CHARIOT A2 Statistical Report

Alexander Ooms
20Dec2022
Version 2.0.
Based on Protocol Version 5.0, 26 Oct 2020.
Based on Statistical Analysis Plan Version 2.0, 07 Jan 2021.
Datalock Date: 24 May 2022.
Version of R: 4.1.0.

Table of Contents

1 INTRODUCTION

This document details the analysis for the main paper(s) reporting results from the CRUK, Merck and The University of Oxford-funded multicentre phase I dose escalation safety study combining the ATR inhibitor M6620 with chemoradiotherapy in oesophageal cancer using time to event continual reassessment method (CHARIOT). The results reported in these papers follow the strategy set out in the Statistical Analysis Plan (include reference to name, version and date of Statistical Analysis Plan (SAP) (Version 2.0, 07Jan2021). Exploratory analyses not pre-specified in the protocol and/or SAP will be expected to follow the broad principles laid down in the SAP and will be reported as post-hoc analyses in this report. This report is limited to CHARIOT Stage A2.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of the analysis strategy; If reported, the analyses will be marked as post-hoc; the source of the suggestion will be acknowledged and the reader will be advised to rely on the pre-specified analysis for the interpretation of the results.

Analysis was carried out using R version 4.1.0 (2021-05-18) and OpenBUGS V3.2.3. Software has been validated and is stored centrally. The R package checkpoint() is used to install R packages as they were on 16 Dec 2022 for future reproducibility. For draft reports, checkpoint will not be run.

Any deviations from the SAP will be described and justified in this report.

1.1 Key Personnel

Author (Trial Statistician): Mr Alexander Ooms

Reviewers (Chief Investigator, Trial Manager, DSMC, TSC, Statistician, as appropriate): Dr Matthew Parkes, Prof Maria Hawkins

Approvers (Author, Senior Statistician, Chief Investigator): Mr Alexander Ooms, Dr Matthew Parkes, Prof Maria Hawkins

2 CHANGES FROM PREVIOUS VERSIONS OF THE STATISTICAL REPORT

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons
V1.0_22Sep2022	Alexander Ooms	Protocol_V5.0_26Oct2020	Not applicable as this is the 1st issue
V2.0_20Dec2022	Alexander Ooms	Protocol_V5.0_26Oct2020	Revised to include feedback from Merck representatives

3 STUDY METHODS

3.1 Software Employed

Analyses were undertaken using R version 4.1.0 (2021-05-18) and OpenBugs V3.2.3.

3.2 Data Quality

Data checks were performed during the entire recruiting process of the trial by both the trial statisitician and the trial team, primarily focussed on data presented dose decision meetings. Details of the final data checks prior to the final data lock can be found in the statistical Trial Master File (sTMF). Checks for missingness of outcome data, implausible values recorded and dates being in sensible ranges were performed. Queries were raised to the trial team and were all closed by the time of the final data lock (24 May 2022).

Derivation of variables and survival times used in this report have been performed as outlined in the SAP. These derivations, the creation of a Final Master Data Files and any other data preparations have been performed in a separate program to the one used to create this final statistical report and can be found in the sTMF.

3.3 Interim Analysis

There were 14 interim dose decisions for Stage A2. The first occurred on 01Jul2019 and the final interim analysis was on 26May2021.

Interim Number	Date	Sample Size at Time of Decision+	Decision
1	01Jul2019	3	Escalate to Schedule 2
2	05Aug2019	5	Escalate to Schedule 3
3	09Sep2019	6	Escalate to Schedule 4

Interim Number	Date	Sample Size at Time of Decision+	Decision
4	16Oct2019	7	Remain on Schedule 4
5	07Nov2019	7	Remain on Schedule 4
6	16Dec2019	8	Remain on Schedule 4
7	17Feb2020	9	Remain on Schedule 4
8	12Mar2020	9	Remain on Schedule 4
9	27Aug2020	9	Remain on Schedule 4
10	26Oct2020	10	De-escalate to Schedule 3
11	14Dec2020	11	Remain on Schedule 3
12	17Feb2021*	12	Remain on Schedule 3
13	11Mar2021	12	Remain on Schedule 3
14	26May2021	14	Remain on Schedule 3

+CH-A2-104 and CH-A2-111 both withdrew before starting treatment, they are not included in the given sample sizes. * Dose Decision made via email.

3.4 Changes to Original Randomisation

This trial was not randomised.

3.5 Deviations from the Original Planned Statistical Analysis Plan

An additional analysis not pre-specified in the Statistical Analysis Plan has been included in this report at the request of the trial's independent Safety Review Committee. This analysis stipulated repeating the primary analysis using a prior "skeleton" (initial guesses of toxicity rates at each dose level) generated from the "getprior" function from the "dfcrm" R package. The results are presented, and compared to the primary analysis using the trial's original skeleton, in the *Additional Analyses Not Specified in the Protocol or the SAP* section of this report.

3.6 Suggested Statistical Methods Section for Publication

This trial used a Time-to-Event Continual Reassessment Method (TiTE-CRM) trial design to evaluate the safety of M6620 in combination with radiotherapy in patients with esophageal cancer in the palliative setting (Stage A1) or chemotherapy (cisplatin and capecitabine) in patients with any metastatic disease in the palliative setting (Stage A2). Patients in A1 were followed up for dose-limiting toxicities (DLTs) for nine weeks, patients in A2 had a DLT window of four weeks. Data is separated by Stage and presented by dosing schedule allocated where appropriate. Trial design parameters used in both stages are given in this table.

Design Parameter	Stage A1	Stage A2
Number of Schedules	6	4
Target Toxicity Level	0.25	0.3
Starting Schedule	1	1
Max Number of Patients	20	20
TiTE Weight Function Used	$w = \frac{1}{2}(\frac{t}{T} + \frac{d}{D})$	$w = \frac{1}{2}(\frac{t}{T} + \frac{d}{D})$
DLT Window Length	61 Days	21 Days
Dose Toxicity Curve Model	Power ($dose_i^{exp(\alpha)}$)	Power ($dose_i^{exp(\alpha)}$)
Priors	$\alpha \sim N(0, 1.158^2)$	$\alpha \sim N(0, 1.158^2)$
Prior Probability of Toxicity on Each Schedule	0.12, 0.15, 0.18, 0.20, 0.22, 0.25	0.17, 0.20, 0.25, 0.30

t = amount of time each patient has been observed, d = amount of M6620 given, T = DLT Window, D = Max M6620 on a given schedule. $dose_i$ *= dose level i, i = 1,…, K. K = 6 for A1, K = 4 for A2.*

The definition of the MTD for both Stages is given as the treatment schedule that is closest to but not above the target toxicity level. During dose decisions, no dose skipping when escalating was permitted, there was no restrictions on de-escalation.

In both stages the starting dose was the lowest dose. A1 examined 6 doses of M6620 whilst keeping the Radiotherapy dose constant (35Gy in 15 Fractions) across schedules. A2 examined 4 doses of M6620 whilst keeping Cisplatin ($60mg/m^2$ per cycle) and Capecitabine ($625mg/m^2$ bd) constant for six cycles of three weeks across schedules.

The primary outcome was to determine the maximum tolerated dose (MTD) for both A1 and A2. Adverse Events and Serious Adverse Events, compliance to all therapies, overall and progression free survival and RECIST are secondary outcome measures in both stages. In-field radiotherapy control was also tabulated to assess the efficacy in Stage A1.

The trial was not randomised or blinded, patients were assigned a treatment schedule based on all available safety data in the TiTE-CRM model producing a recommended dose for the next patient.

The primary safety population included any patient who received at least one dose of M6620. All patients who receive treatment within the study will be evaluable for response.

Data is analysed and reported on all available data, no imputation has been used in any analysis.

Planned early stopping rule were included in this study. These were:

- **Safety**: A Stage will stop for safety if, at any point in the trial, there is sufficient evidence to suggest that schedule 1 is too toxic. More specifically, we will consider schedule 1 to be too toxic if, given all the available data, there is a high probability that the DLT rate is greater than the target toxicity level, (i.e. P(Toxicity at treatment schedule 1 > TTL | data) > 0.95).

- **A1 Success**: Stage A1 will stop for success when either a total of 10 patients have been assigned to a particular treatment schedule or 20 patients have been recruited, whichever occurs first.

- **A2 Success**: The trial will stop for success when either six patients have been assigned to the fourth treatment schedule ($140mg/m^2$ of M6620 (Berzosertib) twice weekly) or 20 patients in total have been recruited, whichever occurs first.

Four sensitivity analyses were presented for each dose decision meeting, they were analysed uisng the TiTE-CRM model as in the primary analysis. For each of these analyses the posterior probabilities of toxicity at each dose level and their associated 95% credible interval were presented. These analyses were:

1. Only using those patients did not miss any of their dose prescribed on their dose schedule, and weighted using the original TiTE-CRM weights, i.e. weighting only according to length of follow-up and not taking account of how much dose has been received
2. Only using those patients who have received at least 75% of the prescribed dose, using the same weight function as in the main analysis
3. Only using those patients who have received at least 75% of the prescribed dose, but using the original TiTE-CRM weights
4. Using the same population and weighting as the primary population but assuming the “Most Toxic” Scenario. All patients currently on treatment within the DLT window have been assigned a DLT.

There are no pre-specified subgroup analyses.

4 RESULTS

4.1 Study Participants

Two participants, CH-A2-104 and CH-A2-111, withdrew before starting so will not be included in the reported result unless otherwise stated.

Figure 1 is the CONSORT diagram for CHARIOT A2, it presents the flow of participants through all stages of the trial: eligibility, registration, allocation and analysis.

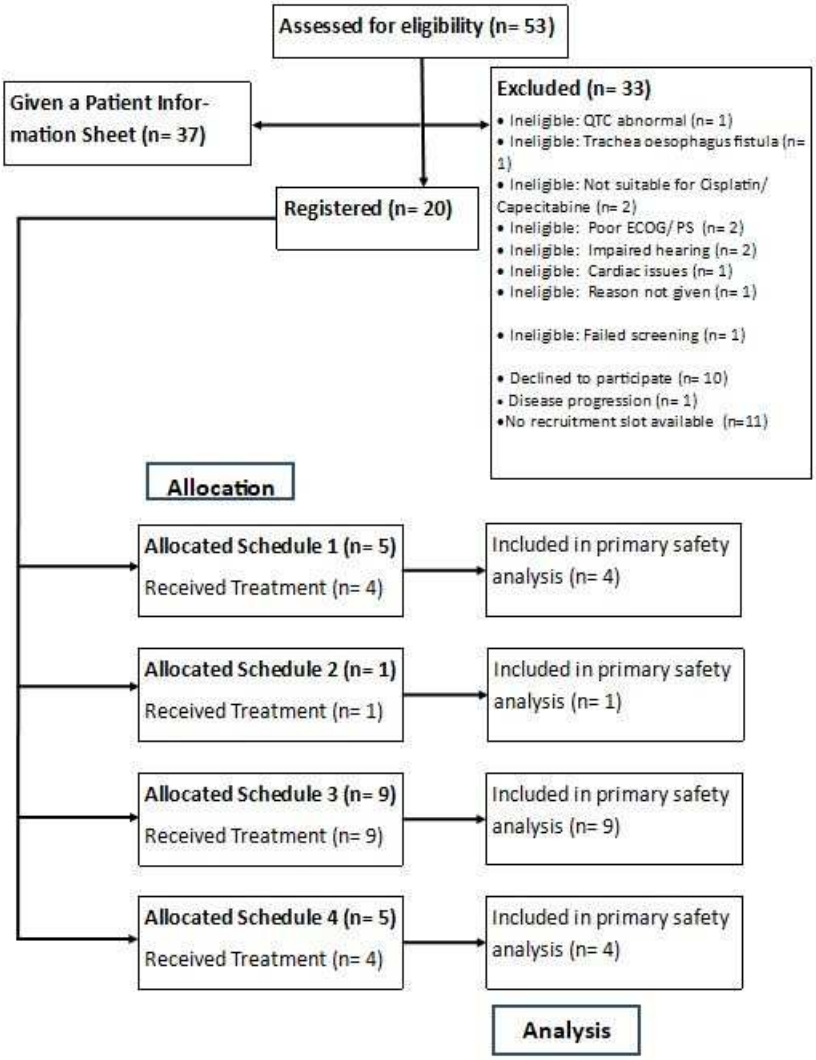


Figure 1: CONSORT Diagram

4.2 Recruitment

The first patient was registered into Stage A2 on 28 December 2018. The final patient was registered on 13 August 2021 and the final study visit was on 21 March 2022. The trial reached its original recruitment target of 20 patients, however two patients withdrew before starting treatment. Two no cost-extensions were granted for this trial: one of 2 years, one of seven months.

4.3 Baseline Characteristics

Baseline characteristics are presented in Table 1, the tumour information is given in Table 2.

Table 1: Baseline characteristics

	Schedule 1 (n=5)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=5)	Total (n=20)
Gender					
Male	3 (60.0)	1 (100.0)	3 (33.3)	2 (40.0)	9 (45.0)
Female	2 (40.0)	0 (0.0)	6 (66.7)	3 (60.0)	11 (55.0)
Age	n=5, 64.0 (6.7)	n=1, 45.0 (NA)	n=9, 63.2 (8.6)	n=5, 54.8 (15.5)	n=20, 60.4 (10.9)
Etnicity					
White British	5 (100.0)	1 (100.0)	9 (100.0)	5 (100.0)	20 (100.0)
Height (cm)	n=5, 169.5 (9.1)	n=1, 166.5 (NA)	n=9, 170.5 (7.5)	n=5, 167.4 (19.3)	n=20, 169.3 (11.0)
Weight (Kg)	n=5, 78.1 (12.4)	n=1, 82.4 (NA)	n=9, 77.1 (11.3)	n=5, 84.6 (27.6)	n=20, 79.5 (16.0)
Smoking Status					
Current smoker	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)
Ex-smoker	1 (20.0)	1 (100.0)	4 (44.4)	3 (60.0)	9 (45.0)
Never smoked	3 (60.0)	0 (0.0)	5 (55.6)	2 (40.0)	10 (50.0)
Site					
Beatson, Glasgow	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (5.0)
Churchill, Oxford	5 (100.0)	0 (0.0)	7 (77.8)	4 (80.0)	16 (80.0)
St James, Leeds	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.0)
Velindre, Cardiff	0 (0.0)	1 (100.0)	1 (11.1)	0 (0.0)	2 (10.0)
Tumour Grade					

	Schedule 1 (n=5)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=5)	Total (n=20)
Well differentiated (G1)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.0)
Moderately differentiated (G2)	1 (20.0)	1 (100.0)	3 (33.3)	0 (0.0)	5 (25.0)
Poorly differentiated (G3)	4 (80.0)	0 (0.0)	0 (0.0)	3 (60.0)	7 (35.0)
Unknown or cannot be assessed (GX)	0 (0.0)	0 (0.0)	5 (55.6)	2 (40.0)	7 (35.0)
Locoregional Disease					
Yes	1 (20.0)	0 (0.0)	6 (66.7)	3 (60.0)	10 (50.0)
No	4 (80.0)	1 (100.0)	3 (33.3)	2 (40.0)	10 (50.0)
Distant Metasases					
Yes	5 (100.0)	1 (100.0)	8 (88.9)	5 (100.0)	19 (95.0)
No	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.0)
Prior Radiotherapy					
Yes	4 (80.0)	0 (0.0)	2 (22.2)	2 (40.0)	8 (40.0)
No	1 (20.0)	1 (100.0)	7 (77.8)	3 (60.0)	12 (60.0)
Prior Systemic Treatment					
Yes	4 (80.0)	1 (100.0)	9 (100.0)	5 (100.0)	19 (95.0)
No	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)

Data are mean (SD) or n (%). Where n=1, SD is N/A.

Table 2: Tumour type

Subject	Primary Tumour Site	Tumour Type	Tumour Grade	HER2 Status	Diagnosis Date
CH-A2-101	Bile Duct	Cholangiocarcinoma	Poorly differentiated (G3)	Unknown/ no data	30Nov2016

Subject	Primary Tumour Site	Tumour Type	Tumour Grade	HER2 Status	Diagnosis Date
CH-A2-102	Uterus	Uterine Leiomyosarcoma	Poorly differentiated (G3)	Not tested	12Aug2013
CH-A2-103	Bladder	Urothelial Cancer	Poorly differentiated (G3)	Not tested	17Nov2017
CH-A2-104	Larynx	Chondrosarcoma	Moderately differentiated (G2)	Unknown/ no data	06Apr2016
CH-A2-105	Thyroid	Papillary Thyroid Cancer	Poorly differentiated (G3)	Unknown/ no data	29Sep2017
CH-A2-106	Duodenum	Duodenum Adenocarcinoma	Moderately differentiated (G2)	Unknown/ no data	06Jan2016
CH-A2-107	Pancreas	Cholangiocarcinoma	Unknown or cannot be assessed (GX)	Unknown/ no data	04Feb2017
CH-A2-108	Right Kidney	Urothelial Cancer	Poorly differentiated (G3)	Not tested	13Jul2018
CH-A2-109	Left Breast	Ductal Breast Cancer	Poorly differentiated (G3)	Negative	27Oct2018
CH-A2-110	Forehead	Melanoma	Unknown or cannot be assessed (GX)	Unknown/ no data	01Jan2001
CH-A2-111	Oesophagus	Oesophageal Adenocarcinoma	Poorly differentiated (G3)	Negative	03Oct2018
CH-A2-112	Left Shoulder	Melanoma	Unknown or cannot be assessed (GX)	Not tested	20Mar2012
CH-A2-113	Back	Melanoma	Unknown or cannot be assessed (GX)	Unknown/ no data	01Sep2013

Subject	Primary Tumour Site	Tumour Type	Tumour Grade	HER2 Status	Diagnosis Date
CH-A2-114	Pancreas	Pancreatic NET	Well differentiated (G1)	Unknown/ no data	28Jun2019
CH-A2-115	Ocular	Choroidal Melanoma	Unknown or cannot be assessed (GX)	Unknown/ no data	01Feb2019
CH-A2-116	Upper Mid Oesophagus	Squamous Cell Carcinoma Oesophagus	Moderately differentiated (G2)	Unknown/ no data	04Dec2018
CH-A2-117	Rectal	Rectal Adenocarcinoma	Moderately differentiated (G2)	Unknown/ no data	01Apr2018
CH-A2-118	Lower Leg NOS	Sarcoma	Unknown or cannot be assessed (GX)	Not tested	13Jan2017
CH-A2-119	Oesophagus	Gastro Oesopahgeal Adenocarcinoma	Moderately differentiated (G2)	Negative	10Nov2020
CH-A2-120	Upper Right Arm	Melanoma	Unknown or cannot be assessed (GX)	Unknown/ no data	01Oct1999

Details on prior therapy, full details on baseline symptoms, prior surgery, prior radiotherapy, and lesions from the baseline CT-scans are given in *Appendix - Baseline*. The most common baseline symptom was Fatigue (9). All baseline scans were done via CT-scan. The mean max diameter of target lesions at baseline was 29.2mm with a standard deviation of 18. Most target lesions were in the Lung (24) or the Liver (4).

A full list of medical history can also be found in *Appendix - Baseline*.

4.3.1 Numbers Analysed

Numbers of participants included in the primary safety analysis and 12 week overall RECIST efficacy reporting are included in Table 3. Twelve week RECIST is considered the main time point for tumour response evaluation defined in the study protocol, other restaging scans undertaken in this trial are reported in *Appendix - Scans*.

Table 3: Numbers analysed

	Schedule 1 (n=5)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=5)	Total (n=20)
Primary Safety	4 (80.0)	1 (100.0)	9 (100.0)	4 (80.0)	18 (90.0)

	Schedule 1 (n=5)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=5)	Total (n=20)
Efficacy (12 Week Overall RECIST)	1 (20.0)	1 (100.0)	3 (33.3)	3 (60.0)	8 (40.0)

4.4 Compliance

4.4.1 Treatment Compliance

4.4.1.1 Capecitabine compliance

Patients were prescribed 625mg/m2 bd, orally for six, three week cycles. The first date of capecitabine treatment in this trial was 09 Jan 2019 and the final date was 20 Dec 2021 The mean duration of Capecitabine treatment was 81.1 days with standard deviation of 53.3.

Capecitabine compliance is presented in Table 4, stoppages and reductions are presented by cycle in Figure 2. All doses of Capecitabine given, including dose reductions, are presented in Figure 3. Ten out of the 18 (56%) patients who started treatment stopped their Capecitabine treatment before the end. The main reasons for early stoppages were Disease Progression and Neutropenia, accounting for 70% (7 out of 10) off all stoppages. 64% (7 out of 10) stoppages occurred in the first two cycles of treatment. A full list of all reductions and modifications to Capecitabine treatment reported as part of this study can be found in *Appendix - Compliance*.

Table 4: Capecitabine compliance

	Schedule 1 (n=4)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=4)	Total (n=18)
Capecitabine % Received					
100%	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.6)
>=90%, <100%	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)
>=75%, <90%	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (5.6)
<75%	3 (75.0)	0 (0.0)	8 (88.9)	4 (100.0)	15 (83.3)
Treatment Duration (Days)	n=4, 50.0 (52.7)	n=1, 132.0 (NA)	n=9, 74.0 (51.2)	n=4, 115.2 (50.0)	n=18, 81.1 (53.3)
Stopped Early					
Yes	3 (75.0)	0 (0.0)	6 (66.7)	1 (25.0)	10 (55.6)
No	1 (25.0)	1 (100.0)	3 (33.3)	3 (75.0)	8 (44.4)
Stopped Reason					
Did Not Stop Early	1 (25.0)	1 (100.0)	3 (33.3)	3 (75.0)	8 (44.4)

	Schedule 1 (n=4)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=4)	Total (n=18)
Disease Progression	2 (50.0)	0 (0.0)	2 (22.2)	1 (25.0)	5 (27.8)
Neutropenia	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	2 (11.1)
Off Study	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.6)
Patient Decision	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)
Unacceptable Toxicity	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.6)
Stopped Cycle					
Cycle 1	2 (66.7)	0 (NaN)	2 (33.3)	0 (0.0)	4 (22.2)
Cycle 2	1 (33.3)	0 (NaN)	1 (16.7)	1 (100.0)	3 (16.7)
Cycle 3	0 (0.0)	0 (NaN)	2 (33.3)	0 (0.0)	2 (11.1)
Cycle 4	0 (0.0)	0 (NaN)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 5	0 (0.0)	0 (NaN)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 6	0 (0.0)	0 (NaN)	1 (16.7)	0 (0.0)	1 (5.6)
Dose Reduction					
Yes	0 (0.0)	1 (100.0)	4 (44.4)	3 (75.0)	8 (44.4)
No	4 (100.0)	0 (0.0)	5 (55.6)	1 (25.0)	10 (55.6)
Reduction Reason					
Adverse Events	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.6)
Decreased Platelet Count	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.6)
Low Neutrophils	0 (0.0)	1 (100.0)	0 (0.0)	1 (25.0)	2 (11.1)
Neutropenia	0 (0.0)	0 (0.0)	2 (22.2)	1 (25.0)	3 (16.7)
No Reduction	4 (100.0)	0 (0.0)	5 (55.6)	1 (25.0)	10 (55.6)
Thrombocytopenia and Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (5.6)

	Schedule 1 (n=4)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=4)	Total (n=18)
Reduction Cycle					
Cycle 1	0 (NaN)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 2	0 (NaN)	1 (100.0)	2 (50.0)	3 (100.0)	6 (33.3)
Cycle 3	0 (NaN)	0 (0.0)	1 (25.0)	0 (0.0)	1 (5.6)
Cycle 4	0 (NaN)	0 (0.0)	1 (25.0)	0 (0.0)	1 (5.6)
Cycle 5	0 (NaN)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 6	0 (NaN)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

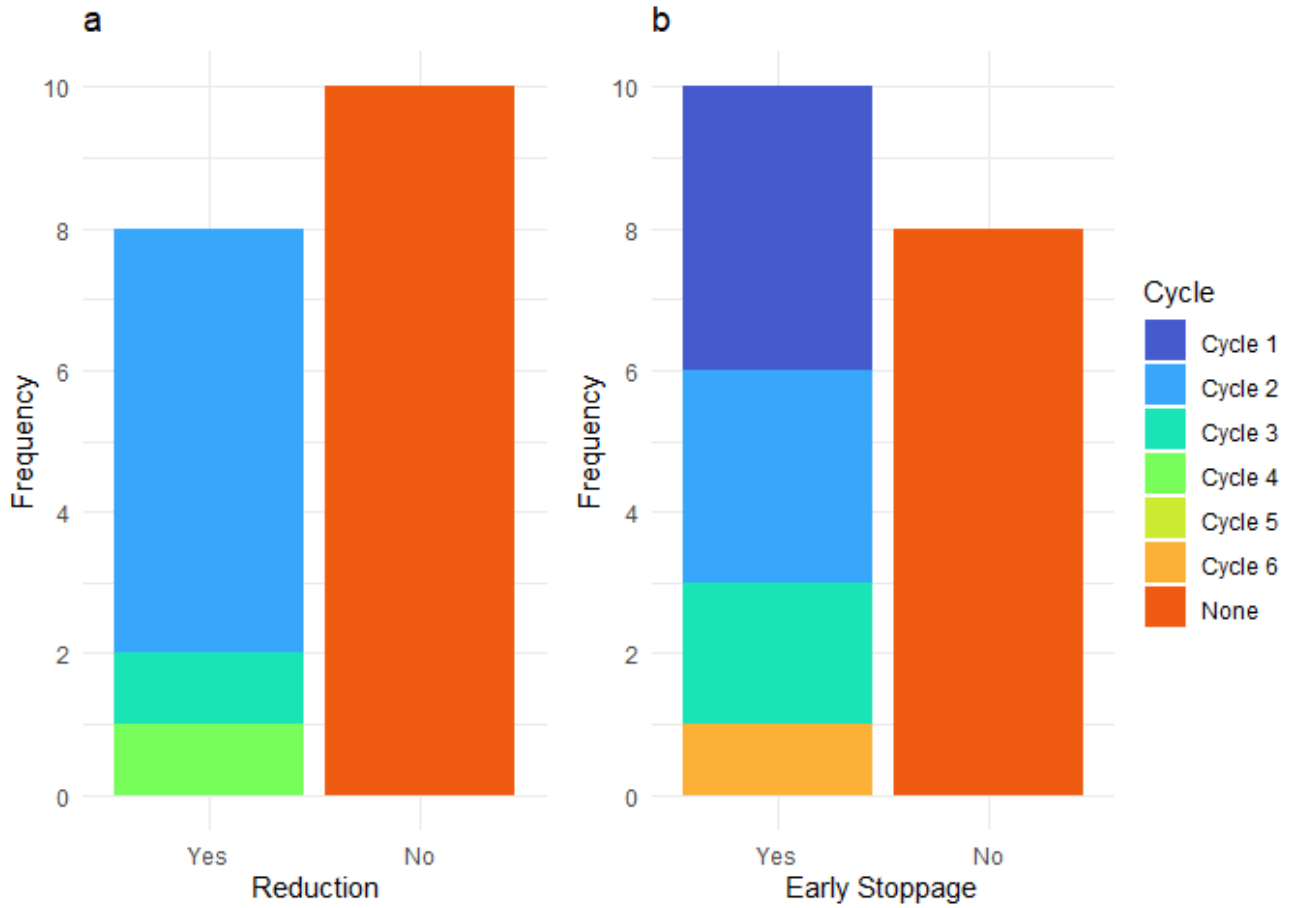


Figure 2: Capecitabine reductions (a) and early stoppages (b) by cycle

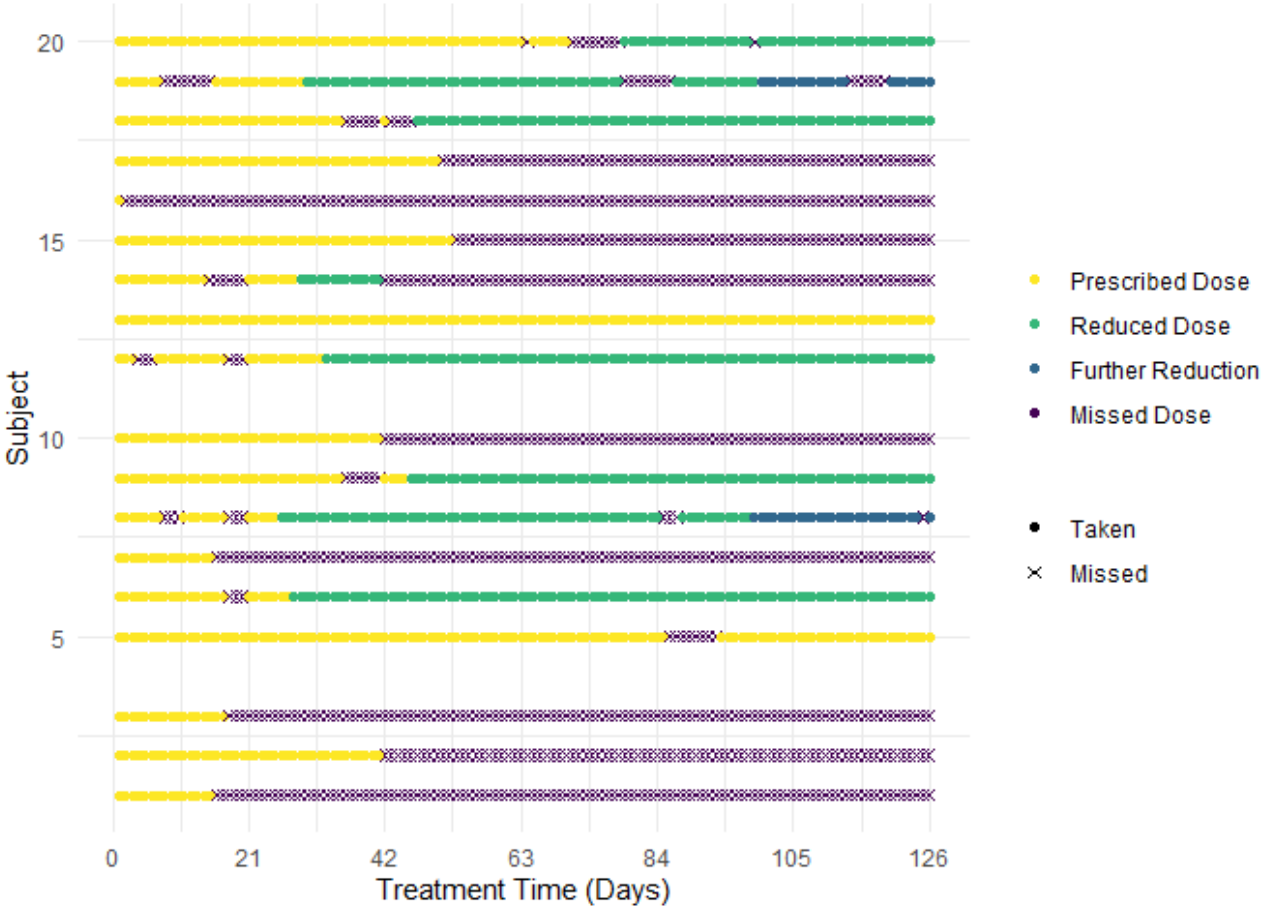


Figure 3: Capecitabine doses received

4.4.1.2 Cisplatin compliance

Patients were prescribed one 60 mg/m2 Cisplatin IV infusion on day one of each three week cycle, for six cycles. The first date of capecitabine treatment in this trial was 09 Jan 2019 and the final date was 30 Nov 2021 The mean duration of Cisplatin treatment was 57.4 days with standard deviation of 49.5.

Cisplatin compliance is presented in Table 5, stoppages and reductions are presented by cycle in Figure 2. All doses of Cisplatin given, including dose reductions, are presented in Figure 5.Nine out of the 18 (50%) patients who started treatment stopped their Cisplatin treatment before the end. The main reasons for early stoppages was Disease Progression 67% (6 out of 9) off all stoppages. A full list of all reasons for delays to Cisplatin treatment reported as part of this study can be found in *Appendix - Compliance*.

Table 5: Cisplatin compliance

	Schedule 1 (n=4)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=4)	Total (n=18)
Cisplatin % Received					
100%	1 (25.0)	0 (0.0)	2 (22.2)	0 (0.0)	3 (16.7)
>=90%, <100%	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.6)

	Schedule 1 (n=4)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=4)	Total (n=18)
>=75%, <90%	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (5.6)
<75%	3 (75.0)	0 (0.0)	6 (66.7)	4 (100.0)	13 (72.2)
Stopped Early					
Yes	3 (75.0)	0 (0.0)	5 (55.6)	1 (25.0)	9 (50.0)
No	1 (25.0)	1 (100.0)	4 (44.4)	3 (75.0)	9 (50.0)
Stopped Reason					
AEs or SAEs	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.6)
Did Not Stop Early	1 (25.0)	1 (100.0)	4 (44.4)	3 (75.0)	9 (50.0)
Disease Progression	2 (50.0)	0 (0.0)	3 (33.3)	1 (25.0)	6 (33.3)
Patient Decision	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)
Unacceptable Toxicity	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.6)
Cycles Received					
1	2 (50.0)	0 (0.0)	2 (22.2)	0 (0.0)	4 (22.2)
2	1 (25.0)	0 (0.0)	1 (11.1)	0 (0.0)	2 (11.1)
3	0 (0.0)	0 (0.0)	2 (22.2)	1 (25.0)	3 (16.7)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6	1 (25.0)	1 (100.0)	4 (44.4)	3 (75.0)	9 (50.0)
Dose Reduction					
Yes	0 (0.0)	1 (100.0)	4 (44.4)	3 (75.0)	8 (44.4)
No	4 (100.0)	0 (0.0)	5 (55.6)	1 (25.0)	10 (55.6)
Reduction Reason					
Low Neutrophils	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (5.6)
Low Platelets	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.6)

	Schedule 1 (n=4)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=4)	Total (n=18)
Neutropenia	0 (0.0)	0 (0.0)	1 (11.1)	2 (50.0)	3 (16.7)
No Reduction	4 (100.0)	0 (0.0)	5 (55.6)	1 (25.0)	10 (55.6)
Thrombocytopenia	0 (0.0)	0 (0.0)	2 (22.2)	1 (25.0)	3 (16.7)
Reduction Cycle					
Cycle 1	0 (NaN)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 2	0 (NaN)	1 (100.0)	2 (50.0)	2 (66.7)	5 (27.8)
Cycle 3	0 (NaN)	0 (0.0)	1 (25.0)	1 (33.3)	2 (11.1)
Cycle 4	0 (NaN)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 5	0 (NaN)	0 (0.0)	1 (25.0)	0 (0.0)	1 (5.6)
Cycle 6	0 (NaN)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

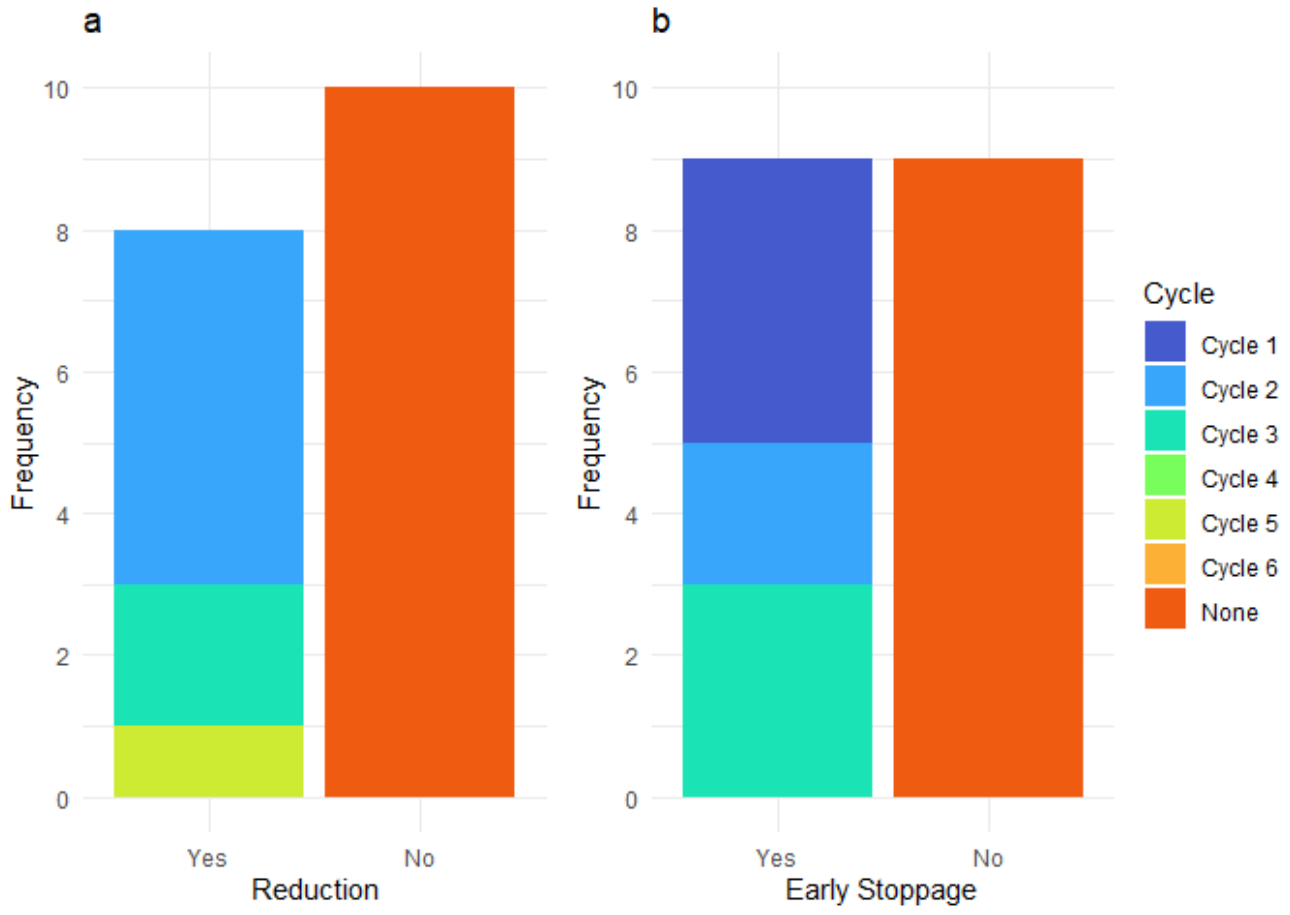


Figure 4: Cisplatin reductions (a) and early stoppages (b) by cycle

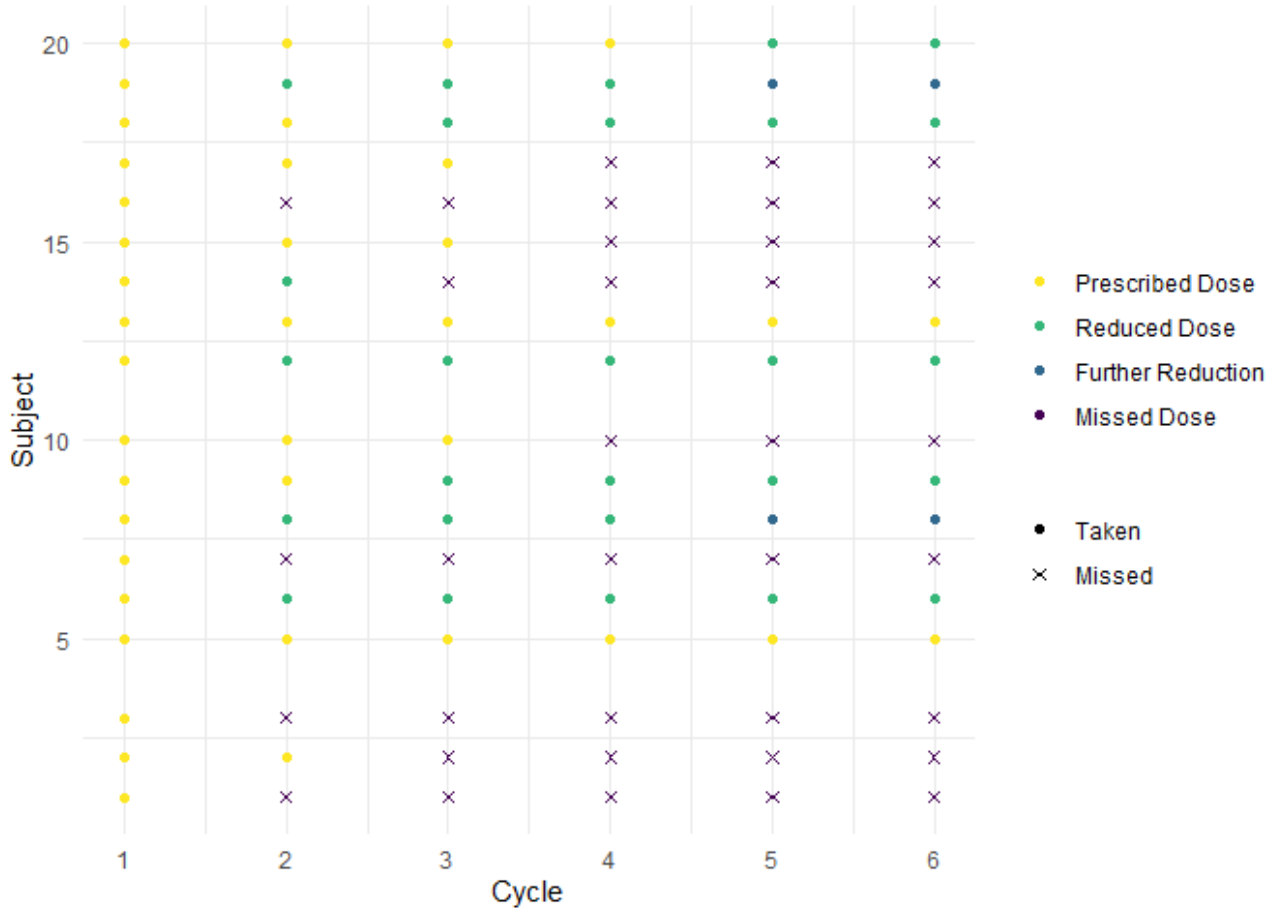


Figure 5: Cisplatin doses received

4.4.1.3 M6620 compliance

M6620 compliance will be reported over the full six cycle treatment and by cycle 1 as compliance in cycle 1 contributes to the TiTE-CRM model used in recommending the next schedule, while the trial was running, and calculating the maximum tolerated dose. Compliance outside of cycle 1 was not used in the model as this was outside of the dose limiting toxicity window of 21 days from starting treatment.

The first dose of M6620 given in Stage A2 was on 10 Jan 2019, the final dose was given on 20 Jul 2021. The mean duration of treatment was 25.4 days with a standard deviation of 18. The average infusion time was 65 minutes with standard deviation 8.

M6620 Compliance - Cycle 1

M6620 compliance is presented in Table 6. A full line-listing of M6620 compliance in Cycle 1 is given in Table 7.

Table 6: M6620 compliance in cycle 1

	Schedule 1 (n=4)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=4)	Total (n=18)
M6620 % Received - Cycle 1					

	Schedule 1 (n=4)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=4)	Total (n=18)
100%	3 (75.0)	0 (0.0)	4 (44.4)	2 (50.0)	9 (50.0)
>=90%, <100%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>=75%, <90%	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (5.6)
<75%	1 (25.0)	0 (0.0)	5 (55.6)	2 (50.0)	8 (44.4)

Table 7: M6620 listing in cycle 1

Subject	Schedule	M6620 Received	M6620 Expected	% Received
CH-A2-101	Schedule 1	180	270	66.7
CH-A2-102	Schedule 1	270	270	100.0
CH-A2-103	Schedule 1	270	270	100.0
CH-A2-104	Schedule 1		270	
CH-A2-105	Schedule 1	270	270	100.0
CH-A2-106	Schedule 2	450	540	83.3
CH-A2-107	Schedule 3	280	420	66.7
CH-A2-108	Schedule 4	560	840	66.7
CH-A2-109	Schedule 4	840	840	100.0
CH-A2-110	Schedule 4	840	840	100.0
CH-A2-111	Schedule 4		840	
CH-A2-112	Schedule 4	560	840	66.7
CH-A2-113	Schedule 3	420	420	100.0
CH-A2-114	Schedule 3	280	420	66.7
CH-A2-115	Schedule 3	280	420	66.7
CH-A2-116	Schedule 3	140	420	33.3
CH-A2-117	Schedule 3	420	420	100.0
CH-A2-118	Schedule 3	420	420	100.0
CH-A2-119	Schedule 3	280	420	66.7

Subject	Schedule	M6620 Received	M6620 Expected	% Received
CH-A2-120	Schedule 3	420	420	100.0

M6620 Compliance - All Cycles

Table 8 gives details of patients who stopped M6620 treatment early and the reason. M6620 compliance is presented in Table 9. A full line-listing of M6620 compliance in Cycle 1 is given in Table 10. All reasons for missed M6620 doses are given in *Appendix - Compliance*. Figure 6 presents M6620 and Cisplatin compliance for all cycles. All doses of M6620 given, including dose reductions, are presented in Figure 7.

Table 8: M6620 treatment total stoppages

Subject	Schedule	Early Stop	Cycle	Reason	% Received
CH-A2-101	Schedule 1	Yes	Cycle 1	Patient Decision	11.1
CH-A2-102	Schedule 1	Yes	Cycle 2	Disease Progression	27.8
CH-A2-103	Schedule 1	Yes	Cycle 1	Disease Progression	16.7
CH-A2-107	Schedule 3	Yes	Cycle 1	Dose Limiting Toxicity	11.1
CH-A2-110	Schedule 4	Yes	Cycle 2	Disease Progression	33.3
CH-A2-114	Schedule 3	Yes	Cycle 2	Disease Progression	22.2
CH-A2-115	Schedule 3	Yes	Cycle 3	Disease Progression	33.3
CH-A2-116	Schedule 3	Yes	Cycle 1	AEs or SAEs	5.6
CH-A2-117	Schedule 3	Yes	Cycle 3	Disease Progression	38.9

Table 9: M6620 full compliance

	Schedule 1 (n=4)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=4)	Total (n=18)
M6620 % Received - All Cycles					
100%	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	2 (11.1)
>=90%, <100%	1 (25.0)	1 (100.0)	0 (0.0)	1 (25.0)	3 (16.7)
>=75%, <90%	0 (0.0)	0 (0.0)	2 (22.2)	1 (25.0)	3 (16.7)
<75%	3 (75.0)	0 (0.0)	5 (55.6)	2 (50.0)	10 (55.6)
Stopped Early					
Yes	3 (75.0)	0 (0.0)	5 (55.6)	1 (25.0)	9 (50.0)

	Schedule 1 (n=4)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=4)	Total (n=18)
No	1 (25.0)	1 (100.0)	4 (44.4)	3 (75.0)	9 (50.0)
Stopped Reason					
AEs or SAEs	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.6)
Did Not Stop Early	1 (25.0)	1 (100.0)	4 (44.4)	3 (75.0)	9 (50.0)
Disease Progression	2 (50.0)	0 (0.0)	3 (33.3)	1 (25.0)	6 (33.3)
Dose Limiting Toxicity	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.6)
Patient Decision	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)
Stopped Cycle					
Cycle 1	2 (66.7)	0 (NaN)	2 (40.0)	0 (0.0)	4 (22.2)
Cycle 2	1 (33.3)	0 (NaN)	1 (20.0)	1 (100.0)	3 (16.7)
Cycle 3	0 (0.0)	0 (NaN)	2 (40.0)	0 (0.0)	2 (11.1)
Cycle 4	0 (0.0)	0 (NaN)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 5	0 (0.0)	0 (NaN)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 6	0 (0.0)	0 (NaN)	0 (0.0)	0 (0.0)	0 (0.0)

Table 10: M6620 full listing

Subject	Schedule	Early Stop	Cycle Stopped	M6620 Received	M6620 Expected	% Received
CH-A2-101	Schedule 1	Yes	Cycle 1	180	1,620	11.1
CH-A2-102	Schedule 1	Yes	Cycle 2	450	1,620	27.8
CH-A2-103	Schedule 1	Yes	Cycle 1	270	1,620	16.7
CH-A2-104	Schedule 1				1,620	
CH-A2-105	Schedule 1	No		1,530	1,620	94.4
CH-A2-106	Schedule 2	No		3,150	3,240	97.2
CH-A2-107	Schedule 3	Yes	Cycle 1	280	2,520	11.1
CH-A2-108	Schedule 4	No		4,060	5,040	80.6

Subject	Schedule	Early Stop	Cycle Stopped	M6620 Received	M6620 Expected	% Received
CH-A2-109	Schedule 4	No		4,760	5,040	94.4
CH-A2-110	Schedule 4	Yes	Cycle 2	1,680	5,040	33.3
CH-A2-111	Schedule 4				5,040	
CH-A2-112	Schedule 4	No		2,975	5,040	59.0
CH-A2-113	Schedule 3	No		2,520	2,520	100.0
CH-A2-114	Schedule 3	Yes	Cycle 2	560	2,520	22.2
CH-A2-115	Schedule 3	Yes	Cycle 3	840	2,520	33.3
CH-A2-116	Schedule 3	Yes	Cycle 1	140	2,520	5.6
CH-A2-117	Schedule 3	Yes	Cycle 3	980	2,520	38.9
CH-A2-118	Schedule 3	No		2,100	2,520	83.3
CH-A2-119	Schedule 3	No		2,240	2,520	88.9
CH-A2-120	Schedule 3	No		2,520	2,520	100.0

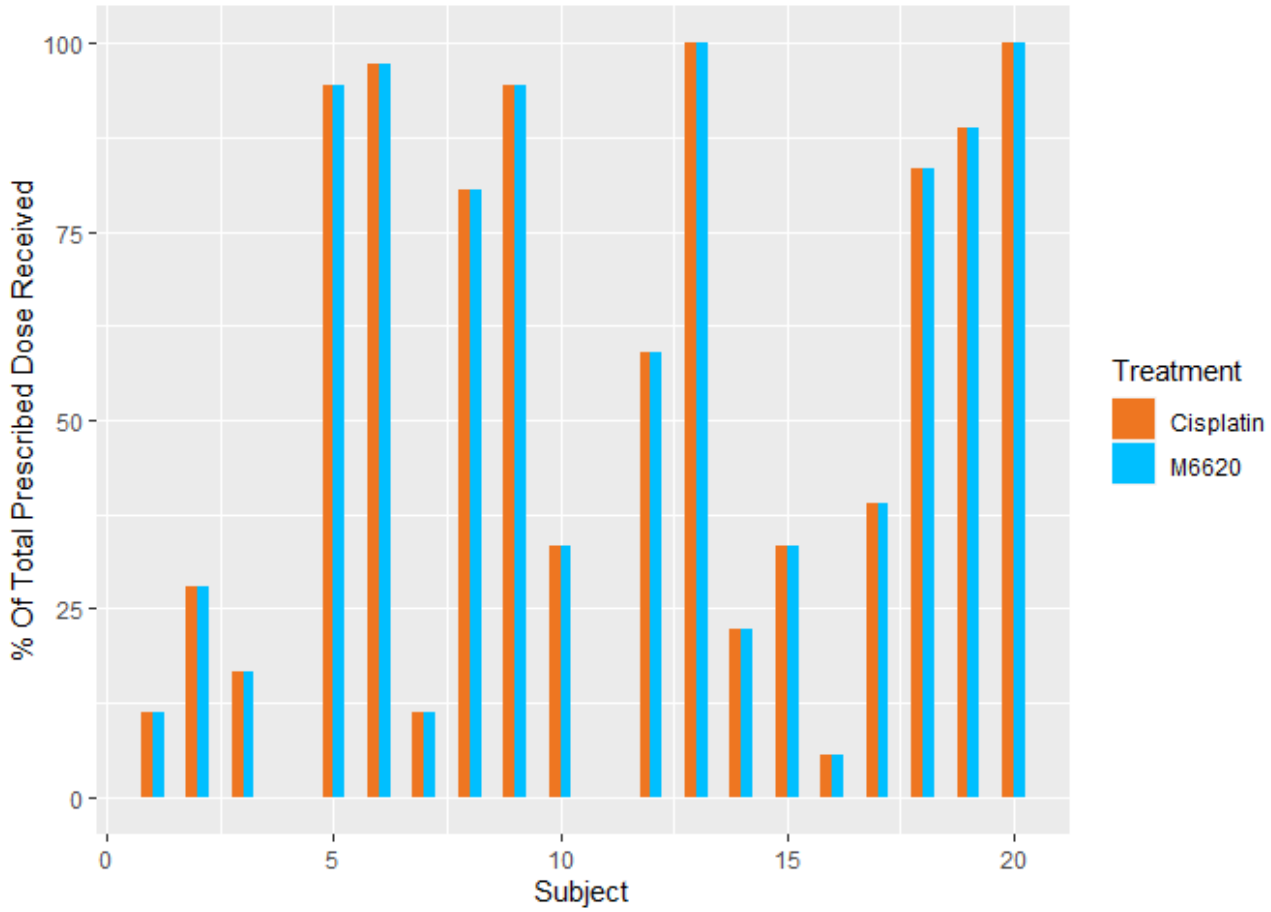


Figure 6: Percentage Cisplatin and M6620 received for each trial participant

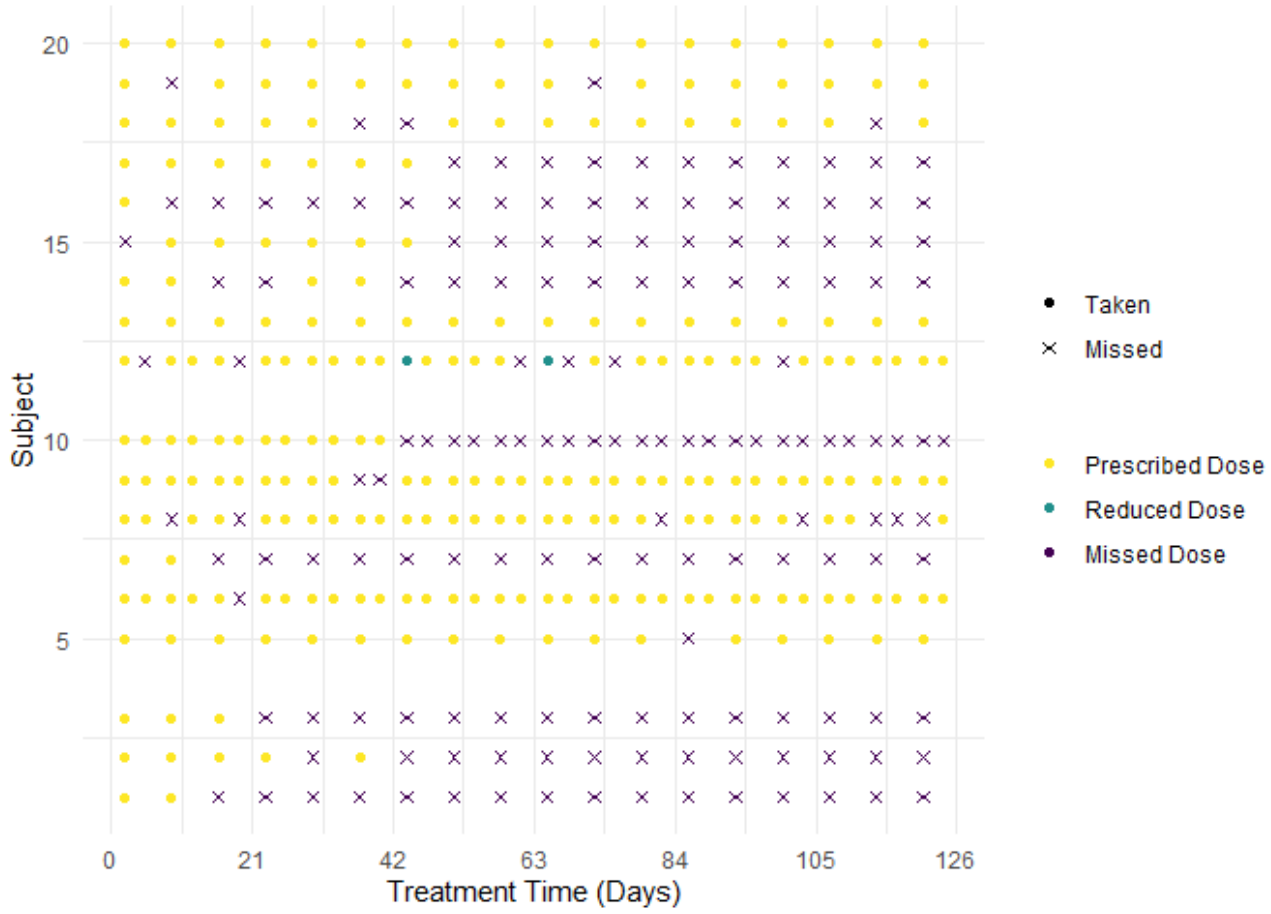


Figure 7: M6620 doses received.

4.4.2 Withdrawals & Protocol Deviations

Two participants, CH-A2-104 and CH-A2-111, withdrew before starting treatment.

Of the 102 deviations reported in Stage A2, 6 of these were important, these are given in Table 11. The full list of deviations is reported in *Appendix - Deviations*.

Table 11: Important protocol deviations

Subject	Site	Date	Description	Action Taken
CH-A2-105	Churchill, Oxford	29 Aug 2019	Cisplatin given to patient in C5D1 after bloods signed off by Dr. Pharmacist noticed bilirubin out of range & team considered this a grade 3 non-haematological toxicity that was considered possibly drug related at the time. If so, Cisplatin should not be given until resolved to G0-1. It was a deviation that this was given. Infusion was stopped, doctor reviewed patient and post hydration was completed and bloods taken. Doctor recommended patient to return following day for liver ultrasound (NAD) and further bilirubin testing, which was decreasing. In retrospect site don't think this is drug related but rather that the patient has gilbert's syndrome and then haemolysed following a blood transfusion.	Important deviation form and CAPA completed by site. PI & co-Is aware. Merck informed. 11Sep2019 update: Reviewed if should have been reported as an SAE. Not applicable, because excluded as related within 24hr period.

Subject	Site	Date	Description	Action Taken
CH-A2-108	Churchill, Oxford	30 Sep 2019	Several patient doses of M6620 were administered on a Monday.	Cycle 1 was discussed with CI at the time - the patient had significant haem toxicity and a number of does were omitted. However, unclear why patient received doses of M6620 on a Monday. Queried with site and unable to give reason. Notified to site as part of Mar2022 deviation review. No further action taken.
CH-A2-110	Churchill, Oxford	03 Feb 2020	Patient CH-A2-110 had all screening assessments performed on 09Jan2020 but trial treatment did not start until 03Feb2020 (screening 25 days prior to treatment, instead of within 21 days prior as per protocol).	Deviation highlighted to site. RN confirmed the dates of screening & C1D1, acknowledged the deviation and will look into how/why this occurred. Update: Site to receive protocol training as part of Stage B refresher SIV. Training set for 02Mar2021 and will include information relating to timing of screening assessments. Update: Site protocol training delivered for key staff on 02Mar2021.
CH-A2-112	Churchill, Oxford	10 Sep 2020	Participant registered to CHARIOT 10Sep2020 and marked by site as eligible. Site identified 11Sep2020 phosphate was out of range 1.56mmol/L (0.7 - 1.45mmol/L) meaning she was ineligible.	Site deem out of range not clinically significant. Patient to be rescreened before treatment start. If ineligible to be withdrawn. CI & PI in agreement. Important deviation form with CAPA completed by site.
CH-A2-113	Churchill, Oxford	23 Oct 2020	Patient received screening CT scan a few hours before consent. In part this occurred due to miscommunication due to some members of the research team having to self-isolate although of course this is not an excuse.	Site to document this occurrence in the source data. Important deviation form to be completed with CAPA 15Dec: Site completed the Deviation form with CAPA and send to CHARIOT. The deviation is now closed.
CH-A2-112	Churchill, Oxford	14 Dec 2020	Patient CH-A2-112 was unintentionally dosed on C3D16 when she had G3 neutropaenia. This has been reported on Ulysses for investigation. She came back for C3D19 and again had G3 neutropaenia and so wasn't dosed. She has already had a dose reduction of capecitabine and cisplatin and M6620. Co-I thought a further reduction wasn't possible. She has only missed one dose and it is not knows what her counts would have been C3D19 if she had not been dosed inappropriately. Site plan C4D1 21Dec2020 if counts have recovered. Request confirmation sponsor in agreement.	OCTO and CI: Agree with plan to assess C4D1. Site to complete important deviation form and investigate what were the circumstances of administering the M6620 when patient neutropenic and establish potential prevention mechanisms. Advised protocol allows a second dose reduction of M6620 allowed to 50% of the starting dose if they've only had a 25% reduction so far. Simon agrees this has not yet been used. Update: CAPA received 04Jan2021. Sub-I suggests protocol retraining for key staff. OCTO to carry out SIV training for site staff in Feb and will ensure that these staff are present. Update: Site protocol training for key staff delivered on 02Mar2021.

4.4.3 Blinding

The CHARIOT trial was not blinded.

4.5 Results

4.5.1 Primary Analysis

The primary analysis is performed using the Time-To-Event Continual Reassessment Method (TiTE-CRM) to established the maximum tolerated dose (MTD) of M6620 in combination with chemotherapy in patients with

metastatic cancer in the palliative setting. For our primary population - all patients who have had any amount of M6620 - the participants go into the CRM model with a weighting defined by both length of follow up and amount of the scheduled dose. The weight function used is $w = \frac{1}{2}\left(\frac{t}{T} + \frac{d}{D}\right)$ with t being time the patient has been followed up for, T is max follow up length, d is number of doses the patient has received and D the maximum number of doses for the schedule they have been prescribed to. If a patient experiences a DLT, they go into the model with a weight of 1. Weight $ $. The pre-defined target toxicity level was 0.3.

Table 12 shows the derivation of the weight used in the TiTE-CRM model for each patient using the weight function $w = \frac{1}{2}\left(\frac{t}{T} + \frac{d}{D}\right)$. Note: all patients have completed their DLT window, therefore $\frac{t}{T} = 1$.

Table 12: Derivation of the patient's TiTE-CRM model weight

Subject	Site	Schedule	M6620 Received	Total M6620	DLT	Weight
CH-A2-101	Churchill, Oxford	Schedule 1	180	270	No DLT	0.833
CH-A2-102	Churchill, Oxford	Schedule 1	270	270	No DLT	1.000
CH-A2-103	Churchill, Oxford	Schedule 1	270	270	No DLT	1.000
CH-A2-104	Churchill, Oxford	Schedule 1		270	No DLT	
CH-A2-105	Churchill, Oxford	Schedule 1	270	270	No DLT	1.000
CH-A2-106	Velindre, Cardiff	Schedule 2	450	540	No DLT	0.917
CH-A2-107	Velindre, Cardiff	Schedule 3	280	420	DLT	1.000
CH-A2-108	Churchill, Oxford	Schedule 4	560	840	No DLT	0.833
CH-A2-109	Churchill, Oxford	Schedule 4	840	840	No DLT	1.000
CH-A2-110	Churchill, Oxford	Schedule 4	840	840	No DLT	1.000
CH-A2-111	Beatson, Glasgow	Schedule 4		840	No DLT	
CH-A2-112	Churchill, Oxford	Schedule 4	560	840	No DLT	0.833
CH-A2-113	Churchill, Oxford	Schedule 3	420	420	No DLT	1.000
CH-A2-114	Churchill, Oxford	Schedule 3	280	420	No DLT	0.833
CH-A2-115	Churchill, Oxford	Schedule 3	280	420	No DLT	0.833
CH-A2-116	Churchill, Oxford	Schedule 3	140	420	DLT	1.000
CH-A2-117	Churchill, Oxford	Schedule 3	420	420	No DLT	1.000
CH-A2-118	St James, Leeds	Schedule 3	420	420	No DLT	1.000
CH-A2-119	Churchill, Oxford	Schedule 3	280	420	No DLT	0.833
CH-A2-120	Churchill, Oxford	Schedule 3	420	420	No DLT	1.000

Note CH-A2-104, CH-A2-111 withdrew before starting treatment.

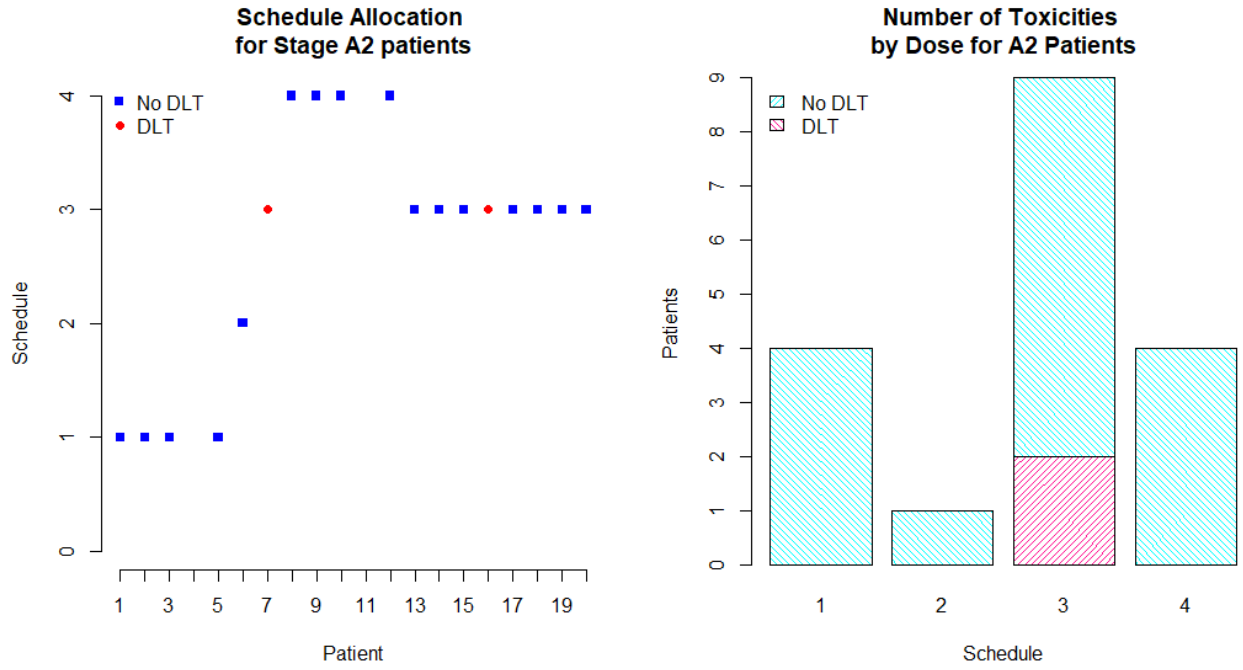


Figure 8: Summaries of Patients' DLT Status and Treatment Schedule in A2

Table 13 presents the posterior probabilities for each schedule along with the corresponding 95% credible intervals and numbers included in the model for each schedule. Figure 9 presents the posteriors graphically. The prior dose toxicity curve is also included as a reference.

Table 13: Posterior Summaries for the primary population, using everyone who took at least one dose of M6620, including 95% credible interval

Schedule	Number of Observations	Posterior Probability	Lower 95% CrI	Upper 95% CrI
1	4	0.091	0.009	0.256
2	1	0.111	0.014	0.291
3	9	0.146	0.026	0.345
4	4	0.185	0.042	0.397

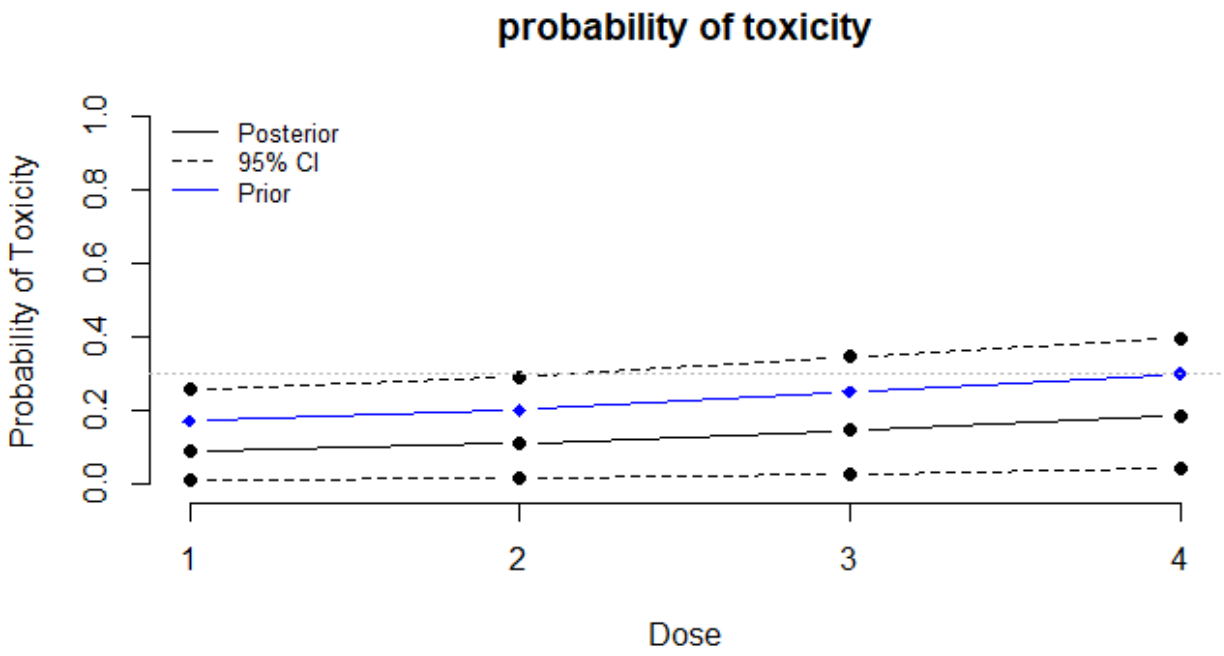


Figure 9: Posterior estimate of the dose toxicity curve, 95% credible interval and prior

The TiTE-CRM model, given the accumulated data, suggests **Schedule 4** is the maximum tolerated dose of M6620 in combination with Chemotherapy of the doses examined in CHARIOT Stage A2. However, due to the difficulty of treatment delivery on Schedule 4 as well as toxicities that occurred outside the DLT window that were considered dose limiting but not falling within the protocol definition of a DLT, the recommended MTD is **Schedule 3**. The posterior probability the DLT rate is >30% in dose level 3 (the Maximum Tolerated Dose) is 0.052.

4.5.2 Supporting Analyses of the Primary Analysis

Four sensitivity analyses were defined it the statistical analysis plan. These were:

1. Only using those patients did not miss any of their dose prescribed on their dose schedule, and weighted using the original TiTE-CRM weights, i.e. weighting only according to length of follow-up and not taking account of how much dose has been received
2. Only using those patients who have received at least 75% of the prescribed dose, using the same weight function as in the main analysis
3. Only using those patients who have received at least 75% of the prescribed dose, but using the original TiTE-CRM weights
4. Using the same population and weighting as the primary population but assuming the “Most Toxic” Scenario. All patients currently on treatment within the DLT window have been assigned a DLT.

As all patients are off study for the final analysis, Sensitivity 4 cannot be completed as part of this report (this was used during the running of the trial). The remaining three sensitivity analyses, numbers of patients included and posterior toxicity estimates are presented in Table 14, Table 15 and Table 16 for sensitivity 1, 2 and 3 respectively.

Table 14: Posterior Summaries for the first sensitivity population, i.e. must have received their full prescribed dose of M6620, weighting only according to length of follow-up and not taking account of how much dose has been received, including 95% credible interval

Schedule	Number of Observations	Posterior Probability	Lower 95% CrI	Upper 95% CrI
1	4	0.149	0.017	0.390
2	1	0.174	0.025	0.425
3	9	0.217	0.041	0.479
4	4	0.261	0.063	0.527

Table 15: Posterior Summaries for the second sensitivity population, i.e. must have received at least 75% of the prescribed dose of M6620, using the same weight function as in the main analysis, including 95% credible interval

Schedule	Number of Observations	Posterior Probability	Lower 95% CrI	Upper 95% CrI
1	3	0.135	0.016	0.363
2	1	0.160	0.024	0.398
3	6	0.201	0.040	0.452
4	2	0.244	0.061	0.502

Table 16: Posterior Summaries for the third sensitivity population, i.e. must have received at least 75% of the prescribed dose of M6620, using the original TiTE-CRM weights, including 95% credible interval

Schedule	Number of Observations	Posterior Probability	Lower 95% CrI	Upper 95% CrI
1	3	0.135	0.016	0.359
2	1	0.159	0.023	0.395
3	6	0.200	0.039	0.449
4	2	0.244	0.060	0.499

All pre-specified supporting analysis results support the main conclusion that the MTD is Schedule 4, however, clinical opinion remains that the MTD is Schedule 3.

4.5.3 Secondary Analysis

4.5.3.1 Toxicity

There were 7 Dose Limiting Toxicities (DLTs) on 2 in this safety study. All DLTs are presented in Table 17.

Table 17: Dose limiting toxicities

Subject	Description	Treatment Week	Grade	m6620 Causality	Cisplatin Causality	Capecitabine Causality	Outcome	Time to Resolve (Days)
CH-A2-107	Pyrexia	Week 2	1	Possibly Related	Possibly Related	Possibly Related	Resolved	4
CH-A2-107	Neutropenia	Week 2	2	Probably Related	Probably Related	Probably Related	Worsened	2
CH-A2-107	Neutropenia	Week 3	3	Probably Related	Probably Related	Probably Related	Resolved	4
CH-A2-107	Neutropenia	Week 3	1	Probably Related	Probably Related	Probably Related	Resolved	14
CH-A2-116	Sepsis	Week 1	3	Probably Related	Definitely Related	Probably Related	Resolved	2
CH-A2-116	Dehydration	Week 1	3	Possibly Related	Definitely Related	Possibly Related	Resolved	4
CH-A2-116	Vomiting	Week 1	3	Possibly Related	Definitely Related	Possibly Related	Resolved	4

There were 5 Serious Adverse Events (SAEs). These are given in full detail in Table 18. There were 11 (55%) deaths observed in Stage A2, full details of these deaths are given in Table 19, all documented causes of death were disease related.

As CH-A2-111 withdrew before starting treatment, survival time is calculated from date of study registration. All other survival times are calculated from the day of starting treatment.

Table 18: Serious adverse events

Subject	Description	Treatment Week	Grade	m6620 Causality	Cisplatin Causality	Capecitabine Causality	Outcome	Time to Resolve (Days)
CH-A2-107	Pyrexia	Week 2	1	Possibly Related	Possibly Related	Possibly Related	Resolved	4
CH-A2-107	Neutropenia	Week 3	3	Probably Related	Probably Related	Probably Related	Resolved	4
CH-A2-116	Sepsis	Week 1	3	Probably Related	Definitely Related	Probably Related	Resolved	2
CH-A2-116	Vomiting	Week 1	3	Possibly Related	Definitely Related	Possibly Related	Resolved	4

Subject	Description	Treatment Week	Grade	m6620 Causality	Cisplatin Causality	Capecitabine Causality	Outcome	Time to Resolve (Days)
CH-A2-119	Chest pain	Week 2	2	Probably Not Related	Probably Not Related	Probably Related	Resolved	0

Table 19: Deaths

Subject	Tumour Type	Cause of Death	Survival Time (Days)
CH-A2-101	Cholangiocarcinoma	Disease related	325
CH-A2-102	Uterine Leiomyosarcoma	Disease related	128
CH-A2-103	Urothelial Cancer	Disease related	84
CH-A2-106	Duodenum Adenocarcinoma	Disease related	434
CH-A2-107	Cholangiocarcinoma	Disease related	427
CH-A2-108	Urothelial Cancer	Disease related	275
CH-A2-111	Oesophageal Adenocarcinoma	Disease related	96
CH-A2-114	Pancreatic NET	Disease related	227
CH-A2-115	Choroidal Melanoma	Disease related	218
CH-A2-117	Rectal Adenocarcinoma	Unclear	249
CH-A2-118	Sarcoma	Disease related	258

A full list of Adverse Events and worst Adverse Events for each patient are presented in *Appendix - Toxicity*. Table 20 summarises the number of AEs each patient who has started treatment has had. It shows the number of AEs that occurred during the first 4 weeks of treatment split by grade, the number of AEs that occurred after week 4 of treatment, the number of AEs either missing time of onset or grade, and the total number of AEs since start of treatment. A summary of AEs by causality and grade is given in Figure 13. The median time taken for AEs to resolve based on complete data was 7 days (IQR 3, 14). Table 21, Table 22, and Figure 10 give information on the worst Adverse Events experienced for each patient. Table 23 gives all Adverse Events classified by MedDRA Organ Class, split by grade; the most commonly effected organ class was General Disorders & Administration Site Conditions with 17.8% of all AEs being from this class. Table 24 gives all AEs by their MedDRA coded event, split by grade; the most common AE was Fatigue (14.9% of all AEs). Figure 11 and Figure 12 graphically present AEs by Organ Class and MedDRA coding respectively. Figure 14 shows the percentage of patients each adverse event occurred in.

Table 20: Summary of adverse avents by patient

Subject	Schedule	In Screening	Grade 1 or 2	Grade 3 or 4	After week 4	Missing	Total AEs
CH-A2-101	1	0	3	1	1	1	6
CH-A2-102	1	0	5	1	3	0	9
CH-A2-103	1	0	7	0	0	0	7
CH-A2-105	1	0	6	0	7	0	13
CH-A2-106	2	0	5	0	16	0	21
CH-A2-107	3	1	8	2	0	0	11
CH-A2-108	4	0	16	1	10	0	27
CH-A2-109	4	0	12	2	7	0	21
CH-A2-110	4	0	15	0	0	0	15
CH-A2-112	4	0	11	3	13	0	27
CH-A2-113	3	0	9	0	6	0	15
CH-A2-114	3	0	2	3	0	0	5
CH-A2-115	3	0	0	1	1	0	2
CH-A2-116	3	0	0	3	0	0	3
CH-A2-117	3	0	2	0	2	0	4
CH-A2-118	3	1	8	1	8	0	18
CH-A2-119	3	0	6	1	19	0	26
CH-A2-120	3	0	4	0	8	0	12

Table 21: Worst grade Adverse Event grade for each patient by dose schedule

	Schedule 1 (n=4)	Schedule 2 (n=1)	Schedule 3 (n=9)	Schedule 4 (n=4)	Total (n=18)
Highest CTCAE Grade					
One	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Two	2 (50.0)	1 (100.0)	2 (22.2)	1 (25.0)	6 (33.3)
Three	1 (25.0)	0 (0.0)	6 (66.7)	2 (50.0)	9 (50.0)
Four	1 (25.0)	0 (0.0)	1 (11.1)	1 (25.0)	3 (16.7)

Table 21: Worst grade Adverse Event grade for each patient by dose schedule

	One (n=0)	Two (n=11)	Three (n=19)	Four (n=3)	Total (n=33)
Adverse Event					
Anaemia	0 (NaN)	2 (18.2)	0 (0.0)	0 (0.0)	2 (6.1)
Blood alkaline phosphatase increased	0 (NaN)	0 (0.0)	1 (5.3)	0 (0.0)	1 (3.0)
Dehydration	0 (NaN)	0 (0.0)	1 (5.3)	0 (0.0)	1 (3.0)
Dyspnoea exertional	0 (NaN)	0 (0.0)	1 (5.3)	0 (0.0)	1 (3.0)
Dysuria	0 (NaN)	1 (9.1)	0 (0.0)	0 (0.0)	1 (3.0)
Embolism	0 (NaN)	0 (0.0)	1 (5.3)	0 (0.0)	1 (3.0)
Fatigue	0 (NaN)	4 (36.4)	0 (0.0)	0 (0.0)	4 (12.1)
Hyperglycaemia	0 (NaN)	0 (0.0)	1 (5.3)	0 (0.0)	1 (3.0)
Hypertension	0 (NaN)	0 (0.0)	1 (5.3)	0 (0.0)	1 (3.0)
Hypophosphataemia	0 (NaN)	0 (0.0)	4 (21.1)	0 (0.0)	4 (12.1)
Neutropenia	0 (NaN)	0 (0.0)	6 (31.6)	3 (100.0)	9 (27.3)
Neutrophil count decreased	0 (NaN)	1 (9.1)	0 (0.0)	0 (0.0)	1 (3.0)
Perineal pain	0 (NaN)	1 (9.1)	0 (0.0)	0 (0.0)	1 (3.0)
Platelet count decreased	0 (NaN)	1 (9.1)	0 (0.0)	0 (0.0)	1 (3.0)
Rash pustular	0 (NaN)	1 (9.1)	0 (0.0)	0 (0.0)	1 (3.0)
Sepsis	0 (NaN)	0 (0.0)	1 (5.3)	0 (0.0)	1 (3.0)
Thrombocytopenia	0 (NaN)	0 (0.0)	1 (5.3)	0 (0.0)	1 (3.0)
Vomiting	0 (NaN)	0 (0.0)	1 (5.3)	0 (0.0)	1 (3.0)

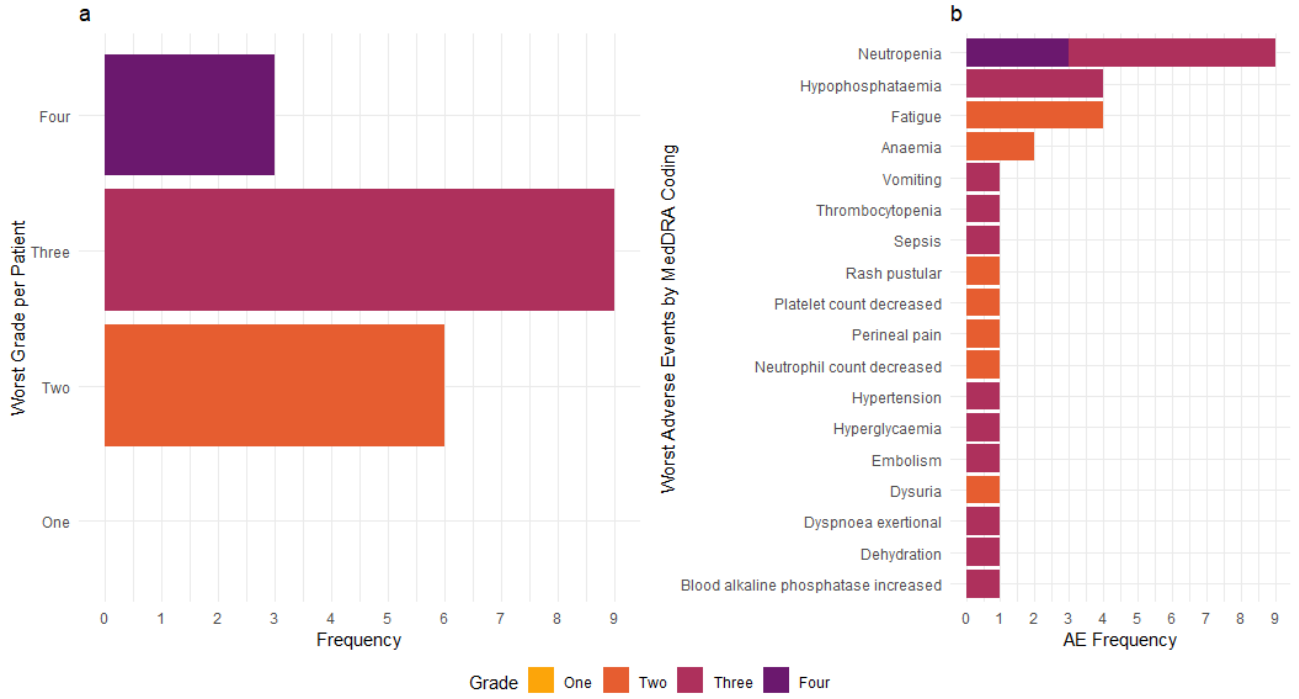


Figure 10: (a) Worst grade Adverse Event grade for each patient (b) Worst Adverse Events for each patient by MedDRA Coding

Table 23: Adverse Events by MedDRA organ class & grade

	One (n=159)	Two (n=54)	Three (n=26)	Four (n=3)	Total (n=242)
Organ Class					
Blood & Lymphatic System Disorders	12 (7.5)	9 (16.7)	13 (50.0)	3 (100.0)	37 (15.3)
Ear and labyrinth disorders	6 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.5)
Eye disorders	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)
Gastrointestinal Disorders	33 (20.8)	5 (9.3)	1 (3.8)	0 (0.0)	39 (16.1)
General Disorders & Administration Site Conditions	27 (17.0)	16 (29.6)	0 (0.0)	0 (0.0)	43 (17.8)
Hepatobiliary	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Infections & Infestations	14 (8.8)	5 (9.3)	1 (3.8)	0 (0.0)	20 (8.3)
Injury; poisoning and procedural complications	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)
Investigations	18 (11.3)	6 (11.1)	1 (3.8)	0 (0.0)	25 (10.3)
Metabolism & Nutrition Disorders	5 (3.1)	4 (7.4)	6 (23.1)	0 (0.0)	15 (6.2)
Musculoskeletal & Connective Tissue Disorders	11 (6.9)	1 (1.9)	0 (0.0)	0 (0.0)	12 (5.0)

	One (n=159)	Two (n=54)	Three (n=26)	Four (n=3)	Total (n=242)
Nervous System Disorders	5 (3.1)	1 (1.9)	0 (0.0)	0 (0.0)	6 (2.5)
Renal and urinary disorders	1 (0.6)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.8)
Reproductive system and breast disorders	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	12 (7.5)	1 (1.9)	1 (3.8)	0 (0.0)	14 (5.8)
Skin and subcutaneous tissue disorders	9 (5.7)	3 (5.6)	0 (0.0)	0 (0.0)	12 (5.0)
Vascular disorders	1 (0.6)	1 (1.9)	3 (11.5)	0 (0.0)	5 (2.1)

Table 24: Adverse Events by MedDRA coding & grade

	One (n=159)	Two (n=54)	Three (n=26)	Four (n=3)	Total (n=242)
MedDRA Coding					
Abdominal pain	1 (0.6)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.8)
Abdominal pain upper	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Adverse drug reaction	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Alanine aminotransferase increased	3 (1.9)	1 (1.9)	0 (0.0)	0 (0.0)	4 (1.7)
Anaemia	4 (2.5)	3 (5.6)	0 (0.0)	0 (0.0)	7 (2.9)
Angular cheilitis	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Arthritis	2 (1.3)	1 (1.9)	0 (0.0)	0 (0.0)	3 (1.2)
Aspartate aminotransferase increased	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)
Asthenia	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Back pain	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)
Blood alkaline phosphatase increased	1 (0.6)	0 (0.0)	1 (3.8)	0 (0.0)	2 (0.8)
Blood phosphorus decreased	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Breast cellulitis	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Catheter site related reaction	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Cellulitis	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.4)
Chest pain	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.4)
Constipation	7 (4.4)	2 (3.7)	0 (0.0)	0 (0.0)	9 (3.7)

	One (n=159)	Two (n=54)	Three (n=26)	Four (n=3)	Total (n=242)
Cough	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)
Decreased appetite	2 (1.3)	4 (7.4)	0 (0.0)	0 (0.0)	6 (2.5)
Dehydration	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (0.4)
Diarrhoea	6 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.5)
Dry mouth	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Dry throat	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Dysgeusia	1 (0.6)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.8)
Dysphagia	1 (0.6)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.8)
Dyspnea on exertion	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Dyspnoea	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Dyspnoea exertional	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (0.4)
Dysuria	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.4)
Embolism	0 (0.0)	1 (1.9)	1 (3.8)	0 (0.0)	2 (0.8)
Epistaxis	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Erythema	3 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)
Fatigue	21 (13.2)	15 (27.8)	0 (0.0)	0 (0.0)	36 (14.9)
Flank pain	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Glomerular filtration rate decreased	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Haemoglobin decreased	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Headache	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Hyperglycaemia	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (0.4)
Hypertension	1 (0.6)	0 (0.0)	2 (7.7)	0 (0.0)	3 (1.2)
Hypocalcaemia	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Hypokalaemia	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Hypomagnesaemia	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Hypophosphataemia	0 (0.0)	0 (0.0)	4 (15.4)	0 (0.0)	4 (1.7)
Jaundice	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Limb discomfort	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

	One (n=159)	Two (n=54)	Three (n=26)	Four (n=3)	Total (n=242)
Lower respiratory tract infection	0 (0.0)	3 (5.6)	0 (0.0)	0 (0.0)	3 (1.2)
Lymphocyte count decreased	1 (0.6)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.8)
Mucosal inflammation	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Muscle spasms	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Muscular weakness	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Musculoskeletal chest pain	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Musculoskeletal pain	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Nasal discomfort	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Nausea	13 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	13 (5.4)
Neuropathy peripheral	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Neutropenia	4 (2.5)	5 (9.3)	11 (42.3)	3 (100.0)	23 (9.5)
Neutrophil count decreased	1 (0.6)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.8)
Oral candidiasis	9 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.7)
Oropharyngeal pain	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Ototoxicity	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Palmar-plantar erythrodysaesthesia syndrome	6 (3.8)	3 (5.6)	0 (0.0)	0 (0.0)	9 (3.7)
Paraesthesia	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Perineal pain	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.4)
Platelet count decreased	4 (2.5)	2 (3.7)	0 (0.0)	0 (0.0)	6 (2.5)
Pollakiuria	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Proctalgia	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Productive cough	1 (0.6)	1 (1.9)	0 (0.0)	0 (0.0)	2 (0.8)
Pulmonary embolism	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Pyrexia	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Rash macular	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Rash pustular	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.4)
Restless legs syndrome	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Rhinitis	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

	One (n=159)	Two (n=54)	Three (n=26)	Four (n=3)	Total (n=242)
Sepsis	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (0.4)
Stoma site extravasation	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Stoma site haemorrhage	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Temperature intolerance	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Thrombocytopenia	4 (2.5)	1 (1.9)	2 (7.7)	0 (0.0)	7 (2.9)
Tinnitus	4 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.7)
Upper respiratory tract infection	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Urinary tract infection	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Vertigo	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Vision blurred	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)
Vomiting	2 (1.3)	1 (1.9)	1 (3.8)	0 (0.0)	4 (1.7)
Weight decreased	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)
White blood cell count decreased	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.4)

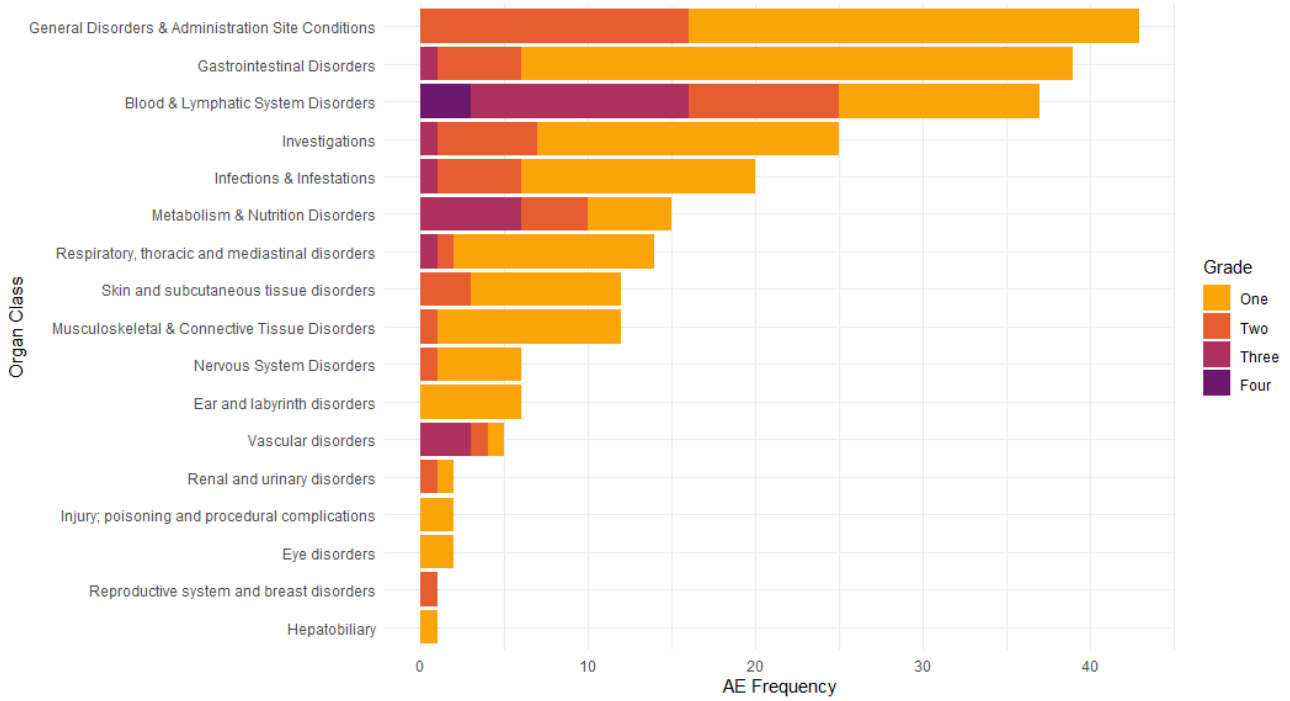


Figure 11: Adverse Events by organ class and grade

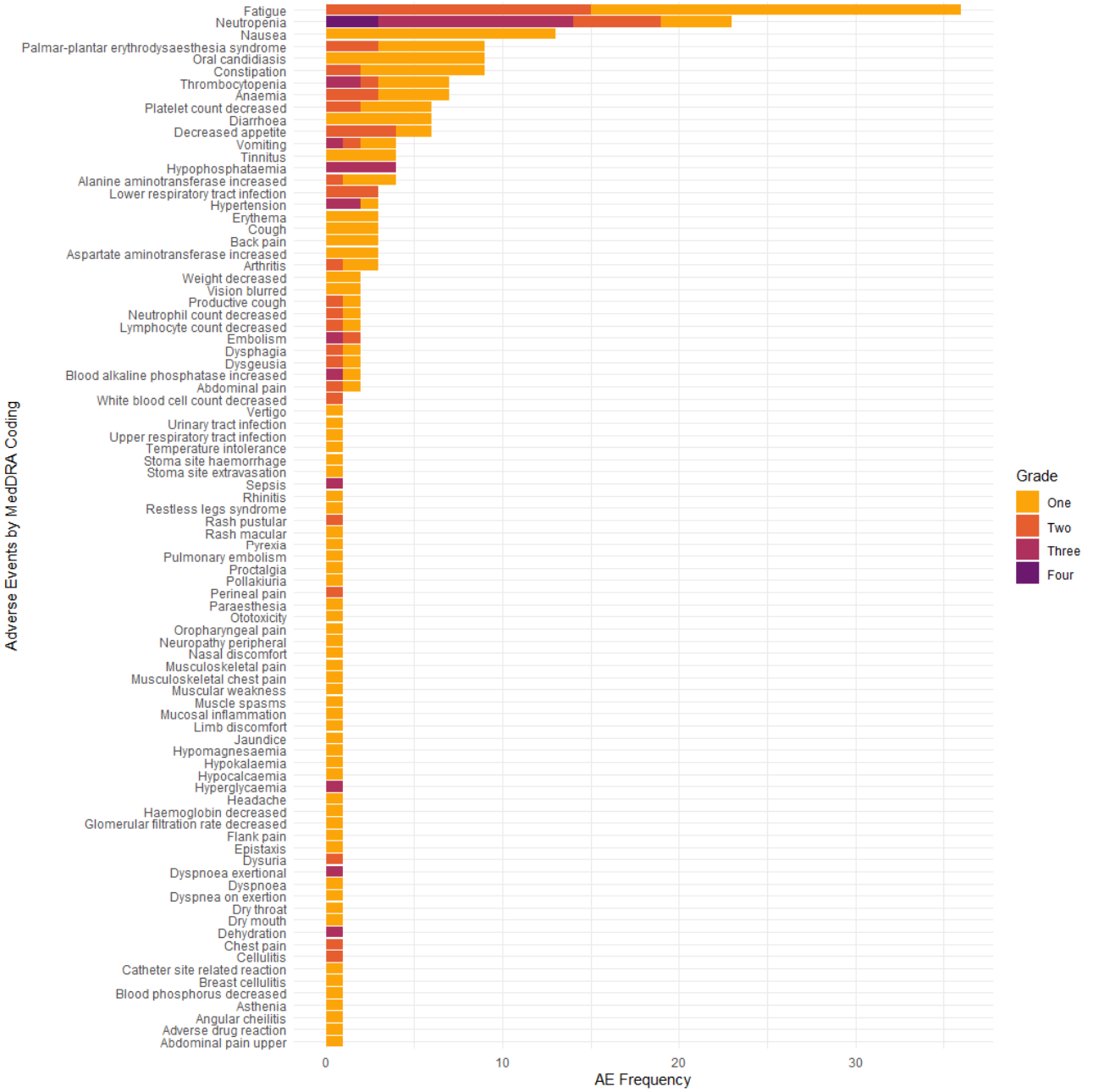


Figure 12: Adverse Events by MedDRA coding and grade

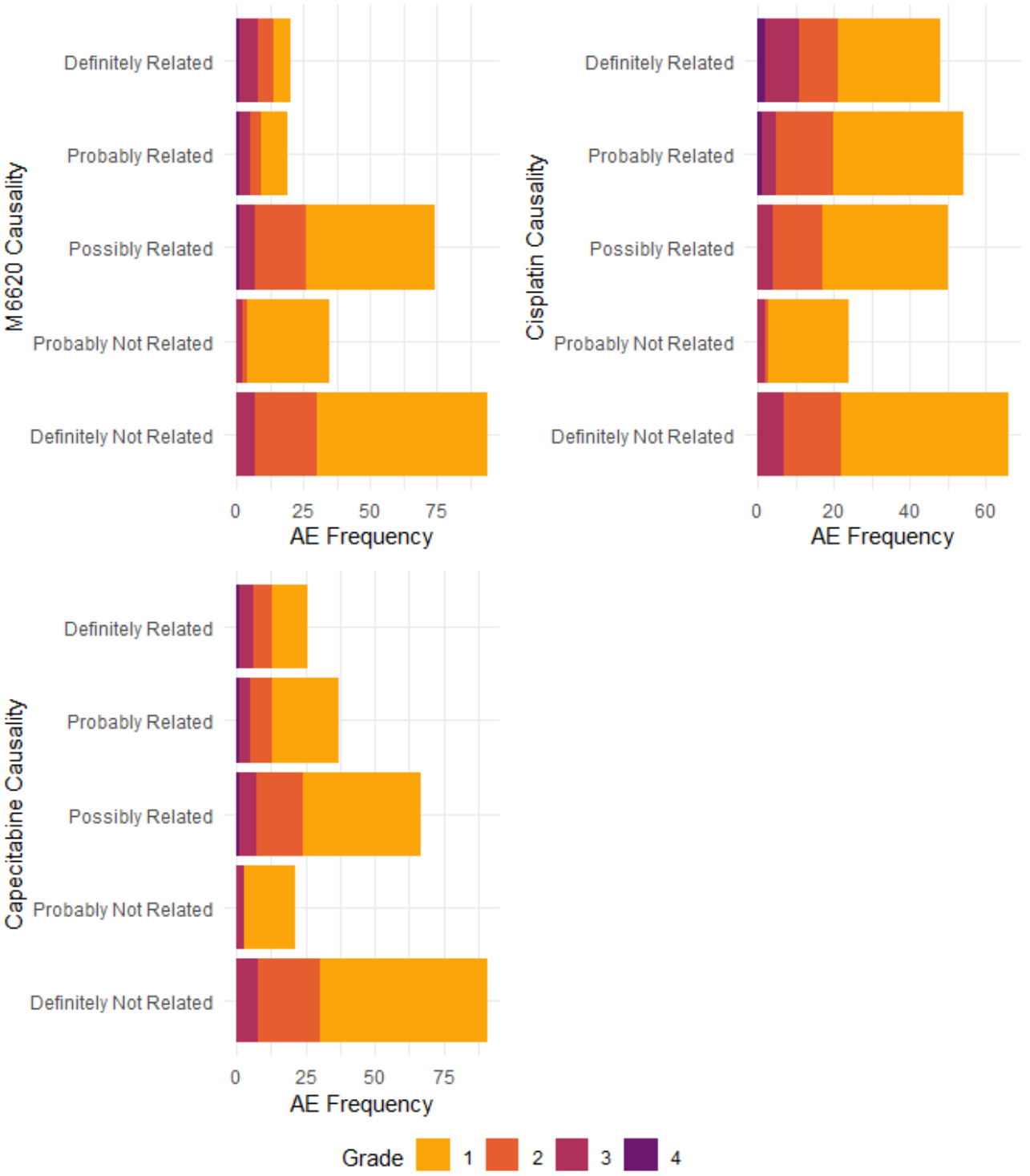


Figure 13: Adverse events by grade and M6620, Capecitabine and Cisplatin causality

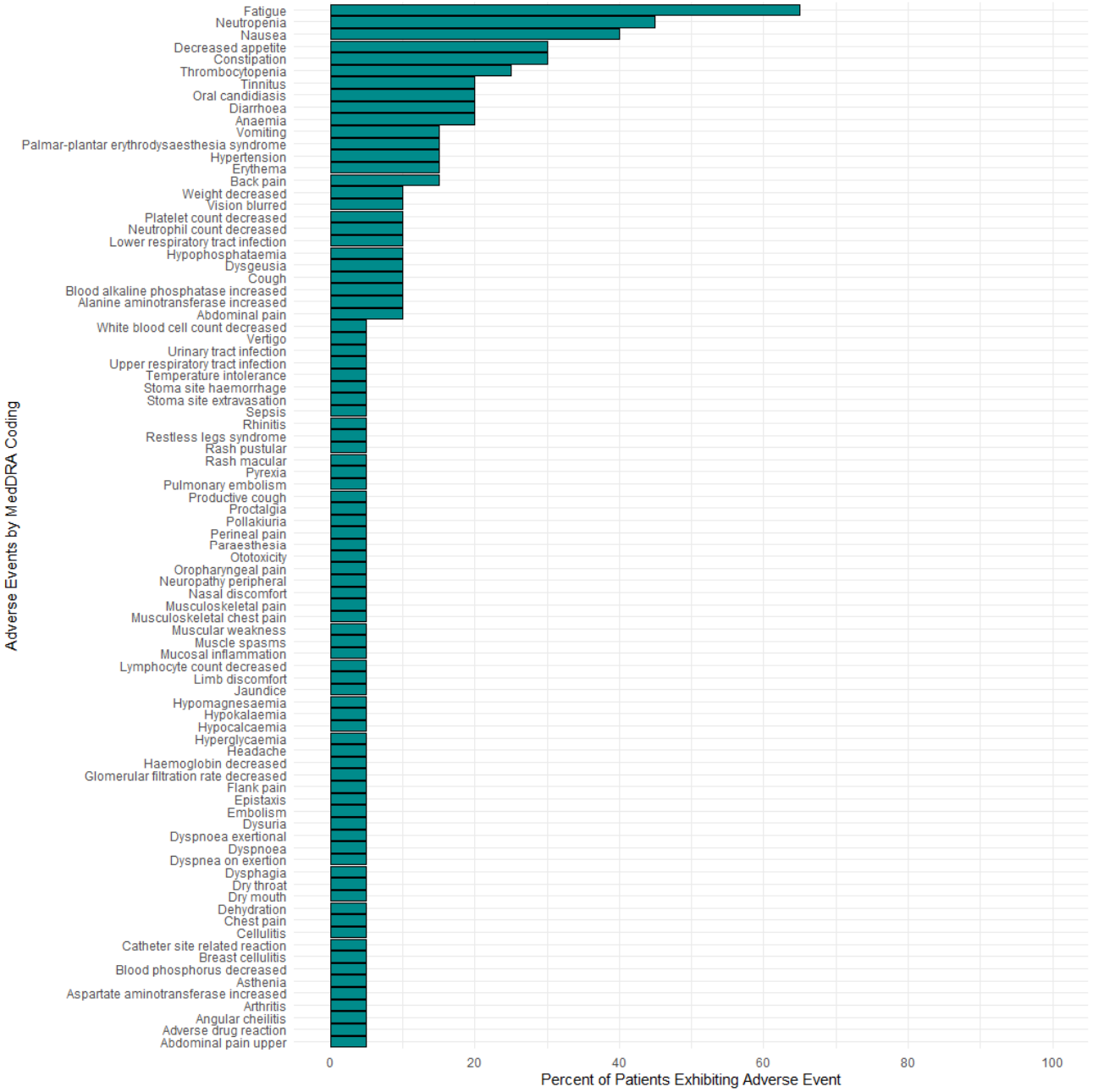


Figure 14: Percentage of patients exhibiting each adverse event

4.5.3.2 Treatment Combination Compliance

Treatment compliance is covered in the *Compliance* section of this report.

4.5.3.3 Efficacy

Efficacy is measured in two ways for Stage A2:

- Objective tumour response (OR) as evaluated by CT scan and quantified by Response Criteria Evaluation (RECIST 1.1) at 12 weeks.
- Progression free survival (PFS) and overall survival (OS)

OR measured by RECIST V1.1 at 12 weeks is presented in Table 25 by assigned dose and overall, and graphically in Figure 15. Results from other, non-12-week scans are presented in *Appendix - Scans*, as are the results from all Target and Non-Target lesion specific scans. Twelve patients had missing data for their 12 week Overall RECIST, two patients (CH-A2-104, CH-A2-111) did not undergo these scans due to withdrawing from the trial before starting treatment, one patient (CH-A2-113) missed their scan in error, and another (CH-A2-118) completed the scan but was not reported to RECIST. The reasons for this missing data from the other patients is unknown. Disease response data at other time points for the patients with missing 12 week RECIST data is presented (where available) in Table 26. Figure 16 presents best overall response, by overall RECIST from any scan.

Table 25: Objective tumour response by RECIST V1.1 at 12 weeks

	Schedule 1 (n=5)	**Schedule 2 (n=1)**	**Schedule 3 (n=9)**	**Schedule 4 (n=5)**	**Total (n=20)**
Overall RECIST at 12 Weeks					
Complete Response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial Response	1 (20.0)	1 (100.0)	0 (0.0)	1 (20.0)	3 (15.0)
Stable Disease	0 (0.0)	0 (0.0)	2 (22.2)	2 (40.0)	4 (20.0)
Progressive Disease	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (5.0)
Not Evaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing Data	4 (80.0)	0 (0.0)	6 (66.7)	2 (40.0)	12 (60.0)

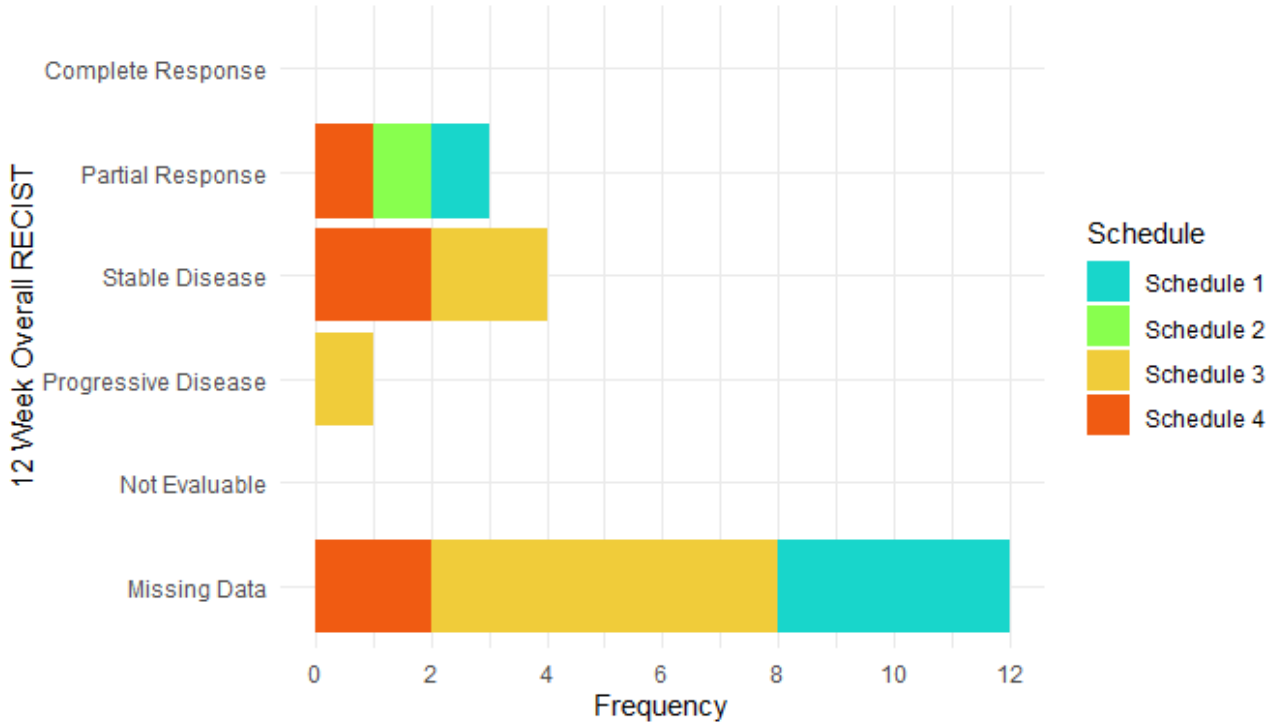


Figure 15: Objective tumour response by RECIST V1.1 at 12 weeks

Table 25: Objective tumour response by RECIST V1.1 at 12 weeks

Subject	Time Point	Sum of Longest Diameters (mm)	Target Response	Non-Target Response	New Lesions	Overall RECIST
CH-A2-101	8 weeks post EOT	102	Progressive Disease	No Non-Target Lesions	No	Progressive Disease
CH-A2-102	6 weeks	187	Progressive Disease	No Non-Target Lesions	No	Progressive Disease
CH-A2-110	6 weeks	113	Progressive Disease	Progressive Disease	Yes	Progressive Disease
CH-A2-113	6 weeks	50	Stable Disease	Non-CR/ Non-PD	No	Stable Disease
CH-A2-113	18 weeks	39	Partial Response	Non-CR/ Non-PD	No	Partial Response
CH-A2-113	8 weeks post EOT	49	Progressive Disease	Non-CR/ Non-PD	No	Progressive Disease

Subject	Time Point	Sum of Longest Diameters (mm)	Target Response	Non-Target Response	New Lesions	Overall RECIST
CH-A2-114	6 weeks	86	Stable Disease	No Non-Target Lesions	Yes	Progressive Disease
CH-A2-115	6 weeks		Progressive Disease	Non-CR/ Non-PD	No	Progressive Disease
CH-A2-117	6 weeks	133	Progressive Disease	Progressive Disease	No	Progressive Disease
CH-A2-118	6 weeks	78	Stable Disease	No Non-Target Lesions	No	Stable Disease
CH-A2-118	18 weeks	86	Progressive Disease	No Non-Target Lesions	No	Progressive Disease
CH-A2-118	8 weeks post EOT	91	Progressive Disease	No Non-Target Lesions	No	Progressive Disease

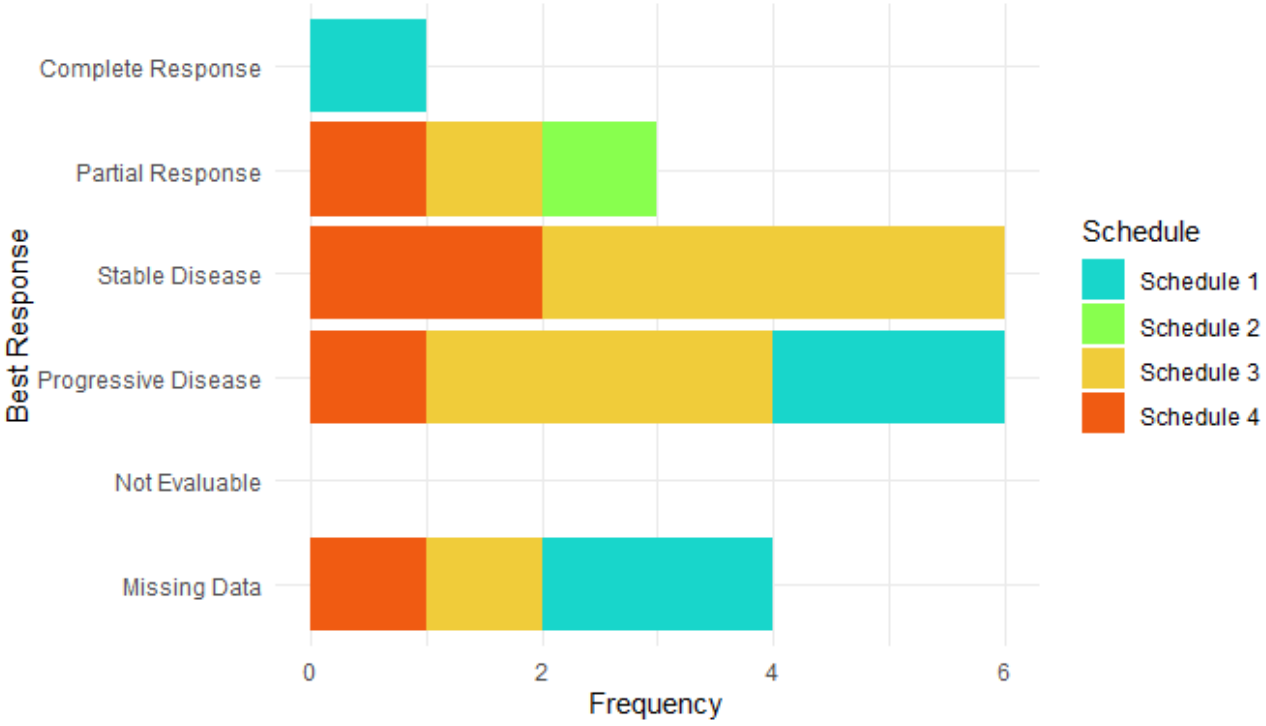


Figure 16: Best response by RECIST

A patient is considered to have progressed if they either had progression or died. Progression free survival is presented in a Kaplan Meier plot in Figure 17 and all data presented graphically in Figure 18. Median progression free survival was 232 days with corresponding 95% confidence lower bound of44, the upper bound is non-calculable . A line listing of progression free survival times and if the observation was censored or not is presented *Appendix - Survival* to this report.

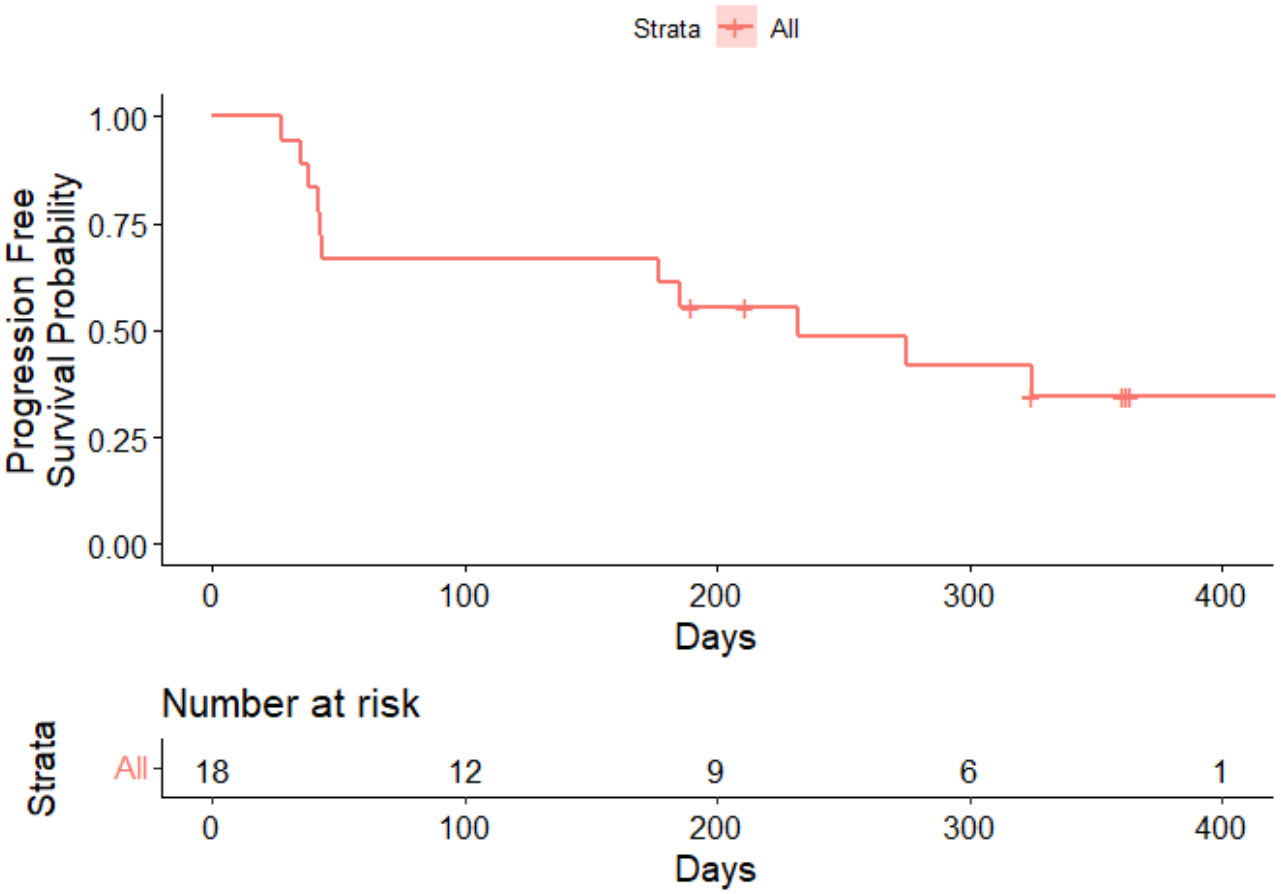


Figure 17: Kaplan Meier plot of progression free survival, censored patients marked

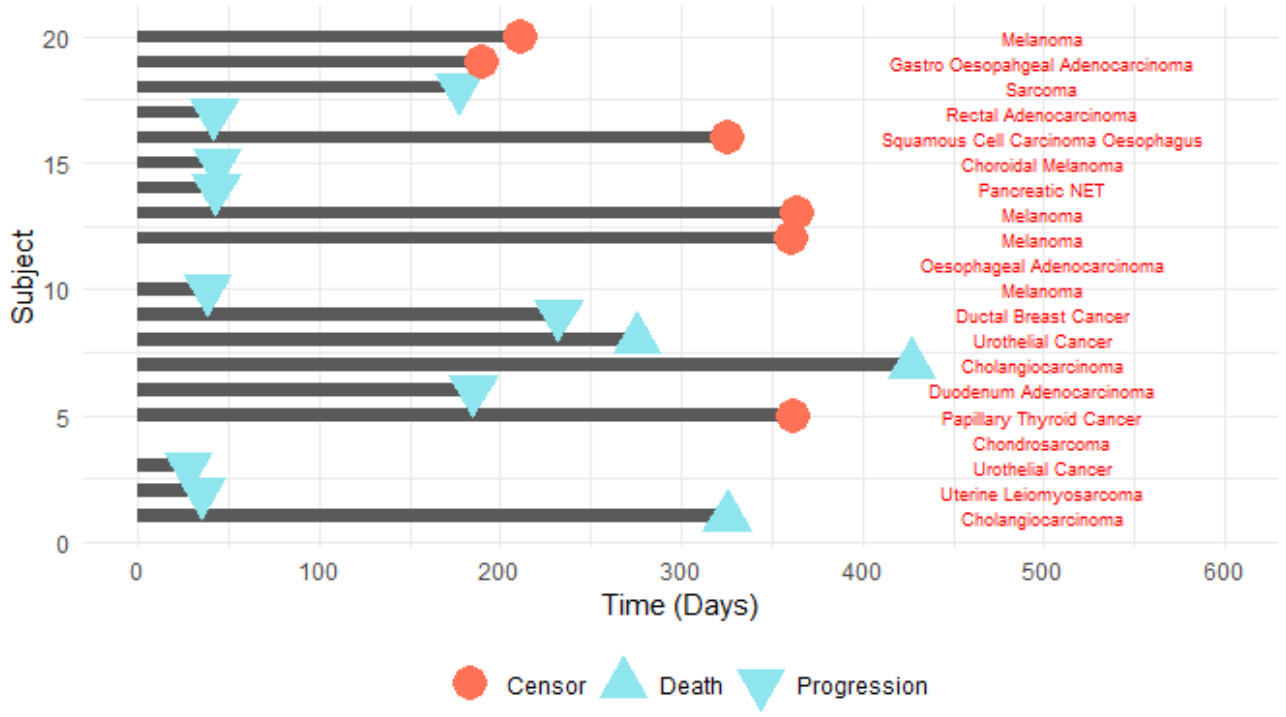


Figure 18: Progression free survival times for all patients, including censoring and tumour type annotations

Overall survival is presented in a Kaplan Meier plot with 95% confidence intervals in Figure 19 and all data presented graphically in Figure 20. Median overall survival was 427 days with corresponding 95% confidence lower bound of249, the upper bound is non-calculable. A line listing of overall survival times and if the observation was censored or not is presented *Appendix - Survival* to this report.

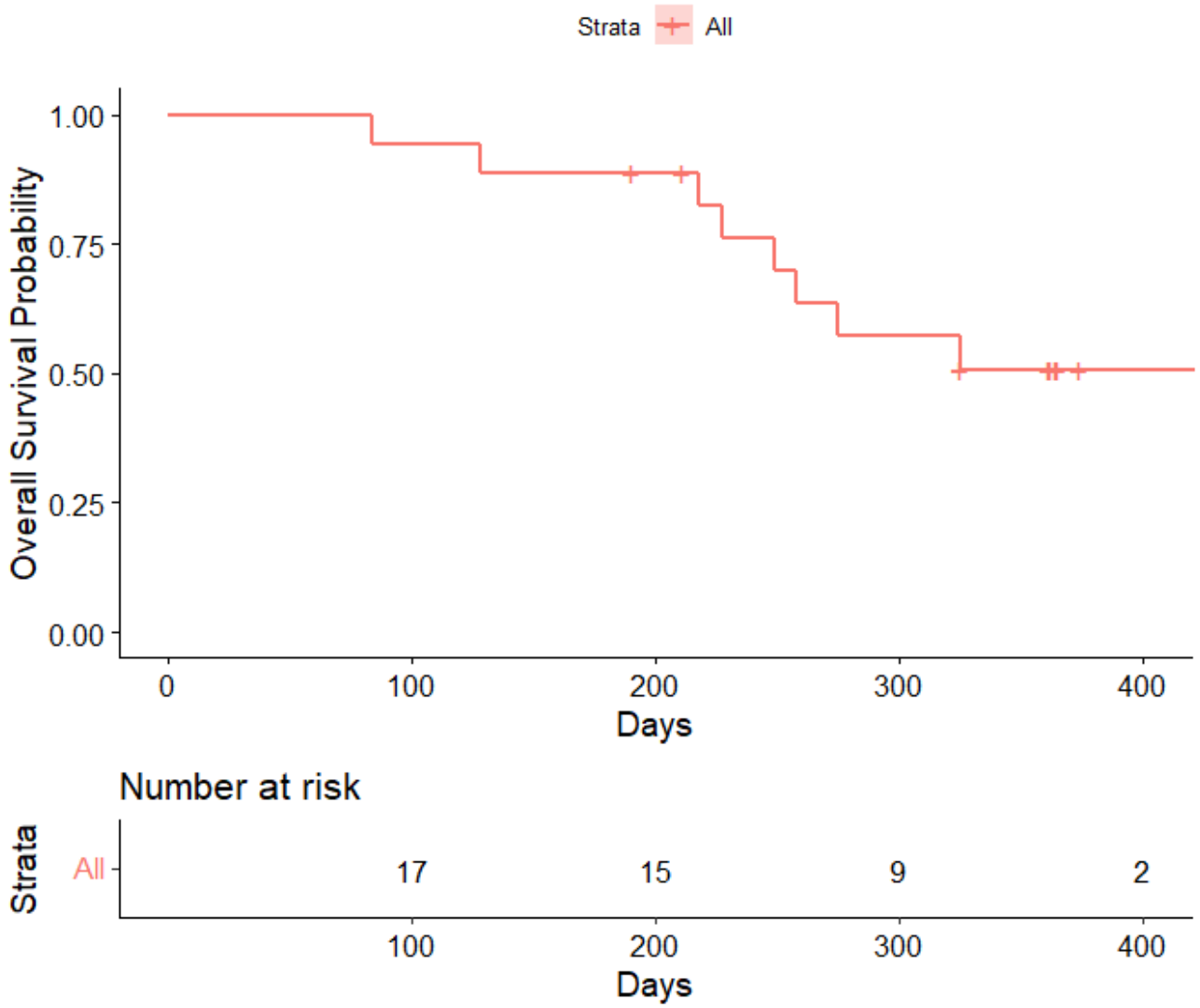


Figure 19: Kaplan Meier plot of overall survival, censored patients marked

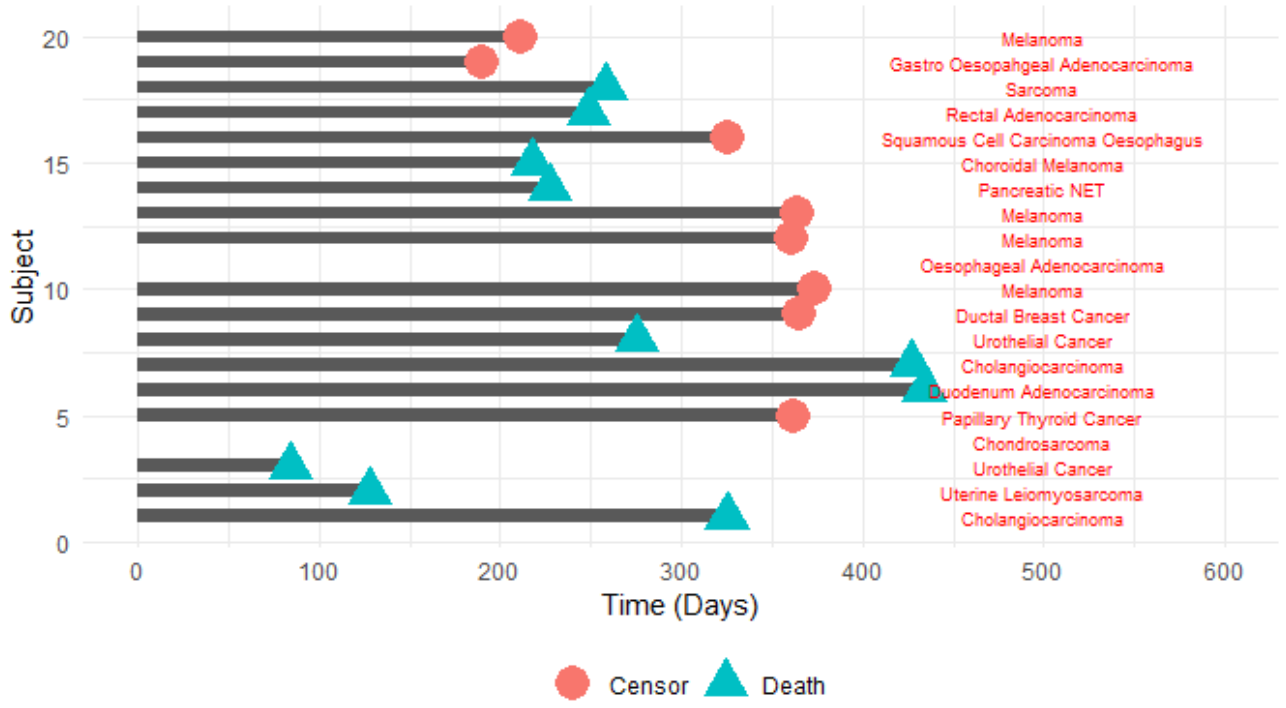


Figure 20: Overall survival times for all patients, including censoring and tumour type annotations

4.6 Safety

Safety is covered in the *secondary outcome* section of this report.

4.7 Concomitant Medication & Post-Trial Treatments

Concomitant medications and post-trial treatments are presented in the *Appendix - Concomitant Medication & Post-Trial Treatments*.

5 ADDITIONAL ANALYSES NOT SPECIFIED IN THE PROTOCOL OR THE SAP

5.1 Additional Analysis Suggested by Safety Review Committee

An analysis not pre-specified in the statistical analysis plan was suggested by CHARIOT's independent Safety Review Committee prior to the final data lock. The suggested analysis was to re-analyse the primary safety data using the TiTE-CRM with a prior skeleton from the "getprior" function in the "dfcrm" R package. This analysis was suggested due to concern that the prior used in the primary analysis may too "flat"; simulation studies prior to the trial opening confirmed that the prior used had acceptable operating characteristics across a range of simulated "true" toxicity scenarios.

Using a halfwidth (desired halfwidth of the indifference intervals) of 0.05 and the existing trial parameters (TTL = 0.3, Prior MTD = Schedule 4, 4 dose levels, model used: 1-parameter power "empiric" model) gives a prior skeleton given in presented in Figure 21 this chunk of R code:

```
getprior(halfwidth = 0.1, target = Target, nu = 4, nlevel = 4, model = "empiric")
## [1] 0.001467223 0.024368001 0.120664288 0.300000000
```

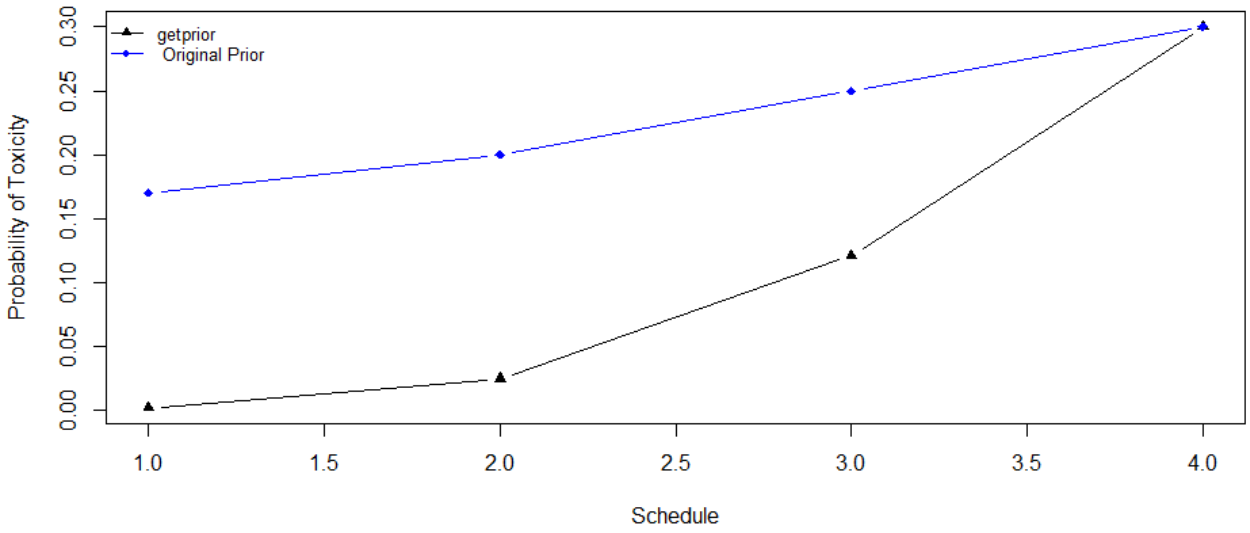


Figure 21: Skeleton from getprior function with original prior included

Table 27 gives the posterior estimates of the replication analysis using the getprior prior. The recommended MTD using the getprior function's recommended prior is Schedule 3, in agreement with the clinical decision to use Schedule 3 as the Recommended Phase II Dose. This additional analysis further supports the final decision of de-escalating from the top dose and choosing Schedule 3 as the MTD of CHARIOT Stage A2.

Table 27: Posterior Summaries for the primary population using the skeleton prior from the dfcrm function. Primary analysis included for reference. Data presented are posterior means and 95% Credible Intervals

Schedule	Number of Observations	Primary Analysis	Get Prior Analysis
1	4	0.091 (0.009, 0.256)	0.007 (0.000, 0.046)
2	1	0.111 (0.014, 0.291)	0.043 (0.001, 0.173)
3	9	0.146 (0.026, 0.345)	0.148 (0.024, 0.369)
4	4	0.185 (0.042, 0.397)	0.322 (0.121, 0.567)

5.2 Maximum Tolerated Dose Discrepancy Analysis

An examination in the difference in clinical opinion of the MTD and recommendation from the TiTE-CRM model used in the primary analysis is performed as part of this report. Whilst there were no DLTs by the definition in the study protocol on Schedule 4, a number of patients experienced toxicities that were considered "near-miss" DLTs, e.g. a toxicity that required missing two consecutive M6620 doses *across* cycles was not a DLT but a toxicity that required missing two consecutive M6620 doses *within* a cycle was. Two patients, CH-A2-108 and CH-A2-112 experienced such "near-miss" DLTs. As a sensitivity analysis to the primary analysis, we present model estimates where these non-DLTs are imputed to be DLTs. The analysis population for this sensitivity is given in Figure 22 and posterior estimates of this analysis are given in Table 28.

The results show that the MTD would still be Schedule 4, however, the final posterior probability of toxicity on Schedule 4 is 0.294, close to the target toxicity level of 0.3. It is also worth considering that had the non-DLTs imputed in this sensitivity analysis been classified as DLTs in the real trial, the course of allocations would have changed. For instance, if both CH-A2-107 and CH-A2-108 had had DLTs, as in Figure 23, at the dose decision meeting for patient CH-A2-109, the next recommended dose would have been Schedule 2 as can be seen from the results in Table 28. This change in patient schedule allocations would have influenced the final MTD recommendation from the CRM model.

It is also possible that had the TMG committee not de-escalated, against the recommendation of the CRM model, more patients would have been treated on Schedule 4 and more patients would have experienced dose limiting toxicities.

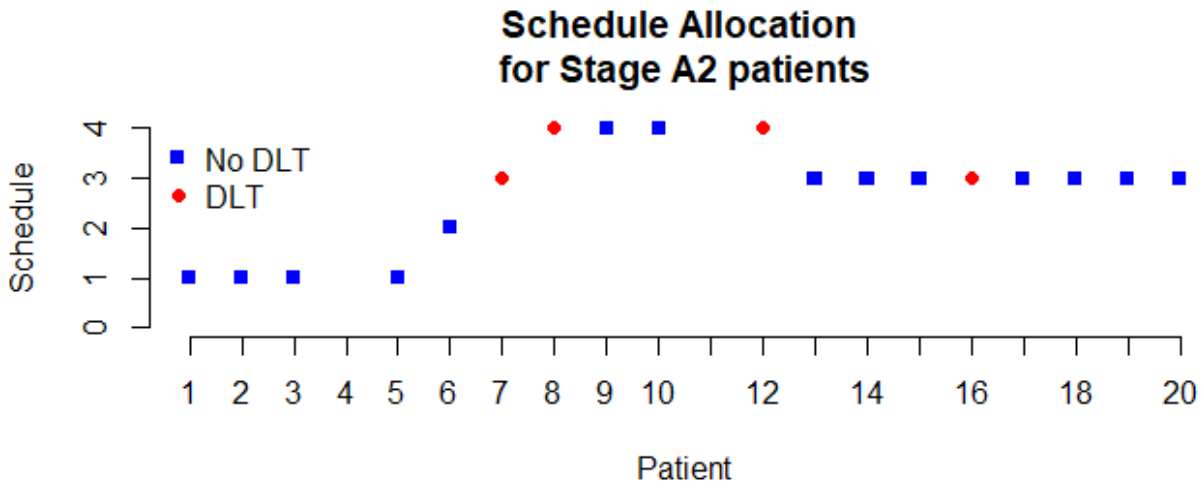


Figure 22: 'Near-miss' DLT imputed population

Table 28: Posterior Summaries for the sensitivity analysis, imputing 'near-miss' DLTs as DLTs, including 95% credible intervals

Schedule	Number of Observations	Posterior Probability	Lower 95% CrI	Upper 95% CrI
1	4	0.173	0.041	0.376
2	1	0.201	0.055	0.411
3	9	0.247	0.082	0.465
4	4	0.294	0.114	0.514

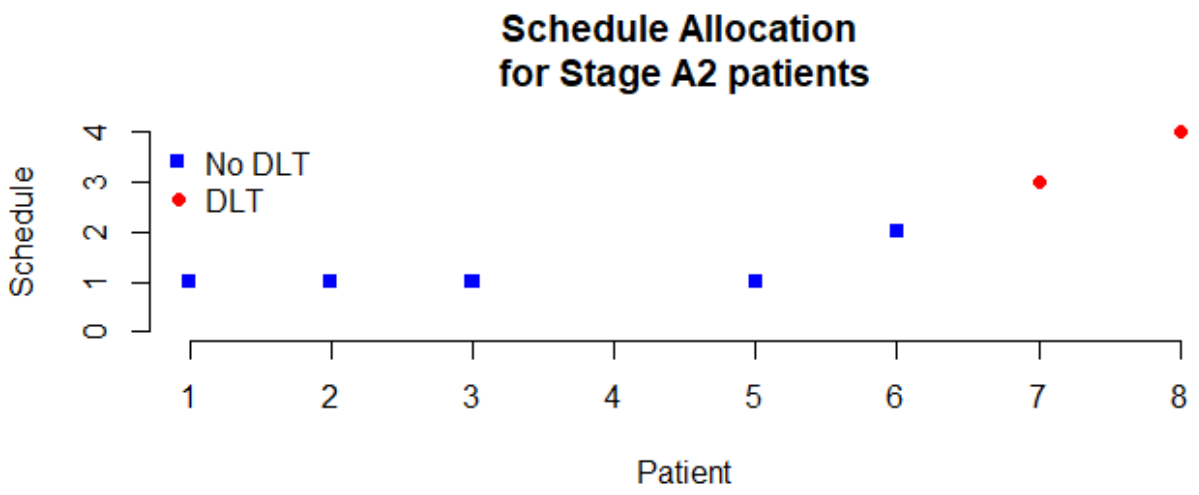


Figure 23: 'Near-miss DLT imputed population up to CH-A2-108

Table 29: Posterior Summaries for the hypothetical dose decision had 107 and 108 had consecutive DLTs, including 95% credible intervals

Schedule	Number of Observations	Posterior Probability	Lower 95% CrI	Upper 95% CrI
1	4	0.256	0.032	0.601
2	1	0.286	0.044	0.630
3	1	0.334	0.068	0.671
4	1	0.381	0.097	0.707

6 EXECUTIVE SUMMARY

Main Analysis

CHARIOT A2 found the combination of M6620, Cisplatin and Capecitabine to be safe at the penultimate dose schedule tested as part of this study (Schedule 3; 140 mg/m^2 M6620 once weekly for six three weeks cycles) in palliative patients with esophageal cancer based on a DLT window of one cycle. Seven Dose Limiting Toxicities (one Pyrexia, three Neutropenia, one Sepsis, one Dehydration, and one Vomiting) were observed in two of the 20 patients recruited over the 32 month recruitment period. Two patients withdrew before starting treatment. One patient who experienced DLTs was on Schedule 3, and the other was on Schedule 4. Table 30 gives the primary estimated posterior means of toxicity for all dose levels given by the 1-parameter power TiTE-CRM model. Five Serious Adverse Events were observed. Figure 24 summarises compliance for all therapies in this stage.

Table 30: Primary results. Data presented are posterior means of toxicity rates and corresponding 95% credible intervals

Schedule	Number of Observations	Primary Analysis
1	4	0.091 (0.009, 0.256)
2	1	0.111 (0.014, 0.291)
3	9	0.146 (0.026, 0.345)
4	4	0.185 (0.042, 0.397)

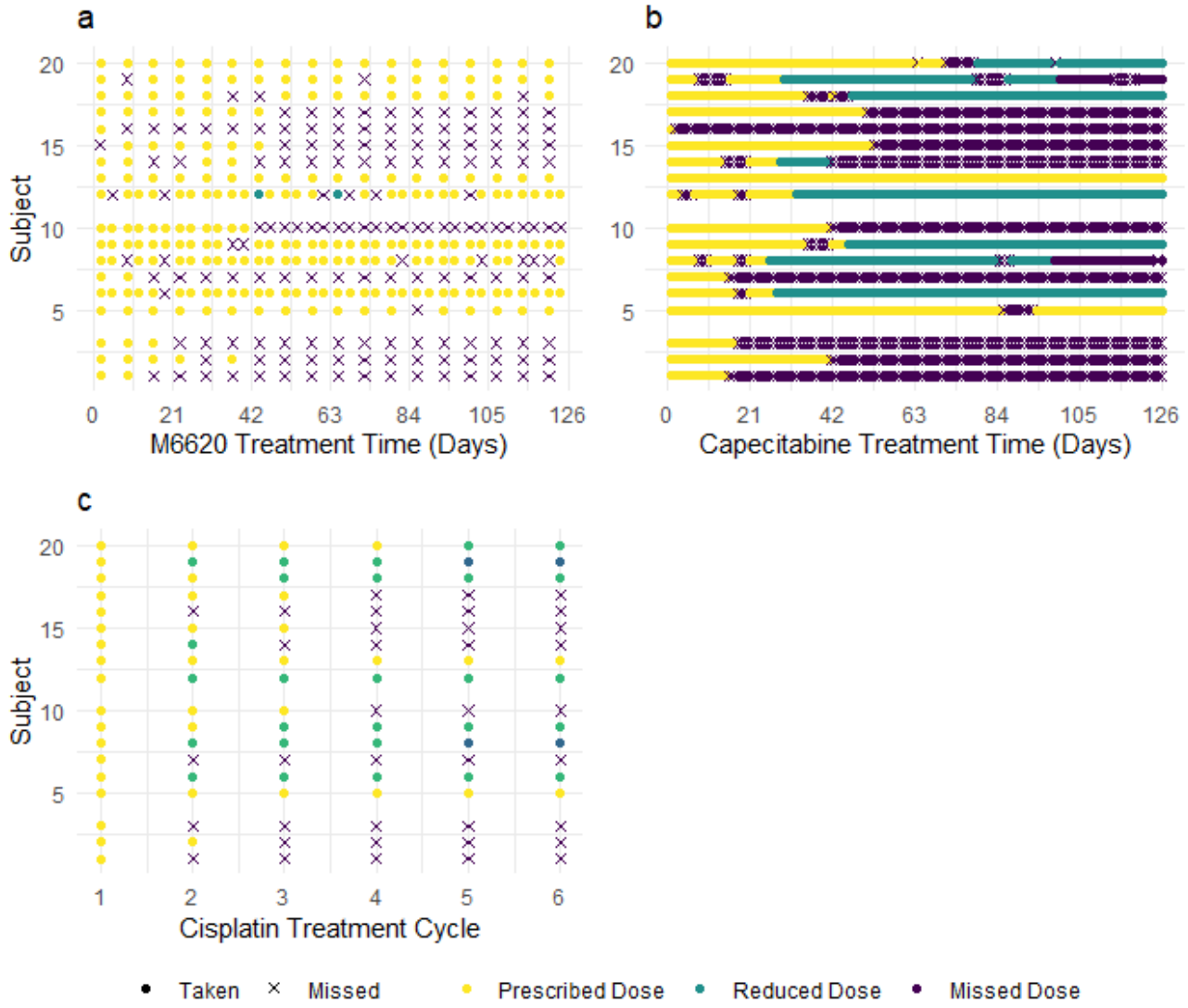


Figure 24: Treatment Compliance Summary: (a) M6620, (b) Capecitabine, (c) Cisplatin

Limitations

This Phase I trial was not blinded or randomised. There was some missing data in the 12 week overall RECIST efficacy outcome. Also, as is usual in Phase I safety studies, no formal power calculation was used to produce the sample size, although this was justified to be sufficient through a simulation study prior to the trial opening.

Data Quality

The overall data quality was excellent for this trial, the primary safety data (required to perform interim analyses and produce dose allocation recommendations) was of high quality throughout the trial. THere was complete safety data within the DLT window and progression/ death was collected until study end, patients who had not died/ progressed were censored in the survival analyses.

Sensitivity

Sensitivity analyses supported the main trial conclusions, including the unplanned sensitivity analysis performed at the suggestion of the trial's Safety Review Committee.

7 APPENDIX

7.1 Appendix - Baseline

Table 31: Prior therapy listing

Subject	Therapy Name	Treatment Duration (Days)
CH-A2-101	Gemcitabine/Cisplatin	350
CH-A2-101	FOLFOX	90
CH-A2-101	Gemcitabine/Cisplatin	60
CH-A2-102	Doxorubicin and Ifosfamide	21
CH-A2-102	Doxorubicin and Ifosfamide	21
CH-A2-102	Gemcitabine and Docetaxel	112
CH-A2-102	Trabectedin	168
CH-A2-102	Gemcitabine and Docetaxel	89
CH-A2-103	Gemcitabine and Cisplatin	12
CH-A2-103	JAVELIN BLADDER 100 Clinical Trial	6
CH-A2-103	PCYC-1128-CA Clinical Trial	42
CH-A2-104	Cyclophosphamide	212
CH-A2-104	CT7001 Tial	117
CH-A2-106	IRMDG	163
CH-A2-107	Capecitabine	14
CH-A2-107	Gemcitabine/Cisplatin	11
CH-A2-108	Gemacitabine and Carboplatin	126
CH-A2-108	Pembrolizumab	107
CH-A2-109	Neoadjuvant FEC-T-Carboplatin	Unknown

Subject	Therapy Name	Treatment Duration (Days)
CH-A2-110	Ipilimumab	4
CH-A2-110	Pembrolizumab	Unknown
CH-A2-111	ECX	6
CH-A2-112	Nivolumab	Unknown
CH-A2-112	Ipilimumab	Unknown
CH-A2-112	Pembrolizumab	Unknown
CH-A2-113	Checkmate 238 CA209238- Ipilimumab	51
CH-A2-113	Nivolumab	26
CH-A2-114	Carboplatin	126
CH-A2-114	Etoposide	126
CH-A2-114	5FU And Irinotecan Modified Degramont (12 Cycles)	168
CH-A2-115	Pembrolizumab Immunotherapy	3
CH-A2-116	Cisplatin	4
CH-A2-116	Capecitabine	4
CH-A2-116	Carboplatin	1
CH-A2-117	Neoadjuvant Folfoxiri	3
CH-A2-117	Rechallenge Folfoxiri with GCSF	Unknown
CH-A2-117	Folfoxiri	Unknown
CH-A2-117	Folfoxiri	4
CH-A2-118	Doxorubicin	4
CH-A2-119	Neo-Adjuvant Flot (Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel)- 5 Cycles	70
CH-A2-120	Pembrolizumab	Unknown
CH-A2-120	Ipilimumab (4 Cycles)	4
CH-A2-120	Bleomycin Electrochemotherapy (1 Course)	Unknown

Table 32: Baseline symptoms listing

Subject	Symptom	Date	Grade
CH-A2-101	Shortness of Breath on Exertion	01 Aug 2017	1
CH-A2-101	Dry Cough	01 Sep 2018	1
CH-A2-101	Intermittent Chest Pain	01 Aug 2017	1

Subject	Symptom	Date	Grade
CH-A2-101	Intermittent Nausea	01 Jul 2016	1
CH-A2-101	Abdominal Cramping	01 Nov 2018	1
CH-A2-101	Abdominal Bruising	01 Dec 2016	1
CH-A2-102	Productive Cough	01 Jan 2016	1
CH-A2-102	Shortness of Breath on Exertion	01 Sep 2017	1
CH-A2-102	Intermittent Fatigue	01 Sep 2017	1
CH-A2-102	Anorexia/Weight Loss	01 Dec 2018	1
CH-A2-102	Lower Respiratory Tract Infection	01 Jan 2016	1
CH-A2-102	Left Atrial Thrombus	14 Feb 2019	2
CH-A2-103	Perineal Pain	01 Feb 2019	1
CH-A2-103	Dysuria	01 Feb 2018	1
CH-A2-103	Intermittent Cough	01 Jan 2013	1
CH-A2-103	Alopecia	01 Jan 2019	1
CH-A2-103	Fatigue	01 Nov 2018	1
CH-A2-103	Neuropathy of Feet	01 Jul 2018	1
CH-A2-104	Central Abdominal Pain	27 Apr 2019	1
CH-A2-104	Dark Urine	27 Apr 2019	1
CH-A2-104	Epigastric Discomfort	01 Apr 2017	1
CH-A2-104	Shortness of Breath on Exertion	01 Nov 2018	1
CH-A2-105	Non-Productive Cough	01 Nov 2017	1
CH-A2-105	Dry Mouth	01 Nov 2017	1
CH-A2-105	Intermittent Reflux	01 Dec 2017	1
CH-A2-105	Lymphopenia	15 May 2018	2
CH-A2-106	Dry Throat	16 Jul 2019	1
CH-A2-106	Bleeding at Stoma Site	17 Jul 2019	1
CH-A2-106	Muscular Pain Buttocks	20 Jul 2019	1
CH-A2-107	Hyperglycemia (Diabetes)	01 Oct 2018	2
CH-A2-107	Arthritis - Hip	01 Jan 2014	1
CH-A2-107	Hypertension	13 Mar 2017	1
CH-A2-107	Eczema	01 Jul 2019	1
CH-A2-107	Acid Reflux	01 Nov 2016	1

Subject	Symptom	Date	Grade
CH-A2-107	Neuropathy To Finger Tips And Toes	01 Dec 2018	1
CH-A2-109	Fatigue	01 Jun 2019	1
CH-A2-110	Fatigue	01 Dec 2019	1
CH-A2-110	Joint Pain	01 Dec 2019	1
CH-A2-111	Hiccups	18 Dec 2019	1
CH-A2-111	Weight Loss	18 Dec 2019	1
CH-A2-111	Nausea	18 Dec 2019	1
CH-A2-111	Fatigue	18 Dec 2019	1
CH-A2-112	Fatigue	01 Jan 2018	1
CH-A2-112	Dry Mouth	01 Feb 2020	1
CH-A2-112	Hot Sweats	01 Jan 2019	1
CH-A2-112	Joint Pain	01 Jan 2018	1
CH-A2-112	Depression	01 Jan 2018	1
CH-A2-114	Epigastric Pain	01 Nov 2020	1
CH-A2-114	Intermittent Constipation	01 Nov 2020	1
CH-A2-114	Fatigue	01 Nov 2020	1
CH-A2-116	Dysphagia	01 Dec 2019	2
CH-A2-116	Tinnitis/Hearing Loss (Bilateral)	01 Jan 2019	2
CH-A2-116	Pain (Deep Chest)	01 Feb 2021	2
CH-A2-117	Fatigue (due to Chemo)	01 Jan 2020	1
CH-A2-117	Fatigue (on Chemo)	01 Jan 2020	2
CH-A2-117	Elevated Alp	25 May 2021	2
CH-A2-117	Constipation	04 Jun 2021	1
CH-A2-119	Ocassional Radiating Pain in the Left Leg	01 May 2021	2
CH-A2-119	Back Pain	01 Jan 2018	1
CH-A2-119	Dysphagia	01 Oct 2020	1
CH-A2-119	Hearing Loss (Acoustic Trauma)	01 Jan 2001	2
CH-A2-120	Right Chest Wall Pain	01 Jun 2021	2
CH-A2-120	Hypertension	01 Oct 2020	2

Table 33: Prior surgery listing

Subject	Procedure	Date
CH-A2-102	Laparotomy With Total Abdominal Hysterectomy	12 Aug 2013
CH-A2-102	Bilateral Salpingo-Oophorectomy	12 Aug 2013
CH-A2-102	Resection Of Subcutaneous Nodule With Clear Margin	12 Aug 2013
CH-A2-102	Left VATS Lower Lobectomy with Complete Resection of Lower Left Lobe Metastases	20 Nov 2013
CH-A2-102	VATS Resection of 2 Right Lower Lobe Pulmonary Metastases	01 Sep 2014
CH-A2-102	Partial Pancreatectomy and Splenectomy	07 Dec 2015
CH-A2-103	Transurethral Resection of Bladder Tumour	01 Nov 2017
CH-A2-104	Left Hemilaryngectomy	02 Jun 2016
CH-A2-105	Thyroidectomy	02 Oct 2017
CH-A2-106	Laparotomy Duodenum	06 Jan 2016
CH-A2-107	Whipple Operation	04 Feb 2017
CH-A2-109	Left Breast Wide Local Excision	22 Mar 2019
CH-A2-110	Resection of Primary Melanoma of the Forehead	01 Jan 2001
CH-A2-110	Right Middle Lobectomy For Right Hilar Nodal Recurrence	01 Jan 2013
CH-A2-112	Wide Local Excision- Left Shoulder	01 Jan 2012
CH-A2-112	Left Neck Dissection	01 Jan 2015
CH-A2-113	Melanoma Excised From Left Back	01 Sep 2013
CH-A2-113	Sentinel Lymph Node Biopsy	01 Sep 2013
CH-A2-113	Lump Removed From Back	18 Jun 2015
CH-A2-113	Further Excision Left Axilla	01 Aug 2016
CH-A2-113	Left Axillary Lymphadenectomy	01 Nov 2016
CH-A2-115	Enucleation and Hyroxyapatite Orbital Implant	06 Feb 2019
CH-A2-116	Oesophagus Biopsy	04 Dec 2018
CH-A2-116	Oesophagus Biopsy	26 Jun 2019
CH-A2-116	Left Lower Lobe Lung Biopsy	08 Aug 2019
CH-A2-116	Rigid Bronchoscopy, Left Vats Lower Lobectomy	23 Oct 2019
CH-A2-116	Oesophago-Gastro-Duodenoscopy Biopsy	26 Feb 2021
CH-A2-116	Endoscopic Ultrasound (EUS)	06 Apr 2021
CH-A2-117	Liver Metastasectomy	01 Jan 2018
CH-A2-118	Right Leg Above Knee Amputation	12 Jan 2017

Subject	Procedure	Date
CH-A2-119	Elective Staging Laparoscopy And Jejunostomy	02 Dec 2020
CH-A2-120	Melanoma Excision- Upper Right Arm	01 Oct 1999
CH-A2-120	Local Recurrence Resected	01 Oct 2012
CH-A2-120	Right Axillary Resection	01 Sep 2020

Table 34: Prior radiotherapy listing

Subject	Site	Setting
CH-A2-101	Abdominal Wall	Radical
CH-A2-102	Right Hilar Mass	Palliative
CH-A2-102	Around Right Stent In Bronchus	Palliative
CH-A2-102	Radiofrequency Ablation to Enlarging Right Upper Lobe Nodule	Palliative
CH-A2-103	Bladder And Left Hip	Palliative
CH-A2-105	Thyroid Bed In Neck	Palliative
CH-A2-105	Thyroid Bed In Neck	Radical
CH-A2-109	Subpleural	Radical
CH-A2-110	Chest Wall	Radical
CH-A2-116	Oesophagus	Radical
CH-A2-119	Oesophagus/Gastro-Oesophageal Junction	Palliative

Table 35: Baseline target scan listing

Subject	Date	Organ	Location	Max Diameter	Assessment Method
CH-A2-101	21 Dec 2018	Lung	Apical Basal Segment, Left Lower Lobe	25	CT-scan
CH-A2-101	21 Dec 2018	Lung	Anterobasal Segment, Right Lower Lobe	16	CT-scan
CH-A2-101	21 Dec 2018	Mediastinum	Subcarinal	18	CT-scan
CH-A2-101	21 Dec 2018	Abdominal Cavity	Retroperitoneal	28	CT-scan
CH-A2-102	14 Feb 2019	Lung	Left Upper Lobe	24	CT-scan
CH-A2-102	14 Feb 2019	Lung	Right Upper Lobe	106	CT-scan
CH-A2-103	01 Apr 2019	Lung	Lingula	24	CT-scan
CH-A2-103	01 Apr 2019	Lung	Right Lower Lobe	22	CT-scan

Subject	Date	Organ	Location	Max Diameter	Assessment Method
CH-A2-104	29 Apr 2019	Lung	Medial Basal Segment Right Lower Lobe	40	CT-scan
CH-A2-104	29 Apr 2019	Lung	Lateral Basal Segment Left Lower Lobe	30	CT-scan
CH-A2-105	24 May 2019	Lung	Left Lower Lobe	12	CT-scan
CH-A2-105	24 May 2019	Lung	Left Upper Lobe	13	CT-scan
CH-A2-106	04 Jul 2019	Lung	Right Upper Lobe	40	CT-scan
CH-A2-106	04 Jul 2019	Lung	Right Middle Lobe	22	CT-scan
CH-A2-107	05 Aug 2019	Liver	Right Lobe	38	CT-scan
CH-A2-107	05 Aug 2019	Pancreas	Pancreas	38	CT-scan
CH-A2-108	11 Sep 2019	Right Kidney	Nodule Posterior and Slightly Cranial to the Upper Pole	30	CT-scan
CH-A2-109	13 Nov 2019	Lung	Right Upper Lobe	16	CT-scan
CH-A2-109	13 Nov 2019	Lung	Left Lower Lobe	10	CT-scan
CH-A2-110	09 Jan 2020	Sternum	Left Prevascular Node	21	CT-scan
CH-A2-110	09 Jan 2020	Lung	Left Hilar Node Posterior to the Left Main Bronchus	33	CT-scan
CH-A2-110	09 Jan 2020	Lung	Lingular Metastasis	30	CT-scan
CH-A2-110	09 Jan 2020	Lung	Left Lower Lobe	17	CT-scan
CH-A2-113	23 Oct 2020	Lung	Left Lower Lobe	19	CT-scan
CH-A2-113	23 Oct 2020	Lung	Right Lower Lobe	21	CT-scan
CH-A2-113	23 Oct 2020	Subcarinal Lymph Node	Subcarinal Lymph Node	25	CT-scan
CH-A2-114	15 Jan 2021	Pancreas	Infiltrating Primary Pancreatic Tumour	81	CT-scan
CH-A2-115	26 Mar 2021	Liver	Peripherally Within Segment VII/VIII	17	CT-scan
CH-A2-117	10 May 2021	Lung	Right Lower Lobe Nodule	29	CT-scan
CH-A2-117	10 May 2021	Liver	Segment VIII	40	CT-scan
CH-A2-117	10 May 2021	Liver	Segment V	30	CT-scan
CH-A2-118	21 Jun 2021	Lung	Right Upper Lobe	28	CT-scan
CH-A2-118	21 Jun 2021	Lung	Left Upper Lobe	25	CT-scan
CH-A2-118	21 Jun 2021	Kidney	Left Kidney Upper Pole	20	CT-scan
CH-A2-120	06 Aug 2021	Lung	Right Lower Lobe Nodule	35	CT-scan

Subject	Date	Organ	Location	Max Diameter	Assessment Method
CH-A2-120	06 Aug 2021	Lung	Left Upper Lobe Nodule	28	CT-scan

Table 36: Baseline non-target scan listing

Subject	Date	Number of Lesions	Lesion Site
CH-A2-103	01 Apr 2019	Multiple Lesions	Lung
CH-A2-103	01 Apr 2019	Single Lesion	Liver
CH-A2-103	01 Apr 2019	Single Lesion	Bladder
CH-A2-103	01 Apr 2019	Multiple Lesions	Bone
CH-A2-104	19 Mar 2019	Multiple Lesions	Bilateral Lung
CH-A2-104	19 Mar 2019	Multiple Lesions	Cystic Lesions In Spleen
CH-A2-106	04 Jul 2019	Single Lesion	Peritoneal
CH-A2-107	05 Aug 2019	Multiple Lesions	Pulmonary Metastases
CH-A2-107	05 Aug 2019	Multiple Lesions	Liver Metastases
CH-A2-108	11 Sep 2019	Single Lesion	Extensive Tumour Throughout Right Kidney
CH-A2-108	11 Sep 2019	Single Lesion	Extensive Retroperitoneal Lymphadenopathy
CH-A2-110	09 Jan 2020	Single Lesion	Left Paratracheal Node
CH-A2-111	02 Mar 2020	Single Lesion	Gastric Mass
CH-A2-111	02 Mar 2020	Multiple Lesions	Pulmonary Nodules
CH-A2-112	28 Aug 2020	Multiple Lesions	Multiple Sclerotic Bone Metastases
CH-A2-112	28 Aug 2020	Single Lesion	Subcutaneous Lesion Anterior to the Left Shoulder
CH-A2-113	23 Oct 2020	Single Lesion	Right Hilar Lymphadenopathy
CH-A2-113	23 Oct 2020	Multiple Lesions	Two Subcutaneous Nodules Over Left Lateral Chest Wall
CH-A2-115	26 Mar 2021	Multiple Lesions	Multiple Poorly Defined Low Attenuation Hepatic Metastases Within Both Lobes
CH-A2-116	21 Apr 2021	Single Lesion	Oesophagus- Mid Oesophagus Invading The Mediastinal Fat
CH-A2-117	10 May 2021	Multiple Lesions	Lung Mets
CH-A2-117	10 May 2021	Single Lesion	Primary Rectal Tumour
CH-A2-117	10 May 2021	Multiple Lesions	Liver Mets
CH-A2-119	21 Jul 2021	Single Lesion	Thickening of the Wall of the Distal Oesophagus Extending into the Stomach
CH-A2-120	06 Aug 2021	Multiple Lesions	Cutaneous Nodules Over The Right Chest Wall And Breast
CH-A2-120	06 Aug 2021	Multiple Lesions	Multifocal Hepatic Metastases

Table 37: Medical history listing

Subject	Description	Date	Status
CH-A2-101	Hypertension	01 Jan 1998	Ongoing with treatment
CH-A2-101	Osteoarthritis- Left Hip	01 Jan 2016	Ongoing without treatment
CH-A2-101	Deep Vein Thrombosis- Right Leg	01 Jan 2016	Ongoing with treatment
CH-A2-101	Benign Prostate Hyperplasia	01 Jan 2018	Ongoing with treatment
CH-A2-101	Left Inguinal Hernia Repair	01 Jan 2016	Resolved
CH-A2-102	Lower Segment Cesarean Section	01 Jan 1993	Resolved
CH-A2-102	Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy	01 Jan 2013	Resolved
CH-A2-102	Left Lower Lung Lobectomy	01 Jan 2013	Resolved
CH-A2-102	Partial Pancreatectomy and Splenectomy	01 Jan 2015	Ongoing with treatment
CH-A2-102	Stent To Right Main Bronchus	01 Dec 2018	Resolved
CH-A2-102	Vats Resection of 2 Right Lower Lobe Pulmonary Mets	01 Sep 2014	Resolved
CH-A2-103	Gout	01 Jan 2008	Ongoing with treatment
CH-A2-103	Hypercholesterolemia	01 Jan 2013	Ongoing with treatment
CH-A2-103	Intermittent Constipation	01 Feb 2018	Ongoing with treatment
CH-A2-103	COPD	01 Jan 2013	Ongoing with treatment
CH-A2-103	Urinary Frequency	01 Oct 2018	Ongoing with treatment
CH-A2-104	Hepatosplenomegaly	09 Apr 2019	Resolved
CH-A2-104	Primary Sclerosing Cholangitis	01 Jan 2016	Ongoing without treatment
CH-A2-104	Pulmonary Embolism	01 Apr 2018	Ongoing with treatment
CH-A2-104	Hypothyroid	01 Jun 2018	Ongoing with treatment
CH-A2-105	Lower Segment Caesarean Section	01 Jan 1972	Resolved
CH-A2-105	Lower Segment Caesarean Section	01 Jan 1974	Resolved
CH-A2-105	Lower Segment Caesarean Section	01 Jan 1979	Resolved
CH-A2-105	Laparoscopic Sterilisation	01 Jan 1981	Resolved
CH-A2-105	Benign Salivary Glandular Tumour	01 Jan 1990	Resolved
CH-A2-105	Total Thyroidectomy	29 Sep 2017	Ongoing with treatment
CH-A2-105	Insomnia	01 Apr 2019	Ongoing with treatment
CH-A2-106	Type 2 Diabetes	01 Jan 2003	Ongoing with treatment
CH-A2-106	Polyposis	01 Jan 1989	Resolved

Subject	Description	Date	Status
CH-A2-106	Reflux	01 Jan 2009	Ongoing with treatment
CH-A2-106	Anxiety	01 Jan 2016	Resolved
CH-A2-106	High Cholesterol	01 Jan 2004	Ongoing with treatment
CH-A2-106	Stomach Pains	01 Jan 2016	Ongoing with treatment
CH-A2-106	Arthritis	01 Jun 2018	Ongoing without treatment
CH-A2-106	Thrombosis	28 Jan 2019	Ongoing with treatment
CH-A2-106	Diarrhoea - Intermittent from Stoma	01 Jan 1999	Ongoing with treatment
CH-A2-106	Vitamin B12 Deficiency	01 Jan 2016	Ongoing with treatment
CH-A2-106	Back Vesicles	01 May 2019	Ongoing without treatment
CH-A2-106	Sebaceous Cyst	01 Jan 1999	Resolved
CH-A2-107	Tonsillectomy	01 Jan 1962	Resolved
CH-A2-107	Rheumatic Fever	01 Jan 1966	Resolved
CH-A2-107	Epilepsy	01 Jan 1968	Resolved
CH-A2-107	Hysterectomy	01 Jan 2003	Resolved
CH-A2-107	Arthritis - Hip	01 Jan 2014	Ongoing without treatment
CH-A2-107	Hypertension	13 Mar 2017	Ongoing with treatment
CH-A2-107	Diabetes	01 Oct 2018	Ongoing with treatment
CH-A2-107	Bowel Twist - Operation	01 Nov 2018	Resolved
CH-A2-107	Neuropathy to Fingertips and Toes	01 Dec 2018	Ongoing without treatment
CH-A2-107	Eczema	01 Jul 2019	Ongoing with treatment
CH-A2-107	Acid Reflux	01 Nov 2016	Ongoing with treatment
CH-A2-108	Appendicectomy	01 Jan 1995	Resolved
CH-A2-108	Hypertension	01 Jan 2016	Ongoing with treatment
CH-A2-108	Bilateral Leg Lymphedema	01 Mar 2019	Resolved
CH-A2-109	Antiphospholipid Syndrome	01 Jun 2017	Ongoing with treatment
CH-A2-109	Pulmonary Embolism	01 Apr 2016	Ongoing with treatment
CH-A2-109	Depression	01 Feb 2016	Ongoing with treatment
CH-A2-110	Asthma	01 Jan 2010	Ongoing with treatment
CH-A2-111	Hyperthyroidism	05 Oct 2017	Ongoing with treatment
CH-A2-112	Epilepsy	01 Jan 1989	Ongoing without treatment
CH-A2-112	Auto Immune Arthritis Secondary to Immunotherapy Treatment	01 Jan 2017	Ongoing without treatment

Subject	Description	Date	Status
CH-A2-112	Left Knee Arthroscopy	01 Jan 2017	Resolved
CH-A2-112	Previous Ruptured Ovarian Cyst	01 Jan 1989	Resolved
CH-A2-112	Constipation	01 Jul 2016	Ongoing without treatment
CH-A2-112	Joint Pain- Generalised	01 Jan 2017	Ongoing with treatment
CH-A2-112	Fatigue	01 Jan 2018	Ongoing without treatment
CH-A2-112	Dry Mouth	01 May 2020	Ongoing without treatment
CH-A2-112	Hot Sweats	01 Jan 2019	Ongoing without treatment
CH-A2-112	Depression	01 Jan 2018	Ongoing with treatment
CH-A2-113	Type 2 Diabetes	01 Jan 2010	Ongoing with treatment
CH-A2-114	Cesarian Section	01 Jan 1974	Resolved
CH-A2-114	Appendectomy	01 Jan 1965	Resolved
CH-A2-114	Osteoporosis	01 Jan 2012	Ongoing without treatment
CH-A2-114	Hysterectomy and Bilateral Salpingo-Oophorectomy	01 Jan 1997	Resolved
CH-A2-114	Splenic Vein Thrombosis	01 Apr 2020	Ongoing with treatment
CH-A2-115	Inflammatory Proctitis	01 Jan 1998	Resolved
CH-A2-115	Hypothyroidism	01 Feb 2020	Ongoing with treatment
CH-A2-116	Febrile Neutropenia	01 Mar 2019	Resolved
CH-A2-118	Olliers Disease	18 Jun 1979	Ongoing without treatment
CH-A2-119	Traumatic Fracture of Lumbar Spine	01 Jan 2018	Resolved
CH-A2-119	Jejunostomy Tube	01 Dec 2020	Resolved
CH-A2-119	Possible Asbestos Exposure (Navy Shipyard)		Resolved
CH-A2-120	Rheumatoid Arthritis	01 Jan 2015	Ongoing with treatment
CH-A2-120	Hypothyroidism	01 Jun 2020	Ongoing with treatment
CH-A2-120	Hypertension	01 Oct 2019	Ongoing with treatment
CH-A2-120	Hypercholesterolaemia	01 Oct 2019	Ongoing with treatment
CH-A2-120	Chest Wall Pain	01 Jun 2021	Ongoing with treatment
CH-A2-120	Transient Ischaemic Attack (TIA)	01 Jan 2020	Resolved
CH-A2-120	Right Chest Wall Rash	01 Jun 2020	Ongoing without treatment

7.2 Appendix - Deviations

Table 38: Deviations listing

Subject	Site	Date	Type	Description	Action Taken
CH-A2-101	Churchill, Oxford	17 Jan 2019	Deviation	End time of infusion not recorded for Cycle 1, week 2 M6620 administration.	Query raised with site. To be notified to clinical team if further instances occur.
CH-A2-101	Churchill, Oxford	06 Feb 2019	Deviation	Coagulation assessment not completed at 2 week FU.	Queried with site - missed in error. Notified to site as part of Mar2022 deviation review.
CH-A2-102	Churchill, Oxford	18 Apr 2019	Deviation	Participant withdrawn from treatment due to disease progression. Site to inform OCTO and safety within 24hours. This did not occur until 09May2019.	Site informed and aware that the early withdrawal form must be completed within 24 hours. Form completed.
CH-A2-103	Churchill, Oxford	25 Apr 2019	Deviation	Infusion end time not recorded in error. Week2 day2.	Notified to site and correct protocol highlighted.
CH-A2-106	Velindre, Cardiff	19 Jul 2019	Deviation	Week 1 Friday physical examination not carried out.	Query raised with site. Response was: "Not carried out as no early phase physician available on a Friday. Patient was feeling well and no concerns to note. On call SHO would have been contacted if any concerns had been raised." No further action taken.
CH-A2-106	Velindre, Cardiff	19 Jul 2019	Deviation	ECOG performance status assessment not done prior to cycle 1 week 1 day 5 (Friday) M6620 administration. This was due to admin error by site.	Site acknowledged the error in the OC when completing data entry. Noted as a deviation in annotation within the CRF. No further action taken.
CH-A2-106	Velindre, Cardiff	26 Jul 2019	Deviation	Performance status not assessed on Friday in weeks 2 and 3. Missed in error.	Notified to site and correct protocol highlighted.
CH-A2-106	Velindre, Cardiff	02 Aug 2019	Deviation	ECOG assessment not completed Friday dose, Week 3.	Notified to site.
CH-A2-107	Velindre, Cardiff	13 Aug 2019	Deviation	Infusion of M6620 duration in Cycle 1 week was 123 minutes (protocol states 60 minutes +/- 10 minutes, unless >600ml when infusion time may be increased by 30 minutes).	Raised as query with site. Response was that infusion was interrupted due to infusion reactions (itching & redness). Patient administered Piriton and infusion was re-started/completed. No further action taken.
CH-A2-106	Velindre, Cardiff	16 Aug 2019	Deviation	Physical exam assessment not completed for Friday visits due to no physician on site. Affected visits: Weeks 4-8.	Notified to site and correct protocol highlighted. Requested provision made for physician to be present on a Firday.
CH-A2-105	Churchill, Oxford	29 Aug 2019	Important Deviation	Cisplatin given to patient in C5D1 after bloods signed off by Dr. Pharmacist noticed bilirubin out of range & team considered this a grade 3 non-haematological toxicity that was considered possibly drug related at the time. If so, Cisplatin should not be given until resolved to G0-1. It was a deviation that this was given. Infusion was stopped, doctor reviewed patient and post hydration was completed and bloods taken. Doctor recommended patient to return following day for liver ultrasound (NAD) and further bilirubin testing, which was	Important deviation form and CAPA completed by site. PI & co-Is aware. Merck informed. 11Sep2019 update: Reviewed if should have been reported as an SAE. Not applicable, because excluded as related within 24hr period.

Subject	Site	Date	Type	Description	Action Taken
				decreasing. In retrospect site don't think this is drug related but rather that the patient has gilbert's syndrome and then haemolysed following a blood transfusion.	
CH-A2-107	Velindre, Cardiff	23 Sep 2019	Deviation	CT scan carried out 4 weeks prior to due date.	Queried with site - no scans performed in Oct 2019. No further action taken.
CH-A2-108	Churchill, Oxford	30 Sep 2019	Important Deviation	Several patient doses of M6620 were administered on a Monday.	Cycle 1 was discussed with CI at the time - the patient had significant haem toxicity and a number of does were omitted. However, unclear why patient received doses of M6620 on a Monday. Queried with site and unable to give reason. Notified to site as part of Mar2022 deviation review. No further action taken.
CH-A2-108	Churchill, Oxford	04 Oct 2019	Deviation	Weight not assessed at week 2 visit. "Missed in error".	Notified to site as part of January 2022 deviation review.
CH-A2-108	Churchill, Oxford	04 Oct 2019	Deviation	Coagulation test not completed at 2 week post-EOT visit.	Notified to site as part of January 2022 deviation review.
CH-A2-106	Velindre, Cardiff	17 Oct 2019	Deviation	Phosphate assessment not completed in error. Week 13.	Notified to site and correct protocol highlighted.
CH-A2-108	Churchill, Oxford	22 Oct 2019	Deviation	Duration missing for M6620 administration during Cycle 2.	Queried with site - not documented in error. Notified to site as part of Apr2022 deviation review. This type of deviation has been assessed by the TMG previously and been deemed to not be an important deviation.
CH-A2-109	Churchill, Oxford	18 Nov 2019	Deviation	Patient received lower than required dose of cisplatin.	Initially, patient should have taken 60mg x 1.82 BSA = 109mg. Site documented dose is 100mg. Patient received a dose reduction in cycle 3, and should have taken 30mg x 1.82 BSA = 54mg . Site documented dose is 50mg. Queried with site - data manager confirmed that documented doses are correct per data on ARIA. Not within 5% tolerance/dose banding. Notified to site as part of Mar2022 deviation review. TMG reviewed 05Jul2022 and confirmed did not meet criteria for important deviation.
CH-A2-109	Churchill, Oxford	19 Nov 2019	Deviation	Patient received lower than required dose of M6620.	Patient should have taken 140mg x 1.82 BSA = 254mg. Site documented dose is 242mg. Queried with site - data manager confirmed that 242mg is documented dose. Notified to site as part of Mar2022 deviation review. TMG reviewed 05Jul2022 and confirmed did not meet criteria for important deviation.
CH-A2-108	Churchill, Oxford	26 Nov 2019	Deviation	Weight not assessed at week 9 visit. "Missed in error".	Notified to site as part of January 2022 deviation review.

Subject	Site	Date	Type	Description	Action Taken
CH-A2-109	Churchill, Oxford	09 Dec 2019	Deviation	Patient received lower than required dose of capecitabine.	Initially, patient should have taken 625mg x 1.82 BSA = 1137mg. Site documented dose is 1000mg. Patient received a dose reduction in cycle 2, and should have taken 313mg x 1.82 BSA = 570mg. Site documented dose is 500mg. Queried with site - data manager confirmed that documented doses are correct per data on ARIA. Not within 5% tolerance/dose banding. Notified to site as part of Mar2022 deviation review. TMG reviewed 05Jul2022 and confirmed did not meet criteria for important deviation.
CH-A2-109	Churchill, Oxford	10 Dec 2019	Deviation	No end time recorded for M6620 infusion, so no duration. Cycle 4, week 11 day 2. Site confirmed end time not documented.	Notified to site as part of Feb 2022 deviations review. Included in TMG review of deviations, but not classed as an important deviation, as no evidence that IMP was not administered correctly. Highlighted that this is a repeating error (3 other instances for A2 patients).
CH-A2-109	Churchill, Oxford	13 Dec 2019	Deviation	Infusion durations exceed 70 mins for some days C2-C3.	Queried with site - no reason recorded. Will be reviewed by TMG as potential important deviation. And notified to site as part of Mar2022 deviation review. Update: TMG agreed no impact to patients of longer infusion time and that deviation does not meet criteria for important classification (14Mar2022).
CH-A2-108	Churchill, Oxford	10 Jan 2020	Deviation	Performance Status not assessed at week 14 visit. "Missed in error".	Notified to site as part of January 2022 deviation review.
CH-A2-110	Churchill, Oxford	03 Feb 2020	Deviation	Stop date of one of pt's con meds not recorded.	Queried with site - not known. Notified to site as part of Apr2022 deviation review.
CH-A2-110	Churchill, Oxford	03 Feb 2020	Important Deviation	Patient CH-A2-110 had all screening assessments performed on 09Jan2020 but trial treatment did not start until 03Feb2020 (screening 25 days prior to treatment, instead of within 21 days prior as per protocol).	Deviation highlighted to site. RN confirmed the dates of screening & C1D1, acknowledged the deviation and will look into how/why this occurred. Update: Site to receive protocol training as part of Stage B refresher SIV. Training set for 02Mar2021 and will include information relating to timing of screening assessments. Update: Site protocol training delivered for key staff on 02Mar2021.
CH-A2-108	Churchill, Oxford	04 Feb 2020	Deviation	Week 8 Tuesday assessments not completed.	Queried with site - due to patient having respiratory tract infection. No further action taken.
CH-A2-109	Churchill, Oxford	07 Feb 2020	Deviation	Pregnancy test not completed at week 12 assessment.	Queried with site - missed in error. Notified to site as part of Mar2022 deviation review.

Subject	Site	Date	Type	Description	Action Taken
CH-A2-109	Churchill, Oxford	07 Feb 2020	Deviation	End time of infusion not recorded for C4 M6620 administration (2 visits).	Queried with site - end time not documented in error. Notified to site as part of Mar2022 deviation review.
CH-A2-110	Churchill, Oxford	03 Mar 2020	Deviation	End time of infusion not recorded (C2, wk5 D2).	Queried with site - not recorded in error. Notified to site as part of Mar2022 deviation review.
CH-A2-109	Churchill, Oxford	16 Mar 2020	Deviation	Infusion duration exceeded 70 minutes.	Queried with site - reason not documented, given in error over 75 mins. Notified to site as part of Mar2022 deviation review. . Review required by TMG. Update: TMG agreed no impact to patients of longer infusion time and that deviation does not meet criteria for important classification (14Mar2022).
CH-A2-110	Churchill, Oxford	23 Mar 2020	Deviation	Participant was withdrawn from treatment due to disease progression 17Mar2020. OCTO were not informed until 23Mar2020. This should have occurred within 24 hours.	Site team informed of deviaiton. Recognised it has occurred during coronavirus where there are other pressures. No further action needed, site aware of process. Withdrawal was not due to safety/DLT and participant is past DLT window= not important deviaton.
CH-A2-109	Churchill, Oxford	23 Mar 2020	Deviation	Cycle 6 end time of infusion not recorded.	Queried with site - stop time not documented in error. Notified to site as part of Mar2022 deviation review.
CH-A2-110	Churchill, Oxford	31 Mar 2020	Deviation	Patient did not attend the site due to COVID-19 outbreak. Haematology & biochemistry bloods done at local GP surgery but all other assessments not done (coagulation, performance status, physical examination and weight).	None.
CH-A2-108	Churchill, Oxford	08 Apr 2020	Deviation	8 week FU assessments not completed - Haematology, Biochemistry, Weight, CT.	Queried with site - patient did not attend due to COVID. No further action taken.
CH-A2-103	Churchill, Oxford	08 Apr 2020	Deviation	8 week FU assessments not completed due to COVID.	Not done due to COVID. No further action taken.
CH-A2-109	Churchill, Oxford	14 Apr 2020	Deviation	Coagulation assessment not completed at 2 weeks post-EOT FU visit.	Notified to site as part of Feb 2022 deviations review and request to ensure all assessments completed per protocol.
CH-A2-109	Churchill, Oxford	20 Apr 2020	Deviation	2 & 8 week FU visits were not done due to COVID.	Queried with site - assessments conducted by phone. Following COVID guidelines. No further actions.
CH-A2-110	Churchill, Oxford	18 May 2020	Deviation	Follow up assessments not carried out as consultation held via telephone due to covid. Affected assessments: PE, Weight, Haematology, Biochemistry. Patient in follow up, so doesn't relate to pre-M6620 assessments.	Notified to site and correct protocol highlighted.
CH-A2-110	Churchill, Oxford	18 May 2020	Deviation	CT-MRI not done at week 8 FU.	Queried with site - not done due to COVID. No further actions.

Subject	Site	Date	Type	Description	Action Taken
CH-A2-109	Churchill, Oxford	08 Jul 2020	Deviation	Target Lesion date & diameter not recorded.	Queried to site - site responded that the lesions were not assessed on this scan. Scan was entered for evidence of DP. Appears to have been done to replace a scan not completed due to COVID, however hasn't fulfilled the point of the RECIST scan. Notified to site as part of Apr2022 deviation review.
CH-A2-112	Churchill, Oxford	28 Aug 2020	Deviation	Patient was re-consented, but PE and ECOG were not completed at re-screening.	Queried with site - notes document that patient was well with no issues at re-screening. Therefore risk to patient low. TMG reviewed 05Jul2022 and confirmed did not meet criteria for important deviation.
CH-A2-112	Churchill, Oxford	10 Sep 2020	Important Deviation	Participant registered to CHARIOT 10Sep2020 and marked by site as eligible. Site identified 11Sep2020 phosphate was out of range 1.56mmol/L (0.7 - 1.45mmol/L) meaning she was ineligible.	Site deem out of range not clinically significant. Patient to be rescreened before treatment start. If ineligible to be withdrawn. CI & PI in agreement. Important deviation form with CAPA completed by site.
CH-A2-112	Churchill, Oxford	14 Sep 2020	Deviation	Participant received phosphate rescreening bloods too early & found to be ineligibile. Site informed rescreening is only allowed once. Blood taken too early as not enough time had been given for the patient to have their vitamin D supplementation washed out which is suspected as the cause of the raised phosphate.	Site informed and aware re-screening can only occur once. CI agree rescreening allowed again, as this rescreening blood test was completed too early in error. This is a agreed deviation of the protocol allowing re-screeening only once.
CH-A2-112	Churchill, Oxford	05 Oct 2020	Deviation	Friday assessments were not carried out in week 1.	Queried with site - patient did not attend. No further action.
CH-A2-112	Churchill, Oxford	12 Oct 2020	Deviation	Infusion end time not recorded for some doses in C2, C3 and C6.	Queried with site - not recorded in error. Notified to site as part of Mar2022 deviation review.
CH-A2-112	Churchill, Oxford	12 Oct 2020	Deviation	C1 and C6 infusion times recorded as over allowable time.	Queried with site - infusion time recorded included flush time, so expected to be within correct tolerance per protocol. Notified to site as part of Mar2022 deviation review. Will need TMG review. Update: TMG agreed no impact to patients of longer infusion time and that deviation does not meet criteria for important classification (14Mar2022).
CH-A2-113	Churchill, Oxford	23 Oct 2020	Important Deviation	Patient received screening CT scan a few hours before consent. In part this occurred due to miscommunication due to some members of the research team having to self-isolate although of course this is not an excuse.	Site to document this occurrence in the source data. Important deviation form to be completed with CAPA 15Dec: Site completed the Deviation form with CAPA and send to CHARIOT. The deviation is now closed.

Subject	Site	Date	Type	Description	Action Taken
CH-A2-113	Churchill, Oxford	23 Oct 2020	Deviation	Phosphate not assessed prior to re-screening.	Queried to site - not completed in error. Notified to site as part of Apr2022 deviation review.
CH-A2-112	Churchill, Oxford	08 Dec 2020	Deviation	Pregnancy test not completed at week 8.	Queried with site - missed in error. Notified to site as part of Mar2022 deviation review.
CH-A2-112	Churchill, Oxford	14 Dec 2020	Important Deviation	Patient CH-A2-112 was unintentionally dosed on C3D16 when she had G3 neutropaenia. This has been reported on Ulysses for investigation. She came back for C3D19 and again had G3 neutropaenia and so wasn't dosed. She has already had a dose reduction of capecitabine and cisplatin and M6620. Co-I thought a further reduction wasn't possible. She has only missed one dose and it is not knows what her counts would have been C3D19 if she had not been dosed inappropriately. Site plan C4D1 21Dec2020 if counts have recovered. Request confirmation sponsor in agreement.	OCTO and CI: Agree with plan to assess C4D1. Site to complete important deviation form and investigate what were the circumstances of administering the M6620 when patient neutropenic and establish potential prevention mechanisms. Advised protocol allows a second dose reduction of M6620 allowed to 50% of the starting dose if they've only had a 25% reduction so far. Simon agrees this has not yet been used. Update: CAPA received 04Jan2021. Sub-I suggests protocol retraining for key staff. OCTO to carry out SIV training for site staff in Feb and will ensure that these staff are present. Update: Site protocol training for key staff delivered on 02Mar2021.
CH-A2-113	Churchill, Oxford	15 Dec 2020	Deviation	M6620 infusion duration exceeded maximum time (total 86 minutes). Week 4 day 2. No reason documented.	Notified to site and correct protocol highlighted. TMG discussed the importance of deviations that extend the maximum window according to the protocol on 14Mar2022. Confirmed that there is no impact to the trial of extending the infusion time. Therefore, does not meet the criteria for an important deviation.
CH-A2-112	Churchill, Oxford	25 Dec 2020	Deviation	Week 10, Day 5 were assessments not completed due to Christmas day (no dose of M6620 given on day5).	This was checked with Maria at the time and it was agreed that the dose couldn't be given due to Xmas. No further actions.
CH-A2-113	Churchill, Oxford	29 Dec 2020	Deviation	Calcium assessment missed in error. Weeks 6, 7, 11.	Notified to site and correct protocol highlighted.
CH-A2-112	Churchill, Oxford	29 Dec 2020	Deviation	Week 11 calcium assessment not done.	Queried with site - missed in error. Notified to site as part of Mar2022 deviation review.
CH-A2-112	Churchill, Oxford	01 Jan 2021	Deviation	Week 11, day 5 assessments not completed due to new years day (no dose of M6620 given on day5).	This was checked with Maria at the time and agreed that the dose couldn't be given due to closures over holiday period. No further action.
CH-A2-112	Churchill, Oxford	08 Jan 2021	Deviation	Week 12 phosphate assessment not done.	Queried with site - missed in error. Notified to site as part of Mar2022 deviation review.
CH-A2-114	Churchill, Oxford	09 Feb 2021	Deviation	GFR not assessed at week 3.	Reported to site as part of December monthly deviations review and

Subject	Site	Date	Type	Description	Action Taken
					requested all protocol assessments completed. Also, suggested updating patient visit sheet, if applicable.
CH-A2-113	Churchill, Oxford	09 Feb 2021	Deviation	MRI scan not completed in error in week 12.	Notified to site and correct protocol highlighted.
CH-A2-114	Churchill, Oxford	09 Feb 2021	Deviation	Weight not assessed at week 3.	Queried to site - not completed in error. Notified to site as part of Apr2022 deviation review.
CH-A2-113	Churchill, Oxford	16 Feb 2021	Deviation	M6620 infusion duration exceeded maximum time. Week 13, day 2 - 72 minutes, no reason documented.	Notified to site and correct protocol highlighted. TMG discussed the importance of deviations that extend the maximum window according to the protocol on 14Mar2022. Confirmed that there is no impact to the trial of extending the infusion time. Therefore, does not meet the criteria for an important deviation.
CH-A2-112	Churchill, Oxford	16 Feb 2021	Deviation	Weight & GFR results not documented.	Queried with site - not documented in error. Notified to site as part of Mar2022 deviation review.
CH-A2-114	Churchill, Oxford	22 Feb 2021	Deviation	Alk phosphatase not assessed at week 4.	Queried to site - not completed in error. Notified to site as part of Apr2022 deviation review.
CH-A2-113	Churchill, Oxford	02 Mar 2021	Deviation	M6620 infusion duration exceeded maximum time. Week 15 day 2 - 74 minutes, flush only was running in error before switching to IMP.	Notified to site and correct protocol highlighted.
CH-A2-114	Churchill, Oxford	09 Mar 2021	Deviation	End time for cycle 2 dose not recorded.	Queried to site - end time not recorded in error. However, confirmed that the administration time was within 1 hour per protocol, therefore not assessed to be a possible important deviation. Notified to site as part of Apr2022 deviation review.
CH-A2-113	Churchill, Oxford	09 Mar 2021	Deviation	No end time recorded for Week 16 and 17 M6620 infusion.	Notified to site and correct protocol highlighted.
CH-A2-114	Churchill, Oxford	10 Mar 2021	Deviation	Patient was withdrawn during cycle 3 due to disease progression, but withdrawal form not received by OCTO within 24 hours. CRF was completed.	Notified to site as soon as identified and form requested for TMF. Update: provided 11Apr2022.
CH-A2-114	Churchill, Oxford	25 Mar 2021	Deviation	Weight not assessed at 2-week FU.	Reported to site as part of December monthly deviations review and requested all protocol assessments completed. Also, suggested updating patient visit sheet, if applicable.
CH-A2-115	Churchill, Oxford	26 Mar 2021	Deviation	Coagulation assessment not completed at screening.	Queried to site - sample underfilled, therefore unsuitable for testing. Notified to site as part of Apr2022 deviation review.

Subject	Site	Date	Type	Description	Action Taken
CH-A2-116	Churchill, Oxford	09 Apr 2021	Deviation	Urea not assessed at screening.	Queried with site - assessment not available. Notified to site as part of Apr2022 deviation review.
CH-A2-115	Churchill, Oxford	09 Apr 2021	Deviation	Site filled in the patient's full DOB on the registration form rather than YOB only.	- Site notified of deviation - Data breach team notified of deviation (ICT1655) - awaiting final response. final response: Closed with no further action.
CH-A2-115	Churchill, Oxford	09 Apr 2021	Deviation	Site sent a histology report with the patients name on the back of one of the scanned pages. This was not identified until the A2 reports were combined to transfer to the data checker.	Page deleted from report as soon as error identified. Attachment deleted from original mail deleted from inbox. Reported to data breach team (ICT1849). Update 29Nov2021: DB team confirmed that case is closed with no further actions.
CH-A2-115	Churchill, Oxford	05 May 2021	Deviation	Duration of M6620 infusion was 83 mins (over the 60 mins +/- 10 mins).	Queried with site. Site response: "dose given over extended period in error". Highlighted to site as part of Feb 2022 deviations review. TMG discussed the importance of deviations that extend the maximum window according to the protocol on 14Mar2022. Confirmed that there is no impact to the trial of extending the infusion time. Therefore, does not meet the criteria for an important deviation.
CH-A2-115	Churchill, Oxford	20 May 2021	Deviation	No end time recorded for M6620 infusion, so no duration. Cycle 2, week 6 day 2. Site confirmed end time not documented in error.	Notified to site as part of Feb 2022 deviations review. Included in TMG review of deviations, but not classed as an important deviation, as no evidence that IMP was not administered correctly. Highlighted that this is a repeating error (4 other instances for A2 patients).
CH-A2-106	Velindre, Cardiff	20 May 2021	Deviation	Patient had 6-month follow up assessment at 6 months post-end of treatment, rather than post-start of treatment.	Queried with site - completed late in error. Notified to site as part of Mar2022 deviation review.
CH-A2-116	Churchill, Oxford	21 May 2021	Deviation	Patient was withdrawn during cycle 3 due to DLT in cycle 2, but withdrawal form not received by OCTO within 24 hours. CRF was completed.	Notified to site as soon as identified and form requested for TMF. Update: provided 11Apr2022.
CH-A2-115	Churchill, Oxford	28 May 2021	Deviation	Patient was withdrawn during cycle 3 due to disease progression, but withdrawal form not received by OCTO within 24 hours. CRF was completed.	Notified to site as soon as identified and form requested for TMF. Update: provided 11Apr2022.
CH-A2-117	Churchill, Oxford	07 Jun 2021	Deviation	Patient took lower than prescribed capecitabine dose during cycle 1 in error.	Site informed OCTO by email 22Jun2021 and confirmed that patient's dose has been rectified. No further action taken.
CH-A2-119	Churchill, Oxford	08 Jul 2021	Deviation	Date of onset of pre-existing medical condition not recorded.	Queried to site - patient unsure of date, so not recorded. Notified to site as part of Apr2022 deviation review.

Subject	Site	Date	Type	Description	Action Taken
CH-A2-119	Churchill, Oxford	08 Jul 2021	Deviation	Physical exam and ECOG assessment not done within 21 days of first dose (following re-consent).	Queried to site - patient re-consented, but tests were not done in error. Notified to site as part of Apr2022 deviation review.
CH-A2-115	Churchill, Oxford	20 Jul 2021	Deviation	CT/MRI not completed at week 8 FU.	Queried with site - site response "missed in error". Highlighted to site as part of Feb 2022 deviations review.
CH-A2-117	Churchill, Oxford	21 Jul 2021	Deviation	Site did not notify OCTO of patient withdrawal within 24 hours.	Site contacted to notify them of the error and request complete withdrawal form. Update: completed and saved to TMF.
CH-A2-117	Churchill, Oxford	27 Jul 2021	Deviation	GFR not calculated at Week 8 (as weight not assessed).	Reported to site as part of December monthly deviations review and requested all protocol assessments completed. Also, suggested updating patient visit sheet, if applicable.
CH-A2-118	St James, Leeds	27 Jul 2021	Deviation	C2-4 infusion time exceeds 70 minutes (but up to 5 minutes).	Queried with site - time accounts for overage in bag & flush. Administration of IMP within the time allowed, but should have been recorded without overage/flush. No further action taken.
CH-A2-117	Churchill, Oxford	27 Jul 2021	Deviation	Weight not assessed at Week 8.	Reported to site as part of December monthly deviations review and requested all protocol assessments completed. Also, suggested updating patient visit sheet, if applicable.
CH-A2-120	Churchill, Oxford	06 Aug 2021	Deviation	Alk Phosphate test missed at screening.	Queried to site - not completed in error. Notified to site as part of Apr2022 deviation review.
CH-A2-118	St James, Leeds	16 Aug 2021	Deviation	ECOG assessment not completed at Weeks 7, 10 and 14.	Queried with site - missed in error. Notified to site as part of Mar2022 deviation review.
CH-A2-120	Churchill, Oxford	16 Aug 2021	Deviation	Dose banding for capecitabine for patient CH-A2-120 has been 6.8% from calculated dose â€“ the protocol says dose banding is permitted as per local hospital policy, assuming it is within 5% of actual calculated dose.	Deviation forwarded to MAH for review. Assessed not to be classed as an important deviation. Requested site either update Aria, or confirm that future doses will not exceed 5%. Also asked to check previous patients, for possible deviations. Awaiting response. Update 15Oct2021: Site confirmed that as far as they know only one patient is affected (A2-120) - to be confirmed. Pt is receiving 1000mg capecitabine which is 6.8% below calculated dose. However, patient will stay on this dose, as this is the closest dose to calculated due to size of capecitabine tablets. Update 02Nov2021: Simon Lord confirmed that no other patients are affected. No other patients to be recruited, so no change to Aria required.

Subject	Site	Date	Type	Description	Action Taken
CH-A2-119	Churchill, Oxford	31 Aug 2021	Deviation	Week 4 assessments not completed within 24 hours of M6620 administration.	Queried to site. Response: Assessment was done on correct date, but M6620 dose could not be given on 01Sep21 as drug was made on 31Aug21 in error, so no longer in date. Aseptic unit were unable to remake dose on 01Sep, so pt was dosed on 02Sep. Test was within 24hrs of cape & cist. Notified to site as part of Apr2022 deviation review.
CH-A2-119	Churchill, Oxford	02 Sep 2021	Deviation	Stop time of infusion not recorded so no duration added (Week 4).	Queried with site - stop time not documented in error. Notified to site as part of Mar2022 deviation review.
CH-A2-119	Churchill, Oxford	02 Sep 2021	Deviation	No M6620 administration duration entered.	Queried to site - end time of infusion not documented, so no duration calculated. Notified to site as part of Apr2022 deviation review. This type of deviation has been previously assessed by the TMG and decided not to be an important deviation.
CH-A2-119	Churchill, Oxford	02 Sep 2021	Deviation	M6620 dose not given within 24hrs of other treatments.	Queried to site. Response: Unable to dose pt on 01Sep as chemotherapy script had not been moved to correct day. Drug was made on 31Aug, so not in date and aseptic couldn't remake drug on 01Sep. Pt had to return for dose on 2Sep21. Notified to site as part of Apr2022 deviation review. TMG reviewed 05Jul2022 and confirmed did not meet criteria for important deviation.
CH-A2-117	Churchill, Oxford	14 Sep 2021	Deviation	CT/MRI assessment not completed at 8 week FU.	Queried with site - not completed in error. Notified to site as part of Apr2022 deviation review.
CH-A2-120	Churchill, Oxford	15 Sep 2021	Deviation	C2 wk5 D2 - end time of M6620 infusion not recorded.	Queried to site - not recorded in error. Notified to site as part of Apr2022 deviation review. This type of deviation has previously been reviewed by the TMG and deemed not to be an important deviation.
CH-A2-118	St James, Leeds	20 Sep 2021	Deviation	Pregnancy test not completed at week 12.	Queried with site - missed in error. Notified to site as part of Mar2022 deviation review.
CH-A2-118	St James, Leeds	20 Sep 2021	Deviation	CT-MRI scan results not entered.	Queried with site - response was that scan was done but not reported to RECIST. Notified to site as part of Mar2022 deviation review.

Subject	Site	Date	Type	Description	Action Taken
CH-A2-118	St James, Leeds	26 Oct 2021	Deviation	Week 17 visit not completed.	Queried with site - visit not completed "at patient request". No further actions taken.
CH-A2-119	Churchill, Oxford	27 Oct 2021	Deviation	Cycle 4 infusion duration recorded as 72 mins.	Queried to site - site responded that the duration included flush time, so administration would have been under an hour. Notified to site as part of Apr2022 deviation review.
CH-A2-117	Churchill, Oxford	07 Dec 2021	Deviation	Late toxicities, palliative intervention, surgical resection and post trial treatment not completed.	Queried to site - data not known. Notified to site as part of Apr2022 deviation review.
CH-A2-120	Churchill, Oxford	14 Dec 2021	Deviation	CT/MRI not done at Week 18 assessment.	Queried with site - not completed in error. Notified to site as part of Apr2022 deviation review.
CH-A2-119	Churchill, Oxford	29 Dec 2021	Deviation	Weight not assessed at Week 2 FU.	Queried to site - not completed in error. Notified to site as part of Apr2022 deviation review.
CH-A2-118	St James, Leeds	30 Dec 2021	Deviation	ECOG assessment not completed at week 12 FU.	Queried with site - missed in error. Notified to site as part of Mar2022 deviation review.

7.3 Appendix - Treatment

Table 39: Capecitabine reductions and modifications listing

Subject	Date	Amount Given	Reason	Type	Cycle
CH-A2-101	18Jan2019	800	patient forgotten to take full dose	Modification	Cycle 1
CH-A2-101	24Jan2019	0	treatment suspended	Modification	Cycle 1
CH-A2-108	04Oct2019	0	fatigue, nausea, dysgeusia, anorexia, abdominal pain	Modification	Cycle 1
CH-A2-108	05Oct2019	0	fatigue, nausea, dysgeusia, anorexia, abdominal pain	Modification	Cycle 1
CH-A2-108	05Oct2019	0	fatigue, nausea, dysgeusia, anorexia, abdominal pain	Modification	Cycle 1
CH-A2-108	06Oct2019	0	fatigue, nausea, dysgeusia, anorexia, abdominal pain	Modification	Cycle 1
CH-A2-108	06Oct2019	0	fatigue, nausea, dysgeusia, anorexia, abdominal pain	Modification	Cycle 1
CH-A2-108	14Oct2019	0	neutropenia	Modification	Cycle 1
CH-A2-108	15Oct2019	0	neutropenia	Modification	Cycle 1
CH-A2-108	15Oct2019	0	neutropenia	Modification	Cycle 1

Subject	Date	Amount Given	Reason	Type	Cycle
CH-A2-108	16Oct2019	0	neutropenia	Modification	Cycle 1
CH-A2-108	16Oct2019	0	neutropenia	Modification	Cycle 1
CH-A2-109	18Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	19Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	19Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	20Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	20Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	21Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	21Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	22Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	22Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	23Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	23Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	24Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	24Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	25Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	25Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	26Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	26Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	27Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	27Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	28Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	28Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	29Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	29Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	30Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	30Nov2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	01Dec2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	01Dec2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	02Dec2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	02Dec2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	03Dec2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	03Dec2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	04Dec2019	500	Pt took the wrong amount in error	Modification	Cycle 1

Subject	Date	Amount Given	Reason	Type	Cycle
CH-A2-109	04Dec2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	05Dec2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	05Dec2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-109	06Dec2019	500	Pt took the wrong amount in error	Modification	Cycle 1
CH-A2-112	05Oct2020	0	Nausea, sickness, fatigue, headache	Modification	Cycle 1
CH-A2-112	05Oct2020	0	Nausea, sickness, fatigue, headache	Modification	Cycle 1
CH-A2-112	06Oct2020	0	Nausea, sickness, fatigue, headache	Modification	Cycle 1
CH-A2-112	06Oct2020	0	Nausea, sickness, fatigue, headache	Modification	Cycle 1
CH-A2-112	07Oct2020	0	Nausea, sickness, fatigue, headache	Modification	Cycle 1
CH-A2-112	19Oct2020	0	Low neutrophils	Modification	Cycle 1
CH-A2-112	20Oct2020	0	Low neutrophils	Modification	Cycle 1
CH-A2-112	20Oct2020	0	Low neutrophils	Modification	Cycle 1
CH-A2-112	21Oct2020	0	Low neutrophils	Modification	Cycle 1
CH-A2-112	21Oct2020	0	Low neutrophils	Modification	Cycle 1
CH-A2-114	09Feb2021	0	Low platelets	Modification	Cycle 1
CH-A2-114	10Feb2021	0	Low platelets	Modification	Cycle 1
CH-A2-114	10Feb2021	0	Low platelets	Modification	Cycle 1
CH-A2-114	11Feb2021	0	Low platelets	Modification	Cycle 1
CH-A2-114	11Feb2021	0	Low platelets	Modification	Cycle 1
CH-A2-114	12Feb2021	0	Low platelets	Modification	Cycle 1
CH-A2-114	12Feb2021	0	Low platelets	Modification	Cycle 1
CH-A2-114	13Feb2021	0	Low platelets	Modification	Cycle 1
CH-A2-114	13Feb2021	0	Low platelets	Modification	Cycle 1
CH-A2-114	14Feb2021	0	Low platelets	Modification	Cycle 1
CH-A2-114	14Feb2021	0	Low platelets	Modification	Cycle 1
CH-A2-115	13Apr2021	0	Forgot to take eve dose	Modification	Cycle 1
CH-A2-115	30Apr2021	0	Forgot to take eve dose	Modification	Cycle 1
CH-A2-117	07Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	08Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	08Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	09Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	09Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	10Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	10Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1

Subject	Date	Amount Given	Reason	Type	Cycle
CH-A2-117	11Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	11Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	12Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	12Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	13Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	13Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	14Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	14Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	15Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	15Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	16Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	16Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	17Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	17Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	18Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	18Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	19Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	19Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	20Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-117	20Jun2021	300	Patient took incorrect dose in error	Modification	Cycle 1
CH-A2-119	10Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	11Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	11Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	12Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	12Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	13Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	13Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	14Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	14Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	15Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	15Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	16Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	16Aug2021	0	Chest pain	Modification	Cycle 1
CH-A2-119	17Aug2021	0	Chest pain	Modification	Cycle 1

Subject	Date	Amount Given	Reason	Type	Cycle
CH-A2-106	02Aug2019	0	Investigator decision. Neutrophils low (0.9 x 10^9/L)	Modification	Cycle 1
CH-A2-106	03Aug2019	0	Investigator decision. Neutrophils low (0.9 x 10^9/L)	Modification	Cycle 1
CH-A2-106	03Aug2019	0	Investigator decision. Neutrophils low (0.9 x 10^9/L)	Modification	Cycle 1
CH-A2-106	04Aug2019	0	Investigator decision. Neutrophils low (0.9 x 10^9/L)	Modification	Cycle 1
CH-A2-106	04Aug2019	0	Investigator decision. Neutrophils low (0.9 x 10^9/L)	Modification	Cycle 1
CH-A2-107	27Aug2019	0	Investigator's advice. The patient had suffered a DLT	Modification	Cycle 1
CH-A2-109	24Dec2019	0	Due to G3 thrombocytopenia and neutropenia	Modification	Cycle 2
CH-A2-109	25Dec2019	0	Due to G3 thrombocytopenia and neutropenia	Modification	Cycle 2
CH-A2-109	25Dec2019	0	Due to G3 thrombocytopenia and neutropenia	Modification	Cycle 2
CH-A2-109	26Dec2019	0	Due to G3 thrombocytopenia and neutropenia	Modification	Cycle 2
CH-A2-109	26Dec2019	0	Due to G3 thrombocytopenia and neutropenia	Modification	Cycle 2
CH-A2-109	27Dec2019	0	Due to G3 thrombocytopenia and neutropenia	Modification	Cycle 2
CH-A2-109	27Dec2019	0	Due to G3 thrombocytopenia and neutropenia	Modification	Cycle 2
CH-A2-109	28Dec2019	0	Due to G3 thrombocytopenia and neutropenia	Modification	Cycle 2
CH-A2-109	28Dec2019	0	Due to G3 thrombocytopenia and neutropenia	Modification	Cycle 2
CH-A2-109	29Dec2019	0	Due to G3 thrombocytopenia and neutropenia	Modification	Cycle 2
CH-A2-109	29Dec2019	0	Due to G3 thrombocytopenia and neutropenia	Modification	Cycle 2
CH-A2-118	10Aug2021	0	treatment deferred for a week	Modification	Cycle 2
CH-A2-118	11Aug2021	0	treatment deferred for a week	Modification	Cycle 2
CH-A2-118	11Aug2021	0	treatment deferred for a week	Modification	Cycle 2
CH-A2-118	12Aug2021	0	treatment deferred for a week	Modification	Cycle 2
CH-A2-118	12Aug2021	0	treatment deferred for a week	Modification	Cycle 2
CH-A2-118	13Aug2021	0	treatment deferred for a week	Modification	Cycle 2
CH-A2-118	13Aug2021	0	treatment deferred for a week	Modification	Cycle 2
CH-A2-118	14Aug2021	0	treatment deferred for a week	Modification	Cycle 2
CH-A2-118	14Aug2021	0	treatment deferred for a week	Modification	Cycle 2
CH-A2-118	15Aug2021	0	treatment deferred for a week	Modification	Cycle 2
CH-A2-118	15Aug2021	0	treatment deferred for a week	Modification	Cycle 2
CH-A2-108	21Oct2019	468	Neutropenia	Reduction	Cycle 2
CH-A2-109	02Jan2020	313	Due to G3 thrombocytopenia and neutropenia	Reduction	Cycle 2
CH-A2-112	02Nov2020	313	Low neutrophils	Reduction	Cycle 2

Subject	Date	Amount Given	Reason	Type	Cycle
CH-A2-114	22Feb2021	313	Neutropenia	Reduction	Cycle 2
CH-A2-119	31Aug2021	469	G3 Neutropenia	Reduction	Cycle 2
CH-A2-106	12Aug2019	469	Additional Prescribing Notes: restart capecitabine and cisplatin with 25% dose reduction both drugs after recovery of neutrophils being 0.5- <1.0.	Reduction	Cycle 2
CH-A2-118	17Aug2021	0	PI delayed treatment	Modification	Cycle 3
CH-A2-118	18Aug2021	0	PI delayed treatment	Modification	Cycle 3
CH-A2-118	18Aug2021	0	PI delayed treatment	Modification	Cycle 3
CH-A2-118	19Aug2021	0	PI delayed treatment	Modification	Cycle 3
CH-A2-118	19Aug2021	0	PI delayed treatment	Modification	Cycle 3
CH-A2-118	20Aug2021	0	PI delayed treatment	Modification	Cycle 3
CH-A2-118	16Aug2021	468	ae	Reduction	Cycle 3
CH-A2-108	20Dec2019	0	Drug suspended due to low blood count	Modification	Cycle 4
CH-A2-108	21Dec2019	0	Drug suspended due to low blood count	Modification	Cycle 4
CH-A2-108	21Dec2019	0	Drug suspended due to low blood count	Modification	Cycle 4
CH-A2-108	22Dec2019	0	Drug suspended due to low blood count	Modification	Cycle 4
CH-A2-108	22Dec2019	0	Drug suspended due to low blood count	Modification	Cycle 4
CH-A2-119	20Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	20Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	21Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	21Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	22Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	22Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	23Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	23Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	24Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	24Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	25Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	25Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4

Subject	Date	Amount Given	Reason	Type	Cycle
CH-A2-119	26Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	26Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-119	27Oct2021	0	Treatment delayed for 1 week due to several low grade toxicities	Modification	Cycle 4
CH-A2-120	19Oct2021	0	Not documented as being taken on patient diary	Modification	Cycle 4
CH-A2-120	26Oct2021	0	Not documented as being taken on patient diary	Modification	Cycle 4
CH-A2-120	27Oct2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	27Oct2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	28Oct2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	28Oct2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	29Oct2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	29Oct2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	30Oct2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	30Oct2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	31Oct2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	31Oct2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	01Nov2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	01Nov2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	02Nov2021	0	On hold due to decreased platelet count	Modification	Cycle 4
CH-A2-120	02Nov2021	469	Grade 2 decreased platelet count	Reduction	Cycle 4
CH-A2-105	29Aug2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	29Aug2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	30Aug2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	30Aug2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	31Aug2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	31Aug2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	01Sep2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	01Sep2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	02Sep2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	02Sep2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	03Sep2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	03Sep2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	04Sep2019	0	1 week break due to high bilirubin	Modification	Cycle 5

Subject	Date	Amount Given	Reason	Type	Cycle
CH-A2-105	04Sep2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	05Sep2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-105	05Sep2019	0	1 week break due to high bilirubin	Modification	Cycle 5
CH-A2-119	24Nov2021	0	G3 Neutropenia	Modification	Cycle 5
CH-A2-119	25Nov2021	0	G3 Neutropenia	Modification	Cycle 5
CH-A2-119	25Nov2021	0	G3 Neutropenia	Modification	Cycle 5
CH-A2-119	26Nov2021	0	G3 Neutropenia	Modification	Cycle 5
CH-A2-119	26Nov2021	0	G3 Neutropenia	Modification	Cycle 5
CH-A2-119	27Nov2021	0	G3 Neutropenia	Modification	Cycle 5
CH-A2-119	27Nov2021	0	G3 Neutropenia	Modification	Cycle 5
CH-A2-119	28Nov2021	0	G3 Neutropenia	Modification	Cycle 5
CH-A2-119	28Nov2021	0	G3 Neutropenia	Modification	Cycle 5
CH-A2-119	29Nov2021	0	G3 Neutropenia	Modification	Cycle 5
CH-A2-119	29Nov2021	0	G3 Neutropenia	Modification	Cycle 5
CH-A2-120	23Nov2021	0	Forgot to take	Modification	Cycle 5
CH-A2-108	02Jan2020	312	Neutropenia	Reduction	Cycle 5
CH-A2-119	09Nov2021	312	Neutropenia	Reduction	Cycle 5
CH-A2-108	29Jan2020	0	Very unwell	Modification	Cycle 6
CH-A2-108	29Jan2020	0	Very unwell	Modification	Cycle 6
CH-A2-108	31Jan2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	01Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	01Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	02Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	02Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	03Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	03Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	04Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	04Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	05Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6

Subject	Date	Amount Given	Reason	Type	Cycle
CH-A2-108	05Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	06Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	06Feb2020	0	Respiratory tract infection - Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	07Feb2020	0	Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	07Feb2020	0	Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	08Feb2020	0	Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	08Feb2020	0	Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	09Feb2020	0	Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	09Feb2020	0	Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	10Feb2020	0	Tx held off for 1 week	Modification	Cycle 6
CH-A2-108	11Feb2020	0	Unwell	Modification	Cycle 6
CH-A2-108	11Feb2020	0	Unwell	Modification	Cycle 6
CH-A2-108	12Feb2020	0	Unwell	Modification	Cycle 6
CH-A2-108	12Feb2020	0	Unwell	Modification	Cycle 6
CH-A2-109	30Mar2020	0	Returned tablets on C6 D19 visit	Modification	Cycle 6
CH-A2-109	31Mar2020	0	Returned tablets on C6 D19 visit	Modification	Cycle 6
CH-A2-109	31Mar2020	0	Returned tablets on C6 D19 visit	Modification	Cycle 6
CH-A2-109	01Apr2020	0	Returned tablets on C6 D19 visit	Modification	Cycle 6
CH-A2-109	01Apr2020	0	Returned tablets on C6 D19 visit	Modification	Cycle 6

Table 40: Cisplatin reductions and modifications listing

Subject	Date	Cycle	Reason
CH-A2-105	08Aug2019	Cycle 4	Received blood transfusion for low haemoglobin
CH-A2-108	02Jan2020	Cycle 5	Neutropenia
CH-A2-109	20Feb2020	Cycle 5	Left breast cellulitis erythema
CH-A2-112	02Nov2020	Cycle 2	Neutropenia
CH-A2-112	30Nov2020	Cycle 3	G3 neutropenia
CH-A2-112	18Jan2021	Cycle 5	G3 neutropenia
CH-A2-114	22Feb2021	Cycle 2	neutropenia
CH-A2-115	04May2021	Cycle 2	bank holiday
CH-A2-115	26May2021	Cycle 3	Delayed due to bank holuday scheduling
CH-A2-119	31Aug2021	Cycle 2	Neutropenia

Subject	Date	Cycle	Reason
CH-A2-119	09Nov2021	Cycle 5	Neutropenia
CH-A2-106	12Aug2019	Cycle 2	Patient had low neutrophils (0.9 x 10^9/L); waiting for recovery

Table 41: Missed M6620 treatment reasons

Subject	Week & Day	Cycle	Reason Treatment Missed
CH-A2-101	week3 day2	Cycle 1	Thrombocytopenia
CH-A2-108	week2 day2	Cycle 1	G2 fatigue, dysguesia, anorexia
CH-A2-108	week3 day5	Cycle 1	G3 neutropenia
CH-A2-112	week1 day5	Cycle 1	Attended local hospital for hydration (discharged same day)
CH-A2-112	week3 day5	Cycle 1	Neutrophil count =0.27, hold off drug
CH-A2-114	week3 day2	Cycle 1	Thrombocytopenia
CH-A2-115	week1 day2	Cycle 1	Grade 3 hypertension
CH-A2-116	week2 day2	Cycle 1	Toxicity to treatment
CH-A2-116	week3 day2	Cycle 1	Toxicity to treatment
CH-A2-119	week2 day2	Cycle 1	Chest pain
CH-A2-106	week3 day5	Cycle 1	Low neutrophils (0.9 x 10^9/L)
CH-A2-107	week1 day5	Cycle 1	Not scheduled
CH-A2-107	week2 day5	Cycle 1	Not scheduled
CH-A2-107	week3 day2	Cycle 1	Patent unwell and admitted to hospital with pyrexia prior to the appointment date
CH-A2-107	week3 day5	Cycle 1	Not scheduled
CH-A2-102	week5 day2	Cycle 2	Not given - bank holiday
CH-A2-109	week6 day2	Cycle 2	Thrombocytopenia
CH-A2-109	week6 day5	Cycle 2	Thrombocytopenia
CH-A2-114	week4 day2	Cycle 2	G3 hypertension
CH-A2-118	week6 day2	Cycle 2	Treatment delay due to AE
CH-A2-112	week9 day5	Cycle 3	G3 neutropenia
CH-A2-115	week8 day2	Cycle 3	off trial
CH-A2-115	week9 day2	Cycle 3	off trial
CH-A2-117	week8 day2	Cycle 3	Withdrawn
CH-A2-117	week9 day2	Cycle 3	Withdrawn

Subject	Week & Day	Cycle	Reason Treatment Missed
CH-A2-118	week7 day2	Cycle 3	due to AST and ALT elevated
CH-A2-108	week12 day5	Cycle 4	Neutropenia
CH-A2-112	week10 day5	Cycle 4	Visit not done
CH-A2-112	week11 day5	Cycle 4	Visit not done
CH-A2-119	week11 day2	Cycle 4	G2 Hand foot syndrome, G2 fatigue, G2 anaemia
CH-A2-105	week13 day2	Cycle 5	High bilirubin
CH-A2-108	week15 day5	Cycle 5	URTI
CH-A2-112	week15 day2	Cycle 5	G3 neutropenia
CH-A2-108	week17 day2	Cycle 6	URTI
CH-A2-108	week17 day5	Cycle 6	URTI
CH-A2-108	week18 day2	Cycle 6	URTI
CH-A2-118	week17 day2	Cycle 6	patient did not attend

7.4 Appendix - Survival

Table 42: Progression free survival times by patient

Subject	Dose	Progression Free Survival (Days)	Censored
CH-A2-101	Schedule 1	325	No
CH-A2-102	Schedule 1	35	No
CH-A2-103	Schedule 1	28	No
CH-A2-105	Schedule 1	362	Yes
CH-A2-106	Schedule 2	185	No
CH-A2-107	Schedule 3	427	No
CH-A2-108	Schedule 4	275	No
CH-A2-109	Schedule 4	232	No
CH-A2-110	Schedule 4	38	No
CH-A2-112	Schedule 4	361	Yes
CH-A2-113	Schedule 3	364	Yes
CH-A2-114	Schedule 3	43	No
CH-A2-115	Schedule 3	44	No
CH-A2-116	Schedule 3	325	Yes

Subject	Dose	Progression Free Survival (Days)	Censored
CH-A2-117	Schedule 3	42	No
CH-A2-118	Schedule 3	177	No
CH-A2-119	Schedule 3	190	Yes
CH-A2-120	Schedule 3	211	Yes

Table 43: Overall survival times by patient

Subject	Dose	Overall Survival (Days)	Censored
CH-A2-101	Schedule 1	325	No
CH-A2-102	Schedule 1	128	No
CH-A2-103	Schedule 1	84	No
CH-A2-105	Schedule 1	362	Yes
CH-A2-106	Schedule 2	434	No
CH-A2-107	Schedule 3	427	No
CH-A2-108	Schedule 4	275	No
CH-A2-109	Schedule 4	365	Yes
CH-A2-110	Schedule 4	374	Yes
CH-A2-112	Schedule 4	361	Yes
CH-A2-113	Schedule 3	364	Yes
CH-A2-114	Schedule 3	227	No
CH-A2-115	Schedule 3	218	No
CH-A2-116	Schedule 3	325	Yes
CH-A2-117	Schedule 3	249	No
CH-A2-118	Schedule 3	258	No
CH-A2-119	Schedule 3	190	Yes
CH-A2-120	Schedule 3	211	Yes

7.5 Appendix - Scans

Table 44: Non-12-week restaging scans

Subject	Time Point	Assessment Done	Reason if Not	Sum of Longest Diameters (mm)	Target Response	Non-Target Response	New Lesions	Overall RECIST
CH-A2-101	8 weeks post EOT	Yes		102	Progressive Disease	No Non-Target Lesions	No	Progressive Disease
CH-A2-102	6 weeks	Yes		187	Progressive Disease	No Non-Target Lesions	No	Progressive Disease
CH-A2-102	8 weeks post EOT	No	Returned to team at Local Hospital. FU was not done					
CH-A2-103	8 weeks post EOT	No	Cancelled due to COVID Pandemic					
CH-A2-104	Other	No	Not Required					
CH-A2-105	6 weeks	Yes		12	Partial Response	No Non-Target Lesions	No	Partial Response
CH-A2-105	18 weeks	Yes		5	Partial Response	No Non-Target Lesions	No	Partial Response
CH-A2-105	8 weeks post EOT	Yes		0	Complete Response	No Non-Target Lesions	No	Complete Response
CH-A2-106	6 weeks	Yes		44	Partial Response	Non-CR/ Non-PD	No	Partial Response
CH-A2-106	18 weeks	Yes		37	Partial Response	Non-CR/ Non-PD	No	Partial Response
CH-A2-106	8 weeks post EOT	Yes		55	Progressive Disease	Non-CR/ Non-PD	Yes	Progressive Disease
CH-A2-107	6 weeks	Yes		77	Stable Disease	Non-CR/ Non-PD	No	Stable Disease
CH-A2-107	18 weeks	No	Patient No Longer Receiving Treatment					
CH-A2-107	Other	No	This Was An Adhoc Assessment					

Subject	Time Point	Assessment Done	Reason if Not	Sum of Longest Diameters (mm)	Target Response	Non-Target Response	New Lesions	Overall RECIST
			- End Of Trial.					
CH-A2-107	8 weeks post EOT	Yes		77	Stable Disease	Non-CR/ Non-PD	No	Stable Disease
CH-A2-108	6 weeks	Yes		20	Partial Response	Non-CR/ Non-PD	No	Partial Response
CH-A2-108	18 weeks	Yes		20	Stable Disease	Progressive Disease	Yes	Progressive Disease
CH-A2-108	8 weeks post EOT	No	Not done due to high risk of COVID-19					
CH-A2-109	6 weeks	Yes		20	Stable Disease	No Non-Target Lesions	No	Stable Disease
CH-A2-109	18 weeks	Yes		25	Progressive Disease	No Non-Target Lesions	No	Progressive Disease
CH-A2-109	Other	Yes			Not Evaluable		No	Not Evaluable
CH-A2-109	During FU	No	Not done due to COVID					
CH-A2-110	6 weeks	Yes		113	Progressive Disease	Progressive Disease	Yes	Progressive Disease
CH-A2-110	8 weeks post EOT	No	CT omitted due to COVID-19 Pandemic					
CH-A2-112	6 weeks	Yes			No Target Lesions	Non-CR/ Non-PD	No	Stable Disease
CH-A2-112	18 weeks	Yes			No Target Lesions	Non-CR/ Non-PD	No	Stable Disease
CH-A2-112	8 weeks post EOT	Yes			No Target Lesions	Non-CR/ Non-PD	No	Stable Disease
CH-A2-113	6 weeks	Yes		50	Stable Disease	Non-CR/ Non-PD	No	Stable Disease
CH-A2-113	18 weeks	Yes		39	Partial Response	Non-CR/ Non-PD	No	Partial Response
CH-A2-113	8 weeks post EOT	Yes		49	Progressive Disease	Non-CR/ Non-PD	No	Progressive Disease

Subject	Time Point	Assessment Done	Reason if Not	Sum of Longest Diameters (mm)	Target Response	Non-Target Response	New Lesions	Overall RECIST
CH-A2-114	6 weeks	Yes		86	Stable Disease	No Non-Target Lesions	Yes	Progressive Disease
CH-A2-115	6 weeks	Yes			Progressive Disease	Non-CR/ Non-PD	No	Progressive Disease
CH-A2-115	8 weeks post EOT	No	Missed In Error					
CH-A2-117	6 weeks	Yes		133	Progressive Disease	Progressive Disease	No	Progressive Disease
CH-A2-117	8 weeks post EOT	No	Missed In Error					
CH-A2-118	6 weeks	Yes		78	Stable Disease	No Non-Target Lesions	No	Stable Disease
CH-A2-118	18 weeks	Yes		86	Progressive Disease	No Non-Target Lesions	No	Progressive Disease
CH-A2-118	Other	No						
CH-A2-118	8 weeks post EOT	Yes		91	Progressive Disease	No Non-Target Lesions	No	Progressive Disease
CH-A2-119	6 weeks	Yes			No Target Lesions	Non-CR/ Non-PD	No	Stable Disease
CH-A2-119	18 weeks	Yes			No Target Lesions	Non-CR/ Non-PD	No	Stable Disease
CH-A2-119	8 weeks post EOT	Yes			No Target Lesions	Non-CR/ Non-PD	No	Stable Disease
CH-A2-120	6 weeks	Yes		68	Stable Disease	Non-CR/ Non-PD	No	Stable Disease
CH-A2-120	18 weeks	No	Not done in error					
CH-A2-120	8 weeks post EOT	Yes		78	Progressive Disease	Progressive Disease	No	Progressive Disease

Table 45: Target lesion restaging scans

Subject	Date	Site	Location	Diameter (mm)	Assessment Method
CH-A2-101	09 Apr 2019	Lung	Left Lower Lobe	27	CT-scan

Subject	Date	Site	Location	Diameter (mm)	Assessment Method
CH-A2-101	09 Apr 2019	Lung	Right Lower Lobe	19	CT-scan
CH-A2-101	09 Apr 2019	Mediastinum	Subcarinal	24	CT-scan
CH-A2-101	09 Apr 2019	Abdominal Cavity	Retroperitoneal	32	CT-scan
CH-A2-102	12 Apr 2019	Lung	Left Upper Lobe	72	CT-scan
CH-A2-102	12 Apr 2019	Lung	Right Upper Lobe	115	CT-scan
CH-A2-105	10 Jul 2019	Lung	Left Lower Lobe	7	CT-scan
CH-A2-105	10 Jul 2019	Lung	Left Upper Lobe	5	CT-scan
CH-A2-105	23 Aug 2019	Lung	Left Lower Lobe	5	CT-scan
CH-A2-105	23 Aug 2019	Lung	Left Upper Lobe	0	CT-scan
CH-A2-105	11 Oct 2019	Lung	Left Lower Lobe	5	CT-scan
CH-A2-105	11 Oct 2019	Lung	Left Upper Lobe	0	CT-scan
CH-A2-105	04 Dec 2019	Lung	Left Lower Lobe	0	CT-scan
CH-A2-105	04 Dec 2019	Lung	Left Upper Lobe	0	CT-scan
CH-A2-106	29 Aug 2019	Lung	Right Upper Lobe	26	CT-scan
CH-A2-106	29 Aug 2019	Lung	Right Middle Lobe	18	CT-scan
CH-A2-106	08 Oct 2019	Lung	Right Upper Lobe Pulmonary Metastasis	22	CT-scan
CH-A2-106	08 Oct 2019	Lung	Right Middle Lobe Metastasis	16	CT-scan
CH-A2-106	19 Nov 2019	Lung	Right Lung Upper Lobe	23	CT-scan
CH-A2-106	19 Nov 2019	Lung	Right Lung Middle Lobe	14	CT-scan
CH-A2-106	17 Jan 2020	Lung	Right Lung Upper Lobe	34	CT-scan
CH-A2-106	17 Jan 2020	Lung	Right Lung Middle Lobe	21	CT-scan
CH-A2-107	23 Sep 2019	Liver	Right Lobe	36	CT-scan
CH-A2-107	23 Sep 2019	Pancreas	Pancreas	41	CT-scan
CH-A2-107	04 Nov 2019	Liver	Right Lobe	44	CT-scan
CH-A2-107	04 Nov 2019	Pancreas	Pancreas	52	CT-scan
CH-A2-107	23 Sep 2019	Liver	Right Lobe	36	CT-scan
CH-A2-107	23 Sep 2019	Pancreas	Pancreas	41	CT-scan
CH-A2-108	07 Nov 2019	Right Kidney	Nodule Posterior and Slightly Cranial to the Upper Pole	20	CT-scan

Subject	Date	Site	Location	Diameter (mm)	Assessment Method
CH-A2-108	20 Dec 2019	Right Kidney	Nodule Posterior and Slightly Cranial to the Upper Pole	14	CT-scan
CH-A2-108	11 Feb 2020	Right Kidney	Nodule Posterior and Slightly Cranial to the Upper Pole	20	CT-scan
CH-A2-109	27 Dec 2019	Lung	Right Upper Lobe	13	CT-scan
CH-A2-109	27 Dec 2019	Lung	Left Lower Lobe	7	CT-scan
CH-A2-109	10 Feb 2020	Lung	Right Upper Lobe	13	CT-scan
CH-A2-109	10 Feb 2020	Lung	Left Lower Lobe	6	CT-scan
CH-A2-109	30 Mar 2020	Lung	Right Upper Lobe	14	CT-scan
CH-A2-109	30 Mar 2020	Lung	Left Lower Lobe	11	CT-scan
CH-A2-109		Lung	Right Upper Lobe		
CH-A2-109		Lung	Left Lower Lobe		
CH-A2-110	13 Mar 2020	Sternum	Left Prevascular Node	26	CT-scan
CH-A2-110	13 Mar 2020	Lung	Left Hilar Node Posterior to the Left Main Bronchus	35	CT-scan
CH-A2-110	13 Mar 2020	Lung	Lingular Metastasis	34	CT-scan
CH-A2-110	13 Mar 2020	Lung	Left Lower Lobe	18	CT-scan
CH-A2-113	29 Dec 2020	Lung	Left Lower Lobe	17	CT-scan
CH-A2-113	29 Dec 2020	Lung	Right Lower Lobe	18	CT-scan
CH-A2-113	29 Dec 2020	Subcarinal Lymph Node	Subcarinal Lymph Node	15	CT-scan
CH-A2-113	23 Mar 2021	Lung	Left Lower Lobe	17	CT-scan
CH-A2-113	23 Mar 2021	Lung	Right Lower Lobe	14	CT-scan
CH-A2-113	23 Mar 2021	Subcarinal Lymph Node	Subcarinal Lymph Node	8	CT-scan
CH-A2-113	19 May 2021	Lung	Left Lower Lobe	18	CT-scan
CH-A2-113	19 May 2021	Lung	Right Lower Lobe	13	CT-scan
CH-A2-113	19 May 2021	Subcarinal Lymph Node	Subcarinal Lymph Node	18	CT-scan
CH-A2-114	10 Mar 2021	Pancreas	Infiltrating Primary Pancreatic Tumour	86	CT-scan
CH-A2-115	27 May 2021	Liver	Peripherally Within Segment VII/VIII	35	Clinical examination
CH-A2-117	20 Jul 2021	Lung	Right Lower Lobe	38	CT-scan

Subject	Date	Site	Location	Diameter (mm)	Assessment Method
CH-A2-117	20 Jul 2021	Liver	Segment VIII	52	CT-scan
CH-A2-117	20 Jul 2021	Liver	Segment V	43	CT-scan
CH-A2-118	09 Aug 2021	Lung	Right Upper Lobe	29	CT-scan
CH-A2-118	09 Aug 2021	Lung	Left Upper Lobe	25	CT-scan
CH-A2-118	09 Aug 2021	Kidney	Left	24	CT-scan
CH-A2-118	01 Nov 2021	Lung	Right Upper Lobe	27	CT-scan
CH-A2-118	01 Nov 2021	Lung	Left Upper Lobe	28	CT-scan
CH-A2-118	01 Nov 2021	Kidney	Left Kidney Upper Pole	31	CT-scan
CH-A2-118	30 Dec 2021	Lung	Right Upper Lobe	27	CT-scan
CH-A2-118	30 Dec 2021	Lung	Left Upper Lobe	31	CT-scan
CH-A2-118	30 Dec 2021	Kidney	Left Kidney Upper Pole	33	Clinical examination
CH-A2-120	28 Sep 2021	Lung	Right Lower Lobe Nodule	37	CT-scan
CH-A2-120	28 Sep 2021	Lung	Left Upper Lobe Nodule	31	CT-scan
CH-A2-120	09 Nov 2021	Lung	Right Lower Lobe Nodule	38	CT-scan
CH-A2-120	09 Nov 2021	Lung	Left Upper Lobe Nodule	31	CT-scan
CH-A2-120	08 Feb 2022	Lung	Right Lower Lobe Nodule	43	CT-scan
CH-A2-120	08 Feb 2022	Lung	Left Upper Lobe Nodule	35	CT-scan

Table 46: Non-Target lesion restaging scans

Subject	Date	Site	Assessment Method	Number of lesions	Assessment
CH-A2-106	29 Aug 2019	Peritoneal Deposit	CT-scan	Single lesion	Present
CH-A2-106	08 Oct 2019	Peritoneal Metastasis	CT-scan	Single lesion	Present
CH-A2-106	19 Nov 2019	Peritoneal Metastasis	CT-scan	Single lesion	Present
CH-A2-106	17 Jan 2020	Peritoneal Metastasis	CT-scan	Single lesion	Present
CH-A2-107	23 Sep 2019	Pulmonary Metastases	CT-scan	Multiple lesions	Present
CH-A2-107	23 Sep 2019	Liver Metastases	CT-scan	Multiple lesions	Present
CH-A2-107	04 Nov 2019	Pulmonary Metastases	CT-scan	Multiple lesions	Present
CH-A2-107	04 Nov 2019	Liver Metastases	CT-scan	Multiple lesions	Present
CH-A2-107	23 Sep 2019	Pulmonary Metastases	CT-scan	Multiple lesions	Present
CH-A2-107	23 Sep 2019	Liver Metastases	CT-scan	Multiple lesions	Present

Subject	Date	Site	Assessment Method	Number of lesions	Assessment
CH-A2-108	07 Nov 2019	Extensive Tumour Throughout Right Kidney	CT-scan	Single lesion	Present
CH-A2-108	07 Nov 2019	Extensive Retroperitoneal Lymphadenopathy	CT-scan	Single lesion	Present
CH-A2-108	20 Dec 2019	Extensive Tumour Throughout Right Kidney	CT-scan	Single lesion	Present
CH-A2-108	20 Dec 2019	Extensive Retroperitoneal Lymphadenopathy	CT-scan	Single lesion	Present
CH-A2-108	11 Feb 2020	Extensive Tumour Throughout Right Kidney	CT-scan	Single lesion	Present
CH-A2-108	11 Feb 2020	Extensive Retroperitoneal Lymphadenopathy	CT-scan	Single lesion	Present
CH-A2-109	08 Jul 2020	Left Breast Skin Has Thickened	CT-scan	Single lesion	Present
CH-A2-109	08 Jul 2020	Left Apical Mass	CT-scan	Single lesion	Present
CH-A2-110	13 Mar 2020	Left Paratracheal Node	CT-scan	Single lesion	Present
CH-A2-112	20 Nov 2020	Sclerotic Bone Lesions	CT-scan	Multiple lesions	Present
CH-A2-112	20 Nov 2020	Subcutaneous Lesion Anterior to the Left Shoulder	CT-scan	Single lesion	Present
CH-A2-112	15 Jan 2021	Multiple Sclerotic Bone Metastases	CT-scan	Multiple lesions	Present
CH-A2-112	15 Jan 2021	Subcutaneous Lesion Anterior to the Left Shoulder	CT-scan	Single lesion	Present
CH-A2-112	26 Feb 2021	Multiple Sclerotic Bone Metastases	CT-scan	Multiple lesions	Present
CH-A2-112	26 Feb 2021	Subcutaneous Lesion Anterior to the Left Shoulder	CT-scan	Single lesion	Present
CH-A2-112	23 Apr 2021	Multiple Sclerotic Bone Metastases	CT-scan	Multiple lesions	Present
CH-A2-112	23 Apr 2021	Subcutaneous Lesion Anterior to the Left Shoulder	CT-scan	Single lesion	Present
CH-A2-113	29 Dec 2020	Right Hilar Lymphadenopathy	CT-scan	Single lesion	Present
CH-A2-113	29 Dec 2020	Two Subcutaneous Nodules Over Left Lateral Chest Wall	CT-scan	Multiple lesions	Present

Subject	Date	Site	Assessment Method	Number of lesions	Assessment
CH-A2-113	23 Mar 2021	Right Hilar Lymphadenopathy	CT-scan	Single lesion	Present
CH-A2-113	23 Mar 2021	Two Subcutaneous Nodules Over Left Lateral Chest Wall	CT-scan	Multiple lesions	Present
CH-A2-113	19 May 2021	Right Hilar Lymphadenopathy	CT-scan	Single lesion	Present
CH-A2-113	19 May 2021	Two Subcutaneous Nodules Over Left Lateral Chest Wall	CT-scan	Multiple lesions	Present
CH-A2-115	27 May 2021	Multiple Poorly Defined Low Attenuation Hepatic Metastases Within Both Lobes	CT-scan	Multiple lesions	Present
CH-A2-117	20 Jul 2021	Lung Mets	CT-scan	Multiple lesions	Present
CH-A2-117	20 Jul 2021	Primary Rectal Tumour	CT-scan	Single lesion	Present
CH-A2-117	20 Jul 2021	Liver Mets	CT-scan	Multiple lesions	Present
CH-A2-119	22 Sep 2021	Thickening of the Wall of the Distal Oesophagus Extending into the Stomach	CT-scan	Single lesion	Present
CH-A2-119	02 Nov 2021	Thickening of the Wall of the Distal Oesophagus Extending into the Stomach	CT-scan	Single lesion	Present
CH-A2-119	29 Dec 2021	Thickening of the Wall of the Distal Oesophagus Extending into the Stomach	CT-scan	Single lesion	Present
CH-A2-119	01 Feb 2022	Thickening of the Wall of the Distal Oesophagus Extending into the Stomach	CT-scan	Single lesion	Present
CH-A2-120	28 Sep 2021	Cutaneous Nodules Over the Right Chest Wall and Breast	CT-scan	Multiple lesions	Present
CH-A2-120	28 Sep 2021	Multifocal Hepatic Metastases	CT-scan	Multiple lesions	Present
CH-A2-120	09 Nov 2021	Cutaneous Nodules Over the Right Chest Wall and Breast	CT-scan	Multiple lesions	Present
CH-A2-120	09 Nov 2021	Multifocal Hepatic Metastases	CT-scan	Multiple lesions	Present

Subject	Date	Site	Assessment Method	Number of lesions	Assessment
CH-A2-120	08 Feb 2022	Cutaneous Nodules Over the Right Chest Wall and Breast	CT-scan	Multiple lesions	Present

7.6 Appendix - Concomitant Medication & Post-Trial Treatments

Table 47: Concomitant Medication

Subject	Medication	Dose	Frequency	Indication	Date
CH-A2-101	Mebeverine	135 mg	Three Times Daily	Abdominal Cramping	01 Dec 2018
CH-A2-101	Amlodipine	10 mg	Once Daily	Hypertension	01 Jan 2004
CH-A2-101	Tamsulosin	400 mcg	Once Daily	Enlarged Prostate	01 Jun 2018
CH-A2-101	Tinzaparin	18000 units	Once Daily	DVT	01 Oct 2016
CH-A2-101	Ibuprofen	400mg	One Dose	Abdominal Cramping	02 Jan 2019
CH-A2-102	Phenoxymethylpenicillin	250mg	Twice Daily	Splenectomy	01 Dec 2015
CH-A2-102	Creon	250000 units	Three Times Daily	Pancreatectomy	01 Dec 2015
CH-A2-102	Paracetamol	1g	When Required	Fever	01 Jan 2017
CH-A2-102	Cough Elixir	10 mls	Three Times Daily	Chest Infection	01 Nov 2018
CH-A2-102	Amoxicillin	500mg	Three Times Daily	Lower Respiratory Tract Infection	28 Feb 2019
CH-A2-102	Tinzaparin	14000 iu	Once Daily	Left Atrial Thrombus	22 Feb 2019
CH-A2-102	Amoxicillin	500mg	Three Times Daily	Lower Respiratory Tract Infection	25 Feb 2019
CH-A2-102	Co-Amoxiclav	625mg	Three Times Daily	Lower Respiratory Tract Infection	25 Feb 2019
CH-A2-102	Co-Amoxiclav	625mg	Three Times Daily	Lower Respiratory Tract Infection	12 Apr 2019
CH-A2-102	Phosphate Sandoz	2 tablets	Twice Daily	Hypophosphatemia	12 Apr 2019
CH-A2-102	Dexamethasone	2mg	Once Daily	Fatigue	17 Apr 2019
CH-A2-102	Dalteparin	12,500	Once Daily	Left Atrial Thrombus	22 Mar 2019
CH-A2-102	Co-Amoxiclav	625 mg	Three Times Daily	Lower Respiratory Tract Infection	30 Apr 2019
CH-A2-103	Oramorph	2.5mls	Twice Daily	Perineal Pain	14 Apr 2019
CH-A2-103	Co Codamol	2 tablets	Four Times Daily	Perineal Pain	28 Mar 2019
CH-A2-103	Morphine Sulphate	20mg	Twice Daily	Perineal Pain	17 Apr 2019
CH-A2-103	Paracetamol	1g	Four Times Daily	Perineal Pain	17 Apr 2019
CH-A2-103	Co-Amoxiclav	65mg	Three Times Daily	UTI	24 Apr 2019

Subject	Medication	Dose	Frequency	Indication	Date
CH-A2-103	Tazocin	4.5	Three Times Daily	UTI	30 Apr 2019
CH-A2-103	Nystatin	100000 units/ml	Twice Daily	Oral Thrush	01 May 2019
CH-A2-103	Gabapentin	300mg	Twice Daily	Perineal Pain	04 May 2019
CH-A2-103	Liquid Oxycodone	7.5 mg	When Required	Perineal Pain	17 May 2019
CH-A2-103	Oxycodone	20 mg	Twice Daily	Perineal Pain	17 May 2019
CH-A2-103	Allopurinol	100 mg	Once Daily	Gout Maintenance	01 Jan 2008
CH-A2-103	Simvastatin	20 mg	Once Daily	Hypercholesterolaemia	01 Jan 2013
CH-A2-103	Tolterodine	2 mg	Twice Daily	Urinary Frequency	01 Nov 2018
CH-A2-103	Salbutamol	2 puffs	When Required	COPD	01 Jan 2013
CH-A2-103	Laxido	1-2 sachets	When Required	Intermittent Constipation	01 Mar 2019
CH-A2-104	Dalteparin	12500 units	Once Daily	Pulmonary Embolism	13 Jul 2018
CH-A2-104	Thyroxine	50 mcg	Once Daily	Hypothyroidism	01 Jul 2018
CH-A2-105	Levothyroxine	100 mcg	Once Daily	Post Thyroidectomy	01 Sep 2017
CH-A2-105	Omeprazole	20 mg	Once Daily	Acid Reflux	01 May 2019
CH-A2-105	Zopiclone	7.5 mg	Once Daily	Insomnia	01 Apr 2019
CH-A2-105	Nystatin	100000 units	Twice Daily	Oral Candida	08 Jun 2019
CH-A2-105	Lactulose	10 ml	When Required	Constipation	06 Jun 2019
CH-A2-105	Blood Transfusion	2 units	One Dose	Low Haemaglobin	07 Aug 2019
CH-A2-105	Metoclopramide	10 mg	When Required	Nausea	25 Jun 2019
CH-A2-105	Nystatin	100000 units	Four Times Daily	Oral Thrush	24 Jul 2019
CH-A2-105	Blood Transfusion	2 units	One Dose	Low Haemaglobin	28 Aug 2019
CH-A2-105	Senna	2 units	Once Daily	Constipation	20 Sep 2019
CH-A2-105	Gelclair	1 dose	When Required	Mucositis	16 Aug 2019
CH-A2-105	Nystatin	100000 units	Twice Daily	Oral Thrush	03 Jul 2019
CH-A2-108	Amlodipine	10 mg	Once Daily	Hypertension	01 Jan 2016
CH-A2-108	Metoclopramide	10 mg	When Required	Nausea- Taken As Required	01 Jan 2016
CH-A2-108	Senna	2 tablets	When Required	Constipation	29 Oct 2019
CH-A2-108	Augmentin	625 mg	Three Times Daily	Prophylactic- Right Lower Lobe	08 Nov 2019
CH-A2-108	Co-Amoxiclav	500 mg/125 mg	Three Times Daily	UTI	20 Jan 2020
CH-A2-108	Doxycycline	100 mg	Twice Daily	Chest Infection	31 Jan 2020
CH-A2-108	Paracetamol	1 g	When Required	Prophylactic	09 Feb 2020

Subject	Medication	Dose	Frequency	Indication	Date
CH-A2-108	Amoxicillin And Clavulanic Acid	625 mg	Three Times Daily	Chest Infection	17 Feb 2020
CH-A2-108	Tazocin	4.5 g	Other	Chest Infection	15 Feb 2020
CH-A2-109	Sertraline	100 mg	Once Daily	Depression	01 Feb 2016
CH-A2-109	Dalteparin	18000 IU	Once Daily	Preventative Treatment For Pulmonary Embolism/Antiphospholipid Syndrome	01 Apr 2016
CH-A2-109	Metoclopramide	10 mg	When Required	Nausea And Vomiting	21 Nov 2019
CH-A2-109	Ondansetron	8 mg	When Required	Nausea And Vomiting (Given After Chemo)	22 Nov 2019
CH-A2-109	Ondansetron	4 mg	One Dose	Nausea And Vomiting	22 Nov 2019
CH-A2-109	Diprobase	1 application	Three Times Daily	Hand And Foot Syndrome	17 Dec 2019
CH-A2-109	Filgrastim	300 units	Once Daily	Neutropenia	27 Dec 2019
CH-A2-109	Augmentin	625 mg	Three Times Daily	Cellulitis	13 Feb 2020
CH-A2-109	Apixaban	5 mg	Twice Daily	Pulmonary Embolism Prophylaxis	20 Mar 2020
CH-A2-110	Ventolin	2 puffs	When Required	Asthma	01 Jan 2010
CH-A2-110	Becotide	1 puff	When Required	Asthma	01 Jan 2010
CH-A2-110	Ibuprofen Cream	1 application	Twice Daily	Back Pain	03 Feb 2020
CH-A2-110	Metoclopramide	10 mg	When Required	Nausea Prophylaxis	03 Feb 2020
CH-A2-110	Difflam	10 mls	When Required	Dry Mouth Prophylaxis	03 Feb 2020
CH-A2-110	Senna	2 tablets	When Required	Constipation	07 Feb 2020
CH-A2-110	Paracetamol	1 g	When Required	Pain	18 Feb 2020
CH-A2-110	Omeprazole	20 mg	Once Daily	Per Trial Protocol- Gastric Protection	21 Feb 2020
CH-A2-110	Chlorphenamine Injection	10 mg	One Dose	Macular Rash	25 Feb 2020
CH-A2-112	Paracetamol	1g	When Required	Joint Pain	01 Nov 2018
CH-A2-112	Oxycontin	90 mg	Twice Daily	Joint Pain	01 Oct 2018
CH-A2-112	Amitriptyline	10mg	Once Daily	Depression	01 Jan 2018
CH-A2-112	Lactulose	10mls	Three Times Daily	Constipation	07 Oct 2020
CH-A2-112	Omeprazole	20mg	Once Daily	Gastritis Prevention	01 Jan 2018
CH-A2-112	Fluoxetine	20 mg	Once Daily	Depression	01 Oct 2018
CH-A2-112	Fleet Enema	133 ml	One Dose	Constipation	12 Oct 2020
CH-A2-112	Senna	2 tablets	Once Daily	Constipation	01 Nov 2020

Subject	Medication	Dose	Frequency	Indication	Date
CH-A2-112	Prednisolone	1 mg	Once Daily	Joint Pain	01 Jan 2018
CH-A2-112	Calci-D	1000 mg	Once Daily	Bone Support	01 Jan 2018
CH-A2-112	Clonidine	0.1 mg	Twice Daily	Migraine	01 Jan 2018
CH-A2-112	Ferrous Fumarate	210 mg	Twice Daily	Iron Deficiency	01 Jan 2018
CH-A2-112	Fleet Enema	133 ml	One Dose	Constipation	09 Oct 2020
CH-A2-112	Fleet Enema	133 ml	One Dose	Constipation	13 Nov 2020
CH-A2-112	Prednisolone	1 mg	Once Daily	Joint Pain	26 Oct 2020
CH-A2-112	Avamys 27.5 Mcg Nasal Spray	27.5 mcg	Unknown	Nasal Congestion	13 Nov 2020
CH-A2-112	Filgrastim	300 mu	Once Daily	Neutropenia	01 Dec 2020
CH-A2-112	Prednisolone	1 mg	Once Daily	Arthritis	18 Dec 2020
CH-A2-112	Filgrastim	480 mu	Once Daily	Neutropenia Prophylaxis	22 Dec 2020
CH-A2-112	Filgrastim	480 mu	Once Daily	Neutropenia Prophylaxis	19 Jan 2021
CH-A2-112	Potassium	2 tablets	Three Times Daily	Hypokalemia	22 Jan 2021
CH-A2-112	Prednisolone	2 mg	Once Daily	Arthritis	20 Apr 2021
CH-A2-113	Metformin	1000 mg	Twice Daily	Type 2 Diabetes	01 Jan 2013
CH-A2-113	Simvastatin	10 mg	Once Daily	Type 2 Diabetes	01 Jan 2010
CH-A2-113	Glicazide	160 mg	Twice Daily	Type 2 Diabetes	01 Jan 2010
CH-A2-113	Senna	15 mg	Once Daily	Constipation	01 Dec 2020
CH-A2-113	Astrazeneca Vaccine	0.5 ml	One Dose	Covid-19 Vaccination (1st Dose)	01 Jan 2021
CH-A2-113	Astrazeneca Vaccine	0.5 ml	One Dose	Covid-19 Vaccination (2nd Dose)	29 Apr 2021
CH-A2-113	Magnesium Aspartate	10 mmol	Twice Daily	Hypomagnesia	16 Mar 2021
CH-A2-114	Pregabalin	150 mg	Twice Daily	Pain	01 Dec 2020
CH-A2-114	Morphine Sr	40 mg	Twice Daily	Pain	01 Jul 2020
CH-A2-114	Apixaban	10 mg	Twice Daily	DVT	01 Jul 2020
CH-A2-114	Creon	5 tablets	Three Times Daily	Pancreatic Enzyme (Malabsorption)	01 Jul 2020
CH-A2-114	Oramorph	20 mg/10 ml	When Required	Pain	01 Jul 2020
CH-A2-114	Paracetamol	1 g	When Required	Pain	01 Jul 2020
CH-A2-114	Lactulose	10 ml	When Required	Constipation	01 Dec 2020
CH-A2-114	Amlodipine	5 mg	Once Daily	Hypertension	23 Feb 2021
CH-A2-115	Amlodipine	5 mg	Once Daily	Hypertension	13 Apr 2021

Subject	Medication	Dose	Frequency	Indication	Date
CH-A2-115	Levothyroxine	125 mg	Once Daily	Hypothyroidism	01 Feb 2020
CH-A2-115	Dalteparin	15000 IU	Once Daily	Pulmonary Embolism	03 Jun 2021
CH-A2-116	Oramorph	2.5 mg	Other	Pain	05 Apr 2021
CH-A2-116	Paracetamol	1 g	Other	Pain	05 Apr 2021
CH-A2-116	Senna	1 tablet	When Required	Constipation	05 Apr 2021
CH-A2-116	Morphine Mr	10 mg	Twice Daily	Pain	19 Apr 2021
CH-A2-116	Famotidine	20 mg	Twice Daily	Stomach Uptake	29 Apr 2021
CH-A2-116	Tazocin	4.5 g	Three Times Daily	Sepsis	04 May 2021
CH-A2-116	Cyclizine	50 mg	Three Times Daily	Anti Sickness	03 May 2021
CH-A2-116	Dexamethasone	4 mg	Once Daily	Vomiting	04 May 2021
CH-A2-117	Paracetamol	500 mg	When Required	Pain in Sacral Area	10 Jun 2021
CH-A2-117	Laxido	1 sachet	When Required	Constipation	04 Jun 2021
CH-A2-117	Filgrastim (Accofil)	48 million units	One Dose	Neutropenia	20 Jul 2021
CH-A2-119	Oramorph	5 mg	Once Daily	Left Leg Pain	01 Jun 2021
CH-A2-119	Ibuprofen	200 mg (2 capsules)	Other	Back Pain	01 Jan 2019
CH-A2-119	Paracetamol	1 tablet	When Required	Back Pain	01 Jan 2019
CH-A2-119	Omeprazole	20 mg	Once Daily	Stomach Protection	01 Feb 2021
CH-A2-119	Filgrastim	48 million units	One Dose	Low Neutrophils	23 Aug 2021
CH-A2-119	Flucloxacillin	250 mg	Four Times Daily	Cellulitis	23 Aug 2021
CH-A2-119	Multivitamins	1 tablet	Once Daily	Vitamin Prophylaxis	01 Oct 2021
CH-A2-119	Red Blood Cells	1 unit	One Dose	Anaemia	21 Oct 2021
CH-A2-119	Flucloxacillin	250 mg	Four Times Daily	Skin Wound	02 Nov 2021
CH-A2-119	Oesophageal Stent Insertion		Unknown	Dysphagia	29 Dec 2021
CH-A2-119	Oesophageal Stent Removal		Unknown	Abdominal Pain	04 Feb 2022
CH-A2-120	Leflunomide	10 mg	Once Daily	Rheumatoid Arthritis	02 Oct 2015
CH-A2-120	Ramipril	10 mg	Once Daily	Hypertension	25 Oct 2019
CH-A2-120	Amlodipine	10 mg	Once Daily	Hypertension	18 Nov 2019
CH-A2-120	Atorvastatin	10 mg	Once Daily	Hypercholesterolaemia	25 Oct 2019
CH-A2-120	Levothyroxine	100 mcg	Once Daily	Hypothyroidism	01 Jun 2020
CH-A2-120	Zapain (30/500 Mg)	1-2 tablets	When Required	Pain	07 Aug 2014

Subject	Medication	Dose	Frequency	Indication	Date
CH-A2-120	Gabapentin	300 mg	Three Times Daily	Pain	11 Aug 2021
CH-A2-120	Prednisolone	10 mg	Once Daily	Rheumatoid Arthritis	03 May 2016
CH-A2-120	Oramorph	5 mg	When Required	Pain	06 Sep 2021
CH-A2-120	Butec Patch	10 mg	Other	Pain	14 Sep 2021
CH-A2-120	Chlorphenamine	4 mg	When Required	Itchy Skin Lesions	05 Feb 2022
CH-A2-118	Paracetamol	1g	When Required	Pain Relief	23 Nov 2017
CH-A2-118	Pregabalin	200mg	Twice Daily	Pain Relief	21 Nov 2017
CH-A2-118	Cetirizine	10mg	Once Daily	Sinusitis	09 Jun 2021
CH-A2-118	Zerobase	11%	When Required	Dermatitis	14 Dec 2017
CH-A2-118	Dermovate	0.05%	When Required	Dermatitis	23 Nov 2017
CH-A2-118	Desogestrel	75mcg	Once Daily	Contraceptive Pill	12 Dec 2018
CH-A2-118	Multivitamins	1Tablet	Once Daily	General Health	30 Mar 2021
CH-A2-118	Dexamethasone	4mg	Twice Daily	Supportive Medication	05 Jul 2021
CH-A2-118	Loperamide	2mg	When Required	Taken in Error	11 Jul 2021
CH-A2-118	Lansoprazole	30mg	Once Daily	Supportive Medication	05 Jul 2021
CH-A2-118	Ondansetron	8mg	Twice Daily	Supportive Medication	05 Jul 2021
CH-A2-118	Dexamethasone	4mg	Twice Daily	Supportive Medication	26 Jul 2021
CH-A2-118	Ondansetron	8mg	Twice Daily	Supportive Medication - Anti Sickness	26 Jul 2021
CH-A2-118	Betnovate	0.025%	Twice Daily	Dermatitis	22 Jul 2021
CH-A2-118	Enoxaparin	130mg	Once Daily	Throembolic Event	20 Aug 2021
CH-A2-118	Cough Syrup	5ml	When Required	Sore Throat	20 Aug 2021
CH-A2-118	Enoxaparin	130mg	Once Daily	Thromboembolic Event	07 Sep 2021
CH-A2-118	Enoxaparin	130mg	Once Daily	Thromboembolic Event	09 Sep 2021
CH-A2-118	Dexamethasone	4mg	Twice Daily	Supportive Medication	17 Aug 2021
CH-A2-118	Dexamethasone	4mg	Twice Daily	Supportive Medication	07 Sep 2021
CH-A2-118	Ondansetron	8mg	Twice Daily	Supportive Medication	27 Sep 2021
CH-A2-118	Aprepitant	125mg	Once Daily	Supportive Medication	18 Oct 2021
CH-A2-118	Ondansetron	8mg	Twice Daily	Supportive Medication	18 Oct 2021
CH-A2-118	Dexamethasone	4mg	Twice Daily	Supportive Medication	18 Oct 2021
CH-A2-106	Apixaban	2.5 mg	Twice Daily	Thrombosis	17 Jun 2019

Subject	Medication	Dose	Frequency	Indication	Date
CH-A2-106	Atorvastatin	10 mg	Once Daily	High Cholesterol	01 Jan 2004
CH-A2-106	Citalopram	20 mg	Once Daily	Anxiety	01 Jan 2016
CH-A2-106	Loperamide	2 mg	When Required	Loose Stools	01 Jan 1999
CH-A2-106	Omeprazole	40 mg	Once Daily	Reflux	01 Jan 2009
CH-A2-106	Sitagliptin	100 mg	Once Daily	Diabetes - Type 2	01 Jan 2019
CH-A2-106	Paracetamol	1 g	When Required	Pain	01 Jan 2016
CH-A2-106	Hydroxocobalamin	1mg/1ml	Other	Vitamin B12 Deficiency	01 Jan 2016
CH-A2-106	Dalteparin	15000 units	Once Daily	Thrombosis	04 Jul 2019
CH-A2-106	Ondansetron	8 mg	Once Daily	Prophylactic Anti-Emetic After Chemotherapy	15 Jul 2019
CH-A2-106	Dexamethasone	4 mg	Twice Daily	Prophylactic Anti-Emetic After Chemotherapy	16 Jul 2019
CH-A2-106	Chlorhexidine Mouthwash	10 ml	When Required	Daily Mouthwash	15 Jul 2019
CH-A2-106	Benzydamine Hcl 0.15 Mouthwash	10 ml	When Required	Sore Mouth	15 Jul 2019
CH-A2-106	Metoclopramide	10 mg	When Required	Nausea	15 Jul 2019
CH-A2-106	Ondansetron	8 mg	Once Daily	Prophylactic Anti-Emetic After Chemotherapy	12 Aug 2019
CH-A2-106	Dexamethasone	4 mg	Twice Daily	Prophylactic Anti-Emetic After Chemotherapy	13 Aug 2019
CH-A2-106	Calcichew	1 tablet	Twice Daily	Hypocalcaemia	03 Sep 2019
CH-A2-106	Dexamethasone	4 mg	Twice Daily	Prohylactic Anti-Emetic After Chemotherapy	03 Sep 2019
CH-A2-106	Ondansetron	4 mg	When Required	To Help Stoma Output Consistency	19 Sep 2019
CH-A2-106	Fusidic Acid	1 application	Three Times Daily	Erythema on Knee	19 Sep 2019
CH-A2-106	Nystatin	1 ml	Four Times Daily	Oral Candida	19 Sep 2019
CH-A2-106	Ondansetron	8 mg	Once Daily	Prophylacti Anti-Emetic After Chemotherapy	23 Sep 2019
CH-A2-106	Dexamethasone	4 mg	Twice Daily	Prophylactic Anti-Emetic After Chemotherapy	24 Sep 2019
CH-A2-106	Nystatin	1 ml	Twice Daily	Oral Candida	04 Oct 2019
CH-A2-106	Flu Vaccination	1 injection	One Dose	Prophylactic Protection	09 Oct 2019
CH-A2-106	Ondansetron	8 mg	Once Daily	Prophylactic Anti Emetic	14 Oct 2019
CH-A2-106	Metoclopramide	10 mg	When Required	Prophylactic Anti Emetic	14 Oct 2019

Subject	Medication	Dose	Frequency	Indication	Date
CH-A2-106	Dexamethasone	8 mg	One Dose	Prophylactic Anti Emetic	14 Oct 2019
CH-A2-106	Dioralyte Rehydration Salts	sachet	When Required	Dehydration	17 Oct 2019
CH-A2-106	Epaderm	1	One Dose	Dry Skin	31 Oct 2019
CH-A2-106	Nystatin	1	Four Times Daily	Oral Thrush	31 Oct 2019
CH-A2-106	Ondansetron	8 mg	Once Daily	Prophylactic Anti-Emetic After Chemotherapy	04 Nov 2019
CH-A2-106	Dexamethasone	4 mg	Twice Daily	Prophylactic Anti-Emetic After Chemotherapy	05 Nov 2019
CH-A2-106	Hydroxocobalamin	1mg/1ml	Other	Vitamin B12 Deficiency	12 Nov 2019
CH-A2-106	Nystatin	1	Four Times Daily	Oral Thrush	09 Dec 2019
CH-A2-107	Humulin	10 units	Once Daily	Diabetes	01 Feb 2019
CH-A2-107	Metformin	500 mg	Twice Daily	Diabetes	01 Nov 2018
CH-A2-107	Gliclazide	80 mg	Once Daily	Diabetes	01 Nov 2018
CH-A2-107	Omeprazole	20 mg	Once Daily	Acid Reflux	01 Nov 2016
CH-A2-107	Amlodipine	5 mg	Once Daily	Hypertension	13 Mar 2017
CH-A2-107	Creon	300 mg	Three Times Daily	Having No Pancreas	13 Mar 2017
CH-A2-107	Diprobase Cream	topical	When Required	Eczema	01 Aug 2019
CH-A2-107	Humulin	12 units	Once Daily	Diabetes	13 Aug 2019
CH-A2-107	Dexamethasone	4 mg`	Twice Daily	Prophylactic Anti-Emetic After Chemotherapy	13 Aug 2019
CH-A2-107	Dexamethasone	2 mg	Twice Daily	Prophylactic After Chemotherapy	14 Aug 2019
CH-A2-107	Metoclopramide	10 mg	When Required	Nausea	16 Aug 2019
CH-A2-107	Chlorhexidine Mouthwash	10 ml	Twice Daily	Mouthwash	12 Aug 2019
CH-A2-107	Chlorphenamine	10 mg	One Dose	Rash To Left Wrist During M6620 Infusion	13 Aug 2019
CH-A2-107	Chlorphenamine	4 mg	One Dose	Prophylactic Anti-Histamine Prior To Treatment	20 Aug 2019
CH-A2-107	Ondansetron	8 mg	When Required	Nausea	20 Aug 2019
CH-A2-107	Tazocin	4.5 g	Three Times Daily	Pyrexia	24 Aug 2019
CH-A2-107	Co-Amoxiclav	625 mg	Three Times Daily	Pyrexia	28 Aug 2019
CH-A2-107	Dalteparin	5000 units	Once Daily	Prophylactic Anticoagulant	24 Aug 2019
CH-A2-107	Cyclizine	50 mg	When Required	Nausea	20 Aug 2019

Subject	Medication	Dose	Frequency	Indication	Date
CH-A2-107	Nystatin	1 ml	Four Times Daily	Oral Thrush	02 Aug 2019
CH-A2-107	Humulin	6 units	Once Daily	Diabetes	27 Aug 2019
CH-A2-107	Humulin	12 units	Once Daily	Diabetes	27 Aug 2019

Table 48: Post trial treatment

Subject	Treatment	Start Date	End Date	Best Response
CH-A2-109	NUC-7738	06 Oct 2020		Unknown
CH-A2-110	Stereotactic Radiosurgery (SRS)	01 Jul 2020		No New Disease- Stable
CH-A2-113	Nucleotide Analogue	29 Jul 2021		Stable Disease
CH-A2-116	Oxaliplatin And Capecitabine	01 Jun 2021		Off due to Complicaion by Oxaliplatin and Acute Neuropathy
CH-A2-116	Nivolumab	26 Aug 2021		
CH-A2-116	Nivolumab	26 Aug 2021	08 Dec 2021	Stable Disease (No Improvement)
CH-A2-107	Capecitabine	04 Dec 2019		Stable Disease

7.7 Appendix - Toxicity

Table 49: All Adverse Events

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-101	Thrombocytopenia			14Jan2019	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-101	Nasal discomfort	17Jan2019	Week 2		1	Possibly Related	Definitely Not Related	Possibly Related	No	No	Persisting
CH-A2-101	Epistaxis	17Jan2019	Week 2	20Jan2019	1	Possibly Related	Definitely Not Related	Possibly Related	No	No	Resolved
CH-A2-101	Thrombocytopenia	24Jan2019	Week 3	30Jan2019	2	Possibly Related	Definitely Related	Possibly Related	No	No	Resolved
CH-A2-101	Neutropenia	30Jan2019	Week 3	06Feb2019	4	Possibly Related	Definitely Related	Possibly Related	No	No	Resolved
CH-A2-101	Nausea	08Mar2019	Cycle 3		1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-102	Lower respiratory tract infection	25Apr2019	Cycle 3		2	Possibly Related	Possibly Related	Possibly Related	No	No	Persisting
CH-A2-102	Decreased appetite	12Apr2019	Week 5 or 6		2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-102	Asthenia	05Apr2019	Week 4		1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-102	Hypophosphataemia	12Apr2019	Week 5 or 6	01May2019	3	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-102	Productive cough	24Apr2019	Cycle 3		2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-102	Dyspnoea exertional	24Apr2019	Cycle 3		3	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-102	Lower respiratory tract infection	15Mar2019	Week 2	22Mar2019	2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Improved
CH-A2-102	Productive cough	22Mar2019	Week 3	24Apr2019	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-102	Fatigue	15Mar2019	Week 5 or 6		2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-103	Glomerular filtration rate decreased	24Apr2019	Week 2	20May2019	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-103	Perineal pain	25Apr2019	Week 2		2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-103	Dysuria	25Apr2019	Week 2		2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-103	Fatigue	30Apr2019	Week 3		2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-103	Temperature intolerance	30Apr2019	Week 3		1	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Persisting
CH-A2-103	Oral candidiasis	01May2019	Week 3	12May2019	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-103	Urinary tract infection	24Apr2019	Week 2	20May2019	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-105	Nausea	04Jun2019	Week 1	21Aug2019	1	Possibly Related	Definitely Related	Definitely Related	No	No	Resolved
CH-A2-105	Mucosal inflammation	16Aug2019	Cycle 4	13Sep2019	1	Possibly Related	Definitely Related	Definitely Not Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-105	Anaemia	04Oct2019	Cycle 6	23Oct2019	2	Definitely Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-105	Jaundice	29Aug2019	Cycle 5	02Oct2019	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-105	Constipation	20Sep2019	Cycle 5	02Oct2019	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-105	Oral candidiasis	08Jun2019	Week 1	15Jun2019	1	Possibly Related	Definitely Related	Definitely Related	No	No	Resolved
CH-A2-105	Constipation	06Jun2019	Week 1	08Jun2019	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-105	Fatigue	04Jun2019	Week 1	23Oct2019	1	Definitely Related	Definitely Related	Definitely Related	No	No	Resolved
CH-A2-105	Dysgeusia	17Jun2019	Week 3	25Jun2019	1	Definitely Related	Definitely Related	Definitely Related	No	No	Resolved
CH-A2-105	Restless legs syndrome	18Jun2019	Week 3	02Jul2019	1	Definitely Not Related	Possibly Related	Definitely Not Related	No	No	Resolved
CH-A2-105	Oral candidiasis	18Jul2019	Cycle 3	20Jul2019	1	Possibly Related	Definitely Related	Possibly Related	No	No	Resolved
CH-A2-105	Oral candidiasis	27Jul2019	Cycle 3	30Jul2019	1	Possibly Related	Definitely Related	Possibly Related	No	No	Resolved
CH-A2-105	Anaemia	16Jul2019	Cycle 3	14Sep2019	2	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-106	Dry throat	16Jul2019	Week 1	16Jul2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	No	Resolved
CH-A2-106	Limb discomfort	17Sep2019	Cycle 3	29Sep2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	N/A; Outside DLT period	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-106	Oral candidiasis	03Oct2019	Cycle 4	11Oct2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Haemoglobin decreased	14Oct2019	Cycle 5	17Oct2019	1	Probably Not Related	Probably Related	Probably Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Stoma site extravasation	16Oct2019	Cycle 5	18Oct2019	1	Probably Not Related	Probably Not Related	Probably Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Blood phosphorus decreased	14Oct2019	Cycle 5	21Oct2019	1	Probably Not Related	Probably Related	Probably Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Rhinitis	29Oct2019	Cycle 5	05Nov2019	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Palmar-plantar erythrodysaesthesia syndrome	28Oct2019	Cycle 5	30Nov2019	1	Probably Not Related	Probably Not Related	Definitely Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Oral candidiasis	31Oct2019	Cycle 5	05Nov2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Fatigue	08Nov2019	Cycle 6	14Nov2019	1	Probably Not Related	Probably Related	Probably Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Flank pain	26Nov2019	After Cycle 6	27Nov2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Stoma site haemorrhage	17Jul2019	Week 1	19Jul2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	No	Resolved
CH-A2-106	Oral candidiasis	09Dec2019	After Cycle 6	16Dec2019	1	Probably Not Related	Probably Related	Probably Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Rash pustular	30Nov2019	After Cycle 6		2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Persisting
CH-A2-106	Musculoskeletal pain	20Jul2019	Week 1	21Jul2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-106	Neutropenia	01Aug2019	Week 3	12Aug2019	1	Probably Not Related	Probably Related	Probably Related	No	No	Resolved
CH-A2-106	Neutropenia	29Aug2019	Week 5 or 6	05Sep2019	1	Probably Not Related	Probably Related	Probably Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Hypocalcaemia	02Sep2019	Cycle 3	05Sep2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Oral candidiasis	19Sep2019	Cycle 3	27Sep2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Erythema	18Sep2019	Cycle 3	22Nov2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-106	Vision blurred	02Sep2019	Cycle 3	27Nov2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-107	Pyrexia	24Aug2019	Week 2	28Aug2019	1	Possibly Related	Possibly Related	Possibly Related	Yes	Yes	Resolved
CH-A2-107	Muscle spasms	01Aug2019	Week 1		1	Probably Not Related	Probably Not Related	Probably Not Related	No	No	Persisting
CH-A2-107	Oral candidiasis	02Aug2019	Screening	18Aug2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	No	Resolved
CH-A2-107	Neutropenia	26Aug2019	Week 2	28Aug2019	2	Probably Related	Probably Related	Probably Related	No	Yes	Worsened
CH-A2-107	Neutropenia	28Aug2019	Week 3	01Sep2019	3	Probably Related	Probably Related	Probably Related	Yes	Yes	Resolved
CH-A2-107	Neutropenia	02Sep2019	Week 3	16Sep2019	1	Probably Related	Probably Related	Probably Related	No	Yes	Resolved
CH-A2-107	Catheter site related reaction	13Aug2019	Week 1	13Aug2019	1	Probably Related	Probably Not Related	Probably Not Related	No	No	Persisting

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-107	Hyperglycaemia	13Aug2019	Week 1		3	Probably Not Related	Probably Not Related	Probably Not Related	No	No	Persisting
CH-A2-107	Nausea	12Aug2019	Week 1	26Aug2019	1	Probably Not Related	Probably Related	Probably Related	No	No	Persisting
CH-A2-107	Fatigue	13Aug2019	Week 1		1	Probably Not Related	Probably Related	Probably Related	No	No	Persisting
CH-A2-107	Muscular weakness	24Aug2019	Week 2	30Aug2019	1	Probably Not Related	Probably Not Related	Probably Not Related	No	No	Persisting
CH-A2-108	Fatigue	29Sep2019	Week 1	03Oct2019	1	Definitely Not Related	Possibly Related	Possibly Related	No	No	Worsened
CH-A2-108	Fatigue	29Oct2019	Week 5 or 6	01Nov2019	2	Possibly Related	Possibly Related	Possibly Related	No	N/A; Outside DLT period	Improved
CH-A2-108	Dry mouth	25Oct2019	Week 4	30Oct2019	1	Possibly Related	Possibly Related	Probably Related	No	No	Resolved
CH-A2-108	Nausea	25Oct2019	Week 4	27Oct2019	1	Possibly Related	Possibly Related	Possibly Related	No	N/A; Outside DLT period	Resolved
CH-A2-108	Constipation	25Oct2019	Week 4	29Oct2019	1	Definitely Not Related	Definitely Related	Definitely Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-108	Nausea	28Oct2019	Week 5 or 6	01Nov2019	1	Possibly Related	Possibly Related	Possibly Related	No	N/A; Outside DLT period	Resolved
CH-A2-108	Fatigue	01Nov2019	Week 5 or 6	14Mar2020	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-108	Cough	08Nov2019	Week 5 or 6	14Nov2019	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-108	Diarrhoea	09Nov2019	Week 5 or 6	10Nov2019	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-108	Neutropenia	11Nov2019	Cycle 3	14Nov2019	2	Definitely Related	Definitely Related	Possibly Related	No	No	Resolved
CH-A2-108	Thrombocytopenia	26Nov2019	Cycle 3	02Dec2019	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-108	Fatigue	03Oct2019	Week 2	06Oct2019	2	Possibly Related	Probably Related	Possibly Related	No	No	Improved
CH-A2-108	Neutropenia	26Nov2019	Cycle 3	06Dec2019	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-108	Weight decreased	29Nov2019	Cycle 3	02Dec2019	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-108	Ototoxicity	02Dec2019	Cycle 4	02Dec2019	1	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Resolved
CH-A2-108	Tinnitus	17Dec2019	Cycle 4	14Mar2020	1	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Resolved
CH-A2-108	Lower respiratory tract infection	29Jan2020	Cycle 6	06Feb2020	2	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-108	Cough	07Feb2020	Cycle 6	08Apr2020	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-108	Neutropenia	20Dec2019	Cycle 4	21Jan2020	3	Definitely Related	Definitely Related	Definitely Related	No	No	Resolved
CH-A2-108	Upper respiratory tract infection	15Jan2020	Cycle 5	22Jan2020	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-108	Nausea	30Sep2019	Week 1	06Oct2019	1	Possibly Related	Probably Related	Possibly Related	No	No	Resolved
CH-A2-108	Dysgeusia	30Sep2019	Week 1	06Oct2019	2	Possibly Related	Probably Related	Possibly Related	No	No	Resolved
CH-A2-108	Decreased appetite	30Sep2019	Week 1	06Oct2019	2	Possibly Related	Probably Related	Possibly Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-108	Abdominal pain	30Sep2019	Week 1	11Oct2019	1	Probably Related	Probably Related	Probably Related	No	No	Resolved
CH-A2-108	Fatigue	07Oct2019	Week 2	24Oct2019	1	Possibly Related	Probably Related	Possibly Related	No	No	Worsened
CH-A2-108	Neutropenia	14Oct2019	Week 3	21Oct2019	3	Definitely Related	Definitely Related	Definitely Related	No	No	Resolved
CH-A2-108	Fatigue	25Oct2019	Week 4	28Oct2019	2	Possibly Related	Possibly Related	Possibly Related	No	N/A; Outside DLT period	Improved
CH-A2-109	Fatigue	21Nov2019	Week 1	23Nov2019	2	Possibly Related	Possibly Related	Possibly Related	No	No	Improved
CH-A2-109	Tinnitus	19Nov2019	Week 1	07Apr2020	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-109	Thrombocytopenia	24Dec2019	Week 5 or 6	02Jan2020	3	Possibly Related	Possibly Related	Possibly Related	No	N/A; Outside DLT period	Resolved
CH-A2-109	Neutropenia	27Dec2019	Week 5 or 6	02Jan2020	3	Possibly Related	Possibly Related	Possibly Related	No	N/A; Outside DLT period	Resolved
CH-A2-109	Vertigo	25Dec2019	Week 5 or 6	26Dec2019	1	Definitely Not Related	Probably Related	Definitely Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-109	Back pain	28Dec2019	Week 5 or 6	02Jan2020	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-109	Fatigue	04Jan2020	Cycle 3	06Jan2020	2	Definitely Not Related	Probably Related	Definitely Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-109	Pollakiuria	30Dec2019	Cycle 3	04Jan2020	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-109	Fatigue	11Jan2020	Cycle 3	20Feb2020	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Worsened

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-109	Breast cellulitis	12Feb2020	Cycle 4	23Feb2020	1	Definitely Related	Definitely Related	Definitely Related	No	N/A; Outside DLT period	Improved
CH-A2-109	Vomiting	22Nov2019	Week 1	25Nov2019	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-109	Fatigue	21Feb2020	Cycle 5	27Feb2020	2	Definitely Not Related	Possibly Related	Definitely Related	No	N/A; Outside DLT period	Improved
CH-A2-109	Fatigue	28Feb2020	Cycle 5		1	Definitely Not Related	Definitely Related	Definitely Related	No	N/A; Outside DLT period	Persisting
CH-A2-109	Erythema	24Feb2020	Cycle 5		1	Definitely Related	Definitely Related	Definitely Related	No	N/A; Outside DLT period	Persisting
CH-A2-109	Nausea	21Nov2019	Week 1	25Nov2019	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-109	Fatigue	24Nov2019	Week 1	03Jan2020	1	Possibly Related	Possibly Related	Possibly Related	No	No	Worsened
CH-A2-109	Thrombocytopenia	03Dec2019	Week 3	13Dec2019	1	Possibly Related	Possibly Related	Definitely Not Related	No	No	Resolved
CH-A2-109	Nausea	13Dec2019	Week 4	17Dec2019	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-109	Palmar-plantar erythrodysaesthesia syndrome	14Dec2019	Week 4	30Dec2019	1	Definitely Not Related	Definitely Not Related	Probably Related	No	No	Resolved
CH-A2-109	Neuropathy peripheral	14Dec2019	Week 4	30Dec2019	1	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Resolved
CH-A2-109	Diarrhoea	13Dec2019	Week 4	14Dec2019	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-110	Back pain	29Jan2020	Week 1		1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-110	Cough	30Jan2020	Week 1		1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-110	Rash macular	24Feb2020	Week 4	24Feb2020	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-110	Decreased appetite	25Feb2020	Week 4		1	Possibly Related	Possibly Related	Possibly Related	No	No	Persisting
CH-A2-110	Fatigue	27Feb2020	Week 4	06Mar2020	2	Definitely Related	Definitely Related	Definitely Related	No	No	Improved
CH-A2-110	Fatigue	06Mar2020	Week 5 or 6		1	Definitely Related	Definitely Related	Definitely Related	No	No	Persisting
CH-A2-110	Dyspnea on exertion	07Mar2020	Week 5 or 6	01Apr2020	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-110	Fatigue	04Feb2020	Week 1	10Feb2020	2	Possibly Related	Definitely Related	Possibly Related	No	No	Improved
CH-A2-110	Nausea	04Feb2020	Week 1	12Feb2020	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-110	Constipation	04Feb2020	Week 1	08Feb2020	1	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Resolved
CH-A2-110	Fatigue	10Feb2020	Week 2	27Feb2020	1	Possibly Related	Definitely Related	Possibly Related	No	No	Worsened
CH-A2-110	Tinnitus	09Feb2020	Week 2	01Apr2020	1	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Resolved
CH-A2-110	Nausea	17Feb2020	Week 3	06Mar2020	1	Possibly Related	Definitely Not Related	Possibly Related	No	No	Resolved
CH-A2-110	Abdominal pain upper	17Feb2020	Week 3	21Feb2020	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-110	Headache	14Feb2020	Week 2	19Feb2020	1	Definitely Not Related	Definitely Not Related	Probably Not Related	No	No	Resolved
CH-A2-112	Fatigue	02Oct2020	Week 1	04Oct2020	2	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Improved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-112	Constipation	11Nov2020	Week 5 or 6	16Nov2020	1	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Neutropenia	23Nov2020	Week 5 or 6	30Nov2020	3	Definitely Related	Definitely Related	Definitely Related	No	No	Resolved
CH-A2-112	Vision blurred	30Nov2020	Cycle 3	30Nov2020	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Fatigue	05Dec2020	Cycle 3	06Dec2020	2	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Improved
CH-A2-112	Fatigue	06Dec2020	Cycle 3	25Dec2020	1	Possibly Related	Probably Related	Probably Related	No	No	Worsened
CH-A2-112	Arthritis	16Dec2020	Cycle 3	21Dec2020	2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Improved
CH-A2-112	Neutropenia	15Dec2020	Cycle 3	21Dec2020	3	Definitely Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Arthritis	21Dec2020	Cycle 4		1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-112	Arthritis	18Dec2020	Week 3	24Dec2020	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Fatigue	25Dec2020	Cycle 4	26Dec2020	2	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Improved
CH-A2-112	Vomiting	02Oct2020	Week 1	03Oct2020	2	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Neutropenia	11Jan2021	Cycle 5	22Jan2021	3	Definitely Related	Definitely Related	Definitely Related	No	No	Persisting
CH-A2-112	Vomiting	16Oct2020	Week 3	16Oct2020	1	Probably Related	Definitely Not Related	Definitely Not Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-112	Neutropenia	16Oct2020	Week 3	19Oct2020	2	Definitely Related	Definitely Related	Definitely Related	No	No	Worsened
CH-A2-112	Neutropenia	02Feb2021	Cycle 5	05Feb2021	3	Definitely Related	Possibly Related	Definitely Not Related	No	No	Improved
CH-A2-112	Neutropenia	05Feb2021	Cycle 5	12Feb2021	2	Definitely Related	Possibly Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Adverse drug reaction	22Jan2021	Cycle 5	23Jan2021	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Fatigue	26Dec2020	Cycle 4	01Apr2021	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Hypokalaemia	22Jan2021	Cycle 5	26Jan2021	1	Probably Not Related	Possibly Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Decreased appetite	02Oct2020	Week 1	03Oct2020	2	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Fatigue	05Oct2020	Week 1	04Dec2020	1	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Worsened
CH-A2-112	Constipation	03Oct2020	Week 1	20Oct2020	2	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Neutropenia	26Oct2020	Week 3	02Nov2020	3	Definitely Related	Definitely Related	Definitely Related	No	No	Resolved
CH-A2-112	Neutropenia	19Oct2020	Week 3	26Oct2020	4	Definitely Related	Definitely Related	Definitely Related	No	No	Improved
CH-A2-112	Dyspnoea	07Nov2020	Week 5 or 6	08Nov2020	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-112	Constipation	06Nov2020	Week 5 or 6	11Nov2020	2	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Improved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-113	Nausea	24Nov2020	Week 1	24Nov2020	1	Definitely Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-113	Fatigue	05Jan2021	Cycle 3	14Feb2021	1	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Worsened
CH-A2-113	Tinnitus	14Feb2021	Cycle 5	14Feb2021	1	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Resolved
CH-A2-113	Diarrhoea	20Feb2021	Cycle 5	21Feb2021	1	Possibly Related	Probably Not Related	Possibly Related	No	No	Resolved
CH-A2-113	Fatigue	15Feb2021	Cycle 5	07Apr2021	2	Possibly Related	Definitely Related	Possibly Related	No	No	Improved
CH-A2-113	Fatigue	08Apr2021	After Cycle 6	04May2021	1	Possibly Related	Definitely Related	Possibly Related	No	No	Improved
CH-A2-113	Hypomagnesaemia	16Mar2021	Cycle 6	23Mar2021	1	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Resolved
CH-A2-113	Fatigue	25Nov2020	Week 1	28Nov2020	1	Probably Related	Probably Related	Definitely Not Related	No	No	Resolved
CH-A2-113	Diarrhoea	27Nov2020	Week 1	27Nov2020	1	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Resolved
CH-A2-113	Constipation	28Nov2020	Week 1	02Dec2020	1	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Resolved
CH-A2-113	Decreased appetite	25Nov2020	Week 1	28Nov2020	1	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Resolved
CH-A2-113	Paraesthesia	04Dec2020	Week 2		1	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Persisting
CH-A2-113	Angular cheilitis	05Dec2020	Week 2	01Jan2021	1	Definitely Not Related	Definitely Not Related	Probably Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-113	Fatigue	17Dec2020	Week 4	19Dec2020	1	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Resolved
CH-A2-113	Diarrhoea	17Dec2020	Week 4	19Dec2020	1	Definitely Not Related	Definitely Related	Definitely Not Related	No	No	Resolved
CH-A2-114	Thrombocytopenia	09Feb2021	Week 3	12Feb2021	3	Probably Related	Probably Related	Probably Related	No	No	Resolved
CH-A2-114	Weight decreased	31Jan2021	Week 2		1	Probably Related	Probably Related	Probably Related	No	No	Persisting
CH-A2-114	Decreased appetite	26Jan2021	Week 1	29Jan2021	2	Probably Related	Probably Related	Probably Related	No	No	Resolved
CH-A2-114	Neutropenia	15Feb2021	Week 4	21Feb2021	4	Probably Related	Probably Related	Probably Related	No	No	Resolved
CH-A2-114	Hypertension	22Feb2021	Week 4	26Feb2021	3	Probably Not Related	Probably Not Related	Probably Not Related	No	No	Resolved
CH-A2-115	Hypertension	13Apr2021	Week 1	19Apr2021	3	Definitely Not Related	Probably Related	Probably Not Related	No	No	Resolved
CH-A2-115	Pulmonary embolism	27May2021	Cycle 3		1	Definitely Not Related	Possibly Related	Possibly Related	No	N/A; Outside DLT period	Persisting
CH-A2-116	Sepsis	04May2021	Week 1	06May2021	3	Probably Related	Definitely Related	Probably Related	Yes	Yes	Resolved
CH-A2-116	Dehydration	02May2021	Week 1	06May2021	3	Possibly Related	Definitely Related	Possibly Related	No	Yes	Resolved
CH-A2-116	Vomiting	02May2021	Week 1	06May2021	3	Possibly Related	Definitely Related	Possibly Related	Yes	Yes	Resolved
CH-A2-117	Back pain	10Jun2021	Week 1	20Jun2021	1	Probably Not Related	Probably Not Related	Probably Not Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-117	Proctalgia	10Jun2021	Week 1	20Jun2021	1	Probably Not Related	Probably Not Related	Definitely Not Related	No	No	Resolved
CH-A2-117	Neutropenia	19Jul2021	Cycle 3	27Jul2021	2	Possibly Related	Definitely Related	Probably Related	No	No	Resolved
CH-A2-117	Blood alkaline phosphatase increased	14Sep2021	After Cycle 6		3	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Persisting
CH-A2-118	Fatigue	09Jul2021	Week 1	14Jul2021	1	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Resolved
CH-A2-118	Alanine aminotransferase increased	17Aug2021	Cycle 3	23Aug2021	2	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-118	Aspartate aminotransferase increased	26Jul2021	Week 4	02Aug2021	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-118	Aspartate aminotransferase increased	09Aug2021	Week 5 or 6	23Aug2021	1	Possibly Related	Probably Related	Possibly Related	No	No	Resolved
CH-A2-118	Oropharyngeal pain	20Aug2021	Cycle 3	22Aug2021	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-118	Embolism	20Aug2021	Cycle 3		2	Possibly Related	Possibly Related	Possibly Related	No	No	Persisting
CH-A2-118	Alanine aminotransferase increased	23Aug2021	Cycle 3	06Oct2021	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-118	Anaemia	31Aug2021	Cycle 3	12Sep2021	1	Possibly Related	Probably Related	Possibly Related	No	No	Resolved
CH-A2-118	Embolism	24Sep2021	Cycle 4	01Nov2021	3	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-118	Aspartate aminotransferase increased	24Sep2021	Cycle 4	06Oct2021	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-118	Constipation	10Jul2021	Week 1	15Jul2021	1	Definitely Not Related	Probably Related	Definitely Not Related	No	No	Resolved
CH-A2-118	Diarrhoea	07Aug2021	Week 5 or 6	07Aug2021	1	Definitely Not Related	Definitely Not Related	Possibly Related	No	No	Resolved
CH-A2-118	Anaemia	09Aug2021	Week 5 or 6	20Aug2021	1	Probably Not Related	Probably Related	Probably Not Related	No	No	Resolved
CH-A2-118	Platelet count decreased	09Aug2021	Week 5 or 6	09Aug2021	2	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-118	Hypophosphataemia	03Jul2021	Screening	12Jul2021	3	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-118	Hypophosphataemia	26Jul2021	Week 4	27Jul2021	3	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-118	Hypophosphataemia	16Aug2021	Cycle 3	17Aug2021	3	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-118	Alanine aminotransferase increased	26Jul2021	Week 4	17Aug2021	1	Possibly Related	Possibly Related	Possibly Related	No	No	Worsened
CH-A2-119	Chest pain	08Aug2021	Week 2	08Aug2021	2	Probably Not Related	Probably Not Related	Probably Related	Yes	No	Resolved
CH-A2-119	Fatigue	20Oct2021	Cycle 4	24Oct2021	2	Probably Related	Probably Related	Probably Related	No	No	Resolved
CH-A2-119	Anaemia	09Nov2021	Cycle 5	01Feb2022	1	Possibly Related	Definitely Related	Probably Related	No	No	Resolved
CH-A2-119	Nausea	11Nov2021	Cycle 5	04Feb2022	1	Probably Not Related	Definitely Related	Possibly Related	No	No	Resolved
CH-A2-119	Lymphocyte count decreased	27Oct2021	Cycle 4	09Nov2021	2	Probably Related	Probably Related	Probably Related	No	No	Improved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-119	White blood cell count decreased	27Oct2021	Cycle 4	09Nov2021	2	Definitely Related	Probably Related	Definitely Related	No	No	Resolved
CH-A2-119	Palmar-plantar erythrodysaesthesia syndrome	20Oct2021	Cycle 4	02Nov2021	2	Probably Not Related	Possibly Related	Definitely Related	No	No	Improved
CH-A2-119	Neutropenia	02Nov2021	Cycle 4	09Nov2021	3	Probably Related	Probably Related	Probably Related	No	N/A; Outside DLT period	Resolved
CH-A2-119	Palmar-plantar erythrodysaesthesia syndrome	02Nov2021	Cycle 4	10Nov2021	1	Definitely Not Related	Definitely Not Related	Definitely Related	No	N/A; Outside DLT period	Worsened
CH-A2-119	Palmar-plantar erythrodysaesthesia syndrome	11Nov2021	Cycle 5	30Nov2021	2	Definitely Not Related	Definitely Not Related	Definitely Related	No	N/A; Outside DLT period	Improved
CH-A2-119	Lymphocyte count decreased	09Nov2021	Cycle 5	15Dec2021	1	Probably Related	Probably Related	Probably Related	No	N/A; Outside DLT period	Resolved
CH-A2-119	Fatigue	04Aug2021	Week 1	20Oct2021	1	Probably Related	Probably Related	Probably Related	No	No	Worsened
CH-A2-119	Palmar-plantar erythrodysaesthesia syndrome	30Nov2021	Cycle 6	06Dec2021	1	Definitely Not Related	Definitely Not Related	Definitely Related	No	N/A; Outside DLT period	Resolved
CH-A2-119	Neutrophil count decreased	30Nov2021	Cycle 6	08Dec2021	1	Probably Related	Probably Related	Probably Related	No	N/A; Outside DLT period	Resolved
CH-A2-119	Abdominal pain	31Jan2022	After Cycle 6	04Feb2022	2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Resolved
CH-A2-119	Palmar-plantar erythrodysaesthesia syndrome	06Dec2021	Cycle 6	15Dec2021	2	Definitely Not Related	Definitely Not Related	Definitely Related	No	N/A; Outside DLT period	Resolved
CH-A2-119	Palmar-plantar erythrodysaesthesia syndrome	15Dec2021	Cycle 6	04Feb2022	1	Definitely Not Related	Definitely Not Related	Definitely Related	No	N/A; Outside DLT period	Resolved
CH-A2-119	Dysphagia	20Dec2021	After Cycle 6	30Dec2021	2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Improved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-119	Dysphagia	30Dec2021	After Cycle 6		1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Persisting
CH-A2-119	Thrombocytopenia	17Aug2021	Week 3	23Aug2021	1	Possibly Related	Probably Related	Possibly Related	No	No	Resolved
CH-A2-119	Neutropenia	23Aug2021	Week 4	31Aug2021	3	Possibly Related	Definitely Related	Possibly Related	No	No	Resolved
CH-A2-119	Cellulitis	23Aug2021	Week 4	31Aug2021	2	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A2-119	Nausea	10Sep2021	Week 5 or 6	24Oct2021	1	Probably Related	Probably Related	Probably Related	No	N/A; Outside DLT period	Resolved
CH-A2-119	Palmar-plantar erythrodysaesthesia syndrome	18Sep2021	Week 5 or 6	20Oct2021	1	Probably Not Related	Possibly Related	Definitely Related	No	N/A; Outside DLT period	Worsened
CH-A2-119	Erythema	21Sep2021	Cycle 3	21Sep2021	1	Probably Not Related	Probably Not Related	Probably Related	No	N/A; Outside DLT period	Resolved
CH-A2-119	Anaemia	06Oct2021	Cycle 3	09Nov2021	2	Possibly Related	Definitely Related	Probably Related	No	No	Improved
CH-A2-120	Platelet count decreased	26Oct2021	Cycle 4	02Nov2021	2	Possibly Related	Probably Related	Probably Related	No	No	Improved
CH-A2-120	Platelet count decreased	02Nov2021	Cycle 4	08Nov2021	1	Possibly Related	Probably Related	Probably Related	No	No	Resolved
CH-A2-120	Platelet count decreased	07Dec2021	Cycle 6	04Jan2022	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-120	Platelet count decreased	16Nov2021	Cycle 5	29Nov2021	1	Possibly Related	Probably Related	Probably Related	No	No	Resolved
CH-A2-120	Blood alkaline phosphatase increased	16Aug2021	Week 1	11Oct2021	1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	Cis Causality	Cape Causality	SAE	DLT	Outcome
CH-A2-120	Alanine aminotransferase increased	24Aug2021	Week 2	31Aug2021	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-120	Hypertension	24Aug2021	Week 2		1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-120	Musculoskeletal chest pain	14Sep2021	Week 5 or 6		1	Definitely Not Related	Definitely Not Related	Definitely Not Related	No	No	Persisting
CH-A2-120	Platelet count decreased	12Oct2021	Cycle 3	26Oct2021	1	Possibly Related	Possibly Related	Possibly Related	No	No	Worsened
CH-A2-120	Neutrophil count decreased	12Oct2021	Cycle 3	26Oct2021	2	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved
CH-A2-120	Anaemia	12Oct2021	Cycle 3		1	Possibly Related	Possibly Related	Possibly Related	No	No	Persisting
CH-A2-120	Fatigue	18Oct2021	Cycle 4	01Feb2022	1	Possibly Related	Possibly Related	Possibly Related	No	No	Resolved

Table 50: Worst graded Adverse Events for each patient

Subject	Grade	Description	Organ Class	M6620 Causality	Cisplatin Causality	Capecitabine Causality
CH-A2-101	4	Neutropenia	Blood & Lymphatic System Disorders	Possibly Related	Definitely Related	Possibly Related
CH-A2-102	3	Hypophosphataemia	Metabolism & Nutrition Disorders	Definitely Not Related	Definitely Not Related	Definitely Not Related
CH-A2-102	3	Dyspnoea exertional	Respiratory, thoracic and mediastinal disorders	Definitely Not Related	Definitely Not Related	Definitely Not Related
CH-A2-103	2	Perineal pain	Reproductive system and breast disorders	Definitely Not Related	Definitely Not Related	Definitely Not Related
CH-A2-103	2	Dysuria	Renal and urinary disorders	Definitely Not Related	Definitely Not Related	Definitely Not Related
CH-A2-103	2	Fatigue	General Disorders & Administration Site Conditions	Definitely Not Related	Definitely Not Related	Definitely Not Related
CH-A2-105	2	Anaemia	Blood & Lymphatic System Disorders	Definitely Related	Definitely Not Related	Definitely Not Related
CH-A2-105	2	Anaemia	Blood & Lymphatic System Disorders	Possibly Related	Possibly Related	Possibly Related

Subject	Grade	Description	Organ Class	M6620 Causality	Cisplatin Causality	Capecitabine Causality
CH-A2-106	2	Rash pustular	Infections & Infestations	Definitely Not Related	Definitely Not Related	Definitely Not Related
CH-A2-107	3	Neutropenia	Blood & Lymphatic System Disorders	Probably Related	Probably Related	Probably Related
CH-A2-107	3	Hyperglycaemia	Metabolism & Nutrition Disorders	Probably Not Related	Probably Not Related	Probably Not Related
CH-A2-108	3	Neutropenia	Blood & Lymphatic System Disorders	Definitely Related	Definitely Related	Definitely Related
CH-A2-108	3	Neutropenia	Blood & Lymphatic System Disorders	Definitely Related	Definitely Related	Definitely Related
CH-A2-109	3	Thrombocytopenia	Blood & Lymphatic System Disorders	Possibly Related	Possibly Related	Possibly Related
CH-A2-109	3	Neutropenia	Blood & Lymphatic System Disorders	Possibly Related	Possibly Related	Possibly Related
CH-A2-110	2	Fatigue	General Disorders & Administration Site Conditions	Definitely Related	Definitely Related	Definitely Related
CH-A2-110	2	Fatigue	General Disorders & Administration Site Conditions	Possibly Related	Definitely Related	Possibly Related
CH-A2-112	4	Neutropenia	Blood & Lymphatic System Disorders	Definitely Related	Definitely Related	Definitely Related
CH-A2-113	2	Fatigue	General Disorders & Administration Site Conditions	Possibly Related	Definitely Related	Possibly Related
CH-A2-114	4	Neutropenia	Blood & Lymphatic System Disorders	Probably Related	Probably Related	Probably Related
CH-A2-115	3	Hypertension	Vascular disorders	Definitely Not Related	Probably Related	Probably Not Related
CH-A2-116	3	Sepsis	Infections & Infestations	Probably Related	Definitely Related	Probably Related
CH-A2-116	3	Dehydration	Metabolism & Nutrition Disorders	Possibly Related	Definitely Related	Possibly Related
CH-A2-116	3	Vomiting	Gastrointestinal Disorders	Possibly Related	Definitely Related	Possibly Related
CH-A2-117	3	Blood alkaline phosphatase increased	Investigations	Definitely Not Related	Definitely Not Related	Definitely Not Related
CH-A2-118	3	Embolism	Vascular disorders	Possibly Related	Possibly Related	Possibly Related
CH-A2-118	3	Hypophosphataemia	Metabolism & Nutrition Disorders	Definitely Not Related	Definitely Not Related	Definitely Not Related
CH-A2-118	3	Hypophosphataemia	Metabolism & Nutrition Disorders	Definitely Not Related	Definitely Not Related	Definitely Not Related

Subject	Grade	Description	Organ Class	M6620 Causality	Cisplatin Causality	Capecitabine Causality
CH-A2-118	3	Hypophosphataemia	Metabolism & Nutrition Disorders	Definitely Not Related	Definitely Not Related	Definitely Not Related
CH-A2-119	3	Neutropenia	Blood & Lymphatic System Disorders	Probably Related	Probably Related	Probably Related
CH-A2-119	3	Neutropenia	Blood & Lymphatic System Disorders	Possibly Related	Definitely Related	Possibly Related
CH-A2-120	2	Platelet count decreased	Investigations	Possibly Related	Probably Related	Probably Related
CH-A2-120	2	Neutrophil count decreased	Investigations	Possibly Related	Possibly Related	Possibly Related

7.8 Appendix – Protocol

Attached overleaf is the combined CHARIOT Trial Protocol.

7.9 Appendix – Statistical Analysis Plan

Attached overleaf is the combined CHARIOT Statistical Analysis Plan.

7.10 Appendix – Statistical Analysis Plan Appendix

Attached overleaf is the appendix for the CHARIOT combined Statistical Analysis Plan, detailing the simulation results.

Full title: A phase I dose escalation safety study combining the ATR inhibitor M6620 (Berzosertib) with chemoradiotherapy in oesophageal cancer & other solid cancers using time to event continual reassessment method

Short title: M6620 (Berzosertib) plus standard treatment in oesophageal and other cancer

Protocol Version & date:	CHARIOT_Protocol_V5.0_26Oct2020
Protocol Number:	OCTO_072
EudraCT Number:	2015-003965-27
IRAS Project ID:	190687
Ethics Number:	16/SC/0395

Sponsor:	University of Oxford
Funders:	CRUK Grant Ref: C43735/A20874 Merck KGaA, Darmstadt Germany
Conflict of Interest statement	None of the protocol authors have declared a potential conflict of interest
Confidentiality Statement	This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Trial Office, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee unless authorised to do so.

Key trial contacts

Chief Investigator

Professor Maria A. Hawkins
Medical Physics and Biomedical Engineering
Malet Place Engineering Building
University College London
Gower Street
London, WC1E 6BT
Email: m.hawkins@ucl.ac.uk

Co-Investigators

Dr Somnath Mukherjee
Consultant Clinical Oncologist
Oxford University Hospitals NHS Trust
Cancer and Haematology Centre
Churchill Hospital
Old Road, Oxford, OX3 7LE
Email: somnath.mukherjee@oncology.ox.ac.uk

Dr Simon Lord
Consultant in Medical Oncology & Senior Clinical Researcher in Experimental Cancer Therapeutics
Department of Oncology
University of Oxford, Old Road Campus Research Building
Off Roosevelt Drive, Oxford, OX3 7DQ
Email: simon.lord@oncology.ox.ac.uk

Prof Tim Maughan
Dr Ester Hammond
Dr Ganesh Radhakrishna
Dr David McIntosh
Dr. Paul Shaw

Oncology Clinical Trial Office (OCTO)

CHARIOT Trial
Oncology Clinical Trials Office (OCTO)
Department of Oncology, The University of Oxford
Old Road Campus Research Building
Oxford OX3 7DQ, UK
Tel: +44 (0)1865 617084
Email: octo-chariot@oncology.ox.ac.uk
Website: http://www.oncology.ox.ac.uk/trial/chariot

Sponsor

University of Oxford Clinical Trials and Research Governance Team
Joint Research Office,
1st Floor, Boundary Brook House
Churchill Drive
Headington
Oxford, OX3 7GB
Email: CTRG@admin.ox.ac.uk

Lead NHS Trust

R&D Department, Oxford University Hospitals NHS Trust
Second Floor, OUH Cowley
Unipart House Business Centre
Garsington Road
Oxford OX4 2PG
E-mail: ouhtma@nhs.net

Statistician	Jane Holmes, Medical Statistician Centre for Statistics in Medicine Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences The University of Oxford Windmill Road Oxford OX3 7LD Tel : 01865 223452 Email: jane.holmes@csm.ox.ac.uk AlexAlexander Ooms, Medical Statistician Centre for Statistics in Medicine Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences The University of Oxford Windmill Road Oxford OX3 7L Tel: 01865 223453 Email: alexalexander.ooms@csm.ox.ac.uk

Trial oversight is provided by the Radiotherapy and Imaging Oversight Committee (RIOC).

RIOC Chairman	Prof Peter Hoskin

Clinical Queries

During office hours: Clinical Queries should be directed to OCTO Trial Manager (details as above) for action.

Out of office hours: Call the Churchill Hospital switchboard on Tel: **01865 741166.** The switchboard team hold emergency contact details for the trial.

Patient Registration: To register a patient on the trial please **scan and email as a PDF attachment the registration form to octo-CHARIOT@oncology.ox.ac.uk**

Protocol Authors and conflict of interest statement

Eleni Frangou[*3]
Claire Brooks[*1]
Maria Hawkins[*1]
Jane Holmes[*3]
Stephanie Levy [*1]
Naomi McGregor[*1]
Alex Ooms[*3]
Usharani Wahengbam[*1]

*There are no relationships/conditions/circumstances that present an actual or potential conflict of interest
[1]University of Oxford, Department of Oncology
[2]Oxford University NHS Trust
[3]University of Oxford, Centre for Statistics in Medicine

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

Full Title of study:	A phase I dose escalation safety study combining the ATR inhibitor M6620 (Berzosertib) with chemoradiotherapy in oesophageal cancer & other solid cancers using time to event continual reassessment method	
Short Title:	M6620 (Berzosertib) plus standard treatment in oesophageal and other cancer	
Trial Acronym:	CHARIOT	
Clinical Phase:	Phase I	
Study Design:	Interventional	
Stage A1	**Objectives**	**Endpoints/ Outcome Measures**
Primary:	To determine the best tolerated M6620 (Berzosertib) treatment schedule (or phase II recommended dose (RPTD)) administered concomitantly with radiotherapy (RT) only in the palliative treatment of oesophageal cancer	Highest treatment schedule resulting in less than 25% dose limiting toxicity (DLT) rate (see section 9.1.2 for DLT definitions)
Secondary:	• To determine the safety and toxicity profile of M6620 (Berzosertib) administered concomitantly with RT only in the palliative treatment of oesophageal cancer • To determine if M6620 (Berzosertib) can be delivered in combination with palliative RT • Efficacy of the combination	• Any toxicity grade ≥3 graded according to CTCAE v4.03 and length of time for toxicity to resolve • Proportion of patients completing at least 75%, 90% and 100% of the planned RT dose • Objective tumour response (OR) as evaluated by CT scan and quantified by Response Criteria Evaluation (RECIST 1.1) & PFS and OS from D1 • In field radiotherapy control
Tertiary:	• Explore tumour characteristics associated with response	• Genotyping of tumours
Stage A2	**Objectives**	**Endpoints/ Outcome Measures**
Primary:	To determine the best tolerated M6620 (Berzosertib) treatment schedule (or phase II recommended dose (RPTD)) administered concomitantly with chemotherapy (Cisplatin and Capecitabine) only in the palliative treatment of solid cancer	Highest treatment schedule resulting in less than 30% dose limiting toxicity (DLT) rate (see section 9.1.2 for DLT definitions)
Secondary:	• To determine the safety and toxicity profile of M6620 (Berzosertib) administered concomitantly with chemotherapy (Cisplatin and Capecitabine) only in the palliative treatment of solid cancer • To determine if M6620 (Berzosertib) can be delivered in combination with palliative chemotherapy • Efficacy of the combination	• Any toxicity grade ≥3 graded according to CTCAE v4.03 and length of time for toxicity to resolve • Proportion of patients completing at least 75%, 90% and 100% of the planned dose • Objective tumour response (OR) as evaluated by CT scan and quantified by Response Criteria Evaluation (RECIST 1.1) & PFS and OS from D1
Stage B	**Objectives**	**Endpoints/ Outcome Measures**
Primary:	To determine the best tolerated M6620 (Berzosertib) treatment schedule (or phase II recommended dose (RPTD)) administered concomitantly with radiotherapy (dCRT) in combination with	Highest treatment schedule resulting in less than 45% dose limiting toxicity (DLT) rate (see section 9.1.2 for DLT definitions)

	cisplatin and capecitabine in the radical treatment of oesophageal cancer	
Secondary:	• To determine the safety and toxicity profile of M6620 (Berzosertib) administered concomitantly with dCRT in combination with cisplatin and capecitabine in the radical treatment of oesophageal cancer • To determine tolerance and ability to deliver M6620 (Berzosertib) in combination with standard dCRT • Efficacy and safety of the combination	• Any toxicity grade ≥3 graded according to CTCAE v4.03 and length of time for toxicity to resolve • Treatment tolerance and deliverability measured by proportion of patients completing at least 80% of the planned chemotherapy dose and at least 20 fractions of RT • Objective tumour response (OR) as evaluated by CT scan and quantified by Response Criteria Evaluation (RECIST 1.1) and endoscopic and biopsy findings & PFS and OS from D1
Tertiary	To explore target effects in tissue	• Change in level of ATR inhibition and apoptosis in M6620 (Berzosertib) treated tissue using IHC. • Genotyping of tumours • Aim to identify markers for oesophageal cancer in the blood
Planned enrolment:	Stage A1: Maximum 20 participants Stage A2: Maximum 20 participants Stage B: Maximum 25 participants	
Target Population:	Stage A1: Oesophageal tumours for palliative radiotherapy Stage A2: Metastatic or advanced inoperable solid tumours for chemotherapy Stage B: Oesophageal tumours for radical chemoradiotherapy	
	Name of drug	**Formulation, dose, route of administration**
Investigational Medicinal Product(s)	M6620 (Berzosertib)	Solution for infusion, 90 – 240 mg/m^2
	Cisplatin	Solution for infusion, 60 mg/m^2
	Capecitabine	Tablet, 625mg/m^2 bd, oral
Other interventions:	Stage A1: Palliative radiotherapy Stage B: Definitive radiotherapy	
Treatment Duration	Stage A1: 3 weeks Stage A2: maximum 18 weeks Stage B: 11 weeks	
Follow-up duration (last study visit from start of treatment)	Stage A1: 12 weeks Stage A2: maximum 26 weeks Stage B: 24 weeks Participants will be followed up through their medical records at 6 and 12 months for Stage A1 & A2	
End of study	For the purpose of the Research Ethics Committee approval the trial end date will be the Last Patient start of treatment for Stage B plus 24 weeks.	

SUMMARY SCHEDULE OF EVENTS STAGE A1

			Week 1							Week 2							Week 3							Week 4[9]	Week 9	Week 12
Study Day	Screening	Post Registration	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	Follow up[8]		
			M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S			
Informed Consent	X																									
Screening assessments[1]	X																									
M6620 (Berzosertib) schedule assignment		X																								
Radiotherapy planning	X																									
Radiotherapy (35GY in 15#)			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X					
M6620 (Berzosertib)				X			X[2]				X			X[2]				X			X[3]					
Haematology/Biochemistry[4]	X		X			X[2]				X			X[2]				X			X[3]				X		
Coagulation	X		X																					X		
DLT assessment[5]						X				X			X[2]				X			X[3]				X	X	
AE assessment[5]			X			X				X			X[2]				X			X[3]				X	X	X
Concurrent medications[5]	X		X			X				X			X[2]				X			X[3]				X	X	X
Physical exam[5]	X		X			X				X			X[2]				X			X[3]				X	X	X
Weight[5]	X		X							X							X							X	X	X
ECG performance status	X		X			X[2]				X			X[2]				X			X[3]				X	X	X
ECG[6]	X		X																					X		X
Vital signs	X		X[7]																							
CT chest abdomen pelvis	X[8]																									X[10]
Collection of archival biopsy																										X[11]

[1] Screening assessments including: pregnancy test (to be repeated for WOCBP 4 weekly during treatment), height and medical history, see section 5.3
[2] Dose schedules -2, -1, 2, 3, 5 & 6 only
[3] Dose schedules -1, 3 & 6 only
[4] Screening and within 24 hours prior to dosing with M6620 (Berzosertib): Haemoglobin, ANC, lymphocytes, WBC, Platelets, Bilirubin, ALP, AST or ALT, urea, Serum creatinine, eGFR, K^+, Na^+
[5] +/- 24 hours, must be prior to dosing with M6620 (Berzosertib); day 4 all patients (excluding weight day 4)
[6] ECG to be carried out at screening, baseline (pre-M6620 (Berzosertib)) week 4 and week 12 and if clinically indicated on treatment
[7] Per clinical requirement
[8] Screening CT only needs to be done if diagnostic CT carried out > 42 days prior to start of treatment
[9] Week 4 follow-up should be 1 week after last dose/fraction (+7 days)
[10] CT Scan can be done up to 7 days prior to the Week 12 visit
[11] Optional

SUMMARY SCHEDULE OF EVENTS STAGE A2

			Cycle 1*			Cycle 2			Cycle 3			Cycle 4			Cycles 5-6[10]	Follow up[11]	
	Screening	Post Registration	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12		2 weeks post EOT	8 weeks post EOT
Informed Consent	X														Repeat assessments done for cycles 3-4 in cycles 5-6 (if applicable)		
Screening assessments[1]	X																
M6620 (Berzosertib) schedule assignment		X															
Capecitabine[2]			X	X	X	X	X	X	X	X	X	X	X	X			
Cisplatin[3]			X[3]			X[3]			X[3]			X[3]					
M6620 (Berzosertib)[4]			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]			
Haematology/Biochemistry[5]	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Coagulation	X		X													X	
ECOG performance status[6]	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Physical Exam[6]	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Weight[6]	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Vital signs	X		X[8]														
ECG[7]	X		X			X			X			X					
Audiogram monitoring[13]		X				X											
Concurrent medications[6]	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
DLT Assessment[6]			X	X	X	X											
AE Assessment[6]			X	X	X	X	X	X	X	X	X	X	X	X		X	X
CT chest abdomen pelvis[9]	X							X						X			X

[1] Screening assessments including: pregnancy test (to be repeated for WOCBP 4 weekly during treatment), height and medical history, see section 5.3

[2] Capecitabine taken bd weeks 1 to 18

[3] Cisplatin given on day 1 (Mon)

[4] M6620 (Berzosertib) given on day 2 only (Tues) dose schedules 1 & 3; M6620 (Berzosertib) given on day 2 & day 5 (Tues/Fri) dose schedules 2 & 4

[5] Check Haem/Biochem within 72 hours prior to cisplatin and 24 hours preceding M6620 (Berzosertib) (only one sample needs to be taken if it satisfies both Cisplatin and M6620 (Berzosertib) requirements): Hb, ANC, lymphocytes, WBC, Platelets, Bilirubin, ALP, AST or ALT, Serum creatinine, Urea, K^+, Na^+, eGFR, Ca, Mg, Phosphate
M6620 (Berzosertib)M6620 (Berzosertib)[6] Assessment done within 24 hours prior to M6620 (Berzosertib) dosing (weight once weekly)

[7] ECG to be carried out at screening, pre-treatment and once per cycle

[8] Per clinical requirement

[9] CT chest abdomen pelvis in weeks 6, 12, 18 and at 8 weeks post EOT. Screening CT only needs to be done if staging CT was carried out > 35 days prior to start of treatment.

[10] Patients can continue with treatment after 4 cycles if CT shows no progression and at the discretion of the PI.

[11] Two week follow-up should be 2 weeks after last dose (+/-7 days); 8 week follow-up should be 8 weeks after last dose (+/- 2 weeks)

[12] If required. *Each cycle lasts 3 weeks

SUMMARY SCHEDULE OF EVENTS STAGE B

			Cycle 1*			Cycle 2			Cycle 3																	Cycle 4										Follow up		
									Week 7					Week 8					Week 9					Week 10					Week 11									
	Screening	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	1	2	3	4	5	8	9	10	11	12	15	16	17	18	19	22	23	24	25	26	29	30	31	32	33	Week 12[13]	Week 18	Week 24
									M	T	W	Th	F	M	T	W	Th	F	M	T	W	Th	F	M	T	W	Th	F	M	T	W	Th	F			
Informed Consent	X																																			
Screening assessments[1]	X																																			
M6620 (Berzosertib) schedule assignment								X																												
Radiotherapy planning				X																																
IMRT (50GY in 25#)									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Capecitabine[2]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Cisplatin (Day 1)			D1			D1			X															X												
M6620 (Berzosertib) (Day 2)			D2			D2				X[4]			X[5]		X			X[6]		X			X[8]		X			X[5]		X			X[7]			
Haematology/Biochemistry[3]	X		X			X			X			X[5]		X			X[6]		X			X[8]		X			X[5]		X			X[7]		X	X	
Coagulation	X		X																															X		
ECOG performance status	X		X	X		X	X		X			X[5]		X			X[6]		X			X[8]		X			X[5]		X			X[7]		X	X	X
Physical Exam[9]	X		X	X		X	X		X			X[5]		X			X[6]		X			X[8]		X			X[5]		X			X[7]		X	X	X
Weight[9]	X		X			X			X					X					X					X					X					X	X	X
Vital signs[9]	X		X	X		X	X		X			X[5]		X			X[6]		X			X[8]		X			X[5]		X			X[7]		X	X	X
ECG[10]	X		X			X			X															X												X
Audiogram monitoring[14]		X				X																														
Concurrent medications[9]	X		X	X		X	X		X			X[5]		X			X[6]		X			X[8]		X			X[5]		X			X[7]		X	X	X
DLT Assessment[9]				X		X	X		X			X[5]		X			X[6]		X			X[8]		X			X[5]		X			X[7]		X	X	X
AE Assessment[9]			X	X		X	X		X			X[5]		X			X[6]		X			X[8]		X			X[5]		X			X[7]		X	X	X
Mellow Score[9]			X	X		X	X		X			X[5]		X			X[6]		X			X[8]		X			X[5]		X			X[7]		X	X	X
Research blood sample		X										X[11]																						X		
Research biopsy												X[11]																								X
CT	X[12]																																			X

[1] Screening assessments including: pregnancy test (to be repeated for WOCBP 4 weekly during treatment), height, medical history, Echo/MUGA and Lung function test, see section 5.3

[2] Capecitabine taken bd weeks 1 to 6; capecitabine taken bd Mon to Fri weeks 7 to 11

[3] Check Haem/Biochem within 72 hours prior to cisplatin and 24 hours preceding M6620 (Berzosertib) (only one sample needs to be taken if it satisfies both Cisplatin and M6620 (Berzosertib) requirements): Hb, ANC, lymphocytes, WBC, Platelets, Bilirubin, ALP, AST or ALT, Serum creatinine, Urea, K^+, Na^+, eGFR, Ca, Mg, Phosphate

[4] Except schedule 1 [5] M6620 (Berzosertib) schedules 3, 4, 5 & 6 only [6] M6620 (Berzosertib) schedules 4, 5 & 6 only [7] M6620 (Berzosertib) schedules 5 & 6 only [8] M6620 (Berzosertib) schedule 6 only

[9] Assessment done within 24 hours prior to M6620 (Berzosertib) dosing; and in weeks 2 & 5 of induction chemotherapy on day 1 or day 2 (excluding weight weeks 2 & 5)

[10] ECG in cycle 1 to be carried out pre-treatment

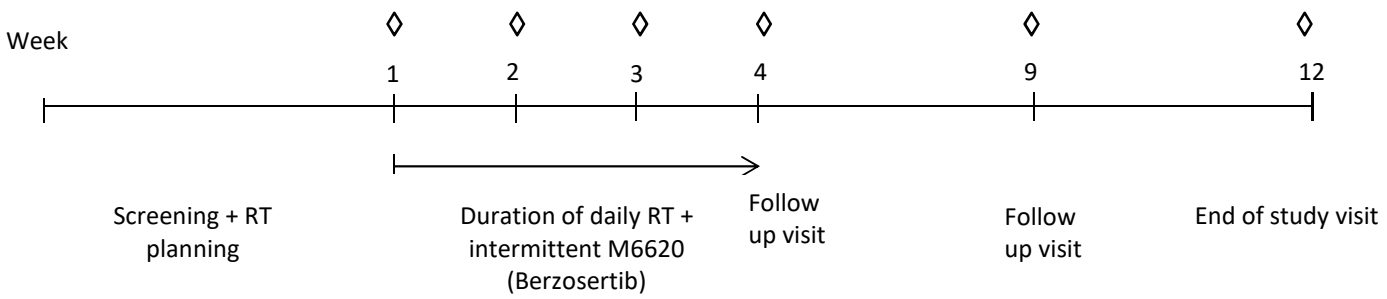
[11] On treatment biopsy/blood sample should be done from radiotherapy fraction 3 to fraction 5 (but up to fraction 7 is permitted if required)

[12] Screening CT only needs to be done if diagnostic CT carried out > 42 days prior to start of treatment

[13] Week 12 follow up to be done one week after last dose/fraction (+7 days) [14]If required. *Each cycle lasts 3 weeks

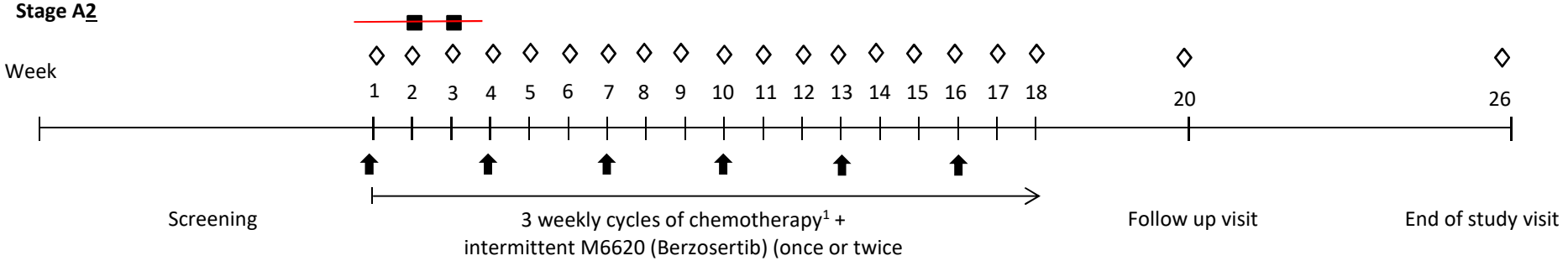
Study Flow Charts

Stage A1



◊ Clinical review and assessment of toxicity before each M6620 (Berzosertib) administration, and at follow up

Stage A2

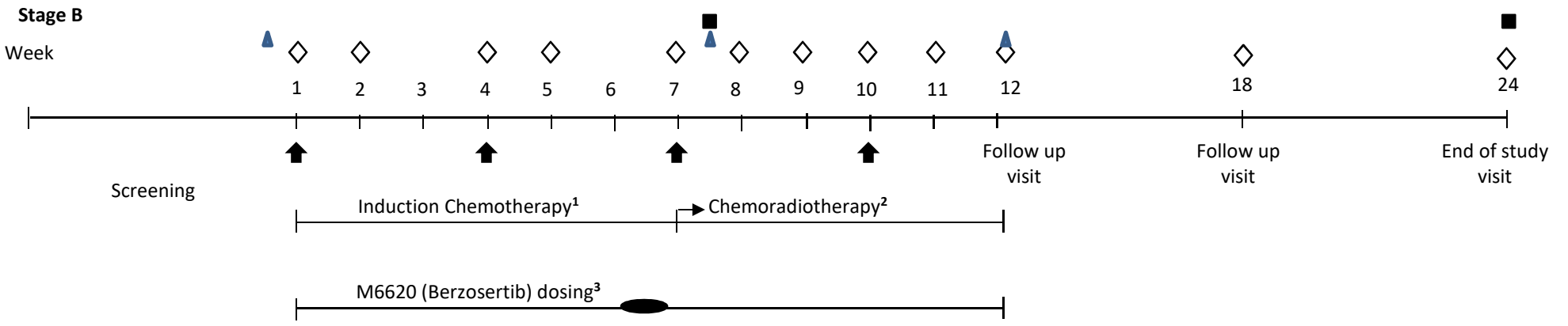


◊ Clinical review and assessment of toxicity before each M6620 (Berzosertib) administration, and

⬆ Cisplatin IV infusion

■

[1] Daily Capecitabine; Cisplatin on day 1 of 21 day cycle



Treatment

[1] Daily Capecitabine; Cisplatin on day 1 of 21 day cycle

[2] Capecitabine (Mon to Fri) and RT (Mon to Fri) for 5 weeks; Cisplatin continues on day 1 of 21 day cycle

[3] On day 2 of 21 day cycle during induction chemotherapy. Assignment of intermittent schedule in week 6 and commencement of intermittent schedule in week 7

ABBREVIATIONS

4DCT	4D computed tomography
4DCECT	4D contrast enhanced computed tomography
ACA	Adenocarcinoma
AE	Adverse Event
BOI	Beginning of infusion
CR	Complete Response
CRT	Chemoradiotherapy
D	Day
dCRT	Definitive Chemoradiotherapy
DLT	Dose Limiting Toxicity
EOI	End of infusion
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
GTV	Gross Tumour Volume
IB	Investigator Brochure
ICRU 62	International Commission on Radiation Units Report 62
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IMRT	Intensity-Modulated Radiation Therapy
mOS	Mean Overall Survival
MA	Marketing Authorisation
MTD	Maximum Tolerated Dose
OAC	Oesophageal Adenocarcinoma
OS	Overall Survival
PI	Principal Investigator
RSI	Reference Safety Information
RT	Radiotherapy
RTTQA	Radiotherapy Trials Quality Assurance
SAR	Serious Adverse Reaction
SCC	Squamous Cell Carcinoma
SmPC	Summary of Product Characteristics
LPLV	last visit of the last patient undergoing the trial
SUSAR	Suspected Unexpected Serious Adverse Drug Reaction
TiTE-CRM	Time to Event Continual Reassessment Method

1 INTRODUCTION

1.1 Background

Oesophageal cancer has been identified by CRUK as a cancer of unmet need, because of persistent low 5-year survival (13%) and lack of research in this disease. The incidence of oesophageal cancer has risen in recent decades, coinciding with a shift in histology and primary tumour location (www.cancerresearchuk.org/cancer-info/cancerstats/types/oesophagus/). In 2010, 8500 people were diagnosed with oesophageal cancer in the UK and in 2011 there were 7600 deaths, making it the 4th most common cause of death in males. In the UK it accounts for around 5% of all cancer deaths (Cancer Research UK, n.d.). Surgery has been the cornerstone of curative treatment of oesophageal adenocarcinoma (OAC) but is only appropriate for 10-20% of the patient population as at presentation the majority of patients are unsuitable for surgery and have locally advanced or metastatic disease irrespective of histologic type. Surgery for squamous cell carcinoma (SCC) is used less often; the proximal nature of the disease making reconstructive surgery more challenging and patients often being less fit as a result of co-existing cardio-pulmonary disease due to the common aetiology of the diseases.

Radical Setting

Definitive chemo-radiotherapy (dCRT) is usually offered to those patients who have non-metastatic oesophageal cancer who are unsuitable for surgery but this modality has been increasingly considered a standard of care for patients with operable SCC [15]. The recently reported SCOPE 1 trial, a CRUK-funded trial which investigated the addition of Cetuximab to standard cisplatin/fluoropyrimidine based dCRT [12], reported unprecedented good outcomes in the standard dCRT arm with a mOS of 25.4 mo and 2-yr OS of 56%. This study demonstrated that with a detailed protocol and a robust radiotherapy trials quality assurance (RTTQA) programme, high quality dCRT can be delivered throughout the UK and lead to outcomes equivalent to that seen in published surgical series. The dCRT outcome was comparable to surgical outcomes despite the patient population in this trial having a relatively poor prognosis. Unfortunately, other chemotherapy regimens have not shown an improved survival over the Cisplatin Fluorouracil combination. There was no increase in median PFS after Oxaliplatin and Fluorouracil (FOLFOX) dCRT when compared with Cisplatin Fluorouracil dCRT 9.7 months (95% CI 8.1–14.5) vs 9.4 months (8.1–10.6) or median OS 20.2 months (95% CI 14.7–25.6),vs 17.5 months (13.9–19.4) respectively[2] highlighting the need for better treatment in this patient group.

A recent study in oesophageal cancer reported patterns of failure after dCRT, assessed by FDG-PET scan in 239 patients [3]. With a median follow-up of 52.6 months, 119 patients (50%) had relapsed locally, 90% of which were within the Gross Tumour Volume (GTV). Having a failure within the GTV (as opposed to all other failure patterns plus patients without failure) influenced OS as well; the median OS time for patients with GTV failure was 23.3 months (95% CI, 20.00-31.32) versus 31.6 months for those with no GTV failure (95% CI, 24.31-not reached; p< .0009). A similar study by Button et al reviewed the patterns of relapse in 145 patients treated with dCRT [4]. Of the 85 (60%) patients who had evidence of relapse after a median on 18 months, 55 had relapse within the irradiated field, 13 relapsed with metastatic disease and 14 had a combination of local and distant disease. Another study assessed patterns of relapse in 274 patients treated in non-randomised trials by TROG between 1985 and 1999[5]. Local failure was observed in 42.3% and distant failure in isolation occurred in 18.1%. In the subgroup with least favourable survival, adenocarcinoma of the lower third of the oesophagus local failure rate (51.5%) dominated over distant failure (36.1%). Taken together, these studies suggest that both local and systemic failures are competing risk factors, and integrating a new agent with the standard dCRT schedule is most likely to succeed if this can enhance the activity of both cisplatin (systemic component) and radiotherapy (local component).

In SCOPE 1[1] patients who were failure free at 24 weeks (76% in the standard arm) had significantly better median overall survival than did those who were not failure free (26.7 mo [24.5–42.7]vs. 8.3 mo [95% CI 6.7–12.5] respectively. The RTOG 0436 study evaluated whether the addition of cetuximab to paclitaxel, cisplatin and RT improved overall survival in patients with oesophageal cancer who are treated without surgery [6]. The study (comparable to SCOPE1) failed to show that adding cetuximab improved survival. However, clinical assessments with endoscopy at 6-8 weeks after completion of therapy were undertaken in all evaluable patients and an analysis of responders (CR versus non CR) were predictive of survival HR=2.2(1.59-2.83) [6].

Palliative setting

dCRT treatment is toxic with a death rate of 2% due to significant life threatening toxicity. Cisplatin is nephrotoxic, and fluoropyrimidines can precipitate acute coronary syndrome therefore CRT is only offered to good performance status (PS) patients with adequate renal function and no significant ischaemic heart disease. Patients unsuitable for CRT may be treated with radiotherapy alone as a non-invasive means of palliating dysphagia and comprise around half of patients referred for RT based treatment.

TROG 03.01, a multinational phase III study in advanced oesophageal cancer (7) comparing palliation of dysphagia and quality of life in patients treated with radiotherapy or chemoradiotherapy (CMT) randomised 220 patients to receive a course of palliative RT [35 Gy in 15 fractions, (n=115) or 30 Gy in 10 fractions (n=105)], or concomitant CRT with Cisplatin and 5FU (D1-4) (n=111). The primary endpoint was the proportion of patients with improved dysphagia measured at week 9 and maintained until week 13. RT alone showed a dysphagia response (at any point) of 68% similar to CMT 74%, (p=0.343). The primary endpoint of dysphagia improvement was achieved in 41% with RT and 47% with CMT (p=0.4163). There was increased toxicity in patients receiving CMT, (nausea (p=0.0019) and vomiting (p=0.0072)). Median survival was 210 days for CRT, 203 days for RT. Although the results of the trial showed equally poor survival in both arms, there were some patients (n=21,

10%) still alive at 2 years post treatment indicating that this is a group of patients who should not be denied active cancer treatment.

Summary of design

This phase I study will test the combination of a novel ATR inhibitor (M6620 (Berzosertib)) with chemoradiotherapy in oesophageal cancer. In the first two cohorts (Stage A1 and A2), we will investigate the safety of combining M6620 (Berzosertib) separately with [1] palliative radiotherapy (RT) for oesophageal cancer (Stage A1) and [2] with cisplatin/capecitabine chemotherapy in patients with advanced inoperable and metastatic solid tumours (Stage A2). In Stage A1, M6620 (Berzosertib) will be given in combination with high dose palliative RT treatment, aiming to deliver M6620 (Berzosertib) twice weekly during RT escalating to a dose of 240mg/m^2. A palliative chemotherapy cohort (Stage A2) will open to recruitment simultaneously where M6620 (Berzosertib) will be given in combination with cisplatin/capecitabine chemotherapy, aiming to deliver M6620 (Berzosertib) twice weekly escalating to a dose of 140mg/m^2 twice weekly. When adequate toxicity and follow-up information to suggest the combinations are tolerable has accumulated, the ATR inhibitor will be tested in the definitive setting (Stage B) in combination with cisplatin/capecitabine and radical RT to identify the Maximum Tolerated Dose (MTD). The MTD found in this study will be taken forward in future phase II studies.

In the palliative setting, we aim to find the schedule associated with no more than 25% Dose Limiting Toxicities (DLTs) in stage A1 on the basis that palliative oesophageal radiotherapy causes approximately 20% grade 3 and 4 toxicity and 30% Dose Limiting Toxicities (DLTs) in stage A2 are derived from capecitabine/cisplatin used in the radical setting (SCOPE1 study [12]).

In the radical setting, we aim to find the schedule associated with no more than 45% DLTs on the basis that conventional oesophageal chemoradiation causes a grade 3 and 4 toxic event rate of 28% haematological toxicity and 63% non-haematological toxicity of which 34% is gastrointestinal as reported in the standard arm of SCOPE1 study (12). Comparable toxicity rates were described in the standard arm of the PRODIGE5/ACCORD17 study (13): grade 3 and 4 neutropenia 29% and grade 3 and 4 dysphagia and oesophagitis 33%.

The trial will find the best optimal dose and dosing schedule using the TiTE-CRM (Time To Event Continual Reassessment Method). The CRM is a model based method for finding the MTD. It assumes that toxicity increases monotonically with increasing dose, and that efficacy also increases with increasing dose. The aim will be to find the dose that causes a DLT with the above specified target toxicity levels. TiTE-CRM is a modified CRM that accounts for the time to event of late onset toxicities. The advantages of a TiTE-CRM are that all current critical toxicity summaries are used when deciding which dose to give the next patient and it is not necessary for a patient to complete the full observation period before consenting the next patient. This results in a better estimation of the MTD and shorter study duration respectively.

1.2 Investigational Medicinal Product(s) used in the study

M6620 (Berzosertib)

M6620 (Berzosertib) is an unlicensed small molecule ATR inhibitor which can be used in combination with DNA damaging agents. In pre-clinical models it has substantial activity when given with DNA damaging drugs or ionising radiation. The clinical agent (M6620 (Berzosertib)) is currently studied in a phase I trial in Oxford and other centres in combination with gemcitabine, cisplatin, gemcitabine/cisplatin and cisplatin/etoposide (see section 1.4)

Cisplatin

Cisplatin is a platinum based chemotherapy drug licensed to treat a number of different types of cancer (see SmPC for more details).

Capecitabine

Capecitabine is a chemotherapy drug licensed to treat a number of different types of cancer, it is a non-cytotoxic pre-cursor of the cytotoxic 5-fluourouracil (see SmPC for more details).

1.3 Pre-clinical rationale

DNA damaging agents (e.g. cisplatin and RT) are key treatments for many solid tumours including oesophageal cancer. Tumours can be resistant to current DNA-damaging based therapies due to the existence of an effective DNA Damage Response (DDR). The DDR consists of a series of molecular events that allow repair of damaged DNA and promote cell survival. ATM (Ataxia Telangiectasia Mutated) and ATR (ATM-and Rad3-related), members of phosphoinositol3-kinase like kinase family (PIKKs), are key components of the DDR. During normal DNA replication, ATR is recruited to stalled replication forks (replication stress) that can progress to DNA double strand breaks if unprotected. The recruitment and activation of ATR leads to cell cycle arrest in S phase whilst DNA is repaired; otherwise nuclear fragmentation occurs and apoptosis is initiated. Therefore, blocking ATR in an environment where replication stress is elevated as a result of treatment with radiotherapy or chemotherapy should improve killing of cancer cells. Consistently, it has been demonstrated that radiation and Cisplatin are more efficacious in tumour cells where kinase dead ATR has been expressed (1, 2).

M6620 (Berzosertib) is a potent inhibitor of ATR (inhibition constant [Ki] <300 pM) that blocks ATR activity in cells, with a concentration resulting in 50% maximal inhibition (IC_{50}) of 20 nM. ATR inhibition enhances the cytotoxic effect of DNA damaging drugs and IR in many cancer cell lines and primary human tumors. In contrast, normal cells tolerate ATR inhibition since they can activate compensatory DDR signaling via the ATM pathway. In xenograft models, M6620 (Berzosertib) markedly enhances the anticancer activity of numerous DNA damaging drugs and IR, often substantially delaying or completely halting tumor progression and promoting tumor regression. Dose range finding studies in mice (with gemcitabine and cisplatin) showed that maximal activity was observed when M6620 (Berzosertib) was administered intravenously at a dose of 20 mg/kg/week, given as a single dose or as two 10-mg/kg doses 3 days apart. Dose-responsive biomarker effects, which correlate with efficacy, support ATR inhibition as the primary mechanism of action.[1]

Consistent with the compensatory role the ATM/p53 pathway plays in response to ATR inhibition in normal cells, defects in this pathway result in increased cell sensitivity to ATR inhibition. In isogenic cell studies it has been shown that loss of ATM itself or one of its principle substrates, p53, can markedly increase cell sensitivity to ATR inhibition. Similarly, in a large panel of 119 genetically-diverse cancer cell lines, *TP53* mutational status was shown to correlate with response to ATR inhibition in combination with DNA damaging agents.

Pires *et al* (10) showed that VE-821 also inhibited ATR-mediated signalling in response to the replication arrest induced by severe hypoxia and that ATR inhibition consistently sensitised tumour cell lines to radiation across a range of oxygen tensions. In addition, it was shown for the first time that treatment with the ATR inhibitor led to a decrease in HIF-1-mediated signalling, suggesting that it could also inhibit the biological consequences of tumour hypoxia such as increased invasion, metastasis and angiogenesis.

Fokas *et al* (11) demonstrated radio-sensitisation and chemosensitisation to gemcitabine using the ATR inhibitor VE-822 in p53 and KRAS mutant pancreatic ductal adenocarcinoma (PDAC) *in vitro* and *in vivo* (VE-822 is another pre-clinical ATR inhibitor chemically identical to M6620 (Berzosertib)). The selectivity of VE-822 was initially demonstrated through selective reduction in CHK1 phosphorylation without inhibition of ATM or DNA-PK signalling pathways. In xenograft experiments, the activity was profound, to the extent that the combination of RT with VE-822 prevented MiaPaCa-2 tumour regrowth in some mice. Importantly, VE-822 did not increase normal cell radiosensitivity and chemosensitivity *in vitro*, similar to the VE-821 studies described previously.

ATR inhibition has not been previously tested specifically on oesophageal cancer cell lines or xenografts. We have recently demonstrated chemosensitisation (cisplatin) and radiosensitisation of ACA and SCC cell lines using VE-822. These data show that the addition of the ATR inhibitor (VE-822) increases sensitivity to radiation as well as cisplatin in 3 oesophageal cell lines (OE21, FLO-1 and OE33) both under normoxic and hypoxic conditions (<0.1% O_2) (Hammond, unpublished data).

1.4 Clinical rationale

There is strong scientific rationale for combining ATR inhibitors with DNA damaging agents such as radiation and cisplatin. In particular, ATR inhibition has been shown to be cytotoxic to tumour cells with an impaired DNA damage response (DDR), such as those with deficiency in the ATM- or p53 pathway [7]. The high incidence of p53 mutations (~89.9% in SCC of the oesophagus and ~72% in ACA) [8, 9] and the fact that cisplatin and radiation are key therapeutics, makes oesophageal cancer an attractive tumour type to test the activity of an ATR inhibitor [8-10]. Given the reported synthetic lethal relationship between ATM and ATR, it is likely that ATR inhibition in

an ATM- or p53- deficient background will offer a specific and effective way of targeting OAC and SCC of the oesophagus, and enhance the current standard of care.

The in vitro and in vivo studies mentioned above, have shown that M6620 (Berzosertib) can enhance sensitivity of cancer cells to chemotherapy and radiotherapy without enhancing radiosensitivity in normal tissue [7, 11]. This tumour selectivity suggests there will be little or no enhancement of radiation toxicity and therefore, is likely to allow delivery of full doses of chemotherapy and radiotherapy. In contrast, recently reported studies in gastro-oesophageal cancer, toxicity due to addition of novel agents resulted in reduction of dose intensity of standard treatment and inferior survival in the experimental arms[1, 12] underlining the importance of this lack of toxicity in normal tissues.

In an ongoing study (VX12-970-001), M6620 (Berzosertib) is being dosed in combination gemcitabine and in combination with cisplatin to determine the MTD of M6620 (Berzosertib) in combination with these agents. To date, 140 mg/m2 of M6620 (Berzosertib) in combination with 75 mg/m2 of cisplatin was tolerated. Also, 210 mg/m2 of M6620 (Berzosertib) in combination with 1000 mg/m2 of gemcitabine was tolerated and is the recommended phase II dose. In another ongoing study (VX13-970-002), M6620 (Berzosertib) at 90 mg/m2 in combination with AUC 5 of carboplatin was tolerated. Also, evaluation of on-target tumor biopsies at these doses demonstrated target engagement as measured by ATR-mediated phosphorylation of Chk1 (P-Chk1).

The trial will be divided into 2 stages, stage A and Stage B. Stage A will consist of 2 parts, part A1 will explore the combination of M6620 (Berzosertib) plus radiotherapy and Stage A2 will explore the combination of M6620 (Berzosertib) plus chemotherapy in the palliative setting. Stage B, will explore the combination of all 3, M6620 (Berzosertib) plus chemoradiotherapy in the radical setting. In Stage A1 of the study M6620 (Berzosertib) will be combined with radiotherapy for the first time and the starting dose will be 140mg/m^2 M6620 (Berzosertib), which has been well-tolerated. Intravenous (IV) administration was shown to be better tolerated than oral administration in dogs and will be used in the study. We have chosen to administer M6620 (Berzosertib) with daily palliative radiotherapy in Stage A1 to study specific interaction of M6620 (Berzosertib) with radiotherapy which is the DNA damaging agent at this stage. In Stage A2 of the study M6620 (Berzosertib) will be combined with Cisplatin and Capecitabine combination chemotherapy for the first time and the starting dose will be 90mg/m^2 M6620 (Berzosertib). We have chosen to administer M6620 (Berzosertib) after chemotherapy to explore possible additional interactions with cisplatin which binds with DNA to form intrastrand crosslinks and adducts that cause changes in the conformation of the DNA and affects DNA replication fluoropyrimidines whose primary mechanism of action is the inhibition of thymidylate synthase. Stage A1 and A2 will give an indication of toxicity profile before administration with radiotherapy, Capecitabine and Cisplatin during chemoradiotherapy. Data from the VERTEX study VX12-970-001 indicates maximum benefit from the chemotherapy and M6620 (Berzosertib) treatment combination comes with administration of M6620 (Berzosertib) between 14 and 36 hours post administration of DNA damaging agent (VERTEX, unpublished results). Therefore we propose to administer M6620 (Berzosertib) 24 hours post cisplatin infusion.

2 TRIAL DESIGN

This will be a single arm, open-label, phase I dose escalation trial using the Time-To-Event Continual Reassessment Method (TiTE-CRM) to find the optimal treatment schedule. The TiTE-CRM method uses critical toxicity summaries of accumulated patient data from all participants treated with at least one dose of the IMP within the corresponding trial stage and for whom up-to-date data has been provided (trial unit will endeavour to ensure contemporaneous data is received for all participants) and it is not necessary for a patient to complete the full observation period before consenting the next patient. This results in a better estimation of the MTD and shorter study duration respectively and is particularly useful in trials involving radiotherapy where the toxicity follow-up phase is longer.

The trial design ensures no treatment schedule skipping and the treatment schedule assigned will be that estimated to be closest to but not above the MTD. However, if the lowest schedule is estimated to be above the MTD we will keep assigning the lowest schedule until we are certain it is too toxic, at which point the trial may start again using a lower dose of drug. When escalating, the treatment schedule cannot skip an untried dose but there will be no restriction on treatment schedule de-escalation. Each escalation decision will be made by the TMG based on the recommendation from the TiTE-CRM model and the accumulated experience of the

recommended schedule. If the TMG is unable to reach a decision or a stopping rule has been met the Safety Review Committee (SRC) will meet.

The trial consists of three stages A1, A2 and B which are described in the following sections. Stages A1 and A2 will run concurrently and will inform the starting dose of M6620 (Berzosertib) for Stage B.

2.1 Stage A1

The aim is to find the M6620 (Berzosertib) treatment schedule when combined with radiotherapy that is associated with no more than 25% dose limiting toxicity rate on the basis that palliative oesophageal radiotherapy is associated with approximately 15-20% grade 3/4 toxicity. Six treatment schedules are proposed. Each schedule comprises a specific combination of dose and dosing frequency. There are two possible M6620 (Berzosertib) doses and three dosing frequencies (see section 8.1). The radiation dose remains consistent across all treatment schedules.

The treatment involves 3 weeks of daily radiotherapy and M6620 (Berzosertib) at a pre-determined frequency dependent on the treatment schedule allocated to the individual patient. The follow-up of a further 6 weeks provides a DLT observation window of a total of 9 weeks. An initial cohort of three patients will receive the starting schedule (lowest dosing frequency) at the starting dose, 140mg/m^2. The fourth patient will not be recruited until all three patients have been followed for the minimum of 9 weeks from the start of radiotherapy or the occurrence of a DLT.

Subsequently, all eligible patients will be continuously recruited and the TiTE-CRM will be used to assign their treatment schedule. To ensure enough information is accumulated to inform the assignment of the treatment schedule to the subsequent patient, recruitment will be managed through allocation of treatment slots (see section 4.4 for further details).

2.1.1. Stage A1 stopping rules

Stage A1 will pause for safety if, at any point in the trial, there is sufficient evidence to suggest that schedule 1 is too toxic. More specifically, we will consider schedule 1 to be too toxic if, given all the available data, there is a high probability that the DLT rate is greater than the target toxicity level of 0.25. If all 3 patients in the first cohort have DLTs then schedule 1 is too toxic and the trial will be re-started. At this point, three extra schedules will be introduced at 90mg/m^2 and varying dosing frequencies, namely (schedule -3, -2 and -1). Once the trial is restarted, the lowest schedule, schedule -3, will be explored first. There will then be 9 treatment schedules to explore (the original 6 plus the 3 dosing frequencies at the lower dose). If the first 3 patients recruited to schedule -3 experience DLTs then the trial will stop. If schedule 1 is found to be too toxic later in the trial when more than 3 patients have been recruited, a SRC meeting will be convened to decide whether the trial should be restarted using the lower dose of 90mg/m^2.

Stage A1 will stop for success when either a total of 10 patients have been assigned to a particular treatment schedule or 20 patients have been recruited, whichever occurs first. When 10 patients in Stage A1 have been assigned to a particular treatment schedule, recruitment will be paused until there are no more than three patients without full follow-up (either DLT or 6 weeks after the end of treatment), i.e. until there is full follow-up information on at least seven patients. If the MTD changes, recruitment may start again.

Based on simulations and assuming a patient will be recruited every 8 weeks, the average number of patients required for Stage A1 is 18, which we aim to recruit in 24 months.

2.2 Stage A2

The aim is to find the M6620 (Berzosertib) treatment schedule when combined with palliative combination chemotherapy (Cisplatin and Capecitabine) that is associated with no more than a 30% dose limiting toxicity rate. Four treatment schedules are proposed. Each schedule comprises a specific combination of dose and dosing frequency. There are two possible M6620 (Berzosertib) doses and two dosing frequencies (see section 8.2). Chemotherapy dose remains consistent across all treatment schedules.

The treatment involves six cycles of chemotherapy with three weekly Cisplatin and Capecitabine and M6620 (Berzosertib) at a pre-determined frequency dependent on the treatment schedule allocated to the individual patient. The follow-up of a further 8 weeks provides a total observation window of 26 weeks. DLT assessments will be carried out during the first 4 weeks of treatment. The MTD will be determined during this period using the TiTE-CRM. An initial cohort of three patients will receive the starting schedule (lowest dosing frequency) at the starting dose. The fourth patient will not be recruited until all three patients have been followed for a minimum of 4 weeks from the start of chemotherapy or until the occurrence of a DLT.
From the fourth patient, all eligible patients will be continuously recruited and the TiTE-CRM will be used to assign their treatment schedule. To ensure enough information is accumulated to inform the assignment of the treatment schedule to the subsequent patient, recruitment will be managed by allocating treatment slots (see section 4.4 for further details).

2.2.1. Stage A2 stopping rules

Stage A2 will stop for safety if, at any point in the trial, there is sufficient evidence to suggest that schedule 1 is too toxic. More specifically, we will consider schedule 1 to be too toxic if, given all the available data, there is a high probability that the DLT rate is greater than the target toxicity level of 0.3. If the first three patients recruited to Stage A2 have DLTs at treatment schedule 1, then the starting schedule (treatment schedule 1) will be deemed too toxic and the trial will stop.

The trial will stop for success when either six patients have been assigned to the fourth treatment schedule (140 mg/m2 of M6620 (Berzosertib) twice weekly) or 20 patients in total have been recruited, whichever occurs first. When six patients in Stage A2 have been assigned to the fourth treatment schedule, recruitment to Stage A2 will be paused until there is full DLT follow-up information on at least five patients. If the MTD has changed, recruitment to Stage A2 may start again.

Based on simulations and assuming a patient will be recruited every 3 weeks, the average number of patients required for Stage A2 is 16, which we aim to recruit in 12 months.

2.3 Stage B

The aim is to find the M6620 (Berzosertib) treatment schedule when combined with chemoradiotherapy that is associated with no more than 45% dose limiting toxicity rate on the basis that conventional oesophageal chemoradiation causes a grade 3 and 4 toxic event rate of 28% haematological toxicity and 63% non-haematological toxicity, of which 34% is gastrointestinal, as reported in the standard arm of the SCOPE1 study. Comparable toxicity rates were described in the standard arm of the PRODIGE5/ACCORD17 study: grade 3 and 4 neutropenia 29% and grade 3 and 4 dysphagia and oesophagitis 33% (13). A maximum of 25 patients will be recruited to Stage B.

There are three proposed M6620 (Berzosertib) treatment schedules (same dose but increasing dosing frequencies) to be explored during Stage B. Before each patient enters Stage B, a TMG will be held to confirm recruitment. If permitted to enrol in the study, the patient will also be assigned a provisional treatment schedule based on the TiTE-CRM's recommendation. If necessary, a confirmation meeting for the M6620 (Berzosertib) treatment schedule assignment will occur prior to the start of chemoradiotherapy 6 weeks after a patient is recruited. This will maximise the accumulation of information on each patient before deciding on the treatment schedule for the subsequent patient.

The dose of M6620 (Berzosertib) in Stage B will be 140mg/m^2, allocation will start on schedule 1, which is the middle of the 3 schedules. Recruitment will be continuous; however, escalation will not occur until at least one patient full DLT window of 24 weeks is complete. At this point escalation to schedule 2 will be possible if it is estimated to be safe, and dose decisions thereafter will be made once each new patient is recruited and confirmed (if there is reason to think their allocation may have changed) when they have been treated for 6 weeks (the induction period which is the same for all schedules). De-escalation to schedule -1 is possible at any point in the trial. Although recruitment will be continuous, the TMG retain the option to pause recruitment should they decide more follow-up data is needed before continuing. This may be, for example, to prevent too many patients being treated with a sub-optimal, or too toxic, schedule. No more than 7 patients will be treated on schedule 1 before there is full follow-up data on at least one patient.

We will recommend starting stage B:

- If 10 patients have been recruited to A1 and it has not restarted at the lower dose
- If 10 patients have been assigned to at least schedule 3 in A2 (i.e. are on any of the schedules with a dose of 140mg/m2) or the stopping rule is satisfied (6 treated on schedule 4)

If one of the above starting rules are satisfied then an SRC meeting will be convened to review the data and may recommend starting stage B.

2.3.1 Stage B stopping rules

Stage B will stop for safety if, at any point in the trial, there is sufficient evidence to suggest that schedule -1 is too toxic. More specifically, we will consider schedule -1 to be too toxic if, given all the available data, there is a high probability that the DLT rate is greater than the target toxicity level of 0.45. There will be no early stopping rules for success. We expect to recruit a minimum of 15 patients.

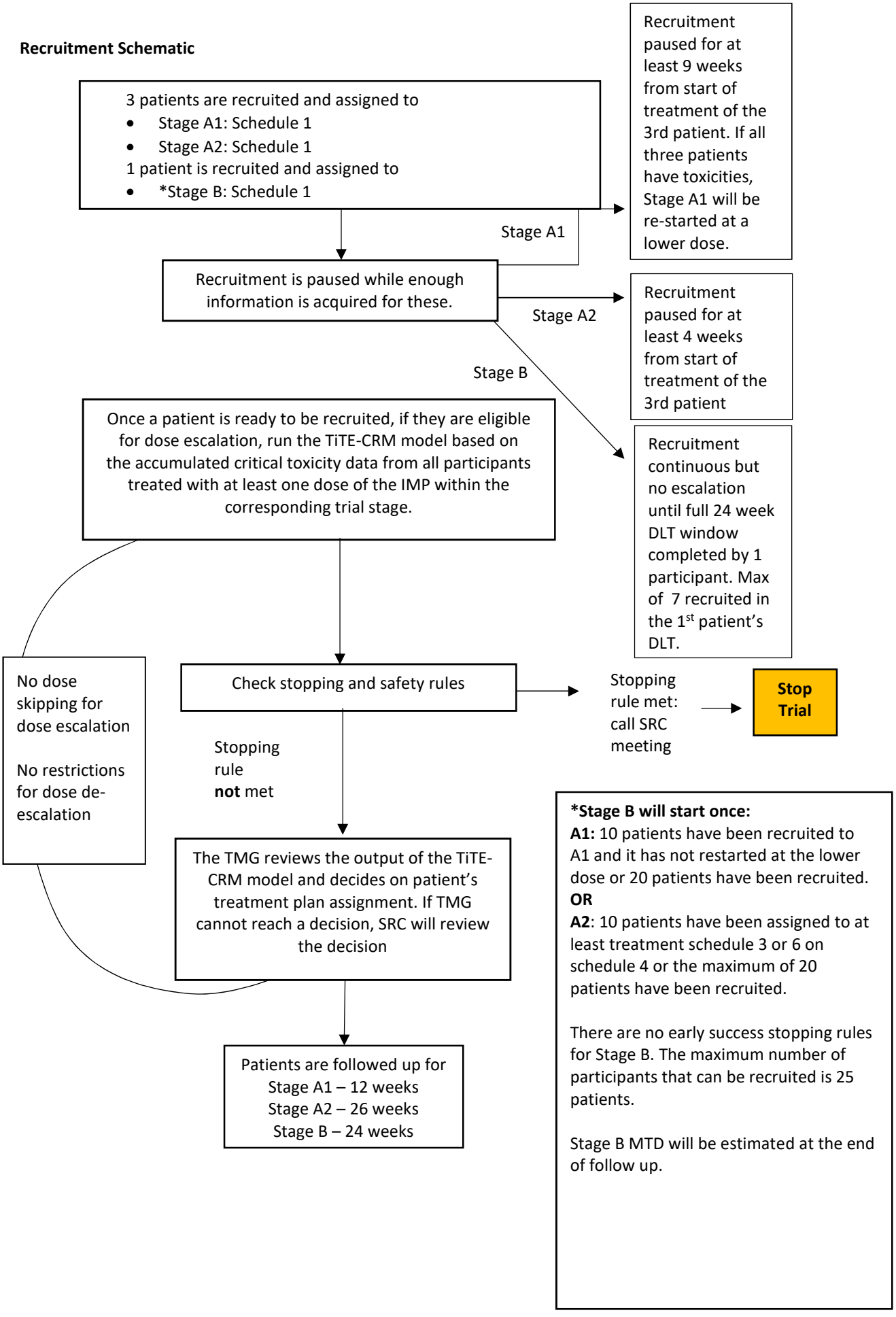
2.4 Duration of patient participation

Stage A1: Participants will be in the study for 12 weeks from first trial dose or intervention to last protocol visit.
Stage A2: Participants will be in the study for maximum of 26 weeks from first trial dose to last protocol visit.
Stage B: Participants will be in the study for 24 weeks from first trial dose or intervention to last protocol visit.

2.5 Post-trial care and follow-up

Following the end of study visit, patients will receive standard care. They may receive further chemotherapy if appropriate as per the standard practice of the clinical care team. Patients in Stage A1 & A2 will be followed for progression free survival, overall survival and late toxicity via routine medical oncology follow up clinics. The physician will be asked to provide these data at 6 and 12 months from the start of treatment for Stage A1 and Stage A2.

2.6 Recruitment Schematic



3 OBJECTIVES AND ENDPOINTS

3.1 Stage A

3.1.1 Stage A1

Primary Objective	Endpoints/ Outcome Measures	Time point(s) for evaluation of end point
• To determine the best tolerated M6620 (Berzosertib) treatment schedule (or phase II recommended dose (RPTD)) administered concomitantly with Radiotherapy only in the palliative treatment of oesophageal cancer	Highest treatment schedule resulting in less than 25% dose limiting toxicity (DLT) rate (see section 9.1.2 for DLT definitions)	• Week 9
Secondary Objectives	**Endpoints/ Outcome Measures**	
• To determine the safety and toxicity profile of M6620 (Berzosertib) administered concomitantly with RT only in the palliative treatment of oesophageal cancer	• Any toxicity grade ≥3 graded according to CTCAE v4.03 and length of time for toxicity to resolve	• During radiotherapy Weeks 1-3 • Week 4, 9 and week 12
• To determine if M6620 (Berzosertib) can be delivered in combination with palliative RT	• Proportion of patients completing at least 75%, 90% and 100% of the planned RT dose	• End of radiotherapy End of Week 3
• Efficacy of the combination	• Objective tumour response (OR) as evaluated by CT scan and quantified by Response Criteria Evaluation (RECIST 1.1) • PFS and OS from D1 • In field radiotherapy control	• 12 weeks • 6 and 12 months
Tertiary Objectives	**Endpoints/ Outcome Measures**	
• Explore tumour characteristics associated with response	• Genotyping of tumours	• Pre-trial archival biopsy

3.1.2 Stage A2

Primary Objective	Endpoints/ Outcome Measures	Time point(s) for evaluation of end point
• To determine the best tolerated M6620 (Berzosertib) treatment schedule (or phase II recommended dose (RPTD)) administered concomitantly with chemotherapy (Cisplatin and Capecitabine) only in the palliative treatment of solid cancer	• Highest treatment schedule resulting in less than 30% dose limiting toxicity (DLT) rate (see section 9.1.2 for DLT definitions)	• Week 4
Secondary Objectives	**Endpoints/ Outcome Measures**	
• To determine the safety and toxicity profile of M6620 (Berzosertib) administered concomitantly with	• Any toxicity grade ≥3 graded according to CTCAE v4.03 and	• During chemotherapy Week 1-18

chemotherapy (Cisplatin and Capecitabine) only in the palliative treatment of solid cancer	length of time for toxicity to resolve	• Week 20, 26
• To determine if M6620 (Berzosertib) can be delivered in combination with palliative chemotherapy	• Proportion of patients completing at least 75%, 90% and 100% of the planned dose	• End of chemotherapy Week 18
• Efficacy of the combination	• Objective tumour response (OR) as evaluated by CT scan and quantified by Response Criteria Evaluation (RECIST 1.1) • PFS and OS from D1	• Week 6, 12, 18, 26 • Week 26 & 12 months

3.2 Stage B

Primary Objective	**Endpoints/ Outcome measures**	**Time point(s) for evaluation of end point**
• To determine the best tolerated M6620 (Berzosertib) treatment schedule (or phase II recommended dose (RPTD)) administered concomitantly with radiotherapy (dCRT) in combination with cisplatin and capecitabine in the radical treatment of oesophageal cancer	Highest treatment schedule resulting in less than 45% dose limiting toxicity (DLT) rate (see section 9.1.2 for DLT definitions)	• Up to Week 24
Secondary Objectives	**Endpoints/ Outcome Measures**	
• To determine the safety and toxicity profile of M6620 (Berzosertib) administered concomitantly with dCRT in combination with cisplatin and capecitabine in the radical treatment of oesophageal cancer	• Any toxicity grade ≥3 graded according to CTCAE v4.03 and length of time for toxicity to resolve	• Up to week 24
• To determine tolerance and ability to deliver M6620 (Berzosertib) in combination with standard dCRT	• Treatment tolerance and deliverability measured by proportion of patients completing at least 80% of the planned chemotherapy dose and at least 20 fractions of RT	• End of induction chemotherapy and dCRT. End of week 11
• Efficacy and safety of the combination	• Objective tumour response (OR) as evaluated by CT scan and quantified by Response Criteria Evaluation (RECIST 1.1) and endoscopic and biopsy findings. • PFS and OS from D1	• 24 weeks
Tertiary/Exploratory Objectives	**Endpoints/ Outcome Measures**	

• To explore target effects in tissue	• Change in level of ATR inhibition and apoptosis in M6620 (Berzosertib) treated tissue using IHC. • Genotyping of tumours • Aim to identify markers for oesophageal cancer in the blood	• Biopsies at baseline, week 7 and 24 • Blood samples at baseline, week 7 and week 12

4 PATIENT SELECTION

Written informed consent must be obtained before any study specific procedures are performed. The Investigator will determine patient eligibility based on the following criteria.

4.1 Eligibility criteria

Inclusion criteria:
A patient will be eligible for inclusion in this study if all of the following criteria apply.

Stage A1

1. Histologically confirmed adenocarcinoma or squamous cell carcinoma of the oesophagus (not including cervical oesophagus).
2. Tumour length 15 cm or less.
3. Any stage of disease that is unsuitable for radical CRT or surgery but suitable for palliative RT.
4. Baseline investigations available: staging CT scan (within 42 days before first study dose) and endoscopy.
5. Previous chemotherapy treatment completed 28 days before first study dose.
6. No oesophageal stent in situ.
7. Any gender, age ≥ 16 years.
8. Life expectancy of at least 12 weeks.
9. ECOG performance score of 0-1.
10. Able to comply with protocol fully - absence of any physical, psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
11. Able to give written (signed and dated) informed consent according to GCP before registration.
12. Haematological and biochemical indices within the ranges shown below:

Lab Test	Value required
Haemoglobin (Hb)	≥ 8.0 g/dL
Platelet count	≥ 100 x 10^9/L
Absolute neutrophil count (ANC)	≥ 1.5 x 10^9/L
Total bilirubin	≤ 1.5 x upper limit of normal unless the subject has known or suspected Gilbert's syndrome
AST (SGOT)/ALT (SGPT)	≤ 2.5 x upper limit of normal; ≤5 X ULN if liver metastases
Estimated glomerular filtration rate	≥40mL/min

Stage A2

1. **Any** histologically confirmed advanced solid tumour that is metastatic or unresectable where investigator considers Cisplatin and Capecitabine based regimen as appropriate.
2. Baseline investigations available: staging CT scan (within 35 days before first study dose).
3. Previous chemotherapy treatment completed 28 days before first study dose.
4. Any gender, age ≥ 16 years.
5. Life expectancy of at least 12 weeks.
6. ECOG performance score of 0-1.

7. Able to comply with protocol fully - absence of any physical, psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
8. Able to give written (signed and dated) informed consent according to GCP before registration.
9. Haematological and biochemical indices within the ranges shown below:

Lab Test	Value required
Haemoglobin (Hb)	≥ 10.0 g/dL
Platelet count	≥ 100 x 10^9/L
Absolute neutrophil count (ANC)	≥ 1.5 x 10^9/L
Total bilirubin	≤ 1.5 x upper limit of normal unless the subject has known or suspected Gilbert's syndrome
AST (SGOT)/ALT (SGPT)	≤ 2.5 x upper limit of normal or ≤5 x ULN in presence of liver metastases
Ca, Mg, Phosphate	Normal limits
Estimated glomerular filtration rate	≥60mL/min

Stage B

1. Histologically confirmed adenocarcinoma or squamous cell carcinoma of the oesophagus including Siewert type 1 or 2 tumours with ≤2cm gastric mucosal extension (not including cervical oesophagus).
2. Tumour length 7cm or less.
3. Suitable for radical CRT and surgery not an option due to being medically unfit or unsuitable for surgery or patient choice.
4. No oesophageal stent in situ.
5. Endoscopically or radiologically documented measureable disease.
6. Diagnostic PET CT scan*
7. Staging CT scan*
   *either CT or PET CT within 42 days of first study dose
8. Adequate respiratory and cardiac function tests for safe delivery of CRT in the opinion of the Principal Investigator, specifically cardiac ejection fraction ≥60% and lung function FEV1 >1 litre or 40% of predicted value or KCO (DLCO/VA) > 40% predicted value.
9. Any gender, age ≥ 16 years.
10. ECOG performance score of 0-1.
11. Able to comply with protocol fully - absence of any physical, psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
12. Able to give written (signed and dated) informed consent according to GCP before registration.
13. Haematological and biochemical indices within the ranges shown below:

Lab Test	Value required
Haemoglobin (Hb)	≥ 10.0 g/dL
Platelet count	≥ 100 x 10^9/L
Absolute neutrophil count (ANC)	≥ 1.5 x 10^9/L
Total bilirubin	≤ 1.5 x upper limit of normal unless the subject has known or suspected Gilbert's syndrome
AST (SGOT)/ALT (SGPT)	≤ 2.5 x upper limit of normal
Ca (corrected), Mg, Phosphate	Normal limits
Estimated glomerular filtration rate	≥60mL/min

Exclusion criteria:
A patient will not be eligible for the trial if any of the following apply:

1. Pregnant or breast-feeding women or women of childbearing potential unless highly effective methods of contraception are used. (see Section 5.2)
2. Untreated and multiple brain metastases.
3. Clinically significant cardiovascular event within 6 months before study entry to include:
    a. congestive heart failure requiring therapy
    b. unstable angina pectoris
    c. myocardial infarction
    d. Class II/III/IV cardiac disease (New York Heart Association)
    e. presence of severe valvular heart disease;
    f. presence of a ventricular arrhythmia requiring treatment
4. History of arrhythmia that is symptomatic or requires treatment (CTCAE 3), symptomatic or uncontrolled atrial fibrillation, despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication are permitted.
5. Uncontrolled hypertension (blood pressure ≥160/100 despite optimal therapy).
6. Second or third degree heart block with or without symptoms.
7. QTc >450 msec in adult male and >470 msec in adult females (by Fridericia's correction) not due to electrolyte abnormality and that does not resolve with correction of electrolytes.
8. History of congenital long QT syndrome.
9. History of torsades de pointes (or any concurrent medication with a known risk of inducing torsades de pointes).
10. Trachea-oesophageal fistula or invasion of the tracheo-bronchial tree.
11. Treatment with any other investigational agent, or treatment in another clinical trial within 28 days prior to treatment start.
12. Strong CYP3A inhibitors and inducers or Haemopoetic growth factors within 14 days before first dose M6620 (Berzosertib).
13. HER2 gastro-oesophageal positive cancer where anti-Her2 therapies may be more appropriate (however patients who have failed anti-HER2 therapy may be eligible for stage A1 and A2).
14. Unable to have or unwilling to change to low molecular weight heparin instead of Warfarin.
15. Other psychological, social or medical condition, physical examination finding or a laboratory abnormality that the Investigator considers would make the patient a poor trial candidate or could interfere with protocol compliance or the interpretation of trial results.
16. Any other active malignancy, with the exception of adequately treated cone-biopsied in situ carcinoma of the cervix uteri and non-melanoma skin lesions.
17. Patients who are known to be serologically positive for active infection with Hepatitis B, Hepatitis C or HIV.

Additional exclusion criteria Stage A1 and B

1. Previous radiotherapy to thorax or upper abdomen.

Additional exclusion criteria Stage A2 and B

1. History of hand-foot syndrome.
2. History of hearing impairment.
3. Live vaccine received within 30 days prior to treatment start.
4. Complete or Partial DPD deficiency.

Additional exclusion criteria Stage B

1. Previous chemotherapy.

4.2 Protocol deviations and waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a clinical study. Changes to the approved protocol need prior approval unless for urgent safety measures.

Investigators must contact OCTO to obtain guidance and/or clarification as necessary if unsure whether the patient satisfies all the entry criteria and to clarify matters of clinical discretion. OCTO will contact the Chief Investigator or clinical coordinators as necessary. Investigators should not request a protocol waiver to enter a patient who does not satisfy the selection criteria.

4.3 Re-screening if patient does not meet inclusion/exclusion criteria first time round

Patients may be re-screened once, for example if a slot is not available.

4.4 Patient registration

Participants will be recruited from patients usually referred from the upper gastrointestinal MDT.

A screening log must be kept of all patients considered for the study including any that are subsequently excluded; the reason for exclusion must be recorded on this form. A copy of the screening log should be sent to the Trial Office on request, but without patient identifiers. The original must be retained on site.

Before entering a patient onto the study the Principal Investigator or designee will confirm eligibility. If in any doubt the Chief Investigator must be consulted before entering the patient. Details of the query and outcome of the decision should be documented.

Patient recruitment will be managed by the allocation of slots and there will be a minimum of 4 weeks between start of treatment for consecutive patients in stage A1 and a minimum of 3 weeks in stage A2. However, the TMG may decide to release a slot sooner if there is sufficient accumulated experience of the current schedule. If the TMG release a slot sooner, the patient can start treatment before the 3 & 4 week minimum treatment gap. In Stage B, recruitment will be managed by the allocation of slots but a pause between the treatment of consecutive patients is not required.

4.5 Registration procedure

The site should contact OCTO to check the availability of a screening slot and if available reserve the slot prior to giving out a Participant Information Sheet. A screening number should be requested prior to screening the patient and the site should register the participant within 2 weeks of receiving the screening number or relinquish the slot unless an extension is agreed with the trial office.

Site staff will complete the trial registration form and email the form with an anonymised copy of the histopathology report to the Trial Office to confirm the patient's eligibility. A copy of the histology report is required for verification of eligibility (which will identify the patient by screening number only). The original copy of the registration form should be stored in the site file and a copy in the patient notes.

M6620 (Berzosertib) dose and schedule assignment will be determined by the TMG before the participant is registered on the trial database. The site (including Principal Investigator, Research Nurse and Trial Pharmacist) will be informed of the dose and treatment schedule by email once a patient is registered by the Trial Office.

5 TRIAL ASSESSMENTS AND PROCEDURES

5.1 Informed consent

Potential participants will be given a current, approved version of the Patient Information Sheet and Consent Form. They will also receive clear verbal information about the study detailing no less than: the nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be explained that they will be free to withdraw from the study at any time, for any reason, without prejudice to future care, and with no obligation to give a reason for withdrawal. They will have at least 24 hours to consider the information provided and the opportunity to question the Investigator, their GP or other independent parties before deciding whether to participate.

The Investigator who obtains consent must be suitably qualified and experienced. All delegates must be authorised by the Principal Investigator to obtain consent. The Investigator is responsible for ensuring that the trial consent procedures comply with current applicable GCP Regulatory and ethical requirements. Informed consent discussions and outcomes must be well documented in the medical record. The Investigator must be

satisfied that the patient has made an informed decision before taking consent. The patient and the Investigator must personally sign and date the current approved version of the informed consent form in each other's presence. A copy of the Patient Information Sheet and signed consent form will be given to the participant. The original signed form will be retained in the Investigator Site File (if local policy permits) at the trial site, with a copy held in the medical record. Patient consent will be checked using the consent notification section in the Patient Registration Form.

5.2 Contraception Requirement and Contraceptive/ Pregnancy counselling

5.2.1 Contraception Requirement

M6620 (Berzosertib) has not been assessed in developmental and reproductive toxicity studies at this stage of development. However, M6620 (Berzosertib) inhibits DNA damage repair and will be administered in conjunction with cytotoxic radiotherapy and chemotherapy, thus the potential for teratogenicity should be considered high. Subjects will be required to take stringent measures to avoid fathering or bearing children while on study drug and for 6 months after discontinuation of M6620 (Berzosertib).

5.2.2 Female participant of child-bearing potential

Female participants of child-bearing potential are required to use highly effective contraceptive measures (see below) from the start of study treatment until a minimum 6 months after completion of all treatment (chemotherapy, radiotherapy and M6620 (Berzosertib)). Highly effective contraceptive methods considered to have a low user dependency* should preferably be used, in particular when contraception is introduced as a result of participation in the clinical trial. The use of birth control methods does not apply if the female partner has a bilateral oophorectomy, hysterectomy or is postmenopausal. Use of a condom by male partners in addition to use of a highly effective contraceptive measure (double barrier method) is not mandated but it can be recommended.

Highly effective contraceptive measures:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable*****)
- Intrauterine device (IUD) in place for at least 90 days prior to start of study drug *****
- Intrauterine hormone-releasing system (IUS) *****
- Bilateral tubal occlusion *****
- Vasectomised partner *****(provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception).

5.2.3 Male participants

Male participants are required to use a condom during treatment (and must avoid donating sperm) for a minimum 6 months after completion of all treatment (chemotherapy, radiotherapy and M6620 (Berzosertib)). Female partners of male participants, who are of child bearing potential, should also consider contraceptive options.

5.2.4 Pregnancy counselling

Participants will be counselled to inform the Investigator of any pregnancy (also applies to female partners of male trial subjects) occurring within 6 months of the last dose of the study drug. If a pregnancy is confirmed female participants will be withdrawn immediately from any ongoing treatment. Participants will be asked to provide follow-up information on the outcome of any pregnancy and infants will be followed up for a year after birth for congenital abnormality (see section 15 for pregnancy reporting requirements).

5.3 Pre-dosing evaluations (all stages)

The majority of evaluations will be standard of care for patients. The following assessments must be performed/obtained within the 2 weeks (+7 days allowed) before the patient receives the first study dose (unless

otherwise specified below). Informed consent must be obtained prior to performing any study specific evaluations. Confirmation of eligibility and registration on study must be completed as soon as possible after consent to allow time for radiotherapy planning in Stage A1.

- Written informed consent
- Demographic details include age, sex, and self-reported race/ethnicity
- Medical History to include cancer history, prior cancer therapies and procedures, reproductive status, smoking history, and clinically significant disease history and concomitant diseases
- Concomitant medications
- Physical examination to include lungs, abdomen, heart, nodal regions, neurological examination and symptom driven examination. Any abnormality identified at baseline should be recorded.
- Mellow score (Stage B only)
- Height, weight and body surface area (BSA)
- ECOG performance status
- Vital signs: systolic/diastolic blood pressure (BP), pulse rate, temperature
- Screening blood tests:
  - Haematology – Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
  - Biochemistry – sodium, potassium, urea, creatinine, bilirubin, ALP, AST or ALT, Ca, Mg, Phosphate
  - Coagulation – INR, APTT or PTT.
- Pregnancy test (in females of child bearing potential only): serum or urine Human Chorionic Gonadotropin (HCG) test to rule out pregnancy at study entry; results must be obtained and reviewed at least 1 week before first dose of IMP. During treatment applicable patients must have pregnancy testing every 4 weeks. Pregnancy test not required for post-menopausal or surgically sterile females.
- Electrocardiogram (ECG)
- Pathology report confirming histological diagnosis (archival diagnostic sample will be requested for analysis see section 7.3.1).

In addition for Stage A1 and A2:

- Staging CT scan within 42 days for Stage A1 and 35 days for Stage A2 of first study dose

In addition for Stage B:

- Staging CT or PET scan within 42 days before first study dose
- Echo cardiogram or MUGA (Multi Gated Acquisition Scan) within 3 months prior to start of treatment
- Lung function tests within 3 months prior to start of treatment

In addition for Stage A2 and B:

- (If required) Audiogram monitoring for patients with significant hearing impairment
- DPD deficiency testing (any time before trial enrolment). This is not required for Stage A2 participants with previous use of Capecitabine.

5.4 Stage A Evaluations

5.4.1 Stage A1 evaluations during the study

Post registration and prior to start of Radiotherapy

- M6620 (Berzosertib) schedule assignment
- Radiotherapy planning (or pre-registration during screening)

Evaluations Week 1:

The following assessments should be done Day 1 and Day 4 (+/-24 hours but must be pre-M6620 (Berzosertib)) unless stated otherwise:

- Venous blood sample within 24 hours prior to M6620 (Berzosertib) including:
  - Haematology – Haemoglobin, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets

  - Biochemistry – sodium, potassium, urea, creatinine, bilirubin, ALP, AST or ALT
- Coagulation – INR, APTT or PTT.
- Adverse Event (AE) Assessment
- Assessment of concomitant medications
- Physical examination
- Weight (Day 1 only)
- ECOG performance status
- Assessment of DLT (Day 4 only)
- ECG (Day 1 prior to treatment)
- On days of M6620 (Berzosertib) monitor patient for reactions for 20 minutes after administration

Evaluation during radiotherapy and concomitant M6620 (Berzosertib) (Weeks 2 - 3)
The following assessments should be done the day before each administration of M6620 (Berzosertib) (+/-24 hours but must be pre-M6620 (Berzosertib)) unless stated otherwise:

- Venous blood sample within 24 hours prior to administration of M6620 (Berzosertib) including:
  - Haematology – Haemoglobin, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
  - Biochemistry – sodium, potassium, urea, creatinine, bilirubin, ALP, AST or ALT
- Assessment of AE
- Assessment of concomitant medications
- Physical examination
- Weight (Day 8 & 15 only)
- ECOG performance status
- Assessment of DLT
- On days of M6620 (Berzosertib) monitor patient for reactions for 20 minutes after administration

Evaluations on Week 4, 9 & 12

- Assessment of AE
- Assessment of concomitant medications
- Physical examination
- Weight
- ECOG performance status
- Assessment of DLT (not week 12)
- Coagulation – INR, APTT or PTT (week 4 only)
- Haematology – Haemoglobin, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets (week 4 only)
- Biochemistry – sodium, potassium, urea, creatinine, bilirubin, ALP, AST or ALT (week 4 only)ECG (weeks 4 & 12 only)
- CT chest, abdomen, pelvis (week 12 only). If disease progression is already identified by CT scan during the follow up period, a repeat CT scan is not necessary at week 12.

5.4.2 Stage A1 evaluations on early withdrawal

Where possible, patients will be followed up as per the follow up visits which should be brought forward to 1, 6 and 9 weeks post end of treatment; including assessments of AEs and DLTs see section 6.

5.4.3 Stage A1 off-Study and Follow-up Evaluations

Where possible, patients will be followed up as per standard of care for 9 weeks post radiotherapy. Patients should be counselled on the continued use of contraception for 6 months following the end of treatment **if appropriate** and encouraged to report any pregnancies to the study team. The clinician in charge will be asked to provide the following information at 6 and 12 months.

- date and cause of death, if applicable
- details of any clinically significant events

- Date and site of progression.
- Further radiotherapy, or other intervention required.

5.4.4 Stage A2 evaluations during the study

Post registration

- M6620 (Berzosertib) schedule assignment
- Audiogram monitoring (if applicable)

Weekly Evaluations during treatment weeks 1 - 18

- Assessment of concomitant medications
- Weight
- ECOG performance status
- Physical examination
- Assessment of AE
- Assessment of DLT (Weeks 1-4 only)
- ECG (once per cycle, week 1 pre-treatment)
- Coagulation – INR, APTT or PTT (week one only, pre-cisplatin)

Additional evaluations during treatment weeks 1 - 18

- Venous blood sample within 72 hours prior to Cisplatin including:
    - Haematology – Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
    - Biochemistry – sodium, potassium, urea, creatinine, bilirubin, ALP and AST or ALT, Ca, Mg, Phosphate

- Venous blood samples within 24 hours prior to M6620 (Berzosertib) administration including:
    - Haematology – Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
    - Biochemistry – sodium, potassium, urea, creatinine, bilirubin, ALP and AST or ALT, Ca, Mg, Phosphate

  Note: only one set of blood tests needs to be done if the timing satisfies both Cisplatin and M6620 (Berzosertib) requirements above.
- On days of M6620 (Berzosertib) monitor patient for reactions for 20 minutes after administration

Additional evaluation Week 4

- Audiogram monitoring (if applicable)

Additional evaluation Week 6, 12, 18

- CT chest abdomen and pelvis to assess response

Evaluations at 2 & 8 week follow up

- Venous blood samples:
    - Haematology – Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
    - Biochemistry – sodium, potassium, urea, creatinine, bilirubin, ALP and AST or ALT, Ca, Mg, Phosphate
- Assessment of concomitant medications
- Weight, ECOG performance status
- Physical examination
- Coagulation – INR, APTT or PTT (week 2 only)
- Assessment of AE
- CT chest abdomen and pelvis to assess response (week 26 only)

5.4.5 Stage A2 evaluations on early withdrawal

Where possible, patients will be followed up as per the follow up visits at 2 and 8 weeks post end of treatment, including assessments of AEs and DLTs (see section 6).

5.4.6 Stage A2 off-Study and Follow-up Evaluations

The final study visit will occur 8 weeks after completion of treatment. Patients should be counselled on the continued use of contraception for 6 months following the end of treatment **if appropriate** and encouraged to report any pregnancies to the study team. The clinician in charge will be asked to provide the following reports at 6 & 12 months.

- date and cause of death, if applicable
- date and site of progression
- details of any clinically significant events
- further chemotherapy or other intervention required

5.5 Stage B evaluations

Post registration and prior to start of Induction chemotherapy

- Research blood sample
- Audiogram monitoring (if applicable)

5.5.1 Stage B evaluations during the study

Evaluations during treatment weeks 1 & 4 (induction chemotherapy + M6620 (Berzosertib)) and weeks 7, 8, 9, 10 & 11 (chemoradiotherapy + M6620 (Berzosertib))

- The following assessments should be done within 24 hours prior to M6620 (Berzosertib) administration: Venous blood samples within 24 hours prior to M6620 (Berzosertib) administration including:
    - Haematology – Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
    - Biochemistry – sodium, potassium, urea, creatinine, bilirubin, ALP and AST or ALT, Ca, Mg, Phosphate
- Assessment of concomitant medications
- Weight
- ECOG performance status
- Vital signs: systolic/diastolic blood pressure (BP), pulse rate, temperature
- Physical examination
- ECG (weeks 1, 4, 7 and 10 pre-cisplatin treatment)
- Coagulation (INR, APTT or PTT, week 1 only pre-cisplatin)
- Mellow score
- Assessment of AE
- Assessment of DLT (not week 1)

The following assessments should be done on days of M6620 (Berzosertib) administration during induction chemotherapy. If problems were identified, this should be continued during chemoradiotherapy:

- Monitor patient for reactions for 20 minutes after administration of M6620 (Berzosertib)

Additional assessments weeks 1, 4, 7 & 10

- Venous blood sample within 72 hours prior to Cisplatin including:
    - Haematology – Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
    - Biochemistry – sodium, potassium, urea, creatinine, bilirubin, ALP and AST or ALT, Ca, Mg, Phosphate

  Note: only one set of blood tests needs to be done if the timing satisfies both Cisplatin and M6620 (Berzosertib) requirements above.

Additional evaluation week 4

- Audiogram monitoring (if applicable)

Additional assessments week 7 (see section 7.3 for details)

- Research endoscopy and biopsy
- Research blood sample

Radiotherapy planning should take place in weeks 2 to 4 and M6620 (Berzosertib) schedule assignment will take place in week 6

Evaluations during induction chemotherapy weeks 2 & 5

Evaluations to be done on day 1 or day 2:

- Assessment of concomitant medications
- ECOG performance status
- Vital signs: systolic/diastolic blood pressure (BP), pulse rate, temperature
- Physical examination
- Mellow score
- Assessment of AE
- Assessment of DLT

Evaluations at weeks 12 & 18

- Venous blood samples:
    - Haematology – Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
    - Biochemistry – sodium, potassium, urea, creatinine, bilirubin, ALP and AST or ALT, Ca, Mg, Phosphate
- Assessment of concomitant medications
- ECOG performance status
- Vital signs: systolic/diastolic blood pressure (BP), pulse rate, temperature
- Coagulation (INR, APTT or PTT, week 12 only)
- Physical examination
- Mellow score
- Assessment of AE
- Assessment of DLT
- Research blood sample (week 12 only)

Evaluations at week 24

- Assessment of concomitant medications
- ECOG performance status
- Vital signs: systolic/diastolic blood pressure (BP), pulse rate, temperature
- Physical examinations
- ECG
- Mellow score
- Assessment of AE
- Assessment of DLT
- Endoscopy and research biopsy
- CT chest abdomen and pelvis to assess response

5.5.2 Stage B evaluations on early withdrawal

Where possible, patients will be followed up as per the follow up visits which should be brought forward to 1, 7 and 13 weeks post end of treatment, including assessments of AEs and DLTs see section 6.

5.5.3 Stage B off-Study and Follow-up Evaluations

The final study visit will occur 13 weeks after completion of treatment. Patients should be counselled on the continued use of contraception for 6 months following the end of treatment **if appropriate** and encouraged to

report any pregnancies to the study team. Sites will report this if notified up until 6m or 13w after last patient treatment whichever is sooner.

6 EARLY PATIENT WITHDRAWAL

The Trial Office should be informed of any early patient withdrawal within 24 hours of the site becoming aware using the Early Withdrawal Form and scan and email as a PDF attachment to octo-safety@oncology.ox.ac.uk. If the reason for early withdrawal is an SAE then an SAE Form will also be required.

6.1 Treatment Withdrawal

During the course of the trial, a patient may withdraw early from treatment. This may happen for a number of reasons, including:

- Unacceptable toxicity
- AE/SAEs requiring discontinuation
- Loss to follow-up
- Significant protocol deviation or inability to comply with trial procedures
- Clinical decision
- Patient decision

When the patient stops treatment early, the 'End of Treatment' Form needs to be completed, and any other relevant CRFs (example SAE Form). Any evaluations carried out on early withdrawal will be captured as per sections 5.4.2, 5.4.5 and 5.5.2. The reason for withdrawing from treatment early should be clearly documented in the medical records.

The end of treatment means the patient will then enter the routine follow up stage of the trial. If M6620 (Berzosertib) treatment is stopped, the patient will continue with standard treatment and will be followed up as part of the trial.

6.2 Consent Withdrawal

Consent withdrawal means that a patient has expressed a wish to withdraw from the study altogether. Under these circumstances, the site needs to document all relevant discussions in the patient notes and notify the Trial Office, which will allow the office to mark all future CRFs as not applicable. The site should inform the Trial Office whether any samples already collected for the study should be destroyed.

Under these conditions, investigators are still responsible to follow up any SAEs till resolution.

6.3 Patient evaluability and replacement

Patients will not be replaced since TiTE-CRM uses accumulated data and all patients will be evaluable for dose escalation decisions. However, the TMG may decide to replace patients if drop-out occurs early in the treatment schedule for reasons other than a DLT.

In Stage B, all patients who receive treatment within the study will be evaluable for response. All participants who receive one dose of M6620 (Berzosertib) will be evaluable for the safety analysis.

Evaluable for Objective Response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated in Appendix B. (Patients who exhibit objective disease progression prior to the end of cycle 1 will be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

7 SAMPLES FOR LABORATORY ANALYSIS

7.1 Samples to be analysed in local Trust's laboratories

Diagnostic Laboratories
Samples for haematology and biochemistry analysis will be labelled with standard patient identifiers and sent to the local hospital diagnostic laboratory. Results will be processed in the standard way and entered into the routine hospital reporting system. Samples will be stored, held, reported and subsequently destroyed in accordance with standard local laboratory practice.

Pathology
The routine diagnostic pathology samples and additional research samples taken at endoscopy will also be labelled, processed and reported according to the standards proposed by the Royal College of Pathologists. An anonymised copy of the diagnostic histopathology/cytology report should be sent to the Trial Office at registration.

7.2 Blood and Tissue samples for translational research

Blood and biopsy samples will be collected in Stage B for translational research concerning the mechanism of action of M6620 (Berzosertib).

7.2.1 Biopsy samples

Tissue samples will be collected at least 24 hours after the first dose of M6620 (Berzosertib) treatment. The samples will be analysed for a signal of ATR inhibition by M6620 (Berzosertib) following induction of the DDR (ATR activity) by Cisplatin or RT treatment.

Tissue should be biopsied from 3 areas of the oesophagus: normal tissue outside the radiotherapy field, normal tissue within the radiotherapy field and tumour tissue within the radiotherapy field. This will allow a comparison of the effect of M6620 (Berzosertib) on healthy tissue, irradiated tissue and tumour tissue.
All participants will have a diagnostic biopsy prior to screening. Baseline FFPE tissue samples will be analysed for common genetic mutations using a cancer panel.
Timepoints for endoscopy and biopsy:

- week 7 day 3, and if M6620 (Berzosertib) given carried out at least 24 hours after the administration of M6620 (Berzosertib) (on treatment biopsy should be taken from fraction 3 to fraction 5 (but up to fraction 7 is permitted if required)
- week 24

Samples will be sent to the central lab for IHC analysis (see Sample Handling Manual for further details). Remaining samples will be returned to Oxford for further IHC markers and storage in Oxford research biobank (details will be in the sampling handling manual).

7.2.2 Research blood samples

Blood samples will be collected to look for biomarkers for ATR inhibition and to identify other DNA, RNA or protein markers present in oesophageal cancer.

Timepoints for research blood samples:

- prior to starting treatment
- week 7 from fraction 3 to fraction 5 (but up to fraction 7 is permitted if required)
- week 12

Samples will be sent to Oxford University Labs for analysis (details will be in the sampling handling manual).

7.3 Labelling and confidentiality of samples sent

All samples sent to analytical Laboratories will be labelled with the trial code, trial patient number, schedule and date/time taken. Should a laboratory receive any samples carrying unique patient identifiers the recipient must immediately obliterate this information and re-label.

7.4 Clinical reporting of exploratory research assay results

The results of the CHARIOT trial research assays are exploratory and are not intended to influence the individual patient's medical care. Findings will not be reported routinely to the responsible clinician except in the unlikely event that the result might be beneficial to the patient's clinical management.

7.5 Trial sample retention at end of study

The Chief Investigator has overall responsibility for custodianship of the trial samples. Laboratories are instructed to retain any surplus samples pending instruction from the Chief Investigator on use, storage or destruction. It is possible that new or alternative assays may be of future scientific interest. At the end of the research study any surplus samples may be retained for use in other projects that have received ethical approval. Hence, any surplus study samples may be transferred to a licensed tissue bank where they will be managed in accordance with applicable host institution policies and the Human Tissue Act (HTA) requirements.

7.6 Withdrawal of consent for sample collection and/or retention

A patient may withdraw consent to provide samples for research at any time without giving a reason. The Investigator must ensure that their wishes are recorded in the medical record and will inform the Trial Office accordingly. The Investigator should discuss with patients the valuable use of samples that have already been provided and under circumstances where these samples have already been processed and anonymised, it would not be possible to destroy such samples.

8 INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)

The trial is investigating the unlicensed drug M6620 (Berzosertib) in combination with the radiotherapy (stage A1); M6620 (Berzosertib) in combination with chemotherapy agents Cisplatin and Capecitabine (stage A2) and M6620 (Berzosertib) with chemoradiotherapy (stage B). For the purposes of the trial, M6620 (Berzosertib), Cisplatin and Capecitabine are all considered IMPs.

8.1 Stage A1 Treatment

Two M6620 (Berzosertib) dose levels and 3 dosing frequencies (treatment schedules) are proposed. Both the dose and frequency of M6620 (Berzosertib) will vary but the administered radiation dose and fractionation schedule will remain unchanged across treatment plans. The treatment schedule will last for 3 weeks and radiotherapy must start on a Monday.

Antiemetics should be prescribed as supporting medication to be available from Day 1 of Radiotherapy, (i.e. Domperidone 20mg tds prn PO 5/7 or Metoclopramide 20mg tds prn PO 5/7, or the preferred standard of care at the institution)

8.1.1 M6620 (Berzosertib) treatment schedules - Stage A1

The starting dose of M6620 (Berzosertib) will be 140mg/m^2 IV once weekly (schedule 1). If schedule 1 is too toxic, the trial will be re-started at 90mg/m^2 (schedule -3). For all schedules see table 8.1. The treatment schedule of M6620 (Berzosertib) will be escalated or de-escalated using the TiTE-CRM model (see section 2 for further details).

Table 8.1

Dose Escalation schedule	
Treatment schedule	Dose** of *M6620 (Berzosertib) and days of the schedule it will be delivered*
-3	90 *mg/m^2* day 2, 9, 16
-2	90 *mg/m^2* day 2, 5, 9, 12, 16
-1	90 *mg/m^2* day 2, 5, 9, 12, 16, 19
1*	140 *mg/m^2* day 2, 9, 16
2	140 *mg/m^2* day 2, 5, 9, 12, 16
3	140 *mg/m^2* day 2, 5, 9, 12, 16, 19
4	240 *mg/m^2* day 2, 9, 16
5	240 *mg/m^2* day 2, 5, 9, 12, 16
6	240 *mg/m^2* day 2, 5, 9, 12, 16, 19

**Starting dose and schedule. 90mg/m^2 dose will only be explored if trial is re-started*
***Doses are stated as exact dose in units. No intermediate dose levels or further splitting of the dose allowed*

8.1.2 Radiotherapy dose and duration –Stage A1

The total dose of radiation will be 35Gy in 15 fractions treated once daily, 5 days a week Monday to Friday and prescribed and recorded per ICRU 62.

8.1.3 Stage A1: Dose Escalation Schema

Schedule -3 – 90 mg/m², 270 mg/m² per plan

	Week 1							Week 2							Week 3						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
ATR Inhibitor		M							M							M					

Schedule -2 – 90 mg/m², 450 mg/m² per plan

	Week 1							Week 2							Week 3						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
ATR Inhibitor		M			M				M			M				M					

Schedule -1 – 90 mg/m², 540 mg/m² per plan

	Week 1							Week 2							Week 3						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
ATR Inhibitor		M			M				M			M				M			M		

Schedule 1 – 140 mg/m² per dose, 420 mg/m² per plan (starting schedule)

	Week 1							Week 2							Week 3						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
ATR Inhibitor		M							M							M					

Schedule 2 – 140 mg/m², 700 mg/m² per plan

	Week 1							Week 2							Week 3						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
ATR Inhibitor		M			M				M			M				M					

Schedule 3 – 140 mg/m², 840 mg/m² per plan

	Week 1							Week 2							Week 3						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
ATR Inhibitor		M			M				M			M				M			M		

Schedule 4 – 240 mg/m², 720 mg/m² per plan

	Week 1							Week 2							Week 3						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
ATR Inhibitor		M							M							M					

Schedule 5 – 240 mg/m², 1200 mg/m² per plan

	Week 1							Week 2							Week 3						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
ATR Inhibitor		M			M				M			M				M					

Schedule 6 – 240 mg/m², 1440 mg/m² per plan

	Week 1							Week 2							Week 3						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
ATR Inhibitor		M			M				M			M				M			M		

8.2 Stage A2 Treatment

Two dose levels and 2 dosing frequencies (treatment schedules) are proposed. Both the dose and frequency of M6620 (Berzosertib) will vary but the Cisplatin and Capecitabine dose and schedule will remain unchanged across treatment plans. The treatment schedule will last for 6 cycles (18 weeks).

8.2.1 M6620 (Berzosertib) treatment schedule – Stage A2

The starting dose of M6620 (Berzosertib) will be 90mg/m^2 IV once weekly (schedule 1). For all schedules see table 8.2. The treatment schedule of M6620 (Berzosertib) will be escalated or de-escalated using the TiTE-CRM model (see section 2 for further details).

Table 8.2

Dose Escalation schedule	
Treatment schedule	Dose of *M6620 (Berzosertib) and days of the schedule it will be delivered*
1	90 *mg/m^2* once a week for 18 weeks (Tuesdays)
2	90 *mg/m^2* twice a week for 18 weeks (Tuesdays and Fridays)
3	140 *mg/m^2* once a week for 18 weeks (Tuesdays)
4	140 *mg/m^2* twice a week for 18 weeks (Tuesdays and Fridays)

**Doses are stated as exact dose in units. No intermediate dose levels or further splitting of the dose allowed*

8.2.2 Chemotherapy dose and duration - Stage A2

Chemotherapy (Weeks 1 – 18)

Cisplatin 60mg/m^2 IV Day 1 of 21-day cycle for 6 cycles
Capecitabine 625mg/m^2 po bd Days 1-21 of 21-day cycle for 6 cycles

8.2.3 Stage A2 Dose escalation schema

Dosing schedule 1,3		**Week 1**							**Week 2**							**Week 3**						
		M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
	Capecitabine	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
	Cisplatin	**C**																				
	ATR Inhibitor		**M**							**M**							**M**					

Repeat this 3 weekly schedule for 6 cycles

Dosing schedule 2, 4		**Week 1**							**Week 2**							**Week 3**						
		M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
	Capecitabine	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
	Cisplatin	**C**																				
	ATR Inhibitor		**M**			**M**				**M**			**M**				**M**			**M**		

Repeat this 3 weekly schedule for 6 cycles

8.3 Stage B Treatment

The dose administered in stage B will be 140mg/m^2 (see section 2.3) and will remain constant whilst three dosing schedules are explored (see table 8.3). The chemotherapy and radiation doses and fractionation schedules will remain unchanged across dosing schedules.

The 11 weeks of treatment consists of 6 weeks of induction chemotherapy (Capecitabine and Cisplatin) with M6620 (Berzosertib) followed by 5 weeks of concomitant chemoradiotherapy (Capecitabine, Cisplatin and radiotherapy) with M6620 (Berzosertib). All patients will receive M6620 (Berzosertib) with induction chemotherapy on Cycle 1 Day 2 and Cycle 2 Day 2. In the last week of chemotherapy patients will be assigned to a M6620 (Berzosertib) treatment schedule to be administered during chemoradiotherapy (see table 8.3 below). Radiotherapy must start on a Monday.

8.3.1 M6620 (Berzosertib) Treatment dose and schedule – Stage B

The dose of M6620 (Berzosertib) in Stage B will be 140mg/m^2, allocation will start on schedule 1.

Table 8.3

Dose Escalation Schedule		
Treatment Schedule	**M6620 (Berzosertib) administration during induction chemotherapy**	**M6620 (Berzosertib) administration during Chemoradiotherapy**
-1	Cycle 1 day 2, Cycle 2 day 2	Days 2, 9, 16, 23, 30
1*	As above	Days 2, 5, 9, 16, 23, 26, 30
2	As above	Days 2, 5, 9, 12, 16, 19, 23, 26, 30, 33

**Starting schedule. Reduced frequency schedule (-1) will only be explored if schedule 1 is too toxic.*

8.3.2 Chemoradiotherapy dose and duration - Stage B

Induction Chemotherapy (Weeks 1 – 6)

Cisplatin 60mg/m^2 IV Day 1 of 21-day cycle for 2 cycles (Days 1 and day 22 of chemotherapy)
Capecitabine 625mg/m^2 po bd Days 1-21 of 21-day cycle for 2 cycles

Concurrent chemoradiotherapy (Weeks 7 – 11)

Cisplatin 60mg/m^2 IV Day 1 of 21-day cycle for 2 cycles (Days 1 and day 22 of chemo**Radio**therapy)
Capecitabine 625mg/m^2 po bd on days receiving radiotherapy (From day 1 to day 33 of chemoradiotherapy **excluding** days not receiving radiotherapy) (Total 25 days of treatment)

8.3.3 Radiotherapy dose and duration - Stage B

The total dose of radiation will be 50Gy in 25 fractions treating once daily, 5 days per week Monday to Friday and prescribed and recorded as per ICRU 62.

8.3.4 Stage B Dose frequency escalation schema

Induction Chemotherapy - All patients

	Week 1							Week 2							Week 3						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Capecitabine	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Cisplatin	C																				
ATR Inhibitor		M																			

	Week 4							Week 5							Week 6						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Capecitabine	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Cisplatin	C																				
ATR Inhibitor		M																			

Chemoradiotherapy dosing frequency escalation schema

		Week 7							Week 8							Week 9							Week 10							Week 11						
		M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Dosing schedule -1	**Capecitabine**	→	→	→	→	→			→	→	→	→	→			→	→	→	→	→			→	→	→	→	→			→	→	→	→	→		
	Cisplatin	C																					C													
	Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
	ATR Inhibitor		M							M							M							M							M					

		Week 7							Week 8							Week 9							Week 10							Week 11						
		M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Dosing schedule 1	**Capecitabine**	→	→	→	→	→			→	→	→	→	→			→	→	→	→	→			→	→	→	→	→			→	→	→	→	→		
	Cisplatin	C																					C													
	Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
	ATR Inhibitor		M			M				M							M							M			M				M					

		Week 7							Week 8							Week 9							Week 10							Week 11						
		M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
Dosing schedule 2	**Capecitabine**	→	→	→	→	→			→	→	→	→	→			→	→	→	→	→			→	→	→	→	→			→	→	→	→	→		
	Cisplatin	C																					C													
	Radiotherapy	X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X			X	X	X	X	X		
	ATR Inhibitor		M			M				M			M				M			M				M			M				M			M		

8.4 Management of M6620 (Berzosertib) drug administration

M6620 (Berzosertib) will be administered intravenously over 60 minutes (±10 minutes) approximately one hour after radiotherapy in stage A1 and B. When the total volume of infusion exceeds 600mL, the infusion may be extended by up to 30 minutes. Intravenous administration of M6620 (Berzosertib) is independent of food intake. When given after chemotherapy, the M6620 (Berzosertib) should be initiated approximately 24 hours (+/- 4hours) after cessation of cisplatin infusion (continue with Capecitabine as prescribed). The cannula should be removed following each infusion. Consideration of a Peripheral Inserted Catheter should be given if there are difficulties accessing a vein.

M6620 (Berzosertib) is associated with infusion-related reactions, e.g., infusion site erythema, infusion site reaction, and catheter site related reaction. Infusion reactions are common with IV administration of drugs used to treat cancer. These reactions occur during or shortly after administration of the drug and are diverse. They may include pruritus, flushing, chills/rigors, urticaria/rash, headache, bronchospasm/dyspnea, and hypotension or hypertension, among others. Infusion-related reactions, nausea, and vomiting are considered adverse drug reactions (ADRs) for MK6620.

The infusion can be mildly irritating so it is necessary to monitor the intravenous catheter site closely for evidence of erythema, tenderness or induration. To minimize the possibility of phlebitis, M6620 (Berzosertib) should be administered through a large bore catheter into a large caliber peripheral vein. The intravenous infusion site should be monitored closely for the development of erythema, induration, purulence, tenderness, or warmth. If any subject develops phlebitis, or signs or symptoms of inflammation that may progress to phlebitis or that the patient cannot tolerate, standard measures should be employed to ameliorate these symptoms (including removal of the infusion catheter and resumption of infusion through a different vein).

If any subject develops pruritus, flushing, or any other symptom suggestive of a systemic infusion reaction, standard measures should be employed to manage these symptoms (e.g. antihistamines and/or steroids, fluid support). Any non-serious reaction such as pruritis, can be prevented in subsequent administration by appropriate desensitizing measures prior to the administration of the study drugs as long as they are not prohibited by protocol (e.g. Corticosteroid and antihistamine combinations that may be used include: 100 mg to 200 mg hydrocortisone intravenously approximately 60 minutes (± 15 minutes) before M6620 (Berzosertib) infusion, and either 10 mg of chlorphenamine intravenously approximately 30 minutes (± 10 minutes) before M6620 (Berzosertib) infusion. Alternative antihistamine and steroid doses, timing, routes of administration and agents may be considered, as long as not prohibited by protocol. In addition, treatment with an H2-blocker (e.g., ranitidine) may be considered for subjects not responsive to a regimen with an H1-blocker. If standard procedures to limit symptoms of an infusion reaction have failed, further re-challenges are prohibited.

Serious acute hypersensitivity reactions have occurred in a few subjects receiving M6620 (Berzosertib). These reactions occurred within minutes of re-exposure to M6620 (Berzosertib), and in cases reported to date, they have occurred during the second infusion. They may include hypotension and mental status changes. All subjects have fully recovered with standard treatment for this reaction, including immediate discontinuation of the inciting infusion and administration of IV corticosteroid and antihistamine, as well as IV fluids and oxygen when clinically indicated. If a serious acute hypersensitivity reaction occurs M6620 (Berzosertib) should be permanently withdrawn and reported as an SAR. For management of M6620 (Berzosertib) toxicity or missed doses see section 9.3.

Laboratory values required for administration of M6620 (Berzosertib) and chemotherapy

Laboratory parameter	Cycle 1 Day 1	Day 1 of subsequent cycles	Other days M6620 (Berzosertib) administered alone or with Capecitabine
Haemoglobin	≥8.0g/dL Stage A1; ≥10.0g/dL Stage A2/B	≥8.0g/dL Stage A1/A2; ≥10.0g/dL Stage B(during radiotherapy)	≥7.0g/dL (if asymptomatic)
Absolute neutrophil count	≥1.5 X 10^9/L	≥1 X 10^9/L	≥1.0 X 10^9/L
Platelet count	≥100 X 10^9/L	≥75 X 10^9/L	≥75 X 10^9/L

AST/ALT	≤2.5 X ULN or ≤5 X ULN if liver metastases	≤2.5 X ULN or ≤5 X ULN if liver metastases	≤2.5 X ULN or ≤5 X ULN if liver metastases or capecitabine given alone
Estimated glomerular filtration rate	≥40mL/min A1 or ≥60mL*/min Stage A2/B	≥60mL/min Stage A2/B	Not required
Total Bilirubin (serum)	≤1.5 X ULN[a]	Not required	Not required

a – unless subject has known or suspected Gilbert's syndrome

* if below 60ml/min, formal Creatinine clearance required (EDTA glomerular function rate, or 24 hours urine collection), and 100% dose cisplatin may be administered if formal result is ≥50ml/min

8.5 Management of capecitabine administration

Patients will be instructed to take capecitabine tablets at a dose of 625mg/m^2 twice a day as per standard practice starting in the evening of day 1 of each cycle (stage A2 and B). For patients who find swallowing capecitabine difficult, it is possible to dissolve the tablets in lukewarm water. The capecitabine tablets should be placed in approximately 200ml of lukewarm water. By stirring for about 15 minutes the tablets should dissolve. There is no stability data for any form of capecitabine suspension, so this should be done immediately prior to use and the solution swallowed immediately, rinsing to ensure all of the contents are ingested. As the solution will have a bitter taste it could be flavoured with a fruit juice or squash, but grapefruit juice should not be used. The solution may also be administered through a naso-gastric tube or other enteral feeding tube. Please note that dissolving capecitabine is outside of its licensed indication.

In addition, it is recommended that patients are carefully monitored for ophthalmologic complications, such as keratitis and corneal disorders, especially if they have a prior history of eye disorders. Treatment of eye disorders should be initiated promptly. For patients with diabetes mellitus, caution must be exercised as it may be aggravated.

Concurrent chemoradiotherapy (Weeks 7-11)

Patients should be instructed to take the drug twice daily as above **only** on the days radiotherapy is delivered.
Where the start of radiotherapy is delayed for scheduling reasons Day 1 of the third cycle of chemotherapy, i.e. Day 1 of the start of concurrent chemotherapy, should also be delayed such that the 2 treatments start together.

Additional dosing requirements are:

- Missed doses/dosing day will not be made up. The next dose must be taken as scheduled. The missed tablets should be brought at next clinic visit to be handed over to the research nurse.
- If a patient vomits after taking the tablets, they should not take another dose. The next doses should be taken as scheduled.
- Doses should NOT be doubled to make up for missed doses.
- Any unused tablets should be returned to pharmacy (via research nurse). All patients are asked to keep a record of their capecitabine use in their diary card.

8.6 Management of cisplatin administration

Cisplatin will be administered on day 1 of a 3 weekly cycle. From weeks 1 to 18 for Stage A2 and 1-11 for Stage B as an intravenous infusion at 60mg/m^2 over 2 hours on treatment days or as per local policy. The hydration regimen for cisplatin administration will be determined by locally agreed pharmacy procedures and guidelines. Pre and post anti-emetics should be given according to local practice for high risk emesis. Laboratory values required for administration of chemotherapy will be as per standard policy (for administration of M6620 (Berzosertib) see section 8.4). Patient monitoring and management of hypersensitivity and extravasation will be as per local hospital policy. Patients with significant hearing impairment will be made aware of potential ototoxicity. For those who choose to be included, it is recommended that audiograms be carried out at baseline and prior to cycle 2. Gastric protection (Proton Pump inhibitor or H2 blocker) is recommended for all patients for duration of therapy and for at least 6 weeks thereafter.

On days of concurrent chemo-radiation, cisplatin should be completed before radiotherapy treatment. Patients may undergo their radiotherapy during the post-hydration following cisplatin, which may be interrupted provided it is completed afterwards.

8.7 Managing delays to Chemotherapy and Radiotherapy

Where the start of radiotherapy is delayed for scheduling reasons Day 1 of the third cycle of chemotherapy, i.e. Day 1 of the start of concurrent chemotherapy, should also be delayed such that the 2 treatments start together. The decision as to the scheduling of chemotherapy as a result of delays to radiotherapy due to machine service days or breakdowns i.e. unscheduled interruptions to radiotherapy should be made at the clinical discretion of the local PI, although the first treatment of radiotherapy must be given on the same first day of cycle 3 of the chemotherapy schedule. Management of hypersensitivity and extravasation will be as per local hospital policy.

8.8 Laboratory values required for administration of chemotherapy

See table in section 8.4**.**

8.9 Calculating and recalculating doses

The dose of M6620 (Berzosertib) will be calculated for each patient based on actual weight. BSA will be calculated according to the DuBois and DuBois formula. The patient's weight should be recorded prior to every chemotherapy or chemoradiotherapy cycle to determine dose of chemotherapy. If a patient's weight changes by ≥ 10% from baseline then drug doses should be recalculated. If a patient's weight changes by <10% the dose may be adjusted according to local policy/clinician's discretion, but is not an absolute requirement.

8.10 Chemotherapy Dose-banding

Dose banding will be permitted as per local hospital policy (assumes dose banding is within 5% of actual calculated dose). The Trials Office will request each site to state upfront whether or not dose banding will be used.

8.11 Dose capping

There will be no dose capping.

8.12 Compliance

Patients will be instructed to keep a record of compliance in terms of their capecitabine treatment, by means of using a study patient diary card provided to the patient by the site. Patients should be asked to bring completed diary cards or other records and all their unused / remaining capecitabine tablets (empty, open or unopened) with them to each clinic visit. Sites should count remaining capecitabine at each visit. The patient diary cards should not be sent to the Trial Office but kept by the centre to monitor patient drug compliance. Compliance of M6620 (Berzosertib) and Cisplatin will be monitored by the patient record.

Accountability logs are required for capecitabine to determine that patients have received at least 80% of the prescribed treatment dose. Returns should be reconciled against the patient diary and the reason for any discrepancy documented. Site staff will collect and count patient returns which must be recorded on the drug accountability log.

8.13 Management of overdose

Overdose of M6620 (Berzosertib) can result in an increase in the severity of M6620 (Berzosertib) toxicities (section 9.3.2). Medical management of overdose should include stopping the chemotherapeutic agents and customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications. An overdose of cisplatin or capecitabine should be managed as per standard policy.

9 TOXICITY MANAGEMENT

9.1 Dose Limiting Toxicity

9.1.1 Reporting a DLT

A dose limiting toxicity is a toxicity that is considered related to M6620 (Berzosertib) or the interaction between M6620 (Berzosertib) and radiotherapy or chemoradiotherapy. **Dose limiting toxicities should be reported within 24 hours of the site becoming aware using the SAE form and scan and email as a PDF attachment to octo-safety@oncology.ox.ac.uk and send an email notification to octo-CHARIOT@oncology.ox.ac.uk.** For management of M6620 (Berzosertib) toxicities see section 9.3. Chemotherapy and radiotherapy toxicities should be managed as per standard practice.

9.1.2 Definition of a DLT

Stage A1

DLTs will be defined as per NCI CTCAE v4.03 and include:

- Absolute neutrophil count (ANC) <0.5 x 10^9/L for >7days
- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C) lasting >3 days
- Infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (absolute neutrophil count <1.0 x 10^9/L)
- Platelets <25 x 10^9/L
- Clinically significant bleeding attributed to grade 3 thrombocytopenia or requiring platelet transfusion
- Grade ≥3 oesophagitis onset within 2 weeks of starting radiotherapy
- Grade ≥3 pneumonitis onset within 3 months of starting radiotherapy
- Grade ≥3 nausea or vomiting not controlled by optimal outpatient anti-emetic treatment
- Grade ≥3 diarrhoea despite optimal outpatient anti-diarrhoeal medication use
- Other grade 3 ≥ effects thought to be directly treatment related to the combination of M6620 (Berzosertib) with radiotherapy
- Any toxicity causing a delay of radiotherapy completion by greater than one week
- Missing 2 consecutive doses of M6620 (Berzosertib) within a cycle due to Grade ≥3 toxicity
- A delay of any of the 3 treatments of 7 days or more within a cycle due to treatment related toxicity
- An elevation of ALT or AST >5 x ULN lasting 8 days or more
- A concurrent elevation of ALT or AST >3 × ULN and total bilirubin >2 × ULN in whom there is no evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevation
- Death due to drug related complications
- Cardiac:

- QTc prolongation (any QTc interval ≥500 msec or any change in QTc interval ≥60 msec from baseline) on ECG, unless related to an electrolyte abnormality and prolongation resolves with correction of electrolyte abnormality

- Any of the following (CTCAE criteria): Grade 2 or greater ventricular arrhythmia (second or third degree AV block), severe sustained/symptomatic sinus bradycardia less than 45 beats per minute (bpm) or sinus tachycardia >120 bpm not due to other causes (e.g., fever), persistent supraventricular arrhythmia (e.g., uncontrolled/new atrial fibrillation, flutter, atrioventricular nodal tachycardia, etc.) lasting more than 24 hours, ventricular tachycardia defined as >9 beats in a row or any length of torsades de pointes (polymorphic ventricular tachycardia with long QTc), or unexplained recurrent syncope

- Symptoms suggestive of congestive heart failure with confirmed Ejection Fraction (EF) <40% (by 2D-echocardiogram or Multiple Gated Acquisition [MUGA] scan)

- Troponin T: level which is consistent with myocardial infarction

Stage A2

DLTs will be defined as per NCI CTCAE v4.03 and include:

- Absolute neutrophil count (ANC) <0.5 x 10^9/L for >7days
- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C) lasting >3 days

- Infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (absolute neutrophil count <1.0 x 10^9/L)
- Platelets <25 x 10^9/L
- Clinically significant bleeding attributed to grade 3 thrombocytopenia or requiring platelet transfusion
- Grade ≥3 nausea or vomiting not controlled by optimal outpatient anti-emetic treatment
- Grade ≥3 diarrhoea despite optimal outpatient anti-diarrhoeal medication use
- Other grade ≥3 effects thought to be directly treatment related to the combination of M6620 (Berzosertib) with chemotherapy
- Missing 2 consecutive doses of M6620 (Berzosertib) within a cycle due to Grade ≥3 toxicity
- A delay of any of the 3 treatments of 7 days or more within a cycle due to treatment related toxicity
- An elevation of ALT or AST >5 x ULN lasting 8 days or more
- A concurrent elevation of ALT or AST >3 × ULN and total bilirubin >2 × ULN in whom there is no evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevation
- Death due to drug related complications
- Cardiac:

- QTc prolongation (any QTc interval ≥500 msec or any change in QTc interval ≥60 msec from baseline) on ECG, unless related to an electrolyte abnormality and prolongation resolves with correction of electrolyte abnormality
- Any of the following (CTCAE criteria): Grade 2 or greater ventricular arrhythmia (second or third degree AV block), severe sustained/symptomatic sinus bradycardia less than 45 beats per minute (bpm) or sinus tachycardia >120 bpm not due to other causes (e.g., fever), persistent supraventricular arrhythmia (e.g., uncontrolled/new atrial fibrillation, flutter, atrioventricular nodal tachycardia, etc.) lasting more than 24 hours, ventricular tachycardia defined as >9 beats in a row or any length of torsades de pointes (polymorphic ventricular tachycardia with long QTc), or unexplained recurrent syncope
- Symptoms suggestive of congestive heart failure with confirmed Ejection Fraction (EF) <40% (by 2D-echocardiogram or Multiple Gated Acquisition [MUGA] scan)
- Troponin T: level which is consistent with myocardial infarction

Stage B

Acute DLTs will be defined as per NCI CTCAE v4.03 and include:

- Absolute neutrophil count (ANC) <0.5 x 10^9/L for >7days
- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever $\geq$38.5°C) lasting >3 days
- Infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (absolute neutrophil count <1.0 x 10^9/L)
- Platelets <25 x 10^9/L
- Clinically significant bleeding attributed to grade 3 thrombocytopenia or requiring platelet transfusion
- Grade ≥3 oesophagitis onset during induction chemotherapy or within 2 weeks of starting radiotherapy
- Grade ≥3 pneumonitis onset within 3 months of starting radiotherapy
- Grade ≥3 nausea or vomiting not controlled by optimal outpatient anti-emetics
- Grade ≥3 diarrhoea despite optimal outpatient anti-diarrheal medication use
- Other grade 3 ≥ effects thought to be directly treatment related to the combination of M6620 (Berzosertib) with chemotherapy or radiotherapy
- Any toxicity causing radiotherapy delivery delay by >3 consecutive fractions
- An elevation of ALT or AST >5 x ULN lasting 8 days or more
- A concurrent elevation of ALT or AST >3 × ULN and total bilirubin >2 × ULN in whom there is no evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevation
- Missing 2 consecutive doses of M6620 (Berzosertib) within a cycle due to Grade ≥3 toxicity
- A delay of any of the 3 treatments of 7 days or more within a cycle due to treatment related toxicity
- Death due to drug related complications
- Cardiac:

- QTc prolongation (any QTc interval ≥500 msec or any change in QTc interval ≥60 msec from baseline) on ECG, unless related to an electrolyte abnormality and prolongation resolves with correction of electrolyte abnormality
- Any of the following (CTCAE criteria): Grade 2 or greater ventricular arrhythmia (second or third degree AV block), severe sustained/symptomatic sinus bradycardia less than 45 beats per minute (bpm) or sinus tachycardia >120 bpm not due to other causes (e.g., fever), persistent supraventricular arrhythmia (e.g.,

uncontrolled/new atrial fibrillation, flutter, atrioventricular nodal tachycardia, etc.) lasting more than 24 hours, ventricular tachycardia defined as >9 beats in a row or any length of torsades de pointes (polymorphic ventricular tachycardia with long QTc), or unexplained recurrent syncope

- Symptoms suggestive of congestive heart failure with confirmed Ejection Fraction (EF) <40% (by 2D-echocardiogram or Multiple Gated Acquisition [MUGA] scan) or a relative decrease >20% from screening assessment of EF or if performed within 12 months
- Troponin T: level which is consistent with myocardial infarction

Late DLTs – onset 6 weeks after completion of radiotherapy will be defined as per RTOG/EORTC late toxicity and Mellow Dysphagia score (Appendix C, D):

- Grade ≥3 lung and heart toxicity
- Grade 3 oesophageal toxicity with an increase in Mellow score by ≥2 since baseline (need to exclude disease progression on CT and/or endoscopy and biopsy)
- Grade 4 oesophageal toxicity

Notes:

- In the event of a Grade 4 neutropenia, a full blood count must be performed no more than 7 days after the onset of the event to determine if a DLT has occurred. Continue to monitor the subject closely until resolution to Grade 3 or less.
- In the event of a Grade 3 or higher elevation in ALT or AST, follow-up laboratory assessments should be performed every 48 to 72 hours until reduced to Grade 2 or less.

9.2 Management of treatment toxicities

In response to a toxicity of unknown or indeterminate causality M6620 (Berzosertib) treatment should be primarily withheld followed by chemotherapy. In the case of M6620 (Berzosertib) or chemotherapy toxicity or dose modification during the concurrent chemoradiotherapy phase patients should continue with RT where possible. The decision as to whether to continue radiotherapy is at the discretion of the treating clinician. If toxicity could be attributable to systemic therapy or radiotherapy, systemic therapy should be withheld first (see section 12.8 for management of radiotherapy toxicities).

Appropriate dose modifications should be considered for all agents if grade 3 or 4 toxicity occurs (see section 9.3 and 9.4 below). In stage A2 dose reductions should not be made beyond 50% of starting dose and the patient should come off study if further Grade 3 or 4 non-haematologic toxicity or Grade 4 haematologic toxicity is then experienced.

9.3 Management of M6620 (Berzosertib) drug toxicities

No dose modifications of M6620 (Berzosertib) may be made (see 9.3.1 for exception in stage A2 below). Treatment may be interrupted because of a non-DLT of Grade 3 or higher, at the discretion of the Investigator. Treatment may be resumed when all toxicities have returned to grade 2 or less, at the discretion of the Investigator. If two consecutive doses of M6620 (Berzosertib) within a cycle are missed due to M6620 (Berzosertib) related Grade ≥3 toxicity, this constitutes a DLT, and no further M6620 (Berzosertib) will be administered. Missed doses due to ≤Grade 2 events, will be classified as non-compliance, not a DLT. A delay of any of the 3 treatments of 7 days or more within a cycle due to treatment related toxicity would be considered a DLT.

If the subject misses a dose of M6620 (Berzosertib) for any reason other than toxicity the dose should not be made up and the scheduling should continue as normal, from the next planned dose of M6620 (Berzosertib), unless it is a Tuesday dose which can be made up on the following day (Wednesday). If radiotherapy is withheld for toxicity or other reasons, M6620 (Berzosertib) should also be withheld and the dosing schedule should continue from the next planned dose once radiotherapy has resumed (see also section 8.4).

In Stage A2, if a patient experiences a DLT, they may continue on trial treatment at the next lowest dose level at the discretion of the treating investigator.

In Stage B, if a patient experiences a DLT, the TMG will convene to decide whether it is appropriate for the patient to continue receiving trial treatment, potentially at a reduced frequency of doses.

9.3.1 Additional guidance Stage A2

In stage A2 M6620 (Berzosertib) must not be dose reduced in the first 4 weeks of treatment but doses may be omitted for toxicity (as above). The M6620 (Berzosertib) dose may be reduced after the 4 week DLT window is complete as follows:

1. For Grade 4 hematologic toxicity: dose of M6620 (Berzosertib) to be reduced by 25%.
2. For Grade 3 non-hematologic toxicity: dose of M6620 (Berzosertib) to be reduced by 25%.
3. For Grade 4 non-hematologic toxicity: dose of M6620 (Berzosertib) to be reduced by 50%.

If the dose of M6620 (Berzosertib) has already been reduced by 25% a further dose reduction of 25% may be made to 50% of starting dose. However no further dose reductions may be made beyond 50% of starting dose and the patient should come off study if further Grade 3 or 4 non-haematologic toxicity or Grade 4 haematologic toxicity is then experienced.

9.3.2 Toxicities associated with M6620 (Berzosertib)

Acute hypersensitivity reactions are a toxicity of M6620 (Berzosertib). Serious acute hypersensitivity reactions have occurred during the second M6620 (Berzosertib) infusion in approximately 5% of subjects administered M6620 (Berzosertib) and should be reported as an Serious adverse reaction (see section 8.4 for management of hypersensitivity reactions). In at least one sixth of patient reactions at the site of infusion were noted including erythema, swelling, pruritus. The most common toxicities reported in patients who have received M6620 (Berzosertib) are: fatigue, abdominal pain, diarrhoea, nausea and vomiting, decreased appetite, cough, headache and fever. Almost all instances of these toxicities occurred in patients who were also receiving chemotherapy in combination with M6620 (Berzosertib). M6620 (Berzosertib) in combination with chemotherapy may exacerbate the risks associated with the chemotherapy. The most frequently noted grade ≥ 2 laboratory abnormalities observed (in combination with chemotherapy) are neutropenia, low lymphocytes, low haemoglobin and elevated ALT/AST. M6620 (Berzosertib) absorbs UV-visible radiation spectrum and is widely distributed including to the skin, so subjects should be cautioned to minimise exposure to the sun and other sources of visible and UV radiation and to take protective measures when necessary. Full range of toxicities can be found in the M6620 (Berzosertib) IB.

9.4 Management of chemotherapy toxicities

Toxicity due to capecitabine or cisplatin administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction) as per standard of care. Once the dose has been reduced, it should not be increased at a later time. Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or worse toxicity occurs. Detailed information can be found in the product SPCs available from www.medicines.org.uk .

9.4.1 Haematological toxicity

Myelosuppression is uncommonly observed with cisplatin and capecitabine. Neutropaenia and thrombocytopaenia should be monitored according to the recommended protocol and appropriate dose modifications made. Anaemia may occur cumulatively with cisplatin and should be corrected during radiotherapy to maintain the haemoglobin ≥10g/dL. The FBC should be taken and reviewed (up to 3 days) prior to Day 1 of each cycle of chemotherapy.

Dose modification for haematological toxicities

Neutrophil / platelet count (10^9/L) **(day 1 of subsequent cycles)**	**Action**
ANC ≥ 1 and/or plts ≥ 75	Full dose drugs
ANC 0.5- <1 and/or plts 50- <75 OR any episode of neutropenic sepsis during the previous cycle	Stop chemotherapy until recovery. Restart with 25% dose reduction cisplatin and capecitabine
ANC <0.5 and/or plts <50	Stop chemotherapy until recovery. Restart with 50% dose reduction cisplatin and capecitabine

9.4.2 Non-haematological toxicity

Gastrointestinal toxicity:
Nausea and vomiting is common following cisplatin, usually starting within 1 hour of treatment and lasting up to 24 hours. Anorexia, nausea and occasional vomiting may persist for up to one week. Nausea occurs less commonly with capecitabine (Diarrhoea occurs with capecitabine and patients should receive advice regarding discontinuation of therapy and use of loperamide or codeine phosphate). Clinicians should be aware of infective causes of diarrhoea (e.g. *Clostridium difficile)*, and patients should be tested in cases of concern. Antibiotic treatment is not recommended routinely but may be required in such circumstances. Stomatitis occurs with capecitabine and patients should receive advice regarding good oral care, and the use of mouthwash (e.g. Corsodyl™).

Anaphylaxis: Reactions to cisplatin therapy have been occasionally reported in patients who were previously exposed to cisplatin. Patients who are particularly at risk are those with a prior history or family history of atopy. Serious reactions may be controlled by IV adrenaline, corticosteroids or antihistamines.

Serum Electrolyte Disturbances: Hypomagnesaemia, hypocalcaemia, hyponatraemia, hypokalaemia and hypophosphataemia have been reported to occur in patients treated with cisplatin and hypomagnesemia may occur and should be monitored according to the protocol.

Other Toxicities: Hair loss is not expected with this combination but may rarely occur with most chemotherapeutic agents. Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. These events may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (haemolytic uraemic syndrome) or cerebral arteritis. There have been reports of optic neuritis, papilloedema and cerebral blindness following treatment with cisplatin.

Non-haematological toxicity dose reductions for Capecitabine and Cisplatin Toxicity	During a course of therapy – Cisplatin and Capecitabine	Dose adjustment for next cycle (% of starting dose)
Grade 1	Maintain dose level for both drugs	100% Cisplatin & Capecitabine
Grade 2		
1st appearance	Interrupt until resolved to grade 0-1	100% Cisplatin & Capecitabine
2nd appearance	Interrupt until resolved to grade 0-1	75% Cisplatin & Capecitabine
3rd appearance	Interrupt until resolved to grade 0-1	50% Cisplatin & Capecitabine
Grade 3		
1st appearance	Interrupt until resolved to grade 0-1	75% Cisplatin & Capecitabine
2nd appearance	Interrupt until resolved to grade 0-1	50% Cisplatin & Capecitabine
3rd appearance	Discontinue treatment permanently	
Grade 4		
1st appearance	Discontinue permanently *Or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1 after discussion with Chief Investigator	50% Cisplatin & Capecitabine

9.4.3 Additional capecitabine toxicities

The following are the recommended dose modifications for toxicity. In addition patients should receive loperamide in case of diarrhoea and mouthwashes and anti-emetics according to local policy. Toxicities should be graded according to CTCAE v4.03. In particular, diarrhoea, nausea, vomiting, stomatitis and skin reactions are to be noted. Please use the

alternative specific toxicity for Hand-foot syndrome (PPE), the frequency of which in patients receiving capecitabine has led to altered toxicity ratings.

Nephrotoxicity

GFR (mls/min) Baseline and prior to Day 1	Capecitabine dose
≥ 50ml/min	100%
30-49 ml/min	75%
< 30ml/min	This group of patients should be withdrawn from trial treatment (please complete withdrawal form at Level 1) and treated according to local investigator choice and continue to complete CRFs

Grade of hand-foot syndrome	
1	Numbness, dysaesthesia/paraesthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt the patient's normal activities.
2	Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living.
3	Moist desquamation, ulceration, blistering and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

If grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-foot syndrome, subsequent doses of capecitabine should be decreased.

Chest pain

For patients with a history of angina please ensure they have GTN spray at home and remain on their cardiac medication. If unexplained chest pain occurs on treatment, capecitabine should be stopped, an ECG performed and cardiac enzymes measured. In the case of angina or myocardial infarction being confirmed this should be managed according to usual local practice. Patients should not recommence capecitabine therapy and further therapy should be discussed with the Chief Investigator. Such cardiac toxicity should be reported through a SAE form.

Hepatotoxicity

Isolated elevation of serum transaminases may be related to capecitabine and will not require dose interruption unless AST/ALT levels are ≥ 5 times ULN. If AST/ALT is above this level, capecitabine will be interrupted till it returns to ≤ 2.5 times ULN.

DPD deficiency

If a patient has not received capecitabine in the past DPD testing should be undertaken as per institutional protocol. Patients with partial or full DPD deficiency are not eligible for the study.

Occasionally (approximately 1-3%) a patient may have a markedly exaggerated toxicity due to reduced 5FU catabolism. If this occurs, await full recovery of toxicities. Further treatment should be discussed with the Chief Investigator or one of the clinical co-investigators.

9.4.4 Additional Cisplatin toxicities

Nephrotoxicity

Cisplatin produces cumulative nephrotoxicity. If a baseline estimate of renal function using the Cockroft & Gault formula predicts the GFR to be ≥ 60mL/min full dose cisplatin should be used. If the estimate is <60mls/min a formal measure of Creatinine clearance should be performed (EDTA or 24 hour urine test) and the appropriate cisplatin dose used (see table below). In the case of a 25% deterioration in estimated renal function (using the Cockroft & Gault formula) on pre-

treatment blood samples a formal Creatinine clearance test should be performed and pending this an appropriate dose reduction in cisplatin should be made. The formal Creatinine clearance result, when available, takes precedent over estimated GFR for subsequent cisplatin dose calculations.

GFR (mls/min) Baseline and prior to Day 1	Cisplatin Dose
≥ 60ml/min	100%
45-59ml/min	50%
30-44 ml/min	Stop Cisplatin. This group of patients if in dose level 1 should be withdrawn from trial treatment (please complete withdrawal form at Level 1) and treated according to local investigator choice and continue to complete CRFs.
< 30ml/min	This group of patients should be withdrawn from trial treatment (please complete withdrawal form at Level 1) and treated according to local investigator choice and continue to complete CRFs

Neurotoxicity/ototoxicity

Neurotoxicity/ototoxicity appears to be cumulative. Prior to each course, any new or progressive symptoms of peripheral neuropathy should be established.

10 OTHER TREATMENTS (NON-IMPS)

10.1 Background systemic therapy

The chemotherapy agents cisplatin and capecitabine are not licensed for use in oesophageal cancer but are used as the standard treatment for oesophageal cancer in the UK. Details of dose administration and toxicity management can be found in the SPC, standard practices and policies apply throughout (Stage B). However, cisplatin and capecitabine are not considered standard practice in stage A2 & B therefore these drugs are considered IMPs for the purpose of this trial.

10.2 Support medication

Pre-medication and supportive medication should be given as per local practice.

10.3 Concomitant medication and non-drug therapies

Concomitant medication may be given as medically indicated. All patients will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the previous 4 weeks prior to the first treatment visit. They must also inform the Investigator about any new medication started while in the trial. Details (including indication, doses, frequency and start / stop dates) of concomitant medication taken during the trial until the completion of the off-study visit must be recorded in the medical record and the appropriate CRF.

10.4 Prohibited therapies

Patients should not be prescribed any other anti-cancer or investigational therapies while participating in this study. In addition, the following should be noted.

- Radiation therapy is permitted as per schedule.
- Oesophageal stent is not permitted.
- Live vaccine is not permitted within 30 days prior to treatment start, for the duration of trial treatment and for 6 weeks after the last administration of IMP dose.

10.5 Potential Drug Interactions

10.5.1 M6620 (Berzosertib)

Drug interaction profile of M6620 (Berzosertib) has not been fully characterised, caution should be used when co-administering medications with M6620 (Berzosertib). Based on its mechanism of action, M6620 (Berzosertib) may increase the frequency or severity of adverse reactions associated with cisplatin.

As M6620 (Berzosertib) is primarily metabolised by CYP3A4, concomitant administration with potent inhibitors or potent inducers of CYP3A4 should be avoided. Up to 14 days prior to receiving study drug and through the duration of the study, the following list of potent CYP3A4 inhibitors or inducers should be avoided. Please note that the following list is not exhaustive:

Potent CYP3A4 inhibitors: Clarithromycin, itraconazole, ketoconazole, mibefradil, hepatitis C virus and HIV protease inhibitors, nefazodone, posaconazole, telithromycin, voriconazole

Potent CYP3A4 inducers: carbamazepine, rifampicin, rifapentine, phenobarbital, phenytoin, primidone, St John's wort

Grapefruit/grapefruit juice, Seville or blood oranges or marmalade – none allowed within 14 days before first dose or during treatment period with M6620 (Berzosertib).

Haemopoetic growth factors - none allowed within 14 days before first dose or prophylactic use with cycle 1.

10.5.2 Capecitabine and Cisplatin

Capecitabine and Cisplatin interact with several medications and the following precautions should be followed:

Drugs to be avoided:

- Cumulative nephrotoxicity may be potentiated by aminoglycoside antibiotics e.g. gentamicin. These should not be administered, if possible, simultaneously or 1-2 weeks after treatment with Cisplatin
- Thymine antivirals and analogues, including Brivudine (would require a 4-week wash out prior to entering in the trial)
- Methotrexate, Bleomycin - Reduce renal excretion of bleomycin and methotrexate which increases their toxicity
- Anti-gout agents (like allopurinol, colchicine, probenecid or sulfinpyrazone) - reduce the efficacy of Capecitabine
- Warfarin - Coumarin derivative anticoagulants (like warfarin) require more frequent monitoring due to altered coagulation parameters, and effects may occur up to several months after initiating Capecitabine therapy. A low molecular weight heparin can be used as a replacement during trial treatment.

The following drugs may require dose modification:

- Ototoxic drugs like aminoglycoside antibiotics or loop diuretics (e.g. furosemide), may increase ototoxic potential of Cisplatin.
- Anti-epileptics; the serum level of phenytoin may be reduced and levels should be monitored and the dose adjusted accordingly - may increase Capecitabine levels
- Folic acid/folinic acid – reduces maximum tolerated dose and may increase Capecitabine toxicity
- Aluminium hydroxide or magnesium hydroxide containing antacids – increase plasma concentrations of Capecitabine and its metabolite 5DFCR (5'-deoxy-5-flurocytidine)
- Interferon alpha – reduces maximum tolerates dose of Capecitabine
- Cytochrome p450 down regulation by Capecitabine may affect the following class of drugs – angiotensin II blockers (losartan, valsartan); oral hypoglycaemic agents (glipizide, tolbutamide, rosiglitazone); NSAIDS (indomethacin, celecoxib, diclofenac, ibuprofen)

Please note that the above contraindications are not exhaustive and investigators should refer to the SPC for full guidance www.medicines.org.uk.

11 DRUG MANAGEMENT

All details regarding M6620 (Berzosertib) packaging, labelling and dispensing will be included in the Pharmacy Manual. Cisplatin and capecitabine should be managed as per local policies and procedures.

11.1 Drug supplies

11.1.1 M6620 (Berzosertib)

M6620 (Berzosertib) will be supplied by MERCK KGAA, DARMSTADT GERMANY in 10ml vials of a 20mg/ml solution for infusion. MERCK KGAA, DARMSTADT GERMANY will ship drug to Fisher Clinical Services where it will be labelled according to applicable regulatory requirements and QP released.

11.1.2 Capecitabine and cisplatin

Cisplatin as a solution for injection and capecitabine as a tablet for oral use should be supplied from trial site's own stock and funded locally.

11.2 Drug ordering

Initial supplies of M6620 (Berzosertib) are sent out by Fisher Clinical Services after they have been informed by the Trial Office that all approvals are in place. Subsequent supplies will be ordered by the Trial office. Pharmacy should request additional shipments of M6620 (Berzosertib) using the drug order form provided. Email the completed form to the Trial Office
(octo-CHARIOT@oncology.ox.ac.uk).

Pharmacy is responsible for monitoring the M6620 (Berzosertib) stock and re-ordering when required. Complete drug orders received by the Trial Office before 4pm will arrive at the Pharmacy within 10 working days.

If a vial of M6620 (Berzosertib) is accidentally destroyed or damaged, i.e. by dropping the vial, damaged packaging or through contamination, the pharmacist should contact the Trial Office for replacement.

11.3 IMP Receipt

A copy of each M6620 (Berzosertib) delivery note and temperature monitoring form should be **scanned and emailed as a PDF attachment to octo-CHARIOT@oncology.ox.ac.uk.** The original should be kept in the Pharmacy File. If supplies are damaged on arrival contact the Trial Office. Damaged supplies should be destroyed on site and a Drug Destruction Log completed.

11.4 Handling and storage

11.4.1 M6620 (Berzosertib)

Unopened vials of single use sterile light protected M6620 (Berzosertib) should be stored at controlled room temperature (15°C to 30°C). It should be retained in the original package to protect from light. Shelf life as instructed on packaging. Following the preparation of diluted M6620 (Berzosertib), intravenous bags should be covered to protect from light and stored in the dark.

The Investigator or an authorised designee will ensure that all the investigational products are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for via drug accountability forms as instructed by the Trial Office.

11.4.2 Capecitabine and cisplatin

Will be handled and stored as per the local practice.

11.5 Labelling

Ensure the phrase "Keep out of reach of children" is used on all medications.

11.5.1 M6620 (Berzosertib)

A 20mg/mL (10mL total volume) M6620 (Berzosertib) sterile solution will be supplied by Merck KGaA, Darmstadt Germany. The responsible Pharmacy will ensure that IMP supplies dispensed for trial use are appropriately labelled as per local practice for infusions in accordance with all applicable regulatory requirements.

11.5.2 Capecitabine and cisplatin:

Labelling will be as per local practice.

11.6 Dosing and dispensing

11.6.1 M6620 (Berzosertib)

M6620 (Berzosertib) will be supplied as 20 mg/mL M6620 (Berzosertib) (in betadex sulfobutyl ether and acetate buffer) to be diluted in Glucose 5% IV infusion before intravenous infusion. M6620 (Berzosertib) solution will be constituted into the individual dosing containers by a qualified member of pharmacy staff. Details of dose preparation will be provided in the Pharmacy Manual (see Formulation Preparation Instructions).

M6620 (Berzosertib) will be administered intravenously over 60 minutes (±10 minutes). When the total volume of infusion exceeds 600mL, the infusion may be extended beyond 60 minutes (as tolerated), but no more than 90 minutes.

11.6.2 Cisplatin and capecitabine

Refer to the Summary of Products Characteristics (SPC) for full prescribing information and details of drug reconstitution, administration and stability (http://www.medicines.org.uk/emc/). Mannitol may be given concurrently with cisplatin or may be given as a short infusion according to local policy.

11.7 Drug accountability

Drug accountability is the responsibility of the site pharmacist listed on the trial delegation log. Full drug accountability records must be maintained for M6620 (Berzosertib), cisplatin and capecitabine. Hospitals may amend the Drug Accountability Logs provided or use their own documentation if it captures all the information requested on the Drug Accountability Logs and has been approved by the Trial Office in advance.

At the conclusion of the study the overall numbers of drug shipped to the centre, the number dispensed and the number destroyed or returned will be provided by the pharmacy. An account must be given of any discrepancy.

11.8 Drug destruction

Chemotherapy drugs will be disposed of as per local hospital policy. Disposal of M6620 (Berzosertib) will be according to the table below.

Used / partially used vials	Disposal at site according to local hospital policy.
Patient returns (Capecitabine only)	Disposal at site according to local hospital policy. Documented on Drug Accountability Log
Expired drug	Any expired drug should be disposed of at site according to local hospital policy. A Drug Destruction Log should be completed.
Drug left unused	Once authorised to do so, any unused drug should be disposed of at site according to local hospital policy. A Drug Destruction Log should be completed.

The original drug destruction logs should be placed in the Pharmacy File and a copy **scanned and emailed to octo-CHARIOT@oncology.ox.ac.uk.**

11.9 Occupational safety

Vein extravasation and accidental spillages should be dealt with according to hospital policy. The product is not expected to pose an occupational safety risk to site staff under normal conditions of use and administration.

12 RADIOTHERAPY (OR CHEMORADIOTHERAPY)

12.1 Dose prescription and fractionation

It is highly recommended that the radiotherapy will be delivered in a single phase, treating each field daily Monday to Friday and prescribed and recorded as per ICRU 50/62. Conformal radiotherapy with a pixel based inhomogeneity correction is essential. Photon energy should be between 6MV and 10MV (energies in excess of 10MV should only be used in exceptional cases due to secondary build-up depth.

Stage A1
Patients recruited to Stage A1 of CHARIOT will receive a planned single-phase treatment delivered with IMRT. If IMRT is not possible then a 3D Conformal approach (meeting the required constraints) should be used. The total dose of radiation will be 35Gy in 15 fractions treating once daily, 5 days a week Monday to Friday and prescribed and recorded as per ICRU 62.

Stage B
Patients recruited to Stage B of CHARIOT should have a single phase inverse-planned IMRT treatment plan produced and treatment delivered with multiple field static or rotational fields.
The total dose of radiation will be 50Gy in 25 fractions treating once daily, 5 days per week Monday to Friday and prescribed and recorded as per ICRU 62.

12.2 Radiotherapy localisation

A contrast enhanced CT (CECT) and depending on the tumour location, this will be followed by 4DCT in treatment position, i.e. supine with their arms above their heads, must be acquired for RT planning. The 4DCT is not mandated for Stage A and imaging will be done as per local policy. Intravenous contrast should be used (providing adequate renal function), to help distinguish the GTV from surrounding tissues; but oral contrast should not be used as it is not helpful in most cases and may interfere with planning calculations. To enable accurate assessment of the doses to organs at risk (OAR) the scan should extend superiorly to at least one CT slice above the apices of the lungs and inferiorly to the iliac crest (L2). Scans for upper third tumours may need to extend superiorly to the tragus.

For Stage B, the planning scan should be performed as per local guidelines ideally within 2 weeks of starting the neoadjuvant phase of chemotherapy. CT slice thickness should be no greater than 3mm. It is recommended that all patients have a CT scan of the thorax, abdomen and pelvis and an endoscopic ultrasound (EUS), noting the full extent of the disease with reference to anatomical landmarks. PET has an established role in the UK in terms of staging oesophageal cancer and can be useful in determining the extent of the disease, but the volume as defined by CT and EUS should not be reduced based on PET findings alone.

12.3 Target volume definition (TVD)

Patients will be divided into two separate groups according to the location of the *centre of the primary tumour*:

a) Proximal tumours (tumours of upper and middle 1/3 oesophagus) defined here as primary tumour whose midpoint is above 32cm ab oral (NB proximal extent of primary being below 15cm is an eligibility criteria).

b) Distal tumours (tumours of distal 1/3 of oesophagus and gastro-oesophageal junction (GOJ)), defined here as being eligible patients with tumours whose midpoint is below 32cm ab oral (NB distal extent of primary being less than 2cm from the GOJ is an eligibility criteria).

This distinction accounts for the need to manually outline the elective nodal regions below the GOJ for the distal tumours. There is also significant movement in this region due to respiration requiring a larger PTV margin. Where possible, the centres are encouraged to use 4DCT planning scans for distal tumours.

Targets are defined following the principles of ICRU 50 and 62. The target volumes are localised on axial slices of the planning 3DCT or 4DCT scan.

Stage A1 - All tumours

Volume	Description
GTV	Consists of the primary tumour and involved nodes deemed treatable and the circumference of the oesophagus at the level of disease. GTV definition is aided by information from EUS, diagnostic spiral CT scan, barium studies and 18-FDG PET scan if available. Encompass 'tumour' seen on the planning CT even if outside the EUS defined disease extent i.e. the GTV should be the most proximal and distal extension of disease as seen on EUS or CT scan. The lateral and anterior-posterior GTV margins are derived from the planning CT scan.
CTVA	GTV is copied and labelled 'CTVA' and is grown manually to include the circumference of the oesophagus superiorly and inferiorly. The superior-inferior margin of CTVA will be 10mm from the edges of GTV.
CTVB	CTVA is copied and labelled 'CTVB'. It is grown by adding 10mm in right-left and anterior-posterior directions using the Treatment Planning System (TPS).

PTV	CTVB is copied and labelled 'PTV' and is grown by adding 10mm in the superior – inferior and 7 mm circumferentially using the TPS (2mm Internal Margin, IM and 5mm Setup Margin, SM).

Stage B - Proximal tumours

Volume	Description
GTVp	Consists of the primary tumour and the circumference of the oesophagus at the level of disease. GTV definition is aided by information from EUS, diagnostic spiral CT scan, barium studies and 18-FDG PET scan. Encompass 'tumour' seen on the planning CT even if outside the EUS defined disease extent i.e. the GTV should be the most proximal and distal extension of disease as seen on EUS or CT scan. The lateral and anterior-posterior GTV margins are derived from the planning CT scan.
GTVn	Consists of involved nodes not in continuity with the tumour. These should be outlined separately and named separately e.g. GTVn1, GTVn2 etc. where more than one GTVn exist. Only the node should be outlined – it is not required to include the full circumference of the oesophagus.
GTVpn	Combine GTVp and all GTVn and the circumference of the intervening oesophagus.
CTVA	GTVp + 20mm sup-inf (manually grown along direction of oesophagus) OR GTVn + 10mm superior-inferior margin (If GTVn is more proximal/distal than GTVp).
CTVB	CTVB = CTVA + 10mm circumferentially (but not superior-inferior), edited for normal structures but NOT beyond CTVC. Normal structures include lung, pericardium, large vessels, trachea, right and left main bronchi, liver and the vertebrae, both above and below the diaphragm.
CTVC	CTVA + 5mm circumferentially (but not superior-inferior) – this is the minimum expansion around CTVA and is respected when CTVB is edited.
PTV	CTVB is copied and labelled 'PTV' and is grown by adding 10mm in the superior – inferior and 7 mm circumferentially using the TPS (2mm Internal Margin, IM and 5mm Setup Margin, SM). Posteriorly this margin may be reduced if the PTV extends across the vertebrae by more than 5mm as the margin for internal movement is not required as tumour cannot move into vertebrae and only setup margin is required.

Stage B - Distal tumours (3DCT)

Volume	Description
GTVp	As for proximal tumour
GTVn	As for proximal tumour
CTVA	GTVp is copied and labelled 'CTVA' and is grown manually to include the circumference of the oesophagus superiorly and inferiorly by 20mm.
CTVN	GTVn is coped and labelled 'CTVn' and is grown by a 5mm margin in all directions (for multiple nodes, label CTVn1, CTVn2 etc). This defines a minimum margin around positive nodes to assist in the delineation of CTVB.
CTVB	CTVA is copied and labelled 'CTVB'. It is grown by adding 10mm in right-left and anterior-posterior directions using the Treatment Planning System. CTVB is edited to exclude lung, pericardium, large vessels and the vertebrae. CTVA is copied and labelled CTVC. It is grown by adding 5 mm circumferential, this contour is then combined with CTVB to create CTVB1. *Below the GOJ* CTVB1 is grown manually to include the volume at risk to a total of 20mm below GTVp and at least 10mm below lowest GTVn. Therefore this volume should include CTVn and the elective nodal regions at high risk of microscopic spread (lymph node stations along the lesser curve to include the para-cardial, and left gastric lymph nodes along the lesser curve of the stomach).
PTV	CTVB1 is copied and labelled 'PTV' and grown 10mm superiorly and 7 mm circumferentially (2mm IM + 5mm SM) and 15mm inferiorly (10mm IM + 5mm SM) using the TPS. Posteriorly this margin may be reduced if the PTV extends across the vertebrae by more than 5mm as the margin for internal movement is not required as tumour cannot move into vertebrae and only setup margin is required.

Distal tumours (4DCT)

The principle involved in 4D planning is to account for intra-fraction motion and therefore generate patient specific volumes. It is expected that sites will have detailed local guidance for acquisition and outlining on 4D dataset, which has been accredited as part of previous trial involvement. Briefly, GTVp. GTVn, CTVA and CTVB contours are generated (as per the distal tumour 3DCT protocol above) on the Maximum Inhalation scan, Maximum Exhalation scan and Reference scan of the 4DCT dataset resulting in the following volumes:

Maximum inhalation scan - GTVp_MaxIn, GTVn_MaxIn, CTVA_MaxIn, CTVB_MaxIn
Maximum exhalation scan – GTVp_MaxEx, GTVn_MaxEx, CTVA_MaxEx, CTVB_MaxEx
Reference scan - GTVp_Ref, GTVn_Ref, CTVA_Ref, CTVB_Ref

ITV is derived by combining CTV_MaxIn, CTVB_MaxEx and CTVB_Ref as the composite CTVB volumes, edited to account for any additional motion seen from all other 4DCT phases (i.e. the editing will result in the ITV only being made bigger, to account for the maximum extent of these motion effects). The above contours must be associated with the reference dataset.

PTV = ITV + SM = ITV + 5mm

Set up margin (SM) is applied for treatment inaccuracies, such as set up error, and for the purpose of this protocol ITV is grown by 5mm in all directions using the TPS. Following the generation of the PTV, outlining of the organs at risk structures and planning should be carried out on the reference data set only. Maximum length of PTV for Stage B = 15cm

12.4 Organs at risk

The organs at risk (OARs) that must be contoured for CHARIOT and the naming convention used in naming these structures are detailed below. The spinal cord should be outlined on slices which include or are within 20mm of the PTV in the superior and inferior directions and a Planning Risk Volume (PRV) for the cord is created to account for positioning error. The full extent of the right and left lungs are outlined, this should be done in such a way that the planning system will be able to calculate a combined lung dose volume histogram (DVH). The whole heart is outlined to the extent of the pericardial sac (if visible). The major blood vessels (superior to the organ) and the inferior vena cava (towards the inferior extent of the heart) are excluded. The whole liver is outlined if the level of its superior edge overlaps with the level of the inferior extent of the PTV. Each kidney is outlined separately if the level of its superior edge overlaps with the level of the inferior extent of the PTV. The whole stomach should be outlined in such a way that a stomach DVH can be produced

12.5 Treatment Plan Optimisation

A single phase IMRT plan (or equivalent if using 3D Conformal approach) should be produced for patients treated in Stage A1 and an inverse-planned IMRT treatment plan should be produced for patients treated in Stage B. Type B algorithms (e.g., collapsed cone, AAA) must be used for dose calculation.

12.6 Dose constraints

Stage A1

All constraints corrected using the linear quadratic equation and are valid only for 35Gy/15# and should not be corrected

Structure	Naming convention*	DVH constraint
PTV	PTV	D99% > 95% V95% > 99%
ICRU Maximum Dose	Please label patient outline as “External”	D1.8cc < 107%
Spinal Cord PRV	SpinalCord_PRV	None
Heart	Heart	Dmean < 23Gy V28Gy < 45%
Combined lungs	Lungs	Dmean < 15Gy V18Gy < 25%
Stomach	Stomach	None
Liver	Liver	Dmean < 26Gy V28Gy<30%
Individual kidneys	Kidney_L and Kidney_R	V18Gy < 25%

Stage B:

The following dose objectives (Warren et al., 2014) and nomenclature (Santanam et al., 2012) should be used:

Structure name	Constraint	Optimal	Mandatory
PTV	V95% (47.5Gy) Dmedian	> 95% 100%	≥ 90% The median should be between 98-102% of the prescription dose.
External	D1.8cc		<107% of highest prescribed dose
SpinalCord_PRV	D0.1cc	< 40Gy	< 42 Gy
Heart	Dmean V30Gy	< 25Gy < 45%	<30Gy -
Lungs (Combined lungs)	Dmean V20Gy	< 17Gy < 20%	<19Gy ≤25%
Stomach_excl_PTV (Stomach excluding PTV)	V50Gy	< 16cc	< 25cc
Liver	Dmean V30Gy	≤28Gy < 30%	≤30Gy -
Kidney_L and Kidney_R (Individual kidneys)	V20Gy	< 25%	≤30%

12.7 Treatment delivery and verification

The treatment should be delivered in a single IMRT (or 3D Conformal approach in Stage A1 only) given the target volume described and the normal tissue constraints above, it is up to the individual participating centre to decide the field arrangements. It is recommended that the best available positional verification methods should be used to ensure correct delivery.

Stage A1

The use of cone beam CT matched to planning CT scans is recommended. The minimum on-treatment verification is for imaging the initial three fractions so that a correction for systematic error can be applied and then continue with weekly imaging. The isocentre should be moved if disagreement is seen in excess of agreed tolerance levels based on local study – typically 5mm.

Stage B

The use of cone beam CT matched to planning CT scans is mandated.

The minimum protocol for verification is on-line imaging of the initial five fractions so that a correction for systematic error can be applied and then continue with minimum weekly imaging thereafter for Stage B patients. The isocentre should be moved if disagreement is seen in excess of agreed tolerance levels based on local study – typically 5mm.

12.8 Management of radiotherapy toxicity

Radiotherapy interruptions will usually not be necessary. However, if radiation is held for any reason, all systemic therapy must also be held, including M6620 (Berzosertib). Interruptions may be kept to a minimum by the use of ancillary therapy and vigorous nutritional support. Interruptions are permitted only on the basis of toxicity. However, if the RT interruptions are due to either technical reasons or due to bank holidays, the schedule should be made up to account for this either on a Saturday or at the end of the treatment.

Toxicity	**Radiotherapy treatment interruption required:**	**Restart radiotherapy:**
Oesophagitis	Grade 4; see management of symptoms below. Aim to limit interruption to 3 treatment days (fractions).	
Haematological toxicity		
Neutrophils	Stop RT treatment if neutrophils <0.5 x 10^9/L or platelet count <25 x 10^9/L and monitor every 48 hours. Note: systemic therapy should be interrupted initially as per local policy.	If levels recover to 0.5 x 10^9/L (neutrophils) and 25 x 10^9/L (platelets)
Platelets		
Non-Haematological toxicity		
All toxicities	Grade 3: stop systemic treatment first and aggressive management should be pursued as per protocol, if no recovery to ≤grade 2 within 48h, consider withholding radiotherapy as follows:	
Vomiting	≥6 episodes of vomiting (≥ grade 3) lasting ≥ 3 days and unresponsive to antiemetics	Resolves to ≤ grade 2
Diarrhoea	An increase from a patients usual bowel habit of ≥ 7 watery stools/day (≥ grade 3) and unresponsive to antidiarrhoeals	Resolves to ≤ grade 2
Weight loss	Loss ≥ 10% (≥ grade 2) of pre-treatment weight	
Other[1]	Grade 3: withhold radiotherapy and chemotherapy	Resolves to ≤ grade 2

[1]Rarely, non-treatment related or unexpected toxicities may require interruption of therapy at the discretion of the treating oncologist. Interruption of therapy may continue until the toxicity has regressed to ≤grade 2 to allow resumption of therapy; however, every effort should be made to limit treatment interruptions to 1-2 weeks

Oesophagitis
If Grade 4 oesophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less. Patients requiring hospitalization because of oesophagitis may have their treatment interrupted. Acute oesophageal toxicity, which typically can occur within 2 weeks of the initiation of treatment and manifests as dysphagia, odynophagia, reflux symptoms, etc. should be pharmacologically managed with the following approach and should be initiated at the first signs or symptoms of oesophageal toxicity. Double PPI dose or start PPI, soluble paracetamol, oramorph, fluconazole and follow local policy. If a patient develops grade 3 oesophagitis in the last week of treatment (i.e., with 5 or fewer radiation treatments remaining), radiation therapy (but not chemotherapy) may continue at the discretion of the treating physician.

If interruption of therapy (< 2 weeks) becomes necessary, radiation therapy should be completed to the prescribed doses. If treatment restarts and there are week-ends left aim to compensate for days lost with treatment Saturdays. No BID fractionation is permitted.

Total number of fractions and elapsed days should be carefully reported. If an interruption of more than 2 weeks is necessary, resumption of treatment is at the discretion of CI. The patient's treatment plan will be considered a major deviation, but follow-up will be continued. Any toxicity that requires a dose reduction must be documented in the patient notes.

12.9 The management of unscheduled gaps in radiotherapy treatment

In the event of unscheduled gaps to radiotherapy treatment, these should be managed as described above (section 12.8)

CHARIOT patients should be managed as Category 1 patients in Stage B and Category 3 in stage A.

Where possible during concurrent chemoradiotherapy phase patients should continue with RT if unable to tolerate chemotherapy in Stage B. Patients should be withdrawn from trial if RT is delayed by greater than 2 weeks.

12.10 Radiotherapy quality assurance

In the first instance, any queries regarding radiotherapy quality assurance for CHARIOT should be addressed to the national Radiotherapy Trials QA group (RTTQA) contact (CHARIOT.RTTQA@wales.nhs.uk or www.rttrialsqa.org.uk).

Centres accredited for SCOPE2 can take part in the trial with no further pre-trial QA required, as these centres will have already completed an outlining and planning exercise, and submitted a process document for review by RTTQA.

Real time review of all patients will not be required instead there will be timely retrospective review of radiotherapy plans in the event of any unexpected or severe toxicity. All images, outlines, plan and dose data (DICOM) should be submitted to the RTTQA contact who will co-ordinate review of the data to check protocol compliance.

13 EVALUATION OF RESPONSE

13.1 Tumour assessment

A clinical and radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before starting the study treatment where applicable. The same methods that detect lesions at baseline will be used to follow these lesions throughout the study. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

Baseline evaluations

These will include radiological measurements of the extent of disease by CT scan or PET-CT scans and endoscopy will also be performed. All areas of disease present must be mentioned (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded on the scan reports. Any non-measurable lesions must be stated as being present.

Evaluations during treatment and at off-study

Tumour assessment will be repeated as per the schedule of events given or more frequently if clinically indicated. All lesions measured at baseline must be measured at subsequent disease assessments, and recorded on the scan reports. All non-measurable lesions noted at baseline must be reported as present or absent. Investigators must ensure that their radiologists are aware of the requirement to follow up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with RECIST (V1.1) criteria.

13.2 Tumour response

To be assigned a status of CR or PR, changes in tumour measurements must be confirmed by two consecutive observations. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after study treatment is started. Should rapid tumour progression occur before the completion of treatment the patient will be classified as having early progression (EP). Tumour response should be classified as “not evaluable” (NE), only when it is not possible to classify it under another response category, e.g., when baseline and/or follow-up assessment is not performed or not performed appropriately. The applicable overall response category for each visit that includes disease assessment must be recorded in the medical record for inclusion in the appropriate CRF in OpenClinica.

13.3 Other definitions of outcome:

Toxic death: Any death to which drug toxicity is thought to have a major contribution.
Early death: Death during the first three weeks of treatment that is not a toxic death.

14 SAFETY REPORTING

The Investigator will monitor each patient for clinical and laboratory evidence of adverse events on a routine basis throughout the study. Should an Investigator become aware of any study drug related SAEs following this period these must also be reported as stated below. Adverse event monitoring starts from the time the patient consents to the study until they complete the trial. All reportable AEs will be followed to a satisfactory conclusion. Any reportable drug-related AEs that are unresolved at the end of treatment visit are to be followed up by the Investigator until resolution or stabilisation. All AEs reported to the Trial Office will be processed according to internal SOPs. The Trial Office may request additional information for any AE as judged necessary.

14.1 Adverse Event Definitions

An Adverse Event or experience (AE) is any untoward medical occurrence in a study subject temporally associated with the administration of an investigational medicinal product (IMP) or a comparator product, whether or not considered related to the IMP or a comparator product. An AE can therefore be any unfavourable and unintended sign, symptom, disease (new or exacerbated) and /or significant abnormal laboratory or physiological observation temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

A Serious Adverse Event (SAE) is any AE, regardless of dose, causality or expectedness, that:

• **Results in death**	
• **Is life-threatening**	This refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• **Requires in-patient hospitalisation or prolongs existing inpatient hospitalisation**	In general, hospitalisation signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.
• **Results in persistent or significant incapacity or disability**	This means a substantial disruption of a person's ability to conduct normal life functions. It does not include experiences of relatively minor medical significance or accidental trauma (e.g. sprained ankle), which do not constitute a substantial disruption.
• **Is a congenital anomaly or birth defect**	
• **Is any other medically important event**	Defined as an event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Any new primary cancer must be reported as an SAE.

An Adverse Drug Reaction (ADR) is an AE which is considered to be causally related to any dose of the IMP. This means that a causal relationship between the IMP and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

An Unexpected Drug Reaction is an adverse drug reaction, the nature or severity of which, is not consistent with applicable product information (referring to information in SPC or IB).

A Suspected Unexpected Serious Adverse Drug Reaction (SUSAR) is a serious adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or SPC for an approved product).

14.2 Clinical laboratory abnormalities and other abnormal assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays and scans) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions given above.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. The

Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

14.3 Determining adverse event causality

The assessment of "relatedness" must be determined by a medically qualified individual and is the responsibility of the PI at site or agreed designee. AEs that will be considered related will include any AE that is documented as possibly, probably or definitely related to protocol treatment. The assessment of relatedness is made using the following:

Classification	Relationship	Definition
drug-related	**Definitely related**	• Starts within a time related to the study drug administration *and* • No obvious alternative medical explanation.
	Probably related	• Starts within a time related to the study drug administration *and* • Cannot be reasonably explained by known characteristics of the patient's clinical state.
	Possibly related	• Starts within a time related to the study drug administration *and* • A causal relationship between the study drug and the adverse event is at least a reasonable possibility.
not drug related	**Probably not related**	• The time association or the patient's clinical state is such that the study drug is not likely to have had an association with the observed effect.
	Definitely not related	• The AE is definitely not associated with the study drug administered.

The Investigator must endeavour to obtain sufficient information to confirm the causality of the adverse event (i.e. relation to surgery, study drug, background treatment, other illness, progressive malignancy etc) and give their opinion of the causal relationship between each AE and study drug. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further specialist opinion.

14.4 Reference safety information (RSI) for assessment of expectedness

- The reference safety information (RSI) for the IMP M6620 (Berzosertib) is section 7 of the IB for M6620 (Berzosertib) and lists all the expected side effects associated with the use of M6620 (Berzosertib).
- The Reference Safety Information for the IMP capecitabine is the SmPC version provided by OCTO (approved for use in this trial by the MHRA).[1]
- The Reference Safety Information for the IMP cisplatin is the SmPC version provided by OCTO (approved for use in this trial by the MHRA).[1]

[1]It is not specified that any particular brand of Capecitabine or Cisplatin must be prescribed, however irrespective of the brand prescribed, the RSI to be referenced is provided by OCTO. N.B: This may not be the latest SmPC version available online.

A copy of the current approved version of the RSI documents for each IMP must be held in the Site File for reference. Any change or update to the RSI during the trial will be made via substantial amendment.

Please note that the list of expected side effects in the SmPCs for cisplatin and capecitabine are those listed for patients receiving standard chemoradiotherapy or chemotherapy alone. It is therefore possible that in this study population, where combination of M6620 (Berzosertib) is used with standard chemoradiotherapy or chemotherapy alone, other side effects may occur, or the patient might suffer a more severe reaction.

14.4.1 Expected adverse events associated with Radiotherapy

Fatigue, oesophagitis, odynophagia, dyspnoea, nausea, vomiting, skin erythema and desquamation. Late toxicity risks of lung fibrosis, oesophageal stricture, oesophageal perforation, cardiac toxicity and secondary malignancy.

14.5 Summary of trial safety reporting requirements

Please note all standard treatment toxicities **must be** reported because the TiTE-CRM trial design is based on an expected frequency of standard treatment toxicities plus M6620 (Berzosertib) related toxicities.

Event	DLT	SAE[1]	AE/SAE	AE/SAE
AE/SAE defined as Dose limiting toxicity (DLT) defined as per NCI CTCAE v4.03	**Email reporting form within 24 hours**		**Report in AE CRF**	**Non reportable**
Absolute neutrophil count (ANC) <0.5 x 10^9/L for >7days	X	X	X	
Febrile Neutropenia (ANC <1.0 x 10^9/L, fever ≥38.5°C) for >3 days	X	X	X	
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (absolute neutrophil count <1.0 x 10^9/L)	X	X	X	
Platelets <25 x 10^9/L (Grade ≥4)	X	X	X	
Clinically significant bleeding attributed to grade 3 thrombocytopenia or requiring platelet transfusion	X	X	X	
Grade ≥3 oesophagitis onset during induction chemotherapy or within 2 weeks of starting radiotherapy	X	X	X	
Grade ≥3 pneumonitis onset within 3 months of starting radiotherapy	X	X	X	
Grade ≥3 elevation of ALT or AST lasting 8 days or more	X	X	X	
A concurrent elevation of ALT or AST >3 × ULN and total bilirubin >2 × ULN in whom there is no evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevation	X	X	X	
Grade ≥3 nausea or vomiting not controlled by optimal outpatient anti-emetic treatment	X	X	X	
Grade ≥3 diarrhoea despite optimal outpatient anti-diarrhoeal medication use	X	X	X	
Other grade ≥ 3 effects thought to be directly treatment related to the combination of M6620 (Berzosertib) with radiotherapy or chemotherapy	X	X	X	
Any toxicity causing a delay of radiotherapy completion by greater than one week for Stage A	X	X	X	
Any toxicity causing radiotherapy delivery delay by ≥3 consecutive fractions for stage B	X	X	X	
Missing 2 consecutive doses of M6620 (Berzosertib) within a cycle due to Grade ≥3 toxicity	X	X	X	
Death due to drug related complications	X	X	X	
Cardiac toxicity: see section 9.1.2	X	X	X	
A delay of any of the 3 treatments of 7 days or more within a cycle due to treatment related toxicity	x	x	x	
AE/SAE defined as late DLT (onset 6 weeks after completion of radiotherapy) as per RTOG/EORTC late toxicity and Mellow Dysphagia score (Appendix C, D)				
Grade ≥3 lung and heart toxicity – onset 6 weeks after completion of radiotherapy	X	X	X	
Grade 3 oesophageal toxicity with an increase in Mellow score by ≥2 since baseline (need to exclude disease progression on CT and/or endoscopy and biopsy) - onset 6 weeks after completion of radiotherapy	X	X	X	

Grade 4 oesophageal toxicity - onset 6 weeks after completion of radiotherapy	**X**	**X**	**X**	
Medically important events in the context of this trial (considered dose limiting and possibly related to M6620 (Berzosertib) combined with Radiotherapy +/- chemotherapy by the TMG)	**Email reporting form within 24 hours**		**Report in AE CRF**	**Non reportable**
Any AE not listed above that is grade ≥3		**X**	**X**	
AE considered more severe than expected		**X**	**X**	
AE Grade <3 that is **unexpected** and thought to be directly treatment related to the combination of M6620 (Berzosertib) with radiotherapy +/- chemotherapy		**X**	**X**	
AE resulting in withdrawal		**X**	**X**	
Any late grade ≥3 toxicities – onset 6 weeks after completion of radiotherapy		**X**	**X**	
Any late grade 2 toxicities – onset 6 weeks after completion of radiotherapy			**X**	
Acute Hypersensitivity reaction		**X**	**X**	
Expected non-dose limiting toxicities	**Email reporting form within 24 hours**		**Report in AE CRF**	**Non reportable**
Anaemia		**If grade≥4**	**X**	
Abdominal pain		**If grade≥4**	**X**	
Cough			**X**	
Decreased appetite		**If grade≥4**	**X**	
Elevated ALT/AST lasting less than 8 days		**If grade≥4**	**X**	
Fatigue		**If grade≥4**	**X**	
Headache			**X**	
Low lymphocytes			**X**	
Infusion-related site reaction		**If grade≥3**	**X**	
Skin rash/discolouration related to sun exposure		**If grade≥4**	**X**	
Grade <3 nausea or vomiting			**X**	
All other AEs, abnormal assessments or laboratory results	**Email reporting form within 24 hours**		**Report in AE CRF**	**Non reportable**
All other AEs, assessments, abnormal laboratory results, if clinically significant		**If grade≥3**	**X**	
AE is life-threatening		**X**	**X**	
AE requires in-patient hospitalisation or prolongs existing inpatient hospitalisation		**X**	**X**	
AE results in persistent or significant incapacity or disability		**X**	**X**	
AE is a congenital anomaly or birth defect		**X**	**X**	
AE is any other medically important event		**X**	**X**	
Disease progression and resultant death	**Email reporting form within 24 hours**		**Report in AE CRF**	**Non reportable**
Hospitalisation (for progression or procedures planned prior to informed consent)				**X**

Clinical symptoms of progression				**X**
Death		**Possibly related directly to M6620 (Berzosertib) or the combination of M6620 (Berzosertib) + radiotherapy +/- chemotherapy**	**Report death and reason on death notification CRF**	

14.6 Suspected Unexpected Serious Adverse Drug Reactions (SUSARs)

All SUSARS must be reported by the Trial Office to the responsible Authority and REC within the required timelines:

- Fatal or life threatening SUSARs will be reported within 7 days of the Trial Office receiving the initial report. Any additional information will be reported within eight days of sending the first report.
- All other SUSARs will be reported within 15 days of the Trial Office receiving the initial report

In addition, other safety issues qualify for expedited reporting where they might materially alter the current risk assessment of an IMP or be sufficient to change IMP administration or the overall conduct of the trial. Chemotherapy SUSARs will be reported via the Yellow Card Scheme.

14.7 Expedited reporting of SAEs

The following SAE reporting requirements apply regardless of the Investigator's assessment of the causality or expectedness of the SAE. All SAEs should be reported on the trial SAE report form (see SAE report form and completion guidelines).

If a Serious Adverse Event occurs that requires reporting, a Serious Adverse Event reporting form should be completed and **scanned and emailed as a PDF attachment** within 24 hours of becoming aware of the event to:

Pharmacovigilance Office, OCTO
Email: octo-safety@oncology.ox.ac.uk
Tel no: +44 (0) 01865 617082

If the SAE has not been reported within the specified timeframe, a reason for lateness must be provided when sending the SAE Report Form.

Investigators should also adhere to their local Trust policy for incident and SAE reporting in research. AEs which are serious must be reported to the Trial Office from the first dose of study medication up to and including 30 days after administration of the last dose of study treatment, or the end of the DLT reporting period, whichever is longer. Any SAE that occurs at any time after completion of treatment or after the designated follow-up period that the Investigator and/or Sub-Investigator consider to be related to any study drug must be reported to the Trial Office.

The Trial Office will be responsible for reporting all SAEs to MERCK KGAA, DARMSTADT GERMANY within 24 hours of receiving an SAE report.

14.8 Follow-up of Serious Adverse Events

A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available. If the SAE is a suspected SUSAR then follow up information must be provided as requested by the Trial Office.

If new or amended information on a reported SAE becomes available, the Investigator should report this on a new SAE form using the completion guidelines. If using the original form to notify further information, you must initial and date all new or amended information so that all changes are clearly identified.

SAEs that are considered to be definitely unrelated to the trial intervention will not be followed up and monitored.

14.9 Reporting Adverse Events on the CRF

All AEs, including Serious AEs must be recorded on the case report forms (CRF) for that patient (unless otherwise specified in section 14.10). The information provided will include date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome and relationship of the AE to study drug. Any concomitant medications or any other therapy used to treat the event must be listed. The Investigator will provide an "other" cause for serious AEs considered to be unrelated to the study drug. Sites should ensure data entered into the CRF is consistent with the SAE report information where applicable.

Each separate AE episode must be recorded. For example, if an AE resolves completely or resolves to baseline and then recurs or worsens again, this must be recorded as a separate AE. For AEs to be considered intermittent, the events must be of similar nature and severity.

AEs occurring from the first dose of study medication up to the end of study visit must be recorded on the CRF. AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. AEs which result in early withdrawal must be reported using the Early Withdrawal Form.

Terms and Grading of Events

All adverse events and toxicities must be graded according to the NCI Common Terminology Criteria for adverse events (NCI-CTCAE) Version 4.0 (currently up to Version 4.03).

14.10 Events exempt from being reported as AE/ SAEs

Progression of underlying disease

Disease progression and resultant death will be captured on the CRF. Adverse events including hospitalisation that are clearly consistent with disease progression will not be reported as individual AE/SAEs. Clinical symptoms of progression will only be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Every effort should be made to document the objective progression of underlying malignancy. In some cases, the determination of clinical progression may be based on symptomatic deterioration. For example, progression may be evident from clinical symptoms, but is not supported by tumour measurements. Or, the disease progression is so evident that the Investigator may elect not to perform further disease assessments.

Death on study

Death on study is to be recorded on the Death CRF. The Investigator must clearly state in the source data if a causal relationship to the study IMP or other protocol treatment intervention is suspected and this should be the primary reason given on the Death CRF. If study treatment or other protocol intervention is suspected an SAE form should also be completed.

Elective admissions and supportive care

Admissions to hospital for patient convenience or for procedures planned prior to informed consent or investigations or treatment as specified in this protocol and standard supportive care are not SAEs, and do not require SAE reporting.

14.11 Informing Investigators of new safety information

The Trial Office or the Chief Investigator will ensure that all investigators are kept informed in a timely manner, as new safety profile information becomes available. Investigators are responsible for briefing their study team and onward transmission to their R&D office as appropriate.

15 PREGNANCY

Expedited reporting is required for pregnancies (in a participant or partner) occurring within 6 months of a participants last dose of the study drug or 13 weeks after last patient treatment, whichever comes sooner. A Pregnancy Form should be completed and scanned and emailed to the Trial Office within the same timelines as an SAE. All reported pregnancies should be followed and the outcome reported using the same form. If the outcome of the pregnancy meets any of the

criteria for seriousness, it must also be reported as an SAE. Examples of pregnancy outcomes that are SAEs include reports of:

- congenital anomalies or developmental delay, in the foetus or the child.
- foetal death and spontaneous abortion.
- suspected adverse reactions in the neonate that are classified as serious.

Women who become pregnant should be withdrawn from trial treatment immediately.

16 DEFINING THE END OF TRIAL

For Stage A1 the last patient last visit (LPLV) will be 9 weeks post end of radiotherapy for Stage A2 LPLV will be 8 weeks post end of chemotherapy, and for Stage B the LPLV will be 13 weeks post end of radiotherapy. However for Stage A1 & A2 this will be followed by the non-interventional phase of follow-up, which will continue for 12 months from start of treatment or when all participants have died (whichever comes first). This will be done via the hospital. But in the longer term this may be carried out via the Health & Social Care Information Centre. For the purpose of the Research Ethics Committee approval the trial end date will be the last patient start of treatment plus 24 weeks for Stage B. The Clinical Study Report (CSR) will be presented within 1 year of end of trial.

The sponsor and the Chief Investigator reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants' best interests.

17 STATISTICAL CONSIDERATIONS

17.1 Sample size and power

Sample size estimates are based on 1,000 simulated TiTE-CRM trials using the same characteristics that the actual trial will be based upon. The patients will not be replaced and the TiTE-CRM will use all accumulated critical toxicity summary data. For Stage A1, to treat 10 patients at a particular treatment plan or reach a maximum of 20 patients, 18 (95% C.I.: (10, 20)) patients are required. For Stage A2, to treat 6 patients at dosing schedule 4 or reach a maximum of 20 patients, 16 (95% C.I.: (11, 20)) are required. Stage B is expected to recruit a minimum of 15 patients and has a maximum sample size of 25.

18 STATISTICAL ANALYSIS PLAN

For all analyses, patients will be included according to the treatment to which they are assigned. All patients, regardless of how much treatment received and follow-up completed, will contribute to analysis.

It is therefore important that every effort is made to encourage patients, including those patients who do not receive/complete their allocated treatment, to attend for follow-up clinic visits to avoid bias in the analysis of the results.

A detailed statistical analysis plan will be available from the time the first patient is recruited and will be finalised before any analysis is undertaken. The analysis plan will be written in accordance with the current OCTRU standard operating procedures and will be finalised and agreed by the trial statistician and the CI. Sites must report any unintended deviations/violations to OCTO according to the procedure outlined during site initiation training.

18.1 Inclusion in analysis

All patients enrolled in the study, will be accounted for and included in the analyses. The number of patients who were not evaluable, who died or withdrew before treatment began will be recorded. The distribution of follow-up time will be described and the number of patients lost to follow-up will be given.

Variables will be analysed to determine whether the criteria for the study conduct are met. This will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol deviations, study drug accountability and other data that impact on the general conduct of the study.

Baseline characteristics will be summarised for all enrolled patients. Patients who died or withdrew before treatment started or do not complete the required safety observations will be described and evaluated separately. Treatment related toxicity will be tabulated by type and grade of toxicity. Evaluable for toxicity: All patients will be evaluable for

toxicity from the time of their first treatment. Adverse events will be summarised by the number of patients experiencing each type of event. The grades and causality will be reported.

18.2 Subgroup analysis

No subgroup analysis is planned.

18.3 Interim Analyses

The trial will use the TiTE-CRM to allocate dose and critical toxicity data will be reviewed prior to deciding the treatment schedule for each patient recruited.

18.4 Procedures for reporting any deviation(s) from the protocol

Any deviations from the original statistical plan will be described and justified in the final report.

18.5 Analysis for Safety

The variables that define the DLTs and safety variables will be summarized by descriptive statistics with patients grouped according to schedule received. Number (with percentages) of patient with and without DLT will also be presented according to schedule.

18.6 Final analysis

Based upon projected accrual rates, this trial (Stage A1, A2 and B) is expected to complete recruitment within 30 months of opening to recruitment. Final analysis for Stage A will be after all patients have been followed up for at least 3 months in Stage A1 and 26 weeks in Stage A2 while for Stage B, it will be performed within 12 months after Stage B last patient start of treatment.

19 TRIAL COMMITTEES

19.1 Trial Management Group (TMG)

The Chief Investigator will chair a TMG responsible for overseeing the successful conduct and publication of the trial. The TMG will include Chief Investigator, Co- Investigators, Radiotherapy Team Representative, Trial Manager, Trial Statistician and others as required. The TMG will meet as necessary to discuss toxicity data and to decide on dose escalation. TMG membership and decision making procedures will be documented in the TMG charter.

19.2 Safety Review Committee

There is no independent Data and Safety Monitoring Committee (DSMC) for this study. The Safety Review Committee (SRC) will be convened as required to review DLTs, review decisions as to the recommended dose to be administered, and review the stop/start rules for each stage. The main outcomes will be analysed as stated above in the analysis plan and will not be analysed as an interim analysis. SRC will have 3 independent members who will attend both open and closed session of the SRC meeting.
The SRC will consist of:

1. Trial Statistician
2. Independent Statistician
3. OCTO trial management representative
4. Either:
    a. One Medical Oncologist and one Clinical Oncologist or
    b. Two Clinical Oncologists

The SRC Charter document for this study will define the exact membership and who should be present for decisions to be made. Further internal or external experts may be consulted by the SRC, as necessary. Any PI can request an ad hoc SRC meeting at any time in order to facilitate the immediate communication of any emerging safety issues during the course of the study.

19.3 Trial Steering Committee

RIOC will act as the TSC. The role of RIOC is to provide oversight for the trial on behalf of the Sponsor and Funder. The TSC will provide overall supervision of the safe and effective conduct of the study. The TSC will review trial progress

against agreed milestones, adherence to protocol, and patient safety, and consider new information. The TSC has the authority to recommend study closure where appropriate.

20 DATA MANAGEMENT

20.1 Database considerations

Data management will be performed via a web-based, bespoke trial database (OpenClinica). OpenClinica is a dedicated and validated clinical trials database designed for electronic data capture. See: http://www.openclinica.org.
The Trial Office will provide sites with instructions and a video link for training purposes.

The participants will be identified by a unique trial specific number and year of birth. Initials, age and gender will be stored as data items within the eCRF but will not be used to identify patient records. These details will be used to assess eligibility and for statistical review of participant demographics. The name and any other identifying detail will NOT be included in any trial data electronic file.

20.2 Case reports forms (CRFs)

The Investigator and study site staff will ensure that data collected on each subject is recorded in the CRF as accurately and completely as possible. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the CRFs from the relevant source data held in the site medical record(s). CRFs entries will not contain any source data (unless otherwise specified in the completion instructions provided by the Trial Office). It is important to ensure that:

- the relevant CRFs are completed.
- all CRF data are verifiable in the source documentation or the discrepancies must be explained.
- CRF sections are completed in a timely fashion, as close to the visit or event being recorded as possible. This trial uses a continual reassessment model for dose escalation, where escalation decisions are made based on all critical toxicity summary data entered to date. It is necessary to enter all participant data as soon as possible to allow accurate assessment of the data and appropriate dose escalation decisions to be made.
- Data queries are resolved and documented by authorised study staff in a timely fashion. The reason for the change or correction should be given where appropriate.
- As much data as possible is entered and cleaned in preparation for each study database lock point.

Note: 'in a timely fashion' means within no more than 5 working days of the initial event and within 14 days of receipt of a data query unless otherwise specified.

If a patient withdraws from the study the Trial Office must be informed within 24 hours using the Early Withdrawal Form, the reason must be noted and the patient must be followed-up as per protocol.

20.3 Accounting for missing, unused, or spurious data.

The statistical analysis plan will describe the procedure for accounting for missing, unused or spurious data.

20.4 Clinical study report

All clinical data will be presented at the end of the study as data listings. These will be checked to confirm the lists accurately represents the data collected during the course of the study. The trial data will then be locked and a final data listing produced. The locked trial data may then be used for analysis and publication. The Clinical Study Report will be based on the final data listings. The Clinical Study Report will include the analysis of the routine survival data collected up to 12 months for Stage A1 and A2. The CSR will be presented within 1 year of end of trial.

21 STUDY SITE MANAGEMENT

21.1 Study site responsibilities

The Principal Investigator (the PI or lead clinician for the study site) has overall responsibility for conduct of the study, but may delegate responsibility where appropriate to suitably experienced and trained members of the study site team. All members of the study site team must complete the Staff Contact and Responsibilities Sheet provided prior to undertaking any study duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

21.2 Study site protocol deviations

The Investigator must document and explain any deviations/violations from the approved protocol. The Investigator should promptly report any important deviations that might impact patient safety, data integrity or be a possible serious breach (see 22.7 below) to the Trial Office.

21.3 Study site set up and activation

The PI leading the investigational study site is responsible for providing all required core documentation. Mandatory Site Training organised by the Trial Office must be completed before the site can be activated. The Trial Office will check to confirm that the site has all the required study information/documentation and is ready to recruit. The site will then be notified once they are activated on the trial database and able to enter patients.

21.4 Arrangements for sites outside the UK

Not applicable

21.5 Study documentation

The Trial Office will provide an Investigator Site File and Pharmacy File to each investigational site containing the documents needed to initiate and conduct the study. The Trial Office must review and approve any local changes made to any study documentation including patient information and consent forms prior to use. Additional documentation generated during the course of the trial, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the trial.

22 REGULATORY AND ETHICAL CONSIDERATIONS

The Sponsor and Investigators will ensure that this protocol will be conducted in compliance with the UK Clinical Trials Regulations[1] and the applicable policies of the sponsoring organisation. Together, these implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive.

22.1 Ethical conduct of the trial and ethics approval

The Protocol, Patient Information Sheet, Consent Form and any other information that will be presented to potential trial patients (e.g. patient card or information that supports or supplements the informed consent) will be reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC). Principal Investigators will be approved by the REC.

22.2 Regulatory Authority approval

This study will be conducted under a UK Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Trials Authorisation (CTA). Approval to conduct the study will be obtained from the Responsible Authority prior to initiating the study.

22.3 NHS Research Governance

Investigators are responsible for ensuring they obtain local Trust management agreement to conduct the trial in accordance with local arrangements and policies.

22.4 Protocol amendments

Amendments are changes made to the research following initial approval. A 'substantial amendment' is an amendment to the terms of the Responsible Authority application (if applicable), the REC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of the investigational medicinal product(s) used in the trial.

Non-substantial amendments are those where the change(s) involve only minor logistical or administrative aspects of the study. All amendments will be generated and managed according to the Trial Office standard operating procedures

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC, regulatory and local approvals must be in place prior to implementation by Investigators. The only exceptions are for changes necessary to eliminate an immediate hazard to study patients (see below).

It is the Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented if appropriate.

22.5 Urgent safety measures

The sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The trial may continue with the urgent safety measures in place. **The Investigator must inform the Trial Office IMMEDIATELY if the study site initiates an urgent safety measure:**

The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the Trial Office to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out. The Trial Office will follow written procedures to implement the changes accordingly.

22.6 Temporary halt

The sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **or** to declare a temporary halt. A temporary halt is defined a formal decision to:

- interrupt the treatment of subjects already in the trial for safety reasons;
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the trial in a timely manner.

The Trial Office will report the temporary halt via an expedited substantial amendment procedure. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

22.7 Serious Breaches

The Medicines for Human Use (Clinical Trials) Regulations require the Sponsor to notify any "serious breaches" to the MHRA within 7 days of the sponsor becoming aware of the breach. A serious breach is defined as "A breach of GCP or the trial protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial"

Investigators must notify the Trial Office within one working day if any serious breach of GCP is suspected. The Trial Office will review the event and, if appropriate a report will be submitted to the REC, Regulatory Authority and the NHS host organisation within 7 days of the Trial Office becoming aware of the breach as per Trials Office SOPs.

22.8 Trial Reports

This protocol will comply with all current applicable Regulatory Authority, Research Ethics Committee and Sponsor reporting requirements.

The Trial Office will determine which reports need to be circulated to Principal Investigators and other interested parties. Study sites are responsible for forwarding trial reports they receive to their local Trust as required.

23 EXPENSES AND BENEFITS

The participating study site may provide reasonable travel expenses incurred for attending additional research visits in excess of standard of care as per local practice. The local arrangements will be explained to the patient during the informed consent discussions prior to trial entry. However, there is no direct study funding to reimburse patient expenses.

24 QUALITY ASSURANCE

24.1 Risk assessment

A risk assessment and a monitoring plan will be prepared before the study opens and will be reviewed throughout the study if necessary in the light of significant changes while the study is ongoing or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

24.2 Monitoring

Regular monitoring will be performed according to the monitoring plan. Data will be evaluated for compliance with the protocol, completeness and accuracy. The Investigator and institutions involved in the study will permit study-related monitoring and provide direct on-site access to all study records and facilities if required. They will provide adequate time and space for the completion of monitoring activities.

Study sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness and timing. The case report data will be validated using appropriate set criteria, range and verification checks. The study site must resolve all data queries in a timely manner. All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the study site for resolution. For other non-critical data items, OCTO staff may resolve data queries centrally providing the correct answer is clear. Such changes will be clearly identified in the CRF and the study site informed.

Study sites will also be monitored remotely and/or by site visit as necessary to ensure their proper conduct of the trial. OCTO staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have. Monitoring reports will be sent to the site in a timely fashion. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance.

If sites are required to provide copies of participant information to the Trial Office for remote monitoring purposes, all patient personal identifiers must be obliterated from the information.

24.3 Audit and Regulatory Inspection

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. It may also be subject to a regulatory inspection. Such audits or inspections may occur at any time during or after the completion of the study. Investigators and their host Institution(s) should understand that it is necessary to allow auditors/inspectors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit. Anyone receiving notification of a Regulatory Inspection that will (or is likely to) involve this trial must inform the Trial Office without delay.

25 RECORDS RETENTION & ARCHIVING

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical trial and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request for the minimum period required by national legislation or for longer if needed. The medical files of trial subjects must be retained in accordance with applicable national legislation and the host institution policy.

Retention and storage of laboratory records for clinical trial samples must also follow these guidelines.
Retention and storage of central laboratory records supporting PD endpoints and the disposition of samples donated via the trial must also comply with applicable legislation and Sponsor requirements.

It is the University of Oxford's policy to store data for a minimum of 5 years. Investigators may not archive or destroy study essential documents or samples without written instruction from the Trial Office.

26 PATIENT CONFIDENTIALITY

Personal data recorded on all documents will be regarded as confidential, and to preserve each patient's anonymity, unique and anonymous trial specific number will be used for identification and year of birth will be recorded on the CRFs. Initials, age and gender will be stored as data items within the eCRF but will not be used to identify patient records. These details will be used to assess eligibility and for statistical review of participant demographics.

The Investigator site must maintain the patient's anonymity in all communications and reports related to the research. The Investigator site team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.
The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s) with the exception of the CRF, where participant initials and Year of Birth may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

27 STUDY FUNDING

The CHARIOT trial is being funded in part by the New Agents Committee (NAC), on behalf of Cancer Research UK (CRUKD/15/011). The Oncology Clinical Trials Office is supported by Cancer Research UK core funding. Merck KGaA, Darmstadt Germany are providing a grant and free M6620 (Berzosertib) to support the study. This study is further supported via the University of Oxford core clinical and research infrastructure underpinned by strategic research programme grant funds. This trial is on the NIHR portfolio. Local research network support should be available at each site taking part to support entry of participants into this trial.

28 SPONSORSHIP AND INDEMNITY

28.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship and authorise the trial commencement once satisfied that all arrangements and approvals for the proper conduct of the trial are in place. A separate study delegation agreement, setting out the responsibilities of the Chief Investigator and Sponsor will be put in place between the parties.

28.2 Indemnity

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

28.3 Contracts/Agreements

This trial is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate. A Clinical Trial Agreement (CTA) will be placed between the Sponsor and participating organisations prior to site activation.
The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the trial as appropriate.

29 PUBLICATION POLICY

The sponsor will retain ownership of all data arising from the trial. The intention is to publish this research in a specialist peer reviewed scientific journal on completion of the study. The results may also be presented at scientific meetings and/or used for a thesis. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the trial and retain final editorial control. Authors will acknowledge that the study was Sponsored by and performed with the support of the Sponsor and other funding bodies as appropriate.

30 REFERENCES

1. Lewis KA, Lilly KK, Reynolds EA, Sullivan WP, Kaufmann SH, Cliby WA. Ataxia telangiectasia and rad3-related kinase contributes to cell cycle arrest and survival after cisplatin but not oxaliplatin. Molecular cancer therapeutics. 2009 Apr;8(4):855-63. PubMed PMID: 19372558. Pubmed Central PMCID: 2690640.
2. Cliby WA, Roberts CJ, Cimprich KA, Stringer CM, Lamb JR, Schreiber SL, et al. Overexpression of a kinase-inactive ATR protein causes sensitivity to DNA-damaging agents and defects in cell cycle checkpoints. The EMBO journal. 1998 Jan 2;17(1):159-69. PubMed PMID: 9427750. Pubmed Central PMCID: 1170367.
3. Ding L, Getz G, Wheeler DA, Mardis ER, McLellan MD, Cibulskis K, et al. Somatic mutations affect key pathways in lung adenocarcinoma. Nature. 2008 Oct 23;455(7216):1069-75. PubMed PMID: 18948947. Pubmed Central PMCID: 2694412.
4. Greenman C, Stephens P, Smith R, Dalgliesh GL, Hunter C, Bignell G, et al. Patterns of somatic mutation in human cancer genomes. Nature. 2007 Mar 8;446(7132):153-8. PubMed PMID: 17344846. Pubmed Central PMCID: 2712719.
5. Abedi-Ardekani B, Kamangar F, Sotoudeh M, Villar S, Islami F, Aghcheli K, et al. Extremely high Tp53 mutation load in esophageal squamous cell carcinoma in Golestan Province, Iran. PloS one. 2011;6(12):e29488. PubMed PMID: 22216294. Pubmed Central PMCID: 3246475.
6. Dulak AM, Stojanov P, Peng S, Lawrence MS, Fox C, Stewart C, et al. Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. Nature genetics. 2013 May;45(5):478-86. PubMed PMID: 23525077. Pubmed Central PMCID: 3678719.
7. He H, Tian D, Guo J, Liu M, Chen Z, Hamdy FC, et al. DNA damage response in peritumoral regions of oesophageal cancer microenvironment. Carcinogenesis. 2013 Jan;34(1):139-45. PubMed PMID: 23027622.
8. Charrier JD, Durrant SJ, Golec JM, Kay DP, Knegtel RM, MacCormick S, et al. Discovery of potent and selective inhibitors of ataxia telangiectasia mutated and Rad3 related (ATR) protein kinase as potential anticancer agents. Journal of medicinal chemistry. 2011 Apr 14;54(7):2320-30. PubMed PMID: 21413798.
9. Reaper PM, Griffiths MR, Long JM, Charrier JD, Maccormick S, Charlton PA, et al. Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR. Nature chemical biology. 2011 Jul;7(7):428-30. PubMed PMID: 21490603.
10. Pires IM, Olcina MM, Anbalagan S, Pollard JR, Reaper PM, Charlton PA, et al. Targeting radiation-resistant hypoxic tumour cells through ATR inhibition. British journal of cancer. 2012 Jul 10;107(2):291-9. PubMed PMID: 22713662. Pubmed Central PMCID: 3394988.
11. Fokas E, Prevo R, Pollard JR, Reaper PM, Charlton PA, Cornelissen B, et al. Targeting ATR in vivo using the novel inhibitor VE-822 results in selective sensitization of pancreatic tumors to radiation. Cell death & disease. 2012;3:e441. PubMed PMID: 23222511. Pubmed Central PMCID: 3542617.
12. Crosby T, Hurt CN, Falk S, Gollins S, Mukherjee S, Staffurth J, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. The lancet oncology. 2013 Jun;14(7):627-37. PubMed PMID: 23623280.
13. Conroy T, Galais MP, Raoul JL, Bouche O, Gourgou-Bourgade S, Douillard JY, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. The lancet oncology. 2014 Mar;15(3):305-14. PubMed PMID: 24556041
14. Knyrim K, Wagner H, Bethge N, Keymling, Vakil N. (1993). A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer. The New England Journal of Medicine; 78:1302-1307. PMID:7692297
15. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R; Guidelines for the management of oesophageal and gastric cancer. Gut. 2011 Nov;60(11):1449-72.

31 APPENDIX A: ECOG PERFORMANCE SCALE

Activity Performance Description	Score
Fully active, able to carry out all on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	1
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	4

32 APPENDIX B: MEASUREMENT OF DISEASE - RECIST CRITERIA

RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS

Objective tumour response and time of progression will be measured according to the RECIST (Response Evaluation Criteria In Solid Tumours) criteria (version 1.1).
Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.
The following paragraphs are a quick reference to the RECIST criteria (version 1.1). The complete criteria are included in the published RECIST document:

Eisenhauer, EA, Therasse, P, Bogaerts, J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247

And also available at: http://www.eortc.be/RECIST

B.1 Measurability of tumour lesions at baseline

B.1.1 Definitions

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - *tumour lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥ 10 mm with CT scan or clinical examination [using callipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres) by use of a ruler or callipers. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- **Non-measurable lesions** - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable.

Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.

- **Target Lesions.** When more than one measurable tumour lesion or malignant lymph node is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be calculated and recorded.
- **Non-target Lesions**. All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

B.1.2 Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

- **Clinical Lesions**. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.
- **Chest X-ray.** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT, MRI.** CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).
- **Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT should be obtained.
- **Endoscopy, Laparoscopy**. The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- **Tumour Markers**. Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.
- **Cytology, Histology**. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g.

with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

B.2 Tumour response evaluation

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later. Refer to the table B1and table B2 below.

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumour markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment, for example where the tumour burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Table B1: Integration of target, non-target and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
Patients with Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumour markers All tumour nodes < 10 mm Documented at least once ≥ 4 weeks from baseline
CR	Non-CR/Non-PD	No	PR	Documented at least once ≥ 4 weeks from baseline
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Patients with Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumour markers All tumour nodes < 10 mm Documented at least once ≥ 4 weeks from baseline
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	

No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression [or evidence of unequivocal disease progression] at that time should be reported as "*symptomatic deterioration"*. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later. The best overall response can be interpreted from Table B2.

Table B2: Response assessment after subsequent scan

Response: First time point	Subsequent time point	BEST overall response	Also requires
CR	CR	CR	Normalization of tumour markers All tumour nodes < 10 mm
CR	PR	SD, PD or PR (see comment*)	
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
NE	NE	NE	

* may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR is PD.

B.2.1 Frequency of tumour re-evaluation

Participants will receive CT scans at baseline and at 24 weeks after the start of treatment as per standard treatment.

B.2.2 Date of progression

This is defined as the first day when the RECIST (version 1.1) criteria for PD are met.

B.3 Reporting of tumour response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death from malignant disease, early death from toxicity, early death from other cause or unknown (not assessable, insufficient data).

Early death is defined as any death occurring before the first per protocol time point of tumour re-evaluation. The responsible investigator will decide if the cause of death is malignant disease, toxicity or other cause.
Patients for whom response is not confirmed will be classified as "unknown", unless they meet the criteria for stable disease (or the criteria for partial response in case of an unconfirmed complete response). Patients' response will also be classified as "unknown" if insufficient data were collected to allow evaluation per these criteria.

33 APPENDIX C: RTOG LATE TOXICITY SCORE

Please refer to
http://www.rtog.org/ResearchAssociates/AdverseEventReporting/RTOGEORTCLateRadiationMorbidityScoringSchema.aspx

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lung	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency/ Continuous O_2/ Assisted ventilation	Death
Heart	None	Asymptomatic or mild symptoms Transient T wave inversion & ST changes Sinus tachycardia >110 (at rest)	Moderate angina on effort Mild pericarditis Normal heart size Persistent abnormal T wave and ST changes Low ORS	Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure Cardiac enlargement EKG abnormalities	Tamponade/ Severe heart failure/ Severe constrictive pericarditis	Death
Oesophagus	None	Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing	Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated	Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilation required	Necrosis/ Perforation Fistula	Death

34 APPENDIX D: MELLOW DYSPHAGIA SCORE

0 = able to eat normal diet / no dysphagia.
1 = able to swallow some solid foods
2 = able to swallow only semi solid foods
3 = able to swallow liquids only
4 = unable to swallow anything / total dysphagia

35 APPENDIX E: PROTOCOL AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
001	V3.0	13Dec2016	Maria Hawkins, Claire Hamill, Stephanie Levy.	Protocol V1.0 28Jun2016 REC approved 19Aug2016. The MHRA and OCTO chemotherapy, pharmacy advisory service (CPAS) initial reviews required changes to protocol V1.0 which updated the protocol to V2.0 10Aug2016. Version 2.0 received MHRA approval 19Aug2016. This was then submitted to the REC as a substantial amendment with additional minor amendments updating the document to V3.0 13Dec2016.
002	V4.0	14May2018	Stephanie Levy	IMP name change from VX-970 to M6620 (Berzosertib). Change in IMP manufacturer. Additional secondary endpoint to Stage A2. Change to definition of end of study. DLT specification updated. Additional minor clarifications or corrections.
004	V5.0	26Oct2020	Maria Hawkins, Jane Holmes, Alex Ooms, Evan Ridgeon, Usha Wahengbam, Steph Levy	Significant design changes to Stage B, including confirmed dose, treatment levels, follow up duration, and escalation/recruitment process. Change in end of trial timepoint, final report, pregnancy follow up. Flexibility in recruitment gaps. PK sampling removed. Eligibility criteria updates. Remove use of carboplatin. Stage A1 archival biopsy added. RSI update. Updates per IB & SmPCs. DLT added, DLT amended & clarity on treatment of patients with DLTs. Hb values corrected. Flexibility in assessments & treatment. RTTQA update. Administrative changes.

CHARIOT

A phase I dose escalation safety study combining the ATR inhibitor M6620 with chemoradiotherapy in oesophageal cancer & other solid cancers using time to event continual reassessment method

Statistical Analysis Plan

Version 2.0 – 07 January 2021

Based on Protocol version V5.0 – 26 October 2020

Trial registration: 2015-003965-27 (EudraCT)

Role	Name	Title	Signature	Date
Author	Alexander Ooms	Trial Statistician		07Jan2021
Author/Approver	Jane Holmes	Senior Trial Statistician		07Jan2021
Reviewer	Maria Hawkins	Chief Investigator		07Jan2021

Oncology Clinical Trials Office (OCTO),
Oxford Clinical Trials Research Unit (OCTRU) &
Centre for Statistics in Medicine (CSM)

CONTENTS

1. INTRODUCTION

This document details the proposed presentation and analysis for the main paper(s) reporting results from the **CRUK, Merck and The University of Oxford-funded multicentre phase I dose escalation safety study**

combining the ATR inhibitor M6620 with chemoradiotherapy in oesophageal cancer using time to event continual reassessment method (CHARIOT). The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

1.1 Key personnel

Author(s) (Trial statistician(s)): Alexander Ooms
Medical Statistician
Centre for Statistics in Medicine
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
The University of Oxford
Windmill Road
Oxford OX3 7LD
Tel.: 01865 737867
Email: **alexander.ooms@ndorms.ox.ac.uk**

Jane Holmes
Medical Statistician
Centre for Statistics in Medicine
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
The University of Oxford
Windmill Road
Oxford OX3 7LD
Tel.: 01865 223452
Email: jane.holmes@csm.ox.ac.uk

Reviewers (Chief Investigator): Maria Hawkins
Professor in Radiation Oncology

Medical Physics and Biomedical Engineering
Malet Place Engineering Building

University College London
Gower Street
London, WC1E 6BT
Tel: 020 8138 7633
m.hawkins@ucl.ac.uk

Approver (Senior Medical Statistician):

1.2 Changes from previous version of SAP

A summary of key changes from earlier versions of SAP, with particular relevance to protocol changes that have an impact on the design, definition, sample size, data quality/collection and analysis of the outcomes will be provided. Include protocol version number and date.

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons
V1.0_10Jul2018	Eleni Frangou Jane Holmes	Protocol_V4.0_14May2018	Not applicable as this is the 1st issue
V2.0_07Jan2021	Alexander Ooms Jane Holmes	Protocol_V5.0_26Oct2020	• Updated to be based on V5.0 of the protocol • Simulation results moved to an Appendix 1 Document • Reference made to Protocol Decision Point Plan and clarification of dose decisions • Change in TiTE CRM's weight function • Change in sensitivity analyses presented at each dose decision • Removal of references to Stage B

Note: All references to Stage B's dose allocation methods have been removed from V2.0 of this Analysis Plan. This is to facilitate dose decisions for Stages A1 and A2 to be based on a finalised SAP while the analysis methods for the redesigned Stage B in V5.0 of the protocol are being considered. This Analysis Plan will be updated to include Stage B's planned analysis methods prior to Stage B opening to recruitment.

2. BACKGROUND AND OBJECTIVES

2.1 Background and rationale

This phase I study will test the combination of a novel ATR inhibitor (M6620) with chemoradiotherapy in oesophageal cancer. In the first two cohorts (Stage A1 and A2), we will investigate the safety of combining M6620 separately with [1] palliative radiotherapy (RT) for oesophageal cancer (Stage A1) and [2] with cisplatin/capecitabine chemotherapy in patients with advanced inoperable and metastatic solid tumours (Stage A2). In Stage A1, M6620 will be given in combination with high dose palliative RT treatment, aiming to deliver M6620 twice weekly during RT escalating to a dose of 240mg/m2. A palliative chemotherapy cohort (Stage A2) will open to recruitment simultaneously where M6620 will be given in combination with cisplatin/capecitabine chemotherapy, aiming to deliver M6620 twice weekly escalating to a dose of 140mg/m2 twice weekly. When we have enough information to suggest the combinations are tolerable, the ATR inhibitor will be tested in the definitive setting (Stage B) in combination with cisplatin/capecitabine and radical RT to identify the MTD. The MTD found in this study will be taken forward in future phase II studies.

In the palliative setting, we aim to find the schedule associated with no more than 25% Dose Limiting Toxicities (DLTs) in stage A1 on the basis that palliative oesophageal radiotherapy causes approximately 20% grade 3 and 4 toxicity, and 30% Dose Limiting Toxicities (DLTs) in stage A2 are derived from capecitabine/cisplatin used in the radical setting (SCOPE1 study).

In the radical setting, we aim to find the schedule associated with no more than 45% DLTs on the basis that conventional oesophageal chemoradiation causes a grade 3 and 4 toxic event rate of 28% haematological toxicity and 63% non-haematological toxicity of which 34% is gastrointestinal as reported in the standard arm of SCOPE1 study (12). Comparable toxicity rates were described in the standard arm of the PRODIGE5/ACCORD17 study: grade 3 and 4 neutropenia 29% and grade 3 and 4 dysphagia and oesophagitis 33%.

The trial will find the best optimal dose and dosing schedule using the TiTE-CRM (Time To Event Continual Reassessment Method). The CRM is a model based method for finding the MTD. It assumes that toxicity increases monotonically with increasing dose, and that efficacy also increases with increasing dose. The aim will be to find the dose that causes a DLT with the above specified target toxicity levels. TiTE-CRM is a modified CRM that accounts for the time to event of late onset toxicities. The advantages of a TiTE-CRM are that all current information is used when deciding which dose to give the next patient and it is not necessary for a patient to complete the full observation period before consenting the next patient. This results in a better estimation of the MTD and shorter study duration respectively.

2.2 Objectives

Stage A1		
Primary Objective	**Endpoints/ Outcome Measures**	**Time point(s) for evaluation of end point**
• To determine the best tolerated M6620 treatment schedule (or phase II recommended dose (RPTD)) administered concomitantly with Radiotherapy only in the palliative treatment of oesophageal cancer	Highest treatment schedule resulting in less than 25% dose limiting toxicity (DLT) rate (see section 9.1.2 for DLT definitions)	• Week 9
Secondary Objectives	**Endpoints/ Outcome Measures**	
• To determine the safety and toxicity profile of M6620 administered concomitantly with RT only in the palliative treatment of oesophageal cancer	• Any toxicity grade ≥3 graded according to CTCAE v4.03 and length of time for toxicity to resolve	• During radiotherapy Weeks 1-3 • Week 4, 9 and week 12
• To determine if M6620 can be delivered in combination with palliative RT	• Proportion of patients completing at least 75%, 90% and 100% of the planned RT dose	• End of radiotherapy End of Week 3
• Efficacy of the combination	• Objective tumour response (OR) as evaluated by CT scan and quantified by Response Criteria Evaluation (RECIST 1.1) • PFS and OS from D1 • In field radiotherapy control	• 12 weeks • 6 and 12 months
Stage A2		
Primary Objective	**Endpoints/ Outcome Measures**	**Time point(s) for evaluation of end point**
• To determine the best tolerated M6620 treatment schedule (or phase II recommended dose (RPTD)) administered concomitantly with chemotherapy (Cisplatin and Capecitabine) only in the palliative treatment of solid cancer	• Highest treatment schedule resulting in less than 30% dose limiting toxicity (DLT) rate (see section 9.1.2 for DLT definitions)	• Week 4
Secondary Objectives	**Endpoints/ Outcome Measures**	
• To determine the safety and toxicity profile of M6620 administered concomitantly with chemotherapy (Cisplatin and Capecitabine) only in the palliative treatment of solid cancer	• Any toxicity grade ≥3 graded according to CTCAE v4.03 and length of time for toxicity to resolve	• During chemotherapy Week 1-18 • Week 20, 26

• To determine if M6620 can be delivered in combination with palliative chemotherapy	• Proportion of patients completing at least 75%, 90% and 100% of the planned dose	• End of chemotherapy Week 18
• Efficacy of the combination	• Objective tumour response (OR) as evaluated by CT scan and quantified by Response Criteria Evaluation (RECIST 1.1) • PFS and OS from D1	• Week 6, 12, 18, 26 • Week 26 & 12 months
Tertiary Objectives	**Endpoints/ Outcome Measures**	
• To evaluate pharmacokinetics (PK) of M6620 when administered in combination with Cisplatin and Capecitabine	• M6620 C_{max} (observed peak plasma concentration) and AUC (area under the plasma concentration time curve) using blood samples when delivered after Capecitabine and Cisplatin administration	• 1st dose of M6620 (C1D2) at the following timepoints: BOI, at 0.5 hours before EOI, at EOI and at 0.5, 1, 2, 3, 6, 23, 47 hours after EOI. For C1D9 and C1D16 doses at the following timepoints: BOI and EOI
Stage B		
Primary Objective	**Endpoints/ Outcome measures**	**Time point(s) for evaluation of end point**
• To determine the best tolerated M6620 treatment schedule (or phase II recommended dose (RPTD)) administered concomitantly with radiotherapy (dCRT) in combination with cisplatin and capecitabine in the radical treatment of oesophageal cancer	Highest treatment schedule resulting in less than 45% dose limiting toxicity (DLT) rate (see section 9.1.2 for DLT definitions)	• Up to Week 24
Secondary Objectives	**Endpoints/ Outcome Measures**	
• To determine the safety and toxicity profile of M6620 administered concomitantly with dCRT in combination with cisplatin and capecitabine in the radical treatment of oesophageal cancer	• Any toxicity grade ≥3 graded according to CTCAE v4.03 and length of time for toxicity to resolve	• Up to week 24
• To determine tolerance and ability to deliver M6620 in combination with standard dCRT	• Treatment tolerance and deliverability measured by proportion of patients completing at least 80% of the planned chemotherapy dose and at least 20 fractions of RT	• End of induction chemotherapy and dCRT. End of week 11
• Efficacy and long term safety of the combination	• Objective tumour response (OR) as evaluated by CT scan and quantified by	• 24 weeks

	Response Criteria Evaluation (RECIST 1.1) and endoscopic and biopsy findings. • PFS and OS from D1	
Tertiary/Exploratory Objectives	**Endpoints/ Outcome Measures**	
• To explore target effects in tissue	• Change in level of ATR inhibition and apoptosis in M6620 treated tissue using IHC. • Genotyping of tumours • Aim to identify markers for oesophageal cancer in the blood	• Biopsies at baseline, week 7 and 24 • Blood samples at baseline, week 7 and week 12

3. STUDY METHODS

3.1 Trial Design/framework

This will be a single arm, open-label, phase I dose escalation trial using the Time-To-Event Continual Reassessment Method (TiTE-CRM) to find the optimal treatment schedule. The trial consists of three stages A1, A2 and B. Stages A1 and A2 will run concurrently and will inform the starting dose of M6620 for Stage B.

3.1.1 General description of the TiTE-CRM design

The TiTE-CRM method is a modified version of the CRM that accounts for late-onset toxicities. It uses all current information when deciding which dose to give the next patient and it is not necessary for a patient to complete the full observation period before consenting the next patient. This results in a better estimation of the MTD and shorter study duration respectively and is particularly useful in trials involving radiotherapy where the toxicity follow-up phase is longer. We assume that:

- A maximum of N subjects are to be recruited
- A target toxicity level, TTL
- K doses $d_1, \dots d_K$ to be explored
- A DLT window of length T
- The maximum amount of dose of M6620 for the patient's allocated treatment schedule D
- A weight function, $\boldsymbol{w}$, associated with T and D denoting a combination of the proportion of the DLT window that has been observed and proportion of the total M6620 they're to receive for each currently enrolled patient
- Prior estimates of DLTs at each dose, also called the skeleton, $\hat{\boldsymbol{\pi}}_{\mathbf{0}} = \{\hat{\pi}_{01}, \dots, \hat{\pi}_{0K}\}$
- Dose toxicity curve (DTC), $g_k(\alpha) = d_k^{exp^{\alpha}}$
- Prior distribution for the parameter of the DTC, $\alpha \sim N(0, \sigma^2)$

At the start of the trial the information on the probability of DLT at each dose level is given by the prior estimates $\hat{\boldsymbol{\pi}}_{\mathbf{0}}$. These estimates are updated after every patient to give the posterior estimates.

Suppose there are J subjects currently enrolled, the available information is the set of doses $\{x_1, \dots, x_J\}$ administered to the J patients, the set of toxicity outcomes $\{y_1, \dots, y_J\}$ where $y_j = 0$ if no toxicity and $y_j = 1$ if toxicity, and the amount of time each patient has been observed $\{u_1, \dots, u_J\}$, where $0 \leq u_j \leq T$. The amount of M6620 given per dose schedule $\{v_1, \dots, v_J\}$, where $0 \leq v_j \leq D$.

The TiTE-CRM model uses a weighted likelihood function given by

$$L(\alpha) = \prod_{j=1}^{J} \left[g_{x_j}(\alpha) * w_j\right]^{y_j} \left[1 - g_{x_j}(\alpha) * w_j\right]^{1-y_j}$$

where

$$w_j = \begin{cases} 1 \text{ if } y_j = 1 \\ \frac{1}{2}\left(\frac{u_j}{T} + \frac{v_j}{D}\right) \text{ if } y_j = 0 \end{cases}$$

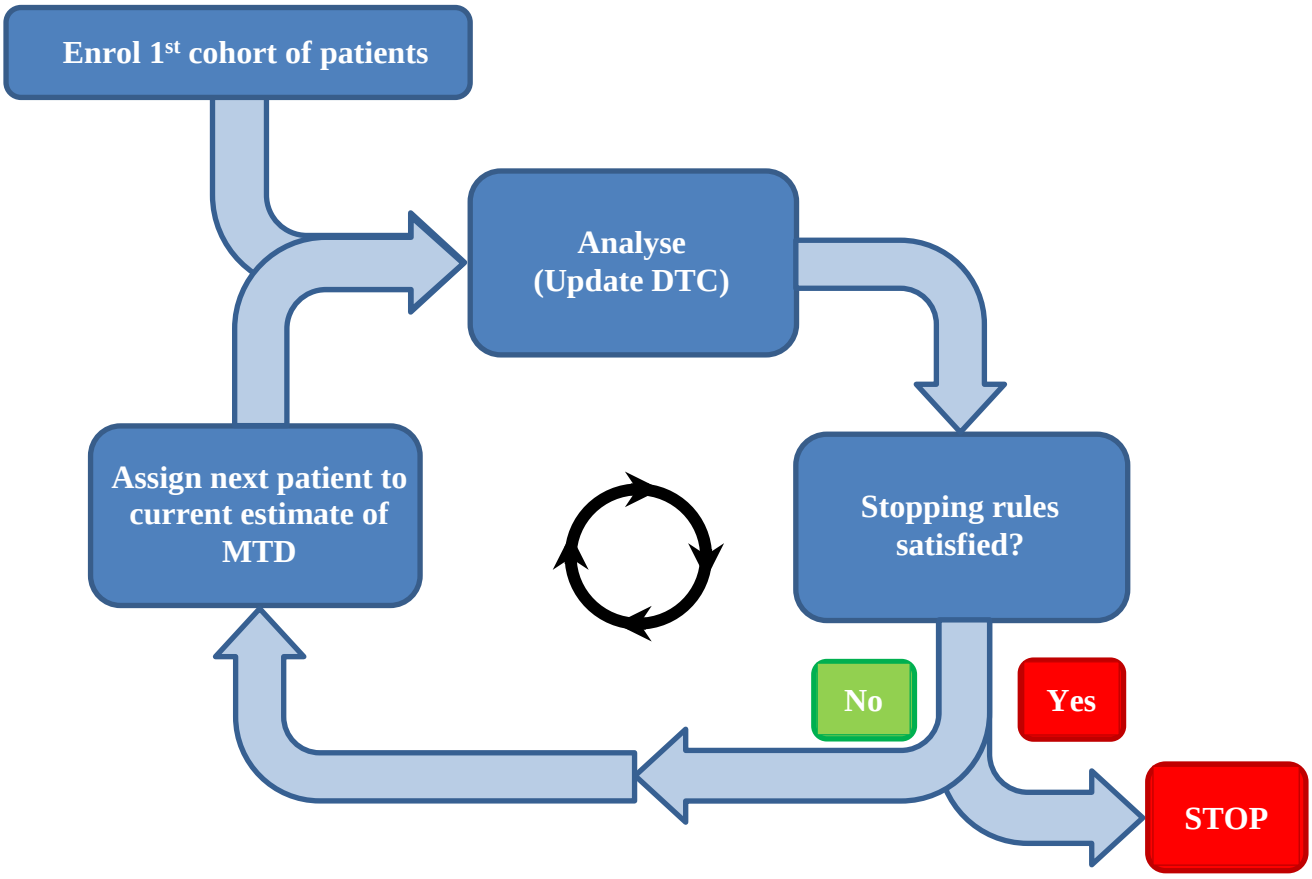
and the posterior expected toxicity at each dose (posterior dose-toxicity curve) is given by

$$\hat{\pi}_k = E(g_k(\alpha)|y) = \int_{-\infty}^{\infty} g_k(\alpha) p(\alpha|y) d\alpha$$

The MTD is defined to be the dose x^* such that $\hat{\pi}_k = TTL$. As each new patient is enrolled, the current best guess at the MTD is calculated based on all data accrued so far, and is the dose suggested for the patient in agreement with the TMG.

In addition the trial may be stopped early if either the drug is found to be too toxic or we are confident in our estimate of the MTD. The flow of patients through a CRM trial is given in Figure 1.

Figure 1: Flow of patients through a CRM trial



3.1.1 Stage A1

The aim is to find the M6620 treatment schedule when combined with radiotherapy that is associated with no more than 25% dose limiting toxicity rate on the basis that palliative oesophageal radiotherapy is associated with approximately 15-20% grade 3/4 toxicity. Six treatment schedules are proposed. Each schedule comprises a specific combination of dose and dosing frequency. There are two possible M6620 doses and three dosing frequencies (see section 4.1.1). The radiation dose remains consistent across all treatment schedules. For the prior estimates of DLT at each treatment schedule, see the skeleton in Table 1.

The treatment involves 3 weeks of daily radiotherapy and M6620 at a pre-determined frequency dependent on the treatment schedule allocated to the individual patient. The follow-up of a further 6 weeks provides a DLT observation window of a total of 9 weeks. An initial cohort of three patients will receive the starting schedule (lowest dosing frequency) at the starting dose, 140mg/m2. The fourth patient will not be recruited until all three patients have been followed for the minimum of 9 weeks from the start of radiotherapy or the occurrence of a DLT.

Subsequently, all eligible patients will be continuously recruited and the TiTE-CRM will be used to assign their treatment schedule. To ensure enough information is accumulated to inform the assignment of the treatment schedule to the subsequent patient, recruitment will be managed through allocation of treatment slots (see Protocol section 4.4 for further details).

Stage A1 stopping rules

Stage A1 will pause for safety if, at any point in the trial, there is sufficient evidence to suggest that schedule 1 is too toxic. More specifically, we will consider schedule 1 to be too toxic if, given all the available data, there is a high probability that the DLT rate is greater than the target toxicity level of 0.25. If all 3 patients in the first cohort have DLTs then schedule 1 is too toxic and the trial will be re-started. At this point, three extra schedules will be introduced at 90mg/m2 and varying dosing frequencies, namely (schedule -3, -2 and -1). Once the trial is restarted, the lowest schedule, schedule -3, will be explored first. There will then be 9 treatment schedules to explore (the original 6 plus the 3 dosing frequencies at the lower dose). If the first 3 patients recruited to schedule -3 experience DLTs then the trial will stop. If schedule 1 is found to be too toxic later in the trial when more than 3 patients have been recruited, a SRC meeting will be convened to decide whether the trial should be restarted using the lower dose of 90mg/m2.

Stage A1 will stop for success when either a total of 10 patients have been assigned to a particular treatment schedule or 20 patients have been recruited, whichever occurs first. When 10 patients in Stage A1 have been assigned to a particular treatment schedule, recruitment will be paused until there are no more than three patients without full follow-up (either DLT or 6 weeks after the end of treatment), i.e. until there is full follow-up information on at least seven patients. If the MTD changes, recruitment may start again.

Based on simulations and assuming a patient will be recruited every 8 weeks, the average number of patients required for Stage A1 is 18, which we aim to recruit in 24 months.

3.1.2 Stage A2

The aim is to find the M6620 treatment schedule when combined with palliative combination chemotherapy (Cisplatin and Capecitabine) that is associated with no more than a 30% dose limiting toxicity rate. Four treatment schedules are proposed. Each schedule comprises a specific combination of dose and dosing frequency. There are two possible M6620 doses and two dosing frequencies (see section4.2.1). Chemotherapy dose remains consistent across all treatment schedules. For the prior estimates of DLT at each treatment schedule see the skeleton in Table 1.

The treatment involves six cycles of chemotherapy with three weekly Cisplatin and Capecitabine and M6620 at a pre-determined frequency dependent on the treatment schedule allocated to the individual patient. The follow-up of a further 8 weeks provides a total observation window of 26 weeks. DLT assessments will be carried out during the first 4 weeks of treatment. The MTD will be determined during this period using the TiTE-CRM. An initial cohort of three patients will receive the starting schedule (lowest dosing frequency) at the starting dose. The fourth patient will not be recruited until all three patients have been followed for a minimum of 4 weeks from the start of chemotherapy or until the occurrence of a DLT.

From the fourth patient, all eligible patients will be continuously recruited and the TiTE-CRM will be used to assign their treatment schedule. To ensure enough information is accumulated to inform the assignment of the treatment schedule to the subsequent patient, recruitment will be managed by allocating treatment slots (see Protocol section 4.4 for further details).

Stage A2 stopping rules

Stage A2 will stop for safety if, at any point in the trial, there is sufficient evidence to suggest that schedule 1 is too toxic. More specifically, we will consider schedule 1 to be too toxic if, given all the available data, there is a high probability that the DLT rate is greater than the target toxicity level of 0.3. If the first three patients recruited to Stage A2 have DLTs at treatment schedule 1, then the starting schedule (treatment schedule 1) will be deemed too toxic and the trial will stop.

The trial will stop for success when either six patients have been assigned to the fourth treatment schedule (140 mg/m2 of M6620 twice weekly) or 20 patients in total have been recruited, whichever occurs first. When six patients in Stage A2 have been assigned to the fourth treatment schedule, recruitment to Stage A2 will be paused until there is full follow-up information on at least five patients. If the MTD has changed, recruitment to Stage A2 may start again.

Based on simulations and assuming a patient will be recruited every 3 weeks, the average number of patients required for Stage A2 is 16, which we aim to recruit in 12 months.

3.1.3 Stage B

The aim is to find the M6620 treatment schedule when combined with chemoradiotherapy that is associated with no more than 45% dose limiting toxicity rate on the basis that conventional oesophageal chemoradiation causes a grade 3 and 4 toxic event rate of 28% haematological toxicity and 63% non-haematological toxicity, of which 34% is gastrointestinal, as reported in the standard arm of the SCOPE1 study. Comparable toxicity rates were described in the standard arm of the PRODIGE5/ACCORD17 study: grade 3 and 4 neutropenia 29% and grade 3 and 4 dysphagia and oesophagitis 33%. A maximum of 25 patients will be recruited to Stage B.

There are three proposed M6620 treatment schedules (same dose but increasing dosing frequencies, section 4.3.1) to be explored during Stage B. M6620 treatment schedule assignment will occur prior to the start of chemoradiotherapy 6 weeks after a patient is recruited. This will maximise the accumulation of information on each patient before deciding on the treatment schedule for the subsequent patient.

The dose of M6620 (Berzosertib) in Stage B will be 140mg/m2, allocation will start on schedule 1, which is the middle of the 3 schedules. Recruitment will be continuous; however, escalation will not occur until at least one patient full DLT window of 24 weeks is complete. At this point escalation to schedule 2 will be possible if it is estimated to be safe, and dose decisions thereafter will be made once each new patient is recruited and confirmed (if there is reason to think their allocation may have changed) when they have been treated for 6 weeks (the induction period which is the same for all schedules). De-escalation to schedule -1 is possible at any point in the trial. Although recruitment will be continuous, the TMG retain the option to pause recruitment should they decide more follow-up data is needed before continuing. This may be, for example, to prevent too many patients being treated with a sub-optimal, or too toxic, schedule. No more than 7 patients will be treated on schedule 1 before there is full follow-up data on at least one patient. The starting dose of M6620 in Stage B will be 140mg/m2 if both A1 and A2 recommend 140mg/m2 otherwise it will be 90mg/m2.

We will recommend starting stage B:

- If 10 patients have been recruited to A1 and it has not restarted at the lower dose
- If 10 patients have been assigned to at least schedule 3 in A2 (i.e. are on any of the schedules with a dose of 140mg/m2) or the stopping rule is satisfied (6 treated on schedule 4)

If one of the above starting rules are satisfied then an SRC meeting will be convened to review the data and may recommend starting stage B.

Stage B stopping rules

Stage B will stop for safety if, at any point in the trial, there is sufficient evidence to suggest that schedule -1 is too toxic. More specifically, we will consider schedule -1 to be too toxic if, given all the available data, there is a high probability that the DLT rate is greater than the target toxicity level of 0.45. There will be no early stopping rules for success. We expect to recruit a minimum of 15 patients.

3.2 Dose allocation

The trial design ensures no treatment schedule skipping and the treatment schedule assigned will be that estimated to be closest to but not above the target toxicity level (TTL). However, if the lowest schedule is estimated to be above the TTL we will keep assigning the lowest schedule until we are certain it is too toxic, at which point the trial may start again using a lower dose of drug. When escalating, the treatment schedule can only increment by one level if escalating to an untried schedule, but there will be no restriction on treatment schedule de-escalation. Each escalation decision will be made by the TMG based on the recommendation from the TiTE-CRM model and the accumulated experience of the recommended schedule. Full details of each dose decision are found in the Protocol Decision Point Plan (V1.0, 28Jun2019) but briefly: TMG to review the dose selected by the statistical model on the basis of the accumulated data and either:

- Confirm the selected dose **or**
- Over-rule the selected dose and choose an alternative dose for the next participant & may convene a meeting of the Safety Review Committee (SRC) **or**
- Agree to convene a meeting of the Safety Review Committee (SRC) for further input as the TMG is unable to reach a decision **or**
  Agree that a protocol defined stopping rule has been met and that the trial should be stopped.

3.3 Stopping rules for toxicity

The same stopping rule for safety applies to all 3 stages of the study: each stage will stop for safety if, at any point in the stage, there is sufficient evidence to suggest that the lowest treatment schedule is too toxic. Specifically, within a particular stage, the lowest schedule will be considered too toxic if, given all the available data, there is a high probability that the DLT rate is greater than the target toxicity level for that stage, i.e. if P(Toxicity at treatment lowest schedule > TTL | data) > 0.95.

3.4 Summary of trial design for all stages

The table summarises the design features of the design for stages A1 and A2, and Figure 1 shows the flow of patients through the trial.

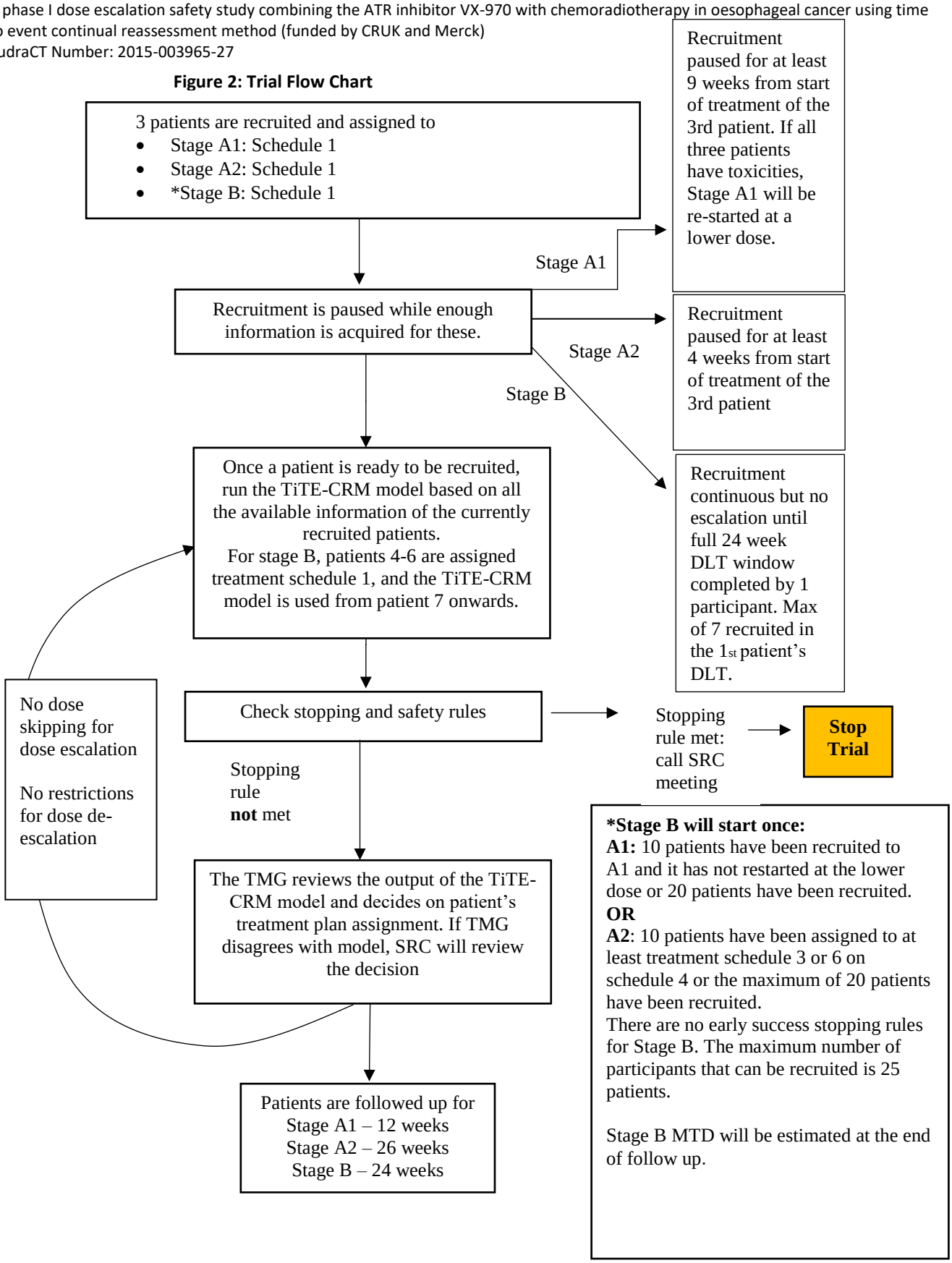
Table 1: Design features for all stages of the study

Assumptions	*A1*	*A2*	*B***
Target toxicity level	0.25	0.30	
Maximum number of subjects	20	20	
Number of treatment schedules	6	4	
Stopping rules	10 on a schedule	6 on schedule 4	
Toxicity stopping rules	P(Toxicity at treatment schedule 1 > TTL | data) > 0.95		
Definition of MTD	Treatment schedule that is closest to but not above the TTL		
Dose escalation rules	No dose skipping when escalating, no restrictions on de-escalation		
Dose toxicity curve	Power curve with prior N(0, 1.158^2)		
DLT window	9 weeks	4 weeks	

Number in first cohort*	3	3
Skeleton	0.12	0.17
	0.15	0.20
	0.18	0.25
	0.20	0.30
	0.22	
	0.25	

*** This is the number assigned the first treatment schedule**
**** Design features for Stage B omitted for this version of the SAP.**

Figure 2: Trial Flow Chart



3.5 Randomisation and Blinding

CHARIOT is not a randomised trial and is open labelled.

3.6 Sample Size

Sample size estimates are based on 1,000 simulated TiTE-CRM trials using the same characteristics that the actual trial will be based upon. The patients will not be replaced and the TiTE-CRM will use all accumulated data. For Stage A1, to treat 10 patients at a particular treatment plan or reach a maximum of 20 patients, 18 (95% C.I.: (10, 20)) patients are required. For Stage A2, to treat 6 patients at dosing schedule 4 or reach a maximum of 20 patients, 16 (95% C.I.: (11, 20)) are required.

3.7 Statistical Interim Analysis, Data Review and Stopping guidelines

This is a schedule finding trial and each time a patient is recruited, an interim analysis of the currently collected data will be performed to recommend the schedule of the newly recruited patient. See Section 3.1 for details.

3.8 Timing of Final Analysis

Based upon projected accrual rates, this trial (Stage A1, A2 and B) is expected to complete recruitment within 30 months of opening to recruitment. Final analysis for Stage A will be after all patients have been followed up for at least 3 months in Stage A1 and 26 weeks in Stage A2 while for Stage B, it will be performed 24 weeks after Stage B last patient start of treatment.

3.9 Blinded analysis

No blinded analysis will be undertaken for this trial as the trial is not randomised and therefore blinded.

3.10 Statistical Analysis Outline

Please refer to Section 3.1.

4. TREATMENT INTERVENTIONS

The trial is investigating the unlicensed drug M6620 in combination with the radiotherapy (stage A1); M6620 in combination with chemotherapy agents Cisplatin and Capecitabine (stage A2) and M6620 with chemoradiotherapy (stage B). For the purposes of the trial, M6620, Cisplatin and Capecitabine are all considered IMPs.

4.1 Stage A1 Treatment

Two M6620 dose levels and 3 dosing frequencies (treatment schedules) are proposed. Both the dose and frequency of M6620 will vary but the administered radiation dose and fractionation schedule will remain unchanged across treatment plans. The treatment schedule will last for 3 weeks and radiotherapy must start on a Monday.

4.1.1 M6620 treatment schedules – Stage A1

The starting dose of M6620 will be 140mg/m^2 IV once weekly (schedule 1). If schedule 1 is too toxic, the trial will be re-started at 90mg/m^2 (schedule -3). For all schedules, see Table 2. The treatment schedule of M6620 will be escalated or de-escalated using the TiTE-CRM model.

Table 2: Stage A1 - Dose Escalation Schedule

Dose Escalation schedule	
Treatment schedule	Dose** of *M6620 and days of the schedule it will be delivered*
-3	90 *mg/m²* day 2, 9, 16
-2	90 *mg/m²* day 2, 5, 9, 12, 16
-1	90 *mg/m²* day 2, 5, 9, 12, 16, 19
1*	140 *mg/m²* day 2, 9, 16
2	140 *mg/m²* day 2, 5, 9, 12, 16
3	140 *mg/m²* day 2, 5, 9, 12, 16, 19
4	240 *mg/m²* day 2, 9, 16
5	240 *mg/m²* day 2, 5, 9, 12, 16
6	240 *mg/m²* day 2, 5, 9, 12, 16, 19

**Starting dose and schedule. 90mg/m² dose will only be explored if trial is re-started*
***Doses are stated as exact dose in units. No intermediate dose levels or further splitting of the dose allowed*

4.2 Stage A2 Treatment

Two dose levels and 2 dosing frequencies (treatment schedules) are proposed. Both the dose and frequency of M6620 will vary but the Cisplatin and Capecitabine dose and schedule will remain unchanged across treatment plans. The treatment schedule will last for 6 cycles (18 weeks).

4.2.1 M6620 Treatment Schedule – Stage A2

The starting dose of M6620 will be 90mg/m² IV once weekly (schedule 1). For all schedules, see Table 3. The treatment schedule of M6620 will be escalated or de-escalated using the TiTE-CRM model.

Table 3: Stage A2 - Dose Escalation Schedule

Dose Escalation schedule	
Treatment schedule	Dose of *M6620 and days of the schedule it will be delivered*
1	90 *mg/m²* once a week for 18 weeks (Tuesdays)
2	90 *mg/m²* twice a week for 18 weeks (Tuesdays and Fridays)
3	140 *mg/m²* once a week for 18 weeks (Tuesdays)
4	140 *mg/m²* twice a week for 18 weeks (Tuesdays and Fridays)

**Doses are stated as exact dose in units. No intermediate dose levels or further splitting of the dose allowed*

4.3 Stage B Treatment

The dose administered in stage B will be 140mg/m2 and will remain constant whilst three dosing schedules are explored. The chemotherapy and radiation doses and fractionation schedules will remain unchanged across dosing schedules.

The 11 weeks of treatment consists of 6 weeks of induction chemotherapy (Capecitabine and Cisplatin) with M6620 (Berzosertib) followed by 5 weeks of concomitant chemoradiotherapy (Capecitabine, Cisplatin and radiotherapy) with M6620 (Berzosertib). All patients will receive M6620 (Berzosertib) with induction chemotherapy on Cycle 1 Day 2 and Cycle 2 Day 2. In the last week of chemotherapy patients will be assigned to a M6620 (Berzosertib) treatment schedule to be administered during chemoradiotherapy. Radiotherapy must start on a Monday.

4.3.1 M6620 Treatment Dose and Schedule – Stage B

The dose of M6620 in Stage B will be confirmed prior to recruitment to stage B and the starting schedule will be treatment schedule 1.

Table 4: Stage B - Dose Escalation Schedule

Dose Escalation Schedule		
Treatment Schedule	**M6620 administration during induction chemotherapy**	**M6620 administration during Chemoradiotherapy**
-1	Cycle 1 day 2, Cycle 2 day 2	Days 9, 16, 23, 30
1	As above	Days 2, 5, 9, 16, 23, 26, 30
2	As above	Days 2, 5, 9, 12, 16, 19, 23, 26, 30, 33

5. STATISTICAL PRINCIPLES

5.1 Statistical Significance and Multiple Testing

There will be no statistical significance level defined for CHARIOT as it is a dose-finding trial and schedule recommendations will be based on the posterior probabilities calculated by the dose-toxicity model using all available data at each time.

5.2 Definition of Analysis Populations

Patients will not be replaced since TiTE-CRM uses all accumulated data and all patients will be evaluable for dose escalation decisions. However, the TMG may decide to replace patients if drop-out occurs early in the treatment schedule for reasons other than a DLT.

All patients who receive treatment within the study will be evaluable for response. All participants who receive at least one dose of M6620 will be evaluable for the safety analysis and included in the TiTE-CRM.

Evaluable for Objective Response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated

in Protocol Appendix B (RECIST criteria). (Patients who exhibit objective disease progression prior to the end of cycle 1 will be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

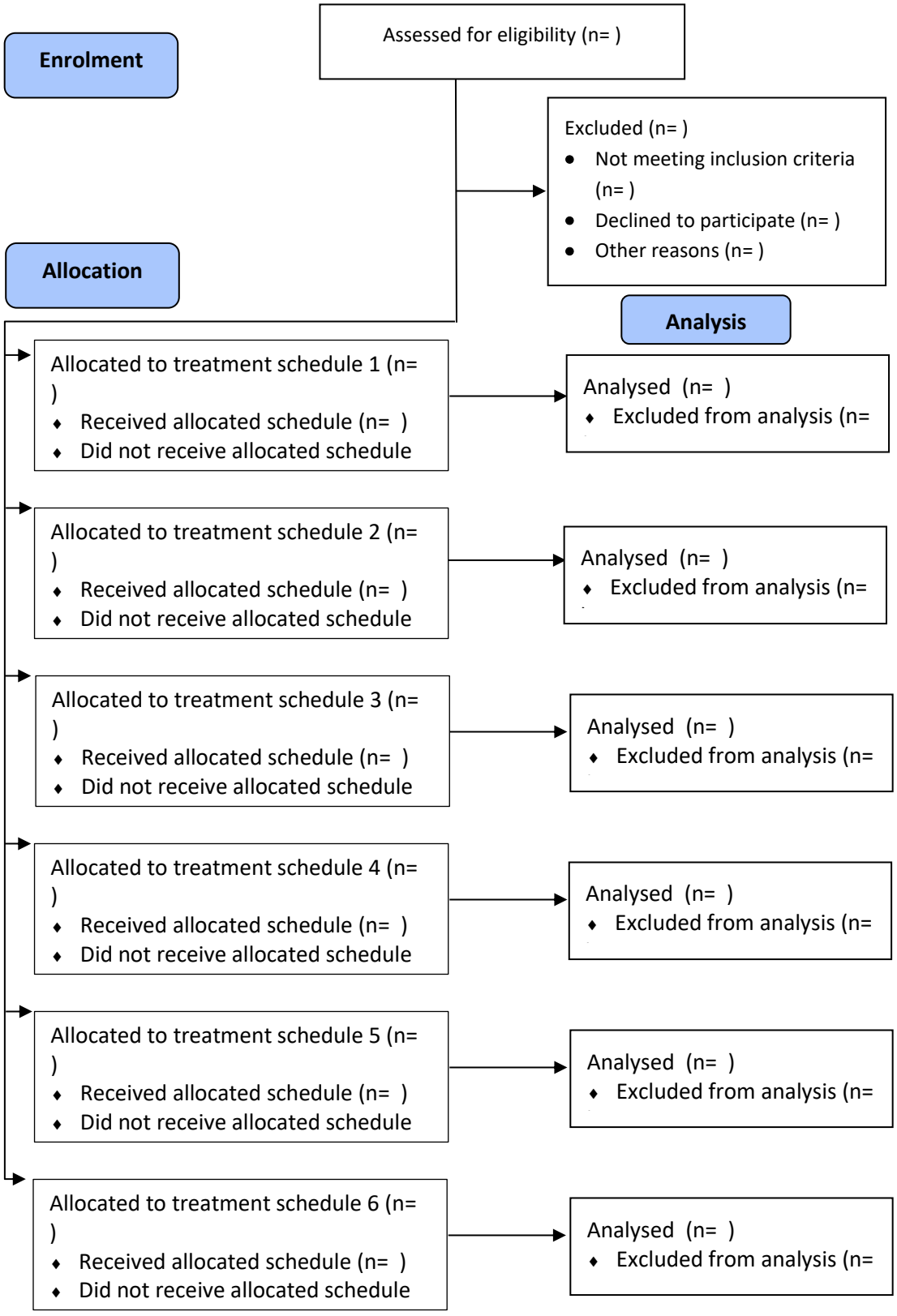
6. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

6.1 Representativeness of Study Sample and Patient Throughput

The flow of participants through each stage of the trial, including numbers of participants assigned to a schedule, receiving intended treatment, completing the study protocol, and analysed for the primary outcome is provided following CONSORT. Protocol violations/deviations and information relating to the screening data including the number of ineligible patients entering the study, together with reasons will be reported. Information on number of participants screened, found to be ineligible (with reasons where available), refused to participate (with reasons where available) will also be included.

A CONSORT diagram will be prepared for each stage. Figure 3 represents an example CONSORT diagram.

Figure 3: Example CONSORT Diagram



6.2 Withdrawal from treatment and/or follow-up

The Trial Office should be informed of any early patient withdrawal within 24 hours of the site becoming aware as described in the Protocol, Section 6. Withdrawals will be summarised, at each stage, but no formal assessments will be performed.

6.2.1 Treatment Withdrawal

During the course of the trial, a patient may withdraw early from treatment. This may happen for a number of reasons, including:

- Unacceptable toxicity
- AE/SAEs requiring discontinuation
- Loss to follow-up
- Significant protocol deviation or inability to comply with trial procedures
- Clinical decision
- Patient decision

The end of treatment means the patient will then enter the routine follow up stage of the trial. If M6620 treatment is stopped, the patient will continue with standard treatment and will be followed up as part of the trial.

6.2.2 Consent Withdrawal

Consent withdrawal means that a patient has expressed a wish to withdraw from the study altogether. Under these circumstances, the site needs to document all relevant discussions in the patient notes and notify the Trial Office, which will allow the office to mark all future CRFs as not applicable. The site should inform the Trial Office whether any samples already collected for the study should be destroyed.

Under these conditions, investigators are still responsible to follow up any SAEs until resolution.

6.3 Baseline Comparability of Randomised Groups

Baseline characteristics will be reported for each stage, including important prognostic, demographic and clinical variables.

Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented.

6.4 Unblinding

The trial is not blinded.

6.5 Description of Compliance with Intervention

Patients will be instructed to keep a record of compliance in terms of their capecitabine treatment, by means of using a study patient diary card provided to the patient by the site. Patients should be asked to bring completed diary cards or other records and all their unused / remaining capecitabine tablets (empty, open or unopened) with them to each clinic visit. The patient diary cards should not be sent to the Trial Office but kept by the centre to monitor patient drug compliance. Compliance of M6620 and Cisplatin will be monitored by the patient record.

Accountability logs are required for capecitabine to determine that patients have received at least 80% of the prescribed treatment dose. Returns should be reconciled against the patient diary and the reason for any

discrepancy documented. Site staff will collect and count patient returns, which must be recorded on the drug accountability log.

Compliance with all study treatments will be summarised for each stage using proportions calculated with respect to the total dose prescribed.

6.6 Reliability

Data derivation/manipulation will be checked to ensure validity of the derived data, where appropriate. Calculations performed using the computer can be checked by hand for the smallest of 5% or 20 observations within the dataset, where appropriate.

7. ANALYSIS

7.1 Outcome Definitions

A table presenting the objectives, outcome measures and evaluation time points for each stage can be found in Section 2.2 of this document.

7.2 Analysis Methods

7.2.1 Primary Outcome (All Stages)

The primary outcome at each stage is to determine the best tolerated treatment schedule of M6620 administered concomitantly with radiotherapy and/or chemotherapy (depending on the stage). The TiTE-CRM model will be used to achieve this as described in Section 1.13. Results will be presented as posterior probabilities and 95% credible intervals of the schedule-toxicity curve, both in tabular form and graphically.

7.2.2 Secondary Outcomes

Safety and Toxicity Profile of the M6620 (All Stages)

The number (proportion) of patients who have had an AE recorded should be reported by schedule group. The number (proportion) of patients who have experienced one, two, three or more AEs will also be provided by schedule group. It is intended that the number of AEs recorded, the number of AEs per grade and the outcome will be reported.

This analysis will be repeated twice: once using serious adverse events (SAEs) and once using serious adverse reactions (SARs). Note: SARs are SAEs that are recorded as being possibly, probably or definitely related to a component of treatment. For SARs, the treatment component the event was related to may also be described.

Details of any SUSARs will be reported in the statistical report; the schedule group for the affected patient will be indicated.

Dose limiting toxicities are classed as SAEs in CHARIOT and will be analysed as described above. Length of time for toxicities to resolve will also be summarised and presented as mean (SD) or median (IQR).

Proportion of patients completing planned dose (All Stages)

To determine the ability to deliver the M6620 with palliative radiotherapy (Stage A1) and palliative chemotherapy (Stage A2), the proportion of patients completing at least 75%, 90% and 100% of the planned dose will be tabulated by schedule group.

To determine tolerance and ability to deliver M6620 in combination with standard definitive chemoradiotherapy in Stage B, the proportion of patients completing at least 80% of the planned chemotherapy dose and at least 20 fractions of radiotherapy will be tabulated by schedule group.

Efficacy of the combination (All Stages)

Objective tumour response will be classified according to the RECIST v1.1 criteria. The number and proportion of patients who achieve Complete Response (CR), Partial Response (PR), (Stable Disease) SD and Progressive Disease (PD) will be reported overall and by treatment schedule.

Overall survival (OS) will be presented by stage using Kaplan Meier graphs along with two-sided 95% confidence intervals. Median and quartile OS will also be presented together with their 2-sided 95% confidence intervals if applicable.

Progression free survival (PFS) will be presented overall by stage using Kaplan Meier graphs along with two-sided 95% confidence intervals. Median and quartile PFS will also be presented together with their 2-sided 95% confidence intervals if applicable.

In field radiotherapy control (Stage A1)

This will be assessed and measured via CT scan response and/or clinical assessment.

Note: *The final statistical report should also include information on the number of participants used in each analysis model, and for the analysis of longitudinal follow-up data, the number of observations used.*

7.2.3 Tertiary Outcomes (Stage A2 and B)

These outcomes will not be analysed as part of this SAP.

7.3 Missing Data

Every effort will be made for complete collection and recording of data. Dose allocation and primary outcome evaluation using the TiTE-CRM model requires complete data; for this reason, a dedicated CRF has been designed, which captures only that data required to run the model.

No data imputation is planned.

7.4 Sensitivity Analysis

There will be four sensitivity analyses presented for each dose decision meeting. They will be analysed using the TiTE-CRM as in the primary analysis. These are:

1. Only using those patients who not missed any of their dose prescribed on their dose schedule, and weighted using the original TiTE-CRM weights, i.e. weighting only according to length of follow-up and not taking account of how much dose has been received
2. Only using those patients who have received at least 75% of the prescribed dose, using the same weight function as in the main analysis
3. Only using those patients who have received at least 75% of the prescribed dose, but using the original TiTE-CRM weights

4. Using the same population and weighting as the primary population but assuming the "Most Toxic" Scenario. All patients currently on treatment within the DLT window have been assigned a DLT.

For each of these analyses we will present the posterior probabilities of toxicity at each dose level and their associated 95% credible interval.

7.5 Pre-specified Subgroup Analysis

No formal subgroup analysis is planned.

7.6 Supplementary/ Additional Analyses and Outcomes

No formal supplementary/additional analyses are planned.

7.7 Health Economics and Cost Effectiveness (where applicable)

No health economics and cost effectiveness analysis is planned.

7.8 Meta-analyses (if applicable)

No meta-analyses are planned.

8. VALIDATION OF THE PRIMARY ANALYSIS

The schedule recommendation for each recruited patient will be calculated using a bespoke, validated program developed in **R** and **OpenBUGS** by Jane Holmes. The program has been validated using another **R** program developed independently by Eleni Frangou. Further, the output from these two programs has been validated using the `titecrm` function in the **R** package `dfcrm`. Details on this package are available here: **https://cran.r-project.org/web/packages/dfcrm/**.

To validate the primary outcome and key secondary outcomes a statistician not involved in the trial will independently repeat the analyses detailed in this SAP. The results will be compared and any discrepancies will be reported in the Statistical report (See OCTRU SOP STATS-005 Statistical Report).

9. SPECIFICATION OF STATISTICAL PACKAGES

All analysis will be carried out using **R**. The relevant package and version number will be recorded in the Statistical report.

10. REFERENCES

Cheung YK, Chappell R. Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics. 2000;56:1177–82.

Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Dore C, Williamson PR, Altman DG, Montgomery A, Lim P. Berlin K, Senn S, Day S, Barbachano Y, Loder E. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. **JAMA.** 2017 Dec 19;318(23):2337-2343. doi: 10.1001/jama.2017.18556.

APPENDIX: GLOSSARY OF ABBREVIATIONS

SAP	Statistical Analysis Plan
DSMC	Data and Safety Monitoring Committee
TSC	Trial Steering Committee

CI Chief Investigator

Appendix 1 - CHARIOT Simulation Results

Table of Contents

Original Simulations

Introduction

During the initial development of CHARIOT, extensive simulations were carried out to determine estimated sample sizes and priors for each Stage. The results of these were initially stored in the Statistical Analysis Plan but have been moved to this appendix with the revisions made to the SAP when making the document V2.0. Table 1 is the original design features of the study from V1.0 of the SAP.

Table 1: Design features for all stages of the study

Assumptions	*A1*	*A2*	*B*
Target toxicity level	0.25	0.30	0.45
Maximum number of subjects	20	20	25
Number of treatment schedules	6	4	6
Stopping rules	10 on a schedule	6 on schedule 4	10 on a schedule
Toxicity stopping rules	P(Toxicity at treatment schedule 1 > TTL | data) > 0.95		
Definition of MTD	Treatment schedule that is closest to but not above the TTL		
Dose escalation rules	No dose skipping when escalating, no restrictions on de-escalation		
Dose toxicity curve	Power curve with prior N(0, 1.158^2)		
DLT window	9 weeks	4 weeks	24 weeks
Number in first cohort*	3	3	3+3
Skeleton	0.12 0.15 0.18 0.20 0.22 0.25	0.17 0.20 0.25 0.30	0.23 0.25 0.30 0.35 0.40 0.45

*** This is the number assigned the first treatment schedule**

Operating Characteristics of the Trial

Sample size estimates are based on 1,000 simulated TiTE-CRM trials using the same characteristics that the actual trial will be based upon. The patients will not be replaced and the TiTE-CRM will use all accumulated data. For each of the stages, simulations are based on the assumptions given in Table 2 and those given previously in Table 1. The assumptions are the same as for the trial, except it also shows the different scenarios of "true" underlying probability of toxicity at each treatment level that were used for simulations. The skeleton is the initial toxicity rate at each schedule that serve as a starting point for the trial, i.e. the initial toxicities at each treatment schedule. For each stage, assuming toxicity rates are the same as the skeleton, the average number of patients recruited are 18 (95% C.I.: (10, 20)), 16 (95% C.I.: (11, 20)) and 22(95% C.I.: (10, 25)) for stages A1, A2 and B respectively. The total combined sample size, for the three stages, is 54 patients (95% C.I.: (41, 65)). It should be noted that the combined sample size is not the sum of each stage's sample size. An additional 4 patients might be required if the starting dose of Stage B proves to be too toxic.

Table 2: Simulation Assumptions

Assumptions	A1				A2				B			
Accrual rate per week	1/8				1/3				1/6			
Skeleton	0.12 0.15 0.18 0.20 0.22 0.25				0.17 0.20 0.25 0.30				0.23 0.25 0.30 0.35 0.40 0.45			
Scenarios	1	2	3	4	1	2	3	4	1	2	3	4
	0.12	0.10	0.00	0.04	0.17	0.10	0.05	0.05	0.23	0.30	0.16	0.04
	0.15	0.20	0.01	0.08	0.20	0.25	0.10	0.15	0.25	0.35	0.25	0.09
	0.18	0.30	0.04	0.16	0.25	0.40	0.15	0.30	0.30	0.40	0.35	0.16
	0.20	0.40	0.08	0.25	0.30	0.55	0.20	0.50	0.35	0.45	0.45	0.25
	0.22	0.50	0.16	0.35					0.40	0.50	0.60	0.35
	0.25	0.60	0.25	0.46					0.45	0.55	0.75	0.45

For each stage of the trial (A1, A2 and B), we simulated 1,000 trials assuming various different scenarios for the true underlying dose toxicity curve. Using the characteristics and assumptions given in Table 1 and Table 2, the operating characteristics of the different stages are given in Tables Table ***3***, Table ***4*** and Table ***5***. The table show the proportion of times each treatment schedule is the recommended schedule at the end of the trial (% recommendation), the proportion of patients treated at each treatment schedule (% treated), the percent of DLTs, and the average trial size.

Table 3: Properties of the trial under various scenarios (based on 1,000 simulations): Stage A1

	% recommendation						% treated						% DLT	Av. trial size
Schedule	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**		
Scenario														
1	17.2	9.2	5.5	6.1	10.3	51.7	35.0	10.2	8.4	7.8	8.8	29.8	18.5	17.6
2	39.9	26.3	14.4	11.3	5.6	2.5	44.6	17.4	12.6	9.4	7.6	8.4	25.7	18.0
3	0.2	1.1	1.3	6.8	8.8	81.8	17.2	7.0	7.5	8.2	10.7	49.4	14.6	18.2
4	9.5	15.7	17.6	19.5	18.4	19.3	24.2	14.8	13.6	12.9	12.8	21.7	22.4	19.5

Table 4: Properties of the trial under various scenarios (based on 1,000 simulations): Stage A2

	% recommendation				% treated				% DLT	Av. trial size
Schedule	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**		
Scenario										
1	13.9	14.5	17.6	54.0	40.5	15.1	14.5	29.8	21.0	15.8
2	18.9	36.2	27.7	17.2	37.5	23.3	18.5	20.8	27.0	17.8
3	0.6	1.5	7.5	90.4	27.8	11.4	13.1	47.6	12.6	12.8
4	6.6	22.7	35.5	35.2	28.3	19.7	21.2	30.9	24.3	16.5

Table 5: Properties of the trial under various scenarios (based on 1,000 simulations): Stage B

	% recommendation						*% treated*						*% DLT*	*Av. trial size*
Schedule	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**		

Scenario														
1	5.4	5.2	6.9	12.3	16.5	53.7	32.9	7.3	9.2	11.2	13.0	26.3	33.4	22.0
2	20.3	15.0	13.4	16.9	14.5	19.9	41.0	11.2	12.4	12.1	10.4	12.8	41.1	21.1
3	3.0	8.9	24.9	30.8	21.9	10.5	28.3	8.4	13.9	17.7	15.2	16.4	41.1	23.7
4	0.0	0.0	0.1	3.0	9.8	87.1	28.8	4.8	5.1	6.4	9.2	45.6	27.2	21.0

Revised Simulations

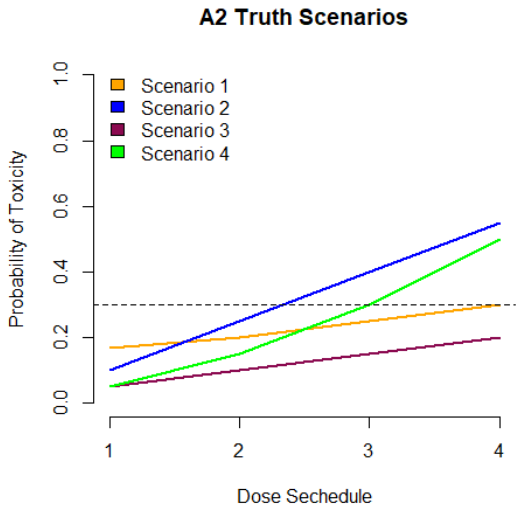
All results in this section have been derived using Version 3.6.1 of R and Version 3.2.3 of OpenBUGS. Code for the results presented here can be found in the sTMF for CHARIOT. "Z:\CSM_CHARIOT\Statistical Analysis\Design\Simulations\PriorsReview_Apr2020".

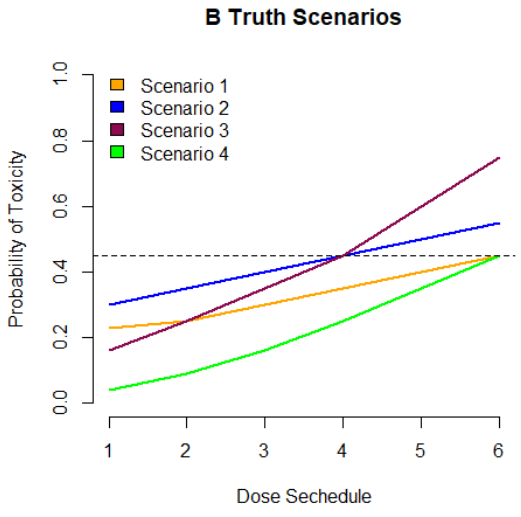
Introduction

In the SRC held on 27Nov2019 questions were raised about the prior for A2. This section is to look at the operating characteristics of the priors for A2 under the same scenarios presented in the SAP but changing steepness of the skeleton and variance and seeing how the operating characteristics are effected.

Truth Scenarios

Stage	A2				B			
Scenario	1	2	3	4	1	2	3	4
	0.17	0.10	0.05	0.05	0.23	0.30	0.16	0.04
	0.20	0.25	0.10	0.15	0.25	0.35	0.25	0.09
	0.25	0.40	0.15	0.30	0.30	0.40	0.35	0.16
	0.30	0.55	0.20	0.50	0.35	0.45	0.45	0.25
					0.40	0.50	0.60	0.35
					0.45	0.55	0.75	0.45





Stage A2

Prior

To fully experiment with a range of priors for both stages we will alter the toxicity skeleton and the variance and examine each proposed prior's performance. For A2 we will look at 5 different skeletons:

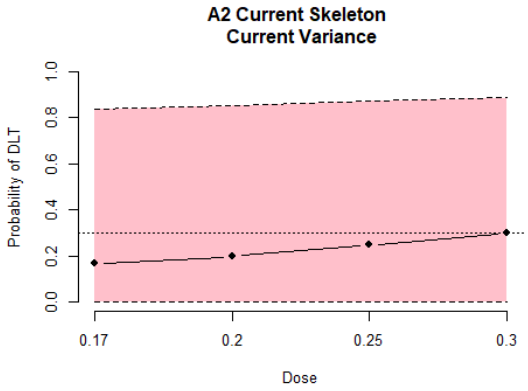
- The current one in use
- A steep skeleton
- A very steep skeleton.
- A coherent skeleton from the "getprior" function from the dfcrm package with dose 4 as the prior guess of the MTD
- A coherent skeleton from the "getprior" function from the dfcrm package with dose 3 as the prior guess of the MTD

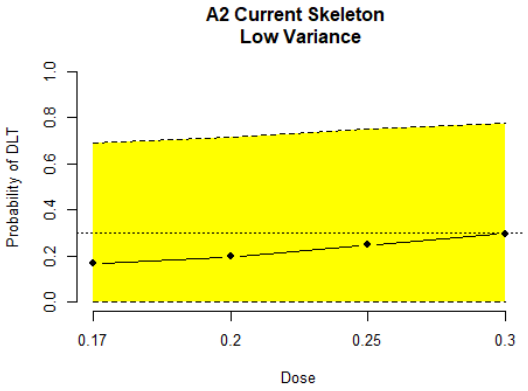
The variances we will use are:

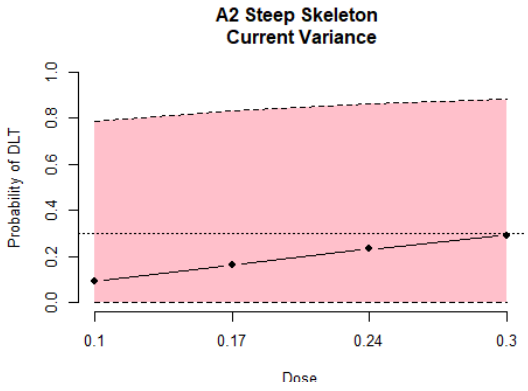
- the original 1.158^2
- a lower variance of 0.8^2.

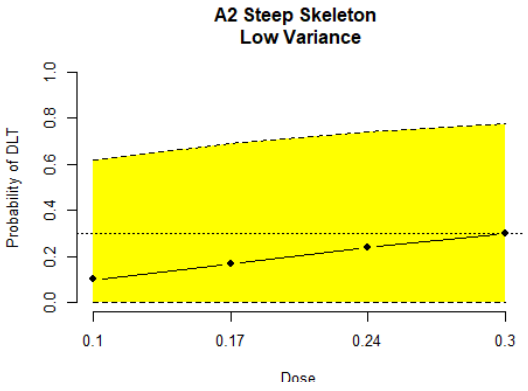
We will look at each combination of these skeletons and variacnce meaning there are 10 priors in total to be examined for A2.

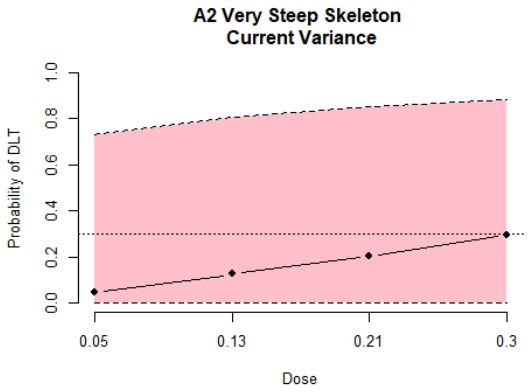
	1	2	3	4
Current Skeleton	0.17	0.2	0.25	0.3
Steep Skeleton	0.1	0.17	0.24	0.3
Very Steep Skeleton	0.05	0.13	0.21	0.3
Coherent Skeleton	0.01	0.05	0.15	0.3
Coherent Toxic Skeleton	0.05	0.15	0.3	0.46

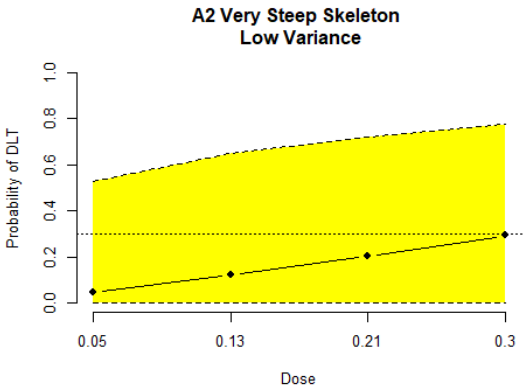

A2 Current Skeleton
Current Variance
Probability of DLT
0.0
0.2
0.4
0.6
0.8
1.0
0.17
0.2
0.25
0.3
Dose

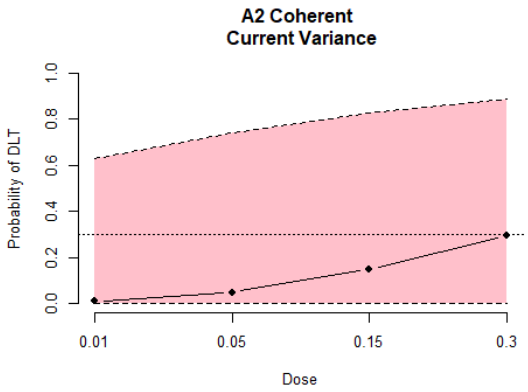

A2 Current Skeleton
Low Variance
Probability of DLT
0.0
0.2
0.4
0.6
0.8
1.0
0.17
0.2
0.25
0.3
Dose

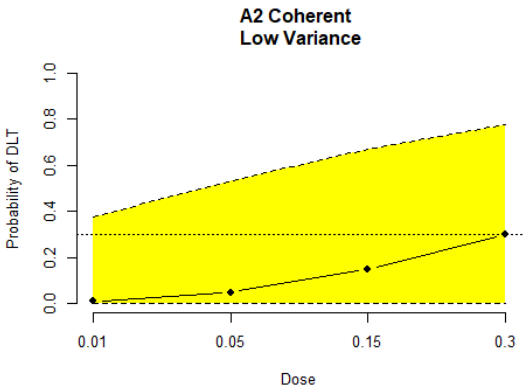

A2 Steep Skeleton
Current Variance
Probability of DLT
0.0
0.2
0.4
0.6
0.8
1.0
0.1
0.17
0.24
0.3
Dose

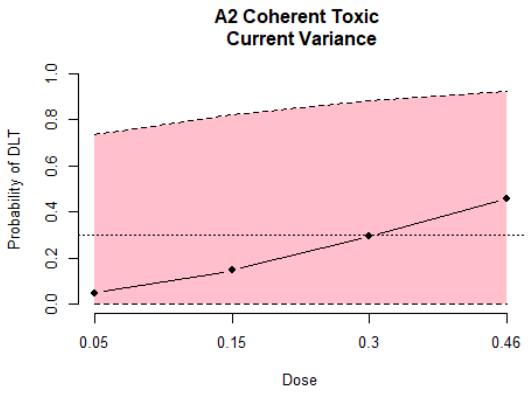

A2 Steep Skeleton
Low Variance
Probability of DLT
0.0
0.2
0.4
0.6
0.8
1.0
0.1
0.17
0.24
0.3
Dose

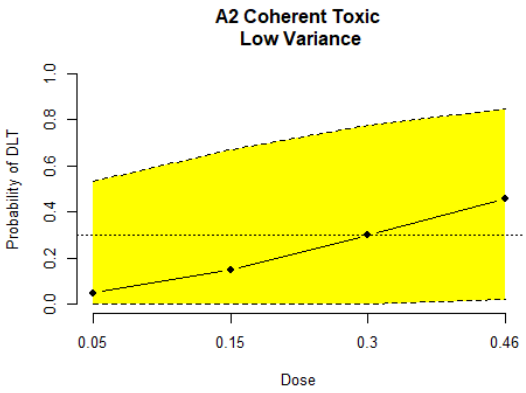

A2 Very Steep Skeleton
Current Variance
Probability of DLT
0.0
0.2
0.4
0.6
0.8
1.0
0.05
0.13
0.21
0.3
Dose


A2 Very Steep Skeleton
Low Variance
Probability of DLT
0.0
0.2
0.4
0.6
0.8
1.0
0.05
0.13
0.21
0.3
Dose


A2 Coherent
Current Variance
Probability of DLT
0.0
0.2
0.4
0.6
0.8
1.0
0.01
0.05
0.15
0.3
Dose


A2 Coherent
Low Variance
Probability of DLT
0.0
0.2
0.4
0.6
0.8
1.0
0.01
0.05
0.15
0.3
Dose





Simulation Results

Based on 1000 simulated trials.

Original Skeleton, Original Variance

	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	13.4	15.6	17.1	53.9	40.8	15.9	15	28.3	19.4	16.16
Scenario 2	20.3	33	24.4	22.3	38.3	24.7	18.6	18.4	30.2	18.23
Scenario 3	0.1	1.8	7	91.1	28	12	13.8	46.2	9.4	13.03
Scenario 4	5.3	18.7	31.7	44.3	28.8	20.3	20.7	30.2	22.7	16.52

Original Skeleton, Low Variance

	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	13	12.8	17.5	56.7	37.8	16.7	16	29.5	18.4	15.98
Scenario 2	19.3	37.1	23.6	20	35.7	25.5	19.8	19	30.7	18.2
Scenario 3	0.9	2.9	7.3	88.9	27.4	12.2	14	46.4	9.8	13.02
Scenario 4	3.9	20	31.7	44.4	26.6	20.3	22	31.1	22.4	16.28

Steep Skeleton, Original Variance

	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	20.9	20.9	14	44.2	44.1	18.6	14.4	22.9	18.4	16.92
Scenario 2	21.1	40.7	21	17.2	38.3	29	17.4	15.3	29.5	18.54
Scenario 3	0.7	5	9	85.3	28.3	13.4	14.9	43.3	8.8	13.59
Scenario 4	5.8	27.1	31.5	35.6	27.3	24.8	22	25.9	22.5	17.15

Steep Skeleton, Low Variance

	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	16.4	19.5	16.5	47.6	40.2	19.9	15.2	24.7	17.7	16.7
Scenario 2	21.4	39.3	21.6	17.7	34.9	30.8	18.7	15.7	29	18.46
Scenario 3	0.5	4	9	86.5	27	13.3	15.8	43.9	9	13.49
Scenario 4	4.2	27.7	32.9	35.2	25.8	25.2	24.3	24.8	22.6	17.4

Very Steep Skeleton, Original Variance

	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	28.4	20.4	18.3	32.9	48.7	18.2	14.9	18.2	18.9	17.52
Scenario 2	23.8	43.5	20.3	12.4	41	29.4	17.2	12.4	29.4	18.75
Scenario 3	1.2	7.9	14.7	76.2	28.3	15.2	18.1	38.4	9.1	14.48
Scenario 4	5.5	32.1	37.2	25.2	27.5	26.2	26.1	20.2	22.7	17.93

Very Steep Skeleton, Low Variance

	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	24.8	21.1	19.7	34.4	43.7	20.6	16.4	19.2	17.9	17.38
Scenario 2	21.7	47.4	21.2	9.7	35.7	33.8	20	10.5	30.1	19.12
Scenario 3	1.8	5.8	14.3	78.1	27.1	14.6	19	39.2	8.5	14.24
Scenario 4	4	30.2	41.6	24.2	24.1	26.4	29.8	19.8	22.1	17.94

Coherent Skeleton, Original Variance

	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	24	21.7	19.2	35.1	42.9	20.9	16.9	19.2	18.1	17.42
Scenario 2	20.5	44.7	23.5	11.3	35.9	31.9	20.3	12	28.6	18.89
Scenario 3	1.3	7	16.5	75.2	26.7	15.5	20.3	37.5	9.8	14.61
Scenario 4	3.9	29.5	39.9	26.7	23.9	26.4	29.4	20.3	22.4	17.84

Coherent Skeleton, Low Variance

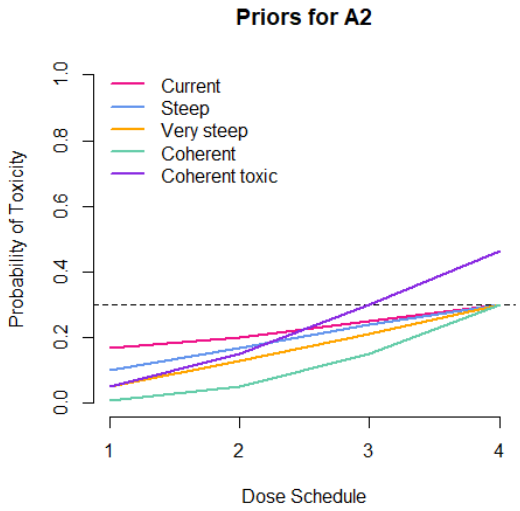
	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	23.5	20.6	20.2	35.7	42.4	20.6	17.5	19.5	18	17.43
Scenario 2	20.9	47.8	20.9	10.4	35.2	33.5	20.7	10.6	29.5	19.07
Scenario 3	0.8	6.3	17.4	75.5	26.5	15	20.3	38.2	9.2	14.53
Scenario 4	3.3	29.3	41.6	25.8	24.2	26.7	29.4	19.7	22.2	18.05

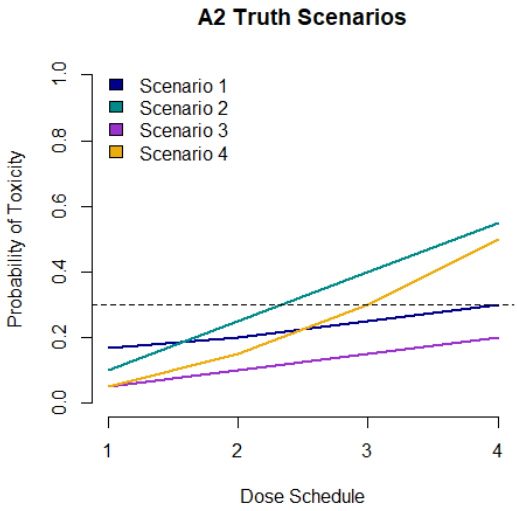
"Toxic" Coherent Skeleton, Original Variance

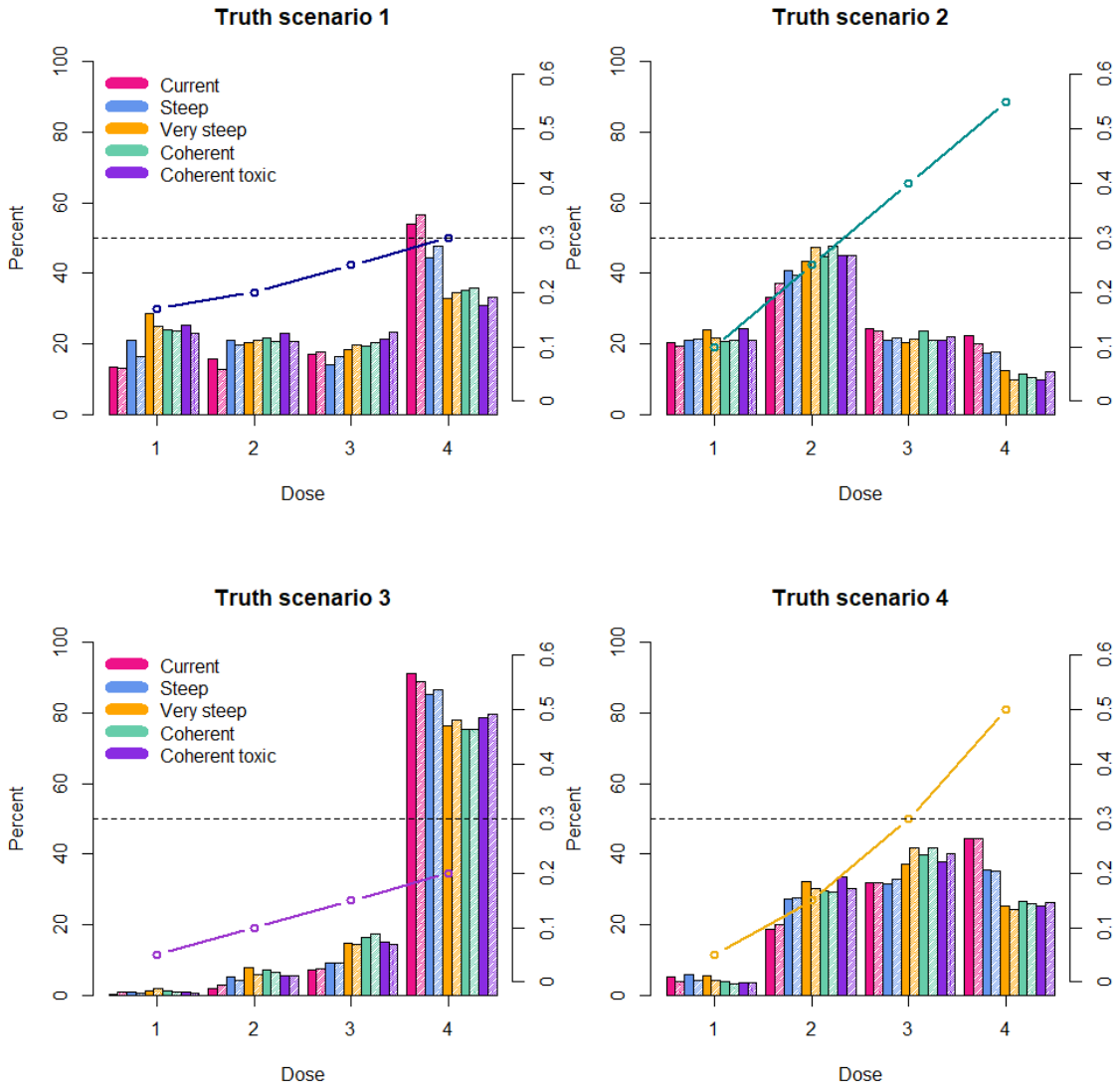
	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	25.3	22.8	21.2	30.7	44	20.8	17.5	17.7	19.8	17.69
Scenario 2	24.2	45	20.9	9.9	36.3	33.5	19.7	10.4	30.6	19.18
Scenario 3	0.7	5.6	15.1	78.6	26.2	14.6	19.6	39.6	8.4	14.23
Scenario 4	3.5	33.5	37.9	25.1	23.9	26.7	29.2	20.1	22.6	17.95

"Toxic" Coherent Skeleton, Low Variance

	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	22.8	20.6	23.3	33.3	42.2	21.1	18.2	18.5	18.3	17.57
Scenario 2	21.1	44.9	22	12	35.1	32.9	20.7	11.2	29	18.96
Scenario 3	0.5	5.5	14.4	79.6	25.7	14.1	20.3	39.8	8.8	14.28
Scenario 4	3.4	30.3	40.1	26.2	24.1	26	29.6	20.3	22.1	17.86







Overall it can be concluded that the current prior used in CHARIOT Stage A2 performs the best of all priors tested when examining non-toxic scenarios which are the most in line with the prior beliefs on how toxic the drug will be. For more toxic scenarios, the current prior used may be suggest escalating to a higher more than other priors, however, the difference in overall characteristics between priors examined here is not sufficient to warrant adopting a new prior. The current prior does best in situations that are believed more likely to arise a priori so this prior will be used for the remainder of the A2 study following this review.

Stage B

Proposed prior and simulation results for Stage B will be added to this section in a SAP Appendix update prior to OCTRU Green Light for Stage B.