CHARIOT A1 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 studycombining 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 A1.

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 11 interim dose decisions for Stage A1. The first occurred on 16Oct2019 and the final interim analysis was on 15Nov2021.

Interim Number	Date	Sample Size at Time of Decision	Decision
1	16Oct2019	3	Escalate to Schedule 2
2	20Nov2019	4	Escalate to Schedule 3
3	19Dec2019	5	Escalate to Schedule 4
4	17Feb2020	6	Escalate to Schedule 5
5	12Mar2020	7	Escalate to Schedule 6
6	27Aug2020	8	Remain on Schedule 6

Interim Number	Date	Sample Size at Time of Decision	Decision
7	14Dec2020	9	Remain on Schedule 6
8	02Feb2021	10	Remain on Schedule 6
9	26May2021	11	Remain on Schedule 6
10	06Sep2021	13	Remain on Schedule 6
11	15Nov2021	15	Remain on Schedule 6

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

Figure 1 is the CONSORT diagram for CHARIOT A1, it presents the flow of participants through all stages of the trial: eligibility, registration, allocation and analysis.

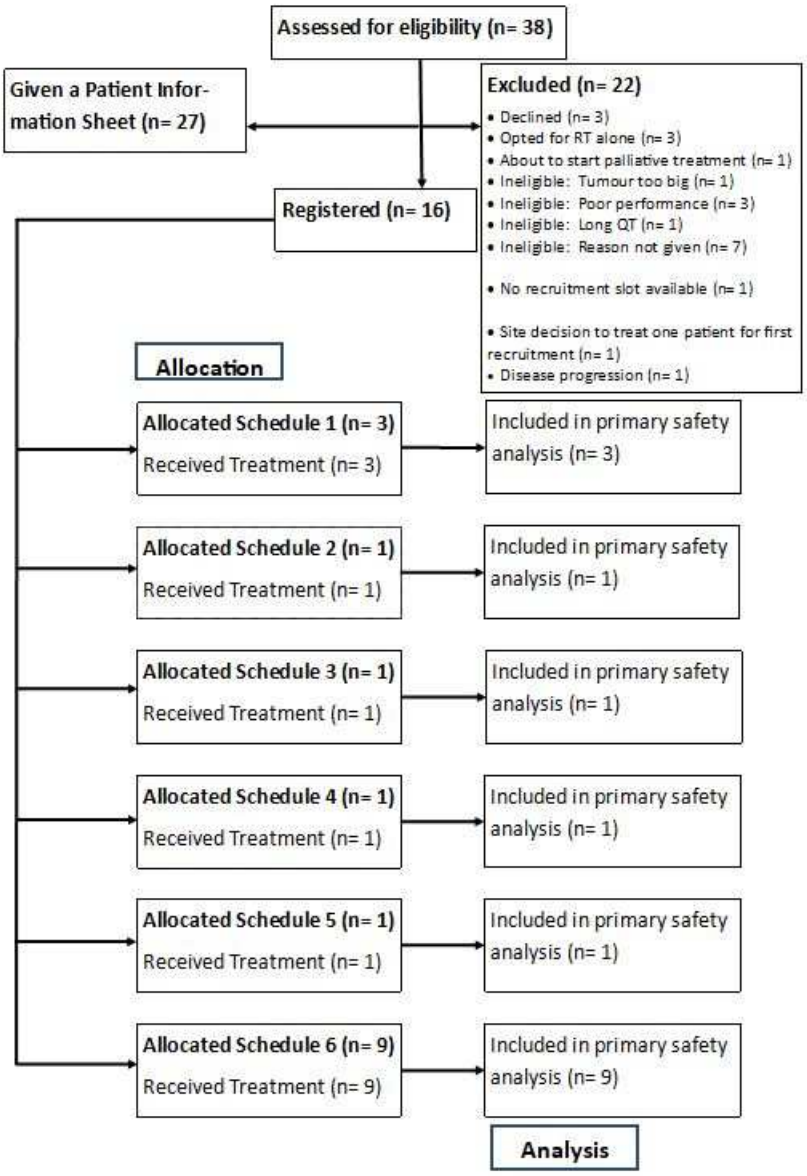

Figure 1: CONSORT Diagram

4.2 Recruitment

The first patient was registered into Stage A1 on 17 May 2019. The final patient was registered on 05 January 2022 and the final study visit was on 31 March 2022. The trial stopped short of its original recruitment target of 20 patients as the planned recruitment period expired, triggering the final trial follow-ups. At this point, nine participants had been recruited to schedule 6, which was one patient short of the early stopping rule for success of recruiting 10 to one schedule (Schedule 6). 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.

Table 1: Baseline characteristics

	Schedule 1 (n=3)	Schedule 2 (n=1)	Schedule 3 (n=1)	Schedule 4 (n=1)	Schedule 5 (n=1)	Schedule 6 (n=9)	Total (n=16)
Gender							
Male	3 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	8 (88.9)	14 (87.5)
Female	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (11.1)	2 (12.5)
Age	n=3, 66.0 (10.4)	n=1, 68.0 (NA)	n=1, 63.0 (NA)	n=1, 67.0 (NA)	n=1, 76.0 (NA)	n=9, 65.2 (12.1)	n=16, 66.2 (10.0)
Etnicity							
White British	3 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	9 (100.0)	16 (100.0)
Smoking Status							
Ex-smoker	2 (66.7)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	6 (66.7)	11 (68.8)
Never smoked	1 (33.3)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	3 (33.3)	5 (31.2)
Site							
Beatson, Glasgow	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (11.1)	2 (12.5)
Christie, Manchester	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	3 (18.8)
Churchill, Oxford	2 (66.7)	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)	5 (31.2)
Velindre, Cardiff	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	5 (55.6)	6 (37.5)
Oesophageal Tumour Location							
Lower thoracic and abdominal portion	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)	8 (50.0)
Mid thoracic portion	1 (33.3)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	2 (22.2)	5 (31.2)

	Schedule 1 (n=3)	Schedule 2 (n=1)	Schedule 3 (n=1)	Schedule 4 (n=1)	Schedule 5 (n=1)	Schedule 6 (n=9)	Total (n=16)
Upper thoracic portion	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (11.1)	3 (18.8)
Tumour Length (cm)	n=2, 9.5 (0.7)	n=1, 5.0 (NA)	n=1, 6.0 (NA)	n=1, 0.5 (NA)	n=1, 3.5 (NA)	n=9, 5.4 (3.5)	n=15, 5.5 (3.4)
Histopathy							
Adenocarcinoma	3 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	6 (66.7)	10 (62.5)
Squamous cell carcinoma	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	3 (33.3)	6 (37.5)
Tumour Grade							
Well differentiated (G1)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.2)
Moderately differentiated (G2)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	3 (18.8)
Poorly differentiated (G3)	0 (0.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	4 (44.4)	8 (50.0)
Unknown or cannot be assessed (GX)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	4 (25.0)
Locoregional Disease							
Yes	3 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	6 (66.7)	13 (81.2)
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	3 (18.8)
Distant Metasases							
Yes	1 (33.3)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	4 (44.4)	6 (37.5)
No	2 (66.7)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	5 (55.6)	10 (62.5)
Prior Radiotherapy							
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (6.2)
No	3 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	8 (88.9)	15 (93.8)

	Schedule 1 (n=3)	Schedule 2 (n=1)	Schedule 3 (n=1)	Schedule 4 (n=1)	Schedule 5 (n=1)	Schedule 6 (n=9)	Total (n=16)
Prior Systemic Treatment							
Yes	2 (66.7)	0 (0.0)	1 (100.0)	1 (100.0)	1 (100.0)	8 (88.9)	13 (81.2)
No	1 (33.3)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (18.8)
Oesophageal Stent							
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	3 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	9 (100.0)	16 (100.0)

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

Details on prior therapy, full details on baseline symptoms and lesions from the baseline CT-scans are given in *Appendix - Baseline*. The most common baseline symptoms were Dysphagia (5) and Hypertension (3). All baseline scans were done via CT-scan. The mean max diameter of target lesions at baseline was 23.7mm with a standard deviation of 9.3. Most target lesions were in the Lymph Nodes (6) or Oesophagus (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 2. 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 2: Numbers analysed

	Schedule 1 (n=3)	Schedule 2 (n=1)	Schedule 3 (n=1)	Schedule 4 (n=1)	Schedule 5 (n=1)	Schedule 6 (n=9)	Total (n=16)
Primary Safety	3 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	9 (100.0)	16 (100.0)
Efficacy (12 Week Overall RECIST)	2 (66.7)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	6 (66.7)	12 (75.0)

4.4 Compliance

4.4.1 Treatment Compliance

4.4.1.1 Radiotherapy Compliance

Patients were prescribed 35Gy in 15 fractions. The first date of radiotherapy in this trial was 27 May 2019 and the final date was 28 Jan 2022 The mean duration of radiotherapy was 18.5 days with standard deviation of 1.1.

Radiotherapy compliance is presented in Table 3. A full line-listing of Radiotherapy compliance is given in Table 4. Only two patients did not receive their full dose, and they only missed one dose each. No patients had their radiotherapy stopped early. All doses of Radiotherapy given, including dose reductions, are presented in Figure 2.

Table 3: Radiotherapy compliance

	Schedule 1 (n=3)	Schedule 2 (n=1)	Schedule 3 (n=1)	Schedule 4 (n=1)	Schedule 5 (n=1)	Schedule 6 (n=9)	Total (n=16)
Radiotherapy % Recevied							
100%	3 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	7 (77.8)	14 (87.5)
>=90%, <100%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (12.5)
>=75%, <90%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<75%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 4: Radiotherapy compliance listing

Subject	Schedule	Fractions Received	% Received
CH-A1-101	Schedule 1	15	100.0
CH-A1-102	Schedule 1	15	100.0
CH-A1-103	Schedule 1	15	100.0
CH-A1-104	Schedule 2	15	100.0
CH-A1-105	Schedule 3	15	100.0
CH-A1-106	Schedule 4	15	100.0
CH-A1-107	Schedule 5	15	100.0
CH-A1-108	Schedule 6	15	100.0
CH-A1-109	Schedule 6	14	93.3
CH-A1-110	Schedule 6	15	100.0
CH-A1-111	Schedule 6	15	100.0
CH-A1-112	Schedule 6	15	100.0
CH-A1-113	Schedule 6	14	93.3
CH-A1-114	Schedule 6	15	100.0
CH-A1-115	Schedule 6	15	100.0
CH-A1-116	Schedule 6	15	100.0

Of the 240 fractions prescribed as part of this trial (15 fractions each for 16 patients treated), there were 2 fractions missed. One was due to a rest day, the other due to concern that the radiotherapy plan might not be representative due to the variation of air in the GI tract near the tumour.

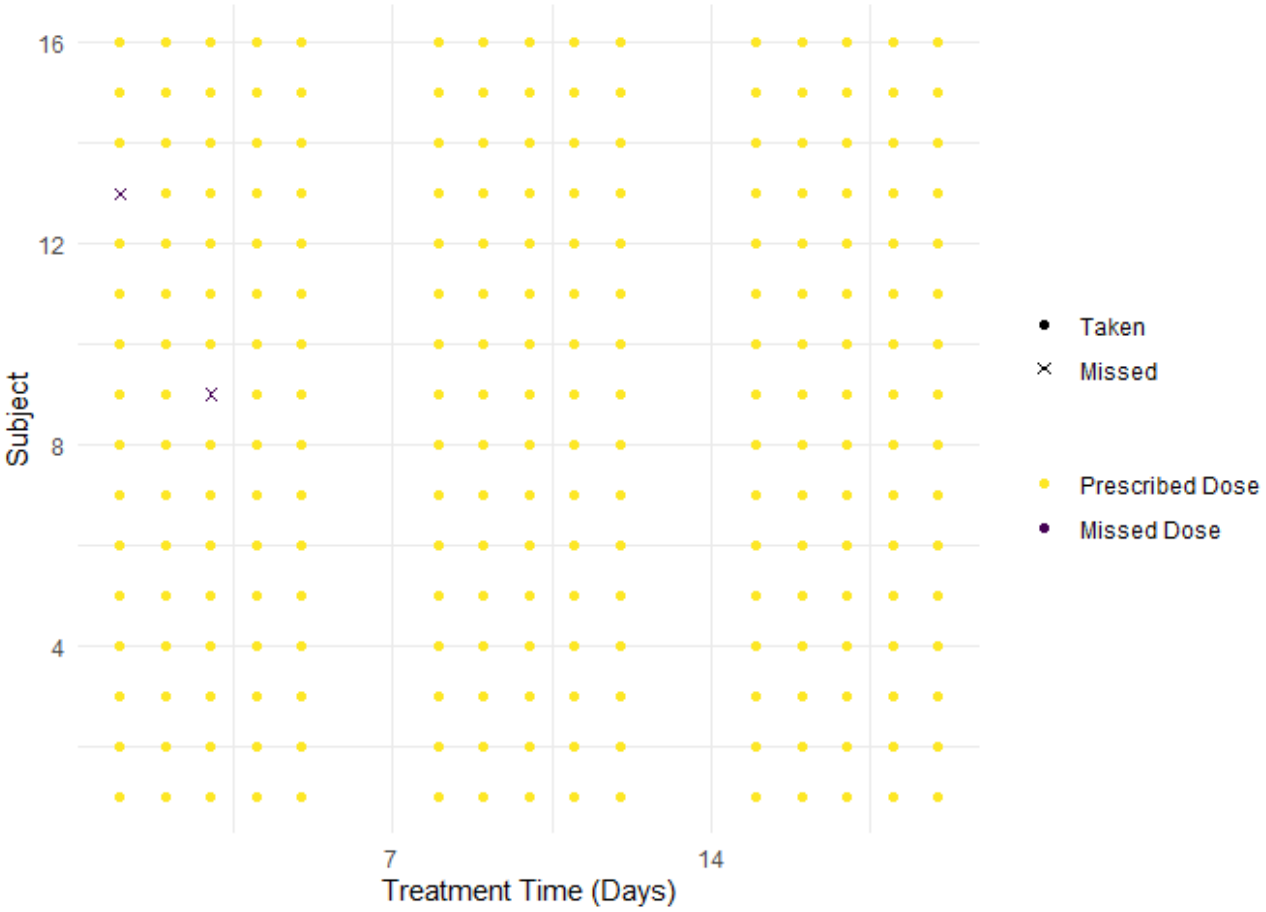

Figure 2: Radiotherapy doses received

4.4.1.2 M6620 Compliance

The first dose of M6620 given in Stage A1 was on 28 May 2019, the final dose was given on 28 Jan 2022. The mean duration of treatment was 15.3 days with a standard deviation of 1.5. The average infusion time was 422 minutes (7 hours) with standard deviation 115.

Table 5 gives details of patients who stopped M6620 treatment early and the reason. M6620 compliance is presented in Table 6. A full line-listing of M6620 compliance is given in Table 7. Figure 3 presents all A1 compliance. CH-A1-114 stopped M6620 treatment due to unacceptable toxicity however this was not considered a DLT, they missed their final of M6620 dose (stopped treatment early) due to ongoing Grade 3 constipation that was considered an SAE. Details of this event and all reasons for missed M6620 doses are given in *Appendix - Compliance*. All doses of M6620 given, including dose reductions, are presented in Figure 4.

Table 5: M6620 treatment stoppages

Subject	Schedule	Early Stop	Early Stop Reason	% Received
CH-A1-105	Schedule 3	Yes	AEs or SAEs	83.3

Subject	Schedule	Early Stop	Early Stop Reason	% Received
CH-A1-114	Schedule 6	Yes	AEs or SAEs requiring discontinuation	83.3

Table 6: M6620 compliance

	Schedule 1 (n=3)	Schedule 2 (n=1)	Schedule 3 (n=1)	Schedule 4 (n=1)	Schedule 5 (n=1)	Schedule 6 (n=9)	Total (n=16)
M6620 % Recevied							
100%	2 (66.7)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	5 (55.6)	9 (56.2)
>=90%, <100%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>=75%, <90%	1 (33.3)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	3 (33.3)	6 (37.5)
<75%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (6.2)

Table 7: M6620 compliance listing

Subject	Schedule	M6620 Received	M6620 Expected	% Received
CH-A1-101	Schedule 1	420	420	100.0
CH-A1-102	Schedule 1	370	420	88.1
CH-A1-103	Schedule 1	420	420	100.0
CH-A1-104	Schedule 2	700	700	100.0
CH-A1-105	Schedule 3	700	840	83.3
CH-A1-106	Schedule 4	720	720	100.0
CH-A1-107	Schedule 5	960	1,200	80.0
CH-A1-108	Schedule 6	1,440	1,440	100.0
CH-A1-109	Schedule 6	1,440	1,440	100.0
CH-A1-110	Schedule 6	1,200	1,440	83.3
CH-A1-111	Schedule 6	1,200	1,440	83.3
CH-A1-112	Schedule 6	1,440	1,440	100.0
CH-A1-113	Schedule 6	960	1,440	66.7
CH-A1-114	Schedule 6	1,200	1,440	83.3
CH-A1-115	Schedule 6	1,440	1,440	100.0

Subject	Schedule	M6620 Received	M6620 Expected	% Received
CH-A1-116	Schedule 6	1,440	1,440	100.0

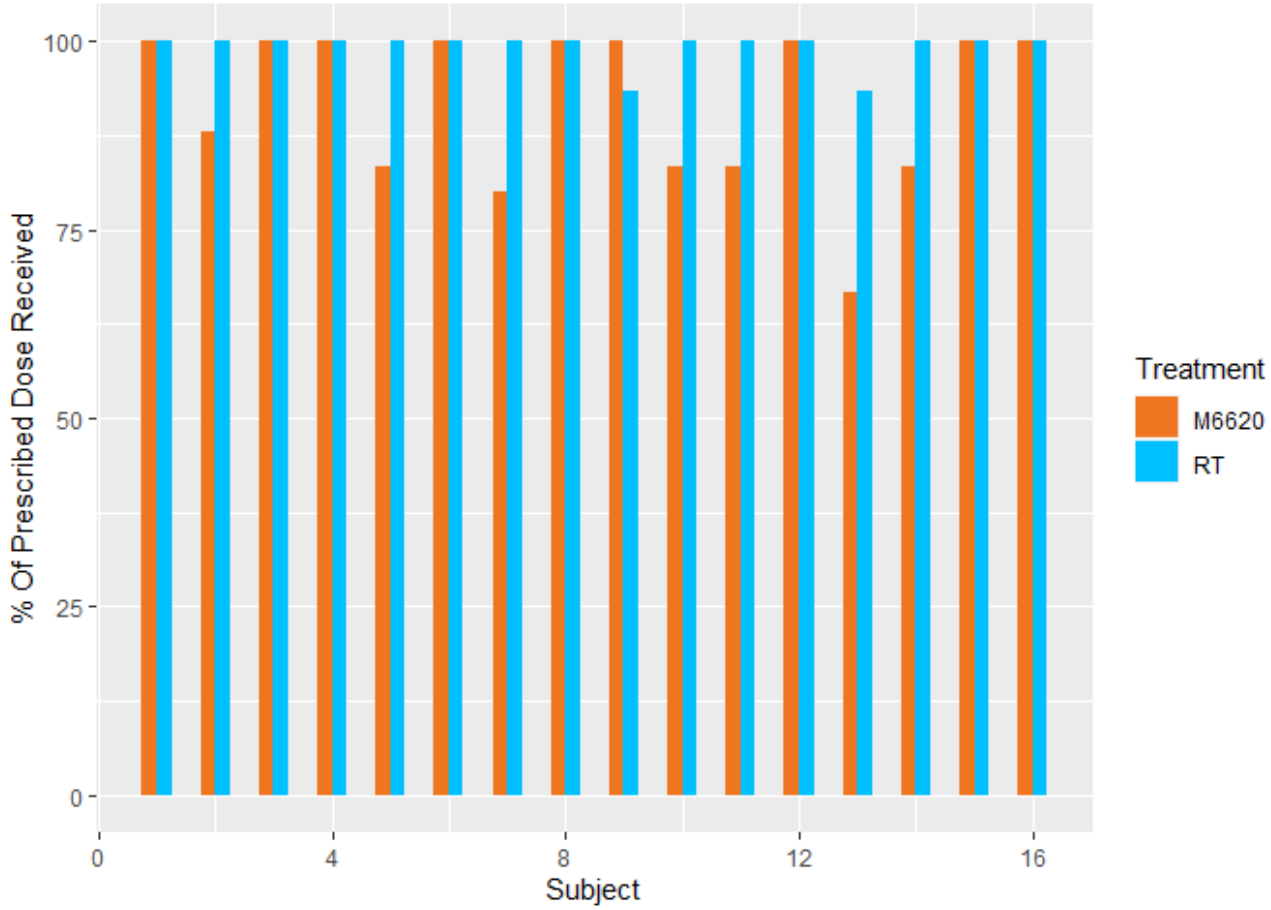

Figure 3: Percentage radiotherapy and M6620 received for each trial participant

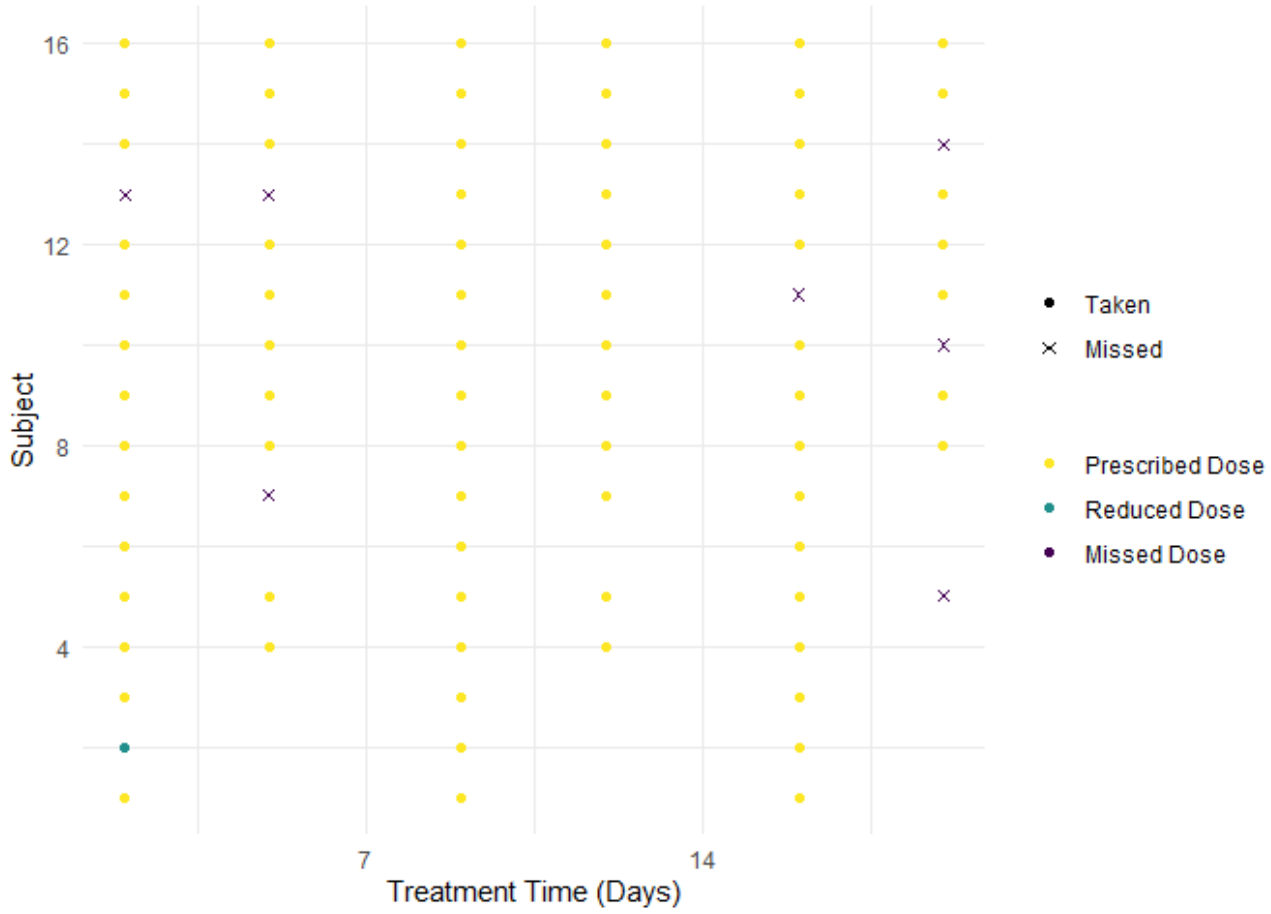

Figure 4: M6620 doses received

4.4.2 Withdrawals & Protocol Deviations

There were no withdrawals from the trial stage.

Of the 57 deviations reported in Stage A1, 3 of these were important, these are given in Table 8. The full list of deviations is reported in *Appendix - Deviations*.

Table 8: Important protocol deviations

Subject	Site	Date	Description	Action Taken
CH-A1-102	Churchill, Oxford		Participant was incorrectly prescribed 90mg/m2 instead of the correctly allocated 140mg/m2 for week 1 of M6620 treatment.	Site: Amend presecription to correct dose for subsequent treatments. Review previous participants treatments to ensure correct. Protocol deviation form to be completed with CAPA. OCTO to review treatment allocation communication with site. Stats & CI informed. 20Aug2019 update: Extra pharmacist allocated to trial. All other participants correctly prescribed. CI

Subject	Site	Date	Description	Action Taken
				confirmation all staff suitably trained. Dr & pharmacist to meet to review C1D1 prescription for each participant. OCTO TSI updated so dose specified on registration & clinical trials screening included as recipient. Deviation description sent to CI for review. CI's response: "As the delay was due to a technical reasons (need for vascular access- portacath insertion), and not due to a medical issue - and subject tolerated treatment, the overall impact to wellbeing/safety is minimal and the impact to trial integrity is minimal also. The accuracy of the data collected from the patient can be use to inform trial endpoints."
CH-A1-111	Christie, Manchester		Screening assessments completed >21 days prior to first dose. This was due to delay to treatment because the patient required a portacath to be inserted.	Site notified and requested to complete deviation reporting form and CAPA. Received 21Jul2021. CAPA: Site has addressed the issue by managing the timelines for clinic consent and planning scans in advance, so this can be conducted closer to C1D1 date and within 21 day window.
CH-A1-114	Christie, Manchester		The TMG met to make a dose decision for this patient on 06Sep2021. However, the trial team consulted the wrong section of the charter in error. There are two different quoracy rules, depending on whether a dose decision is being made or not.	The CI was notified as soon as the error was spotted and the TMG emailed with the dose decision report to request review from another clinician not present at the meeting. One of the clinician members reviewed the report and sent written agreement with the

Subject	Site	Date	Description	Action Taken
			This meant that there were one too few medics available for the dose decision. This mistake was not spotted until after the meeting, but before the patient had started on treatment.	TMG's dose decision. All correspondence was saved in the TMG dose decision meeting folder, along with a file note explaining the deviation and resolution. A protocol deviation form was also filled in and filed in the patient folder, with a CAPA. CAPA details: a checklist was added to the dose decision meeting agenda template to ensure that the necessary members are present in order to make a dose decision in future.

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 radiotherapy in patients with oesophageal 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. $w \in [0,1]$. The pre-defined target toxicity level was 0.25.

Table 9 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 $\frac{t}{T} = 1$ for all patients.

Table 9: Derivation of the patient's TiTE-CRM model weight

Subject	Site	Schedule	M6620 Received	Total M6620	DLT	Weight
CH-A1-101	Churchill, Oxford	Schedule 1	420	420	No DLT	1.000
CH-A1-102	Churchill, Oxford	Schedule 1	370	420	No DLT	0.940
CH-A1-103	Christie, Manchester	Schedule 1	420	420	No DLT	1.000

Subject	Site	Schedule	M6620 Received	Total M6620	DLT	Weight
CH-A1-104	Churchill, Oxford	Schedule 2	700	700	No DLT	1.000
CH-A1-105	Churchill, Oxford	Schedule 3	700	840	No DLT	0.917
CH-A1-106	Beatson, Glasgow	Schedule 4	720	720	No DLT	1.000
CH-A1-107	Velindre, Cardiff	Schedule 5	960	1,200	No DLT	0.900
CH-A1-108	Velindre, Cardiff	Schedule 6	1,440	1,440	No DLT	1.000
CH-A1-109	Velindre, Cardiff	Schedule 6	1,440	1,440	No DLT	1.000
CH-A1-110	Velindre, Cardiff	Schedule 6	1,200	1,440	No DLT	0.917
CH-A1-111	Christie, Manchester	Schedule 6	1,200	1,440	No DLT	0.917
CH-A1-112	Velindre, Cardiff	Schedule 6	1,440	1,440	No DLT	1.000
CH-A1-113	Churchill, Oxford	Schedule 6	960	1,440	No DLT	0.833
CH-A1-114	Christie, Manchester	Schedule 6	1,200	1,440	No DLT	0.917
CH-A1-115	Beatson, Glasgow	Schedule 6	1,440	1,440	No DLT	1.000
CH-A1-116	Velindre, Cardiff	Schedule 6	1,440	1,440	No DLT	1.000

Note CH-A1-102 had less treatment due to being prescribed the incorrect dose for their first infusion. They did not miss a dose.

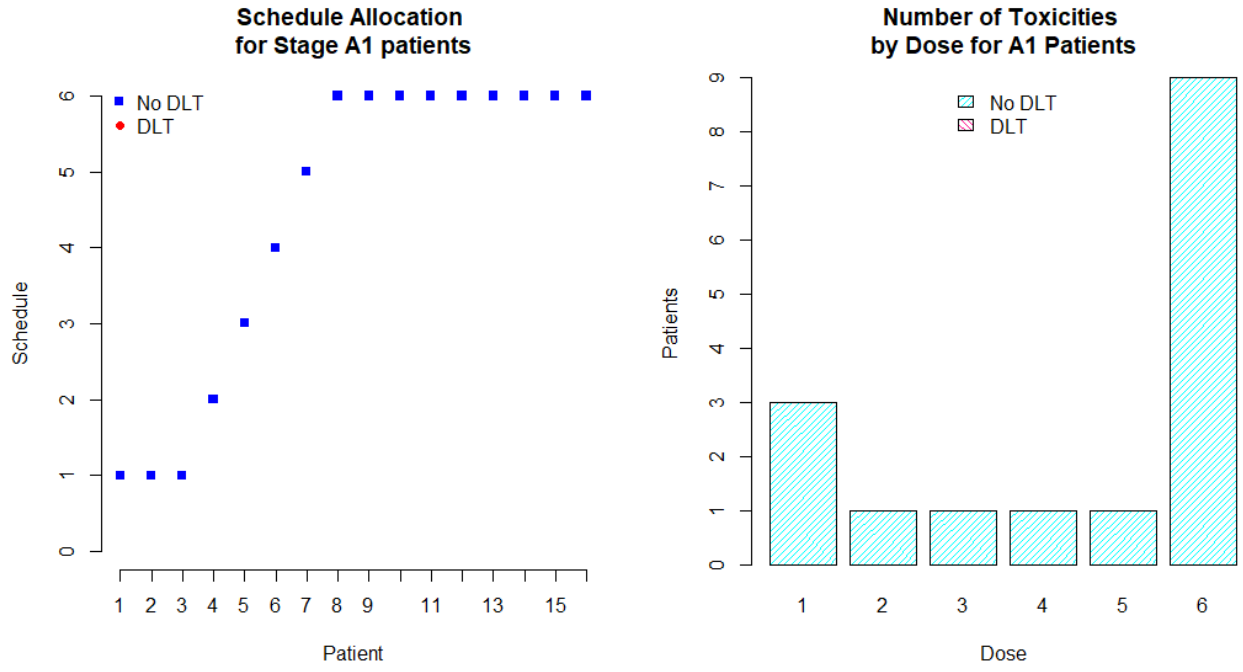

Figure 5: Summaries of Patients' DLT Status and Treatment Schedule in A1

Table 10 presents the posterior probabilities for each schedule along with the corresponding 95% credible intervals and numbers included in the model for each schedule. Figure 6 presents the posteriors graphically. The prior dose toxicity curve is also included as a reference.

Table 10: 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	3	0.008	0	0.064
2	1	0.012	0	0.085
3	1	0.016	0	0.108
4	1	0.019	0	0.124
5	1	0.023	0	0.140
6	9	0.029	0	0.165

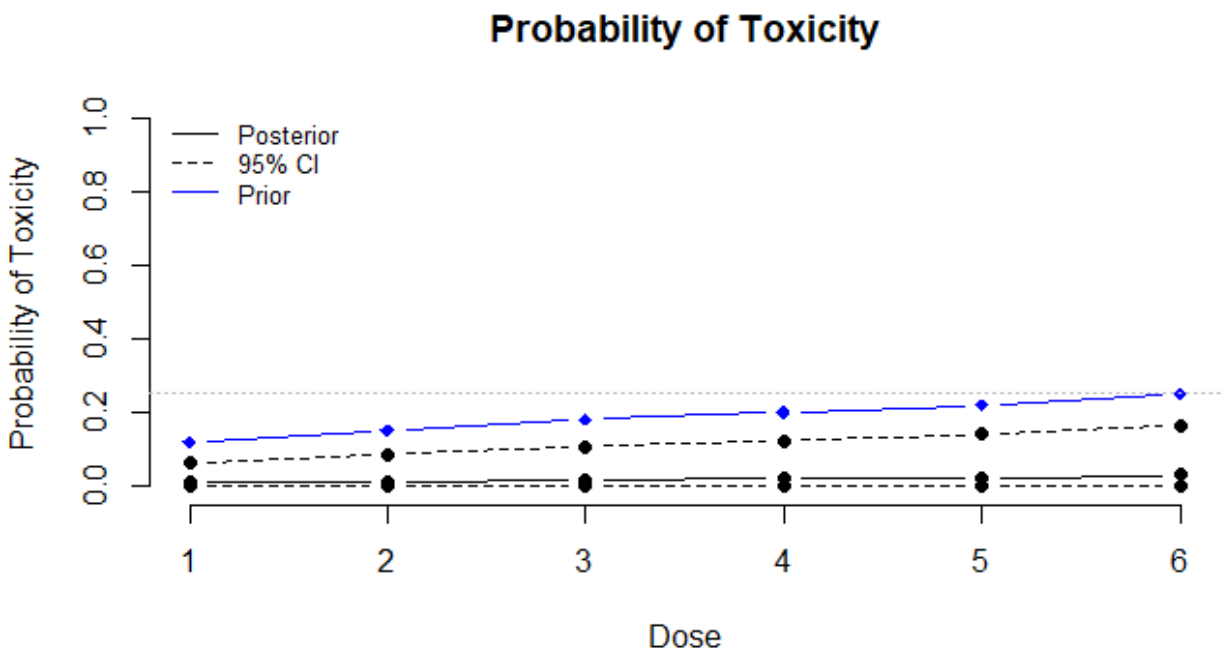

Figure 6: Posterior estimate of the dose toxicity curve, 95% credible interval and prior

The TiTE-CRM model, given the accumulated data, suggests **Schedule 6** is the maximum tolerated dose of M6620 in combination with Radiotherapy of the doses examined in CHARIOT Stage A1. The posterior probability the DLT rate is >25% in dose level 6 (the Maximum Tolerated Dose) is 0.005.

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 11, Table 12 and Table 13 for sensitivity 1, 2 and 3 respectively.

Table 11: Posterior Summaries for the first sensitivity population, i.e. must have receieved 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	2	0.018	0	0.139
2	1	0.024	0	0.171
3	0	0.031	0	0.203
4	1	0.036	0	0.224
5	0	0.041	0	0.244
6	5	0.050	0	0.275

Table 12: Posterior Summaries for the second sensitivity population, i.e. must have receieved 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	0.009	0	0.074
2	1	0.013	0	0.098
3	1	0.018	0	0.122
4	1	0.021	0	0.139
5	1	0.025	0	0.156
6	8	0.031	0	0.183

Table 13: Posterior Summaries for the third sensitivity population, i.e. must have receieved 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	0.008	0	0.066
2	1	0.012	0	0.087
3	1	0.016	0	0.110
4	1	0.019	0	0.126
5	1	0.023	0	0.143
6	8	0.029	0	0.168

All pre-specified supporting analysis results support the main conclusion that the MTD is Schedule 6.

4.5.3 Secondary Analysis

4.5.3.1 Toxicity

There were 0 Dose Limiting Toxicities (DLTs) in this safety study.

There were 3 Serious Adverse Events (SAEs). These are given in full detail in Table 14. There were 9 (56.2%) deaths observed in Stage A1, full details of these deaths are given in Table 15, all documented causes of death were disease related.

Table 14: Serious Adverse Events

Subject	Description	Treatment Week	Grade	m6620 Causality	RT Causality	Outcome	Time to Resolve (Days)
CH-A1-110	Maculopapular Rash	Week 3	3	Possibly Related	Possibly Related	Improved	8
CH-A1-114	Rig accidentally fallen out	Week 5-9	3	Definitely Not Related	Definitely Not Related	Resolved	2
CH-A1-114	Constipation	Week 1	3	Probably Not Related	Probably Not Related	Resolved	27

Table 15: Deaths

Subject	Cause of Death	Survival Time (Days)
CH-A1-101	Disease related	168

Subject	Cause of Death	Survival Time (Days)
CH-A1-104	Disease related	394
CH-A1-106	Disease related	561
CH-A1-107	Disease related	263
CH-A1-108	Cause of Death Not Documented	403
CH-A1-110	Disease related	363
CH-A1-112	Disease related	315
CH-A1-113	Disease related	93
CH-A1-116	Disease related	105

A full list of Adverse Events and worst Adverse Events for each patient are presented in *Appendix - Toxicity*. Table 16 summarises the number of AEs each patient who has started treatment has had. It shows the number of AEs that occurred during the first 9 weeks of treatment split by grade, the number of AEs that occurred after week 9 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 10. The median time taken for AEs to resolve based on complete data was 7 days (IQR 2.75, 21.25). Table 17, Table 18, and Figure 7 give information on the worst Adverse Events experienced for each patient. Table 19 gives all Adverse Events classified by MedDRA Organ Class, split by grade; the most commonly effected organ class was Gastrointestinal Disorders with 27.7% of all AEs being from this class. Table 20 gives all AEs by their MedDRA coded event, split by grade; the most common AE was Dysphagia (8.9% of all AEs). Figure 8 and Figure 9 graphically present AEs by Organ Class and MedDRA coding respectively. Figure 11 shows the percentage of patients each adverse event occurred in.

Table 16: Summary of Adverse Events by patient

Subject	Schedule	In Screening	Grade 1 or 2	Grade 3 or 4	After week 9	Total AEs
CH-A1-101	1	2	0	0	0	2
CH-A1-102	1	0	4	0	0	4
CH-A1-103	1	0	3	0	2	5
CH-A1-104	2	0	3	0	0	3
CH-A1-105	3	0	5	1	0	6
CH-A1-106	4	0	3	0	0	3
CH-A1-107	5	0	4	0	0	4
CH-A1-108	6	0	6	1	0	7
CH-A1-109	6	0	7	2	1	10
CH-A1-110	6	1	10	3	0	14

Subject	Schedule	In Screening	Grade 1 or 2	Grade 3 or 4	After week 9	Total AEs
CH-A1-111	6	0	4	2	0	6
CH-A1-112	6	0	10	0	0	10
CH-A1-113	6	0	3	0	0	3
CH-A1-114	6	0	5	5	0	10
CH-A1-115	6	0	6	0	0	6
CH-A1-116	6	0	6	1	1	8

Table 17: Worst grade Adverse Event grade for each patient by dose schedule

	Schedule 1 (n=3)	Schedule 2 (n=1)	Schedule 3 (n=1)	Schedule 4 (n=1)	Schedule 5 (n=1)	Schedule 6 (n=9)	Total (n=16)
Highest CTCAE Grade							
One	1 (33.3)	1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)	2 (22.2)	6 (37.5)
Two	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (18.8)
Three	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	6 (66.7)	7 (43.8)
Four	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 17: Worst grade Adverse Event grade for each patient by dose schedule

	One (n=28)	Two (n=7)	Three (n=16)	Four (n=0)	Total (n=51)
Adverse Event					
Abdominal pain upper	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Arthralgia	2 (7.1)	0 (0.0)	1 (6.2)	0 (NaN)	3 (5.9)
Blood sodium decreased	0 (0.0)	0 (0.0)	1 (6.2)	0 (NaN)	1 (2.0)
Blood urea increased	0 (0.0)	0 (0.0)	1 (6.2)	0 (NaN)	1 (2.0)
Chest pain	0 (0.0)	1 (14.3)	0 (0.0)	0 (NaN)	1 (2.0)
Chills	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Constipation	0 (0.0)	1 (14.3)	1 (6.2)	0 (NaN)	2 (3.9)
Cough	2 (7.1)	0 (0.0)	0 (0.0)	0 (NaN)	2 (3.9)
Decreased appetite	2 (7.1)	0 (0.0)	0 (0.0)	0 (NaN)	2 (3.9)
Diarrhoea	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Dry skin	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)

	One (n=28)	Two (n=7)	Three (n=16)	Four (n=0)	Total (n=51)
Dysphagia	2 (7.1)	0 (0.0)	0 (0.0)	0 (NaN)	2 (3.9)
Dysphonia	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Dyspnoea	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Erythema	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Eye pain	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Fatigue	0 (0.0)	1 (14.3)	2 (12.5)	0 (NaN)	3 (5.9)
Gastrostomy tube site complication	0 (0.0)	0 (0.0)	1 (6.2)	0 (NaN)	1 (2.0)
Hypertension	0 (0.0)	1 (14.3)	0 (0.0)	0 (NaN)	1 (2.0)
Hyponatraemia	0 (0.0)	0 (0.0)	1 (6.2)	0 (NaN)	1 (2.0)
Lacrimation increased	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Lymphocyte count	0 (0.0)	0 (0.0)	1 (6.2)	0 (NaN)	1 (2.0)
Lymphopenia	0 (0.0)	0 (0.0)	2 (12.5)	0 (NaN)	2 (3.9)
Nausea	1 (3.6)	1 (14.3)	0 (0.0)	0 (NaN)	2 (3.9)
Neuropathy peripheral	2 (7.1)	0 (0.0)	0 (0.0)	0 (NaN)	2 (3.9)
Oesophagitis	1 (3.6)	0 (0.0)	1 (6.2)	0 (NaN)	2 (3.9)
Oropharyngeal pain	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Pain	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Pyrexia	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Rash	1 (3.6)	0 (0.0)	1 (6.2)	0 (NaN)	2 (3.9)
Rash generalised	0 (0.0)	0 (0.0)	1 (6.2)	0 (NaN)	1 (2.0)
Rash maculo-papular	0 (0.0)	0 (0.0)	2 (12.5)	0 (NaN)	2 (3.9)
Squamous cell carcinoma of skin	0 (0.0)	1 (14.3)	0 (0.0)	0 (NaN)	1 (2.0)
Transaminases increased	1 (3.6)	0 (0.0)	0 (0.0)	0 (NaN)	1 (2.0)
Urinary tract infection	0 (0.0)	1 (14.3)	0 (0.0)	0 (NaN)	1 (2.0)
Vomiting	2 (7.1)	0 (0.0)	0 (0.0)	0 (NaN)	2 (3.9)

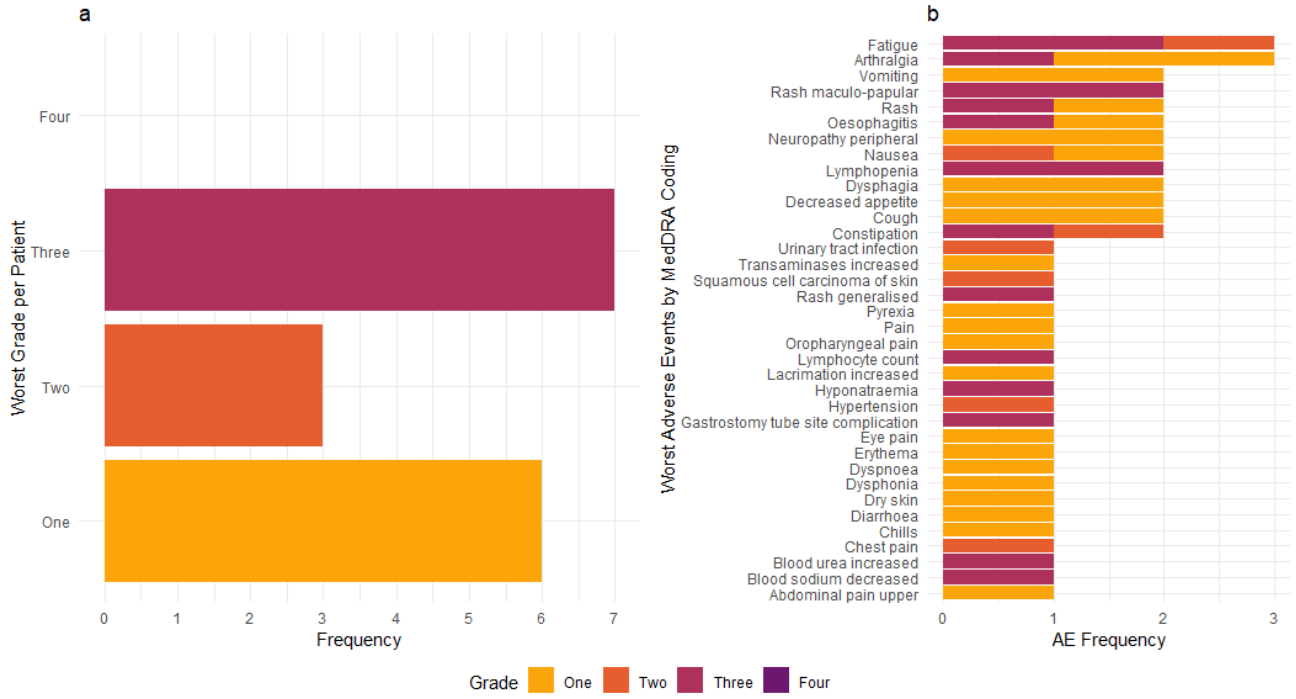

Figure 7: (a) Worst grade Adverse Event grade for each patient (b) Worst Adverse Events for each patient by MedDRA Coding

Table 19: Adverse Events by MedDRA organ class & grade

	One (n=66)	Two (n=19)	Three (n=16)	Four (n=0)	Total (n=101)
Organ Class					
Blood & Lymphatic System Disorders	1 (1.5)	2 (10.5)	2 (12.5)	0 (NaN)	5 (5.0)
Eye disorders	2 (3.0)	0 (0.0)	0 (0.0)	0 (NaN)	2 (2.0)
Gastrointestinal Disorders	20 (30.3)	6 (31.6)	2 (12.5)	0 (NaN)	28 (27.7)
General Disorders & Administration Site Conditions	6 (9.1)	2 (10.5)	2 (12.5)	0 (NaN)	10 (9.9)
Infections & Infestations	1 (1.5)	2 (10.5)	0 (0.0)	0 (NaN)	3 (3.0)
Injury; poisoning and procedural complications	0 (0.0)	1 (5.3)	1 (6.2)	0 (NaN)	2 (2.0)
Investigations	4 (6.1)	0 (0.0)	3 (18.8)	0 (NaN)	7 (6.9)
Metabolism & Nutrition Disorders	4 (6.1)	1 (5.3)	1 (6.2)	0 (NaN)	6 (5.9)
Musculoskeletal & Connective Tissue Disorders	3 (4.5)	0 (0.0)	1 (6.2)	0 (NaN)	4 (4.0)
Neoplasms benign; malignant and unspecified	0 (0.0)	1 (5.3)	0 (0.0)	0 (NaN)	1 (1.0)
Nervous System Disorders	5 (7.6)	1 (5.3)	0 (0.0)	0 (NaN)	6 (5.9)

	One (n=66)	Two (n=19)	Three (n=16)	Four (n=0)	Total (n=101)
Psychiatric disorders	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Respiratory, thoracic and mediastinal disorders	11 (16.7)	0 (0.0)	0 (0.0)	0 (NaN)	11 (10.9)
Skin and subcutaneous tissue disorders	8 (12.1)	2 (10.5)	4 (25.0)	0 (NaN)	14 (13.9)
Vascular disorders	0 (0.0)	1 (5.3)	0 (0.0)	0 (NaN)	1 (1.0)

Table 20: Adverse Events by MedDRA coding & grade

	One (n=66)	Two (n=19)	Three (n=16)	Four (n=0)	Total (n=101)
MedDRA Coding					
Abdominal pain upper	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Anaemia	1 (1.5)	1 (5.3)	0 (0.0)	0 (NaN)	2 (2.0)
Arthralgia	2 (3.0)	0 (0.0)	1 (6.2)	0 (NaN)	3 (3.0)
Arthralgia	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Blood creatinine increased	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Blood sodium decreased	0 (0.0)	0 (0.0)	1 (6.2)	0 (NaN)	1 (1.0)
Blood urea increased	1 (1.5)	0 (0.0)	1 (6.2)	0 (NaN)	2 (2.0)
Campylobacter infection	0 (0.0)	1 (5.3)	0 (0.0)	0 (NaN)	1 (1.0)
Chest pain	0 (0.0)	1 (5.3)	0 (0.0)	0 (NaN)	1 (1.0)
Chills	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Constipation	2 (3.0)	1 (5.3)	1 (6.2)	0 (NaN)	4 (4.0)
Cough	4 (6.1)	0 (0.0)	0 (0.0)	0 (NaN)	4 (4.0)
Decreased appetite	3 (4.5)	0 (0.0)	0 (0.0)	0 (NaN)	3 (3.0)
Dehydration	0 (0.0)	1 (5.3)	0 (0.0)	0 (NaN)	1 (1.0)
Dermatitis	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Diarrhoea	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Dry skin	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Dry throat	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Dyspepsia	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Dysphagia	6 (9.1)	3 (15.8)	0 (0.0)	0 (NaN)	9 (8.9)

	One (n=66)	Two (n=19)	Three (n=16)	Four (n=0)	Total (n=101)
Dysphonia	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Dyspnoea	2 (3.0)	0 (0.0)	0 (0.0)	0 (NaN)	2 (2.0)
Erythema	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Eye pain	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Fatigue	3 (4.5)	1 (5.3)	2 (12.5)	0 (NaN)	6 (5.9)
Gastrostomy tube site complication	0 (0.0)	0 (0.0)	1 (6.2)	0 (NaN)	1 (1.0)
Headache	3 (4.5)	0 (0.0)	0 (0.0)	0 (NaN)	3 (3.0)
Hypertension	0 (0.0)	1 (5.3)	0 (0.0)	0 (NaN)	1 (1.0)
Hypomagnesaemia	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Hyponatraemia	0 (0.0)	0 (0.0)	1 (6.2)	0 (NaN)	1 (1.0)
Insomnia	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Lacrimation increased	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Lymphocyte count	0 (0.0)	0 (0.0)	1 (6.2)	0 (NaN)	1 (1.0)
Lymphopenia	0 (0.0)	1 (5.3)	2 (12.5)	0 (NaN)	3 (3.0)
Nausea	4 (6.1)	1 (5.3)	0 (0.0)	0 (NaN)	5 (5.0)
Neuropathy peripheral	2 (3.0)	0 (0.0)	0 (0.0)	0 (NaN)	2 (2.0)
Oesophagitis	2 (3.0)	1 (5.3)	1 (6.2)	0 (NaN)	4 (4.0)
Oropharyngeal pain	3 (4.5)	0 (0.0)	0 (0.0)	0 (NaN)	3 (3.0)
Pain	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Pyrexia	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Rash	3 (4.5)	1 (5.3)	1 (6.2)	0 (NaN)	5 (5.0)
Rash generalised	1 (1.5)	1 (5.3)	1 (6.2)	0 (NaN)	3 (3.0)
Rash maculo-papular	1 (1.5)	0 (0.0)	2 (12.5)	0 (NaN)	3 (3.0)
Rhinitis	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)
Sciatica	0 (0.0)	1 (5.3)	0 (0.0)	0 (NaN)	1 (1.0)
Spinal fracture	0 (0.0)	1 (5.3)	0 (0.0)	0 (NaN)	1 (1.0)
Squamous cell carcinoma of skin	0 (0.0)	1 (5.3)	0 (0.0)	0 (NaN)	1 (1.0)
Transaminases increased	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)

	One (n=66)	Two (n=19)	Three (n=16)	Four (n=0)	Total (n=101)
Urinary tract infection	0 (0.0)	1 (5.3)	0 (0.0)	0 (NaN)	1 (1.0)
Vomiting	3 (4.5)	0 (0.0)	0 (0.0)	0 (NaN)	3 (3.0)
Weight decreased	1 (1.5)	0 (0.0)	0 (0.0)	0 (NaN)	1 (1.0)

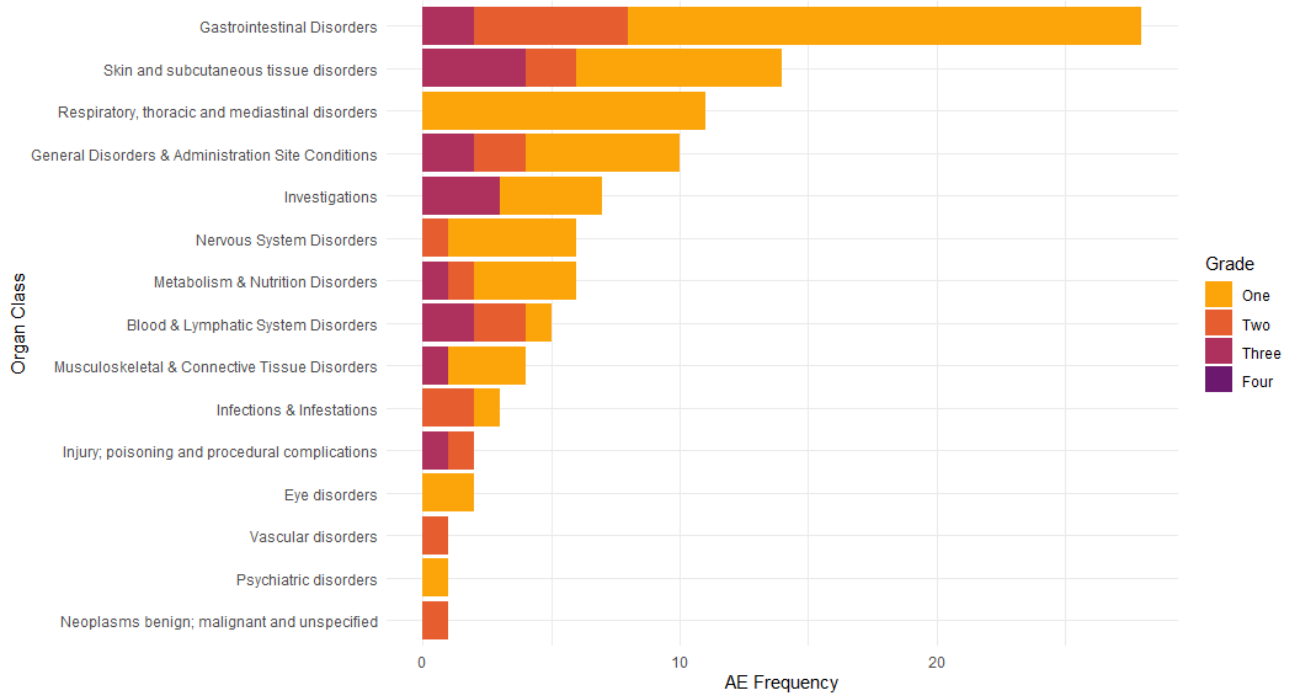

Figure 8: Adverse Events by organ class and grade

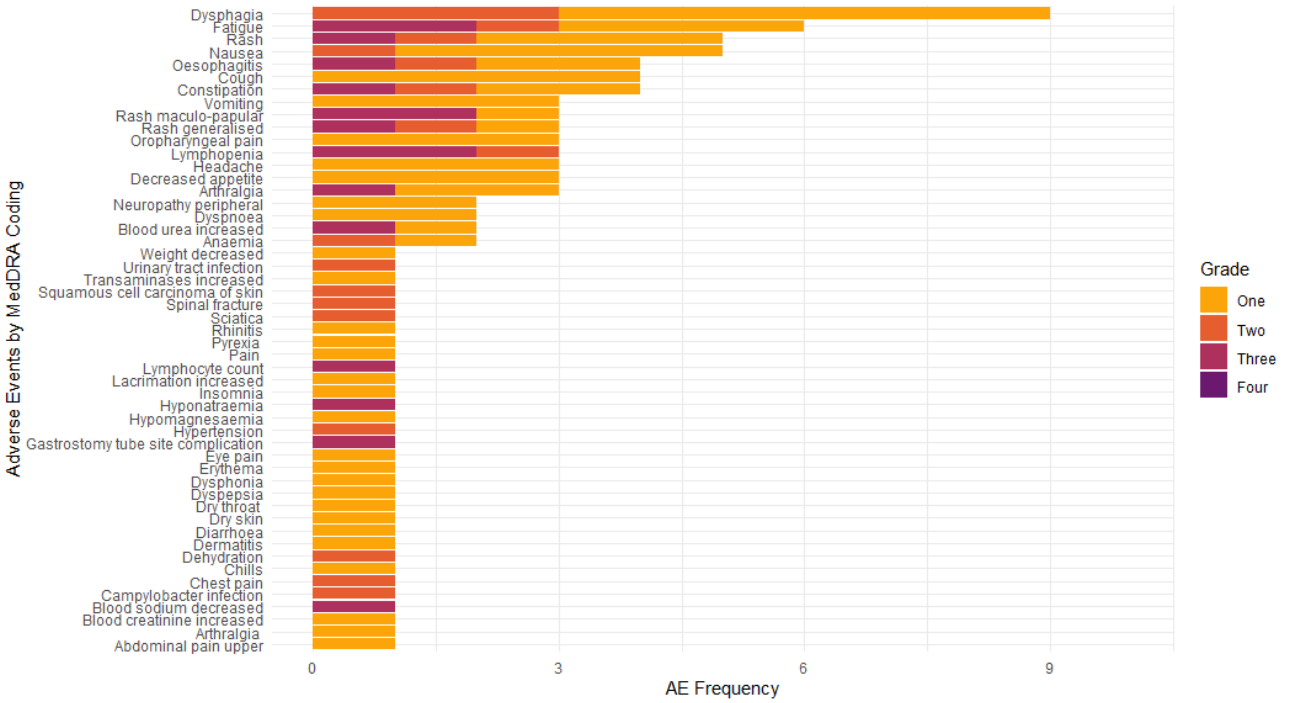

Figure 9: Adverse Events by MedDRA coding and grade

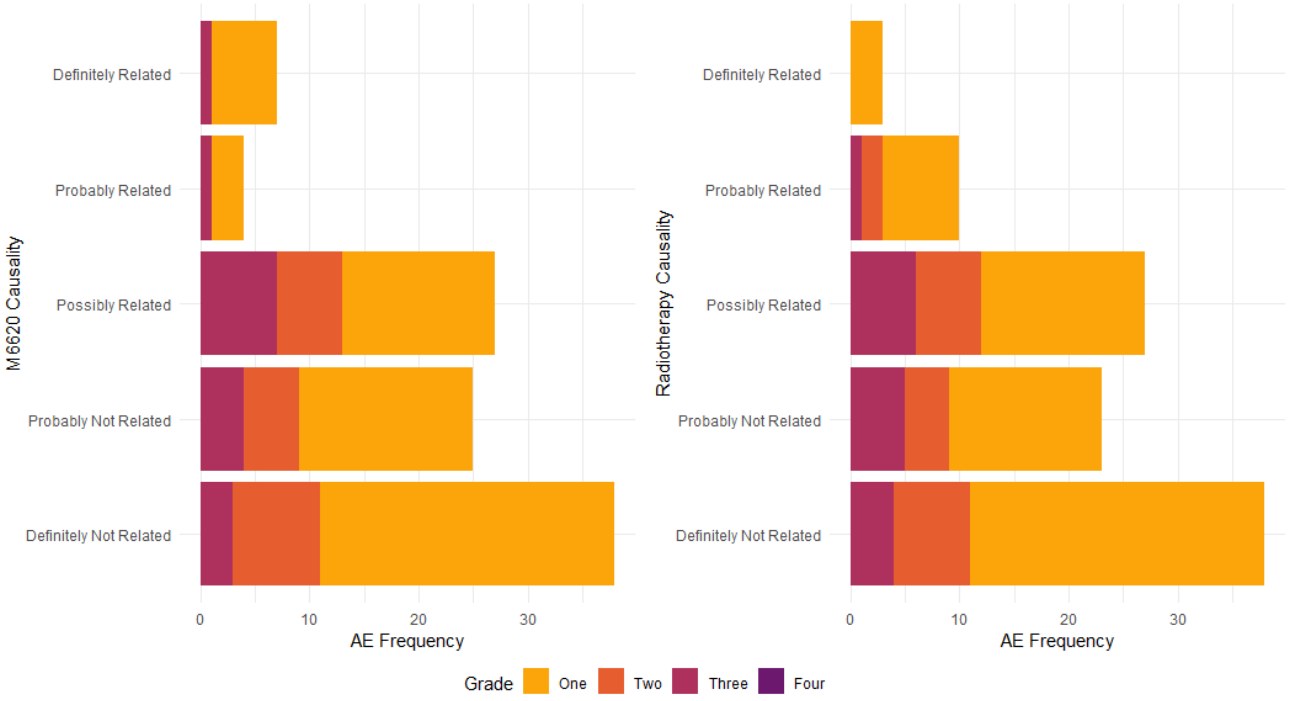

Figure 10: Adverse Events by grade and M6620 and radiotherapy causality

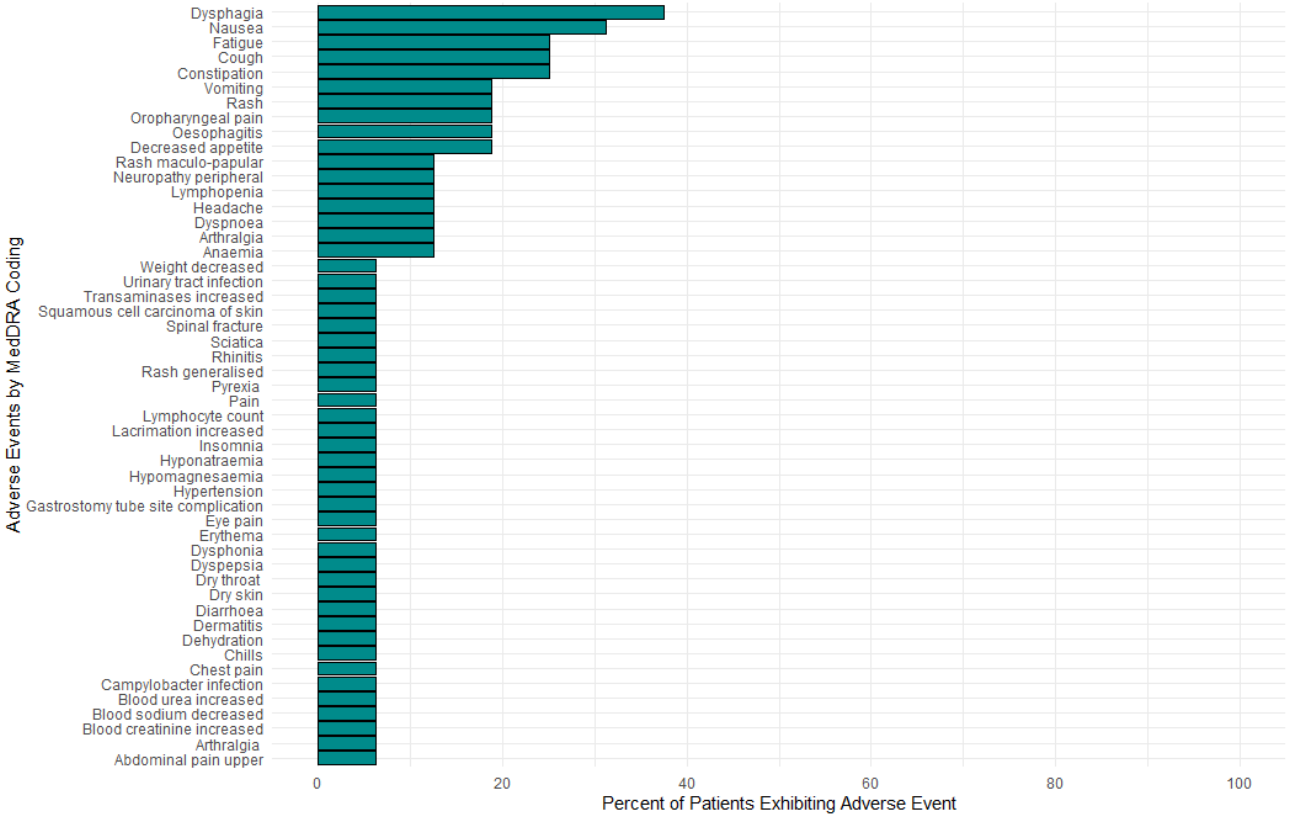

Figure 11: Percentage of patients exhibiting each adverse event

4.5.3.2 Treatment Combination Compliance

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

4.5.3.3 Efficacy of the Combination

Efficacy is measured in three ways for Stage A1:

- 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)
- In-field radiotherapy control.

OR measured by RECIST V1.1 at 12 weeks is presented in Table 21 by assigned dose and overall, and graphically in Figure 12. 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. Four patients had missing data for their 12 week Overall RECIST, three of these patients (CH-A1-101, CH-A1-108, CH-A1-115) had a scan 8 weeks post end of treatment, one had overall progressive disease (CH-A1-101), one had overall partial response (CH-A1-108), and the final one (CH-A1-115) had complete response. There is no scan data on the final patient (CH-A1-116) with missing 12 week overall RECIST data as they did not have a trial scan due to CHARIOT being completed. Figure 13 presents best overall response, by overall RECIST from any scan.

Table 21: Objective tumour response by RECIST V1.1 at 12 weeks

	Schedule 1 (n=3)	Schedule 2 (n=1)	Schedule 3 (n=1)	Schedule 4 (n=1)	Schedule 5 (n=1)	Schedule 6 (n=9)	Total (n=16)
Overall RECIST at 12 Weeks							
Complete Response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial Response	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (12.5)
Stable Disease	1 (33.3)	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)	2 (22.2)	6 (37.5)
Progressive Disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	2 (22.2)	3 (18.8)
Not Evaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (6.2)
Missing Data	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	4 (25.0)

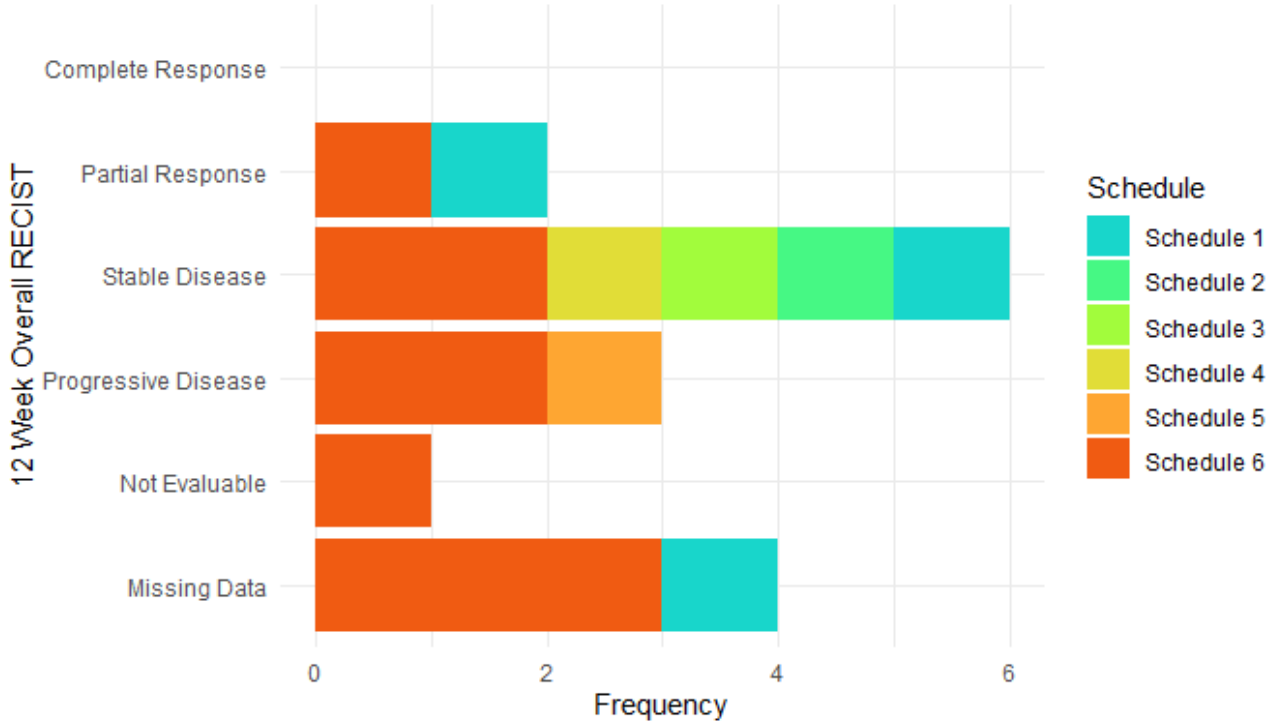

Figure 12: Objective tumour response by RECIST V1.1 at 12 weeks

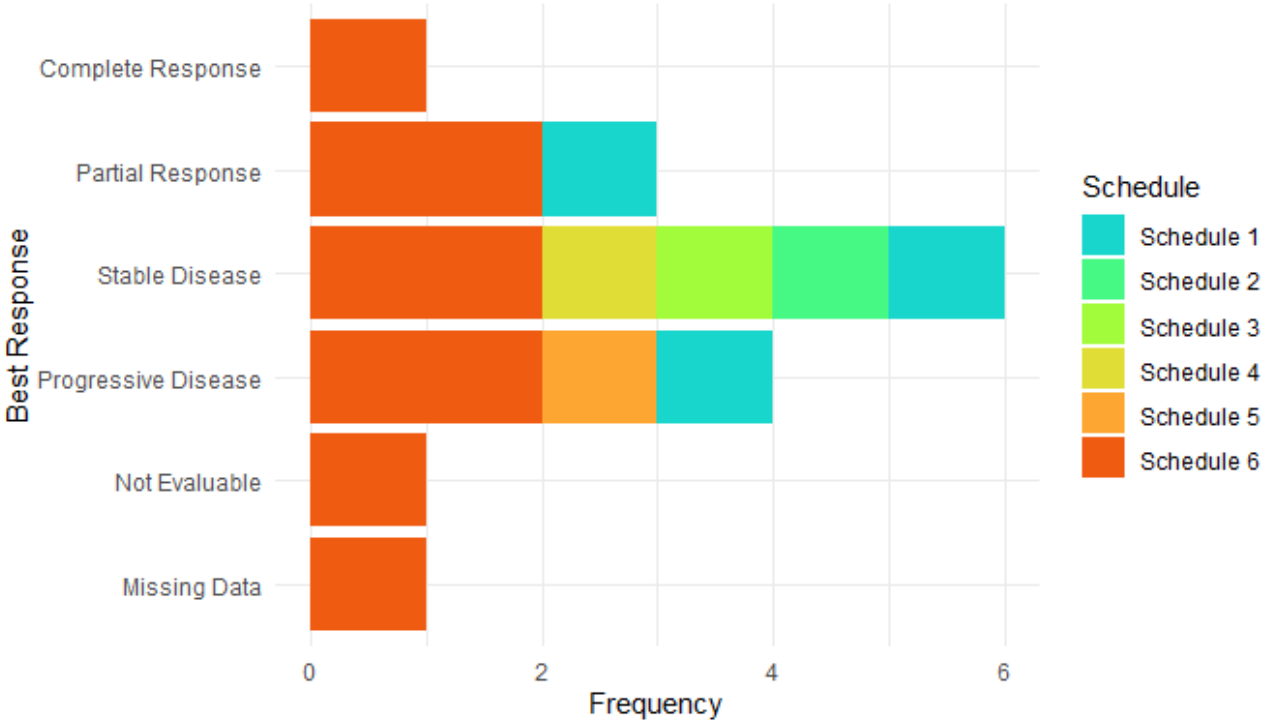

Figure 13: Best response by RECIST

A patient is considered to have progressed if they either had progression or died. Progression free survival is presented in a Kaplan Meier plot with 95% confidence intervals in Figure 14 and all data presented graphically in Figure 15. Median progression free survival was 226 days with corresponding 95% confidence interval of (175, 342). A line listing of progression free survival times and if the observation was censored or not is presented *Appendix - Survival* to this report.

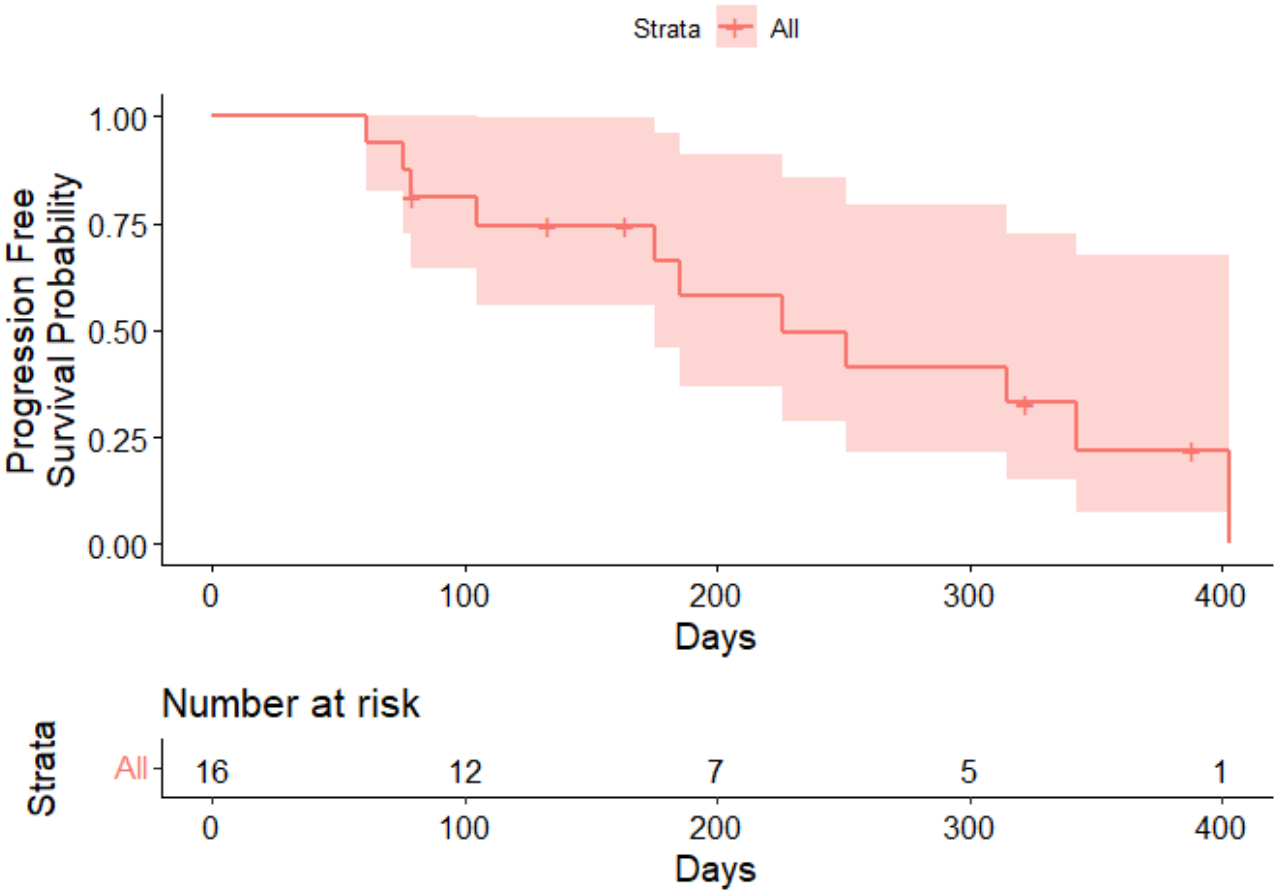

Figure 14: Kaplan Meier plot of progression free survival, censored patients marked

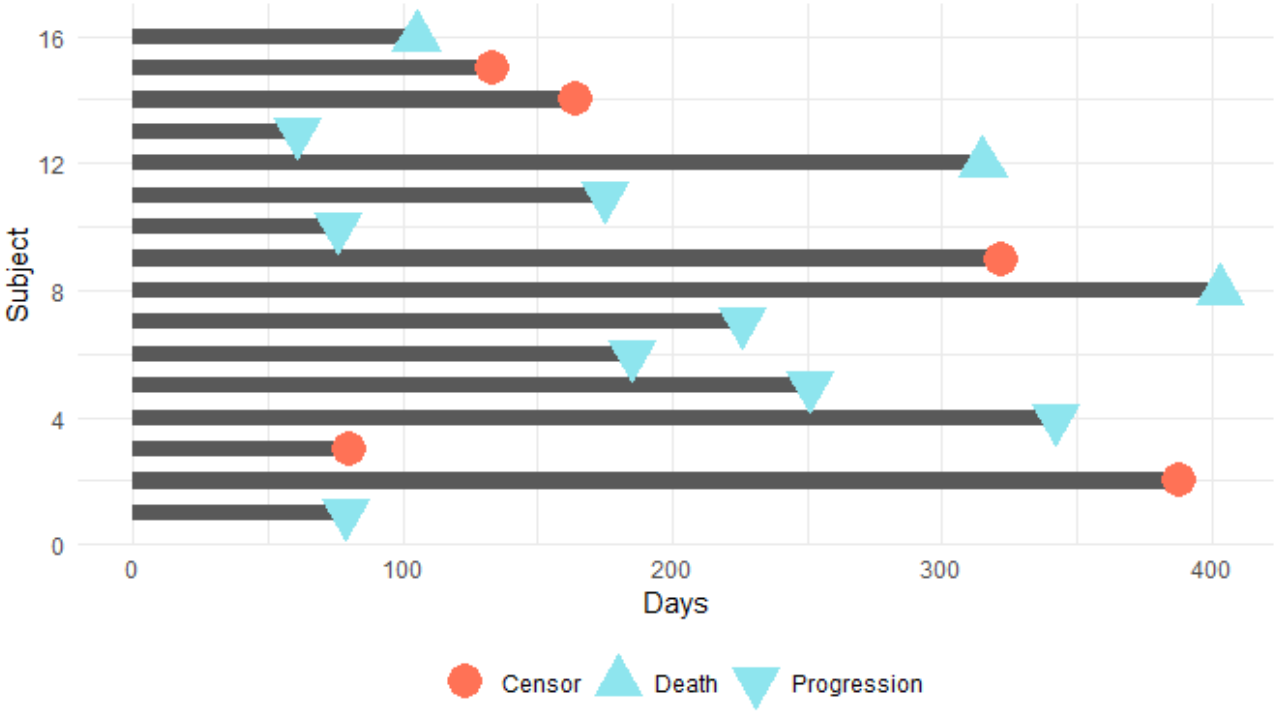

Figure 15: Progression free survival times for all patients, including censoring

Overall survival is presented in a Kaplan Meier plot with 95% confidence intervals in Figure 16 and all data presented graphically in Figure 17. Median overall survival was 394 days with corresponding 95% confidence interval of (263, 403). A line listing of overall survival times and if the observation was censored or not is presented *Appendix - Survival* to this report.

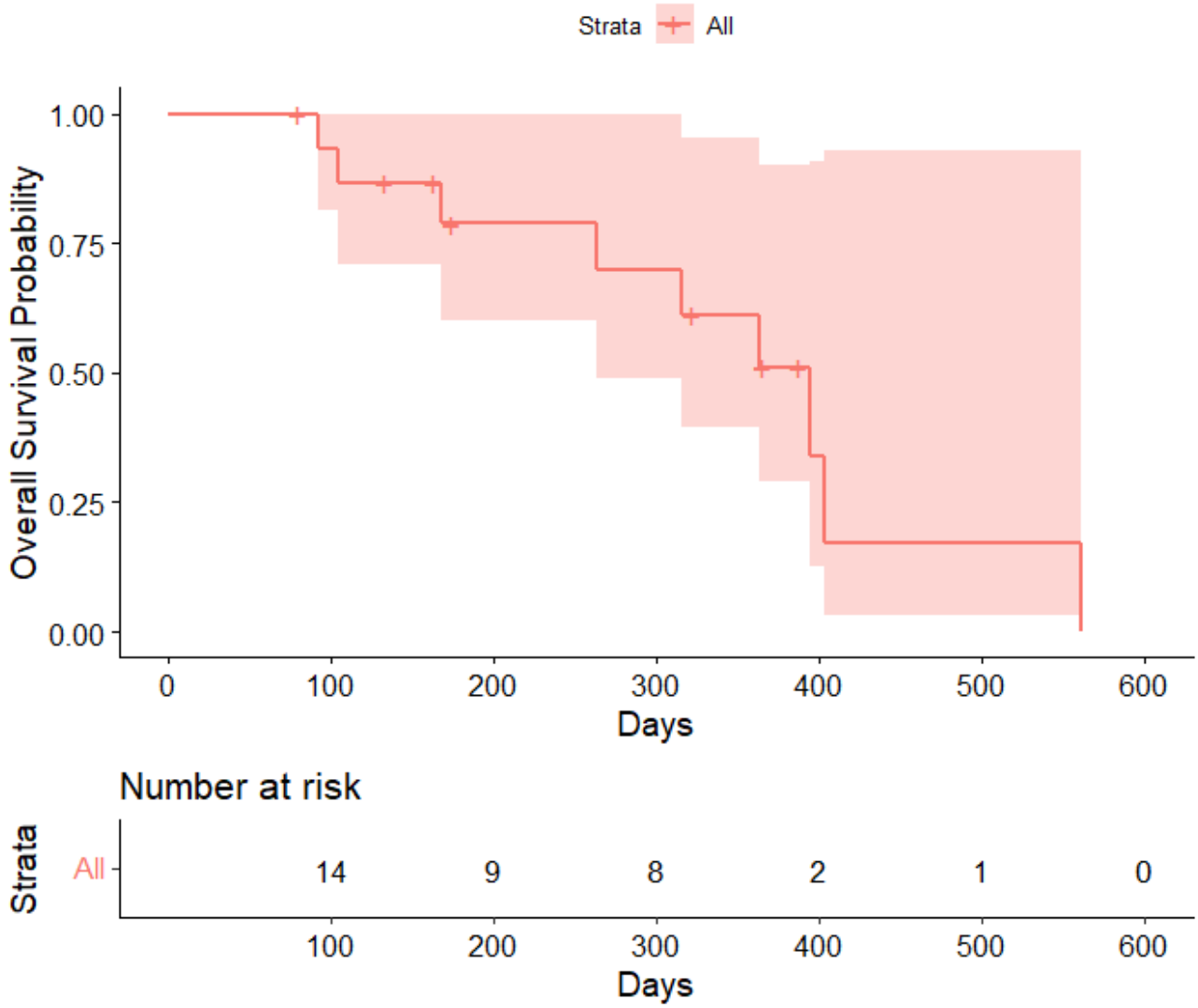

Figure 16: Kaplan Meier plot of overall survival, censored patients marked

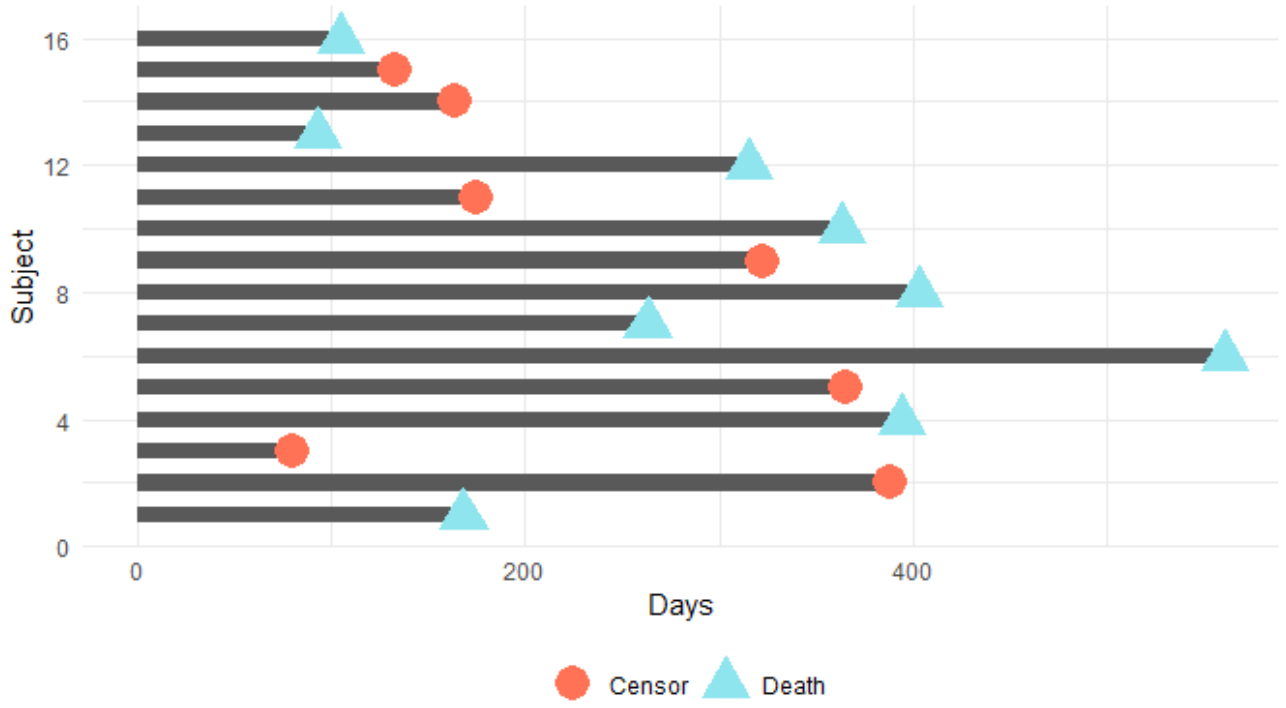

Figure 17: Overall survival times for all patients, including censoring

In field radiotherapy control is presented in Table 22. Disease response if control was observed is presented in Table 23.

Table 22: In field radiotherapy control at 12 weeks

	Schedule 1 (n=3)	Schedule 2 (n=1)	Schedule 3 (n=1)	Schedule 4 (n=1)	Schedule 5 (n=1)	Schedule 6 (n=9)	Total (n=16)
In Field Radiotherapy Control							
Yes	2 (66.7)	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	2 (22.2)	6 (37.5)
No	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	4 (44.4)	6 (37.5)
Missing Data	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (33.3)	4 (25.0)

Table 23: Disease response, for patients with in field radiotherapy control observed at 12 weeks

	Schedule 1 (n=3)	Schedule 2 (n=1)	Schedule 3 (n=1)	Schedule 4 (n=1)	Schedule 5 (n=1)	Schedule 6 (n=9)	Total (n=16)
In Field Radiotherapy Control Response							
Complete Response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial Response	2 (66.7)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	4 (25.0)

	Schedule 1 (n=3)	Schedule 2 (n=1)	Schedule 3 (n=1)	Schedule 4 (n=1)	Schedule 5 (n=1)	Schedule 6 (n=9)	Total (n=16)
Stable Disease	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (12.5)
Progressive Disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not Evaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing Data/ No Radiotherapy Control	1 (33.3)	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	7 (77.8)	10 (62.5)

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

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 = 0.25, Prior MTD = Schedule 6, 6 dose levels, model used: 1-parameter power "empiric" model) gives a prior skeleton given in presented in Figure 18 this chunk of R code:

```
getprior(halfwidth = 0.1, target = Target, nu = 6, nlevel = 6, model = "empiric")
##       [1]       2.499992e-12       3.799171e-07       2.799941e-04       1.081272e-02       8.166297e-02
## [6] 2.500000e-01
```

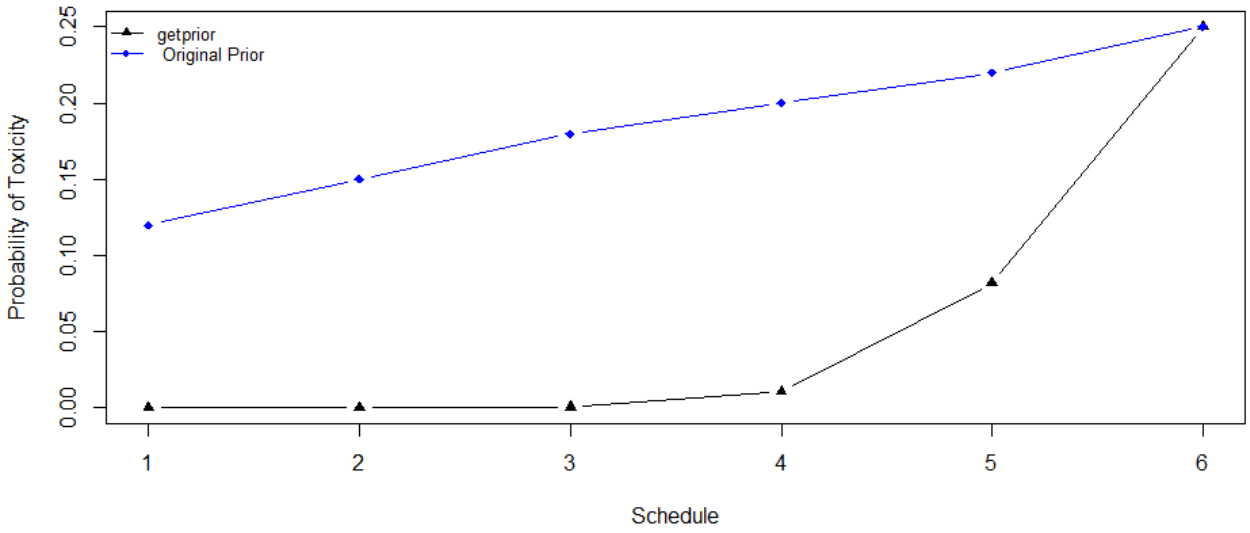

Figure 18: Skeleton from getprior function with original prior included

Table 24 gives the posterior estimates of the replication analysis using the getprior prior. The posterior mean estimated DLT rates at each dose level differ slightly between the primary analysis and this reanalysis but the conclusion remains the same: the maximum tolerated dose is Schedule 6.

Table 24: 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	3	0.008 (0.000, 0.064)	0.000 (0.000, 0.000)
2	1	0.012 (0.000, 0.085)	0.000 (0.000, 0.000)
3	1	0.016 (0.000, 0.108)	0.000 (0.000, 0.000)
4	1	0.019 (0.000, 0.124)	0.001 (0.000, 0.008)
5	1	0.023 (0.000, 0.140)	0.008 (0.000, 0.070)
6	9	0.029 (0.000, 0.165)	0.041 (0.000, 0.230)

6 EXECUTIVE SUMMARY

Main Analysis

CHARIOT A1 found the combination of M6620 and radiotherapy to be safe at the highest dose schedule tested as part of this study (Schedule 6; 240 mg/m^2 M6620 twice weekly for three weeks) in palliative patients with esophageal cancer, no Dose Limiting Toxicities were observed in the 16 patients recruited over the 32 month recruitment period. Table 25 gives the primary estimated posterior means of toxicity for all dose levels given by the 1-parameter power TiTE-CRM model. Three Serious Adverse Events were observed. Compliance to both

prescribed M6620 and radiotherapy was excellent across all dosing schedules. Figure 19 summarises compliance for all therapies in this stage.

Table 25: Primary results. Data presented are posterior means of toxicity rates and corresponding 95% credible intervals

Schedule	Number of Observations	Primary Analysis
1	3	0.008 (0.000, 0.064)
2	1	0.012 (0.000, 0.085)
3	1	0.016 (0.000, 0.108)
4	1	0.019 (0.000, 0.124)
5	1	0.023 (0.000, 0.140)
6	9	0.029 (0.000, 0.165)

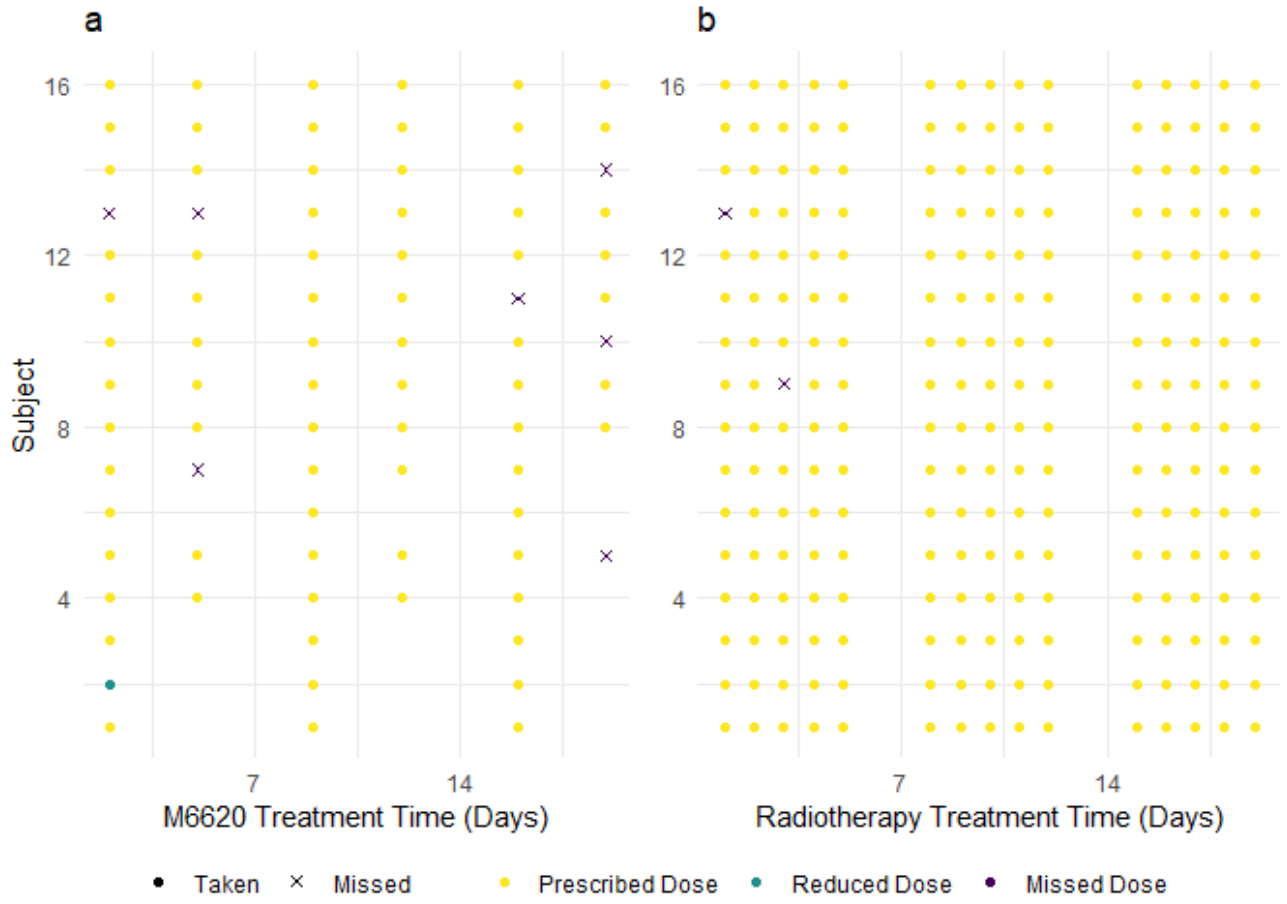

Figure 19: Treatment Compliance Summary: (a) M6620, (b) Radiotherapy

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. The trial stage did not reach its full sample size or hit an early stopping rule (one patient more required to hit the stopping rule of requiring 10 on the highest dose), however the trial team and independent safety review committee felt the trial conclusions is not weakened by this, the precision of the estimated toxicity rates at each dose schedule will be affected, however.

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

All 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 26: Prior therapy listing

Subject	Therapy Name	Treatment Duration (Days)
CH-A1-101	Oxaliplatin (Ludwig Trial)	154
CH-A1-101	Capecitabine (Ludwig Trial)	154
CH-A1-101	Durvalumab (Ludwig Trial)	154
CH-A1-101	Tremelimumab	1
CH-A1-102	Durvalumab (Ludwig clinical trial)	14
CH-A1-102	Capecitabine (Ludwig clinical trial)	126
CH-A1-102	Oxaliplatin (Ludwig clinical trial)	6
CH-A1-105	Cisplatin	106
CH-A1-105	Capecitabine	106
CH-A1-106	ECX	3
CH-A1-106	ECX (cisplatin ommitted for Carboplatin)	1
CH-A1-107	Carboplatin/Capecitabine	103
CH-A1-108	carboplatin/capecitabine	64

Subject	Therapy Name	Treatment Duration (Days)
CH-A1-110	carboplatin	68
CH-A1-110	capecitabine	68
CH-A1-111	Capecitabine	122
CH-A1-111	Oxaliplatin	122
CH-A1-112	oxaliplatin	85
CH-A1-113	Cisplatin (6 cycles)	6
CH-A1-113	Capecitabine (6 cycles)	84
CH-A1-113	Trastuzumab (6 cycles)	6
CH-A1-113	Rechallenge oxaliplatin (3 cycles)	3
CH-A1-113	Rechallenge capecitabine (3 cycles)	42
CH-A1-113	Docetaxel (5 cycles)	5
CH-A1-114	Oxaliplatin and Capecitabine	42
CH-A1-115	Oxaliplatin/ Capecitabine	6
CH-A1-116	Flouorouracil	Unknown
CH-A1-116	Leucovorin	Unknown
CH-A1-116	Oxaliplatin	Unknown
CH-A1-116	Docetaxel	Unknown

Table 27: Baseline symptoms listing

Subject	Symptom	Date	Grade
CH-A1-101	Dysphasia	26 Mar 2019	1
CH-A1-101	Intermittent Fatigue	14 Jan 2019	1
CH-A1-101	Intermittent Cough	26 Mar 2019	1
CH-A1-101	Cold Hypersensitivity	01 Jan 2019	1
CH-A1-102	Dysphagia	30 May 2019	1
CH-A1-102	Occasional pruritus	20 Dec 2018	1
CH-A1-102	Cold Hypersensitivity	14 May 2019	1
CH-A1-102	Pins and needles in fingers and toes	11 Apr 2019	1
CH-A1-102	Numbness in Feet	14 May 2019	1
CH-A1-102	Reflux	14 May 2019	1

Subject	Symptom	Date	Grade
CH-A1-102	Hypertension	01 Jan 2003	1
CH-A1-104	Cough	04 Sep 2019	1
CH-A1-104	Dysphagia	01 Jul 2019	2
CH-A1-104	Gastro-oesophageal reflux	01 Jul 2019	1
CH-A1-104	Back Pain	16 Sep 2019	1
CH-A1-106	Lethargy		1
CH-A1-106	Hearing Loss	21 Oct 2019	1
CH-A1-106	Dysphagia	19 Jun 2019	1
CH-A1-107	Oesophageal reflux	01 Aug 2019	1
CH-A1-107	Occasional pain felt in hiatus hernia	01 Aug 2019	1
CH-A1-109	Dysphagia	01 Jan 2020	1
CH-A1-110	Hypertension	01 Jan 2011	1
CH-A1-110	Rash	22 Dec 2020	1
CH-A1-110	Atrial Fibrillation	01 Jan 2011	1
CH-A1-111	Neck Pain (Intermittent)	01 Jun 2020	1
CH-A1-111	Hypertension	01 Jan 2000	1
CH-A1-112	Gastro-oesophageal reflux	01 Aug 2003	1
CH-A1-113	Dysphagia	01 Jan 2019	1
CH-A1-114	Odynophagia	01 Mar 2021	1
CH-A1-116	Iliac Metastases	02 Jun 2021	

Table 28: Baseline target scan listing

Subject	Date	Organ	Location	Max Diameter (mm)	Assessment Method
CH-A1-101	18 Apr 2019	Lymph Node	Lateral Node Left Lupraclavicular Fossa	20	CT-scan
CH-A1-102	07 Jun 2019	Lymph Node	Coeliac Axis	18	CT-scan
CH-A1-103	17 Jul 2019	Oesophagus	Lower Thoracic	45	CT-scan
CH-A1-104	14 Oct 2019	Lymph Node	Right Inferior Pulmonary Vein	29	CT-scan
CH-A1-104	14 Oct 2019	Lymph Node	Left Inferior Pulmonary Vein	25	CT-scan
CH-A1-107	19 Feb 2020	Gastric Lymph Node	Left	15	CT-scan
CH-A1-108	18 Mar 2020	Lymph Node	Anterior Mediastinal	31	CT-scan

Subject	Date	Organ	Location	Max Diameter (mm)	Assessment Method
CH-A1-111	05 Feb 2021	Oesophagus	Lower	25	CT-scan
CH-A1-113	23 Jun 2021	Liver	Segment VIII	15	CT-scan
CH-A1-113	23 Jun 2021	Lymph Node	Coeliac Lymph Node	20	CT-scan
CH-A1-114	21 Aug 2021	Oesophagus	Para-Oesophageal Lymph Node	11	CT-scan
CH-A1-115	05 Oct 2021	Oesophagus	Lower	30	CT-scan

Table 29: Baseline non-target scan listing

Subject	Date	Number of Lesions	Lesion Site
CH-A1-101	18 Apr 2019	Single Lesion	Right Paratracheal Node
CH-A1-101	18 Apr 2019	Single Lesion	Para-Oesophageal Node
CH-A1-102	07 Jun 2019	Multiple Lesions	Pulmonary Nodules
CH-A1-102	07 Jun 2019	Multiple Lesions	Mediastinal and Hilar Nodes
CH-A1-102	07 Jun 2019	Single Lesion	Liver
CH-A1-104	14 Oct 2019	Single Lesion	Mid-Oesophageal Primary
CH-A1-105	11 Nov 2019	Single Lesion	Upper Oesophageal Primary Tumour
CH-A1-106	19 Dec 2019	Single Lesion	Oesophagus
CH-A1-107	19 Feb 2020	Single Lesion	Mid Oesophagus
CH-A1-108	18 Mar 2020	Single Lesion	Oesophagus
CH-A1-109	26 Aug 2020	Single Lesion	Gastro-Oesophageal
CH-A1-110	08 Dec 2020	Single Lesion	Oesophagus
CH-A1-111	05 Feb 2021	Single Lesion	Paratracheal Lymph Node
CH-A1-112	26 May 2021	Single Lesion	Oesophagus
CH-A1-115	05 Oct 2021	Multiple Lesions	Mediastinal Nodes
CH-A1-116	22 Dec 2021	Single Lesion	Left Iliac Bone Metastases

Table 30: Medical history listing

Subject	Description	Date	Status
CH-A1-101	Hypertension	01 Jan 2010	Ongoing with treatment
CH-A1-101	Regurgitate Vomiting	01 Aug 2018	Ongoing without treatment
CH-A1-101	Pruritus (Back Of Neck)	28 Apr 2019	Ongoing with treatment

Subject	Description	Date	Status
CH-A1-102	Appendectomy	01 Jan 1979	Resolved
CH-A1-103	Right Knee Arthritis	01 Mar 2019	Ongoing with treatment
CH-A1-103	Dysphagia	01 Dec 2018	Ongoing without treatment
CH-A1-103	Septic Arthritis	01 Mar 2019	Resolved
CH-A1-103	Weight Loss	01 Dec 2018	Resolved
CH-A1-103	Ruptured Aaa	01 Jan 2008	Resolved
CH-A1-104	Chronic Obstructive Pulmonary Disease	01 Jan 2015	Ongoing with treatment
CH-A1-104	Obstructive Sleep Apnea		Ongoing with treatment
CH-A1-104	Gout		Ongoing without treatment
CH-A1-104	High Cholesterol	01 Jan 2014	Ongoing with treatment
CH-A1-104	Chronic Back Pain Due To Vertebra (Mid Thoracic)	01 Jan 2000	Ongoing with treatment
CH-A1-104	Low Back Pain Due To Osteoarthritis	01 Jan 2016	Ongoing with treatment
CH-A1-104	High Alcohol		Ongoing without treatment
CH-A1-104	Dysphagia	01 Jul 2019	Ongoing without treatment
CH-A1-104	Cough	04 Sep 2019	Ongoing without treatment
CH-A1-104	Reflux Gastroesophageal	01 Jul 2019	Ongoing with treatment
CH-A1-104	Peripheral Vascular Disease (PVD)	01 Apr 2017	Ongoing with treatment
CH-A1-104	Hypertension	01 Jan 2014	Ongoing with treatment
CH-A1-104	Erectile Dysfunction	01 Jan 2019	Ongoing with treatment
CH-A1-105	Osteoarthritis Left Knee	01 May 2019	Ongoing with treatment
CH-A1-106	Dysphagia	20 Jun 2019	Ongoing without treatment
CH-A1-107	Atrial Fibrillation	01 Jan 2016	Ongoing without treatment
CH-A1-107	Tinnitus	01 Jan 1970	Ongoing without treatment
CH-A1-107	Peripheral Neuropathy	01 Jan 1990	Ongoing without treatment
CH-A1-107	Floaters In Visual Fields	01 Jan 2010	Ongoing without treatment
CH-A1-107	Raised Lump On Left Calf Above Ankle	01 Feb 2020	Ongoing without treatment
CH-A1-107	Dry Skin On Hands And Feet	01 Jan 2010	Ongoing without treatment
CH-A1-107	Dry Eczema Patch On Midline of Chest	01 Jan 2020	Ongoing without treatment
CH-A1-108	COPD	01 Jan 2002	Ongoing without treatment
CH-A1-108	Oesteoporosis	01 Feb 2014	Ongoing with treatment

Subject	Description	Date	Status
CH-A1-108	Rectal Cancer	01 Mar 2004	Resolved
CH-A1-108	Fracture To Left Hip	30 Oct 2016	Resolved
CH-A1-108	Swelling Of Left Ankle	17 Dec 2019	Ongoing without treatment
CH-A1-108	Leucopenia	26 Nov 2019	Resolved
CH-A1-108	Lymphopenia	15 Oct 2019	Resolved
CH-A1-108	Gastric Reflux	01 Jul 2019	Ongoing with treatment
CH-A1-109	Weight Loss	01 Aug 2019	Ongoing without treatment
CH-A1-109	Hypertension	01 Jan 2010	Ongoing with treatment
CH-A1-109	Benign Micturition Syncope	01 Jan 2017	Ongoing with treatment
CH-A1-109	Occasional Constipation	01 Jan 2012	Ongoing with treatment
CH-A1-109	Depression	01 Jan 2017	Ongoing with treatment
CH-A1-109	Constipation	01 Jan 2008	Ongoing with treatment
CH-A1-109	Indigestion	01 Jan 2020	Ongoing with treatment
CH-A1-109	High Cholesterol	01 Jan 2010	Ongoing with treatment
CH-A1-110	Basal Cell Carcinoma	01 Jun 2012	Ongoing without treatment
CH-A1-110	Atrial Fibriallation	01 Jan 2011	Ongoing with treatment
CH-A1-110	Rash	22 Dec 2020	Ongoing with treatment
CH-A1-110	Hypertension	01 Jan 2011	Ongoing with treatment
CH-A1-110	Anaemia	01 Oct 2020	Ongoing without treatment
CH-A1-110	Bilateral Pitting Oedema To Knees	01 Jan 2020	Ongoing without treatment
CH-A1-110	High Cholesterol	01 Jan 2010	Ongoing with treatment
CH-A1-110	Gout	01 Jan 2018	Ongoing with treatment
CH-A1-111	Hypertension	01 Jan 2000	Ongoing with treatment
CH-A1-111	Neck Pain (Intermittent)	01 Jun 2020	Ongoing with treatment
CH-A1-112	Type 2 Diabetes	01 Jan 2017	Ongoing with treatment
CH-A1-112	Hypertension	01 Jan 2019	Ongoing with treatment
CH-A1-112	Depression	01 Jan 2016	Ongoing with treatment
CH-A1-112	Osteoarthritus	01 Aug 2003	Ongoing without treatment
CH-A1-112	Obesity	01 Jan 2011	Ongoing without treatment
CH-A1-113	Anxiety	01 Jan 2009	Ongoing with treatment
CH-A1-113	Pain	01 Jan 2012	Ongoing with treatment

Subject	Description	Date	Status
CH-A1-113	Insomnia	01 Jan 2019	Ongoing with treatment
CH-A1-113	Nausea	01 Jan 2019	Ongoing with treatment
CH-A1-113	Hernia Repair	01 Jan 1971	Resolved
CH-A1-113	Fracture Right Tibia and Fibula	01 Jan 1996	Resolved
CH-A1-113	Hypertension	09 Mar 2000	Ongoing without treatment
CH-A1-114	Bilateral Inguinal Hernia Repair	01 Jan 2019	Resolved
CH-A1-114	Odynophagia	01 Mar 2021	Ongoing with treatment
CH-A1-115	Ischaemic Heart Disease	01 Jan 2016	Resolved
CH-A1-115	Angioplasty	01 Jan 2016	Resolved
CH-A1-115	Hypertension	01 Jan 2016	Ongoing with treatment
CH-A1-116	Gastric Pain	01 Jun 2021	Ongoing with treatment
CH-A1-116	Nausea	01 Sep 2021	Ongoing with treatment
CH-A1-116	Back Pain	01 Dec 2021	Ongoing without treatment

7.2 Appendix - Deviations

Table 31: Deviations listing

Subject	Site	Date	Type	Description	Action Taken
CH-A1-102	Churchill, Oxford		Deviation	Screening coagulation sample not obtained. The comment within the source says 'sample underfilled, unsuitable for testing for coagulation'	Flagged to TM. No further action taken
CH-A1-102	Churchill, Oxford		Important Deviation	Participant was incorrectly prescribed 90mg/m2 instead of the correctly allocated 140mg/m2 for week 1 of M6620 treatment.	Site: Amend presecription to correct dose for subsequent treatments. Review previous participants treatments to ensure correct. Protocol deviation form to be completed with CAPA. OCTO to review treatment allocation communication with site. Stats & CI informed. 20Aug2019 update: Extra pharmacist allocated to trial. All other participants correctly prescribed. CI confirmation all staff suitably trained. Dr & pharmacist to meet to review C1D1 prescription for each participant. OCTO TSI updated so dose specified on registration & clinical trials screening included as recipient.
CH-A1-102	Churchill, Oxford		Deviation	Site did not carry out ECOG assessment at week 2 visit in error.	Identified by OCTO data checker. Deviation highlighted to site by email.
CH-A1-103	Christie, Manchester		Deviation	Duration of M6620 infusion was recorded as 74 minutes (4 minutes over allowable duration of 60 mins +/- 10 minutes).	OCTO requested confirmation of total volume of infusion (total time may be extended by up to 30 mins if >600ml). Site confirmed that this was 400ml,

Subject	Site	Date	Type	Description	Action Taken
					therefore a deviation has occurred. Site notified of deviation via email.
CH-A1-104	Churchill, Oxford		Deviation	Coag assessment done on day 2 of treatment (due on day 1).	Queried to site - missed on day 1 in error. Notified to site as part of Mar2022 deviation review.
CH-A1-105	Churchill, Oxford		Deviation	Duration of infusion not recorded for day 16.	Queried to site - end of infusion time not recorded. Notified to site as part of Mar2022 deviation review.
CH-A1-105	Churchill, Oxford		Deviation	Site did not carry out coagulation test at week 4 FU. 20-Dec-2019	Identified by OCTO data checker. Deviation highlighted to site by email.
CH-A1-106	Beatson West of Scotland Cancer Centre		Deviation	Date of onset missing for 1 condition in PMH.	Queried to site - site response "dates unknown". Notified to site as part of Apr2022 deviation review.
CH-A1-104	Churchill, Oxford		Deviation	QTc assessment missing from week 12 FU.	Queried to site. Response - "did not print properly on ECG". Notified to site as part of Mar2022 deviation review.
CH-A1-104	Churchill, Oxford		Deviation	Date of CT scan more than 14 days before assessment due date for Week 12 FU.	Queried to site - scan was "requested early in error". Notified to site as part of Mar2022 deviation review.
CH-A1-106	Beatson West of Scotland Cancer Centre		Deviation	Exact date of deviation (visit) unknown - to update when entered in OpenClinica. PI self reported W12 follow up conducted in full over phone to prevent participant attending hospital during covid-19. Assessments missed: ECG, Physical, Weight. CT was completed.	No action required. Site correctly following local policies per covid19 & did not miss assessments in error. Deviations included in update to TMG.
CH-A1-107	Velindre Cancer Centre		Deviation	Week 9 and 12 follow up visits performed over the phone due to covid. Site following covid procedures. Week 9 = 21Apr2020 (missed - ECOG, Physical Exam, Weight) Week 12 = Not recorded in CRF, but concurrent CT scan carried out 07May2020 (missed - ECOG, Physical Exam, Weight, ECG)	No action taken, site correctly following local policies per covid19 & did not miss assessments in error. Deviations included in update to TMG.
CH-A1-108	Velindre Cancer Centre		Deviation	ECG was not carried out at 4 week FU.	Identified by OCTO data checker. Deviation highlighted to site by email and requested that site ensure all assessments are carried out at each trial visit.
CH-A1-108	Velindre Cancer Centre		Deviation	Site did not complete in-person assessments at week 6 and 12 FU as the appointments were held as a telephone consultations due to COVID.	No action required. Site correctly following local policies per covid19 & did not miss assessments in error. Deviations included in update to TMG.
CH-A1-103	Christie, Manchester		Deviation	Potassium assessment was not done due to haemolysis of sample. Should have been repeated.	Identified by OCTO data checker. Deviation highlighted to site by email.
CH-A1-109	Velindre Cancer Centre		Deviation	Alk phosphatase assessment not done at week 2 assessment in error.	Identified by OCTO data checker. Deviation highlighted to site by email.

Subject	Site	Date	Type	Description	Action Taken
CH-A1-109	Velindre Cancer Centre		Deviation	Site did not perform week 3 Friday performance status assessment in error.	Identified by OCTO data checker. Deviation highlighted to site by email.
CH-A1-109	Velindre Cancer Centre		Deviation	Duration of M6620 infusion 74 mins (10 mins over).	Query raised with site. Response was that patient had to be re-cannulated.
CH-A1-109	Velindre Cancer Centre		Deviation	Site did not do DLT assessment at week 4 FU in error.	Identified by OCTO data checker. Deviation highlighted to site by email.
CH-A1-109	Velindre Cancer Centre		Deviation	Week 4 FU ECG not done in error.	Identified by OCTO data checker. Deviation highlighted to site by email.
CH-A1-109	Velindre Cancer Centre		Deviation	Site did not perform ECG at week 12 FU in error.	Identified by OCTO data checker. Deviation highlighted to site by email.
CH-A1-110	Velindre Cancer Centre		Deviation	Site did not carry out phosphate assessment at screening in error. Note, that this is not an eligibility criterion.	Identified by OCTO data checker. Deviation highlighted to site by email.
CH-A1-110	Velindre Cancer Centre		Deviation	RTTQA summary received by OCTO at end of the trial noted "5mm circumferential PTV margin (7mm in protocol) - recorded as deviation from protocol." This is the first that OCTO was made aware of this deviation.	No further actions taken. RTTQA liaised with site at the time.
CH-A1-115	Beatson West of Scotland Cancer Centre		Deviation	Weight assessment not completed at Week 12 FU.	Queried to site - missed in error. Notified to site as part of monthly deviations review (RH).
CH-A1-110	Velindre Cancer Centre		Deviation	Week 2 ECOG assessment not done in error.	Notified to site at Nov monthly review and requested to ensure all assessments carried out. Site has confirmed that patient treatment sheet shave been updated to ensure assessments not missed in the future.
CH-A1-111	Christie, Manchester		Deviation	Site used alternative method for GFR calculation than that specified in protocol (C&G).	Notified to site at Nov monthly review and requested to ensure correct equation used. Also notified to all sites as part of recruitment update, as data checker has raised queries for other patients where the same error has occurred.
CH-A1-110	Velindre Cancer Centre		Deviation	Week 4 FU ECG not done.	Notified to site at Nov monthly review and requested to ensure all assessments carried out. Site has confirmed that patient treatment sheet shave been updated to ensure assessments not missed in the future.
CH-A1-110	Velindre Cancer Centre		Deviation	6 month FU visit not completed.	Queried to site - "missed in error". Notified to site as part of Mar2022 deviation review.
CH-A1-111	Christie, Manchester		Important Deviation	Screening assessments completed >21 days prior to first dose. This was due to delay to treatment because the patient required a portacath to be inserted.	Deviation description sent to CI for review. CI's response: "As the delay was due to a technical reasons (need for vascular access- portacath insertion), and not due to a medical issue - and subject tolerated treatment, the overall impact to wellbeing/safety is minimal

Subject	Site	Date	Type	Description	Action Taken
					and the impact to trial integrity is minimal also. The accuracy of the data collected from the patient can be use to inform trial endpoints." Site notified and requested to complete deviation reporting form and CAPA. Received 21Jul2021. CAPA: Site has addressed the issue by managing the timelines for clinic consent and planning scans in advance, so this can be conducted closer to C1D1 date and within 21 day window.
CH-A1-111	Christie, Manchester		Deviation	Site did not complete ECOG assessment at week 1 (Friday) in error.	Identified by OCTO data checker. Deviation highlighted to site by email.
CH-A1-111	Christie, Manchester		Deviation	Site did not complete Week 2 ECOG assessment prior to Friday dose in error.	Identified by OCTO data checker. Deviation highlighted to site by email.
CH-A1-110	Velindre Cancer Centre		Deviation	Week 12 FU ECG not done in error. Logged as 'not required' by site.	Identified by OCTO data checker. Deviation highlighted to site by email.
CH-A1-112	Velindre Cancer Centre		Deviation	Screening phosphate assessment missed.	Query raised with site. Assessment missed in error. All other biochem assays correctly done.
CH-A1-116	Velindre Cancer Centre		Deviation	CTCAE grade not listed for baseline symptom.	Queried with site - "grade not documented and doctor no longer at Velindre". Notified to site as part of Apr2022 deviations review.
CH-A1-112	Velindre Cancer Centre		Deviation	The PI accidentally copied my personal email address (ruth.harman@oncology.ox.ac.uk) into an email whose title contained a trial participantâ€™s full name (first and surname). He meant to copy his colleague (also called Ruth), and didnâ€™t realised his email system had auto-filled my email address instead of hers. The PI sent an email almost immediately later apologising that the email was sent to me in error and to please delete it. I responded that I would do so immediately and did (at 17:17). However, the PI then attempted to recall the email (17:18), which unfortunately didnâ€™t solve the issue as (a) I had already read and deleted it and (b) the recall notice contained the title of the original email in the subject. I deleted the recall messages as well (17:19). Since this was sent to my personal email address, I was the only person who saw the email.	Emails and recall notice have been deleted from my inbox and deleted items folders permanently. Notified site of the deviation by email and confirmed that it would be reported to the data breach team. Details emailed to DB team same day [ICT1791]. Update (29Nov2021): DB team have closed the issue with no further actions.
CH-A1-107	Velindre Cancer Centre		Deviation	The data manager accidentally forwarded a copy of the patient's RT report when requesting that a CRF was unlocked to answer a data query.	Email and attachment has been deleted from the trial inbox and deleted items folders permanently. Notified site of the deviation by email and confirmed that it would be reported to the data breach team. PI has confirmed that he will be speaking to the team internally.

Subject	Site	Date	Type	Description	Action Taken
					Details emailed to DB team same day [ICT1797]. PI reported to IGO at site, who notified OCTO that internal conversations were taking place. Response from DB team - incident closed. No further actions.
CH-A1-107	Velindre Cancer Centre		Deviation	No stop date recorded for one of pt's conmeds ("site has confirmed "unknown").	Notified to site at Nov monthly review with action to ensure all con med dates are recorded.
CH-A1-112	Velindre Cancer Centre		Deviation	Week 2 physical exam missed in error.	Notified to site at Nov monthly review and requested to ensure all assessments carried out.
CH-A1-113	Churchill, Oxford		Deviation	Alk phosphatase assessment not completed for Fri visit at week 1.	Queried to site - "missed in error". Notified to site as part of Mar2022 deviation review.
CH-A1-113	Churchill, Oxford		Deviation	Weight not assessed at Week 2.	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-A1-113	Churchill, Oxford		Deviation	GFR not assessed at Week 2 (although note added to say that GFR was >90).	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-A1-113	Churchill, Oxford		Deviation	Alk phosph assessment not done at week 3 visit.	Queried to site - "missed in error". Notified to site as part of Mar2022 deviation review.
CH-A1-109	Velindre Cancer Centre		Deviation	12 month FU completed early (by 2 months).	Consulted PL, who confirmed that this would be a deviation. Although no appropriate window for completing this visit given in the protocol.
CH-A1-105	Churchill, Oxford		Deviation	6 month FU carried out more than 6 months from start of treatment (8 months).	Consulted PL, who confirmed that this would be a deviation. Although no appropriate window for completing this visit given in the protocol.
CH-A1-114	Christie, Manchester		Important Deviation	The TMG met to make a dose decision for this patient on 06Sep2021. However, the trial team consulted the wrong section of the charter in error. There are two different quoracy rules, depending on whether a dose decision is being made or not. This meant that there were one too few medics available for the dose decision. This mistake was not spotted until after the meeting, but before the patient had started on treatment.	The CI was notified as soon as the error was spotted and the TMG emailed with the dose decision report to request review from another clinician not present at the meeting. One of the clinician members reviewed the report and sent written agreement with the TMG's dose decision. All correspondence was saved in the TMG dose decision meeting folder, along with a file note explaining the deviation and resolution. A protocol deviation form was also filled in and filed in the patient folder, with a CAPA. CAPA details: a checklist was added to the dose decision meeting agenda template to ensure that the necessary

Subject	Site	Date	Type	Description	Action Taken
					members are present in order to make a dose decision in future.
CH-A1-114	Christie, Manchester		Deviation	GFR calculation carried out using alternative equation to that specified in protocol (i.e. not Cockroft-Gault). Visits affected - Screening, week 1, 2 & 3.	All sites emailed as part of recruitment update email on 02Dec2021 to notify that this deviation had occurred and to ensure that future calculations are completed using C-G.
CH-A1-115	Beatson West of Scotland Cancer Centre		Deviation	INR assessment not completed at screening.	Queried to site - "missed in error". Notified to site as part of Mar2022 deviation review.
CH-A1-115	Beatson West of Scotland Cancer Centre		Deviation	Patient received M6220 infusion around 3 hours after RT completed (protocol says "approximately one hour" after radiotherapy).	Deviation reported along with a second administration deviation. Actions apply to both issues. CI, clinical leads and Merck contacted. Advice regarding future administration forwarded to site. Reviewed by CI and assessed to not be an important deviation. Email saved to patient folder of trial inbox.
CH-A1-115	Beatson West of Scotland Cancer Centre		Deviation	Rate of M6620 infusion was reduced from 60 to 90 minutes due to pain and infusion reactions. However, completion time was closer to 2 hours. Site wish to complete all infusions over 90 minutes for this patient.	Deviation reported along with a second administration deviation. CI, clinical leads and Merck contacted. Advice regarding future administration forwarded to site. - Merck suggested pre-medicating the patient with corticosteroids and antihistamine for next the infusion(s). Please refer to the protocol section 8.4 carefully. - Merck advised Sponsor to consider possible infusion site reaction with potential drug extravasation. Recommend to cautiously assess the intravenous line before next infusion. - Prof Mukherjee recognised that 90 mins for future infusions would be ideal as it is tolerable for the patient. - 90min infusion is fine from Merck side as it is mentioned in the IB that the infusion time may be extended to 90 mins to minimize the infusion related reactions. However, please note the IB also mentions that it should not go over the 90 mins (please ensure to report as protocol deviations every time) - In case of non-resolution or worsening of reactions, Merck recommends Sponsor considers checking for thrombosis and consider central access (if possible) or include pre-medication with anti-histamine and/or steroids. Reviewed by CI and assessed not to be an important deviation. Email saved in patient folder of inbox.
CH-A1-115	Beatson West of Scotland Cancer Centre		Deviation	DLT assessment not done at Week 4 FU.	Queried to site - reason provided by site 'pt not dosed at this week'. Notified to site as part of Mar2022 deviation review.

Subject	Site	Date	Type	Description	Action Taken
CH-A1-114	Christie, Manchester		Deviation	Date of CT 2 weeks after week 12 FU visit.	Queried to site - scan requested out of required window in error. Notified to site as part of Mar2022 deviation review.
CH-A1-116	Velindre Cancer Centre		Deviation	Dates of both Tues & Fri GFR assessments the same and not within 24 hours of dose.	Queried with site - "this is the date documented". Notified to site as part of Apr2022 deviation review.
CH-A1-116	Velindre Cancer Centre		Deviation	Phosphate assessment not completed in week 1.	Queried with site - "missed in error". Notified to site as part of Apr2022 deviation review.
CH-A1-116	Velindre Cancer Centre		Deviation	Friday ECOG assessment not carried out.	Queried with site. Response was that reason was "not documented". Notified to site as part of Apr2022 deviations review.
CH-A1-116	Velindre Cancer Centre		Deviation	Patient was unable to attend for 12 week FU visit, so this was conducted via telephone.	Site notified OCTO of arrangements in the first instance and made appropriate arrangements given the circumstances. No further actions.
CH-A1-116	Velindre Cancer Centre		Deviation	Number of days of treatment not entered for prior systemic treatment.	Queried with site - "not documented". Notified to site as part of Apr2022 deviation review.
CH-A1-104	Churchill, Oxford		Deviation	Date of onset missing for 3 conditions in PMH.	Queried to site - site response "dates unknown". Notified to site as part of Mar2022 deviation review.

7.3 Appendix - Treatment

Table 32: Missed M6620 treatment with reason

Subject	Reason Treatment Missed
CH-A1-105	Due to G3 esophagitis
CH-A1-107	Patient became febrile (38.7oC), neutrophilia, atrial fibrillation, chest wheeze
CH-A1-110	Decreased sodium
CH-A1-111	Withheld due to AEs
CH-A1-113	G3 Hypertension
CH-A1-113	G3 Hypertension
CH-A1-114	Patient had ongoing constipation and was under inpatient admission on scheduled dose date.

7.4 Appendix - Survival

Table 33: Progression free survival times by patient

Subject	Dose	Progression Free Survival (Days)	Censored
CH-A1-101	Schedule 1	79	No
CH-A1-102	Schedule 1	388	Yes
CH-A1-103	Schedule 1	80	Yes
CH-A1-104	Schedule 2	342	No
CH-A1-105	Schedule 3	251	No
CH-A1-106	Schedule 4	185	No
CH-A1-107	Schedule 5	226	No
CH-A1-108	Schedule 6	403	No
CH-A1-109	Schedule 6	322	Yes
CH-A1-110	Schedule 6	76	No
CH-A1-111	Schedule 6	175	No
CH-A1-112	Schedule 6	315	No
CH-A1-113	Schedule 6	61	No
CH-A1-114	Schedule 6	164	Yes
CH-A1-115	Schedule 6	133	Yes
CH-A1-116	Schedule 6	105	No

Table 34: Overall survival times by patient

Subject	Dose	Overall Survival (Days)	Censored
CH-A1-101	Schedule 1	168	No
CH-A1-102	Schedule 1	388	Yes
CH-A1-103	Schedule 1	80	Yes
CH-A1-104	Schedule 2	394	No
CH-A1-105	Schedule 3	365	Yes
CH-A1-106	Schedule 4	561	No
CH-A1-107	Schedule 5	263	No
CH-A1-108	Schedule 6	403	No
CH-A1-109	Schedule 6	322	Yes
CH-A1-110	Schedule 6	363	No
CH-A1-111	Schedule 6	175	Yes

Subject	Dose	Overall Survival (Days)	Censored
CH-A1-112	Schedule 6	315	No
CH-A1-113	Schedule 6	93	No
CH-A1-114	Schedule 6	164	Yes
CH-A1-115	Schedule 6	133	Yes
CH-A1-116	Schedule 6	105	No

7.5 Appendix - Scans

Table 35: Non-12-week restaging scans

Subject	Time Point	Sum of Longest Diameters (mm)	Target Response	Non-Target Response	Overall RECIST	Response in RT Field
CH-A1-101	8 weeks post EOT		Progressive disease	Progressive disease	Progressive disease	Disease control not observed in RT field
CH-A1-104	During FU		Not evaluable	Non-CR/ Non-PD	Progressive disease	Disease control not observed in RT field
CH-A1-105	During FU		No target lesions	Non-CR/ Non-PD	Progressive disease	Disease control not observed in RT field
CH-A1-106	Other		No target lesions	Progressive disease	Progressive disease	Disease control not observed in RT field
CH-A1-108	8 weeks post EOT	15	Partial response	Complete response	Partial response	Disease control not observed in RT field
CH-A1-110	8 weeks post EOT		No target lesions	Non-CR/ Non-PD	Progressive disease	Disease control not observed in RT field
CH-A1-111	During FU		Stable disease	Progressive disease	Progressive disease	Stable disease
CH-A1-115	8 weeks post EOT	0	Complete response	Non-CR/ Non-PD	Complete response	Disease control not observed in RT field

Table 36: Target lesion restaging scans

Subject	Date	Site	Location	Diameter (mm)	Assessment Method
CH-A1-101	15 Aug 2019	Lymph Node	Lateral Node In Left Supraclavicular Fossa	26	CT-scan
CH-A1-102	09 Sep 2019	Lymph Node	Coeliac Axis	16	CT-scan
CH-A1-104	23 Dec 2019	Lymph Node	Right Inferior Pulmonary Vein	24	CT-scan
CH-A1-104	23 Dec 2019	Lymph Node	Left Inferior Pulmonary Vein	20	CT-scan
CH-A1-104	28 Sep 2020	Lymph Node	Right Inferior Pulmonary Vein		CT-scan
CH-A1-104	28 Sep 2020	Lymph Node	Left Inferior Pulmonary Vein		CT-scan
CH-A1-113	12 Sep 2021	Liver	Segment VIII		CT-scan
CH-A1-113	12 Sep 2021	Lymph Node	Coeliac Lymph Node		CT-scan
CH-A1-115	10 Jan 2022	Oesophagus	Lower	0	CT-scan
CH-A1-103	08 Oct 2019	Oesophagus	Lower Thoracic	31	CT-scan
CH-A1-111	07 May 2021	Oesophagus	Circumferential Lower Thickening	27	CT-scan
CH-A1-111	17 Aug 2021	Oesophagus	Lower	27	CT-scan
CH-A1-114	30 Dec 2021	Oesophagus	Para-Oesophageal Lymph Node	5	CT-scan
CH-A1-107	07 May 2020	Gastric Lymph Node	Left	19	CT-scan
CH-A1-108	10 Jun 2020	Lymph Node	Anterior Mediastinal	15	CT-scan

Table 37: Non-Target lesion restaging scans

Subject	Date	Site	Assessment Method	Number of lesions	Assessment
CH-A1-101	15 Aug 2019	Right Paratracheal Node	CT-scan	Single lesion	Present
CH-A1-101	15 Aug 2019	Para-Oesophageal Node	CT-scan	Single lesion	Present
CH-A1-102	09 Sep 2019	Pulmonary Nodules	CT-scan	Multiple lesions	Present
CH-A1-102	09 Sep 2019	Mediastinal And Hilar Nodes	CT-scan	Multiple lesions	Absent
CH-A1-102	09 Sep 2019	Liver	CT-scan	Single lesion	Present
CH-A1-104	23 Dec 2019	Mid-Oesophageal Primary	CT-scan	Single lesion	Present
CH-A1-104	28 Sep 2020	Mid-Oesophageal Primary	CT-scan	Single lesion	Present
CH-A1-105	17 Feb 2020	Upper Oesophageal Primary Tumour	CT-scan	Single lesion	Present
CH-A1-106	23 Mar 2020	Oesophageal	CT-scan	Single lesion	Present
CH-A1-106	08 Jul 2020	Oesophageal	CT-scan	Single lesion	Present
CH-A1-115	10 Jan 2022	Mediastinal Nodes	CT-scan	Multiple lesions	Present

Subject	Date	Site	Assessment Method	Number of lesions	Assessment
CH-A1-111	07 May 2021	Paratracheal Lymph Node	CT-scan	Single lesion	Present
CH-A1-111	17 Aug 2021	Paratracheal Lymph Node	CT-scan	Single lesion	Present
CH-A1-107	07 May 2020	Mid Oesophageal	CT-scan	Single lesion	Present
CH-A1-108	10 Jun 2020	Oesophageal Tumour	CT-scan	Single lesion	Absent
CH-A1-109	19 Nov 2020	Gastro-Oesophageal	CT-scan	Single lesion	Present
CH-A1-110	29 Mar 2021	Oesophageal Tumour	CT-scan	Single lesion	Present
CH-A1-110	22 Jun 2021	Oesphageal Tumour	CT-scan	Single lesion	Present
CH-A1-112	25 Aug 2021	Lower Oesophagus	CT-scan	Single lesion	Present
CH-A1-105	04 Nov 2020	Upper Oesophageal Primary Tumour	CT-scan	Single lesion	Present

7.6 Appendix - Concomitant Medication & Post-Trial Treatments

Table 38: Concomitant Medication

Subject	Medication	Dose	Frequency	Indication	Date
CH-A1-101	Omeprazole	20 mg	Other	Gastric Reflux Prophylaxis	28 May 2019
CH-A1-101	Amlodipine	5 mg	Once Daily	Hypertension	01 Jan 2010
CH-A1-101	Ramipril	10 mg	Other	Hypertension	01 Jan 2010
CH-A1-101	Cetirizine	10 mg	Other	Pruritus	18 May 2019
CH-A1-102	Ramipril	10 mg	Once Daily	Hypertension	01 Jan 2014
CH-A1-102	Omeprazole	20 mg	When Required	Reflux	01 Oct 2018
CH-A1-102	Morphine Sulphate	7 mg	When Required	Chest Pain	02 Jul 2019
CH-A1-102	Sucralfate	1 g	When Required	Chest Pain	02 Jul 2019
CH-A1-102	Metaclopramide	10 mg	Three Times Daily	Nausea	01 Jul 2019
CH-A1-104	Omeprazole	20 mg	Once Daily	Gastric Reflux	01 Jul 2019
CH-A1-104	Lisinopril	2.5 mg	Once Daily	Hypertension	01 Jan 2014
CH-A1-104	Amlodipine	10 mg	Once Daily	Hypertension	01 Jan 2014
CH-A1-104	Atorvastatin	10 mg	Once Daily	High Cholesterol	01 Jan 2014
CH-A1-104	Salbutamol	100 mcg	When Required	COPD	01 Jan 2015
CH-A1-104	Sildenafil	100 mg	When Required	Erectile Dysfunction	01 Jan 2019
CH-A1-104	Salmeterol	25 mcg	Twice Daily	COPD	01 Jan 2015
CH-A1-104	Clarithromycin	500 mg	Twice Daily	Pneumonia	07 Oct 2019

Subject	Medication	Dose	Frequency	Indication	Date
CH-A1-104	Atimos Modulite	12 mcg	Twice Daily	COPD	01 Sep 2019
CH-A1-104	Aspirin	75 mg	Once Daily	PVD	01 Apr 2017
CH-A1-104	Ibuprofen	200 mg	Once Daily	Back Pain	01 Jan 2015
CH-A1-104	Paracetamol	1 g	Twice Daily	Back Pain	01 Jan 2015
CH-A1-104	Ibuprofen	400 mg	Once Daily	Back Pain	01 Nov 2019
CH-A1-105	Paracetamol	1 g	When Required	Pain From Osteoarthritis	26 Nov 2019
CH-A1-105	Paracetamol	1 g	Four Times Daily	Esophagitis	11 Dec 2019
CH-A1-105	Ibuprofen	400 mg	Four Times Daily	Rhinitis And Cough Prophylaxis	16 Feb 2020
CH-A1-113	Omeprazole	20 mg	Once Daily	Gastro-Protection	01 Jan 2019
CH-A1-113	Trazadone	50 mg	Once Daily	Anxiety	01 Jan 2019
CH-A1-113	Zopiclone	7.5 mg	When Required	Insomnia	01 Apr 2021
CH-A1-113	Tramadol	50 mg	When Required	Pain	01 Feb 2021
CH-A1-113	Metoclopramide	10 mg	When Required	Nausea	01 Jan 2019
CH-A1-113	Gaviscon	1 tablet	When Required	Gastro-Protection	01 Jan 2019
CH-A1-113	Amlodipine	5 mg	Once Daily	Hypertension	13 Jul 2021
CH-A1-113	Perindopril	4 mg	Once Daily	Hypertension	19 Jul 2021
CH-A1-113	Amlodipine	10 mg	Once Daily	Hypertension	19 Jul 2021
CH-A1-113	Laxido	1 sachet	Twice Daily	Constipation	19 Jul 2021
CH-A1-113	Fentanyl Patch	12 mcg	Unknown	Pain	15 Jul 2021
CH-A1-113	Amlodipine	5 mg	Once Daily	Hypertension	09 Aug 2021
CH-A1-113	Gabapentin	100 mg	Twice Daily	Pain	27 Jul 2021
CH-A1-113	Dexamethasone	4 mg	Once Daily	Pain	27 Jul 2021
CH-A1-113	Fentanyl Patch	24 mcg	Unknown	Pain	20 Jul 2021
CH-A1-115	Bisoprolol	5mg	Once Daily	Hypertension	26 Jul 2021
CH-A1-115	Aspirin	75mg	Once Daily	Hypertension	26 Jul 2021
CH-A1-115	Rosuvastatin	10mg	Once Daily	Hypertension	26 Jul 2021
CH-A1-115	Ramipril	2.5mg	Once Daily	Hypertension	26 Jul 2021
CH-A1-103	Co-Codamol	8mg	Once Daily	Right Knee Arthritis	01 Mar 2019
CH-A1-103	Senna	2 tablets	When Required	Constipation	29 Jul 2019
CH-A1-111	Amlodipine	10mg	Once Daily	Hypertension	01 Jan 2000
CH-A1-111	Perindopril	8mg	Once Daily	Hypertension	01 Jan 2000

Subject	Medication	Dose	Frequency	Indication	Date
CH-A1-111	Omeprazole	20mg	Once Daily	Prophylactic	01 Jun 2020
CH-A1-111	Paracetamol	1000mg	When Required	Neck Pain	01 Jun 2020
CH-A1-111	Pfizer Covid-19 Vaccination	0.3ml	Other	Prophylactic	24 Feb 2021
CH-A1-111	Chlorphenamine	1%	Twice Daily	Skin Rash	08 Mar 2021
CH-A1-111	Hydrocortisone Cream	4mg	Other	Skin Rash	08 Mar 2021
CH-A1-114	Paracetamol Suspension	1g	Four Times Daily	Odynophagia	01 Mar 2021
CH-A1-114	Senna Liquid	15mg	Once Daily	Constipation	01 Oct 2021
CH-A1-114	Docusate 12.5mg/5ml	25mg	Twice Daily	Constipation	04 Oct 2021
CH-A1-114	Glycerol Suppository	4g	Twice Daily	Constipation	04 Oct 2021
CH-A1-114	Glycopyrronium	200mcg	Other	Excess Mucous Production	05 Oct 2021
CH-A1-114	Scopoderm Patch	1.5mg	Other	Excess Mucous Production	05 Oct 2021
CH-A1-114	Phosphate Enema	1 enema	Once Daily	Constipation	14 Oct 2021
CH-A1-114	Lactulose	10ml	Three Times Daily	Constipation	14 Oct 2021
CH-A1-114	Clarithromycin	500mg	Twice Daily	Campylobacter Jejuni Infection	15 Oct 2021
CH-A1-114	0.8 Saline + 4% Dextrose Solution	1000ml	When Required	Dehydration + Urea Rise	14 Oct 2021
CH-A1-107	Omeprazole	40 mg	Once Daily	Acid Reflux	01 Aug 2019
CH-A1-107	Difflam Mouthwash	10 ml	Four Times Daily	Sore Throat	28 Feb 2020
CH-A1-107	Paracetamol	1 g	When Required	Pyrexia	28 Feb 2020
CH-A1-107	Doxycycline	200 mg	One Dose	Pyrexia	28 Feb 2020
CH-A1-107	Doxycycline	100 mg	Twice Daily	Pyrexia	29 Feb 2020
CH-A1-107	Metaclorpamide	10 mg	When Required	Nausea, Vomiting	04 Mar 2020
CH-A1-108	Omeprazole	20mg	Once Daily	Gastric Reflux	01 Jul 2019
CH-A1-108	Adcal	1 TABLET	Twice Daily	Oesteoporosis	01 Jan 2016
CH-A1-108	Paracetamol	2 tablets	Three Times Daily	Soreness In Lower Oesophagus	06 Apr 2020
CH-A1-108	Cocodamol	30/500mg	Four Times Daily	Spinal Fracture	11 May 2020
CH-A1-108	Oramorph	10mg/5mls	Four Times Daily	Spinal Fracture	18 May 2020
CH-A1-108	Paracetamol	1g	Four Times Daily	Spinal Fracture	25 May 2020
CH-A1-109	Omeprazole	20mg	Unknown	Indigestion	01 May 2020
CH-A1-109	Bendroflumethiazide	2.5mg	Unknown	Hypertension	01 Jan 2010
CH-A1-109	Simvastatin	20mg	Once Daily	High Cholesterol	01 Jan 2010
CH-A1-109	Amlodipine	10mg	Unknown	Hypertension	01 Jan 2010

Subject	Medication	Dose	Frequency	Indication	Date
CH-A1-109	Doxazosin	4mg	Once Daily	Benign Micturition Syncope	01 Jan 2017
CH-A1-109	Fibrogel	1 sachet	When Required	Constipation	01 Jan 2008
CH-A1-109	Mirtazapine	45mg	Unknown	Depression	01 Jan 2017
CH-A1-109	Irbesartan	300mg	Unknown	Hypertension	01 Jan 2010
CH-A1-109	Ensure Drinks	1 drink	Twice Daily	Weight Loss	11 Sep 2020
CH-A1-109	Metoclopramide	10mg	Three Times Daily	Nausea	16 Sep 2020
CH-A1-109	Zopiclone	3.75mg	When Required	Insomnia	18 Sep 2020
CH-A1-109	Ensure Drinks	1 drink	Once Daily	Weight Loss	01 Oct 2020
CH-A1-109	Flu Jab	Unknown	One Dose	Prevent Flu	23 Oct 2020
CH-A1-110	Dermol 500	1 application	Once Daily	Soap Substitute For Dry Skin	22 Dec 2020
CH-A1-110	Synalar Cream	1 application	When Required	Eczema	30 Dec 2020
CH-A1-110	Exocream	1 application	Twice Daily	Eczema	30 Dec 2020
CH-A1-110	Epiderm Cream	1 application	Four Times Daily	Rash And Dry Skin	02 Jan 2021
CH-A1-110	Chlorphenamine	4mg	When Required	Rash	30 Dec 2020
CH-A1-110	Paracetamol	1000mg	When Required	Headache	11 Jan 2021
CH-A1-110	Lisinopril	40mg	Once Daily	Hypertension	01 Jan 2011
CH-A1-110	Amlodipine	5mg	Once Daily	Hypertension	01 Jan 2011
CH-A1-110	Atenolol	25mg	Once Daily	Hypertension	01 Jan 2011
CH-A1-110	Atorvastatin	20mg	Once Daily	High Cholesterol	01 Jan 2010
CH-A1-110	Allopurinol	200mg	Once Daily	Gout	01 Jan 2018
CH-A1-110	Dalteparin	12,500 IU	Once Daily	Atrial Fibrillation	14 Sep 2020
CH-A1-110	Aveeno Cream	1 application	Four Times Daily	Dry Skin	22 Dec 2020
CH-A1-110	Loratadine	10mg	Once Daily	Rash	19 Jan 2021
CH-A1-110	Hydrocortisone Cream	1%	Unknown	Rash	19 Jan 2021
CH-A1-110	Ensure Drinks	2 drinks	Twice Daily	Dysphagia	01 Jan 2020
CH-A1-110	Soluable Paracetamol	1g	Four Times Daily	Dysphagia	26 Jan 2021
CH-A1-110	Magnesium Supplement	1 tablet	Once Daily	Decreased Magnesium	25 Jan 2021
CH-A1-110	Ibuprofen	400mg	When Required	Dysphagia	26 Jan 2021
CH-A1-110	Betnovate Cream	1 application	Twice Daily	Maculopapular Rash	05 Feb 2021
CH-A1-110	Epaderm	1 application	Twice Daily	Maculopapular Rash	05 Feb 2021
CH-A1-110	Chlorphenamine	4mg	Twice Daily	Maculopapular Rash	11 Feb 2021

Subject	Medication	Dose	Frequency	Indication	Date
CH-A1-110	Soluable Paracetamol	1000mg	Twice Daily	Dysphagia	11 Feb 2021
CH-A1-112	Empagliflozin	10mg	Once Daily	Diabetes	11 May 2021
CH-A1-112	Citalopram	40mg	Once Daily	Depression	01 Jan 2016
CH-A1-112	Propranolol	40mg	Once Daily	Hypertension	01 Jan 2019
CH-A1-112	Metformin	500mg	Three Times Daily	Diabetes	01 Jan 2017
CH-A1-112	Atorvastatin	40mg	Once Daily	Hypertension	01 Jan 2019
CH-A1-112	Linagliptin	5mg	Once Daily	Diabetes	25 Jan 2021
CH-A1-112	Lansoprazole	15mg	Once Daily	Gastroesophageal Reflux	01 Nov 2019
CH-A1-112	Peptac Liquid	10ml	Four Times Daily	Gastroesophageal Reflux	12 Apr 2021
CH-A1-112	Ensure Compact Liquid	200ml	When Required	Nutritional Supplement	11 May 2021
CH-A1-112	Metoclopramide	10mg	When Required	Nausea	15 Jun 2021
CH-A1-112	Loperamide	2mg	When Required	Diarrhoea	16 Jun 2021
CH-A1-112	Paracetamol	1g	Four Times Daily	Stomach Pain	28 Jun 2021
CH-A1-112	Aveeno	1 application	When Required	Dry Skin	01 Jul 2021
CH-A1-112	Otrivine Antistin Eye Drops	1 drop	Four Times Daily	Watery Eyes	01 Jul 2021
CH-A1-112	Cetirizine Hydrochloride	10mg	Once Daily	Watering Eyes	24 Jun 2021
CH-A1-112	Amitripyline	10mg	Once Daily	Numbness/Peripheral Neuropathy	06 Aug 2021
CH-A1-112	Sertraline	50mg	Once Daily	Depression	27 Aug 2021
CH-A1-116	Co-Codamol	30MG	Four Times Daily	Gastric Pain	01 Jun 2021
CH-A1-116	Ondansetron	8MG	When Required	Nausea	10 Sep 2021
CH-A1-116	Metoclopramide	10MG	When Required	Nausea	03 Nov 2021
CH-A1-116	Difflam Mouthwash	10ml	Four Times Daily	Poor Dentition	14 Jan 2022
CH-A1-116	Chlorhexidine	10ml	Twice Daily	Poor Dentition	14 Jan 2022
CH-A1-116	Senna	7.5mg	When Required	Constipation	14 Jan 2022
CH-A1-116	Oramorph	2.5ml	Twice Daily	Hip Pain	08 Apr 2022
CH-A1-116	Amitriptyline	10mg	Once Daily	Hip Pain	23 Mar 2022
CH-A1-116	Amitriptyline	20mg	Once Daily	Hip Pain	31 Mar 2022
CH-A1-116	Amitriptyline	30mg	Once Daily	Hip Pain	07 Apr 2022

Table 39: Post trial treatment

Subject	Treatment	Start Date	End Date	Best Response
CH-A1-102	Experimental Drug RP2	22 Oct 2019	17 Dec 2019	Stable Disease
CH-A1-104	Carboplatin	05 Feb 2020	03 Jun 2020	Ongoing Disease Response
CH-A1-104	Paclitaxel	05 Feb 2020	03 Jun 2020	Ongoing Disease Response
CH-A1-104	Carboplatin and Paclitaxel- 6 Cycles	05 Feb 2020		Good Response
CH-A1-104	Radiotherapy - 20Gy, 5#	01 Aug 2020		Disease Progression
CH-A1-105	Cisplatin	10 Sep 2020	01 Oct 2020	Evidence of Local and Metastatic Disease Response at Cycle 3
CH-A1-105	Capecitabine	22 Oct 2020		Evidence of Local and Metastatic Disease Response at Cycle 3
CH-A1-105	Oxaliplatin	22 Oct 2020		Evidence of Local and Metastatic Disease Response at Cycle 3
CH-A1-106	ECX Peripheral	07 Aug 2020		Static Disease

7.7 Appendix - Toxicity

Table 40: All adverse events

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	RT Causality	SAE	DLT	Outcome
CH-A1-101	Chills	27May2019	Screening	27May2019	1	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A1-101	Neuropathy peripheral	20May2019	Screening		1	Definitely Not Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-102	Chest pain	02Jul2019	Week 3	11Jul2019	2	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A1-102	Nausea	01Jul2019	Week 2	03Aug2019	2	Possibly Related	Definitely Not Related	No	No	Resolved
CH-A1-102	Fatigue	15Jul2019	Week 3	03Aug2019	2	Probably Not Related	Possibly Related	No	No	Improved
CH-A1-102	Fatigue	04Aug2019	Week 5-9		1	Possibly Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-103	Dyspepsia	23Jul2019	Week 1		1	Probably Not Related	Possibly Related	No	No	Was persisting at last contact
CH-A1-103	Constipation	27Jul2019	Week 1	13Sep2019	1	Probably Not Related	Probably Not Related	No	No	Resolved
CH-A1-103	Squamous cell carcinoma of skin	01Sep2019	Week 5-9	22Oct2019	2	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Resolved
CH-A1-103	Cough	04Oct2019	After week 9		1	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Was persisting at last contact
CH-A1-103	Urinary tract infection	11Oct2019	After week 9		2	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Was persisting at last contact

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	RT Causality	SAE	DLT	Outcome
CH-A1-104	Dysphonia	11Dec2019	Week 5-9		1	Definitely Not Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-104	Dysphagia	01Dec2019	Week 5-9		1	Definitely Not Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-104	Dyspnoea	01Dec2019	Week 5-9		1	Definitely Not Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-105	Oesophagitis	09Dec2019	Week 3	12Dec2019	3	Definitely Not Related	Possibly Related	No	No	Resolved
CH-A1-105	Dysphagia	06Dec2019	Week 2	27Dec2019	1	Definitely Not Related	Possibly Related	No	No	Resolved
CH-A1-105	Oesophagitis	12Dec2019	Week 3	14Dec2019	2	Possibly Related	Possibly Related	No	No	Resolved
CH-A1-105	Dermatitis	12Dec2019	Week 3	27Dec2019	1	Definitely Not Related	Possibly Related	No	No	Resolved
CH-A1-105	Rhinitis	10Feb2020	Week 5-9		1	Definitely Not Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-105	Cough	10Feb2020	Week 5-9		1	Definitely Not Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-106	Arthralgia	25Jan2020	Week 3	26Jan2020	1	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A1-106	Cough	14Jan2020	Week 2	14Jan2020	1	Probably Not Related	Probably Not Related	No	No	Resolved
CH-A1-106	Arthralgia	31Jan2020	Week 4	05Mar2020	1	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A1-107	Oropharyngeal pain	28Feb2020	Week 1	03Mar2020	1	Definitely Not Related	Definitely Not Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	RT Causality	SAE	DLT	Outcome
CH-A1-107	Pyrexia	28Feb2020	Week 1	29Feb2020	1	Definitely Not Related	Probably Not Related	No	No	Resolved
CH-A1-107	Vomiting	03Mar2020	Week 2	04Mar2020	1	Definitely Related	Definitely Related	No	No	Resolved
CH-A1-107	Cough	02Mar2020	Week 2		1	Definitely Related	Definitely Related	No	No	Was persisting at last contact
CH-A1-108	Lymphopenia	30Mar2020	Week 2		3	Possibly Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-108	Fatigue	04Apr2020	Week 2		1	Definitely Related	Possibly Related	No	No	Was persisting at last contact
CH-A1-108	Oesophagitis	04Apr2020	Week 2	27Apr2020	1	Definitely Not Related	Possibly Related	No	No	Resolved
CH-A1-108	Oropharyngeal pain	04Apr2020	Week 2	27Apr2020	1	Definitely Not Related	Possibly Related	No	No	Resolved
CH-A1-108	Spinal fracture	19Apr2020	Week 5-9		2	Definitely Not Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-108	Constipation	14May2020	Week 5-9		1	Definitely Not Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-108	Dry throat	10Apr2020	Week 3	02Jun2020	1	Definitely Not Related	Possibly Related	No	No	Resolved
CH-A1-109	Vomiting	09Sep2020	Week 1	09Sep2020	1	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A1-109	Anaemia	24Nov2020	After week 9		2	Probably Not Related	Probably Not Related	No	No	Was persisting at last contact
CH-A1-109	Blood creatinine increased	11Sep2020	Week 1	14Sep2020	1	Probably Not Related	Probably Not Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	RT Causality	SAE	DLT	Outcome
CH-A1-109	Blood sodium decreased	14Sep2020	Week 2	06Oct2020	3	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A1-109	Nausea	16Sep2020	Week 2	25Sep2020	1	Probably Not Related	Probably Not Related	No	No	Resolved
CH-A1-109	Weight decreased	11Sep2020	Week 1	03Nov2020	1	Possibly Related	Possibly Related	No	No	Resolved
CH-A1-109	Insomnia	14Sep2020	Week 2	01Oct2020	1	Probably Not Related	Probably Not Related	No	No	Resolved
CH-A1-109	Lymphopenia	14Sep2020	Week 2	21Sep2020	2	Probably Not Related	Possibly Related	No	No	Worsened
CH-A1-109	Lymphopenia	21Sep2020	Week 3		3	Probably Not Related	Possibly Related	No	No	Was persisting at last contact
CH-A1-109	Oropharyngeal pain	25Sep2020	Week 3	27Sep2020	1	Probably Not Related	Probably Not Related	No	No	Resolved
CH-A1-110	Anaemia	11Jan2021	Screening		1	Definitely Not Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-110	Hypomagnesaemia	21Jan2021	Week 2	05Feb2021	1	Possibly Related	Possibly Related	No	No	Resolved
CH-A1-110	Rash maculo-papular	02Feb2021	Week 3	10Feb2021	3	Possibly Related	Possibly Related	Yes	No	Improved
CH-A1-110	Hyponatraemia	28Jan2021	Week 3	04Feb2021	3	Possibly Related	Probably Not Related	No	No	Resolved
CH-A1-110	Rash	10Feb2021	Week 5-9	17Feb2021	2	Possibly Related	Possibly Related	No	No	Improved
CH-A1-110	Rash	17Feb2021	Week 5-9		1	Probably Not Related	Probably Not Related	No	No	Was persisting at last contact
CH-A1-110	Dysphagia	13Jan2021	Week 1	26Jan2021	1	Definitely Not Related	Probably Related	No	No	Worsened

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	RT Causality	SAE	DLT	Outcome
CH-A1-110	Dysphagia	26Jan2021	Week 3		2	Definitely Not Related	Probably Related	No	No	Was persisting at last contact
CH-A1-110	Headache	11Jan2021	Week 1	11Jan2021	1	Probably Not Related	Possibly Related	No	No	Resolved
CH-A1-110	Rash generalised	18Jan2021	Week 2	22Jan2021	3	Probably Not Related	Possibly Related	No	No	Resolved
CH-A1-110	Rash generalised	22Jan2021	Week 2	26Dec2021	2	Probably Not Related	Possibly Related	No	No	Improved
CH-A1-110	Rash generalised	26Jan2021	Week 3		1	Possibly Related	Possibly Related	No	No	Was persisting at last contact
CH-A1-110	Dysphagia	26Jan2021	Week 3	28Jan2021	2	Definitely Not Related	Probably Related	No	No	Improved
CH-A1-110	Dysphagia	28Jan2021	Week 3		1	Probably Not Related	Probably Related	No	No	Was persisting at last contact
CH-A1-111	Dyspnoea	24Feb2021	Week 1		1	Probably Not Related	Probably Not Related	No	No	Was persisting at last contact
CH-A1-111	Rash maculo-papular	07Mar2021	Week 2	11Mar2021	3	Probably Related	Probably Related	No	No	Improved
CH-A1-111	Lymphocyte count	08Mar2021	Week 3		3	Possibly Related	Possibly Related	No	No	Was persisting at last contact
CH-A1-111	Rash maculo-papular	11Mar2021	Week 3	18Mar2021	1	Probably Related	Possibly Related	No	No	Resolved
CH-A1-111	Fatigue	12Mar2021	Week 3		1	Possibly Related	Probably Not Related	No	No	Was persisting at last contact
CH-A1-111	Arthralgia	12Mar2021	Week 3		1	Probably Not Related	Possibly Related	No	No	Was persisting at last contact

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	RT Causality	SAE	DLT	Outcome
CH-A1-112	Nausea	14Jun2021	Week 1	19Jun2021	1	Definitely Not Related	Definitely Related	No	No	Resolved
CH-A1-112	Transaminases increased	24Jun2021	Week 2		1	Possibly Related	Probably Not Related	No	No	Was persisting at last contact
CH-A1-112	Diarrhoea	16Jun2021	Week 1	17Jun2021	1	Probably Related	Probably Not Related	No	No	Resolved
CH-A1-112	Lacrimation increased	23Jun2021	Week 2	04Jul2021	1	Possibly Related	Definitely Not Related	No	No	Resolved
CH-A1-112	Abdominal pain upper	26Jun2021	Week 2		1	Probably Not Related	Probably Related	No	No	Was persisting at last contact
CH-A1-112	Vomiting	26Jun2021	Week 2	26Jun2021	1	Probably Not Related	Probably Related	No	No	Resolved
CH-A1-112	Eye pain	23Jun2021	Week 2	04Jul2021	1	Possibly Related	Definitely Not Related	No	No	Resolved
CH-A1-112	Dry skin	01Jul2021	Week 3	30Jul2021	1	Possibly Related	Possibly Related	No	No	Resolved
CH-A1-112	Decreased appetite	18Jun2021	Week 1		1	Probably Not Related	Possibly Related	No	No	Was persisting at last contact
CH-A1-112	Neuropathy peripheral	14Jun2021	Week 1		1	Possibly Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-113	Hypertension	13Jul2021	Week 1		2	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Was persisting at last contact
CH-A1-113	Constipation	15Jul2021	Week 1		2	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Was persisting at last contact
CH-A1-113	Dysphagia	31Jul2021	Week 3		1	Definitely Not Related	Definitely Not Related	No	N/A; Outside DLT period	Was persisting at last contact

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	RT Causality	SAE	DLT	Outcome
CH-A1-114	Dysphagia	28Sep2021	Week 1		2	Possibly Related	Possibly Related	No	No	Was persisting at last contact
CH-A1-114	Fatigue	13Oct2021	Week 3	19Oct2021	3	Possibly Related	Possibly Related	No	No	Resolved
CH-A1-114	Gastrostomy tube site complication	30Oct2021	Week 5-9	01Nov2021	3	Definitely Not Related	Definitely Not Related	Yes	No	Resolved
CH-A1-114	Nausea	30Sep2021	Week 1		1	Probably Related	Probably Related	No	No	Was persisting at last contact
CH-A1-114	Constipation	28Sep2021	Week 1	25Oct2021	3	Probably Not Related	Probably Not Related	Yes	No	Resolved
CH-A1-114	Blood urea increased	04Oct2021	Week 2	12Oct2021	1	Possibly Related	Probably Not Related	No	No	Resolved with sequelae
CH-A1-114	Blood urea increased	13Oct2021	Week 3	20Oct2021	3	Possibly Related	Probably Not Related	No	No	Resolved
CH-A1-114	Fatigue	13Oct2021	Week 3	20Oct2021	3	Possibly Related	Probably Not Related	No	No	Resolved with sequelae
CH-A1-114	Campylobacter infection	15Oct2021	Week 3		2	Possibly Related	Probably Not Related	No	No	Was persisting at last contact
CH-A1-114	Dehydration	14Oct2021	Week 3	19Oct2021	2	Possibly Related	Probably Not Related	No	No	Resolved
CH-A1-115	Erythema	26Oct2021	Week 1	26Oct2021	1	Definitely Related	Definitely Not Related	No	No	Resolved
CH-A1-115	Decreased appetite	29Oct2021	Week 1	01Nov2021	1	Possibly Related	Definitely Not Related	No	No	Resolved
CH-A1-115	Pain	26Oct2021	Week 1	26Oct2021	1	Definitely Related	Definitely Not Related	No	No	Resolved

Subject	Description	Start Date	Treatment Week	End Date	Grade	M6620 Causality	RT Causality	SAE	DLT	Outcome
CH-A1-115	Dysphagia	04Nov2021	Week 2	08Nov2021	1	Definitely Not Related	Probably Related	No	No	Resolved
CH-A1-115	Oesophagitis	12Nov2021	Week 3	23Dec2021	1	Definitely Not Related	Probably Related	No	No	Resolved
CH-A1-115	Rash	20Nov2021	Week 5-9	04Dec2021	1	Probably Not Related	Definitely Not Related	No	No	Resolved
CH-A1-116	Rash	13Jan2022	Week 1		3	Definitely Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-116	Headache	16Jan2022	Week 1	19Jan2022	1	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A1-116	Nausea	24Jan2022	Week 2		1	Possibly Related	Probably Not Related	No	No	Was persisting at last contact
CH-A1-116	Headache	26Jan2022	Week 3	25Feb2022	1	Definitely Not Related	Definitely Not Related	No	No	Resolved
CH-A1-116	Decreased appetite	07Feb2022	Week 4		1	Possibly Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-116	Sciatica	01Mar2022	Week 5-9	24Mar2022	2	Probably Not Related	Probably Not Related	No	No	Resolved
CH-A1-116	Rash	14Mar2022	Week 5-9		1	Definitely Related	Definitely Not Related	No	No	Was persisting at last contact
CH-A1-116	Arthralgia	24Mar2022	After week 9		3	Probably Not Related	Probably Not Related	No	No	Was persisting at last contact

Table 41: Worst graded Adverse Events for each patient

Subject	Grade	Description	Organ Class	M6620 Causality	RT Causality
CH-A1-101	1	Chills	General Disorders & Administration Site Conditions	Definitely Not Related	Definitely Not Related
CH-A1-101	1	Neuropathy peripheral	Nervous System Disorders	Definitely Not Related	Definitely Not Related
CH-A1-102	2	Chest pain	General Disorders & Administration Site Conditions	Definitely Not Related	Definitely Not Related
CH-A1-102	2	Nausea	Gastrointestinal Disorders	Possibly Related	Definitely Not Related
CH-A1-102	2	Fatigue	General Disorders & Administration Site Conditions	Probably Not Related	Possibly Related
CH-A1-103	2	Squamous cell carcinoma of skin	Neoplasms benign; malignant and unspecified	Definitely Not Related	Definitely Not Related
CH-A1-103	2	Urinary tract infection	Infections & Infestations	Definitely Not Related	Definitely Not Related
CH-A1-104	1	Dysphonia	Respiratory, thoracic and mediastinal disorders	Definitely Not Related	Definitely Not Related
CH-A1-104	1	Dysphagia	Gastrointestinal Disorders	Definitely Not Related	Definitely Not Related
CH-A1-104	1	Dyspnoea	Respiratory, thoracic and mediastinal disorders	Definitely Not Related	Definitely Not Related
CH-A1-105	3	Oesophagitis	Gastrointestinal Disorders	Definitely Not Related	Possibly Related
CH-A1-106	1	Arthralgia	Musculoskeletal & Connective Tissue Disorders	Definitely Not Related	Definitely Not Related
CH-A1-106	1	Cough	Respiratory, thoracic and mediastinal disorders	Probably Not Related	Probably Not Related
CH-A1-106	1	Arthralgia	Musculoskeletal & Connective Tissue Disorders	Definitely Not Related	Definitely Not Related
CH-A1-107	1	Oropharyngeal pain	Respiratory, thoracic and mediastinal disorders	Definitely Not Related	Definitely Not Related
CH-A1-107	1	Pyrexia	General Disorders & Administration Site Conditions	Definitely Not Related	Probably Not Related
CH-A1-107	1	Vomiting	Gastrointestinal Disorders	Definitely Related	Definitely Related
CH-A1-107	1	Cough	Respiratory, thoracic and mediastinal disorders	Definitely Related	Definitely Related
CH-A1-108	3	Lymphopenia	Blood & Lymphatic System Disorders	Possibly Related	Definitely Not Related
CH-A1-109	3	Blood sodium decreased	Investigations	Definitely Not Related	Definitely Not Related

Subject	Grade	Description	Organ Class	M6620 Causality	RT Causality
CH-A1-109	3	Lymphopenia	Blood & Lymphatic System Disorders	Probably Not Related	Possibly Related
CH-A1-110	3	Rash maculo-papular	Skin and subcutaneous tissue disorders	Possibly Related	Possibly Related
CH-A1-110	3	Hyponatraemia	Metabolism & Nutrition Disorders	Possibly Related	Probably Not Related
CH-A1-110	3	Rash generalised	Skin and subcutaneous tissue disorders	Probably Not Related	Possibly Related
CH-A1-111	3	Rash maculo-papular	Skin and subcutaneous tissue disorders	Probably Related	Probably Related
CH-A1-111	3	Lymphocyte count	Investigations	Possibly Related	Possibly Related
CH-A1-112	1	Nausea	Gastrointestinal Disorders	Definitely Not Related	Definitely Related
CH-A1-112	1	Transaminases increased	Investigations	Possibly Related	Probably Not Related
CH-A1-112	1	Diarrhoea	Gastrointestinal Disorders	Probably Related	Probably Not Related
CH-A1-112	1	Lacrimation increased	Eye disorders	Possibly Related	Definitely Not Related
CH-A1-112	1	Abdominal pain upper	Gastrointestinal Disorders	Probably Not Related	Probably Related
CH-A1-112	1	Vomiting	Gastrointestinal Disorders	Probably Not Related	Probably Related
CH-A1-112	1	Eye pain	Eye disorders	Possibly Related	Definitely Not Related
CH-A1-112	1	Dry skin	Skin and subcutaneous tissue disorders	Possibly Related	Possibly Related
CH-A1-112	1	Decreased appetite	Metabolism & Nutrition Disorders	Probably Not Related	Possibly Related
CH-A1-112	1	Neuropathy peripheral	Nervous System Disorders	Possibly Related	Definitely Not Related
CH-A1-113	2	Hypertension	Vascular disorders	Definitely Not Related	Definitely Not Related
CH-A1-113	2	Constipation	Gastrointestinal Disorders	Definitely Not Related	Definitely Not Related
CH-A1-114	3	Fatigue	General Disorders & Administration Site Conditions	Possibly Related	Possibly Related
CH-A1-114	3	Gastrostomy tube site complication	Injury; poisoning and procedural complications	Definitely Not Related	Definitely Not Related

Subject	Grade	Description	Organ Class	M6620 Causality	RT Causality
CH-A1-114	3	Constipation	Gastrointestinal Disorders	Probably Not Related	Probably Not Related
CH-A1-114	3	Blood urea increased	Investigations	Possibly Related	Probably Not Related
CH-A1-114	3	Fatigue	General Disorders & Administration Site Conditions	Possibly Related	Probably Not Related
CH-A1-115	1	Erythema	Skin and subcutaneous tissue disorders	Definitely Related	Definitely Not Related
CH-A1-115	1	Decreased appetite	Metabolism & Nutrition Disorders	Possibly Related	Definitely Not Related
CH-A1-115	1	Pain	General Disorders & Administration Site Conditions	Definitely Related	Definitely Not Related
CH-A1-115	1	Dysphagia	Gastrointestinal Disorders	Definitely Not Related	Probably Related
CH-A1-115	1	Oesophagitis	Gastrointestinal Disorders	Definitely Not Related	Probably Related
CH-A1-115	1	Rash	Skin and subcutaneous tissue disorders	Probably Not Related	Definitely Not Related
CH-A1-116	3	Rash	Skin and subcutaneous tissue disorders	Definitely Related	Definitely Not Related
CH-A1-116	3	Arthralgia	Musculoskeletal & Connective Tissue Disorders	Probably Not Related	Probably Not 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.

7.11 Appendix – Radiotherapy Trials Quality Assurance (RTTQA) Summary

Attached overleaf is the RTTQA summary for CHARIOT A1.

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.

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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

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*There are no relationships/conditions/circumstances that present an actual or potential conflict of interest
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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

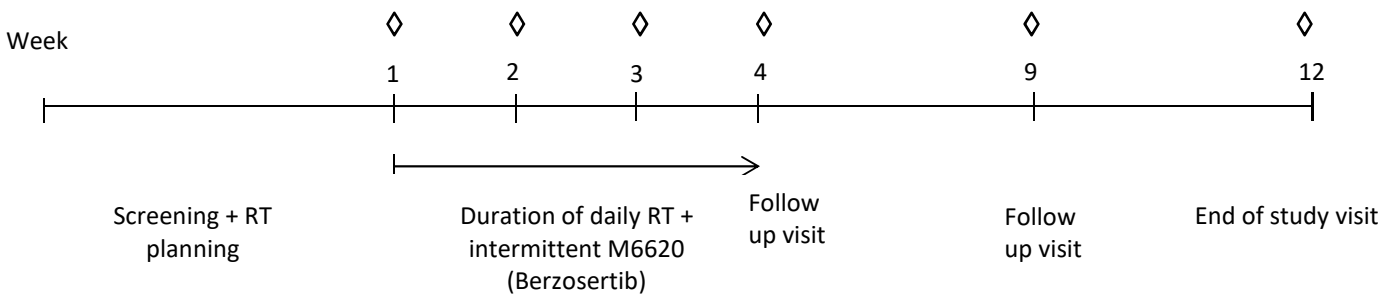
[11] On treatment biopsy/blood sample should be done from radiotherapy fraction 3 to fraction 5 (but up to fraction 7 is permitted if required)

[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

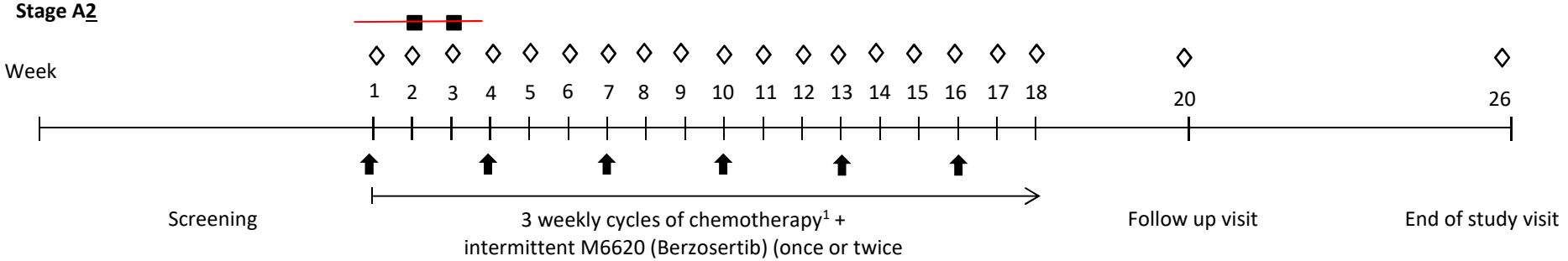
Study Flow Charts

Stage A1



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

Stage A2

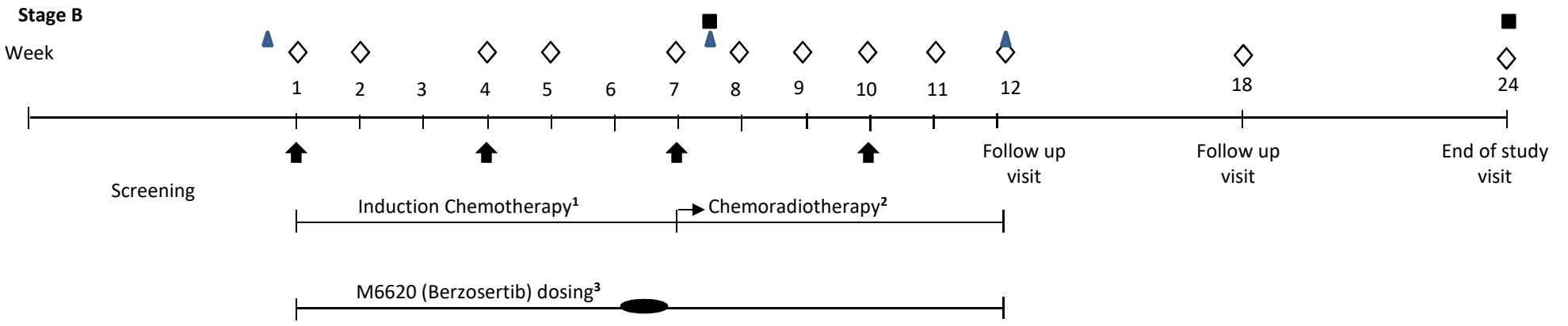


◊ Clinical review and assessment of toxicity before each M6620 (Berzosertib) administration, and

⬆ 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.

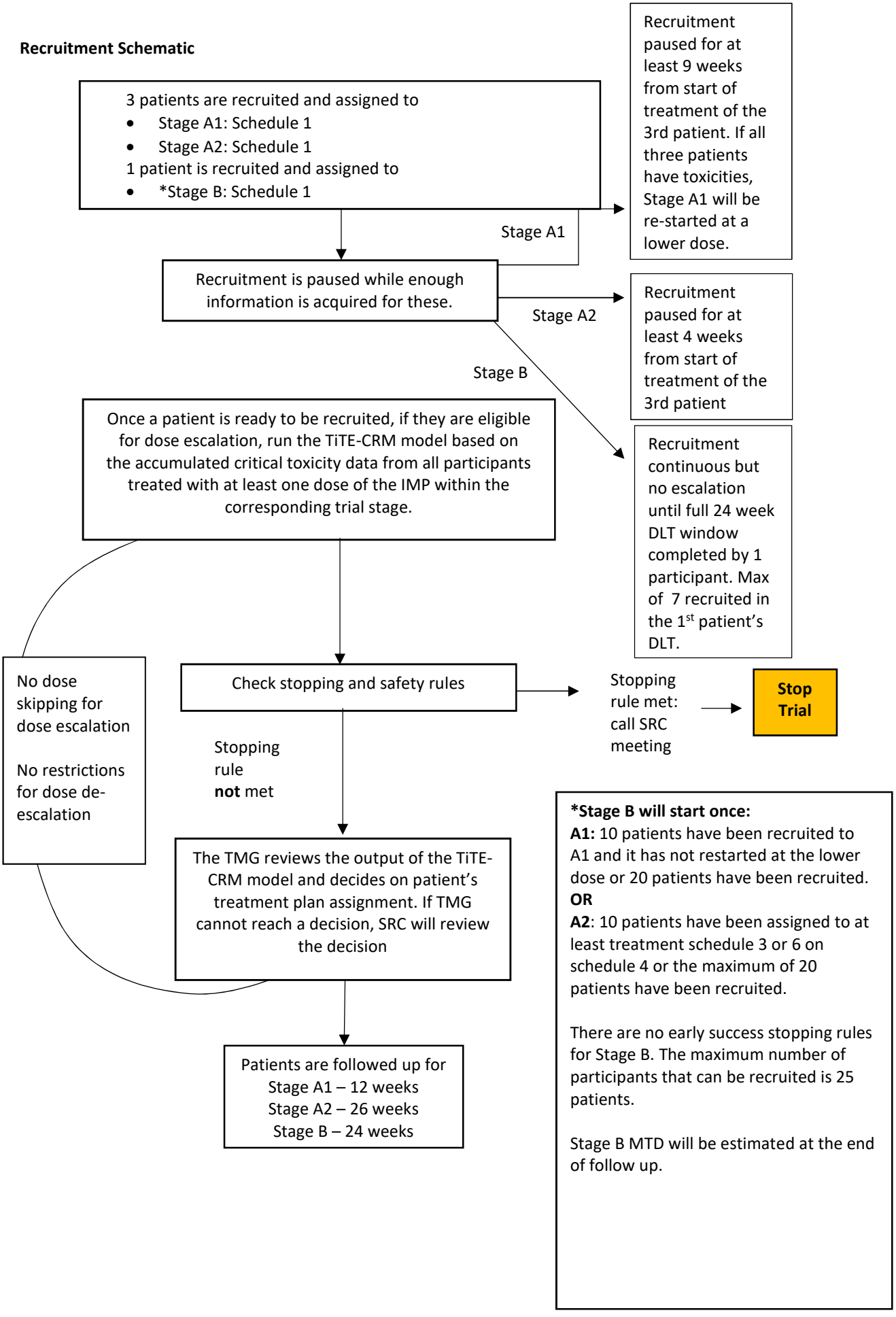
2.4 Duration of patient participation

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

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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.

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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

$$w_j = \begin{cases} 1 \text{ if } y_j = 1 \\ \frac{1}{2}\left(\frac{u_j}{T} + \frac{v_j}{D}\right) \text{ if } y_j = 0 \end{cases}$$

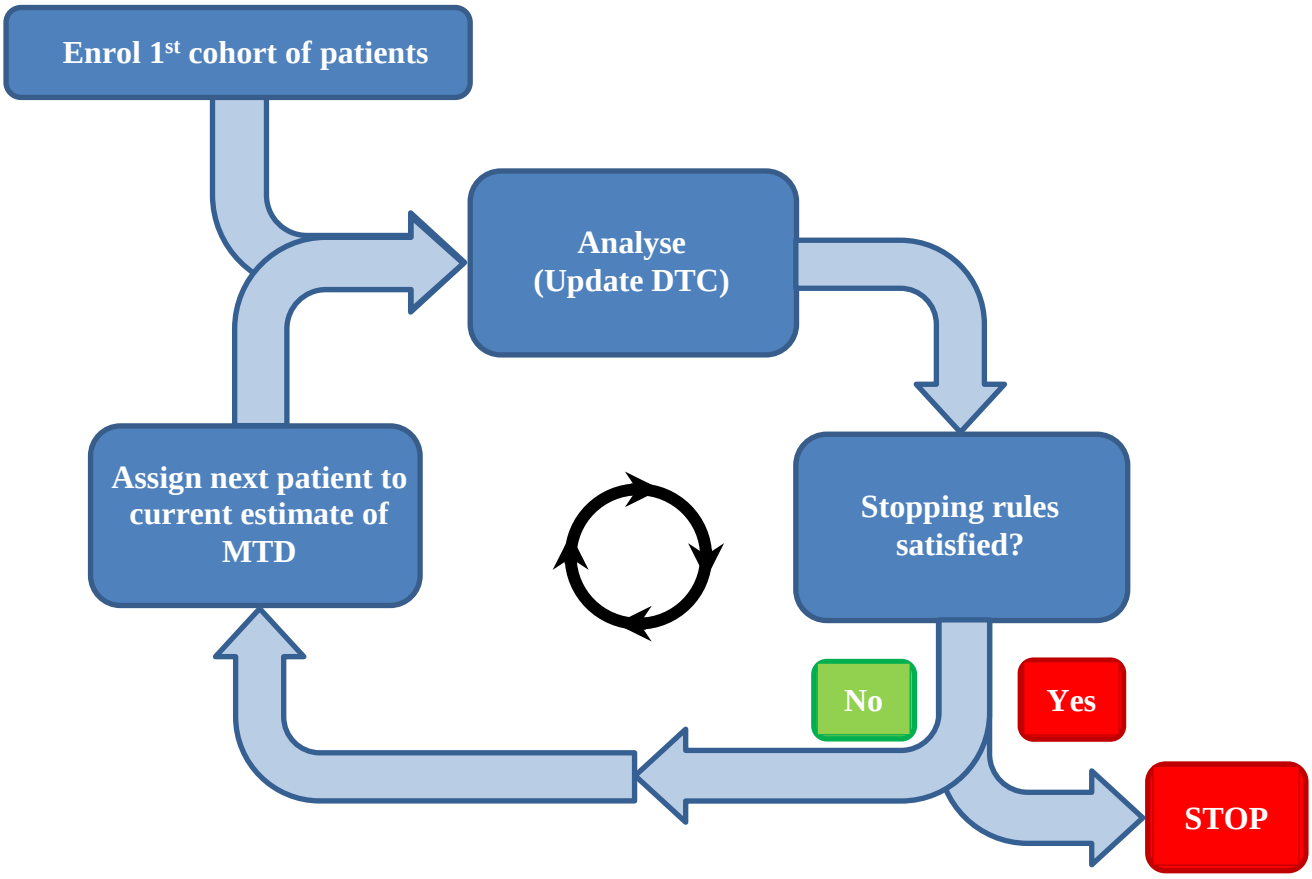
and the posterior expected toxicity at each dose (posterior dose-toxicity curve) is given by

$$\hat{\pi}_k = E(g_k(\alpha)|y) = \int_{-\infty}^{\infty} g_k(\alpha) p(\alpha|y) d\alpha$$

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.

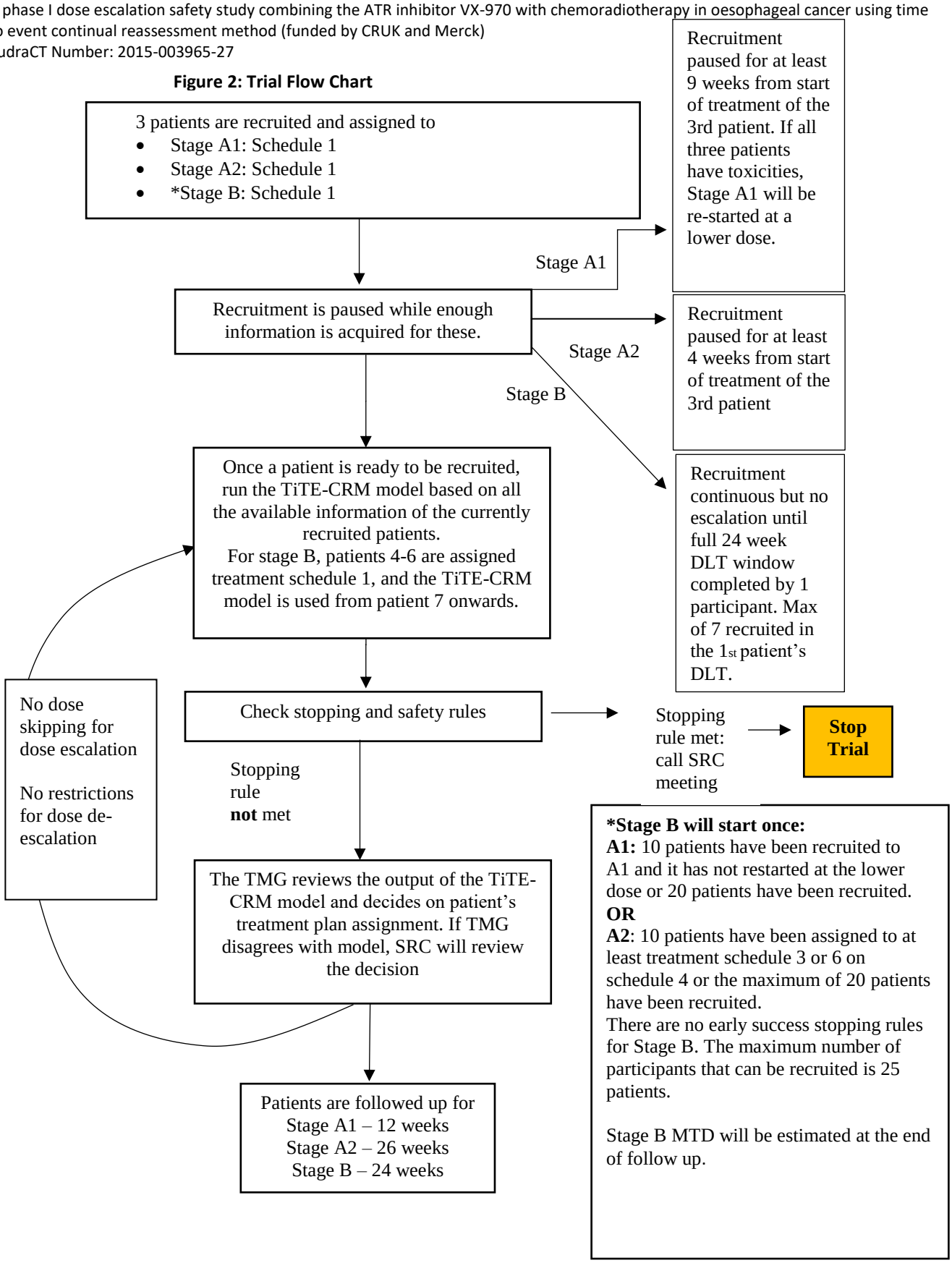
Table 1: Design features for all stages of the study

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.

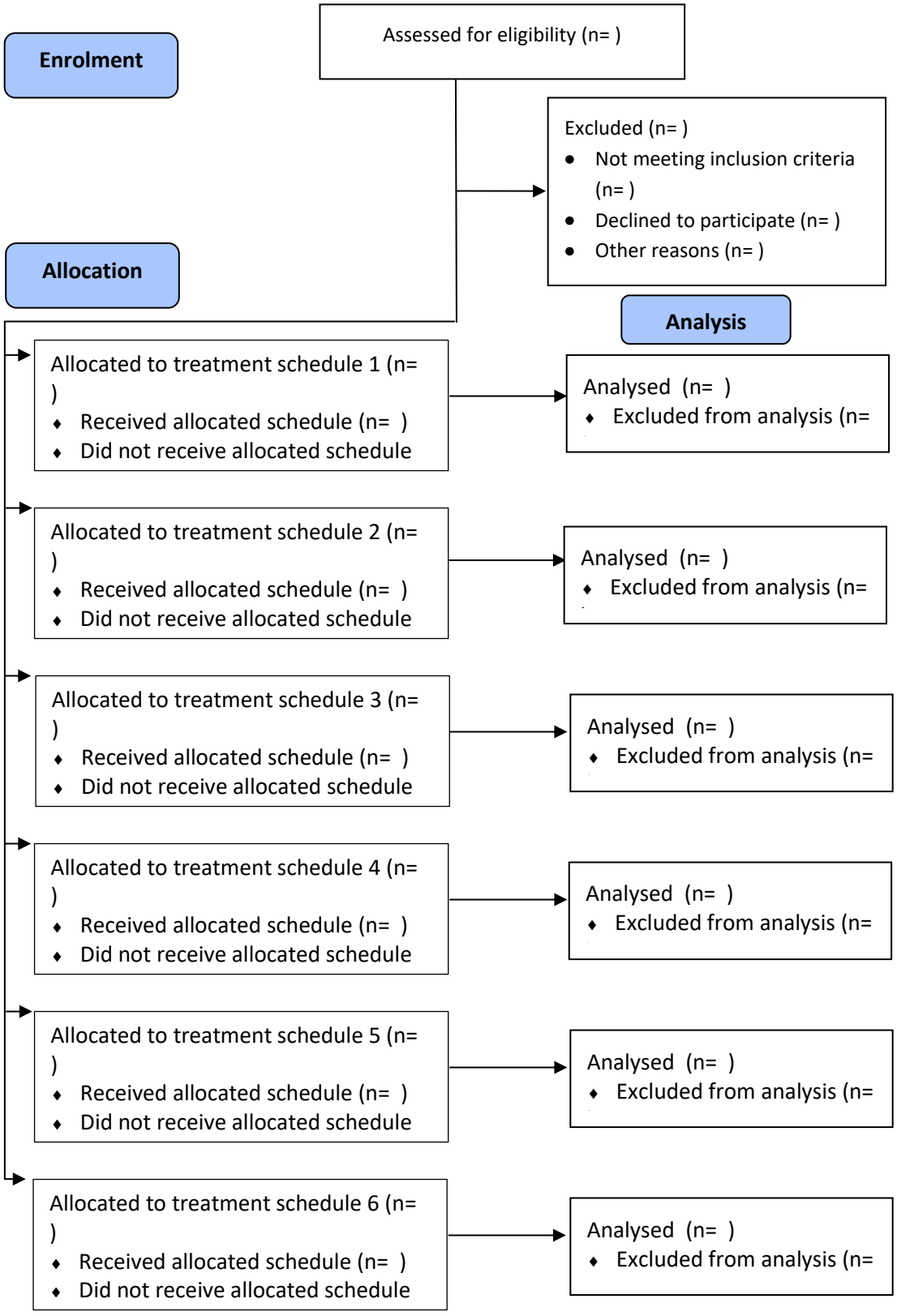
6. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

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

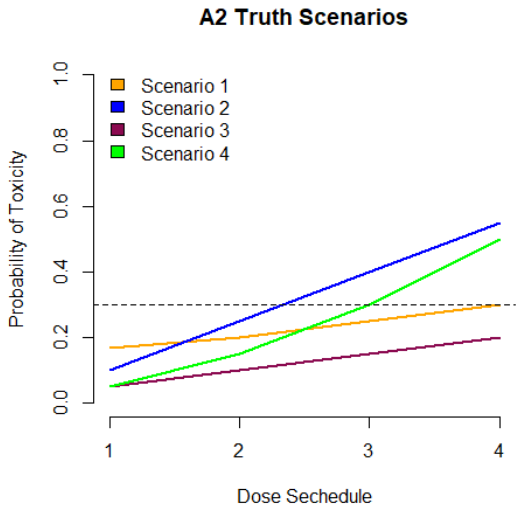
All results in this section have been derived using Version 3.6.1 of R and Version 3.2.3 of OpenBUGS. Code for the results presented here can be found in the sTMF for CHARIOT. "Z:\CSM_CHARIOT\Statistical Analysis\Design\Simulations\PriorsReview_Apr2020".

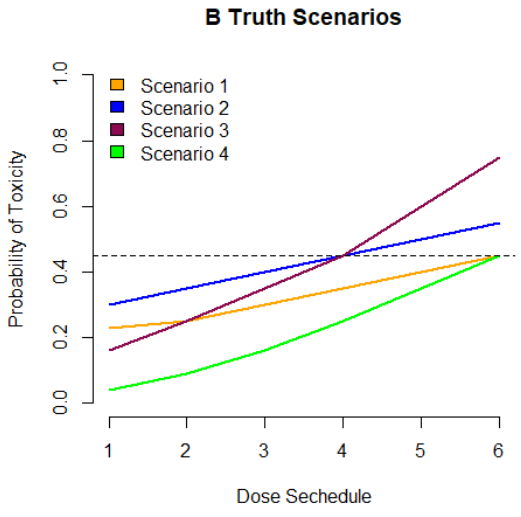
Introduction

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:

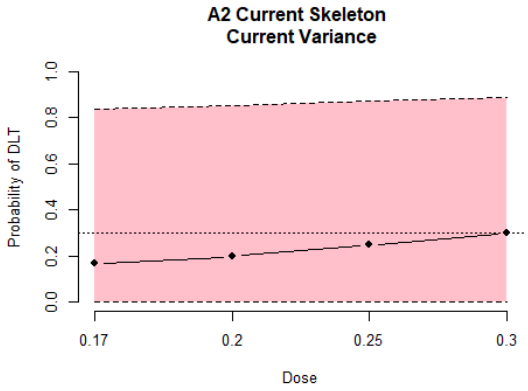
- The current one in use
- A steep skeleton
- A very steep skeleton.
- A coherent skeleton from the "getprior" function from the dfcrm package with dose 4 as the prior guess of the MTD
- A coherent skeleton from the "getprior" function from the dfcrm package with dose 3 as the prior guess of the MTD

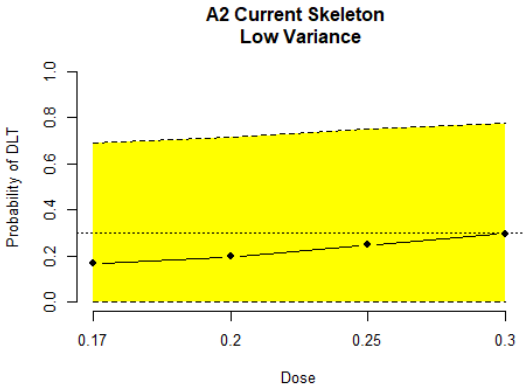
The variances we will use are:

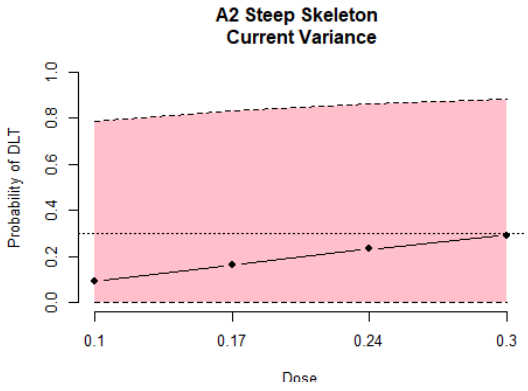
- the original 1.158^2
- a lower variance of 0.8^2.

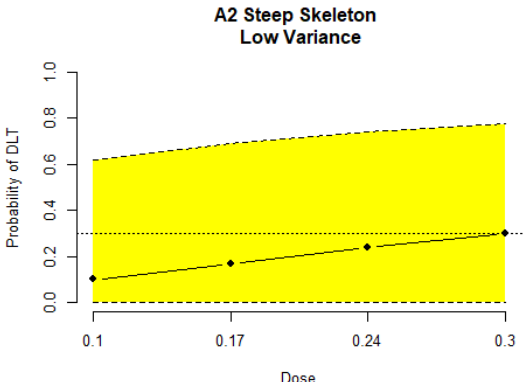
We will look at each combination of these skeletons and variacnce meaning there are 10 priors in total to be examined for A2.

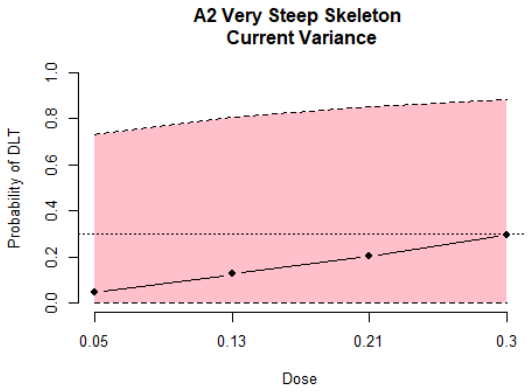
	1	2	3	4
Current Skeleton	0.17	0.2	0.25	0.3
Steep Skeleton	0.1	0.17	0.24	0.3
Very Steep Skeleton	0.05	0.13	0.21	0.3
Coherent Skeleton	0.01	0.05	0.15	0.3
Coherent Toxic Skeleton	0.05	0.15	0.3	0.46


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
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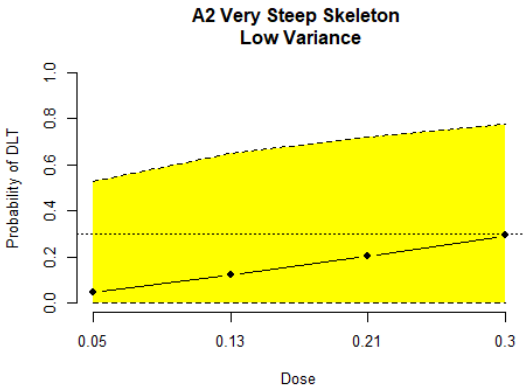
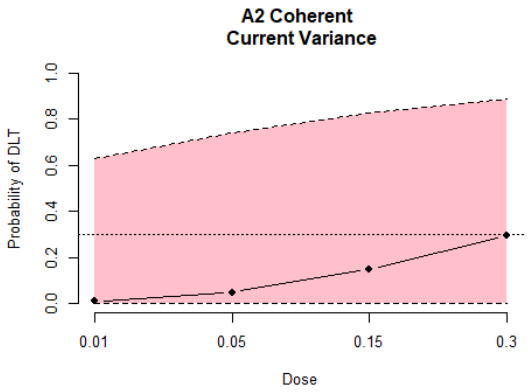
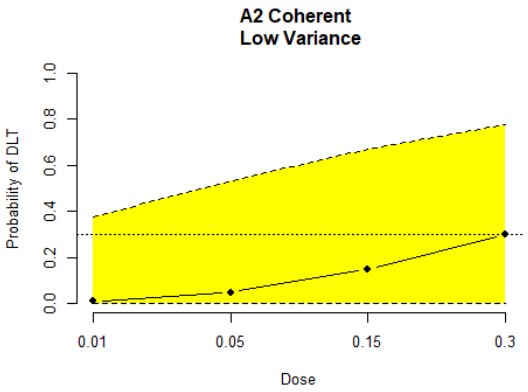
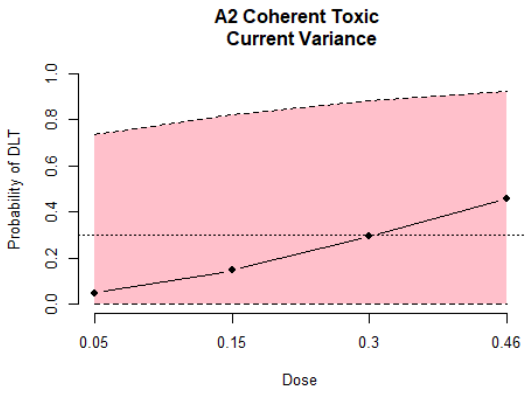
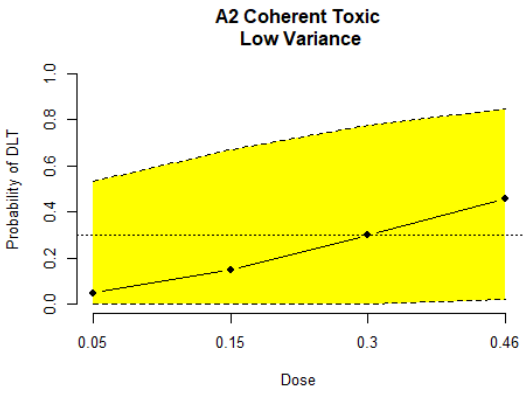
0.2
0.4
0.6
0.8
1.0
0.05
0.13
0.21
0.3
Dose


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

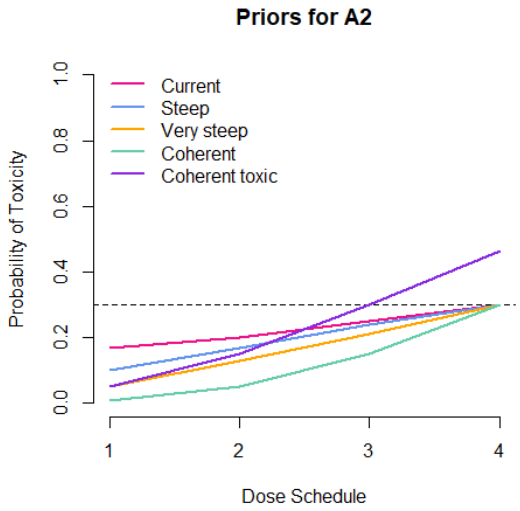
	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	23.5	20.6	20.2	35.7	42.4	20.6	17.5	19.5	18	17.43
Scenario 2	20.9	47.8	20.9	10.4	35.2	33.5	20.7	10.6	29.5	19.07
Scenario 3	0.8	6.3	17.4	75.5	26.5	15	20.3	38.2	9.2	14.53
Scenario 4	3.3	29.3	41.6	25.8	24.2	26.7	29.4	19.7	22.2	18.05

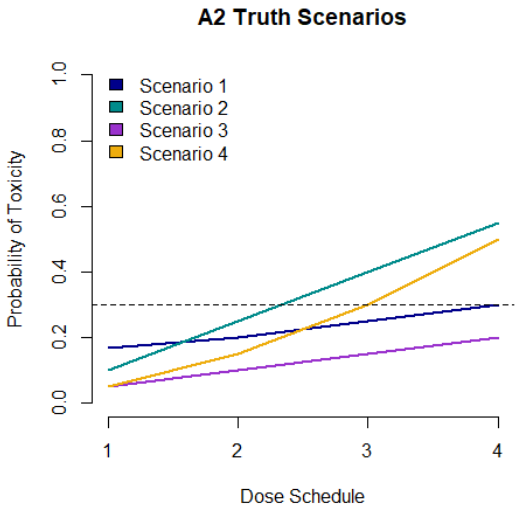
"Toxic" Coherent Skeleton, Original Variance

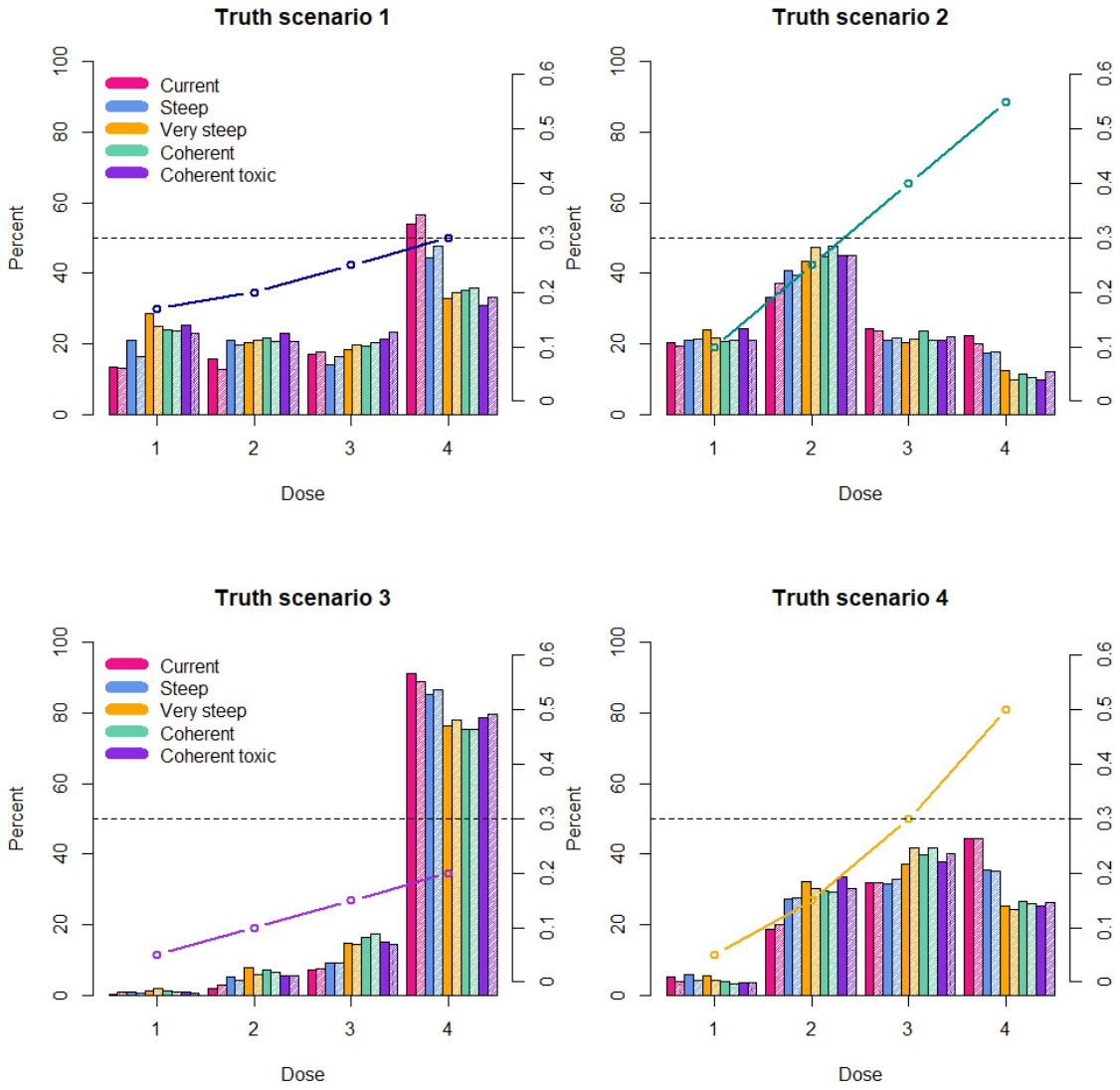
	% Recommendation				% Treated				% DLT	Av. Trial Size
Schedule	1	2	3	4	1	2	3	4		
Scenario 1	25.3	22.8	21.2	30.7	44	20.8	17.5	17.7	19.8	17.69
Scenario 2	24.2	45	20.9	9.9	36.3	33.5	19.7	10.4	30.6	19.18
Scenario 3	0.7	5.6	15.1	78.6	26.2	14.6	19.6	39.6	8.4	14.23
Scenario 4	3.5	33.5	37.9	25.1	23.9	26.7	29.2	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.

CHARIOT Radiotherapy Quality Assurance Summary (Stage A1)

Patients recruited to Stage A1 of CHARIOT were prescribed a radiotherapy dose of 35Gy in 15 fractions. Approval from the Radiotherapy Trials Quality Assurance (RTTQA) group was required for centres to recruit to Stage A1 of CHARIOT. This report summarises the radiotherapy quality assurance programme for patients within the trial.

Pre-Trial Quality Assurance

RTTQA approval for participation in CHARIOT was streamlined based on the completion of pre-trial benchmarking exercises for SCOPE2 or NeoSCOPE, to reduce the barriers to centres opening to the trial as far as possible. In all, five radiotherapy centres were given RTTQA approval through the streamlining process.

The use of 4DCT was permitted for use within CHARIOT, with streamlined approval based on the completion of the corresponding pre-trial benchmarking exercises for SCOPE2 or NeoSCOPE.

Table 1 summarises the QA status of each centre participating in Stage A1 of CHARIOT.

Table 1: Summary of Pre-Trial Quality Assurance Approvals for Centres Participating in CHARIOT Stage A1

Centre Name	**SCOPE2 Centre #**	**Lower-third Outlining Status**	**Lower 3rd 4DCT Outlining Status**	**Planning Exercise Status**
Oxford, Churchill	121	Approved (NeoSCOPE)	Approved (NeoSCOPE)	Approved (SCOPE2)
Glasgow, Beatson	067	Approved (SCOPE2)	Approved (SCOPE2)	Approved (SCOPE2)
Leeds, St James	182	Approved (NeoSCOPE)	Approved (SCOPE2)	Approved (SCOPE2)
Cardiff, Velindre	001	Approved (SCOPE2)	Approved (SCOPE2)	Approved (SCOPE2)
Manchester, Christie	006	Approved (SCOPE2)	Approved (SCOPE2)	Approved (SCOPE2)

On-Trial Quality Assurance

The radiotherapy plan data for all patients recruited to Stage A1 of CHARIOT were subject to timely retrospective review. RTTQA reviewers assessed the delineation of target volumes and organs at risk, as well as the final treatment plan, with feedback given to the recruiting centre in advance of the 10th treatment fraction.

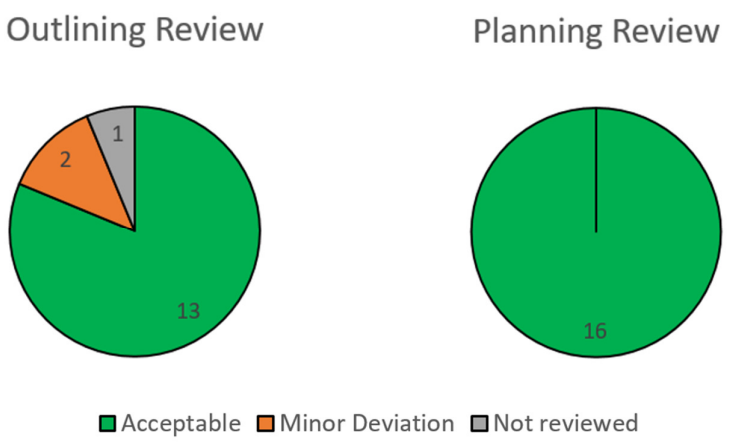


Figure 1: QA Outcome for outlining and planning review for on-trial patients in Stage A1

Figure 1 summarises the outcomes of the on-trial reviews for the 16 patients recruited to Stage A1. Minor deviations from protocol were recorded for 2 cases. Both deviations were related to the incorrect growth of margins for target volumes.

One case was not reviewed within the agreed timescales due to the availability of clinical staff to review the case. Arrangements were made for cross-cover to reduce the likelihood of this reoccurring.

Radiotherapy treatment plan review found all 16 cases met the dose objectives for the trial, and displayed an acceptable dose distribution. Centres used the CHARIOT Plan Assessment Form (PAF) to submit dose-volume histogram (DVH) data for each patient recruited to Stage A1 of the trial. The reported DVH statistics were independently verified as part of the plan review process. Table 2 summarises the data submitted for all 16 patients recruited to Stage A1 of CHARIOT.

Conclusion

The CHARIOT RTTQA programme verified that the delineation of target volumes and organs at risk, as well as the optimisation of the radiotherapy treatment plan met the specifications laid out in the CHARIOT trial protocol. Deviations from protocol were recorded in 12.5% of on-trial cases, emphasising the need for ongoing quality assurance checks in radiotherapy clinical trials.

Table 2: DVH statistics reported through plan assessment forms for each on-trial patient

Patient number	GTV Volume (cm^3)	PTV Volume (cm^3)	PTV D99% (Gy)	PTV V95% (%)	External D1.8cc (%)	SpinalCord_PRV D0.1cc (Gy)	Heart Dmean (Gy)	Heart V28Gy (%)	Lungs Dmean (Gy)	Lungs V18Gy (%)	Liver Dmean (Gy)	Liver V28Gy (%)	Kidney_L V18Gy (%)	Kidney_R V18Gy (%)
CH-A1-101	107.7	642.7	33.5	99.5	103.1	30.8	18.3	13.5	10.6	11.1	8.0	13.5	0.0	0.0
CH-A1-102	23.4	257.8	33.7	100.0	103.3	26.8	13.6	11.8	3.0	4.7	3.8	2.6	0.0	0.0
CH-A1-103	75.0	548.3	33.8	99.9	103.3	27.0	17.8	10.8	8.0	8.2	12.8	7.1	Not outlined	0.0
CH-A1-104	109.1	563.9	33.9	99.9	104.8	32.3	20.0	18.8	8.6	12.2	0.9	0.0	0.0	0.0
CH-A1-105	12.4	222.9	34.0	99.5	105.7	34.5	0.1	0.0	3.1	4.5	0.0	0.0	0.0	0.0
CH-A1-106	56.5	417.2	34.8	100.0	105.0	27.4	16.3	12.1	9.0	12.3	8.3	2.3	0.0	0.0
CH-A1-107	51.3	377.0	33.3	99.1	104.9	24.3	9.6	7.1	8.4	6.3	0.6	0.0	Not outlined	Not outlined
CH-A1-108	63.1	482.8	31.8	91.7	104.9	32.9	5.2	5.6	8.7	11.7	Not outlined	Not outlined	Not outlined	Not outlined
CH-A1-109	283.7	912.7	33.6	99.7	103.8	27.7	12.4	11.0	3.9	2.2	12.4	4.8	0.0	0.0
CH-A1-110	65.3	408.8	32.3	95.6	104.1	30.6	6.2	2.7	8.9	10.3	0.4	0.0	Not outlined	Not outlined
CH-A1-111	39.7	375.2	33.4	99.5	104.3	23.5	15.9	10.2	6.5	7.5	5.8	1.4	0.0	0.0
CH-A1-112	74.8	462.1	33.5	99.6	104.6	24.1	13.4	5.4	8.9	7.2	8.4	1.7	Not outlined	Not outlined
CH-A1-113	124.4	690.7	34.1	100.0	106.3	24.5	15.9	7.9	8.1	11.4	7.1	1.7	0.0	0.0
CH-A1-114	43.5	396.1	33.4	99.2	104.4	30.6	18.5	22.5	8.4	6.7	Not outlined	Not outlined	Not outlined	Not outlined
CH-A1-115	30.2	350.0	34.1	98.7	101.8	27.4	14.4	7.5	8.9	7.1	6.3	1.5	Not outlined	Not outlined
CH-A1-116	48.1	352.1	33.3	99.2	103.8	18.0	9.8	5.4	4.9	5.1	11.0	3.5	Not outlined	Not outlined