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

Summary

EudraCT number	2015-003965-27
Trial protocol	GB
Global end of trial date	04 April 2022

Results information

Result version number	v1 (current)
This version publication date	08 April 2023
First version publication date	08 April 2023
Summary attachment (see zip file)	Stage A1 Full Results (CHARIOT_StatisticalReportA1_Final_V2.0_20Dec2022.pdf) Stage A2 Full Results (CHARIOT_StatisticalReportA2_Final_V2.0_20Dec2022.pdf)

Trial information

Trial identification

Sponsor protocol code	OCTO-072

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03641547
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Research Governance, Ethics & Assurance, Boundary Brook House, Churchill Drive, Headington , Oxford, United Kingdom, OX3 7GB
Public contact	CHARIOT Trial Manager, Oncology Clinical Trials Office, University of Oxford, +44 1865617018, octo-CHARIOT@oncology.ox.ac.uk
Scientific contact	CHARIOT Trial Manager, Oncology Clinical Trials Office, University of Oxford, +44 1865617018, octo-CHARIOT@oncology.ox.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2022
Global end of trial reached?	Yes
Global end of trial date	04 April 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Stage A1: to find the best tolerated dose of the drug M6620 in combination with palliative radiotherapy in patients with oesophageal cancer.

Stage A2: to find the best tolerated dose of the drug M6620 in combination with palliative cisplatin/capecitabine chemotherapy in patients with advanced solid tumours.

Stage B: to find the best tolerated M6620 treatment schedule in combination with curative chemoradiotherapy in patients with oesophageal cancer.

Protection of trial subjects:

The protocol was conducted in compliance with the UK Clinical Trials Regulations, the Principles of Good Clinical Practice (GCP) 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 investigational medicinal products under the European Union Clinical Trials Directive.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 36
Worldwide total number of subjects	36
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	18
From 65 to 84 years	17
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Stage A1 (cohort 1): 16 patients were recruited between 17May2019 and 05Jan2022.
Stage A2 (cohort 2): 20 patients were recruited between 28Dec2018 and 18Aug2021.
Stage B: 0 patients were recruited to this cohort due to lack of funding available.

Pre-assignment

Screening details:

Stage A1 (cohort 1): 16 patients were recruited between 17May2019 and 05Jan2022.
Stage A2 (cohort 2): 20 patients were recruited between 28Dec2018 and 18Aug2021.
Stage B: 0 patients were recruited to this cohort due to lack of funding available.

Period 1

Period 1 title	Stage A1 & Stage A2 (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	A2 - Dose level 1

Arm description:

Cisplatin/capecitabine + M6620 (Berzosertib) administered at 90 mg/m2 once a week for 18 weeks.

Arm type	Experimental
Investigational medicinal product name	M6620 (Berzosertib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

M6620 (Berzosertib) administered IV at 90 mg/m2 once a week for 18 weeks.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Cisplatin was administered at 60mg/m2 IV on day 1 of each 21-day cycle for 6 cycles.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was administered at 625mg/m2 PO BD on days 1-21 of a 21-day cycle for 6 cycles.

Arm title	A2 - Dose level 2

Arm description:

Cisplatin/capecitabine + M6620 (Berzosertib) administered at 90 mg/m2 twice a week for 18 weeks.

Arm type	Experimental

Investigational medicinal product name	M6620 (Berzosertib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:
M6620 (Berzosertib) administered IV at 90 mg/m2 twice a week for 18 weeks.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:
Cisplatin was administered at 60mg/m2 IV on day 1 of each 21-day cycle for 6 cycles.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Capecitabine was administered at 625mg/m2 PO BD on days 1-21 of a 21-day cycle for 6 cycles.

Arm title	A2 - Dose level 3

Arm description:
Cisplatin/capecitabine + M6620 (Berzosertib) administered at 140 mg/m2 once a week for 18 weeks.

Arm type	Experimental
Investigational medicinal product name	M6620 (Berzosertib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:
M6620 (Berzosertib) administered IV at 140 mg/m2 once a week for 18 weeks.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:
Cisplatin was administered at 60mg/m2 IV on day 1 of each 21-day cycle for 6 cycles.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Capecitabine was administered at 625mg/m2 PO BD on days 1-21 of a 21-day cycle for 6 cycles.

Arm title	A2 - Dose level 4

Arm description:
Cisplatin/capecitabine + M6620 (Berzosertib) administered at 140 mg/m2 twice a week for 18 weeks.

Arm type	Experimental

Investigational medicinal product name	M6620 (Berzosertib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

M6620 (Berzosertib) administered IV at 140 mg/m2 twice a week for 18 weeks.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Cisplatin was administered at 60mg/m2 IV on day 1 of each 21-day cycle for 6 cycles.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was administered at 625mg/m2 PO BD on days 1-21 of a 21-day cycle for 6 cycles.

Arm title	A1 - Dose level 1

Arm description:

Radiotherapy + M6620 (Berzosertib) administered at 140 mg/m2 on days 2, 9, 16.

Arm type	Experimental
Investigational medicinal product name	M6620 (Berzosertib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

M6620 (Berzosertib) administered IV at 140 mg/m2 on days 2, 9, 16.

Arm title	A1 - Dose level 2

Arm description:

Radiotherapy + M6620 (Berzosertib) administered at 140 mg/m2 on days 2, 5, 9, 12, 16.

Arm type	Experimental
Investigational medicinal product name	M6620 (Berzosertib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

M6620 (Berzosertib) administered IV at 140 mg/m2 on days 2, 5, 9, 12, 16.

Arm title	A1 - Dose level 3

Arm description:

Radiotherapy + M6620 (Berzosertib) administered at 140 mg/m2 on days 2, 5, 9, 12, 16, 19.

Arm type	Experimental

Investigational medicinal product name	M6620 (Berzosertib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

M6620 (Berzosertib) administered IV at 140 mg/m2 on days 2, 5, 9, 12, 16, 19.

Arm title	A1 - Dose level 4

Arm description:

Radiotherapy + M6620 (Berzosertib) administered at 240 mg/m2 on days 2, 9, 16.

Arm type	Experimental
Investigational medicinal product name	M6620 (Berzosertib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

M6620 (Berzosertib) administered IV at 240 mg/m2 on days 2, 9, 16.

Arm title	A1 - Dose level 5

Arm description:

Radiotherapy + M6620 (Berzosertib) administered at 240 mg/m2 on days 2, 5, 9, 12, 16.

Arm type	Experimental
Investigational medicinal product name	M6620 (Berzosertib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

M6620 (Berzosertib) administered IV at 240 mg/m2 on days 2, 5, 9, 12, 16.

Arm title	A1 - Dose level 6

Arm description:

Radiotherapy + M6620 (Berzosertib) administered at 240 mg/m2 on days 2, 5, 9, 12, 16, 19.

Arm type	Experimental
Investigational medicinal product name	M6620 (Berzosertib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

M6620 (Berzosertib) administered IV at 240 mg/m2 on days 2, 5, 9, 12, 16, 19.

Number of subjects in period 1	A2 - Dose level 1	A2 - Dose level 2	A2 - Dose level 3
Started	5	1	9
Completed	2	1	4
Not completed	3	0	5
Patient decision	1	-	-
Disease progression	1	-	3
Adverse event, non-fatal	-	-	2
Did not start treatment	1	-	-

Number of subjects in period 1	A2 - Dose level 4	A1 - Dose level 1	A1 - Dose level 2
Started	5	3	1
Completed	3	3	1
Not completed	2	0	0
Patient decision	-	-	-
Disease progression	1	-	-
Adverse event, non-fatal	-	-	-
Did not start treatment	1	-	-

Number of subjects in period 1	A1 - Dose level 3	A1 - Dose level 4	A1 - Dose level 5
Started	1	1	1
Completed	1	1	1
Not completed	0	0	0
Patient decision	-	-	-
Disease progression	-	-	-
Adverse event, non-fatal	-	-	-
Did not start treatment	-	-	-

Number of subjects in period 1	A1 - Dose level 6
Started	9
Completed	9
Not completed	0
Patient decision	-
Disease progression	-
Adverse event, non-fatal	-
Did not start treatment	-

Baseline characteristics

Reporting groups	
Reporting group title	A2 - Dose level 1
Reporting group description: Cisplatin/capecitabine + M6620 (Berzosertib) administered at 90 mg/m2 once a week for 18 weeks.	
Reporting group title	A2 - Dose level 2
Reporting group description: Cisplatin/capecitabine + M6620 (Berzosertib) administered at 90 mg/m2 twice a week for 18 weeks.	
Reporting group title	A2 - Dose level 3
Reporting group description: Cisplatin/capecitabine + M6620 (Berzosertib) administered at 140 mg/m2 once a week for 18 weeks.	
Reporting group title	A2 - Dose level 4
Reporting group description: Cisplatin/capecitabine + M6620 (Berzosertib) administered at 140 mg/m2 twice a week for 18 weeks.	
Reporting group title	A1 - Dose level 1
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 140 mg/m2 on days 2, 9, 16.	
Reporting group title	A1 - Dose level 2
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 140 mg/m2 on days 2, 5, 9, 12, 16.	
Reporting group title	A1 - Dose level 3
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 140 mg/m2 on days 2, 5, 9, 12, 16, 19.	
Reporting group title	A1 - Dose level 4
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 240 mg/m2 on days 2, 9, 16.	
Reporting group title	A1 - Dose level 5
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 240 mg/m2 on days 2, 5, 9, 12, 16.	
Reporting group title	A1 - Dose level 6
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 240 mg/m2 on days 2, 5, 9, 12, 16, 19.	

Reporting group values	A2 - Dose level 1	A2 - Dose level 2	A2 - Dose level 3
Number of subjects	5	1	9
Age categorical Units: Subjects			
Adults (18-64 years)	3	1	3
From 65-84 years	2	0	6
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	2	0	6
Male	3	1	3

Ethnicity Units: Subjects			
White British	5	1	9
Smoking status Units: Subjects			
Ex-smoker	1	1	4
Never smoked	3	0	5
Current smoker	1	0	0
Locoregional Disease Units: Subjects			
Yes	1	0	6
No	4	1	3
Distant Metastases Units: Subjects			
Yes	5	1	8
No	0	0	1
Prior Radiotherapy Units: Subjects			
Yes	4	1	9
No	1	0	0
Prior Systemic Treatment Units: Subjects			
Yes	4	1	9
No	1	0	0
Tumour grade Units: Subjects			
Well differentiated (G1)	0	0	1
Moderately differentiated (G2)	1	1	3
Poorly differentiated (G3)	4	0	0
Unknown or cannot be assessed (GX)	0	0	5

Reporting group values	A2 - Dose level 4	A1 - Dose level 1	A1 - Dose level 2
Number of subjects	5	3	1
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	0
From 65-84 years	2	0	1
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	3	0	0
Male	2	3	1
Ethnicity Units: Subjects			
White British	5	3	1
Smoking status Units: Subjects			
Ex-smoker	3	2	1
Never smoked	2	1	0
Current smoker	0	0	0

Locoregional Disease Units: Subjects			
Yes	3	3	1
No	2	0	0
Distant Metastases Units: Subjects			
Yes	5	1	0
No	0	2	1
Prior Radiotherapy Units: Subjects			
Yes	5	0	0
No	0	3	1
Prior Systemic Treatment Units: Subjects			
Yes	5	2	0
No	0	1	1
Tumour grade Units: Subjects			
Well differentiated (G1)	0	1	0
Moderately differentiated (G2)	0	1	0
Poorly differentiated (G3)	3	0	1
Unknown or cannot be assessed (GX)	2	1	0

Reporting group values	A1 - Dose level 3	A1 - Dose level 4	A1 - Dose level 5
Number of subjects	1	1	1
Age categorical Units: Subjects			
Adults (18-64 years)	1	1	1
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	1	0
Male	1	0	1
Ethnicity Units: Subjects			
White British	1	1	1
Smoking status Units: Subjects			
Ex-smoker	1	0	1
Never smoked	0	1	0
Current smoker	0	0	0
Locoregional Disease Units: Subjects			
Yes	1	1	1
No	0	0	0
Distant Metastases Units: Subjects			
Yes	0	1	0
No	1	0	1

Prior Radiotherapy Units: Subjects			
Yes	0	0	0
No	1	1	1
Prior Systemic Treatment Units: Subjects			
Yes	1	1	1
No	0	0	0
Tumour grade Units: Subjects			
Well differentiated (G1)	0	0	0
Moderately differentiated (G2)	0	0	0
Poorly differentiated (G3)	1	1	1
Unknown or cannot be assessed (GX)	0	0	0

Reporting group values	A1 - Dose level 6	Total	
Number of subjects	9	36	
Age categorical Units: Subjects			
Adults (18-64 years)	2	18	
From 65-84 years	6	17	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	1	13	
Male	8	23	
Ethnicity Units: Subjects			
White British	9	36	
Smoking status Units: Subjects			
Ex-smoker	6	20	
Never smoked	3	15	
Current smoker	0	1	
Locoregional Disease Units: Subjects			
Yes	6	23	
No	3	13	
Distant Metastases Units: Subjects			
Yes	4	25	
No	5	11	
Prior Radiotherapy Units: Subjects			
Yes	8	27	
No	1	9	
Prior Systemic Treatment Units: Subjects			
Yes	8	32	
No	1	4	

Tumour grade Units: Subjects			
Well differentiated (G1)	0	2	
Moderately differentiated (G2)	2	8	
Poorly differentiated (G3)	4	15	
Unknown or cannot be assessed (GX)	3	11	

End points

End points reporting groups

Reporting group title	A2 - Dose level 1
Reporting group description: Cisplatin/capecitabine + M6620 (Berzosertib) administered at 90 mg/m2 once a week for 18 weeks.	
Reporting group title	A2 - Dose level 2
Reporting group description: Cisplatin/capecitabine + M6620 (Berzosertib) administered at 90 mg/m2 twice a week for 18 weeks.	
Reporting group title	A2 - Dose level 3
Reporting group description: Cisplatin/capecitabine + M6620 (Berzosertib) administered at 140 mg/m2 once a week for 18 weeks.	
Reporting group title	A2 - Dose level 4
Reporting group description: Cisplatin/capecitabine + M6620 (Berzosertib) administered at 140 mg/m2 twice a week for 18 weeks.	
Reporting group title	A1 - Dose level 1
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 140 mg/m2 on days 2, 9, 16.	
Reporting group title	A1 - Dose level 2
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 140 mg/m2 on days 2, 5, 9, 12, 16.	
Reporting group title	A1 - Dose level 3
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 140 mg/m2 on days 2, 5, 9, 12, 16, 19.	
Reporting group title	A1 - Dose level 4
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 240 mg/m2 on days 2, 9, 16.	
Reporting group title	A1 - Dose level 5
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 240 mg/m2 on days 2, 5, 9, 12, 16.	
Reporting group title	A1 - Dose level 6
Reporting group description: Radiotherapy + M6620 (Berzosertib) administered at 240 mg/m2 on days 2, 5, 9, 12, 16, 19.	

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

End point title	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[1]
End point description: Highest treatment schedule resulting in less than 25% dose limiting toxicity (DLT) rate	
End point type	Primary
End point timeframe: 9 weeks	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There are 2 different stages in the baseline period - Stage A1 and Stage A2. The Stages in are independent of each other and so analyses relating to the two sets of arms are reported separately.

End point values	A1 - Dose level 1	A1 - Dose level 2	A1 - Dose level 3	A1 - Dose level 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	1	1	1
Units: Dose Limiting Toxicities	0	0	0	0

End point values	A1 - Dose level 5	A1 - Dose level 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	9		
Units: Dose Limiting Toxicities	0	0		

Attachments (see zip file)	A1 DLTs/A1_Allocation.PNG A1 Primary Results/A1_PrimaryResults.PNG

Statistical analyses

Statistical analysis title	TiTE-CRM

Statistical analysis description:

The primary analysis is performed using the Time-To-Event Continual Reassessment Method (TiTE-CRM). Giving posterior estimates for the probability of toxicity (DLT) at each dose level

Comparison groups	A1 - Dose level 1 v A1 - Dose level 2 v A1 - Dose level 3 v A1 - Dose level 4 v A1 - Dose level 5 v A1 - Dose level 6
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Post prob of tox at dose level 6
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.165

Notes:

[2] - Bayesian TiTE-CRM

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

End point title	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[3]

End point description:

Highest treatment schedule resulting in less than 30% dose limiting toxicity (DLT) rate

End point type	Primary

End point timeframe:

4 Weeks

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: There are 2 different stages in the baseline period - Stage A1 and Stage A2. The Stages in are independent of each other and so analyses relating to the two sets of arms are reported separately.

End point values	A2 - Dose level 1	A2 - Dose level 2	A2 - Dose level 3	A2 - Dose level 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	1	9	4
Units: Dose Limiting Toxicities	0	0	2	0

Attachments (see zip file)	A2 DLTs/A2_Allocation.PNG A2 Primary Results/A2_PrimaryResults.PNG

Statistical analyses

Statistical analysis title	TiTE-CRM (A2)

Statistical analysis description:

The primary analysis is performed using the Time-To-Event Continual Reassessment Method (TiTECRM). Giving posterior estimates for the probability of toxicity (DLT) at each dose level

Comparison groups	A2 - Dose level 1 v A2 - Dose level 2 v A2 - Dose level 3 v A2 - Dose level 4
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Post prob of tox at dose level 4
Point estimate	0.185
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.042
upper limit	0.397

Notes:

[4] - Bayesian TiTE-CRM

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Stage A1 (cohort 1): adverse events were reported from first dose of IMP to patients' 12-week follow up visit.
Stage A2 (cohort 2): adverse events were reported from first dose of IMP to follow up visit at 8 weeks post-end of treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Stage A1 (cohort 1)

Reporting group description:

Patients administered M6620 (Berzosertib) in combination with palliative radiotherapy in oesophageal cancer.

Reporting group title	Stage A2 (cohort 2)

Reporting group description:

Patients administered M6620 (Berzosertib) in combination with cisplatin/capecitabine chemotherapy in metastatic or advanced inoperable solid tumours.

Serious adverse events	Stage A1 (cohort 1)	Stage A2 (cohort 2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	3 / 18 (16.67%)	
number of deaths (all causes)	9	11	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Gastrostomy tube site complication	Additional description: Rig accidentally fallen out		
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			

subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Stage A1 (cohort 1)	Stage A2 (cohort 2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	18 / 18 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Neoplasms benign; malignant and unspecified			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	1 / 16 (6.25%)	4 / 18 (22.22%)	
occurrences (all)	1	5	
General disorders and administration site conditions			
General Disorders & Administration Site Conditions			
subjects affected / exposed	7 / 16 (43.75%)	13 / 18 (72.22%)	
occurrences (all)	10	43	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	0 / 16 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	8 / 16 (50.00%)	8 / 18 (44.44%)	
occurrences (all)	11	14	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	1 / 16 (6.25%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Investigations			
Investigations			
subjects affected / exposed	4 / 16 (25.00%)	8 / 18 (44.44%)	
occurrences (all)	7	25	
Injury, poisoning and procedural complications			
Injury; poisoning and procedural complications			
subjects affected / exposed	2 / 16 (12.50%)	1 / 18 (5.56%)	
occurrences (all)	2	2	
Nervous system disorders			
Nervous System Disorders			

subjects affected / exposed occurrences (all)	4 / 16 (25.00%) 6	5 / 18 (27.78%) 6	
Blood and lymphatic system disorders Blood & Lymphatic System Disorders subjects affected / exposed occurrences (all)	 3 / 16 (18.75%) 5	 12 / 18 (66.67%) 37	
Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0	 4 / 18 (22.22%) 6	
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 2	 2 / 18 (11.11%) 2	
Gastrointestinal disorders Gastrointestinal Disorders subjects affected / exposed occurrences (all)	 13 / 16 (81.25%) 28	 12 / 18 (66.67%) 39	
Hepatobiliary disorders Hepatobiliary subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0	 1 / 18 (5.56%) 1	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	 6 / 16 (37.50%) 14	 4 / 18 (22.22%) 12	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0	 2 / 18 (11.11%) 2	
Musculoskeletal and connective tissue disorders Musculoskeletal & Connective Tissue Disorders subjects affected / exposed occurrences (all)	 3 / 16 (18.75%) 4	 7 / 18 (38.89%) 12	
Infections and infestations			

Infections & Infestations subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 3	10 / 18 (55.56%) 20	
Metabolism and nutrition disorders Metabolism & Nutrition Disorders subjects affected / exposed occurrences (all)	5 / 16 (31.25%) 6	10 / 18 (55.56%) 15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 January 2017	Amendment_001: Substantial amendment following review of protocol by MHRA and Chemotherapy Pharmacy Advisory Service (CPAS) during initial submission process and prior to obtaining approvals to proceed.
15 May 2018	Amendment_002: Substantial amendment following change of IMP name from VX-970 to M6620 and manufacturer from Vertex Pharmaceutical Inc. to Merck KGaA. Included, *Additional secondary endpoint to Stage A2 (in-field radiotherapy control) *Change in PI at two recruiting NHS sites and additional NHS recruiting site *Update to definition of end of study *Clarification of DLT definition wording *Update to ionising radiation exposure assessment due to one site having a higher standard of care dose than initially planned for *Minor clarifications/corrections to trial documents.
08 August 2018	Amendment_003: Substantial amendment following changes to IMP supply chain (manufacturing and assembly sites, drug distribution and transport, QC/QP release).
27 October 2020	Amendment_004: Substantial amendment to change design of Stage B. Including, *Fewer treatment levels *Confirmation of dosage based on data from Stages A1 and A2 *Reduced follow up period *IB update and Reference Safety Information *Update to DLT definitions *Clarification of treatment for patients experiencing DLT *Clarification on data used in treatment allocation decisions *Increased flexibility in gaps between participant treatment start dates (Stage A1 & A2) *Removal of Carboplatin for Cisplatin toxicity *Removal of PK sampling endpoint (Stage A2) *Changes to eligibility criteria to allow patients with larger tumours to participate *Collection of Stage A1 archival biopsy samples *Reduction in requirement to monitor for reactions after M6620 administration if prior administrations have shown no reaction *Haemoglobin values requirements for M6620 administration corrected *Correction of RTTQA oversight details *Change in PI at an NHS recruiting site *Patient cards updated with out of hours guidance *Minor clarifications/corrections to trial documents.
03 August 2021	Amendment_005: Change of PI at NHS recruiting site.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported