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)

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1. INTRODUCTION

This document details the proposed presentation and analysis for the main paper(s) reporting results from the **CRUK, Merck and The University of Oxford-funded multicentre phase I dose escalation safety study combining the ATR inhibitor M6620 with chemoradiotherapy in oesophageal cancer using time to event continual reassessment method (CHARIOT)**. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

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

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

1.1 Key personnel

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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

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

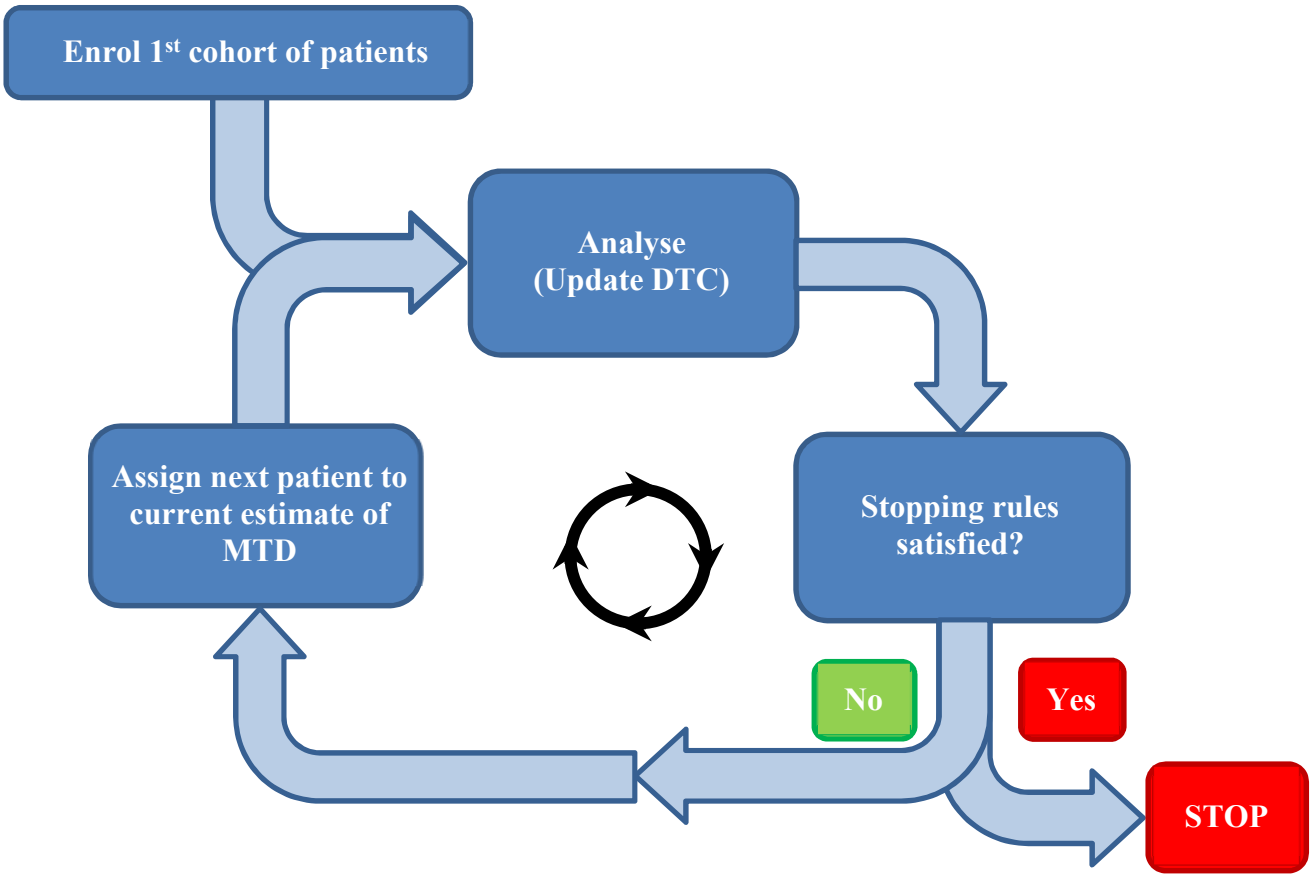
and the posterior expected toxicity at each dose (posterior dose-toxicity curve) is given by

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

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.

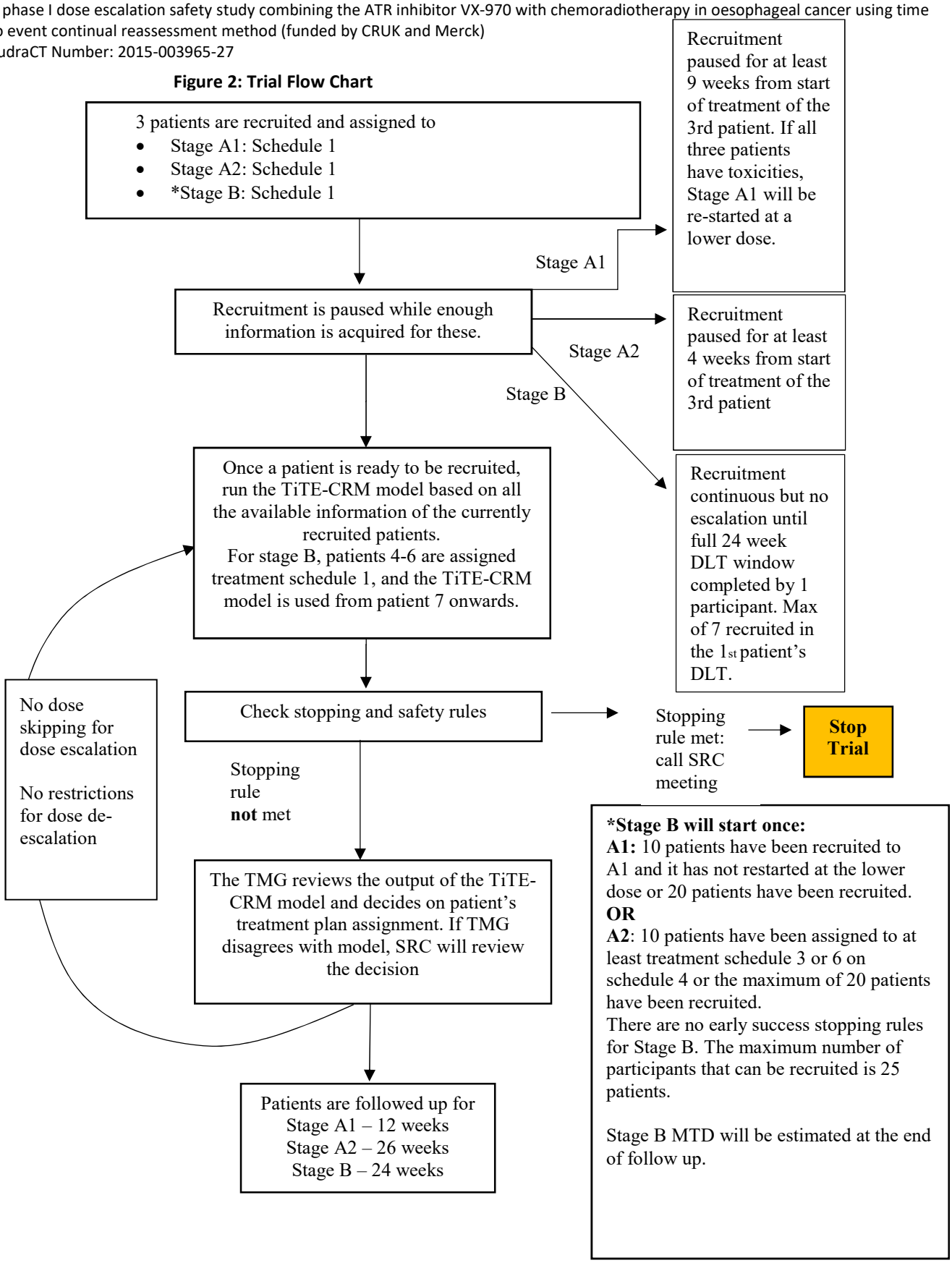
Table 1: Design features for all stages of the study

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.

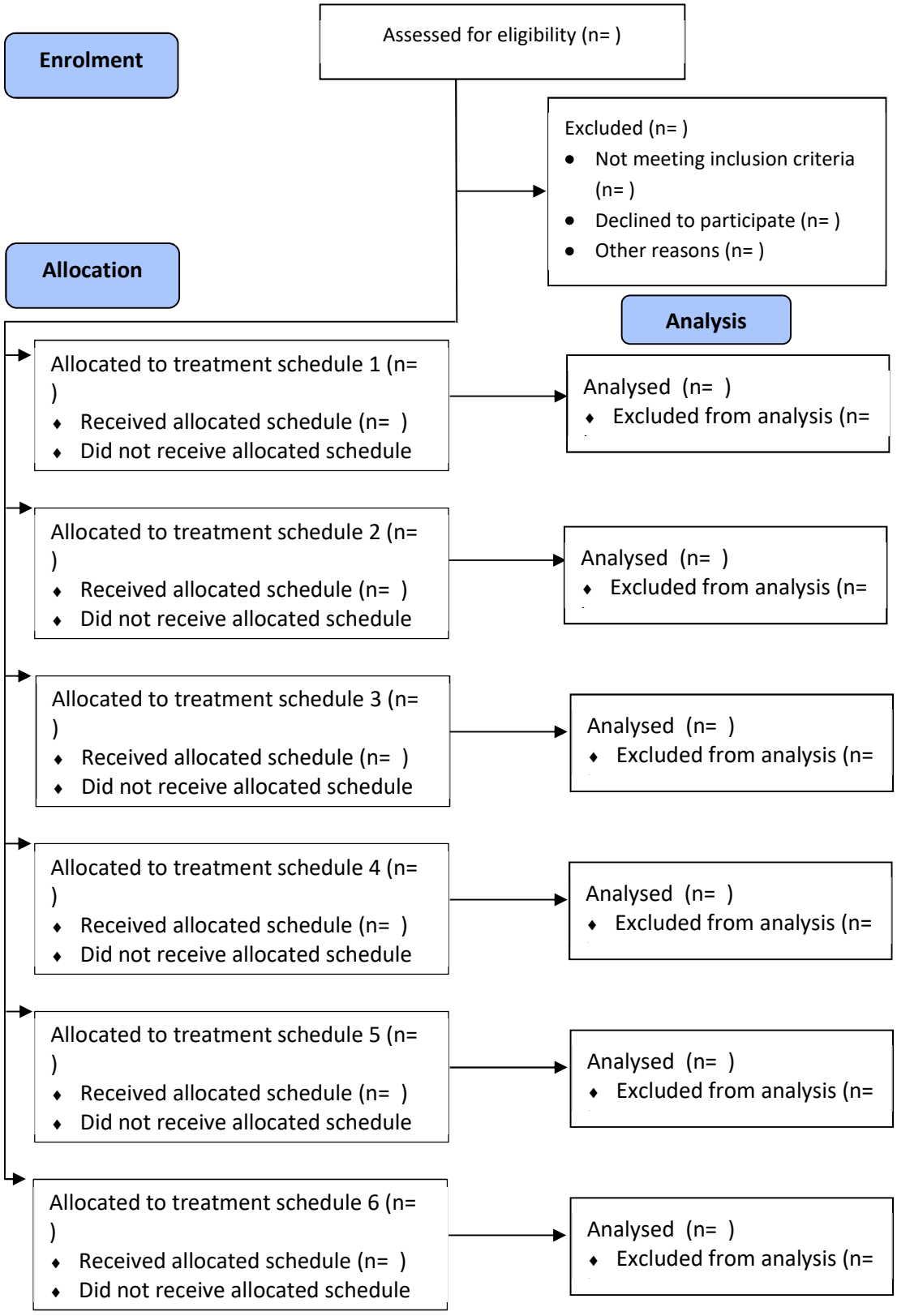
6. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

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