CRAIN

A phase 1b TiTE-CRM dose escalation clinical trial of tolinapant (ASTX660) in combination with standard radical chemoradiotherapy in cervical cancer

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FUNDER

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Protocol Information

This protocol describes the CRAIN trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non-trial participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This trial will be conducted in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CRT	Cisplatin & Radiotherapy
CTA	Clinical Trial Authorisation
CTC	Circulating Tumour Cell
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DMP	Data Management Plan
GCP	Good Clinical Practice
IAP	Inhibitor of Apoptosis Protein
IB	Investigator Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
PBMCs	Peripheral Blood Mononuclear Cells
PI	Principal Investigator
REC	Research Ethics Committee
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SCTU	Southampton Clinical Trials Unit
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TTL	Target Toxicity Level
WOCBP	Women Of Child Bearing Potential

KEYWORDS
Cervical cancer; Tolinapant; Chemoradiation; Chemoradiotherapy; Cisplatin;

TRIAL SYNOPSIS

Short title:	CRAIN
Full title:	A phase 1b TiTE-CRM dose escalation clinical trial of tolinapant in combination with standard radical chemoradiotherapy in cervical cancer.

Phase:	Phase 1b
Population:	Women aged 16 or over with histologically proven adenocarcinoma or squamous cell carcinoma of the cervix stage IB2/IB3/IIA1/IIA2/IIB/IIIA/IIIB/IIIC1 suitable for radical treatment with radiotherapy and cisplatin, with a ECOG Performance Status 0-1. **Inclusion Criteria** 1. Histologically confirmed adenocarcinoma or squamous cell carcinoma of the cervix stage IB2/IB3/IIA1/IIA2/IIB/IIIA/IIIB/IIIC1* *(*any stage IIIC1 patients must have treatment planned with the same volume and tissue constraints as node negative patients. In stage IIIA patients inguinal nodes may be included but patients with extended field volumes to include para-aortic nodes would not be eligible).* 2. Suitable for radical treatment with radiotherapy and cisplatin (using a standard dose of 45Gy in 25 daily fractions over 5 weeks with weekly cisplatin 40mg/m^2). 3. Adequate haematological parameters: • Haemoglobin ≥ 90 g/L • Neutrophil count ≥ 1.5 x 10^9/L • Platelets ≥ 100 x 10^9/L 4. Adequate biochemical parameters: • Bilirubin ≤ 1.5 x ULN • AST and ALT ≤2.0 x ULN • ALP ≤ 2.5 x ULN • Lipase and Amylase ≤1.2 x ULN • Estimated GFR (calculated using the CKD-EPI formula or other accepted formula) or measured directly as ≥ 50 mL/min 5. Age 16 years or over. 6. ECOG Performance Status of 0-1. 7. Willing and able to give written informed consent. **Exclusion Criteria** 8. Previous pelvic radiotherapy. 9. Liver cirrhosis, or chronic liver disease Child-Pugh Class B or C. 10. Women who are pregnant or breast feeding (Women of child bearing potential (WOCBP) must have a negative serum pregnancy test at screening). 11. Patients of child-bearing potential who are not able to use a method of contraception as detailed in section 4.6. 12. Any investigational medicinal product (IMP)within 30 days prior to consent 13. Major surgery within 30 days prior to enrolment. 14. Hypersensitivity to tolinapant, excipients of the drug product, or other components of the study treatment regimen. 15. Patients with known HIV infection. 16. Patients with known active hepatitis B virus (HBV; chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test) or hepatitis C. Patients with past HBV infection or resolved HBV infection (defined as the

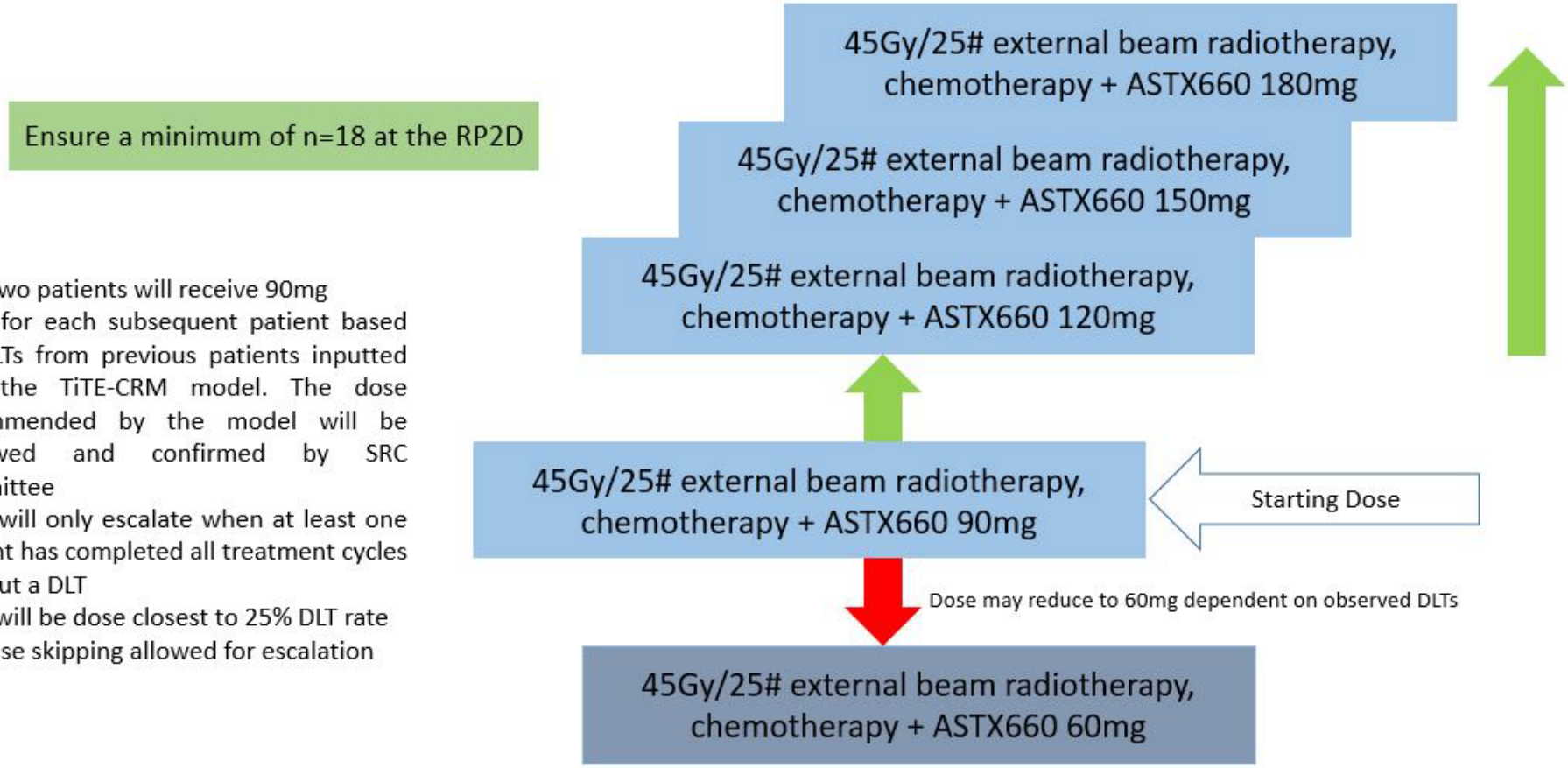
	presence of hepatitis B core antibody and the absence of HBsAg) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. 17. Coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, unstable arrhythmias, unstable angina, left bundle branch block, third degree heart block, pacemakers or congestive cardiac failure (New York Heart Association ≥ grade 2) within 6 months prior to enrolment. 18. Any patient who has received a live vaccine within 4 weeks of initiation of their treatment (COVID-19 vaccination is allowed). 19. Conditions requiring systemic treatment with either corticosteroids (≥ 20 mg daily prednisolone or equivalent) or other immunosuppressive medications within 14 days of study drug administration. 20. Prior anticancer treatments or therapies within the indicated time window prior to first dose of study treatment (tolinapant), as follows: a. Cytotoxic chemotherapy or radiotherapy within 3 weeks prior and any encountered treatment-related toxicities (excepting alopecia) not resolved to Grade 1 or less. b. Skin directed treatments, including topicals and radiation within 2 weeks prior. c. Monoclonal antibodies within 4 weeks prior and any encountered treatment-related toxicities not resolved to Grade 1 or less. d. Small molecules or biologics (investigational or approved) within the longer of 2 weeks or 5 half-lives prior to study treatment and any encountered treatment-related toxicities not resolved to Grade 1 or less. e. At least 6 weeks must have elapsed since CAR-T infusion and subjects must have experienced disease progression, and not have residual circulating CAR-T cells in peripheral blood (based on local assessment). Any encountered treatment-related toxicities must have resolved to Grade ≤1. 21. Patients taking a QT prolonging agent (with the exception of palonesetron/Akynzeo when used as part of a cisplatin antiemetic regime), see appendix for example list. 22. Use of a concomitant medication which is a strong CYP3A4 inhibitor. 23. Abnormal left ventricular ejection fraction (LVEF) of <50% on echocardiogram (ECHO). 24. History of long QTc syndrome or ventricular arrhythmias including ventricular bigeminy. 25. Screening 12-lead electrocardiogram (ECG) with measurable QTc interval of ≥470 msec (according to either Fridericia's or Bazett's correction). 26. Any other active malignancy. 27. Any known active covid-19 infection at the time of consent.	
Primary Objective and Endpoints:	To establish the maximum tolerated safe dose of tolinapant in combination with Cisplatin & Radiotherapy (CRT) to aid dose selection for a phase II trial	Measured using the estimated rate of Dose limiting toxicities (DLT) at each dose level using a TiTE-CRM Bayesian model. DLTs will be categorised using the Common Terminology Criteria for Adverse Events (CTCAE) version 5 over 12 weeks from the start of treatment. See the full list of defined DLTs given in section 3.3.

Secondary Objectives and Endpoints:	To determine the safety and tolerability of the combination of CRT+tolinapant To assess the response rates to CRT+tolinapant To ensure the addition of tolinapant does not interfere with planned delivery of CRT	Measured by the number of drug related Adverse Events (AEs) and Serious Adverse Events (SAEs) graded by CTCAEv5 at each dose level. Complete and partial response rates at three months from completion of chemoradiation as assessed by measurements on MRI scan using RECIST version 1.1 Relative dose intensity of planned courses of CRT and total chemotherapy delays
Tertiary Objectives and Endpoints:	To evaluate on-target effects of tolinapant To explore tissue and liquid biomarkers which may predict response to tolinapant	Target activation with suppression of cellular inhibitor of apoptosis 1 (cIAP1) in peripheral blood mononuclear cells (PBMCs) Response in relation to changes in circulating tumour cell (CTC) level, cDNA, tissue gene expression and plasma cytokines eg Interleukin 2, Tumour Necrosis Factor β
Translational Objectives and Endpoints	1. Monitoring pharmacokinetics of tolinapant 2. Identification of markers of therapy response 3. Identification of predictors of response to tolinapant + CRT 4. Identification of patients with hypoxic tumours 5. Identification of genetic factors affecting treatment response	Patient response data in relation to changes seen in tissue and liquid biomarkers. (Further details for endpoint assessment methods for translational objectives can be seen in the trial laboratory manual)
Rationale:	The standard treatment for locally advanced cervical cancer is radical cisplatin based chemoradiation. Tolinapant is a dual antagonist of the inhibitors of apoptosis proteins (IAPs) XIAP and cIAP1. It is a novel agent which has a different mode of action to both cisplatin and radiation and has been shown to have synergistic effects with cisplatin and radiotherapy with a lack of significant overlapping toxicities in vitro. There is then good reason to propose that improved results will be achieved with the combination of cisplatin chemoradiation and tolinapant.	
Trial Design:	This is a phase 1b open-label, multi-centre study to characterise the safety and tolerability and initial evidence for clinical activity of tolinapant when administered in combination with cisplatin based CRT to women with newly diagnosed cancer of the cervix.	
Sample size:	The actual number of patients required and the duration of the trial will depend on any toxicities observed and dose escalation decisions, utilising a TiTE-CRM design. However, the phase 1 trial will recruit a maximum of 42 patients across six sites over	

	24 months and will include a minimum of 18 patients treated at the recommended phase II dose.
Investigational Medicinal Product/s:	Tolinapant (also known as ASTX660)
Non- Investigational Medicinal Product/s:	Cisplatin
Dosage Regimen / Duration of Treatment:	The treatment schedule is planned to last 7 weeks. Dose levels for tolinapant which will be assessed in the TiTE-CRM are: Level 1: 60mg; Level 2: 90mg (starting level); Level 3: 120mg; Level 4: 150mg; Level 5: 180mg. Escalation will be guided by emerging safety data and decision by the Safety Review Committee (SRC).
Total Number of Sites:	6

TRIAL SCHEMA

A phase Ib TiTE-CRM dose escalation clinical trial of tolinapant in combination with standard radical chemoradiotherapy in cervical cancer.



- First two patients will receive 90mg
- Dose for each subsequent patient based on DLTs from previous patients inputted into the TiTE-CRM model. The dose recommended by the model will be reviewed and confirmed by SRC committee
- Dose will only escalate when at least one patient has completed all treatment cycles without a DLT
- MTD will be dose closest to 25% DLT rate
- No dose skipping allowed for escalation

SCHEDULE OF OBSERVATIONS AND PROCEDURES

	Screening Phase	Treatment Phase							Follow up Phase	
		External Beam RT Treatment Week 1	External Beam RT Treatment Week 2	External Beam RT Treatment Week 3	External Beam RT Treatment Week 4	External Beam RT Treatment Week 5	Brachytherapy Week 1	Brachytherapy Week 2	Follow up visit 1	Follow up visit 2
Trial Week[1]	**-2-0 weeks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**12** (± 2 week)	**18** (± 2 week)
Informed consent[2]	x									
Inclusion / exclusion criteria	x									
Medical history	x									
Physical exam	x						x	x	x	X[3]
ECOG performance status	x	x	x	x	x	x	x	x	x	x
Electrocardiogram	x									
Echocardigram	x									
Serum biochemistry[4]	X	x	x	x	x	x	x			
Haematology[5]	x	x	x	x	x	x	x			
Serology – HBV and HCV	x									
Pregnancy test for WOCBP[6]	x			x		x				
Translational tissue samples[7]	x						x			
Translational blood samples	x	x	x	x	x	x	x	x	x	
Translational urine samples	x	x		x		x	x		x	x
Diagnostic imaging assessment (MRI)	X[8]					x				X
CT scan to assess for metastases[9]	x									
Disease Assessment Questions[10]	x					x				x
Adverse event assessment	x	x		x		x		x	x	X
Concomitant medication record	x								x	x
Tolinapant[11]		x		x		x				
PK sampling[12]		xxxxxx								
External beam radiotherapy (standard 5 week course)[13]		x	x	x	x	x				
Cisplatin (40 mg/m^2)		x	x	x	x	x				
Brachytherapy[14]							x	x		

[1]Treatment weeks of CRT and tolinapant should always be scheduled to start on a Monday, cisplatin can be given on any day throughout the week.

[2]Consent may be taken up to 14 days prior to Treatment day 1, week 1 and must be completed before any screening procedures take place.

[3]Vaginal adhesions should be assessed as part of the physical exam at the follow up 2 visit to inform the disease assessment.

[4]Serum biochemistry including renal (urea, sodium, potassium, creatinine), liver (AST and ALT, ALP and bilirubin), bone (including serum albumin and calcium), thyroid profiles (including T4, T3, TSH) and lipids, lipase and amylase. Bloods can be taken up to one working day in advance.

[5]Full blood count (FBC) to include haemoglobin, white blood cell count, absolute neutrophil, lymphocytes and platelet counts. Bloods can be taken up to one working day in advance.

[6]Must be serum test at screening. Urine/serum test at week 3 and week 5

[7] Archival FFPE block to have been collected within 3 months prior to day 1 and should be sent as soon as possible after consent. New tissue biopsy to be collected at week 1 Brachytherapy

[8]Screening scan not required if done within 8 weeks prior to day 1

[9]Baseline imaging assessing for metastases can be done via CT alone or combined PET-CT, and does not need to be repeated if done within 8 weeks prior to day 1

[10]Assessment of fecal urgency (RT-ARD Score) at screening, Radiotherapy week 5 and follow up 2. Assessment of vaginal dilator use at follow up 2 only.
[11]To be taken for 7 consecutive days as an outpatient. Tolinapant can be taken with or without food, with the exception of PK days. On days with PK sampling, patients should refrain from eating (including soup) or drinking milk or juice for at least 2 hours prior to ingesting study drug(s) and 2 hours after ingesting study drug (4 hour fasting window).
[12]6 PK samples should be taken across day 4 and day 5 of week 1. Please see Laboratory Manual for further information.
[13]Daily cone beam CT imaging will be used to inform the delivery of the radiotherapy, as per standard of care and according to local site policy. External beam radiotherapy should be administered in line with EMBRACE or INTERLACE processes.
[14]Brachytherapy schedules may vary according to local site policy in line with section 6.1, however all brachytherapy treatments should be carried out within the 2 week window. Brachytherapy should be image guided (utilizing up to 3 MRI scans and 4 CT scans) as per standard of care and according to local site policy.

1 INTRODUCTION

1.1 BACKGROUND

CRAIN is a phase 1b trial to determine the maximum tolerated dose (MTD) of the Inhibitor of Apoptosis Proteins (IAP) inhibitor tolinapant combined with cisplatin & radiotherapy (CRT) and to then determine whether there is a signal of efficacy sufficient to justify further study of the combination, in the primary treatment of cervical cancer.

Cervical cancer is the fourth most common cancer in women, with an estimated 266,000 deaths worldwide in 2012 (1), where almost nine out of ten (87%) cervical cancer deaths occur in less developed countries. Current standard of care in the UK for locally advanced cervical cancer is concurrent chemoradiotherapy with weekly cisplatin, yet 5-year overall survival rates are only around 65% with a distant relapse rate of 50% (2). This treatment is associated with long term side effects in around half of patients with up to 15% suffering from grade 3-4 toxicity (3).

Evasion of apoptosis is one of the hallmarks of cancer (4) and apoptosis is a key mechanism for programmed cell death that is dysregulated in many tumour types. IAPs are key regulators of antiapoptotic and pro-survival signalling pathways, which are often overexpressed in cancer cells and associated with tumour progression and resistance to treatment (5). Tolinapant is an IAP antagonist, which is chemically distinct from first generation peptidomimetic SMAC mimetics and shows balanced inhibition across the subtypes of IAP: cIAP1, cIAP2 and XIAP (6). A putative mechanism of action of tolinapant is via down-regulation of NF-kB which is an important regulator in cervical cancer.

1.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

Inhibitors of Apoptosis Proteins are considered attractive targets for anti-cancer therapy. Antagonists of these proteins have the potential to switch pro-survival signalling pathways such as TNFa signalling, in cancer cells towards cell death, thus promoting apoptosis. Tolinapant, developed by Taiho Oncology, is a novel antagonist of cIAP1/2 and XIAP currently in clinical trials for treating advanced solid tumours i.e. head and neck squamous cell carcinoma (HNSCC), cervical carcinoma and other tumour types that are characterized by a molecular feature that may confer sensitivity to tolinapant, and various lymphomas. In vitro studies in four cervical cancer models (Hela, Caski, SiHa, Me180) indicate that tolinapant reduces clAP1 protein levels and induces co-incidental apoptosis (6-40% induction over baseline; Promega RealTime-Glo™ Annexin V Apoptosis Assay). Radiation (2Gy) or cisplatin alone induced apoptosis in all cell lines (radiation range 15-66% over baseline; cisplatin 10-40%). The combination of tolinapant, cisplatin and radiation significantly enhanced apoptosis observed versus radiation alone across the panel. Induction of apoptosis correlated with significantly reduced clonogenic survival following treatment with tolinapant, cisplatin and radiation versus radiotherapy alone. Initial in vivo studies indicated that reduced clAP1 protein levels in Me180 xenografts established in Balb-c nude mice. Combining tolinapant with chemo(cisplatin)-radiotherapy enhanced response versus chemo-radiotherapy alone whilst having no impact on acute gastro-intestinal (GI) toxicity analysed via crypt assay.
Tolinapant is currently being investigated in an open-label, multi-centre study; ASTX660-01. The objectives of the Phase 1 part of the study were to assess safety, preliminary clinical activity, pharmacokinetics, pharmacodynamics, identify the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) in subjects with advanced solid tumours (head and neck squamous cell carcinoma and cervical carcinoma) or lymphoma. Phase 1 enrolment is complete, with a total of 45 subjects all of whom have discontinued study treatment. The dose of tolinapant was escalated from 15 mg/day to 270 mg/day (fixed dose) using an intermittent dosing schedule (7 days on/7 days off × 2 of each 28-day cycle). The 210 mg/day dose was determined as the MTD and 180 mg/day as the RP2D. Dose limiting toxicities (DLTs) included asymptomatic Grade 3 lipase increased or hyperlipaemia with or without Grade 3 amylase increased at the 210 mg/day and 270 mg/day dose level. The most common study treatment-related AEs (≥10%) were nausea (22%), pruritus (18%), vomiting (18%), and fatigue (13%). In addition, rash (including rash maculo-papular) was reported in >10% of subjects. The most common Grade 3 AE related to study treatment was lipase increased (6.7%); all other Grade 3 AEs occurred in 1 subject (2.2%) each, including hyponatremia and hypophosphatemia (both in the same subject), hyperlipasemia, lymphopenia, increased amylase, and anaemia. No subjects in Phase 1 in any dose group had Grade 4 or 5 AEs related to study treatment or SAEs related to study treatment. At the RP2D, tolinapant achieved target therapeutic exposure based on preclinical models. (Astex Pharmaceuticals ASTX660 Investigator Brochure, v7, 18th August 2021).

As of the cut-off date (4th June 2019) for reporting of the phase 2, the peripheral T-cell lymphoma (PTCL) and cutaneous T cell lymphoma (CTCL) cohorts are enrolling; all other cohorts have completed enrolment. All subjects

received tolinapant at the RP2D 180 mg/day (fixed dose) orally once daily at the same intermittent dosing regimen as Phase 1. 107 subjects have been treated in the Phase 2 part of the ASTX660-01 study: Head and neck squamous cell carcinoma (HNSCC; N=14), Diffuse large B-cell lymphoma (DLBCL; N=16), PTCL (N=26), CTCL (N=23), other tumour types with a molecular rationale (N=14), and cervical cancer (N=14). The most common study treatment related AEs were increased lipase and hyperlipaemia (N=36; 33.6%), maculo-papular rash (N=33; 30.8%), increased amylase (N=31; 29.0%), and increased alanine aminotransferase (N=16; 15.0%). The most common Grade ≥3 AE related to study treatment included increased lipase and hyperlipaemia (N=17; 15.9%), maculo-papular rash (N=17; 15.9%), and increased amylase (N=10; 9.3%). A total of 50 subjects experienced SAEs in Phase 2, with the most common events including pneumonitis (N=5 [4.7%]), acute kidney injury (N=3 [2.8%]), and maculo-papular rash (N=3[2.8%]). The most common SARs included pneumonitis (N=5; 4.7%), maculo-papular rash (N=3; 2.8%), and pancreatitis (N=2; 1.9%); all other SARs were observed in 1 subject (0.9%) each. (Astex Pharmaceuticals ASTX660 Investigator Brochure, v7 18th August 2021).

Preclinical studies performed using tolinapant in combination with cisplatin and radiotherapy (RT) showed an inhibition of tumour growth and enhanced survival in multiple HPV+/- head and neck squamous cell carcinoma models (7). Additional data using a syngeneic mouse oral cancer model also showed tolinapant in combination induced tumour growth inhibition compared to RT alone and tolinapant alone (7). *In vitro* studies by Professor Kaye Williams (co-investigator) in 4 cervical cancer models (Hela, Caski, SiHa, Me180) indicate that tolinapant inhibits cIAP1 expression and induces co-incidental apoptosis (6-40% induction over baseline; Promega RealTime-Glo™ Annexin V Apoptosis Assay). Radiation (2Gy) or cisplatin alone induced apoptosis in all cell lines (RT range 15-66% over baseline; cisplatin 10-40%). The combination of tolinapant, cisplatin and radiation significantly enhanced apoptosis observed versus radiation alone across the panel. Induction of apoptosis correlated with significantly reduced clonogenic survival following treatment with tolinapant, cisplatin and radiation versus radiotherapy alone. Initial *in vivo* studies indicated that tolinapant inhibited cIAP1 expression in Me180 xenografts established in Balb-c nude mice. Combining tolinapant with chemo(cisplatin)-radiotherapy enhanced response versus chemoradiotherapy alone whilst having no impact on acute gastro-intestinal (GI) toxicity analysed via crypt assay.

There is therefore a strong rationale to combine tolinapant with CRT. Improvement in loco-regional control is closely related to survival improvement in cervical cancer hence this study has the potential to improve survival in a population of relatively young active women.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 2.1 PRIMARY TRIAL OBJECTIVE AND ENDPOINT

The CRAIN trial primary objective is to establish the maximum tolerated safe dose of tolinapant in combination with Cisplatin & Radiotherapy (CRT) to aid dose selection for a phase II trial. The primary end point is dose limiting toxicities, as defined in the table below and in section 3.3. Any tolinapant related deaths will be recorded as a DLT at the time of death. Any patient who discontinues treatment early, for any reason not attributable to a DLT, will be included in the analysis as a patient without a DLT, unless the SRC decide they should be replaced based on the amount of treatment they had received.

2.2 2.2 TABLE OF ENDPOINT/OUTCOMES

	Objective	Outcome Measures	Summary method(s)
Primary:	To establish the maximum tolerated safe dose of tolinapant in combination with Cisplatin & Radiotherapy (CRT) to aid dose selection for a phase II trial	Estimated rate of Dose limiting toxicities (DLT) at each dose level. DLTs will be categorised using the Common Terminology Criteria for Adverse Events (CTCAE) version 5 over 12 weeks from the start of treatment. See the full list of defined DLTs given in section 3.3.	TiTE-CRM Bayesian model showing estimates of DLT risks at each dose level and the probability of each dose being unsafe.

Secondary:	To determine the safety and tolerability of the combination of CRT+tolinapant	Number of drug related AEs and SAEs graded by CTCAEv5 at each dose level.	AEs summarised by system organ class, split by AEs related and unrelated to tolinapant at each dose level.
	To assess the response rates to CRT+tolinapant	Complete and partial response rates at three months from completion of chemoradiation as assessed by measurements on MRI scan using RECIST version 1.1	Summarised using frequency and percentages of complete and partial response rates.
	To ensure the addition of tolinapant does not interfere with planned delivery of CRT	Relative dose intensity of planned courses of CRT and total chemotherapy delays	Summary of the relative dose intensity across all patients. Frequency and percentages of delays or disruption to CRT.
Tertiary:	To evaluate on-target effects of tolinapant	Target activation with suppression of cellular inhibitor of apoptosis 1 (cIAP1) in peripheral blood mononuclear cells (PBMCs)	Summary of cIAP inhibition seen in patient PBMCs. Any other tertiary endpoints and summary methods will be experimental.
	To explore tissue and liquid biomarkers which may predict response to tolinapant	Response in relation to changes in CTC level, cDNA, tissue gene expression and plasma cytokines eg Interleukin 2, Tumour Necrosis Factor β	A summary of the changes in tissue and liquid biomarkers will be correlated with patient response data. A further exploratory aim of the study is to develop a suitable summary methodology for future trials.

3 TRIAL DESIGN

3.1 TRIAL DESIGN OVERVIEW:

This is a phase 1b open-label, multi-centre study to characterise the safety and tolerability and initial evidence for clinical activity of tolinapant when administered in combination with cisplatin based CRT to women with newly diagnosed cancer of the cervix.

3.2 STUDY TREATMENTS:

CRT using a standard dose of 45Gy in 25 daily fractions (with nodal boosting performed using a simultaneous integrated boost (SIB) for radiologically positive nodes to a total dose of 55-60Gy in 25 daily fractions) over 5 weeks with once weekly cisplatin 40mg/m^2. This is followed by brachytherapy for which common schedules will be a further 28Gy in 4 fractions high-dose-rate or 34Gy in 2 fractions pulsed- dose-rate.

Tolinapant will be administered in fixed dose capsules of 30mg or 90mg taken orally daily for seven consecutive days as an outpatient (followed by seven consecutive days off) prior to radiotherapy on alternate weeks (weeks 1, 3, 5) during chemoradiation. Tolinapant can be taken with or without food, with the exception of PK days. On days with PK sampling, patients should refrain from eating (including soup) or drinking milk or juice for at least 2 hours prior to ingesting study drug(s) and 2 hours after ingesting study drug (4 hour fasting window).

3.3 DEFINITION OF DOSE LIMITING TOXICITY:

The DLT assessment period is 12 weeks from the start of treatment.

Any of the following events occurring after the first dose of tolinapant will constitute a DLT if, in the opinion of the investigator, the event is defined as **definitely or probably** related to tolinapant:

- Grade 4 neutropenia ≥7 days duration
- Grade 3 or 4 febrile neutropenia (neutrophils <1000/mm3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour AND/OR life-threatening consequences with urgent intervention indicated)
- Grade 3 or 4 neutropenia associated with a separate event of bacteriologically proven sepsis happening at the same time
- Grade 3 or 4 thrombocytopenia
- Death

Any other grade 3 or 4 adverse event will constitute a DLT if, in the opinion of the investigator, the event is defined as **definitely or probably** related to tolinapant.

In all cases of a suspected DLT, clinical judgement will be the final arbiter as to whether the event should be categorised as such.

3.4 DOSE ESCALATION AND DETERMINATION OF MTD:

The phase 1b dose finding trial will be a single arm, open-label, multi-centre trial that will use the two-stage time-to event continual reassessment method (TiTE-CRM) to find the optimal dose of tolinapant in combination with CRT. This will be defined as the dose where the number of patients experiencing a DLT is closest to the target toxicity rate of 25%.

Dose levels for tolinapant which will be assessed in the TiTE-CRM are: Level 1: 60mg; Level 2: 90mg (starting level); Level 3: 120mg; Level 4: 150mg; Level 5: 180mg. No dose skipping is allowed (i.e., it is only possible to escalate to an adjacent dose). Escalation will be guided by emerging safety data and decision by the SRC.

A maximum of 42 patients will be recruited and treated according to the dose defined by the TiTE-CRM. The first patient recruited will be assigned 90mg as this will allow for a dose reduction to 60mg for future patients if the first patients experience excess toxicity. The TiTE-CRM will identify the MTD based on the assessment of dose limiting toxicities (DLTs).

The TiTE-CRM design utilises a one parameter logistic model and linear weights. Meaning that information accrued through the DLT assessment period (12 weeks from the start of treatment) is given weight equal to the proportion if the assessment period that has passed. Any patient experiencing a DLT will be included in the analysis as a full patient equivalent, regardless of the timing of the event.

The treatment schedule is planned to last 7 weeks, with an additional 5 weeks follow up for DLTs. Linear weighting will be used in the TiTE-CRM. For example:

- At trial week 12 (i.e. completion of treatment and 5 weeks of follow-up): in the absence of a DLT this would account for a full patient tolerable outcome
- At trial week 6: in the absence of a DLT this would account for 0.5 equivalent of a tolerable outcome

The trial will stop for success if 15 concurrent patients are treated at the current recommendation for the MTD, whilst also ensuring a total of at least 18 patients have been treated at the recommended phase II dose. The trial will stop for safety if there is sufficient evidence to suggest that dose level 1 (60mg) is too toxic i.e. a posterior probability of DLT of 35% or higher is found reflecting a 10% increase over the expected toxicity rate based on published experience (3).

3.5 DEFINITION OF END OF TRIAL

All patients will be followed up until trial week 18.

End of Trial is defined as when the last patient has had their last trial visit and all data to answer the research objectives have been collected.

4 SELECTION AND ENROLMENT OF PARTICIPANTS

4.1 CONSENT

Prior to any study specific procedures, each patient must provide written informed consent, which should be signed by an Investigator and the patient. Patients will keep a copy of the information sheet and signed consent form.

Consent to enter the trial must be sought from each participant only after a full explanation has been given, a Participant Information Sheet offered and time allowed for consideration. Signed participant consent must be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if they feel it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Upon completion of the informed consent form, a copy will be given to the participant, a copy stored in the participant's medical notes and the original filed in the site trial file. Only if informed consent has been provided for the SCTU to receive this information should a copy of the consent form be sent to the SCTU via email to monitorsctu@ soton.ac.uk using a secure nhs.net email address, safesend or encrypted mail to allow for central monitoring.

4.2 INCLUSION CRITERIA

1. Histologically confirmed adenocarcinoma or squamous cell carcinoma of the cervix stage IB2/IB3/IIA1/IIA2/IIB/IIIA/IIIB/IIIC1* (using the revised 2018 FIGO staging classification for cervical cancer) **any stage IIIC1 patients must have treatment planned with the same volume and tissue constraints as node negative patients. In stage IIIA patients inguinal nodes may be included but patients with extended field volumes to include para-aortic nodes would not be eligible.*
2. Suitable for radical treatment with radiotherapy and cisplatin (using a standard dose of 45Gy in 25 daily fractions over 5 weeks with weekly cisplatin 40mg/m2).
3. Adequate haematological parameters
    - Haemoglobin ≥ 90 g/L
    - Neutrophil count ≥ 1.5 x 10^9/L
    - Platelets ≥ 100 x 10^9/L
4. Adequate biochemical parameters
    - Bilirubin ≤ 1.5 x ULN
    - AST and ALT ≤2.0 x ULN
    - ALP ≤ 2.5 x ULN
    - Lipase and Amylase ≤1.2 x ULN
    - Estimated GFR (calculated using the CKD-EPI formula or other accepted formula) or measured directly as ≥ 50 mL/min
5. Age 16 years or over
6. ECOG Performance Status of 0-1
7. Willing and able to give written informed consent

4.3 EXCLUSION CRITERIA

8. Previous pelvic radiotherapy
9. Liver cirrhosis, or chronic liver disease Child-Pugh Class B or C
10. Women who are pregnant or breast feeding (WOCBP must have a negative serum pregnancy test at screening)
11. Patients of child-bearing potential who are not able to use a method of contraception as detailed in section 4.6

12. Any investigational medicinal product within 30 days prior to consent
13. Major surgery within 30 days prior to enrolment
14. Hypersensitivity to tolinapant, excipients of the drug product, or other components of the study treatment regimen
15. Patients with known HIV infection
16. Patients with known active hepatitis B virus (HBV; chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test) or hepatitis C. Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody and the absence of HBsAg) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA
17. Coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, unstable arrhythmias, unstable angina, left bundle branch block, third degree heart block, pacemakers or congestive cardiac failure (New York Heart Association ≥ grade 2) within 6 months prior to enrolment
18. Any patient who has received a live vaccine within 4 weeks of initiation of their treatment (COVID-19 vaccination is allowed).
19. Conditions requiring systemic treatment with either corticosteroids (≥ 20 mg daily prednisolone or equivalent) or other immunosuppressive medications within 14 days of study drug administration
20. Prior anticancer treatments or therapies within the indicated time window prior to first dose of study treatment (tolinapant), as follows:
    a. Cytotoxic chemotherapy or radiotherapy within 3 weeks prior and any encountered treatment-related toxicities (excepting alopecia) not resolved to Grade 1 or less.
    b. Skin directed treatments, including topicals and radiation within 2 weeks prior.
    c. Monoclonal antibodies within 4 weeks prior and any encountered treatment-related toxicities not resolved to Grade 1 or less.
    d. Small molecules or biologics (investigational or approved) within the longer of 2 weeks or 5 half-lives prior to study treatment and any encountered treatment-related toxicities not resolved to Grade 1 or less.
    e. At least 6 weeks must have elapsed since CAR-T infusion and subjects must have experienced disease progression, and not have residual circulating CAR-T cells in peripheral blood (based on local assessment). Any encountered treatment-related toxicities must have resolved to Grade ≤1.
21. Patients taking a QT prolonging agent (with the exception of palonesetron/Akynzeo when used as part of the chemotherapy antiemetic regime), see appendix for example list.
22. Use of a concomitant medication which is a strong CYP3A4 inhibitor.
23. Abnormal left ventricular ejection fraction (LVEF) of <50% on echocardiogram (ECHO).
24. History of long QTc syndrome or ventricular arrhythmias including ventricular bigeminy.
25. Screening 12-lead electrocardiogram (ECG) with measurable QTc interval of ≥470 msec (according to either Fridericia's or Bazett's correction).
26. Any other active malignancy.
27. Any known active covid-19 infection at the time of consent.

4.4 SCREEN FAILURES

Patients who are found to be screen failures will have their initials, year of birth and reasons for failure recorded on a screening form. The screening log should be scanned and emailed to the SCTU trial specific email address on a monthly basis. Due to timescales of patients starting treatment, re-screening is not expected for this trial.

4.5 REGISTRATION PROCEDURES

This is a single arm trial so no randomisation will be performed.

Prior to approaching a potential trial participant, sites should contact SCTU to ascertain if a dose slot is available. If available this slot can then be placed on hold while the patient is approached for consent and screened for eligibility.

Once screening assessments have been completed and the patient has been deemed eligible by a delegated clinician, the patient will be registered on the trial specific RAVE database to generate a patient ID. SCTU should then be notified so the dose slot can be formally allocated to the patient prior to starting treatment.

4.6 CONTRACEPTION

Women of child-bearing potential must agree to use one of the following methods of contraception effective from the first administration of all study drugs, throughout the trial and for six months afterwards:

- sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject),
- bilateral tubal occlusion,
- vasectomized partner.
- A barrier method such as male or female condom (with or without spermicide), cap or diaphragm

Where appropriate, and according to local institutional policy, investigators should discuss with and advise patients on the need for cryopreservation of oocytes for future fertility as part of standard of care prior to trial entry.

Contraception and pregnancy testing is not applicable for women who are considered to be of non-reproductive potential (i.e. post-menopausal, permanently sterile or having a congenital/acquired condition that prevents childbearing).

5 TRIAL OBSERVATIONS AND PROCEDURES

5.1 SCREENING PROCEDURES

- Informed consent
- Inclusion / exclusion criteria
- Medical history including demographics (including ethnicity), previous and concurrent relevant diseases and medications
- Physical exam
- ECOG performance status
- Electrocardiogram
- Echocardiogram including assessment of ejection fraction
- Serum biochemistry including renal (urea, sodium, potassium, creatinine), liver (AST and/or ALT, ALP and bilirubin), bone (including serum albumin and calcium), thyroid profiles (including T4, T3, TSH) and lipids, lipase and amylase
- Haematology including Full blood count to include haemoglobin, white blood cell count, absolute neutrophil, lymphocytes and platelets counts
- Serology – HBV and HCV
- Pregnancy test for WOCBP (serum test)
- Translational tissue (Archival FFPE block) and blood samples (CTCs, cfDNA, PBMCs, plasma for cytokines) as detailed in the CRAIN lab manual
- Translational urine collection as detailed in the CRAIN lab manual
- Imaging assessment (MRI) including response assessment by RECIST v1.1
- CT scan to assess for metastases (can be CT alone or PET-CT combined)
- Disease assessment questions (faecal urgency assessment)
- Adverse event assessment by CTCAEv5
- Concomitant medication record

5.2 TRIAL PROCEDURES

External Beam RT Treatment Week 1

- ECOG performance status
- Serum biochemistry including renal (urea, sodium, potassium, creatinine), liver (AST and/or ALT, ALP and bilirubin), bone (including serum albumin and calcium), thyroid profiles (including T4, T3, TSH) and lipids, lipase and amylase

- Haematology including full blood count to include haemoglobin, white blood cell count, absolute neutrophil, lymphocytes and platelet counts
- Translational blood samples (PBMCs, plasma for cytokines)
- Translational urine collection as detailed in the CRAIN lab manual
- Adverse event assessment by CTCAEv5
- Tolinapant
- PK sampling as detailed in the CRAIN lab manual
- Daily cone beam CT imaging to inform the radiotherapy delivery
- External beam radiotherapy (standard 5 week course)
- Cisplatin (40 mg/m^2)

External Beam RT Treatment Week 2

- ECOG performance status
- Serum biochemistry including renal (urea, sodium, potassium, creatinine), liver (AST and/or ALT, ALP and bilirubin), bone (including serum albumin and calcium), thyroid profiles (including T4, T3, TSH) and lipids, lipase and amylase
- Haematology bloods including full blood count to include haemoglobin, white blood cell count, absolute neutrophil, lymphocytes and platelet counts
- Translational blood samples (CTCs, cfDNA)
- Daily cone beam CT imaging to inform the radiotherapy delivery
- External beam radiotherapy (standard 5 week course)
- Cisplatin (40 mg/m^2)

External Beam RT Treatment Week 3

- ECOG performance status
- Pregnancy test for WOCBP (urine/serum test)
- Serum biochemistry including renal (urea, sodium, potassium, creatinine), liver (AST and/or ALT, ALP and bilirubin), bone (including serum albumin and calcium), thyroid profiles (including T4, T3, TSH) and lipids, lipase and amylase
- Haematology bloods including full blood count to include haemoglobin, white blood cell count, absolute neutrophil, lymphocytes and platelet counts
- Translational blood samples (PBMCs, plasma for cytokines)
- Translational urine collection as detailed in the CRAIN lab manual
- Adverse event assessment by CTCAEv5
- Tolinapant
- Daily cone beam CT imaging to inform the radiotherapy delivery
- External beam radiotherapy (standard 5 week course)
- Cisplatin (40 mg/m^2)

External Beam RT Treatment Week 4

- ECOG performance status
- Serum biochemistry including renal (urea, sodium, potassium, creatinine), liver (AST and/or ALT, ALP and bilirubin), bone (including serum albumin and calcium), thyroid profiles (including T4, T3, TSH) and lipids, lipase and amylase
- Haematology bloods including full blood count to include haemoglobin, white blood cell count, absolute neutrophil, lymphocytes and platelet counts
- Translational blood samples (CTCs, cfDNA)
- Daily cone beam CT imaging to inform the radiotherapy delivery
- External beam radiotherapy (standard 5 week course)
- Cisplatin (40 mg/m^2)

External Beam RT Treatment Week 5

- ECOG performance status
- Pregnancy test for WOCBP (urine/serum test)
- Serum biochemistry including renal (urea, sodium, potassium, creatinine), liver (AST and/or ALT, ALP and bilirubin), bone (including serum albumin and calcium), thyroid profiles (including T4, T3, TSH) and lipids, lipase and amylase
- Haematology bloods including full blood count to include haemoglobin, white blood cell count, absolute neutrophil, lymphocytes and platelet counts
- Translational blood samples (PBMCs, plasma for cytokines)
- Translational urine collection as detailed in the CRAIN lab manual
- Imaging assessment (MRI) including response assessment by RECIST v1.1
- Disease Assessment questions (faecal urgency assessment)
- Adverse event assessment by CTCAEv5
- Tolinapant
- Daily cone beam CT imaging to inform the radiotherapy delivery
- External beam radiotherapy (standard 5 week course)
- Cisplatin (40 mg/m^2)

Brachytherapy Week 1

- Physical exam
- ECOG performance status
- Serum biochemistry including renal (urea, sodium, potassium, creatinine), liver (AST and/or ALT, ALP and bilirubin), bone (including serum albumin and calcium), thyroid profiles (including T4, T3, TSH) and lipids, lipase and amylase
- Haematology bloods including full blood count to include haemoglobin, white blood cell count, absolute neutrophil, lymphocytes and platelet counts
- Translational tissue (new biopsy)
- Translational blood samples (PBMCs, plasma for cytokines)
- Translational urine collection as detailed in the CRAIN lab manual
- Brachytherapy Planning Imaging (MRI/CT)
- Brachytherapy

Brachytherapy Week 2

- Physical exam
- ECOG performance status
- Adverse event assessment by CTCAEv5
- Translational blood samples (CTCs/cfDNA)
- Brachytherapy Planning Imaging (MRI/CT)
- Brachytherapy

5.3 FOLLOW UP

Follow up 1 at trial week 12

- Physical exam
- ECOG performance status
- Translational blood samples (CTCs, cfDNA, PBMCs, plasma for cytokines)
- Translational urine collection as detailed in the CRAIN lab manual
- Adverse event assessment by CTCAEv5
- Concomitant medication record

Follow up 2 at trial week 18

- Imaging Assessment (MRI) as per standard care, including response assessment by RECIST v1.1
- Physical exam (including assessment of vaginal adhesions)
- ECOG performance status

- Disease Assessment questions (faecal urgency assessment and use of vaginal dilators)
- Translational urine collection as detailed in the CRAIN lab manual
- Adverse event assessment by CTCAEv5
- Concomitant medication record

5.4 DEVIATIONS AND SERIOUS BREACHES

Any trial protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the local R&D Office immediately. SCTU will then advise of and/or undertake any corrective and preventative actions as required.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and/or the trial protocol will immediately be reported to the regulatory authorities and other organisations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

5.5 TRIAL TREATMENT DISCONTINUATION AND PARTICIPANT WITHDRAWAL

Participants may withdraw voluntarily from the trial or the Principal Investigator/Treating Healthcare Provider may discontinue a participant from the trial treatment for appropriate medical reasons.

5.5.1 Discontinuation of Trial Treatment

A participant may withdraw, or be withdrawn, from trial treatment for the following reasons:

- Pregnancy*
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the trial intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g. infectious disease) illness

*In the case of pregnancy, the investigator must immediately notify the Sponsor of this event. In all cases, the study drug will be permanently discontinued in an appropriate manner.

Where possible, participants discontinued from tolinapant only should continue with the trial-associated processes as per the Schedule of Observations and Procedures.

Full details of the reason for trial treatment discontinuation should be recorded in the eCRF and the participants medical record.

5.5.2 Trial Withdrawal

The participant/legal representative is free to withdraw consent from the trial at any time without providing a reason, and without their medical care or legal rights being adversely affected.

Investigators should explain to participants the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, participants who have withdrawn from trial treatment should continue with relevant trial-associated processes as per the Trial Schedule of Observations and Procedures. If participants additionally withdraw consent for this, they should revert to standard clinical care/follow up as deemed by the responsible clinician. It would remain useful for the trial team to continue to collect any routine data (i.e., data that can be collected with no impact on the participant beyond standard clinical care/follow-up), and this will continue unless the participant explicitly requests otherwise. If this is requested, this constitutes complete withdrawal from the trial and should be recorded as end of study for the participant in the relevant eCRF and in their medical record, and no further data should be collected for this participant.

5.6 TRANSLATIONAL SAMPLES

5.6.1 Biopsies

- Pre-treatment biopsies (1 per patient)
- Brachytherapy biopsies (1 per patient)

Pre-treatment archival biopsy processed as formalin-fixed paraffin-embedded (FFPE) blocks will be collected from all patients where consent has been obtained.

A second biopsy will be taken at brachytherapy after completion of 5 weeks external beam chemoradiation using information from the week 5 MRI scan to direct biopsies from likely viable tumour sites. Central storage will be at the Manchester Cancer Research Centre HTA licensed Tissue Bank (HTA licence number 30004).

A section from the diagnostic FFPE tissue biopsy will be taken for haematoxylin and eosin staining to confirm presence of tumour and determine percentage of tumour cells. Further sections will be immunohistochemically stained for a number of markers associated with cell proliferation (Ki67), apoptosis (cytokeratin-18, caspase-3) and immune cells (macrophages; CD68). Images will be analysed using automated image analysis programmes available in house (Definiens and InForm). Additional sections will be used for DNA and RNA extraction and sequenced using Clariom array, for genomic analyses. The transcriptomics will be used to develop and test existing apoptotic and immunomodulatory signatures (8). In addition, principal component analysis and hierarchical clustering will be used to compare the gene expression between responders and non-responders since molecular subtyping of cervical cancer may have value in stratification for response over traditional histopathological categorisation (9).

5.6.2 Blood

All study participants will be asked for translational blood samples. One sample will be to study "on-target" effects of tolinapant by measuring cIAP levels in PBMCs. The rest will enable biomarker discovery. This data will enable powering of a future phase II study for biomarker validation, thus enabling both biomarker and clinical development to occur in parallel.

Pre- and post-treatment blood samples will be collected for blood based biomarker analysis. Potential biomarkers of apoptosis include circulating tumour cells (CTCs), circulating free DNA (cfDNA), DNA nucleosomes and cytokeratins (proteomics). CTCs have been implicated in other solid tumours as a prognostic factor with an interest in the dynamic changes in CTC level being associated with treatment response (10). CTCs have been detected in women with cervical cancer and there is a suggestion that they are related to a poor prognosis (11). There are preliminary data that dynamic changes in cfDNA may be associated with response to chemoradiation (12). Blood samples will be analysed for CK18 and M30/M65 by multiplex plate-based sandwich ELISAs chemiluminescent arrays. Response to tolinapant and apoptotic rate will be measured using CK18 and its caspase-cleaved fragments. The ratio of CK18 and M30/M65 can be used to determine the mode of cell death (necrosis v apoptosis), leading to study of the mode of action of treatment (13). Since baseline levels of CK18 biomarkers can be variable, and drug-induced changes can be acute and transitory, it is important to take multiple pre-treatment samples less than 7 days apart, plus early post-treatment samples where possible to mitigate for reproducibility. Data from a previous study with tolinapant has shown immunomodulatory effects with release of inflammatory cytokines eg Interleukin 2, INF γ and TNF β on treatment. Weekly plasma samples will be used to investigate this further. A separate laboratory protocol will be produced to outline the methods in detail.

Any samples remaining once trial analyses are complete will be stored appropriately for future use, if patient consent allows. Southampton CTU will keep record of the conditions of consent for each patient sample. If a patient does not give consent for their samples to be used outside of the trial or subsequently withdraws consent for their samples to be used, Southampton CTU will inform the relevant central laboratory who will be responsible for destroying the samples and confirming this in writing to Southampton CTU once done.

5.6.3 Imaging Scans

As per standard of care, all patients with uterine cervix cancer will receive three diagnostic MRI scans during the time period of this study. If the patient provides optional consent, participating centres will acquire

additional research sequences during these scan times. A short visual grading assessment (VGA) will be required to assure quality assurance and highlight any problems with acquisition. Details regarding the acquisition parameters and VGAs can be found in the Imaging Manual. These steps minimise technical errors and test reproducibility.

In order to research the quantitative imaging biomarkers, the scan images of at least 20 patients will be centrally analysed. Tumour volumes-of-interest will be drawn to allow summary measures to be compared between visits. Quantitative measures will be calculated on a voxel-by-voxel basis using in house software and compared between visits.

5.6.4 Urine

Translational studies will explore the urine biomarkers associated with treatment response and toxicity. Genomic aberrations detected in urinary cell-free DNA (ucfDNA) have been demonstrated to be the same as those in primary tumours. Therefore, urine could be an easily accessible source of genetic material that reflects the genomic aberrations of cancer (14). More importantly, urine has a distinct advantage as a non-invasive sample source over tissue and blood (14), especially for patients who need repeated sampling to monitortreatment response and toxicity. As urine contains lower levels of protein than blood, the isolation of DNA fragments may be technically easier (15). ucfDNA has been studied in urological cancers like bladder and prostate but also in non-urological cancers such as breast, lung, colon and hepatocellular carcinoma (16). It has been established that DNA released from cells into the circulation can be filtered through the kidney into urine. ucfDNA can provide reliable and reproducible information on cancer-specific DNA alterations, a finding that has potential for monitoring of treatment response. Dynamic changes in ucfDNA will be quantified and mapped. This should enable development of sensitive and specific ucfDNA biomarkers from the urine that provide information about an individual patient's tumour response and organ-specific toxicities. A separate laboratory protocol will be produced to outline the methods in detail.

Any samples remaining once trial analyses are complete will be stored appropriately for future use, if patient consent allows. Southampton CTU will keep record of the conditions of consent for each patient sample. If a patient does not give consent for their samples to be used outside of the trial or subsequently withdraws consent for their samples to be used, Southampton CTU will inform the relevant central laboratory who will be responsible for destroying the samples and confirming this in writing to Southampton CTU once done.

6 TREATMENTS

6.1 TREATMENT SCHEDULE

6.1.1 Cisplatin Administration

CRT treatment weeks should always start on a Monday, however cisplatin can be given on any day within the week. Weekly cisplatin dose should be 40mg/m^2 and in line with local practicecan be dose banded and does not need to be given prior to radiotherapy.

6.1.2 External Beam Radiotherapy Administration

External beam radiotherapy administration should be a standard dose of 45Gy in 25 daily fractions over 5 weeks with nodal boosting performed using a simultaneous integrated boost (SIB) for radiologically positive nodes to a total dose of 55-60Gy in 25 daily fractions. The QA programme for the study will be co-ordinated by the National Radiotherapy Trials QA (RTTQA) Group. The CRAIN trial is streamlined through participation in the INTERLACE trial and EMBRACE.

6.1.2.1 Pre-Accrual QA

The following QA will be completed before opening the trial at each centre. Please contact RTTQA for all relevant documentation and datasets necessary for completion of the RT QA programme.

A) Facility Questionnaire: to be completed and submitted online
B) Brachytherapy Dosimetry Audit

C) EBRT Dosimetry Audit
D) EBRT outlining (benchmark) case: Outlining case 1 used for the INTERLACE trial is available to download from the RTTQA website. This should be completed by the radiotherapy lead from each participating site.
E) EBRT Planning (benchmark) case: Planning case 2 used for the INTERLACE trial is available to download from the RTTQA website. This should be completed by each participating site.
F) Brachytherapy example case (dummy run): each centre will be asked to submit an anonymised example case they have treated recently to complete their brachytherapy outlining and planning QA.

6.1.2.2 On-trial QA

There are no on-trial RT QA requirements for the CRAIN trial.

6.1.3 Brachytherapy Administration

This is followed by brachytherapy for which common schedules will be a further 28Gy in 4 fractions high-dose-rate or 34Gy in 2 fractions pulsed- dose-rate, or equivalent.

6.1.4 Tolinapant Administration

Tolinapant in fixed dose capsules of 30 or 90 mg taken orally daily for seven consecutive days as an outpatient (followed by seven consecutive days off) prior to radiotherapy on alternate weeks (weeks 1, 3, 5) during chemoradiation. Tolinapant can be taken with or without food, with the exception of PK days. On days with PK sampling, patients should refrain from eating (including soup) or drinking milk or juice for at least 2 hours prior to ingesting study drug(s) and 2 hours after ingesting study drug (4 hour fasting window). When a patient is registered, they will be allocated to a dose level of tolinapant, they will continue to take this dose of tolinapant throughout their participation in the CRAIN trial. The dose levels of tolinapant that will be used in this trial are detailed in the table below.

Dose Level	**Tolinapant**
Level 1	60 mg
Level 2 (Starting level)	90 mg
Level 3	120 mg
Level 4	150 mg
Level 5	180 mg

6.2 IMP SUPPLY

Taiho Oncology, Inc will be supplying tolinapant free of charge to include clinical trial packaging, labelling and distribution to participating sites. Tolinapant will be supplied as hydroxypropyl methylcellulose (HPMC) capsules that contain either 30 or 90 mg of tolinapant. The capsules are provided in induction-sealed bottles. Each bottle will contain 14 capsules. Study drug must be kept secure at site in temperature-controlled refrigerator between 2°C and 8°C.

Re-ordering will be completed using the Endpoint drive system (see pharmacy manual for details). A maximum of 50 bottles can be ordered at a time.

6.3 ADMINISTRATION

Cisplatin is given intravenously with pre and post hydration once weekly during the five weeks of radiotherapy, according to local institutional standard practice and in line with EMBRACE or INTERLACE processes.

Tolinapant in fixed dose capsules of 30 or 90 mg taken orally daily for seven consecutive days as an outpatient (followed by seven consecutive days off) prior to radiotherapy on alternate weeks (weeks 1, 3, 5) during chemoradiation. At each tolinapant administration week, the patients clinical condition should be reviewed by a delegated clinician prior to prescribing and dispensing.

Patients will receive a diary to record the specific time each dose has been taken and to record reasons for any missed doses. The patients will be instructed to bring the diary and any remaining capsules or empty bottles to the clinic at their next visit. The study staff will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules should be returned to the pharmacy department after week 1,3 and 5 to be counted and recorded within the patient dispensing and returns log.

Tolinapant can be taken with or without food, with the exception of PK days. On days with PK sampling, patients should refrain from eating (including soup) or drinking milk or juice for at least 2 hours prior to ingesting study drug(s) and 2 hours after ingesting study drug (4 hour fasting window).

If a subject forgets to take or misses a dose at their usual time, they may still take the dose up to 8 hours after this time. After that time, they should skip the dose for that day and wait until the next day to resume their normal dosing schedule.

6.4 DRUG ACCOUNTABILITY LOGS

An accountability log will be required for the IMP (tolinapant) supplied for this trial. A patient specific dispensing and returns logs for tolinapant will also be required. These logs will be supplied to sites by SCTU.

Any returned capsules must not be re-dispensed to any patient and should be held by site until the accountability logs have been reviewed by a monitor. Following monitor review, resolution of any inconsistencies, and subsequent SCTU approval returned IMP can be destroyed as per local practice and documented on the tolinapant destruction log.

Cisplatin will be supplied from standard hospital stock and as such there is no requirement for drug accountability logs.

6.5 CONCOMITANT MEDICATIONS

Information on any treatment/medications (including those given as standard of care) received by the participant, along with dose, frequency and therapeutic indication, from prior to starting trial treatment up to 12 weeks after the last dose of tolinapant will be recorded in the electronic case report form (eCRF).

6.6 PROHIBITED AND RESTRICTED THERAPIES DURING THE TRIAL

If there is a clinical indication for any medication or vaccination specifically prohibited during the trial then discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision regarding medication or vaccination rests with the investigator and/or subject's primary physician. Decision for the participant to continue on the trial therapy requires mutual agreement of the investigator, sponsor and the subject.

No other investigational medicinal products should be received whilst on study.

Prohibited concomitant medication:

- Other anticancer treatments, including other investigational drugs or therapies.
- QT prolonging agents (with the exception of palonesetron/Akynzeo when used as part of the chemotherapy antiemetic regime)
- Strong CYP3A4 inhibitors or inducers

Due to the risk of potential cIAP-related liver injury, statins and other medications that can affect liver function should be used with caution.

Guidance on vaccines, including for COVID-19:

- Administration of a live, attenuated vaccine within the four weeks prior to enrolment or for five months after the last dose of tolinapant is prohibited
- The benefit of using the currently authorized COVID-19 vaccines is likely to outweigh any potential risk
- It is the investigator's decision on whether to administer COVID-19 vaccines based on the risk of COVID-19 infection/complications and for potential benefit from vaccination, general condition of

the patient and the severity of COVID-19 outbreak in a given area or region and in accordance with the vaccine label

- Institutional guidelines should be considered in the decision making
- Vaccines are considered concomitant medication and must be reported on the Concomitant Medication eCRF as per protocol instructions
- Where available, details regarding COVID-19 vaccination (such as vaccination date, anatomic site, laterality, and manufacturer) should be captured in the patient's case notes

6.7 RISKS ASSOCIATED WITH TOLINAPANT

Identified Risks	Severity	Action to Take with tolinapant
Pneumonitis	Grade 1	Continue without modification
	Grade 2	If event occurs during week 1 interrupt study treatment until recovery to Grade $\leqslant$1. If not recovered to Grade $\leqslant$1 by week 3 or if event subsequently worsens to grade 2 later in treatment, permanently discontinue study treatment. If event occurs after week 1, permanently discontinue study treatment.
	Grades 3 or 4	Permanently discontinue study treatment.
Rash maculo-papular	Grade 1	Continue without modification
	Grade 2	If event occurs during week 1 interrupt study treatment until recovery to Grade $\leqslant$1. If not recovered to Grade $\leqslant$1 by week 3 or if event subsequently worsens to grade 2 later in treatment, permanently discontinue study treatment. If event occurs after week 1, permanently discontinue study treatment.
	Grade 3	If event occurs during week 1 interrupt study treatment until recovery to Grade $\leqslant$1. If not recovered to Grade $\leqslant$1 by week 3 or if event subsequently worsens to grade 2 later in treatment, permanently discontinue study treatment. If event occurs after week 1, permanently discontinue study treatment.
Pancreatitis	Any grade	Permanently discontinue study treatment.
AEs that are classified as related to tolinapant or its interaction with CRT	Grade 1 or 2	Continue without modification
	Grade 3	If event occurs during week 1, clinicians can interrupt study treatment until recovery to Grade $\leqslant$1 if clinically indicated. If not recovered to Grade $\leqslant$1 by week 3 or if event subsequently worsens to grade 2 later in treatment, permanently discontinue study treatment. If event occurs after week 1, permanently discontinue study treatment.
	Grades 4	Permanently discontinue study treatment.

6.8 DOSE DELAYS AND MODIFICATIONS FOR TOXICITY

If a patient experiences any expected or unexpected related toxicity from tolinapant, tolinapant administration may be delayed as per the guidelines in section 6.7. Tolinapant treatment can only be delayed in week 1 and must recommence in week 3 if the patient has recovered to a suitable grade of toxicity. If tolinapant administration cannot recommence at week 3, tolinapant should be permanently discontinued.

A delay in CRT should only be done when clinically indicated or in the case of a trial-related dose limiting toxicity.

7 SAFETY

7.1 DEFINITIONS

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

Adverse Event (AE): any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered.

All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure (IB) for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the IB/SmPC which occur in a more severe form than anticipated are also considered to be unexpected. Reports which add significant information on specificity or severity of a known documented adverse event are to be considered unexpected.

Serious Adverse Event (SAE) or **Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** any untoward medical occurrence or effect that at any dose:

- **Results in death**
- **Is life-threatening***
- **Requires hospitalisation, or prolongation of existing hospitalisation****
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- Important medical events***.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient 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.

** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Note: *It is the responsibility of the Principal Investigator (PI) or delegate to grade an event as 'not serious' (AE) or 'serious' (SAE).*

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

In addition to the definition above, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform

Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. Elevations in liver biochemistry that meet Hy's Law criteria are reported as SAEs, using the important medical event serious criterion if no other criteria are applicable.

7.2 TRIAL SPECIFIC REQUIREMENTS

All Adverse Events (AEs) should be reported on the AE eCRF. Any abnormal lab values that are deemed not clinically significant by a delegated clinician do not need to be reported as AEs (unless considered relevant by the treating clinician).

7.2.1 Seriousness

A complete assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

All reportable adverse events that fulfil the criteria definition of 'serious' in protocol section 7.1, must be reported to SCTU using the Serious Adverse Event Report Form. Specific exceptions to this (as listed below) should be recorded as AEs rather than SAEs.

7.2.2 Exceptions:

For the purposes of this trial, the following SAEs **do not** require reporting to SCTU using the Serious Adverse Event Report Form:

- Death due to cervical cancer
- Hospitalisation for elective treatment of a pre-existing condition (the pre-existing condition needs to have been captured within the medical history CRF).
- Standard of care hospital admissions for the administration of brachytherapy (any prolongation of hospital stay beyond the expected admission due to AE should be reported as an SAE).
- Adenocarcinoma or squamous cell carcinoma of the cervix disease progression (unless this progression is deemed related to the trial in which case, it should be reported as an SAE).

7.3 CAUSALITY

A complete assessment of the causality must always be made by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

If any doubt about the causality exists, the local investigator should inform SCTU who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality, SCTU will classify the event as per the worst-case classification and if onward reporting is required, the MHRA will be informed of both parties' points of view.

Relationship	Description	Denoted
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	SAR/ SUSAR

Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR/ SUSAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR/ SUSAR

7.4 EXPECTEDNESS

Expectedness assessments are made against the approved Reference Safety Information (RSI). The RSI for this trial is specified within the document versions listed in the tables below:

Name of Product	IB	Section /Table No.	Manufacturer	Date of text revision DD-MMM-YYYY
Tolinapant (also known as ASTX660)	IB v7	Table 52	Astex Pharmaceuticals, Inc.	18-Aug-2021

The nature and/or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available then the AE should be recorded as 'unexpected'.

7.5 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the SCTU in the first instance.

7.5.1 Reporting Details

Any questions concerning adverse event reporting should be directed to the SCTU in the first instance.

7.5.1.1 Adverse Events

All reportable AEs should be recorded on the eCRF as per the trial specific requirements listed in Section 7.2.

All adverse events should also be recorded in the patient's medical records.

7.5.1.2 Serious Adverse Events

For all reportable SAEs, an SAE report form should be completed with as much detail as possible (including any relevant anonymised treatment forms and/or investigation reports) and emailed to SCTU immediately but at least within 24 hours of site becoming aware of the event. The SCTU will forward on received reports to Taiho Clinical Safety and Risk Management at taihoctsafetyreporting@taihooncology.com within 1 working day of becoming aware of the event

Or

Contact SCTU by phone for advice and then email a scanned copy of the SAE report form completed as above.

SAE REPORTING CONTACT DETAILS

Please email a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event

ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 5154 (Mon to Fri 09:00 – 17:00)

The event term should be the most appropriate medical term or concept (which the SCTU will code to MedDRA) and grades given in accordance with the NCI CTCAE v5.

Additional information should be provided as soon as possible as it is received if all information was not included at the time of reporting.

7.5.2 Time Frame For Reporting, Follow Up and Post-trial SAEs

The reporting requirement for all AEs and SAEs affecting participants applies:

- Between provision of informed consent, and the first dose of tolinapant: for all AEs and SAEs that are considered by the investigator to be related to trial procedures
- Between the first dose, and 30 days after the last dose of tolinapant: for AEs and SAEs

All unresolved adverse events should be followed by the investigator until one of the end of trial criteria is met (i.e. lost to follow up, withdrawal, end of study at trial week 18 etc.). At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this trial. The investigator should notify the trial sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated trial participation that may reasonably be related to this trial.

7.5.3 Pre-existing Conditions

Medically significant pre-existing conditions (prior to informed consent) should not be reported as an AE unless the condition(s) worsens during the trial. The condition, however, must be reported on the Medical History eCRF. Any adverse events that occur after Informed Consent should be recorded on the AE eCRF as per safety reporting section.

7.5.4 Pregnancy

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

If a participant becomes pregnant whilst taking part in the trial or during a stage where the foetus could have been exposed to an IMP (up to 6 months following IMP administration), the investigator must ensure that the participant and the participant's healthcare professional are aware that follow up information is required on the outcome of the pregnancy.

Follow-up is of course, dependent on obtaining informed consent for this from the participant.

Women having radical chemoradiation for cervical cancer are all screened for pregnancy before commencing treatment and informed of the risk of pregnancy.

During chemoradiation ovarian function is impaired and the endometrium irradiated to preclude a successful implantation. During the subsequent brachytherapy the uterine cavity is probed and very high dose radiation delivered to the cavity.

Following radical chemoradiation for cervical cancer women will undergo complete ovarian failure and will be infertile.

The nature of the disease and treatment therefore means that concerns about pregnancy during drug exposure are minimal.

If the participant leaves the area, their new healthcare professional should also be informed.

7.6 RESPONSIBILITIES

7.6.1 Principal Investigator (PI)

The PI, or medically qualified doctor who is registered on the delegation of responsibility log, is responsible for:

1. Using medical judgement in assigning seriousness, causality and whether if requested, the event/reaction was anticipated using the Reference Safety Information approved for the trial.
2. Ensuring that all SAEs are recorded and reported to the SCTU immediately, or at a least within 24 hours, of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with the SCTU if a record of receipt is not received within 1 working day of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the SCTU in line with the requirements of the protocol.

7.6.2 Chief Investigator (CI) / delegate or independent clinical reviewer:

The CI, or delegated clinical reviewer, is responsible for:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether if requested, the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Upon request review Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.

7.6.3 Sponsor / delegate

The Sponsor, or delegate, is responsible for:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Checking causally related events against the approved RSI, in place at time of event onset.
4. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
5. Reporting all SAEs, SARs and SUSARs to Taiho Clinical safety and risk management at taihoctsafetyreporting@taihooncology.com with in 1 working day of awareness.
6. Ensuring that expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC are within the required timelines.
7. Providing SUSAR submission confirmation to Taiho Clinical safety and risk management at taihoctsafetyreporting@taihooncology.com
8. Notifying Investigators of SUSARs that occur within the trial.
9. Regularly checking for and notifying PIs of updates to the Reference Safety Information for the trial.

10. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

7.7 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken the CI/Sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and REC of the measures taken and the circumstances giving rise to those measures.

7.8 DEVELOPMENT SAFETY UPDATE REPORTS (DSUR)

SCTU will prepare DSURs at the molecule level. These will be shared with the Sponsor for providing, as necessary, to the Competent Authority (the MHRA in the UK), and the appropriate REC.

The report will be submitted within 60 days of the Development International Birth Date of the trial each year until the trial is declared ended.

8 STATISTICS AND DATA ANALYSES

8.1 DESIGN, SIMULATIONS AND SAMPLE SIZE

The trial uses a two-stage TiTE-CRM design. The first two/three participants will be given dose level 2 (90mg) and followed up for 7 weeks after starting tolinapant; if no DLT occurs and the SRC agree, the next participants recruited after the SRC decision will receive dose level 3 (120mg), and so on. On average 2 patients are expected to be recruited per month with defined dose slots available per dose level. Once a DLT occurs, the TiTE-CRM model will be used to recommend the next dose. Once the TiTE-CRM model is in use eligible patients will be continuously recruited and the TiTE-CRM model used to recommend the assigned dose of tolinapant. The actual number of patients required and the duration of trial will depend on any toxicities observed and dose escalation decisions. However, a maximum of 42 patients will be recruited and treated.

Statisical design and simulations

Given the relatively long assessment period for dose limiting toxicities (DLTs) of 12 weeks, a time-to-event (TiTE) CRM design (18) was deemed appropriate. This design allows for dose escalation without having to wait for full information from every participant enrolled, hence shortening the length of the study. Some key elements of the decision-making process and simulation results for the design are detailed below.

Targeted toxicity level

The current treatment is given with curative intent. Therefore, it was deemed important not to create an excessive number of toxicities that could disrupt current treatment. DLTs for existing treatment is thought to be in the range 5 to 15% (19). The target toxicity level (TTL) was therefore chosen as 25% as an acceptable rate above this.

Number of doses

Five doses were chosen, from 60mg to 180mg in fixed dose 30mg increases, according to previous results from Taiho Oncology Inc, where 180mg was recommended as the phase 2 dose when used as monotherapy (ASTX660 Investigator Brochure). These doses were thought to cover a range of outcomes from a low number of dose-limiting toxicities (DLTs) to those plausibly at, but potentially beyond, the TTL.

Starting dose level

The second dose (90mg) was chosen as the starting dose. This dose was thought to have DLT rate below the TTL, while also allowing for de-escalation, if needed.

Stopping rules
Two stopping rules were developed as part of the design simulations.

Firstly, once a fifteenth consecutive participant was recommended a given dose, no more participants were recruited. Fifteen was chosen as the limit as, under simulations for a number of scenarios, this meant fewer than 10% of trials would have chosen an MTD different to the dose with fifteen consecutive participants. In addition, the trial will review the safety of at least 18 patients at the recommended phase II dose. Therefore the trial will stop for success if 15 concurrent patients are treated at the current recommendation for the MTD, whilst also ensuring a total of at least 18 patients have been treated at the recommended phase II dose.

The second stopping rule was for safety and was to stop the trial if the DLT rate was estimated to be 35% or more for the lowest dose. The figure of 35% was chosen as it is 10% above the upper limit of what was deemed an acceptable toxicity rate, allowing for some overestimation of the DLT rate for the lowest rate if it was still within the acceptable range of DLT rates.

Sample size
As a result of the stopping rules, all simulated toxicity scenarios averaged 24-29 participants, while a maximum of 42 patients was deemed suffient to estimate the MTD and be able to recruit additional patients to ensure 18 are treated at the recommended phase II dose.

Weighting
TiTE CRM requires specification of the weighting i.e., how much a participant contributes to the recommended next dose when the DLT assessment period is not complete. This design uses a linear weighting, meaning that information accrued through the DLT assessment period is given weight equal to the proportion of the assessment period that has passed.

8.2 STATISTICAL ANALYSIS PLAN (SAP)

All participants will be accounted for. The definition of an evaluable patient for safety is any patient who has received any exposure to tolinapant.

Dose-limiting toxicities are defined in Section 3.3. A safety review committee will be responsible for confirming trial dose escalations within the trial, informed by the dose-toxicity model and safety data. The SRC will decide if patients should be replaced based on the amount of treatment received.

If a fifteenth consecutive participant was recommended a given dose and 18 patients had been treated at the likely recommended phase II dose, no more participants would be recruited. All participants would then be followed up until a DLT or 12 weeks, the model would then be updated with this information, and this would be used to inform the SRC's decision on the final recommended phase II dose.

At the end of this phase dose finding data will be summarised descriptively, including baseline characteristics for participants. Dose delivery and toxicities will be reported. Toxicities will be reported by cohort, including type, number, range and worst grade. Complete and partial response rates at 3 months after treatment will also be summarised descriptively along with relative dose intensity.

The parameters of the dose-toxicity model will be described alongside Bayesian posterior point estimates of the risk of toxicity at each dose and corresponding 95% credible intervals.

All analysis will be done in R, Stata or SAS.

9 TRANSLATIONAL RESEARCH

9.1 TRANSLATIONAL RESEARCH SAMPLES AND SCANS

Sites will be provided with a CRAIN Trial Laboratory Manual for a detailed description of sample collection, handling and shipment processes. Research scan acquisition and sharing will be detailed in the CRAIN Imaging Manual. A 'CRAIN Translational Samples Dispatch Log' needs to be maintained for each patient documenting the collection, storage and shipment of translational samples.

1. **Archival FFPE tumour samples**: will be collected at screening on all patients where consent has been obtained.
2. **Blood samples:** these will be taken at baseline, RT Treatment weeks 1, 2, 3, 4, 5, Brachytherapy Weeks 1, 2 and Follow up visit 1.
3. **Biopsy:** these will be taken at Brachytherapy Week 1
4. **MRI scan images:** Routine diagnostic imaging is taken at baseline, RT Treatment week 5 and Follow up visit 2 as part of standard of care. If the patient provides optional consent, additional research sequences will be acquired and the images will form part of the translational research.

Central blood and tumour sample processing and storage will be at the Manchester Cancer Research Centre at The University of Manchester (MCRC), the Cancer Research UK Manchester Institute and Resolian Bioanalytics (on behalf of Taiho). All samples will be identified via a unique trial ID number, with linked anonymisation.

In addition, patients will also be asked to sign consent for transfer of samples for use in future analyses, as yet to be defined, linked to the overall objectives of the CRAIN trial with collaborators in other research groups who may be in the UK or abroad and in either the academic or commercial sector. All such work would maintain patient confidentiality and anonymisation in presentation of data.

Electronic data generated such as diagnostic imaging or reports from the various trial sites will be imported onto the Christie NHS Trust servers using trusted and dedicated NHS pathways. The network is already used on a daily basis to securely transfer data between NHS PACS at different sites. This imaging data, alongside data generated at the Christie NHS Trust, will be pseudonymised and a pseudonymised key will link the study ID to the participant's name. See Imaging Manual for further information.

There is an established and ethics approved software programme that links the Christie NHS Hospital and the University of Manchester servers. Pseudonymised imaging data is routinely transferred from the Christie to the University of Manchester by the Radiotherapy Related Research group. Both servers can only accessed by authorised computers with dedicated username/password privileges. These privileges will be determined by the principal/chief investigator.

9.2 TRANSLATIONAL ANALYSIS

Objectives	Analysis Timepoint	Sample Used
Monitoring pharmacokinetics of tolinapant	End of trial	PK samples
Identification of markers of therapy response	End of trial	Immune Markers
Identification of predictors of response to tolinapant + CRT	End of trial	Immune markers
		Diagnostic biopsy
		Brachytherapy biopsy
		MRI imaging
Identification of patients with hypoxic tumours	End of trial	Diagnostic biopsy
Identification of genetic factors affecting treatment response	End of trial	Genomic samples
		Diagnostic biopsy

		Brachytherapy biopsy

Future Endpoints:
Remaining blood and tissue samples will be stored under HTA regulations for future ethically approved studies.

10 REGULATORY

10.1 CLINICAL TRIAL AUTHORISATION

This trial has a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA).

11 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the trial should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the trial without giving reasons must be respected.

After the participant has entered the trial, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and trial follow-up without giving reasons and without prejudicing their further treatment.

11.1 SPECIFIC ETHICAL CONSIDERATIONS

The SCTU uses the electronic data capture tool called RAVE, which will be used in the CRAIN trial for sites to input anonymised trial data. The servers that this database will be held on are based in the USA and therefore being stored outside of the UK and EEA. The Patient Information Sheet and Informed Consent Form shall highlight to patients where the data shall be held.

11.2 ETHICAL APPROVAL

The trial protocol has received the favourable opinion of a Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries.

11.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the participant information sheet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

11.4 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the trial. The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On e/CRFs participants will not be identified by their names, but by an identification code.

12 SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial task allocation matrix.

The duties assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Non-Commercial Agreement.

12.1 INDEMNITY

For NHS sponsored research HSG (96) 48 reference no.2 applies. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

12.2 FUNDING

The CRAIN trial is funded by Cancer Research UK with provision of tolinapant by Taiho Oncology, Inc.

12.3 SITE PAYMENTS

The payments assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Non-Commercial Agreement.

This study is adopted onto the NIHR portfolio. This enables Trusts to apply to their comprehensive local research network for service support costs, if required.

12.4 PARTICIPANT PAYMENTS

Participants will not be paid for participation in this trial.

13 TRIAL OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group (TMG), the Trial Steering Committee (TSC) and the Safety Review Committee (SRC).

13.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the trial, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the trial.

The CRAIN TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

13.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet in person or virtually at least yearly and have at least one further teleconference meeting during the year. The majority of members of the TSC, including the Chair, should be independent of the trial.

The CRAIN TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

13.3 SAFETY REVIEW COMMITTEE (SRC)

The SRC will consist of:

- Chief Investigator
- Principal Investigators and representatives from site
- Independent statistician
- Independent clinician

- Trial Statistician
- Trial Manager

The SRC Charter for this study will define the exact membership and who should be present for decisions to be made. Further experts may be consulted by the SRC as necessary. The SCTU Senior Quality Assurance Manager (or other suitable delegated member of the QRT team) and Sponsor representative should always be present at the SRC if there are safety issues for discussion.

Recruitment will be limited to three patients before the first SRC. Once two evaluable patients have received at least 7 weeks of treatment each, the SRC will review and assess the safety and toxicity of all patients. The SRC will determine whether the trial should continue, however there will be no pause in recruitment up to the maximum of three patients whilst the review takes place. The SRC will also decide the recommended dose for future patients, the maximum number of patients to recruit on that dose and the minimum amount of data required before meeting again (this avoids too many patients being treated on the same dose). The SRC can also meet at any other time if deemed necessary, especially if there are any safety concerns. The decisions that are likely to be made by the SRC are recorded in Appendix E.

14 DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with the current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the trial and for any participant- specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Participant Information Sheet and Informed Consent Form will outline the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the electronic case report forms (eCRF). ECRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The original laboratory reports must be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the trial specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created.

Data queries will either be automatically generated within the eCRF, or manually raised by the trial team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis.

15 DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved

proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

16 MONITORING

16.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Data queries on eCRFs will be raised to site either automatically or manually by STCU staff via the database. Sites should respond to queries on the database and provide an explanation/resolution to any discrepancies within the required timeframe. Queries and responses are recorded within the database audit trail. There are a number of monitoring principles in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

For central monitoring, Informed Consent Forms will be scanned and sent to SCTU via secure electronic means; to the nhs.net secure account for SCTU, by SafeSend or by encrypted email to a University email account with limited access. Drug accountability forms will be sent electronically to SCTU to allow for review prior to onsite monitoring.

16.2 CLINICAL SITE MONITORING

Sites will be monitored as per the CRAIN Trial Monitoring Plan. Sites will be contacted by the SCTU Trial Team/ Monitoring Team to arrange a monitoring visit and request that patient records to be reviewed be made available. Where on-site monitoring is not permitted due to the COVD-19 pandemic, alternative strategies such as remote monitoring will be deployed. These will be fully described in the trial monitoring plan. Clinical site monitoring frequency will be determined by the recruitment figures at each participating centre as detailed in the Trial Monitoring Plan. Triggered site monitoring will occur where required.

16.3 SOURCE DATA VERIFICATION

Upon receipt of a request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to trial staff and departments (e.g. pharmacy).

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the trial, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the trial site without informed consent.

16.4 SOURCE DATA

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

16.5 AUDITS AND INSPECTIONS

The trial may be participant to inspection and audit by University Hospital Southampton NHS Foundation Trust (UHS) (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, UK Policy Framework for Health & Social Care Research, applicable contracts/agreements and national regulations.

17 RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. All source documents will be retained for a period of 25 years following the end of the trial.

Sites are responsible for archiving the ISF and participants' medical records.

The Sponsor is responsible for archiving the TMF and other relevant trial documentation.

18 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

19 REFERENCES

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20 APPENDICES

20.1 APPENDIX A: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE V5)

Please go to the following website to access the CTCAE Version 5

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

20.2 APPENDIX B: RECIST

Please go to the following website to access RECIST Version 1.1:

https://recist.eortc.org/

20.3 APPENDIX C: ECOG PERFORMANCE STATUS

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

20.4 APPENDIX D: MANAGEMENT OF TOLINAPANT-SPECIFIC ADVERSE EVENTS

Expected side effects – Expected Adverse Events are recorded in the IB as per the versions specified in section 6.4. Please refer to these approved documents for full list of expected side effects.

20.5 APPENDIX E: DOSE MODIFICATION, RECRUITMENT OF ADDITIONAL PATIENTS & SELECTION OF THE RECOMMENDED PHASE II DOSE

All dose modifications will be guided by safety data from all trial participants. The SRC will decide, based on the safety and pharmacokinetic data specified, how the trial will proceed. The likely courses of action are:

- **Recruit additional patients into the study and dose escalate to the next highest available dose (dose skipping is not allowed). This will be considered if:**
  - There is no concern of significant toxicity in trial patients and
  - The TiTE-CRM model recommends a dose escalation
- **Recruit additional patients into the study at the current dose. This will be considered if:**
  - There is no concern of significant toxicity in trial patients and
  - The TiTE-CRM model recommends continuing at the current dose

- **Recruit additional patients into the study and dose reduce to any dose below the current dose. This will be considered if:**
  - There is concern of significant toxicity in trial patients or
  - The TiTE-CRM model recommends a dose de-escalation
- **Stop evaluation of the study at the current dose level due to unacceptable toxicity. This will be considered if:**
  - There is major concern of significant toxicity in trial patients or
  - There is sufficient evidence to suggest that dose level 1 (60mg) is too toxic i.e. has a posterior probability of DLT of 35% or higher
- **Stop evaluation of the study and recommend the phase II dose. This will be considered if:**
  - There is no concern of significant toxicity in trial patients at the recommended dose and
  - A total of at least 18 patients have been treated at the recommended phase II dose

20.6 APPENDIX F: DRUGS THAT CAN PROLONG THE QT INTERVAL

Antimicrobials	**Antipsychotics** (all have some risk)
Erythromycin	Risperidone
Clarithromycin	Fluphenazine
Moxifloxacin	Haloperidol
Fluconazole	Pimozide
Ketoconazole	Chlorpromazine
Antiarrhythmics	Quetiapine
Dronedarone	Clozapine
Sotalol	**Antidepressants**
Quinidine	Citalopram/escitalopram
Amiodarone	Amitriptyline
Flecainide	Clomipramine
	Dosulepin
Others	Doxepin
Methadone	Imipramine
Protein kinase inhibitors e.g. sunitinib	Lofepramine
Some antimalarials	**Antiemetics**
Some antiretrovirals	Domperidone
Telaprevir	Droperidol
Boceprevir	Ondansetron/Granisetron

Drugs that can prolong the QT interval.
This list is not exhaustive but is designed to give examples of more commonly used drug classes

21 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
v1 08-JUN-2022	First version of the protocol.
v2 09-DEC-2022	Eligibility criteria updated to allow some stage IIIC patients Allowance for additional brachytherapy planning imaging Allowance of PET-CT or CT at baseline Inclusion of RTTQA information and dose slot allocation information Allowable time window of baseline MRI and CT imaging increased Clarification that amended FIGO classification 2018 to be used Clarification treatment phase is 7 rather than 6 weeks
v3 06-JUN-2023	Change in required contraception methods (agreed with TMG and sponsor) Addition of translational urine collection Removal of requirement for bi-dimensional measurements as this is not part of RECIST 1.1 Prohibited therapies updated to allow for a cisplatin anti-emetic regime (agreed with TMG) Clarification of actions to take with trial treatment following related AEs. Inclusion of requirement to review safety bloods prior to treatment each week. Tolinapant Reference Safety Information updated
v4 25-OCT-2023 (not accepted by MHRA, not implemented at site)	Details surrounding radiation boosting for patients with radiologically positive nodes added Clarification of the tolinapant prescribing, dispensing and returns process added Hospital admissions for standard of care brachytherapy added as an SAE exception Stages IIA1, IIA2 and IIIA added to inclusion criteria Lipase removed from eligibility criteria Clarity provided over safety bloods required to be checked by a clinician prior to prescribing each week Reference Safety Information updated
v5 15-DEC-2023	Changes requested by MHRA in response to protocol v4: Lipase reinstated as an eligibility criteria Identification of bloods requiring clinician review prior to dispensing removed NHS email address update Follow up visit windows increased to 2 weeks
v6 12-JUL-2024	Definition of sexual abstinence reinstated
V7 06-SEP-2024	Administrative name change from Astex to Taiho throughout protocol Updated email address for completed ICFs to be sent to