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| **A phase I/II study of first line ganetespib with pemetrexed/platinum, in patients with malignant pleural mesothelioma** | |
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**Please note:** This trial protocol must not be applied to patients treated outside the MESO‑02 trial. UCL CTC can only ensure that approved trial investigators are provided with amendments to the protocol.

Aldeyra Therapeutics, Inc. and Madrigal Pharmaceuticals, Inc (formerly Synta Pharmaceuticals Corp.) are providing free of charge ganetespib and are supporting study coordination through the Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) – the coordinating centre for the trial. Problems relating to this trial should be referred, in the first instance, to the UCL CTC.

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# PROTOCOL SUMMARY

## Summary of Trial Design

|  |  |
| --- | --- |
| **Title:** | A phase I/II trial of first line ganetespib with pemetrexed/platinum, in patients with malignant pleural mesothelioma |
| **Short Title/acronym:** | MESO-02 |
| **EUDRACT no:** | 2012-001598-10 |
| **Sponsor name & reference:** | University College London – UCL/12/0158 |
| **CTA no:** | 20363/0317/001-0001 |
| **REC no:** | 12/EM/0448 |
| **Funder name** | Madrigal Pharmaceuticals Inc (formerly Synta Pharmaceuticals Corp.) |
| **CR UK reference number** | A15183 |
| **ISRCTN/Clinicaltrials.gov no:** | NCT01590160 |
| **Design:** | **Phase I**: 3 dose cohorts (pemetrexed/cisplatin with ganetespib, followed by maintenance ganetespib), 3+3 design.  Additional patients will be treated with ganetespib and pemetrexed/carboplatin in an accelerated titrated design, to confirm the MTD in patients given carboplatin instead of cisplatin.  **Phase II:** multicentre randomised phase II trial of pemetrexed/platinum (cis or carbo) with ganetespib followed by maintenance ganetespib, vs. pemetrexed/platinum (cis/carbo) alone, in patients with malignant pleural mesothelioma.  The trial will no longer proceed to phase II following the business decision by Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) to cease development of ganetespib in this population. |
| **Overall aim:** | The primary aim of the phase I trial is to find the maximum tolerated dose of ganetespib, and use this with the number of chemotherapy cycles administered to determine the most appropriate dose of ganetespib for the phase II trial.  The primary aim of the phase II trial is to determine whether the addition of ganetespib to pemetrexed/platinum improves progression free survival. Secondary aims are to examine whether ganetespib affects tumour response rate, overall survival, or toxicity. |
| **Primary endpoint (phase I):** | Dose-limiting toxicities during Cycles 1 & 2; and number of cycles of pemetrexed/platinum given. |
| **Primary endpoint (phase II):** | Progression free survival  The trial will no longer proceed to phase II following the business decision by Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) to cease development of ganetespib in this population. |
| **Secondary endpoints (phase I):** | * To examine the number of cycles of pemetrexed/platinum chemotherapy administered. * To examine the frequency of all Adverse Events graded by NCI-CTCAE version 4. * To evaluate the incidence of Dose Limiting Toxicities (DLTs) according to each ganetespib dose cohort. * To examine the objective tumour response according to meso-modified RECIST, and the overall response rate. * To examine biomarkers for response, progression and survival within a translational research substudy (see section 2.2.3 for more details). |
| **Secondary endpoints (phase II):** | * To examine the frequency of all Adverse Events graded by NCI-CTCAE version 4, in particular those with ≥ grade 3 * To examine the objective tumour response according to meso-modified RECIST, and the overall response rate. * To examine overall survival. * To examine the number of chemotherapy cycles (pemetrexed/platinum (cis or carbo)) completed; and for patients who stop before 6 cycles, the reasons for stopping early.   The trial will no longer proceed to phase II following the business decision by Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) to cease development of ganetespib in this population. |
| **Target accrual:** | Phase I: maximum 27 patients for cisplatin; and 18 for carboplatin  Phase II: 110 patients (55 per arm) |
| **Inclusion & exclusion criteria:** | Patient Inclusion Criteria  * Histopathological confirmation of malignant pleural mesothelioma * Measurable disease using meso-modified RECIST criteria **(CT scan must be within 28 days of registration/randomisation)** * Performance status ECOG 0-1 * Age at least 18 years * Adequate haematological status:   + Haemoglobin 100g/L or greater   + Neutrophil count ≥2.0 x 109/L   + Platelets ≥100 x 109 /L * Adequate organ function:   + Bilirubin ≤1.5x ULN, ALP ≤2.5x ULN, ALT or AST ≤1.5x ULN   + Serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥ 60ml/min (C&G or EDTA) (appendix 4) * Chemotherapy naïve * Negative serum pregnancy test for female patients of child-bearing potential. * Male subjects and women of child-bearing potential must agree to use an acceptable method of birth control for the duration of the trial and for 6 months after the last trial treatment cycle has finished. * Ability to understand and willing to sign the written informed consent to participate (including donation of diagnostic biopsy tissue for research) * Ability to comply with the requirements of the protocol  Patient Exclusion Criteria  * Prior exposure to other investigational or commercial agents or therapies administered with the intent of treating the patient’s malignancy. This includes crizotinib, other ALK-targeted agents, and any Hsp90 inhibitor (e.g. ganetespib). Prior valproic acid is acceptable but only if there has been at least 30 days wash-out period * Evidence of CNS metastases that in the opinion of the investigator should receive local treatment prior to systemic cytotoxic chemotherapy * Uncontrolled intercurrent illness including but not limited to: * Symptomatic neurological illness * Active uncontrolled systemic infection considered opportunistic, life threatening or clinically significant at the time of treatment * Significant pulmonary disease or hypoxia * Psychiatric illness/social situations that would limit compliance with trial requirements * Human immunodeficiency virus (HIV)-positive patients * Known hepatitis B or C infection * Uncontrolled diabetes mellitus * Serum potassium, magnesium, and calcium levels no more than 10% outside the Sites normal reference ranges * Known serious cardiac illness including but not confined to: * Clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling temporary pacemaker * Ventricular tachycardia or a supraventricular tachycardia that requires treatment with a Class Ia anti-arrhythmic drug (e.g., quinidine, procainamide, disopyramide) or Class III anti-arrhythmic drug (e.g. sotalol, amiodarone, dofetilide). Use of other anti-arrhythmic drugs is permitted. * Use of medications that have been linked to the occurrence of torsades de pointes (see Appendix 5 for the list of such medications) * Second- or third-degree atrioventricular (AV) block unless treated with a permanent pacemaker * Complete left bundle branch block (LBBB) * History of long QT Syndrome or a family member with this condition * QTc >470ms (average of triplicate ECG recordings); a consistent method of QTc calculation must be used for each patient's QTc measurements. QTcF (Fridericia's formula) is preferred * The patient has a history of prior gastrointestinal illness or disorder. * The patient has a history of prior malignant tumour, unless the patient has been without evidence of disease for at least three years, or the tumour was a non-melanoma skin tumour or in situ cervix carcinoma * Pregnant women or those who are lactating * Pre-planned surgery or procedures that would interfere with the conduct of the trial * Patients who have had surgery (does not include pleurodesis or pleurectomy) within 28 days of randomisation should not be included * Previous treatment of mesothelioma with systemic chemotherapy * Receipt of extensive radiation therapy, systemic chemotherapy, or other anti-neoplastic therapy within 4 weeks before enrolment is not allowed. However, drain site radiotherapy is allowed * Significant weight loss (≥10% body weight) within the 4 weeks prior to Cycle 1 Day 1. * Patients who have had a yellow fever vaccination in the previous 30 days. * Other medications, severe acute/chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into this study. |
| **Planned number of sites:** | Phase I: 4-5 centres  Phase II:~20 centres, in the UK |
| **Treatment summary:** | **Phase I trial, three ganetespib dose cohorts, each with 3 or 6 patients:**   * **Cohort 1:**100mg/m2 IV on day 1 and day 15 of each cycle * **Cohort 2:** 150mg/m2 IV on day 1 and day 15 of each cycle * **Cohort 3:** 200mg/m2 IV on day 1 and day 15 of each cycle   All patients in each cohort will receive pemetrexed (500mg/m2 IV on Day 1 every 21 days with vitamin B12 and folate supplementation as standard) and cisplatin 75mg/m2 IV day 1 every 21 days.  Additional patients will be treated with ganetespib and pemetrexed/carboplatin in an accelerated titrated design, to confirm the MTD in patients given carboplatin instead of cisplatin    **Randomised phase II**  **Arm A:** Patients will receive pemetrexed (500mg/m2 IV day 1 with vitamin B12/folate supplementation), cisplatin (75mg/m2 IV day 1) or carboplatin (AUC5), and ganetespib (using the dose and schedule from Phase I) every three weeks. Chemotherapy will continue for a maximum of 6 cycles, unless the patient has disease progression, toxicity, or withdraws from the trial.  **Arm B**: Patients will receive pemetrexed/platinum (cis or carbo) for a maximum of 6 cycles (as in Arm A). |
| **Anticipated duration of recruitment:** | Phase I: 6 months  Phase II: 24 months |
| **Duration of patient follow up:** | Phase I: last assessment 30 days after Day 21 of the last chemotherapy.  Phase II: patients will be followed-up until death or the trial results are available. |
| **Definition of end of trial :** | As the trial will no longer proceed to phase II following the business decision by Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) to cease development of ganetespib in this population, the End of Trial will now be defined as 12 months after the last patient visit. |
| **Translational component:** | * Formalin fixed paraffin embedded (FFPE) diagnostic tissue blocks will be collected from **all** patients, where available, who are enrolled into this clinical trial (phase I and II). * Blood samples will be obtained, at baseline and on progression, from all patients in the cisplatin and carboplatin cohort used to confirm MTD * Blood samples will be obtained from all patients in the Phase II trial at baseline and on progression.   The collection of these samples will enable high quality RNA and DNA extraction for future pharmacogenomics studies. |

## Trial Schema

The trial aims to examine the efficacy and safety of first-line ganetespib when used concurrently with pemetrexed/platinum. We will initially conduct a phase I trial, before embarking on the randomised phase II trial. The trial is therefore in two stages:

* Phase I trial: to find the maximum tolerated dose of ganetespib in this patient group.
* Randomised Phase II trial: to evaluate the efficacy and safety of ganetespib (using the dose from the phase I trial) versus pemetrexed/platinum alone.

### Phase I trial

The phase I trial will have 3 cohorts, each with 3 or 6 patients.

* **Cohort 1:** 100mg/m2 IV on day 1 and day 15 of each cycle
* **Cohort 2:** 150mg/m2 IV on day 1 and day 15 of each cycle
* **Cohort 3:** 200mg/m2 IV on day 1 and day 15 of each cycle

Patients will receive a maximum of 6 cycles of treatment, each cycle lasts 21 days:

**Day 1**

* IV ganetespib -1 hour infusion at the current cohort dose
* Pemetrexed 500mg/m2 IV – infused over 10 minutes with vitamin B12 and folate supplementation as standard. Pemetrexed should be administered immediately after completion of the ganetespib infusion.
* Cisplatin 75mg/m2 IV infused over 2 hours Cisplatin should be administered approximately 30 minutes after completion of the pemetrexed infusion.

**Day 15**

* IV ganetespib – 1 hour infusion at the current cohort dose

\*DuBois and DuBois formula is the recommended method to be used for calculation of BSA

After completing 6 cycles of chemotherapy/ganetespib patients could receive maintenance ganetespib if there are no signs of disease progression. Patients who have only completed 4 cycles of treatment without disease progression may be treated with maintenance ganetespib if their treating clinician agrees there is benefit. Please contact UCL CTC if a patient has received less than 4 cycles of treatment but maintenance ganetespib is deemed appropriate.

Maintenance ganetespib should be given on Day 1 and 15 of each 21-day cycle.

* Subsequent cohorts will not start until all patients in the previous cohort have completed at least 2 cycles and been assessed for toxicity and the occurrence of a dose limiting toxicity (DLT) in cycles 1 and 2.
* If patients decide to withdraw before finishing cycle 2 (for reasons other than toxicity), or they have progression or symptom deterioration before cycle 2 they will be replaced.
* If the dose schedule in Cohort 2 or 3 is found to be tolerable (whichever is the highest), further 3/6 patients will be recruited (total number of patients treated at the MTD will be 9) and given the same dose, to confirm tolerability and safety before proceeding to phase II.
* Intermediary doses may also be explored between cohorts 1 and 2, and 2 and 3 if DLTs are experienced at the higher dose.
* The chosen dose to be used in the phase II trial will be influenced by the number of DLTs (see section 7.3.1 for definitions), overall toxicity, and the number of cycles of chemotherapy administered (to be examined by an Independent Data Monitoring Committee). This dose will not be chosen until all patients in phase I have completed at least 2 cycles.

*Using carboplatin instead of cisplatin*

There will be additional patients to be treated with carboplatin (AUC5) instead of cisplatin. If treatment with carboplatin is confirmed to be safe and tolerable, the option of treating patients with either cisplatin or carboplatin during phase II will be taken. The evaluation will be done as follows (using an accelerated titrated phase I design):

* 1 patient to be given carboplatin, with 100 mg/m2 IV ganetespib and pemetrexed.
* If there are no DLTs, the second patient is given 150 mg/m2 IV ganetespib.
* If a DLT occurs at either ganetespib dose, a 3+3 dose escalation design will begin (as with cisplatin).
* If there are no DLTs at the two low ganetespib doses, the next 3 patients are given 200 mg/m2 IV ganetespib, expanded to 6 if there are 0 or 1 DLTs among the first 3. If there are 2 or 3 DLTs among the first 3 patients the MTD would be the next lowest ganetespib dose.

**Day 1**

* IV ganetespib -1 hour infusion at the proposed MTD
* Pemetrexed 500mg/m2 IV – infused over 10 minutes with vitamin B12 and folate supplementation as standard. Pemetrexed should be administered immediately after completion of the ganetespib infusion.
* Carboplatin AUC5 IV infused over 30 minutes. Carboplatin should be administered approximately 30 minutes after completion of the pemetrexed infusion.

**Day 15**

* IV ganetespib – 1 hour infusion at the proposed MTD

\*DuBois and DuBois formula is the recommended method to be used for calculation of BSA

### Moving from Phase I to Phase II

On completion of the Phase I trial, the trial results will be reviewed with regards to the safety profile and delivery of standard chemotherapy (see section 7.3.1). There will also be a review by Synta Pharmaceuticals Corp. of their support, in light of results from other trials of ganetespib currently in progress, before the decision is made to proceed to the randomised Phase II trial. A substantial amendment would then be submitted to the MHRA and Research Ethics Committee with the relevant sections of this protocol changed accordingly and approval sought before moving into the Phase II trial.

**The trial will no longer proceed to phase II following the business decision by Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) to cease development of ganetespib in this population.**

### Randomised phase II Trial

**Arm B Chemotherapy**

**(55 patients)**

**Pemetrexed**

500mg/m2 IV

day 1 every 21 days

(with vitamin B12/folate supplementation)

+

**Cisplatin**

75mg/m2 IV**or Carboplatin** AUC5

day 1 every 21 days

**Randomisation**

**Arm A Chemotherapy**

**(55 patients)**

**Ganetespib**

*Using the dose from Phase I*

+

**Pemetrexed**

500mg/m2 IV

day 1 every 21 days

(with vitamin B12/folate supplementation)

+

**Cisplatin**

75mg/m2 IV

**or Carboplatin** AUC5

day 1 every 21 days

**Patients with pathologically confirmed malignant pleural mesothelioma**

**(110 patients)**

**Follow up every 6 weeks until one year from the start of treatment**

**For those who survive to 12 months without progression, follow up would be every 12 weeks thereafter until death or until the trial results are reported, whichever is sooner.**

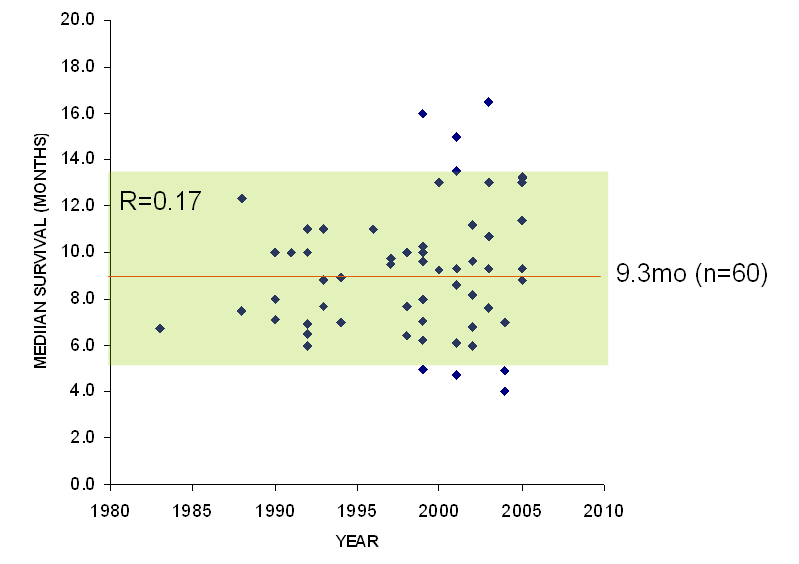
# Introduction

## Background

**Mesothelioma**Malignant pleural mesothelioma (MPM) is a rapidly lethal cancer arising from the parietal pleural mesothelium, and is associated with exposure to asbestos. Once a rare disease, it is increasing in incidence in the UK and presently, is more common than either melanoma or carcinoma of the cervix (CancerStats Monograph 2004). MPM is characterized by local invasion of adjacent structures including the chest wall, mediastinum, diaphragm and pericardium resulting in progressive shortness of breath. Three histological subtypes of mesothelioma are described; epithelioid (the most common and more favourable), sarcomatoid, and biphasic. Median survival with best supportive care alone is approximately 6-9 months. Most cases of mesothelioma present in the advanced setting. The survival benefit associated with radical surgery (extrapleural pneumonectomy, EPP) in the management of mesothelioma has not yet been formally evaluated in the form of a definitive randomised clinical trial. Accordingly, there is no evidence to refute the possibility that improved survival observed in patients undergoing EPP could be attributed to selection bias in this relatively rare patient sub-population. The UK MARS trial confirmed the feasibility randomising patients to radical surgery and radiotherapy versus best supportive care following induction chemotherapy (Treasure et al 2009).

**First line chemotherapy of mesothelioma**

Mesothelioma remains incurable and rapidly lethal. Over the last 25 years there has been no consistent improvement in 5 year survival. Systemic therapy with cytotoxic drugs is the mainstay of treatment. Clinical and pathological factors can significantly impact prognosis leading to misleadingly high survival estimates in both phase II and phase III trials settings. Fennell et al reported a statistical validation of the EORTC prognostic score which demonstrates a clear impact of clinical and pathological factors on clinical outcome (Fennell et al 2005). For example, a bias towards PS 0-1 patients can result in greater median survival estimates.



*Figure 1. Metadata showing survival associated with 60 mesothelioma phase II/III clinical trials over the last 25 years. There is a symmetrical distribution about the median of 9.3 months and a correlation coefficient strongly suggesting a therapeutic plateau.*

Objective response rates for single cytotoxic agents range from 10 to 20%. For combination therapy, response rates typically range between 20-40%. Meta-analysis suggests that response rates are higher for platinum versus non-platinum containing chemotherapy (Fennell et al 2008). Despite the existence of a large number of phase II clinical studies previously conducted, there exists no robust randomised data confirming a survival advantage over best supportive care. This was addressed by UK MSO-1 study randomizing vinorelbine versus mitomycin/vindesine/cisplatin versus active symptom control (Muers et al 2008). This trial failed to demonstrate a statistically benefit for chemotherapy. However this study has been criticised for not employing standard therapy (see below), and being underpowered to detect a statistically significant effect of vinorelbine which demonstrated a trend to 2 months improved survival. Two recent phase III clinical trials have demonstrated some improvement in median survival over single platinum for pemetrexed/cisplatin (9.3 vs. 12.1 months) (Vogelzang et al 2003) or raltitrexed/cisplatin (8.8 vs. 11.4 months) (van Meerbeck et al 2005). Pemetrexed/cisplatin has been now adopted as the standard of care in front-line mesothelioma, and therefore the control arm of choice in randomised clinical trials. The optimal timing of front line therapy has not been clearly defined. A randomised study comparing early versus delayed therapy failed to demonstrate a statistically significant difference in survival, however a trend to shorter survival was evident and concluded a potential benefit of early intervention (O’Brien et al 2006).

**Apoptosis and Chemotherapy**

Cytotoxic therapy relies in part on the induction of programmed cell death or apoptosis for efficacy. Anti-cancer activity is typically limited by intrinsic apoptosis resistance in incurable, metastatic solid tumours (Fennell et al 2004a). MPM typically exhibits significant insensitivity to induction of apoptosis, however the molecular basis of this phenotype has not been fully elucidated (Fennell et al 2004b). There is an urgent need for novel, active treatments for MPM. It is likely that conventional cytotoxic therapy alone has reached a therapeutic plateau as seen in non-small cell lung cancer (Fennell et al 2004a). Better understanding of MPM biology, coupled to targeted therapies selected rationally as opposed to empirically has the potential to improve the outlook of patients with this malignancy. However, the rapid evaluation of such promising compounds is essential.

**Targeting HSP90 as a strategy for treating mesothelioma**

MPM is a very apoptosis resistant cancer, and this plays a significant factor in drug resistance (Mohiuddin et al 2002, Fennell 2011). In mesothelioma, anti-apoptotic survival signals are mediated predominantly through receptor tyrosine kinases (RTKs) which signal through the PI3K/AKT axis (Altomare et al 2005) and are critical for maintaining viability; these include MET (Jagadeeswaran et al 2006) and AXL (Ou et al 2011a). Mesotheliomas are addicted to these growth factors, at least in preclinical models and simultaneous targeting of their signalling pathways is a rational approach to treatment; this can be achieved through heatshock protein 90 (HSP90) inhibition (Workman et al 2004). HSP90 belongs to a class of molecular chaperone proteins that help modulate cellular responses to environmental stress (Whitesell et al 2005).

AKT protein in Mesothelioma is regulated by HSP90. Inhibition of HSP90 leads to dissociation of the client protein PDK1 and inhibition of AKT, a critical downstream kinase of PDK1 (Pespeni et al 2007). Accordingly, HSP90 inhibition has potential for efficiently inducing Mesothelioma apoptosis. Recent data has confirmed this, showing that HSP90 inhibition is effective against mesothelioma in preclinical model (Ou et al 2011b, Okamoto et al 2008). Furthermore, HSP90 inhibition suppresses signalling via MET, as well as EGFR, ERBB3, AXL, EPHA7, and EPHB2 (Ou et al 2011b). This parallel targeting of growth factor signals, contributes to the preclinical activity in Mesothelioma cells (Ou et al 2011b).

HSP90 inhibition results in destabilization of the client protein thymidylate synthase (TS) (Lee et al 2006). TS has been strongly implicated as a critical regulator of resistance to anti-folates including pemetrexed (Longley et al 2001, Wu et al 2010). Furthermore, inhibition of HSP90 has been shown to synergize with cisplatin (Solar et al 2007). Based on available data from 400 patients treated, ganetespib appears to have a relatively safe profile as monotherapy and in combination. Critically, and based on its unique chemistry, ganetespib is the first potent but well tolerated HSP90, that lacks the toxicity profile seen previously with other agents such as 17AAG (Prioa et al 2011, Bansal et al 2010). Ganetespib is expected to exhibit efficacy in mesothelioma by virtue of its activity on critical survival pathways in this cancer, and on the basis of known synergies with antifolates and platinum chemotherapy. This provides sound justification for its evaluation in mesothelioma.

Receptor tyrosine kinases such as MET, AXL, EGFR, IGF1-R and ERBB3 are constitutively activated in subsets of mesothelioma, and signal through the PI3 kinase and AKT. These signals appear to be essential for sustaining proliferation, and cell survival. PI3K and AKT are client proteins for heatshock protein 90 (HSP90). Inhibition of HSP90 leads to a down regulation of MET, EGFR, and AXL as well as suppression of activation signals downstream of RTKs in mesothelioma, including inactivation of AKT and S6 (Ou et al 2011). This leads to induction of apoptosis and reduced proliferation in mesothelioma cells.

**Ganetespib - Pharmacology**

Ganetespib, 5-[2, 4-dihydroxy-5-(1 methylethyl) phenyl]-2, 4 dihydro-4-(1-methyl-1H indol-5 yl)-3H-1, 2, 4 triazole-3-one, is a novel triazolone heterocyclic compound. It is a synthetic small molecule that binds to the ATP pocket in the N-terminus of Hsp90 and demonstrates significant activity for down-regulating Hsp90 client protein levels. This ability to impact a broad array of important oncogenes and cell signalling kinases is reflected in ganetespib’s activity across a wide variety of tumour cell types.

Solid tumours typically exhibit regions of poor oxygen supply, or hypoxia, due to disorganised tumour microvasculature limiting the efficient circulation of blood within the tissue. The hypoxia-inducible transcription factor 1α (HIF1A) is activated by low oxygen conditions and is found in high levels in malignant tumours but not in normal tissues. HIF1A is a known client protein of Hsp90 and both its basal and induced levels are potently down-regulated by in vitro ganetespib treatment. Further, in in-vivo mouse models, ganetespib was shown to penetrate deeply into hypoxic regions of the tumours far from the nearest vessels and induce apoptosis. (15)

**Clinical Experience**

As of 21 September 2015, 1,524 individuals (patients and normal, healthy volunteers) have received at least 1 dose of ganetespib. A total of 402 patients have been treated with single-agent ganetespib..

The MTD for once weekly dosing in solid tumours was established at 216 mg/m2 ganetespib administered 3 weeks consecutively of a 4-week cycle. The recommended dose for twice weekly dosing in patients with solid tumours is 150 mg/m2 ganetespib administered 3 weeks consecutively of a 4-week cycle.

The doses selected for further study in patients with hematologic malignancies were 200 mg/m2 once weekly and 90 mg/m2 twice weekly administered continuously without a rest week.

A phase II trial using ganetespib in 95 patients with advanced non-small cell lung cancer (previously treated) was presented at ASCO 2011 (Wong et al 2011), indicating promising efficacy and that it was tolerable. 29% of patients (19/95) were still on treatment at the end of the trial. The main endpoint was progression-free survival rate at 16 weeks which was 24%, 95% CI 14-36%. This has now led to a phase II/III trial of ganetespib and docetaxel as second-line treatment.

**Adverse Effects**

As per data reported in the Investigator Brochure (version 11, 13 November 2015), approximately 99.5% of the patients in the largest pooled data set (single-agent studies, n=402) experienced at least 1 AE; 92.5% experienced at least 1 treatment-related event. The most frequently reported AEs were related to gastrointestinal toxicity, and included diarrhoea (80.1%), nausea (44.5%), decreased appetite (31.6%), vomiting (27.4%), constipation (21.9%), and abdominal pain (20.9%). Non gastrointestinal-related events that occurred frequently have included fatigue (53.5%), headache (20.4%), and anaemia (21.1%). Approximately 2/3 (68.4%) of these patients experienced an event that was a Grade ≥3; 31.3% experienced a Grade ≥3 treatment-related event. Approximately 39./8% experienced at least 1 serious adverse event (SAE); 8.2% of patients had at least 1 treatment-related SAE.

Additional to the events listed above, 1 patient suffered a gastrointestinal perforation leading to death. This was assessed as being related to ganetespib.

Ganetespib administered as a single agent had a favorable safety profile and was devoid of liver toxicities and visual impairment associated with other Hsp90 inhibitors across all studies. In addition, there was no evidence of myelosuppressive effect with documented decrease in

neutrophil count associated with ganetespib administration; this is favorable for the use of

ganetespib in combination with chemotherapeutic agents.

## Trial Design

### Phase I trial

**Primary objective:**

To find the most tolerable dose of ganetespib in combination with standard pemetrexed/ platinum in patients with mesothelioma.

**Secondary objectives:**

* To examine the number of cycles of pemetrexed/platinum chemotherapy administered.
* To examine the frequency of all Adverse Events graded by NCI-CTCAE version 4.
* To evaluate the incidence of Dose Limiting Toxicities (DLTs) according to each ganetespib dose cohort.
* To examine the objective tumour response according to meso-modified RECIST, and the overall response rate.
* To examine biomarkers for response, progression and survival within a translational research substudy (see section 2.2.3 for more details).

Both safety (i.e. the observed number of DLTs per cohort and the overall toxicity profile) and the number of chemotherapy cycles administered would be used to determine the final dose of ganetespib to be used in the phase II trial.

**Design:**

In the phase I trial, 3 or 6 patients per dose cohort will be used. A further 3 or 6 (to give a total of 9 in the cohort) would be allocated to the maximum tolerated dose.

In parallel to this, additional patients will be treated with ganetespib, pemetrexed and carboplatin (AUC5). If treatment with carboplatin is confirmed to be safe and tolerable, the option of treating patients with either cisplatin or carboplatin during phase II will be taken, because these two drugs have similar effects (and in practice clinicians choose one or the other, depending on expected patient tolerability).

### Randomised phase II trial

The phase II trial will not start until the dose of ganetespib has been determined by the phase I stage, and there has been agreement by the Sponsor and Synta Pharmaceuticals Corp. to continue to phase II. The decision to allow the option of treating patients with pemetrexed/carboplatin instead of pemetrexed/cisplatin during phase II (at the treating clinician’s discretion) will also be made at this time.

**The trial will no longer proceed to phase II following the business decision by Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) to cease development of ganetespib in this population.**

**Primary objective:**To examine whether Progression Free Survival (PFS) is improved in patients given ganetespib, compared to those given pemetrexed/platinum (cisplatin or carboplatin) alone (a trial of superiority).

**Secondary objectives:**

* To examine the frequency of all Adverse Events graded by NCI-CTCAE version 4, in particular those with events of greater than or equal to grade 3.
* To examine the objective tumour response according to meso-modified RECIST, and the overall response rate.
* To examine overall survival.
* To examine the number of chemotherapy cycles (pemetrexed/cisplatin or pemetrexed/carboplatin) completed; and for patients who stop before 6 cycles, the reasons for stopping early.
* To examine biomarkers for response, progression and survival within a translational research substudy (see section 2.2.3 for more details).

**Design:**A randomised multicentre phase II clinical trial. Patients will be randomised 1:1 to two treatment arms.

In **Arm A** (experimental arm), patients will receive pemetrexed (500mg/m2IV) and cisplatin (75mg/m2 IV) or carboplatin (AUC5) on Day 1, and ganetespib Day 1 and 15. Maintenance ganetespib may be prescribed if appropriate. Patients receive ganetespib at the dose indicated by the phase I trial.

In **Arm B** (control arm), patients will receive pemetrexed (500mg/m2 IV) and cisplatin (75mg/m2 IV) or carboplatin (AUC5) on Day 1

All patients enrolled in the trial should receive B12 and folate vitamin supplementation, in line with usual practice.

### Translational research

Formalin fixed paraffin embedded (FFPE) diagnostic tissue blocks will be collected from **all** patients, where available, who are enrolled into this clinical trial, to enable high quality RNA and DNA extraction for future pharmacogenomics studies. FFPE tissue will be used to build a tissue microarray to study putative predictive biomarkers. See section 20 for details

Tissue blocks will be retained for the trial. However, requests for the return of the block will be considered (provided there is tissue remaining) during the course/end of the trial once cores have been obtained.

Blood samples will be collected for translational research at baseline and on progression from patients in the cisplatin and carboplatin cohort used to confirm MTD.

Blood samples will be collected in the phase II trial at baseline and on progression to isolate circulating free tumour DNA from blood for future pharmacogenomics studies.

Some biomarkers will be evaluated during the trial, and considered with published evidence. It is possible that one biomarker strongly predicts response, and if this is the case there will be a review of the trial design with the Independent Data Monitoring Committee, to consider whether the patient population (the remaining patients to be recruited) should be enriched for this marker (i.e. only marker positive patients would be eligible).

## Trial activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

* Research Ethics Committee approval
* Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)
* ‘Adoption’ into NIHR portfolio NHS permission
* Adequate funding for central coordination
* Confirmation of sponsorship
* Adequate insurance provision

# Selection of Sites/Site Investigators

## Site selection

In this protocol trial **‘site’** refers to the hospital where trial-related activities are conducted.

Sites must be able to comply with:

* Trial treatment, imaging, clinical care, follow up schedules and all requirements of the trial protocol
* Requirements of the Research Governance Framework and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)
* Data collection requirements - data sent to CTC within **2 weeks for the phase I trial** and within **1 month for the phase II trial** of the patient being seen.

In addition Site must have:

* Previous experience in early phase trials
* Facilities to provide **24 hour medical advice** for trial patients.

## Selection of Principal Investigator and other investigators at sites

Sites must have an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site, ethics committee and regulatory authority, to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating mesothelioma.

## Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). An up-to-date, signed copy of the CV for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

## Site initiation and activation

### Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI, the pharmacy lead and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by site visit for the phase I trial. Site Initiation for the Phase II trial may be performed by either site visit or teleconference. This is in addition to any investigator meetings that may take place during the phase I and phase II trials.

### Required documentation

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by UCL CTC trial team:

* Trial specific Site Registration Form (identifying relevant local staff)
* All relevant institutional approvals (e.g. local NHS permission/confirmation of capacity and capability)
* A completed site delegation log that is signed and dated by the PI
* A copy of the PI’s current CV that is signed and dated, with details of GCP training (or separate GCP certificate if not detailed in CV)
* A copy of the prescription sheet to be used in the trial
* A copy of the drug accountability log if CTC template not used

The UCL CTC trial team will ensure that, for UK sites:

* If the site was not included in the original CSP application, the Part C is updated and the R&D form is resubmitted to CSP (who will notify the lead CLRN of the new site)
* An SSI form is transferred to the site via IRAS
* If the site was not included on the original REC application, a substantial amendment is submitted to and approved by the REC
* If the site was not included on the original CTA application, the CTA is updated and the MHRA notified at the next substantial amendment to the MHRA

In addition, the following agreements must be in place:

* For UK sites: a signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually a NHS Trust)

### Site activation letter

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

Once the site has been activated by UCL CTC, the PI is responsible for ensuring:

* adherence to the most recent version of the protocol;
* all relevant site staff are trained in the protocol requirements;
* appropriate recruitment and medical care of patients in the trial;
* timely completion and return of CRFs (including assessment of all adverse events);
* prompt notification and assessment of all serious adverse events;
* that the site has facilities to provide **24 hour medical advice** for trial patients.

# Informed consent

Sites are responsible for assessing a patient’s capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form.

Sites must assess a patient’s ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

The PI, or other appropriately trained site staff (where delegated by the PI), are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheet for the trial should be discussed with the patient. A minimum of twenty four hours must be allowed for the patient to consider and discuss participation in the trial. Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Site Staff are responsible for:

* checking that the correct (current approved) version of the patient information sheet and consent form are used;
* checking that information on the consent form is complete and legible;
* checking that the patient has completed/initialled all relevant sections and signed and dated the form;
* checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient;
* checking that an appropriate member of staff has made dated entries in the patient’s medical notes relating to the informed consent process (i.e. information given, consent signed etc.);
* following registration/randomisation: adding the patient trial number to all copies of the consent form(s), which should be filed in the patient’s medical notes and investigator site file
* giving the patient a copy of their signed consent form, patient information sheet, and patient contact card;

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 13.0 (Withdrawal of patients).

# Selection of Patients

## Pre-registration (phase I) & pre-randomisation (phase II) Evaluation

There are a number of assessments and procedures that must be performed to ensure a patient’s suitability for participation in the trial. Please see section 8.1 for full details of the pre‑registration (phase I) or pre-randomisation (phase II) investigations which are required prior to patient entry.

## Screening Log

A screening log must be maintained by the site and kept in the Investigator Site File. This must record each patient screened for the trial and the reasons why they were not registered or randomised in the trial if this is the case. A copy of the log must be sent to UCL CTC when requested, with patient identifiers removed prior to sending.

## Patient Eligibility

There will be no exception to the eligibility requirements at the time of registration (phase I) /randomisation (phase II). Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Queries in relation to the eligibility criteria must be addressed prior to calling/faxing for registration/randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

## Patient Inclusion Criteria

1. Histopathological confirmation of malignant pleural mesothelioma
2. Measurable disease using meso-modified RECIST criteria **(CT scan must be within 28 days of registration/randomisation)** – (appendix 6)
3. Performance status ECOG 0-1
4. Age at least 18 years
5. Adequate haematological status:
   * Haemoglobin 100g/L or greater
   * Neutrophil count ≥2.0 x 109/L
   * Platelets ≥100 x 109 /L
6. Adequate organ function:
   * Bilirubin ≤1.5x ULN, ALP ≤2.5x ULN, ALT or AST ≤1.5x ULN
   * Serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥ 60ml/min (C&G or EDTA) (appendix 4)
7. Chemotherapy naïve
8. Negative serum pregnancy test for female patients of child-bearing potential.
9. Male subjects and women of child-bearing potential must agree to use an acceptable method of birth control for the duration of the trial and for 6 months after the last trial treatment cycle has finished. (See section 5.6 for details)
10. Ability to understand and willing to sign the written informed consent to participate (including donation of diagnostic biopsy tissue for research)
11. Ability to comply with the requirements of the protocol

## Patient Exclusion Criteria

1. Prior exposure to other investigational or commercial agents or therapies administered with the intent of treating the patient’s malignancy. This includes crizotinib, other ALK-targeted agents, and any Hsp90 inhibitor (e.g. ganetespib). Prior valproic acid is acceptable but only if there has been at least 30 days wash-out period
2. Evidence of CNS metastases that in the opinion of the investigator should receive local treatment prior to systemic cytotoxic chemotherapy
3. Uncontrolled intercurrent illness including but not limited to:
   * Symptomatic neurological illness
   * Active uncontrolled systemic infection considered opportunistic, life threatening or clinically significant at the time of treatment
   * Significant pulmonary disease or hypoxia
   * Psychiatric illness/social situations that would limit compliance with trial requirements
   * Human immunodeficiency virus (HIV)-positive patients
   * Known hepatitis B or C infection
   * Uncontrolled diabetes mellitus
4. Serum potassium, magnesium, and calcium levels no more than 10% outside the Sites normal reference ranges
5. Known serious cardiac illness including but not confined to:
   * Clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling temporary pacemaker
   * Ventricular tachycardia or a supraventricular tachycardia that requires treatment with a Class Ia anti-arrhythmic drug (e.g., quinidine, procainamide, disopyramide) or Class III anti-arrhythmic drug (e.g., sotalol, amiodarone, dofetilide). Use of other anti-arrhythmic drugs is permitted.
   * Use of medications that have been linked to the occurrence of torsades de pointes (see Appendix 5 for the list of such medications)
   * Second- or third-degree atrioventricular (AV) block unless treated with a permanent pacemaker
   * Complete left bundle branch block (LBBB)
   * History of long QT Syndrome or a family member with this condition
   * QTc >470ms (average of triplicate ECG recordings); a consistent method of QTc calculation must be used for each patient's QTc measurements. QTcF (Fridericia's formula) is preferred
6. The patient has a history of prior malignant tumour, unless the patient has been without evidence of disease for at least three years, or the tumour was a non-melanoma skin tumour or in situ cervix carcinoma
7. The patient has a history of prior gastrointestinal illness or disorder.
8. Pregnant women or those who are lactating
9. Pre-planned surgery or procedures that would interfere with the conduct of the trial
10. Patients who have had surgery (does not include pleurodesis or pleurectomy) within 28 days of randomisation should not be included
11. Previous treatment of mesothelioma with systemic chemotherapy
12. Receipt of extensive radiation therapy, systemic chemotherapy, or other anti-neoplastic therapy within 4 weeks before enrolment is not allowed. However, drain site radiotherapy is allowed
13. Significant weight loss (≥10% body weight) within the 4 weeks prior to Cycle 1 Day 1.
14. Patients who have had a yellow fever vaccination in the previous 30 days.
15. Other medications, severe acute/chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into this study.

## Pregnancy and Birth Control

Ganetespib may involve currently unforeseeable risks to pregnant women, to an unborn child (an embryo or a foetus), or to children of nursing women. In an animal study, pregnant rats given ganetespib daily had side effects such as decreased weight gain and/or weight loss, and an increase in embryonic deaths.

Men who are participating in this trial need to understand the possible danger of taking a drug whose effects on the foetus are unknown.

Due to insufficient data on the effects of ganetespib in combination with pemetrexed/cisplatin or carboplatin during pregnancy and lactation, all patients must consent to use one of the following acceptable methods of contraception for the duration of trial treatment, and until 6 months after the last treatment cycle has finished. Acceptable methods of effective contraception for this trial are (women of childbearing potential, or men who have partners of childbearing potential):

* Established use of oral, injected or implanted hormonal methods of contraception.
* Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository). The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:
  + Failure rates indicate that, when used alone, the diaphragm or condom are **not** highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.
  + However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and must not be used alone.
* Male sterilisation (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomised male partners must be the sole partner for that patient. Please note that sterilisation is not usually regarded as completely reliable enough on its own to ensure that pregnancy can never occur.

Absolute and continuous abstinence: When this is in line with the preferred and usual lifestyle of the patient. Please note that periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. The method(s) of contraception used must be stated in the patient medical notes and CRFs.

### Pregnancy Testing

A baseline serum pregnancy test (beta-HCG) must be obtained within 1 week prior to the first dose of trial treatment for women of child-bearing potential. If a patient becomes pregnant, she must be immediately withdrawn from the trial.

A woman of childbearing potential is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

* undergone a hysterectomy or bilateral oophorectomy/salpingectomy
* been postmenopausal for 24 consecutive months (i.e. who has had menses at any time in the preceding 24 consecutive months without an alternative medical cause)

If a patient or the partner of a male trial patient becomes pregnant during the trial UCL CTC must be informed immediately (See section 10.0 Pharmacovigilance for details on the reporting procedure)). A female patient who becomes pregnant and her treating physician should have an immediate and thorough discussion to evaluate pregnancy in the context of drug exposure. All trial treatment should be stopped immediately.

# Registration (phase I) and Randomisation (phase II) Procedures

Patient registration (phase I) or randomisation (phase II) will be undertaken centrally at UCL CTC and this must be performed prior to commencement of any trial treatment/intervention.

|  |  |
| --- | --- |
| Registration/Randomisation telephone number: | 020 7679 9870 |
| UCL CTC Office hours: | 09:00 to 17:00 Monday to Friday |

## Registration to the phase I trial

Sites with a potential patient for the phase I trial must telephone the UCL CTC before taking consent to ensure there is an available place in a cohort. Patients within a cohort will be registered consecutively on a first-come first-serve basis.

Following pre-treatment evaluations (as detailed in section 8.1), confirmation of eligibility and consent of a patient at a site, the registration form must be fully completed prior to telephoning UCL CTC to register the patient into the trial. The eligibility criteria will be reviewed during the registration telephone call using the same form at UCL CTC.

A trial number will be assigned for the patient during the call and must be recorded at site by the caller.

UCL CTC will email confirmation of the patient’s inclusion in the trial, their trial number to the main contact and pharmacy***.*** Case report forms will be sent via e-mail to the main contact at site if requested. Once a patient has been registered onto the trial they must be provided with the following:

* A copy of their signed consent form and patient information sheet
* A patient contact card. Site on-call contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial

## Randomisation to the phase II trial

Minimisation will be used as the method of randomisation, stratified for recruiting centre, performance status (0 vs. 1) and histological subtype (epithelial versus non-epithelial). A randomisation programme will be developed by the UCL CTC specifically for the trial.

Following pre-treatment evaluations (as detailed in section 8.1), confirmation of eligibility and consent of a patient at a site, the randomisation form must be fully completed prior to telephoning UCL CTC to register the patient into the trial. The eligibility criteria will be reviewed during the registration telephone call using the same form at UCL CTC.

A trial number and treatment allocation will be assigned during the call.

UCL CTC will email confirmation of the patient’s inclusion in the trial, their trial number and trial treatment allocation to the main contact and pharmacy. Case report forms will be sent to the main contact at site if requested.   
  
Once a patient has been randomised onto the trial they must be provided with the following:

* A copy of their signed consent form and patient information sheet
* A patient contact card. Site on-call contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial

**The trial will no longer proceed to phase II following the business decision by Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) to cease development of ganetespib in this population.**

## Initial trial drug supply

Refer to Summary of Drug Arrangements (SoDA) for details of initial supply of ganetespib for the trial. Pemetrexed, cisplatin and carboplatin will be supplied from hospital stocks. Folic Acid, vitamin B12 and loperamidewill also be supplied from hospital stock.

# 

# Trial Treatment

## Treatment summary

For the purpose of this protocol, the IMPs are ganetespib, pemetrexed, cisplatin and carboplatin and the NIMPs are folic acid, vitamin B12 and loperamide.

## Summary Treatment Schedule

## Phase I trial

The phase I trial will have 3 cohorts:

* Cohort 1: 100 mg/m2 IV ganetespib given on day 1 and day 15 of each cycle
* Cohort 2: 150 mg/m2 IV ganetespib given on day 1 and day 15 of each cycle
* Cohort 3: 200 mg/m2 IV ganetespib given on day 1 and day 15 of each cycle

Patients will receive a maximum of 6 cycles of treatment, each cycle lasts 21 days:

**Day 1**

* IV ganetespib - 1 hour infusion at the current cohort dose
* Pemetrexed 500mg/m2 IV - infused over 10 minutes with vitamin B12 and folate supplementation as standard. Pemetrexed should be administered immediately after completion of the ganetespib infusion.
* Cisplatin 75mg/m2 IV infused over 2 hours Cisplatin should be administered approximately 30 minutes after completion of the pemetrexed infusion.

**Day 15**

* IV ganetespib - 1 hour infusion at the current cohort dose

\* DuBois and DuBois formula is the recommended method to be used for calculation of BSA

After completing 6 cycles of chemotherapy/ganetespib patients could receive maintenance ganetespib if there are no signs of disease progression. Patients who have only completed 4 cycles of treatment without disease progression may be treated with maintenance ganetespib if their treating clinician agrees there is benefit. Please contact UCL CTC if a patient has received less than 4 cycles of treatment but maintenance ganetespib is deemed appropriate.

Maintenance ganetespib should be given on Day 1 and 15 of each 21-day cycle.

**Loperamide must be given prophylactically** at the start of each cycle of treatment (i.e. prior to day 1 and 15 of ganetespib administration). Loperamide 2mg must be given (starting approximately 1-2 hours) before ganetespib administration, and repeated every 4 hours for the first 12 hours.

Schedules for hydration and electrolytes can based on locally agreed pharmacy procedures and guidelines. Pre-hydration can be started prior to ganetespib administration.

Patients should be strongly encouraged to maintain liberal oral fluid intake during therapy, especially during the initial 14 days of each treatment cycle.

Chemotherapy will be continued to a maximum of 6 cycles or patient withdrawal due to unacceptable toxicity, patient refusal or progressive disease.

Summary of drug administration per cycle (phase I)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Week 1 | | | | | | | Week 2 | | | | | | | Week 3 | | | | | | |
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| Ganetespib\* IV | X |  |  |  |  |  |  |  |  |  |  |  |  |  | X |  |  |  |  |  |  |
| Pemetrexed  500mg/m2 IV | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cisplatin  75mg/m2 IV | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

\*Dose determined by which cohort the patient has been assigned to at registration

### Determining the ganetespib dose from the phase I trial to be used in phase II (maximum tolerated dose, MTD)

DLTs used to determine dose-escalation or expanding the cohort size will be based on those seen in treatment Cycles 1 and 2.

* In each cohort, if there are no DLTs among the first 3 patients, then the next cohort will commence.
* If there is 1 DLT, another 3 patients will be added to the current cohort.
  + If there are no further DLTs (i.e. 1 DLT in 6 patients), the next cohort can commence.
  + If at least 2 out of the 6 patients have a DLT, the trial dose escalation stops and no higher dose is used.

The dose to be used in Phase II will be the highest dose in the phase I where there is an acceptable safety profile and where either 0 DLTs were experienced in 3 patients or only 1 DLT was experienced out of 6 patients. In order to confirm tolerability and safety and establish the MTD, a further 3/6 patients will be recruited to receive this same dose of ganetespib, to give a total of 9 with that dose.

*Using carboplatin instead of cisplatin*

There will be additional patients to be treated with carboplatin (AUC5) instead of cisplatin. If treatment with carboplatin is confirmed to be safe and tolerable, the option of treating patients with either cisplatin or carboplatin during phase II will be taken. The evaluation will be done as follows (using an accelerated titrated phase I design):

* 1 patient to be given carboplatin, with 100 mg/m2 IV ganetespib and pemetrexed,
* If there are no DLTs, the second patient is given 150 mg/m2 IV ganetespib.
* If a DLT occurs at either ganetespib dose, a 3+3 dose escalation design will begin (as with cisplatin).
* If there are no DLTs at the two low ganetespib doses, the next 3 patients are given 200 mg/m2 IV ganetespib, expanded to 6 if there are 0 or 1 DLTs among the first 3. If there are 2 or 3 DLTs among the first 3 patients the MTD would be the next lowest ganetespib dose.

Only a DLT occurring on Days 1-21 of Cycle 1 (out of the maximum of 6 cycles) will be considered for dose-escalation. If multiple toxicities are seen, the dose administered should be based on the most severe toxicity

Carboplatin schedule:

**Day 1**

* IV ganetespib -1 hour infusion at the proposed MTD
* Pemetrexed 500mg/m2 IV – infused over 10 minutes with vitamin B12 and folate supplementation as standard. Pemetrexed should be administered immediately after completion of the ganetespib infusion.
* Carboplatin AUC5 IV infused over 30 minutes. Carboplatin should be administered approximately 30 minutes after completion of the pemetrexed infusion.

**Day 15**

* IV ganetespib – 1 hour infusion at the proposed MTD

\*DuBois and DuBois formula is the recommended method to be used for calculation of BSA

Dose Limiting Toxicities: Definition

Toxicities will be graded in severity according to the guidelines outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. In order to be declared a dose-limiting toxicity, an adverse experience must be related (definitely, probably, or possibly) to ganetespib therapy.

Only a DLT occurring on Days 1-21 of Cycles 1 or 2 (out of the maximum of 6 cycles) will be considered for dose-escalation. If multiple toxicities are seen, the dose administered should be based on the most severe toxicity.

A DLT is defined as any of the following:

* Ganetespib related grade 3 or 4 non-hematologic events except diarrhoea, nausea and vomiting
* Ganetespib related diarrhoea, nausea or vomiting ≥ Grade 3) that lasts longer than 48 hours despite maximal medical therapy
* Ganetespib related grade 4 thrombocytopenia or neutropenia (> 7 days)
* Ganetespib related febrile neutropenia
* Any drug related adverse experience, regardless of CTCAE grade, leading to an interruption of ganetespib for greater than 14 days
* Any clinically significant toxicity leading to dose reduction for ganetespib

A dose reduction for pemetrexed or cisplatin, or a change to carboplatin for cisplatin toxicity will be reviewed by members of the Trial Management Group on a case-by-case basis, to determine whether it should be classified as a DLT or not, since some patients normally have dose modifications for these two drugs.

Supportive care measures for nausea, vomiting, diarrhoea, or dehydration:

Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating clinician including but not limited to the items outlined below.

**Diarrhoea:**

In integrated data from Studies 9090-07 and 9090-08, 48% of patients treated with both ganetespib and docetaxel experienced at least 1 AE of diarrhoea compared to 15% of patients treated with docetaxel alone. In single-agent studies, approximately 78% of ganetespib patients experienced this event. The postulated mechanism of action is inhibition of EGFR in cells that line the GI tract, leading to a transient secretory diarrhoea, limited to 24 to 48 hours following ganetespib infusion. This AE is manageable with loperamide. Prophylactic use of loperamide can reduce the occurrence of diarrhoea from >80% to approximately 40%.

These broad, general management principles are necessary to proactively try and avoid more serious complications by active management of diarrhoea. However, guidelines such as these should never replace sound clinical judgment.

Experience suggests that diarrhoea is an expected drug class effect for Hsp90 inhibitors and it typically starts 2 to 3 hours following administration of ganetespib in most subjects. However, when appropriately managed with anti-diarrhoeal treatment, it is generally mild to moderate and its duration limited to 24 hours.

**Diarrhoea must be proactively managed for all patients treated with ganetespib to avoid complications or worsening of the subject’s condition. Without appropriate prophylactic treatment, the diarrhoea can be prolonged, severe and lead to severe dehydration and other complications.** Loperamide must be given **prophylactically** at the start of each cycle of treatment (i.e. prior to day 1 and 15 of ganetespib administration). Loperamide 2mg must be given (starting approximately 1-2 hours) before ganetespib administration, and repeated every 4 hours for the first 12 hours. This treatment may be continued for up to 24 hours in the absence of symptoms of diarrhoea. Due to inter-patient variability, adjustment to this regimen should be made on a case-by-case basis.

In the event of diarrhoea, patients should take loperamide at an initial 4 mg dose (irrespective of the timing of the last prophylactic dose), followed by 2mg doses every 4 hours. In the presence of uncomplicated grade 1 or 2 diarrhoea, loperamide should be continued until the patient is free from diarrhoea for 12 hours. Total daily dose should not exceed 16mg (eight capsules).

If mild to moderate diarrhoea persists after 24 hours despite treatment with loperamide, a cocktail of atropine-diphenoxylate or equivalent and loperamide may be considered. Loperamide 2 mg may be alternated with one tablet of atropine-diphenoxylate every 3 hours.

For Grade 3 or 4 diarrhoea or complicated Grade 1 or 2 (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration), IV fluids should be used as appropriate, as well as prophylactic antibiotics. Hospitalisation is recommended

**Ganstrointestinal perforation (GIP):**

A safety review of ganetespib found 11 out of 1509 exposed to ganetespib with a reported SAE which included GI perforation in the narrative. 6 of the cases were unrelated or unlikely related and the remaining 5 were reported as having a least a possible attribution to ganetespib.

If there are underlying gastrointestinal comorbidities then serious or fatal gastrointestinal perforation events have been seen. It is recommended ganetespib should be used with care in patients exhibiting the following:

* Intra-abdominal malignancies
* Active gastrointestinal disorders or require concomitant procedures that predispose to GI perforation
* Recent transmural inflammatory conditions, GI ulcers, GI strictures, obstruction, fistulae and/or GIabscess formation.

If GIP is identified or suspected, study agents should be discontinued.

**Neutropenia:**

If an Investigator determines a patient is at risk for severe neutropenia or febrile neutropenia, granulocyte-colony stimulating factor (G-CSF) may be used prophylactically beginning with the first cycle. Granulocyte colony stimulating factor (G-CSF) prophylactic use is recommended during subsequent treatment cycles in case of neutropenia lasting more than 7 days, febrile neutropenia, or documented infection with neutropenia. Assessments during treatment cycles should evaluate peripheral blood cell counts on Day 1 and Day 15 of each cycle. If severe neutropenia (Grade 3 or 4) is found on any of these days, it is very likely that neutropenia has lasted more than 7 days and, therefore, the use of prophylactic G-CSF in subsequent cycles is recommended.

**Severe or Complicated Neutropenia:**

For treatment of febrile neutropenia, guidance is provided below, or consider using widely used and accepted guidance such as:

*Management of Febrile Neutropenia: ESMO Clinical Practice Guidelines. De Naurois J, Novitzky-Basso I, Gill MJ, Marti Marti F, Cullen MH, and Roila F, on behalf of the ESMO Guidelines Working Group. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Annals of Oncology 21 (Supp 5): v252-256, 2010; NCCN Clinical Practice Guidelines in Oncology, Myeloid Growth Factors, Version 2.2013,* [*www.nccn.org*](http://www.nccn.org)*.*

Occurrence of Grade 2, Grade 3, or Grade 4 neutropenia (ANC ≤1500/mm³) on **Day 1 (any cycle)**

* Delay ganetespib dosing until neutrophil recovery to at least Grade 1. Use of G-CSF is recommended. Re-evaluate in 1 week.
* Use of prophylactic G-CSF in subsequent cycles is recommended.

Grade 2 and Grade 3 neutropenia (ANC 500 - 1500/mm³) on **Day 15 (any cycle)**

* Administer ganetespib without delay or dose modification

Occurrence of Grade 4 neutropenia (ANC<500/mm³) on **Day 15 (any cycle)** or febrile neutropenia defined as follows: neutropenia: ANC<1000/mm3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour. Grade 4 febrile neutropenia: Life-threatening consequences; urgent intervention indicated.

* Delay ganetespib dosing until neutrophil recovery to at least Grade 3. Use of G-CSF on Day 15 is recommended, followed by re-evaluation in 2-3 days. If neutropenia improves to ≤Grade 3, administer ganetespib as delayed Day 15 dose. If neutropenia is still Grade 4, skip ganetespib Day 15 dose.
* If necessary, delay the start of the next treatment cycle by up to 3 days
* Use of prophylactic G-CSF in subsequent cycles is recommended.

**Nausea/vomiting:**

Nausea and vomiting should be treated aggressively, and strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. In particular, the use of antiemetics including 5HT3 antagonists and/or aprepitant plus dexamethasone is encouraged.). Patients should be strongly encouraged to maintain liberal oral fluid intake during therapy, especially during the initial 14 days of each treatment cycle. Investigators are advised to note that ondansetron has been linked to QTc prolongation and the occurrence of torsades de pointes. Therefore it should not be used in patients being treated with ganetespib. The use of all other serotonin 5 HT3 antagonists is acceptable (e.g., palonosetron, granisetron, tropisetron). Please refer to appendix 5.

**Ocular toxicity:**

Ocular toxicity manifested as visual disturbances, has been reported for several Hsp90 inhibitors. Based on safety data as of 22 September 2014, this was not the case

with ganetespib administration. Of the 6241 patients treated with ganetespib (single-agent and combination-treatment studies) as of 20 September 2013, 8 (1%) patients experienced an event of blurred vision and 5 (<1%) experienced an event of visual impairment that was assessed as related. In patients treated with single-agent ganetespib (N=402), 6 patients (2%) experienced treatment-related blurred vision and 4 patients (<1%) experienced treatment-related visual impairment.

In studies using single-agent ganetespib, eye disorders including visual disturbances regardless of relationship to treatment included: blurred vision (5%), visual impairment (2%), and conjunctivitis, cataract, eye pain, visual acuity reduced, vitreous floaters, conjunctival

hemorrhage, dry eye, eyelid edema, periorbital edema, scotoma, blindness, chromatopsia,

conjunctival hyperemia, diplopia, eye swelling, eyelid ptosis, glaucoma, night blindness, ocular hyperemia, photopsia, and retinal degeneration (all <1%).

**QTc prolongation**:

"If a patient has a reported Grade 3 QTc prolongation (QTc ≥501 ms) of any ECG (an average of triplicate recordings), the patient may continue ganetespib treatment at a reduced dose of 80% after the QTc has decreased to at least <470 ms.

If a patient has a reported Grade 4 QTc prolongation (QTc ≥501 ms or >60 ms change from baseline and torsades de pointes, or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia) or repeated Grade 3 or higher QTc prolongation, the patient must discontinue treatment with ganetespib.

Patients with QTc prolongation of Grade 3 severity or higher should be closely monitored during the first 72 hours post ganetespib infusion (i.e., electrolytes, concomitant medications) and at subsequent cycles of ganetespib treatment.

While the QTc prolongation is Grade 3 or higher, patients will have ECGs performed in triplicate until the QTc interval returns to baseline or ≤ Grade 2

**Pancreatic events:**

A low incidence of grade 3 amylase and lipase events have been reported in other studies. All abdominal events or symptoms must be monitored closely for pancreatic disorder (including amylase levels).

**Liver:**

In the pooled data from 402 patients who received single-agent ganetespib, AEs of elevated AST and ALT were reported in 16% and 15% of patients, respectively. An AE of elevated alkaline phosphatase was reported in 16% of these patients and an AE of elevated bilirubin was reported in 6%. Grade ≥3 elevations of AST were reported in 5% of patients, Grade ≥3 elevations of alkaline phosphatase were reported in 4% of patients, and Grade ≥3 elevations of ALT and bilirubin were reported in 2% of patients. Higher prevalence of transitory increase of liver enzymes in patients treated with single-agent ganetespib is likely due to baseline disease characteristics of this patient population. In general, these patients were treated in Phase 1 dose-escalation studies and Phase 2 studies of advanced disease (different malignancy types) with multiple lines of prior cancer treatment. Patients in the 9090-08 study were treated for secondline advanced NCSLC.

None of the patients reported concomitant elevations of ATs ≥3× the upper limit of normal

(ULN) and bilirubin ≥2× ULN with alkaline phosphatase <2× ULN (Hy’s Law).

Liver toxicity in the 1st-generation geldanamycin-derivative Hsp90 inhibitors is an off-target

effect. According to a study by Cysyk, the presence of benzoquinone moiety in the molecule is the suspected cause of liver toxicity [Cysyk, Chem Res Toxicol, 2006]. Ganetespib does not contain the benzoquinone moiety and, therefore, liver toxicity is not expected. This correlates with the safety information collected to date.

### Randomised Phase II trial

Summary of drug administration per cycle (phase II)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Week 1 | | | | | | | Week 2 | | | | | | | Week 3 | | | | | | |
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| Ganetespib\* IV  (Arm A only) | X |  |  |  |  |  |  |  |  |  |  |  |  |  | X |  |  |  |  |  |  |
| Pemetrexed  500mg/m2 IV  (Arm A and B) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cisplatin  75mg/m2 IV  **or**  carboplatin  AUC5 IV  (Arm A and B) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

\*The ganetespib IV dose to be used in the phase II trial will be determined only after patients in phase I have had at least 2 cycles of therapy and the data has been reviewed by the Independent Data Monitoring Committee.

Patients will receive a maximum of 6 cycles of treatment, each cycle lasts 21 days:

**Arm A:**

Day 1

* IV ganetespib - 1 hour infusion at the dose determined by the phase I
* Pemetrexed 500mg/m2 IV - infused over 10 minutes with vitamin B12 and folate supplementation as standard. Pemetrexed should be administered immediately after completion of the ganetespib infusion.
* Cisplatin 75mg/m2 IV infused over 2 hours. Cisplatin should be administered approximately 30 minutes after completion of the pemetrexed infusion ***OR*** Carboplatin AUC5 IV infused over 30 minutes. Carboplatin should be administered approximately 30 minutes after completion of the pemetrexed infusion.

Day 15

* IV ganetespib - 1 hour infusion at the dose determined by the phase I

After completing 6 cycles of chemotherapy/ganetespib patients could receive maintenance ganetespib if there are no signs of disease progression. Patients who have only completed 4 cycles of treatment without disease progression may be treated with maintenance ganetespib if their treating clinician agrees there is benefit. Please contact UCL CTC if a patient has received less than 4 cycles of treatment but maintenance ganetespib is deemed appropriate.

Maintenance ganetespib should be given on Day 1 and 15 of each 21-day cycle.

**Arm B:**

Day 1

* Pemetrexed 500mg/m2 IV - infused over 10 minutes with vitamin B12 and folate supplementation as standard.
* Cisplatin 75mg/m2 IV infused over 2 hours Cisplatin should be administered approximately 30 minutes after completion of the pemetrexed infusion ***OR*** Carboplatin AUC5 IV infused over 30 minutes. Carboplatin should be administered approximately 30 minutes after completion of the pemetrexed infusion.

\* DuBois and DuBois formula is the recommended method to be used for calculation of BSA

## Pharmacy responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the PI, who may delegate this responsibility to the local pharmacist or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the site staff delegation log.

Ganetespib supplied for the MESO-02 trial is for MESO-02 patients only and must not be used outside the context of this protocol.

### Temperature Excursions

All temperature excursions outside the storage conditions specified in the IB for ganetespib (also refer to the latest version of the SoDA) must be reported to UCL CTC as per the ‘Pharmacy Procedure for Reporting Temperature Excursions’ (see Pharmacy Site File).

Upon identifying an excursion:

* all affected trial stock must be quarantined IMMEDIATELY
* the ‘Notification of Temperature Excursion’ form must be completed and e-mailed to [ctc.excursions@ucl.ac.uk](mailto:ctc.excursions@ucl.ac.uk) or faxed to +44 (0)20 7679 9871.

**Please note that UCL CTC must be informed immediately if a patient has been administered drug affected by a temperature excursion.**

### Drug accountability

The Pharmacy Lead must ensure that appropriate records are maintained.

These records must include accountability for each drug including receipt (for ganetespib only), dispensing, returned medication and destruction of returned/unused medication as per the Summary of Drug Arrangements document. Template accountability forms will be supplied, however, sites may be permitted to use their own drug accountability records providing the same information is captured, as a minimum. Such in-house records must be submitted to UCL CTC for review and authorisation for use prior to patient enrolment.

Copies of completed drug accountability logs must be submitted to UCL CTC for all trial patients upon request. Also refer to section 12.2 (Central Monitoring).

## Ganetespib

Ganetespib (formerly called STA-9090) is a novel, injectable, synthetic small molecule being developed by Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.). Ganetespib inhibits heat shock protein 90 (Hsp90), a molecular chaperone protein that modulates cellular homeostasis and responses to environmental stress by regulating the post-translational folding of its protein substrates (referred to as Hsp90 client proteins). Because many of these client proteins function in signal transduction pathways implicated in the development of cancer, Hsp90 is considered an attractive target for cancer therapy

Ganetespib is provided as the Ganetespib Drug Product, 25 mg/mL for dilution and infusion in 2 different vials sizes; 300mg and 400mg.

300mg vials contain 12mL of deliverable volume (12.84 mL total including an overage per USP requirements) and 400mg vials contain 16mL of deliverable volume (17.12 mL total including an overage per USP requirements). Both are equivalent to a concentration of 25 mg/mL in a PEG 300, polysorbate 80 and dehydrated alcohol non‑aqueous solvent system. The drug product is a colorless to slightly yellow, clear solution, essentially free of visible particles.

Chemical name: 5-[2,4-dihydroxy-5-(1-methylethyl)phenyl]-2,4-dihydro-4-(1-methyl-1*H*-indol-5-yl)-3*H*-1,2,4-triazole-3-one

Molecular formula / weight: C20H20N4O3/ 364.40 g/mol

Pharmaceutical form: 25mg/ml

Supplier: Aldeyra Therapeutics, Inc. and Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.)

Unit strength: 25mg/ml

License status: Unlicensed. No marketing authorisation in the EU

Posology: Taken as indicated. Depends on allocation to dose cohort for phase I. Phase II dose will be determined from the phase I results

Duration of use: Ganetespib will be administered as a 60-minute IV infusion on day 1 and day 15, of each 21-day chemotherapy cycle, for up to 6 cycles

Container: **400mg/vial** - 30mL type I amber glass vial fitted with a 20mm stopper and sealed with a red coloured cap.

**300mg/vial** - 30mL type I amber glass vial fitted with a 20mm stopper and sealed with a dark blue coloured cap.

Storage conditions: Please refer to the Summary of Drug Arrangements

Route of administration: Intravenous infusion

**Dosage and Frequency**

The dosage and frequency for ganetespib (to given on day 1 and day 15 of each cycle) for each cohort in the phase I trial is given below:

* Cohort 1: 100 mg/m2 IV ganetespib
* Cohort 2: 150 mg/m2 IV ganetespib
* Cohort 3: 200 mg/m2 IV ganetespib

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Week 1 | | | | | | | Week 2 | | | | | | | Week 3 | | | | | | |
| Day | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
| Ganetespib | X |  |  |  |  |  |  |  |  |  |  |  |  |  | X |  |  |  |  |  |  |
| Pemetrexed  500mg/m2 IV | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cisplatin  75mg/m2 IV | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

**Administration**

Ganetespib must be diluted in 5% glucose prior to administration. Infusion solutions must be stored at ambient room temperature and exposure to direct light should be avoided. The diluted solution must be used within 4 hours of preparation. The diluted drug product should be a clear, colourless solution, essentially free of visible particles. The appropriate administration instructions per the preparation guidelines must be carefully followed prior to use. Refer to the Summary of Drug Arrangements for detailed ganetespib preparation guidelines. Ganetespib infusion will be administered over approximately 60 minutes. The amount of ganetespib administered will be determined by calculating the subject’s body surface area, and will be recalculated on Day 1 of each cycle during the course of the study. The DuBois and DuBois formula is the recommended method to be used for the calculation of BSA. Other methods are allowed, however this should be documented on the relevant CRF accordingly.

*Use of Vascular Access Devices*

Only the use of vascular access devices (VADs) (such as ports and peripherally‑inserted central catheters [PICCs]) containing silicone are permitted.  Use of VADs with catheters made of any other material is not allowed.  Following each ganetespib administration through a VAD, care should be taken to flush the line using 5% dextrose after each dose of study drug.  Follow institutional clinical practice for flushing and care of subjects utilising VADs.

**Randomised phase II trial**

In the randomised phase II trial, patients randomised to receive ganetespib will be given the dose chosen from the phase I trial.

## Pemetrexed

Pemetrexed will be given as an intravenous infusion at a dose of 500mg/m2 IV over 10 minutes on day 1 every 21 days during the treatment. Pemetrexed should be administered immediately after completion of the ganetespib infusion. To reduce the incidence and severity of pemetrexed-related skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4mg of dexamethasone administered orally twice a day.

Pemetrexed should be administered in accordance with local schedules for hydration and electrolytes, based on locally agreed pharmacy procedures and guidelines. Pre-hydration can be started prior to ganetespib administration.

Dose banding to ±5% is acceptable.

## Cisplatin

Cisplatin will be given at as an intravenous infusion at a dose of 75mg/m2 infused over 2 hours on day 1 every 21 days during the treatment. Cisplatin should be administered approximately 30 minutes after completion of the pemetrexed infusion. Cisplatin should be administered in accordance with local schedules for hydration, antiemetics and electrolytes, based on locally agreed pharmacy procedures and guidelines. Pre-hydration can be started prior to ganetespib administration. Prior to each course, the absence of symptoms of peripheral neuropathy should be established.

Dose banding to ±5% is acceptable.

## Carboplatin

Carboplatin will be given at as an intravenous infusion at a dose of AUC5 infused over 30 minutes on day 1 every 21 days during the treatment. Carboplatin should be administered approximately 30 minutes after completion of the pemetrexed infusion. Carboplatin should be administered in accordance with local schedules for supportive medication.

Dose banding to ±5% is acceptable.

## Vitamin supplementation

All patients receiving pemetrexed containing regimens should receive the following prophylactic treatments:

* 350 – 1000 micrograms oral folic acid daily. At least five doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and daily dosing must continue during pemetrexed treatment, and for 21 days after the last dose.
* 1000 micrograms of intramuscular vitamin B12 every 9 weeks. The first dose starting in the week preceding the first dose of pemetrexed. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.

Alternative locally approved schedules for folate and vitamin B12 supplementation may be considered if deemed appropriate by the treating clinician. Vitamin B12 and folic acid supplementation products do not fall within the definition of investigational medicinal products.

## Anti-emetics

The use of anti-emetics should be as per local practice for cisplatin, carboplatin and pemetrexed administration.

If patients have acute uncontrolled emesis then admission for intravenous fluid support should be given.

## Prophylactic antibiotics

It is advised that all patients should receive prophylactic antibiotics during each cycle to minimise the risk of neutropenic sepsis and respiratory infection. Please refer to section 7.12.4 and 7.13.1 for possible interactions.

## Dose modifications

### Ganetespib reductions (phase I only)

Before each dose of trial drug, the patient should be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), Version 4.0 <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>. Dose reductions due to previously established or new toxicities observed at any time are to be managed as described in the sections below.

**Dose re-escalations are not allowed.**

**If treatment is delayed because of toxicity for >28 days from the date of the last dose received, then trial treatment should be terminated.**

* If a toxicity can be identified from a particular drug then only that drug should be reduced. Otherwise all three drugs (ganetespib, cisplatin/carboplatin and pemetrexed) should be reduced.

Up to two dose reductions of ganetespib may occur before the patient must be withdrawn from the trial

If a dose delay is necessary for a particular drug on Day 1 all other drugs should also be delayed to ensure the treatment combination is given concurrently.

.The following table summarises dose reductions according to adverse event:

|  |  |
| --- | --- |
|  | **Ganetespib Administration** |
| **Non-Hematologic Toxicity** |  |
| * Any Grade 1 or 2 toxicity | Maintain dose level; delay or omit dose for Grade 2 toxicity as needed in order to avoid greater clinical significance |
| * Unresolved Grade 3 or 4 toxicity within a maximum of 2 weeks from last planned administration | Discontinue treatment |
| **Gastrointestinal toxicity** |  |
| * Grade 1 or 2 | Maintain dose level |
| * Grade 3 or 4 | Delay until recovery; Reduce to 80% if recurrent toxicity or if optimal prophylactic measures have failed to control symptoms |
| **Fatigue and Asthenia** |  |
| * Grade 1 or 2 | Maintain dose level |
| * Grade 3 or 4 | Reduce to 80% if recurrent |
| **QTc Prolongation – see also section 8.2** |  |
| * Grade 1 or 2 | Maintain dose level |
| * Grade 3 (≥ 501ms - average of triplicate ECGs) | Reduce dose to 80% after QTc has decreased to at least <470ms. |
| * If repeated Grade 3, or 4 | Discontinue |
| * Grade 4 (QTc ≥501ms or >60 ms change from baseline and torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia | Discontinue |
| While the QTc prolongation is Grade 3 or higher, patients will have ECGs performed in triplicate until the QTc interval returns to baseline or ≤ Grade 2. | |
| **Hematologic Toxicity** |  |
| * Grade 1 and 2 * ANC ≥ 0.5 x 109/L * Platelet count ≥ 50.0 × 109/L and <75.0 x 109/L * Haemoglobin is > 80 g/L * Platelet count <50.0 × 109/L, * Haemoglobin is <80 g/L | Maintain dose level  Delay until recovery |
| * ANC <0.5 x 109/L |  |
| * Febrile neutropenia |  |
| Hepatic function (no hepatic metastasis) |  |
| * ALT or AST >3 × ULN but ≤5 × ULN and total bilirubin ≤2 × ULN | Reduce dose to 80% |
| * ALT or AST >5.0 - 20.0 x ULN and total bilirubin ≤2 × ULN | Reduce to 80% and delay until recovery to at least ≤3 × ULN |
| * ALT or AST >3 × ULN and total bilirubin >2.0 × ULN | Discontinue |
| Hepatic function (with hepatic metastasis) |  |
| * ALT or AST >5 × ULN but ≤8 × ULN and total bilirubin ≤2 × ULN | Reduce dose to 80% |
| * ALT or AST >8.0 - 20.0 x ULN and total bilirubin ≤2 × ULN | Reduce to 80% and delay until recovery to at least ALT or AST <5 × ULN \* |
| * ALT or AST >5 × ULN and total bilirubin >2.0 × ULN | Discontinue |
| Clinical Chemistry[1]: |  |
| * Any Grade 1 or 2 toxicity | Maintain dose level |
| * Any Grade 3 or 4 toxicity – not clinically significant | Maintain dose level |
| * Any Grade 3 or 4 toxicity – clinically significant | Delay until recovery\* |
| Renal |  |
| * Serum Creatinine between 1.5 - 3 x ULN or CLcr[2]≤ 50 mL/min≥ 30 mL/min | Maintain dose level |
| * Serum Creatinine > 3 x ULN or CLcr[2] ≤ 30 mL/min | Delay until recovery\* |
| NOTE: related toxicities are recovered when their severity grade resolves to ≤ 1 or to the severity grade assessed at baseline. Related hematologic toxicities are recovered when: ANC ≥ 1.5 x 109/L; Platelet count ≥75.0 x 109/L. Haemoglobin is ≥ 90 g/L. Treatment should be restarted as per the guidelines provided in this table. For recurrent toxicities, dose reduction to 80% may be considered.  \* Start next cycle at reduced dose (80%).  [1] Clinical chemistry includes both amylase and lipase levels.  [2 ]CLcr: calculated creatinine clearance using Cockcroft Gault – see appendix 4 | |

### Ganetespib reductions (phase II only)

The ganetespib dose reduction schedule in the previous section will be modified before the phase II begins (in a revised protocol as part of a substantial amendment).

### Pemetrexed/cisplatin dose reduction guidelines

The dose modification schedules should be followed as closely as possible but these are recommendations only and clinical judgement should be used in individual cases.

#### Pemetrexed/cisplatin doses to be administered in the presence of renal toxicity

|  |  |  |
| --- | --- | --- |
|  | **Day 1 (% of previous dose**) | |
| **GFR (ml/min) (EDTA or C&G)** | **Cisplatin** | **Pemetrexed** |
| ≥60 | 100% | 100% |
| 45-59 | 75% | 100% |
| <45 | Discontinue | Discontinue |

#### Pemetrexed/cisplatin doses to be administered in the presence of haematological, non-haematological, or neurological toxicities

Dose adjustments at the start of a subsequent cycle should be based on haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy. Treatment should be delayed to allow sufficient time for recovery. Upon recovery, it is recommended patients are retreated using the guidelines in the tables below.

#### Doses in the presence of Haematological Toxicity

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  | **Day 1 (% of previous dose)** | |
| **ANC (x109/L)** |  | **Platelets (x109/L)** | **Cisplatin** | **Pemetrexed** |
| ≥ 0.5 | and | ≥ 50 | 100% | 100% |
| <0.5 | and | ≥ 50 | 75% | 75% |
| Any | and | <50 | 75% | 75% |
| Any | and | <50 with bleedinga | 50% | 50% |
| Febrile neutropenia | and | Any | 75% | 75% |
| Recurrence of decreased neutrophil count of CTCAE v4.0 Grade 3 or 4 after 2 dose reductions | or | Recurrence of decreased platelet count of CTCAE v4.0 Grade 3 or 4 after 2 dose reductions | Discontinue patient from trial | Discontinue patient from trial |

a Criteria meet the CTCAE version 4.0 definition of ≥ Grade 3 bleeding. Dose reduction is maintained into subsequent cycles.

#### Doses in the presence of Non-Haematological Toxicity

|  |  |  |
| --- | --- | --- |
|  | **Day 1 (% of previous dose)** | |
| **Grade (CTCAE v 4.0)** | **Cisplatin** | **Pemetrexed** |
| ≤ 2 (Except for nausea/  vomiting and alopecia) | 100%\*\* | 100%\*\* |
| ≥ 3 toxicities except:  (i) mucositis (see box below) (ii) neurotoxicity (see table below)  (iii) nausea/vomiting and alopecia  and any diarrhoea requiring hospitalisation irrespective of grade | Delay\* until recovery to baseline, then resume treatment at 75% of previous dose | Delay\* until recovery to baseline, then resume treatment at 75% of previous dose |
| Grade 3 or 4 mucositis | 100% | 50% |

\*If delay is >28 days the patient will be withdrawn from the protocol treatment

\*\*Investigator discretion to whether a particular non-haematological toxicity requires dose reduction or treatment delay.

#### Doses in the presence of Neurosensory Toxicity

|  |  |  |
| --- | --- | --- |
|  | **Day 1 (% of previous dose)** | |
| **Grade (CTCAE v 4.0)** | **Cisplatin** | **Pemetrexed** |
| 0-1 | 100% | 100% |
| 2 | 50% | 100% |
| 3 | Discontinue | Discontinue |
| 4 | Discontinue | Discontinue |

#### Dose Reductions for Cisplatin Induced Ototoxicity

In cases of significant clinical hearing loss, cisplatin therapy should be reduced or stopped. The clinician will make the decision regarding cisplatin dosing and also whether to continue pemetrexed alone or to withdraw the patient. A change to carboplatin may be permitted if deemed appropriate by the treating clinician; further treatment with ganetespib will cease.

#### Dose Reductions for carboplatin

The neutrophil count should be is at least 2.0 x109/L and the platelet count at least 100 x109/L prior to each cycle of treatment.

In case of a glomerular filtration rate of ≤ 20 ml/min, carboplatin should not be administered at all.

Local guidelines should be used for other dose reductions.

#### Dose reductions related to changes in patient weight – all drugs

The doses for all drugs should be re-calculated prior to each cycle of treatment. The amount of drug administered will be determined by calculating patient body surface area, and will be recalculated when there is ≥ 10% change in patient weight during the course of the study

**Doses will be capped to a maximum of 2m2 for BSA.**

## Drug Interactions

### Interactions Common to all Cytotoxics

Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation treatment is frequent. The high intra-individual variability of the coagulation status during diseases and the possibility of interaction between oral anticoagulants and anti-cancer chemotherapy require increased frequency of INR (International Normalised Ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.

Supportive equipment should be available to control anaphylactic reactions.

### Ganetespib (also refer to the latest version of ganetespib Investigator brochure and SoDA)

Substrates of CYP3A4 or CYP2C19 Results of a clinical drug-drug interactions study, examining the effect of ganetespib on the pharmacokinetics of the CYP2C19-sensitive probe omeprazole, show a modest (20%) increase in omeprazole exposure when co-administered with ganetespib. In vitro data implies expectation of greater interaction with CYP2C19 substrates than with CYP3A4 substrates. In addition, PK data for docetaxel in combination with ganetespib was comparable to reference literature. Since docetaxel is a sensitive CYP3A4 substrate, an effect of ganetespib on other CYP3A4 substrates is unlikely.

Caution is advised when sensitive narrow therapeutic range CYP3A4 or CYP2C19 substrates are concomitantly administered.

In mice, ganetespib did not show marked pharmacokinetic interactions when co-administered with paclitaxel, docetaxel, erlotinib, fulvestrant, BEZ235, AZD6244, bortezomib, or irinotecan. Vemurafenib exposure via oral administration was more than 2 fold lower when ganetespib was co-administered compared to administration of vemurafenib alone to mice.

Based on the Caco-2 permeability assay, ganetespib is a P-gp substrate. Since ganetespib’s potential as a P-gp inhibitor has not yet been determined, caution with concomitant P-gp substrates is recommended

**QTc prolongation**

**The use of any medication that has the potential for QTc prolongation and has been linked to the occurrence of torsades de pointes is strictly prohibited.** See Appendix 5 for a list of drugs with a risk of torsades de pointes. Investigators are advised to note that ondansetron has been linked to QTc prolongation and the occurrence of torsades de pointes. Therefore it should not be used in patients being treated with ganetespib. The use of all other serotonin 5 HT3 antagonists is acceptable (e.g., palonosetron, granisetron, tropisetron).

Medications that have the potential of prolonging the QT interval but are not linked to the occurrence of torsades de pointes should be avoided or used with caution. The decision to use such a medication should be made by the Investigator, taking into consideration the patient’s medical history and current QTc values.

**Interaction with potential co-medications**

A panel of potential co-medication (atorvastatin, dexamethasone, fentanyl, furosemide, morphine and warfarin) and combination (fulvestrant and 5-fluorouracil) drugs was evaluated for potential drug-drug interactions (DDIs) with ganetespib via hepatic metabolism using human cryopreserved hepatocytes suspensions. Ganetespib CL was not affected by any of the co-medications tested at clinically relevant dosage. Ganetespib did not markedly affect theCYP3A4-mediated metabolism of atorvastatin, dexamethasone, fentanyl, warfarin and fulvestrant, CYP2C9-mediated metabolism of warfarin, or dihydropyrimidine dehydrogenase mediated metabolism of 5-fluorouracil. Ganetespib at 20μM appeared to inhibit UGT-mediated metabolism of furosemide (UGT1As) and morphine (mainly UGT2B7) at clinically relevant concentrations of these co-medications.

*In vivo* DDI potentials between ganetespib and other oncology drugs that are possibly co-administered in clinic (paclitaxel, docetaxel, erlotinib, fulvestrant, BEZ235, AZD6244, bortezomib, irinotecan and vemurafenib) were investigated in female SCID mice. None of these drugs altered the ganetespib pharmacokinetics. Similarly, no apparent pharmacokinetic alterations were observed for these co-administered drugs (differences were within variations), except vemurafenib, with ganetespib, suggesting no pharmacokinetic interactions between ganetespib and these drugs under the study conditions used. Vemurafenib exposure via oral administration was more than 2 fold lower when ganetespib was co-administered compared to administration of vemurafenib alone to mice.

### Pemetrexed

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic drugs (e.g., aminoglycoside, loop diuretics, platinum compounds, cyclosporin) could potentially result in delayed clearance of pemetrexed. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

Concomitant administration of substances that are also tubularly secreted (e.g., probenecid, penicillin) could potentially result in delayed clearance of pemetrexed. Caution should be made when these drugs are combined with pemetrexed. If necessary, creatinine clearance should be closely monitored. Creatinine clearance must be ≥ 45ml/min in order for dosing of Pemetrexed.

In patients with *normal renal function* (creatinine clearance ≥ 80ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen >1600mg/day) and aspirin at higher dosage (≥1.3g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. Therefore, caution should be made when administering higher doses of NSAIDs or aspirin at higher dosage concurrently with pemetrexed to patients with normal function (creatinine clearance ≥ 80ml/min).

In patients with *mild to moderate renal insufficiency* (creatinine clearance from 45 to 79ml/min) the concomitant administration of pemetrexed with NSAIDs (e.g., ibuprofen) or aspirin at higher dosage should be avoided for 2 days before, on the day of, and 2 days following pemetrexed administration

In the absence of data regarding potential interaction with NSAIDs having longer half-lives, such as piroxicam or rofecoxib, the concomitant administration with pemetrexed should be avoided for at least 5 days prior to, on the day, and at least 2 days following pemetrexed administration.  If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression and gastrointestinal toxicity.

Pemetrexed undergoes limited hepatic metabolism. Results from in vitro studies with human liver microsomes indicated that pemetrexed would not be predicted to cause clinically significant inhibition of the metabolic clearance of drugs metabolised by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

Concomitant Use Contra-Indicated

Yellow fever vaccine: Risk of fatal generalised vaccinale disease.

Concomitant Use Not Recommended

Live attenuated vaccines (except yellow fever): Risk of systemic, possibly fatal, disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (poliomyelitis).

### Cisplatin

Concomitant administration of aminoglycoside antibiotics, cephaloridine or frusemide may result in increased ototoxicity or nephrotoxicity. Ototoxicity may be enhanced with prior simultaneous cranial irradiation and may be related to peak plasma concentration of cisplatin.

Cisplatin causes immunosuppression. Concomitant use of live vaccines may lead to generalised systemic reaction.

The literature indicates that cisplatin may reduce renal excretion of bleomycin and methotrexate (probably due to cisplatin-induced nephrotoxicity), and thus increase their toxicity.

## Support and Concomitant medication

All concomitant medications during the trial will be recorded in the CRF with indication and dates of administration.

Appropriate pre-hydration and anti-emetic prophylaxis must be administered prior to each dose of cisplatin/carboplatin.

Full supportive care measures will be offered to treat any emerging DLTs. Supportive care measures including those directed at controlling symptoms resulting from mesothelioma are allowed.

Any other anticancer therapies should not be given until disease progression or withdrawal from the study medication, e.g., biologic therapy, chemotherapy, and radiation therapy, including palliative radiotherapy for painful metastases. Patients who require radiation therapy for palliative care may be allowed to continue on ganetespib, at the clinician’s discretion.

### Medications Used with Caution

* Medications associated with QTc prolongation should be used with caution. The decision whether or not such a medication may be used should be taken in the context of the patient’s medical history and QTc values at screening. Please also refer to appendix 5
* Ganetespib is a substrate of the P-glycoprotein (P-gp) efflux transporter.  Since ganetespib’s potential as a P-gp inhibitor has not yet been determined, caution with concomitant P-gp substrates is recommended.
* Caution is advised when sensitive narrow therapeutic range CYP3A4 or CYP2C19 substrates are concomitantly administered.
* Refer to the following link for CYP2C19 and CYP3A4, and P-glycoprotein (P-gp) interactions: <http://www.pharmacologyweekly.com/content/pages/drug-reference-table-cyp-p450-ugt-enzymes-transporters-ab>

### Permitted Concomitant Treatment

After confirmation and documentation that a subject has met all the inclusion criteria and none of the exclusion criteria, supportive care treatments (transfusions, etc.) can be prescribed as medically appropriate. The following treatments are permitted during the study:

* Erythropoietin or other specific red blood cell growth factors. Transfusion of blood products.
* Steroids (inhaled, topical, or for physiologic replacement, or for short term treatment of conditions such as allergic reactions and asthma flares, or for appetite stimulation). A standard 3-5 day course of dexamethasone following the institutions standard of care for the prevention of chemotherapy-induced nausea and vomiting is allowed. In addition glucocorticoid daily doses (oral) ≤ 1.5 mg dexamethasone (or equivalent) are allowed.

Other concomitant medications may be given as clinically indicated. Please consult with the CTC regarding any questions about concomitant medications.

## Management of Events of Special Interest associated with ganetespib

### Management of Gastrointestinal Adverse Events

These broad general management principles are necessary to proactively attempt to avoid more serious complications by active management of diarrhoea syndrome. However, guidelines such as these should not replace sound clinical judgment.

Experience suggests that diarrhoea is an expected drug class effect for Hsp90 inhibitors and it typically starts 2 to 3 hours following administration of ganetespib. However, when appropriately managed with anti-diarrhoea treatment, it is generally mild to moderate and its duration limited to 24 hours.

**For all subjects, it is strongly recommended that diarrhoea be managed proactively to avoid complications or worsening of the subject’s condition. Without appropriate prophylactic treatment, the diarrhoea can be prolonged and lead to severe dehydration and other complications.**

**Loperamide must be given prophylactically** at the start of each cycle of treatment (i.e. prior to day 1 and 15 of ganetespib administration). Loperamide 2mg must be given (starting approximately 1-2 hours) before ganetespib administration, and repeated every 4 hours for the first 12 hours. Due to inter-patient variability, adjustment to this regimen should be made on a case-by-case basis.

In the event of diarrhoea, patients should take loperamide at an initial 4 mg dose (irrespective of the timing of the last prophylactic dose), followed by 2 mg doses every 4 hours. In the presence of uncomplicated grade 1 or 2 diarrhoea, loperamide should be continued until the patient is free from diarrhoea for 12 hours. Total daily dose should not exceed 16mg (eight capsules).

For Grade 3 or 4 diarrhoea or complicated Grade 1 or 2 (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration), IV fluids should be used, as well as prophylactic antibiotics. Hospitalisation is recommended.

**Nausea/vomiting:** Nausea and vomiting should be treated aggressively, and strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. In particular, the use of antiemetics including 5HT3 antagonists and/or aprepitant plus dexamethasone is encouraged. Patients should be strongly encouraged to maintain liberal oral fluid intake during therapy, especially during the initial 14 days of each treatment cycle.

### Management of Neutropenia

**Neutropenia:** If an Investigator determines a patient is at risk for severe neutropenia or febrile neutropenia, granulocyte-colony stimulating factor (G-CSF) may be used prophylactically beginning with the first cycle. Granulocyte colony stimulating factor (G-CSF) prophylactic use is recommended during subsequent treatment cycles in case of neutropenia lasting more than 7 days, febrile neutropenia, or documented infection with neutropenia.

Assessments during treatment cycles should evaluate peripheral blood cell counts on Day 1 and Day 15 of each cycle. If severe neutropenia (Grade 3 or 4) is found on any of these days, it is very likely that neutropenia has lasted more than 7 days and, therefore, the use of prophylactic G-CSF in subsequent cycles is recommended.

### Severe or Complicated Neutropenia:

For treatment of febrile neutropenia, guidance is provided below, or consider using widely used and accepted guidance such as:

*Management of Febrile Neutropenia: ESMO Clinical Practice Guidelines. De Naurois J, Novitzky-Basso I, Gill MJ, Marti F, Cullen MH, and Roila F, on behalf of the ESMO Guidelines Working Group. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Annals of Oncology 21 (Supp 5): v252-256, 2010; NCCN Clinical Practice Guidelines in Oncology, Myeloid Growth Factors, Version 2.2013,* [*www.nccn.org*](http://www.nccn.org)*.*

Occurrence of Grade 2, Grade 3, or Grade 4 neutropenia (ANC ≤1500/mm³) on **Day 1 (any cycle)**

* Delay ganetespib dosing until neutrophil recovery to at least Grade 1. Use of G-CSF is recommended. Re-evaluate in 1 week.
* Use of prophylactic G-CSF in subsequent cycles is recommended.

Grade 2 and Grade 3 neutropenia (ANC 500 - 1500/mm³) on **Day 15 (any cycle)**

* Administer ganetespib without delay or dose modification

Occurrence of Grade 4 neutropenia (ANC<500/mm³) on **Day 15 (any cycle)** or febrile neutropenia defined as follows: neutropenia: ANC<1000/mm3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour. Grade 4 febrile neutropenia: Life-threatening consequences; urgent intervention indicated.

* Delay ganetespib dosing until neutrophil recovery to at least Grade 3. Use of G-CSF on Day 15 is recommended, followed by re-evaluation in 2-3 days. If neutropenia improves to ≤Grade 3, administer ganetespib as delayed Day 15 dose. If neutropenia is still Grade 4, skip ganetespib Day 15 dose.

If necessary, delay the start of the next treatment cycle by up to 3 days

Use of prophylactic G-CSF in subsequent cycles is recommended.

### Ganetespib Premedication and Management of Hypersensitivity Reactions

The use of the 3-day corticosteroid premedication regimen is strongly recommended for all patients

Generally, ganetespib does not require premedication for hypersensitivity reactions. However, ganetespib contains a surfactant (polysorbate 80) that has been associated with hypersensitivity reactions in other medications administered by infusion. Symptoms have included pruritus, flushing, shortness of breath, chest tightness, dizziness, headache, increased systolic blood pressure and heart rate.

If an infusion reaction is suspected, the following is provided as guidance only; treatment should be based on clinical presentation.  Institution specific premedication and/or treatment procedures and regimens may also be appropriate in lieu of these guidelines:

**Mild or moderate symptoms**:

* Stop ganetespib administration
* Give IV dexamethasone and chlorphenamine/diphenhydramine HCl or therapeutic equivalent
* After recovery from symptoms, resume ganetespib infusion; a reduced flow rate may be considered
* In subsequent cycles, consider optimising the premedication regimen (e.g, begin steroids the day before infusion or increase the dose of steroids)

**Severe symptoms** (such as hypotension requiring pressor therapy or IV fluids, angioedema, respiratory distress requiring bronchodilator therapy, or generalised urticaria):

* Stop ganetespib administration
* Give IV dexamethasone and chlorphenamine/diphenhydramine HCl or therapeutic equivalent
* Add adrenaline (1:1000) or bronchodilators as indicated
* Reschedule dose administration for the following day
* In subsequent cycles, optimise the premedication regimen (e.g., begin steroids the day before infusion or increase the dose of steroids) and reduce the flow rate of the ganetespib infusion

If severe symptoms recur with optimal premedication, treatment with ganetespib should be discontinued.

Example of infusion premedication regimen:

* Dexamethasone 12 mg by mouth (PO) and diphenhydramine HCl 25-50 mg PO approximately 12 to 24 hours prior to the next dose of study drug
* Repeat dexamethasone 12 mg PO and diphenhydramine HCl 25 to 50 mg PO approximately 4 to 6 hours prior to the re-challenge

## Medical drug-specific advice for ganetespib (24 hours)

|  |  |  |
| --- | --- | --- |
| **Ganetespib** | **Office hours**  09:00 to 17:00 Monday to Friday, excluding Bank Holidays | **All other times**  Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) |
|  | UCL CTC  020 7679 9105 | * 001-770-419-1025 * 001-404-723-2754 |

## Clinical management after treatment discontinuation

The management and subsequent treatment of patients who withdraw consent, stop protocol treatment early due to toxicity or any other reason, or on completion of protocol chemotherapy, will be left to the discretion of the clinician. Any additional treatment should be documented on the ‘Additional treatment’ CRF. Please refer to section 13 (Withdrawal of Patients) for further details.

## Drug provision after the end of the trial

Subsequent treatment after discontinuation or completion of trial treatment, and subsequent therapy of any kind should that occur, will be left to the discretion of the clinician. Any additional treatment must be documented on the ‘Additional treatment’ CRF.

# Assessments - Appendices 2 and 3

## Pre-registration (phase I) / pre-randomisation (phase II) assessments

The following assessments or procedures are required prior to patient entry.

The CT scan must be performed no more than 28 days prior to registration/randomisation. All other screening procedures should be performed within 7 days before registration/randomisation.

* Pathological confirmation of malignant pleural mesothelioma
* Complete physical examination and medical history
* Concomitant medication check
* Vital signs, including heart rate, respiratory rate, blood pressure and body temperature
* Height and body weight
* ECOG Performance status
* Oncological profile including FBC, haematocrit, haemoglobin, RCC, white cell count with differential, platelets, sodium, potassium, urea, creatinine, chloride, bicarbonate, bilirubin, ALP, AST or ALT, LDH, albumin, total protein, calcium, phosphate, magnesium
* Urinalysis (pH, protein, blood, ketones, glucose)
* 12 lead Electrocardiogram (ECG), this is the baseline ECG value – see below
* Adverse event check
* CT scan (chest and abdomen). Scan within 28 days of registration/randomisation.
* If female and of child-bearing potential, a negative serum pregnancy test (See Section 5.6)
* Collection of archival paraffin embedded formalin fixed diagnostic tissue is mandatory for this trial. All tissue blocks will be analysed centrally for RNA/DNA extraction, as well as generation of a virtual tissue library and tissue microarray to facilitate biomarker discovery and assessment of chemoresistance. See Section 20 for details of sending the tissue sample to the central laboratory.
* Blood sample for translation research (Phase I: only patients in cisplatin cohort used to confirm MTD and cohort treated with carboplatin run in parallel. Phase II: all patients). See Section 20 for details

*12-lead electrocardiogram (ECG)*

* If the first test results in QTc >470msec, repeat ECGs as necessary to determine eligibility

## Assessments during treatment (phase I and phase II)

The assessments detailed below must be performed at the beginning of each cycle, before starting ganetespib:

* Physical examination
* ECOG Performance status
* Concomitant medication check
* Vital signs, including heart rate, respiratory rate, blood pressure and body temperature
* Height and body weight
* Oncological profile including FBC, haematocrit, haemoglobin, RCC, white cell count with differential, platelets, sodium, potassium, urea, creatinine, chloride, bicarbonate, bilirubin, ALP, AST or ALT, LDH, albumin, total protein, calcium, phosphate, magnesium.
  + **The ANC must be ≥2.0 x 109/L, and platelets must be ≥100 x 109/L before the start of cycle 1.**
  + Haematocrit, haemoglobin, red cell count, white cell count with differential, platelet count also required on Day 15 of Cycles 1 and 2 only. Day 15 bloods are not required for subsequent cycles unless clinically indicated.
  + Bloods may be taken up to 2 days prior to treatment.
* If female and of child-bearing potential, a serum pregnancy test if test at baseline taken >1 week prior to 1st dose of ganetespib
* Urinalysis (pH, protein, blood, ketones, glucose, glucose). **Urinalysis also required on Day 15 of Cycle 1 only in the Phase I trial.**
* Assessment of adverse events, which have occurred since pre-registration/randomisation or the start of the previous treatment cycle.
* 12-lead ECG performed pre-dose on Day 1 of every treatment cycle.
* For Cycle 1, ECG also performed approximately 24 hours (±2 hours) after ganetespib administration. If there is QTc prolongation >500msec, a post-infusion ECG should be done at 24 hours (±2 hours) for all subsequent cycles until the ECG returns to baseline. If there is no prolongation, the 24-hour ECG is not required at subsequent cycles.
* Chest x-ray (except where CT is performed), post cycle 1, 3 and 5.
* CT- chest and abdomen post cycle 2, 4, 6 only. CT scans should then be completed every 6 weeks for the first year (i.e. 12 months from Day 1 of chemotherapy), then 12 weekly thereafter. Tumour response to be evaluated by Chest CT scan. Response assessments will be based on the meso-modified RECIST criteria (appendix 6). CT scans may be requested from sites in pseudo-anonymised form to supplement tumour measurement data for overall examination of objective tumour response according to meso-modified RECIST criteria.

If a patient has a reported Grade 3 QTc prolongation (QTc ≥501 ms) of any ECG (an average of triplicate recordings), the patient may continue ganetespib treatment at a reduced dose of 80% after the QTc has decreased to at least <470 ms.

If a patient has a reported Grade 4 QTc prolongation (QTc ≥501 ms or >60 ms change from baseline and torsades de pointes, or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia) or repeated Grade 3 or higher QTc prolongation, the patient must discontinue treatment with ganetespib.

Patients with QTc prolongation of Grade 3 severity or higher should be closely monitored during the first 72 hours post ganetespib infusion (i.e., electrolytes, concomitant medications) and at subsequent cycles of ganetespib treatment.

While the QTc prolongation is Grade 3 or higher, patients will have ECGs performed in triplicate until the QTc interval returns to baseline or ≤ Grade 2.

The end of treatment assessments should be done on Day 21 (± 3 days) of the last treatment cycle.

## Assessments following completion of trial treatment (phase I only)

All patients should attend their final trial visit 30 days (± 7 days) after Day 21 of the last cycle of treatment, for the following investigations:

* Physical examination
* Concomitant medication check
* Vital signs, including heart rate, respiratory rate, blood pressure and body temperature
* Height and body weight
* ECOG Performance status
* Oncological profile including FBC, Haematocrit, haemoglobin, RCC, white cell count with differential, platelets, sodium, potassium, urea, creatinine, chloride, bicarbonate, bilirubin, ALP, AST or ALT, LDH, albumin, total protein, calcium, phosphate, magnesium
* Urinalysis (including pH, protein, blood, ketones, glucose).
* Assessment of Adverse events, which have occurred since the start of the previous treatment cycle.
* Blood sample for translation research (cisplatin and carboplatin cohort used to confirm MTD only). See Section 20 for details

## Assessments following completion of trial treatment (phase II only)

Follow up assessments start 6 weeks after Day 21 of the last cycle of treatment. These 6-weekly (± 7 days) assessments occur during the first year (since the start of treatment, i.e. 12 months from Day 1 of chemotherapy Cycle 1). For patients who survive to 12 months, follow up will be every 12 weeks (± 7 days) thereafter until death or until the trial results are available, whichever is sooner.

* Physical examination
* Concomitant medication check
* Vital signs, including heart rate, respiratory rate, blood pressure and temperature
* ECOG Performance Status
* Assessment of Adverse events, which have occurred since previous follow up visit.
* CT- chest and abdomen and tumour response. Response assessment will be based on the meso-modified RECIST criteria (appendix 6). CT scans may be requested from sites in pseudo-anonymised form to supplement tumour measurement data for overall examination of objective tumour response according to meso-modified RECIST criteria.
* Blood sample for translation research (all phase II patients). See Section 20 for details

All efforts should be made by the Site to contact the patient’s GP to assess their condition, if a patient fails to attend a clinic or cannot be followed up at site.

Progression may be determined clinically or radiologically, but sites are encouraged to have documented radiological progression.

1. **Data Management and Data Handling Guidelines**

Data will be collected from sites on version controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC. Data entered onto CRFs must be verifiable from source data at site.

Examples of source documents are hospital records which include laboratory and other clinical reports etc. Some data will be recorded directly on the CRFs (i.e. no prior written or electronic record of data) and it will be considered to be the source document.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, CT scan images, etc.) are being submitted to UCL CTC, the patient’s trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending to maintain confidentiality.

Please note that, for this trial, patients will be asked to consent to their date of birth and NHS number being supplied to UCL CTC. This is:

* So that, clinical trial data can be linked to hospital records if needed, without the use of the patient’s full name

## Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

All entries must be clear, legible and written in ball point pen. Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used.

The use of abbreviations and acronyms must be avoided.

Once completed the original CRFs must be sent to UCL CTC and a copy kept at site.

## Imaging

The UCL CTC will contact sites to arrange transfer of CT scan images via disc for selected patients if deemed of scientific interest. CT scan images must be transferred to the UCL CTC in **pseudo-anonymised** form i.e. with all patient identifiers (name, DOB, NHS number, hospital number) removed.

* **CT scan images** should include:
  + The patient’s trial ID (MES-XXX)
  + The date of the scan
* **Electronic file names** should include:
  + The name of the trial (MESO\_02)
  + The patient’s trial ID MES-XXX
  + The date of the scan

**Pseudo-anonymised** CT scans should be uploaded onto a disc (do not send by email) and sent by recorded delivery to the following address:

**MESO-02 Trial Coordinator**

Cancer Research UK and UCL Cancer Trials Centre

90 Tottenham Court Road

London W1T 4TJ

## Missing Data

To avoid the need for unnecessary data queries, CRFs must be checked at site to ensure there are no blank fields before sending to UCL CTC. When data are unavailable because a measure has not been taken or test not performed, enter “ND” for not done. If an item was not required at the particular time the form relates to, enter “NA” for not applicable. When data are unknown enter the value “NK” (only use if every effort has been made to obtain the data).

## Timelines for data return

CRFs must be completed at site and returned to UCL CTC as soon as possible after patient visit and within **2 weeks for the phase I trial** and within **1 month for the phase II trial** of the patient being seen.

Sites who persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to a ‘for cause’ monitoring visit. See section 12.3 (‘For cause’ on-site monitoring) for details.

## Data Queries

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Query Reports will be sent to the data contact at site. Further guidance on how data contacts should respond to Data Queries can be found on the Query Reports.

# Pharmacovigilance

## Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting” and ICH GCP E6:

Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial 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 a trial treatment, whether or not related to that trial treatment.

Adverse Reaction (AR)

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between a trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

* Results in death
* Is life threatening (the term “life-threatening” 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 that hypothetically might have caused death if it were more severe)
* Requires in-patient hospitalisation or prolongs existing hospitalisation
* Results in persistent or significant disability/incapacity
* Is a congenital anomaly or birth defect
* Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the reference safety information (RSI).

## Reporting Procedures

### All Adverse Events (AEs)

All adverse events that occur between informed consent and 30 days after administration of the last dose of trial treatment must be recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the trial specific SAE Report. Also refer to section 10.2.2 (Serious Adverse Events (SAEs)).

Pre-existing conditions do not qualify as adverse events unless they worsen.

Overdoses

All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and CRFs. Overdoses resulting in an adverse event are classified as SAEs and must be reported to UCL CTC according to SAE reporting procedures. The fact that an overdose has occurred must be clearly stated on the SAE Report. Also refer to section 10.2.2 (Serious Adverse Events (SAEs)).

Sites must inform UCL CTC immediately when an overdose has been identified. Also refer to section 11 (Incident Reporting and Serious Breaches).

Adverse Event Term

An adverse event term must be provided for each adverse event, using free text for the actual diagnoses or primary symptom reported, and using the term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 available online at: <http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40>.

Severity

Severity of each adverse event must be determined by using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 as a guideline, wherever possible. The criteria are available online at:

<http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40>

In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria:

1 = Mild (awareness of sign or symptom, but easily tolerated)

2 = Moderate (discomfort enough to cause interference with normal daily activities)

3 = Severe (inability to perform normal daily activities)

4 = Life threatening (immediate risk of death from the reaction as it occurred)

5 = Fatal (the event resulted in death)

Causality

The PI, or other delegated site investigator, must perform an evaluation of causality for each adverse event.

Causal relationship to each trial treatment must be determined as follows:

* **None**

There is no evidence of any causal relationship.

* **Unlikely**

There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of a trial treatment). There is another reasonable explanation of the event (e.g. the patient’s clinical condition, other concomitant treatments).

* **Possibly**

There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of a trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant treatments).

* **Probably**

There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

* **Definitely**

There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

UCL CTC will consider events evaluated as possibly, probably or definitely related to be adverse reactions.

### Serious Adverse Events (SAEs)

All SAEs that occur between the signing of informed consent and 30 days post the last trial treatment administration (or after this date if the site investigator feels the event is related to a trial treatment) must be submitted to UCL CTC by fax within **24 hours** of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

Exemptions from SAE Report Submission

For this trial, the following events are exempt from requiring submission on an SAE Report, but must be recorded in the relevant section(s) of the trial CRFs:

* + events that occur after 30 days post last trial treatment administration that are:
  + not considered to be side-effects of the trial treatment
  + not SAE related to pregnancies
  + disease progression (including disease related deaths)

Please note that hospitalisation for elective treatment or palliative care does not qualify as an SAE. However, if during either of these types of hospitalisation and event occurs which meets SAE criteria, the event should be reported. For example, the subject is hospitalised for chemotherapy administration and during that time experiences a heart attack, the heart attack would require immediate submission on an SAE Report.

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| **Completed SAE Reports must be faxed within 24 hours of becoming aware of the event to UCL CTC**  **Fax: +44 (0)20 7679 9871** |

**Adverse Event Reporting Flowchart**



SAE Follow-Up Reports

All SAEs must be followed-up until resolution and until there are no further queries. The PI, or other delegated site investigator, must provide follow-up SAE Reports if the SAE had not resolved at the time the initial report was submitted.

SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the RSI (list of expected adverse events in the approved IB for ganetespib and SPCs for pemetrexed, carboplatin and cisplatin).

The CI, or their delegate (e.g. a clinical member of the TMG), will be contacted to review the SAE and to perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

UCL CTC will submit all reports of SAEs, occurring in patients exposed to ganetespib, to Synta Pharmaceuticals Corporation within 24 hours of receipt of the minimum data elements.

## SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the MHRA and the REC within 7 calendar days for initial reports of fatal/life threatening events (with a follow-up report within a further 8 calendar days) and 15 calendar days for all other events. Where there are conflicting evaluations of causal relationship by the site and UCL CTC/CI, both opinions will be reported.

UCL CTC will submit all ganetespib-related SUSAR reports to Synta Pharmaceuticals Corporation concurrent with submission to the MHRA and the REC.

Informing Sites of SUSARs

UCL CTC will inform all PIs of any SUSARs that occur on the trial. PIs will receive expedited SUSAR reports that must be processed according to local requirements.

UCL CTC will forward reports received from Synta Pharmaceuticals Corporation regarding ganetespib-related SUSARs that have occurred on other trials to all PIs. These must be processed according to local requirements and filed with the applicable IB.

## Safety Monitoring

UCL CTC will provide safety information to the TMG and the IDMC on a periodic basis for review.

Trial safety data will be monitored to identify:

* new adverse reactions to the trial treatment regimen or individual trial treatments;
* a higher incidence in rare adverse events than is stated in the IB/SPC for a trial treatment
* trial related events that are not considered related to the trial treatment regimen.

Should UCL CTC identify or suspect any issues concerning patient safety at any point throughout the trial, the CI or TMG will be consulted for their opinion.

## Pregnancy

If a female patient or the female partner of a male patient becomes pregnant at any point during the trial, a completed trial specific Pregnancy Report must be submitted to UCL CTC by fax within **24 hours** of learning of its occurrence. The site must request consent from the pregnant patient/partner to report information regarding the pregnancy, using the trial-specific pregnancy monitoring information sheets and informed consent forms for trial patients and the partners of trial patients. If consent is not given, the notification that a pregnancy has occurred will be retained by UCL CTC, however no further action will be taken on the information detailed in the report.

|  |
| --- |
| **All pregnancies must be reported by faxing a completed Pregnancy Report within 24 hours of becoming aware of the pregnancy to UCL CTC**  **Fax: +44 (0)20 7679 9871** |

Pregnancy Follow-Up Reports

All pregnancies, where consent has been given, must be followed-up until an outcome is determined. Follow-up Pregnancy Reports must be submitted to UCL CTC by fax within **24 hours** of learning of the outcome. Reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

SAEs during Pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. **Refer to section 10.2.2 (Serious Adverse Events (SAEs)) for details.**

Pregnancy Report Processing at UCL CTC

UCL CTC will submit a report to the MHRA and the REC **should the pregnancy outcome meet the definition of a SUSAR. Refer to section 10.3 (SUSARs) for details.**

UCL CTC will submit all reports of pregnancies, occurring in patients or partners of trial patients exposed to ganetespib, to Synta Pharmaceuticals Corporation within 24 hours of receipt of the minimum data elements about the pregnancy.

## Development Safety Update Reports (DSURs)

Safety data obtained from the trial will be included in DSURs that UCL CTC **will submit to the MHRA and the REC.**

UCL CTC will provide Synta Pharmaceuticals Corporation with DSURs that include information regarding ganetespib concurrent with submission to the MHRA and the REC.

# Incident Reporting and Serious Breaches

## Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. UCL CTC may require a report on the incident(s) and a form will be provided if the organisation does not have an appropriate document (e.g. Trust Incident Form).

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

## Serious Breaches

Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a potential or actual serious breach has been identified, UCL CTC will inform the MHRA within 7 calendar days of becoming aware of the breach.

Sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches).

UCL CTC will use an organisation’s history of non-compliance to make decisions on future collaborations.

# Trial Monitoring and Oversight

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

UCL CTC will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

## On-Site Monitoring

The degree of on-site monitoring will be proportionate to the objective, purpose, phase, design, size, complexity, endpoints and risks associated with the trial.

Sites will be sent a letter in advance confirming when a routine monitoring visit is due. The letter will include a list of the documents to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit is likely to occur.

The Trial Coordinator will conduct routine monitoring visits.

The frequency and level of monitoring will be specified in the Trial Monitoring Plan which may be updated during the trial.

**Monitoring Follow up**

Following a monitoring visit, the Trial Monitor/Trial Coordinator will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified, (this may be delegated to an appropriate member of staff).

## Central Monitoring

**Sites will be requested to submit screening logs and staff delegation logs to UCL CTC on request and these will be checked for consistency and completeness.** (Also refer to section 3.4.2: Required documentation and section 5.2, Screening Logs).

Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Checks of the criteria listed on the randomisation form will be undertaken by an appropriately trained UCL CTC staff member prior to randomisation.

**Copies of the drug accountability logs will be collected at UCL CTC for all trial patients**. Sites will be required to submit logs following the patient’s completion in the trial or on request if not collected previously at an on-site monitoring visit. (Also refer to section 7.4.2 Pharmacy Responsibilities)

**Sites will be requested to conduct quality control checks of documentation** held within the Investigator Site File and Pharmacy Site File at the frequency detailed in the trial monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Data received at UCL CTC will be subject to review in accordance with section 9.4 (Data Queries).

Where monitoring/central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (e.g. evidence of an overdose having been administered, indication that stopping rules for an IMP were not observed following an adverse reaction, etc.), the matter will be raised urgently with site staff and escalated as appropriate refer to section 11 (Incident Reporting and Serious Breaches) and 12.3 (‘For cause’ on-site monitoring) for further details.

## ‘For Cause’ On-Site Monitoring

Additional on-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit, a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit will likely occur.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. See section 11, (Incident Reporting and Serious Breaches), for details.

## Oversight Committees

### Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and MESO-02 trial staff from UCL CTC (see page 2). The TMG will be responsible for overseeing the trial. The group will meet regularly but no less than twice a year and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Lung Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individuals. All members will be required to sign the MESO-02 TMG charter.

### Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder(s) and Sponsor. All members will be required to sign the TSC charter.

### Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held at least once per year to review interim analyses, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC. All members will be required to sign the IDMC charter.

## Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 10.0 (Pharmacovigilance).

# Withdrawal of Patients

In consenting to the trial, patients are consenting to trial treatment, assessments, follow-up and data collection.

Discontinuation of Trial Treatment for clinical reasons

A patient may be withdrawn from trial treatment whenever continued participation is no longer in the patient’s best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include:

* Disease progression whilst on therapy
* Unacceptable toxicity
* Treatment delay > 28 days
* Intercurrent illness which prevents further treatment
* Patient choice
* Any alterations in the patient’s condition which justifies the discontinuation of treatment in the site investigator’s opinion
* New cancer treatment or radiotherapy
* Pregnancy

In the randomised phase II trial these patients remain within the trial for the purposes of follow-up and data analysis according to the treatment option to which they have been allocated. In the phase I trial, these patients may be replaced with another patient depending on the reason for discontinuation of trial treatment. Potential replacement of withdrawn patients will be discussed between the UCL CTC and CI or among the wider TMG.

If a patient expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. If the patient gives a reason for their withdrawal, this should be recorded.

Future Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected, with the exception of safety data, and recorded on the relevant CRF. In this event details should be recorded in the patient’s hospital records, no further CRFs must be completed and no further data other than safety data sent to UCL CTC.

Losses to Follow-Up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for follow-up via GP. Details of participating trial sites can be obtained from the UCL CTC trial team who must be informed of the transfer of care and follow up arrangements.

If a patient is lost to follow-up at a site every effort should be made to contact the patient’s GP to obtain information on the patient’s status.

# Trial Closure

## End of Trial

As the trial will no longer proceed to phase II following the business decision by Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) to cease development of ganetespib in this population, the End of Trial will now be defined as 12 months after the last patient visit.

The UCL CTC will advise sites on the procedure for closing the trial at the site.

## Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained for a minimum of 5 years after the end of the trial, in accordance with national legislation and for the maximum period of time permitted by the site.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

## Early discontinuation of trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 12.4.2 TSC and 12.4.3 IDMC). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

## Withdrawal from trial participation by a site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for all patients recruited into the trial at that site and other responsibilities continue as per CTSA.

# Statistical Considerations

## Endpoints

### Phase I trial

Primary outcome measures:

* The number of patients with a dose-limiting toxicity
* The number of cycles of platinum/pemetrexed that patients complete

Secondary outcome measures:

* Toxicities, according to CTCAE grade (version 4); all grades and events will be examined
* Tumour response; the number with a complete or partial response, stable disease, or disease progression

### Randomised phase II trial

Primary outcome measure:

Progression-free survival (PFS); calculated as the time between the date of randomisation and date of first radiological progression or death (from any cause), whichever occurs first. Patients who have not died or progressed will be censored at the date last seen alive (i.e. the last assessment). We will also analyse the data where patients are censored at the last radiological assessment. PFS is an appropriate primary endpoint for phase II trials of mesothelioma (Francart et al 2006).

Secondary outcome measures:

* Time to progression: taken from the time of randomisation to time of objective tumour progression.
* Toxicity: the proportion of patients who have a grade 3 or 4 event, according to CTCAE version 4, for each type of event. The proportion with any grade 3 or 4 event.
* Time to treatment failure: the time of randomisation to time of objective tumour progression, death, stopping ganetespib/chemotherapy, or start of a new anticancer treatment whichever comes first
* Overall survival: taken as the time from randomisation until the time of death (from any cause).
* The number of cycles of platinum/pemetrexed that patients complete, and for those who have less than 6 cycles, the reasons for stopping early
* The objective tumour response according to meso-modified RECIST (Byrne and Nowak 2004), and the overall response rate
* Translational research biomarkers for response, progression and survival, (see section 2.2.3 for more details).

## Sample size (phase II trial)

The median PFS associated with pemetrexed and cisplatin is 5.7 months, from a randomised phase III trial (Vogelzang et al 2003). In the proposed trial, we aim to detect a hazard ratio of 0.65 or lower by adding Ganetespib to pemetrexed and cisplatin, i.e. a median PFS of at least 8.8 months. With 80% power and one-sided test of statistical significance at the 10% level, the sample size in each arm is 55 patients, with 2 years of recruitment and 1 year of follow up after the end of recruitment (using the approach described by Rubinstein et al 2005). **N=110 in total** (which should be associated with at least 96 PFS events). Calculation from “PS Power and Sample Size” software (Dupont & Plummer 1997). Using carboplatin is expected to have a similar effect as cisplatin.

## Safety monitoring during the phase II trial

A severe cumulative toxicity rate (grade ≥3) of more than 33% is judged to be unacceptable. As soon as we see 25 patients with a severe toxicity in either arm (defined above), the lower one-sided 95% confidence interval associated with this is 34% (p-value <0.05), i.e. the true toxicity rate is likely to be greater than the acceptable rate of 33%. This is used to help guide whether the observed rate in the sample of patients is consistent with the unacceptable true rate, and not due to chance. Because there will be a control group, we will also compare the toxicity rates between the two trial arms to confirm whether there is a higher adverse event rate in the Ganetespib arm, and examine the confidence intervals for the differences or relative risks. However, all types and all grades of toxicities will be monitored during the trial regardless of whether the unacceptable cut-off is met or not. An Independent Data Monitoring Committee (IDMC) will review the data regularly, about every 6 months (or more frequent if they choose), and set up extra IDMC meetings when judged to be necessary. The assessment of toxicity by the IDMC would be based on all available data, and they will determine whether the trial should be stopped early based on the whole toxicity profile as well as other relevant information.

The trial will no longer proceed to phase II following the business decision by Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) to cease development of ganetespib in this population.

## Statistical analysis

### Phase I trial

* The maximum tolerated dose (MTD) will be specified, and the number of dose-limiting toxicities (DLTs) and number of chemotherapy cycles administered will be summarised in each ganetespib dose cohort. The Trial Management Group and IDMC will use this information to determine which dose should be used for the phase II trial. If, for example, there are no DLTs in any dose cohort, the ganetespib dose used in a phase II trial could be the one where the highest number of chemotherapy cycles can be delivered.
* The maximum toxicity grade for each type of adverse event will be obtained for each patient, and summarised in a table.
* The number of patients who complete 1 up to 6 cycles of platinum/pemetrexed therapy will be summarised in a table for each dose cohort.
* The best tumour response for each patient will also be summarised in a table, according to complete or partial responders, those with stable disease, those who progress, and those whose disease status is not evaluable.

### Randomised phase II trial

**Efficacy analyses**

* Progression-free survival, overall survival, time-to-progression and time-to-treatment failure, will each be analysed using Kaplan-Meier curves, and the hazard ratios estimated for ganetespib versus chemotherapy (with 95% confidence intervals and p-values). Methods such as the log rank test using Efron's method for ties and Cox regression will be used. The primary hazard ratio for PFS will be estimated without adjustment for any other variables. We will also examine the HR with adjustment for the stratification factors used in the randomisation (i.e. recruiting centre, performance status, and histological subtype). All 110 patients should be enrolled before the final analysis can be performed.
* It is expected that an effect as large as a hazard ratio of 0.65 for PFS might translate to a more moderate but meaningful improvement in overall survival (to be examined in a subsequent phase III trial). At the end of the phase II trial, the one-sided p-value for the observed PFS hazard ratio would be compared against a cut-off of 0.10 to help determine whether a larger trial is justified (this is the cut-off upon which the sample size is based).
* The best tumour response will be compared between the treatment arms using a Fishers exact or chi-squared test. Focus will be on patients who have a complete or partial response.
* An exploratory analysis will be based on obtaining the observed proportion of patients who experience no vomiting and the number of patients who do not require the use of rescue anti-nausea medication. We will also obtain the observed proportion of patients who experience vomiting and use rescue medication for the 120 hours after the platinum and pemetrexed administration.

The trial will no longer proceed to phase II following the business decision by Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) to cease development of ganetespib in this population.

**Interim analyses**

There are no formal planned interim analyses of progression-free survival. However, if accrual is much slower than expected (e.g. <3 patients per month after several centres have been activated for at least 4 months), the trial statistician and IDMC will examine the PFS data for futility after about half the number of expected events have occurred or half the patients have been recruited and followed up for at least 2 months (whichever occurs first). The analysis will include estimation of the conditional probability of detecting a hazard ratio of 0.65 with a p-value of 0.10 using the current data and making the assumption that the trial continues as planned. If the conditional probability is judged to be low (e.g. <15%), then consideration would be given to stopping the trial early.

There will also be an IDMC review of the results after 50% patients have been recruited (and followed for 2 months), to see whether there are biomarkers that strongly predict response/outcomes. If there is such a marker, the IDMC and trial investigators will decide whether only marker positive patients should be recruited for the remainder of the trial, and also whether the sample size needs to increase. If this does occur, a substantial amendment will be submitted.

**Safety analyses**

* For each type of adverse event, the maximum toxicity grade will be obtained for each patient, and summarised in a table. Focus will be on those with a grade 3 or 4 event. Toxicity rates will be compared between the treatment arms using Fisher’s exact test or a chi-squared test, depending on whether the number of observed events is small or not.
* The proportion of patients with any grade 3 or 4 event will also be compared, as above, between the two treatment arms.
* The proportion of patients who complete 6 cycles of platinum/pemetrexed therapy will be compared, using a chi-squared test between the two treatment arms.

# Ethical and Regulatory Approvals

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

* the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
* Human Rights Act 1998
* General Data Protection Regulation (GDPR) 2018
* Data Protection Act 2018
* Freedom of Information Act 2000
* Human Tissue Act 2004
* Medicines Act 1968
* Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
* Good Manufacturing Practice
* the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

## Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled ‘Ethical Principles for Medical Research Involving Human Subjects’ (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial. The trial has received a favourable opinion from the East Midlands Research Ethics Committee. UCL CTC will submit Annual Progress Reports to the REC, which will commence one year from the date of ethical approval for the trial.

## Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA.

## Site Approvals

Evidence of approval from the Trust R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

## Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approval, as appropriate for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments.

## Patient Confidentiality & Data Protection

Patient identifiable data, including initials, date of birth and NHS number will be required for the registration (phase I) /randomisation (phase II) process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the General Data Protection Regulation (GDPR) 2018 and the Data Protection Act 2018 with the Data Protection Officer at UCL.

# Sponsorship and Indemnity

## Sponsor Details

|  |  |
| --- | --- |
| Sponsor Name: | University College London |
| Address: Joint Research Office  Gower Street  London  WC1E 6BT | |
| Sponsor Contact: | Director of Research Support |
| Tel: | 020 3447 9995/2178 (unit admin) |
| Fax: | 020 3447 9937 |

## Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor’s Insurers, via the Sponsor’s office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

# Funding

Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp.) is providing the following for the trial:

* Ganetespib (also provided by Aldeyra Therapeutics, Inc. as the IMP has since been in-licensed)
* supporting the central coordination of the trial through UCL CTC

CR UK has provided endorsement for the trial (ref no. A15183) via the Clinical Trials Award & Advisory Committee (CTAAC).

# Publication Policy

The data resulting from the trial will be published in peer reviewed medical journals. The publications will be authorised by the CI and the TMG. The named authors will include the CI, Trial Coordinator, TMG members, trial statistician and co-investigators. Aldeyra Therapeutics, Inc. and Madrigal Pharmaceuticals Inc. (formerly Synta Pharmaceuticals Corp., USA) will be acknowledged in the publication and will be able to review the draft manuscript prior to publication. The drug companies will be given 30 days to review the data. Sites may not publish trial results prior to first publication by the named authors and need written consent from the TMG and CI to do so.

The ClinicalTrials.gov (or equivalent unique trial I.D.) will be quoted in all publications relating to trial. The data will be owned by the UCL CTC.

# Translational Research

Diagnostic Tissue Samples

Formalin fixed paraffin embedded (FFPE) diagnostic tissue blocks must be forwarded from the local site to the central laboratory for **all** patients, where available and consent has been given, for pharmacogenomic analyses.

Blocks will be requested from the relevant pathology department by the treating clinician, who will also forward a copy of the patient’s consent form to the pathologist in order for the block to be sent to the central laboratory.

**Procedure**

* Cancer trials office will supply the ‘safeboxes’ for specimen transportation to sites when a patient is randomised.
* Send paraffin embedded tissue block. Specimen/s to be labelled with: biopsy reference number and patient trial number.
* Enclose a copy of the pathology report, ensuring that all identifiers are obscured other than biopsy reference number and add the patient trial number.
* These should be placed into plastic slide carrier boxes - which should also be labelled with the patient trial number.
* Container is then to be sealed in a ‘safebox’ and posted to:

MESO-02 TRIAL

C/O Professor Dean Fennell

University of Leicester

The Thoracic oncology Research Group

University of Leicester

Cancer Studies, Hodgkin Building

PO BOX 138

Lancaster Road

Leicester LE1 9HN

Blood Samples

Patients in the cisplatin and carboplatin cohort used to confirm MTD and all patients in the phase II trial, must consent to provide blood samples for the isolation of circulating free tumour DNA for future pharmacogenomics studies. A 15mL sample will be collected at baseline and at the time of progression.

Samples must be processed at each site to isolate plasma, the buffy coat and packed red blood cells. These are to be stored at -80OC. Samples will be shipped to the central lab at the end of the trial.

Please refer to the laboratory manual for further details.

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**Synta studies:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Protocol No. /Phase** | **Study Description** | **Enrolled (Received ganetespib)**  **(n)** | **Dose Levels - Ganetespib** | **Dosing Schedule** | **Study Status** |
|  | | |
| **9090-07**  *Phase 1* | Open-label dose-escalation in solid tumors to determine the PKs of once-weekly dosing with ganetespib plus docetaxel | 27  (27) | 150 mg/m2 + 60 mg/ m2 OR 75 mg/m2 docetaxel  200 mg/m2 + 75 mg/ m2 docetaxel  150 mg/m2 + 75 mg/ m2 docetaxel | Day 1- combo tx  Day 15- ganetespib  2 wks+1 wk rest  Day 1, 4, 15 | Enrollment Completed |
| **9090-08**  *Phase 2B/3* | Randomized, open-label study in Stage IIIb or IV NSCLC | 385  (196) | Arm A (control):  docetaxel 75 mg/m2  Arm B (experimental): ganetespib 150 mg/m2 + docetaxel 75 mg/m2. | 75 mg/m2  Day 1, 3 wk cycle  Ganetespib Days 1 and 15, each 3-wk cycle  Docetaxel Day 1 of each 3-wk cycle | Enrollment Completed |
| **9090-13**  Phase 1 | Thorough QT/ECG study in healthy male volunteers | 50  (48) | 200 mg/m2 | Sequence-randomized single-dose, 3-way crossover of 200 mg/m2 ganetespib vs 400 mg moxifloxacin PO vs vehicle placebo control | CSR final |

Appendix 1: Abbreviations

|  |  |
| --- | --- |
| ABPI | Association of British Pharmaceutical Industry |
| **ADL** | Activities of Daily Living |
| **AE** | Adverse Event |
| **ALP** | Alkaline phosphatase |
| **ALT** | Alanine transaminase |
| **ANC** | Absolute Neutrophil Count |
| **AR** | Adverse Reaction |
| **AST** | Aspartate aminotransferase |
| **ATC** | Anatomical therapeutic chemical classification system |
| **AUC** | Area Under the Curve |
| **CEA** | Carcinoembryonic Antigen |
| **CI** | Chief Investigator |
| **CR** | Complete response |
| **CRF** | Case Report Form |
| **CRUK** | Cancer Research UK |
| **CT** | Computerised Tomography |
| **CTA** | Clinical Trial Authorisation |
| **CTAAC** | Clinical Trials Advisory & Awards Committee |
| **CTCAE** | see NCI CTCAE |
| **CTSA** | Clinical Trial Site Agreement |
| **CXR** | Chest X-Ray |
| **DFS** | Disease Free Survival |
| **DLT** | Dose limiting toxicity |
| **DPA** | Data Protection Act |
| **DSUR** | Development Safety Update Reports |
| **ECG** | Electrocardiogram |
| **ECOG** | Eastern Cooperative Oncology Group |
| **ECMC** | Experimental Cancer Medicine Centre |
| **EDTA** | Ethylene Diamine Tetra Acetate |
| **EPP** | Extrapleural Pneumonectomy |
| **EudraCT** | European Clinical Trials Database |
| **FBC** | Full Blood Count |
| **GDPR** | General Data Protection Regulation 2018 |
| **GFR** | Glomerular Filtration Rate |
| **GLP** | Good laboratory practice |
| **Hb** | Haemoglobin |
| **IB** | Investigator’s Brochure |
| **ICH GCP** | International Conference of Harmonisation-Good Clinical Practice |
| **IDMC** | Independent Data Monitoring Committee |
| **IMP** | Investigational Medicinal Product |
| **INR** | International Normalised Ratio |
| **IV** | Intravenous |
| **LDH** | Lactic Dehydrogenase |
| **LFT** | Liver Function Tests |
| **LLN** | Lower Limit of Normal |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **MPM** | Malignant pleural mesothelioma |
| **MRC** | Medical Research Council |
| **MREC** | Multicentre Research Ethics Committee |
| **MRI** | Magnetic Resonance Image |
| **NCI CTCAE** | National Cancer Institute Common Terminology Criteria for Adverse Events |
| **NCRI** | National Cancer Research Institute |
| **NCRN** | National Cancer Research Network |
| **NRES** | National Research Ethics Service |
| **OS** | Overall Survival |
| **PA** | Posteroanterior |
| **PD** | Progressive Disease |
| **PFS** | Progression Free Survival |
| **PI** | Principal Investigator |
| **PO** | By mouth |
| **PR** | Partial Response |
| **RECIST** | Response Evaluation Criteria in Solid Tumours |
| **SAE** | Serious Adverse Event |
| **SAR** | Serious Adverse Reaction |
| **SD** | Stable Disease |
| **SoDA** | Summary of Drug Arrangements |
| **SOP** | Standard operating procedure |
| **SPC** | Summary of Product Characteristics |
| **SSI** | Site Specific Information |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TMF** | Trial Master File |
| **TMG** | Trial Management Group |
| **TSC** | Trial Steering Committee |
| **UCL CTC** | CR UK and UCL Cancer Trials Centre |
| **U&E** | Urea and Electrolyte |
| **ULN** | Upper Limit of Normal |
| **WBC** | White Blood Cells |

Appendix 2: Schedule of Investigations – Phase I Trial. Each chemotherapy cycle is 21 days (3 weeks)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Assessment** | **Screening**  (assessments within 7 days except CT) | Pre-Cycle = Prior to administration of ganetespib and chemotherapy | | | | | |  | **Maintenance**  **Ganetespib (21 day cycle)** | **Day 21 of last treatment cycle**  (±3 days) | **30 days after Day 21 of the last treatment cycleg**  (±7 days) |
| **Pre - Cycle 1** | **Pre - Cycle 2** | **Pre - Cycle 3** | **Pre - Cycle 4** | **Pre - Cycle 5** | **Pre - Cycle 6** |
| Informed consent | X |  |  |  |  |  |  | Maintenance ganetespib (if appropriate) |  |  |  |
| Medical history and concomitant medication check | X | Xa | Xa | Xa | Xa | Xa | Xa | Xa | Xa | Xa |
| Clinical/physical examination (including height and weight) | X | X | X | X | X | X | X | X | X | X |
| ECOG performance status | X | X | X | X | X | X | X | X | X | X |
| Oncological profileb | X | X  & Day 15b2 | X  & Day 15b2 | X | X | X | X | X | X | X |
| Serum pregnancy test (females only) | X | Xc |  |  |  |  |  |  |  |  |
| Urine analysis | X | X  & Day 15 | X | X | X | X | X | X | X | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X |
| Chest X-rayd |  | X |  | X |  | X |  |  |  |  |
| CT scan – Chest and abdomen (RECIST) e | X |  | X |  | X |  | X  (close to Day 21 of cycle 6) | X e |  |  |
| 12 Lead ECGf | X | Xh | X | X | X | X | X | X |  |  |
| Adverse events check | X | X | X | X | X | X | X | X | X | X |
| Diagnostic tissue sample | X |  |  |  |  |  |  |  |  |  |
| Translational blood samplei | X | Further blood sample to be taken at time of progression | | | | | | | | | |

a = Medical history not required after screening; Concomitant check required from Pre-cycle 1 onwards only

b = Oncological profile - Haematocrit, haemoglobin, RCC, white cell count with differential, platelets, sodium, potassium, urea, creatinine, chloride, bicarbonate, bilirubin, ALP, AST or ALT, LDH, albumin, total protein, calcium, phosphate, magnesium. Bloods may be taken up to 2 days prior to treatment.

b2 = Day 15 of Cycles 1 and 2 the following required: Haematocrit, haemoglobin, RCC, white cell count with differential, platelets

c = Repeat only if baseline test date >1 week prior to 1st dose of ganetespib

d =Chest x-ray - **post** cycles 1, 3 and 5

e = CT scan –screening CT within 28 days of registration. CT scan during treatment to be completed **post** cycles 2, 4, and 6. CT scans ever 6 weeks for the first year (i.e. 12 months from Day 1 of chemotherapy) then 12-weekly thereafter.

f = At screening and Day 1 of each cycle. Repeat ECGs where clinically indicated. While the QTc prolongation is Grade 3 or higher, patients will have ECGs performed in triplicate until the QTc interval returns to baseline or ≤Grade 2. Please also refer to section 7.3.1 on QTc prolongation.

g = After this, patients are managed according to usual local practise

h = ECG also performed approx. 24 hr (±2 hr) after ganetespib administration. If QTc prolonged >500msec, post-infusion ECG should be done at 24 (±2hr) for all subsequent cycles

i = Patients in cisplatin and carboplatin cohort used to confirm MTD only

Appendix 3: Schedule of Investigations – Phase II Trial. Each chemotherapy cycle is 21 days (3 weeks)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Assessment** | **Screening** (assessments within 7 days except CT) | Pre-Cycle = Prior to administration of ganetespib and chemotherapy | | | | | |  | **Maintenance**  **Ganetespib (21 day cycle)** | **Day 21 of last treatment cycle**  (±3 days) | **Follow-up trial assessmentsh**  (±7 days) |
| **Pre - Cycle 1** | **Pre - Cycle 2** | **Pre - Cycle 3** | **Pre - Cycle 4** | **Pre - Cycle 5** | **Pre - Cycle 6** |
| Informed consent | X |  |  |  |  |  |  | Maintenance ganetespib (if appropriate) |  |  |  |
| Medical history and concomitant medication check | X | Xa | Xa | Xa | Xa | Xa | Xa | X | Xa | Xa |
| Clinical/physical examination (including height and weight) | X | X | X | X | X | X | X | X | X | X |
| ECOG performance status | X | X | X | X | X | X | X |  | X | X |
| Oncological profileb | X | X  & Day 15b2 | X  & Day 15b2 | X | X | X | X | X | X |  |
| Serum pregnancy test (females only) | X | Xc |  |  |  |  |  |  |  |  |
| Urine analysis | X | X  & Day 15 | X | X | X | X | X | X | X |  |
| Vital signs | X | X | X | X | X | X | X | X | X | X |
| Chest X-rayd |  | X |  | X |  | X |  |  |  |  |
| CT scan – Chest and abdomen (RECIST) e | X |  | X |  | X |  | X  (close to Day 21 of cycle 6) | X |  | X |
| 12 Lead ECGf | X | X | X | X | X | X | X | X | X |  |
| Adverse events check | X | X | X | X | X | X | X | X | X | X |
| Diagnostic tissue sample | X |  |  |  |  |  |  |  |  |  |
| Translational blood sample | X | 1 further blood sample taken at time of progression | | | | | | | | | |

a = Medical history not required after screening; Concomitant check required from Pre-cycle 1 onwards only

b = Oncological profile - Haematocrit, haemoglobin, RCC, white cell count with differential, platelets, sodium, potassium, urea, creatinine, chloride, bicarbonate, bilirubin, ALP, AST or ALT, LDH, albumin, total protein, calcium, phosphate, magnesium. Bloods may be taken up to 2 days prior to treatment.

b2 = Day 15 of Cycles 1 and 2 the following required: Haematocrit, haemoglobin, RCC, white cell count with differential, platelets

c = Repeat only if baseline test date >1 week prior to 1st dose of ganetespib

d =Chest x-ray - **post** cycles 1, 3 and 5

e = CT scan – screening CT within 28 days of randomisation. CT scan during treatment to be completed **post** cycles 2, 4, and 6. CT scans ever 6 weeks for the first year (i.e. 12 months from Day 1 of chemotherapy) then 12-weekly thereafter.

f = At screening and Day 1 of each cycle. Repeat ECGs where clinically indicated

g = After this, patients are managed according to usual local practise

h = Follow-up visit - starting 6 weeks after ‘Day 21 of the last chemo cycle’, and6 weekly during the first year from Day 1 of chemotherapy Cycle 1. For those who survive to 12 months without progression, follow up would be every 12 weeks thereafter until death or until the trial results are available, whichever is sooner.

Appendix 4: Cockcroft & Gault Formula

**If creatinine measured in µmol/l:**

**Males:** 1.23 x (140 - age) x actual body weight (kg)

serum creatinine (µmol/l)

**Females:** 1.05 x (140 - age) x actual body weight (kg)

serum creatinine (µmol/l)

**If creatinine measured in mg/%**

**Males:** (140 - age) x actual body weight (kg)

72 x serum creatinine

**Females:** (140 - age) x actual body weight (kg) x 0.85

72 x serum creatinine

Appendix 5: Drugs With Risk Of Torsades De Pointes

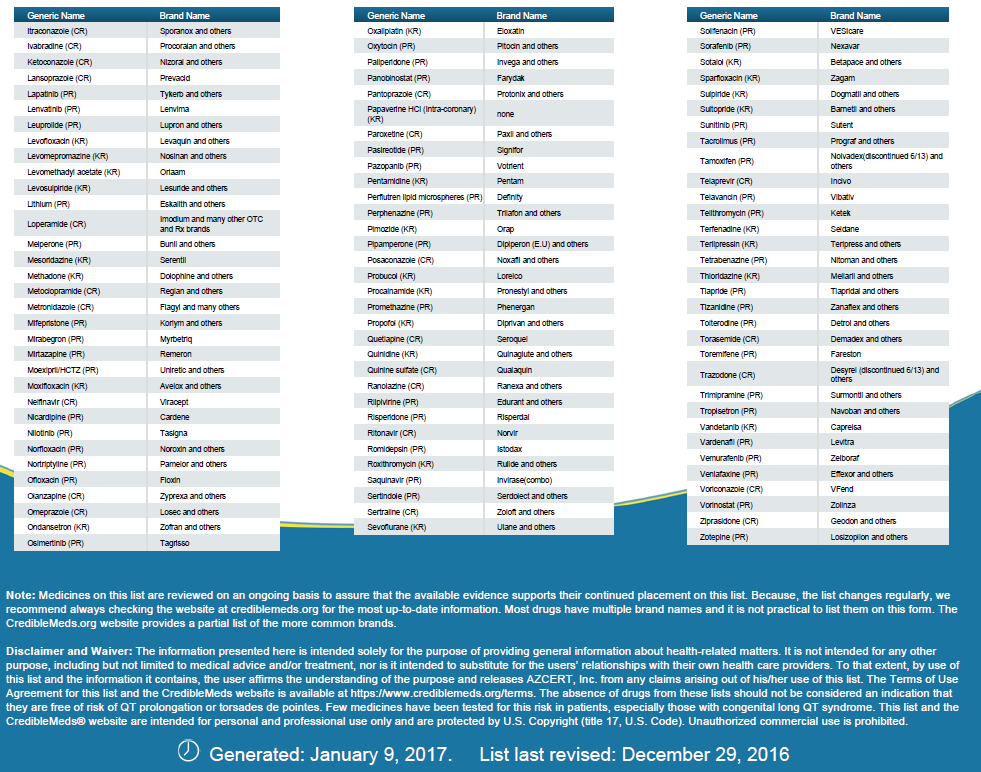
Substantial evidence supports the conclusion that these drugs, when used as directed in labeling, can prolong the QT interval and can have a risk of Torsades de pointes (TdP) in some patients

This list was obtained from the Arizona Center for Education and Research on Therapeutics (AZCERT) website https://www.crediblemeds.org/ (last accessed 09 January 2017). Please refer to the website for the most up-to-date information.



List continued on next page.

Source: www.QTdrugs.org

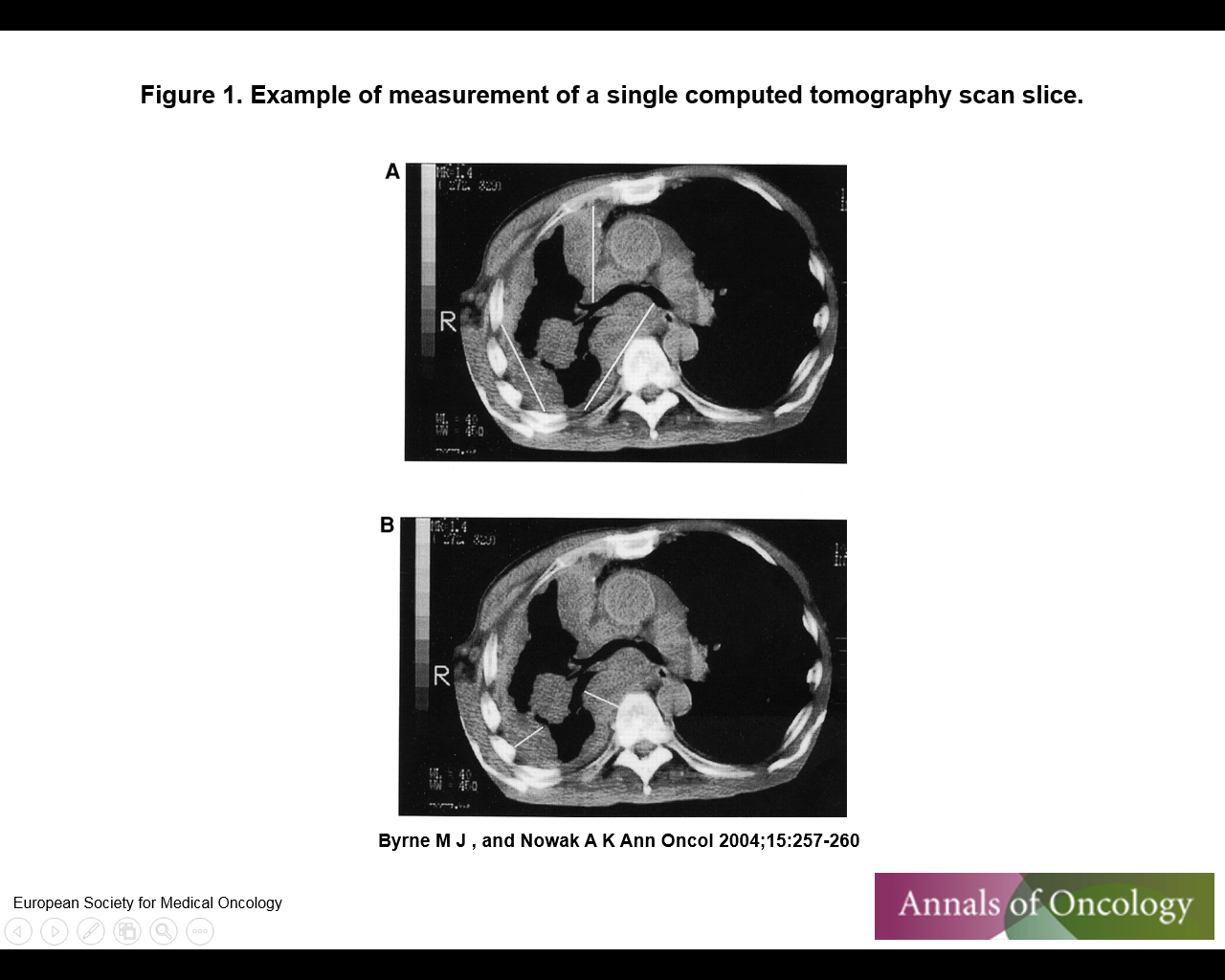
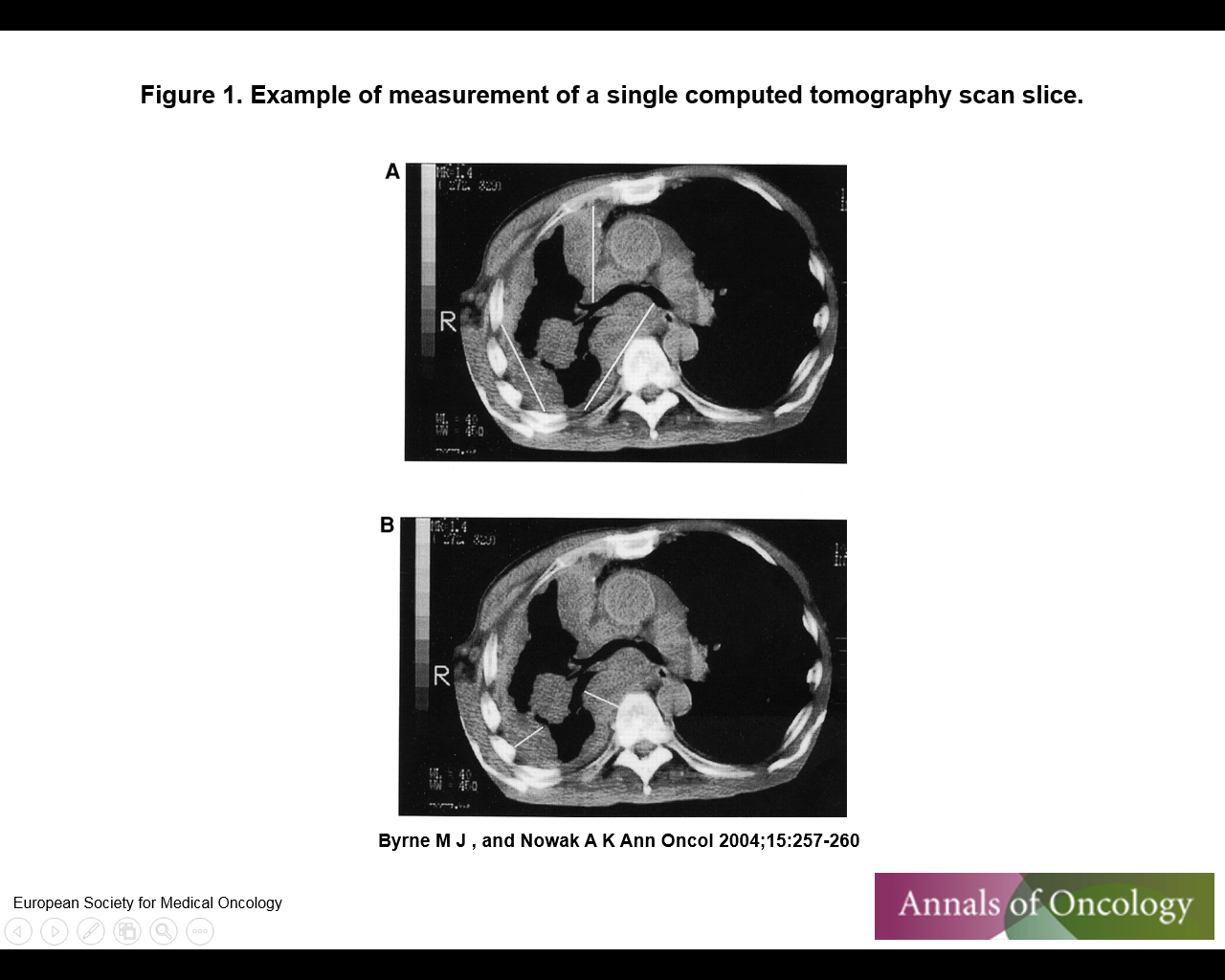


Source: www.QTdrugs.org

Appendix 6 Meso - Modified RECIST criteria

**Pleural uni-dimensional lesions:**

* Tumour thickness measurement should be made perpendicular to the chest wall or mediastinum
* Measurements should be taken at two positions at three separate levels on transverse cuts of the CT scan
* Transverse cuts should be at least 1cm apart and related to anatomical landmarks in the thorax for reproducible assessments at later time points
* If measurable tumour is present, transverse cuts in the upper thorax above the main bronchi is preferred



Lines represent suggested measurement sites perpendicular to fixed structures, chest wall and vertebral column, according to Modified RECIST criteria

**Bi-dimensional lesions**

* To be measured according to RECIST 1.1
* A maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.
* Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm);
* Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan

**Non-measurable**

* Pleural effusions are not considered measurable
* All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions.

The uni- dimensional and bi-dimensional measurements are summated to produce the **total tumour burden.**

**Assessment of tumour response**

Tumour response for modified RECIST criteria is defined as:

|  |  |
| --- | --- |
| **Response** | **Response Parameters** |
| CR | Complete disappearance of all target lesions with no evidence of tumour elsewhere. |
| PR | A ≥30% reduction in the total tumour measurement |
| PD | An increase of at least 20% in the total tumour measurement against the nadir measurement (the smallest sum on the study), plus an absolute increase of at least 5 mm  or    The appearance of one or more new lesions |
| SD | Not meeting the criteria for PR or PD |

Reference:

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Appendix 7: Protocol Version History

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Protocol:** | | **Amendments:** | |  |
| **Version no.** | **Date** | **Amendment no.** | **Summary of main changes from previous version.** | |
| 2.0 | 20-03-2013 | 1.0 | * Section 2.1 (ganetespib) – updated in line with v8.0 of the IB: no. of patients being treated with ganetespib and the number of new studies. Adverse Events has also been updated with new events and the percentages reported has now changed as the sample size increased. * Section 4.1 updated in line with CTC template – sites must assess a patient’s ability to understand verbal explanations and written information in English.  If local interpreters are not available and fully informed consent is not deemed possible, the patient should not be considered for the trial * Section 7.3.1 – updated in line with v8.0 of the IB: (Events of special interest), updated instructions for investigators regarding neutropenia. * Section 7.5 – Ganetespib administration – ‘D5W’ American terminology changed to ‘5% Glucose’ to concentration of solution when making infusion. * Section 7.14.1 – Management of severe or complicated neutropenia – recommendation of GCSF prophylactic use during subsequent treatment cycles in cases of Neutropenia lasting more than 7 days * Section 7.14.2 - Ganetespib pre-medication and management of hypersensitivity reactions – minor edits in line with IB: upon recover patients may also or re-schedule patient for re-treatment * Section 9.0 updated in line with CTC template – data in CRFs should be verifiable by source date * Section 9.1 and 9.4 updated in line CTC template – instruction regarding CRF corrections and update regarding the use of query sheets * Section 10.0 updated in line with CTC template: UCL CTC will consider events evaluated as possibly, probably or definitely related to be adverse reactions * Section 10.0 updated - ‘Exemptions from SAE Report Submission’ updated to include events that occur after 30 days post last trial treatment administration that are not considered to be side-effects of the trial treatment and are not AEs of special interest. * Section 12.2 updated in line with CTC template – Central Monitoring – Data received at UCL CTC will be subject to review in accordance with section 9 | |
| 3.0 | 14-05-2013 | 2.0 | * Updated Front Page with Clinicaltrials.gov number * Section 1.1 updated with Clinicaltrials.gov number * Section 1.1 – Units for Haemoglobin changed from g/dL to g/L in accordance with the new national units * Section 1.2 – Trial Schema – Mosteller formula for calculation of BSA changed to Dubois and Dubois * Section 4.0 – updated in line with new CTC template - Sites must assess a patient’s ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. * Section 5.3 – Patient Eligibility – updated in line with new CTC template - Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). * Section 5.4 - Units for Haemoglobin changed from g/dL to g/L in accordance with the new national units * Section 7.3 – Phase I trial - Mosteller formula for calculation of BSA changed to Dubois and Dubois * Section 7.3.2 – Randomised Phase II trial - Mosteller formula for calculation of BSA changed to Dubois and Dubois * Section 7.5 – Ganetespib - Ganetespib infusion now supplied in 2 different vials sizes; 300mg and 400mg. Container and Storage conditions added for 300mg vial. * Section 7.5 – Administration - The DuBois and DuBois formula is the recommended method to be used for the calculation of BSA. * Section 7.11.1 – Ganetespib dose reductions – ANC values for Haematological Toxicity clarified * Section 7.11.3 – Pem/Cis dose reduction guidelines - The dose modification schedules should be followed as closely as possible but these are recommendations only and clinical judgement should be used in individual cases. * Section 9 – Data Management - Some data will be recorded directly on the CRFs (i.e. no prior written or electronic record of data) and it will be considered to be the source document. * Section 12.1 – On-Site Monitoring – Key areas for assessment during on site monitoring removed altogether and referenced to the trial monitoring plan document. * Section 12.2 – Central Monitoring - Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). * Section 13 – Withdrawals – Discontinuation - Patient withdrawing to further trial treatment changed to Patient Choice. Withdrawal of consent for data collection changed to Future Data Collection - If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected, with the exception of safety data, and recorded on the relevant CRF * Section 16 – Ethical and Regulatory Approvals – updated in line with new CTC template. * Section 16.3 - updated in line with new CTC template - Site Approvals reference to Lead CLRN removed * Section 17.1 – Sponsor Details updated * Section 20 – Translational Research – Address for diagnostic tissue samples updated. | |

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| 3.1 | 07-08-2013 | N/A  **non- substantial** | * Change in Trial Coordinator’s name * 7.3 – clarification loperamide is administered prior to day 1 and 15 ganetespib administration * 7.11 clarification the two dose reductions that can occur before a patient must be withdrawn refers to ganetespib only * 7.14.2 - chlorphenamine added as an alternative to diphenhydramine * 7.15 - correction to the telephone number for drug-specific advice for ganetespib, and alternative numbers added * 8.1, 8.2 & 8.3 – typographical errors amended * Appendix 2 – table corrected to match protocol |
| 4.0 | 19-03-2014 | 3.0 | * Change in title from cisplatin to platinum to reflect option of using carboplatin in phase II * Change in TMG members * Section 1.1 - Summary of trial design updated to reflect changes in main protocol * Sections 1.2, 2.2, 7.3 - details added to include additional patients to be registered to receive ganetespib, pemetrexed and carboplatin in the phase I. This group will be recruited concurrently with the group of patients used to confirm the MTD. * Section 1.2.3, 2.2.2, 7.3.2. - updated to reflect the option of using carboplatin in the phase II * Section 2.1 – Clinical experience and Adverse Events updated in line with new version of IB for ganetespib * Sections 2.2.3, 8.1, 8.3, 8.4, 20 and Appendix 2 – update to schedule of blood sample collection for translational research * Section 5.5 – Patient Exclusion criteria updated in line with version 9.0 of IB for ganetespib * Section 6.3 – updated to include carboplatin (to be supplied from hospital stock) * Section 7.1 – update to include carboplatin as IMP * Section 7.3.1 – updated to clarify definition of DLTs * Section 7.3.1 – updated to clarify accelerated titrated phase I design * Section 7.3.1, 7.15.1, 7.15.2, 7.15.3 – Management of events of special interest updated in line with version 9.0 of IB for ganetespib * Section 7.5 – ganetespib storage conditions updated in line with version 9.0 of IB for ganetespib * Section 7.8 – new section to add dosing details for carboplatin * Section 7.12.1 – dose modifications for ganetespib updated in line with version 9.0 of IB * Section 7.12.3.7 – new section added for dose modifications for carboplatin * Section 7.13.2 drug interaction section updated for ganetespib in line with version 9.0 of IB * Section 7.13.5 - new section added for drug interactions for carboplatin * Section 7.14, 7.14.1 – Medications used with caution updated in line with version 9.0 of IB for ganetespib * Section 8.2, Appendices 2 and 3 – Schedule of ECG and dose modifications in the event of QTc prolongation updated in line with version 9.0 of IB for ganetespib * Section 15 – Statistical considerations updated to reflect the option of using carboplatin in phase II * Section 21 – references updated to include Synta studies * Appendix 5 – new appendix listing drugs with a risk of Torsades de Pointes |
| 5.0 | 30-09-2015 | 5.0 | * Change to Trial Coordinator * Update to exclusion criteria to reflect new safety data * Section 2.1 - Background clinical information and adverse effects for ganetespib have been updated to reflect new data. * Section 2.2.3 – Changes to translational blood sample evaluation and use of results affecting future sample analysis. * Section 7.3 – clarification – DLT assessments for the carboplatin arm will be made after 1 cycle * Section 7.3.1 – Update and additional information for ocular, liver and gastrointestinal perforation toxicities * Section 7.7 – Symptom review for cisplatin added prior to treatment * Section 7.12.3.7 – Information on use of local guidelines for dose reduction of carboplatin * Section 7.13.1 – Instructions on availability of equipment for anaphylaxis * Section 7.15.1 – New information for prophylactic use of Loperamide * Section 7.15.4 – addition of information for premedication regimen * Section 8.2 – change to required ANC value at Day 1 assessment and additional information explaining requirement to take Day 15 bloods. * Section 10.1 – Updated to reflect use of RSI in defining SUSARs * Section 15.4.2 – Additional information relating to interim analysis and timing of IDMC. * Appendix 5 – information relating to Torsades de pointes updated to reflect new data since last update * Appendix 6 – Additional appendix added to protocol outlining meso-modified criteria and what is required when reporting trial CT scans. |
| 6.0 | 09Jan2017 | 6.0 | * Change in trial statistician * Change in trial oversight * Change in trial coordinator * Change in drug company name from Synta Pharmaceuticals Corp to Madrigal Pharmaceuticals Inc. following reverse merger * Decision by not to proceed with continuing the phase II of the trial included in relevant sections of protocol as follows: 1.1 Summary of trial design; 1.2. Trial Schema; 2.2 Trial Design; 6.2 Randomisation to the phase II trial; 15.3 Safety Monitoring during the phase II trial; and 15.4.2 Randomised phase II trial * Section 2.1 – number of patients exposed to ganetespib updated in line with IB version 11, 13Nov2015 * Section 7.16 Out-of-hours drug advice contact numbers for ganetespib updated * Section 7.3 – loperamide guidance in line with IB v11 – to allow treatment to continue for up to 24 hours * Section 7.3 and 7.12.1 – Dose modifications and frequency of ECG recordings relating to QTc prolongation updated in line with IB v11 * Appendix 2 – Scheduling of CT assessments reworded to reflect that outlined in section 8.2 * Appendix 2 – Additional wording regarding the frequency of ECG assessments in case of QTc prolongation * Appendix 5 – updated in line with IB v11 |
| 7.0 | 26Oct2018 | 7.0 | * Section 7.5 Drug company information updated to reflect change in IMP sourcing information for gantespib * Sections 8.1, 8.2 and 8.4 – additional information regarding the sharing of pseudo-anonymised CT scan images for selected trial participants * Section 9.2 – new section on Imaging * Section 16 – updated in line with General Data Protection Regulation (GDPR) 2018 and Data Protection Legislation 2018 * Sections 1.1 and 14.1 - End of trial definition updated * New reference added for modified RECIST 1.1 |