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Phase I open-label trial of intraperitoneal paclitaxel in combination with intravenous cisplatin and oral capecitabine in patients with advanced gastric cancer and peritoneal metastases (IPGP study): study protocol

Sina Vatandoust,[1,2] Tim Bright,[1,2] Amitesh Chandra Roy,[1,2] David Watson,[1,2] Susan Gan,[1,2] Jeff Bull,[1] Muhammad Nazim Abbas,[1] Christos Stelios Karapetis[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Sina Vatandoust;
sina.vatandoust@sa.gov.au

ABSTRACT

Introduction Gastric cancer with peritoneal metastasis has a poor outcome. Only a few studies have specifically investigated this group of patients. Japanese researchers have shown that chemotherapy with intraperitoneal paclitaxel (IPP) and oral S-1 (tegafur/gimeracil/oteracil) is active and well tolerated. These results have been achieved in a specific genetic pool (Japanese population), using regimens that may not be available in other parts of the world. We have designed this phase I trial to investigate IPP in combination with a standard chemotherapy combination in these patients.

Methods We use a 3+3 expanded cohort dose escalation until a predefined number of dose-limiting toxicities are reached. Patients will have an intraperitoneal catheter placed surgically after trial enrolment. Chemotherapy includes a maximum of six cycles (21 days) of capecitabine (X) (1000 mg/m^2 two times a day, days 1–14)+cisplatin (C) (intravenous 80 mg/m^2 day 1) and IPP (days 1 and 8) with the following doses: cohort-1: 10 mg/m^2, cohort-2: 20 mg/m^2 and cohort-3: 30 mg/m^2. Primary endpoint is to determine the maximum tolerated dose of IPP. Secondary endpoints include determining the safety and tolerability of IPP in combination with C and X, overall response rates, ascites response rate, progression-free survival, overall survival and effects on quality of life. Important inclusion criteria include age ≥18 years, human epidermal growth factor receptor 2 non-amplified gastric adenocarcinoma with histological or cytology-proven peritoneal involvement and adequate organ function. Exclusion criteria include previous malignancy within 5 years, recent abdominal or pelvic radiation treatment, significant abdominal adhesions or sepsis.

Ethics and dissemination The study is approved by Southern Adelaide Clinical Human Research Ethics Committee. A manuscript will be prepared for publication on the completion of the trial. This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), and the NHMRC Australian Code for the Responsible Conduct of Research (©Australian Government 2007), and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008.

Trial registration number ACTRN12614001063606.

Strengths and limitations of the study

- Currently, there are limited data to guide treatment in patients with gastric cancer and peritoneal metastases.
- This study investigates a novel treatment: intraperitoneal paclitaxel in combination with standard chemotherapy (capecitabine and cisplatin).
- Based on the results of this study, future studies will be designed to investigate the efficacy of this approach and to improve the outcomes in this population.
- Not investigating the pharmacokinetics of intraperitoneal paclitaxel is a potential limitation of our study.

INTRODUCTION

Gastric cancer

Gastric cancer is among the most common cancers and the second most frequent cause of cancer death worldwide.[1] While responses can be achieved with chemotherapy, the cancer often develops resistance within 6 months. The median survival for the combination chemotherapy regimens including cisplatin and the fluoropyrimidine, capecitabine—which is considered one of the standard systemic chemotherapy regimens for advanced gastric cancer—is 10.5 months.[2]

Table 1 Combination chemotherapy regimens using paclitaxel in advanced gastric cancer

Regimen (reference)	RR	PFS (months)	OS (months)
Paclitaxel+platinum[21–27]	22%–46%	2.9–6	7.5–13.8
Paclitaxel+fluoropyrimidine[28–32]	32%–66%	3–9	9.9–14
Paclitaxel+fluoropyrimidine + platinum[33–36]	51%–66%	4–9	6–14

OS, median overall survival; PFS, progression-free survival; RR, response rate.

Peritoneal involvement in gastric cancer

Advanced gastric cancer can spread via the transcoelomic route to involve the peritoneum and ascites often develops as a consequence. There have been few studies looking specifically at this group of patients with malignant ascites or peritoneal disease. Due to lack of measurable disease, some of these patients are ineligible for clinical trials. The few studies that have looked at this subgroup of patients have shown poor survival. Some of the regimens studied in this group of patients include modified fluorouracil, leucovorin and oxaliplatin leading to 1-year survival of 27.2%,[3] and sequential methotrexate/ fluorouracil (5FU) leading to 1-year survival of 16%.[4]

Paclitaxel in advance gastric cancer

In advanced gastric cancer, including cases with malignant ascites, paclitaxel has shown good response rates.[5] The response rate to paclitaxel monotherapy has been reported to be 17%–28%.[6–9] Combination chemotherapy regimens using paclitaxel have also been studied in a number of phase II studies (table 1).

Intraperitoneal paclitaxel

In ovarian cancer, a phase III randomised trial showed survival advantage for intravenous paclitaxel plus intraperitoneal (IP) cisplatin and paclitaxel over intravenous paclitaxel plus cisplatin.[10] Paclitaxel has been shown to have distinct pharmacokinetic advantages when given via an IP route. These include high IP concentration of the drug, as well as a longer half-life in the peritoneal cavity, compared with that observed with intravenous administration.[11] This makes IP paclitaxel a compelling option for use in patients with peritoneal involvement from advanced gastric cancer.

Studies in Japan have reported that IP paclitaxel is well tolerated and active in patients with gastric cancer and peritoneal involvement.[12] In a series of 100 patients, the median survival was 23 months, and the 12-month survival was 80%.[13] The chemotherapy regimen used consisted of weekly intravenous paclitaxel at 50 mg/m^2, IP paclitaxel at 20 mg/m^2 and oral S1 (tegafur/gimeracil/oteracil) given on a 14-day regimen of 80 mg/m^2 per day repeated every 3 weeks. It is of note that S1 may not be available for this indication in other parts of the world.

Rational for phase I study

The mentioned results have been achieved in a different genetic pool (Japanese population) using regimens that are not available in other parts of the world. We have designed this phase I trial to investigate the maximum tolerated dose (MTD) of IP paclitaxel in combination with one of the standard chemotherapy combinations (cisplatin and capecitabine) in this patient population.

Justification of IP paclitaxel dose and escalation schedule

The MTD and recommended dose available from previous phase I study by Ishigami *et al*[12] is certainly informative but because we are suggesting the use of IP paclitaxel in a new combination and in a different genetic pool, these doses may not be accurate. Therefore, we have elected to start the IP paclitaxel from 10 mg/m^2 which is one dose level lower than recommended dose by Ishigami *et al*. In our study, regardless of the IP paclitaxel, patients receive a standard regimen for their disease; therefore, despite the low starting dose of IP paclitaxel, undertreatment is not a concern. The next dose levels are to be increased in 10 mg/m^2 increments to 30 mg/m^2, unless the MTD is achieved.

RECENTLY PUBLISHED STUDIES

In a randomised phase III trial, Ishigami *et al*[14] enrolled patients with gastric cancer with peritoneal metastasis. Patients were randomised to receive IP and intravenous paclitaxel plus S-1 or S-1 plus cisplatin. In this study, median survival was not significantly different between the two arms.

Yonemura *et al*[15] showed that neoadjuvant laparoscopic hyperthermic IP chemoperfusion with docetaxel and cisplatin and neoadjuvant IP/systemic chemotherapy with S-1, docetaxel and cisplatin can lead to reduced Peritoneal Cancer Index in patients with gastric cancer with peritoneal metastasis.

METHODS

Aim and objectives

Primary objective

1. To determine the MTD of IP paclitaxel in patients with advanced gastric cancer and peritoneal involvement

Secondary objectives

To determine:

2. Rates of toxicities (based on Common Terminology Criteria for Adverse Events [CTCAE V.4.0]).[16]
3. Rates of IP catheter complications.
4. 12-month survival.
5. Median survival.

6. Progression-free survival (PFS) (based on Response Evaluation Criteria in Solid Tumours [RECIST] V.1.1 criteria).[17]
7. Objective response rate (complete response rate+partial response rate [based on RECIST 1.1 criteria]).
8. Ascites response (based on imaging).
9. Effects of treatment on quality of life (based on average scores for aspects of HRQL during treatment as assessed by the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) [V.4]).[18]
10. Quality of life (based on average scores as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach [EORTC STO22]).[19]
11. Tissue banking for biomarker analysis.

DESIGN

Open-label, single-centre, phase I trial with standard 3+3 dose escalation design.

SUBJECT POPULATION

Target population

Subjects with stage IV gastric cancer with biopsy-proven or cytology-proven peritoneal involvement.

Inclusion criteria

1. Age≥18 years.
2. A diagnosis of gastric cancer proven by histopathology and either:
   - Biopsy-proven peritoneal metastases or
   - Cytology consistent with malignant ascites: in which case patient must have ≥1 area of peritoneal metastasis apart from the ascites.
3. Subject must not have received previous chemotherapy for metastatic gastric cancer.
   - Previous adjuvant chemotherapy for gastric cancer is allowed.
4. Adequate bone marrow function (platelets>100×10^9/L, absolute neutrophil count >1.5×10^9/L)
5. Adequate liver function (serum bilirubin ≤1.5 upper limit normal and transaminases≤3 ULN).
6. Adequate renal function (serum creatinine ≤1.5 upper normal limit or creatinine clearance ≥50 mL/min (using Cockcroft-Gault equation).
7. Negative pregnancy test for female patients if of potential childbearing age.
8. Eastern Cooperative Oncology Group Performance Score 0, 1 or 2.
9. Staging CT scan of chest/abdomen/pelvis within 30 days of registration.
10. Study treatment both planned and able to start within 30 days of registration.
11. Willing and able to comply with all study requirements, including treatment (able to swallow tablets), and required assessments.
12. Signed, written informed consent.

Exclusion criteria

1. Contraindications to investigational chemotherapy regimen including allergies to any of the chemotherapy medications.
2. Any comorbidities or conditions that the investigator considers the patient should not participate in the study.
3. Life expectancy of less than 3 months.
4. History of another malignancy within 5 years prior to registration. Patients with a history of adequately treated cervical carcinoma-in-situ, basal cell carcinoma of the skin, squamous cell carcinoma of the skin or superficial transitional cell carcinoma of the bladder are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 5 years after definitive primary treatment.
5. Significant intercurrent illness that will interfere with the chemotherapy during the trial such as:
   a. Known HIV infection.
   b. Active infection.
   c. Myocardial infarction within the previous 6 months or significant cardiac disease resulting in an inability to tolerate the intravenous fluid load as required for the administration of cisplatin.
   d. Severe lung disease which in the investigator's opinion would limit the patient's ability to tolerate large volumes of intra-abdominal fluids.
6. Peripheral neuropathy of any grade (based on CTCAE V.4.0).
7. Clinically significant sensorineural hearing impairment or tinnitus which may be exacerbated by cisplatin (audiometric abnormalities without corresponding clinical deafness will not be grounds for exclusion).
8. Previous abdominal or pelvic radiation treatment.
   a. Recent (<4 weeks) abdominal or pelvic radiation treatment; patients who have received palliative radiation to gastric/oesophageal area are not excluded if total radiation received is less than 30 Gy and radiation is completed more than 4 weeks prior to commencing study treatments.
9. Significant intra-abdominal adhesions as determined by the surgeon at time of staging laparoscopy.
10. Active intra-abdominal sepsis.
11. Medical or psychiatric condition that compromises the ability of patients to give informed consent.
12. Pregnancy, lactation or inadequate contraception. Women must be postmenopausal, infertile or use a reliable means of contraception. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to registration. Men must have been surgically sterilised or use a barrier method of contraception during treatment and for the subsequent 3 months after treatment.

Screening

Written informed consent (online supplementary file 1) must be signed and dated by the subject, and signed and dated by the investigator, prior to any study-specific screening investigations being performed.

Entry to this study is conditional on confirmation of tumour peritoneal involvement through either biopsy or cytology. Patients must have a staging CT scan of chest/abdomen/pelvis within 30 days of registration.

Registration

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. There will be no exceptions made to these eligibility requirements at the time of registration. Subjects must be registered before starting study treatment. Treatment should be planned to start within 28 days after registration. Registration should be done after all screening assessments have been performed and the responsible investigator has both verified the subject's eligibility, and signed the completed registration form. Once the registration process has been completed, the subject will be assigned a subject study number.

TREATMENT PLAN

IP paclitaxel is the study intervention in this trial; intravenous cisplatin and oral capecitabine are required standard concomitant interventions.

Administration of study treatments

IP catheter

IP catheter insertion

Patients will have an IP catheter placed surgically after trial enrolment. The IP catheter is placed surgically, under general anaesthesia. The port should be secured to the anterior abdominal wall or the costal margin to enable easy access. The catheter should be tunnelled through the rectus sheath and muscle and secured to minimise the risk of an ascitic leak.

Possible adverse effects of IP catheter

- Infection.
- Abdominal pain.
- Development of intra-abdominal adhesions.
- Risk of organ perforation.
- IP catheter blockage: in the event that the catheter is blocked and is not opened with conservative management including flushing with normal saline or simple manoeuvring, then this will be considered a rate-limiting toxicity and the catheter will be removed.

Endoscopic biopsy

Before the surgery for IP catheter insertion, four endoscopic biopsies of the primary gastric tumour should be taken as well as biopsies of the peritoneal disease. These biopsy specimens are to be stored as fresh tissue in RNAlater in separate containers for any and all later molecular analyses.

Chemotherapy

Paclitaxel

Preparation for IP administration: paclitaxel, at the appropriate dose, will be diluted in 250–500 mL of 0.9% sodium chloride injection or 5% dextrose injection.

Stability: the infusion should be completed within 24 hours of preparation of the solution and any residue discarded. Diluted solutions should be refrigerated if not used immediately to decrease the likelihood of microbial contamination.

Cisplatin

Preparation: the 10 mg and 50 mg vials should be reconstituted with 10 mL or 50 mL of sterile water for injection, The United States Pharmacopoeia (USP), respectively. Each mL of the resulting solution will contain 1 mg of cisplatin. Cisplatin should be diluted in 1 L of normal saline.

Stability: infusion should be completed within 24 hours of preparation and any residue discarded.

Capecitabine

Preparation: a combination of the 500 mg and 150 mg tablets will be administered to reach the desired dose of 1000 mg/m^2.

Chemotherapy regimen and doses

Each cycle will be 21 days and includes the following combination:

- *Capecitabine* (oral) 1000 mg/m^2 two times a day, days 1– 14 every 21 days.
- *Cisplatin* at 80 mg/m^2 day (intravenous), day 2 every 21 days.
- *Paclitaxel* will be given on day 1 and day 8 of a 21 day cycle. The dose of paclitaxel will vary depending on the cohort as follows (table 2).

Table 2 Dosing of intraperitoneal paclitaxel based on 3+3 design

Cohort	No of patients	Paclitaxel dose given on day 1 and day 8 of a 21 day cycle
1	3	10 mg/m^2
2	3	20 mg/m^2
3	6	30 mg/m^2

If no dose-limiting toxicity is seen after three patients have completed treatment in *cohort 3*, this cohort will be expanded to six patients if maximum tolerated does has not been reached. There will be no further dose escalation after *cohort 3*.
If no dose-limiting toxicity is seen after three patients have completed treatment in *cohort 1*, patients will commence enrolment into *cohort 2*.
If no dose-limiting toxicity is seen after three patients have completed treatment in cohort 2, patients will commence enrolment into *cohort 3*.

Dose modifications

Dose modifications for cisplatin and capecitabine will be based on Eviq guidelines (https://www.eviq.org.au) (online supplementary file 2). Adverse events (AEs) are graded according to CTCAE V.4.0. In general, treatment should be withheld during AEs of severity G3-4, and not restarted until the AE has resolved to G0-1, at the investigator's discretion. Day 1 treatment may be delayed for a maximum of 14 days. If the AE has not resolved to G0-1 after delaying day 1 treatment for 14 days, then study treatment should be discontinued. Treatment should not be delayed or modified for alopecia of any grade.

Specified dose reductions apply to all subsequent doses of study drug. If a patient experiences several adverse events (SAEs) with differing recommendations, then the modification that results in the longest delay and lowest dose should be used.

Dose escalations or dose re-escalations after reductions for AEs are prohibited.

Rechallenge

If patients experience a suspected drug-related AE, they can interrupt the study medication until the symptoms resolve and then can reintroduce the study medication at the same dose. If the reaction reappears, then the study medication is to be discontinued permanently.

Concomitant medications/treatments

Include medications and treatments recommended, permitted (including rescue medication) and prohibited before and/or during the trial.

Recommended

The following medications and treatments are *recommended* in this study (table 3):

Table 3 Recommended medication before chemotherapy

Each cycle:		
Day 1		
Aprepitant	165 mg (PO)	60 min before chemotherapy
Palonosetron	0.25 mg (intravenous bolus)	30 min before chemotherapy
Fexofenadine	120 mg (PO)	60 min before treatment
Ranitidine	150 mg (PO)	The night before and the morning of chemotherapy
Dexamethasone	12 mg (PO)	Once a day with or after food
Days 2, 3		
Dexamethasone	8 mg (PO)	Once a day with or after food
Day 8		
Fexofenadine	120 mg (PO)	60 min before treatment
Ranitidine	150 mg (PO)	The night before and the morning of chemotherapy
Dexamethasone	20 mg (PO)	The night before and the morning of chemotherapy

PO, per os.

Permitted

Antidiarrhoeal and analgesics are *permitted* in this study:

Prohibited

The following medications should not be used during this study. Subjects who require treatment with any of these agents will usually need to discontinue study treatment, and should be discussed with the study chair:

- Radiation to abdomen/pelvis.
- Operations/procedures involving abdomen/pelvis.
- Other investigational treatments.

Concomitant medication reporting

Concomitant medications will not be recorded during the study.

Treatment discontinuation

Study treatment will be permanently discontinued for any of the following reasons:

- Progressive disease is documented by a site investigator.
- Unacceptable toxicity as determined by the patient or site investigator.
- Delay of day 1 treatment for >21 days due to treatment-related AEs. For delays>21 days due to reasons other than treatment-related AEs, contact the study chair to discuss treatment continuation.
- The investigator determines that the continuation of treatment is not in the patient's best interest.
- Occurrence of an exclusion criterion affecting patient safety, for example, pregnancy or psychiatric illness.
- Required use of a concomitant treatment that is not permitted, as defined in *Exclusion criteria*.
- Failure to comply with the protocol.
- The patient declines further study treatment, or withdraws their consent to participate in the study.

The reasons for discontinuing treatment will be documented in the subject's medical record.

Follow-up of subjects who stop study treatment should continue. All end-of-treatment assessments must be performed within 30 days after the end of study treatment. A safety assessment should be performed to include any AEs occurring within 30 days after the last dose of study treatment.

Subsequent treatment

Treatment after the discontinuation of study treatment is at the discretion of the patient's clinician.

Table 4 Schedule of assessments

	Screening	Run in	Baseline	On treatment	After third cycle	End of treatment and 30-day safety assessment	Follow-up after treatment	End of study
	14–28 days prior to registration	Within 14 days prior to registration	Within 7 days prior to registration	Within 3 days prior to: day 1 and day 8 of every cycle	Within 7 days after end of day 8 of third cycle	Within 30 days after end of treatment	Every 12 weeks after end of treatment	2 years after registration
Informed consent	X							
Clinic assessment	X		X	X		X	X	X
Haematology	X		X	X				
Biochemistry	X		X	X				
Imaging CT	X				X	X	X	
Adverse events				X				
Endoscopy and biopsy		X						
IP catheter insertion		X						
Patient status			X	X		X	X	X
Quality of life assessments			X		X	X	X	X

ASSESSMENT PLAN

Schedule of assessments

Schedule of assessments is outlined in Table 4.

OUTCOMES, ENDPOINTS AND OTHER MEASURES

Maximum tolerated dose

- MTD is defined as the highest dose level at which ≤33% of patients experience dose-limiting toxicity (DLT)[20]
- DLTs are defined as
  - Grade 3 or higher febrile neutropenia.
  - Grade 3 or higher thrombocytopenia with bleeding.
  - Grade 3 or higher neurological toxicity (excluding ototoxicity [hearing deficit and tinnitus]).
  - Grade 3 or higher non-haematological toxicities (not including fatigue, alopecia, nausea, vomiting, elevated liver transaminases, palmar plantar erythrodysesthesia and other capecitabine-related skin toxicity, hearing deficit and tinnitus).
  - Grade 4 neutropenia lasting >7 days.
  - Grade 4 thrombocytopenia.
  - Grade 4 increased liver transaminases.
- Recommended phase 2 dose defined as: dose equal to the MTD (as defined above), or cohort 3 if the MTD is not reached.

Adverse events (worst grade according to National Cancer Institute CTCAE V.4.0)

- Rate of toxicities based on CTCAE V.4.0 and the rate of catheter complications. See *Safety Reporting* for the definition of an AE, and reporting of SAEs.
- The National Cancer Institute CTCAE V.4.0 will be used to classify and grade the intensity of AEs after each treatment cycle.
- The investigator's assessment of attribution to the study drug: IP paclitaxel.

Overall response rate

Defined as complete response rate plus partial response rate (both defined according to RECIST 1.1).

Progression-free survival (disease progression or death)

PFS is defined as the interval from the date of registration to the date of first evidence of disease progression or death, whichever occurs first. Disease progression is defined according to RECIST 1.1

Overall survival (death from any cause)

Overall survival is defined as the interval from the date of registration to date of death from any cause, or the date of last known follow-up alive.

Effects of treatment on quality of life

Based on average scores for aspects of HRQL during treatment as assessed by the FACT-Ga (V.4) and EORTC STO22.

SAFETY REPORTING

Definitions

An AE is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. AEs include the following:

- All suspected adverse drug or device reactions.
- All reactions from drug or device.

- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses.
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).

Any untoward event that occurs after the protocol-specified reporting period which the investigator believes may be related to the drug or device. AEs must be reported as AEs even if they do not meet SAE criteria.

An SAE is any untoward medical occurrence that at any dose:

- results in death.
- is life threatening (ie, the subject is at risk of death at the time of the event).
- requires inpatient hospitalisation or prolongation of existing hospitalisation.
- results in persistent or significant disability or incapacity.
- is a congenital anomaly/birth defect.
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol.

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is related to the drug or device and is unexpected (ie, not listed in the investigator brochure or approved product information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the subject information sheet and informed consent form or elsewhere in the protocol.

Reporting of SAEs (including SUSARs)

The investigator is responsible for reporting all SAEs (including SUSARs) occurring during the study to the principal investigators (through FMC Medical Oncology Clinical Trials Unit) within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention.

The principal investigators must notify the local Human Research Ethics Committees as required.

Pregnancy

In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. Pregnancies occurring up to 6 months after the completion of the study drug must also be reported to the investigator. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Pregnancy occurring in the partner of a patient participating in the study and up to 90 days after the completion of the test drug should also be reported to the principal investigators. The partner should be counselled and followed as described above.

STATISTICAL CONSIDERATIONS

This is an open-label phase 1 study with a standard 3+3 dose escalation design, therefore does not require sample size justification. The dose escalation is continued until the predefined number of DLT is reached.

ADMINISTRATIVE ASPECTS

Recruitment of participants

Patients attending oncology clinics within the Southern Adelaide Health Services that are potential candidates for the study will be given a patient information sheet by a member of the research team inviting them to participate in the study. Subjects willing to participate will meet with a study investigator to sign a consent form.

Consent

Involved clinicians will initially approach eligible patients to determine their interest in the study. Potential study subjects will be given a study patient information sheet. The purpose, requirements and risks of the study will be explained in a clear manner. Before witnessing the consent form, the investigator will discuss the study with the potential study subject to ensure that they fully understand the study risks, procedures and requirements.

Confidentiality

The study will be conducted in accordance with applicable privacy acts and regulations. All data generated in this study will remain confidential. All information will be stored securely at the clinical trials unit and will only be available to people directly involved with the study and who have signed a confidentiality agreement.

Protocol amendments

Changes and amendments to the protocol can only be made by the principal investigators. Approval of amendments by the Institutional Human Research Ethics Committee (HREC) is required prior to their implementation.

Data handling and record keeping

All trial data required for the monitoring and analysis of the study will be recorded on the case report forms (CRF). All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated. All study-related documentation will be maintained for 15 years following completion of the study.

Study monitoring

Data from this study will be monitored by FMC Medical Oncology Clinical Trials Unit. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness.

Audit and inspection

This study may be subject to audit or inspection by representatives of regulatory bodies.

Publication policy

The principal investigators will appoint a writing committee to draft manuscript(s) based on the trial data. Manuscript(s) will be submitted to peer-reviewed journal(s). All publications must receive prior written approval from the principal investigators prior to submission.

Author affiliations
[1]Medical Oncology, Flinders Medical Centre, Bedford Park, South Australia, Australia
[2]School of Medicine, Flinders University, Adelaide, South Australia, Australia

Contributors SV, TB, ACR, DW, JB and CSK were involved in study conception, design, planning, and conduct of the study and manuscript writing. SG was involved in writing the manuscript. MNA was involved in the conduct of the study and writing manuscript. All authors were involved in the final approval of the manuscript. All authors agreed to be accountable for all aspects of the work.

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