A Phase I, Open label Study to Assess the Safety and Tolerability of KU-0059436 in Combination with Carboplatin and of KU-0059436 in Combination with a Paclitaxel/Carboplatin (TC) doublet and KU-0059436 in combination with Paclitaxel in the Treatment of Patients with Advanced Solid Tumours

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Primary objective· • To investigate the safety and tolerability and establish either the dose of KU-0059436 which causes inhibition of PARP in combination with an active dose of carboplatin or the maximum tolerated dose (MTD) of KU-0059436 in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON46952

Source
ToetsingOnline

Brief title
Safety,Tolerability of KU-0059436,Carboplatin - Paclitaxel in Solid tumours

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
matastatic disease, solid tumours

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: de sponsor: AstraZeneca

Intervention

Keyword: Phase I, Poly ADP-ribose polymerase inhibitor, Safety and tolerability, Solid tumours

Outcome measures

Primary outcome

Safety data, including laboratory parameters and adverse events, will be collected for all patients in order to determine the toxicity, reversibility of toxicity, and dose limiting toxicity of orally administered KU-0059436 when given in combination with i.v. carboplatin, in combination with i.v. paclitaxel and carboplatin and in combination with i.v. paclitaxel.

Secondary outcome

Although tumour response is not the primary endpoint of this study, patients with measurable disease will be assessed by RECIST criteria. Pharmacokinetic data will also be collected.

Study description

Background summary

Preliminary results from an ongoing phase I study (EudraCT 2005-001435-29) have illustrated that KU-0059436 can effectively inhibit the PARP enzyme.

Inhibition of PARP affects the repair of DNA damage. Whilst the ability to repair DNA is desirable in most cases, in cancer therapy it may enable tumour cells to recover from chemotherapy thus preventing effective treatment.

The potential to effectively inhibit the DNA repair in tumour cells following cytotoxic agents may potentiate the effects of chemotherapy and lead to better responses in some tumours. This concept is supported by the preclinical studies.

Carboplatin exerts its cytotoxic and therapeutic effect primarily by forming intrastrand and DNA adducts with adjacent guaninine residues in tumour cell DNA, thereby inhibiting tumour growth.

A combination of carboplatin with KU-0059436 may be an effective anti-cancer combination and warrants further investigation.

The paclitaxel / carboplatin combination is standard treatment for advanced ovarian cancer. It has also been found to give a high response rate in patients with metastatic / recurrent triple negative breast cancer, including patients with prior exposure to taxanes and those with large volume disease. It is therefore expected that the addition of paclitaxel to the KU-0059436 and carboplatin administration will lead to the best possible clinical outcome for these patients.

Study objective

Primary objective·
• To investigate the safety and tolerability and establish either the dose of KU-0059436 which causes inhibition of PARP in combination with an active dose of carboplatin or the maximum tolerated dose (MTD) of KU-0059436 in combination with paclitaxel / carboplatin and validate this in specific patient populations.

Secondary objectives·
• To identify the Dose Limiting Toxicity (DLT) of the combination of KU-0059436 and paclitaxel / carboplatin.·
• To determine the plasma pharmacokinetic profile of:
- KU-0059436 alone
- KU-0059436 in combination with carboplatin
- KU-0059436 in combination with paclitaxel / carboplatin
- KU-0059436 in combination with paclitaxel
• To investigate the pharmacodynamic profile over time in surrogate tissue of KU-0059436 when given in combination with a paclitaxel/carboplatin (TC) doublet.
• To determine the safety profile of KU-0059436 in combination with paclitaxel given at two dose levels.
To enable a preliminary assessment of the anti-tumour activity of KU-0059436 when given in combination with paclitaxel / carboplatin in specific patient

populations.
• To determine the safety and tolerability profile of the KU-0059436 Melt-Extrusion (tablet) formulation in combination with a paclitaxel / carboplatin (TC) doublet.

Exploratory objective·
•To investigate exploratory biomarkers in whole blood, serum, urine and tumour biopsies (on treatment and historical) to ascertain if there are any which differentiate treatment effects, and to investigate their correlation with disease progression/response to therapy or an improved understanding of the disease.

Study design

This is an open-label multi-centre, phase I study of KU-0059436 when administered orally in combination with carboplatin and in combination with paclitaxel / carboplatin.

The study consists of a dose escalation phase to establish the appropriate dose to be used in the dose expansion phase. The dose expansion phase of the study will establish the safety and tolerability of the established dose.

The dose escalation phase consists of 3 parts:
Part I: KU-0059436 (continuous) + carboplatin
Part IIa: KU-0059436 (continuous) + paclitaxel / carboplatin
Part IIb: KU-0059436 (continuous) + paclitaxel
Part III: KU-0059436 (discontinuous) + paclitaxel / carboplatin - this part of the study will only be initiated if a dose of carboplatin AUC 5 or above cannot be achieved in part II.
Part IV: KU-0059436 (discontinuous) + paclitaxel / carboplatin - this part of the study will only be initiated if the 1st expansion dose is not appropriate for futher phase II/III studies.

Intervention

Dose escalation phase:
Part I:
Cycle 1 will be of 28 days* duration. KU-0059436 will be administered twice daily for 28 days. Carboplatin will be administered on day 8. All subsequent cycles will be of 21 days* duration with carboplatin being administered on day 1 at least 1 hour after the patient has taken their KU-0059436 capsules. Starting dose is 50 mg bd KU-0059436 and 4 mg/ml.min Carboplatine

Part IIa:
Cycle 1 will be of 28 days' duration and all subsequent cycles will be of 21 days' duration. KU-0059436 will be administered twice daily for 28 days.

Paclitaxel, followed by carboplatin, will be administered on day 8, at least 1 hour after the patient has taken their KU-0059436 capsules. All subsequent cycles, KU-0059436 will be administered twice daily for 21 days, with paclitaxel and carboplatin administration on day 1. In case 50 mg KU-0059436 twice daily is not tolerated then 50 mg KU-0059436 once daily may be tested in a dose escalating scheme.
Starting dose of KU-0059436 and carboplatin is the maximum tolerated dose of Part I. Starting dose of paclitaxel is 90 mg/m2.

Part IIb:
Cycle 1 will be of 35 days* duration. KU-0059436 will be administered twice daily for 28 days. Paclitaxel will be administered on days 8, 15 and 22, at least 1 hour after intake of the KU-0059436 capsules. All subsequent cycles will be of 28 days* duration with paclitaxel being administered on day 1, 8 and 15 at least 1 hour after the patient has taken their KU-0059436 capsules
Starting dose is 100 mg bd KU-0059436 and 80 mg/m2 paclitaxel

Part III:
Each cylce will be of 21 days' duration. KU-0059436 capsules or tablets will be administered once or twice daily for a certain number of days in the cycle, followed by a rest period. Paclitaxel and carboplatin will be administered on day 1, at least 1 hour after the patient has taken their KU-0059436 capsule/tablet.
Starting dose of KU-0059436 and paclitaxel is the maximum tolerated dose of Part II. Starting dose of carboplatin will be 4 mg/ml.min.

Part IV: (will only be initiated if the 1st expansion dose is not appropriate for further phase II/III studies)
Each cylce will be of 21 days' duration. KU-0059436 capsules or tablets will be administered once or twice daily for a certain number of days in the cycle, followed by a rest period. Paclitaxel and carboplatin will be administered on day 1, at least 1 hour after the patient has taken their KU-0059436 capsule/tablet. Other discontinuous KU-0059436 schedules consisting of KU-0059436 (capsule or tablet) administered for any pre-defined number of days, up to 20 days, within each treatment cycle may be explored with carboplatin and paclitaxel.
Starting dose of KU-0059436 will be determined by the Investigators and the sponsor. Starting dose of carboplatin will be 4 mg/ml.min and of paclitaxel will be 175 mg/m2.

Expansion Phase (following part III and/or part IV of the study):
Each cycle will be of 21 days' duration. The maximum tolerated dose established in Part III will be selected for dose expansion.

In the event that carboplatin/paclitaxel is permanently discontinued on the basis of carboplatin/paclitaxel related toxicity or patients have completed the required treatment course, treatment with KU-0059436 may continue alone, at the

discretion of the Investigator and in consultation with the sponsor. The optimal recommended monotherapy dose is 400 mg b.d. continuously.

Study burden and risks

Screening procedures: medical history, physical exam, vital signs (pulse, blood pressure, respiratory rate, temperature), ECOG preformance status, ECG, CT scan or NMRI of the thorax and abdomen, chest X-ray, hematology and biochemistry test, biomarker, urine test and pregnancy test

Before start of chemotherapy: hematology and biochemistry test, physical exam, urine test, adverse event assessment and concomitant medication. During treatment CT scan or NMRI of the chest and abdomen will done every 2 cycles.

During cycle 1 the patient will come weekly to the clinic (day 8, 15 and 22) for hematology and biochemistry test, adverse event assessment and concomitant medication. Patients participating in part IIb will need to come twice a week for hematology and biochemistry tests.

Additional pharmacokinetic blood samples will be taken on day 1, 4 and 8. Also two pharmacokinetic blood samples will be taken on day 9 (24 hours after paclitaxel and/or carboplatin administration) and on day 10 (48 hours after Carboplatin administration).

In part III pharmacokinetic blood samples will be taken before treatment on day 1 of cycle 1 and periodically over about 8 hours. Depending on the treatment schedule, further pharmacokinetic samples may be taken on day 2 and day 8 of cycle 1. Certain treatment schedules may result in a sample being taken on day 18. In that case no samples will be taken on day 2 and day 8.

Pharmacodynamic blood samples will be taken before treatment on day 1 of cycle 1 and periodically over about 4 hours on day 1 of cycle 1. Depending on the treatment schedule, further pharmacodynamic blood sampling may occur on days 2, 8, 10-12 and 15 of cycle 1 and before treatment on day 1 of cycle 2. Certain treatment schedules may result in a sample being taken on day 18. In that case, no pharmacodynamic samples will be taken on days 2 and 8.

During the subsequent cycles the patient will need to come weekly to the clinic (day 8 and 15) for hematology and biochemistry test, adverse event assessment and concomitant medication.

At the last visit: physical exam, vital signs, ECOG, ECG, CT scan or NMRI of the chest and abdomen, hematology and biochemistry test, urine test, adverse event assessment and concomitant medication.

Contacts

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SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Full informed consent
2. Dose escalation phase: male or female patients with a histologically or cytologically diagnosed malignant solid tumour
Non-randomised dose expansion phase: female patients with histologically or cytologically diagnosed metastatic triple-negative breast cancer (platinum naive) and female patients with histologically or cytologically diagnosed ovarian cancer, where further treatment with platinum based chemotherapy is indicated.
Randomised dose expansion phase: female patients with histologically or cytologically diagnosed measurable metastatic breast cancer and female patients with histologically or cytologically diagnosed measurable ovarian cancer, where further treatment with platinum based chemotherapy is indicated.
3. Adequate bone marrow, hepatic and renal function, including the following:

a. hemoglobin >= 10.0 g/dl, ANC >= 1500x10 6/l, platelets >= 100.000x10 6/l;
b. total bilirubin <= 1,25 x upper normal limit
c. AST (SGOT), ALT (SGPT) ,= 2,5 x upper normal limit
d. creatinine <= 1,5 x upper normal limit
4. Creatinine clearance (Cockcroft-Gault) within normal range (> 60 ml/min)
5. Age >= 18 years
6. PS <= 2
7. Female patients with reproductive potential must have a negative urine or serum pregnancy test within 7 days of start of study.
8. The patient is willing to comply with the protocol for the duration of the study, including hospital visits for treatment and scheduled follow-up visits and examinations.
9. Life expectancy of at least 12 weeks.

Exclusion criteria

1. Any chemotherapy, radiotherapy (except for palliative reasons), endocrine therapy or immunotherpay within 4 weeks prior to study entry (or a longer period depending on the defined characteristics of the agents used). Patients may continue the use of biphosphonates for bone disease and corticosteroids provided the dose is stable before and during the study. Heavily pre-treated patients (> 2 courses of previous chemotherapy and/or extensive irradiation leading to bone marrow deficiency) will be excluded from the study.
Bone marrow deficiency is defined as the occurence of one or other of the events below:
- treatment delay in previous chemotherapy courses due to bone marrow toxicity.
- previous chemotherapy courses requiring growth factor support.
2. Dose escalation phase: more than 2 previous courses of platinum-containing chemotherapy
Non-randomised dose expansion phase: more than 2 courses of platinum-containing chemotherapy, except for metastatic triple negative breast cancer patients who must have had no previous platinum-containing chemotherapy.
Randomised dose expansion phase: patients where platinum therapy is not indictaed
3. Major surgery within 4 weeks of starting the study and patients must have recovered from the effects major surgery.
4. Patients with an active second primary cancer, except adequately treated basal skin cancer or carcinoma in-situ of the cervix. An active second primary cancer is defined as one with a disease free interval of <3 years
5. Pre-existing peripheral neuropathy > grade 1.
6. Any co-existing medical condition that in the investigator's judgement will substantially increase the risk associated with the patient's participation in the study.
7. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or compliance with the study protocol.
8. Symptomatic or known brain metastases.
9. Gastrointestinal disorders likely to interfere with absorption of the study drug.
10. Patients who are unable to swallow oral medication.
11. Patients with a history of allergic reactions to carboplatin, platinum containing compounds or mannitol.

12. Persistent toxicities (grade 2 or greater) from any cause.
13. Pregnant or breast-feeding women.
14. Patients with hepatic disease, e.g. patients with known serologically positive Hepatitis B or Hepatitis C as they may be more at risk of toxicity from KU-0059436.
15. Immunocompromised patients, e.g. patients who are known to be serologically positive for HIV.
16. Treatment with any investigational product during the last 30 days

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-07-2007
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	KU-0059436 Gelucire 44/14 (capsules)
Generic name:	KU-0059436
Product type:	Medicine
Brand name:	KU-0059436 Melt-Extrusion (tablets)
Generic name:	KU-0059436

Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-04-2007
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-06-2007
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-12-2007
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-01-2008
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-02-2008
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-02-2008
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-05-2008
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	14-10-2008
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-03-2009
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-08-2009
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-11-2009
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-02-2010
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-05-2010
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-06-2010
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-09-2010
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-12-2010
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	12-09-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-11-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-03-2012
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-11-2012
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	04-05-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Not approved Date:	14-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-09-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	10-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	16-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-03-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-000939-26-NL
CCMO	NL16955.031.07