Phase II and Pharmacological Study with Wee-1 inhibitor AZD1775 Combined with Carboplatin in Patients with p53 Mutated Epithelial Ovarian Cancer that Show Early Relapse (<3 months) or Progression during Standard First Line Treatment with Carboplatin - Paclitaxel Combination Therapy. With an additional safety and preliminary anti-tumor activity cohort of Wee-1 inhibitor AZD1775 Combined with Carboplatin in Patients with p53 Mutated Epithelial Ovarian Cancer, non-small cell lung cancer (NSCLC), sm

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Objective of the phase II POP study:To determine the safety and preliminary anti-tumor activity of AZD1775 in combination with carboplatin in p53 mutated epithelial ovarian cancer in a 21 day schedule.Objectives of the additional safety and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms female benign
Study type	Interventional

Summary

ID

NL-OMON47848

Source
ToetsingOnline

Brief title
M10 MKO (NKI name of trial) AZD1775

Condition

- Reproductive neoplasms female benign

Synonym
(non-)small cell lung cancer, cervical cancer, endometrial cancer, lung cancer, ovarian cancer, p53 mutated epithelial ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: AstraZeneca

Intervention

Keyword: AZD1775, carboplatin, p53, Several tumor types

Outcome measures

Primary outcome

Proof of concept trial:

To determine the safety and preliminary anti-tumor activity of MK-1775 in

combination with carboplatin in p53 mutated epithelial ovarian cancer in a 21

day schedule.

Additional safety and preliminary activity cohorts:

To determine the safety and preliminary anti-tumor activity (RECIST 1.1) of

AZD1775 in combination with carboplatin in p53 mutated epithelial ovarian

cancer, NSCLC, SCLC, cervical, and endometrial cancer, in a 21 day schedule

Secondary outcome

Phase II POP trial:

- To determine the pharmacokinetics of MK-1775 in plasma and of carboplatin in plasma and ultrafiltrates.

- To determine pharmacodynamic changes induced by MK-1775 in combination with carboplatin in both surrogate tissues (skin) and tumor tissue.

Additional safety and preliminary activity cohorts:

- To determine the time to progression.

- To determine the pharmacodynamic changes induced by AZD1775 in combination with carboplatin in circulating tumor cells (CTC).

Study description

Background summary

Platinum-based drugs are used in first line treatment of epithelial ovarian cancer. Despite high overall initial response rates, resistance or early relapse can occur. MK-1775 is a potent and selective inhibitor of Wee-1 kinase, a kinase that regulates the G2/M checkpoint. Since most human cancers retain p53-related G1 checkpoint abnormalities, they are dependent on the G2 checkpoint. Annulment of the G2 checkpoint may therefore make p53 deficient tumor cells more susceptible to anti-cancer agents. Therefore only patients with established p53 mutated pathway that have shown early relapse (< 3 months) or recurrence during standard platinum based treatment will be eligible for this proof-of-concept trial and receive carboplatin in combination with AZD1775.
As of 21 November 2016, this phase I study has been finished and reported(2). A total of 202 patients were enrolled. Monotherapy AZD1775 was well tolerated and the maximum tolerated dose (MTD) was not reached. The MTDs and biologically effective doses were established for AZD1775 combined with each combination. Of the 176 patients evaluable for efficacy, 94 (53%) had stable disease as best

response, and 17 patients (10%) achieved a partial response. AZD1775 was safe and tolerable as single agent and in combination with chemotherapy at doses associated with target engagement. In addition to this first-in-human phase I study, a proof-of-concept phase II study was conducted in patients with platinum refractory or early relapsed (<3 months) ovarian cancer. Results show promising anti-tumor effects with an ORR of 43% (95%- confidence interval (CI), 22-66%), including 1 patient with a prolonged complete response. It demonstrated manageable toxicity with fatigue (87%), nausea (78%), thrombocytopenia (70%), diarrhea (70%) and vomiting (48%) as most common adverse events (1).

Study objective

Objective of the phase II POP study:
To determine the safety and preliminary anti-tumor activity of AZD1775 in combination with carboplatin in p53 mutated epithelial ovarian cancer in a 21 day schedule.

Objectives of the additional safety and preliminary activity cohorts:
To determine the safety and preliminary anti-tumor activity (RECIST 1.1) of AZD1775 in combination with carboplatin in p53 mutated epithelial ovarian cancer, NSCLC, SCLC, cervical, and endometrial cancer, in a 21 day schedule

Study design

Study design POP trial:
This study is a multi-center, open label, single arm phase II and pharmacological study with carboplatin in combination with MK-1775 administered as second-line therapy to patients with p53 mutated epithelial ovarian cancer that show relapse or progression after standard first line treatment with carboplatin - paclitaxel combination therapy. Carboplatin will be administered at a dose resulting in AUC 5. The safe and tolerable dose of MK-1775 is currently being established in a phase I study with MK-1775(MK1775-001: EudraCT No. 2009-017054-12 / NL20803.031.07 - NKI M07MKC).

Each treatment cycle consists of 21 days. At day 1 of each cycle, carboplatin (AUC 5) will be administered in a 30 min infusion. MK-1775 will be administered as capsules BID for two and a half days starting concomitantly with each administration of chemotherapy.

Eligible patients must have p53 mutated pathway determined by IHC at the participating hospitals according to specific guidelines provided by the NKI and with second review of digitally uploaded images in the central database by pathologists of the NKI. Sequencing will also be performed at a later time point at the NKI. (Additional tumor tissue will be sent to Roche for retrospective concordance testing with AmpliChip p53 assay.) Patients must have

p53 mutated pathway confirmed by sequencing to be evaluable for the study. Patients that have entered the study based on positive p53 by IHC, but which cannot be confirmed by sequencing (negative for p53 mutation by sequencing) may continue treatment, but will not be considered evaluable for the study.

A Simon two-stage design will be used whereby in the first stage (Step A) 18 eligible patients will be recruited. In case of sufficient response (evaluated by RECIST or CA-125 levels), an additional cohort of 14 eligible patients will be included in the second stage (Step B), to a total of 32 patients.

Study design additional safety and preliminary activity cohorts:
The additional safety and preliminary anti-tumor activity cohort is a multi-center, open-label, non-randomized, single arm, cohort study in patients with confirmed p53 mutated epithelial ovarian cancer, NSCLC, SCLC, cervical, and endometrial cancer who previously received carboplatin and showed recurrence on or within 6 months of this treatment. Patients are allowed to have received second line treatment as well.

In the additional safety and preliminary anti-tumor activity cohort a minimum of 10 patients will be recruited per tumor type. If no partial responses have been documented in a defined tumor type that tumor type will be closed for further recruitment. If at least one patient shows a PR, or better, recruitment may continue until 29 patients have been included per tumor type.

Intervention

Treatment with carboplatin and Wee1 inhibitor AZD1775. Carboplatin will be administered at a dose resulting in AUC 5. The safe and tolerable dose of AZD1775 is currently being established in a phase I study with AZD1775(MK1775-001: EudraCT No. 2009-017054-12 / NL20803.031.07 - NKI M07MKC). Each treatment cycle consists of 21 days. At day 1 of each cycle, carboplatin (AUC 5) will be administered in a 30 min infusion. AZD1775 will be administered as capsules BID for two and a half days starting concomitantly with each administration of chemotherapy. A dose of 225mg AZD1775 is found to be safe and tolerable.

Study burden and risks

Patients participating may be hospitalized for about 2 days in the first week of the first cycle, however this will depend on the individual study teams. Blood for hematology, and serum chemistry (total for cycle 1: approximately 100 mL) will be drawn. The patient will undergo a physical exam and will have to visit the hospital (or be contacted by the hospital) once every week.
Patients are at risk for carboplatin related side effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion criteria for phase II POP trial:
1. p53 mutated (determined by IHC and later by sequencing) epithelial ovarian cancer
2. measurable disease on CT scan or elevated CA-125 levels that can be monitored
3. patients previously received standard 1st line platinum therapy (combined with paclitaxel) for epithelial ovarian cancer, and showed recurrence on or within 3 months of this treatment
4. age > 18 years
5. WHO performance status lower or equal to 1;Additional inclusion criteria for the safety and activity cohort:
1. histological or cytological proof of advanced epithelial ovarian cancer, NSCLC, SCLC, cervical and endometrial cancer (with proven p53 mutation).
2. previously treated with (standard) (1st) line platinum-based therapy (, and showed recurrence on or within 6 months after the end of this treatment.;3. Patients are allowed to

have received second line non-platinum containing therapy after recurrence on 1st line treatment. No more than 2 lines of pre-treatment with cytotoxic chemotherapy are allowed.
4. Eligible patients will have p53 mutation determined by sequencing of exons 2-10. See chapter 10 for additional information and Appendix XI +XII
5. Able and willing to undergo a fresh tumor biopsy (if p53 status is already known , tumor biopsy is still mandatory) .

Exclusion criteria

1. symptomatic cerebral or leptomeningeal metastases
2. current participation or previous participation in a study with an investigational compound, or chemo- and/or radiotherapy within 28 days of receiving first dose of study medication
3. patient must not have prior radiation therapy to more than 30% of the bone marrow and must have recovered for at least 3 weeks from the hematologic toxicity of prior radiotherapy.
4. more than 2 prior cytotoxic chemotherapy regimens

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-11-2010
Enrollment:	155
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable

Generic name:	AZD1775

Ethics review

Approved WMO Date:	19-03-2010
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	31-05-2010
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-07-2010
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-08-2010
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-09-2010
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-09-2010
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-01-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-02-2011
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	14-03-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-03-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-03-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	20-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	19-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-05-2020
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	EUCTR2010-019106-16-NL
ClinicalTrials.gov	NCT01164995
CCMO	NL31685.031.10

Study results

Date completed:	07-04-2023
Actual enrolment:	56