A pilot phase I open-label study to assess the safety and tolerability of Olaparib, a poly-(ADP-ribose)polymerase (PARP) inhibitor, in combination with melphalan for the treatment of patients with homologous recombination deficient metastatic solid tumors

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To perform a pilot study to determine the feasibility of conducting a two-arm phase I trial and to determine the recommended dose level for phase II (RP2D) study and assess the safety of the combination olaparib and melphalan in patients with...

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

Summary

ID

NL-OMON37339

Source
ToetsingOnline

Brief title
Olaparib and Melphalan, fase 1

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym

advanced, solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: A Sister's Hope

Intervention

Keyword: Homologous Recombination Deficiency, phase I, solid tumors

Outcome measures

Primary outcome

Primary end point:

• Recommended phase II dose determined by the dose limiting toxicity (DLT)

graded using the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE)

version 4

Secondary outcome

Secondary end points:

• Pharmacokinetics of the combination of olaparib and melphalan in two cohorts

• Pharmacodynamics: measuring PARP activity and γH2AX-RAD51 foci (plasma and

potential tumor)

• Assess objective response rates via RECIST in patients with measurable

disease

Study description

Background summary

Homologous recombination is an essential pathway for genomic integrity as it

repairs DNA double strand breaks error-free. Within this pathway BRCA1 and -2 play important roles. Inactivation of either of these genes predisposes patients to cancer. Cancers associated with BRCA1 or -2 inactivation can*t repair double strand breaks. These tumors are therefore more likely to benefit from therapy that induces these lesions such as bifunctional alkylators and Poly(ADP)Ribose Polymerase 1 (PARP1) inhibitors. Array CGH classifiers can distinguish tumors that are associated with loss of BRCA1 or -2. In this trial we will investigate feasibility of a combination of olaparib (a PARP1 inhibitor) and melphalan in BRCA1 or -2¬ mutation carriers or patients that have a BRCA like CGH tumor.

Study objective

To perform a pilot study to determine the feasibility of conducting a two-arm phase I trial and to determine the recommended dose level for phase II (RP2D) study and assess the safety of the combination olaparib and melphalan in patients with advanced solid tumors that have hallmarks of BRCA-1 or -2 deficiency.

Study design

This is a pilot open label phase I study assessing the orally administered olaparib in combination with melphalan i.v. Two cohorts will be investigated. In one cohort we will escalate melphalan in olaparib treated patients. In the other cohort we will escalate the olaparib dose in melphalan-treated patients. The study will consist of a dose escalation phase to establish the dose that can safely be administered and is recommended for phase II testing. In an expansion phase further safety and tolerability of the combination olaparib and melphalan will be evaluated. To assess pharmacokinetics, single agent olaparib will be administered on day 0 in cycle 1 as an internal control for PK. Furthermore efficacy will be analyzed in a more restricted patient population most likely to benefit from the combination. Allocation to cohorts occurs by patient and physician preference until one of the cohorts is full.

Intervention

The dose escalation phase will follow a traditional 3+3 design in two cohorts. In cohort 1 melphalan will be escalated on the background of an effective olaparib dose. If after escalating melphalan to the current dose used for treating multiple myeloma patients (25 mg/m2) no DLT has been observed olaparib will be escalated to the currently recommended dose. If still no DLT has been observed melphalan will be escalated beyond 25 mg/m2 following modified Fibonnaci increments. In cohort 2 olaparib will be escalated in combination with low dose melphalan. If no DLT occurs, melphalan will be increased to the current single agent dose.

Study burden and risks

Patient will experience the side effects of the study treament with olaparib and melphalan. Patients will be hospitalised for the first cycle of treatment because of close monitoring of vital signs the first 2 hours after melphalan infusion and for pharmacokinetic sampling.
In the first cycle patient will be seen on the out patient clinic on day 4, 8 and 15.
In the second and subsequent cycles patients will be seen on day 1 (dosing), day 8 and 15.
Patient will be asked to participate in the optional investigations of biomarker and pharmacogenetic research. This will include a tumor biopsy (3 timepoints), blood sampling (5 times x 10 ml) and urine sampling (4 times). For these investigation as seperate informed consent will be asked.

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

- Before patient registration, written informed consent must be given
- Male or female patients with a histologically or cytologically diagnosed metastatic or locally advanced malignant solid tumor having hallmarks of BRCA-1 or -2 deficiency:
o BRCA-1 or -2 mutation carriers with any tumor
o Breast cancer patients with a BRCA-likeCGH tumor
- Patients must have progressed despite standard therapy.
- Age > 18 years
- Performance status (PS): <2 (ECOG scale) and a life expectancy of at least 12 weeks
- Patients must be able to swallow oral medication.
- Female patients of childbearing age must have a negative urine or serum pregnancy test within 7 days prior to start of study.
- Laboratory requirements within 7 days prior to start of treatment:
Haematology:
-Haemoglobin >10.0 g/dl (6.2 mmol/l)
-absolute neutrophil count >1.5 x 109/L
-platelets >100 x 109/L;
Biochemistry:
-Total bilirubin : <1.25 x upper normal limit;
-AST (SGOT), ALT (SGPT) : <2.5 x upper limit of normal (ULN); in case of liver metastases < 5 * ULN
-Serum creatinine clearance >= 50 ml/min (Cockroft-Gault)
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

Exclusion criteria

- Patients having received any chemotherapy, radiotherapy (except for palliative reasons), biological therapy or investigational compound administered within four weeks prior to start of study treatment or patients not recovered from adverse events due to agents administered more than 4 weeks earlier.
- Patients having symptomatic brain metastases. A scan to confirm the absence of brain metastases is not required.
- Patients having gastrointestinal disorders likely to interfere with absorption of the study drug (e.g. partial bowel obstruction or malabsorption).
- Patients should not require treatment with inhibitors or inducers of Cytochrome P450 system.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2012
Enrollment:	60
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Alkeran
Generic name:	Melphalan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Olaparib
Generic name:	Olaparib

Ethics review

Approved WMO Date:	21-02-2012
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-03-2012
Application type:	First submission
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	EUCTR2011-005278-46-NL
CCMO	NL39007.031.11