ENGOT-ov11/MILO study (MEK Inhibitor in Low-grade Serous Ovarian Cancer): A Multinational, Randomized, Open-label Phase 3 Study of MEK162 vs. Physician*s Choice Chemotherapy in Patients with Recurrent or Persistent Low-grade Serous Carcinomas of the Ovary, Fallopian Tube or Primary Peritoneum

Published: 19-12-2013
Last updated: 24-04-2024

Primary: • Demonstrate superior efficacy (increased progression-free survival [PFS]) of MEK162 vs. physician*s choice of selected chemotherapies (liposomal doxorubicin, paclitaxel and topotecan)Key Secondary: • Demonstrate superior efficacy (...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON45111

Source
ToetsingOnline

Brief title
ENGOT-ov11/MILO study

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
Ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: Array BioPharma Inc.
Source(s) of monetary or material Support: Array Biopharma;Inc.

Intervention

Keyword: Chemotherapy, MEK162, Ovarian Cancer

Outcome measures

Primary outcome

Primary:

• Progression-free survival as determined by the blinded independent central review (BICR). The local Investigator assessments will be used as supportive analyses

Secondary outcome

• Overall survival

• Objective response rate (ORR) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1

• Duration of response (DOR)

• Disease control rate (DCR), defined as having achieved a best response of complete response (CR) or partial response (PR), or stable disease (SD) documented at Week 24 or later

• Incidence and severity of adverse events (AEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI

CTCAE), Version 4.03

• Changes in clinical laboratory parameters

• Assessment by the quality-of-life (QOL) questionnaires European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-OV28 and Functional Assessment of Cancer Therapy (FACT)/Gynecologic Oncology Group (GOG)-Neurotoxicity (NTX)

• Plasma concentration-time profiles and model-based PK parameters of MEK162 (and metabolite AR00426032, if feasible) in a subset of the patients randomized to receive MEK162

• During the crossover period, after failure of physician*s choice chemotherapy in the randomized period:

o Progression-free survival as determined by local Investigator assessments

o Objective response rate as defined by RECIST, Version 1.1

o Duration of response

o Incidence and severity of AEs, graded according to the NCI CTCAE, Version 4.03

o Changes in clinical laboratory parameters

o Assessment by the QOL questionnaires EORTC QLQ-C30, EORTC QLQ-OV28 and FACT/GOG-NTX

Exploratory:

• In tumor tissue, if available and as feasible:

o Mutations in cancer-associated and

chemotherapy-metabolism-related genes

o Levels and activation states of apoptosis-related proteins and

associated messenger ribonucleic acid (mRNA) transcripts

o Levels and activation states of rat sarcoma viral oncogene

(RAS)/v-Raf murine sarcoma viral oncogene (RAF)/mitogen-activated protein

kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling

pathway proteins, and associated mRNA transcripts and regulatory molecules

• In blood samples, as feasible:

o Genetic variant analysis of the UGT1A1 gene in a subset of the

patients randomized to receive MEK162

Study description

Background summary

Low-grade serous carcinomas of the overay, fallopian tube and primary peritoneum are rare tumors for which current therapies have limited efficacy. A Phase 2 study evaluating the MEK inhibitor selumetinib showed an objective response rate of 15%, a clinical benefit rate of 81% and a median progression-free survival of 11 months. This Phase 3 is designed to evaluate the efficacy of the MEK inhibitor MEK162 in patients with recurrent or persisten LGS carcinoma of the ovary, fallopian tube or primary peritoneum. Previous studies with this inhibitor in patients with other types of cancer have shown that there is more chance of longer progression-free survival or longer overall survival

Study objective

Primary:
• Demonstrate superior efficacy (increased progression-free survival [PFS]) of MEK162 vs. physician*s choice of selected chemotherapies (liposomal doxorubicin, paclitaxel and topotecan)

Key Secondary:
• Demonstrate superior efficacy (increased overall survival [OS]) of MEK162 vs.

physician*s choice of selected chemotherapies

Other Secondary:
• Obtain additional estimates of the efficacy of MEK162 vs. physician*s choice of selected chemotherapies
• Characterize the safety profile of MEK162 vs. physician*s choice of selected chemotherapies
• Assess the effect on global health status of MEK162 vs. physician*s choice of selected chemotherapies
• Characterize the plasma pharmacokinetics (PK) of MEK162 in this patient population

Exploratory:
• Assess possible predictive biomarkers of clinical activity for MEK162

Study design

Note: As of 01 April 2016, screening and randomization into the study were discontinued
This multinational, randomized, open-label Phase 3 study will evaluate MEK162 vs. physician*s choice of selected chemotherapies in patients with LGS carcinomas of the ovary, fallopian tube or primary peritoneum who have recurrent or persistent disease following at least 1 prior platinum-based chemotherapy treatment and no more than 3 prior lines of chemotherapy. Patients who have achieved a CR following therapy and who subsequently experience a return of cancer cells after last therapy are said to have recurrent disease. Persistent disease refers to residual cancer growths or cells that persist during and following last therapy.
This study will have 2 periods, a randomized period and a crossover period to MEK162 treatment after failure of physician*s choice chemotherapy treatment in the randomized period.

Randomized Period
Prior to randomization, central pathology review of the patient*s archival histological tumor specimen obtained at Screening will be required to confirm diagnosis of LGS carcinoma. If adequate archival tumor sample is not available for confirmation of LGS carcinoma diagnosis, a tumor biopsy will be required with additional consent. Only those patients with confirmed LGS carcinoma per central pathology review and meeting all eligibility criteria will be randomized. All patients must have measurable disease as defined by RECIST, Version 1.1, per the BICR.
Patients will be stratified by their last platinum-free interval (PFI; <= 182 days vs. > 182 days) and number of prior systemic regimens (1 to 2 vs. > 2) and then randomized 2:1 to receive MEK162 or physician*s choice chemotherapy (liposomal doxorubicin, paclitaxel or topotecan). Platinum-free interval is the period of time from the date of last platinum dose to the date of progressive disease (PD) on that regimen (defined as radiological and/or clinical

progression; an increase in cancer antigen [CA]-125 alone is not sufficient) or initiation of subsequent therapy, whichever occurred first. Non-platinum maintenance therapy (e.g., extending taxane treatment) is not counted as another subsequent therapy. Platinum-free interval for the most recent platinum therapy will need to be calculated prior to randomization for stratification purposes. Prior systemic regimens include both chemotherapy regimens and hormonal therapy regimens given by all routes of administration. For the purpose of stratification, front-line therapy may include neoadjuvant and adjuvant therapy and will be counted as 1 prior systemic regimen. The randomization schedule will be created and managed by an independent statistician not assigned to support the study and will be implemented via an external Interactive Web Response System (IWRS).
Once a patient is randomized, efficacy, safety and global health status will be assessed at specified time points. Tumor tissue, if available after central pathology review and with patient consent, will be assessed for mutations and copy number variations in cancer-associated (including RAS/RAF) and chemotherapy-metabolism-related genes. With patient consent, tumor tissue may also be analyzed for exploratory biomarkers. In addition, a subset of patients randomized to receive MEK162 will have pre- and postdose blood samples collected on specified days in order to characterize the plasma PK of MEK162 in this patient population. This same subset of patients, with patient consent, will also have a predose blood sample drawn for genetic variant analysis of the UDP-glucuronosyl transferase (UGT)1A1 gene to investigate the effect of UGT1A1 genetic variant on MEK162 exposure. With patient consent, these blood samples may also be analyzed for exploratory biomarkers.
As of Protocol Version 6 (date 15 March 2017), BICR review of tumor assessments will no longer be performed; tumor assessments in both the randomized and crossover periods will be conducted by the study sites according to institutional standards. Results of tumor assessments will be retained in patient files only and no longer be entered into the eCRFs. All laboratory assessments will be performed by a central laboratory as well as the local laboratory if more rapid results are required for treatment decisions or patient safety. All patients will be followed for approximately 30 days after the last dose of study drug for safety. After the Safety Follow-up period, patients will be discontinued from the study

Crossover Period
As of Protocol Version 6, crossover from physician*s choice chemotherapy treatment to MEK162 treatment will no longer be permitted.
The study will have an independent Data Monitoring Committee (DMC) to review safety data at regular intervals, as well as to perform the interim efficacy analysis. An interim efficacy analysis for futility will be conducted following a prespecified number of events.

Intervention

Patients randomized to MEK162 treatment will take 45 mg orally (PO) twice daily

(BID) with water, continuously, starting on Day 1. Patients should be fasted 1 hour before and 1 hour after each dose.

Patients randomized to the physician*s choice chemotherapy arm will receive one of the following therapies, if available and if approved for treatment of ovarian cancer within a given country:
• Liposomal doxorubicin 40 mg/m2 intravenously (IV) on Day 1 of every 28 day cycle
• Paclitaxel 80 mg/m2 IV on Days 1, 8 and 15 of every 28 day cycle
• Topotecan 1.25 mg/m2 IV on Days 1 through 5 of every 21 day cycle

Patients randomized to the physician*s choice chemotherapy arm should receive a therapy considered appropriate by the Investigator given the patient*s medical history, prior treatment(s) and other relevant factors. At least 3 days prior to randomization, the Investigator must declare which physician*s choice chemotherapy the patient will receive if randomized to this treatment arm.

Patients must receive their first dose of study drug within 5 days of randomization.
Patients will receive premedication prior to chemotherapy infusions per institutional standards. Hematologic growth factors may be given per institutional standards.
For an individual patient, the dose of study drug may be reduced or interrupted as appropriate based on protocol defined treatment modifications.

Study burden and risks

The benefits of treatment is to increase progression-free survival of the patient.

Contacts

Public
Array BioPharma Inc.

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US
Scientific
Array BioPharma Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

•Written informed consent
•Diagnosis of LGS carcinoma of the ovary, fallopian tube or primary peritoneum (invasive micropapillary serous carcinoma or invasive grade 1 serous carcinoma), confirmed histologically and verified by central pathology review.;•Recurrent or persistent measurable disease that has progressed (defined as radiological and/or clinical progression; an increase in cancer antigen [CA]-125 alone is not sufficient) on or after last therapy (i.e., chemotherapy, hormonal therapy, surgery) and is not amenable to potentially curative intent surgery, as determined by the patient's treating physician.;•Must have received at least 1 prior platinum-based chemotherapy regimen but have received no more than 3 lines of prior chemotherapy regimens, with no limit to the number of lines of prior hormonal therapy.;•Available archival tumor sample (excisional or core biopsy) for confirmation of LGS carcinoma diagnosis. If adequate archival tumor sample is not available, willingness to consent to tissue biopsy.;•Suitable for treatment with at least one of the physician's choice chemotherapy options (liposomal doxorubicin, paclitaxel or topotecan) as determined by the Investigator.;•Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.;•Other protocol-defined inclusion criteria exist.

Exclusion criteria

•History or current evidence of retinal vein occlusion (RVO), or current risk factors for RVO.;•Prior therapy with a MEK or BRAF inhibitor.;•History of Gilbert's syndrome.;•Impaired cardiovascular function or clinically significant cardiovascular diseases.;•Uncontrolled or symptomatic brain metastases that are not stable or require steroids, are potentially life-threatening or have required radiation within 28 days prior to first dose of study treatment.;•Concomitant malignancies or previous malignancies with less than a 5-year disease-free interval at the time of first dose of study treatment; patients with adequately resected basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or

ductal carcinoma in situ may be enrolled irrespective of the time of diagnosis.;•Known positive serology for the human immunodeficiency virus (HIV), active hepatitis B and/or active hepatitis C.;•Other protocol-defined exclusion criteria exist.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-11-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Caelyx
Generic name:	L01DB - Liposomal doxorubicin - SUB33393
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MEK162
Generic name:	ARRY-438162
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Paclitaxel - SUB09583MIG

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Potactasol
Generic name:	L01XX17 - Topotecan - SUB11191MIG
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-12-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-05-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-06-2015
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-08-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-06-2017
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2013-000277-72-NL
ClinicalTrials.gov	NCT01849874
CCMO	NL46689.042.13

Study results

Results posted: 24-10-2019

First publication
01-01-1900