The MILO Study-ENGOT OV-11
Clinical Study ARRAY 162-311

The MILO Study (MEK Inhhibitor in Low-grade Serous Ovarian Cancer

A Multinational, randomized, open-label Phase 3 Study of MEK 162 vs Physician's choice chemotherapy in patients with recurrent of persistent low-grade serous carconimas of the ovary, fallopian tube or primary peritoneum

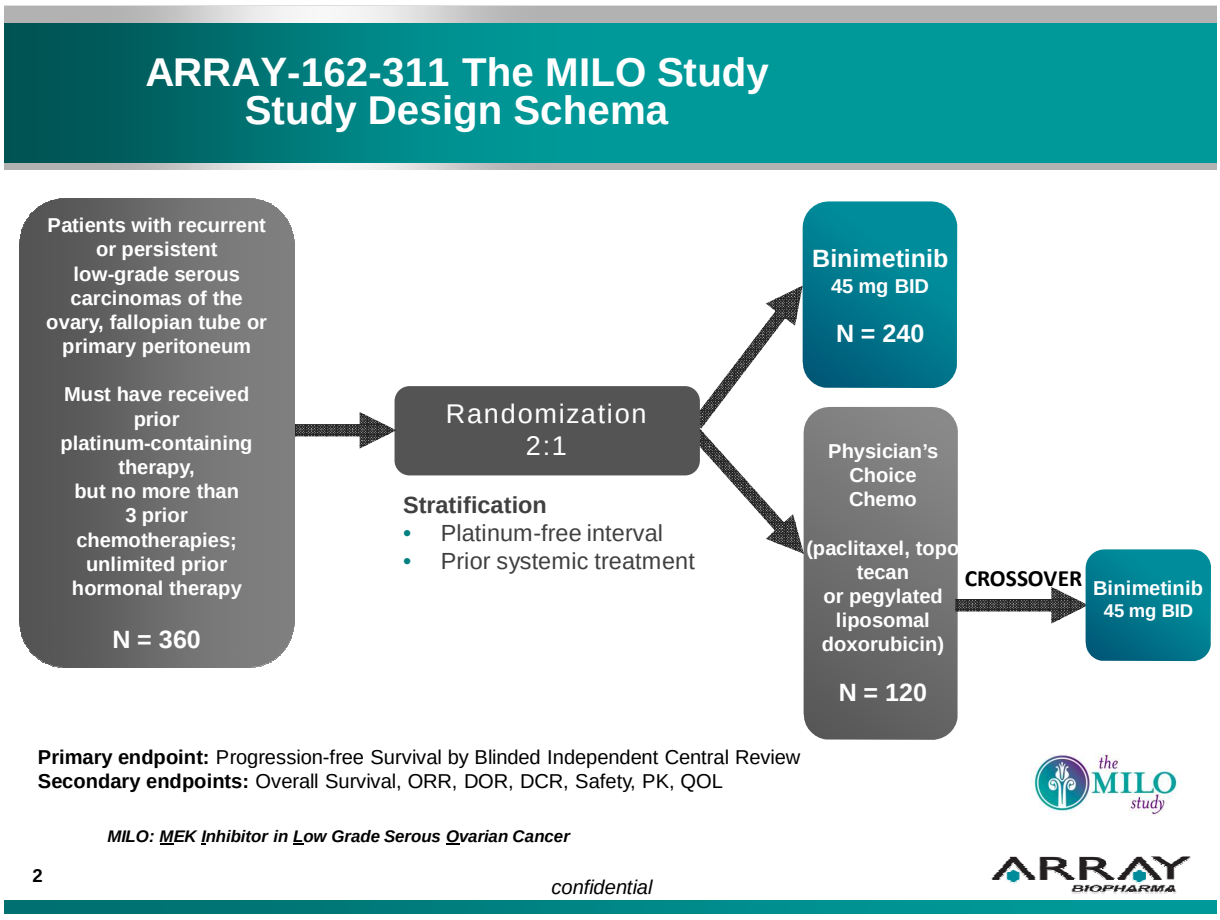
Protocol Version 1:	01 February 2013
Protocol Version 2:	29 May 2013
Protocol Version 3:	16 September 2013
Protocol Version 4:	03 October 2014
EudraCT Number:	2013-000277-72
IND Number:	116,725

Sponsor: Array BioPharma Inc
International Coordinating Center: BGOG
Italian Coordinating Center: INT-Napoli

FOURTH PROGRESS REPORT MITO

June 2016

Clinical Trials Unit – National Cancer Institute of Naples



Study Objectives

Primary:

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

Secondary:

• Obtain additional estimates of the efficacy (including overall survival [OS]) 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
• During the crossover period, after failure of physician's choice chemotherapy in the randomized period:
o Assess the efficacy of MEK162
o Characterize the safety profile of MEK162
o Assess the effect on global health status of MEK162

Exploratory:

• Assess possible predictive biomarkers of clinical activity for MEK162

Study design

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

Patients randomized to MEK162 treatment will take 45 mg orally (PO) twice daily (BID) with water irrespective of food, continuously, starting on Day 1.

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. Approximately 3 days prior to randomization, the Investigator must declare which physician's choice chemotherapy the patient will receive if randomized to this treatment arm.

Crossover Period

Patients who crossover from physician's choice chemotherapy treatment to MEK162 treatment will take 45 mg PO BID with water irrespective of food, continuously, starting on Day 1 of the crossover period.

Statistical Considerations

The required sample size is based on the following considerations. The historical median PFS for patients with LGS ovarian cancer treated with chemotherapy is approximately 7 months (Gershenson DM et al. Gynecol Oncol 2009;114:48-52). An improvement of 4.7 months (median PFS of 11.7 months; hazard ratio [HR] = 0.60) would be considered clinically meaningful. In order to have 90% power to detect this improvement using a group-sequential design with 1 interim futility analysis, a 1-sided log-rank test with α = 0.025 requires a minimum of 195 events (PD or death). Assuming uniform accrual at a rate of 11 patients per month (for an accrual duration of approximately 27.3 months) and an additional 2 months of follow-up, approximately 300 patients will be randomized.

An interim futility analysis of PFS will be performed after a minimum of approximately 78 events have been observed. The analysis of PFS will be performed using a stratified log-rank test that includes the stratification factors that were used during the randomization process.

ENROLLMENT TERMINATED 01/04/2016 DUE TO FUTILITY

FINAL ENROLLMENT MITO 1 APRIL 2016

SITE ID	CITY	INSTITUTE	SITE STATUS	PTS SCREENED	FAILURES	RANDOM
2083	Naples	Istituto Pascale	Activated	5	2	**3**
2084	Milan	Istituto Tumori Milan	activated	2	0	**2**
2143	Roma	Policlinico Umberto I	activated	1	1	**0**
2086	Roma	Policlinico A Gemelli	activated	8	5	**3**
2214	Aviano	Centro Riferimento Oncologico,	activated	1	1	**0**
2115	Naples	University "Federico II“	activated	1	1	**0**
2114	Faenza (RA)	Unità Operativa di Oncologia	activated	1	0	**1**
2211	Bologna	AOU Bologna	activated	2	0	**2**
2116	Roma	Regina Elena	activated	2	2	**0**
2210	Catania	Azienda Ospedaliera "Cannizzaro"	activated	1	0	**1**
TOTALS						**12**