ENGOT OV-27

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Efficacy and Safety of Farletuzumab (MORAb-003) in Combination with Carboplatin plus Paclitaxel or Carboplatin plus Pegylated Liposomal Doxorubicin (PLD) in Subjects with Low CA125 Platinum-Sensitive Ovarian Cancer

Protocol Version 1: 11 November 2014
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Sponsor: Morphotek
International Coordinating Center: BGOG
Italian Coordinating Center: INT-Napoli

FOURTH PROGRESS REPORT MITO

JUNE 2017

Clinical Trials Unit – National Cancer Institute of Naples

Data contained in this report are CONFIDENTIAL
for Investigators participating in the trial and cannot be divulged.

Study Objectives

Primary:
The primary objective of the study is to demonstrate that farletuzumab has superior efficacy compared to placebo in improving progression-free survival (PFS) as determined by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 when added to 1 of 2 standard chemotherapy regimens (carboplatin plus paclitaxel or carboplatin plus PLD) in subjects with platinum-sensitive ovarian cancer in first relapse who have a cancer antigen 125 (CA125) ≤ 3x the upper limit of normal (ULN) (105 U/mL) at study entry.

Secondary:
- To assess the effect of farletuzumab on overall survival (OS) in this population
- To assess the effect of farletuzumab in prolonging second platinum-free interval longer than first platinum-free interval
- To assess the effect of farletuzumab on best objective response (OR) rate, time to response (TTR) and duration of response (DR) by RECIST 1.1 criteria
- To assess the safety and tolerability of farletuzumab
- To assess the pharmacokinetics and exposure-response relationships between farletuzumab and PFS and OS

Exploratory:
- To explore blood CA125 change pattern during study
- To explore biomarkers that may correlate with the efficacy-related endpoints and farletuzumab mechanism of action
- To explore expression of CA125 and folate receptor alpha in blood, urine, and tissue to correlate to disease characteristics, exposure, efficacy-related endpoints, farletuzumab mechanism of action, and other biomarkers

Study design
MORAb-003-011 is a global, multicenter, double-blind, randomized placebo-controlled study.
Subjects will be enrolled in a targeted 1:1 stratification ratio into 1 of 2 chemotherapy treatment arms at the investigator's discretion: carboplatin plus paclitaxel or carboplatin plus PLD, and then randomized in a 2:1 ratio to receive weekly farletuzumab 5 mg/kg or placebo (ie, Test Article). All subjects will receive a loading dose for the first 2 weeks of 10 mg/kg Test Article (farletuzumab or placebo). Subjects will be stratified at randomization by individual chemotherapy treatment regimen (targeted 1:1 ratio) and platinum-free interval following first-line therapy (6-12 months vs >12-36 months). The enrollment and accumulative PFS events in each chemotherapy stratum will be closely monitored to ensure the required number of PFS events is achieved in each chemotherapy stratum. The minimum enrollment for each chemotherapy stratum is 105 subjects. Once the minimum number of subjects is enrolled, one chemotherapy stratum might be closed to enrollment before the other chemotherapy stratum to ensure that the targeted 1:1 ratio does not become significantly imbalanced.
All subjects must have CA125 ≤ 3xULN (105 U/mL) confirmed at Screening for study entry using a central laboratory designated by the sponsor to assure a standardized assay is used (Architect CA125 II assay). An archival tumor tissue sample taken at the time of initial diagnosis of ovarian cancer will be provided at Screening for analysis. In addition, blood and urine samples will be collected at time points throughout the study for other supporting exploratory analyses.

The study will consist of 4 phases: Screening, Combination Treatment, Maintenance Treatment, and Follow-up. At the end of the Combination Treatment Phase, subjects who have not experienced disease progression will enter the Maintenance Treatment Phase until disease progression. Subjects who discontinue Test Article for reasons other than disease progression will be followed radiographically until documentation of disease progression or start of any new anticancer therapy and should still be followed for OS. An independent data monitoring committee (DMC) will be utilized to monitor the safety profile, and to enhance safety oversight.

Number of Subjects

A total of 210 subjects are planned for enrollment, including 140 subjects in thefarletuzumabarm, and 70 subjects in the placebo arm.

Inclusion Criteria

1. Female subjects whoare at least18 years of age at the time of informed consent
2. CA125≤3xULN(105 U/mL) confirmed within 2 weeks of randomization using a centralized laboratory assay
3. A histologically confirmed diagnosis of high-grade serous epithelial ovarian cancer including primary peritonealandfallopian tube malignancies; all other histologies, including mixed histology, are excluded
4. Have been treated with debulking surgeryand a first–line platinum based chemotherapy regimen
5. Maintenance therapy during the first platinum-free interval is allowed; however, the last dose must have been at least 21 days prior toRandomization.
6. Must have evaluabledisease by computed tomography (CT) or magnetic resonance imaging (MRI) scan, according to RECIST 1.1(subjects with measurable disease per RECIST 1.1 or radiographically visible and evaluable disease). Subjects with only ascites or pleural effusion are excluded.
7. Must have relapsed radiographicallywithin ≥6 months and ≤36 months of completion of first-line platinum chemotherapy and should be randomized within 16 weeks of radiographic relapse
8. Must be a candidate for treatment with either carboplatin plus paclitaxel or carboplatin plus PLD
9. Have a life expectancy of at least6 months, as estimated by the investigator
10. Other significant medical conditions must be well-controlled and stable in the opinion of the investigator for at least 30 days prior toRandomization
11. Have an Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
12. Subjects being enrolled to receive paclitaxel plus carboplatin treatment must have neuropathic function (sensory and motor) ≤ Grade 2 according to the National Cancer Institute's(NCI) Common Terminology Criteria for Adverse Events(CTCAE) v4.03
13. Laboratory results within the 2 weeks prior toRandomization must be as follows:
    - Absolute neutrophil count (ANC)≥ 1,500cells/mm3
    - Platelet count≥ 100,000 cells/mm3
    - Hemoglobin≥ 9 g/dL
    - Creatinine<1.5xULN (CTCAE Grade 1)
    - Bilirubin< 1.5xULN (CTCAE Grade 1)
    - Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) <3xULN (CTCAE Grade 1)
    - Alkaline Phosphatase < 2.5xULN (CTCAE Grade 1)
    - Baseline albumin ≥Lower Limit of Normal

14. Subjects of childbearing potential must be surgically sterile or consent to use a medically acceptable method of contraception throughout the study period. All females will be considered to be of childbearing potential unless they are postmenopausal (eg, amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy). If a patient of childbearing potential is neither surgically sterile nor postmenopausal, contraceptive measures must start either before or at Screening and continue throughout the entire study period and for 5 months after the last dose of Test Article is administered. Pregnant and/or lactating females are excluded

Subjects must provide written informed consent and be willing and able to comply with all aspects of the protocol

Exclusion Criteria

1. Known central nervous system (CNS) tumor involvement
2. Evidence of other active invasive malignancy requiring treatment other than surgery in the past 3 years
3. Clinically significant heart disease (eg, congestive heart failure of New York Heart Association Class 3 or 4, angina not well controlled by medication, or myocardial infarction within 6 months)
4. Electrocardiogram (ECG) demonstrating clinically significant arrhythmias that are not adequately medically managed (Note: subjects with chronic atrial arrhythmia, ie, atrial fibrillation or paroxysmal supraventricular tachycardia [SVT], are eligible)
5. Active serious systemic disease, including active bacterial or fungal infection
6. Active viral hepatitis or active human immunodeficiency virus (HIV) infection. Asymptomatic positive serology is not exclusionary
7. Other concurrent immunotherapy (eg, immunosuppressants or chronic use of systemic corticosteroids with the exception that low-dose corticosteroids [50 mg/day prednisone or equivalent corticosteroid] are allowed; these should be discussed with the Medical Monitor)
8. Known allergic reaction to a prior monoclonal antibody therapy or have any documented Anti-Drug Antibody (ADA) response
9. Previous treatment with farletuzumab or other folate receptor targeting agents
10. Previous treatment with cancer vaccine therapy
11. For subjects being enrolled to receive PLD plus carboplatin, prior treatment with anthracyclines or anthracenodiones
12. Breast-feeding, pregnant, or likely to become pregnant during the study
13. Any medical or other condition that, in the opinion of the investigator, would preclude the subject's participation in a clinical study
14. Patients who have had secondary debulking surgery

Currently enrolled in another clinical study or used any investigational drug or device within 30 days (or 5x half-life for investigational drugs where the half-life is known)preceding informed consent

Number of Subjects

A total of 210 subjects are planned for enrollment, including 140 subjects in the farletuzumab arm, and 70 subjects in the placebo arm.

ENROLLMENT FACTS AND FIGURES AS OF 31/05/2017

GLOBALLY: 136/210 PTS RANDOMIZED

ENGOT: 54 RANDOMIZED

MITO: 19 RANDOMIZED

MITO Report by Centre

Codice centro	Centro	Città	Status	Pts screened	Screen failures	Pts randomized
70010	Istituto Nazionale Tumori - IRCCS Pascale	Napoli	Open	1	1	0
70020	AOU Bologna Policlinico S.Orsola-Malpighi	Bologna	Open	5	0	5
70030	Policlinico Univeristario Gemelli	Roma	Open	7	2	5
70040	Istituto Nazionale Tumori Regina Elena	Roma	Open	3	1	2
70050	Istituto Nazionale Tumori - Milano	Milano	Open	7	3	2
70060	AO Ospedale Policlinico Universitario Consorziale	Bari	Open	0	0	0
70070	Ospedale Santa Maria della Misericordia	Perugia	Open	0	0	0
70080	AOU Federico II	Napoli	Open	3	1	2
70090	Ospedale San Raffaele	Milano	Open	2	0	2
70100	AO SG Moscati	Avellino	Inactive	0	0	0
70110	Policlinico Umberto I La Sapienza	Roma	Open	5	4	1
70120	Seconda Università i	Napoli	Not yet open			
TOTALS				**33**	**12**	**19**