PSSV Presentation

TRIO 014 Study

A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, MULTI-CENTER, PHASE II STUDY OF ADDING AMG 479, A FULLY HUMAN MONOCLONAL ANTIBODY AGAINST INSULIN-LIKE GROWTH FACTOR TYPE 1 RECEPTOR (IGF-1R) TO FIRST LINE CHEMOTHERAPY IN PATIENTS WITH OPTIMALLY DEBULKED ( < 1 cm ) EPITHELIAL OVARIAN CANCER.

TRIO 015 Study

A MULTICENTER OPEN LABEL PHASE II STUDY OF THE EFFICACY AND SAFETY OF AMG 479, A FULLY HUMAN MONOCLONAL ANTIBODY AGAINST INSULIN-LIKE GROWTH FACTOR TYPE 1 RECEPTOR (IGF-1R) AS SECOND LINE THERAPY IN PATIENTS WITH RECURRENAT PLATINUM-SENSITIVE OVARIAN CANCER
Sponsor

- **CIRG** (Cancer International Research Group), a division of **TRIO** (Translational Research In Oncology)

- Test article AMG 479 provided by AMGEN
Ovarian cancer: course of disease

Diagnosis

Initial surgery

Systemic (IV or IP) chemotherapy

Recurrence (75% within first 20 Mo)

Additional surgery could be performed

Recurrence (within 4-6 Mo)

Systemic (IV or IP) chemotherapy

Carbo/cisplatin + taxol or taxotere

> 6 Mo: Carbo/cisplatin

< 6 Mo: other cytotox
GCIG 2005 Definition of CA 125 Progression

- **Definition of progression on first line therapy and recurrence according to CA 125:** according to radiological tumor assessment but can also be based upon serum CA 125 (defined below) but tumor measurements should take precedence over CA 125.

- **EVALUATION OF PROGRESSION/RECURRENT ACCORDING TO CA 125**
  - Patients with elevated CA 125 pretreatment and normalization of CA 125 must show evidence of CA 125 ≥ 2 ULN on two occasions at least one week apart
  - or
  - Patients with elevated CA 125 pretreatment, which never normalizes must show evidence of CA 125 ≥ 2 Nadir on two occasions at least one week apart
  - or
  - Patients with CA 125 in the normal range pretreatment must show evidence of CA 125 ≥ 2 ULN on two occasions at least one week apart.

- Elevated values must be confirmed by two separate measurements obtained at least one week apart. CA 125 progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA4, 5) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

- A patient may be declared to have progressive disease on the basis of either the objective appearance of a new lesion on radiological tumor assessment or the CA 125 criteria. The date of progression will be the date of the earlier of the two events if both are documented.
IGF-1R in ovarian cancer

- **IGF-1**: insulin like growth factor 1: growth factor of which production by liver is stimulated by growth hormon
- IGF-1 could bind insulin receptor and **IGF-1R** (high affinity)
- **IGF-1R**: tyrosine kinase with transduction signal overlapping with HER-2, involving mTOR
- IGF-1R is overexpressed on ovarian tumors, and in particular on ovarian epithelial cells
- IGF-1 and IGF-1R are important mitogens in ovarian carcinogenesis.
- *In vitro* overexpression of IGF-1R was found to induce malignant transformation of the cells.
AMG 479

- Monoclonal antibody specific for IGF-1R
- Inhibits binding of IGF-1 and IGF-2
- Inhibits signal through IGF-1R
- Currently in phase I trials:
  - First in human in advanced malignancies
  - In combination with panitumumab and gemcitabine
  - In Ewing’s sarcoma
AMG 479: List of AE related

Very Common (10% or more):
- feeling tired
- Rash
- Thrombocytopenia
- anorexia

Common (less than 10%):
- diarrhea, nausea, vomiting
- inflammation of mucous membranes
- dizziness
- decreased appetite or loss of appetite
- joint or muscle pain
- headache
- anemia
- chills, fever
- high blood sugar
- flushing
TRIO 014

TRIO 014: If debulked < 1 cm

- Carbo/cisplatin + taxol or taxotere

Systemic (IV or IP) chemotherapy

Recurrence

Initial surgery

Diagnosis

Systemic (IV or IP) chemotherapy

Additional surgery could be performed

> 6 Mo: Carbo/cisplatin

< 6 Mo: other cytotox
TRIO 014: Study rational

- Progress could be done to improve therapeutic approaches for ovarian cancers.
- Expression of IGF-1R seems similar in ovarian tumors despite the heterogeneity of this cancer.
- Ligands for IGF-1R are mitogens involved in carcinogenesis of ovarian tumors.
- Preclinical *in vitro* and *in vivo* results demonstrate that AMG 479 interferes with the growth and survival of tumors.
- There is no significant overlap in the toxicity profiles of AMG 479 and paclitaxel and carboplatin.
- This drug combination allows to combine a cytostatic drug AMG 479 to a cytotoxic approach with paclitaxel and carboplatin.
- Preliminary phase I results show that AMG 479 is associated to a good safety profile and may have a clinical benefit in cancer patients.
TRIO 014: Study Design

Double-blinded, 160 patients (2x80)
Determine the value of adding AMG 479 to paclitaxel and carboplatin first line chemotherapy in patients with optimally debulked (<1 cm) FIGO stage III and IV (positive pleural cytology only) ovarian epithelial (including fallopian tube and primary peritoneal) carcinoma.
TRIO 014: study design

- Approx. 160 subjects
- Subjects are randomized 1:1 to receive
  - Paclitaxel + carboplatin + AMG 479 vs Paclitaxel + carboplatin + placebo
- Stratification factors
  - Stage of disease (III vs IV)
  - Histology (papillary serous vs non-serous)
- Safety interim analysis: through 1st cycle of the 12 first patients
- One interim analysis at 64 PFS events:
  - to provide a PFS estimate for each treatment arm
  - to provide an estimate of the hazard ratio with respect to PFS in this patient population to assist in the overall clinical development of AMG 479.
TRIO 014: Inclusion Criteria (1/3)

- Histologically-confirmed optimally debulked (< 1 cm) FIGO stage III or stage IV ovarian epithelial (including fallopian tube and primary peritoneal) carcinoma.
- Prior surgical debulking, with the aim of maximal surgical cytoreduction and optimally debulked (no residual tumor > 1 cm)
- Stage IV disease if a positive pleural cytology is the only extra peritoneal disease.
- Paraffin block (or 10 – 20 unstained slides) and fresh frozen surgical/biopsy specimens of the primary tumor required at baseline.
- No prior systemic treatment in the primary disease treatment setting.
- Female ≥ 18 years of age or legal age.
- ECOG performance status ≤ 2.
Adequate organ and bone marrow function as evidenced by:
- hemoglobin $\geq 9.0 \text{ g/dL}$,
- absolute neutrophil count $\geq 1.5 \times 10^9/L$,
- platelet count $\geq 100 \times 10^9/L$,
- serum creatinine $\leq 1.5 \times \text{ ULN}$ and measured or calculated creatinine clearance $\geq 60 \text{ mL/min}$
- AST and ALT $\leq 2.5 \times \text{ ULN}$
- total bilirubin $\leq 1.5 \times \text{ ULN}$ unless increase is due to Gilbert’s disease or similar syndrome involving slow conjugation of bilirubin

Non diabetic patients or Type 1 or 2 Diabetic Patients:
- Diabetes must be controlled with HgbA1c $< 8\%$ and fasting blood glucose level $< 160 \text{ mg/dL}$.
Patient must be willing and able to comply with all study procedures.

Informed consent obtained.

Patients should be able to commence systemic therapy within 6 weeks of cytoreductive surgery.

Life expectancy > 12 weeks.

Adequate coagulation parameters (within 14 days prior to randomization), International Normalized Ratio (INR) ≤1.5; Activated Prothrombin Time (APTT) ≤ 1.5 x ULN.
TRIO 014: Exclusion Criteria (1/3)

- Non-epithelial ovarian cancer, including malignant mixed Mullerian tumors
- Borderline tumors (tumors of low malignant potential).
- Planned intraperitoneal cytotoxic chemotherapy.
- Prior systemic anticancer therapy for ovarian cancer.
- Any previous radiotherapy to the abdomen or pelvis.
- Patients with synchronous primary endometrial carcinoma, or a past history of primary endometrial carcinoma, are excluded unless ALL of the following criteria for describing the endometrial carcinoma are met: Stage ≤ Ib, no more than superficial myometrial invasion, no lymphovascular invasion, not poorly differentiated (i.e., not Grade 3 or papillary serous or clear cell).
TRIO 014: Exclusion Criteria (2/3)

- Diagnosis of any second malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or in situ carcinoma of the cervix uteri.
- Prior treatment with a humanized monoclonal antibody anticancer therapeutic.
- Prior treatment with investigational treatment targeted to IGF axis including, but not limited to, CP 751,871, IM-A12, RO4858696.
- Previous exposure to AMG 479.
- Anticipation of a need for a major surgical procedure (e.g., impending bowel obstruction, gastrointestinal perforation) or radiation therapy during the study.
- History of hypersensitivity to recombinant proteins.
- Treatment with radiotherapy, surgery, or an investigational agent within 4 weeks of randomization.
TRIO 014: Exclusion Criteria (3/3)

- Any of the following within 6 months prior to study enrollment: myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, NYHA class III or IV congestive heart failure, cerebrovascular accident or transient ischemic attack, grade ≥ 2 peripheral neuropathy, pulmonary embolism, deep vein thrombosis, or other thromboembolic event.

- History of brain metastases, spinal cord compression, or carcinomatous meningitis.

- Patient of child-bearing potential is pregnant or is breast feeding.

- Patient of child-bearing potential is not willing to use adequate contraceptive precautions.

- Known active infection, or on antiretroviral therapy for HIV disease.

- Known positive test for chronic hepatitis B or C infection.

- Any other underlying physical or mental condition...

- Refusal or inability to give informed consent to participate in the study.

- Other severe acute or chronic medical or psychiatric condition, or significant laboratory abnormality requiring further investigation in the judgment of the investigator.
TRIO 014: main objectives

- This study will determine the value of adding AMG 479 to paclitaxel and carboplatin first line chemotherapy in patients with optimally debulked (<1 cm) FIGO stage III and IV (positive pleural cytology only) ovarian epithelial (including fallopian tube and primary peritoneal) carcinoma.

- **Primary Objective**
  - To estimate whether the addition of AMG 479 to paclitaxel and carboplatin chemotherapy improves progression free survival (PFS) when compared to paclitaxel and carboplatin chemotherapy alone.

- **Secondary Objectives**
  - To assess time to progression (TTP),
  - To assess overall survival (OS),
  - To assess the safety profile of AMG 479,
  - To assess health-related quality of life (HRQL),
  - To assess the pharmacokinetics (PK) of AMG 479 and paclitaxel/carboplatin,
  - To assess patients for the development of anti-AMG 479 antibodies.
TRIO 014: exploratory objectives

- To explore the relationship between PFS and levels of IGF-1, IGFBP3 and growth hormone (GH) in serum collected predose AMG 479,
- To explore the relationship between PFS and the expression of genes that encode signalling proteins in baseline tumor tissue and circulating tumor cells. These will include IGF-1R, INR, IGF-1, IGF-2, IRS-1, IGFBP1, PI3K, AKT and PTEN,
- To explore the potential effects of mutations in genes involved in signal transduction resulting from activation of the IGF-1R. These will include PTEN, PI3K, b-raf, K-ras, N-ras and H-ras.
Procedures: Screening

- Informed consent
- Medical history
- Physical exam
- ECG
- Hematology (WBC, ANC, platelets, hemoglobin)
- Fasting Blood Glucose and HbA1C
- Coagulation factors (PT, PTT, INR or aPTT)
- Blood chemistry (ALT, AST, total bilirubin and creatinine)
- Pregnancy test (If applicable)
- Quality of Life Questionnaire (FACT-O)
- Radiological Tumor Assessment
- Tumor sample: Paraffin block (or 10 – 20 unstained slides) AND Fresh frozen surgical/biopsy specimen
Procedures: Under Study

- Day 1 of each cycle (except *)
- Physical exam
- Hematology (WBC, ANC, platelets, hemoglobin )
- Fasting Blood Glucose and HbA1C *
- Coagulation factors (PT, PTT, INR or aPTT) *
- Blood chemistry (ALT, AST, total bilirubin and creatinine)
- Radiological Tumor Assessment * (every 12 weeks) – Images will be sent to a central reader
- CA 125
- Quality of Life (FACT-O) *

- Could continue AMG 479 until 12 cycles after premature permanent discontinuation of paclitaxel and carboplatin
## Blood sampling

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<th><strong>Mandatory</strong></th>
<th><strong>Sodium</strong></th>
<th><strong>Potassium</strong></th>
<th><strong>Catecholamines</strong></th>
<th><strong>Lipids</strong></th>
<th><strong>Proteins</strong></th>
<th><strong>Carbohydrates</strong></th>
<th><strong>Miscellaneous</strong></th>
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<tr>
<td>Anti-AMG 479 antibodies</td>
<td>Serum</td>
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<td>IGF-1, IGFBP3, GH</td>
<td>Serum</td>
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<td>AMG 479 Pharmacokinetics</td>
<td>Serum</td>
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### Intensive PK for paclitaxel and carboplatin (20 pts on selected sites)

- **PK sample for paclitaxel:**
  - Day 1, Cycle 4: Pre-dose, 1.5 hr post infusion, 5 min prior to the end of infusion, and then 0.1, 1, 6, 24 and 48 hours after the end of infusion
  - Day 1, Cycle 4: Pre-dose, 0.5 hr post infusion, 5 min prior to the end of infusion, and then 0.1, 1, 6, 24 and 48 hours after the end of infusion.

# Optional

- **Pharmacogenomics**
  - Whole Blood
  - Pre 1st Dose

- **Circulating Tumor Cells**
  - Whole Blood
  - Day 1 of cycles 1, and 2 (predose)
TRIO 014: EOS

- Physical exam
- Anti-AMG 479 antibodies
- AMG 479 PK
- Radiological Tumor Assessment
- CA 125
- Quality of Life (FACT-O)
TRIO 14: follow-up

- Tumor assessments and CA 125: every 12 (±1) weeks during study treatment up to 3 years after randomization.
- Follow-up visits: every 3 months from the end of study treatment visit for patients who have not progressed until 36 months of follow-up (from the date of randomization). PE and FACT-O
- After disease progression, F/U for survival status every 6 months for the first 5 years in the study and yearly thereafter to a maximum of 10 years.
TRIO 014

- 40 sites
- USA, Canada, Spain, France, Germany, Israel, Ireland?
- FPFV on early August
- Enrollment: 12 months
- Interim analysis: about 10 months after LPFV
Ongoing competitive trial

- ICON-7
- Phase III in patients with newly diagnosed ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer
- Double blinded: Paclitaxel + carboplatin +/- bevacizumab
- Similar target population
- Competitive in France, Germany, Canada, USA
Documents to retrieve from sites

During the PSSV or just after the PSSV

- Confidentiality Agreement signed and dated by PI (2 originals), one for both studies
- English current CVs of PI and Sub-Inv. duly dated and signed
- Study staff list including PI, Sub-Investigator, Study Nurse, Data Manager or Study Coordinator, Pharmacist, Radiologist and satellite sites if any (surname, first name, phone/fax numbers and email address)
- Financial contract contact
- FDA 1572 form
- Initial Financial Disclosure Form (PI and Sub-investigators)
- IRB/IEC member list (FWA number for US sites)
- GCP statement from IRB/IEC
- Laboratory accreditation / certification
- Payee Information Form