STUDY SYNOPSIS

Name of Sponsor/Company

TRIO (formerly CIRG)

Test Generic Name/Drug Name

AMG479 (Ganitumab)

Study Number

TRIO 015

Title

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 recurrent platinum-sensitive ovarian cancer

Investigator(s), study site(s)

The study was conducted over a total of 35 sites in 7 countries:

Canada: 4 sites
France: 5 sites
Germany: 3 sites
Ireland: 4 sites
Israel: 1 site
Spain: 3 sites
United States of America (USA): 15 sites

The recruitment was completed over 20 sites. A complete list of study investigators can be found in Appendix 13.1.4.

Publication (reference)

Ref Poster ASCO 2013

Studied period (Years) Phase of the Study II

21-JAN-2009 / 23-MAY-2013 (LPLV)

Objectives

Primary Objective

- To obtain an estimate of the objective response rate (ORR) as per Response Evaluation Criteria in Solid Tumors (RECIST) for subjects treated with AMG 479 with measurable disease and/or Gynecologic Cancer Intergroup (GCIG) CA 125 response criteria for subjects with non-measurable disease and history of a CA 125 recurrence in patients with recurrent platinum-sensitive ovarian epithelial (including fallopian tube and primary peritoneal) carcinoma failing frontline chemotherapy.

Secondary Objectives

- To assess clinical benefit response (CBR), progression free survival (PFS), time to tumor progression (TTP), time to tumor marker (CA 125) progression (TTMP), and overall survival (OS) in patients with recurrent platinum-sensitive ovarian epithelial (including fallopian tube and primary peritoneal) carcinoma failing frontline chemotherapy
- To evaluate the safety profile of single agent AMG 479
- To assess health-related quality of life (HRQL)
- To assess the pharmacokinetics (maximum plasma concentration [Cmax] and minimum plasma concentration [Cmin]) of AMG 479 and paclitaxel/carboplatin (Note: These results will be presented separately)
- To assess patients for the development of anti-AMG 479 antibodies including neutralizing antibodies (Note: These results will be presented separately)

Exploratory Objectives

- To explore the relationship between response and levels of IGF-1, IGFBP3 and growth hormone (GH) in plasma collected predose AMG 479,
- To explore the relationship between response and the expression of genes that encode signaling 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, and
- To explore the potential effects of mutations in genes involved in signal transduction resulting from activation of IGF-1R. These will include PTEN, PI3K, b-raf, K-ras, N-ras and H-ras.

Note: These results will be presented separately.

Study design

Multicenter open label phase II clinical trial of AMG 479 administered at 18 mg/kg intravenously (IV) every 3 weeks until disease progression.

Number of subjects planned/enrolled

60 patients planned / 61 patients enrolled

Indication

Second line therapy in patients with advanced platinum-sensitive ovarian epithelial (including fallopian tube and primary peritoneal) carcinoma.

Main Inclusion Criteria

Female ≥ 18 years of age, or legal age, with histologically-confirmed ovarian epithelial (including fallopian tube and primary peritoneal) carcinoma. Prior treatment with at most one treatment regimen in the primary treatment setting. Platinum-sensitive disease defined by recurrence or progression of disease > 6 months after completion of prior platinum based chemotherapy. Subjects with recurrence or progression > 24 months after completion of prior platinum-based chemotherapy were excluded. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. Non Diabetic Patients Type 1 or 2 given the potential impact of AMG479 on the insulin receptor pathway.

Adequate coagulation parameters (within 21 days prior to randomization), International Normalized Ratio (INR) ≤ 1.5, and prothrombin time (PT) or (activated) partial thromboplastin time (aPTT) ≤ 1.5 x upper limit of normal (ULN). Adequate organ and bone marrow function as evidenced by:

- hemoglobin ≥ 9.0 g/dL,
- absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L,
- platelet (PLT) count ≥ 100 x 10^9/L,
- Serum creatinine ≤ 1.5 x ULN or measured or calculated creatinine clearance ≥ 60 mL/min
- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
- total bilirubin ≤ 1.5 x ULN unless increase is due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin

Treatments

Patients received AMG 479 IV (lot numbers below) at the dose of 18 mg/kg, on Day 1 of each 21-day cycle.

Country	Lot #
Canada	1007708, 1020163, 1022709
USA	1007707, 1019659
Germany	1008281, 1012559, 1015277
France	1008281, 1012559, 1015277
Israel	1015277
Ireland	1008281, 1012559, 1015277, 1017928, 1025599

Duration of treatment

Patients continued to receive study treatment until one of the following occurred:

- Disease progression (defined per radiological tumor assessment using RECIST criteria and/or CA 125 progression fulfilling the GCIG criteria.),
- Unacceptable toxicity, or
- Withdrawal of consent, or
- Sponsor decision to stop the study.

Criteria for evaluation - Efficacy Parameter

The primary efficacy parameter was the ORR as per RECIST and/or GCIG CA 125. For secondary efficacy objectives of the study, CBR, PFS, TTP, TTMP, and overall survival OS were assessed. Both independent radiology and investigator measurements were assessed for all tumor-related parameters.

Disease progression was defined as per RECIST version 1.0 and/or CA 125 progression fulfilling the GCIG criteria agreed in November 2005.

Criteria for evaluation - Safety Parameter

Safety was assessed by physical exams, interim history and laboratory assessments. Adverse Events (AE's) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.

The period of observation for collection and reporting of adverse events/serious adverse events extends from the time the patient signs the informed consent form until 30 days after the last dose of any study treatment.

Serious adverse events (SAEs) were also collected and reported if they occurred

> 30 days after the last dose of any study treatment and were thought to be possibly related to study treatment/study procedure.

Criteria for evaluation – Quality of Life

To assess the quality of life, the patients completed FACT-O forms at baseline, at the onset of every cycle up to disease progression or up to 1 year after first dose (whatever occurred first), every 3 months after 1 year of treatment, until treatment discontinuation, at disease progression (i.e., at the End of Treatment [EOT] visit), and at the 36 month visit if patient was still alive.

Statistical methods

The sample size of 60 patients will allow for an evaluation of the safety of AMG 479 and provide estimates for the median PFS, TTP, TTMP as well as ORR, CBR, TMRR and OS in patients with recurrent platinum-sensitive ovarian cancer that receive AMG 479 as second-line therapy. The sample size of 60 subjects was chosen due to the fact that ovarian cancer is a heterogeneous group of diseases which includes multiple different histological types: clear cell carcinomas, mucinous adenocarcinomas, endometrioid adenocarcinomas, or papillary serous carcinomas. Thus, the sample size of 60 subjects is needed to identify signals of clinical activity among these differing histological subtypes.

Results – Study Subjects Characteristics

The end of the accrual was reached on 07-MAY-2010, with a total of 61 patients registered in the study at 20 sites. All the patients received at least one dose of AMG 479.

Fifty-nine patients discontinued the study treatment because of ovarian cancer progression. One patient withdrew consent from study participation after having received 2 cycles of AMG 479 with no dose modification. One patient discontinued the study treatment because of an AE (Grade 3 deafness).

A total of 271 cycles had been administered among the 61 patients, which corresponds to a mean of 4.4 cycles per patient or to a median of 3 cycles per patient.

The median age at study entry was 62 years of age (range: 35.3 to 83.8 years) and 50.8% of patients were between ages 50 to 65 years. In the majority of cases, the cancer, at initial diagnosis, was staged as stage IIIC (72%), with a histologic type papillary serous (69%) poorly differentiated (74%). The mean time between initial diagnosis of the ovarian cancer and the registration into the trial was of 20.4 months.

As per eligibility criteria all the patients received only one regimen of chemotherapy before study entry. All except two patients underwent at least one surgery for ovarian cancer prior to enrolment. The results of this initial surgical procedure was mainly a disease optimally debulked as only 18.3% of the patients had a status of residual disease ≥ 1 cm.

Results - Efficacy

The final analysis was performed with a total of 60 PFS events (corresponding to 58 progressions) reported by investigators, 53 PFS events (corresponding to 45 progressions) identified by Independent Radiology Committee (IRC). Tumor Marker progression was reported for 23 patients (37.8%) and death for 19 patients (31.1%).

In this study the best overall response according to RECIST (INV) and CA 125 was one CR (1.7%) and 13 SD (21.7%) with an ORR of 1.6% (95% CI: 0.0% to 8.8%). The best

overall response as based on RECIST as assessed by the independent reader and CA 125 showed no CR, one PR (1.8%), and 14 SD (25.5%) with an ORR of 1.6% (95% CI: 0.0% to 8.8%). These results did not approach the historical results noted for bevacizumab in a second-line ovarian cancer in a phase II setting (ORR between 15.9% and 21%; Burger, 2007; Cannistra, 2007).

One complete response was observed per the investigator but was not confirmed by the independent reader who considered this as a partial response. For the IRC only one patient has no lesion at baseline compared to five as per investigators, which may explain why the IRC reports more SD and less PD than investigators. When examining the best overall response on CA 125 alone, two CR were observed.

At 16 weeks, the clinical benefit rate according to RECIST (INV) and CA 125 was 1.7% (95% CI, 0.0% to 8.9%) and the CBR according to RECSIT (IRC) and CA 125 was 5.5% (95% CI, 1.1% to 15.1%). The highest clinical benefit rate reported was 11.9% (95% CI, 4.9% to 22.9%) and was recorded according to CA 125 at 16 weeks.

In this study, the median PFS based on investigator-assessed RECIST and CA 125 for the Intent-to-Treat (ITT) Population was 1.9 months (95% CI, 1.45 to 2.10 months) and the median PFS based on an independent-review using RECIST and CA 125 was 2.0 months (95% CI, 1.77 to 2.10 months). These results did not approach the historical results noted for single agent platinum-based chemotherapy in recurrent ovarian cancer (between 5.8 and 8.4 months; Pfisterer, 2006; González-Martín, 2005).

The median TTP based on the investigator assessment was 2.0 months (95% CI, 1.91 to 2.17 months) and the median TTP based on the IRC was 2.1 months (95% CI, 1.97 to 2.76 months).

The median TTMP was 5.0 months (95% CI, 2.76 to 12.81 months).

The median overall survival (based on 19/61 patients) in the ITT population was 21.0 months (95% CI, 19.45 to - months).

Results – Safety

All but one patient (60/61, 98.4%) reported one or more treatment-emergent AEs during this study. The most frequently reported AEs (>20% of patients; regardless of relationship) were: fatigue (34.4%), abdominal pain (31.1%), diarrhea (27.9%), nausea (26.2%), constipation (24.6%), and asthenia (24.6%). The majority of patients reported AEs that were mild (Grade 1) or moderate (Grade 2) in intensity. Grade 3 or Grade 4 AE PTs reported in more than one subject each included hypersensitivity, arthralgia, abdominal pain, asthenia, and headache.

Most patients (50/61, 82.0%) had at least one AE that was considered by the investigator as being related to study drug treatment. The most frequently reported related AEs (>10%) were: asthenia (23.0%), fatigue (21.3%), diarrhea (14.8%), nausea (14.8%), chills (11.5%), and headache (11.5%). Hypersensitivity and arthralgia were the only drug-related Grade 3 or Grade 4 AE PTs reported by more than one patient each.

One patient had an AE that led to treatment withdrawal during this study. Patient 220301 (a 75-year old female) had a SAE of Grade 3 deafness that began approximately 6 months after her first dose of AMG 479 and led to her withdrawal from the study

One fatal treatment-emergent AE was reported during this study. Patient 003902 had a fatal treatment-emergent AE of congestive cardiac failure that was considered by the investigator as being related to treatment with AMG 479.

Twelve SAEs were reported for nine patients (9/61, 14.8%). With the exception of intestinal obstruction in two patients, each SAE PT was reported in one patient each.

Most of these SAEs were Grade 3 or 4 in severity and most were not considered by the investigator as being related to treatment with AMG 479.

Although no other significant events were identified in the protocol, certain safety assessments were scheduled to monitor the important identified and potential risks related to AMG 479:

- No patients experienced AEs of thrombocytopenia, neutropenia, venous thromboembolic events, hyperglycemia, increased ALT, or increased AST during the study.
- Hearing loss (corresponding PT: deafness) was reported as a SAE for one patient (220301).
- Immunogenicity (corresponding PT: hypersensitivity) was reported for eight patients. None of these AEs was serious. All nine AEs of hypersensitivity were considered by the investigator as being related to treatment with AMG 479; all nine hypersensitivity AEs resolved during the study.
- Rash (PTs: rash, dermatitis, dermatitis allergic) was reported for eight patients. Rash was considered by the investigator as being related to treatment with AMG 479 in five of the eight patients; the rashes were all Grade 1 or Grade 2 in intensity and all resolved (or resolved with sequelae) during the study. One of these patients (087705) had a SAE with a PT of dermatitis.
- Infusion reaction (corresponding PT: infusion-related reaction) was reported for one patient (200315) during the study. This AE was Grade 2 in intensity and was not considered to be serious. The AE resolved within 1 day and was considered by the investigator as being related to treatment with AMG 479.

Hematologic abnormalities (i.e., anemia, thrombocytopenia, and neutropenia) were noted for several subjects during the study but in most cases did not result in clinically meaningful changes and were not reported as AEs.

No clinically meaningful changes were observed in vital signs, ECOG, or weight results during the study.

Results – Other data

Across the majority of FACT-O scores and sub-scores, results suggested that patient-reported quality of life was not negatively impacted by treatment with AMG 479.

Conclusions

- One complete response was observed per the investigator but was none by the independent reader who considered this case as a partial response. For the IRC only one patient had no lesion at baseline compared to 5 as per investigators. When examining the best overall response on CA 125 alone, two CR were observed.
- The highest clinical benefit rate according to CA 125 was noted at 16 weeks: 11.9% (95% CI, 4.9% to 22.9%).
- The median PFS based on investigator-assessed RECIST and CA 125 for the ITT population was 1.9 months (95% CI, 1.45 to 2.10 months) and the median PFS based on an independent-review using RECIST and CA 125 was 2.0 months (95% CI, 1.77 to 2.10 months). The last event for both assessments occurred at 11.14 months.
- Most patients had TTP events when assessed by the investigator (58/61, 95.1%; ITT population) and by the independent reviewer (45/61, 73.8%; ITT population). The median TTP based on the investigator assessment was 2.0 months (95% CI, 1.91 to 2.17 months) and the median TTP based on the IRC was 2.1 months (95% CI, 1.97 to 2.76 months).

- Tumor marker progression events were reported for less than half (23/61, 37.7%) patients in the ITT population. The median TTMP was 5.0 months (95% CI, 2.76 to 12.81 months).
- The median overall survival (based on 19/61 patients) in the ITT population was 21.0 months (95% CI, 19.45 to -- months).
- Across the majority of FACT-O scores and sub-scores, results suggested that patient-reported quality of life was not negatively impacted by treatment with AMG 479.
- Therapy with AMG 479 was well tolerated in this study.
- The most frequently reported AEs (>20% of patients; regardless of relationship) were: fatigue, abdominal pain, diarrhea, nausea, constipation, and asthenia.
- Twelve SAEs were reported for nine patients (9/61, 14.8%) and one patient had a fatal treatment-emergent AE during this study.
- No patients experienced AEs of thrombocytopenia, neutropenia, venous thromboembolic events, hyperglycemia, increased ALT, or increased AST during the study.
- Hematologic abnormalities (i.e., anemia, thrombocytopenia, and neutropenia) were noted for several subjects during the study but in most cases did not result in clinically meaningful changes and were not reported as AEs.
- No clinically meaningful changes were observed in vital sign, ECOG, or weight results during the study.