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Final results of a phase 3 study of trebananib plus weekly paclitaxel in recurrent ovarian cancer (TRINOVA-1): Long-term survival, impact of ascites, and progression-free survival-2☆,☆☆,☆☆☆

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HIGHLIGHTS

- Trebananib did not improve overall survival in the intent-to-treat population.
- Trebananib improved overall survival in patients with baseline ascites.
- Trebananib prolonged time to second disease progression.

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ABSTRACT

Purpose. Trebananib, a peptibody that blocks binding of angiopoietin-1 and -2 to Tie2, significantly prolonged progression-free survival (PFS) in patients with recurrent epithelial ovarian cancer in the phase 3 TRINOVA-1 study. We report overall survival (OS) in the intent-to-treat population and clinically relevant subgroups and time to second disease progression (PFS-2).

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Patients and methods. Women with recurrent disease (platinum-free interval < 12 months) were randomized to receive intravenous paclitaxel 80 mg/m^2 (3 weeks on/1 week off) plus intravenous trebananib 15 mg/kg or placebo, weekly. OS in the intent-to-treat population was a key secondary endpoint. Exploratory analysis of PFS-2 was conducted according to guidance by the European Medicines Agency.

Results. Median OS was not significantly improved with trebananib compared with placebo (19.3 versus 18.3 months; HR, 0.95; 95% CI, 0.81–1.11; $P = 0.52$) in the intent-to-treat population (n = 919). In subgroup analysis, trebananib improved median OS compared with placebo (14.5 versus 12.3 months; HR, 0.72; 95% CI, 0.55–0.93; $P = 0.011$) in patients with ascites at baseline (n = 295). In the intent-to-treat population, trebananib significantly improved median PFS-2 compared with placebo (12.5 versus 10.9 months; HR, 0.85; 95% CI, 0.74–0.98; $P = 0.024$). The incidence and type of adverse events in this updated analysis was consistent with that described in the primary analysis; no new safety signals were detected.

Conclusions. OS was not significantly longer in the intent-to-treat population, although there was an improvement in OS in patients with ascites receiving trebananib. PFS-2 confirmed that the PFS benefit associated with trebananib was maintained through the second disease progression independent of the choice of subsequent therapy.

1. Introduction

First-line treatment with a platinum/taxane combination therapy is effective in the treatment of ovarian cancer, but recurrence/relapse is frequent and outcomes are poor, particularly for those patients with a platinum-free interval < 12 months [1]. In addition to poor overall survival (OS), ovarian cancer is often associated with debilitating symptoms. More than one third of patients diagnosed with the disease have malignant ascites, which can result in abdominal pain, dyspnea, nausea, vomiting, and anorexia [2,3]. Presence of ascites plays a major role in progression of ovarian cancer and is associated with poor prognosis [2,3].

The tumor microenvironment and, specifically, tumor angiogenesis, is involved in ovarian cancer development, progression, and metastasis [4]. Angiogenesis is controlled by growth factors, including the vascular endothelial growth factor (VEGF) pathway and angiopoietin-Tie2 receptor axis. The angiopoietin axis is distinct from the VEGF pathway; angiopoietin 1 (Ang1) and angiopoietin 2 (Ang2) regulate angiogenesis and vascular remodeling by interacting with the endothelial receptor tyrosine kinase, Tie2 [5]. Evidence suggests that the Ang2 pathway plays a role in the pathophysiology of ovarian cancer [6–8] and upregulation of Ang2 is correlated with poor prognosis in women with recurrent ovarian cancer [9]. Several antiangiogenic agents that target the VEGF pathway have been shown to improve progression-free survival (PFS) in patients with ovarian cancer; however, a statistically significant improvement in OS has not been demonstrated [10–18].

Trebananib (AMG 386) is a peptide-Fc fusion protein that binds Ang1 and Ang2, thus preventing their ligand-receptor interaction with Tie2 [19]. In a randomized, placebo-controlled, double-blind, phase 3 study (TRINOVA-1), women with recurrent ovarian cancer receiving paclitaxel plus trebananib 15 mg/kg once weekly (QW) had significantly prolonged PFS (primary endpoint) compared with patients who received paclitaxel plus placebo (7.2 versus 5.4 months; hazard ratio [HR], 0.66; 95% CI, 0.57–0.77; $P < 0.0001$) [20] without impairment of quality of life [21]. We report the mature analysis of OS in this study. Additionally, we provide results from a subgroup analysis that evaluated outcomes in patients with/without ascites and an exploratory analysis of time to second disease progression (PFS-2).

2. Methods

2.1. Patients

Eligibility criteria for TRINOVA-1 have been reported previously [20]. Briefly, women (≥18 years) were eligible if they had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [22]; as a result, patients with only ascites or pleural effusion at baseline were excluded from the study. Women were eligible if they had ≤3 prior lines of anticancer therapy, Gynecologic Oncology Group (GOG) performance status ≤1, and platinum-free interval ≤ 12 months. Women with primary platinum-refractory disease (disease progression during the first 6 cycles or within 6 months after the beginning of primary platinum-based treatment) were excluded. The protocol was approved by each center's independent ethics committee. Patients provided written informed consent.

2.2. Study design and treatment

This randomized, double-blind, phase 3 study was conducted at 179 centers globally. Patients were randomly assigned in a 1:1 ratio to receive intravenous paclitaxel 80 mg/m^2 once weekly (3 weeks on/1 week off) plus either intravenous trebananib 15 mg/kg or intravenous placebo once weekly. Randomization was stratified based on platinum-free interval (≤6 months versus >6 to 12 months), presence/absence of measurable disease per RECIST, and geographic region (North America, Western Europe/Australia, rest of world). Study treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or death. Dose modifications for paclitaxel were based on attributed toxic effects and allowed for a reduction in dose of 15 mg/m^2 per level. Dose reductions for trebananib and placebo were not permitted.

2.3. Assessments

Disease was assessed with computed tomography/magnetic resonance imaging of at least the chest, abdomen, and pelvis before cycle 1 and every 8 ± 1 weeks for up to 2 years from time of randomization and then every 6 ± 1 months thereafter until disease progression. Imaging was evaluated by the investigator per RECIST version 1.1. The presence or absence of ascites at baseline (i.e., within 28 days before randomization) was determined by the investigator at study randomization and recorded using the electronic case report form. Adverse events (AEs) occurring from start of treatment until the safety follow-up visit (30–37 days after last dose) were recorded and graded using the Common Terminology Criteria for Adverse Events, version 3.0 [23]. Health-related quality of life (HRQoL) was evaluated using Functional Assessment of Cancer Therapy–Ovary (FACT-O) and EQ-5D instruments [24,25].

2.4. Statistical analyses

As previously described [20], the planned population size of 900 patients (followed up until at least 510 patients had disease progression or died) was estimated to provide 90% statistical power to detect a 33%