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Original Research

ENGOT-ov-6/TRINOVA-2: Randomised, double-blind, phase 3 study of pegylated liposomal doxorubicin plus trebananib or placebo in women with recurrent partially platinum-sensitive or resistant ovarian cancer

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Abstract ***Aims:*** Trebananib, a peptide-Fc fusion protein, inhibits angiogenesis by inhibiting binding of angiopoietin-1/2 to the receptor tyrosine kinase Tie2. This randomised, double-blind, placebo-controlled phase 3 study evaluated whether trebananib plus pegylated liposomal doxorubicin (PLD) improved progression-free survival (PFS) in patients with recurrent epithelial ovarian cancer.
Methods: Women with recurrent ovarian cancer (platinum-free interval ≤12 months) were randomised to intravenous PLD 50 mg/m^2 once every 4 weeks plus weekly intravenous trebananib 15 mg/kg or placebo. PFS was the primary end-point; key secondary end-points were objective response rate (ORR) and duration of response (DOR). Owing to PLD shortages, enrolment was paused for 13 months; the study was subsequently truncated.
Results: Two hundred twenty-three patients were enrolled. Median PFS was 7.6 months (95% CI, 7.2–9.0) in the trebananib arm and 7.2 months (95% CI, 4.8–8.2) in the placebo arm, with a hazard ratio of 0.92 (95% CI, 0.68–1.24). However, because the proportional hazards assumption was not fulfilled, the standard Cox model did not provide a reliable estimate of the hazard ratio. ORR in the trebananib arm was 46% versus 21% in the placebo arm (odds ratio, 3.43; 95% CI, 1.78–6.64). Median DOR was improved (trebananib, 7.4 months [95% CI, 5.7–7.6]; placebo, 3.9 months [95% CI, 2.3–6.5]). Adverse events with a greater incidence in the trebananib arm included localised oedema (61% versus 32%), ascites (29% versus 9%) and vomiting (45% versus 33%).
Conclusions: Trebananib demonstrated anticancer activity in this phase 3 study, indicated by improved ORR and DOR. Median PFS was not improved. No new safety signals were identified.
Trial registration: ClinicalTrials.gov, NCT01281254

1. Introduction

First-line platinum/taxane therapy is effective in the treatment of ovarian cancer [1]. However, the risk of recurrence is high, and outcomes for these patients are poor [2,3]. For patients with recurrence following first-line platinum-based therapy, pegylated liposomal doxorubicin (PLD) represents an effective non-platinum second-line therapy [4–8]. All patients will experience disease progression, underscoring the need to improve outcomes.

Angiogenesis is a multifactorial process that plays a key role in tumour growth, development and metastasis [2]. Two distinct pathways are important regulators of angiogenesis: the vascular endothelial growth factor (VEGF) pathway and the angiopoietin-Tie2 receptor axis [9–11]. Agents targeting the VEGF pathway have been shown to improve progression-free survival (PFS) in patients with ovarian cancer but have not been shown to prolong overall survival (OS) [12–20]. Preclinical studies support the angiopoietin pathway as an important target in ovarian cancer [11]. Angiopoietin-1 and angiopoietin-2 regulate angiogenesis and vascular remodelling both in normal ovarian physiology and in tumours [11].

Trebananib (AMG 386) is a peptide-Fc fusion protein that binds angiopoietin-1 and angiopoietin-2, preventing their interaction with the Tie2 receptor [21,22]. In a phase 1b study, trebananib plus either PLD or topotecan was tolerable in patients with recurrent ovarian cancer, with evidence of antitumour activity [23]. Trebananib combined with weekly paclitaxel has shown antitumour activity in women with recurrent