Randomized, phase II, placebo-controlled trial of onartuzumab and/or bevacizumab in combination with weekly paclitaxel in patients with metastatic triple-negative breast cancer


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Background: Increased hepatocyte growth factor/MET signaling is associated with an aggressive phenotype and poor prognosis in triple-negative breast cancer (TNBC). We evaluated the benefit of adding onartuzumab, a monoclonal anti-MET antibody, to paclitaxel with/without bevacizumab in patients with TNBC.

Patients and methods: Women with metastatic TNBC were randomized to receive onartuzumab plus placebo plus weekly paclitaxel (OP; n = 60) or onartuzumab plus bevacizumab plus paclitaxel (OBP; n = 63) or placebo plus bevacizumab plus paclitaxel (BP; n = 62). The primary end point was progression-free survival (PFS); additional end points included overall survival (OS), objective response rate (ORR), and safety. This trial was hypothesis generating and did not have power to detect minimum clinically meaningful differences between treatment arms.

Results: There was no improvement in PFS with the addition of onartuzumab to BP [hazard ratio (HR), 1.08; 95% confidence interval (CI) 0.69–1.70]; the risk of a PFS event was higher with OP than with BP [HR, 1.74; 95% CI 1.13–2.68]. Most patients had MET-negative tumors (88%); PAM50 subtype analysis showed basal-like tumors in 68% of samples. ORR was higher in the bevacizumab arms (OBP: 42.2%; 95% CI 28.6–57.1; BP: 54.7%; 95% CI 41.0–68.4) compared with OP (27.5%; 95% CI 15.9–40.6). The primary end point was progression-free survival (PFS); additional end points included overall survival (OS), objective response rate (ORR), and safety. This trial was hypothesis generating and did not have power to detect minimum clinically meaningful differences between treatment arms.

Conclusion: This study did not show a clinical benefit of the addition of onartuzumab to paclitaxel with/without bevacizumab in patients with predominantly MET-negative TNBC.

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Key words: bevacizumab, MET, triple-negative breast cancer, onartuzumab, paclitaxel, phase II

introduction

Triple-negative breast cancers (TNBCs) are associated with an aggressive clinical course and poorer outcome than other breast cancers [1, 2]. TNBC remains a significant challenge to treat; chemotherapy is effective in some cases, with pathologic complete response (pCR) rates of around 50% reported [3, 4]. However, TNBCs have a worse outcome overall, particularly if pCR is not achieved [1, 5]. The addition of bevacizumab to chemotherapy in patients with metastatic TNBC significantly increased objective response rate (ORR) and progression-free survival (PFS) versus chemotherapy alone, but the lack of an overall survival (OS) benefit led to controversy about the therapeutic indication [6].

MET signaling plays a vital role in tissue remodeling and its dysregulation has been implicated in many tumors, affecting cell proliferation, invasion, metastasis, and survival [7]. The MET pathway is frequently activated in TNBCs and/or basal-like tumors [8–12].

Onartuzumab (MetMab; Genentech, South San Francisco, CA) is a recombinant, humanized, monovalent, anti-MET monoclonal
antibody, which selectively blocks ligand binding and hepatocyte growth factor (HGF)-dependent signaling [13]. Because the HGF/MET pathway has been implicated in the upregulation of vascular endothelial growth factor (VEGF) expression, dual MET and VEGF inhibition may provide an improved clinical benefit. This phase II study evaluated the efficacy and safety of onartuzumab plus bevacizumab plus paclitaxel (OBP), and onartuzumab plus placebo plus paclitaxel (OP), relative to placebo plus bevacizumab plus paclitaxel (BP) in patients with TNBC.

methods

study design

OAM4861g was a randomized, double-blind, placebo-controlled study in patients with metastatic or locally recurrent (LR) TNBC. Treatment comprised 28-day cycles of paclitaxel (90 mg/m² days 1, 8, and 15), with onartuzumab (10 mg/kg days 1 and 15) or placebo, and bevacizumab (10 mg/kg days 1 and 15) or placebo until disease progression (PD), unacceptable toxicity, or death. No onartuzumab/bevacizumab dose reductions were permitted; paclitaxel dose modifications were allowed per standard practice. Patients who discontinued paclitaxel for toxicity could continue onartuzumab/placebo and bevacizumab/placebo.

Patients were randomized to treatment (1:1:1) using an interactive voice/web-based system stratified according to the number of metastatic sites (<3 versus ≥3), line of therapy (first versus second), and disease-free interval for first-line patients (≤6 versus >6 months).

The protocol was approved by the institutional review board of each participating center and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Patients provided written informed consent.

patients

Eligibility criteria were ≥18 years; histologically confirmed TNBC; ≤1 prior therapy for metastatic TNBC; measurable/non-measurable metastatic/LR disease not amenable to resection with curative intent; Eastern Cooperative Oncology Group performance status ≤1; consent to providing tumor tissue; and adequate hematologic, renal, and liver function. Exclusion criteria were systemic anticancer therapy within 3 weeks before day 1, cycle 1; previous taxanes for metastatic breast cancer; prior antiangiogenic or anti-MET/anti-HGF therapy; prior endocrine or human epidermal growth factor receptor 2-directed therapy; or untreated central nervous system metastases.

assessments

Computed tomography scans were obtained at baseline and every two cycles. Disease status per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was assessed by investigators.

Onartuzumab and bevacizumab serum samples were assessed centrally using validated enzyme-linked immunosorbent assays. Paclitaxel/6-OH-paclitaxel plasma samples were analyzed centrally using a validated liquid chromatography tandem mass spectrometry method.

Tumor tissue (archival permitted) was collected for confirmation of TNBC and evaluation of MET expression. MET immunohistochemistry (IHC) was carried out centrally with the CONFIRM SP44 anti-MET rabbit monoclonal primary antibody (Ventana Medical Systems, Inc., Tucson, AZ) on a Ventana Benchmark XT platform. Staining intensity was evaluated using an IHC scoring system [14]. MET positivity was defined as a score of...
2+/3+ based on the 50% cutoff developed for non-small-cell lung cancer (NSCLC) [15]. The MET status was determined centrally after randomization and before unblinding, IHC for epidermal growth factor receptor (EGFR), cytokeratin 5, and phosphatase and tensin homolog (PTEN) was carried out on a Ventana autostainer using antibodies 3G6 (Ventana), AF 138 (Covance Biologics, Princeton, NJ), and 138G6 (Cell Signaling Technology, Beverly, MA), with CCI retrieval conditions. Cases were scored using an H-score algorithm [16].

Formalin-fixed, paraffin-embedded (FFPE) sections were macrodissected to enrich for neoplastic tissue followed by RNA extraction [17] using the high-pure FFPE RNA Micro Kit (Roche Applied Sciences, Indianapolis, IN). NanoString gene expression data were collected using a custom 400-gene breast cancer panel for PAM50 analysis [18].

### statistical analysis

The primary end point was investigator-assessed PFS, defined as the time from randomization to PD/relapse (RECIST v1.1), or death on study from any cause, whichever occurred first. OS was defined as the time from randomization to death from any cause. Median PFS/OS were estimated by the Kaplan–Meier methodology. For each pairwise comparison of the OBP or OP arm versus the BP arm, an estimate of the hazard ratio (HR) and 95% confidence interval (CI) was determined using a Cox regression model stratified by the randomization stratification factors. Log-rank test (stratified) was used to compare survival between the arms. ORR was defined as the proportion of patients with a complete or partial response on two consecutive assessments ≥4 weeks apart (RECIST v1.1); 95% CI were computed using the Blyth-Still-Casella method. Adverse events (AEs) were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (v 4.0). Onartuzumab concentrations were compared with simulated results based on a population pharmacokinetic (PK) model [19]. Bevacizumab concentrations were compared with predictions from a bevacizumab PK model [20].

The study was designed to accrue ~180 patients. Efficacy analyses were planned after 126 investigator-assessed PFS events. This trial was hypothesis generating and did not have power to detect minimum clinically meaningful differences between treatment arms. Based on 84 PFS events for the comparison of each onartuzumab-containing arm versus the BP arm, the study had 80% power to detect, at a one-sided significance level of 0.025, an HR of 0.54 for each onartuzumab-containing arm relative to the BP arm. No adjustments for multiple comparisons were made.

### results

#### patient demographics

From March 2011 to March 2013, 185 patients were randomized to receive OBP (n = 63), OP (n = 60), or BP (n = 62) (Figure 1). Baseline demographics were balanced across the arms (Table 1). The MET status was determined in 178 patients (96%), of whom 22 (12%) had MET-positive tumors (IHC 2+/3+).

#### efficacy

As of 22 March 2013, 133 patients (71.9%) had experienced a PFS event and 17 were receiving treatment (six OBP, two OP, nine BP). Median PFS was 7.3 months with OBP, 5.4 months with OP, and 7.2 months with BP (Table 2). Compared with BP, the risk of a PFS event was higher with OP (stratified HR, 1.74; 95% CI 1.13–2.68; P = 0.011) and similar with OBP (stratified HR, 1.08; 95% CI 0.69–1.70; P = 0.730) (Figure 2A; Table 2).

Objective response was evaluated in 149 patients with measurable disease at baseline. ORR was 42.2% (95% CI 28.6–57.1) with OBP, 27.5% (95% CI 15.9–40.6) with OP, and 54.7% (95% CI 41.0–68.4) with BP (Table 2).

At the data cutoff date, 76 deaths (41.1%) were recorded: 27 with OBP, 26 with OP, and 23 with BP. Median OS was 14.7 months, 13.4 months, and 17.4 months, respectively (Table 2). OS was numerically shorter with OBP (stratified HR, 1.36; 95% CI 0.75–2.46; P = 0.316) and OP (stratified HR, 1.92; 95% CI 1.03–3.59; P = 0.038), than with BP (Table 2; Figure 2B).

#### exploratory end points

Exploratory analyses examined the effect of baseline characteristics on PFS (supplementary Figure S1, available at Annals of Oncology).
Oncology online) and OS. Results were similar across most subgroups. Analysis of the impact of MET IHC was limited by the low number of patients with MET-positive tumors (one IHC 3+, 21 IHC 2+).

PAM50 analysis identified 68% of the 165 TNBC samples as basal like. Median PFS in this subgroup was 6.4 months with OBP, 4.4 months with OP, and 6.2 months with BP (supplementary Figure S2, available at Annals of Oncology online).

Compared with BP, the risk of a PFS event was higher with OP (stratified HR, 1.61; 95% CI 0.89−2.90) and similar with OBP (stratified HR, 1.05; 95% CI 0.54−2.04). Median OS was 14.7 months with OBP, 10.8 months with OP, and 14.6 months with BP. Compared with BP, the risk of an OS event was higher with OP (stratified HR, 1.72; 95% CI 0.77−3.81) and similar with OBP (stratified HR, 1.07; 95% CI 0.45−2.53), but these differences were not statistically significant. Basal-like tumors showed high EGFR and low PTEN expression (supplementary Figure S3, available at Annals of Oncology online).

pharmacokinetics

Mean serum onartuzumab concentrations were similar in the two onartuzumab-containing arms (supplementary Table S1, available at Annals of Oncology online), and were consistent with simulated data (90% CI 154–583 µg/ml steady-state peak; 26.1–149 µg/ml steady-state trough). Observed bevacizumab serum concentrations were similar in the two bevacizumab-containing arms; at steady-state, most fell within the 90% CI of the predicted concentration−time profile. Plasma paclitaxel/6-OH−paclitaxel concentrations were similar among treatment arms (not shown).

safety

Median dose intensity was 100% for onartuzumab and bevacizumab. Median paclitaxel dose intensity was 97.8%, 97.2%, and 93.5% in the BP, OP, and OBP arms, respectively.

Most common AEs in the onartuzumab-containing arms were peripheral edema, alopecia, and fatigue (Table 3). Peripheral edema was reported by 58.1% and 58.6% of OBP and OP patients, versus 17.7% of BP patients. Alopecia, epistaxis, and diarrhea were the most frequent AEs in the bevacizumab-containing arms.

Patients receiving OBP were most likely to have an AE leading to treatment withdrawal; most often peripheral edema that led to onartuzumab withdrawal (five patients; 8.1%). Serious AEs occurred in more patients receiving OBP than OP or BP (32% versus 22% versus 24%), as did Grade 3−5 AEs (71% versus 50% versus 61%) (Table 3). Five AEs resulted in death, three (4.8%) with OBP (sepsis, dural fistula, and

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aDisease progression, relapse, or death.
bBased on 149 randomized patients with measurable disease at baseline.
BP, placebo plus bevacizumab plus paclitaxel; CR, complete response; HR, hazard ratio; NE, not estimable; OBP, onartuzumab plus bevacizumab plus paclitaxel; OP, onartuzumab plus placebo plus paclitaxel; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.
Of the known AEs associated with bevacizumab, gastrointestinal perforation occurred in two patients (3.2%) receiving OBP, and venous thromboembolic events were reported in eight patients (12.9%) receiving OBP or BP, and in three patients (5.2%) receiving OP. Most common thromboembolic events were pulmonary embolism (11 patients; 6.0%) or deep vein thrombosis (six patients; 3.3%).

**Discussion**

The addition of onartuzumab to BP or to paclitaxel did not improve PFS, OS, or ORR compared with BP in advanced TNBC. Patients in the bevacizumab arms experienced increased ORR and PFS versus the OP arm, in keeping with previous trial results, although bevacizumab is not standard of care for TNBC in many countries. Analyses by patient baseline characteristics revealed similar results across most subgroups.

Analyses according to MET IHC score were inconclusive owing to the low proportion of patients with MET-positive tumors. Comparison of outcomes in the OBP and BP arms suggested no negative impact of onartuzumab in patients with MET-negative disease. The question of a positive treatment effect in patients with MET-positive tumors could not be answered and was not explained by dose intensity, PK, safety, or AE findings. An NSCLC trial of onartuzumab plus erlotinib also demonstrated a benefit for patients with MET-positive tumors but potentially worse outcome in MET-negative disease, which was not explained by patterns of PD, PK, or safety [15]. There are a number of hypotheses for the potentially deleterious effect of onartuzumab in MET-negative tumors. It is conceivable that alternative pathways of MET activation exist such that MET might act as a tumor suppressor in MET-negative disease and as an oncogene in MET-positive disease.

**Figure 2.** Kaplan–Meier curves of (A) PFS and (B) OS in the randomized population. BP, placebo plus bevacizumab plus paclitaxel; OBP, onartuzumab plus bevacizumab plus paclitaxel; OP, onartuzumab plus placebo plus paclitaxel.
In conclusion, the addition of onartuzumab to BP or to paclitaxel did not improve PFS, OS, or ORR compared with BP in patients with advanced TNBC and predominantly MET-negative tumors.

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**disclosure**

HK, TRW, YX, DSS, SM, and MC are employees of Roche/Genentech. HK, TRW, YX, and DSS are shareholders of Roche/Genentech. VD has received honoraria from Roche/Genentech. MC has received honoraria from Novartis, Servier, Menari, and Roche, and research funding from Novartis. DAY has received honoraria from Genentech. VV has received honoraria and research funding from Roche/Genentech. GR has received honoraria from Roche. PS has received research funding from AstraZeneca, Novartis, Genentech, Oncogenex, and Astellas. All remaining authors have declared no conflicts of interest.

**references**

Derived neutrophil lymphocyte ratio may predict benefit from cisplatin in the advanced biliary cancer: the ABC-02 and BT-22 studies

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Background: The superiority of cisplatin and gemcitabine (CisGem) chemotherapy over gemcitabine (Gem) alone in patients with advanced biliary tract cancer (ABC) has been demonstrated in two randomised trials; ABC02 and the Biliary Tract (BT) 22 study. We used a combined dataset from these two trials to investigate the derived neutrophil-to-lymphocyte ratio (dNLR), which is thought to be a prognostic factor associated with clinical outcomes in several solid tumours, including ABC.

Methods: White blood cell (WBC) and absolute neutrophil count (ANC) were available for 379 of 410 patients from ABC-02 and all 83 patients in BT-22. The dNLR was calculated as ANC/(WBC-ANC), as previously specified. We examined the association between dNLR and overall survival (OS) and progression-free survival (PFS), as well as comparing the treatment effect in two patient groups defined by their dNLR level. A high dNLR was defined as ≥3.0, which was approximately the upper tertile value.

Results: A total of 462 individual patient records were analysed, 328 with baseline dNLR <3 and 134 with dNLR ≥3. There were 443 deaths in the cohort, and all surviving patients had a dNLR <3. There was strong evidence that dNLR was closely associated with both OS (hazard ratio (HR), 1.62; 95% confidence interval (CI) 1.32–2.01) and PFS (HR, 1.40; 95% CI 1.13–1.72). There was limited evidence (P = 0.10) of a differential effect of CisGem on OS between the two dNLR groups, but this was clearest in the ABC-02 dataset (P = 0.06). There was good evidence (P = 0.008) of an association between low baseline dNLR and long-term survival on a CisGem regimen. There was also good evidence of an association between ECOG performance status (split at 0 and 1 versus 2) on both OS (P < 0.001) and PFS (P = 0.01), but there was no evidence of a differential treatment effect, with both groups receiving benefit from the addition of cisplatin.

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