Poster discussion presentations
(Wed, 23 Sep, 17:00–18:00)

Breast cancer

5016 POSTER DISCUSSION

Efficacy in patient subgroups in RIBBON-1, a randomized, double-blind, Phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC)

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Background: In 2 prior Phase III trials (E2100 and AVADO), B in combination with taxanes (T) as first-line therapy for MBC improved progression-free survival (PFS) compared with T alone. In RIBBON-1, the addition of B to standard first-line chemotherapy regimens also improved PFS in MBC patients (pts).
Methods: Pts were randomized 2:1 to B+chemotherapy vs. placebo (pl)+chemotherapy. Prior to randomization, investigators chose capecitabine (Cap) (2000 mg/m^2 x 14 d), taxane (nab-paclitaxel 260 mg/m^2, or docetaxel (D) 75 or 100 mg/m^2), or anthracycline (Ant) (doxorubicin [A] or epirubicin [E] combinations-AC, EC, FAC, FEC)-based chemotherapy given q3 wk. B or pl was administered at 15 mg/kg q3 wk.
Key eligibility criteria: MBC or locally recurrent disease, no prior cytotoxic treatment for MBC, ECOG PS 0–1, HER2-negative disease, no CNS mets. The 1º endpoint was investigator-assessed PFS. The Cap cohort and pooled T or Ant (T+Ant) cohorts were independently powered and analyzed using 2-sided stratified log-rank test (Cap: 80% power to detect HR = 0.75; T+Ant: 90% power to detect HR = 0.7).
Results: 1237 pts (Cap = 615; T = 307; Ant = 315) were enrolled. Addition of B improved PFS (Cap: pl 5.7 mo, B 8.6 mo, p = 0.0002; T+Ant: pl 8.0 mo, B 9.2 mo, p < 0.0001). In prespecified subgroups, HRs favored B arms of the respective chemotherapies.

	Cap n = 615	T+Ant n = 622
All patients	0.67 (0.55, 0.82)	0.66 (0.54, 0.81)
Age, yr		
<65	0.67 (0.53–0.84)	0.63 (0.50–0.78)
⩾65	0.69 (0.47–1.02)	0.83 (0.52–1.34)
Triple negative		
Yes	0.72 (0.49–1.06)	0.78 (0.53–1.15)
No	0.68 (0.54–0.86)	0.61 (0.48–0.77)
No. of metastatic sites		
<3	0.63 (0.49–0.83)	0.65 (0.49–0.86)
⩾3	0.74 (0.55–0.98)	0.64 (0.48–0.85)
Bone-only disease		
Yes	0.47 (0.26–0.87)	0.39 (0.18–0.88)
No	0.70 (0.57–0.86)	0.72 (0.59–0.89)
Visceral involvement		
Yes	0.72 (0.57–0.90)	0.68 (0.54–0.86)
No	0.58 (0.40–0.83)	0.63 (0.42–0.94)
Disease-free interval		
<12 mo	0.81 (0.54–1.21)	0.62 (0.45–0.85)
⩾12 mo	0.63 (0.51–0.79)	0.69 (0.53–0.89)
Prior adjuvant chemotherapy		
Yes	0.64 (0.51–0.80)	0.67 (0.50–0.90)
No	0.80 (0.54–1.18)	0.64 (0.49–0.85)
Prior adjuvant taxane		
Yes	0.62 (0.45–0.84)	0.65 (0.39–1.07)
No	0.72 (0.56–0.92)	0.66 (0.53–0.83)

Conclusions: The overall treatment effect of combining B with capecitabine, taxanes, or anthracyclines in RIBBON-1 is seen across the prespecified clinically relevant subgroups. These results are consistent with the findings of E2100 and AVADO and suggest that B with standard chemotherapies provides benefit to HER2-negative MBC pts with differing clinical characteristics and disease history.

5017 POSTER DISCUSSION

Multinational study (n = 2041) of first-line bevacizumab (Bev) plus taxane-based chemotherapy (CT) for locally recurrent or metastatic breast cancer (LR/mBC): updated results of MO19391

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Background: Three randomised phase III trials (E2100, AVADO, RIBBON-1) have shown that Bev combined with first-line CT significantly improves PFS versus CT alone. The open-label, multicentre MO19391 trial further assessed safety and efficacy of first-line Bev combined with taxane-based therapy in a broader patient (pt) population, representative of general oncology practice.
Materials and Methods: Eligible pts had HER2-negative LR/mBC (or trastuzumab-pretreated HER2-positive LR/mBC), ECOG PS 0–2, no prior CT for LR/mBC and no evidence of CNS metastases. Pts received Bev 10 mg/kg q2w or 15 mg/kg q3w combined with a taxane (alone or with another CT) or non-anthracycline CT according to the physician's decision, until disease progression, unacceptable toxicity or withdrawal. The primary endpoint was safety (CTCAE v3.0); secondary endpoints included TTP and OS.
Results: Between Sept 2006 and data cut-off for this analysis (March 2009), 2041 pts were treated. Median age was 54 years (range 21–93). Most pts (76%) received taxane-based therapy with Bev, predominantly paclitaxel or docetaxel monotherapy. Mean duration of therapy was 7.0±4.7 months for Bev and 4.7±3.1 months for CT. Grade (G) 3–5 adverse events (AEs) occurring at any G in >15% of pts (related or unrelated to Bev) are shown below. The incidences of ⩾G3 predefined Bev-related AEs of special interest were: DVT in 0.3% (all G3); thrombosis in <0.1% (G3); GI perforation in 0.2% (<0.1% G3, <0.1% G4, 0.1% G5); CHF in 0.1% (G3); impaired healing in 0.2% (0.1% G3, 0.1% G4); cerebral haemorrhage in <0.1% (G5), pulmonary embolism in 0.4% (0.1% G3, 0.2% G4, <0.1% G5); hypertension in 3.0% (3.0% G3, <0.1% G4). Median TTP is 9.5 months (95% CI: 9.1–10.0). OS data are still immature (78% of pts alive at data cut-off).

	AE (%)		
	G3	G4	G5
Pts with ⩾1 AE	48.4	15.4	3.4
Neutrophil count decreased	9.9	5.2	0
WBC count decreased	7.2	1.6	0
Fatigue	4.9	0	0
Hypertension	4.0	0.1	0
Alopecia	2.9	0	0
Stomatitis	2.0	0	0
Hb decreased	1.6	0.1	0
Diarrhoea	1.6	<0.1	0
Neuropathy	1.6	0	<0.1
Proteinuria	1.0	<0.1	0
Anorexia	0.9	0	0
Nausea	0.7	<0.1	0
Constipation	0.5	<0.1	0
Headache	0.4	0	0
Epistaxis	0.2	<0.1	0

*Related or unrelated to Bev.

Conclusions: In this large study, safety and efficacy of Bev combined with taxane-based therapy was similar to E2100 and AVADO results. Bev has minimal impact on the safety profile of CT. Hypertension >G3 was reported in 0.1% of pts (4% G3) and only 1 pt (<0.1%) had Bev-related cerebral haemorrhage. No new Bev-related safety signals were observed. Roche sponsored MO19391.

5018 POSTER DISCUSSION

Quality of life (QoL) in patients (pts) treated with bevacizumab (BV) and taxane therapy for locally recurrent (LR) or metastatic breast cancer (mBC)

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Background: In the randomised, double-blind, phase III AVADO study, addition of two different doses of the anti-VEGF therapy BV (Avastin®) to docetaxel (D) significantly improved PFS and response rates compared with placebo (PL) and D in the first-line treatment of mBC. Another phase III trial, E2100, showed significant improvements in efficacy on addition of BV to paclitaxel (PAC) in this setting. In addition, an FDA pre-specified statistical analysis showed a significantly better QoL in pts treated with BV+PAC. In both studies, BV had only limited impact on the known safety profile of the taxanes used.
Materials and Methods: In AVADO, pts completed a Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire, comprising generic and breast cancer-specific components, at baseline (n = 656 of 736 enrolled), weeks 9 (n = 570), 15 (n = 510) and 33 (n = 289). The present exploratory QoL analysis is based on the same imputation rule recommended by the FDA for the E2100 study, which imputed missing QoL scores (due to death or disease progression) with zero (worst possible).
Results: We show here results for TOT-B (total FACT-B score) and for TOI-B (trial outcome index; including physical and functional well-being generic elements and the breast cancer-specific subscale). Baseline TOT-B and TOI-B scores were balanced between arms. Mean changes to baseline scores were significantly better in BV+D treatment arms compared with PL+D except for week 9 with 15 mg/kg BV and week 33 with 7.5 mg/kg BV (Table).
Conclusions: Patients treated with BV in combination with taxanes as first-line treatment for mBC experienced significantly better QoL changes at most timepoints compared with those treated with PL+D. This is consistent with E2100 data, which also demonstrated significantly better scores in the BV+PAC arm compared with PAC alone.

	Mean change from baseline (95% CI); p value vs PL + D		
Assessment	PL + D	BV 7.5 mg/kg + D	BV 15 mg/kg + D
Week 9			
TOI-B (n = 615)	−11.4 (−14.7, −8.2)	−7.0 (−9.8, −4.2); **0.0220**	−8.8 (−11.6, −6.0); **0.3224**
TOT-B (n = 611)	−15.8 (−21.0, −10.6)	−10.1 (−14.7, −5.5); **0.0412**	−12.0 (−16.5, −7.5); **0.4587**
Week 15			
TOI-B (n = 590)	−19.9 (−23.7, −16.1)	−12.5 (−15.7, −9.3); **0.0041**	−12.0 (−15.2, −8.8); **0.0050**
TOT-B (n = 587)	−29.4 (−35.6, 23.1)	−17.9 (−23.1, −12.8); **0.0042**	−17.0 (−22.1, −11.8); **0.0094**
Week 33			
TOI-B (n = 535)	−34.3 (−39.1, −29.6)	−29.4 (−34.1, −24.7); **0.0866**	−25.2 (−29.8, −20.6); **0.0092**
TOT-B (n = 532)	−56.0 (−63.6, 48.3)	−48.2 (−55.9, −40.5); **0.1001**	−40.6 (−48.1, −33.1); **0.0080**

5019 POSTER DISCUSSION

Pegylated liposomal doxorubicin and Bevacizumab as first-line therapy for locallyrecurrent or metastatic breast cancer – a multicenter, single-arm phase II trial of the Swiss Group for Clinical Cancer Research (SAKK)

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Background: Bevacizumab in combination with taxanes has become a standard first-line treatment of advanced breast cancer in some countries, but there is no information on its use in combination with pegylated lipsomal doxorubicin in metastatic breast cancer. Therefore, we performed a multicenter, single-arm phase II trial to evaluate the toxicity and efficacy of pegylated liposomal doxorubicin (PLD) and bevacizumab (B) as first-line treatment in advanced breast cancer.
Methods: PLD at a dose of 20 mg/m^2 and B at 10 mg/kg were infused on days 1 and 15 of each 4-week cycle for a maximum of 6 cycles. Thereafter, B monotherapy was continued at the same dose until progression or toxicity. Primary endpoint was the occurrence of specific toxic events known to strongly interfere with quality of life, i.e. severe cardiac toxicity, any grade 4/5 toxicity, and selected grade 3 nonhematological toxicities (hand-foot-syndrome, cognitive disturbance, CNS hemorrhage, and mucositis/stomatitis). Secondary endpoints included overall response, progression free survival (PFS), time to treatment failure, and duration of response. Eligibility criteria included documentation of metastatic or inoperable breast cancer; measurable disease according to RECIST; erbB2-negativity; LVEF of $\geqslant$55%; WHO performance status 0 or 1. The study used a Herndon's two-stage design with 14 and 29 patients for stages 1 and 2, respectively. The promising rate of primary toxicity was <15% and the uninteresting rate >33%. The type I error probability was 5% and the power 80%.
Results: The trial had to be stopped prematurely because of toxicity after the enrollment of 41 evaluable patients. Among these patients, 16 (39%) had grade 3 hand-foot syndrome, 3 grade 3 mucositis and 1 grade 4 cardiac toxicity. A total of 18/41 (44%, exact 95% c.i. 28−60%) of all patients had a primary toxicity. Most frequent grade 2 toxicities were hand-foot syndrome (15), mucositis (14), fatigue (5), hypertension (4) and pain (4).
Best overall response rate was 23.3% (exact 95% c.i. 12−39%), median PFS was 7.5 months (95% c.i. 4.6−8.1 months). Median overall survival is 15.9 months (95% c.i. 14.0−21.5 months) at a median follow-up of 14.3 months; the 1-year survival rate is 70% (95% c.i. 52−82%).
Conclusions: The combination of 2-weekly PLD and B in advanced breast cancer is surprisingly toxic and only modestly active and should not be further investigated.

5020 POSTER DISCUSSION

Pharmacokinetics (PK), safety, and efficacy of trastuzumab (T)-DM1, a HER2 antibody-drug conjugate (ADC), in patients with HER2+ metastatic breast cancer (MBC): phase I and phase II trial results

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Background: The ADC T-DM1 combines the biological activity of T with targeted delivery of a potent anti-microtubule agent, DM1, to HER2+ cancer cells. DM1 and T are linked via a highly stable MCC thioether linker. Preclinical studies showed activity of T-DM1 in lapatinib (L)-resistant breast cancer cells, and in T-sensitive and T-refractory breast tumor models.
Key PK and safety results are presented from Phase I and II (NCT00679211, Genentech, Inc.) trials of T-DM1 in pts with HER2+ MBC who had progressed on T + chemotherapy.
Methods: In Phase I, successive cohorts of pts received escalating doses of T-DM1 wkly or every 3 wks (q3w) until maximum tolerated dose (MTD)