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)

was determined for each schedule. In Phase II, pts received T-DM1 at 3.6 mg/kg q3w (the MTD). Noncompartmental PK parameters, after multiple dosing, are shown.
Results: In Phase I, 24 pts enrolled in the q3w cohort, with median age 50.5 yrs; 0% had ECOG PS ⩾2; pts received a median of 91.6 wks prior T treatment (tx). Transient thrombocytopenia (TCP) was the dose-limiting toxicity. In Phase II, as of 7/31/08, 112 pts had enrolled, with median age 54.5 yrs; 8.0% had ECOG PS ⩾2; pts received a median 76.6 wks prior T; 55.4% received prior L.
PK (latest data): For q3w dosing at MTD, in Phase I and Phase II respectively, T-DM1 half-lives were 3.5 and 3.7 days; clearance rates were 12.9 and 8.56 mL/day/kg; steady state C_{max} levels at Cycle 4 were 79.2 and 70.2 ug/mL; C_{min} was ~1 ug/mL in both trials. For wkly dosing at 2.4 mg/kg (wkly MTD) C_{max} was lower and there was greater cumulative T-DM1 exposure.
Safety: In the Phase I q3w cohort, the Gr 3−4 drug-related AEs were TCP (12.5%), and Gr 3 neutropenia and pulmonary hypertension (1 pt each). No cardiac toxicity requiring tx modification, or Gr > 1 nausea, vomiting, alopecia or neuropathy, were reported. In Phase II, the most common Gr 3−4 related AEs were TCP (7.1%), and Gr 3 hypokalemia (3.6%) and fatigue (2.7%), with no Gr ⩾3 cardiac dysfunction.
Efficacy: In Phase I (final data), 5 of 15 (33%) pts treated at MTD had partial responses after a median of 11 doses T-DM1. This compares with the following formerly presented interim Phase II data: 33 (43.4%) responses (partial or complete), 29 (38.2%) confirmed by follow-up (F/U) imaging, among 76 pts with ⩾6 months F/U or who discontinued (8/29/08 data-cut).
Conclusions: T-DM1 has single-agent activity in pts with previously-treated, HER2+ MBC and is well tolerated at the MTD, with minimal accumulation after multiple dosing q3w. A Phase III trial (EMILIA) is enrolling MBC pts with prior HER2-directed therapy for randomization to tx with T-DM1 or capecitabine + L.

5021 POSTER DISCUSSION

Everolimus (RAD001) in combination with weekly paclitaxel and trastuzumab in patients (pts) with HER-2-overexpressing metastatic breast cancer (MBC) with prior resistance to trastuzumab: a multicenter phase I clinical trial

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Background: Resistance to trastuzumab (H) may be associated with loss/deregulation of PTEN or activating mutations in the PI3K/AKT pathway. Preclinically, everolimus (E), an oral inhibitor of mTOR, enhances efficacy and reverses resistance to H, and demonstrates synergistic activity with paclitaxel (T). The objective of this study was to establish the feasible doses/regimens of E in combination with T and H in heavily pretreated HER2+ MBC pts.
Methods: A multicenter, Novartis sponsored, phase I clinical trial (NCT00426556) was conducted using 2 regimens of a triple combination: T 80 mg/m^2, IV on days 1, 8 and 15 q4w; H 4 mg/kg loading dose, followed by weekly 2 mg/kg IV and E either daily (d) (5 and 10 mg) and weekly (w) (30, 50 and 70 mg).
Results: As of March 30th 2009, 33 pts were enrolled (9 still ongoing): 6 pts in the E 5 mg/d cohort, 17 in the 10 mg/d, and 10 in the 30 mg/w. Pts characteristics were: median age 55 y-o; visceral disease in 79% of pts; median No. of prior chemo-lines for metastatic disease 3 (range 0−17); H-resistance in 97% of pts; prior taxanes in 94% of pts (39% taxane-resistant); prior anthracyclines in 76% of pts; and 48% of pts refractory or resistant to lapatinib. Mean duration of study treatment was 24 wks in the 5−10 mg/d and 31 wks in the 30 mg/w cohorts. G3−4 neutropenia occurred in 3 (50%), 8 (47%) and 4 (40%) pts in the 5 mg/d, 10 mg/d and 30 mg/w cohorts, respectively with 2 cases of febrile neutropenia. G3 stomatitis occurred in 1 pt (17%), in the 5 mg/d cohort, 3 pts (18%) in the 10 mg/d, and 3 pts (30%) in the 30 mg/w. G3 asthenia/fatigue was observed in 2 pts (33%) in the 5 mg/d, 3 pts (18%) pts in the 10 mg/d, and 2 pts (20%) in the 30 mg/w cohorts. Thirty pts were evaluable for efficacy. In the 5−10 mg/d cohorts (N = 21), we observed 2 CRs, 7 PRs, 11 SDs and 1 PD, for an overall response rate (ORR) of 43%. In the 30 mg/w cohort (N = 9) we observed 3 PRs, 5 SDs and 1 PD. Most of the pts benefited from treatment, independently of taxane resistance (ORR = 56% in pts resistant to H and prior taxanes in the 5−10 mg/d cohorts).
Conclusions: E in combination with T and H has an acceptable safety profile and confirms high promising anticancer activity. The phase I part of the study is completed and E 10 mg daily has been selected as the recommended dose and schedule for further development. Final results, PK and biomarker data will be presented.

5022 POSTER DISCUSSION

A retrospective study on the efficacy of elliptinium acetate in metastatic breast cancer patients

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Background: Elliptinium acetate (Celiptium®) is a synthesized member of the class of ellipticines who demonstrated clinical activity as salvage treatment in advanced or metastatic breast cancer. Our study aimed to analyse retrospectively the efficacy of Celiptium administered in breast cancer patients and, in a forthcoming genomic study, to evaluate the correlation between the responsiveness to this inhibitor of topoisomerase II and the expression of spliceosomes.
Material and Methods: We assessed the outcome of all patients (pts) who had received elliptinium acetate from 1991 to 2001 at Institute Gustave-Roussy. We considered pts' and pathologic tumor characteristics [age, histologic type and grade (G), estrogens receptors (ER)] and response evaluation according to WHO criteria.
Results: 306 metastatic breast cancer patients resistant to anthracyclines received elliptinium acetate. Median age at diagnosis was 51 years (range 29−78), ER were positive in 49%, negative in 24% and unknown in 27% of pts. Number of metastases sites at administration of Celiptium included one site in 21%, two sites in 37% and more than three sites in 42% of pts. Distribution of metastases type is as follow: 16% of pts presented visceral metastases, 25% non-visceral and 59% mixed. Celiptium was administered the most frequently in combination with etoposide/mitomycin in 70% of pts. The majority of pts (71%) received elliptinium-based chemotherapy as second or third metastatic line. Median number of administered cycles was 3 (range 1−10). The rate of response was of 26% [7% (22 pts) complete remission (CR), 19% (57 pts) partial remission]; 23% (71 pts) presented stable disease, 45% (139 pts) progression disease and 6% (17 pts) non-evaluable (treatment refusal or toxicity). Concerning the correlation of response to ER, we registered CR in 10% (15 pts) of positive ER pts, and in 6% (4 pts) of negative ER pts. A total of 45% of pts with CR received Celiptium as second line metastatic. The median treatment free interval was 1 month [0−81] and the median progression free survival was 3 months [0−87]. The median survival after administration of elliptinium-based chemotherapy was of 6 months [0–119].
Conclusion: Elliptinium acetate is a low cost antineoplastic agent that proved significant efficacy in metastatic breast cancer resistant to anthracyclines, and acceptable toxicity. Ongoing studies on gene expression profile will aim at identifying patients who are particularly sensitive to such drug family.

5023 POSTER DISCUSSION

Ixabepilone/epiribicin combination as therapy for metastatic breast cancer – a phase Ib study

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Background: Ixabepilone (ixa) and epirubicin (epi) are active agents in metastatic breast cancer (MBC), used either as monotherapy or as part of a combination therapy. The primary objective of this study was to determine the maximum tolerated doses (MTD) and recommended phase II dose (RP2D) of a combination of ixa and epi.
Methods: Patients (pts) with locally advanced, recurrent or MBC with cumulative dose of ⩽300 mg/m^2 for doxorubicin, and ⩽450 mg/m^2 for