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

epirubicin, and ⩾3 months of progression free interval after anthracycline therapy were eligible. To determine the MTD, RP2D, cohorts of 3−6 pts received ixa/epi at 25/75, 30/75 and 35/75 mg/m^2, respectively, as IV Q 3 wk doses, until disease progression, unacceptable toxicity, or discontinuation by Investigator or patient request. An additional 24 pts were enrolled at MTD and followed for >6 months for progression free survival (PFS).
Results: Forty-two pts (median age: 57; range 33−69) were enrolled, 95% receiving the combination in the first line metastatic setting. Six pts each were enrolled at 25/75 mg/m^2 and 35/75 mg/m^2 dose cohort, and 30 pts at 30/75 mg/m^2, receiving a total of 249 cycles (median 6, range 1−10). All pts were evaluable for safety and efficacy analysis. Grade 3/4 neutropenia occurred in 6/6 at 25/75 mg/m^2, 6/6 at 35/75 mg/m^2 and 29/30 at 30/75 mg/m^2. Only 1 pt developed febrile neutropenia. No deaths or grade 4 non-hematological toxicities were reported. Frequent grade 3 drug-related toxicities included: asthenia (12%); vomiting and peripheral neuropathy (each, 7%); nausea, mucosal inflammation, pyrexia and hypersensitivity (each, 5%). The MTD (£ 33% DLTs in cycle 1) was 30 mg/m^2 of ixa and 75 mg/m^2 of epi.
Objective responses were observed at all dose levels in 18/32 (56%) pts with measurable disease; 2/10 pts with non-measurable disease had complete response. Median time to response was 11.6 wks (range: 5.3−26 wks). Among 18 pts with measurable disease, duration of response was ⩾4 mo for 13 pts and ⩾6 mo for 11 pts (range 1−17 mo). For the remaining 21 pts, 17 had stable disease (⩾6 wks from start of therapy to PD) and 4 had PD. PFS (time from 1st dose to date of PD or death), was ⩾6 mo in 27 (64%), ⩾9 mo in 18 (43%) and ⩾10 mo in 11 (26%) pts (range 0.5−17.9 mo).
Conclusions: Ixa/epi combination is an active first line MBC regimen with a manageable safety profile. The RP2D is 30 mg/m^2 of ixabepilone and 75 mg/m^2 of **epirubicin**.

5024 POSTER DISCUSSION

Dose adjusting capecitabine minimises side effects while maintaining efficacy: retrospective review of capecitabine for pretreated metastatic breast cancer

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Background: Capecitabine (X) monotherapy is considered standard treatment in patients with metastatic breast cancer (MBC) for whom anthracycline and taxane therapy is not indicated. Dose adjustment of X is easy to implement due to its twice-daily oral administration. A number of retrospective analyses have shown that, in patients receiving X monotherapy, or X in combination with docetaxel (T), dose modification of X is effective in the management of adverse events (AEs), without compromising efficacy. We performed a retrospective review of a large data set to consolidate the impact of X dose modification on efficacy and safety outcomes.
Methods: Data from four phase II X monotherapy trials (N = 319; X 1,255 mg/m^2 b.i.d. every 14 days q3w), one phase III XT combination trial (N = 511; X 1,250 mg/m^2 b.i.d. every 14 days, T 75 mg/m^2 day 1, q3w) and an analysis of consecutive patients receiving X outside of a clinical trial (N = 141), all with pretreated MBC, were reviewed. In the phase II and III trials, dose reductions were implemented for recurrent treatment-related AEs of NCIC-CTC ⩾grade 2, as previously described (O'Shaughnessy et al. J Clin Oncol 2002;20:2812−23); the dose of X was initially reduced by 25%, and subsequently by 50%. Patients receiving X consecutively were grouped according to starting dose, most commonly full dose (1,250 mg/m^2 b.i.d.), a 10% reduction (1,125 mg/m^2 b.i.d.), or a 20% reduction (1,000 mg/m^2 b.i.d.).
Results: Dose reductions were required in 41% (n = 131) of patients receiving X monotherapy (to ~941 mg/m^2) and 65% (n = 163) of patients receiving XT (80% of these patients required dose reductions of both X and T, to ~950 mg/m^2 and ~55 mg/m^2, respectively). Time to disease progression and overall survival were similar, or even slightly longer, amongst patients receiving lower doses of X versus full dose X in all of the studies examined. In addition, reduced X doses were associated with a lower incidence of treatment-related AEs, specifically hand-foot syndrome, diarrhoea, and stomatitis.
Conclusions: These data show that the dose of X can be reduced, either when used as monotherapy or in combination with T, without compromising efficacy in terms of time to progression or overall survival. Together these data support the use of dose reducing X, including the possibility of starting at a lower dose (<1,250 mg/m^2), in order to reduce the incidence of AEs.

5025 POSTER DISCUSSION

A dose escalating study of cabazitaxel (XRP6258) in combination with capecitabine, in patients (pts) with metastatic breast cancer (MBC) progressing after anthracycline and taxane therapy

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Background: Cabazitaxel (X), a new taxoid showed activity in taxane resistant MBC. Capecitabine (C) is approved in MBC pts pretreated with anthracycline and taxane.
Methods: A standard 3+3 escalation scheme explored doses of combined intravenous X (Day (D) 1) with oral C twice daily (D1to14), every 3 weeks (q3w). The study objectives were the identification of dose limiting toxicities (DLTs), recommended dose (RD) of the combination, assessment of safety, pharmacokinetics (PK) and activity at the RD in an expanded cohort.
Results: 33 MBC pts pretreated with taxane and anthracycline were enrolled and treated (15 in the dose escalation part and 18 at the RD). This population had a median age 55 [34−74], ECOG-PS 0/1: 21/12, in first or second line chemotherapy, median of 3 (1−6) organs involved (mainly: bone, liver, lymph nodes). In the escalation part, X+C were administered at 3 dose levels (DL), as shown in the table.

X+C (mg/m^2)	N	N pts with DLT at cycle (cy) 1/DLT Type
DL1: 20+825	6	1/grade (Gr) 4 neutropenia lasting more than 7 D
DL2: 20+1000	3	0
DL3: 25+1000	6	2/Gr 4 neutropenia lasting more than 7 D

DL2 was defined as the RD and the expansion cohort was initiated. PK analysis did not show any drug-drug interaction with this schedule of administration. Overall, out of the 33 pts (170cy), the main Gr3−4 toxicities (N pts) were asthenia (5), hand-foot syndrome (4), neutropenia (20), febrile neutropenia (1), neutropenic infection (1), neutropenic colitis (1), no toxic death. Efficacy was observed at each DL with a total of 1 complete response, 5 partial responses (PR) and 21 stabilizations (including 6 unconfirmed PR).
Conclusions: X was safely combined to C. X at 20 mg/m^2 D1 + C at 1000 mg/m^2 twice a D (D1−14), q3w is the RD. Final results for efficacy and safety will be presented.

5026 POSTER DISCUSSION

Ibandronate is effective in metastatic bone pain reduction regardless of previous bisphosphonate treatment

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Background: Phase III trials have already proved the efficacy of intravenous and oral ibandronate in significantly reducing bone pain due to metastatic bone disease in breast cancer patients for up to 2 years. An ongoing non-interventional study in Germany is currently assessing this pain relieving effectiveness of i.v. and oral ibandronate regardless of previous bisphosphonate treatment in the real life setting. An interim analysis based on 1897 documented cases is now available.
Patients and Methods: Breast cancer patients (age: 63.3 11.9 years) were treated for 24 weeks with i.v. ibandronate 6 mg every 4 weeks or daily oral ibandronate 50 mg. For detailed subgroup analysis, the total collective was divided according to the previous treatment: bisphosphonate-naive (n = 1219), or previous treatment with ibandronate (n = 213), or other bisphosphonates (n = 465) respectively. Bone pain was assessed using a visual analog scale (VAS, range: 0 [no pain] to 10 [maximum pain]). Analgetic medication was determined additionally.
Results: At the end of the observational period, 66% of the total collective experienced an overall pain score reduction of 10−40%, intravenous formulation and oral formulation being comparably effective. The greatest pain reduction was observed in bisphosphonate-naive patients (69% reported improved bone pain scores). At baseline, patients who had received ibandronate pretreatment had lower Bone pain scores (2.8±2.2) than patients who were bisphosphonate naive (3.5±2.4) or were treated with other bisphosphonates (3.2±2.5).