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