With the limitations of small sample size and lack of control for diurnal variations of sNTX, our retrospective analysis does not support the hypothesis that, in the setting of IB use, systemic over-suppression of bone turn-over as revealed by biochemical markers, is associated with development of ONJ. Prospective trials to identify pts' characteristics and markers predictive for ONJ are needed.

**2105** POSTER

**An accelerated loading regimen for trastuzumab leads to early higher than steady-state serum concentrations**

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**Background:** Serum concentrations of trastuzumab (Herceptin®; H) normally take 18−24 weeks to reach steady-state levels with currently used regimens (qw or q3w). Achieving higher than steady-state H concentrations earlier in the course of treatment could result in earlier benefits including tumour shrinkage in patients (pts) with HER2-positive metastatic breast cancer (MBC). To investigate this further, we examined the pharmacokinetics (PK) and tolerability of a novel higher-dose loading regimen of H, based on PK simulation.
**Methods:** Pts with HER2-positive MBC were given a 6 mg/kg iv loading dose of H on days 1, 8 and 15, followed by 6 mg/kg q3w from day 22. Blood samples for PK analysis were collected at various time points within the first 4 cycles (12 weeks). All PK data were analysed by non-linear mixed-effect modelling (population PK). Safety and efficacy analyses were also performed.
**Results:** PK was analysed in 71/72 enrolled pts (median age 59 years; median weight 69.75 kg; 56 pts had received previous chemotherapy [CT]: 46 for early breast cancer, 10 for MBC, 16 pts had no prior CT). In cycle 1, predicted exposure levels were already higher than previously reported steady-state exposure levels with conventional dosing regimens (Charoin et al 2004) (table).

| PK parameter | Units | Median level | | |
|---|---|---|---|---|
| | | Cycle 1 | Cycle 5 | Conventional regimen |
| $AUC_{0-3wks}$ | mg·day/L | 2712.9 | 1996.3 | 1793 |
| $C_{max}$ | mg/L | 235.8 | 203.4 | 189 |
| $C_{min}$ | mg/L | 119.8 | 54.9 | 47.3 |

The regimen was well tolerated, with 3 pts (4.2%) withdrawing due to adverse events. One pt experienced a drop in left ventricular ejection fraction to <40% and no pts experienced symptomatic heart failure. The response rate (RR) was 26.8% (11/41 evaluable pts), with a median time to progression (TTP) of 7.7 months.
**Conclusions:** This regimen achieved higher than steady-state serum concentrations of H during the first q3w treatment cycle without diminished tolerability. RR was higher and TTP was longer than previously seen with monotherapy. Treatment with this intensive loading dose regimen of H has the potential to improve efficacy and maximise synergies when combined with CT.

**References**

Charoin JE, et al. (2004) Population pharmacokinetic analysis of trastuzumab (Herceptin) following long-term administration using different regimens. Poster 33 presented at the Population Approach Group in Europe 13th Meeting, Uppsala, Sweden, 17−18 June, 2004. Available at: http://www.page-meeting.org.

**2106** POSTER

**Randomized clinical comparison of weekly or every-3-week 130-nanometer albumin-bound paclitaxel vs. every-3-week docetaxel as first-line therapy in patients with metastatic breast cancer**

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**Background:** 130-nanometer albumin-bound- (nab-) paclitaxel (Abraxane®) combines paclitaxel with albumin without solvents or altering either component. A cross analysis of 2 clinical trials comparing solvent-based (SB) paclitaxel 175 mg/m$^2$ every 3 weeks (q3w) to nab-paclitaxel (Gradishar et al, JCO, 2005) and SB docetaxel (Jones et al, JCO, 2005) suggested comparable antitumor activity between nab-paclitaxel and SB docetaxel and better tolerability with nab-paclitaxel in patients (pts) with metastatic breast cancer (MBC). The aim of this study was to compare the toxicity and antitumor activity of 3 regimens of nab-paclitaxel (q3w and 2 weekly) with each other and that of SB docetaxel in MBC.
**Methods:** In this open-label study, first-line pts with MBC were randomly assigned to nab-paclitaxel 300 mg/m$^2$ q3w (A); nab-paclitaxel 100 mg/m$^2$ (B) or 150 mg/m$^2$ (C) days 1, 8, and 15, q28 days (q 3/4 w); or SB docetaxel 100 mg/m$^2$ q3w (D). The primary endpoints were overall response rate (complete response + partial response), evaluated every 8 weeks and toxicity. Progression-free survival (PFS) was also determined.
**Results:** 302 pts [median age, 54 years; 99% Caucasian; 75% post-menopausal; Eastern Collaborative Oncology Group (ECOG) Performance Score (PS) $\leqslant$2 (94% $\leqslant$1)] either had at least 2 response assessments (94%) or had discontinued due to progressive disease (PD; 6%). The efficacy results at the time of a planned interim analysis conducted in November, 2006 are shown in the Table. Neutropenia (N) was greater with D than with A, B, or C ($p < .001$). Grade 4 N was: (A) 4%, (B) 3%, (C) 7%, and (D) 74%. Febrile neutropenia (FN) was: (A) 1%, (B) 1%, (C) 1%, and (D) 7%. Gr 3 peripheral neuropathy was: (A) 14%, (B) 7%, (C) 12%, and (D) 5%.

Efficacy results[a]

| | (A) nab-Pac 300 mg/m$^2$ q3w (n = 76) | (B) nab-Pac 100 mg/m$^2$ q3/4w (n = 76) | (C) nab-Pac 150 mg/m$^2$ q3/4w (n = 74) | (D) Solvent-based Doc 100 mg/m$^2$ q3w (n = 74) |
|---|---|---|---|---|
| Overall response rate (CR + PR) | 25 (33%) | 44 (58%) | 46 (62%) | 27 (36%) |
| P-value vs. D[b] | Not calculated | 0.004 | 0.016 | – |
| P-value vs. B[b] | <0.001 | – | 0.424 | – |
| P-value vs. C[b] | <0.001 | – | – | – |
| Number of pts with PFS event | 23 (30%) | 25 (33%) | 19 (26%) | 33 (45%) |
| Median PFS (months) | >10.6 | 9.3 | 9.2 | 7.3 |
| 95% CI | 7.3–>10.6 | 7.1–>10.6 | 8.1–>10.8 | 5.6–8.4 |

[a]Pac, paclitaxel; Doc, docetaxel; CR, complete response; PR, partial response.
[b]P-value based on a Cochran-Mantel-Haenszel test stratified by study site.

**Conclusions:** The response rates of q3w nab-paclitaxel and solvent-based docetaxel were comparable. Q 3/4 w nab-paclitaxel resulted in higher response rates than SB docetaxel. Grade 4 N and FN were less frequent with nab-paclitaxel as compared with solvent-based docetaxel. At the time of this interim analysis, all 3 nab-paclitaxel regimens have a longer PFS than SB docetaxel. Current data will be presented for toxicity and from a radiological review of response data and PFS. As of 10 April 2007, 146 (49%) of PFS events had occurred, and it is projected that sufficient events ($\geqslant$80%) for a final PFS analysis will occur by August, 2007.