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).

There was a reduction (mean 9.2%) in analgetic use for all patients during ibandronate treatment.
Conclusions: The study shows that in clinical practice intravenous as well as oral ibandronate is a valuable and well-tolerated treatment option for breast cancer patients with metastatic bone disease.

5027 POSTER DISCUSSION

A randomized, phase III trial exploring the effects of neoadjuvant sequential treatment with steroidal (exemestane) and non-steroidal (anastrozole) aromatase inhibitors on biomarkers in post-menopausal women with hormone receptor positive locally advanced breast cancer (LABC)

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Background: Despite many large randomised trials assessing adjuvant aromatase inhibitor (AI) treatment for postmenopausal breast cancer patients, optimal endocrine strategy remains unknown. Neoadjuvant endocrine studies provide the opportunity to model appropriate study design in a more expeditious manner. Several adjuvant trials are exploring sequential AI strategies. This study compared the effect of two sequences of AI use [steroidal (exemestane, *E*) and non-steroidal (anastrozole, *A*)] on serological and pathological biomarkers, when given in the neoadjuvant setting to patients with LABC.
Methods: 30 postmenopausal women with ER and/or PR positive disease were randomised to receive either *E* followed by *A*, or *A* followed by *E*. Each drug was given for 8 weeks. Serum estrone sulphate, and estradiol levels, as well as intra-tumoural Ki67 were evaluated at baseline, 8 weeks, and 16 weeks. Clinical response, patient preference, & quality of life were also assessed.
Results: Despite rapid falls in sex steroid levels with AI use, there was no difference in estradiol, estrone sulphate or Ki67 levels between groups. There was no significant difference in toxicities, or in quality of life scores. Overall clinical response rate was 68% & clinical benefit was 93%. There was a trend towards improved clinical response in the *A* followed by *E* group. The majority of patients expressed a preference of treatment.
Conclusions: Neither sequence of steroidal or non-steroidal AI appears to offer a significant advantage over the other. A trend towards improved clinical response in patients treated with *A* followed by *E* is hypothesis generating and needs confirmation in larger trials.

5028 POSTER DISCUSSION

Neoadjuvant concomitant radio-endocrine therapy for locally-advanced receptor positive elderly breast cancer: an Indian experience

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Background: Locally-advanced breast cancer patients – commonest presentation in developing countries – are conventionally addressed with neoadjuvant chemotherapy, irrespective of hormonal status. Cost and toxicity of chemotherapy often leads to non-compliance. Objective of this study was to evaluate a less expensive, better tolerated neoadjuvant strategy, by combined Radio-hormonal manipulation, to achieve down staging, adequate enough for MRM or even to allow conservative surgery (BCS) in ER+ postmenopausal patients.
Primary end point of the study is overall response of tumor and axillary node(s) to neoadjuvant treatment. Secondary endpoint is the feasibility of BCS.
Materials and Methods: Between June 2007 and October 2008, a total of 221 patients aged >60 years with core biopsy confirmed, receptor positive, invasive adenocarcinoma of breast, who are not amenable to BCS (T_2-T_4, N_1-N_2, M_0) were placed on daily Tamoxifen 20 mg (n = 156) or if HER 2 positive, Letrozole 2.5 mg, (n = 65). Concomitant Radiotherapy (50 Gy in 25 F over 5 weeks) with individualised CT-based planning was started after 3 months of hormone therapy in 217/221 patients. 4 patients were excluded, as they developed systemic metastasis. After completion of radiotherapy, hormonal agent was continued until disease progression. 2–4 weeks after radiotherapy i.e. around 20–24 weeks from the initiation of hormone treatment, patients were assessed for tumor response by clinical examination, mammography and also metastatic work up once again for feasibility of surgery. Surgery consisted of tumerectomy with level II axilla dissection or MRM depending on residual tumor: breast ratio and patient's choice.
Results: All patients completed treatment. Tumor response was evaluated as per RECIST criteria by monthly clinical examination. More than 50% tumor shrinkage was noted prior to radiotherapy in 48/156 (31%) patients on Tamoxifen and 28/65 (43%) on Letrozole. 2–4 weeks after radiotherapy complete and partial remission were achieved in 71/217 and 130/217 patients respectively – stable disease in 16/217 patients. Surgery was possible in 201/217 (92%) patients – BCS in 126/217 (58%) patients, MRM in 75/217 (35%). Pathological CR was noted in 65/217 (30%) patients. No patients had more than RTOG Grade 2 skin toxicity.
Conclusions: Judicious integration of systemic and local therapy is the key to success in breast cancer management. In this single institute study neoadjuvant radio-hormone therapy proved to be an effective, non-toxic, well-tolerated, inexpensive, patient-compliant treatment option, which, till date remains nearly untrodden ground in world literature.

5029 POSTER DISCUSSION

Motesanib (AMG 706) in combination with paclitaxel or docetaxel: phase 1b study in patients with locally recurrent, unresectable or metastatic breast cancer

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Background: Motesanib, an oral inhibitor of angiogenesis, selectively targets VEGF receptors 1, 2, and 3; PDGF and Kit receptors. This ongoing phase 1b open-label dose-finding study determines the maximum-tolerated dose (MTD), safety, pharmacokinetics (PK), and efficacy of motesanib plus paclitaxel (P) or docetaxel (D) in patients (pts) with advanced breast cancer (ClinicalTrials.gov ID NCT00322400; sponsor: Amgen Inc.).
Methods: Pts with ECOG 0/1 and $\leqslant$1 prior chemotherapy regimen for metastatic breast cancer are eligible. Pts were treated with (until toxicity or disease progression) motesanib (50 or 125 mg) QD orally continuously from cycle 1 day 3 plus either P (Arm A) 90 mg/m^2 on days 1, 8, and 15 of each 28-day cycle; or D (Arm B) at either 100 mg/m^2 on day 1 of every 21-day cycle; or at 75 mg/m^2 with motesanib at MTD (125 mg). Objective response (OR) per RECIST was assessed every 8 (Arm A) or 6 wks (Arm B).
Results: 33 pts (Arm A, n = 10; Arm B, n = 23) have received $\geqslant$1 dose of motesanib. Median age is 51 (range 28–66) yrs. 5 dose-limiting toxicities (all grade [gr] 3) occurred in 4 pts: abnormal liver function test and deep vein thrombosis (Arm A, 125 mg), fatigue (Arm A, 125 mg), gallbladder enlargement (Arm B, 125 mg+D 75 mg/m^2), and migraine (Arm B, 125 mg). The motesanib MTD has not been reached; the target dose is 125 mg QD. 28 (85%) pts had motesanib-related adverse events (AEs). The most common (highest gr) AEs were: diarrhea, Arm A/B 60%/61% (gr 3, 0%/13%); fatigue, 30%/26% (gr 3, 10%/4%); hypertension, 20%/22% (gr 3, 10%/4%); and nausea, 10%/26% (no gr 3). No related AE $\geqslant$gr 4 was reported. 2 deaths occurred on study (Arm B; 50 and 125 mg, n = 1 each); neither was considered to be motesanib-related. Motesanib PK parameters were generally within the range described for single-agent motesanib treatment. PK profiles of P and D showed high interpatient variability; AUC was higher in some pts after motesanib coadministration. Efficacy at data cutoff in pts with measurable disease at baseline is shown (Table).

	Best OR, n (%)	
	Arm A (n = 7)	Arm B (n = 18)
Partial response	2 (29)	5 (28)
Stable disease (SD)	2 (29)	9 (50)
SD $\geqslant$24 wks	0	3 (17)
Duration of response, median days (range)	169 (58+, 169)	198 (96, 337+)

Conclusions: Motesanib in combination with P or D appears to be tolerable and shows evidence of antitumor activity in pts with advanced breast cancer. Coadministration with either P or D had no major effect on motesanib PK.