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Overall survival analysis of a randomized phase III trial comparing nab-paclitaxel with solvent-based paclitaxel in patients with metastatic breast cancer previously treated with anthracycline

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Background: Nanoparticle albumin-bound (nab)-paclitaxel demonstrated superior antitumor activity compared with solvent-based paclitaxel in a phase III trial of patients with metastatic breast cancer (MBC). The current retrospective analysis aimed to determine the efficacy of nab paclitaxel in patients with MBC previously treated with anthracycline.

Material and Methods: This was a retrospective analysis of a randomized, phase III efficacy trial of nab-paclitaxel (CA-012). Patients (⩾18 years of age) received either nab-paclitaxel 260 mg/m^2 or solvent-based paclitaxel 175 mg/m^2 intravenously every 3 weeks for treatment of MBC.

Results: Of 460 patients randomized, 351 (76%) had received prior anthracycline therapy in the metastatic or adjuvant setting (176 and 175 were randomized to nab-paclitaxel and solvent-based paclitaxel, respectively). A total of 245 patients received prior anthracycline therapy specifically in the metastatic setting (115 and 130 were randomized to nab-paclitaxel and solvent-based paclitaxel, respectively). The overall response rate, time to disease progression, and overall survival were significantly higher for patients randomized to nab-paclitaxel compared with solvent-based paclitaxel for patients with any prior anthracycline therapy, and for those with prior anthracycline therapy for metastatic disease.

Safety profiles of nab-paclitaxel and solvent-based paclitaxel were similar. The most frequent grade 3/4 adverse event was neutropenia. Treatment-related grade 3 sensory neuropathy was more frequent in the nab-paclitaxel arm but improved to grades 1/2 in 22 days (median) and was readily managed.

Conclusions: Patients treated with nab-paclitaxel had a ~30% reduction in the risk of disease progression compared with solvent-based paclitaxel, regardless of prior anthracycline exposure. Additionally, nab-paclitaxel prolonged survival in patients with MBC that was resistant to anthracycline after treatment in the adjuvant or metastatic setting. Nab-paclitaxel is an effective option for the treatment of MBC in patients previously treated with anthracycline.

	Metastatic anthracycline			Metastatic or adjuvant anthracycline		
	Nab-paclitaxel (n = 115)	Solvent-based paclitaxel (n = 130)	P-value	Nab-paclitaxel (n = 176)	Solvent-based paclitaxel (n = 175)	P-value
ORR, %	27.0	13.8	0.010	34.1	18.3	0.002
TTP, weeks	21.0	15.7	0.011	23.0	16.6	0.004
Median OS, weeks	56.4	46.7	0.022	65.0	52.4	0.049

ORR = Overall response rate; TTP = Time to progression; OS = Overall survival.

Friday, 18 April 2008 12:30–14:30

POSTER SESSION

Targeted treatment

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Colloidal immunochemogene formulation SEVINA-VI composed of anti-MUC1 MAbs, clamp PNA against mRNA of eIF3c, and vinorelbine in stealth liposomes induce PCD in HRBC resistant to trastuzumab, cetuximab, and taxanes

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Background: HRBC with overexpressed MUC-1 causes resistance to tyrosine kinase inhibitors (TKIs). Upregulated eIF3c and bcl-2 cause potent chemoresistance inhibiting induction of PCD in HRBC. Our aim is to circumvent all these resistant factors.

Materials and Methods: We developed xenograft animal models from TKI resistant HRBC cells, obtained from stage-V patients overexpressing eIF3c, MUC1, and bcl-2. We formulated stealth liposomal anti-MUC1 Mab in the biological recognition layer, vinorelbine in the lipid phase, and clamp PNA anti-eIF3c oligomers composed of 6 mer homopyrimidine triplex [(PNA)2/RNA) for hybridization to 5′ end (Leader), and 10 mer purine/pyrimidine dublex (PNA/RNA) for hybridization to the 3′-end (Trailer)of the AUG start codon region on the mRNA, in the polar phase. The human HRBC xenograft animal models were treated with SEVINA-VI.

Results: Post-treatment, downregulated glycosylated MUC1 blocked binding of TKIs, by inhibiting direct steric hindrance onto HER2, EGFR, and IGF-IR. Inhibition of MUC1 phosphorylation, blocked downstream signaling pathways Ras/Raf/Erk1/2/MAPK, PI3K/AKT, VEGF, and MMP-2. ADCC was induced. The clamp PNA hybridized to the leader, and trailer region of the AUG start codon region on mRNA eIF3c forming Watson-crick double helices, and steric hindrance of the translation machinery inhibiting expression of eIF3c, after assembly inhibition of the 80 ribosome initiation complex. The RNA helicase activity of eIF3c has been silenced, disabling cellular cap-dept scanning/initiation. It inhibited mTOR preventing downstream activation of mRNA translation and blocked ribosome biogenesis inhibiting S6K1, and 4E-BPI, which led to inhibition of ribosomal protein, elongation factors, and ODC/cyclinD1. Thus, chemoresistant 4E-BPI induced by taxanes was inhibited. Cycline/CDK2-p27 and p53 were upregulated, inhibiting CDK1/2 and cyclinD1 activity. Signal transduction initiated by VEGF was inhibited, and translation of antiapoptotic FLIPS, and c-myc was blocked. Type I PCD or apoptosis was induced. Vinorelbine phoshorylated bcl-2 leading to its inactivation, and subsequent circumvention of oncogene addiction. Furthermore, it released beclin-1 inducing typeII PCD or autophagy. Also, vinorelbine by depolymerizing MT blocked cell cycle at G2/M. TEM exhibited type III PCD or necrosis. DNA and metabolic activity of tumor cells were blocked.

Conclusion: SEVINA-VI has circumvented oncogene transcriptional intervention in HRBC resistant to TKIs, and taxanes via protein translational inhibition of eIF3c downstream of mTOR pathways, and downregulation of MUC1, which led to induction of ADCC, and PCD in synergy with cytostatic agent vinorelbine.

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Growth and molecular interactions of the anti-EGFR antibody cetuximab and the DNA cross-linking agent cisplatin: new prospects in the treatment of triple-negative/basal-like breast cancer

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Background: Two prominent hallmarks of triple-negative/basal-like breast carcinomas – a subtype of breast cancer-gene expression signature associated with poor relapse-free and overall survival – are overexpression of the Epidermal Growth Factor Receptor (EGFR) and high sensitivity to DNA-damaging agents. The interaction between EGFR inhibitors (*i.e.,* monoclonal antibodies and small molecule tyrosine kinase inhibitors) and DNA cross-linking agents (*e.g.,* platinum derivatives) may represent a promising combination for the treatment of triple-negative/basal-like breast tumors that are dependent upon EGFR-signaling.

Methods: We evaluated the growth and molecular interactions of Cetuximab (Erbitux®) and cisplatin in the gefitinib-resistant MDA-MB-468 breast cancer cell line, an in vitro model system showing many of the recurrent basal-like molecular abnormalities including ER-PR-HER2-negative status, *TP53* deficiency, EGFR overexpression, *PTEN* loss, and constitutive activation of the MEK/ERK pathway.

Results: Low-scale phospho-proteomic approaches (*i.e.,* Phospho-Receptor Tyrosine Kinase [RTK] and Phospho-Mitogen-Activated Protein Kinases [MAPKs] Array Proteome Profiler™ capable to simultaneously identify the relative levels of phosphorylation of 42 different RTKs and 23 different MAPKs and other serine/threonine kinases, respectively) revealed the ability of Cetuximab, as single agent, to paradoxically induce hyperphosphorylation of EGFR while concomitantly deactivating p42/44 (ERK1/ERK2) MAPK. Concurrent treatment with sub-optimal doses of Cetuximab significantly enhanced cisplatin-induced apoptosis. However, a mathematical assessment of the nature of the interaction revealed a loss of synergism when employing high-dose Cetuximab. ELISA-based quantitative analyses demonstrated that simultaneous exposure to high-dose Cetuximab and cisplatin triggered a complete depletion of the EGFR protein accompanied by a drastic up-regulation of the DNA repair protein BRCA1.

Conclusions: Although these results preclinically support, at least in part, ongoing clinical trials for "triple-negative/basal-like" metastatic breast cancer patients who are receiving either Cetuximab alone *versus* Cetuximab plus carboplatin (http://www.clinicaltrials.gov/ct/show/NCT00232505), they further suggest that treatment schedules, Cetuximab doses, and

BRCA1 status should be carefully considered when combining Cetuximab and platinum derivatives in sporadic basal-like breast carcinomas.

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mTOR inhibitor nanoparticle albumin-bound (nab®) rapamycin is effective in a breast cancer xenograft model

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Background: The mammalian target of rapamycin (mTOR) is involved in the control of cellular growth and proliferation and is an important target in tumor therapy. Rapamycin is currently available in 2 oral forms, and its use as an anticancer agent has been hampered by poor solubility, low oral bioavailability, and dose-limiting intestinal toxicity. Here we report on a novel albumin-bound nanoparticle form of the mTOR inhibitor rapamycin for IV administration and its antitumor activity in a breast tumor xenograft model.

Material and Methods: A nanoparticle form of rapamycin was prepared using Abraxis' proprietary *nab*-technology. Repeated-dose toxicity of *nab*-rapamycin was determined in Sprague-Dawley rats with dose levels of 0, 20, 40, 90, 120, and 180 mg/kg (n = 5M/5F per group) on a q4d×3 schedule. Pharmacokinetics (PK) of *nab*-rapamycin was investigated in Sprague-Dawley rats at dose levels of 1, 15, 30, and 45 mg/kg. Antitumor activity of *nab*-rapamycin was examined using MX-1 breast tumor xenograft (n = 5) treated with 40 mg/kg *nab*-rapamycin with a 3× wkly/4wks schedule. Tumor growth data were analyzed by ANOVA.

Results: Injectable *nab*-rapamycin was successfully prepared with a mean particle size of ~90 nm. *Nab*-rapamycin administered IV was well tolerated in rats at dose levels up to 90 mg/kg/dose on a q4d×3 schedule, with no significant clinical signs of toxicity, and no observed hypercholesterolemia and hypertriglyceridemia. *Nab*-rapamycin exhibited linear pharmacokinetics with respect to dose and rapid tissue distribution, typical of *nab*-drugs, e.g. *nab*-paclitaxel and *nab*-docetaxel. *Nab*-rapamycin was highly effective against MX-1 breast tumor xenograft with a TGI of 88% ($P < 0.0001$, ANOVA).

Conclusions: *Nab*-rapamycin (ABI-009) was well tolerated at repeated doses up to 90 mg/kg in rats (540 mg/m^2) with no remarkable toxicity. *Nab*-rapamycin displayed linear PK and high antitumor activity *in vivo* in an aggressive breast cancer xenograft model.

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Nanoparticle albumin-bound paclitaxel in 3 dosing schedules with bevacizumab as first line therapy for HER2-negative metastatic breast cancer: an interim safety analysis

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Background: Nanoparticle (nab) paclitaxel (P) at 260 mg/m^2 every 3 weeks (q3wk) is more effective than Cremophor-EL based P (Gradishar et al. JCO 2005). Weekly uninterrupted administration of P is superior to q3wk P in metastatic breast cancer (MBC) (Seidman et al. JCO 2008). When added to weekly P as 1st-line therapy for MBC, bevacizumab (bev) improves response rate (RR) and time to progression (TTP) (Miller et al. NEJM 2007).

Methods: This randomized phase II trial compares nab-P at 260 mg/m^2 q3wk (arm A) vs. 260 mg/m^2 q2wk with filgrastim (arm B) vs. 130 mg/m^2 weekly, all with bev (15 mg/kg q 3 wks in arm A, 10 mg/kg q 2 wks in arms B and C), as 1st-line therapy for patients (pts) with HER2(−) MBC. Premedication for hypersensitivity reaction (HSR) was not planned. A protocol specified safety analysis was performed after ⩾40 pts in each arm had completed ⩾12 wks of therapy. 132 pts are now evaluable for toxicity, 109 for response.

Results: The median age was 57 (range 29−85); 81% are post-menopausal, 86% have visceral dominant disease, 61% had prior adjuvant and/or neo-adjuvant chemotherapy, 38% with taxane. 763 cycles have been delivered (median 6, range 1−19). Some dose reduction has been necessary (% pts): Arm A: 24%, B: 40%, C: 34%. Dose delays have occurred in all arms (% pts): A: 29%, B: 30%, C: 64%. Significant and similar efficacy (RR) is noted in all arms: A: 39% (95% CI 24−55%), B: 31% (95% CI 16−46%), and C: 37% (95% CI 21−53%); median TTP was 7.5, 7.9, and 8.3 months, respectively. Any category of grade 3 toxicity was seen in 42% of pts in arm A, 44% of pts in arm B, and 45% of pts in arm C. The most common grade 3/4 toxicities are sensory neuropathy (A: 13%, B: 26%, C: 23%) and fatigue (A: 11%, B: 16%, C: 5%). More bone pain was noted in arm B (p = 0.037). One HSR was noted due to nab-P (arm A) 3 days post-infusion, and 1 due to bev (arm C). Grade 4 non-heme toxicity has occurred in only 3% of pts. Seven of 43 pts (16%) treated on arm B withdrew due to cumulative toxicity, predominantly fatigue, anorexia, neuropathy, epistaxis, skin and nail changes. Bev toxicity included grade 3 hypertension in 2%, 1 deep vein thrombosis; proteinuria of > grade 1 was not encountered.

Conclusions: All schedules of nab-P + bev are active as 1st-line therapy for HER2(−) MBC. Due to increased events in this protocol-specified safety analysis, arm B has closed. Accrual continues on arms A and C. Updated results will be presented.

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Analysis of cardiac events in a single institution series of 155 patients who completed adjuvant Trastuzumab

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Background: Following interim results of HERA (2005) patients with HER2 positive breast cancer now receive adjuvant Trastuzumab (T) post chemotherapy (CT) as standard practice, however there is an increased potential for cardiac dysfunction (CD) during treatment which requires close monitoring.

Method: A single institution series of patients treated with T from Sept 2005–Dec 2006. Cardiac function was monitored by MUltiple Gated Acquisition scan every 3 months. If baseline LVEF (BL) <55% an echo/cardiology assessment was performed before T. A proforma was created for data collection and SPSS used for data entry/analysis.

Results: 155 patients received T, including 13 (8.4%) over 65 years old and there was no significant difference (NS) between age and CD, nor number of cycles of T given. 154 patients had anthracycline based CT but type of CT was NS. 107 (69%) had radiotherapy.

BL ranged from 47−80%, was normal in 148 (95.5%), <50% in two and 50−54% in 5 patients. All 7 with abnormal BL had further CD during T, but 5 (71.4%) recovered and completed T. In comparison 124 (83.8%) with normal BL completed T and 19 (12.8%) had CD. There was a significant difference (SD) in BL and development of CD (p < 0.001), but NS in BL and completion of T (p = 0.602). Although a total of 129 (83.2%) completed T, it was suspended in 38 (24.5%) since 7 developed MBC, 5 had adverse effects and 26 (16.8%) had CD. Of the 26 with CD, 12 (46.2%) completed T; 6 (23.1%) resumed but had further CD and discontinued. 19 (73%) with CD had normal BL but on completion LVEF was normal in only 9 (5.8%) compared with 96 (74.4%) who did not have CD. NS between CD and survival.

The time from CT to T was 3−84 weeks, median 14.5. 62 (41.1%) started T <12 weeks from CT; there was NS in start of T and BL/final LVEF, CD or cycles given, but a SD in MBC/death if time lag was >12 weeks (p = 0.048). Following T, 7 patients (4.5%) have died, 3 (1.9%) have MBC but 145 (93.5%) are alive and well.

Conclusions: Cardiac monitoring is crucial with T, and caution needed when BL is abnormal as this may predict further CD. Although 26/155 developed CD, the majority improved when T was stopped and 12/26 completed T despite CD. Age alone was not associated with CD and discontinuing T, which is reassuring in an ageing population. Disparities in time lag from CT to T was due to early implementation in UK, but showed a significant increase in MBC/death if T started >12 wks after CT, which has implications for practice.

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Ixabepilone overcomes multiple mechanisms of drug resistance including overexpression of class III β tubulin and breast cancer resistance protein

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Background: Microtubule inhibitors are highly active agents but their therapeutic benefits are significantly curtailed by innate or acquired drug resistance, which is frequently multifactorial. Ixabepilone, a semi-synthetic derivative of epothilone B is the first of a new class of microtubule agent designed to have reduced susceptibility to multiple mechanisms of drug