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

resistance including MDR1, MRP1 and tubulin mutation. Recently, two additional resistance mechanisms had emerged: overexpression of class III β tubulin (TUBB3) and breast cancer resistance protein (BCRP), a member of the ABC transporter family. We tested whether ixabepilone retains activity in tumor cell lines that overexpress these two resistance proteins.

Methods: Cancer cell lines overexpressing TUBB3 were evaluated in vivo in mice for sensitivity to ixabepilone, docetaxel and vinorelbine. These include DU4475 and PAT-21 breast (MDR1 negative), as well as H1155 and LX-1 lung cancer lines. BCRP overexpressing HEK293 cell line was studied in vitro for sensitivity to ixabepilone, paclitaxel and mitoxantrone.

Results: Efficacy evaluation in nude mice demonstrated that the 4 xenografts overexpressing TUBB3 were resistant to docetaxel and vinorelbine, yielding antitumor efficacy ranging 0.2−0.9 and 0.1−0.3 log cell kill (LCK), respectively. In contrast, ixabepilone was active in all 4 tumors, yielding 1.6−4.2 LCK (Table 1) when tested at their maximum tolerated doses (MTD). The BCRP overexpressing HEK293/BCRP cell line demonstrated resistance to paclitaxel and mitoxantrone by 9.8-fold (IC50 = 26.4 nM) and 4.1-fold (IC50 = 8.7 nM), respectively, in comparison with the vector-transfected control line. This resistance can be reversed by fumitremorgin C, a selective inhibitor of BCRP. In contrast, ixabepilone was far less susceptible to the BCRP-mediated resistance, resulting in a resistance factor of only 1.9-fold (IC50 = 4.1 nM).

Conclusion: Ixabepilone demonstrated reduced susceptibility to multiple resistance mechanisms affecting agents commonly used in breast cancer. These include overexpression of TUBB3, BCRP, MDR1 and MRP1, and β-tubulin mutations. Together, these results suggest ixabepilone may offer breast cancer patients a potentially valuable treatment option.

Table 1. Comparison of the antitumor efficacy of ixabepilone, docetaxel and vinorelbine in 4 human tumor xenografts overexpressing TUBB3

	Antitumor efficacy (Log Cell Kill)		
Tumors	Ixabepilone	Docetaxel	Vinorelbine
H1155	4.2	0.2	0.1
DU4475	2.6	0.9	0.2
Pat-21	1.6	0.3	0.3
LX-1	2.6	0.5	0.1

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Possible targets for dasatinib sensitivity in triple negative breast cancer

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Background: Triple-negative breast cancers (TNBCs) lack expression of oestrogen, progesterone, and HER-2 receptors. At present there is no specific targeted therapy for this sub-type of breast cancer. The multi-target kinase inhibitor, dasatinib, has shown promising results in inhibiting growth of triple negative breast cancer cells in vitro. To identify the specific target or targets which are responsible for sensitivity to dasatinib we have compared sensitivity to imatinib, sunitinib and dasatinib in triple negative breast cancer cell lines.

Materials and Methods: Imatinib, sunitinib and dasatinib were tested in TNBC cell lines (MDA-MB-231, BT20, HCC1937) using the acid phosphatase proliferation assay. IC50 values were determined using CalcuSyn software.

Results: The TNBC cell lines displayed the greatest resistance to imatinib, which targets Bcr-Abl, PDGFR and c-Kit (Table). The TNBC cell lines showed greater sensitivity to sunitinib, although still in the 6−10 μM range. Sunitinib targets PDGFR, VEGFR, c-Kit, FLT3, CSF-1R, and RET. As previously reported, the TNBC cell lines display significant sensitivity to the multi-target kinase inhibitor dasatinib, which targets Src, Abl, PDGFR, Kit, and EphA receptors.

IC50 values for multi-target kinase inhibitors in TNBC

	MDA-MB-231	BT-20	HCC-1937
Imatinib (μM)	23.6±2.0	32.6±3.6	27.3±2.0
Sunitinib (μM)	6.7±1.4	9.3±2.5	9.1±1.8
Dasatinib (μM)	0.04±0.01	2.5±0.6	0.13±0.07

Conclusions: TNBC cells are sensitive to dasatinib and based on response to other multi-target kinase inhibitors with overlapping target specificities, our results suggest that sensitivity to dasatinib in triple negative breast cancer is due to inhibition of Src kinase and/or EphA receptors.

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Combination of nab®-paclitaxel and bevacizumab eradicates large orthotopic breast tumors and metastasis to lymph nodes and lungs

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Background: *Nab*-paclitaxel (Abraxane®, *nab*-pac) is an albumin-bound 130-nm particle form of paclitaxel that demonstrated greater efficacy and was well tolerated compared to solvent-based paclitaxel (Taxol®) and docetaxel (Taxotere®) in preclinical and clinical studies. We have previously shown that reactionary angiogenesis induced by chemotherapy correlated with increased VEGF production in tumors, and the combination of *nab*-pac and anti-VEGF-A antibody (bevacizumab, bev) has superior efficacy against both primary tumors and metastasis than monotherapies in medium-sized MDA-MB-231 tumors (~230 mm^3) (Ran et al., AACR 2007, #2201). Herein, we studied the combination of *nab*-pac and bev on the growth and metastasis of large-sized (450–600 mm^3) breast tumors.

Materials and Methods: Luciferase-tagged MDA-MB-231-Luc$^+$ human breast carcinoma cells were implanted into mammary fat pads of *nu/nu* mice and allowed to reach an size of 450–600 mm^3, before treatment with *nab*-pac at 10 or 30 mg/kg on the qd×5 schedule for 1, 2 or 3 cycles separated by one week. Bev (4 mg/kg) was administered either concurrently with or after *nab*-pac treatment; and either continued for the duration of the experiment or discontinued after cessation of *nab*-pac therapy. Primary tumor growth was monitored and metastases to lymph nodes and lungs analyzed by monitoring luciferase activity.

Results: Complete regressions and total elimination of metastasis were achieved in 100% of mice bearing large orthotopic MDA-MB-231-Luc$^+$ tumors after treatment with 2 cycles of concurrent 30 mg/kg *nab*-pac and 4 mg/kg bev. Three cycles of combined therapy with 10 mg/kg *nab*-pac resulted in 80% regressions and 98% reduction in metastatic burden. Bev effect was optimal when administered concurrently with *nab*-pac and continued for the duration of the experiment. Bev administered sequentially after *nab*-pac delivered no benefits of the combined therapy.

Conclusions: Repetitive cycles of *nab*-paclitaxel given concurrently with bevacizumab at 4 mg/kg can eradicate both large primary tumors (450–600 mm^3) and lymphatic and pulmonary metastases in an aggressive breast cancer xenograft model. The suppression of paclitaxel-induced reactionary angiogenesis by bevacizumab can significantly enhance the antitumor and antimetastatic efficacy of Abraxane (*nab*-paclitaxel).

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First-line trastuzumab (H), oral vinorelbine (NVBo) and capecitabine (X) combination therapy for HER2-positive metastatic breast cancer (MBC): efficacy and safety in a multinational phase II study

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Background: In HER2-positive MBC, H combined with chemotherapy has shown high efficacy. In HER2-negative MBC, doublet combinations of NVBo and X are active and well tolerated. Therefore we evaluated a triple combination (NVBo+X+H) as first-line therapy for HER2-positive MBC.

Methods: Key eligibility criteria for this multicentre, single-arm trial were: IHC 3+ or FISH+ disease, documented measurable MBC with no previous chemotherapy exposure, relapse >6 months after completing (neo)adjuvant chemotherapy, Karnofsky PS greater than or equal to 70, age greater than or equal to18 years. Each 3-week cycle consisted of NVBo 80 mg/m^2 (first cycle at 60 mg/m^2 in the absence of G3/4 neutropenia) days 1 and 8;