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;