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

572 Poster

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

V. Trieu[1], T. De[1], A. Yang[1], J. Cordia[1], B. Grim[1], S. Ci[1], P. Nguyen[1], N. Desai[1]. [1]*Abraxis BioScience LLC, R&D, Los Angeles, USA*

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.

573 Poster

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

A.D. Seidman[1], A.K. Conlin[1], M.E. Moynahan[1], A. Bach[1], T. Troso-Sandoval[1], S. Sugarman[1], A. Forero[2], R. Kerr[3], G. Wright[4], C.A. Hudis[5]. [1]*Memorial Sloan-Kettering Cancer Center, Medicine, New-York NY, USA;* [2]*University of Alabama at Birmingham, Medical Oncology, Birmingham AL, USA;* [3]*Southwest Regional Cancer Center, Medical Oncology, Austin TX, USA;* [4]*Florida Cancer Insitute, Medical Oncology, Hudson FL, USA;* [5]*Memorial Sloan-Kettering Cancer Center, Medicine, New York NY, USA*

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.

574 Poster

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

C. Farrell[1], A. Wardley[1], H. Lander[2], A. McGurk[3], H. Mitchell[2], V. Lau[4], J. Loncaster[2], B. Magee[2], A. Stewart[2], P. Burt[2]. [1]*Christie Hospital NHS Foundation Trust, Medical Oncology, Manchester, United Kingdom;* [2]*Christie Hospital NHS Foundation Trust, Clinical Oncology, Manchester, United Kingdom;* [3]*Christie Hospital NHS Foundation Trust, Pharmacy, Manchester, United Kingdom;* [4]*Christie Hospital NHS Foundation Trust, Nursing, Manchester, United Kingdom*

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.

575 Poster

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

F. Lee[1], H. Shen[2], H. Lee[3], M. Wen[1], K. Covello[1], J. Gan[2], C. Raventos-Suarez[1], R. Kramer[1]. [1]*Bristol-Myers Squibb Company, Oncology Drug Discovery, Princeton New Jersey, USA;* [2]*Bristol-Myers Squibb Company, Non-Clinical Pharmacokinetics, Princeton New Jersey, USA;* [3]*Bristol-Myers Squibb Company, Oncology Biomarker Team, Princeton New Jersey, USA*

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