## Wednesday, 22 October 2008 15:00–16:00

PLENARY SESSION 2

# Proffered paper session

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### Preclinical evaluation of 64Cu labeled bevacizumab by PET/CT imaging in tumor models

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**Background:** Bevacizumab (Avastin) is an antibody targeted vascular endothelial growth factor (VEGF), an angiogenesis factor, for clinical practice as an anti-cancer therapeutic drug. This study is to test if Avastin could be used as an efficient diagnostic imaging agent for preclinical practice in various tumor animal models.
**Method and Materials:** Avastin was conjugated to a macrocyclic ligand (DOTA) and radiolabeled with a positron emitter, 64Cu. The microPET/CT imaging was conducted in xenograft tumor models established from MiaPaca2 (pancreatic), MDA-MB-231 (breast), and HT29 (lung) cancer cell lines. 64Cu-DOTA-Avastin was administered intravenously at a dose of 250 μCi/50 μg antibody into each cancer model. The mouse was imaged with a microPET and microCT scanners at 1 h, 4 h, 24 h and 44 h post-injection. The 18FDG was injected one day before the administration of 64Cu-Avastin in the same mouse, and the images were acquired at 1 h and 4 h for comparison with 64Cu-Avastin imaging.
**Results:** The images confirmed the high accumulation of radiolabeled 64Cu-DOTA-Avastin in tumor for pancreatic cancer model. PET imaging successfully detected the tumors with a clear contour. The location and shape of the tumors in animal model were evaluated by quantitative imaging data analysis. Similar results were observed in breast and lung cancer models as well. The images also showed that 64Cu-DOTA-Avastin could detect tumors in earlier stages and smaller sizes than with 18FDG imaging dose. The conventional hot spots seen with 18FDG imaging – such as, brain, muscle, kidney and bladder – do not appear on 64Cu-DOTA-Avastin images, with much less activity in the heart.
**Conclusion:** 64Cu-DOTA-Avastin can be used as a tumor diagnostic agent by PET imaging in preclinical research. The radiolabeled tracer is highly sensitive in pancreatic, breast, and lung cancer animal models. The tumor-tissue contrast and in vivo bio-distribution are superior to the current clinical standard 18FDG imaging.

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### Advantages of a modified continual reassessment method (CRM) for dose finding studies: experience in ongoing phase I trials with ABT-263

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**Background:** ABT-263 is a novel, BH3 mimetic that binds with high affinity (Ki ⩽ 1 nM) & inhibits antiapoptotic Bcl-2 proteins, & displays potent mechanism-based activity (EC50 ⩽ 1 μM) against human tumor cell lines from lymphoid & small cell lung cancers (SCLC). Preclinical toxicities include decreased spermatogenesis, circulating lymphocytes & circulating platelet survival, mediated by Bcl-w, Bcl-2 & Bcl-XL, respectively.
**Objective:** Determine the maximum tolerated dose (MTD) of ABT-263 in a modified continuous reassessment method (CRM) versus traditional 3+3 phase 1 design.
**Materials and Methods:** Safety & PK of fixed ABT-263 doses given 14 d per 21 d cycle were studied in 3 phase 1 trials [M06–814 (3+3 design), M06–822 & M06–873 (CRM)] of patients with relapsed or refractory lymphoma, SCLC/solid tumors, & chronic lymphocytic leukemia (CLL). ABT-263 dose began at 10 mg & escalated to define MTD. In traditional 3+3 design, if 0/3 subjects experiences a dose limiting toxicity (DLT), 3 subjects are enrolled at the next dose, typically 25−40% higher. If a DLT occurs in 1/3 subjects, 3 added subjects are enrolled at the same dose. If DLTs occur in ⩾2/6 subjects, MTD is the previous lower dose. CRM uses cumulative data to adjust the model and determine MTD adaptively.
**Results:** 39, 33 and 14 patients, respectively, enrolled in M06–814 (10–440 mg), M06–822 (10–475 mg) & M06–873 (10–250 mg). In M06–814, 1 (worsening cough), 2 (incr ALT, & thrombocytopenia) & 1 (worsening pleural effusion) DLTs were observed at 160, 315 & 440 mg, respectively. In M06–822, 2 thrombocytopenia DLTs occurred, 1 at each of the 325 & 425 mg doses; 1 DLT of fatal respiratory failure occurred at 10 mg. In M06–873, 3 DLTs were observed: 2 at 110 mg (thrombocytopenia & tumor lysis); 1 at 250 mg (thrombocytopenia). Dose-finding continues based on real time CRM to estimate MTD. In ABT-263 phase 1 trials, CRM was more efficient than 3+3 design, e.g., the 10 mg cohort in M06–822 would have expanded to 6 before escalating to 14 mg (40% increase), & a dose less than 110 mg would have been prematurely declared as MTD in M06–873.
**Conclusions:** With CRM modeling, dose escalation is based on cumulative toxicity data, minimizing subjects on potentially low, inefficacious or high supraMTD doses. In ABT-263 phase 1 disease specific trials, CRM estimates MTD more effectively than traditional 3+3 design in that dose escalation is less confounded by potential noise in the clinical data with an adaptive design.

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### Clinical attrition rates for kinase inhibitors in oncology

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Attrition rates within oncology have previously been reported to be high in comparison to other disease indications. Some reports in the literature claim that only 5% of oncology agents that enter clinical development may be expected to reach the market (Kola, I. and Landis, J. Nature Reviews Drug Discovery. 3, 711–716 (2004)). Such high failure rates have clear implications for drug development and the access of patients to new medicines. We hypothesised that high attrition rates, specifically within oncology, may be due the historic dominance of cytotoxic agents, which inherently have a low therapeutic window. To test this hypothesis we analysed the clinical attrition rates for all therapeutic classes within cancer over the period 1995–2007 (over 800 drugs) and compared the data to attrition rates for one class of molecularly targeted therapeutics, kinase inhibitors (over 150 drugs). Our analysis showed that the clinical attrition rate within oncology, i.e. the overall percentage of drugs entering Phase I trials that do not reach the market, for all therapeutic classes was 77%. We also showed that the Phase II to Phase III transition had the lowest transition probability. Phase I to Phase II transition was 0.8, Phase II to Phase III was 0.49 and Phase III to market was 0.59. In contrast, kinase inhibitors showed a clear improvement in phase transition probabilities at each of the key clinical phases. Phase I to Phase II transition was 0.88, Phase II to Phase III was 0.75 and Phase III to market was 0.83. Consequently the overall Phase I to market attrition rate for kinase inhibitors was seen to improve drastically to 45%. In addition to the improved attrition rates, kinase inhibitors were also associated with improved timelines to market (approximately 21 months faster to market). Improvements in attrition rates with kinase inhibitors may be linked to a number of key factors, including improved clinical trial design, patient stratification, the use of more representative pre-clinical animal models and the use of biomarkers. Overall, this study has demonstrated that the evolution of molecularly targeted therapeutics, as exemplified by kinase inhibitors, with specific mechanisms of action and improved toxicity profiles has resulted in improved attrition rates during clinical development in cancer.

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### A Phase I single dose escalation study of the novel Polo-like kinase 1 inhibitor BI 6727 in patients with advanced solid tumours

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**Background:** BI 6727 is a novel highly potent and selective inhibitor of the serine-threonine Polo-like kinase 1 (Plk1), a key regulator of cell cycle progression. BI 6727 is a second generation dihydropteridinone derivative with distinct pharmacokinetic (PK) properties. Objectives of this trial are the assessment of the maximum tolerated dose (MTD) and overall safety, PKs and preliminary efficacy of BI 6727 given intravenously.
**Materials and Methods:** Sequential cohorts of three to six patients with advanced or metastatic solid tumors received a single 1-hour infusion of BI 6727 per treatment course following a toxicity guided dose escalation