

anticipated to achieve broad antitumor efficacy without perturbing insulin signaling/glucose homeostasis.

Methods: Sequential cohorts of three to six subjects with advanced solid tumors received MEDI-573 as an IV infusion with consecutive dose escalations. Subjects had KPS ≥ 60 and adequate hematologic, renal and hepatic function. Study (NCT00816361, sponsor: MedImmune, LLC) objectives included determinations of MTD, safety characteristics, pharmacokinetics (PK), pharmacodynamics (PD), and tumor response.

Results: 17 subjects (7M/10F), median age 58 yrs were treated (15 evaluable for DLT). No DLTs, drug-related serious adverse events or toxicity patterns have been reported to date. CTC grade 1–2 adverse events considered treatment-related have included decreased appetite and fatigue (24% each), anemia and diarrhea (18% each), leukopenia, nausea, and vomiting (12% each), thrombocytopenia, abdominal pain, systolic hypertension, pyrexia, back pain, and exertional dyspnea (6% each). No significant changes in plasma glucose, insulin, or growth hormone levels have been reported. MEDI-573 exhibited a dose-proportional increase in exposure over the range of doses tested and achieved the anticipated pharmacodynamic effects (including free IGF-1 and IGF-2 suppression). Stable disease spanning 12 weeks or more was seen in 5/13 subjects (range 12–30+ weeks), including 1 subject each with Ewing's sarcoma (18w) and liposarcoma (30w+). To date, anti-drug antibodies have not been reported. An expansion cohort (bladder cancer) biomarker focused phase is ongoing at doses that completely suppressed IGF ligands in the circulation.

Conclusions: In this study of 17 subjects, MEDI-573 has shown acceptable safety and favorable PK profiles. It did not directly or through compensatory mechanisms induce changes in glucose, insulin or growth hormone, which are endocrine liabilities observed with other IGF targeting strategies. MEDI-573 appears to have antitumor activity in some multiply refractory subjects. Continued clinical development is being pursued at doses that deplete IGF-1/-2 in the peripheral circulation.

16, 17 and 18 November 2010

POSTER SESSION

Late breaking posters

4LB LATE BREAKING POSTER A first synthesis of [^{18}F]-lapatinib: a new agent for positron emission tomographic studies of kinase receptors

G.L. Griffiths¹, F. Basuli¹, H. Wu¹, C. Li¹, J.L. Tatum², J.H. Doroshow².
¹NHLBI, IPDC, Rockville MD, USA; ²NCI, NIH, Bethesda, USA

Lapatinib ditosylate (Tykerb[®]) is a new drug from GlaxoSmithKline approved for treatment of advanced metastatic breast cancer in combination chemotherapy in patients who have failed Herceptin[®] and other initial therapies, and is also under investigation in other tumor indications. It is an epidermal growth factor receptor (EGFR) and ErbB-2 (Her2/neu) tyrosine kinase inhibitor. Lapatinib contains a fluorine atom in a *meta*-position on one benzyl ring, and ideally, if an ^{18}F atom could be placed here it would result in a chemically identical radiofluorinated analog of the approved drug. The total synthesis of an ^{18}F -lapatinib analog represents a significant overall radiochemical challenge while the generation of the required 3- ^{18}F fluorobenzylbromide intermediate, itself, has not yet been reported. We based our approach to [^{18}F]-lapatinib on ether bond formation between 3- ^{18}F fluorobenzylbromide and a *Boc*-protected Lapatinib fragment, followed by deprotection of the *N-Boc* secondary amino protecting group with TFA. In order to synthesize 3- ^{18}F fluorobenzylbromide a series of arylodonium salts of 3-formylbenzene with different counter-ions [PhPhCHO] X^+ (where $\text{X} = \text{Cl}, \text{Br}, \text{OTf}$) were prepared and radiolabeling of the precursors with ^{18}F was investigated using different bases, different temperatures, and in presence of the free radical scavenger, TEMPO. The best conversion (~80%) was obtained using CsHCO_3 at a reaction temperature of 110°C. 3- ^{18}F Fluorobenzaldehyde thus obtained was then converted to 3- ^{18}F Fluorobenzylbromide and treatment with *Boc*-protected lapatinib precursor fragment in the presence of K_2CO_3 at 100 °C for 10 minutes in a microwave followed by *Boc* deprotection afforded [^{18}F]lapatinib (**1**) (65%, uncorrected, isolated). The overall radiochemical yield of the reaction starting from the radiofluorination of the iodonium salt was 5–10% (uncorrected) in a 130 minute synthesis time. The availability of the [^{18}F]-lapatinib, which represented a heretofore complex and unresolved radiochemical challenge will enable future PET imaging studies related to lapatinib uses.



5LB LATE BREAKING POSTER Anti-tumor activity of MPC-9528, GMX1778 and APO866: Namp1 inhibitors of three different structural classes

J.J. Boniface¹, V.R. Baichwal¹, L. DeMie¹, J.P. Green¹, W.R. Judd¹, J.W. Lockman¹, D.I. Papac¹, R.T. Terry-Lorenzo¹, J.A. Willardsen¹, R.O. Carlson¹. ¹Myrex Inc., Research, Salt Lake City, USA

Background: Nicotinamide phosphoribosyltransferase (Namp1) catalyzes the rate limiting step in the recycling of nicotinamide to NAD. Increased metabolic demands and higher activity of NAD consuming enzymes, such as PARPs, make cancer cells rely more upon Namp1. We compare MPC-9528, GMX1778 and APO866, which represent three structural classes of selective Namp1 inhibitors.

Material and Methods: In vitro and cellular Namp1 activity was measured using a coupled biochemical reaction based on fluorescent resorufin. Viability was measured by cellular ATP levels. Cellular Namp1 activity was measured by NAD levels and detection of nuclear poly(ADP-ribose) (PAR). Xenografts were performed in nu/nu mice.

Results: Namp1 enzyme was potently inhibited in vitro with IC_{50} values of 0.06, 0.1 and 0.4 nM for MPC-9528, GMX1778 and APO866, respectively. Cellular IC_{50} values were 0.2, 3.0 and 0.4 nM by measure of NAD and 0.1, 0.6 and 0.4 nM by measure of PAR for MPC-9528, GMX1778 and APO866, respectively. In 72 hour viability assays in HCT116 cells, MPC-9528, GMX1778 and APO866 exhibited IC_{50} values of 0.4, 2.0 and 1.5 nM, respectively. However, in an HCT116 xenograft model, oral administration of a maximally tolerated dose (MTD) of 75 mg/kg of MPC-9528 on days 1 and 10 gave comparable tumor regression as weekly oral dosing of GMX1778 at 250 mg/kg. Pharmacokinetic (PK) studies indicated that the C_{max} and AUC were approximately 1.5 and 4 fold greater for GMX1778 than MPC-9528. In vivo anti-tumor activity was not observed for GMX1778 at 100 mg/kg despite a comparable C_{max} and 3 fold greater AUC than was obtained for MPC-9528 at 75 mg/kg. The in vivo activities of MPC-9528 and APO866 were also compared in the HCT116 xenograft model. Administration of MPC-9528 orally at its daily MTD of 10 mg/kg for 21 days induced tumor regression, while APO866 dosed IP at its reported MTD of 20 mg/kg twice daily for 4 consecutive days per week for 3 weeks resulted in only tumor growth inhibition, but no regression. PK studies indicated that C_{max} and AUC were approximately 15 and 4-fold greater, respectively, for APO866 than MPC-9528.

Conclusions: This study demonstrates that Namp1 inhibitors with comparable in vitro activities, but different structures, display widely different anti-tumor activity in vivo.

6LB LATE BREAKING POSTER The Namp1 inhibitor MPC-9528 and the PARP inhibitor olaparib synergize in killing a BRCA-deficient cancer cell line

R.T. Terry-Lorenzo¹, T.C. Fleischer¹, J.W. Lockman¹, J.J. Boniface¹, J.A. Willardsen¹, R.O. Carlson¹. ¹Myrex Inc., Research, Salt Lake City, USA

Background: MPC-9528, a tumoral agent with picomolar potency, is an inhibitor of nicotinamide phosphoribosyltransferase (Namp1). Namp1 catalyzes the first step in NAD synthesis from nicotinamide, and when Namp1 is inhibited, cellular NAD levels are depleted. NAD is an essential substrate for the enzyme poly(ADP-ribose) polymerase (PARP), and PARP activity is diminished following Namp1 inhibition. PARP inhibitors such as olaparib selectively kill cells with impaired homologous recombination due to BRCA deficiency. Because MPC-9528 and olaparib inhibit PARP by different mechanisms, we hypothesized that, when combined, these two agents would synergize in killing BRCA-deficient cells dependent upon PARP for survival.

Material and Methods: Cellular NAD was measured using a coupled enzymatic assay. PARP activity was assessed using an imaging-based assay for detection of nuclear poly(ADP ribose) deposition. Cell viability was assessed by measuring ATP levels. In drug combination experiments, synergy, antagonism, or additivity was assessed using the MacSynergy program.