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—SUPPLEMENT TO—

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2010 ASCO Annual Meeting Proceedings

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2010 ASCO Annual Meeting Proceedings

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2504

Clinical Science Symposium, Sun, 8:00 AM - 9:30 AM

First-in-human phase I safety, pharmacokinetic (PK), and pharmacodynamic (PD) analysis of the oral MEK-inhibitor AS703026 (two regimens [R1] in patients (pts) with advanced solid tumors. J. Delord, N. Houede, A. Awada, A. Taamma, S. J. Faivre, T. Besse-Hammer, A. Italiano, C. Vignaud, M. Donica, E. Raymond; Institut Claudius Regaud, Toulouse, France; Institut Bergonié, Bordeaux, France; Institut Jules Bordet, Brussels, Belgium; Merck Serono S.A., Geneva, Switzerland; Beaujon Hospital, Clichy, France; Jules Bordet Institute, Brussels, Belgium; Service Inter-Hospitalier de Cancérologie et Service de Gastroentéropancréatologie, Hôpital Beaujon, Clichy, France

Background: AS703026 is a highly selective and potent noncompetitive inhibitor of MEK1/2. AS703026 exhibited strong antiproliferative activity in tumor cell lines with activated mitogen-activated protein kinase (MAPK) signalling, and antitumor efficacy in numerous human tumor xenograft models. This phase I trial was initiated to determine the maximum tolerated dose (MTD) of two AS703026 R. **Methods:** Pts with solid tumors received oral, fixed doses of AS703026 once a day, on days 1-5, 8-12, and 15-19 (R1) or days 1-15 (R2), of 21-day cycles. Accelerated then modified Fibonacci dose-escalation processes were applied for each R. PK samples and pre- and post-dose peripheral blood mononuclear cells (PBMC) for the measurement of phosphorylated extracellular signal-regulated kinase (pERK) were collected for all pts. **Results:** As of November 1, 2009, 68 pts (36 pts R1, 32 pts R2) received AS703026 across 10 dose levels [range 1-94 mg/day]. Pt characteristics were median age [range] 60 yrs [34-75] R1, 62 yrs [43-77] R2; males 56% R1, 55% R2; ECOG PS (0/1) 56%/44% R1, 55%/46% R2. Most frequent tumors were colorectal (42% R1, 36% R2) and melanoma (14% R1, 12% R2). Pts received a median of 2 cycles [range] in both R [1-6, R1, 1-11, R2]. Most common adverse events (all grades): asthenia (49% R1, 50% R2), diarrhea (40% R1, 28% R2), acne-like skin reactions (37% R1, 41% R2), nausea (34% R1, 25% R2), constipation (26% R1, 16% R2), vomiting (23% R1, 25% R2). At 28 mg/day, 1/6 pts experienced a DLT (grade 3 liver function test elevation). Visual disturbances were reported at 94 mg/day (66% R1, 33% R2). Plasma concentrations and exposures increased proportionally with dose, with a median t_{max} of 1.5 hours [range 0.5-4.0] after intake. Complete pERK inhibition was observed in PBMC 2 hours post-intake at doses ≥ 28 mg/day. Two confirmed partial responses (at 68 and 94 mg/day) were reported in previously-treated melanoma pts. **Conclusions:** AS703026 showed a good safety and PK profile with complete target inhibition in PBMCs at doses ≥ 28 mg/day. MTD has not been reached; dose escalation is ongoing. Interestingly, antitumor activity has been observed prior to reaching the MTD.

2506

Oral Abstract Session, Tue, 9:30 AM - 12:30 PM

Safety and antitumor activity of biweekly MDX-1106 (Anti-PD-1, BMS-936558/ONO-4538) in patients with advanced refractory malignancies. M. Sznol, J. D. Powderly, D. C. Smith, J. R. Brahmer, C. G. Drake, D. F. McDermott, D. P. Lawrence, J. D. Wolchok, S. L. Topalian, I. Lowy; Yale Cancer Center, New Haven, CT; Carolina BioOnco Institute, Huntersville, NC; University of Michigan Cancer Center, Ann Arbor, MI; Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Beth Israel Deaconess Medical Center, Boston, MA; Massachusetts General Hospital Cancer Center, Boston, MA; Memorial Sloan-Kettering Cancer Center, New York, NY; Johns Hopkins University School of Medicine, Baltimore, MD; Medarex, Inc., Bloomington, NJ

Background: Programmed death-1 (PD-1), a T-cell inhibitory receptor, may suppress antitumor immunity. MDX-1106, a fully human IgG4 PD-1 blocking antibody, has shown antitumor activity and limited toxicity after intermittent dosing (Brahmer et al., ASCO 2009). This multicenter trial evaluates safety, antitumor activity, pharmacokinetics (PK), and immunological correlates of extended biweekly dosing. **Methods:** Patients (pts) had treatment refractory metastatic non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma (MEL), or prostate cancer (CRPC), and no history of autoimmune disease. Escalation of biweekly MDX-1106 dosing at 1, 3, or 10 mg/kg IV was studied. Enrollment at the MTD was expanded to 16 pts in each indication, plus colon cancer. Tumor assessments after every 4 doses (one cycle) used RECIST. Pts received up to 12 treatment cycles, until progression (PD) or complete response (CR). Clinically stable pts with early PD could continue until further PD or deterioration. **Results:** Four, 4, and 8 pts accrued at 1, 3, and 10 mg/kg, respectively. MTD was not reached. Grade 1/2 drug-related adverse events in > 2 pts included fatigue (9 pts/56.3%), nausea (4 pts/25.0%), and diarrhea, xerostomia, and pruritus (3 pts/18.8% each). One possibly drug-related SAE, myelodysplastic syndrome, rapidly emerged in a MEL pt previously treated with cytotoxic chemotherapy. As of Dec 2009, 6/16 (37.5%) evaluable pts had objective tumor responses, including 3 at 1 mg/kg (RCC/CR, RCC/PR, MEL/PR), 2 at 3 mg/kg (NSCLC/PR, MEL/PR) and one at 10 mg/kg (MEL/PR). All responses are ongoing (3-13+ mo). Preliminary PK estimates of trough/peak antibody levels after 2 cycles are ~ 25/40, 50/110, 150/300 μ g/ml for 1, 3, and 10 mg/kg, respectively. Expansion cohort enrollment at 10 mg/kg is nearly complete, and the 1 and 3 mg/kg cohorts have been expanded with 16 MEL pts each. Grade 3/4 adverse events remain uncommon. **Conclusions:** MDX-1106 administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg. Correlative tumor and immunologic studies are underway. Objective responses with limited toxicity in multiple malignancies warrant further investigation of PD-1 blockade.

2505

Clinical Science Symposium, Sun, 8:00 AM - 9:30 AM

Phase I dose-escalation study of E6201, a MEK-1 inhibitor, in advanced solid tumors. M. J. Borad, C. E. Akerele, R. K. Ramanathan, D. W. Northfelt, L. Reidman, D. Verbel, K. Feit, D. D. Von Hoff, R. Tibes; Mayo Clinic Arizona, Scottsdale, AZ; Eisai, Woodcliff Lake, NJ; Virginia G. Piper Cancer Center and TGen, Scottsdale, AZ; Virginia G. Piper Cancer Center at Scottsdale Healthcare and TGen, Scottsdale, AZ

Background: E6201 is a potent inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK)-1 and MEK kinase-1, with anticancer activity in preclinical models. **Methods:** This phase I, open-label study evaluated E6201 MTD in advanced solid tumors. Inclusion criteria were ECOG PS ≤ 1 and adequate bone marrow, renal, and liver function. Sequential cohorts of 3-6 subjects were given E6201 30-min IV infusion on Days 1, 8, and 15 of a 28-day cycle starting at 20 mg/m² and increasing in 100% increments up to 320 mg/m² until Grade 2 toxicities or 1 DLT was observed. Doses were then increased by $\leq 50\%$ up to 720 mg/m² or until the MTD was determined. Blood samples were collected on days 1 and 15 for PK analysis. PD assessment included evaluation of CTC, serum IL-6 and IL-8 levels, and effects on proliferation and signal transduction pathway in skin and tumor biopsies. **Results:** 25 subjects (median age 66.6 [range 44-87] yr) received E6201 doses from 20 to 40, 80, 160, 320, and 480 mg/m². At 480 mg/m², 2 subjects had DLTs (QTc prolongation [Grade 3] and confusional state [Grade 4]). E6201 was reduced to 400 mg/m², at which 1 subject had CNS toxicity (dizziness). Therefore, the 320 mg/m² cohort was expanded to 3 additional subjects (total 6); 1 subject had 1 DLT (Grade 2 QTc prolongation) and Grade 2 CNS toxicities (dizziness, dysarthria, ataxia), confirming 320 mg/m² as the MTD. Most frequent AEs across doses were nausea (16%), constipation, dizziness, peripheral edema, and vomiting (all 12%, all Grade 1/2). E6201 was rapidly eliminated (mean $t_{1/2}$ = 2.47-5.60 hr). Exposure to E6201 was dose related and comparable on days 1 and 15. A trend for decreasing IL-6 and IL-8 levels was observed without clear dose dependency or duration of effect. Surrogate tissue (skin) biopsies were not informative. One subject with metastatic ocular melanoma had stable disease (> 10 months) (B-Raf wild-type) and another, with B-Raf mutant papillary thyroid cancer, a partial remission. **Conclusions:** The E6201 MTD of 320 mg/m² IV once weekly for 3 out of a 4-week cycle was well tolerated in patients with advanced solid tumors. An expansion phase at MTD will continue to assess efficacy and determine the optimal schedule using biomarker-driven endpoints and tumor response.

2507

Oral Abstract Session, Tue, 9:30 AM - 12:30 PM

A Cancer Research UK phase I study evaluating safety, tolerability, and biological effects of chimeric anti-CD40 monoclonal antibody (MAb), Chi Lob 7/4. P. W. Johnson, N. M. Steven, F. Chowdhury, J. Dobbey, E. Hall, M. Ashton-Key, E. Hodges, C. H. Ottensmeyer, A. Williams, M. Glennie; Southampton Experimental Cancer Medicine Centre, Southampton, United Kingdom; Institute for Cancer Studies, University of Birmingham, Birmingham, United Kingdom; Experimental Cancer Medicine Centre, Southampton, United Kingdom; Drug Development Office, Cancer Research UK, London, United Kingdom; Department of Histopathology, Southampton University Hospitals, Southampton, United Kingdom; Department of Immunology, Southampton University Hospitals, Southampton, United Kingdom; University of Southampton School of Medicine and Experimental Cancer Medicine Centre Southampton, Southampton, United Kingdom

Background: Expression of CD40 on a range of malignancies and the role of CD40 signaling in antigen presentation make it an attractive target for MAb therapy. Potential mechanisms of action for agonistic anti-CD40 include direct cytotoxic effects on tumor cells, recruitment of immune effectors and conditioning of antigen-presenting cells (Schultze and Johnson. Lancet, 1999, 354:1225). Preclinical studies showed anti-CD40 can eradicate lymphoma in immunocompetent hosts, inducing rapid CD8+ T-cell responses independent of CD4+ T-cell help. The response provided protection against re-challenge without further treatment. Notably, therapeutic activity improved when animals with a higher tumor burden were treated. (French et al Nat Med, 1999, 5:548). We have made an agonistic IgG1 chimeric anti-CD40 MAb, Chi Lob 7/4. The affinity is 0.2 nM, comparable to the parent murine MAb (0.1 nM). The aims of the study are to establish maximum tolerated dose (MTD), toxicity profile, biologically-active dose and pharmacokinetics, identify dose limiting toxicity and propose a dose for phase II evaluation. **Methods:** Eligible patients (pts) have histologically proven CD40+ solid tumors or diffuse large B-cell lymphoma resistant to conventional therapy. Chi Lob 7/4 is given by intravenous infusion weekly for 4 doses starting at 0.5 mg/dose. Planned dose escalation is in cohorts of 3 pts until MTD or biological effect, defined as reduction of peripheral blood CD19+ B-cells to 10% or less of baseline. Nineteen patients have been recruited to the dose escalation study, reaching 160 mg/dose. An expanded cohort at this dose will test efficacy in different tumor types. Enzyme linked immunosorbent assays were developed and validated to quantitate Chi-Lob 7/4 in serum and test for anti-chimeric MAb responses. Pharmacodynamic assessments include quantitation of T-, NK-, and B-cell numbers and activation in peripheral blood by flow cytometry, measurement of a panel of cytokines in plasma by Luminex technology, enumeration, and phenotypic assessment of human plasmacytoid and myeloid dendritic cells by a novel 6 color flow cytometry panel.