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Meeting Proceedings

ASCO

IN MEMORIAM
B.J. Kennedy, MD

The 2003 Meeting Proceedings Is Dedicated
to the Memory of B.J. Kennedy, MD,
ASCO Founding Member and Past President

800 Poster Discussion, Tue, 8:00 AM - 12:00 PM

A phase II study of E7070 in patients with metastatic, recurrent, or refractory head and neck squamous cell carcinoma (HNSCC): Clinical activity and post-treatment modulation of Rb phosphorylation. *R. I. Haddad, G. I. Shapiro, L. Weinstein, T. Wieczorek, N. Bhattarcharya, M. Loda, J. L. Faucher, H. Raftopoulos, M. Oster, M. Posner; Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital, Boston, MA; Columbia University, New York, NY*

E7070 is a synthetic sulfonamide that targets the G1 phase of the cell cycle. It causes depletion of cyclin E, upregulation of p53 and p21Waf1/Cip1, as well as inhibition of cdk2 phosphorylation. All of these events contribute to hypophosphorylation of the retinoblastoma (Rb) protein and cause a blockade in the G1/S transition. We conducted a phase II study of E7070 in patients with noncurable HNSCC. Patients received 700 mg/m2 over one hour every 3 weeks. Fifteen patients were treated with a median age of 59 years. A total of 39 cycles of E7070 were delivered, median 2.6 per patient. Six patients had progressive disease (PD) after 2 cycles and 3 patients had PD after one cycle. Five patients showed stable disease (SD) after 2 cycles and went on to receive 1 (2 patients), 2 (2 patients) and 3 additional cycles (1 patients), respectively, before showing PD. One patient remains on study and has received 5 cycles with SD. A fine needle aspirate (FNA) was obtained from 5 patients prior to treatment and within 24 hrs after the completion of the first 3-hr infusion to determine whether the phosphorylation of Rb was modulated in tumor cells following drug exposure. Aspirates were subjected to immunohistochemistry with phospho-specific anti-Rb antibodies directed at the T821, S795 and S807/811 cdk2- and cdk4-specific phosphorylation sites.Among the 3 patients with informative samples, results were as follows: E7070 demonstrated very limited activity against SCCHN.However,our data suggest that cdk activity can be inhibited in tumor cells, resulting in a post-treatment modulation of Rb phosphorylation. In the absence of cytotoxic activity, more frequent administration of E7070 may be required to sustain Rb hypophosphorylation and cytostatic growth arrest.

patient	antibody	% (2+,3+) pre-treatment	% (2+,3+) post-treatment	Clinical Outcome
1	Anti-Rb [pT821]	32	5	PD after 2 cycles
	Anti-Rb [pS795]	86	21	
2	Anti-Rb [pT821]	13	0	SD after 2cycles PD after 4
	Anti-Rb [pS795]	41	0	
3	Anti-Rb [pS807/811]	80	0	SD after 4 cycles. Still on study
	Anti-Rb [pS795]	80	5	
	Anti-Rb [Total]	70	50	

801 Poster Discussion, Tue, 8:00 AM - 12:00 PM

Phase I study of the proteasome inhibitor bortezomib and pegylated liposomal doxorubicin in patients with refractory hematologic malignancies. *R. Z. Orlowski, P. M. Voorhees, R. Garcia, M. Hall, J. Adams, D. Esseltine, C. Dees; Univ of North Carolina at Chapel Hill, Chapel Hill, NC; Millennium Pharmaceuticals, Inc., Cambridge, MA*

The proteasome is involved in intracellular protein degradation, and is a novel target for therapy of hematologic malignancies. Proteasome inhibitors also block activation of several survival pathways, including NF-KB and p44/42-MAPK, that may limit the effectiveness of anthracyclines, suggesting such combinations might have enhanced anti-tumor efficacy. We sought to evaluate the maximum tolerated dose(MTD), dose limiting toxicity(DLT), pharmacokinetics, and pharmacodynamics of the proteasome inhibitor bortezomib(B;Velcade) and pegylated, liposomal doxorubicin(D;Doxil) in patients(pts) with hematologic malignancies. B was given as an intravenous bolus at 0.90–1.30-mg/m^2 on days-1, -4, -8, and -11 of a 3-week cycle, and D on day-4 at 30-mg/m^2. The MTD was defined based on cycle-1, while responses were evaluated every 2 cycles. 19 pts have been treated, and have included 14 multiple myeloma(MM) pts. A mean of 4.4 cycles (range 1–10) has been administered, with 15 pts evaluable for toxicity. At 0.90-mg/m^2 a pt with Crohns disease had grade(g)-3 diarrhea, hypotension, confusion and syncope, but no other DLTs were noted at this or other levels, and the MTD has yet to be defined. All other non-hematologic drug-related toxicities during cycle-1 have been g-1/2 in intensity. G-3/4 toxicities in later cycles included fatigue, palmar plantar erythrodysesthesia, cytopenias, and neuropathy. Of 10 evaluable MM pts complete responses(CR) have been observed in 3, near-CR in 1, partial responses(PR) in 3, 1 pt each had a minor response or stable disease, while one progressed. Five of these pts, including two of the CRs, had disease that previously progressed, or did not respond to anthracycline-based therapy, and five are continuing treatment. Also, one pt with relapsed acute myeloid leukemia had a PR. Early results from this study suggest that BD may be well-tolerated and active in patients with multiple myeloma, and possibly other hematologic malignancies. Accrual is continuing to define the MTD and DLT.

802 Poster Discussion, Tue, 8:00 AM - 12:00 PM

A phase I trial of an oral histone deacetylase inhibitor, MS-275, in advanced solid tumor and lymphoma patients. *Q. C. Ryan, D. Headlee, A. Sparreboom, W. Figg, S. Zhai, J. Trepel, A. Murgo, Y. Elsayed, J. Karp, E. Sausville; National Cancer Institue, Bethesda, MD; Cancer Institute of New Jessy, New Brunswick, NJ; The Sidney Kimmel Cancer Center at Johns Hopkins, Baltimore, MD*

We are conducting a Phase I trial using MS-275, an orally administered, synthetic histone deacetylase inhibitor, in advanced solid tumor and lymphoma patients. The trial initially used a daily x 28, repeated every six weeks, dosing schedule with an accelerated titration design, beginning at 2 mg/m2 (i.e., 1/10 of rat maximal tolerated dose (MTD)). However, in humans the MTD was exceeded at the 1st dose level, with grade 3 AST, hyposphosphatemia, hypoalbuminemia, pleural effusion and epigastric pain. Preliminary evidence of a substantially longer half-life of MS-275 in humans as compared to preclinical species likely accounts for this finding. A once q14 day schedule was then implemented, also starting at 2 mg/m2 but escalating with 2 mg/m2 increments. To date, 20 patients have been treated on this schedule. Although escalated to level 5 (10 mg/m2 q 2 wk), the MTD has not yet been reached. Frequent grade 1–2 toxicities include fatigue (50%); nausea (50%); hypoalbuminemia (35%), headache (35%), anxiety (30 %), dyspepsia (30%), vomiting (30%); dysgeusia (20%), anemia (20%), fever (20%), and hyponatremia (20%). Besides the first course toxicities, hypoalbuminemia and progressive fatigue as a continuing effect of MS-275 occurred, especially at higher dose levels, and are of concern for long term dosing. Peak plasma concentrations were observed at 6 - 24 h after dosing, suggesting slow absorption, and in the range of 10 - 50 ng/ml. This concentration is within the range that might affect proliferation of certain cell types preclinically. Dose dependence of exposure to MS-275 occurred, but no further increase in area under the curve at doses above 6 mg/m2 was evident. This phenomenon likely involves nonlinear, apparent saturable absorption processess. Increased histone H3 acetylation in peripheral blood mononuclear cells was apparent at all dose levels, by immunofluorescent analysis. Based on these data, a new oral schedule, weekly x4, repeated every six weeks, as well as an intravenous formulation are being developed.

803 Poster Discussion, Tue, 8:00 AM - 12:00 PM

A phase I study of the oral mTOR inhibitor RAD001 as monotherapy to identify the optimal biologically effective dose using toxicity, pharmacokinetic (PK) and pharmacodynamic (PD) endpoints in patients with solid tumours. *A. O'Donnell, S. Faivre, I. Judson, C. Delbado, C. Brock, H. Lane, N. Shand, K. Hazell, J.-P. Armand, E. Raymond; Royal Marsden Hospital, Sutton, UK; Institute Gustave Roussy, Villejuif, France; Novartis Pharma AG, Basel, Switzerland*

RAD001, a novel derivative of rapamycin, interacts with the mTOR protein kinase to inhibit downstream signalling proteins crucial to cell cycle progression. Pre-clinical *in vitro* and *in vivo* studies have shown dose dependent inhibition of tumour growth and reduced tumour vascularity, as well as the ability to potentiate the activity of a number of cytotoxics including paclitaxel and gemcitabine. Methods: This phase I dose escalation study was performed to identify the optimal biologically effective dose based on toxicity, PK and PD assessments using the biomarker p70 S6 kinase 1 (S6K1) activity in peripheral blood mononuclear cells (PBMCs). Indication of activity was also sought using conventional and PET imaging. Treatment with RAD001 was given orally, once weekly. Results: Cohorts of 4 patients were treated at each of 4 dose levels: 5, 10, 20 and 30mg. (7M:9F; Median age 60y, Range 32–75 y) RAD001 was well tolerated with only mild degrees (Gr 1/2) of anorexia, fatigue, rash, mucositis, headache, hyperlipidemia and gastrointestinal disturbance. PK results are consistent with prior experience (renal transplant and healthy subject studies): AUC increasing in proportion to dose, a plateau in Cmax occurring at doses ≥20mg and a terminal $t_{1/2}$ of 26—38 hours. 4 patients (hepatocellular 10mg; fibrosarcoma 10mg; NSCLC x 2, 30mg) have stable disease >16 weeks. A responding patient with NSCLC showed a reduction in ^{18}FDG uptake on PET scanning after week 3. S6K1 activity in PBMCs was inhibited for 3—5 days at 5 and 10 mg dose levels. At doses ≥20mg 7/8 patients exhibited inhibition for at least 7 days. Conclusions: Weekly administration of 20mg RAD001 in patients, gives plasma concentrations and sustained S6K1 inhibition equivalent to the PK levels and PD changes that correlate with anti-tumour effects in rodents treated with this schedule. Doses above 20mg result in only marginally increased inhibition. Combination studies have been initiated and we continue to explore the PD impact of mTOR inhibition in human tumours.