Wednesday 29 September 15:00–16:00

PLENARY SESSION 2

Proffered papers

28 ORAL

Molecular and clinical analysis of response to Imatinib for locally advanced dermatofibrosarcoma protuberans

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Background: Dermatofibrosarcoma protuberans (DFSP) is a cutaneous malignant tumor that is typically associated with a translocation between chromosomes 17 and 22 that places the platelet-derived growth factor-B (PDGFB) under the control of the collagen 1A1 promoter. This translocation results in overexpression of PDGFB, with resultant autocrine/paracrine activation of the platelet-derived growth factor receptor beta (PDGFRB). Treatment with imatinib mesylate has been reported to be effective in several cases of metastatic DFSP. The purpose of this study was to evaluate the cytogenetic and kinase activation profiles in a series of DFSP, and to determine whether these biological features correlate with clinical responses to imatinib.
Patients and Methods: 10 patients with DFSP were treated with imatinib at 800mg daily. Eight patients had locally advanced DFSP and 2 had metastatic disease. Clinical responses were evaluated using SWOG criteria by either CT, clinical photography or by palpation using ultrasound to confirm clinical measurements. PDGFB genomic evaluations were performed by karyotyping and fluorescence *in situ* hybridization, and PDGFRB activation was determined by immunoblotting for phosphorylated and total forms of PDGFRB.
Results: Each of 8 patients with locally advanced DFSP had karyotypic and/or FISH evidence of t(17;22), and showed a clinical response to imatinib. Two of these patients had complete clinical responses (CR). The two patients with metastatic disease had fibrosarcomatous histology and karyotypes that were substantially more complex than those reported generally in locally advanced DFSP. In one of these patients, the metastatic DFSP had t(17;22), and this patient had a partial response to imatinib but progressed after 7 months of therapy. The other patient with metastatic disease lacked the t(17;22), and this patient did not show a clinical response to imatinib. Resections of residual DFSP, in 2 patients with major clinical responses, revealed persistence of the t(17;22) in approximately 20% of the cells. Notably, there was minimal phospho-PDGFRB in the untreated DFSP, despite the documented presence of a PDGFB autocrine/paracrine mechanism.
Conclusions: Imatinib has clinical activity against both localized and metastatic DFSP with t(17;22). However, DFSP-like tumors that lack t(17;22) may not respond to imatinib. The t(17;22)-induced PDGFB overexpression results in relatively weak PDGFRB activation, perhaps accounting for the low proliferative activity and the gradual nature of the clinical responses to PDGFRB inhibition.

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A phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of OGX-011, a 2′-methoxyethyl phosphorothioate antisense to clusterin, in patients with prostate cancer prior to radical prostatectomy

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Background: The *clusterin* gene encodes a cytoprotective chaperone protein that promotes cell survival. *Clusterin* is expressed in a variety of cancers including prostate, increases in response to apoptotic stimuli, and in pre-clinical models confers a resistant phenotype. OGX-011 (Oncogenex Technologies Inc) is a 2nd generation antisense complimentary to *clusterin* mRNA that inhibits expression of *clusterin* in xenograft models and thereby increases sensitivity to therapy. The objective of this first-in-man study was to determine phase II dose based on target regulation effect in addition to standard toxicity parameters.
Methods: Patients having localized prostate cancer with high-risk features and candidates for prostatectomy were enrolled to this dose escalation trial. OGX-011 was given by IV infusion over 2 hrs at a starting dose of 40mg on days 1, 3, 5, 8, 15, 22, and 29. Buserelin and flutamide were started on day 1. Prostatectomy was performed day 30–36. OGX-011 plasma PK and prostate tissue concentrations were determined. Prostate tissues, lymph nodes, and serial samples of peripheral blood mononuclear cells and serum were assessed for *clusterin* expression.
Results: 25 patients were enrolled to 6 cohorts with doses of OGX-011 up to 640mg delivered. Toxicity was limited to grade 1 or 2, including fevers, rigors, fatigue and transient AST and ALT elevations. Plasma PK analysis showed linear increases in AUC and Cmax with a t1/2 of approximately 2 hrs. Prostate tissue concentrations of OGX-011 increased with dose, and tissue concentrations associated with preclinical effect could be achieved. Dose dependent decreases in prostate cancer cell *clusterin* expression were observed by rtPCR, in situ hybridization and immunohistochemistry (IHC). At 640mg dosing, *clusterin* mRNA was decreased to a mean of 8% (SD=4%) compared with lower dose levels and historical controls as assessed by rtPCR on laser captured microdissected cancer cells. By IHC, mean% cancer cells staining 0 intensity for *clusterin* protein at 640mg dosing was 54% (SD=24%) compared with 2–15% for lower dose levels and historical controls.
Conclusions: OGX-011 is well tolerated and can inhibit *clusterin* expression in primary prostate cancers. The recommended phase II dose for OGX-011 is 640mg based on pharmacokinetic parameters and target regulation results. Phase II studies of OGX-011 in combination with hormone and chemotherapy are planned in patients with prostate, breast and lung cancers. Supported by a grant from the U.S. Department of Defense and coordinated by the NCIC-CTG.

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A phase I clinical trial of HGS-ETR1, an agonist monoclonal antibody to TRAIL-R1, in patients with advanced solid tumors

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Background: HGS-ETR1 (TRM-1) is a fully-human monoclonal antibody that is agonistic to the Tumor Necrosis Factor Apoptosis-Inducing Ligand Receptor 1 (TRAIL-R1). TRAIL-R1 is expressed on the surface of a wide variety of human tumor cells. When TRAIL R1 is bound by its native ligand, TRAIL, or an agonistic antibody, it can induce apoptosis through the extrinsic pathway. Preclinical studies show that HGS-ETR1 induces apoptosis in a range of human tumor cell lines in vitro and inhibits tumor growth in human tumor xenograft models.
Methods: Patients with advanced refractory solid tumors were or will be treated with HGS-ETR1 by iv infusion once every 28 or 14 (10 mg/kg only) days.
Results: To date 37 patients have received 69 cycles (doses) in the on-going trial of HGS-ETR1 across 7 dose cohorts ranging from 0.01 mg/kg to 10.0 mg/kg q28 days. The median number of cycles is 2 (1 to 7+). Primary tumor types include lung, colon, esophagus, prostate, renal, pancreas and thyroid. In general, HGS-ETR1 has been well-tolerated. One patient with pre-existing Grade 2 peripheral neuropathy treated at the 0.01 mg/kg dose had worsening of symptoms to Grade 3. Another patient developed a reversible acute lung injury (Grade 4) after treatment at the 10 mg/kg dose. Both events were considered possibly drug-related; no other Grade 3/4 toxicities have been attributed to HGS-ETR1. Five patients have had radiographic evidence of stable disease lasting through at least 2 (n=1), 4 (n=3) or 6 (n=1) treatment cycles. Preliminary pharmacokinetic results are linear up to 1.0 mg/kg and are non-linear at 3.0 mg/kg. At the 3 mg/kg dose, HGS-ETR1 concentrations increased less than proportionally to dose, with a mean (SD) T1/2b of 24.9 (16.1) days and CL of 6.2 (3.3) mL/day/kg.
Conclusions: HGS-ETR1 is well-tolerated and the maximum tolerated dose has not been reached. Enrollment to the final cohort of 10 mg/kg every 14 days is planned.