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NPI-2358 (a novel vascular disrupting agent) Phase 1 dose escalation trial with an RP2D cohort

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Background: NPI-2358 is a vascular disrupting agent (VDA) functioning through inhibition of tubulin polymerization leading to tumor vascular endothelial destabilization. NPI-2358 selectively induces tumor vascular collapse producing tumor regression alone and in combination with other standard of care oncology therapies in preclinical tumor models. Preclinical and clinical data suggest VDAs may have significant potential in treating NSCLC in combination with standard of care agents and angiogenesis inhibitors. Preclinical data indicate NPI-2358 may have advantages in terms of safety profile and activity. Based on the outcomes reported herein of the first-in-human study of NPI-2358 in patients with advanced solid tumors and lymphomas, a Phase 1/2 trial has been initiated in patients with NSCLC in combination with docetaxel.
Methods: Patients were treated with a weekly IV infusion of NPI-2358 for 3 weeks in 4-week cycles. The dose of NPI-2358 was escalated from 2 to 30 mg/m^2. A dynamic accelerated dose titration (DADT) study design was used, in which the dose of NPI-2358 was escalated in cohorts, in which any cohort could consist of 1 patient provided no $\geqslant$Grade 2 adverse event is reported in the prior cohort, otherwise the cohort consisted of at least 3 patients. In addition to weekly safety monitoring, ECG, ECHO and PK were obtained on D1 & D15. DCE-MRI were performed at baseline, Day 2 and at optional time points on study to assess changes in tumor blood flow as estimated by the volume transfer constant (Ktrans). A recommended Phase 2 dose (RP2D) was selected based on safety and pharmacodynamic data, at which point enrollment began in an RP2D cohort.
Results: 31 subjects were enrolled. 30 mg/m^2 was selected as the RP2D, based on adverse events of nausea, vomiting, fatigue, fever, tumor pain and transient elevations in blood pressure, as well as DCE-MRI data. DCE-MRI demonstrated decreases in Ktrans beginning at 13.5 mg/m^2, and a 16−82% decrease in patients evaluated at 30 mg/m^2. Decreasing Ktrans over multiple treatment cycles was seen in the two patients that underwent repeat DCE-MRI imaging. Eight patients (26%) had stable disease for two or more cycles: pancreatic adenocarcinoma, colorectal carcinoma, anal squamous cell carcinoma, adrenocortical carcinoma, melanoma, liposarcoma and hemangiopericytoma (2). Mean Cmax and $AUC_{0-\infty}$ increased from 34.4 ng/mL to 610 ng/mL, and from 101 to 3998 ng/mL$\times$hr respectively. No drug accumulation was observed; T1/2 was 5.8 h, clearance was 34.1$\pm$26.4 L/h and distributive volume was 210.7$\pm$60.8 L.
Conclusions: At the RP2D NPI-2358 produced tolerable toxicities, while eliciting biological effects as evidenced by a decrease in tumor blood flow, tumor pain and adverse events. Effects on blood flow appeared to increase with increasing dose and time on treatment. Cmax and AUC increased with dose, without drug accumulation. NPI-2358 is currently proceeding into Phase 1b/2 trials in solid tumor malignancies.

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Assessment of predictive biological markers with an oral angiogenic receptor tyrosine kinase (RTK) inhibitor, TSU-68, in the Phase I/II study for advanced hepatocellular carcinoma (HCC)

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Background: TSU-68 is an oral anti-angiogenesis compound that inhibits VEGFR-2 and PDGFR. HCC is well known for most hypervascular tumors, and some anti-angiogenic agents exhibit efficacy at some level. However, a useful biological marker which can predict responders to each agent has still not been substantially reported. We performed an open-label phase I/II study to evaluate the safety and efficacy of TSU-68 in advanced HCC. To explore the predictive biological makers, 40 factors in patients' plasma were analyzed and compared between the PD group and non-PD group.
Patients and methods: Patients who are not candidates for conventional therapy were eligible. In the phase I portion, the safety and pharmacokinetics were assessed by a stepwise study design based on the hepatic function. In phase II, efficacy was assessed at the dose determined at phase I. The response rate was assessed by RECIST. Forty factors involving angiogenic related proteins were measured on day 1 and 28 and we analyzed the relationship between those expression levels and the best response or time to progression (TTP). Cut-off levels for evaluating TTP were determined by receiver operating characteristic (ROC) curve.
Results: Twelve pts were enrolled in phase I. Dose limiting toxicities were found with 400 mg bid and the dose was de-escalated to 200 mg bid, which provided biologically active levels. Phase II assessment was performed on all 35 pts, with 23 pts additionally enrolled. Common toxicities were: hypoalbuminemia, diarrhea, abdominal pain, fever, AST/ALT elevation, most grade 1 or 2. Only one pt discontinued administration due to toxicities. Response rate (CR+PR) was 8.6%, disease control rate (CR+PR+SD) was 51.4%. Tumor necroses were observed in 9 pts (25.7%). The analysis of plasma biomarkers of 35 pts revealed that high expression levels of PDGF, VCAM-1, and LDH at baseline correlated with disease control rate compared to low expression levels. Moreover, the TTP with higher levels of LDH and PDGF group were significantly longer than other patients ($p < 0.0001$, Log-rank test).
Conclusions: TSU-68 exhibits promising anti-tumor efficacy with a highly safe profile even in heavily pretreated advanced HCC with cirrhosis. The biomarker analysis shows that baseline level of angiogenic factors PDGF, VCAM-1 or LDH in plasma correlated with clinical outcome of phase I/II study. These markers could provide a useful biological maker to predict the response of TSU-68 in HCC.

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The BH4 domain is required for proangiogenic function of bcl-2

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Background: We have previously demonstrated that overexpression of bcl-2 in melanoma cells exposed to hypoxia enhances angiogenesis through Hypoxia Inducible Factor (HIF)-1-mediated-Vascular Endothelial Growth Factor (VEGF) expression. Although it is well established in which domains map the prosurvival function of bcl-2, whether the same or distinct domains of bcl-2 account for the antiapoptotic and proangiogenic activities is not fully understood.
Materials and Methods: Expression vectors encoding the human wild type bcl-2, two inactivating point mutations into the BH1 and BH2 domains and the bcl-2 deleted of the amino-terminal BH4 domain were used for stable and transient transfection of M14 human melanoma line. VEGF and HIF-1α protein expression was evaluated by ELISA and western blot analyses, respectively. For transcriptional activity experiments, luciferase constructs containing VEGF 1511-bp proximal promoter or HIF-1-like 808-bp sequences were used. In vitro HUVEC proliferation and morphogenesis, and in vivo matrigel assays were performed by using Conditioned Medium (CM) from the different lines exposed to hypoxia (1% oxygen, 24 h). Microvessel density and VEGF transcripts were evaluated by immunohistochemical staining and real-time absolute quantitative RT-PCR, respectively in tumors obtained after injection of different cell lines in nude mice.
Results: We showed that the activation of HIF-1/VEGF proangiogenic signaling by bcl-2 under hypoxia requires the BH4 domain but not the BH1 and BH2 domains, which abrogate the interaction of bcl-2 with bax. In keeping with this, CM obtained from cells expressing bcl-2 deleted of the BH4 domain markedly reduced in vitro angiogenesis-related endothelial cell functions and in vivo neovascularization when compared to the effect induced by CM derived from cells overexpressing wild type bcl-2. Notably, deletion of BH4 domain also abrogated the ability of bcl-2 to increase the microvessel density and VEGF production in human tumor xenografts. Finally, exogenous application of the BH4 cell permeable peptide was sufficient to induce HIF-1-mediated VEGF protein expression in melanoma cells exposed to hypoxia.
Conclusions: Together, these results show a regulation of angiogenesis by bcl-2 through a mechanism that requires the BH4 domain, and suggest the development of new antiangiogenic agents targeting the BH4 domain of bcl-2.