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A phase I dose-escalation study of the fully human monoclonal antibody MNRP1685A (anti-NRP1) administered intravenously to patients with advanced solid tumors

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Background: Neuropilin-1 (NRP1) is required for vascular remodeling and blood vessel maturation. NRP1 is expressed by endothelial and stromal support cells in almost all human tumor types tested, and by a subset of tumor cells. Anti-NRP1 is a human synthetic phage IgG1 antibody that blocks binding of a number of b-domain ligands, including VEGF, VEGF-B and PlGF, to NRP1. Anti-NRP1 blocks maturation of blood vessels and keeps blood vessels more dependent on VEGF for survival. In preclinical studies, anti-NRP1 shows substantial anti-tumor activity when combined with anti-VEGF.
Methods: Patients with advanced solid tumors were treated with anti-NRP1 intravenously every three weeks using a 3+3 dose escalation design. Objectives were to study safety, pharmacokinetics (PK), and pharmacodynamics (PD), and to determine the maximum tolerated or administered dose.
Results: Thirty-two patients were enrolled in 7 dose-escalation cohorts at doses of 2, 5, 10, 15, 20, 30 and 40 mg/kg. The most frequent drug-related adverse event was acute infusion reaction (Grade 1 and 2) manifested initially by rigors, pyrexia, headaches, hypotension and hypertension. With dexamethasone premedication (Days −1 and 1) anti-NRP1 infusions were well tolerated with main symptoms of pruritus and rash. Other Grade 1 and 2 adverse events observed in more than 1 patient were fatigue and myalgia. One dose-limiting toxicity of Grade 3 upper gastrointestinal bleeding (20 mg/kg) was observed. One Grade 3 thrombocytopenia coinciding with unrelated Grade 3 fungemia was observed in the 30 mg/kg cohort. Anti-NRP1 showed nonlinear PK with more-than-dose proportional increases in exposure, consistent with broad expression of the target. Target exposure, based on preclinical studies, was achieved with every 3-week dosing starting at 15 mg/kg. One patient with rectal cancer was on study for a total of one year with stable disease. Eight other patients had stable disease for 4 to 6 cycles. Placental Growth Factor (PlGF) has been identified as possible PD marker for anti-vascular agents. Anti-NRP1 resulted in sustained elevation of PlGF starting at 10 mg/kg.
Conclusions: Anti-NRP1 is generally well tolerated with acute infusion reaction as the main adverse event. PK is non-linear throughout the dose range consistent with broad target expression. Estimated target exposure was achieved with every 3-week dosing. Elevation of PlGF as a PD marker of systemic NRP1 pathway inhibition was observed.

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The oral MEK1/MEK2 inhibitor, GSK1120212, effectively inhibits the MAPK pathway: pharmacokinetic, pharmacodynamic, and clinical response relationship

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Background: GSK1120212 is a reversible and highly selective allosteric inhibitor of MEK1/MEK2. The objectives of the First-in-Human study are to define the maximum tolerated dose (MTD), and to evaluate the pharmacokinetic, pharmacodynamic (PD), and response rate of GSK1120212 in advanced solid tumors and lymphoma. In Part 1 of this 3-part study, the MTD and recommended phase II dose (RP2D) were identified as 3 mg QD and 2 mg QD, respectively.
Materials and Methods: GSK1120212 is given orally on a daily basis (QD). In Part 2, GSK1120212 was administered in patients (pts) with selected tumor types to further evaluate safety, tolerability, and clinical activity at the RP2D. In Part 3, biological activity was evaluated using FDG-PET scans or tumor biopsies collected pre-dose and after 15 days of dosing across a range of doses below the MTD.
Results: GSK1120212 exposure increases with dose in an approximately dose-proportional manner, has a small peak:trough ratio of ~ 2, and an effective half life of ~ 4.5 days. Steady state is reached by ~ day 15. Based on day 15 mean trough levels ($C_{trough,ss}$) observed at the 2 mg dose level, the majority of subjects (>83%) are predicted to exceed the antiproliferation IC_{90} of B-RAF-mutant cell lines, which defined the preclinical target exposure level. In the 20 evaluable pts with B-RAF-mutant melanoma, 2 complete responses (CRs) and 6 partial responses (PRs) were observed (preliminary response rate = 40%). In 22 evaluable pancreatic cancer pts, 1 PR and 9 SDs were observed; 5 of these pts had a CA19−9 decrease of >55%. Twenty-three of 25 melanoma pts and 9 of 15 pancreatic cancer pts dosed at 2 mg QD achieved $C_{trough,ss}$ above the preclinical target exposure level. In 20 evaluable paired biopsies from pts with melanoma or other solid tumors pERK, ppERK, and Ki67 generally decreased with increasing dose (0.5−2.0 mg QD), whereas p27 generally increased. SUV_{max} was reduced by 4−48% after a 2-week treatment at doses of 0.5 to 2.5 mg QD in 6 melanoma pts with evaluable FDG-PET data.
Conclusions: The long effective half life and small peak:trough ratio of GSK1120212 allow constant target inhibition within a narrow range of exposure. The RP2D achieves preclinical target exposure level, modulates relevant PD markers, and is associated with durable clinical activity in specific tumor types.

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Clinical, pharmacokinetic (PK) and pharmacodynamic (PD) results of first-in-man phase I trial of the orally available MEK-inhibitor MSC1936369 (AS703026) in patients (pts) with advanced solid tumors

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Background: MSC1936369 is a highly selective non-competitive inhibitor of MEK1/2 with anti-proliferative activity in tumor cell lines and in human tumor xenografts with mitogen-activated protein kinase (MAPK) signaling. The primary objective of this ongoing phase I trial is to determine for each of 2 different dosing schedules (S) the maximum tolerated dose (MTD).
Methods: Pts with solid tumors received MSC1936369 orally once/day (d), either on d 1−5, 8−12, and 15−19 (S1) or on d 1−15 (S2) of a 21-d cycle. In each S independently, a 3+3 design with accelerated dose escalation was followed after grade 2 toxicity by a modified Fibonacci scheme. PK samples and peripheral blood mononuclear cells (PBMC) to measure phosphorylated extracellular signal-regulated kinase (pERK) were collected for all pts.
Results: A total of 85 pts were dosed, 43 across 11 dose levels (DL) in S1 and 42 across 13 DLs in S2. DLs ranged between 1 and 195 mg/d. Pt characteristics: median age [range] 59 yrs [34−75] S1, 62 yrs [35−77] S2; males 58% S1, 64% S2; ECOG PS (0/1) 60%/40% S1, 50%/50% S2. Most frequent tumors: colorectal (42% S1, 33% S2) and melanoma (12% S1, 26% S2). Pts received a median of 2 cycles in both S [range 1−8, S1, 1−11, S2]. Most common adverse events (⩾15% of pts in at least 1 S) were grade 1−2: skin rash, diarrhea, asthenia, nausea, vomiting and peripheral edema. At 28 mg/d (S1), 1/6 pts experienced a dose-limiting toxicity (DLT) (grade 3 liver function test elevation). Visual disturbances were reported in 23% pts in S1 and 29% in S2, with some cases of serous macular detachment. One pt at 120 mg/d (S1) developed in cycle 3 grade 2 retinal vein occlusion, which was considered DLT. Plasma concentrations increase with dose, median t_{max} 1 hour (hrs) [0.5−4.0 hrs]. At doses ⩾28 mg/d pERK inhibition in PBMC was >80% at 2 hrs, around 80% at 8 hrs and 50% at 24 hrs. BRAF status is available for 11/17 melanoma pts: 6 are mutated and 5 wild-type. Tumor shrinkage was reported in 4 melanoma pts (3 mutated and 1 wild-type), 3 of whom (all BRAF mutated) had partial responses (PR).
Conclusions: Adverse events associated with MSC1936369 are usually mild to moderate and reversible during treatment or after dosing interruption. Cohort expansion in S1 at 120 mg/d and dose escalation in S2 are ongoing. PK seems dose proportional, >50% target inhibition lasts up to 8 hrs post dosing, 3 PRs are reported in BRAF mutated melanoma.