In GIST, activating mutations in KIT exon 9 or 11 occur in ~80% of patients. Tyrosine kinase inhibitors (TKIs) such as imatinib, sunitinib and regorafenib have markedly improved treatment of GIST. However, most GIST patients develop resistance mutations in exon (ex) 13, 14, 17 or 18. PLX9486 is a novel TKI with activity against primary KIT mutations (ex 9 and 11) and against activation loop mutations (ex 17 and 18).

**Mechanism**
PLX9486 has complementary mutant selectivity versus other KIT TKIs. PLX9486 is >150 fold selective for mutant vs. WT KIT. Combinations of PLX9486 with either pazopanib (PLX3397) or sunitinib potentially inhibit all common primary and secondary KIT mutations.

**Clinical Study Design/Methods**
Phase 1 open-label, multi-dose, dose escalation in two Parts.

**Part 1 Objectives:**
- Evaluate PLX9486 single agent safety & pharmacokinetics (PK).
- Establish single agent maximum tolerated dose/recommended phase 2 dose (MTD/RP2D).
- Evaluate efficacy by ORR by RECIST 1.1, including Duration of Response (DOR) and Progression-Free Survival (PFS).
- Exploratory: Assess changes in circulating tumor DNA (ctDNA) and other biomarkers in peripheral blood & tumor tissue.

**Part 2 Objectives:**
- Assess efficacy of a. single agent PLX9486 @ RP2D in GIST and other solid tumors with a KIT mutation, and b. combinations (PLX9486+sunitinib; PLX9486+PLX3397) in GIST.
- Assess the safety & tolerability of the combinations.
- Secondary:
  - Assess PK of the combinations with or without food
- Exploratory: See Part 1

**Results**

**Adverse Events**

**Patient Characteristics**

**Circulating Tumor DNA**
Cell-free DNA from patient plasma was sequenced with a targeted panel to identify mutations in cDNA.

**Conclusions**
PLX9486 as single agent selectively inhibits a spectrum of KIT mutations including difficult to treat exon 13/18 activation loop variants.
PLX9486 single agent RP2D = 500 mg QD (MTD not reached);
predicted efficacy exposure observed; well tolerated.
Interim results in heavily pretreated GIST patients (100% ≥ 3 prior regimens) at doses ≥ 500 mg daily: 1 PR; CBR of 57%; median PFS of 20.86 weeks (95% CI: 9.5-46).

**Study Progress and Interim Results**
Interim results for GIST patients (all having ≥ 3 prior regimens) treated with single agent PLX9486 @ ≥ 500 mg daily:
- 1 PR; CBR of 57%; median PFS of 20.86 weeks (95% CI: 9.5-46).
- **Part 3:** No drug drug interaction with PLX9486; food has negligible effect on steady state PK (in contrast with single-dose results).

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