A Phase I Pharmacokinetic (PK) and Pharmacodynamic (PD) Study of PLX9486, A Novel KIT Inhibitor with Potent Activity Against Exon 17/18 Activation Loop Mutations in Patients with Gastrointestinal Stromal Tumor (GIST)

CTOS Abstract ID: 2771952 J Trent[1], A Wagner[2], W Tap[3], A Shields[4], A Patnaik[5], G Tinoco[6], G Michelson[7], E Martin[7], O Alcantar[7], M Pelayo[7], C Zhang[7], B West[7], P Severson[7]

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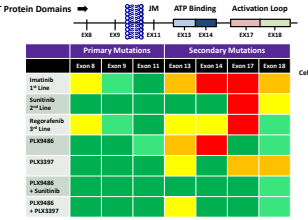
Plexxikon

Background

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 pexidartinib (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:

- Primary:
  - Evaluate PLX9486 single agent safety & pharmacokinetics (PK)
  - Establish single agent maximum tolerated dose/recommended phase 2 dose (MTD/RP2D)
- Secondary: 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:

- Primary:
  - 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
  - Assess ORR, DOR, PFS, and Clinical Benefit Rate (CBR = sum rates of complete response [CR] + partial response [PR] + stable disease [SD] @ 16 weeks)
- Exploratory: See Part 1

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Results

Patient Characteristics

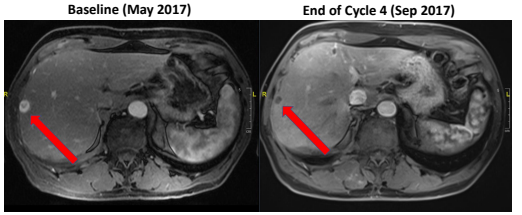
	All (n=36)	Part 1 (n=24)	Part 2b (n=12)
Age, median [range]	60.5 [39-82]	53.5 [39-79]	63 [49-82]
Sex, male, n (%)	24 (67%)	15 (62.5%)	9 (75%)
GIST, n (%)	31 (86%)	20 (83%)	11 (92%)
Prior regimens, median [range]	4 [1-10]	4 [3-10]	4 [1-7]
Prior imatinib, n (%)	31 (86%)	20 (83%)	11 (92%)
Prior sunitinib, n (%)	29 (81%)	20 (83%)	9 (75%)
Prior regorafenib, n (%)	25 (69%)	18 (75%)	7 (58%)
Prior pazopanib, n (%)	4 (11%)	3 (13%)	1 (8%)
Prior ponatinib, n (%)	4 (11%)	3 (13%)	1 (8%)
Prior sorafenib, n (%)	3 (8%)	3 (13%)	0 (0%)

Adverse Events

Adverse Events (AEs)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)	All Grades
Fatigue	7	5	1	0	13
Diarrhoea	8	2	0	0	10
Nausea	10	0	0	0	10
AST increased	9	0	0	0	9
ALT increased	5	2	0	0	7
Vomiting	5	0	0	0	5
Decreased appetite	5	0	0	0	5
Anaemia	1	2	1	0	4
Oedema peripheral	4	0	0	0	4
ALP increased	4	0	0	0	4
Weight decreased	4	0	0	0	4
Hair colour changes	4	0	0	0	4

AEs shown are those possibly related to PLX9486 or PLX3397 that occurred in ≥ 4 (10%) patients.

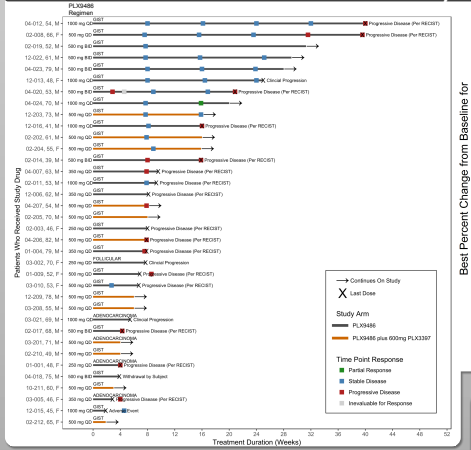
Patient 04-024

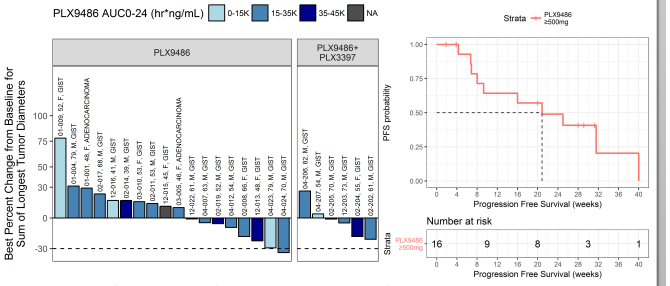


Patient History

- 70 year old Caucasian male
- diagnosed with GIST in 2014
- identified KIT exon 11 (V559A) mutation s/p resection
- treated with:
  - imatinib -- best response – PR; discontinued due to toxicity
  - sunitinib -- best response – PR; discontinued due to toxicity
  - nilotinib -- best response – SD; discontinued due to toxicity
  - PLX9486 at 1000 mg QD single agent started May 2017
    - after 2 cycles scans indicated a 12% decrease in lesion size
    - after 4 cycles scans indicated a 33% decrease in lesion size
      - PR per RECIST 1.1

Study Progress and Interim Results





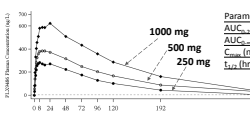
Interim results for GIST patients (all having ≥ 3 prior regimens) treated with single agent PLX9486 @ ≥ 500 mg daily:

- 1 PR; CBR of 57%; median PFS of 20.86 weeks (95% CI: 9.5-46)

Data cutoff Oct 2017

Pharmacokinetics

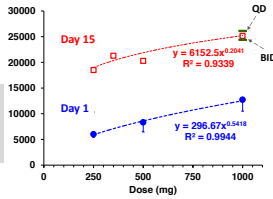
Single Dose PK



Parameter	250 mg Fasted (N=9)	250 mg Fed (N=9)	500 mg Fasted (N=9)	1000 mg Fasted (N=9)
AUC_{0-24} (hr*ng/mL)	5980	10100	8130	12600
$AUC_{0-\infty}$ (hr*ng/mL)	30500	55000	52700	87700
C_{max} (ng/mL)	298	603	396	630
$t_{1/2}$ (hr)	48.6	49.1	66.2	71.4

- Dose dependent (< dose-proportional) increase in C_{max} & AUC
- Long $t_{1/2}$ (2-3 days); food effect increased $AUC_{0-\infty}$ by 80%

Repeat Dose PK



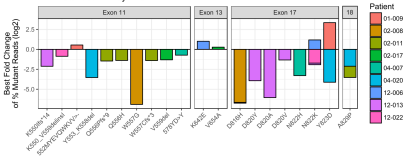
Efficacious exposure range ~ **12,000–36,000** hr*ng/mL based on GIST PDX models expressing various exon 17 mutations

- *Part 1*: 2-3 fold accumulation at steady state; modest increase (~40%) in systemic exposure at steady state from 250 to 1000 mg; further dose increase is not expected to significantly improve AUC
- *Part 2*: No drug-drug interaction with PLX3397; food has negligible effect on steady state PK (in contrast with single-dose results)

Circulating Tumor DNA

Cell-free DNA from patient plasma was sequenced with a targeted panel to identify mutations in ctDNA.

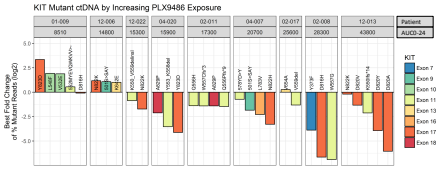
- ctDNA levels track with tumor burden (right)
- KIT mutations in Exons 11, 17 & 18 show a decreasing trend with PLX9486 treatment (below)

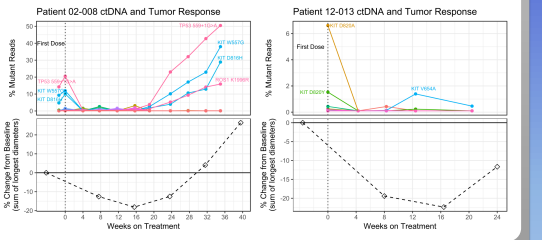


- Exception 1: patient 01-009 (low exposure)
- Exception 2: patient 12-006 (low exposure and co-occurring exon 13 mutation)

- Consistent with preclinical PLX9486 selectivity data, no decreases were observed for circulating mutations in exon 13 of KIT

- ctDNA reductions trend with PLX9486 exposure (C1D15, hr*ng/mL)





Conclusions

- PLX9486 as single agent selectively inhibits a spectrum of KIT mutations including difficult to treat exon 17/18 activation loop variants
- PLX9486 single agent RP2D = 500 mg QD (MTD not reached); predicted efficacious exposure achieved; well tolerated
- Interim results in heavily pretreated GIST patients (100% ≥ 3 prior regimens) @ doses ≥ 500 mg daily: 1 PR; CBR of 57%; median PFS of 5 months
- Changes of KIT ctDNA matched the selectivity profile of PLX9486 and trended with both tumor response and PLX9486 exposure
- Combination (PLX9486+PLX3397) selectively inhibits all common primary and secondary KIT mutations
- Combination RP2D likely 500 mg PLX9486 + 600 mg PLX3397 daily with food; combination MTD not reached; predicted efficacious exposure achieved; clinical benefit demonstrated in patients who progressed on multiple TKIs; well tolerated
- Sunitinib combination in planning
- Further accrual in earlier line patients is planned