A phase I pharmacokinetic and pharmacodynamic study of PLX9486 alone and in combination with the KIT inhibitors pexidartinib (pexi) or sunitinib in patients with advanced solid tumors and gastrointestinal stromal tumor (GIST)

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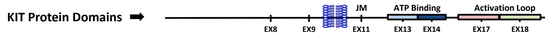
Background

GISTs have a unique dependence on oncogenic KIT signaling with ~80% showing KIT mutations in exons 9 or 11 upon diagnosis. Inhibition of these primary activating mutations with tyrosine kinase inhibitors (TKI) markedly improves survival of GIST patients. However, most GIST patients develop resistance mutations in exon 13, 14, 17 or 18. While mutations in exons 13-14 are moderately sensitive to 2nd and 3rd line treatments, there are no approved therapies that potently inhibit mutations in exons 17-18 (activation loop). PLX9486 is a novel TKI with activity against primary KIT mutations (ex 9 and 11) and against activation loop mutations. 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 and address all common primary and secondary KIT mutations.



Cell-based assay, IC50s (μM)

	Primary Mutations			Secondary Mutations			
	Exon 8	Exon 9	Exon 11	Exon 13	Exon 14	Exon 17	Exon 18
Imatinib (1st Line)							
Sunitinib (2nd Line)							
Regorafenib (3rd Line)							
PLX9486							
Pexidartinib							
PLX9486 + Pexidartinib							
PLX9486 + Sunitinib							

≤ 10 | ≤ 3 | ≤ 1 | ≤ 0.15 | ≤ 0.10

Trial Design and Methodology

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 Objective Response Rate (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 single agent PLX9486 @ RP2D in GIST and other solid tumors with KIT mutations
  - Assess combination PLX9486 + pexidartinib in GIST
  - Assess combination PLX9486 + sunitinib 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

Methodology: standard 3+ 3 dose escalation for single agent and combination; GIST patients who had progressed after imatinib; 28 day DLT window – general non-hematologic DLT criteria: any grade ≥ 3 (AE/Lab) toxicity despite adequate supportive care; exceptions made for clinically insignificant or short lived events; Hem DLT: grade 3+ neutropenia, thrombocytopenia; grade 4 anemia

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Results

Patient Characteristics

	All (n= 44)	Part 1 (n= 24)	Part 2b (n= 12)	Part 2e (n= 8)
Age, Median [range]	58.5 [39-82]	53.5 [39-79]	63 [49-82]	56 [44-78]
Sex, Male, n (%)	27 (61%)	15 (62%)	9 (75%)	3 (38%)
GIST, n (%)	39 (89%)	20 (83%)	11 (92%)	8 (100%)
Prior Regimens, Median [range]	4 [1-10]	4.5 [3-10]	4 [1-7]	2.5 [1-7]
Prior Imatinib, n (%)	37 (84%)	20 (83%)	11 (92%)	8 (100%)
Prior Sunitinib, n (%)	33 (75%)	20 (83%)	9 (75%)	5 (63%)
Prior Regorafenib, n (%)	28 (64%)	18 (75%)	7 (58%)	4 (50%)
Prior Pazo or Pona, n (%)	9 (20%)	6 (25%)	2 (17%)	2 (25%)

Adverse Events

Part 1: PLX9486 Dose Escalation

AE Term	Grade 1-2, n (%)	Grade 3-4, n (%)	All Grades, n (%)
Fatigue	11 (46%)	1 (4%)	12 (50%)
Diarrhea	9 (38%)	0	9 (38%)
Nausea	7 (29%)	0	7 (29%)
AST increased	7 (29%)	0	7 (29%)
ALT increased	5 (21%)	0	5 (21%)
Alk phos raised	5 (21%)	0	5 (21%)
Vomiting	4 (17%)	0	4 (17%)
Edema limbs	4 (17%)	0	4 (17%)
Hair color changes	4 (17%)	0	4 (17%)
CPK increased	2 (8%)	1 (4%)	3 (12%)
Hypophosphatemia	2 (8%)	1 (4%)	3 (12%)
Weight loss	3 (12%)	0	3 (12%)
Dysgeusia	3 (12%)	0	3 (12%)
Headache	3 (12%)	0	3 (12%)
Alopecia	3 (12%)	0	3 (12%)

AE's at least possibly related to PLX9486 in >10% of patients

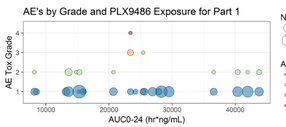
Part 2b: PLX9486 + Pexidartinib

AE Term	Grade 1-2, n (%)
Hair color changes	5 (42%)
Fatigue	4 (33%)
Decreased appetite	4 (33%)
Anemia	3 (25%)
Diarrhea	3 (25%)
Nausea	3 (25%)
ALT increased	3 (25%)
AST increased	3 (25%)
Weight loss	2 (17%)
Rash maculo-papular	2 (17%)
Hypertension	2 (17%)

Part 2e: PLX9486 + Sunitinib

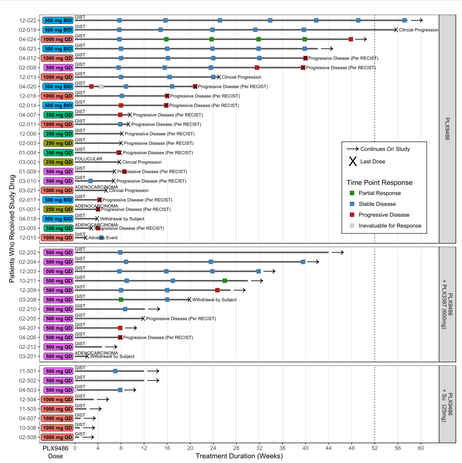
AE Term	Grade 1-2, n (%)
Nausea	2 (17%)

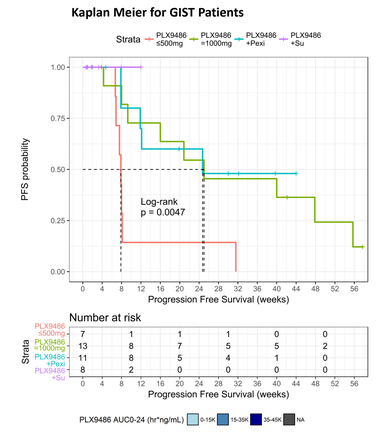
No grade 3-4 AE's in the combination groups



DLTs:
Part 1 – Single grade 3 anemia
Part 2b – None
Part 2e – None to Date

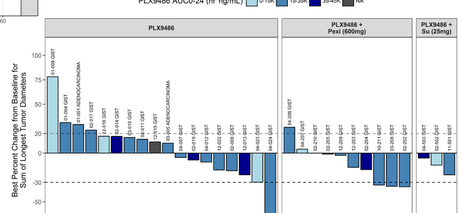
Study Progress and Interim Results



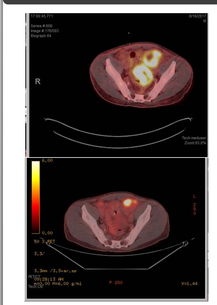


Interim results for GIST patients:

Metric	≤ 500mg PLX9486	1000mg PLX9486	PLX9486 + Pexidartinib
Median PFS (months)	2	6	6
Number of PR's	0	1	3
Clinical Benefit Rate @ 16 weeks	1/7 (14%)	7/11 (64%)	6/9 (67%)



Patient Vignette



- 55 year old male diagnosed with GIST in 2016
- KIT exon 11 (N566_P573del), TP53 and RB1 mutations identified at diagnosis
- Imatinib + MEK162 → PR, discontinued MEK162 due to AE
- Continued Imatinib → PD (Aug 2017)
- Started PLX9486 + Pex (Sep 2017)
- After 2 cycles, scans indicated a 34% decrease
- ctDNA analysis confirmed KIT exon 11 and TP53 mutations
- ctDNA also revealed KIT exon 17 and 18 resistance mutations
- ctDNA mutations were not detectable after one cycle of combination treatment

Conclusions

- PLX9486 single agent was tested @ 250, 350, 500 & 1000 mg (QD & 500 BID); is well tolerated and selectively inhibits a spectrum of KIT mutations including difficult to treat exon 17-18 activation loop variants.
- Interim results in heavily pretreated GIST patients @ 1000 mg daily resulted in 1 PR, a CBR of 64% and a median PFS of 6 months; significantly better than at lower doses.
- Combination of 500 mg PLX9486 + 600 mg pexidartinib was studied both fed and fasted; achieved 3 PR's and a CBR of 67%, with interim PFS of 6 months.
- In patients treated with single agent PLX9486, changes in KIT mutant ctDNA matched the selectivity profile of PLX9486 with reduction in ctDNA levels of exons 11, 17/18
- The addition of pexidartinib to PLX9486 did not result in additional reduction of exon 13/14 ctDNA levels at the doses studied.
- Accrual to the PLX9486 + sunitinib cohorts is ongoing (continuous QD dosing for both agents); dose levels tested so far include 500 & 1000 mg PLX9486 + 25 mg sunitinib fed. Planned dosing up to 1000 mg PLX9486 + 37.5 mg sunitinib
- The combination of PLX9486 with either pexidartinib or sunitinib is generally well tolerated and toxicities are typically grade 1 or 2 in nature and reversible
- Given these interim results, it is anticipated that the selectivity profile and potency of a PLX9486 + Sunitinib combination will achieve broader and more durable coverage of primary and secondary KIT mutations.

Pharmacokinetics

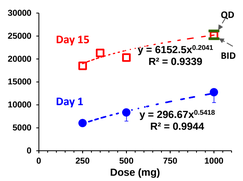
Single Dose PK

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
$C_{max,ss}$ (ng/mL)	298	603	396	630
$t_{1/2}$ (hr)	48.6	49.1	66.2	71.4

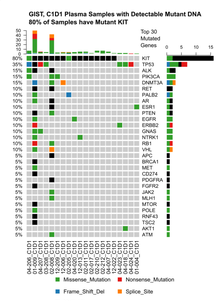
- Dose dependent (< dose-proportional) increase in C_{max} & AUC
- Long $t_{1/2}$ (2-3 days); food effect increased $AUC_{0-\infty}$ by 80%

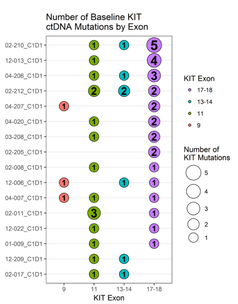
Repeat Dose PK

- *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
- *Parts 2b & 2e:* No drug-drug interaction with Pexi or Su; food has negligible effect on steady state PK of PLX9486 (in contrast with single-dose results)



Circulating Tumor DNA





Far Left: GIST patients present with a high prevalence of circulating KIT mutations at study entry (80% of C1D1 samples with detectable ctDNA).

Left: At baseline, all KIT-mutant GISTs had at least 2 KIT mutations (range 2-7). Notably, 14 of 16 patients had 1 or more mutations in exons 17-18:

- Most of these patients have progressed on 1st, 2nd and 3rd lines
- Demonstrates the need for a targeted therapy with activity against exons 17-18

Two patients without exon 17-18 mutations presented with mutations in exon 13-14.

Right: After starting therapy with PLX9486 (alone or with Pexi), a majority of KIT exon 17-18 circulating mutant alleles are reduced. Exon 17-18 alleles are even decreasing in several patients that have both 13-14 & 17-18 resistance mutations.

- suggests that most sub clones have either 13-14 or 17-18 in addition to the primary mutation.