The Potent and Selective KIT Inhibitor PLX9486 Dosed in Combination with Sunitinib Demonstrates Promising Progression Free Survival (PFS) in Patients with Advanced Gastrointestinal Stromal Tumor (GIST): Final Results of a Phase 1/2 Study

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Gastrointestinal Stromal Tumors (GIST) and KIT Signaling

Incidence

- Estimated 4,000-6,000 new cases per year in US*
- Represents approximately 80% of GI sarcomas
- High frequency of metastatic disease

Treatment of metastatic disease

- High unmet medical need remains for imatinib-refractory patients
  - Sunitinib, regorafenib, and ripretinib have mPFS of ≤ 6 mos with ORR < 10%

KIT signaling

- ~ 80% of GIST shows KIT mutations in exons 9 or 11 at diagnosis
- KIT mutations confer sensitivity to tyrosine kinase inhibitors (TKIs)
- Imatinib-refractory patients commonly develop resistance mutations in exons 13, 14, 17, or 18

*** ACS 2020 Statistics**

Potent, Selective Targeting of KIT Mutations in GIST

PLX9486

- Novel type I (active conformation) TKI with activity against primary KIT mutations (exons 9 & 11) and activation loop mutations (exons 17 & 18)
  - > 150-fold more selective for mutations in exons 17 & 18 vs. wild type

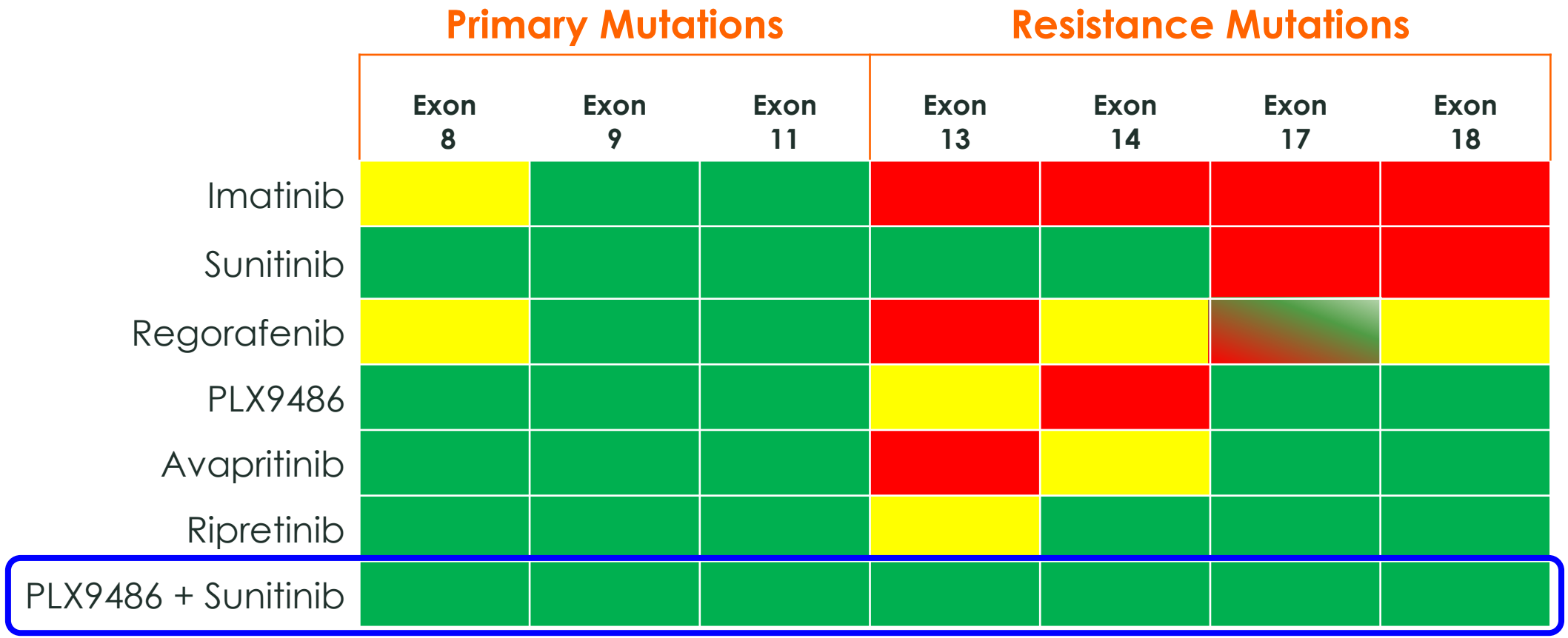
Sunitinib

- Sunitinib is a type II (inactive conformation) TKI that inhibits KIT primary mutations and secondary mutations (exons 13 & 14)

PLX9486 + Sunitinib

- Complementary type I and type II binding create synergistic potential
- PLX9486 + sunitinib combination therapy may have activity against a broader spectrum of KIT mutations by blocking both active and inactive conformations

PLX9486 + Sunitinib Combination Creates Complementary Profiles Against KIT Resistance Mutations



Ref: Plexxikon, Data on file; Serrano, BJC 2019
Evans, Sci Transl Med 2017; Trent CTOS 2018;
Smith, Proc AACR 2018

Study PLX121-01: Phase 1/2 Study of PLX9486 + Sunitinib

Eligibility

- Relapsed/Refractory GIST
- Previous imatinib treatment

Design for Part 2e

- 3+3 dose escalation
- 3 combination dose levels based on PLX9486 single agent experience

NCT#02401815

Part 2e: PLX9486 + Sunitinib

All doses PO once daily

Primary Objective

Characterize the safety and tolerability of combination in patients with GIST

Secondary Objectives

Overall response rate per RECIST v1.1

Clinical benefit rate (CBR): CR + PR + SD ≥ 16 weeks

Exploratory Objective

Changes in circulating tumor DNA (ctDNA) and correlation with response and survival

Criteria for Dose Limiting Toxicities

Assessed during Cycle 1 (28 days)

Nonhematologic

- Gr ≥ 3 AE of laboratory toxicity despite adequate supportive care

Hematologic

- Gr 4 anemia, neutropenia, or thrombocytopenia
- Gr 3 neutropenia/thrombocytopenia lasting > 7 days

Follow-up Complete in All Patients Treated in PLX121-01

Part 1
Single-agent PLX9486 dose escalation
N = 24

Part 2b
PLX9486 + pexidartinib
N = 12

Part 2e
PLX9486 + Sunitinib
N = 18 with previously treated GIST

Dose Level 1	Dose Level 2	Dose Level 3
PLX9486 500 mg + Sunitinib 25 mg N = 3	PLX9486 1000 mg + Sunitinib 25 mg N = 5	PLX9486 1000 mg + Sunitinib 37.5 mg N = 10
AE (Gr3 anemia), n = 1 Subject withdrawal, n = 1 Other, n = 1*	Disease progression / Clinical progression n = 5	Disease progression, n = 4 Other, n = 3* Subject withdrawal, n = 1 Death (sepsis), n = 1

*Four patients continued to receive treatment via Expanded Access

- 51 pts treated on study
  - 24 pts with single-agent PLX9486**
  - 18 pts with PLX9486+sunitinib

**Wagner et. al, ASCO 2018

db snapshot: 10July2020

Demographics and Prior Therapy: Heavily Pretreated GIST Patients

	Total (N=18)	Dose Level 1 (n=3)	Dose Level 2 (n=5)	Dose Level 3 (n=10)
Age, Median (range)	62 (44 – 78)	57 (46 – 68)	55 (44 – 78)	62 (53 – 65)
Sex, male, n(%)	9 (50)	0	3 (60)	6 (60)
Prior Regimens, Median (range)	3 (1 – 6)	2 (1 – 2)	3 (1 – 6)	4 (1 – 5)
Imatinib, n (%)	18 (100)	3 (100)	5 (100)	10 (100)
Sunitinib, n (%)	13 (72)	1 (33)	4 (80)	8 (80)
Regorafenib, n (%)	12 (67)	0	4 (80)	8 (80)
Ripretinib, n (%)	5 (28)	1 (33)	1 (20)	3 (30)
≥ 3 prior lines, n (%)	12 (67)	0	4 (80)	8 (80)
Prior treatment with PLX9486 (previously enrolled on another arm)	**3 (17)**	0	0	**3 (30)**

DL 1 = PLX9486 500 mg + Sunitinib 25 mg; DL 2 = PLX9486 1000 mg + Sunitinib 25 mg; DL3 = PLX9486 1000 mg + Sunitinib 37.5 mg
All doses PO once daily

db snapshot: 10July2020

TEAE ≥ Gr 3 Reported in ≥ 2 Patients and Corresponding All Grade AEs

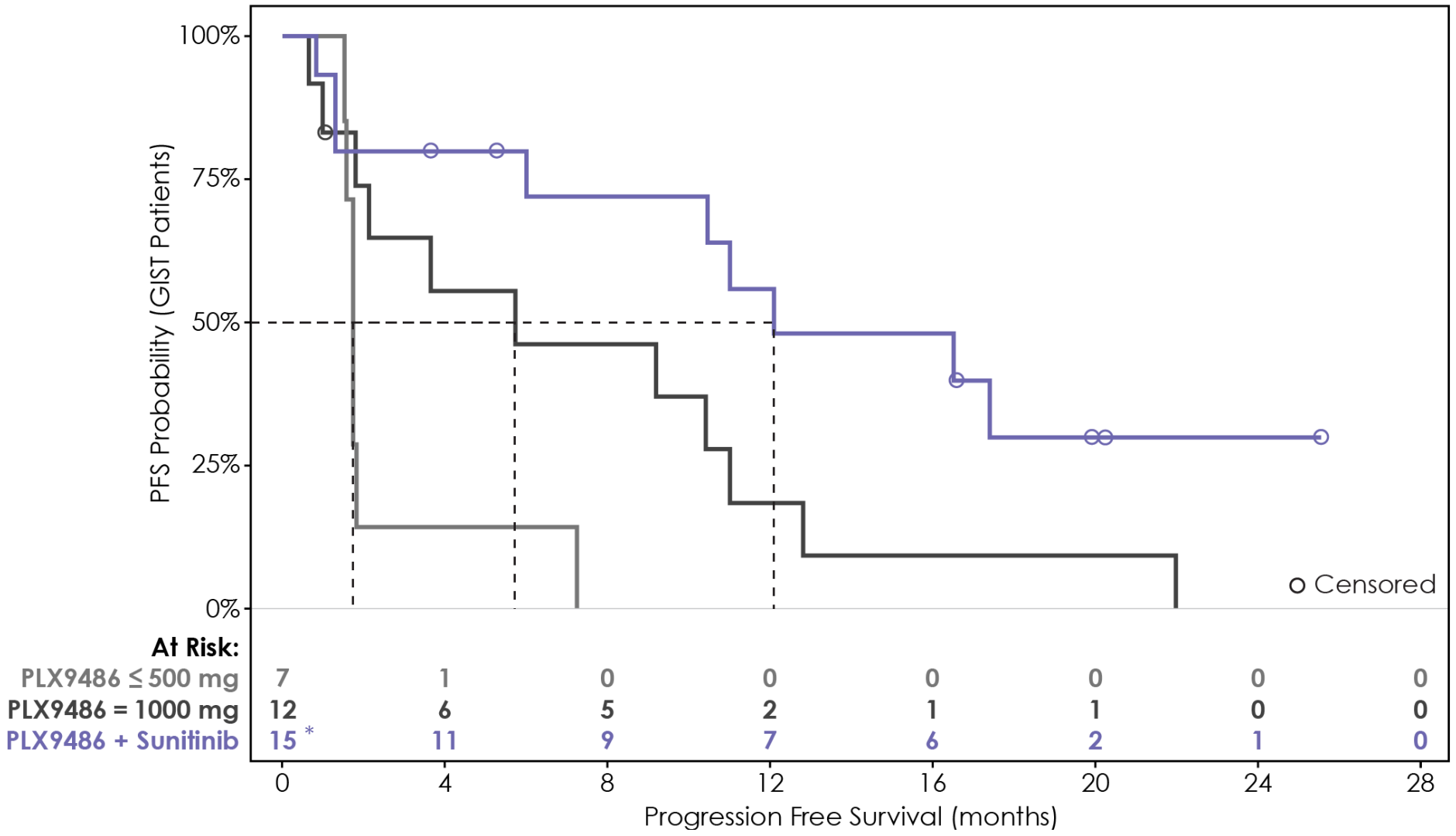
Preferred term, n	Total (n=18)		Dose Level 1 (n=3)		Dose Level 2 (n=5)		Dose Level 3 (n=10)	
	Any Gr	Gr ≥ 3	Any Gr	Gr ≥ 3	Any Gr	Gr ≥ 3	Any Gr	Gr ≥ 3
Diarrhea	13	2	3	0	2	1	8	1
Anemia	9	5	3	1	2	1	4	3
Hypophosphatemia	7	3	1	1	3	1	3	1
Fatigue	7	2	1	0	2	0	4	2
Hypertension	7	2	0	0	3	2	4	0
Lymphopenia	3	2	1	0	0	0	2	2

DL 1 = PLX9486 500 mg + Sunitinib 25 mg; DL 2 = PLX9486 1000 mg + Sunitinib 25 mg; DL3 = PLX9486 1000 mg + Sunitinib 37.5 mg

db snapshot: 10July2020

- Combination safety profile generally similar to that of single-agent sunitinib (Demetri et al, Lancet 2006)
- Severe events do not appear to be dose-dependent
- Dose modification guidelines for treatment-related AEs allowed majority of patients to remain on treatment
  - One patient had a treatment-related AE leading to withdrawal of study treatment (gr 3 anemia)
  - Three patients required dose reduction
- One AE (sepsis) leading to death (not related to study treatment; post-operative complication)

PLX9486 + Sunitinib: 12-Month mPFS in Heavily Pretreated GIST Patients



- Estimated 12 month mPFS in PLX9486-naïve patients receiving combination
- Improvement in mPFS in patients receiving higher dose of single-agent PLX9486
- In subset of patients with ≥ 2 prior therapies (n=11), estimated PFS remains 12 months

* excludes combination therapy patients who had previously received PLX9486

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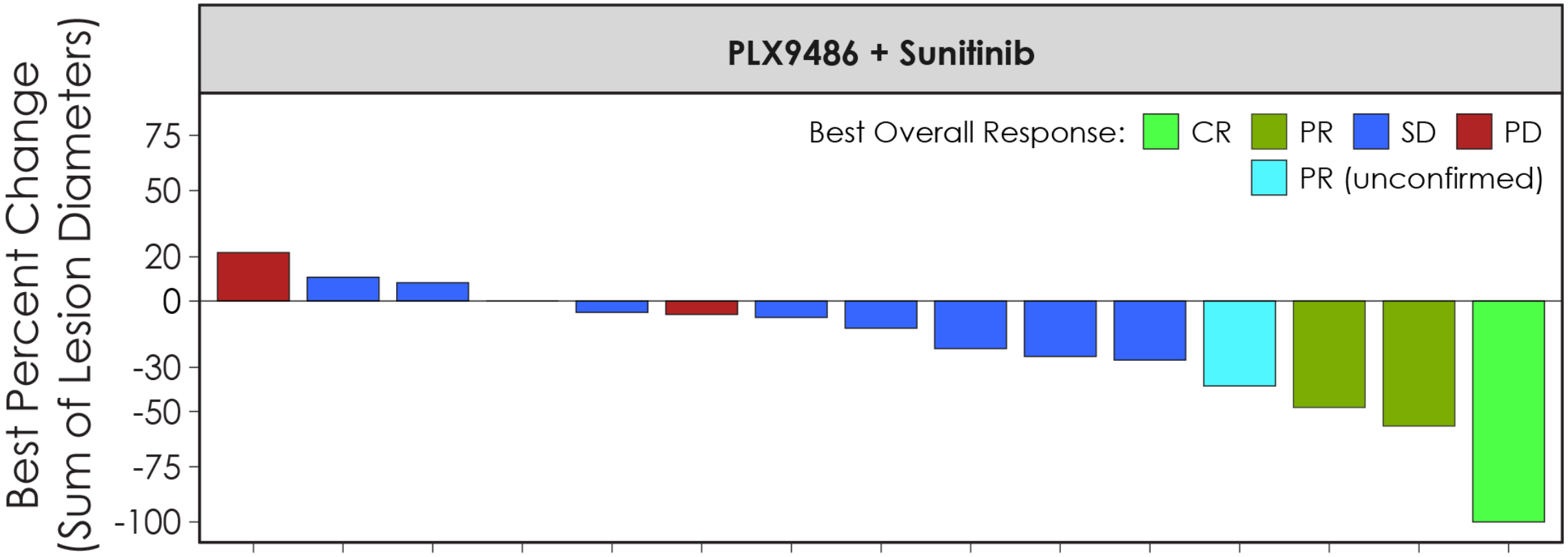
PLX9486 + Sunitinib: Clinical Benefit Observed in Majority of Patients

Best Overall Response: **ORR = 20%** (1 CR, 2PR)
CBR = 80%



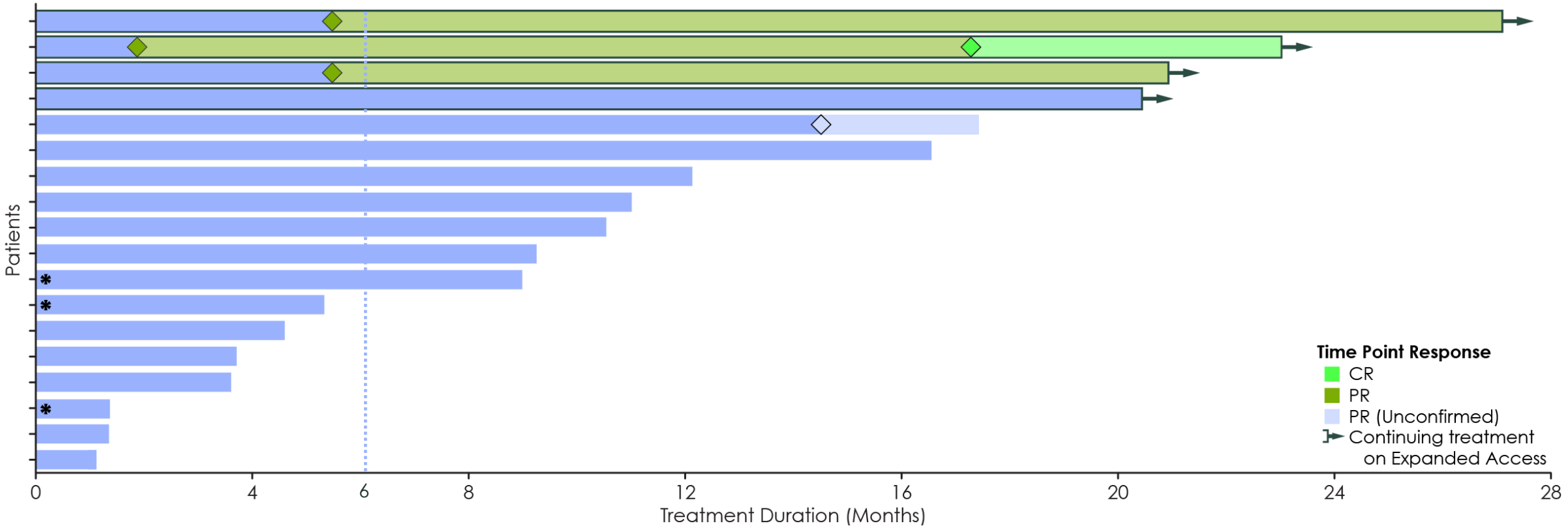
- Excludes combination therapy patients who had previously received PLX9486

ORR: Overall Response Rate (CR+PR)
CBR: Clinical benefit rate (CR+PR+SD at 16 weeks)

db snapshot: 10July2020

Durable Responses in Patients Treated with PLX9486 + Sunitinib

- The median duration of PLX9486 + sunitinib treatment was 10 months (range: 1 to 27 months)
- Four patients remain on therapy, including 1 CR and 2 PR
- In patients achieving confirmed response, responses were durable >18 months



*patient previously received PLX9486

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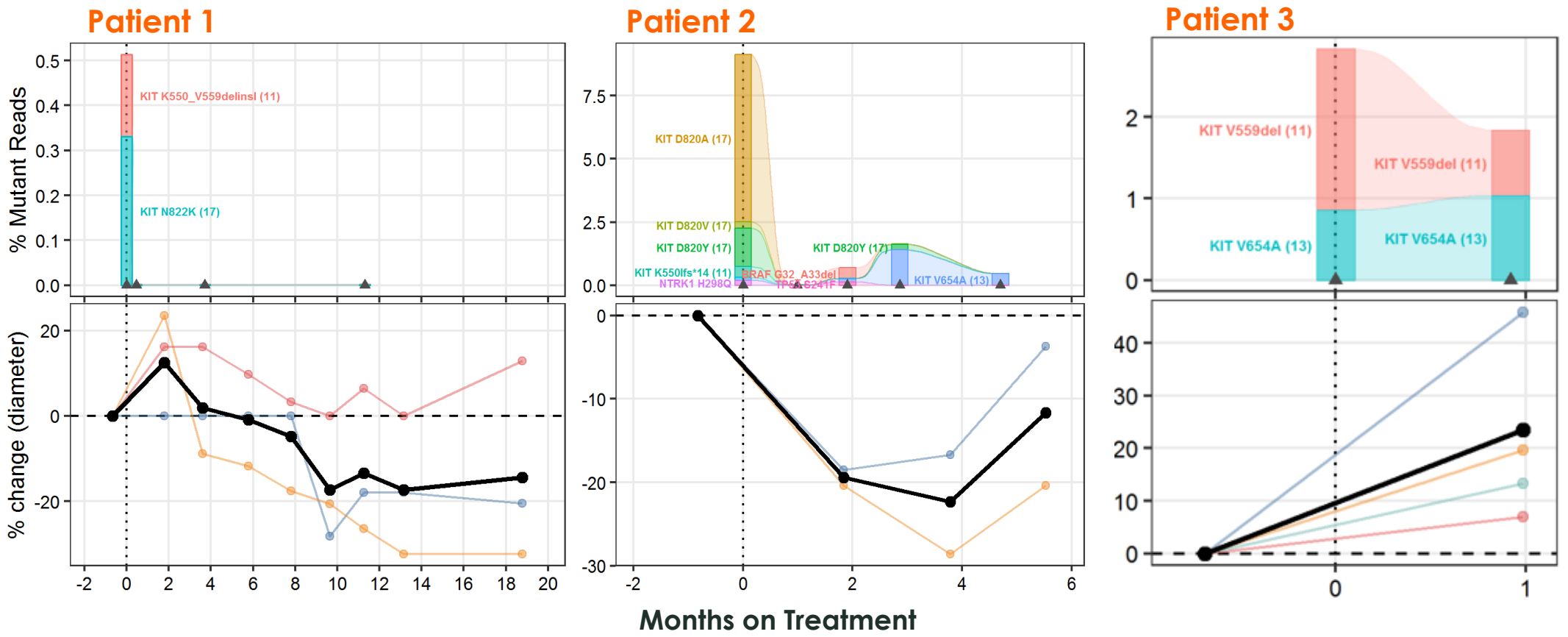
PLX9486 Monotherapy Exploratory Analysis: Changes in ctDNA Support Specificity of Kinase Inhibition

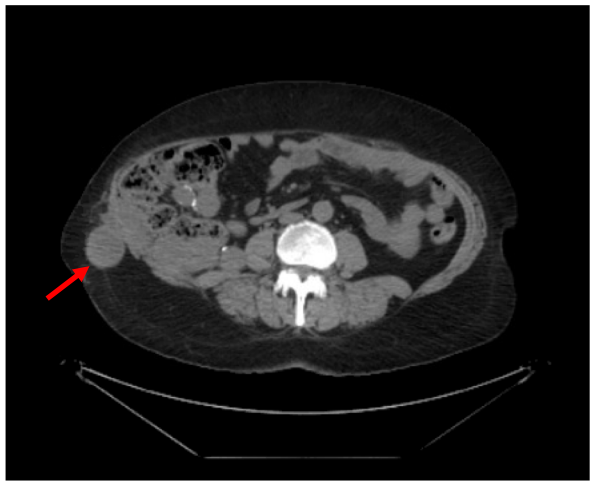


Black line: represents average of Sum of Product Diameters
Individual lesions represented in color

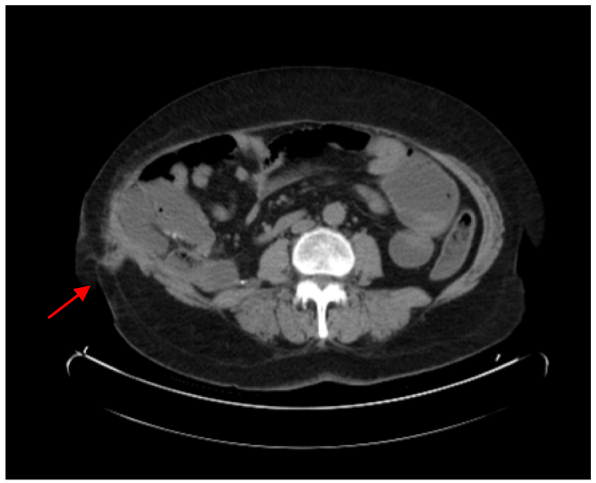
db snapshot: 10July2020

Patient Achieved Complete Response Following Three Prior Therapies When Treated at RP2D of PLX9486 + Sunitinib

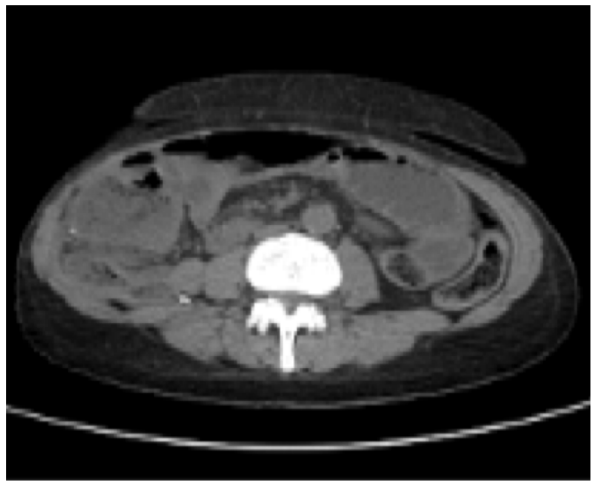
Study Entry



PR – Cycle 3



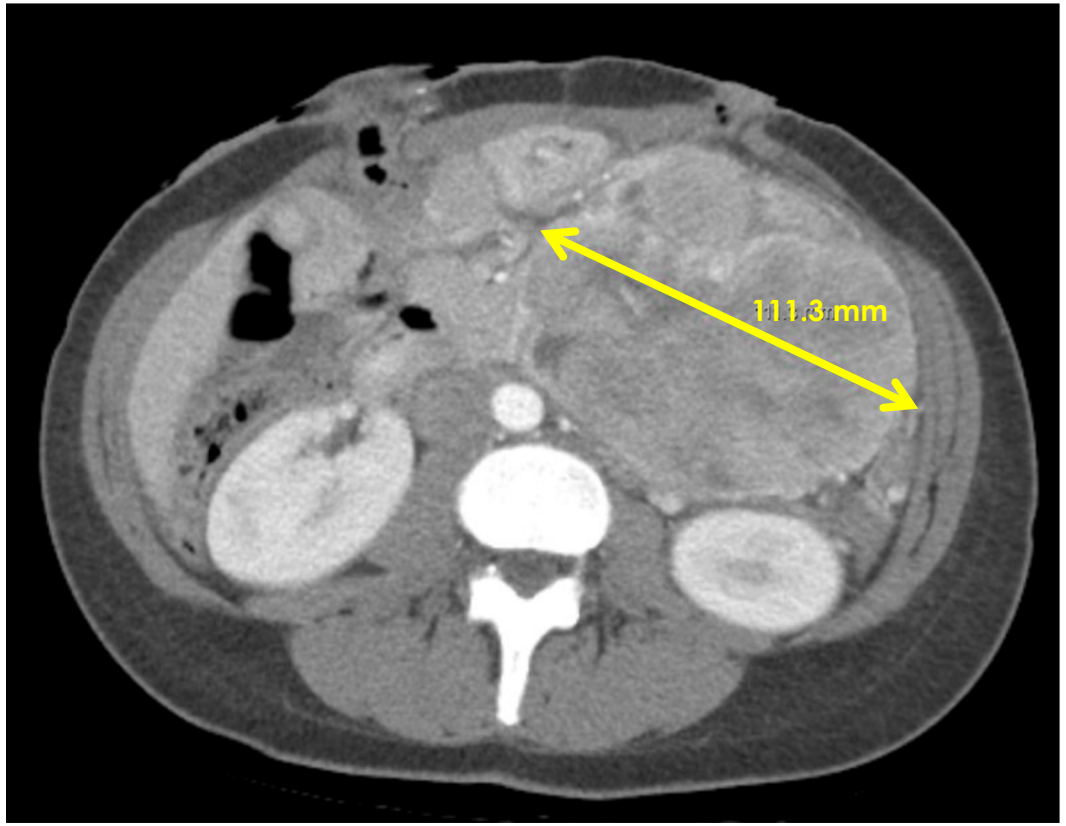
CR – Cycle 18



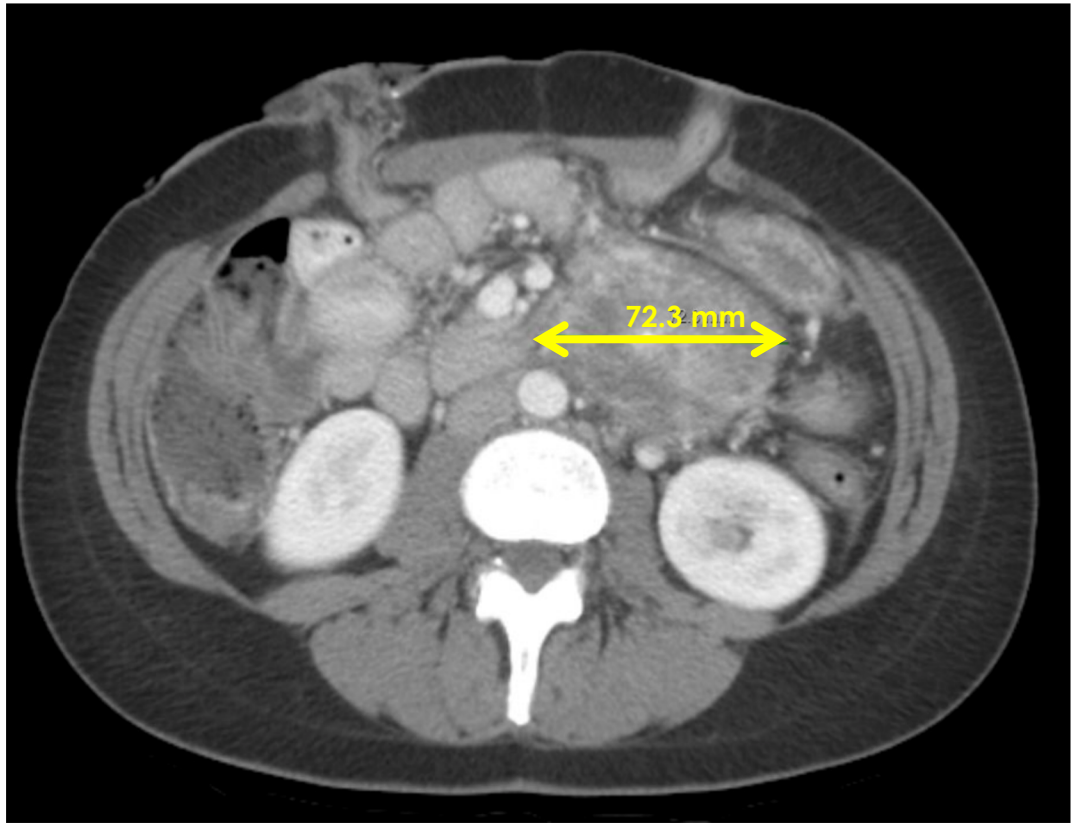
- 65 yr old female previously refractory to imatinib (PD) and sunitinib (PD); intolerant to regorafenib
- Metabolically active right abdominal and subcutaneous masses
- Mutation status (ctDNA): Exon 11 & 17
- Continues on treatment > 27 months

Patient Achieved Partial Response Following Imatinib Treatment When Treated with PLX9486 + Sunitinib

Study Entry



Continued PR - one year later



- 46 yr old female previously treated with imatinib (PD); Hepatic and abdominal disease at Study Entry
- Mutation status (ctDNA): Exon 11 & 17
- SD after 2 months on treatment, deepening to PR 7 months post treatment initiation
- Continues on treatment > 32 months

Conclusions

- **PLX9486 + sunitinib combination was well-tolerated in heavily pretreated GIST patient population**
  - MTD of combination not reached
  - Recommended Phase 2 dose: PLX9486 1000 mg + sunitinib 37.5 mg PO once daily
  - Safety profile of combination similar to single agent sunitinib
- **PLX9486 + sunitinib was clinically active in heavily pretreated GIST patient population**
  - 20% ORR with 1 complete and 2 partial responses (n=15)
  - 12-month median PFS (n=15)
- **ctDNA data provides clinical evidence of PLX9486 mechanism of action**
  - On-target effect demonstrated in patients receiving PLX9486 monotherapy
  - Changes in ctDNA associated with tumor response and PFS
- **Specificity and tolerability of PLX9486 permits combination of complementary type I and type II KIT inhibitors to drive improved activity in a difficult to treat patient population**
- **Further exploration of the combination in GIST is warranted as well as in other KIT-driven indications**

ACKNOWLEDGEMENTS

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