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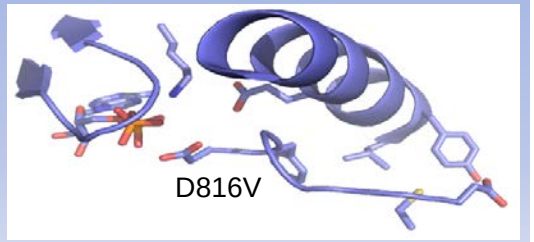
PLX9486 for CRUK Combinations Alliance

OCTOBER 2017

PLX9486: Targeting Mutant KIT
Exon 17 Mutations

- **Unmet Need:**
  Exon 17 mutated KIT resistant to approved KIT inhibitors
- **Selectivity:**
  PLX9486 targets mutant KIT, including exon 17 mutations, but spares wild-type KIT
- **Opportunities:**
  Mastocytosis (90% KIT^{D816V})
  - U.S. incidence 1500-3000 per year

  Resistant GIST (Frequently involves exon 17 mutations)
  - U.S. incidence 3300-6000 per year
- **Status:**
  Single-agent RP2D established; Phase 1b combination dose escalation with pexidartinib ongoing



KIT Exon 17 mutants - not just in GIST

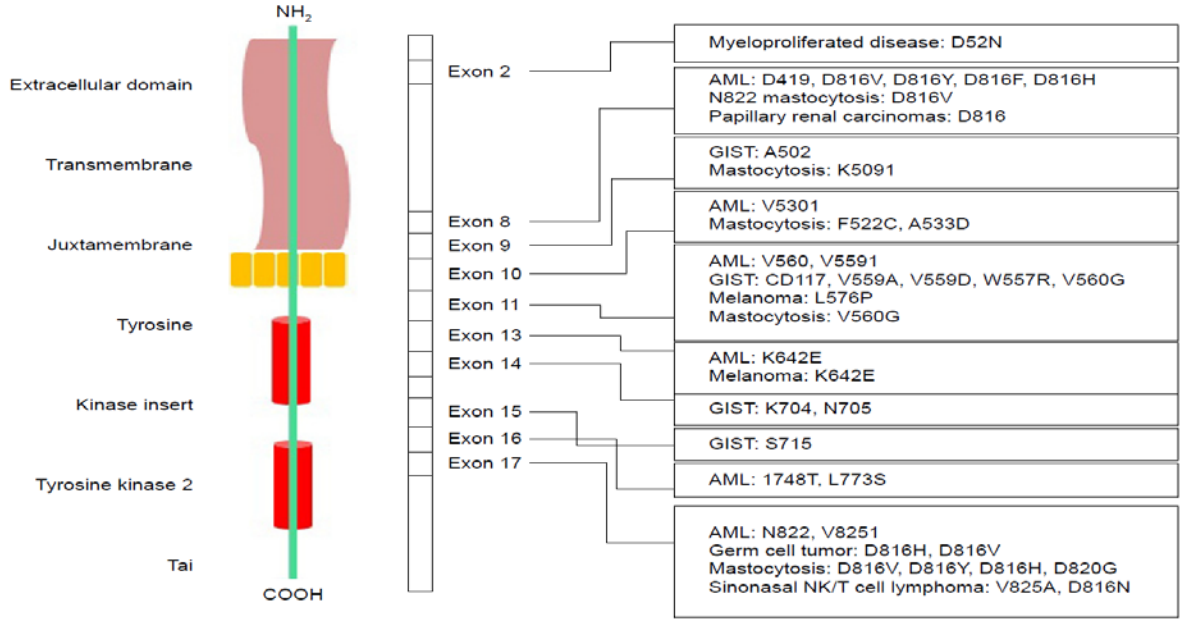


Figure 1 KIT cDNA and protein structure in different cancers and their respective mutations.
Abbreviations: cDNA, complementary DNA; AML, acute myeloid leukemia; GIST, gastrointestinal stromal tumor.

Germ Cell tumors (GCT)
Exon 17 >> exon 11
Seminoma (30%) >> non-seminoma (4%)

Babaei 2016, Bagrodia 2016

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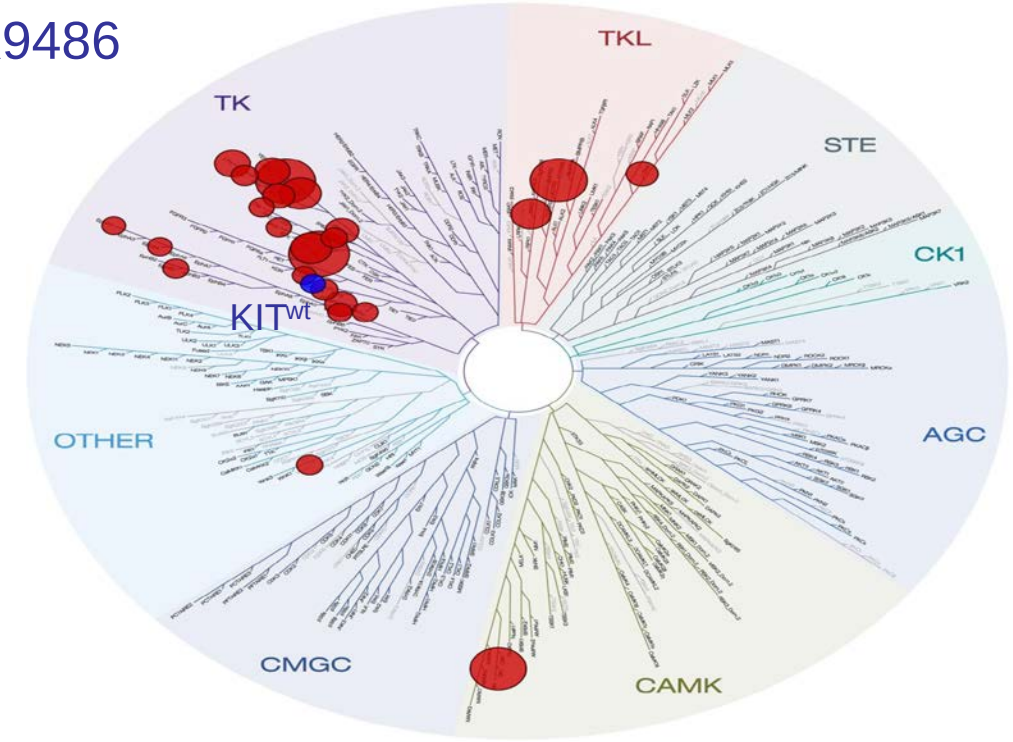
PLX9486 - Rationale for Collaboration with Combinations Alliance

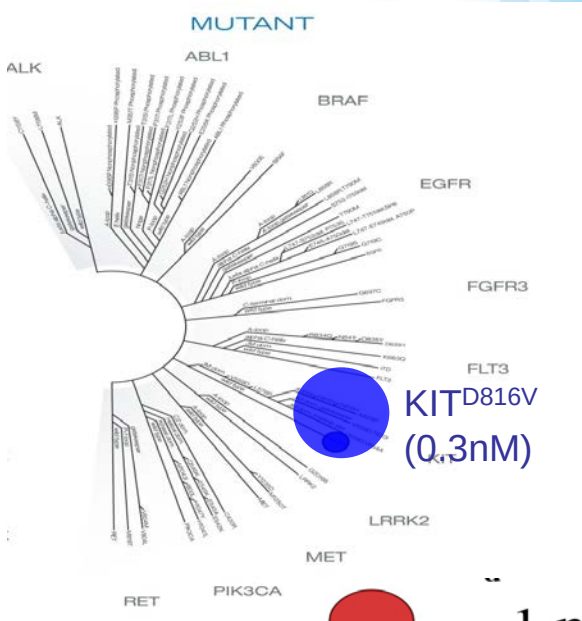
- Due to its selectivity, PLX9486 may be the most combinable KIT Exon 17 inhibitor in clinical development
- Plexxikon is developing PLX9486 primarily in combinations for the treatment of GIST
- SOC for non-GIST Exon 17 mutant tumors is varied, presents opportunities for combinations:
  - KITm AML: high-dose chemo, hypomethylating agents
  - KITm melanoma: PD-1/PD-L1
  - Germ cell tumors/seminomas: neo/adjuvant chemo; refractory
  - Mastocytosis: TNF, methotrexate, steroids

PLX9486 is Selective versus the Kinome

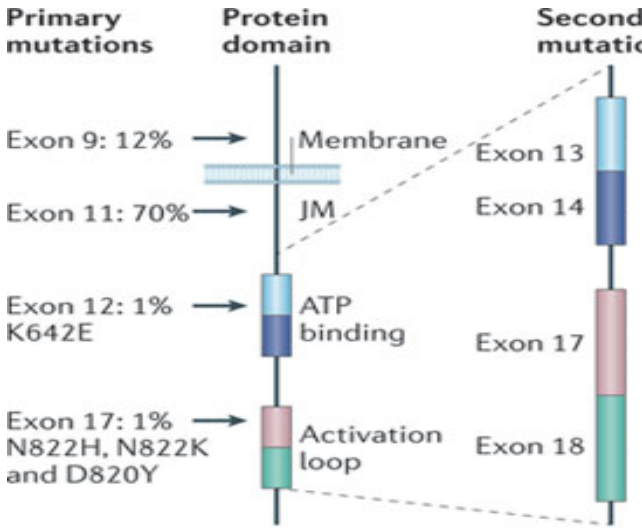
Mutant >> wild-type, other kinases

PLX9486





Imatinib is Active on Primary KIT Mutations in GIST (first-line treatment)



Drug sensitivity		
Primary Mutations		imatinib
Exon 8	D419DEL	
Exon 9	Y503A/F504Y	
Exon 11	W557K558DEL	
Secondary Mutations		
Exon 13	K642E	
Exon 13	V654A	
Exon 14	T670I	
Exon 17	D816V	
Exon 18	A829P	

Green: Sensitive Red: Resistant

Adapted from *Nature Reviews Cancer 2011*

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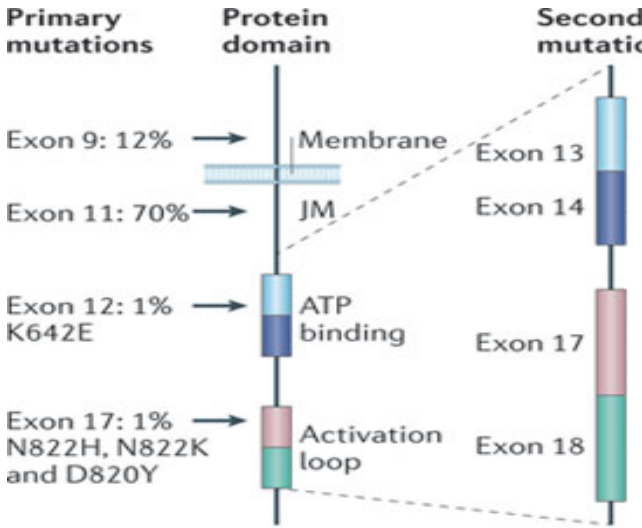
Sunitinib is Active on Gatekeeper KIT Mutation in GIST (second-line treatment)



Drug sensitivity

Primary Mutations		imatinib	sunitinib
Exon 8	D419DEL		
Exon 9	Y503A/F504Y		
Exon 11	W557K558DEL		
Secondary Mutations			
Exon 13	K642E		
Exon 13	V654A		
Exon 14	T670I		
Exon 17	D816V		
Exon 18	A829P		

← Gatekeeper Mutation

Green: Sensitive Red: Resistant

Adapted from *Nature Reviews Cancer 2011*

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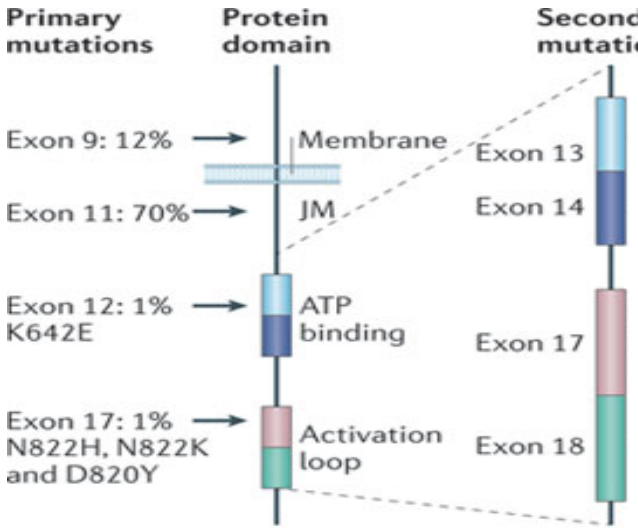
Regorafenib has Broad Activity on KIT Mutations in GIST (third-line treatment)



Drug sensitivity

Primary Mutations		imatinib	sunitinib	sorafenib
Exon 8	D419DEL			
Exon 9	Y503A/F504Y			
Exon 11	W557K558DEL			
Secondary Mutations				
Exon 13	K642E			
Exon 13	V654A			
Exon 14	T670I			
Exon 17	D816V			
Exon 18	A829P			

Green: Sensitive Red: Resistant

Adapted from *Nature Reviews Cancer 2011*

Note: Sorafenib is a surrogate for regorafenib activity

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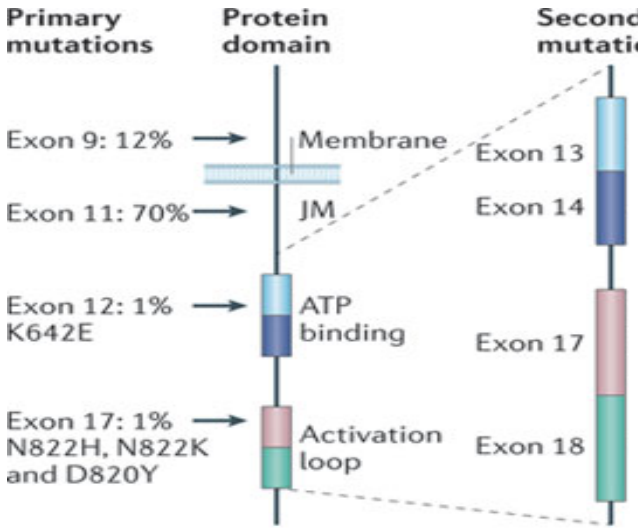
PLX9486 Has Complementary Mutant Selectivity Versus Other KIT Inhibitors

PLX9486 is >150-fold selective for mutant vs WT KIT



Drug sensitivity

Complementary

Primary Mutations		imatinib	sunitinib	sorafenib	PLX3397	PLX9486
Exon 8	D419DEL					
Exon 9	Y503A/F504Y					
Exon 11	W557K558DEL					
Secondary Mutations						
Exon 13	K642E					
Exon 13	V654A					
Exon 14	T670I					
Exon 17	D816V					
Exon 18	A829P					

Green: Sensitive Red: Resistant

Adapted from *Nature Reviews Cancer 2011*

Note: Sorafenib is a surrogate for regorafenib

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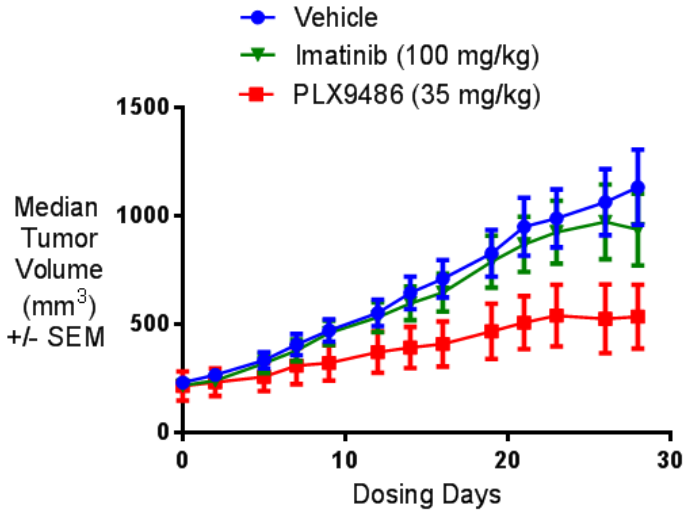
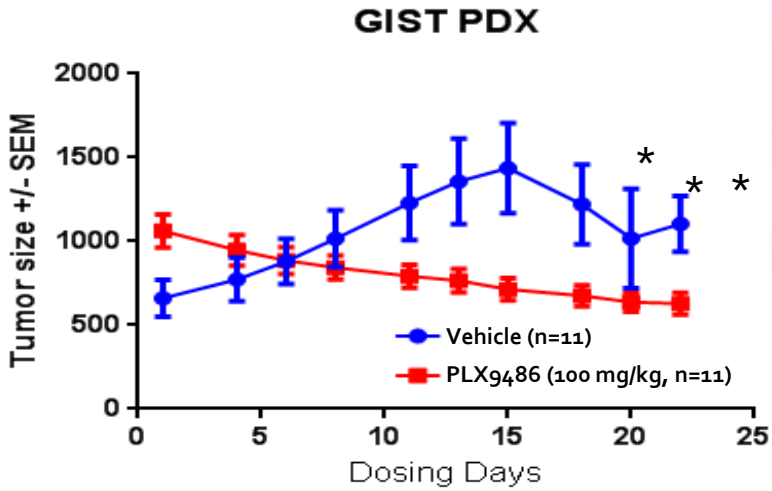
PLX9486 shows regression of large GIST PDX tumors with Kit exon 17 activating mutation (similar to D816V)

Kit mutations: Y823D (exon 17) + del W557K558 (exon 11)





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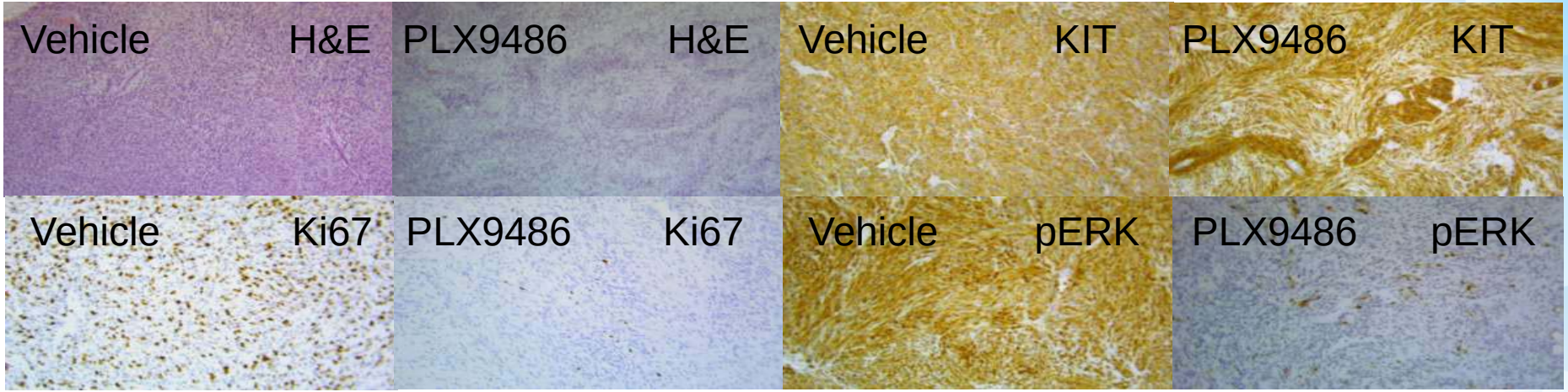
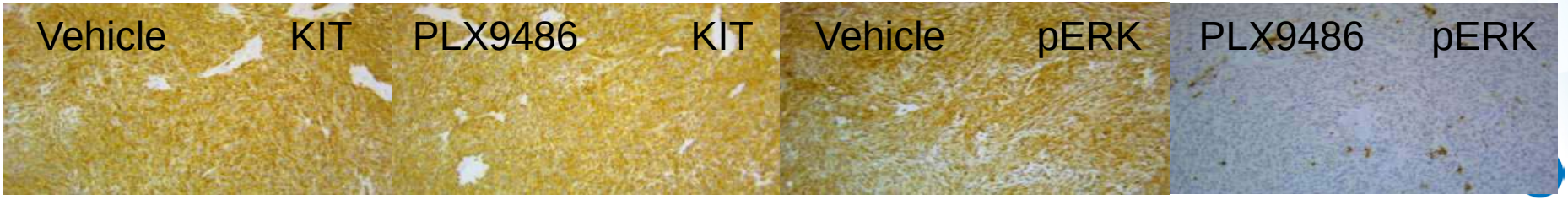
PLX9486 Blocks Proliferation and KIT pathway
Histology of PDX tumors

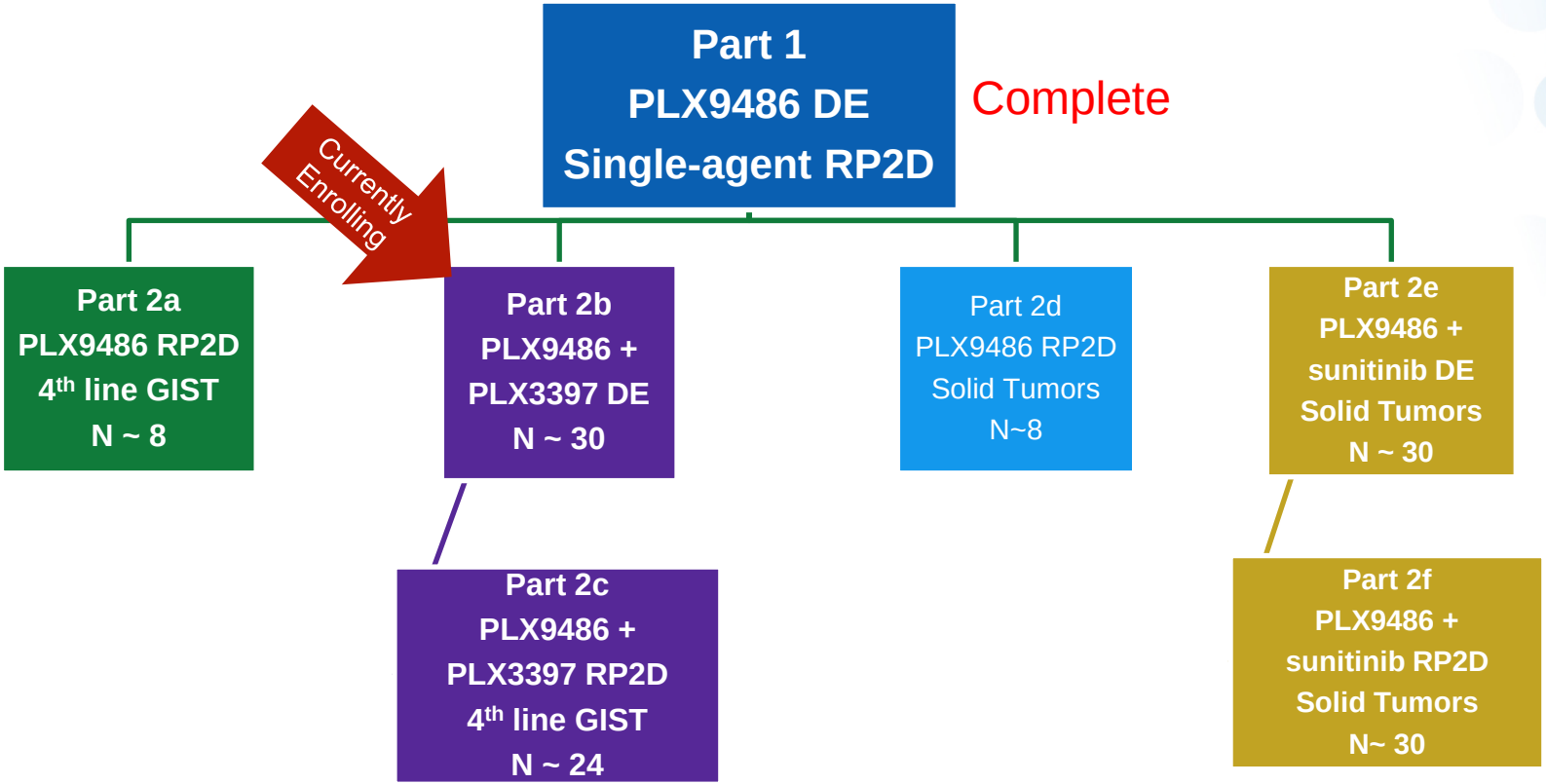
Tumors Harvested on Last Day of Dosing



Tumors (previously untreated) Harvested 2 Hours After Treatment



PLX9486 Clinical Development Plans



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PLX9486 Combinations Alliance

- Phase 1 Data to be presented at Connective Tissue Oncology Society meeting, Nov. 8-11, 2017
  - Will be available to ECMC members when embargo is lifted
- Plexxikon is soliciting proposals for SOC combinations in KIT mutant cancers
  - 1st line or refractory settings
  - Access to rare patient populations and genomic testing
- Further information is available under CDA
- Questions? Please contact us:
  - Marguerite Hutchinson, Sr. Director, Business Development: mhutchinson@plexxikon.com