PLX7486 Background Information

October 2015

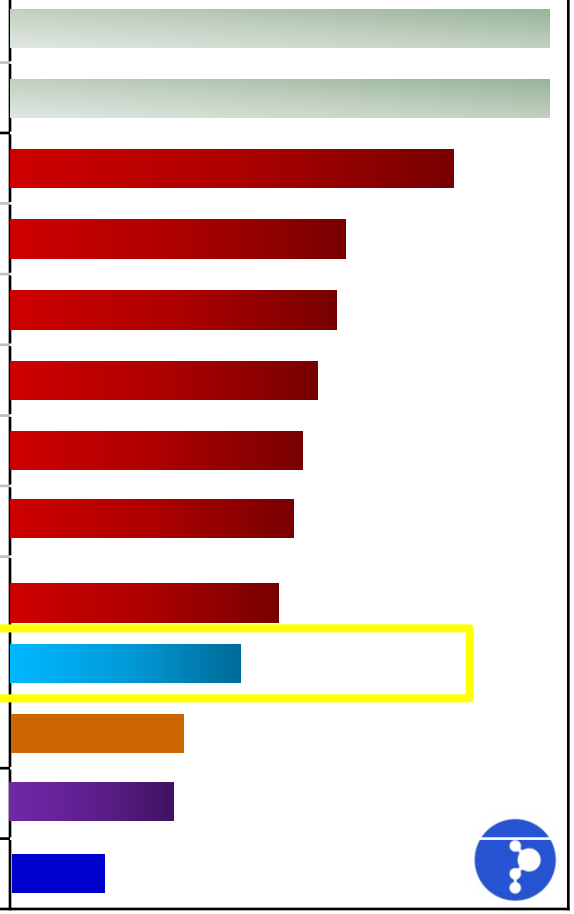
Candidate for

CRUK Combinations Alliance

Plexxikon

Plexxikon's Development Pipeline

Compound	Target	Cancer Indication	Stage of Development
			Pre-IND / Ph1 / Ph2 / Ph3
Vemurafenib + Cobimetinib	BRAF + MEK	Metastatic Melanoma	
Vemurafenib	BRAF	Adjuvant Melanoma	
PLX3397	FMS	PVNS (TGCT)	
PLX3397 + RT + TMZ	FMS, KIT	Adjuvant GBM	
*PLX3397 + eribulin**	*FMS, KIT*	*Metastatic Breast Cancer*	
*PLX3397 + paclitaxel**	*FMS, KIT*	*Neoadjuvant Breast (I-SPY2)*	
PLX3397 + pembro	FMS	Melanoma, Solid Tumors	
PLX3397 + paclitaxel (Q4 2015)	FMS, KIT	Advanced Ovarian Cancer	
PLX3397 (2016) - China	KIT	KIT-mutant Melanoma	
PLX7486	TRK, FMS	Solid Tumors, Pain	
PLX9486	KIT-Mutant	GIST, KIT-mutant tumors	
PLX8394	BRAF	BRAF-mutant tumors	
PLX51107 (2016)	BRD4	Leukemia	

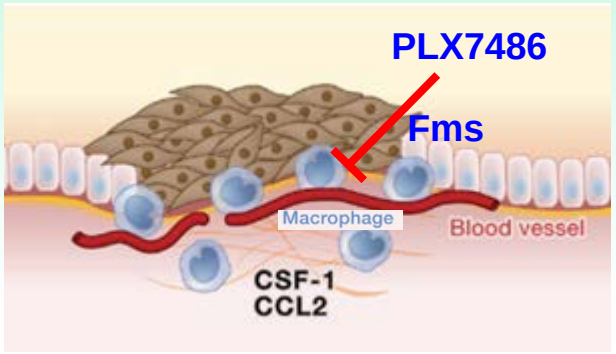


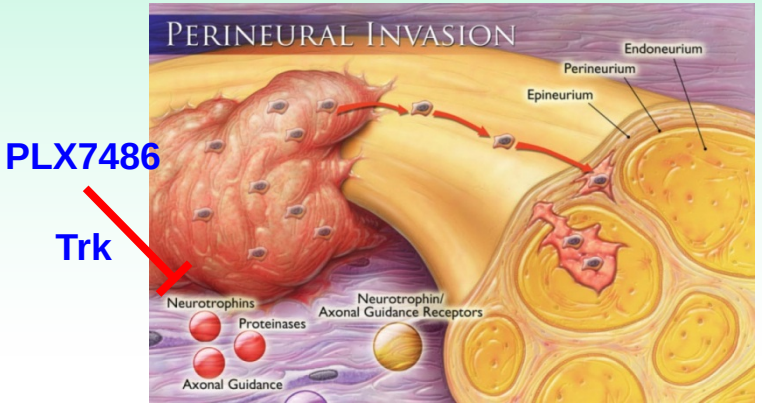
** IST*

PLX7486, First-in-Class Dual Trk/Fms Inhibitor

Orally administered, potent and selective,
attractive pharmaceutical properties

- Single-agent efficacy potential
  - Tumors driven by Trk or Fms pathway mutations
- Suppress tumor microenvironment (single-agent or combo)
  - Tumor ⇔ Nerve and Tumor ⇔ Inflammation
  - Targeting tumors with infiltrating **macrophages** (Fms), **perineural invasion** and consequent severe **pain** (Trk)
  - Melanoma, head & neck, pancreatic, many other cancers





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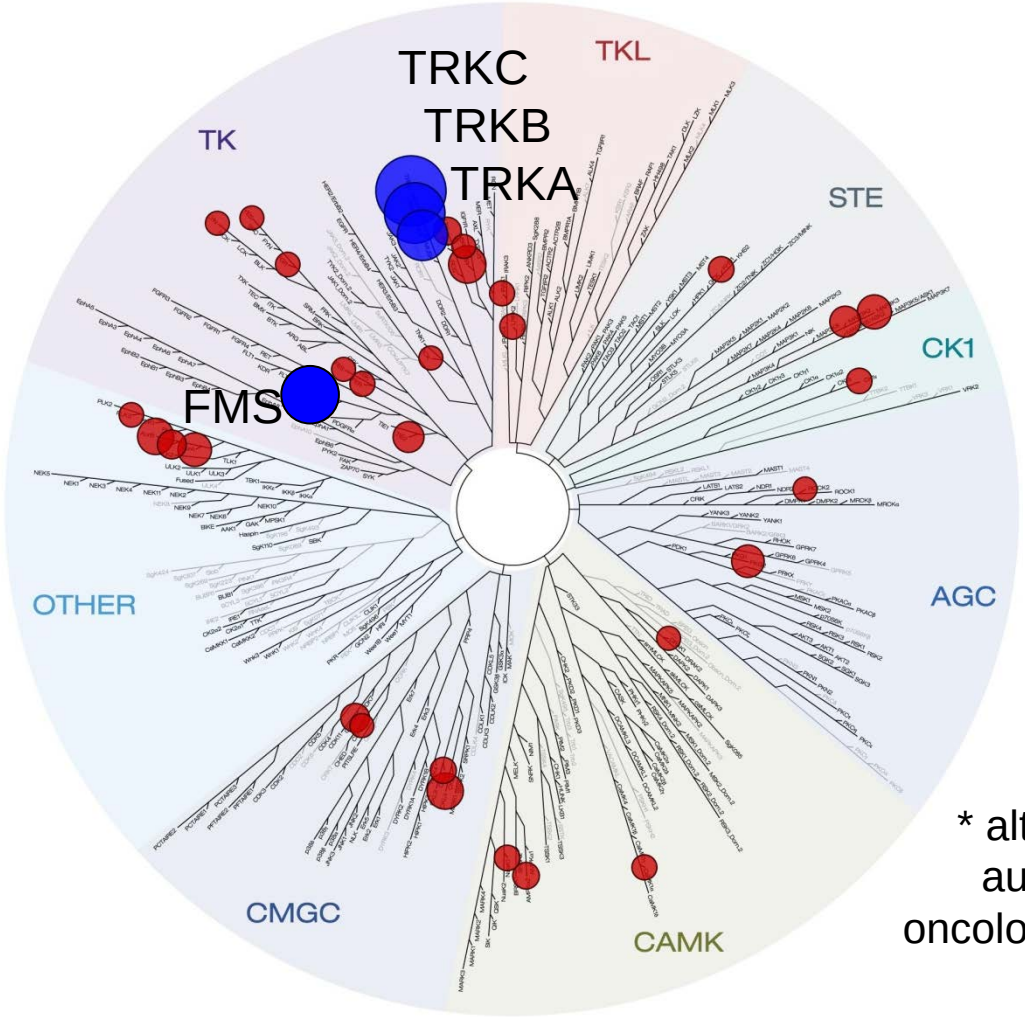
PLX7486 is a very selective kinase inhibitor

Invitrogen screen ~ 250 human kinases



IC_{50}'s

- < 10nM
  TRK A, B, C; FMS
- 80nM-1µM
  MAP3K2, AURKB, MAP3K3, AURKA *
- > 1µM
  240+ kinases

* although an off-target of PLX7486, aurora kinase is a well-recognized oncology target involved in cell division

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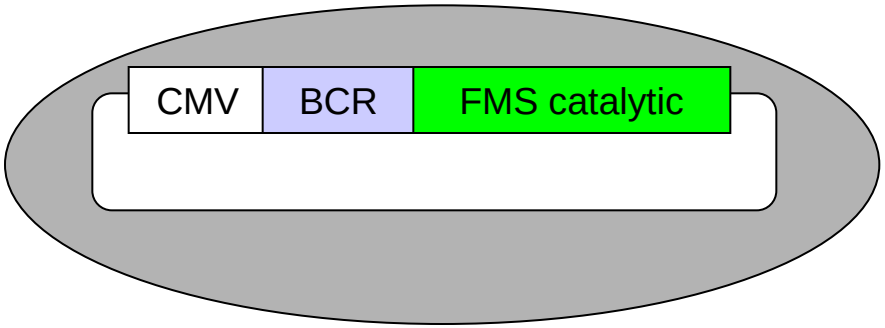
Customized Assay System for Fms/Trk Activity:
Ba/F3 Cells Transfected with Bcr-Fms or Bcr-TrkA,B,C

Cell-Based AND *in vivo* Assay



Bcr-Chimera Ba/F3 cells: "Bcr-Fms"

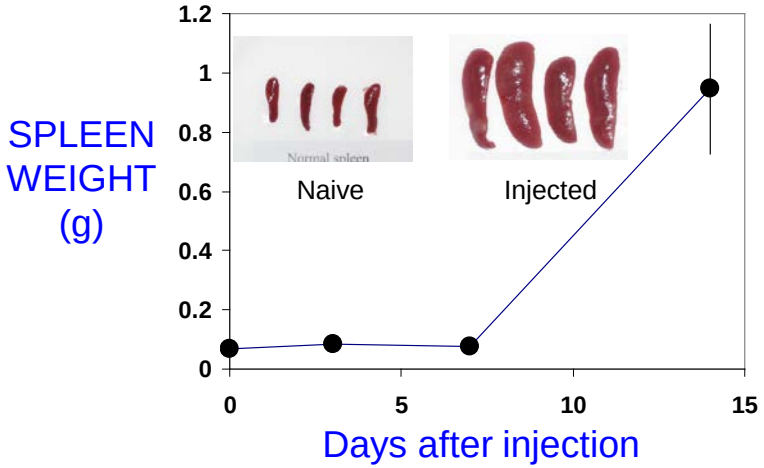
in vivo Assay

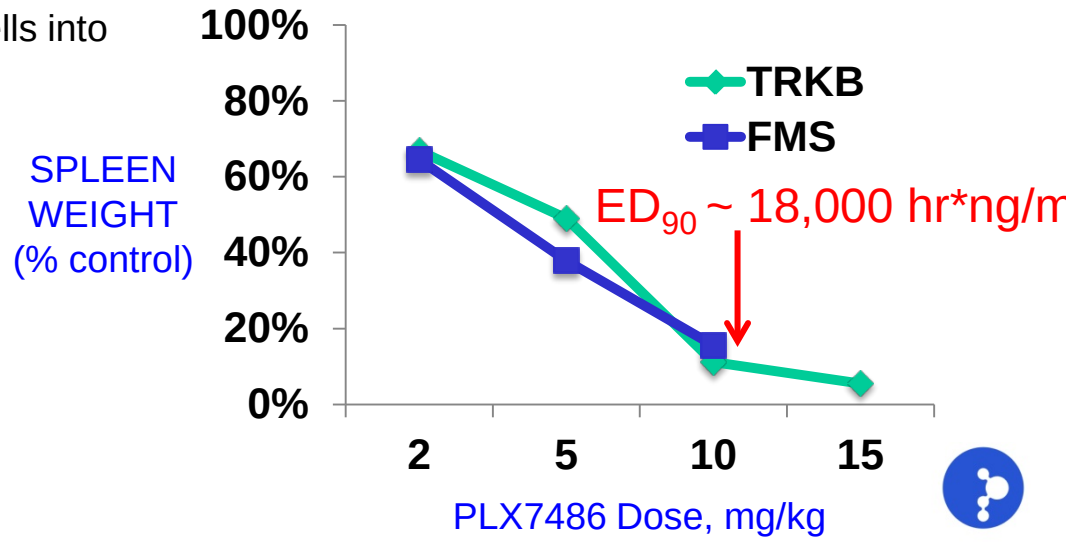
Inject cells into mice i.v.

Cell-Based Assay

Cell Proliferation IC_{50} (μM)	
Bcr-Fms	0.01
Bcr-TrkA	0.03
Bcr-TrkB	0.008
Bcr-TrkC	0.004

in vivo Bcr-Fms Splenomegaly Model





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Trk Kinases are Important Cancer Drug Targets

TrkA = receptor for neuronal growth factor (NGF)

- Potential role in perineural invasion (PNI) and validated role in pain

TrkB = receptor for brain-derived neurotrophic factor (BDNF), neurotrophin-4 (NT-4), NT-5

- Pro-oncogenic through suppression of caspase-associated anoikis

TrkC = receptor for neurotrophin-3 (NT-3)

- Overexpression or mutational activation may have role in promoting tumor survival, proliferation and invasion of certain cancers

Patients with **Trk-fusion**-driven tumors:

Single-agent efficacy potential for PLX7486

Tumor type	Subtype	How often	Which Trk	Example 'driver' fusions	
Salivary	MASC	up to 100%	TrkC	ETV6-NTRK3	
Breast	secretory	up to 100%	TrkC	ETV6-NTRK3	
Fibrosarcoma	congenital	up to 100%	TrkC	ETV6-NTRK3	
Nephroma	congenital	up to 100%	TrkC	ETV6-NTRK3	
Lung		rare	TrkA	MPRIP-NTRK1 CD74-NTRK1	TRIM24-NTRK2
Colorectal		rare	TrkA	TPM3-NTRK1	
Thyroid	PTC, rad	rare	TrkA,C	TPR-NTRK1 TPM3-NTRK1	ETV6-NTRK3 RBPMS-NTRK3
Glioma / Astrocytoma	GBM	rare	TrkB,A	QKI-NTRK2 NACC2-NTRK2 AFAP1-NTRK2	BCAN-NTRK1 NFASC-NTRK1
Cholangio		rare	TrkA	RABGAP1L-NTRK1	
HNSCC		rare	TrkB	PAN3-NTRK2	LYN-NTRK3
Melanoma	spitzoid	rare	TrkA	TP53-NTRK1 LMNA-NTRK1	
Sarcoma		rare	TrkA	TPM3-NTRK1	

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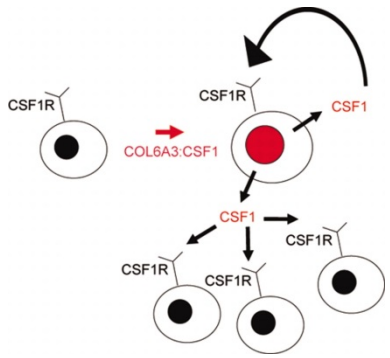
Additional opportunities for PLX7486
Overexpression of TRK, CSF1

- Adenoid Cystic Carcinoma (ACC) Ivanov, S. V. *et al. Oncogene* **32**, 3698-3710 (2013).
  - Overexpression of TRK-C and/or its ligand, NT-3
- Cylindromas Rajan, A. *et al. Oncogene* **30**, 4243-4260 (2011).
  - Overexpression of TRK-B and TRK-C
- Tenosynovial Giant Cell Tumor (aka Pigmented Villonodular Synovitis)
  - Rare synovial tumor of joints & tendon sheaths
  - Incidence ~600 cases per year in US, often young adults
  - Clonal neoplasm resulting in synovial overexpression of CSF1
    - Frequently due to genetic translocation: t(1;2) CSF1:COL6A3
    - Propagation of neoplastic clone (autocrine)
    - Reactive inflammatory process with proliferation & recruitment of CSF1R-expressing cells: macrophages, giant cells, osteoclasts

West, R. et al *PNAS USA* **103**, 690-695 (2006).



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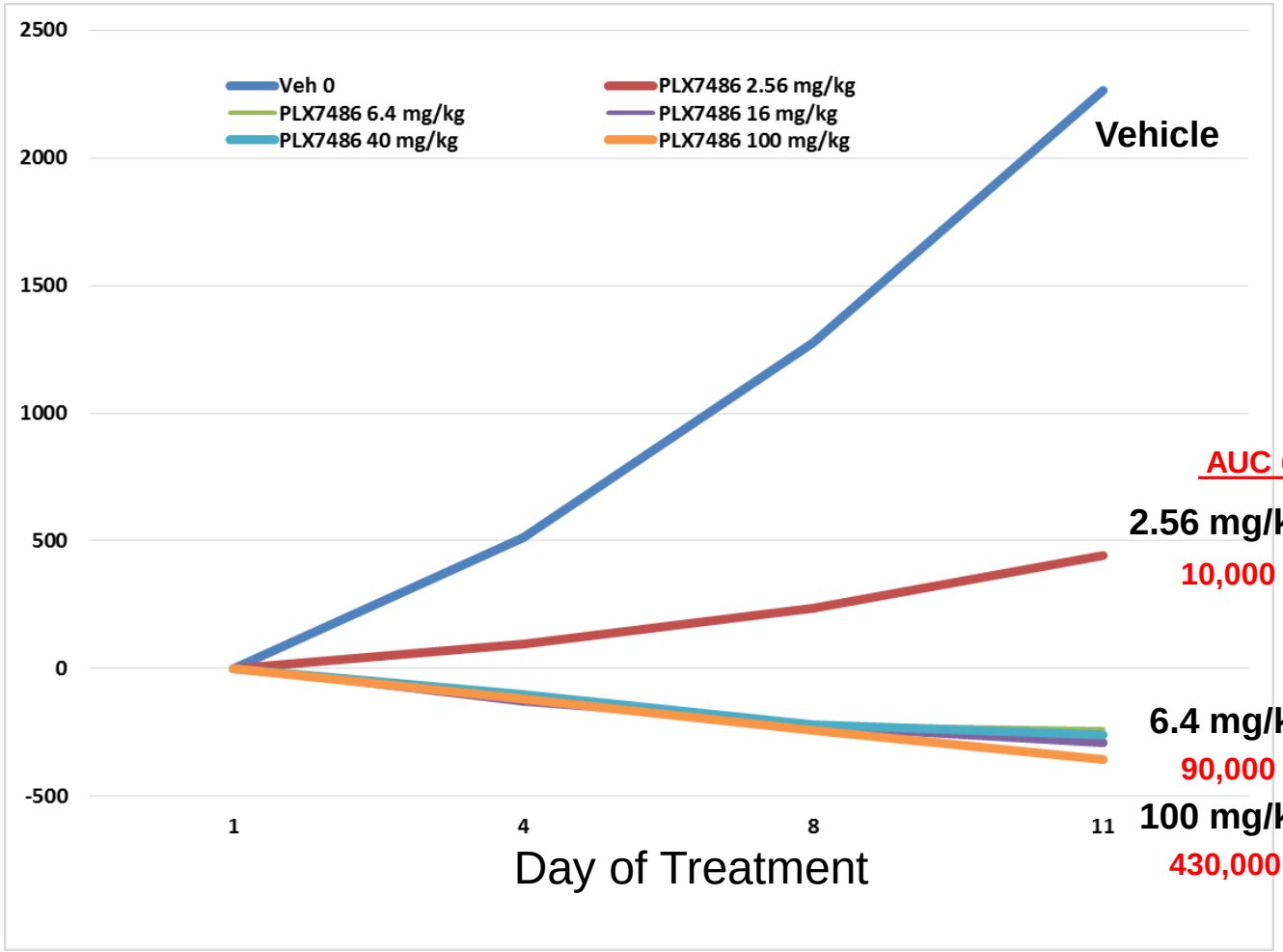
Efficacy of PLX7486 in KM12 Model

CRC cell line with TPM3-NTRK1 fusion



AUC 0-24

2.56 mg/kg PLX7486

10,000 hr*ng/mL

6.4 mg/kg PLX7486

90,000 hr*ng/mL (max efficacy)

100 mg/kg PLX7486

430,000 hr*ng/mL

Current mean clinical exposure: 90,000 hr*ng/mL

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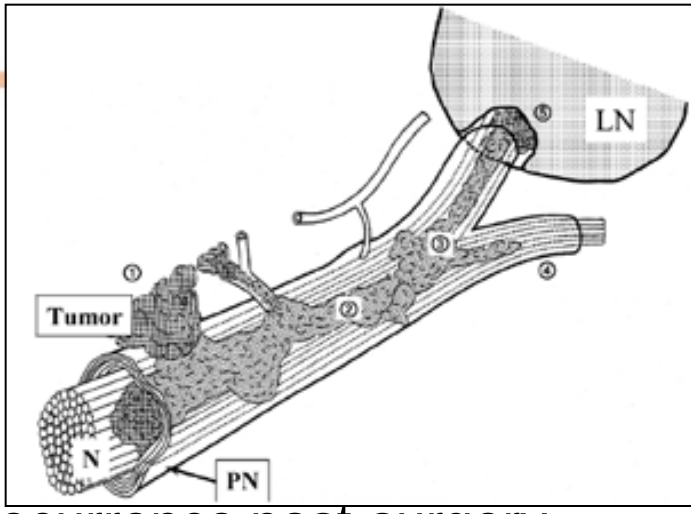
Addressing Perineural Invasion (PNI) & Pain



PNI is present in notorious tumor types

- Pancreatic, prostate, head & neck
- Local and referred cancer-associated pain

Anti-Tumor Goals for Trk inhibition:

- Combo regimens to reduce tumor spread and recurrence post-surgery
- Combo regimens to inhibit tumor/nerve interaction and enhance chemo/radiation efficacy

Validated Role in Pain

- Patients with inactivating mutations of NGF and TRKA are insensitive to pain
- rhNGF induces severe pain at injection site
- Anti-NGF Ab being developed for pain indications
  - Tanezumab, Ph 3 in Osteoarthritis and Chronic Back Pain

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PLX7486: Changing TRKs

Reasons for a new development plan

- Old plan
  - Determine single agent RP2D
    - Enroll TRK-fusion cancer patients
  - Determine RP2D in combo with Gem/Abraxane
    - Enroll pancreatic cancer patients
- Challenges
  - TRK fusion mutations are uncommon (e.g. ~1.5% of NSCLC) and requires large scale screening to identify patients
  - Combination studies for pancreatic CA challenging due to evolving treatment regimens; many additional combinations unexplored
- New plan: Partner with CRUK
  - Stratified Medicines to identify TRK-fusion lung cancers
  - Combinations alliance to test multiple hypotheses
    - Role of perineural invasion
    - Additional value based on pioneering studies with PLX3397 as FMS inhibitor

PLX7486 Phase 1 Trial: Protocol PLX119-01 (first in human)

- Single-agent, 3+3 design, dose-escalation of PLX7486 TsOH in all solid tumors
- 40 patients dosed at 9 dose levels so far, no DLTs
- Dose escalation ongoing
- < 10% of patients with drug-related Grade 3 AEs; no SAEs
- Reported AEs are consistent with other kinase inhibitors; some may be consistent with on-target activity
- In dose expansion, enrollment will be limited to patients with NTRK-implicated tumors