

LOXO-101
Loxo Oncology, Inc

Oncologic Drugs Advisory Committee
Pediatric Subcommittee

June 29, 2016

Developing LOXO-101 in Children with TRK Fusion Cancers

Josh Bilenker, MD

Chief Executive Officer
Loxo Oncology, Inc.

Agenda

◆ Drug and Target Rationale

- LOXO-101 is a highly selective TRK family inhibitor designed to spare off-targets and avoid on-target CNS issues

◆ Clinical Data

- LOXO-101 induces dramatic responses in adults and children with TRK fusion cancers, independent of context

◆ Pediatric Opportunities

- TRK fusions occur at high frequencies in rare tumors; their prevalence in other cancers is less well understood

◆ Patient Identification

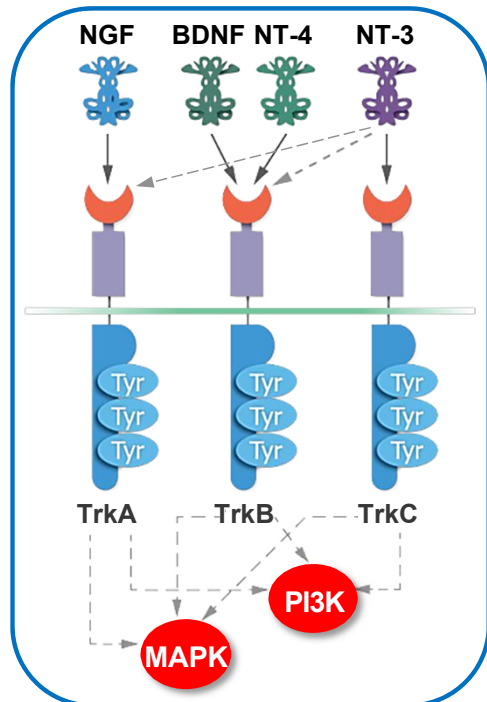
- Comprehensive molecular testing provides the best opportunity for TRK fusion detection and requires stakeholder alignment

TRK Fusions are Oncogenic and Signal Through Canonical Downstream Pathways

◆ Normal TRK Proteins

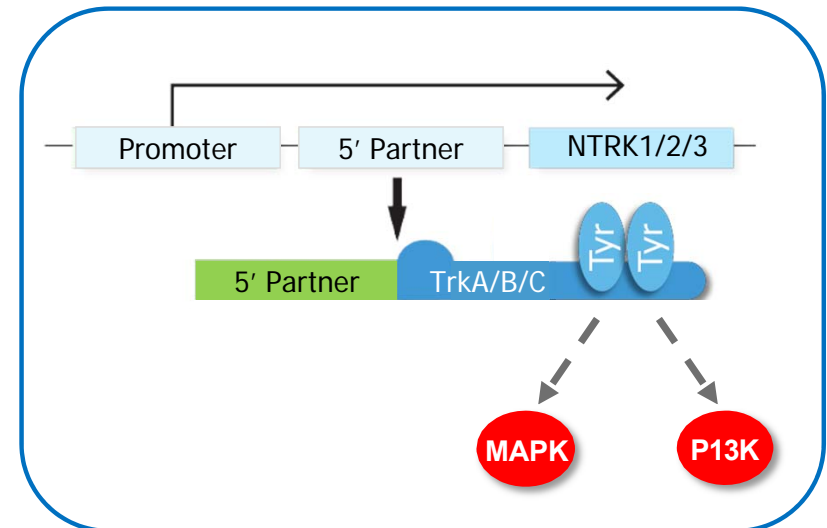
Family of neurotrophin receptors

- TRKA (*NTRK1*) → Pain, thermoregulation
- TRKB (*NTRK2*) → Movement, memory, mood, appetite, body weight
- TRKC (*NTRK3*) → Proprioception



◆ TRK Fusions

- 5' fusion partner leads to erroneous expression
- 3' TRK kinase signals independent of ligand activation

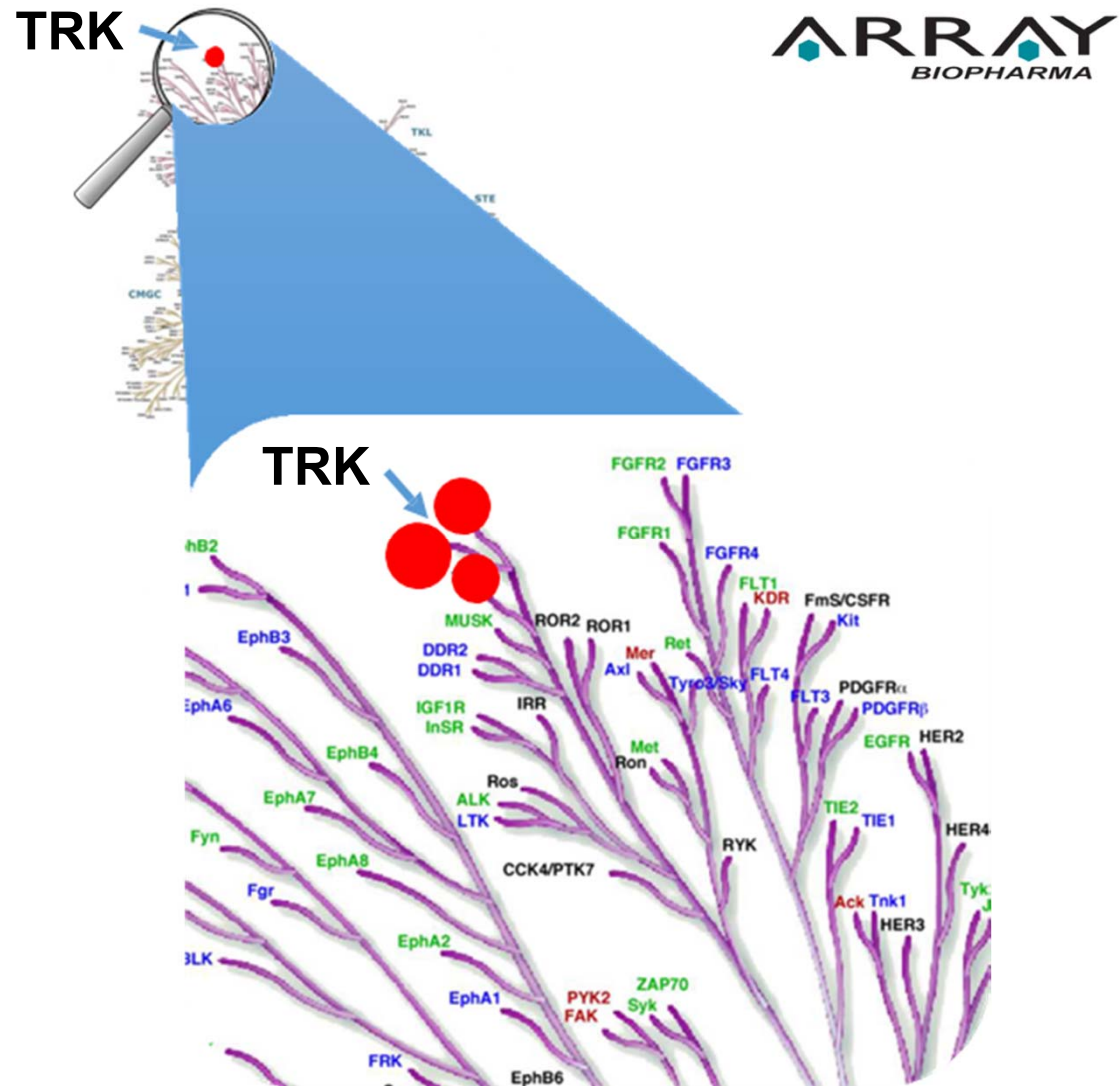


LOXO-101

A Rationally Designed Selective TRK Inhibitor

Highly potent against
TRKA, TRKB, TRKC
(5-11 nM IC₅₀)

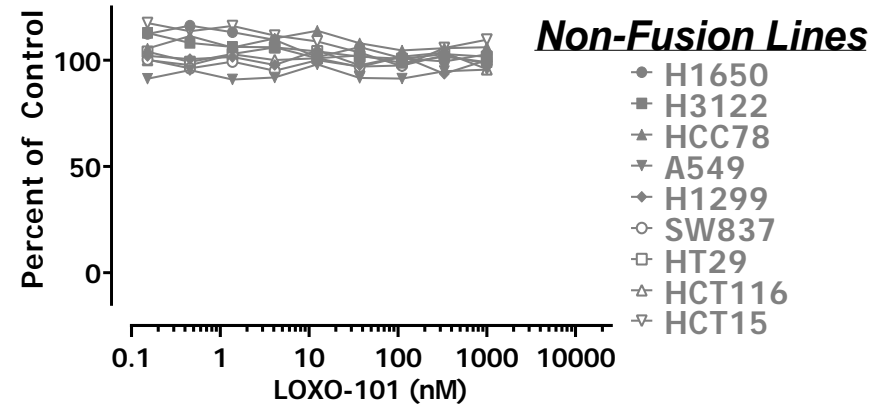
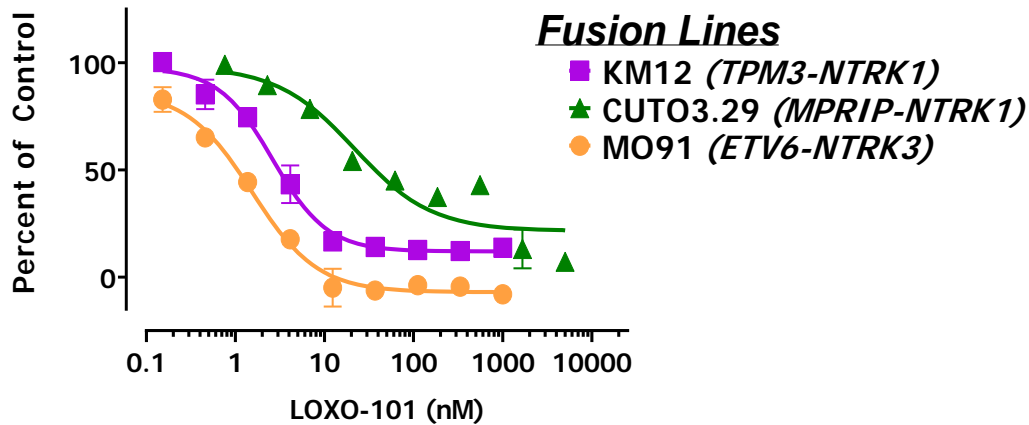
Highly selective:
limited inhibition of other
kinases and >1,000x selective
over other off targets



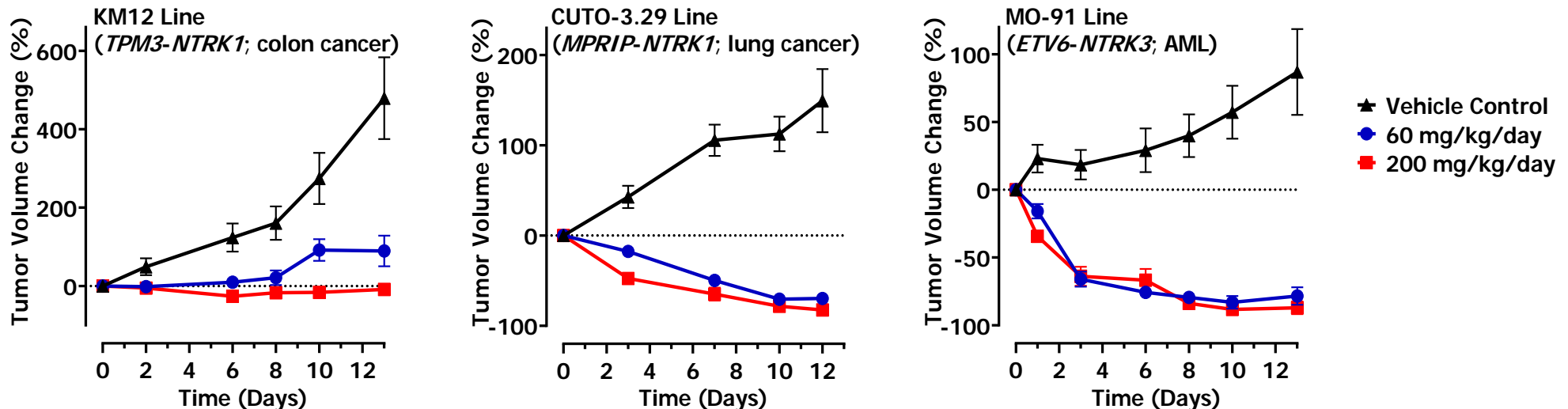
Chartier M, Chénard T, Barker J, Najmanovich R. (2013) Kinome Render: a stand-alone and web-accessible tool to annotate the human protein kinome tree. *PeerJ* 1:e126.

LOXO-101 *In Vitro* and *In Vivo* Activity

In Vitro: Potency in TRK Fusion Cell Models; Spares Unselected Cell Models



In Vivo: Tumor Regressions in TRK Fusion Xenografts



Courtesy of the Doebele lab. Doebele et al. *Cancer Discov.* 2015 Oct;5(10):1049-57;
 Hong D et al. Proc AACR-NCI-EORTC Molecular Targets Meeting 2015.

LOXO-101 Clinical Trials Enrichment for NTRK Fusions

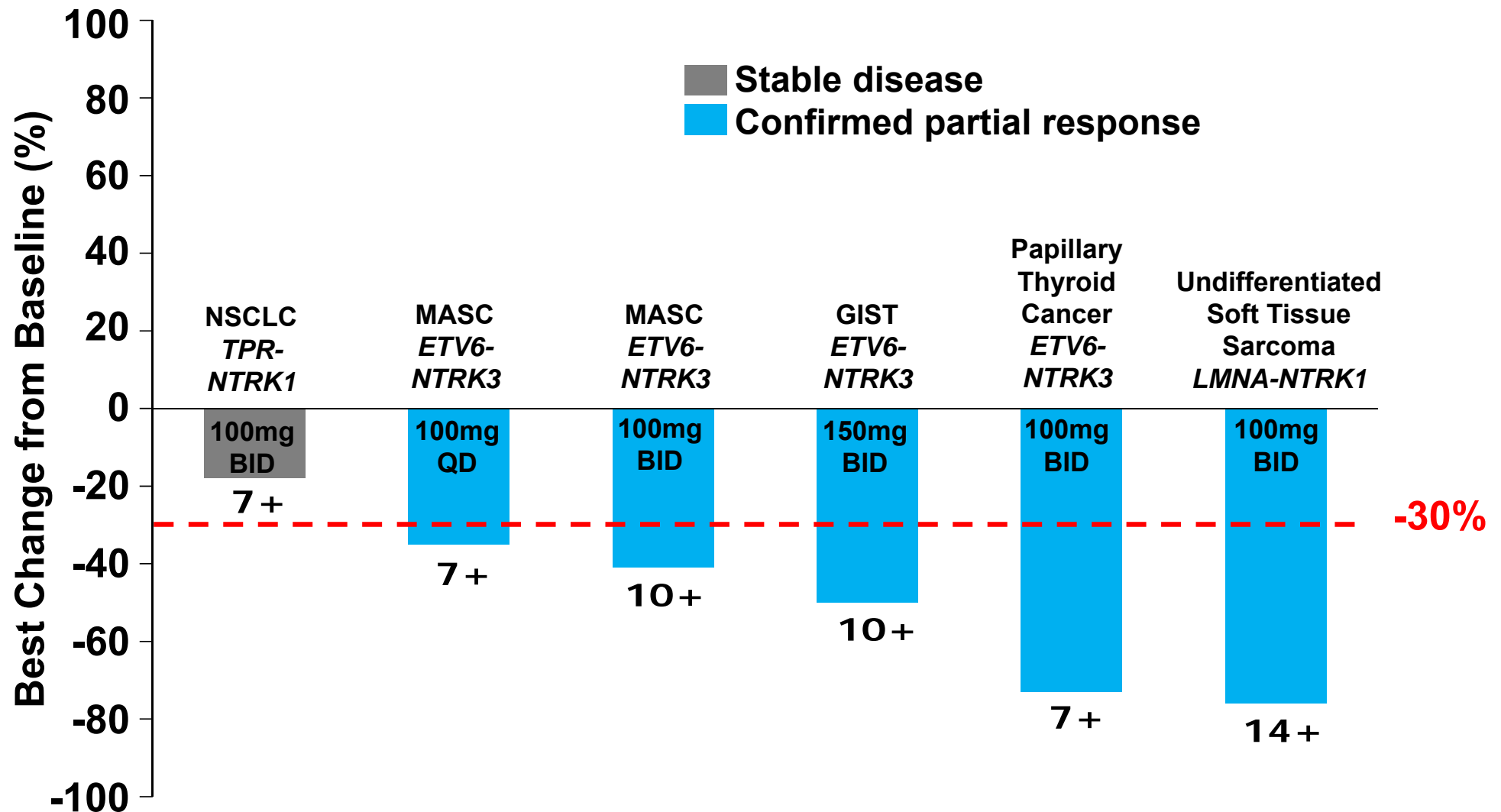
- ◆ **Phase 1 Adult Study**
 - 6 NTRK fusions updated AACR Apr 2016
- ◆ **Phase 1 Pediatric Study (Scout Trial)**
 - 1st NTRK fusion case report Apr 2016
- ◆ **Phase 2 Basket Study Adult/Adolescent (≥ 12 years) (Navigate Trial)**
 - Enrolling NTRK fusions only
- ◆ **NCI-MATCH Adult Study**
 - LOXO-101/ NTRK fusion arm opening ~Jul 2016
- ◆ **NCI-MATCH Pediatric Study**
 - LOXO-101/ NTRK fusion arm anticipated ~late 2016

LOXO-101 Phase 1 Adult Clinical Safety

- ◆ **Doses: 50mg QD, 100mg QD, 200mg QD, 100mg BID, 150mg BID**
- ◆ **MTD not yet established; 100mg BID selected for Phase 2**
- ◆ **Preliminary safety**
 - **Gr 3/4 events uncommon across doses, relatedness unclear (increased ALT/AST, anemia)**
 - **Gr 1/2 events suggest potential transient dizziness associated with C_{max} (dizziness, fatigue, increase AST/ALP)**
- ◆ **AE interpretation complicated by patients unselected for TRK fusion status**

LOXO-101

Phase 1 Adult Experience in NTRK Fusions

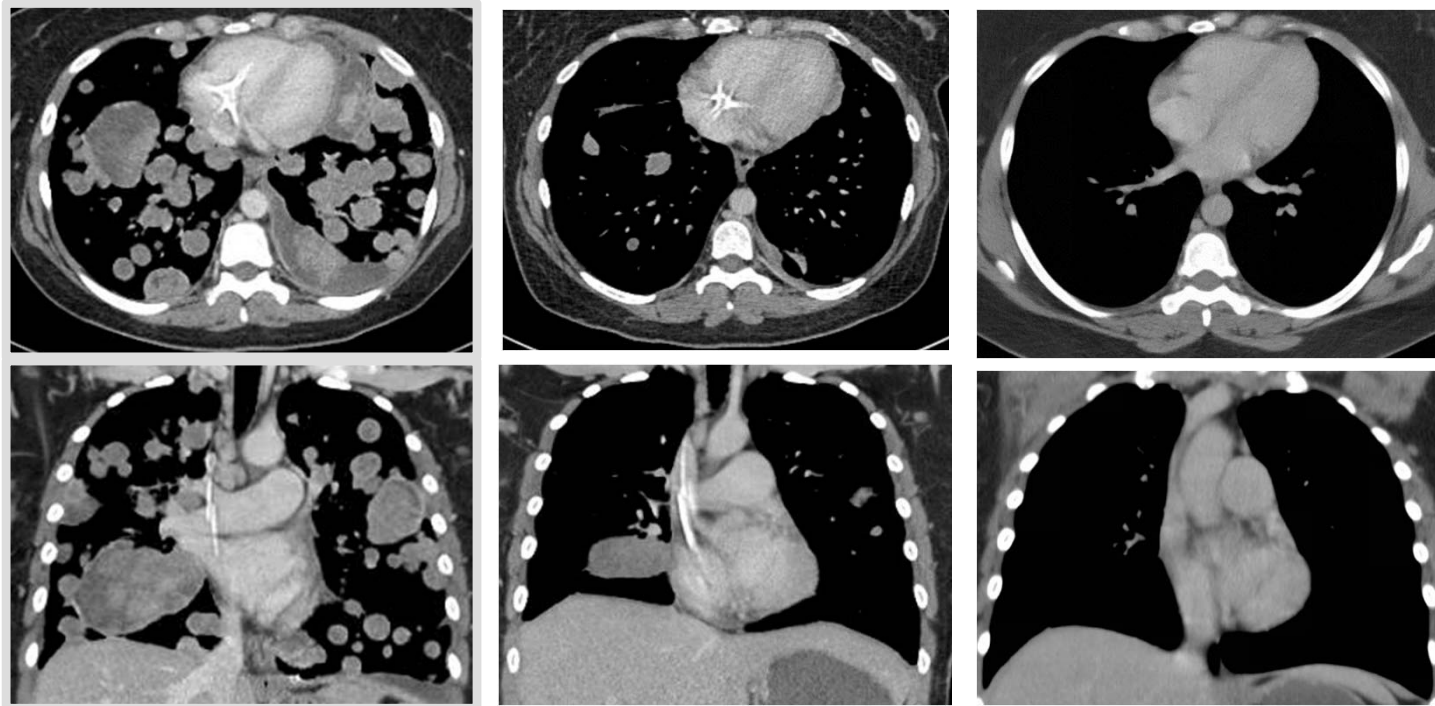


Note: Ongoing cycle number noted for each patient below each bar; 28-day cycles. RECIST v1.1.

Hong D et al. Proc AACR Annual Meeting 2016. Abstr CT008.

Data cutoff March 25, 2016.

Case Study: LMNA-NTRK1 Fusion Soft Tissue Sarcoma



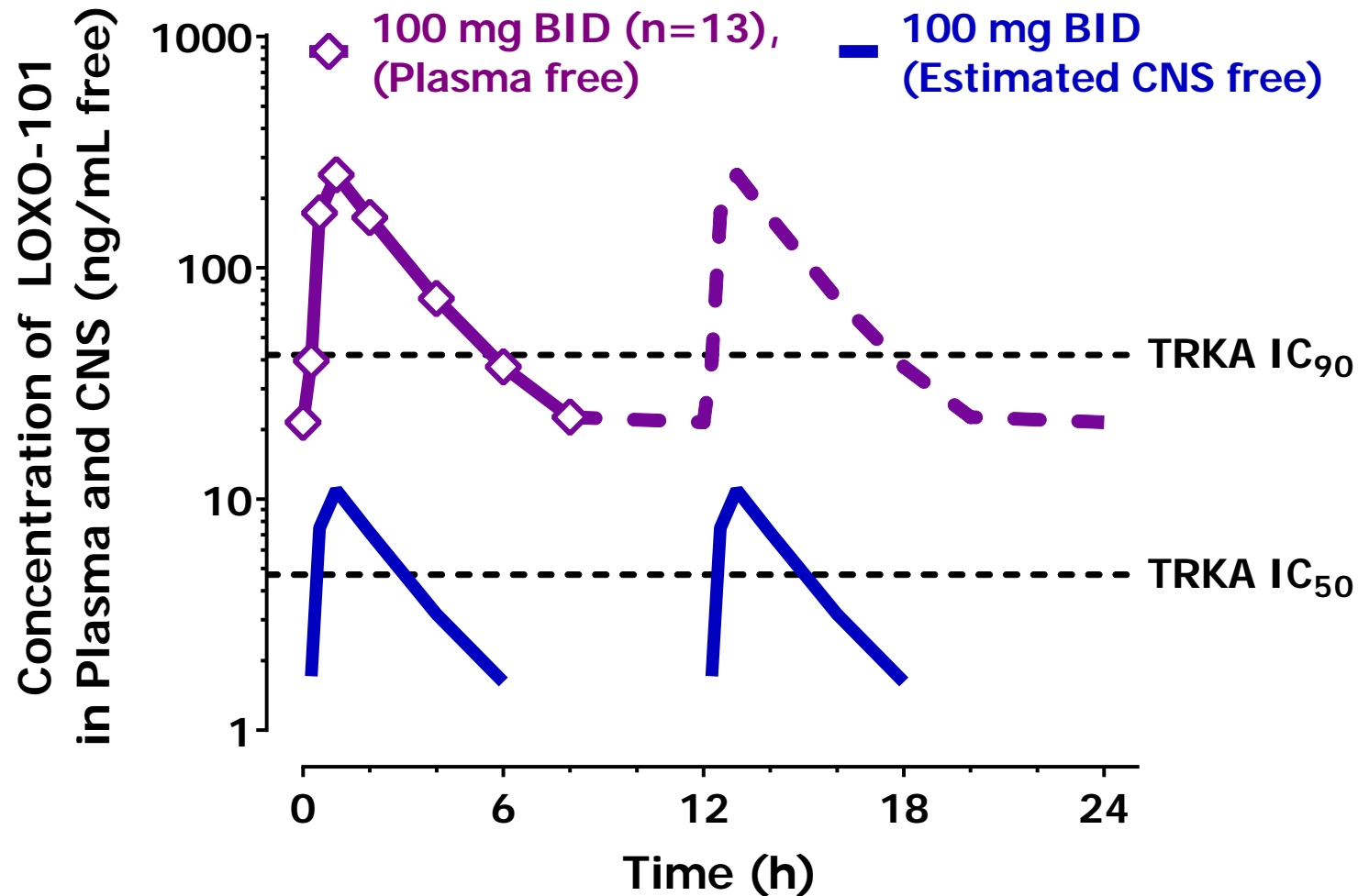
Study baseline

Study cycle 3 day 1

Study cycle 13 day 1

- ◆ 41-year-old female with undifferentiated sarcoma
- ◆ Progressed on prior chemotherapy and investigational therapy
- ◆ 100mg BID
- ◆ Rapid resolution of dyspnea and hypoxemia

LOXO-101 Adult Phase 1 Exposures

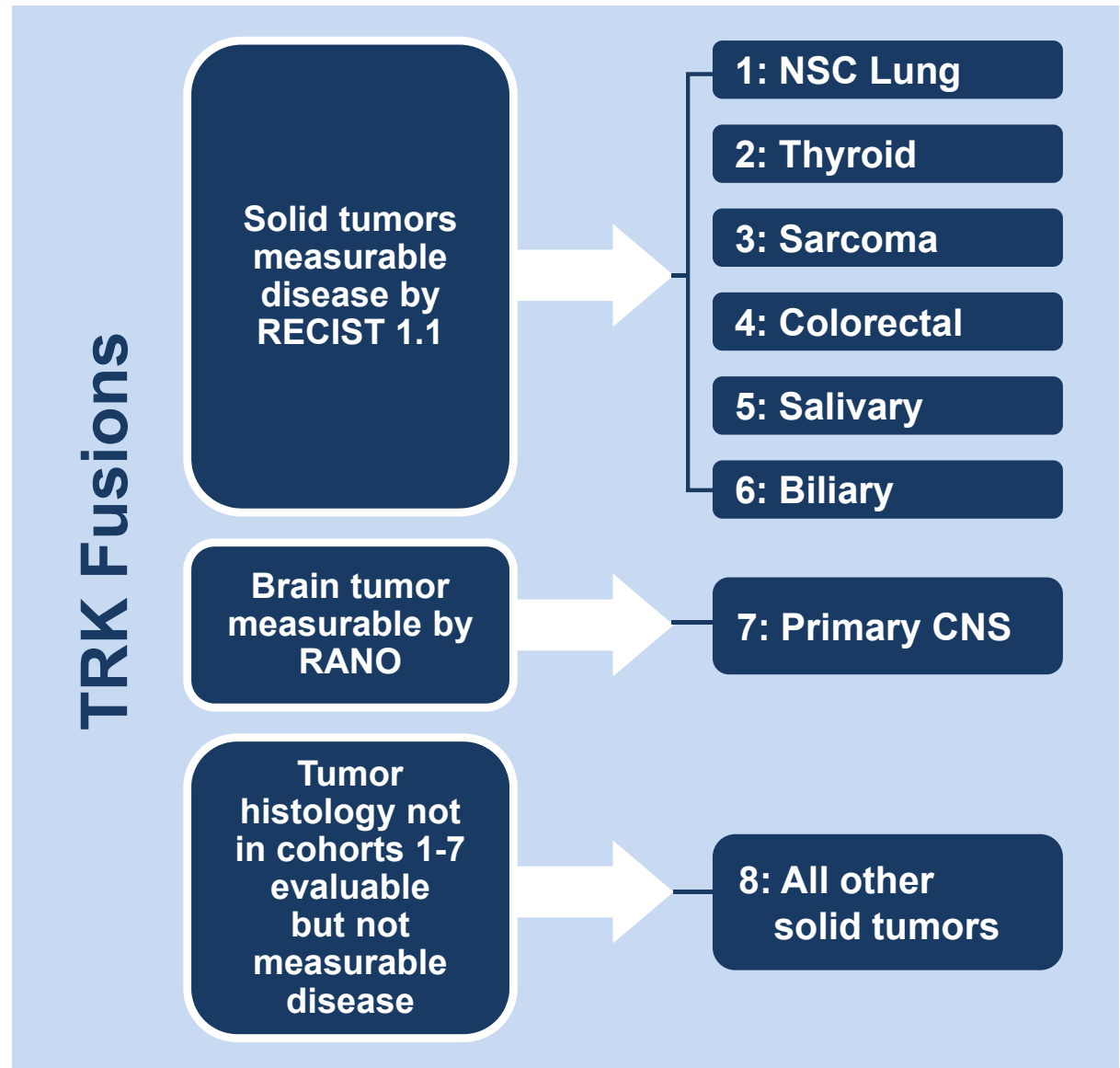


Protein binding	~70%
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$t_{1/2}$	~2 h
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LOXO-101 Phase 2 Navigate Basket Trial

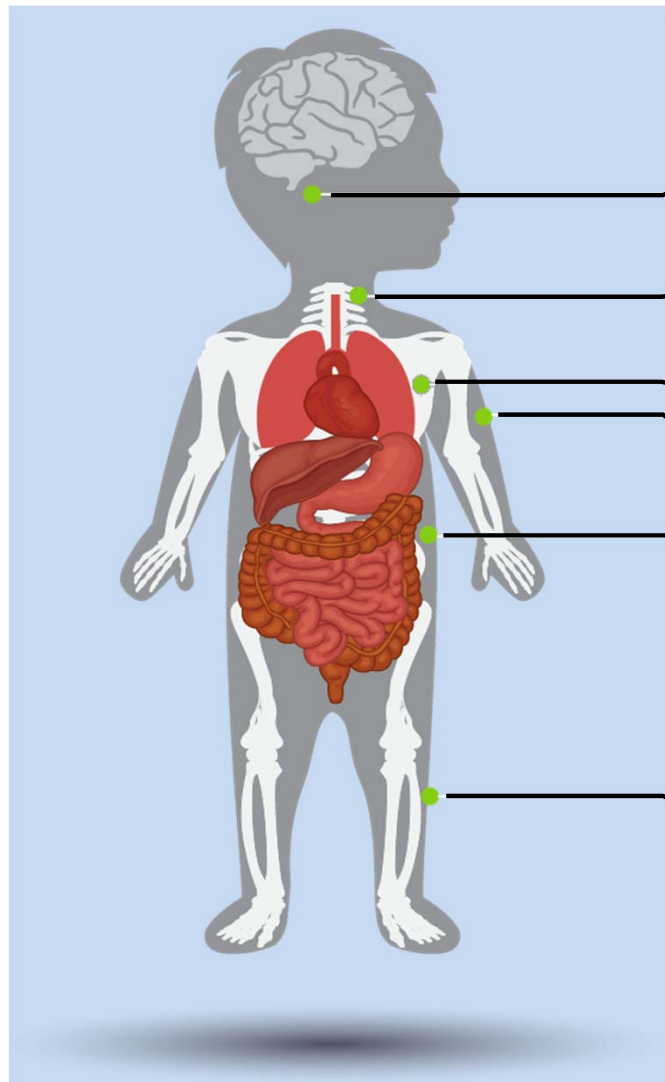
- ◆ Age ≥ 12
- ◆ 100mg BID
- ◆ Primary endpoint: ORR
- ◆ TRK fusion patients eligible by local testing methods
- ◆ Multinational trial in ~30 sites with access to comprehensive testing
- ◆ First patient enrolled October 2015



LOXO-101 Program Observations

- ◆ **NTRK 1, 2 and 3 fusions have been identified and treated**
- ◆ **TRK fusion cancers are diverse**
 - **>46 fusion partners in literature, with novel partners identified in LOXO-101 trials**
 - **>10 anatomic diagnoses in LOXO-101 trials**
- ◆ **Context independent efficacy**
- ◆ **Currently enrolling patients in adult P1, adult P2 and pediatric P1 trials**

Pediatric Cancers and NTRK Gene Fusions



DIPG and other High-Grade Gliomas¹

4% of DIPG

40% (4/10) HGG in infants <3

Papillary thyroid cancer²

7 of 28 younger patients

(25%) TRK fusion positive

Secretory breast carcinoma³

>90% of tumors have *ETV6-NTRK3* fusion

Infantile Fibrosarcoma^{4,5}

>85% of tumors have *ETV6-NTRK3* fusion

Congenital Mesoblastic Nephroma⁶

100% of cellular subtype exhibit *ETV6-NTRK3*

Sarcoma⁷

Myopericytic/ haemangiopericytic morphology indicative of TRK fusion

1. Wu G et al. *Nat Genetics* 2016. 2. Prasad ML et al. *Cancer* 2016. 3. Tognon C et al. *Cancer Cell* 2002. 4. Orbach D. *E Journal Cancer* 2016. 5. Wong V. *J Natl Cancer Inst.* 2016 6. Demellawy *Pathology* 2016. 7. Haller F et al. *J Pathol.* 2016.

Infantile Fibrosarcoma (IFS)

- ◆ Most common soft tissue sarcoma in children < 1 year
- ◆ >70% ETV6-NTRK3; case report of NTRK1 fusion
- ◆ Typically cured by surgical resection and chemotherapy, but
 - Surgery can be associated with disfigurement and limb compromise
 - Chemotherapy has variable activity and is associated with toxicity and late effects
 - XRT: Growth and late effect concerns
- ◆ Areas of unmet need
 - Neo adjuvant treatment in locally advanced disease
 - Refractory locally advanced disease
 - Metastatic disease



Case Study: ETV6-NTRK3 Infantile Fibrosarcoma



Study Baseline



Study Cycle 2 Day 1



Study Cycle 3 Day 1

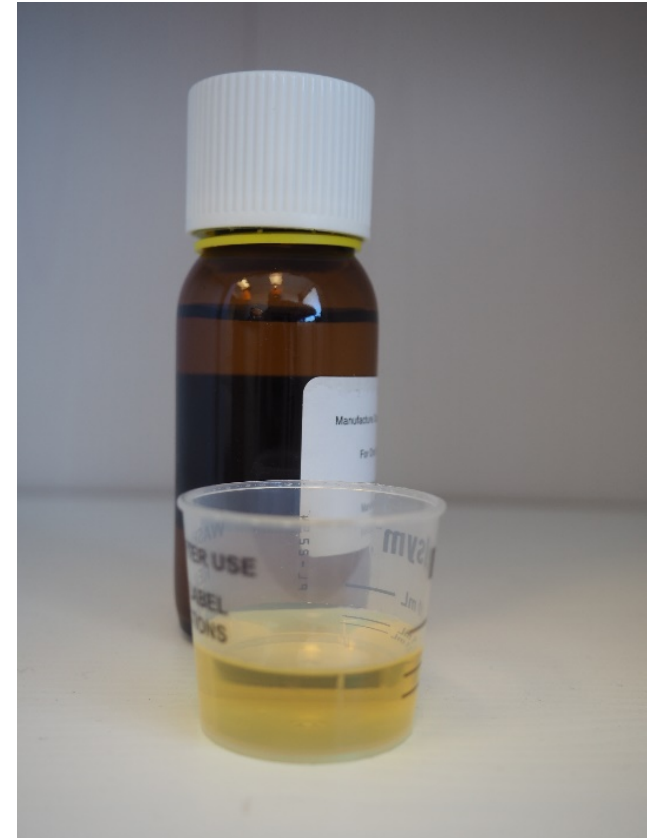
- ◆ 16-month-old female with prior surgery x 3 and multi-agent chemotherapy
- ◆ 100mg BID/ adult equivalent dose with liquid formulation
- ◆ 90% reduction in tumor volume by MRI; confirmed RECIST PR
- ◆ Again achieving normal developmental milestones

Neuroblastoma: Awaiting Clinical Validation

- ◆ Tumor of the neural crest
- ◆ TRK expression correlates with prognosis
 - Some cases contain novel TRKA splice variant (TrkAIII) that appears constitutively active
 - No reported TRK fusions
- ◆ In preclinical models, TRK inhibitors do not cause regressions
 - Suggest that combination therapy may be best
- ◆ In a clinical study of lestaurtinib, 2 objective responses
- ◆ Ongoing LOXO-101 Phase 1 trial and other sponsor trials are capable of answering the single agent activity question soon

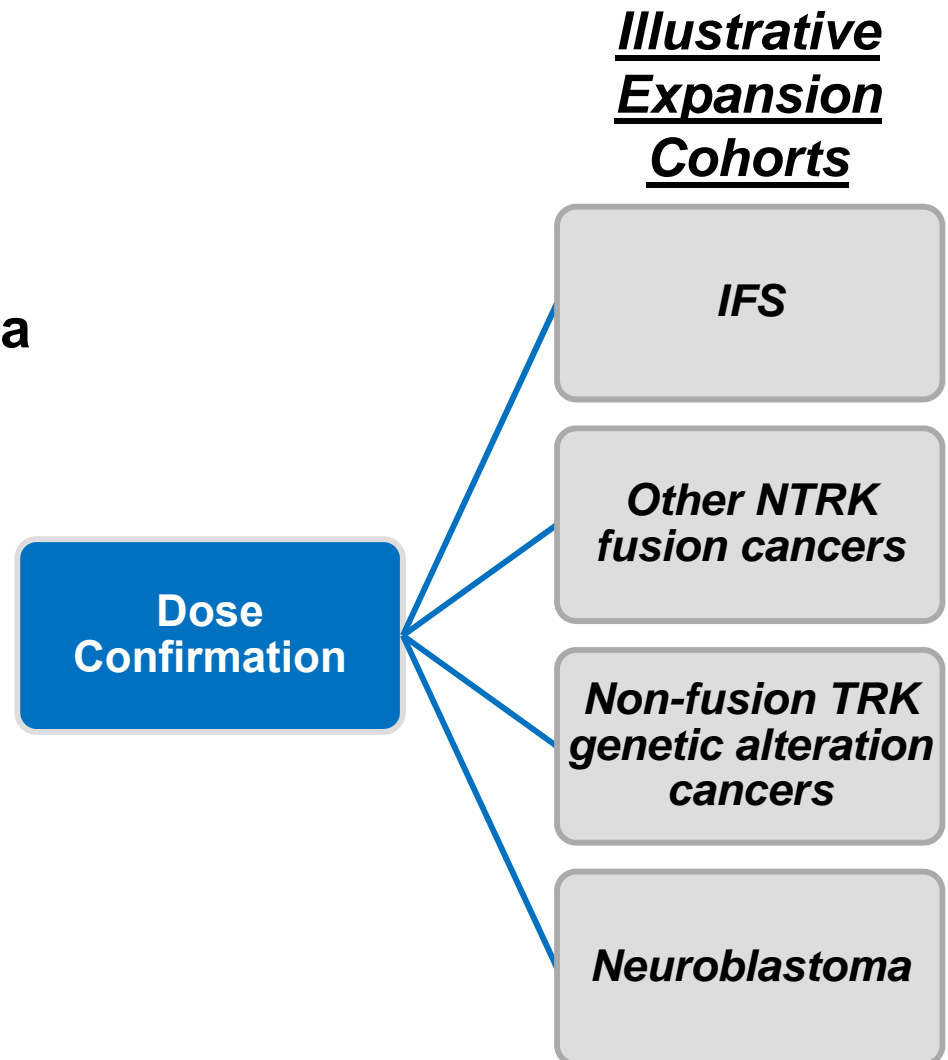
Liquid Formulation and Pediatric Dosing

- ◆ LOXO-101 amenable to taste masked liquid formulation; 25mg and 100mg capsules also available to pediatric patients
- ◆ Employed physiologic-driven PK modeling approach (SimCyp®), by age and weight
- ◆ Phase 1 study targeting exposures equivalent to adult recommended phase 2 dose 100mg PO BID



LOXO-101 Pediatric Phase 1 Scout Trial

- ◆ Rolling-6 dose escalation trial
- ◆ Ages 1-21 years in unselected refractory cancer; as young as 1 month for infantile fibrosarcoma or congenital mesoblastic nephroma
- ◆ Cohort 1 dose: targets equivalent exposure to adult Phase 2 dose
 - Intra-subject dose escalation permitted by real-time PK
- ◆ Expansion cohorts planned
- ◆ First patient enrolled: December 2015



Pediatric Development

Key Questions and Next Steps

- ◆ **Integrating data with the adult program (e.g. thyroid cancer, sarcoma)**
- ◆ **Streamlined trial designs**
 - **Phase 1/ 2 expansion model**
- ◆ **LOXO-101 selected as TRK fusion arm of pediatric MATCH trial**

Detecting NTRK Fusions Requires Attention and Commitment

- ◆ **The perfect NTRK gene fusion test does not exist**
- ◆ **Comprehensive genomic profiling**
 - Hypothesis free
 - Utilizes scarce tumor to full potential
 - Can include all actionable targets
 - RNA>DNA for fusions
 - Requires institutional commitment
- ◆ **Connectivity between lab medicine and clinical investigators**

Conclusions

- ◆ **NTRK joining the canon of other validated fusion oncogenes**
- ◆ **LOXO-101 is a well-tolerated, purpose-built, highly selective inhibitor of TRK A, B, C**
- ◆ **Early clinical experience in pediatrics appears consistent with the adult experience: context- and partner-independent efficacy**
- ◆ **Loxo Oncology is committed to accelerated pediatric development**

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Supporting Slides

Role of TRKA, TRKB, and TRKC in Embryonic Development

- ◆ **TRKA (nociceptive neurons)**
 - **Knock-out mice 99% neuron loss in DRG**
- ◆ **TRKB (trigeminal ganglia and dorsal root ganglia, motor neurons)**
 - **Knock-out mice 25-55% loss in trigeminal ganglia, 30-50% loss in DRG, 35% loss in motor neurons**
- ◆ **TRKC (large myelinated axons)**
 - **Knock-out mice devoid of axon collaterals projecting to motor pools**

Inherited Kinasopathies

- ◆ **TRKA mutation: Congenital Insensitivity to Pain with Anhidrosis (CIPA)**
 - Self-mutilation and trauma
- ◆ **Case report of a child with a TRKB mutation**
 - Developmental delay, impairment of short term memory, impaired nociception and obesity

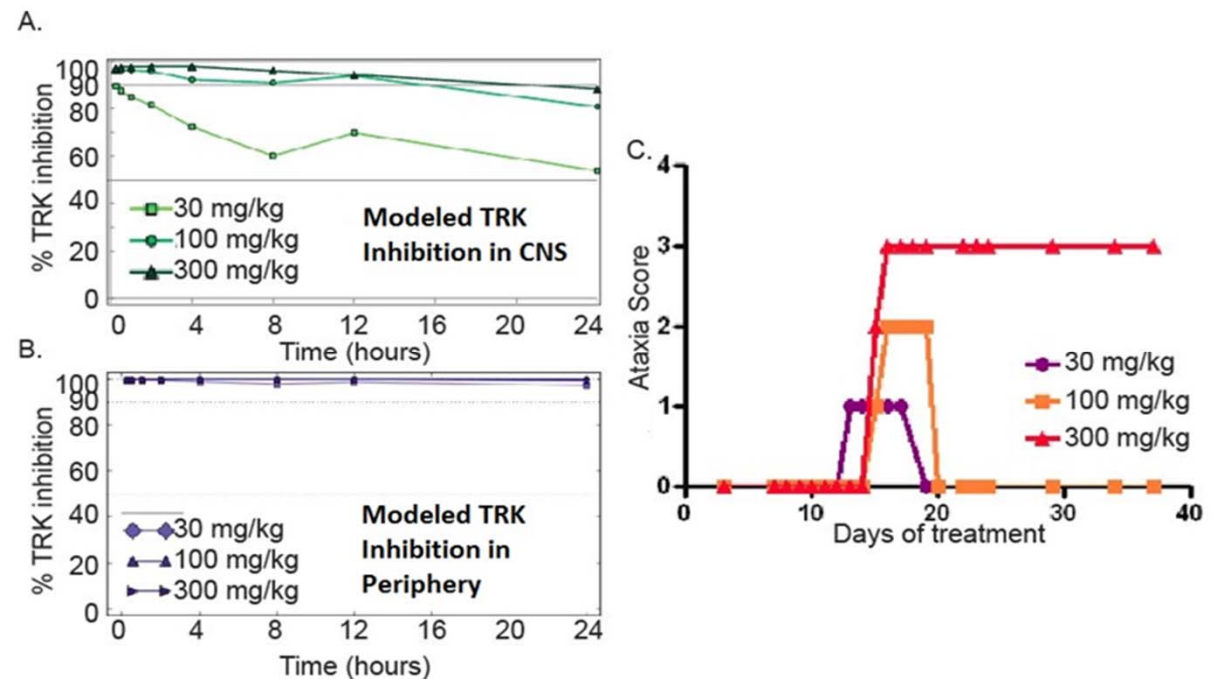
CNS Toxicity Reported for a Different, Brain-Penetrant TRK Inhibitor

- ◆ Phase 1 study of PHA-848125AC, a TRK and CDK inhibitor
- ◆ Highly brain-penetrant compound: brain/plasma >1 in rodents and non-rodents
- ◆ Two dosing schedules, necessitated by CNS tox
 - 7 days on / 7 days off; escalating doses associated with increasing severity of tremors and ataxia (Gr3/4)
 - 4 days on / 3 days off; 3 weeks on / 1 week off; tremors (Gr2)
- ◆ Neurotoxicity correlated with dose and schedule

LOXO-101: Selected for Favorable CNS Toxicity Profile

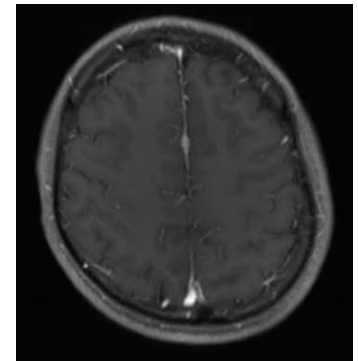
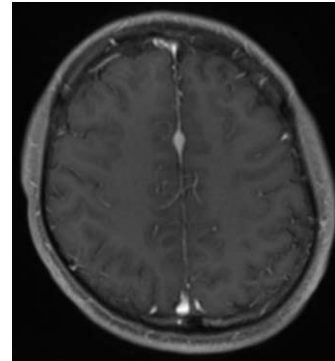
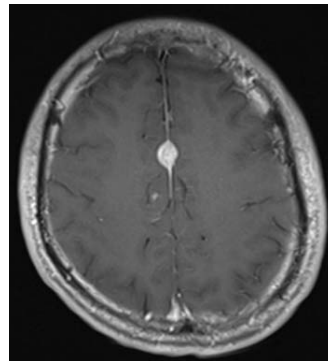
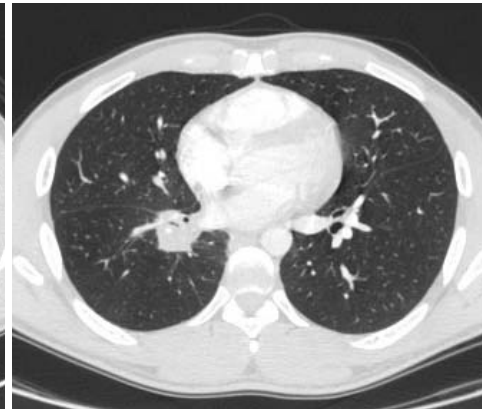
- ◆ TRKB important for normal movement, memory, mood and cognition
- ◆ Explored CNS PK-PD relationships in dedicated rat models
- ◆ Gait and behavior changes associated with deep and sustained target coverage across species

- ◆ Conclusion:
Optimal drug profile would deliver high *transient* brain levels and *sustained* peripheral levels



Preliminary Evidence of Brain Penetration

- ◆ 28 yo male progressed through cisplatin and etoposide
- ◆ TPR-NTRK1 non-small cell lung cancer
- ◆ 100mg BID
- ◆ Resolution of cough and pain
- ◆ Currently on study in cycle 7



Study baseline

Study cycle 3 day 1

Study cycle 7 day 1

Pediatric Phase 1 Study

◆ Study Design

- Phase 1, multicenter, open-label, rolling 6 dose escalation study in pediatric patients with advanced solid or primary CNS tumors
- LOXO-101 administered BID
- Cohort 1 targets equivalent of adult 100mg BID exposure
- Dose by age/ body weight nomogram; intra-subject dose escalation/ de-escalation
- Expansion cohorts planned, but to be defined based on signal seeking during Phase 1 portion

◆ Pharmacokinetics assessed C1D1 and C2D1

◆ Escalation may continue for CNS tumors

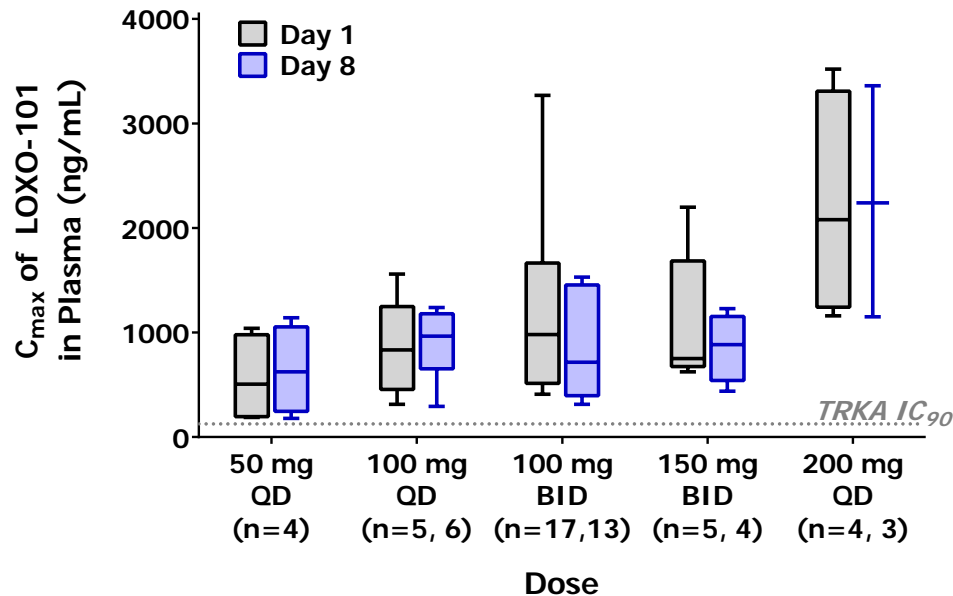
Pediatric Dosing Informed By Simcyp Modeling (20 mg/mL)

Example: Cohort 1

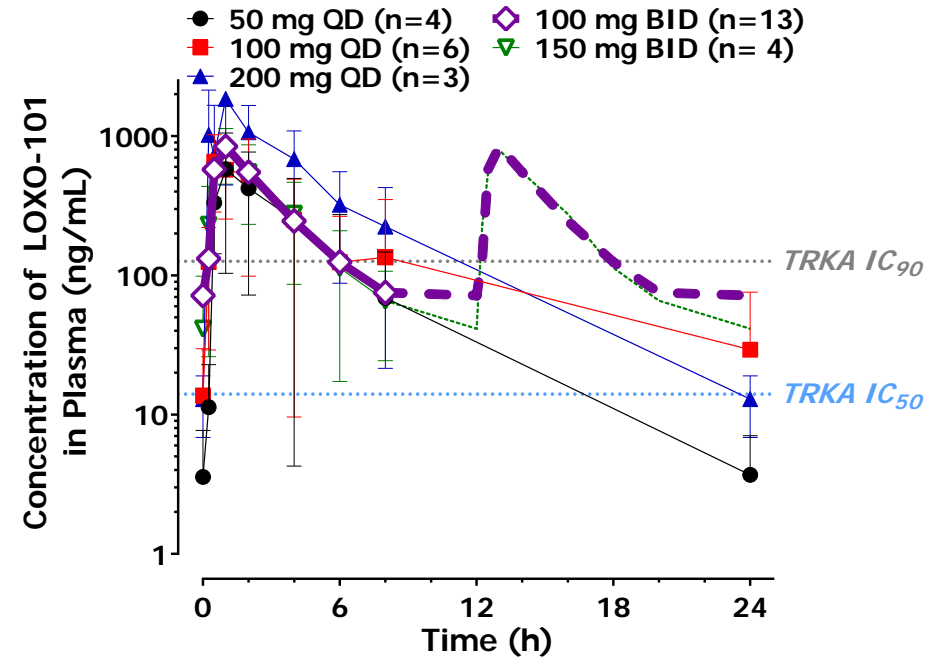
Patient's Age	<u>Volume (mL)</u>				
	6 mo-1 yr	1-2 yr	2-6 yr	6-12 yr	12-18 yr
Target dose (mg/m ²):	13.9	23.5	39.4	72.8	125
Patient's BSA (m ²)					
0.25 to 0.35	0.2	0.4	0.6	1.1	1.9
0.35 to 0.45	0.3	0.5	0.8	1.5	2.5
0.45 to 0.55	0.3	0.6	1.0	1.8	3.1
0.55 to 0.65	0.4	0.7	1.2	2.2	3.7
0.65 to 0.75	0.5	0.8	1.4	2.5	4.4
0.75 to 0.9	0.6	0.9	1.6	2.9	5.0
0.9 to 1.1	0.7	1.2	2.0	3.6	5.0
1.1 to 1.3	0.8	1.4	2.4	4.4	5.0
1.3 to 1.5	1.0	1.6	2.8	5.0	5.0
1.5 to 1.7	1.1	1.9	3.2	5.0	5.0
1.7 to 1.9	1.2	2.1	3.5	5.0	5.0
1.9 to 2	1.4	2.3	3.9	5.0	5.0

LOXO-101 Exposure Adult Phase 1

LOXO-101 C_{MAX}



LOXO-101 EXPOSURE OVER TIME



- ◆ Linear PK profile following oral administration shows high plasma exposure and no accumulation
- ◆ Slow off-rate; T_{1/2} = 160 min

The horizontal line representing TRKA IC₉₀ refers to the total plasma concentration of LOXO-101 that is associated with an unbound concentration of LOXO-101 that is equal to its IC₉₀ for inhibition of NGF-stimulated activity in a cellular assay. The IC₉₀ values for TRKB and TRKC are not shown, but are similar to those of TRKA. Dotted lines in the right panel are inferred PK from the evening BID dose.

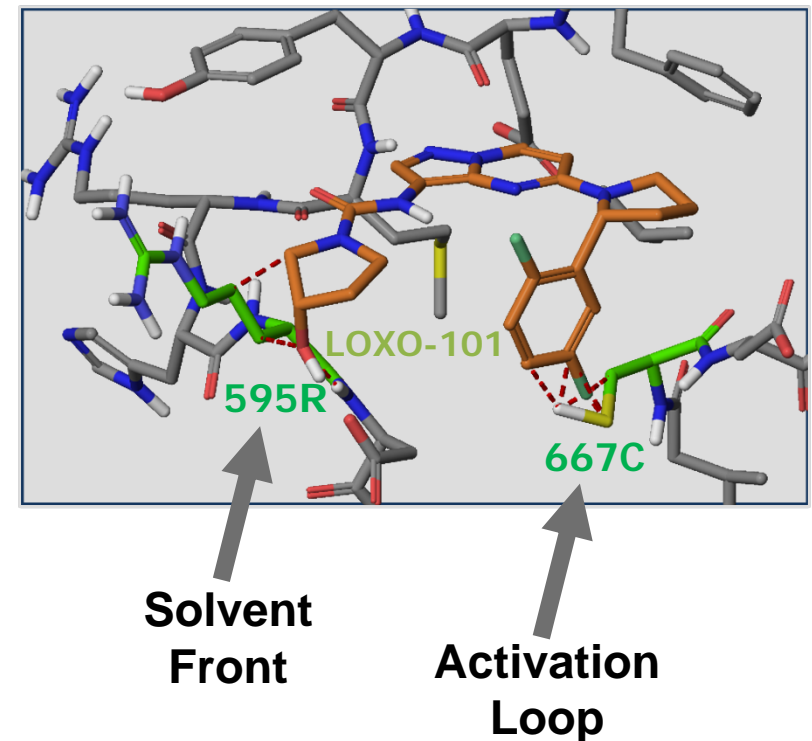
Pediatric Phase 1 Study

Neurological Exam (eCRF)

Neurologic Symptom	Specify	Response	CTCAE Grade
Cognitive disturbance		<input type="radio"/> Not Done <input type="radio"/> Not Present <input type="radio"/> Present	<input type="radio"/> Grade 1 <input type="radio"/> Grade 2 <input type="radio"/> Grade 3 <input type="radio"/> Grade 4
Concentration impairment		<input type="radio"/> Not Done <input type="radio"/> Not Present <input type="radio"/> Present	<input type="radio"/> Grade 1 <input type="radio"/> Grade 2 <input type="radio"/> Grade 3 <input type="radio"/> Grade 4
Dizziness (lightheadedness, spinning sensation)		<input type="radio"/> Not Done <input type="radio"/> Not Present <input type="radio"/> Present	<input type="radio"/> Grade 1 <input type="radio"/> Grade 2 <input type="radio"/> Grade 3 <input type="radio"/> Grade 4
Ataxia (lack of coordination of muscle movements)		<input type="radio"/> Not Done <input type="radio"/> Not Present <input type="radio"/> Present	<input type="radio"/> Grade 1 <input type="radio"/> Grade 2 <input type="radio"/> Grade 3 <input type="radio"/> Grade 4
Extrapyramidal disorder (involuntary muscle movements)		<input type="radio"/> Not Done <input type="radio"/> Not Present <input type="radio"/> Present	<input type="radio"/> Grade 1 <input type="radio"/> Grade 2 <input type="radio"/> Grade 3 <input type="radio"/> Grade 4
Lethargy		<input type="radio"/> Not Done <input type="radio"/> Not Present <input type="radio"/> Present	<input type="radio"/> Grade 1 <input type="radio"/> Grade 2 <input type="radio"/> Grade 3 <input type="radio"/> Grade 4
Memory impairment		<input type="radio"/> Not Done <input type="radio"/> Not Present <input type="radio"/> Present	<input type="radio"/> Grade 1 <input type="radio"/> Grade 2 <input type="radio"/> Grade 3 <input type="radio"/> Grade 4
Neuralgia (pain around nerve or group of nerves)		<input type="radio"/> Not Done <input type="radio"/> Not Present <input type="radio"/> Present	<input type="radio"/> Grade 1 <input type="radio"/> Grade 2 <input type="radio"/> Grade 3 <input type="radio"/> Grade 4
Paresthesia (loss of DTR)		<input type="radio"/> Not Done <input type="radio"/> Not Present <input type="radio"/> Present	<input type="radio"/> Grade 1 <input type="radio"/> Grade 2 <input type="radio"/> Grade 3 <input type="radio"/> Grade 4
Peripheral sensory neuropathy (tingling, numbness, etc.)		<input type="radio"/> Not Done <input type="radio"/> Not Present <input type="radio"/> Present	<input type="radio"/> Grade 1 <input type="radio"/> Grade 2 <input type="radio"/> Grade 3 <input type="radio"/> Grade 4
Somnolence (Sleepiness, drowsiness)		<input type="radio"/> Not Done <input type="radio"/> Not Present <input type="radio"/> Present	<input type="radio"/> Grade 1 <input type="radio"/> Grade 2 <input type="radio"/> Grade 3 <input type="radio"/> Grade 4

Acquired Resistance to Kinase Inhibitors

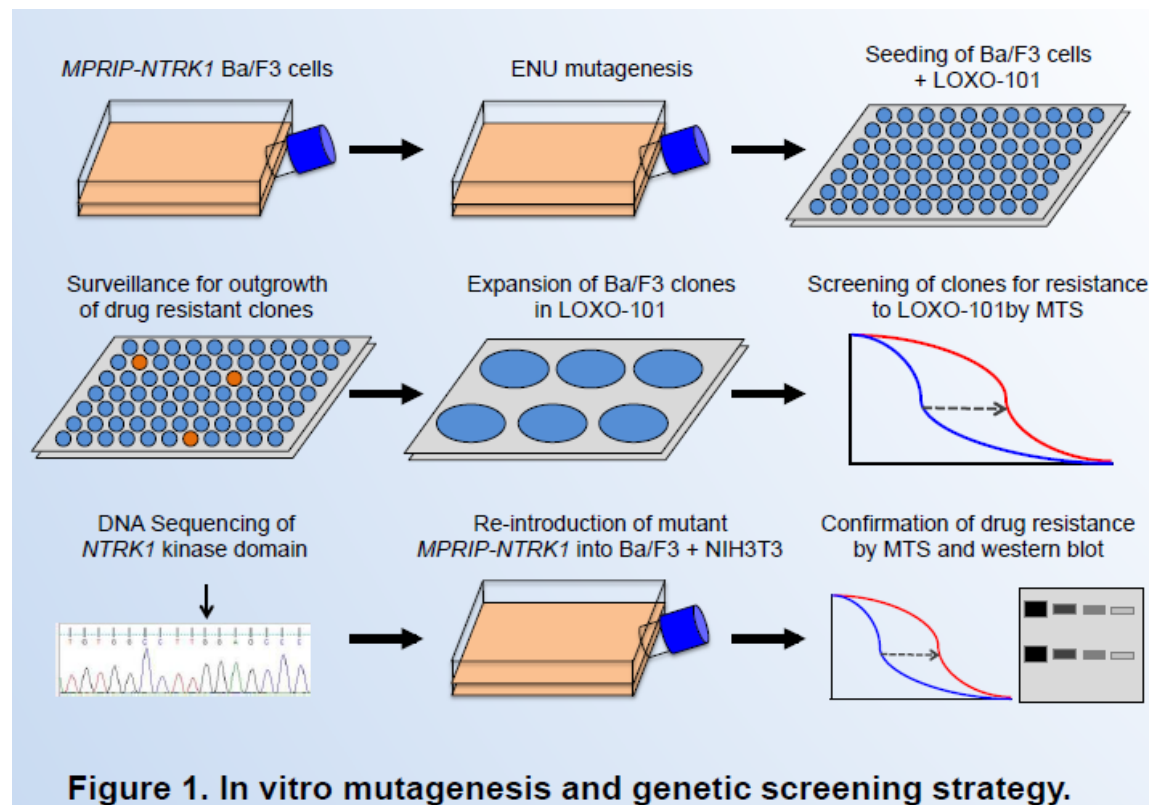
- ◆ Universally encountered with targeted therapies
- ◆ As of this presentation, no LOXO-101 responder has progressed
- ◆ Case reports: two patients with tumor progression after initial response to a different TRK inhibitor in the clinic^{1,2}
 - Patient 1: NTRK1 G595R (solvent front) + Y667C
 - Patient 2: NTRK3 G623R (solvent front)
- ◆ Paralogous of ALK-G1202R and ROS1-G2032R



1. Russo et al. *Cancer Discovery*. Published OnlineFirst on November 6, 2015; DOI: 10.1158/2159-8290.
2. Drilon et al. *Annals of Oncology*. Advance Access published February 15, 2016

ASCO 2016 Abstract LB-118

“Identification of TRKA and TRKB kinase domain mutations that induce resistance to a pan-TRK inhibitor,” Adriana Estrada-Bernal, Anh T. Le, Brian Tuch, Tatiana G. Kutateladze, and Robert C. Doebele



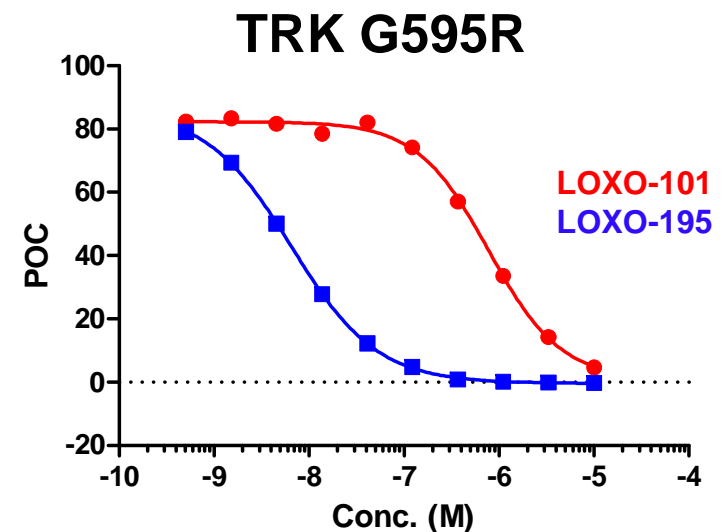
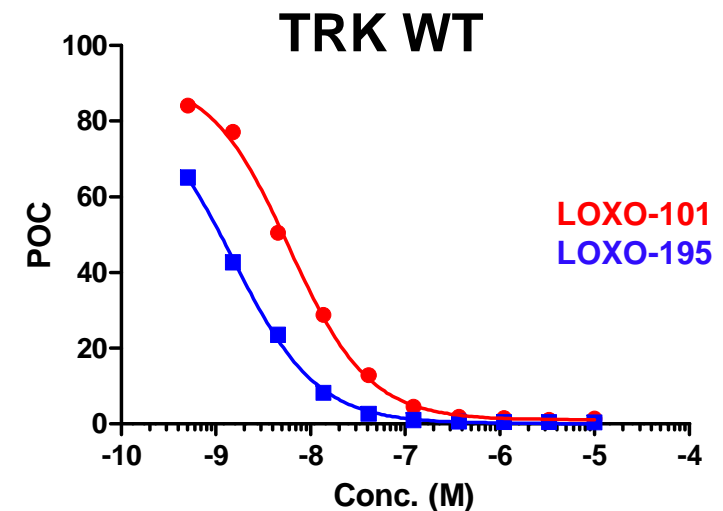
LOXO-195: 2nd Generation TRK Inhibitor

◆ LOXO-195

- Highly potent: nanomolar in cell against TRKA, TRKB, TRKC
- Highly selective: >1,000x
- Chemically distinct from LOXO-101

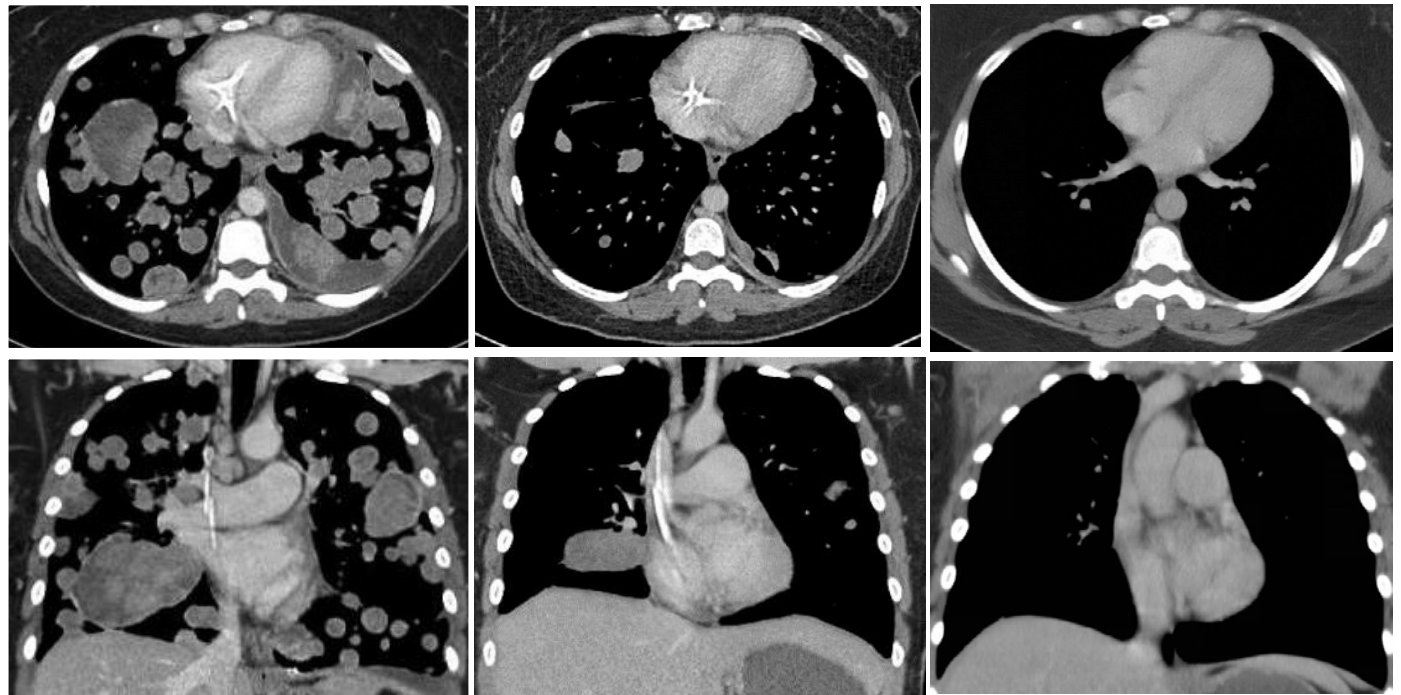
◆ LOXO-195 active against all acquired resistance mutations identified to date

◆ Entering Phase 1 in 2017



Patient #1: LMNA-NTRK1 Fusion Soft Tissue Sarcoma

- ◆ 41 yo female with undifferentiated sarcoma progressed through epirubicin, ifosfamide, sorafenib, and doxorubicin
- ◆ 100mg BID
- ◆ Rapid resolution of dyspnea and hypoxemia
- ◆ Confirmed partial response
- ◆ Currently on study in cycle 14



Study
baseline

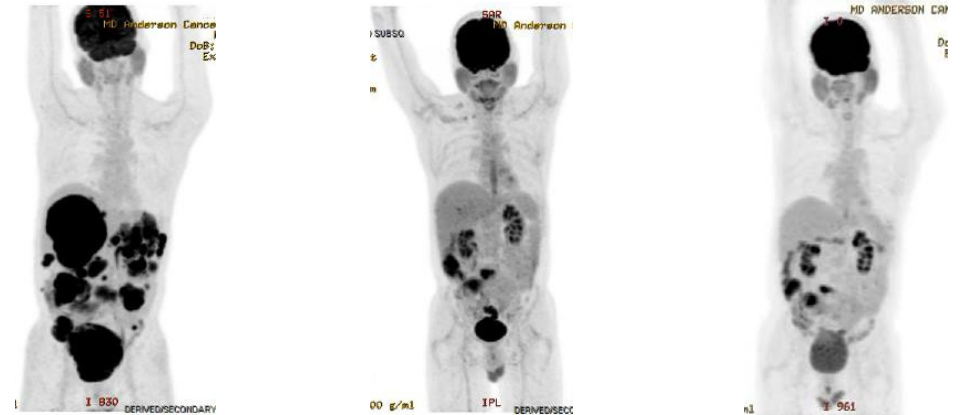
Study cycle 3
day 1

Study cycle 13
day 1

Patient #2: ETV6-NTRK3 Fusion GIST

- ◆ 55 yo male with GIST progressed through imatinib, sunitinib, sorafenib, nilotinib, and regorafenib
- ◆ 150mg BID
- ◆ Confirmed partial response
- ◆ Currently on study in cycle 10

PET



Study
baseline

Study cycle 3
day 1

Study cycle 9
day 1

CT



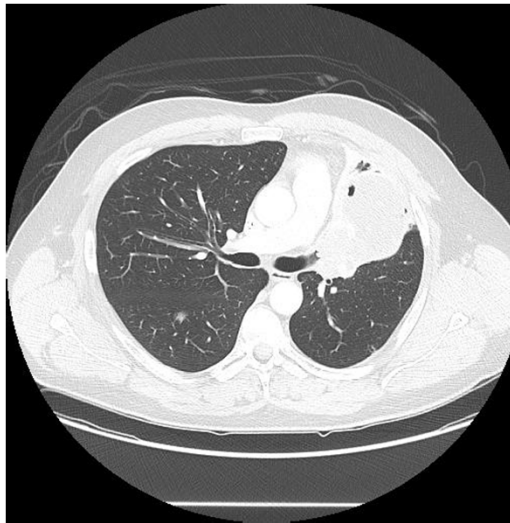
Study
baseline

Study cycle 5
day 1

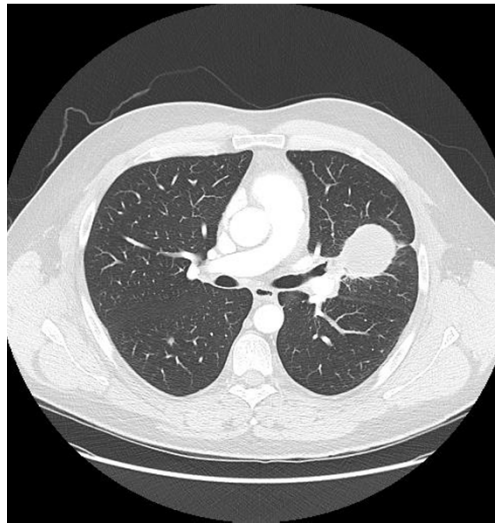
Study cycle 9
day 1

ETV6-NTRK3 Fusion Mammary Analogue Secretory Carcinoma of the Salivary Gland (MASC)

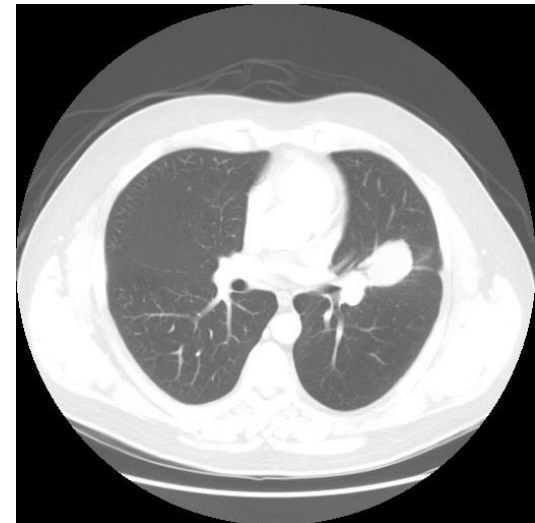
- ◆ 33 yo male progressed through docetaxel, carboplatin and 5FU
- ◆ 100mg BID
- ◆ Confirmed partial response
- ◆ Currently on study in cycle 10



Study baseline



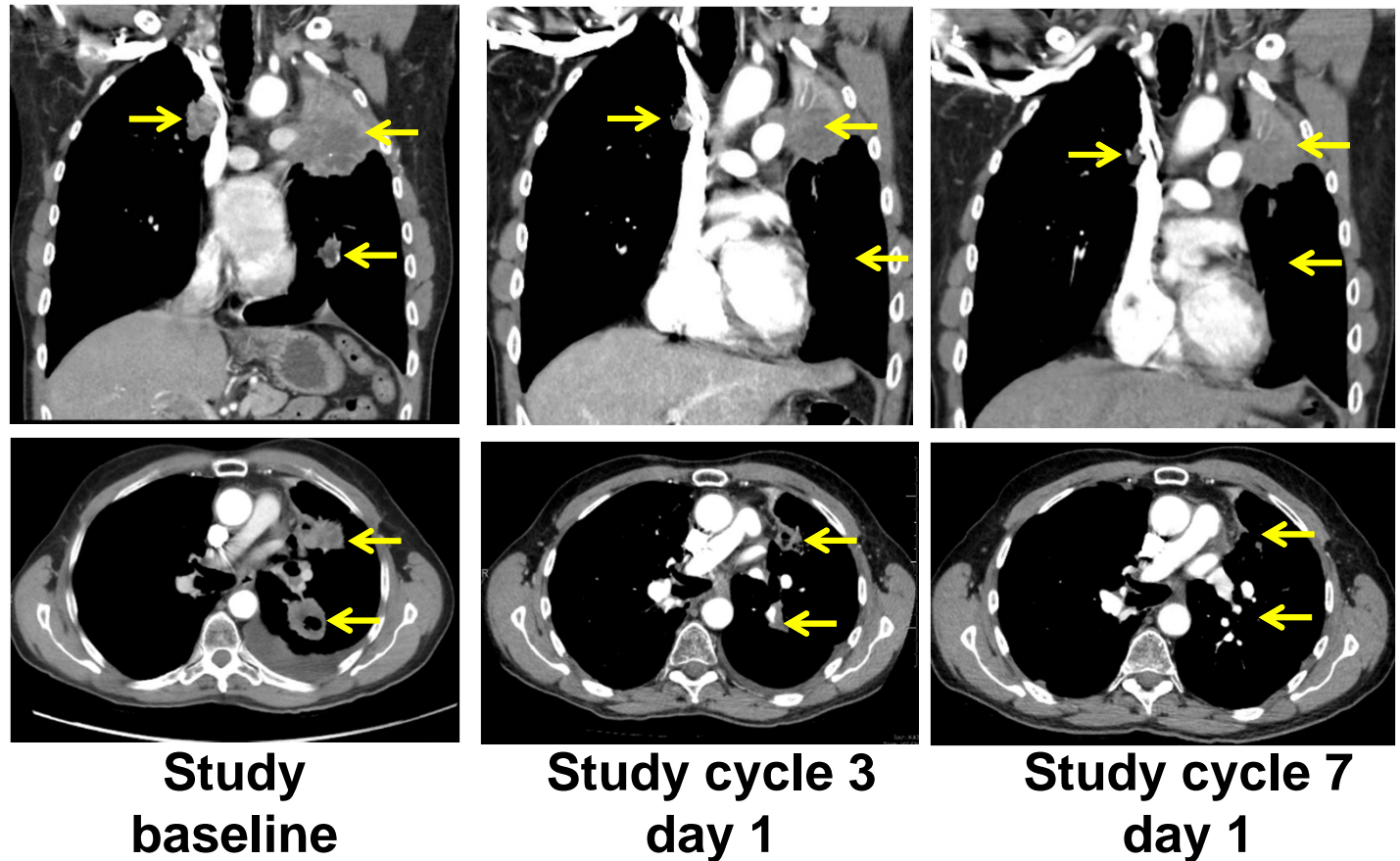
Study cycle 3 day 1



Study cycle 9 day 1

ETV6-NTRK3 Fusion Mammary Analogue Secretory Carcinoma of the Salivary Gland (MASC)

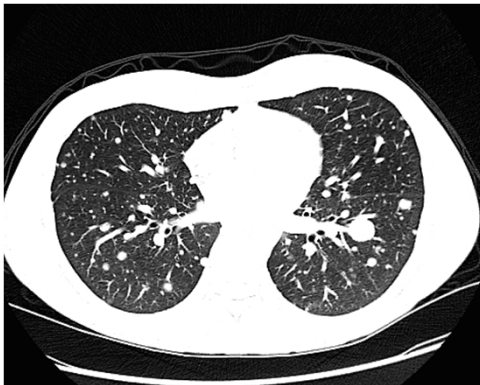
- ◆ 66 yo male progressed through radiotherapy, dasatinib, GDC-0941+ erlotinib, and ABBV-399
- ◆ 100mg QD*
- ◆ Confirmed partial response
- ◆ Currently on study in cycle 7



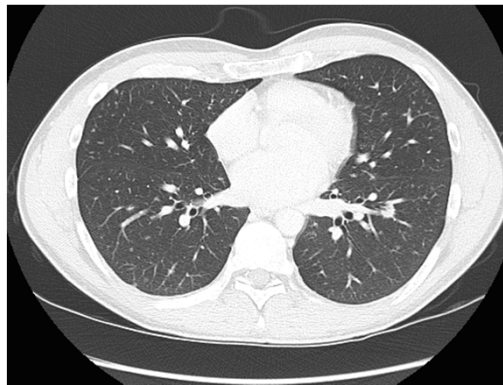
* Patient enrolled at 100mg BID and dose reduced to 100mg QD on C1D2 due to transient dizziness possibly related to drug.

Patient #5: ETV6-NTRK3 Fusion Papillary Thyroid Cancer

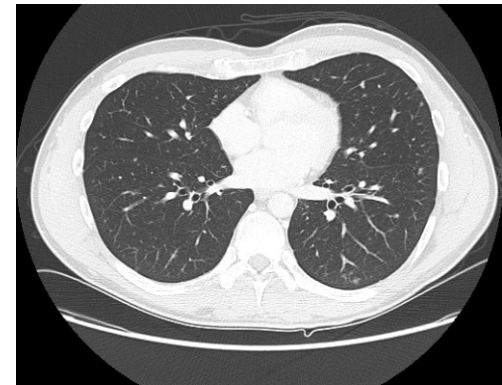
- ◆ 33 yo male progressed through RAI, pazopanib, trametinib
- ◆ 100mg BID
- ◆ Confirmed partial response
- ◆ Rapid improvement cervical lymphadenopathy
- ◆ Currently on study in cycle 7



Study
baseline



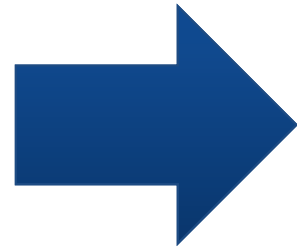
Study cycle 3
day 1



Study cycle 7
day 1

The “Perfect” Diagnostic Test

- ◆ Minimally invasive
- ◆ Comprehensive
- ◆ Sensitive/ few false negatives
- ◆ Specific/ few false positives
- ◆ Straightforward specimen handling
- ◆ Low cost but well reimbursed
- ◆ Easily interpreted
- ◆ Affects clinical decision making

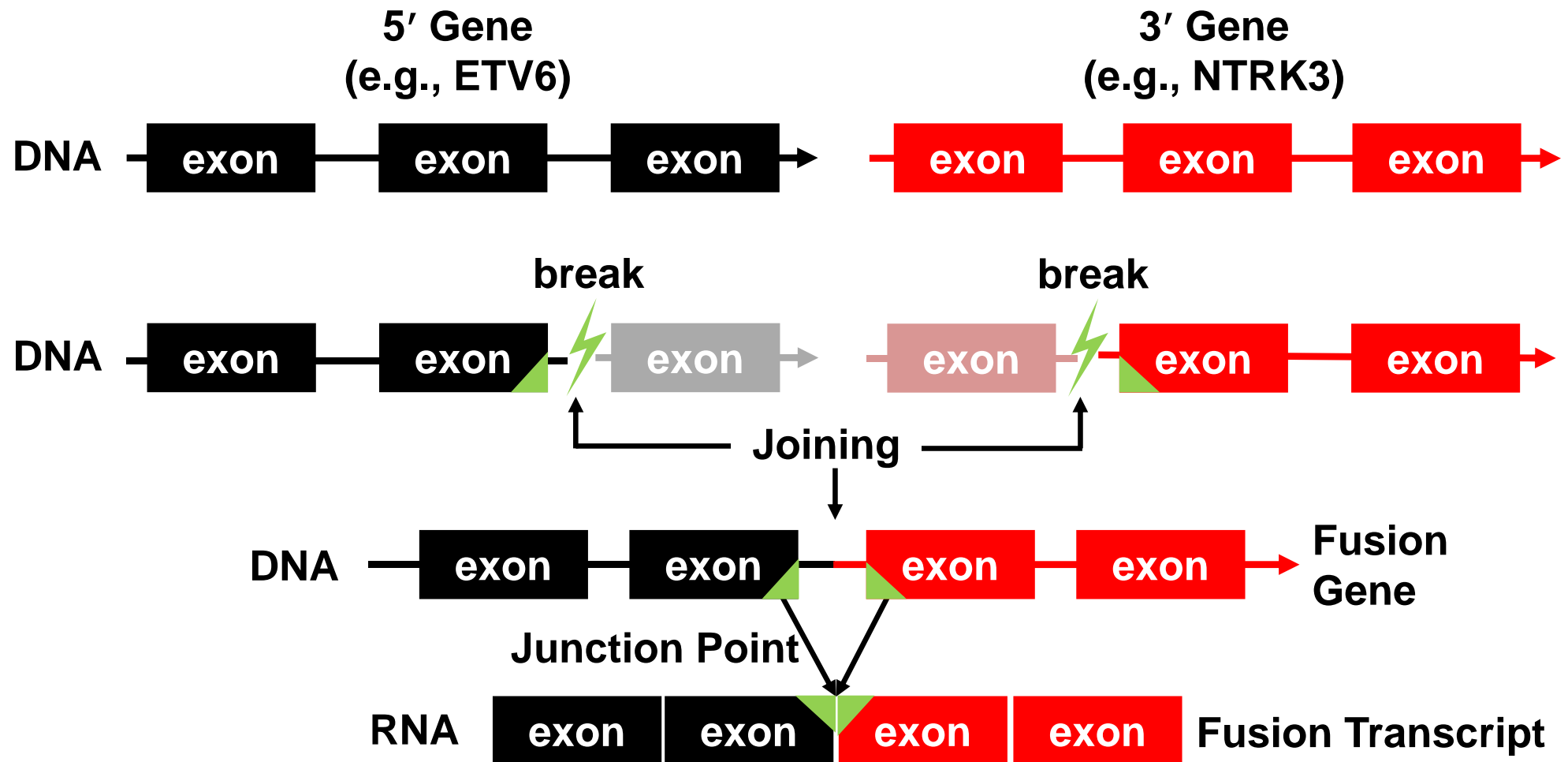


??

The Perfect NTRK Gene Fusion Test Does Not Exist

	Pros	Cons	Comment
NGS	Comprehensive, hypothesis free	Gene fusions require deliberate and challenging assay design	RNA > DNA for fusion sensitivity
RT-PCR	Proven, inexpensive	Too many TRK fusion partners	Only find fusions you know to look for
FISH (break apart)	Built for fusions	Single-plex, fusion partner not ID'd	3 NTRK genes = 6 probes/ colors
IHC	Proven, inexpensive	Single-plex, “positive” does not necessarily = fusion	ALK gene fusion success story

Gene Fusions: Intronic Events Living in an Exon-focused World



- ◆ Nihilism: “Introns aren’t worth the sequencing cost/ attention.”

Thesis: The True Burden of NTRK-driven Cancers Cannot Be Known Without Comprehensive Testing

Children and Adolescents		
Tumor Type	NTRK Fusion Reported	Other Oncogenic Drivers
ALL	✓	ABL, FLT3, JAK2, MLL, PDGFRB, RUNX1
AML	✓	FLT3,NPM1,NRAS, PDGFRA
Bone Tumor**		ATM, BRCA2, FLI1, DDIT3, TP53
Brain and CNS	✓	ACVR1, BRAF, EGFR, MET, PDGFRA
Hodgkin Lymphoma		JAK2, REL
Melanoma	✓	ALK, ROS1, BRAF, RET
Neuroblastoma*		ALK
NHL		ALK, BCL, CARD11,MYC, MYD88
Ovarian Germ Cell Tumors		KIT, RAC1, miRNAs
Retinoblastoma		RB1
Rhabdomyosarcoma	✓	PAX3/7
Other Sarcomas	✓	SSX1/2, CHOP, TEC
Testicular Germ Cell Tumors		KIT, KRAS
Thyroid Carcinoma	✓	BRAF, RET
Wilms Tumor		WT1, WTX

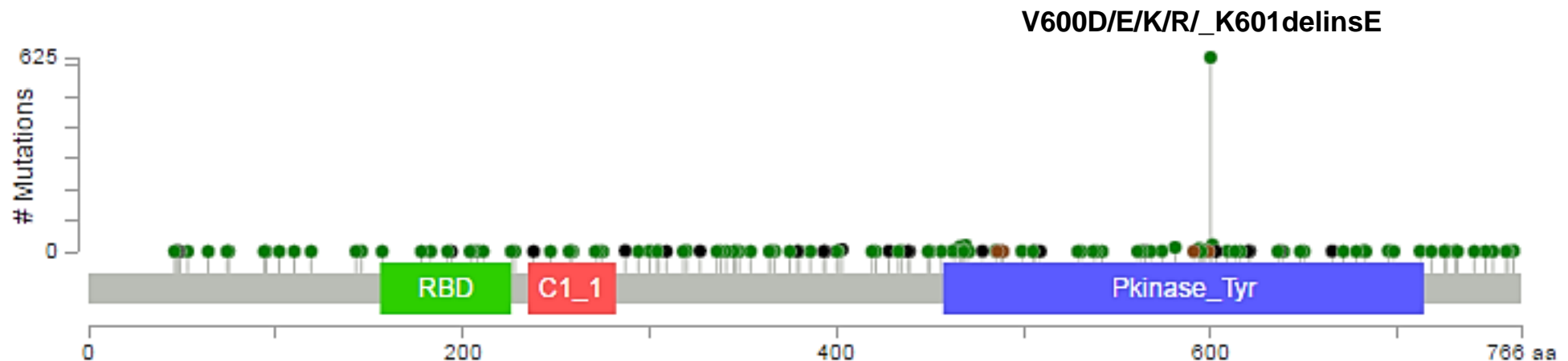
*Includes ganglioneuroblastoma; ** Includes osteosarcoma and Ewing sarcoma.

“Hotspot” Signal is a Tell For Actionability

◆ BRAF V600

BRAF:

BRAF_HUMAN



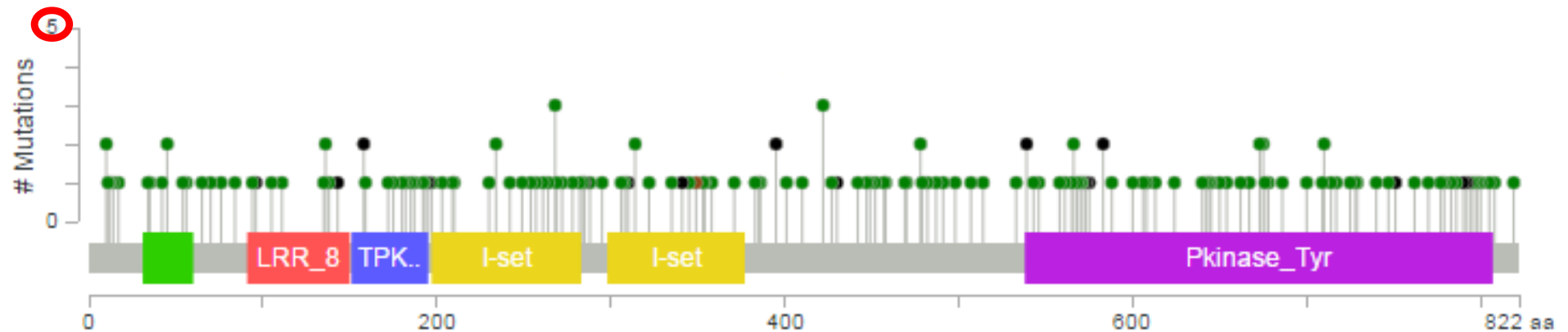
Source: cBioportal.

Lack of “Hotspot” Signal for NTRK

◆ e.g. NTRK2

NTRK2:

NTRK2_HUMAN



Source: cBioportal.

Other Variables Indicative of Driver Point Mutation Biology

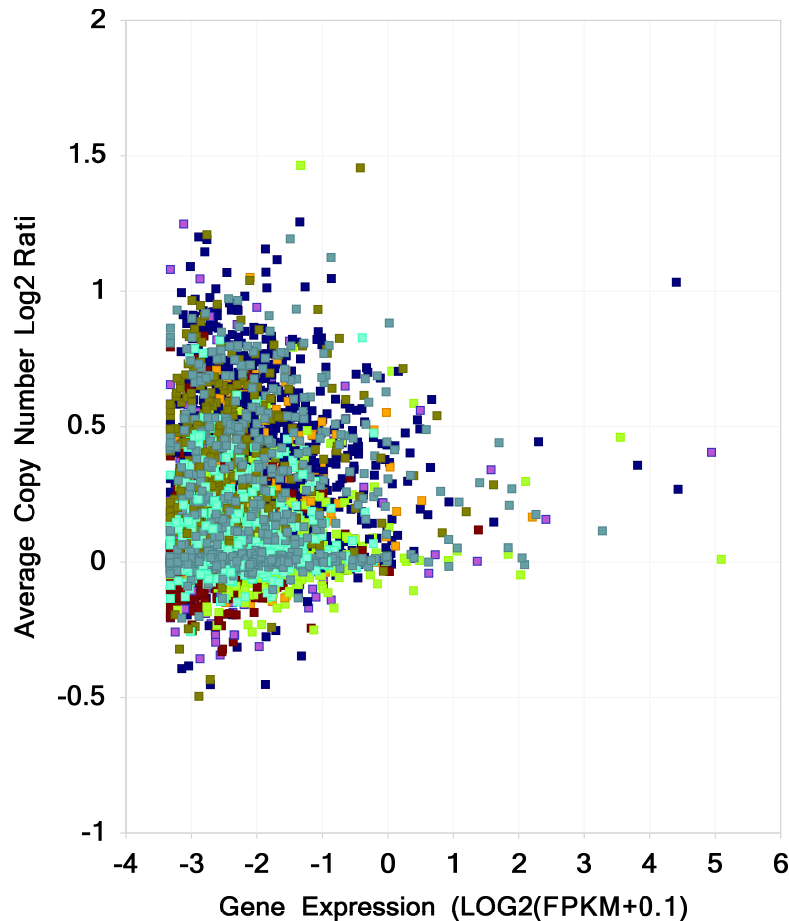
- ◆ **Non-synonymous**
- ◆ **Expressed**
- ◆ **Occurs in kinase domain**
- ◆ **Occurs in the absence of other known oncogenic drivers**

Loxo Oncology ASCO 2015 Poster

- ◆ **Identification of Tropomyosin Kinase Receptor (TRK) Point Mutations in Cancer**
- ◆ **Nisha Nanda, Tim Fennell, Barb Brandhuber, Brian B. Tuch, Jennifer A. Low**
- ◆ **May 2015**
- ◆ **Methods**
 - **Studied 1,823 distinct mutations, including public domain data and private databases**
- ◆ **Conclusions**
 - **No “hotspot” point mutations**
 - **Most reported NTRK mutations have no detectable expression**
 - **Only a small minority worth of further study**

NTRK Amplification and Expression are Uncorrelated, in Contrast to HER2

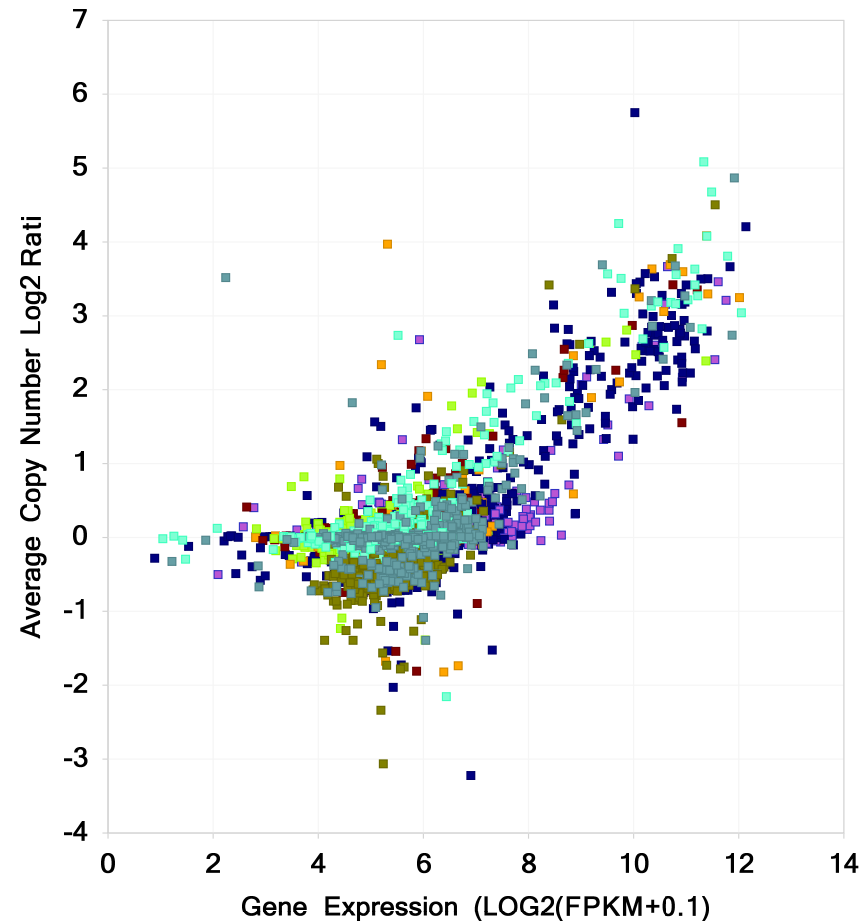
NTRK1



Color by Disease

- Bladder Urothelial Carcinoma
- Breast invasive carcinoma
- Cervical squamous cell carcinoma and endocervical adenocarcinoma
- Colon adenocarcinoma

HER2



- Head and Neck squamous cell carcinoma
- Ovarian serous cystadenocarcinoma
- Stomach adenocarcinoma
- Uterine Corpus Endometrial Carcinoma

Summary of Preclinical Pharmacology/ Toxicology

◆ Rat toxicology

- Single dose with 14-day recovery
- 7-day dose range finding (DRF) with no recovery
- 28-day DRF with no recovery
- 42-day DRF with no recovery
- 28-day DRF with 28-day recovery

◆ Monkey toxicology

- 7-day DRF with no recovery
- 14-day DRF with no recovery
- 14-day DRF with no recovery
- 28-day DRF with 28-day recovery

◆ Safety Pharmacology

- In vitro hERG
- In vivo cardiovascular assessment - telemetry-instrumented conscious rat and monkey
- 48-day mouse neurobehavioral study (rotorod)
- 42-day rat neurobehavioral study (rotorod)
- Rat Irwin test
- Rat respiratory function study
- Rat gastrointestinal motility study
- Rat gastric secretion study

LOXO-101 Preclinical Safety

- ◆ **Completed 28-day GLP studies: equivalent to human age 12**
- ◆ **4Q16: plan additional toxicology in 7-day-old rat, dosed to 56-day-old: equivalent to human neonate to young adult**
 - **Bone length**
 - **Histopathology**
 - **Reproductive endpoints/ mating trial**
 - **Behavioral**

Recent FDA Publication on Juvenile Animal Studies

An FDA oncology view of juvenile animal studies in support of initial pediatric trials for anticancer drugs



John K. Leighton*, Haleh Saber, Gregory Reaman, Richard Pazdur

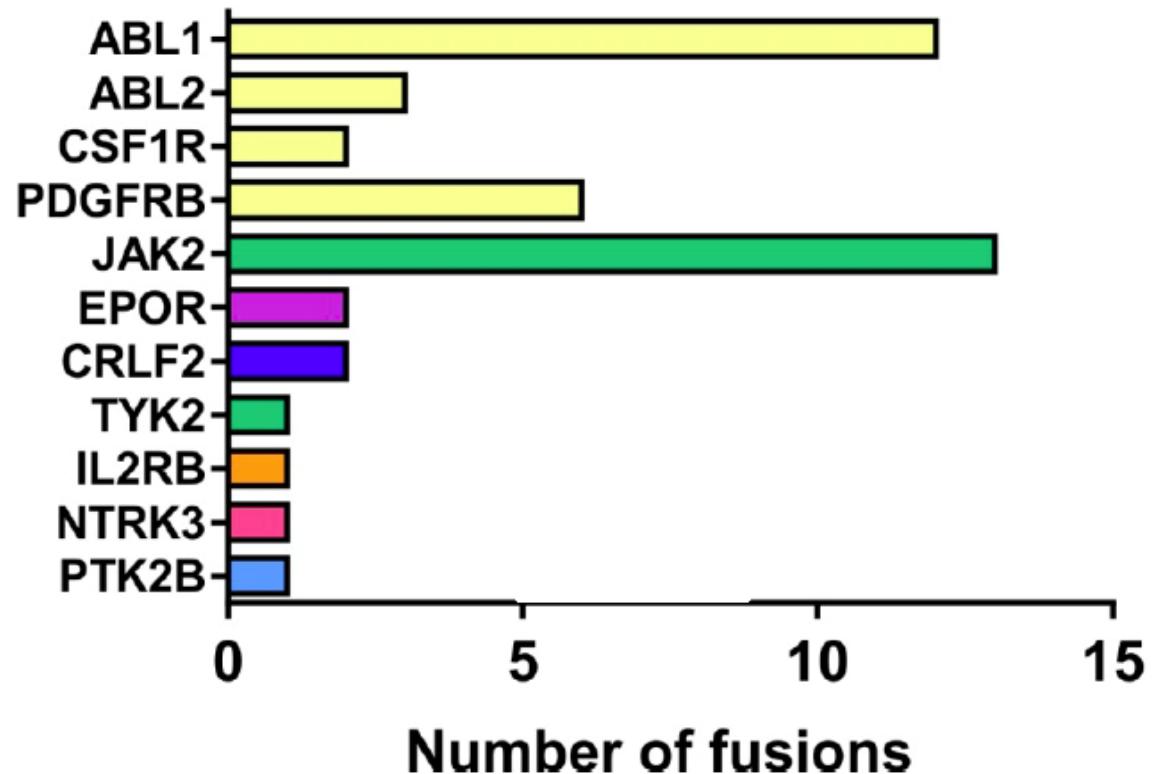
US Food and Drug Administration, Center for Drug Evaluation and Research, Office of Hematology and Oncology Products, 10903 New Hampshire Ave, Silver Spring, MD 20903, United States

Regulatory Toxicology and Pharmacology 79 (2016) 142–143

- ◆ ICH S9 states that “[s]tudies in juvenile animals are not usually conducted in order to support inclusion of pediatric populations for the treatment of cancer”
- ◆ FDA OHOP analysis
 - Juvenile animal studies have not provided useful information, consistent with ICH S9
 - Studies did not affect first in pediatric trials
- ◆ Longitudinal follow up required to assess emergence of aberrant development
- ◆ Generally short life expectancy complicates analysis
- ◆ Developmental toxicities are best assessed after a drug has demonstrated sufficient clinical activity

Philadelphia Chromosome-like Childhood Acute Lymphoblastic Leukemia (Ph-like ALL)

- ◆ *BCR-ABL*-negative with similar gene expression pattern and poor outcome
- ◆ Comprehensive genomic profiling of 152 patients with Ph-like ALL
 - 44 different rearrangements
 - 11 tyrosine kinase, cytokine or cytokine receptor genes
 - 91% of patients possess kinase-activating mutation
 - One patient with *ETV6-NTRK3* fusion



Roberts, *NEJM* 2014 371: 1005-15.

Cui, *J Med Chem* 2011 54:6342-63.

Courtesy of Kathryn Roberts, ASH 2014Mullighan lab, St Jude.

Adult Phase 1 Interim Safety (Regardless of Attribution)

DOSE	100 MG BID (N=24)		TOTAL (N=43)	
Adverse Events (AEs)*	Gr 3/4 n (%)	All Gr n (%)	Gr 3/4 n (%)	All Gr n (%)
Fatigue	0	5 (21)	2 (5)	14 (33)
Constipation	0	3 (13)	1 (2)	10 (23)
Dizziness	0	6 (25)	0	10 (23)
Anemia	1 (4)	4 (17)	3 (7)	8 (19)
Increased AST	1 (4)	5 (21)	4 (9)	8 (19)
Cough	0	4 (17)	0	8 (19)
Diarrhea	0	4 (17)	0	8 (19)
Increased ALP	0	5 (21)	1 (2)	7 (16)
Dyspnea	1 (4)	3 (13)	1 (2)	7 (16)
Nausea	0	4 (17)	0	7 (16)
Abdominal pain	0	3 (13)	1 (2)	6 (14)
Increased ALT	1 (4)	4 (17)	2 (5)	6 (14)
Anxiety	0	2 (8)	0	5 (12)
Hypertension	0	4 (17)	1 (2)	5 (12)
Peripheral edema	0	2 (8)	0	5 (12)
Pyrexia	0	2 (8)	0	5 (12)
Vomiting	0	2 (8)	0	5 (12)
Hyperkalemia	1 (4)	1 (4)	2 (5)	3 (7)
Delirium	1 (4)	1 (4)	2 (5)	2 (5)
Pleural effusion	1 (4)	1 (4)	2 (5)	2 (5)
Syncope	0	0	2 (5)	2 (5)

*Treatment-emergent adverse events (reported by > 10% of total subjects) or any Grade 3-4 events that occurred in at least 2 patients.

Pediatric Gliomas

- ◆ **Significant unmet medical need in Diffuse Intrapontine Glioma and High Grade Glioma**
 - Median OS of 12-15 months; 20% 2-year survival
 - No treatment to date has altered natural history of disease
- ◆ ***ACVR1*, *TP53* and *ATRX* genes are frequently mutated**
- ◆ ***NTRK1*, *NTRK2*, and *NTRK3* identified in up to 40% of samples in patients < 3 years of age**
- ◆ **Low grade gliomas may have 2% of tumors harboring an *NTRK* fusion**