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 IC\textsubscript{50})

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

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

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

**Fusion Lines**
- KM12 (*TPM3-NTRK1*; colon cancer)
- CUTO3.29 (*MPRI-P-NTRK1*)
- MO91 (*ETV6-NTRK3*)

**Non-Fusion Lines**
- H1650
- H3122
- HCC78
- A549
- H1299
- SW837
- HT29
- HCT116
- HCT15

**In Vivo:** Tumor Regressions in TRK Fusion Xenografts

**Fusion Lines**
- KM12 (*TPM3-NTRK1*; colon cancer)
- CUTO3.29 (*MPRI-P-NTRK1*; lung cancer)
- MO91 (*ETV6-NTRK3*; AML)

**Non-Fusion Lines**
- Vehicle Control
- 60 mg/kg/day
- 200 mg/kg/day

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 ($\geq 12$ 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 Cmax (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.

Data cutoff March 25, 2016.
Case Study: LMNA-NTRK1 Fusion Soft Tissue Sarcoma

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


Data cutoff March 25, 2016.
LOXO-101 Adult Phase 1 Exposures

- 100 mg BID (n=13), (Plasma free)
- 100 mg BID (Estimated CNS free)

Protein binding ~70%
$t_{1/2}$ ~2 h

Data cutoff March 25, 2016.
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 Gliomas
- 4% of DIPG
- 40% (4/10) HGG in infants <3

Papillary thyroid cancer
- 7 of 28 younger patients (25%) TRK fusion positive

Secretory breast carcinoma
- >90% of tumors have ETV6-NTRK3 fusion

Infantile Fibrosarcoma
- >85% of tumors have ETV6-NTRK3 fusion

Congenital Mesoblastic Nephroma
- 100% of cellular subtype exhibit ETV6-NTRK3

Sarcoma
- Myopericytic/haemangiopericytic morphology indicative of TRK fusion

References:
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

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 (TrkAlIII) 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

Illustrative Expansion Cohorts

- IFS
- Other NTRK fusion cancers
- Non-fusion TRK genetic alteration cancers
- Neuroblastoma

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

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

<table>
<thead>
<tr>
<th>Patient's Age</th>
<th>6 mo-1 yr</th>
<th>1-2 yr</th>
<th>2-6 yr</th>
<th>6-12 yr</th>
<th>12-18 yr</th>
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</thead>
<tbody>
<tr>
<td>Target dose (mg/m²):</td>
<td>13.9</td>
<td>23.5</td>
<td>39.4</td>
<td>72.8</td>
<td>125</td>
</tr>
<tr>
<td>Patient's BSA (m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25 to 0.35</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
<td>1.1</td>
<td>1.9</td>
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<tr>
<td>0.35 to 0.45</td>
<td>0.3</td>
<td>0.5</td>
<td>0.8</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>0.45 to 0.55</td>
<td>0.3</td>
<td>0.6</td>
<td>1.0</td>
<td>1.8</td>
<td>3.1</td>
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<tr>
<td>0.55 to 0.65</td>
<td>0.4</td>
<td>0.7</td>
<td>1.2</td>
<td>2.2</td>
<td>3.7</td>
</tr>
<tr>
<td>0.65 to 0.75</td>
<td>0.5</td>
<td>0.8</td>
<td>1.4</td>
<td>2.5</td>
<td>4.4</td>
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<tr>
<td>0.75 to 0.9</td>
<td>0.6</td>
<td>0.9</td>
<td>1.6</td>
<td>2.9</td>
<td>5.0</td>
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<tr>
<td>0.9 to 1.1</td>
<td>0.7</td>
<td>1.2</td>
<td>2.0</td>
<td>3.6</td>
<td>5.0</td>
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<tr>
<td>1.1 to 1.3</td>
<td>0.8</td>
<td>1.4</td>
<td>2.4</td>
<td>4.4</td>
<td>5.0</td>
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<tr>
<td>1.3 to 1.5</td>
<td>1.0</td>
<td>1.6</td>
<td>2.8</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>1.5 to 1.7</td>
<td>1.1</td>
<td>1.9</td>
<td>3.2</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>1.7 to 1.9</td>
<td>1.2</td>
<td>2.1</td>
<td>3.5</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>1.9 to 2</td>
<td>1.4</td>
<td>2.3</td>
<td>3.9</td>
<td>5.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>
Linear PK profile following oral administration shows high plasma exposure and no accumulation.

Slow off-rate; T1/2 = 160 min

The horizontal line representing TRKA IC\textsubscript{90} refers to the total plasma concentration of LOXO-101 that is associated with an unbound concentration of LOXO-101 that is equal to its IC\textsubscript{90} for inhibition of NGF-stimulated activity in a cellular assay. The IC\textsubscript{90} 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)

<table>
<thead>
<tr>
<th>Neurologic Symptom</th>
<th>Specify</th>
<th>Response</th>
<th>CTCAE Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive disturbance</td>
<td>□ Not Done □ Not Present □ Present</td>
<td>□ Grade 1 □ Grade 2 □ Grade 3 □ Grade 4</td>
<td></td>
</tr>
<tr>
<td>Concentration impairment</td>
<td>□ Not Done □ Not Present □ Present</td>
<td>□ Grade 1 □ Grade 2 □ Grade 3 □ Grade 4</td>
<td></td>
</tr>
<tr>
<td>Dizziness (lightheadedness, spinning sensation)</td>
<td>□ Not Done □ Not Present □ Present</td>
<td>□ Grade 1 □ Grade 2 □ Grade 3 □ Grade 4</td>
<td></td>
</tr>
<tr>
<td>Ataxia (lack of coordination of muscle movements)</td>
<td>□ Not Done □ Not Present □ Present</td>
<td>□ Grade 1 □ Grade 2 □ Grade 3 □ Grade 4</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal disorder (involuntary muscle movements)</td>
<td>□ Not Done □ Not Present □ Present</td>
<td>□ Grade 1 □ Grade 2 □ Grade 3 □ Grade 4</td>
<td></td>
</tr>
<tr>
<td>Lethargy</td>
<td>□ Not Done □ Not Present □ Present</td>
<td>□ Grade 1 □ Grade 2 □ Grade 3 □ Grade 4</td>
<td></td>
</tr>
<tr>
<td>Memory impairment</td>
<td>□ Not Done □ Not Present □ Present</td>
<td>□ Grade 1 □ Grade 2 □ Grade 3 □ Grade 4</td>
<td></td>
</tr>
<tr>
<td>Neuralgia (pain around nerve or group of nerves)</td>
<td>□ Not Done □ Not Present □ Present</td>
<td>□ Grade 1 □ Grade 2 □ Grade 3 □ Grade 4</td>
<td></td>
</tr>
<tr>
<td>Paresthesia (loss of DTR)</td>
<td>□ Not Done □ Not Present □ Present</td>
<td>□ Grade 1 □ Grade 2 □ Grade 3 □ Grade 4</td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy (tingling, numbness, etc.)</td>
<td>□ Not Done □ Not Present □ Present</td>
<td>□ Grade 1 □ Grade 2 □ Grade 3 □ Grade 4</td>
<td></td>
</tr>
<tr>
<td>Somnolence (Sleepiness, drowsiness)</td>
<td>□ Not Done □ Not Present □ Present</td>
<td>□ Grade 1 □ Grade 2 □ Grade 3 □ Grade 4</td>
<td></td>
</tr>
</tbody>
</table>
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. Patient 1: NTRK1 G595R (solvent front) + Y667C
  2. Patient 2: NTRK3 G623R (solvent front)
- Paralogs of ALK-G1202R and ROS1-G2032R

1. Russo et al. Cancer Discovery. Published OnlineFirst on November 6, 2015; DOI: 10.1158/2159-8290.
ASCOC 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
Patient #3: 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
Patient #4:
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

<table>
<thead>
<tr>
<th></th>
<th>Pros</th>
<th>Cons</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGS</td>
<td>Comprehensive, hypothesis free</td>
<td>Gene fusions require deliberate and</td>
<td>RNA &gt; DNA for fusion sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>challenging assay design</td>
<td></td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Proven, inexpensive</td>
<td>Too many TRK fusion partners</td>
<td>Only find fusions you know to look for</td>
</tr>
<tr>
<td>FISH (break apart)</td>
<td>Built for fusions</td>
<td>Single-plex, fusion partner not ID’d</td>
<td>3 NTRK genes = 6 probes/ colors</td>
</tr>
<tr>
<td>IHC</td>
<td>Proven, inexpensive</td>
<td>Single-plex, “positive” does not necessarily = fusion</td>
<td>ALK gene fusion success story</td>
</tr>
</tbody>
</table>
Gene Fusions: Intrinsic Events Living in an Exon-focused World

- 5’ Gene (e.g., ETV6)
  - DNA: exon → exon → exon
- 3’ Gene (e.g., NTRK3)
  - DNA: exon → exon → exon

- Fusion Gene
- Fusion Transcript

- Junction Point

- Nihilism: “Introns aren’t worth the sequencing cost/attention.”
# Thesis: The True Burden of NTRK-driven Cancers Cannot Be Known Without Comprehensive Testing

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

*Includes ganglioneurblastoma; ** Includes osteosarcoma and Ewing sarcoma.
“Hotspot” Signal is a Tell For Actionability

◆ BRAF V600

Source: cBioportal.
Lack of “Hotspot” Signal for NTRK

- e.g. NTRK2

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
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

**Color by Disease**
- Purple: Bladder Urothelial Carcinoma
- Blue: Breast invasive carcinoma
- Orange: Cervical squamous cell carcinoma and endocervical adenocarcinoma
- Red: Colon adenocarcinoma
- Green: Head and Neck squamous cell carcinoma
- Brown: Ovarian serous cystadenocarcinoma
- Cyan: Stomach adenocarcinoma
- Teal: 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

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

*Courtesy of Kathryn Roberts, ASH 2014 Mullighan lab, St Jude.*
## Adult Phase 1 Interim Safety (Regardless of Attribution)

<table>
<thead>
<tr>
<th>Adverse Events (AEs)*</th>
<th>100 MG BID (N=24)</th>
<th>TOTAL (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr 3/4 n (%)</td>
<td>All Gr n (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (4)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Increased AST</td>
<td>1 (4)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>1 (4)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (4)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>1 (4)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>4 (17)</td>
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<tr>
<td>Peripheral edema</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>2 (8)</td>
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<tr>
<td>Vomiting</td>
<td>0</td>
<td>2 (8)</td>
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<tr>
<td>Hyperkalemia</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Delirium</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*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**, an **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

Taylor *Cancer Res* 2014; Waren KE *Front Oncol* 2012; Wu *Nat Genet* 2014; Jones *Nat Genet* 2012.