UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 8-K
CURRENT REPORT PURSUANT TO
SECTION 13 OR 15(d) OF THE
SECURITIES EXCHANGE ACT OF 1934

Date of Report: June 3, 2017
(Date of earliest event reported)

LOXO ONCOLOGY, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware
(State or Other Jurisdiction of Incorporation)

001-36562
(Commission File Number)

46-2996673
(IRS Employer Identification No.)

281 Tresser Blvd., 9th Floor
Stamford, CT
(Registrant’s Telephone Number, Including Area Code)

06901
(Zip Code)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒
On June 3, 2017, Loxo Oncology, Inc. (“Loxo Oncology”) issued two press releases. One press release announced updated clinical data for Loxo Oncology’s ongoing larotrectinib trials as reported by study investigators at the 2017 American Society of Clinical Oncology Annual Meeting (“ASCO”) in Chicago. The second press release announced a clinical proof of concept publication for next-generation TRK inhibitor LOXO-195. A copy of the press releases are furnished as Exhibit 99.1 and 99.2, respectively, to this report and incorporated herein by reference. A copy of the slides presented by the study investigators at ASCO are furnished as Exhibit 99.3 and Exhibit 99.4 to this report and incorporated herein by reference.

On June 4, 2017, Loxo Oncology held an investor conference call. A copy of the slides presented during the investor conference call are furnished as Exhibit 99.5 to this report and incorporated herein by reference.

The information furnished with this report, including Exhibit 99.1, Exhibit 99.2, Exhibit 99.3, Exhibit 99.4 and Exhibit 99.5, shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (“Exchange Act”), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference into any other filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

**Item 9.01 Financial Statements and Exhibits**

(d) Exhibits.

<table>
<thead>
<tr>
<th>Exhibit Number</th>
<th>Description of Exhibit</th>
</tr>
</thead>
<tbody>
<tr>
<td>99.3</td>
<td>Slides presented by study investigators on June 3, 2017.</td>
</tr>
<tr>
<td>99.4</td>
<td>Slides presented by study investigators on June 5, 2017.</td>
</tr>
<tr>
<td>99.5</td>
<td>Slides presented by Loxo Oncology on June 4, 2017.</td>
</tr>
</tbody>
</table>
Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Loxo Oncology, Inc.

Date: June 5, 2017

By: /s/ Jennifer Burstein

Name: Jennifer Burstein

Title: Vice President of Finance and principal financial officer
STAMFORD, Conn., June 3, 2017 — Loxo Oncology, Inc. (Nasdaq: LOXO), a biopharmaceutical company innovating the development of highly selective medicines for patients with genetically defined cancers, today announced interim clinical data from all three ongoing larotrectinib (LOXO-101) clinical trials in patients whose tumors harbor tropomyosin receptor kinase (TRK) fusions. These data, demonstrating a 76 percent confirmed objective response rate (ORR) across tumor types, are being presented today at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago (abstract LBA2501). The larotrectinib pediatric data, included in this presentation, are also being presented in a separate oral presentation on Monday, June 5th (abstract 10510).

“Larotrectinib delivers consistent and durable responses in TRK fusion patients across all ages, regardless of tumor context, and does so with few side effects,” said David Hyman, M.D., the NAVIGATE global principal investigator and chief of the early drug development service at Memorial Sloan Kettering Cancer Center who will present the data at ASCO. “In this way, the larotrectinib-TRK fusion story fulfills the promise of precision medicine, where tumor genetics rather than tumor site of origin define the treatment approach. It is now incumbent upon the clinical oncology and pathology communities to examine our testing paradigms, so that TRK fusions and other actionable biomarkers become part of the...”
standard patient workup."

The ASCO presentation includes adult and pediatric patients with RECIST-evaluable TRK fusion cancers enrolled across all three larotrectinib clinical trials, and employs an April 14, 2017 data cut-off. These patients will serve as the basis for the larotrectinib New Drug Application (NDA), which the company expects to submit in late 2017 or early 2018 for evaluation by the U.S. Food and Drug Administration (FDA). The primary analysis for the NDA will rely upon central, independent radiology review, which will be performed in the second half of 2017. The company plans to announce these data, which will also include additional patient follow-up, before the end of 2017.

Larotrectinib received Breakthrough Therapy Designation from the FDA in July 2016, “for the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments.”

“The Loxo Oncology team is proud to have contributed to these important data presentations at ASCO,” said Josh Bilenker, M.D., chief executive officer of Loxo Oncology. “We are grateful to the patients, families, and clinical trial teams who help push the boundaries of available care through their participation in clinical trials. We hope that larotrectinib is the first of many new medicines we develop together.”

### Key Data Presented at ASCO

The primary efficacy outcome measure for the analysis presented at ASCO is objective response rate (ORR) as measured by RECIST v 1.1. Key secondary endpoints include duration of response (DOR), progression-free survival (PFS) and safety. The data presented at ASCO, summarized below, are based on response assessments as performed by each respective clinical trial site (local, investigator-assessed radiology). A separate response assessment performed by independent radiologists, not yet conducted, will be required to support global regulatory filings.

Consistent with written FDA correspondence, TRK fusion patients enrolled in Loxo Oncology’s Phase 1 adult trial, Phase 2 trial (NAVIGATE), and Phase 1/2 pediatric trial (SCOUT) contributed to the primary efficacy analysis. The data presented are based on the intent to treat (ITT) principle, using the first 55 TRK fusion patients with RECIST-evaluable disease enrolled to the three clinical trials, regardless of prior therapy or tumor tissue diagnostic method.

Forty-three adult and 12 pediatric patients were enrolled, identified by 15 different lab tests. TRK fusion patients carried primary diagnoses of appendiceal cancer, breast cancer, cholangiocarcinoma, colorectal cancer, gastrointestinal stromal tumor (GIST), infantile fibrosarcoma, lung cancer, mammary analogue secretory carcinoma of the salivary gland, melanoma, pancreatic cancer, thyroid cancer, and various sarcomas. One patient had central nervous system (CNS) metastases at study entry.

<table>
<thead>
<tr>
<th>Objective Response Rate</th>
<th>Enrolled Patients with Confirmatory Response Data Available (n=50)</th>
<th>All Enrolled Patients (n=55)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective Response Rate (ORR = PR+CR)</strong></td>
<td>76% <em>(95% CI: 62% — 87%)</em></td>
<td>78% <em>(95% CI: 65% — 88%)</em></td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>64%</td>
<td>65%*</td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>12%</td>
<td>13%*</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>12%</td>
<td>11%</td>
</tr>
</tbody>
</table>

* Includes unconfirmed responses with confirmatory scans pending (4 PR, 1 CR). All patients with unconfirmed responses remain in response and ongoing on study.
As shown in the above table, the confirmed ORR is 76 percent in 50 patients for whom follow-up was sufficiently long to include a confirmatory scan. The ORR is 78 percent when an additional 5 patients, recently enrolled with unconfirmed PR (n=4) and CR (n=1), are included. ORR was generally consistent across tumor types, TRK gene fusions, and various diagnostic tests. In the pediatric setting, lorotrectinib showed promising activity in the pre-surgical management of patients with infantile fibrosarcoma, with 3 patients treated to best response, which allowed for subsequent referral to surgery with curative intent.

Median DOR and PFS have not been reached. Ninety-three percent of all responding patients either remain on drug or received surgery with curative intent. Seventy-five percent of all patients enrolled either remain on drug or received surgery with curative intent.

The safety data presented at ASCO encompass the entire lorotrectinib safety database in cancer patients (n=125) intended to support an NDA. The most common treatment-emergent adverse events, regardless of relationship to lorotrectinib, included fatigue (15% Grade 1, 18% Grade 2, 5% Grade 3), dizziness (22% Grade 1, 4% Grade 2, 2% Grade 3), nausea (20% Grade 1, 5% Grade 2, 2% Grade 3), and anemia (8% Grade 1, 9% Grade 2, 9% Grade 3). Seven (13%) of patients required a dose reduction due to an adverse event. Of note, all patients requiring dose reduction experienced tumor regression (1 CR, 5 PR, 1 SD), which has continued on the reduced dose. Nearly all of the dose reductions were due to infrequent neurocognitive adverse events, likely a result of off-target TRK inhibition in the CNS. No patients discontinued lorotrectinib due to an adverse event.

Six patients responded to lorotrectinib but subsequently progressed, a pattern referred to as “acquired resistance.” Progression biopsies from five of six patients indicate a consistent mechanism of acquired resistance, namely a solvent front mutation. A solvent front mutation is an amino acid substitution in a kinase that reduces the binding potency of a targeted drug. In the case of NTRK1 and NTRK3, these solvent front amino acid substitutions are denoted as G595R and G623R, respectively. The presence of an acquired resistance mutation in a primary activating oncogene suggests that the involved cancer cell remains dependent on the aberrant signaling pathway that had been successfully drugged previously. LOXO-195, Loxo Oncology’s next-generation selective TRK inhibitor, was designed to address solvent front and other acquired resistance mutations to potentially induce new responses in TRK fusion dependent cancers with acquired resistance mutations.

About the ASCO Presentations

These data are being presented in two oral presentations at ASCO.

- “The efficacy of lorotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers.” This includes the integrated database across the three lorotrectinib clinical trials and is being presented by Dr. David Hyman, Memorial Sloan Kettering Cancer Center, during the Session entitled, “Developmental Therapeutics — Clinical Pharmacology and Experimental Therapeutics,” from 1:15 — 4:15PM CT on Saturday, June, 3, 2017 (Abstract LBA2501).

- “A pediatric phase I study of lorotrectinib, a highly selective inhibitor of the tropomyosin receptor kinase (TRK) family.” This focuses specifically on the pediatric Phase 1 clinical trial data, included in the aforementioned data set, and is being presented by Dr. Theodore Laetsch, University of Texas Southwestern Medical Center, during the Session entitled, “Pediatric Oncology II,” from 8:00 — 11:00AM CT on Monday, June, 5, 2017 (Abstract 10510).

The presentations will be available online at http://www.loxooncology.com/asco at the time of their scheduled presentation at ASCO.

Conference Call and Webcast Information

Loxo Oncology will host a conference call and live webcast with slides and Q&A on Sunday, June 4, 2017 at 5:30 p.m. CT to discuss the lorotrectinib data. Loxo Oncology management will be joined by the
primary investigators of the larotrectinib clinical development program, Dr. David Hyman and Dr. Alex Drilon of Memorial Sloan Kettering Cancer Center, and Dr. Theodore Laetsch of University of Texas Southwestern Medical Center. To participate in the conference call, please dial (877) 930-8065 (domestic) or (253) 336-8041 (international) and refer to conference ID 14447513. A live webcast of the presentation will be available at http://ir.loxooncology.com/. A replay of the webcast will be available shortly after the conclusion of the call and archived on the company’s website for 90 days following the call.

About Larotrectinib (LOXO-101)

Larotrectinib is a potent, oral and selective investigational new drug in clinical development for the treatment of patients with cancers that harbor abnormalities involving the tropomyosin receptor kinases (TRKs). Growing research suggests that the NTRK genes, which encode for TRKs, can become abnormally fused to other genes, resulting in growth signals that can lead to cancer in many sites of the body. In an analysis of 53 RECIST-evaluable TRK fusion adult and pediatric patients, larotrectinib demonstrated a 76 percent confirmed objective response rate (ORR), across many different types of solid tumors. Larotrectinib has been granted Breakthrough Therapy Designation Rare Pediatric Disease Designation and Orphan Drug Designation by the U.S. FDA. For additional information about the larotrectinib clinical trials, please refer to www.clinicaltrials.gov. Interested patients and physicians can contact the Loxo Oncology Physician and Patient Clinical Trial Hotline at 1-855-NTRK-123 or visit www.loxooncologytrials.com.

About TRK Fusion Cancer

TRK fusions are chromosomal abnormalities that occur when one of the NTRK genes (NTRK1, NTRK2, NTRK3) becomes abnormally connected to another, unrelated gene (e.g. ETV6, LMNA, TPM3). This abnormality results in uncontrolled TRK signaling that can lead to cancer. TRK fusions occur rarely but broadly in various adult and pediatric solid tumors, including appendiceal cancer, breast cancer, cholangiocarcinoma, colorectal cancer, GIST, infantile fibrosarcoma, lung cancer, mammary analogue secretory carcinoma of the salivary gland, melanoma, pancreatic cancer, thyroid cancer, and various sarcomas. TRK fusions can be identified through various diagnostic tests, including targeted next-generation sequencing (NGS), immunohistochemistry (IHC), polymerase chain reaction (PCR), and fluorescent in situ hybridization (FISH). For more information, please visit www.TRKtesting.com.

About Loxo Oncology

Loxo Oncology is a biopharmaceutical company innovating the development of highly selective medicines for patients with genetically defined cancers. Our pipeline focuses on cancers that are uniquely dependent on single gene abnormalities, such that a single drug has the potential to treat the cancer with dramatic effect. We believe that the most selective, purpose-built medicines have the highest probability of maximally inhibiting the intended target, thereby delivering best-in-class disease control and safety. Our management team seeks out experienced industry partners, world-class scientific advisors and innovative clinical-regulatory approaches to deliver new cancer therapies to patients as quickly and efficiently as possible. For more information, please visit the company’s website at www.loxooncology.com.

Forward Looking Statements

This press release contains “forward-looking” statements within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. Forward-looking statements can be identified by words such as: “anticipate,” “intend,” “plan,” “goal,” “seek,” “believe,” “project,” “estimate,” “expect,” “strategy,” “future,” “likely,” “may,” “should,” “will” and similar references to future periods. These statements are subject to numerous risks and uncertainties that could cause actual results to differ materially from what we expect. Examples of forward-looking statements include, among others, statements we make regarding the timing and success of our clinical trials, the potential therapeutic benefits and economic value of our lead product candidate or other product candidates, and timing of
future filings. Further information on potential risk factors that could affect our business and its financial results are detailed in our most recent Quarterly Report on Form 10-Q, and other reports as filed from time to time with the Securities and Exchange Commission. We undertake no obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.

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Loxo Oncology Announces Clinical Proof of Concept Publication for Next-Generation TRK Inhibitor LOXO-195

STAMFORD, Conn., June 3, 2017 — Loxo Oncology, Inc. (Nasdaq: LOXO), a biopharmaceutical company innovating the development of highly selective medicines for patients with genetically defined cancers, today announced the online publication of a new research brief in Cancer Discovery outlining the preclinical rationale for LOXO-195 and clinical proof-of-concept data from the first two patients treated. LOXO-195 was developed to treat patients with TRK fusion cancers who become resistant while receiving another TRK inhibitor, such as Loxo Oncology’s larotrectinib.

“This publication highlights the potential for LOXO-195 to extend the period of durable disease control for patients with TRK fusion cancers,” said Josh Bilenker, M.D., chief executive officer of Loxo Oncology. “We believe that today’s ASCO presentation establishes larotrectinib as the clear first choice for patients with TRK fusion cancers. However, over time, patients will require new treatment options, since oncogene-addicted metastatic cancers ultimately evade targeted therapies. We have been relentless in the development of LOXO-195 so that it could be ready in time for the current larotrectinib clinical trial participants and future patients who depend upon us to realize the full potential of TRK inhibition in the management of advanced cancer.”

LOXO-195 was designed to address anticipated mechanisms of acquired resistance in cancers exposed to a prior TRK inhibitor, including “solvent front” mutations (e.g. NTRK1 G595R, NTRK3 G623R), which are not well-addressed by existing investigational agents. LOXO-195 will be developed as a sequential treatment, to follow larotrectinib or another TRK inhibitor, to extend the total time of benefit from TRK inhibition.

The Cancer Discovery research brief provides early but encouraging evidence that the sequential use of larotrectinib followed by LOXO-195 could extend the total duration of disease control for patients with TRK fusion cancers. An analogous paradigm has already been established for other oncogene-addicted tumors, such as those driven by androgen and estrogen signaling, EGFR mutations and ABL gene fusions. The brief describes the first two patients with TRK fusion cancers who responded to larotrectinib but later relapsed. An adult with colorectal cancer and a child with infantile fibrosarcoma were biopsied at the time of tumor progression and found to have a solvent front TRK mutation in the existing TRK fusion, which explained the diminished activity of larotrectinib. As no other treatment options exist to address TRK fusion solvent front mutations, Loxo Oncology, in collaboration with the U.S. FDA, enabled these patients to access LOXO-195 through emergency use Investigational New Drug applications (INDs). Both patients responded to LOXO-195, with minimal adverse events reported.

A formal LOXO-195 IND was recently cleared by the U.S. FDA, and a Phase 1/2 trial is opening globally.

About LOXO-195

LOXO-195 is a potent, oral and selective investigational new drug in clinical development for the treatment of patients with cancers that have acquired resistance to initial TRK therapy such as larotrectinib. Growing research suggests that the NTRK genes, which encode for TRKs, can become abnormally fused to other genes, resulting in growth signals that can lead to cancer in many sites of the body. Though drugs such as larotrectinib can induce durable responses in these patients, the cancer may eventually begin to grow again. This phenomenon is called “acquired resistance,” in that the cancer has acquired features conferring resistance to the initial therapy that was once effective. Emerging data in the field of TRK inhibition suggest that acquired resistance may emerge due to TRK kinase point mutations,
such as those in the solvent front domain, xDFG domain, or gatekeeper region. LOXO-195 was designed to address these new point mutations and induce a new response in the patient’s cancer. Interested patients and physicians can contact the Loxo Oncology Physician and Patient Clinical Trial Hotline at 1-855-NTRK-123 or email clinicaltrials@loxooncology.com.

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The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers

Hyman DM,¹ Laetsch TW,² Kummar S,³ DuBois SG,⁴ Farago AF,⁵ Pappo AS,⁶ Demetri GD,⁷ El-Deiry WS,⁸ Lassen UN,⁹ Dowlati A,¹⁰ Brose MS,¹¹ Boni V,¹² Turpin B,¹³ Nagasubramanian R,¹⁴ Cruickshank S,¹⁵ Cox MC,¹⁵ Ku NC,¹⁵ Hawkins DS,¹⁶ Hong DS,¹⁷ Drilon AE¹

¹Memorial Sloan Kettering Cancer Center, New York, NY; ²University of Texas Southwestern, Dallas, TX; ³Stanford University School of Medicine, Palo Alto, CA; ⁴Dana-Farber Cancer Institute/Boston Children’s Cancer and Blood Disorders Center, Boston, MA; ⁵Massachusetts General Hospital, Boston, MA; ⁶St. Jude Children’s Research Hospital, Memphis, TN; ⁷Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; ⁸Fox Chase Cancer Center, Philadelphia, PA; ⁹Hvidovre Hospital, Copenhagen, Denmark; ¹⁰UH Cleveland Medical Center, Cleveland, OH; ¹¹Department of Otorhinolaryngology: Head and Neck Surgery, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; ¹²START Madrid COCC, Hospital HM Universitario Sanchinarro, Madrid, Spain; ¹³Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; ¹⁴Nemours Children’s Hospital, Orlando, FL; ¹⁵Lava Oncology, Inc., San Francisco, CA; ¹⁶Seattle Children’s Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA; ¹⁷The University of Texas MD Anderson Cancer Center, Houston, TX.
Role of TRK in normal biology and cancer

Neurotrophin family of receptors

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

TRK fusions

- Ligand binding domain (LBD) replaced by 5' fusion partner
- Drives overexpression and ligand-independent activation

TRK uncommonly expressed in normal tissues or cancer
Fusion drives abnormally high expression and activation of TRK kinase domain
TRK fusions found in diverse cancer histologies

- Brain cancers (glioma, GBM, astrocytoma)
- Thyroid cancer
- Lung cancer
- Secretory breast cancer
- Pancreatic Cholangiocarcinoma
- GIST
- Colon Melanoma
- Sarcoma (multiple)

- Gliomas
- Thyroid cancer
- Infantile fibrosarcoma
- Congenital nephroma
- Spitz nevi
- Sarcoma (multiple)

Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually.
Detecting TRK fusions

- Several modalities:
  - DNA & RNA NGS, FISH, IHC
- Large NTRK introns (compared to ALK, ROS1, RET) make DNA-based detection challenging
- Loxo/Ventana developing Pan-TRK IHC companion diagnostic (CDx)
- NGS “universal” CDx tests under FDA review include TRK fusion detection*

*FoundationOne, Oncomine Universal Dx

More Info: www.TRKtesting.com
Larotrectinib

- Larotrectinib is the first and only selective pan-TRK inhibitor in clinical development
- Highly potent against TRKA, TRKB, TRKC
  - 5–11 nM IC$_{50}$ in cellular assays
- Highly selective
- Development timeline
  - March 2015: 1st TRK-fusion patient treated
  - July 2016: breakthrough therapy designation
  - February 2017: pivotal enrollment complete
Larotrectinib TRK fusion development program

**Adult phase I**
- Age ≥18 years
- Advanced solid tumors

**SCOUT: pediatric phase I/II**
- Age ≤21 years
- Advanced solid tumors

**navigate: adult/adolescent phase II ‘basket’ trial**
- Age ≥12 years
- Advanced solid tumors
- TRK fusion positive

N=8

n=12

n=35

N=55 TRK fusion patients

- TRK fusion status determined by local CLIA (or similarly accredited) laboratories
- Primary endpoint
  - Best objective response rate (ORR)
  - RECIST v1.1 per investigator assessment
- Secondary endpoints
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Safety
- Dosing
  - Single-agent larotrectinib, administered predominantly at 100 mg BID continuously
  - Treatment beyond progression permitted if patient continuing to benefit

Data cut-off: April 14, 2017
### Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=55)</th>
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<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (47)</td>
</tr>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>45.0 (0.3–76.0)</td>
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<tr>
<td><strong>Age group, n (%)</strong></td>
<td></td>
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<tr>
<td>&lt;2 years</td>
<td>6 (11)</td>
</tr>
<tr>
<td>2–6 years</td>
<td>5 (9)</td>
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<td>1 (2)</td>
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<tr>
<td>15–39 years</td>
<td>12 (22)</td>
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<tr>
<td>≥40 years</td>
<td>31 (56)</td>
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<td><strong>ECOG PS, n (%)</strong></td>
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<tr>
<td>0</td>
<td>27 (49)</td>
</tr>
<tr>
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<td>22 (40)</td>
</tr>
<tr>
<td>2</td>
<td>6 (11)</td>
</tr>
<tr>
<td><strong>No. of prior systemic chemotherapies, n (%)</strong></td>
<td></td>
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<tr>
<td>0–1</td>
<td>30 (55)</td>
</tr>
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<td>2</td>
<td>8 (15)</td>
</tr>
<tr>
<td>≥3</td>
<td>17 (31)</td>
</tr>
<tr>
<td><strong>CNS metastases, n (%)</strong></td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
Diversity of cancers treated - 17 unique types

- Peripheral nerve sheath tumor: 4%
- Sarcoma, NOS: 4%
- Myopericytoma: 4%
- Cholangiocarcinoma: 4%
- Spindle cell sarcoma: 5%
- GIST: 5%
- Melanoma: 7%
- Lung: 7%
- Colon: 7%
- Thyroid: 9%
- Infantile fibrosarcoma (IFS): 13%
- Salivary gland: 22%
- Inflammatory myofibroblastic kidney tumor: 2%
- Breast: 2%
- Pancreatic myofibromatosis: 2%
Clinical activity of larotrectinib in patients with TRK fusion cancers

<table>
<thead>
<tr>
<th></th>
<th>Enrolled patients with confirmatory response data available (n=50)</th>
<th>All enrolled patients (n=55)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate</strong> (95% CI)</td>
<td>76% (62–87%)</td>
<td>78% (65–88%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>64%</td>
<td>65%*</td>
</tr>
<tr>
<td>Complete response</td>
<td>12%</td>
<td>13%*</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12%</td>
<td>11%</td>
</tr>
</tbody>
</table>

*Includes unconfirmed responses with confirmatory scans pending (4 PR, 1 CR). All remain in response and ongoing on study.
Efficacy of larotrectinib in TRK fusion cancers

Objective response rate (95% CI) 76% (62–87%)

- Partial response 64%
- Complete response 12%
- Stable disease 12%
- Progressive disease 12%

*Patient had TRK solvent front resistance mutation (NTRK3 G522R) at baseline due to prior therapy. **Pathologic CR.

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Efficacy regardless of age

- Adult patients
- Pediatric patients

*Patient had TRK solvent front resistance mutation (NTRK3 G52R) at baseline due to prior therapy. *Pathologic OR.

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Efficacy regardless of tumor type

*Patient had TRK solvent front resistance mutation (NTRK3 G522R) at baseline due to prior therapy. *Pathologic CR.

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Efficacy regardless of NTRK gene

*Patient had TRK solvent front resistance mutation (NTRK3 G523R) at baseline due to prior therapy. *Pathologic CR.

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Efficacy regardless of fusion partner

- NTRK1
- LMNA
- TPM3
- TPR
- CTRC
- PDE4DIP
- IRF2BP2
- SQSTM1
- PPL
- TRIM63

Maximum change in tumor size (%)

*Patient had TRK solvent front resistance mutation (NTRK3 G32R) at baseline due to prior therapy. *Pathologic CR.

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Duration of larotrectinib therapy

93% of responding patients and 75% of all patients remain on treatment or underwent surgery with curative intent.
Median duration of response not reached

Median follow-up 5.8 months

In patients with confirmed complete or partial response (n=38)

Hyman, LBA2501

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Median progression-free survival not reached

Median follow-up 7.7 months

N=55 12/55 3/27 0/11 0/6 0/1 17

In primary analysis population (n=55) Hyman, LBA2501
SQSTM1-NTRK1 lung cancer patient

45F NSCLC & paraneoplastic hypertrophic osteoarthropathy

Prior therapy: platinum/pemetrexed

Larotrectinib ongoing in month 8, resolution of paraneoplastic symptoms
ETV6-NTRK3 infantile fibrosarcoma patient

2F infantile fibrosarcoma

2 cycles of vincristine/actinomycin-D/cyclophosphamide → progression → leg amputation was only alternative option

4 cycles larotrectinib → referred for surgery

Pathologic complete response with clear margins

No functional deficit post-surgery

Baseline

Cycle 3
ETV6-NTRK3 secretory breast cancer patient

Baseline | Day 6 | Day 20

14F, prior therapy: 4 lines of chemotherapy and repeated resections
Treated with larotrectinib under expanded access
### Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Treatment-emergent AEs (%)*</th>
<th>Treatment-related AEs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Increased AST</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

7 (13%) patients required dose reductions – all maintained tumor regression (1 CR, 5 PR, 1 SD) on reduced dose. No discontinuations for adverse events.
LOXO-195 to Address TRK Acquired Resistance

TRKA G595R

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Fusion</th>
<th>Resistance mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Colorectal</td>
<td>LMNA-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>NSCLC</td>
<td>TPR-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Sarcoma*</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>IFS</td>
<td>ETV6-NTRK3</td>
<td>TRKC G623R</td>
</tr>
<tr>
<td>Cholangio+</td>
<td>LMNA-NTRK1</td>
<td>TRKA F589L* + GNAS Q227H</td>
</tr>
</tbody>
</table>

TRK solvent front mutations detected in 5 of 6 patients with acquired resistance. First 2 patients successfully treated with LOXO-195.
Larotrectinib conclusions

- Consistent and durable antitumor activity in TRK fusion cancers
  - ORR: 76% (12% CRs)
  - 6-month landmark DOR: 91%
  - Minimal side effects for patients

- Notable elements of larotrectinib program
  - Potentially the first new targeted therapy developed in a tissue type-agnostic manner
  - First new targeted therapy developed simultaneously in adults and pediatrics
  - Rapid path from first patient to last patient enrolled (24 months)
  - New Drug Application (NDA) to be submitted in late 2017 or early 2018
  - Real-time elucidation of convergent acquired resistance mechanism and treatment with LOXO-195

- For patients with TRK fusion cancer, larotrectinib may offer a potential new standard of care
  - Routine pan-cancer screening will be important to identify these patients, as well as those with other tumor-agnostic biomarkers (MSI-H)
Acknowledgements

- Patients and their families, many of whom traveled long distances to participate in these studies
- National Institutes of Health P30 CA008748
- Marie-Josée and Henry R. Kravis Center for Molecular Oncology
A pediatric phase 1 study of larotrectinib, a highly selective inhibitor of the tropomyosin receptor kinase (TRK) family

Laetsch TW,1 DuBois SG,2 Nagasubramanian R,3 Turpin B,4 Mascarenhas L,5 Federman N,6 Reynolds M,7 Smith S,7 Cruickshank S,7 Cox MC,7 Pappo AS,8 Hawkins DS9

1University of Texas Southwestern/Children’s Health, Dallas, TX; 2Dana-Farber/Boston Children’s Cancer and Blood Disorders Center, Boston, MA; 3Nemours Children’s Hospital, Orlando, FL; 4Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 5Children’s Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA; 6University of California, Los Angeles, Los Angeles, CA; 7Laxo Oncology, Inc., South San Francisco, CA; 8St. Jude Children’s Research Hospital, Memphis, TN; 9Seattle Children’s Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA
Role of TRK in normal biology and cancer

Neurotrophin family of receptors

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

TRK fusions

- Ligand binding domain (LBD) replaced by 5’ fusion partner
- Drives overexpression and ligand-independent activation

TRK uncommonly expressed in normal tissues or cancer
Fusion drives abnormally high expression and activation of TRK kinase domain
Pediatric cancers and TRK fusions

- Gliomas
- Thyroid cancer
- Secretory breast carcinoma
- Infantile fibrosarcoma
- Spitz nevi
- Congenital mesoblastic nephroma
- Various sarcomas

Rare neoplasm with high TRK fusion frequency
Larotrectinib (LOXO-101)

- Larotrectinib is the first and only selective pan-TRK inhibitor in clinical development
- Highly potent against TRKA, TRKB, TRKC (5–11 nM IC\textsubscript{50} in cellular assays)
- Highly selective
- Responses seen in adult patients with TRK fusions
- Recommended phase 2 dose in adults is 100 mg BID continuously
- Liquid formulation for pediatric patients
Pediatric phase I trial design (SCOUT)

Eligibility

- 1 month – 21 years of age
- Relapsed/refractory solid tumor (including CNS) or locally advanced IFS
- Evaluable or measurable disease by RECIST v1.1
- Karnofsky/Lansky status ≥50
- Adequate organ function

Objectives

- Safety, including dose-limiting toxicities (DLTs)
- Pharmacokinetics
- Maximum tolerated dose (MTD)
- Antitumor activity

Modified rolling 6 design

- Patients with TRK fusion continue to enroll to current dose level during DLT evaluation
- Intrapatient dose escalation allowed
- Target AUC₀⁻²⁴ ≥50% of adults at RP2D
- TRK fusion status determined by local CLIA (or similarly accredited) laboratories

Data cut-off: April 14, 2017

---

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Laetsch, 10510
## Patient and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>5 (21)</td>
</tr>
<tr>
<td>1–2 years</td>
<td>2 (8)</td>
</tr>
<tr>
<td>2–12 years</td>
<td>10 (42)</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>7 (29)</td>
</tr>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>4.5 (0.1–18.0)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>12 (50)</td>
</tr>
<tr>
<td><strong>Extent of disease at study enrollment, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>10 (42)</td>
</tr>
<tr>
<td><strong>No. of prior systemic therapies, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (29)</td>
</tr>
<tr>
<td>1</td>
<td>6 (25)</td>
</tr>
<tr>
<td>≥2</td>
<td>11 (46)</td>
</tr>
</tbody>
</table>
### Range of histologies treated

<table>
<thead>
<tr>
<th>Cancer types, n (%)</th>
<th>TRK fusion (n=17)</th>
<th>Non-TRK fusion (n=7)</th>
<th>Total (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile fibrosarcoma (IFS)</td>
<td>8 (47)</td>
<td>0</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Soft tissue sarcoma, various</td>
<td>7 (41)</td>
<td>0</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Primary CNS</td>
<td>0</td>
<td>5 (71)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2 (12)</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>0</td>
<td>1 (14)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>0</td>
<td>1 (14)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>
Dose escalation

Dose level 1 (starting)
100 mg BID AED*
(n=4)

Dose level 2
150 mg BID AED*
(n=11)

Dose level 3
100 mg/m² BID
max 100 mg (n=9)

Interim PK analysis
Protocol modification to only BSA-based dosing

Recommended Phase 2 Dose
100 mg/m² BID
max 100 mg

No DLTs

No DLTs

No DLTs

*Adult equivalent doses by SimCyp modeling
Pharmacokinetics

Concentration-time

Larotrectinib in plasma (ng/mL)

Time (hours)

Adults (100 mg, BID, n=29)

Pediatric (solution formulation) (100 mg/m², max: 100 mg, BID, n=9)

Pediatric (capsule formulation) (100 mg/m², max: 100 mg, BID, n=3)

AUC₀–2₄ in patients treated with 80–125 mg/m² BID

Estimated plasma AUC₀–2₄ (ng*h/mL)

Age (years) and mean BID dose

n=6

n=9*

n=5

n=29

<2

2–11

12–18

Adult

(99 mg/m²)

(98 mg/m²)

(95 mg/m²)

(100 mg)

*One patient included in both <2 and 2–11 year categories (due to aging while on study)
## Treatment-emergent AEs related to study drug

### 100 mg/m² (n=9)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gr 1</th>
<th>Gr 2</th>
<th>Gr 3</th>
<th>Gr 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>33%</td>
<td>-</td>
<td>11%</td>
<td>-</td>
<td>44%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22%</td>
<td>-</td>
<td>11%</td>
<td>-</td>
<td>33%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>11%</td>
<td>11%</td>
<td>-</td>
<td>-</td>
<td>22%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11%</td>
<td>11%</td>
<td>-</td>
<td>-</td>
<td>22%</td>
</tr>
<tr>
<td>Anemia</td>
<td>22%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>22%</td>
</tr>
<tr>
<td>Constipation</td>
<td>22%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>22%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>-</td>
<td>-</td>
<td>11%</td>
<td>-</td>
<td>11%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11%</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>11%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11%</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>11%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11%</td>
</tr>
</tbody>
</table>

### Total (n=24)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gr 1</th>
<th>Gr 2</th>
<th>Gr 3</th>
<th>Gr 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>17%</td>
<td>-</td>
<td>4%</td>
<td>-</td>
<td>21%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8%</td>
<td>4%</td>
<td>4%</td>
<td>-</td>
<td>17%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>33%</td>
<td>4%</td>
<td>-</td>
<td>-</td>
<td>38%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13%</td>
<td>8%</td>
<td>-</td>
<td>-</td>
<td>21%</td>
</tr>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>4%</td>
<td>-</td>
<td>-</td>
<td>17%</td>
</tr>
<tr>
<td>Constipation</td>
<td>13%</td>
<td>4%</td>
<td>-</td>
<td>-</td>
<td>17%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>21%</td>
<td>4%</td>
<td>4%</td>
<td>-</td>
<td>29%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>21%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>21%</td>
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<td>17%</td>
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<td>-</td>
<td>-</td>
<td>17%</td>
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<tr>
<td>Blood creatinine increased</td>
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<td>-</td>
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<td>13%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8%</td>
<td>4%</td>
<td>-</td>
<td>-</td>
<td>13%</td>
</tr>
</tbody>
</table>

*In ≥10% of patients*
High response rate in children with TRK fusions

Note: 3 Non-TRK fusion patients not shown due to clinical disease progression without post-baseline tumor measurements. 4 TRK fusion patients not shown due to having non-measurable disease (n=2) or no disease assessment yet continuing treatment (n=2). #Pathologic CR
Efficacy regardless of tumor type

Non-TRK fusion

TRK fusion

Maximum change in tumor size (%)

Note: 3 Non-TRK fusion patients not shown due to clinical disease progression without post-baseline tumor measurements. 4 TRK fusion patients not shown due to having non-measurable disease (n=2) or no disease assessments yet (n=2). #Pathologic CR

Laetsch, 10510

Presented at: ASCO Annual Meeting '17 #ASC017

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Efficacy regardless of TRK gene

Note: 3 Non-NTRK fusion patients not shown due to clinical disease progression without post-baseline tumor measurements. 4 TRK fusion patients not shown due to having non-measurable disease (n=2) or no disease assessments yet (n=2). *Pathologic CR
Efficacy regardless of fusion partner

![Graph showing efficacy of fusion partners](image)

Note: 3 Non-NTRK fusion patients not shown due to clinical disease progression without post-baseline tumor measurements. 4 TRK fusion patients not shown due to having non-measurable disease (n=2) or no disease assessments yet/continuing treatment (n=2). *Pathologic CR
Clinical activity of larotrectinib

<table>
<thead>
<tr>
<th></th>
<th>TRK fusions (n=17)*</th>
<th>Non-fusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Confirmatory response data available (n=11)</td>
<td>All patients (n=13)</td>
</tr>
<tr>
<td><strong>Objective response rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>91% (59–100%)</td>
<td>92%** (64–100%)</td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
<td>64%</td>
<td>62%**</td>
</tr>
<tr>
<td><strong>Complete response</strong></td>
<td>27%</td>
<td>31%**</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*4 patients not evaluable due to having non-measurable disease (n=2) or no disease assessments yet/continuing treatment (n=2)

**Includes unconfirmed responses with confirmatory scans pending (1 PR, 1 CR). Both remain in response and ongoing on study.
Responses occur early and are durable

- Treatment after surgery
- Treatment ongoing
- Pathologic CR
- Post-surgery observation
- Time to first response

*Only patient with TRK fusion to develop PD
Confirmed TRKC G623R solvent front resistance mutation
Patient re-responded to LOXO-195*

*Patients had non-measurable disease at baseline
Rapid response in infant with ETV6-NTRK3 infantile fibrosarcoma (IFS)

- Baseline
- After four doses
- Before Cycle 3

31 do infant with IFS of the scalp
Rapid recurrence following surgical resection
Marked clinical improvement after four doses of larotrectinib
CR after 2 cycles of larotrectinib
Remains on therapy after 2 cycles
Rapid and durable response in patient with metastatic STRN-NTRK2 fusion sarcoma

11 yo girl with retroperitoneal undifferentiated sarcoma harboring STRN-NTRK2 fusion

Refactory to vincristine/doxorubicin/cyclophosphamide, ifosfamide/etoposide, sorafenib, and vincristine/irinotecan

PR after 1 cycle of larotrectinib with rapid clinical improvement

Remains in response after 13 cycles
ETV6-NTRK3 infantile fibrosarcoma patient

2 yo girl with infantile fibrosarcoma
2 cycles of vincristine/actinomycin-D/cyclophosphamide → progression → leg amputation was only alternative option
4 cycles larotrectinib → referred for surgery
Pathologic complete response with clear margins
No functional deficit post-surgery
Larotrectinib is active and well-tolerated in children with TRK fusion cancers

- Larotrectinib demonstrated a favorable tolerability profile and histology-independent activity in pediatric patients harboring TRK fusions
- Recommended phase 2 dose in children: 100 mg/m² BID continuously, cap 100 mg/dose
  - No DLTs at any dose level
  - Similar exposure to adults at RP2D
  - Highly active
- Phase 2 portion of trial is enrolling globally (Abstract TPS10577)
  - Infantile fibrosarcoma
  - Other CNS and extracranial TRK fusion solid cancers
Acknowledgements

The authors would like to thank

- Patients and their families
- Research staff

Funded by Loxo Oncology, Inc
2017 ASCO Conference Call
June 4, 2017
Forward Looking Statements

This presentation and the accompanying oral presentation contain "forward-looking" statements within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. Forward-looking statements can be identified by words such as: "anticipate," "intend," "plan," "goal," "seek," "believe," "project," "estimate," "expect," "strategy," "future," "likely," "may," "should," "will" and similar references to future periods. Examples of forward-looking statements include, among others, statements we make regarding our future financial performance, business plans and objectives, timing and success of our clinical trials, our ability to obtain regulatory approval or the timing of regulatory filings, the potential therapeutic benefits and economic value of our lead product candidate and second generation product candidate, potential growth opportunities, the timing or success of commercialization, financing plans, competitive position and industry environment.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, projections, anticipated events and trends, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict and many of which are outside of our control. Our actual results and financial condition may differ materially from those indicated in the forward-looking statements. Therefore, you should not rely on any of these forward-looking statements. Important factors that could cause our actual results and financial condition to differ materially from those indicated in the forward-looking statements include, among others, the following: those related to our future financial performance, our ability to raise additional funding when needed, our ability to develop and maintain partnerships, our ability to identify and develop new products in a timely manner, the outcome, cost and timing of our product development activities and clinical trials, market size and acceptance of our targeted small molecule therapeutics and diagnostics, our ability to maintain, protect and enhance our brand and intellectual property, our ability to continue to stay in compliance with applicable laws and regulations, our ability to scale our business and make key hires and such other factors as discussed under the section titled "Risk Factors" and elsewhere in our annual report on Form 10-K and quarterly reports on Form 10-Q that we filed with the Securities and Exchange Commission ("SEC") as well as our other filings and the documents incorporated by reference therein, with the SEC.

Any forward-looking statement made by us in this presentation and the accompanying oral presentation is based on information currently available to us and speaks only as of the date on which it is made. We undertake no obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.

Certain information in this slide deck on larotrectinib is derived from the presentation made at the 2017 ASCO Annual Meeting by Dr. Hyman, an independent third-party investigator.
<table>
<thead>
<tr>
<th>Program Indication</th>
<th>Stage of Development</th>
<th>Key Milestones</th>
<th>Eligible US patients/yr¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larotrectinib (LOXO-101)</td>
<td>Pred.</td>
<td>Will form the basis of NDA expected to be filed in late 2017 / early 2018</td>
<td>1,500-5,000</td>
</tr>
<tr>
<td></td>
<td>Phase 2 Basket Trial &quot;NAVIGATE&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pediatric Phase 1/2 Trial &quot;SCOUT&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adult Phase 1 Trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOXO-195</td>
<td>Pred.</td>
<td>Clinical proof-of-concept recently published</td>
<td>1,500-5,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase 1 starting now</td>
<td></td>
</tr>
<tr>
<td>LOXO-292</td>
<td>Pred.</td>
<td>Phase 1 ongoing</td>
<td>&lt;5,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential clinical data by YE 2017</td>
<td></td>
</tr>
<tr>
<td>FGFR2/3</td>
<td>Pred.</td>
<td>Lead optimization ongoing</td>
<td></td>
</tr>
</tbody>
</table>

¹ Estimated number of late-line eligible patients per year in U.S.
Agenda

• Review of larotrectinib data presented at ASCO
  – Dr. David Hyman, MSKCC
  – Dr. Alex Drilon, MSKCC
  – Dr. Theodore Laetsch, UT Southwestern

• Ongoing larotrectinib development activities

• LOXO-195

• LOXO-292

• Upcoming milestones / Q&A
The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers

Hyman DM,1 Laetsch TW,2 Kummar S,3 DuBois SG,4 Farago AF,5 Pappo AS,6 Demetri GD,7 El-Deiry WS,8 Lassen UN,9 Dowlati A,10 Brose MS,11 Boni V,12 Turpin B,13 Naganubramanian R,14 Cruickshank S,15 Cox MC,15 Ku NC,15 Hawkins DS,16 Hong DS,17 Drilon AE1

1Memorial Sloan Kettering Cancer Center, New York, NY; 2University of Texas Southwestern, Dallas, TX; 3Stanford University School of Medicine, Palo Alto, CA; 4Dana-Farber Cancer Institute/Boston Children’s Cancer and Blood Disorders Center, Boston, MA; 5Massachusetts General Hospital, Boston, MA; 6St. Jude Children’s Research Hospital, Memphis, TN; 7Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; 8Fox Chase Cancer Center, Philadelphia, PA; 9Rigshospitalet, Copenhagen, Denmark; 10UH Cleveland Medical Center, Cleveland, OH; 11Division of Otolaryngology–Head and Neck Surgery, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; 12KISTT Madrid CIOLII, Hospital HM Universitario Sanchaeramo, Madrid, Spain; 13Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 14Nation’s Children’s Hospital, Orlando, FL; 15Cancer Oncology, Inc., San Francisco, CA; 16Seattle Children’s Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA; 17The University of Texas MD Anderson Cancer Center, Houston, TX
Larotrectinib

- Larotrectinib is the first and only selective pan-TRK inhibitor in clinical development
- Highly potent against TRKA, TRKB, TRKC
  - 5–11 nM IC_{50} in cellular assays
- Highly selective
- Development timeline
  - March 2015: 1^{st} TRK-fusion patient treated
  - July 2016: breakthrough therapy designation
  - February 2017: pivotal enrollment complete
Larotrectinib TRK fusion development program

**Adult phase I**
- Age ≥18 years
- Advanced solid tumors

**SCOUT: pediatric phase I/II**
- Age ≤21 years
- Advanced solid tumors

**NAVIGATE: adult/adolescent phase II 'basket' trial**
- Age ≥12 years
- Advanced solid tumors
- TRK fusion positive

- **n=8**
- **n=12**
- **N=55 TRK fusion patients**

- TRK fusion status determined by local CLIA (or similarly accredited) laboratories

- **Primary endpoint**
  - Best objective response rate (ORR)
  - RECIST v1.1 per investigator assessment

- **Secondary endpoints**
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Safety

- **Dosing**
  - Single-agent larotrectinib, administered predominantly at 100 mg bid continuously
  - Treatment beyond progression permitted if patient continuing to benefit

Data cut-off: April 14, 2017
Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (47)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>45.0 (0.3–76.0)</td>
</tr>
<tr>
<td>Age group, n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>6 (11)</td>
</tr>
<tr>
<td>2–6 years</td>
<td>5 (9)</td>
</tr>
<tr>
<td>6–15 years</td>
<td>1 (2)</td>
</tr>
<tr>
<td>15–39 years</td>
<td>12 (22)</td>
</tr>
<tr>
<td>≥40 years</td>
<td>31 (56)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27 (49)</td>
</tr>
<tr>
<td>1</td>
<td>22 (40)</td>
</tr>
<tr>
<td>2</td>
<td>6 (11)</td>
</tr>
<tr>
<td>No. of prior systemic chemotherapies, n (%)</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>30 (55)</td>
</tr>
<tr>
<td>2</td>
<td>8 (15)</td>
</tr>
<tr>
<td>≥3</td>
<td>17 (31)</td>
</tr>
<tr>
<td>CNS metastases, n (%)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
Diversity of cancers treated - 17 unique types

- Infante fibrosarcoma (IFS): 13%
- Salivary gland: 22%
- Colon: 7%
- Thyroid: 9%
- Lung: 7%
- Melanoma: 7%
- GIST: 5%
- Spindle cell sarcoma: 5%
- Cholangiocarcinoma: 4%
- Myopericytoma: 4%
- Sarcoma, NOS: 4%
- Peripheral nerve sheath tumor: 4%
- Pancreatic myofibromatosis: 2%
- Inflammatory myofibroblastic kidney tumor: 2%
- Appendix: 2%
- Breast: 2%
Clinical activity of larotrectinib in patients with TRK fusion cancers

<table>
<thead>
<tr>
<th>Objective response rate (95% CI)</th>
<th>Enrolled patients with confirmatory response data available (n=50)</th>
<th>All enrolled patients (n=55)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>64% (62–87%)</td>
<td>65%*</td>
</tr>
<tr>
<td>Complete response</td>
<td>12%</td>
<td>13%*</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12%</td>
<td>11%</td>
</tr>
</tbody>
</table>

*Includes unconfirmed responses with confirmatory scans pending (4 PR, 1 CR). All remain in response and ongoing on study.
Efficacy of larotrectinib in TRK fusion cancers

<table>
<thead>
<tr>
<th>Objective response rate (95% CI)</th>
<th>Patient with available response data evaluable (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>64%</td>
</tr>
<tr>
<td>Complete response</td>
<td>12%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12%</td>
</tr>
</tbody>
</table>

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

*Patient had TRK solvent front resistance mutation (NTRK1 G922R) at baseline due to prior therapy. *Pathologic CR.
Efficacy regardless of age

*Patient had TRK solvent front resistance mutation (NTRK) G82R at baseline due to prior therapy. *Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Efficacy regardless of tumor type

*Patient had TRK solvent front resistance mutation (NTRK1 G626R) at baseline due to prior therapy. *Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Efficacy regardless of NTRK gene

*Patient had TRK solvent front resistance mutation (NTRK) G623R at baseline due to prior therapy. *Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Efficacy regardless of fusion partner

*Patient had TRK solvent front resistance mutation (NTRK1-G82R) at baseline due to prior therapy. *Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Duration of larotrectinib therapy

93% of responding patients and 75% of all patients remain on treatment or underwent surgery with curative intent.
### Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Treatment-emergent AEs (%)</th>
<th>Treatment-related AEs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Increased AST</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

7 (13%) patients required dose reductions – all maintained tumor regression (1 CR, 5 PR, 1 SD) on reduced dose. No discontinuations for adverse events.
SQSTM1-NTRK1 lung cancer patient

Baseline

Cycle 4

45F NSCLC & paraneoplastic hypertrophic osteoarthropathy
Prior therapy: platinum/pemetrexed
Larotrectinib ongoing in month 8, resolution of paraneoplastic symptoms
ETV6-NTRK3 secretory breast cancer patient

Baseline | Day 6 | Day 20

14F, prior therapy: 4 lines of chemotherapy and repeated resections
Treated with larotrectinib under expanded access
ETV6-NTRK3 infantile fibrosarcoma patient

Baseline

Cycle 3

2F infantile fibrosarcoma
2 cycles of vincristine/ actinomycin-D/ cyclophosphamide → progression
→ leg amputation was only alternative option
4 cycles larotrectinib → referred for surgery
Pathologic complete response with clear margins
No functional deficit post-surgery
**LOXO-195 to Address TRK Acquired Resistance**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Fusion</th>
<th>Resistance mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Colorectal</td>
<td>LMNA-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>NSCLC</td>
<td>TPR-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Sarcoma*</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>IPS</td>
<td>ETV6-NTRK3</td>
<td>TRKC G623R</td>
</tr>
<tr>
<td>Cholangio*</td>
<td>LMNA-NTRK1</td>
<td>TRKA F589L* + GNAS Q227H</td>
</tr>
</tbody>
</table>

**TRK solvent front** mutations detected in 5 of 6 patients with acquired resistance. First 2 patients successfully treated with LOXO-195.
Larotrectinib conclusions

- Consistent and durable antitumor activity in TRK fusion cancers
  - ORR: 76% (12% CRs)
  - 6-month landmark DOR: 91%
  - Minimal side effects for patients

- Notable elements of larotrectinib program
  - Potentially the first new targeted therapy developed in a tissue type-agnostic manner
  - First new targeted therapy developed simultaneously in adults and pediatrics
  - Rapid path from first patient to last patient enrolled (24 months)
  - New Drug Application (NDA) to be submitted in late 2017 or early 2018
  - Real-time elucidation of convergent acquired resistance mechanism and treatment with LOXO-195

- For patients with TRK fusion cancer, larotrectinib may offer a potential new standard of care
  - Routine pan-cancer screening will be important to identify these patients, as well as those with other tumor-agnostic biomarkers (MSI-H)
Path to Regulatory Filings

- Clinical
  - Independent radiology review to be conducted 2H 2017
  - NDA filing will utilize a later data cut-off date relative to ASCO data
  - Trials continue to enroll as mechanism of expanded access

- CMC scale-up and stability testing ongoing
  - Dictates the expiration date of the commercial product

- Long-term toxicology ongoing

- Clinical pharmacology studies ongoing
  - Drug-drug interactions
  - Food effect
  - ADME

- NDA submission expected in late 2017 or early 2018 –
- MAA submission expected in 2018 –
Larotrectinib Diagnostics Strategy

- Multiple diagnostic relationships are likely

- Focused on immunohistochemistry (IHC) and next-generation sequencing (NGS)

  - **IHC**
    - Collaboration announced with Roche Ventana
    - Loxo/Ventana are creating pan-TRK test
    - 8,500+ installed base of Ventana instruments worldwide

  - **NGS**
    - Multiple players in an evolving space
    - Keys for Loxo: (1) TRK fusion panel inclusion, (2) FDA path, (3) Payor traction
LOXO-195: Structurally Distinct, Similarly Selective
LOXO-195 Clinical Development

- Clinical proof-of-concept established in *Cancer Discovery* publication
  - First 2 emergency use patients with PRs
  - 1 additional emergency use patient (unpublished) with limited duration of treatment amidst clinical deterioration
  - 3 remaining larotrectinib RECIST progressions: 2 patients remain on larotrectinib post-progression, 1 patient with clinical deterioration too rapid for LOXO-195 initiation

- IND cleared by FDA

- Phase 1/2 trial startup in process
  - Co-locate at high enrolling larotrectinib sites
  - Co-locate at other sites with TRK fusion patients

- Plan to address patients with TRK fusion cancers harboring solvent front mutations, xDFG mutations, and gatekeeper mutations
LOXO-292 (RET)
LOXO-292 Phase 1 Trial Design

**Dose Escalation**

- Advanced RET-altered solid tumor
  - Any prior TKIs that inhibit RET
  - ~30 patients

**Expansion Cohorts**

1. Advanced RET-fusion NSCLC
   - ≥1 Prior TKI that inhibit RET
   - ~15 patients

2. Advanced RET-fusion NSCLC
   - No prior TKI that inhibits RET
   - ~15 patients

3. Advanced RET-mutant MTC
   - ≥1 prior TKI that inhibit RET
   - ~15 patients

4. Advanced RET-mutant MTC
   - No prior TKI that inhibits RET
   - ~15 patients

5. Advanced RET-altered solid tumor, any of:
   - Disease not measurable
   - Other RET-altered tumors
   - RET mutation-neg. MTC
   - Any prior TKIs that inhibit RET
   - ~15 patients

NSCLC = Non-small cell lung cancer
MTC = Medullary thyroid cancer
LOXO-292 Clinical Development

- First patient enrolled in Phase 1 clinical trial in May 2017
  - Early human pharmacokinetic data is in line with preclinical predictions

- Opportunity for patient enrichment in Phase 1
  - Growing target awareness
  - Detection technology is relatively straightforward

- Expect single agent activity at biologically relevant doses

- Potential for initial clinical data by YE 2017
# Milestones and Capitalization

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>UPDATE</th>
<th>DEC 2016 GUIDANCE</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larotrectinib (LOXO-101, TRK)</td>
<td>Complete enrollment for primary efficacy analysis dataset</td>
<td>Early 2017</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Present Phase 1/2 pediatric clinical data</td>
<td>Mid-2017</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Present interim data for integrated TRK fusion NDA database (local radiology)</td>
<td>...</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Announce final data for integrated TRK fusion NDA database (central radiology)</td>
<td>2H 2017</td>
<td>On plan</td>
</tr>
<tr>
<td></td>
<td>Submit NDA with US FDA</td>
<td>Late 2017 / Early 2018</td>
<td>On plan</td>
</tr>
<tr>
<td>LOXO-195 (TRK)</td>
<td>Initiate Phase 1 study</td>
<td>Mid-2017</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Assuming availability of appropriate patients, potential for initial clinical data</td>
<td>By Year End 2017</td>
<td>✓</td>
</tr>
<tr>
<td>LOXO-292 (RET)</td>
<td>Initiate Phase 1 study</td>
<td>Early 2017</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Potential for initial clinical data</td>
<td>By Year End 2017</td>
<td>On plan</td>
</tr>
</tbody>
</table>

- NASDAQ: LOXO
- Shares Outstanding*: 26.2M basic, 3.0M options ($17.63 weighted avg strike price)
- Cash, cash equivalents, and investments*: $244.3M

* As of Q1 2017 10-Q
Q&A