SINGAPORE 2016 ESMO ASIA

Clinical safety and activity from a Phase 1 study of LOXO-101, a selective TRKA/B/C inhibitor, in solid-tumor patients with NTRK gene fusions

David S. Hong[1], Afshin Dowlati[2], Howard A. Burris, III[3], James J. Lee[4], Marcia S. Brose[5], Anna F. Farago[6], Todd M. Bauer[3], Matthew Taylor[7], Alice T. Shaw[6], Steve Smith[8], Nisha Nanda[8], Scott Cruickshank[8], Michael C. Cox[8], Robert C. Doebele[9]

[1]MD Anderson Cancer Center, Houston, TX
[2]University Hospitals Case Medical Center, Cleveland, OH
[3]Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN
[4]University of Pittsburgh Medical Center, Pittsburgh, PA
[5]University of Pennsylvania, Philadelphia, PA
[6]Massachusetts General Hospital, Boston, MA
[7]Oregon Health & Science University, Portland, OR
[8]Loxo Oncology, South San Francisco, CA
[9]University of Colorado, Aurora, CO

DISCLOSURE SLIDE

Travel and accommodations expenses supported by Loxo Oncology

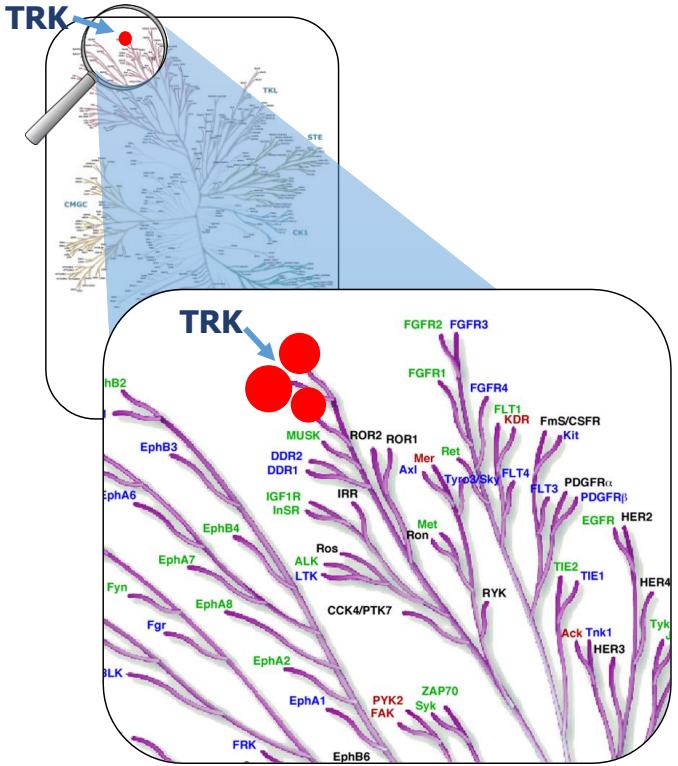
I am an investigator on numerous Phase 1 studies of molecularly targeted agents, including other NTRK-targeting compounds

TRK FUSIONS ARE FOUND ACROSS HUMAN CANCER

TRK fusion frequency		
<5%	5–25%	>75%
CNS ✓ Astrocytoma ✓ Brain low-grade glioma ✓ Glioblastoma GI ✓ Colorectal cancer ✓ Cholangiocarcinoma ✓ GIST ✓ Pancreatic cancer Head and neck ✓ Squamous cell carcinoma Lung ✓ Adenocarcinoma ✓ Large cell neuroendocrine Other ✓ Acute myeloid leukemia ✓ Breast invasive carcinoma ✓ Melanoma ✓ Sarcoma	✓ Congenital mesoblastic nephroma ✓ Papillary thyroid cancer ✓ Pontine glioma ✓ Spitz tumors	✓ Mammary analogue secretory carcinoma (MASC) of the salivary glands ✓ Secretory breast carcinoma ✓ Infantile fibrosarcoma

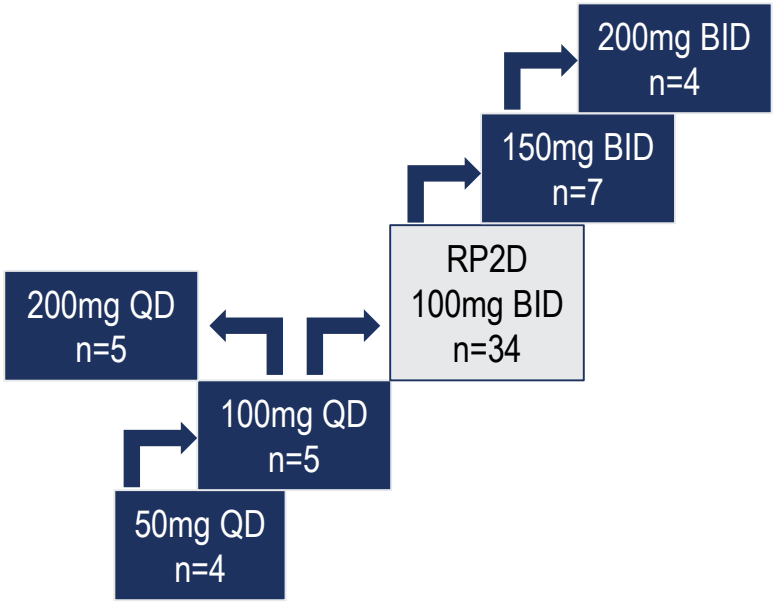
LAROTRECTINIB (LOXO-101)

- First and only selective TRK inhibitor
- Highly potent against TRKA, TRKB, TRKC (5-11 nM IC50)
- Highly selective: limited inhibition of other kinases and >1,000x selective over non-kinase off targets
- Highly soluble and bioavailable
- Moderately protein-bound
- Two clinical formulations: capsule and liquid



STUDY DESIGN

- Ongoing dose escalation study
  - Advanced or metastatic solid tumors
  - ECOG 0/1, normal organ function
  - QD or BID oral fixed, continuous dosing, 28-day cycles
- Outcome measures
  - Safety and tolerability
  - Pharmacokinetics measured at cycle 1, days 1 and 8
  - Efficacy assessments conducted every other cycle starting C3D1



Data cutoff 10-Nov-2016

BASELINE CHARACTERISTICS

Characteristics		Subjects (N= 59)
Median age (range), years		59.0 (19 – 82)
Sex	Male / Female	34 (58%) / 25 (42%)
Race	White / Black / Other	49 (83%) / 7 (12%) / 3 (5%)
Tumor Type*	Non-small cell lung	9 (15%)
	Soft tissue sarcoma	8 (14%)
	Colon	5 (8%)
	Salivary gland	5 (8%)
	Breast	4 (7%)
	Pancreatic	4 (7%)
ECOG Status	0 / 1 / 2 / 3 / Unknown	16 (27%) / 39 (66%) / 1 (2%) / 1 (2%) / 2 (3%)
Prior systemic anticancer therapy, n (%)		58 (98%)
Median number of regimens (range)		3 (0-24)

TRK-fusion positive		
	Mammary analogue secretory carcinoma (ETV6-NTRK3)	3
	GIST (ETV6-NTRK3)	2
	Soft tissue sarcoma (LMNA-NTRK1)	1
	Thyroid (ETV6-NTRK3)	1
	NSCLC (TPR-NTRK1)	1
	Total	8

*Includes n=3 each of thymic and thyroid. Includes n=2 each of GIST, gastric, hepatocellular, and head/neck. Includes n=1 each of anal, appendix, unknown, cholangiocarcinoma, gallbladder, glioma, melanoma, mesothelioma, small cell lung cancer, and uterine.

LAROTRECTINIB PHASE 1 INTERIM TREATMENT-EMERGENT ADVERSE EVENTS

Regardless of attribution to study drug

DOSE	100 MG BID (N=34)		TOTAL (N=59)	
Adverse Events (AEs)*	Gr 3/4	All Gr	Gr 3/4	All Gr
	n (%)	n (%)	n (%)	n (%)
Fatigue	2 (6%)	10 (29%)	4 (7%)	22 (37%)
Dizziness	1 (3%)	10 (29%)	1 (2%)	17 (29%)
Anemia	3 (9%)	10 (29%)	5 (8%)	15 (25%)
Dyspnea	2 (6%)	7 (21%)	3 (5%)	15 (25%)
Nausea	0	8 (24%)	0	13 (22%)
Cough	0	6 (18%)	0	12 (20%)
Constipation	0	5 (15%)	1 (2%)	11 (19%)
Arthralgia	0	8 (24%)	1 (2%)	10 (17%)
Increased AST	1 (3%)	7 (21%)	4 (7%)	10 (17%)
Decreased appetite	1 (3%)	5 (15%)	2 (3%)	10 (17%)
Pyrexia	0	7 (21%)	1 (2%)	10 (17%)
Vomiting	0	6 (18%)	0	10 (17%)
Diarrhea	0	5 (15%)	0	9 (15%)
Lymphocyte count decreased	2 (6%)	5 (15%)	2 (3%)	6 (10%)
Pneumonia	2 (6%)	3 (9%)	2 (3%)	4 (7%)

*Treatment-emergent adverse events (reported by > 15% of total subjects) or any Grade 3-4 events that occurred in at least 2 patients at 100 mg BID.

SUMMARY OF BEST RESPONSE FOR PATIENTS WITH TRK FUSIONS

Data as of 10-Nov-2016

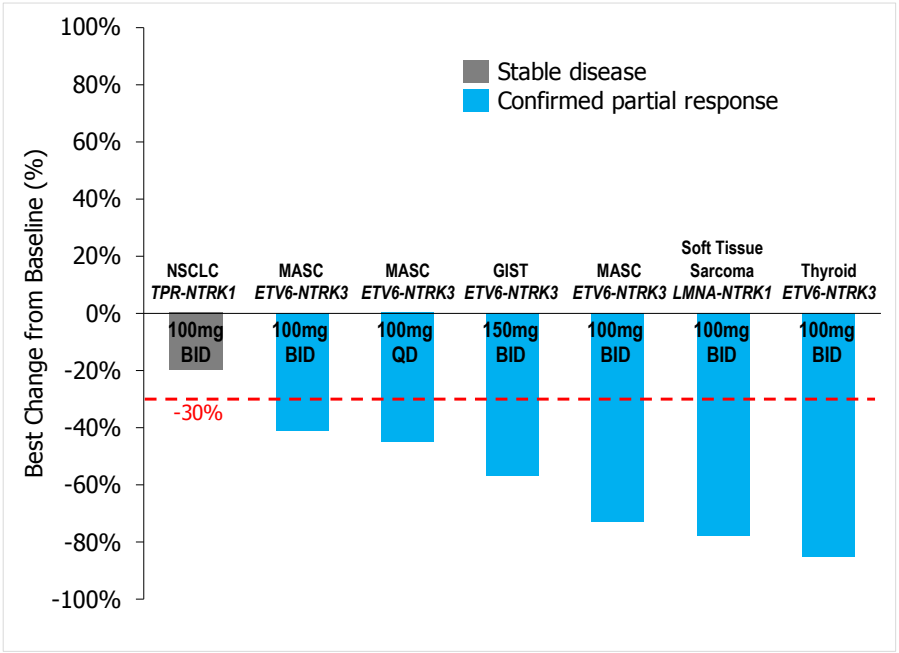
	N=7*
CR	0
PR	6
SD	1
PD	0
Off-study prior to first response assessment	0
Overall Response Rate	86% (6/7)

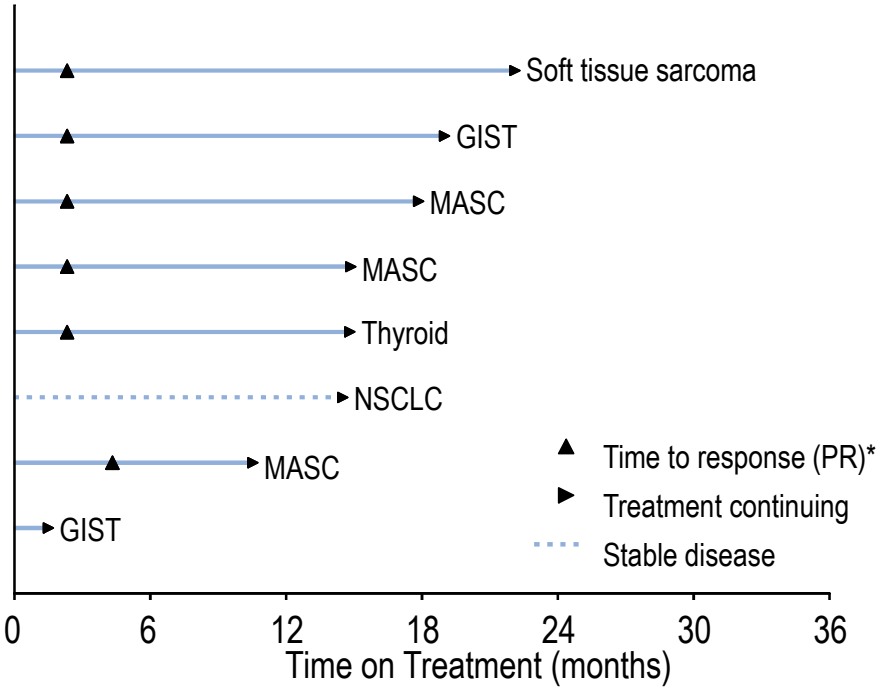
CR = complete response (confirmed)
PR = partial response (confirmed)

SD = stable disease
PD = progressive disease
RECIST v1.1

* Excludes 1 recently enrolled patient, on study for less than 8 weeks as of November 10, 2016.
Note: Of the other 51 patients, a total of 7 (14%) continue to receive larotrectinib, ranging from 2 to 22 cycles. A total of 44 (86%) discontinued treatment. 32 patients discontinued within the first 2 cycles, and 12 patients discontinued after more than 2 cycles (range 3-11 cycles).

BEST RESPONSE TO LAROTRECTINIB AND DURATION OF THERAPY FOR PATIENTS WITH TRK FUSIONS





SINGAPORE 2016 ESMO ASIA

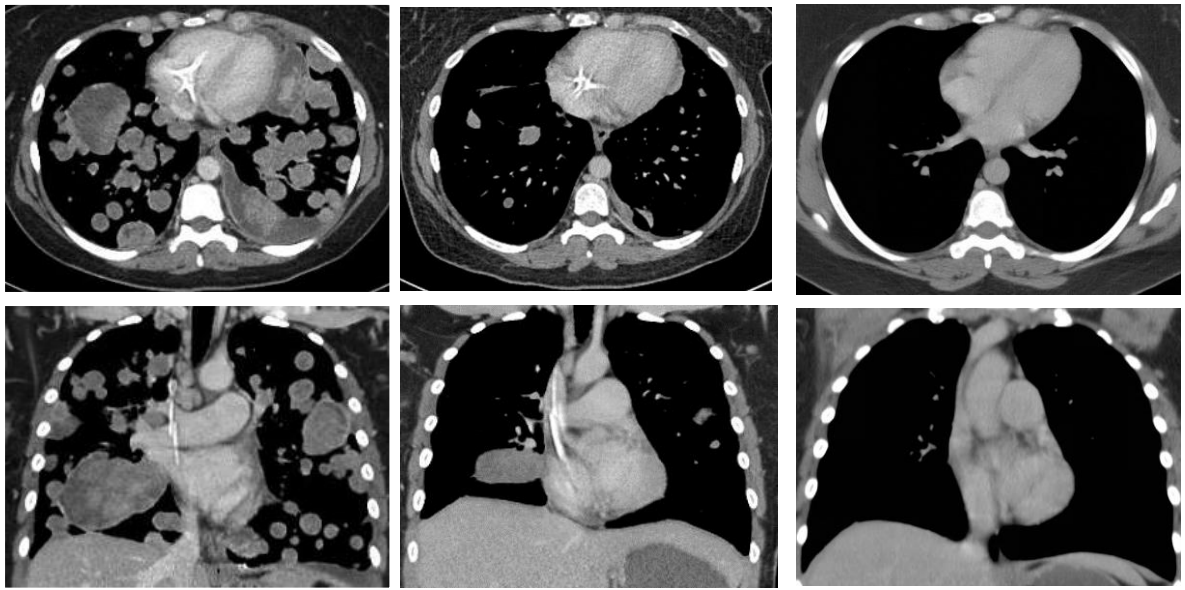
Data cutoff November 10, 2016.

* PR=partial response. Response is based on the investigator's assessment using RECIST 1.1.

FIRST TRK FUSION TREATED WITH LAROTRECTINIB

LMNA-NTRK1 fusion soft tissue sarcoma

- 42 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 22



Study baseline | Study cycle 3 day 1 | Study cycle 13 day 1

Doebele et al. Cancer Discov. 2015 Oct;5(10):1049-57.

CONCLUSIONS

- Larotrectinib is a purpose-built, oral, selective and potent TRK inhibitor
- Larotrectinib is well tolerated, with few adverse events likely related to drug
- Larotrectinib appears broadly active against TRK fusion cancers in this Phase 1 study
- Confirmed RECIST responses observed in 6 of 7 evaluable patients, with tumor regression in all 7
- Encouraging durability signal: All TRK fusion patients remain on study with most past one year
- Larotrectinib Phase 2 basket trial currently enrolling patients with TRK gene fusions

NAVIGATE TRIAL

Larotrectinib Phase 2 Basket Study

- Solid tumors, including CNS tumors, with TRK fusion based on local or pre-existing testing
- Enrolling patients ≥ 12 yo; ECOG 0-3
- Dose: 100mg BID
- Primary endpoint: Best ORR
- Global study: Active in US, EU, and Asia (South Korea, Singapore, Japan)
- Patient assistance for trial travel and logistics

ACKNOWLEDGEMENTS

- Larotrectinib patients and their families and caregivers
- Co-investigators and study support staffs
- This trial sponsored and supported by Loxo Oncology
- Larotrectinib invented by Array BioPharma