ESMO ADVANCED COURSE ON NTRK GENE FUSION: A NEW TARGET IN PRECISION TREATMENT OF CANCER

Larotrectinib: Clinical Data

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Lyon, 13-14 September 2019
DISCLOSURE OF INTEREST

Advisory boards and honorarium: Bayer and Pfizer
Grants: none
Stocks: none
Others: none
LAROTRECTINIB IS A SELECTIVE, CNS-ACTIVE TRK INHIBITOR

- Larotrectinib is a highly potent small-molecule inhibitor of TRKA, TRKB, and TRKC (5–11 nM IC₅₀ in cellular assays)
- Demonstrated activity in CNS disease¹
- Liquid formulation allows dosing of children as young as at birth and delivers equivalent pharmacokinetics to capsules

Patients with TRK fusion cancer: Available dataset

**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 cancer

Primary
- n=8
- n=12
- n=35
- n=55

Supplementary
- n=2
- n=25
- n=40
- n=67

**122 patients with TRK fusion cancer**

- **TRK fusion status** determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - Best objective response rate (RECIST 1.1)
- **Secondary endpoints**
  - Duration of response
  - Progression-free survival
  - Safety
- **Dosing**
  - Single-agent larotrectinib, administered predominantly at 100 mg BID continuously
  - Treatment beyond progression permitted if patient continuing to benefit

Data cutoff: 30 July 2018

BID, twice-daily; CLIA, clinical laboratory improvement amendments; RECIST, Response Evaluation Criteria In Solid Tumors

Lassen et al. ESMO 2018. Investigator response assessments, as of 30 July 2018
Diversity of cancers treated

Primary dataset (n=55)

- Appendix: 9%
- Bone sarcoma: 13%
- Breast: 19%
- Cholangiocarcinoma: 16%
- Colon: 10%
- Congenital mesoblastic nephroma: 5%
- Gastrointestinal stromal tumor: 5%
- Infantile fibrosarcoma: 7%
- Lung: 5%
- Melanoma: 4%
- Thyroid: 4%
- Unknown primary: 4%
- Pancreas: 2%

Supplementary dataset (n=67)

- Appendix: 1%
- Bone sarcoma: 1%
- Breast: 19%
- Cholangiocarcinoma: 16%
- Colon: 10%
- Congenital mesoblastic nephroma: 7%
- Gastrointestinal stromal tumor: 6%
- Infantile fibrosarcoma: 4%
- Lung: 4%
- Melanoma: 4%
- Thyroid: 3%
- Unknown primary: 3%
- Pancreas: 3%
- Salivary gland: 3%
- Small round cell sarcoma: 3%
- Spindle cell sarcoma: 1%
- Stromal sarcoma: 1%
- Sarcoma NOS: 1%
- Unknown primary: 1%
- Peripheral nerve sheath: 1%
- Inflammatory myofibroblastic tumor: 1%
- Myopericytoma: 1%
- Inflammatory myofibroblastic kidney tumor: 1%
- Not determined: 1%

Subtypes of soft tissue sarcoma

Lassen et al. ESMO 2018. Investigator response assessments, as of 30 July 2018
Integrated dataset: Larotrectinib is efficacious regardless of tumor type

Infantile fibrosarcoma
Soft tissue sarcoma
Thyroid
Salivary gland
Melanoma
Breast
Appendix
Pancreas
Cholangiocarcinoma
Gastrointestinal stromal tumor
Colon
Lung
Congenital mesoblastic nephroma
Unknown primary
Bone sarcoma

Maximum change in tumor size (%)

-100 0 10 20 30 40 50

Infantile fibrosarcoma
Soft tissue sarcoma
Thyroid
Salivary gland
Melanoma
Breast
Appendix
Pancreas
Cholangiocarcinoma
Gastrointestinal stromal tumor
Colon
Lung
Congenital mesoblastic nephroma
Unknown primary
Bone sarcoma

Note: Two patients not shown here. These patients discontinued treatment prior to any post-baseline tumor measurements.

CR, complete response; ORR, objective response rate; PR, partial response

ORR (95% CI)‡ 81% (72–88%)

Best response‡

| PR | 63% |
| CR | 17% |

‡Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment

*Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; #Surgical CR; †RECIST 1.1

Lassen et al. ESMO 2018. Investigator response assessments, as of 30 July 2018
Integrated dataset: Larotrectinib is efficacious regardless of age

Maximum change in tumor size (%)

- **Integrated‡ (n=109)**
  - ORR (95% CI)†: 81% (72–88%)
  - Best response†:
    - PR: 63%
    - CR: 17%

‡Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment
†Age <21 years *Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; #Surgical CR; †RECIST 1.1

Note: Two patients not shown here. These patients discontinued treatment prior to any post-baseline tumor measurements.

CR, complete response; ORR, objective response rate; PR, partial response
Larotrectinib Efficacy and Safety in Adult TRK Fusion Cancer Patients

- David S. Hong,1 Shivaani Kummar,2 Anna F. Farago,3 Ulrik Lassen,4 Jordan Berlin,5 Russell Schilder,6 Ray McDermott,7 Jyoti Patel,8 Afshin Dowlati,9 Robert C. Doebele,10 Daniel S.W. Tan,11 James J. Lee,12 Shivani Nanda,13 Barrett H. Childs,13 Nora C. Ku,14 Alexander Drilon,15,16 David M. Hyman15,16

1. The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 2. Stanford Cancer Institute, Stanford University, Palo Alto, CA, USA; 3. Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; 4. Department of Oncology, Rigshospitalet, Copenhagen, Denmark; 5. Vanderbilt University, Nashville, TN, USA; 6. Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA; 7. St Vincent’s University Hospital and Cancer Trials Ireland, Dublin, Ireland; 8. University of Chicago, Chicago, IL, USA; 9. Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, OH, USA; 10. Department of Medicine, Division of Medical Oncology, University of Colorado, Denver, Aurora, CO, USA; 11. National Cancer Center, 11 Hospital Drive, Singapore 169610, Singapore; 12. University of Pittsburgh Medical Center, Pittsburgh, PA, USA; 13. Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ, USA; 14. Loxo Oncology, Inc., South San Francisco, CA, USA; 15. Memorial Sloan Kettering Cancer Center, New York, NY, USA; 16. Weill Cornell Medical College, New York, NY, USA

Abstract 3122 presented at ASCO 2019
Adult Patient Characteristics

- As of July 30, 2018, adult patients (N=83) with TRK fusion cancer across 12 different tumor types had been treated with larotrectinib
- The median age was 57.0 years (range, 19.9–80.0 years)
  - Most TRK fusions involved NTRK1 (40%) or NTRK3 (57%)

*One patient had cancer of unknown primary origin.
GIST, gastrointestinal stromal tumor; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.

Patient population by tumour type*

- Salivary gland 23%
- Colon 7%
- Thyroid 19%
- Lung 13%
- Soft tissue sarcoma 14%
- GIST 5%
- Breast 2%
- Pancreas 1%
- Appendix 1%
- Cholangiocarcinoma 2%
- Bone sarcoma 2%
- Melanoma 7%

Hong DS, et al. ASCO 2019; abstract 3122
### Patient Characteristic

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Median 57.0</td>
</tr>
<tr>
<td></td>
<td>Range 19.9–80.0</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male 41 (49%)</td>
</tr>
<tr>
<td></td>
<td>Female 42 (51%)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>0 27 (33%)</td>
</tr>
<tr>
<td></td>
<td>1 47 (57%)</td>
</tr>
<tr>
<td></td>
<td>2 9 (11%)</td>
</tr>
<tr>
<td>NTRK fusions†, n (%)</td>
<td>1 33 (40%)</td>
</tr>
<tr>
<td></td>
<td>2 2 (2%)</td>
</tr>
<tr>
<td></td>
<td>3 47 (57%)</td>
</tr>
<tr>
<td>Prior anticancer therapies, n (%)</td>
<td>Systemic therapy 64 (77%)</td>
</tr>
<tr>
<td></td>
<td>Surgery 76 (92%)</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy 53 (64%)</td>
</tr>
<tr>
<td>Number of prior systemic therapies, n (%)</td>
<td>0 17 (20%)</td>
</tr>
<tr>
<td></td>
<td>1–2 41 (49%)</td>
</tr>
<tr>
<td></td>
<td>≥3 25 (30%)</td>
</tr>
</tbody>
</table>

†NTRK fusion was not determined for one patient.
**Efficacy Results**

- ORR per IRC was 68% (95% CI 55–79); 17% had a complete response, 51% had partial response, 15% had stable disease, 12% had progressive disease, and 5% were non-evaluable.
  - ORR per investigator assessment was 76% (95% CI 64–85). Responses were observed irrespective of tumor type.
- At a median follow-up of 17.5 and 17.2 months by IRC and investigator assessment, respectively, the median duration of response for patients with confirmed responses had not been reached (ranges identical, 1.9+ to 38.7+ months); 79% (by IRC) and 76% (by investigator assessment) of responders were estimated to be in response longer than 12 months.
- At a median follow-up of 13.6 months, median progression-free survival (investigator assessment) was 25.8 months (range, 0.03+ to 39.7+ months) and median overall survival had not been reached (range, 0.03+ to 40.7+ months).
- The median duration of treatment was 7.4 months; at data cut-off, 63% remained on treatment and 30% had discontinued due to disease progression.

### Efficacy of larotrectinib in adult patients with TRK fusion cancer

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Independent review-assessed patients (n=65)</th>
<th>Investigator-assessed patients (n=74)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>11 (17%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>33 (51%)</td>
<td>49 (66%)*</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (15%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8 (12%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Not determined</td>
<td>—</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>3 (5%)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Overall response rate</strong></td>
<td>44 (68%)</td>
<td>56 (76%)</td>
</tr>
</tbody>
</table>

Data presented are as of July 30, 2018.

*Nine patients non-evaluable due to lack of post-baseline assessment. †Includes seven patients with a partial response pending confirmation. CI, confidence interval; IRC, independent review committee; ORR, objective response rate; TRK, tropomyosin receptor kinase.
Best change in Tumor Size in Adult Patients with TRK Fusion Cancer (n=72*)

Best change in tumor size, per investigator assessment. Data cut off: July 30, 2018. Three patients with 0% change in tumor size: colon, thyroid, and salivary gland.

*11 patients had no available tumor measurements.

GIST, gastrointestinal stromal tumor; TRK, tropomyosin receptor kinase.

Hong DS, et al. ASCO 2019; abstract 3122
Secondary Efficacy Endpoints (Investigator Assessed)


At median follow-up of 17.2 months, median duration of response was not reached.

At median follow-up of 13.6 months, median progression-free survival was 25.8 months and median overall survival was not reached.

Hong DS, et al. ASCO 2019; abstract 3122
Duration of Treatment

Data cut-off: July 30, 2018. Circles denote category of first response, per investigator assessment.

Hong DS, et al. ASCO 2019; abstract 3122
Conclusions

- Selective inhibition of TRK with larotrectinib elicited a high and durable response rate and tumor-agnostic efficacy in adults with TRK fusion cancer.
- Larotrectinib was well tolerated in adult patients with TRK fusion cancer, with the majority of adverse events being grade 1 and 2.
- These data provide strong evidence in support of testing for TRK fusions in adult patients with advanced solid tumors, regardless of the site of primary diagnosis.
Activity of Larotrectinib in TRK Fusion Cancer Patients with Brain Metastases or Primary Central Nervous System Tumors

- Alexander Drilon,1 Steven G. DuBois,2 Anna F. Farago,3 Birgit Geoerger,4 Juneko E. Grilley-Olson,5 David S. Hong,6 Davendra Sohal,7 Cornelis M. van Tilburg,8 David S. Ziegler,9 Nora C. Ku,10 Michael C. Cox,10 Shivani Nanda,11 Barrett H. Childs,11 Francois Doz12

1. Memorial Sloan Kettering Cancer Center, New York, NY, USA; Weill Cornell Medical College, New York, NY, USA;
2. Dana-Farber/Boston Children’s Cancer and Blood Disorders Center, Boston, MA, USA; 3. Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; 4. Gustave Roussy, Department of Pediatric and Adolescent Oncology, Université Paris-Sud, Université Paris-Saclay, Villejuif, France;
5. University of North Carolina Hospitals, Chapel Hill, NC, USA;
6. The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 7. Cleveland Clinic, Cleveland, OH, USA;
8. Hopp Children’s Cancer Center Heidelberg (KITZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany; 9. Sydney Children’s Hospital, Randwick, Australia;
12. Institut Curie, University Paris Descartes, Paris, France.

Abstract 2006 presented at ASCO 2019
**Methods**

**Pediatric phase I/II trial**
(SCOUT, NCT02637687)
- Age 1 month to 21 years
- Locally advanced or metastatic solid tumours or CNS tumours

**Adult/adolescent phase II basket trial**
(NAVIGATE, NCT02576431)
- Age ≥12 years
- Advanced solid tumours
- TRK fusion cancer

**Adult phase I trial**
(NCT02576431)
- Age ≥18 years
- Advanced solid tumours

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**Endpoints**

**Objective response rate**
**Intracranial response‡**

**Objective responses**
- RECIST 1.1 or RANO
- Serial MRI/CT brain
  - required with baseline intracranial disease

**Initial larotrectinib dose**
- 100 mg or 100 mg/m² (maximum of 100 mg) BID

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*Data cutoff: February 19, 2019. †Data cutoff date July 30, 2018. ‡In tumor for patients with brain metastases; not a formal endpoint. §SCOUT trial: neurologically stable and on stable dose of steroids.
RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors.

Clinicopathologic Features: Non-Primary CNS Solid Tumors with Brain Metastases

Frequency of brain metastases in TRK fusion-positive solid tumors: 5% (n=6/121*)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>Male</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>65 years (25–76)</td>
</tr>
<tr>
<td>Prior therapies, n (%)</td>
<td></td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>Prior CNS radiotherapy/surgery</td>
<td></td>
</tr>
<tr>
<td>Yes†</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>No</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>Number of prior systemic therapies, median (range)</td>
<td>2 (0–5)</td>
</tr>
<tr>
<td>Patients with measureable intracranial brain lesions</td>
<td>3 (50%)</td>
</tr>
</tbody>
</table>

*All TRK fusion-positive patients treated with larotrectinib. †2 patients received radiation for intracranial disease >1 year prior to larotrectinib, 1 of whom also underwent surgery for intracranial disease >1 year prior to larotrectinib. ‡Thyroid cancer: 1 papillary and 1 follicular. NSCLC, non-small cell lung cancer.

Overall Response to Larotrectinib in TRK Fusion-Positive Solid Tumors with Brain Metastases

Overall efficacy n=5 evaluable patients‡

<table>
<thead>
<tr>
<th>Objective response rate*</th>
<th>60% (95% CI: 15–95)</th>
</tr>
</thead>
</table>

Best overall response†, n (%)

| Partial response         | 3 (60%)§            |
| Stable disease           | 2 (40%)             |
| Progressive disease      | 0 (0%)              |

Data cutoff date July 30, 2018. *Overall (systemic) response by RECIST 1.1 including intracranial and extracranial disease when applicable. †Investigator assessment based on RECIST 1.1. ‡1 patient not shown here initiated treatment with larotrectinib but has not yet had an on-treatment scan to evaluate response. §One patient pending confirmation. RECIST, Response Evaluation Criteria In Solid Tumors.

Larotrectinib in TRK Fusion-Positive Solid Tumors with Brain Metastases: Treatment Duration

Data cutoff date July 30, 2018. Disease assessments were performed by investigators. Intracranial target tumor responses in patients with measurable disease, based on RECIST 1.1 sum of longest diameter. *Nontarget PD in asymptomatic leptomeningeal focus.

NE, not evaluable; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Larotrectinib in TRK Fusion-Positive Solid Tumors with Brain Metastases: Intracranial Response

Data cutoff date July 30, 2018.

Clinicopathologic Features: Primary CNS Tumors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (55%)</td>
</tr>
<tr>
<td>Male</td>
<td>8 (45%)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td></td>
</tr>
<tr>
<td>Pediatric*</td>
<td>10 years (1–79)</td>
</tr>
<tr>
<td>Adult</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Prior therapies, n (%)</td>
<td></td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>15 (83%)</td>
</tr>
<tr>
<td>Surgery or radiotherapy</td>
<td>13 (72%)</td>
</tr>
<tr>
<td>Number of prior systemic therapies, median (range)</td>
<td>1 (0–6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>6 (32%)</td>
</tr>
<tr>
<td>Glioma</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>Glioneuronal</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Not otherwise specified</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Grade (High/Low/Unknown), n</td>
<td></td>
</tr>
<tr>
<td>6/0/0†</td>
<td></td>
</tr>
<tr>
<td>1/3/0</td>
<td></td>
</tr>
<tr>
<td>2/0/1</td>
<td></td>
</tr>
<tr>
<td>1/1/1</td>
<td></td>
</tr>
<tr>
<td>1/0/1</td>
<td></td>
</tr>
</tbody>
</table>

*Pediatric age range 1–16 years; adult age range 31–79 years. †Histology based on initial CRF entries. For select tumors, WHO grade, IDH mutation status, MGMT methylation status, and 1p/19q co-deletion status will be clarified in a future report. ‡3 cases were entered as "unknown grade"; however, these glioblastomas were assumed to be grade III. §One patient not determined.
# Investigator-Assessed Efficacy of Larotrectinib in TRK Fusion-Positive Primary CNS Tumors

## n=14 evaluable patients

<table>
<thead>
<tr>
<th>Objective response rate</th>
<th>36% (95% CI: 13–65)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best overall response</strong>, n (%)</td>
<td></td>
</tr>
<tr>
<td>Complete response†</td>
<td>2 (14%)‡</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (21%)‡</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Disease control rate ≥ 16 weeks</strong>, n (%)</td>
<td>11 (79%)</td>
</tr>
<tr>
<td><strong>Disease control rate ≥ 24 weeks</strong>, n (%)</td>
<td>10 (71%)</td>
</tr>
<tr>
<td><strong>Progression-free survival, median</strong></td>
<td>11.0 months (95% CI: 2.8, NE)</td>
</tr>
</tbody>
</table>

Data cutoff date February 19, 2019. *Investigator assessment based on RANO or RECIST 1.1. †Pending confirmation. ‡All responses were seen in pediatric cases (ORR 45%, n=5/11). §Disease control rate = complete response + partial response + stable disease. **In 18 patients with median follow-up of 4.4 months. CI, confidence interval; RANO, Response Assessment in Neuro-Oncology. Drilon A, et al. ASCO 2019; abstract 2006
Larotrectinib in TRK Fusion-Positive Primary CNS Tumors: Response and Treatment Duration by Age Group

Best change in tumor response*

Treatment duration

Data cutoff date February 19, 2019. Disease assessments were performed by investigators. *Tumor responses in patients with measurable disease and tumor values recorded at data cutoff, based on RANO sum of products of diameters, unless noted otherwise. †Based on RECIST 1.1 sum of longest diameter. CR, complete response; NE, not evaluable; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Larotrectinib in TRK Fusion-Positive Primary CNS Tumors: Response and Treatment Duration

Best change in tumor response*

- Maximum change in tumor size (%)

- Time (months)

- Treatment duration

- Range: 0.03+ to 16.6+ months

Data cutoff date February 19, 2019. Disease assessments were performed by investigators. *Tumor responses in patients with measurable disease and tumor values recorded at data cutoff, based on RANO sum of products of diameters, unless noted otherwise. †Based on RECIST 1.1 sum of longest diameter. CR, complete response; NE, not evaluable; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Conclusions

- Larotrectinib is active in patients with TRK fusion-positive cancers with intracranial disease

- **Confirmed responses and durable disease control are achieved**
  - in patients with solid tumors metastatic to the brain
  - in patients with primary CNS tumors of various histologies and grades

These results support testing for TRK fusions across patients with various cancers, including those with primary CNS tumors.
Larotrectinib Efficacy and Safety in Pediatric TRK Fusion Cancer Patients

- Cornelis M. van Tilburg,1 Steven G. Dubois,2 Catherine M. Albert,3 Noah Federman,4 Ramamoorthy Nagasubramanian,5 Birgit Geoerger,6 Daniel Orbach,7 Stefan Bielack,8 Neerav Shukla,9 Brian Turpin,10 Michela Casanova,11 Sheri L. Spunt,12 Hope Qamoos,13 Shivani Nanda,14 Barrett H. Childs,14 Michael C. Cox,13 Alberto Pappo,15 Theodore W. Laetsch,16 and Leo Mascarenhas17

1. Hopp Children’s Cancer Center Heidelberg (KiTZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany; 2. Dana-Farber/Boston Children’s Cancer and Blood Disorders Center, Boston, MA, USA; 3. Seattle Children’s Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; 4. University of California, Los Angeles, CA, USA; 5. Nemours Children's Hospital, Orlando, FL, USA; 6. Gustave Roussy, Department of Pediatric and Adolescent Oncology, Université Paris-Sud, Université Paris-Saclay, Villejuif, France; 7. Institut Curie, SIREDO Oncology Center (Care, Innovation and research for children and AYA with cancer), PSL Research University, Paris, France; 8. Pediatrics 5 (Oncology, Hematology, Immunology), Klinikum Stuttgart-Olgahospital, Stuttgart, Germany; 9. Marie-Josée and Henry R. Kravis Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 10. Division of Pediatric Hematology/Oncology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA; 11. Paediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 12. Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA; 13. Loxo Oncology, Inc., South San Francisco, CA, USA; 14. Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ, USA; 15. Department of Oncology, St. Jude Children’s Research Hospital, Memphis, TN, USA; 16. University of Texas, Southwestern Medical Center/Children’s Health, Dallas, TX, USA; 17. Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA.

Abstract 10010 presented at ASCO 2019
Study Design: Pediatric Subset

**SCOUT:** (NCT02637687) pediatric/adolescent phase 1–2 study
- Age ≤21 years
- Advanced solid tumors
- TRK fusion cancer

**Navigator:** (NCT02576431) Adult/adolescent phase 2 study
- Age ≥12 years
- Advanced solid tumors
- TRK fusion cancer

### 38 children and adolescents (aged <18 years) with non-CNS TRK fusion cancer
- n=35

### Data cut-off: July 30, 2018

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

- **Primary endpoint**
  - Objective response rate (RECIST 1.1; investigator-assessed)

- **Secondary endpoints**
  - Duration of response
  - PFS
  - OS
  - Safety

- **Dosing**
  - Adult equivalent doses of 100 mg BID (Cohort 1; n=3) and 150 mg BID (Cohort 2; n=6) by SimCyp® modeling
  - 100 mg/m² BID (Cohort 3; n=29); maximum dose 100 mg BID

BiD, twice daily; CLIA, Clinical Laboratory Improvement Amendments; CNS, central nervous system; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TRK, tropomyosin receptor kinase.
## Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>2.3 (0.1–14.0)</td>
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<tr>
<td>Female/Male, n (%)</td>
<td>20/18 (53/47)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30 (79)</td>
</tr>
<tr>
<td>1</td>
<td>5 (13)</td>
</tr>
<tr>
<td>2</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Prior therapies, n (%)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>23 (61)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>26 (68)</td>
</tr>
<tr>
<td>Number of prior systemic therapies, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12 (32)</td>
</tr>
<tr>
<td>1–2</td>
<td>20 (53)</td>
</tr>
<tr>
<td>≥3</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Disease status at enrollment, n (%)</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>19 (50)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>19 (50)</td>
</tr>
</tbody>
</table>
Pediatric Population by Tumor Type and NTRK Fusion (N=38)

**Tumor types**
- Infantile fibrosarcoma: 47%
- Other soft tissue sarcoma: 42%
- Melanoma: 3%
- Thyroid: 5%
- Congenital mesoblastic nephroma: 3%

**NTRK fusion partners**
- NTRK1: 47%
- NTRK2: 5%
- NTRK3: 47%
- ETV6: 45%
- TPM3: 24%
- RBPMS: 3%
- STRN: 3%
- LMNA: 11%
- PDE4DIP: 3%
- EML4: 3%
- SQSTM1: 3%
- IRF2BP2: 3%
- TPR: 5%

NTRK, neurotrophic tyrosine receptor kinase.

van Tilburg CM, et al. ASCO 2019; abstract 10010
Best Change in Tumor Size in Pediatric Patients with TRK Fusion Cancer (N=34)

Data cut-off: July 30, 2018. *Melanoma patient at 0% change; †Includes two patients pending confirmation; #Pathologic CR; four patients were non-evaluable due to insufficient time on study. CR, complete response; INV, investigator; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TRK, tropomyosin receptor kinase.

ORR per INV 94%
CR 35%
PR† 59%
SD 6%

van Tilburg CM, et al. ASCO 2019; abstract 10010
Duration of Treatment (N=38)*

- Median time to response: 1.8 months
- Median duration of treatment was 10.24 months.
- Five patients discontinued treatment post-surgery without progression, two with pCR.
- pCR, pathologic complete response.

33 of 38 patients (87%) remained on treatment or underwent surgery with curative intent.

van Tilburg CM, et al. ASCO 2019; abstract 10010
Secondary Efficacy Endpoints

### Duration of response
- Median: NE (range 1.6+, 26.7+)
- 84% of responders estimated DOR ≥1 year
- Median duration of follow-up: 8.9 months

### Progression-free survival
- Median: NE (range 0.03+, 27.6+)
- Median follow-up: 10.7 months

### Overall survival
- Median: NE (range 0.6+, 27.6+)
- Median duration of follow-up: 12.3 months

Data cut-off: July 30, 2018. DOR, duration of response; NE, not estimable.
Conclusions

- Larotrectinib treatment resulted in a high and durable response rate in pediatric patients with TRK fusion cancer.
- Larotrectinib was well tolerated in the pediatric population with TRK fusion cancer.
  - Longer term follow-up of patient safety profile is required.
- Larotrectinib reduces the need for mutilating/disfiguring surgery in certain pediatric patients with TRK fusion cancer.
- Routine testing for NTRK gene fusions in pediatric patients with cancer is recommended in the appropriate clinical context.

NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.
Activity of Larotrectinib in Sarcoma Patients with TRK Fusion Cancer

- Noah Federman1, Daniel Orbach2, Shivaani Kummar3, Alexander Drilon4, Ulrik Lassen5, Birgit Geoerger6, Cornelis M. van Tillburg7, Theodore W. Laetsch8, Steven G. Dubois9, Ramamoorthy Nagasubramanian10, Neerav Shukla4, Michela Casanova11, Soledad Gallego12, Stefan Bielack13, Atrayee Basu-Mallick14, Mohamad Farid15, Jyoti Patel16, Vicki Keedy17, Scott Cruickshank18, Nora C. Ku18, Michael C. Cox18, Alberto Pappo19, George D. Demetri20, Douglas S. Hawkins21

1. Departments of Pediatrics and Orthopedics, Jonsson Comprehensive Cancer Center, UCLA David Geffen School of Medicine, Los Angeles, CA, USA; 2. Institut Curie, SIREDO Oncology Center, PSL University, Paris, France; 3. Stanford Cancer Center, Palo Alto, CA, USA; 4. Memorial Sloan Kettering Cancer Center, New York, NY, USA; 5. Rigshospitalet, Copenhagen, Denmark; 6. Gustave Roussy Cancer Center, Villejuif, France; 7. Hopp Children’s Cancer Center at the NCT Heidelberg (KITZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany; 8. University of Texas Southwestern Medical Center/Children’s Health, Dallas, TX, USA; 9. Dana-Farber/Boston Children’s Cancer and Blood Disorders Center and Harvard Medical School, Boston, MA, USA; 10. Nemours Children’s Hospital, Orlando, FL, USA; 11. Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; 12. Hospital Universitario Vall d’Hebron, Barcelona, Spain; 13. Olgahospital, Klinikum Stuttgart, Stuttgart, Germany; 14. Thomas Jefferson University, Philadelphia, PA, USA; 15. National Cancer Centre, Singapore; 16. University of Chicago, Chicago, IL, USA; 17. Vanderbilt University School of Medicine, Nashville, TN, USA; 18. Loxo Oncology Inc., South San Francisco, CA; 19. St Jude Children’s Research Hospital, Memphis, TN, USA; 20. Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; 21. Seattle Children’s Hospital, University of Washington, Fred Hutchinson Cancer Research Center Seattle, WA, USA.

Presented in 2018 at SIOP 2018 by: Dr Noah Federman, UCLA, USA
TRK FUSION SARCOMA PATIENTS (N=51) – SUBTYPES*

- Infantile fibrosarcoma (35%)
- GIST (10%)
- Spindle cell (14%)
- NOS (8%)
- Inflammatory myofibroblastic tumor (10%)
- Peripheral nerve sheath (8%)
- Myopericytoma (4%)
- Infantile myofibromatosis (2%)
- Not determined (2%)
- Spindle, epithelioid (2%)
- Small round cell (2%)
- Stromal (2%)
- Lipofibromatosis (2%)

* Based on Investigator assessment

Presented in 2018 at SIOP 2018 by: Dr Noah Federman, UCLA, USA
EFFICACY OF LAROTRECTINIB IN PATIENTS WITH TRK FUSION SARCOMA

Investigator response assessments, as of 30 July 2018

Presented in 2018 at SIOP 2018 by: Dr Noah Federman, UCLA, USA
Conclusion

- Oncogenic $NTRK$ gene fusions can be detected in sarcomas
  - Frequency of $NTRK$ gene fusions vary with type of sarcoma
- Larotrectinib demonstrates robust antitumor activity across the spectrum of TRK fusion sarcomas, including complete responses, in adult and pediatric patients
  - ORR of 93% (n=46) in the integrated dataset, per investigator assessment
- Responses to larotrectinib therapy were generally durable in TRK fusion sarcomas
  - The median duration of response has not yet been reached with a median follow-up of 17.5 months in the primary dataset
- Prolonged larotrectinib therapy was well tolerated
- Genomic profiling with assays capable of identifying $NTRK$ gene fusions should be strongly considered in patients with sarcomas when determining systemic treatment options, especially in the setting of recurrence

Presented in 2018 at SIOP 2018 by: Dr Noah Federman, UCLA, USA
Activity of Larotrectinib in TRK Fusion Lung Cancer

Anna F. Farago¹, Shivaani Kummar², Victor Moreno³, Jyoti Patel⁴, Ulrik Lassen⁵, Lee Rosen⁶, Nora C. Ku⁷, Michael C. Cox⁷, Shivani Nanda⁸, Barrett H. Childs⁸, David M. Hyman⁹, and Alexander Drilon⁹

¹Massachusetts General Hospital Cancer Center, Boston, MA, USA; ²Stanford Cancer Institute, Stanford, CA, USA; ³START MADRID-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain; ⁴University of Chicago, Chicago, IL, USA; ⁵Department of Oncology, Rigshospitalet, Copenhagen, Denmark; ⁶UCLA, Los Angeles, CA, USA; ⁷Loxo Oncology, South San Francisco, CA, USA; ⁸Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA; ⁹Memorial Sloan Kettering Cancer Center, New York, NY, USA

Presented in Sep 2019 at WCLC by: Dr Anna F. Farago, Massachusetts General Hospital Cancer Center, Boston, USA
Methods

Adult phase I trial (NCT02122913)
• Age ≥18 years
• Advanced solid tumours

Adult/adolescent phase II ‘basket’ trial (NAVIGATE; NCT02576431)
• Age ≥12 years
• Advanced solid tumours
• TRK fusion cancer

12 patients with TRK fusion lung cancer

Dosing
• Larotrectinib, 100 mg BID continuously
• 28-day cycles

Endpoints
• Primary endpoint
  • Best objective response rate (RECIST 1.1)
• Secondary endpoints
  • Duration of response
  • Progression-free survival
  • Overall survival
  • Safety

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Median age, range</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.0 (25–76)</td>
<td>38.0 (25–76)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (50)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTRK fusion, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTRK1</td>
<td>9 (75)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>NTRK2</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>3 (25)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Brain metastases at baseline, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (50)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TRK fusion status determined by local CLIA (or similar accredited laboratories)
BID, twice daily; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.

Data cut off February 19 2019

Presented in Sep 2019 at WCLC by: Dr Anna F. Farago, Massachusetts General Hospital Cancer Center, Boston, USA
Larotrectinib is active in TRK fusion lung cancer

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=12)</th>
<th>Patients with brain metastases (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>75%</td>
<td>67%</td>
</tr>
<tr>
<td>CR, n</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PR, n</td>
<td>8*</td>
<td>4*</td>
</tr>
<tr>
<td>SD, n</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

*PR pending confirmation in 1 patient. Investigator assessments as of 19 February 2019.

CR, complete response; ORR, objective response rate; PR, partial response;

SD, stable disease.

† Nontarget PD in asymptomatic leptomeningeal focus

Median duration of response not reached (range, 7.4* to 17.6* months) (median follow-up of 12.8 months)

Median treatment duration was 9.2 months (range, 0.03–28.5) (median follow-up of 12.8 months)

Presented in Sep 2019 at WCLC by: Dr Anna F. Farago, Massachusetts General Hospital Cancer Center, Boston, USA
Conclusion

- Larotrectinib demonstrated robust activity in patients with advanced TRK fusion lung cancer
- Larotrectinib showed activity in patients with brain metastases
- Larotrectinib was well tolerated with AEs predominantly being grade 1–2
- These results support routine testing for TRK fusions in patients with NSCLC

TRK fusions are rare oncogenic drivers in lung cancer. Due to the high global prevalence of this disease, there may be a substantial number of patients able to benefit from TRK inhibitors.
Activity of larotrectinib in patients with TRK fusion GI malignancies

Michael Nathenson¹,
George Demetri¹, Ulrik Lassen², David Hong³, Valentina Boni⁴, John Deeken⁵, Afsin Dowlati⁶, Michael Cox⁷,
Nora Ku⁷, Scott Cruickshank⁷, Hope Qamoos⁷, and Alexander Drilon⁸

¹ Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA;
² Rigshospitalet, Copenhagen, Denmark; ³ MD Anderson Cancer Center, Houston, TX, USA;
⁴ Centro Integral Oncologico Clara Campal, Madrid, Spain; ⁵ Inova Health Care Services, Falls Church, VA, USA;
⁶ University Hospitals of Cleveland, Cleveland, OH, USA;
⁷ Loxo Oncology, South San Francisco, CA, USA; ⁸ Memorial Sloan Kettering Cancer Center, New York, NY, USA.

World GI Cancer Conference 2018
# Patient and Disease Characteristics in the GI-cancer Subset

Nathenson M, et al. World GI Cancer Conference 2018

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N=12</th>
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</thead>
<tbody>
<tr>
<td>Median age (range) years</td>
<td>56 (32–74)</td>
</tr>
<tr>
<td>Gender female: male, n</td>
<td>7:5</td>
</tr>
<tr>
<td>Tumor type, n</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>4</td>
</tr>
<tr>
<td>GIST*</td>
<td>4</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>1</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>1</td>
</tr>
<tr>
<td>Appendix</td>
<td>1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1</td>
</tr>
<tr>
<td>Fusion partners</td>
<td></td>
</tr>
<tr>
<td>TPM3-NTRK1</td>
<td>4</td>
</tr>
<tr>
<td>LMNA-NTRK1</td>
<td>3</td>
</tr>
<tr>
<td>CTRC-NTRK1</td>
<td>1</td>
</tr>
<tr>
<td>PLEKHA6-NTRK1</td>
<td>1</td>
</tr>
<tr>
<td>ETV6-NTRK3</td>
<td>3</td>
</tr>
<tr>
<td>Prior therapies</td>
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</tr>
<tr>
<td>All therapies, median (range)</td>
<td>3 (2-14)</td>
</tr>
<tr>
<td>Systemic therapies, median (range)</td>
<td>2 (0-9)</td>
</tr>
</tbody>
</table>

*One patient initially diagnosed as GIST was determined to have peri-rectal undifferentiated soft tissue sarcoma*
Efficacy

*One patient initially diagnosed as GIST was determined to have peri-rectal undifferentiated soft tissue sarcoma

Note: Investigator assessment

Nathenson M, et al. World GI Cancer Conference 2018
Suggested workflow for molecular testing in colorectal carcinoma.

MSI/ MMR Assessment

- MSS/ MMR-P
  - NGS Testing of tumor*
    - Or KRAS/ NRAS mutation analysis*
  - MLH1 Promoter hypermethylation
    - Wild-type BRAF
    - Fusion testing*
  - No MLH1 promoter hypermethylation
    - BRAF V600E
    - MLH1 Germline testing
      - NGS Testing of tumor*
- MSI-H/ MLH1 Deficient
  - MSH2, MSH6, PMS2 Only deficient
  - MMR Gene germline testing

*For colorectal carcinoma with distant metastases

Activity of Larotrectinib in Patients with Advanced TRK Fusion Thyroid Cancer

Marcia S. Brose¹, Catherine M. Albert², Steven G Waguespack³, Maria E. Cabanillas³, Patrick C. Ma⁴, Davendra Sohal⁵, Michael C. Cox⁶, Nora C. Ku⁶, and Lori J. Wirth⁷

¹ Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA;
² Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA;
³ University of Texas MD Anderson Cancer Center, Houston, TX, USA;
⁴ West Virginia University Cancer Institute, West Virginia University, Morgantown, WV, USA;
⁵ Cleveland Clinic, Cleveland, OH, USA;
⁶ Loxo Oncology Inc., South San Francisco, CA, USA;
⁷ Massachusetts General Hospital, Boston, MA, USA
Patient and Disease Characteristics in the Thyroid cancer Subset

<table>
<thead>
<tr>
<th>Characteristic</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) years</td>
<td>57 (15-75)</td>
</tr>
<tr>
<td>Gender female: male, n</td>
<td>3:4</td>
</tr>
<tr>
<td>Histology type, n</td>
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</tr>
<tr>
<td>Papillary</td>
<td>5</td>
</tr>
<tr>
<td>Follicular</td>
<td>1</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>1</td>
</tr>
<tr>
<td>Fusions, n</td>
<td></td>
</tr>
<tr>
<td>TPM3-NTRK1</td>
<td>1</td>
</tr>
<tr>
<td>PPL-NTRK1</td>
<td>1</td>
</tr>
<tr>
<td>IRF2BP2-NTRK1</td>
<td>1</td>
</tr>
<tr>
<td>ETV6-NTRK3</td>
<td>4</td>
</tr>
<tr>
<td>Prior therapies</td>
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</tr>
<tr>
<td>Thyroidectomy</td>
<td>7</td>
</tr>
<tr>
<td>Systemic treatment</td>
<td>5</td>
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<td>I-131</td>
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</table>
# Efficacy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gene fusion</th>
<th>Histology</th>
<th>Measurable disease</th>
<th>Best response</th>
<th>DOT (months)</th>
<th>DOR (months)</th>
<th>Ongoing treatment</th>
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</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>33</td>
<td>ETV6-NTRK3</td>
<td>Papillary</td>
<td>Yes</td>
<td>PR</td>
<td>&gt;28.7</td>
<td>&gt;27.0</td>
<td>Yes</td>
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<td>Patient 2</td>
<td>15</td>
<td>TPM3-NTRK1</td>
<td>Papillary</td>
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<td>-</td>
<td>&gt;16.6</td>
<td>-</td>
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<tr>
<td>Patient 3</td>
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<td>ETV6-NTRK3</td>
<td>Papillary</td>
<td>No</td>
<td>-</td>
<td>&gt;15.7</td>
<td>-</td>
<td>Yes</td>
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<tr>
<td>Patient 4</td>
<td>75</td>
<td>ETV6-NTRK3</td>
<td>Papillary</td>
<td>Yes</td>
<td>PR</td>
<td>&gt;14.7</td>
<td>&gt;8.3</td>
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<tr>
<td>Patient 5</td>
<td>65</td>
<td>PPL-NTRK1</td>
<td>Papillary</td>
<td>Yes</td>
<td>CR</td>
<td>&gt;13.8</td>
<td>&gt;12.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 6</td>
<td>63</td>
<td>ETV6-NTRK3</td>
<td>Follicular</td>
<td>Yes</td>
<td>PR</td>
<td>&gt;12.9</td>
<td>&gt;9.3</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 7</td>
<td>57</td>
<td>IRF2BP2-NTRK1</td>
<td>Anaplastic</td>
<td>Yes</td>
<td>PR</td>
<td>7.7</td>
<td>3.7</td>
<td>No</td>
</tr>
</tbody>
</table>

Based on IRC assessment of February 19, 2018
Efficacy

* Does not include 2 patients with non-measureable disease

Brose MC, et al. ATA 2018
Duration of Response

- Patient 1: Papillary, first response
- Patient 2: Papillary, first response
- Patient 3: Papillary, first response
- Patient 4: Papillary, first response
- Patient 5: Papillary, first response
- Patient 6: Follicular, first response
- Patient 7: Anaplastic, progression

Data cutoff: February 19, 2018

Brose MC, et al. ATA 2018
CONCLUSION

- TRK fusions can occur with any of the NTRK genes in a wide variety of cancers
- TRK inhibition with larotrectinib yields high response rates in TRK fusion cancer, including those that are heavily pre-treated
- Responses with larotrectinib therapy are generally durable and clinically meaningful
- Prolonged larotrectinib therapy is associated with minimal toxicity
- Molecular tumor profiling with assays capable of identifying TRK fusions, ideally to identify NTRK gene fusions at DNA or RNA level should be strongly considered when determining systemic treatment options, especially in the setting of metastatic disease, and in the absence of known activating mutations
THANK YOU FOR YOUR ATTENTION

ulrik.lassen@regionh.dk

Department of Oncology
Rigshospitalet, Copenhagen, Denmark