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

Larotrectinib: Clinical Data

Ulrik Lassen, Professor, MD, PHD. Rigshospitalet, Copenhagen, Denmark

Barcelona, 21-22 October 2019
DISCLOSURE OF INTEREST

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

- Larotrectinib is a highly potent small-molecule inhibitor of TRKA, TRKB, and TRKC (5–11 nM IC$_{50}$ in cellular assays)
- Demonstrated activity in CNS disease$^1$
- Liquid formulation allows dosing of children as young as at birth and delivers equivalent pharmacokinetics to capsules

Integrated dataset: Larotrectinib is efficacious regardless of age

Integrated\(^\ddagger\) (n=109)

<table>
<thead>
<tr>
<th>Best response(^\ddagger)</th>
<th>Adult patients</th>
<th>Pediatric patients(^\ddagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>63%</td>
<td>93.2% (95% CI: 72–88%)</td>
</tr>
<tr>
<td>CR</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

\(^\ddagger\)Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment

\(^\ddagger\)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

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

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Abstract 3122 presented at ASCO 2019
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

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

122 patients with TRK fusion cancer

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
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 \textit{NTRK1} (40%) or \textit{NTRK3} (57%).

*One patient had cancer of unknown primary origin.
GIST, gastrointestinal stromal tumor;
\textit{NTRK}, neurotrophic tyrosine receptor kinase;
TRK, tropomyosin receptor kinase.
## Patient Characteristic

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

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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

• 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

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

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.

Data cut-off: July 30, 2018

van Tilburg CM, et al. ASCO 2019; abstract 10010
# 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>
</tr>
<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%
- Thyroid: 5%
- Melanoma: 3%
- Congenital mesoblastic nephroma: 3%

NTRK fusion partners

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

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.

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.
Durability of response with larotrectinib in adult and paediatric patients with TRK fusion cancer

David M. Hyman,1 Cornelis M. van Tilburg,2 Catherine M. Albert,3 Daniel S.W. Tan,4 Birgit Geoerger,5 Anna F. Farago,6 Theodore W. Laetsch,7 Shivaani Kummar,8 François Doz,9 Ulrik Lassen,10 Steven G. DuBois,11 Ray McDermott,12 Leo Mascarenhas,13 Jordan Berlin,14 Erin R. Rudzinski,15 Michael C. Cox,16 Shivani Nanda,17 Barrett H. Childs,17 Alexander Drilon,1 David S. Hong18

1. Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA. 2. Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany. 3. Seattle Children's Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. 4. National Cancer Center, Singapore. 5. Gustave Roussy Cancer Center, Université Paris-Sud, Université Paris-Saclay, Villejuif, France. 6. Massachusetts General Hospital Cancer Center, Boston, MA, USA. 7. University of Texas, Southwestern Medical Center/Children's Health, Dallas, TX, USA. 8. Stanford Cancer Institute, Stanford University, Palo Alto, CA, USA. 9. Institut Curie, SIREDO Oncology Center (Care, Innovation and research for children and AYA with cancer), Paris Descartes University, Paris, France. 10. Rigshospitalet, Copenhagen, Denmark. 11. Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA. 12. St. Vincent's University Hospital and Cancer Trials Ireland, Dublin, Ireland. 13. Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA. 14. Vanderbilt University, Nashville, TN, USA 15. Seattle Children’s Hospital and University of Washington Medical Center, Seattle, WA, USA. 16. Loxo Oncology, Inc., South San Francisco, CA, USA. 17. Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ, USA. 18. The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Presented at the European Society for Medical Oncology Congress
September 27–October 1, 2019, Barcelona, Spain
Patients with TRK fusion cancer: Available dataset

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

**SCOUT: paediatric phase I/II**
- Age ≤21 years
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**NAVIGATE: adult/adolescent phase II ‘basket’ trial**
- Age ≥12 years
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- TRK fusion cancer

<table>
<thead>
<tr>
<th>Primary</th>
<th>Supplementary</th>
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<tbody>
<tr>
<td>n=8</td>
<td>n=4</td>
</tr>
<tr>
<td>n=12</td>
<td>n=38</td>
</tr>
<tr>
<td>n=35</td>
<td>n=62</td>
</tr>
<tr>
<td>n=55</td>
<td>n=104</td>
</tr>
</tbody>
</table>

159 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 lorotrectinib, administered predominantly at 100 mg BID continuously
  - Treatment beyond progression permitted if patient continuing to benefit

Data cut-off: 19 February 2019

BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; RECIST, Response Evaluation Criteria In Solid Tumors; TRK, tropomyosin receptor kinase.

Hyman DM, et al. ESMO 2019