MEETING SUMMARY
CTOS 2019, Tokyo, Japan

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SARCOMA UPDATE
NOVEMBER 2019
Please note: The views expressed within this presentation are the personal opinion of the author. They do not necessarily represent the views of the author’s academic institution or the rest of the SARCOMA CONNECT group.

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TOP 3 HIGH-IMPACT SARCOMA PRESENTATIONS AT CTOS 2019
ENTRECTINIB IN NTRK FUSION-POSITIVE SARCOMA: INTEGRATED ANALYSIS OF PATIENTS ENROLLED IN STARTRK-2, STARTRK-1 AND ALKA-372-001

Liu SV, et al. CTOS 2019 Abstract #3255999
Neutrotrophic receptor tyrosine kinase (NTRK) gene fusions in NTRK1, NTRK2, and NTRK3 act as oncogenic drivers and potential therapeutic targets across a broad range of tumour types, including sarcomas.

Entrectinib is a CNS-active, potent inhibitor of all TRK proteins (TRK A/B/C) as well as ROS1 and ALK.

This presentation reports integrated efficacy data from 3 trials of entrectinib focusing on patients with sarcoma and safety from the integrated safety population.

ALK, anaplastic lymphoma kinase; CNS, central nervous system; NTRK, neurotrophic tyrosine receptor kinase; TRK, tyrosine receptor kinase

Liu SV, et al. CTOS 2019 Abstract #3255999
ENTRECTINIB IN NTRK FUSION POSITIVE SARCOMA
INTEGRATED ANALYSIS DESIGN

**Efficacy population***
Adult patients with NTRK fusion-positive, TRK inhibitor-naïve solid tumours \( N=54 \)

- **Phase I** (ALKA-372-001)
  - Phase I dose-escalation study
  - \( NTRK \) fusion-positive patient
  - \( n=1 \)

- **Phase I** (STARTRK-1)
  - Phase I dose-escalation study
  - \( NTRK \) fusion-positive patients
  - \( n=2 \)

- **Phase II** (STARTRK-2)
  - Phase II, multicentre, global basket study
  - Entrectinib 600mg once daily, 28-day cycle
  - \( NTRK \) fusion-positive patients
  - \( n=51 \)

**Safety populations**

- \( NTRK \) fusion-positive patients receiving entrectinib \( n=68 \)
- Patients receiving entrectinib (all tumour types and gene rearrangements) \( N=355^\dagger \)

**Primary endpoints (BICR)**
- ORR
- DoR

**Secondary endpoints (BICR)**
- PFS and OS
- Intracranial ORR and DoR
- Safety and tolerability

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*Patients with at least 6 months of follow-up

†All patients from ALKA-372-001, STARTRK-1, STARTRK-2 and STARTRK-NG (regardless of tumour type or gene rearrangement) who received ≥ 1 entrectinib dose

§Patients with measurable and non-measurable CNS lesions at baseline

BICR, Blinded independent central review; CNS, central nervous system; DoR, duration of response; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, overall survival; PFS, progression free survival; TRK, tyrosine receptor kinase

**ENTRETRACTINIB IN NTRK FUSION POSITIVE SARCOMA**

**PATIENT POPULATION**

<table>
<thead>
<tr>
<th>Patients with NTRK-fusion positive sarcomas*</th>
<th>N = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with NTRK1 gene fusions</td>
<td>53.8%</td>
</tr>
<tr>
<td>Patients with NTRK3 gene fusions</td>
<td>46.2%</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>53 (21-81)</td>
</tr>
<tr>
<td>Patients with ≥ 2 prior systemic therapies</td>
<td>46.2%</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>61.5%</td>
</tr>
<tr>
<td>1</td>
<td>38.5%</td>
</tr>
<tr>
<td>CNS metastases at baseline</td>
<td>0</td>
</tr>
</tbody>
</table>

*Six subtypes of STS were identified: cervical adenosarcoma, dedifferentiated chondrosarcoma, endometrial stromal sarcoma, follicular dendritic cell sarcoma, gastrointestinal stromal tumour, malignant peripheral nerve sheath tumour*

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NTRK, neurotrophic tyrosine receptor kinase; STS, soft tissue sarcoma

Liu SV, et al. CTOS 2019 Abstract #3255999
Median treatment duration was 4.6 months

<table>
<thead>
<tr>
<th>Response by BICR using RECIST v1.1</th>
<th>N = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (ORR)*, % (95% CI)</td>
<td>46.2 (19.22-74.87)</td>
</tr>
<tr>
<td>Partial response, N (%)</td>
<td>6 (46.2)</td>
</tr>
<tr>
<td>Stable disease, N (%)</td>
<td>4 (30.8)</td>
</tr>
<tr>
<td>Progressive disease, N (%)</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Median duration of response, months (95%CI)</td>
<td>10.3 (4.6-15.0)</td>
</tr>
<tr>
<td>Median progression free survival, months (95%CI)</td>
<td>11.0 (6.5-15.7)</td>
</tr>
<tr>
<td>Median overall survival, months (95%CI)</td>
<td>16.8 (10.6-20.9)</td>
</tr>
</tbody>
</table>

*2 patients had missing/unevaluable data

BICR, blinded independent central review; CI, confidence interval; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate
Liu SV, et al. CTOS 2019 Abstract #3255999
ENTRECTINIB IN NTRK FUSION POSITIVE SARCOMA

SAFETY RESULTS

• Treatment-related AEs lead to:-
  – Dose reduction: 27.3% of patients
  – Dose interruption: 25.4% of patients
  – Treatment discontinuation: 3.9% of patients

<table>
<thead>
<tr>
<th>Treatment-related adverse events, %</th>
<th>Safety population† N = 355</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>60.5</td>
</tr>
<tr>
<td>Grade 3</td>
<td>27.6</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3.4</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0</td>
</tr>
</tbody>
</table>

Most frequently reported TRAEs

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Dysgeusia</td>
<td>41.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>23.7</td>
</tr>
</tbody>
</table>

†All patients from ALKA-372-001, STARTRK-1, STARTRK-2 and STARTRK-NG (regardless of tumour type or gene rearrangement) who received ≥ 1 entrectinib dose

AEs, adverse events; NTRK, neurotrophic tyrosine receptor kinase; TRAEs, treatment-related adverse events

Liu SV, et al. CTOS 2019 Abstract #3255999
In this integrated analysis of global multicentre clinical trials, entrectinib was well tolerated and induced clinically meaningful, durable response in patients with NTRK-fusion positive sarcomas.
LAROTRECTINIB EFFICACY AND SAFETY IN PATIENTS WITH TRK FUSION SARCOMAS

Demetri GD et al. CTOS 2019 Abstract #3254588
LAROTREXCTINIB FOR TRK FUSION SARCOMA

BACKGROUND

• **NTRK** gene fusions are rare oncogenic drivers in a diverse range of tumour types, including sarcomas, but are nearly pathognomonic in infantile fibrosarcoma

• **Larotrectinib** is a highly selective TRK inhibitor with robust activity and is well tolerated in children and adults with TRK fusion cancer, irrespective of tumour type

• This presentation reports updated efficacy and safety data for larotrectinib in patients with TRK fusion sarcomas

NTRK, neurotrophic tyrosine receptor kinase; TRK, tyrosine receptor kinase

Demetri GD, et al. CTOS 2019 Abstract #3254588
LAROTREXCTINIB FOR TRK FUSION SARCOMA

POOLED ANALYSIS

**NCT02122913**: Phase 1 dose escalation study in adults with advanced solid tumours

**SCOUT: NCT02637687**: Phase 1/2 dose escalation study in paediatric patients with advanced solid tumours

**NAVIGATE: NCT02576431**: Phase 2, open-label, basket study in adults/adolescents with NTRK-fusion positive solid Tumors

69 patients with TRK fusion sarcoma

**Primary endpoint**
Best objective response rate (ORR) according to RECIST v1.1 as assessed by independent radiology review committee

**Secondary endpoints:**
Overall response rate (investigator assessment)
Duration of response
Progression-free survival
Safety

**Dosing:**
Larotrectinib 100mg BID predominantly*

*one patient in phase I trial received 150 mg BID and most paediatric patients received 100 mg/m² BID

Data cut-off: 19 February 2019

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BID, twice a day; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumours; TRK, tyrosine receptor kinase

### LAROTREXTOINIB FOR TRK FUSION SARCOMA - PATIENT POPULATION

<table>
<thead>
<tr>
<th>Patients with TRK fusion sarcoma treated with larotrectinib</th>
<th>n = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sarcoma type, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>GIST</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Infantile fibrosarcoma</td>
<td>29 (42)</td>
</tr>
<tr>
<td>Other STS*</td>
<td>36 (52)</td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>5.2 (0.1-61.0)</td>
</tr>
<tr>
<td><strong>Paediatric (&lt;18 years), n (%)</strong></td>
<td>48 (70)</td>
</tr>
<tr>
<td><strong>NTRK gene fusion, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>NTRK1</td>
<td>24 (35)</td>
</tr>
<tr>
<td>NTRK2</td>
<td>2 (3)</td>
</tr>
<tr>
<td>NTRK3</td>
<td>42 (61)</td>
</tr>
<tr>
<td>Unconfirmed</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Previous treatment†, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>42 (61)</td>
</tr>
<tr>
<td>Prior systemic therapy</td>
<td>50 (72)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Treatment naive</td>
<td>9 (13)</td>
</tr>
</tbody>
</table>

*Including: spindle cell, inflammatory myofibroblastic tumour, malignant peripheral nerve sheath tumour, myopericytoma, epithelioid spindle, stromal tumour, synovial, lipofibromatosis, infantile myofibromatosis, adult fibrosarcoma, and not otherwise specified; †patients may have received more than one prior therapy

GIST, gastrointestinal stromal tumour; NTRK, neurotrophic tyrosine receptor kinase; STS, soft tissue sarcoma

Demetri GD, et al. CTOS 2019 Abstract #3254588
LAROTRECTINIB FOR TRK FUSION SARCOMA

RESULTS

<table>
<thead>
<tr>
<th>Response according to investigator assessment</th>
<th>n = 68 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall response rate</strong></td>
<td>60 (88)</td>
</tr>
<tr>
<td>Paediatric patients (&lt; 18 years) (n=47)</td>
<td>44 (94)</td>
</tr>
<tr>
<td>Adults (≥ 18 years) (n=21)</td>
<td>16 (76)</td>
</tr>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response*</td>
<td>16 (24)</td>
</tr>
<tr>
<td>Partial response†</td>
<td>44 (65)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

- Median duration of response not reached (range 1.6+ to 44.2+ months) with a median follow up of 15.6 months
- Treatment duration ranged from 0.1 to 47.2+ months, 68% (n=47) of patients still receiving treatment at data cut-off
- Adverse events mostly grade 1-2

*2 patients pending confirmation and 3 patients with pathologic complete response; †7 patients pending confirmation

RECIST, Response Evaluation Criteria in Solid Tumours
Demetri GD, et al. CTOS 2019 Abstract #3254588
LAROTRECTINIB FOR TRK FUSION SARCOMA

CONCLUSIONS

• Larotrectinib treatment resulted in robust and durable responses in both adult and paediatric patients with TRK fusion sarcomas, regardless of histology

• A favourable safety profile was observed with larotrectinib

• To determine the biology of the more favourable response observed in paediatric patients compared with adult patients, further investigation is warranted

• These data support the clinical importance of identifying NTRK gene fusions in patients with sarcomas

TRK, tyrosine receptor kinase
Demetri GD, et al. CTOS 2019 Abstract #3254588
THE RADIO-ENHANCER HAFNIUM OXIDE NANOPARTICLE, NBTXR3 ACTIVATED BY RADIATION THERAPY IN PATIENTS WITH LOCALLY ADVANCED SOFT TISSUE SARCOMA: A PHASE 2/3 TRIAL

Bonvalot S, et al. CTOS 2019 Abstract #3250148
NBTXR3 ACTIVATED BY RADIATION THERAPY

BACKGROUND

• NBTXR3 (hafnium oxide nanoparticles) is a first in class radio-enhancer

• NBTXR3 augments the effective radiotherapy (RT) dose deposited within tumour cells when activated by ionising radiation to increase cancer cell death compared to RT alone

• This presentation reports on the preoperative efficacy and safety of NBTXR3 activated by RT in patients with locally advanced soft tissue sarcoma (STS) in the extremity and trunk wall

RT, radiotherapy; STS, soft tissue sarcoma
Bonvalot S, et al. CTOS 2019 Abstract #3250148
**NBTXR3 ACTIVATED BY RADIATION THERAPY**

**STUDY DESIGN**

**Soft tissue sarcoma (STS) of the extremity or trunk wall**
- Age ≥18 years old
- Locally advanced STS, newly diagnosed or relapsed tumour
- High-risk tumour
- Unresectable tumour or unfeasible carcinologic resection
- WHO score of 0 to 2

**Primary endpoint:**
- pCRR# following EORTC guidelines

**Secondary endpoints:**
- Safety
- Carcinologic resection (surgical margin, R0, ...)
- pR
- Limb amputation rate

**Arm A**
NBTXR3* activated by EBRT**

**Arm B**
EBRT** alone

N=180†

1:1

14 patients excluded from the ITT full analysis set: 3 did not have STS (2 in Arm A, 1 in Arm B), 1 (in Arm A) was not eligible for preoperative RT

*IT injection of a dose, 10% of baseline tumour volume

**50Gy, 25 fractions x 2 Gy, over 5 weeks

#Pathological response evaluated by an independent central pathological review board

EBRT, external beam radiotherapy; EORTC, European Organisation for Research and Treatment of Cancer; IT, intratumoural injection; ITT, intention-to-treat; pCRR, pathological complete response rate; pR, pathological response; R0, negative surgical margin; RT, radiotherapy; STS, soft tissue sarcoma; WHO, World Health Organisation

Bonvalot S, et al. CTOS 2019 Abstract #3250148; Bonvalot S, et al. ESMO 2018 Abstract #LBA66 (oral presentation)
Efficacy Results, N (%) | Arm A NBTXR3 activated by RT N=87 | Arm B RT alone N=89 | P-value
---|---|---|---
pCRR | 14 (16.1) | 7 (7.9) | 0.044
R0 resection rate | 67 (77.0) | 57 (64.0) | 0.042

Safety Results, N (%) | Arm A NBTXR3 activated by RT N=89 | Arm B RT alone N=90
---|---|---
Most common grade 3-4 TEAE
Post operative wound complication | 8 | 8

Most common grade 3-4 TRAE
Skin injury | 5 (5.6) | 4 (4.4)
Serious adverse events | 35 (39.3) | 27 (30.0)

AEs related to NBTXR3
Injection site pain | 4 (4.5) | NA
Hypotension | 4 (4.4) | NA

pCRR, pathological complete response rate; R0, negative surgical margin; RT, radiotherapy; TEAE, treatment-emergent adverse events; TRAE, treatment-related adverse events
Bonvalot S, et al. CTOS 2019 Abstract #3250148
This registration trial of NBTXR3 combined with EBRT improved pCCR and increased R0 resection compared to EBRT alone

NBTXR3 combined with EBRT was well tolerated with a safety profile consistent with EBRT alone

EBRT, external beam radio therapy; pCRR, pathological complete response rate; R0, negative surgical margin
Bonvalot S, et al. CTOS 2019 Abstract #3250148
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