Entrectinib in NTRK fusion-positive breast cancer: integrated analysis of patients enrolled in STARTTRK-2, STARTTRK-1 and ALKA-372-001

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1. NTRK gene family
2. NTRK2, NTRK3 lead to the expression of truncated receptors in the TRK (tyrosine kinase domain) proteins NTRK1, TRKA, and TRKB, respectively, with constitutively active kinase function
3. NTRK fusions act as oncogenic drivers, and are potential therapeutic targets across a broad range of tumor types including breast cancer
4. NTRK gene fusions occur in ~0.3% of solid tumors
5. Entrectinib is a novel small-molecule CNS active, and potent inhibition of TR Kang, AXL and ROSS1 designed to cross the blood-brain-barrier
6. In August 2019 the US Food and Drug Administration granted accelerated approval to entrectinib for the treatment of adults and pediatric patients (>12 years) with solid tumors that have an NTRK gene fusion

OBJECTIVES
● To present integrated efficacy data from three trials of entrectinib in NTRK fusion-positive solid tumors focusing on the cohort of patients with breast cancer.

METHODS
● Patients with locally advanced/metastatic NTRK fusion-positive solid tumors (with or without baseline CNS disease) were included by nuisance and board-diagnostic platforms were enrolled in three global phase 1/2 entrectinib trials at 150 sites in 15 countries:
- STARTRK-1 [NCT02097810]
- STARTRK-2 [NCT02568267]
- ALKA-372-001 [EudraCT 2012-000148-88]

● The data cut-off for this analysis was 31 May 2018.
● The efficacy evaluable population included adult patients with at least 6 months of follow-up.
● The safety evaluable population included all patients enrolled across clinical trials who had received at least 1 dose of entrectinib.

● Disease burden was assessed by blinded independent central review (BICR) using RECIST v1.1 after cycle 1 (8 weeks) then every 8 weeks.
● Primary endpoints were objective response rate (ORR) and duration of response (DOR) by BICR.
● Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety.

RESULTS
Patient populations
● The overall efficacy-evaluable population consisted of 54 adult patients with locally advanced or metastatic NTRK fusion-positive solid tumors, including 12 patients with breast cancer CNS disease.

Patient populations
● Ten different tumor types and >19 histopathologies were identified (Table 1).

Number of prior systemic therapies, n (%)
- 0 33 (61.1)
- 1 16 (29.6)
- 2 3 (5.6)

● The safety-evaluable population included 355 patients enrolled across clinical trials who had received at least 1 dose of entrectinib.

● Breast cancer patients were shown in Figure 1.

● The most frequently reported TRAEs were dysgeusia (41.4%), fatigue (27.9%), dizziness (25.4%) and constipation (23.7%)

CONCLUSIONS
● In this integrated analysis of global multicenter clinical trials, entrectinib induced clinically meaningful, durable responses in patients with NTRK fusion-positive tumors including breast cancer.

- BICR ORR
- 57.4% in patients with NTRK fusion-positive solid tumors
- 83.3% in patients with NTRK fusion-positive breast cancer

- Entrectinib was well tolerated, with a manageable safety profile; most TRAEs were managed with dose interruption/reduction and the discontinuation rate was low.

Table 1. Baseline characteristics
<table>
<thead>
<tr>
<th>Patients with NTRK fusion-positive breast cancer (N=54)</th>
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<tbody>
<tr>
<td>Female, n (%)</td>
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<tr>
<td>Median age, years (range)</td>
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<tr>
<td>Baseline CNS lesions present, n (%)</td>
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<tr>
<td>Number of prior systemic therapies, n (%)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>ECOG PS of 0 or 1</td>
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<td>Previous radiology to the brain, n (%)</td>
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<tr>
<td>Histological subtype</td>
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<td>Hereditary</td>
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Table 2. Efficacy and safety

<table>
<thead>
<tr>
<th>TRAE</th>
<th>Incidence %</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>27.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>25.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>23.7</td>
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Figure 1. Adult patients with NTRK fusion-positive solid tumors

Figure 2. NTRK fusion-positive breast cancer

Figure 3. Duration of response in patients with NTRK fusion-positive breast cancer

Figure 4. Individual responses by BICR in patients with NTRK fusion-positive breast cancer