#104

An updated analysis of the clinical efficacy and safety of entrectinib in *NTRK* fusion-positive sarcoma

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BACKGROUND

- Neurotrophic tyrosine receptor kinase (*NTRK1/2/3*) gene fusions lead to constitutively active tropomyosin receptor kinases (TRK) with oncogenic potential across a number of tumor types.[1,2]
- *NTRK* gene fusions occur at low frequencies in a range of common cancers, including <1% of patients with sarcoma.[3]
- Entrectinib is a central nervous system (CNS)-active potent inhibitor of TRKA/B/C, ROS1 and ALK.[4,5]
- In an updated integrated analysis (data cut-off: 31 Oct 2018) of three multicenter, single-arm trials (ALKA-372-001 [EudraCT 2012-000148-88], STARTRK-1 [NCT02097810], and STARTRK-2 [NCT02568267]), entrectinib demonstrated strong and durable responses in a cohort of 74 patients with 12 solid tumor types harboring *NTRK* gene fusions:[6]
  - Confirmed objective response rate (ORR), 63.5% (n=47/74)
  - Median duration of response (DoR), 12.9 months (95% CI 9.3–not estimable [NE]); median progression-free survival (PFS), 11.2 months (95% CI 8.0–15.7); median overall survival (OS), 23.9 months (95% CI 16.0–NE)
  - Intracranial (IC) ORR, 50% (n=8/16); median IC DoR, 8.0 months (95% CI 6.7–NE); median PFS, 8.9 months (95% CI 5.9–14.3).
- Here we present an analysis focused on the *NTRK* fusion-positive sarcoma cohort.

METHODS

- Patients were aged ≥18 years with locally advanced/metastatic TRK inhibitor-naïve *NTRK* fusion-positive solid tumors, with or without baseline CNS metastases.
- Response was assessed by blinded independent central review (BICR) using RECIST v1.1, after cycle 1 (4 weeks) and every 8 weeks thereafter.
- Co-primary endpoints (by BICR) were confirmed ORR and DoR. Secondary endpoints included PFS by BICR, OS, and safety.

RESULTS

Patients

- Of the 18 patients with *NTRK* fusion-positive sarcoma who received entrectinib, 16 were evaluable for efficacy, of these:
  - 93.8% had an ECOG PS of 0 or 1
  - 75% had received ≥1 line of prior systemic therapy in the metastatic setting.
- Baseline characteristics are summarized in **Table 1**.

Table 1. Baseline characteristics

Characteristic	*NTRK* fusion-positive sarcoma (N=16)
Median age, years (range)	50.5 (21–81)
Male / Female, n (%)	8 (50.0) / 8 (50.0)
Race, n (%) Asian / White	2 (12.5) / 14 (87.5)
ECOG PS, n (%) 0 / 1 / 2	9 (56.3) / 6 (37.5) / 1 (6.3)
NTRK gene fusion, n (%) *NTRK1 / NTRK3*	9 (56.3) / 7 (43.8)
Previous therapy in any setting, n (%) Chemotherapy / targeted therapy / RT / brain RT	15 (93.8) 13 (81.3) / 4 (25.0) / 8 (50.0) / 1 (6.3)
CNS mets at baseline confirmed by BICR, n (%)	2 (12.5)
Prior lines of therapy in metastatic setting†, n (%) 0 / 1 / 2 / ≥3	4 (25.0) / 6 (37.5) / 4 (25.0) / 2 (12.5)
Histology, n (%)	
Angiosarcoma	1 (6.3)
Cervical adenosarcoma	1 (6.3)
Chondrosarcoma	1 (6.3)
Endometrial stromal sarcoma	1 (6.3)
Follicular dendritic cell sarcoma	1 (6.3)
MPNST	1 (6.3)
GIST	2 (12.5)
Spindle cell sarcoma	4 (25.0)
Undifferentiated pleomorphic sarcoma	1 (6.3)
Sarcoma, NOS*	3 (18.8)

*1 patient with sarcoma NOS and 2 patients with sarcoma NOS with carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements.
†Patients may have received (neo)adjuvant therapy that would not count as a line of therapy, and could have received >1 prior therapy; GIST, gastrointestinal stromal tumor; MPNST, malignant peripheral nerve sheath tumor; NOS, not otherwise specified; RT, radiotherapy

Overall efficacy in the *NTRK* fusion-positive sarcoma cohort

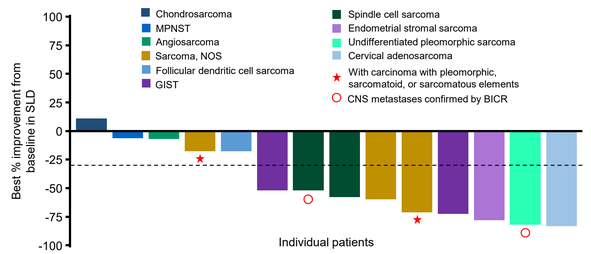
- After a median follow-up of 17.74 months (95% CI 9.95–22.57), the confirmed ORR was 56.3% (95% CI 29.9–80.3; **Table 2**).
- The majority of patients with sarcoma experienced a reduction in tumour lesion size, including those with CNS metastases at baseline (**Figure 1**).

Table 2. Overall efficacy by sarcoma tumor histology

Response	n (%)	Sarcoma tumor histology
BICR ORR	**9 (56.3)** (95% CI 29.9–80.3)	• Cervical adenosarcoma (1) • Endometrial stromal sarcoma (1) • GIST (2) • Spindle cell sarcoma (2) • Undifferentiated pleomorphic sarcoma (1) • Sarcoma, NOS (1) • Sarcoma, NOS with carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements (1)
PR	9 (56.3)	• As above
SD	4 (25.0)	• Angiosarcoma (1) • Follicular dendritic cell sarcoma (1) • MPNST (1) • Sarcoma, NOS with carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements (1)
PD	1 (6.3)	• Chondrosarcoma (1)
Missing/unevaluable	2 (12.5)	• Spindle cell sarcoma (2)

†PD, progressive disease; PR, partial response; SD, stable disease

Figure 1. Best change from baseline in tumor SLD per BICR in patients with *NTRK* fusion-positive sarcoma



Patients who were not evaluable, or those with missing SLD percent change were excluded from the plot. Patient with chondrosarcoma was recorded as PD due to progression in the lungs (non-target lesion); assessment of target lesions indicated SD. SLD, sum of longest diameter.

- In the 9 responders (all PR), median time to response was 0.95 months (95% CI 0.9–2.8; **Figure 2**) and median DoR was 9.3 months (95% CI 4.6–15.0).
- Median PFS was 10.1 months (95% CI 6.5–11.2; **Figure 3**), median OS was 16.8 months (95% CI 10.6–20.9; **Figure 4**).

Figure 2. Time on treatment and timing of events in patients with *NTRK* fusion-positive sarcoma

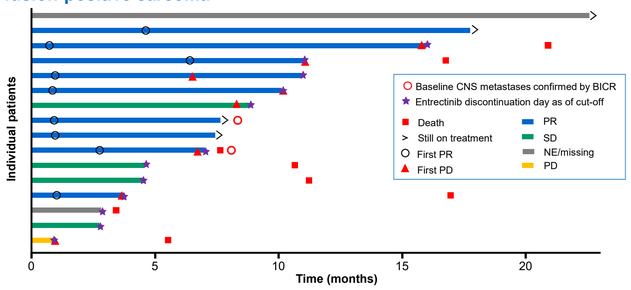


Figure 3. PFS per BICR in patients with *NTRK* fusion-positive sarcoma

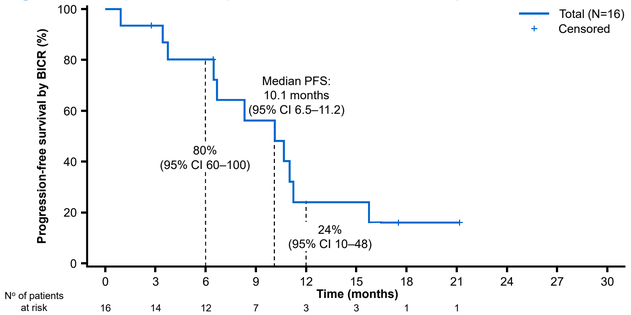
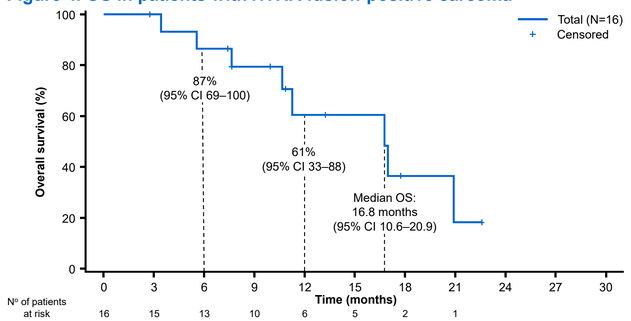


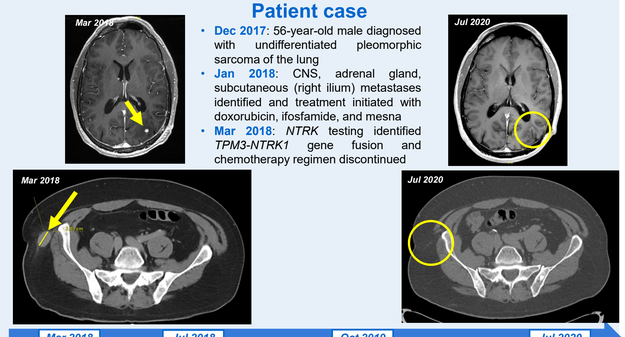
Figure 4. OS in patients with *NTRK* fusion-positive sarcoma



- Among 2 patients with baseline CNS metastases (confirmed by BICR):
  - 1 patient (undifferentiated pleomorphic sarcoma, received prior radiotherapy [RT] <2 months prior) had an overall PR and IC PR (IC DoR, 1.9 months)
  - 1 patient (spindle cell sarcoma, no prior RT) had an overall PR and IC non-complete response/non-PD (non-measurable CNS metastases).
- No patients in the sarcoma efficacy dataset (n=16), either with or without baseline CNS metastases, had a CNS progression event while on treatment.*

*As regular CNS scans in patients without baseline CNS metastases were not mandated by the protocol, CNS follow-up for patients in this subgroup was not comprehensive, but based on imaging elicited by symptomatic progression or routine CNS scans where customary. Patients with baseline CNS metastases underwent regular CNS scans.

Patient case



- **Dec 2017**: 56-year-old male diagnosed with undifferentiated pleomorphic sarcoma of the lung
- **Jan 2018**: CNS, adrenal gland, subcutaneous (right ilium) metastases identified and treatment initiated with doxorubicin, ifosfamide, and mesna
- **Mar 2018**: *NTRK* testing identified *TPM3-NTRK1* gene fusion and chemotherapy regimen discontinued

Safety

- The safety-evaluable *NTRK* fusion-positive sarcoma cohort comprised 18 patients, of whom 16 (88.9%) reported a TRAE; there were no grade 5 TRAEs
  - Most frequently reported TRAEs were dysgeusia (44.4%), dizziness (38.9%), fatigue (33.3%), peripheral edema (27.8%), and weight gain (27.8%)
  - Dose reductions, interruptions, and discontinuations due to TRAEs occurred in 22.2%, 16.7%, and 5.6% of patients, respectively
  - Dose intensity was maintained in the sarcoma cohort during the study, with a median of 1.5 missed doses and a median dose intensity of 97.0%.
- Safety findings in the sarcoma cohort are consistent with previous reports.[7]

CONCLUSIONS

Entrectinib continued to achieve clinically meaningful, durable responses, demonstrating overall efficacy in patients with *NTRK* fusion-positive sarcoma.

Strong and durable intracranial responses were induced, with a lack of scan-confirmed CNS progression or development of new lesions in patients with and without baseline CNS metastases.

Entrectinib was well tolerated, with a manageable safety profile.

Although *NTRK* fusion-positive sarcoma is rare the evidence demonstrates that entrectinib is an effective treatment option, supporting the value of screening patients with sarcoma for *NTRK* gene fusions.

SUMMARY

56.3%
ORR in *NTRK* fusion-positive sarcoma

12.5% baseline CNS mets

Responses seen in patients with/without baseline CNS mets

Rapid **onset** and long **duration** of response
Median TTR: **0.95 mos**
DoR: **9.3 mos**

16.8 months
Median OS

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Disclosures
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