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MEETING SUMMARY
CTOS 2019, Tokyo, Japan

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SARCOMA UPDATE
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DISCLAIMER

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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

ENTRECTINIB IN *NTRK* FUSION POSITIVE SARCOMA

BACKGROUND

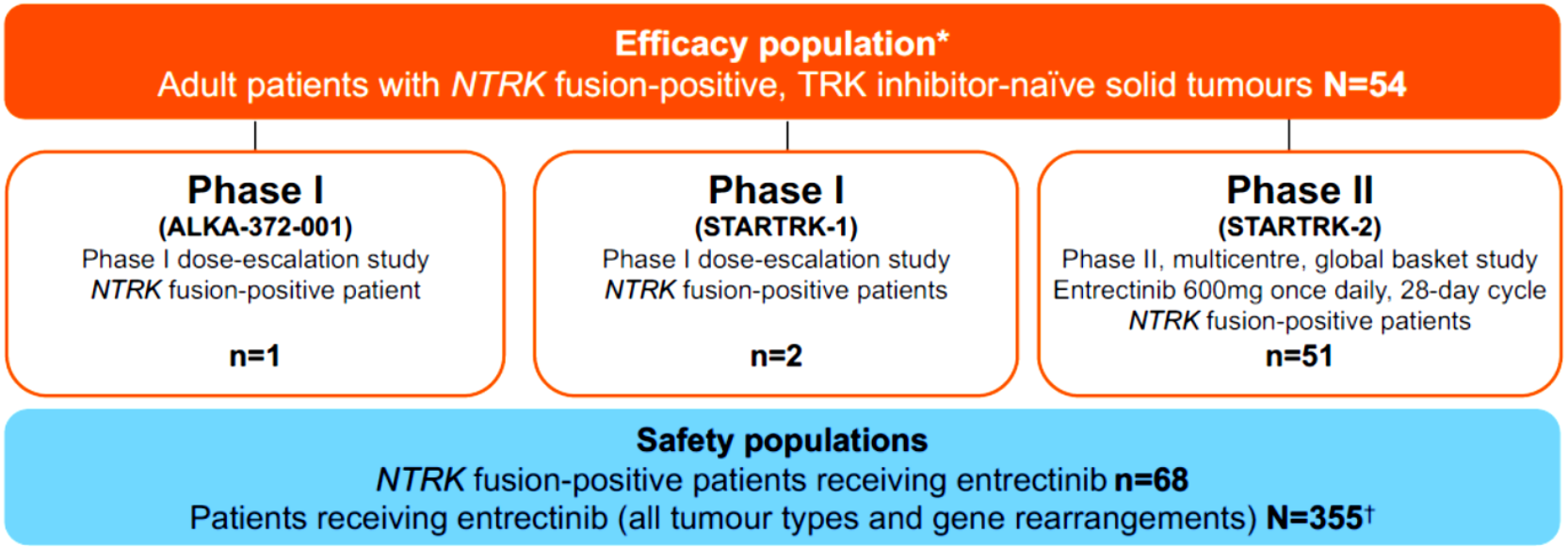
- Neutrotrophic receptor tyrosine kinase **(*NTRK*) gene fusions in *NTRK1*, *NTRK2*, and *NTRK3* act as oncogenic drivers and potential therapeutic targets** across a broad range of tumour types, including sarcomas
- **Entrectinib** is a CNS-active, **potent inhibitor of all TRK proteins** (TRK A/B/C) as well as ROS1 and ALK
- This presentation **reports integrated efficacy data from 3 trials of entrectinib** focussing 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



Primary endpoints (BICR)
- ORR
- DoR

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

*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

Liu SV, et al. Oral presentation CTOS 2019. Abstract #3255999; https://www.oncnet.com/sites/oncnet.com/files/2019-07/O-024-Siena-MED.pdf: Accessed 25 Nov 2019

ENTRECTINIB IN *NTRK* FUSION POSITIVE SARCOMA

PATIENT POPULATION

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

*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

ENTRECTINIB IN *NTRK* FUSION POSITIVE SARCOMA

EFFICACY RESULTS

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- Median treatment duration was 4.6 months

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

*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

Treatment-related adverse events, %	Safety population† N = 355
Grade 1 or 2	60.5
Grade 3	27.6
Grade 4	3.4
Grade 5	0
Most frequently reported TRAEs	
Dysgeusia	41.4
Fatigue	27.9
Dizziness	25.4
Constipation	23.7

†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

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ENTRECTINIB IN *NTRK* FUSION POSITIVE SARCOMA

CONCLUSION

- 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**

NTRK, neurotrophic tyrosine receptor kinase

Liu SV, et al. CTOS 2019 Abstract #3255999

LAROTRECTINIB EFFICACY AND SAFETY IN PATIENTS WITH TRK FUSION SARCOMAS

Demetri GD et al. CTOS 2019 Abstract #3254588

LAROTRECTINIB 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

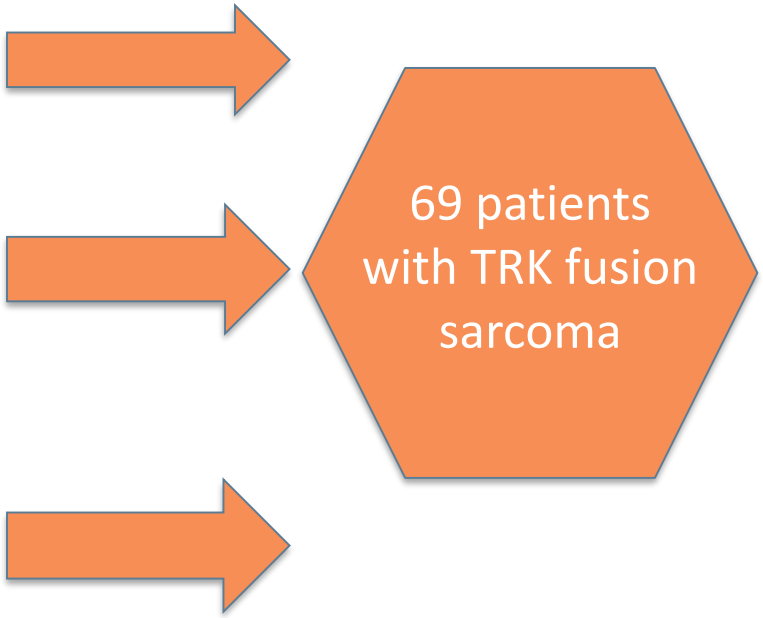
LAROTRECTINIB FOR TRK FUSION SARCOMA

POOLED ANALYSIS

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

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

NAVIGATE: NCT02576431: Phase 2, open-label, basket study in adults/adolescents with NTRK-fusion positive solid Tumors [3]



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*

Data cut-off: 19 February 2019[4]

*one patient in phase I trial received 150 mg BID and most paediatric patients received 100 mg/m^2 BID

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

1. Hong DS, et al. Ann Oncol 2019;30(2):325-31; 2. Laetsch TW, et al. Lancet Oncol 2018;19(5):705-14;
3. Drilon A, et al. N Engl J Med 2018;378(8):731-39; 4. Demetri GD, et al. CTOS 2019 Abstract #3254588

LAROTRECTINIB FOR TRK FUSION SARCOMA - PATIENT POPULATION

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

*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

Response according to investigator assessment RECIST v1.1	n = 68 n (%)
Overall response rate	60 (88)
Paediatric patients (< 18 years) (n=47)	44 (94)
Adults (≥ 18 years) (n=21)	16 (76)
Best overall response	
Complete response*	16 (24)
Partial response†	44 (65)
Stable disease	5 (7)
Progressive disease	2 (3)

- 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

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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

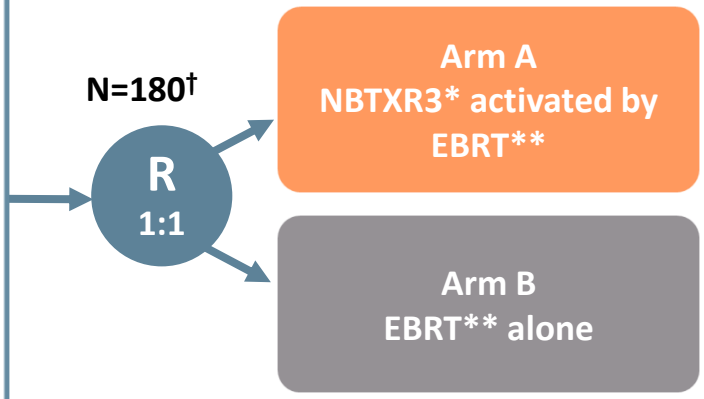
Bonvalot S, et al. CTOS 2019 Abstract #3250148

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

†4 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 radio therapy; 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)

NBTXR3 ACTIVATED BY RADIATION THERAPY

RESULTS

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

NBTXR3 ACTIVATED BY RADIATION THERAPY
CONCLUSION

- 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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