Entrectinib in *NTRK* Fusion-Positive Sarcoma: Integrated Analysis of Patients Enrolled in STARTRK-2, STARTRK-1 and ALKA-372-001

Stephen V Liu,[1] Luis Paz-Ares,[2] James Hu,[3] Jürgen Wolf,[4] Byung Chul Cho,[5] Maciej Krzakowski,[6] Christine H Chung,[7] Manish Patel,[8] Matthew Taylor,[9] Harald Zeuner,[10] Amine Aziez,[10] Xinhui Huang,[11] Stuart Osborne,[10] Anna Farago[12]

1. Georgetown University, Washington, DC, USA; 2. Hospital Universitario 12 de Octubre, Madrid, Spain; 3. University of Southern California/Norris Cancer Center, Los Angeles, CA, USA; 4. Center for Integrated Oncology, University Hospital of Cologne; 5. Yonsei Cancer Center, Seoul, Republic of Korea; 6. Maria Skłodowska-Curie Institute of Oncology, Warsaw, Poland; 7. Moffitt Cancer Center, Tampa, FL, USA; 8. University of Minnesota, Department of Medicine, Minneapolis, MN, USA; 9. Oregon Health & Science University, Portland, OR, USA; 10. F. Hoffmann-La Roche, Basel, Switzerland; 11. Genentech, San Francisco, CA, USA; 12. Massachusetts General Hospital, Boston, MA, USA

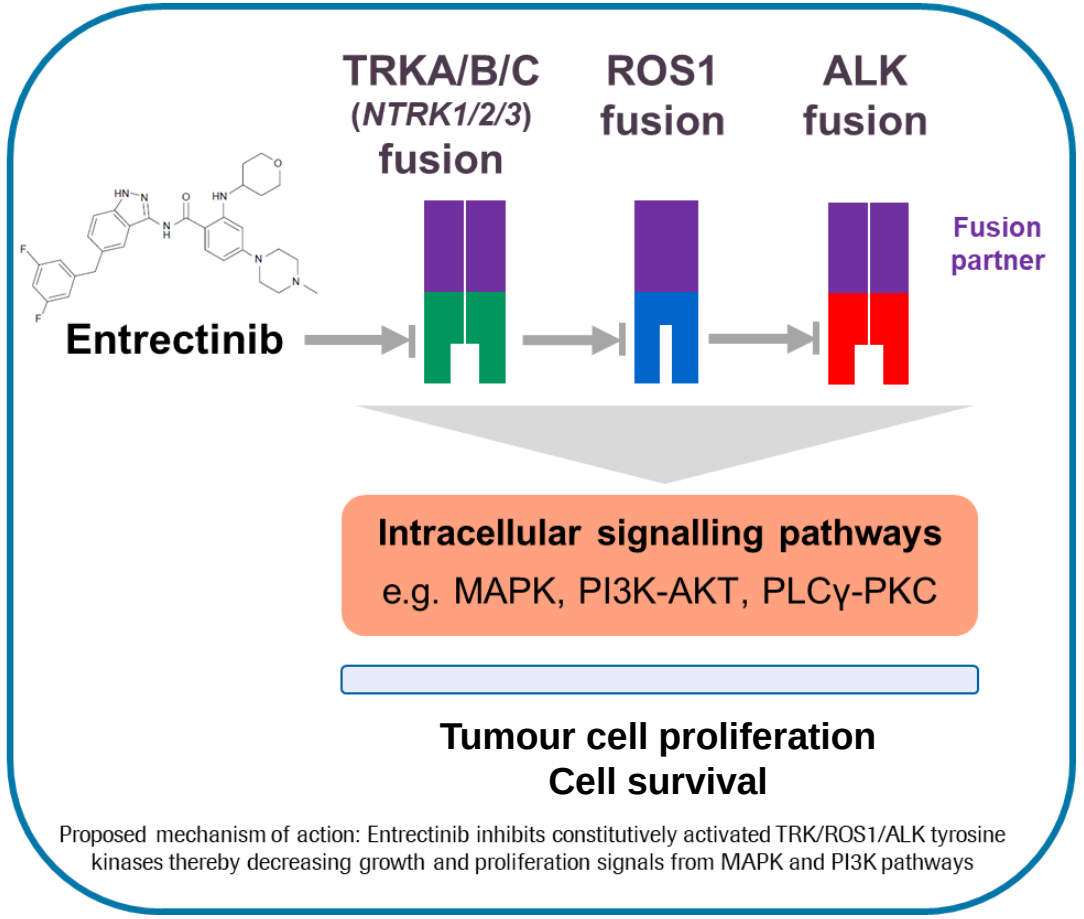
Disclosures

- Stephen Liu declares the following potential conflicts of interest
  - consulting fees from Apollomics, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, G1 Therapeutics, Genentech/Roche, Janssen, Lilly, MSD, Pfizer, Regeneron, Taiho, and Takeda
  - sponsored research agreements from AstraZeneca, Bayer, Blueprint, Bristol-Myers Squibb, Clovis, Corvus, Genentech/Roche, Lilly, Lycera, Merck, Molecular Partners, OncoMed, Pfizer, Rain Therapeutics, Spectrum, and Turning Point Therapeutics
  - the ALKA-372-001, STARTRK-1, STARTRK-2 and STARTRK-NG studies were funded by Ignyta/F. Hoffmann-La Roche Ltd (EudraCT 2012-000148-88; NCT02097810; NCT02568267; NCT02650401)

- Editorial assistance in the preparation of these slides was provided by Gardiner-Caldwell Communications, Macclesfield, UK and was funded by F. Hoffmann-La Roche

Background

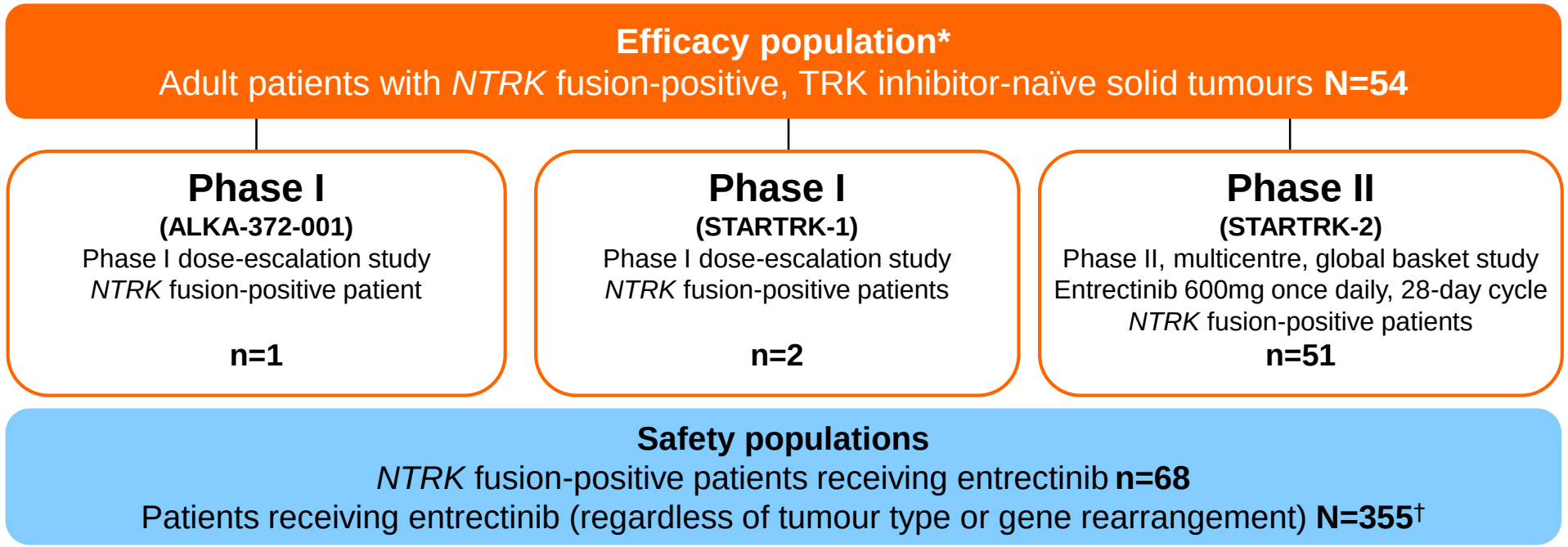
- Fusions in the ***NTRK1/2/3***, ***ROS1*** and ***ALK*** genes act as drivers of certain cancers[1–4]
- **Entrectinib** is an **oral, potent** and **selective** inhibitor of **TRK, ROS1 and ALK** tyrosine kinases, designed to **penetrate** and **remain in** the **CNS**
  - it is a weak P-glycoprotein substrate[5–7]
  - as such, entrectinib achieved **therapeutic levels in the CNS**[6,7]
- Clinical activity has been seen in adult and paediatric solid tumours with target gene fusions (*ROS1*+, *NTRK*+), even in patients with **brain metastases** or in **primary brain** tumours[8–11]
- Here, we report on the activity of **entrectinib in *NTRK* fusion-positive sarcomas** from an integrated analysis of three clinical studies



ALK, anaplastic lymphoma kinase; CNS, central nervous system; (N)TRK, (neurotrophic) tropomyosin receptor kinase

1. Amatu, et al. ESMO Open 2016; 2. Vaishnavi, et al. Cancer Discov 2014; 3. Lin, et al. J Thorac Oncol 2017
4. Le & Gerber. Semin Cancer Biol 2017; 5. Menichincheri, et al. J Med Chem 2016; 6. Ardini, et al. Mol Cancer Ther 2016
7. Fischer, et al. AAPS PharmSci 360 2019; 8. Doebele, et al. J Thorac Oncol 2018
9. Demetri, et al. Ann Oncol 2018; 10. Siena, et al. ASCO 2019; 11. Robinson, et al. ASCO 2019

Design of integrated analysis across phase I/II trials of entrectinib



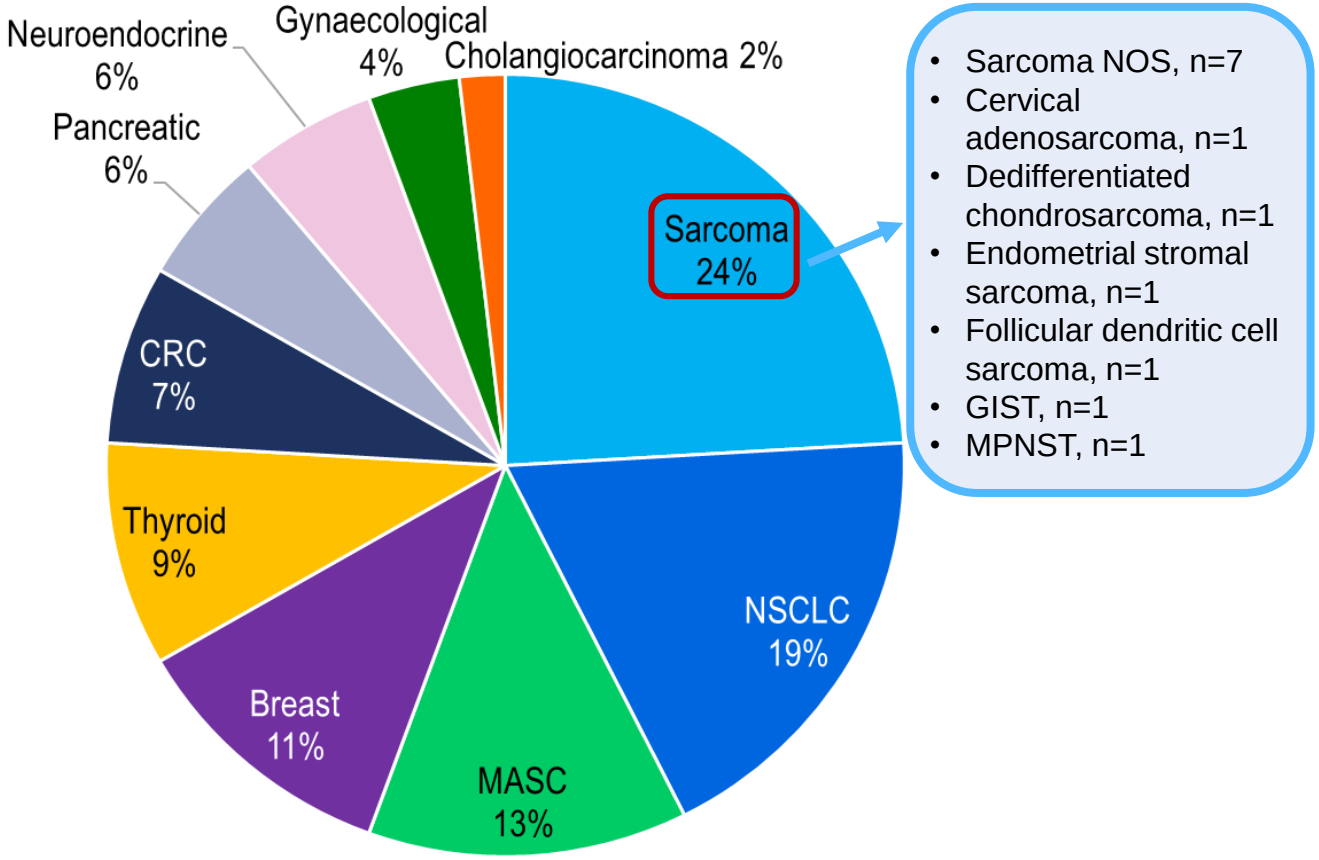
Primary endpoints (BICR)
- ORR
- DoR

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

Data cut-off: 31 May 2018
*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; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Baseline characteristics: adult patients with *NTRK* fusion-positive solid tumours

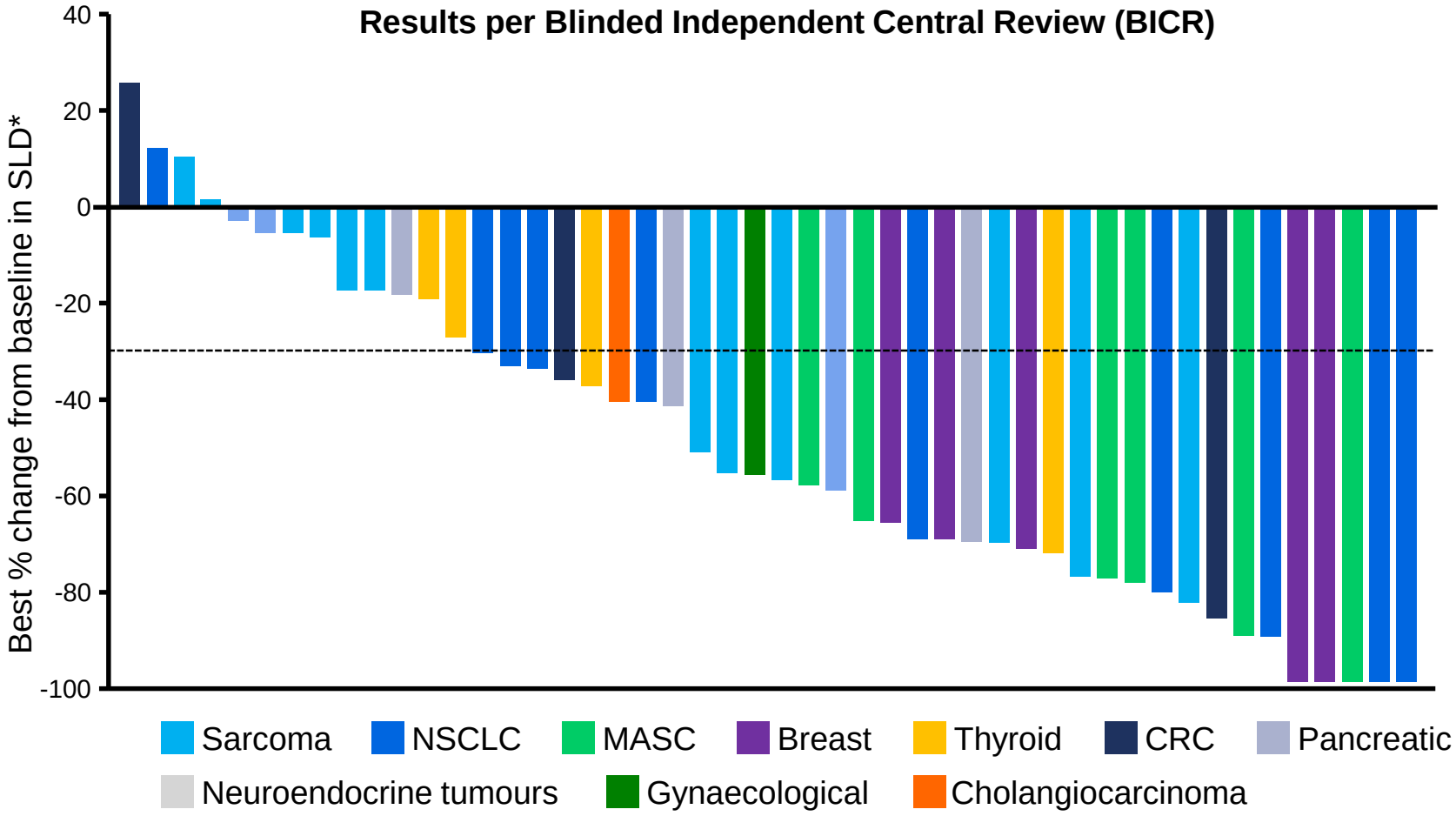
Baseline characteristics		*NTRK*+ All patients (n=54)[1]	*NTRK*+ sarcoma (n=13)*
Age, years	Range	21–83	21–81
Sex	Female Male	59% 41%	62% 38%
Race	White Asian	80% 13%	92% 8%
ECOG PS	0 1 2	43% 46% 11%	62% 38% 0
Prior lines of systemic therapy	0/1 ≥2	57% 43%	54% 46%
CNS metastases at baseline		22%	0



Data cut-off: 31 May 2018
*In patients with sarcomas, gene fusions were: *NTRK1*,7 patients (53.8%); *NTRK3*, 6 patients (46.2%)
CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GIST, gastrointestinal stromal tumour; MASC, mammary analogue secretory carcinoma; MPNST, malignant peripheral nerve sheath tumour; NOS, not otherwise specified; NSCLC, non-small cell lung cancer

1. Doebele, et al. Lancet Oncology 2019

Entrectinib activity in *NTRK* fusion-positive solid tumours: individual responses by tumour type



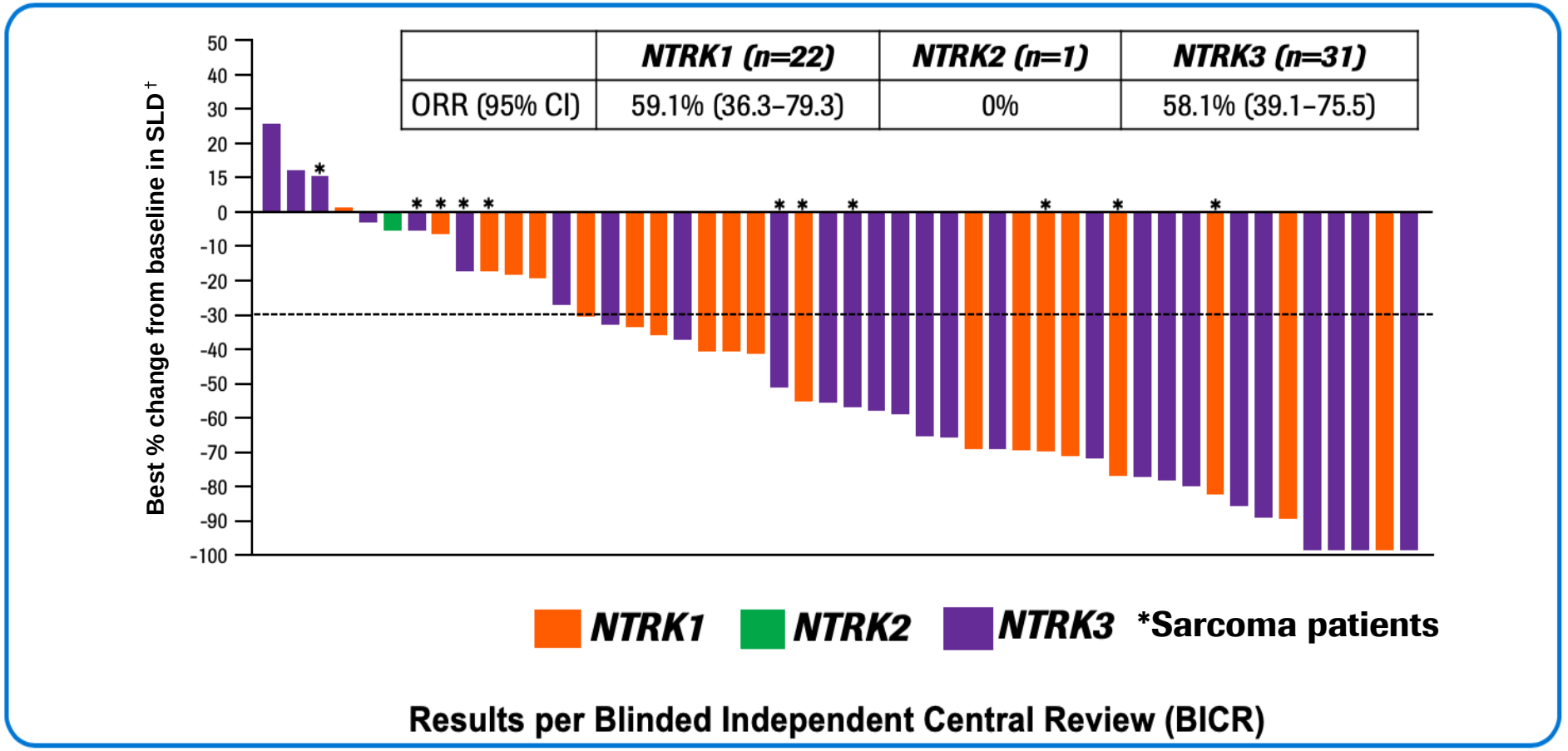
Efficacy outcomes by BICR	*NTRK*+ patients (n=54)
ORR,† % (95% CI)	**57.4 (43.2–70.8)**
CR, n (%)	4 (7.4)
Median DoR, mos (95% CI)	10.4 (7.1–NR)
Median PFS, mos (95% CI)	11.2 (8.0–14.9)
Median OS, mos (95% CI)	20.9 (14.9–NR)

NTRK+ patients with CNS metastases (n=11)	
Intracranial ORR, %	**54.5**
CR, %	27.3
Median intracranial PFS, mos	14.3

Data cut-off: 31 May 2018; patients (n=6) without matched pre/post therapy scans were excluded from the plot
*Best change at any single timepoint; †Confirmed responses only
CI, confidence interval; CR, complete response; NR, not reached; SLD, sum of the longest diameters

Doebele et al. Lancet Oncology 2019

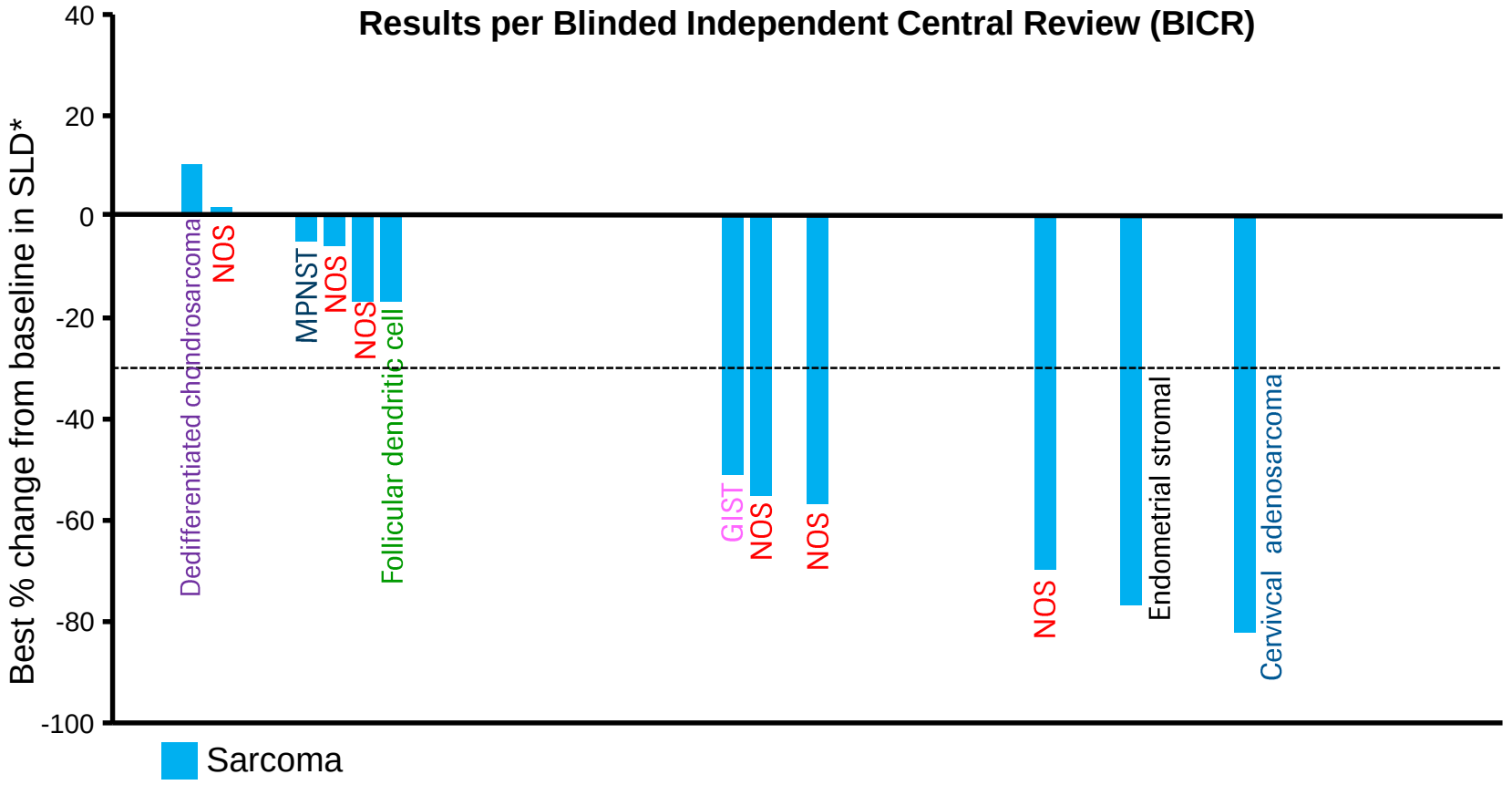
Entrectinib activity in *NTRK* fusion-positive sarcoma: regardless of specific *NTRK* gene (1, 2 or 3)



Data cut-off: 31 May 2018; patients (n=6) without matched pre/post therapy scans were excluded from the plot

†Best change at any single timepoint

Entrectinib activity in adult patients with *NTRK* fusion-positive sarcomas



Efficacy outcomes by BICR	*NTRK+* sarcoma patients (n=13)
ORR,† % (95% CI)	**46.2 (19.22–74.87)**
PR, n	6
SD, n	4
Disease progression, n	1
Missing/unevaluable,‡ n	2
Median DoR, mos (95% CI)	10.3 (4.6–15.0)
Median PFS, mos (95% CI)	11.0 (6.5–15.7)
Median OS, mos (95% CI)	16.8 (10.6–20.9)
Median treatment duration, mos	4.6

Data cut-off: 31 May 2018

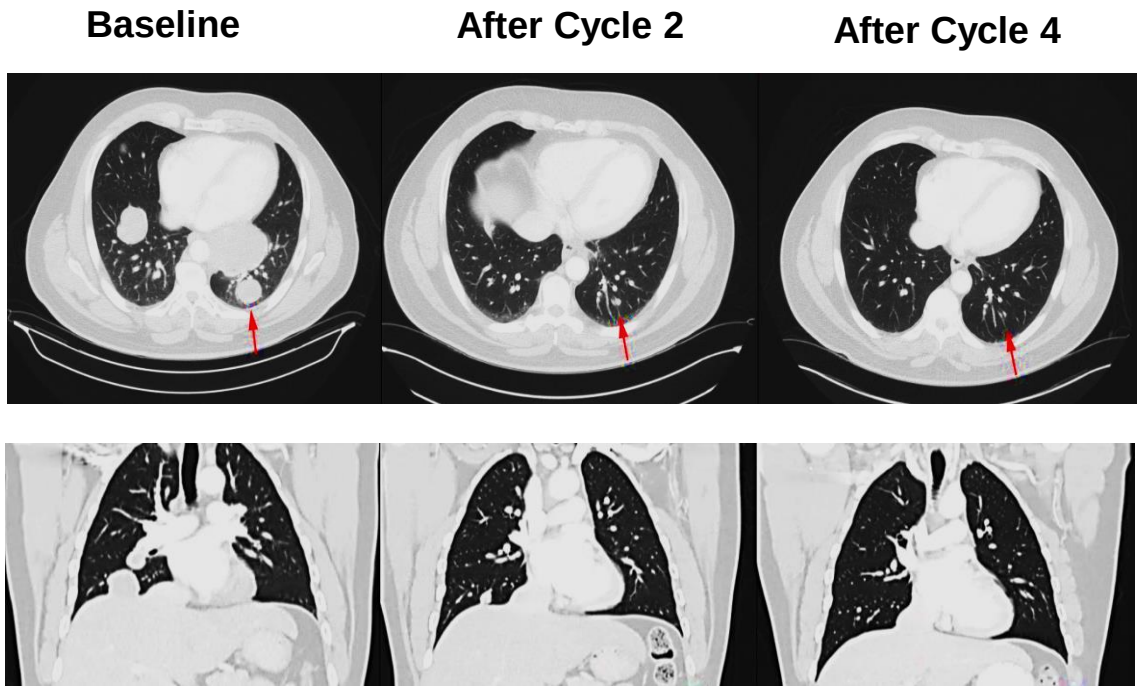
*Best change at any single timepoint; †Confirmed responses only; ‡Missing/unevaluable includes patients having on-study scans that could not be evaluated and patients who discontinued prior to obtaining adequate scans to evaluate or confirm response

GIST, gastrointestinal stromal tumour; MPNST, malignant peripheral nerve sheath tumour; NOS, not otherwise specified; PR, partial response

Entrectinib activity in a patient with undifferentiated sarcoma harbouring an *NTRK1* fusion

- 48-year-old male with sarcoma of the right thigh
- Underwent primary resection which showed undifferentiated sarcoma, positive for SMA, negative for CD31, CD34, desmin, keratins, S100
- Evaluated for adjuvant chemotherapy but baseline scans identified multiple lung metastases
- NGS identified *TPM3-NTRK1* gene fusion
- In STARTRK-2 the patient received entrectinib 600 mg orally, once daily
- CT scan on cycle 2 showed a PR per RECIST v1.1
  - 80% tumour reduction from baseline observed while on-study

Clinical response



CT, computed tomography; NGS: next-generation sequencing; RECIST, Response Evaluation Criteria in Solid Tumours

Safety overview

- Most treatment-related AEs were grade 1/2 and reversible
- In the overall safety population, treatment-related AEs:
  - grade 1/2: 60.5%
  - grade 3: 27.6%
  - grade 4: 3.4%
  - no grade 5 treatment-related AEs
- Treatment-related AEs leading to:
  - dose reduction: 27.3%
  - dose interruption: 25.4%
  - discontinuation from treatment: 3.9%
- Treatment-related AEs reported in the *NTRK* fusion-positive and the overall safety populations were comparable

Treatment-related AEs reported in ≥10% of patients	Overall safety population (N=355)*		*NTRK* fusion-positive safety population (n=68)†§	
Patients, n (%)	**Grade 1/2**	**Grade 3**	**Grade 1/2**	**Grade 3**
Dysgeusia	146 (41.1)	1 (0.3)	32 (47.1)	0
Constipation	83 (23.4)	1 (0.3)	19 (27.9)	0
Fatigue	89 (25.1)	10 (2.8)	19 (27.9)	5 (7.4)
Diarrhoea	76 (21.4)	5 (1.4)	18 (26.5)	1 (1.5)
Oedema peripheral	49 (13.8)	1 (0.3)	16 (23.5)	1 (1.5)
Dizziness	88 (24.8)	2 (0.6)	16 (23.6)	1 (1.5)
Blood creatinine increased	52 (14.6)	2 (0.6)	12 (17.7)	1 (1.5)
Paresthesia	67 (18.9)	0	11 (16.2)	0
Nausea	74 (20.8)	0	10 (14.7)	0
Vomiting	48 (13.5)	0	9 (13.2)	0
Arthralgia	42 (11.8)	2 (0.6)	8 (11.8)	0
Myalgia	52 (14.6)	2 (0.6)	8 (11.8)	0
Weight increased	51 (14.4)	18 (5.1)	8 (11.8)	7 (10.3)
AST increased	35 (9.9)	3 (0.8)	7 (10.3)	0
Muscular weakness	22 (6.2)	3 (0.8)	6 (8.8)	1 (1.5)
Anaemia	27 (7.6)	16 (4.5)	5 (7.4)	8 (11.8)

Data cut-off: 31 May 2018

*The safety population comprises 355 patients who received ≥1 dose of entrectinib and includes the NTRK fusion-positive population (n=68); †The *NTRK* fusion-positive safety population comprises all patients with an *NTRK* fusion-positive tumour who have received ≥1 dose of entrectinib; §In the NTRK fusion-positive safety population, there were five grade 4 treatment-related AEs in 3 patients (1 increased AST; 1 increased ALT; 1 increased blood uric acid; 2 hyperuricaemia)

AE, adverse event; ALT, alanine aminotransaminase; AST, aspartate aminotransferase

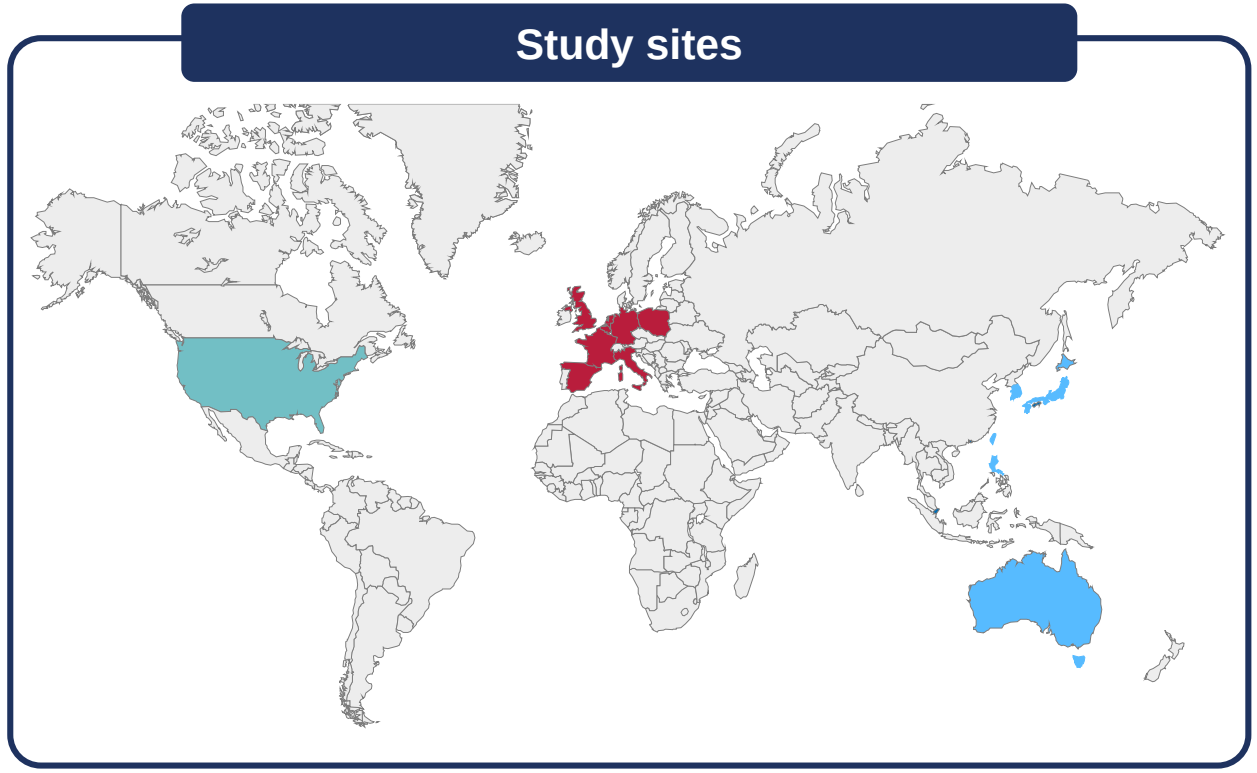
Doebele, et al. Lancet Oncology 2019

Conclusions

- In this integrated analysis of global multicentre clinical trials, entrectinib was well tolerated and induced clinically meaningful, durable responses in adult patients with *NTRK* fusion-positive sarcomas
  - ORR 46.2%
  - median DoR 10.3 months
- Entrectinib was well tolerated, with a manageable safety profile
  - most treatment-related AEs were managed with dose interruption/reduction and the discontinuation rate was low
- These efficacy data should encourage broader *NTRK* screening of adult patients with sarcomas who may benefit from treatment with entrectinib

Acknowledgements

- Thank you to all the patients and investigators who participated in these studies



Integrated analysis

STARTRK-2: 150+ sites in 15 countries
STARTRK-1: 10 sites in USA, Spain, South Korea
ALKA-372-001: 2 sites in Italy
STARTRK-NG: sites in US

North America	Europe	Asia Pacific
USA	Belgium	Australia
	France	Hong Kong
	Germany	Japan
	Italy	**South Korea**
	The Netherlands	Singapore
	Poland	Taiwan
	Spain	
	UK	