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TRK FUSION-POSITIVE CANCER HIGHLIGHTS FROM ASCO 2022

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JUNE 2022

DISCLOSURES

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This content is supported by an independent educational grant from Bayer.

Disclosures: **Prof. David S. Hong** has received honoraria from the following:

- ***Research/Grant Funding :*** AbbVie, Adaptimmune, Adlai-Nortye, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Deciphera, Eisai, Endeavor, Erasca, Roche, Fate Therapeutics, Genentech, Genmab, Ignyta, Infinity, Kite, Kyowa Kirin, Eli Lilly, LOXO, Merck, Medimmune, Mirati, Mologen, Navier, NCI-CTEP, Novartis, Numab, Pfizer, Pyramid Bio, SeaGen, Takeda, TCR2, Teckro, Turning Point Therapeutics, VM Oncology
- ***Consulting, Speaker, or Advisory Role:*** Abbvie, Adaptimmune, Alpha Insights, Acuta, Alkermes, Amgen, Aumbiosciences, Axiom, Baxter, Bayer, Boxer Capital, BridgeBio, COR2ed, COG, Cowen, Ecor1, Gennao Bio, Genentech, Gilead, GLG, Group H, Guidepoint, HCW Precision, Immunogen, Infinity, Janssen, Liberium, MedaCorp, Medscape, Numab, Oncologia Brasil, Pfizer, Pharma Intelligence, POET Congress, Prime Oncology, RAIN, SeaGen, ST Cube, Takeda, Tavistock, Trieza Therapeutics, Turning Point Therapeutics, WebMD, YingLing Pharma, Ziopharm

SELECTED ABSTRACTS FROM ASCO 2022

- Updated clinical efficacy and safety data from the currently approved first-generation TRK inhibitors:
  - **larotrectinib**: Long-term efficacy and safety of larotrectinib in a pooled analysis of patients with tropomyosin receptor kinase fusion cancer. Presented by *Drilon A.E. et al.*
  - **entrectinib**: Updated analysis of the efficacy and safety of entrectinib in patients with locally advanced/metastatic *NTRK* fusion-positive solid tumors.
    Presented by *Krzakowski M.J. et al.*

- Preliminary and promising clinical evidence for a next-generation TRK inhibitor:
  - **ICP-723**: Safety, pharmacokinetics, and clinical efficacy of ICP-723, a highly selective next-generation pan-TRK inhibitor, in patients with solid tumor. Presented by *Wei XL. et al.*

NTRK, neurotrophic receptor tyrosine kinase; Trk, tropomyosin receptor kinase

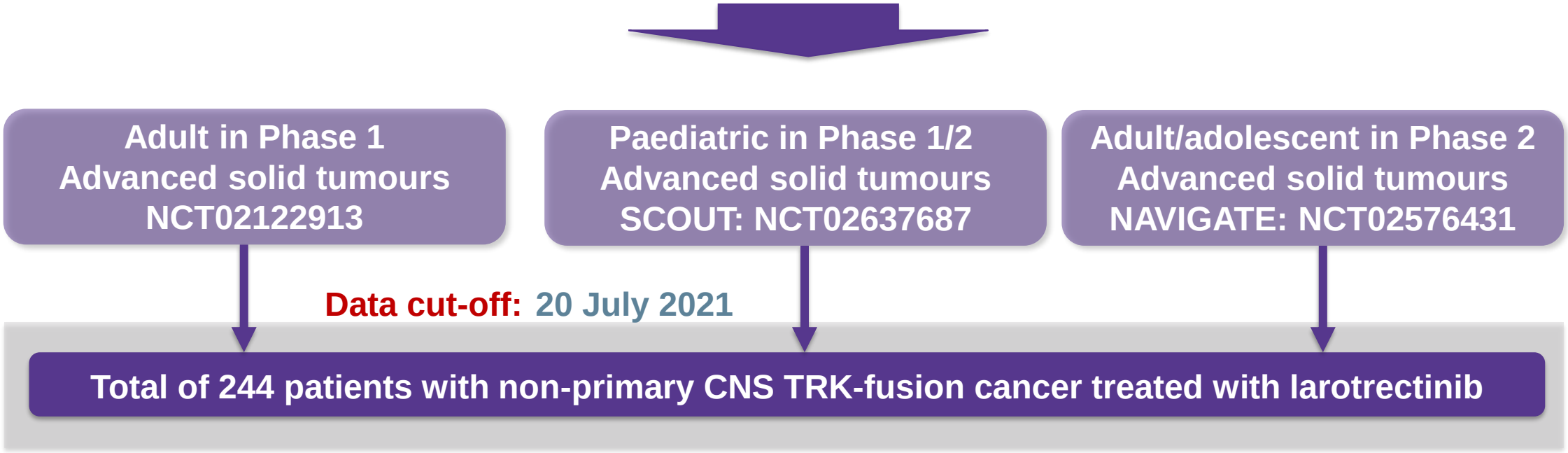
LONG-TERM EFFICACY AND SAFETY OF LAROTRECTINIB IN A POOLED ANALYSIS OF PATIENTS WITH TROPOMYOSIN RECEPTOR KINASE (TRK) FUSION CANCER

Drilon AE, et al.

ASCO 2022. Abstract #3100. Poster presentation

BACKGROUND

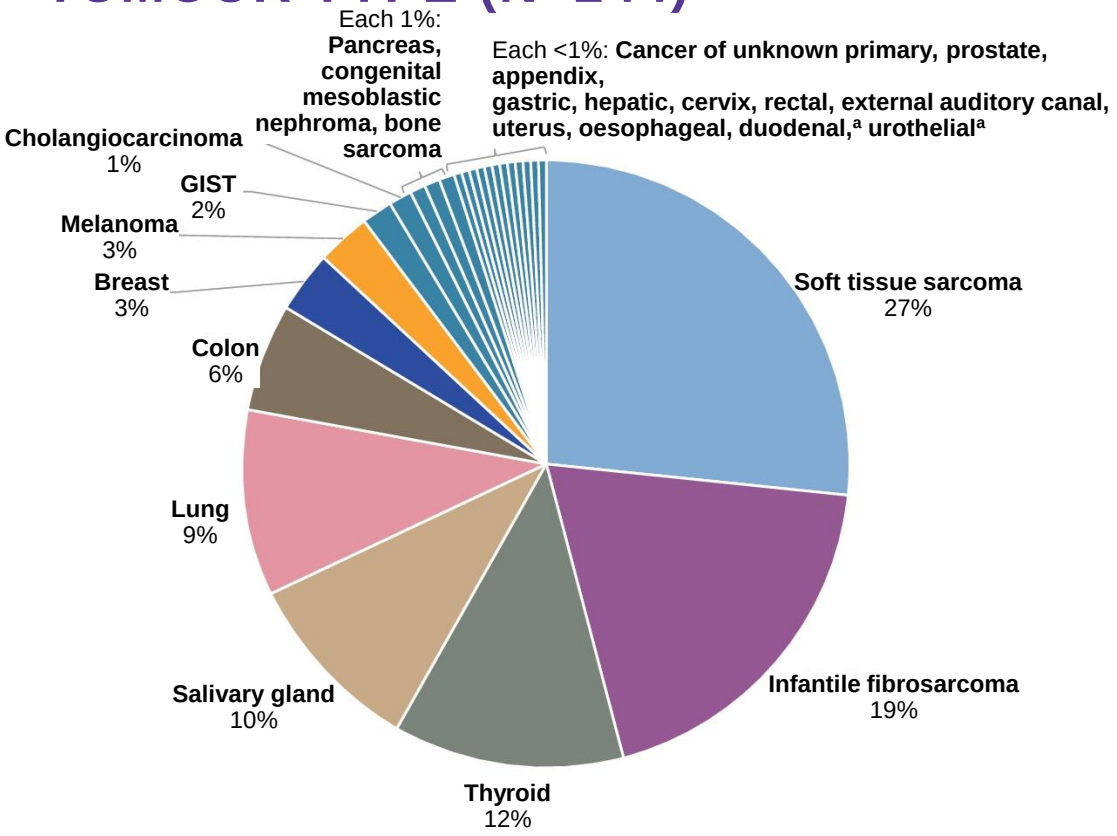
larotrectinib = first-in-class, highly selective, CNS-active TRK inhibitor approved to treat adult and paediatric patients with TRK fusion cancer



CNS, central nervous system; TRK, tropomyosin receptor kinase

INTEGRATED DATASET: VARIOUS TUMOUR TYPES TREATED WITH LAROTRECTINIB WITH HIGH ORR

PATIENT POPULATION BY TUMOUR TYPE (N=244)



[a] Tumour types not represented in previous integrated data cut

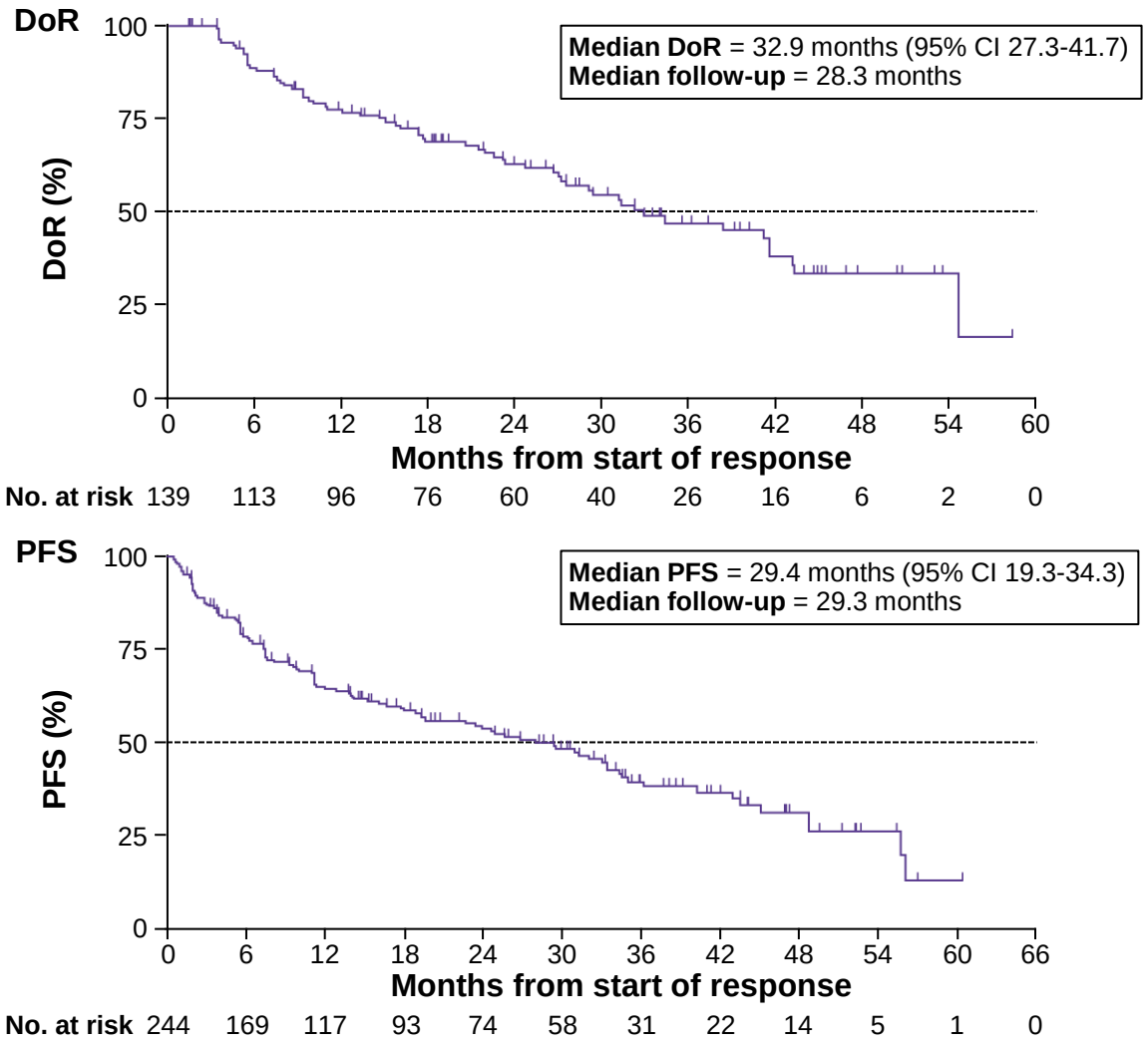
EFFICACY ASSESSMENTS

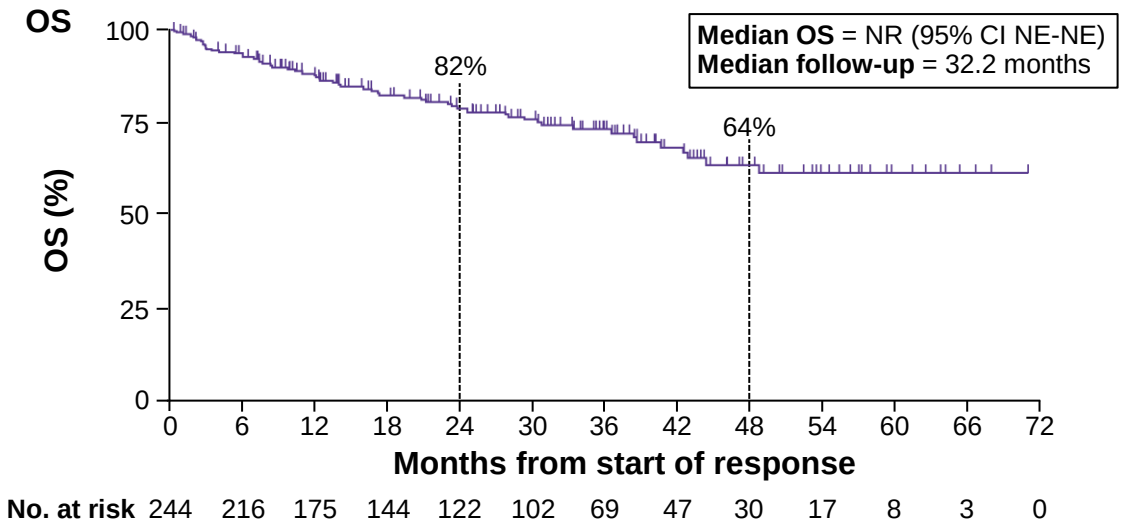
	Integrated dataset
Evaluable patients, n	244
ORR, % (95% CI)	69 (63-75)
Best response, n (%)	
Complete response	51 (21)
Pathological complete response	13 (5)
Partial response	104 (43)
Stable disease	41 (17)
Progressive disease	20 (8)
Not determined[b]	15 (6)

[b] Patients who discontinued study drug without evaluable post-baseline assessments

CI, confidence interval; GIST, gastrointestinal stromal tumour; ORR, objective response rate

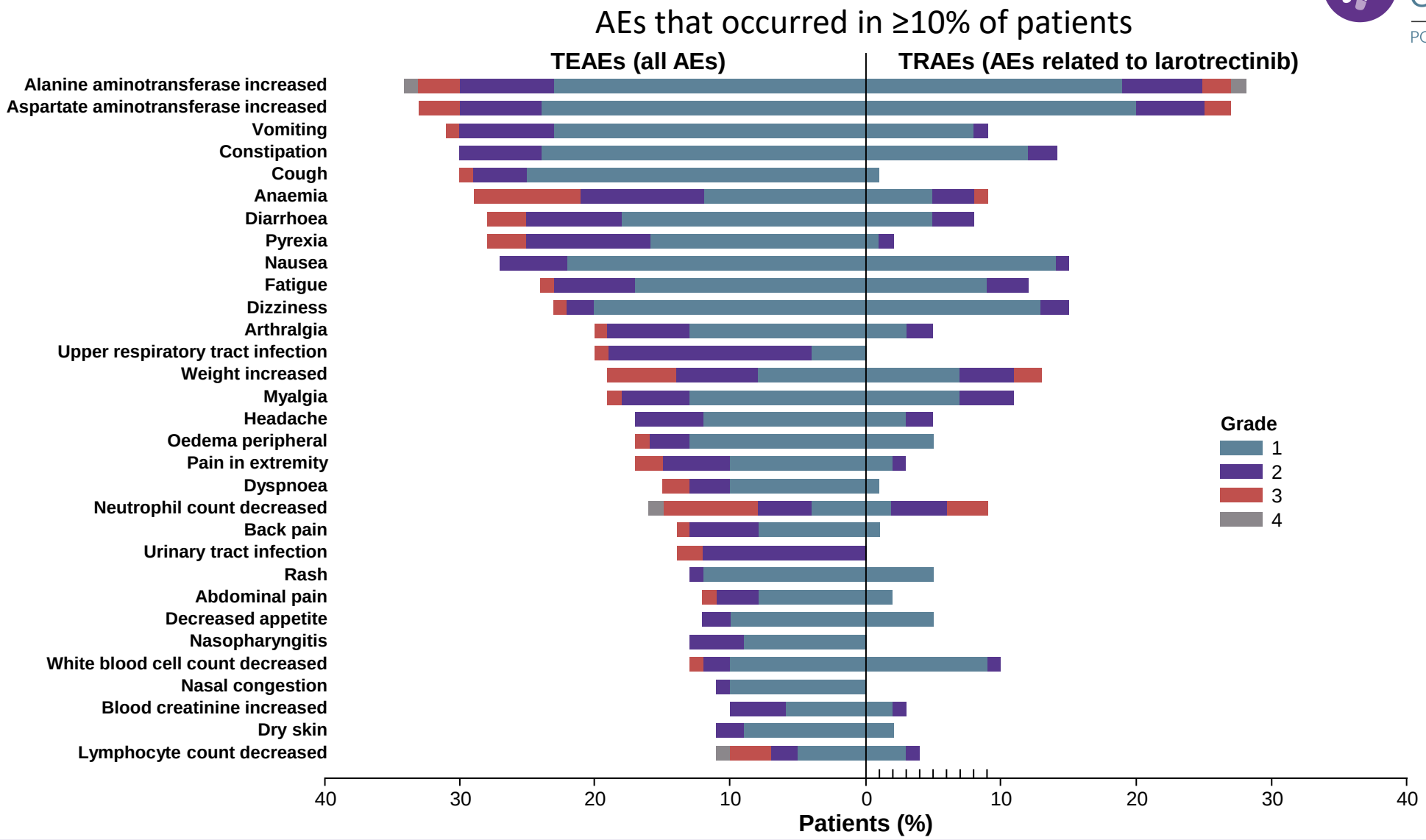
EFFICACY: DoR, PFS, AND OS IN PATIENTS WITH TRK FUSION CANCER





CI, confidence interval; DoR, duration of response; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase

SAFETY: NO NEW SIGNAL IDENTIFIED



AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

UPDATED ANALYSIS OF THE EFFICACY AND SAFETY OF ENTRECTINIB IN PATIENTS WITH LOCALLY ADVANCED/METASTATIC *NTRK* FUSION-POSITIVE SOLID TUMORS

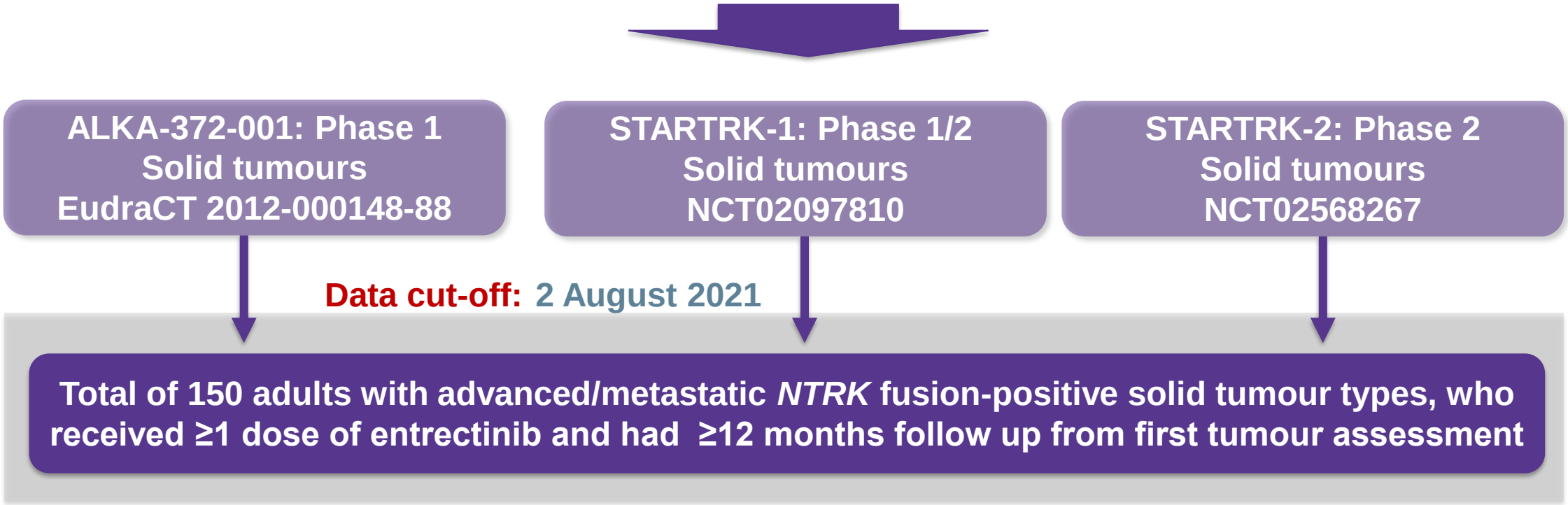
Krzakowski MJ, et al.

ASCO 2022. Abstract #3099. Poster presentation

NTRK, neurotrophic receptor kinase

BACKGROUND

entrectinib = CNS-active, potent inhibitor of TRK, ROS1 and ALK tyrosine kinase



ALK, anaplastic lymphoma kinase; CNS, central nervous system; *NTRK*, neurotrophic receptor tyrosine kinase; ROS1, ROS proto-oncogene 1; TRK, tropomyosin receptor kinase

PATIENT CHARACTERISTICS AND KEY EFFICACY RESULTS

- **Patient characteristics:**
  - 150 patients with 17 different *NTRK* fusion-positive tumours types
  - Median survival follow-up: 30.6 months
- **Efficacy:**
  - Time-to-event endpoints
    - Median DoR was **20.0 months** (Table)
    - Median PFS was **13.8 months** and median OS was **37.1 months** (Table)

Overall efficacy

Parameter	Efficacy population (N=150)	Baseline CNS mets[a] (n=31)	No baseline CNS mets[a] (n=119)
ORR[b], n (%) [95% CI]	92 (**61.3**) [53.1-69.2]	19 (**61.3**) [42.2-78.2]	73 (**61.3**) [52.0-70.1]
Complete response, n (%)	25 (16.7)	2 (6.5)	23 (19.3)
Partial response, n (%)	67 (44.7)	17 (54.8)	50 (42.0)
Stable disease, n (%)	15 (10.0)	4 (12.9)	11 (9.2)
Progressive disease, n (%)	18 (12.0)	2 (6.5)	16 (13.4)
Non-CR / non-PD, n (%)	7 (4.7)	0	7 (5.9)
Missing / unevaluable[c], n (%)	18 (12.0)	6 (19.4)	12 (10.1)
Median DoR[b], months [95% CI)	20.0 [13.2-31.1]	17.2 [9.0-33.3]	20.0 [14.8-NE]
Median PFS[b], months [95% CI)	13.8 [10.1-20.0]	11.7 [4.9-30.3]	13.8 [10.2-20.4]
Median OS, months [95% CI)	37.1 [27.2-NE]	20.0 [7.9-NE]	40.5 [30.4-NE]

[a] CNS metastases status at baseline per investigator. [b] Assessed by BICR per RECIST v1.1. [c] Includes patients with unevaluable on-study scans or those who discontinued treatment prior to obtaining adequate scans to evaluate or confirm response

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; mets, metastases; NE, not estimable; NTRK, neurotrophic receptor tyrosine kinase; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

SAFETY: NO NEW SIGNAL IDENTIFIED

- **Safety:**
  - Safety analysis set = 235 patients
  - Median dose intensity: 93.7% (range 11.8-106.1)
  - TRAEs:
    - Mostly grade 1/2
    - Most frequent: dysgeusia (36.6%), diarrhoea (29.8%), weight increase (28.5%)
    - Led to dose interruption: 32.8%
    - Led to dose reduction: 24.3%
    - Led to dose discontinuation: 7.2%

TRAE, treatment-emergent adverse event

SAFETY, PHARMACOKINETICS, AND CLINICAL EFFICACY OF ICP-723, A HIGHLY SELECTIVE NEXT-GENERATION PAN-TRK INHIBITOR, IN PATIENTS WITH SOLID TUMOR

Wei XL, et al.

ASCO 2022. Abstract #3106. Poster presentation

TRK, tropomyosin receptor kinase

ICP-723 IS A POTENT NEXT-GENERATION TRK INHIBITOR

- **Mechanism of action**:
  - Potent inhibitor of wild-type TRKA/B/C
  - Highly active against resistant mutations (G595R, F589L or G667C/A/S)

- **Clinical development status:**
  - First-in-human trial ongoing (first patient enrolled in September 2020) to evaluate the safety, tolerability, PK and preliminary efficacy of ICP-723 (NCT04685226)

PK, pharmacokinetic; TRKA/B/C, tropomyosin receptor kinase A/B/C

STUDY DESIGN

A multicentre, open-label, non-randomised, phase 1/2 clinical trial of ICP-723 in the treatment of advanced solid tumours

Phase 1:

- Dose escalation study with 28-day continuous dosing
- Objective: evaluate safety, tolerability and PK of ICP-723 in advanced solid tumours

Phase 2:

- Objective: Preliminary evaluation of the clinical efficacy in *NTRK* treatment naïve patient

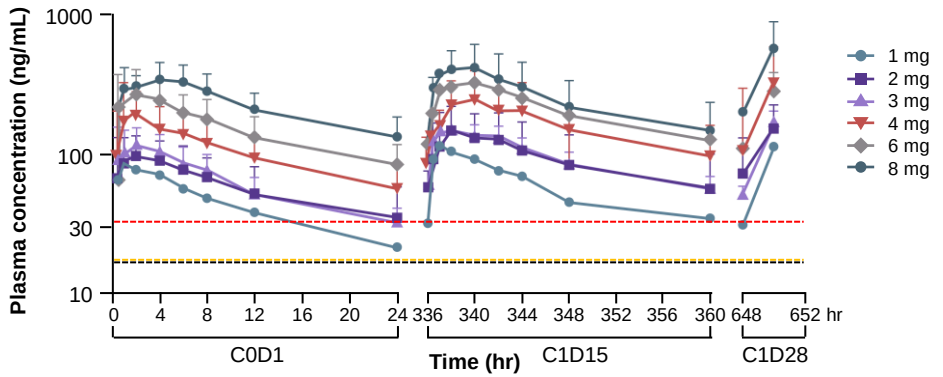
Cut off date: 11 February 2022

→ 17 patients in phase 1 dose escalation treated with ICP-723 at dose levels from 1 mg QD to 8 mg QD

NTRK, neurotrophic receptor tyrosine kinase; PK, pharmacokinetic; QD, once a day

RESULTS: SAFETY, PK AND EFFICACY

- **Safety**
  - DLT has not been observed in the six dose groups (1, 2, 3, 4, 6 and 8 mg)
  - Most treatment-related adverse events (TRAEs) were Grade 1-2
  - Grade 3 TRAEs were reported in three patients. No Grade 4 or Grade 5 TRAEs were observed
  - The most common TRAEs (>20%) were asthenia, increased ALT, increased AST and anaemia
  - Grade 3 TRAEs were increased ALT, increased AST, increased CPK, neutrophil count decreased and pain
- **Pharmacokinetic (PK) analysis**
  - The plasma concentrations of ICP-723 over time on day 1 and day 15 are shown in the figure below
  - Plasma exposure to ICP-723 increased in a dose proportional manner across the dosage levels



Plasma concentration versus time profiles

- **Efficacy**
  - Among the six patients with *NTRK* fusion, the ORR was 66.7% (four PR), the DCR was 100% (Table). There was no response in patients without *NTRK* fusion, but there were SD patients
    - All the *NTRK* fusion positive patients treated with ICP-723 at dose levels of 4 mg and above (n=4) responded to the treatment (ORR: 100%)
  - Among the four PR patients, the remission depth gradually deepened with higher dose
  - All patients who achieved shrunk SD or above have maintained sustained responses to the date of data cut-off
  - One patient achieved PR with the target brain lesion shrunk from 10 mm to 3 mm with 5 months DoR to date. The signal of oedema region markedly reduced after treatment
- **Efficacy assessment in *NTRK* fusion (+) patients**

	Total (N=16[a])	*NTRK* fusion (+) (N=6)	*NTRK* fusion (-) (N=6)
ORR (CR+PR+uPR), n (%)[b]	4 (25.0)	4 (66.7)	0 (0.0)
DCR (CR+PR+uPR+SD), n (%)	11 (68.8)	6 (100.0)	4 (80.0)
BOR, n (%)			
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	3 (18.8)	3 (50.0)	0 (0.0)
uPR	1 (6.3)	1 (16.7)	0 (0.0)
SD	7 (43.8)	2 (33.3)	4 (80.0)
PD	5 (31.3)	0 (0.0)	1 (20.0)
NE	0 (0.0)	0 (0.0)	0 (0.0)

[a] There was one patient non-evaluable for efficacy analysis, for whom tumour scan not performed. b The ORR will be 80% (four PR out of five patients) if excluding the patient who was considered not being able to form RNA fusion. All the NTRK fusion positive patients treated with ICP-723 at dose levels of 4 mg and above responded to the treatment (ORR: 100%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BOR, best overall response; C, cycle; CPK, creatine phosphokinase; CR, complete response; D, day; DCR, disease control rate; DLT, dose-limiting toxicity; DoR, duration of response; hr, hour; NE, non evaluable; NTRK, neurotrophic receptor tyrosine kinase; ORR, objective response rate; PD, progressive disease; PR, partial response; uPR, unconfirmed partial response; SD, stable disease

CONCLUSIONS

CONCLUSIONS

- **First generation TRK inhibitors:**
  - larotrectinib and entrectinib demonstrate a robust clinical efficacy with a manageable safety profile in various solid tumour types
  - larotrectinib and entrectinib show a high survival benefit (PFS and OS) and high response rate with long durability in patients with *NTRK* fusion-positive solid tumours
- **Next generation TRK inhibitors:**
  - Are required to overcome the resistance mechanisms seen with larotrectinib and entrectinib
  - ICP-723 could be an effective and well-tolerated second-generation TRK inhibitor
    - Phase 2 investigation is ongoing with *NTRK* fusion positive patients, including those who developed acquired resistance to first-generation TRK inhibitor
- **Testing is critical in order to find patients:**
  - Presence of *NTRK* gene fusions must be tested for in order to identify patients who can benefit from larotrectinib and entrectinib

NTRK, neurotrophic receptor tyrosine kinase; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase

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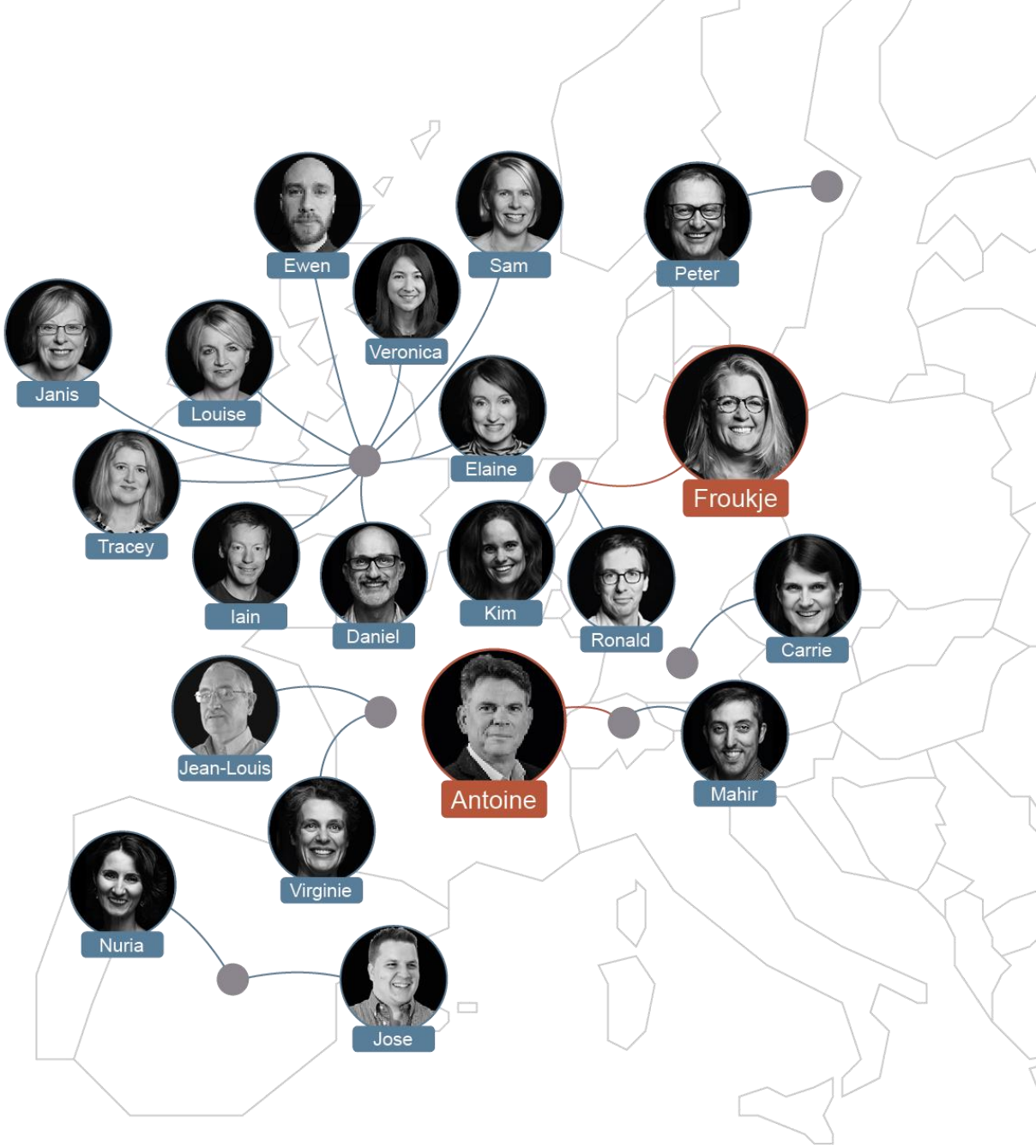

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