Efficacy and Safety of Larotrectinib in a Pooled Analysis of Patients (Pts) With Tropomyosin Receptor Kinase (TRK) Fusion Cancer With an Extended Follow-Up

463P

Ray McDermott[1], Cornelis M. van Tilburg[2], Jessica J. Lin[3,4], Shivaani Kummar[5†], Daniel S. W. Tan[6], Catherine M. Albert[7], Jordan Berlin[8], Ulrik Lassen[9], Francois Doz[10,11], Birgit Geoerger[12], Leo Mascarenhas[13], Noah Federman[14], Ricarda Norenberg[15], Laura Dima[16], Chiara E. Mussi[17], Esther De La Cuesta[18], Theodore W. Laetsch[19], David S. Hong[20], Alexander Drilon[21,22]

[1]St Vincent's University Hospital and Cancer Trials Ireland, Dublin, Ireland; [2]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; [4]Harvard Medical School, Boston, MA, USA; [5]Stanford Cancer Center, Stanford University, Palo Alto, CA, USA; [6]Division of Medical Oncology, National Cancer Centre Singapore, Duke-NUS Medical School, Singapore, Singapore; [7]Seattle Children's Hospital and University of Washington School of Medicine, Seattle, WA, USA; [8]Vanderbilt University Medical Center, Nashville, TN, USA; [9]Department of Oncology, Rigshospitalet, Copenhagen, Denmark; [10]SIREDO Oncology Center (Care, Innovation and Research for Children and AYA with Cancer), Institut Curie, Paris, France; [11]Université Paris Cité, Paris, France; [12]Gustave Roussy Cancer Center, Department of Pediatric and Adolescent Oncology, Université Paris-Saclay, INSERM U1015, Villejuif, France; [13]Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA, USA; [14]David Geffen School of Medicine, University of California, Los Angeles, CA, USA; [15]Chrestos Concept GmbH & Co. KG, Essen, Germany; [16]Bayer HealthCare SAS, Medical Affairs, La Garenne-Colombes, France; [17]Bayer S.p.A., Milan, Italy; [18]Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ, USA; [19]The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA; [20]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [21]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [22]Weill Cornell Medical College, New York, NY, USA
[†]Current affiliation: Oregon Health & Science University, Portland, OR, USA

BACKGROUND

- Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in multiple adult and paediatric tumour types, occurring with varying frequencies from ~90% in rare cancers, such as infantile fibrosarcoma and secretory breast cancer, to <1% in more common cancers, such as non-small cell lung cancer, colorectal adenocarcinoma and cutaneous melanoma.[1,2]
- Larotrectinib is a first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor approved by the US Food and Drug Administration and European Medicines Agency, and in 48 countries worldwide, for adult and paediatric patients with TRK fusion cancer.[3,4]
- In an integrated analysis of 244 patients with non-primary CNS TRK fusion cancer, larotrectinib demonstrated an independent review committee (IRC)-assessed objective response rate (ORR) of 69%, at a data cut-off of 20 July 2021.[5]
- To better determine outcomes in a more mature dataset with a longer follow-up, we report an updated analysis on the first 164 patients with TRK fusion cancer enrolled, with a data cut-off of July 2021. The investigator-assessed analysis of this cohort of patients, with a data cut-off of 15 July 2019, was initially presented at ESMO 2020.[6]

METHODS

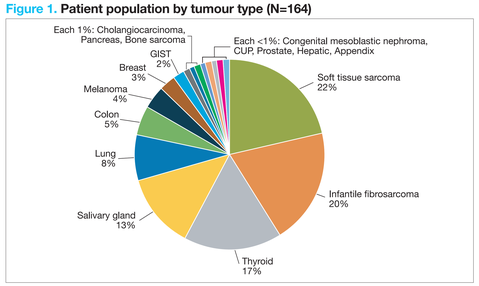
- Data for this analysis were pooled from three clinical trials (NCT02576431, NCT02122913 and NCT02637687) of patients with non-primary CNS TRK fusion cancer treated with larotrectinib.
- Larotrectinib was administered at a dose of 100 mg twice daily to most adult patients and 100 mg/m^2 (maximum dose 100 mg twice daily) to most paediatric patients.
- The primary endpoint was ORR as assessed by IRC using the Response Evaluation Criteria in Solid Tumors v1.1.
- The data cut-off for this analysis was 20 July 2021.

RESULTS

Patients

- The first 164 patients that were enrolled between February 2015 and February 2019 were evaluated for efficacy by IRC.
- There were 17 different tumour types in this dataset. The most common were soft tissue sarcoma (22%), infantile fibrosarcoma (20%), thyroid (17%), salivary gland (13%) and lung (8%; **Figure 1**).

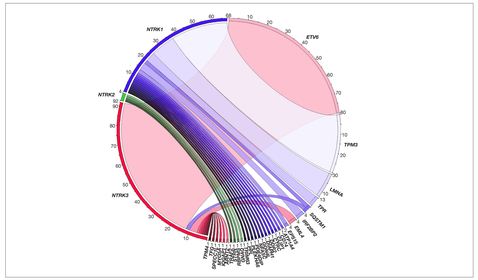
Figure 1. Patient population by tumour type (N=164)



CUP, cancer of unknown primary; GIST, gastrointestinal stromal tumour.

- There were 30 unique fusion partners, with *ETV6* being the most common (n=80; 49%; **Figure 2**).
- The median age was 42.0 years (range 0–84) and the median number of prior systemic therapies was 1 (range 0–10; **Table 1**).
- Fourteen patients (9%) had CNS metastases at baseline.

Figure 2. *NTRK* fusion partner distribution



NTRK, neurotrophic tyrosine receptor kinase. Created using Circos (Krzywinski[7]).

Table 1. Baseline characteristics

Characteristic	N=164
Age, median (range), years	42.0 (0–84)
Paediatric (<18 years), n (%)	55 (34)
Adult (≥18 years), n (%)	109 (66)
Sex, n (%)	
Male	80 (49)
Female	84 (51)
Known CNS metastases at baseline, n (%)	14 (9)
ECOG or equivalent Lansky PS, n (%)	
0	80 (49)
1	62 (38)
2	19 (12)
3	3 (2)
***NTRK* gene fusion,** n (%)	
NTRK1	68 (42)
NTRK2	4 (2)
NTRK3	92 (56)
Prior therapies, n (%)[†]	
Surgery	125 (76)
Radiotherapy	75 (46)
Systemic therapy[‡]	122 (74)
Prior systemic therapies, median (range)	1 (0–10)
Prior systemic therapies, n (%)[‡]	
0	41 (25)
1	48 (29)
2	32 (20)
≥3	43 (26)
Best response to prior systemic therapy, n (%)	
Complete response	3 (2)
Partial response	9 (7)
Stable disease	40 (33)
Progressive disease	22 (18)
Other[§]	48 (39)

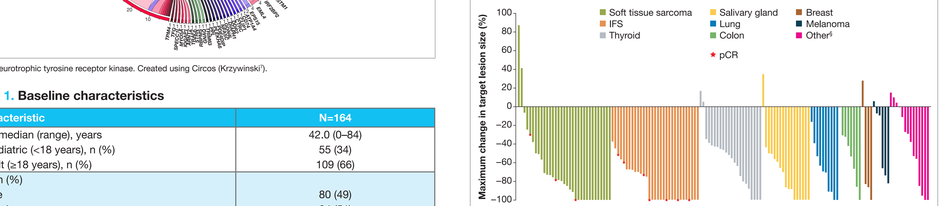
[†]Patients may be counted in more than one row. [‡]Due to a discrepancy in the Case Report Form, the table reflects one patient who had the number of prior systemic therapies reported as "1", but that patient actually reported "No" to prior systemic therapies. [§]Other includes unknown and not evaluable.
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; *NTRK*, neurotrophic tyrosine receptor kinase; PS, Performance Status.

Efficacy

- Larotrectinib achieved an ORR of 74% (95% confidence interval [CI] 67–81) and was efficacious regardless of tumour type (**Figure 3**).
  - Among the 14 patients with baseline CNS metastases, the ORR was 86% (95% CI 57–98).
  - Among the 109 adult patients, the ORR was 67% (95% CI 57–76).
- With the longer follow-up, 17 patients (10%) had an improved best overall response compared with the July 2019 data cut.

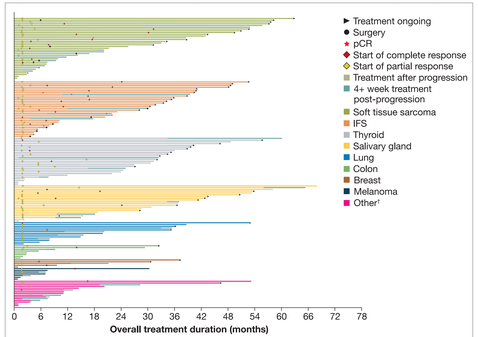
Figure 3. Maximum change in target lesion size in patients with TRK fusion cancer[†]

	Overall	Patients with CNS metastases
Evaluable patients, n	164	14
ORR, % (95% CI)	74 (67–81)	86 (57–98)
Best response, n (%)		
Complete response	40 (24)	1 (7)
Pathological complete response	10 (6)	0
Partial response	72 (44)	11 (79)
Stable disease	22 (13)	1 (7)
Progressive disease	13 (8)	0
Not determined[‡]	7 (4)	1 (7)



[†]There are 159 patients shown in the figure as five patients had no measurable lesions assessed by IRC. [‡]Patients who discontinued study drug without evaluable post-baseline assessments. [§]Other includes tumours that are less than 3% of the total as defined in Figure 1.
CI, confidence interval; CNS, central nervous system; IFS, infantile fibrosarcoma; IRC, independent review committee; ORR, objective response rate; pCR, pathological complete response; TRK, tropomyosin receptor kinase.

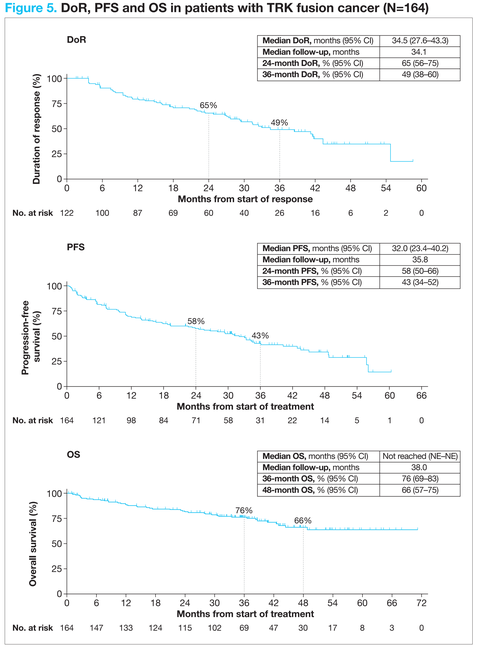
Figure 4. Treatment duration in patients with TRK fusion cancer (N=164)



[†]Other includes tumours that are less than 3% of the total as defined in Figure 1. IFS, infantile fibrosarcoma; pCR, pathological complete response; TRK, tropomyosin receptor kinase.

- The treatment duration ranged from 0.1 to 67.9 months (**Figure 4**).
- The median time to response was 1.8 months (range 0.9–16.2).
- The median duration of response (DoR) and progression-free survival (PFS) were 34.5 months (95% CI 27.6–43.3) and 32.0 months (95% CI 23.4–40.2), respectively. The 48-month overall survival (OS) rate was 66% (95% CI 57–75) (**Figure 5**).
  - Among the 109 adult patients, the median DoR, PFS, and OS were 41.5 months (95% CI 29.2–not estimable [NE]), 30.8 months (95% CI 15.2–43.5), and 48.7 months (95% CI 38.7–NE), respectively.

Figure 5. DoR, PFS and OS in patients with TRK fusion cancer (N=164)

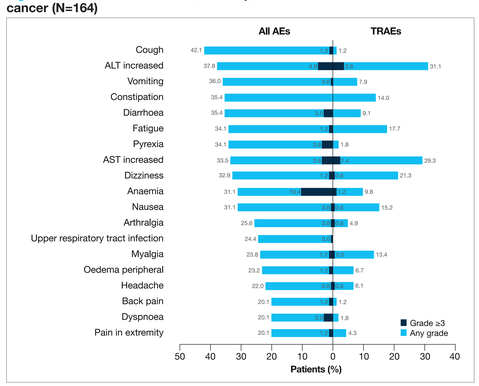


CI, confidence interval; DoR, duration of response; NE, not estimable; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase.

Safety

- Treatment-related adverse events (TRAEs) were mainly Grade 1–2 (**Figure 6**).
- Thirty-two patients (20%) had Grade 3–4 TRAEs. The most common were decreased neutrophil count and increases in alanine aminotransferase and aspartate aminotransferase.
- Three patients (2%) discontinued treatment due to TRAEs (increases in alanine aminotransferase and aspartate aminotransferase, emotional poverty and decreased neutrophil count).

Figure 6. AEs that occurred in ≥20% of patients with TRK fusion cancer (N=164)



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event; TRK, tropomyosin receptor kinase.

CONCLUSIONS

- With a 3-year follow-up, larotrectinib demonstrated durable and deepening responses, extended survival benefit and a favourable safety profile.
- These results highlight the importance of identifying *NTRK* gene fusions in patients with cancer.

74% ORR by IRC
34.5 mo Median DoR
32.0 mo Median PFS
66% 48-month OS

References

1. Amatu A, et al. *Ann Oncol*. 2019;30:viii5–viii15.
2. Forsythe A, et al. *Ther Adv Med Oncol*. 2020;12:1–10.
3. Bayer. VITRAKVI US PI. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210861s006lbl.pdf. Accessed 7 July 2022.
4. Bayer VITRAKVI SmPC. 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/vitrakvi-epar-product-information_en.pdf. Accessed 7 July 2022.
5. Drilon A, et al. ASCO. 2022:3100.
6. McDermott R, et al. ESMO. 202:1955P.
7. Krzywinski M, et al. *Genome Res*. 2009;19:1639–1645.

Acknowledgements

We thank the patients and their families, many of whom travelled long distances to participate in these studies. Medical writing assistance was provided by Anastasija Pesevska, PharmD, and editorial and typesetting assistance was provided by George Chappell, MSc, both of Scion (London, UK), supported by Bayer Healthcare Pharmaceuticals, Inc.

Disclosures

These studies were funded by Bayer Healthcare Pharmaceuticals, Inc. and Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company. The presenting author discloses: advisory boards: Amgen, Bayer, BMS, Clovis, Janssen, and Pfizer; invited speaker: Astellas, Ipsen, and MSD; research interests: Astellas, Bayer, BMS, Clovis, MSD, and Regeneron; financial interests: Stella, Bayer, BMS, Clovis, MSD, and Regeneron.

Scan QR code for a video overview of the poster or to download the poster.

Presented by: Ray McDermott, ray.mcdermott@tuh.ie