Parametric Survival Extrapolations of Larotrectinib and Entrectinib for *NTRK* Fusion Cancers

Sean D. Sullivan, PhD

THE CHOICE INSTITUTE

School of Pharmacy

Disclosures

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- Member of Bayer Advisory Board.

Tumor-agnostic treatment: an issue of sample size

- Few studies compare survival benefits of tumour-agnostic treatments between patients.
- Given its rarity, *NTRK*-fusion studies include multiple cancer types to reach a reliable sample size.
- Larotrectinib has previously demonstrated improvements in life expectancy and health utility in patients with *NTRK* fusion-positive metastatic non-small cell lung cancer compared with entrectinib.[1]

Given the heterogeneity of outcomes between cancer types and treatments, how can doctors make informed decisions?

Can extrapolation of small sample sets be made reliably to solve this?

1. Suh K, Carlson JJ, Xia F, Williamson T, Sullivan SD. Comparative effectiveness of larotrectinib versus entrectinib for the treatment of metastatic NTRK gene fusion cancers. J Comp Eff Res. 2022 Oct;11(14):1011-1019. doi: 10.2217/cer-2021-0247. Epub 2022 Aug 22. PMID: 35993247.

Objective and methods

Objective

Assess the potential long-term effectiveness of larotrectinib vs. entrectinib in adults (≥18 years) with either CRC, STS or brain metastases by extrapolating clinical data prior to the initiation of TRK inhibitor treatment.

Model type

- A partitioned survival model using three health states:
  - Progression-free
  - Progression
  - Death

Data sources

- Single arm Phase 1/2 trials[1]
  - Larotrectinib: NCT02122913, NCT02637687 & NCT02576431; data cut off July 2020
  - Entrectinib: published data and conference proceedings[2,3,4]: 2012-000148-88; NCT02097810; NCT02568267; data cut-off October 2018
- Published literature for health state utility values in CRC and STS

Model outcomes

- Life years
- QALYs

CRC, colorectal cancer; STS, soft tissue carcinoma; TRK, tyrosine kinase; PFS, progression-free survival; QALYs; quality-adjusted life years

1. Suh K et al. J Comp Eff Res 2022;11:1011–1019 . 2. Patel M, Siena S, Demetri G et al. Efficacy and safety of entrectinib in NTRK fusion-positive gastrointestinal cancers: updated integrated analysis of three clinical trials (STARTRK-2, STARTRK-1 and ALKA-372-001). Ann. Oncol. 31, S232–S233 (2020). 3. Chawla S, Paz-Ares L, Patel M et al. An updated analysis of the clinical efficacy and safety of entrectinib in NTRK fusion-positive sarcoma. Presented at: 2020 CTOS Virtual Meeting, November 18–21, 2020 4. Rolfo CD, De Braud FG, Doebele RC et al. Efficacy and safety of entrectinib in patients (pts) with NTRK-fusion-positive (NTRK-fp) solid tumors: an updated integrated analysis. J. Clin. Oncol. 38(Suppl. 15), 3605 (2020)

Clinical trial data formed the baseline model inputs

Outcome results from clinical studies

Colorectal cancer	Larotrectinib (n=8) [1]	Entrectinib (n=7) [2]
Age, median (range)	69 (54, 84)	59.5 (31, 75)*
Male, n (%)	3 (37.5)	6 (50.0)*
Median PFS, months (95% CI)	NR	2.4 (1.0, 16.0)
Median OS, months (95% CI)	NR	16.0 (2.4, NR)
ORR	37.5%	28.6%
Stable disease	62.5%	0.0%

Soft tissue sarcoma	Larotrectinib (n=23) [1]	Entrectinib (n=16) [3]
Age, median (range)	41 (26, 48)	50.5 (21, 81)
Male, n (%)	11 (47.8)	8 (50.0)
Median PFS, months (95% CI)	NR	10.1 (6.5, 11.2)
Median OS, months (95% CI)	NR	16.8 (10.6, 20.9)
ORR	52.2%	56.3%
Stable disease	26.1%	25.0%

Brain metastasis at baseline	Larotrectinib (n=14) [1]	Entrectinib (n=16) [4]
Median PFS, months (95% CI)	NR	6.7 (4.7, NR)
Median OS, months (95% CI)	NR	14.3 (7.6, NR)
ORR	85.7%	50.0%
Stable disease	7.1%	Not available

CI: confidence interval; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression free survival
*based on Gastrointestinal carcinomas (n=12) as Colorectal cancer-specific characteristics not presented. References to be added from manuscript.

1. Cost-Effectiveness in Health and Medicine(2nd Edition). Oxford University Press, NY, USA (2017). 2. Bayer US LLC. Data on file. (2020). 3. Patel M et al. Efficacy and safety of entrectinib in *NTRK* fusion-positive gastrointestinal cancers: updated integrated analysis of three clinical trials (STARTRK-2, STARTRK-1 and ALKA-372-001).Ann. Oncol.31, S232–S233 (2020). 4. Chawla S, Paz-Ares L, Patel Met al. An updated analysis of the clinical efficacy and safety of entrectinib in *NTRK* fusion-positive sarcoma. Presented at:2020 CTOS Virtual Meeting, November 18–21, 2020.

Health state utility values used to estimate QALYs

On-treatment utilities were calculated as a weighted average of the utility for those in pre-progression, with and without responsive disease based on the overall response rate for each treatment

	Progression-free / stable disease	Progressive Disease
Colorectal cancer, base case (95% CI) [1]	0.82 (0.78, 0.86)	0.64 (0.55, 0.75)
Larotrectinib on-treatment utility	0.83	
Entrectinib on-treatment utility	0.83	

	Progression-free / stable disease	Progressive Disease
Soft tissue sarcoma, base case (95% CI) [2]	0.43 (0.39, 0.47)	0.30 (0.26, 0.34)
Larotrectinib on-treatment utility	0.50	
Entrectinib on-treatment utility	0.50	

1. Rolfo CD, De Braud FG, Doebele RC et al. Efficacy and safety of entrectinib in patients (pts) with *NTRK*-fusion-positive (*NTRK*-fp) solid tumors: an updated integrated analysis. J. Clin. Oncol. 38(Suppl. 15), 3605 (2020). 2. Farkkil¨a N, Sintonen H, Saarto T et al. Health-related quality of life in colorectal cancer. Colorectal Dis. 15(5), e215–e222 (2013).

Model shows an improvement in life years and QALYs in both OS and PFS

Base case results

Colorectal cancer	Larotrectinib	Entrectinib
Life-years (LYs), mean (95% CrI)		
Progression-free	1.16 (0.50, 2.28)	0.35 (0.14, 0.64)
Post-progression	0.95 (0.00, 4.03)	0.18 (0.00, 1.25)
TOTAL	**2.11 (0.84, 5.10)**	**0.53 (0.17, 1.60)**
QALYs, mean (95% CrI)		
Progression-free	0.97 (0.41, 1.90)	0.29 (0.12, 0.53)
Post-progression	0.61 (0.00, 2.52)	0.11 (0.00, 0.82)
TOTAL	**1.58 (0.66, 3.47)**	**0.41 (0.14, 1.10)**

Soft tissue sarcoma	Larotrectinib	Entrectinib
Life-years (LYs), mean (95% CrI)		
Progression-free	2.08 (1.22, 3.41)	0.66 (0.37, 1.12)
Post-progression	4.99 (1.00, 10.30)	0.60 (0.00, 1.81)
TOTAL	**7.07 (3.31, 12.34)**	**1.26 (0.64, 2.44)**
QALYs, mean (95% CrI)		
Progression-free	1.03 (0.61, 1.72)	0.33 (0.18, 0.56)
Post-progression	1.50 (0.31, 3.16)	0.18 (0.00, 0.54)
TOTAL	**2.53 (1.40, 4.21)**	**0.51 (0.30, 0.88)**

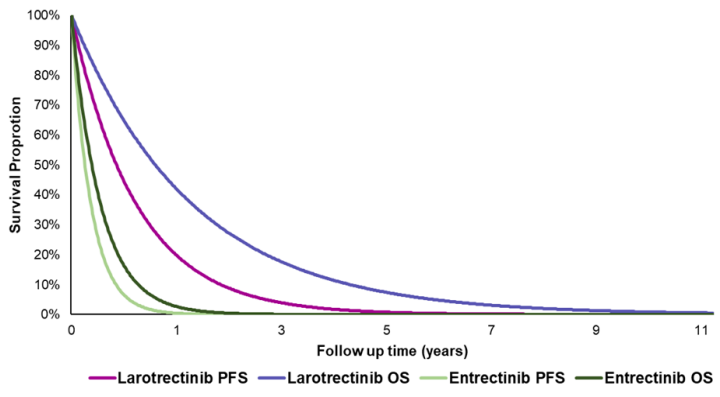
Brain metastasis at baseline	Larotrectinib	Entrectinib
Life-years (LYs), mean (95% CrI)		
Progression-free	1.91	0.80
Post-progression	0.85	0.86
TOTAL	**2.76**	**1.66**

CrI: credible interval; QALY: quality-adjusted life-year

Models estimate that larotrectinib improves progression-free and overall survival vs. entrectinib in *NTRK*-fusion positive cancers

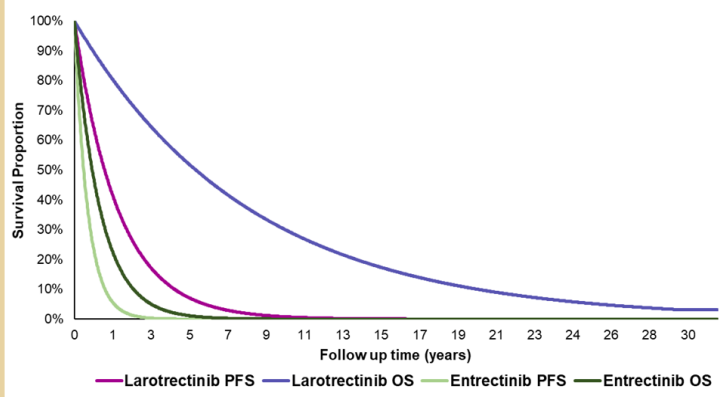
Parametric extrapolations of progression-free and overall survival

A) Colorectal cancer



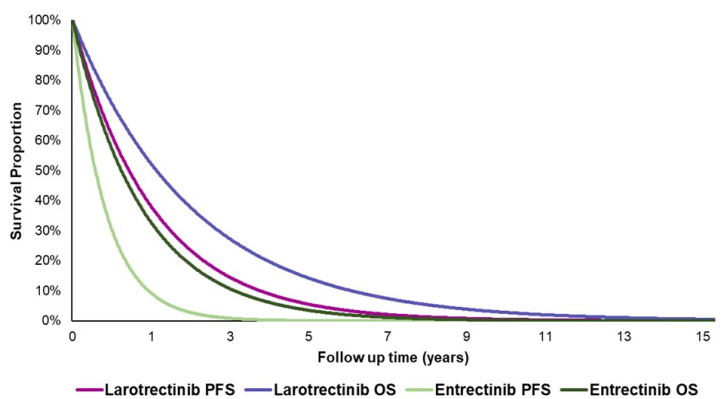
Larotrectinib led to a gain of 0.81 LYs and 0.77 LYs in progression-free and overall survival vs. entrectinib

B) Soft tissue sarcoma



Larotrectinib led to a gain of 1.42 and 4.39 LYs in the progression-free and overall survival vs. entrectinib

C) Brain metastasis at baseline



Larotrectinib led to a gain of 2.76 and 1.66 LYs in the progression-free and overall survival vs. entrectinib

NTRK: Neurotrophic tropomyosin receptor kinase; LYs: life years

Conclusions

> Model shows larotrectinib vs. entrectinib is expected to provide additional:

- Life years in *NTRK* fusion-positive metastatic CRC and STS, and brain metastases
- QALYs in *NTRK* fusion-positive metastatic CRC and STS

> The ability to compare treatments in rare diseases can help clinicians and decision-makers assess the potential clinical value of treatment options beyond larotrectinib and entrectinib.

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Thank you

Please take this opportunity to ask questions