The Potential Long-Term Comparative Effectiveness of Larotrectinib vs. Entrectinib for Treatment of Fusion-Positive Cancers in Children and Young Adults

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Introduction

- Larotrectinib and entrectinib are approved for pediatric and adult patients with *NTRK* gene fusion-positive cancers.[1,2]
- Previous comparative effectiveness studies have demonstrated promising results for larotrectinib compared to entrectinib in adult patients with metastatic *NTRK* gene-fusion cancers.[3-5]
- A recent analysis of entrectinib in children and young adults (<22 years of age) with fusion-positive tumors (*NTRK*, *ROS1*, or *ALK*) was conducted.[6]
- There are no studies that have compared larotrectinib to entrectinib in the pediatric and young adult population.

Objective

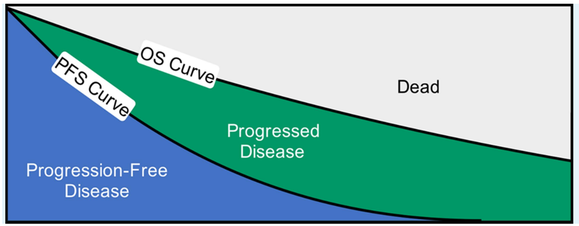
- This study aimed to estimate and compare expected life-years (LYs) and quality-adjusted life-years (QALYs) for pediatric and young adult patients with primary CNS solid tumors or infantile fibrosarcoma eligible to receive larotrectinib (primary CNS / infantile fibrosarcoma) or entrectinib (primary CNS / extracranial solid tumors).

Methods

Modeling Approach

- Partitioned survival models were developed to project long-term comparative effectiveness of larotrectinib vs. entrectinib (Figure 1).
- PFS and OS were estimated from parametric survival distributions (Exponential, Weibull, Log-logistic, and Log-normal).
- QALYs were estimated by adjusting the time spent in the pre-progression and post-progression health states by utility values derived from publicly available literature (Table 1).[7]
- Probabilistic sensitivity analysis with 5,000 simulations were run to obtain 95% credible intervals (CrI).
- Outcomes (LYs, QALYs) were discounted at 3%.

Figure 1. Model Schematic



Methods

Larotrectinib Data Source

- Larotrectinib survival data were derived from an updated July 2022 analysis of 86 pediatric and young adult (<22 years of age) patients who were *NTRK* gene-fusion positive from the larotrectinib clinical trials program (NCT02122913, NCT02637687 NCT02576431).[8]
- The tumor types for primary CNS and extracranial solid tumors observed in the entrectinib study were used to select larotrectinib patients to improve the comparability of the two treatment groups.[6]
  - There were 37 patients with primary CNS (43%) and 49 patients with infantile fibrosarcoma (57%).

Entrectinib Data Source

- Survival data for 26 patients treated with entrectinib were informed from NCT02650401, the majority of whom were *NTRK* gene-fusion positive (n=15, 58%) followed by *ROS1* (n=8, 31%) and *ALK* (n=3, 12%)
- Most patients had primary CNS tumors (n=16, 62%) and 10 had extracranial solid tumors (38%)
- In the base case, we imputed entrectinib OS for the study population by applying the entrectinib OS to PFS ratio observed in the adult population exclusively to the entrectinib PFS in the study population.[9]
- In the scenario analysis, we imputed entrectinib OS for the study population by applying the larotrectinib OS to PFS ratio observed in the same population to entrectinib PFS.

Table 1. On-Treatment Health State Utility Values and Response Rates*

	Larotrectinib	Entrectinib
Central nervous system tumors in children (response rate)	0.71 (66%)	0.69 (58%)

*On-treatment utilities were calculated as a weighted average of the utility for those in pre-progression, with no evidence of disease and recurrent disease based on the response rate for each treatment.

Results

- Exponential curve fits were used based on goodness-of-fit and clinical plausibility for PFS and OS (Figures 2 and 3).

Figure 2. Extrapolated Progression Free Survival

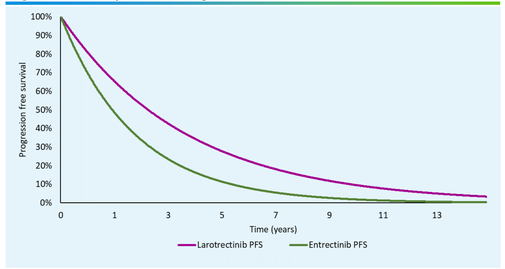
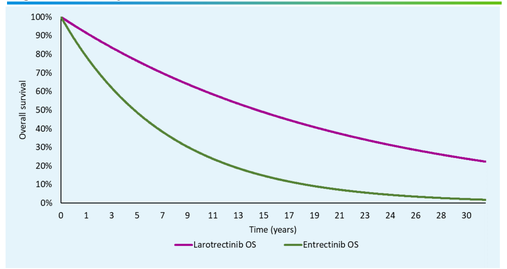


Figure 3. Extrapolated Overall Survival



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Results

- In the treatment of fusion-positive cancers in children and young adults, larotrectinib resulted in gains of 9.70 total LYs compared to entrectinib, which translated to gains of 3.87 total QALYs (Table 2).
- Specifically, for PFS, patients treated with larotrectinib gained 1.85 LYs and 1.35 QALYs compared to entrectinib
- In the scenario analysis, larotrectinib resulted in gains of 12.69 total LYs and 4.83 total QALYs compared to entrectinib

Table 2. Survival and Quality-Adjusted Survival Outcomes

(95% CrI)	Larotrectinib	Entrectinib (Base Case)	Entrectinib (Scenario)
Pre-Progression LYs	4.50 (3.23, 6.21)	2.66 (2.11, 3.36)	2.66 (1.91, 3.67)
Post-Progression LYs	13.16 (6.67, 19.56)	5.30 (2.39, 14.52)	2.31 (0.70, 10.79)
Total LYs	17.66 (11.45, 24.03)	7.96 (4.49, 17.88)	4.97 (2.71, 14.28)
Pre-Progression QALYs	3.18 (2.01, 4.75)	1.82 (1.26, 2.56)	1.82 (1.17, 2.72)
Post-Progression QALYs	4.21 (0.00, 14.83)	1.70 (0.00, 8.77)	0.74 (0.00, 5.11)
Total QALYs	7.39 (2.45, 17.99)	3.52 (1.43, 10.84)	2.57 (1.30, 7.29)

Conclusions

- In pediatric and young adult patients with metastatic fusion-positive tumors, larotrectinib may produce substantial life expectancy and quality-adjusted life-year gains compared to entrectinib.
- Additional data with more mature data and larger sample size will further inform this comparison.

Limitations

- We used an unadjusted naïve direct comparison in the absence of direct comparative data.
- While the majority of entrectinib patients were *NTRK* gene-fusion positive, patients with *ROS1* and *ALK* gene fusions were included due to the inability to separate them from the analysis.
- Due to the lack of publicly available data on entrectinib in patients <22 years of age, OS was imputed.
- The sample sizes for larotrectinib and entrectinib estimates were small.
- The larotrectinib arm consisted of primary CNS and infantile fibrosarcoma patients compared to primary CNS and extracranial solid tumors for entrectinib
- Comparative safety differences were not evaluated.
- There is uncertainty as to how the comparative effectiveness results will translate to clinical practice outside of Phase 1 and 2 trials

Disclosures

This study is sponsored by Bayer AG. The sponsor was involved in the study design and writing of the report.