The Potential Long-Term Comparative Effectiveness of Larotrectinib and Entrectinib for Second-Line Treatment of TRK Fusion-Positive Metastatic Lung Cancer

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ABSTRACT

BACKGROUND: Larotrectinib and entrectinib are FDA-approved therapies for patients with non-small cell lung cancer (NSCLC) with neurotrophic receptor tyrosine kinase gene fusion (TRK fusion-positive) whose cancer has metastasized and progressed. Early evidence indicates that these targeted therapies may offer dramatic survival benefits versus traditional cytotoxic regimens, but it remains uncertain how larotrectinib and entrectinib compare with each other.

OBJECTIVE: To simulate and compare expected life-years and quality-adjusted life-years (QALYs) for both TRK inhibitors.

METHODS: We developed a partitioned survival model to project the long-term comparative effectiveness of larotrectinib versus entrectinib in second-line treatment of metastatic NSCLC. Larotrectinib survival data were derived from a 13-month follow-up of 12 patients with TRK fusion-positive NSCLC in the NCT02122913 (phase 1) and NCT02576431 (NAVIGATE) trials. Entrectinib survival data were derived from a 13-month follow-up of 10 patients with TRK fusion-positive NSCLC in the ALKA-372-001, STARTRK-1, and STARTRK-2 trials. For larotrectinib and entrectinib progression-free survival and overall survival (OS), in-trial survival was extrapolated using parametric curve fits. Exponential fits were selected for all survival models based on minimal Bayesian information criteria and clinical plausibility. Lifetime survival curves were used to estimate expected mean/median survival. QALYs were estimated by applying preprogression and postprogression health state utilities derived from the literature.

RESULTS: In the base case, treatment with larotrectinib and entrectinib resulted in 5.4 and 1.2 median preprogression life-years and 7.0 and 1.8 median total life-years, respectively. Mean preprogression life-years (QALYs) were 7.5 (5.0) and 1.9 (1.2), and mean total life-years (QALYs) were 9.2 (5.8) and 4.4 (2.4), respectively.

CONCLUSIONS: Among TRK inhibitors for metastatic NSCLC, larotrectinib is estimated to provide improved life-year and QALY outcomes versus entrectinib based on parametric extrapolations of in-trial survival data. Our analysis is limited by lack of NSCLC-specific data on entrectinib OS, the small samples of patients with NSCLC in the trials, and a cross-trial comparison. Future studies should re-evaluate the comparative effectiveness of larotrectinib versus entrectinib as more patients are treated and as long-term survival data mature.

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What is already known about this subject

- Early evidence indicates that the receptor tyrosine kinase (TRK) inhibitors larotrectinib and entrectinib may offer dramatic survival benefits versus traditional cytotoxic regimens for treatment in TRK fusion-positive metastatic non-small cell lung cancer (NSCLC).
- No study has evaluated the potential comparative effectiveness of larotrectinib versus entrectinib for second-line treatment of TRK fusion-positive metastatic NSCLC.

What this study adds

- We used larotrectinib and entrectinib clinical trial data and simulation modeling to project the potential long-term comparative effectiveness of the 2 FDA-approved TRK inhibitors for treatment in TRK fusion-positive metastatic NSCLC.
- We found that larotrectinib is expected to provide improved life-year and quality-adjusted life-year outcomes compared with entrectinib based on parametric extrapolations of in-trial survival data.
- Future studies should reevaluate the comparative effectiveness of larotrectinib and entrectinib as greater numbers of patients are treated and as long-term survival data mature.

Larotrectinib and entrectinib are therapies approved by the U.S. Food and Drug Administration (FDA) for adult patients with neurotrophic receptor tyrosine kinase gene fusion (TRK fusion-positive) found in multiple solid tumor types whose cancer has metastasized and progressed. Entrectinib also was approved for treatment in adults with non-small cell lung cancer (NSCLC) with ROS1 fusion-positive tumors. Emerging evidence indicates that these targeted therapies may offer potentially dramatic survival benefits for patients compared with traditional cytotoxic regimens.^{1,2}

Guidelines recommend that patients who initiate on either larotrectinib or entrectinib do not use the alternate TRK inhibitor as a subsequent line of treatment, that is, clinicians and patients need to decide between these 2 products for their only chance at using a TRK inhibitor.³ However, data on larotrectinib and entrectinib comparative effectiveness and safety remain uncertain, in part because of the design of the clinical

research programs used to support FDA approval. Both clinical research programs employed single-arm, basket trial designs without concurrent or historical control groups in relatively small populations of patients.^{1,2} The trial populations were relatively similar across key characteristics, and the available data to date indicate longer median progression-free (PFS) and overall survival (OS) in samples of all patients treated across tumor types with larotrectinib (median PFS=28.3 months, median OS=44.4 months) as compared with entrectinib (median PFS=11.2 months, median OS=20.9 months).^{1,2} In small samples of patients with NSCLC, larotrectinib median PFS and OS were not reached (n=12), while entrectinib median PFS was 14.9 months, and OS results have not been reported (n=10).

Of importance to clinicians and decision makers is that extrapolation of within-trial survival outcomes using standard parametric curve fit methods can provide more comprehensive estimates of the potential comparative effectiveness of larotrectinib and entrectinib in treatment for NSCLC and can allow for estimation on mean life expectancy and quality-adjusted life-years (QALYs).⁴ The objective of this study was to use available evidence to extrapolate and compare expected life-years and QALYs for both TRK inhibitors in metastatic NSCLC to inform initial stakeholder considerations about potential comparative effectiveness.

Methods

Approach Overview

We developed a partitioned survival simulation model in Microsoft Excel (version 16.16.12, Redmond, WA) to project long-term comparative effectiveness of larotrectinib and entrectinib in second-line treatment of metastatic NSCLC.⁵ The simulation evaluated preprogression and OS over a lifetime horizon (maximum 50-year follow-up, to age 102 years). The model was populated with larotrectinib and entrectinib survival, response, and health-related quality of life data drawn from several clinical trials reported at recent major oncology conferences. It should be noted that all source studies had limited sample size (n<60) and median follow-up duration (13 months).^{2,6} We modeled parametric curve fits to in-trial PFS and OS data to project long-term survival outcomes.^{4,7} Outcomes included expected 3-, 5-, and 10-year survival proportions as well as mean expected life-years over a lifetime horizon.

Larotrectinib Survival Data Sources

Larotrectinib OS and PFS data were derived from a 13-month follow-up of 12 patients with TRK fusion-positive NSCLC in the NCT02122913 (phase 1) and NCT02576431 (NAVIGATE) trials.² Among patients in this sample, median age was 52.0 years; 50% (n=6) were female; 92% (n=11) had ≥1 previous systemic therapy; 50% (n=6) had 3 or more systemic therapies; and 8% (n=1) had no previous systemic therapy.

Entrectinib Survival Data Sources

Entrectinib NSCLC PFS data were derived from a 13-month follow-up of 10 patients with TRK fusion-positive NSCLC in the ALKA-372-001, STARTRK-1, and STARTRK-2 trials.⁶ Among patients in this sample, median age was 62.5 years, 50% (n=5) were female, 30% (n=3) had 1 previous systemic therapy, 40% (n=4) had 2 or more systemic therapies, and 30% (n=3) had no previous systemic therapy.

While there have been reports of entrectinib OS pooled across TRK fusion-positive tumor types, there have not been reports of entrectinib OS data in the subgroup of patients with TRK fusion-positive NSCLC. To model survival in the absence of such data, we imputed entrectinib OS by applying the same monthly ratio of OS to PFS observed in patients receiving larotrectinib to entrectinib PFS outcomes in ALKA-372-001, STARTRK-1, and STARTRK-2 trials.⁶ This approach resulted in a mean of 4.38 expected life years—74% greater than the mean life-years estimated from the model (2.52) when OS was derived from pooled entrectinib results across 54 patients with any TRK fusion-positive tumor type in the ALKA-372-001, STARTRK-1, and STARTRK-2 trials and extrapolated with an exponential curve fit.

Parametric Survival Curve Fits

In-trial survival outcomes were extrapolated using parametric curve fits (Weibull, exponential, log-logistic, gamma) for larotrectinib PFS and OS as well as entrectinib OS.⁷ For entrectinib PFS, an exponential model was fit to the median PFS estimate for 10 patients with TRK fusion-positive NSCLC.⁶ This approach was taken in the absence of publicly reported Kaplan-Meier survival curves showing monthly survival proportions over the 13-month follow-up period.

Based on minimal Bayesian information criteria, clinical plausibility, and visual inspection, exponential fits were selected to simulate long-term survival in all PFS and OS survival models. Lifetime survival curves were used to estimate expected mean and median PFS and OS. Lifetime survival curves were designed so that survival age-based mortality rates could not be lower than those for the general public as reported in U.S. life tables.⁸ If parametric curve fit annual mortality rates were less than that of U.S. life tables for a given mean age of the cohort, then mortality rates reverted to those of the life tables.

Health State Utility Values for Estimation of QALYs

Health state utility values for preprogression and postprogression health states (0.66 and 0.47, respectively) were derived from a societal based valuation study of 100 people in the United Kingdom using standard gamble methods.⁹ These values were applied to survival time in preprogression and postprogression states to estimate expected QALYs over a lifetime horizon.

FIGURE 1 Parametric Extrapolations of Larotrectinib and Entrectinib Overall and Progression-Free Survival

Note: This figure shows the curve fits used to calculate base case model outcomes. The annual mortality rates for the larotrectinib and entrectinib arms were less than that for aged-matched adults in U.S. life tables beginning in months 275 and 281 of follow-up, so mortality rates reverted to those from the life table from that point forward—consequently, the sharply declining curves.

Scenario Analyses

Due to the small samples of patients with NSCLC in the larotrectinib ($n=12$) and entrectinib ($n=10$) trials and the limited median follow-up duration of 13 months, there was a high degree of uncertainty about long-term survival with both therapies. As such, we undertook sensitivity analyses with wide uncertainty ranges to explore the implications of alternative survival outcomes that might be demonstrated with larger samples tracked over longer follow-up periods. Specifically, we evaluated survival and QALY outcomes in scenarios where (a) larotrectinib OS hazard was increased by 30% (i.e., less favorable survival) versus the base case larotrectinib OS function, and (b) entrectinib OS was decreased by 30% (i.e., more favorable survival) versus the base case entrectinib OS function. The magnitude of variation in survival functions ($\pm 30\%$) was arbitrarily selected as a large but statistically plausible deviation in survival outcomes as compared with the base case. We took this approach in absence of reported 95% confidence intervals for survival outcomes. Furthermore, it would be

expected that survival function confidence intervals derived from samples of 10 or 12 patients that could have highly variable survival durations would result in such extreme values that they would not be informative in our sensitivity analyses.

Using the sensitivity analyses survival functions previously described, we conducted 3 additional pairwise comparisons of larotrectinib and entrectinib: (1) sensitivity analysis of larotrectinib survival versus base case entrectinib survival, (2) base case larotrectinib survival versus sensitivity analysis of entrectinib survival, and (3) sensitivity analysis of larotrectinib survival versus sensitivity analysis of entrectinib survival. These comparisons would assess (a) comparative effectiveness under less favorable larotrectinib survival, (b) comparative effectiveness under more favorable entrectinib survival, and (c) comparative effectiveness under an extreme scenario with less favorable larotrectinib survival and more favorable entrectinib survival, respectively. We conducted these analyses recognizing the possibility that if all resulted in positive incremental survival outcomes for larotrectinib, it could reinforce the likely favorable comparative effectiveness of larotrectinib

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TABLE 1 Base Case and Scenario Analysis Comparative Effectiveness Estimates for Larotrectinib Versus Entrectinib in TRK Fusion-Positive Metastatic Non-Small Cell Lung Cancer^a

Scenario	Larotrectinib Outcomes		Entrectinib Outcomes		Difference in Outcomes	
	Preprogression	Total	Preprogression	Total	Preprogression	Total
Base case	7.49 (5.00)	9.15 (5.78)	1.85 (1.23)	4.38 (2.43)	5.64 (3.77)	4.77 (3.36)
Alternative scenario 1: larotrectinib 30% increase in PFS and OS hazard	6.02 (4.02)	7.44 (4.69)	1.85 (1.23)	4.38 (2.43)	4.17 (2.79)	3.05 (2.27)
Alternative scenario 2: entrectinib 30% decrease in PFS and OS hazard	7.49 (5.00)	9.15 (5.78)	2.56 (1.70)	6.77 (3.75)	4.93 (3.30)	2.38 (2.03)
Alternative scenario 3: combination of scenarios 1 and 2	6.02 (4.02)	7.44 (4.69)	2.56 (1.70)	6.77 (3.75)	3.46 (2.32)	0.67 (0.95)

^aOutcomes are reported as life-years (QALYs).

OS=overall survival; PFS=progression-free survival; QALYs=quality-adjusted life-years.

versus entrectinib in the treatment for TRK fusion-positive NSCLC that would likely be demonstrated in the base case.

Results

Base Case Survival Results

In the base case, treatment with larotrectinib and entrectinib resulted in a median of 5.4 and 1.3 preprogression life-years and a median of 7.0 and 1.8 total-life years, respectively (Figure 1). Mean preprogression life-years were 7.5 and 1.9, and mean total life-years were 9.2 and 4.4, respectively (Table 1). Projected OS proportions at 3, 5, and 10 years were 75%, 61%, and 37% with larotrectinib, and 35%, 22.4%, and 13.2% with entrectinib (Figure 1).

Base Case Quality-Adjusted Survival Results

In the base case, treatment with larotrectinib and entrectinib resulted in mean preprogression QALYs of 5.0 and 1.2 and mean total QALYs of 5.8 and 2.4, respectively (Table 1).

Sensitivity Analysis Survival Results

Scenario 1: Sensitivity Analysis of Larotrectinib Survival (–30%) Versus Base Case Entrectinib Survival. In scenario 1, treatment with larotrectinib and entrectinib resulted in 5-year survival proportions of 53% and 22%, respectively. Mean preprogression life-years were 6.0 and 1.9, and mean QALYs were 4.0 and 1.2, respectively (Table 1). Mean total life-years were 7.4 and 4.4, and mean QALYs were 4.7 and 2.4, respectively (Table 1).

Scenario 2: Base Case Larotrectinib Survival Versus Sensitivity Analysis of Entrectinib Survival (+30%). In scenario 2, treatment with larotrectinib and entrectinib resulted in 5-year survival proportions of 61% and 35%, respectively. Mean preprogression life-years were 7.5 and 2.6, and mean QALYs were 5.0 and 1.7, respectively (Table 1). Mean total life-years were 9.2 and 6.8, and mean QALYs were 5.8 and 3.7, respectively (Table 1).

Scenario 3: Sensitivity Analysis of Larotrectinib Survival (–30%) Versus Sensitivity Analysis of Entrectinib Survival (+30%). In scenario 3, treatment with larotrectinib and entrectinib resulted in 5-year survival proportions of 53% and 35%, respectively. Mean preprogression life-years were 6.0 and 2.6, and mean QALYs were 4.0 and 1.7, respectively (Table 1). Mean total life-years were 7.4 and 6.8, and mean QALYs were 4.7 and 3.7, respectively (Table 1).

Discussion

Using emerging clinical data, we set out to develop comparative effectiveness estimates of larotrectinib and entrectinib in patients with TRK fusion-positive metastatic NSCLC. We undertook this analysis to better inform clinical and health care system reimbursement decisions, in part because both of these targeted, tumor-agnostic agents were FDA-approved with very limited clinical evidence.

We found that among TRK fusion protein-targeted therapies for metastatic NSCLC, larotrectinib is estimated to provide improved life-year and QALY outcomes versus entrectinib using extrapolations of in-trial survival data. Larotrectinib survival gains remain highly uncertain, but scenario analyses suggested that gains are expected to persist under a range of clinically plausible survival effects. Future studies should re-evaluate the comparative outcomes of larotrectinib and entrectinib as more patients are treated, survival data mature, and real-world evidence studies are conducted in TRK fusion-positive NSCLC.

In the past 20 years, the treatment landscape in advanced NSCLC has evolved from a few traditional chemotherapeutic options with limited effectiveness to now include many innovative products ranging from immunotherapeutics to agents targeted to a variety of tumors molecular profiles.³ Five years ago, patients with TRK fusion-positive tumors were limited to untargeted products. With the arrival of the first TRK inhibitors, larotrectinib and entrectinib, these patients can potentially achieve unprecedented response rates and survival outcomes.^{2,6} However, the choice between TRK inhibitors is

critical as guidelines recommend that patients receive only 1 of the 2 available treatment options. Given the evidence available in the peer-reviewed literature and conference proceedings, coupled with the estimates provided here, larotrectinib may be the optimal treatment option for patients who are TRK fusion-positive who have no satisfactory alternative treatments or that have progressed following cytotoxic treatment.

Limitations

Our analysis has several important limitations that should be noted. First, in-trial survival data were derived from small samples tracked for a median of 13 months.^{2,6} As such, there is a high degree of uncertainty about how well survival data from these samples will generalize to larger samples of patients with TRK fusion-positive NSCLC treated with larotrectinib or entrectinib. Recognizing this issue, we conducted a series of sensitivity analyses that widely varied the OS hazard functions for each agent and found that larotrectinib was still expected to result in a potentially clinically meaningful gain in survival versus entrectinib even if the larotrectinib hazard was increased by 30% and the entrectinib hazard was decreased by 30%.

Second, there is limited publicly reported data about OS outcomes in patients with TRK fusion-positive NSCLC treated with entrectinib. To deal with this, we imputed entrectinib OS by applying the same monthly ratio of OS to PFS that was modeled for larotrectinib to the parametric extrapolation of in-trial PFS for entrectinib. This approach closely replicated reported OS in a pooled sample of TRK fusion-positive tumors treated with entrectinib and is also expected to minimize differences in comparative survival between larotrectinib versus entrectinib—an important factor to mitigate bias in our incremental analyses.⁶

Finally, this study involves a naive, direct (cross-trial) comparison of survival with larotrectinib and entrectinib. As samples were not derived from a single randomized trial, there is possible imbalance in prognostic factors between samples. For example, median age in the larotrectinib sample (52.0 years) was lower than median age in the entrectinib sample (62.5 years). This imbalance may account for some fraction of the more favorable survival we demonstrated for larotrectinib versus entrectinib. Still, given the relatively short survival duration of all patients diagnosed with advanced NSCLC, this imbalance likely only explains a limited amount of the mean survival differences we estimated. For example, U.S. life tables for the general public demonstrate that mortality rates for persons aged 52 years is only 1.09-fold greater than those aged 62 years, and our sensitivity analyses examined incremental outcomes under much larger uncertainty ranges.⁸ It is also possible that there are unmeasured prognostic factors that could vary between samples, which could impact comparative effectiveness estimates.

Our results should be interpreted with these notes in mind, and comparative effectiveness should be reassessed using rigorous observational research designs as each agent has increased real-world use in clinical practice.

Conclusions

Among TRK inhibitors for treatment of metastatic NSCLC, larotrectinib is estimated to provide improved life-year and QALY outcomes compared with entrectinib based on parametric extrapolations of in-trial survival data. Our analysis is limited by a paucity of NSCLC-specific data on entrectinib OS; the small sample size of patients with NSCLC in source trials; and a naive, direct (cross-trial) comparison. Future studies should re-evaluate the comparative effectiveness of larotrectinib and entrectinib as greater numbers of patients are treated and as long-term survival data mature.

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