EE453

# Cost-Effectiveness Analyses of Repotrectinib in TKI-Naïve Patients with *ROS1+* Advanced Non-Small Cell Lung Cancer

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## Background

- Non-small-cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for 80-85% of all cases. Symptoms are usually unnoticeable until the lung cancer has progressed to advanced stages, for which mutational testing has become an integral part of guiding treatment. [1]
- Receptor tyrosine kinase 1 fusions (*ROS1+*) are present in 1-2% of tumors among all patients with NSCLC. *ROS1* fusions are associated with responsiveness to certain tyrosine kinase inhibitors (TKIs), which block tyrosine kinases and reduce the cell growth and division associated with cancer progression.
- Currently available treatments for TKI-naïve patients with *ROS1+* NSCLC include repotrectinib, entrectinib, and crizotinib.
- Repotrectinib is a next-generation orally administered ROS1 TKI with demonstrated durable efficacy (a confirmed objective response rate of 79%) in TRIDENT-1, a phase I/II global, open-label, single-arm trial. Progression-free survival (PFS) and safety were secondary end points. However, overall survival (OS) data were immature and European Quality of Life 5 Dimensions (EQ-5D) utility weights were not available at the time of analysis. [2]

## Objective

This study aims to establish a health technology assessment (HTA) acceptable framework to evaluate cost-effectiveness of repotrectinib versus standard of care (SoC) in TKI-naïve patients with *ROS1+* advanced NSCLC, in light of major challenges in the available clinical evidence.

## Methods

The model takes a hypothetical United Kingdom (UK) National Health Service (NHS) perspective and estimates life years (LY), quality-adjusted life years (QALY), costs, and incremental cost per QALY of repotrectinib versus SoC over a 30-year time horizon at a 3.5% annual discount rate, based on a pre-specified study protocol.

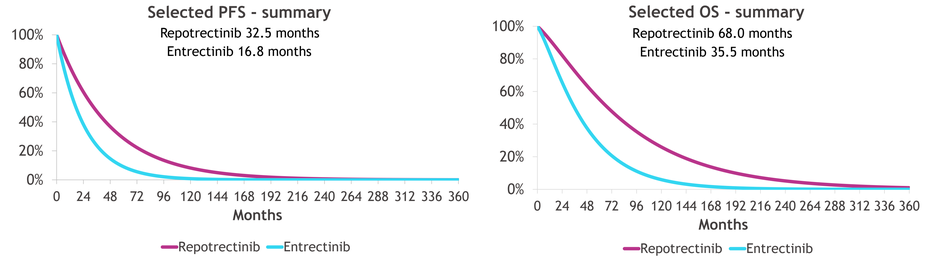
- The base case comparator is entrectinib, with a scenario evaluating cost-effectiveness versus crizotinib.
- Model structure features a partitioned survival approach comprising 3 health states (pre-progression, post-progression, and dead) with 30-day cycles for transitions.

### *Modeling survival*

- Repotrectinib PFS was estimated by parametric fitting of the individual participant data (IPD) from TRIDENT-1 (data cutoff date of October 15, 2023). [2] Standard parametric survival models (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, and generalized gamma) were fitted to estimate long-term/lifetime outcomes. Exponential model was selected based on the assessment of the fit and clinical plausibility. (**Figure 1**)
- An unanchored matching-adjusted indirect comparison (MAIC) informed by a systematic literature review [3, 4] was undertaken to estimate hazard ratio (HR) for PFS with entrectinib (or crizotinib in the scenario analysis) versus repotrectinib utilizing published studies (ALKA-372-001, STARTRK-1, and STARTRK-2 for entrectinib, [5] PROFILE 1001, OO-1201, AcSé, METROS, and EUCROSS for crizotinib [4, 6]) and TRIDENT-1 IPD. The HR for repotrectinib PFS was estimated to be 0.52 relative to entrectinib and 0.44 relative to crizotinib.
- Given the immaturity of OS data from TRIDENT-1 at the time of the analysis, PFS was used as a surrogate to estimate OS based on an analysis using United States (US) data from the Flatiron database. (**Figure 1**) [7] This analysis found that patients who had progressed had 2.7 times the hazard of death compared to those who had not progressed. A calibration exercise was undertaken utilizing the parametric exponential PFS and OS curves for entrectinib, which estimated the HR of mortality for patients who have not progressed to be 0.28.

## Methods (cont.)

**Figure 1.** Survival curves




### *Costs*

- Drug acquisition costs for treatments were calculated based on dosing in product labels and the relative dose intensity (RDI) from pivotal studies, [2, 5] packaging prices published by British National Formulary, [8] and extrapolated time on treatment based on trial data. Repotrectinib used recommended phase 2 dose and assumed parity acquisition cost with entrectinib.
- Drug administration costs were differentiated for first versus subsequent cycles and oral versus intravenous administration, using the respective service codes. [9, 10]
- Monitoring costs were included for pre-progression and post-progression health states, with the resource utilization sourced from the entrectinib National Institute for Health and Care Excellence (NICE) submission. [11]
- Adverse event (AE) rates were multiplied by NHS reference costs of respective service codes for managing AEs to derive total AE costs. [9]
- Costs of post-progression therapies were calculated assuming one additional therapy after progressing on the primary treatment and received over a fixed treatment duration. Utilization of post-progression therapy was based on data from TRIDENT-1 on patients receiving subsequent TKIs or chemotherapy. (**Table 2**) [12]
- End-of-life cost was modeled as a one-off cost (£13,569) for palliative care for the proportion of patients who were dying in each model cycle, equivalent to 90 days of hospital care. [10, 11]
- All costs were represented in 2024 values (**Table 1**).

**Table 1.** Drug acquisition, administration, monitoring, and AE costs

| Drug acquisition | Cost | Packaging | Dose | RDI | Admin/cycle |
|---|---|---|---|---|---|
| Repotrectinib | £5,160.00 | 240 x 40 mg | 160 mg[a] | 86% | 60 |
| Entrectinib | £5,160.00 | 90 x 200 mg | 600 mg | 91% | 30 |
| **Administration** | **Oral** | **IV** | | | |
| First cycle | £237.03 | £519.04 | | | |
| Subsequent cycles | £10.60 | £402.66 | | | |
| **Monitoring** | **Unit cost** | **Pre-progression** | | **Post-progression** | |
| | | % patients per month | Frequency per month | % patients per month | Frequency per month |
| Outpatient visit | £45.86 | 100 | 0.75 | 100 | 1.00 |
| GP visit | £224.89 | 10 | 0.10 | 28 | 1.00 |
| Cancer nurse | £130.05 | 20 | 1.00 | 10 | 1.00 |
| CT | £175.27 | 30 | 0.75 | 5 | 0.75 |
| Chest x-ray | £41.84 | 30 | 0.75 | 30 | 0.75 |
| Complete blood count | £3.24 | 100 | 0.75 | 100 | 1.00 |
| Biochemistry | £1.69 | 100 | 0.75 | 100 | 1.00 |
| **Adverse event** | **Unit cost** | **Repotrectinib** | **Entrectinib** | | |
| Anemia | £471.34 | 3.8% | 0.0% | | |
| Dyspnea | £600.45 | 0.5% | 0.0% | | |
| Increased weight | £0.00 | 1.6% | 11.2% | | |
| Nausea | £0.00 | 0.5% | 0.0% | | |
| Neutropenia | £0.00 | 0.0% | 2.2% | | |

[a] Recommended phase 2 dose: 160 mg orally once daily for 14 days then 160 mg twice daily.

**Key**: AE – adverse event; CT – computed tomography; GP – general practitioner; IV – intravenous; NICE – National Institute for Health and Care Excellence; RDI – relative dose intensity.

**Table 2.** Utilization of subsequent therapy

| Subsequent therapy | Utilization by treatment arm | | Time on treatment (month) |
|---|---|---|---|
| | Repotrectinib | Entrectinib | |
| Entrectinib | 21.4% | 0.0% | 3.96 [12] |
| Crizotinib | 21.4% | 42.9% | 5.65 [12] |
| Platinum doublet therapy | 57.1% | 57.1% | 3.30 [11] |

### *Utilities*

- EQ-5D utility weights were mapped from European Organisation for Research and Treatment of Cancer (EORTC) data in TRIDENT-1 for pre- and post-progression health states (0.84 and 0.79 respectively; same across treatment arms owing to a lack of availability of utility data for all model comparators). [13]
- Utility decrements due to grade 3 or 4 AEs were based on previous NICE submissions and assumptions. [11, 14] Neutropenia (-0.09) and anaemia (-0.07) were the events with an impact on utility weights.

## Results

### *Base case*

- Patients on repotrectinib achieved better outcomes (4.91 QALYs and 6.01 LYs) than those on entrectinib (2.82 QALYs and 3.46 LYs).
- Using parity price, total costs for repotrectinib and entrectinib were £186,462 and £132,892, respectively, with an incremental cost-effectiveness ratio (ICER) of £25,621/QALY. (**Table 3**)

**Table 3.** Base case results

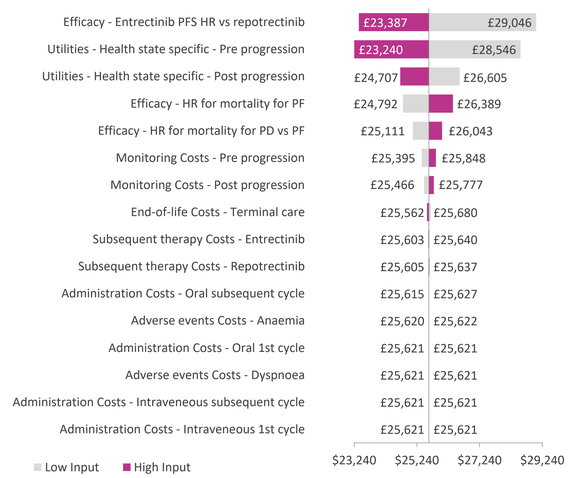
| Outcome | Repotrectinib | Entrectinib | Incremental |
|---|---|---|---|
| Costs | £186,462 | £132,892 | £53,569 |
| Median PFS (months) | 32.5 | 16.8 | 15.8 |
| Median OS (months) | 68.0 | 35.5 | 32.5 |
| QALYs | 4.91 | 2.82 | 2.09 |
| LYs | 6.01 | 3.46 | 2.55 |
| ICER/QALY | - | - | £25,621 |

**Key:** ICER – incremental cost-effectiveness ratio; LY – life year; OS – overall survival; PFS – progression-free survival; QALY – quality-adjusted life year.

### *Scenario and sensitivity analyses*

- The ICER increased with shorter time horizons, with £26,351/QALY over 20 years and £30,996/QALY over 10 years.
- The ICER remained stable when entrectinib PFS was modeled by parameterization of digitized trial data (assuming exponential model) instead of the MAIC, alternative parameterization models were selected for repotrectinib PFS, subsequent therapy costs were excluded, or when health state utilities were based on the entrectinib NICE submission rather than the mapping study.
- The comparison versus crizotinib led to an ICER of £11,521, with 2.51 incremental QALYs and 3.06 incremental LYs.
- When considering the NICE disease severity modifier, the QALY shortfall calculated for patients with ROS1 advanced NSCLC justifies a QALY weight between 1.2 and 1.7 based on outcomes reported for current SoC treatments [11, 14]. The corresponding ICER for repotrectinib would fall within the range of £15,069 to £21,348.
- The deterministic sensitivity analysis also confirmed robustness of results, with the most impactful parameters being the HR for entrectinib PFS vs repotrectinib and health state utilities (pre- and post-progression). (**Figure 2**)
- Probabilistic sensitivity analysis with 1,000 simulations generated an 83.2% probability for repotrectinib to be cost-effective at a willingness-to-pay threshold of £30,000/QALY.

**Figure 2.** One-way sensitivity analysis




## Conclusions and Limitations

- Repotrectinib would be a cost-effective option for TKI-naïve patients with *ROS1+* advanced NSCLC, with cost-effectiveness ratios below the NICE threshold of £30,000 per QALY.
- These findings were robust across a variety of scenarios and sensitivity analyses.
- Limitations
  - OS for repotrectinib and comparators was estimated using PFS surrogacy due to the fact that repotrectinib OS data were immature at the time of the analysis.
  - The HRs for PFS between repotrectinib and the comparators were based on the best available MAIC results at the time of model development, due to lack of availability of head-to-head data.
  - Direct EQ-5D utility weights were not available from TRIDENT-1, and thus utilities were mapped from trial-reported EORTC data using a mixed adjusted model.
  - Due to variation in post-progression therapy utilization, the model applied a simplified approach by assigning a one-off post-progression treatment cost based on utilization and a fixed treatment duration for the included subsequent therapies. This was equally applied to all treatment arms, which potentially underestimated duration and costs of the subsequent treatment.

## Disclosures

This research was sponsored by BMS. AL and YY are employees of BMS. SC, KO, BF, QL, EW and KM are employees of Cencora, which received funds from BMS to conduct the research.

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