Cost per PFS-based responder for TKI-naive patients receiving repotrectinib or entrectinib in *ROS1* fusion positive (*ROS1*+) non-small cell lung cancer (NSCLC) in the United States (US)

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Reginald Villacorta[1], Rick Szymialis[1], Yong Yuan[1], Matthew Martin[2], Karissa Johnston[2]

[1]Bristol Myers Squibb, Lawrenceville, NJ, USA ;

[2]Broadstreet Health Economics and Outcomes Research, Vancouver, BC, Canada

Background

- This study evaluated the economic value of repotrectinib vs entrectinib, both of which are approved and recommended first-line treatments for *ROS1*+ advanced non-small cell lung cancer (aNSCLC) patients who are *ROS1* tyrosine kinase inhibitor (TKI)-naïve.[1]
- Repotrectinib demonstrated durable clinical activity in the TRIDENT-1 trial (NCT03093116) - a phase 1/2, open-label, multi-center, first-in-human study – as a treatment for participants with advanced solid tumors harboring *ALK*, *ROS1*, or *NTRK1-3* rearrangements.[2-4]
- No head-to-head randomized clinical trials (RCTs) have been conducted that directly compare outcomes for *ROS1* TKIs recommended for TKI-naïve patients in the US – such as repotrectinib, entrectinib, and crizotinib.[1]
- The relative efficacy of these agents was recently assessed via unanchored MAICs between: (1) repotrectinib and entrectinib, and (2) repotrectinib and crizotinib, among *ROS1* TKI-naïve patients with *ROS1*+ aNSCLC.[5,6]

Objectives

Primary: To characterize the costs and effects of repotrectinib vs entrectinib for the treatment of patients with *ROS1*+ aNSCLC who are *ROS1* tyrosine kinase inhibitor (TKI)-naïve, over a short-term (3-year) time horizon and from a societal perspective.

Exploratory: To estimate long-term (15-year) costs and effects of repotrectinib vs entrectinib for the treatment of patients with *ROS1*+ aNSCLC who are *ROS1* TKI-naïve.

Methods

- A partitioned survival model (PSM) was employed that evaluated multiple economic outcomes, incorporating cost per progression-free survival (PFS)-based responder (CPR), number needed to treat (NNT), cost of preventing an event (COPE), and long-term economic outcomes.
- A 3-year time horizon was chosen in the base case for CPR and NNT outcomes given its clinical relevance in aNSCLC,[4,7] while a 15-year horizon considered long-term outcomes, such as overall costs and difference in progression-free life years.
- Parametric models were applied to individual patient data (IPD) from TRIDENT-1 to estimate PFS, DoR, and OS outcomes. IPD were adjusted according to MAIC weights estimated by Wolf et al., 2025 and hazard ratios (HRs) were applied to estimate comparators curves.[5]

Cost per PFS-based responder (CPR)

- CPR was calculated by dividing the total treatment cost by the probability of remaining progression-free at 3 years, based on the PFS curves, and reflects the cost of sustaining patients in a progression-free state.

Number needed to treat (NNT)

- NNT was estimated using restricted mean survival time (RMST) to capture the average progression-free survival time within the 3-year time horizon, accounting for the cumulative differences in time spent progression-free.[8] While interpretation of the NNT is context-dependent, a literature review identified a median NNT of 5 (range: 2-20) in a sample of oncology studies reporting on PFS.
- The NNT_{ARR}, which captures the local treatment effect, is also presented.[9]

Cost of preventing an event (COPE)

- The COPE is the product of the NNT and total treatment costs per patient and represents the financial investment necessary to prevent a progression or death in a given time period e.g., 3 years.
- Drug costs were calculated based on Wholesale Acquisition Costs (WAC)[10] and DoR data from TRIDENT-1, with HRs used to estimate comparator DoR. Drug costs were adjusted for dose reductions based on treatment patterns described in US package inserts.[3,11]
- HCRU, AE management, and lost productivity were incorporated to capture the societal perspective. HCRU rates differed for pre- and post-progression states, with post-progression costs informed by OS data. AE management costs were derived from the literature,[7,12,13] and lost productivity accounted for absenteeism, presenteeism, and workforce participation.[14-16] Subsequent treatment costs were applied to the cohort in the post-progression state.
- One-way sensitivity analysis (OWSA) and scenario analyses were conducted to assess the robustness of key model parameters on outcomes. A sensitivity analysis was also run comparing repotrectinib against crizotinib by applying MAIC weights estimated for a pooled crizotinib population.[5]

Results

Cost per PFS-based responder (CPR)

- At 3 years, PFS probabilities were 0.42 for repotrectinib and 0.22 for entrectinib. **Costs per PFS-based responder were $2,108,603 for repotrectinib and $2,780,560 for entrectinib**, with annualized costs of $702,868 and $926,853, respectively.

Table 1 PFS-based CPR analysis repotrectinib vs entrectinib (3-year time horizon)

	Repotrectinib	Entrectinib
Total costs	$888,049	$609,901
Drug-related costs	$753,266	$451,232
Healthcare costs	$79,871	$93,812
Productivity loss	$54,913	$64,856
Responders	0.42	0.22
Cost per responder	$2,108,603	$2,780,560
Cost per responder per year	$702,868	$926,853

Footnote: 'Responders' refers to PFS probability at 3-year time horizon. 'Cost per responder' refers to total cost divided by % responders at 3-year time horizon. 'Cost per responder per year' refers to the cost per responder divided by the time horizon (3 years).

Number needed to treat (NNT)

- The NNT_{RMST} was 4 (95% CI: 3.7 to 5.0) based on the best-fitting parametric model (Weibull) applied to repotrectinib PFS data and a HR-adjusted curve for entrectinib, indicating that treating four patients with repotrectinib would prevent one progression/death over a 3-year time horizon.
- The NNT_{RMST} ranged from 7 (95% CI: 6.1 to 8.3) at a 2-year time horizon to 3 (95% CI: 2.2 to 3.4) at a 5-year time horizon.
- The NNT_{ARR} was 5 (95% CI: 1.6 to -4.7).

Cost of preventing an event (COPE)

- The COPE based on NNT_{RMST} (NNT_{ARR}) was $1,306,871 ($1,506,052) over a 3-year time horizon. With an NNT_{RMST} of 4, the COPE represents the cost of treating 4 patients with repotrectinib rather than entrectinib.

Long-term economic impact

- Total costs over the 15-year time horizon were $1,313,488 for repotrectinib compared to $914,718 for entrectinib, driven primarily by drug-related costs.
- Treatment with repotrectinib resulted in a gain of 0.92 PFLYs vs entrectinib.

Table 2 Long-term economic impact results for repotrectinib vs entrectinib

	Repotrectinib	Entrectinib	Incremental analysis
Total costs	$1,313,488	$914,718	$398,770
Drug-related costs	$942,914	$500,761	$442,153
Healthcare costs	$116,972	$137,343	-$20,371
Productivity loss	$253,602	$276,614	-$23,012
Progression-free life years	2.88	1.97	0.92

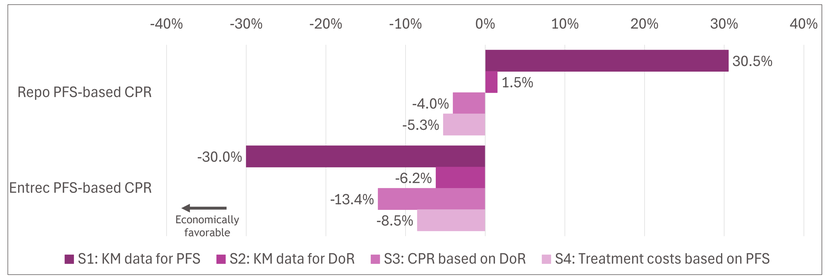
Footnote: Long-term results were estimated over a 15-year time horizon.

Scenario analysis

- Modelling KM data for PFS (repotrectinib and entrectinib) had the biggest overall impact on outcomes, resulting in 3-year PFS probabilities of 0.33 and 0.32, NTT_{RMST} of 3, and a higher (lower) CPR of $2,752,197 ($1,946,527) for repotrectinib (entrectinib) (Table 3).
- Despite a smaller difference in PFS probabilities at 3 years, the alternative NNT_{RMST} favors repotrectinib due to the RMST tracking the difference in the area under the PFS curve, which is larger when modelling KM data vs parametric models.

Results, continued

Figure 1 Scenario analysis – PFS-based CPR results



Footnote: The four key scenarios were: (S1) PFS based on KM data instead of parametric models for repotrectinib and HRs for comparators; (S2) DoR based on KM data instead of parametric models for repotrectinib and HRs for comparators; (S3) CPR based on DoR instead of PFS; and (S4) treatment costs based on PFS instead of DoR.

Acronyms: PFS, progression-free survival; DoR, duration of response; CPR, cost per PFS-based responder.

Table 3 Scenario analysis full results

	Repotrectinib						Entrectinib			
Scenario	**Total costs**	**Respond-ers**	**CPR**	**NNT_{RMST}**	**COPE**	**PFLYs**	**Total costs**	**Respond-ers**	**CPR**	**PFLYs**
BC	$0.89M	0.42	$2.11M	4	$1.31M	2.11	$0.61M	0.22	$2.78M	1.72
1	$0.91M	0.33	$2.75M	3	$0.85M	2.14	$0.62M	0.32	$1.95M	1.58
2	$0.90M	0.42	$2.14M	4	$1.52M	2.11	$0.57M	0.22	$2.61M	1.72
3	$0.89M	0.44	$2.02M	4	$1.31M	2.11	$0.61M	0.25	$2.41M	1.72
4	$0.84M	0.42	$2.00M	4	$1.33M	2.11	$0.56M	0.22	$2.54M	1.72

Acronyms: BC, base case; CPR, cost per PFS-based responder; NNT_{RMST}, number needed to treat; COPE, cost of preventing an event; PFLYs, progression-free life years.

- **OWSA** demonstrated that the most sensitive parameters for the CPR analysis were time horizon, PFS HR, drug pack cost, and DoR HR.
- Results of the **sensitivity analysis vs crizotinib** aligned with the comparison vs entrectinib, with repotrectinib outperforming crizotinib by a larger magnitude.

Conclusions

- Repotrectinib demonstrated a lower cost per PFS-based responder compared to entrectinib, with annualized costs substantially lower, reinforcing its economic advantage in managing *ROS1*+ aNSCLC.
- With an NNT_{RMST} of 4, repotrectinib shows a strong ability to delay disease progression or death compared to entrectinib, highlighting its clinical effectiveness in extending PFS.
- Model outcomes were particularly sensitive to the time horizon and efficacy assumptions, underscoring the need to define a clinically valid time period and to ensure the integration of robust efficacy data.
- Our analyses suggest that patients with *ROS1*+ aNSCLC benefit from prolonged disease control with repotrectinib, while payers gain from its improved cost efficiency relative to entrectinib.
- These results highlight the clinical and economic benefit of repotrectinib vs entrectinib in the US.

Limitations

- Short-term outcomes were based on a 3-year time horizon, reflecting a period covering commonly reported DoR for repotrectinib and entrectinib.[4,7] Alternative time horizons may be of interest to various stakeholders.
- Due to immature OS data from TRIDENT-1 and resulting lack of comparative evidence, OS was assumed equivalent between treatments; results should be interpreted with caution.

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Email: <reginald.villacorta@bms.com>