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What Did Time Reveal? Evaluating the Accuracy of Parametric Model Predictions Against Long-Term Observed Data for Larotrectinib

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INTRODUCTION

- **Larotrectinib** is a tumour-agnostic treatment that targets neurotrophic tyrosine receptor kinase (*NTRK*) fusion-positive tumors[1]. Its regulatory and health technology assessment (HTA) approvals were supported by single-arm basket trials with limited data due to the rarity of these cancers[2,3,4].
- **Long-term survival predictions** are critical for cost-effectiveness (CE) evaluations, yet limited trial data require extrapolation methods that may introduce considerable uncertainty[5].
- **Assessing the accuracy of these predictions** is essential to inform robust clinical and policy decisions[5,6].

OBJECTIVES

- We aim to **compare parametric survival model predictions** used in HTA submissions for larotrectinib **with observed** overall survival (OS) and investigator-assessed progression-free survival (PFS) from pooled trial **data with longer follow-up** (FU).

METHODS

- HTA submissions to the National Institute for Health Care Excellence (NICE) and other agencies were based on the **2018 dataset** (*N* = 102 patients)[7].
- A **Weibull distribution** was used by the sponsor to **extrapolate** OS and PFS in a CE model.
- Prediction accuracy was evaluated by comparing CE model outputs with 95% confidence intervals (CIs) of observed outcomes from the **2024 data readout**, representing a 61.6-month increase in median survival FU.
- Accuracy was assessed at timepoints corresponding to **~10% patient risk milestones**[8].

RESULTS

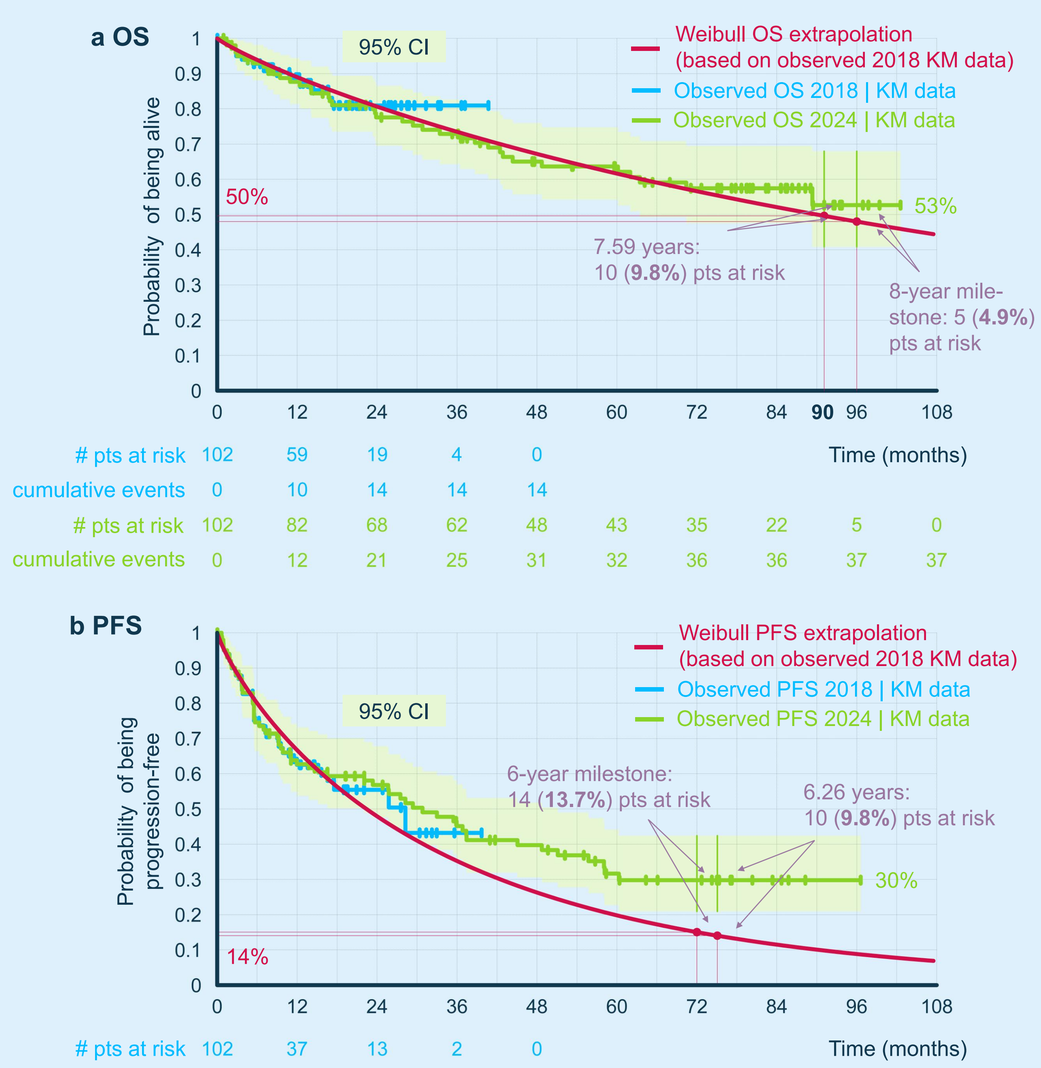
- The analysis pooled adult and pediatric patient-level data from three larotrectinib clinical trials (*N* = 102). Mean age was 37.1 years (standard deviation, 26.6; shown in **Table 1**). Fifteen tumor types were included, with the most common being soft tissue sarcoma (20.6%), salivary gland carcinoma (16.7%), and infantile fibrosarcoma (12.7%).
- The median FU time for OS, estimated using the reverse Kaplan-Meier (KM) method, increased from 15.6 months at the 2018 data cut to 77.2 months at the 2024 data cut – reflecting a 61.6-month difference.
- At 7.59 years, corresponding to the ~10% risk milestone (10 patients at risk), the 2018 **OS** Weibull extrapolation predicted 50% OS versus 53% observed – an underestimation of 3 percentage points, within the 95% CI of the 2024 OS KM estimate. At the rounded 8-year milestone, the underestimation rises to 5 percentage points, still within the 95% CI. Both time points are shown in **Figure 1 a**.
- The 2018 OS Weibull model predicted a **median OS** of **90 months** (observed not reached).
- In contrast, for **PFS**, the 2018 Weibull extrapolation underestimated outcomes more substantially. At 6.26 years (10 patients at risk), predicted PFS was 14% versus 30% observed – a 16 percentage-point difference, falling outside the 95% CI of the 2024 PFS KM estimate. At the rounded 6-year milestone, the underestimation remains sizable at 15 percentage points. Both time points are shown in **Figure 1 b**, with divergence from the KM curve evident from year 3 onwards.

TABLE 1 Baseline patient characteristics common to both data cuts (2018 and 2024).

Characteristics	Value (*N* = 102)
Age	
Mean (SD)	37.1 (26.6)
Age category, *n* (%)	
< 1 year	9 (8.8)
≥ 1 and ≤ 5	10 (9.8)
> 5 and ≤ 11	8 (7.8)
> 11 and ≤ 17	7 (6.9)
> 17 and ≤ 44	22 (21.6)
> 44 and ≤ 64	26 (25.5)
> 64 and ≤ 74	14 (13.7)
> 74	6 (5.9)
Sex, *n* (%)	
Male	54 (52.9)
Female	48 (47.1)
Race, *n* (%)	
White	74 (72.6)
Black	5 (4.9)
Asian	4 (3.9)
All others	19 (18.6)
Primary tumor site, *n* (%)	
Appendix	1 (1.0)
Bone sarcoma	2 (2.0)
Breast	1 (1.0)
Cholangiocarcinoma	2 (2.0)
Colon	6 (5.9)
Congenital mesoblastic nephroma	1 (1.0)
GIST	4 (3.9)
IFS	13 (12.7)
Lung	7 (6.9)
Melanoma	7 (6.9)
Pancreas	1 (1.0)
Primary CNS	9 (8.8)
Salivary gland	17 (16.7)
Soft tissue sarcoma	21 (20.6)
Thyroid	10 (9.8)
Baseline ECOG, *n* (%)	
0	47 (46.1)
1	44 (43.1)
2	11 (10.8)
Disease extent at enrollment, *n* (%)	
Locally advanced	16 (15.7)
Metastatic	77 (75.5)
Other	9 (8.8)
Tumor stage at diagnosis, *n* (%)	
I	10 (9.8)
II	16 (15.7)
III	25 (24.5)
IV	25 (24.5)
Not reported	26 (25.5)

SD, standard deviation; GIST, gastrointestinal stromal tumor; IFS, infantile fibrosarcoma; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group.

FIGURE 1 a, b Comparison of 2018 and 2024 PFS and OS Kaplan-Meier data with 2018 Weibull PFS and OS predictions.



CONCLUSIONS

- While the **Weibull model** provided **reasonably projected OS**, it **underestimated PFS**. The model's median OS estimate is considered conservative, given the underestimation of OS prediction.
- These results highlight the **need for improved modelling approaches in HTA submissions** to better inform clinical and policy decisions.

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