HTA368

When less is more? Learnings from a recent NICE submission utilizing a novel predictive individual-level surrogacy approach to predict overall survival (OS) in the absence of trial-level evidence

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INTRODUCTION AND OBJECTIVE

- OS predictions over a lifetime horizon are required for cost-effectiveness analyses (CEA) for health technology assessment; however, data in the oncology setting are often immature or unavailable at the time of reimbursement submission.
- In the absence of long-term follow-up from a randomized controlled trial (RCT), NICE recommend trial-level surrogacy (level-1) to predict OS treatment effects (**Figure 1**).[1] For novel targeted treatments, this may be challenging to establish given limited number of RCTs in the target population.
- This study describes the experience of a recent NICE appraisal using a novel patient-level approach to predict OS based on the association with progression-free survival (PFS) (level-2) for KRAS^{G12C}-mutated second-line (2L) non-small cell lung cancer (NSCLC).[2]

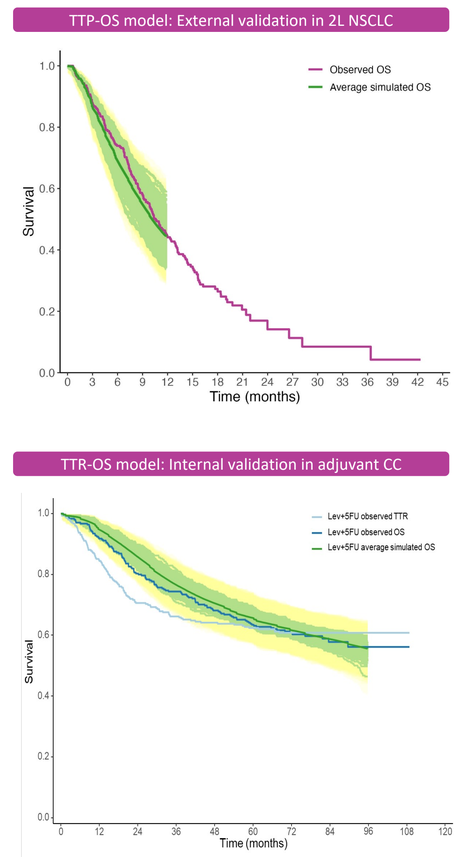
Figure 1: NICE surrogacy evidence hierarchy

Level 1: Trial-level surrogacy • The technology's effect on the surrogate outcome corresponds to commensurate effect on the final endpoint across many RCTs	Not feasible due to lack of RCTs in KRAS^{G12C}-mutated population
Level 2: Patient/cohort-level surrogacy • Strong association between surrogate outcome and final endpoint at the individual patient level	**This method was further developed to allow prediction of OS**
Level 3: Biological plausibility • Biology and pathophysiological studies make it plausible that changes in the surrogate outcome will lead to changes in the final endpoint	KRAS mutation provides strong basis

METHODS

- Public NICE draft guidance documents for TA1076 were reviewed, and drivers of decision-making were assessed.
- The manufacturer estimated PFS-OS and time to progression (TTP)-OS surrogacy based on a single-arm Phase-I/IIb trial in the target population (KRAS^{G12C}-mutated 2L NSCLC) using a copula-based predictive individual-level surrogacy model.[3] OS was predicted for Phase-III RCT arms using patient characteristics, progression status, and surrogacy relationship.
- Internal validation results proved that OS in the single-arm trial was well-predicted, with the TTP-OS model performing better than the PFS-OS one.[3]
- External validation results (**Figure 2**) for TTP-OS surrogacy in a similar 2L NSCLC population also showed good fit to observed survival, despite population differences that could not be adjusted for (KRAS status missing).[3]
- The model was further refined and subsequently validated in a separate dataset to explore time to recurrence (TTR)-OS surrogacy in adjuvant colon cancer (CC), with performance comparable to alternative methodological approaches (**Figure 2**).[4]

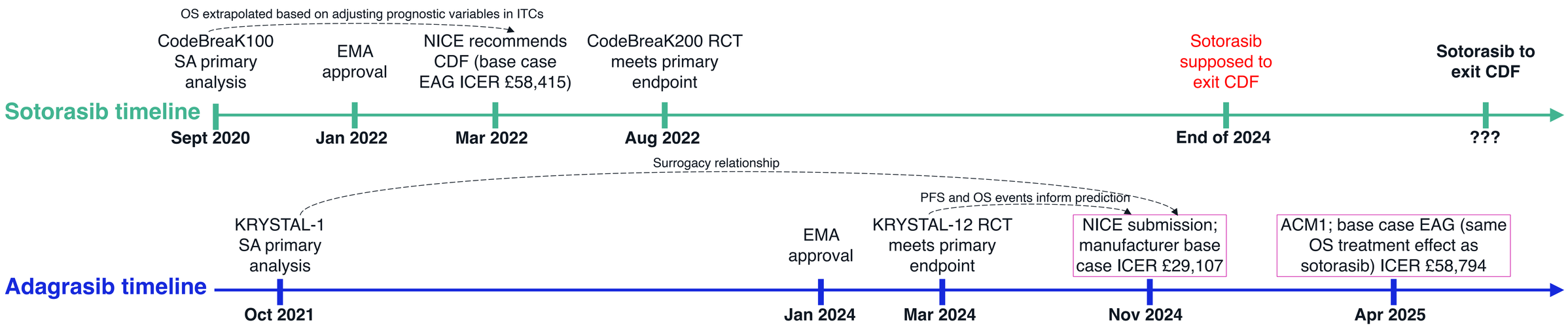
Figure 2: Predictive individual-level surrogacy model validation in 2L NSCLC and adjuvant CC



RESULTS

- Despite minimal methodological critiques, NICE considered the **level-2 surrogacy-based OS predictions incorporating death events from an RCT** (KRYSTAL-12) inappropriate for decision-making despite robust internal validation results: "no evidence to suggest that PFS benefits translate to OS benefits, or that PFS is a reliable surrogate for OS in [the target population]."[2] External validation in 2L KRAS-unselected NSCLC was also available[3] but not considered sufficient for the KRAS-mutated target population.
- External assessment group (EAG) assessors assumed no OS benefit and the technology was not recommended for routine use or for the Cancer Drugs Fund (CDF) despite PFS benefits versus standard of care from the RCT (KRYSTAL-12; hazard-ratio: 0.58, p<0.0001) and favorable efficacy based on an indirect treatment comparison versus another KRAS inhibitor (sotorasib) currently in the CDF (**Figure 3**). EAG base case assumed same effect of adagrasib on OS as docetaxel.
- Sotorasib was recommended for CDF based on a single-arm trial and a base case EAG ICER of £58,415; OS results for the RCT (CodeBreaK200) became available after the NICE decision. The technology was supposed to exit the CDF in late 2024 but as of October 2025 is still in the CDF, with exit date unknown.

Figure 3: Timelines for sotorasib and adagrasib regulatory approval and NICE submission



ACM, appraisal committee meeting; CDF, Cancer Drugs Fund; EAG, external assessment group; EMA, European Medicines Agency; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; RCT, randomized controlled trial; SA, single-arm.

TAKEAWAYS

- This experience suggests that early evidence from a single-arm trial using unanchored comparisons may be preferable when first to market, as compared to evidence from an RCT leveraging OS predictions based on level-2 surrogacy in the target population, despite robust internal and external validation results.
- Although trial-level surrogacy represents the highest level of evidence, it may not always be feasible to estimate. A recent NICE publication suggests that there is a lack of consensus regarding best surrogacy methods in the absence of trial-level evidence.[5] Guidance is warranted to compare OS extrapolations from unanchored matching-adjusted comparisons (sotorasib) versus RCTs with PFS available where OS predictions are informed by level-2 surrogacy from earlier phase trials in the target population (adagrasib). Rejection of all evidence other than level-1 surrogacy has implications for patient access and wait time, particularly for targeted therapies.
- Data collection in the CDF in light of demonstrated benefits in PFS can provide an opportunity for patient access and reduced clinical uncertainty. However, our experience suggests inconsistencies in NICE's decision-making relative to sotorasib which was recommended for CDF, wherein despite more favorable PFS effects for adagrasib, NICE assumed lack of OS benefit for adagrasib based on sotorasib. Assumption of OS comparability is further complicated given previously published issues with CodeBreaK200.[6]
- NICE technology appraisal process is intended to be based on best available evidence. Therefore, when equivalence is assumed without properly exploring additional evidence, this brings into question the robustness of the assessment and transparency in the decision-making process.

1. Bujkiewicz S, et al. Multivariate meta-analysis of summary data for combining treatment effects on correlated outcomes and evaluating surrogate endpoints. NICE DSU Technical Support Document 20. 2019:121. 2. National Institute for Health and Care Excellence. Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [TA1076]. 3. Berardi A, et al. Estimation and validation of a predictive patient-level surrogacy model between progression-free survival (PFS) and overall survival (OS) in patients with pre-treated advanced or metastatic (a/m) non-small cell lung cancer (NSCLC) with a KRASG12C mutation. Presented at: ISPOR Europe; 2024; Barcelona. 4. Berardi A, et al. Predicting overall survival (OS) from time to recurrence (TTR) using a copula-based patient-level surrogacy model with parametric marginal survival distributions: application to adjuvant treatment of patients with colon cancer. Presented at: ISPOR US; 2025; Montreal. 5. National Institute for Health and Care Excellence. Surrogate endpoints in cost-effectiveness analysis for use in health technology assessment 2025. 6. Ranganathan S, et al. Lancet Oncol. 2024;25(5):549-552.

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