# 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 *KRAS$^{G12C}$* mutation

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## Background & objective

### Background

- Cost-effectiveness analyses for health technology assessment require OS predictions over a lifetime horizon
- When OS follow-up is limited and/or considered highly immature in a randomized controlled trial (RCT) evaluating a new intervention, trial-level surrogacy between PFS and OS can be used to predict OS treatment effects
- For patients with pre-treated *KRAS$^{G12C}$*-mutated a/m-NSCLC, there is insufficient evidence from multiple RCTs to assess trial-level surrogacy (only CodeBreaK 200)[1]
- Existing trial-level surrogacy for the broader NSCLC population may not be applicable to the target population[2,3]
- Individual-level surrogacy between PFS (or time to progression [TTP]) and OS can be used to predict OS[4] if individual patient data (IPD) are available with outcomes of interest in the relevant target population and relevant interventions
  - IPD were available from one clinical trial in the target population (KRYSTAL-1, evaluating adagrasib[5])
  - IPD were available from one clinical trial in a related population (SAPPHIRE, evaluating docetaxel[6])

### Objective

- To estimate and validate a predictive individual-level surrogacy model between PFS (or TTP) and OS in patients with pre-treated *KRAS$^{G12C}$*-mutated a/m-NSCLC

## Methods framework: Patient-level surrogacy & survival prediction

### Step 1: Estimate relationship between TTP & OS using joint frailty copula model (Emura 2017)[7]

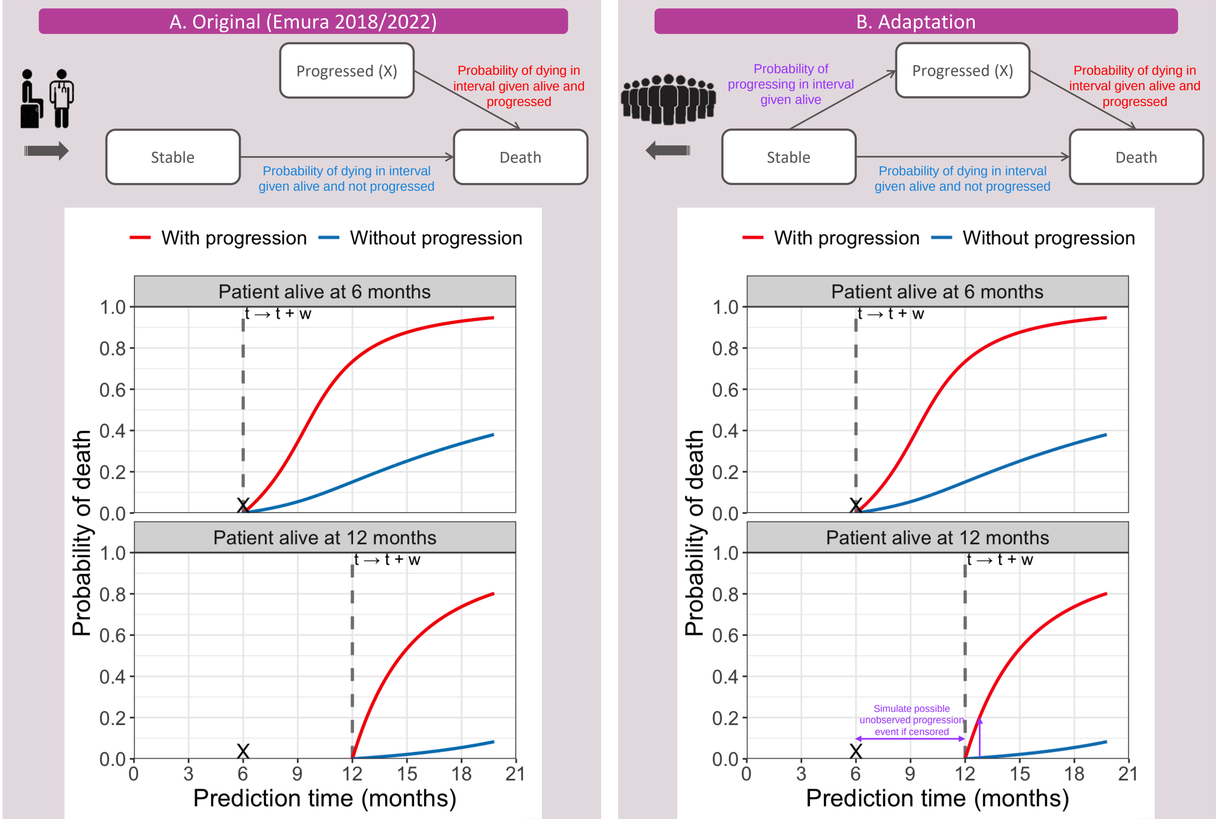
- Baseline hazards estimated using cubic M-splines (3 equally spaced internal knots) adjusted for covariates
- Intra-subject dependence captured through Clayton copula (couples marginal TTP and OS distributions)
- **Adaptation:** In absence of numerous studies for study-specific frailty terms, patient-level random effects can be used

### Step 2a: Predict OS using dynamic simulation given progression status and death events (Figure 1)

- Use conditional failure function (CFF) to predict death conditional on progression status and covariates (Emura 2018, 2022)[8,9]
- **Adaptation:** Rather than predicting risk of death for 1 patient alive in clinic, simulate OS event times for alive individuals in cohort
  - For each patient, to emulate regular check-ins in study, simulate deaths based on CFF in intervals, stopping at maximum timeframe (defined based on available follow-up)
  - Update CFF in each interval and simulate possible progression events for patients censored without it occurring (TTP model only, due to PFS and death events being competing risks)

### Step 2b: Use Monte Carlo simulation and propagate uncertainty

**Figure 1. Prediction of OS based on progression status and known death events (original Emura model and adaptation)**




## Evidence base & Analysis

### Evidence base

- PFS and OS were available in terms of IPD from:
  - *Target population*: KRYSTAL-1 phase 2 cohort A (N=116), investigating adagrasib in patients with aNSCLC with *KRAS$^{G12C}$* mutation previously treated with a platinum-based regimen and an anti-PD-1/PD-L1 therapy[5]
  - *Related population*: SAPPHIRE, a phase 3 RCT comparing sitravatinib+nivolumab to docetaxel in patients with a/m NSCLC with unknown *KRAS* mutation previously treated with a checkpoint inhibitor with/after platinum-based chemotherapy. Only the IPD for the docetaxel arm (N=293) were considered of interest[6]
- Covariates were identified based on clinical expert opinion from previous analyses of KRYSTAL-1: Eastern Cooperative Oncology Group (ECOG) performance score (PS), age, sex, disease stage, histology (squamous vs non-squamous), and smoking status
- Between-study differences in terms of these covariates and any study design or analysis factors were summarized

### Analysis

- The individual-level association between PFS (or TTP) and OS was evaluated using KRYSTAL-1 based on the Emura 2017 model (Step 1)[7]
  - The base case model included ECOG PS only. Sensitivity analyses explored the impact of including additional covariates (i.e., age ≥65 years and sex), where covariate levels within KRYSTAL-1 had limited sample size
  - The base case model censored TTP/PFS/OS when 5% or less of patients were still at risk of a PFS/TTP event to avoid over-reliance on the tails of the distributions, where very few patients remained at risk of events
- OS was predicted for KRYSTAL-1 (internal validation) and SAPPHIRE (external validation) using the adapted process (Step 2; Figure 1B):
  - KRYSTAL-1 PFS-OS model: Using progression status but not subsequent progression events from KRYSTAL-1/SAPPHIRE
  - KRYSTAL-1 TTP-OS model: Using progression status and subsequent progression events from KRYSTAL-1/SAPPHIRE
- Restricted mean survival time (RMST) up to max simulated time was compared for the predicted and observed OS. Relative differences in RMST (ΔRMST) at the maximum simulated time were compared across models to assess goodness of fit to the observed data

## Results

### Association between PFS (or TTP) and OS based on KRYSTAL-1

- In the models fit to KRYSTAL-1, τ was 0.62 (95% CI: 0.42, 0.79) in the PFS model and 0.38 (0.18, 0.63) in the TTP model (**Figure 2**)
- Sensitivity analyses including additional covariates (age ≥65 years and sex) yielded very similar results, suggesting that the number of covariates had minimal impact on results, while increasing the leverage of patient subgroups with very low event numbers

### OS prediction of adagrasib for KRYSTAL-1 - Internal validation

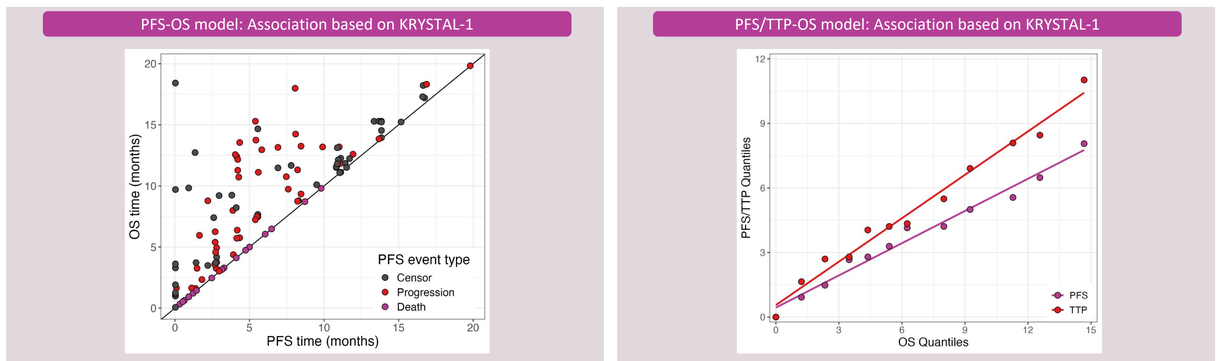
- KRYSTAL-1 adagrasib OS was well-predicted by both the TTP-OS (ΔRMST -0.15%) and PFS-OS (ΔRMST -4.63%; **Figure 3**; **Table 1**) models, although the TTP-OS model resulted in the smallest difference in RMST

### OS prediction of docetaxel for SAPPHIRE - External validation

- Analogously, SAPPHIRE docetaxel OS was predicted better by the TTP-OS model (ΔRMST -3.62%) than the PFS-OS model (ΔRMST -8.52%; **Figure 3**; **Table 1**)

## Results: Association between PFS (or TTP) & OS

**Figure 2. Individual-level relationship between PFS-OS and PFS/TTP-OS for KRYSTAL-1**




OS, overall survival; PFS, progression-free survival; TTP, time to progression

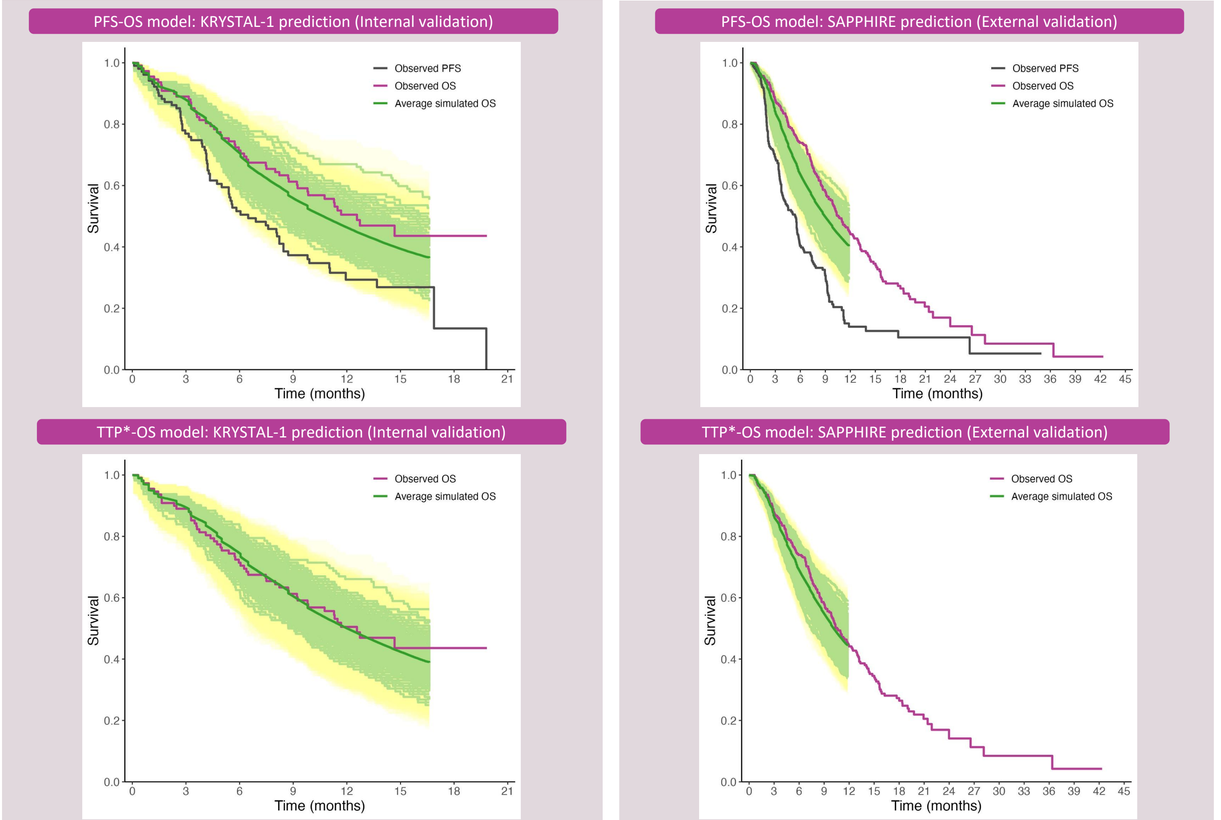
## Results: Validation of predicted OS

**Table 1. Predicted OS for KRYSTAL-1 adagrasib (internal validation) and SAPPHIRE docetaxel (external validation)**

| Model | Validation | Treatment | Source | RMST[a] | RMST (95% CI) | RMST Δ | RMST relative Δ |
|---|---|---|---|---|---|---|---|
| PFS-OS | Internal | Adagrasib | KRYSTAL-1 observed OS | Up to 16 months | 10.72 (9.63, 11.80) | -0.50 | -4.63% |
| | | | KRYSTAL-1 predicted OS | | 10.22 (8.91, 11.53) | | |
| | External | Docetaxel | SAPPHIRE observed OS | Up to 11 months | 8.35 (7.95, 8.74) | -0.71 | -8.52% |
| | | | SAPPHIRE predicted OS | | 7.64 (6.97, 8.30) | | |
| TTP-OS | Internal | Adagrasib | KRYSTAL-1 observed OS | Up to 16 months | 10.72 (9.63, 11.80) | -0.02 | -0.15% |
| | | | KRYSTAL-1 predicted OS | | 10.70 (9.37, 12.03) | | |
| | External | Docetaxel | SAPPHIRE observed OS | Up to 11 months | 8.35 (7.95, 8.74) | -0.32 | -3.62% |
| | | | SAPPHIRE predicted OS | | 8.05 (7.41, 8.68) | | |

[a] Calculated based on time at which less than 5% of patients are at risk of progression (PFS/TTP); CI, confidence interval; OS, overall survival; PFS, progression-free survival; RMST, restricted meal survival time; TTP, time to progression

**Figure 3. Predicted OS for KRYSTAL-1 adagrasib and SAPPHIRE docetaxel using KRYSTAL-1 PFS-OS or TTP-OS models**




*TTP was also available from IPD (not illustrated here); OS, overall survival; PFS, progression-free survival; TTP, time to progression

## Discussion

### Key findings

- In the target population, both PFS and TTP were associated with OS, although the strength of the association was only moderate[10]
- PFS-OS association was stronger than TTP-OS association, which was likely driven by inclusion of deaths in the PFS definition
- Internal validation suggests that the TTP model was better at predicting OS than the PFS model, which may be driven by addition of simulated subsequent progression events to the model for TTP, not feasible for PFS due to competing risk of progression and death
- The TTP-OS KRYSTAL-1 model predicted OS for adagrasib well from KRYSTAL-1 (internal validation)
- The TTP-OS KRYSTAL-1 model predicted OS for docetaxel well from SAPPHIRE (external validation), despite some differences between the populations that were not feasible to adjust for (i.e., *KRAS* missing in SAPPHIRE)

### Limitations

- Covariates were selected based on expert opinion but there is a risk of potential residual bias due to missing covariates
- Sample size in KRYSTAL-1 was limited, and several covariates (disease stage, histology [squamous vs non-squamous], and smoking status) were not included due to the small proportion of patients presenting these characteristics in KRYSTAL-1 and SAPPHIRE trials
- Extreme (low or high) event counts for patients with these covariates led to a high degree of leverage on the model parameters, resulting in unstable estimates. Therefore, a simpler model with ECOG PS only as covariate was preferred

### Future research

- The role of residual heterogeneity between OS and PFS and the copula parameter (α parameter) requires further investigation when applied to a single study
- The individual-level surrogacy approach was adapted from the meta-analytic one given the limited evidence available (1-2 trials). It would be of interest to validate the relationship using a meta-analysis model in the future with additional trials, particularly for docetaxel, which has a different mechanism of action compared to adagrasib

## Conclusion

- The individual-level surrogacy model shows that PFS/TTP and OS were moderately correlated for the patients with pre-treated *KRAS$^{G12C}$*-mutated a/m-NSCLC treated with adagrasib in KRYSTAL-1
- This relationship, combined with a dynamic simulation, may be useful to predict OS for adagrasib and docetaxel in the target population for clinical trials where PFS or TTP data are available, but OS follow-up is limited, and trial-level surrogacy is not feasible

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