Conditional Overall Survival (OS) Simulations With a Joint Tumor Size (TS)-OS Model to Support Oncology Development Decision Making

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Introduction

Tumor-size (TS)-overall survival (OS) models characterize the relationship between TS dynamics and OS in oncology to support drug development decision making.[1,2]

TS-OS models can generate conditional simulations of long-term OS, fully accounting for and extrapolating early TS and OS data.

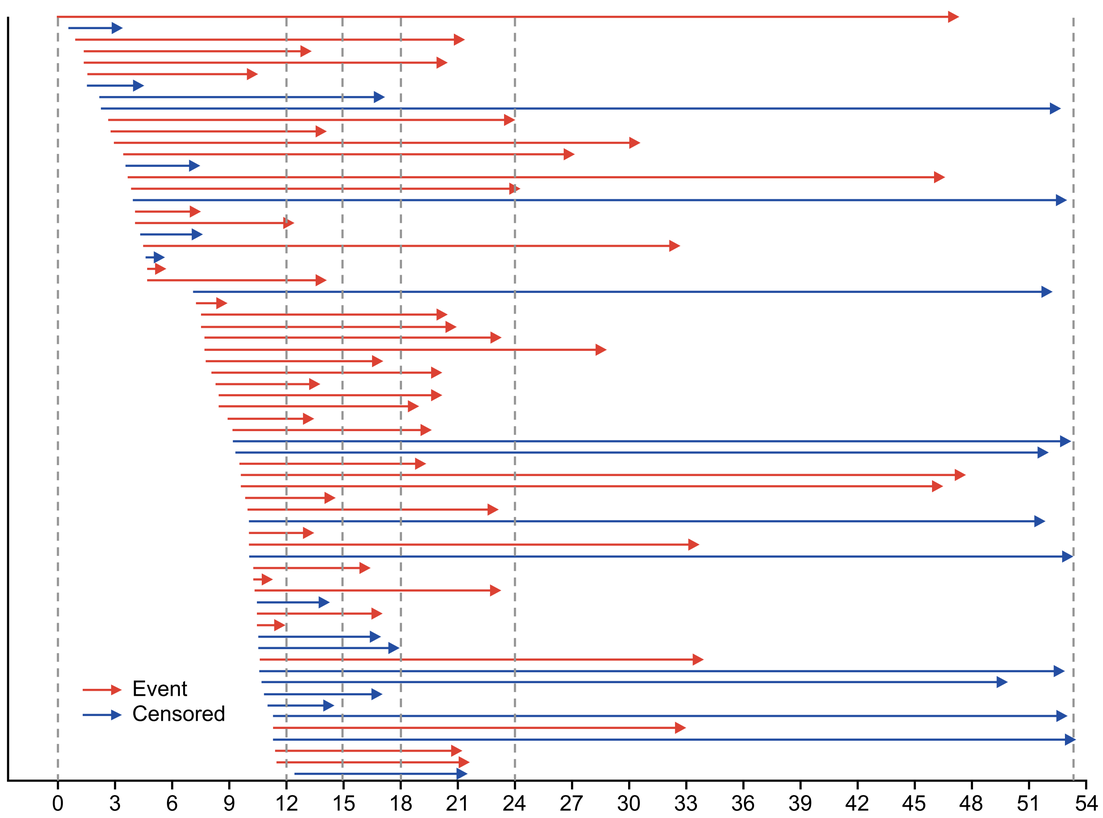
Objective

This study aimed to investigate the impact of data cut-off time (i.e., interim data length of follow-up time to inform the conditional simulations) on the quality of conditionally simulated OS.

Additionally, it aimed to inform clinical development to allow robust OS predictions that can be used for decision making.

Methods

Figure 1. Illustration of individual follow-up periods in final dataset relative to the time of study start



Event=1 is OS event, while event=0 is a censored observation (end of follow-up before OS event occurred). Time of study start defined as first patient first record. OS; overall survival.

Study design

- This was a *post hoc* analysis using the final dataset for the single-arm GARNET study (NCT02715284) with ~4-year follow-up of dostarlimab in patients with non-small cell lung cancer (N=67).
- Hypothetical 'interim datasets' were created with varying follow-up times by censoring OS data and removing TS data after cut-off dates 1, 1.25, 1.5 or 2 years after study start.
  - Cut-off dates <1 year after first patient first visit were not explored because enrollment lasted ~1 year (**Figure 1**).
- To each 'interim' GARNET dataset, a TS-OS model was fitted by estimating TS parameters based on the interim datasets. All OS parameters and the covariate effects on TS parameters were fixed to the estimated value of the TS-OS model developed on feladilimab data.[3] This model was an intermediate step in the development of an integrated feladilimab + GARNET TS-OS model (described in Struemper et al. 2023[3]).
  - Reflects prospective application in which new, immature OS data are not sufficient to re-estimate OS parameters.
- The TS-OS model consisted of a log-normal OS distribution, with a Stein model to characterize the TS dynamics over time.[3,4]

Conditional simulations of the long-term OS

- For each patient and simulation repetition, samples (N=1000) were generated from the patient's individual uncertainty in *post hoc* TS parameters (**Figure 2**).

Figure 2. Conditional simulation TS-OS workflow

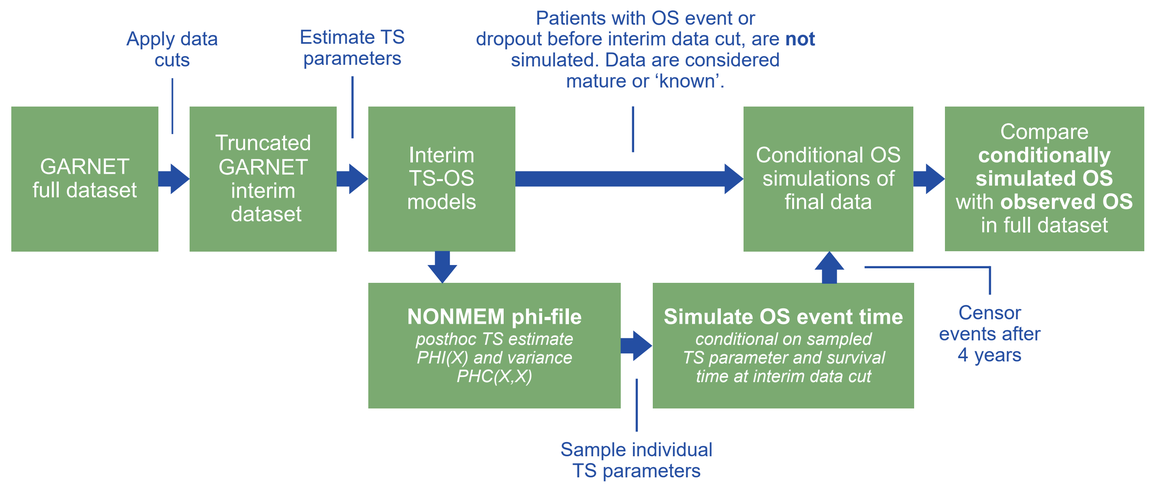
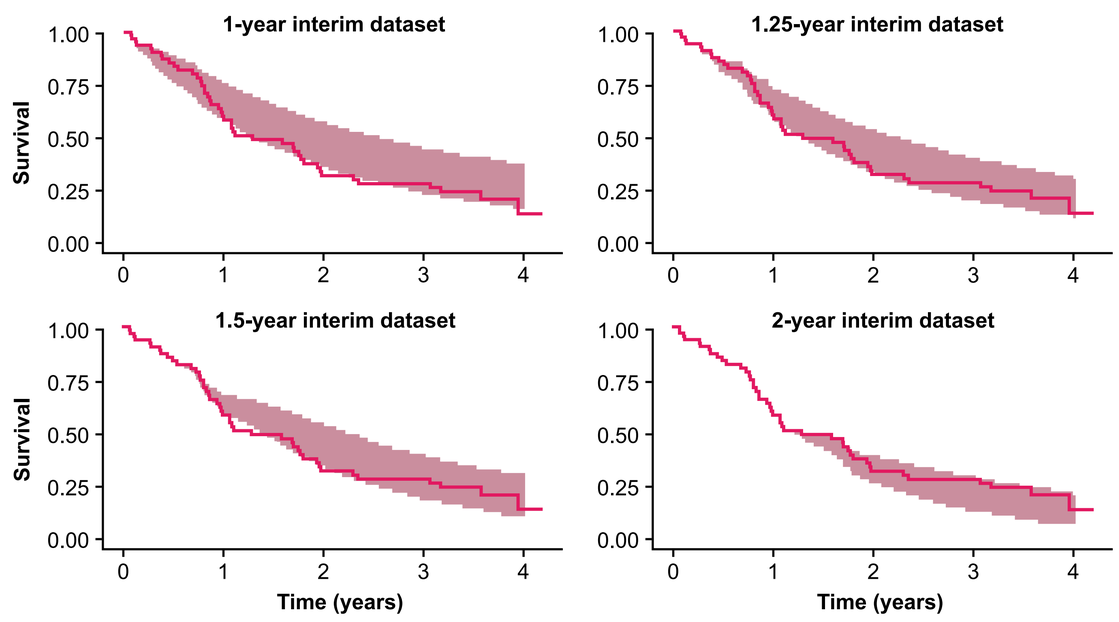


Illustration includes the comparison with the observed OS in the final dataset to evaluate the predictive success of the conditional simulations. OS, overall survival; TS, tumor size.

- Based on these conditionally sampled TS parameters, the individual OS distribution was obtained.
- A sample from the individual OS distribution was taken, conditional on the available interim OS data that the TS-OS model was based on.
  - Patients that had already experienced the OS event in the interim dataset were not re-simulated, and OS events would be sampled only in the future (i.e., if an individual already survived for 200 days in the interim dataset, the simulated OS event for that individual always occurred after 200 days).
- Simulated OS events after 4 years were treated as censored at 4 years in line with GARNET follow-up.
- The 95% prediction interval from each conditional simulation was visually compared to the observed 4-year OS data using a Kaplan-Meier survival plot.

Results

Figure 3. Comparison of conditional simulated OS and Kaplan-Meier curve of OS in final GARNET dataset



95% prediction interval shown as shaded area; Kaplan-Meier curve of OS in final GARNET dataset shown as solid line. OS, overall survival.

- Compared to a model estimated on the full GARNET dataset, the TS-OS models fitted to the 'interim' datasets had higher estimates for the treatment-specific TS parameters[3] tumor growth rate (*kg*) (+14–39%) and tumor shrinkage rate (*ks*) (+28–65%) for dostarlimab (**Table 1**).
  - This is likely related to the behavior of the Stein model; long-term stable TS levels can be 'fitted' only with equally low values of *kg* and *ks*.
- Despite the difference in TS parameters when 'censoring' the TS and OS data, the conditional simulations adequately predicted long-term OS for all cut-off dates (ranging from 1–2 years after study start for a 4-year total study duration, **Figure 3**).
  - This is likely because both *kg* and *ks* were included as predictors of OS (with opposite direction of effect) in the TS-OS model, resulting in a similar prediction of OS with dostarlimab despite lower *kg* and *ks*.
  - The presence of covariates on both OS and TS parameters in the TS-OS model likely contributes to its predictive performance.[3]

Table 1. Estimated tumor size parameters for TS-OS model applied to full dataset and hypothetical 'interim datasets' at earlier cut-offs

	Final dataset (±4-year follow-up)	Interim data-cut follow-up (years)			
		1	1.25	1.5	2
No. total TS observations	460	156	234	303	363
No. of patients	67	66	67	67	67
Mean no. TS observations per patient	6.9	2.4	3.5	4.5	5.4
	Parameter estimates [relative standard error %]				
Log(TSb)	4.00 [1.96]	4.06 [1.90]	4.07 [1.88]	4.06 [1.88]	4.05 [1.89]
Log(*kg*)	−4.91 [3.95]	−4.78 [7.02]	−4.68 [5.75]	−4.71 [4.25]	−4.58 [2.94]
Log(*ks*)	−4.21 [6.19]	−3.96 [11.0]	−3.71 [7.35]	−3.83 [6.47]	−3.75 [5.86]

Follow-up period for the interim data cuts calculated as time since first patient first record. Therefore, the follow-up time for individual patients will be lower, depending on the time between first patient first record and their individual first record. *kg*, tumor growth rate per week; *ks*, tumor shrinkage rate per week; OS, overall survival; TS, tumor size; TSb, baseline TS in mm.

Conclusions

Conditional simulations using a TS-OS model can leverage early TS and OS data from an ongoing study to forecast OS at the study end.

We obtained adequate OS predictions at 1 year post study start (i.e., around the time of last patient first visit) in GARNET.

We identified a possible dependence of the Stein model on the follow-up time, likely related to parameter values that were needed to fit the long-term stable TS profiles observed in some patients in GARNET.

Although *kg* was the most significant predictor of OS, the inclusion of *ks* as a predictor for OS appeared necessary for adequate long-term predictive performance of GARNET.

The presented simulation framework could be extended, for example via simulation of patient enrollment, to determine minimal follow-up required to obtain adequate OS predictions.

Disclosures

SCG: Paid consultant for GSK. MM: Paid consultant for GSK. CR: Employee of and holds stock in GSK. AM: Employee of GSK. SAGV: Employee of and holds stock in GSK. TMP: Paid consultant for GSK. HS: Employee of and holds stock in GSK.

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Abbreviations

kg, tumor growth rate; *ks*, tumor shrinkage rate; OS, overall survival; TS, tumor size; TSb, baseline TS.

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