Development of a joint tumor size (TS)−overall survival (OS) modeling and simulation (M&S) framework supporting oncology development decision making

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Introduction

Decision making regarding early oncology development programs is often based on overall response rate endpoints due to immature overall survival (OS) data, despite critical importance of OS endpoint for regulatory pathways.

Joint modeling and simulation (M&S) of the individual longitudinal tumor size (TS) and OS has the potential to bridge this gap by establishing the predictive relationship of TS parameters to OS and quantifying the direct impact of patient characteristics in often heterogeneous patient populations on OS to simulate OS comparisons to control arms or historic controls.[1,2,3]

Objective

Here we describe the development of a joint TS-OS M&S framework and its evaluation based on immuno-oncology (IO) and chemotherapy responses in patients with non-small cell lung cancer (NSCLC).

Methods

- The TS-OS dataset included 254 ≥second-line NSCLC patients (187 from the feladilimab [FELAD] studies NCT02723955, NCT03693612, and NCT03739710; 67 from the dostarlimab [DOSTAR] study NCT02715284) and 1163 TS observations, including chemotherapy (CHEMO), immune agonist, and checkpoint inhibitor monotherapy and combination arms (IO-COMBO, **Table 1**)

Table 1. NSCLC data

Study	Treatment Arm	No. of patients	No. of TS observations
INDUCE 1 NCT02723955	Feladilimab (FELAD)	52	161
INDUCE 1 NCT02723955	Feladilimab and docetaxel (FELAD+CHEMO)	8	40
INDUCE 1 NCT02723955	Feladilimab and IO* (IO-COMBO)	14	39
INDUCE-2 NCT03693612	Feladilimab and IO* (IO-COMBO)	9	41
ENTRÉE Lung Part 2 NCT03739710	Feladilimab and docetaxel (FELAD+CHEMO)	70	304
ENTRÉE Lung Part 2 NCT03739710	Docetaxel (CHEMO)	34	118
GARNET NCT02715284	Dostarlimab (DOSTAR)	67	460

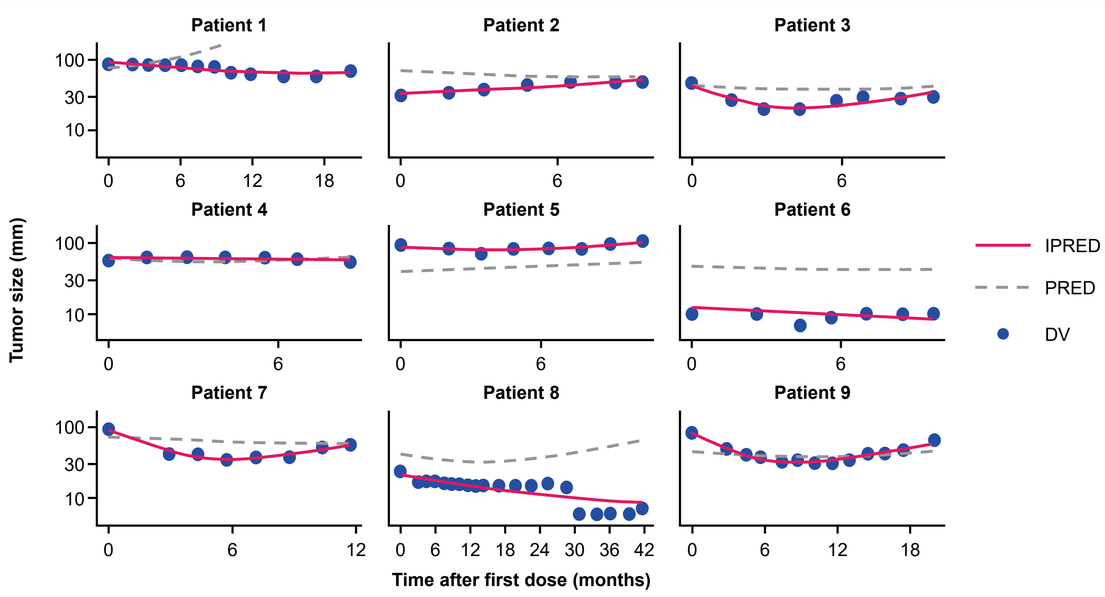
*IO was bintrafusp alfa, cobolimab (TIM-3), tremelimumab (CTLA-4), dostarlimab (PD-1), or GSK3174998 (OX40). CHEMO, chemotherapy; DOSTAR, dostarlimab; FELAD, feladilimab; IO-COMBO, immuno-oncology combination; NSCLC, non-small cell lung cancer; TS, tumor size.

- In this *post hoc* analysis, the proposed TS-OS model characterizes TS dynamics via a Stein model[4] − with parameters baseline TS (TSb), tumor shrinkage rate (*ks*) and tumor growth rate (*kg*) − and links the resulting TS parameters and patient baseline characteristics to an accelerated failure time (AFT) log-normal survival model.[3]
- Simultaneous joint estimation of TS and OS model parameters was performed in NONMEM® 7.5 using consecutive stochastic approximation expectation maximization (SAEM) and importance sampling (IMP) estimation methods.
- Various combinations of TS link parameters and baseline characteristics were tested in a covariate analysis using stepwise forward inclusion (α=0.01) followed by backward elimination (α=0.001).
- Goodness of fit plots and Kaplan-Meier visual predictive checks were used to evaluate the TS-OS model.

Results

- The model was iteratively developed with data from the FELAD program then evaluated with external DOSTAR data, followed by a final model update using the combined TS-OS dataset.
- The TS model rate constants *ks* and *kg* were estimated separately for five treatment categories: FELAD, CHEMO, FELAD+CHEMO, DOSTAR, IO-COMBO. Individual TS profiles were captured adequately by the Stein model (**Figure 1**).

Figure 1. Individual fit plots for TS profiles of select patients with at least six TS observations, showing the diversity of TS profile shapes that are captured by the Stein model



DV, observed TS; IPRED, individual predicted TS; PRED, population predicted TS; TS, tumor size.

- In the final model (**Table 2**), the covariates on TS were number of target lesions and hemoglobin at baseline on TSb and alkaline phosphatase at baseline on *kg*. For OS, the covariates were *kg*, *ks*, TSb, age at baseline, albumin at baseline, number of prior lines of therapy, and neutrophil-to-lymphocyte ratio at baseline. The statistically most significant predictor of log(OS) was *kg*. Any treatment differences in OS were driven by differences in treatment-specific TS parameters (*kg* and *ks*); no TS-independent treatment effect on OS was needed.

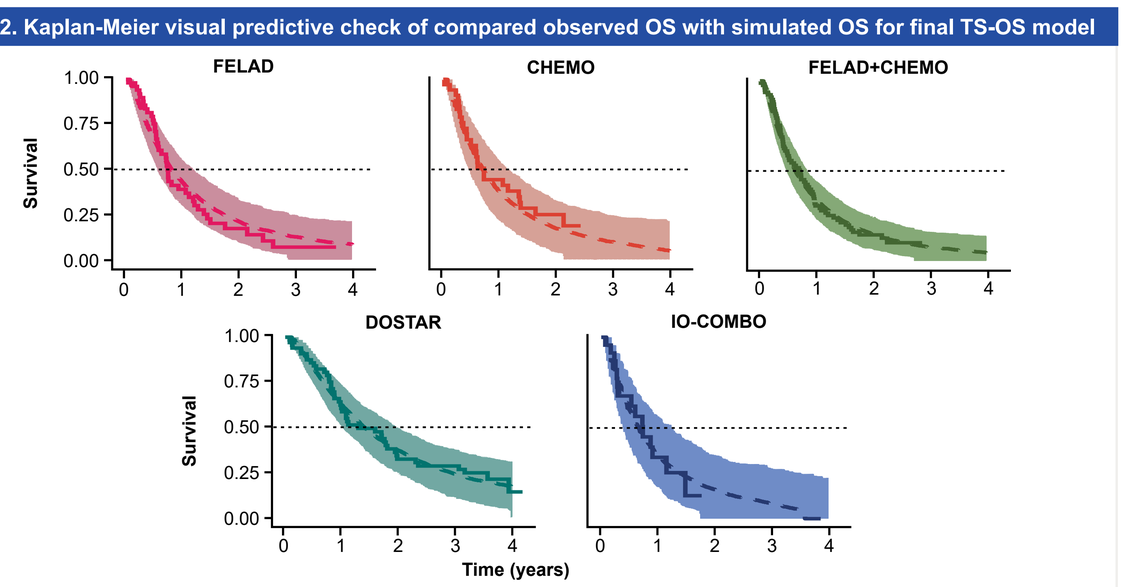
Table 2. TS-OS Model Parameters

Parameter	Estimate	RSE (%)	95% CI
TS parameters per treatment arm			
Log(TSb)	4.30	0.967	4.22 − 4.38
Log(*kg*) FELAD	−4.78	4.52	−5.20 − −4.35
Log(*ks*) FELAD	−7.84	16.2	−10.3 − −5.35
Log(*kg*) FELAD+CHEMO	−4.21	3.46	−4.50 − −3.93
Log(*ks*) FELAD+CHEMO	−3.79	6.79	−4.29 − −3.28
Log(*kg*) DOSTAR	−5.03	3.49	−5.37 − −4.68
Log(*ks*) DOSTAR	−4.22	5.90	−4.70 − −3.73
Log(*kg*) IO-COMBO	−4.43	5.72	−4.92 − −3.93
Log(*ks*) IO-COMBO	−5.21	12.3	−6.48 − −3.95
Log(*kg*) CHEMO	−4.06	5.81	−4.52 − −3.60
Log(*ks*) CHEMO	−3.62	10.4	−4.36 − −2.88
Effect number of target lesions on TSb [/lesion]*	0.195	12.7	0.147 − 0.243
Effect hemoglobin on TSb†	−0.645	41.3	−1.17 − −0.123
Effect alkaline phosphatase on *kg*†	0.576	30.2	0.235 − 0.917
Impact of TS on OS			
Effect log(*kg*) on log(OS)*	−0.800	7.84	−0.923 − −0.677
Effect TSb on log(OS) [/mm]*	−0.00303	43.8	−0.00563 − −0.000430
Effect log(*ks*) on log(OS)*	0.0858	43.5	0.0126 − 0.159
Other OS parameters (log-normal survival model)			
Scale parameter of log-normal survival distribution	5.65	25.3	2.85 − 8.46
Shape parameter of log-normal survival distribution	−0.479	20.6	−0.672 − −0.286
Effect Albumin on log(OS) [L/g]*	0.0315	28.0	0.0143 − 0.0488
Effect Neutrophil-to-Lymphocyte ratio on log(OS)*	−0.00936	44.3	−0.0175 − −0.00124
Effect second or higher line of therapy on log(OS)*	−0.109	–	–
Effect log(age) on log(OS)*	−0.942	35.4	−1.60 − −0.289
Inter-individual variability TS model (ω^2)			
ω^2 TSb	0.337	9.50	0.274 − 0.400
Covariance (TSb, *kg*)	−0.0144	376	−0.120 − 0.0916
ω^2 *kg*	1.14	15.2	0.798 − 1.48
Covariance (TSb, *ks*)	−0.0827	100	−0.246 − 0.0802
Covariance (*kg*, *ks*)	0.510	38.3	0.128 − 0.892
ω^2 *ks*	1.71	22.3	0.962 − 2.45
Residual error TS model (σ^2)			
Additive error on TS	13.2	17.3	8.75 − 17.7
Proportional error on TS	0.0106	13.0	0.00791 − 0.0133

Covariates on log(OS) are included using an accelerated failure time parameterisation; negative coefficients represent that at higher values of the covariate, the survival time decreases. *linear relationship; †power relationship. CHEMO, chemotherapy; CI, confidence interval; DOSTAR, dostarlimab; FELAD, feladilimab; IO-COMBO, immuno-oncology combination; *kg*, tumor growth rate per week; *ks*, tumor shrinkage rate per week; OS, overall survival; RSE, relative standard error; TS, tumor size in mm; TSb, baseline tumor size in mm.

- As part of the model development, we compared our TS-OS M&S framework with a TS-OS modeling framework based on a large set of NSCLC data described in Chan et al.[2] and noted specific similarities and differences.
  - Both frameworks use the Stein TS model linked to a log-normal survival model, which allowed us to test the *kg* to OS link parameter from Chan et al. on our data. Fixing the OS parameters based on the estimates from Chan et al. while estimating the TS parameters with a joint TS-OS approach resulted in an adequate fit of the FELAD data and confirmed the applicability of the TS-OS approach across development programs.
  - However, when modeling the combined FELAD and DOSTAR data, we noticed that the inclusion of *ks* as a TS-OS link parameter improved predictive performance of OS for the long term follow-up in DOSTAR (**Figure 2, see companion poster no. I-50**).[5]

Figure 2. Kaplan-Meier visual predictive check of compared observed OS with simulated OS for final TS-OS model



Dotted line marks 50% survival; solid lines show observed OS; dashed lines show median of predicted survival; shaded areas show 2.5th to 97.5th percentile of predicted survival distribution. CHEMO, chemotherapy; DOSTAR, dostarlimab; FELAD, feladilimab; IO-COMBO, immuno-oncology combination; OS, overall survival; TS, tumor size.

- Because the OS events introduce an informative dropout/missingness of TS data in patients with fast tumor growth, joint TS-OS modeling is preferred versus separate or two-stage modeling of TS data to avoid biased estimates of TS parameters.[6,7] This was confirmed here, as the two-stage approach estimated *kg* parameters were −18% to −57% lower than joint TS-OS modeling (**Table 3**).

Table 3. Impact of joint TS-OS versus separate TS modeling on the estimates of tumor growth parameter *kg*

Treatment group	*kg* population estimate (week^{-1})		Difference in *kg* two-stage versus joint model
	Joint TS-OS model	Two-stage (separate TS and OS models)	
FELAD	0.00842	0.00688	−18%
CHEMO	0.01729	0.00958	−45%
FELAD + CHEMO	0.01480	0.00729	−51%
DOSTAR	0.00656	0.00282	−57%
IO-COMBO	0.01195	0.00695	−48%

CHEMO, chemotherapy; DOSTAR, dostarlimab; FELAD, feladilimab; IO-COMBO, immuno-oncology combination; *kg*, tumor growth rate; OS, overall survival; TS, tumor size.

- In a separate investigation and additional model evaluation, the final model has been applied to extrapolate TS responses to OS with conditional simulations to investigate the impact of various data cut-offs on prediction precision.[7]

Conclusions

The TS-OS model characterized differences in OS across five different treatment categories using the same link functions for the influence of TS parameters and OS in patients with NSCLC, with *kg* as the most significant predictor.

The use of patient characteristics as covariates on both OS and TS parameters is expected to further promote the predictive performance of the TS-OS model, especially when analyzing sparse, immature data or when predicting TS-OS results for a study design tailored to a different distribution of patient characteristics compared to a modelled earlier study.

Our work further supports the potential of TS-OS modeling as a tool to leverage early TS data to obtain insights on long-term treatment effects, such as OS.[5]

The TS-OS M&S framework was applied to predict first-line NSCLC data from the PERLA study (NCT04581824; head-to-head DOSTAR + CHEMO vs pembrolizumab + CHEMO, to be published separately), with plans to further validate and expand the framework with additional data sources.

This framework can be applied to support decision making by:

- Accurately predicting OS and hazard ratio (HR) for an ongoing trial based on immature OS data.[5]
- Benchmarking internal single arm trial results by calculating HR against OS results digitized from literature.
- Predicting OS and HR for a future trial with known *ks* and *kg* estimates for treatment arms of interest and assuming a certain distribution of baseline patient characteristics.
- Assessing the impact of inclusion/exclusion criteria on OS outcome via the modelled effect of patient characteristics.

Disclosures

HS, employee of and holds stock in GSK. MM, paid consultant for GSK. SCG, paid consultant for GSK. CR, employee of and holds stock in GSK. AM, employee of GSK. TMP, paid consultant for GSK. SAGV, employee of and holds stock in GSK.

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Abbreviations

AFT, accelerated failure time; CHEMO, chemotherapy; CI, confidence interval; DOSTAR, dostarlimab; DV, observed TS; FELAD, feladilimab; HR, hazard ratio; IMP, importance sampling; IO, immuno-oncology; IO-COMBO, IO combination; IPRED, individual predicted TS; *kg*, tumor growth rate; *ks*, tumor shrinkage rate; M&S, modeling and simulation; NSCLC, non-small cell lung cancer; OS, overall survival; PRED, population predicted TS; RSE, relative standard error; TS, tumor size; TSb, baseline TS; SAEM, stochastic approximation expectation maximization.

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