Comparison of two-stage and joint TGI-OS modelling using data from six clinical studies in metastatic non-small cell lung cancer patients

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Introduction

- Tumor growth inhibition (TGI)-overall survival (OS) models have been shown to predict OS distributions and study outcomes (OS hazard ratio (HR)) in several cancers and settings [1].
- Tumor growth rate (KG) using a biexponential TGI model has been proposed as an exploratory endpoint to support early decisions using a two-stage TGI-OS model [2, 3].
- However, KG estimation and two-stage TGI-OS models may be prone to estimation bias. Joint TGI-OS modeling has been proposed as a better approach [4].

Objectives

- To compare the performances of the two modeling approaches: joint and two-stage in the prediction of OS and HR using tumor dynamics in patients with metastatic non-small cell lung cancer (NSCLC) patients.

Methods

- Pooled data from six clinical studies [5] were used to assess the two methods in 3699 NSCLC patients with non-missing baseline characteristics and a total of 21684 tumor size data (sum of longest diameters, SLD). Patients with no post-baseline scan were included.
- In the two-stage approach individual parameters of the longitudinal process were estimated (using NONMEM™ version 7.3.0) followed by a parametric regression analysis (using R). The latter included the individual tumor growth rate (log(KG)) as well as the baseline covariates, hence leading to a TGI-OS model as previously described [5, 6].
- The joint model consisted of the same two sub-models (using Monolix 2020R1), but all model parameters are estimated in one step, hence providing unbiased parameters of the longitudinal and survival submodels at stake [4]. Although KG was the best TGI metric in the two-stage approach [5, 6], additional metrics such as the current continuous SLD (SLD(t)) and the SLD derivative (SLDslope(t)) were evaluated in the joint modelling approach.
- The estimates provided by the two approaches were compared as well as their predictive performances.
- Trials were replicated 500 times and OS distributions and HR comparing atezolizumab-containing arms to their respective controls (median and 95% prediction interval) were calculated.

Results

- For the two methods, KG estimates were very similar (**Table 1**) and OS data followed a log-logistic distribution. As previously observed, among all tested variables log(KG) was found to be the best predictor of OS [5, 6].
- In both approaches, the same covariates were selected in the final TGI-OS model (**Table 2**): patients with slower tumor growth, better ECOG, lower C-reactive protein, neutrophil to lymphocyte ratio, LDH, metastatic sites, no liver metastasis, positive PD-L1 status, 1st-line therapy, higher albumin, Asian, tended to have longer survival. (**Figure 1**).
- The OS distributions were well captured for each treatment arm using both models (**Figure 2**).
- Finally, the predicted HR were similar with the two approaches and indicated good model performance across the 6 studies (**Table 3**), with observed HR within the 95% prediction intervals for most of the studies.
- Eventually, joint modelling approach provided slightly larger prediction intervals.

Table 1. Comparison of parameter estimates between Two-stage and Joint TGI models – Longitudinal model

		Two-stage model	Joint model
Parameter	**Unit**	**Estimate (RSE%)**	**Estimate (RSE%)**
BSLD	mm	69.2 (1.1)	69.5 (1.1)
KG Atezo+CnP	1/w	0.00103 (3.9)	0.00121 (3.9)
KG CnP		0.00145 (4.8)	0.00163 (4.8)
KG Atezo+CP		0.00110 (5.5)	0.00128 (5.5)
KG Atezo+CP+B		0.000875 (5.5)	0.00103 (5.6)
KG CP+B		0.00135 (5.7)	0.00152 (5.7)
KG Atezo+C/C+P		0.00116 (11)	0.00132 (9.8)
KG C/C+P		0.00165 (11)	0.00183 (10)
KG Atezo		0.00143 (5.0)	0.0017 (5.0)
KG Doce		0.00178 (5.7)	0.00219 (5.5)
KS Atezo+CnP	1/w	0.00593 (3.9)	0.00642 (3.9)
KS CnP		0.00645 (4.7)	0.00693 (4.7)
KS Atezo+CP		0.00557 (5.5)	0.00615 (5.4)
KS Atezo+CP+B		0.00598 (5.3)	0.00642 (5.3)
KS CP+B		0.00622 (5.6)	0.00656 (5.6)
KS Atezo+C/C+P		0.00405 (10)	0.00445 (10)
KS C/C+P		0.00452 (12)	0.00497 (11)
KS Atezo		0.00187 (6.0)	0.00228 (6.2)
KS Doce		0.00303 (6.8)	0.00373 (6.6)
ω^2 BSLD	-	0.652 (1.2)	0.655 (1.3)
ω^2 KG	-	0.849 (1.7)	0.882 (1.7)
ω^2 KS	-	0.848 (1.9)	0.843 (2.0)
Residual	mm	6.43 (0.63)	6.38 (0.64)

BSLD: baseline tumor burden, KG: tumor growth rate; KS: tumor shrinkage, RSE: relative standard error of parameter estimate, residual: residual error; ω^2: variance of inter-individual variability; - not applicable. Atezo : atezolizumab; Doce : docetaxel; C/C : cisplatin or carboplatin; P : pemetrexed; CnP : carboplatin + nab-paclitaxel; CP : carboplatin + paclitaxel; B : bevacizumab

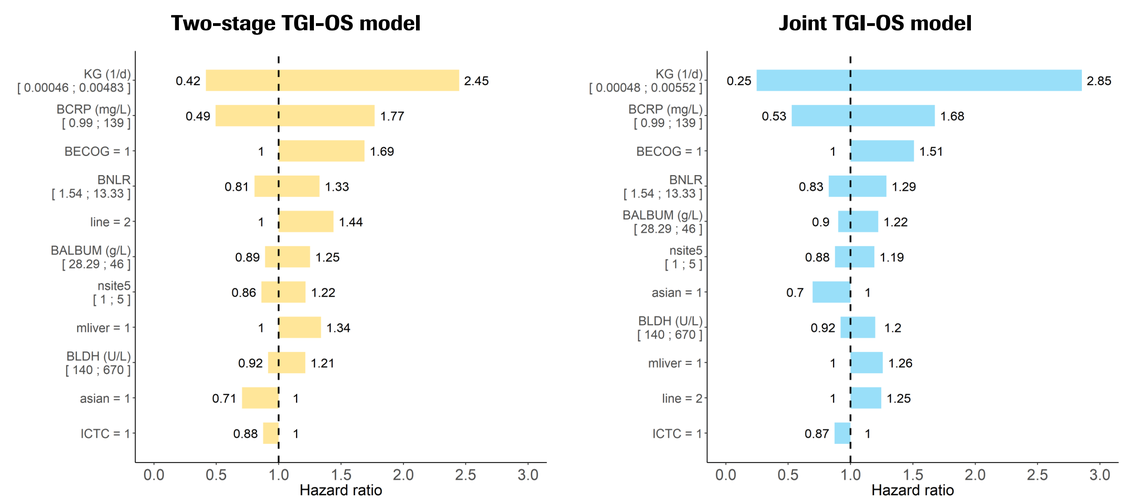
Table 2. Comparison of parameter estimates between Two-stage and Joint TGI-OS multivariate models – OS model

		Two-stage model		Joint model	
Parameter	**Unit or Group**	**Estimate (RSE%)**	**p**	**Estimate (RSE%)**	**p**
Scale	day	644 (3.3)	2.56E-210	750 (3.2)	2.96E-220
logKG	-	0.756 (3.6)	2.35E-166	1.000 (4.1)	6.35E-135
CRP	mg/L	0.258 (7.1)	1.15E-44	0.233 (8.5)	1.21E-31
ECOG	1 vs. 0	0.524 (8.8)	4.73E-30	0.411 (9.9)	5.99E-24
2d line	2+ vs. 1	0.365 (13)	8.14E-15	0.221 (18)	2.36E-08
NLR	-	0.231 (15)	1.63E-11	0.206 (18)	1.78E-08
LMET	Yes vs. No	0.293 (19)	1.58E-07	0.231 (24)	2.26E-05
Asian	Yes vs. No	-0.347 (19)	2.08E-07	-0.363 (24)	2.41E-05
NSITES	-	0.214 (20)	8.72E-07	0.191 (25)	6.07E-05
ALBU	g/L	-0.7 (22)	3.53E-06	-0.627 (27)	2.59E-04
LDH	U/L	0.18 (22)	6.08E-06	0.169 (25)	4.79E-05
ICTC	IC or TC > 0 vs. IC and TC = 0	-0.133 (27)	1.59E-04	-0.137 (29)	5.87E-04
Shape	-	1.75 (1.2)	<2.96E-220	1.70 (1.1)	<2.96E-220

Survival time was analyzed in days; RSE: relative standard error of parameter estimate; p: Wald test p-value. KG: tumor growth rate; CRP: C-Reactive Protein, ECOG: Eastern Cooperative Oncology Group, 2d line: second line of therapy, LMET: Liver metastasis, NLR: Neutrophil to Lymphocyte ratio, NSITE: number of metastatic site up to 5 sites, ALBU: albumin level, LDH: Lactate dehydrogenase level, ICTC: PD-L1 status, shape: intercept, scale: standard deviation of log(OS)

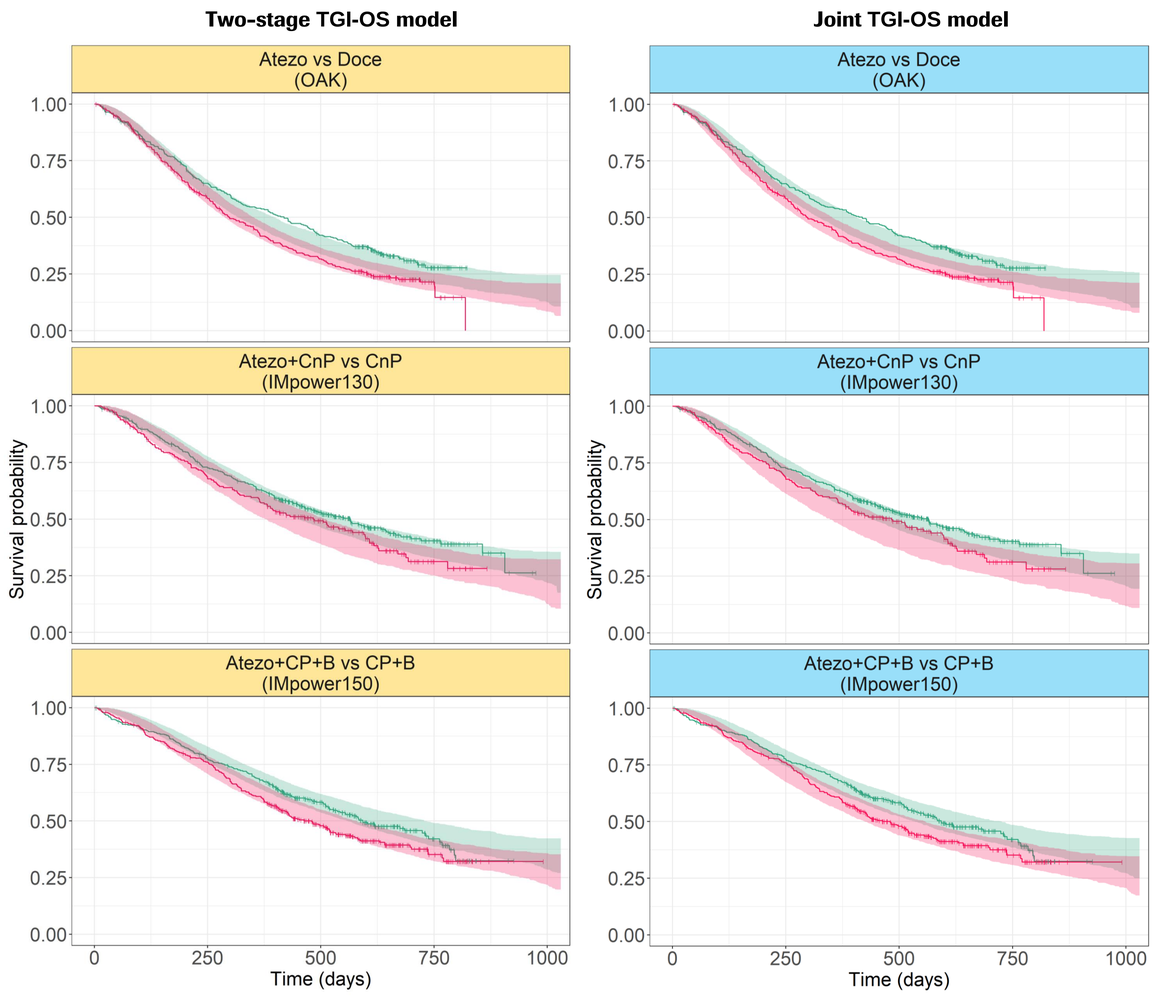
Results

Figure 1. Tornado plot of covariate effects on the TGI-OS model



KG: tumor growth rate; CRP: C-Reactive Protein, ECOG: Eastern Cooperative Oncology Group, 2d line: second line of therapy, NLR: Neutrophil to Lymphocyte ratio, liver met: liver metastasis, NSITE: number of metastatic site up to 5 sites, ALBU: albumin level, LDH: Lactate dehydrogenase level, ICTC: PD-L1 status; For continuous covariates effects are centered around medians, edges of bars represent 5th and 95th percentiles of the covariate distributions

Figure 2. Evaluation of the Overall Survival Model: OS distributions by experimental vs. control for 3 studies



Lines: observed Kaplan-Meier distributions; Shaded areas are 95% prediction intervals;
Atezo : atezolizumab; Doce : docetaxel; CnP : carboplatin + nab-paclitaxel; CP : carboplatin + paclitaxel; B : bevacizumab

Table 3. Simulations of Overall Survival Hazard Ratios for each study and Comparison of Two-stage and Joint models performances

			Two-stage model	Joint model
Treatment (Study)	N	Observed HR	Predicted HR [95% PI]	Predicted HR [95% PI]
Atezo vs Doce (OAK)	364/373	0.76	0.89 [0.79-0.99]	0.87 [0.75-1.0)
Atezo vs Doce (POPLAR)	134/127	0.66	0.84 [0.69-1.05]	0.85 [0.66-1.1]
Atezo+C/C+P vs C/C+P (IMpower132)	160/140	0.83	0.85 [0.72-1.02]	0.82 [0.68-0.99]
Atezo+CnP vs CnP (IMpower130)	437/214	0.85	0.86 [0.66-1.11]	0.87 [0.67-1.14]
Atezo+CnP vs CnP (IMpower131)	317/309	0.88	0.78 [0.67-0.91]	0.81 [0.67-0.97]
Atezo+CP vs CP+B (IMpower150)	384/370	0.88	0.90 [0.78-1.05]	0.88 [0.74-1.03]
Atezo+CP+B vs CP+B (IMpower150)	370/370	0.80	0.82 [0.69-0.95]	0.79 [0.66-0.94]

Atezo : atezolizumab; Doce : docetaxel; C/C : cisplatin or carboplatin; P : pemetrexed; CnP : carboplatin + nab-paclitaxel; CP : carboplatin + paclitaxel; B : bevacizumab

Conclusions

Overall, the two approaches led to similar results in terms of impact of KG and baseline prognostic factors on OS, prediction of OS distributions, and finally prediction of HR (treatment effect) for all studies. Operating characteristics in support to early decisions are being evaluated for the joint modelling approach in comparison with the two stage one [2, 3],

References

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