A model-based survival meta-analysis for indirect comparison of immune therapy efficacy in NSCLC

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Objective

The aim of this research was to perform an indirect comparison of immunotherapy efficacy based on the published clinical study outcomes in advanced non-small cell lung cancer (NSCLC) via model-based meta-analysis (MBMA) based on flexible survival models with non-proportional hazards.

Introduction

- Overall survival (OS) is a 'gold standard' endpoint for the efficacy assessment in oncology clinical trials [1]. However, indirect comparison of the study outcomes based on OS measures may be challenging or not informative if it is based on the standard pairwise meta-analysis techniques.
- In general, high heterogeneity in inclusion criteria, disease and patient characteristics as well as limited observation time in particular studies complicates analysis of the pooled aggregated data or meta-analysis.

Methods

Survival data analyzed

- The published Kaplan-Meier survival curves were digitized via an updated approach by Wei et al. [3]. A set of covariates was introduced to represent the data – treatment type for NSCLC (chemotherapy or immune-checkpoint inhibition (ICI): PD-1 therapy, PD-L1 therapy, PD-1/chemo and PD-L1/chemo combinations), treatment line (first line and second line+), PD-L1 status (positive for at least 1% expression by means of Tumor Proportion Score).
- The dataset incorporated the OS data of 20 phase II and III clinical studies (11626 subjects). The data on chemotherapy as well as immune therapy and its combinations (nivolumab, atezolizumab, pembrolizumab, avelumab, durvalumab) were collected.
- To reduce possible bias in parameter estimates due to unbalanced data the studies with published long-term outcomes (>24 months) were selected.

Survival modeling

- To perform the analysis, Cox proportional hazards (PH) models as well as flexible survival models from mexhaz package in R were used to describe patient survival based on the following hazard function formulation [2]:

$$h(t|Z) = exp\left\{\beta_0 + \sum_{k=1}^{M}\beta_k Z_k + \sum_{l=1}^{L}\left(\beta_{lo} + \sum_{m=1}^{N}\beta_{lm}Z_m\right)NS_l(t)\right\}$$

- The flexible fully parametric exponential survival models incorporated time-variable cubic splines for covariate coefficient description representing non-PH effects as well as random effects as a shared frailty.
- Model selection was performed via a stepwise covariate search towards LRT test, AIC assessment, parameter identifiability check and a set of visual model diagnostics.
- Patient survival comparison was performed via forward simulations of survival function for up to 36 months in different scenarios.
- Current research extended the previous analysis introducing the updated NSCLC study data, applying covariate search techniques for model building, testing non-PH effects [4].

Results

Model evaluation

- The initial analysis via Cox PH models provided the following list of included covariates - treatment type (chemotherapy, PD-1, PD-L1), combinatorial therapy option, PD-L1 status and therapy line.
- For this model, the diagnostics with Schoenfeld residuals (Figure 1, black) suggested that some of covariate effects should vary in time representing non-PH effects:

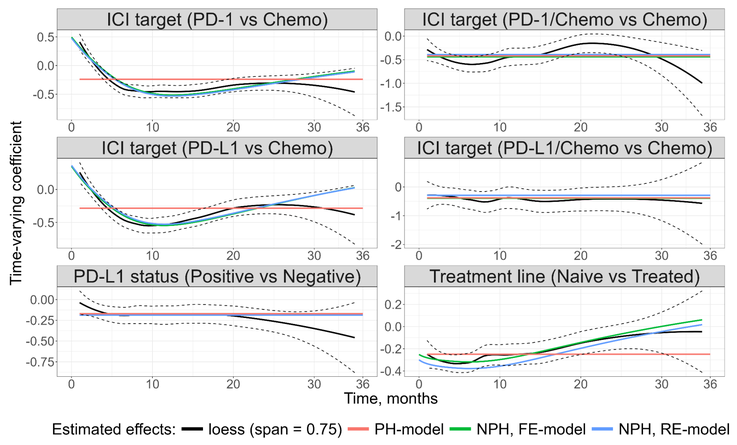

FIGURE 1. Time-variable model coefficients according to Schoenfeld residuals. The outcomes suggest that flexible models provide a better description of covariate effects.

- Then, the flexible survival models were qualified representing time-varying covariate effects with natural splines with 2 knots (Figure 1, green and blue *vs.* red for exponential PH model).
- The final model incorporated random effects (Figure 1, blue). Parameters were statistically identifiable (Table 1), and the model provided adequate description of the data (Figure 2).

Parameter	Estimate	StdErr	p.value
Intercept	-12.062	0.818	< 2.2E-16
NS_1	9.569	0.517	< 2.2E-16
NS_2	20.725	1.635	< 2.2E-16
NS_3	7.081	0.321	< 2.2E-16
PDL1_status_Positive	-0.188	0.031	2.08E-09
ICIs_targetPDL1/Chemo	-0.290	0.115	0.0119
ICIs_targetPD1/Chemo	-0.390	0.055	1.55E-12
*ICIs_targetPD1*NS_1*	*-1.087*	*0.103*	*< 2.2e-16*
*ICIs_targetPD1*NS_2*	*0.619*	*0.145*	*1.88E-05*
*ICIs_targetPD1*NS_3*	*-0.729*	*0.109*	*2.21E-11*
*ICIs_targetPDL1*NS_1*	*-1.034*	*0.114*	*< 2.2E-16*
*ICIs_targetPDL1*NS_2*	*0.542*	*0.162*	*0.000829*
*ICIs_targetPDL1*NS_3*	*-0.489*	*0.122*	*6.00E-05*
Line_NaiveNS_1*	*-0.290*	*0.093*	*0.00185*
Line_NaiveNS_2*	*-0.428*	*0.147*	*0.00368*
Line_NaiveNS_3*	*0.208*	*0.098*	*0.0337*
Study random eff. [log(sd)]	-2.582	0.277	< 2.2E-16

TABLE 1. Optimal flexible model parameter table. Time-variable effects are shown in italic

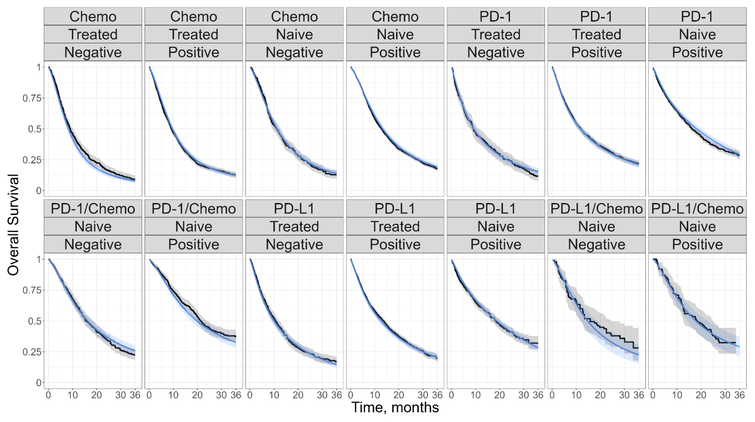

FIGURE 2. Goodness-of-fit plots according to the used covariate stratification.

Hazard ratio analysis

- The hazard ratio analysis for the final model suggested that ICI monotherapy provided a higher risk of death comparing to Chemo at first 6 months, while ICI/Chemo combination resolved this effect (Figure 3).

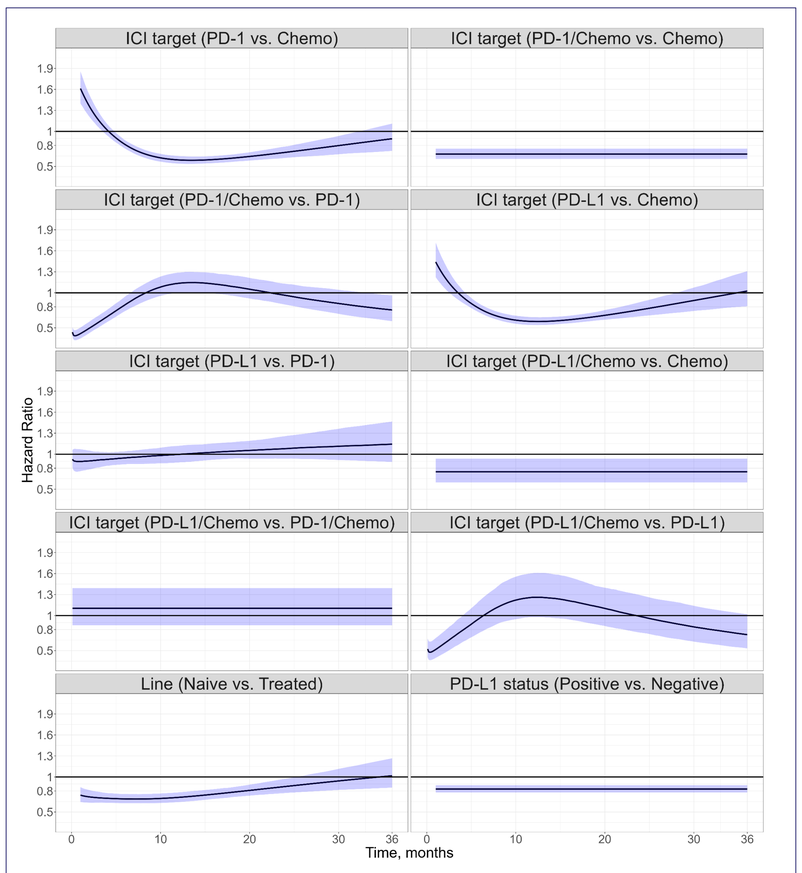

FIGURE 3. Time-variable hazard ratio analysis for the covariate levels included in the final flexible survival model.

Patient survival prediction

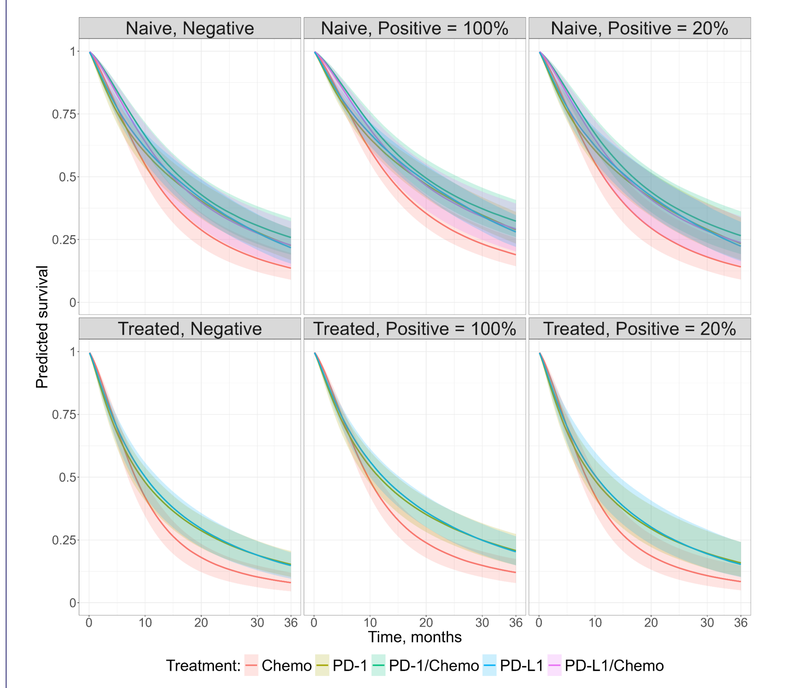

FIGURE 4. Posterior prediction check for survival simulations using the final flexible model with random effects.

- According to the applied simulation scenarios for a combined cohort of naïve patients containing 20% of PD-L1 positive subjects the median survival times of 11.5 (9.6-14.8), 14.9 (11.8-21.2), 15.7 (12.3-21.1), 16.7 (13.4-22.0), 15.3 (11.5-20.8) months were predicted for chemotherapy, PD-1, PD-L1, PD-1/chemo and PD-L1/chemo treatments, respectively.
- A high variability of OS predictions shows that PD-1 and PD-L1 immunotherapies can be hardly differentiated representing similar efficacy in the tested scenarios.

Conclusions

- The proposed MBMA survival analysis methodology based on the flexible fully parametric exponential survival models with constant and time-varying covariate effects provides a comprehensive basis for the indirect comparison of time-to-event outcome measures.
- Finally, application of the methodology for the NSCLC immunotherapy shows noninferiority of PD-1 vs. PD-L1 efficacy in the tested simulation scenarios.

References

[1] Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Guidance for Industry. FDA CDER/CBER, 2018.
[2] Charvat, H., & Belot, A. (2021). mexhaz: An R Package for Fitting Flexible Hazard-Based Regression Models for Overall and Excess Mortality with a Random Effect. Journal of Statistical Software, 98(14), 1–36.
[3] Wei Y, Royston P. Reconstructing time-to-event data from published Kaplan-Meier curves. Stata J. 2017;17(4):786-802.
[4] Sergey Gavrilov et al. Survival Model-based Meta-Analysis Framework for the Indirect Comparison of Anti-Cancer Therapy Efficacy. Page Meeting 2021. Abstr 9697.

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