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Comparison of three indirect overall survival (OS) modeling approaches in predicting long-term OS benefit in randomized controlled trials: a case study from the RELATIVITY-047 study

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Abstract

- OBJECTIVES: Overall survival [OS] is essential in cost-effectiveness analyses; however, it may not be available from the initial database-locks [DBLs] of a randomized trial. This research compared predicted long-term mean OS gains between the arms of the phase 3 RELATIVITY-047 study (nivolumab [NIVO]+relatlimab [RELA] versus NIVO) obtained from extrapolated OS using reported trial data and from three approaches indirectly modeling OS from progression free survival [PFS].
- METHODS: Initial DBL (DBL1) for RELATIVITY-047 study only reported PFS, whereas the successive DBL (DBL2) reported both PFS and OS. Two indirect approaches employed a semi-Markov model to estimate the OS for both arms of the study using the estimated post-progression survival from the NIVO arm of CheckMate 067 study assuming similar subsequent treatment patterns between the trials and the two arms of RELATIVITY-047. The third approach predicted OS through a surrogacy relationship between PFS-OS and extrapolated OS for NIVO from CheckMate 067. All indirect approaches used PFS data from the initial DBL of RELATIVITY-047. OS data from the trial was extrapolated using parametric models and adjusted with background mortality to generate a benchmark for the indirect methods. Projections over a time horizon of 40 years were compared.
- RESULTS: Lognormal and gamma distributions were used to extrapolate OS data for NIVO+RELA and NIVO from RELATIVITY-047, respectively. Mean OS gain with NIVO+RELA versus NIVO was estimated as 3.1 years using reported trial data and ranged between 1.1-1.8 years using the indirect methods. As a sensitivity analysis, shortening the time-horizon to 30-years for projections only slightly affected the underestimation margins of mean OS gain by indirect methods (2.9 years with reported trial data versus 1.1-1.7 years with indirect methods).
- CONCLUSION: This case study showed that in the absence of reported OS data from a trial, indirect methods can be conservative options for subsequent cost-effectiveness analyses by underestimating underlying long-term mean survival benefit.

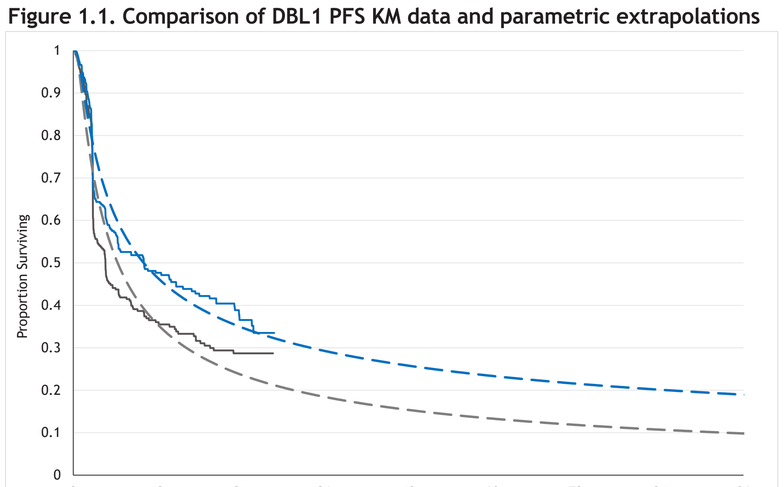
Introduction

- Overall survival (OS) and progression-free survival (PFS) results remain primary outcomes in evaluating efficacy in advanced stage oncology trials. Along with treatment duration, they are key contributors of cost-effectiveness estimates in reimbursement evaluations.
- As treatment innovation advances, particularly with the invention of immune-checkpoint inhibitors, prolonged survival beyond initially planned trial follow-up presents a challenge to early clinical and economic assessment of treatments and their consideration for subsequent regulatory and reimbursement approvals.
- Visibility of potential value of a new intervention from early trial results, particularly when it has a different mechanism of action from the existing treatments, can be an important tool in demonstrating its benefit to patients and evaluating the potential cost of delaying the decision of its adoption.
- Extrapolations of immature data represent potentially significant sources of uncertainty in evaluating new therapies, even when the pivotal trial data include a control treatment with robust survival data with longer follow-up available from other sources.
- Prior methods of extrapolating available early phase data[1] have depended on available but immature OS data (i.e., had not reached the median); however, in some cases, particularly for settings with effective subsequent treatment options, early trial evaluations may include no reports of OS outcomes.
- Ultimately, projected survival methods must be judged in treatment specific cases for their consistency and clinical plausibility with respect to the realization of the trial data after the extrapolations are made.

Objective

- Given available PFS estimates from RELATIVITY-047 trial's DBL1, we sought to construct reasonable long-term estimates of OS by multiple methods. We also compared the potential sources and spread of uncertainty behind the corresponding mean survival estimates from these methods.
- To evaluate the performance of the candidate methods, we visually compared their predictions with the OS data reported in RELATIVITY-047 trial's DBL2[3]. We also compared the estimated long-term mean survivals from the proposed methods with those obtained from parametric extrapolations from the DBL2 OS data.

Figure 1.1. Comparison of DBL1 PFS KM data and parametric extrapolations



Methods

- Observed efficacy data from RELATIVITY-047 trial's DBL1 was only PFS and an estimate of treatment effect on PFS (statistically significant hazard ratio (HR) comparing Relatlimab (Rela) + Nivolumab (Nivo) to Nivo was 0.75 with 95% confidence interval: 0.62-0.92).[2]
- Three methods of constructing estimates of OS were developed using the PFS data from DBL1 and the data for Nivo arm from CheckMate 067 trial:
  - 1. A semi-Markov Process Model (sMPM)
  - 2. A "Sum of means" (SoM) approach
  - 3. A Surrogacy approach (predicting an OS HR from the observed PFS HR)
- Each of the approaches was used to generate a predicted OS curve over a 40-year time horizon, area under which provided estimates of mean survival.
- Age- and sex-adjusted background mortality rates were used to cap the extrapolations to ensure that models' predictions remain clinically plausible over the entire time horizon

1) The sMPM approach:

- A detailed sMPM with three-health states (progression-free, post-progression and death) was developed. Observed PFS data from RELATIVITY-047 study was used to model the transitions from progression-free state to post-progression and death.
- Data for estimating the transitions from post-progression state to death (Gompertz distribution for post-progression survival) and the proportion of PFS events that were deaths were both taken from the Nivo arm of the CheckMate 067 study (6.5-year follow-up data).[4]
- Parametric survival analysis was performed on each set of observed PFS data to estimate weekly transition probabilities from the progression-free state. PFS data in RELATIVITY-047 study were best fit by generalized gamma models.
- Each weekly cohort transitioning from progression-free state to post-progression state was modeled with a tunnel state where patients remained until death.

2) The SoM approach:

- A second simplified model was constructed using indirectly estimated mean PPS for Nivo-treated patients in CheckMate 067 study.
- Mean PPS was estimated by dividing the difference between the mean OS (Gompertz distribution) and mean PFS (generalized gamma distribution) by the estimated proportion of patients experiencing progression before death. Extrapolations were carried out for 40 years in calculating each of the key three parameters of this method.
- For each arm of RELATIVITY-047 trial, the mean PPS estimated from CheckMate 067 study was multiplied with the corresponding estimated proportion of patients that would experience progression before death and combined with estimated mean PFS to generate a corresponding mean OS. Extrapolation of PFS data in RELATIVITY-047 trial was based on generalized gamma form for both arms.
- The OS curve for Nivo arm in CheckMate 067 study was scaled accordingly using proportional hazards assumption to construct OS curves for Rela + Nivo and Nivo arms of RELATIVITY-047 trial that met their corresponding target mean OS.

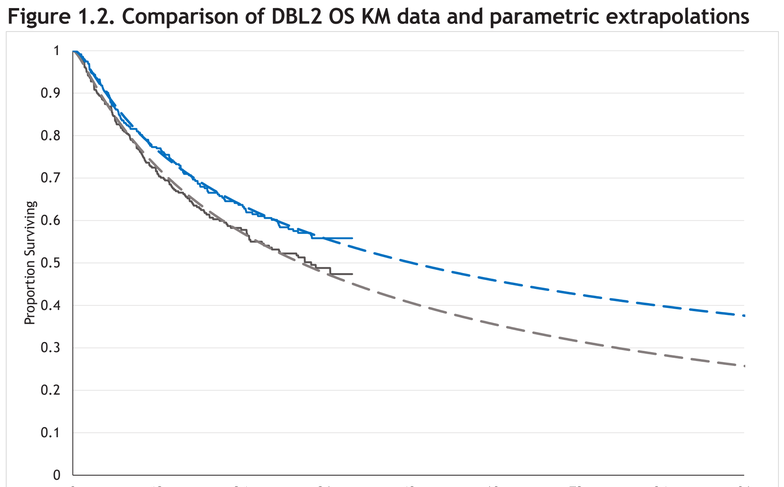
3) The Surrogacy approach:

- Using the statistical model developed by Leung et al.[5] the reported PFS HR was used to predict the OS HR between Rela + Nivo and Nivo. Specifically, the equation used to predict OS HR from PFS HR was $\ln(HR_{OS}) = -0.09 + 0.46 * \ln(HR_{PFS})$.
- The predicted OS HR was 0.801 and applied to the modeled OS curve (Gompertz distribution) of Nivo arm from the CheckMate 067[4] trial to estimate the OS for Rela + Nivo arm of RELATIVITY-047 trial. This method assumed similar OS results for Nivo arms between the two studies which could not be evaluated at the time of DBL1 for RELATIVITY-047 trial.

Modeling DBL2 OS in RELATIVITY-047 Trial:

- Observed OS data from DBL2 were used to develop independent parametric survival estimates as a benchmark for the OS data predicted from DBL1 PFS.
- Functional forms were selected independently for each arm. Based on minimum Akaike and Bayesian information criteria, lognormal and gamma distributions emerged as corresponding best-fits to the observed OS data for Rela + Nivo and Nivo, respectively.

Figure 1.2. Comparison of DBL2 OS KM data and parametric extrapolations



Results

- Mean forecasted OS gains with Rela + Nivo versus Nivo are presented in **Table 1**.
- **Figures 1.1 and 1.2** present comparisons of observed Kaplan-Meier (KM) data and parametric fits. Figure 1.1 presents the PFS from DBL1 while Figure 1.2 presents the OS from DBL2.
- **Figures 2.1-2.3** present the constructed OS curves derived by the three approaches. Each graph presents the constructed curves compared with the observed KM data for OS from DBL2.
- Generally, the proposed OS prediction methods (range between 1.1-1.8 years) underestimated the difference in the extrapolated mean survival (3.1 years by extrapolation of best independent parametric fits).
- Across all models and extrapolations, incremental mean OS estimations were not significantly affected in a sensitivity analysis that shortened the time-horizon of extrapolation to 30-years (2.9 years with the extrapolations from reported trial data versus 1.1-1.7 years with the proposed models).

Table 1. Predicted mean OS (years) from PFS for each of the three methods compared with the mean OS predicted from the extrapolations based on observed OS data released in DBL2 of RELATIVITY-047 trial. Mean OS predictions are based on 40-years of extrapolation.

	Mean OS (years)			Median OS (years)	
	Nivo	Rela + Nivo	Δ†	Nivo	Rela + Nivo
Constructed OS curves (from DBL1 PFS data):					
1) sMPM	8.41	9.54	1.1	2.66	3.62
2) SoM	8.47	10.26	1.8	2.32	3.10
3) Surrogacy	10.98	12.80	1.8	3.39	7.21
OS data released at DBL2:					
Parametric extrapolation*	6.70	9.77	3.1	2.70	4.04

*: Rela + Nivo uses LogNormal, Nivo uses generalized gamma.
†Δ: Incremental mean OS between Rela + Nivo and Nivo in RELATIVITY-047 study

Limitations

- In RELATIVITY-047 study, parametric curves do not capture the trend in the reported PFS data accurately (by visual inspection) and this could have contributed to the underprediction of incremental mean OS by the sMPM and SoM approaches.
- The selection of parametric fits for the DBL2 OS data relied on independent models which were chosen based on statistical criteria without accounting for further decision criteria (e.g., consistency in functional forms of the extrapolated curves between the arms) that would be considered in a cost-effectiveness analysis.

Conclusions

- While each of the constructed approaches overestimated the mean OS for Nivo arm, the sMPM approach provided the most accurate predictions for Rela + Nivo compared with extrapolations based on actual OS from DBL2.
- For each method, the estimated incremental survival benefit with Rela+Nivo versus Nivo was lower than the incremental survival benefit obtained by parametric survival extrapolations from DBL2
- Surrogacy approach resulted in large overestimations for mean and median OS for both arms of RELATIVITY-047 study when compared with extrapolations based on actual DBL2 OS data. Overestimation of OS curves and correspondingly the mean OS from the surrogacy model in RELATIVITY-047 trial can be accounted to differences between the patient populations and the observed OS profiles in Nivo arms of the two trials
- This case study showed that in the absence of reported OS data from a trial, indirect methods of OS estimation can be used for cost-effectiveness analyses by providing a range of (conservative) estimates of long-term incremental mean survival between the arms.

References

1. Paly VF, et al. Long-term survival extrapolation for nivolumab (anti-PD-1) in advanced melanoma (AM) from trial data: A response-stratified approach. 11th EADO Meeting; 28-31 October 2015; Marseille, France.
2. Tawbi HA, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med*. 2022 386:24—34.
3. Long GV, et al. Relatlimab and nivolumab versus nivolumab in previously untreated metastatic or unresectable melanoma: Overall survival and response rates from RELATIVITY-047 (CA224-047). ASCO Plenary Series; 15 March 2022.
4. Data on file: Parametric analysis of OS data from 6.5 year follow-up DBL for CheckMate 067.
5. Leung L, et al. Progression-free survival as a surrogate endpoint for overall survival in previously untreated advanced melanoma: A correlation meta-analysis of randomized controlled trials. Poster presentation at Virtual ISPOR EU Conference, 30 November – 3 December 2021

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Figure 2.1. Comparison of sMPM-constructed OS curves with the DBL2 OS KM data

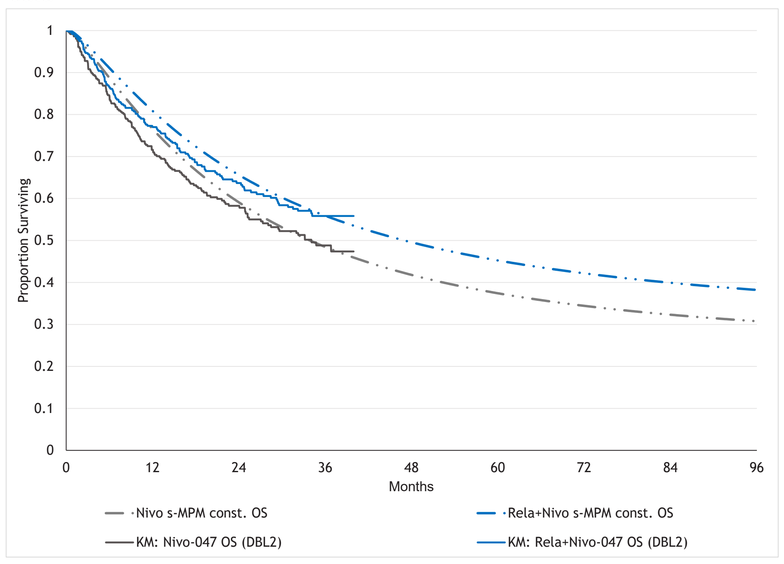


Figure 2.2. Comparison of SoM-constructed OS curves with the DBL2 OS KM data

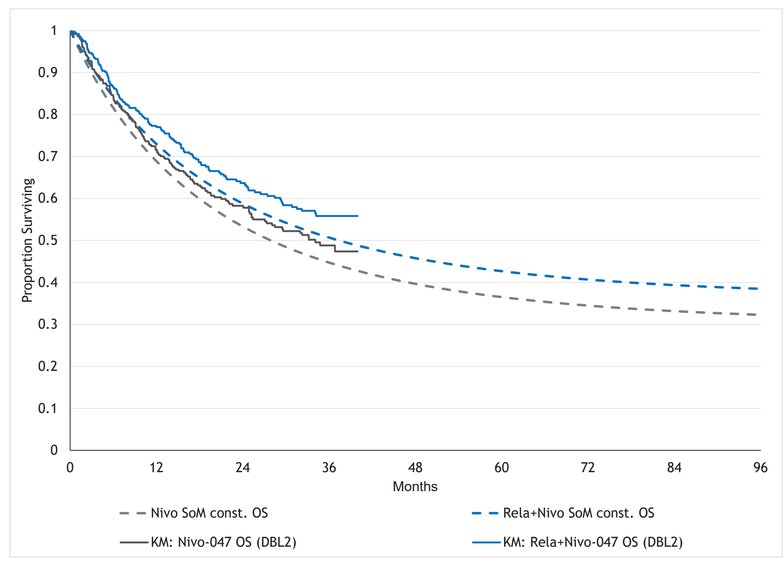
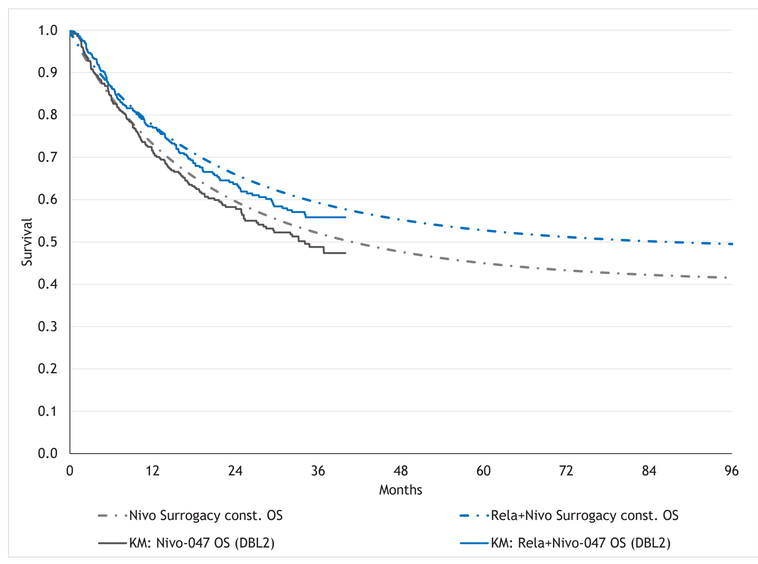


Figure 2.3. Comparison of surrogacy-constructed OS curves with DBL2 OS KM data



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