CO18

Exploring Endpoint Correlation between Progression Free Survival (PFS) and Overall Survival (OS) in Previously Untreated Metastatic Melanoma using Pseudo Individual Patient Data (IPD)

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Background and Objective

- Although overall survival (OS) is the gold standard endpoint in oncology clinical trials, considerable follow-up may be necessary to demonstrate a treatment benefit
- A way to address this challenge is to use clinically relevant intermediate endpoints such as progression-free survival (PFS), which can mature sooner, as a surrogate for OS
- Establishing surrogacy between two endpoints involves showing both:[1]
  - —Treatment-level association between the surrogate endpoint and OS, and
  - —Individual-level association between the surrogate endpoint and OS, which requires individual patient data (IPD) that is not always readily accessible
- Most surrogacy analyses in the literature[2,3] report a treatment-level correlation, but not an individual-level correlation because they do not have access to IPD. Reporting both correlations strengthens our understanding of the relationship between the candidate surrogate endpoint and the true endpoint
- In the absence of IPD, we developed a novel approach to estimate the individual-level correlation between PFS and OS, capitalizing on the access to pseudo-IPD through digitization of Kaplan-Meier (KM) curves using an SLR database that was previously completed in untreated metastatic melanoma[4]
- Our approach aims to jointly utilize the independently reconstructed PFS and OS pseudo-IPD to resolve one of the main challenges of obtaining individual-level correlation with digitized data, which is the lack of connection between the PFS and OS data due to their separate reporting of KM curves

Methods

Data Acquisition

- We systematically searched MEDLINE®, Embase, and CENTRAL from database inception to October 20, 2020 for RCTs reporting OS and either PFS or time-to-progression (TTP) in adults (≥18 years old) with previously untreated advanced, unresectable stage III/IV melanoma
- KM curves were digitized from the publications using *Grab It!*, a plot digitizer tool to extract data from figures, from which pseudo-IPD for OS and PFS endpoints were separately reconstructed using the Guyot algorithm
- The follow-up time for each arm of each trial was divided into non-overlapping intervals, and for each interval m, the conditional survival probability was calculated based on the scanned survival proportions: $S(t_{m+1})/S(t_m)$
- The result was a marginal survival distribution for both OS and PFS. In order to draw inference into their joint distribution, we used a three health-state model and insights from the Li and Zhang model (2015)[5]

Three Health-State Model

- The three health-state model for OS and PFS is illustrated in **Figure 1**
- *TTP* is the time from start of therapy to progression, OS_{orig} is the time from start of therapy to death, and *OS'* is the time from progression to death. This implies:

$$PFS = min(TTP, OS_{orig})$$

$$OS = PFS + I_{PFS!=OS_{orig}}\, OS'$$

where $I_{PFS!=OS_{orig}}$ is an indicator variable attaining the value of 0 if $PFS = OS_{orig}$ and 1 otherwise

- Li and Zhang (2015)[5] assume that the random outcomes defined above other than PFS follow Weibull distributions with independent scale parameters (λ_i) and a common shape parameter (κ):

$$TTP \sim Weibull(\kappa, \lambda_1)$$

$$OS_{orig} \sim Weibull(\kappa, \lambda_2)$$

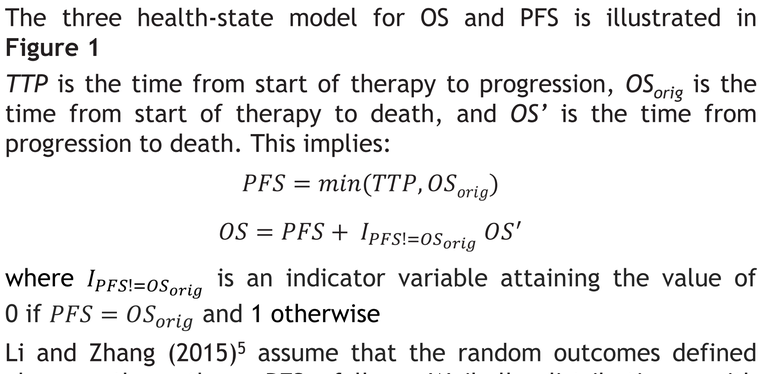
$$OS' \sim Weibull(\kappa, \lambda_3)$$

- They demonstrate that q, the proportion of patients who progress before dying, can be derived from λ_1 and λ_2:

$$q = Prob(PFS = TTP) = Prob(TTP < OS) = \frac{\lambda_1}{\lambda_1 + \lambda_2}$$

- We used the resulting closed-form equation for calculating the Pearson's correlation between OS and PFS on the basis of λ_1, λ_2, and λ_3

Figure 1. Three health-state model for OS and PFS



Start of therapy implies that a patient is progression-free. h^{SD} is the hazards from start of therapy to death, h^{SP} is the hazards from start of therapy to progressed disease, and h^{PD} is the hazard from progressed disease to death.

Methods (continued)

Bayesian Regression Model

- The number of events (r_{jm}) and hazard rate (h_{jm}) in interval m ($[t_m, t_{m+1}]$) of study j is described by

$$r_{jm} \sim bin(p_{jm}, n_{jm})$$

$$h_{jm} = -ln(1 - p_{jm})/\Delta t_{jm}$$

where n_{jm} is the number at risk at t_{jm}, p_{jm} is the event probability, and Δt_{jm} is the length of the interval

- The log hazard rate can be predicted using the following regression model:

$$ln(h_{jm}) = \beta_{0j} + \beta_{1j}\, ln(t)$$

which bears the following relation to the parameters defined by Li and Zhang[5]:

$$\kappa = \beta_{1j} + 1$$

$$\lambda = \frac{e^{\beta_{0j}}}{\kappa}$$

- Therefore, the log-transformed hazard rate for each transition is described by:

$$ln(h_{jm}^{SP}) = \beta_{0j} + \beta_{1j}\, ln(t)$$

$$ln(h_{jm}^{SD}) = \beta_{2j} + \beta_{1j}\, ln(t)$$

$$ln(h_{jm}^{PD}) = \beta_{3j} + \beta_{1j}\, ln(t)$$

- The prior distributions of the β_{ij} were assumed to be independent and normally distributed with a mean of 0 and a variance of 10,000, and each trial arm was modelled independently to avoid imposing homogeneity on the studies

Estimation Procedure

- Our data did not distinguish whether a patient leaving the healthy state was progressing or dying, but we could determine the number or proportion of patients leaving the healthy state (h) or entering the death state (d)
- Therefore, we used the following approach for each arm of each trial:
  1. Estimate the transitions between health states using several stipulated values of q:
     - Number transitioning from start of therapy to progression $= qh$
     - Number transitioning from start of therapy to death $= h - qh$
     - Number transitioning from progression to death $= d - (h - qh)$
  2. Choose the best fitting value of q based on deviance information criterion (DIC)
  3. Use that value to estimate the Weibull parameters and calculate a correlation
- This procedure was implemented as a Markov Chain Monte Carlo simulation in JAGS v4.3
- Model fit was assessed by comparing the curve predicted by the best-fitting model for each arm of each trial to the reported curve visually, and based on whether the 95% CI of the difference in restricted mean survival time (RMST) between the two curves covered 0 (good fit) or not (poor fit)
- Meta-regression was performed on the Fisher transformed correlations to estimate the overall correlation based on (1) the entire evidence base, and then (2) the curves for which the model fit was good based on both visual inspection and RMST

Results

- The SLR, which has been described previously,[4] included 49 arms from 24 trials published from 2000 to 2020
- The proportion of patients experiencing progression prior to death (mean=0.816, standard error=0.011) was generally higher for modern treatments (0.70–0.94 across 36 arms) and lower in control arms
- Based on the 95% CI coverage of 0 on the difference in RMST, four curves from two trials had poor model fit for PFS and three curves from three trials had poor model fit for OS
- Based on visual inspection between the predicted and reported curves, thirteen curves from eight trials had poor model fit for OS
- Overall, 31 of 49 OS/PFS pairs had good fit for both curves. See **Figure 2** and **Figure 3** for examples of good fitting curves.
- When the meta-regression was conducted for the full evidence base (**Figure 4**), the estimated correlation between OS and PFS was 0.987 (95% confidence interval [CI]: 0.979, 0.992)
- When the meta-regression was restricted to the 31 curves with good model fit, the estimated correlation was 0.986 (95% CI: 0.975, 0.992)
- IQWiG criteria requires lower bound of the 95% CI on the correlation estimate to be greater than 0.85; hence, the correlation between PFS and OS was concluded as strong

Results (continued)

- Model predictions on an equally-spaced discrete time basis were illustrated for PFS and OS using the reported data in the control arm of CheckMate 067

Figure 2. Observed (red) vs. predicted (black) OS from PFS via three-state model in the ipilimumab arm of CheckMate 067

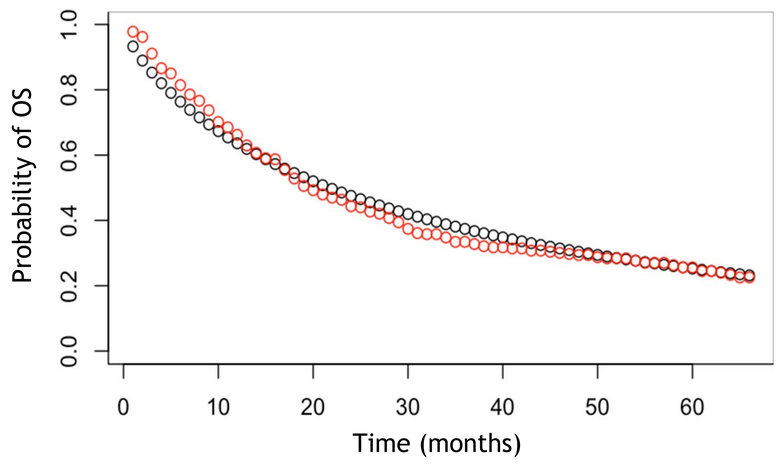


Figure 3. Observed (red) vs. predicted (black) PFS via three-state model in the ipilimumab arm of CheckMate 067

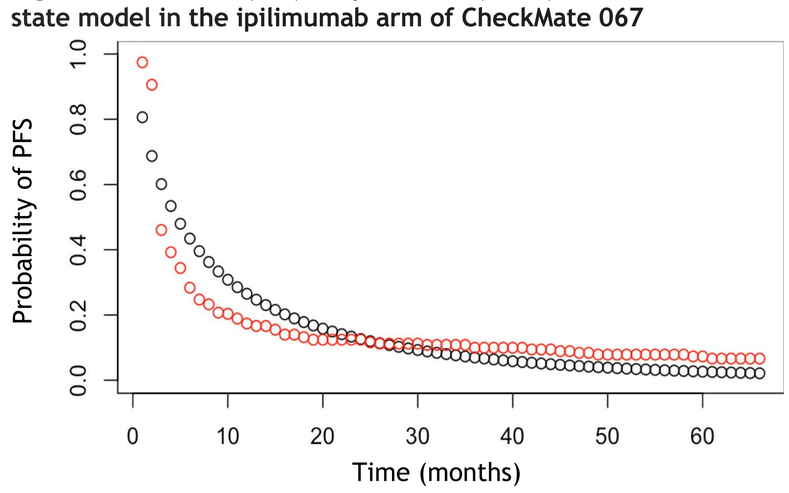
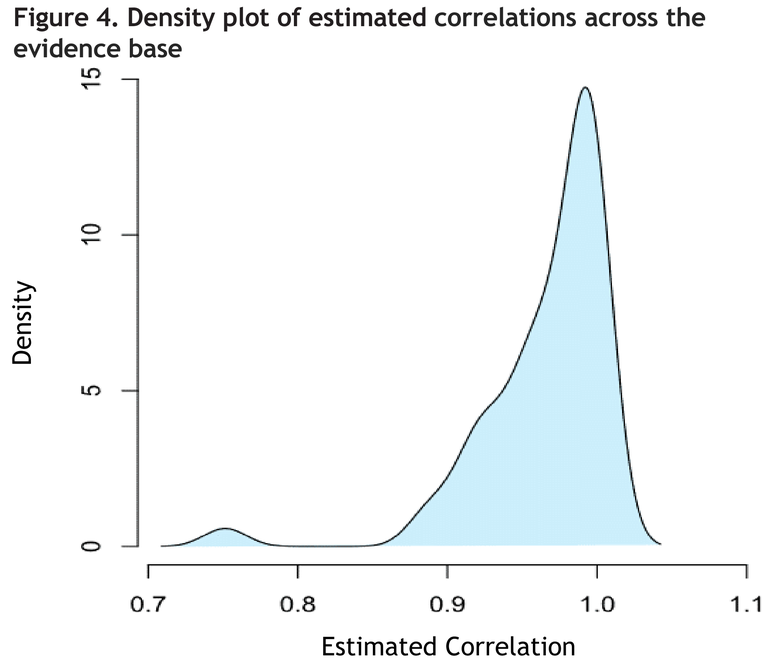


Figure 4. Density plot of estimated correlations across the evidence base



Conclusions

- The estimated endpoint correlation between PFS and OS was strong (0.986) in previously untreated advanced melanoma patients
  - —Although not all trial arms met the model assumptions, the estimate was stable when the analysis was restricted to studies considered to have good model fit (either 95% CI coverage of 0 on the difference in RMST, or reported curves were visually well-fitted by the model)
- Overall, this study presents additional evidence supporting the use of PFS as a surrogate for OS in previously untreated melanoma
- The three-state model can also be utilized directly in eliciting post-progression survival from PFS and OS, and in cost effectiveness assessments where IPD is missing
- Two directions for future research:
  - —To develop a procedure with fewer assumptions as our approach required the strong assumption that the main three time-to-event outcomes followed a Weibull distribution with a shared shape parameter
  - —To investigate the model validity in capturing survival trend and estimate underlying correlation between two endpoints using synthetic data

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