

Can Bayesian Informative Priors Improve Extrapolation of Immature Overall Survival? A Case Study in Advanced Melanoma

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Background

- Novel oncology treatments often undergo health technology assessments (HTAs) based on immature trial data due to high unmet need. In these situations, extrapolation of overall survival (OS) with parametric survival models (PSMs) can be subject to large uncertainty.
- The use of Bayesian informative priors (IPs) for long-term OS extrapolation can reduce uncertainty,¹ which can reduce risk in HTA decision-making.
- This case study in newly diagnosed BRAF^{V600} mutation-positive advanced melanoma (aM-BRAF^{V600}) investigates whether Bayesian PSM using IPs provide more accurate extrapolations compared with standard PSMs.

Objectives

- Compare the accuracy of OS extrapolation using PSMs or Bayesian PSMs, with respect to available long-term OS reference data.

Methods

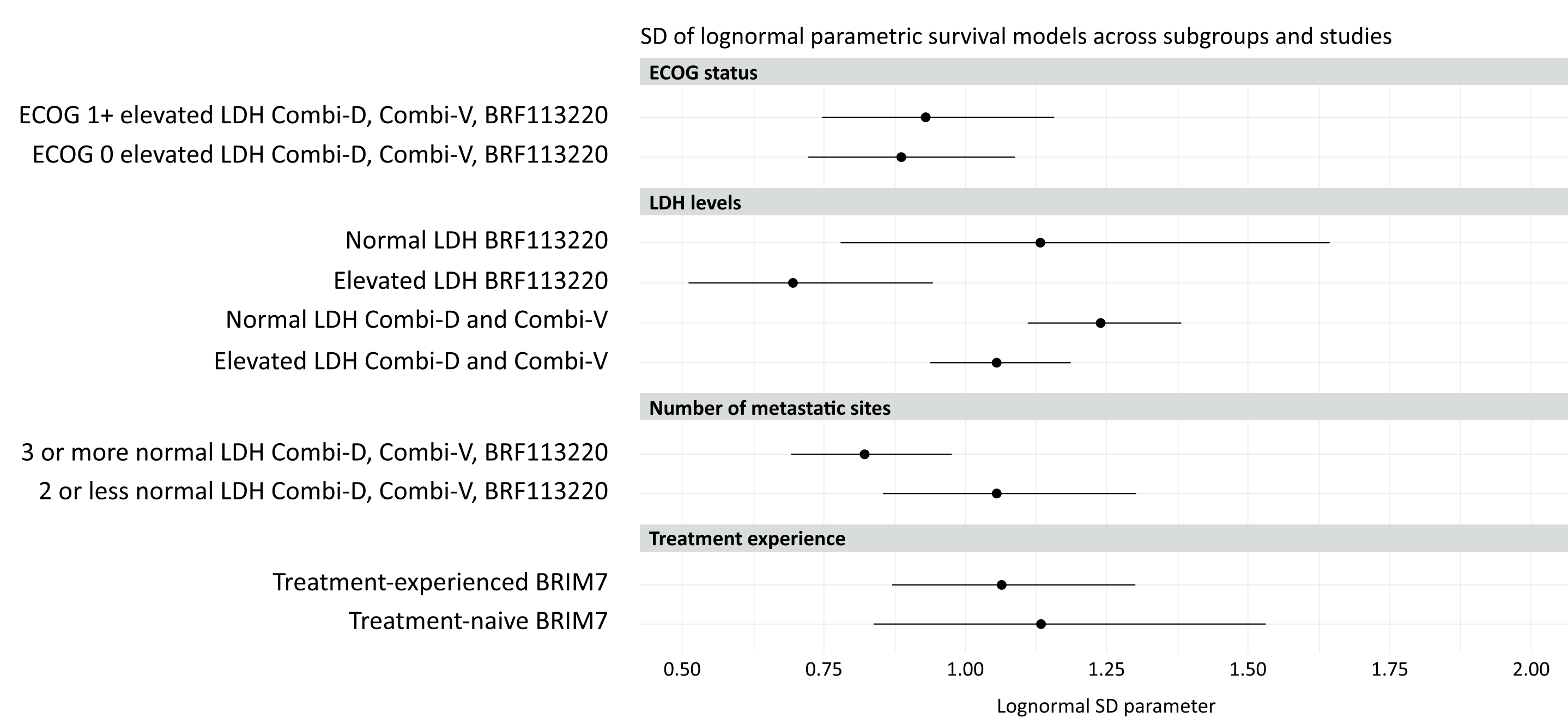
- The coBRIM trial was selected for this case study and was identified from a targeted literature review of aM-BRAF^{V600} clinical trials.
- CoBRIM is a phase III trial of cobimetinib + vemurafenib in patients with newly diagnosed aM-BRAF^{V600} with long-term OS data available (at least five years since the last patient was randomized).²
 - OS data from the active arm of the coBRIM trial were digitized, followed by generation of reconstructed individual patient-level data (RIPD) using the Guyot et al. algorithm.³ Two datasets were then created.
 - Reference dataset.** As obtained from the RIPD, with the long-term OS data used to compare the accuracy of PSMs vs. Bayesian PSMs.
 - Immature dataset.** Truncated using the median OS time (22.5 months) reported in Ascierto et al.² as the truncation time. Patients with reported time after the simulated truncation time were considered to have been censored. This dataset was used to provide immature OS data on which PSMs/Bayesian PSMs were fitted.
- Five other trials with long-term OS data investigating combination regimens with a BRAF- and MEK-targeted agent in patients with aM-BRAF^{V600} were used to derive IPs (BRF113220, BRIM-7, Combi-D, Combi-V, and DREAMseq).⁴⁻⁸
- The IPs were derived by pooling the ancillary parameters obtained from parametric fits (Weibull, Gompertz, log-logistic, and lognormal distributions) fitted on the RIPD from the five trials mentioned above, through meta-analysis. The method presented by Soikkeli et al. 2019⁹ was then used to incorporate IPs into the Bayesian PSMs.
 - Ahead of the pooling, heterogeneity in the ancillary parameter estimates obtained in the different trials was assessed through forest plots.
- Accuracy of PSMs and Bayesian PSMs was then evaluated comparing the restricted mean (RM) from the reference dataset with the RM derived from the PSMs and Bayesian PSMs fitted on the immature dataset.

Results

Derivation of informative priors

- The lognormal and log-logistic distribution consistently achieved the best fits of the OS long-term data in the BRF113220, BRIM-7, Combi-D, Combi-V, and DREAMseq trials.
- Heterogeneity in the ancillary parameters was noted across LDH levels (**Figure 1**), suggesting that the trials used to derive IPs for the overall population should have a relatively comparable LDH distribution (normal vs. elevated) to what was observed in the coBRIM trial.

Figure 1. Forest Plot of Ancillary Parameters across Subgroup of Interest Using the Lognormal Distribution



Abbreviations: ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; SD = standard deviation

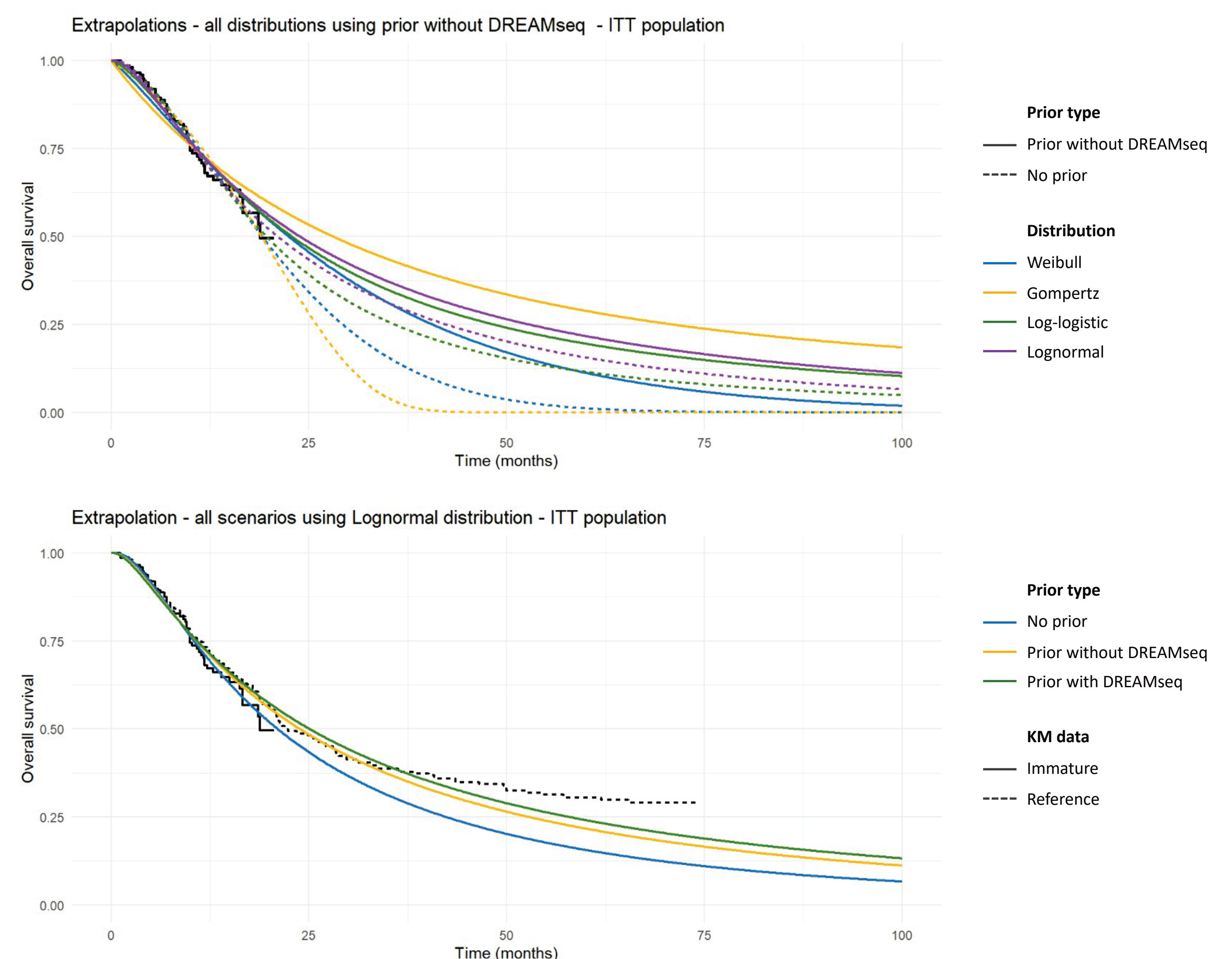
- Two scenarios for IPs derivation were explored. In Scenario 1 the following trials were considered: Combi-V, Combi-D, BRF113220 and treatment-naïve data from BRIM-7. In Scenario 2, DREAMseq was also considered, since, by trial design, patients could only receive a specific combination of immunotherapies as subsequent therapy upon progression (potentially causing heterogeneity in the ancillary parameter estimates).⁶

Results (Cont'd)

Accuracy of PSMs and BPSMs

- An overlay of the long-term survival extrapolations across parametric distributions without or with using IPs (based on scenario 1) is presented in **Figure 2**. The Bayesian PSMs obtained with IPs based on scenario 2 yielded similar results and are not presented.
- Figure 2** also compares the lognormal survival extrapolations (best fitting model) obtained for PSM and Bayesian PSM with the Kaplan-Meier data for the immature coBRIM dataset and the mature coBRIM dataset.

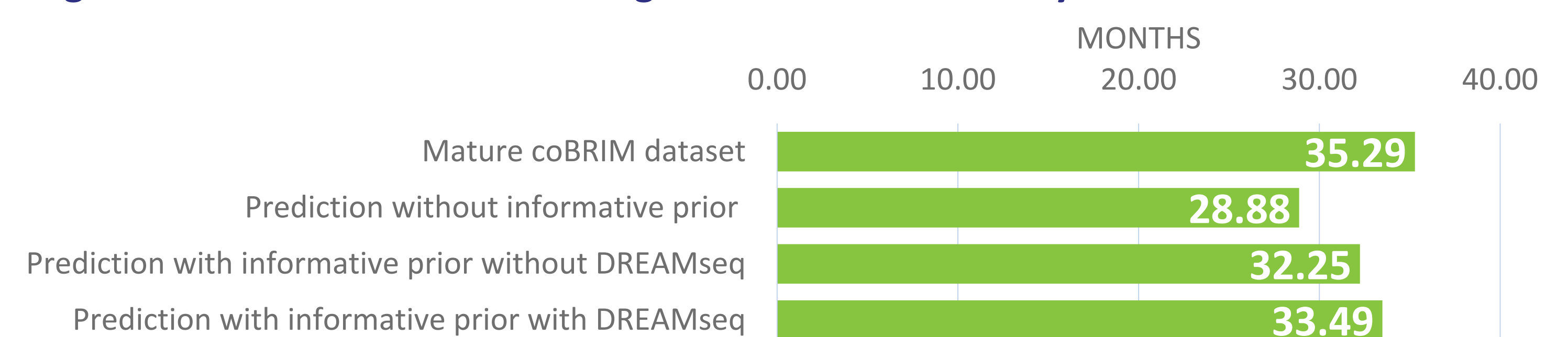
Figure 2. (A). Overlay of Long-term Extrapolations across Parametric Distribution with (BPSMs – solid line) and without (PSM – dashed lines) using IPs. (B) Long-term Extrapolation with (BPSM) and without (PSM) Using IPs Compared to the Immature coBRIM OS (dotted line) and the Reference coBRIM OS (solid line)



Abbreviation: ITT = intent to treat

- Figure 3** compares the RM estimated with the mature coBRIM data with the RM obtained without IPs and with IPs. The RM estimates obtained using the IPs are closer to the mature dataset.

Figure 3. Comparison of RM Estimates between the coBRIM Mature Data and the Lognormal Distribution Fitted Using PSM with no IPs or Bayesian PSM with IPs.



Discussion

- Bayesian PSMs with IPs provided more accurate survival projections and RM estimates and reduced variability in projections based on different parametric distributions (**Figure 2-3**).
 - Some deviation of the Bayesian PSM projection from the observed long-term survival was observed beyond 37 months (**Figure 2**).
 - The impact of alternative IPs including or excluding DREAMseq trial was limited in terms of estimated RM and survival probabilities.
- Evaluating heterogeneity of the ancillary parameters included in the IPs is recommended to ensure that meaningful IPs are used, and alternative IP scenarios can be tested.
 - Heterogeneity can also be handled by fitting Bayesian PSMs with IPs to data specific to the subgroups of interest.

Conclusions

- Use of Bayesian PSMs can improve extrapolation of immature OS data when suitable IPs can be formulated from prior studies.

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