

Projecting median survival times for studies with immature survival data to support accelerated approval considerations of treatments in multiple myeloma

Letao Li^{1*}, John Maringwa¹, Chandni Valiathan¹

Clinical Pharmacology & Pharmacometrics, Janssen Research & Development, LLC. ^{*}Intern at the time of preparation.

Abstract

Background: In relapsed/refractory multiple myeloma (RRMM), new therapies often receive accelerated approval based on early response endpoints like overall response rate (ORR), which are available sooner than the clinical endpoint e.g., progression-free survival (PFS). The correlation between median PFS (mPFS) and ORR was explored based on summary-level published clinical trials data to help inform decisions. Often, ORR is available but mPFS missing e.g., due to immature PFS (mPFS not reached). This study investigated if PFS Kaplan-Meier (KM) data available at the time of publication could reliably be used to project the mPFS, thereby boosting the information to quantify the relationship between mPFS and ORR. Studies that reported both KM curves and mPFS helped to validate the approach. Weibull and Exponential models were applied on fractions of KM data to project the mPFS and compare that with reported values. The relationship between mPFS and ORR was then assessed on a subset of Phase 3 studies, based on reported data and data augmented with projected mPFS when missing. Results from this study may help researchers to enrich reported data through imputation of mPFS if unreported or PFS is immature, potentially improving precision of the mPFS-ORR correlation estimate and reducing bias by inclusion of more data. Further, recommendations on the amount information required to reliably project mPFS for immature PFS are provided to help practitioners decide on when, or whether, it is advisable to use the imputed information.

Methods: 140 studies identified from a systematic literature review (SLR) of studies investigating treatments for RRMM were leveraged. The Weibull and Exponential models were used to project mPFS on subsets of data created by omitting fractions of data from the end of each study to mimic immature survival data. The projected mPFS were then compared with reported data. Graphical and numerical metrics were used to qualify and compare models, and the best-chosen model was used to project mPFS for further use. A selected set of Phase 3 studies was used to quantify the relationship between mPFS and ORR, based on (1) reported data only and (2) reported data augmented with data points for which ORR was reported and mPFS imputed from the chosen model.

Results: Using the full data (Table 1), strong correlation between reported and projected mPFS was identified for both models. Overall, based on model diagnostics, the Weibull tended to describe the data better and hence was preferred for mPFS projections. When at least 70% of data was retained (Table 1, Figure 3), the relationship between projected and reported mPFS was strong, reflected by R-square >0.80. In Phase 3 studies, the R-square (95% , confidence interval (CI)) between mPFS and ORR was 0.83 (0.75, 0.89) based on reported data and it was similar but slightly more precise when including imputed mPFS.

Conclusions: Parametric time-to-event models may reliably project median survival times to enrich information and improve precision on estimates as opposed to excluding studies with immature survival data, risking bias. At least about 70% of information from the expected full KM curve may be required to reliably project mPFS if PFS is immature. The relationship between mPFS and ORR remained consistent after including imputed data and there may be gains in precision through the supplementary information.

Rationale

- Strong relationships between early and clinical endpoints often support accelerated approvals in multiple myeloma.
- ORR may be available but mPFS missing because either it was not reported in sources or PFS was immature at publication time (mPFS not yet reached, see example in Figure 1).
- Excluding studies with immature survival data may hinder appropriate depiction of the relationship between the early and clinical endpoint, because of reduced information and potential biases that may ensue.
- Approaches to impute missing median survival times to maximize information for inferences may potentially help improve precision on estimates and hence are warranted.

Objective

To assess if parametric time-to-event models can be applied on available KM data to project mPFS in a reliable manner when it is not reported or in the case of immature survival data.

Methods

- A SLR identified 140 studies for investigational and approved antimyeloma therapies, published between 2007 and 2023, that were used to validate the approach considered here.
- Studies that reported both KM curves and mPFS with study arms that had ≥ 10 KM data points and ≥ 20 patients at randomization were included in the analysis.
- Subsets of data were created by excluding fractions of data from the end of each KM curve to reflect reduced information and mimic immature survival data scenarios (Table 1).

- 36 (/140) international, randomized, controlled, parallel-design Phase 3 studies, that reported both mPFS and ORR were selected to correlate the early and clinical endpoint.
- 9 study arms (/186) from 4 studies (/140) with similar characteristics as the 36 studies above reported ORR but not mPFS, since it was either not reported or PFS was immature (Figure 4); models were then used to project the missing mPFS in these study arms.

Table 1. Some data were excluded from the full set to mimic reduced information and the mPFS was projected based on those subsets of data.

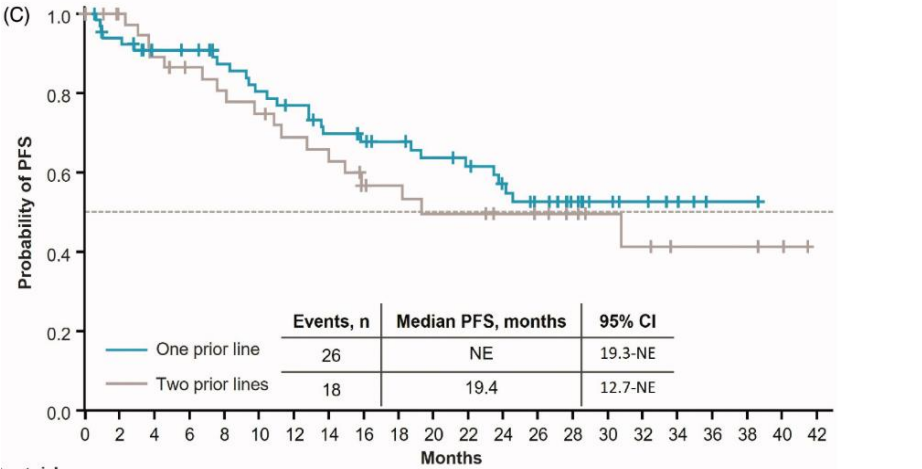
Data included* to project mPFS	# arms with immature PFS/# study arms (%)	Weibull, R-square	Exponential, R-Square
100% (Full data)	7/186 (3.7)	0.87	0.85
90%	17/182 (9.3)	0.87	0.84
80%	24/165 (14.5)	0.86	0.81
70%	34/149 (22.8)	0.82	0.76
60%	38/113 (33.6)	0.77	0.70
50%	36/78 (46.2)	0.73	0.64

*10% of data points are sequentially deleted to mimic reduced information settings.

Statistical methods

- The relationship between mPFS and ORR/projected mPFS was quantified by the proportion of variation in mPFS explained by ORR/projected mPFS (R-Square); the log transformation was considered if it helped to better linearize the relationship.
- The Weibull and Exponential models described the hazard of progression/death [1] on full or subsets of KM data (Table 1) per study arm, weighted by the number of patients at risk when reported, otherwise no censoring was assumed.
- The closed-form solution for the median survival time for both models enabled a convenient way to project the mPFS.
- Diagnostic plots of reported vs model-projected mPFS, median prediction error (MPE) and root mean square error (RMSE) capturing the discrepancy between reported and projected mPFS helped to evaluate model adequacy, enabling comparison between models and to assess the impact on projecting mPFS of the amount of information used (Table 1).

Figure 1. Example of reported KM curves. The blue line exemplifies immature PFS showing that the mPFS was not yet reached.



Results and Discussion

- Model diagnostics suggested that in general, both models described the full data (R-Square ≥ 0.85 , Table 1) in a satisfactory manner.
- In general, graphical and numerical diagnostics (Table 1, Figure 2 & 3) tended to favor the Weibull as a somewhat better model to describe trends in the data. Figure 2 illustrates that the Weibull model captured trends in the full data well.
- When applied to subsets of data, the Weibull consistently had a larger R-Square compared to the Exponential and the difference appeared to widen when information decreased (Table 1, Figure 3). Weibull was therefore selected to make mPFS projections for augmentation with reported data.
- For Weibull, with $\geq 70\%$ of data ($\leq 22.8\%$ of study arms with immature data), R-Square was relatively large (>0.80 , Figure 3).

Figure 2. Illustrative fit of Weibull model in selected study arms shows a satisfactory description of the full data.

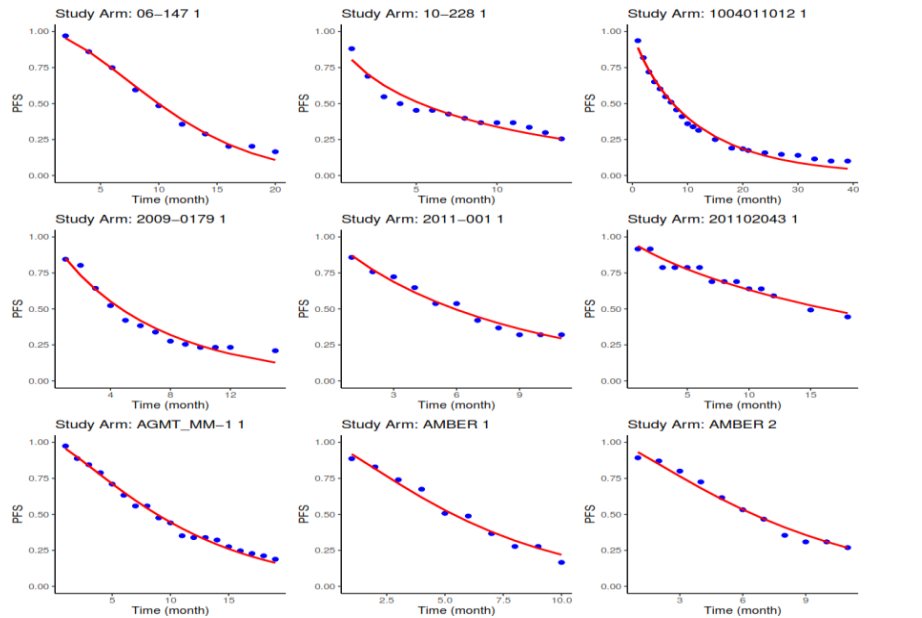
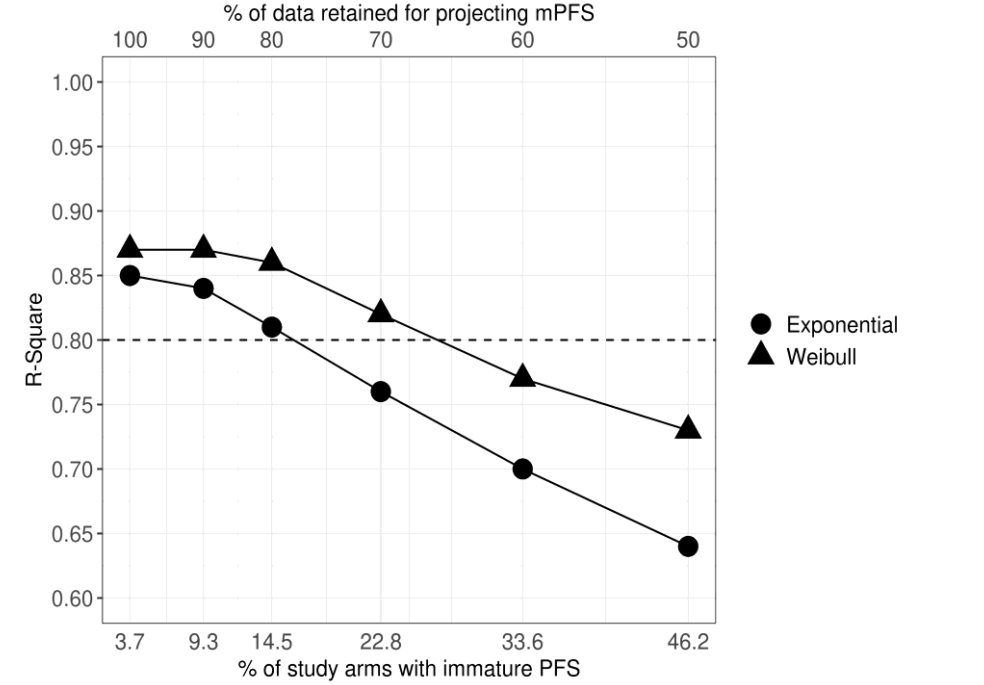


Figure 3. The R-square quantified the relationship between reported and model-projected mPFS to compare between models and across subsets of data (see Table 1).



- Figure 4 shows the Weibull model fit to KM data in the 9 Phase 3 study arms that had missing mPFS while ORR was available and shows that the model described trends in the data well; mPFS was then projected from the model (blue line).
- The fully reported Phase 3 data (both mPFS and ORR available, Figure 5, left) was then augmented with the model-projected mPFS and reported ORR data (red points Figure 5, right) to provide an extended analysis data set (Figure 5, right).

Figure 4. The Weibull model fit (red line) and mPFS projections (blue line) on Phase 3 study arms that had ORR but missing mPFS.

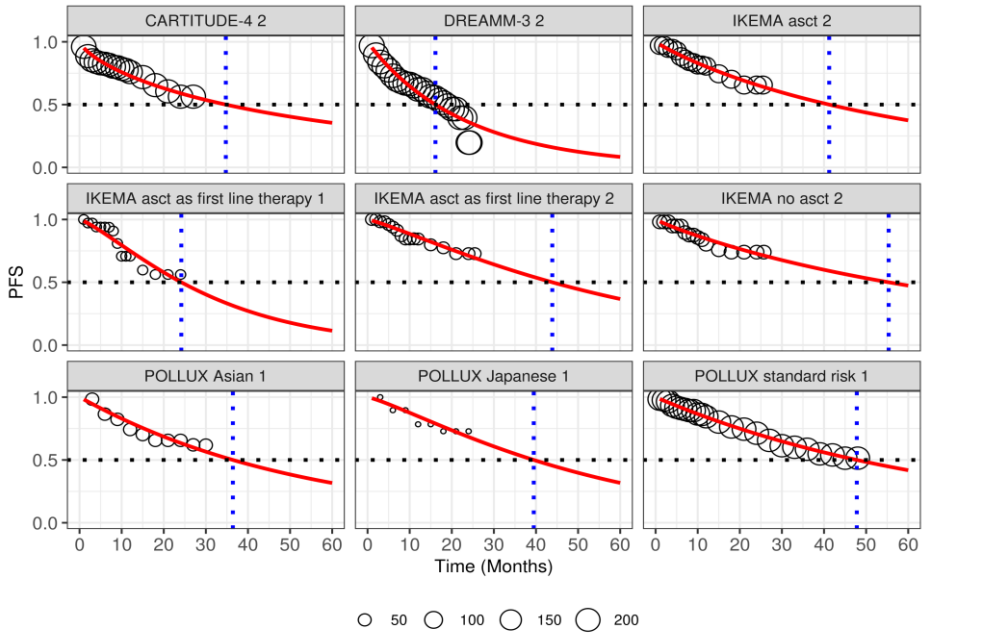
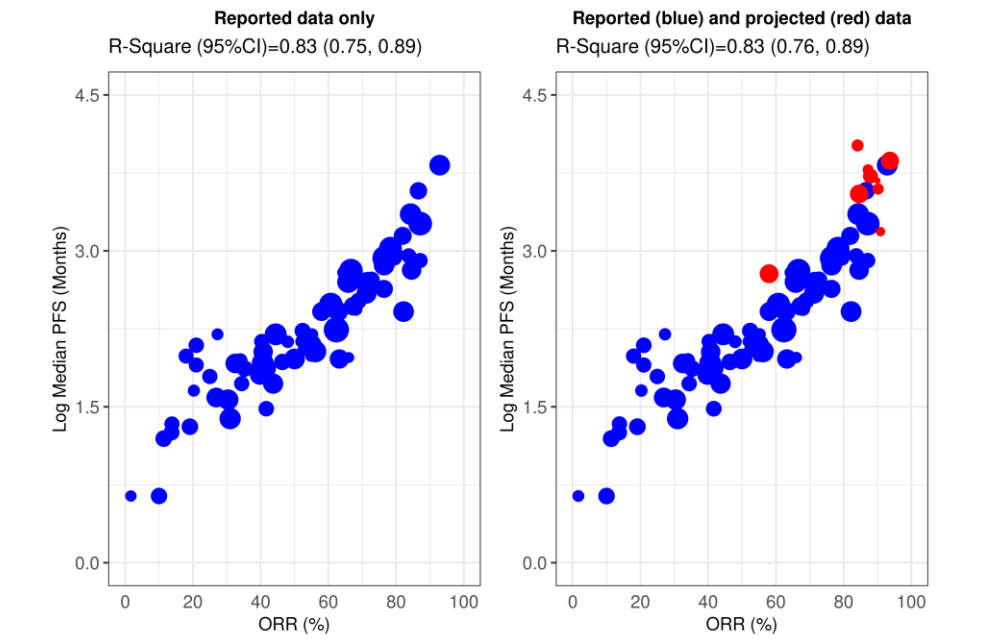


Figure 5. Log mPFS related to ORR based on reported Phase 3 data and reported data augmented with imputed mPFS data.



- The R-square relating log mPFS to ORR was 0.83 based on reported data only and was similar when including imputed mPFS (Figure 5), suggesting a strong relationship.
- CI's associated with the extended data where somewhat narrower (Figure 5), commensurate with potential gains in precision.

Conclusion

With at least 70% of the expected KM information over time, the Weibull model may reliably be used to project missing mPFS when not reported or PFS is immature, subsequently boosting the amount of information to quantify the relationship between early (ORR) and clinical endpoint (PFS) in support of accelerated approval of treatments in RRMM.

References

- Collett, D. Modelling Survival Data in Medical Research. 2nd ed. Boca Raton: Chapman & Hall/CRC, 2003.