Inferring the proportion of durable responders to targeted oncology therapies in combination regimens using Bayesian parametric mixture survival models

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Background

- Many current clinical trials in oncology are designed to evaluate the efficacy of novel therapies used in combination with conventional treatment or current standard of care, for example, targeted therapy plus chemotherapy versus chemotherapy alone, dual immunotherapy versus immuno-monotherapy, etc.
- Intuitively, the cohort of patients receiving the intervention should be split into patients who exhibit a control-like response, and patients who attain markedly improved survival outcomes as a result of favorable response to the novel agent
- Bayesian formulations of parametric mixture models (B-PMMs) provide an appealing method to capture this phenomenon in the survival outcomes

Methods

- PMMs represent the patient population as a combination of two latent subpopulations with disparate survival curves, and are therefore convenient for modelling heterogeneity in time to event outcomes, at least in principle
  - in practice, PMM estimates can be unreliable even with large cohorts and long follow-up [1-3]
  - the performance of PMMs can be greatly improved by integrating external information via a Bayesian framework, where *a priori* knowledge is represented by specified prior distributions
- To impose our expectation that one latent subpopulation of the experimental arm will exhibit a survival pattern similar to that of the control arm, we use a standard parametric survival model fitted to the control arm data as the corresponding prior distribution for "non-responders" to the intervention in the B-PMMs
  - for the second subpopulation, which represents "responders" to the intervention, a weakly informative prior distribution necessitating markedly improved survival outcomes compared to the overall population is used
- We applied the B-PMMs to digitized[4] 5-year progression-free survival (PFS) data from the phase 3 CLEOPATRA trial comparing a trastuzumab and docetaxel regimen with and without the targeted therapy pertuzumab (PER+TRA+DOC vs TRA+DOC) in HER2-positive metastatic breast cancer[5]
- We use Weibull and log-normal distributions for "responder" and "non-responder" survival functions, to reflect our belief of monotonic and non-monotonic hazards for these respective subpopulations
- To assess the robustness of the B-PMMs with respect to specification of the prior distributions, we explored three alternative scenarios for prior expectation of the proportion of responders to PER:
  - a uniform distribution (vague prior, reflecting no *a priori* knowledge)
  - a beta distribution with mean 30% (optimistic; moderately informative but modest uncertainty)
  - a logit-normal distribution with mean 30% (optimistic; strongly informative; misleading)

Results and Discussion

- The B-PMMs based on uniform and beta prior distributions for the proportion of responders to PER yield clinically plausible estimates for the survival curves of both latent subpopulations (Fig 1) and for the mixture fraction, and are highly consistent with one another (Table 1)
  - in contrast, the model based on a logit-normal prior, which was an erroneous representation of the responder fraction and did not allow high enough variance for the model predictions to deviate from this misspecification, gives a significantly greater estimate for the mixture fraction. Nonetheless, the incorrectness of the logit-normal model is readily diagnosed from the goodness-of-fit (Table 1)
- Thus, strongly informative priors, such as logit-normal distributions with low variance, should only be used in mixture survival models when there is clear justification (i.e., based on relevant external data) for having precise *a priori* belief
- Whereas, we have shown that a well-formulated B-PMM featuring a somewhat misspecified moderately informative prior distribution that allows for modest uncertainty, such as the beta example herein, can yield reliable posterior estimates

Table 1: Summary of B-PMM predictions using various different choices of prior distribution for the proportion of responders to PER, and deviance information criteria (DIC). Estimates are reported as posterior means and 95% credible intervals

Prior distribution	Proportion of responders to PER	5-year non-responder survival	5-year overall population survival	DIC
Uniform	15.9 [6.6-25.5]	9.8 [6.1-14.2]	21.0 [16.3-26.0]	2445.4
Beta	18.0 [10.3-27.0]	9.1 [5.7-12.9]	21.7 [17.8-26.2]	2445.4
Logit-normal	26.4 [21.9-31.1]	7.3 [4.7-10.6]	24.8 [21.0-28.8]	2450.4

Figure 1: B-PMM survival functions for the overall population and latent subpopulations, using a beta distribution for the proportion of responders, compared to Kaplan-Meier estimates from trial observations

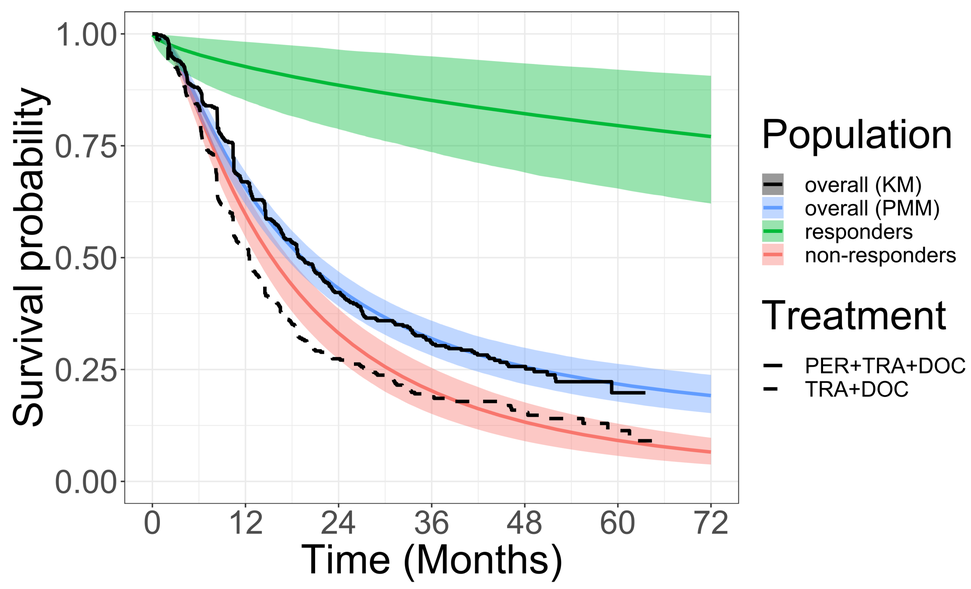
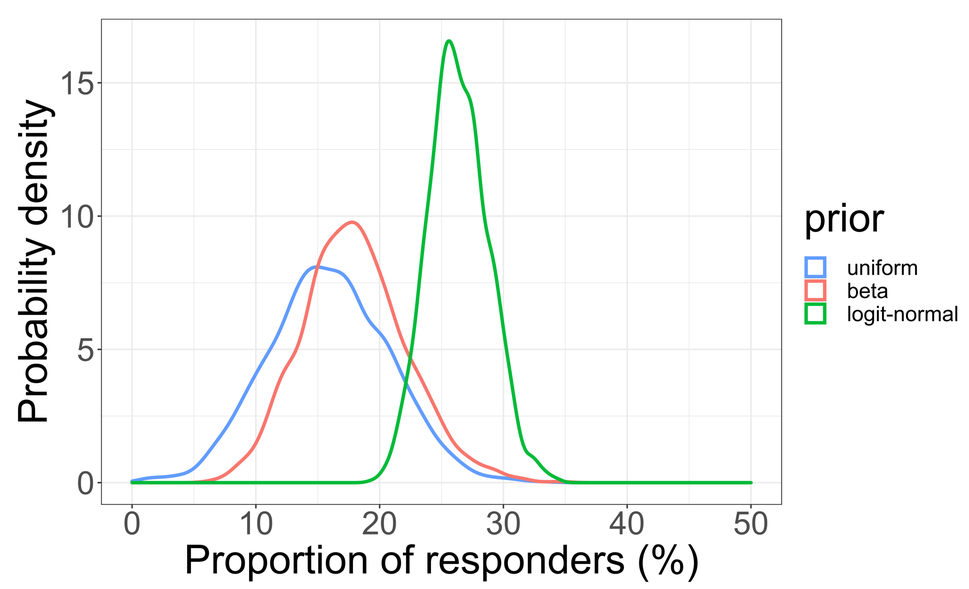


Figure 2: Posterior probability densities for the proportion of responders to PER under various different choices for the prior distribution of this parameter



Conclusions

- B-PMMs can be used to infer the proportion of patients who achieve a durable survival benefit attributable to a novel oncology therapy used in a combination regimen
- B-PMMs appear generally robust to moderate perturbations in component prior distributions
  - strongly informative prior distributions should be derived from relevant external data sources and/or validated by clinical experts since they can have a significant influence on model predictions
  - weakly or moderately informative prior distributions can be used for certain parameters in the absence of external data sources to derive more specific *a priori* expectation
- Further work will investigate the use of alternative assumptions and data sources within B-PMMs (e.g., historical trial data on duration of response to inform responder survival patterns in an immature study dataset)

REFERENCES

[1] Chen T-T. Predicting analysis times in randomized clinical trials with cancer immunotherapy. *BMC Med Res Methodol* 2016; 16(1): 12.

[2] Federico Paly V, et al. Heterogeneity in survival with immune checkpoint inhibitors and its implications for survival extrapolations: a case study in advanced melanoma. *MDM Policy Pract.* 2022; 7(1): 23814683221089659.

[3] Heeg B, et al. Bayesian hierarchical model-based network meta-analysis to overcome survival extrapolation challenges caused by data immaturity. *J Comp Eff Res* 2012; 12(3): e220159.

[4] Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012: 12(1):9.

[5] Swain SM et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015; 372: 724.