Bayesian parametric mixture cure models with delayed treatment effects

and application to targeted therapies in advanced ovarian cancer

MSR45

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Background

- **Mixture cure models** (MCMs) are commonly employed to analyze **survival heterogeneity** in oncology studies[1,2], but the standard assumption of cure at randomization may restrict their clinical interpretability and result in **biased estimates** for the **cure fraction**
  - patients with **advanced cancers** have non-zero tumor burden and are thus uncured at baseline, and responses to therapies are delayed[3]

Objectives

- We extended conventional parametric MCMs to **relax the baseline cure assumption** and instead allow an initial period during which all patients are classified as "uncured" (i.e., have disease-related hazard[1,2]), by incorporating a **cure delay time** parameter
- We demonstrated the proposed method with application to reconstructed **progression-free survival** (PFS) data for first-line maintenance olaparib or placebo plus bevacizumab in the predefined subgroup of patients with homologous recombination deficiency-positive **advanced ovarian cancer** from the final analysis of the randomized phase III PAOLO-1 study, with 61.8 months minimum follow-up duration[4]

Methods

- We formulated an extended MCM wherein the cure delay time is a **threshold** parameter in a **change-point** survival model[5,6]
  - at the cure delay time, a proportion of surviving patients become classified as statistically cured (i.e., have zero disease-related hazard)
  - the other patients continue to follow the parametric (Weibull) distribution representing survival in the latent uncured subpopulation
- The model was estimated in a **Bayesian** framework with marginalization[7] of the cure delay time parameter in monthly intervals
  - i.e., a set of models characterized by alternative values for the cure delay time, weighted by the marginal probabilities, were estimated simultaneously
  - a weakly informative[8] beta-binomial prior distribution was specified for the cure delay time, with a domain ranging from 0 (in which case, the model reduces to the standard MCM) to 36 months
- Estimates for the cure fraction and effective **cure timepoint**[9,10] (here defined as when only <5% of uncured patients remain event-free) were compared to those from a conventional MCM

Results

- The most probable cure delay time for the olaparib (N=255) and placebo (N=132) cohorts, with 86.0% and 32.6% marginal posterior probability, were 23 [90% credible interval (CrI): 23-24] and 25 [90% CrI: 8-26] months, respectively (Fig. 1)
- The estimated cure fraction for the olaparib cohort was 42.1% [95% CrI: 35.7-48.6%] in the extended MCM and 43.3% [95% CrI: 36.1-50.0%] in the standard MCM; and for the placebo cohort was 19.3% [95% CrI: 15.7-24.6%] in the extended MCM and 20.5% [95% CrI: 13.8-28.0%] in the standard MCM
- Estimated 3-year PFS in the uncured subpopulation of the olaparib cohort was 40.8% [95% CrI: 32.4-50.2%] in the extended MCM and 25.5% [95% CrI: 18.4-34.4%] in the standard MCM (Fig. 2)
- Estimated effective cure timepoint for the olaparib cohort was 68 [95% CrI: 57-85] months in the extended MCM vs 58 [95% CrI: 49-70] months in the standard MCM

Figure 1: Prior and posterior marginal probabilities for the cure delay time

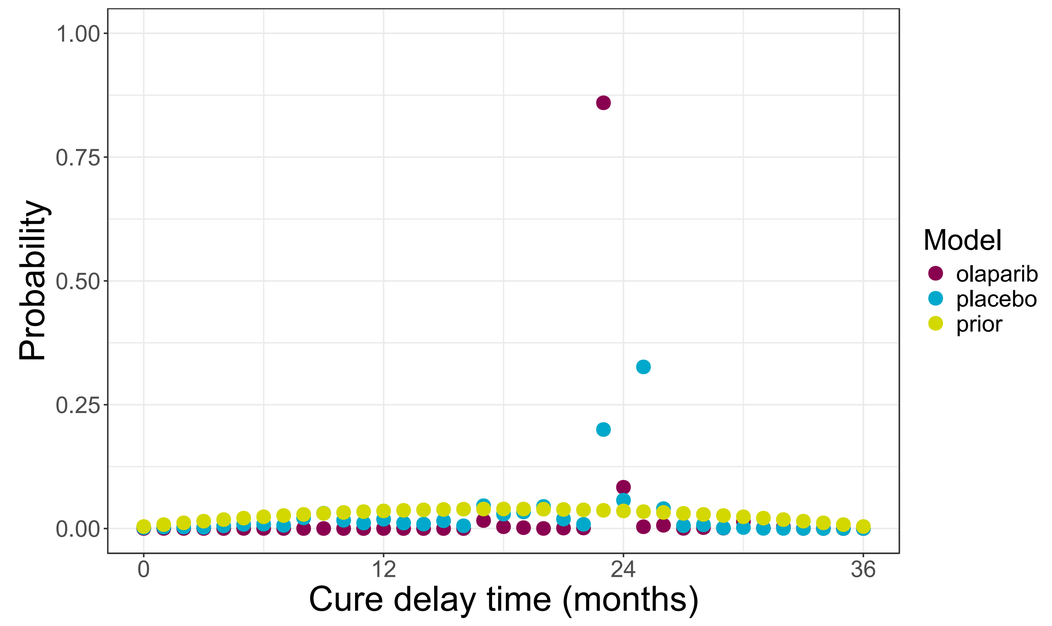
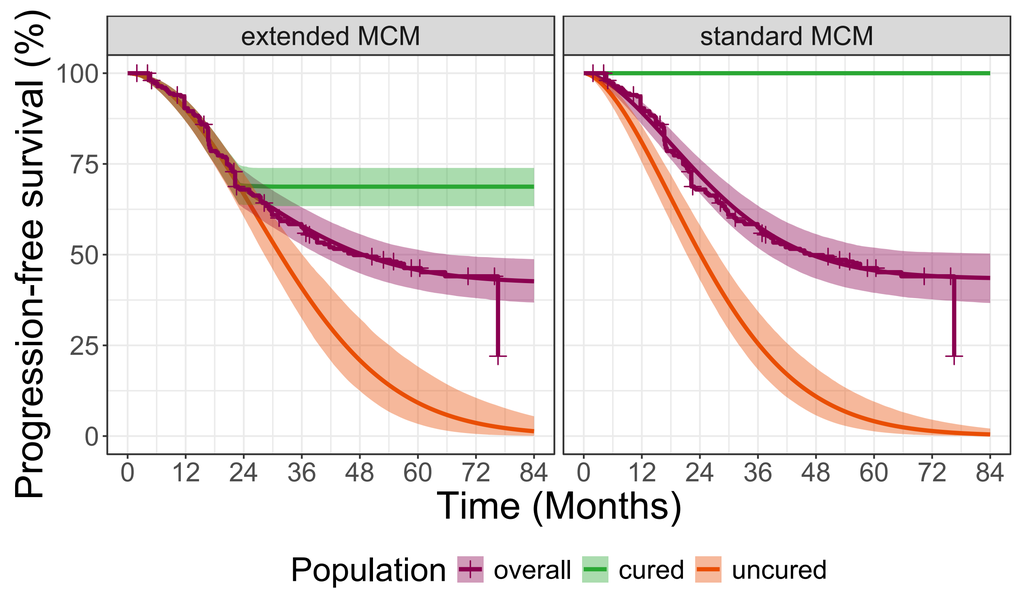


Figure 2: Posterior PFS estimates for the olaparib cohort from an MCM with delayed cure effect and a standard MCM



Shaded areas indicate 95% credible intervals in the Bayesian models.
Kaplan-Meier estimates for the overall population are also shown (step function). Crosses indicate censoring.

Discussion

- The MCM with delayed cure effect essentially infers the time at which a **latent subpopulation** of **statistically cured patients becomes identifiable** from an abrupt reduction in the hazard, which has a simplified representation as a discontinuity within the model
- In PAOLO-1, the cure delay time was very strongly identifiable in the olaparib arm, but more weakly identifiable in the smaller placebo arm
  - in general, **identifiability** of the **cure delay time** depends on both the sample size and survival pattern - specifically, inference is aided by the **emergence** of a **strong survival plateau** at a **well-defined time**
  - hence, the cure delay time is a highly population-specific property
- The extended (vs standard) MCM yields less pessimistic estimates for survival in the uncured subpopulation, and so predicts **a later cure timepoint** and **slightly smaller cure fraction**
- Reasonable uncertainty levels and similarity of the posterior distribution for the cure delay time between the two treatment arms of PAOLO-1 support **robustness** of the extended MCMs

Conclusions

- Extending **MCMs** to incorporate a **delayed cure effect** provides a more **clinically plausible** representation of underlying survival heterogeneity for studies in **advanced cancers**, and can:
  - yield **more realistic estimates** for the **proportion of cured patients** and for the **cure timepoint**, at which the remaining population are essentially free of disease-related hazard
  - infer the time at which the presence of curative effects becomes identifiable at a population level from survival observations
  - allow more accurate assessment of value for therapies that have curative potential

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