MSR11

Accounting for Cure Rates Estimated from Progression Free Survival (PFS) in Long-Term Overall Survival (OS) Projections: A Case Study from Previously Treated Advanced Cancers

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OBJECTIVES

- To devise a conservative and clinically plausible mixture cure modeling (MCM) framework for the analysis of overall survival (OS) data by embedding earlier statistical signs of cure derived from the progression free survival (PFS) data.
- To compare the predictive performance of standard parametric models (SPMs) and proposed MCM framework for long-term OS projections in a case study including various later-line advanced stage cancers treated with Pembrolizumab (shortly Pembro. hereafter).

INTRODUCTION

- Uncertainty in long-term survival projections borne by the limited trial follow-up and model choice is an important and common factor in health technology assessments. Reliable and clinically plausible long-term survival projections are critical for the authorities responsible for the allocation of healthcare resources.[1]
- In clinical trials, OS is widely regarded as the gold standard endpoint measuring a treatment's benefit for patients. In addition to regulators, it is also valued valued by patients, clinicians, and payers as it guides treatment selection by its direct impact also on quality of life, however mature OS data are often unavailable from the trials at the time of decision-making.[2]
- Progression-free survival (PFS) is often used as a primary endpoint in oncology trials due to its ability to provide an earlier measure of treatment efficacy and predict OS. Events contributing to the definition of PFS occur earlier and more frequent than OS events, allowing PFS reach statistical maturity faster than OS.[3]
- MCMs, though well established for survival analysis in statistical literature, are less familiar in clinical research. They are flexible frameworks analyzing cancer survival under heterogeneity borne by patients' achievement of long-term remission or statistical cure in a clinical trial or real-world cohort.[4]
- With advancements in standard of care of oncology, while OS data may not exhibit early signs of plateauing behavior, PFS data for the same cohort may display survival plateaus indicating the existence of long-term survivors who are also at minimal risk of clinical progression before death. This difference in tail behaviors of PFS and OS curves may result from the confounding effects of subsequent treatments on OS and lags in the follow-up durations required for the maturity of PFS and OS data.
- In the treatment of advanced cancers, especially in settings where patients were exposed or refractory to multiple prior lines of treatments, achieving a statistical cure after progression may be unlikely due to limited subsequent treatment options.
- Despite recent transformation of treatment landscape for advanced cancers with immune checkpoint inhibitors; head & neck squamous cell carcinoma, cervical cancer, esophageal cancer, endometrial cancer and hepatocellular carcinoma remain as aggressive malignancies with poor prognosis and limited long-term survival, highlighting the need for innovative modelling approaches to better capture to long-term clinical potential and economic value of novel agents, particularly in previously treated settings.[5]
- In the absence of statistical maturity needed to tackle the OS data with MCMs, long-term OS projections based on PFS-based cure rates can be more accurate and reflective of clinical reality in cost-effectiveness evaluations as analysis of PFS data by MCMs assume cured patients to be also free of risk of progression.
- Compared to SPMs, MCMs offer several advantages in health economic evaluations:
  a. Ability to capture survival plateaus for long-term projections
  b. Analyze survival heterogeneity with respect to cause of death (cancer-related vs. non-cancer related), and with respect to risk of progression
  c. Offer clinical insights on the survival trend of the uncured subgroup, long-term quality of life and reduced disease burden that may not be inferable directly from Kaplan-Meier (KM) curves

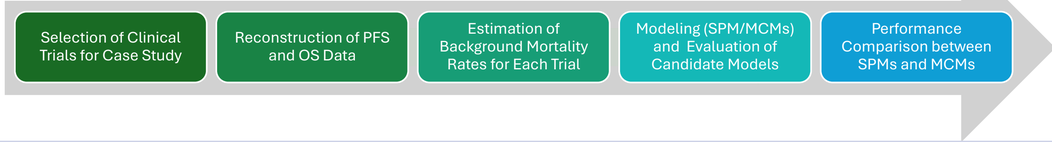
METHODS

- Five published registrational trials were included in a case study based on their role in supporting FDA approval of Pembro. for treatment of different tumor types (**Table 1**):
  a. KEYNOTE-012 (Mehra et al. 2018, head & neck cancer)
  b. KEYNOTE-158 (Chung et al. 2019, cervical cancer)
  c. KEYNOTE-181 (Kojima et al. 2020, esophageal cancer)
  d. KEYNOTE-224 (Kudo et al. 2018, hepatocellular cancer)
  e. KEYNOTE-775 (Marth et al. 2022, endometrial cancer)
- Time-to-event outcomes for PFS and OS from the experimental arms of the listed trials in the case study were reconstructed using the Guyot algorithm.
- The case study focused only on the data from the experimental arms of the clinical trials investigating Pembro. as a monotherapy or in combination with chemotherapy. The rationale behind this restriction was to capture the curative potential of Pembro. containing regimens due to its mechanism of action. Furthermore, assuming patients are unlikely to be retreated with an immune checkpoint inhibitor after progression on Pembro. treatment, the low possibility of achieving cure after progression in later line settings may imply closeness of the cure-rates estimated from the PFS data to the underlying cure rates that would be estimated from the OS data with longer follow-up.
- Background mortality rates for MCMs were derived from publicly available country-specific life tables and adjusted to the mean baseline age and gender distribution of the trial populations.
- For simplicity, in each trial, the country contributing to the majority of patient enrolment was assumed to be representative of the baseline demographics of the entire trial cohort when deriving background mortality rates. Similarly for each trial, published data with the longest possible follow-up were used for survival modelling, ensuring higher reliability for extrapolations and data maturity for the estimated cure-rates.
- Long-term OS projections were based on two modelling approaches[6]:
  a. **SPMs:** As a benchmark to be compared against the proposed MCM approach, SPMs suggested by NICE Technical Support Documents 14 and 21 were fitted directly to OS data using *flexsurvreg* package in R. In the SPMs there was no possibility of cure, however background mortality rates were incorporated into modeling with SPMs to avoid clinically implausible projections and to maintain consistency with the handling of background mortality rates in MCMs.
  b. **MCMs:** MCMs were fitted to PFS and OS data using *flexsurvcure* package in R. First, using reconstructed PFS, a cure fraction was estimated. Then, under the fixed cure rate obtained from the PFS data, MCMs were fitted to the reconstructed OS data. This approach ensured consistency between the cure rates informing the extrapolations of both endpoints while maintaining a hierarchical order between the PFS and OS of the uncured subgroup.
- For each trial, long-term OS extrapolations were based on a sufficiently long lifetime horizon to capture the health outcomes of the cured subgroup. More specifically, for each trial, the lifetime horizon was calculated as the difference between 100 years and the reported mean/median baseline age of the corresponding population.
- Model selection was guided by NICE Technical Support Documents 14 and 21[6,7] considering:
  a. Akaike Information Criterion (AIC)/Bayesian Information Criterion (BIC)
  b. Visual inspection of candidate fits and their hazard predictions to the reported survival and underlying hazard trends, respectively
- For each trial, mean OS was calculated over a lifetime horizon as the area under the best-fitting SPMs and MCMs to the OS data.

CONCLUSIONS

- Incorporating PFS-derived cure rates into OS projections while OS data were in the process of maturing with little-to-no sign of plateau can generate significantly higher estimates of mean OS compared to modeling OS with SPMs assuming no possibility of cure.
- The proposed framework improves the clinical plausibility of long-term OS projections while aligning them with expected mortality patterns and reducing structural uncertainty.

Figure 1: Schematic Flow of Study Selection and Modeling Process



RESULTS

- The best-fitting SPMs varied across studies while log-normal (for 3 trials) and log-logistic (for 2 trials) distributions emerged as the most frequent, best-fitting models. The best-fitting MCMs across studies showed higher variation across studies as 4 different models emerged as best-fits (**Table 2**).
- Compared to SPMs, incorporating cure fractions derived from PFS-data into the analysis of OS data improved the statistical fit criteria, selected models' visual fit to the observed and their long-term clinical plausibility by accounting for survival heterogeneity borne by the cured subgroup (**Table 2** and **Figure 3**).
- Estimated cure fractions ranged from 3.3% (95% CI: 1.5% – 7.0%) in esophageal cancer to 21.9% (95% CI: 16.1 – 29.1%) in endometrial cancer. Within the range of estimated cure fractions across five trials, in head & neck cancer, estimated cure fraction was relatively moderate: 11.9% (95% CI: 7.7% –17.8%)
- Across all studies, compared to SPMs, MCMs parameterized with fixed cure rates estimated from PFS-data generated higher OS estimates across the entire time horizon leading to higher mean OS projections (**Figure 4**).
- In Figure 2, the KM curves for PFS and OS from the experimental arms of the pivotal trials are displayed. As shown in Figure 2, for each trial, PFS data exhibit a clearer plateauing behavior than the OS data.

Table 1. Summary of trials included in the case study with respect to tumor, experimental therapy, line of treatment, setting, baseline age, and time horizon used for survival projections

Study name	Advanced Cancer Setting	Treatment	LOT	Baseline age	Time-horizon (years)
Mehra et. al. (2018)	Head and Neck	Pembrolizumab	2L+	60[1]	40
Chung et. al. (2019)	Cervical	Pembrolizumab	2L+	46[1]	54
Kojima et. al. (2020)	Esophageal	Pembrolizumab	2L+	63[1]	37
Kudo et. al. (2022)	Liver	Pembrolizumab	2L	67.4[2]	32.6
Marth et. al. (2024)	Endometrial	Lenvatinib Plus Pembrolizumab	1L	63[1]	37

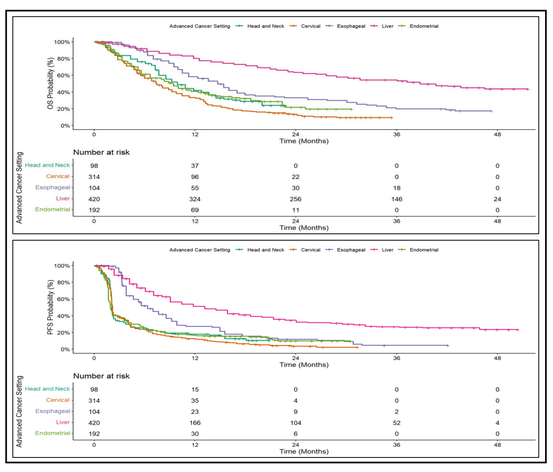
LOT = Line of Treatment; 1 = Median; 2 = Mean, 1L: First line, 2L: Second line, 2L+: Second line and beyond

Table 2. Best-fitting SPMs and MCMs, and their corresponding statistical goodness of fit criteria (AIC/BIC)

Study	SPM			MCM			
	Distribution	AIC	BIC	Distribution	AIC	BIC	Cure Rate (95% CI)
Mehra et al. (2018)	Log-normal	306	312	Log-normal	304	311	11.9% (7.7%, 17.8%)
Chung et al. (2019)	Log-logistic	163	168	Weibull	162	168	11.7% (6.3%, 20.6%)
Kojima et al. (2020)	Log-logistic	467	475	Log-logistic	467	474	3.3% (1.5%, 7%)
Kudo et al. (2022)	Log-normal	245	250	Generalized Gamma	240	248	4.6% (1.3%, 14.8%)
Marth et al. (2024)	Log-normal	1014	1022	Log-normal	1015	1024	21.9% (16.1%, 29.1%)

SPM = Standard Parametric Models; MCM = Mixture Cure Models; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CI = Confidence Interval

Figure 2. Kaplan–Meier (KM) curves for OS and PFS reported from the registrational trials of Pembrolizumab used in the case study



KM = Kaplan-Meier; OS = Overall Survival; PFS = Progression-free Survival;

- Across all trials in the case study, estimated mean OS from the selected MCMs was ≥0.53 life years higher than the estimated mean OS from selected SPMs. For head and neck, and cervical cancers, this difference was up to 2-3 life years.
- Selected MCMs generated similar or slightly improved AIC/BIC scores compared with selected SPMs, emphasizing the statistical value of accounting for earlier signs of cure from PFS data in modeling OS.

Figure 3. Comparison of reported KM-curves for OS, long-term OS projections from SPMs and MCMs using cure rates derived from the PFS data in the corresponding experimental arms of five trials in the case study

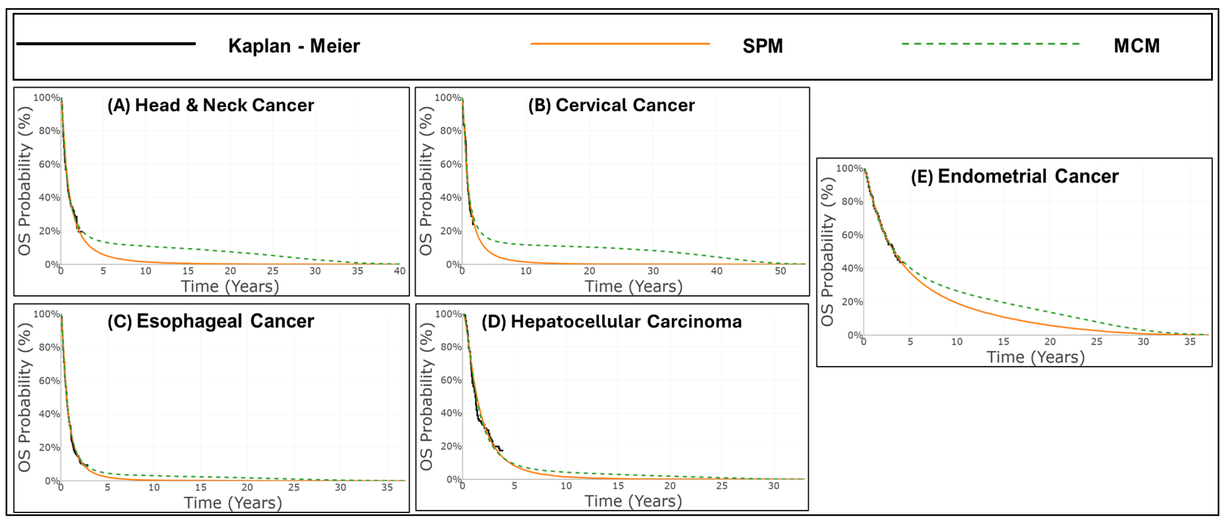
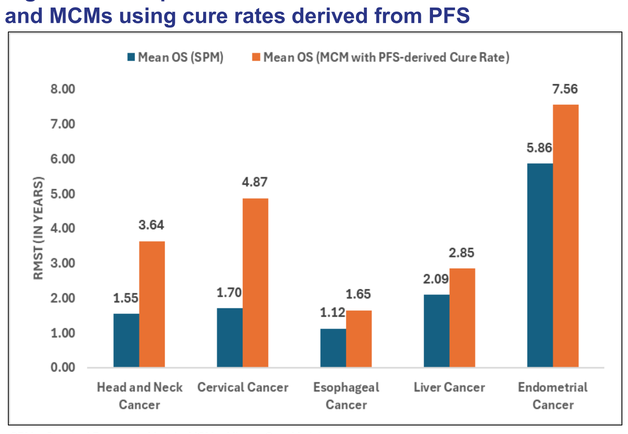


Figure 4: Comparison of mean OS estimated from SPMs and MCMs using cure rates derived from PFS



SPM = Standard Parametric Models; MCM = Mixture Cure Models

- In Figure 3, extrapolations highlight noticeable differences between the two modelling approaches. In the absence of cure assumption, SPMs, despite the consideration of background mortality rates, exhibit faster decline trends over time compared to MCM. On the other hand, MCMs due to accounting for fixed "cured" fractions, exhibit slower and steadier drops in OS rates
- In head & neck, cervical and endometrial cancers, the separation between the selected SPMs and MCMs were highly apparent from the end of the follow-up indicating the maturity and immediate impact of the cure-rates obtained from the PFS data.

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DISCLOSURES:

SP, SK, BS, and MK, the authors, declare that they have no conflict of interest

ACKNOWLEDGMENTS:

The findings and opinions expressed in this study are solely those of the authors and are independent of the views of Iovance Biotherapeutics, Inc.

PRESENTED AT: International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe 2025 Meeting | 9-12 November, 2025 | Glasgow, Scotland, UK