
Proceedings Paper:
Cranmer, H., Shields, G. and Bullement, A. orcid.org/0000-0001-7091-0972 (2019) PCN224 Treatment benefit discontinuation : comparison of a partitioned survival analysis and a semi-Markov multi-state model approach using an oncology case study. In: Value in Health. ISPOR Europe 2019, 02-06 Nov 2019, Copenhagen, Denmark. Elsevier BV , S479-S479.

https://doi.org/10.1016/j.jval.2019.09.420

PCN224

Treatment Benefit Discontinuation: Comparison of a Partitioned Survival Analysis and a Semi-Markov Multi-State Model Approach Using an Oncology Case Study

Cranmer H[1], Shields G[2, 3], Bullement A.[4]

[1]Takeda UK, High Wycombe, UK; [2]University of Manchester, Manchester, UK; [3]Azurite Research, Sheffield, UK; [4]Delta Hat, Nottingham, UK.

Background

- To determine the value of cancer treatments across a patient's lifetime, the short-term outcomes observed in clinical trials often require extrapolation to inform the long-term trends.
  - The more immature the trial data, the more uncertain the extrapolation as the extrapolation methods have limited information from which to predict outcomes.
- Many treatments for cancer are associated with a benefit that is expected to extend beyond the clinical trial period – either due to the sustained efficacy of treatment or because patients remain on treatment beyond the clinical trial cut-off. However, the treatment benefit is not expected to extend indefinitely – particularly when the model time horizon far exceeds the duration of treatment.
- The partitioned survival analysis (PartSA) three-state model was identified as the most common model structure in oncology (see also #PCN106).[1] Applying standard techniques within a PartSA structure assumes that the treatment effect over time is the same regardless of a patient occupying the pre-progression or progressed disease health state.
  - Therefore, the survival rate over time does not reflect the increasing proportion of patients in the progressed health state.
- However, a more flexible model structure, such as a multi-state model (MSM) allows for the treatment effect to differ for patients in each health state – perhaps reflecting a more realistic pathway.
- Within a PartSA, the guidance from the UK health technology appraisal (HTA) body is to explore the impact of: (1) no treatment benefit in the extrapolation period, (2) the same benefit as during the trial and (3) a diminishing treatment benefit.[1] These scenarios are often not supported by clinical rationale.
- In line with this guidance, we consider comparing three scenarios exploring treatment benefit reduction in a PartSA framework. We then compare these results with unadjusted results from a semi-Markov MSM.

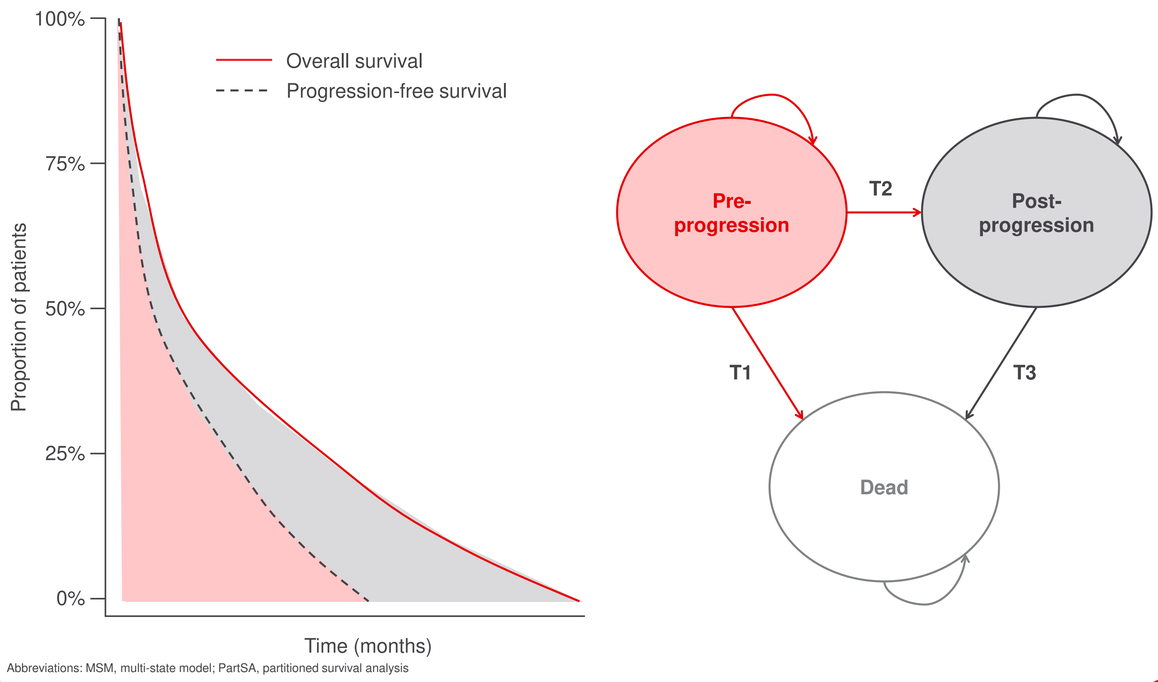
Objective

- To compare the clinical and economic outcomes associated with three scenarios around the treatment benefit in a PartSA structure and to compare this with the outcomes of a semi-Markov MSM structure.

Methods

- **Figure 1** presents the model structures. A full description of the economic models is presented in #PCN103

Figure 1. Concept of the PartSA and MSM approaches

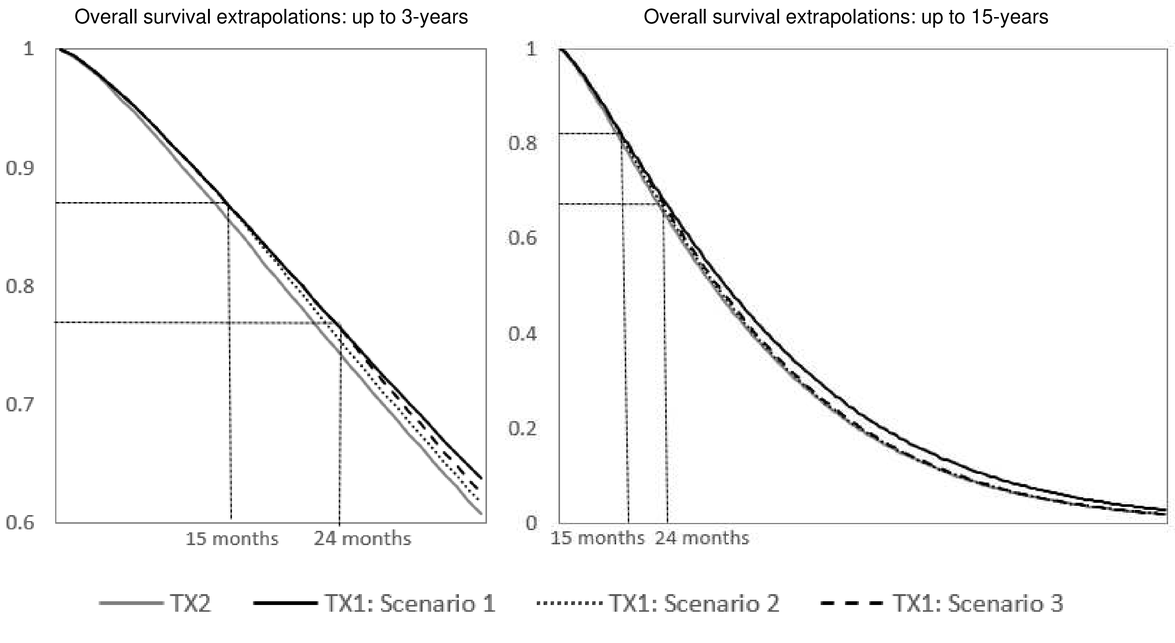


Abbreviations: MSM, multi-state model; PartSA, partitioned survival analysis

Treatment benefit scenarios

- Three scenarios were explored within the PartSA framework:
  - 1) A constant treatment benefit for the duration of the model time horizon
  - 2) No treatment benefit beyond the median follow-up period (15-months)
  - 3) No treatment benefit beyond the maximum follow-up period (24-months)
- As TX1 is the treatment of interest, scenarios (2) and (3) used TX2 as the reference treatment and reduced the survival benefit for TX1 to TX2 after 15- and 24-months, respectively. This is a method commonly applied in PartSA when exploring treatment benefit discontinuation.
- **Figure 2** presents the extrapolated overall survival curves for TX1 and TX2 under each of the treatment benefit scenarios.

Figure 2. Treatment benefit discontinuation scenarios in the PartSA



Abbreviations: PartSA, partitioned survival analysis

Results

- Table 1 and Table 2 present the clinical and economic outcomes predicted from each of the scenarios and model structures.
- The PartSA is associated with ICERs of £342,474, £803,992 and £653,301 for each of the scenarios, respectively. Whereas, the MSM is associated with an ICER of £416,030.

Table 1. Clinical outcomes associated with TX1

	Pre-progression life years	Progressed disease life years	Total life years
PartSA			
Scenario 1	2.44	1.97	4.41
Scenario 2	2.44	1.74	4.18
Scenario 3	2.44	1.78	4.22
Semi-Markov MSM	2.41	1.07	3.48

Abbreviations: MSM, multi-state model; PartSA, partitioned survival analysis

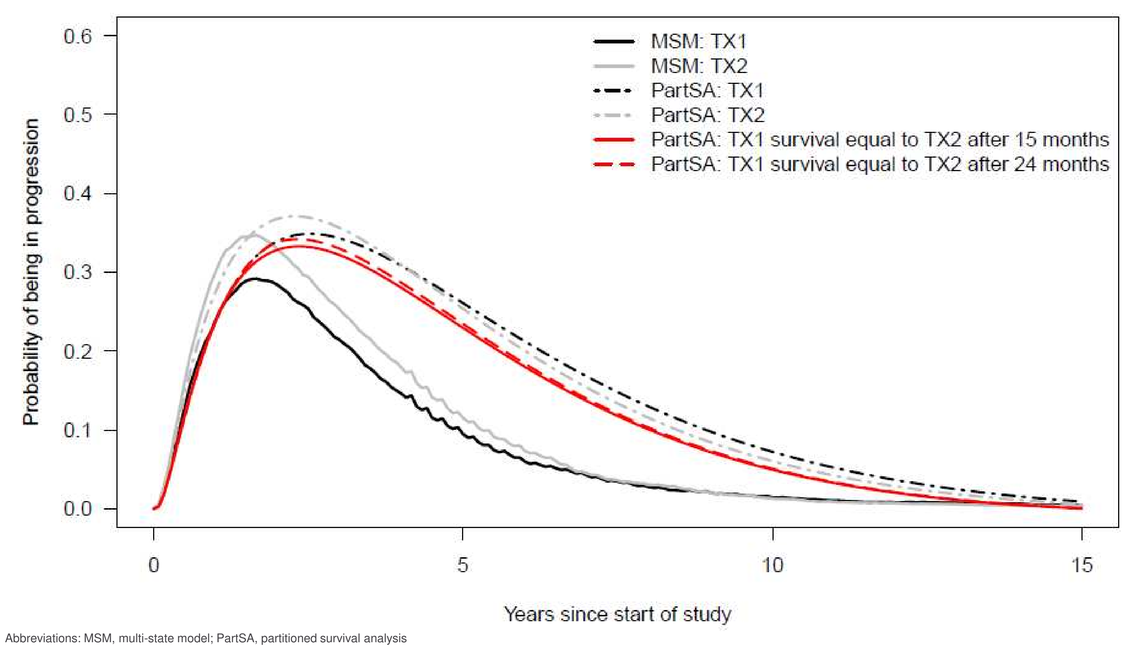
Table 2. Cost-effectiveness results

	Incremental costs	Incremental QALYs	ICER
PartSA			
Scenario 1	£78,045	0.23	£342,474
Scenario 2	£72,031	0.09	£803,992
Scenario 3	£72,994	0.11	£653,301
Semi-Markov MSM	£78,199	0.19	£416,030

Abbreviations: ICER, incremental cost-effectiveness ratio; MSM, multi-state model; PartSA, partitioned survival analysis; QALY, quality adjusted life year

- Figure 3 presents the proportion of patients in the progressed disease health state over time for each of the scenarios within the PartSA and the semi-Markov model structure.
- Although curtailing the treatment benefit in scenario (2) and (3) reduces the proportion of patients in the progressed disease health state over time, this still remains noticeably higher than predicted in the MSM structure. Therefore, the PartSA may still be over-estimating long-term survival.
  - Note: this may be because these methods only reduce the survival rate for TX1 to that of TX2. Whereas, it is likely that the treatment benefit of TX2 would also decline over time. However, within a PartSA framework there is limited ability to account for this without inclusion of external data.
- In the PartSA model by ~15-years all patients have moved to the death health state. Whereas, in the semi-Markov MSM model all patients have reached this health state by ~10-years.

Figure 3. Proportion of patients in the progressed health state over time



Abbreviations: MSM, multi-state model; PartSA, partitioned survival analysis

Conclusions

- The commonly used PartSA framework often assumes a constant treatment effect across the model time horizon. Due to the assumptions underpinning the structure, this treatment effect does not change based on the evolving proportion of patients off-treatment or progressed over time.
- The UK guidance requires exploration into the impact of this assumption on results. However, scenarios presented are often arbitrary. For example: there may be no justification with relation to the time point at which the treatment effect is assumed to stop or the duration of the treatment effect after treatment discontinuation. Furthermore, often the treatment effect of the intervention is explored and not the treatment effect of the comparators.
- Attempting to incorporate some dependency between endpoints (for example: linking the treatment benefit to progression or treatment discontinuation) within a PartSA contradicts the underlying PartSA structure. If the treatment effect on survival is expected to be related to other outcomes (like progression or time on treatment) then this questions the choice of PartSA as the preferred model structure.
- A more flexible model structure, such as an MSM (in this case study) allows a separate treatment effect to be modelled for patients in the pre-progression health state vs. those patients in the progressed disease health state. Therefore, the overall survival within the model evolves over time as more patients enter the progressed disease health state.
  - This example uses a model structure defined by progression. However, other outcomes like duration of treatment may better reflect some pathways.
- Therefore, in pathways where the treatment effect on survival is likely to evolve over time a more flexible model structure should be considered. This study highlights that exploring treatment benefit discontinuation scenarios within a PartSA framework may still over estimate long-term survival.

References

1. Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU Technical Support Document 19. Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. 2017. Available at: http://www.nicedsu.org.uk. Last updated: 2 June 2017. Accessed: 26 September 2019.

Abbreviations

HTA, health technology appraisal; ICER, incremental cost-effectiveness ratio; MSM, multi-state model; OS, overall survival; PartSA, partitioned-survival analyses; PFS, progression-free survival; QALY, quality adjusted life year

Acknowledgments

The authors received no specific funding for this work and declare that they have no conflict of interest

ISPOR Europe 2019, Copenhagen, Denmark, 2-6 November, 2019