# Impact of model approach on economic evaluation of nivolumab plus chemotherapy for advanced gastric, gastro-oesophageal junction and oesophageal cancer

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## Introduction

- Patients with advanced gastric (GC), gastro-oesophageal junction (GOJC) and oesophageal adenocarcinoma (OAC) have historically been limited to chemotherapy, where median survival is less than one year[1,2]
- However, several studies in patients with locally advanced or metastatic GC demonstrate the potential for prolonged survival and/or long-term remission in a small proportion of patients[1,3-7]
- Immuno-oncology (I-O) therapies such as nivolumab (in combination with chemotherapy) have the potential to provide survival benefit over a longer period, increasing the proportion of patients with prolonged long-term survival[4,5,8]
- CheckMate 649 evaluated nivolumab plus chemotherapy versus chemotherapy in patients with previously untreated advanced GC, GOJC and OAC. In patients with PD-L1 combined positive score (CPS) ≥5, nivolumab plus chemotherapy demonstrated a significant improvement in overall survival (OS) versus chemotherapy (HR 0.70, 95% CI: 0.61-0.81) with 31.0% of patients surviving at two years compared with 18.6% for chemotherapy
- The standard approach for economic evaluation of oncology therapies with available OS data is the three-state partitioned survival model (PSM). However, this approach is unable to explicitly model populations with mixed outcomes, which is crucial when assessing a population where some patients may experience long-term remission while others may not
- By contrast, a semi-Markov model (SMM) can facilitate modelling progression-specific outcomes, including the impact of time since- and time of-progression on the rate of mortality, facilitating evaluation of the impact of long-term remission and more granular assessment of patients with heterogenous outcomes

## Objectives

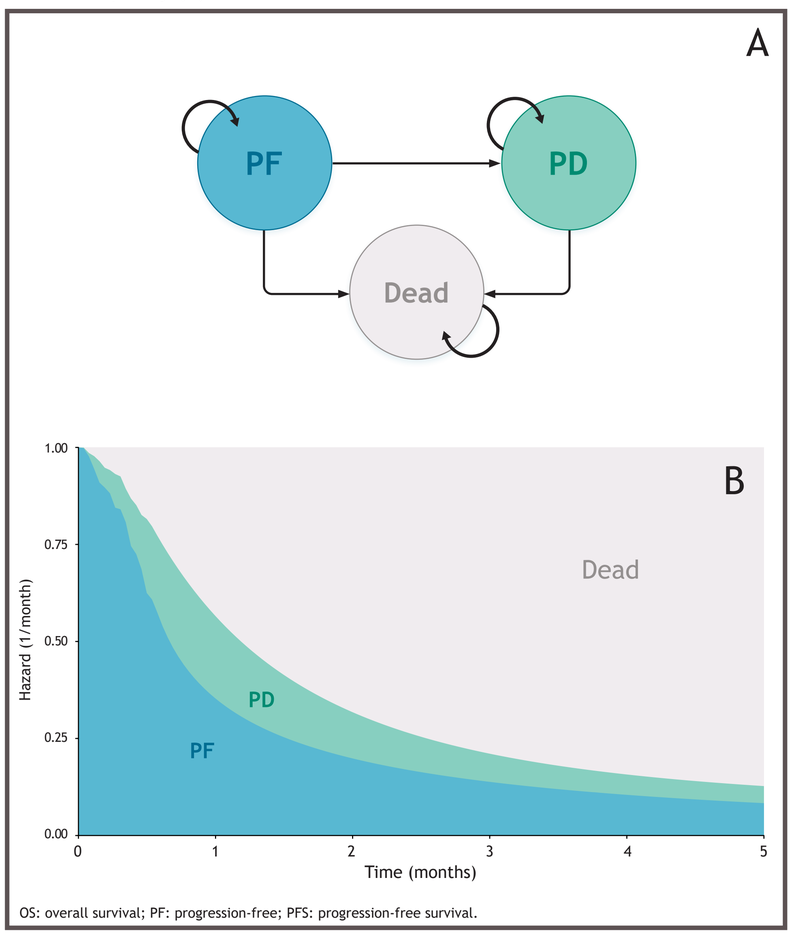
- To assess PSM and SMM economic modelling approaches, comparing clinical outcomes and disease management cost accrual in patients with gastric-oesophageal cancer, using data from CheckMate 649

## Methods

### Partitioned survival model

- A three-state PSM was developed with mutually exclusive health states representing progression-free disease, post-progression and death (**Figure 1**)
- The health state occupancy is determined by survival curves, namely progression-free survival (PFS) and overall survival (OS) functions (**Figure 1**; illustrative data depicted). These health states reflect disease severity and determine use of healthcare resources, health-related quality of life and mortality rates
- Clinical inputs: PFS and OS
  - PFS: probability of remaining alive and progression-free conditional upon time from model start
  - OS: probability of remaining alive conditional upon time from model start

**Figure 1. Partitioned survival model structure (A) and illustrative health state occupancy (B)**



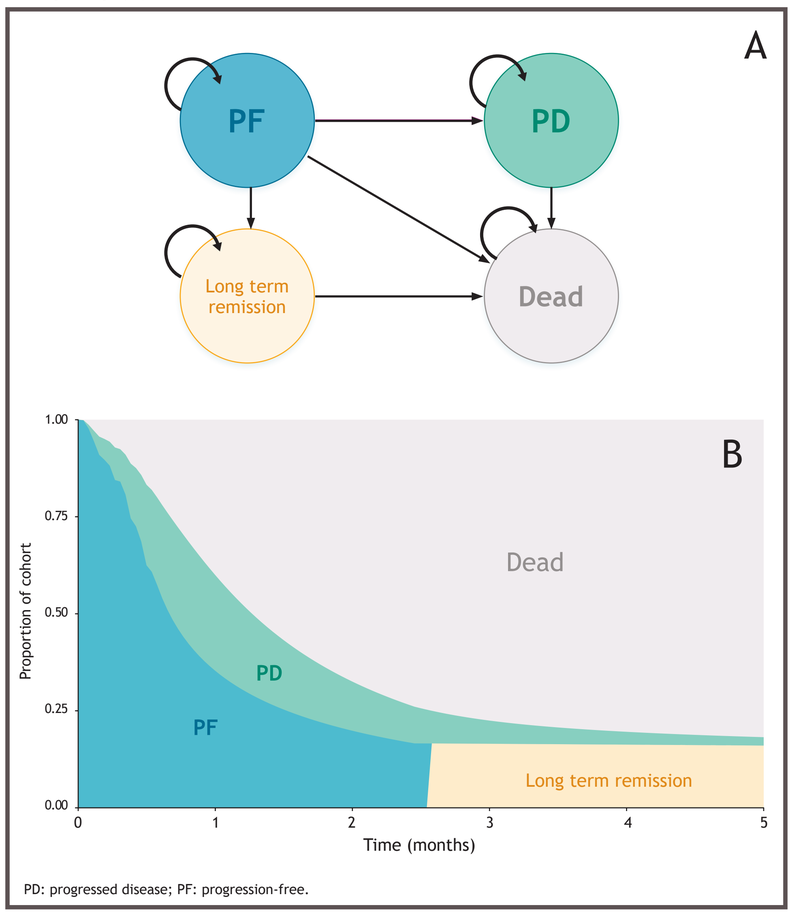

OS: overall survival; PF: progression-free; PFS: progression-free survival.

## Methods (continued)

### Semi-Markov model

- An SMM was developed including four health states: all patients entered the model in the pre-progression state and remained there until death, disease progression or until they moved into the long-term remission health state (**Figure 2**)
- Long-term remission is an additional health state included in the SMM; it does not allow movement to any other state but death. Those patients still progression-free after 30 months are classified as in long-term remission, which was considered appropriate:
  - The hazard profiles showed a sharp change in hazard across all treatments and outcomes and can adequately be described using the mixture cure model with long-term remission state as seen in the advanced gastro-oesophageal setting
  - Few deaths were observed after 30 months, and patients were defined as in long-term remission at that point
  - Patients in the long-term remission state are subject to general population mortality rates which are applied instead of disease-specific mortality in the economic model
- The SMM health state occupancy is represented in **Figure 2** (illustrative data depicted)

**Figure 2. Semi-Markov model structure (A) and illustrative health state occupancy (B)**




PD: progressed disease; PF: progression-free.

### Model inputs

- Clinical effectiveness inputs were informed by the PD-L1 CPS ≥5 subgroup of CheckMate 649 (**Table 1**)
- Drug costs were not included as subject to a confidential PAS and would not be anticipated to vary between the two economic models

**Table 1. Clinical parameters and variables in both models**

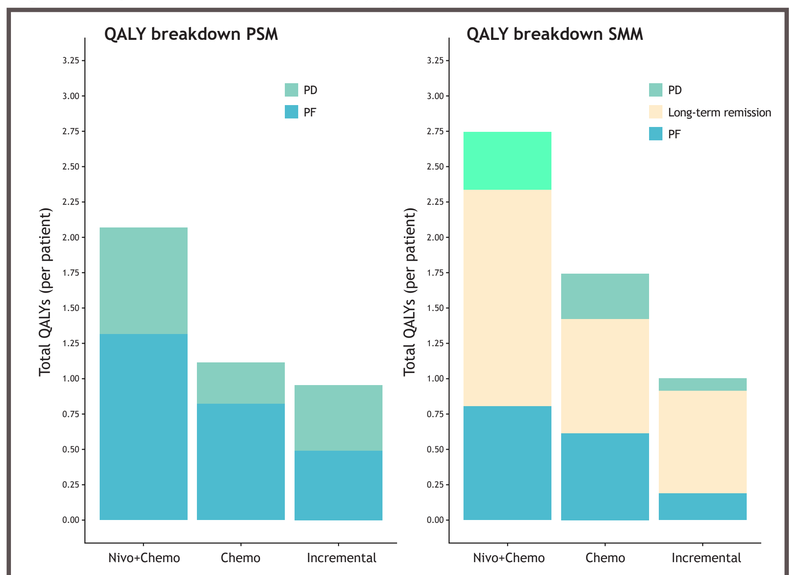
| Clinical parameter and variables[1] | PSM | SMM |
|---|---|---|
| **Time horizon** | Lifetime, up to 40 years | |
| **Discount rate** | 3.5% | |
| **Cycle lenght** | 14 days, no half-cycle correction required | |
| **Baseline age** | Derived from CheckMate 649 | |
| **Proportion male** | 69.5% | |
| **Stopping rule** | 2 years | |
| **Resource use** | Derived for NICE (England) setting | |
| **PF** | £102.81 on treatment; £42.67 off treatment | |
| **PD** | £626.22 | |
| **End of life cost** | £5,387 | |
| **Extrapolation method** | | |
| PFS | Semi-parametric fitted to CheckMate 649 data; Kaplan-Meier to 6.44 months log-normal fitting | PF -> PD/Dead<br>Semi-parametric fitted to CheckMate 649 data; Kaplan-Meier to 6.44 months log-normal fitting<br>PF -> LTR<br>100% PF at 2.5 years<br>LTR -> Dead<br>General population mortality |
| OS | Semi-parametric fitted to CheckMate 649 data; Kaplan-Meier to 6.44 months Gompertz fitting | PD/Dead -> Dead<br>Logistic model conditional upon progression time and log progression time fitted to CheckMate 649 data<br>PD -> Dead<br>Log-logistic fitted to CheckMate 649 data from progression |
| **Treatment discontinuation** | Time on treatment Kaplan-Meier curves derived from CheckMate 649 patient-level data | |
| **Subsequent therapies** | Second-line palliative chemotherapy: single-agent taxane | |
| **Adverse events (AE)** | Derived from CheckMate 649 | |
| **Health state utility values** | Derived from CheckMate 649 | |

LTR: long-term response OS: overall survival; PD: progressed disease; PD/Dead: post-PFS pseudo-state; PF: progression-free; PFS: progression-free survival.

## Results

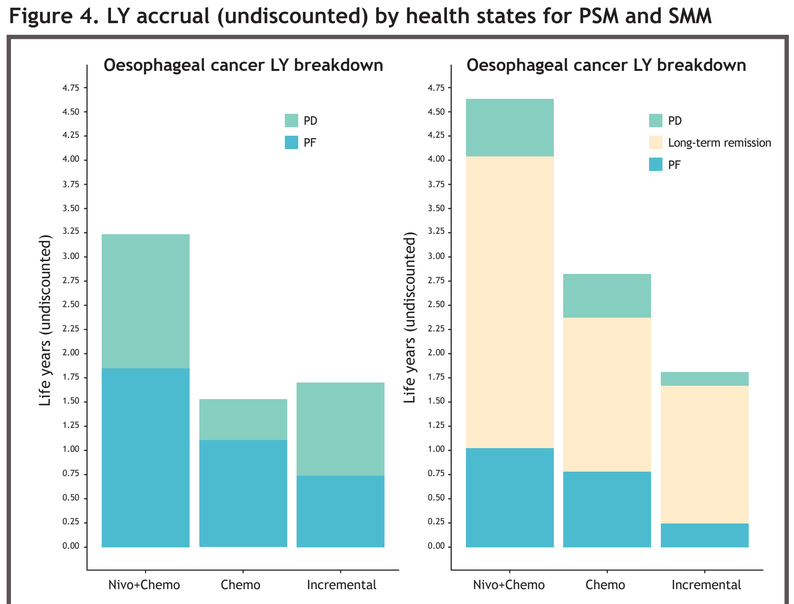
- The SMM predicted larger LY and QALY accrual for both NIVO+CHEMO and CHEMO, but incremental benefits were similar to the PSM approach (undiscounted LYs: 1.81 versus 1.70; discounted QALYs: 1.00 versus 0.96) (**Figure 3** and **4**)
- In the PSM, the majority of the survival benefit was accrued in the progressed state; almost all survival benefit in the SMM was accrued during the long-term remission state (**Figure 3** and **4**)
- As a result of reduced time in the pre-progression and progressed states, disease management costs were reduced in the SMM approach (**Figure 5**)

**Figure 3. QALY accrual (discounted) by health states for PSM and SMM**



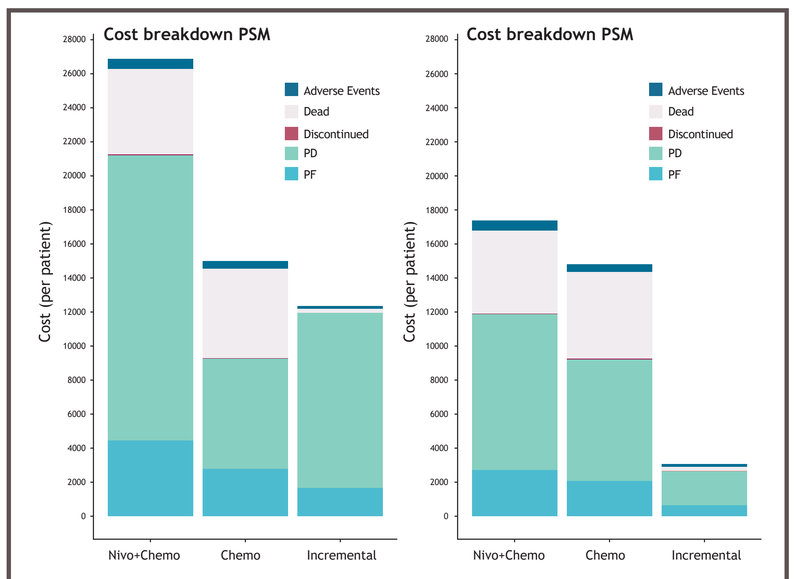

Chemo: chemotherapy; Nivo: nivolumab; PD: progressed disease; PF: progression-free; PSM: partitioned survival model; QALY: quality-adjusted life year; SMM: semi-Markov model.

**Figure 4. LY accrual (undiscounted) by health states for PSM and SMM**




Chemo: chemotherapy; LY: life year; Nivo: nivolumab; PD: progressed disease; PF: progression-free, PSM: partitioned survival model; SMM: semi-Markov model.

**Figure 5. Disease management cost accrual (discounted) by health state for SMM and PSM**




Chemo: chemotherapy, Nivo: nivolumab; PD: progressed disease; PF: progression-free, PSM: partitioned survival model; SMM: semi-Markov model

## Conclusions

- Although providing similar incremental survival, the SMM was more able to model populations with mixed outcomes by reflecting mortality rates stratified by progression status and a long-term remission state
- This illustrates the suitability of SMM over PSM in demonstrating the long-term benefits of I-O therapy

## References

1. Davidson M, et al. Clin Colorectal Cancer. 2018;17(3):223-30
2. Office for National Statistics. Cancer survival by stage at diagnosis for England. 2019
3. Chau I, et al. Ann Oncol. 2009;20(5):885-91
4. Chen L-T, et al. Journal of Clinical Oncology. 2020;38(4_suppl):383
5. Chen L-T, et al. Gastric Cancer. 2020;23(3):510-9
6. Ford HER, et al. The Lancet Oncology. 2014;15(1):78-86
7. Shankaran V, et al. Adv Ther. 2021;38(1):707-20
8. Janjigian YY, et al. Lancet. 2021;398(10294):27-40

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