How good are cost-effectiveness model predictions when compared to longer follow-up data? An example of nivolumab studies in the first-line gastro-oesophageal setting

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Introduction

Recommendations by the National Institute for Health and Care Excellence (NICE) are informed by the assessment and interpretation of the evidence using a range of scientific evidence;[1] as was the case for **TA857** and **TA865**, two first-line gastro-oesophageal NICE health technology assessments (HTAs). Both received positive recommendations based on the positive survival benefits reported by the informing trials and accompanying cost-effectiveness analysis, detailed below.

At the time of submission to NICE the overall survival (OS) data for both TAs was immature; consequently, in order to provide timely access to novel therapies, such as immunotherapies, the clinical data required extrapolation to predict long-term survival.

The critical measure of efficacy for economic evaluation of life-extending products is the mean survival time of the cohort, which is represented by the area under the survival curve (AUC). Where follow-up is incomplete, validation of the AUC of the extrapolative models can only be undertaken up to a time limit due to the current extent of follow-up. This time-limited AUC is also known as the restricted mean survival time (RMST). The non-parametric Kaplan-Meier estimator may be used to estimate RMST, particularly where patient-level data are not available to inform a flexible parametric model over the observed follow-up.

TA857:[2] Nivolumab with platinum- and fluoropyrimidine-based chemotherapy was recommended in January 2023 as an option for untreated HER2-negative, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score (CPS) of 5 or more, only if the company provides it according to the commercial arrangement.

TA865:[3] Nivolumab with fluoropyrimidine-based and platinum-based combination chemotherapy, was recommended in February 2023 as an option for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma (OSCC) in adults whose tumours express PD-L1 at a level of 1% or more, only if: pembrolizumab plus chemotherapy is not suitable, and the company provides nivolumab according to the commercial arrangement.

Objectives

The objective of this cost-effectiveness study was to compare the RMST OS values from the extrapolation models informing TA857 and TA865 to those of Kaplan-Meier estimates from later data-cuts of the informing trials in order to evaluate whether the extrapolations used in the HTA submissions were consistent with the developing data at increased follow-up.

Methods

To provide timely access to nivolumab for both indications, it was necessary to extrapolate OS, observed in the phase 3 trials which informed the clinical evidence for the technical assessments, to estimate the total benefit of the treatment.

Parametric survival models informed by immature patient-level data were used to develop the models selected by the company, evidence assessment group (EAG) and considered by the NICE assessment committee (AC) to inform **TA857** and **TA865**.

To provide a robust and transparent assessment of parametric extrapolations for OS, the company applied the methodologies suggested by the NICE decision support unit (DSU) and Bagust and Beale (2014).[4,5] An overview of the approach is summarised below:

Characterise the available data (CheckMate 649 [TA857], CheckMate 648 [TA865])

Describe trends in the available data

Assess **viability** of accelerated failure time and proportional hazards models

Assess **suitability** of standard statistical models outlined in technical support document (TSD) 14[5]

If standard statistical models are not indicated, consider[6-8]:
- A relative survival framework
- A piecewise framework
- A flexible non-statistical framework (splines)
- A mixture framework

Assess appropriateness of parametric models of extrapolation based on:
- Goodness-of-fit statistics (Akaike Information Criterion [AIC]/Bayesian Information Criterion [BIC])
- Non-parametric or smoothed representations of patient level data
- Examination of log-cumulative hazard plots.
- Assessment of clinical validity.
- Consideration of external data (e.g. within-class in similar indications)

Select most **plausible** models, and other **valid** models for sensitivity analysis

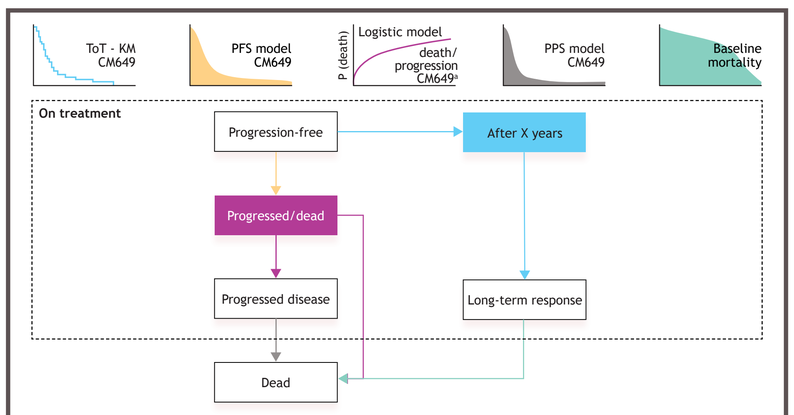
Choice of models for the HTAs

TA857

The company submission for **TA857**[9] was informed by data from the July 2020 database lock (DBL) of CheckMate 649, minimum follow-up of 12.1 months.

- To capture the long-term trends in survival suggested by the data and present in other immunotherapy indications, the company presented a 4-state semi-Markov model (SMM) (**Figure 1**).
- The SMM described progression-free survival (PFS) via a piecewise Kaplan-Meier (KM)/parametric relative survival model to a nominated time, after which survivors without progression were assumed in "long-term response" (LTR) and given a rate of mortality equal to the general population and no risk of progression.
- For those who progressed or died from the progression-free state, the proportion moving to the progressed-disease versus the dead state was determined by a logistic regression model upon the probability of an observed PFS-ending event being death in the patient-level data.
- The models used for PFS were based on KM data to 6.4 months and log-logistic relative survival thereafter, with the cut time being chosen after the last of the initial 4-cycle assessment windows and so away from any abrupt discontinuities in PFS.
- OS after progression was predicted by a fully parametric log-logistic relative survival model.

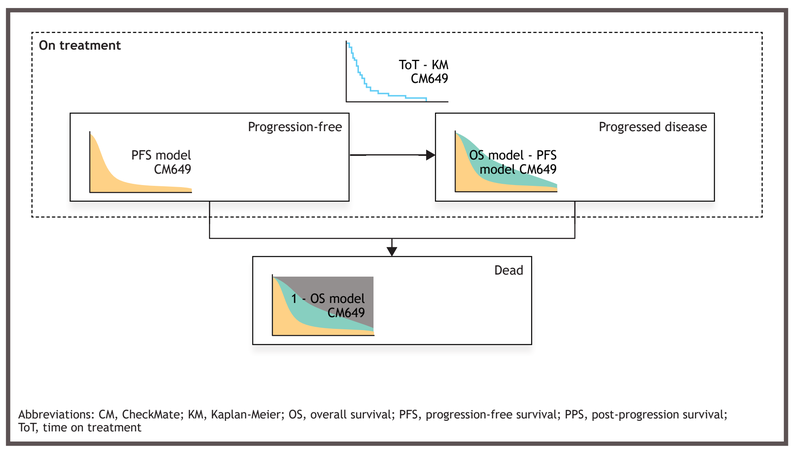
Figure 1. 4-state semi-Markov model, TA857



[a]Logistic model of PFS event being death, conditional upon PFS-ending event being observed and time of observation
[b]Equal to general population mortality in base case
Abbreviations: CM, CheckMate; KM, DBL, database lock; Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; ToT, time on treatment

- In their initial assessment report, the EAG removed the LTR state from the SMM as they thought that the company's model was unnecessarily complicated but did not alter the selected survival extrapolations.
- At the first committee meeting, the AC requested that the model be rebuilt as a 3-state partitioned survival model (PSM) that directly uses OS data, in part to simplify the model and improve calibration of the OS to the observed data.
- Implementing the PSM (**Figure 2**), the company chose a piecewise KM/Gompertz model for OS, whilst the EAG chose a piecewise KM/generalised Gamma model. At this stage, data from the July 2021 DBL were available and utilised for model fitting.

Figure 2. Partitioned survival model, TA857



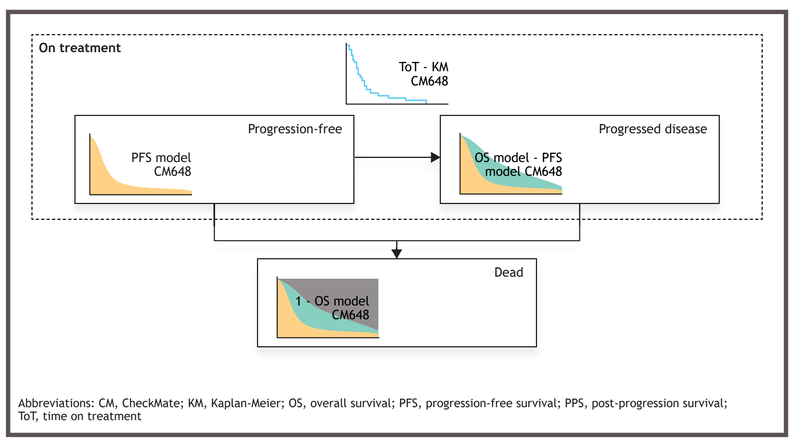
Abbreviations: CM, CheckMate; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; ToT, time on treatment

TA865

The company submission for **TA865** was informed by data from the October 2021 DBL of CheckMate 648, giving a minimum follow-up of 20 months.

- A three-state PSM was used (**Figure 3**), with OS modelled using a piecewise KM, lognormal model with cut time at 6.9 months, as single parametric models were incapable of representing the hazard profiles observed in trial; the lognormal distribution was chosen considerate of clinically expected long-term outcomes in the CHEMO arm, in addition to internal goodness of fit.
- The EAG preferred a fully parametric log-logistic model, despite poor fit in the first six months.

Figure 3. Partitioned survival model, TA865

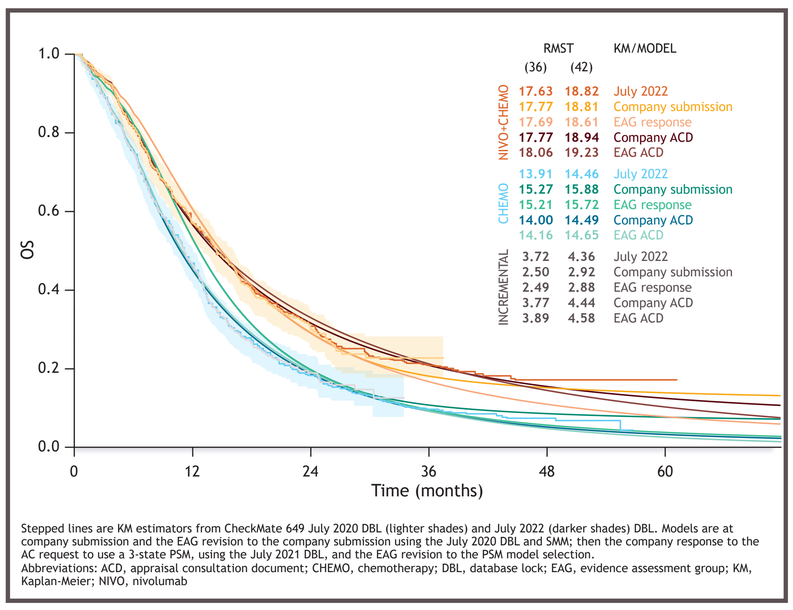


Abbreviations: CM, CheckMate; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; ToT, time on treatment

Validation results

- In **TA857**, data from the July 2022 DBL were used to estimate RMST to 36 and 42 months, with the results shown in **Figure 4**. Enrolment to the nivolumab plus chemotherapy (NIVO + CHEMO) arm occurred over two years, and at this DBL the minimum follow-up was 36 months; 42-month data is subject to some uninformative administrative censoring but is useful in suggesting trends in model error into extrapolation.
- To the restriction times available with current follow-up, the difference between the company submission and EAG response models were minor, both predicting (NIVO + CHEMO) RMST well. However, both over-predicted for CHEMO.
- The appraisal consultation document (ACD) models, using a PSM framework, validated better to the CHEMO arm.
- The EAG model overpredicted at 42 months for CHEMO; however, this was also true of the EAG NIVO + CHEMO model.
- Both company models validated well to RMST at current follow-up.

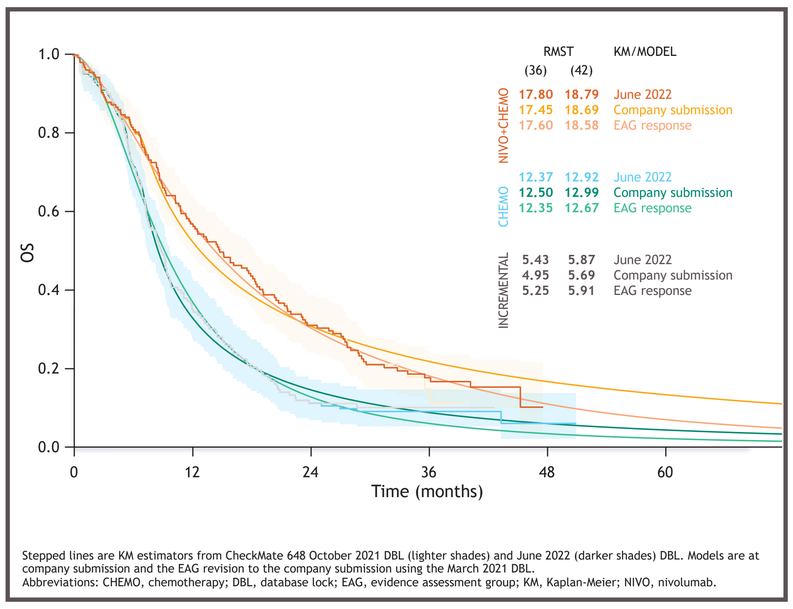
Figure 4. Model predictions and KM estimators for TA857



Stepped lines are KM estimators from CheckMate 649 July 2020 DBL (lighter shades) and July 2022 (darker shades) DBL. Models are at company submission and the EAG revision to the company submission using the July 2020 DBL and SMM; then the company response to the AC request to use a 3-state PSM, using the July 2021 DBL, and the EAG revision to the PSM model selection.
Abbreviations: ACD, appraisal consultation document; CHEMO, chemotherapy; DBL, database lock; EAG, evidence assessment group; KM, Kaplan-Meier; NIVO, nivolumab

- In **TA865**, data from the June 2022 DBL were used to estimate RMST to 36 and 42 months, with the results shown in **Figure 5**. Enrolment to this trial occurred over 27 months, and at the June 2022 DBL minimum follow-up was 30 months; KM estimates of OS to 36 months and 42 months are therefore subject to some administrative censoring, but as can be seen by the close overlay of the KM estimators in **Figure 5**, censoring was uninformative for at least 14 months beyond minimum follow-up at the October 2021 DBL, so it is expected that the KM estimator up to 42 months is unbiased.
- To the restriction times available with current follow-up, the EAG shows underestimation of RMST for both arms, and this underestimation appears to be increasing.
- The company model agreed well with observed data, slightly under-predicting the difference in RMST between arms at both restriction times.

Figure 5. Model predictions and KM estimators for TA865



Stepped lines are KM estimators from CheckMate 648 October 2021 DBL (lighter shades) and June 2022 (darker shades) DBL. Models are at company submission and the EAG revision to the company submission using the March 2021 DBL.
Abbreviations: CHEMO, chemotherapy; DBL, database lock; EAG, evidence assessment group; KM, Kaplan-Meier; NIVO, nivolumab.

Conclusions

- Continued follow-up validates predictions used in the models informing both **TA865** and **TA857**
- In **TA857**, all models predicted accurately for NIVO + CHEMO, whilst the PSM improved prediction for chemotherapy and increased the predicted difference in RMST between NIVO + CHEMO and CHEMO.
- In **TA865**, the company and EAG models show better fit to opposite arms of the trial, neutralising incremental differences in predictions. The largest differences in prediction are at longest follow-up, where uncertainty in the survival data is highest.
- The decisions based upon the economic analyses informing both technical assessments are validated by additional follow-up.

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