A COMPARISON OF THREE SURVIVAL MODELS TO ESTIMATE THE COST-EFFECTIVENESS OF CANCER IMMUNOTHERAPY IN THE TREATMENT OF ADVANCED MELANOMA (AM)

Introduction
Recent phase III clinical trial evidence has demonstrated that nivolumab improves overall survival (OS) versus dacarbazine in previously untreated patients with BRAF-AM (1). While trial data only extend to 12.8 months, they demonstrate divergence of survival curves. These are not well approximated with traditional survival methods, as they have monotonic hazard functions that don’t capture plateaus in survival well.

To date, the cost-effectiveness of nivolumab when compared to existing treatments for AM has not been evaluated. Ipilimumab is the main comparator in Australia. As real-world data has demonstrated a plateau in survival for patients receiving ipilimumab (2), it is unknown which methods will best approximate the long-term survival of patients receiving this treatment.

Mixed Cure models have been used in the statistical literature to model survival plots with long plateaus where there is a sub-set of long-term survivors (3). This method may be a useful alternative to traditional methods of parametric survival analysis to investigate the divergence of survival curves seen in patients receiving immunotherapy for advanced melanoma (AM).

Aims
1. To compare three methods for extrapolating survival curves for previously-untreated patients receiving nivolumab versus ipilimumab for BRAF wild-type advanced melanoma (AM, comprising unresectable and/or metastatic melanoma).
2. To compare the impact of each method on incremental cost-effectiveness ratios (ICERs).

Methods
- A state-transition Markov model was used to simulate the history of Australian BRAF-AM patients. Patient-level data from 203 patients with AM receiving nivolumab in study CA209066 (nivolumab versus dacarbazine) were used to estimate the risks of progression and death.
- Weibull, log-logistic and a Weibull mixture cure model (MCM) were fitted to extrapolate trial data for overall survival (OS) and progression-free survival (PFS) up to a 10 year time horizon.
- Head-to-head trial data were not available at the time of analysis. To estimate transition probabilities for subjects receiving ipilimumab, hazard ratios were drawn from an indirect comparison of nivolumab versus ipilimumab (using data from trials CA209066 and MDX010-020) and applied to underlying survival distributions.
- Models were evaluated using Akaike’s Information Criterion (AIC) and a naïve comparison of the extrapolated ipilimumab survival functions with observed long-term survival data from published studies.
- ICERs were estimated using utilities from an EQ-5D survey utilised in the pivotal trial (CA209066). Costs of managing AM were estimated from a survey of Australian clinicians regarding healthcare utilisation. The cost of ipilimumab was based on the reimbursement price in Australia. The cost of nivolumab was based on expected reimbursement prices in Australia.
- The cost-effectiveness of nivolumab compared to ipilimumab varied greatly depending on the choice of model ranging from $AUD 23,492 to 63,885 per QALY.
- AIC scores for the weibull, log-logistic and MCM were 336.47, 335.30 and 776.20, for OS and 511.39, 479.38 and 1421.63 for PFS, respectively.
- Compared to ipilimumab, nivolumab therapy was estimated to yield 0.66, 1.58, 2.49 years of life (discounted) and 0.54, 1.30, 2.10 quality adjusted years of life (discounted) per person over a ten-year time horizon based on the weibull, log-logistic and MCM survival models, respectively.
- The log-logistic survival model most closely approximated real-world data on the long-term survival of patients receiving ipilimumab.

Results
- To compare three methods for extrapolating survival curves for previously-untreated patients receiving nivolumab versus ipilimumab for BRAF wild-type advanced melanoma (AM, comprising unresectable and/or metastatic melanoma).
- The choice of parametric model has a large effect on predicted ICERs and should be well justified based on internal and external validation.
- Due to the short period of follow-up time in this study, the MCM introduced the greatest potential for error.

Key Findings
- The log-logistic survival model most closely approximated real-world data on the long-term survival of patients receiving ipilimumab.
- ICERs varied by AUD$50,000 per QALY gained, which substantially impacted conclusions about the cost-effectiveness of nivolumab.
- The choice of parametric model has a large effect on predicted ICERs and should be well justified based on internal and external validation methods.

References