Comparison of Long-Term Overall Survival With Extrapolated Overall Survival for Pembrolizumab Assessed by Australian Reimbursement Authorities

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Background and Objectives

For PD(L)-1 inhibitors, overall survival (OS) is a key driver of clinical- and cost-effectiveness. Submissions to the reimbursement authorities often require the extrapolation of observed OS data from the pivotal clinical trial to project patients' survival beyond the trial period, and typically over their lifetime. This extrapolation is necessary to value cost-effectiveness of new medicines and inform decision-making.

A recent study compared long-term OS data for PD(L)-1 inhibitors with manufacturer- and Evidence Review Group (ERG)-extrapolations presented in UK National Institute for Health and Care Excellence (NICE) submissions with corresponding long-term follow-up OS data.[1] The analysis showed that overall, OS extrapolations preferred by the ERGs tended to predict OS reasonably well when compared to more mature data, although on average they appeared to underestimate OS slightly.

The aims of this study are:

- To analyse the differences in extrapolations accepted by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) for pembrolizumab submissions compared with what has been subsequently observed in long-term trial follow-up
- To understand whether the time horizon accepted by the PBAC adequately captures the treatment benefit and value of pembrolizumab

Methodology

To focus on treatments with a high disease burden and budget impact, the study was limited to treatment areas with disease incidence greater than 500 patients per year in Australia. A search was conducted for pembrolizumab public summary documents (PSD) as well as published long-term OS data with at least 2 years median follow-up.

The sponsor-preferred and PBAC-accepted extrapolation methodology and model time horizon reported in the relevant PSDs were extracted. To compare the accuracy of OS projections vs the most mature published data, published KM OS data (using the most recent published follow-up) was digitised using WebPlotDigitizer[2] software and overlaid with the sponsor-preferred and PBAC-accepted extrapolations

To quantify the difference between initial OS extrapolations and the most mature trial data, the proportion of patients alive at two time points were considered:

1. The proportion of patients alive at the maximum follow-up time point based on the initial KM curve as reported in the relevant PSD
2. The proportion of patients alive at the midpoint between the maximum follow-up of the initial and most mature KM curve as reported in the relevant long-term follow-up data report

Results

- The review identified two relevant pembrolizumab PBAC submissions based on trials with subsequent longer-term data (**Table 1**)
  1. Patients with previously untreated advanced non–small cell lung cancer (NSCLC) with a PD-L1 tumour proportion score of 50% based on KN-024
  2. Patients with advanced melanoma previously untreated and BRAF^{V600} wild-type or up to one previous systemic therapy with a BRAF^{V600} mutation based on KN-006. Notably, the long-term data for KN-006 was in a broader population and also included first line BRAF^{V600} mutation positive patients. As such, a sensitivity analysis was included, which compared the submission indication population with the BRAF^{V600} wild-type subgroup

Table 1. Extrapolation Methodology Used in the PBAC Submissions

Included Submission	PSDs	Pivotal Trial (long-term data report)	Indication	Sponsor Extrapolation Method and Time Horizon	PBAC-accepted Extrapolation Method and Time Horizon
NSCLC	March and November 2017 March and July 2018	KN-024[3]	Previously untreated metastatic NSCLC with a PD-L1 tumour proportion score of ≥50%	KM to 7.4 months, log-logistic to 7.5 years	KM to 25.1 months, exponential to 7.5 years
Melanoma	March 2016, November 2016	KN-006[4]	Advanced melanoma, first line in BRAF^{V600} wild-type or second line with a BRAF^{V600} mutation	KM to 22.8 months, log-logistic to 4.6 years, exponential to 7 years	KM to 22.8 months, exponential to 5 years

Source: Pembrolizumab July 2018 NSCLC PSD **Table 1**; Pembrolizumab November 2016 melanoma PSD **Figure 3**, **Table 9**; Pembrolizumab November 2017 NSCLC PSD **Figure 2**, **Figure 3**, **Table 11**; Reck et al 2019; Robert et al 2019.

KM, Kaplan-Meier; NSCLC, non–small cell lung cancer; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, public summary document.

- In both NSCLC and melanoma, the sponsor-preferred and PBAC-accepted extrapolation methods underestimated the OS of pembrolizumab compared with the longer-term follow-up data (**Table 2**)
- The PBAC-accepted extrapolation underestimated OS to a greater extent compared with the sponsor-preferred extrapolation (**Table 2**)

NSCLC

- At the end of the original KM (33 months), sponsor-preferred extrapolation and PBAC-accepted extrapolation underestimated OS by 3.0% and 5.2%, respectively
- At midpoint between original and most mature KMs (40.5 months), sponsor-preferred extrapolation and PBAC-accepted extrapolation underestimated OS by 4.9% and 9.1%, respectively
- The PBAC-accepted extrapolation resulted in 0.44 fewer life-years compared with the sponsor-preferred extrapolation

Melanoma

- At the end of the original KM (36 months), sponsor-preferred extrapolation and PBAC-accepted extrapolation underestimated OS by 7.7% and 12.6%, respectively, compared with long-term OS in the intention to treat (ITT) population
- At midpoint between original and most mature KMs (49 months), sponsor-preferred extrapolation and PBAC-accepted extrapolation underestimated OS by 9.7% and 18.3%, respectively, compared with the long-term ITT OS data
- Similar results were observed for the comparison with the long-term BRAF^{V600} wild-type subgroup
- The PBAC-accepted extrapolation resulted in 0.55 fewer life-years compared with the sponsor-preferred extrapolation

Table 2. Absolute Change in OS% Between Extrapolated KM and Most Mature KM for Melanoma

Comparison	NSCLC	Melanoma (ITT)	Melanoma (BRAFwt)
Maximum reported OS time (months)			
Original KM	33	36	36
Most mature KM	48	62	62
Absolute change in OS % from most mature KM at end of original KM vs:[a]			
Sponsor-preferred extrapolation	-3.0%	-7.7%	-5.7%
PBAC-accepted extrapolation	-5.2%	-12.6%	-10.6%
Absolute change in OS % from most mature KM at midpoint between original and most mature KMs vs:[a]			
Sponsor-preferred extrapolation	-4.9%	-9.7%	-8.7%
PBAC-accepted extrapolation	-9.1%	-18.3%	-17.2%

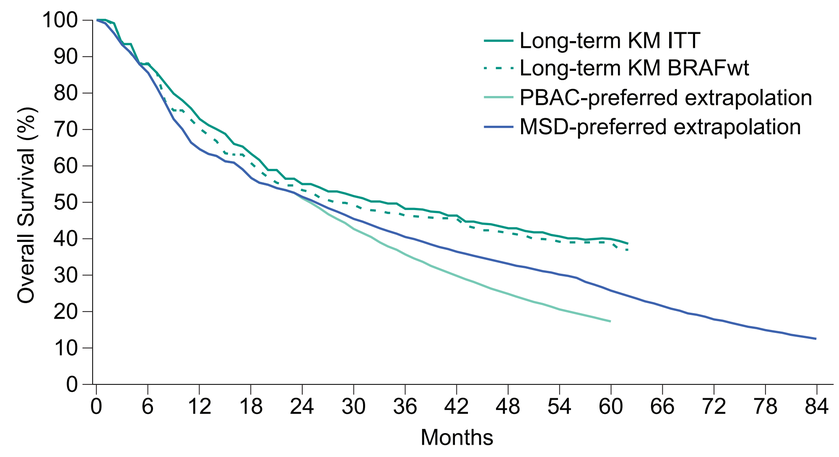
Source: Pembrolizumab November 2016 melanoma PSD **Figure 3**; Pembrolizumab November 2017 NSCLC PSD **Figure 2**; Reck et al 2019; Robert et al 2019, **Figure 2A**.

BRAFwt, BRAF wild-type; ITT, intention to treat; KM, Kaplan-Meier; NSCLC, non–small cell lung cancer; OS, overall survival; PBAC, Pharmaceutical Benefits Advisory Committee.

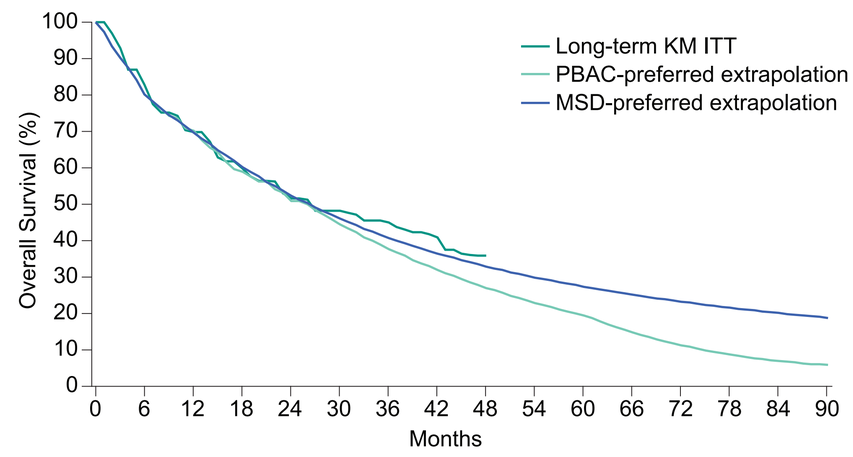
[a]A negative value here indicates that the extrapolation underestimated OS, whereas a positive value here shows the extrapolation overestimated OS.

Figure 1. Comparison of Observed and Extrapolated OS

Melanoma



NSCLC



Source: Pembrolizumab November 2016 melanoma PSD **Figure 4** and **5**; Pembrolizumab November 2017 NSCLC PSD **Figure 3**; Robert et al 2019, **Figure 2A**, Supplementary **Figure S2B**; https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes. Reck et al 2019.

Discussion and Conclusions

- This study is the first to compare OS extrapolation with more mature OS data for PD(L)-1 inhibitors evaluated by the PBAC in Australia
- For pembrolizumab in NSCLC and melanoma, the PBAC-accepted extrapolation underestimated OS to a greater extent than the sponsor-preferred extrapolation when compared with the more mature data
- The results of this analysis broadly align with Bullement et al[1] where on average, OS extrapolations employed by manufacturers and ERGs in NICE evaluations appeared to underestimate OS
- Notably, when compared to the corresponding NICE STAs for melanoma (TA366), sponsor-preferred extrapolation was more conservative than ERG-preferred extrapolation and identical for NSCLC (TA447).[1] In contrast, the PBAC-accepted extrapolations underestimated OS to a greater extent compared with ERG-preferred extrapolations
- A limitation of the analysis in melanoma was that the long-term data for KN-006 was in a broader population than what was originally modelled. However, sensitivity analyses in the BRAF^{V600} wild-type subgroup produced similar results supporting the validity of this comparison
- Unlike Bullement et al,[1] our analysis was limited to pembrolizumab. Further analyses in other PD(L)-1 inhibitors would determine if our findings are consistent across other PD(L)-1 inhibitor submissions evaluated by the PBAC
- The longer-term data shows a "plateauing" effect of pembrolizumab on OS, which is consistent with what has previously been observed for PD(L)-1 inhibitors.[5-7] This suggests that the time horizons recommended by the PBAC (5 years in melanoma and 7.5 years in NSCLC) do not adequately capture the OS treatment benefit of pembrolizumab
- Overall, the underestimation of OS and relatively short time horizons preferred by the PBAC suggest that the value of pembrolizumab in these indications may have been underestimated
- The results of this analysis may help evidence-based valuing of cost-effectiveness for future PD(L)-1 inhibitor submissions

References

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Presented at Virtual ISPOR Asia Pacific 2020; September 14-16, 2020.