EE349

Cost-Effectiveness of First-Line Treatment with Pembrolizumab for Unresectable or Metastatic MSI-H/dMMR Colorectal Cancer (CRC) in the United States Based on 5-year follow-up data

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Background

- Colorectal cancer (CRC) is the second most common cancer in terms of mortality (~881,000 deaths estimated in 2018) and third most diagnosed cancer worldwide[1]
- In the United States, there were an estimated 1.4 million people living with CRC in 2020 and in 2023 it is expected that CRC will contribute 7.8% of all new cancer cases and 8.6% of all cancer deaths[2]
- Keytruda® (pembrolizumab) is a monoclonal antibody which enhances the anti-tumor immune response by inhibiting the interaction between the programmed death 1 (PD-1) receptor and its ligands PD-L1 and PD-L2[3]
- In 2020, pembrolizumab was approved by the Food and Drug Administration (FDA) for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC[4]
- The approval was based on the KEYNOTE-177 trial which enrolled 307 patients randomized to receive first-line (1L) pembrolizumab or SoC. Crossover to pembrolizumab after disease progression was permitted[5]
- Previous economic evaluations for this indication were based on interim analyses (data cut-off: 19 February 2020) from KEYNOTE-177.[4] Long term follow-up data (data cut-off: July 17, 2023) are now available[5]

Objective

- To re-evaluate the cost-effectiveness of pembrolizumab versus SoC as 1L treatment for patients with MSI-H/dMMR CRC from the perspective of the US healthcare system, using additional long-term follow-up data from KEYNOTE-177

Method

Economic model

- A partitioned survival (PartSA) modeling approach with three mutually exclusive health states: pre-progression, post-progression, and death was used in the base case. The modelling approach was consistent with previous publications[5]
- The model adopted a lifetime time horizon (40 years) with adjustment for half-cycle correction, an annual discount rate of 3% for costs and health outcomes and took a US health care system perspective
- Sensitivity and scenario analyses were performed including evaluating an alternative three-state semi-Markov state-transition model (STM) structure and evaluating results from a societal perspective

Cost parameters

- Direct medical costs (in $2020) were assessed from the US health system perspective, including drug acquisition and monitoring (1L and subsequent therapies) disease monitoring, adverse event management and end of life

Clinical parameters – efficacy and subsequent therapy

- The clinical data for progression-free (PFS), overall (OS), and post-progression survival (PPS) along with the subsequent therapy data were updated using the 5-year follow-up of the KEYNOTE-177 trial
- Despite the additional follow-up, survival outcomes were still not fully mature and therefore required extrapolation. Published guidance was followed to select appropriate parametric survival distributions.[6,7] In the base case, two-piece parametric curves were fit to the pembrolizumab and SoC OS and PFS data using exponential distribution from 52 weeks and Weibull distribution from 20 weeks onward, respectively (Figure 1)
- Survival outcomes were not adjusted for treatment crossover, but the model did include the cost of PD-1 inhibitors used as subsequent therapies (based on RWE), reflecting the current treatment landscape

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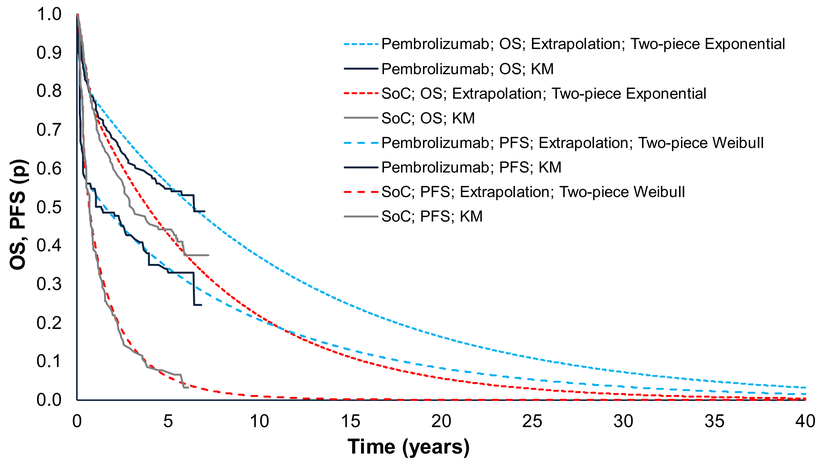
Figure 1. OS and PFS curves for pembrolizumab and SoC



Key: *KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; SoC, standard of care*

Results

Base case analysis

- Based on the long-term follow up data, pembrolizumab continues to demonstrate improved overall survival while delaying progression when compared to SoC as observed in the KEYNOTE-177 trial (Table 1)
- Pembrolizumab was cost saving with a reduced total cost by $15,843 (discounted), compared to SoC. Additional 1L drug acquisition costs were offset by savings in administration, disease management, AE monitoring and subsequent therapy costs

Results based on previous data cuts

- In a previous analysis using second interim analysis (IA2) data, the incremental QALYs were 1.61 and the incremental costs were $11,270, which resulted in an ICER of $6,984 versus SoC[5] (Table 2)

Table 1. Discounted results of the base case analysis

Therapeutic strategy	Costs	LYs	QALYs	Incremental costs	Incremental QALYs	ICER ($/QALY)
SoC	$446,060	5.22	4.06			
Pembrolizumab	$430,217	7.43	5.99	-$15,843	1.93	Dominates

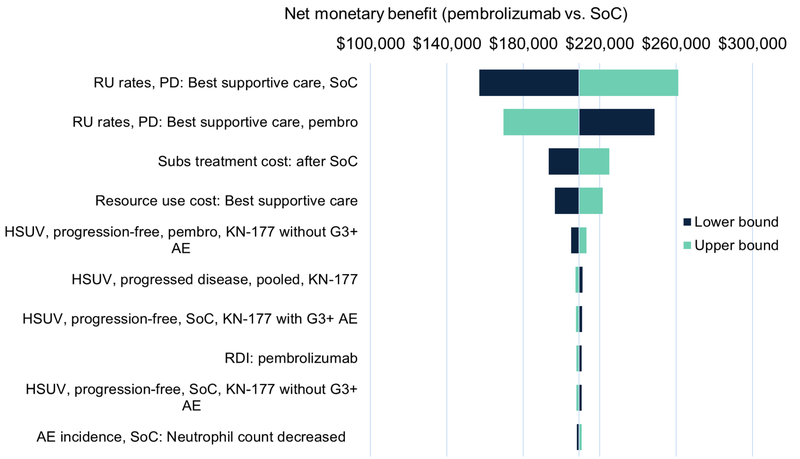
Table 2. Discounted results of the analysis using IA2 data cut

Therapeutic strategy	Costs	LYs	QALYs	Incremental costs	Incremental QALYs	ICER ($/QALY)
SoC	$370,465	4.12	3.23			
Pembrolizumab	$381,735	5.94	4.85	$11,270	1.61	**$6,984**

Sensitivity and scenario analyses

- The probabilistic sensitivity analysis (PSA) results were consistent with the deterministic analysis. At a willingness-to-pay threshold of $100,000, there was a 99.9% probability of pembrolizumab being cost-effective versus SoC
- Using KN-177 trial based subsequent therapy data increased incremental costs to -$10,176, with pembrolizumab still remained cost-saving versus SoC
- Using the societal perspective resulted in additional cost-savings from productivity gains due to delayed progression and death. This resulted in incremental costs of -$239,478
- The one-way sensitivity analysis (OWSA) showed that of the univariate parameters explored, the ICER was most sensitive to the resource use frequency of best supportive care in the 'post-progression' state. The ICER was also sensitive to subsequent treatment costs for the SoC arm (Figure 2)
- Use of the 3-health state STM structure resulted in a gain of 2.27 QALYs and additional cost of $18,147 for pembrolizumab leading to an ICER of $7,991 versus SoC

Figure 2. Tornado plot of pembrolizumab vs. SoC



Key: *AE, adverse events; G3, grade 3; HSUV, health state utility value; PD, progressed disease; PF, progression-free; RDI, relative dose intensity; RU, resource use; SoC, standard of care*

Conclusion

- These updated results demonstrate that pembrolizumab remains a highly cost-effective treatment option for 1L MSI-H mCRC patients when incorporating additional 5-year follow-up data from KEYNOTE-177
- The results were robust to a range of sensitivity and scenario analyses explored. Key assumptions include using OS outcomes unadjusted for treatment crossover and including the cost of subsequent PD-1 inhibitor use
- The 5-year follow-up data addressed the uncertainties associated with long-term outcomes with the IA2 survival data, demonstrating that pembrolizumab is still cost-saving as a 1L therapy for CRC patients in the US when compared to SoC
- Previous cost-effectiveness estimates using IA2 are shown to be conservative when compared to this study. The authors suggest this was intended, by using conservative extrapolations to mitigate uncertainty from the immature data
- The choice of model structure had little impact on model results, while the 3-health state STM structure yielded a slightly higher ICER due to post-progression survival assumptions translating to increased incremental costs
- Two-piece models fitted to OS in the base case had a poor visual fit but were retained as they produced clinically plausible extrapolations

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