Cost-effectiveness of pembrolizumab as first-line (1L) treatment for patients with microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) unresectable or metastatic colorectal cancer (CRC) from public payer perspective in Mexico

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Introduction

In Mexico, colorectal cancer (CRC) ranks fourth among the most common cancers.[1] In 2020, a total of 14,901 new cases were registered, which corresponds to an incidence of 10.6 and a mortality rate of 5.4 per 100,000 inhabitants.[1] CRC with MSI-H (microsatellite instability-high)/dMMR (mismatch repair deficient) represents approximately 12 to 15% of all CRC cases, and 4% of metastatic CRC cases.[1,2] Patients with MSI-H/dMMR CRC are a distinct population in which the disease is driven by a high mutational burden and a specific tumor neoantigen burden mediated by MSI and common defects in the MMR.[4] The prognosis for these patients has been poor, in part due to the lack of an approved first-line treatment specific to this population.[3] Recent scientific evidence suggests that MSI-H/-dMMR tumors respond much less to conventional chemotherapy and are associated with high toxicity.[3]

MSI-H/dMMR cancers demonstrate a high positive regulation of PD-1 and PD-L1 expression, therefore providing a scientific basis for PD-1 blockade with pembrolizumab.[4] Hence this CRC subgroup represents a group of patients who may benefit from treatment with pembrolizumab, which is designed to address the unique biology of this disease.[4]

The KEYNOTE-177 Phase 3 trial has marked a significant milestone as the first global study to establish the efficacy of Pembrolizumab in patients with advanced or metastatic MSI-H/dMMR CRC.[5] The study demonstrated a compelling and clinically meaningful improvement in progression-free survival (PFS) as compared to standard of care (SOC) (HR=0.60 [95% CI: 0.45, 0.80]) and an overall survival (OS) OS hazard ratio [HR] 0·74; 95% CI 0·53–1·03; p=0·036 of , nearly doubling the duration of progression-free status for patients and resulting in a 40% reduction in the risk of disease progression.[5] Notably, the observed difference in PFS rates became increasingly pronounced over time, underlining the sustained impact of Pembrolizumab in this patient population.[5]

Objective

This study evaluated the cost-effectiveness of pembrolizumab monotherapy vs. SoC as per KEYNOTE-177 Phase 3 trial for MSI-H/dMMR CRC from a Mexican public healthcare system perspective.

Methodology

A five-stage Markov model was developed including PFS, post-surgery progression free, post-surgery progressed disease, progressed disease, and death (Figure 1), and using efficacy and safety data from KEYNOTE-177 trial based on IA2. Utility inputs used were derived through primary analyses of the EuroQoL five-dimension five-level questionnaire (EQ-5D-5L) data collected in the KEYNOTE-177 trial using the Mexican algorithm. In case of surgical survival outcomes are taken from the literature given the limited data available from the trial.[6]

Treatment costs were obtained from the hospital "Instituto Mexicano del Seguro Social" and are available in the official journal of the federation. Acquisition and medical costs, and costs related to adverse events and subsequent therapies were obtained from government institutions and reported in US dollars. A 5-year time horizon was adopted due to the natural history of the disease in the country. . Alternate scenarios were tested in the sensitivity analyses, performing 1000 iterations, to test the robustness of the results. Outcomes were expressed in incremental cost-effectiveness ratio (ICER) per life years gained according to local HTA guideline, results showed cost-effectiveness even though without reflecting the discount of 5%.
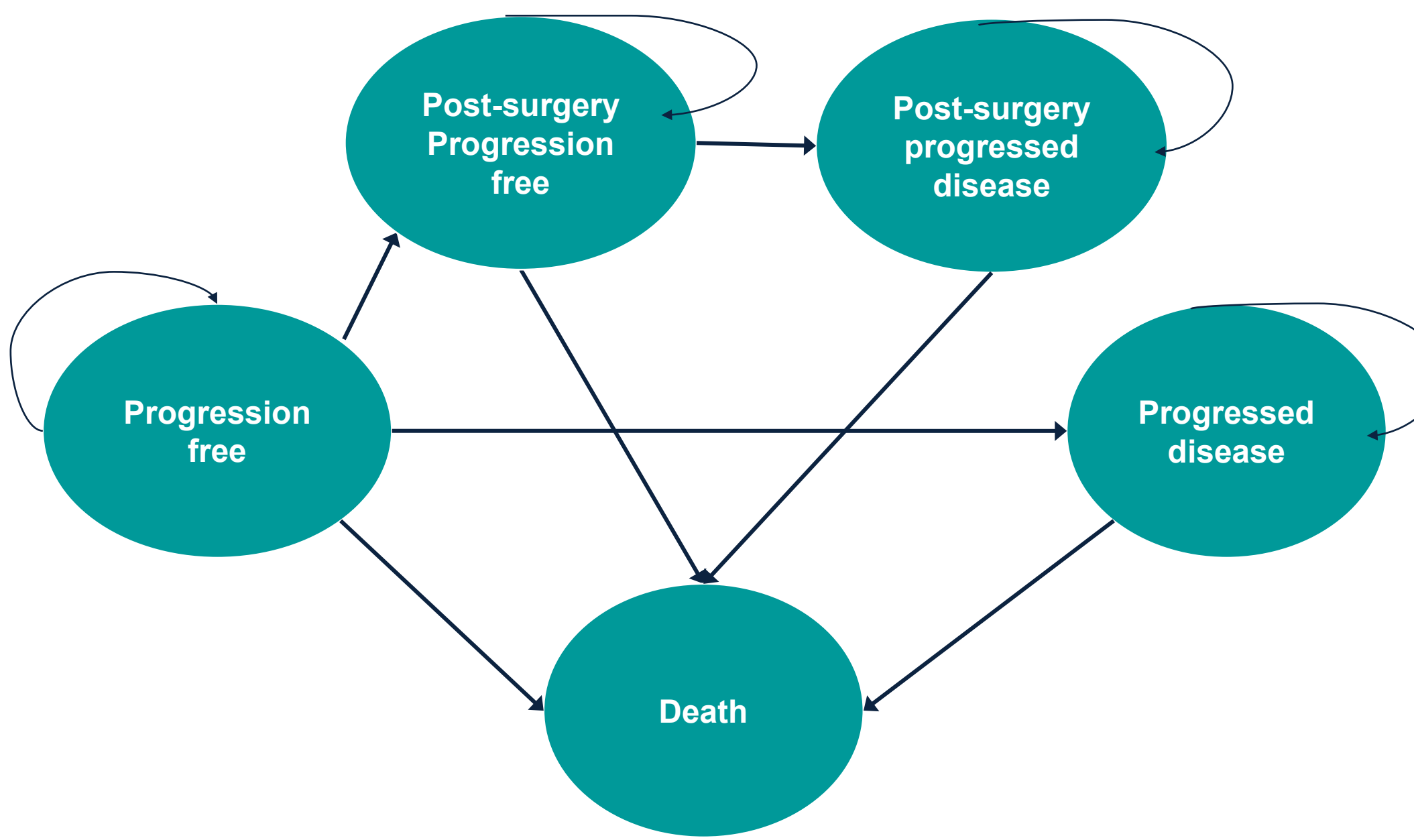

Figure 1. Markov Model that represents the disease transition in each stage

Results

Base case analysis

Over a 5-year time horizon, pembrolizumab as monotherapy increases the total life years gained (LY) by 0.685, mainly derived from increases in the progression free state (1.011 LYs), post-surgery progression free (0.014 LYs), post-surgery progressed disease (0.011 LYs) and a decrease in progressed disease state (0.351 LYs). This translates to a total cost of pembrolizumab of $161,864 USD vs $145,091 USD for SoC, with an incremental cost of $16,773 USD, resulting ICER of 24,492 USD per LY, which is equivalent to 1.68 GDP per capita (1 GDP is equal to $14,537).

Table 1 shows the years of life gained or lost for each stage of the disease. In the pembrolizumab arm, patients remain in the progression-free stage for longer time with 1,987 LY. While the stage in which the SoC remains the longest is in the progression stage with 0.976 LY.

Category	LYs Standard of care	LYs Pembrolizumab	Difference
Progression free	0.976	1.987	1.011
Progressed disease	1.241	0.890	-0.351
Post-surgery progression free	0.164	0.178	0.014
Post-surgery progressed disease	0.132	0.143	0.011
Total LYs	**2.513**	**3.198**	**0.685**

Table 1. Life years gained per stage of disease

On the other hand, treatment with pembrolizumab could result in savings in the management of adverse events, treatment administration, monitoring costs, and the subsequent treatment costs, with the results being consistent between the time spent in the progression stage and the accumulated costs. Table 2 shows the disaggregated and total direct costs for both therapies.

Category	Standard of Care	Pembrolizumab	Difference
Acquisition	$ 39,193	$ 118,819	$ 79,626
Administration	$ 10,916	$ 5,471	-$ 5,446
Adverse Events	$ 1,175	$ 553	-$ 621
Surgery	$ 766	$ 773	$ 7
Monitoring	$ 45,142	$ 35,455	-$ 9,687
Subsequent treatment	$ 47,899	$ 793	-$ 47,106
Total	**$145,091**	**$ 161,864**	**$ 16,773**

Table 2. Disaggregated direct costs of Pembrolizumab monotherapy vs SoC

Sensitivity analyses

The tornado diagram of the deterministic sensitivity analysis shows that the variable that most influences the change in the ICER is the subsequent cost of treatments after SoC. (Figure 2)
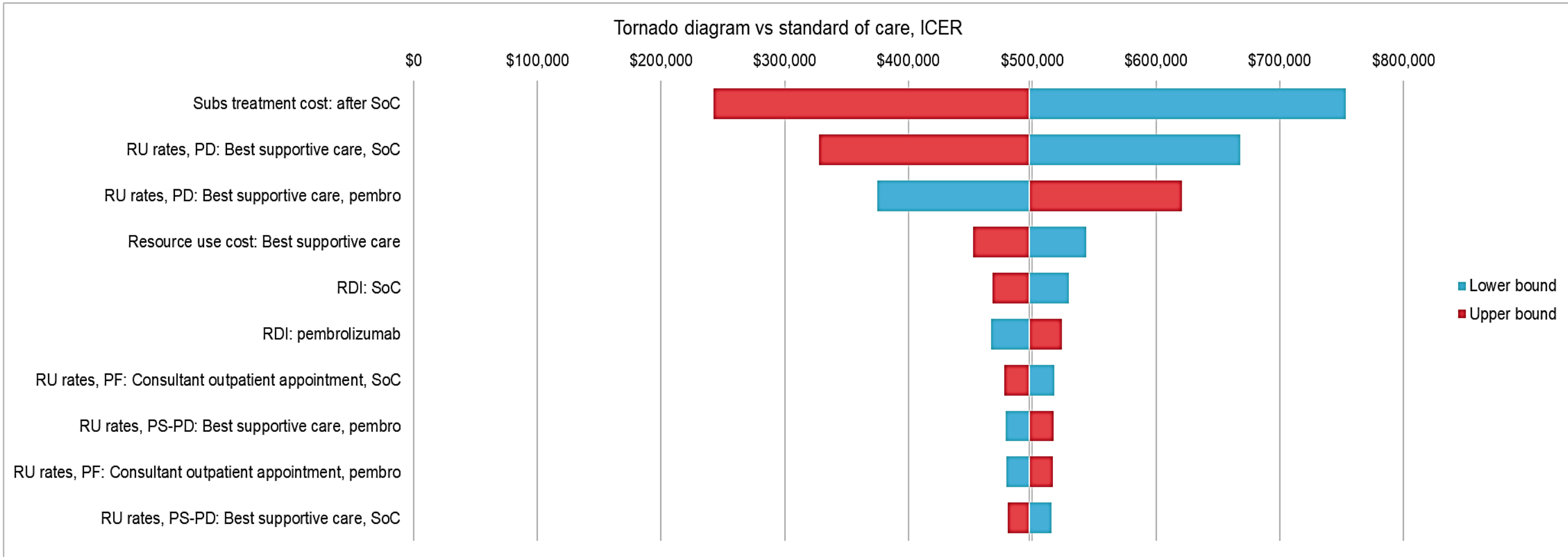

Figure 2. Tornado Diagram

Conclusion

From a Mexico's public payer perspective, the cost-effectiveness of pembrolizumab as a first-line treatment for patients with unresectable or metastatic MSI-H/dMMR colorectal cancer is evident when compared with the standard of care. The introduction of pembrolizumab as a therapeutic option represents an investment of $16,773 USD per 0.6 life-years which is traduced in an ICER of $24,492 USD.

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