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ORIGINAL RESEARCH

Cost-Effectiveness of Pembrolizumab as an Adjuvant Treatment in Colombia for Melanoma Patients with Lymph Node Involvement After Complete Resection

Cesar Lopez-Vinueza · Juan Urrego-Reyes · Fredy R. S. Gutierrez · Victoria Wurcel · Shujing Zhang · Shan Jiang · Ruixuan Jiang · Angela Zambrano Harvey · Praveen Dhankhar · Baanie Sawhney · Gargi Baluni · Shrishti Jain · Debosmita Bhadra

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ABSTRACT

Introduction: The KEYNOTE-054 trial found that adjuvant treatment with pembrolizumab improved recurrence-free survival versus placebo in completely resected high-risk stage III melanoma patients. We assessed the cost-effectiveness of adjuvant pembrolizumab in Colombia compared with watchful waiting, a widely used strategy despite the high risk of recurrence with surgery alone.

Methods: A four-health state [recurrence-free (RF), locoregional recurrence (LR), distant metastases (DM), and death) Markov model was developed to assess the lifetime medical costs and outcomes (3% annual discount), along with cost-effectiveness ratios (ICERs). The transitions from the RF and LR states were modeled using KEYNOTE-054 data, and those from the DM state were modeled using data from the KEYNOTE-006 trial and a network meta-analysis of advanced treatments received after adjuvant pembrolizumab and watchful waiting. The health state utilities were derived from KEYNOTE-054 Euro-QoL data and literature. Costs are expressed in 2021 Colombian pesos (COP).

Results: Over a 46-year time horizon, patients on adjuvant pembrolizumab and watchful waiting were estimated to gain 9.69 and 7.56 quality-adjusted life-years (QALYs), 10.83 and 8.65 life-years (LYs), and incur costs of COP 663,595,726 and COP 563,237,206, respectively. The proportion of LYs spent in RF state was 84.63% for pembrolizumab and 72.13% for watchful waiting, yielding lower subsequent treatment, disease management, and terminal care costs for pembrolizumab. Adjuvant pembrolizumab improved survival by 2.18 LYs and 2.13 QALYs versus watchful waiting. The ICER per QALY was COP 47,081,917, primarily driven by recurrence rates and advanced melanoma treatments. The deterministic sensitivity analysis results were robust and consistent across various reasonable inputs and alternative scenarios. At a willingness-to-pay threshold of COP

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C. Lopez-Vinueza (✉) · J. Urrego-Reyes · F. R. S. Gutierrez
MSD Colombia, Calle 127A #53A-45 T3 P8, 110111 Bogota, Colombia
e-mail: cesar.lopez2@merck.com

V. Wurcel
MSD Argentina, Buenos Aires, Argentina

S. Zhang · S. Jiang · R. Jiang
Merck & Co., Inc., Rahway, NJ, USA

A. Zambrano Harvey
Fundación Valle de Lili, Cali, Colombia

P. Dhankhar · B. Sawhney · G. Baluni · S. Jain · D. Bhadra
CHEORS, North Wales, PA, USA

69,150,201 per QALY, the probability of pembrolizumab being cost-effective was 65.70%. ***Conclusion***: Pembrolizumab is cost-effective as an adjuvant treatment compared to watchful waiting among patients with high-risk stage III melanoma after complete resection in Colombia.

Keywords: Melanoma; Adjuvant treatment; Cost-effectiveness; Pembrolizumab; Colombia; Latin America; High-risk stage III

Key Summary Points

Why carry out this study?

The KEYNOTE-054 trial demonstrated that pembrolizumab as an adjuvant therapy improved recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) in patients with completely resected stage III melanoma versus placebo.

The study evaluates the cost-effectiveness of pembrolizumab in Colombia, against watchful waiting using both the RFS and DMFS data from the KEYNOTE-054 trial.

What was learned from the study?

At the given willingness-to-pay (WTP) threshold for Colombia, adjuvant treatment with pembrolizumab was found to be cost-effective.

The patients receiving pembrolizumab in the adjuvant setting were projected to experience fewer recurrences and thereby accrue fewer costs in the locoregional recurrence (LR) and distant metastases (DM) health states compared to the watchful waiting.

Most of the life-years (LYs) and quality-adjusted life-years (QALYs) were gained because patients treated with pembrolizumab spent more time in the RF state, and fewer of them progressed to DM as compared to watchful waiting.

INTRODUCTION

Melanoma is one of the most common forms of skin cancer, accounting for most skin cancer deaths globally [1]. The incidence of melanoma has increased over the years across the world [2]. In 2020, approximately 57,043 patients died from melanoma worldwide [3]. Melanoma is responsible for 32.5 disability-adjusted life-years (DALYs) per 100,000 in southern Latin America [4]. In Colombia, the 5-year prevalence of melanoma diagnosed among men and women was 5268 in 2020, reflecting an incidence of 10.35 per 100,000 [5].

Surgery is the primary treatment for stage III melanoma with clinically positive nodes, even though it alone is insufficient to achieve a cure in most patients [6–8]. Despite the high risk of disease recurrence, a watchful waiting treatment approach in completely resected stage III patients with melanoma continues to be one of the most common treatment approaches in Colombia due to limited access to newer therapies in clinical practice.

The introduction of immune checkpoint inhibitors, anti-programmed death-1 (PD-1) monoclonal antibodies, and targeted drugs active in BRAF-positive (BRAF+) mutated melanoma have increased the effectiveness of the treatment in the adjuvant setting for high-risk stage III melanoma patients [9–16]. Pembrolizumab is a high-affinity monoclonal antibody that blocks the activity of the PD-1 receptor, reactivating the tumor-specific cytotoxic T-lymphocyte response [11, 12]. According to Colombia's regulatory agency, National Institute for Drug and Food Surveillance (INVIMA), pembrolizumab is approved in the adjuvant setting for the treatment of patients with cutaneous melanoma metastatic to lymph node (> 1 mm) who have undergone complete resection, including total lymphadenectomy [17].

The efficacy and safety of pembrolizumab were evaluated in interim analyses of the KEYNOTE-054 trial, a phase 3 randomized study conducted in collaboration with the European Organization for Research and Treatment of Cancer (EORTC) comparing pembrolizumab

and placebo as an adjuvant treatment for completely resected high-risk stage III melanoma [stage IIIA (lymph node involvement > 1 mm), IIIB, and IIIC] [8].

The results from the EORTC-1325/KEYNOTE-054 trial confirmed the effectiveness of pembrolizumab as an adjuvant therapy for stage III melanoma following complete resection, by providing a significant and clinically meaningful improvement in both recurrence-free survival (RFS) and distant metastases-free survival (DMFS) at a 42.3-month median follow-up. [8] The clinical results were leveraged to inform the assessment of the cost-effectiveness of adjuvant pembrolizumab treatment of patients with stage III melanoma in Colombia compared with watchful waiting. The survival analysis findings from the trial were fitted to determine the transition probabilities within the model. This evaluation will support the Colombian healthcare decision-makers and payers in making informed, efficient decisions regarding funding and reimbursement of pembrolizumab for this indication [8, 18].

METHODS

Population and Patient Characteristics

Adult patients (age 18 years or older) with complete resection of high-risk stage III melanoma with lymph node involvement were considered the overall target population, consistent with the enrollment criteria in the KEYNOTE-054 trial [8]. The baseline characteristics of patients were taken from the KEYNOTE-054 trial with the exception of mean body weight, which was based on the National Survey of the Nutritional Situation in Colombia (ENSIN). [8, 19] The patient characteristics and data sources are summarized in Table S1 of Appendix 1 (see Supplementary Material).

Model Structure and Analysis

The state transition diagram in Fig. 1 illustrates the health states and allowable transitions in the cost-effectiveness model, developed using

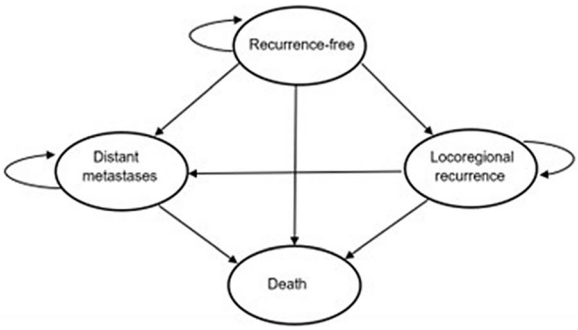

Fig. 1 Model schematic

Microsoft Excel® 2016, which used a Markov cohort structure. The model consists of four mutually exclusive health states [recurrence-free (RF), locoregional-recurrence (LR), distant metastases (DM), and death] to track patients' disease course and survival over time. Patients with stage III melanoma who have undergone complete resection enter the model in the RF state and may experience LR, DM, or death (death can either occur pre- or post-recurrence).

The economic evaluation was conducted from the perspective of the Colombian healthcare payer based on the Institute for Health Technology Assessment (IETS) guidelines [20]. Therefore, only direct health care costs were considered, expressed in Colombian Peso (COP). Wherever required, the original cost values were inflation-adjusted to 2021 prices using the health component of the Consumer Price Index (CPI) from the Bank of the Republic (Colombia) [21]. Watchful waiting was considered the sole comparator to pembrolizumab as an adjuvant treatment for melanoma, based on the current clinical practice in Colombia.

The analysis used a 46-year time horizon to capture all relevant costs and benefits [8]. A cycle length of 1 week was used to account for differences in the frequency of treatment administration (e.g., every 2 weeks for nivolumab maintenance; every 3 weeks for pembrolizumab, the combination of nivolumab and ipilimumab, and BRAF inhibitors) [9–16].

The expected costs, quality-adjusted life years (QALYs), and life years (LYs) gained were estimated for each treatment arm. The

incremental cost-effectiveness ratio (ICER) of pembrolizumab versus watchful waiting was evaluated in terms of incremental cost per QALY and incremental cost per life year. In the base-case analysis, costs and effectiveness were discounted at 3% annually, consistent with the World Health Organization guidelines [22].

A series of scenario and deterministic sensitivity analyses (DSA) was conducted to evaluate the robustness of the ICER. Probabilistic sensitivity analysis (PSA) was conducted to estimate the probability of pembrolizumab being cost-effective relative to watchful waiting based on the willingness-to-pay (WTP) threshold (COP 69,150,201 per QALY) for Colombia, which is three times the gross domestic product per capita (COP 23,050,067) [22, 23]. For the PSA, a Monte Carlo simulation with 1000 iterations was conducted, and, in each iteration, the model inputs were randomly drawn from the specified distributions (Table 1). Whenever available, the standard error (SE) of the distribution selected for the parameters varied was obtained directly from the data source that informed the mean value. If the data were unavailable, each parameter's SE was assumed to be 20% of the mean value. Appendix 3 (see Supplementary Material) provided more information on the scenario analyses, DSA and PSA.

Inputs

Transition Probabilities

The transition probabilities in the Markov model (shown in Table 1) were based on patient-level data from the KEYNOTE-054 trial, a network meta-analysis comparing the efficacy of pembrolizumab in KEYNOTE-006 to other advanced melanoma treatments, and a targeted literature search for relevant clinical inputs not estimable from the trial data [8, 24]. Appendix 2 (see Supplementary Material) presents detailed information regarding all health state transitions and data sources.

For the three transitions starting from the RF state, i.e., RF → LR, RF → DM, and RF → death, a parametric multistate modeling approach was followed to estimate the transition probabilities [25, 26]. The base-case analysis modeled the cause-specific hazards in each treatment arm using generalized gamma for RF → LR, Gompertz for RF → DM, and exponential for RF → death [27]. For the weekly transitions from RF → death in each treatment arm, exponential models were fitted, due to the small number of direct transitions from RF to death observed in the KEYNOTE-054 trial, and were subject to the constraint that the risk must be at least as high as all-cause Colombian mortality [28]. Figure 2(I) presents the observed and long-term predictions of RFS for both model arms.

Following second interim analysis (IA2) of the KEYNOTE-054 trial, patient-level time-to-event data were used to estimate exponential rates and standard errors for transitions starting from the LR state to DM or death, and exponential models were fitted for each treatment arm [18, 29]. The analytical sample was restricted to patients who experienced LR as their first RFS failure event. In scenario analyses, transition probabilities from the LR state based on the Flatiron database were explored [30].

For each adjuvant treatment arm, the probability of the transition from DM → death was estimated based on the expected mix of first-line treatments for advanced melanoma in Colombia. For both adjuvant treatment arms, the expected overall survival (OS) within the DM state was calculated as a market share-based weighted average of expected OS associated with different first-line advanced melanoma treatment regimens (Table 3), and was then converted into a weekly hazard of DM → death. Similarly, the expected progression-free survival (PFS) was also estimated for each adjuvant treatment arm. Figure 2(ii) and (iii) presents the long-term predictions of DMFS and OS for both model arms, respectively.

Adverse Events

The medical costs and health disutilities associated with the drug-related adverse events (AEs) of grade 3 or higher with a frequency of at least 5% (all grades) in either the pembrolizumab or watchful waiting arm of the KEYNOTE-054 trial were included in the model. Diarrhea of grade 2 or higher was also included because of the high expected cost of managing the AE. The risks and the mean durations of the

Table 1 Model inputs

Parameters		Base-case values		Scenario values		Sensitivity analyses performed	Estimation approach/data sources Pembrolizumab
		Pembrolizumab	Watchful waiting	Pembrolizumab	Watchful waiting		
Transition probabilities	RF → LR	Generalized gamma Location = 8.1178 Scale = 4.8581 Shape = − 0.9719	Generalized gamma Location = 6.2939 Scale = 3.6677 Shape = − 0.9301	Proportional hazard models with time-constant or with time-varying treatment effect Gompertz Shape = − 0.0159 Rate = 0.0030 Log normal Location = 8.5676 Scale = 3.4803	 Gompertz Shape = − 0.0182 Rate = 0.0057 Log normal Location = 6.8879 Scale = 2.8333	PSA[b] (multinormal)	Separate parametric extrapolation for each transition from RF state accounting for competing risks based on patient-level data from KEYNOTE-054 *Note:* The distributions generalized gamma and Gompertz were used to model the base case transitions from RF → LR and RF → DM, respectively. Other distributions were explored in the scenario analysis
	RF → DM	Gompertz Shape = − 0.0091 Rate = 0.0036	Gompertz Shape = − 0.0126 Rate = 0.0079	Proportional hazard models with time-constant or with time-varying treatment effect Log normal Location = 6.9377 Scale = 2.8093	 Log normal Location = 5.5748 Scale = 2.2648	PSA[b] (multinormal)	
	RF → Death[a]	0.00009	0.00002	–		Varied by ± 10% PSA[b] (normal)	Exponential rate based on data from KEYNOTE-054 trial
	LR → DM	0.01062	0.00893				
	LR → Death[a]	0.00078	0.00045				
	DM → Death[a]	0.0060 for rechallenge- and IO-eligible if RF → DM ≥ 18 months, else 0.0079 for OI-ineligible	0.0059	0.0054 for rechallenge- and IO-eligible if RF → DM ≥ 18 months, else 0.0072 for OI-ineligible	0.0054	OS and PFS varied by ± 10% PSA [b] (pembrolizumab: normal; HR: log-normal)	Exponential rate based on first-line subsequent treatments mix for advanced melanoma and associated PFS and OS based on NMA of clinical trials

Table 1 continued

Parameters		Base-case values		Scenario values		Sensitivity analyses performed	Estimation approach/data sources Pembrolizumab
		Pembrolizumab	Watchful waiting	Pembrolizumab	Watchful waiting		
Costs	Adverse events costs (one-off)	193,566.72	65,329.25	–		Varied by ± 10%	ISS (2001) Tariff Manual and the SOAT Tariff Manual [35, 38]
	Disease management, per cycle					PSA [b] (gamma)	
	RF, years 1–2; 3–5; 6–10	31,864.57; 30,670.30; 311.68					
	LR	21,966.81					
	Pre-progression DM	27,778.15					
	Post-progression DM	96,780.61					
	Disease management, one-time cost						
	Salvage surgery cost at LR entry	2,269,168.23					
	DM entry	1,419,937.33					
	Terminal care	9,846,941.51					Prada and Contreras (2018) [39]
	Drug administration						ISS (2001) Tariff Manual and Santa Fe Foundation Fee Tariff Manual [35]
	First hour chemo infusion for IV drugs	240,461.00					
	Additional hour chemo infusion for IV drugs	63,261.00					
	Subsequent chemo infusion for IV drugs	240,461.00					
	Drug acquisition	See Table 2		Assume 400 mg Q6W dosing of pembrolizumab		Patient weight varied by ± 10%	SISMED 2021 and dosing schedules according to the product clinical trials/clinical trials [33]
				Allow for vial sharing			
				Do not apply to adjuvant pembrolizumab			

Table 1 continued

Parameters		Base-case values		Scenario values		Sensitivity analyses performed	Estimation approach/data sources
		Pembrolizumab	Watchful waiting	Pembrolizumab	Watchful waiting		Pembrolizumab
Utilities	Health state utility values			Alternative source for all health states		Varied by ± 10%	
	RF without toxicity	0.923				PSA[b] (health state: ß; AE-related disutilities: normal)	KEYNOTE-054 trial [18]
	LR	0.860		Alternative source for post-progression DM state			
	Pre-progression DM	0.837		Apply age-adjusted disutility			
	Post-progression DM	0.590					Beusterien et al. [32]
	QALY decrement from AEs (one-off)	− 0.0022	− 0.0006	Do not apply QALY decrement from AEs			KEYNOTE-054 trial [18]

AE Adverse events, *DM* distant metastases, *DSA* deterministic sensitivity analysis, *HR* hazard ratio, *ISS* Social Security Institute, *IV* intravenous, *LR* locoregional recurrence, *NMA* network meta-analysis, *OS* overall survival, *PFS* progression-free survival, *PSA* probabilistic sensitivity analysis, *RDI* relative dose intensity, *RF* recurrence-free, *SISMED* Drug and Medical Device Price Information System, *SOAT* Compulsory Traffic Accident Insurance

[a]Transition probability to death constrained to be at least as high as all-cause mortality from the life tables for Colombia [28]

[b]The variability of the selected distributions was based on standard errors or variance–covariance from original data sources. For costs, the standard errors were assumed to be equal to 20% of the base-case values

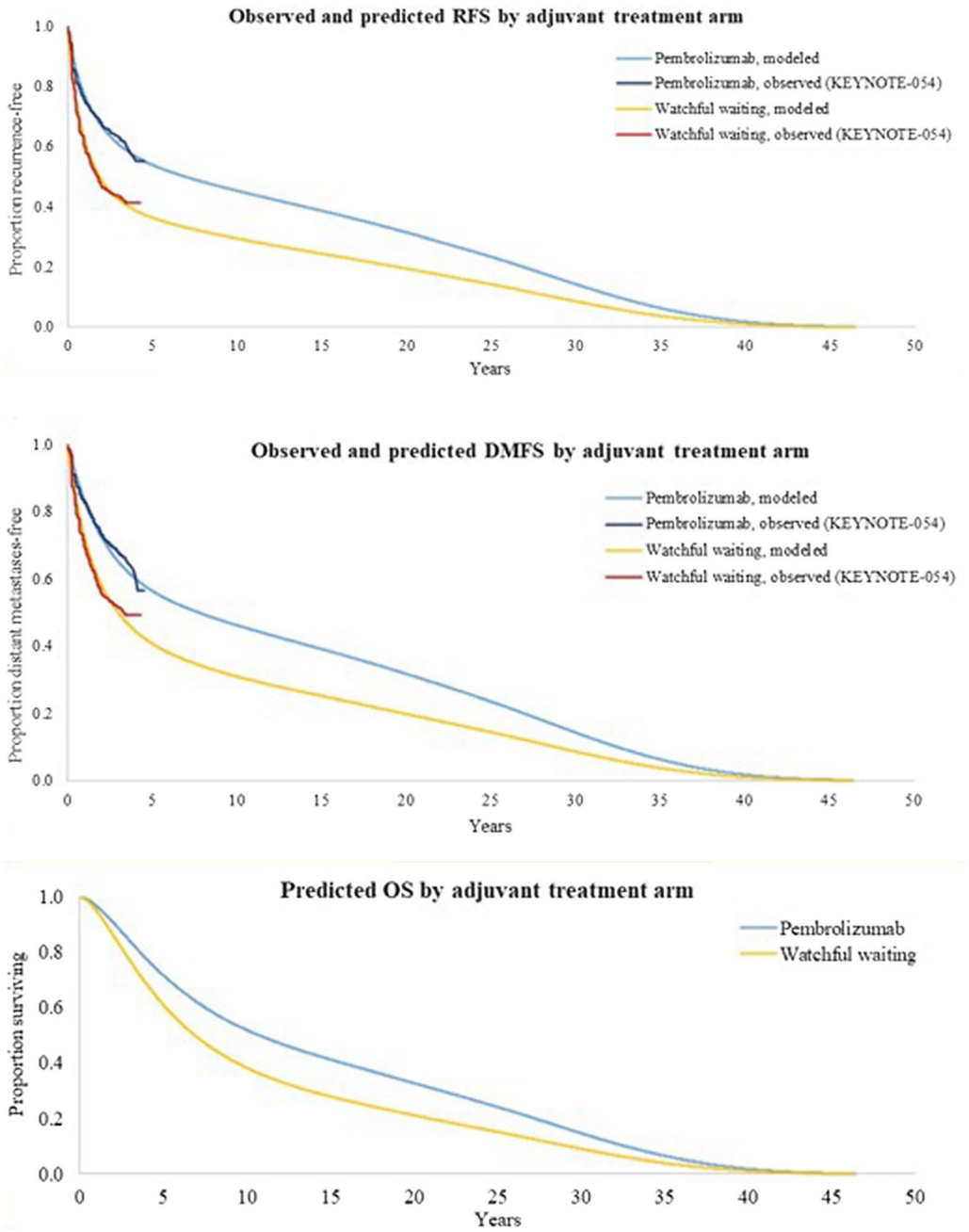

Fig. 2 Long-term outcomes under base-case parametric distribution assumptions: (I) RFS, (ii) DMFS, (iii) OS. *DMFS* distant metastases-free survival, *OS* overall survival, *RFS* Recurrence-free survival

included AEs in each arm were obtained from the KEYNOTE-054 trial [8].

Health Utilities

The utilities for the RF, LR, and DM pre-progression states and the AE-related disutility were assessed through an Argentinian algorithm applied to EQ-5D-3L KEYNOTE-054 data after

Table 2 Drug regimens and unit costs

Drugs	Dosing schedule[a]	Unit cost, COP (strength, mg)
Pembrolizumab	200 mg IV Q3W (as adjuvant, up to 18 cycles)	10,850,000 (100)
Ipilimumab	3 mg/kg IV (with nivolumab, 1 mg/kg) Q3W, up to 4 doses	13,544,406 (50)
Nivolumab	240 mg IV Q2W as monotherapy	2,066,137 (40)
	1 mg/kg IV Q3W followed by ipilimumab (up to 4 doses); 3 mg/kg IV Q2W starting 3 weeks after last ipilimumab dose	5,165,343 (100)
Vemurafenib	960 mg twice daily oral in combination with cobimetinib	27,060 (240)
Cobimetinib	60 mg (3 tablets of 20 mg) per day for the first 21 out of 28 days oral in combination with vemurafenib	208,120 (20)
Dabrafenib	150 mg twice daily oral in combination with trametinib	98,781 (50)
		148,171 (75)
Trametinib	2 mg once daily oral in combination with dabrafenib	98,109 (0.5)
		392,437 (2)

COP Colombian Peso, *IV* intravenous, *kg* kilogram, *mg* milligram, *Q2W, Q3W* once every *n* weeks
Source of drug costs: SISMED 2021 Database [33]
[a]Dosing for weight-based therapies was approximated without vial-sharing, and was calculated based on method of moments using an estimated distribution across weight categories

Table 3 Market shares of first-line regimens in the advanced melanoma setting by adjuvant treatment and eligibility for rechallenge/IOs

First-line regimens in advanced setting	First-line market shares, by adjuvant treatment arm		
	Pembrolizumab Rechallenge-eligible[a]	Pembrolizumab IO-eligible[b]	Watchful Waiting IO-eligible[b]
Pembrolizumab	100.0%	20.3%	20.0%
Nivolumab	0.0%	20.3%	20.0%
Nivolumab + ipilimumab	0.0%	25.4%	33.0%
Vemurafenib + cobimetinib	0.0%	0.0%	7.0%
Dabrafenib + trametinib	0.0%	33.9%	20.0%

IO Immunotherapy
[a]*Rechallenge-eligible* patients who transitioned to the DM state from the RF state after 18 months of adjuvant pembrolizumab treatment initiation were eligible to rechallenge with pembrolizumab in the first-line advanced setting
[b]*IO-eligible* patients who transitioned to the DM state immediately after adjuvant pembrolizumab treatment initiation either from RF or LR were not eligible to rechallenge with pembrolizumab but were eligible to use other immuno-oncology (IO) therapies

Table 4 Market shares of second-line regimens for advanced melanoma by adjuvant treatment and eligibility for rechallenge/IOs

Second-line regimens in advanced setting	Second-line market shares, by adjuvant treatment arm		
	Pembrolizumab Rechallenge-eligible	Pembrolizumab IO-eligible	Watchful Waiting IO-eligible
Pembrolizumab	0.0%	0.0%	10.0%
Ipilimumab	13.3%	0.0%	10.0%
Nivolumab	0.0%	0.0%	10.0%
Nivolumab + ipilimumab	30.0%	30.0%	23.0%
Vemurafenib + cobimetinib	3.3%	14.0%	10.0%
Dabrafenib + trametinib	45.0%	37.0%	20.0%
No active treatment[a]	8.3%	19.0%	17.0%

IO Immunotherapy

[a]In both adjuvant treatment arms, a proportion of patients was assumed to receive no active second-line treatment due to death or rapid progression after the first-line regimen

pooling both arms, considering the similarities between the populations of Colombia and Argentina (Table 1) [18, 31]. The utility associated with the DM state was computed as a weighted average of the pre- and post-progression DM state. The utility of post-progression DM was informed by Beusterien et al., because the DM follow-up in KEYNOTE-054 IA2 was expected to be too limited to capture average utility over the entire post-progression disease course until death [32]. The AE-related disutility, calculated as a function of treatment-specific AE risks, mean durations of the AEs, and the AE-related disutility value, was applied as a one-time QALY decrement in the first model cycle.

Costs

Drug acquisition and administration costs per infusion of adjuvant pembrolizumab were calculated as a function of the list price per drug unit (COP 10,850,000 per 100 mg vial), defined dosing for the medication, relative dose intensity, and unit cost of drug administration (Table 2). The list price per vial was retrieved from the Drug and Medical Device Price Information System (SISMED) and was validated from the regulated price database of the Ministry of Health and Social Protection of Colombia (Minsalud) [33, 34]. The dosing schedule of pembrolizumab in the adjuvant setting was assumed to be a flat dose of 200 mg every 3 weeks (Q3W) for up to 18 cycles (1 year), consistent with the treatment protocol used in the KEYNOTE-054 trial [8]. The relative dose intensity (99.9%), as reflected in the pembrolizumab arm of KEYNOTE-054, was applied to the drug acquisition cost per infusion of adjuvant pembrolizumab to account for any delay or interruptions in administration [18]. Drug administration cost per 30-min infusion of pembrolizumab was extracted from the Social Security Institute (ISS) (2001) Tariff Manual and adjusted for inflation [35].

The proportion of patients remaining on treatment over time at each scheduled infusion was based on the observed Kaplan–Meier (KM) curve for time on treatment (ToT) in the KEYNOTE-054 trial [18]. In the trial, patients in the adjuvant pembrolizumab arm received treatment for up to 1 year or until completion of all 18 doses (i.e., beyond the 1-year treatment period).

The average cost of crossover/rechallenge was calculated and applied as a one-time cost at

Table 5 Base-case results

Costs and outcomes	Pembrolizumab	Watchful waiting	Incremental
Costs, COP	663,595,726	563,237,206	100,358,520
Adjuvant treatment (RF state)	306,598,457	0	306,598,457
Drug acquisition	303,238,228	0	303,238,228
Drug administration	3,360,229	0	3,360,229
Adjuvant treatment (LR state)	6,246,108	80,003,559	− 73,757,451
Drug acquisition	6,177,652	79,126,743	− 72,949,091
Drug administration	68,456	876,815	− 808,360
Subsequent treatment (DM state)	335,345,955	465,310,147	− 129,964,192
Drug acquisition	332,615,984	460,850,792	− 128,234,808
Drug administration	2,729,971	4,459,354	− 1,729,384
Adverse event	193,567	65,329	128,237
Disease management	11,106,548	12,173,017	− 1,066,470
Terminal care	4,105,092	5,685,154	− 1,580,062
Life years	10.827	8.646	2.180
Recurrence-free	9.163	6.237	2.926
Locoregional recurrence	0.327	0.536	− 0.209
Distant metastases	1.337	1.874	− 0.537
Quality-adjusted life years	9.687	7.555	2.132
Recurrence-free	8.458	5.757	2.701
Locoregional recurrence	0.281	0.461	− 0.180
Distant metastases	0.950	1.338	− 0.388
AE-related disutility	− 0.0022	− 0.0006	− 0.0016
Incremental cost-effectiveness ratio			
Cost per life year			46,026,437
Cost per QALY			47,081,917

AE Adverse event, *COP* Colombian Peso, *DM* distant metastases, *LR* locoregional recurrence, *LY* life year, *RF* recurrence-free, *QALY* quality-adjusted life year

entry into the LR state. This represented a plausible approach given the high frequency of crossover in the placebo arm. The mean ToT for the crossover/rechallenge regimen was based on the observed mean ToT among patients in KEYNOTE-054 who initiated crossover/rechallenge within the LR state [18]. The weekly exponential rate of discontinuation was calculated based on this mean ToT and the protocol-defined maximum duration of crossover/rechallenge (i.e., 2 years).

The model applied drug acquisition and administration costs associated with subsequent therapies as a one-time cost upon entry into the

DM state. List prices of drugs used in the advanced melanoma setting were retrieved from SISMED for 2021 (Table 2) [33]. The base-case model assumed that vial-sharing is not allowed for drugs with weight-based dosing in the advanced melanoma setting. Under this assumption, the number of vials required per infusion was estimated based on log-normal distributions of the patient weight in Colombia. [19] The standard deviation for weight was assumed to be based on the proportion of the standard deviation and mean patient weight characteristics from the KEYNOTE-006 trial, applied to the mean weight of the Colombian population [24]. Drug administration cost was based on the ISS (2001) Tariff and the Santa Fe Foundation Fee Tariff Manual [35]. Additionally, the drug administration cost for ipilimumab (in combination with nivolumab) included only the fixed administration cost for subsequent infusion, irrespective of the infusion time. The approved dosing schedules, type of administration, and infusion time for each advanced regimen were obtained from the Food and Drug Administration (FDA) Highlights of Prescribing Information [9, 10, 12–16]. Oral drug combinations were assumed to have no administration cost according to IETS guidelines [20].

For first-line treatment regimens for advanced melanoma, the exponential rate of PFS failure was used to approximate the treatment discontinuation rate up to the label-recommended maximum duration where applicable. The mean ToT was assumed to be 21 weeks for all second-line advanced regimens [36]. As an exception, ipilimumab as monotherapy or in combination was capped at the maximum duration of 12 weeks based on the dosing schedules recommended by National Institute for Health and Care Excellence and the FDA label [10, 37]. Based on the estimated discontinuation rate and (when applicable) the maximum duration of each drug component in a regimen, the model estimated the mean total cost of each treatment regimen in the first- and second-line settings. The drug cost in the advanced setting was calculated for each adjuvant treatment arm as a weighted average of the first- and second-line market shares, based on Colombian market research and expert inputs, and their respective costs. BRAF inhibitors' market shares were subject to the restriction that they should not exceed the percentage of BRAF+ patients enrolled in the KEYNOTE-054 trial [8]. The market shares of regimens for use in the first- and second-line advanced melanoma settings in Colombia (approved by INVIMA) are presented in Tables 3 and 4.[17]

The cost of AE management was applied as a one-time cost in the first model cycle and was based on treatment-specific AE risks and the unit costs per episode for included AEs. Unit costs of AEs were obtained from the ISS (2001) Tariff Manual, and an inflation adjustment factor of 30% was applied to the cost [35]. The cost for management of increased alanine aminotransferase was obtained from the Compulsory Traffic Accident Insurance (SOAT) Tariff Manual [38].

The costs for resource use elements in the RF, LR, and DM states were obtained from the ISS (2001) Tariff Manual and the SOAT Tariff Manual (Table 1) [35, 38]. Medical resource use per week in the RF state included outpatient provider visits and radiologic assessments. The frequencies of resource use elements were based on the clinical expert opinion in Colombia and the KEYNOTE-054 trial, and were time-varying to account for recommended reductions in the frequency of screening among patients who had remained RF for longer periods. Following LR, a one-time cost for salvage surgery was applied based on the proportion of patients who received lymphadenectomy, skin lesion resection, in-transit metastases resection, or other surgery after LR in the KEYNOTE-054 trial [8]. Apart from the salvage surgery, the medical resources used per week in the LR state included outpatient provider visits and radiologic assessments.

For the patients who transitioned to the DM state, a one-time cost was applied based on medical resources associated with first-line treatment initiation. The DM state in the model encompasses both pre- and post-progression DM; therefore, the recurring medical resource use associated with pre-and post-progression DM based on resource use while receiving and not receiving treatment was considered. The

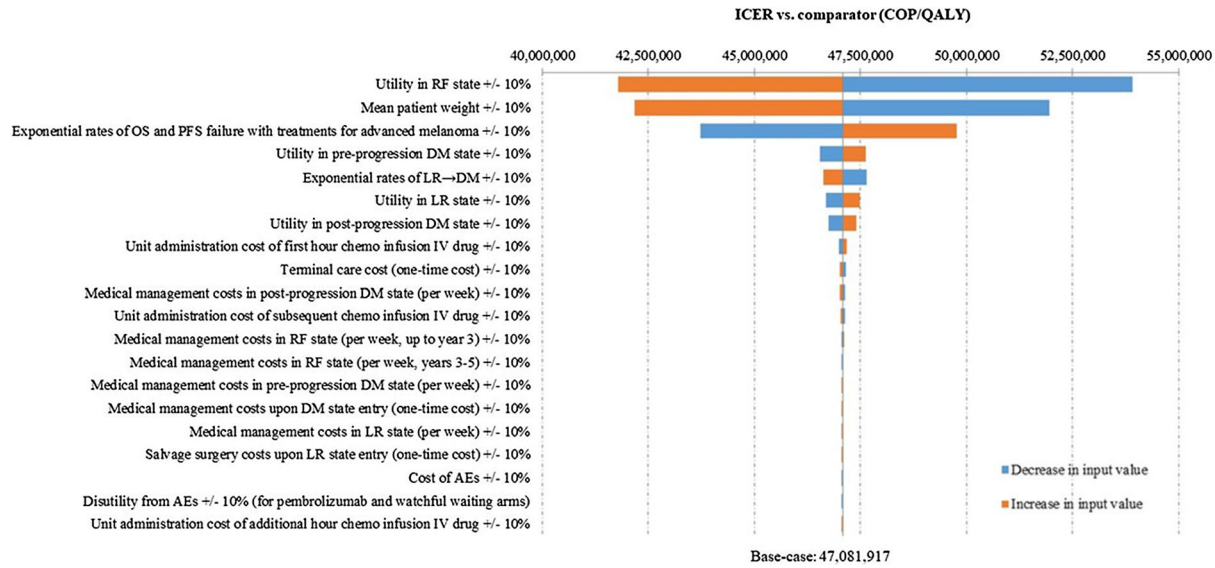

Fig. 3 Tornado diagram for the incremental cost-effectiveness ratio of adjuvant pembrolizumab versus watchful waiting. *AE* Adverse events, *DM* distant metastases, *DMFS* distant metastases-free survival, *IV* intravenous, *LR* locoregional recurrence, *OS* overall survival, *PFS* progression-free survival, *RF* recurrence-free, *RFS* recurrence-free survival

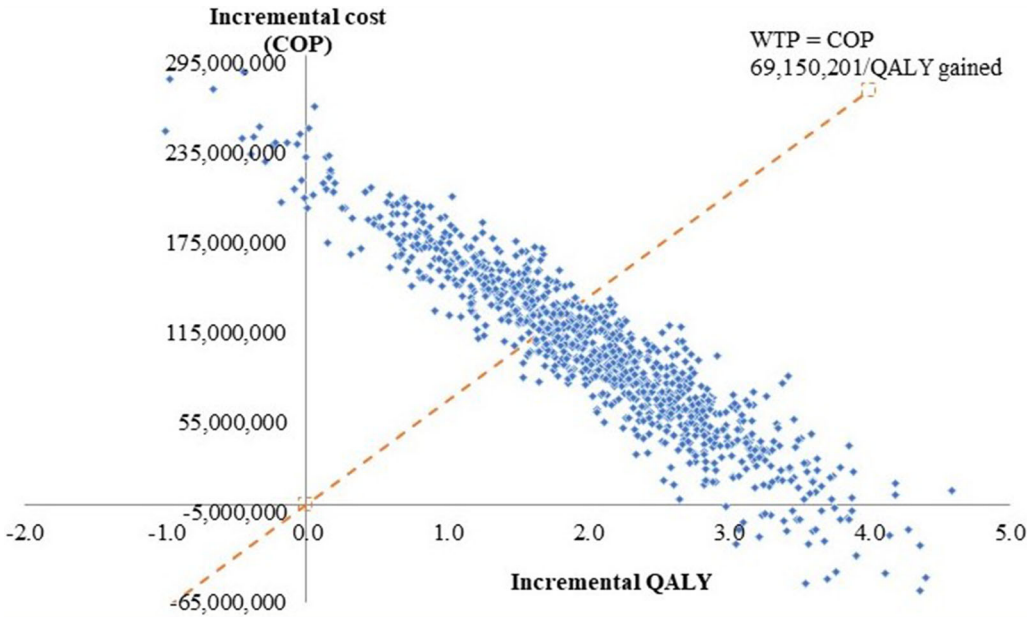

Fig. 4 Scatterplots of incremental costs and effectiveness for pembrolizumab versus watchful waiting across 1000 iterations of the probabilistic sensitivity analysis. *COP* Colombian Peso, *QALY* quality-adjusted life year, *WTP* willingness-to-pay

disease management costs per week in the DM state were computed as a weighted average of resource use associated with pre- versus post-progression DM, based on the proportion of

time spent in the pre- and post-progression DM states.

Patients transitioning from the DM state to death were assumed to incur a one-time cost associated with palliative/terminal care. The terminal care cost was based on the cost of management during the last 3 months before death, as reported by Prada and Contreras (2018), and were inflation-adjusted to 2021 prices [21, 39].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any authors.

RESULTS

Base Case

Over the 46-year lifetime horizon, the total costs were COP 663,595,726 for pembrolizumab and COP 563,237,206 for watchful waiting. Total QALYs were estimated to be 9.69 for pembrolizumab and 7.56 for watchful waiting, and the total LYs were estimated to be 10.83 and 8.65 years, respectively, for pembrolizumab and watchful waiting. Therefore, the patients treated with adjuvant pembrolizumab were projected to gain 2.18 additional LYs and 2.13 additional QALYs relative to those in the watchful waiting arm. The proportion of total LYs spent in the RF state was 84.63% in the pembrolizumab arm compared with 72.13% in the watchful waiting arm. The discounted base-case results are presented in Table 5.

The adjuvant treatment with pembrolizumab projected an increase of COP 100,358,520 in the total costs, driven by adjuvant treatment costs and subsequent treatment costs in the advanced melanoma setting, the latter being lower for pembrolizumab. The disease management and terminal care costs were also lower in the pembrolizumab arm, reflecting the lower incidence of disease recurrence and reduced mortality achieved with pembrolizumab. The resulting ICERs were COP 47,081,917 per QALY gained, and COP 46,026,437 per LY gained for pembrolizumab versus watchful waiting. As the ICER was within Colombia's WTP threshold of COP 69,150,201 per QALY, pembrolizumab is a cost-effective adjuvant treatment.

Scenario Analyses and Deterministic Sensitivity Analysis

To assess the robustness of the model results, scenario analyses and DSA were conducted by varying one model input or assumption at a time. The inputs and settings varied in the scenario analyses are reported in Table S6 of Appendix 3 (see Supplementary Material), along with the base-case inputs and settings, accompanied by the resulting ICERs.

Across the scenario analyses, the incremental cost per QALY for pembrolizumab versus watchful waiting ranged from COP 10,406,890 to COP 65,285,578. The scenario that explored parametric models with a time-varying treatment effect with Weibull and Gompertz distribution used to model the transitions RF → LR and RF → DM for both adjuvant pembrolizumab and watchful waiting resulted in the lowest ICER per QALY. The highest ICER value was obtained when the transitions RF → LR and RF → DM were modeled using Gompertz distribution, fitted individually to adjuvant pembrolizumab, and watchful waiting.

The DSA results are reported in Table S7 of Appendix 3 (see the Supplementary Material) and are presented graphically in a tornado diagram (Fig. 3). The sensitivity analyses presented in the tornado diagrams were sorted in the decreasing order of range (widest to the narrowest) of ICER values to highlight parameters with the strongest influence on the cost-effectiveness results. Within the DSA, the ICER was observed to be the most sensitive to the utility associated with the RF state, with ICERs ranging from COP 41,786,793 to COP 53,913,739 per QALY for pembrolizumab versus watchful waiting when varying the utility by 10%. The three most impactful parameters affecting the ICER were the utility associated with the RF state, the patients' mean weight, and the exponential rates of OS and PFS failure with

treatments for advanced melanoma. The ICERs obtained for all the scenario analyses, and the DSA were within the WTP threshold for Colombia.

Probabilistic Sensitivity Analysis

Table S8 of Appendix 3 (see Supplementary Material) reports the PSA results, and Fig. 4 presents scatterplots of the simulated incremental cost and QALY pairs for pembrolizumab versus watchful waiting. Across the 1000 iterations of the PSA, the average incremental cost was COP 102,962,328, and the average incremental QALY gain was 2.042 for pembrolizumab versus watchful waiting. The resulting probabilistic ICER per QALY for pembrolizumab versus watchful waiting was COP 50,423,958 and was within Colombia's WTP threshold of COP 69,150,201 per QALY. Based on the 1000 replicates shown in Fig. 4, pembrolizumab had a 65.70% probability of being cost-effective versus watchful waiting.

DISCUSSION

Over a lifetime model horizon, adjuvant pembrolizumab in Colombia following complete resection of stage III melanoma with lymph node involvement is expected to yield substantial improvements in QALYs and LYs. Therefore, pembrolizumab was cost-effective compared to watchful waiting with an ICER below the WTP threshold of Colombia (COP 69,150,201 per QALY) [22, 23]. Adjuvant treatment with pembrolizumab is predicted to incur lower costs in the DM state (COP 335,345,955 vs. COP 465,310,147) and increased survival and QALYs in the overall analysis compared to the watchful waiting. By delaying recurrence, pembrolizumab is expected to result in approximately 2 additional LYs and to provide about 2 additional QALYs per treated patient for a reasonable incremental cost. The proportion of total LYs spent without recurrence was superior for pembrolizumab (84.63% in the adjuvant pembrolizumab compared with 72.13% for watchful waiting), yielding lower costs in the advanced setting and savings in total costs of subsequent treatments, disease management, and terminal care compared to watchful waiting. Results from the DSA and PSA supported the base-case findings.

Even though published literature assessing pembrolizumab's cost-effectiveness as an adjuvant melanoma treatment is available for the United States (US), and other Latin American countries, such as Argentina, none was available for Colombia [40, 41]. Therefore, we evaluated the cost-effectiveness of pembrolizumab from the perspective of a Colombian healthcare payer for the adjuvant treatment of melanoma patients with lymph node involvement who have undergone complete resection, using newer evidence (i.e., KEYNOTE-054 IA2), and for inputs specific to Colombia, such as patient weight, drug costs, monitoring costs, market shares and life tables [18, 20]. The cost-effectiveness of adjuvant treatment with pembrolizumab in Colombia aligns with the conclusions from similar studies conducted in the US and Argentina. However, the LYs gained with adjuvant pembrolizumab treatment in Colombia (2.18) were less than those for the US (3.39) and Argentina (2.94). This difference in the LYs is likely due to the different advanced treatment options available in each country and the overall higher mortality rates reported in Colombia, which could be attributed to differences in the healthcare resources between countries [28, 42, 43].

Additionally, the US and Argentina analyses were performed using the first interim analysis (IA1) outcomes, which consisted of only the RFS data from the KEYNOTE-054 trial with a 15-month median follow-up [44]. In contrast, the Colombian analysis was based on the updated RFS and DMFS evidence from the second interim analysis (IA2) of the KEYNOTE-054 trial (with more than 3 years of follow-up data) to support decision-makers' recommendations about financing cancer treatments involving pembrolizumab through economic evidence.

The economic evaluation is based on a well-established Markov modeling approach that has been commonly used in published cost-effectiveness analyses of adjuvant therapies for melanoma and prior health technology

appraisals of adjuvant/neoadjuvant therapies in other oncology indications [40, 41].

The clinical inputs were obtained from KEYNOTE-054 IA2, representing a 42.3-month median follow-up (compared to the 15-month median follow-up in IA1). The inclusion of longer-term RFS data, as well as the DMFS data, helped in addressing the uncertainty surrounding the long-term survival extrapolations in the model. Additionally, the ToT in the adjuvant pembrolizumab arm was precisely estimated based on observed KM data from the KEYNOTE-054 trial and did not require extrapolation.

To verify the results of the cost-effectiveness model, internal quality control procedures were undertaken by the model developers to ensure that the mathematical calculations were performed correctly and were consistent with the model specifications. The model's validity was assessed by comparing modeled efficacy outcomes against the sources that informed the efficacy inputs. In particular, the RFS and DMFS curves predicted for the pembrolizumab and the watchful waiting arms were plotted alongside the observed KM curves for RFS and DMFS to ensure that the curves were well-aligned during the trial period of the KEYNOTE-054 trial. External validations of pembrolizumab's survival projections and feedback from two clinical experts were also considered to support the plausibility of the base-case survival projections for watchful waiting (Appendix 2 in Supplementary Material).

As with any pharmacoeconomic evaluation, this model is subject to some limitations which need to be acknowledged. First, due to the memoryless property of Markov models, it was not feasible to track the length of time spent in intermediate health states (i.e., LR and DM). To address this limitation, the transition probabilities starting from these two health states were therefore modeled using constant exponential rates that did not vary as a function of time spent in these states. Additionally, the KEYNOTE-054 trial could not inform OS data because the secondary endpoint of OS was not part of the pre-specified IA2, so it was assumed that adjuvant pembrolizumab would have no ongoing therapeutic benefit post-disease recurrence. The analysis was based on a Colombian payer perspective, and only the direct medical care costs were considered. Including a societal perspective by considering the indirect costs, such as productivity loss, could strengthen the cost-effectiveness analysis of adjuvant pembrolizumab. The base-case utility of post-progression DM was extracted from Beusterin et al. (a UK-based report) instead of a Colombian source, and the population representativeness from Colombia in the KEYNOTE-054 trial may be low and thus affect the generalizability of the results [32]. To address this limitation, Latin American data related to the quality of life for pre-progression states and AE-related disutility, as well as Colombian-specific epidemiological and cost data, were included in the model. Even though newer drugs have been approved for the adjuvant treatment of melanoma in Colombia, the model used watchful waiting as the base-case comparator. The rationale for using watchful waiting to compare with pembrolizumab is that access to these newer therapies in clinical practice is limited. Watchful waiting was the only comparator with direct, head-to-head evidence versus pembrolizumab from the KEYNOTE-054 trial. Thus, while emerging evidence supports the effectiveness of the new adjuvant treatment options, we evaluated the cost-effectiveness of the most widely used comparator, watchful waiting compared to pembrolizumab, to demonstrate that adjuvant pembrolizumab treatment for melanoma is a worthwhile and long-term choice for Colombia's healthcare system.

Economic evaluations are a key tool to choose how the resources of the healthcare system in Colombia should be allocated, given their scarcity and the high costs associated with the new health technologies, which are, therefore, a threat to the system's financial sustainability. This study has very important implications for health financing and clinical practice as pembrolizumab proves to be the first cost-effective immunotherapy in Colombia. This is crucial for both the decision-makers and clinicians to be able to provide an effective treatment for patients with stage III melanoma with lymph node involvement aligned with the WTP threshold in the country.

CONCLUSIONS

From the perspective of a Colombian healthcare payer, pembrolizumab represents a clinically- and cost-effective adjuvant treatment with an ICER below the WTP threshold. Patients receiving pembrolizumab in the adjuvant setting are projected to experience fewer recurrences and incur fewer costs in the LR and DM health states relative to watchful waiting. Adjuvant treatment with pembrolizumab results in an incremental gain in LYs and QALYs because fewer patients treated with pembrolizumab progressed to the DM state compared to watchful waiting. The cost-effectiveness of pembrolizumab was robust in probabilistic simulations and across various alternative scenarios and parameter values.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to its proprietary nature. Further information about the data and conditions for access can be obtained from the corresponding author.

REFERENCES

1. Gray-Schopfer V, Wellbrock C, Marais R. Melanoma biology and new targeted therapy. Nature. 2007;445:851–7.

2. Loria D, Abriata M, Santoro F, Latorre C. Cutaneous melanoma in Argentina: an analysis of its characteristics and regional differences. eCancer Med Sci. 2020;1017:14.

3. Global Cancer Observatory. Globocan 2020, World factsheet. https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf.

4. Karimkhani C, Green A, Nijsten T, et al. The global burden of melanoma: Results from the Global Burden of Disease Study 2015. Br J Dermatol. 2017;177(1):134–40.

5. Global Cancer Observatory. Globocan 2020, Colombia Factsheet. https://gco.iarc.fr/today/data/factsheets/populations/170-colombia-fact-sheets.pdf.

6. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline—Update 2016. Eur J Cancer. 2016;63:201–17.

7. National Comprehensive Cancer Network (NCCN) Melanoma. NCCN clinical practice guidelines in oncology. Version 2. 2018. https://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf.

8. Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group: Clinical study reportEORTC protocol 1325-MG/KEYNOTE-054. https://clinicaltrials.gov/ct2/show/record/NCT02362594.

9. Opdivo (nivolumab): Highlights of Prescribing Information. Initial U.S. Approval: Bristol-Myers Squibb Company. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125554s099lbl.pdf.

10. Yervoy (ipilimumab): Highlights of Prescribing Information. Initial U.S. Approval: Bristol-Myers Squibb Company. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s115lbl.pdf.

11. Keytruda: EPAR—Product Information. https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf.

12. Keytruda (pembrolizumab): Highlights of Prescribing Information. Initial U.S. Approval: Merck Sharp & Dohme Corp. 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s105lbl.pdf.

13. Cotellic (cobimetinib): Highlights of Prescribing Information. Initial U.S. Approval: Genentech. 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206192s002lbl.pdf.

14. Zelboraf (vemurafenib): Highlights of Prescribing Information. Initial U.S. Approval: Genentech. 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202429s009lbl.pdf.

15. Mekinist (Trametinib): Highlights of Prescribing Information. Initial U.S. Approval: Novartis. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204114s007lbl.pdf.

16. Tafinlar (Dabrafenib): Highlights of Prescribing Information. Initial U.S. Approval: Novartis. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202806s008lbl.pdf.

17. National Institute for Food and Drug Surveillance (INVIMA). Product Data. https://consultaregistro.invima.gov.co/Consultas/consultas/consreg_encabcum.jsp.

18. Eggermont A, Blank C, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): Distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. Lancet Oncol. 2021;22(5):643–54.

19. Ministry of Health and Social Protection (Minsalud). National Survey of the Nutritional Situation in Colombia (ENSIN). 2015. https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/ED/GCFI/libro-ensin-2015.pdf.

20. Institute for Health Technology Assessment (IETS). Handbook Methodological for Assessment of Heath Techonologies. https://www.iets.org.co/.

21. Bank of The Republic—Colombia. Consumer Price Index. 2021. https://www.banrep.gov.co/es/estadisticas/indice-precios-consumidor-ipc.

22. World Health Organisation (WHO). Guide to Cost-effectiveness Analysis. 2003. http://apps.who.int/iris/bitstream/handle/10665/42699/9241546018.pdf?sequence=1.

23. National Administrative Department of Statistics (DANE). Quarterly National Gross Domestic Product—GDP. Main Results for Fourth Quarter of 2021. 2022 February 15. https://www.dane.gov.co/files/investigaciones/boletines/pib/presen_rueda_de_prensa_PIB_IVtrim21.pdf.

24. Schachter J, Ribas A, Long G, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017;390(10105):1853–62.

25. Williams C, Lewsey J, Briggs A, Mackay D. Cost-effectiveness analysis in R using a multi-state modeling survival analysis framework: a tutorial. Med Decis Making. 2017;37(4):340–52.

26. Williams C, Lewsey J, Mackay D, Briggs A. Estimation of survival probabilities for use in cost-effectiveness analyses: a comparison of a multi-state modeling survival analysis approach with partitioned survival and markov decision-analytic modeling. Med Decis Making. 2017;37(4):427–39.

27. National Institute for Health and Care Excellence. DSU Technical Support Document 19: Partitioned survival analysis for decision modelling in health care: a critical review. 2017 June 2. http://nicedsu.org.uk/technical-support-documents/partitioned-survival-analysis-tsd/.

28. United Nations (UN). Department of Economic and Social Affairs Population Division. World Population Prospects. 2022. https://population.un.org/wpp/Download/Standard/Mortality/.

29. Hinchliffe S, Lambert P. Flexible parametric modelling of cause-specific hazards to estimate cumulative incidence functions. BMC Med Res Methodol. 2013;13:13.

30. Flatiron Health Database2018. http://www.flatiron.com/real-world-evidence.

31. Augustovski F, Irazola V, Velazquez A, Gibbons L, Craig B. Argentine valuation of the EQ-5D health states. Value Health. 2009;12(4):587–96.

32. Beusterien K, Szabo S, Kotapati S, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. Br J Cancer. 2009;101(3):387–9.

33. Drug and Medical Device Price Information System (SISMED). Drug Cost Database2021. https://web.sispro.gov.co/WebPublico/Consultas/ConsultarCNPMCadenaComercializacionCircu2yPA_028_2_2.aspx.

34. Ministry of Health and Social Protection of Colombia (Minsalud). Medicines regulation prices. 2021. https://www.minsalud.gov.co/salud/MT/Paginas/medicamentos-regulacion-precios.aspx.

35. Social Security Institute (ISS). Tariff Manual. 2001. https://lexsaludcolombia.files.wordpress.com/2010/10/tarifas-iss-2001.pdf.

36. National Institute for Health and Care Excellence (NICE). Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma [TA319]. 2014.

37. National Institute for Health and Care Excellence. NICE Pathway: Melanoma. https://pathways.nice.org.uk/pathways/melanoma#path=view%3A/pathways/melanoma/managing-melanoma.xml&content=view-index.

38. Federation of Colombian Insurers (SOAT). Tariff Manual. https://fasecolda.com/cms/wp-content/uploads/2021/01/Manual-tarifario-2021.pdf.

39. Prada S, Contreras J. Last-year-of-life expenditure of patients diagnosed with cancer. Colomb J Cancerol. 2018;22(1):3–7.

40. Bensimon A, Zhou Z, Jenkins M, et al. Cost-effectiveness of pembrolizumab for the adjuvant treatment of resected high-risk stage III melanoma in the United States. J Med Econ. 2019;22(10):981–93.

41. Wurcel V, Scherrer E, Aguiar-Ibanez R, et al. Cost-effectiveness of pembrolizumab for the adjuvant treatment of melanoma patients with lymph node involvement who have undergone complete resection in Argentina. Oncol Ther. 2021;9(1):167–85.

42. National Center for Health Statistics. National Vital Statistics Report. https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_04.pdf.

43. National Institute of Statistics and Censuses (INDEC). Abbreviated tables of mortality by sex and age 2008–2010. Total for the country and provinces. Demographic Analysis Series No 372013.

44. Eggermont A, Blank C, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med. 2018;378(19):1789–801.