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

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Supplementary Materials

APPENDIX 1. PATIENT CHARACTERISTICS

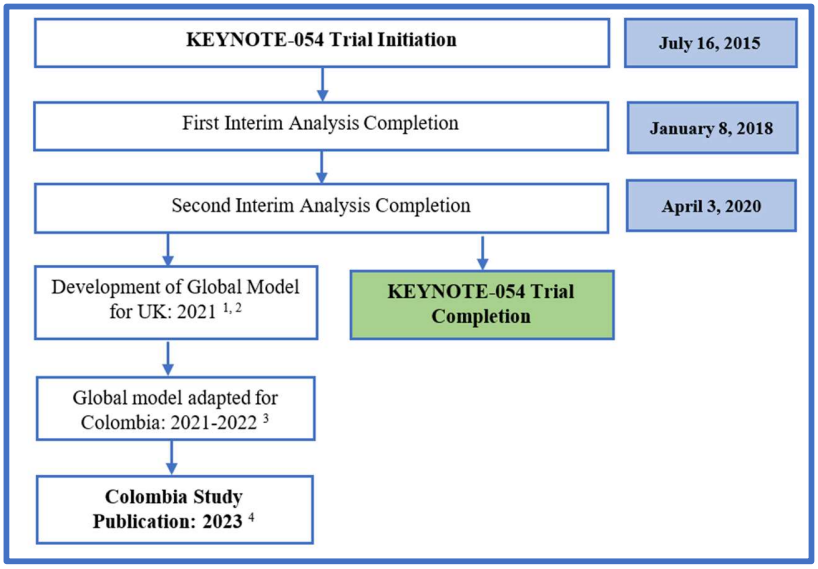
The age and gender distribution of the model cohort were based on the reported characteristics of the KEYNOTE-054 trial population.[1] The KEYNOTE-054 trial also provided information on the proportion of BRAF-positive (BRAF+) patients, a factor used to calculate market shares of subsequent therapies for advanced melanoma. The KEYNOTE-054 trial was conducted internationally and involved patients from North America, Europe, Australia/ New Zealand, and other regions (representing less than 5% of the participants). Therefore, to adapt the economic model to Colombia, the mean body weight for Colombian patients was based on information from the National Survey of Nutritional Situation (ENSIN).[2] The patient weight inputs were used within the model to compute the required dosage of weight-based treatment options in the advanced melanoma setting. Table S1 summarizes the patient characteristics considered in the model along with the corresponding data sources. Figure S1 presents the process followed from the initiation of the KEYNOTE-054 trial till the publication of this study.

Table S1. Patient Characteristics

Characteristics	Value	Source
Median age (years)	54.0	KEYNOTE-054[1] (Sample size = 1,019 with 514 patients for pembrolizumab and 505 patients for watchful waiting)
Percent female	38.4%	
Percent BRAF+	49.8%	
Weight (kg), mean (standard deviation)	65.4 (12.8)[1]	ENSIN [2]

Abbreviations: ENSIN, National Survey of Nutritional Situation; kg, Kilogram.
Note:
(1) The standard deviation of patient weight was based on the proportion of the standard deviation and mean patient weight characteristics from the KEYNOTE-006 trial, applied to mean Colombian weight.[3]

Figure S1. Flow Diagram of the Study Process



Abbreviations: UK, United Kingdom.
Notes: The process followed to develop the cost-effectiveness study for Colombia:
(1) Decision on the model structure
(2) Inclusion of model inputs from KEYNOTE-054 trial, network meta-analysis of advanced melanoma and real world evidence wherever appropriate
(3) Adaptation of model based on Colombia local data and context; including discussions with local scientific leaders
(4) Analyses of main results and sensitivity analyses for Colombia

APPENDIX 2. TRANSITIONS PROBABILITIES

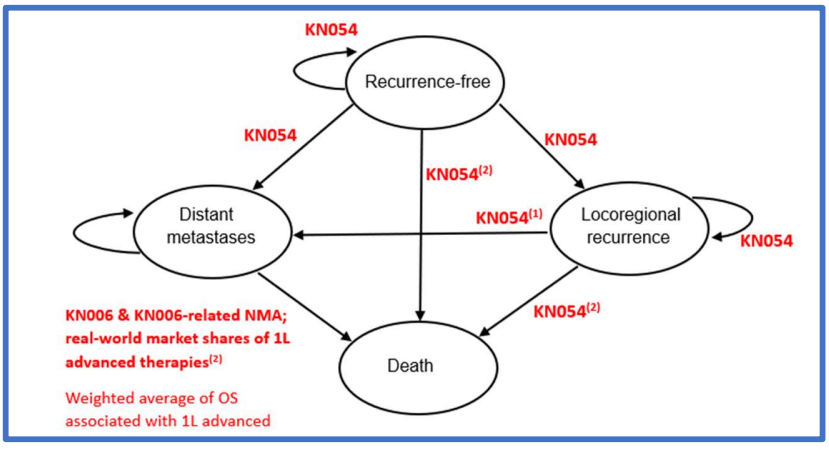
The transition probabilities were calculated using primary analyses of patient-level data from the KEYNOTE-054 trial, a systematic literature review, a network meta-analysis (NMA) comparing pembrolizumab's effectiveness in KEYNOTE-006 to that of other advanced melanoma treatments, and a targeted literature search for pertinent clinical inputs that could not be estimated using trial data. [1, 3] The state transition diagram in Figure S2 serves as an illustration of the set of permissible transitions, and Table S2 summarizes the corresponding data sources.

Table S2. Summary of Health State transitions Considered in the Economic Model

Transition(s)	Estimation Approach	Data Source(s)
RF → LR RF → DM RF → Death(1)	▪ Based on a parametric multistate modeling approach in which different parametric functions were fitted to each of the three individual transitions starting from RF, accounting for competing risks ▪ In the base case, separate parametric models were fitted for each treatment arm of KEYNOTE-054	▪ Patient-level data from KEYNOTE-054 ▪ Life tables for Colombia - *for transitions to death [4]*
LR → DM LR → Death(1)	▪ Transition probabilities starting from LR were estimated using exponential distributions separately fitted for each treatment arm of KEYNOTE-054	▪ Patient-level data from KEYNOTE-054 ▪ Life tables for Colombia - *for transitions to death [4]*
DM → Death(1)	▪ In each adjuvant treatment arm, the transition probability from DM to death was estimated based on the expected mix of subsequent treatments for advanced melanoma, and the efficacy of these subsequent treatments in terms of mean OS	▪ Patient-level OS and PFS data for pembrolizumab 2 mg/kg in KEYNOTE-006 ▪ NMA comparing treatments for advanced melanoma in terms of OS and PFS ▪ Life tables for Colombia - *for transitions to death* [4]

Abbreviations: DM, distant metastases; LR, locoregional recurrence; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RF, recurrence-free.
Notes:
(1) Transition probabilities to death were constrained to be at least as high as all-cause mortality, as estimated from life tables given the age and gender distribution of the cohort at each cycle.

Figure S2. Model schematic with a Summary of sources Used to Inform Transition Probabilities



Abbreviations: 1L, first-line; KN006, KEYNOTE-006; KN054, KEYNOTE-054; NMA, Network Meta-Analysis; OS, overall survival.
Notes:
[1] In a scenario analysis, the transition probability from locoregional recurrence to distant metastases was instead informed by real-world evidence from the Flatiron database.[5]
[2] All transition probabilities to death were constrained to be at least as high as all-cause mortality, as estimated from the Colombian mortality rates from World Population Prospects 2022 from the UN database, given the age and gender distribution of the cohort at each cycle.[4]

Transitions from RF to LR, DM, or death

The three transitions starting from the recurrence-free (RF) state were fitted using a parametric multistate modeling approach to estimate the transition probabilities.[6], [7] Cause-specific hazards of transitions for the pembrolizumab and watchful waiting were estimated based on parametric models fitted separately to data from the pembrolizumab and placebo arms of the KEYNOTE-054 trial, respectively.[1] Within each weekly cycle, the probability of each transition (and the composite probability of any recurrence-free survival [RFS] failure event) was calculated as a function of all three cause-specific hazards.

Standard survival analysis methods were used to fit parametric models to each of the three individual health state transitions with one modification to account for competing risks: while analyzing time to each specific type of RFS failure (either type of recurrence or death), the two competing failure types were treated as censoring events.[8, 9]

Estimation of cause-specific hazards for each individual transition starting from the recurrence-free state

In each treatment arm, transitions from RF to locoregional recurrence (LR) and from RF to distant metastases (DM) were modelled using six distinct parametric functions, including the exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma distributions. Due to the low number of direct transitions from RF to death observed in the KEYNOTE-054 study, exponential models were fitted to the transition from RF to death in each treatment arm.[10] Parameter estimates associated with all parametric models are presented in Table S3. In order to select base-case parametric functions, all thirty-six possible combinations of parametric functions for RF→LR and RF→DM were considered.

Table S3. Parametric Models for Transitions starting from the Recurrence-free State, Separately Fitted to Each Arm of the KEYNOTE-054 Trial

Distribution	Parameter	Parameter Estimates for Pembrolizumab			Parameter Estimates for Watchful Waiting (i.e., Placebo)		
		RF → LR	RF → DM	RF → Death	RF → LR	RF → DM	RF → Death
Exponential	Rate	0.0011	0.0019	0.0001	0.0020	0.0035	0.00002
Weibull	Shape	0.5515	0.6495	-	0.5996	0.6940	-
	Scale	3978.7	1057.4	-	1198.2	391.16	-
Log-normal	Log mean	8.5676	6.9377	-	6.8879	5.5748	-
	Log standard deviation	3.4803	2.8093	-	2.8333	2.2648	-
Log-logistic	Shape	0.5791	0.7019	-	0.6550	0.8116	-
	Scale	2887.4	731.27	-	768.15	230.82	-
Gompertz	Shape	-0.0159	-0.0091	-	-0.0182	-0.0126	-
	Rate	0.0030	0.0036	-	0.0057	0.0079	-
Generalized gamma	Mu	8.1178	6.9865	-	6.2939	5.6795	-
	Sigma	4.8581	2.1727	-	3.6677	2.0669	-
	Q	-0.9719	0.4753	-	-0.9301	0.2304	-

Abbreviations: DM, distant metastases; LR, locoregional recurrence; RF, recurrence-free.

Selection of Base-case Parametric Functions

According to the NICE Decision Support Unit (DSU) Technical Support Document (TSD), evaluating model fit is more difficult for multistate models than for partitioned survival models because the target outcomes of interest (such as the proportions of people who experience the composite endpoint) are determined by a combination of survival models rather than by a single survival model.[8]

Therefore, all the 36 feasible combinations of parametric functions for RF→LR and RF→DM were taken into account while selecting the base case parametric functions. In accordance with recommendations in the NICE DSU TSD 14, the base case parametric functions were selected such that the same functional form was used to model each health state transition in both the pembrolizumab and watchful waiting arms.[11] The rationale for this approach was to prevent the extrapolated portion of the RFS curves from following significantly divergent trajectories for the two model arms. Base case parametric functions were chosen based on the following criteria:

1. Fit based on mean squared error (MSE) versus observed RFS: Akaike information criterion (AIC), a fit statistic commonly used in partitioned survival models, is not a suitable measure of fit with observed data when modelling competing risks.[6] This is due to the fact that transition probabilities in the context of competing risks are decided by the cause-specific hazards of all competing events, rather than just by the

cause-specific hazards of a single event. As a result, the AICs associated with various parametric distributions for the cause-specific hazards of a certain event do not provide sufficient information to evaluate fit. MSE was therefore used as an alternative diagnostic test to assess fit of the predicted RFS curve vs. the observed KM curve during the within-trial period in each treatment arm.

2. Fit based on MSE versus observed DMFS: The secondary endpoint of DMFS was evaluated as part of the second interim analysis (IA2) of KEYNOTE-054. The MSE of the predicted DMFS curve vs. the observed DMFS KM curve was therefore also assessed for different combinations of parametric functions for RF→LR and RF→DM. (Of note, predicted RFS in the Markov model depends only upon the transition probabilities starting from the RF state, while predicted DMFS also depends upon the transition probabilities starting from the LR state)
3. Visual assessment of fit: Predictions generated by different combinations of parametric functions were also visually verified against the observed data in each treatment arm, following the approach used by William et al. (2017).[6] Specifically, predicted vs. observed cumulative incidence (CI) curves were plotted for both RF→LR and RF→DM.
4. Plausibility of long-term extrapolations: External data from the European Organisation For Research And Treatment Of Cancer (EORTC) 18071 trial were used to assess the appropriateness of different possible combinations of parametric functions in the watchful waiting arm. EORTC 18071 was a phase 3 trial comparing adjuvant ipilimumab vs. placebo in patients with resected stage III melanoma.[12, 13] Observed RFS, DMFS, and overall survival (OS) at 7 years in the placebo arm of this trial were respectively compared with predicted RFS, DMFS, and OS at 7 years in the watchful waiting arm of the model. (Predicted DMFS is a function of transition probabilities starting from the recurrence-free and locoregional recurrence states, while predicted OS is a function of all transition probabilities in the model.) Ten-year OS projections in the watchful waiting arm were also externally validated against the composite stage III OS curve presented in the Evidence Review Group (ERG) report for TA553.[14] Using digitized OS curves by the American Joint Committee on Cancer (AJCC) 7th Edition stage from the 2010 Surveillance, Epidemiology, and End Results (SEER) database, the ERG generated a composite stage III OS curve as a weighted average of the stage IIIA, IIIB, and IIIC OS curves based on the proportions of patients in each of these stages in KEYNOTE-054.[15]

Because longer-term empirical data were not available for adjuvant pembrolizumab, the plausibility of long-term extrapolations in the pembrolizumab arm was assessed based on clinical expert opinion and based on OS data for adjuvant nivolumab in the CheckMate 238 trial.[16]

Based on these results, the generalized gamma function for RF→LR and Gompertz function for RF→DM appeared to provide the best balance between goodness-of-fit with observed data and plausible long-term extrapolations in each treatment arm, as explained below:

Fit statistics: Among all thirty six possible combinations of parametric functions, the generalized gamma / Gompertz combination was ranked second in the watchful waiting arm in terms of both MSE versus observed RFS and MSE versus observed DMFS. In the pembrolizumab arm, most combinations of parametric functions (including generalized gamma / Gompertz) yielded comparably low MSEs relative to observed RFS and DMFS; the choice of base-case parametric distributions therefore prioritized fit within the watchful waiting arm and clinical plausibility in both arms.

Visual assessment of fit: Visual assessment also supported the choice of generalized gamma and Gompertz as the base case parametric functions for RF→LR and RF→DM, respectively. In the pembrolizumab arm, combinations of parametric functions that used generalized gamma or Gompertz for RF→LR appeared to achieve the best fit with the observed CI of RF→LR, although close fits were also achieved with other combinations of functions that used log-normal, log-logistic, or Weibull for RF→LR. In the watchful waiting arm, certain combinations of parametric functions that used either Gompertz or generalized gamma for RF→LR yielded a close visual fit with the observed CI of RF→LR. The Figure S3 presents the predicted and observed CIs of transitions from the RF state under the base case parametric distributions.

The base-case analysis therefore modeled the cause-specific hazards in each treatment arm using: generalized gamma for RF→LR; Gompertz for RF→DM; and exponential for RF → death.

External validations of survival projections for watchful waiting: Base-case predictions of RFS, DMFS, and OS at 7 years in the watchful waiting arm (i.e., 33.1%, 35.8%, and 49.6%, respectively) were comparable to the reported 7-year RFS (30.9%; 95% confidence interval [CI]: 26.7-35.2), DMFS (36.9%; 95% CI: 32.4-41.4), and OS (51.3%; 95% CI: 46.5-55.9) in the placebo arm of the EORTC 18071 trial.[13] Base-case predictions of OS in the watchful waiting arm at 1, 2, and 3 years (95.0%, 86.2%, and 77.0%) were also comparable to the reported OS for the placebo arm of

the COMBI-AD trial at these time points (94%, 83%, and 77%).[17] At 10 years, predicted OS was 40.4% for watchful waiting, which closely aligned with 10-year OS according to the composite stage III OS curve presented in the TA553 ERG report (~39.8%).[14] Figure S4 presents the predicted OS curve for watchful waiting alongside the digitized KM OS curves from the EORTC 18071 trial and the ERG report. As shown, the cost-effectiveness model predicted higher OS for watchful waiting relative to both of these external sources during the first 7 to 8 years, which is expected given the crossover protocol of KEYNOTE-054 and recent advances in the treatment of advanced melanoma. The predicted OS curve closely aligned with the ERG curve between 8 and 10 years but crossed the EORTC 18071 curve starting from ~7 years; the latter result may be due to the small numbers of patients at risk at the tail of the EORTC 18071 curve (i.e., 63 patients at 8 years, 9 patients at 9 years).[13]

Feedback from two clinical experts also supported the plausibility of the base-case survival projections for watchful waiting. Clinician A noted that 40% of patients in the target population are expected to survive to the 10-year timepoint without adjuvant therapy; under the base-case parametric distributions, 10-year OS was predicted to be 40.4% under the watchful waiting strategy. Clinician A favored the Gompertz/Gompertz combination of distributions as providing the most plausible extrapolation of OS for watchful waiting, while Clinician B favored the Gompertz/log-normal combination. The base-case combination of distributions (generalized gamma/Gompertz) yielded OS predictions for watchful waiting that were in-between the OS predictions from the Gompertz/Gompertz and Gompertz/log-normal combinations (the latter two combinations of distributions were each tested in scenario analyses).

External validations of survival projections for pembrolizumab: Figure S5 presents the predicted OS curve for adjuvant pembrolizumab alongside the digitized OS curve for adjuvant nivolumab in the CheckMate 238 trial.[16] External OS data for adjuvant nivolumab in CheckMate 238 supported the plausibility of OS extrapolations for pembrolizumab under the base-case parametric functions. As shown, predicted OS for pembrolizumab was slightly above observed OS for nivolumab before crossing nivolumab OS at ~4 years. Given differences in the disease stages of patients in KEYNOTE-054 (completely resected stage IIIA [>1 mm], IIIB and IIIC) versus CheckMate 238 (completely resected stage IIIB, IIIC, or IV), base-case OS predictions for pembrolizumab were considered reasonable if not conservative when using nivolumab OS from CheckMate 238 as a benchmark.

During consultations with clinical experts, the base-case combination of distributions (generalized gamma/Gompertz) was one of three combinations highlighted by Clinician B as yielding plausible long-term OS projections for

pembrolizumab. (The other two combinations cited by Clinician B were Gompertz/Gompertz and log-normal/Gompertz, with the latter being the most plausible for pembrolizumab. Both of these combinations were tested in scenario analyses.)

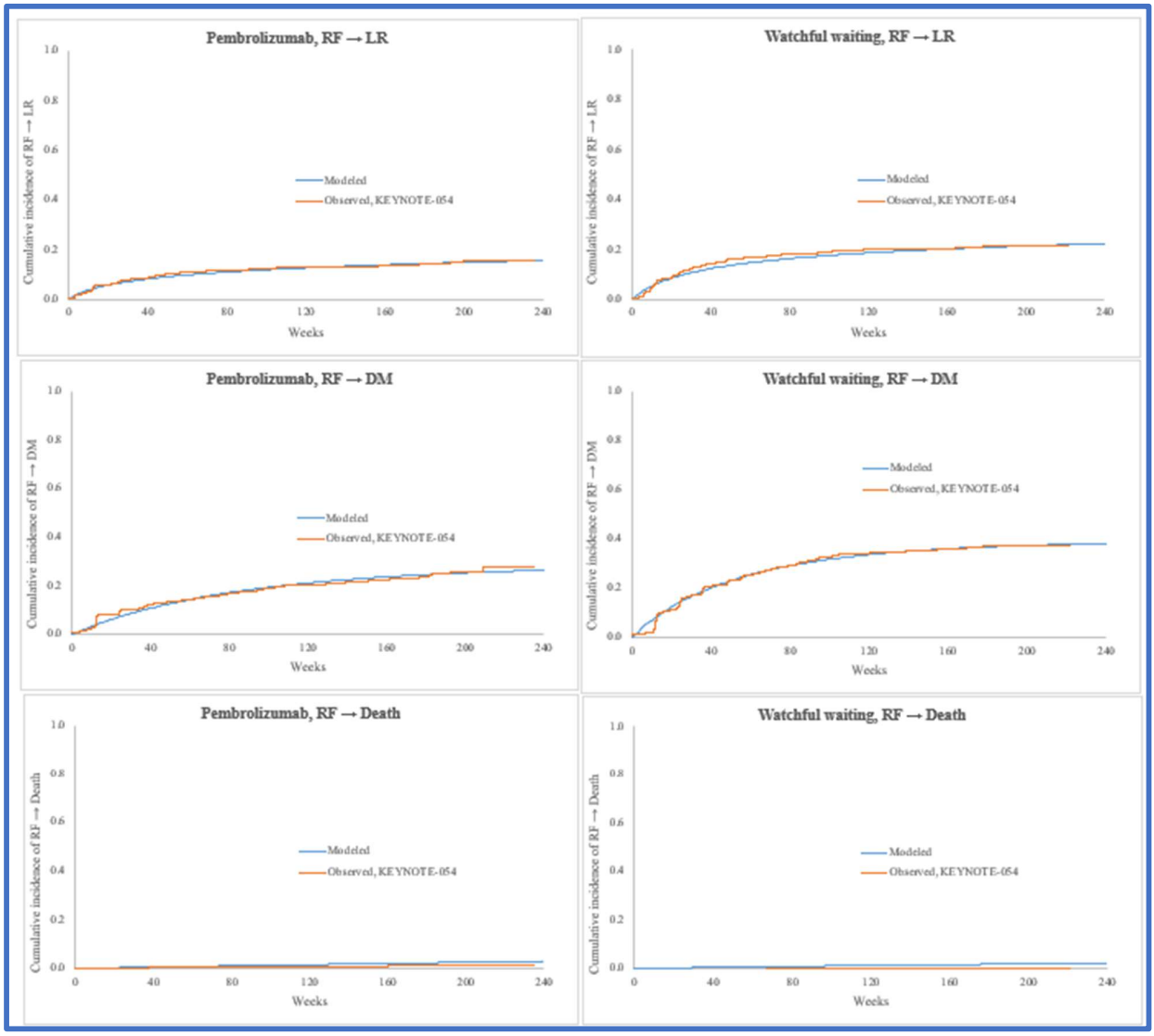
The Table S4 presents the list of external sources used to compare the projections of RFS, DMFS and OS.

Table S4. Sources Used to Validate Modelled Survival Projections

Source	Description	Used to Validate:
EORTC 18071 [12, 13]	Phase III comparing adjuvant ipilimumab vs. placebo in patients with resected stage III melanoma. Data available up to 7 years.	RFS, DMFS and OS projections for watchful waiting
CheckMate 238 [16]	Phase III trial comparing adjuvant nivolumab vs adjuvant ipilimumab in patients with resected stage III melanoma. Data available up to 4 years.	RFS, DMFS and OS projections for pembrolizumab
COMBI-AD [18, 19]	Phase III trial comparing adjuvant dabrafenib + trametinib vs vemurafenib in patients with BRAF V600 mutation positive stage III melanoma. Data available up to 3 years.	RFS, DMFS and OS projections for watchful waiting
TA553 original ERG report [14]	Composite curve of 10-year OS for patients with stage III melanoma, produced by ERG in review of original company submission. Based on data from 2010 SEER database by disease stage, weighted by the percentage of patients for each disease stage in KEYNOTE-054. MSD have been unable to replicate the original source data, but a digitized version of the curve from the ERG's report has been used.	OS projections for watchful waiting
SEER 2000-2017 [15]	Real world data reported by NCI SEER Program. Survival rates by time since diagnosis (2000-2017), weighted by proportion of males and females in KEYNOTE-054. Data available up to 10 years.	OS projections for watchful waiting
AJCC v8 (Gershenwald et al, 2017) [20]	Real world data on melanoma-specific survival by stage III subgroups (based on AJCC 8th edition cancer staging), weighted by staging distribution in KEYNOTE-054. Data available up to 10 years.	OS projections for watchful waiting

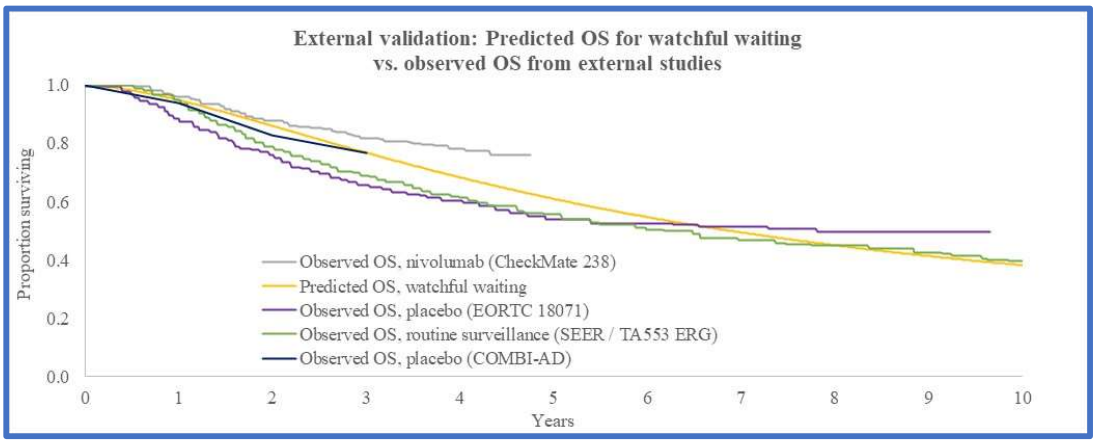
Abbreviations: AJCC, American Joint Committee on Cancer; DMFS, distant metastasis free survival; EORTC, European Organisation For Research And Treatment Of Cancer; ERG, Evidence Review Group; NCI, National Cancer Institute; OS, overall survival; RFS, recurrence free survival; SEER, Surveillance, Epidemiology, and End Results; TA, Technology Appraisal.

Figure S3. Predicted vs. observed Cumulative Incidences of Transitions from the RF State Under the Base case Parametric Distributions



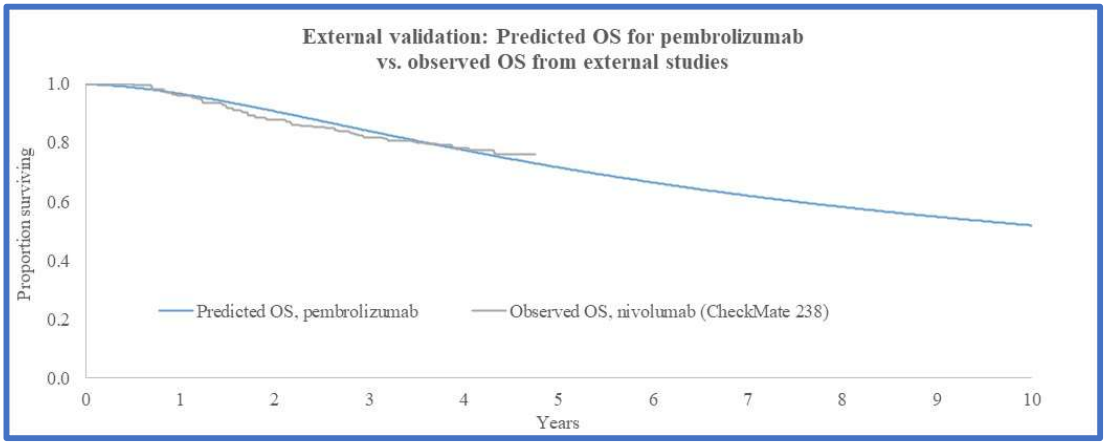
Abbreviations: DM, distant metastases; LR, locoregional recurrence; RF, recurrence-free.

Figure S4. External Validations of Predicted OS in the Watchful Waiting Arm



Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; ERG, Evidence Review Group; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results, TA, Technology Appraisal.

Figure S5. External Validations of Predicted OS in the Pembrolizumab Arm



Abbreviation: OS, overall survival.

Alternative Parametric Modeling Approaches

Alternative parametric distributions for the cause-specific hazards of RF→LR and RF→DM, in the pembrolizumab and watchful waiting arms, were explored in scenario analysis. Table S5 lists the specific combinations of distributions tested in scenario analyses, and the rationale for considering each of these alternative scenarios.

Table S5. Alternative Parametric Distributions Tested in Scenario Analyses

Distributions Used for RF→LR and RF→DM in Scenario Analyses	Rationale for Scenario
Gompertz and Gompertz	In both treatment arms, the Gompertz/Gompertz combination yielded the highest survival projections out of all possible combinations. Long-term OS predictions from this combination were considered by one of the two consulted clinical experts to be overly optimistic for the watchful waiting arm. However, according to both MSE and visual assessment, Gompertz/Gompertz yielded the best fit with observed RFS and DMFS in the watchful waiting arm among all possible combinations of distributions
Gompertz and Log-normal	This combination of distributions was cited by Clinician B as yielding the most plausible long-term extrapolation of OS for watchful waiting, although it was considered too pessimistic by Clinician A. In terms of MSE, this combination was ranked as having the fourth and seventh best fit with observed RFS and DMFS, respectively, in the watchful waiting arm
Log-normal and Gompertz	This combination of distributions was cited by Clinician B as yielding the most plausible long-term extrapolation of OS for pembrolizumab. In terms of MSE, this combination was ranked as having the third and fourth best fit with observed RFS and DMFS, respectively, in the watchful waiting arm
Generalized gamma and Log-normal	In terms of MSE, this combination of distributions yielded the best fit with observed RFS (and the fourth best fit with observed DMFS) in the pembrolizumab arm. Clinician A indicated that the survival predictions from this combination were reasonable if not pessimistic for pembrolizumab. Clinician B considered this combination to be overly pessimistic for pembrolizumab.

Abbreviations: DM, distant metastases; DMFS, distant metastases-free survival; LR, locoregional recurrence; MSE, mean squared error; OS, overall survival; RF, recurrence-free; RFS, recurrence-free survival.

Additionally, the following two proportional hazards modeling approaches were tested as scenario analyses to further explore uncertainty in the estimation of transition probabilities starting from the RF state:

- Proportional hazards models with a time-constant treatment effect: This alternate method used proportional hazards parametric models (exponential, Weibull, or Gompertz) with a time-constant hazard ratio for the pembrolizumab vs. watchful waiting arms to determine cause-specific hazards.
- Proportional hazards models with a time-varying treatment effect: In this alternate strategy, cause-specific hazards in the watchful waiting and pembrolizumab arms were calculated using proportional hazards parametric models that included a time-varying hazard ratio for watchful waiting vs. pembrolizumab. Specifically, a different treatment effect is assumed during vs. after the first year following initiation of adjuvant therapy, given the protocol-defined maximum treatment duration of 1 year. Due to the limited follow-up data available from KEYNOTE-054 trial as of the present data cutoff date, other potential inflection points in the hazard ratio were not taken into account.

Under both approaches, an exponential model with a time-constant treatment effect was used for transitions from RF→ death given the small number of events observed in the KEYNOTE-054 trial. Scenario analyses based on these alternative modeling approaches used Weibull for RF→LR, Gompertz for RF→DM, and exponential for RF→ death.

Transitions from LR to DM, or death

The patient-level time-to-event data for the IA2 of the KEYNOTE-054 trial were used to estimate exponential rates and standard errors for transitions starting from the LR state, and exponential models were fitted for each treatment arm. [10, 21]Only those patients who experienced LR as their first RFS failure event were considered in the sample. Patients in the placebo arm of the KEYNOTE-054 IA2 trial who experienced LR and satisfied all crossover requirements were given the option to switch to pembrolizumab if clinically necessary. The patients in the adjuvant pembrolizumab arm who experienced LR more than 6 months after finishing a year of adjuvant therapy were allowed to rechallenge with pembrolizumab. The estimated transition probabilities included the effect of crossover/rechallenge on the risk of DM or death because no adjustments were made for rechallenge or crossover regimens within the LR state. Given the large proportion of patients in the placebo arm who experienced LR and switched to pembrolizumab, this represented a conservative approach. In contrast, only a small proportion of patients in the pembrolizumab arm received rechallenge among those who had LR.[1]

Transitions from DM to death

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 the adjuvant treatment arms. The cost of second-line therapies for advanced melanoma was considered in the model; however, survival within the DM state was assumed to depend on the choice of first-line therapies only.

Estimation of the Hazard Rate of Death from Distant Metastases by Adjuvant Treatment Arm

Patients transitioning from RF→DM state after 18 months of adjuvant pembrolizumab treatment initiation were eligible to rechallenge with pembrolizumab, and those transitioning less than 18 months were allowed to use other immuno-oncology (IO) therapies in the first-line advanced setting. Patients transitioning from LR→DM state after adjuvant pembrolizumab treatment initiation (at any time point) were eligible to use IO therapies other than pembrolizumab. However, in the case of rechallenge-ineligibility and IO-ineligibility in the DM state, the patients received targeted therapies such as BRAF inhibitors.

For first-line treatment options in the pembrolizumab arm, exponential models of OS and PFS were fitted to patient-level data from the pembrolizumab 10 mg/kg Q3W arm (first-line sub-group only) of the KEYNOTE-006 trial.[3] Hazard ratios (HRs) for OS and PFS vs. pembrolizumab were obtained from an NMA of trials conducted in advanced

melanoma for other advanced treatment regimens.[22-28] The predicted OS in the DM state for both adjuvant treatment arms was computed as a weighted average of the expected OS associated with various first-line advanced melanoma treatment regimens. The weekly risk of DM death was then calculated from the predicted OS. Similarly, the predicted PFS for each adjuvant treatment group was also predicted.

APPENDIX 3. SCENARIO AND SENSITIVITY ANALYSES

Scenario analyses were performed by changing one model input or assumption at a time to evaluate the model outputs' robustness. The Table S6 reports the base case inputs and settings, the resulting ICERs, and the inputs and settings that were altered in the scenario analyses.

DSA is used to assess parameter uncertainty in health economic modeling by varying the base case value of each parameter between the lower and upper bound, then plotting the impact on the outcome (ICER in this case) in a tornado diagram. Therefore, DSA provides useful information regarding which parameters are most influential. The results for the DSA are presented in Table S7.

PSA is a quantitative method to account for the joint impact of uncertainty associated with several model inputs at a time. The point estimate of each input parameter value is considered in the base case analysis, whereas in the PSA, these parameters are represented as distributions around the point estimate, which can be summarized using a few parameters (such as mean and standard deviation for a normal distribution). In general, different distributions are appropriate for various types of variables and are supported, whenever possible, by data from source research. In a PSA, the model is 'run' to produce outputs (cost and health outcome), which are recorded using a set of input parameter values chosen at random from each distribution. This is done repeatedly (usually 1,000–10,000 iterations), producing a distribution of outcomes that may be analyzed by plotting it on the cost–effectiveness plane. The proportion of results that fall favorably (i.e., are deemed cost-effective) in respect to a specific cost-effectiveness threshold is one of a PSA's primary outputs. An acceptability cost-effectiveness curve could be used to illustrate the results of the PSA.

The results obtained from 1,000 Monte Carlo iterations for the PSA are presented in Table S8.

Table S6. Scenario Analysis Results for the Incremental Cost-effectiveness Ratio of Adjuvant Pembrolizumab vs. Watchful Waiting

Scenario	Base-case Setting/ Parameter	ICER (COP/QALY) for Scenario Analyzed
Annual Discount rate (costs, LYs and QALYs)		
2.5%	Annual discount rate for costs and effectiveness: 3.0%	43,429,941
3.5%		50,903,084
5.0%		63,369,605
Distribution used to fit parametric models individually to each treatment arm for RF→LR and RF→DM		
Gompertz and Gompertz	Distribution used for RF→LR and RF→DM: Generalized gamma and Gompertz	65,285,578
Gompertz and Log-normal		38,531,006
Log-normal and Gompertz		39,605,095
Generalized gamma and Log-normal		34,656,190
Transitions from RF state		
Apply treatment effect waning	Do not apply treatment effect waning	56,624,531
Use parametric models with a time-constant treatment effect with distribution used for RF→LR and RF→DM: Weibull and Gompertz for both arms	Use parametric models fitted individually to each treatment arm with distribution used for RF→LR and RF→DM: Generalized gamma and Gompertz	31,924,762
Use parametric models with a time-varying treatment effect with distribution used for RF→LR and RF→DM: Weibull and Gompertz for both arms		10,406,890
Transitions from LR state		
Use estimates from Flatiron	Use KEYNOTE-054 data	46,101,026
Differentiate by timing of LR (<5 vs. ≥5 months)	Do not differentiate by timing of LR (<5 vs. ≥5 months)	52,584,454
Transitions from DM state		
Source for OS and PFS for pembrolizumab in advanced setting: KEYNOTE-006 (Previously untreated subgroup (1L))	KEYNOTE-006 (All-comer population (1L+))	41,566,586
Subsequent therapies for advanced melanoma		
Include costs of first-line advanced regimens only	Include costs of first- and second-line advanced regimens	58,989,244
Drug acquisition and administration costs		
Assume 400 mg Q6W dosing of pembrolizumab	Pembrolizumab dosing schedule of 200 mg IV Q3W	48,374,343
Do not apply relative dose intensity to adjuvant pembrolizumab	Apply relative dose intensity to adjuvant pembrolizumab	47,190,062
Allow vial-sharing	Do not allow vial-sharing	52,681,497
Utilities		
All health state utilities based on KEYNOTE-054 Argentine population (incl. post-progression DM)	KEYNOTE-054 Argentine population for RF, LR and pre-progression DM, and Beusterien et al. (2009) for post-progression DM	48,475,617
All health state utilities based on KEYNOTE-054 (incl. post-progression DM)		51,327,177
Apply age-adjusted disutility	Do not apply age-adjusted disutility	50,357,409
Do not apply AE-related disutility	Apply AE-related disutility	47,046,293

Abbreviations: AE, Adverse Events; COP, Colombian Peso; DM, Distant Metastases; ICER, Incremental Cost-effectiveness Ratio; IV, intravenous; LR, Locoregional Recurrence; LY, Life Year; mg, Milligram; OS, Overall Survival; PFS, Progression-free Survival; QALY, Quality-adjusted Life Year; Q#W, Once every [#] weeks; RF, Recurrence-free; 1L, First-line.

Table S7. Results for the Incremental Cost-effectiveness Ratio of Adjuvant Pembrolizumab vs. Watchful Waiting of the Deterministic Sensitivity Analysis

Parameter Varied	ICER (COP/QALY) for Lower Bound of Input Value	ICER (COP/QALY) for Upper Bound of Input Value
Efficacy and transition probabilities		
Exponential rates of LR→DM +/- 10%	47,639,832	46,624,892
Exponential rates of LR→Death +/- 10%	47,130,295	47,039,561
Exponential rates of OS and PFS failure with treatments for advanced melanoma +/- 10%	43,726,429	49,769,035
Drug administration costs		
Unit administration cost of first hour chemo infusion IV drug +/- 10%	46,990,070	47,173,764
Unit administration cost of additional hour chemo infusion IV drug +/- 10%	47,082,496	47,081,338
Unit administration cost of subsequent chemo infusion IV drug +/- 10%	47,134,599	47,029,234
Mean patient weight +/- 10%	51,949,238	42,187,679
Disease management costs		
Medical management costs in RF state (per week, up to year 3) +/- 10%	47,048,064	47,115,770
Medical management costs in RF state (per week, years 3-5) +/- 10%	47,057,593	47,106,240
Medical management costs in RF state (per week, years 5-10) +/- 10%	47,081,398	47,082,436
Salvage surgery costs upon LR state entry (one-time cost) +/- 10%	47,089,840	47,073,994
Medical management costs in LR state (per week) +/- 10%	47,093,082	47,070,751
Medical management costs upon DM state entry (one-time cost) +/- 10%	47,093,630	47,070,203
Medical management costs in pre-progression DM state (per week) +/- 10%	47,101,429	47,062,404
Medical management costs in post-progression DM state (per week) +/- 10%	47,140,329	47,023,505
Terminal care cost (one-time cost) +/- 10%	47,156,044	47,007,790
AE-related costs		
Cost of AEs +/- 10%	47,075,901	47,087,933
Utilities		
Utility in RF state +/- 10%	53,913,739	41,786,793
Utility in LR state +/- 10%	46,688,100	47,482,435
Utility in pre-progression DM state +/- 10%	46,554,026	47,621,917
Utility in post-progression DM state +/- 10%	46,760,785	47,407,490
Disutility from AEs +/- 10% (for pembrolizumab and watchful waiting arms)	47,078,352	47,085,482

Abbreviations: AE, Adverse Events; COP, Colombian Peso; DM, Distant Metastases; ICER, Incremental Cost-effectiveness Ratio; IV, Intravenous; LR, Locoregional Recurrence; OS, Overall Survival; PFS, Progression-free Survival; QALY, Quality-adjusted Life Year; RF, Recurrence-free.

Table S8. Results for Incremental Costs and Effectiveness for Pembrolizumab vs. Watchful Waiting across 1,000 Iterations of the Probabilistic Sensitivity Analysis

Average incremental costs (COP)	102,962,328
Average incremental QALYs	2.042
Average ICER (COP/QALY)	50,423,958
Probability of pembrolizumab being cost-effective at WTP of COP 69,150,201/QALY	65.70%

Abbreviations: COP, Colombian Peso; ICER, Incremental Cost-effectiveness Ratio; QALY, Quality-adjusted Life Year; WTP, Willingness-to-pay.

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