# COST-EFFECTIVENESS OF NIVOLUMAB (NIVO) AND NIVO IN COMBINATION WITH IPILIMUMAB (IPI) IN FIRST-LINE TREATMENT OF ADVANCED MELANOMA IN COLOMBIA: ANALYSIS USING 78-MONTH OVERALL SURVIVAL FROM CHECKMATE 067

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## Background

- In Colombia in 2013, melanoma was still a rare tumour, being diagnosed in approximately 4.5/100,000 individuals per year. Unfortunately, its case-fatality was relatively high, making melanoma a much more fatal cancer here than in the high incidence areas of the world.[1] Comparatively, in Colombia in 2020, the 5-year prevalence of melanoma diagnosed among men and women was 5,268, reflecting an increased annual incidence of 10.35/100,000 individuals.[2]
- The treatment landscape for advanced, non resectable melanoma has transformed over the last decade with the development and approval of non-chemotherapy systemic treatments including immune checkpoint inhibitors (I-O therapies) and targeted therapies (BRAF inhibitors, mitogen-activated protein kinase (MEK) inhibitors).[3]
- Despite recent advances in long-term overall survival (OS) in some populations, long-term, quality survival remains elusive for many patients.
- Results from the 78-month data of the CheckMate 067 trial showed that NIVO+IPI had significantly longer progression-free survival (PFS) (HR = 0.79 [95%CI, 0.64-0.96]) and a non-statistically significant improvement for OS (HR = 0.83 [95%CI, 0.67-1.03]) versus NIVO.[4,5] Results from this trial have also showed that the combination regimen has similar efficacy across patient subgroups.
- Given the addition of NIVO monotherapy and the NIVO+IPI combination regimen to the variety of existing treatments available for patients with advanced melanoma, it is important to synthesize the available evidence across all treatments and evaluate the cost-effectiveness of these regimens.

## Objective

The objective of this study is to evaluate the cost-effectiveness of NIVO and NIVO+IPI versus pembrolizumab (PEM), and dabrafenib+trametinib (DAB+TRAM) in the first-line treatment of patients with advanced melanoma from the Colombian payer perspective.

## Methods

### Model Structure

- A three-state partitioned survival model was developed which considered time-varying hazard ratios to estimate costs, life-years (LYs), and quality-adjusted LYs (QALYs) over a 30-year time horizon.
- The competing treatments considered in the analysis included NIVO, NIVO+IPI, PEM, and DAB+TRAM.
- Costs and health outcomes were discounted at 5% annually, to align with Instituto de Evaluación Tecnológica en Salud (IETS) guidelines.[6]

**Figure 1. Parametric OS Extrapolations for NIVO**

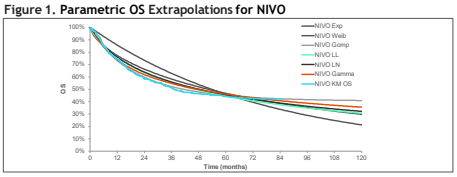
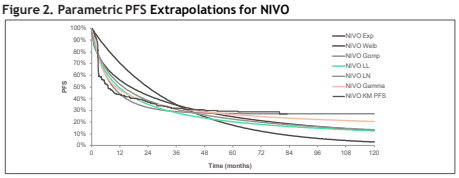



**Figure 2. Parametric PFS Extrapolations for NIVO**




### Survival Projections

- Survival projections for all competing treatments were estimated based on the relative treatment effects estimated in the NMA, which are represented by time-varying HRs relative to NIVO.
  - For both OS and PFS, it was found that HRs significantly changed over time for key comparators included in the analysis, so an NMA that could capture these variations was considered more appropriate than an NMA considering constant HR.
- The NIVO reference survival curves were estimated via parametric survival analysis of the CheckMate 067 OS and PFS 78-month data. Based on Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistical estimations of goodness-of-fit, observed fit, and the appropriateness of the underlying hazard, the Gompertz distribution was deemed the best fit based on the 78-month data analysis (Figure 1 and Figure 2).
- The time-varying relative treatment effects for OS and PFS were applied to the NIVO reference survival curves until the end of the observed data included in the NMA.
- The OS and PFS estimates produced by the model are presented in Figure 3 and Figure 4, respectively. These projections include Colombia-specific age-adjusted background mortality,[7] and the treatment effects estimated in the NMA.

**Figure 3. OS Extrapolations, Adjusted for Background Mortality**

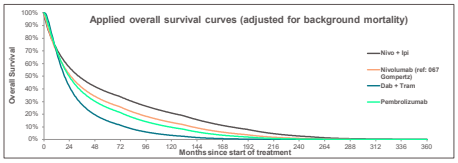
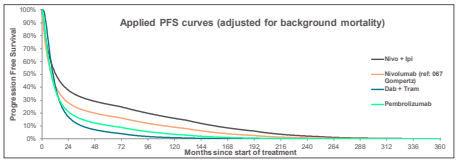



**Figure 4. PFS Extrapolations, Adjusted for Background Mortality**




### Drug Acquisition and Administration Costs

- Treatment-specific drug acquisition and administration costs per month were based on the number of treatment cycles per month, dosage per administration, and cost per package. The dosage required for infusion therapies was estimated using the mean patient mass of 66 kg.[8]
  - Treatment costs for infusion-based therapies were rounded up to the nearest vial required to account for wastage. A 3 mg/kg dose was used for NIVO in both monotherapy and for maintenance when in combination with IPI.
  - For infusion drugs, administration costs included general chemotherapy infusion administration costs (COL$634,700 per session). Oral drugs were assumed to have a monthly administration cost of zero.
- Treatment durations for NIVO and NIVO+IPI were directly estimated using the 78-month follow-up time-to-treatment discontinuation (TTD) data from the Checkmate 067 study. Due to the lack of available data, it was assumed that PEM TTD was equivalent to that of NIVO.
  - For PD-1 agents (NIVO, NIVO+IPI, PEM) a 2-year stopping rule was applied to the trial-observed TTD curve.
  - A treat to progression with a maximum duration approach was applied to DAB+TRAM, as median treatment durations are generally aligned with the PFS shape of the extrapolations for BRAF+MEK combination therapy.

### Subsequent Treatment Costs

- After progression following first-line treatment, it was assumed that, for each comparator, a proportion of patients received second-line treatment.
- Subsequent therapy post-progression was based on a distribution of subsequent treatments, including the option for no treatment. In the base case, the distribution of therapy received was based on BRAF mutation status-specific distributions estimated by clinical experts in Colombia.
  - These BRAF-specific distributions were then weighted by the proportion of the population that is BRAF wild type (WT) (70%) and BRAF mutant (30%),[9] to allow for an all-comer analysis (Table 1).
  - The mean cost of subsequent therapy was calculated from the monthly cost of treatment and the duration of subsequent therapy (assumed 21 weeks duration based on PFS from Zimmer 2017;[10] IPI was assumed a fixed duration of 10.5 weeks based on Checkmate 067). The cost, proportion, and duration were weighted together to estimate a mean cost of follow-up treatment per month.

**Table 1. Subsequent Treatment Distribution**

| Subsequent Therapy | Initial Therapy | | | |
|---|---|---|---|---|
| | NIVO | NIVO+IPI | PEM | DAB+TRAM * |
| NIVO | - | 6% | 16% | 9.2% |
| IPI | - | - | - | 27.3% |
| VEM | 25% | 15% | 25% | 19.3% |
| DAB | 25% | 15% | 25% | - |
| DAB+TRAM | 14% | 11% | 14% | - |
| PEM | 16% | 14% | 16% | - |

Source: Colombian clinical expert opinion; * Robert et al., (2019).[11]
Note: Weighted average of distributions for BRAF mutant and WT patients based on expert opinion.

### Disease Management Costs

- Disease management costs included healthcare encounters outside of regularly scheduled administration encounters, assigned on the basis of progression status (pre/post) and treatment status (on/off) (Table 2).
- One time event costs at the time of progression and death were also applied.
- Monthly and one-time event costs were derived from resource use estimates informed by key opinion leaders (KOLs). Unit costs were based on 2022 list prices.[12]

**Table 2. Disease Management Costs**

| Category | Cost Per Month (COL$) |
|---|---|
| Pre-progression - On treatment | 1,624,270 |
| Pre-progression - Off treatment | 1,119,266 |
| Post-progression - On treatment | 1,791,688 |
| Post-progression - Off treatment | 1,791,688 |
| Disease progression (one time cost) | 3,339,248 |
| Death (one time cost) | 948 |

### Adverse Events

- The frequency of grade 3/4 adverse events (AEs) by treatment was included as inputs to more fully capture the impact on cost and quality of life associated with being on treatment. Frequencies of AEs were based on the clinical trials.[4,11,13]
- The costs for grade 3/4 AEs were assumed to be equivalent to the hospitalization costs associated with that event (*i.e.*, a grade 3/4 AE will result in hospitalization). Costs were obtained from the Manual Tarifario SOAT de Salud (2022) from Colombia (Table 3).[12]

**Table 3. Adverse Event Costs and Utility Decrements**

| Adverse Event | Cost Per Event (COL$) | Utility Decrement |
|---|---|---|
| Abdominal pain | 3,500,000 | -0.130 |
| Atrial fibrillation | 4,500,000 | -0.170 |
| Autoimmune colitis | 5,600,000 | -0.170 |
| Autoimmune hepatitis | 5,600,000 | -0.170 |
| Autoimmune thyroiditis | 4,500,000 | -0.170 |
| Colitis | 5,600,000 | -0.170 |
| Dehydration | 5,600,000 | -0.130 |
| Diabetic ketoacidosis | 12,000,000 | -0.170 |
| Diarrhea | 5,600,000 | -0.130 |
| Enterocolitis | 7,500,000 | -0.170 |
| Febrile neutropenia | 16,500,000 | -0.170 |
| Guillain-Barré syndrome | 120,000,000 | -0.170 |
| Malabsorption | 12,500,000 | -0.170 |
| Myocardial infarction | 65,000,000 | -0.170 |
| Pancreatitis | 45,000,000 | -0.170 |
| Pulmonary embolism | 45,000,000 | -0.170 |
| Pneumonia | 35,000,000 | -0.170 |
| Respiratory failure | 45,000,000 | -0.170 |
| Syncope | 15,000,000 | -0.170 |
| Upper abdominal pain | 5,500,000 | -0.130 |
| Vomiting | 3,500,000 | -0.130 |

### Health-Related Quality of Life

- Utility analysis based on EQ-5D data collection in the CheckMate 067 trial (78-month follow-up) was used in the model using United Kingdom tariffs (Colombian-specific tariffs were not available), in alignment with Colombian IETS guidelines.[6]
- Utilities were estimated for the progression-free and post-progression health states, via longitudinal regression adjusting for baseline utility observed in the trial, time until death (Table 4).
- Differences in the regression coefficient for the assigned treatment arm were assumed to be associated with differential toxicity. The NIVO treatment arm was applied as the reference case in this model and separate AE-specific decrements were applied.
- Additional AE decrements were assigned for each event, regardless of which treatment triggered the event, and these were weighted by the treatment-specific and line-specific frequency of events to derive a treatment-specific toxicity decrement while patients remained on treatment (Table 3).[14]

**Table 4. Utility Weights**

| Health State | Utility |
|---|---|
| Pre-progression | 0.807 |
| Post-progression | 0.782 |
| Month prior to death | -0.374 |

### Sensitivity Analyses

- One-way sensitivity analyses were performed on model parameters including utility inputs, discount rates, disease management costs, and AE costs for the ICUR of NIVO vs. DAB+TRAM, NIVO vs. PEM, NIVO+IPI vs. DAB+TRAM, and NIVO+IPI vs. PEM.
- Additional scenarios were conducted to examine the impact of assumptions on time horizon (20 years), survival assumptions (use independently fit parametric survival curves from CheckMate 067 for NIVO+IPI and NIVO), and subsequent treatment (no active treatment assumed).
- Probabilistic sensitivity analysis was also conducted.

## Results

### Base Case

- NIVO was associated with cost savings (COL$2,457,700,118 and COL$69,259,660), higher LYs (3.33 vs. 2.28 and 3.01), and higher QALYs (2.62 vs. 1.76 and 2.36) compared to DAB+TRAM and PEM, respectively (Table 5).
  - NIVO was the dominant treatment option compared to DAB+TRAM and PEM.
- NIVO+IPI was associated with higher LYs (4.09 vs. 2.28 and 3.01), and higher QALYs (3.19 vs. 1.76 and 2.36) compared to DAB+TRAM and PEM, respectively (Table 5).
  - NIVO+IPI was the dominant treatment option compared to DAB+TRAM (cost savings of COL$2,385,137,437).
  - NIVO+IPI was the cost-effective treatment option compared to PEM, with an incremental cost-utility ratio (ICUR) of COL$3,986,610 per QALY, falling below the cost-effectiveness threshold of COL$27,000,000 per QALY (equivalent of 1 x GDP per capita in Colombia) with incremental costs of COL$3,303,021.

**Table 5. Base Case Results**

| Tx | LYs | QALYs | Total Costs (COL$) | NIVO vs Comparator | | | NIVO+IPI vs Comparator | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Marginal costs (COL$) | Marginal QALYs | ICUR | Marginal costs (COL$) | Marginal QALYs | ICUR |
| NIVO | 3.334 | 2.623 | 200,752,516 | | | | | | |
| NIVO+ IPI | 4.089 | 3.190 | 273,315,197 | | | | | | |
| DAB+ TRAM | 2.283 | 1.756 | 2,658,452,634 | -2,457,700,118 | 0.868 | Dominant | -2,385,137,437 | 1.434 | Dominant |
| PEM | 3.008 | 2.361 | 270,012,176 | -69,259,660 | 0.262 | Dominant | 3,303,021 | 0.829 | 3,986,610 |

### Sensitivity Analysis

- Across all one-way sensitivity analyses for NIVO vs. DAB+TRAM, NIVO vs. PEM, and NIVO+IPI vs. DAB+TRAM, the results showed NIVO-based therapy to be the dominant treatment option.
- The top 7 parameters to which the ICUR was most sensitive in one-way sensitivity analysis are presented in Figure 5 for NIVO+IPI vs. PEM. The ICUR was most sensitive to changes in the utility values and discount rates; however, all ICURs fell below the COL$27,000,000/QALY cost-effectiveness threshold, and NIVO+IPI remained the cost-effective treatment option.
- In scenario analyses, the model results were robust and aligned with those in the base case analysis.
- To understand the impact of the uncertainty in the model, probabilistic sensitivity analysis was conducted performing 1,000 replications of the model. The results are presented on an incremental cost-effectiveness plane (Figure 6 and Figure 7) and showed the robustness of the base case results.

**Figure 5. One-Way Sensitivity Analysis, NIVO+IPI vs. PEM**

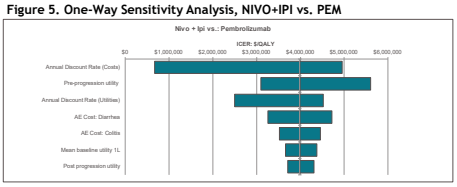



**Figure 6. Incremental Cost-Effectiveness Scatterplot, NIVO+IPI vs. DAB+TRAM & NIVO vs. DAB+TRAM**

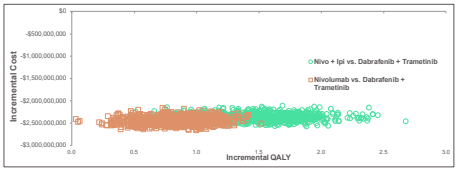
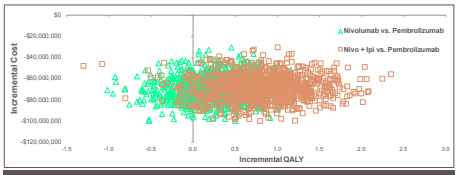



**Figure 7. Incremental Cost-Effectiveness Scatterplot, NIVO+IPI vs. PEM & NIVO vs. PEM**




## Discussion and Limitations

- The availability of long-term data, including survival and treatment duration, has allowed the survival extrapolation to be precisely estimated. Estimations of the reference OS and PFS curves for nivolumab were based on CheckMate 067 data with 78 months of follow-up. The best fitting parametric distributions were selected based on statistical metrics of goodness-of-fit, visual inspection of the extrapolated curves, and plausibility of the combined expressions of OS and PFS within a given treatment arm. While several distributions provided similar fits to the observed data, there was considerable variability in the extrapolated tails. This is not uncommon given the difference distributional assumptions in the shape of the underlying hazard functions. When secondary distribution selections were tested in sensitivity analysis, while estimates of total QALYs and costs by treatment arm shifted, the incremental estimates for NIVO and NIVO+IPI vs. comparators were not found to be particularly sensitive.
- Based on the observed survival data across treatments, it was found that HRs significantly changed over time for key comparators included in the analysis, so an NMA that could capture these variations was considered more appropriate than an NMA considering constant HRs. However, the findings of this NMA should be interpreted with some caution. Note that while NIVO and PEM are expected to be similar given their similar molecular makeup, survival projections for PEM are potentially underestimated due to the IPI arm in Keynote-006 reporting higher OS than the IPI arm in the CheckMate 067 study (as the link between PEM to the network depends on the comparison to IPI).

## Conclusion

- NIVO and NIVO+IPI are the cost-effective and dominant treatment options compared to DAB+TRAM and PEM for the first-line treatment of advanced melanoma patients in Colombia.

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## Disclosures

- Virgilio Barco, Javier Garcia, and Laura McDonald are employees of BMS and/or hold stocks/shares in BMS.
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