Cost-effectiveness analysis of nivolumab plus ipilimumab versus pembrolizumab plus axitinib for the first-line treatment of intermediate- and poor-risk advanced renal cell carcinoma patients in Colombia

EE81

Nishit Dhanji,[1] Gijs van de Wetering,[2] Vivian Guiot,[3] Virgilio Barco,[4] Andres Mejia,[3] Jessica R. May,[5] Javier Garcia,[6] Matthew Dyer,[5]

[1]OPEN Health, Oxford, UK; [2]OPEN Health, Rotterdam, Netherlands; [3]Bristol Myers Squibb, Bogota, Colombia; [4]A Bristol Myers Squibb, Cali, Colombia; [5] Bristol Myers Squibb, Uxbridge, UK; [6] Bristol Myers Squibb, Princeton, USA

Introduction

Renal Cell Carcinoma

- Renal Cell Carcinoma (RCC) is the most common type of kidney cancer, accounting for 80-90% of all kidney malignancies.[1]
- Approximately one-third of RCC patients present with advanced or metastatic RCC (aRCC) at diagnosis, of which approximately 77% are classified as intermediate or poor (I/P)-risk with worse outcomes than patients in the favorable-risk population based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk model.[2,3]
- In Colombia, tyrosine kinase inhibitors (TKI) such as sunitinib (SUN) have been the standard of care for patients with first-line (1L) aRCC. However, recently standard of care treatment has evolved from TKI monotherapy to combination therapies, including immuno-oncologic (IO) agents.[4]

Nivolumab plus ipilimumab and pembrolizumab plus axitinib

- Dual IO therapy nivolumab plus ipilimumab (NIVO+IPI) and IO+TKI combination therapy pembrolizumab plus axitinib (PEM+AXI) have shown to improve overall survival (OS) and progression-free survival (PFS) compared to SUN in their pivotal phase 3, randomized, open-label trials (CheckMate 214 and KEYNOTE-426, respectively):
  - NIVO+IPI resulted in improved OS compared to SUN (hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.58-0.81) based on 60-month follow-up data.[5]
  - PEM+AXI has demonstrated improved OS compared to SUN (HR, 0.64; 95% CI, 0.52-0.80) based on 23-month minimum follow-up data.[6,7]

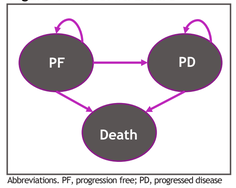
Objective

- To assess the cost-effectiveness (CE) of NIVO+IPI compared to PEM+AXI in I/P 1L aRCC patients in Colombia from a payer perspective, utilizing a novel approach to estimate comparative efficacy, involving a matching-adjusted indirect comparison (MAIC) to account for imbalances of treatment effect modifiers between the two trials.

Methods

Model Structure and Population of Interest

Figure 1. Model Structure



Abbreviations. PF, progression free; PD, progressed disease

- A partitioned survival model was developed for CE assessment. The model comprised of three distinct health states; progression free (PF), progressed disease (PD), and death as the absorbing state **(Figure 1)**.
- **Perspective:** Colombian payer
- **Population:** I/P, age (65 years), gender (61.5% male) and weight (59kg).
- **Cycle length:** 7 days, with half cycle correction.
- **Time horizon**: lifetime (40 years).
- The analysis was performed in line with guidelines by the Instituto de Evaluación Tecnológica en Salud (local HTA authority in Colombia) with a 5% discount rate for both costs and effects[8].

Treatment Efficacy

- Individual patient-level data (IPD) from CheckMate 214 (60-month data base lock) was used to inform the efficacy for NIVO+IPI in the study.
- In the absence of IPD from KEYNOTE-426, Kaplan-Meier (KM) plots were digitized to generate pseudo-IPD to inform the efficacy for PEM+AXI.
- Due to the lack of head to head clinical evidence between NIVO+IPI and PEM+AXI, a MAIC that accounted for any imbalance in observed treatment effect modifiers (TEMs) was performed.
- Two MAICs were conducted using different sets of TEMs to assess the robustness of the analysis and sensitivity to the inclusion of different TEMs **(Table 1)**.

Survival analysis

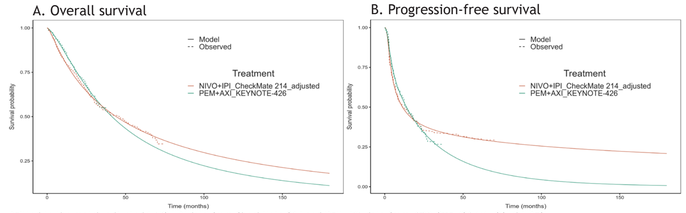
- To extrapolate efficacy outcomes over a lifetime horizon, a range of parametric survival curves were fitted to the adjusted KM survival data, which accounted for non-proportional hazards over time.
- The base case extrapolations were determined according to commonly used statistical fit criteria (Akaike and Bayesian information criterion), visual inspection, comparison to observed landmark survival estimates and external evidence **(Figure 2)**.
- The log-normal distribution was selected to extrapolate OS and the spline 2 knot (hazard) was used for PFS. The same distributions were used for NIVO+IPI and PEM+AXI.
- Time to discontinuation (TTD) was defined by the trial-reported TTD curve for NIVO+IPI, the spline 2 knot (probit) model was chosen to extrapolate TTD for NIVO+IPI. In the absence of reported TTD data for PEM+AXI, PFS was used as a proxy for TTD, as concurrence between PFS and TTD has been reported[9] to inform drug-related costs.

Table 1. Treatment effect modifiers (base case and scenario)

	Un. CM 214 (%)	*P*-value (inter)	KN-426 (%)	Mat. CM 214 Base (%)	Mat. CM 214 Scen (%)
Sarcomatoid features	13.22	0.048	18.17**	18.17	-
Age < 65	61.87	0.028	62.49**	62.49	-
Metastases lymph	48.05	0.224	49.83	49.83	49.83
IMDC intermediate-risk	78.75	-	81.76	81.76	81.76
IMDC poor-risk	21.25	0.151	18.24	-	18.24
Sex male	72.61	0.159	72.94**	72.94	-
Metastases lung	69.78	0.309	73.65	-	73.65
Metastases bone	20.43**	0.590	27.03	-	27.03
Metastases liver	20.90	0.728	16.89	-	16.89

* In KN-426 this was only tested in 67% of subjects; the percentage presents the proportion of positive/total number of tests.** Information for KN-426 was only available for the intention-to-treat (ITT) population, a similar proportion was assumed in the intermediate-poor population compared to the ITT. Abbreviations. Un, unmatched; CM, CheckMate; inter, interaction; KN, KEYNOTE; mat, matched; scen, scenario; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium

Figure 2. Survival models used in the base case vs reported data[a]



[a]Fitted to the match-adjusted NIVO+IPI data from CheckMate 214 and PEM+AXI data from KEYNOTE-426 (a), OS, (b) PFS

Costs and utilities

- For each treatment, drug acquisition costs were obtained from the Circular de precios (01/02/2022)[10] and treatment dosing was informed by its respective pivotal trials and summary of product characteristics **(Table 2)**.
- For NIVO+IPI, NIVO was administered for a maximum duration of 60 months, with IPI being stopped after four doses, for PEM+AXI, patients could not receive PEM beyond 24 months, but could continue treatment with AXI until 60 months.
- Disease management resource use (outpatient visits, monitoring tests & scans) was based on clinical expert opinion input and costs were Colombian-specific, in 2022 Colombian Peso (Col $), where available.
- All Grade 3-4 adverse events for NIVO+IPI and PEM+AXI from CheckMate 214 and KEYNOTE-426 were included and costs were Colombian-specific (2022 Col$) where available.
- Treatment-specific health state utility values were based on EuroQol 5-dimensions 3-level (EQ-5D-3L) data from the CheckMate 214 trial using Argentinian tariffs in the absence of Colombian tariffs[11].
- Utility values in the PF health state were 0.874 for NIVO+IPI and 0.833 for PEM+AXI. In the PD health state this was 0.852 for NIVO+IPI and 0.834 for PEM+AXI. PEM+AXI was assumed to have the same utility as that of SUN from CheckMate 214 as no statistically significant health-related quality of life benefit has been demonstrated for PEM+AXI versus SUN.[12-15]

Table 2. Drug acquisition costs and dosing

Treatment	Drug	Dose admin, dosing, admin frequency	Pack size	Cost per pack
NIVO+IPI	NIVO (induction)	IV, 3mg/kg Q3W for 4 cycles	10mg/ml, 4ml	Col$ 2,211,153
	IPI (induction only)	IV, 1mg/kg Q3W for 4 cycles	5 mg/ml, 10 ml	Col$ 14,508,643
	NIVO (maintenance)	IV, 240mg, Q2W	10 mg/ml, 10 ml	Col$ 5,527,882
PEM+AXI	PEM	IV, 200mg, Q3W	25mg/ml	Col$ 3,183,996
	AXI	Oral, 5mg, BID	1mg, 56 tablets	Col$ 2,670,199

Abbreviations. BID, twice a day; Q2W, once every two weeks; Q3W, once every three weeks; wks, weeks; mg, milligrams; ml, milliliters; NIVO, nivolumab; IPI, ipilimumab; PEM, pembrolizumab; AXI, axitinib

Outcomes

- Model outcomes included total costs, life-years (LYs), quality-adjusted life-years (QALYs), incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR).
- In addition to the base case analysis, deterministic sensitivity analyses (DSA) (based on 95% CIs estimated using standard errors [SE], where for parameters with unknown SE, 10% of their base case estimate were considered as SE) and probabilistic sensitivity analysis were conducted.
- To test the robustness of the base case results, scenario analyses were conducted to test assumptions around PEM+AXI health state utility, maximum treatment duration for NIVO, alternative survival extrapolations, alternative MAICs and time horizon.

Results

Matching-Adjusted Indirect Treatment Comparison

- The similarity assessment between CheckMate 214 and KEYNOTE-426 highlighted the presence of heterogeneity for several potential TEMs, including age, sarcomatoid features, lymph, lung bone and liver metastases, IMDC risk status, and sex.
- The interaction analyses identified sarcomatoid features, age group, lymph metastases, IMDC group, and sex as variables with a meaningful association level with the treatment effect.
- Baseline characteristics of the matched population closely aligned with the KEYNOTE-426 baseline characteristics indicating a successful matching.

Economic Analysis

- The economic model estimated 3- and 5-year PFS at 35.8% and 31.7%, respectively, and OS at 57% and 44% for NIVO+IPI, which is in line with observed data in the CheckMate 214 trial.
- NIVO+IPI was associated with cost savings (COL$ 292,884,798), higher LYs (4.70 vs 4.25), and higher QALYs (4.08 vs 3.54) versus PEM+AXI, resulting in NIVO+IPI dominating PEM+AXI **(Table 3)**.

Table 3. Base case discounted costs and health outcomes for NIVO+IPI vs PEM+AXI

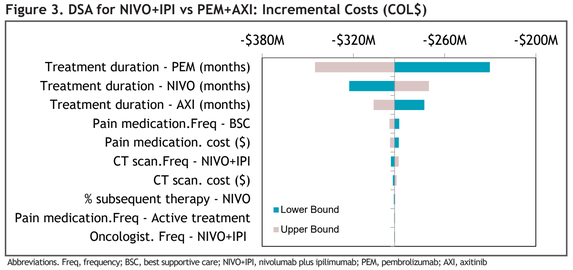
	NIVO+IPI	PEM+AXI
Total Costs (COL$)	$679,580,383	$972,465,181
Total QALYs	4.08	3.54
Total LYs	4.70	4.25
Incremental costs (COL$)	-$292,884,798	
Incremental QALYs	0.54	
Incremental LYs	0.44	
ICUR (COL$/QALY)	**Dominant**	
ICER (COL$/LY)	**Dominant**	

Abbreviations. LY, life-year; QALY, quality adjusted life-year; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; NIVO+IPI, nivolumab plus ipilimumab; PEM+AXI, pembrolizumab plus axitinib

Sensitivity analyses

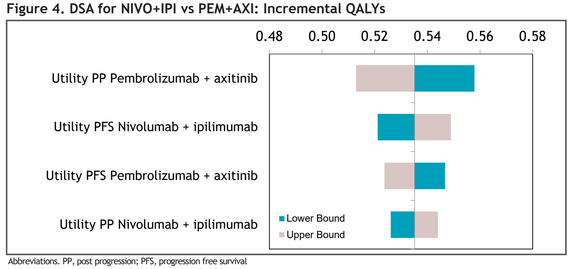
- The DSA showed that uncertainty around the maximum treatment duration for PEM, NIVO and AXI had the highest impact on incremental costs **(Figure 3)**.
- The most influential parameters for incremental QALYs between the treatments were the utilities for both the PF and PD health states, with the PD utility for PEM+AXI being the most influential, followed by the PF utility for NIVO+IPI **(Figure 4)**.
- The PSA showed a consistent result compared to the deterministic base case. In 96% of the 1,000 simulations NIVO+IPI was associated with lower total costs and higher total QALYs than PEM+AXI **(Figure 5)**.
- The base case results were robust to alternative scenarios as NIVO+IPI remained dominant when: (i) selecting the second-best fitting survival curves for extrapolations, (ii) an alternative MAIC (when different TEMs) were used, (iii) a naïve comparison (no MAIC) was applied, (iv) no stopping rule for the treatment duration of NIVO+IPI was adopted, (v) the utilities for PEM+AXI were assumed to be identical between treatments, and (vi) 5- and 10-year time horizon.

Figure 3. DSA for NIVO+IPI vs PEM+AXI: Incremental Costs (COL$)



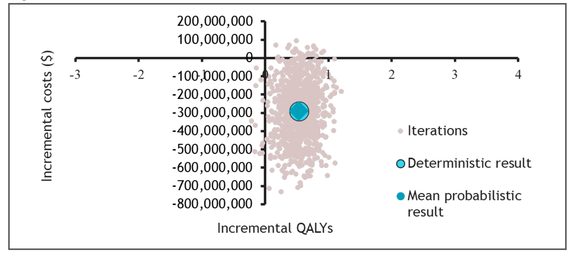
Abbreviations. Freq, frequency; BSC, best supportive care; NIVO+IPI, nivolumab plus ipilimumab; PEM, pembrolizumab; AXI, axitinib

Figure 4. DSA for NIVO+IPI vs PEM+AXI: Incremental QALYs



Abbreviations. PP, post progression; PFS, progression free survival

Figure 5. Scatter Plot of Simulated Incremental Costs and QALYs



Conclusions

- This analysis utilizes robust methods for adjusting for baseline differences between relevant clinical trials, as well as accounting for non-proportional hazards over time and extrapolating survival outcomes over a long-term horizon
- Over a 40-year time horizon, NIVO+IPI generated more LYs and was predicted to have higher OS and PFS compared to PEM+AXI
- This analysis shows that NIVO+IPI is estimated to be a life-extending and potentially cost-saving 1L treatment option when compared with PEM+AXI for I/P aRCC patients in Colombia

References

1. Ljungberg B, et al. *Eur Urol*. 2015;67:913-924.
2. Heng DY, et al. *J Clin Oncol*. 2009;27:5794-5799.
3. Heng DY, et al. *Lancet Oncol*. 2013;14:141-148.
4. Smaletz O. *Int Braz J Urol*. 2015;41(5):835-843
5. Motzer RJ, et al. *Cancer*. 2022;128(11):2085-2097.
6. Rini B, et al. *J Clin Oncol*. 2021;39: 4500-4500
7. Powles T, et al. Lancet Oncol. 2020;21(12):1563-1573
8. Faria R, Mejia A. *IETS*. 2014
9. Bensimon AG, et al. *Curr Med Res Opin*. 2020;36(9):1507-1517.
10. Colombian Ministry of Health: Circular de precios (01/02/2022)
11. Augustovski AF, et al. Value in health. 20009: 587-596.
12. European Medicines Agency. Assessment report Keytruda, in Assessment report. 2015.
13. NICE, Single Technology Appraisal Pembrolizumab with axitinib for untreated advanced renal cell carcinoma [ID1426] Committee papers. 2019.
14. Bedke J, et al. EAU 2020 QOL. 2020.
15. Bedke J., et al. *Eur Urol*. 2022;82(4):427-439.

Presented at ISPOR 2023; May 7-10, 2023; Boston, MA

Email: Matthew.Dyer@bms.com