ORIGINAL ARTICLE
ARTIGO ORIGINAL

Immunotherapy-based first-line treatment of intermediate- and poor-risk advanced renal cell carcinoma: number needed to treat and cost of preventing an event from the perspective of the Brazilian private healthcare system

Tratamento baseado em imunoterapia para primeira linha do carcinoma renal avançado com risco intermediário ou alto: número necessário a tratar e custo para prevenir um evento na perspectiva do sistema privado de saúde brasileiro

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DOI: 10.21115/JBES.v13.n3.p258-67

Keywords:
renal cell carcinoma, axitinib, ipilimumab, nivolumab, pembrolizumab, costs and cost analysis, health care costs

ABSTRACT

Objective: To perform an analysis over time of the number needed to treat (NNT) and the cost of preventing an event (COPE) for nivolumab + ipilimumab (NIVO+IPI) and pembrolizumab + axitinib (PEMBRO+AXI) as first-line treatments for advanced renal cell carcinoma patients with intermediate or poor-risk, under the Brazilian private healthcare system perspective. **Methods:** The NNT for overall survival (OS) and progression-free survival (PFS) from 12-month to maximum available follow-up from CheckMate 214 and KEYNOTE-426 studies were used to estimate the COPE. Treatment costs were estimated considering the labeled dosing and median PFS as a proxy for treatment duration. **Results:** The OS NNT for NIVO+IPI decreased from 12 to 8 and for PEMBRO+AXI increased slightly from 7 to 8 at 12 and 42 months, respectively. For PFS, NNT for NIVO+IPI decreased from 15 to 6, and for PEMBRO+AXI increased from 7 to 10 at 12 and 30 months. The estimated treatment cost is R$ 638,620 for an estimated median of 11.2 months of NIVO+IPI treatment and R$ 966,818 for 13.8 months of PEMBRO+AXI treatment. COPE for OS at 12 and 42 months was R$ 7,663,440 and R$ 5,108,960 with NIVO+IPI and R$ 6,047,417 and R$ 7,734,547 with PEMBRO+AXI. For PFS, COPE at 12 and 30 months was R$ 9,579,300 and R$ 3,831,720 with NIVO+IPI and R$ 6,047,417 and R$ 9,668,184 with PEMBRO+AXI. **Conclusions:** Treatment with NIVO+IPI results in lower COPE than PEMBRO+AXI from month 18 onwards, driven by lower treatment costs and improved NNT over time with NIVO+IPI.

Palavras-chave:
carcinoma renal, axitinibe, ipilimumabe, nivolumabe, pembrolizumabe, custos e análise de custo, custos de cuidados de saúde

RESUMO

Objetivo: Analisar ao longo do tempo o número necessário a tratar (NNT) e o custo para prevenir um evento (COPE) para nivolumabe + ipilimumabe (NIVO+IPI) e pembrolizumabe + axitinibe (PEMBRO+AXI) na primeira linha de tratamento do carcinoma de células renais avançado com risco intermediário ou alto na perspectiva do sistema suplementar de saúde brasileiro. **Métodos:** O NNT

Received on: 10/25/2021.**Approved for publication on:** 11/19/2021.
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Funding: The study was supported by Bristol Myers Squibb, Brazil.
Conflict of interests: Ana Paula Casagrande Drozda Oliveira, Lucienne Pereira Del Grossi Neusquen, Matthew T. D. Dyer, and Jessica R. May are employees of Bristol Myers Squibb. Camila Finardi Roubik is a contracted employee of Bristol Myers Squibb.
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para sobrevida global (SG) e sobrevida livre de progressão (SLP) para 12 meses até o máximo de tempo de seguimento disponível dos estudos CheckMate 214 e KEYNOTE-426 foi usado para estimar o COPE. Custos de tratamento foram estimados considerando a dosagem em bula e a mediana de SLP como aproximação para duração de tratamento. **Resultados:** O NNT de SG para NIVO+IPI reduziu de 12 para 8 e para PEMBRO+AXI subiu de 7 para 8 em 12 e 42 meses, respectivamente. Para SLP, NIVO+IPI teve redução de 15 para 6 e para PEMBRO+AXI aumentou de 7 para 10 em 12 e 30 meses. O custo estimado é de R$ 638.620 para mediana de 11,2 meses de tratamento com NIVO+IPI e de R$ 966.818 para 13,8 meses com PEMBRO+AXI. O COPE para SG foi de R$ 7.663.440 e R$ 5.108.960 com NIVO+IPI e de R$ 6.047.417 e R$ 7.734.547 com PEMBRO+AXI para 12 e 42 meses. Para SLP, foi de R$ 9.579.300 e R$ 3.831.720 com NIVO+IPI e de R$ 6.047.417 e R$ 9.668.184 com PEMBRO+AXI em 12 e 30 meses. **Conclusões:** O tratamento com NIVO+IPI resulta em menor COPE, em comparação com PEMBRO+AXI, a partir de 18 meses de seguimento, justificado por menor custo de tratamento e melhora do NNT ao longo do tempo com NIVO+IPI.

Introduction

Kidney cancers represent 2.4% of all diagnosed cancers among men and 1.6% among women in Brazil (IARC, 2020; Sung *et al.*, 2021). GLOBOCAN estimate showed an age-adjusted incidence for 100,000 men and women in Brazil of 5.8 and 3.3, respectively, and mortality of 2.4 and 1.2, respectively (IARC, 2020; Sung *et al.*, 2021). These statistics include parenchymal and renal pelvis tumors, though renal cell carcinoma (RCC) comprises approximately 80%-90% of those tumors (Escudier *et al.*, 2019; NCCN, 2021). Clear cell RCC (ccRCC) is the most common histological subtype and represents 80% of malignant renal tumors in adults (Escudier *et al.*, 2019; Hsieh *et al.*, 2017). About two-thirds of diagnoses occur at the local stage, partially attributed to an incidental diagnosis of asymptomatic tumors by image exams conducted for urological or other reasons (ACS, 2021; Muglia & Prando 2015). However, around 20% of these patients will relapse and develop metastatic RCC (mRCC) during follow-up (Ljungberg *et al.*, 2011). In addition, many RCC tumors are already at an advanced stage at the first presentation, being nearly 38% in Brazil (Aguiar *et al.*, 2016).

Immunotherapy and targeted therapies, sometimes with radical nephrectomy, are the main treatment options for metastatic disease (ACS, 2021; Escudier *et al.*, 2019; NCCN, 2021). The first-line systemic treatment algorithm of advanced RCC is defined by a risk stratification of patients' prognosis at favorable-, intermediate- or poor-risk disease (Heng *et al.*, 2013; Heng *et al.*, 2009), depending on the number of clinical and laboratory risk factors present (Escudier *et al.*, 2019; NCCN, 2021). Based on 2020 ESMO Guidelines, for first-line treatment of metastatic ccRCC, pembrolizumab plus axitinib (PEMBRO+AXI) and nivolumab plus cabozantinib are recommended for all risk categories, while nivolumab plus ipilimumab (NIVO+IPI) is recommended for intermediate- and poor-risk (I/P-risk) patients (ESMO, 2020). In this guideline, if the recommended combined treatments are not available or contraindicated, sunitinib (all risks), pazopanib (all risks), tivozanib (favorable-risk), and cabozantinib (I/P-risk) are alternative options. The Brazilian Society of Clinical Oncology (SBOC) guideline recommends the following options for I/P-risk patients: NIVO+IPI, cabozantinib monotherapy, nivolumab plus cabozantinib, avelumab plus axitinib, and PEMBRO+AXI (Fay *et al.*, 2021). Sunitinib or pazopanib are the alternative options for those with no access to immunotherapy (Fay *et al.*, 2021).

In Brazil, between 2013 and 2016, 79% of metastatic RCC (mRCC) patients in public and private institutions received first-line systemic treatment, mostly with sunitinib (56.5%) (Bergerot *et al.*, 2018). Notably, an estimate of premature deaths that could be averted by treating patients with immunotherapy (NIVO+IPI) in the Brazilian Public Health System (SUS) showed that over ten years, approximately 1,040 patients with metastatic ccRCC would die prematurely due to lack of access to immunotherapy (Lenz *et al.*, 2019).

NIVO+IPI and PEMBRO+AXI have shown improved progression-free survival (PFS) and overall survival (OS) compared with sunitinib in first-line treatment of advanced ccRCC (Powles *et al.,* 2020; Albiges *et al.,* 2020). Recently, Botrel *et al.*, 2021 compared the number needed to treat (NNT) and the cost of preventing an event (COPE) between PEMBRO+AXI and NIVO+IPI as first-line treatments of advanced RCC from the private health system perspective. Both analyses were conducted over a 12-month time horizon, using the I/P-risk patient subgroup data from the KEYNOTE-426 study (Rini *et al.*, 2019b) for PEMBRO+AXI, and the CheckMate 214 study for NIVO+IPI (Motzer *et al.*, 2018). The 12-month follow-up choice was justified by claiming that PEMBRO+AXI did not have available data for a longer follow-up period. Currently, both studies have already presented results for an extended analysis. Results for median follow-ups of 30.6 months and 42.8 months are now available for KEYNOTE-426 (Powles *et al.*, 2020; Rini *et al.*, 2021). Furthermore, CheckMate 214 is the phase III immunotherapy-based clinical trial with longer follow-up available; published data of 4 years minimum follow-up was available when this study was developed (Albiges *et al.*, 2020). Considering the available longer follow-up data, the objective of this study is to perform an extended analysis of NNT and COPE for NIVO+IPI and PEMBRO+AXI as first-line treatment of I/P-risk patients with advanced RCC from the Brazilian private health system perspective.

METHODS

General description

The study compares the COPE (Maharaj, 2008) of two first-line treatment strategies for I/P-risk advanced RCC, NIVO+IPI and PEMBRO+AXI over time.

The NNT for PFS and OS from 12 months to the longer follow-up available for I/P-risk patients at the time of study development (at 6-month intervals) from the corollary studies for each treatment combination (CheckMate 214 and KEYNOTE-426 for NIVO+IPI and PEMBRO+AXI, respectively) were used to estimate the COPE. NNT is calculated as the inverse of absolute risk reduction for each treatment combination versus sunitinib. COPE is calculated by multiplying the treatment cost in a specific time by the NNT.

Clinical data sources and data extraction

CheckMate 214 for NIVO+IPI (Albiges *et al.,* 2020; Motzer *et al.*, 2018; Tannir *et al.*, 2019) and KEYNOTE-426 for PEMBRO+AXI (Powles e*t al.*, 2020; Rini *et al.*, 2019b; Rini *et al.*, 2021) were chosen as the data sources to assess effectiveness. Both studies are phase III randomized clinical trials investigating the effect of immunotherapy combinations on the first-line treatment of advanced ccRCC compared with sunitinib. Patients included were characterized according to IMDC risk stratification, based on the number of presented risk factors among six predictors, as favorable- (0 factor), intermediate- (1 or 2), or poor-risk (3 to 6) (Heng *et al.*, 2009). Randomization was stratified by risk in both studies.

In CheckMate 214, the primary outcome analysis considered the I/P-risk patients (Albiges *et al.*, 2020; Motzer *et al.*, 2018), while in KEYNOTE-426, the primary analysis was performed for the intention-to-treat (ITT) population, including all risk categories; however, subgroup analyses for the I/P-risk subgroup were also reported (Powles *et al.*, 2020; Rini *et al.*, 2019b). In CheckMate 214, 1,096 patients were randomized, 550 were allocated to NIVO+IPI, and 546 to sunitinib. Of those, 425 and 422 patients, respectively, were classified as I/P-risk patients (Motzer *et al.*, 2018). In KEYNOTE-426, 861 patients were randomized (432 to PEMBRO+AXI and 429 to sunitinib); 294 and 298 of those patients were classified as I/P-risk, respectively (Rini *et al.*, 2019b). Patients' characteristics were well balanced between groups within each study (Motzer *et al.*, 2018; Rini *et al.*, 2019b).

PFS and OS rates in each time point were extracted from the publications with the longest follow-up data or Kaplan-Meier curve available for the I/P-risk patients from CheckMate 214 (median follow-up of 55 months, minimum follow-up of 48 months) (Albiges *et al.*, 2020) and KEYNOTE-426 (median follow-up of 30.6 months) (Powles *et al.*, 2020). For KEYNOTE-426, the OS rate at month 42 for I/P-risk patients was later reported in a conference presentation at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting (Rini *et al.*, 2021); however, the PFS rate was not reported for I/P-risk patients. In both studies, data from the comparator arm (sunitinib) was also extracted to estimate the NNT. NNT was rounded up for all analysis and reporting (McQueen, 2011). OS and PFS rates used are presented in Table 1.

Table 1. PFS and OS rates and NNT per time point for I/P-risk patients

Outcome	CheckMate 214				KEYNOTE-426			
	NIVO + IPI	SUN	ARR	NNT#	PEMBRO + AXI	SUN	ARR	NNT#
	OS rate (%)				OS rate (%)			
12 months	80.3	71.8	8.5	12	86.7	72.0	14.7	7
18 months	73.8	59.6	14.2	8	75.5	63.2	12.3	9
24 months	66.4*	52.4*	14.0	8	69.2*	55.8*	13.4	8
30 months	59.6	47.2	12.4	9	61.3	48.9	12.4	9
36 months	54.5	43.6	10.9	10	-	-	-	-
42 months	52.0	39.2	12.8	8	50.6*	37.6*	13.0	8
48 months	50.0*	35.8*	14.2	8	-	-	-	-
	PFS rate (%)				PFS rate (%)			
12 months	49.6	42.8	6.8	15	55.8*	40.9*	14.9	7
18 months	42.8	32.5	10.3	10	44.5	33.2	11.3	9
24 months	36.4*	25.1*	11.3	9	34.3*	22.7*	11.6	9
30 months	35.8	19.0	16.8	6	28.4	17.7	10.7	10
36 months	34.5	17.3	17.2	6	-	-	-	-
42 months	34.1	14.8	19.3	6	-	-	-	-
48 months	32.7*	12.3*	20.4	5	-	-	-	-

OS rate and PFS rate were extracted from Kaplan-Meier curves for intermediate-/poor-risk patients in each study. *Data extracted directly from publication; ARR, absolute risk reduction; #Absolut number; NNT, number needed to treat; NIVO+IPI, nivolumab + ipilimumab; OS, overall survival; PEMBRO+AXI, pembrolizumab + axitinib; PFS, progression-free survival; SUN, sunitinib.

The data available in curves were extracted using the WebPlotDigitizer software version 4.4 (Rohatgi, 2020).

Costs

Treatment costs for each time point were estimated considering the dosing and cycle duration defined by the Brazilian approved labels of NIVO+IPI and PEMBRO+AXI, assuming a mean corporal weight of 70 kg per patient (Cortellini *et al*., 2019). All costs are presented as Brazilian Reais (R$), 2021.

Drug acquisition costs were obtained from the official price list of the Medicines Market Regulation Chamber (*Câmara de Regulação do Mercado de Medicamentos* – CMED), considering the factory price with 18% of tax (*Imposto sobre Circulação de Mercadorias e Serviços* – ICMS) (Anvisa, 2021). Units needed for each presentation were estimated considering cycle or month, using the combination of drug presentations with the minimum possible waste.

In the base case analysis, median PFS (mPFS) for I/P-risk patients for NIVO+IPI (Albiges *et al*., 2020) and PEMBRO+AXI (Rini *et al*., 2021) were used to estimate treatment costs. If mPFS was longer than 12 months, costs were limited to 12-month treatment for the 12-month follow-up estimate. The use of mPFS should be considered a conservative analysis for NIVO+IPI as previous studies have demonstrated a treatment-free interval for patients who had discontinued treatment and had not received subsequent systemic anticancer therapy or died (McDermott *et al*., 2018; Regan *et al*., 2020). To date, no treatment-free interval has been reported for PEMBRO+AXI, and previously it has been reported congruence between time on treatment and mPFS for this regimen (Bensimon *et al.,* 2020).

An alternative scenario analysis was performed using median duration of treatment (mDOT) for the ITT population as reported from both studies. The mDOT was not chosen as the base case because it was not available for I/P-risk patients. Moreover, for the longer follow-up of KEYNOTE-426 (median follow-up = 30.6 months), the authors reported only the total treatment exposure in person-months (7,715.4 person-months). This could be converted only to mean DOT by dividing it by the number of patients (n= 432), resulting in a mean DOT of 17.86 months (Powles *et al*., 2020). This value would be much higher than the one reported for NIVO+IPI (mDOT of 7.9 months with median follow-up = 55 months) (Albiges *et al.,* 2020). Thus, the mDOT reported for the 12.8 months follow-up of KEYNOTE-426 was used in the scenario analysis (9.2 months for pembrolizumab and 9.6 months for axitinib) (Rini *et al*., 2019).

For all analyses, a month was considered as 30 days and a year as 52 weeks. The treatment protocols for each medication, units and presentations needed to complete the estimated dose per cycle or application are presented in Table 2.

The base case analysis considered only drug acquisition costs, but an additional analysis including monitoring costs, as defined by the microcosting described by Botrel *et al*., 2021, was also performed. The monitoring costs proposed are R$ 4,785.62 in the first cycle and R$ 4,322.39 per subsequent cycle (Botrel *et al*., 2021). Monitoring costs were deemed to be equal between interventions and to remain constant while on treatment. Noteworthy, the microcosting used for monitoring cost did not include adverse event management (Botrel *et al*., 2021).

COPE analysis

COPE is the product of NNT and treatment cost. It was calculated considering the NNT to prevent one death (OS) and the NNT to prevent one progression or death (PFS) for NIVO+IPI and PEMBRO+AXI, both versus sunitinib. NNT was estimated from 12 months to maximum available time points.

In the base case, COPE calculation used the treatment costs estimated for I/P-risk patients' mPFS. As mPFS with PEMBRO+AXI was longer than 12 months, the annual PEMBRO+AXI treatment costs were used for the 12-month time point (Table 2). In the scenario analysis considering ITT mDOT for treatment costs estimation, this correction was not required since the mDOT for both treatments is under 12 months.

RESULTS

NNT

The estimated number of patients needed to be treated to prevent one's death, and the number of patients needed to be treated to prevent one's death or progression event at month 12 to maximum available follow-up for NIVO+IPI and PEMBRO+AXI, both vs. SUN, are presented in Table 1. The NNT for OS was reasonably stable for PEMBRO+AXI, rising from 7 at the 12-month time point to 8 at the 42-month OS time point. In contrast, for NIVO+IPI, NNT for OS became more favorable with longer follow-up time, decreasing from 12 at the 12-month cut to 8 at the 42- and 48-month evaluations. For PFS, a similar phenomenon was seen with NIVO+IPI, starting with a NNT of 15 at the 12-month analysis, reducing by nearly two-thirds to 6 at the 30-month evaluation and later to 5 at the 48-month assessment. Conversely, NNT of PEMBRO+AXI increased over time from 7 at the 12-month analysis to 10 at the 30-month follow-up.

Cost per treatment

The cost estimates are presented in Table 2. Considering the mPFS for I/P-risk patients with each therapy combination, the estimated cost per treatment in the base case is R$ 638,620 for a median 11.2 months of treatment with NIVO+IPI and R$ 966,818 for a median 13.8 months of treatment with PEMBRO+AXI. With the addition of the monitoring costs, the NIVO+IPI treatment cost is R$ 734,176, and PEMBRO+AXI treatment cost is R$ 1,053,729.

Table 2. Drug presentations, dosing, and treatment costs

Drug	**Nivolumab**	**Ipilimumab**	**Pembrolizumab**	**Axinitinib**
Commercial Name	**Opdivo**	**Yervoy**	**Keytruda**	**Inlyta**
Presentations	100 mg/10 mL (10 mg/mL) solution, single vial 40 mg/4 mL (10 mg/mL) solution, single vial	50 mg/10 mL (5 mg/mL) solution, single vial	100 mg/4 mL (25 mg/mL) solution, single-dose vial	5 mg tablets, 60 tablets per unit
Price per unit (R$)	100 mg: 9,269.37 40 mg: 3,707.75	19,576.59	16,684.92	21,697.22
Dosing	*I:* 3 mg/kg (210 mg) Q3W, 4 cycles *M:* 240 mg Q2W	1mg/kg (70 mg) Q3W, 4 cycles	200 mg Q3W	5 mg twice a day
Presentation units per cycle/month	*I:* 1 un. of 100 mg and 3 un. of 40 mg *M:* 2 un. of 100 mg and 1 un. of 40 mg	2 un. per cycle (total 100 mg)	2 un. per cycle	1 un. per month
Cost per cycle/month (R$)	*I:* 20,392.62 *M:* 22,246.49	39,153.18	33,369.84	21,697.22/month
Treatment costs based on median PFS (base case)				
Median PFS	11.2 months		13.8 months	
Median treatment doses	22*	4*	20*	828 tablets†
Units per treatment ‡	*I:* 4 un. of 100 mg + 12 un. of 40 mg *M:* 36 un. of 100 mg + 18 un. of 40 mg	8 un.	40 un.	13.8 un.
Cost per treatment (R$)	*I:* 81,570.48 *M:* 400,436.82 *Total:* 482,007.30	156,612.72	667,396.80	299,421.64
Total cost per treatment combination (R$)	638,620		966,818	
Cost per treatment with monitoring costs (R$) §	734,176		1,053,729	
Treatment costs based on median treatment duration (scenario analysis)				
mDOT (ITT population)	7.9 months‖		9.2 months¶	9.6 months¶
Median treatment doses	14‖	4‖	14*	576 tablets†
Units per treatment‡	*I:* 4 un. of 100 mg + 12 un. of 40 mg *M:* 20 un. of 100 mg + 10 un. of 40 mg	8 un.	28 un.	9.6 un.
Cost per treatment (R$)	*I:* 81,570.48 *M:* 222,464.90 *Total:* 304,035.38	156,612.72	467,177.76	208,293.31
Total cost per treatment combination (R$)	460,648		675,471	
Cost per treatment with monitoring costs (R$) §	521,625		736,448	
Annual estimates				
Annual cost (R$)	526,500.28	156,612.72	600,657.12	263,259.60*
Annual cost per treatment combination (R$)	683,113		863,917	
Annual cost per treatment combination with monitoring costs (R$) §	787,314		937,861	

*Median treatment doses estimated considering median treatment duration in months and cycle duration. †Median treatment doses estimated multiplying median treatment duration in months by the number of tablets per month. ‡ Units needed to cover the dose needed for the treatment duration, keeping the relation between dose and units needed per cycle. § Monitoring costs added considering treatment duration in each study (Botrel *et al.*, 2021). ‖ Median duration of treatment and doses for the intention-to-treat population reported by the study (Albiges *et al.*, 2020). ¶ Median duration of treatment for each drug for the intention-to-treat population reported by the study (Rini *et al.*, 2019b). I, induction, M, maintenance; mDOT, median duration of treatment; PFS, progression-free survival; Q2W, every two weeks; Q3W, every three weeks; un., unit.

Considering the mDOT of each therapy combination for the scenario analysis, the estimated cost per treatment is R$ 460,648 for a median 7.9 months of treatment with NIVO+IPI and R$ 675,471 for a median 9.2 months of treatment with PEMBRO and 9.6 months of treatment with AXI. Adding monitoring costs, the treatment cost based on mDOT of NIVO+IPI is R$ 521,625 and of PEMBRO+AXI is R$ 736,448.

COPE

The COPE in the base case analysis using treatment costs based on mPFS for I/P-risk patients and NNT for OS and PFS at each time point considered is presented in Table 3. An additional analysis including monitoring costs is also presented. The COPE for OS of NIVO+IPI decreased from R$ 7,663,440 at month 12 to R$ 5,108,960 at month 42. For PEMBRO+AXI, COPE for OS increased from R$ 6,047,417 at month 12 to R$ 7,734,547 at month 42 for the base case analysis.

The COPE for PFS decreased over time with NIVO+IPI, from R$ 9.579,300 at the 12-month follow-up to R$ 3,831,720 at the 30-month follow-up. Conversely, for PEMBRO+AXI, the COPE increased from R$ 6,407,417 to R$ 9,668,184 at 12- and 30-month follow-up, respectively. Additional follow-up available for NIVO+IPI showed a continued COPE reduction of R$ 3,193,100 at month 48.

The scenario analysis using treatment costs based on mDOT, with or without monitoring costs, is presented in Table 4. COPE values for this scenario are lower than the base case for all therapies and time points. At months 12 and 42, the COPE for OS with NIVO+IPI was R$ 5,527,777 and R$ 3,685,185, respectively, and with PEMBRO+AXI was R$ 4,728,298 and R$ 5,403,769, respectively. For PFS, the COPE with NIVO+IPI was R$ 6,909,772 and R$ 2,763,889 at months 12 and 30, further reducing to R$ 2,303,241 at month 48. For PEMBRO+AXI, the COPE increased from R$ 4,728,298 at month 12 to R$ 6,754,711 at month 30.

Discussion

This study demonstrated that the NNT and COPE for OS and PFS vary with the follow-up time used to estimate the event rates for PEMBRO+AXI and NIVO+IPI as first-line treatments for I/P-risk patients with advanced RCC. Overall, NIVO+IPI showed the lowest COPE in all analyses, except for the 12-month time point. The result was driven by the NNT decrease for NIVO+IPI with time for OS and PFS and its lower treatment cost. The NNT reduction with time represents the durable effect of the combination of two immuno-oncology agents. For PFS, specifically, a change in shape is visible in the Kaplan-Meier curve from 18 months onwards, with a plateau

Table 3. COPE for OS and PFS estimates for NIVO+IPI and PEMBRO+AXI as first-line treatments for I/P-risk patients

Outcome	Base case (R$)			With monitoring costs (R$)		
	NIVO +IPI	PEMBRO+AXI	Relative COPE increase*	NIVO +IPI	PEMBRO+AXI	Relative COPE increase*
Treatment cost†	638,620	966,818		734,176	1,053,729	
COPE – OS						
12 months‡	7,663,440	6,047,417	-21.1%	8,810,110	6,565,024	-25.5%
18 months	5,108,960	8,701,366	70.3%	5,873,407	9,483,565	61.5%
24 months	5,108,960	7,734,547	51.4%	5,873,407	8,429,836	43.5%
30 months	5,747,580	8,701,366	51.4%	6,607,582	9,483,565	43.5%
36 months	6,386,200	-	-	7,341,758	-	-
42 months	5,108,960	7,734,547	51.4%	5,873,407	8,429,836	43.5%
48 months	5,108,960	-	-	5,873,407	-	-
COPE – PFS						
12 months‡	9,579,300	6,047,417	-36.9%	11,012,637	6,565,024	-40.4%
18 months	6,386,200	8,701,366	36.3%	7,341,758	9,483,565	29.2%
24 months	5,747,580	8,701,366	51.4%	6,607,582	9,483,565	43.5%
30 months	3,831,720	9,668,184	152.3%	4,405,055	10,537,295	139.2%
36 months	3,831,720	-	-	4,405,055	-	-
42 months	3,831,720	-	-	4,405,055	-	-
48 months	3,193,100	-	-	3,670,879	-	-

*Relative COPE increasing calculated with the difference of COPE for PEMBRO+AXI minus COPE of NIVO+IPI divided by the COPE from NIVO+IPI. †Treatment cost considering mPFS from each study. ‡At the 12-month time point, the annual treatment cost from PEMBRO+AXI was used (R$ 863,917 without monitoring costs and R$ 937,861 with monitoring costs), as mPFS was longer than the landmark time point. COPE, cost of preventing an event; NIVO+IPI, nivolumab + ipilimumab; mPFS, median progression-free survival; NNT, number needed to treat; OS, overall survival; PFS, progression-free survival; PEMBRO+AXI, pembrolizumab + axitinib.

observed from approximately 24 months in the CheckMate 214 trial that is not observed for sunitinib (Albiges *et al*., 2020). Also, based on the latest PFS curve for I/P-risk patients from KEYNOTE-426, no plateau for PFS was observed for both PEMBRO+AXI and sunitinib groups (Powles *et al*., 2020).

Botrel *et al*., 2021 conducted a NNT and a COPE analysis with PEMBRO+AXI and NIVO+IPI in the first-line treatment of I/P-risk patients with mRCC. The study indicated that PEMBRO+AXI would be a better treatment option than NIVO+IPI, with the lower values of NNT and COPE for OS and PFS at 12-month follow-up. The present study shows the results for subsequent follow-up time based on analysis with more mature OS and PFS data for both therapies (Albiges *et al*., 2020; Powles *et al*., 2020; Rini *et al*., 2021). Our results show that the NNT of each therapeutic option varies with time and becomes more favorable or with the same magnitude for NIVO+IPI compared with PEMBRO+AXI beyond 12 months. Supported by lower treatment costs and lower NNT for NIVO+IPI with time, COPE was considerably lower for NIVO+IPI from month 18 onwards in all analyses, reflecting a difference in treatment effect for patients over time with NIVO+IPI versus sunitinib.

There are some differences between the analysis conducted in this study and that published recently by Botrel *et al*., 2021. Botrel *et al*., 2021 used the area under the PFS curve until 12 months as a proxy for time on treatment from an interim analysis based on shorter follow-up for both studies. Reviewing acquisition costs used in this study, the choice of nivolumab dosing (2 x 100 mg/10 mL vials + 1 x 40 mg/4 mL vial) resulted in 30 mg excess dose compared with our study, leading to a 9% overestimation of its actual cost per cycle in the induction phase. These differences may explain the variation in results observed in this current study and the study by Botrel *et al*., 2021 for the 12-month time point.

From month 18 onwards, the difference in NNT for OS between NIVO+IPI and PEMBRO+AXI is reduced, and the same NNT value is reached at the 42-month time point. For PFS, the NNT of NIVO+IPI drops below the NNT of PEMBRO+AXI in the 30-month time point analysis. Thus, the potential superiority of PEMBRO+AXI at month 12 for OS and PFS, shown by our and Botrel *et al*., 2021 analyses, was no longer seen in the subsequent time points analyzed in this study. On the contrary, COPE was lower for NIVO+IPI than PEMBRO+AXI in all subsequent time points for both OS and PFS analysis. Noteworthy, the OS NNT and COPE for NIVO+IPI decreased or remained relatively stable until the maximum time point analyzed (48 months). A reduction in PFS NNT and COPE for NIVO+IPI was also observed from the 18-month to

Table 4. COPE for OS and PFS estimates for NIVO+IPI and PEMBRO+AXI for I/P-risk patients as first-line treatments using median duration of treatment for treatment cost estimates

Outcome	Base case (R$)			With monitoring costs (R$)		
	NIVO +IPI	PEMBRO+AXI	Relative COPE increase*	NIVO +IPI	PEMBRO+AXI	Relative COPE increase*
Treatment cost†	460,648	675,471		521,625	736,448	
COPE – OS						
12 months	5,527,777	4,728,298	-14.5%	6,259,497	5,155,134	-17.6%
18 months	3,685,185	6,079,240	65.0%	4,172,998	6,628,030	58.8%
24 months	3,685,185	5,403,769	46.6%	4,172,998	5,891,582	41.2%
30 months	4,145,833	6,079,240	46.6%	4,694,623	6,628,030	41.2%
36 months	4,606,481	-	-	5,216,248	-	-
42 months	3,685,185	5,403,769	46.6%	4,172,998	5,891,582	41.2%
48 months	3,685,185	-	-	4,172,998	-	-
COPE – PFS						
12 months	6,909,722	4,728,298	-31.6%	7,824,372	5,155,134	-34.1%
18 months	4,606,481	6,079,240	32.0%	5,216,248	6,628,030	27.1%
24 months	4,145,833	6,079,240	46.6%	4,694,623	6,628,030	41.2%
30 months	2,763,889	6,754,711	144.4%	3,129,749	7,364,478	135.3%
36 months	2,763,889	-	-	3,129,749	-	-
42 months	2,763,889	-	-	3,129,749	-	-
48 months	2,303,241	-	-	2,608,124	-	-

* Relative COPE increasing calculated with the difference of COPE for PEMBRO+AXI minus COPE of NIVO+IPI divided by the COPE from NIVO+IPI. †Treatment cost considering mDOT from ITT population of each study. COPE, cost of preventing an event; NIVO+IPI, nivolumab + ipilimumab; mDOT, median duration of treatment; NNT, number needed to treat; OS, overall survival; PFS, progression-free survival; PEMBRO+AXI, pembrolizumab + axitinib.

48-month time point. The OS NNT and COPE for PEMBRO+AXI went on the other way and increased or remained relatively stable until the maximum follow-up analyzed (42 months). An increase in the PFS NNT and COPE for PEMBRO+AXI was also observed from 12-month to 30-month analyses.

The COPE estimation is an alternative to cost-effectiveness analysis. It is simpler to conduct and easier to interpret by decision-makers as it represents the cost for every event potentially avoided by the treatment of interest (Maharaj, 2008). However, COPE does not represent a complete economic evaluation. It ignores several elements included in a full cost-effectiveness analysis, such as the modeling of the disease course over time, estimation of costs and consequences possibly including the disease impact on quality of life, alternative treatments under the same assumptions, and estimation of the incremental cost-effectiveness ratio between alternatives (Brazil, 2014). However, it provides rapid insight into the drug cost at a population level for the given effectiveness as determined by the randomized controlled trial (Maharaj, 2008).

We must emphasize that the comparison between therapies in this study is a naive, unadjusted comparison and should not be used to prove the treatments' clinical or economic superiority. Possible differences in potential confounding factors, including baseline characteristics, between the studies may impact the NNT result. Still, the COPE estimated for each therapy individually should not have significant problems with confounding, even with data extracted for only a subgroup of patients, as the PFS and OS are originated from randomized clinical trials with randomization stratified by risk. Therefore, the analysis provides an approximate estimate of each treatments' efficiency. As mDOT was not published for the I/P-risk patients in the clinical trials, we used mPFS for I/P-risk patients to estimate the treatment costs in the base case analysis, which may have overestimated the treatment costs and consequently the COPE results, especially for NIVO+IPI. There is evidence that NIVO+IPI treated patients experienced survival time free of therapy (including subsequent anticancer therapy) despite treatment discontinuation, suggesting that the base case with the mPFS approach may be conservative for this therapeutic option (McDermott *et al*., 2018; Regan *et al*., 2020).

Moreover, data from CheckMate 214 at a minimum follow-up of 4 years (median follow-up = 55 months) showed that only 53 (10%) of 547 patients in the NIVO+IPI arm (ITT patients) were reported to continue therapy (Albiges *et al*., 2020). At this follow-up, 31% of patients in the ITT group and 32.7% in the I/P-risk subgroup had not progressed (Albiges *et al*., 2020). So far, no treatment-free survival or treatment-free interval was published for PEMBRO+AXI.

A scenario analysis was added to consider mDOT for the ITT population of each study as an approximation for time on treatment cost calculation, which produced lower COPE estimates for both treatments. This scenario analysis also has some limitations; it was based on treatment duration in the ITT population, not specific to I/P-risk patients, and mDOT for PEMBRO+AXI was reported only for a limited median follow-up of 12.8 months from KEYNOTE-426 (Rini *et al*., 2019b). Furthermore, mDOT may also underestimate the actual treatment cost compared with mean DOT, considering that mean DOT for PEMBRO+AXI was approximately 18 months in the longer follow-up based on reported mean treatment exposure (Powles *et al.,* 2020), resulting in much higher COPE results for PEMBRO+AXI than the ones presented in this article. Therefore, the base case based on mPFS for time on treatment approximation was considered balanced for PEMBRO+AXI given the concurrence between PFS and time on treatment in both arms of KEYNOTE-426 reported by a cost-effectiveness analysis previously published (Bensimon *et al*., 2020).

As mentioned before, the microcosting used in this study for monitoring cost did not include adverse event management. A recent network meta-analysis including NIVO+IPI and PEMBRO+AXI analyzed the rates of ≥ grade 3 adverse event to measure treatment toxicity (Mori *et al*., 2021). Compared with sunitinib, NIVO+IPI was the only treatment associated with a significantly lower likelihood of toxicity (OR 0.50, 95% credible interval 0.39-0.64); based on analysis of the treatment ranking, it was highly likely that NIVO+IPI had the lowest rate of serious AEs (Mori *et al*., 2021). A recently published study reported that NIVO+IPI was associated with lower costs of managing grade ≥ 3 adverse events than PEMBRO+AXI from a United States healthcare payer perspective (McGregor *et al*., 2021). Therefore, if adverse event management were included in the microcosting, an even larger difference between NIVO+IPI and PEMBRO+AXI COPE results should be noted from 18 months onwards, and the absence of AE management in our study could be considered conservative.

This study limited the analysis to immunotherapy-based studies, given the paradigm shift in the treatment of mRCC since the introduction of regimens based on immunotherapy (Rini *et al*., 2019a). This analysis did not include other recommended immunotherapy-based regimens for the treatment of first-line advanced RCC, including nivolumab plus cabozantinib and avelumab plus axitinib (ESMO, 2020; Fay *et al*., 2021; NCCN, 2021). The nivolumab plus cabozantinib combination, which showed improved PFS and OS compared with sunitinib (Choueiri *et al*., 2021), was not considered because the Brazilian regulatory agency has not yet approved it. The avelumab plus axitinib combination was not included because the OS data were still immature at the most recent publication, not showing significant benefit for this outcome, with a median follow-up for OS of approximately 19 months (Choueiri *et al*., 2020). Finally, our study compared the NNT

and COPE of NIVO+IPI versus PEMBRO+AXI through different time points using more mature data from CheckMate 214 and KEYNOTE-426, respectively. The results showed that NNT and COPE are parameters that vary with the time point chosen, highlighting that a single follow-up analysis should be interpreted with caution.

Conclusion

This analysis, with extended follow-up time points to assess NNT and COPE from NIVO+IPI and PEMBRO+AXI as first-line treatments for I/P-risk patients with advanced RCC from the Brazilian private health system perspective, showed that the NNT and COPE for PFS and OS may vary per the time point chosen in the analysis. From month 18 to 42, NNT for OS for NIVO+IPI was approximately the same as for PEMBRO+AXI. The NNT for PFS, on the other hand, inverted relative to PEMBRO+AXI from the 12-month time point, after which NIVO+IPI had a lower NNT that continued to decrease with increasing follow-up time. Although the true COPE for NIVO+IPI and PEMBRO+AXI may be underestimated due to limited data available, regardless of the approach used to calculate treatment costs, the treatment with NIVO+IPI results in lower COPE than PEMBRO+AXI from month 18 onwards. This reduction in COPE for NIVO+IPI is mainly driven by improved NNT of NIVO+IPI over time compared with stable or increased NNT of PEMBRO+AXI over time, as well as lower treatment costs of the double immunotherapy option, suggesting that NIVO+IPI may be a therapy with better efficiency over longer follow-up time.

Acknowledgments

We would like to acknowledge Frederico José Bighetti Magro, who at the time of the analysis was an employee of Bristol Myers Squibb (Brazil), for leading and supporting the planning of this article.

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