Pembrolizumab plus axitinib and nivolumab plus ipilimumab as first-line treatments of advanced intermediate- or poor-risk renal-cell carcinoma: a number needed to treat analysis from the Brazilian private perspective

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ABSTRACT

Background: Considering clinical benefits of new combination therapies for metastatic renal-cell carcinoma (mRCC), this study aims to calculate the number needed to treat (NTT) and the cost of preventing an event (COPE) for pembrolizumab plus axitinib (P + A), and nivolumab plus ipilimumab (N + I) as first-line treatments, from the Brazilian private perspective.

Methods: Overall survival (OS) and progression-free survival (PFS) data for intermediate- and poor-risk groups were obtained from KEYNOTE-426 and CHECKMATE-214 trials for P + A and N + I, respectively, versus sunitinib as mRCC first-line treatment.

Results: Considering a 12-month time horizon, 6 patients should be treated with P + A to prevent one death with sunitinib use, resulting in a COPE of 3,893,903 BRL. Using N + I, NNT for 12-month OS rate was 13 compared to sunitinib, with a COPE of 6,357,965 BRL. Regarding PFS data, NNT was also 6 when comparing P + A versus sunitinib, with an estimated COPE of 3,893,903 BRL. Estimated NNT was 20 comparing N + I and sunitinib, resulting in a COPE of 10,172,744 BRL. Cost differences between two treatment options, reached more than 6 million BRL for PFS, and 2 million BRL for OS.

Conclusion: At the 12-month landmark, P + A suggests better economic scenario versus N + I as first-line mRCC treatment option for intermediate- and poor-risk groups, through indirect comparison using sunitinib as a common comparator.

Introduction

Renal-cell carcinoma (RCC) is the most frequent type of kidney cancer, representing about 90% of cases. Clear cell RCC is the most common histological subtype and accounts for most cancer-related deaths1. According to the International Agency for Research on Cancer, incidence and mortality rates for kidney neoplasms of 4.5 and 1.8 per 100,000 inhabitants worldwide were expected for 2018, respectively. In Brazil, kidney cancer incidence and mortality rates of 4.3 and 1.6 per 100,000 inhabitants were estimated for the same year2.

When diagnosed in early stages, the surgical treatment with partial or radical nephrectomy is indicated. However, a relevant percentage of patients with RCC are diagnosed in late stages3,4. In Brazil, a study showed 37.9% of advanced or metastatic RCC (mRCC) at diagnosis4. For those cases, systemic treatments with immunotherapy or targeted agents are recommended1. According to Close-Up International database, patterns of care vary greatly and while 79% of mRCC patients receive first-line therapy, only 20% are treated with second-line therapy in Brazil5.

First-line treatment option for mRCC is dependent on risk classification according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria, which classifies patients as having favorable, intermediate- or poor-risk through six predictors of poor survival6. Based on Brazilian, European and American guidelines, those classified as favorable-risk disease may receive pazopanib, sunitinib or the combination of pembrolizumab plus axitinib or avelumab plus axitinib. For those with intermediate- or poor-risk disease, first-line treatment options may involve the use of pembrolizumab plus axitinib, nivolumab plus ipilimumab, avelumab plus axitinib, cabozatinib, sunitinib, or pazopanib7,8. In clinical trials, pembrolizumab plus axitinib and nivolumab plus ipilimumab demonstrated to improve overall survival (OS) when compared to sunitinib for mRCC patients9-11. Furthermore, OS data were
not yet mature in the study of avelumab plus axitinib combination, in the time this study was developed\textsuperscript{12}.

RCC imposes a relevant economic burden for patients and society. In France, a mean direct cost of 71,185 EUR per patient with metastatic disease was estimated in a lifetime horizon\textsuperscript{13}. Considering only drug-related costs, a mean of 32,951 EUR per patient with metastatic disease was observed in Finland\textsuperscript{14}. These studies were conducted before the advent of immunotherapy; thus, the current disease burden may be even higher. Previous studies have evaluated the cost-effectiveness of the new first-line treatment option for mRCC\textsuperscript{15,16}, but these analyzes did not involve a cost perspective similar to that of Brazil.

In a setting of continuous technological and scientific development, the increase on costs caused by the incorporation of innovation threatens the sustainability of healthcare delivery and the consequent financial constraints cause wide variations in patterns of care for cancer patients\textsuperscript{5}. Considering that financial resources are limited in healthcare systems, economic and clinical evaluations are complements and needed to an adequate decision-making process\textsuperscript{17}. Different strategies may be used in economic analyses, such as cost-effectiveness, cost-utility, cost-minimization, cost-benefit, and cost of preventing an event (COPE) or cost-consequence, calculated based on the number needed to treat (NNT)\textsuperscript{18}. Despite the importance of economic analyses, the complexity of some models may impose comprehension difficulties by clinicians and non-economist policy-makers\textsuperscript{19}.

Considering that economic evaluations aim to compare alternative technologies in terms of both costs and consequences, NNT and further calculation of COPE represent a simpler way to assess these aspects\textsuperscript{20}. NNT evaluates the impact of a drug on a given disease outcome, representing the number of patients required to be treated to produce a beneficial result or to prevent a harmful event in one additional patient. The measure is calculated as the inverse of the absolute risk reduction of an event\textsuperscript{20–22}. COPE is calculated through the product of NNT and treatment-related costs\textsuperscript{20}. These analyses have been previously used to understand economic oncological issues in Brazil\textsuperscript{23}.

Given the clinical benefits shown by using the combination of pembrolizumab plus axitinib and nivolumab plus ipilimumab, both compared to sunitinib as first-line treatments for mRCC, to understand its economic impact seems to be meaningful for the decision-making process. Therefore, the aim of the present study was to calculate the NNT and COPE of pembrolizumab plus axitinib and nivolumab plus ipilimumab as mRCC first-line treatments, considering the Brazilian private healthcare system perspective.

### Methods

#### Study population

This analysis was conducted considering the population and clinical data obtained from KEYNOTE-426 (NCT02853331) and CHECKMATE-214 (NCT02231749) trials. These studies were selected as they were both registration trials of current available options and reached mature data on OS\textsuperscript{10,11,24–27}. KEYNOTE-426 (NCT02853331) and CHECKMATE-214 (NCT02231749) are phase 3 open-label trials, comparing pembrolizumab plus axitinib and nivolumab plus ipilimumab versus sunitinib, respectively, as first-line of mRCC treatment. KEYNOTE-426 was designed to assess OS and progression free survival (PFS) among all IMDC risk groups, while CHECKMATE-214 assessed OS, objective response rate and PFS among patients with intermediate or poor prognostic risk\textsuperscript{10,11,24–27}.

In both trials, patients with advanced clear-cell RCC, older than 18 years and without a previous systemic treatment were included. Subjects were classified through the IMDC risk group as favorable, intermediate- and poor-risk\textsuperscript{10,11,24–25}. IMDC is a prognostic model built to predict survival through six characteristics assessed before treatment (treatment time, performance status, hemoglobin, calcium, neutrophil, and platelets; Supplementary Table 1). Each characteristic counts as one point and the sum classifies the patient as favorable (total score = 0), intermediate- (total score ranging from 1 to 2) and poor-risk (total score ranging from 3 to 6).

The coprimary endpoints were evaluated among intermediate- and poor-risk patients in the CHECKMATE-214 while the efficacy endpoints were assessed in the intention-to-treat population in the KEYNOTE-426, which included all patients who underwent randomization regardless of IMDC classification. Due to the limitation of the available data, this study used only data for intermediate- and poor-risk groups from both studies in order to compare populations as similar as possible, since the combination of ipilimumab and nivolumab is only approved for these patients.

Two independent studies were selected due to the lack of head-to-head studies comparing the two interventions of interest. It is important to note that avelumab plus axitinib as mRCC first-line treatment was excluded from this analysis as the OS data are still immature after a minimum follow-up of 13 months\textsuperscript{12}. Other treatment options for advanced RCC, such as nivolumab plus cabozantinib\textsuperscript{28}, do not yet have regulatory approval for use in Brazil.

#### Study outcomes

OS and PFS were the outcomes of interest. Due to the limitation of the available data for the population of interest, this study used 12-month OS and PFS rates. KEYNOTE-426 and CHECKMATE-214 define PFS as the time from randomization to the first documented progressive disease (PD) or death, whichever occurred first. PD was described as ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, an absolute increase of ≥5 mm and the appearance of one or more new lesions. OS was defined as the time from randomization to death due to any cause\textsuperscript{10,11,24–25}. As CHECKMATE-214 publication only reports rounded percentages, OS and PFS were described in the same way in this study.

For these analyses, one year was considered as a 52-week period, and one month as a 30-day period. NNT was calculated considering a 12-month period for both studies due to shorter follow-up period available for intermediate- and poor-risk patients in KEYNOTE-426.
Costs

Cycles duration and doses used in the cost calculation were defined in accordance with local labels of pembrolizumab plus axitinib and nivolumab plus ipilimumab, considering a mean weight of 70 kg per patient.

Since the median PFS was shorter than 12 months in both studies, mean treatment duration for the one-year time horizon was calculated as the area under the curve (AUC) of PFS for each therapeutic scheme of the analysis, assuming that treatment is interrupted at the time of disease progression. The software Engauge Digitizer Tool Version 12 was used to calculate X and Y coordinates. The curves were further rebuilt in Microsoft Excel, in order to perform tendency analysis and equation f(x) assessment. Equations and limits (0, 12) were statistically analyzed using a derived equation.

Drugs and monitoring costs were considered, however adverse events management costs were not included. Drug costs used are the ex-factory price with 18% of goods and services tax (Imposto sobre Circulação de Mercadorias e Serviços, ICMS) for 2019, obtained from the official list published by the Medicines Market Regulation Chamber (CMED). For the monitoring costs, a micro-costing approach was developed and the resource utilization related to imaging and laboratory tests, biological product administration fee and medical appointment was estimated based on products’ labels, clinical trials, and guidelines from the Brazilian Society of Clinical Oncology (Supplementary Table 2). The microcosting was based on the Brazilian Classification of Medical Procedures (Classificação Brasileira Hierarquizada de Procedimentos Médicos) published by the Brazilian Medical Association (Associação Médica Brasileira). All costs were reported in Brazilian Real (BRL).

NNT and COPE analysis

The NNT to prevent one death (OS) or to prevent death or disease progression (PFS) at 12 months was calculated as shown in the Equation (1). Considering that COPE is the product of NNT and treatment cost, COPE estimates were calculated as described in Equation (2). The NNT = 1 ÷ (Proportion of patients who achieved outcome in intervention arm – Proportion of patients who achieved outcome in control arm)

\[
NNT = \frac{1}{(p_{intervention} - p_{control})}
\]

Formula to estimate the number needed to treat. NNT: number needed to treat.

\[
COPE = \frac{\text{Treatment cost in a specific time period} \times \text{Number needed to treat}}{n}
\]

Formula to estimate the cost of preventing an event. COPE: cost of preventing an event.

In order to understand variability of measures, 95% confidence intervals (95%CI) were calculated using the rationale for a sample proportion. We used the formula described in Equation (3), where \(\hat{p}\) is the sample proportion, \(n\) is the sample size, and \(z\) is the appropriate value from the standard normal distribution for desired confidence level.

\[
CI = \hat{p} \pm z \sqrt{\frac{p(1-p)}{n}}
\]

Formula to estimate 95% confidence intervals. CI: confidence interval.

Results

General characteristics of study population

Table 1 shows the general characteristics of patients included in both studies at baseline. Baseline demographics and disease characteristics were as expected for a trial involving patients with mRCC and were balanced between the groups in the KEYNOTE-426. Baseline characteristics were similar in the two treatment groups, and the characteristics of the intermediate- and poor-risk patients were similar to those of the intention-to-treat population in the CHECKMATE-214. The patient’s characteristics that are prognostic or risk factors for the treatment-independent outcome had similar distribution between the two clinical trials. Given the properties of the NNT, between-trial or indirect comparisons based on the NNT of individual trials should be avoided when there are differences in baseline risk. In this way, the results of this study should be interpreted with caution because the likely differences in study design or patients’ characteristics between KEYNOTE-426 and CHECKMATE-214 can influence how well the intervention arm works.

OS and PFS

The 12-month OS and PFS rates for intermediate- or poor-risk groups are described in Table 2. Regarding OS, the combination of pembrolizumab plus axitinib showed better 12-month OS rate when compared to sunitinib (87% vs. 71%) and a similar pattern was observed for nivolumab plus ipilimumab, showing better 12-month OS rates when compared to sunitinib (80% vs 72%). For 12-month PFS rate, both combination therapies presented lower frequency of disease progression compared to sunitinib. However, the between-group difference in the CHECKMATE-214 study did not meet the prespecified threshold for statistical significance in the first interim analysis. The 12-month PFS rates were estimated at 56% for pembrolizumab plus axitinib arm and 40% at sunitinib arm, in KEYNOTE-426 trial. Considering CHECKMATE-214, 12-month PFS rates were 41% in nivolumab plus ipilimumab arm and 36% in sunitinib arm.

Cost of treatment

Total estimated cost, considering drug treatment for mean PFS and monitoring, was 623,025 BRL for pembrolizumab plus axitinib and 508,637 BRL for nivolumab plus ipilimumab. The mean treatment duration estimated through the AUC of PFS was 8.76 months for pembrolizumab plus axitinib and 8.34 months for nivolumab plus ipilimumab. Tables 3 and 4
show therapeutic regimen characteristics and parameters used to calculate drug costs, respectively. Monitoring costs were considered similar in both groups, estimated at 4,785.62 BRL in the first cycle of treatment and 4,322.39 BRL per subsequent cycle (Supplementary Table 2).

**NNT and COPE per outcome**

For the 12-month OS rate, a total of 6 (95%CI: 5.27–7.66) patients must be treated with pembrolizumab plus axitinib to prevent one death over a period of 12 months after
more efficient treatment option than nivolumab plus axitinib. This study suggests that pembrolizumab plus axitinib is a promising option for mRCC patients who are treated with a first-line therapy as pembrolizumab plus axitinib versus sunitinib resulted in a COPE of 3,893,903 BRL (95%CI: 3,283,339–4,772,368). The NNT for 12-month OS rate was 13 (95%CI: 10.18–16.20) for PFS, and 2 million BRL for OS.

The NNT for favorable risk group was 20 (95%CI: 15.46–28.31) patients to be treated with ipilimumab plus nivolumab to prevent one disease progression or death when compared to sunitinib, which results in a COPE of 10,172,744 BRL (95%CI: 7,863,528–14,399,513). Table 5 shows the NNT and COPE results related to 12-month OS and PFS from KEYNOTE-426 and CHECKMATE-214.

Discussion

This study suggests that pembrolizumab plus axitinib is a more efficient treatment option than nivolumab plus ipilimumab with lower values of NNT and COPE for 12-month OS and PFS. Lower NNT values indicate the need for fewer patients to be treated to obtain an additional benefit in terms of death and disease progression avoided. Likewise, lower values of COPE mean lower costs to obtain this additional benefit. COPE analysis showed a difference greater than 2 and 6 million BRL for OS and PFS, respectively, with pembrolizumab plus axitinib versus nivolumab plus ipilimumab against sunitinib as mRCC first-line treatment. In the absence of a threshold for evaluating NNT, these values should be interpreted considering the context of the evaluation since a high NNT may be considered acceptable for a severe event.

Previous analysis have assessed the relationship between clinical and economic benefits of pembrolizumab, axitinib, nivolumab and ipilimumab, isolated or in combination for mRCC management, using traditional strategies such as cost-effectiveness and cost-utility analyses. In Brazil, the National Sanitary Agency (Agência Nacional de Vigilância Sanitária – ANVISA) is responsible for registering new drugs, an exclusive task of the State that intervenes in the production-consumption relationship by establishing legal rules for granting this registration. Contrary to what occurs in other countries, the registration of a drug in Brazil does not require any analysis of the product’s economic viability. After regulatory approval of the new drug, the decision on whether or not to use the product in an institution’s therapeutic arsenal is left to the regional payers, who is often not a health professional or has a background in health economics. In this context, the calculation of NNT and COPE are intended to be more user-friendly measures aiming to assess costs and consequences of the adoption of different technologies in this process. Despite previous comparative publications available to treat mRCC, simpler and more practical pharmacoeconomic analyzes for health decision-making process in Brazil are needed.
Even after improvement on mRCC management, high costs are still imposed to healthcare system, patients and the whole society\textsuperscript{41}. Some novel tools to optimize the cost/ effectiveness of immunotherapy in RCC have been proposed, such as fixed dose assessment, determination of biomarkers to promote early treatment cessation and the improvement of treatment length. However, these initiatives have not been successful on decreasing disease burden yet. In example, Soerensen et al.\textsuperscript{42} did not find a significant difference on total healthcare costs per patients after implementing targeted therapy for mRCC management in Denmark. Thus, the proposal of further initiatives to decrease disease costs still needs to be promoted.\textsuperscript{3}

The present study evaluated 12-month OS and PFS rates in the intermediate-to-poor risk groups in KEYNOTE-426 and CHECKMATE-214. OS is considered as a universally accepted direct measure of a clinical benefit, while PFS may be used as a surrogate or direct measure of a clinical improvement in studies assessing cancer management. The 12-month OS and PFS were reported in the publications with less uncertainty due to censoring\textsuperscript{11,26,27}. The analysis was restricted to the IMDC intermediate- and poor-risk groups as nivolumab plus ipilimumab was only approved in this population. In general, three quarters of patients with mRCC have intermediate- or poor-risk clinical characteristics\textsuperscript{43}.

In this analysis, patients were assumed to be treated until progression in the 12-month study period. To estimate the mean treatment duration, Kaplan–Meier curves for PFS were extracted from the pivotal clinical trials. The mean PFS was then estimated by calculating the area under each PFS Kaplan Meier curve, assuming that treatment is interrupted at the time of disease progression\textsuperscript{44,45}. The AUC approach accurately estimated the mean time to progression (proxy of treatment duration) with censoring appropriately considered. The outcomes, PFS and OS rates for each treatment arm at 12 months were extracted from the Kaplan Meier curves.

The study has some limitations. The actual time on treatment may be different than PFS used to calculate study variables, however, mean treatment durations were not available in the KEYNOTE-426 and CHECKMATE-214 publications. In the absence of a head-to-head comparison between pembrolizumab plus axitinib and nivolumab plus ipilimumab, an indirect treatment comparison was conducted with sunitinib as a common comparator. There are not concerning differences between the two studies in terms of the targeted study population, but differences that were not accounted in the studies design and in the characteristics of the patients can generate differences in baseline risk of the study population, which interferes with the NNT result. Furthermore, patient reported outcomes were not considered by the authors to assess efficacy of two treatment strategies due to the unavailability of published data so far. It is also important to highlight that NNT and COPE shown in the present analysis only refers to Brazilian scenario, since other countries may have different pricing policies, reducing generalizability of data.

A major limitation that also needs to be highlighted is that adverse events management costs were not included in this analysis. The authors decided not to consider this variable due to the likely regional variations in patients’ care and the lack of published primary data indicating their resource utilization and costs. In addition, reports from clinical trials used to perform the present analysis only presents results for total safety population, making the analysis of the subgroup of interest, intermediate- and poor-risk mRCC, unfeasible. However, it is important to state that treatment strategies compared have different safety profile. Nivolumab plus ipilimumab is expected to have higher frequency of immune-related adverse events due to the addition of anti-CTLA-4 therapy, whereas pembrolizumab plus axitinib generally has higher rates of grade $\geq 3$ adverse events due to the tyrosine kinase inhibitor. Increased lipase level is the most frequently observed grade 3 or 4 adverse event for the combination nivolumab plus ipilimumab, while hypertension was the most frequent for the association of pembrolizumab and axitinib\textsuperscript{10,11}.

A study conducted from the Brazilian private healthcare system perspective calculated a monthly average adverse event costs per patient for nivolumab of 199.83 BRL, representing only 0.5% of total treatment costs\textsuperscript{46}. The available data suggest that adverse event management costs may not significantly impact the conclusion. On the other hand, the difference in the tolerability profile between pembrolizumab plus axitinib and nivolumab plus ipilimumab can cause different economic burdens for the Brazilian health system. Given the importance of the topic, future research should address this issue. Moreover, future research can evaluate the number needed to harm (NNH), which indicates how many people need to be treated for one patient to have an adverse event. NNH analysis evaluates the risk associated with the treatments and can inform the decision making from a different perspective.

In addition, future studies can assess other relevant outcomes related to efficacy of treatment strategies such as response rate, time to disease progression, disease-free survival, and objective responses. One of the potential advantages of an immunotherapy-based strategy for RCC is obtaining long-term responses. The longer follow-up of the studies, including the 42-month follow-up of the CHECKMATE-214, indeed demonstrated that 35% of patients are progression free after 3 years of therapy\textsuperscript{27}. This potential long-term benefit of immunotherapies is also important for cost-benefit analyses and further work is needed to address this question. In the present study, unavailability of long-term data on the included clinical trials does not allow to estimate differences in other follow-up periods.

Conclusions

Considering the absence of head-to-head trials comparing pembrolizumab plus axitinib and ipilimumab plus nivolumab, an indirect analysis was performed using sunitinib as common comparator. Pembrolizumab plus axitinib and nivolumab plus ipilimumab shows better clinical scenario in a 12-month period than sunitinib among intermediate- and poor-risk mRCC. Beyond the already known improvement of OS and PFS, pembrolizumab plus axitinib may promote a reduction in the cost per event avoided.
Transparency

Declaration of funding

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Declaration of financial/other relationships

TEAB declares no conflict of interest. DLJ receives speaker fees from Roche, Janssen, Astellas, MSD, Bristol-Myers Squibb and Libbs, as well as consultant fees from Janssen, Bristol-Myers Squibb and Libbs. MDA, LCH, CRPDV and DDVF are formal employees at MSD.

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Author contributions

TEAB and DLJ contributed to conception, design or planning of the study, analysis of the data, interpretation of the results, drafting the manuscript and critically reviewing or revising the manuscript for important intellectual content. MDA and LCH contributed to conception, design or planning of the study, analysis of the data, interpretation of the results and critically reviewing or revising the manuscript. CRPDV contributed to analysis of the data, acquisition of the data, interpretation of the results, drafting of the manuscript, critically reviewing or revising the manuscript for important intellectual content. DDVF contributed to acquisition of the data, interpretation of the results and critically reviewing or revising the manuscript for important intellectual content.

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