Cost-effectiveness of pembrolizumab + axitinib versus nivolumab + ipilimumab as first-line treatment of advanced renal cell carcinoma in the Private Healthcare System in Brazil

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Introduction

- Approximately 431 thousand new cases of kidney cancer were diagnosed in 2020, of which 11,971 occurred in Brazil (1,2).
- Twenty percent of Brazilian patients are diagnosed in metastatic stage (3). Of these, 74% present intermediate or poor-risk disease, which means a worst prognosis (4).
- Treatments for renal cell carcinoma are constantly evolving, being the current gold standard for the first-line metastatic scenario the combotherapies, encompassing the combination of two immunotherapies or an immunotherapy plus a tyrosine kinase inhibitor (TKI) (5).
- In Brazil's Private Healthcare System, intravenous (IV) oncological drugs approved by the regulatory agency are automatically reimbursed. However, when the treatment involves an oral drug, it must go through the health technology assessment (HTA) process for reimbursement approval, which includes a cost-effectiveness analysis as mandatory evidence (6).

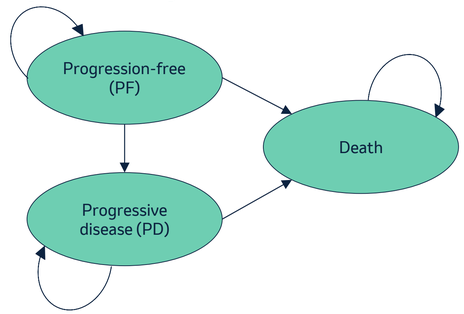
Objective

- To evaluate the cost-effectiveness of pembrolizumab (IV) + axitinib (oral) versus nivolumab (IV) + ipilimumab (IV) as first-line treatments in patients with advanced renal cell carcinoma (aRCC) at intermediate/poor IMDC (International Metastatic RCC Database Consortium) risk under the perspective of the Private Healhcare System of Brazil.

Methods

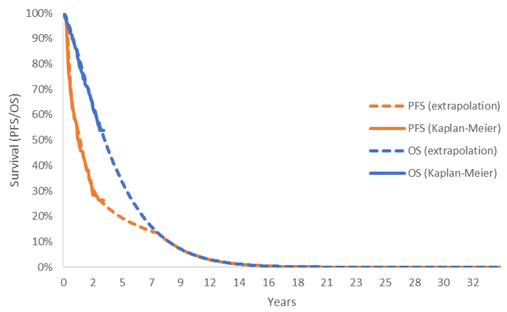
- Pembrolizumab + axitinib was compared to nivolumab + ipilimumab because the latter was the only combotherapy of mandatory coverage at the time of the analysis, as it is composed by two IV drugs.
- A three-state partitioned survival model (PSM) was developed in Excel to estimate the clinical effectiveness and expected medical costs associated with the first-line treatment of aRCC at intermediate/poor IMDC with pembrolizumab + axitinib versus nivolumab + ipilimumab over a lifetime horizon.
- The simulated cohort could transition through three health states: progression free (PF), progressive disease (PD) and death.
- Movement between health states was determined by PFS and OS data for patients treated with pembrolizumab + axitinib in the phase III clinical trial KEYNOTE-426 (7), with extrapolation based on fitted parametric functions (data cutoff: Jan 6, 2020).
- Each cycle lasted four weeks and a 5% annual discount rate was applied to costs and benefits (8).
- Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection, were used to select the best-fitted parametric functions, using Lifelines library (Python 3).

Figure 1. Model diagram.



- Weibull distribution was selected as the best fit for OS and Spline distribution was selected for PFS.
- Because of the PSM approach, PD is defined as the difference between PFS and OS. A limit is built into the model whereby PFS cannot exceed OS; if PFS is estimated to be greater than OS at any time on any model arm, PD is assumed to be zero, and PFS is assumed to be equal to OS.

Figure 2. Modeled PFS and OS for pembrolizumab + axitinib.



- Data from a network meta-analysis (Riaz et al., 2021) were used to project the survival functions of nivolumab + ipilimumab. To this end, the PFS and OS curves of pembrolizumab + axitinib were adjusted according to the hazard ratio (HR) available in the meta-analysis.

Table 1. Hazard ratios (HR) of pembrolizumab + axitinib versus nivolumab + ipilimumab – intermediate/poor IMDC risk (9).

Outcome	HR	95% confidence interval
Overall survival	0.95	0.70-1.30
Progression free survival	0.91	0.69-1.19

- PFS data was used as proxy for treatment duration.
- The dosage and maximum duration were those described in the Brazilian labels:
  - Pembrolizumab + axitinib: pembrolizumab 200 mg every 3 weeks up to 24 months and axitinib 5 mg twice a day.
  - Nivolumab + ipilimumab: nivolumab 3 mg/kg every 3 weeks for 4 cycles then 240 mg every 2 weeks and ipilimumab 1 mg/kg every 3 weeks up to 4 cycles.
- Utilities were derived from patient level data from KEYNOTE-426 using the EQ-5D-3L questionnaire. The values were 0.803 for PF and 0.756 for PD, already considering decrements because of adverse event (AE).
- In case of disease progression, patients received cabozantinib, the second-line available in the Private Healthcare System in Brazil.
- The costs of drugs were retrieved from the official price list of CMED (Medicines Market Regulation Chamber) considering the mandatory taxes (18% ICMS - tax on circulation of goods and services).
- Other cost elements included were drugs infusion procedure, AE management, disease management, subsequent therapy, and end-of-life care costs, sourced from CBHPM (Brazilian Hierarchical Classification of Medical Procedures) table and from D-TISS (Supplementary Health Information Exchange Data Panel).

Table 2. Drugs acquisition and monthly costs.

Drug	Acquisition cost PF - ICMS 18%[1]	Monthly cost[2]
Pembrolizumab	R$ 18,501	R$ 48,313
Axitinib	R$ 24,060	R$ 18,997
Ipilimumab	R$ 21,708	R$ 55,680
Nivolumab (in combination)	R$ 4,111	R$ 31,983
Nivolumab (as monotherapy)	R$ 4,111	R$ 47,927
Cabozantinib[3]	R$ 41,680	R$ 33,081

[1]CMED price list of 22/04/2022.
[2]One month was considered as containing 4 weeks. Includes acquisition and administration price.
[3]Second-line treatment.
Mean weight: 67.17 kg (10).
ICMS: *imposto de circulação sobre mercadorias e serviços*.
PF: *preço fábrica* (factory price).

- For reference, 1.00 Brazilian real (R$) equals approximately 0.19 United States dollar (U$) in January 2023.

Results

- The deterministic analysis estimated a similar clinical benefit for pembrolizumab + axitinib (2.58 QALYs) and nivolumab + ipilimumab (2.49 QALYs).
- Pembrolizumab + axitinib (R$ 1,489,180) cost less than nivolumab+ipilimumab (R$ 1,585,160), with estimated savings of R$ 95,980.

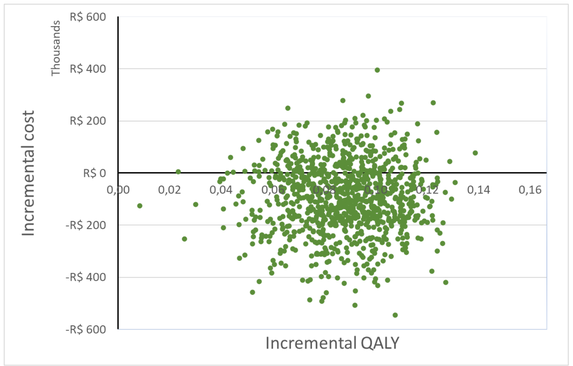
Table 3. Cost-effectiveness results.

Treatment	Cost	Incremental cost	QALYs	Incremental QALY
Nivolumab + Ipilimumab	R$ 1,585,160		2.49	
Pembrolizumab + Axitinib	R$ 1,489,180	-R$ 95,980	2.58	+0.09

QALY: quality-adjusted life-years.

- One-way sensitive analysis showed that drug costs and utilities were the parameters with the greatest impact on results.
- Probabilistic sensitivity analyses estimated that pembrolizumab + axitinib was dominant over nivolumab + ipilimumab in 74.6% of the simulations.

Figure 3. Incremental cost-effectiveness plane.



Conclusions

- Pembrolizumab + axitinib is likely cost-effective in comparison to nivolumab + ipilimumab for patients with intermediate/poor prognostic IMDC risk aRCC from a Brazilian Private Healthcare System perspective.

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