An incremental effectiveness analysis of avelumab in combination with axitinib for the treatment of first-line advanced renal cell carcinoma in Portugal

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SCOPE

- **To evaluate the incremental life-years (LYs) and quality-adjusted LYs (QALYs) with avelumab + axitinib compared with sunitinib or pazopanib in patients with International Metastatic Renal Cell Carcinoma (RCC) Database Consortium (IMDC) intermediate- or poor-risk disease and compared with temsirolimus in those with poor-risk disease in the first-line treatment of advanced renal cell carcinoma (aRCC) in Portugal**

CONCLUSIONS

- **In the selected populations, avelumab + axitinib resulted in increased LYs and QALYs compared with sunitinib, pazopanib, or temsirolimus in the first-line treatment of aRCC in Portugal**

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BACKGROUND

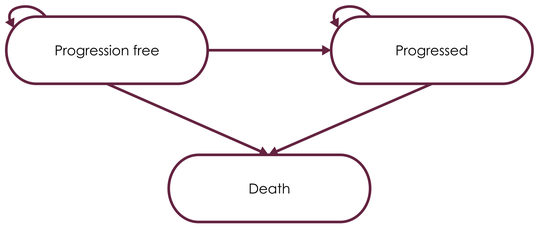
- RCC accounts for >90% of kidney cancers, with approximately 80% presenting as clear cell carcinoma within kidney tubules[1]
- Latest incidence of RCC in Portugal was estimated to be 10.14 per 100,000, with a total of 1,018 new cases observed in 2018[2]
- Avelumab is a fully human immunoglobulin G1 monoclonal antibody (with an intact Fcγ region) that inhibits the immune checkpoint protein PD-L1[3]
- Avelumab in combination with axitinib was approved by the European Commission for the first-line treatment of adult patients with aRCC[3]
- We assessed the effectiveness of avelumab + axitinib compared with pazopanib or sunitinib in patients with IMDC intermediate- or poor-risk disease and temsirolimus in those with poor-risk disease in untreated clear cell aRCC in Portugal, as requested by Portuguese authorities during their health technology assessment review

METHODS

Economic model

- A partitioned-survival model was used to assess patient evolution among 3 health states: progression-free survival (PFS), postprogression survival (PPS), and death (**Figure 1**)
- LYs and QALYs were estimated for treatment with avelumab + axitinib or the comparators in patients with aRCC
- The analysis was conducted from the Portuguese perspective, assuming a 40-year time horizon and a 4% discount rate, according to Portuguese methodological guidelines[4]
- Deterministic and probabilistic sensitivity analyses were conducted to assess the robustness of results

Figure 1. Partitioned-survival model structure



Clinical data

- Data for avelumab + axitinib and sunitinib are based on the JAVELIN Renal 101 study, a 2-arm randomized phase 3 trial comparing avelumab + axitinib vs sunitinib in adults with aRCC[5]
- Parametric functions were chosen to extrapolate overall survival (OS), PFS, and time on treatment (TOT) according to goodness-of-fit criteria and clinical plausibility (**Table 1**)
- For comparison between avelumab + axitinib vs pazopanib or temsirolimus, OS and PFS were modeled using hazard ratios (HRs) obtained from a systematic literature review and a network meta-analysis (NMA); TOT for these comparators was assumed to be equal to PFS (**Table 2**)
- For pazopanib, NMA estimates by risk subgroup (intermediate and poor) were pooled using the inverse variance method[6]
- Due to lack of data for temsirolimus, the relative effect estimated for patients with poor-risk disease was applied to the intermediate- or poor-risk disease reference curve

Table 1. Summary of key parameters and modeling extrapolation options

	Avelumab + axitinib	Sunitinib	Pazopanib	Temsirolimus
OS	Weibull	Weibull	NMA (RE)	NMA (RE)
PFS	Lognormal	Lognormal		
TOT*	Exponential	Lognormal	Equal to PFS	Equal to PFS

NMA, network meta-analysis; **OS**, overall survival; **PFS**, progression-free survival; **RE**, random effects; **TOT**, time on treatment.
*TOT for avelumab and axitinib was extrapolated separately.

Table 2. NMA results (avelumab + axitinib vs comparator arm)[7]

	Pazopanib (intermediate- or poor-risk disease)	Temsirolimus (poor-risk disease)
HR for OS (95% CI)	0.79 (0.58-0.99)	0.65 (0.32-1.28)
HR for PFS (95% CI)	0.66 (0.49-0.83)	0.31 (0.20-0.49)

HR, hazard ratio; **NMA**, network meta-analysis; **OS**, overall survival; **PFS**, progression-free survival.

Utilities

- Utility weights, stratified by progression status, were estimated by applying the EQ-5D-5L Portuguese value set[8] to the patient-reported outcome results from JAVELIN Renal 101
- Utility scores estimated for the sunitinib arm were used for the comparators not included in the trial (**Table 3**)
- Disutilities due to adverse events (AEs) were obtained from the literature[9]

Table 3. Mean utility score per health state

Health state	Score
PFS	0.840 (0.821-0.858)
PPS	0.812 (0.795-0.829)

PFS, progression-free survival; **PPS**, postprogression survival.

Adverse events

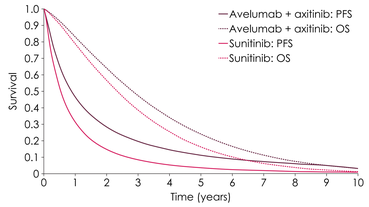
- The impact of grade 3 or 4 AEs was incorporated into the model
  - For avelumab + axitinib and for sunitinib, AE incidence was obtained from the JAVELIN Renal 101 clinical trial[5]
- For pazopanib and temsirolimus, AE rates were sourced from published literature[10,11]

RESULTS

Base-case scenario

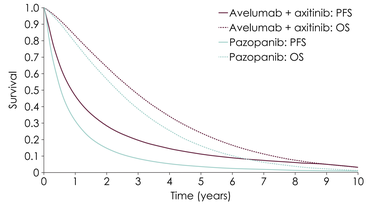
- Survival projections indicate that treatment with avelumab + axitinib prolongs both PFS and OS in patients with aRCC
- Avelumab in combination with axitinib increased average life expectancy by 0.57 undiscounted LYs, enabling a discounted gain of 0.48 LYs or 0.41 QALYs compared with sunitinib (**Figure 2**, **Table 4**)
- Compared with pazopanib, the estimated average gain was 0.56 undiscounted LYs, allowing a discounted increase of 0.47 LYs or 0.39 QALYs (**Figure 3**, **Table 4**)
- Compared with temsirolimus, avelumab + axitinib increased average life expectancy by 0.96 undiscounted LYs, enabling a discounted gain of 0.81 LYs or 0.70 QALYs (**Figure 4**, **Table 4**)

Figure 2. Base-case extrapolation of OS and PFS (avelumab + axitinib vs sunitinib)



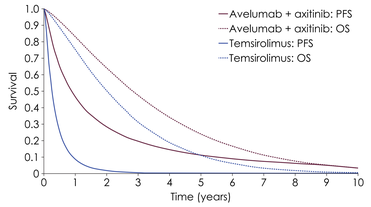
OS, overall survival; **PFS**, progression-free survival.

Figure 3. Base-case extrapolation of OS and PFS (avelumab + axitinib vs pazopanib)



OS, overall survival; **PFS**, progression-free survival.

Figure 4. Base-case extrapolation of OS and PFS (avelumab + axitinib vs temsirolimus)



OS, overall survival; **PFS**, progression-free survival.

Table 4. Base-case effectiveness

	Avelumab+ axitinib	Sunitinib	Pazopanib	Temsirolimus	Incremental vs		
					Sunitinib	Pazopanib	Temsirolimus
TOT (undiscounted years)	1.57*	1.21	1.12	0.43	0.36	0.46	1.14
LYs (undiscounted)	3.45	2.88	2.89	2.49	0.57	0.56	0.96
LYs	3.12	2.64	2.65	2.31	0.48	0.47	0.81
PFS	1.76	1.07	1.05	0.42	0.69	0.71	1.34
PPS	1.36	1.57	1.61	1.89	−0.21	−0.24	−0.53
QALYs	2.58	2.17	2.18	1.87	0.41	0.39	0.70

LYs, life-years; **PFS**, progression-free survival; **PPS**, postprogression survival; **QALYs**, quality-adjusted life-years; **TOT**, time on treatment.
*The value presented is for avelumab; patients continued receiving axitinib for 1.71 years.

Sensitivity analyses

- Deterministic sensitivity analyses showed that the results were sensitive to OS and PFS extrapolation options
  - Pazopanib and temsirolimus comparison results were also sensitive to HR estimates
- Probabilistic sensitivity analysis was conducted (1,000 simulations)
  - Compared with sunitinib, incremental QALYs ranged between 0.198 (25th percentile) and 0.600 (75th percentile)
  - Compared with pazopanib, incremental QALYs ranged between 0.364 (25th percentile) and 0.421 (75th percentile)
  - Compared with temsirolimus, incremental QALYs ranged between 0.646 (25th percentile) and 0.753 (75th percentile)

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DISCLOSURES At the time of the study, **L. S. Miguel**, **B. Pinheiro**, **R. Lopes**, and **M. Borges** were working at Centro de Estudos de Medicina Baseada na Evidência, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal. **M. Kearney** is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany. **G. Zanotti** is an employee of Pfizer. **R. Hart** and **S. Smith** are employees of BresMed Health Solutions. **ACKNOWLEDGMENTS** This study was funded by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.