REVIEW ARTICLE
ARTIGO DE REVISÃO

Comment on: 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

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

Letícia Paula Leonart[1], Bruno Salgado Riveros[1], Felipe Berlinski[1], Maria Aparecida do Carmo Rego[1]

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Dear Editor,

We read with great interest the article by Oliveira *et al.*, 2021. In this study, the authors calculated the number needed to treat (NNT) and the cost of preventing an event (COPE) for nivolumab + ipilimumab (NIV+IPI) and pembrolizumab + axitinib (PEM+AXI) as first-line treatments for advanced renal cell carcinoma patients with intermediate or poor-risk according to the International Metastatic RCC Database Consortium (IMDC), under the Brazilian private healthcare system perspective. A similar analysis had been previously performed by Botrel *et al.*, 2021, considering data from 12 months of follow-up, which was the evidence available at the time. In the study by Oliveira *et al.*, (2021), a longer follow-up was considered (up to 48 months for NIV+IPI and 42 months for PEM+AXI), according to updated data from pivotal studies of both combo therapies (CheckMate 214 for NIV+IPI and KEYNOTE-426 for PEM+AXI) (Albiges *et al.*, 2020; Powles *et al.*, 2020; Rini *et al.*, 2021).

Oliveira *et al.* (2021) and Botrel *et al.* (2021) calculated the NNT as the inverse of absolute risk reduction for each treatment combination *versus* sunitinib, the comparator drug in both pivotal studies. COPE was calculated by multiplying the treatment cost in a specific time by the NNT. These definitions show that the estimated costs are closely related to the NNT values to prevent a case of disease progression and death, compared to sunitinib. The authors indirectly compared the NNT estimated for NIV+IPI and for PEM+AXI, concluding that the NNT to avoid disease progression of NIV+IPI would be better (i.e., lower) than that of PEM+AXI in the longer follow-up (30 months). However, the authors reached this conclusion without considering the uncertainty of estimates, i.e., without calculating a confidence interval. Therefore, we recalculated the NNT estimates, considering the corresponding 95% confidence intervals (95% CIs) for a more thorough assessment.

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1. MSD Brasil, São Paulo, SP, Brazil.
Corresponding author: Letícia Paula Leonart. Telefone: (11) 95596-3256. E-mail: leticia.paula.leonart.garmatter@merck.com

The NNT to prevent a disease progression and the NNT to prevent death are here calculated as presented by Oliveira *et al.* (2021). The 95% CIs were calculated using the rationale for a sample proportion. The formula is described in Equation (1), where p is the sample proportion, n is the sample size (considering the intermediate or poor-risk population of each randomized trial), and z is the appropriate value from the standard normal distribution for desired confidence level (Triola 2007).

$$CI\ 95\% = p \pm z\sqrt{\frac{p(1-p)}{n}} \quad (1)$$

We present the results from the shorter (12 months) to the longer (42 months for overall survival and 30 months for progression-free survival) follow-ups, according to the data described by Oliveira *et al.* (2021). The NNT and the corresponding 95% CI are presented in Table 1.

According to our recalculation, there would be a difference in the NNT (no overlapping CIs) for the 12 months' time point, favoring PEM + AXI for both averted progression and death. When considering the other follow-ups, no difference between groups is noted (overlapping CIs).

We recognize the efforts of Oliveira *et al.* (2021) in updating the analysis as soon as more mature data from the clinical trials were available. However, before jumping to any conclusion suggesting the superiority of NIV + IPI regarding NNT and, consequently, COPE, one cannot ignore the uncertainty of the results inherent to any clinical study based on a population sample. Indeed, the data show that NIV + IPI has a reduced performance during the first year of treatment that improves from this time onwards. However, it is impossible to claim superiority compared to PEM + AXI, as no uncertainty was considered by the authors.

Table 1. PFS and OS rates and NNT per time point for intermediate/poor risk patients

	CheckMate 214				KEYNOTE-426			
Outcome	**NIV + IPI**	**SUN**	**ARR**	**NNT (CI 95%)**	**PEM + AXI**	**SUN**	**ARR**	**NNT (CI 95%)**
	OS rate (%)				OS rate (%)			
12 months	80.3	71.8	8.5	***12 (10-16)***	86.7	72.0	14.7	***7 (6-9)***
18 months	73.8	59.6	14.2	8 (7-9)	75.5	63.2	12.3	9 (7-11)
24 months	66.4	52.4	14.0	8 (7-9)	69.2	55.8	13.4	8 (7-10)
30 months	59.6	47.2	12.4	9 (7-10)	61.3	48.9	12.4	9 (7-11)
42 months	52.0	39.2	12.8	8 (7-10)	50.6	37.6	13.0	8 (7-10)
	PFS rate (%)				**PFS rate (%)**			
12 months	49.6	42.8	6.8	***15 (12-20)***	55.8	40.9	14.9	***7 (6-9)***
18 months	42.8	32.5	10.3	10 (9-13)	44.5	33.2	11.3	9 (8-12)
30 months	36.4	25.1	11.3	9 (8-11)	34.3	22.7	11.6	9 (8-12)
30 months	35.8	19.0	16.8	6 (6-8)	28.4	17.7	10.7	10 (8-13)

OS and PFS data were extracted from Olivera et al. (2021).

Results of NNT in ***bold and italics*** present no overlapping confidence intervals between NIVO + IPI and PEM + AXI.

ARR: absolute risk reduction; CI: confidence interval; NNT: number needed to treat; NIV+IPI: nivolumab + ipilimumab; OS: overall survival; PEM+AXI: pembrolizumab + axitinib; PFS: progression-free survival; SUN: sunitinib.

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