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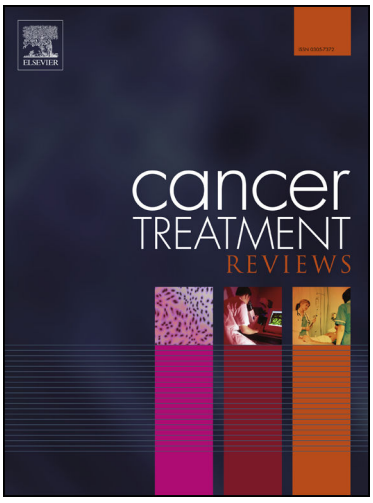

Hot Topic

Response to " *Analysis of the association between prospectively collected immune-related adverse events and survival in patients with solid tumor treated with immune-checkpoint blockers, taking into account immortal-time bias"*

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Letter to the editor

Title: Response to **"***Analysis of the association between prospectively collected immune-related adverse events and survival in patients with solid tumor treated with immune-checkpoint blockers, taking into account immortal-time bias"*

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Letter to the editor:

The search of predictive biomarkers for immune checkpoint inhibitor (ICIs) therapy remains a topic of major interest in oncology research. Previous studies have suggested that the development of immune-related adverse events (irAEs) can be associated with efficacy of ICIs in different cancer types[1 2 3]. However, statistical caveats such as the immortal-time bias or the publication bias may have overestimated this association[4]. Recently, Kfoury *et al* have analysed 577 patients treated with anti-PD-(L)1 antibodies at Gustave Roussy Institute to evaluate the association of irAEs and efficacy outcomes after correctly accounting for immortal-time bias[5]. Authors concluded that development of irAEs was associated with improved overall survival (OS) using a time-dependent Cox model (hazard ratio: 0.56, 95% confidence interval (CI) 0.41-0.75; p=0.0001) but not using a 12-week landmark analysis (p=0.26). Similar results were obtained in terms of progression-free survival (PFS).

Aiming to validate those findings, we have reviewed information from 403 patients treated with anti-PD-(L)1 antibodies in clinical trials or as per standard practice at Vall D'Hebron Institute of Oncology (VHIO) from 2015 to 2021. Different tumour types were included in this analysis (29.8% head and neck, 20.8% melanoma, 19.1% colorectal, 10% lung, and 20.3% others). To estimate the association between irAEs grade $\geq$ 2 and survival endpoints (PFS and OS), three different methods were used: i) unadjusted analysis using the standard Cox model, ii) time-dependent Cox model and iii) landmark analysis at 4 and 12-weeks[6]. Survival endpoints were calculated since the first dose of ICIs treatment, and all analyses were stratified by tumor type.

Among the 403 patients analyzed, 95 (23.6%) developed irAEs grade $\geq$ 2 with a median time to onset of 2.3 months (95%CI 1.2 -3.8) in a median follow-up period of 27.1 months. Efficacy results are summarized in Table 1. In terms of OS, the time-dependent Cox model analysis showed an association between irAEs grade $\geq$ 2 and OS (HR: 0.63; 95%CI 0.44-0.92). The landmark analysis was strongly influenced by the selected time-point, at 4-weeks the estimation showed a trend towards a protective effect in patients developing irAEs grade $\geq$ 2 (HR: 0.68; 95%CI 0.36-1.31), but not at 12 weeks (HR=1.06). On the other hand, the unadjusted analysis overestimated the risk reduction in patients with irAEs grade $\geq$ 2 (HR: 0.42; 95%CI 0.29-0.60). For the PFS endpoint, the only analysis that showed a significant association was the unadjusted analysis. An inconclusive association was found in the time-dependent Cox model analysis (HR: 0.85; 95%CI 0.61-1.16) and, again, heterogenous results were obtained using different time-points in the landmark analysis.

In conclusion, our data validates the results presented by *Kfoury et al* providing more evidence of the association between irAEs and OS outcomes. Results in the PFS endpoint could not be validated. In addition, our results confirm the impact of different statistical methods on final conclusions. Unadjusted analyses do not properly address immortal-time bias and previous studies that used this standard methodology have overestimated the magnitude of the association between irAEs and efficacy outcomes. The landmark analysis emerged as an alternative to deal with this bias, although, two important drawbacks have to be considered: i) there is significant reduction in the statistical power and ii) the selection of the time-point can strongly influence the results. The time-dependent Cox model analysis is the recommended statistical approach to evaluate the association between irAEs and efficacy outcomes.

Table 1: Hazard ratio with 95%CI of the association between immune-related adverse events grade $\geq$ 2 and survival endpoints.

Endpoint	Unadjusted analysis	Time-covariate Cox model	4-weeks landmark analysis	12-weeks landmark analysis
OS	0.**42 (0.29 – 0.60)**	**0.63 (0.44 – 0.92)**	0.68 (0.36 – 1.31)	1.06 (0.67 – 1.67)
PFS	0.**46 (0.35 – 0.61)**	0.85 (0.61 – 1.16)	1.08 (0.68 – 1.69)	1.49 (0.94 – 2.35)

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Confict of interest statement

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