IMMUNE RELATED ADVERSE EVENTS ASSOCIATED WITH IMMUNE CHECKPOINTS INHIBITORS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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BACKGROUND: Immune checkpoints inhibitors (ICIs) are monoclonal antibodies acting as a "on switch" of the T cells and increasing the immune system response against cancer cells. Promising results from clinical trials led to their approval in several advanced cancers, as metastatic melanoma, and small and non-small cell lung cancer. However, enhancing immune response could increase the risk of immune-related adverse drug reactions (irADR), especially on gastro-intestinal tract, skin, liver, lung, endocrine glands and cardiovascular system.

OBJECTIVE: The objective of this study is to report preliminary results of the systematic review in the perspective to evaluate the incidence and relative risk of irADR related to ICIs though direct and indirect meta-analysis.

MATERIALS AND METHODS: A systematic review on the irADR associated with ICIs was performed through PubMed, Web Of Science, Scopus and clinicaltrials.gov to select all relevant clinical trials on the following ICIs: atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, pidilizumab and tremelimumab.

We included all articles relative to ICIs published before the start date of the literature search. Two investigators evaluated all potentially eligible studies separately, and discordances were resolved through discussion between the two investigators. In case uncertainty or doubt about eligibility remained, a third reviewer made the final decision. The following data were extracted from all eligible studies: study phase and methodology, patients characteristics, indication of ICI use and diseases staging, mono or combined therapies, previous chemotherapy/radiotherapy, nature and severity of irADR.

All included studies will be used to calculate the incidence of irADR, while the comparative studies will be used to perform direct and network meta-analyses to compare the risk of irADR associated to each of the different studied ICIs. The Cochrane risk of bias tool will be used for the quality assessment of the comparative studies.

RESULTS: A total of 2,965 references were initially retrieved. After duplicates removal, screening of title abstract and full text, a total of 126 clinical trials met the inclusion criteria: 98 with definite information about irADR and 30 for which a mail will be sent to the authors for additional data. A total of 20,636 patients were included in these trials, 5,176 patients treated with non-ICI comparators or placebo, and 15,460 treated with ICIs, namely: 7,280 with ipilimumab, 3,545 with nivolumab, 2,615 with pembrolizumab, 1,292 with tremelimumab, and 1,303 with other ICIs. All these studies will be thus used to calculate the incidence of irADR.

A total of 50 phase I clinical trials, 10 phase I/II, 43 phase II, 3 phase II/III, 20 phase III was found. Among a total of 23 comparative studies, which will be used for direct and network meta-analyses, 19 studies have compared the drugs of interest to a not-ICI therapy and 4 compared two or more ICI therapies between them, for a total of 8,121 patients treated with ICIs in comparative studies.

DISCUSSION/CONCLUSION: These preliminary results showed that a significant amount of clinical trials on ICIs were identified. The data on irADR of these studies will provide valuable evidence to calculate the incidence and assess the risk of irADR related to ICIs administration, and will contribute to better characterise their risk/benefit profile.