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Mini Review

Safety and efficacy of immune checkpoint inhibitors in cancer patients with pre-existing autoimmune disease

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The advent of immune checkpoint inhibitors (ICI) targeting CTLA-4 and PD-1/PD-L1 pathways has revolutionized cancer treatment with significantly improved outcomes across a spectrum of cancers [1,2]. Although ICI therapy offers significant clinical benefits, these treatments can also lead to various immune-related adverse events (irAEs) that may negatively impact patient outcomes. Although the precise mechanism of irAE is not fully understood, they demonstrate many clinical features similar to autoimmune diseases. IRAEs are thought to result from bystander effects of activated T-cells, cross-reactivity between tumor and host tissues, and the role of the gut microbiome in immune activation [3]. Consequently, patients with pre-existing autoimmune diseases (AID) have been excluded from clinical trials due to concerns about exacerbation of autoimmune disease and risk of immune toxicity. While patients with AID have an increased risk for adverse events with ICI, there is no clear basis for broad and rather non-specific exclusions that are integrated into clinical trials involving ICI. As a result of this, there are no standard guidelines for real-world use of these agents in this patient population. The significance of this issue cannot be underestimated, as up to 25% of patients diagnosed with cancer have pre-existing autoimmune disease, and oncologists frequently encounter this patient population [4].

We conducted a systematic review and meta-analysis of existing data to compare the safety and efficacy of ICI treatment in cancer patients with and without autoimmune disease [5]. We found that autoimmune disease flares occurred in 36% in any cancer and 23% in non-small cell lung cancer (NSCLC) **(Table 1)**. Interestingly, the incidence of autoimmune flares was similar across different categories of autoimmune disorders based on primary organ system that is affected, suggesting a more uniform risk profile than assumed, which was unexpected and represents a novel finding.

De novo irAEs were reported in 41% of cancer patients with autoimmune disease compared to 29% in those without autoimmune disease. Consistent with prior observations, pre-existing autoimmune disease was associated with a higher risk of irAE in all cancer patients (RR 1.38; 95% CI, 1.16-1.65) and in NSCLC patients (RR 1.51; 95% CI, 1.12-2.03). The incidence of these *de novo* irAE was again similar across different categories of autoimmune disorders.

Current literature suggests that most ICI-related toxicities in patients with autoimmune disease are mild and manageable without discontinuing therapy [6,7]. Our meta-analysis supports this finding as rates of permanent ICI discontinuation were generally low. We also addressed whether high-grade *de novo* irAEs occur more frequently in the autoimmune population compared to general population. Across all types of cancers, the incidence of grade 3-4 *de novo* irAE was 12% in the autoimmune

Table 1. Summary results of meta-analysis.

Outcomes	All cancers (n=11,567)			NSCLC (n=3774)		
	Pooled incidence (95% CI)		Relative risk (95% CI)	Pooled incidence (95% CI)		Relative risk (95% CI)
	AID (n=1157)	No AID (n=10410)		AID (n=250)	No AID (n=3524)	
Autoimmune flare	36% (27%-46%)			23% (9%-40%)		
De novo irAE	41% (31%-52%)	29% (21%-38%)	RR **1.38** (1.16-1.65)	40% (23%-57%)	34% (21%-48%)	RR **1.51** (1.12-2.03)
Grade 3-4 *de novo* irAE	12% (9%-15%)	9% (6%-12%)	RR 1.38 (0.84-2.26)	12% (6%-21%)	7% (5%-8%)	RR **1.95** (1.01-3.75)
Objective response rate	33% (23%-44%)	29% (19%-41%)	RR 1.21 (0.88-1.86)	24% (11%-40%)	19% (11%-30%)	RR **1.56** (1.19-2.04)
ICI discontinuation	15% (10%-20%)	5% (2%-9%)	RR **1.61** (1.12-2.31)	10% (5%-14%)	3% (0%-8%)	RR 2.22 (0.77-6.41)

disease population compared to 9% in those without autoimmune disease. A similar incidence was observed among NSCLC patients, where 12% of patients with autoimmune disease experienced grade 3-4 *de novo* irAE compared to 7% in those without autoimmune disease, representing nearly a two-fold increase in risk (RR 1.95, 95%CI 1.01-3.75). Interestingly, these patients also showed a better tumor response with 56% more likely to achieve a complete or partial response compared to those without autoimmune disease. However, when considering all cancers collectively, we did not find a significant difference in both *de novo* grade 3-4 irAE and tumor response based on autoimmune disease status. This highlights the fact that the relationship between irAE and response may be tumor dependent.

Our study has important implications for clinicians who treat patients with cancer and those who treat autoimmune disease, since it highlights that autoimmune disease is not an absolute contraindication for ICI therapy. Instead, it emphasizes the importance of a balanced approach weighing the benefits and risks of ICI treatment. By identifying that NSCLC patients with autoimmune disease are more likely to respond to ICI treatment, our study provides valuable insights that can help clinicians make more informed treatment decisions regarding candidacy for therapy.

In the broader clinical context, our findings challenge the exclusionary criteria for cancer patients with pre-existing autoimmune disease from ICI clinical trials and underscore the need for prospective studies that includes cancer patients with autoimmune disease. A review of eligibility criteria on ClinicalTrials.gov for 142 advanced NSCLC immunotherapy clinical trials conducted between 2016 and 2023 showed that 40% of the trials excluded patients solely based on a history of autoimmune disease [8,9]. Given the growing number of cancer patients with autoimmune disease and the lack of clear guidelines for their treatment, our study highlights the urgent need for designing protocols and algorithms for safe use of immunotherapy while maintaining efficacy in this population. This aligns with the advocacy efforts of national organizations, including the American Society of Clinical Oncology (ASCO), Friends of Cancer Research (FOCR), and LUNGevity, which have called for more inclusive criteria and excluding only those on immunosuppressants or with active autoimmune disease. Additionally, prospective trials like the ongoing National Cancer Institute (NCI) sponsored trial (NCT03816345), which evaluates nivolumab in patients with autoimmune diseases and includes rigorous assessments of autoimmune disease flares and irAEs by specialists, will provide more detailed information on adverse events and impact of ICI therapy on cancer patients with autoimmune diseases. Observational data suggest that combining tocilizumab with ICI may effectively manage irAEs and prevent autoimmune disease flare-ups. In a multi-center retrospective study, initiation of IL-6R inhibitor was associated with a 73% improvement in irAEs and a stable overall response rate [10]. Currently, there are several active Phase I and II clinical trials evaluating the efficacy and safety of the combination of tocilizumab with ICI in cancer patients (NCT04940299, NCT03999749, NCT04375228, NCT03424005). Data from these studies would provide proof of concept that may extend to the autoimmune disease population [11].

In summary, our study highlights the importance of pre-existing autoimmune disease as a predictor for both treatment response and toxicity when evaluating the risks and benefits of ICI therapy in cancer patients. Further research that includes this population and focuses on immunotherapeutic strategies is crucial. Awaiting such studies, we recommend a thorough assessment of patient's autoimmune disease activity before ICI initiation, close monitoring, and collaboration with rheumatologists to optimize immunosuppressive therapy. We anticipate that developing targeted approaches to immunotherapy will improve outcomes for this underrepresented group.

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