Incidence of Treatment-Related Adverse Events from Immune Checkpoint Inhibitors: A Meta-Analysis of Randomized Clinical Trials

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Introduction

- Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by enhancing the immune system's ability to fight tumors. ICIs targeting Programmed cell Death Protein 1 (PD-1), Programmed cell Death Ligand 1 (PD-L1), and Cytotoxic T-lymphocyte Antigen 4 (CTLA-4) pathways are effective across various cancer types.(1)
- ICIs are however associated with treatment-related adverse events (TRAEs) which may necessitate treatment discontinuation. Understanding the safety profile of ICIs is essential to manage TRAEs effectively.(2)

Objective

- This study aimed to conduct a meta-analysis to estimate the incidence of grade ≥ 3 TRAEs and treatment discontinuation due to TRAEs in cancer patients receiving ICI therapies, either as monotherapy or in combination regimens.

Methods

- A systematic literature review was performed to identify registrational phase II/III randomized controlled trials (RCTs) of the US FDA-approved ICIs across tumor types.
- Data on incidence of grade ≥ 3 TRAEs and treatment discontinuation due to TRAEs was meta-analyzed using random- and fixed-effects analyses.
- Meta-analyses were carried out at a pan-tumor level for various ICI classes (PD-1/PD-L1 inhibitors, CTLA-4 inhibitors, ICI + chemotherapy combination, ICI + tyrosine kinase inhibitor [TKI] combination etc.) irrespective of tumor or treatment types. Subgroup analyses were carried out by tumor type - melanoma, lung, renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), gastrointestinal (GI), and others.
- Statistical analyses was carried out in R (version 4.3.0) using the meta package (v 8.0-2; Balduzzi et al, 2019).(3)

Results

- A total of 72 trials involving 51,061 patients treated with ICIs across 14 tumor types were included.

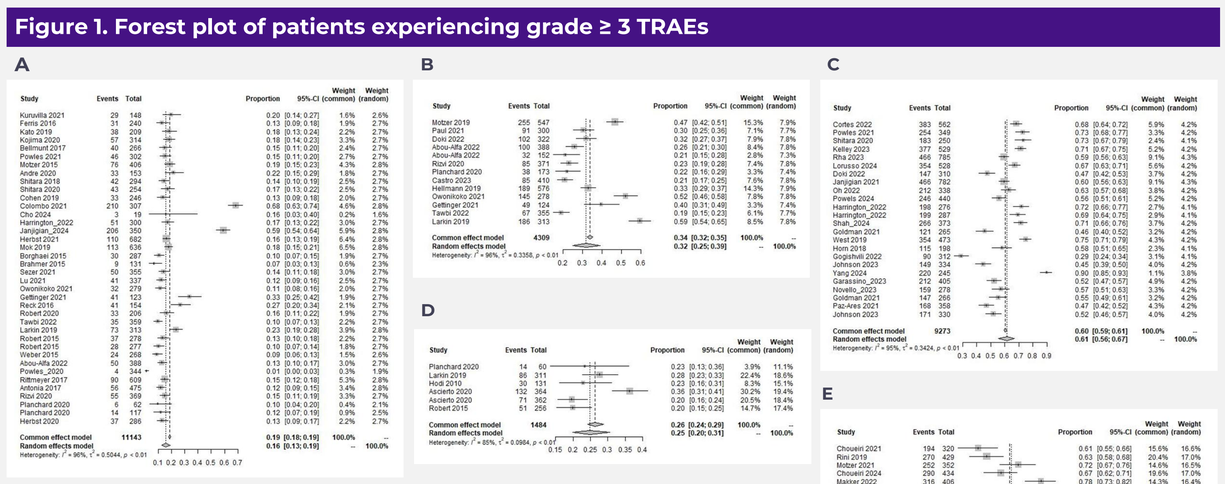
Incidence of grade ≥ 3 TRAEs

- The meta-analysis estimated grade ≥ 3 TRAEs in 16% of patients treated with PD-1/PD-L1 monotherapies, 25% with CTLA-4 monotherapies, and higher rates with combination therapies – 32% (ICI + ICI), 61% (ICI + chemotherapy), and 70% (ICI + TKI) (**Figure 1**).
- Pooled estimates showed wide variability across cancers, with lower incidence (7–15%) for PD-1/PD-L1 monotherapy and substantially higher rates (>60%) for combination regimens. ICI + TKI combinations had the greatest incidence, particularly in endometrial (77%) and RCC (66%) (**Figure 2**).

Discontinuation of treatment due to TRAEs by cancer type

- The meta-analysis estimated treatment discontinuation due to TRAEs in 7% of patients receiving PD-1/PD-L1 monotherapies, 14% with CTLA-4 monotherapies, 18% with ICI + ICI combinations, 14% with ICI + chemotherapies, and 5% with ICI + TKI regimens (**Figure 3, Figure 4**).
- Discontinuation rates were generally low with PD-1/PD-L1 monotherapy (6–8%) but higher with combination regimens – up to 31% with ICI + chemotherapy in GI cancers and 26% with ICI + ICI in melanoma (Figure 4). Despite higher toxicity, pooled discontinuation with ICI + TKI regimens remained modest (~5%), notably in renal cell carcinoma (**Figure 4**).

Figure 1. Forest plot of patients experiencing grade ≥ 3 TRAEs



A. Pan tumor: PD-1/ PD-L1; B. Pan tumor: ICI + ICI; C. Pan tumor: ICI + Chemo / ICI+ ICI + Chemo; D. Pan tumor: CTLA-4; E. Pan tumor: ICI + KI

Figure 2. Patients experiencing grade ≥ 3 TRAEs

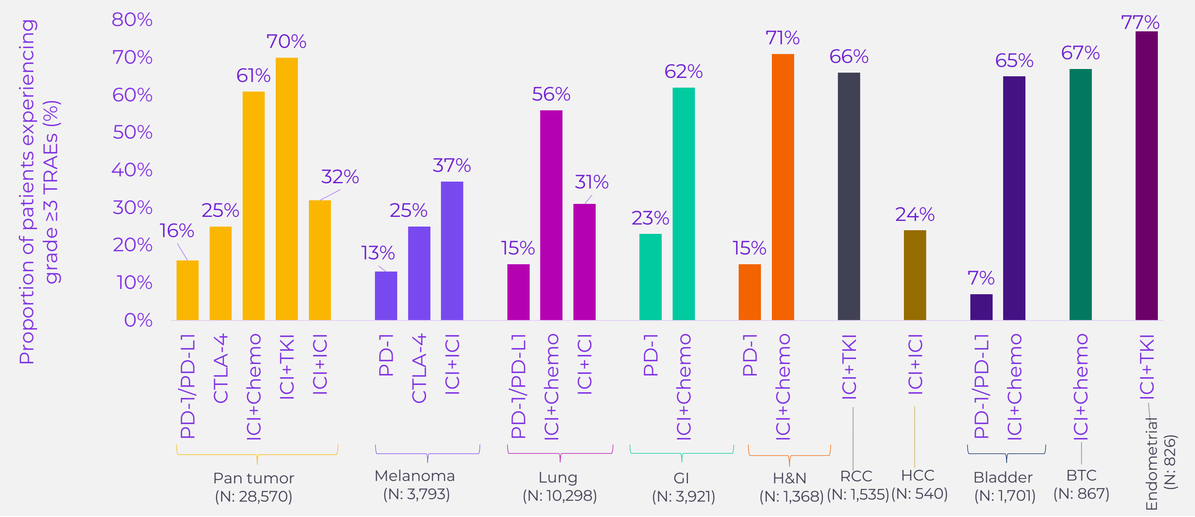
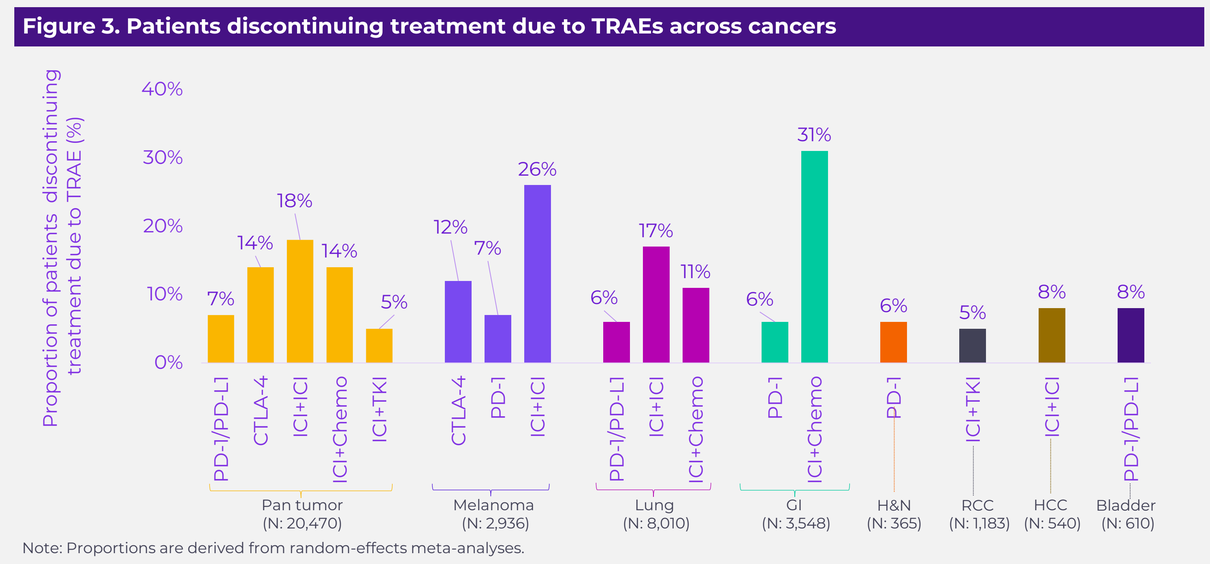
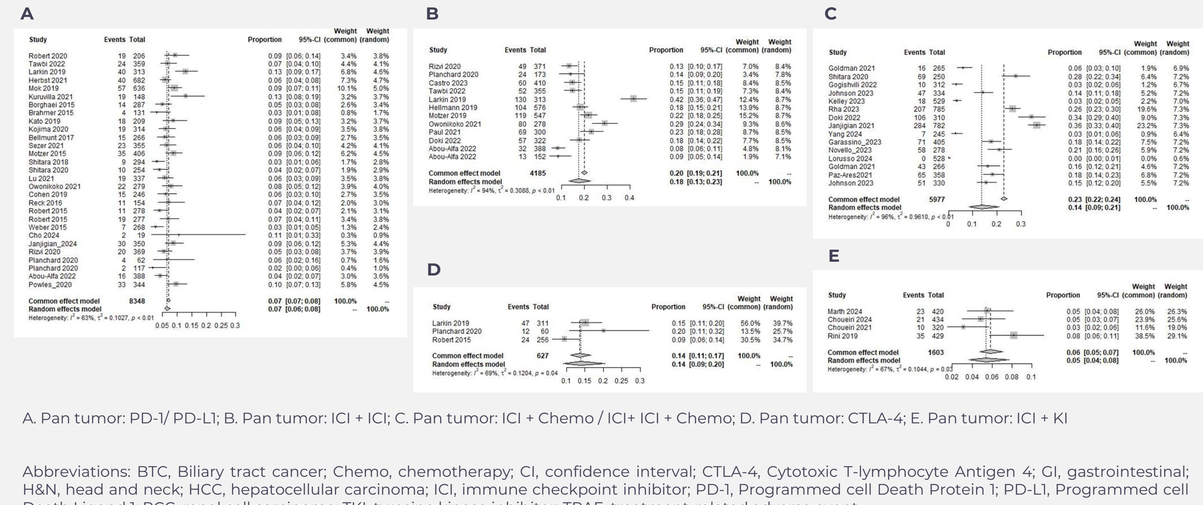


Figure 3. Patients discontinuing treatment due to TRAEs across cancers



Note: Proportions are derived from random-effects meta-analyses.

Figure 4. Forest plot of treatment discontinuations due to TRAEs



A. Pan tumor: PD-1/ PD-L1; B. Pan tumor: ICI + ICI; C. Pan tumor: ICI + Chemo / ICI+ ICI + Chemo; D. Pan tumor: CTLA-4; E. Pan tumor: ICI + KI

Abbreviations: BTC, Biliary tract cancer; Chemo, chemotherapy; CI, confidence interval; CTLA-4, Cytotoxic T-lymphocyte Antigen 4; GI, gastrointestinal; H&N, head and neck; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; PD-1, Programmed cell Death Protein 1; PD-L1, Programmed cell Death Ligand 1; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event.

Discussion & Conclusion

- The incidence of grade ≥ 3 TRAEs and treatment discontinuations due to TRAEs varied considerably by ICI regimen and the underlying malignancy.
- ICI monotherapies (PD-1/PD-L1, CTLA-4) had lower TRAE rates, while combination regimens – especially ICI + TKI and ICI + chemotherapy – showed higher rates, reaching up to 77%.
- Discontinuation due to TRAEs followed a similar trend. However, ICI + TKI regimens showed low discontinuation despite high TRAE incidence, suggesting better management of TRAEs or tolerability of adverse events in patients treated with ICI + TKI.
- These findings provide a comparative overview of the safety burden associated with ICIs and highlight the importance of toxicity management, especially in ICI combination regimens.

References: 1. Marei HE, et al. Cancer Cell Int. 2023;23:64., 2. Ouyang T, et al. Front Oncol. 2021;11:621639. , 3. 3. Balduzzi S, et al. Evid Based Ment Health. 2019;22(4):153–160

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