774P - Immune checkpoint inhibitor monotherapy and the risk of venous thromboembolism in cancer: A systematic review and meta-analysis

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BACKGROUND

- Nine immune checkpoint inhibitors (ICI) are FDA approved for the treatment of more than a dozen cancers.
- The toxicity landscape of immune checkpoint inhibitor (ICI) therapy continues to be under investigation
- The risk of venous thromboembolism (VTE) with ICI monotherapy remains unexplored.

METHODS

- MEDLINE and EMBASE databases were searched through 25th April 2022 to identify full text publications of phase 2/3 randomized controlled trials (RCTs) assessing ICI monotherapy compared to either chemotherapy or placebo and reporting adverse events.
- Primary outcome of interest was VTE risk.
- Binary outcome data were pooled using a fixed-effect Peto method.
- Treatment effect estimates were expressed as odds ratio (OR) and 95% confidence intervals (CI).
- Additional analyses were conducted by types of VTE (deep vein thrombosis [DVT], pulmonary embolism [PE]), and class of ICI [PD1, PDL1]).
- A sensitivity analysis was also conducted using empirical informative priors within the Bayesian framework.

RESULTS

- This meta-analysis included 45 RCTs that met the inclusion criteria and reported VTE events as shown in Table 1.
- Of those 45 RCTs, 35 trials compared ICI monotherapy with chemotherapy in a total of 19696 patients, whereas 10 trials compared ICI monotherapy with placebo in 7191 patients (Table 2).
- The incidence of VTE events with ICI monotherapy was 1.09% (95 % CI: 0.91%-1.27%) as shown in Figure 1.
- Compared to chemotherapy, the risk of VTE events in ICI monotherapy was not statistically significant (OR: 0.87, 95% CI: 0.69-1.09).
- Compared to placebo, the risk of VTE events with ICI monotherapy was not statistically significant (OR: 0.95, 95% CI: 0.56-1.61) as shown in Figure 2.

Table 1. Baseline trial characteristics

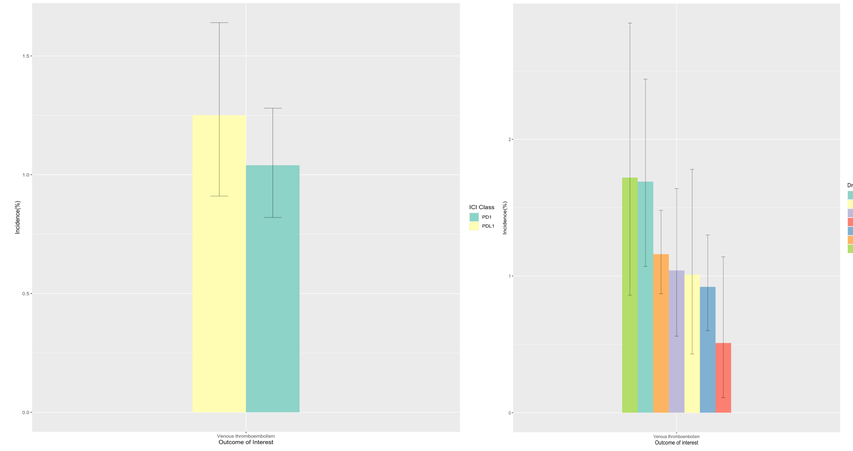
	Studies
Total number of trials	45
Total number of participants	26887
Trial by Type of Control N (%)	
vs Chemotherapy	35 (77.8%)
vs Placebo	10 (22.2%)
Trial by Phase N (%)	
Phase I	5 (11.1%)
Phase II	9 (20.0%)
Phase II/III	31 (68.9%)
Trial by Cancer Types N (%)	
NSCLC	17 (37.8%)
Gastric/Esophageal	6 (13.3%)
Urothelial	4 (8.9%)
Melanoma	6 (13.3%)
Head and Neck	3 (6.7%)
Others*	9 (20.0%)
Trial by ICI Class N (%)	
PD1	28 (62.2%)
PDL1**	13 (28.9%)
CTLA – 4**	5 (8.9%)
Trial by ICI Drug N (%)	
Pembrolizumab	15 (33.3%)
Atezolizumab	4 (8.9%)
Nivolumab	12 (26.7%)
Durvalumab***	6 (13.3%)
Cemiplimumab	1 (2.2%)
Tremelimumab***	3 (4.4%)
Avelumab	3 (6.7%)
Ipilimumab	2 (4.4%)

Abbreviations: NSCLC: non-small cell lung cancer
*Others include Ovarian, Breast, and Colorectal cancer in the ICI vs Chemotherapy arm; Prostate, Mesothelioma, Small Cell Lung Cancer and Renal Cell Carcinoma in the ICI vs Placebo arm.
**1 clinical trial used both PDL1 and CTLA-4 monotherapy in separate arms
***1 clinical trial used both Tremelimumab and Durvalumab monotherapy in separate arms.

Table 2. Summary of Findings

Comparison	Outcome	Participants (RCTs)	Relative Risk (95% CI)	Anticipated Absolute Risk	
				Risk with control	Risk Difference with ICI
ICI vs Chemotherapy	Venous Thromboembolism	19696 (35 RCTs)	OR 0.87 (0.69 to 1.09)	16 per 1,000	2 fewer per 1,000 (from 5 fewer to 1 more)
	Deep Vein Thrombosis	15215 (24 RCTs)	OR 0.71 (0.43 to 1.18)	5 per 1,000	1 fewer per 1,000 (from 3 fewer to 1 more)
	Pulmonary Embolism	19696 (35 RCTs)	OR 0.90 (0.69 to 1.17)	12 per 1,000	1 fewer per 1,000 (from 4 fewer to 2 more)
ICI vs Placebo	Venous Thromboembolism	7191 (10 RCTs)	OR 0.95 (0.56 to 1.61)	8 per 1,000	0 fewer per 1,000 (from 3 fewer to 5 more)
	Deep Vein Thrombosis	4745 (7 RCTs)	OR 0.49 (0.16 to 1.44)	4 per 1,000	2 fewer per 1,000 (from 3 fewer to 2 more)
	Pulmonary Embolism	7191 (10 RCTs)	OR 1.27 (0.67 to 2.39)	5 per 1,000	1 more per 1,000 (from 1 fewer to 6 more)

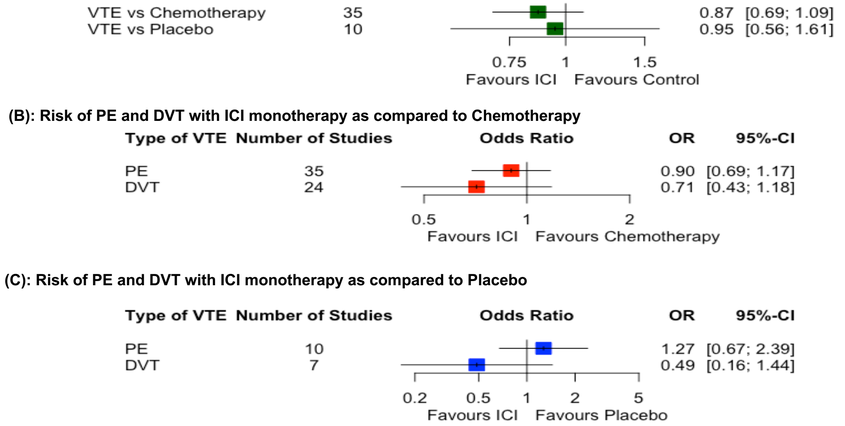
Figure 1: Pooled Incidence of VTE events



(A): Incidence of VTE by ICI Class

(B): Incidence of VTE by ICI Drugs

Figure 2: Risk of VTE with ICI monotherapy



CONCLUSIONS

- ICI monotherapy may not be associated with an increased risk of VTE in patients with cancer when compared to either chemotherapy or placebo.

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