

# Incidence and Risk of Hematological Adverse Events Associated With Immune Checkpoint Inhibitors: A Systematic Literature Review and Meta-Analysis

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# Abstract

Background: Immune checkpoint inhibitors (ICIs) have been a breakthrough in cancer therapy. ICI therapy is generally better tolerated than cytotoxic chemotherapy; however, hematological adverse events (AEs) have not been fully analyzed. Hence, we performed a meta-analysis to evaluate the incidence and risk of ICI-related hematological AEs.

Methods: A systematic literature search was performed using Pub-Med, EMBASE, Cochrane Library, and the Web of Science Core Collection. Phase III randomized controlled trials (RCTs) involving ICI combination regimens were selected. The experimental group received ICIs with systemic treatment, and the control group received only the same systemic treatment. Odds ratios (ORs) for anemia, neutropenia, and thrombocytopenia were calculated using a randommodel meta-analysis.

Results: We identified 29 RCTs with 20,033 patients. The estimated incidence rates for anemia of all grades and grades III-V were 36.5% (95% confidence interval (CI) 30.23 - 42.75) and 4.1% (95% CI 3.85 - 4.42), respectively. The incidence of neutropenia (all grades 29.7%, grades III-V 5.3%) and thrombocytopenia (all grades 18.0%, grades III-V 1.6%) was also calculated.

Conclusion: Treatment with ICIs seemed unlikely to increase the incidence of anemia, neutropenia, and thrombocytopenia in all grades. However, programmed cell death-1 receptor ligand inhibitors signifi-

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cantly increased the risk of grades III-V thrombocytopenia (OR 1.53; 95% CI 1.11 - 2.11). Further research is needed to examine the potential risk factors.

Keywords: Immune checkpoint inhibitor; Hematological toxicities; Immune-related adverse events; Meta-analysis

### Introduction

Immune checkpoint inhibitors (ICIs) have shown significant efficacy in various cancers, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), melanoma, classical Hodgkin lymphoma, head and neck squamous cell carcinoma, urothelial cancer, and renal cell carcinoma [1-3]. Approved ICIs include monoclonal antibodies against programmed cell death-1 receptor (PD-1), its ligand (PD-L1), and cytotoxic T lymphocyte antigen-4 (CTLA-4). In addition to the consistent and significant clinical effects achieved by enhancing the immune response to control malignancies, ICIs also induce severe multiple organ system toxicities. These include hematopoietic system, which may cause intolerance resulting in an immune response against autologous tissue [4, 5]. These adverse events (AEs), termed immune-related AEs (irAEs), are primarily associated with dysregulation of T-cell function. Frequently reported clinical hematological complications include neutropenia, immune thrombocytopenia (ITP), autoimmune hemolytic anemia, and immune thrombocytopenic purpura. Generally, hematological side effects associated with conventional chemotherapies can be managed with appropriate supportive care; however, AEs from ICIs can be severe and, if neglected, can lead to conditions that have poor prognosis.

Although multicenter clinical data analyses, case series analyses, and meta-analyses have been conducted on the hematological AEs of ICI therapies [6-8], to the best of our knowledge, no meta-analysis using randomized controlled trials (RCTs) has focused on concomitant anticancer therapies. ICIs are being extensively used for a wide range of cancers, in combination with other anticancer agents or in two-drug

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regimens. Hematological complications, such as anemia, can occur in patients with advanced cancer; hence, it is important to determine the hematological toxicities associated with ICIs for the selection of treatment regimens and management of AEs. Therefore, we performed a systematic review and metaanalysis of RCTs to estimate the incidence of hematological AEs and their association with ICIs.

## **Materials and Methods**

#### Systematic search for locating studies and selection

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9, 10] and registered in the University Hospital Medical Information Network Center Clinical Trial Registry (Japan) (UMIN000046032) [11]. Institutional review board approval and patient informed consent were waived since this was a review study. This study was conducted in compliance with all the applicable institutional ethical guidelines for the care.

In the electronic search, we systematically queried Pub-Med, EMBASE, Cochrane Central Register of Controlled Trials, and the Web of Science Core Collection (up to August 16, 2021) for RCTs reporting anemia, neutropenia, and thrombocytopenia with ICIs. The search formulas are presented in Supplementary Material 1 (www.thejh.org). Two investigators (AM and KT-M) independently screened the candidate articles by checking the title and abstract after uploading the citation list into Endnote X9 software (Thomson Reuters, Philadelphia, PA, USA). The inclusion criteria were as follows: 1) patients clinically diagnosed with hematological cancer or other solid tumors; 2) ICI monotherapy with systemic treatment as the experimental group and only the same systemic treatment for the control group; 3) study with three arms where ICI was included in at least one arm; 4) published study designed as a phase III RCT; and 5) evaluation of hematological AEs in the study. The exclusion criteria were as follows: 1) studies with no data on anemia, neutropenia, and thrombocytopenia; 2) republished research literature; 3) studies published in languages other than English; and 4) conference abstracts. Disagreements in assessing the cases or data were resolved via discussion between the two investigators.

### **Data extraction**

The total number of patients treated with ICIs and the number of patients who developed grade I-V anemia, neutropenia, and thrombocytopenia (Supplementary Material 2, www.thejh.org) in each treatment arm were collected from the eligible RCTs. If a study included more than two comparable arms, we selected only one comparable pair to evaluate the effect of ICIs. We also included grade  $\geq$  3 anemia, neutropenia, and thrombocytopenia. AEs were graded according to the Common Terminology Criteria for Adverse Events system [12]. Data were extracted in standardized tables by one reviewer (TO) and verified by a second reviewer (AM).

#### Data synthesis and statistical analyses

A meta-analysis evaluating the contribution of ICIs to the incidence of hematological AEs was performed using randomeffects models. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the risk of hematological toxicity associated with ICIs. Heterogeneity was assessed using the I<sup>2</sup> statistic. Heterogeneity was indicated by I<sup>2</sup>, where 0% indicated no heterogeneity and 100% indicated the strongest heterogeneity. Statistical analyses were performed using Review Manager 5.4 (Cochrane Community, London, UK). We also conducted subgroup analyses based on ICI type (PD-1, PD-L1 inhibitor and CTLA-4 inhibitor) and cancer type. In addition, we assessed the risk of hematological toxicity between ICI + cytotoxic agents and ICI + non-cytotoxic agents. The Cochrane Risk of Bias Tool was used to evaluate the risk of bias for each RCT [13]. Two reviewers (TO and AM) independently assessed RCT quality.

### Results

#### Summary of systematic review and meta-analysis

Of the 5,471 candidate articles, 120 were reviewed in detail (Fig. 1). Of the 120 articles, 19 were excluded, and 71 of the 101 selected articles had insufficient data to assess ICI-related hematological AEs. Finally, 29 RCTs were included in this meta-analysis (Supplementary Material 3, www.thejh.org) [14-42]. The characteristics of the included studies are summarized in Supplementary Material 3 (www.thejh.org). The overall risk of bias for most evaluated studies was low (Supplementary Material 4, www.thejh.org). Visual inspection of funnel plots was also assessed (Supplementary Material 5, www.thejh.org). There was no clear risk of publication bias in the included studies.

The PD-1 inhibitor was used in 10 studies involving 3,901 patients, the PD-L1 inhibitor was evaluated in 14 studies involving 4,713 patients, and the CTLA-4 inhibitor was assessed in five studies involving 2,057 patients. Tumor types of the eligible studies included NSCLC (n = 7), breast cancer (n = 5), gastric cancer (n = 4), SCLC (n = 3), myeloma (n = 3), urothelial cancer (n = 3), melanoma (n = 2), and ovarian cancer (n = 2).

#### Incidence of hematological complications treated with ICIs

The incidence of anemia, neutropenia, and thrombocytopenia for ICIs with subsequent systemic therapy was analyzed. A total of 29 RCTs involving 20,033 patients with grade I-V anemia and 28 RCTs involving 19,522 patients with grade III-V anemia were evaluated. The estimated incidence rates for grades I-V and III-V anemia were 36.5% (95% CI 30.2 - 42.8) and 4.1% (95% CI 3.9 - 4.4), respectively (Fig. 2).

Regarding neutropenia, 25 RCTs involving 17,536 patients and 26 RCTs involving 18,310 patients were evaluated for grade I-V and III-V neutropenia. The estimated incidence rates for grade I-V and grade III-V neutropenia were 29.7% (95% CI 24.8 - 34.6) and 5.3% (95% CI 3.9 - 6.7), respectively (Fig. 2). In



Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection process.

subgroup analyses based on ICI type, no significant difference in heterogeneity was observed for grade I-V neutropenia (P = 0.69).

Regarding thrombocytopenia, 18 RCTs involving 12,575 patients and 23 RCTs involving 15,562 patients were evaluated for grade I-V and III-V thrombocytopenia. The estimated incidence rates for grade I-V and grade III-V thrombocytopenia were 18.0% (95% CI 15.0 - 20.1) and 1.6% (95% CI 1.1 - 2.1), respectively (Fig. 2).

# Risk of hematological complications associated with ICI treatment

The risk of anemia, neutropenia, and thrombocytopenia in

each RCT that compared ICI plus systemic treatment with the same systemic treatment only as controls was evaluated. Compared with the control arms, treatment with ICIs did not increase the incidence of grade I-V anemia (OR 1.05; 95% CI 0.98 - 1.14, I<sup>2</sup> = 26%) (Fig. 3). The ORs of grade I-V neutropenia and thrombocytopenia were 1.10 (95% CI 1.01 - 1.19, I<sup>2</sup> = 23%) and 1.15 (95% CI 1.02 - 1.31, I<sup>2</sup> = 37%), respectively (Fig. 3). We also analyzed the data based on ICI types. For grade I-V anemia, neutropenia, and thrombocytopenia, no differences were observed among the ICI types (P > 0.05) (Supplementary Material 6, www.thejh.org).

Cases of severe or life-threatening anemia, neutropenia, and thrombocytopenia were infrequent, but their frequency varied depending on the type of ICIs and concomitant medi-



**Figure 2.** Mechanism of action of immune checkpoint inhibitors and hematological complications of immune checkpoint inhibitors. CTLA-4: cytotoxic T lymphocyte antigen-4; MHC: major histocompatibility complex; PD-1: programmed cell death-1 receptor; PD-L1: PD-1 ligand 1; TCR: T-cell receptor.

cation. In grade III-V hematological AEs, CTLA-4 inhibitor and PD-1 inhibitor did not increase the risk; however, PD-L1 inhibitor significantly increased the risk of thrombocytopenia (OR 1.53; 95% CI 1.11 - 2.11,  $I^2 = 0\%$ ) (Supplementary Material 7, www.thejh.org). Nevertheless, no significant difference was observed in each group in this analysis ( $I^2 = 38.2\%$ , P = 0.20). Grades III-V thrombocytopenia induced by PD-L1 inhibitor was more frequent when ICIs were combined with cytotoxic agents than in combination with non-cytotoxic agents (Supplementary Material 7, www.thejh.org).

# Subgroup analysis of the risk of hematological toxicities based on cancer type

The incidence of hematological AEs did not significantly differ according to the type of cancer. Subgroup analysis revealed that some combinations of ICIs and cancer type increased the incidence of hematological AEs, with a significant increase in grade III to V thrombocytopenia, especially in the combination of PD-L1 and NSCLC (OR 2.85; 95% CI 1.17 - 6.96, I<sup>2</sup> = 0%) (Supplementary Material 8, www.thejh.org). However, the small number of RCTs included in individual categories should be interpreted with caution.

## Discussion

ICIs have revolutionized cancer therapy by providing antitumor effects in various types and stages of cancer that are not achievable with existing drugs. Consequently, many clinical trials are underway to expand their indications. ICI therapies are generally better tolerated, and their associated toxicity can be managed with appropriate supportive care compared to cytotoxic chemotherapy. Agents that inhibit coinhibitory immune checkpoint molecules, such as PD-1, activate the immune response to control malignancy. However, ICIs may also induce an immune response against self-tissues, leading to various AEs. Clinically, this manifests as autoimmune diseaselike side effects including skin, gastrointestinal, liver, lung, and endocrine toxicity. These AEs, called irAEs, are primarily associated with dysregulated T-cell functions. Our study analyzed only anemia, neutropenia, and thrombocytopenia due to ICIs. However, other life-threatening hematological irAEs such as aplastic anemia, hemophagocytic lymphohistiocytosis and acquired hemophilia A after ICIs have also been reported [43, 44], but these AEs were not analyzed. We performed a systematic review and meta-analysis of ICI trials in patients with cancer and evaluated the incidence of hematotoxicity in different ICIs, combination of each ICI and other systemic chemotherapy, and tumor types. Hematological abnormalities are frequently seen in cancer patients. The strength of this study was only phase III RCTs that compared the add-on effect of ICIs on the control arm were extracted, resulting in more accurate risk for ICI-related cytopenias.

The mechanisms underlying the risk of immunotherapyrelated cytopenia are currently unclear, but multiple mechanisms may be involved. Patients with urothelial cancer or NSCLC may have previously received platinum-based chemotherapy, which may explain the high incidence of cytopenia. Kasamatsu et al reported that patients with chronic ITP had a significantly higher frequency of the PDCD1 +7209 TT genotype, a single nucleotide polymorphism in PD -1, which is possibly related to our results [44]. Drug-related autoimmune

		ICI		Cont	rol		Odds Ratio	Odds Ratio
а.	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
	Cortes, J. 2020	275	562	129	281	4.5%	1.13 [0.85, 1.50]	
	Galsky, M. D. 2020	85	453	63	390	3.3%	1.20 [0.84, 1.72]	
	Gandhi, L. 2018	190	405	98	202	3.6%	0.94 [0.67, 1.31]	
	Govindan, R. 2017	192	475	167	473	5.0%	1.24 [0.96, 1.62]	<b>—</b>
	Gutzmer, R. 2020	41	230	40	281	2.1%	1.31 [0.81, 2.10]	
	Hodi, F. S. 2010	41	380	27	132	1.7%	0.47 [0.28, 0.80]	
	Horn, L. 2018	202	198	69	196	2.7%	1.44 [0.96, 2.16]	
	Janjigian, t. t. 2021	203	224	1/1	224	5.8%	1.22 [0.97, 1.94]	
	Julie, R. 2020	193	202	190	206	4.170	0.90[0.71,1.31]	
	Lee N Y 2021	214	349	204	344	1196	1 10 [0.91 1 49]	
	Mateos M V 2019	35	122	204	123	1 7 %	0 72 [0 42 1 24]	
	Miles D. 2021	120	431	62	218	3.2%	0.97 [0.68, 1.39]	
	Mittendorf, E. A. 2020	65	164	66	167	2.3%	1.00 [0.65, 1.56]	
	Moore, K. N. 2021	285	642	269	644	6.2%	1.11 [0.89, 1.39]	_ <b>_</b>
	Nishio, M. 2021	138	291	120	274	3.7%	1.16 [0.83, 1.61]	
	Powles, T. 2020	39	344	23	345	1.7%	1.79 [1.04, 3.07]	
	Powles, T. 2021	242	349	229	342	3.9%	1.12 [0.81, 1.54]	
	Pujade-Lauraine, E. 2021	55	182	43	177	2.1%	1.35 [0.85, 2.15]	
	Reck, M. 2016	184	562	212	561	5.5%	0.80 [0.63, 1.02]	
	Robert, C. 2015.2	24	247	16	251	1.2%	1.58 [0.82, 3.05]	
	Rudin, C. M. 2020	108	223	125	223	3.1%	0.74 [0.51, 1.07]	
	Schmid, P. 2018	130	460	116	430	4.3%	1.07 [0.79, 1.43]	
	Schmid, P. 2020	430	781	215	389	5.5%	0.99 [0.78, 1.27]	
	Shitara, K. 2020	124	250	117	244	3.3%	1.07 [0.75, 1.52]	
	Socinski, M. A. 2018	121	393	108	394	4.1%	1.18 [0.87, 1.60]	
	Sugawara, S. 2021	18	213	92	2/5	3.2%	0.80 [0.55, 1.14]	
	Usmani, S. Z. 2019	30	104	32	148	1.0%	1.07 [0.62, 1.84]	
	West, H. 2019	275	473	(1	131	2.970	1.15 [0.76, 1.70]	
	Total (95% CI)		10901		9132	100.0%	1.05 [0.98, 1.14]	•
	Total events	4101		3223				*
	Heterogeneity: Tau <sup>2</sup> = 0.01; •	Chi <sup>2</sup> = 37.6	63, df=	28 (P = 0	.11); <b>P</b> ≊	= 26%		
	Test for overall effect: Z = 1.4	41 (P = 0.1	6)					0.2 0.5 1 2 5
			~					Higher risk without ICL Higher risk with ICI
			,					Higher risk without ICI Higher risk with ICI
b		ICI		Contr	ol		Odds Ratio	Higher risk without ICI Higher risk with ICI Odds Ratio
b	Study or Subgroup	ICI Events	Total	Contro Events	ol Total	Weight	Odds Ratio M-H, Random, 95% CI	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup Cortes, J. 2020	ICI Events 231	Total 562	Contro Events 107	ol Total 281	Weight 5.3%	Odds Ratio M-H, Random, 95% CI 1.13 (0.85, 1.52)	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup Cortes, J. 2020 Galsky, M. D. 2020	ICI Events 231 58	Total 562 453	Contro Events 107 27	ol <u>Total</u> 281 390	Weight 5.3% 2.5%	Odds Ratio M-H, Random, 95% Cl 1.13 (0.85, 1.52) 1.97 (1.22, 3.19)	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup Cortes, J. 2020 Galsky, M. D. 2020 Gandhi, L. 2018	ICI Events 231 58 114	Total 562 453 405	Contro Events 107 27 49	ol Total 281 390 202	Weight 5.3% 2.5% 3.5%	Odds Ratio M-H, Random, 95% CI 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.22 [0.83, 1.80]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup Cortes, J. 2020 Galsky, M. D. 2020 Gandhi, L. 2018 Govindan, R. 2017	ICI Events 231 58 114 123 70	Total 562 453 405 475	Contro Events 107 27 49 111 74	ol Total 281 390 202 473	Weight 5.3% 2.5% 3.5% 5.3%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.14 [0.85, 1.53] 4.07 [0.71, 1.61]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup Cortes, J. 2020 Galsky, M. D. 2020 Gandhi, L. 2018 Govindan, R. 2017 Horn, L. 2018 Janijidan X Y. 2021	ICI Events 231 58 114 123 78 191	Total 562 453 405 475 198 792	Contro Events 107 27 49 111 74	ol 281 390 202 473 196 767	Weight 5.3% 2.5% 3.5% 5.3% 3.2% 7.2%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.14 [0.85, 1.53] 1.07 [0.71, 1.61] 1.08 [0.82, 1.22]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b _	Study or Subgroup Cortes, J. 2020 Galsky, M. D. 2020 Gandhi, L. 2018 Govindan, R. 2017 Horn, L. 2018 Janjigian, Y. Y. 2021 Jotte, P. 2020	ICI Events 231 58 114 123 78 191 124	Total 562 453 405 475 198 782 234	Contro Events 107 27 49 111 74 181 125	ol <u>Total</u> 281 390 202 473 196 767 224	Weight 5.3% 2.5% 3.5% 5.3% 3.2% 7.2% 4.9%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.14 [0.85, 1.53] 1.07 [0.71, 1.61] 1.05 [0.83, 1.32] 0.99 [0.72, 1.25]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b _	Study or Subgroup Cortes, J. 2020 Galsky, M. D. 2020 Gandhi, L. 2018 Govindan, R. 2017 Horn, L. 2018 Janjigian, Y. Y. 2021 Jotte, R. 2020 Lee, N.Y. 2021	ICI Events 231 58 114 123 78 191 124 107	Total 562 453 405 475 198 782 334 348	Contro Events 107 27 49 111 74 181 125 101	ol 281 390 202 473 196 767 334 344	Weight 5.3% 2.5% 3.5% 5.3% 3.2% 7.2% 4.8% 4.6%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.14 [0.85, 1.53] 1.07 [0.71, 1.61] 1.05 [0.83, 1.32] 0.99 [0.72, 1.35] 1.07 [0.77, 1.48]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup Cortes, J. 2020 Galsky, M. D. 2020 Gandhi, L. 2018 Govindan, R. 2017 Horn, L. 2018 Janjigian, Y. Y. 2021 Jotte, R. 2020 Lee, N. Y. 2021 Mateos, M. V. 2019	ICI Events 231 58 114 123 78 191 124 107 49	Total 562 453 405 475 198 782 334 348 122	Contre Events 107 27 49 111 74 181 125 101 33	ol 281 390 202 473 196 767 334 344 123	Weight 5.3% 2.5% 3.5% 5.3% 3.2% 7.2% 4.8% 4.8% 2.0%	Odds Ratio <u>M-H, Random, 95% Cl</u> 1.13 (0.85, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80) 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32) 0.99 (0.72, 1.35) 1.07 (0.77, 1.48) 1.83 (1.07, 3.14)	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup Cortes, J. 2020 Galsky, M. D. 2020 Gandhi, L. 2018 Govindan, R. 2017 Horn, L. 2018 Janjigian, Y. Y. 2021 Jotte, R. 2020 Lee, N. Y. 2021 Mateos, M. V. 2019 Miles, D. 2021	ICI Events 231 58 114 123 78 191 124 107 49 93	Total 562 453 405 475 198 782 334 348 122 431	Contro Events 107 27 49 111 74 181 125 101 33 46	ol 281 390 202 473 196 767 334 344 123 218	Weight 5.3% 2.5% 3.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 3.3%	Odds Ratio <u>M-H, Random, 95% Cl</u> 1.13 (0.85, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80) 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32) 0.99 (0.72, 1.35) 1.07 (0.77, 1.48) 1.83 (1.07, 3.14) 1.03 (0.69, 1.53)	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mittendorf, E. A. 2020	ICI Events 231 58 114 123 78 191 124 107 49 93 65	Total 562 453 405 475 198 782 334 348 122 431 164	Contro Events 107 27 49 111 74 181 125 101 33 46 61	ol 281 390 202 473 196 767 334 344 123 218 167	Weight 5.3% 2.5% 3.5% 5.3% 3.2% 7.2% 4.8% 4.6% 3.3% 2.0% 3.3%	Odds Ratio M-H, Random, 95% Cl 1.13 (0.85, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80) 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32) 0.99 (0.72, 1.35) 1.07 (0.77, 1.48) 1.83 (10.79, 3.14) 1.03 (0.69, 1.53) 1.14 (0.73, 1.78)	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Mileos, D. 2021   Miles, D. 2021   Millendorf, E. A. 2020   Moore, K. N. 2021	ICI Events 231 58 114 123 78 191 124 107 49 93 65 200	Total 562 453 405 475 198 782 334 348 122 431 164 642	Contro Events 107 27 49 111 74 181 125 101 33 46 61 198	ol <u>Total</u> 281 390 202 473 196 767 334 344 123 218 167 644	Weight 5.3% 2.5% 3.5% 5.3% 3.2% 7.2% 4.8% 4.6% 3.3% 2.0% 3.3% 2.8% 7.1%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.14 [0.85, 1.53] 1.07 [0.71, 1.61] 1.05 [0.83, 1.32] 0.99 [0.72, 1.35] 1.07 [0.77, 1.48] 1.83 [1.07, 3.14] 1.03 [0.69, 1.53] 1.14 [0.73, 1.78] 1.02 [0.80, 1.29]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Miles, D. 2021   Milles, D. 2021   Mittendorf, E. A. 2020   Moore, K. N. 2021   Nishio, M. 2021	ICI Events 231 58 114 123 78 191 124 107 49 93 65 200 50	Total 562 453 405 475 198 782 334 348 122 431 164 642 291	Contro Events 107 27 49 111 74 181 125 101 33 46 61 198 41	ol 281 390 202 473 196 767 334 123 218 167 644 274	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 3.3% 2.8% 7.1% 2.7%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.14 [0.85, 1.53] 1.07 [0.71, 1.61] 1.05 [0.83, 1.32] 0.99 [0.72, 1.35] 1.07 [0.77, 1.48] 1.83 [1.07, 3.14] 1.03 [0.69, 1.53] 1.14 [0.73, 1.78] 1.02 [0.80, 1.29] 1.18 [0.76, 1.85]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b _	Study or Subgroup Cortes, J. 2020 Galsky, M. D. 2020 Gandhi, L. 2018 Govindan, R. 2017 Horn, L. 2018 Janjigian, Y. Y. 2021 Jotte, R. 2020 Lee, N. Y. 2021 Mateos, M. V. 2019 Miles, D. 2021 Mittendorf, E. A. 2020 Moore, K. N. 2021 Nishio, M. 2021 Powles, T. 2021	ICI Events 231 58 114 123 78 191 124 107 49 93 65 2000 50 50 128	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349	Contro Events 107 27 49 111 74 181 125 101 33 46 61 198 41 132	ol Total 281 390 202 473 196 767 334 123 218 167 644 274 342	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 3.3% 2.8% 7.1% 2.7% 5.0%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.14 [0.85, 1.53] 1.07 [0.71, 1.61] 1.05 [0.83, 1.32] 0.99 [0.72, 1.35] 1.07 [0.77, 1.48] 1.83 [1.07, 3.14] 1.03 [0.89, 1.53] 1.14 [0.73, 1.78] 1.02 [0.80, 1.29] 1.18 [0.75, 1.85] 0.92 [0.68, 1.25]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b _	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mittendorf, E. A. 2020   Noser, K. N. 2021   Nishio, M. 2021   Powles, T. 2021   Pujade-Lauraine, E. 2021	ICI Events 231 58 114 123 78 191 124 107 49 93 65 200 50 50 200 50 200 50 200 50 200 50 200 50 200 50 200 20	Total 562 453 405 198 782 334 348 122 431 164 642 291 349 182	Contro Events 107 27 49 111 74 181 125 101 33 46 61 193 46 61 132 26	ol 281 390 202 473 196 767 334 123 218 167 644 274 342 177	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 3.3% 2.8% 7.1% 2.7% 5.0% 1.7%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.13 (0.85, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80] 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32] 0.99 (0.72, 1.35) 1.07 (0.77, 1.48) 1.83 (1.07, 3.14) 1.83 (1.07, 3.14) 1.03 (0.69, 1.53] 1.14 (0.73, 1.78] 1.02 (0.80, 1.29] 0.92 (0.68, 1.25] 0.97 (0.54, 1.74]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b .	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mittendorf, E. A. 2020   Moore, K. N. 2021   Nishio, M. 2021   Powles, T. 2021   Puljade-Lauraine, E. 2021   Reck, M. 2016	ICI Events 231 58 114 123 78 191 124 107 49 93 65 200 50 50 128 26 249	Total 562 453 405 198 782 334 348 122 431 164 642 291 349 182 562	Contro Events 107 27 49 111 74 181 125 101 33 46 61 198 41 132 26 281	ol 281 390 202 473 196 767 334 144 123 218 167 644 274 342 177 561	Weight 5.3% 2.5% 3.5% 5.3% 3.2% 7.2% 4.8% 2.0% 3.3% 2.8% 7.1% 5.0% 1.7% 7.1%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.12 [0.85, 1.53] 1.07 [0.71, 1.61] 1.05 [0.83, 1.32] 0.99 [0.72, 1.35] 1.07 [0.77, 1.48] 1.83 [1.07, 3.14] 1.03 [0.69, 1.53] 1.14 [0.73, 1.78] 1.02 [0.80, 1.29] 0.92 [0.68, 1.25] 0.97 [0.54, 1.74] 0.79 [0.63, 1.00]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup Cortes, J. 2020 Galsky, M. D. 2020 Gandhi, L. 2018 Govindan, R. 2017 Horn, L. 2018 Janjigian, Y. Y. 2021 Jotte, R. 2020 Lee, N. Y. 2021 Mateos, M. V. 2019 Miles, D. 2021 Mittendorf, E. A. 2020 Moore, K. N. 2021 Nishio, M. 2021 Powles, T. 2021 Powles, T. 2021 Pujade-Lauraine, E. 2021 Reck, M. 2016 Robert, C. 2015.2	ICI Events 58 114 123 78 191 124 107 49 93 65 200 50 128 260 202 202 202	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 562 247	Contre Events 107 27 49 111 74 181 125 101 33 46 61 198 41 132 266 281 19	ol 281 390 202 473 196 767 334 344 123 218 167 644 274 342 177 561 251	Weight 5.3% 2.5% 3.5% 5.3% 7.2% 4.8% 2.0% 3.3% 2.8% 7.1% 2.7% 5.0% 1.7% 7.1% 1.4%	Odds Ratio M-H, Random, 95% Cl 1.13 (0.86, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80) 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32) 0.99 (0.72, 1.35) 1.07 (0.77, 1.48) 1.83 (1.07, 3.14) 1.03 (0.89, 1.53) 1.14 (0.73, 1.78) 1.02 (0.80, 1.29) 1.18 (0.75, 1.85) 0.92 (0.68, 1.25) 0.97 (0.54, 1.74) 0.79 (0.63, 1.00) 1.08 (0.56, 2.07)	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup Cortes, J. 2020 Galsky, M. D. 2020 Gandhi, L. 2018 Govindan, R. 2017 Horn, L. 2018 Janjigian, Y. Y. 2021 Jotte, R. 2020 Lee, N. Y. 2021 Mateos, M. V. 2019 Miles, D. 2021 Mittendorf, E. A. 2020 Moore, K. N. 2021 Nishio, M. 2021 Powles, T. 2021 Pujade-Lauraine, E. 2021 Reck, M. 2016 Robert, C. 2015.2 Rudin, C. M. 2020	ICI Events 58 114 123 78 191 124 107 49 93 65 200 50 128 26 249 20 20 131	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 562 247 223	Contre Events 107 27 49 111 74 181 125 101 333 46 61 198 41 132 266 281 19 120	ol 281 390 202 473 196 767 334 123 218 167 644 274 342 274 342 274 342 274 342 274 342 251 223	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 3.3% 2.8% 7.1% 2.7% 5.0% 1.7% 7.1% 1.4% 3.7%	Odds Ratio M-H, Random, 95% Cl 1.13 (0.85, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80) 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32) 0.99 (0.72, 1.35) 1.07 (0.77, 1.48) 1.03 (0.69, 1.53) 1.14 (0.73, 1.78) 1.02 (0.80, 1.29) 1.18 (0.75, 1.85) 0.92 (0.68, 1.25) 0.97 (0.54, 1.74) 0.79 (0.63, 1.00) 1.08 (0.56, 2.07) 1.22 (0.84, 1.78)	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Moore, K. N. 2021   Nishio, M. 2021   Powles, T. 2021   Pujade-Lauraine, E. 2021   Reck, M. 2016   Robert, C. 2015.2   Rudin, C. M. 2020   Schmid, P. 2018	ICI Events 231 54 114 123 78 191 124 107 49 93 65 200 50 128 26 249 20 249 20 131	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 562 247 223 460	Contre Events 107 27 49 111 74 181 125 101 33 46 61 198 41 132 266 281 19 120 65	ol 281 390 202 473 196 767 334 196 767 334 123 218 167 644 274 342 177 561 221 223 430	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 3.3% 2.8% 7.1% 2.7% 5.0% 1.7% 1.4% 3.7% 4.2%	Odds Ratio M-H, Random, 95% Cl 1.13 (0.85, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80) 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32) 0.99 (0.72, 1.36) 1.07 (0.77, 1.48) 1.03 (0.69, 1.53) 1.14 (0.73, 1.78) 1.02 (0.80, 1.29) 1.18 (0.75, 1.85) 0.92 (0.68, 1.25) 0.97 (0.54, 1.74) 0.79 (0.63, 1.00) 1.08 (0.56, 2.07) 1.22 (0.84, 1.78) 1.60 (1.13, 2.26)	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b .	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mittendorf, E. A. 2020   Moore, K. N. 2021   Nishio, M. 2021   Puigade-Lauraine, E. 2021   Reck, M. 2016   Robert, C. 2015.2   Rudin, C. M. 2020   Schmid, P. 2018   Schmid, P. 2020	ICI Events 231 568 114 123 78 191 124 107 49 93 365 200 50 128 26 249 200 50 128 26 249 200 131 102 365	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 291 349 182 247 223 460 781	Contre Events 107 27 49 111 74 181 125 101 33 46 61 198 41 132 26 281 198 120 65 183	ol 281 390 202 473 196 767 334 144 123 218 167 644 274 342 177 561 223 430 389	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 2.8% 7.1% 2.8% 5.0% 1.7% 7.1% 5.0% 1.4% 3.7% 4.2% 6.8%	Odds Ratio M-H, Random, 95% Cl 1.13 (0.85, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80) 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32) 0.99 (0.72, 1.35) 1.07 (0.77, 1.48) 1.83 (1.07, 3.14] 1.03 (0.69, 1.53) 1.14 (0.73, 1.78) 1.02 (0.80, 1.29) 1.18 (0.75, 1.85) 0.92 (0.68, 1.25) 0.97 (0.54, 1.74] 0.97 (0.54, 1.74] 0.97 (0.54, 1.74] 1.08 (0.56, 2.07) 1.22 (0.84, 1.78] 1.60 (1.13, 2.26] 0.99 (0.77, 1.26)	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b .	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mittendorf, E. A. 2020   Moore, K. N. 2021   Puishio, M. 2021   Powles, T. 2021   Reck, M. 2016   Robert, C. 2015.2   Rudin, C. M. 2020   Schmid, P. 2018   Schmid, P. 2020   Shitara, K. 2020	ICI Events 231 588 114 123 78 191 124 107 49 93 365 200 50 128 26 249 200 50 128 26 249 200 50 131 102 365 94	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 562 247 223 460 781 254	Contre Events 107 27 49 111 74 181 125 101 33 46 61 198 41 132 26 281 198 120 65 183 102	ol 281 390 202 473 196 767 334 123 218 167 644 274 342 177 561 223 430 389 244	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 2.8% 7.1% 2.8% 5.0% 1.7% 7.1% 5.0% 1.4% 3.7% 4.2% 6.8% 3.9%	Odds Ratio M-H, Random, 95% CI 1.13 (0.85, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80) 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32) 0.99 (0.72, 1.35) 1.07 (0.77, 1.48) 1.83 (1.07, 3.14) 1.03 (0.69, 1.53) 1.14 (0.73, 1.78) 1.02 (0.80, 1.29) 1.18 (0.75, 1.85) 0.92 (0.68, 1.25) 0.97 (0.54, 1.74) 0.79 (0.63, 1.00) 1.08 (0.56, 2.07) 1.22 (0.84, 1.78) 1.60 (1.13, 2.26) 0.99 (0.77, 1.26) 0.82 (0.57, 1.17)	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mitendorf, E. A. 2020   Moore, K. N. 2021   Nishio, M. 2021   Powles, T. 2021   Pujade-Lauraine, E. 2021   Reck, M. 2016   Robert, C. 2015.2   Rudin, C. M. 2020   Schmid, P. 2020   Shitara, K. 2020   Socinski, M.A. 2018	ICI Events 231 58 114 123 78 191 124 107 49 93 50 50 50 50 50 128 266 249 20 131 102 365 94 76	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 562 247 223 460 781 254 393	Contre Events 107 27 49 111 74 181 125 101 33 46 61 198 41 132 26 281 199 120 65 183 102 72 72	ol 281 390 202 473 196 767 334 123 218 167 644 274 342 177 561 223 430 389 244 394	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 2.8% 7.1% 2.7% 5.0% 1.7% 7.1% 1.4% 3.7% 4.2% 6.8% 3.9% 4.0%	Odds Ratio <u>M-H, Random, 95% CI</u> 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.14 [0.85, 1.53] 1.07 [0.71, 1.61] 1.05 [0.83, 1.32] 0.99 [0.72, 1.35] 1.07 [0.77, 1.48] 1.83 [1.07, 3.14] 1.03 [0.69, 1.53] 1.14 [0.73, 1.78] 1.02 [0.80, 1.29] 1.18 [0.75, 1.85] 0.92 [0.68, 1.25] 0.97 [0.54, 1.74] 0.79 [0.63, 1.00] 1.08 [0.56, 2.07] 1.22 [0.84, 1.78] 1.60 [1.13, 2.26] 0.99 [0.77, 1.26] 0.82 [0.57, 1.17] 1.07 [0.75, 1.53]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mitendorf, E. A. 2020   Moore, K. N. 2021   Powles, T. 2021   Powles, T. 2021   Powles, T. 2021   Robert, C. 2015.2   Rudin, C. M. 2020   Schmid, P. 2018   Schmid, P. 2020   Shitara, K. 2020   Socinski, M. A. 2018   Sugawara, S. 2021	ICI Events 231 58 114 123 78 191 124 107 49 93 65 200 50 50 200 50 200 50 200 50 200 50 200 50 200 50 50 200 50 50 50 8 49 70 50 50 50 50 50 50 50 50 50 50 50 50 50	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 562 247 223 460 781 254 393 273	Contre Events 107 27 49 111 74 181 125 101 33 46 61 198 41 132 26 281 199 120 65 183 102 72 37	ol 281 390 202 473 196 767 334 123 218 167 644 274 342 177 561 223 430 389 244 394 275	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 3.3% 7.1% 2.7% 5.0% 1.7% 7.1% 1.4% 3.7% 4.2% 6.8% 3.9% 4.0% 2.6%	Odds Ratio M-H, Random, 95% CI 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.14 [0.85, 1.53] 1.07 [0.71, 1.61] 1.05 [0.83, 1.32] 0.99 [0.72, 1.35] 1.07 [0.77, 1.48] 1.83 [1.07, 3.14] 1.03 [0.69, 1.53] 1.14 [0.73, 1.78] 1.02 [0.80, 1.29] 1.18 [0.75, 1.85] 0.92 [0.68, 1.25] 0.97 [0.54, 1.74] 0.79 [0.63, 1.00] 1.08 [0.56, 2.07] 1.22 [0.84, 1.78] 1.60 [1.13, 2.26] 0.99 [0.77, 1.26] 0.82 [0.57, 1.17] 1.07 [0.75, 1.53] 1.55 [0.98, 2.45]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b.	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jate, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mateos, M. V. 2019   Miles, D. 2021   Nishio, M. 2021   Powles, T. 2021   Powles, T. 2021   Powles, T. 2021   Reck, M. 2016   Robert, C. 2015.2   Rudin, C. M. 2020   Schmid, P. 2020   Shitara, K. 2020   Socinski, M. A. 2018   Sugawara, S. 2021   Usmani, S. Z. 2019	ICI Events 231 58 114 123 78 191 124 107 49 93 65 200 50 128 26 249 200 50 128 26 249 20 131 102 365 59 4 476 53 32	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 562 247 223 460 781 254 393 273 154	Contre Events 107 279 111 74 181 125 101 33 46 61 198 41 132 26 281 19 120 65 183 102 281 19 120 65 183 102 272 37 26	ol 281 390 202 473 196 767 334 123 218 167 644 274 342 177 561 251 251 251 251 251 251 251 25	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 2.0% 2.0% 2.8% 7.1% 2.7% 5.0% 1.7% 7.1% 1.4% 3.7% 4.2% 6.8% 3.9% 4.0% 2.6% 1.8%	Odds Ratio M-H, Random, 95% CI 1.13 [0.85, 1.52] 1.97 [1.22, 3.19] 1.22 [0.83, 1.80] 1.14 [0.85, 1.53] 1.07 [0.71, 1.61] 1.05 [0.83, 1.32] 0.99 [0.72, 1.35] 1.07 [0.77, 1.48] 1.83 [1.07, 3.14] 1.03 [0.69, 1.53] 1.14 [0.73, 1.78] 1.02 [0.80, 1.29] 1.18 [0.75, 1.85] 0.92 [0.68, 1.25] 0.97 [0.54, 1.74] 0.79 [0.63, 1.00] 1.08 [0.56, 2.07] 1.22 [0.84, 1.78] 1.60 [1.13, 2.26] 0.99 [0.77, 1.26] 0.99 [0.77, 1.26] 0.82 [0.57, 1.17] 1.07 [0.75, 1.53] 1.55 [0.98, 2.45] 1.23 [0.69, 2.19] 4.29 [0.20, 2.01]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b.	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jate, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mateos, M. V. 2019   Miles, D. 2021   Nishio, M. 2021   Powles, T. 2021   Powles, T. 2021   Powles, T. 2021   Reck, M. 2016   Robert, C. 2015.2   Rudin, C. M. 2020   Schmid, P. 2018   Schmid, P. 2020   Shitara, K. 2020   Socinski, M. A. 2018   Sugawara, S. 2021   Usmani, S. Z. 2019   West, H. 2019	ICI Events 231 58 114 123 78 191 124 107 49 93 65 200 50 128 260 200 50 128 260 249 20 131 102 365 94 476 53 32 227	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 562 247 223 460 781 254 393 273 154 473	Contre Events 107 27 49 111 74 181 125 101 33 46 61 198 41 132 26 281 19 120 65 183 102 265 53	ol Total 281 390 202 473 196 767 334 123 218 167 644 274 342 177 561 251 223 430 389 244 394 275 148 131	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 2.0% 3.3% 2.8% 7.1% 2.7% 5.0% 1.7% 7.1% 1.4% 3.7% 4.2% 6.8% 3.9% 4.0% 2.6% 1.8% 3.4%	Odds Ratio M-H, Random, 95% Cl 1.13 (0.86, 1.52) 1.97 [1.22, 3.19] 1.22 (0.83, 1.80) 1.14 (0.85, 1.53] 1.07 [0.71, 1.61] 1.05 (0.83, 1.32] 0.99 (0.72, 1.35] 1.07 (0.77, 1.48] 1.83 (1.07, 3.14] 1.03 (0.89, 1.53] 1.14 (0.73, 1.78] 1.02 (0.80, 1.29] 1.18 (0.75, 1.85] 0.92 (0.68, 1.25] 0.97 (0.54, 1.74] 0.79 (0.63, 1.00] 1.08 (0.56, 2.07] 1.22 (0.84, 1.78] 1.60 (1.13, 2.26] 0.99 (0.77, 1.26] 0.82 (0.57, 1.17] 1.07 (0.75, 1.53] 1.55 (0.98, 2.45] 1.23 (0.69, 2.19] 1.36 (0.92, 2.01]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b.	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janjigian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mateos, M. V. 2019   Miles, D. 2021   Moore, K. N. 2021   Powles, T. 2021   Pujade-Lauraine, E. 2021   Reck, M. 2016   Robert, C. 2015.2   Rudin, C. M. 2020   Schmid, P. 2018   Schmid, P. 2020   Shitara, K. 2020   Socinski, M. A. 2018   Sugawara, S. 2021   Usmani, S. Z. 2019   West, H. 2019   Total (95% CI)	ICI Events 231 558 114 123 78 191 124 107 93 65 200 50 128 266 249 20 131 102 365 94 76 53 32 227	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 562 247 223 460 781 254 393 273 154 473 9558	Contre Events 107 27 49 111 74 181 125 101 33 46 61 198 41 132 26 281 19 120 65 183 102 272 37 26 53	ol Total 281 390 202 473 196 767 334 123 218 167 644 274 342 177 561 251 251 251 251 251 251 251 25	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 2.0% 3.3% 2.8% 7.1% 2.7% 5.0% 1.7% 5.0% 1.4% 3.7% 4.2% 6.8% 3.9% 4.0% 2.6% 1.8% 3.4%	Odds Ratio M-H, Random, 95% Cl 1.13 (0.85, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80) 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32) 0.99 (0.72, 1.35) 1.07 (0.77, 1.48) 1.83 (1.07, 3.14) 1.03 (0.69, 1.53) 1.14 (0.73, 1.78) 1.02 (0.80, 1.29) 1.18 (0.75, 1.85) 0.92 (0.68, 1.25) 0.97 (0.54, 1.74) 0.79 (0.63, 1.00) 1.08 (0.56, 2.07) 1.22 (0.84, 1.78) 1.60 (1.13, 2.26) 0.99 (0.77, 1.26) 0.82 (0.57, 1.17) 1.07 (0.75, 1.53) 1.55 (0.98, 2.45) 1.23 (0.69, 2.19) 1.36 (0.92, 2.01) 1.00 (1.01, 1.49)	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b.	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janijgian, Y. Y. 2021   Jotte, R. 2020   Lee, N.Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mittendorf, E. A. 2020   Moore, K. N. 2021   Powles, T. 2021   Pujade-Lauraine, E. 2021   Reck, M. 2016   Robert, C. 2015.2   Rudin, C. M. 2020   Schmid, P. 2018   Schmid, P. 2018   Sugawara, S. 2021   Usmani, S. Z. 2019   West, H. 2019   Total (95% CI)   Total events	ICI Events 231 358 114 123 78 191 124 107 93 65 200 50 128 260 50 128 260 249 20 131 102 365 94 766 53 32 227	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 562 247 223 460 781 254 393 273 154 473 <b>9558</b>	Contre Events 107 27 49 111 74 181 125 101 336 61 198 41 132 266 281 19 120 65 183 102 272 37 26 53	ol Total 281 390 202 473 196 767 334 123 218 167 644 274 342 177 561 251 223 430 389 244 394 294 394 275 148 131 7978	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 2.8% 7.1% 2.7% 5.0% 1.7% 5.0% 1.4% 3.7% 4.2% 6.8% 3.9% 4.0% 2.6% 1.8% 3.4%	Odds Ratio M-H, Random, 95% Cl 1.13 (0.85, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80) 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32) 0.99 (0.72, 1.35) 1.07 (0.77, 1.48) 1.03 (0.69, 1.53) 1.14 (0.73, 1.78) 1.02 (0.80, 1.29) 1.18 (0.75, 1.85) 0.92 (0.68, 1.25) 0.97 (0.54, 1.74) 0.79 (0.63, 1.00) 1.08 (0.56, 2.07) 1.22 (0.84, 1.78) 1.60 (1.13, 2.26) 0.99 (0.77, 1.26) 0.99 (0.77, 1.26) 0.99 (0.77, 1.53) 1.55 (0.98, 2.45) 1.23 (0.69, 2.19) 1.36 (0.92, 2.01) <b>1.10 [1.01, 1.19]</b>	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI
b.	Study or Subgroup   Cortes, J. 2020   Galsky, M. D. 2020   Gandhi, L. 2018   Govindan, R. 2017   Horn, L. 2018   Janijgian, Y. Y. 2021   Jotte, R. 2020   Lee, N. Y. 2021   Mateos, M. V. 2019   Miles, D. 2021   Mittendorf, E. A. 2020   Moore, K. N. 2021   Powles, T. 2021   Pujade-Lauraine, E. 2021   Reck, M. 2016   Robert, C. 2015.2   Rudin, C. M. 2020   Schmid, P. 2018   Schmid, P. 2018   Sugawara, S. 2021   Usmani, S. Z. 2019   West, H. 2019   Total (95% CI)   Total events   Heterogeneity: Tau <sup>2</sup> = 0.01*	ICI Events 231 231 124 123 78 191 124 107 93 65 200 50 128 266 249 20 131 102 365 94 76 53 32 227 2986 Chi² = 31	Total 562 453 405 475 198 782 334 348 122 431 164 642 291 349 182 562 247 223 460 781 254 393 273 154 473 <b>9558</b> 27. df =	Contre Events 107 27 49 111 74 181 125 101 336 61 198 41 132 266 281 19 120 65 183 102 72 37 26 53 2270 24 (P = 5	ol Total 281 390 202 473 196 767 334 123 218 167 644 274 342 177 561 251 223 430 389 244 394 275 148 131 7978	Weight 5.3% 2.5% 5.3% 3.2% 7.2% 4.8% 4.6% 2.0% 3.3% 2.8% 7.1% 2.7% 5.0% 1.7% 7.1% 1.4% 3.7% 4.2% 6.8% 3.9% 4.0% 3.9% 4.2% 6.8% 3.9% 4.2% 6.8% 3.9% 4.2% 6.8% 3.9% 4.2% 6.8% 3.9% 4.2% 6.8% 3.9% 4.2% 6.8% 3.9% 4.2% 6.8% 3.9% 4.2% 6.8% 3.9% 4.2% 6.8% 3.2% 5.0%	Odds Ratio M-H, Random, 95% Cl 1.13 (0.85, 1.52) 1.97 (1.22, 3.19) 1.22 (0.83, 1.80) 1.14 (0.85, 1.53) 1.07 (0.71, 1.61) 1.05 (0.83, 1.32) 0.99 (0.72, 1.35) 1.07 (0.77, 1.48) 1.03 (0.69, 1.53) 1.14 (0.73, 1.78) 1.02 (0.80, 1.29) 1.18 (0.75, 1.85) 0.92 (0.68, 1.25] 0.97 (0.54, 1.74) 0.79 (0.63, 1.00) 1.08 (0.56, 2.07) 1.22 (0.84, 1.78) 1.60 (1.13, 2.26) 0.99 (0.77, 1.26) 0.99 (0.77, 1.73) 1.55 (0.98, 2.45] 1.23 (0.69, 2.19) 1.36 (0.92, 2.01] 1.10 [1.01, 1.19]	Higher risk without ICI Higher risk with ICI Odds Ratio M-H, Random, 95% CI

Figure 3. The forest plot of the odds ratio of grade I-V hematological adverse events comparing the additional immune checkpoint inhibitor use with control therapy. (a) Anemia. (b) Neutropenia. (c) Thrombocytopenia. CI: confidence interval.

C		ICI		Contr	ol		Odds Ratio	Odds Ratio
•	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
	Galsky, M. D. 2020	53	453	21	390	4.2%	2.33 [1.38, 3.93]	
	Gandhi, L. 2018	77	405	30	202	5.1%	1.35 [0.85, 2.13]	
	Govindan, R. 2017	84	475	81	473	7.5%	1.04 [0.74, 1.45]	
	Horn, L. 2018	36	198	33	196	4.3%	1.10 [0.65, 1.85]	
	Janjigian, Y. Y. 2021	157	782	145	767	9.9%	1.08 [0.84, 1.39]	
	Jotte, R. 2020	92	334	93	334	7.5%	0.99 [0.70, 1.38]	
	Lee, N. Y. 2021	46	348	41	344	5.3%	1.13 [0.72, 1.77]	
	Mateos, M. V. 2019	26	122	20	123	3.1%	1.39 [0.73, 2.66]	
	Mittendorf, E. A. 2020	12	164	5	167	1.3%	2.56 [0.88, 7.43]	
	Moore, K. N. 2021	138	642	136	644	9.4%	1.02 [0.78, 1.34]	
	Nishio, M. 2021	50	291	27	274	4.5%	1.90 [1.15, 3.13]	
	Powles, T. 2021	98	349	99	342	7.7%	0.96 [0.69, 1.33]	
	Reck, M. 2016	68	562	92	561	7.5%	0.70 [0.50, 0.98]	
	Rudin, C. M. 2020	60	223	51	223	5.6%	1.24 [0.81, 1.91]	
	Shitara, K. 2020	29	250	29	244	4.0%	0.97 [0.56, 1.68]	
	Socinski, M. A. 2018	59	393	47	394	5.9%	1.30 [0.86, 1.97]	
	Usmani, S. Z. 2019	13	154	12	148	2.1%	1.04 [0.46, 2.37]	
	West, H. 2019	138	473	29	131	5.2%	1.45 [0.92, 2.29]	+
	Total (95% CI)		6618		5957	100.0%	1.15 [1.02, 1.31]	◆
	Total events	1236		991				
	Heterogeneity: Tau <sup>2</sup> = 0	.03; Chi <sup>z</sup> :	= 26.83	), df = 17	(P = 0.0)	06); <b>I<sup>2</sup> =</b> 37	'%	
	Test for overall effect: Z	= 2.20 (P	= 0.03	)	-			U.2 U.5 1 2 5
								Figher lisk without ICL Figher lisk with ICL

Figure 3. (continued) The forest plot of the odds ratio of grade I-V hematological adverse events comparing the additional immune checkpoint inhibitor use with control therapy. (a) Anemia. (b) Neutropenia. (c) Thrombocytopenia. CI: confidence interval.

phenomena of ICIs are associated with the direct activation of autoreactive T and B cells and suppression of T-reg cells [45]. In the case of anemia, a study reported that the activation of B cell clones with hemolytic action on erythrocytes causes anemia [45]. In the case of platelets, immune-related thrombocytopenia (irTCP), including ITP, caused by ICI, is considered. IrTCP is mediated by platelet autoantibodies, which accelerate platelet destruction and inhibit platelet production. The proclivity to develop platelet-reactive antibodies arises from diverse mechanisms. In this study, it is remarkable that the risk of grade III-V thrombocytopenia was significantly higher than that of other hematological toxicities. Furthermore, we found a significant increase in grade III-V thrombocytopenia in the combination of PD-L1 and NSCLC. Strikingly, this finding is consistent with a previous study [46], which showed platelets, during their frequent interaction with tumor cells, ingest PD-L1 and present it on their surface using platelets from NSCLC patients. Tyler et al also showed that grade III or higher thrombocytopenia caused by ICI also affected overall survival reduction compared with thrombocytopenia caused by other causes, and the median (interquartile) time to grade III thrombocytopenia was 72.5 days [47]. Since several reports have linked the development of irAEs to prolonged OS, irTCP is likely to have a significant impact on the clinical course, and it is important to identify and appropriately manage patients at higher risk [48-53]. Previous studies have reported that smoking status, cancer type (melanoma and lung cancer), body mass index (> 25), and low-grade thrombocytopenia prior to ICI therapy were significantly associated with the development of grade III or higher thrombocytopenia of any etiology and early intervention is required for such patients [48]. Future studies are needed to determine the relationship between response rates for ICIs and cytopenia.

Our study had several limitations. First, it was a studylevel meta-analysis and was not based on individual patient data. Consequently, a comprehensive analysis, adjusting for baseline factors such as performance status, age, prior treatment, and other disparities that exist between trials was not possible. Second, the clinical studies included in our analysis included cancers with different levels of risk of hematotoxicity. There were not a sufficient number of RCTs to analyze for each ICI drug. Unfortunately, the newer PD-1 inhibitors (dostarlimab; zimberelimab; sintilimab) were not included in the present analyses because they were not well reported at the time of our literature search. Lastly, hematotoxicity may occur due to a variety of common exposures, medications, and concomitant conditions that influence the platelet count. Past and concurrent chemotherapy are the major causes of mild to life-threatening hematotoxicity.

In conclusion, the present meta-analysis is one of the few attempts to systematically estimate the incidence of hematotoxicity associated with immunotherapy in patients with cancer using a comprehensive search analysis. Treatment with ICIs seemed unlikely to increase the incidence of anemia, neutropenia, and thrombocytopenia in all grades, but PD-L1 inhibitors may be associated with a high risk of grade III-V thrombocytopenia. For the safe use of these drugs, periodic checks and appropriate management of toxicity are required. Further studies are needed to clarify the pathogenesis and risk factors of ICI-associated hematotoxicity.

### **Supplementary Material**

#### Suppl 1. Search formulas.

Suppl 2. Common Terminology Criteria for Adverse Events

v5.0 for hematological adverse events.

**Suppl 3.** Overview of the included studies in the meta-analysis.

**Suppl 4.** Risk of bias across studies assessed using the Cochrane risk of bias tool.

**Suppl 5.** Funnel plots assessing publication bias for odds ratio of immune checkpoint inhibitor-induced hematological adverse events.

**Suppl 6.** Subgroup analysis based on immune checkpoint inhibitor type.

**Suppl 7.** Result of meta-analysis on odds ratios of grade III-V anemia, neutropenia and thrombocytopenia comparing the additional ICI use with control therapy as per different types of ICIs

Suppl 8. Subgroup analysis based on cancer type.

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None to declare.

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This study did not receive any funding.

# **Conflict of Interest**

The authors declare that they have no conflict of interest.

# **Informed Consent**

Not applicable.

# **Author Contributions**

All authors made a substantial contribution to the design of the study, interpreted the data, and reviewed the manuscript; TO, AM and KM performed data extraction and analyses and wrote the first draft. All authors critically revised the paper for important intellectual content, approved the final version, and agreed with the submission.

# **Data Availability**

All data generated or analyzed during this study are included in this published article.

# Abbreviations

ICIs: immune checkpoint inhibitors; AEs: adverse events;

RCTs: randomized controlled trials; ORs: odds ratios; CI: confidence interval; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; PD-1: programmed cell death-1 receptor; PD-L1: programmed cell death-1 receptor ligand; CTLA-4: cytotoxic T lymphocyte antigen-4; irAE: immune-related AE; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; irTCP: immune-related thrombocytopenia; ITP: immune thrombocytopenia

## References

- Onoi K, Chihara Y, Uchino J, Shimamoto T, Morimoto Y, Iwasaku M, Kaneko Y, et al. Immune checkpoint inhibitors for lung cancer treatment: a review. J Clin Med. 2020;9(5):1362. doi pubmed pmc
- Lopez-Beltran A, Cimadamore A, Blanca A, Massari F, Vau N, Scarpelli M, Cheng L, et al. Immune checkpoint inhibitors for the treatment of bladder cancer. Cancers (Basel). 2021;13(1):131. doi pubmed pmc
- 3. Togasaki K, Sukawa Y, Kanai T, Takaishi H. Clinical efficacy of immune checkpoint inhibitors in the treatment of unresectable advanced or recurrent gastric cancer: an evidence-based review of therapies. Onco Targets Ther. 2018;11:8239-8250. doi pubmed pmc
- Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, Berdelou A, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer. 2016;54:139-148. doi pubmed
- Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158-168. doi pubmed
- 6. Petrelli F, Ardito R, Borgonovo K, Lonati V, Cabiddu M, Ghilardi M, Barni S. Haematological toxicities with immunotherapy in patients with cancer: a systematic review and meta-analysis. Eur J Cancer. 2018;103:7-16. doi pubmed
- Kramer R, Zaremba A, Moreira A, Ugurel S, Johnson DB, Hassel JC, Salzmann M, et al. Hematological immune related adverse events after treatment with immune checkpoint inhibitors. Eur J Cancer. 2021;147:170-181. doi pubmed
- Wilson NR, Lockhart JR, Garcia-Perdomo HA, Oo TH, Rojas-Hernandez CM. Management and outcomes of hematological immune-related adverse events: systematic review and meta-analysis. J Immunother. 2022;45(1):13-24. doi pubmed
- 9. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700. doi pubmed pmc
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi pubmed pmc
- 11. UMIN Center. UMIN Clinical Trials Registry (UMIN-

CTR). Available at: https://www.umin.ac.jp/ctr/ctrregist. htm.

- 12. Diane MF Savarese. Common terminology criteria for adverse events. Up To Date.
- Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. doi pubmed pmc
- Yang JC, Shepherd FA, Kim DW, Lee GW, Lee JS, Chang GC, Lee SS, et al. Osimertinib plus durvalumab versus osimertinib monotherapy in EGFR T790M-positive NSCLC following previous EGFR TKI therapy: CAURAL brief report. J Thorac Oncol. 2019;14(5):933-939. doi pubmed
- 15. Galsky MD, Arija JAA, Bamias A, Davis ID, De Santis M, Kikuchi E, Garcia-Del-Muro X, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebocontrolled phase 3 trial. Lancet. 2020;395(10236):1547-1557. doi pubmed
- Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378(22):2078-2092. doi pubmed
- Govindan R, Szczesna A, Ahn MJ, Schneider CP, Gonzalez Mella PF, Barlesi F, Han B, et al. Phase III trial of ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-small-cell lung cancer. J Clin Oncol. 2017;35(30):3449-3457. doi pubmed
- Gutzmer R, Stroyakovskiy D, Gogas H, Robert C, Lewis K, Protsenko S, Pereira RP, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF(V600) mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;395(10240):1835-1844. doi pubmed
- Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-723. doi pubmed pmc
- Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, Huemer F, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018;379(23):2220-2229. doi pubmed
- 21. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, Wyrwicz L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27-40. doi pubmed pmc
- 22. Jotte R, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodriguez-Abreu D, Hussein M, Soo R, et al. Atezolizumab in Combination With Carboplatin and Nab-Paclitaxel in Advanced Squamous NSCLC (IMpower131): Results From a Randomized Phase III Trial. J Thorac Oncol. 2020;15(8):1351-1360. doi pubmed
- 23. Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJ, Krainer M, et al. Ipilimumab versus

placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15(7):700-712. doi pubmed pmc

- 24. Lee NY, Ferris RL, Psyrri A, Haddad RI, Tahara M, Bourhis J, Harrington K, et al. Avelumab plus standardof-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, doubleblind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol. 2021;22(4):450-462. doi pubmed
- 25. Mateos MV, Blacklock H, Schjesvold F, Oriol A, Simpson D, George A, Goldschmidt H, et al. Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183): a randomised, open-label, phase 3 trial. Lancet Haematol. 2019;6(9):e459-e469. doi pubmed
- 26. Miles D, Gligorov J, Andre F, Cameron D, Schneeweiss A, Barrios C, Xu B, et al. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. Ann Oncol. 2021;32(8):994-1004. doi pubmed
- Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, Koehler A, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020;396(10257):1090-1100. doi pubmed
- Moore KN, Bookman M, Sehouli J, Miller A, Anderson C, Scambia G, Myers T, et al. Atezolizumab, bevacizumab, and chemotherapy for newly diagnosed stage III or IV ovarian cancer: placebo-controlled randomized phase III trial (IMagyn050/GOG 3015/ENGOT-OV39). J Clin Oncol. 2021;39(17):1842-1855. doi pubmed pmc
- 29. Nishio M, Barlesi F, West H, Ball S, Bordoni R, Cobo M, Longeras PD, et al. Atezolizumab plus chemotherapy for first-line treatment of nonsquamous NSCLC: results from the randomized phase 3 IMpower132 trial. J Thorac Oncol. 2021;16(4):653-664. doi pubmed
- Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, Kalofonos H, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383(13):1218-1230. doi pubmed
- 31. Powles T, Csoszi T, Ozguroglu M, Matsubara N, Geczi L, Cheng SY, Fradet Y, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as firstline therapy for advanced urothelial carcinoma (KEY-NOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(7):931-945. doi pubmed
- 32. Pujade-Lauraine E, Fujiwara K, Ledermann JA, Oza AM, Kristeleit R, Ray-Coquard IL, Richardson GE, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinumrefractory ovarian cancer (JAVELIN Ovarian 200): an

open-label, three-arm, randomised, phase 3 study. Lancet Oncol. 2021;22(7):1034-1046. doi pubmed

- Reck M, Luft A, Szczesna A, Havel L, Kim SW, Akerley W, Pietanza MC, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. J Clin Oncol. 2016;34(31):3740-3748. doi pubmed
- Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320-330. doi pubmed
- 35. Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csoszi T, Cheema PK, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. J Clin Oncol. 2020;38(21):2369-2379. doi pubmed pmc
- 36. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Dieras V, et al. Atezolizumab and nabpaclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379(22):2108-2121. doi pubmed
- Schmid P, Cortes J, Pusztai L, McArthur H, Kummel S, Bergh J, Denkert C, et al. Pembrolizumab for early triplenegative breast cancer. N Engl J Med. 2020;382(9):810-821. doi pubmed
- 38. Shitara K, Van Cutsem E, Bang YJ, Fuchs C, Wyrwicz L, Lee KW, Kudaba I, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. JAMA Oncol. 2020;6(10):1571-1580. doi pubmed pmc
- Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodriguez-Abreu D, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288-2301. doi pubmed
- 40. Sugawara S, Lee JS, Kang JH, Kim HR, Inui N, Hida T, Lee KH, et al. Nivolumab with carboplatin, paclitaxel, and bevacizumab for first-line treatment of advanced nonsquamous non-small-cell lung cancer. Ann Oncol. 2021;32(9):1137-1147. doi pubmed
- Usmani SZ, Schjesvold F, Oriol A, Karlin L, Cavo M, Rifkin RM, Yimer HA, et al. Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185): a randomised, open-label, phase 3 trial. Lancet Haematol. 2019;6(9):e448-e458. doi pubmed
- 42. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, Kopp HG, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment

for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(7):924-937. doi pubmed

- 43. Gidaro A, Palmieri G, Donadoni M, Mameli LA, La Cava L, Sanna G, Castro D, et al. A diagnostic of acquired hemophilia following PD1/PDL1 inhibitors in advanced melanoma: the experience of two patients and a literature review. Diagnostics (Basel). 2022;12(10):2559. doi pubmed pmc
- 44. Kasamatsu T, Ino R, Takahashi N, Gotoh N, Minato Y, Takizawa M, Yokohama A, et al. PDCD1 and CTLA4 polymorphisms affect the susceptibility to, and clinical features of, chronic immune thrombocytopenia. Br J Haematol. 2018;180(5):705-714. doi pubmed
- 45. Hinterleitner C, Strahle J, Malenke E, Hinterleitner M, Henning M, Seehawer M, Bilich T, et al. Platelet PD-L1 reflects collective intratumoral PD-L1 expression and predicts immunotherapy response in non-small cell lung cancer. Nat Commun. 2021;12(1):7005. doi pubmed pmc
- Kroll MH, Rojas-Hernandez C, Yee C. Hematologic complications of immune checkpoint inhibitors. Blood. 2022;139(25):3594-3604. doi pubmed pmc
- Haddad TC, Zhao S, Li M, Patel SH, Johns A, Grogan M, Lopez G, et al. Immune checkpoint inhibitor-related thrombocytopenia: incidence, risk factors and effect on survival. Cancer Immunol Immunother. 2022;71(5):1157-1165. doi pubmed pmc
- Maillet D, Corbaux P, Stelmes JJ, Dalle S, Locatelli-Sanchez M, Perier-Muzet M, Duruisseaux M, et al. Association between immune-related adverse events and longterm survival outcomes in patients treated with immune checkpoint inhibitors. Eur J Cancer. 2020;132:61-70. doi pubmed
- 49. Zhou X, Yao Z, Yang H, Liang N, Zhang X, Zhang F. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. BMC Med. 2020;18(1):87. doi pubmed pmc
- 50. Shafqat H, Gourdin T, Sion A. Immune-related adverse events are linked with improved progression-free survival in patients receiving anti-PD-1/PD-L1 therapy. Semin Oncol. 2018;45(3):156-163. doi pubmed
- Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother Cancer. 2019;7(1):306. doi pubmed pmc
- 52. Ricciuti B, Genova C, De Giglio A, Bassanelli M, Dal Bello MG, Metro G, Brambilla M, et al. Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis. J Cancer Res Clin Oncol. 2019;145(2):479-485. doi pubmed