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Comparison of efficacy discrepancy between early-phase clinical trials and phase III trials of PD-1/PD-L1 inhibitors

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ABSTRACT

Background Phase III clinical trials are pivotal for evaluating therapeutics, yet a concerning failure rate has been documented, particularly impacting oncology where accelerated approvals of immunotherapies are common. These failures are predominantly attributed to a lack of therapeutic efficacy, indicating overestimation of results from phase II studies. Our research aims to systematically assess overestimation in early-phase trials involving programmed cell death-1 (PD-1)/programmed cell death-ligand 1(PD-L1) inhibitors compared with phase III trials and identify contributing factors.

Methods We matched 51 pairs of early-phase and phase III clinical trials from a pool of over 9,600 PD-1/PD-L1 inhibitor trials. The matching criteria included identical treatment regimens, cancer types, treatment lines, and biomarker enrichment strategies. To assess overestimation, we compared the overall response rates (ORR) between early-phase and phase III trials. We established independent variables related to eligibility criteria, and trial design features of participants to analyze the factors influencing the observed discrepancy in efficacy between the two phases through univariable and multivariable logistic analyses.

Result Early-phase trial outcomes systematically overestimated the subsequent phase III results, yielding an odds ratio (OR) comparing ORR in early-phase versus phase III: 1.66 (95% CI: 1.43 to 1.92, p<0.05). This trend of inflated ORR was consistent across trials testing PD-1/PD-L1 monotherapies and combination therapies involving PD-1/PD-L1. Among the examined factors, the exclusion of patients with autoimmune diseases was significantly associated with the disparity in efficacy between early-phase trials and phase III trials (p=0.023). We calculated a Ward statistic of 2.27 to validate the effectiveness of the model.

Conclusion These findings underscore the tendency of overestimation of efficacy in early-phase trials involving immunotherapies. The observed differences could be attributed to variations in the inclusion of patients with autoimmune disorders in early-phase trials. These insights have the potential to inform stakeholders in the future development of cancer immunotherapies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Substantial failure rate in phase III clinical trials, especially in oncology, prompts ethical and resource concerns. This is primarily attributed to a lack of therapeutic efficacy in phase III studies.

WHAT THIS STUDY ADDS

⇒ Outcomes of early-phase clinical trials of programmed cell death-1 (PD-1)/programmed cell death-ligand 1(PD-L1) inhibitors have been systematically overestimated compared with subsequent phase III results.

⇒ Exclusion of patients with autoimmune diseases in early-phase trials has been demonstrated to be the significant determinant of overestimation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings provide insights in the design of future clinical trials for cancer immunotherapy. Further investigations are warranted to assess the effectiveness of cancer immunotherapies in patients with pre-existing autoimmune disorders to enhance our understanding and optimize treatment outcomes.

INTRODUCTION

Phase III clinical trials hold immense importance in assessing the efficacy and safety of emerging therapeutics,[1] with positive outcomes serving as a gateway to regulatory approval.[2] However, a documented failure rate of approximately 40% in phase III trials has led to substantial resource wastage and ethical concerns, as patients may be exposed to ineffective treatments.[3–5] This issue is particularly alarming in the field of oncology, where a substantial proportion of oncology drugs have received accelerated approval based on early-phase clinical data,[5] notably observed with programmed cell death-1 (PD-1)/programmed cell death-ligand 1(PD-L1)t inhibitors.[6] Immunotherapy has become the mainstream approach in cancer treatment, with thousands of ongoing clinical trials in this field.[7] Nonetheless, according to the US Food and Drug Administration, among the 36 accelerated approvals involving

PD-1/PD-L1, 8 have already been withdrawn from the market.[8]

The primary cause of these failures has been attributed to a lack of therapeutic efficacy, constituting 55% of phase III failures.[5] Essentially, this implies the results were overestimated in phase II studies, but could not be reproduced on a larger scale in phase III trials. This pattern of overestimation has been consistently observed in cancer and other indications.[9–14] In the context of chemotherapy and targeted therapy in cancer, it has been suggested that factors related to study design and sample size may be implicated, although only preliminary analyses were conducted.[15 16] In other indications like rheumatoid arthritis, overestimation has been linked to eligibility criteria of the study population.[17]

Currently, there is a notable gap in systematic research within the field of oncology, particularly in the booming PD-1/PD-L1 arena, to identify the precise factors influencing overestimation. Therefore, our research aims to comprehensively assess the extent of overestimation in early-phase trials compared with phase III clinical trials involving PD-1/PD-L1 inhibitors and explore potential factors contributing to this systematic overestimation. This research endeavor is anticipated to yield valuable insights with implications for the design of future clinical trials related to immunotherapies.

METHOD

Search strategy

We conducted searches on major clinical trial registration platforms including the US' ClinicalTrials.gov (https://www.clinicaltrials.gov/), the European Union's EudraCT (https://www.clinicaltrialsregister.eu/), Japan's UMIN-CTR (https://www.umin.ac.jp/ctr/), Australia's ANZCTR (https://www.anzctr.org.au/) and China's CDE (http://www.chinadrugtrials.org.cn/) platforms. To compile a comprehensive data set, we accessed the "trialcube" database of Pharmcube,[18] a pharmaceutical data repository that amalgamates studies registered on aforementioned platforms on a daily basis. We identified over 9,600 clinical trials by conducting standardized searches for drugs targeting PD-1/PD-L1 as of February 14, 2023.

We subsequently narrowed our focus to 3,105 phase III trials, for which we obtained the trial outcomes by searching for the registered numbers of each study across various databases, including PubMed, Web of Science, and scientific conferences related to oncology, such as American Society of Clinical Oncology and European Society for Medical Oncology. The data extraction was completed by April 16, 2023. Among the 852 phase III trials with available outcomes, we further conducted matching with early-phase trials (see below in the "Matching strategy" section). The variables of interest in these trials included trial phase, treatment regimens, indications, lines of therapies, inclusion and exclusion criteria, primary outcomes and efficacy outcomes regarding overall response rates. Majority of the PD-1/PD-L1 products have been approved for certain indications in major countries.

Matching strategy

After identifying relevant literature on clinical trials, we deployed a matching process to pair the phase III trials with early-phase trials. Our matching criteria were guided by the following principles: (1) same regimens involving PD-1/PD-L1 inhibitors; (2) same types of cancer, including well-defined molecular types if specified; (3) identical number of lines of treatment, (4) in case where PD-L1 expression or microsatellite instability signature was relevant to the study. These criteria needed to align between at least one study group in the paired trials (eg, both trials involved patients with PD-L1 expression larger than 1%); and (5) the early-phase trials had to be cited as in the published literature of the phase III trial. Following these principles outlined above, we identified and paired 51 sets of clinical trials. The early-phase trials primarily consisted of phase II trials. In cases where phase II trials meeting the criteria could not be found, we extended our search to include phase I trials within the same context. These 51 sets comprised 23 pairs involving monotherapies of PD-1/PD-L1 inhibitors and 28 pairs with combination regimens (figure 1).

Data extraction

Trial characteristics were retrieved from various sources, including literature, ClinicalTrials.gov, EudraCT, and official trial reports. The primary outcome of efficacy in our study was overall response rates (ORR) in both early-phase and phase III clinical trials. ORR was chosen as it provides an objective measure of drug activity, focusing on the immediate responses without considering long-term effects. It can be evaluated in various single-arm studies, enabling the comparison of single arms between paired trials. Other trial characteristics included sample size, the number of study centers, and the year of publication. In addition, we conducted an extraction of eligibility criteria, encompassing the following factors: life expectancy greater than 3 or 6 months, the requirement for representative tumor specimens, the presence of measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, adequate hematologic function, adequate hepatic function, adequate renal function, PD-L1 tumor cells or immune cells status determined by immunohistochemistry, biomarker expression of targeted cancer, central nervous system disorders (including metastasis), currently active infection, prior chemotherapy treatment, prior immunotherapy treatment, prior immunosuppressive therapy, history of malignancies other than the cancer of interest, history of autoimmune diseases, history of interstitial pulmonary diseases, history of hepatitis virus infection, history of HIV infection, history of cardiovascular diseases, history of organ transplantation, vaccination within the past weeks, pregnancy or lactation status.

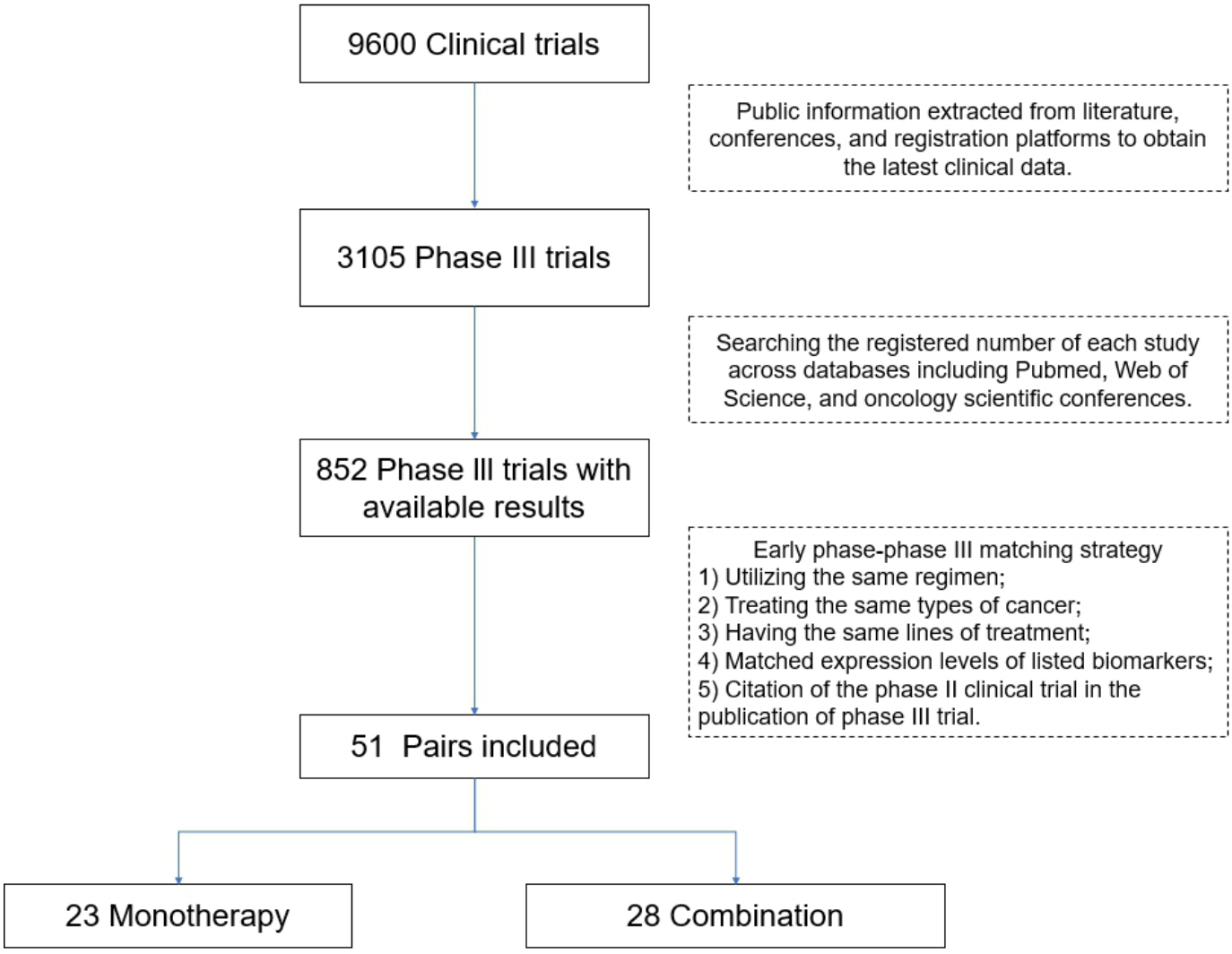

Figure 1 Flow chart of study screening, selection, and matching process for programmed cell death-1 (PD-1)/programmed cell death-ligand 1(PD-L1)-related clinical trials.

Data analysis

To explore potential differences in efficacy between early-phase and phase III trials, we first compared the ORR between early-phase studies and corresponding phase III studies using scatter plots. Forest plots were created to visually display the odds ratio (OR) and associated CIs for each trial's ORR in early-phase trials relative to phase III trials with a random effects model. Furthermore, funnel plots were generated to investigate the relationship between study size and effect size. All analyses were performed individually for each clinical trial. Given that our analysis was conducted at the level of individual study arms, and some study arms originated from the same clinical trials, calculations of heterogeneity were infeasible.

To analyze the factors that might influence the disparities in efficacy between early-phase and phase III trials, we introduced a dichotomous variable called ORv. ORv served as the dependent variable, representing the CI of the OR for ORR in early-phase trials relative to phase III trials, as calculated during the meta-analysis. This variable was assigned a value of 1 if the CI of OR was entirely to the right of 1, and a value of 0 if the CI had a fraction less than 1.

For the independent variables, we defined a set of variables related to phase, clinical trial design, and eligibility criteria of the study population, aiming to investigate their impact on the differences in efficacy between early-phase and phase III trials. These variables were defined as binary, with a value of 1 indicating the presence of a particular characteristic or difference between early-phase and corresponding phase III trials, and a value of 0 indicating its absence.

Finally, we employed a univariable logistic regression approach, analyzing each independent variable separately to assess its significant contribution to the differences in efficacy between early-phase and phase III trials. To ensure the adequacy of our model fit, we used likelihood ratio tests and the Akaike information criterion, prioritizing models that strike an optimal balance between simplicity and explanatory power. We also conducted multivariable logistic regression analysis on variables that demonstrated significance in the univariate

analysis, as well as on variables that were closely related. The model's effectiveness was further evaluated using the Ward statistic. Variance inflation factor was calculated to assess potential issues of collinearity among the variables. To mitigate the risk of false positives, the Benjamini-Hochberg method was applied, enabling us to control the false discovery rate and ensure the reliability of our p value findings. All statistical analyses were executed using RStudio V.4.2.3 and Stata V.17. A two-sided p value <0.05 was considered statistically significant.

Risk of bias

In our assessment of included randomized trials, we applied the Cochrane Collaboration's Risk of Bias Assessment Tool to rigorously evaluate six key types of bias: selection, performance, detection, attrition, reporting, and other potential biases.[19] To guarantee the objectivity and precision of our evaluation, each study was independently by two independent researchers. In cases where their assessments differed, the researchers engaged in detailed discussions to achieve a consensus. The outcome of this process was the categorization of each study based on the risk of bias, which was designated as low, high, or unclear for each bias type. An "unclear risk of bias" categorization was applied in situations where the information provided was either insufficient or inadequately detailed, rendering a definitive assessment of bias risk unfeasible.

RESULTS

Comparison of outcomes between early-phase and phase III trials

A visual examination of the ORR of early-phase and phase III trials assessing the identical treatment regimens indicated an overestimation of ORR values in early-phase trials compared with phase III trials, as depicted in figure 2. This trend of inflated ORR in early-phase trials was consistent across trials testing

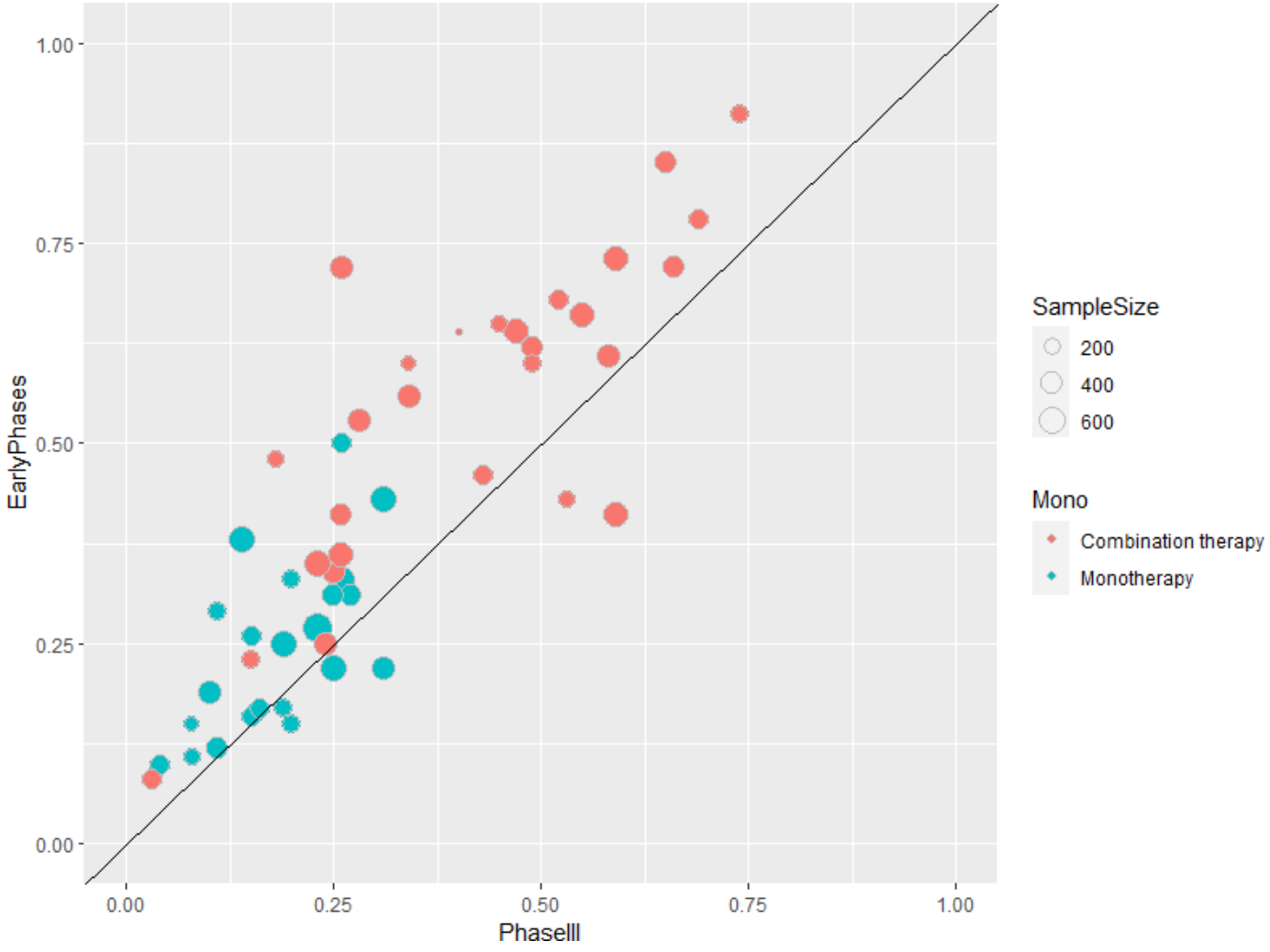

Figure 2 Comparative analysis of overall response rates between early-phase and phase III studies. Green dots represent studies that use monotherapy with programmed cell death-1 (PD-1)/programmed cell death-ligand 1(PD-L1) inhibitors, and red marks denote those involving combination therapies. The size of each dot corresponds to the total number of participants of the two selected arms in both early-phase and phase III studies.

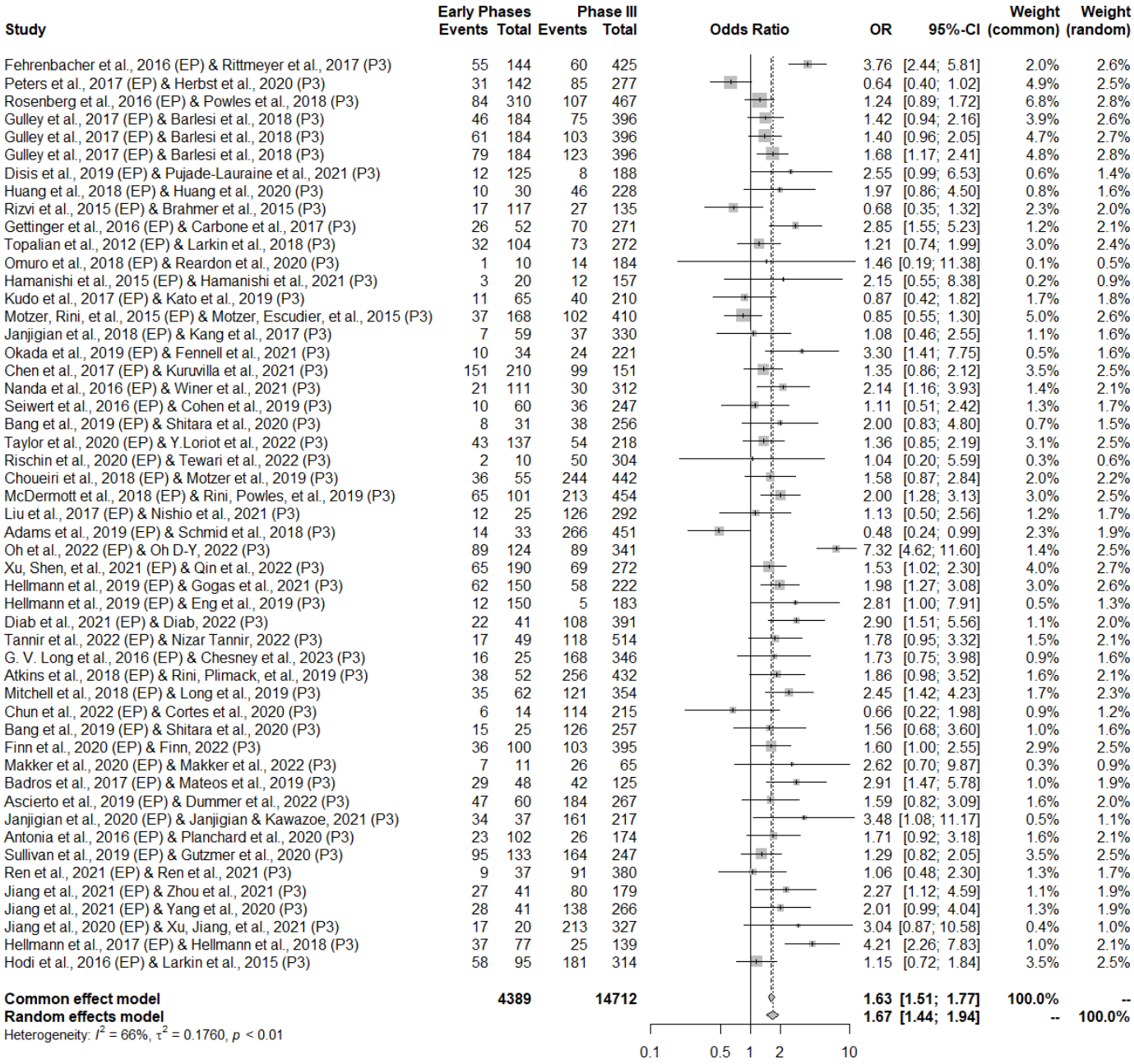

Figure 3 Random-effect model analysis for outcome comparison between early-phase and phase III trials involving anti-PD-1/PD-L1 inhibitors. Forest plots visualizing ORs of objective response rates with±95% CIs in early-phase studies compared with phase III studies. Each row presents data for a specific treatment regimen used in a particular population for a specific type of cancer as the unit of analysis. The squares represent the paired evaluation of outcomes in matched early-phase and phase III trials, and the bars (lines) represent the 95% CI for each comparison. Summary estimates are depicted as diamonds at the bottom of the plot, encompassing±95% CI. Results from heterogeneity analysis are displayed beneath the plot. CRC, carcinoma of colon and rectum; EP: Early-phase trials; HCC, hepatic cell cancer; HL, Hodgkin's lymphoma; HNSCC, head and neck squamous cell carcinoma; MPM, malignant pleural mesothelioma; NSCLC, non-small-cell lung cancer; P3: Phase III trials; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand; RCC, renal cell cancer; TNBC, triple-negative breast cancer; 1/2/3 L: first/second/third-line therapy.

PD-1/PD-L1 monotherapies and combination therapies involving PD-1/PD-L1.

To quantify this overestimation, the random-effects model analysis reveals an OR of overestimation is 1.67 (95% CI: 1.44 to 1.94, p<0.01, figure 3). Dissecting this further, trials using single agent PD-1/PD-L1 inhibitors showed an OR of 1.45 (95% CI: 1.18 to 1.79, p<0.01), while trials incorporating combination drug regimens demonstrated a more pronounced OR of 1.85 (95% CI: 1.52 to 2.25, p<0.01). Further reinforcing these results, sensitivity analyses, which included stepwise exclusion (refer to online supplemental figure 1) and subgroup analyses (see online supplemental figure 2), consistently yielded an OR greater than 1, substantiating the robustness of our findings.

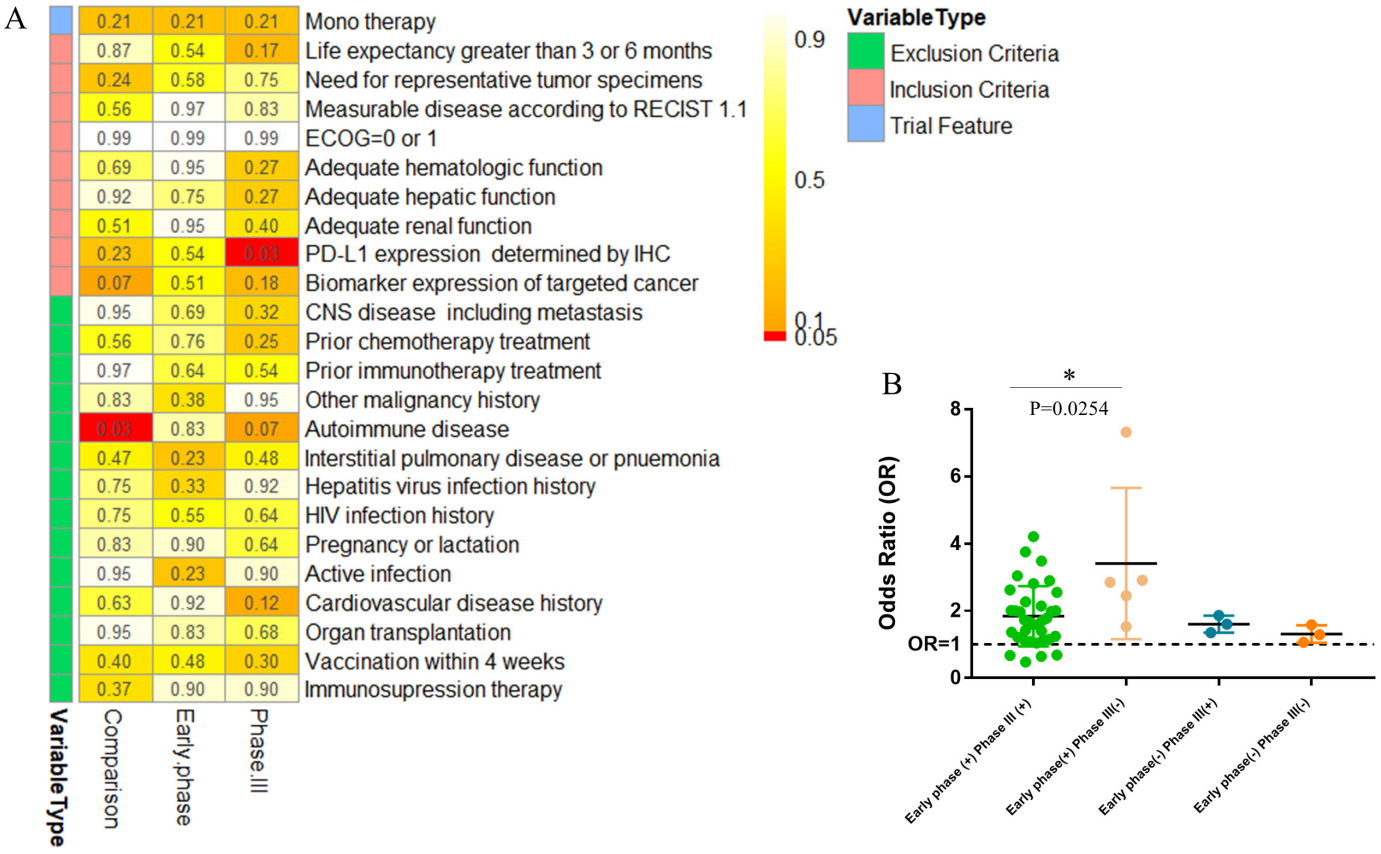

Figure 4 Exploratory analysis of efficacy differences between early-phase and phase III trials involving PD-1/PD-L1 immunotherapies. (A) Heat map visualizing the association of the evaluated variables and the observed efficacy differences. Color coding and numeric indicators within each cell represent the p values of each determinant, as determined through univariable analysis. This analysis tests the null hypothesis (H0) that the CI of OR lies entirely to the right of 1. (B) Scatter plot to investigate the impact of the inclusion or exclusion of patients with autoimmune diseases in the eligibility criteria on the overestimation of efficacy in early-phase trials versus phase III trials. Each dot indicates one pair of trials, plotting the OR for overall response rates in early-phase compared with phase III on the y-axis, against the eligibility criteria of patients with autoimmune diseases on the x-axis. The labels on the x-axis are marked with (+) to denote "trials that included an exclusion criterion for patients with autoimmune diseases" and (–) to indicate the absence of such a criterion. CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group Performance Status; IHC, immunohistochemistry; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand; RECIST: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.

Factors contributing to discrepancies in efficacy between early-phase and phase III trials

To explore the reasons behind the efficacy overestimation in early-phase trials, determinants that contribute to the observed differences between early-phase and phase III trials were investigated (figure 4). Among the selected factors, exclusion of patients with autoimmune diseases stood out as the sole variable significantly influencing the disparity in efficacy (p=0.023). The computed Wald statistic was 2.27 for the exclusion criteria of autoimmune diseases, indicating a significant deviation from the null hypothesis at the 0.05 level and substantiating its role in the overestimation of efficacy in early-phase trials compared with phase III trials. Further strengthening our findings, we conducted multivariable logistic analysis incorporating several variables including the exclusion criteria of autoimmune diseases (online supplemental table 4). These analyses consistently demonstrate that the exclusion of patients with pre-existing autoimmune diseases markedly influence the overestimation of efficacy in these trials.

To further delineate this correlation, we stratified the trial pairs based on their inclusion and exclusion criteria regarding autoimmune diseases in both early-phase and phase III studies. The analysis revealed that trials which excluded patients with autoimmune diseases in the early phase but not in phase III exhibited a significantly elevated OR for efficacy discrepancy when contrasted with trials that consistently applied autoimmune disease exclusion criteria across both phases.

Risk of bias

Individual study outcomes (online supplemental table 1) and risk of bias assessments (online supplemental table 2) are listed in the supplementary tables. A majority of the studies analyzed were assigned a low risk of bias. The most frequently encountered issue contributing to an unclear risk of bias designation stemmed from insufficient

information regarding random-sequence generation. None of the studies included in our analysis were classified as having a high risk of bias, affirming the methodological rigor of the research underpinning our findings.

DISCUSSION

This study demonstrates that early-phase clinical trials for PD-1/PD-L1 inhibitors in tumor treatment tend to yield higher efficacy estimates compared with phase III trials. Our analysis indicates an OR of 1.67 (95% CI: 1.44 to 1.94, p<0.01) for the overestimation of ORR in these early-phase trials. This pattern of early-phase results not alighting with phase III outcomes is not exclusive to oncology, but is also observable in various other diseases,[9–14 16 17 20–22] including autoimmune diseases (such as rheumatoid arthritis, psoriatic arthritis and Crohn's disease, multiple sclerosis, and systemic lupus erythematosus) and certain malignancies (like pancreatic cancer, and cutaneous T-cell lymphoma). Our findings, therefore, add to a growing body of evidence suggesting caution in interpreting early-phase trial results as definitive indicators of phase III trial outcomes. However, the reason for this inconsistency was less known.

Our findings indicate that excluding patients with autoimmune disorders was significantly associated with the discrepancy of effect estimation, in contrast to other criteria which show minimal impact. Specifically, the ORR in early-phase trials was significantly higher than the paired phase III trials, when patients with autoimmune disorders were excluded in early-phase trials but not in phase III trials. However, other variables, including inclusion criteria, and baseline characteristics, on the difference in efficacy between early-phase and phase III trials, did not demonstrate statistically significant impact on the efficacy variance. Given the larger sample size of phase III studies, these observed differences likely stem from an overestimation of treatment efficacy in early-phase studies, rather than an underestimation in phase III data.

The interplay between autoimmune diseases and cancer risk is multifaceted, with the risk profile varying among different autoimmune disorders. While a generalized increase in cancer risk is observed, the extent and nature of this risk differ across various conditions.[23] For instance, patients with systemic lupus erythematosus have an increased risk of developing solid tumors like bladder, endometrial, and cervical cancers, as well as hematological malignancies. Additionally, inflammatory myopathies, within 3 years of diagnosis, reveal a 74.6% likelihood of progressing to malignancies, with a pronounced risk for ovarian cancer.[23 24] In addition, many drugs used to treat autoimmune diseases have carcinogenic properties. Cyclophosphamide has been classified as a Group 1 carcinogen by the WHO.[25] Despite of these, it remains to be thoroughly investigated whether the underlying autoimmune condition alters the characteristics of tumors in a manner that significantly impacts the efficacy of pharmacological treatments.

The integration of tumor immunotherapy with treatment for autoimmune diseases in patients with cancer presents a complex challenge, particularly regarding the safety of immunotherapy. Concerns focus on the potential for recurrence of autoimmune diseases and emergence of immune-related adverse events, which may be severe. Consequently, patients with autoimmune diseases are often excluded from clinical trials. Recent evidence indicated that immune checkpoint inhibitors are safe for well-managed autoimmune diseases, such as rheumatoid arthritis.[26] Despite an increased overall risk of immune-related adverse reactions, the incidence of severe adverse events and mortality risks does not appear to be elevated.

Moreover, the antitumor efficacy of immunotherapy for patients with autoimmune diseases poses another challenge. In our study, early-phase trials overestimate the efficacy of immunotherapy, potentially skewed by excluding autoimmune disease patients. This suggests that the efficacy might be lower in the recruited patients with previously autoimmune diseases in paired phase III trials. Unfortunately, the lack of baseline data on immune diseases in these studies hampers further validation of this finding. Literature review indicate that immune checkpoint inhibitors in patients with a history of autoimmune disease can trigger relapses and necessitate immunosuppressive therapy, thereby affecting their efficacy.[27–29] Moreover, the efficacy of PD-1/PD-L1 inhibitors in these patients may be reduced due to the pre-existing immune system dysregulation. Altered immune state, characterized by prolonged hyperactivity and exposure to interferons, has been featured in these patients.[30 31] Downregulated PD-1 expression in both CD4+ and CD8+ T cells,[32 33] as well as increased levels of anti-PD-1 antibodies,[34] has been detected and potentially undermines the effectiveness of PD-1/PD-L1 inhibitor therapies in treating tumors. While some studies reported comparable efficacy in autoimmune and non-autoimmune patients,[35 36] these were limited to the use of ipilimumab in melanoma, and could not fully address our concerns. Further meticulously designed trials are needed to directly validate the response of these patients to immunotherapy.

To enhance the validity of our results in assessing the efficacy of PD-1/PD-L1 inhibitors, we employed rigorous sensitivity analyses. A stepwise exclusion method was applied to each study, confirming the stability of the combined OR and the robustness of our meta-analysis findings (online supplemental figure 1). Subgroup analysis, considering factors like treatment regimen, PD-L1 expression, treatment stages, cancer types, and study characteristics, consistently yielded OR values greater than 1, aligning with our primary conclusion (online supplemental figure 2).

Our study has several limitations. First, our independent variables were all dichotomous, neglecting the details of some quantitative variables, such as participant number, blood count and liver function measures, and PD-L1 expression. The latter is particularly important but cannot be quantified due to the inconsistent descriptions of

PD-L1 expression level in each clinical trial, thus limiting our ability to assess its impact on efficacy differences. Some important factors, though recognized as potential confounders in literature, were unable to be analyzed due to lack of data, such as concurrent antibiotic utilization. Second, the heterogeneity among trials and potential publication bias were noted as concerns. Given the lack of data availability, we were not be able to precisely quantify the heterogeneity and publication bias. Third, possibility for experiment-wise error, especially in early phase trials with smaller sample sizes, could not be neglected. Smaller sample size may make the results susceptible to random errors, leading to unstable or biased outcomes. Fourth, ORR was used as an integrated efficacy endpoint in our analysis, due to its feasibility to be retrieved from both early-phase trials and phase III trials. Its limitations in reflecting survival outcomes were acknowledged, and it is rarely considered as the primary endpoint in phase III trials. Finding better indicators to replace ORR and comparing the differences in survival outcomes between early-clinical trials and phase III clinical trials for immunotherapies still pose a significant challenge.

In conclusion, our systematic literature review suggests a possible overestimation of efficacy in early-phase cancer immunotherapy trials, partly attributable to the exclusion of autoimmune patients. We analyzed 51 pairs of early-phase and phase III clinical trials, the largest cohort to date, focusing on PD-1/PD-L1 as a therapeutic agent across diverse cancer types. This underscores the importance of our findings in guiding future development in immunotherapy. Due to the concerns regarding potential diminished efficacy, inclusion of patients with autoimmune diseases from trials raises uncertainties. We recommend designing future trials specifically for these patients to deepen our understanding and improve treatment outcomes.

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Supplementary Table 1. ORRs and assessing criteria of clinical trials included in the analysis

Regimen	Cancer Type	Line	Biomarker	study							
				Phase2	Phase 2 ORR	N(Responder/total)	assessing criteria	Phase3	Phase 3 ORR	N(Responder/total)	assessing criteria
Atezolizumab	NSCLC	2L	TC1/2/3 or IC1/2/3	(Fehrenbacher et al., 2016)	38%	55/144	RECIST v1.1	(Rittmeyer et al., 2017)	14%	60/425	RECIST v1.1
Atezolizumab	NSCLC	1L	TC2/3	(Peters et al., 2017)	22%	31/142	RECIST v1.1	(Herbst et al., 2020)	31%	85/277	RECIST v1.1
Atezolizumab	Bladder cancer	2L	TC2/3	(Rosenberg et al., 2016)	27%	84/310	RECIST v1.1, imRECIST	(Powles et al., 2018)	23%	107/467	RECIST v1.1
Avelumab	NSCLC	2L	PD-L1(1%)	(Gulley et al., 2017)	25%	46/184	RECIST v1.1	(Barlesi et al., 2018)	19%	75/396	RECIST v1.1
Avelumab	NSCLC	2L	PD-L1(50%)	(Gulley et al., 2017)	33%	61/184	RECIST v1.1	(Barlesi et al., 2018)	26%	103/396	RECIST v1.1
Avelumab	NSCLC	2L	PD-L1(80%)	(Gulley et al., 2017)	43%	79/184	RECIST v1.1	(Barlesi et al., 2018)	31%	123/396	RECIST v1.1
Avelumab	Ovarian cancer	2L	PD-L1	(Disis et al., 2019)	10%	12/125	RECIST v1.1, irRECIST	(Pujade-Lauraine et al., 2021)	4%	8/188	RECIST v1.1,
Camrelizumab	Esophageal cancer	2L	PD-L1	(Huang et al., 2018)	33%	10/30	RECIST v1.1	(Huang et al., 2020)	20%	46/228	RECIST v1.1
Nivolumab	NSCLC	2L	PD-L1	(Rizvi et al., 2015)	15%	17/117	RECIST v1.1	(Brahmer et al., 2015)	20%	27/135	RECIST v1.1
Nivolumab	NSCLC	2L	PD-L1>5%	(Gettinger et al., 2016)	50%	26/52	RECIST v1.1	(Carbone et al., 2017)	26%	70/271	RECIST v1.1
Nivolumab	Melanoma	2L	PD-L1	(Topalian et al., 2012)	31%	32/104	RECIST v1.0	(Larkin et al., 2018)	27%	73/272	RECIST v1.1
Nivolumab	Glioblastoma	2L	/	(Omuro et al., 2018)	11%	1/10	RANO	(Reardon et al., 2020)	8%	14/184	RANO
Nivolumab	Ovarian Cancer	2L	PD-L1	(Hamanishi et al., 2015)	15%	3/20	RECIST v1.1	(Hamanishi et al., 2021)	8%	12/157	RECIST v1.1
Nivolumab	Esophageal cancer	2L	PD-L1	(Kudo et al., 2017)	17%	11/65	RECIST v1.1	(Kato et al., 2019)	19%	40/210	RECIST v1.1
Nivolumab	RCC	2L	PD-L1	(Motzer, Rini, et al., 2015)	22%	37/168	RECIST v1.1	(Motzer, Escudier, et al., 2015)	25%	103/410	RECIST v1.1
Nivolumab	Gastric cancer	2L	PD-L1	(Janjigian et al., 2018)	12%	7/59	RECIST v1.1	(Kang et al., 2017)	11%	37/330	RECIST v1.1
Nivolumab	MPM	2L	PD-L1	(Okada et al., 2019)	29%	10/34	RECIST v1.1, mRECIST	(Fennell et al., 2021)	11%	24/221	RECIST v1.1, mRECIST
Pembrolizumab	HL	HSCT	PD-L1	(Chen et al., 2017)	72%	151/210	RRC	(Kuruvilla et al., 2021)	66%	99/151	RRC
Pembrolizumab	TNBC	2L	PD-L1	(Nanda et al., 2016)	19%	21/111	RECIST v1.1	(Winer et al., 2021)	10%	30/312	RECIST v1.1

Pembrolizumab	HNSCC	2L	PD-L1	(Seiwert et al., 2016)	16%	10/60	RECIST v1.1	(Cohen et al., 2019)	15%	36/247	RECIST v1.1, imRECIST
Pembrolizumab	Gastric cancer	1L	PD-L1≥1%	(Bang et al., 2019)	26%	8/31	RECIST v1.1	(Shitara et al., 2020)	15%	38/256	RECIST v1.1
Pembrolizumab	Bladder cancer	2L	PD-L1	(Taylor et al., 2020)	31%	43/137	RECIST v1.1	(Y.Loriot et al., 2022)	25%	55/218	RECIST v1.1
Cemiplimab	Cervix cancer	2L	PD-L1	(Rischin et al., 2020)	17%	2/10	RECIST v1.1	(Tewari et al., 2022)	16%	50/304	RECIST v1.1
Avelumab+Axitinib	RCC	1L	PD-L1	(Choueiri et al., 2018)	66%	36/55	RECIST v1.1	(Motzer et al., 2019)	55%	244/442	RECIST v1.1
Atezolizumab+bevacizumab	RCC	1L	PD-L1	(McDermott et al., 2018)	64%	65/101	RECIST v1.1	(Rini, Powles, et al., 2019)	47%	213/454	RECIST v1.1
Atezolizumab+Chemotherapy	NSCLC	1L	/	(Liu et al., 2017)	46%	12/25	RECIST v1.1	(Nishio et al., 2021)	43%	126/292	RECIST v1.1
Atezolizumab+Paclitaxel(Albumin bound)	TNBC	1L	PD-L1	(Adams et al., 2019)	41%	14/33	RECIST v1.1	(Schmid et al., 2018)	59%	266/451	RECIST v1.1
Gemcitabine+cisplatin+durvalumab+tremelimumab	Billary tract cancer	1L	PD-L1	(Oh et al., 2022)	72%	89/124	irRECIST	(Oh D-Y, 2022)	26%	89/341	RECIST v1.1
Camrelizumab+rivocerarib	HCC	1L	PD-L1	(Xu, Shen, et al., 2021)	34%	65/190	RECIST v1.1	(Qin et al., 2022)	25%	69/272	RECIST v1.1
Atezolizumab+Cobimetinib	Melanoma	1L	PD-L1/BRAF	(Hellmann et al., 2019)	41%	62/150	RECIST v1.1	(Gogas et al., 2021)	26%	58/222	RECIST v1.1
Atezolizumab+Cobimetinib	CRC	3L	PD-L1/ BRAF/RAS	(Hellmann et al., 2019)	8%	12/150	RECIST v1.1	(Eng et al., 2019)	3%	5/183	RECIST v1.1
Nivolumab+bempegaldesleukin	Melanoma	1L	PD-L1/BRAF	(Diab et al., 2021)	53%	22/41	RECIST v1.1	(Diab, 2022)	28%	108/391	RECIST v1.1
Nivolumab+bempegaldesleukin	RCC	1L	PD-L1	(Tannir et al., 2022)	35%	17/49	RECIST v1.1	(Nizar Tannir, 2022)	23%	118/514	RECIST v1.1
Pembrolizumab+talimogene laherparepvec	Melanoma	2L	/	(G. V. Long et al., 2016)	62%	16/25	RECIST v1.1	(Chesney et al., 2023)	49%	168/346	irRECIST
Pembrolizumab+Axitinib	RCC	1L	PD-L1	(Atkins et al., 2018)	73%	38/52	RECIST v1.1	(Rini, Plimack, et al., 2019)	59%	256/432	RECIST v1.1
Pembrolizumab+Epacadostat	Melanoma	1L	PD-L1/IDO1	(Mitchell et al., 2018)	56%	35/62	RECIST v1.1	(Long et al., 2019)	34%	121/354	RECIST v1.1
Pembrolizumab+Chemotherapy	TNBC	1L	PD-L1 ≥1%	(Chun et al., 2022)	43%	6/14	RECIST v1.1	(Cortes et al., 2020)	53%	114/215	RECIST v1.1
Pembrolizumab+Chemotherapy	Gastric cancer	1L	PD-L1	(Bang et al., 2019)	60%	15/25	RECIST v1.1	(Shitara et al., 2020)	49%	126/257	RECIST v1.1
Pembrolizumab+Lenvatinib	HCC	1L	AFP	(Finn et al., 2020)	36%	36/100	RECIST v1.1	(Finn, 2022)	26%	103/395	RECIST v1.1
Lenvatinib+Pembrolizumab	endometrial cancer	1L	MSI-H/dMMR	(Makker et al., 2020)	64%	7/11	RECIST v1.1	(Makker et al., 2022)	40%	26/45	RECIST v1.1
Pembrolizumab+pomalido	MM	3L	PD-L1/CD3	(Badros et al.,	60%	29/48	International	(Mateos et al.,	34%	43/125	International

mide+dexamethasone				2017)			Myeloma Working Group criteria	2019)			Myeloma Working Group criteria
Pembrolizumab+Dabrafenib+trametinib	Melanoma	1L	PD-L1/BRAF	(Ascierto et al., 2019)	78%	47/60	RECIST v1.1	(Dummer et al., 2022)	69%	184/267	RECIST v1.1
Pembrolizumab+trastuzumab	Gastric cancer	1L	PD-L1/HER2	(Janjigian et al., 2020)	91%	34/37	RECIST v1.1	(Janjigian & Kawazoe, 2021)	74%	161/217	RECIST v1.1
Durvalumab+Tremelimumab+Chemotherapy	NSCLC	1L	PD-L1 TC <25%	(Antonia et al., 2016)	23%	23/102	RECIST v1.1	(Planchard et al., 2020)	15%	26/174	RECIST v1.1
Atezolizumab+cobimetinib+vemurafenib	Melanoma	1L	PD-L1/BRAF	(Sullivan et al., 2019)	72%	95/133	RECIST v1.1	(Gutzmer et al., 2020)	66%	164/247	RECIST v1.1
Sintilimab+IBI305	HCC	1L	α-fetoprotein	(Ren et al., 2021)	25%	9/37	RECIST v1.1, mRECIST	(Ren et al., 2021)	24%	91/380	RECIST v1.1, mRECIST
Sintilimab+chemotherapy	NSCLC-Squamous	1L	PD-L1	(Jiang et al., 2021)	65%	27/41	RECIST v1.1	(Zhou et al., 2021)	45%	80/179	RECIST v1.1
Sintilimab+chemotherapy	NSCLC-Non Squamous	1L	PD-L1	(Jiang et al., 2021)	68%	28/41	RECIST v1.1	(Yang et al., 2020)	52%	138/266	RECIST v1.1
Oxaliplatin+Sintilimab+Capecitabine	Gastric cancer	1L	PD-L1	(Jiang et al., 2020)	85%	17/20	RECIST v1.1	(Xu, Jiang, et al., 2021)	65%	213/327	RECIST v1.1
Nivolumab+Ipilimumab	NSCLC	1L	PD-L1	(Hellmann et al., 2017)	48%	37/77	RECIST v1.1	(Hellmann et al., 2018)	36%	50/139	RECIST v1.1
Ipilimumab+Nivolumab	Melanoma	1L	PD-L1/BRAF	(Hodi et al., 2016)	61%	58/95	RECIST v1.1	(Larkin et al., 2015)	58%	181/314	RECIST v1.1

Supplement Table 2 Table of primary endpoints and week intervals for tumor assessment of clinical trials included in the analysis

Regimen	Cancer Type	study					
		Phase2	Primary Endpoint	Intervals for tumor assessment	Phase3	Primary Endpoint	Intervals for tumor assessment
Atezolizumab	NSCLC	(Fehrenbacher et al., 2016)	OS	Every 6 weeks for 36 weeks, followed by 9-weeks interval	(Rittmeyer et al., 2017)	OS	Every 6 weeks for 36 weeks, followed by 9-weeks interval
Atezolizumab	NSCLC	(Peters et al., 2017)	ORR	Every 6 weeks for 12 months, followed by 9-weeks interval	(Herbst et al., 2020)	OS	Every 6 weeks for 48 weeks, followed by 9-weeks interval
Atezolizumab	Bladder cancer	(Rosenberg et al., 2016)	ORR	Every 9 weeks for 12 months, followed by 12-weeks interval	(Powles et al., 2018)	OS	Every 9 weeks for 54 weeks, followed by 12-weeks interval
Avelumab	NSCLC	(Gulley et al., 2017)	BOR	Every 6 weeks	(Barlesi et al., 2018)	OS	Every 6 weeks for 12 months, followed by 12-weeks interval
Avelumab	NSCLC	(Gulley et al., 2017)	BOR	Every 6 weeks	(Barlesi et al., 2018)	OS	Every 6 weeks for 12 months, followed by 9-weeks interval
Avelumab	NSCLC	(Gulley et al., 2017)	BOR	Every 6 weeks	(Barlesi et al., 2018)	OS	Every 6 weeks for 12 months, followed by 9-weeks interval
Avelumab	Ovarian cancer	(Disis et al., 2019)	BOR	Every 6 weeks	(Pujade-Lauraine et al., 2021)	OS/PFS	Every 8 weeks until disease progression
Camrelizumab	Esophageal cancer	(Huang et al., 2018)	Safety	Every 8 weeks for 6 months,	(Huang et al., 2020)	OS	Every 8 weeks

				followed by 12-weeks interval			
Nivolumab	NSCLC	(Rizvi et al., 2015)	ORR	Every 6 weeks until disease progression	(Brahmer et al., 2015)	OS	Every 6 weeks
Nivolumab	NSCLC	(Gettinger et al., 2016)	ORR	Every 3 months until documented progression	(Carbone et al., 2017)	OS	Every 6 weeks for 48 weeks, followed by 12-weeks interval
Nivolumab	Melanoma	(Topalian et al., 2012)	Safety	unknown	(Larkin et al., 2018)	ORR/OS	Every 6 weeks for 1 year, followed by 12-weeks interval
Nivolumab	Glioblastoma	(Omuro et al., 2018)	Safety	Every 6 weeks for 12 weeks, followed by 8-weeks interval	(Reardon et al., 2020)	OS	Every 6 weeks for 12 weeks, followed by 8-weeks interval
Nivolumab	Ovarian Cancer	(Hamanishi et al., 2015)	ORR	Every 2 months for 1 year or until PD, progression	(Hamanishi et al., 2021)	OS	Every 8 weeks for 48 weeks, followed by 12-weeks interval
Nivolumab	Esophageal cancer	(Kudo et al., 2017)	ORR	Every 6 weeks for 1 year, followed by 12-weeks interval	(Kato et al., 2019)	OS	Every 6 weeks for 1 year, followed by 12-weeks interval
Nivolumab	RCC	(Motzer, Rini, et al., 2015)	ORR	Every 6 weeks for 12 months, followed by 12-weeks interval	(Motzer, Escudier, et al., 2015)	OS	Every 8 weeks for 1 year, followed by 12-weeks interval
Nivolumab	Gastric cancer	(Janjigian et al., 2018)	ORR	Every 6 weeks for 24 weeks, followed by 12-weeks interval	(Kang et al., 2017)	OS	Every 6 weeks for 14 months, followed by 12-weeks interval

Nivolumab	MPM	(Okada et al., 2019)	ORR	Every 6 weeks	(Fennell et al., 2021)	OS/PFS	Every 6 weeks
Pembrolizumab	HL	(Chen et al., 2017)	ORR	Every 12 weeks	(Kuruvilla et al., 2021)	OS/PFS	Every 12 weeks
Pembrolizumab	TNBC	(Nanda et al., 2016)	ORR	Every 8 weeks	(Winer et al., 2021)	OS	Every 9 weeks for 12 months, followed by 12-weeks interval
Pembrolizumab	HNSCC	(Seiwert et al., 2016)	ORR	unknown	(Cohen et al., 2019)	OS	6 weeks for 1 year, and then 9 weeks
Pembrolizumab	Gastric cancer	(Bang et al., 2019)	ORR	Every 6 weeks for 1 year, followed by 9-weeks interval	(Shitara et al., 2020)	OS/PFS	Every 6 weeks
Pembrolizumab	Bladder cancer	(Taylor et al., 2020)	Safety	24^{th} week	(Y.Loriot et al., 2022)	OS/PFS	unknown
Cemiplimab	Cervix cancer	(Rischin et al., 2020)	Safety	Every 8 weeks	(Tewari et al., 2022)	OS	Every 4 weeks at beginning, then every 6 weeks
Avelumab+Axitinib	RCC	(Choueiri et al., 2018)	Safety	Every 6 weeks for 1 year, followed by 12-weeks interval	(Motzer et al., 2019)	OS/PFS	Every 6 weeks for 18 months, followed by 12-weeks interval
Atezolizumab+bevacizumab	RCC	(McDermott et al., 2018)	PD/PFS	Every 12 weeks	(Rini, Powles, et al., 2019)	OS/PD/PFS	Every 6 weeks for 78 weeks, followed by 12-weeks interval
Atezolizumab+Chemotherapy	NSCLC	(Liu et al., 2017)	Safety	unknown	(Nishio et al., 2021)	OS/PFS	Every 6 weeks for 48 weeks, followed by 9-weeks interval

Atezolizumab+Paclitaxel(Albumin bound)	TNBC	(Adams et al., 2019)	Safety	Every 4 weeks for 1 year, followed by 8-weeks interval	(Schmid et al., 2018)	OS/PFS	Every 8 weeks for 12 months, followed by 12-weeks interval
Gemcitabine+cisplatin+durvalumab+tremelimumab	Billary tract cancer	(Oh et al., 2022)	ORR	Every 6 weeks	(Oh D-Y, 2022)	OS	unknown
Camrelizumab+rivoceranib	HCC	(Xu, Shen, et al., 2021)	ORR	8 weeks for 48 weeks, and then 12 weeks	(Qin et al., 2022)	OS/PFS	unknown
Atezolizumab+Cobimetinib	Melanoma	(Hellmann et al., 2019)	ORR	Every 8 weeks	(Gogas et al., 2021)	ORR/OS	Every 8 weeks for 80 weeks, followed by 12-weeks interval
Atezolizumab+Cobimetinib	CRC	(Hellmann et al., 2019)	ORR	Every 8 weeks	(Eng et al., 2019)	OS/PFS	Every 8 weeks until PD
Nivolumab+bempegaldesleukin	Melanoma	(Diab et al., 2021)	Safety	Every 8 weeks	(Diab, 2022)	PFS	unknown
Nivolumab+bempegaldesleukin	RCC	(Tannir et al., 2022)	ORR	Every 8 weeks	(Nizar Tannir, 2022)	ORR/OS	unknown
Pembrolizumab+talimogene laherparepvec	Melanoma	(G. V. Long et al., 2016)	Safety	unknown	(Chesney et al., 2023)	OS/PFS	Every 12 weeks
Pembrolizumab+Axitinib	RCC	(Atkins et al., 2018)	Safety	Every 6 weeks for 66 weeks, followed by 12-weeks interval	(Rini, Plimack, et al., 2019)	OS/PFS	Every 6 weeks for 54 weeks, followed by 12-weeks interval
Pembrolizumab+Epacadostat	Melanoma	(Mitchell et al., 2018)	ORR	Every 9 weeks for 18 months, followed by 12-weeks interval	(Long et al., 2019)	OS/PFS	Every 9 weeks for 102 weeks, followed by 12-weeks interval
Pembrolizumab+Chemotherapy	TNBC	(Chun et al., 2022)	Safety	unknown	(Cortes et al., 2020)	OS/PFS	Every 8 weeks for 24 weeks,

							followed by 9-weeks interval
Pembrolizumab+Chemotherapy	Gastric cancer	(Bang et al., 2019)	ORR	Every 6 weeks for 1 year, followed by 9-weeks interval	(Shitara et al., 2020)	OS/PFS	Every 6 weeks
Pembrolizumab+Lenvatinib	HCC	(Finn et al., 2020)	ORR	Every 6 weeks for 24 weeks, followed by 9-weeks interval	(Finn, 2022)	OS/PFS	unknown
Lenvatinib+Pembrolizumab	endometrial cancer	(Makker et al., 2020)	ORR	Every 8 weeks	(Makker et al., 2022)	OS/PFS	Every 6 weeks for 24 weeks, followed by 9-weeks interval
Pembrolizumab+pomalidomide+dexamethasone	MM	(Badros et al., 2017)	Safety	unknown	(Mateos et al., 2019)	OS/PFS	unknown
Pembrolizumab+Dabrafenib+trametinib	Melanoma	(Ascierto et al., 2019)	ORR/PFS	Every 6 weeks for 18 months, followed by 12-weeks interval	(Dummer et al., 2022)	PFS	unknown
Pembrolizumab+trastuzumab	Gastric cancer	(Janjigian et al., 2020)	PFS	Every 9 weeks	(Janjigian & Kawazoe, 2021)	OR/PFS	Every 6 weeks
Durvalumab+Tremelimumab+Chemotherapy	NSCLC	(Antonia et al., 2016)	ORR	Every 8 weeks for 12 months, followed by 6-months interval	(Planchard et al., 2020)	OS	Every 8 weeks for 12 months, followed by 6-months interval
Atezolizumab+cobimetinib+vemurafenib	Melanoma	(Sullivan et al., 2019)	Safety	Every 4 weeks	(Gutzmer et al., 2020)	PFS	Every 8 weeks for 24 months, followed by 12-weeks interval
Sintilimab+IBI305	HCC	(Ren et al.,	OS/PFS	Every 6 weeks	(Ren et al.,	OS/PFS	Every 6 weeks

		2021)		for 48 weeks, followed by 12-weeks interval	2021)		for 48 weeks, followed by 12-weeks interval
Sintilimab+chemotherapy	NSCLC-Squamous	(Jiang et al., 2021)	ORR	Every 9 weeks	(Zhou et al., 2021)	OS/PFS	Every 9 weeks for 48 weeks, followed by 12-weeks interval
Sintilimab+chemotherapy	NSCLC-Non Squamous	(Jiang et al., 2021)	ORR	Every 9 weeks	(Yang et al., 2020)	OS/PFS	Every 9 weeks for 48 weeks, followed by 12-weeks interval
Oxaliplatin+Sintilimab+Capecitabine	Gastric cancer	(Jiang et al., 2020)	ORR	Every 9 weeks	(Xu, Jiang, et al., 2021)	OS	unknown
Nivolumab+Ipilimumab	NSCLC	(Hellmann et al., 2017)	ORR	Every 6 weeks for 24 weeks, followed by 12-weeks interval	(Hellmann et al., 2018)	OS/PFS	Every 6 weeks for 24 weeks, followed by 12-weeks interval
Ipilimumab+Nivolumab	Melanoma	(Hodi et al., 2016)	ORR	Every 6 weeks for 1 year, followed by 12-weeks interval	(Larkin et al., 2015)	OS/PFS	Every 6 weeks for 49 weeks, followed by 12-weeks interval

Supplementary Table 3. Cochrane standards for assessing risk of bias in included studies

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personell (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
(Fehrenbacher et al., 2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Rittmeyer et al., 2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Peters et al., 2017)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
(Herbst et al., 2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Rosenberg et al., 2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Powles et al., 2018)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Gulley et al., 2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Barlesi et al., 2018)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
(Gulley et al., 2017)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Barlesi et al., 2018)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Gulley et al., 2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Barlesi et al., 2018)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Disis et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Pujade-Lauraine et al., 2021)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Huang et al., 2018)	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk
(Huang et al., 2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Rizvi et al., 2015)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Brahmer et al., 2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Gettinger et al., 2016)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
(Carbone et al., 2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Topalian et al., 2012)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk

(Larkin et al., 2018)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Omuro et al., 2018)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Reardon et al., 2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Hamanishi et al., 2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Hamanishi et al., 2021)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Kudo et al., 2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Kato et al., 2019)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
(Motzer, Rini, et al., 2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Motzer, Escudier, et al., 2015)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
(Janjigian et al., 2018)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Kang et al., 2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Okada et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Fennell et al., 2021)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Chen et al., 2017)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
(Kuruvilla et al., 2021)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Nanda et al., 2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Winer et al., 2021)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
(Seiwert et al., 2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Cohen et al., 2019)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
(Bang et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Shitara et al., 2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Taylor et al., 2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Y.Loriot et al., 2022)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Rischin et al., 2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Tewari et al., 2022)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Choueiri et al., 2018)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk

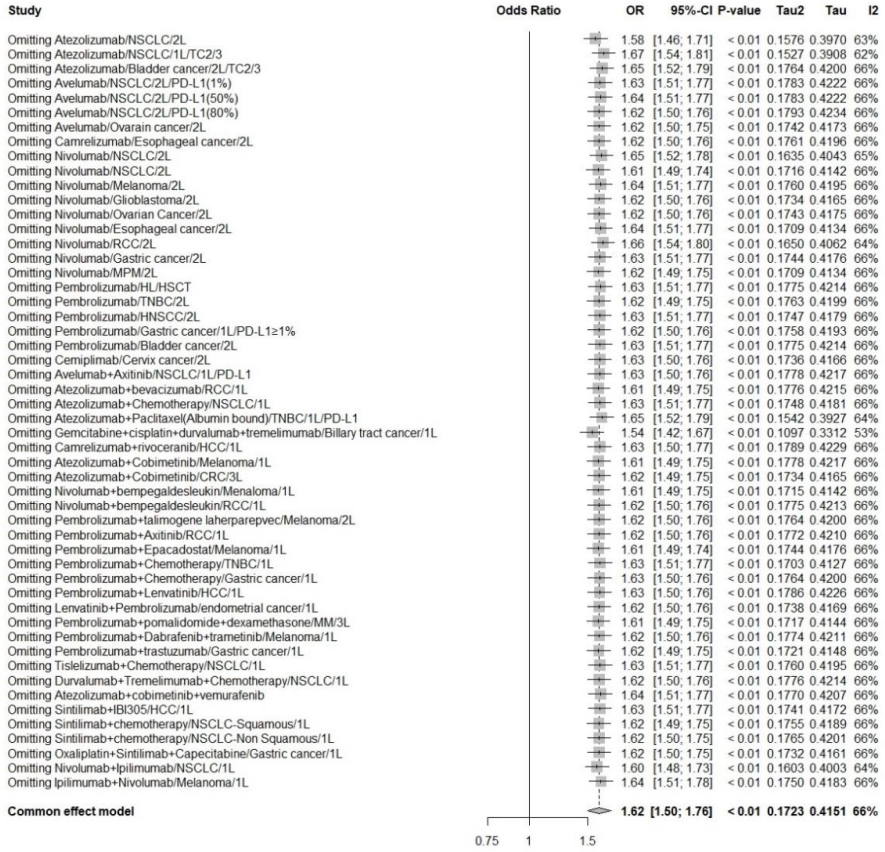
(Motzer et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(McDermott et al., 2018)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Rini, Powles, et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Liu et al., 2017)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Nishio et al., 2021)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Adams et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Schmid et al., 2018)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
(Oh et al., 2022)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
(Oh D-Y, 2022)	unknown	unknown	unknown	unknown	unknown	unknown
(Xu, Shen, et al., 2021)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Qin et al., 2022)	unknown	unknown	unknown	unknown	unknown	unknown
(Hellmann et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Gogas et al., 2021)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
(Hellmann et al., 2019)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Eng et al., 2019)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
(Diab et al., 2021)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Diab, 2022)	unknown	unknown	unknown	unknown	unknown	unknown
(Tannir et al., 2022)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Nizar Tannir, 2022)	unknown	unknown	unknown	unknown	unknown	unknown
(G. V. Long et al., 2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Chesney et al., 2023)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Atkins et al., 2018)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Rini, Plimack, et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Mitchell et al., 2018)	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
(Long et al., 2019)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
(Chun et al., 2022)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk

(Cortes et al., 2020)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
(Bang et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Shitara et al., 2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Finn et al., 2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Finn, 2022)	unknown	unknown	unknown	unknown	unknown	unknown
(Makker et al., 2020)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
(Makker et al., 2022)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Badros et al., 2017)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
(Mateos et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Ascierto et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Dummer et al., 2022)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Janjigian et al., 2020)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
(Janjigian & Kawazoe, 2021)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
(Antonia et al., 2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Planchard et al., 2020)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Sullivan et al., 2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Gutzmer et al., 2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
(Ren et al., 2021)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Ren et al., 2021)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
(Jiang et al., 2021)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Zhou et al., 2021)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
(Jiang et al., 2021)	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Yang et al., 2020)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Jiang et al., 2020)	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
(Xu, Jiang, et al., 2021)	unknown	unknown	unknown	unknown	unknown	unknown
(Hellmann et al., 2017)	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk

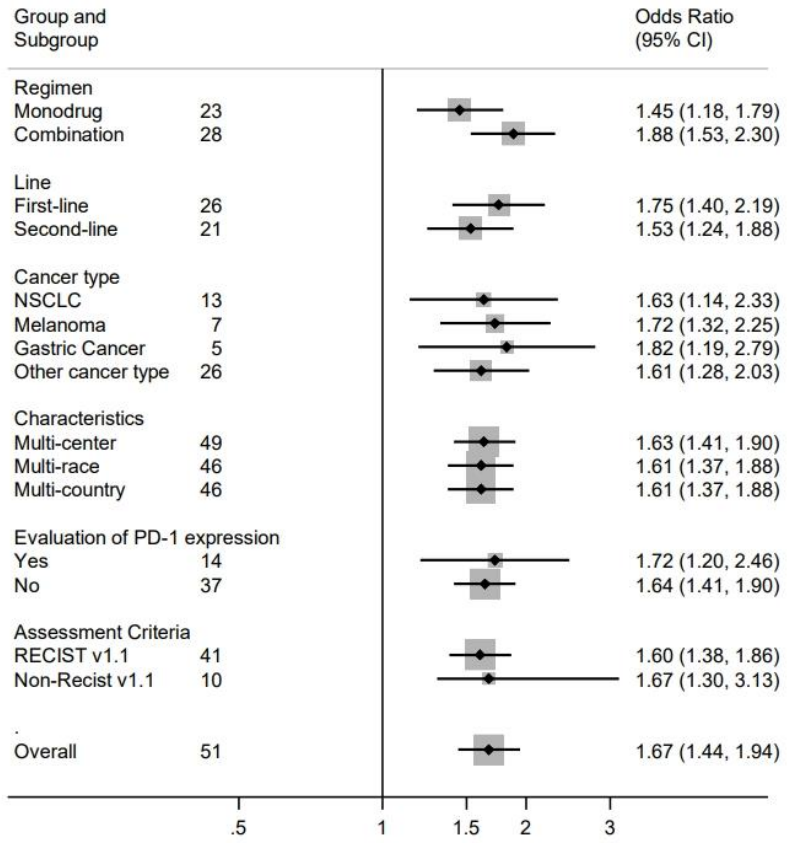
(Hellmann et al., 2018)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
(Hodi et al., 2016)	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk
(Larkin et al., 2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Supplementary Table 4. Multinomial logistics models for determinants of overestimation.

Models	Estimate	Standard Error	P value
Multinomial Logistic Model 1			
Autoimmune disease	2.205818	0.935784	**0.0184139***
Other malignancy history	-0.29868	0.799317	0.7086488
PD-1 expression of tumor cells or immune cells	-1.24573	0.787039	0.1134648
Size	0.001129	0.002598	0.6637954
Multinomial Logistic Model 2			
Autoimmune disease	2.206813	0.936306	**0.01842643***
PD-1 expression of tumor cells or immune cells	-1.18696	0.782397	0.12924528
Prior immunotherapy treatment	0.247124	1.018564	0.80829974
Size	0.001393	0.002509	0.57878478
Multinomial Logistic Model 3			
Autoimmune disease	2.099053	0.927734	**0.02366291***
PD-1 expression of tumor cells or immune cells	-1.17903	0.783309	0.13227475
Immunosupressive therapy	0.438969	0.705617	0.53387211
Size	0.00177	0.002581	0.49279497



Supplementary Figure 1. Stepwise exclusion approach to evaluate sensitivity.



Supplementary Figure 2. subgroup analysis. combined results of these subgroups were statistically significant and consistent with the original conclusion of the meta-analysis.

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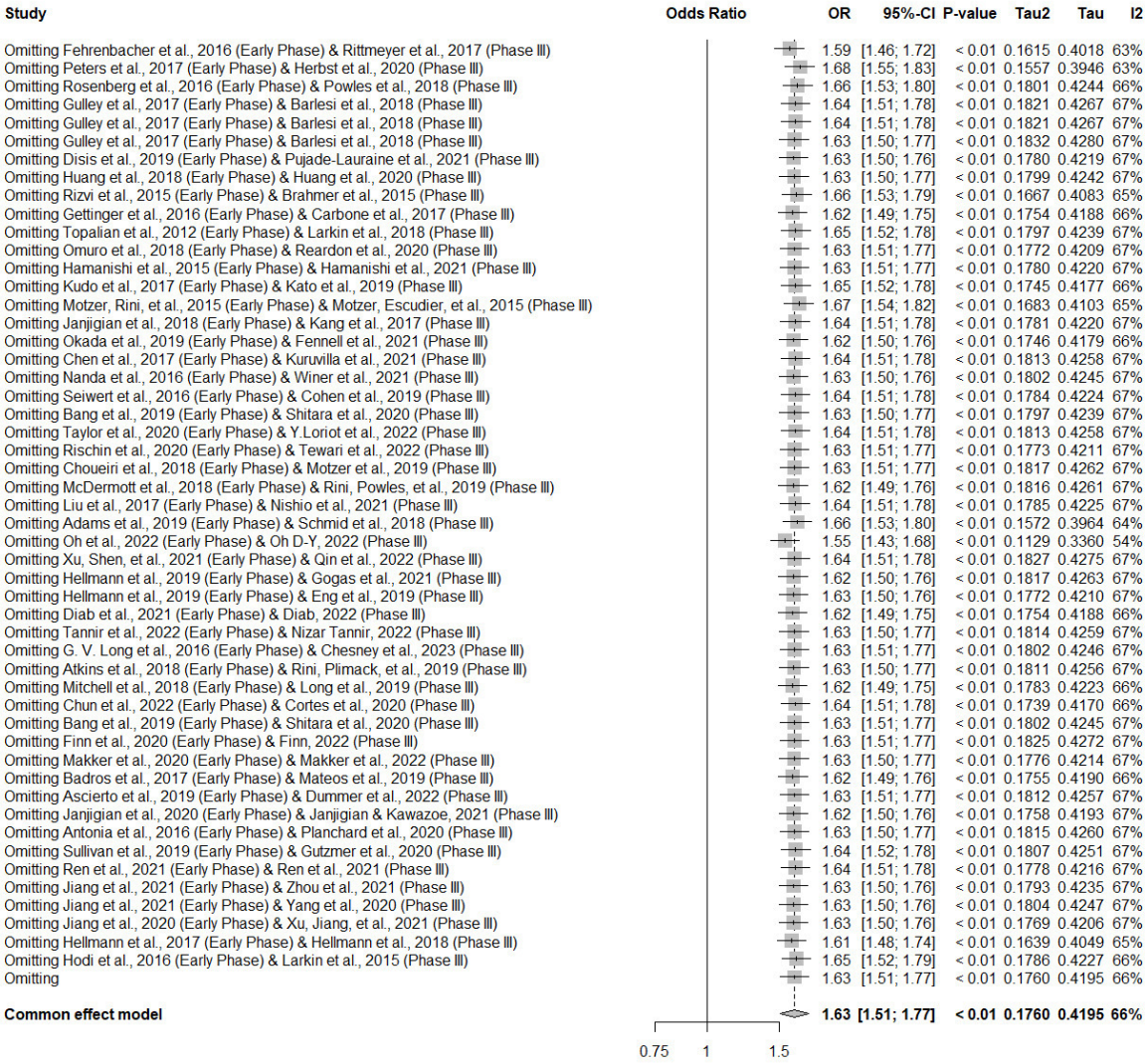
Study
Odds Ratio
OR 95%-CI P-value Tau2 Tau I2
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Omitting Peters et al., 2017 (Early Phase) & Herbst et al., 2020 (Phase III) 1.68 [1.55; 1.83] < 0.01 0.1557 0.3946 63%
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Omitting 1.63 [1.51; 1.77] < 0.01 0.1760 0.4195 66%
Common effect model 1.63 [1.51; 1.77] < 0.01 0.1760 0.4195 66%
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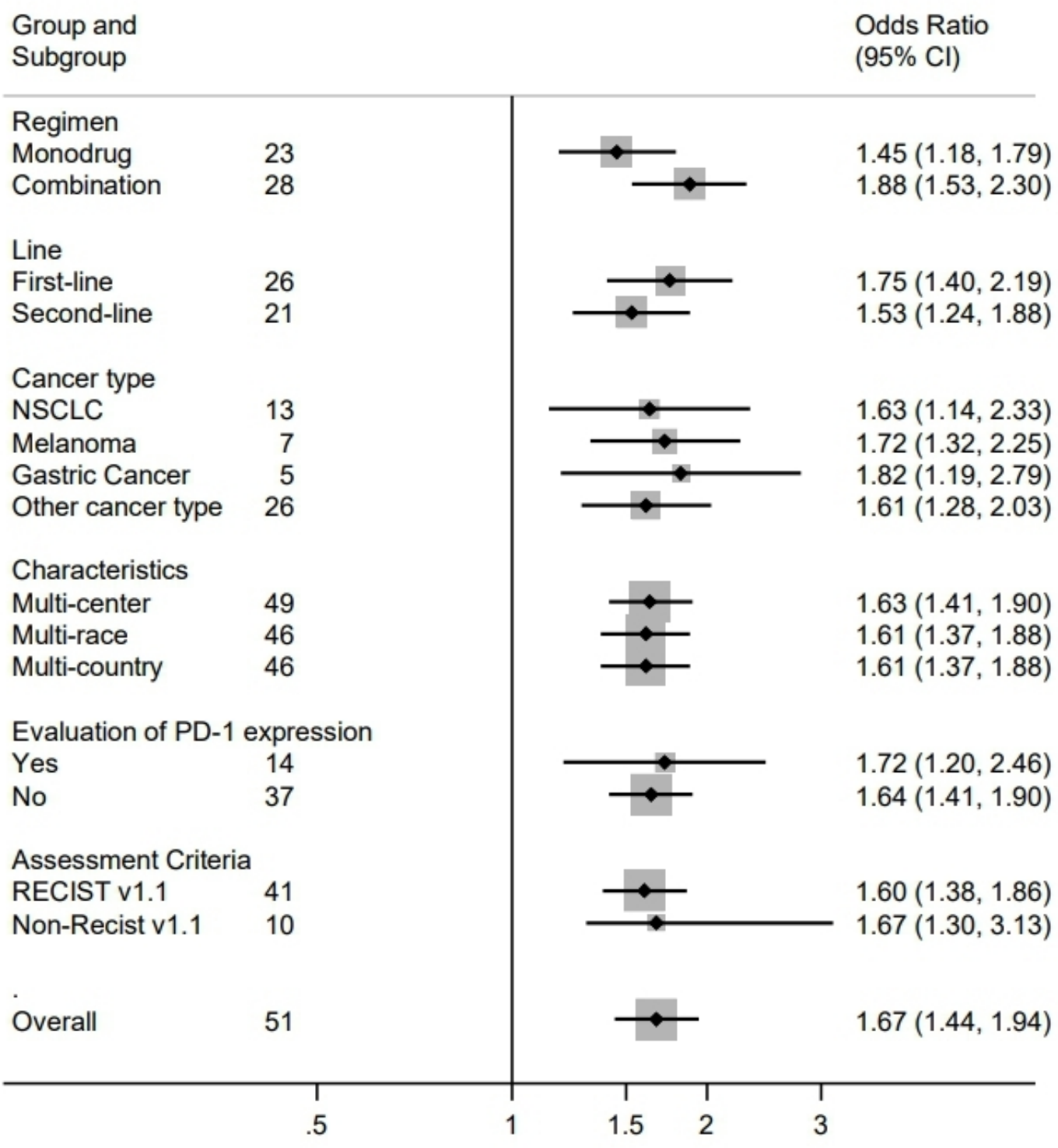
1.5


Group and Subgroup
Odds Ratio (95% CI)
Regimen
Monodrug 23 1.45 (1.18, 1.79)
Combination 28 1.88 (1.53, 2.30)
Line
First-line 26 1.75 (1.40, 2.19)
Second-line 21 1.53 (1.24, 1.88)
Cancer type
NSCLC 13 1.63 (1.14, 2.33)
Melanoma 7 1.72 (1.32, 2.25)
Gastric Cancer 5 1.82 (1.19, 2.79)
Other cancer type 26 1.61 (1.28, 2.03)
Characteristics
Multi-center 49 1.63 (1.41, 1.90)
Multi-race 46 1.61 (1.37, 1.88)
Multi-country 46 1.61 (1.37, 1.88)
Evaluation of PD-1 expression
Yes 14 1.72 (1.20, 2.46)
No 37 1.64 (1.41, 1.90)
Assessment Criteria
RECIST v1.1 41 1.60 (1.38, 1.86)
Non-Recist v1.1 10 1.67 (1.30, 3.13)
Overall 51 1.67 (1.44, 1.94)
.5
1
1.5
2
3