Anti-tumor efficacy and safety of immune checkpoint inhibitors in combination with other anticancer therapy in solid tumors

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Abstract

Cancer is a leading cause of death worldwide, with 10 million deaths reported in 2020. Despite the ongoing development and implementation of diverse therapeutic approaches, a definitive cure remains elusive. Recent efforts have been focused on developing anticancer agents that specifically target tumorigenic molecular pathways. Specifically, immune checkpoint inhibitors (CPIs), such as programmed death 1 (PD-1) inhibitors, programmed death ligand 1 (PD-L1) inhibitors, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors have demonstrated efficacy against various tumor types and have been approved by the US Food and Drug Administration (FDA) and other global regulatory agencies.

Despite the acknowledged clinical efficacy of these CPIs, monotherapy exhibits a response rate of approximately 20% against solid tumors. Therefore, further improvements in treatment outcomes are required. In light of this background, there is a strong impetus to explore combination therapies involving CPIs and other anticancer drugs with a distinct mode of action, such as cytotoxic anticancer agents and molecular-targeted agents. These combination therapies anticipated to synergistically enhance the antitumor efficacy of CPIs by inducing immunogenic cell-death (ICD) with the release of tumor antigens by cytotoxic anticancer drugs, or modulating the tumor microenvironment by molecular-targeted drugs. Encouragingly, clinical efficacy of PD-1/PD-L1 inhibitors in combination with other anticancer drugs has been reported in certain solid tumors, which may bring about a breakthrough in future cancer treatments. Nonetheless, definitive conclusions regarding the contribution of combining PD-1/PD-L1 inhibitors with other anticancer drugs to improve antitumor efficacy from a clinical perspective have yet to be reached.

In contrast, CPIs, including PD-1/PD-L1 inhibitors, are associated with a relatively low incidence of serious organ-specific adverse events (AEs), distinct from conventional chemotherapies and multi-kinase inhibitors. These AEs manifest as autoimmune or inflammatory disease-like reactions and called immune-related adverse events (irAEs). Hence, when developing or introducing combination therapies involving CPIs and other anticancer drugs with distinct modes of action, up-to-date knowledge concerning safety risks and appropriate management strategies is required based on the profile of the combination drugs. However, a comprehensive comparison of the incidence of clinically significant AEs between CPI monotherapy and CPI-based combination therapies has not yet been sufficiently conducted.

In the first research (Research 1), we conducted a systematic review and meta-analysis to evaluate the contribution of combinations of PD-1/PD-L1 inhibitors and anticancer

drugs to the improved clinical antitumor efficacy. The tumor response rate, known as objective response rate (ORR), was used as an indicator, as it is considered the most appropriate parameter for assessing the antitumor efficacy of a treatment in clinical settings. Additionally, we performed a subgroup analysis to identify favorable modes of action for concomitant anticancer drugs when combined with PD-1/PD-L1 inhibitors. Our search encompassed electronic databases search, such as ClinicalTrials.gov, Medline (PubMed), and ASCO/ESMO annual meeting libraries. We included randomized or non-randomized trials designed to evaluate the efficacy and safety of combination therapies involving PD-1/PD-L1 inhibitors and other anticancer drugs. Meta-analysis used random effects models to pool the results.

Sixteen studies involving 3793 patients were included in the primary analysis. These studies have a monotherapy group with PD-1/PD-L1 inhibitors as the control group or the in-study arm/cohort (1863 patients in the combination group with PD-1/PD-L1 inhibitors and 1930 patients in PD-1/PD-L1 inhibitor monotherapy). The pooled results showed that the combination of PD-1/PD-L1 inhibitors and other anticancer drugs significantly improved the ORR (risk ratio [RR]: 1.79, 95% confidence interval [CI]: 1.46, 2.20). In the subgroup analysis, PD-1/PD-L1 inhibitor plus DNA-synthesis or microtubule inhibitor led to a statistically significant improvement in the ORR compared to PD-1/PD-L1 inhibitor monotherapy.

In the second research (Research 2), we conducted a systematic review and meta-analysis to evaluate the RR of organ-specific irAEs and common AEs related to PD-1/PD-L1 inhibitors in patients treated with combination of PD-1/PD-L1 inhibitors and chemotherapy or molecular-targeted anticancer therapy, in comparison to those treated with PD-1/PD-L1 monotherapy for solid tumors. Additionally, subgroup analyses were conducted based on the mode of action of concomitant anticancer drugs to identify differences in the RR of the AEs of interest. The electronic databases identical to those used for the Research 1 were employed. We included randomized controlled trials (RCTs) designed to assess the safety and efficacy of combination therapies involving PD-1/PD-L1 inhibitors and other anticancer drugs. Meta-analysis was performed using random effects models to pool the results.

The primary analysis included sixteen relevant clinical studies comprising 4232 patients (2071 patients in the PD-1/PD-L1 inhibitor-based combination therapy and 2161 patients in PD-1/PD-L1 inhibitor monotherapy). Serious organ-specific irAEs were infrequent (ranging from 0 to 2.2%) even when PD-1/PD-L1 inhibitors were combined with other anticancer drugs. The incidence of serious colitis (RR: 2.47, 95% CI: 1.14, 5.37) was significantly higher in the combination therapy group than in the

monotherapy group. Among the common AEs associated with PD-1/PD-L1 inhibitors, the incidence of serious fever, non-serious fever, fatigue, nausea, decreased appetite, vomiting, diarrhea, dyspnea, and rash significantly increased in the combination therapy group. In the subgroup analysis based on the modes of action of concomitant anticancer drugs, the combination of PD-1/PD-L1 inhibitors and DNA synthesis inhibitors significantly increased the risk of serious colitis compared to PD-1/PD-L1 inhibitor monotherapy.

Overall, the combination of PD-1/PD-L1 inhibitors and other anticancer drugs is expected to confer significant benefits in terms of improved efficacy compared to PD-1/PD-L1 inhibitor monotherapy. However, careful attention should be paid to the increased risk of certain AEs. Therefore, vigilant monitoring of AEs and implementation of appropriate clinical management strategies, guided by the mode of action of the combination drugs are essential.

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Abbreviations

AEs	Adverse events
ALK	Anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
BCG	Bacillus Calmette-Guérin
BRAF	B-Raf proto-oncogene
BTK	Bruton's tyrosine kinase
CI	Confidence interval
CPIs	Immune checkpoint inhibitors
CPS	Combined Positive Score
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DNA	Deoxyribonucleic acid
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
EGFR	Epidermal growth factor receptor
ESMO	European Society for Medical Oncology
FDA	US Food and Drug Administration
GEJ	Gastroesophageal junction
ICD	Immunogenic cell death
IDO	Indoleamine 2,3-dioxygenase
irAE	Immune-related adverse events
MAPK	Mitogen-activated protein kinase
MDSCs	Myeloid-derived suppressor cells
MEK	Mitogen-activated extracellular signal-regulated kinase
MMAE	Monomethyl auristatin E
MMP-9	Matrix metalloproteinase 9
NA	Not applicable
NK	Natural killer
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews Registry
RCTs	Randomized controlled trials

RoB 2.0	Cochrane Collaboration risk-of-bias tool 2.0
RR	Risk ratio
SmPC	Summary of Product Characteristics
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
TKI	Thymidine kinase inhibitor
Treg	T cells and regulatory T cells
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

1. Introduction

Cancer is the leading cause of death worldwide, with 10 million deaths from cancer in 2020 [1]. Although various therapies are being developed and put into clinical practice, they are still far from being cured. Recent efforts have been made to develop anticancer agents that specifically target tumorigenic molecular pathways. Notably, significant progress has been made in the field of anticancer drugs, wherein molecular target drugs and immunotherapies, alongside conventional cytotoxic chemotherapies, have exhibited remarkable advancements. Specifically, immune checkpoint inhibitors (CPIs) such as anti-programmed death 1(PD-1) antibodies (pembrolizumab and nivolumab), anti-programmed death-ligand 1(PD-L1) antibodies (atezolizumab, avelumab and durvalumab) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody (ipilimumab) have demonstrated efficacy across various tumor types, and have been approved by the US Food and Drug Administration (FDA) and other regulatory agencies globally [2, 3].

PD-1 is predominantly expressed on activated or exhausted T cells, B cells, and NK cells. PD-L1, a PD-1 ligand, is constitutively expressed in many tissues, but is known to be enhanced in tumor cells and immune cells that infiltrate cancer tissues. The interaction between PD-1 and PD-L1 transduces immunosuppressive signals and reduces the activity of tumor-reactive T cells, and anti PD-1/PD-L1 antibodies have been shown to exert anti-tumor effects through this inhibitory mechanism [4]. CTLA-4 is expressed on tumor-reactive T cells and regulatory T cells (Treg), which transmit inhibitory signals to tumor-reactive T cells through interaction with dendritic cell-surface B7 (CD80/86) to support the maintenance of its inhibitory function on Treg. Anti CTLA-4 antibodies have been shown to exert anti-tumor effects by inhibiting cancer immune responses [5, 6].

Despite the acknowledged clinical efficacy of these CPIs, monotherapy exhibits a limited response rate of approximately 20% against solid tumors, including breast, colon, lung, urothelial, and prostate cancers [7]. Therefore, further improvements in treatment outcomes are required. The factors that affect the responsiveness to monotherapy with CPIs have not been elucidated. However, unlike in so-called “inflamed tumors” where T cells infiltrate the tumor tissue, the antitumor efficacy of CPIs is thought to be limited when T cells remain in the tumor stroma (immune excluded tumor) or when T cells are absent from the tumor site (immune desert) [8]. Given this background, combination therapy with CPIs and existing anticancer agents with different mechanisms of action (e.g., cytotoxic anticancer agents and molecular targeted agents) is being actively attempted. Combination therapy is not only expected

to have a mere additive effect on standard therapies with established efficacy and safety, but it is also expected to synergistically enhance the anti-tumor efficacy of CPIs. For instance, the potential synergistic effects can be derived from inhibiting the production of immunosuppressive cells (e.g., Treg cells and myeloid-derived suppressor cells [MDSCs]) and their associated humoral factors, such as immunosuppressive cytokines and other endogenous immunosuppressive molecules. The synergistic effects can also be attributed to the induction of ICD with the release of tumor antigens followed by T-cell infiltration into tumor sites and T-cell activation by enhancing the function of antigen-presenting cells.

Nonclinical studies have reported that cyclophosphamide (an alkylating agent), doxorubicin (an anthracycline), and oxaliplatin (a platinum-based agent) induce ICDs and/or T-cell infiltration into tumors, potentially leading to sensitization of tumors to CPIs [9, 10]. In addition, cyclophosphamide, taxanes (e.g., paclitaxel and docetaxel), and gemcitabine (a cytidine analog) have been reported to suppress Treg. Doxorubicin, docetaxel, gemcitabine, and 5-fluorouracil (a fluoropyrimidine-based agent) have been reported to suppress MDSCs [11]. Among the anticancer drugs that have been shown to induce ICD in nonclinical studies, DNA synthesis inhibitors such as alkylating agents, platinum agents, DNA antimetabolites, and taxanes are expected to enhance the efficacy of CPIs in clinical settings [12]. In contrast, it has also been reported that the same agents can have a negative impact on the anti-tumor immune response [13, 14]; therefore, no clear conclusion has been drawn on the clinical significance of combination therapy on anti-tumor efficacy. Similarly, recent years have witnessed the efficacy of combination therapy involving PD-1/PD-L1 inhibitors and molecular targeted drugs such as anti-VEGF antibody and multi-kinase inhibitors in solid tumors, resulting in FDA and other regional regulatory authority approvals. However, it is still controversial if the tumor response of PD-1/PD-L1 inhibitors in combination with molecular-targeted drugs such as anti-VEGF antibody and multi-kinase inhibitors can be enhanced compared to those of PD-1/PD-L1 inhibitor monotherapies.

On the other hand, CPIs, including PD-1/PD-L1 inhibitors, are associated with relatively low incidence yet serious or fatal organ-specific adverse events (AEs), distinct from conventional cytotoxic chemotherapies and multi-kinase inhibitors. These AEs manifest as autoimmune or inflammatory disease-like reactions termed immune-mediated adverse reactions or immune-related adverse events (irAEs) [15]. The typical organ-specific irAEs associated with PD-1 inhibitors (pembrolizumab, nivolumab) and PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab) are specified in the European Medicines Agency (EMA)-approved Summary of Product Characteristics

(SmPCs) and the FDA-approved U.S. package inserts. These irAEs include immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies (adrenal insufficiency, hypophysitis, thyroiditis, hyperthyroidism, and hypothyroidism, type 1 diabetes mellitus), immune-related nephritis with renal dysfunction and immune-related skin adverse reactions (immune-mediated rash or dermatitis, exfoliative dermatitis including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms). Furthermore, other clinically significant organ-specific irAEs, with an incidence of less than 1%, are documented with warnings and precautions. These include cardiovascular disorders (myocarditis, pericarditis, and vasculitis), nervous system disorders (meningitis, encephalitis, myelitis, demyelination, and myasthenic syndrome/myasthenia gravis, Guillain-Barre syndrome, nerve paresis, and autoimmune neuropathy), ocular disorders (uveitis, iritis and other ocular inflammatory toxicities), gastrointestinal disorders (pancreatitis, gastritis, and duodenitis), musculoskeletal and connective tissue disorders (myositis/polymyositis, rhabdomyolysis, arthritis, and polymyalgia rheumatica), and endocrinopathies (hypoparathyroidism).

When developing or introducing combination therapy involving CPIs and other anticancer drugs with distinct mode of action, up-to-date knowledge concerning safety risks and appropriate management are required based on the profile of the combination drugs. However, a comprehensive evaluation comparing the incidence of clinically significant AEs between CPI monotherapy and CPI-based combination therapies with other anticancer drugs has not been sufficiently conducted.

The objective of this study was to analyze and assess the enhanced clinical efficacy and increased safety risks associated with PD-1/PD-L1 inhibitor-based combination therapy in comparison to PD-1/PD-L1 monotherapy based on clinical trials in solid tumors.

2. Anti-tumor efficacy of PD-1/PD-L1 inhibitors in combination with other anticancer drugs in solid tumors: a systematic review and meta-analysis (Research 1)

2.1. Objective

This Research 1 was aimed to evaluate the contribution of combinations of PD-1/PD-L1 inhibitors and anticancer drugs to the improved clinical antitumor efficacy. The tumor response rate, known as the objective response rate (ORR), served as the primary indicator, as it is considered the most appropriate parameter for assessing the antitumor efficacy of a treatment in clinical settings. Additionally, we performed a subgroup analysis to identify favorable modes of action for concomitant anticancer drugs when combined with PD-1/PD-L1 inhibitors.

2.2. Materials and method

2.2.1. Search strategy

This meta-analysis was based on randomized controlled trials (RCTs) designed to compare FDA-approved combination therapies of anti PD-1/PD-L1 inhibitors as of December 2020 (i.e., nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) in addition to anticancer drug therapies with a comparator arm of either PD-1/PD-L1 inhibitor or other anticancer drug monotherapy. Non-randomized trials were included if multiple treatment arms or cohorts of combination of either of the PD-1/PD-L1 inhibitors plus other anticancer drug-containing therapies and either of the PD-1/PD-L1 inhibitors or other anticancer drug monotherapy were within the same study. To evaluate the benefit of contribution of PD-1/PD-L1 inhibitors and non-immunomodulatory intent anticancer drugs for the clinical tumor response in solid organ cancers, the following criteria were applied to select clinical studies to be evaluated in this study: (i) RCT or multi-arm/cohort studies that compared the efficacy of combination therapy of PD-1/PD-L1 inhibitor (nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) plus anticancer drug with a control group; (ii) studies with PD-1/PD-L1 inhibitor monotherapy or non PD-1/PD-L1 inhibitor treatment group as a control group; and (iii) studies in which efficacy data of ORR were published or disclosed. Clinical trials that met the following criteria were excluded: (i) trials in patients with hematological cancers; (ii) trials in which immunotherapy (vaccines, CPIs other than the above PD-1/PD-L1 inhibitors, cytokines, and treatments with immunostimulatory effects such as Bacillus Calmette-Guérin (BCG)s and indoleamine 2,3-dioxygenase (IDO) inhibitors) were included as study intervention; (iii) trials in

which anticancer procedures (radiotherapy, tumorectomy, etc.) were included as study intervention, and (iv) trials evaluating adjuvant or neo-adjuvant therapy.
The clinical trials evaluated in this study were searched and extracted using the multiple strategies. As a primary data source, we utilized ClinicalTrials.gov (https://ClinicalTrials.gov) using each of the drug names (nivolumab including [nivolumab or BMS-936558 or MDX-1106 or MDX-1106-04 or nivolumab BMS or ONO-4538 or Opdivo], pembrolizumab including [pembrolizumab or Keytruda or ambrolizumab or lambrolizumab or mDX-400 or MK-3475 or SCH-900475], atezolizumab including [atezolizumab or MPDL-3280A or PRO-304397 or RG-7446 or RO-5541267 or Tecentriq], avelumab including [avelumab or MSB-0010682 or MSB-0010718C or PF-06834635 or Bavencio], and durvalumab including [durvalumab or MEDI-4736 or Imfinzi]) as the key words. Among the registered trials with their study results, we identified trials with a combination therapy containing PD-1/PD-L1 inhibitors as the treatment group, except for those in hematologic cancers. We also used PubMed (https://pubmed.ncbi.nlm.nih.gov/) as a secondary data source and searched for clinical trials on solid tumors in which article type was registered as "Clinical Trial" using (pembrolizumab or nivolumab or atezolizumab or avelumab or durvalumab) and (clinical or trial) and (combination or plus or with) as the search terms. Furthermore, as a third data source, the ASCO Meeting Library (https://meetinglibrary.asco.org/) and the European Society for Medical Oncology (ESMO (https://oncologypro.esmo.org/meeting-resources) were referenced using the search terms, including (nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) and (clinical or trial) and (combination or plus or with) to find clinical trials with solid tumor subjects in the abstract of the Annual Meetings.
Clinical trials extracted on the data cut-off date (December 31, 2020) according to the above procedures were eligible for assessment. The language was restricted to English.

2.2.2. Data extraction and quality of evidence

We screened the names and designs of the clinical trials for the records derived from ClinicalTrials.gov or the titles and abstracts derived from the other data sources, followed by assessment of eligibility based on the full texts. Disagreements about eligibility were resolved through discussion. The primary indicator was tumor response rate (i.e., objective response rate; ORR). The tumor response rate was defined as the proportion of subjects whose objective response is confirmed complete response or partial response. For response rate, we collected the exact number of events and the total number of subjects included in the analysis. We also identified all the trials by

ClinicalTrials.gov identification number (i.e., NCT number), identification number in other local study registration, or first author and the year of publication, and extracted the following information from the reports: NCT number or other local study identification number, first author, publication year, intervention of experimental treatment and control groups, number of subjects enrolled in each group, study phase, subject allocation (i.e., randomized or non-randomized), and tumor type/disease condition. A single reviewer performed the initial data extraction using a standardized data collection form and second reviewer carefully checked them. Discrepancies were resolved through a discussion between them.

The quality and risk of bias of RCTs were assessed with the revised Cochrane Collaboration risk-of-bias tool (RoB 2.0) [16]. Nonrandomized cohort studies were assessed using the Newcastle-Ottawa Scale [17], ranging between zero up to nine stars. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for the purpose of this analysis [18]. The review protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols-INPLASY (registration number: INPLASY2022100004).

2.2.3. Statistical analysis

The meta-analysis was performed using the RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). All analyses were performed using a random effects model because study cohorts were expected to be different (e.g., multiple tumor types) and treatment regimens were not identical among studies. Analyses were conducted for the following groups: PD-1/PD-L1 inhibitor plus other anticancer drugs vs. control therapies, and PD-1/PD-L1 inhibitor plus other anticancer drugs vs. PD-1/PD-L1 inhibitor monotherapies. Subsequently, subgroup analyses by mode of action of the concomitant anticancer drugs, PD-1 or PD-L1 inhibitors, and tumor types were performed. For all analyses, pooled risk ratios for ORR with 95% CI in the intention-to-treat (ITT) population were calculated, and $P<0.05$, using a two-sided test, was considered statistically significant. Heterogeneity among studies was assessed using the Q test and I^2 index, and statistically significant heterogeneity was considered at $P<0.05$ or $I^2>50\%$. Lastly, publication bias was evaluated by drawing a funnel plot of the effect size for each trial against the reciprocal of SE.

2.3. Results

2.3.1. Study selection and characteristics

The evaluated trials were identified as described in Figure 1. For the 22 studies that have been reported in duplicate, we only included the report with the most recent or most complete profile of ORR data as the data source. The main characteristics of the 36 studies included in the analysis are summarized in Table 1 and Supplementary Table 1. Among the 36 studies, five studies with nivolumab (10 combination therapy groups), 15 studies with pembrolizumab (15 combination therapy groups), 11 studies with atezolizumab (11 combination therapy groups), two studies with avelumab (two combination therapy groups), and four studies with durvalumab (four combination therapy groups) were extracted. Thirty trials were randomized. Fifteen trials (44%) were in patients with lung cancer (including 13 non-small cell lung cancer [NSCLC]), followed by three trials each for ovarian cancer, colorectal cancer, and gastric or gastroesophageal junction cancer.

The anticancer drugs frequently used in combination with PD-1/PD-L1 inhibitors included cisplatin or carboplatin (13 studies), bevacizumab (6 studies), paclitaxel or nab-paclitaxel (6 studies), acalabrutinib (5 studies), 5-FU (4 studies), pemetrexed (4 studies) and capecitabine (4 studies). We categorized the anticancer drugs into four main types and other targeted therapies based on the mode of action: DNA synthesis inhibitors, microtubule inhibitors, kinase inhibitors, and angiogenesis inhibitors. DNA synthesis inhibitors included platinum-based chemotherapies (cisplatin and carboplatin), antimetabolites (5-FU, capecitabine, etoposide, pemetrexed, gemcitabine, and CC-486 (oral azacytidine), pegylated liposomal doxorubicin, and decitabine plus tetrahydrouridine. Microtubule polymerization inhibitors included taxanes (paclitaxel and nab-paclitaxel). Kinase inhibitors included epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (erlotinib and osimertinib), Bruton's tyrosine kinase (BTK) inhibitor (acalabrutinib), and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor (cobimetinib). Angiogenesis inhibitors included bevacizumab. Hedgehog inhibitor (vismodegib), matrix metalloproteinase 9 (MMP-9) inhibitor (andecaliximab), an antibody–drug conjugate (ADC) of anti-transmembrane glycoprotein NMB, the cytotoxic agent monomethyl auristatin E (MMAE) (glembatumumab vedotin), and an ADC of anti-HER2 trastuzumab and the cytotoxic agent emtansine (DM1) (trastuzumab emtansine) were categorized as other targeted therapies. There were 16 studies in which the PD-1/PD-L1 inhibitor monotherapy group was set as the control group or the in-study arm or cohort.

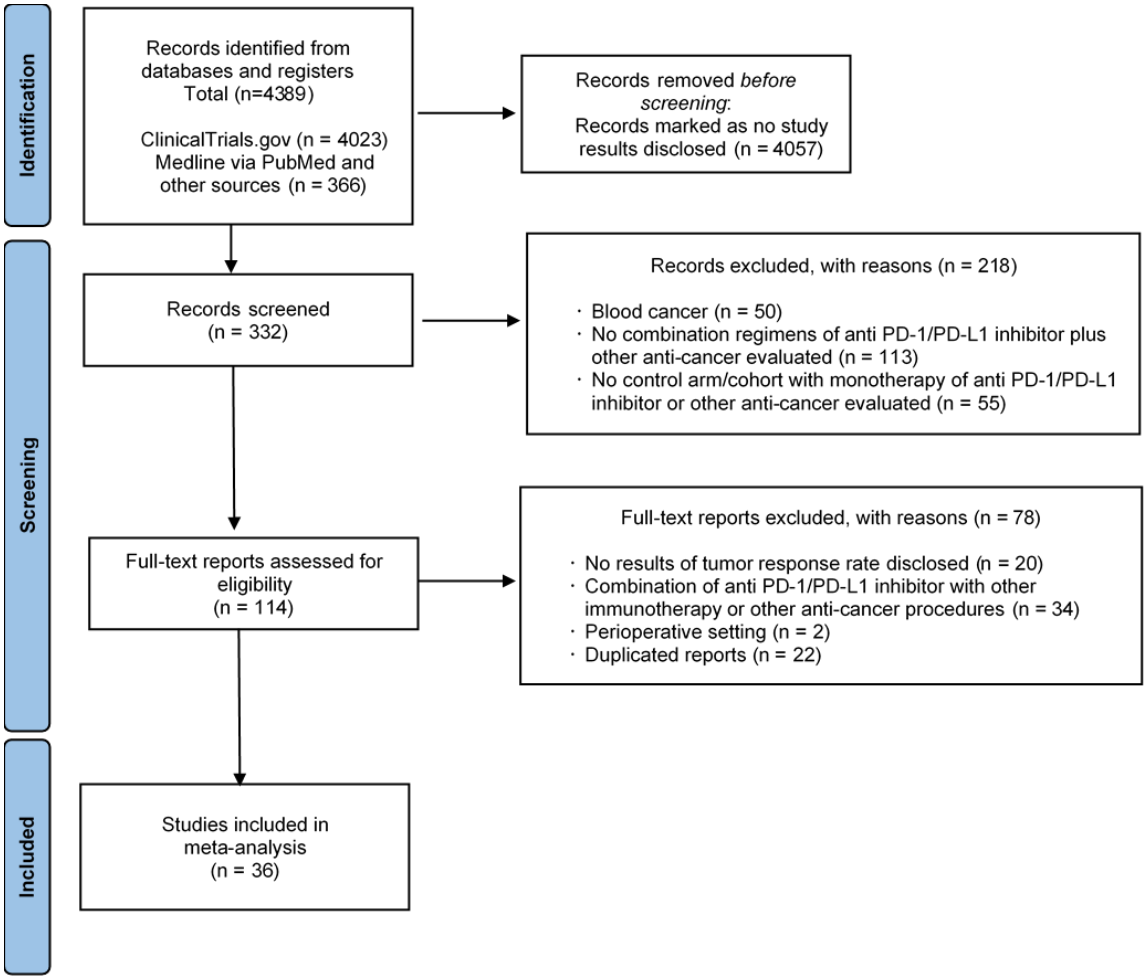

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of selecting clinical trials for Research 1

Table 1 Characteristics of the included studies in Research 1

Parameter	Category	All studies (N=36)		Studies with CPI mono arm/cohort (N=16)		Reference
		No. studies	No. combo groups	No. studies	No. combo groups	
Name of CPI	Nivolumab	5	10	4	9	[19-21]
	Pembrolizumab	15	15	7	7	[23-31]
	Atezolizumab	11	11	3	3	[32-40]
	Avelumab	2	2	1	1	
	Durvalmab	4	4	1	1	[41, 42]
Mode of action of CPI	PD-1 inhibitor	19	24	11	16	[19-31]
	PD-L1 inhibitor	17	17	5	5	[32-42]
Development phase	Phase 1 or 1/2	4	9	2	7	[19-22]
	Phase 2	17	17	9	9	[23, 24, 26, 28, 29, 32, 40]
	Phase 3	15	15	5	5	[25, 27, 30, 31, 33-39, 41, 42]
Study type	Randomized	30	35	13	18	[20-22, 24-42]
	Non-randomized	6	6	3	3	[19, 23]

Parameter	Category	All studies (N=36)		Studies with CPI mono arm/cohort (N=16)		Reference
		No. studies	No. combo groups	No. studies	No. combo groups	
Tumor type	Lung cancer	15	20	4	9	[20-22, 28-31, 33, 34, 37, 41, 42]
	Ovarian cancer	3	3	1	1	
	Gastric/GEJ cancer	3	3	3	3	[23, 27]
	Colorectal cancer	3	3	1	1	[38]
	Head & neck cancer	2	2	2	2	[25]
	Skin cancer	2	2	0	0	
	Breast cancer	2	2	0	0	[35, 36, 40]
	Urothelial cancer	2	2	2	2	[24, 39]
	Biliary tract cancer	1	1	1	1	[19]
	Renal cell carcinoma	1	1	1	1	[32]
	Pancreatic cancer	1	1	0	0	[26]
	Glioblastoma	1	1	1	1	
Combination drug	Cisplatin/Carboplatin	13	16	6	9	[19-23, 25, 27, 29-31, 33, 34, 39, 42]
	Bevacizumab	6	6	3	3	[20, 21, 32, 33]
	Paclitaxel/nab-paclitaxel	6	7	1	2	[20, 21, 30, 33-36]
	Acalabrutinib	5	5	3	3	[24, 26]

Parameter	Category	All studies (N=36)		Studies with CPI mono arm/cohort (N=16)		Reference
		No. studies	No. combo groups	No. studies	No. combo groups	
	5-FU	4	4	3	3	[23, 25, 27]
	Capecitabine	4	4	2	2	[23, 27]
	Pemetrexed	4	4	1	1	[20-22, 29]
	Gemcitabine	3	3	3	3	[19-21, 39]
	Etoposide	3	3	0	0	[31, 37, 42]
	Andecaliximab	1	1	1	1	
	CC-486	1	1	1	1	[28]
	Cobimetinib	1	1	1	1	[38]
	Decitabine	1	1	1	1	
	Tetrahydrouridine	1	1	1	1	
	Erlotinib	1	1	1	1	[20, 21]
	Pegylated liposomal doxorubicin	1	1	1	1	
	Glembatumumab vedotin	1	1	0	0	
	Osimertinib	1	1	0	0	[41]
	Vismodegib	1	1	0	0	
	Trastuzumab emstasine	1	1	0	0	[40]

CPI, immune checkpoint inhibitor; PD-1, programmed death 1; PD-L1, programmed death ligand 1; GEJ, gastroesophageal junction

2.3.2. Quality assessment

The RoB 2.0 results for randomized studies are shown in Supplementary Figure 1, where 27 out of 30 randomized studies had low risk and the remaining 3 studies were assessed as having some concerns (due to insufficient information of D1 randomization process and/or D4 measurement of the outcome) for performance. Of the 6 non-randomized cohort studies assessed using the Newcastle-Ottawa scale, 3 studies had a score 9 and 3 studies had a score 7, and therefore were deemed to be robust with regards to bias arising from patient selection, comparability of study groups, and outcome assessment (Supplementary Table 2). The funnel plot (Supplementary Figure 2) for the ORR revealed no obvious asymmetry, indicating no remarkable publication bias in the analysis. Meanwhile, the PRISMA checklist for our meta-analysis is given in Supplementary Table 3.

2.3.3. Benefit of PD-1/PD-L1 inhibitors and anticancer drugs for tumor response

Initially, 36 studies, involving 6774 patients in the combination therapy groups with PD-1/PD-L1 inhibitors plus other anticancer drugs and 6131 patients in the control group were included in the meta-analysis on anticancer effect in clinical settings by ORR. The pooled results showed that the ORR was significantly improved by the combination therapy of PD-1/PD-L1 inhibitors with other anticancer drugs (RR: 1.45; 95% CI: 1.30, 1.62; P<0.00001) (Figure 2), although caution is required to interpret the results due to very high heterogeneity (P<0.00001, I^2=74%).

We also analyzed the pooled effect of combination therapy on anti-tumor efficacy (ORR) in 16 trials having a monotherapy group with PD-1/PD-L1 inhibitors as the control group or the in-study arm/cohort (1863 patients in the combination group with PD-1/PD-L1 inhibitors plus other anticancer drugs and 1930 patients in the control group with PD-1/PD-L1 inhibitor monotherapy). The main characteristics of the 16 studies included in the analysis are summarized in Table 1 and Supplementary Table 1. The pooled results showed that combination therapy with PD-1/PD-L1 inhibitors plus other anticancer drugs significantly improved the ORR compared to monotherapy with PD-1/PD-L1 inhibitors (RR: 1.79; 95% CI: 1.46, 2.20; P<0.00001; I^2=44%) (Figure 3).

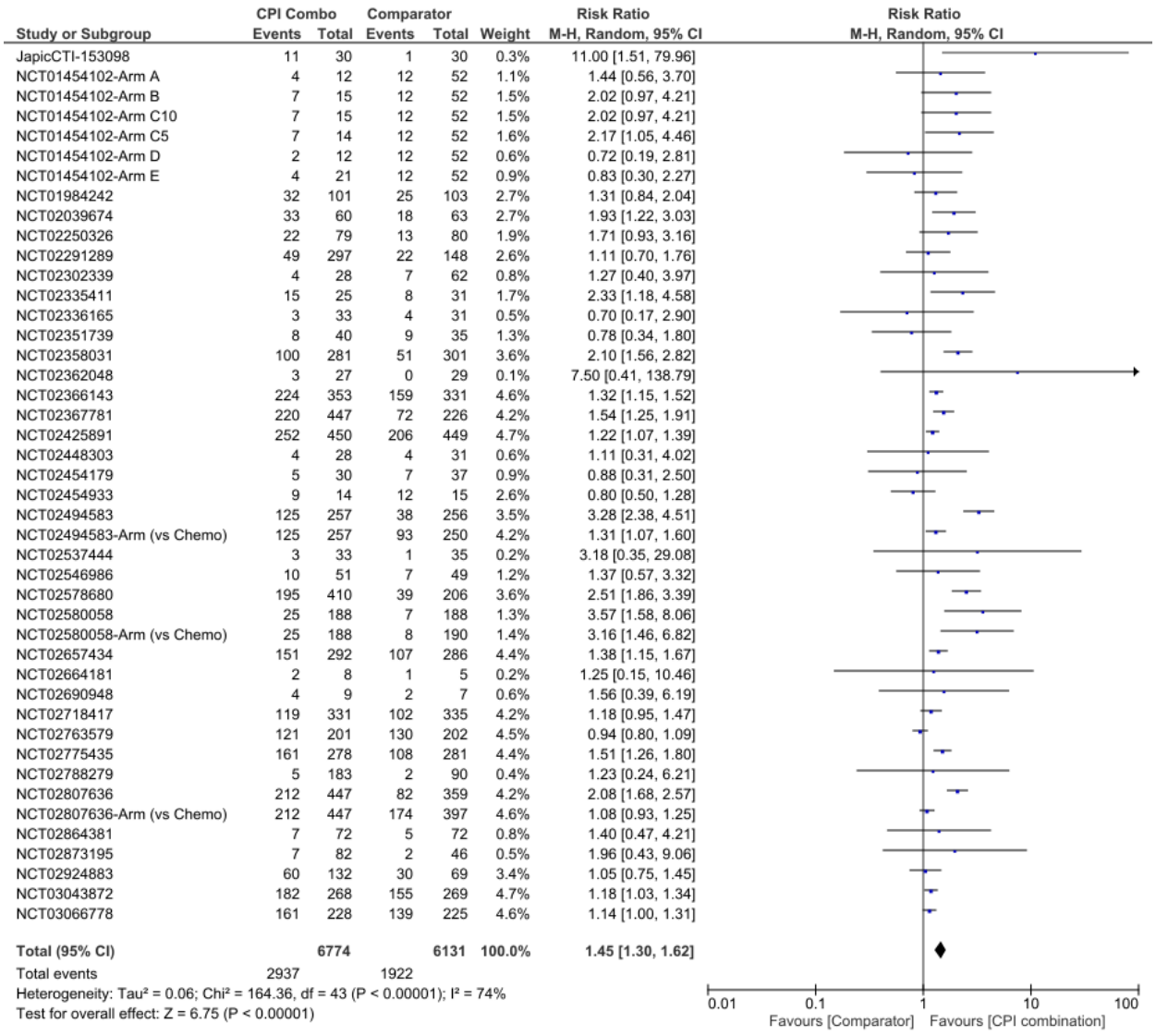

Figure 2 Meta-analysis of ORR for all identified studies

Abbreviations: ORR, overall response rate; CPI, immune checkpoint inhibitor

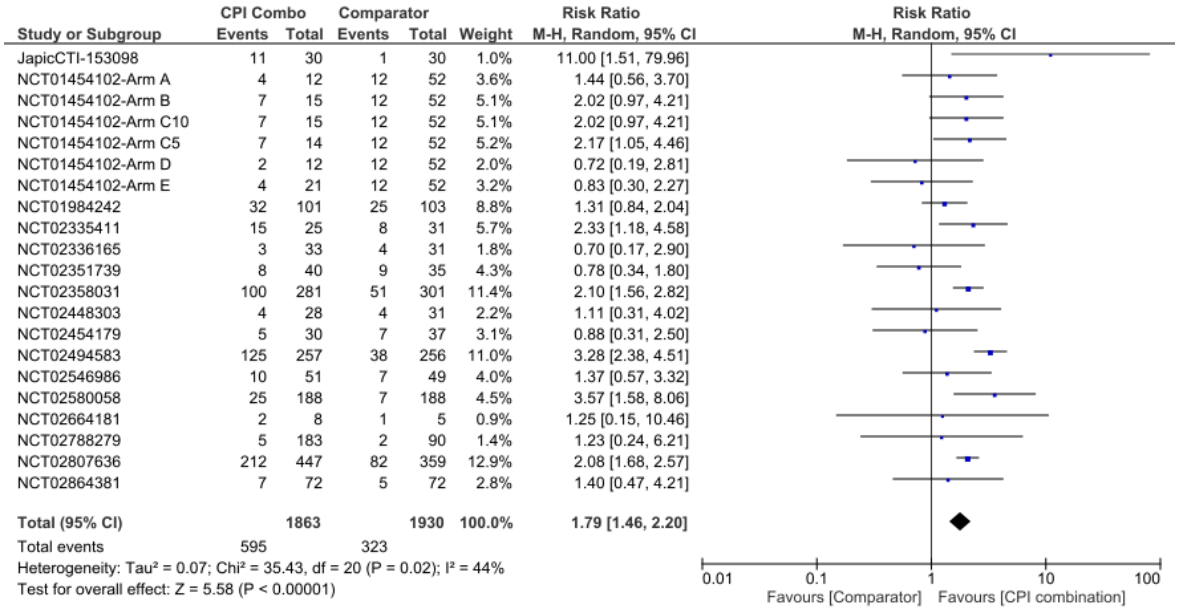

Figure 3 Meta-analysis of ORR for all studies with PD-1/PD-L1 monotherapy arm

Abbreviations: ORR, overall response rate; CPI, immune checkpoint inhibitor

2.3.4. Subgroup analyses

Given our primary research question in this study and based on the findings, we focused on combination therapy to enhance the anti-tumor efficacy of CPIs in further analysis. A subgroup analysis of the mode of action of the combination drugs was conducted in 16 studies in which a PD-1/PD-L1 inhibitor monotherapy group was set. The results of the subgroup analysis for ORR are summarized in Figure 4. PD-1/PD-L1 inhibitor plus anticancer drugs with DNA-synthesis inhibitory effect or microtubule inhibitory effect led to a statistically significant improvement in ORR compared to PD-1/PD-L1 inhibitor alone. In contrast, it was suggested that PD-1/PD-L1 inhibitor plus molecular targeted agents with anti-angiogenic or kinase-inhibitory effects did not significantly improve the ORR compared to PD-1/PD-L1 inhibitor alone.

Subgroup analyses by other factors such as the target molecule of CPI (PD-1 or PD-L1) and tumor type were also conducted, and the results are summarized in Table 2. The combination of PD-1/PD-L1 inhibitor and anticancer drugs showed significantly improved ORR consistently across all subgroups.

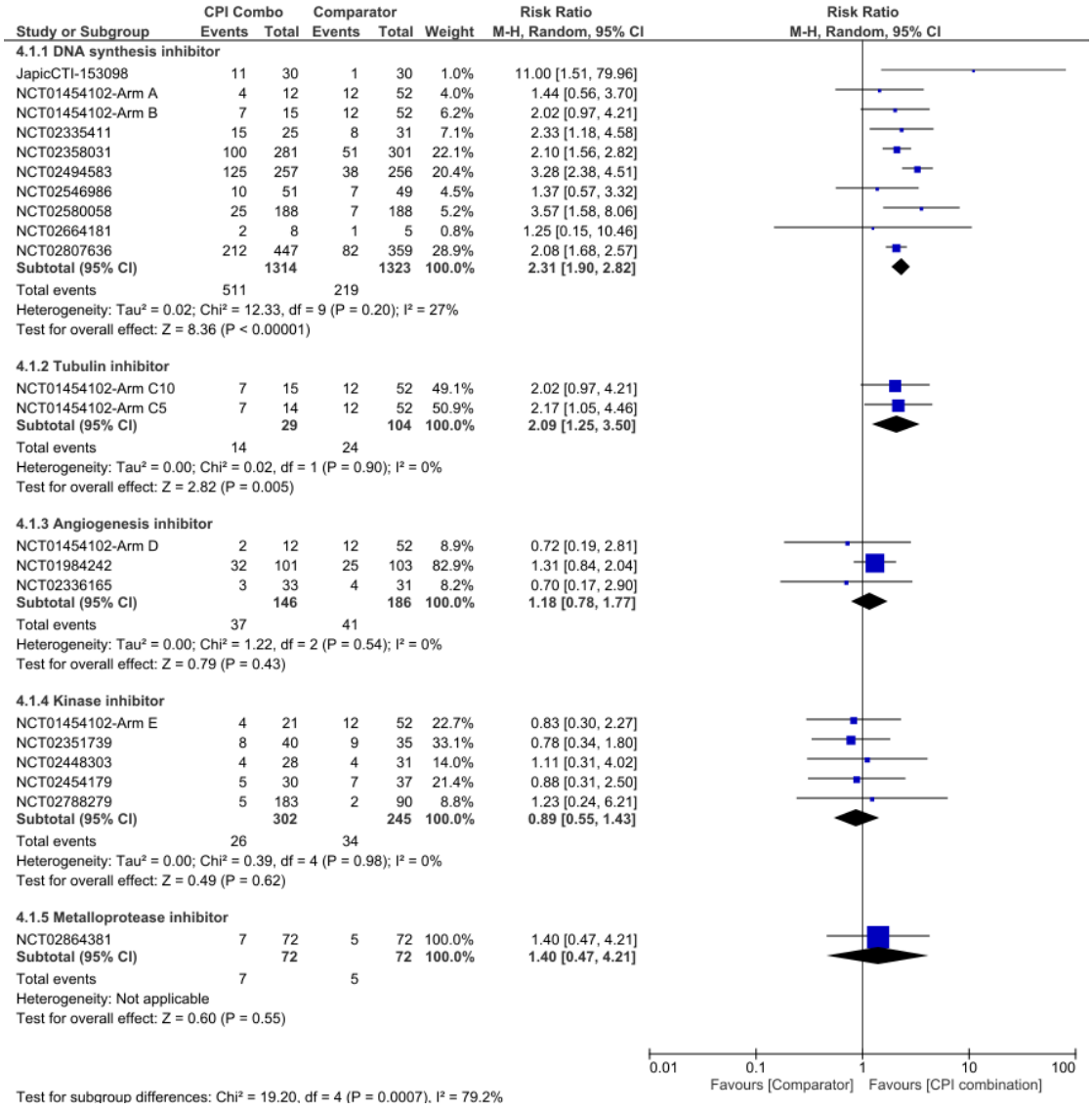

Figure 4 Subgroup analysis of ORR according to the mode of action of concomitant anticancer drugs for all studies with PD-1/PD-L1 monotherapy arm

Abbreviations: ORR, overall response rate; CPI, immune checkpoint inhibitor

Table 2 Subgroup analysis of ORR according to CPI type and tumor type for all studies with PD-1/PD-L1 monotherapy arm

Subgroup	**Number of studies/arms included**	**Number of responder/Total**		**Risk Ratio (95%CI) P-value Heterogeneity I^2**
		CPI Combination	**Comparator**	
ORR based on the CPI type				
Combination with PD-1 inhibitor	11/16	318/911	203/1159	1.75 (1.34, 2.28) <0.0001 45%
Combination with PD-L1 inhibitor	5/5	277/952	120/771	1.78 (1.20, 2.64) 0.004 49%
ORR based on the tumor type				
Lung cancer	4/9	47/176	84/397	1.57 (1.15, 2.14) 0.005 0%
Gastric or GEJ cancer	3/3	147/354	51/359	2.73 (1.86, 4.02) <0.00001 25%
Other tumors	9/9	401/1333	188/1174	1.70 (1.25, 2.32) 0.0008 55%

ORR, objective response rate; CPI, immune checkpoint inhibitor; PD-1, programmed death 1; PD-L1, programmed death ligand 1; GEJ, gastroesophageal junction

2.4. Discussion

This meta-analysis was conducted based on clinical trials on solid tumors, which evaluated the efficacy of combination therapy of CPI (PD-1/PD-L1 inhibitor) and anticancer drugs with ORR from public databases and published reports. Thirty-six trials having a comparator group were identified, and the pooled analysis showed that combination therapy led to a significantly improved ORR. However, the 36 studies included a mixture of trials in which an CPI monotherapy group was set as the control group and those in which non-CPI agents were set as the control group. Therefore, we conducted a further pooled analysis, including 16 trials in which an CPI monotherapy group was set as the control group based on our primary research question of investigating whether the combination of CPI with other anticancer therapies contributes to clinical anti-tumor efficacy compared with CPI alone. The results showed that combination therapy led to a significantly improved ORR. These indicated that combination therapies of PD-1/PD-L1 inhibitor plus anticancer drugs did not have a negative effect on the anti-tumor activity of PD-1/PD-L1 inhibitor but were associated with favorable clinical outcomes by additive or synergistic modes of action.

Subsequently, a subgroup analysis for all 16 studies having PD-1/PD-L1 monotherapy arm was performed according to the mode of action of the anticancer drugs used in combination with PD-1/PD-L1 inhibitors. The mode of actions of the evaluated anticancer drugs were classified into DNA-synthesis inhibitors, microtubule inhibitors, angiogenesis inhibitors, kinase inhibitors and MMP-9 inhibitor as the other targeted therapy. The results of the subgroup analysis indicated that the combination of PD-1/PD-L1 inhibitors and anticancer drugs with inhibitory effects on DNA synthesis or microtubule formation had a statistically significant improvement in ORR. These results suggest that these potential ICD-inducible agents, including DNA-synthesis inhibitors and microtubule inhibitors, can be considered as favorable anticancer drugs when concomitantly used with a PD-1/PD-L1 inhibitor. This is in line with the hypothesis that combinations of CPI and ICD-inducible agents may show clinically enhanced anti-tumor activities compared to CPI monotherapies, as reported in non-clinical studies. In contrast, the subgroup analysis suggested that combination therapy with molecular targeted agents with anti-angiogenic or kinase-inhibitory effects did not necessarily significantly improve the ORRs of PD-1/PD-L1 inhibitor alone. Regarding EGFR tyrosine kinase inhibitors, it was previously reported that PD-L1 expression is reduced by EGFR inhibitors in NSCLC cell lines with activated EGFR. In addition, oncogenic EGFR signaling has been suggested to have a role in the remodeling of the tumor microenvironment to trigger the immune escape response [43]. According to a meta-

analysis based on clinical trials of anti PD-1/PD-L1 antibodies in advanced NSCLC patients who previously received first-line tyrosine kinase inhibitor (TKI) therapy, anti-PD-1/PD-L1 antibodies significantly prolonged overall survival compared to docetaxel in the overall population and in the EGFR-wild type subgroup, but not in the EGFR-mutant subgroup [44]. There is also little evidence available that pleads molecular targeted anticancer agents have shown to induce ICD except for some TKIs such as small molecule anaplastic lymphoma kinase (ALK)/c-ros oncogene 1 (ROS1) inhibitor crizotinib [45]. Thus far, potential involvement of the specific molecular targeted anticancer agents evaluated in our subgroup analysis of angiogenesis inhibitor (bevacizumab), kinase inhibitor (erlotinib, acalabrutinib, cobimentinib) and metalloprotease inhibitor (andecaliximab) in ICD have not been established. The role of PD-1/PD-L1 blockade in EGFR mutation, other oncogenic gene mutations or oncogenic proteins in solid tumors is still conflicting and the mechanisms remain to be elucidated; therefore, there is a need for future research and updated meta-analyses based on clinical trials to evaluate the efficacy of targeted therapies plus PD-1/PD-L1 inhibitors.

A strength of this review is that it assessed the clinical anti-tumor efficacy of PD-1/PD-L1 inhibitor plus potential ICD inducers or other molecular targeted therapies compared with PD-1/PD-L1 inhibitor alone (based on so-called add-on trials) in the meta-analysis. Importantly, we also analyzed the pooled effect of combination therapy from 16 trials that involved 1863 patients in the combination group and 1930 patients in PD-1/PD-L1 inhibitor monotherapy.

However, the following limitations must be considered in this meta-analysis. First, moderate to high heterogeneity was observed among the trials, and we should carefully interpret the results of the pooled effects. Second, a part of clinical trials included in the analyses were not randomized. While the pooled data extracted from each of these non-randomized trials for the comparison were obtained from similar populations (same tumor type), we need to interpret these group comparisons with caution. Third. unmeasured confounding factors as well as confounding by tumor type, treatment line, presence or absence of metastatic diseases, or target indication may exist. This is partly attributable to the limited number of clinical trials eligible for the present study.

3. Immune-related and common adverse events with PD-1/PD-L1 inhibitors combined with other anticancer therapy for solid tumors: a systematic review and meta-analysis (Research 2)

3.1. Objective

This Research 2 was aimed to evaluate the relative risk of organ specific irAEs and common AEs associated with PD-1/PD-L1 inhibitors as the primary indicators in patients treated with PD-1/PD-L1 inhibitor-based combination therapies compared to those treated with PD-1/PD-L1 inhibitor monotherapy for solid tumors. Additionally, subgroup analyses were conducted based on the mode of action of concomitant anticancer drugs to identify differences in the relative risk of the AEs of interest.

3.2. Materials and methods

3.2.1 Search strategy

This systematic review and meta-analysis followed the PRISMA reporting guidelines [18]. The study protocol is available online at the International Prospective Register of Systematic Reviews registry (PROSPERO: registration number CRD42022379088).

The clinical trials evaluated in this study were RCTs that evaluated the safety and efficacy of FDA-approved PD-1/PD-L1 inhibitor (i.e., nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab) in combination with other anticancer drugs for solid tumors. A systematic search was performed using multiple databases from their inception until August 10, 2022. As a primary data source, we used ClinicalTrials.gov (https://ClinicalTrials.gov), employing drug names as key search terms (nivolumab including [nivolumab or BMS-936558 or MDX-1106 or MDX-1106-04 or nivolumab BMS or ONO-4538 or Opdivo], pembrolizumab including [pembrolizumab or Keytruda or ambrolizumab or lambrolizumab or mDX-400 or MK-3475 or SCH-900475], atezolizumab including [atezolizumab or MPDL-3280A or PRO-304397 or RG-7446 or RO-5541267 or Tecentriq], avelumab including [avelumab or MSB-0010682 or MSB-0010718C or PF-06834635 or Bavencio], and durvalumab including [durvalumab or MEDI-4736 or Imfinzi]). Additionally, Medline (PubMed) served as a secondary data source with registered article type classified as "Randomized Controlled Trial". The search terms used were (pembrolizumab or nivolumab or atezolizumab or avelumab or durvalumab) and (clinical or trial) and (combination or plus or with). Furthermore, the American Society of Clinical Oncology [ASCO] Meeting Library (https://meetinglibrary.asco.org/) and the European Society for Medical Oncology [ESMO] (https://oncologypro.esmo.org/meeting-resources) were referenced as a third

data source, utilizing the same search terms as used for PubMed to identify relevant clinical trials presented in the abstracts of their annual meetings.

3.2.2. Study selection

Clinical trials that met the following criteria were included: (i) RCTs evaluating the safety and efficacy of PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) in combination with anticancer drugs; (ii) trials with a PD-1/PD-L1 inhibitor monotherapy arm; and (iii) trials reporting the incidence of AEs (non-serious/serious AEs and/or grade 3-4 AEs according to the Common Terminology Criteria for Adverse Events [CTCAE]) in both the combination and the monotherapy groups. Clinical trials that met the following criteria were excluded: (i) trials involving patients with hematological cancers; (ii) trials evaluating immunotherapy (e.g., vaccines, CPIs other than the aforementioned PD-1/PD-L1 inhibitors, cytokines, and treatments with immunostimulatory effects like Bacillus Calmette-Guérin [BCG] and indoleamine 2,3-dioxygenase [IDO] inhibitors) as a component of combination therapy; (iii) trials incorporating anticancer procedures (e.g., radiotherapy, tumorectomy) as study interventions; (iv) trials evaluating adjuvant or neo-adjuvant therapy; (v) reports solely focused on subgroup analysis; (vi) trials with disparate PD-L1 inhibitor dosing regimens between the combination and monotherapy groups, (vii) trials randomized subjects with different PD-L1 expression levels (such as CPS scores) into different groups; and (viii) trials with less than ten subjects evaluated in both groups. Additionally, literature reports were limited to the original English language.

3.2.3. Data extraction

We identified and extracted the names and designs of the clinical trials from the records derived from ClinicalTrials.gov and the titles and abstracts derived from the other data sources, followed by assessments of eligibility based on the full texts. The primary indicators were the incidence of typical organ-specific irAEs that were acknowledged to be infrequent but serious in CPIs (such as pneumonia, pneumonitis, immune-related lung disease, immune-mediated hepatitis, autoimmune hepatitis, colitis, autoimmune colitis, colitis ulcerative, cardiac failure, immune-mediated myocarditis, autoimmune myocarditis, myocardial infraction, pericardial disease/pericardial effusion, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, myositis, myasthenia gravis, immune-mediated dermatitis, toxic epidermal necrolysis [TEN], Stevens-Johnson syndrome [SJS], autoimmune nephritis, and nephritis), along with 12

common AEs (abdominal pain, decreased appetite, diarrhea, nausea, vomiting, fatigue, pyrexia/fever, arthralgia, cough/productive cough, dyspnoea, pruritus, and rash) described as very common AEs (defined as a frequency of 10% or more) in the EMA-approved SmPCs at least four out of the five PD-1/PD-L1 inhibitors of interest [46, 47, 48, 49, 50]. The secondary indicators comprised an overview of AEs (incidence of serious AEs, non-serious AEs, and Grade 3 or 4 AEs).

To calculate the incidence and perform a pooled analysis of the primary and secondary indicators, we collected the number of events and total number of subjects included in the analysis. We identified all trials using the ClinicalTrials.gov identification number (i.e., NCT number), first author and publication year, and recorded the intervention of experimental and control groups, number of subjects enrolled in each group, study phase, and tumor type/disease condition. A single reviewer performed the initial data extraction using a standardized data collection form, and a second reviewer carefully checked the data. Discrepancies were resolved through discussions. The quality and risk of bias were assessed using the revised Cochrane Collaboration risk-of-bias tool (RoB 2.0) [16]. Publication bias was assessed visually using a funnel plot.

3.2.4. Statistical analysis

Statistical analysis was performed using RevMan, version 5.4 (The Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark). All analyses were performed using a random-effects model owing to the expected heterogeneity among the study cohorts, which encompassed various tumor types and treatment lines. Analyses were conducted for the following groups: PD-1/PD-L1 inhibitor combined with other anticancer drugs versus PD-1/PD-L1 inhibitor monotherapy. Subsequently, if a statistically significant increase in the risk ratio (RR) was observed in PD-1/PD-L1 inhibitor-based combination therapy compared to PD-1/PD-L1 inhibitor monotherapy, exploratory subgroup analyses were conducted based on the modes of action of the concomitant anticancer drugs. For all analyses, pooled RRs for the incidence of AEs with 95% CI were calculated in the ITT population, and $P<0.05$, employing a two-sided test, was considered statistically significant. Heterogeneity among studies was assessed using the Q test and I^2 index, and statistically significant heterogeneity was considered at $P<0.05$ or $I^2>50\%$.

3.3. Results

3.3.1. Study characteristics

Eighteen studies were eligible for inclusion, as shown in Figure 5. The characteristics

of each trial were summarized in Table 3 and Supplementary Table 4. Out of the 18 studies, nine utilized pembrolizumab, four utilized nivolumab, three utilized atezolizumab, while avelumab and durvalumab were each utilized in one study. The cancer types reported in two or more studies were non-small-cell lung cancer (NSCLC) (five studies), urothelial or bladder cancer (four studies), gastric or gastroesophageal junction adenocarcinoma, and head and neck cancer (two studies each). The concomitant anticancer drugs used in combination with PD-1/PD-L1 inhibitors, as reported in two or more studies, were cisplatin or carboplatin (five studies), bevacizumab (four studies), acalabrutinib and gemcitabine (three studies each), and 5-FU and pemetrexed (two studies each). The number of study arms categorized by the mode of action of concomitant anticancer drugs are as follows: ten arms for DNA synthesis inhibitors (cisplatin, carboplatin, gemcitabine, 5-FU, pemetrexed, capecitabine, CC-486, and pegylated liposomal doxorubicin), seven arms for kinase inhibitors (acalabrutinib, cobimetinib, dasatinib, erlotinib, and lenvatinib), four arms for anti-VEGF antibody (bevacizumab), and two arms for other molecular targeted drugs (andecaliximab and olaparib). Furthermore, there was one arm for microtubule inhibitors (paclitaxel).

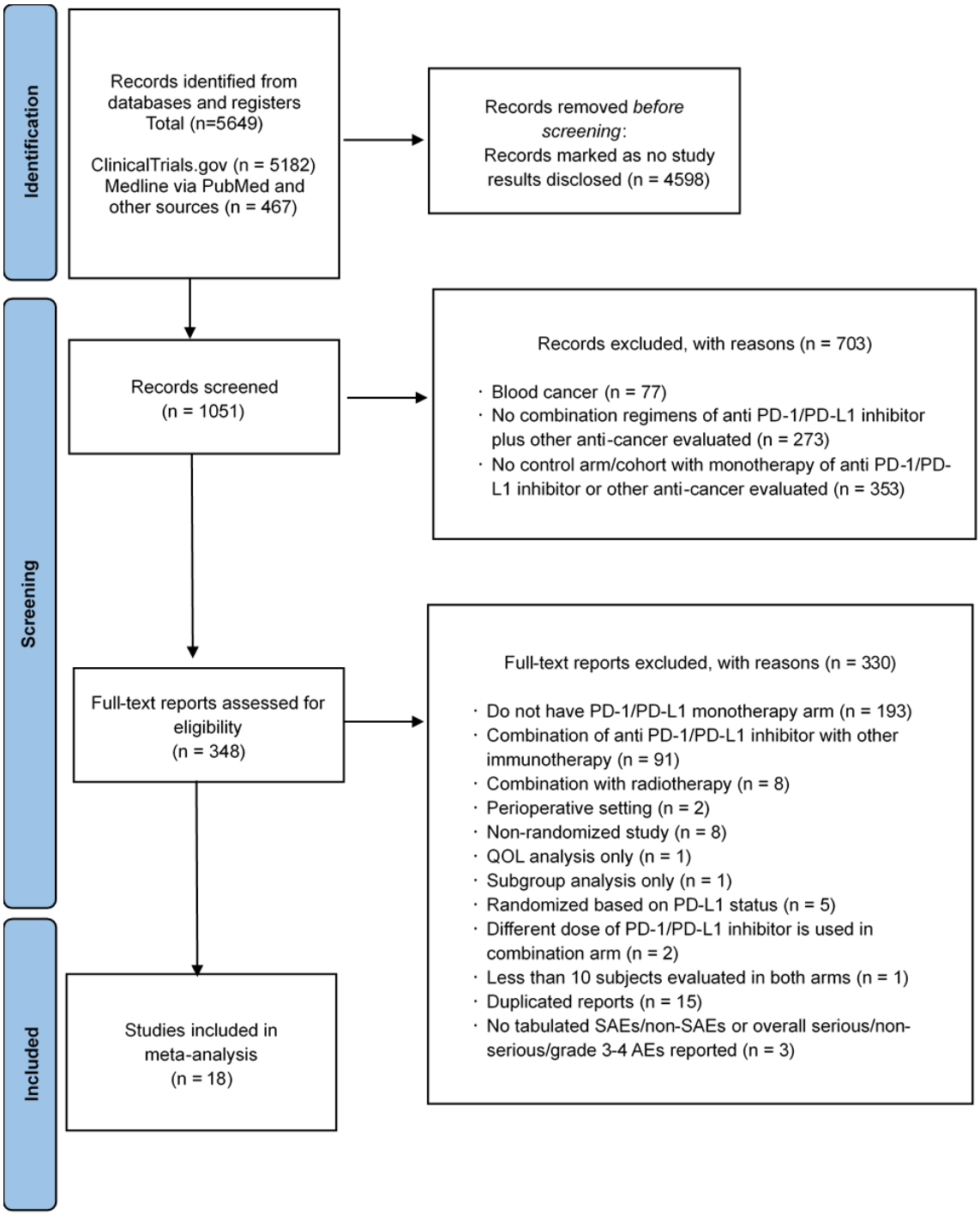

Figure 5 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of selecting clinical trials for Research 2

Table 3 Characteristics of the included studies in Research 2

Parameter	Category	All studies (N=18)		Reference
		No. studies	No. combo arms	
Name of CPI	Pembrolizumab	9	9	[24, 25, 27, 28, 51-53]
	Nivolumab	4	9	[54, 55]
	Atezolizumab	3	3	[32, 38, 39, 56]
	Avelumab	1	1	[57]
	Durvalumab	1	1	[58]
Mode of action of CPI	PD-1 inhibitor	13	18	[24, 25, 27, 28, 51-55]
	PD-L1 inhibitor	5	5	[32, 38, 39, 56-58]
Development phase	Phase 1 or 1/2	2	7	[54]
	Phase 2	9	9	[24, 28, 32, 51, 52, 55, 58]
	Phase 3	7	7	[25, 27, 38, 39, 53, 56, 57]
Tumor type	NSCLC	5	10	[28, 54]
	Urothelial/bladder cancer	4	4	[24, 39, 53, 58]
	Gastric/GEJ cancer	2	2	[27, 55]
	Head & neck cancer	2	2	[25, 52]
	Advanced cancer	1	1	
	Colorectal cancer	1	1	[38, 56]
	Glioblastoma	1	1	[51]
	Ovarian cancer	1	1	[57]
	Renal cell carcinoma	1	1	[32]
Combination drug	Cisplatin/Carboplatin	5	7	[25, 27, 39, 53, 54]
	Bevacizumab	4	4	[32, 51, 54]
	Acalabrutinib	3	3	[24, 52]
	Gemcitabine	3	3	[39, 53, 54]
	5-FU	2	2	[25, 27]
	Pemetrexed	2	2	[54]
	Cobimetinib	1	1	[38, 56]

Parameter	Category	All studies (N=18)		Reference
		No. studies	No. combo arms	
	Andecaliximab	1	1	[55]
	Capecitabine	1	1	[27]
	CC-486	1	1	[28]
	Dasatinib	1	1	
	Erlotinib	1	1	[54]
	Lenvatinib	1	1	
	Olaparib	1	1	[58]
	Paclitaxel	1	1	[54]
	Pegylated liposomal doxorubicin	1	1	[57]

CPI, immune checkpoint inhibitor; PD-1, programmed death 1; PD-L1, programmed death ligand 1; NSCLC, non-small-cell lung cancer; GEJ, gastroesophageal junction.

3.3.2. Quality assessment

The results of the RoB 2.0 assessment are presented in Supplementary Figure 3, showing that out of 18 studies, 17 exhibited low risk, while the remaining 1 study raised a concern due to insufficient information regarding the D1 randomization process. Funnel plots were shown in Supplementary Figure 4 to assess publication bias. No obvious asymmetry was observed, indicating the absence of significant publication bias. Furthermore, the PRISMA checklist for our meta-analysis was presented in Supplementary Table 5.

3.3.3. Organ-specific immune-related adverse events

In total, 4232 patients (2071 received combination therapy and 2161 received monotherapy) were included in the analysis, comprising 21 combination therapy groups from 16 studies. These studies provided incidence data for organ-specific irAEs of interest. The incidence and RR for each organ-specific irAE, both serious and non-serious, in the combination therapy group compared with the monotherapy group were summarized in Table 4.

Among the organ-specific irAEs of interest, the most common serious events (incidence of ≥1.0% in the combination therapy group) occurring more frequently in the combination therapy group than in the monotherapy group were pneumonia (2.2% in the combination therapy group; 1.8% in the monotherapy group) and colitis (1.0% in the combination therapy group; 0.3% in the monotherapy group). The most common non-serious organ-specific irAEs (with an incidence of ≥1.0% in the combination therapy group) occurring more frequently in the combination therapy group than in the monotherapy group were pneumonia (2.2% in the combination therapy group; 1.7% in the monotherapy group), hypothyroidism (14.4% in the combination therapy group; 9.4% in the monotherapy group), and hyperthyroidism (1.8% in the combination therapy group; 1.1% in the monotherapy group).

Among these, only serious colitis showed a statistically significant increase in RR in the combination therapy group compared to the monotherapy group (RR: 2.47; 95% CI: 1.14, 5.37; P=0.02). A subgroup analysis of serious colitis based on the mode of action of concomitant anticancer drugs is shown in Figure 6. PD-1/PD-L1 inhibitor plus DNA synthesis inhibitors exhibited a statistically significant increase in RR for the incidence of serious colitis compared with PD-1/PD-L1 inhibitor monotherapy. In contrast, combination with anticancer drugs from other categories of mode of action (i.e., tubulin inhibitor, kinase inhibitor, anti-VEGF antibody, and other molecular targeted drugs) did not significantly increase the RR for the incidence of serious colitis compared to PD-

1/PD-L1 inhibitor monotherapy, although the results should be interpreted with caution owing to the low number of patients experiencing the event, ranging from 0 to 3 in both treatment groups.

Table 4 The incidence and risk ratio for serious/non-serious organ-specific irAE of interest in the combination therapy group compared to the monotherapy group

Event name		**Incidence (95% CI)**		**RR (95% CI)**	I^2 **%**	**P-value**
		Combination (n=2071)	**PD-1/PD-L1 inhibitor monotherapy (n=2161)**			
Pneumonia	Serious	2.2 (1.6-3.0)	1.8 (1.3-2.5)	1.22 (0.79, 1.88)	0	0.37
	Non-serious	2.2 (1.6-3.0)	1.7 (1.2-2.4)	1.36 (0.89, 2.09)	0	0.16
Pneumonitis	Serious	1.0 (0.6-1.5)	1.3 (0.9-1.9)	0.92 (0.51, 1.66)	0	0.79
	Non-serious	0.4 (0.2-0.8)	0.8 (0.5-1.3)	1.36 (0.59, 3.13)	0	0.48
Immune-related lung disease	Serious	0.2 (0.1-0.5)	0.2 (0.1-0.5)	0.81 (0.22, 2.98)	NA	0.75
	Non-serious	0	0	Not estimable	NA	NA
Immune mediated hepatitis	Serious	0.5 (0.3-0.9)	0.1 (0-0.4)	2.68 (0.75, 9.61)	0	0.13
	Non-serious	0	0	Not estimable	NA	NA
Autoimmune hepatitis	Serious	0.3 (0.1-0.6)	0.2 (0.1-0.5)	1.17 (0.40, 3.42)	0	0.78
	Non-serious	0	0	Not estimable	NA	NA
Colitis	Serious	1.0 (0.6-1.5)	0.3 (0.1-0.6)	2.47 (1.14, 5.37)	0	0.02
	Non-serious	0	0	Not estimable	NA	NA
Autoimmune colitis	Serious	0.05 (0-0.3)	0.05 (0-0.3)	0.88 (0.09, 8.36)	0	0.91
	Non-serious	0.1 (0-0.3)	0	7.27 (0.78, 67.92)	0	0.08

Event name		Incidence (95% CI)		RR (95% CI)	I^2 %	P-value
		Combination (n=2071)	PD-1/PD-L1 inhibitor monotherapy (n=2161)			
Colitis ulcerative	Serious	0.05 (0-0.3)	0.3 (0.1-0.6)	0.97 (0.01, 146.10)	82	0.99
	Non-serious	0	0	Not estimable	NA	NA
Cardiac failure	Serious	0.2 (0.1-0.5)	0.4 (0.2-0.7)	0.87 (0.22, 3.36)	8	0.84
	Non-serious	0.2 (0.1-0.5)	0.1 (0-0.3)	2.27 (0.39, 13.13)	0	0.36
Immune mediated myocarditis	Serious	0.05 (0-0.3)	0	3.03 (0.12, 74.07)	NA	0.50
	Non-serious	0	0	Not estimable	NA	NA
Autoimmune myocarditis	Serious	0.05 (0-0.3)	0	3.26 (0.13, 79.69)	NA	0.47
	Non-serious	0	0	Not estimable	NA	NA
Myocardial infraction	Serious	0.5 (0.2-0.9)	0.2 (0.1-0.5)	1.85 (0.69, 4.97)	0	0.22
	Non-serious	0	0	Not estimable	NA	NA
Pericardial disease/effusion	Serious	0.2 (0.1-0.5)	0.5 (0.2-0.8)	1.17 (0.46, 2.97)	0	0.75
	Non-serious	0	0	Not estimable	NA	NA
Hypothyroidism	Serious	0.2 (0.1-0.5)	0.4 (0.2-0.7)	0.68 (0.20, 2.33)	0	0.54
	Non-serious	14.4 (12.9-16.0)	9.4 (8.2-10.7)	1.31 (0.88, 1.93)	67	0.18
Hyperthyroidism	Serious	0.1 (0-0.3)	0.3 (0.1-0.7)	1.01 (0.34, 3.03)	0	0.98
	Non-serious	1.8 (1.3-2.5)	1.1 (0.7-1.6)	1.79 (0.91, 3.50)	11	0.09

Event name		Incidence (95% CI)		RR (95% CI)	I^2 %	P-value
		Combination (n=2071)	PD-1/PD-L1 inhibitor monotherapy (n=2161)			
Hypophysitis	Serious	0.3 (0.1-0.6)	0.1 (0-0.4)	1.54 (0.46, 5.14)	0	0.49
	Non-serious	0.05 (0-0.3)	0	11.54 (0.50, 267.09)	NA	0.13
Adrenal insufficiency	Serious	0.2 (0.1-0.5)	0.4 (0.2-0.8)	0.95 (0.38, 2.42)	0	0.92
	Non-serious	0.05 (0-0.3)	0	3.06 (0.13, 74.21)	NA	0.49
Myositis	Serious	0	0.05 (0-0.3)	0.34 (0.01, 8.23)	NA	0.50
	Non-serious	0	0	Not estimable	NA	NA
Myasthenia gravis	Serious	0.05 (0-0.3)	0.05 (0-0.3)	1.37 (0.15, 12.45)	0	0.78
	Non-serious	0	0	Not estimable	NA	NA
Immune mediated dermatitis	Serious	0	0.05 (0-0.3)	0.34 (0.01, 8.23)	NA	0.50
	Non-serious	0	0	Not estimable	NA	NA
Toxic epidermal necrolysis	Serious	0	0	Not estimable	NA	NA
	Non-serious	0	0	Not estimable	NA	NA
Stevens-Johnson syndrome	Serious	0.1 (0-0.3)	0	3.04 (0.32, 29.12)	0	0.34
	Non-serious	0	0	Not estimable	NA	NA
Autoimmune nephritis	Serious	0.1 (0-0.3)	0	2.81 (0.29, 26.97)	0	0.37
	Non-serious	0	0	Not estimable	NA	NA

Event name		Incidence (95% CI)		RR (95% CI)	I^2 %	P-value
		Combination (n=2071)	PD-1/PD-L1 inhibitor monotherapy (n=2161)			
Nephritis	Serious	0.1 (0-0.3)	0.2 (0.1-0.5)	0.92 (0.23, 3.77)	0	0.91
	Non-serious	0	0	Not estimable	NA	NA

irAE, immune-related adverse event; PD-1, programmed death 1; PD-L1, programmed death ligand 1; RR, risk ratio; CI, confidence interval; NA, not applicable.

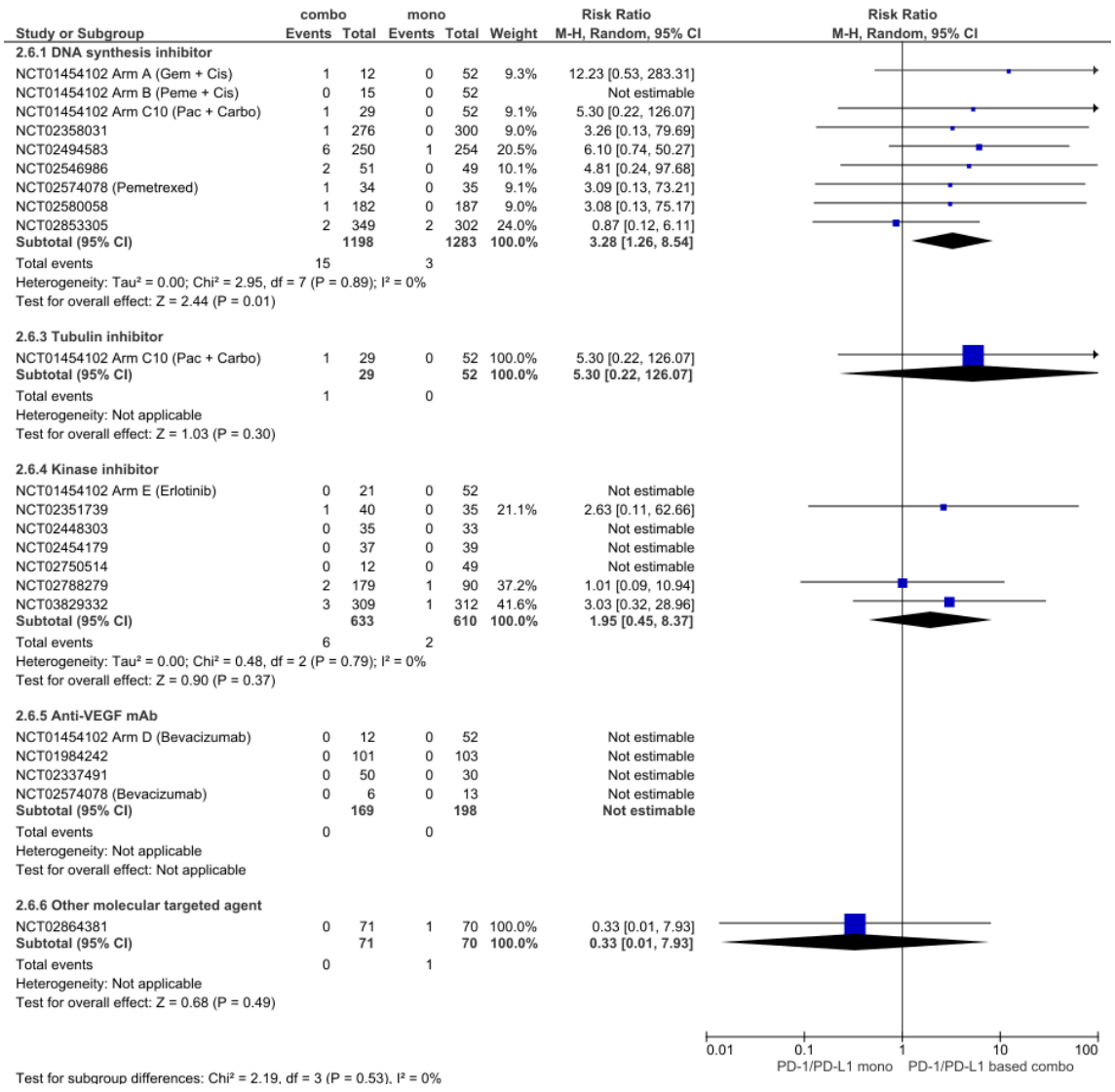

Figure 6 Subgroup analysis of serious colitis according to the mode of action of concomitant anticancer drugs

3.3.4. Major adverse events very commonly reported in the PD-1/PD-L1 monotherapies

Studies identical to those included for organ-specific irAEs were analyzed for 12 common AEs. The incidence and RR for each serious/non-serious common AEs of interest in the combination therapy group compared with the monotherapy group were summarized in Table 5.

The most common serious events (with an incidence of ≥1.0% in the combination therapy group) occurring more frequently in the combination therapy group than in the monotherapy counterpart were pyrexia/fever, diarrhea, vomiting, nausea, fatigue and abdominal pain. The most common non-serious events (with an incidence of ≥10% in the combination therapy group) that occurred more frequently in the combination therapy group than in the monotherapy group were pyrexia/fever, nausea, fatigue, diarrhea, decreased appetite, vomiting, rash, dyspnea, and abdominal pain. Among these, AEs that showed a statistically significant increased RR in the combination therapy group compared to the monotherapy group were serious fever (RR: 1.81; 95% CI: 1.1, 2.9; P=0.01) and the following non-serious events: fatigue (RR: 1.32; 95% CI: 1.2, 1.5; P<0.0001), nausea (RR: 1.95; 95% CI: 1.6, 2.3; P<0.00001), decreased appetite (RR: 1.57; 95% CI: 1.4, 1.8; P<0.00001), vomiting (RR: 1.89; 95% CI: 1.6, 2.3; P<0.00001), dyspnea (RR: 1.19; 95% CI: 1.0, 1.4; P=0.03), rash (RR: 1.49; 95% CI: 1.1, 2.0; P=0.006), diarrhea (RR: 1.66; 95% CI: 1.4, 2.0; P<0.00001), and pyrexia/fever (RR: 1.42; 95% CI: 1.2, 1.7; P<0.0001).

Subgroup analyses evaluating the aforementioned nine AEs based on the modes of action of the concomitant anticancer drugs were summarized in Table 6 (forest plots are shown in Supplementary Figure 5-13). The combination of PD-1/PD-L1 inhibitors and DNA synthesis inhibitors was associated with a statistically significant increase in the RR for serious and non-serious pyrexia/fever, non-serious fatigue, nausea, decreased appetite, vomiting, and diarrhea compared with PD-1/PD-L1 inhibitor monotherapy. Furthermore, PD-1/PD-L1 inhibitors combined with tubulin inhibitors resulted in a statistically significant increase in the RR for non-serious fatigue and pyrexia/fever. PD-1/PD-L1 inhibitors combined with kinase inhibitors showed a statistically significant increase in the RR for non-serious nausea, decreased appetite, vomiting, dyspnea, rash, diarrhea, and pyrexia/fever. Finally, PD-1/PD-L1 inhibitors combined with anti-VEGF antibodies showed a statistically significant increase in the RR for non-serious nausea.

Table 5 The incidence and risk ratio for serious/non-serious common adverse events of interest in the combination therapy group compared to the monotherapy group

Event name		**Number of events**		**RR (95% CI)**	I^2 **%**	**P-value**
		Combination (n=2071)	**PD-1/PD-L1 inhibitor monotherapy (n=2161)**			
Fatigue	Serious	1.2 (0.8-1.8)	0.7 (0.4-1.1)	1.56 (0.84, 2.87)	0	0.16
	Non-serious	38.1 (36.0-40.2)	29.9 (26.0-31.9)	1.32 (1.16, 1.50)	55	<0.0001
Nausea	Serious	1.4 (0.9-1.9)	0.8 (0.5-1.3)	1.33 (0.71, 2.48)	0	0.37
	Non-serious	44.0 (41.9-46.2)	20.4 (18.7-22.2)	1.95 (1.61, 2.34)	65	<0.00001
Decreased appetite	Serious	0.9 (0.6-1.4)	0.6 (0.3-1.0)	1.09 (0.43, 2.74)	20	0.86
	Non-serious	30.0 (28.1-32.1)	19.4 (17.7-21.1)	1.57 (1.35, 1.83)	38	<0.00001
Vomiting	Serious	1.5 (1.1-2.2)	0.9 (0.5-1.4)	1.53 (0.86, 2.73)	0	0.15
	Non-serious	25.9 (24.1-27.9)	13.5 (12.1-15.0)	1.89 (1.55, 2.30)	41	<0.00001
Cough/productive cough	Serious	0.2 (0.1-0.5)	0.05 (0-0.3)	2.09 (0.45, 9.66)	0	0.35
	Non-serious	16.9 (15.3-18.5)	17.5 (16.0-19.2)	1.13 (0.98, 1.29)	6	0.10
Dyspnea	Serious	1.4 (0.9-1.9)	1.5 (1.0-2.1)	1.05 (0.62, 1.77)	0	0.87
	Non-serious	15.2 (13.6-16.8)	14.9 (13.4-16.4)	1.19 (1.02, 1.39)	10	0.03
Rash	Serious	0.2 (0.1-0.5)	0.05 (0-0.3)	2.30 (0.56, 9.53)	0	0.25
	Non-serious	19.2 (17.5-20.9)	12.2 (10.9-13.7)	1.49 (1.12, 1.97)	63	0.006
Diarrhea	Serious	1.7 (1.2-2.3)	0.8 (0.5-1.3)	1.62 (0.87, 3.03)	0	0.13
	Non-serious	32.9 (30.9-35.0)	18.5 (16.9-20.2)	1.66 (1.37, 2.03)	57	<0.00001

Event name		Number of events		RR (95% CI)	I^2 %	P-value
		Combination (n=2071)	PD-1/PD-L1 inhibitor monotherapy (n=2161)			
Abdominal pain	Serious	1.1 (0.7-1.6)	0.9 (0.6-1.4)	1.03 (0.55, 1.91)	0	0.93
	Non-serious	12.5 (11.1-14.0)	10.0 (8.8-11.4)	1.26 (0.97, 1.64)	35	0.09
Pyrexia/fever	Serious	2.6 (2.0-3.4)	1.2 (0.8-1.8)	1.81 (1.13, 2.89)	0	0.01
	Non-serious	15.7 (14.2-17.4)	10.7 (9.4-12.1)	1.42 (1.20, 1.67)	2	<0.0001
Arthralgia	Serious	0.1 (0-0.3)	0.3 (0.1-0.6)	0.55 (0.17, 1.82)	0	0.33
	Non-serious	9.9 (8.6-11.3)	9.2 (8.0-10.5)	1.21 (0.95, 1.54)	27	0.12
Pruritus	Serious	0.1 (0-0.3)	0.05 (0-0.3)	1.72 (0.3, 10.8)	0	0.56
	Non-serious	12.7 (11.2-14.2)	13.4 (12.0-14.9)	1.00 (0.80, 1.26)	25	0.97

PD-1, programmed death 1; PD-L1, programmed death ligand 1; RR, risk ratio; CI, confidence interval; NA, not applicable.

Table 6 Subgroup analysis of selected adverse events of interest according to the mode of action of concomitant anticancer drugs

Subgroup	No. studies/arms included	Number of events, n/N		RR (95% CI)	I^2 (%)	P-value
		Combination	PD-1/PD-L1 inhibitor monotherapy			
Serious pyrexia/fever						
DNA synthesis inhibitor	7/9	33/1198	17/1283	1.93 (1.08, 3.48)	0	0.03
Tubulin inhibitor	1/1	1/29	0/52	5.30 (0.22, 126.07)	NA	0.30
Kinase inhibitor	7/7	16/633	3/610	2.90 (0.99, 8.48)	0	0.05
Angiogenesis inhibitor	4/4	3/169	4/198	0.67 (0.15, 2.96)	0	0.60
Other molecular-targeted drug	1/1	2/71	2/70	0.99 (0.14, 6.81)	NA	0.99
Non-serious pyrexia/fever						
DNA synthesis inhibitor	7/9	180/1198	133/1283	1.42 (1.15, 1.75)	0	0.001
Tubulin inhibitor	1/1	9/29	6/52	2.69 (1.06, 6.80)	NA	0.04
Kinase inhibitor	7/7	113/633	64/610	1.62 (1.17, 2.24)	10	0.004
Angiogenesis inhibitor	4/4	23/169	30/198	0.87 (0.52, 1.45)	0	0.59
Other molecular-targeted drug	1/1	10/71	4/70	2.46 (0.81, 7.49)	NA	0.11
Non-serious fatigue						
DNA synthesis inhibitor	7/9	492/1198	374/1283	1.51 (1.29, 1.77)	54	<0.00001
Tubulin inhibitor	1/1	23/29	28/52	1.47 (1.08, 2.01)	NA	0.02
Kinase inhibitor	7/7	186/633	153/610	1.20 (0.91, 1.58)	58	0.19

Subgroup	No. studies/arms included	Number of events, n/N		RR (95% CI)	I^2 (%)	P-value
		Combination	PD-1/PD-L1 inhibitor monotherapy			
Angiogenesis inhibitor	4/4	89/169	95/198	1.14 (0.93, 1.41)	0	0.21
Other molecular-targeted drug	1/1	22/71	25/70	0.87 (0.54, 1.39)	NA	0.55
Non-serious nausea						
DNA synthesis inhibitor	7/9	645/1198	265/1283	2.39 (1.85, 3.07)	73	<0.00001
Tubulin inhibitor	1/1	12/29	17/52	1.27 (0.71, 2.27)	NA	0.43
Kinase inhibitor	7/7	180/633	113/610	1.60 (1.29, 1.98)	0	<0.0001
Angiogenesis inhibitor	4/4	60/169	46/198	1.58 (1.02, 2.46)	17	0.04
Other molecular-targeted drug	1/1	27/71	17/70	1.57 (0.94, 2.61)	NA	0.08
Non-serious decreased appetite						
DNA synthesis inhibitor	7/9	399/1198	253/1283	1.78 (1.41, 2.25)	58	<0.00001
Tubulin inhibitor	1/1	10/29	9/52	1.99 (0.92, 4.34)	NA	0.08
Kinase inhibitor	7/7	173/633	123/610	1.37 (1.11, 1.69)	0	0.003
Angiogenesis inhibitor	4/4	26/169	23/198	1.74 (0.95, 3.20)	3	0.08
Other molecular-targeted drug	1/1	24/71	20/70	1.18 (0.72, 1.94)	NA	0.50
Non-serious vomiting						
DNA synthesis inhibitor	7/9	359/1198	191/1283	2.04 (1.47, 2.81)	67	< 0.0001
Tubulin inhibitor	1/1	9/29	7/52	2.31 (0.96, 5.54)	NA	0.06

Subgroup	No. studies/arms included	Number of events, n/N		RR (95% CI)	I^2 (%)	P-value
		Combination	PD-1/PD-L1 inhibitor monotherapy			
Kinase inhibitor	7/7	128/633	63/610	1.88 (1.41, 2.51)	0	< 0.0001
Angiogenesis inhibitor	4/4	28/169	19/198	1.84 (0.99, 3.40)	0	0.05
Other molecular-targeted drug	1/1	22/71	18/70	1.21 (0.71, 2.04)	NA	0.49
Non-serious dyspnea						
DNA synthesis inhibitor	7/9	165/1198	186/1283	1.08 (0.81, 1.43)	48	0.59
Tubulin inhibitor	1/1	15/29	17/52	1.58 (0.94, 2.67)	NA	0.09
Kinase inhibitor	7/7	110/633	88/610	1.37 (1.06, 1.79)	0	0.02
Angiogenesis inhibitor	4/4	29/169	38/198	1.17 (0.74, 1.83)	0	0.50
Other molecular-targeted drug	1/1	10/71	9/70	1.10 (0.47, 2.53)	NA	0.83
Non-serious rash						
DNA synthesis inhibitor	7/9	212/1198	152/1283	1.44 (0.96, 2.16)	69	0.08
Tubulin inhibitor	1/1	10/29	15/52	1.20 (0.62, 2.31)	NA	0.60
Kinase inhibitor	7/7	155/633	73/610	1.73 (1.04, 2.88)	64	0.04
Angiogenesis inhibitor	4/4	30/169	39/198	1.10 (0.70, 1.72)	1	0.69
Other molecular-targeted drug	1/1	0/71	0/70	Not estimable	NA	-
Non-serious diarrhea						
DNA synthesis inhibitor	7/9	349/1198	249/1283	1.42 (1.09, 1.86)	63	0.009

Subgroup	No. studies/arms included	Number of events, n/N		RR (95% CI)	I^2 (%)	P-value
		Combination	PD-1/PD-L1 inhibitor monotherapy			
Tubulin inhibitor	1/1	14/29	15/52	1.67 (0.95, 2.96)	NA	0.08
Kinase inhibitor	7/7	266/633	103/610	2.19 (1.63, 2.93)	36	< 0.00001
Angiogenesis inhibitor	4/4	53/169	39/198	1.75 (0.87, 3.51)	37	0.11
Other molecular-targeted drug	1/1	14/71	9/70	1.53 (0.71, 3.31)	NA	0.28

PD-1, programmed death 1; PD-L1, programmed death ligand 1; RR, risk ratio; CI, confidence interval; NA, not applicable.

3.3.5. Overall safety events

As secondary indicators, a meta-analysis was performed on the safety summary encompassing overall serious AEs, non-serious AEs, and Grade 3-4 AEs. The analysis of serious AEs included 5043 patients (2528 received PD-1/PD-L1 inhibitor-based combination therapy and 2515 received PD-1/PD-L1 inhibitor monotherapy) from 22 combination therapy groups in 17 studies. The analysis of non-serious AEs included 4236 patients (2075 received PD-1/PD-L1 inhibitor-based combination therapy and 2161 received PD-1/PD-L1 inhibitor monotherapy) from 21 combination therapy groups in 16 studies. Furthermore, the analysis of Grade 3-4 AEs included 1605 patients (899 received PD-1/PD-L1 inhibitor-based combination therapy and 706 received PD-1/PD-L1 inhibitor monotherapy) from six combination groups in six studies.

The results of each safety indicator of interest were summarized in Table 7, demonstrating statistically significant increased RRs for overall serious AEs (RR: 1.30; 95% CI: 1.18, 1.42; P<0.00001), non-serious AEs (RR: 1.04; 95% CI: 1.02, 1.06; P=0.0006), and Grade 3-4 AEs (RR: 1.66; 95% CI: 1.41, 1.96; P<0.00001) in combination therapy compared with monotherapy. Additionally, subgroup analyses based on the modes of action of the concomitant drugs revealed that the combination of PD-1/PD-L1 inhibitors with DNA synthesis inhibitors or kinase inhibitors was associated with a statistically significant increase in the RR for the incidence of overall serious AEs compared with PD-1/PD-L1 inhibitor monotherapy. Similarly, the combination of PD-1/PD-L1 inhibitors with DNA synthesis inhibitors or anti-VEGF antibodies showed a statistically significant increase in the RR for the incidence of overall non-serious AEs compared with PD-1/PD-L1 inhibitor monotherapy. Lastly, the combination of PD-1/PD-L1 inhibitors with DNA synthesis inhibitors, kinase inhibitors, or anti-VEGF antibodies exhibited a statistically significant increase in the RR for the incidence of Grade 3-4 compared to PD-1/PD-L1 inhibitor monotherapy. Forest plots were shown in Supplementary Figure 14-16.

Table 7 Incidence and risk ratio of overall adverse events, including 95% CI and number of trials in each analysis

Event name	Number of studies/arms included	Incidence % (95% CI), n/N		RR (95% CI)	I^2 %	P- value
		Combination	PD-1/PD-L1 inhibitor monotherapy			
Any serious adverse events	17/22	51.5 (49.5-53.4), 1301/2528	40.3 (38.4-42.2), 1013/2515	1.30 (1.18, 1.42)	39	<0.00001
Any non-serious adverse events	16/21	94.8 (93.8-95.7), 1967/2075	90.1 (88.8-91.4), 1948/2161	1.04 (1.02, 1.06)	49	0.0006
Grade 3-4 adverse events	6/6	73.3 (70.3-76.2), 659/899	40.7 (37.0-44.4), 287/706	1.66 (1.41, 1.96)	53	<0.00001

PD-1, programmed death 1; PD-L1, programmed death ligand 1; RR, risk ratio; CI, confidence interval; NA, not applicable.

3.4. Discussion

The emergence of CPIs has brought about revolutionary changes in therapeutic options for various cancer types that have remained stagnant for decades. On the other hand, since the response rate with CPI monotherapy is limited to a subset of patients with most tumor types studied to date, attempts have been made in non-clinical and clinical studies to enhance the antitumor effect by combining CPIs with other anticancer drugs, including conventional chemotherapies and molecular targeted drugs. Among conventional chemotherapies, some have suggested the potential to enhance the antitumor response of CPI by triggering ICD and a direct or indirect stimulation of immune effectors. Additionally, combination therapy with PD-1/PD-L1 inhibitors with multi-kinase inhibitors has attracted great interest in recent years, and numerous preclinical and translational studies have suggested the potential involvement of the immune system in the mode of action of kinase inhibitors.

For instance, in melanoma cell lines harboring constitutively active mitogen-activated protein kinase (MAPK) pathway due to the common BRAFV600E mutation, the expression of anti-inflammatory cytokines is induced, and cytotoxic T cells are partially inactivated [59]. This phenotype can be attributed to the effects of kinase inhibitors, such as BRAF inhibitors and MEK inhibitors, which have been reported to modulate the tumor microenvironment by increasing tumor antigen expression, promoting tumor-infiltrating T lymphocytes, and suppressing the expression of immunosuppressive cytokines [60, 61, 62]. Encouraging response rates were reported in a phase 1b clinical trial evaluating the combination of vemurafenib (a BRAF inhibitor) or cobimetinib (a MEK inhibitor) with atezolizumab in patients with $BRAF^{v600}$-mutated metastatic melanoma [63]. Similarly, the inhibition of EGFR has been shown to affect the tumor immune microenvironment [64], and an increase in tumor-infiltrating lymphocytes (TILs) has been observed in tumor tissue samples from EGFR mutated-positive NSCLC patients previously treated with EGFR-TKI [65]. Furthermore, VEGF-A, a proangiogenic molecule produced by the tumors, plays a pivotal role in the development of an immunosuppressive microenvironment. Voron et al. suggested that VEGF-A produced in the tumor microenvironment enhances the expression of PD-1 and other inhibitory checkpoints associated with CD8+ T cell exhaustion, an effect that can be reversed by anti-angiogenic drugs targeting VEGF-A–VEGFR [66].

Consequently, the combination of VEGF inhibitors and CPIs might bring a sense of expectancy in the synergistic antitumor activity, and several clinical trials have evaluated this therapeutic approach using PD-1/PD-L1 inhibitors in combination with VEGF or VEGFR targeted drugs. In patients with previously untreated advanced clear-

cell renal-cell carcinoma, the combination of pembrolizumab or avelumab with axitinib, an oral VEGFR-1/2/3 inhibitor, demonstrated significant PFS prolongation compared to the standard therapy of sunitinib monotherapy and thus have approved by health authorities and is now recognized as one of the standard therapies [67, 68].

As mentioned earlier, the combination of PD-1/PD-L1 inhibitors and diverse anticancer drugs is expected to enhance the antitumor efficacy. Certain combination therapies have become the standard therapy, yielding substantial benefits for patients. However, caution should also be exercised when introducing combination therapy involving different modes of action, as it may introduce new safety risks that are not observed in monotherapy. A comprehensive assessment of the clinically significant safety risks associated with PD-1/PD-L1 inhibitor-based combination therapy compared with monotherapy has not yet been fully conducted.

In this study, we performed a meta-analysis to assess the incidence of organ-specific irAEs of special interest for CPIs and common AEs for PD-1/PD-L1 inhibitors in combination therapy with anticancer drugs compared to PD-1/PD-L1 monotherapy. We also analyzed how the incidence of AEs differed based on the mode of action of concomitant anticancer drugs, utilizing available data from RCTs.

Regarding treatment with PD-1/PD-L1 inhibitors, the incidence of organ-specific serious/non-serious irAEs of interest was rare, as expected based on previous reports [69, 70]. When compared with PD-1/PD-L1 inhibitor monotherapy, there was no significant increase in the incidence of organ-specific irAEs, except for serious colitis, observed in combination therapy. The gastrointestinal tract, including the large intestine, is a complex barrier in the human. It plays a crucial role in defending against pathogens, while regulating immune tolerance to intestinal microflora and food. CPI-induced gastrointestinal AEs tend to occur early, typically within one month of treatment initiation [71, 72]. The proposed mechanisms for CPI-induced colitis involve hyperactivation of effector T cells, infiltration of lymphocytes, and an increase in circulating memory T cells, leading to a proinflammatory state and the manifestation of autoimmune-type symptoms [73, 74]. Furthermore, studies have indicated a substantial increase in the expression of inflammatory cytokines such as IFN-γ and TNFα, which can induce cell death in the intestinal wall, among patients with CPIs-induced colitis [75].

Gastrointestinal and intestinal disorders, including enterocolitis/colitis are commonly reported AEs in patients treated with conventional chemotherapy. Patients receiving chemotherapy may experience severe infectious and noninfectious colitis. Infectious colitis is primarily caused by *Clostridium difficile* infection. Noninfectious enterocolitis

typically manifests as neutropenic enterocolitis (typhlitis) or ischemic enterocolitis. Neutropenic enterocolitis typically manifests one to two weeks after the initiation of myelosuppressive chemotherapy, corresponding to the nadir of neutrophil count. It has been commonly reported that various DNA synthesis inhibitors, such as cisplatin, cytosine arabinoside, gemcitabine, vincristine, doxorubicin, gemcitabine, cyclophosphamide, and 5-FU have been implicated. Ischemic colitis is a rare complication of cancer chemotherapy. Initially, few cases were reported in patients treated with docetaxel and carboplatin-paclitaxel regimens. It is characterized by the acute onset of abdominal pain with or without neutropenia, fever and diarrhea [76]. The intestinal microflora is also known to undergo changes following chemotherapy, as well as CPI treatment, and has been associated with inflammatory bowel diseases such as ulcerative colitis, infective colitis as well as experimental models of colitis [77].

Subgroup analyses based on the mode of action of concomitant anticancer drugs revealed a statistically significant increase in the incidence of serious colitis when PD-1/PD-L1 inhibitors were combined with DNA synthesis inhibitors compared with PD-1/PD-L1 inhibitor monotherapy. Attention should be paid to the possibility that the gastrointestinal toxicities caused directly or indirectly by myelosuppressive DNA synthesis inhibitors may overlap with the disruption of immune homeostasis caused by PD-1/PD-L1 inhibitors.

Regarding common AEs associated with PD-1/PD-L1 inhibitor monotherapy, the following events were significantly increased in the PD-1/PD-L1 inhibitor-based combination therapy group compared to the PD-1/PD-L1 inhibitor monotherapy group: serious pyrexia/fever, and eight non-serious events including pyrexia/fever, fatigue, nausea, decreased appetite, vomiting, diarrhea, dyspnea, and rash. These events are well-recognized side effects of most anticancer treatments, irrespective of their mode of actions [78, 79]. Fever is an important indicator and is often the only sign or symptom of infection in patients with chemotherapy-induced neutropenia. Gastrointestinal toxicities, such as decreased appetite, vomiting, nausea, and diarrhea, are AEs that occur during the course of anticancer treatment. The pathophysiology underlying gastrointestinal syndromes, including fever, is complex and likely results from various mechanisms, including mucosal tissue damage and changes in the available surface area of the epithelium for digestion and absorption. Bacterial overgrowth has also been identified as a significant cause of clinical diarrhea, which increases the risk of opportunistic infections [77].

Cutaneous AEs are among the most prevalent irAEs observed with both PD-1/PD-L1 and CTLA-4 inhibitors [80]. Several studies have indicated that dermatological toxicity

occurs soon after treatment initiation [81].

Subgroup analyses based on the mode of action of concomitant anticancer drugs revealed a statistically significant RR for the incidence of rash when PD-1/PD-L1 inhibitors were combined with kinase inhibitors compared with PD-1/PD-L1 inhibitor monotherapy. Owing to the significant role of EGFR signaling in the skin, dermatological AEs have frequently been associated with EGFR tyrosine kinase inhibitors. EGFR is expressed in the epidermal cells, outer root sheath cells, and basal cells of sebaceous and sweat glands of normal skin tissue, and contributes to epidermal turnover. Inhibitors of EGFR phosphorylation in epidermal cells hinder normal keratinocyte growth and migration and induce apoptosis. Subsequently, the release of chemoattractants from the inflammatory cells recruits leukocytes, leading to an inflammatory response in the skin as a secondary event [82, 83]. It is also known that BRAF inhibitors and other multikinase inhibitors frequently cause hand-foot syndrome and skin disorders, including rash, although the detailed mechanism remains unclear [84]. Reports have shown that cutaneous toxicities associated with targeted therapies predominantly involve EGFR inhibitors and other multi-kinase inhibitors, thereby compromising the quality of life (QoL) of patients treated with targeted therapy compared to chemotherapy [85].

Current evidence supports the overlap of immune-related mechanisms between rash and skin disorders caused by PD-1/PD-L1 inhibitors and kinase inhibitors.

In summary, most events that exhibited a statistically significant increase in the combination therapy group compared with the monotherapy group were well recognized for both anticancer chemotherapies and kinase inhibitors, suggesting that the established management strategies employed for each monotherapy can be applied.

The strength of this systematic review and meta-analysis lies in its assessment of the frequencies of clinically significant AEs in PD-1/PD-L1 inhibitors combined with anticancer drugs compared to PD-1/PD-L1 inhibitor monotherapy based solely on RCTs, which are considered the highest-quality clinical trials. As a result, the heterogeneity among most trial results was low to moderate.

However, the following limitation should be considered in this meta-analysis: First, AEs classified as organ-specific irAEs may encompass events arising from factors other than CPIs and concomitant anticancer treatment (e.g., primary disease, infection, and continued toxicity of prior therapy). Second, unmeasured confounding factors, as well as confounding factors related to tumor type, treatment line, presence or absence of metastatic diseases, or target indication may exist.

4. Overall Discussion

We conducted systematic reviews and meta-analyses to examine the efficacy (Research 1) and safety (Research 2) of PD-1/PD-L1 inhibitors in combination with other anticancer drugs compared to PD-1/PD-L1 inhibitor monotherapy. Our aim was to enhance our understanding of the benefit-risk profile of these emerging anticancer treatments. For the primary meta-analysis in each study, we utilized data from 16 randomized or non-randomized trials, encompassing 3793 patients, to evaluate the anti-tumor response rate (ORR). Additionally, we utilized data from 16 randomized controlled trials, including 4232 patients, to evaluate the incidence of organ-specific irAEs and common AEs associated with PD-1/PD-L1 inhibitors. All of these patients received either PD-1/PD-L1 inhibitor monotherapy or PD-1/PD-L1 inhibitor-based combination therapy.

Our study is notable for comparing the efficacy and safety between PD-1/PD-L1 inhibitor-based combination therapy and PD-1/PD-L1 inhibitor monotherapy, with a specific focus on the mode of action of concomitant anticancer drugs. Previous meta-analyses assessed the antitumor efficacy and/or risk of irAEs in patients treated with any CPI (including ipilimumab), CPI-CPI combination or CPI-based anticancer therapy, compared to standard of care or control treatments, regardless of the mode of action [86, 87] In contrast to previous studies, we observed an improved ORR with the combination of PD-1/PD-L1 inhibitors and DNA synthesis inhibitors or tubulin inhibitors compared to PD-1/PD-L1 inhibitor monotherapy. Additionally, we identified an increased risk of serious colitis with PD-1/PD-L1 inhibitors and DNA synthesis inhibitors compared to PD-1/PD-L1 inhibitor monotherapy. These findings are likely owing to our access to more comprehensive response data and AE data obtained from ClinicalTrials.gov and publications.

Our findings carry significant implications for healthcare providers including clinicians and pharmacists, scientists, professionals in regulatory and industry fields across various specialties. The impressive advancements made in recent years regarding the scientific understanding of the interaction between tumor and immune system have laid the groundwork for the rational development of drugs, therapeutic strategies, and patient stratification in solid tumors. While anticancer agents can enhance the immunogenicity of tumor cells through antigenicity and adjuvanticity [88], these mechanisms have predominantly been established in preclinical or translational research. Our results provide clinical evidence supporting the use of combination therapy involving PD-1/PD-L1 inhibitors and chemotherapies categorized as ICD inducers, which can augment tumor response and benefit patients with solid tumors.

This would encourage investigators, pharmaceutical companies, and health authorities to focus on the development of such combination strategies.

Furthermore, as the utilization of PD-1/PD-L1 inhibitors in combination with other anticancer drugs continues to expand, non-oncology specialists will increasingly be called upon to manage the infrequent but clinically significant organ specific irAEs, as well as the more prevalent common AEs associated with immune activation. In addition to clinically significant AEs such as pneumonitis and myelosuppression, which should be considered as potential risks in anticancer therapies, our study highlights the importance of managing serious colitis when patients are treated with a combination of PD-1/PD-L1 inhibitors and DNA synthesis inhibitors. A multidisciplinary clinical approach will enable better assessment of the benefits and risks for patients, considering the anticipated efficacy and toxicity associated with each component of the combination therapy.

5. Conclusion

This study demonstrated that the combination of PD-1/PD-L1 inhibitors with DNA synthesis inhibitors or microtubule inhibitors significantly enhanced the ORR in comparison to PD-1/PD-L1 inhibitor monotherapy. Additionally, it revealed that the combination therapy was associated with an increased risk of clinically significant AEs, such as serious colitis. Overall, the combination of PD-1/PD-L1 inhibitors and other anticancer drugs is expected to confer significant benefits in terms of improved efficacy compared to PD-1/PD-L1 inhibitor monotherapy. However, careful attention should be paid to the increased risk of certain clinically significant AEs. Therefore, close monitoring of AEs and considerable planning for their management and treatment are imperative when designing and implementing novel PD-1/PD-L1 inhibitor-based combination therapies.

6. References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249. doi: 10.3322/caac.21660.
2. Seebacher NA, Stacy AE, Porter GM, et al. Clinical development of targeted and immune based anticancer therapies. J Exp Clin Cancer Res. 2019;38(1):156. doi: 10.1186/s13046-019-1094-2.
3. Ribas A and Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350-1355. doi: 10.1126/science.aar4060.
4. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion. Nat Med. 2002;8(8):793-800. doi: 10.1038/nm730.
5. Chambers CA and Allison JP. Costimulatory regulation of T cell function. Curr Opin Cell Biol. 1999;11(2):203-210. doi: 10.1016/s0955-0674(99)80027-1.
6. Wing K, Onishi Y, Prieto-Martin P, et al. CTLA-4 control over Foxp3+ regulatory T cell function. Science. 2008;322(5899):271-275. doi: 10.1126/science.1160062.
7. Ott PA, Hodi FS, Kaufman HL, et al. Combination immunotherapy: a road map. J Immunother Cancer. 2017;5:16. doi: 10.1186/s40425-017-0218-5.
8. Chen DS and Mellman I. Elements of cancer immunity and the cancer–immune set point. Nature. 2017;541(7637):321-330. doi: 10.1038/nature21349.
9. Galluzzi L, Buqué A, Kepp O, et al. Immunogenic cell death in cancer and infectious disease. Nat Rev Immunol. 2017;17(2):97-111. doi: 10.1038/nri.2016.107.
10. Pfirschke C, Engblom C, Rickelt S, et al. Immunogenic chemotherapy sensitizes tumors to checkpoint blockade therapy. Immunity. 2016;44(2):343-354. doi: 10.1016/j.immuni.2015.11.024.
11. Galluzzi L, Senovilla L, Zitvogel L, et al. The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov. 2012;11(3):215-233. doi: 10.1038/nrd3626.
12. Galluzzi L, Humeau J, Buqué A, et al. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. Nat Rev Clin Oncol. 2020;17(12):725-741. doi: 10.1038/s41571-020-0413-z.
13. Shalapour S, Font-Burgada J, Di Caro G, et al. Immunosuppressive plasma cells impede T-cell-dependent immunogenic chemotherapy. Nature. 2015;521(7550):94-98. doi: 10.1038/nature14395.
14. Bruchard M, Mignot G, Derangère V, et al. Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and

promotes tumor growth. Nat Med. 2013;19(1):57-64. doi: 10.1038/nm.2999.
15. Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019;16(9):563-580. doi: 10.1038/s41571-019-0218-0.
16. Sterne JAC, Savovic´ J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:I4898. doi: 10.1136/bmj.l4898.
17. Wells GA, Shea B, O'Connell, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.
19. Ueno M, Ikeda M, Morizane C, et al. Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study. Lancet Gastroenterol Hepatol. 2019;4(8):611-621. doi: 10.1016/S2468-1253(19)30086-X.
20. Rizvi NA, Hellmann MD, Brahmer JR, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non–small-cell lung cancer. J Clin Oncol. 2016;34(25):2969-2979. doi: 10.1200/JCO.2016.66.9861.
21. Gettinger S, Rizvi NA, Chow LQ, et al. Nivolumab monotherapy for first-line treatment of advanced non–small-cell lung cancer. J Clin Oncol. 2016;34(25):2980-2987. doi: 10.1200/JCO.2016.66.9929.
22. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016;17(11):1497-1508. doi: 10.1016/S1470-2045(16)30498-3.
23. Bang YJ, Kang YK, Catenacci DV, et al. Pembrolizumab alone or in combination with chemotherapy as firstline therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: results from the phase II nonrandomized KEYNOTE-059 study. Gastric Cancer. 2019;22(4):828-837. doi: 10.1007/s10120-018-00909-5.
24. Zhang T, Harrison MR, O'Donnell PH, et al. A randomized Phase 2 trial of pembrolizumab versus pembrolizumab and acalabrutinib in patients with platinum-resistant metastatic urothelial cancer. Cancer. 2020;126(20):4485-4497. doi:

10.1002/cncr.33067.
25. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019;394(10212):1915-1928. doi: 10.1016/S0140-6736(19)32591-7.
26. Overman M, Javle M, Davis RE, et al. Randomized phase II study of the bruton tyrosine kinase inhibitor acalabrutinib, alone or with pembrolizumab in patients with advanced pancreatic cancer. Immunother Cancer. 2020;8(1):e000587. doi: 10.1136/jitc-2020-000587.
27. Shitara K, Van Cutsem EV, Bang YJ, 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: 10.1001/jamaoncol.2020.3370.
28. Levy BP, Giaccone G, Besse B, et al. Randomised phase 2 study of pembrolizumab plus CC-486 versus pembrolizumab plus placebo in patients with previously treated advanced non-small cell lung cancer Levy a BP. Eur J Cancer. 2019;108:120-128. doi: 10.1016/j.ejca.2018.11.028.
29. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;378(22):2078-2092. doi: 10.1056/NEJMoa1801005.
30. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. N Engl J Med. 2018;379(21):2040-2051. doi: 10.1056/NEJMoa1810865.
31. Rudin CM, Awad MM, Navarro A, 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: 10.1200/JCO.20.00793.
32. McDermott DF, Huseni MA, Atkins MB, et al. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. Nat Med. 2018;24(6):749-757. doi: 10.1038/s41591-018-0053-3.
33. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288-2301. doi: 10.1056/NEJMoa1716948.
34. West H, McCleod M, Hussein M, 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: 10.1016/S1470-2045(19)30167-6.

35. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379(22):2108-2121. doi: 10.1056/NEJMoa1809615.
36. Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21(1):44-59. doi: 10.1016/S1470-2045(19)30689-8.
37. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220-2229. doi: 10.1056/NEJMoa1809064.
38. Eng C, Kim TW, Bendell J, et al. Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2019;20(6):849-861. doi: 10.1016/S1470-2045(19)30027-0.
39. Galsky MD, Arija JÁA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395(10236):1547-1557. doi: 10.1016/S0140-6736(20)30230-0.
40. Emens LA, Esteva FJ, Beresford M, et al. Trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo in previously treated, HER2-positive advanced breast cancer (KATE2): a phase 2, multicentre, randomised, double-blind trial. Lancet Oncol. 2020;21(10):1283-1295. doi: 10.1016/S1470-2045(20)30465-4.
41. Yang JCH, Shepherd FA, Kim DW, 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: 10.1016/j.jtho.2019.02.001.
42. Paz-Ares L, Dvorkin MD, Chen Y, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (Caspian): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394(10212):1929-1939. doi: 10.1016/S0140-6736(19)32222-6.

43. Akbay EA, Koyama S, Carretero J, et al. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. Cancer Discov. 2013;3(12):1355-1363. doi: 10.1158/2159-8290.CD-13-0310.
44. Lee CK, Man J, Lord S, et al. Checkpoint inhibitors in metastatic EGFR-mutated non–small cell lung cancer—A meta-analysis. J Thorac Oncol. 2017;12(2):403-407. doi: 10.1016/j.jtho.2016.10.007.
45. Liu P, Zhao L, Pol J, et al. Crizotinib-induced immunogenic cell death in non-small cell lung cancer. Nat Commun. 2019;10(1):1486. doi: 10.1038/s41467-019-09415-3.
46. Bristol-Myers Squibb Pharma EEIG. Opdivo (nivolumab) [summary of product characteristics]. European Medicines Agency web site. https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo. Revised April 2020. Accessed November 26, 2022.
47. Merck Sharp & Dohme B.V. Keytruda (pembrolizumab) [summary of product characteristics]. European Medicines Agency web site. https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda. Revised March 2020. Accessed November 26, 2022.
48. Roche Registration GmbH. Tecentriq (atezolizumab) [summary of product characteristics]. European Medicines Agency web site. https://www.ema.europa.eu/en/medicines/human/EPAR/tecentriq. Revised April 2022. Accessed November 26, 2022.
49. Merck Europe B.V. Bavencio (avelumab) [summary of product characteristics]. European Medicines Agency web site. https://www.ema.europa.eu/en/medicines/human/EPAR/bavencio. Revised July 2020. Accessed November 26, 2022.
50. AstraZeneca AB. Imfinzi (durvalumab) [summary of product characteristics]. European Medicines Agency web site. https://www.ema.europa.eu/en/medicines/human/EPAR/imfinzi. Authorized September 2018. Accessed November 26, 2022.
51. Nayak L, Molinaro AM, Peters K, et al. Randomized phase II and biomarker study of pembrolizumab plus bevacizumab versus pembrolizumab alone for patients with recurrent glioblastoma. Clin Cancer Res. 2021;27(4):1048-1057. doi: 10.1158/1078-0432.CCR-20-2500.
52. Taylor MH, Betts CB, Maloney L, et al. Safety and efficacy of pembrolizumab in combination with acalabrutinib in advanced head and neck squamous cell carcinoma: Phase 2 proof-of-concept study. Clin Cancer Res. 2022;28(5):903-914.

doi: 10.1158/1078-0432.CCR-21-2547.
53. Powles T, Csőszi T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(7):931-945. doi: 10.1016/S1470-2045(21)00152-2.
54. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18(1):31-41. doi: 10.1016/S1470-2045(16)30624-6.
55. Shah MA, Cunningham D, Metges JP, et al. Randomized, open-label, phase 2 study of andecaliximab plus nivolumab versus nivolumab alone in advanced gastric cancer identifies biomarkers associated with survival. J Immunother Cancer. 2021;9(12):e003580. doi: 10.1136/jitc-2021-003580.
56. Schröder C, Lawrance M, Li C, et al. Building external control arms from patient-level electronic health record data to replicate the randomized IMblaze370 control arm in metastatic colorectal cancer. JCO Clin Cancer Inform. 2021;5:450-458. doi: 10.1200/CCI.20.00149.
57. Pujade-Lauraine E, Fujiwara K, Ledermann JA, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. Lancet Oncol. 2021;22(7):1034-1046. doi: 10.1016/S1470-2045(21)00216-3.
58. Rosenberg JE Rosenberg, Park SH, Kozlov V, et al. Durvalumab plus olaparib in previously untreated, platinum-ineligible patients with metastatic urothelial carcinoma: A multicenter, randomized, phase II trial (BAYOU). J Clin Oncol. 2023;41(1):43-53. doi: 10.1200/JCO.22.00205.
59. Sumimoto H, Imabayashi F, Iwata T, et al. The BRAF-MAPK signaling pathway is essential for cancer-immune evasion in human melanoma cells. J Exp Med. 2006;203(7):1651-6. doi: 10.1084/jem.20051848.
60. Frederick DT, Piris A, Cogdill AP, et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. Clin Cancer Res. 2013; 19(5): 1225–1231. doi: 10.1158/1078-0432.CCR-12-1630.
61. Wilmott JS, Long GV, Howle JR, et al. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clin Cancer Res. 2012;18(5):1386-94. doi: 10.1158/1078-0432.CCR-11-2479.

62. Vella LJ, Pasam A, Dimopoulos N, et al. MEK inhibition, alone or in combination with BRAF inhibition, affects multiple functions of isolated normal human lymphocytes and dendritic cells. Cancer Immunol Res. 2014;2(4):351-60. doi: 10.1158/2326-6066.CIR-13-0181.
63. Sullivan RJ, Hamid O, Gonzalez R, et al. Atezolizumab plus cobimetinib and vemurafenib in BRAF-mutated melanoma patients. Nat Med. 2019;25(6):929-935. doi: 10.1038/s41591-019-0474-7.
64. Brea EJ, Oh CY, Manchado E, et al. Kinase regulation of human MHC Class I molecule expression on cancer cells. Cancer Immunol Res. 2016;4(11):936-947. doi: 10.1158/2326-6066.CIR-16-0177.
65. Isomoto K, Haratani K, Hayashi H, et al. Impact of EGFR-TKI treatment on the tumor immune microenvironment in EGFR mutation-positive non-small cell lung cancer. Clin Cancer Res. 2020;26(8):2037-2046. doi: 10.1158/1078-0432.CCR-19-2027.
66. Voron T, Colussi O, Marcheteau E, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. J Exp Med. 2015;212(2):139-48. doi: 10.1084/jem.20140559.
67. Rini B, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma N Engl J Med. 2019;380(12):1116-1127. doi: 10.1056/NEJMoa1816714.
68. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380(12):1103-1115. doi: 10.1056/NEJMoa1816047.
69. Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ. 2018;360:k793. doi: 10.1136/bmj.k793.
70. Raschi E, Gatti M, Gelsomino F, et al. Lessons to be learnt from real-world studies on immune-related adverse events with checkpoint inhibitors: A clinical perspective from pharmacovigilance. Target Oncol. 2020;15(4):449-466. doi: 10.1007/s11523-020-00738-6.
71. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012;30(21):2691-7. doi: 10.1200/JCO.2012.41.6750.
72. Sznol M, Ferrucci PF, Hogg D, et al. Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. J Clin Oncol. 2017;35(34):3815-3822. doi: 10.1200/JCO.2016.72.1167.

73. Dougan M. Checkpoint blockade toxicity and immune homeostasis in the gastrointestinal tract. Front Immunol. 2017;8:1547. doi: 10.3389/fimmu.2017.01547.
74. Tang L, Wang J, Lin N, et al. Immune checkpoint inhibitor-associated colitis: From mechanism to management. Front Immunol. 2021;12:800879. doi: 10.3389/fimmu.2021.800879.
75. Luoma AM, Suo S, Williams HL, et al. Molecular pathways of colon inflammation induced by cancer immunotherapy. Cell. 2020;182(3):655-671.e22. doi: 10.1016/j.cell.2020.06.001.
76. Khunger A and Estfan B. Gastrointestinal complications of chemotherapy. Handbook of Cancer Treatment-Related Toxicities. 2022; Chapter 6, 29-50.
77. Gibson RJ and Keefe DMK. Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies. Support Care Cancer. 2006;14(9):890-900. doi: 10.1007/s00520-006-0040-y.
78. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol. 2018;36(14):1443-1453. doi: 10.1200/JCO.2017.77.6211.
79. Kuderer NM, Desai A, Lustberg MB, et al. Mitigating acute chemotherapy-associated adverse events in patients with cancer. Nat Rev Clin Oncol. 2022;19(11):681-697. doi: 10.1038/s41571-022-00685-3.
80. Sibaud V. Dermatologic reactions to immune checkpoint inhibitors: Skin toxicities and immunotherapy. Am J Clin Dermatol. 2018;19(3):345-361. doi: 10.1007/s40257-017-0336-3.
81. 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: 10.1056/NEJMra1703481.
82. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer. 2006;6(10):803-12. doi: 10.1038/nrc1970.
83. Albanell J, Rojo F, Averbuch S, et al. Pharmacodynamic studies of the epidermal growth factor receptor inhibitor ZD1839 in skin from cancer patients: histopathologic and molecular consequences of receptor inhibition. J Clin Oncol. 2002;20(1):110-24. doi: 10.1200/JCO.2002.20.1.110.
84. Lacouture M and Sibaud V. Toxic side effects of targeted therapies and immunotherapies affecting the skin, oral mucosa, hair, and nails. Am J Clin Dermatol. 2018;19(Suppl 1):31-39. doi: 10.1007/s40257-018-0384-3.

85. Rosen AC, Case EC, Dusza SW, et al. Impact of dermatologic adverse events on quality of life in 283 cancer patients: a questionnaire study in a dermatology referral clinic. Am J Clin Dermatol. 2013;14(4):327-33. doi: 10.1007/s40257-013-0021-0.
86. Ma X, Zhang Y, Wang S, et al. Immune checkpoint inhibitor (ICI) combination therapy compared to monotherapy in advanced solid cancer: A systematic review. J Cancer. 2021;12(5): 1318-1333. doi: 10.7150/jca.49174.
87. Peng M, Li X, Lei G, et al. The efficacy and safety of immune checkpoint inhibitor combination therapy in lung cancer: a systematic review and meta-analysis. Onco Targets Ther. 2018;11:7369-7383. doi: 10.2147/OTT.S177318.
88. Galon J and Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov. 2019;18(3):197-218. doi: 10.1038/s41573-018-0007-y.

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8. Appendix

Supplementary Table 1 Characteristics of eligible trials included in the analyses for Research 1

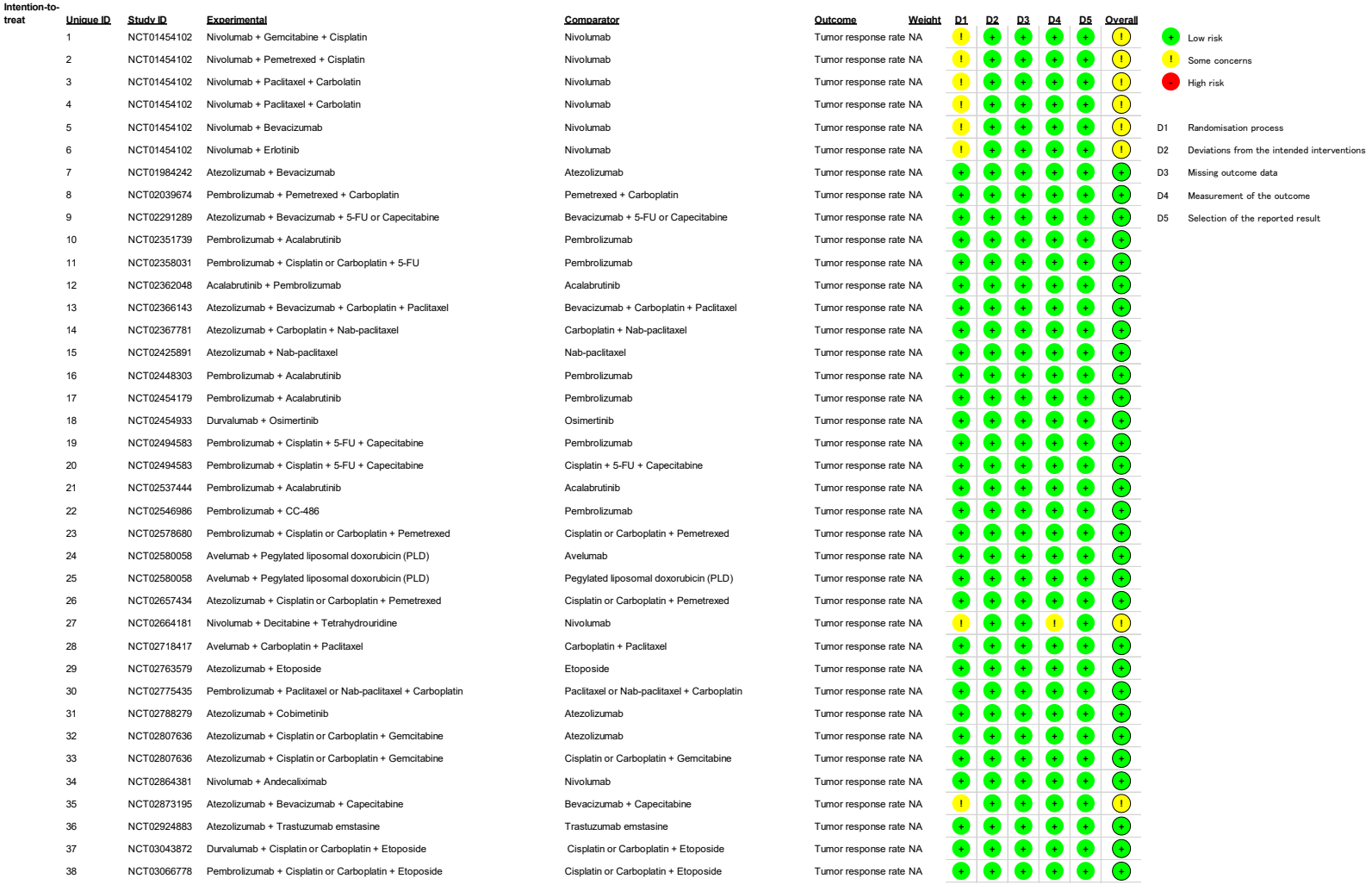
Study Identifier	Author	Phase	Randomized trial (Yes/No)	Tumor type	Response events per arm	Non-CPI MoA Types
JapicCTI-153098	Ueno et al. 2019	1	No	Biliary tract cancer	Nivo: 1/30 Nivo + cisplatin+ gemcitabine: 11/30	DNA synthesis inhibitor
NCT01454102	Rizvi et al. 2016 Gettinger et al. 2016	1	Yes	Non-small cell lung cancer	Nivo (Arm F): 12/52 Nivo + gemcitabine + cisplatin (Arm A):4/12 Nivo + pemetrexed + cisplatin (Arm B):7/15 Nivo + paclitaxel + carboplatin (Arm C10):7/15 Nivo + paclitaxel + carboplatin (Arm C5):7/14 Nivo + bevacizumab (Arm D):2/12 Nivo + erlotinib (Arm E):4/21	DNA synthesis inhibitor DNA synthesis inhibitor Tubulin inhibitor + DNA synthesis inhibitor Tubulin inhibitor + DNA synthesis inhibitor Angiogenesis inhibitor EGFR inhibitor
NCT01984242	McDermott et al. 2018	2	Yes	Renal cell carcinoma	Atezo: 25/103 Atezo + bevacizumab: 32/101	Angiogenesis inhibitor
NCT02039674	Langer et al. 2016	1/2	Yes	Non-small cell Lung cancer	Pemetrexed + carboplatin: 18/63 Pembro + pemetrexed + carboplatin: 33/60	DNA synthesis inhibitor
NCT02250326	NA	2	No	Non-small cell lung cancer	Nab-paclitaxel: 13/80 Druva + nab-paclitaxel: 22/79	Tubulin inhibitor
NCT02291289	NA	2	Yes	Colorectal cancer	Bevacizumab + 5-FU or capecitabine: 22/148 Atezo + bevacizumab + 5-FU or capecitabine: 49/297	Angiogenesis inhibitor DNA synthesis inhibitor
NCT02302339	NA	2	No	Melanoma	Glembatumumab vedotin: 7/62 Nivo or Pembro + glembatumumab vedotin: 4/28	ADC targeting cancer cells expressing transmembrane glycoprotein NMB (GPNMB).
NCT02335411	Bang et al. 2019	2	No	Gastric or gastroesophageal junction adenocarcinoma	Pembro: 8/31 Pembro + cisplatin + 5-FU + capecitabine: 15/25	DNA synthesis-inhibitor
NCT02336165	NA	2	No	Glioblastoma	Druva: 4/31 Durva + bevacizumab:3/33	Angiogenesis inhibitor

Study Identifier	Author	Phase	Randomized trial (Yes/No)	Tumor type	Response events per arm	Non-CPI MoA Types
NCT02351739	Zhang et al. 2020	2	Yes	Urothelial cancer	Pembro: 9/35 Pembro + acalabrutinib: 8/40	BTK inhibitor
NCT02358031	Burtness et al. 2019	3	Yes	Head and neck cancer	Pembro: 51/301 Pembro + cisplatin or carboplatin + 5-FU: 100/281	DNA synthesis inhibitor
NCT02362048	Overman et al. 2020	2	Yes	Pancreatic cancer	Acalabrutinib: 0/29 Acalabrutinib + pembro: 3/27	BTK inhibitor
NCT02366143	Socinski et al. 2018	3	Yes	Non-small cell lung cancer	Bevacizumab + carboplatin + paclitaxel: 159/331 Atezo + bevacizumab + carboplatin + paclitaxel: 224/353	Angiogenesis inhibitor DNA synthesis inhibitor Tubulin inhibitor
NCT02367781	West et al. 2019	3	Yes	Non-small cell lung cancer	Carboplatin + nab-paclitaxel: 72/226 Atezo + carboplatin +nab-paclitaxel: 220/447	DNA synthesis inhibitor Tubulin inhibitor
NCT02425891	Schmid et al. 2020 Schmid et al. 2018	3	Yes	Breast cancer	Nab-paclitaxel: 206/449 Atezo + nab-paclitaxel: 252/450	Tubulin inhibitor
NCT02448303	NA	2	Yes	Non-small cell lung cancer	Pembro: 4/31 Pembro + Acalabrutinib: 4/28	BTK inhibitor
NCT02454179	NA	2	Yes	Head and neck cancer	Pembro: 7/37 Pembro + Acalabrutinib: 5/30	BTK inhibitor
NCT02454933	Yang et al. 2019	3	Yes	Non-small cell lung cancer	Osimertinib: 12/15 Durva + Osimertinib: 9/14	EGFR inhibitor
NCT02494583	Shitara et al. 2020	3	Yes	Gastric adenocarcinoma	Pembro: 38/256 Pembro + cisplatin + 5-FU + capecitabine: 125/257 Placebo + cisplatin + 5-FU + capecitabine: 93/250	DNA synthesis inhibitor
NCT02537444	NA	2	Yes	Ovarian cancer	Acalabrutinib: 1/35 Acalabrutinib + Pembro: 3/33	BTK inhibitor
NCT02546986	Levy et al. 2018	2	Yes	Non-small cell lung cancer	Pembro: 7/49 Pembro + CC-486: 10/51	DNA synthesis inhibitor
NCT02578680	Gandhi et al.2018	2	Yes	Non-small cell lung cancer	Cisplatin or carboplatin + pemetrexed: 39/206 Pembro + cisplatin or carboplatin + pemetrexed: 195/410	DNA synthesis inhibitor
NCT02580058	NA	3	Yes	Ovarian cancer	Ave: 7/188 Pegylated liposomal doxorubicin (PLD): 8/190 Ave + PLD: 25/188	DNA synthesis inhibitor

Study Identifier	Author	Phase	Randomized trial (Yes/No)	Tumor type	Response events per arm	Non-CPI MoA Types
NCT02657434	NA	3	Yes	Non-small cell lung cancer	Cisplatin or carboplatin + pemetrexed: 107/286 Atezo + cisplatin or carboplatin + pemetrexed: 151/292	DNA synthesis inhibitor
NCT02664181	NA	2	Yes	Non-small cell lung cancer	Nivo: 1/5 Nivo + decitabine + Tetrahydrouridine: 2/8	DNA synthesis inhibitor DNA methyltransferase inhibitor
NCT02690948	NA	1/2	No	Basal cell skin cancer	Vismodegib: 2/7 Pembro + Vismodegib:4/9	Hedgehog inhibitor
NCT02718417	NA	3	Yes	Ovarian cancer	Carboplatin + paclitaxel: 102/335 Ave + carboplatin + paclitaxel:119/331	DNA synthesis inhibitor Tubulin inhibitor
NCT02763579	Horn et al. 2018	3	Yes	Non-small cell lung cancer	Etoposide: 130/202 Atezo + etoposide: 121/201	DNA synthesis inhibitor
NCT02775435	Paz-Ares et al. 2018	3	Yes	Non-small cell lung cancer	Paclitaxel or nab-paclitaxel + carboplatin: 108/281 Pembro + paclitaxel or nab-paclitaxel + carboplatin:161/278	Tubulin inhibitor DNA synthesis inhibitor
NCT02788279	Eng et al. 2019	3	Yes	Colorectal cancer	Atezo: 2/90 Atezo + Cobimetinib: 5/183	MEK inhibitor
NCT02807636	Galsky et al. 2020	3	Yes	Urothelial cancer	Atezo: 82/359 Atezo + cisplatin or carboplatin + gemcitabine: 212/447 Cisplatin or carboplatin + gemcitabine: 174/397	DNA synthesis inhibitor
NCT02864381	NA	2	Yes	Gastric or gastroesophageal junction adenocarcinoma	Nivo: 5/72 Nivo + Andecaliximab: 7/72	Anti MMP-9 monoclonal antibody
NCT02873195	NA	2	Yes	Colorectal cancer	Bevacizumab + capecitabine: 2/46 Atezo + bevacizumab + capecitabine: 7/82	Angiogenesis inhibitor DNA synthesis inhibitor
NCT02924883	Emens et al. 2020	2	Yes	Breast cancer	Trastuzumab emstasine: 30/69 Atezo + trastuzumab emstasine: 60/132	HER2 inhibitor
NCT03043872	Paz-Ares et al. 2019	3	Yes	Small-cell lung cancer	Cisplatin or carboplatin + etoposide : 155/269 Durva + cisplatin or carboplatin + etoposide: 182/268	DNA synthetase inhibitor

Study Identifier	Author	Phase	Randomized trial (Yes/No)	Tumor type	Response events per arm	Non-CPI MoA Types
NCT03066778	Rudin et al.2020	3	Yes	Small-cell Lung cancer	Cisplatin or carboplatin + etoposide: 139/225 Pembro + cisplatin or carboplatin + etoposide: 161/228	DNA synthesis inhibitor

NA, not applicable; MoA, mode of action; Nivo, nivolumab; Pembro, pembrolizumab; Atezo, atezolizumab; Ave, avelumab; Durva, Durvalumab; EGFR, epidermal growth factor receptor; BTK, Bruton's tyrosine kinase; MEK, mitogen-activated extracellular signal-regulated kinase; MMP-9, matrix metalloproteinase 9.



Supplementary Figure 1　Risk of bias in each randomized trial according to the Cochrane RoB 2.0 tool

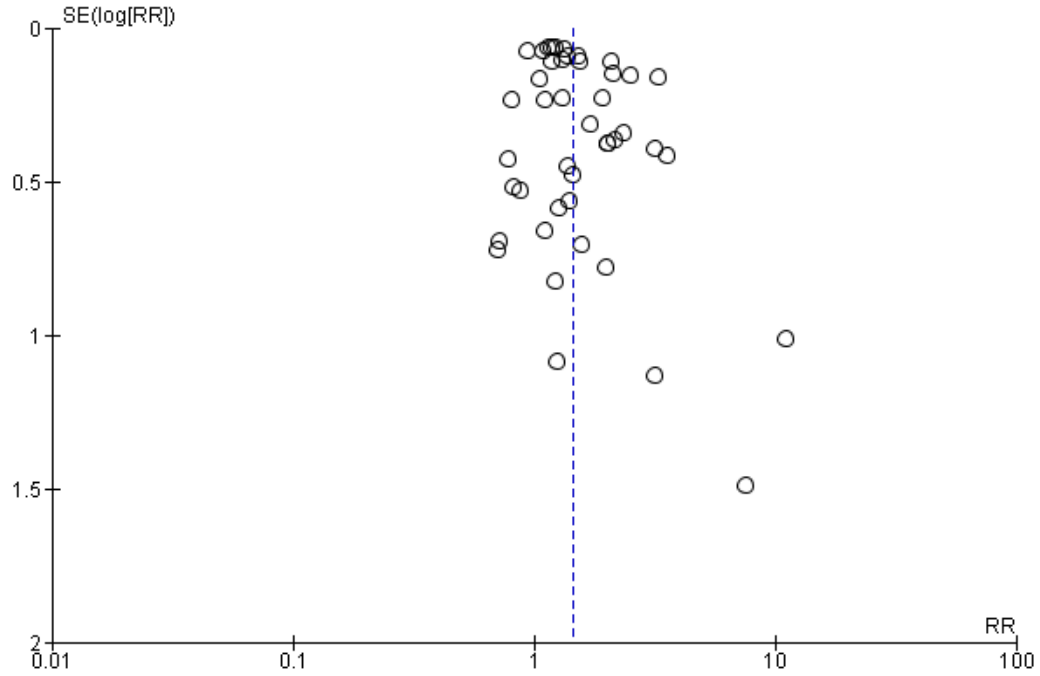
Supplementary Table 2 Newcastle-Ottawa Scale[a] Scoring of Non-randomized trials in the Meta-analysis

Study Identifier	Author	Study Type	Selection	Comparability	Outcome	Total Score (n/9)
JapicCTI-153098	Ueno et al. 2019 [14]	Cohort of unresectable or recurrent biliary tract cancer	***	*	***	7
NCT02250326	NA	Cohort of advanced non-small cell lung cancer	****	**	***	9
NCT02302339	NA	Cohort of unresectable Stage III or Stage IV melanoma	****	**	***	9
NCT02335411	Bang et al. 2019 [19]	Cohort of advanced gastric or GEJ adenocarcinoma	****	**	***	9
NCT02336165	NA	Cohort of glioblastoma	***	*	***	7
NCT02690948	NA	Cohort of unresectable or metastatic basal cell carcinoma	***	*	***	7

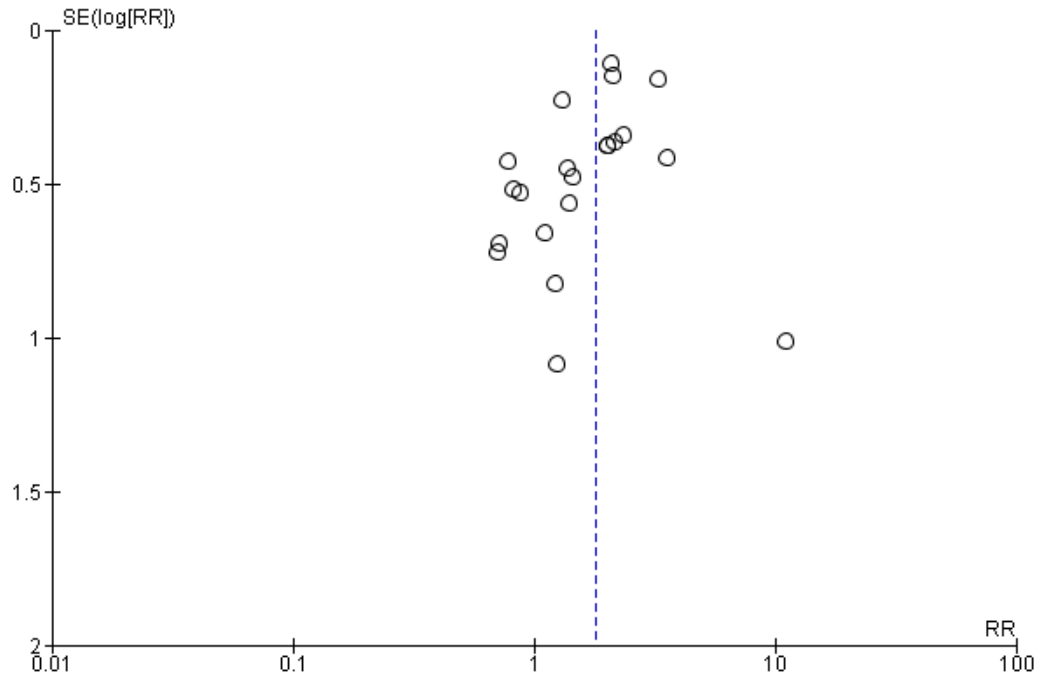
NA, not applicable; GEJ, gastroesophageal junction

a, Possible scores are 0–4 asterisks for selection, 0–2 asterisks for comparability, and 0–3 asterisks for outcome, regarding risk of bias, *with indicating a low score

****indicating the highest score.



Supplementary Figure 2-1 Funnel plot of studies included in the meta-analysis of ORR for all identified studies



Supplementary Figure 2-2 Funnel plot of studies included in the meta-analysis of ORR for all studies with PD-1/PD-L1 monotherapy arm

Supplementary Table 3　PRISMA Checklist for Research 1

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction, Line 20-51
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction, Line 52-54
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Search strategy, Line 1-21
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Search strategy, Line 23, 32, and 36, 37
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Search strategy, Line 22-40

Topic	No.	Item	Location where item is reported
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction and quality of evidence, Line 1-4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Data extraction and quality of evidence, Line 10-12
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Data extraction and quality of evidence, Line 4-7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Data extraction and quality of evidence, Line 8-13
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction and quality of evidence, Line 16-18

Topic	No.	Item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Statistical analysis, Line 8-12
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Statistical analysis, Line 2-6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Data extraction and quality of evidence, Line 6-7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Data extraction and quality of evidence, Line 16-18; Statistical analysis, Line 1-2, 10-13
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Data extraction and quality of evidence, Line 16-18; Statistical analysis, Line 1-2, 10-13
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Statistical analysis, Line 7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not Applicable

Topic	No.	Item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Data extraction and quality of evidence, Line 16-18; Statistical analysis, Line 12-13
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not Applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Study selection and characteristics, Line 1-4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Study selection and characteristics, Line 1-4
Study characteristics	17	Cite each included study and present its characteristics.	Study selection and characteristics, Line 3-29
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Quality assessment, Line 1-8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Benefit of PD-1/PD-L1 inhibitors and anticancer drugs for tumor response, Line 1-13
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Study selection and characteristics, Line 4-29

Topic	No.	Item	Location where item is reported
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Benefit of PD-1/PD-L1 inhibitors and anticancer drugs for tumor response, Line 1-13; Subgroup analyses, Line 1-13
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not Applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not Applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Quality assessment, Line 7-8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not Applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion, Line 1-46
	23b	Discuss any limitations of the evidence included in the review.	Discussion, Line 52-60
	23c	Discuss any limitations of the review processes used.	Discussion, Line 55-59
	23d	Discuss implications of the results for practice, policy, and future research.	Conclusion, Line 6-10
OTHER INFORMATION			

Topic	No.	Item	Location where item is reported
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Data extraction and quality of evidence, Line 20-22
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Data extraction and quality of evidence, Line 20-22
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not Applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding
Competing interests	26	Declare any competing interests of review authors.	Declaration of Conflicting Interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not Applicable

PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			

Topic	No.	Item	Reported?
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

Supplementary Table 4 Characteristics of eligible trials included in the analyses for Research 2

Study Identifier	Author	Phase	Tumor type	Treatment arms	MoA Types of combo drug	Incidence of SAEs	Incidence of Grade 3/4 AEs	Available incidence data per non-serious/serious AEs (Yes/No)
NCT01454102	Hellmann et al. 2017	1	NSCLC	Nivo Nivo + GEM + CDDP Nivo + pemetrexed + CDDP Nivo + paclitaxel + CBDCA Nivo + bevacizumab Nivo + erlotinib	 DNA synthesis inh. DNA synthesis inh. Tubulin inh., DNA synthesis inh. Angiogenesis inh. EGFR inh.	23/52 4/12 10/15 17/29 3/12 11/21	-	Yes
NCT01984242	McDermott et al. 2018	2	Renal cell cancer	Atezo Atezo + bevacizumab	 Angiogenesis inh.	37/103 49/101	41/103 64/101	Yes
NCT02337491	Nayak et al. 2021	2	Glioblastoma	Pembrolizumab Pembrolizumab + bevacizumab	 Angiogenesis inh.	22/50 10/30	-	Yes
NCT02351739	Zhang et al. 2020	2	Urothelial cancer	Pembro Pembro + acalabrutinib	 Kinase inh.	15/35 23/40	19/34 30/39	Yes
NCT02358031	Burtness et al. 2019	3	Head and neck cancer	Pembro Pembro + CDDP/CBCDA + 5-FU	 DNA synthesis inh.	123/300 165/276	-	Yes
NCT02448303	NA	2	NSCLC	Pembro Pembro + acalabrutinib	 Kinase inh.	12/33 18/35	-	Yes
NCT02454179	Taylor et al. 2022	2	Head and neck cancer	Pembro Pembro + acalabrutinib	 Kinase inh.	12/39 25/37	-	Yes
NCT02494583	Shitara et al. 2020	3	Gastric adenocarcinoma	Pembro Pembro + CDDP + 5-FU + CAP	 DNA synthesis inh.	93/254 122/250	-	Yes
NCT02546986	Levy et al. 2018	2	NSCLC	Pembro Pembro + CC-486	 DNA synthesis inh.	20/49 23/51	27/49 40/51	Yes
NCT02574078	NA	1/2	NSCLC	Nivo Nivo + bevacizumab Nivo Nivo + pemetrexed	 Angiogenesis inh. DNA synthesis inh.	6/13 1/6 15/35 16/34	-	Yes
NCT02580058	Pujade-Lauraine et al. 2021	3	Ovarian cancer	Ave Avelumab + PLD	 DNA synthesis inh.	71/187 75/182	-	Yes
NCT02750514	NA	2	Advanced cancer	Nivolumab Nivolumab + Dasatinib	 Kinase inh.	28/49 7/12	-	Yes
NCT02788279	Eng et al. 2019 Schröder et al. 2021	3	Colorectal cancer	Atezo Atezo + Cobimetinib	 Kinase inh.	15/90 71/183	28/90 109/179	Yes
NCT02807636	Galsky et al. 2020	3	Urothelial cancer	Atezo Atezo + CDDP/CBCDA + GEM	 DNA synthesis inh.	152/354 234/453	148/354 383/453	No
NCT02853305	Powles et al. 2021	3	Urothelial cancer	Pembro Pembro + CDDP/CBCDA + GEM	 DNA synthesis inh.	145/302 188/349	-	Yes

Study Identifier	Author	Phase	Tumor type	Treatment arms	MoA Types of combo drug	Incidence of SAEs	Incidence of Grade 3/4 AEs	Available incidence data per non-serious/serious AEs (Yes/No)
NCT02864381	Shah et al 2021	2	Gastric or gastroesophageal junction adenocarcinoma	Nivo Nivo + Andecaliximab	Anti MMP-9 mAb	38/70 42/71	-	Yes
NCT03459846	Rosenberg et al. 2022	2	Bladder cancer	Durva Durva + Olaparib	PARP inh.	- -	24/76 33/76	No
NCT03829332	NA	3	NSCLC	Pembro Pembro + Lenvatinib	Kinase inh.	106/312 175/309	-	Yes

NA, not applicable; MoA, mode of action; NSCLC, non-small cell lung cancer; Nivo, nivolumab; Pembro, pembrolizumab; Atezo, atezolizumab; Ave, avelumab; Durva, Durvalumab; GEM, gemcitabine, CDDP, cisplatin; CBDCA, carboplatin; EGFR, epidermal growth factor receptor; BTK, Bruton's tyrosine kinase; MEK, mitogen-activated extracellular signal-regulated kinase; MMP-9, matrix metalloproteinase 9; ORR, objective response rate; OS, overall survival; PFS, progressive free survival; SAE, severe adverse event; AE adverse event.

Supplementary Table 5 PRISMA Checklist for Research 2

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1 Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction, Line 22-34
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction, Line 35-39
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Study selection, Line 1-18
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Search strategy Line 5-20
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Search strategy, 9-20
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction, Line 1-10
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Data extraction, Line 15-18
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Data extraction, Line 10-12
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Data extraction, Line 12-15

Topic	No.	Item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction, Line 18-20
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Statistical analysis, Line 10-12
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Data extraction, Line 10-15
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Data extraction, Line 10-12
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Data extraction, Line 18-20; Statistical analysis, Line 1-4, 13-14
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Data extraction, Line 18-20; Statistical analysis, Line 1-4, 13-14
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Statistical analysis, Line 1-4, 8-9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not Applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Data extraction, Line 18-20; Statistical analysis, Line 13-14
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not Applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Study characteristics, Line 1; Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Study characteristics, Line 1; Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Study characteristics, Line 1-10; Table 1; Suppl Table A3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Quality assessment, 1-5; Suppl Figure A1, A2

Topic	No.	Item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Study characteristics, Line 1-10; Table 1; Suppl Table A3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Organ-specific immune-related adverse events, 1-11; Adverse events commonly reported in the PD-1/PD-L1 monotherapies, 1-18; Overall safety endpoints, 1-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Organ-specific immune-related adverse events, 1-11; Adverse events commonly reported in the PD-1/PD-L1 monotherapies, 1-18; Overall safety endpoints, 1-15
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not Applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not Applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Quality assessment, Line 1-7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not Applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion Line 1-89
	23b	Discuss any limitations of the evidence included in the review.	Discussion Line 99-104
	23c	Discuss any limitations of the review processes used.	Discussion Line 99-104
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion Line 89-93
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Search strategy Line 1-4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Search strategy Line 1-4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not Applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding, Line 1

Topic	No.	Item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	Declaration of conflicting interests, Line 1-3
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not Applicable

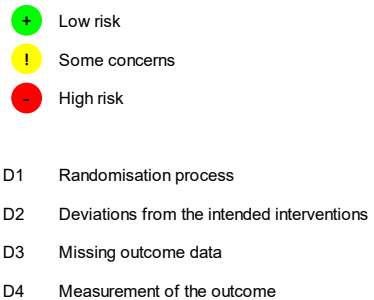
PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

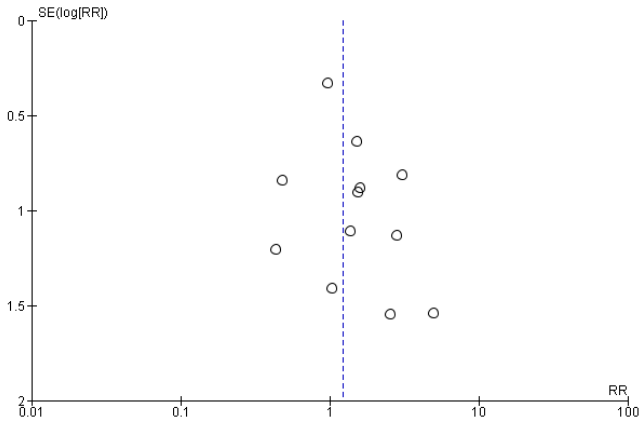
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

Intention-to-treat

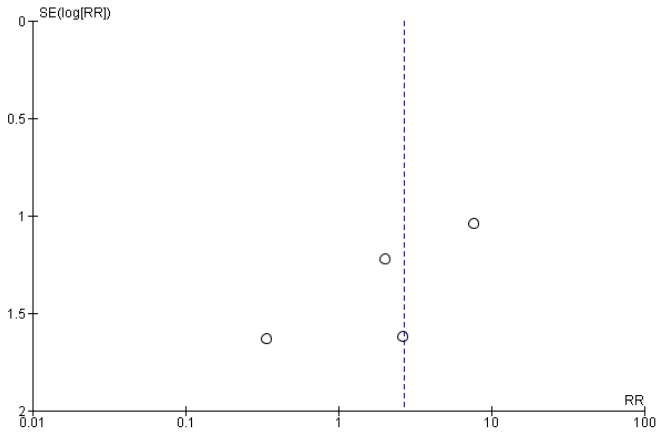
Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
1	NCT01454102	Nivolumab + Gemcitabine + Cisplatin	Nivolumab	Adverse event incidence	NA	!	+	+	+	+	!
2	NCT01454102	Nivolumab + Pemetrexed + Cisplatin	Nivolumab	Adverse event incidence	NA	!	+	+	+	+	!
3	NCT01454102	Nivolumab + Paclitaxel + Carbolatin	Nivolumab	Adverse event incidence	NA	!	+	+	+	+	!
4	NCT01454102	Nivolumab + Paclitaxel + Carbolatin	Nivolumab	Adverse event incidence	NA	!	+	+	+	+	!
5	NCT01454102	Nivolumab + Bevacizumab	Nivolumab	Adverse event incidence	NA	!	+	+	+	+	!
6	NCT01454102	Nivolumab + Erlotinib	Nivolumab	Adverse event incidence	NA	!	+	+	+	+	!
7	NCT01984242	Atezolizumab + Bevacizumab	Atezolizumab	Adverse event incidence	NA	+	+	+	+	+	+
8	NCT02337491	Pembrolizumab + bevacizumab	Pembrolizumab	Adverse event incidence	NA	+	+	+	+	+	+
9	NCT02351739	Pembrolizumab + Acalabrutinib	Pembrolizumab	Adverse event incidence	NA	+	+	+	+	+	+
10	NCT02358031	Pembrolizumab + Cisplatin or Carboplatin + 5-FU	Pembrolizumab	Adverse event incidence	NA	+	+	+	+	+	+
11	NCT02448303	Pembrolizumab + Acalabrutinib	Pembrolizumab	Adverse event incidence	NA	+	+	+	+	+	+
12	NCT02454179	Pembrolizumab + Acalabrutinib	Pembrolizumab	Adverse event incidence	NA	+	+	+	+	+	+
13	NCT02494583	Pembrolizumab + Cisplatin + 5-FU + Capecitabine	Pembrolizumab	Adverse event incidence	NA	+	+	+	+	+	+
14	NCT02546986	Pembrolizumab + CC-486	Pembrolizumab	Adverse event incidence	NA	+	+	+	+	+	+
15	NCT02574078	Nivolumab + bevacizumab	Nivolumab	Adverse event incidence	NA	+	+	+	+	+	+
16	NCT02574078	Nivolumab + pemetrexed	Nivolumab	Adverse event incidence	NA	+	+	+	+	+	+
17	NCT02580058	Avelumab + Pegylated liposomal doxorubicin (PLD)	Avelumab	Adverse event incidence	NA	+	+	+	+	+	+
18	NCT02750514	Nivolumab + Dasatinib	Nivolumab	Adverse event incidence	NA	+	+	+	+	+	+
19	NCT02788279	Atezolizumab + Cobimetinib	Atezolizumab	Adverse event incidence	NA	+	+	+	+	+	+
20	NCT02807636	Atezolizumab + Cisplatin or Carboplatin + Gemcitabine	Atezolizumab	Adverse event incidence	NA	+	+	+	+	+	+
21	NCT02853305	Pembrolizumab + CDDP/CBCDA + GEM	Pembrolizumab	Adverse event incidence	NA	+	+	+	+	+	+
22	NCT02864381	Nivolumab + Andecaliximab	Nivolumab	Adverse event incidence	NA	+	+	+	+	+	+
23	NCT03459846	Durvalumab + Olaparib	Duruvalumab	Adverse event incidence	NA	+	+	+	+	+	+
24	NCT03829332	Pembrolizumab + Lenvatinib	Pembrolizumab	Adverse event incidence	NA	+	+	+	+	+	+



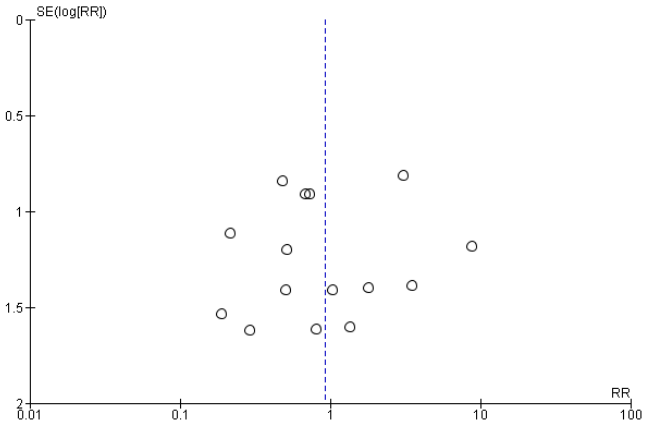
Supplementary Figure 3 Risk of bias in each randomized trial according to the Cochrane RoB 2.0 tool



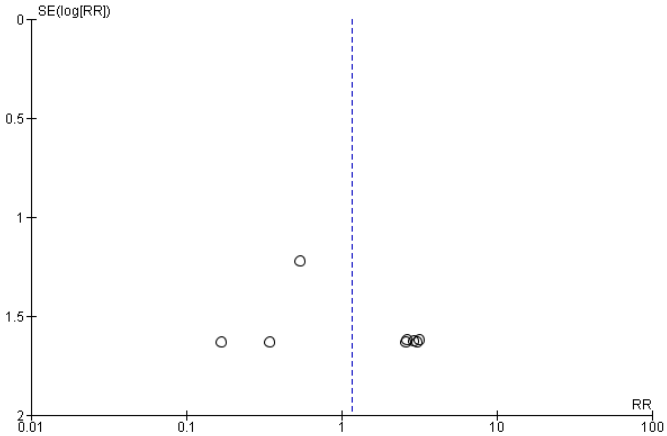
Serious pneumonia



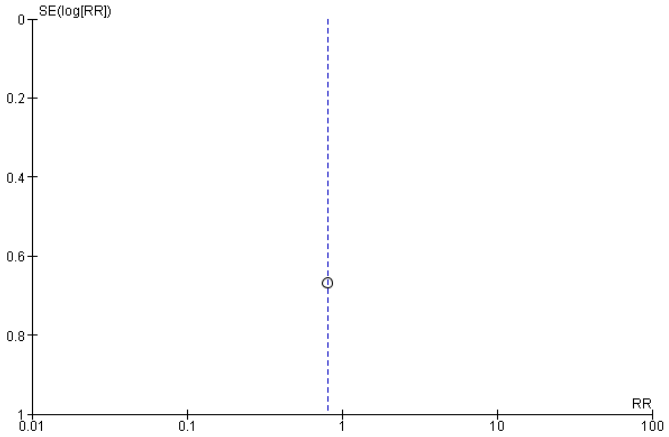
Serious immune-mediated hepatitis



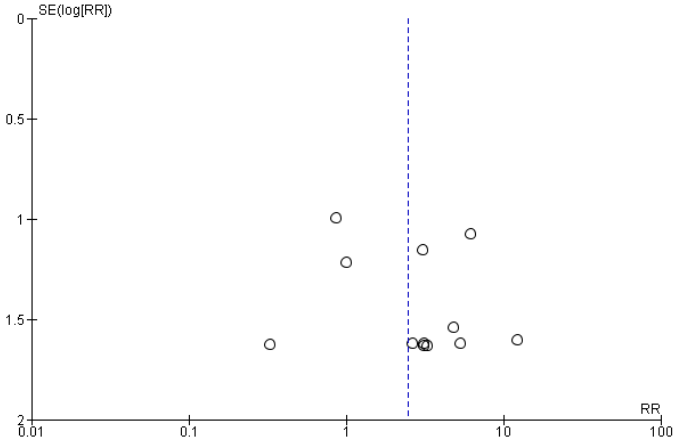
Serious pneumonitis



Serious autoimmune hepatitis

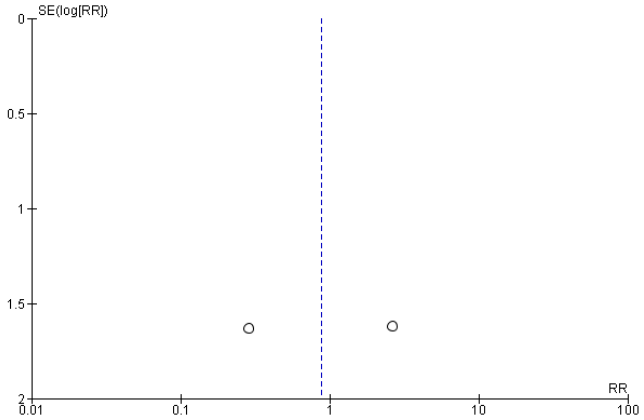


Serious immune-related lung disease

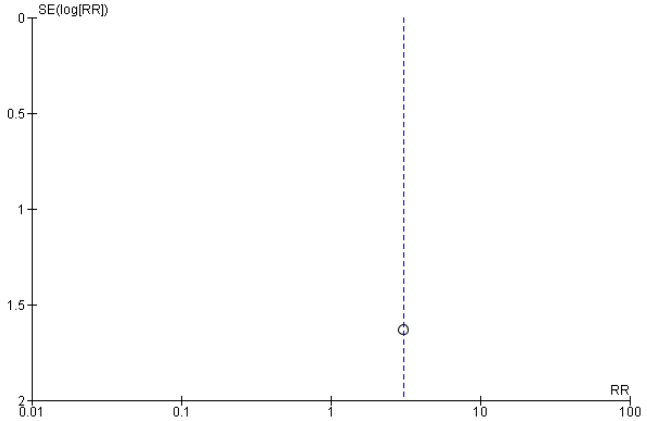


Serious colitis

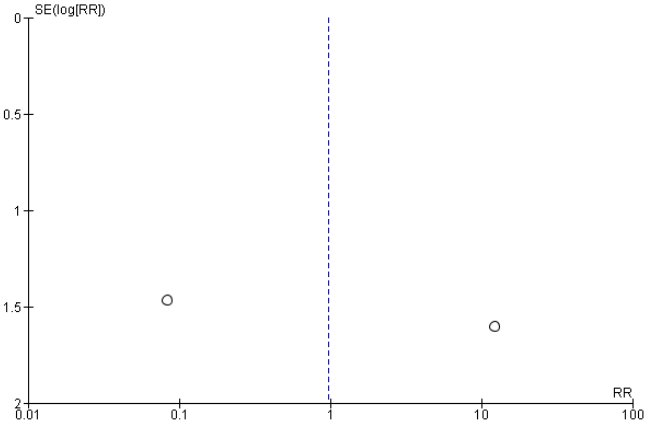
Supplementary Figure 4 Funnel plot of studies included in the meta-analysis



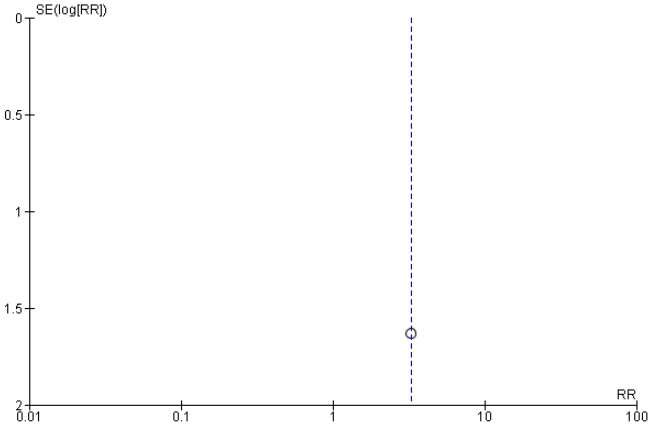
Serious autoimmune colitis



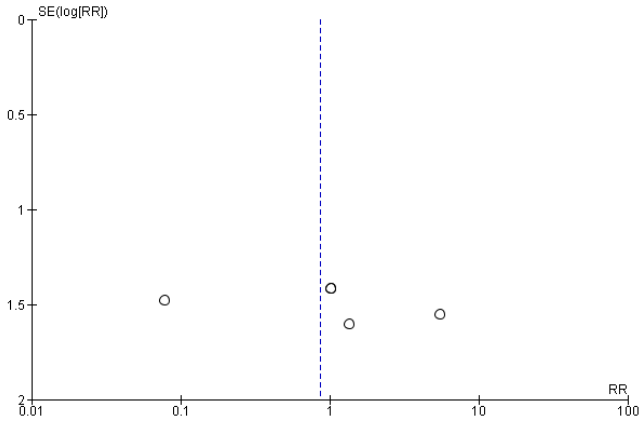
Serious immune-mediated myocarditis



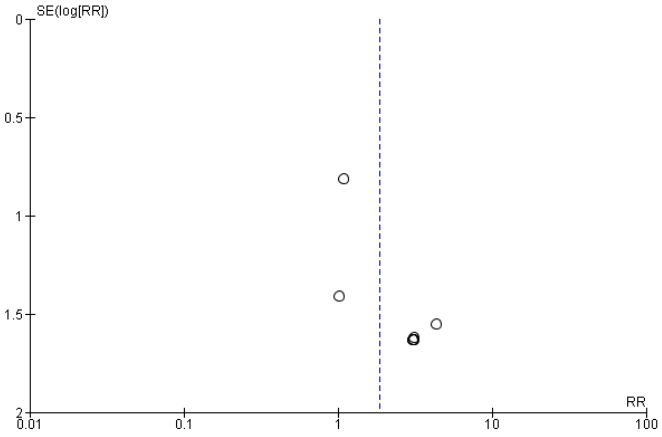
Serious colitis ulcerative



Serious autoimmune myocarditis

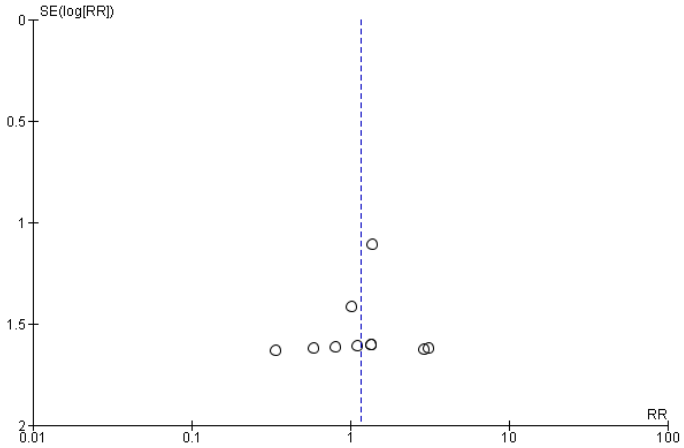


Serious cardiac failure

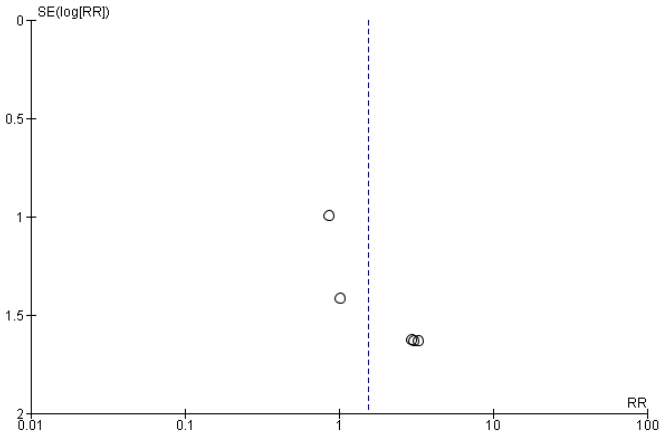


Serious myocardial infraction

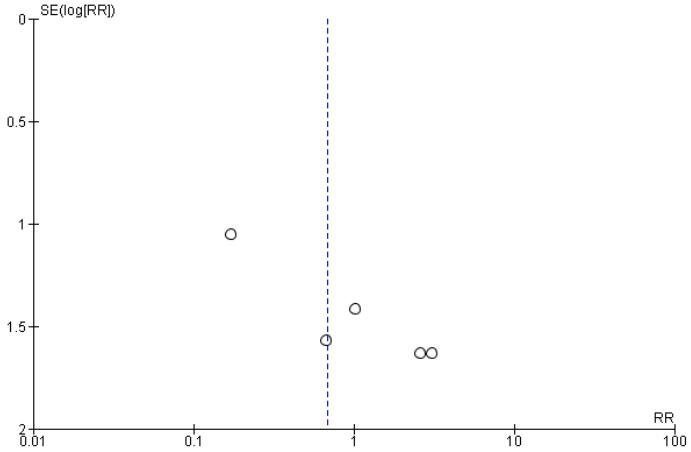
Supplementary Figure 4 Funnel plot of studies included in the meta-analysis



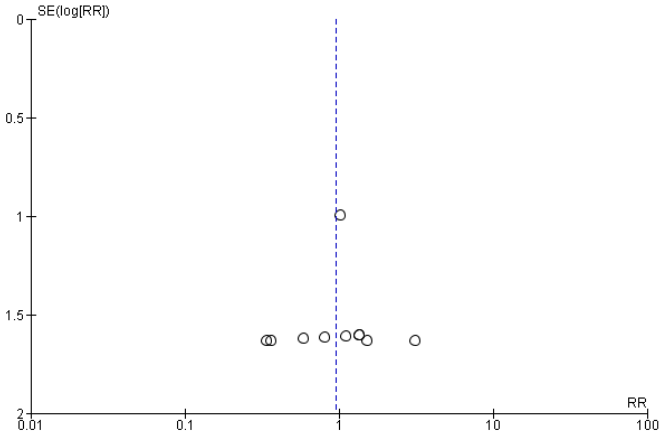
Serious pericardial disease/pericardial effusion



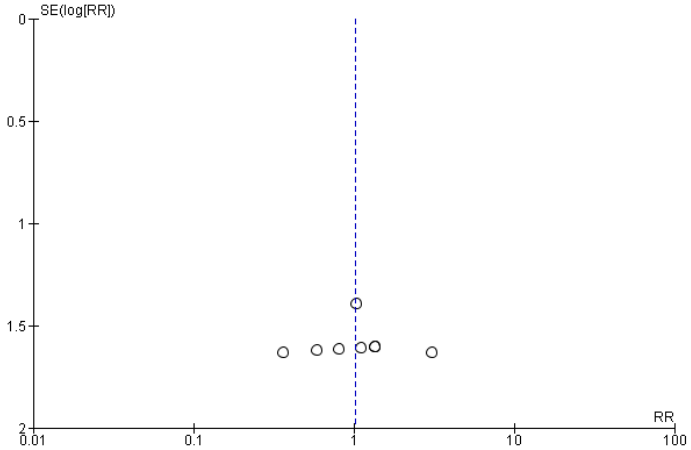
Serious hypophysitis



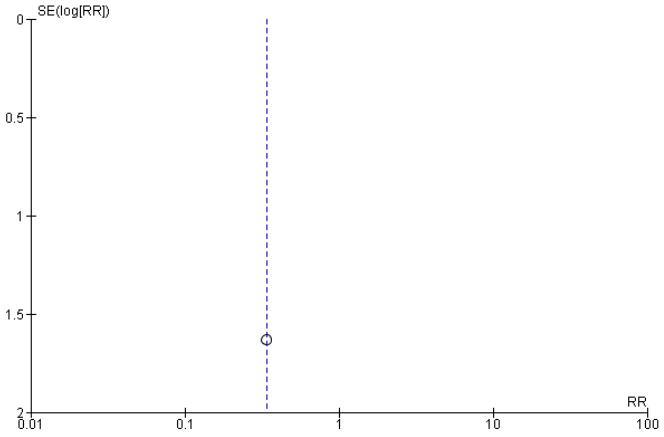
Serious hypothyroidism



Serious adrenal insufficiency

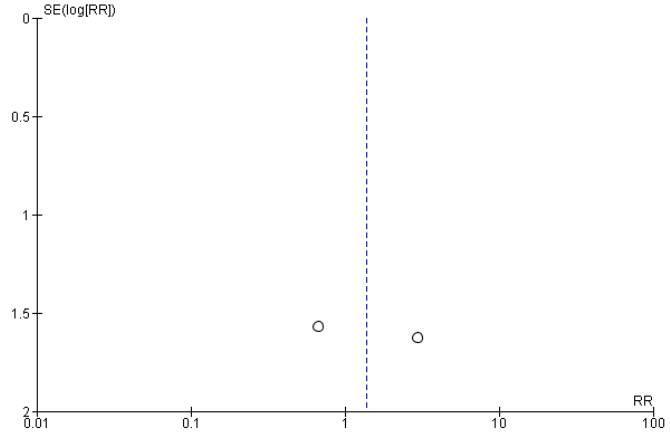


Serious hyperthyroidism

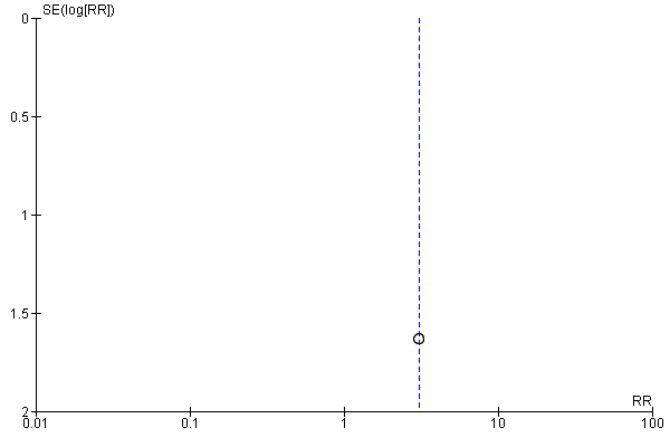


Serious myositis

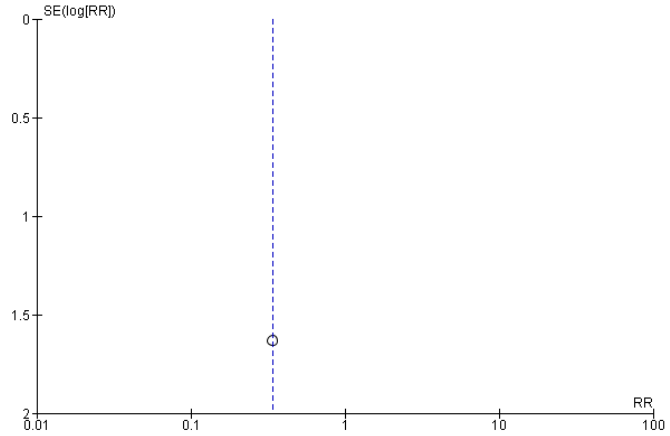
Supplementary Figure 4　Funnel plot of studies included in the meta-analysis



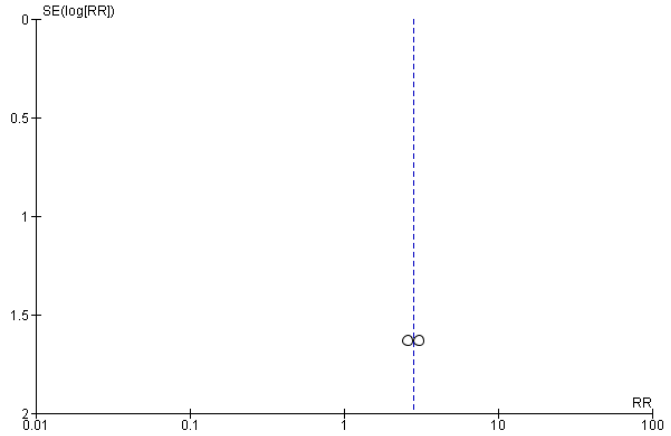
Serious myasthenia gravis



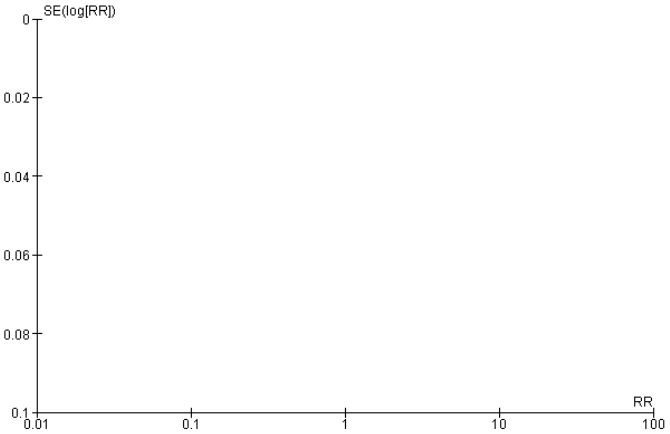
Serious SJS



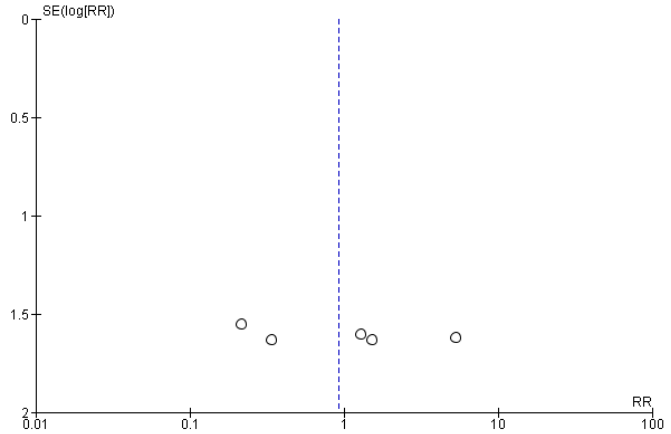
Serious immune-mediated dermatitis



Serious autoimmune nephritis

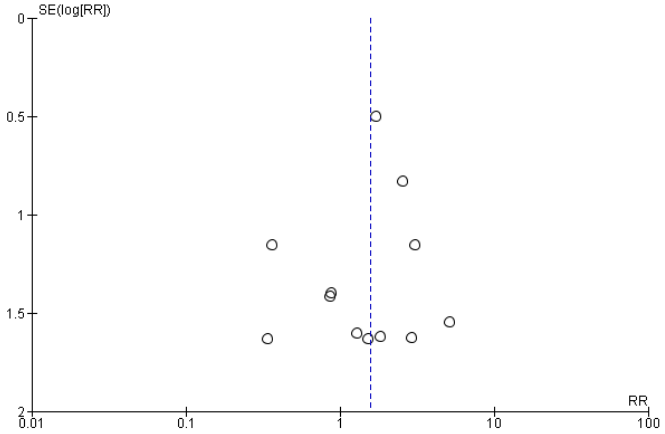


Serious TEN

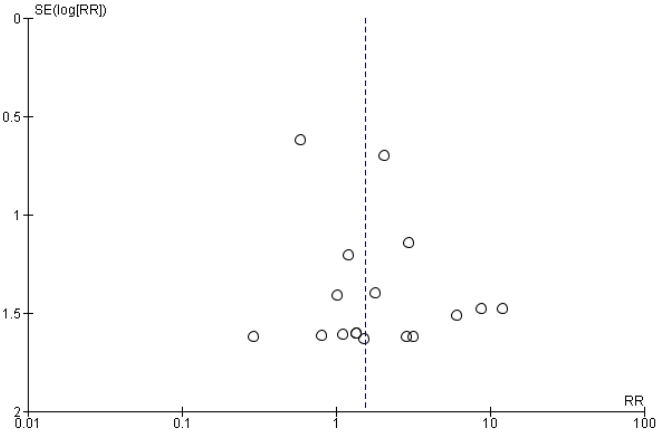


Serious nephritis

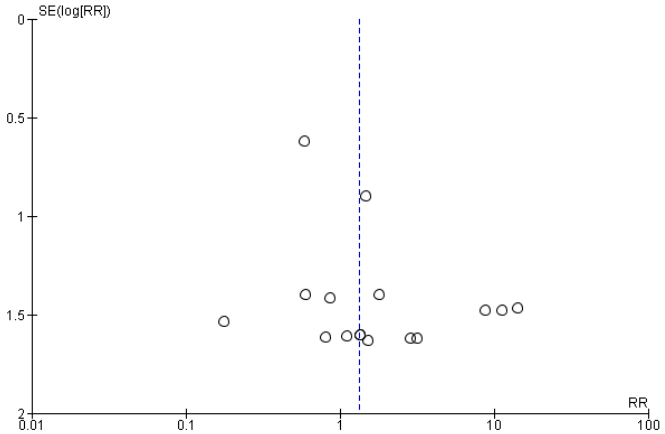
Supplementary Figure 4　Funnel plot of studies included in the meta-analysis



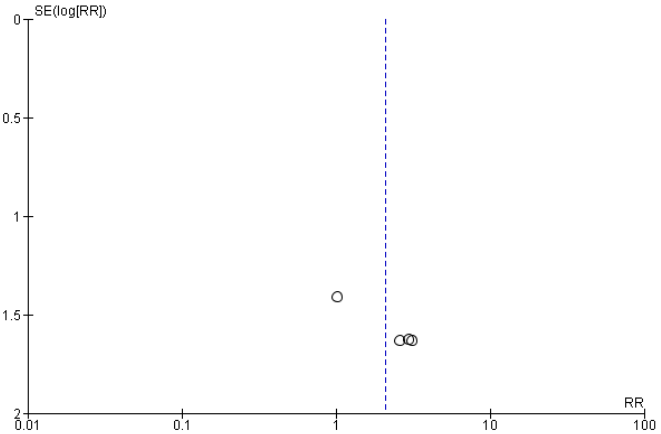
Serious fatigue



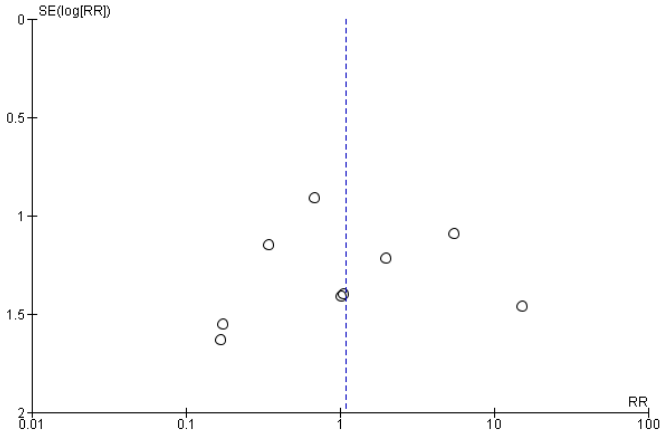
Serious vomiting



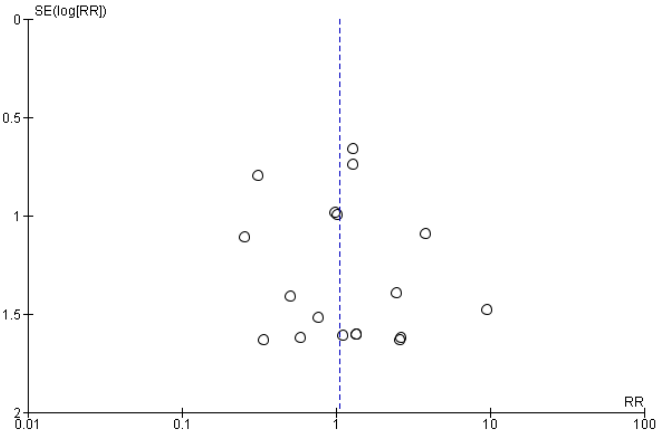
Serious nausea



Serious cough/productive cough

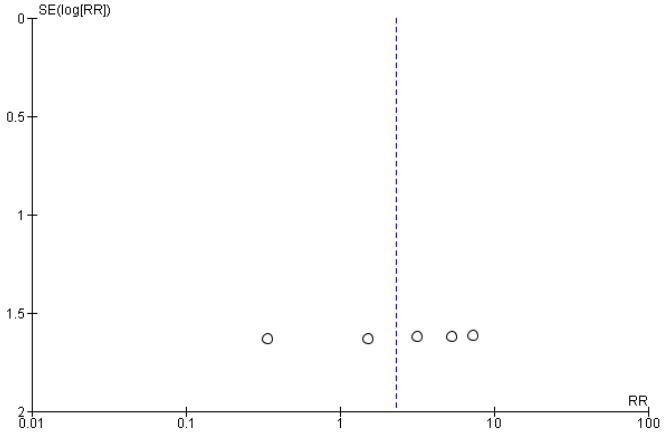


Serious decreased appetite

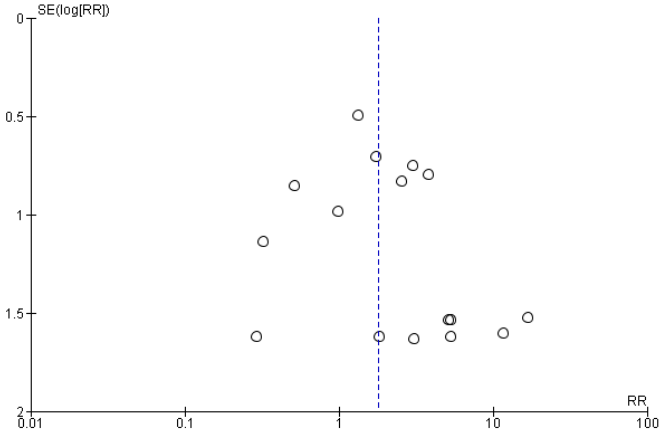


Serious dyspnea

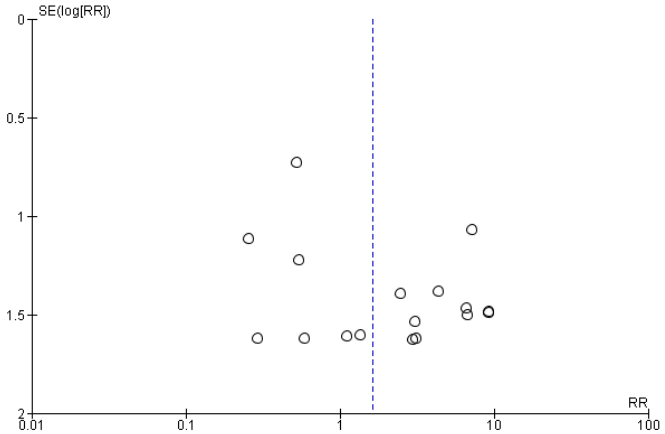
Supplementary Figure 4　Funnel plot of studies included in the meta-analysis



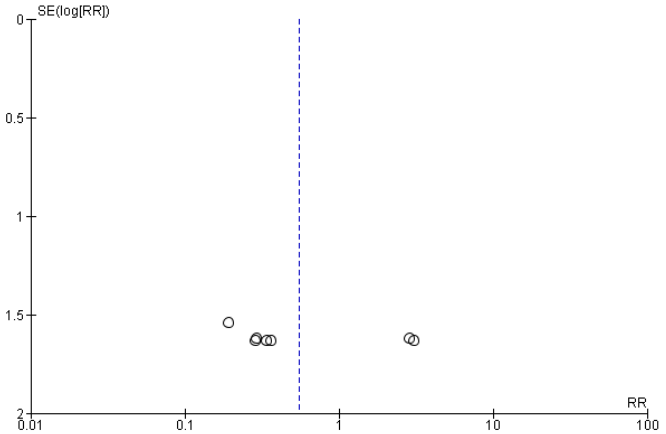
Serious rash



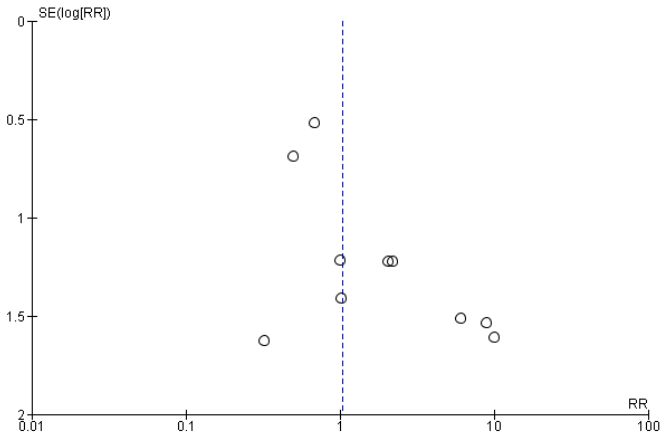
Serious pyrexia/fever



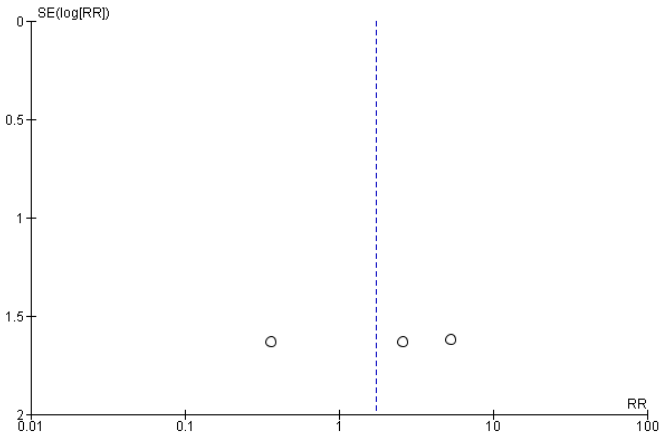
Serious diarrhea



Serious arthralgia

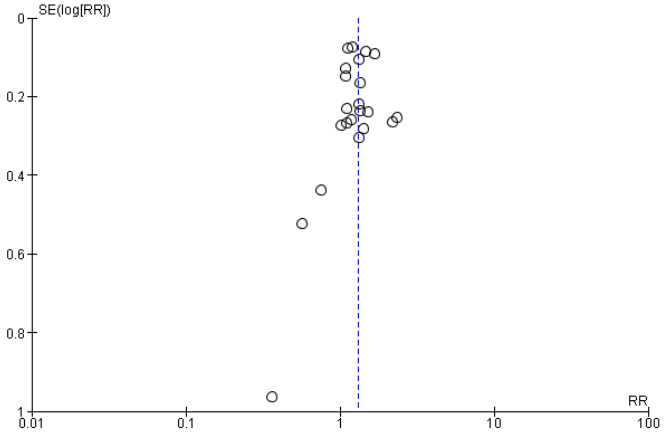


Serious abdominal pain

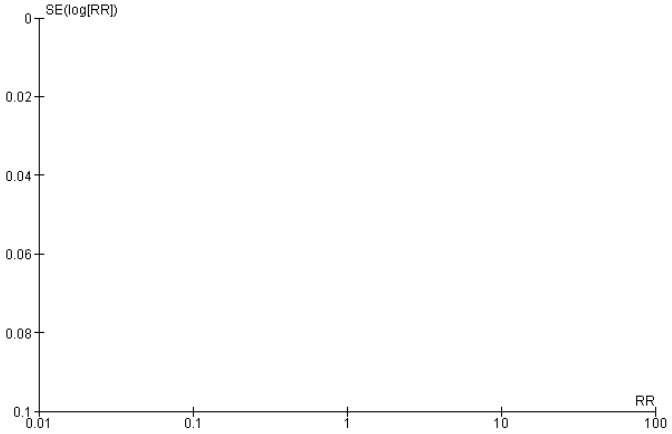


Serious pruritus

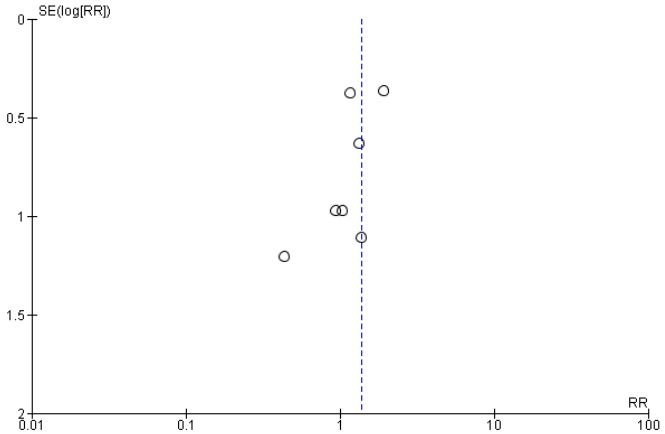
Supplementary Figure 4 – Funnel plot of studies included in the meta-analysis



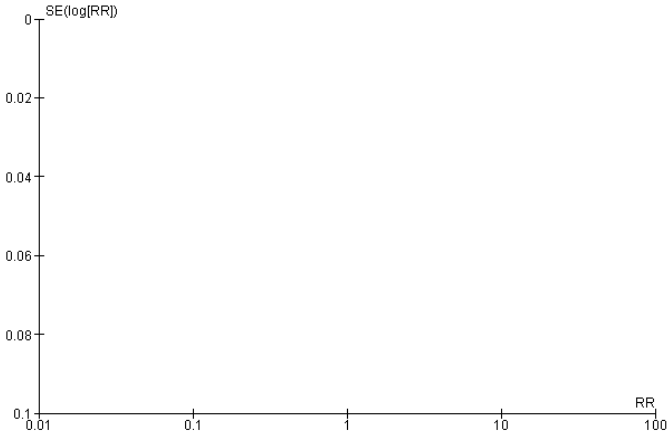
Serious adverse events; Total



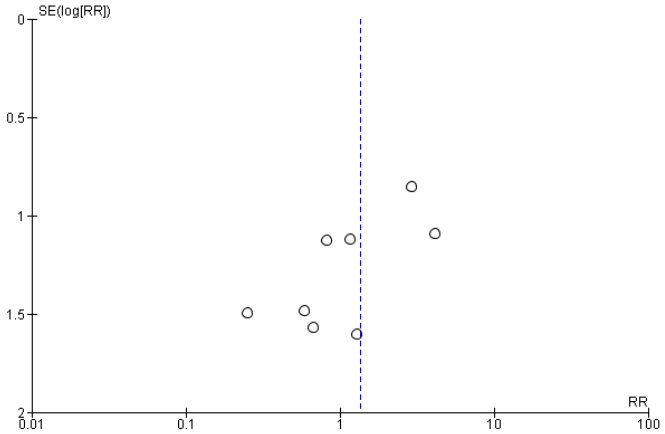
Non-serious immune-related lung disease



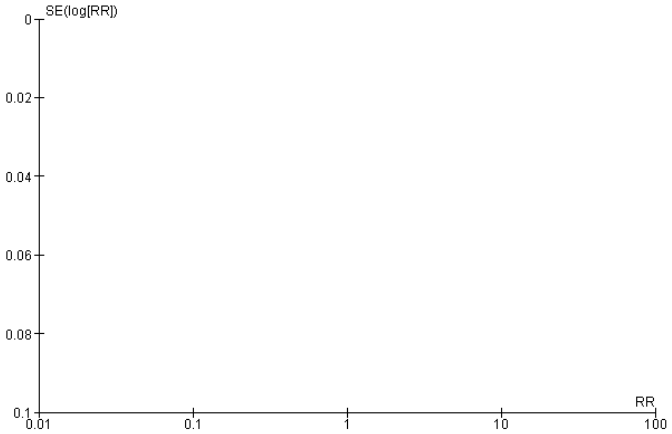
Non-Serious pneumonia



Non-serious immune-mediated hepatitis

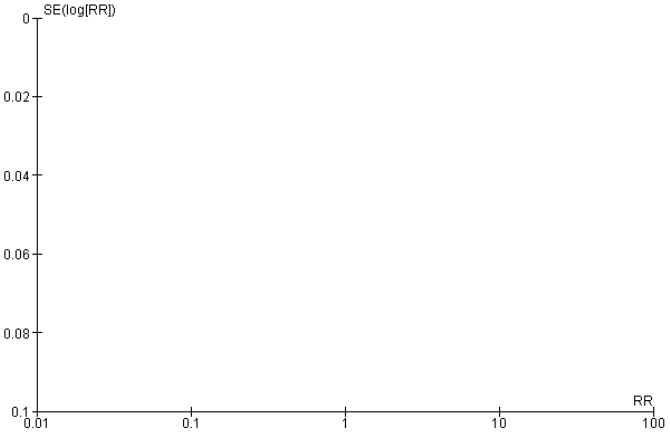


Non-serious pneumonitis

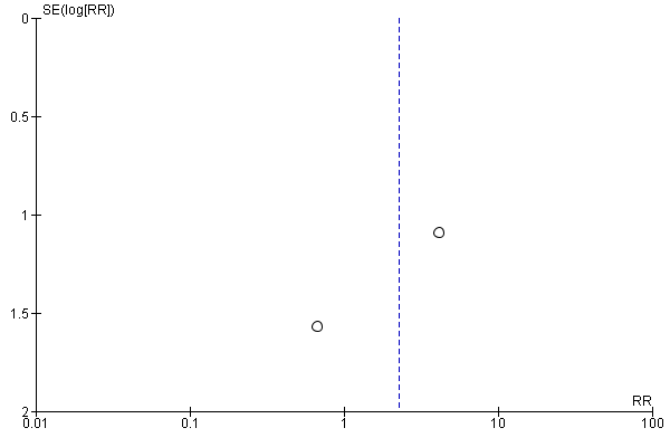


Non-serious autoimmune hepatitis

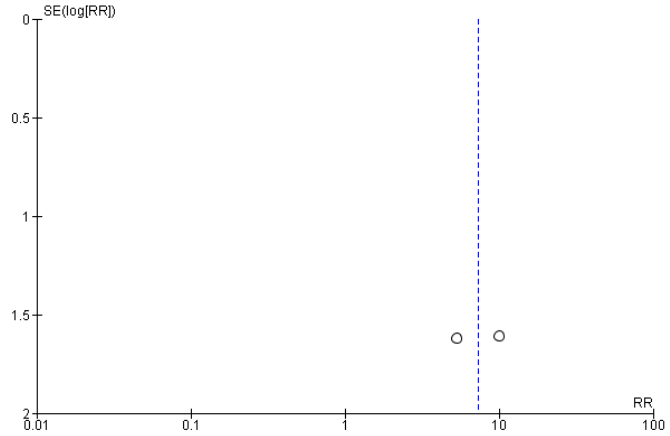
Supplementary Figure 4　Funnel plot of studies included in the meta-analysis



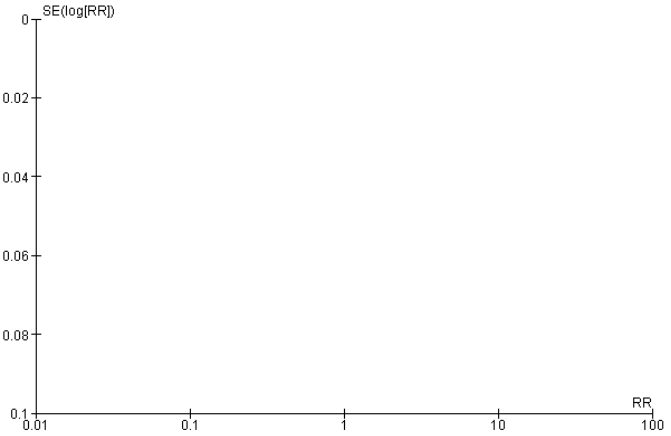
Non-serious colitis



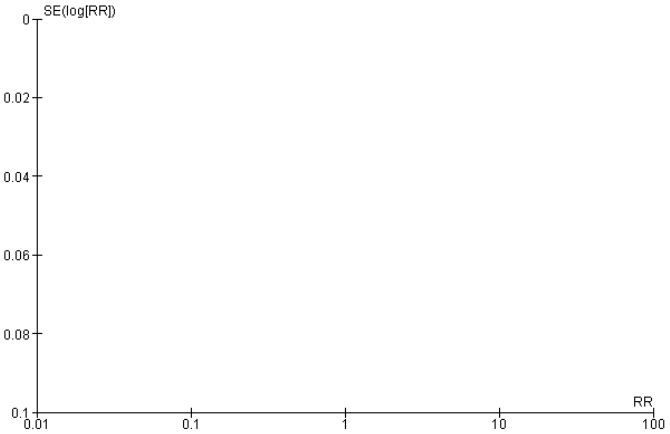
Non-serious cardiac failure



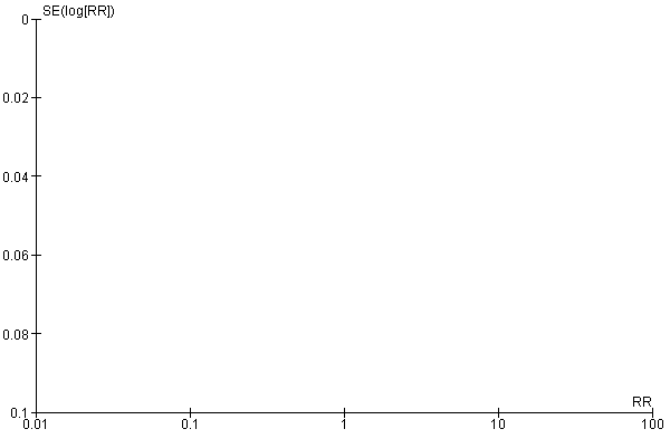
Non-serious autoimmune colitis



Non-serious immune-mediated myocarditis

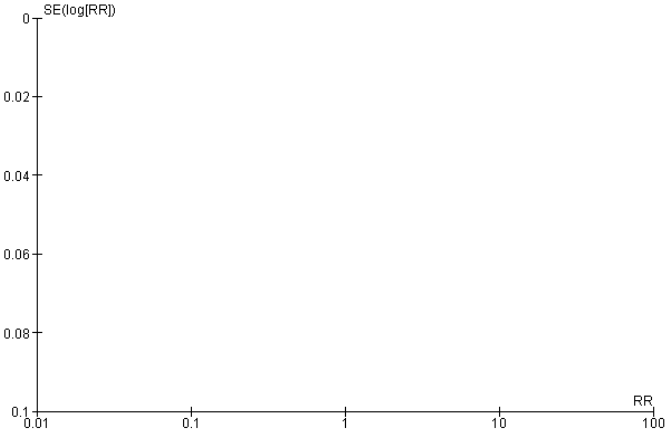


Non-serious colitis ulcerative

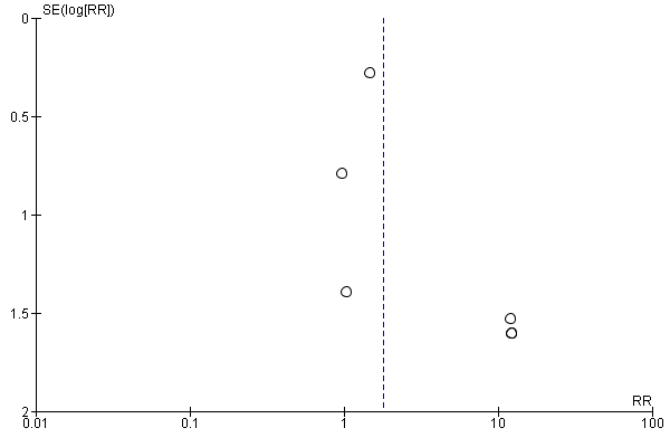


Non-serious autoimmune myocarditis

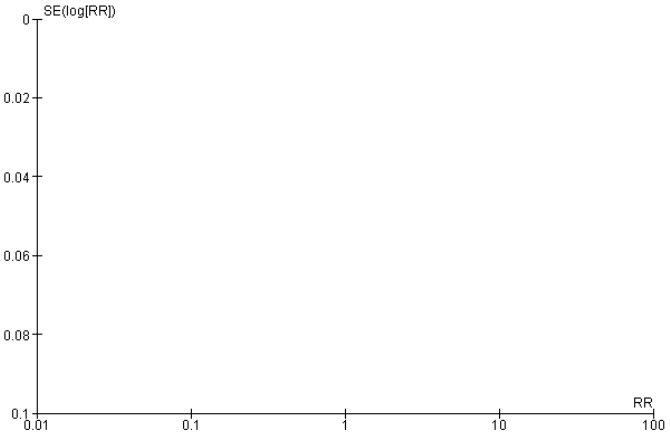
Supplementary Figure 4　Funnel plot of studies included in the meta-analysis



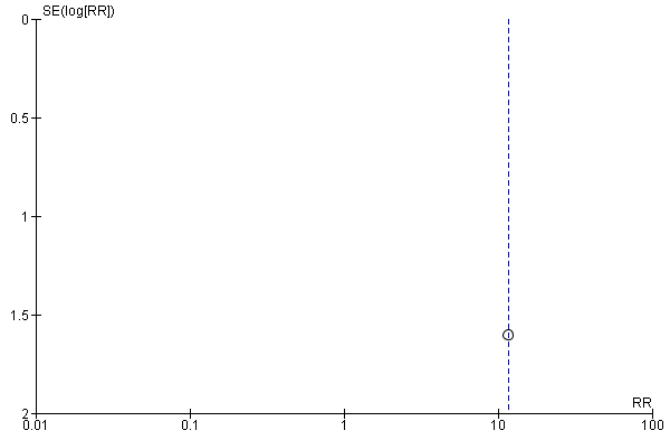
Non-serious myocardial infraction



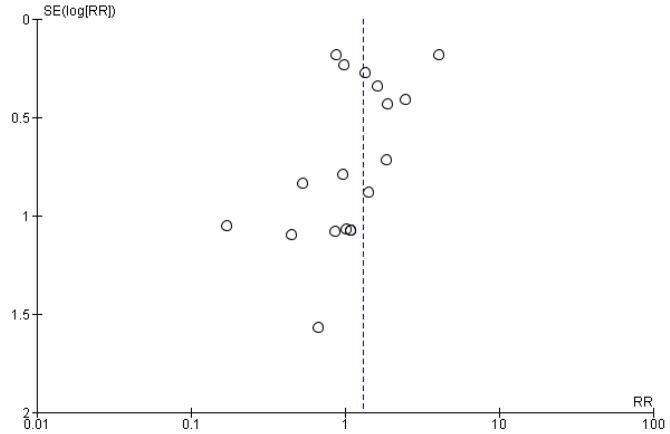
Non-serious hyperthyroidism



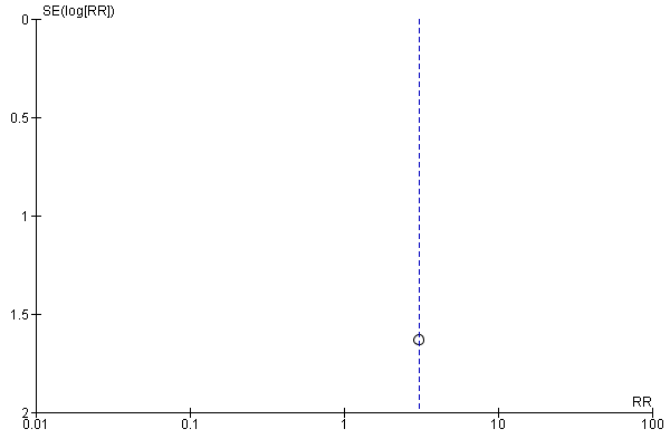
Non-serious pericardial disease/pericardial effusion



Non-serious hypophysitis

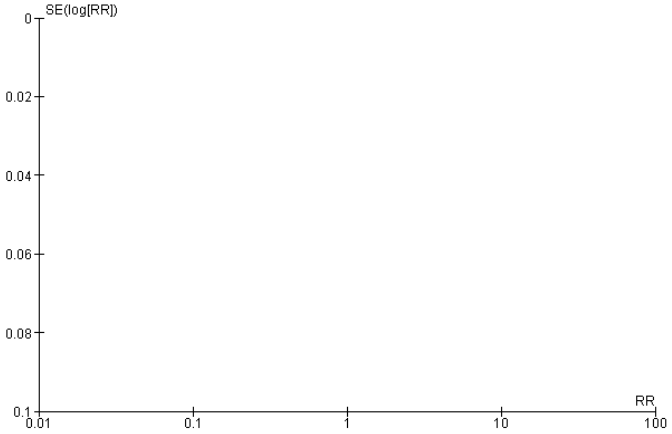


Non-serious hypothyroidism

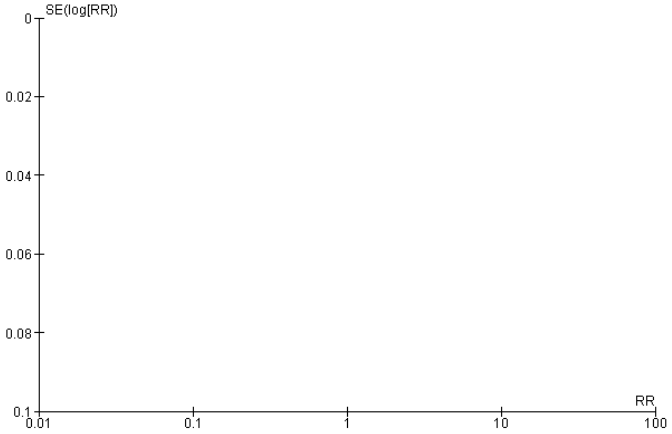


Non-serious adrenal insufficiency

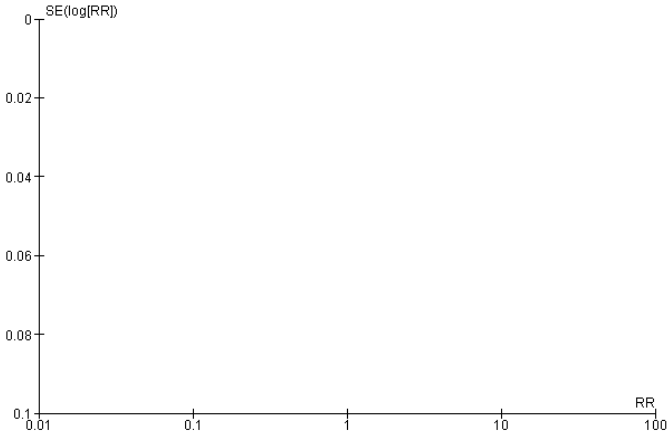
Supplementary Figure 4　Funnel plot of studies included in the meta-analysis



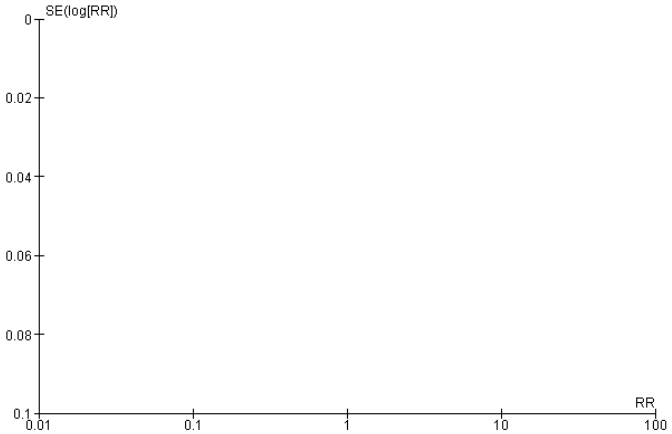
Non-serious myositis



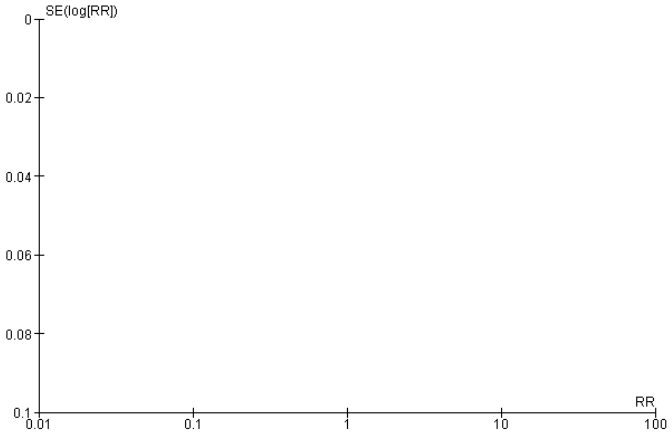
Non-serious TEN



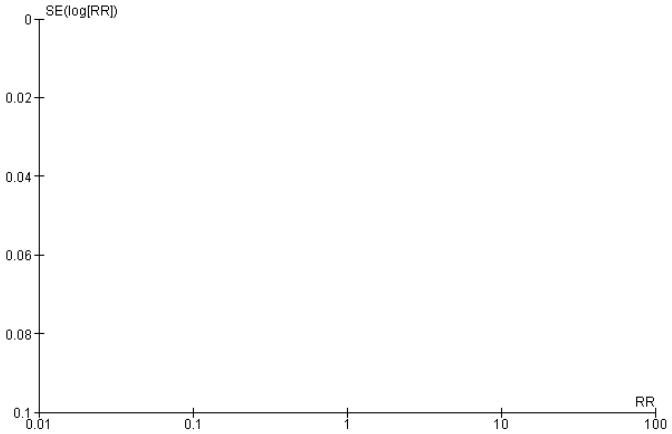
Non-serious myasthenia gravis



Non-serious SJS

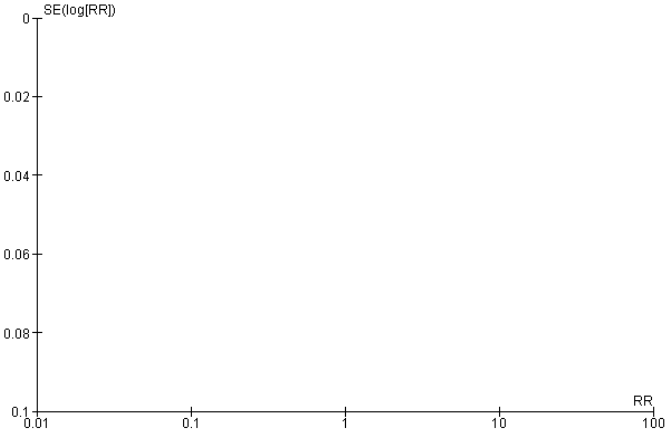


Non-serious immune-mediated dermatitis

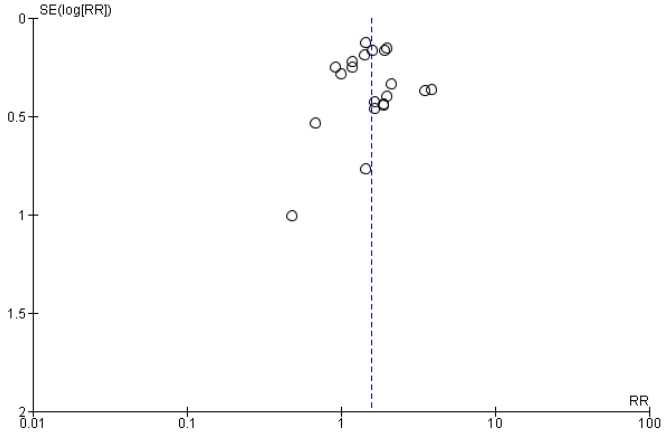


Non-serious autoimmune nephritis

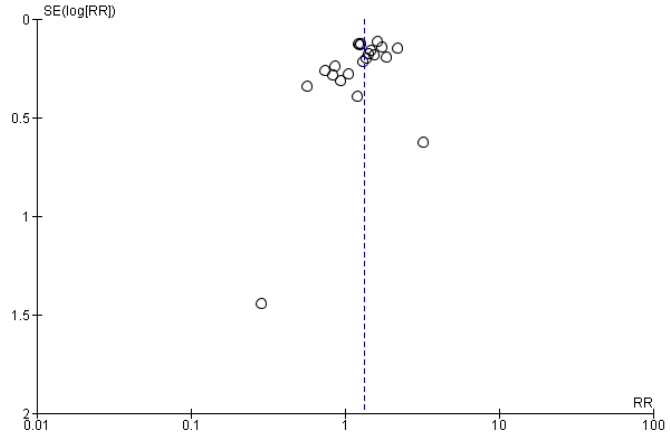
Supplementary Figure 4　Funnel plot of studies included in the meta-analysis



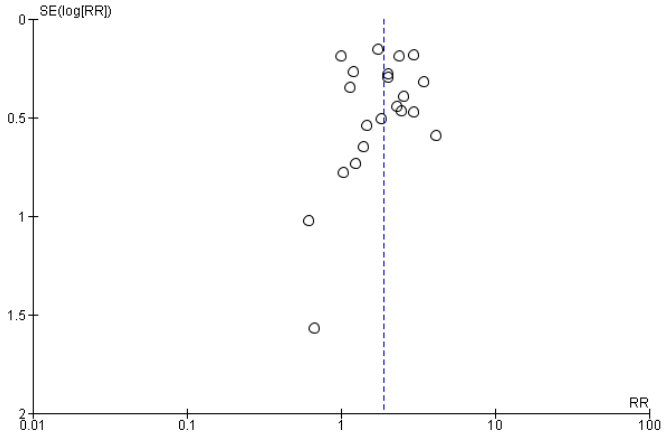
Non-serious nephritis



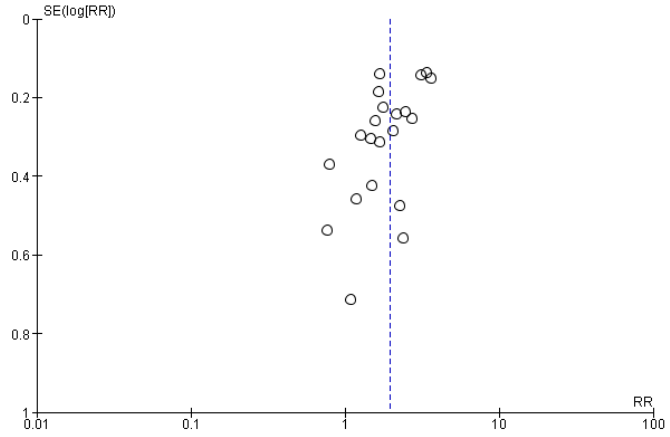
Non-serious decreased appetite



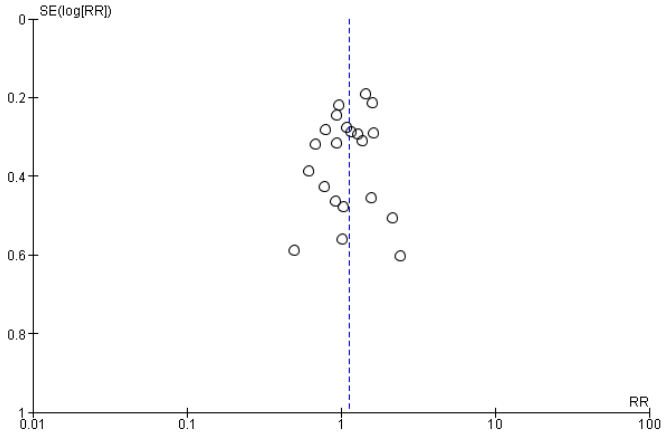
Non-serious fatigue



Non-serious vomiting

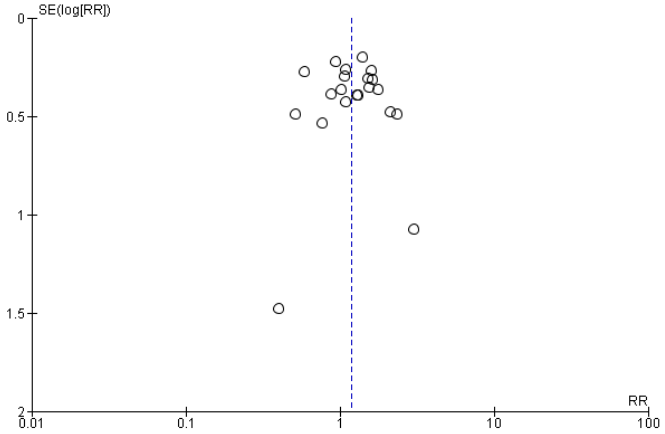


Non-serious nausea

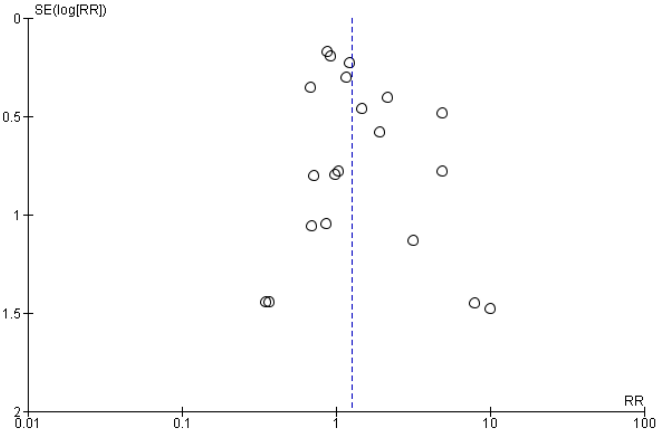


Non-serious cough/productive cough

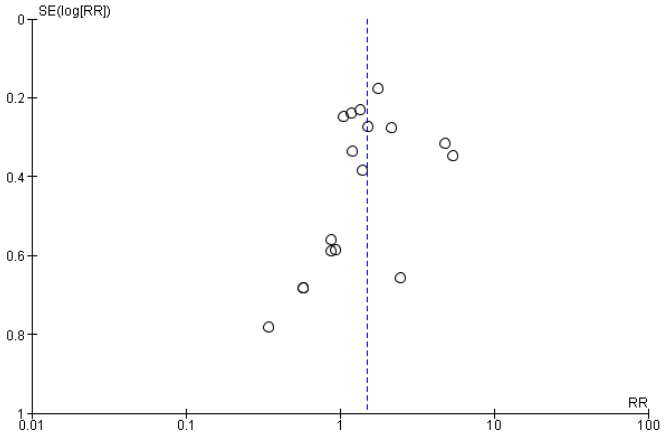
Supplementary Figure 4　Funnel plot of studies included in the meta-analysis



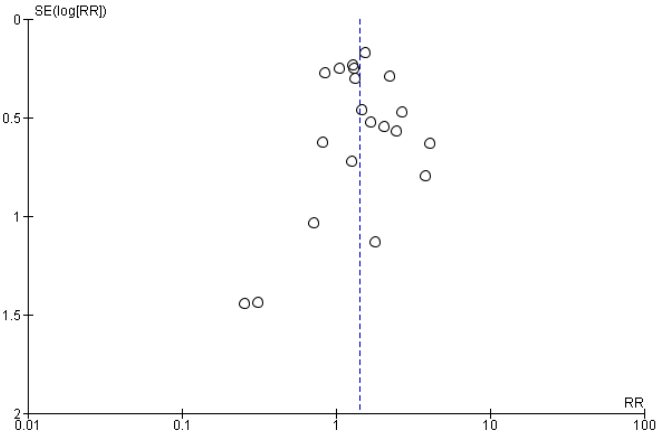
Non-serious dyspnea



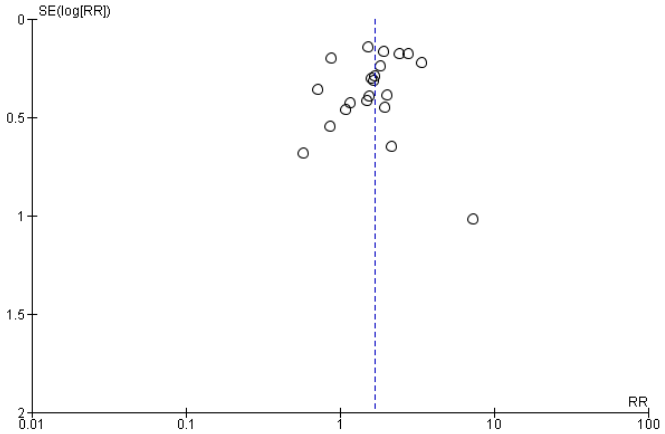
Non-serious abdominal pain



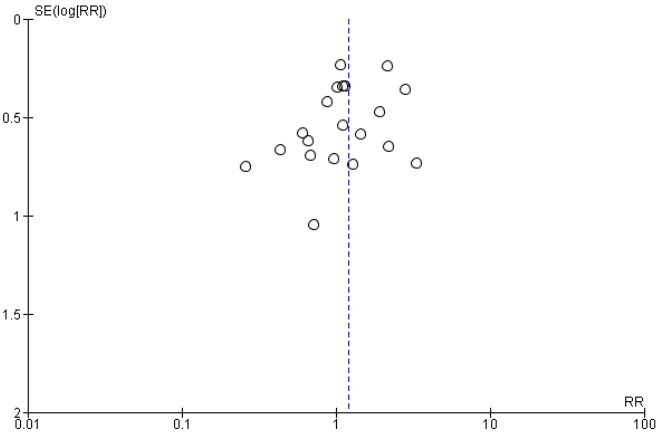
Non-serious rash



Non-serious pyrexia/fever

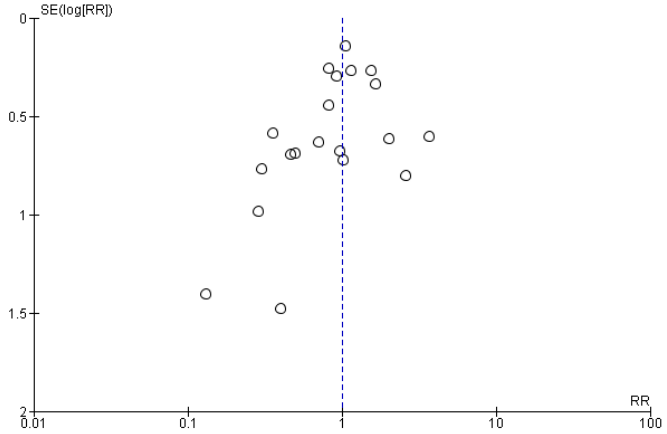


Non-serious diarrhea

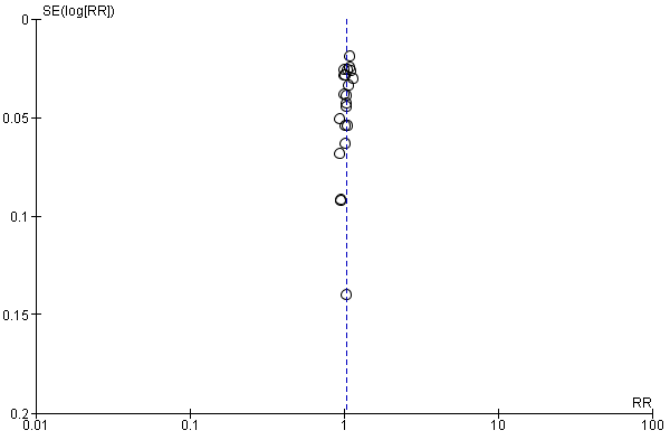


Non-serious arthralgia

Supplementary Figure 4　Funnel plot of studies included in the meta-analysis

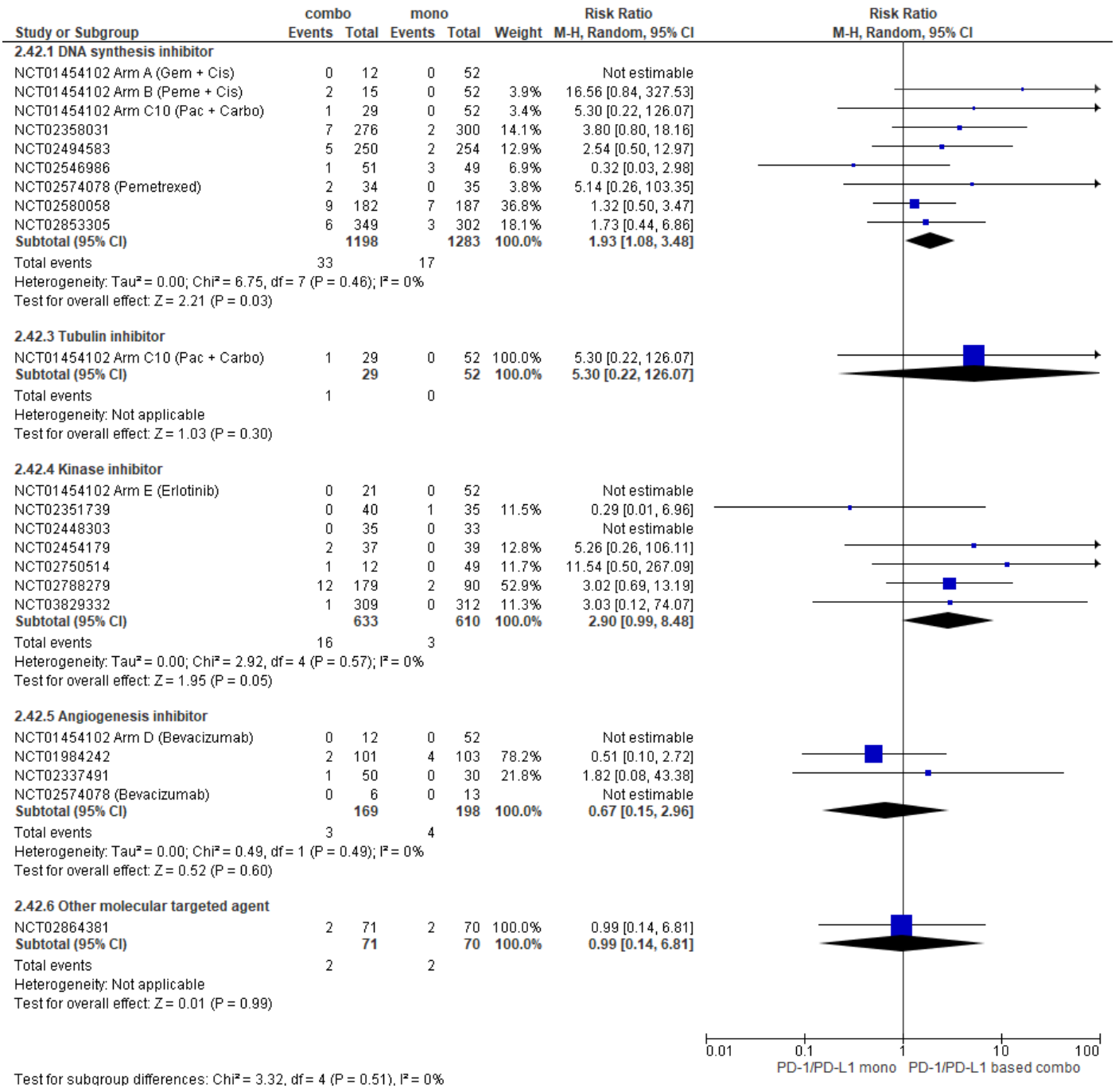


Non-serious pruritus

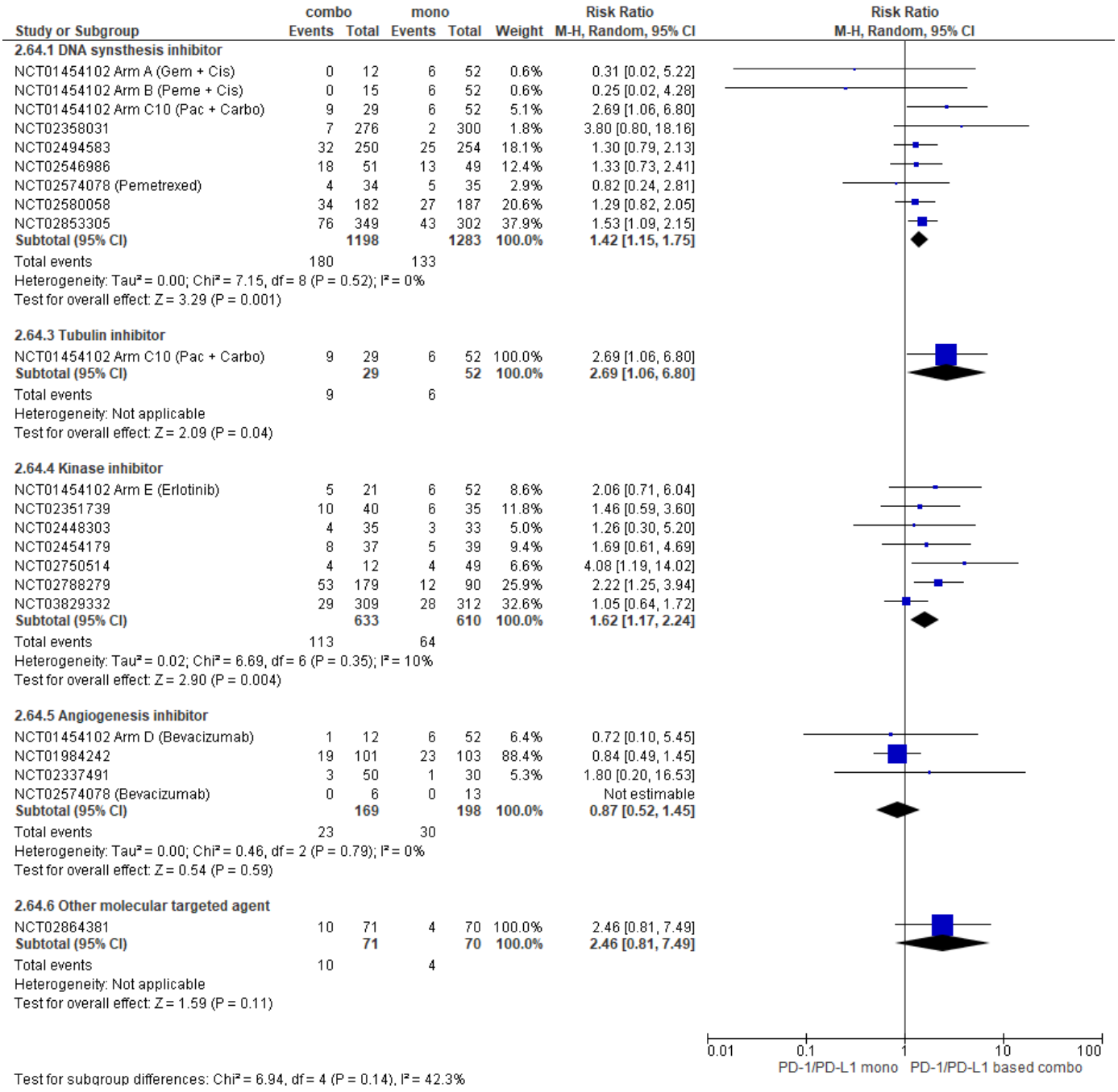


Non-serious adverse events; Total

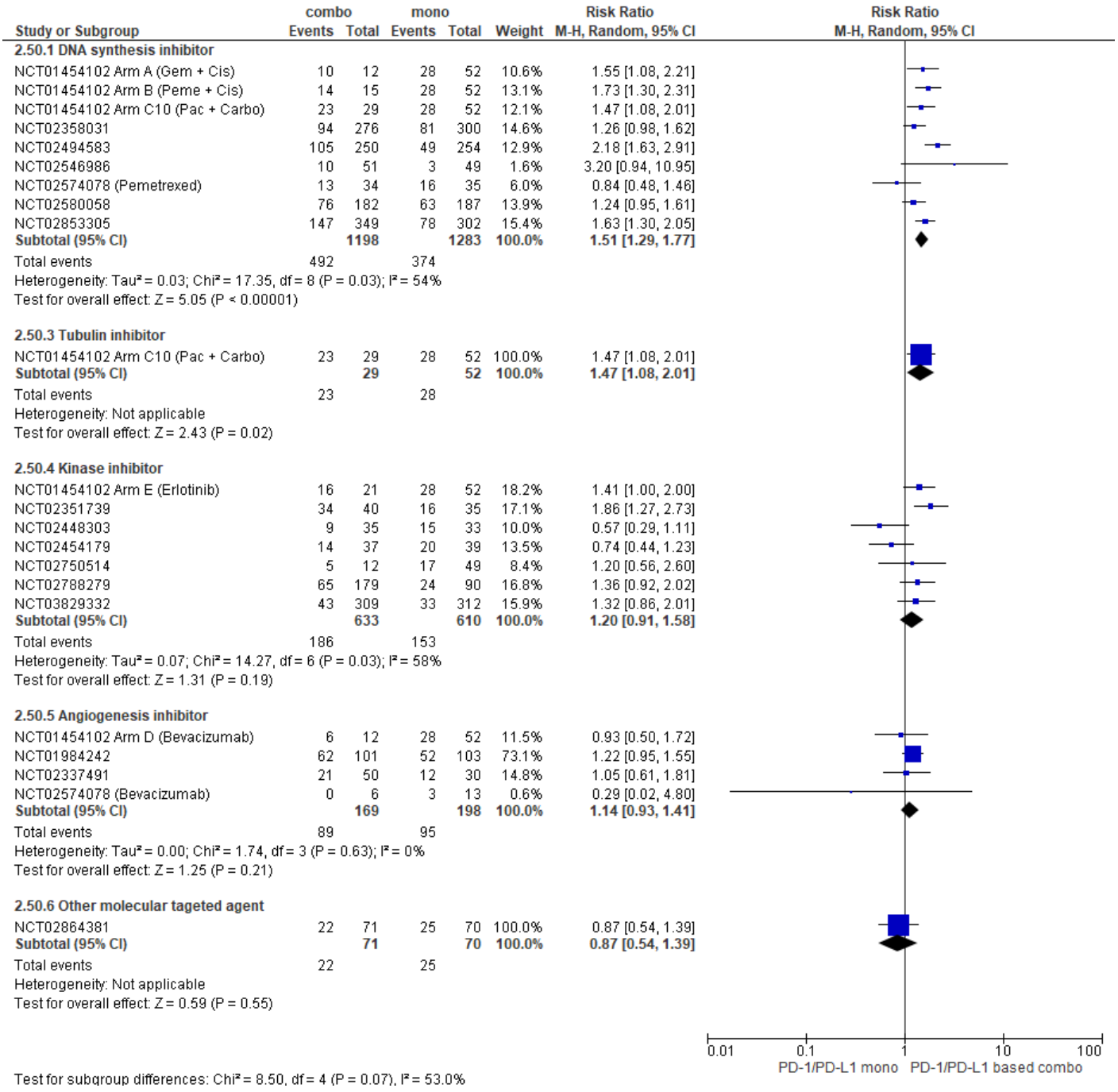
Supplementary Figure 4　Funnel plot of studies included in the meta-analysis



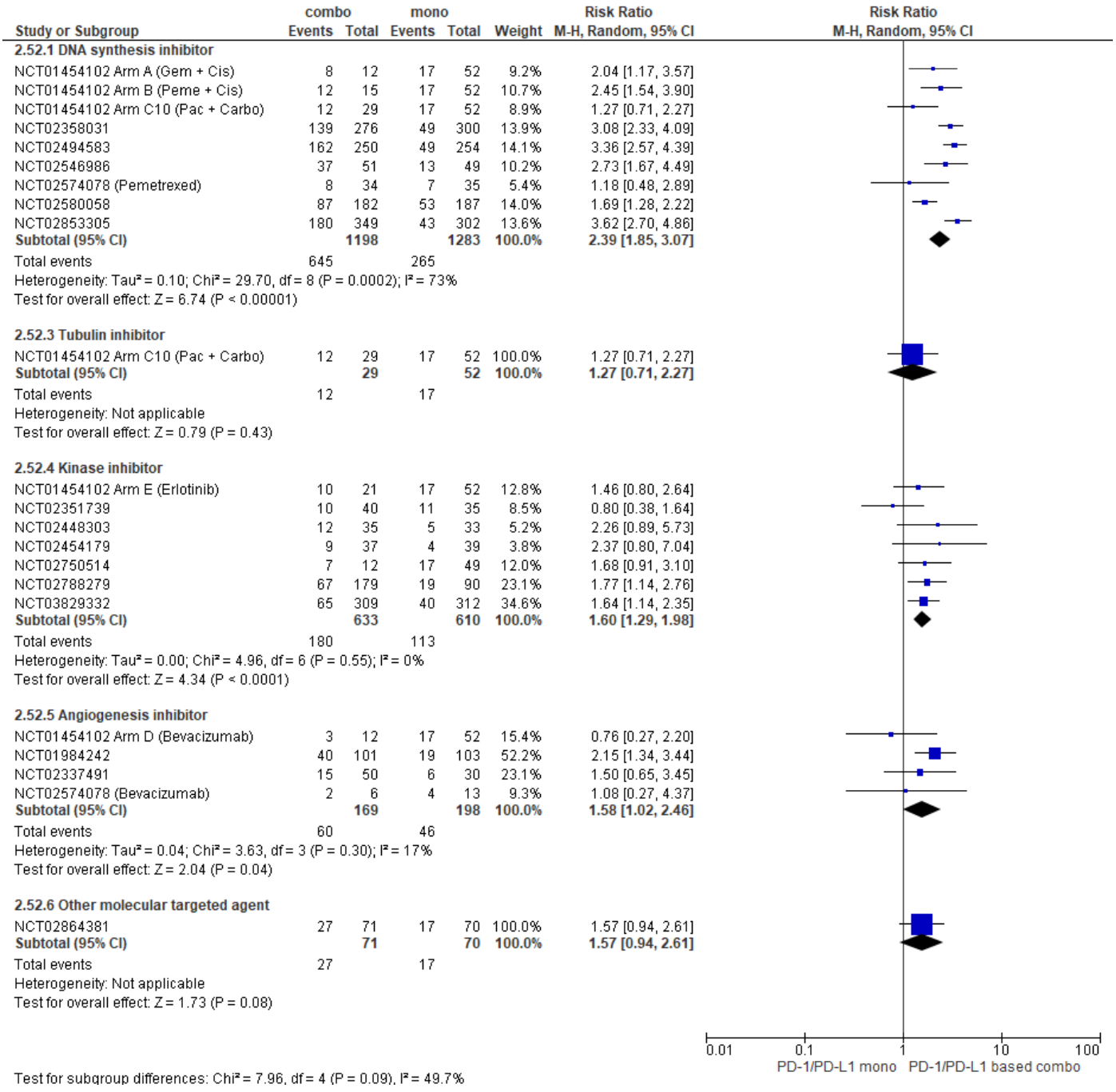
Supplementary Figure 5 Subgroup analysis of serious pyrexia/fever according to the mode of action of concomitant anticancer drugs



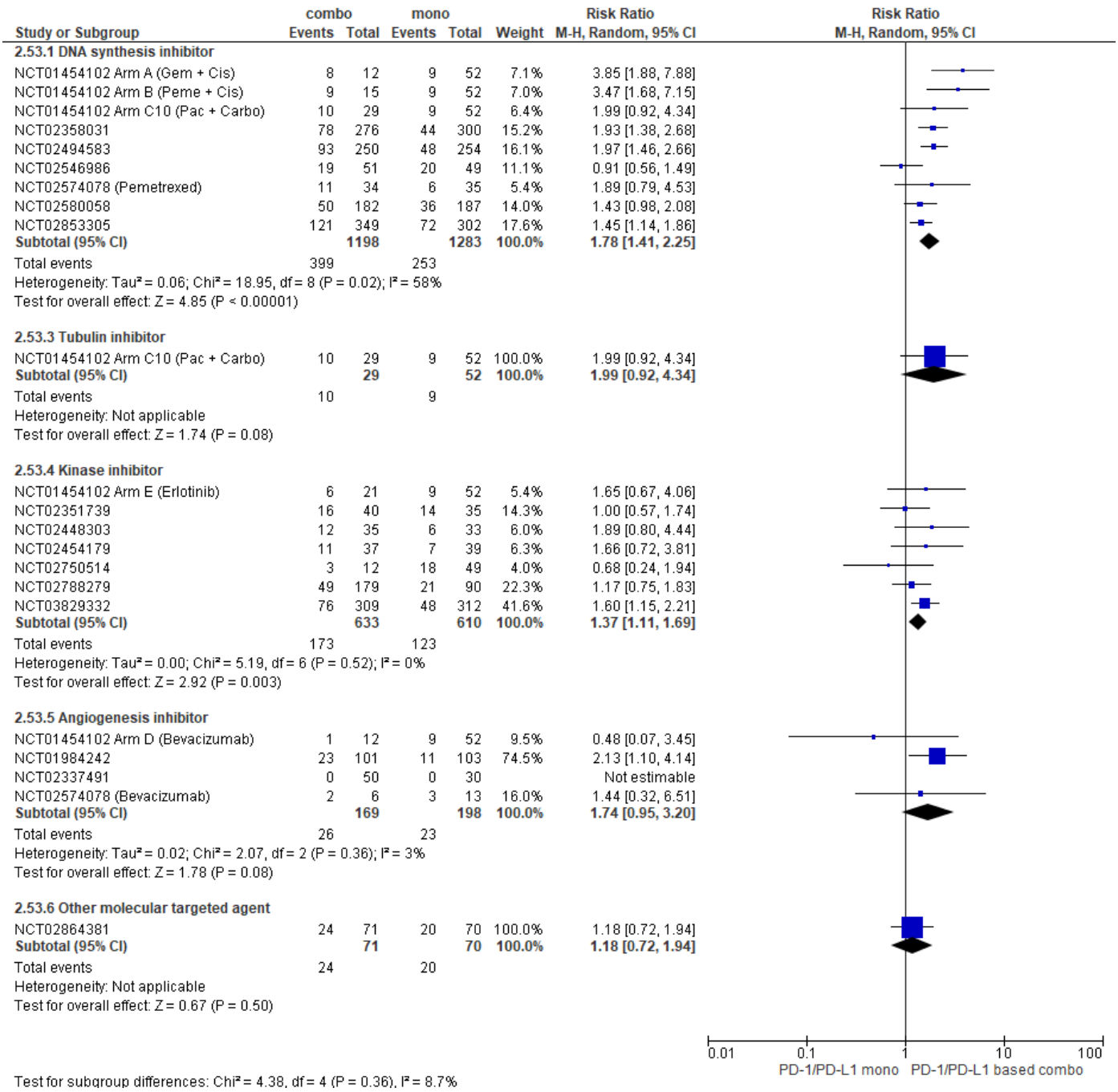
Supplementary Figure 6 Subgroup analysis of incidence of non-serious pyrexia/fever according to the mode of action of concomitant anticancer drugs



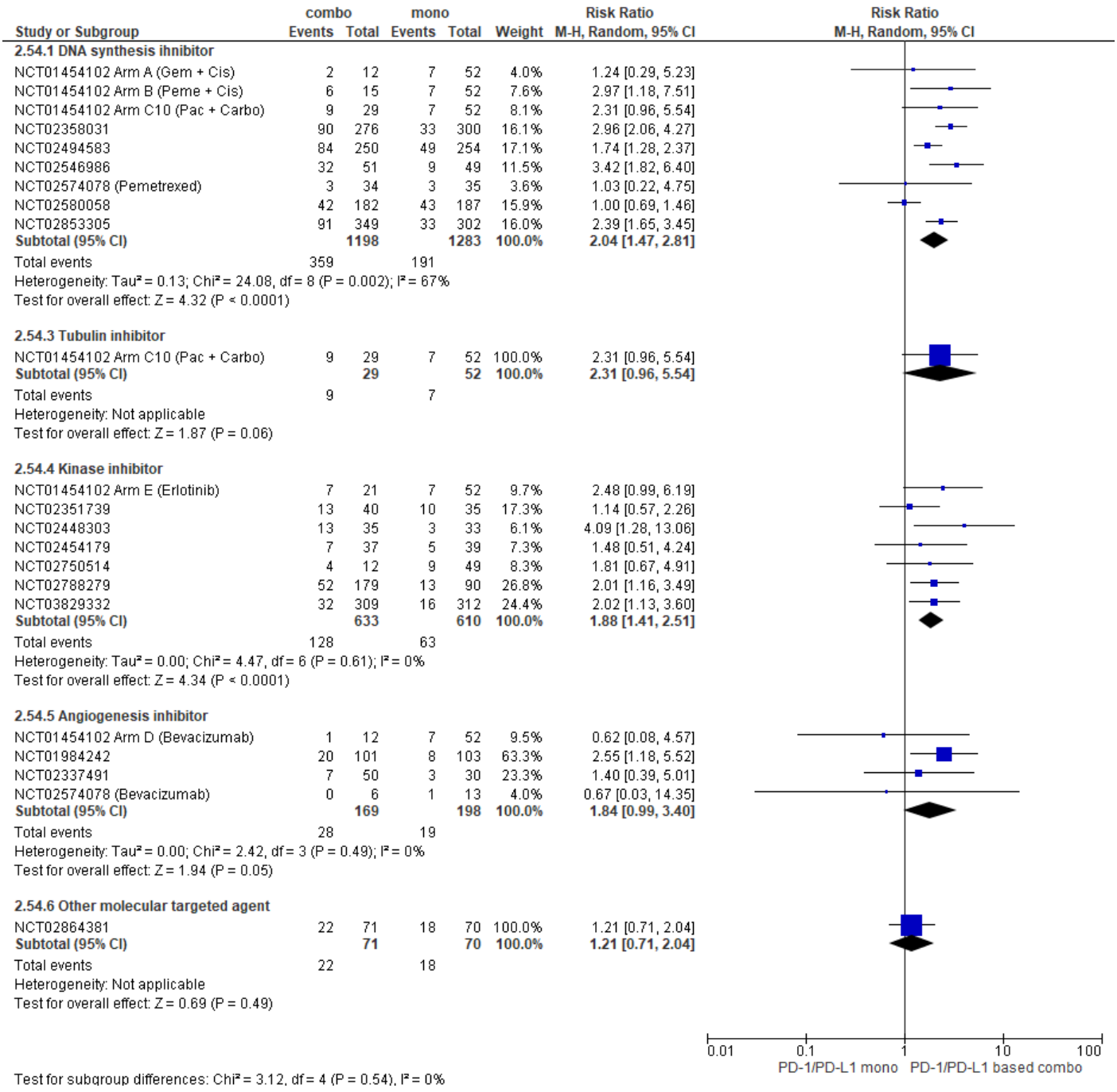
Supplementary Figure 7 Subgroup analysis of incidence of non-serious fatigue according to the mode of action of concomitant anticancer drugs



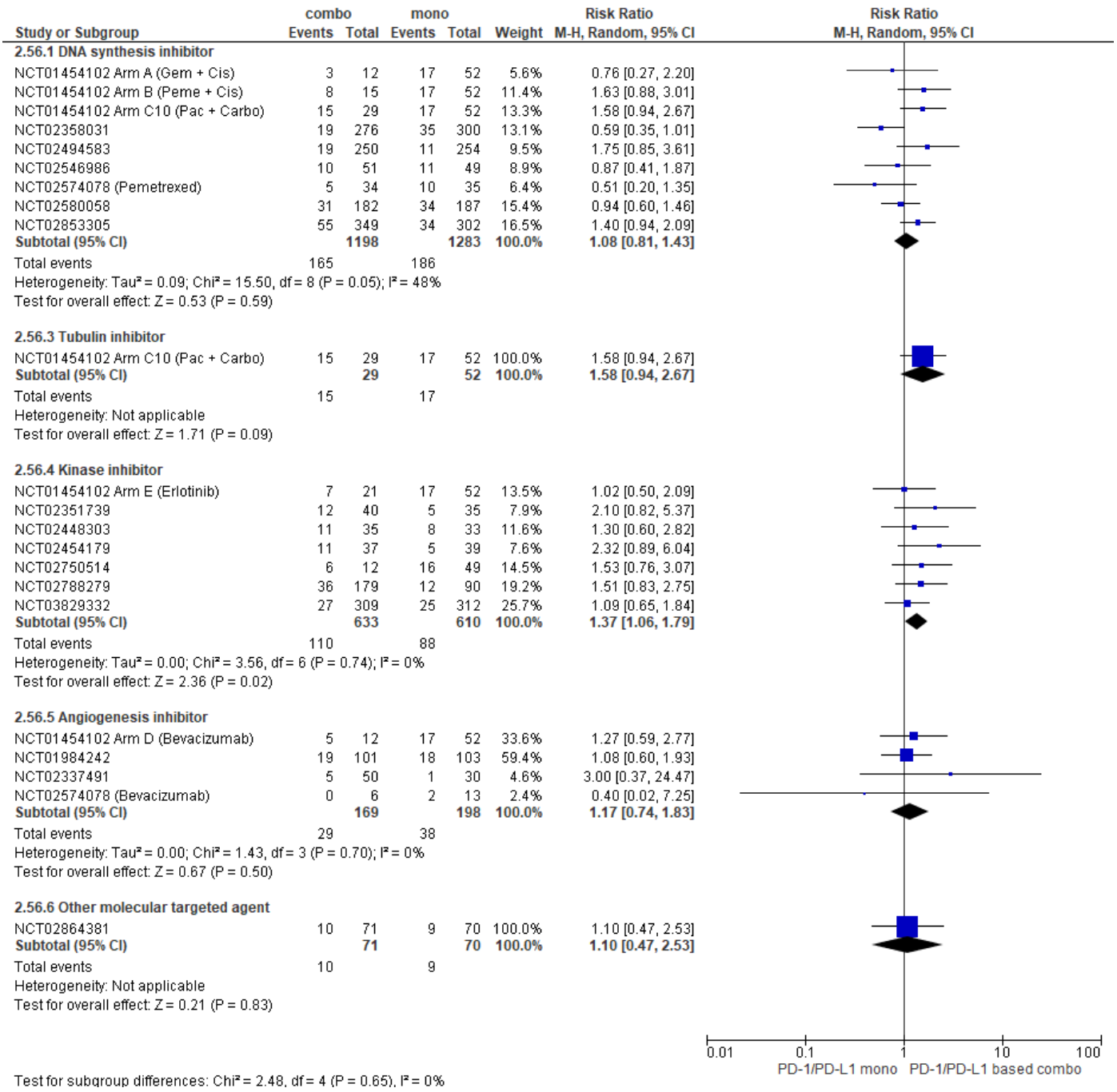
Supplementary Figure 8 Subgroup analysis of non-serious nausea according to the mode of action of concomitant anticancer drugs



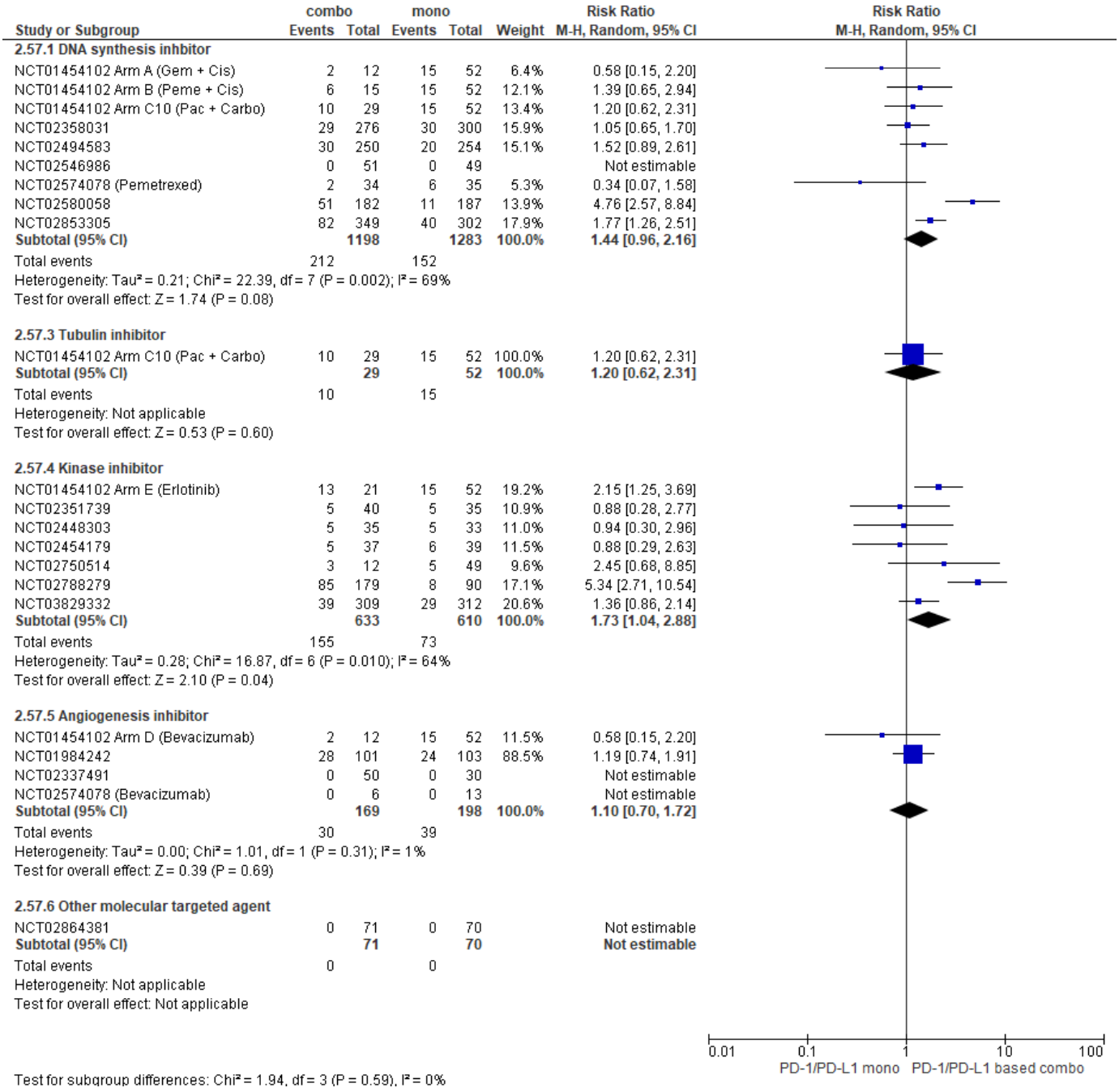
Supplementary Figure 9 Subgroup analysis of non-serious decreased appetite according to the mode of action of concomitant anticancer drugs



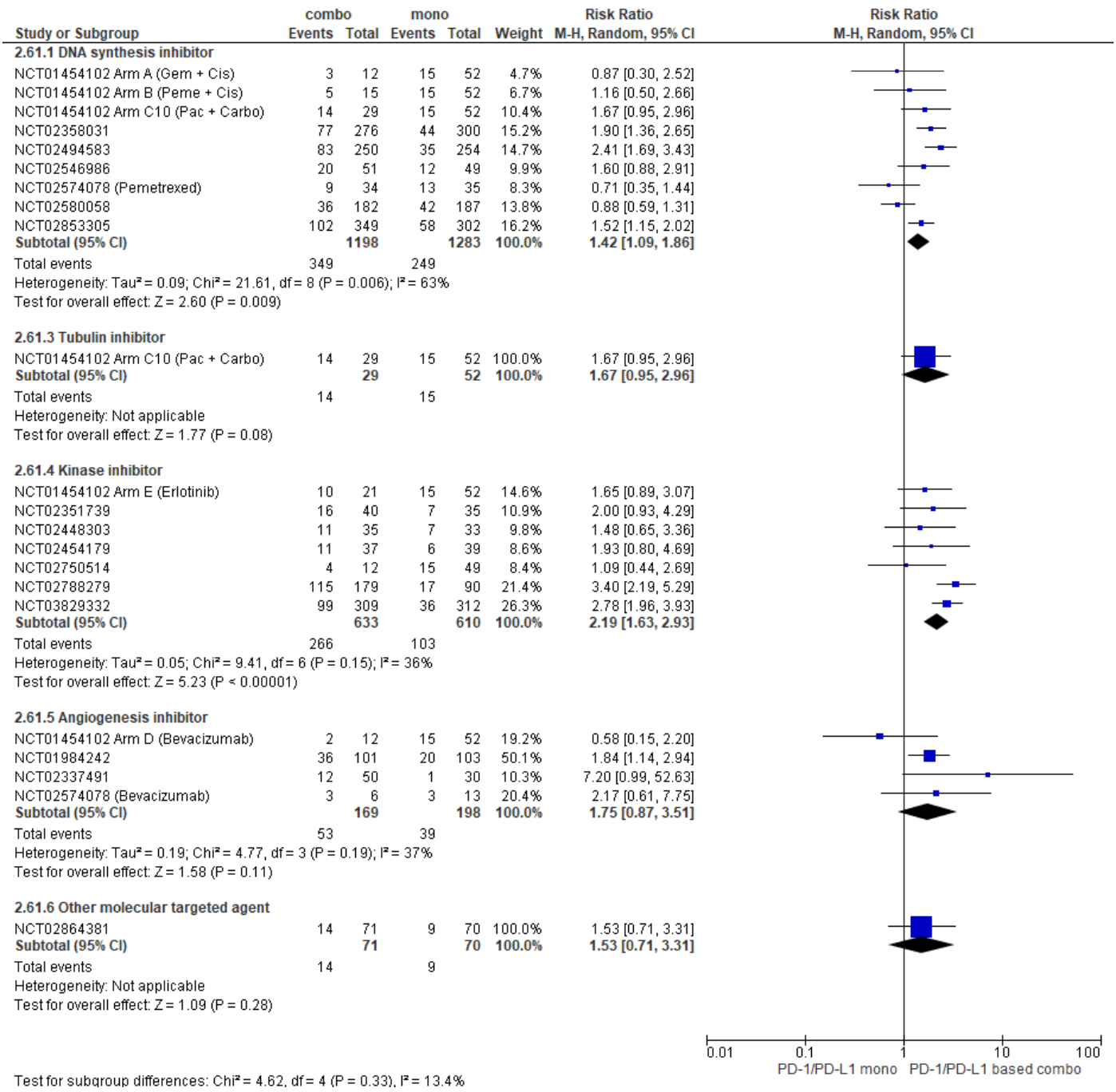
Supplementary Figure 10 Subgroup analysis of non-serious vomiting according to the mode of action of concomitant anticancer drugs.



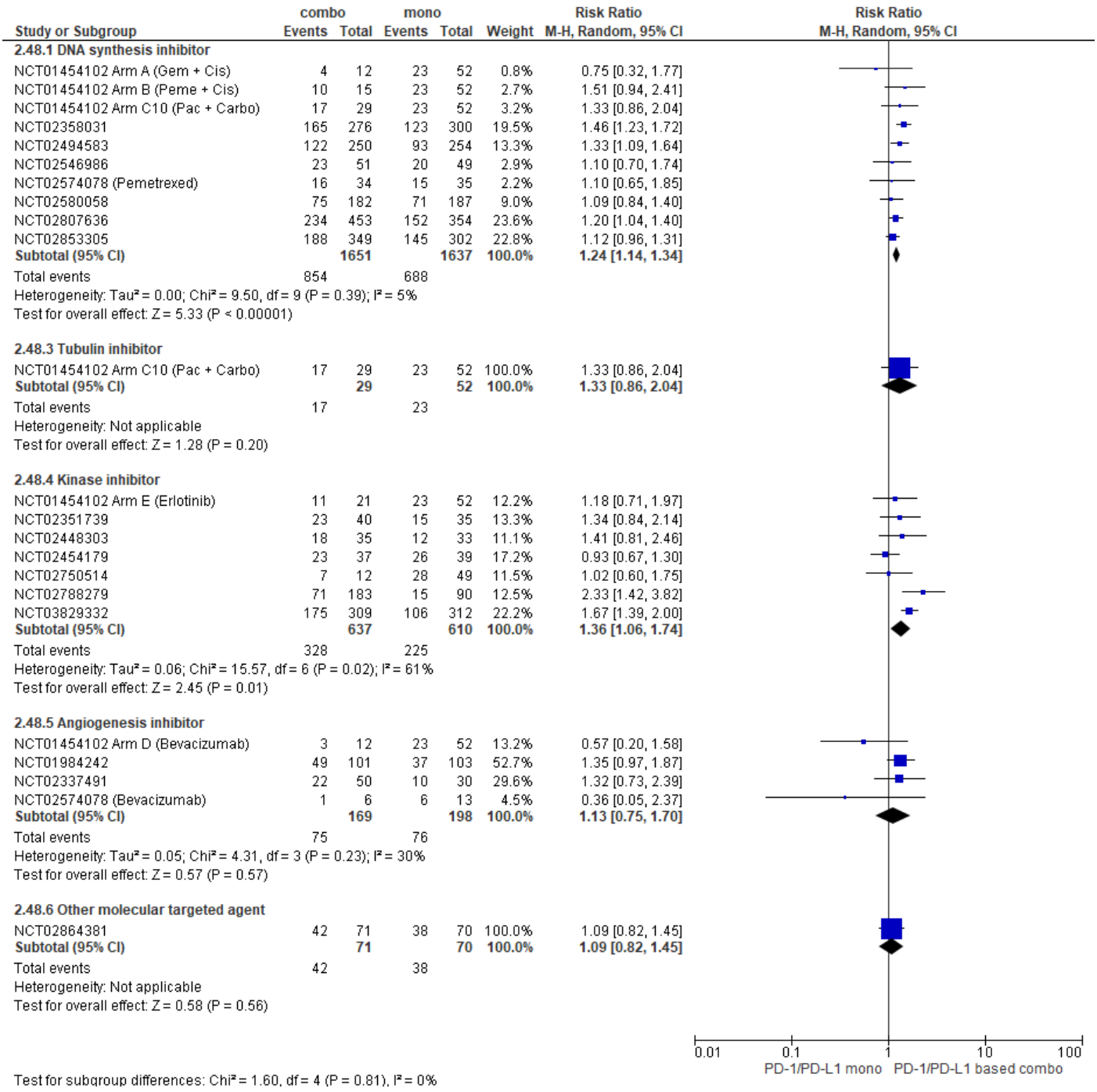
Supplementary Figure 11 Subgroup analysis of non-serious dyspnea according to the mode of action of concomitant anticancer drugs



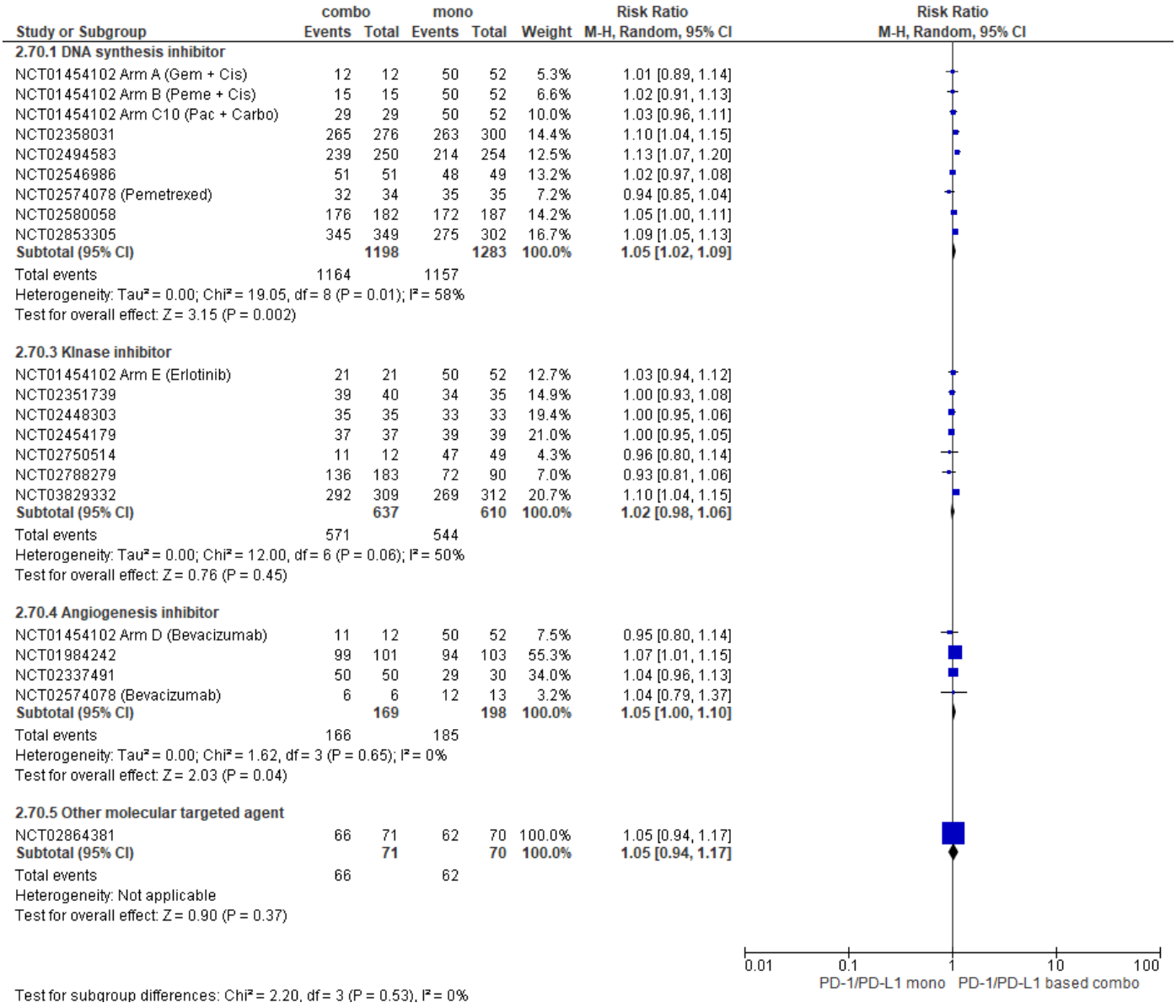
Supplementary Figure 12 Subgroup analysis of non-serious rash according to the mode of action of concomitant anticancer drugs



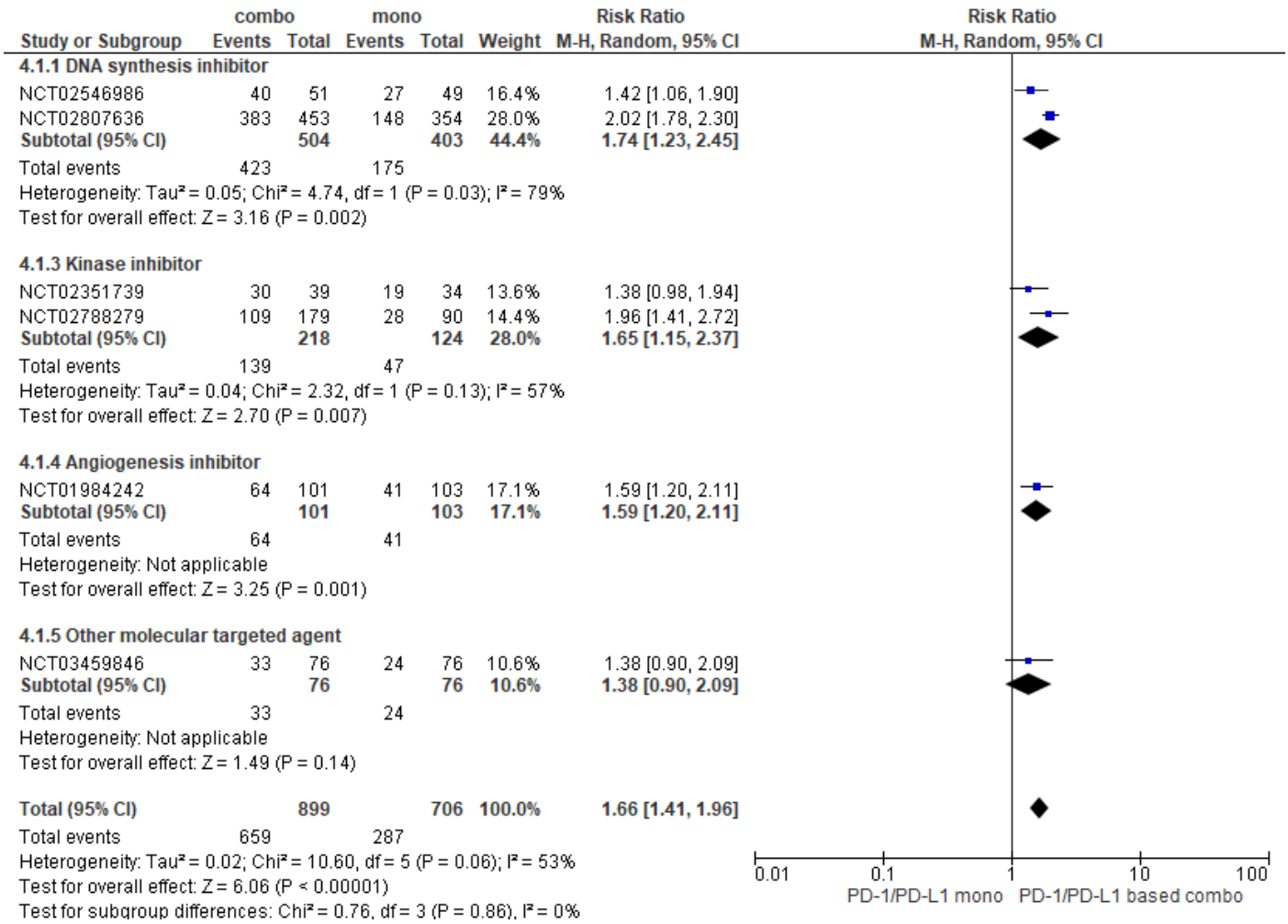
Supplementary Figure 13 Subgroup analysis of non-serious diarrhea according to the mode of action of concomitant anticancer drugs



Supplementary Figure 14 Subgroup analysis of overall serious AEs according to the mode of action of concomitant anticancer drugs



Supplementary Figure 15 Subgroup analysis of overall non-serious AEs according to the mode of action of concomitant anticancer drugs



Supplementary Figure 16 Subgroup analysis of overall Grade 3 or 4 AEs according to the mode of action of concomitant anticancer drugs