Cancer Control
Volume 29: 1–12

DOI: 10.1177/10732748221140694
journals.sagepub.com/home/ccx
SAGE

Anti-Tumor Efficacy of Anti-PD-1/PD-L1 Antibodies in Combination With Other Anticancer Drugs in Solid Tumors: A Systematic Review and Meta-Analysis

Takashi Inoue, MS[1,2] and Mamoru Narukawa, PhD[1]

Abstract

Background: The clinical efficacy of immune checkpoint inhibitors (CPIs) has been proven; however, it is also known that their efficacy as monotherapy is limited, with a response rate of 20% or less in solid tumors. The combination of CPIs and anticancer agents has been actively attempted in solid tumors area. In this systematic review and meta-analysis, we aimed to find favorable combination therapies of programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitors in terms of anti-tumor efficacy in clinical settings.

Methods: An electronic database search was performed using ClinicalTrials.gov, PubMed, and ASCO/ESMO annual meeting libraries. We included randomized or non-randomized trials designed to evaluate the efficacy and safety of combination therapies of PD-1/PD-L1 inhibitors and other anticancer drug-containing therapies. All clinical studies selected were solid tumors with objective response rate (ORR) data. The quality of the evidence was assessed with the Cochrane risk of bias tool or the Newcastle-Ottawa Scale. Meta-analysis used random effects models to pool results.

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 (relative risk [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 alone.

Conclusions: It was suggested that combinations of PD-1/PD-L1 inhibitors and potential immunogenic cell death (ICD) inducers improve the clinical anti-tumor efficacy, although updated meta-analyses based on the results of ongoing clinical trials are further needed.

Keywords

solid tumors, objective response rate, immune checkpoint inhibitor, PD-1 inhibitor, PD-L1 inhibitor, systematic review, meta-analysis

Introduction

Cancer is the leading cause of death worldwide, accounting to approximately 9.6 million deaths worldwide in 2018.[1] Although various novel therapies are being developed and introduced into clinical practice, there is currently no specific cure for cancer. Recent efforts have been made to develop

[1]Department of Clinical Medicine (Pharmaceutical Medicine), Graduate School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo, Japan
[2]Development, Astellas Pharma Inc, Chuo-ku, Tokyo, Japan

Corresponding Author:
Takashi Inoue, Department of Clinical Medicine (Pharmaceutical Medicine), Graduate School of Pharmaceutical Sciences, Shirokane 5-9-1, Minato-ku, Tokyo 108-8641, Japan.
Email: inoue.takashi@kitasato-u.ac.jp

anticancer agents that specifically target tumorigenic molecular pathways. Moreover, CPIs in addition to conventional cytotoxic chemotherapy agents have advanced significantly. In particular, PD-1 antibodies (pembrolizumab, nivolumab), or PD-L1 antibodies (atezolizumab, avelumab, and durvalumab), and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4; ipilimumab) have shown efficacy in several cancers and have been approved by the US Food and Drug Administration (FDA) and other regulatory agencies as CPIs.[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]

The clinical efficacy of CPIs has been proven in clinical settings; however, it is also known that their efficacy as monotherapy is limited to a subset of patients with most tumor types studied to date. Moreover, it has a response rate of 20% or less in many solid tumors, including breast, colon, lung, urothelial, and prostate cancer, thus warranting further improved outcomes.[7] 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 (eg, 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 (eg, 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 (eg, 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. It is also necessary to consider that combinations of drugs with different mechanisms of action are associated with enhanced safety risks.

In this study, we conducted a meta-analysis to evaluate the contribution of combinations of anticancer drugs and CPIs to the improved clinical tumor response and anti-tumor efficacy, particularly the anticancer drugs that may induce ICDs and other molecular targeted agents.

Materials and Methods

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 (ie, 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 American Society of Clinical Oncology (ASCO) Meeting Library (https://meetinglibrary.asco.org/) and the European Society for Medical Oncology (ESMO) Meeting Resources (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.

Data Extraction and Quality of Evidence

Two independent reviewers (TI and MN) 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 endpoint was tumor response rate (ie, 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 (ie, 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 (ie, randomized or non-randomized), and tumor type/disease condition. A single reviewer (TI) performed the initial data extraction using a standardized data collection form and second reviewer (MN) carefully checked them. Discrepancies were resolved through a discussion between them.

The quality and risk of bias of randomized controlled trials (RCTs) were assessed with the revised Cochrane Collaboration's risk of bias tool (RoB 2.0).[15] Non-randomized cohort studies were assessed using the Newcastle-Ottawa Scale,[16] ranging between zero up to 9 stars. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for the purpose of this analysis.[17] The review protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols [INPLASY] (registration number: INPLASY2022100004).

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 (eg, 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 $P < .05$, 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 $P < .05$ 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.

Results

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

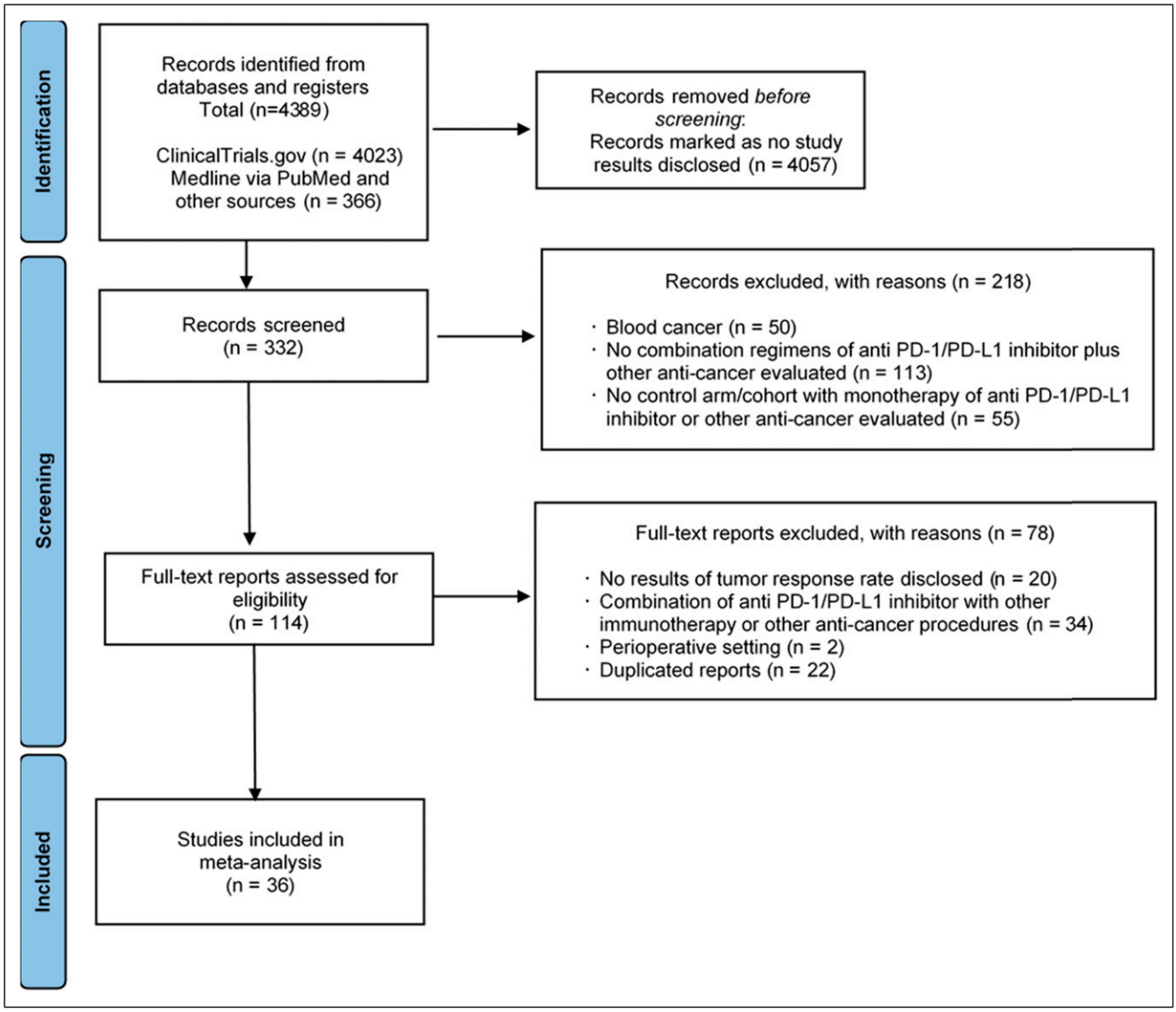

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of selecting clinical trials for this analysis.

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, 5 studies with nivolumab (10 combination therapy groups), 15 studies with pembrolizumab (15 combination therapy groups), 11 studies with atezolizumab (11 combination therapy groups), 2 studies with avelumab (2 combination therapy groups), and 4 studies with durvalumab (4 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 3 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 4 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

Table 1. Characteristics of the Included Studies.

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	18-20
	Pembrolizumab	15	15	7	7	21-29,38
	Atezolizumab	11	11	3	3	30-37,41
	Avelumab	2	2	1	1	
	Durvalumab	4	4	1	1	39,40
Mode of action of CPI	PD-1 inhibitor	19	24	11	16	18-29,38
	PD-L1 inhibitor	17	17	5	5	30-34,35-37,39,41
Development phase	Phase 1 or 1/2	4	9	2	7	18,19,20,21
	Phase 2	17	17	9	9	30,22,23,25,27,28,37
	Phase 3	15	15	5	5	24,31-34,26,41,29,35,36,39-40
Study type	Randomized	30	35	13	18	19,20,30,21,23-38,39-41
	Non-randomized	6	6	3	3	18,22
Tumor type	Lung cancer	15	20	4	9	19,20,21,31,32,39,27,28,41,29,40,38
	Ovarian cancer	3	3	1	1	
	Gastric/GEJ cancer	3	3	3	3	22,26
	Colorectal cancer	3	3	1	1	35
	Head & neck cancer	2	2	2	2	24
	Skin cancer	2	2	0	0	
	Breast cancer	2	2	0	0	33,34,37
	Urothelial cancer	2	2	2	2	23,36
	Biliary tract cancer	1	1	1	1	18
	Renal cell carcinoma	1	1	1	1	30
	Pancreatic cancer	1	1	0	0	25
	Glioblastoma	1	1	1	1	
Combination drug	Cisplatin/Carboplatin	13	16	6	9	18,19,21,22,24,28,29,31,32,36,38,40
	Bevacizumab	6	6	3	3	19,30,31
	Paclitaxel/nab-paclitaxel	6	7	1	2	19,31-34,29
	Acalabrutinib	5	5	3	3	23,25
	5-FU	4	4	3	3	22,24,26
	Capecitabine	4	4	2	2	22,26
	Pemetrexed	4	4	1	1	19,21,28
	Gemcitabine	3	3	3	3	18,19,36
	Etoposide	3	3	0	0	41,40,38
	Andecaliximab	1	1	1	1	
	CC-486	1	1	1	1	27
	Cobimetinib	1	1	1	1	35
	Decitabine	1	1	1	1	
	Tetrahydrouridine	1	1	1	1	
	Erlotinib	1	1	1	1	19
	Pegylated liposomal doxorubicin	1	1	1	1	
	Glembatumumab vedotin	1	1	0	0	
	Osimertinib	1	1	0	0	39
	Vismodegib	1	1	0	0	
	Trastuzumab emstasine	1	1	0	0	37

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

(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 monoclonal antibody bound with the cytotoxic agent monomethyl auristatin E (MMAE) (glembatumumab vedotin), and

an ADC of anti-HER2 trastuzumab bound with 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.

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.

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 < .00001) (Figure 2), although caution is required to interpret the results due to very high heterogeneity (P < .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 < .00001; I^2 = 44%) (Figure 3).

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.

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

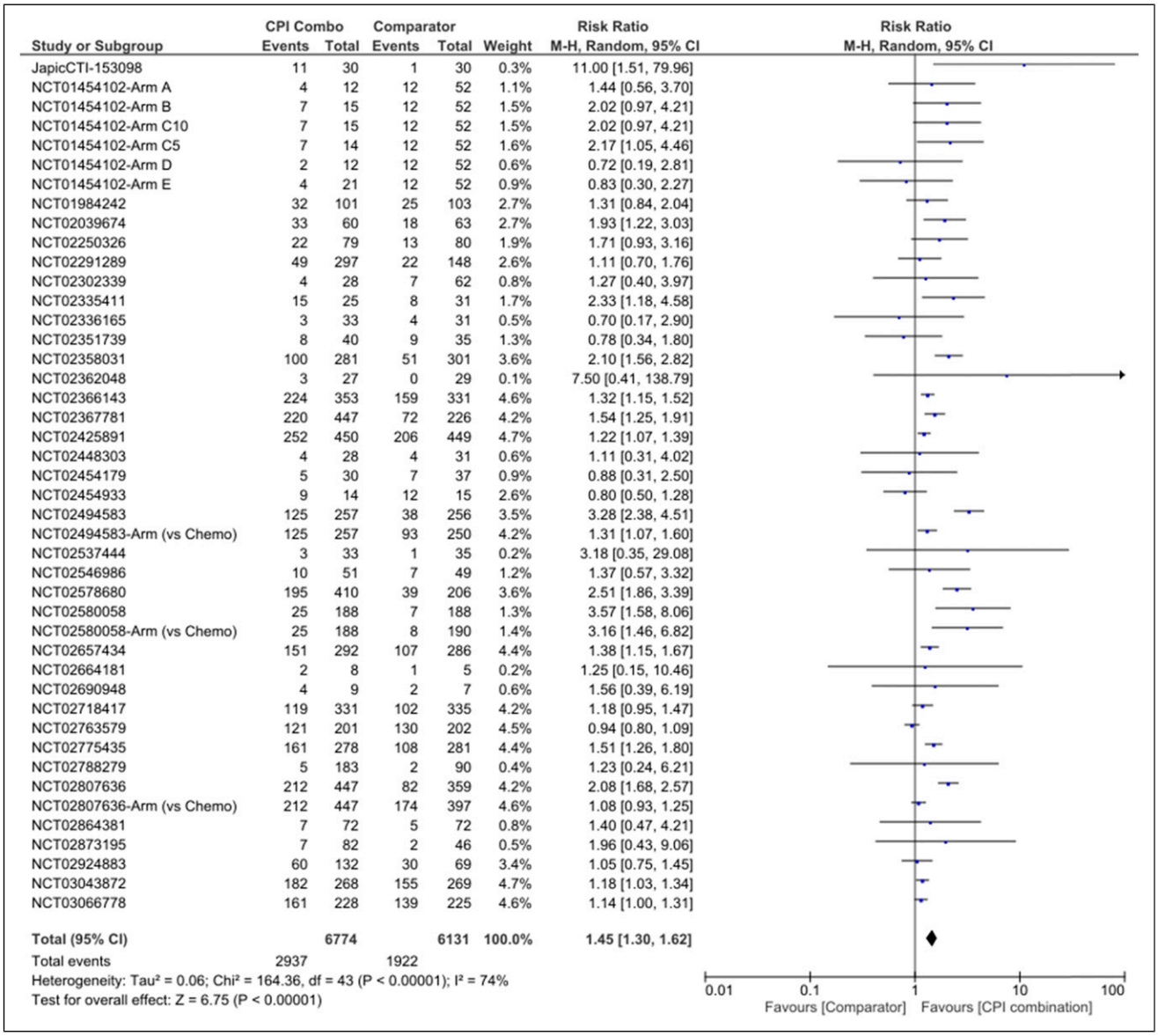

Figure 2. Meta-analysis of ORR for all identified studies. Abbreviations: ORR, overall response rate; CPI, immune checkpoint inhibitor.

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.[42] 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.[43] 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.[44] 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.

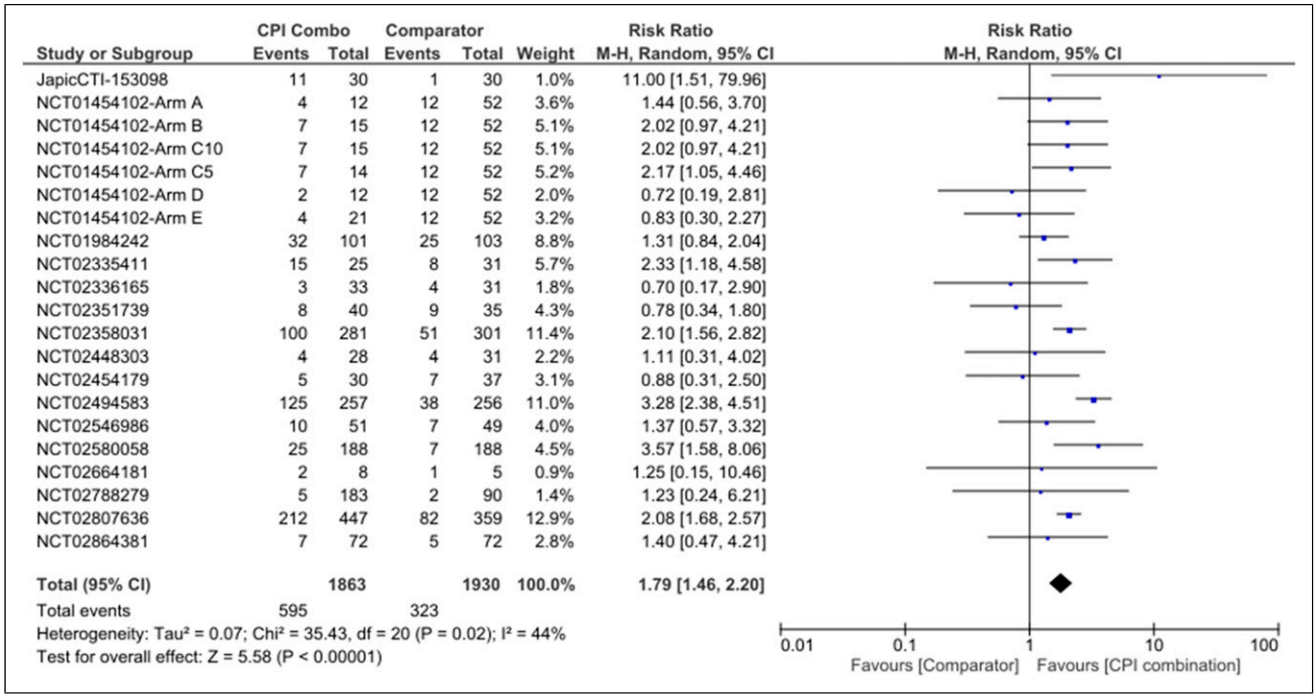

Figure 3. Meta-analysis of ORR for all studies with PD-1/PD-L1 monotherapy arm. Abbreviations: ORR, overall response rate; CPI, immune checkpoint inhibitor.

Table 2. Other Subgroup Analysis of ORR 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) <.0001 45%
Combination with PD-L1 inhibitor	5/5	277/952	120/771	1.78 (1.20, 2.64) .004 49%
ORR based on the tumor type				
Lung cancer	4/9	47/176	84/397	1.57 (1.15, 2.14) .005 0%
Gastric or GEJ cancer	3/3	147/354	51/359	2.73 (1.86, 4.02) <.00001 25%
Other tumors	9/9	401/1333	188/1174	1.70 (1.25, 2.32) .0008 55%

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

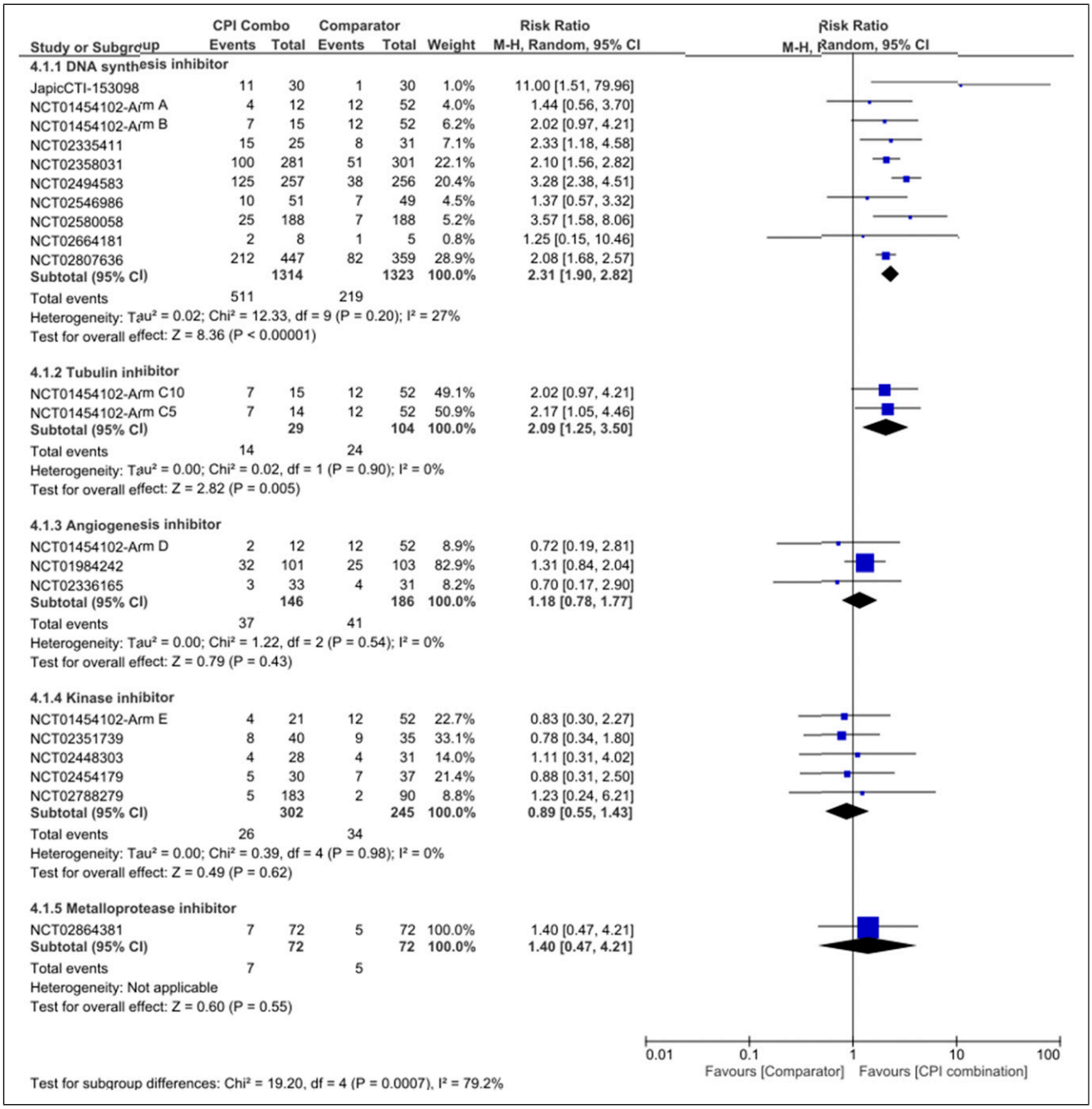

Figure 4. Meta-analysis of ORR by type of combination therapy for all studies with PD-1/PD-L1 monotherapy arm. Abbreviations: ORR, overall response rate.

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.

Conclusion

In the current study, we revealed that PD-1/PD-L1 inhibitor plus chemotherapies with DNA-synthesis inhibitory effect or microtubule inhibitory effect which are reported to induce immunogenic cell death 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-L inhibitor plus molecular targeted agents such as anti-angiogenic or kinase-inhibitory effects did not necessarily significantly improve the ORRs compared to PD-1/PD-L1 inhibitor alone. Although an updated meta-analysis based on the results of ongoing clinical trials of PD-1/PD-L1 inhibitors and other anticancer agents is needed, these findings will serve to help researchers and clinicians determine what kind of agents will improve clinical antitumor efficacy in combination with PD-1/PD-L1 inhibitors in the future.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

Author Contributions

Takashi Inoue: conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing-original draft, writing-editing. Mamoru Narukawa: data curation, investigation, writing-editing.

Declaration of Conflicting Interests

Takashi Inoue is an employee of Astellas Pharma Inc.; however, employment in the company has not influenced the results and discussion presented in this paper. The other authors declare no competing interests.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

The conducted research is not related to either human or animal use.

ORCID iD

Takashi Inoue https://orcid.org/0000-0001-5409-8961

Supplemental Material

Supplementary material for this article is available on the online.

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer.* 2019;144(8):1941-1953. doi:10.1002/ijc.31937.
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, 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, 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, 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 byanticancer 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. 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.
16. 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
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.

37. 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.
38. 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.
39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.