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Efficacy and safety of combination immunotherapy for malignant solid tumors: A systematic review and meta-analysis

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ABSTRACT

Background: Combination immunotherapy has become an actively growing field of clinical investigation.
Methods: We searched for clinical trials of combination immunotherapy and calculated the pooled hazard ratio (HR), odds ratio (OR) of clinical outcomes and safety by subgroups of different combination regimens.
Results: Totally 28 clinical trials were analyzed. The study showed that the pooled HRs of overall survival and progression-free survival for combination therapy were 0.77 (95% CI: 0.70 − 0.84, $p < 0.001$) and 0.72 (95% CI: 0.66 − 0.79, $p < 0.001$) while the pooled OR of high-grade adverse effects was 1.45 ($p = 0.004$). Subgroup analysis showed that the HR of overal survival were 0.74 ($p = 0.005$), 0.79 ($p < 0.001$), 0.70 ($p = 0.003$) and 0.85 ($p = 0.052$) for immunotherapy combined with immunotherapy, chemotherapy, targeted therapy and radiotherapy group, respectively.
Conclusions: The meta-analysis indicated that combination immunotherapy could bring more clinical benefits with increased high-grade adverse effects.

1. Introduction

In recent years, remarkable progress has been made in tumor treatment with the discovery of immunotherapy, which has been used to a wide range of solid tumors such as melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), small cell lung cancer (SCLC), squamous-cell carcinoma of the head and neck, urothelial carcinoma and prostate cancer (Ferris et al., 2016; Kantoff et al., 2010; Motzer et al., 2015; Reck et al., 2016b; Robert et al., 2015a,b; Sharma et al., 2016). In 2013, *Science* magazine announced immunotherapy a turning point in cancer treatment (Couzin-Frankel, 2013). Immunotherapy stimulates and enhances antitumor responses to inhibit tumor growth or kill tumor cells by active or passive ways such as immune checkpoint blockade (ICB), antitumor vaccine, adoptive immunotherapy, cytokine, etc. Among them, ICB, which restores antitumor effects by blocking cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), T cell immunoglobulin mucin 3 (TIM-3), lymphocyte activation gene 3 (LAG-3), indoleamine 2,3 dioxygenase (IDO) and other inhibitory receptor-ligand interactions, is most promising due to its unprecedented durable responses and manageable adverse events (AEs) (Pennock and Chow, 2015). Particularly, anti-CTLA-4 antibodies (ipilimumab), anti-PD-1 antibodies (nivolumab and pembrolizumab) and anti-PD-L1 antibodies (atezolizumab, avelumab and durvalumab) have been approved for clinical use.

Despite the remarkable progress that has been achieved, the efficacy of immunotherapy is not entirely satisfactory. Even for ICB, there are approximately 60%–70% of patients who do not respond to monotherapy (Larkin et al., 2015; Larkins et al., 2017; Robert et al., 2015a,b; Topalian et al., 2012, 2014). Immune tolerance may be the main reason for the phenomenon. Therefore, combination strategies are necessary to overcome the resistance and enlarge the clinical utility of immunotherapy. It is demonstrated that traditional treatments such as chemotherapy, radiotherapy and targeted therapy have immunomodulatory effects (Demaria et al., 2015; Fukumura et al., 2018; Pfirschke et al., 2016) and combination therapies with immunotherapy may achieve synergistic effects and thus maximize clinical efficacy. Some combinatorial regimens are demonstrated statistically significant improvements in survival and have been approved in clinical

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application (e.g., ipilimumab + nivolumab for melanoma and NSCLC, pembrolizumab + pemetrexed and platinum-based drug for non-squamous NSCLC) (Gandhi et al., 2018; Hodi et al., 2016; Wolchok et al., 2017).

Nevertheless, it remains controversial whether combination therapy with immunotherapy is superior to monotherapy indeed, because not all studies showed significant improvement (Hodi et al., 2014; Reck et al., 2016a) and some even showed reduction of efficacy (Hodi et al., 2010). Besides, the increased AEs and the added costs of combinatorial regimens make it doubtful. It is of great significance to explore the efficacy and safety of combination therapy from evidence-based medicine but there are few relevant studies. We conducted a systematic review and meta-analysis of clinical data that compared the combination immunotherapy with monotherapy and explored relevant mechanisms to guide the application of combination approaches.

2. Methods

2.1. Search strategy

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2015). Three researchers (Yuhan Wei, Mengqi Li and Qi Du) searched for relevant studies on PubMed, EMBASE and the Central Registry of Controlled Trials of the Cochrane Library. We also searched abstracts from the meetings of American Society of Clinical Oncology (ASCO). Proposed MeSH terms were: “immunotherapy OR immune therapy OR immune checkpoint inhibitor OR immune checkpoint blockade OR immune vaccine OR nivolumab OR ipilimumab OR pembrolizumab OR atezolizumab OR tremelimumab OR avelumab OR durvalumab” AND “combination OR combined with OR plus” AND “tumor OR cancer OR carcinoma OR neoplasm OR malignancy OR sarcoma”. Qualifier was “clinical trial”. The language was restricted to English. The cut-off date was February 20, 2019.

2.2. Eligibility

The inclusion criteria was as follows: (1) prospective study; (2) phase II or III clinical trials; (3) the subjects of the trials must be patients with histologically or cytologically confirmed malignant solid tumor; (4) the experimental intervention group was immunotherapy + immunotherapy, immunotherapy + chemotherapy, immunotherapy + targeted therapy or immunotherapy + radiotherapy; (5) the study should analyze the efficacy and safety of combination immunotherapy versus monotherapy; (6) the study must present any of the following measurements: overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and the rate of grade 3–5 AEs. Where multiple articles analyzed the same trial, the most recent data was used.

2.3. Data extraction

Relevant information was extracted independently by two reviewers (Yuhan Wei and Qi Du) according to a predefined form including study characteristics, patient characteristics, treatment regimens and outcome data. Data from relevant appendix was extracted as well. All disagreements were resolved by discussion with a third reviewer (Teng Li). The primary outcomes were OS, PFS and secondary outcomes were ORR, DCR and the rate of grade 3–5 AEs. An exploratory analysis included evaluating the survival benefit of combination immunotherapy according to PD-L1 expression.

2.4. Statistical analysis

Two reviewers (Yuhan Wei and Qi Du) independently assessed the risk of bias using the Cochrane Reviewer Handbook. Any discrepancy was resolved by consensus. The evaluation of the risk of bias was conducted by Review Manager (RevMan5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Statistical analysis, forest plots, detection of publication bias and sensitivity analysis were done with Stata SE 12 (Stata Corporation, College Station, TX, USA). We calculated the pooled hazard ratio (HR) and 95% CI for PFS and OS and the pooled odds ratio (OR) and 95% CI for ORR and DCR and the rate of grade 3–5 AEs. An exploratory analysis evaluating the pooled HR of OS according to PD-L1 expression bounded by 1% was done as well. I-squared (I^2) tests were used to evaluate the heterogeneity between trials. Either $p < 0.1$ or $I^2 > 50\%$ indicated the existence of heterogeneity, then the randomized-effects model was used. Otherwise, the fixed-effects model was used. $p < 0.05$ was considered statistically significant. The publication bias was assessed by both Bag’s test and Egger’s test.

3. Results

3.1. Search results

A total of 5462 original articles as well as 452 ASCO meeting abstracts were obtained from electronic searches. After screening, duplicates and irrelevant studies were excluded and 24 original articles and 4 ASCO conference abstracts remained for final meta-analysis (Fig. 1).

3.2. Main characteristics and the risk of bias in the included studies

Totally 28 clinical trials published from 2011 to 2019 involving 14,070 patients were identified in the systematic evaluation, including seven immunotherapy + immunotherapy (D’Angelo et al., 2018; Hodi et al., 2016, 2014; Hodi et al., 2010; Motzer et al., 2018a,b; Peters et al., 2016; Wolchok et al., 2017), thirteen immunotherapy + chemotherapy (eleven full-text articles (Borghaei et al., 2019; Gandhi et al., 2018; Govindan et al., 2017; Hersh et al., 2011; Horn et al., 2018; Lynch et al., 2012; Paz-Ares et al., 2018; Reck et al., 2013, 2016a; Robert et al., 2011; Schmid et al., 2018) and two ASCO meeting abstracts (Borghaei et al., 2018; Jotte et al., 2018)), five immunotherapy + targeted therapy (four full-text articles (McDermott et al., 2018; Motzer et al., 2019; Rini et al., 2019; Socinski et al., 2018) and one ASCO meeting abstracts (Motzer et al., 2018a,b) and three immunotherapy + radiotherapy (two full-text articles (Kwon et al., 2014; Slovin et al., 2013) and one ASCO meeting abstracts (Theelen et al., 2018)). There were seven different tumor types such as NSCLC (N = 9), melanoma (N = 6), RCC (N = 5), SCLC (N = 4), prostate cancer (N = 2), breast cancer (N = 1) and sarcoma (N = 1). There were 21 trials done in first-line settings and seven with second or additional lines of therapy (Table 1, Supplementary Table S1). The assessment of risk of bias was presented in Supplementary Fig. S1.

3.3. Efficacy

Among 28 identified studies, 19 trials reported OS with 23 comparisons; 23 trials reported PFS with 27 comparisons; data on ORR were available in 27 trials with 31 comparisons; 21 trials with 25 comparisons provided data of DCR. Randomized-effects model was used in all measurements because of the significant heterogeneity.

Overall analysis indicated that combination immunotherapy could significantly improve OS (HR = 0.77, 95% CI: 0.70 − 0.84, $p < 0.001$), PFS (HR = 0.72, 95% CI: 0.66 − 0.79, $p < 0.001$), ORR (OR = 1.79, 95% CI: 1.45–2.21, $p < 0.001$) and DCR (OR = 1.32, 95% CI: 1.08–1.63, $p = 0.008$) in comparison to monotherapy.

Subgroup analysis demonstrated that immunotherapy + immunotherapy was associated with better OS (HR = 0.74, 95% CI: 0.59 − 0.91, $p = 0.005$), PFS (HR = 0.72, 95% CI: 0.53 − 0.97, $p = 0.031$), ORR (OR = 2.33, 95% CI: 1.33–4.05, $p = 0.003$) and DCR (OR = 1.54, 95% CI: 1.03–2.29, $p = 0.034$) compared to monotherapy.

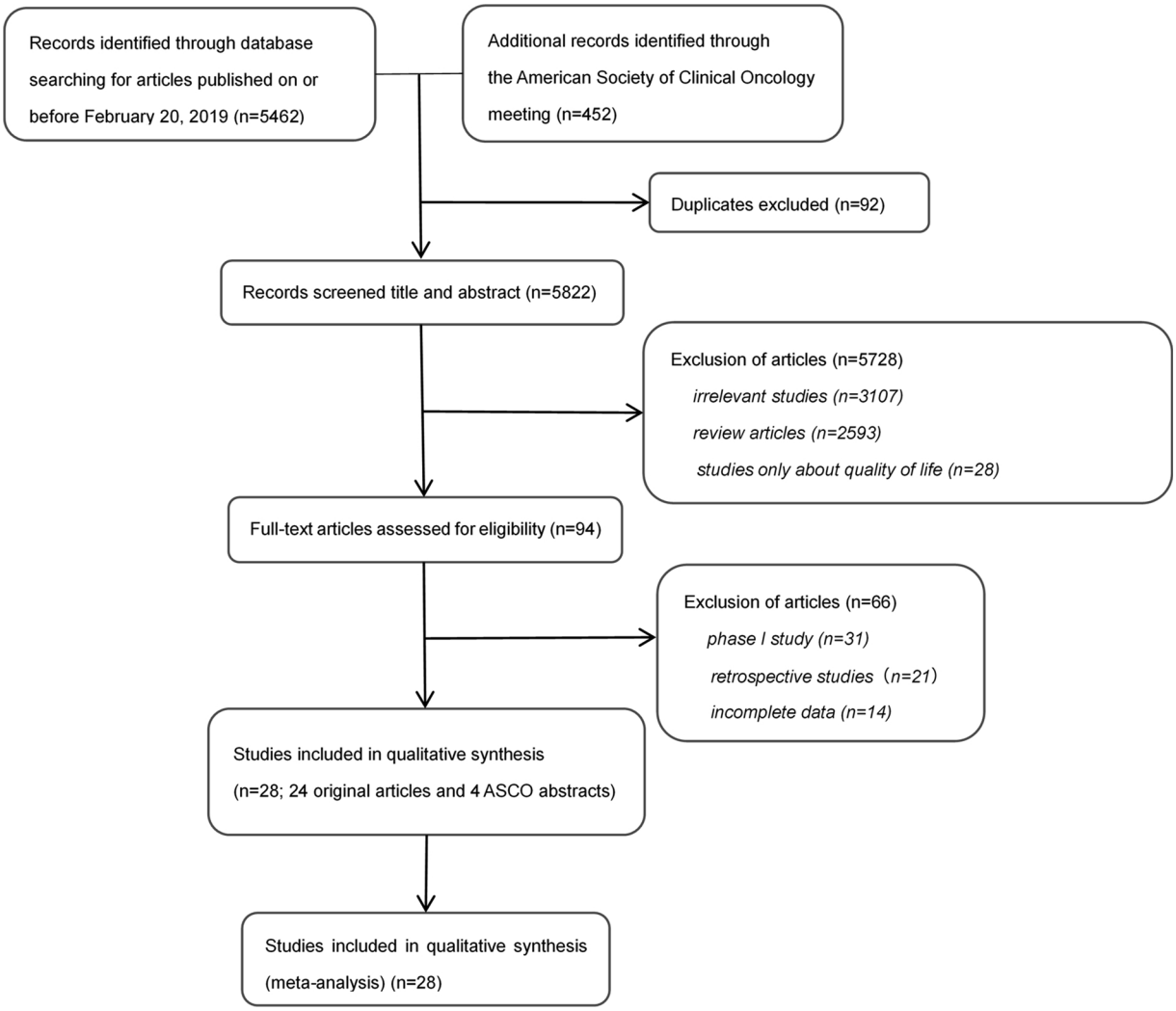


Fig. 1. Flow diagram representing the selection process.

Immunotherapy + chemotherapy could significantly prolong OS (HR = 0.79, 95% CI: 0.70 − 0.89, $p < 0.001$), PFS (HR = 0.72, 95% CI: 0.65 − 0.80, $p < 0.001$), improve ORR (OR = 1.56, 95% CI: 1.22–2.01, $p < 0.001$) when compared with immunotherapy or chemotherapy alone, but didn't increase DCR (OR = 1.10, 95% CI: 0.78–1.53, $p = 0.591$). Immunotherapy + targeted therapy brought more clinical benefits in OS (HR = 0.70, 95% CI: 0.55 − 0.88, $p = 0.003$), PFS (HR = 0.73, 95% CI: 0.64 − 0.84, $p < 0.001$) and ORR (OR = 1.88, 95% CI: 1.28–2.78, $p = 0.001$) and DCR (OR = 1.58, 95% CI: 1.28–1.95, $p < 0.001$) than targeted therapy. In addition, PFS (HR = 0.69, 95% CI: 0.60 − 0.80, $p < 0.001$) was significantly longer in the immunotherapy + radiotherapy group than that in monotherapy group, while OS improvement was marginally significant (HR = 0.85, 95% CI: 0.72–1.00, $p = 0.052$), ORR (OR = 0.87, 95% CI: 0.05–14.78, $p = 0.921$) and DCR (OR = 1.56, 95% CI: 0.59–4.12, $p = 0.369$) were not statistically improved (Fig. 2 and Fig. 3).

When grouped by tumor types, OS was significantly prolonged in melanoma, RCC and NSCLC groups (pooled HR were 0.75, 0.64 and 0.76, respectively). Combination immunotherapy was associated with longer PFS in RCC, NSCLC, breast cancer, SCLC and prostate cancer groups (pooled HR were 0.77, 0.66, 0.80, 0.81 and 0.70, respectively). For melanoma, RCC, NSCLC and breast cancer groups, the pooled OR of ORR were 2.30, 1.91, 1.91 and 1.50, which were superior to monotherapy (Supplementary Fig. S2, S3).

Four RCTs were available for analysis of OS according to PD-L1 expression bounded by 1%. For patients of PD-L1 < 1%, the pooled HR of survival was 0.66 (95% CI: 0.55 − 0.80, $p < 0.001$). For patients of PD-L1 ≥ 1%, the pooled HR of survival was 0.53 (95% CI: 0.43 − 0.64, $p < 0.001$) (Supplementary Fig. S5).

3.4. Toxicity

In total 22 trials reported the incidence of grade 3–5 AEs. Randomized-effects model was used because of the substantial heterogeneity. It showed that the rate of grade 3–5 AEs in the combination group was significantly higher than that in the monotherapy group (OR = 1.45, 95% CI: 1.12–1.86, $p = 0.004$).

According to the subgroup analysis, immunotherapy + immunotherapy, immunotherapy + chemotherapy and immunotherapy + targeted therapy were associated with higher risk of the incidence of grade 3–5 AEs with the pooled OR of 1.81, 1.51 and 1.16, respectively. However, the rate of grade 3–5 AEs did not increase in immunotherapy + radiotherapy (OR = 0.93). Moreover, melanoma and NSCLC groups had higher incidence of grade 3–5 AEs. Main adverse events included general adverse events related to immune activation (diarrhea, fatigue and rash) and organ specific adverse events (colitis, hepatitis, pneumonia, hypothyroidism and hypophysitis) (Baxi et al., 2018), among which the rate of grade 3–5 diarrhea, fatigue and colitis drastically increased in all combination regimens (Fig. 4).

Table 1
Main characteristics of included studies.

Author	Year	Phase	Tumor	Line	Sample Size		Age	Interventions
					Arms	N		
Hodi FS	2016	II	Melanoma	1 L	Study	95	64	Nivolumab + ipilimumab
					Control	47	67	Ipilimumab
Wolchok JD	2017	III	Melanoma	1 L	Study	314	61	Nivolumab + ipilimumab
					Control	316	60	Nivolumab
					Control	315	62	Ipilimumab
Antonia SJ	2016	I/II	SCLC	2L	Study	54	61	Nivolumab + ipilimumab
					Control	98	63	Nivolumab
Motzer RJ	2018	III	RCC	1 L	Study	550	62	Nivolumab + ipilimumab
					Control	546	62	Sunitinib
Hodi FS	2010	III	Melanoma	2L	Study	403	55.6	Ipilimumab + gp100
					Control	137	56.8	Ipilimumab + placebo
					Control	136	57.4	Gp100
Hodi FS	2014	II	Melanoma	1 L/2L	Study	123	61	Ipilimumab + sargramostim
					Control	122	64	Ipilimumab
D'Angelo SP	2018	II	Sarcoma	2L	Study	42	57	Nivolumab + ipilimumab
					Control	43	56	Nivolumab
Borghaei H*	2018	III	NSCLC	1 L	Study	177	–	Nivolumab + platinum doublet chemotherapy
					Control	186	–	Platinum doublet chemotherapy
Schmid P	2018	III	Breast cancer	1 L	Study	451	55	Atezolizumab + na**b**-paclitaxel
					Control	451	56	Na**b**-paclitaxel
Jotte R*	2018	III	Squamous NSCLC	1 L	Study	343	–	Atezolizumab + carboplatin + na**b**-paclitaxel
					Control	340	–	Carboplatin + na**b**-paclitaxel
Horn L	2018		SCLC	1 L	Study	201	64	Atezolizumab + carboplatin + etoposide
					Control	202	64	Carboplatin + etoposide
Paz-Ares L	2018	III	Squamous NSCLC	1 L	Study	278	–	Pembrolizumab + carboplatin-paclitaxel/na**b**-paclitaxel
					Control	281	–	Carboplatin-paclitaxel/na**b**-paclitaxel
Gandhi L	2018	III	Non-squamous NSCLC	1 L	Study	410	65	Cisplatin/carboplatin + pemetrexed + pembrolizumab
					Control	206	63.5	Cisplatin/carboplatin + pemetrexed
Govindan R	2017	III	Squamous NSCLC	1 L	Study	388	64	Paclitaxel + carboplatin + ipilimumab
					Control	361	64	Paclitaxel + carboplatin
Reck M	2016	III	SCLC	1 L	Study	478	62	Etoposide + cisplatin/carboplatin + ipilimumab
					Control	476	63	Etoposide + cisplatin/carboplatin
Borghaei H	2019	II	Non-squamous NSCLC	1 L	Study	60	62.5	Pembrolizumab + pemetrexed + carboplatin
					Control	63	63.2	Pemetrexed + carboplatin
Reck M	2013	II	SCLC	1 L	Study	43	–	Paclitaxel + carboplatin + concurrent-ipilimumab
					Study	42	–	Paclitaxel + carboplatin + phased-ipilimumab
					Control	45	–	Paclitaxel + carboplatin
Lynch TJ	2012	II	NSCLC	1 L	Study	70	59	Paclitaxel + carboplatin + concurrent-ipilimumab
					Study	68	61	Paclitaxel + carboplatin + phased-ipilimumab
					Control	66	62	Paclitaxel + carboplatin
Robert C	2011	III	Melanoma	1 L	Study	250	57.5	Ipilimumab + dacarbazine
					Control	252	56.4	Dacarbazine
Hersh EM	2011	II	Melanoma	1 L	Study	35	60	Ipilimumab + dacarbazine
					Control	37	66	Ipilimumab
Rini BI	2019	III	RCC	1 L	Study	432	62	Pembrolizumab + axitinib
					Control	429	61	Sunitinib
Motzer RJ	2019	III	RCC	1 L	Study	442	62	Avelumab + axitinib
					Control	444	61	Sunitinib
McDermott DF	2018	II	RCC	1 L	Study	101	62	Atezolizumab + bevacizumab
					Control	101	61	Sunitinib
Motzer RJ*	2018	III	RCC	1 L	Study	454	–	Atezolizumab + bevacizumab
					Control	461	–	Sunitinib
Socinski MA	2018	III	Non-squamous NSCLC	1 L	Study	356	63	Atezolizumab + bevacizumab + paclitaxel + carboplatin
					Control	336	63	Bevacizumab + paclitaxel + carboplatin
Slovin SF	2013	I/II	Prostate cancer	2L	Study	34	66	Ipilimumab 10 mg/kg + radiotherapy
					Control	16	65	Ipilimumab
Kwon ED	2014	III	Prostate cancer	2L	Study	399	69	Radiotherapy + ipilimumab
					Control	400	67.5	Radiotherapy
Theelen W*	2018	II	NSCLC	2L	Study	32	–	Pembrolizumab + SBRT
					Control	32	–	Pembrolizumab

Abbreviation: SCLCsmall-cell lung cancer; RCCrenal cell carcinoma; NSCLCnon-small-cell lung cancer; 1 Lfirst line; 2Lsecond line or beyond; SBRTstereotactic body radiotherapy.

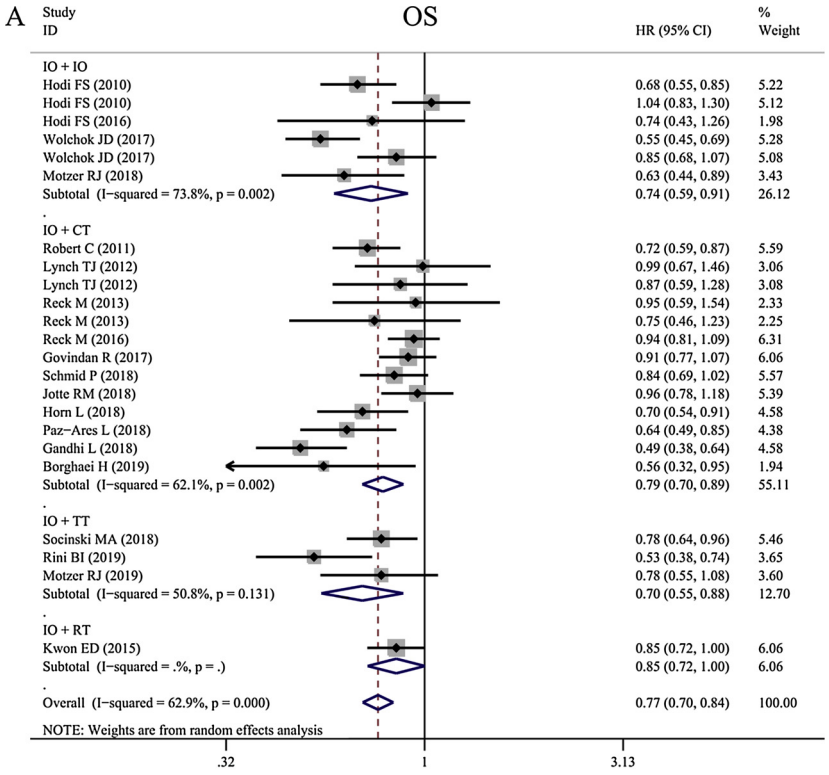
* showed on ASCO; - unclear.

3.5. Publication bias and sensitivity analysis

There was no publication bias based on our analysis. The funnel plot was basically symmetrical and the *p*-values of both the Bag's test and the Egger's test were over 0.05 in each outcome measurement. Sensitivity analysis was conducted for all outcomes and revealed that no individual study appeared to change the pooled effect estimate dramatically (Supplementary Fig. S4).

4. Discussion

Despite the durable responses observed in tumor immunotherapies, most patients do not respond to the initial treatment (primary resistance) and some of the responders relapse after a period of response



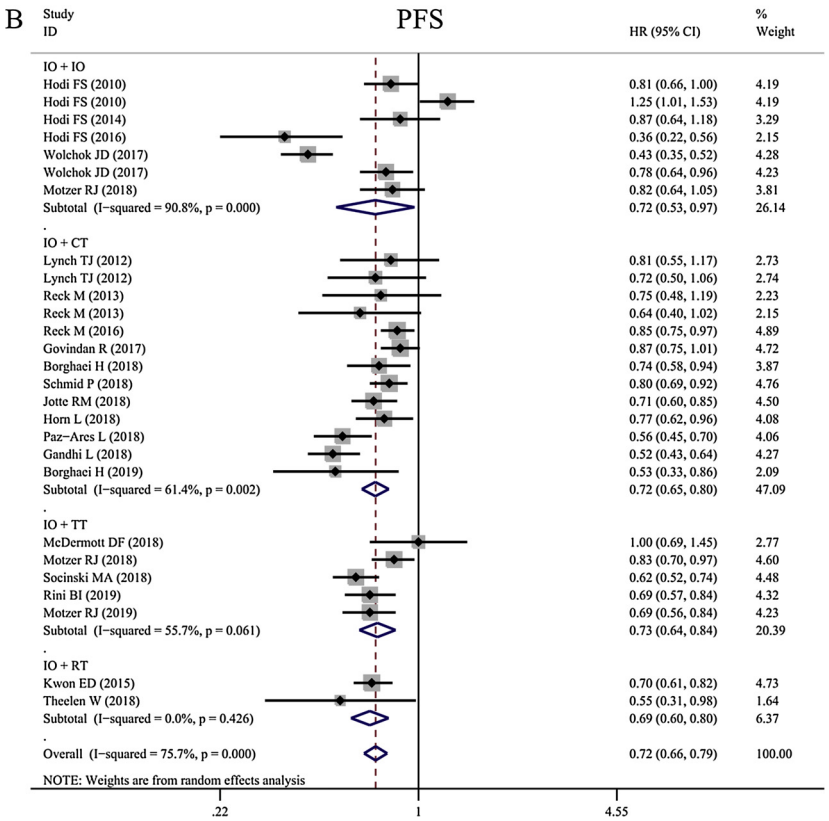


Fig. 2. Subgroup analysis of OS and PFS by combination regimens. **A,** OS; **B,** PFS. IO, immunotherapy; CT, chemotherapy; RT, radiotherapy; TT, targeted therapy; CRT, chemoradiotherapy.

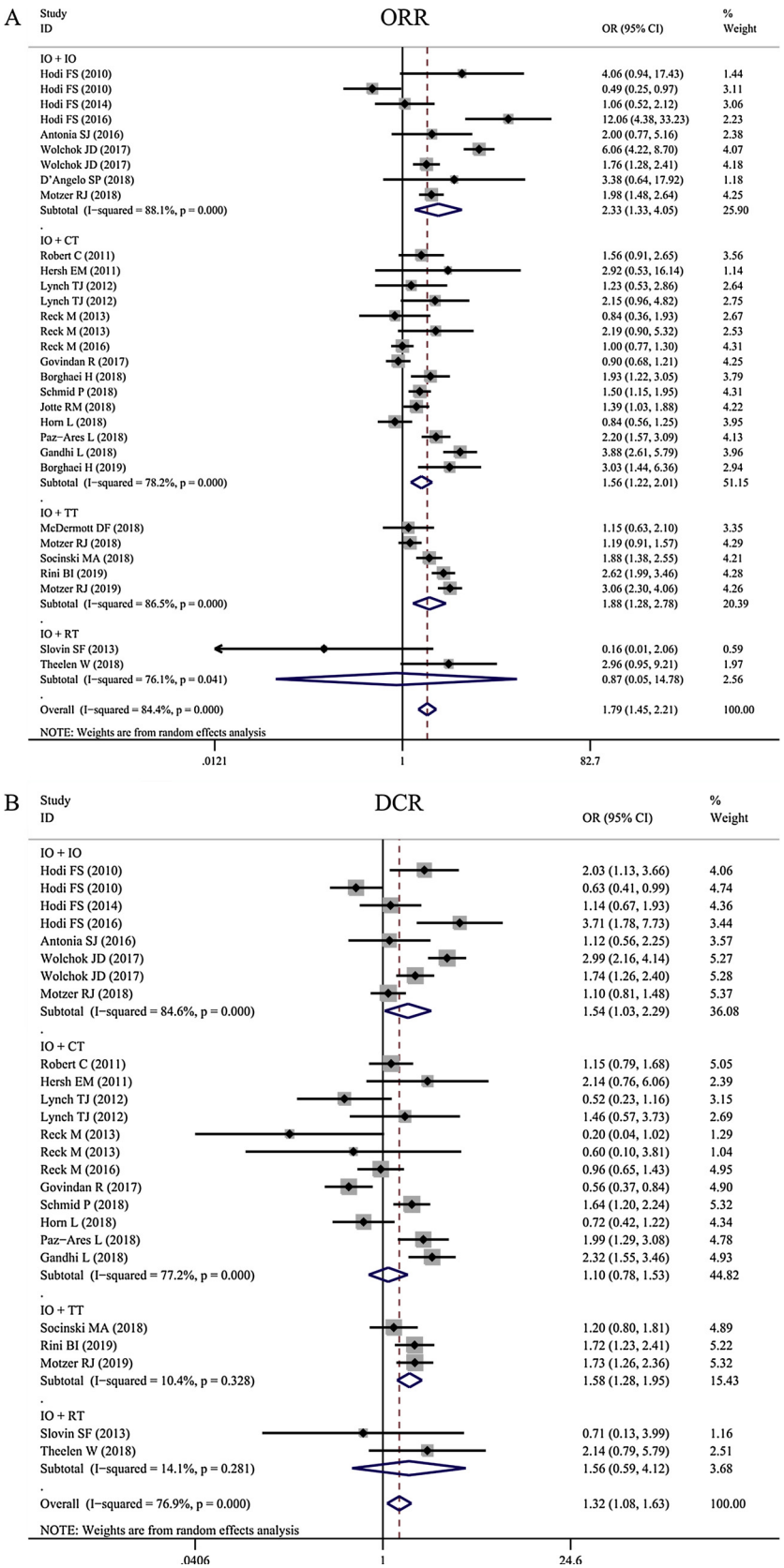


Fig. 3. Subgroup analysis of ORR and DCR by combination regimens. **A,** ORR; **B,** DCR. IO, immunotherapy; CT, chemotherapy; RT, radiotherapy; TT, targeted therapy; CRT, chemoradiotherapy.

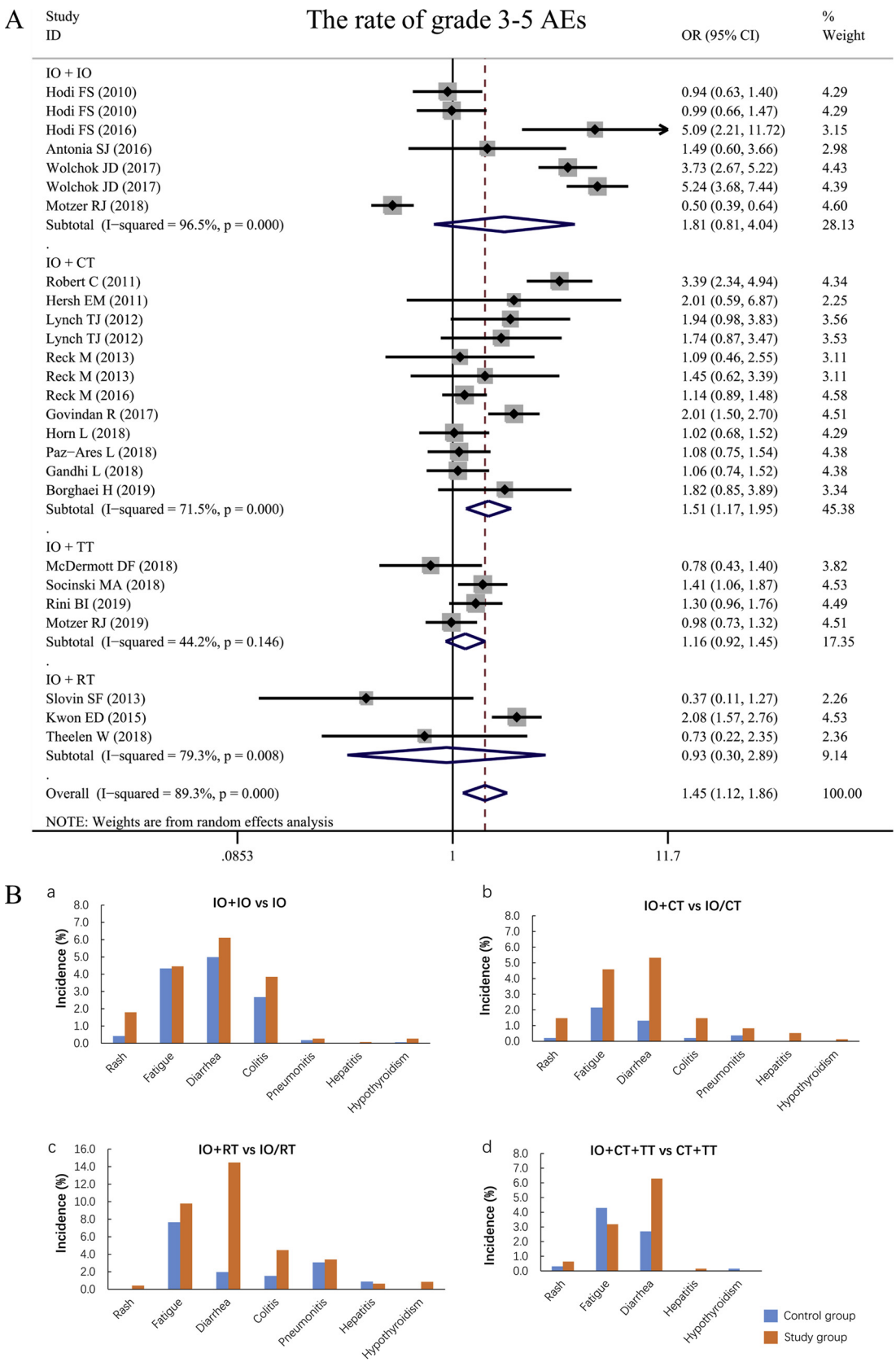


Fig. 4. A, OR of grade 3–5 AEs rates. **B,** Incidence of grade 3–5 irAEs. IO, immunotherapy; CT, chemotherapy; RT, radiotherapy; TT, targeted therapy; CRT, chemoradiotherapy.

(acquired resistance) (Sharma et al., 2017). Insufficient infiltration of cytotoxic T lymphocytes, lack of tumor-associated antigens (TAAs) and activation of other immunosuppressive pathways are major causes of resistance to immunotherapy. Researchers tried to overcome the resistance to improve clinical benefits of immunotherapy. Chemotherapy, radiotherapy and targeted therapy have immunomodulatory effects. Their clinical utilities in combination with immunotherapy to achieve synergetic effects and improve clinical outcomes have been hot research topics at present. However, it remains controversial as outcomes regarding the efficacy and safety of combination immunotherapy are not always consistent. Our meta-analysis showed that combination immunotherapy could significantly improve the anti-tumor efficacy. Although the incidence of adverse events above grade 3 increased, it was manageable.

The combination of different immunotherapies is an actively growing field of clinical investigation, as many studies showed great clinical efficacy. In checkmate 067 and 069, the combination group was associated with significantly better responses and longer PFS: the ORR of nivolumab + ipilimumab combination group were 58% and 59%, respectively and PFS were 11.5 months and NR (not reached), respectively (Hodi et al., 2016; Wolchok et al., 2017). We further confirmed this in the meta-analysis. Our study showed that combination immunotherapy resulted in a significantly improved ORR and OS. Among all immunotherapy + immunotherapy research, CTLA-4 blockade + PD-1 blockade is most frequent in research: CTLA-4 blockade primarily acts at sites of priming of T cell (e.g., tumor draining lymph nodes). It blocks the competitive inhibition signal of CTLA-4, inhibits the function of regulatory T cell (Treg), thus promoting T cell activation. PD-1/PD-L1 blockade primarily acts in inflamed peripheral tissues (e.g., tumor) by blocking the binding of PD-1 on T cells to PD-L1 on tumor cells to reverse the depletion of T cells and restore the activity of T cells (Fig. 5A) (Hargadon et al., 2018; Wei et al., 2018). Distinct mechanisms that act on different targets and at different stages of T cell differentiation make it possible to realize synergistic effect. In addition, tumor vaccines or immune cellular therapy stimulating T cells, combined with immune checkpoint inhibitors releasing brake of T cell, may improve therapeutic efficacy (Dammeijer et al., 2016). All above explain our results very well. However, NCT00094653 showed that gp100 vaccine + ipilimumab did not improve therapeutic efficacy. On the contrary, additional gp100 appeared to attenuate responses (Hodi et al., 2010). Researchers demonstrated that it was due to a persisting antigen depot produced by gp100 that primes T cells and induces T cell isolation, dysfunction and deletion, thus reducing the efficacy of ICB. Researchers further proved that non-persistent, virus, or water-based vaccine would not cause this inhibitory effect and could play a synergistic role with ICB (Hailemichael et al., 2013, 2018).

Whether the combination of immunotherapy and chemotherapy exert synergetic effects is highly concerned by researchers. Our meta-analysis gave a positive answer: immunotherapy + chemotherapy did show significantly longer survival than chemotherapy alone (HR = 0.79). Among them, Keynote-189, which evaluated the combination of pembrolizumab with pemetrexed and platinum-based drug in the treatment of advanced non-squamous NSCLC, showed that the combination regimen extended the median PFS by 3.9 months (8.8 months vs 4.9 months) and reduced the risk of death by 51% (HR for survival: 0.49), and ORR in the combined group was significantly superior to that in the single group (47.6% vs 18.9%). More importantly, additional pembrolizumab does not increase the incidence of adverse events (Gandhi et al., 2018). In addition to the direct cytotoxic effects on tumor cells, some chemotherapeutic agents can also stimulate immune system. This mainly including: increasing tumor antigenicity by releasing TAAs, inducing immunogenic cell death (ICD) with releasing damage-associated molecular patterns (DAMPs) and eliminate immunosuppressive cells such as Treg and myeloid-derived suppressor cell (MDSC) (Fig. 5B) (Pfirschke et al., 2016; Sistigu et al., 2014). In addition, several studies reported upregulation of PD-L1 on tumor cells induced by chemotherapy (Galluzzi et al., 2015; Peng et al., 2015), which may be one of the mechanisms of resistance to chemotherapy. Blocking PD-1/PD-L1 signaling pathway may reverse the resistance. Therefore, the combination can play a facilitating role. It is worth noting that different chemotherapeutic drugs have different immune mechanisms and effect duration, so it is particularly important to select appropriate drugs, dosage and timing of administration to improve the efficacy of combination therapy. The optimal combination therapy strategy is still under exploration.

In recent years, studies have reported abscopal effect of radiotherapy, that is, regression of non-irradiated metastatic lesions at a distance from the primary site of irradiation (Fig. 5C). This phenomenon is closely related to immune responses, which gives researchers an idea for immunotherapy + radiotherapy combination to improve clinical efficacy. The analysis showed that immune + radiotherapy only prolonged the PFS yet did not show statistically significant improvements on OS and ORR. Dying tumor cells after radiation can release TAAs so that irradiative tumor can be converted to in situ vaccine. They may also release danger signals and chemokines, promote the infiltration of dendritic cells (DCs) and cytotoxic T lymphocytes and enhance antitumor immune responses (Demaria et al., 2015). On the other hand, the radiation can also attract immunosuppressive cells such as Treg to tumor microenvironment, making negative regulation of the immune system, which may explain the rarity of abscopal effect (Muroyama et al., 2017). Preclinical studies showed that radiotherapy combined with immunotherapy may improve the response rate of distal tumors and enhance the anti-tumor effect (Dovedi et al., 2017; Hao et al., 2016; Twyman-Saint Victor et al., 2015). Current exploration of immunotherapy combined with radiotherapy is still in its early stage.

This study showed that immunotherapy + targeted therapy increased PFS and OS by 27% and 30%, respectively. Anti-angiogenesis therapy and immune system interact with each other as well: Anti-angiogenesis therapy induced normalization of abnormal tumor vascular, thereby reducing tumor microenvironment hypoxia, promoting the infiltration of $CD8^+$ T lymphocytes and transforming immunosuppressed microenvironment into immune-activated microenvironment to improve the effect of immunotherapy (Fukumura et al., 2018). Meanwhile, immune cells promote the normalization of tumor blood vessels as well. The mutual regulation between tumor blood vessel normalization and immune reprogramming forms positive circulation and induces long-lasting anti-tumor immunity (Huang et al., 2018). Immunotherapy combined with anti-angiogenic drugs is a promising approach, with a large number of relevant clinical trials ongoing.

In the presence of remarkable efficacy, we also found that combination immunotherapy appeared to increase toxicity. The most common AEs were diarrhea, fatigue and colitis, etc. Therefore, in the implementation of the combination regimens, attention should be paid to the prevention, early detection and proper management of these side effects. In addition, the cost-utility analysis of the combination should be concerned.

What's more, there is no satisfactory biomarker for immunotherapy with high sensitivity and specificity up to now. The exploratory analysis indicated that patients with PD-L1 ≥ 1% derived more survival benefits than those with PD-L1 < 1%, which was consistent with previous studies (Fehrenbacher et al., 2016; Motzer et al., 2018a,b). Nevertheless, in some studies, such as Keynote-407, the survival benefit of pembrolizumab in combination with chemotherapy was independent from PD-L1 expression (Paz-Ares et al., 2018). TMB as another promising biomarker has showed some clinical predictive value in some clinical trials (Carbone et al., 2017). Nevertheless, IMpower133 showed that the OS and PFS benefits of first-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer were consistent in patients with mutations greater or less than 10 and 16 mutations per megabase (Horn et al., 2018). Because of the complex interactions between tumor immune system, the predictive effects of these biomarkers vary by tumor types and drug regimens and there is not yet an

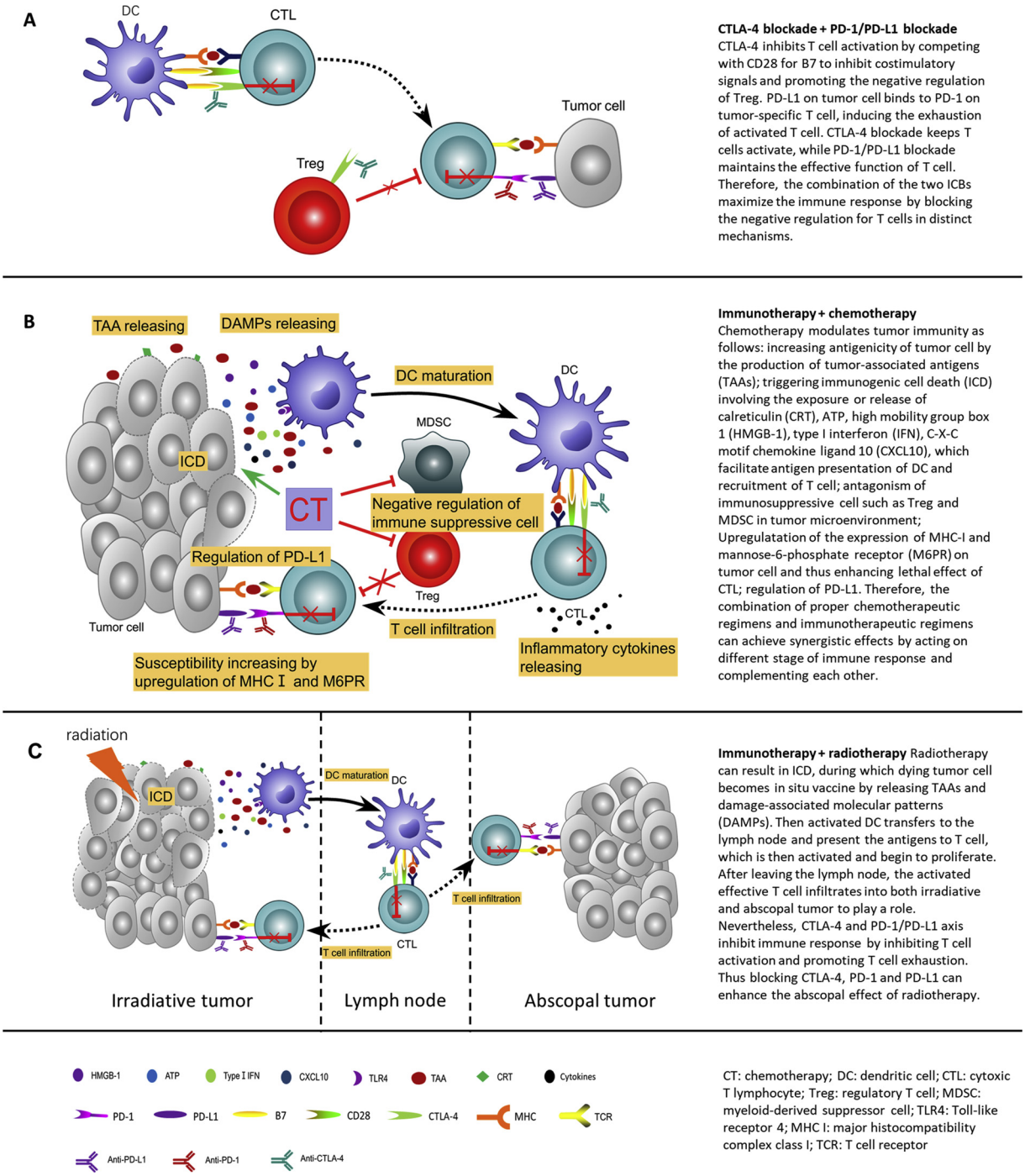


Fig. 5. Relevant mechanisms. **A,** CTLA-4 blockade + PD-1/PD-L1 blockade; **B,** Immunotherapy + chemotherapy; **C,** Immunotherapy + radiotherapy.

appropriate cut-off for these biomarkers to distinguish the efficacy of ICB (Havel et al., 2019). It was found that PD-L1 expression and TMB were independent predictors of the response and a multivariate model containing PD-L1 expression and TMB could improve the sensitivity and specificity of the prediction (Hellmann et al., 2018). A predictive model that takes into account multiple factors may be necessary for patient selection.

Although some important conclusions have been drawn from this study, we must pay attention to its limitations: 1. Differences in combination regimens, drug dosage, lines of treatment and tumor histotype may lead to heterogeneity between studies; 2. Two I/II studies were included; 3. Some subgroups, such as the immunotherapy + radiotherapy group, had small sample sizes; 4. The follow-up time of some studies was not long enough, resulting in lack of long-term outcome data. We expect more complete follow-up data in the future to confirm our results.

To maximize the benefits for patients, how to optimize the therapeutic mode, select the appropriate treatment population and weigh the risks and benefits should be taken into account in future study designs and clinical practice to ensure the selection of the best beneficial population, the most synergistic combinatorial regimes and the most appropriate sequencing of therapies.

5. Conclusion

Combination immunotherapy significantly improved survival.

Though the adverse effects above grade 3 increased, they were manageable in clinic. Further research is required to identify sensitive biomarkers, as well as explore more combinatorial regimens, dosages and sequencing of therapies for combination therapy.

Conflict of interest statement

There is no potential conflict of interest to disclose.

Authors' contributions

Qin Li contributed to the design of the study and was responsible for the integrity of the data and accuracy of the data analysis. Yuhan Wei, Qi Du and Mengqi Li collected and extracted the clinical data. Qi Du and Teng Li were responsible for the statistical analysis. Li Li, Xueke Fan, Yingrui Li, Seyed Kariminia prepared the figures and tables. Yuhan Wei, Qi Du and Xiaoyue Jiang wrote the manuscript. All authors contributed to the review and approved the paper. All authors agreed to be accountable for the content of this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2019.04.008.

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