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Efficacy and safety of PD-1/PD-L1 inhibitors for natural killer/T-cell lymphoma: a single-arm meta-analysis

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Abstract

Background With the advent of asparaginase-based drugs, patients with natural killer/T-cell lymphoma (NKTCL) have achieved excellent efficacy. However, the prognosis is poor in patients with advanced disease, and even worse in relapse/refractory patients. This meta-analysis aimed to evaluate the efficacy and safety of PD-1/PD-L1 inhibitor monotherapy or combination treatment strategies in patients with NKTCL.

Method Seven databases were extensively searched from inception to November 2023 and updated in April 2024, with no language restrictions. The pooled overall response rate (ORR), overall survival (OS), progression-free survival (PFS), and treatment-related adverse events (AEs) were calculated via a random effects model. Heterogeneity was tested utilizing the I-square (I^2) test and Cochrane's Q test. Subgroup analysis was used to compare the effects of single PD-1/PD-L1 inhibitors or combination treatment in NKTCL patients.

Results A total of thirteen single-arm studies involving 460 patients were enrolled. The results revealed that the pooled ORR was 62% (95% CI: 48-76%). In terms of survival outcomes, the pooled 1-year OS was 67% (95% CI: 47-87%) and the 2-year OS was 47% (95% CI: 24-69%). Moreover, the 1-year and 2-year PFS rates were 66% (95% CI: 48-84%) and 59% (95% CI: 34-84%), respectively. With regard to treatment toxicity, the pooled incidence of all-grade AEs was 86% (95% CI: 79–93%), and the pooled incidence of grade 3 or higher AEs was 29% (95% CI: 22–36%). Leukopenia and hypoalbuminemia were identified as the most common hematologic and non-hematologic adverse events, respectively.

Conclusion Evidence suggests that PD-1/PD-L1 inhibitors are promising treatment options for newly diagnosed NKTCL patients. PD-1/PD-L1 inhibitors combined with chemotherapy or chidamide has demonstrated superior clinical efficacy in patients with relapsed/refractory NKTCL.

Trial registeration Open Science Framwork: osf.io/2bwh3.

Keywords Natural killer/T-cell lymphoma, PD-1/PD-L1, Immune checkpoint inhibitor, Efficacy and safety, Meta-analysis

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Background

Natural killer/T-cell lymphoma (NKTCL) represents a rare, aggressive subtype of non-Hodgkin lymphoma (NHL) characterized by Epstein–Barr virus infection [1]. It has a clear geographic and ethnic predisposition, with a predilection for East Asian and Latin American populations [2]. NKTCL mainly affects extranodal sites, predominantly the upper respiratory and gastrointestinal tract [3].

Asparaginase-based chemotherapy and standard radiotherapy have dramatically improved the outcomes of NKTCL patients, especially early-stage patients [4]. However, patients with advanced-stage disease have a dismal clinical outcome, with a 5-year survival rate of only 30–40% [5]. Over 10% of NKTCL patients have primary resistance to asparaginase therapies, leading to a high recurrence rate [6]. Moreover, for those recurrent or refractory NKTCL patients, the median survival period is only 6.4 months [7]. Hence, there is an urgent need for innovative and rational approaches, especially for patients with R/R disease and for populations with advanced-stage disease and high-risk disease manifestations. Recently, small molecule targeted therapies, including immune checkpoint inhibitors (ICIs), and cellular therapy have brought hope for relapsed/refractory NKTCL [3, 8].

The most common immune checkpoints are PD-1 and PD-L1. Our previous study has revealed that PD-L1 expression has clinical significance and prediction of treatment response in NKTCL [9]. However, not all patients show good response to ICIs. Meanwhile, there is controversial in different studies as the relation of PD-1/PD-L1 expression with treatment response [10, 11]. Therefore, we have to think deeply about whether patients benefit from the use of PD-1/PD-L1 inhibitors.

Considering that individual studies might not be sufficient to support clinical practice, we sought to perform an objective synthesis of the potential effects of these therapies. We thus performed a comprehensive systematic review and meta-analysis to evaluate the efficacy and safety of PD-1/PD-L1 inhibitor monotherapy or combination therapy in patients with NKTCL.

Methods

This single-arm meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12] (Additional file: Table S1) and was registered in OSF (osf.io/2bwh3, https://osf.io/).

Search strategy

We systematically and comprehensively searched foreign language databases (PubMed, Embase, Web of Science, and Cochrane Library) and Chinese databases (CNKI and WanFang). We also retrieved clinicalTrial.gov, dissertations databases and grey literature up to April 2024 without language restrictions. Clinical trial registers was searched to identify unpublished studies, and the reference lists of included trials were investigated for additional eligible studies. The search strategy was based on Mesh terms and their variants. The following keywords were used: "NK/T-cell lymphoma", "immune checkpoint inhibitor", "nivolumab", "pembrolizumab", "toripalimab", "sintilimab", "tislelizumab", "camrelizumab", "cemiplimab", "atezolizumab", "avelumab", "durvalumab", and "sugemalimab". No restriction in language was applied. The detailed search strategies used in PubMed can be found in Additional file: Table S2.

We also contacted a content expert and industry representatives and searched conference abstracts for additional information.

Selection criteria

Studies were eligible if they met the following criteria: (1) Population: Patients diagnosed with primary or recurrent NK/T-cell lymphoma. (2) Intervention: PD-1/PD-L1 inhibitor monotherapy or combination treatment. (3) Study type: randomized controlled trial, prospective clinical trial, or retrospective study. (4) Outcomes: objective response rate (ORR), overall survival (OS), and progression-free survival (PFS). Exclusion criteria comprised: (1) Other types of patients: peripheral T-cell lymphoma, TFH-derived neoplasma, etc. (2) cell and animal studies, reviews, case reports, or editorials. (3) Exact outcome data were not provided.

Data extraction and quality assessment

Two researchers extracted data from the eligible studies, and the information collected from each included study was as follows: (1) study data: first author, publication year, registration number, and trial design; (2) patient data: total number, median age, stage, and disease status (newly diagnosed NKTCL or relapse/refractory patients); (3) intervention data: drug of immune checkpoint inhibitors, dose, period, and combination regimens; and (4) main outcomes: ORR, OS, and PFS. The two authors independently chose the Methodological Index for Non-randomized Studies (MINORS) to evaluate the quality of the single-arm trials included [13] and the Newcastle Ottawa Quality Assessment Scale (NOS) to assess the quality of the eligible retrospective studies [14]. Any differences will be handled by consensus.

Statistical analysis

STATA 18.0 statistical software (StataCorp LLC, College Station, TX, USA) was used to integrate the evidence. Hazard ratio (HR) was used in estimating OS for each study. Odd ratio (OR) with 95% confidence intervals

(CIs) was used for dichotomous data, and mean differenes (MDs) with 95% Cls were used for continuous data. Given the wide range of high heterogeneity between studies, we conducted pooled analysis of the included studies based on random effects models.

Subgroup analyses were performed to identify sources of heterogeneity. Sensitivity analysis was performed to evaluate the data stability using statistical models (fixed- vs. random-effects models). Finally, we investigated the possibility of publication bias by using funnel plots. The asymmetry of the funnel plot was assessed by Egger's and Begg's tests, and $P<0.05$ indicated significant publication bias.

Results

Study selection and characteristics

A comprehensive search of seven databases yielded 1079 records, including 710 studies in foreign language databases, 318 studies in the Chinese database, and 51 studies were from clinical trials.gov. After removing duplicate studies, 39 studies were eligible for full-text review. Finally, the remaining 13 articles were included in this study. The selection process is presented in Fig. 1.

The thirteen single-arm studies with a total of 460 patients were all published between 2021 and 2024. Twelve studies were prospective clinical trials, and one study [15] was a retrospective case series. The

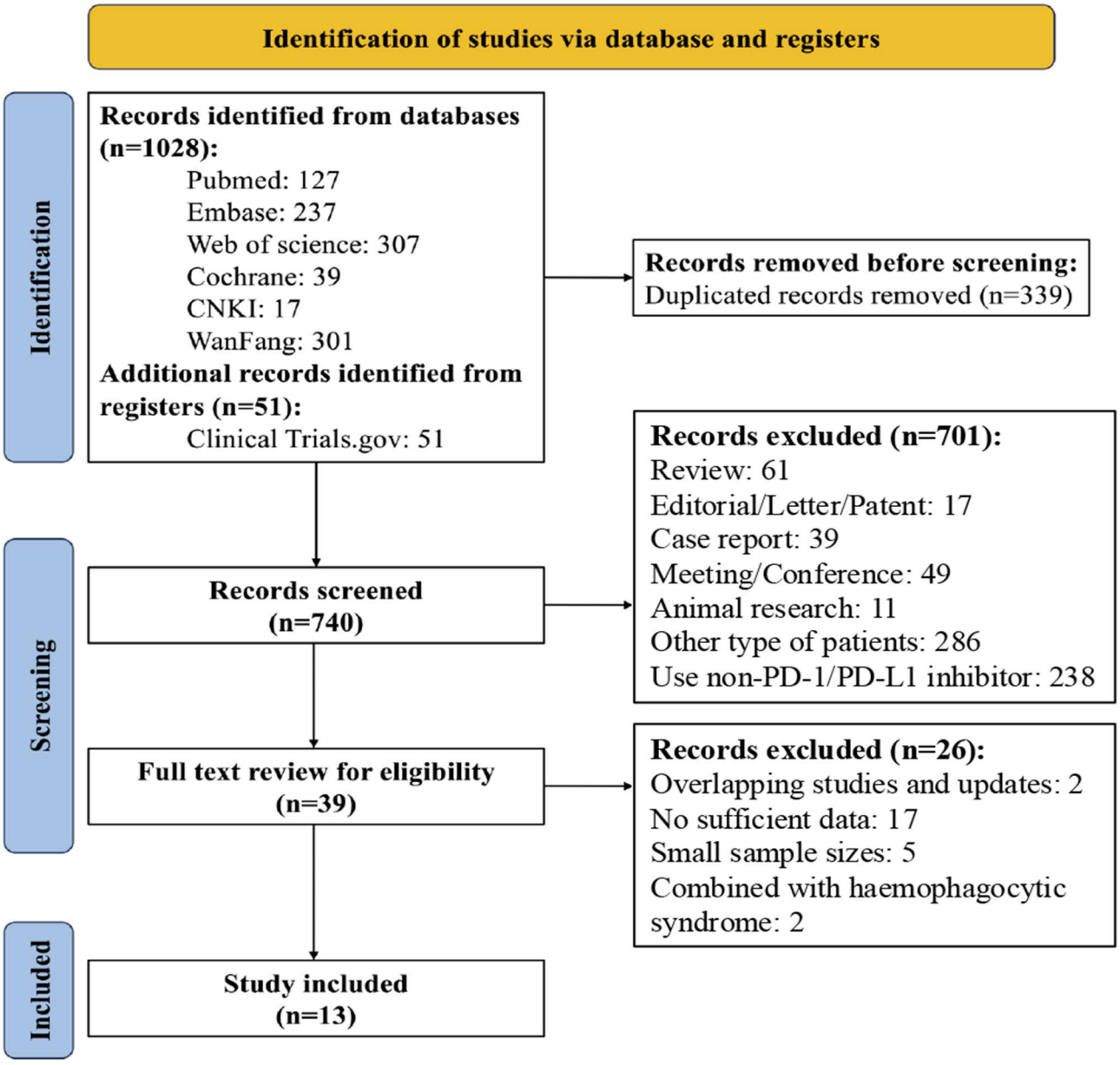

Fig. 1 Flow diagram

largest sample sizes included 80 patients and the smallest enrolled 16 patients. Most of the studies were only investigator-assessed response rates, while one study [16] also reported independent radiologic review committee (IRRC) -assessed antitumor activity. Among them, four studies [11, 17, 18] enrolled newly diagnosed NKTCL patients, and others enrolled relapsed/refractory patients who previously failed to respond to asparaginase-based regimens or chemoradiotherapy. Seven studies used sintilimab [11, 17–22], two used pembrolizumab [15, 23], two used tislelizumab [24, 25], one used sugemalimab [16], and one used avelumab [26]. In addition, six studies reported PD-1/PD-L1 inhibitor monotherapy, and seven studies utilized combination regimens, including combinations of chemotherapy ($n=4$) and histone deacetylase inhibitor (HDACi) ($n=3$). Three studies analyzed the relationship between PD-L1 expression and treatment response, and only one study analysed PD-1 expression on tumor-infiltrating lymphocytes and response to treatment.

In total, there were 460 extranodal NKTCL patients, 297 patients (64.6%) had Ann Arbor stage III/IV disease. There were 125 extranodal NKTCL patients treated with PD-1 inhibitor monotherapy, 101 patients treated with single PD-L1 inhibitor, and 234 patients treated with PD-1 inhibitor combination therapy. The median age ranged from 36.5 to 60 years, the percentage of males ranged from 37.5 to 80%, and the median follow-up time ranged from 3.2 to 38.3 months. The details are summarized in Table 1.

Quality assessment

The quality of 12 of including studies was assessed using the MINORS tool, of which two studies scored 14 points,

Table 1 Characteristics of the single-arm studies included

Study	Design (register number)	Patient status	Patient number	Median age (years)	Male (%)	Stage III/IV (%)	Intervention	Median follow-up (month)	ORR (95%CI)	CR (%)
Tao 2021	NCT03228836	R/R	28	37 (19–65)	17 (60.7%)	67.9%	sintilimab 200 mg every 3w	30.4 (27.5–31.9)	75% (55.1–89.3%)	21.4%
Chan 2023	Prospective	R/R	16	57 (41–83)	6 (37.5%)	62.5%	Pembrolizumab 200 mg every 3w	24 (1–51)	50%	44%
Lee 2023	Retrospective	R/R	59	60 (22–87)	37 (62.7%)	76.3%	Pembrolizumab	3.2	40.7%	28.8%
Bachy 2023	NCT03493451	R/R	22	47.5 (24–76)	14 (63.6%)	63.6%	Tislelizumab 200 mg every 3w	12.5 (8.3–13.9)	31.8% (13.9–54.9%)	18.2%
Huang 2023	NCT03595657	R/R	80	48 (29–74)	51 (63.8%)	67.5%	Sugemalimab 1200 mg every 3w	18.7	44.9% (33.6–56.6%)	35.9%
Kim 2020	NCT03439501	R/R	21	54 (24–78)	13 (62%)	81%	Avelumab 10 mg/kg every 4 weeks	15.7	38%	24%
Xiong 2024	NCT04096690	Newly diagnosed	22	51 (24–74)	16 (73%)	100%	Sintilimab 200 mg plus pegaspargase 2500IU/m^2 every 3w	30	68% (47–84%)	59%
Sun 2023	NCT03936452	Newly diagnosed	58	48 (20–70)	36 (62.1%)	0	Sintilimab 200 mg plus pegaspargase 2500 IU/m^2 and anlotinib 12 mg sandwiched with radiotherapy	22.5	87.8% (75.2–95.4%)	87.8%
Tao 2023	Prospective	R/R	33	48 (18–76)	25 (75.8%)	88%	Sintilimab 200 mg plus anlotinib 8 mg and pegaspargase 2500U/m^2	NA	81.8%	45.5%
Tian 2024	NCT04127227	Newly diagnosed	34	39 (32–55)	25 (74%)	100%	Sintinimab 200 mg plus P-GEMOX every 3w	21 (13–32)	100%	85%
Yan 2023	NCT03820596	R/R	37	48 (20–72)	NA	70.3%	Sintilimab 200 mg plus chidamide every 3w	38.3 (0.9–51.5)	58.3%	44.4%
Yan 2021	Prospective	Newly diagnosed	30	49 (21–81)	NA	40%	Sintilimab 200 mg plus chidamide every 3w	8.8 (0.3–24.3)	100%	100%
Zhang 2022	NCT04038411	R/R	20	36.5 (17–60)	16 (80%)	75%	Tislelizumab 200 mg plus chidamide 20 mg, lenalidomide 25 mg and etoposide 100 mg every 3w	NA	94.7%	50%

*NA: no available

five studies scored 15 points, and five studys scored 16 points. The quality of one retrospective study was assessed using NOS and the score was 6. Details of the risk of bias assessment are summarized in Additional file: Table S3. Overall, all studies were rated high, suggesting that there was a low risk of bias.

Assessment of the therapeutic efficacy and ORR

Treatment response rates were recorded in eleven studies, ranging from 31.8 to 100%. The analysis adopted a random-effects model and showed significant heterogeneity ($I^2 = 91.3\%$, $P < 0.001$) and a pooled ORR of 62% (95% CI: 48-76%) (Fig. 2(a)). As considerable heterogeneity existed between studies, possible sources of heterogeneity were further explored by subgroup analysis.

Subgroup analysis were conducted based on treatment. Six studies of PD-1/PD-L1 inhibitor monotherapy reported ORR data. Pooled ORR of patients receiving PD-1 inhibitors alone was 50% (95% CI: 30-69%), compared to 43% (95%CI: 34-53%) with PD-L1 inhibitors alone. Three trials of combined PD-1/PD-L1 inhibitors with chemotherapy reported ORR data. The pooled ORR was 82% (95% CI: 72–92%), which was significantly different from that of patients not treated with chemotherapy. Two studies combining PD-1/PD-L1 inhibitors with HDACi was reported ORR data, with a pooled ORR of 77% (95% CI: 41–100%) (Fig. 3(a)). We performed efficacy comparisons and analyses in patients with relapsed or refractory disease, demonstrating that combination group has a higher ORR compared with monotherapy (79% vs. 47%) (Figure S1(a)).

Efficacy evaluation of OS

OS for 1-year (from 5 studies) and 2-year (from 3 studies) were further pooled from single-arm studies. The pooled 1-year OS was 67% (95% CI: 47-87%, $I^2 = 90\%$), and the 2-year OS was 47% (95% CI: 24-69%, $I^2 = 84.5\%$) (Fig. 2(b)).

Subgroup analysis revealed that the newly diagnosed patients yielded the better 1-year OS compared with relapsed/refractory patients (91% vs. 61%) (Fig. 4).

Efficacy evaluation of PFS

PFS data for 1 year (8 studies) and 2 years (5 studies) were pooled respectively. The results revealed that one-year PFS rates of 66% (95% CI: 48-84%, I^2=93.5%) and two-year PFS rates of 59% (95% CI: 34-84%, I^2=94.2%) (Fig. 5(a)).Two studies provided eligible median PFS data, including specified 95% confidence intervals. The pooled median PFS was 2.06 months (95% CI: 1.21–2.91, $I^2 = 0.0\%$) (Fig. 5(b)).

Subgroup analysis revealed that the pooled 1-year PFS rate was 30% (95% CI: 19-42%, $I^2 = 16.6\%$) in patients treated with PD-1/PD-L1 inhibitor alone, which was significantly lower than patients treated with combination therapy. Among populations received with PD-1/PD-L1 inhibitors combined with chemotherapy, the pooled 1-year PFS was 74% (95% CI: 59–88%, $I^2 = 77.1\%$). The pooled 1-year PFS was 91% (95% CI: 83-99%, $I^2 = 0.0\%$) in patients treated with PD-1/PD-L1 inhibitors combined with HDACi (Fig. 3(b)). In all relapsed/refractory NKTCL patients, the 1-year PFS rate was also higher in the combination group than in the monotherapy (71% vs. 30%) (Figure S1(b)).

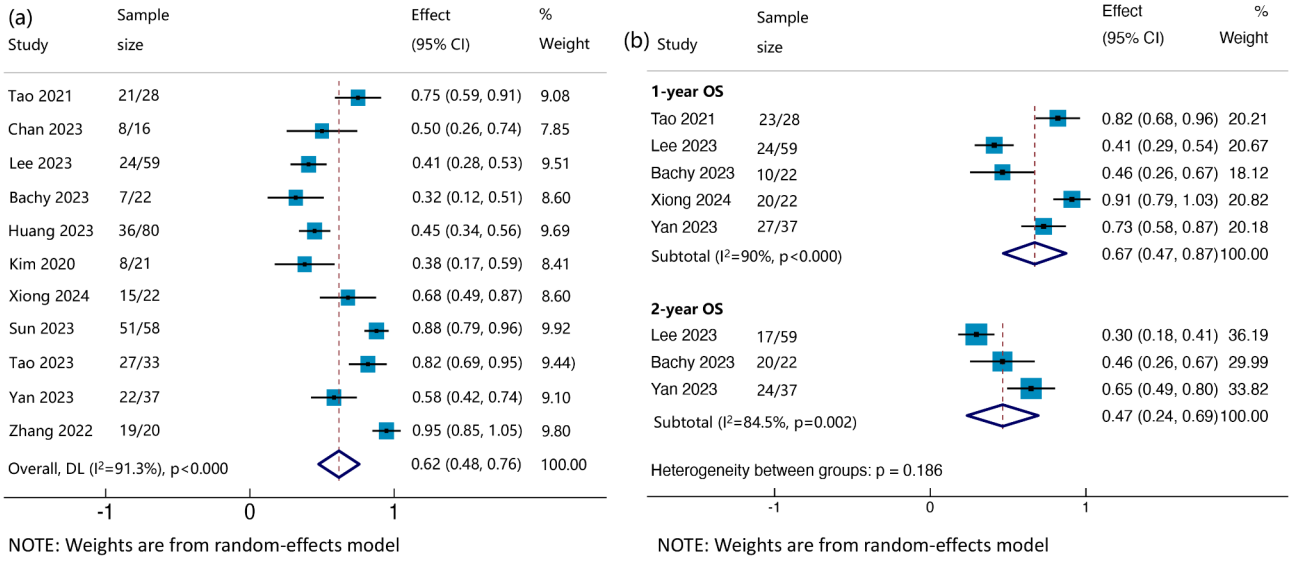

Fig. 2 The pooled results of (**a**) ORR and (**b**) OS

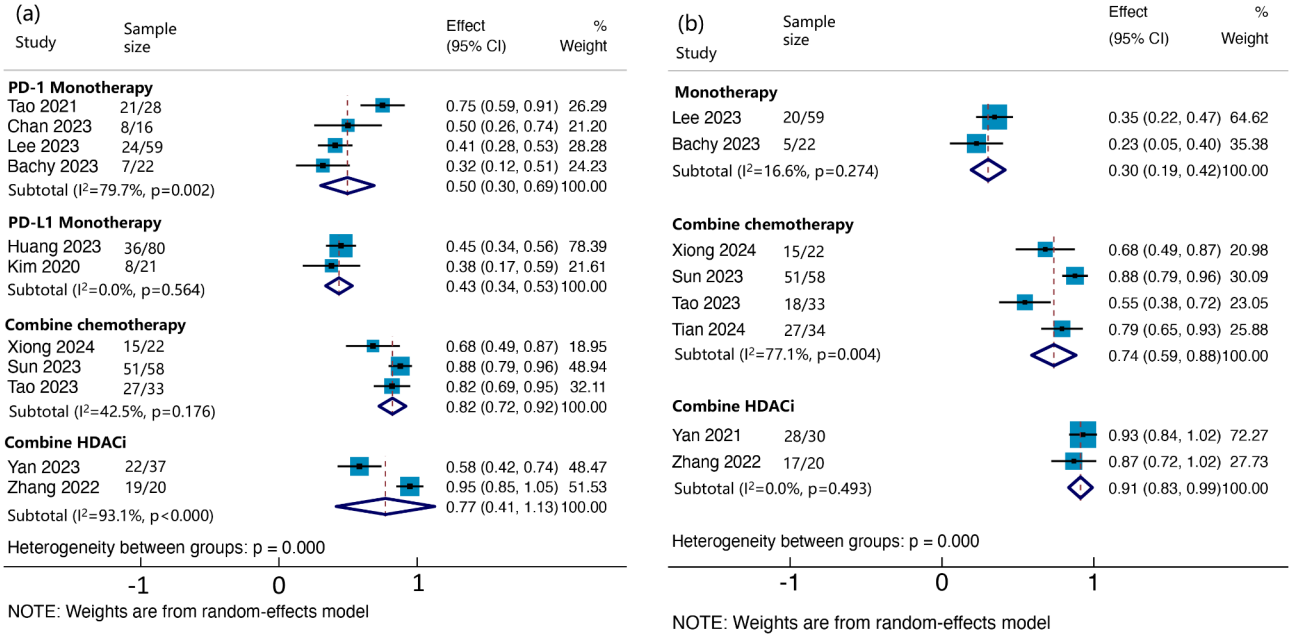

Fig. 3 Subgroup analysis as per treatment regimens for survival outcomes: (**a**) ORR; and (**b**) 1-year PFS

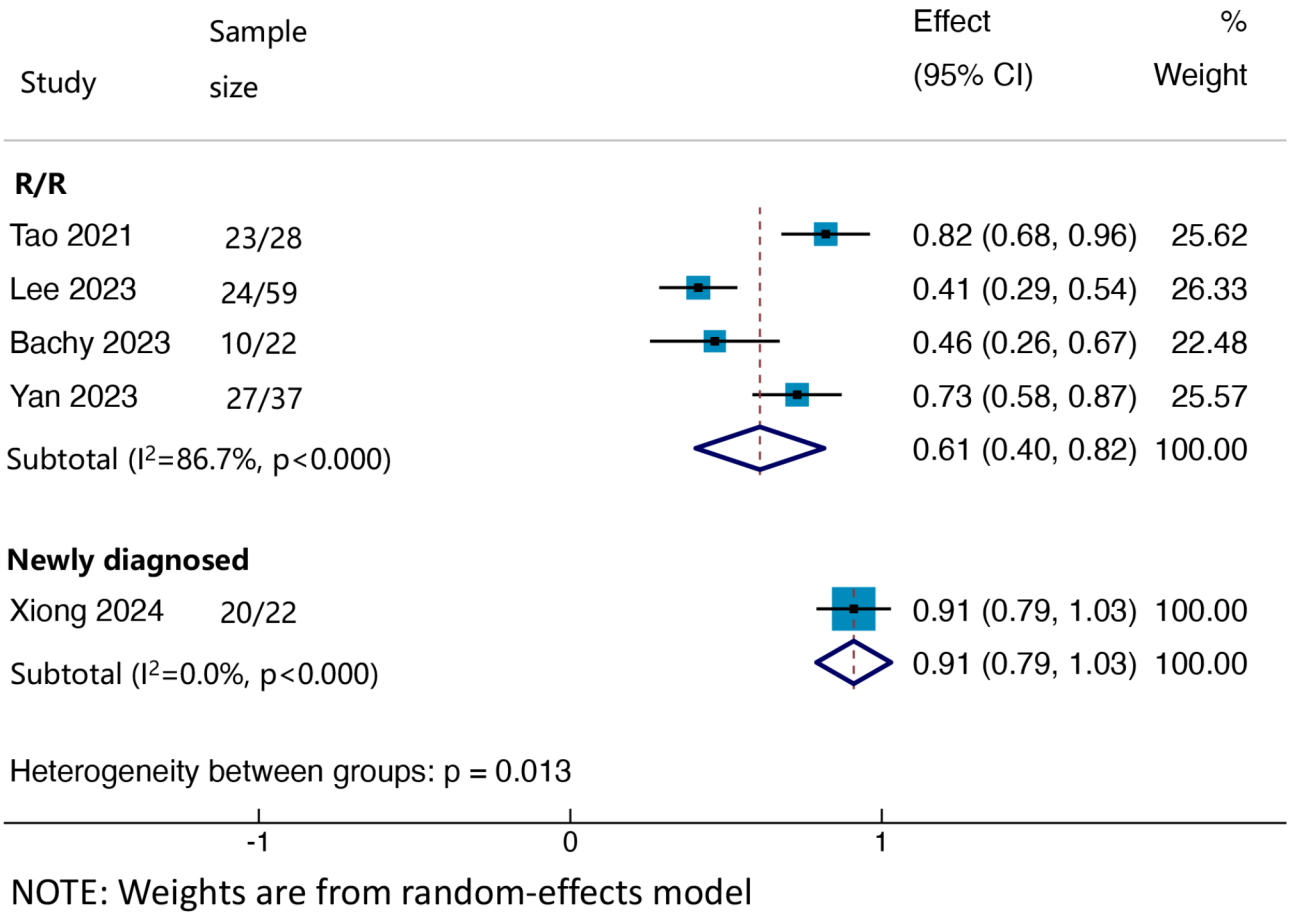

Fig. 4 Subgroup analysis of 1-year OS in newly diagnosed and relapse/refractory NKTCL patients

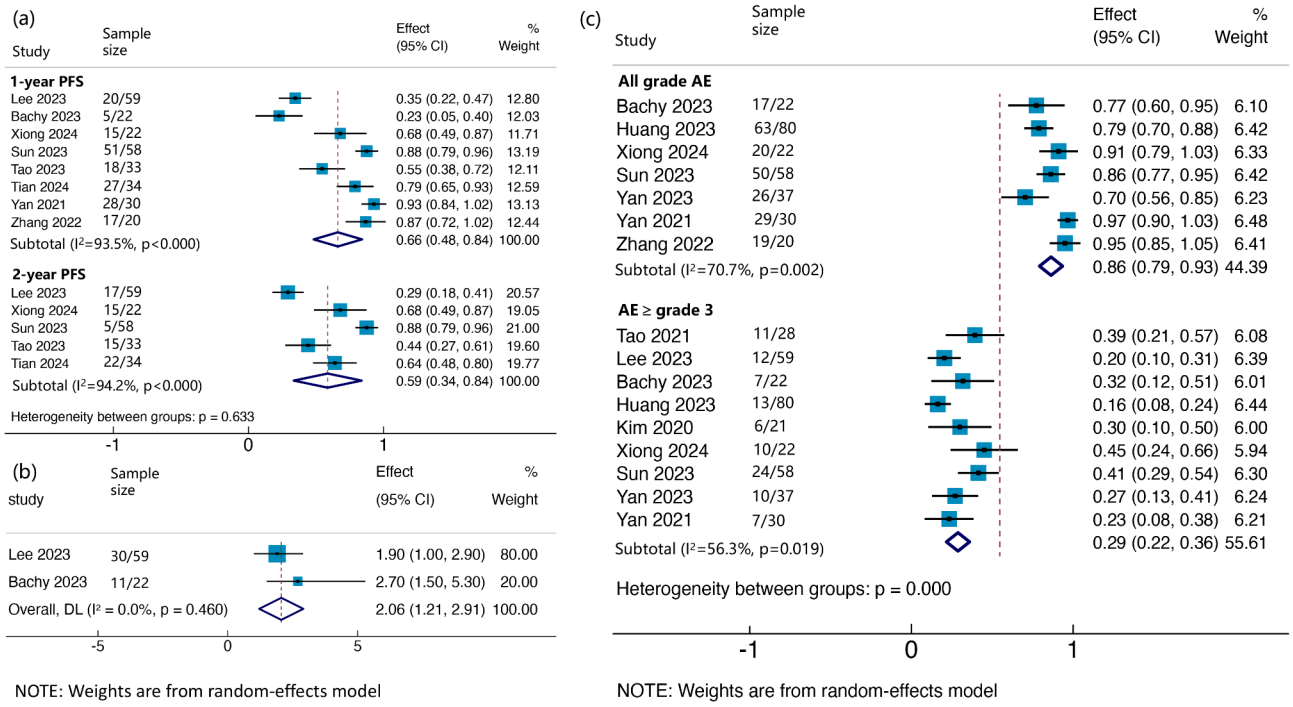

Fig. 5 The pooled results of (**a**) 1-year and 2-year PFS; (**b**) median PFS and (**c**) AE

Adverse events

Seven studies reported the total number of treatment-related adverse effects, and the pooled all-grade AE was 86% (95% CI: 79–93%, $I^2 = 70.7\%$). Nine studies included grade 3 or more AE, and the pooled incidence of AE≥ grade 3 was 29% (95% CI: 22–36%, $I^2 = 56.3\%$) (Fig. 5(c)). Adverse events were graded according to the National Cancer Institute Comon Toxicity Criteria for AEs (CTCAE). We found that leukopenia was the most common haematological AEs of all grades, with a pooled incidence of 55% (95% CI: 24-85%). Other common AEs included anemia and neutropenia in 46% (95% CI: 17-75%) and 44% (95% CI: 16-71%), respectively. Among the non-hematologic AEs, hypoalbuminemia was the most common, occurring in 70% (95% CI: 41-100%), while other AEs such as anorexia and nausea were also relatively high. The most common grade 3 or higher hematological AEs were neutropenia, liver aminotransferase levels elevation, and hyperglycemia were common grade 3 or higher non-hematological AEs. Immune-related adverse events were reported in five studies, with a pooled incidence of all-grade irAEs of 37% (95% CI: 14-60%), with hypothyroidism being the most common at 28% (95% CI: 11-46%). The detailed pooled rates of these AEs and the number of included studies are detailed in Table 2.

Subgroup analysis showed that the pooled all-grade AE was 78% (95% CI: 71-86%, $I^2 = 0.0\%$) for NKTCL patients treated with PD-1/PD-L1 inhibitors alone. The pooled percentage of all-grade AEs was 88% (95% CI: 81–95%, $I^2 = 0.0\%$) in patients treated with PD-1/PD-L1 inhibitors combined with chemotherapy. The pooled incidence of all-grade AEs was 89% (95% CI: 76-89%, $I^2 = 81.1\%$) in patients who receive PD-1/PD-L1 inhibitors combined with HDACi (Fig. 6(a)). Notably, the combination treatment group showed some significant differences in AEs compared to the monotherapy. Specifically, the incidence of leukopenia (71% vs. 31%), elevated hepatic aminotransferase levels (55% vs. 16%), and anorexia (55% vs. 10%) was higher in the combination therapy group, but the incidence of hyperglycemia was relatively lower (15% vs. 25%). The pooled incidence of AE≥ grade 3 was 28% (95% CI: 16-40%, I2 = 44.5%) in patients treated with PD-1 inhibitor alone, while those with PD-L1 inhibitor alone was 20% (95% CI: 8-32%, $I^2 = 37.6\%$). The pooled AE≥ grade 3 was 42% (95% CI: 32–53%, $I^2 = 0.0\%$) in populations of combined PD-1/PD-L1 inhibitors with chemotherapy. Overall, 25% (95% CI: 15-36%, $I^2 = 0.0\%$) of the patients who received PD-1/PD-L1 inhibitors combined with HDACi had grade 3 or higher AE (Fig. 6(b)). Among grade 3 or higher AEs, neutropenia (21% vs. 7%), hepatic aminotransferase levels elevation(19% vs. 3%), and diarrhea (10% vs. 2%) were also higher in the combination therapy group.

Sensitivity analysis

Sensitivity analysis using the fixed effects model yielded corresponding results, which are detailed in the Fig. 7.

Table 2 Treatment-related adverse events and immune-related adverse events of the studies included

Organ	Adverse events	Treatment	All Grades		≥ 3 Grades	
			N	Effect (95%CI)	*N*	Effect (95%CI)
Hematological	Anemia	Monotherapy	2	13% [0%, 28%]	1	9% [0%, 21%]
		Combination therapy	5	59% [28%, 90%]	4	10% [2%, 19%]
		Overall	7	46% [17%, 75%]	5	10% [3%, 17%]
	Thrombocytopenia	Monotherapy	3	9% [0%, 21%]	4	3% [0%, 5%]
		Combination therapy	6	31% [16%, 45%]	5	9% [2%, 16%]
		Overall	9	23% [12%, 34%]	9	5% [2%, 8%]
	Neutropenia	Monotherapy	3	16% [10%, 21%]	4	7% [0%, 14%]
		Combination therapy	6	58% [29%, 87%]	6	21% [7%, 35%]
		Overall	9	44% [16%, 71%]	10	14% [7%, 20%]
	Leukopenia	Monotherapy	2	31% [11%, 51%]	2	3% [0%, 9%]
		Combination therapy	3	71% [48%, 93%]	3	19% [7%, 32%]
		Overall	5	55% [24%, 85%]	5	12% [2%, 23%]
Endocrine	Hypothyroidism	Monotherapy	3	20% [2%, 38%]	2	1% [0%, 3%]
		Combination therapy	4	32% [13%, 51%]	0	
		Overall	7	26% [13%, 40%]	2	1% [0%, 3%]
	Hyperglycemia	Monotherapy	1	25% [9%, 41%]	0	
		Combination therapy	3	15% [7%, 23%]	1	5% [0%, 15%]
		Overall	4	17% [10%, 24%]	1	5% [0%, 15%]
Liver	LFTs elevation	Monotherapy	3	16% [5%, 27%]	2	3% [0%, 5%]
		Combination therapy	7	55% [27%, 82%]	2	19% [0%, 39%]
		Overall	10	40% [17%, 63%]	4	7% [0%, 14%]
Gastrointestinal	Diarrhea	Monotherapy	1	2% [0%, 5%]	1	2% [0%, 5%]
		Combination therapy	3	15% [7%, 23%]	1	10% [0%, 23%]
		Overall	4	11% [1%, 21%]	2	3% [0%, 10%]
	Appetite loss	Monotherapy	1	10% [0%, 23%]	0	
		Combination therapy	4	55% [27%, 83%]	0	
		Overall	5	46% [16%, 76%]	0	
	Nausea	Combination therapy	6	40% [28%, 51%]	0	
		Overall	6	40% [28%, 51%]	0	
	Fatigue	Monotherapy	2	10% [0%, 20%]	2	6% [1%, 12%]
		Combination therapy	3	34% [20%, 47%]	0	
		Overall	5	23% [10%, 36%]	2	6% [1%, 12%]
Dermatologic	Skin rash	Monotherapy	2	8% [0%, 16%]	1	1% [0%, 4%]
		Combination therapy	3	13% [0%, 30%]	2	2% [0%, 5%]
		Overall	5	10% [2%, 19%]	3	2% [0%, 4%]
	Edema	Overall	3	12% [0%, 26%]	0	
	Hypoalbuminemia	Overall	3	70% [41%, 100%]	2	2% [0%, 5%]
	Infusion-related reaction	Overall	4	9% [2%, 16%]	2	2% [0%, 5%]
irAE	All		5	37% [14%, 60%]		
	Hypothyroidism		4	28% [11%, 46%]		

LFTs: liver function tests

Publication bias

The funnel plot for ORR was symmetric, indicating no publication bias because of Egger's test ($P = 0.12$) and Begg's test ($P = 0.161$) (Fig. 8). We failed to assess publication bias of other pooled outcomes due to the small number of included studies.

Discussion

This comprehensive systematic review reported the effectiveness and safety of PD-1/PD-L1 inhibitors in patients with NKTCL, confirming the good efficacy and broad prospects of PD-1/PD-L1 inhibitors in clinical application.Clinical studies have shown potential efficacy with PD-1/PD-L1 inhibitors in NKTCL patients. For example, pembrolizumab, sintilimab, tislelizumab, sugemalimab and avelumab were all found to be highly effective and well tolerated in R/R NKTCL patients [16, 19, 24, 26].

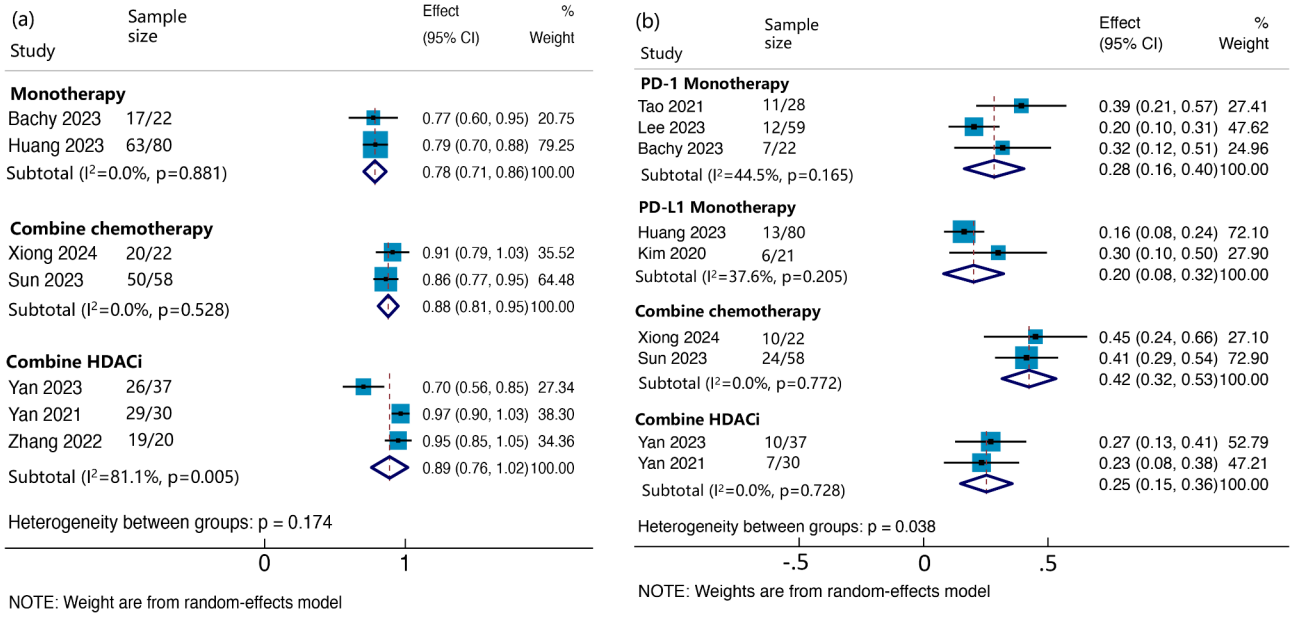

Fig. 6 Subgroup analysis as per treatment regimens for (**a**) all adverse events and (**b**) above grade 3 adverse events

For a long time, many oncologists have believed different ICIs, whether PD-1 or PD-L1 inhibitors, to be equally efficious and clinically interchangeable [27].

Laboratory and clinical findings have confirmed that the combination of anti-PD-1 antibodies with chemotherapy, radiotherapy, targeted therapy, and epigenetic regulators might have a synergistic effect on enhancing treatment efficacy [6]. In light of this evidence, a series of clinical trials have used PD-1/PD-L1 inhibitors combined with chemotherapy or HDACi for treating patients with newly diagnosed or relapsed/refractory NKTCL [18, 21, 22, 25, 28]. Our report also reported the efficacy of PD-1/PD-L1 inhibitors alone with combination therapy. First, the pooled ORRs of patients treated with PD-1 blockade alone, PD-L1 inhibitors alone, combined with chemotherapy, or combined with HDACi were 50%, 43%, 82%, and 77%, respectively. The pooled 1-year PFS rates were 30%, 74%, and 91%, respectively. The results showed that combination therapy can significantly improve the ORR and 1-year PFS rate. To minimize the potential impact of a patient's disease status on the assessment of treatment effectiveness, we performed efficacy comparisons in R/R NKTCL patients. The results confirmed that the combination therapy was more effective than the monotherapy in all patients with R/R NKTCL disease. At the same time, we conducted an in-depth analysis of treatment-related adverse events and found that most of them were grade 1 or 2 AEs, while the incidence of grade 3 or 4 AEs was low, and no grade 5 AEs occurred. Hematologic AEs, such as leukopenia, anemia, and neutropenia, as well as non-hematologic AEs, such as gastrointestinal effects (anorexia, nausea) and hepatic symptom (elevated hepatic transaminases) occur frequently. In particular, combination therapy may lead to serious hematologic, gastrointestinal, and nutritional origin AEs, so monitoring and appropriately managing these AEs when using combination regimens.

Second, though no significant differences were observed between PD-1 inhibitor alone and PD-L1 inhibitor alone regarding ORR, PD-1 inhibitors alone seems to have slightly better efficacy. The underlying mechanism remains to be well explored, but the possible reason is the interaction of PD-L1 or PD-L2 with PD-1 all may suppress T cell activation. To our knowledge, PD-1 inhibitors can block the interaction between PD-1 and PD-L1/2, while PD-L1 inhibitors can only hinder the binding PD-1 to PD-L1, and tumor cells can also evade immune surveillance through the PD-1/PD-L2 axis to exert a pro-tumor effect [29]. Many meta-analyses conducted by other teams also found no obvious difference in efficacy of PD-1 + chemo versus PD-L1 + chemo regimens, possibly due to limited sample size and the number of randomized controlled trials included [27, 30]. However, further studies are needed to confirm this discovery and excavate the underlying mechanisms.

Third, several studies have reported the correlation of treatment response rates with patients' clinical characteristics. The results suggested that the treatment response rate was not related to Ann arbor stage, extranodal nasal type, distant lymph node metastasis, tumor mutational burden, soluble PD-1/PD-L1, and plasma EBV-DNA. Three studies displayed that patients with high PD-L1 expression of tumor tissues were more responsive to ICI treatment, while one study comfirmed that PD-1

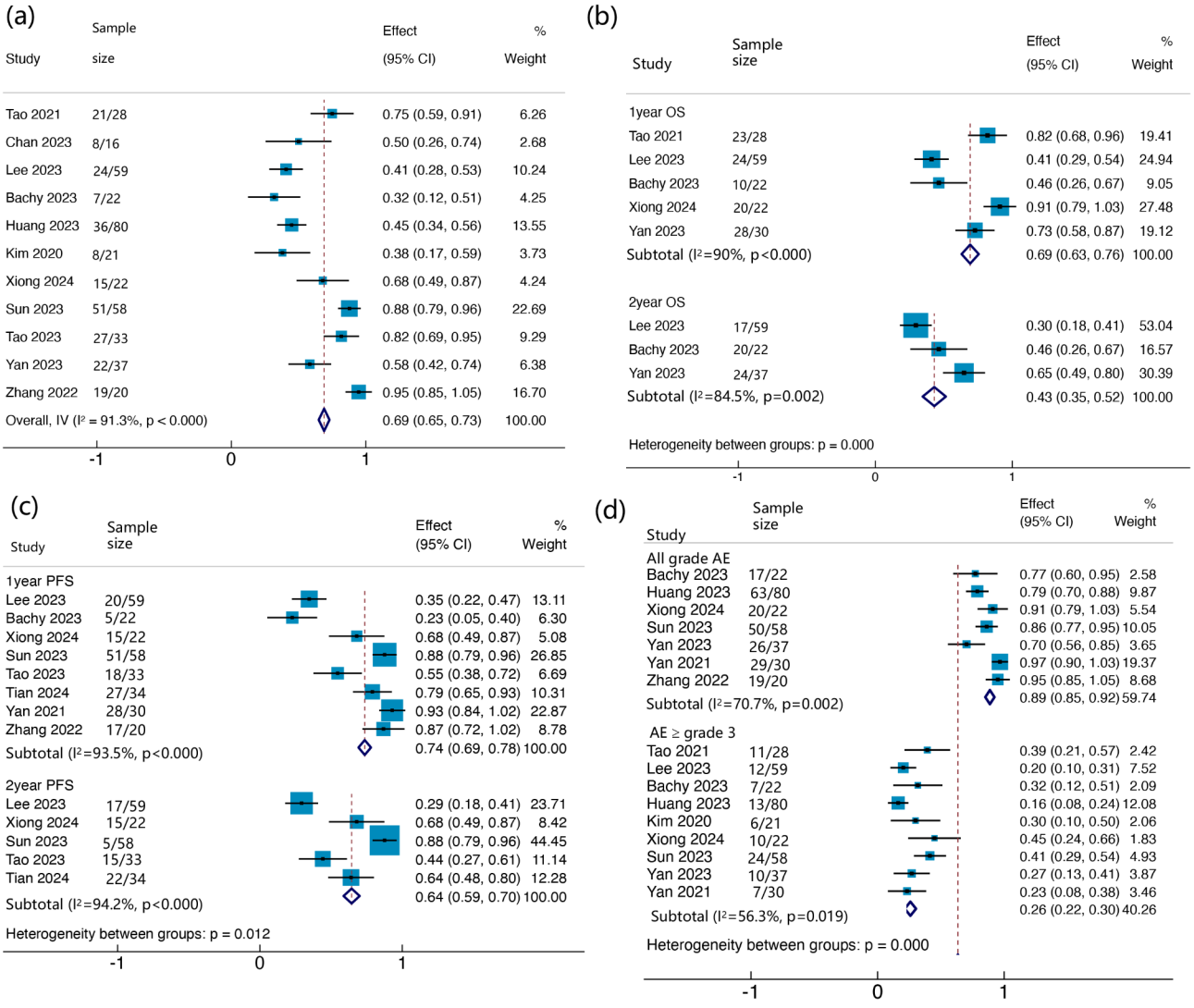

Fig. 7 Sensitivity analysis of ORR, OS, PFS and AE in fixed-effects model

expression on tumor-infiltrating lymphocytes was associated with poor response to treatment. The reason might be that PD-1 and PD-L1 are co-expressed on the surface of APCs, and PD-L1/PD-1 cis interaction attenuate the PD-1 signaling of T cells and inhibit the ability of antitumor activity [11, 22, 26, 31]. Due to the different calculation methods of PD-L1 expression level, the results could not be synthesized for analysis. Therefore, there is warranted to investigate the predictive value of PD-L1 and PD-1 expression for clinical response in a larger patients cohort.

Previous systematic review have not conclusively quantified the benefits and risks of PD-1/PD-L1 inhibitors combination with other regimens in comparison with single ICI in NKTCL patients. They only included several case reports and three clinical studies to investigate the efficacy of pembrolizumab and anti-PD-1 treatments in R/R NKTCL patients [32]. In contrast, our study all enrolled single-arm clinical trials, which were significantly larger sample size and more credible.

To our knowledge, our study is the largest meta-ananlysis to date using PD-1/PD-L1 inhibitors in NKTCL patients, with largest sample sizes and almost all clinical trials. However, there are several shortcomings. First, due to the short time to market of PD-L1 inhibitors and the short time of application of ICIs in NKTCL, especially in relapsed/refractory patients, there is a lack of corresponding randomized controlled trials. Second, all the studies included in our analysis are single-arm designs, which limits the ability to draw definitive conclusions about adverse events through inter-group comparisons. Therefore, we can only assess the pooled efficacy and safety of PD-1/PD-L1 inhibitors, without making direct comparisons between treatment modalities. Next, the use of subgroup analyses could not account for all sources of heterogeneity. Finally, the limited availability of only two

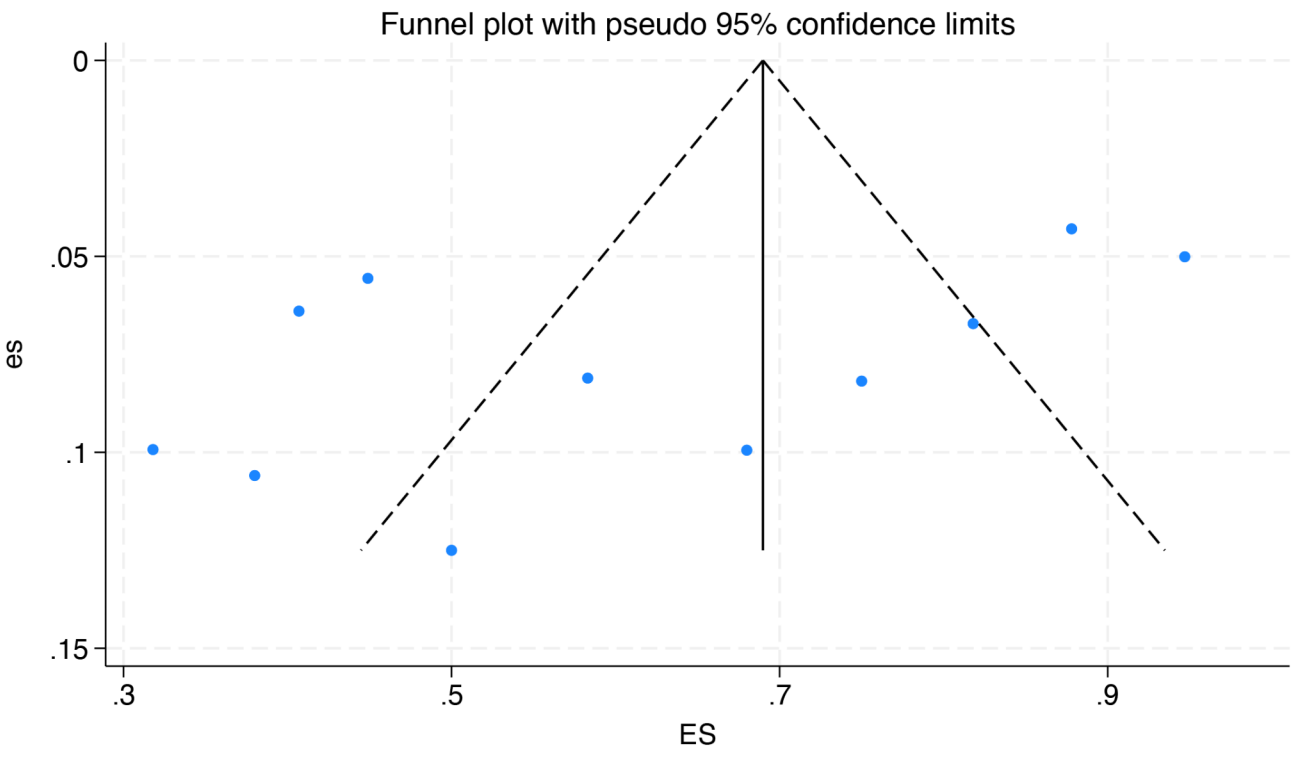

Fig. 8 Funnel plot asymmetry test for publication bias

studies completely reporting median PFS outcome weakened the stability of our conclusions [15, 24]. In view of the current single-arm studies, large-scale and high-quality randomized controlled trials are necessary to validate the prospect of PD-1/PD-L1 blockade combination therapy and thus choose the optimal treatment.

Conclusion

PD-1/PD-L1 inhibitors has promising efficacy in patients with newly diagnosed and R/R NKTCL. PD-1/PD-L1 inhibitors combined with chemotherapy or chidamide exhibited excellent clinical efficacy in patients with R/R NKTCL.

Supplementary Information

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Supplementary Material 1

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Author contributions
YJ: Conceptualization; Formal analysis; Methodology; Writing-original draft; Writing-review&editing.XXY: Formal analysis; Methodology; Software; Writing-review&editing.MYF: Data curation; Resources; Validation.WXM: Data curation; Investigation; Validation.XCG: Conceptualization; Supervision; Writing-original draft; Writing-review&editing.All the authors contributed to the article and approved the submitted version.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

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References

1. Siegel RL, Xiong J et al. Cancer Statistics, 2021. CA Cancer J Clin: Genomic and Transcriptomic Characterization of Natural Killer T Cell Lymphoma. Cancer Cell 2020, 37(3):403–419.e406.
2. Zhou J, et al. Super-enhancer-driven TOX2 mediates oncogenesis in natural Killer/T cell lymphoma. Mol Cancer. 2023;22(1):69.
3. Tse E, et al. How we treat NK/T-cell lymphomas. J Hematol Oncol. 2022;15(1):74.
4. Qi SN, van Doesum JA,Extranodal Natural Killer/T-cell Lymphoma, Nasal Type: Diagnosis and Treatment. Hemasphere 2021, 5(2):e523;, Zhang Y et al. First-line non-anthracycline-based chemotherapy for extranodal nasal-type NK/T-cell lymphoma: a retrospective analysis from the CLCG. Blood Adv: Sequential

P-GEMOX and radiotherapy for early-stage extranodal natural killer/T-cell lymphoma: A multicenter study. Am J Hematol 2021, 96(11):1481–1490.
5. Qi SN, Fox CP,Survival outcomes of patients with extranodal natural-killer T-cell lymphoma: a prospective cohort study from the international T-cell Project. Lancet Haematol 2020, 7(4):e284-e294;, Wang L et al. First-line immunochemotherapy for extranodal natural killer/T cell lymphoma. Lancet Haematol: Extranodal natural-killer T-cell lymphoma: experience from China. Lancet Haematol 2020, 7(6):e441.
6. He L, et al. Advances and challenges of immunotherapies in NK/T cell lymphomas. iScience. 2023;26(11):108192.
7. Tian XP, Li YQ et al. Novel target and treatment agents for natural killer/T-cell lymphoma. J Hematol Oncol: Single-Cell Analysis Reveals Malignant Cells Reshape the Cellular Landscape and Foster an Immunosuppressive Microenvironment of Extranodal NK/T-Cell Lymphoma. Adv Sci (Weinh) 2023, 10(36):e2303913.
8. Kwong Y-L, et al. PD1 Blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing L-asparaginase. Blood. 2017;129(17):2437–42.
9. Feng Y, et al. The expression and clinical significance of programmed cell death receptor 1 and its ligand in tumor tissues of patients with extranodal nasal NK/T cell lymphoma. Sci Rep. 2022;12(1):36.
10. Chen Z, et al. Genomic features reveal potential benefit of adding anti-PD-1 immunotherapy to treat non-upper aerodigestive tract natural killer/T-cell lymphoma. Leukemia. 2024;38(4):829–39.
11. Xiong J, et al. Anti-metabolic agent Pegaspargase plus PD-1 antibody sintilimab for first-line treatment in advanced natural killer T cell lymphoma. Signal Transduct Target Ther. 2024;9(1):62.
12. Page MJ, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
13. Slim K, et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003;73(9):712–6.
14. The Newcastle-Ottawa. Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp]
15. Lee JY et al. Pembrolizumab for Patients with Relapsed or Refractory Extranodal NK/T-Cell Lymphoma in Korea. Cancer research and treatment: 2023.
16. Huang H, et al. Sugemalimab monotherapy for patients with relapsed or refractory extranodal natural Killer/T-Cell lymphoma (GEMSTONE-201): results from a Single-Arm, multicenter, phase II study. J Clin Oncol. 2023;41(16):3032–41.
17. Sun P et al. A phase II study of sintilimab, anlotinib, and pegaspargase sandwiched with radiotherapy as first-line therapy in patients with newly diagnosed, stage I-II extranodal natural-killer/T-cell lymphoma. American Journal of Hematology: 2023, 98(7):1043–1051; Tian XP: First-line sintilimab with pegaspargase, gemcitabine, and oxaliplatin in advanced extranodal natural killer/T cell lymphoma (SPIRIT): a multicentre, single-arm, phase 2 trial. Lancet Haematol 2024.
18. Yan G, et al. Novel induction therapy for newly diagnosed extranodal natural Killer/t cell lymphoma (ENKTL) treated by anti-pd-1 antibody plus histone deacetylase inhibitor followed by Pgemox regimen. Blood. 2021;138(SUPPL 1):137.
19. Tao R, et al. Sintilimab for relapsed/refractory extranodal NK/T cell lymphoma: a multicenter, single-arm, phase 2 trial (ORIENT-4). Signal Transduct Target Ther. 2021;6(1):365.
20. Tao R et al. Anti-PD-1 antibody sintilimab in combination with anlotinib and Pegaspargase as a highly effective salvage regimen for the treatment of relapsed or refractory natural killer /T-Cell lymphoma. Blood 2023, 142.
21. Yan G et al. PD-1 Antibody (Sintilimab) Plus Histone Deacetylase Inhibitor (Chidamide) for the Treatment of Refractory or Relapsed Extranodal Natural Killer/T Cell Lymphoma, Nasal Type (r/r ENKTL): Updates of the Phase Ib/II Scent Study. Blood: 2023, 142.
22. Gao Y, et al. Sintilimab (anti-PD-1 antibody) plus Chidamide (histone deacetylase inhibitor) in relapsed or refractory extranodal natural killer T-cell lymphoma (SCENT): a phase Ib/II study. Signal Transduct Target Ther. 2024;9(1):121.
23. Chan T, et al. Pembrolizumab in relapsed/refractory extranodal NK/T cell lymphoma and mature T cell lymphoma: A prospective phase II study. Blood. 2023;142:1726.
24. Bachy E, et al. Treating relapsed/refractory mature T- and NK-cell neoplasms with Tislelizumab: a multicenter open-label phase 2 study. Blood Adv. 2023;7(16):4435–47.
25. Zhang L, et al. ANTI-PD-1-ANTIBODY (TISLELIZUMAB) COMBINED WITH DEACETYLASE INHIBITOR (CHIDAMIDE), LENALIDOMIDE AND ETOPOSIDE FOR THE TREATMENT OF REFRACTORY/RELAPSED EXTRANODAL NATURAL KILLER/T CELL LYMPHOMA. NASAL HemaSphere. 2022;6:2168–9.
26. Kim SJ, et al. Avelumab for the treatment of relapsed or refractory extranodal NK/T-cell lymphoma: an open-label phase 2 study. Blood. 2020;136(24):2754–63.
27. Li H, et al. Efficacy and safety of first-line PD-1/PD-L1 inhibitor combinations for extensive-stage small-cell lung cancer: a bayesian network meta-analysis. Ther Adv Med Oncol. 2023;15:17588359231189430.
28. Cai C, Q, Tian X, P, et al. Sintilimab plus P-Gemox (Pegaspargase, gemcitabine and Oxaliplatin) regimen for Newly-Diagnosed advanced, extranodal natural Killer/T cell lymphoma, nasal type: A multicenter, phase 2 cohort of the Open-Label spirit study. BloodLancet Haematol. 20222024;140(2299–2301). e336-e344.
29. Chen L, et al. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. J Clin Invest. 2015;125(9):3384–91.
30. Yu H, et al. Efficacy and safety of PD-L1 inhibitors versus PD-1 inhibitors in first-line treatment with chemotherapy for extensive-stage small-cell lung cancer. Cancer Immunol Immunother. 2022;71(3):637–44.
31. Zhao Y, et al. Antigen-Presenting Cell-Intrinsic PD-1 neutralizes PD-L1 in cis to attenuate PD-1 signaling in T cells. Cell Rep. 2018;24(2):379–e390376.
32. Rivera-Francia VM, et al. Use of PD-1 Blockade in refractory/relapsed natural killer T-cell lymphomas: a systematic review and synthesis of case reports. Leuk Lymphoma. 2024;65(1):37–47.

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