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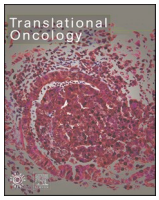

A systematic review and meta-analysis of immune checkpoint therapy in relapsed or refractory non-Hodgkin lymphoma; a friend or foe?

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ABSTRACT

Over the last decades, a revolution has occurred in oncology with the development of immune checkpoint inhibitors (ICIs). Following tremendous successes in solid tumors, interest has risen to explore these inhibitors in hematologic malignancies; while Hodgkin's lymphoma (HL) has shown overwhelming achievements, available data on different types of non-Hodgkin's lymphoma (NHL) vary considerably. To the best of our knowledge, no meta-analysis has assessed the efficacy and safety of ICI therapy in relapsed or refractory NHL patients. Meta-analysis of the included studies ($n = 29$) indicated PD-1 may probably be the more attractive ICI target rather than PD-L1 and CTLA-4 in NHL patients. Also, there is a plausible correlation between NHL subtypes and response to ICI therapy. While MF, ENKTL, RT, and PMBCL showed promising responses to ICI monotherapy, neither FL nor DLBCL had satisfactory responses; further necessitating novel strategies such as the application of ICIs in combination with other treatment strategies. Notably, among different combinations, BTK inhibitors showed an obvious improvement as compared to ICI monotherapy in both FL and DLBCL, however, the best results were obtained when ICI was combined with anti-CD20 monoclonal antibodies. Finally, while most NHL patients who received ICI treatment have experienced mild AEs, larger trials with long-term follow-up are required to confirm the safety, as well as the efficacy, of ICI therapy in NHL patients.

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous malignancy of either immature and mature lymphoid cells, mainly (>85%) originated from a clonal proliferation of the B lineage. According to prognosis, it can be categorized into aggressive NHL (aNHL) or fast-progressing, and indolent NHL (iNHL) or slow-progressing. Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) are the most common aggressive and indolent subtypes, accounting for about one-third and one-fifth of all NHL patients respectively [1]. Despite therapeutic improvement, 30–50% of patients still fail to respond to standard treatments or relapse after remission. The prognosis for refractory DLBCL patients is extremely poor, with a dismal median overall survival (OS) of 6.3 months and objective response rate (ORR) of 26% after salvage treatment [2], further highlighting an urgent need for alternative therapies that improve outcomes and provide durable responses in relapsed or refractory NHL patients.

Immune checkpoints are members of the regulatory molecules family which physiologically are critical for inhibiting self-immune responses [3]. However, during the carcinogenic process, immune checkpoint mechanisms are often activated to suppress immune-mediated destruction [4], and interestingly, the trace of dysregulated expression of

Abbreviations: AEs, Adverse events; BCL, B-cell lymphoma; CNSL, Central nervous system lymphoma; CR, Complete response; CTCL, Cutaneous T-cell lymphoma; DCR, Disease control rate; DLBCL, Diffuse large B-cell lymphoma; DOR, Duration of response; ENKTL, Extranodal natural killer (NK)/T celllymphoma; FL, Follicular lymphoma; HL, Hodgkin's lymphoma; MCL, Mantel cell lymphoma; MF, Mycosis fungoides; MZL, Marginal zone lymphoma; NHL, Non-Hodgkin lymphoma; PD, Progressive disease; PFS, Progression-free survival; PMBCL, Primary mediastinal large B-cell lymphoma; PR, Partial response; PTCL, Peripheral T-cell lymphomas; RT, Richter transformation; SD, Stable disease; SS, Sézary syndrome; TCL, T-cell lymphoma; TRAE, Treatment-related adverse event.

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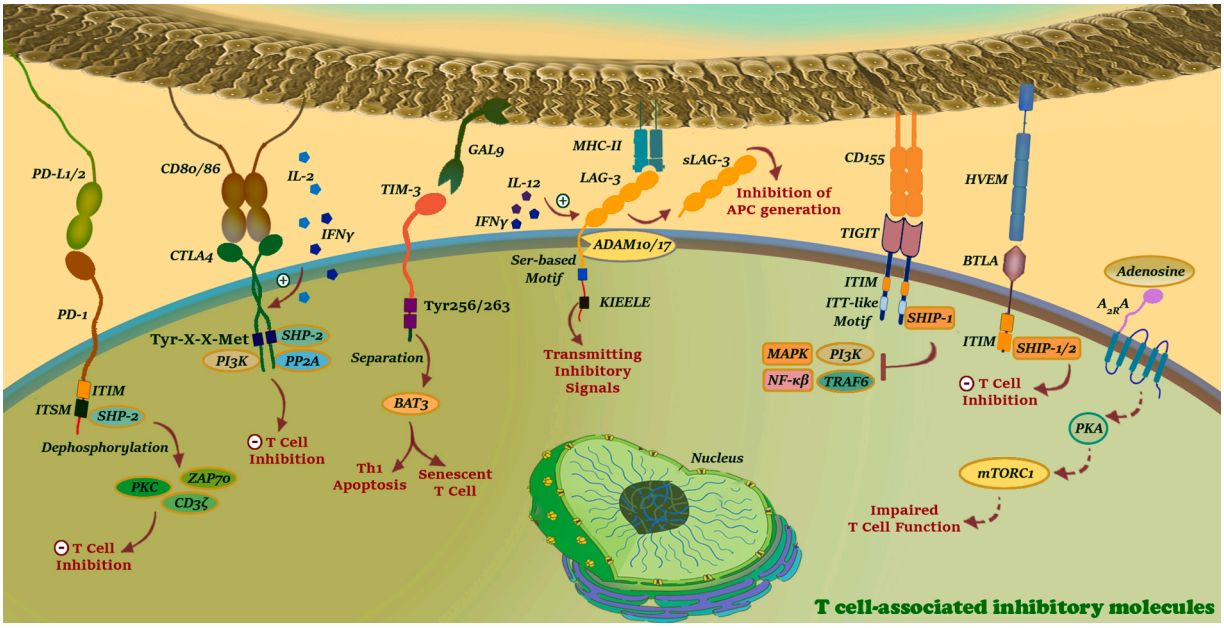

Fig. 1. An overview of immune checkpoint interactions, their structure, and roles. Various immune checkpoints that interact with their ligands and/ or receptors and initiate inhibitory signals are depicted. The engagement of PD-1 with PD-L1/2 and CTLA-4 with CD80/86 could result in SHP-2 recruitment and dephosphorylation of activating agents such as PKCθ, CD3ζ, and ZAP70. The TIGIT/CD155 and BTLA/HVEM interactions could also induce the recruitment of SHP-1/2 which consequently inhibits PI3K, MAPK, and NF-κB signaling. The binding of MHC-II to LAG-3 could lead to an inhibitory signal derived by the KIEELE amino acid sequence in the cytoplasmic tail of LAG-3. The activities of ADAM10/17 could lead to the production of sLAG-3 which could suppress the APC generation. Also, TIM-3/GAL-9 causes the BAT-3 to separate from Tyr256 and 263 and promotes the Th1 apoptosis and T cell senescence. Moreover, the interaction of A2AR and adenosine results in impaired T cell functions.

immune checkpoints such as programmed cell death 1 (PD-1) and its ligands (PD-L1/2), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), lymphocyte activation gene 3 (LAG-3), and T-cell immunoglobulin and mucin domain-containing protein-3 (TIM-3) has been observed in a wide range of human cancers [5]. PD-1 is a monomeric molecule with an intracellular domain containing an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM) motif, as well as an extracellular immunoglobulin-like domain [6]. Following interaction with its ligands, PD-L1 (CD274; B7-H1) and PD-L2 (CD273; B7-DC), PD-1 can inhibit TCR/CD28 signaling by recruiting SHP-2 (phosphatase) to the ITSM motif. SHP-2 dephosphorylates signaling molecules including PKCθ, CD3ζ, and ZAP70, and therefore, inhibits T cells activation [7]. CTLA-4 (CD152) is a member of the immunoglobulin gene superfamily and is highly similar to the co-stimulatory CD28 molecule with the same ligands, B7.1 (CD80) and B7.2 (CD86). However, it has an opposite function, and its affinity for binding to the ligands is significantly higher [8,9]. After the activation of T cells, CTLA-4 is translocated to cell surface remarkably. Moreover, cytokines like IFNγ and IL-2 can increase the expression of CTLA-4 [10]. Upon interaction with B7.1/B7.2, CTLA-4 initiates the inhibitory activities by different strategies including competing with the stimulatory function of CD28 and disrupting the stimulatory kinase cascade by recruiting a phosphatase [11,12]. An overview of PD-1, CTLA-4, as well as other immune checkpoints like LAG-3, TIM-3, and TIGIT (T cell immunoreceptor with Ig and ITIM domains) interactions, structure, and roles are depicted in Fig. 1.

Accordingly, immunotherapies focusing on immune checkpoints which are able to counteract the abovementioned inhibitory signals could be a dramatic approach to regulate the immunosuppressive tumor microenvironment and boost the anti-tumor immune reactions [13]. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies (mAbs) that change the exhausted T-cell phenotype into an activated one [14] via targeting immune checkpoint molecules such as PD-1, its ligands (PD-L1 and PD-L2), CTLA-4. Following tremendous successes in metastatic melanoma [15,16], the efficacy of pembrolizumab and nivolumab (PD-1 inhibitors), durvalumab, avelumab, and atezolizumab (PD-L1 inhibitors), and tremelimumab and ipilimumab (CTLA-4 inhibitors) were explored and approved in a wide range of human cancers including non-small cell lung cancer (NSCLC), hepatocellular carcinoma, gastric cancers, renal cell carcinoma, ovarian cancer, urothelial carcinoma, cervical cancer, triple-negative breast cancer, head and neck cancer, and colorectal cancer [17,18]. In light of these impressive results in solid tumors [5,13,19], interest has risen to explore ICIs in hematologic malignancies; notably, Hodgkin's lymphoma (HL) has shown overwhelming success [20] to the extent that the food and drug administration (FDA) approved pembrolizumab and nivolumab for this lymphoma [21].

Several clinical trials have investigated the ORR and adverse events (AEs) of ICI therapy in NHLs, but the available data on different types of this neoplasm draw a diverse picture. Such diversity in results makes it difficult to ascertain whether ICIs can provide effective and durable responses in this group of diseases or not. Although Apostolidis et al. reviewed the rationale and biological principles behind immune checkpoint inhibition in NHLs [22], few articles reviewed the task, and to the best of our knowledge, no meta-analysis has assessed the effectiveness and safety of ICI therapy in relapsed or refractory NHL patients. The current review aims to summarize the original data obtained from relevant clinical trials, and also to answer some critical questions; how effective are ICIs as monotherapies in relapsed or refractory NHLs? Which subtypes of NHL are most likely to benefit from ICIs? What are the most effective types of drugs? Can the combination of ICIs and other treatment strategies improve their functions? Finally, we provide a more comprehensive picture of ICI therapy in NHL patients in terms of its efficacy and safety by overcoming the limitations of individual studies,

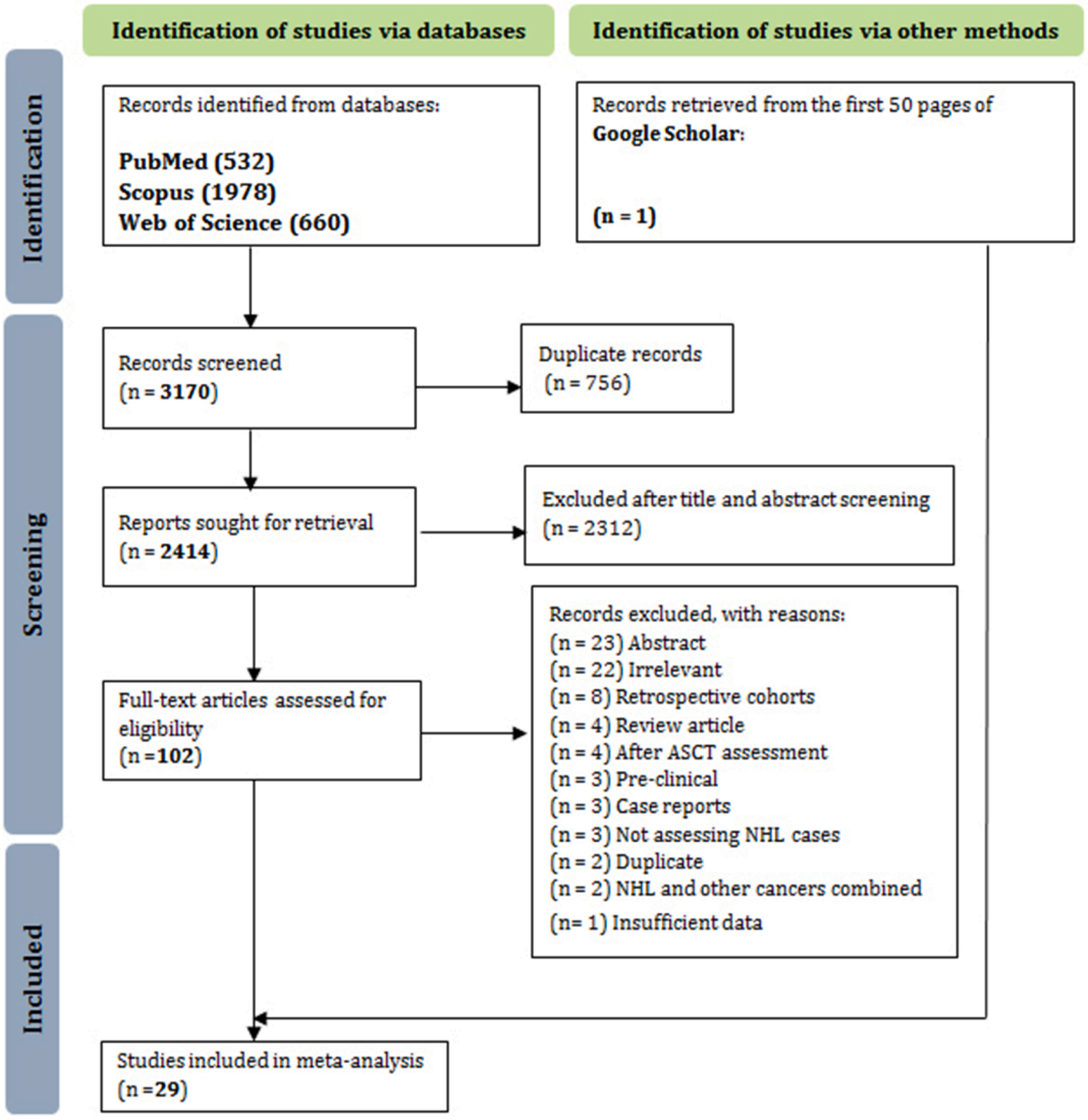

Fig. 2. Study selection flowchart.

such as a small sample size and insufficient statistical power.

Methods

Identification of studies

The search was conducted on PubMed, Web of Science, and Scopus from their inception to February 5, 2022. The first 50 pages of Google Scholar were also screened. Detailed search terms utilized to retrieve published articles specifically for each database are provided in the Supplementary file. Selection of the articles was carried out in two steps; first, two independent researchers screened the titles and abstracts of articles found through the search engines, and then, the full texts of the articles selected in the first step were reviewed to remove those that did not fit the current study. Disagreements raised in the selection process were resolved through discussion with a third researcher.

Eligibility criteria

The eligibility criteria were described as follows: (1) the study must be a clinical trial related to the efficacy or safety of ICIs treating relapsed, refractory or high-grade NHL; (2) the full text of the study must be available; (3) the study must be in English. The exclusion criteria were described as follows: (1) studies with insufficient data; (2) retrospective studies, review articles, letters, case reports, case series, *in-vitro* studies, pre-clinical studies, editorials, and expert opinions; (3) evaluate the efficiency of ICIs after autologous stem cell transplantation (ASCT).

Data collection

Data extraction and the methodological quality assessment of eligible studies were performed by two researchers independently, and any disagreement were resolved through a discussion with a third researcher. The following data were extracted: title, author, year of publication, origin country, phase, number of arms, type of NHL, number of patients, patients inclusion criteria, age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, stage of disease, prior Hematopoietic Stem Cell Transplantation (HSCT), the median duration of follow up, the median duration of treatment, disease refractory to the most recent regimen, prior line of therapy, ICI name, dose and schedule, the data of concomitant therapy, all-grade, grade $\geq$3 and serious adverse events (AEs), the median time to any response, duration

Table 1
The characteristics of the included studies.

	First author	Year	Identifier	Phase	Type of ICIs	Type of NHL	No. of Pts.	Median Age	Median follow-up (month)	Median prior line of therapy	Ref.
B-NHLs											
1	Advani et al.	2018	NCT02953509	Ib	Magrolimab	DLBCL	15	60 [44–82]	6.2 [1.9–13.9]	4 [2–10]	[24]
						FL	7	59 [44–75]	8.1 [1.9–16.4]	4 [2–9]	
2	Ansell et al. [#1]	2009	NCT00089076	I	Ipilimumab	FL	14	56 [37–79]		3 [1–4]	[25]
						DLBCL	3				
						MCL	1				
3	Ansell et al. [#2]	2019	NCT02038933	II	Nivolumab	DLBCL	121	[24-86]			[26]
4	Armand et al. [#1]	2019	NCT01953692	Ib	Pembrolizumab	PMBCL	21	31 [22–62]	29.1 [0.6–49.6]	3 [2–9]	[27]
			NCT02576990	II	Pembrolizumab	PMBCL	53	33 [20–61]	12.5 [0.1–25.6]	3 [2–8]	
5	Armand et al. [#3]	2021	NCT02038946	II	Nivolumab	FL	92	67 [37-87]		3 [2–10]	[28]
6	Davis et al.	2020	NCT02304458	I/II	Nivolumab	DLBCL	3				[29]
						Non-Hodgkin, NOS	1				
						BL	3				
						PMBCL	3				
7	Ding et al.	2017	NCT02332980	II	Pembrolizumab	RT	9	69 [46–78]	11	5[1,10]	[30]
8	Gregory et al.	2021	NCT02684617	Ib	Pembrolizumab	DLBCL	38	64.5 [39–85]			[31]
9	Grzegorz et al.	2021	NCT03003520	II	Durvalumab	DLBCL	43	62	6.2		[32]
					Durvalumab	DLBCL	3	66	14.0		
10	Herrera et al.	2020	NCT02401048	Ib/II	Durvalumab	FL	27	57 [31–79]	17.0 [1.8–28.1]	2 [1–7]	[33]
						GCB DLBCL	16	68 [22–82	17.5 [0.2–23.6]		
						Non-GCB DLBCL	16	67 [39-82]			
						Unspecified DLBCL	2				
11	Mei et al.	2020	NCT03346642	II	Camrelizumab	PMBCL	27	30 [18–45]	24.8 [3.2–32.4]	3 [1–6]	[34]
12	Morschhauser et al.	2021	NCT02631577	Ib/II	Atezolizumab	FL	38	61.5 [38–79]	35.9 [3–47]		[35]
13	Nastoupil et al.	2022	NCT02446457	II	Pembrolizumab	FL	30	64 [43-84]	34.9 [8.8–48.5]	1 [1–4]	[36]
14	Panayiotidis et al.	2022	EudraCT:2016–003,579–22	II	Atezolizumab	MCL	30	67 [49–84]	13.7 [95% CI:9.5–18.3]	2 [1–8]	[37]
						MZL	21	68 [47–87]	16.7 [95% CI: 12.6–21.6]	2 [1–7]	
						WM	4	63 [56–67]	11.4 [95% CI: 1.3–15.3]	4 [1–4]	
15	Ribrag et al.	2021	NCT02549651	Ib	Durvalumab	DLBCL	32	68 [41-87]		2 [1–4]	[38]
16	Tuscano et al.	2019	NCT01729806	I	Ipilimumab	BCL	33	62 [33–78]		4 [1–7]	[39]
17	Westin et al.	2014	NCT00904722	II	Pidilizumab	FL	30	61 [35–79]	15·4 [IQR 10·1–21]	1 [1–4]	[40]
18	Younes et al.	2019	NCT02329847	I/IIa	Nivolumab	FL	40	62 [52·5–70]		3 [2.5–4]	[41]
						DLBCL	45	64 [46–74]		3 [2–3]	
						RT	20	67.5 [56–70·5]		2 [1–3]	
19	Zinzani et al.	2017	NCT01953692	Ib	Pembrolizumab	PMBCL	18	30 [22 to 62]		3 [2–6]	[42]
20	Zinzani et al.	2019	NCT02581631	II	Nivolumab	PMBCL	30	35.5 [19-83]	11.1	2 [2–5]	[43]
T-NHLs											
21	Khodadoust et al.	2020	NCT02243579	II	Pembrolizumab	MF	9	66.9 [44-85]	58 weeks	4	[44]
						SS	15				
22	Kim et al.	2020	NCT03439501	II	Avelumab	ENKTL	21				[45]

(continued on next page)

Table 1 (*continued*)

	First author	Year	Identifier	Phase	Type of ICIs	Type of NHL	No. of Pts.	Median Age	Median follow-up (month)	Median prior line of therapy	Ref.
								54 [24–78]			
23	Querfeld et al.	2021	NCT02890368	I	TTI-621	CTCL	35	62 [58−70]		3 [1 − 5]	[46]
24	Shi et al.	2021	NCT03502629	II	Geptanolimab [GB226]	PTCL	102	52.5 [18–78]	4.06 [0.30–22.9]		[47]
25	Tao et al.	2021	NCT03228836	II	Sintilimab	ENKTL	28	37 [9–65]	30.4 [27.5–31.9]	3 [IQR 2–4.5]	[48]
B- and T- NHLs											
26	Ansell et al. [#3]	2021	NCT02663518	I	TTI-621	DLBCL	35				[49]
						FL	11				
						MCL	5				
						Others B-NHLs	4				
						PTCL	12				
						MF	24				
						SS	5				
27	Armand et al. [#2]	2021	NCT01592370	Ib	Nivolumab+Ipilimumab	FL	5	66 [24–87]		3 [1–16]	[50]
						DLBCL	11				
						Systematic T-NHL	5	56 [29–72]		4 [1–11]	
						CTCL	6				
					Nivolumab+Lirilumab	FL	6	62 [27-86]		3 [1–7]	
						DLBCL	26				
						Systematic T-NHL	6	70 [31–79]		2 [1–9]	
						CTCL	3				
28	Barta et al.	2019	NCT02535247	II	Pembrolizumab	PTCL	7	71 [18-88]	5.9 [95% CI, 0–18]	2 [1–9]	[51]
						FL	4				
						MF	3				
						Other TCLs	3				
29	Lesokhin et al.	2016	NCT01592370	Ib	Nivolumab	DLBCL	11	65 [23–74]	22.7 weeks	3[1–12]	[52]
						FL	10		91.4 weeks		
						Other BCL	10				
						MF	13	61 [30-81]	42.9 weeks		
						PTCL	5		44.0 weeks		
						SS CTCL	3				

DLBCL: Diffuse large B-cell lymphoma; GCB: Germinal-center B-cell-like; FL: Follicular lymphoma; MCL: Mantel cell lymphoma; PTCL: Peripheral T-cell lymphomas; PMBCL: Primary mediastinal large B-cell lymphoma; ENKTL: Extranodal natural killer (NK)/T cell lymphoma; MZL: Marginal zone lymphoma; CTCL: Cutaneous T-cell lymphoma; SS: Sézary syndrome; MF: Mycosis fungoides; RT: Richter transformation; BCL: B-cell lymphoma; TCL: T-cell lymphoma; WM:Waldenstrom'smacroglobulinaemia; No. of Pts: Number of patients.

of response (DOR), overall response rate (ORR), complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and target lesion size change.

Quality assessment

Two researchers used Methodological Index for Non-Randomized Studies (MINORS) to assess the quality of studies [23]. As all of the included studies were non-randomized controlled trials, eight items were evaluated for each study. Items were scored as 0, 1, or 2 depending on whether it was not reported, reported but inadequate, or reported adequately; therefore, the highest possible score for every study was 16, and a score ≤ 12 was considered at high risk of bias. A third researcher was consulted if the first two researchers could not reach an agreement.

Data synthesis and analysis

Our primary objective was to investigate the ORR, DCR, and PD following the administration of ICIs in patients with relapsed or refractory NHL. The secondary outcome was the pooled risk of adverse events. We used Cochrane's Q test to examine the between-study heterogeneity and estimate the I^2 statistics. A random-effect model was utilized whenever an obvious heterogeneity was observed ($I^2 > 50\%$), otherwise, the fixed-effect model was applied. Since no heterogeneity was observed among our analyses, a fixed-effect model was utilized for all statistics. Furthermore, we conducted subgroup analysis according to the monotherapy of immune checkpoint inhibitors or in combination with conventional therapies, type of NHL, and type of ICI.

Results

Study selection

PRISMA guidelines were followed to select studies as shown in Fig. 2. A total of 3170 studies were initially searched: 532 studies from PubMed, 660 studies from Web of Science, and 1978 studies from Scopus. Of these, 756 studies were excluded due to duplication. Among the remaining 2414 studies, 2312 studies were excluded because they were not related to the aim of this study as determined by the title and

Table 2
MINORS scale for quality assessment of included studies.

		Year	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the study's aim	Loss to follow-up less than 5%	Prospective calculation of study size	Total
1	Advani et al.	2018	2	2	2	2	0	2	2	2	14
2	Ansell et al. [#1]	2009	2	2	2	2	0	0	1	0	9
3	Ansell et al. [#2]	2019	2	2	2	2	0	2	2	2	14
4	Ansell et al. [#3]	2021	2	2	2	2	0	0	0	0	8
5	Armand et al. [#1]	2019	2	2	2	2	0	2	2	2	14
6	Armand et al. [#2]	2021	2	2	2	2	0	1	0	2	11
7	Armand et al. [#3]	2021	2	2	2	2	0	1	2	2	13
8	Barta et al.	2019	2	2	2	2	0	2	2	0	12
9	Davis et al.	2020	2	2	2	2	0	2	2	0	12
10	Ding et al.	2017	2	2	2	2	0	2	2	2	14
11	Gregory et al.	2021	2	2	2	2	0	2	2	2	14
12	Grzegorz et al.	2021	2	2	2	0	0	2	2	2	12
13	Herrera et al.	2020	2	2	2	2	0	2	2	2	14
14	Khodadoust et al.	2020	2	2	2	2	0	2	1	2	13
15	Kim et al.	2020	2	2	0	2	0	0	2	2	10
16	Lesokhin et al.	2016	2	2	2	2	0	2	2	2	14
17	Mei et al.	2020	2	2	2	2	0	2	2	2	14
18	Morschhauser et al.	2021	2	2	2	2	0	2	2	2	14
19	Nastoupil et al.	2022	2	2	2	2	0	2	2	2	14
20	Panayiotidis et al.	2022	2	2	2	2	0	2	1	2	13
21	Querfeld et al.	2021	2	2	2	1	2	1	2	0	12
22	Ribrag et al.	2021	2	1	2	2	0	0	2	0	9
23	Shi et al.	2021	2	2	2	2	0	2	1	2	13
24	Tao et al.	2021	2	2	2	2	0	2	2	2	14
25	Tuscano et al.	2019	2	2	2	2	0	1	2	2	14
26	Westin et al.	2014	2	2	0	2	2	2	2	2	14
27	Younes et al.	2019	2	2	2	2	0	1	1	2	12
28	Zinzani et al.	2017	2	0	2	2	0	0	2	2	10
29	Zinzani et al.	2019	2	2	2	2	2	2	2	2	16

abstract of each study. Next, 102 studies were reviewed, among which 74 studies were excluded according to specific exclusion criteria: only abstract was available (n = 23), irrelevant publications (n = 22), retrospective cohort (n = 8), review article (n = 4), trials after ASCT (n = 4), case reports (n = 3), pre-clinical study (n = 3), not assessing NHL patients (n = 3), duplicate (n = 2), and NHL analysis along with other cancers (n = 2). Thereafter, 28 full-texts remained. Of note, an additional study was retrieved from the screening of the first 50 pages of Google Scholar engine, and finally, a total of 29 studies were included in the meta-analysis.

Characteristics of the selected studies and quality assessment

While most of the included studies were published in 2016–2022, two were investigated in 2009 and 2014. All studies were single-arm-designed clinical trials. A total of 1334 confirmed relapsed/refractory NHL patients, with the age range of 30–71 years, participated in our selected studies. In total, 153 patients were treated with CD47 inhibitors, and 1181 patients were treated with PD-1, PD-L1, or CTLA-4 inhibitors, among them 480 patients received nivolumab, 210 patients received pembrolizumab, 139 patients received durvalumab, 54 patients received ipilimumab, 27 patients received nivolumab+ipilimumab, and 271 patients received other types of drugs. The characteristics of the included studies are summarized in Table 1.

The quality assessment of studies is presented in Table 2. All included studies (n = 29) provided the information on a clearly stated aim, and 27 studies provided the information on the inclusion of consecutive patients, prospective collection of data, and endpoints appropriate to the aim of the study. Furthermore, 19 studies had a follow-up period appropriate to the aim of the study, 22 studies provided information on loss to follow up less than 5%, 23 studies reported prospective calculation of the study size, and only 3 studies noted an unbiased assessment of the study endpoint. Overall, all trials scored between 8 and 16 points, 5 of them were considered at high risk of bias.

Efficacy of ICIs as monotherapy in relapsed or refractory NHL patients

Although some studies have reported promising outcomes of ICIs as monotherapy in NHL patients [53–55], there are controversial results about their efficacies as single agents. Given this, it is of great interest to investigate whether ICI monotherapy can increase response rates and duration of response in NHL patients. Through analysis of 15 trials which assessed ICI monotherapy either in B- or T-NHL patients pooled DCR was 59.22% (95% CI: 54.72–63.66; Fig. 3A); of note, ORR was 24.61% (95% CI: 20.54–28.87; Fig. 3B) and SD rate was 26.67% (95% CI: 22.69–30.82; Fig. 3C). Despite promising DCR, pooled PD rate was 40.78% (95% CI: 36.34–45.28; Fig. 3D); highlighting the fact that ICI monotherapy is unlikely to be effective at least in some subgroups of NHL patients. A growing body of evidence has discussed that multiple factors such as type of ICIs and tumor may influence outcomes of ICI monotherapy in NHL patients [20,56]; that's why it was intriguing to investigate whether types of ICIs or tumor are in charge of different outcomes in NHL patients.

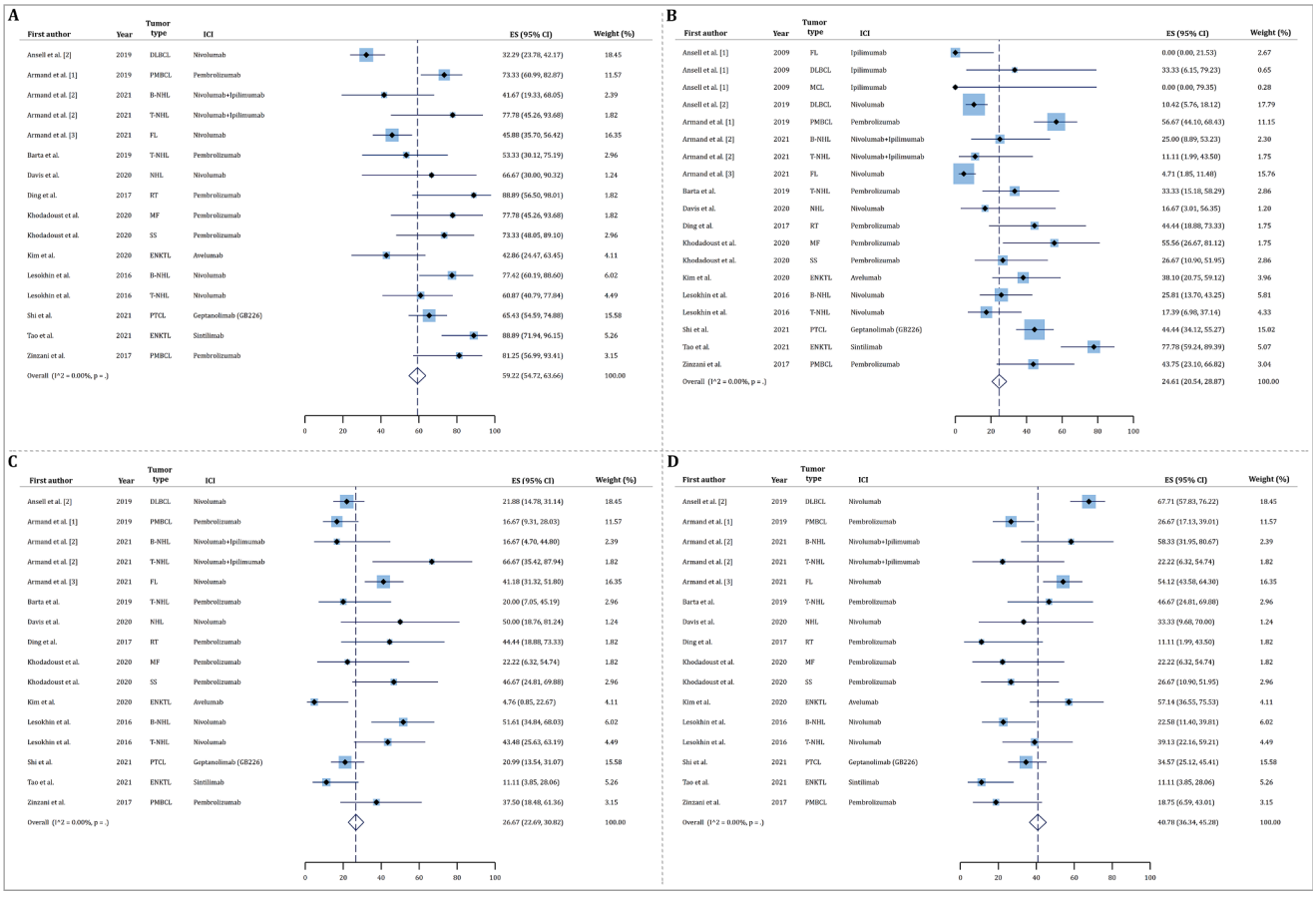

Fig. 3. Forest plots of effect size (ES) comparing pooled (A) disease control rate (DCR), (B) overall response rate (ORR), (C) stable disease (SD) rate, and (D) progressive disease (PD) of ICIs monotherapy in relapsed or refractory NHL.

Efficacy of ICIs based on drug types

It has been reported that targeting PD-1, PD-L1 or CTLA-4 may provide different outcomes in melanoma [57], gastric cancer [58], and hepatocellular carcinoma [59]; thus hypothesizing whether the application of different ICIs was associated with different efficacies in NHL patients. After subgroup analysis based on various ICIs, pembrolizumab and nivolumab were the most investigated drugs, proposing that PD-1 may probably be the more attractive ICI target rather than PD-L1 and CTLA-4 in NHL patients. Notably, pembrolizumab, as a potent PD-1 inhibitor, was the best drug with DCR of 74.24% (95% CI: 65.63–82.10; Fig. 4A), ORR of 47.49% (95% CI: 38.28–56.77; Fig. 4B), and PD rate of only 25.76% (95% CI: 17.90–34.37; Fig. 4C). Nivolumab, on the other hand, had more than 2-fold PD rate compared to pembrolizumab; while PD rate in NHL patients who received nivolumab was 53.67% (95% CI: 47.07–60.22; Fig. 4C), DCR was 46.33% (95% CI: 39.78–52.93; Fig. 4A). Notably, ORR achieved by nivolumab was only 9.17% (95% CI: 5.42–13.59; Fig. 4B). All in all, the results of our study showed that pembrolizumab outperforms nivolumab in spite of the fact that both of them target PD-1; however, this conclusion may have a bias as the subgroups of NHLs were different in the studies which investigated the efficacies of these agents.

Apart from pembrolizumab and nivolumab, there are also several other studies which have assessed other PD-1 inhibitors; for example, one study which evaluated PD-1 targeting using sintilimab in extranodal natural killer (NK)/T cell lymphoma (ENKTL) patients [48] showed an impressive response, but further studies are needed to give an accurate assessment of its effectiveness in NHL patients. Also, 2 other studies investigated avelumab (PD-L1 inhibitor) and ipilimumab (CTLA-4 inhibitor) in NHL patients, but there isn't enough evidence to make a definitive judgment about their safeties and efficacies.

Efficacy of ICIs based on NHL types

Based on the knowledge that NHL is a heterogeneous tumor, it seems interesting to find that whether there is any correlation between NHL subtypes and response to ICI therapy. To make a better conclusion, we first classified the included studies according to B and T lineages; overall, we found that being NHL patients of either T or B lineage does not affect the outcomes of ICI therapy obviously. In T-NHL subtypes, while Mycosis fungoides (MF) had the best DCR of 82.04% (95% CI: 61.95–96.45), ENKTL followed by peripheral T-cell lymphomas (PTCL) had the best ORR of 61.21% (95% CI: 46.72–74.82) and 43.75% (95% CI: 32.49–55.30) respectively. On the other hand, in B-NHL subtypes, Richter transformation (RT) with DCR of 88.89% (95% CI: 56.50–98.01), and PD rate of 11.11% (95% CI: 1.99–43.50) showed a promising response to ICI monotherapy. Primary mediastinal large B-cell lymphoma (PMBCL) also showed a favorable response, however, neither FL nor DLBCL had satisfactory results.

DLBCL was the worst with the lowest DCR of 34.85% (95% CI: 25.70–44.53) together with the highest PD rate of 24.65% (95% CI: 15.25–35.32). The results in FL did not appear to be much better than DLBCL, as DCR and PD rate was 53.46% (95% CI: 42.94–63.85) and 46.54% (95% CI: 36.15–57.06), respectively. No data was existed for Burkitt's lymphoma patients exclusively. Taken together, while some subtypes of NHL showed promising outcomes with ICI monotherapy, the others didn't; further necessitating novel strategies such as the application of ICIs in combination with other treatment strategies in more resistant cases. To provide a better overview, we represented the response to ICI therapies in various NHL subgroups, separately in T- and B-NHL, in Fig. 5. Forest plots of ES comparing DCR, ORR, and PD between different subtypes of NHL were represented in Supplementary Fig. 1.

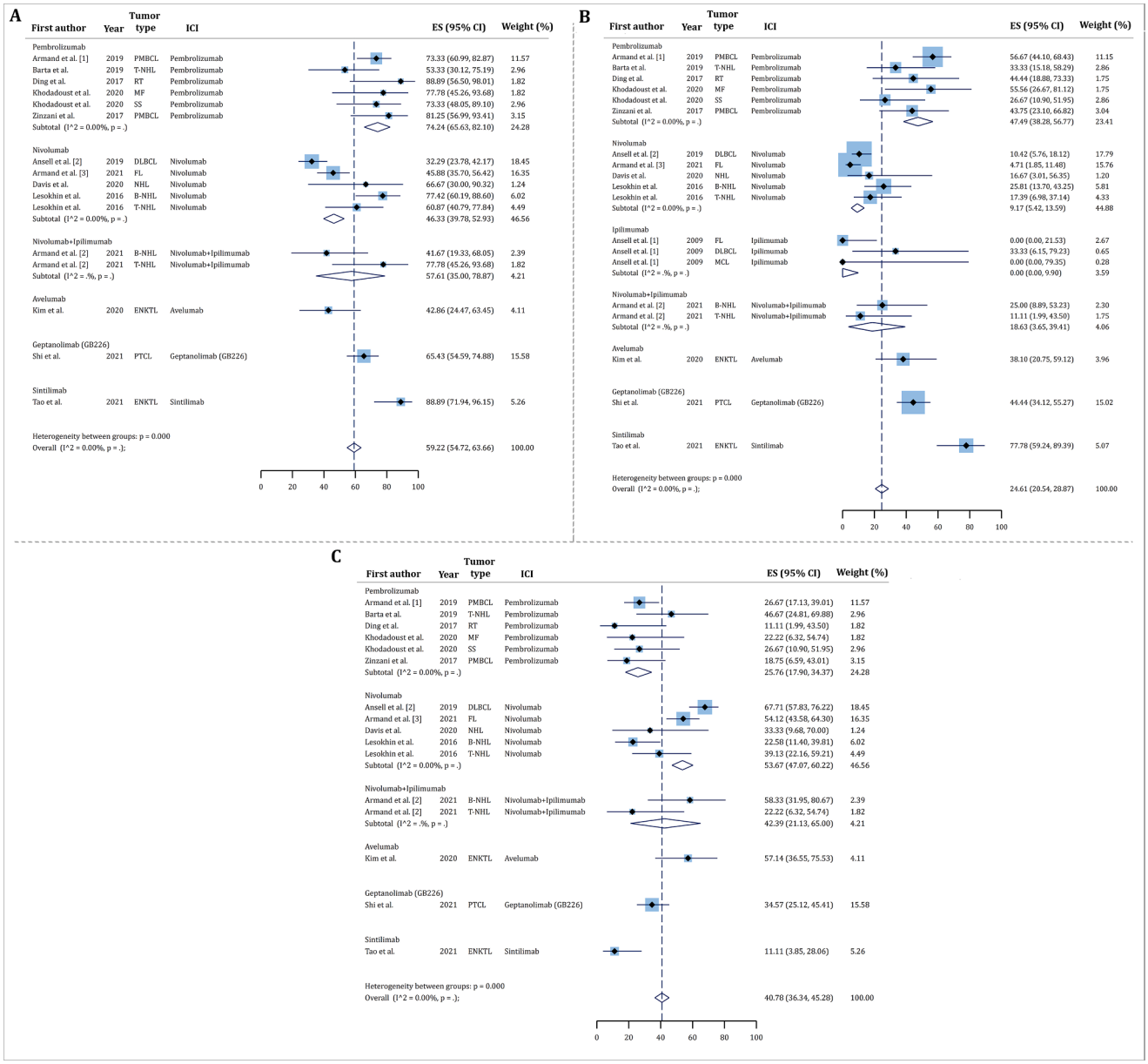

Fig. 4. Forest plots of effect size (ES) comparing pooled (A) disease control rate (DCR), (B) overall response rate (ORR), and (C) progressive disease (PD) of different ICIs in relapsed or refractory NHL.

Efficacy of ICIs in combination with other treatment strategies in relapsed or refractory NHL patients

It has been reported that ICIs in combination with other treatment strategies may provide better outcomes in various types of tumors including colorectal cancer [60], hepatocellular carcinoma [61], and triple-negative breast cancer [62]. We found that while overall results represent beneficial outcomes in the combinational strategies, there were controversies based on either the combination strategy or tumor type.

Among different combinations, Bruton's tyrosine kinase (BTK) inhibitors and anti-CD20 monoclonal antibodies were the most investigated strategies. While the combination with BTK inhibitors did not show an obvious improvement as compared to single treatment (DCR: 60.64% vs. 59.22%; ORR: 36.23% vs. 24.61%; and PD: 39.36% vs. 40.78%), the results were more effective in the combination of ICIs and anti-CD20 monoclonal antibodies. As depicted in Fig. 6A and B, both DCR and ORR greatly improved as compared with ICI monotherapy (DCR: 78.55% vs. 59.22%; ORR: 50.36% vs. 24.61%). Along with increased responses, PD rate was also decreased in NHL patients who received ICIs in combination with anti-CD20 monoclonal antibodies (PD: 21.45% vs. 40.78%; Fig. 6C). Another study took a step forward and investigated this combination-plus-chemotherapy with or without IMiD; of note, the addition of chemotherapy either with or without IMiD had impressive results with ORR of 100% (95% CI: 43.85–100) and 97.30% (95% CI: 86.18–99.52), respectively (Fig. 6).

The combination of ICIs with Killer-cell immunoglobulin-like receptors (KIR) or CTLA-4-plus-STAT3 inhibitors, on the other hand, didn't have acceptable results; indeed, not only they didn't improve the outcomes of ICIs monotherapy but also decreased its ORR rate to 18.28% (95% CI: 5.46–35.12) and 9.09% (95% CI: 2.53–27.81), respectively (Fig. 6). Apart from targeting PD-1, PD-L1, and CTLA-4, two other studies have investigated the efficacy of CD47 inhibitors either as a monotherapy or in combination with anti-CD20 monoclonal antibodies which their results are depicted in Supplementary Fig. 2.

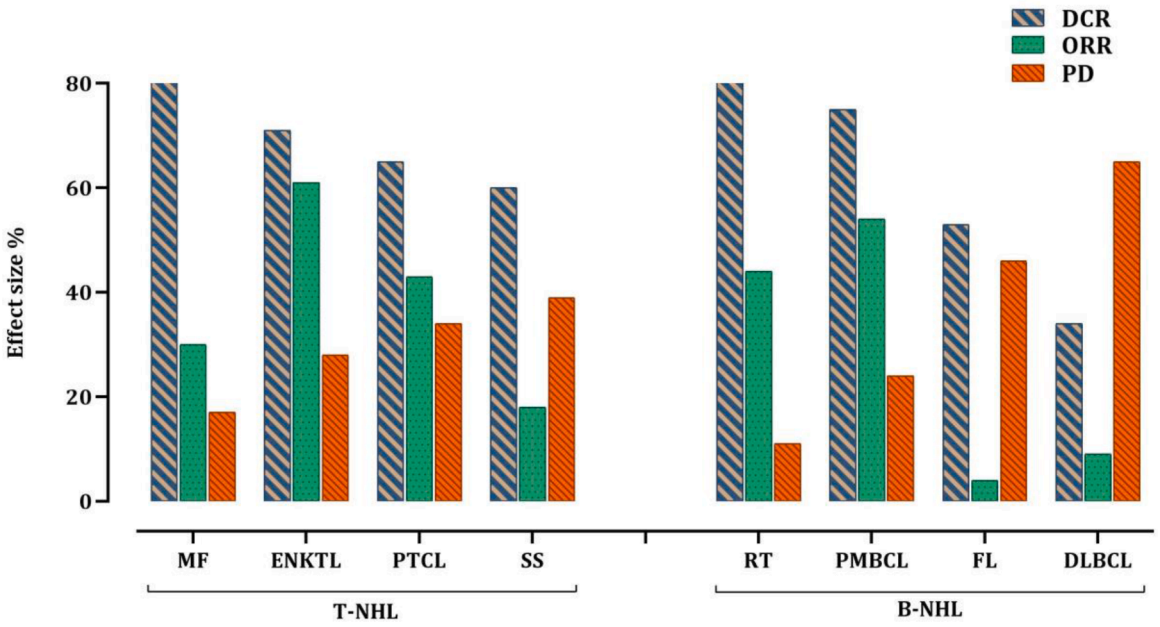

Fig. 5. An overview of the response to ICI therapies between different subtypes of relapsed or refractory NHL, separately in T- and B-NHL.

Efficacy of ICIs in combination in relapsed or refractory FL and DLBCL patients

Since ICI monotherapy almost failed in FL and DLBCL which are the most prevalent subtypes, we aimed to take a closer look at their combination therapy. Among different combinations, BTK inhibitors showed an obvious improvement as compared to a single treatment in both FL (ORR: 2.92% vs. 31.16%; PD: 54.12% vs. 26.48%) and DLBCL (ORR: 6.12% vs. 32.69%; PD: 67.71% vs. 54.88%). However, the best results were obtained when ICI was combined with anti-CD20 monoclonal antibodies. In FL, the combination of ICI and anti-CD20 increased the ORR to 66.10%, while decreasing the PD to 6.90%. Notably, adding IMiD to this combination further enhanced the ORR to 83.87%. The best results were obtained in DLBLC when ICI is combined with anti-CD20 monoclonal antibodies +chemotherapy, either alone or in combination with IMiD. To provide a better overview, we represented the response FL and DLBCL to ICIs in combination with other treatment strategies in Fig. 7. The forest plots of ES comparing pooled ORR and PD between single and combined-modal ICI therapy were depicted in Supplementary Figs. 3 and 4.

Safety of ICI therapy in relapsed or refractory NHL patients

Pooled treatment-related adverse event (TRAE) was 69.00% (95% CI: 64.73–73.13), while grade ≥3 and serious TRAEs were 22.33% (95% CI: 18.68–26.19) and 12.95% (95% CI: 8.95–17.52), respectively; indicating that the majority of AEs were relatively mild. Leukopenia and increased AST were the most prevalent AEs with the rate of 24.53% (95% CI: 17.33–32.44) and 22.83% (95% CI: 11.30–36.51) respectively, followed by lymphopenia (18.32%), hypothyroidism (18.15%), headache (17.64%), anorexia (15.87%), hypocalcemia (15.54%), fatigue (15.47%), fever (13.23%), nausea (11.97%), hyperglycemia (10.79%), and diarrhea (10.31%). The most common grade ≥3 AE, on the other hand, was lymphopenia (4.85%). The other common grade ≥3 AEs were neutropenia (3.98%), thrombocytopenia (2.17%), upper respiratory tract infection (1.93%), and dyspnea/wheezing (1.77%). The rest of grade ≥3 AEs rarely occurred. Detailed on total and garde≥3 are provided in Fig. 8 and Supplementary Table 1. To provide a deeper overview, we also analyzed and compared the AEs based on each ICI (Fig. 8B).

Discussion

Despite therapeutic improvements in the treatment strategies over the past decades, human malignancies still remain one of the leading causes of person-years of life lost worldwide. First introduced by William B. Coley in the 1890s [63], immunotherapies take advantage of the patients' immune system to improve tumor eradication [64]; however, cancers are able to evade the immune-mediated destruction, and interestingly, the trace of dysregulated expression of immune checkpoints such as PD-1 and its ligands (PD-L1/2), CTLA-4, T-cell immunoglobulin and mucin domain containing protein-3 (TIM-3), and lymphocyte-activation gene-3 (LAG-3) has been observed in a wide range of human cancers [65]. Thus, immunotherapeutic agents targeting immune checkpoints are considered a dramatic approach to boost the anti-tumor immune reactions. Following great successes in solid tumors such as non-small cell lung cancer, melanoma, renal cell carcinoma [66], and squamous cell carcinoma of the head and neck [67], interest has risen to explore these inhibitors in hematologic malignancies. Notably, patients with relapsed or refractory HL showed promising outcomes to PD-1 inhibitors probably due to the PD-L1 and PD-L2 up-regulation in >95% of cases during the immune escape [68]. While ICIs are a logical treatment option for HL patients, there are controversial results about their efficacies in NHL ones.

The results of our meta-analysis revealed that ICI monotherapy in refractory or relapsed NHL patients, after receiving at least one prior line of therapy, could partially control disease progression with a pooled DCR of 59.22%; while some studies have reported remarkable responses, the others failed to achieve favorable outcomes, which may be explained, at least partially, by the variation in drug types, the aggressiveness of the NHL subtypes, differences in the line of treatment, and the expression of the drug targets in the tumor microenvironment. The results of subgroup analysis based on various ICIs revealed that pembrolizumab and nivolumab (potent PD-1 inhibitors) were the most investigated drugs, proposing that PD-1 may probably be the more attractive ICI target rather than PD-L1 and CTLA-4 in NHL patients. Furthermore, as represented in Table 3, most of the ongoing clinical trials are designed to investigate the efficacies of PD-1 inhibitors, mainly nivolumab, either as a single agent or in combination with other ICIs and/or anti-cancer agents. Inline, Ribas et al. have claimed that PD-1 inhibitors outperform PD-L1 inhibitors as they inhibit the binding of

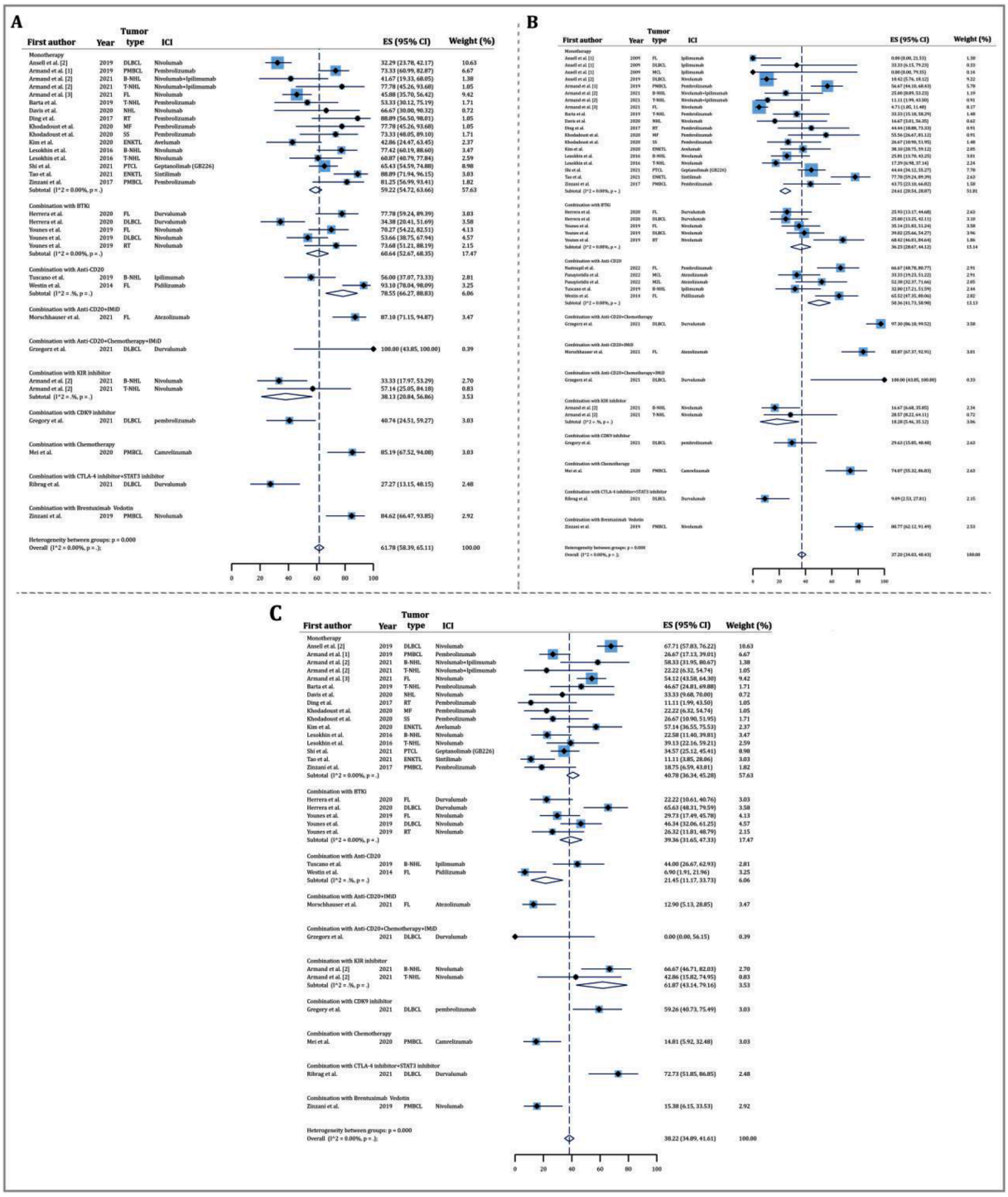

Fig. 6. Forest plots of effect size (ES) comparing pooled (A) disease control rate (DCR), (B) overall response rate (ORR), and (C) progressive disease (PD) of ICIs in combination with other lines of therapies in relapsed or refractory NHL.

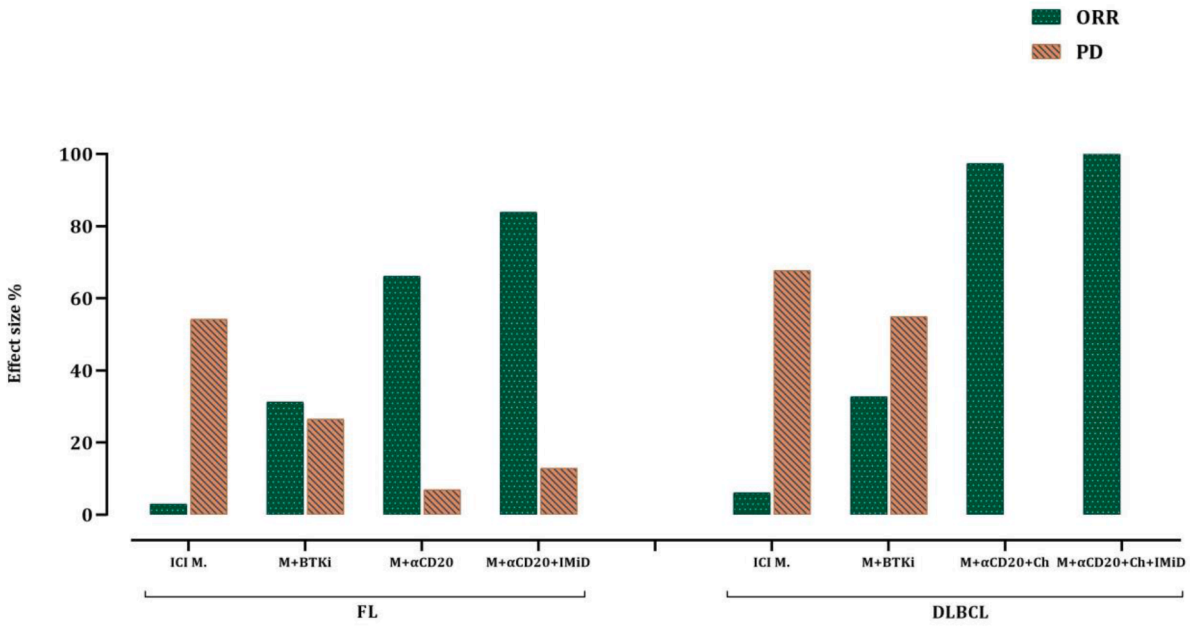

Fig. 7. An overview of comparing the overall response rate (ORR) and progressive disease (PD) of ICIs, either as monotherapy or in combination with other lines of therapy separately in FL and DLBCL. PD of monotherapy+αCD20+chemotherapy and monotherapy+αCD20+chemotherapy+IMiD have not reported. M: Monotherapy; Ch: Chemotherapy.

PD-L2 to PD-1, as well [69]. Accordingly, recent studies indicated that PD-1 inhibitor sintilimab [48] controlled the disease more effectively than avelumab (PD-L1 inhibitor) [45] in the treatment of ENKTL, partially due to the variability of PD-L1 expression by the tumor tissue.

As represented in Fig. 4, the results of our study showed that pembrolizumab outperforms nivolumab in spite of the fact that both of them target PD-1; however, this conclusion may have a bias as the subgroups of NHLs were different in the studies which investigated the efficacies of these agents. For example, PD of nivolumab was lower than pembrolizumab in T-NHL patients (39.13% [52] vs. 46.67% [51]); shedding light on the plausible correlation between NHL subtypes and response to ICI therapy. Except for FL and DLBCL, the results of subgroup analysis revealed that most types of NHLs, being patients of either T or B lineage, respond favorably to ICIs mainly targeting PD-1. In T-NHL subtypes, we found that patients with MF had the best DCR together with the lowest PD in response to PD-1 inhibitors pembrolizumab and nivolumab (Fig. 5); this finding can be justified by the high expression of PD-1 in malignant T-cells of MF patients [70,71]. ENKTL, a highly aggressive subtype of T-NHL as a result of PD-L1 overexpression [72], also responds well to ICIs targeting PD-1/PD-L1 interaction.

On the other hand, in B-NHL subtypes, PMBCL and RT showed a promising response to ICI monotherapy using PD-1 inhibitor pembrolizumab. Notably, around 30–80% of patients with PMBCL have PD-L1 overexpression [73], and encouraging results of ICIs targeting PD-1/PD-L1 interaction led to the approval of pembrolizumab by the US-FDA in PMBCL patients after failure of 2 or more lines of therapy. RT –which is the progression of CLL into aggressive lymphoma (DLBCL; RT-DLBCL)– is associated with a poor prognosis. While tumor cells in RT express high levels of PD-1 [74], its expression is rare in de novo DLBCL, which is consistent with the observed differences in the efficacy of PD-1 inhibitors in patients with RT and de novo DLBCL [52]. Moreover, in contrast to other B-cell lymphomas, PD-L1 and PD-L2 are infrequently expressed by either DLBCL or FL tumor cells [75,76]; turning these subtypes into the least responding NHLs to ICIs monotherapy.

Despite the initial enthusiasm regarding ICI monotherapy in NHL patients, randomized trials of ICIs monotherapy failed to demonstrate an obvious improvement in response rate, particularly in DLBCL and FL. Accordingly, as represented in Table 3, most of the ongoing clinical trials are planned to investigate the efficacy of ICIs in combined-modal strategies. Dual checkpoint blockade with anti-PD-1 and CTLA-4 monoclonal antibodies, with or without STAT3 inhibitors, did not show promising clinical activity in DLBCL and FL [77]. Although a pre-clinical study showed that BTK inhibitor ibrutinib had a synergistic antitumor activity with PD-1 blockade [78], this combination failed to improve clinical outcomes in RT, FL, and DLBCL patients [33,41]. In contrast, a favorable clinical activity has been reported when a PD-1 inhibitor was co-administrated with an anti-CD20 monoclonal antibodies [36,37, 39, 40]. Of note, the effect of this combination was further enhanced by adding chemotherapy [79], IMiD [80], or both [79]; however, larger studies are needed to confirm these results.

The results of our meta-analysis confirmed the favorable safety profile and adequate toleration of ICIs in NHL patients. As represented in Fig. 8, the majority of AEs were grade 1 or 2 and manageable. The most prevalent drug-related AEs were leukopenia, increased AST, lymphopenia, and hypothyroidism. On the other hand, the most common grade $\geq$3 AEs that patients experienced during ICI treatment included lymphopenia, neutropenia, and thrombocytopenia. Nevertheless, to confirm the safety of ICI therapy in NHL patients' larger trials with long-term follow-up are required. In spite of our best efforts to present a complete and practical study, the type of inhibitors, intervention time, cycles of receiving the drug, line of ICI therapy, and previous treatments of patients varied between eligible studies, which may have affected the results of the meta-analysis.

Conclusion

To the best of our knowledge, no study has performed a meta-analysis of the existing clinical trials of ICI therapy in relapsed or refractory NHL patients, and this article is the first study conducted to evaluate the efficacy and safety of this approach in these patients. In conclusion, we found that PD-1 may probably be the more attractive ICI target rather than PD-L1 and CTLA-4 in NHL patients. Moreover, there is a plausible correlation between NHL subtypes and response to ICI therapy. While most types of NHLs, either with T or B origin, respond favorably mainly to PD-1 inhibitors, neither FL nor DLBCL had satisfactory responses to ICI monotherapy; further necessitating the

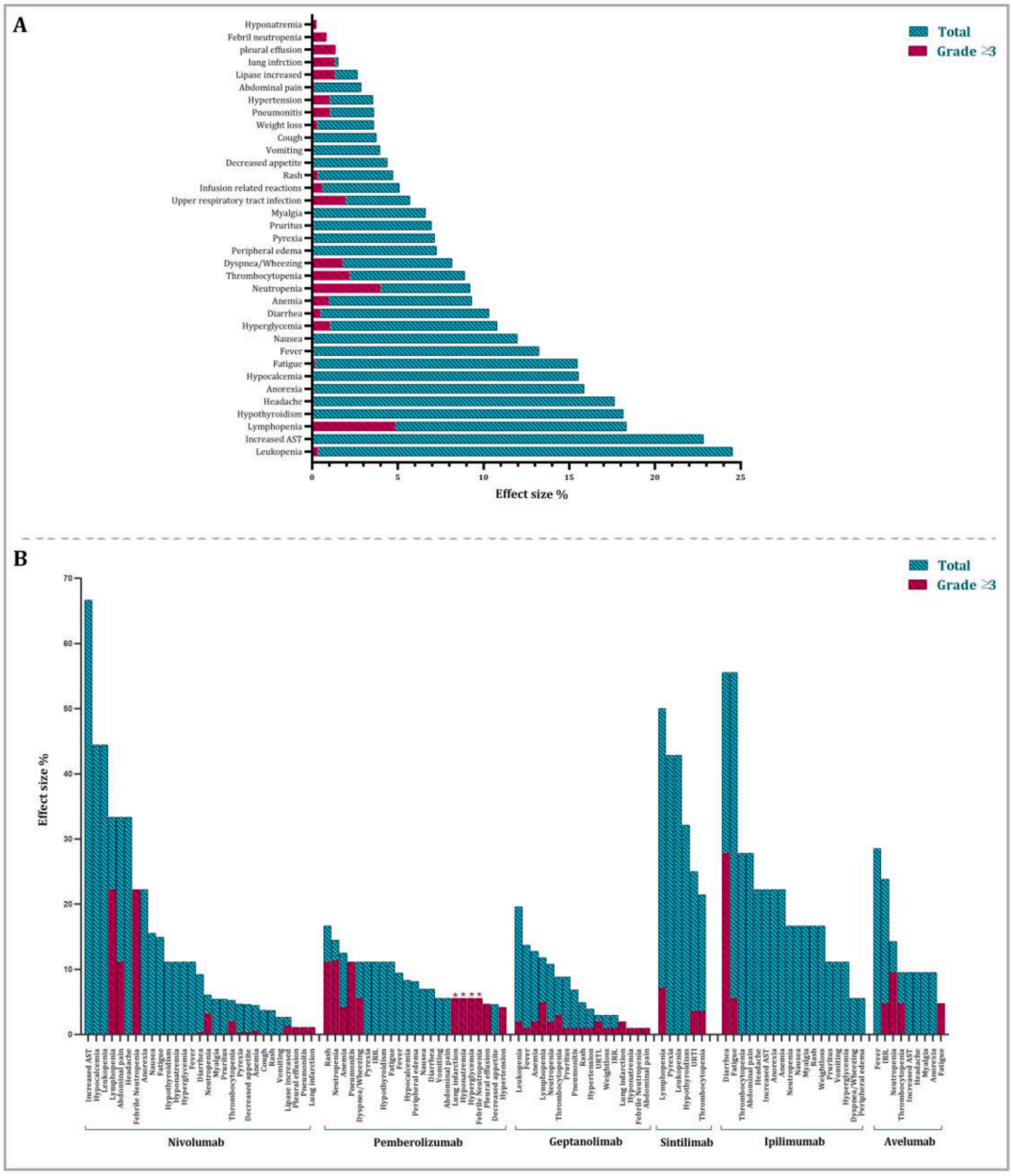

Fig. 8. (A) An overview of total and garde≥3 AEs of ICI therapy in relapsed or refractory NHL cases. (B) Safety of ICI therapy based on each drug.

application of ICIs in combination with other treatment strategies, in particular ICIs-plus-anti-CD20 monoclonal antibodies. Although there remains much to learn about the efficacy of ICI therapy in NHL, an important question for oncologists is: whether the expression pattern of the immune checkpoints on tumors or immune cells is the determinant factor in NHL patients? It is necessary to keep in mind that response to therapy is ongoing and ever-changing during the course of a patient's disease whether due to physiological factors or therapeutic approaches applied to eradicate the tumor; thus initial examinations to determine the expression of the immune checkpoint molecules using flow cytometry or immunohistochemistry (IHC) seem an essential step before ICI treatment. Finally, while most NHL patients who received ICI treatment have experienced mild AEs, larger trials with long-term follow-up are required to confirm the safety, as well as the efficacy, of ICI therapy in NHL patients.

CRediT authorship contribution statement

Zeinab Davoodi-Moghaddam: Investigation, Writing – original draft, Writing – review & editing. **Farideh Jafari-Raddani:** Investigation, Writing – original draft, Writing – review & editing. **Maryam Noori:** Investigation, Data curation, Writing – review & editing. **Davood Bashash:** Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 3
Ongoing clinical trials investigating the efficacy of ICIs in NHL patients.

NCT number	Condition	No.	Intervention	Phase	Status	Location
PD-1 inhibitors						
NCT03258567	NHL, LPDs	40	Nivolumab	II	Recruiting	USA
NCT04205409	NHL, Hematologic malignancies	20	Nivolumab	II	Recruiting	USA
NCT03432741	NHL, HL, Stage IV breast cancer	39	Nivolumab+Pembrolizumab	I	Recruiting	USA
NCT03884998	DLBCL, FL, MZL, RT, LPL, CLL	21	Nivilomab+Copansilib	I	Recruiting	USA
NCT05255601	NHL, HL	68	Nivolumab+Relatlimab	I/II	Not yet recruiting	Multicenter
NCT03770416	CNSL	40	Nivolumab+Ibrutinib	II	Recruiting	USA
NCT03061188	NHL, Stage IV solid tumor	15	Nivolumab+Veliparib	I	Active, not recruiting	USA
NCT03038672	B-NHL, HL	106	Nivolumab+Varlilumab	II	Suspended	USA
NCT02581631	NHL	146	Nivolumab+Brentuximab Vedotin	I/II	Unknown	USA
NCT01703949	NHL, HL	40	Nivolumab+Brentuximab Vedotin	II	Recruiting	USA
NCT03015896	NHL, HL	102	Nivolumab+Lenalidomide	I/II	Recruiting	USA
NCT03749018	Aggressive B-NHL	30	Nivolumab+EPOCH-R	II	Recruiting	USA
NCT03704714	NHL	30	Nivolumab+EPOCH-R	I/II	Recruiting	USA
NCT03620578	NHL, B-cell lymphoma	97	Nivolumab+EPOCH-R	II	Active, not recruiting	Multicenter
NCT03310619	NHL	77	Nivolumab+JCAR017	I/II	Recruiting	Multicenter
NCT05272384	B-NHL, HL	27	Nivolumab+Decitabine+Cedazuridine	I	Not yet recruiting	USA
NCT02978625	Lymphomas, Skin cancers	68	Nivolumab+Talimogene+Laherparepvec	II	Recruiting	USA
NCT03366272	NHL	388	Nivolumab+Rituximab+Gemcitabine+Oxaliplatin	II/III	Recruiting	Multicenter
NCT01716806	PTCL, HL	180	Nivolumab+brentuximabvedotin+bendamustine+dacarbazine	II	Recruiting	USA
NCT03843294	DLBCL, HL	18	Nivolumab+TAA-T cells	I	Recruiting	USA
NCT04539444	rr NHL	10	Tislelizumab+CD19/22 CART cell	II	Recruiting	China
NCT03207867	DLBCL, Solid tumors	376	Spartalizumab+NIR178	II	Recruiting	Multicenter
PD-L1 inhibitors						
NCT03310619	NHL	77	Durvalumab+JCAR017	I/II	Recruiting	Multicenter
CTLA-4 inhibitors						
NCT01919619	NHL, Hematologic malignancies	41	Ipilimumab+Lenalidomide	II	Active, not recruiting	USA
NCT00586391	B-NHL, CLL, ALL	14	Ipilimumab+CD19 CART cell	I	Active, not recruiting	USA
PD-1-plus-CTLA-4 inhibitors						
NCT03297606	NHL, Solid tumors	720	Nivolumab+Ipilimumab+other anti-cancer drugs	II	Recruiting	Multicenter
NCT02693535	NHL, Solid tumors	3581	Nivolumab+Ipilimumab+other anti-cancer drugs	II	Recruiting	Multicenter
PD-1-plus-LAG-3 inhibitors						
NCT02061761	DLBCL, HL	107	Nivolumab+Relatlimab	I/II	Active, not recruiting	Multicenter
NCT05255601	NHL, HL	68	Nivolumab+Relatlimab	I/II	Not yet recruiting	Multicenter

NHL: Non-Hodgkin lymphoma; HL: Hodgkin's lymphoma; LPDs: Lymphoproliferative disorders; LPL: Lymphoplasmacytic lymphoma; CLL: Chronic lymphocytic leukemia; ALL: Acute lymphoblastic Leukemia; CNSL: Central nervous system lymphoma; rr: refractory/relapsed; DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma; RT: Richter transformation; MZL: Marginal zone lymphoma; PTCL: Peripheral T-cell lymphomas.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2023.101636.

References

[1] K. Chaudhari, S. Rizvi, B.A. Syed, Non-Hodgkin lymphoma therapy landscape, Nat. Rev. Drug Discov. 18 (9) (2019) 663–664.
[2] M. Crump, et al., Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood, J. Am. Soc. Hematol. 130 (16) (2017) 1800–1808.
[3] D.J. Palmieri, M.S. Carlino, Immune checkpoint inhibitor toxicity, Curr. Oncol. Rep. 20 (9) (2018) 1–12.
[4] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (5) (2011) 646–674.
[5] M.J. Sanaei, et al., The application of nano-medicine to overcome the challenges related to immune checkpoint blockades in cancer immunotherapy: recent advances and opportunities, Crit. Rev. Oncol. Hematol. 157 (2021), 103160.
[6] T. Okazaki, T. Honjo, PD-1 and PD-1 ligands: from discovery to clinical application, Int. Immunol. 19 (7) (2007) 813–824.
[7] G.J. Freeman, Structures of PD-1 with its ligands: sideways and dancing cheek to cheek, Proc. Natl. Acad. Sci. 105 (30) (2008) 10275–10276.
[8] A. Kosmaczewska, et al., Expression and functional significance of CTLA-4, a negative regulator of T cell activation, Arch. Immunol. Ther. Exp. 49 (1) (2001) 39–46 (Warsz.).
[9] P.S. Linsley, et al., CTLA-4 is a second receptor for the B cell activation antigen B7, J. Exp. Med. 174 (3) (1991) 561–569.
[10] C. Jago, et al., Differential expression of CTLA-4 among T cell subsets, Clin. Exp. Immunol. 136 (3) (2004) 463–471.
[11] M.L. Alegre, K.A. Frauwirth, C.B. Thompson, T-cell regulation by CD28 and CTLA-4, Nat. Rev. Immunol. 1 (3) (2001) 220–228.
[12] J.C.D. Schwartz, et al., Structural mechanisms of costimulation, Nat. Immunol. 3 (5) (2002) 427–434.
[13] E. Masoumi, et al., The application of immune checkpoint blockade in breast cancer and the emerging role of nanoparticle, J. Control. Release 340 (2021) 168–187.
[14] K. Suresh, et al., Immune checkpoint immunotherapy for non-small cell lung cancer: benefits and pulmonary toxicities, Chest 154 (6) (2018) 1416–1423.
[15] C. Robert, et al., Pembrolizumab versus ipilimumab in advanced melanoma, N. Engl. J. Med. 372 (26) (2015) 2521–2532.
[16] J. Weber, et al., Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma, N. Engl. J. Med. 377 (19) (2017) 1824–1835.
[17] H. Hatic, D. Sampat, G. Goyal, Immune checkpoint inhibitors in lymphoma: challenges and opportunities, Ann. Transl. Med. 9 (12) (2021).
[18] H. Memon, B.M. Patel, Immune checkpoint inhibitors in non-small cell lung cancer: a bird's eye view, Life Sci. 233 (2019), 116713.
[19] M.J. Sanaei, et al., Recent advances in immune checkpoint therapy in non-small cell lung cancer and opportunities for nanoparticle-based therapy, Eur. J. Pharmacol. 909 (2021), 174404.
[20] G. Hess, Checkpoint inhibition in non-Hodgkin's lymphoma, Oncol Res Treat. 40 (11) (2017) 662–672.
[21] B. Hu, R. Jacobs, N. Ghosh, Checkpoint inhibitors Hodgkin lymphoma and non-Hodgkin lymphoma, Curr. Hematol. Malig. Rep. 13 (6) (2018) 543–554.

[22] J. Apostolidis, et al., Current clinical applications and future perspectives of immune checkpoint inhibitors in non-Hodgkin lymphoma, J. Immunol. Res. 2020 (2020) 1–18.
[23] K. Slim, et al., Methodological index for non-randomized studies (MINORS): development and validation of a new instrument, ANZ J. Surg. 73 (9) (2003) 712–716.
[24] R. Advani, et al., CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma, N. Engl. J. Med. 379 (18) (2018) 1711–1721.
[25] S.M. Ansell, et al., Phase I Study of Ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with relapsed and refractory B-cell non-Hodgkin lymphoma, Clin. Cancer Res. 15 (20) (2009) 6446–6453.
[26] S.M. Ansell, et al., Nivolumab for relapsed/refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation: a single-arm, phase II study, J. Clin. Oncol. 37 (6) (2019) 481.
[27] P. Armand, et al., Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma, J. Clin. Oncol. 37 (34) (2019) 3291.
[28] P. Armand, et al., Efficacy and safety results from CheckMate 140, a phase 2 study of nivolumab for relapsed/refractory follicular lymphoma, Blood 137 (5) (2021) 637–645.
[29] K.L. Davis, et al., Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1–2 trial, Lancet Oncol. 21 (4) (2020) 541–550.
[30] W. Ding, et al., Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. blood, J. Am. Soc. Hematol. 129 (26) (2017) 3419–3427.
[31] G.P. Gregory, et al., Pembrolizumab plus dinaciclib in patients with hematologic malignancies: the phase 1b KEYNOTE-155 study, Blood Adv. (2022).
[32] G.S. Nowakowski, et al., Safety and efficacy of durvalumab with R-CHOP or R-2-CHOP in untreated, high-risk DLBCL: a phase 2, open-label trial, Int. J. Hematol. 115 (2) (2022) 222–232.
[33] A.F. Herrera, et al., Safety and activity of ibrutinib in combination with durvalumab in patients with relapsed or refractory follicular lymphoma or diffuse large B-cell lymphoma, Am. J. Hematol. 95 (1) (2020) 18–27.
[34] Q. Mei, et al., Camrelizumab plus gemcitabine, vinorelbine, and pegylated liposomal doxorubicin in relapsed/refractory primary mediastinal B-cell lymphoma: a single-arm, open-label, Phase II trial, Clin. Cancer Res. 26 (17) (2020) 4521–4530.
[35] F. Morschhauser, et al., Obinutuzumab-atezolizumab-lenalidomide for the treatment of patients with relapsed/refractory follicular lymphoma: final analysis of a Phase Ib/II trial, Blood Cancer J 11 (8) (2021) 147.
[36] L.J. Nastoupil, et al., Safety and activity of pembrolizumab in combination with rituximab in relapsed or refractory follicular lymphoma, Blood adv. 6 (4) (2022) 1143–1151.
[37] P. Panayiotidis, et al., A phase-II study of atezolizumab in combination with obinutuzumab or rituximab for relapsed or refractory mantle cell or marginal zone lymphoma or Waldenström's macroglobulinemia, Leuk. Lymphoma. 63 (5) (2022) 1–12.
[38] V. Ribrag, et al., A Phase 1b Study to evaluate the safety and efficacy of durvalumab in combination with tremelimumab or danvatirsen in patients with relapsed or refractory diffuse large B-cell lymphoma, Clin. Lymphoma Myeloma Leuk. 21 (5) (2021) 309–317, e3.
[39] J.M. Tuscano, et al., A phase I study of the combination of rituximab and ipilimumab in patients with relapsed/refractory B-cell lymphoma, Clin. Cancer Res. 25 (23) (2019) 7004–7013.
[40] J.R. Westin, et al., Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial, lancet oncol. 15 (1) (2014) 69–77.
[41] A. Younes, et al., Safety and activity of ibrutinib in combination with nivolumab in patients with relapsed non-Hodgkin lymphoma or chronic lymphocytic leukaemia: a phase 1/2a study, The Lancet Haematol. 6 (2) (2019) e67–e78.
[42] P.L. Zinzani, et al., Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma, Blood 130 (3) (2017) 267–270.
[43] P.L. Zinzani, et al., Nivolumab combined with brentuximab vedotin for relapsed/refractory primary mediastinal large B-cell lymphoma: efficacy and safety from the phase II checkmate 436 study, J. Clin. Oncol. 37 (33) (2019) 3081.
[44] M.S. Khodadoust, et al., Pembrolizumab in relapsed and refractory mycosis fungoides and sézary syndrome: a multicenter phase II study, J. Clin. Oncol. 38 (1) (2020) 20.
[45] S.J. Kim, et al., Avelumab for the treatment of relapsed or refractory extranodal NK/T-cell lymphoma: an open-label phase 2 study, Blood 136 (24) (2020) 2754–2763.
[46] C. Querfeld, et al., Intralesional TTI-621, a novel biologic targeting the innate immune checkpoint CD47, in patients with relapsed or refractory mycosis fungoides or sezary syndrome: a multicentre, phase 1 study, Lancet Haematol 8 (11) (2021) E808–E817.
[47] Y. Shi, et al., Efficacy and safety of geptanolimab (GB226) for relapsed or refractory peripheral T cell lymphoma: an open-label phase 2 study (gxplore-002), J. Hematol. Oncol. 14 (1) (2021) 1–13.
[48] R. Tao, et al., Sintilimab for relapsed/refractory extranodal NK/T cell lymphoma: a multicenter, single-arm, phase 2 trial (ORIENT-4), Signal Transduct, Target. Ther. 6 (1) (2021) 365.
[49] S.M. Ansell, et al., Phase I study of the CD47 blocker TTI-621 in patients with relapsed or refractory hematologic malignancies, Clin. Cancer Res. 27 (8) (2021) 2190–2199.
[50] P. Armand, et al., A phase 1b study of dual PD-1 and CTLA-4 or KIR blockade in patients with relapsed/refractory lymphoid malignancies, Leukemia 35 (3) (2021) 777–786.
[51] S.K. Barta, et al., Phase II study of the PD-1 inhibitor pembrolizumab for the treatment of relapsed or refractory mature T-cell lymphoma, Clin. Lymphoma Myeloma Leuk. 19 (6) (2019) 356.
[52] A.M. Lesokhin, et al., Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study, J. Clin. Oncol. 34 (23) (2016) 2698.
[53] Y.L. Kwong, et al., PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing L-asparaginase. Blood, J. Am. Soc. Hematol. 129 (17) (2017) 2437–2442.
[54] X. Li, et al., Activity of pembrolizumab in relapsed/refractory NK/T-cell lymphoma, J. Hematol. Oncol. 11 (1) (2018) 1–8.
[55] L. Nayak, et al., PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. blood, J. Am. Soc. Hematol. 129 (23) (2017) 3071–3073.
[56] Z.Y. Xu-Monette, J. Zhou, K.H. Young, PD-1 expression and clinical PD-1 blockade in B-cell lymphomas, Blood 131 (1) (2018) 68–83.
[57] M.S. Carlino, J. Larkin, G.V. Long, Immune checkpoint inhibitors in melanoma, Lancet 398 (10304) (2021) 1002–1014.
[58] K. Kono, S. Nakajima, K. Mimura, Current status of immune checkpoint inhibitors for gastric cancer, Gastric Cancer 23 (4) (2020) 565–578.
[59] X. Liu, S. Qin, Immune checkpoint inhibitors in hepatocellular carcinoma: opportunities and challenges, Oncologist 24 (Suppl 1) (2019) S3–S10.
[60] R. Cohen, et al., Immune checkpoint inhibition in colorectal cancer: microsatellite instability and beyond, Target Oncol. 15 (1) (2020) 11–24.
[61] A.L. Cheng, et al., Challenges of combination therapy with immune checkpoint inhibitors for hepatocellular carcinoma, J. Hepatol. 72 (2) (2020) 307–319.
[62] D. Kwapisz, Pembrolizumab and atezolizumab in triple-negative breast cancer, Cancer Immunol. Immunother. 70 (3) (2021) 607–617.
[63] W.B. Coley, The treatment of inoperable sarcoma by bacterial toxins (the mixed toxins of the streptococcus erysipelas and the bacillus prodigiosus), Proc. R. Soc. Med. 3 (Surg_Sect) (1910) 1–48.
[64] W.C. Dempke, et al., Second-and third-generation drugs for immuno-oncology treatment—the more the better? Eur. J. Cancer 74 (2017) 55–72.
[65] D. Bashash, et al., Resistance to immunotherapy in human malignancies: mechanisms, research progresses, challenges, and opportunities, J. Cell. Physiol. 237 (1) (2022) 346–372.
[66] R.J. Motzer, et al., Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, N. Engl. J. Med. 378 (14) (2018) 1277–1290.
[67] L.Q. Chow, et al., Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort, J. Clin. Oncol. 34 (32) (2016) 3838.
[68] A.Y. Lin, J.M. Schnitter, L.I. Gordon, Immune checkpoint blockade for the treatment of Hodgkin lymphoma, ImmunoTargets Ther. 11 (2022) 1.
[69] A. Ribas, J.D. Wolchok, Cancer immunotherapy using checkpoint blockade, Science 359 (6382) (2018) 1350–1355.
[70] F. Çetinözman, et al., Differential expression of programmed death-1 (PD-1) in Sézary syndrome and mycosis fungoides, Arch. Dermatol. 148 (12) (2012) 1379–1385.
[71] D.A. Wada, et al., Programmed death 1 is expressed in cutaneous infiltrates of mycosis fungoides and sézary syndrome, Am. J. Hematol. 86 (3) (2011) 325–327.
[72] J.-.C. Jo, et al., Expression of programmed cell death 1 and programmed cell death ligand 1 in extranodal NK/T-cell lymphoma, nasal type, Ann. Hematol. 96 (1) (2017) 25–31.
[73] S. Tomassetti, R. Chen, S. Dandapani, The role of pembrolizumab in relapsed/refractory primary mediastinal large B-cell lymphoma, Ther Adv Hematol 10 (2019), 2040620719841591.
[74] A. Behdad, et al., PD-1 is highly expressed by neoplastic B-cells in Richter transformation, Br. J. Haematol. 185 (2) (2019) 370–373.
[75] S. Muenst, et al., Diagnostic and prognostic utility of PD-1 in B-cell lymphomas, Dis. Markers 29 (1) (2010) 47–53.
[76] D.D. Twa, et al., Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell lymphoma blood, J. Am. Soc. Hematol. 123 (13) (2014) 2062–2065.
[77] S. Ansell, et al., A phase 1 study of nivolumab in combination with ipilimumab for relapsed or refractory hematologic malignancies (checkmate 039), Blood 128 (22) (2016) 183.
[78] I. Sagiv-Barfi, et al., Therapeutic antitumor immunity by checkpoint blockade is enhanced by ibrutinib, an inhibitor of both BTK and ITK, Proc. Natl. Acad. Sci. 112 (9) (2015) E966–E972.
[79] G.S. Nowakowski, et al., Safety and efficacy of durvalumab with R-CHOP or R2-CHOP in untreated, high-risk DLBCL: a phase 2, open-label trial, Int. J. Hematol. 115 (2) (2021) 1–11.
[80] F. Morschhauser, et al., Obinutuzumab-atezolizumab-lenalidomide for the treatment of patients with relapsed/refractory follicular lymphoma: final analysis of a Phase Ib/II trial, Blood Cancer J 11 (8) (2021) 1–7.