Review

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Immune Checkpoint Blockade and Biomarkers of Response in Lymphoma: A Case-Illustrated Narrative Review

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Abstract: Immune checkpoint blockade (ICB) has revolutionized the prognosis of several advanced-stage solid tumors. However, its success has been far more limited in hematological malignancies and is mostly restricted to classical Hodgkin lymphoma (cHL) and primary mediastinal B cell lymphoma (PMBCL). In patients with non-Hodgkin lymphoma (NHL), response to PD-1/PD-L1 ICB monotherapy has been relatively limited, although some subtypes are more sensitive than others. Numerous predictive biomarkers have been investigated in solid malignancies, such as PD-L1 expression, tumor mutational burden (TMB) and microsatellite instability (MSI), among others. This case-illustrated review aims to appraise the current knowledge on PD-1/PD-L1 ICB efficacy in lymphoid malignancies, when used either as monotherapy or combined with other agents, and describes potential biomarkers of response in this specific setting.

Keywords: Hodgkin lymphoma; non-Hodgkin lymphoma; PD1/PD-L1 checkpoint inhibitors; tumor mutational burden; predictive biomarkers

1. Introduction

The tumor microenvironment (TME), consisting of T cells, tumor-associated macrophages (TAMs), dendritic cells (DCs), neutrophils, natural killer (NK) and stromal cells, is thought to play a significant role in the development and progression of many cancers, as well as in tumor escape from the immune system. Accumulation of somatic mutations during oncogenesis has been shown to result in the presentation of neoantigens at the tumor cell surface, which can elicit tumor-specific CD4+ and CD8+ T cells with antitumor potential [1]. Many studies have demonstrated that tumor evasion is, at least in part, mediated by inhibition of antitumor T-cell responses, mostly via upregulation of immune checkpoint molecules [2–4]. The understanding of these resistance mechanisms led to the delineation of the concept of immune checkpoint blockade (ICB).

More precisely, interaction between the immune checkpoint (IC) molecule programmed cell death protein-1 (PD1) expressed by activated tumor-infiltrating T cells and its ligands (PD-L1 and PD-L2) expressed by surrounding tumor and TME cells commonly leads to down-regulation of neoantigen-specific T cell responses. Blocking these interactions is a frequently used therapeutic approach to restore the anti-tumor effect of the host immune system [5,6].

In lymphoproliferative disorders, PD-1 is frequently expressed on tumor cells themselves as in tumor-infiltrating lymphocytes (TILs), while its ligands may be upregulated by tumor cells (some B-

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cell or T-cell lymphoma) but also TME cells such as TAMs, mast cells and mesenchymal cells [7–9]. PD-1 blockade using nivolumab or pembrolizumab has dramatically improved the prognosis of relapsed/refractory (r/r) classical Hodgkin Lymphoma (cHL) and is nowadays a well-recognized therapeutic option in this setting [10–12]. On the other hand, efficacy of PD-1 or PD-L1 blockade in non-Hodgkin Lymphoma (NHL) has shown disappointingly low response rates, except for some specific subsets of NHL, such as primary mediastinal B cell lymphoma (PMBCL) [13], primary testicular lymphoma (PTL) or primary central nervous system lymphoma (PCNSL) [14,15]. Interestingly, these NHL subsets have been shown to be highly infiltrated by T cells [16,17]). Of note, the different anti-PD-1/PD-L1 antibodies used in the clinic vary in their IgG isotypes and affinity to the various Fc gamma receptors (FcγRs) expressed on immune cells (Table 1), however, whether these changes translate into different clinical benefit is not well-established [18]. A persistent challenge remains the identification of predictive biomarkers of response to PD-1/PD-L1 ICB in this setting.

Here, we present the clinical case of a patient suffering from an aggressive NHL with multiple relapses who was treated successfully with ICB. We then describe clinical efficacy of PD-1/PD-L1 ICB as monotherapy and in combination with other agents for different lymphoma subtypes.

Table 1. PD-1 / PDL-1 antibodies evaluated in lymphoma.

Target	Name	Pharmaceutical company	Isotype	Approval status	Year Indication
PD-1	Nivolumab (Opdivo®)	Bristol-Myers Squibb	IgG4 $S_{228}P$	FDA / EMA [25,64]	2018, cHL
	Pembrolizumab (Keytruda®)	Merck	IgG4 $S_{228}P$	FDA / EMA [23,28,81]	2018, cHL, PMBCL
	Tislelizumab (BGB-A317)	BeiGene	IgG4mut, FcγR null	China NMPA [39]	2019, cHL
	Camrelizumab (AiRuiKa™)	Hengrui	IgG4 $S_{228}P$	China NMPA [35]	2019, cHL
	Sintilimab (Tyvyt®)	Innovent Biologics, Eli Lilly	IgG4 κ	China NMPA [33]	2018, cHL
	Zimberelimab (AB122)	Gloria Biosciences, Arcus Biosciences, Taiho Pharmaceutical Co	IgG4	China NMPA [41]	2021, cHL
	Penpulimab (AK105)	Akeso Biopharma	IgG1, FcγR null	China NMPA [42]	2021, cHL
PD-L1	Atezolizumab (Tecentriq®)	Roche	IgG1mut, FcγR null	-	-
	Avelumab (Bavencio®)	Merck KGaA/Pfizer	IgG1	-	-

Abbreviations: cHL, classical Hodgkin lymphoma; FDA, Food and Drug Administration; EMA, European Medicines Agency; NMPA, National Medical Products Administration; PMBCL, primary mediastinal B cell lymphoma.

2. Clinical case

A 71-year-old man with known chronic kidney disease (CKD) had incidentally been diagnosed with grade 1 stage IVA follicular lymphoma (FL) 16 years prior. The FLIPI score at this time was at 3/5 (meeting criteria for age, stage, and > 4 nodal areas involved). Initial radiological and pathology workup are reported in (Figures 1 and 2). As the GELF criteria were not initially met (GELF score 0/7), the patient did not receive any treatment and was observed for almost 3 years. Subsequently, he received R-CHOP (rituximab, cyclophosphamide, hydroxyadriamycine, vincristine and prednisone) with rituximab maintenance, R-ICE (rituximab, ifosfamide, carboplatin and etoposide), rituximab-bendamustine, pelvic VMAT radiotherapy and idelalisib for progression of disease. Over this period, in addition to multiple infectious issues, the patient developed end-stage CKD requiring hemodialysis.

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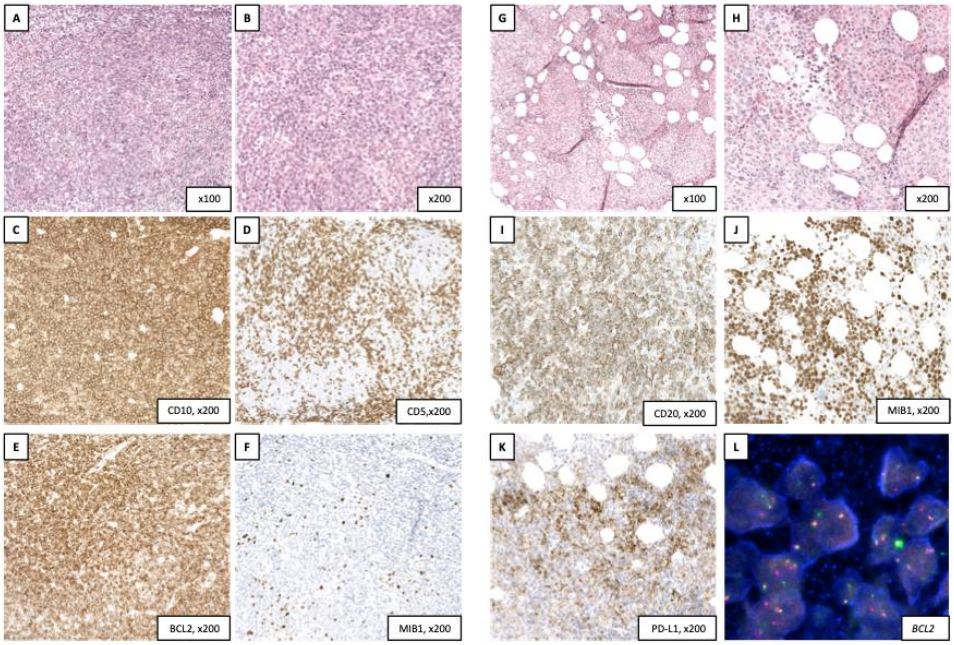

Figure 1. Transformation of a follicular lymphoma (A-F) into a DLBCL with high PD-L1 expression (G-L). (A-F) Follicular lymphoma diagnosed on a retroperitoneal lymph node biopsy. H&E sections (A and B) showing a vaguely nodular lymphoid proliferation composed mainly of centrocytes with rare centroblasts (grade I). The nodular architecture is better highlighted in immunohistochemistry with a T-cell marker (CD5, D). The tumor cells are diffusely reactive to CD10 (C) and Bcl2 (E) with a very low proliferation index (5%, F).G-L. Transformation into a DLBCL with PD-L1 expression in a bone marrow core biopsy. H&E sections (G and H) showing a replacement of the hematopoietic lineages by a diffuse lymphoid proliferation consisting of large-size and atypical cells. The tumor cells retain a CD20 positivity (I) with half of them showing a PD-L1 expression (K). Proliferation index is high (70%, J). FISH analysis confirms a BCL2 rearrangement (L). *Abbreviations: BCL-2, B-cell lymphoma 2; DLBCL, diffuse large B-cell lymphoma; FISH, fluorescence in situ hybridization; H&E, hematoxylin & eosin; PD-L1, programmed death-ligand 1.*

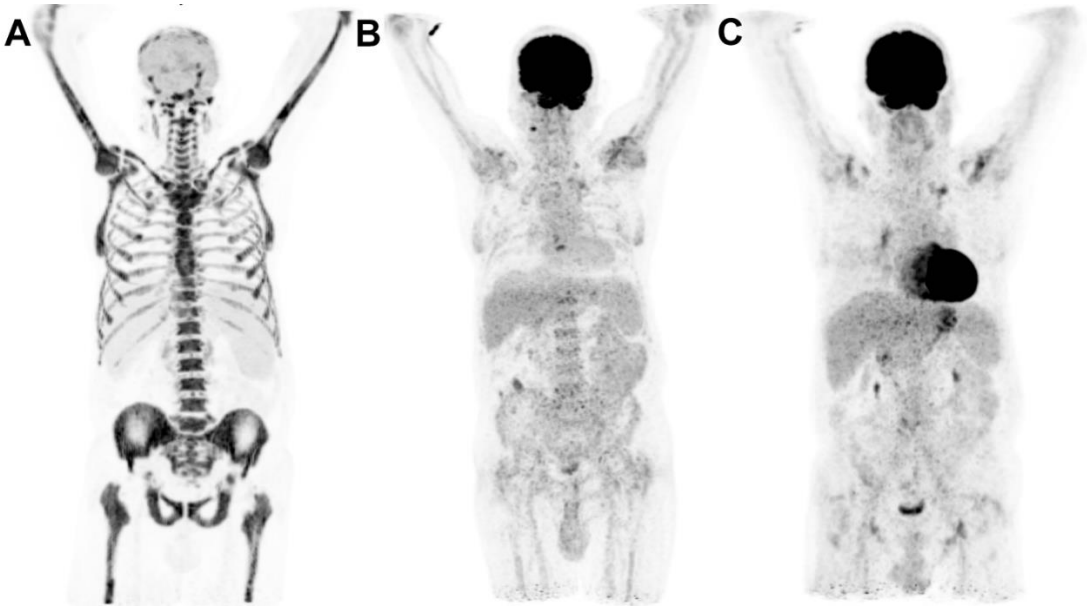

Figure 2. PET-CT response assessment of transformed FL on PD-1 ICB. A. Intense bone marrow diffuse metabolism and mild lymph nodes, at diagnosis of transformation; B. 3-month response assessment; C. 9-month response assessment**.** *Abbreviations: FL, follicular lymphoma; ICB, immune*

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checkpoint blockade; PD-1, programmed death-1; PET-CT, positron emission tomography and computed tomography; SUV max, maximum standardized uptake value.

While on idelalisib, the patient was admitted severely unwell with febrile grade IV pancytopenia associated with significant dyspnea. A PET-CT reported intensely diffuse osteo-medullary hypermetabolic activity, with a mixed response in the known areas of lymphadenopathy. A diagnosis of high-grade transformation of prior FL was confirmed on a bone marrow biopsy, with positivity for CD20 and PD-L1 expression over 50% of cells (Figure 1). Despite a poor performance status (ECOG 4) and significant comorbidities (Cumulative Illness Rating Scale (CIRS) score of 14), the patient strongly opted to pursue a new palliative therapeutic option. He received one cycle of rituximab (375 mg/m2) and cyclophosphamide (1000mg/m2), followed by pembrolizumab 200mg and rituximab repeated every 3 weeks. This therapeutic choice was based on published results obtained from a small phase 2 study in Richter syndrome [19]. Surprisingly, the patient's general state and hematological counts dramatically improved and complete metabolic response was achieved at 3 months (Figure 2). Tumor sequencing using a 400-gene capture panel (2.9 Mb) to a bone marrow sample revealed a TMB of 6.75 mutations/Mb (Supplement Figure S1). We tried to prospectively monitor the patient's response measuring circulating tumor DNA in plasmatic samples collected 3 and 6 months after the first pembrolizumab infusion, but we were not able to reach a sequencing depth that enabled us to reach the desired sensitivity (<1%). The patient received a total of twenty-four months of pembrolizumab and achieved a sustained clinical and metabolic remission. Unfortunately, the patient died from an infectious complication whilst still in remission, three years after aggressive transformation from FL.

3. Clinical efficacy of ICB in lymphomas

3.1. Classical Hodgkin lymphoma(cHL)

3.1.1. PD-1/PD-L1 ICB as monotherapy

Safety and activity of PD-1 ICB was first tested by Ansell et al. (2015) in a phase 1 study on 23 heavily pretreated cHL patients who received biweekly nivolumab, a PD-1 inhibitor, demonstrating an impressive 87% overall response rate (ORR) and 17% complete metabolic response rate (CMR) [11,20]. Larger studies subsequently confirmed the efficacy of PD-1 ICB monotherapy in r/r cHL either using nivolumab (Maruyama et al 2017, 2020: [21,22]) or pembrolizumab (KEYNOTE-013: 2016, 2020: [23,24]). All trials showed similar results in r/r cHL patients, including those relapsing after autologous stem cell transplantation (ASCT) and those ineligible for ASCT (CheckMate 205: 2016, 2018, 2021: [10,25–27]; KEYNOTE-087: 2017, 2019, 2021: [12,28,29]). At 5-year follow-up, both CheckMate 205 and KEYNOTE-087 trials demonstrated sustained responses, with a median PFS of 15 months and 13.7 months, respectively. Additionally, a subgroup analysis of the KEYNOTE-087 trial demonstrated efficacy of pembrolizumab after treatment with the anti-CD30 antibody drug conjugate brentuximab vedotin (BV) (ORR 82%) [30]. Based on these results, the FDA approved nivolumab (2016) and pembrolizumab (2017) for r/r cHL for patients relapsing after ASCT and BV [31]. More recently, the phase 3 KEYNOTE-204 study (2021) compared pembrolizumab and BV in patients with r/r cHL either following ASCT or in patient ineligible for ASCT. Pembrolizumab showed increased median progression-free survival (PFS) over BV (13.2 months versus 8.3 months) with a median follow-up time of 25.7 months [32].

In addition to nivolumab and pembrolizumab, several other PD-1 inhibitors have been investigated in r/r cHL early-phase trials. PD-1/PD-L1 antibodies vary in their IgG isotypes. PD-1 IgG4 antibodies include nivolumab, pembrolizumab, sintilimab, camrelizumab, tislelizumab and zimberelimab; with ORR ranging from 42% to 91% [33–41] (Table 2), while penpulimab, an IgG1 antibody, demonstrated an ORR of 89% with 47% CR in a multicenter phase I/II trial [42]. To our knowledge, avelumab, an IgG1 anti-PD-L1 antibody, is the only anti-PD-L1 antibody that has been tested in this setting, achieving 42% ORR and 19% CR respectively [43].

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3.1.2. PD-1/PD-L1 ICB in combination with chemotherapy

Frontline setting

Assuming that PD-1/PD-L1 ICB may prime the TME for induction of antitumor T cell responses before patients receive cytotoxic agents, both sequential and concomitant combinations of ICB with conventional chemotherapy have been evaluated in the frontline setting. Ramchandren et al. (2019) evaluated a sequential approach of four cycles of single agent nivolumab followed by twelve cycles of nivolumab given concomitantly with doxorubicin, vinblastine and dacarbazine (N-AVD) in patients with newly diagnosed advanced-stage cHL (cohort D of CheckMate 205). In this phase 2 cohort, 69% of patients achieved an ORR with 18% of CMR at the end of nivolumab monotherapy, which improved to 84% ORR and 67% CMR after completion of N-AVD [44]. N-AVD has also been investigated in early unfavorable stage cHL in a phase 2 trial conducted by the German Hodgkin Study Group (2020); patients were randomized in two groups receiving either four cycles of nivolumab monotherapy followed by 2 cycles of N-AVD (sequential group) or six cycles of N-AVD (concomitant group). Responses were consolidated by 30-Gy involved-site radiotherapy in both groups. After 2 cycles of therapy, ORR and CMR were 100% and 96% with N-AVD and 85% and 51% with nivolumab monotherapy. At the end of therapy, 100% and 90% of patients belonging to concomitant group achieved an ORR and CMR, respectively, while patients enrolled within the sequential group reached 98% ORR and 94% CMR [45]. A sequential strategy of pembrolizumab monotherapy followed by combination with AVD has similarly been evaluated in unfavorable or advanced-stage cHL patients. CMR were 37%, 100% and 100% respectively after pembrolizumab monotherapy, two additional cycles of combined therapy and after treatment completion [46]. A frontline randomized phase 3 study comparing the N-AVD regimen to BV-AVD in patients with advanced stage cHL is currently ongoing, with an estimated completion date in 2024 (NCT03907488). Another ongoing non-randomized phase 2 study (NCT03617666) is investigating safety and efficacy of avelumab in first line high-risk cHL. All patients will receive four doses of avelumab followed by two cycles of ABVD (doxorubicin, bleomycine, vinblastine and dacarbazine) with further treatment administered with a PET-adapted approach [47]. As approximatively twenty percent of newly diagnosed cHL patients are ineligible for intensive chemotherapy regimen and consequently at risk of experiencing worse outcomes [48,49], Cheson and colleagues (2020) investigated the combination of 8 cycles of BV with nivolumab for older (> 60 years) or chemo-ineligible newly diagnosed cHL patients. The trial was prematurely closed after an interim analysis failed to show that the combination met the predefined ORR criteria (ORR > 68%) [50]. However, 61% of all evaluable patients displayed an objective response and 48% achieved CMR, demonstrating that this well-tolerated combination is active in this frail population.

Relapsed / refractory setting

Herrera and colleagues (2018) enrolled 62 r/r cHL patients in the first-salvage setting. In this phase 1/2 study, patients were treated with a nivolumab and BV combination for up to four cycles. This regimen was well tolerated and achieved an ORR of 82%, with 61% of CMR [51]. Extended 3-year follow-up confirmed durability of responses with an estimated 77% 3-years PFS after a median follow-up of 34.3 months [52]. A phase 3 trial further investigating this regimen versus BV alone in r/r or ASCT-ineligible cHL patients was closed due to insufficient enrolment (NCT03138499). Three other trials investigated the role of PD-1 ICB combined with standard salvage chemotherapy. Herrera et al. (2019) evaluated a PET-guided strategy in the ASCT-eligible r/r setting, combining nivolumab to ICE as a bridge to transplant regimen starting with six cycles of biweekly ICB monotherapy followed either by ASCT for patients achieving CMR, or two cycles of nivolumab-ICE in non-complete responders, consolidated thereafter by ASCT for those achieving CMR with the combined therapy regimen [53]. Among 43 evaluable patients, 34 patients received nivolumab alone, and nine received nivolumab-ICE. At the end of the nivolumab monotherapy, the ORR was 81%, including 71% patients in CMR. All non-complete responders (n=9) subsequently treated with nivolumab-ICE displayed an objective response, with 89% (n=8) achieving CMR [53,54]. Bryan et al. (2021) reported

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similar response rates in a phase 2 study evaluating the efficacy of combined pembrolizumab with ICE followed by ASCT consolidation [55]. Finally, Moskowitz et al. (2021) demonstrated efficacy of salvage pembrolizumab, gemcitabine, vinorelbine and liposomal doxorubicin (GVD) immunochemotherapy, achieving 95% CMR prior to ASCT [56]. Atezolizumab, a PD-L1 inhibitor, was scarcely tested as monotherapy in lymphoma ([57], NCT03120676), but its efficacy in combination with BeGEV regimen (bendamustine, gemcitabine, vinorelbine) is currently being investigated (NCT05300282).

Patients with r/r HL who undergo ASCT have an expected 60% 18-months PFS [58–60]. Lepik et al. evaluated the utility of nivolumab and bendamustine administered for up to three cycles in heavily pretreated r/r cHL patients failing at least 2 lines of prior therapy, including nivolumab monotherapy. Among all enrolled patients (n=30), 26 achieved a response (ORR: 87%) and 17 a CMR (57%) [61]. To our knowledge, only one trial investigated the role of PD-1/PD-L1 ICB as consolidative therapy in the post-ASCT setting. In a phase 2 study, Armand et al. administered pembrolizumab every 3 weeks for up to eight cycles starting no later than two months after ASCT; PFS and OS assessed at 18 months were 82% and 100%, respectively [62].

3.1.3. PD-1/PD-L1 ICB combined with other agents

In solid malignancies, combination of PD-1/PD-L1 inhibitors with other ICB molecules have shown superior efficacy compared to single agent ICB [63]. Combination of nivolumab with other ICBs, such as ipilumumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibitor, or lirilumab, an antibody targeting the killer cell Ig-like receptors (KIR) expressed by NK cells, did not seem to significantly improve response rate in 31 r/r cHL patients enrolled in phase 1 CheckMate 039 trial (2016, 2021). An ORR of 74% with 23% of CMR was achieved for the nivolumab/ipilimumab combination and 76% ORR, including 24% CMR, was obtained for the nivolumab/lirimumab combination [64,65]. The safety and efficacy of a triple combination of nivolumab, ipilimumab and BV was tested in a phase 1/2 trial conducted by Diefenbach et al. (2020) in patients with r/r cHL in comparison with nivolumab-BV or ipilimumab-BV. The triple regimen was associated with increased toxicity without clinical benefit; the respective ORR were 82% with triple therapy, 89% in the nivolumab-BV group and 76% in the ipilimumab-BV group [66]. Potentially more promising are PD-1/PD-L1 ICB and histone deacetylase inhibitors (HDACi) combinations. The combination of pembrolizumab with entinostat has been investigated in 22 r/r cHL patients by Sermer et al. (2020, 2021) in a phase 2 trial with an ORR of 86% [67,68]. Similarly, a phase 2 trial with camrelizumab, another PD-1 inhibitor, combined with decitabine demonstrated improved response rates (ORR 95%, CMR 79%) compared to camrelizumab monotherapy (ORR 89%, CMR 32%) [37,38].

Various combination of PD-1/PD-L1 ICB with novel immunotherapies are currently under investigation in early phase trials. A first report of pembrolizumab combined to AFM-13, a CD30-CD16 bispecific antibody stimulating innate immune cells, such as NK and macrophages, achieved an impressive 83% ORR in r/r cHL patients who had received a median of three prior lines of therapy [69,70]. A recent phase 1 study evaluating the benefit of adoptive cellular therapy consisting of tumor-associated antigen (TAA)-specific T cells enrolled 10 patients with r/r HL (n=8 active disease, n=2 adjuvant after ASCT) to receive TAA-specific T cells (autologous or allogenic) with nivolumab given as a priming agent in six out of the 10 patients. Among patients with active disease, one patient achieved CMR and seven had stable disease (SD) at 3 months [71]. In addition, there is growing evidence that chimeric antigen receptor (CAR) T cell-fitness may be improved by the adjunction of PD1 ICB. With the limitation of a small sample size (n=12), PD1 ICB administration after CD30 CAR T cell therapy in CD30+ lymphoma patients (n=9 cHL, n=1 angioimmunoblastic T-cell lymphoma, n=2 gray zone lymphoma) suggested improved efficacy (ORR 86% versus 100%; CR 27% versus 80%) [72]. Similarly, the role of anti-PD1 therapy after CD30 CAR T cell treatment is currently being evaluated in r/r cHL patients (NCT04134325) [73,74]. Recently, Timmerman et al. (2022) demonstrated that the association of favezelimab (lymphocyte activating gene-3 (LAG-3) ICB) and pembrolizumab could be an effective therapeutic option for patients progressing under PD-1 ICB (ORR 31%, CR 7%) [75].

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Other combination approaches in the r/r cHL setting are ongoing, such as nivolumab with ruxolitinib (NCT03681561) and nivolumab/pembrolizumab combined with radiation (NCT04419441).

Table 2. PD-1 / PDL-1 ICB monotherapy prospective studies by lymphoma subtype.

Lymphoma Subtype	Studies	N	Study population	Therapy	ORR (%)	CR (%)	Median PFS (months)	Median OS (months)	Median follow-up (months)	Specifi cities
Classical Hodgkin lymphoma (cHL)	Ansell 2015, [11,20] Phase 1	23	R/R (prior ASCT or allo-SCT)	Nivolumab 3mg/kg q2wks*	87	17	NR† (86% at 6 months)	NR†	21.5	
	Maruyama 2017, 2020, [21,22] Phase 2	17	R/R (prior ASCT and BV)	Nivolumab 3mg/kg q2wks*	88	31	11.7 (60% at 6 months)	NR (80% at 3-year)	38.8	
	KEYNOTE-013, Armand 2016, 2020 *et al.*, [23,24], Phase 2B	31	R/R after BV failure	Pembrolizumab 10 mg/kg q2wks*	58	19	11.4 (30% at 2 year)	NR(81% at 3-year)	52.8	
	CheckMate 205, Younes 2016, Armand 2018, Ansell 2021, [10,25–27], Cohort A, B, C, Phase 2	243	R/R after: A. ASCT (n = 63) B. ASCT + BV (n = 80) C. BV + ASCT ± BV (n = 100)	Nivolumab 3 mg/kg q2wks*	71	21	15 (18% at 5-year)	NR(71% at 5-year)	58	
	KEYNOTE-087, Ansell 2017, Chen 2019, Chen 2021, [12,28,29], Phase 2	210	R/R after: A. ASCT + BV (n = 69) B. Salvage chemo + BV (n = 89) (*ineligibility for SCT owing to chemorefractory disease)* C. ASCT (n = 60)	Pembrolizumab 200 mg q3wks*	71	28	13.7 (14% at 5-year)	NR(71% at 5-year)	62.9	
	KEYNOTE-204, Kuruvilla 2021, [32], Phase 3	304	R/R (ineligible or relapsed after ASCT)	Pembrolizumab 200 mg q3wks versus BV 1.8 mg/kg q3wks*	Pembrolizumab: 66 BV: 54	Pembrolizumab: 25 BV: 24	13.2 (for pembrolizumab) 8.3 (for BV)	NA	25.7	
	JAVELIN Hodgkin trial, Herrera 2021, [43], Phase 1B	31	R/R (ineligible or relapsed after ASCT)	Avelumab with four dose levels and 2 dosing schedules (q2wks or q3wks)	42	19	5.7 (18% at 1-year)	NA	NA	Dose levels/schedules: 70, 350, and 500 mg q2wks; 500 mg q3wks; 10 mg/kg q2wks
	Song 2019, Song 2022, [39,40], Phase 2	70	R/R (ineligible or relapsed after ASCT)	Tislelizumab 200 mg q3wks*	87	67	31.5 (41% at 3-year)	NR(85% at 3-year)	33.8	
	Song 2019, Wu 2021, [35,36], Phase 2	75	R/R (ineligible or relapsed after ASCT)	Camrelizumab 200 mg q2wks*	76	28	22.5 (67% at 1-year)	NR(83% at 3-year)	36.2	
	Nie 2019, Liu 2021, [37,38], Cohort 1	19	R/R after more than 2 therapies	Camrelizumab 200 mg q3wks monotherapy*	90	32	15.5 (42% at 2-year)	NR (63% at 2-year)	34.5	

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	Phase 2		lines, anti-PD1 naïve							
	ORIENT-1, Shi 2019, Su 2020, [33,34], Phase II	96	R/R after more than 2 therapies lines (including ASCT)	Sintilimab 200mg q2wks*	80	29	18.6 (78% at 6 months)	NR(96% at 2-year)	26.7	
	Armand 2019, [62], Phase II	30	R/R after ASCT	Pembrolizumab 200 mg q3wks × 8 cycles as maintenance after ASCT	NA	NA	NR (82% at 18 months)	NR (100% at 18 months)	NA	
	Song 2022, [42], Phase I/II	85	R/R (including ASCT)	Penpulimab 200mg q2wks* (maximum of 24 months)	89	47	NR (72% at 1 year)	NR (100% at 18 months)	15.8	
	Lin 2022, [41], Phase II	85	R/R (including ASCT)	Zimberelimab (GLS-010) q2wks* (maximum of 24 months)	91	33	NR (78% at 1 year)	NR (99% at 1 year)	15.8	
Follicular lymphoma (FL)	Barraclough 2019, Hawkes 2021, [110,111], Phase 2	39	Newly diagnosed, stage III-IV, grade 1-3a FL	Nivolumab 240mg 2-weekly × 4 cycles If CR: N 240mg monotherapy × 4 cycles, maintenance N 480mg 4-weekly × 12 cycles If < CR: N 240mg + rituximab 375mg/m² 2-weekly × 4 cycles, maintenance N+R (N 480mg 4 weekly ×12 cycles; R 12 weekly × 8 cycles).	92	54	NR (72% at 1 year)	NR (96% at 1 year)	17.5	
	CheckMate 140, Armand 2021, [86], Phase 2 R/R	92	R/R (after failure of at least 2 prior lines of therapy)	Nivolumab 3 mg/kg q2wks*	4	1	2.2	NA	NA	minimal follow-up of 12 months
Diffuse large B-cell lymphoma (DLBCL)	Ansell 2019, [77], Phase 2	121	R/R (ineligible or relapsed after ASCT)	Nivolumab 3 mg/kg q2wks*	10 (all groups) ‡	3 (all groups) §	ASCT failed (n = 87):1.9 ASCT ineligible (n = 34): 1.4	ASCT failed (n = 87):12.2 ASCT ineligible (n = 34): 5.8	ASCT failed: 9 ASCT ineligible: 6	
Primary mediastinal B-cell lymphoma (PMBCL)	KEYNOTE-013, Zinzani 2017, Armand 2019, [14,80] Phase 1B	21	R/R PMBCL	Pembrolizumab 10mg/kg (n=11) 200 mg (n= 10) q3wks*	48	33	10.4	31.4	29.1	
	KEYNOTE-170, Armand 2019, [14]	53	R/R PMBCL	Pembrolizumab 200 mg q3wks*	45	13	5.5	NR	12.5	

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	Phase 2									
Extranodal natural killer / T-cell lymphomas (ENKTL)	**Kim 2020,** [84], Phase 2	21	R/R ENKTL	Avelumab 10 mg/kg q2wks*	38	24	2.7	NR	15.7	Response significantly associated with the expression of PD-L1 by tumor tissue
	ORIENT-4, Tao 2021, [85], Phase 2	28	R/R ENKTL	Sintilimab 200 mg q3wks*	75	21	NA	NR(79% at 2 year)	30.4	
Hematologic malignancies	**Lesokhin 2016,** [76], Phase 1	81	R/R B-cell lymphoma, TCL, MM (inclusive after ASCT)	Nivolumab 1 or 3mg/kg q2wks*	FL (n = 10): 40 DLBCL (n = 11): 36 TCL (n = 23): 17 MM (n = 27): 4	FL (n = 10): 10 DLBCL (n = 11): 18 TCL (n = 23): 0 MM (n = 27): 4	FL (n = 10): NR DLBCL (n = 11): 7 TCL (n = 23): 10 MM (n = 27): 10	NA	16.7	
	Frigault 2020, [79], Phase 2	29	R/R DLBCL + PMBCL after ASCT as maintenance	Pembrolizumab 200 mg q3wks × 8 cycles	N/A	59% at 18 months	NR (59% at 18 months)	NR (93% at 18 months)	NA	
	Davids 2020, [78], Phase 1	28	Relapsed hematologic malignancies after allo-SCT	Nivolumab 0.5-3 mg/kg q2wks*	29	4	3.7	21.4	11	
	Ding 2017, [19], Phase 2	25	relapsed or progressive CLL (n=16) + CLL with RT (n=9)	Pembrolizumab 200mg q3wks*	CLL: 0 RT: 44	CLL: 0 RT: 11	CLL: 2.4 RT: 5.4	CLL: 4.3 RT: NR	11	
	Khodadoust 2020, [207], Phase 2	24	R/R MF (n=9) and SS (n=15)	Pembrolizumab 2 mg/kg q3wks#	MF: 56 SS: 27	MF: 0 SS: 7	MF: 12 SS: 12	MF: NR SS: NR	NA	
	Chong 2018, [100], Phase 1/2	12	R/R B-cell NHL after CAR-T cells therapy	Pembrolizumab 200mg q3wks*	27	9	NA	NA	NA	

* until progression or unacceptable toxicity; † PFS and OS are data of the first article with the 10 months follow-up. ‡ ORR within groups: ASCT failed (n = 87): 9; ASCT ineligible (n = 34): 1; § CR within groups: ASCT failed (n = 87): 3; ASCT ineligible (n = 34): 0; # until progression or unacceptable toxicity or investigator choice. Abbreviations: allo-SCT, allogeneic stem cell transplantation; ASCT, Autologous stem cell transplantation; BV, brentuximab-vedotin; CLL, chronic lymphocytic leukemia; CMR, complete metabolic response; CR; complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MF, mycosis fungoid; MM, multiple myeloma; NR, not reached; N/A, not data available; PCNSL, primary central nervous system lymphoma; PMBCL, primary mediastinal B-cell lymphoma; q2wks, every two weeks; q3wks, every three weeks; RT, Richter transformation; SS, Sézary syndrome; TCL, T-cell lymphoma.

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3.2. Non-Hodgkin lymphoma (NHL)

3.2.1. PD-1/PD-L1 ICB as monotherapy

Aggressive NHL

First tested in a range of various hematological malignancies, nivolumab achieved an ORR of 36% and a CMR of 18% in the eleven r/r diffuse large B cell lymphoma (DLBCL) patients enrolled in a phase 1 study [76]. Single agent activity was further evaluated in DLBCL patients relapsing after ASCT (ORR 9%) or ineligible for ASCT (ORR 1%) [77]. Nivolumab monotherapy was also tested in various hematologic malignancies relapsing after allogeneic stem cell transplantation (allo-SCT), demonstrating an ORR of 29% [78]. In contrast to cHL, maintenance treatment with pembrolizumab administered after ASCT in DLBCL and PMBCL patients did not show any clinical benefit [79]. A randomized phase 3 trial investigating tislelizumab, a PD-1 inhibitor, as maintenance in DLBCL after ASCT is planned (NCT04799314). Even though the benefit of PD-1/PD-L1 inhibitors as monotherapy in r/r aggressive NHL has been disappointing, better activity has been observed in patient subsets, such as PMBCL, PCNSL and PTL [14,15,76]. Benefit from pembrolizumab was demonstrated in r/r PMBCL with 45-48% ORR and 13-33% CMR in KEYNOTE-013 and KEYNOTE-170 trials, respectively [80,81]. These results led to accelerated approval of pembrolizumab for r/r PMBCL by the FDA. Nivolumab demonstrated activity in 4 patients with r/r PCNSL and 1 patient with PTL CNS recurrence; all 5 patients had clinical and radiographic responses to the monotherapy [15]. Efficacy in these specific aggressive NHL subgroups is likely due their particular biology. This will be described in further details in the biomarker section. Pembrolizumab has also been tested in 9 patients experiencing Richter transformation (RT) with ORR 44% and CMR 11% [19].

PD-1/PD-L1 ICB demonstrated modest results in natural killer NK / T-cell NHL. In a phase 1 trial, conducted in 23 r/r T-cell NHL patients, nivolumab monotherapy achieved an ORR of 17% with no CR observed [76]. In comparison to T-cell NHL, pembrolizumab showed slightly improved activity in cutaneous T cell lymphoma (CTCL) (ORR 38%) [82] and in a series of seven r/r extranodal NK / T-cell lymphomas (ENKTL) patients, two of them achieving CR [83]. This initial signal of activity in r/r ENKTL was recently confirmed by two phase 2 trials evaluating avelumab, a PD-L1 inhibitor, (ORR 38%) and sintilimab, a PD-1 inhibitor, (ORR 75%) [84,85].

Indolent B NHL

PD-1/PD-L1 ICB has also been evaluated in indolent lymphomas. Lesokhin et al. (2016) administered single agent nivolumab in 10 r/r FL patients (ORR 40%) [76], but this result was not confirmed in a larger phase 2 study conducted by Armand et al. (CheckMate-140) (ORR 4 %) [86]. To date, other indolent lymphoid malignancies such as chronic lymphocytic leukemia (CLL), marginal cell lymphoma (MZL) and Waldenström macroglobulinemia (WM) have not shown significant response rates with PD-1/PD-L1 ICB [19,87,88].

3.2.2. PD-1/PD-L1 ICB in combination with other agents

Aggressive NHL

Frontline setting

PD-1/PD-L1 ICB does not seem to add much benefit to frontline immunochemotherapy in newly diagnosed DLBCL. The combination of atezolizumab with frontline R-CHOP was tested in 40 DLBCL patients (ORR 87.5%, CMR 77.5%) [89,90]. Similarly, pembrolizumab in combination with R-CHOP achieved an ORR of 90%, including 77% CMR, in 30 patients with either DLBCL or grade 3b FL [91]. Finally, a durvalumab (another PD-L1 inhibitor) and R-CHOP combination reached similar results (ORR 97%, CMR 68%) [92]. An ongoing phase 3 trial is currently investigating nivolumab combined with DA-EPOCH-R versus DA-EPOCH=R in newly diagnosed patients with PMCBL (NCT04759586).

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Relapse / refractory setting

Various therapeutic combinations including PD-1/PD-L1 ICB have been investigated in the r/r NHL setting. Nivolumab with ipilimumab or lirilumab did not show any clinical activity in the 27 r/r NHL patients enrolled the phase 1 CheckMate 039 trial (2016, 2021) (ORR 13% and CMR 3% for B-NHL, ORR 22% and no CMR for T-NHL) [64,65]. A phase 1/2 trial tested nivolumab combined with ibrutinib, a Bruton kinase inhibitor (BTKi), in r/r CLL (ORR 61%), RT (ORR 65%), DLBCL (ORR 36%) and FL (ORR 33%) [93]. In another trial, pembrolizumab with acalabrutinib (BTKi) or dinaciclib, a cycline kinase inhibitor (CDKi), in r/r DLBCL resulted in an ORR of 26% and 21%, respectively [94,95]. Durvalumab in combination with ibrutinib resulted in a similarly modest improvement in ORR (13% for germinal center origin DLBCL and 38% for non-germinal center origin DLBCL) [96].

PD-1/PD-L1 ICB combined to CD19 CAR T cells appears promising in early-phase trials, notably in the phase 1/2 ZUMA 6 study (2020) combining atezolizumab with axicabtagene ciloleucel in DLBCL patients (ORR 75%) [97], in a trial combining a single dose of nivolumab with various CD19 CAR T cells in 11 patients with r/r B-NHL (n=1 Burkitt lymphoma, n=10 DLBCL) (ORR 82%) [98] and in a trial combining pembrolizumab (at diverse moment) and tisagenlecleucel (CD19 CAR T cells) in 12 r/r DLBCL (ORR: days 15 of treatment: 50%, days 8 of treatment: 25%, days-1 of treatment: 25%) [99]. By contrast, the treatment of pembrolizumab in 12 patients with NHL progressing or relapsing after CD19 CAR T cells achieved an ORR of 27%, including only one patient with CR [100]. Durvalumab administered either prior to (n= 6) or after (n= 9) CD19 CAR T (JCAR014) cell infusion in 13 evaluable r/r B-cell NHL patients lead to an ORR of 50% with 42% CMR [101]. Finally, dual targeting CD19/CD22 CAR T cell therapy associated with pembrolizumab were evaluated in 19 r/r B-cell NHL patients, with an ORR of 65% with 55% CMR [102].

Other combined regimens of PD-1/PD-L1 ICB with either other ICB, targeted agents (tazemetostat [103], venetoclax [104]), novel anti-CD 20 and anti-CD27 antibodies (obinutuzumab [105], varlimumab (NCT03038672)), CD20/CD3 bispecific antibodies(glofitamab [106], monetuzumab) (NCT02500407)) are under investigation in this setting (Table 3).

In r/r PMBCL patients, the phase 2 CheckMate 436 trial (2019, 2021) evaluated nivolumab with BV (n=30), reporting an ORR of 73% and 37% CMR. Responses were durable at extended follow-up with a 2-year PFS of 56% [107,108]. A phase 1 study testing the addition of nivolumab and lenalidomide to immunochemotherapy in PCNSL is now recruiting (NCT04609046). In advanced ENKTL, a combined sintilimab, pegasparaginase, gemcitabine and oxaliplatin regimen has demonstrated an acceptable toxicity profile and promising efficacy in a phase 1 study [109]; a phase 2 trial is currently ongoing (NCT04127227).

With the exception of CAR T cell therapy and specific for NHL subtypes, PD-1/PD-L1 ICB do generally not add much clinical benefit when combined to other active agents in r/r NHL setting.

Indolent B NHL

Frontline setting

A phase 2 trial combining nivolumab with rituximab in newly diagnosed patients with advanced grade 1-3A FL, showed a favorable toxicity profile and high ORR (92%) in 39 patients [110,111]. Atezolizumab in combination with the anti-CD20 antibody obinutuzumab was tested with in association with bendamustin (in 40 previously untreated FL patients requiring therapy), achieving a 75% CR rate, even though this combination showed an inacceptable toxicity profile, with fatal adverse events occurring in five patients (pneumonia, sudden death, cardiac arrest (due to severe immune-mediated myocarditis and bronchiolitis obliterans), gastrointestinal tract/biliary adenocarcinoma, progressive multifocal leukoencephalopathy) [112,113].

Relapse / refractory setting

PD-1/PD-L1 ICB have been extensively tested in the r/r setting of indolent lymphomas, with no or only modest results. A phase 2 study tested pembrolizumab combined with rituximab in 30

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patients with r/r FL, and achieved a 67% ORR and 50% CR [114,115]. Similarly, a combination regimen of the PD-1 inhibitor pidilizumab with rituximab administered in 30 r/r FL patients demonstrated an ORR of 66% and 52% CR [116]. However, the combination of atezolizumab plus obinutuzumab achieved a less convincing result in r/r FL (ORR 54%, CR 23%) [105]. Atezolizumab with obinutuzumab and lenalidomide resulted in 78% ORR and 72% CR rate [117]. The LYSA group investigated atezolizumab, obinutuzumab and venetoclax in r/r FL and MZL with a reported ORR of 54% and 67%, respectively [87]. Durvalumab in combination with ibrutinib resulted in modest response rates (ORR 26%) in 27 r/r FL patients [96]. Finally, nivolumab added to ibrutinib administered to 5 r/r CLL patients showed 60% ORR with only partial responses achieved [118,119].

Table 3. PD-1 / PDL-1 ICB combination prospective studies by lymphoma subtype.

Lymphoma subtype	Studies	N	Study population	Therapy	ORR (%)	CR (%)	Median PFS (months)	Median OS (months)	Median follow-up (months)	Specifi cities
Classical Hodgkin lymphoma (cHL)	**CheckMate 205, Ramchandren 2019,** [44] Cohort D, Phase 2	51	Untreated advanced stage	Nivolumab 240 mg q2wks × 4 doses followed by nivolumab-AVD × 6 cycles	84	67	NR (92% at 9 months)	NR (98% at 9 months)	11.1	
	NIVAHL Trial, Bröckelmann2 022, [45], Phase 2	109	Untreated early stage and unfavorable	Groupe 1: Nivolumab 240 mg q2wks + AVD × 4 cycles Groupe 2: Nivolumab × 4 cycles monotherapy, nivolumab-AVD × 2 cycles, AVD only × 2 cycles, followed by 30-Gy involved-site radiotherapy	96	87	NA 1: 100% at 1-year 2: 98% at 1-year	NA 1: 100% at 1-year 2: 100% at 1-year	13	
	Cheson 2020, [50] Phase 2	46	Untreated, > 60 years old or younger and ineligible for chemothera py	Nivolumab 3 mg/kg + BV 1.8 mg/kg q3wks × 8 cycles	61	48	18.3	NR	21.2	
	Allen 2021, [46], Phase 2	30	Untreated early unfavorable and advanced-stage	Pembrolizum ab 200 mg q3wks for 3 cycles, AVD × 4-6 cycles	100	NA	NR	NR	22.5	

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Nie 2019, Liu 2021 *et al.*, [37,38], Cohort 1 combination, Phase 2	67	R/R after more than 2 therapies lines	Cohort 1 combination; anti-PD1 naïve: (n=42): decitabine (10 mg/d, days 1 to 5) plus camrelizumab 200mg q3wks* Cohort 2 (n=25); anti-PD1 resistant: decitabine plus camrelizumab*	1: 95 2: 52	1: 71 2: 28	1: 89% at 1-year 2: 59% at 1-year	1: 63% at 2-year 2: NA	34.5	
Herrera 2019, Mei 2022, [53,54], Phase 2	43	R/R first salvage therapy and bridge to ASCT	Nivolumab 3 mg/kg q2wks × 6 cycles +/- ICE. PET-CT after C3 and C6. After C6, pts in CR: ASCT, not in CR: N-ICE for 2 cycles	93	91	NA (72% at 2-year)	NA (95% at 2-year)	NA	Among 9 patients who received N-ICE: ORR 100%, CR 89%
Bryan 2021, [55], Phase 2	42	R/R prior to ASCT	Pembrolizumab 200mg q2wks + ICE × 2 cycles, stem cell mobilization/ collection, pembrolizumab 200mg × 1 cycle	97	NA	26.9 (88% at 2-year)	NR (95% at 2-year)	27	
Diefenbach 2020, [66], Phase 1/2	64	R/R	BV 1.8 mg/kg + ipilimumab 3 mg/kg or nivolumab 3 mg/kg or nivolumab 3 mg/kg and ipilimumab 1 mg/kg*	BV + Ipi 76 BV + Nivo 89 BV + Ipi/Nivo 82	BV + Ipi 57 BV + Nivo 61 BV + Ipi/Nivo 73	BV + Ipi 14.4 (61% at 1 year) BV + Nivo NR (70% at 1 year) BV + Ipi/Nivo NR (80% at 1 year)	NR	BV + Ipi: 31.2 BV + Nivo: 28.8 BV + Ipi/ Nivo: 20.4	
Sermer 2020, Sermer 2021, [67,68], Phase 2	22	R/R (heavily pretreated, previous ICB therapy accepted)	Entinostat 5-7 mg orally q1wks + pembrolizumab 200mg q3wks	86	45	NA (72% at 1 year)	NA	8.4	

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Lepik 2020, [61], Phase 2	30	R/R after Nivolumab monotherapy	Nivolumab 3 mg/kg on D1,14 + bendamustine (90 mg/m2) on D1, 2 of a 28-day cycle for up to 3 cycles	87	57	10.2 (23% at 2 year)	NA (97% at 2 year)	25	
Herrera 2018, Advani 2021, [51,52] Phase 1/2	62	R/R in initial salvage therapy before ASCT	BV + Nivolumab 3 mg/kg q3wks × 4 cycles	82	61	NR (77% at 3 year)	NR (93% at 3 year)	34.3	
Moskowitz 2021, [56], Phase 2	38	R/R after first line therapy, prior to ASCT	Pembrolizumab 200 mg + GVD q3wks × 2-4 cycles	100	95	NA	NA	13.5	
Ansell 2019, Bartlett 2020, [69,70], Phase 1B	24	R/R, CD30 positive, 3-7 prior lines of therapy including BV	Pembrolizumab 200 mg q3wks + AFM13 dose escalation schedules	83	37	NA (77% at 6 months)	NA	NA	
Dave 2022, [71], Phase 1	10	R/R inclusive after ASCT, allo-SCT, BV, prior ICB) (n=8 active disease, n=2 adjuvant after ASCT)	TAA-Ts + Nivolumab in 6 patients*		1 CR 7 SD at 3 months			41 (adjuvant arm) and 12.6 (active disease arm)	Nivolumab priming impacted TAA-T recognition and persistence.
CheckMate 039, Ansell 2016, Armand 2021, [64,65], Phase 1B	52	R/R after ≥2 prior lines of therapy, independent of ASCT	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg q3wks or nivolumab 3 mg/kg + liriliumab 3 mg/kg q4wks*	Nivo/Ipi: (n = 31) 74 Nivo/Liri (n = 21) : 76	Nivo/Ipi: (n = 31) 23 Nivo/Liri: (n = 21): 24	Nivo/Ipi: NR Nivo/Liri: NR	NA	Nivo/Ipi: 18 Nivo/Liri: 11	
Timmerman 2022, [75], Phase I/II (cohort 2)	29	R/R after anti-PD1 therapy	Favezelimab 800mg q3wks + pembrolizumab 20mmg q3wks for up to 35 cycles	31	7	9 (39% at 1 year)	26 (91% at 1 year)	N/A	

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Follicular lymphoma (FL)	**Younes 2017, Younes 2022,** [112,113] Phase 1/2	40	FL grade 1, 2 or 3a disease requiring therapy	Obinutuzumab 1000 mg on days 1, 8 and 15 of cycle 1 and day 1 of cycles 2-6, bendamustine 90 mg/m² on days 1 and 2 of cycles 1-6, and atezolizumab 840 mg on days 1 and 15 of cycles 2-6 (28-day cycles). Maintenance in pts with CR or PR consisted of obinu 1000 mg on day 1 of every other month and atezo 840 mg on days 1 and 2 of each month*	NA	75%	NA (81% at 3 year)	NA (89% at 3 year)	40.4	Grade 5 (fatal) adverse events reported in five patients
	Westin 2014, [116], Phase 2	30	Relapsed FL rituximab sensible	Rituximab 375 mg/m2 weekly for 1 cycle + pidilizumab 3 mg/kg q4wks for 12 doses	66	52	18.8	NA	15.4	
	Nastoupil 2017, Nastoupil 2022, [114,115], Phase 2	30	Relapsed FL rituximab sensible	Pembrolizumab 200 mg q3wks for up to 16 cycles + rituximab 375 mg/m2 weekly for 1 cycle	67	50	12.6	NR (97% at 3 year)	35	
	Morschhauser 2021, [117], Phase 1B/2	32	R/R FL (grade 1–3a)	Obinutuzumab 1000 mg + atezolizumab 840 mg + lenalidomide 15mg (in the expansion phase) or 20mg × 6 cycles, if CR/PR/SD maintenance*	78 (at the end of the induction)	72 (at the end of the induction)	NA (68% at 3 year)	NA (90% at 3 year)	30 (lenalidomide 15mg) 14.2 (lenalidomide 20mg)	

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Diffuse large B-cell lymphoma (DLBCL)	**Younes 2018, Younes 2019,** [89,90], Phase 1/2	40	Untreated advanced DLBCL	atezolizumab 1200mg q3wks + R-CHOP × 8 cycles	NA	78	NA (75% at 2 year)	NA (86% at 2 year)	21.3
	Smith 2020, [91], Phase 1	30	Untreated DLBCL or grade 3b FL	Pembrolizumab 200 mg + R-CHOP q3wks × 6 cycles	90	77	NA (83% at 2 year)	NA (84% at 2 year)	25.5
	Nowakowski 2022, [92], Phase 2	37	High-risk DLBCL (IPI ≥3/NCCN-IPI ≥4)	Durvalumab 1125mg q3wks+ R-CHOP × 6-8 cycles, then durvalumab consolidation *	97	68	NA (68% at 1 year)	NA	NA
	Palomba 2022, [103], Phase 1B	43	R/R DLBCL	Atezolizumab 1200 mg + tazemetostat 800 mg orally twice daily q3wks	16	7	2	13	23.7
	ZUMA 6, Jacobson 2020, [97], Phase 1/2	28	R/R DLBCL	Atezolizumab 1200mg + KTE-C19 (axi-cel)	75	46	NR	NR	10.2
	PORTIA trial, Jäger 2021, [99], Phase 1B	12	R/R DLBCL	Pembrolizumab q3wks for up to 6 doses either days +15, +8, or –1 of tisagenlecleucel	Days+15: 50 Days+8 25 Days-1 25	Days+15: 0 Days+8 25 Days-1 25	NA	NA	4
	Witzig 2019, [94], Phase 1/2	61	R/R DLBCL	Pembrolizumab 200mg q3wks + acalabrutinib 100mg BID*	26	7	1.9	NA	NA
	Alexander trial, Osborne 2020, [102], Phase 1	29	R/R DLBCL	Pembrolizumab 200mg q3wks + AUTO3 (bispecific CAR T targeting CD19/22)	69	52	NA	NA	NA
Primary mediastinal B-cell lymphoma (PMBCL)	**CheckMate 436, Zinzani 2019, Zinzani 2021,** [107,108], Phase 2	30	R/R PMBCL	Nivolumab 240 mg and BV 1.8 mg/kg q3wks*	73	37	26 (56% at 1 and 2 year)	NR (76% at 2 year)	11.1
Multiple hematologic	**CheckMate 039, Ansell**	78	R/R hematologic malignancie	Nivolumab 3 mg/kg + ipilimumab	Nivo/Ipi: B-	Nivo/Ipi: B-	Nivo/Ipi: B-NHL (n = 16)	NA	Nivo/Ipi: 18

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malignancies	2016, Armand 2021, [64,65], Phase 1B		s (≥2 prior lines of therapy) independent of ASCT	1 mg/kg q3wks or nivolumab 3 mg/kg + liril umab 3 mg/kg q4wks*	NHL (n = 16) 19 T-NHL (n=11): 9 Nivo/ Liri B-NHL (n = 32) : 13 T-NHL (n=11): 22	NHL (n = 16) 6 T-NHL (n=11): 0 Nivo/Liri B-NHL (n = 32): 3 T-NHL (n=11): 0	1 T-NHL (n=11): 2 Nivo/Liri B-NHL (n = 32): 1 T-NHL (n=11): 6	Nivo/Liri: 11
	Younes 2019, [93], Phase 1/2A	141	R/R CLL, SLL, FL, DLBCL	Ibrutinib + nivolumab 3 mg/kg q2wks*	CLL/SLL (n = 36) : 61, FL (n = 40) : 33, DLBCL (n = 45) : 36 RT (n = 20) : 65	CLL/SLL (n = 36): 0 FL (n = 40): 10 DLBCL (n = 45): 16 RT (n = 20): 10	CLL/SLL (n = 36): NR FL (n = 40): 9.1 DLBCL (n = 45): 2.6 RT (n = 20):5.0	CLL/SLL (n = 36): NR FL (n = 40): NR DLBCL (n = 45): 13.5 RT (n = 20): 10.3	19.7
	Palomba 2022, [105], Phase 1B	49	R/R FL + R/R DLBCL	Atezolizumab 1200 mg + obinutuzumab 1000 mg	FL (n = 26): 54 DLBCL(n = 23): 17	FL (n = 26): 23 DLBCL(n = 23): 4	FL (n = 26): 9 DLBCL(n = 23): 3	FL (n = 26): NA DLBCL (n = 23): 9	NA

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Jain 2016, Jain 2018, [118,119], Phase 2 (cohort 1)	28	R/R FL + RT	Nivolumab 3 mg/kg q2wks × 24 cycles + ibrutinib 420 mg*	FL (n=5): 60 RT (n = 23): 43	FL (n=5): 0 RT (n = 23): 35	FL (n=5): NR RT (n = 23): NA	FL (n=5): NR RT (n = 23): 13.8	NA	
LYSA trial, Herbaux 2020, Herbaux 2021, [87,104], Phase 2	136	R/R DLBCL (cohort 1) and R/R iNHL (FL + MZL) (cohort 2)	Obinutuzumab 1 g × 8 cycles + atezolizumab 1.2 g q3wks × 24 cycles + venetoclax 800mg/j (on D8) × 24 cycles	DLBCL (n=58): 24 FL (n=58): 54 MZL (n=20): 67	DLBCL (n=58): 18 FL (n=58): 30 MZL (n=20): 17	NA	NA	DLBCL: 9 FL: 14.5 MZL: 11.9	
Hutchings 2019, [106], Phase 1B	36	R/R B- NHL (DLBCL, transformed FL, MCL, PMBCL, LPL, iNHL)	Atezolizumab 1200mg + CD-20-TCB antibody (RG6026) q3wks	36	17	NA	NA	NA	Ongoing trial
KEYNOTE-155, Gregory 2022, [95], Phase 1B	72	R/R hematologic malignancies	Pembrolizumab 200 q3wks + dinaciclib (dose escalation)*	CLL (n = 17): 29 DLBCL (n = 38): 21 MM (n = 17): 0	CLL (n = 17): 0 DLBCL (n = 38): 11 MM (n = 17): 0	CLL (n = 17): 5.2 DLBCL (n = 38): 2.1 MM (n = 17): 1.6	CLL (n = 17): 21.7 DLBCL (n = 38): 7.9 MM (n = 17): 10.5	NA	Dinaciclib dose levels (7 mg/m2, 10 mg/m2, 14mg/m2)
Herrera 2020, [96], Phase 1/2	61	R/R FL + R/R DLBCL	Durvalumab 10 mg/kg q2wks + ibrutinib 560mg once daily (dosing according to phase 1B)*	FL (n=29): 26 Non-GCB DLBCL (n=16): 38 GCB-DLBCL (n=16): 13	FL (n=29): 4 Non-GCB DLBCL (n=16): 31	FL (n=29): 10.2 Non-GCB DLBCL (n=16): 4.1 GCB-DLBCL (n=16): 2.9	FL (n=29): NR Non-GCB DLBCL (n=16): 7.3 GCB-DLBCL (n=16): 5.5	FL: 17 DLBCL: 17.5	

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				GCB-DLBCL (n=16): 6					
Hirayama 2020, [101], Phase 1	13	R/R B-cell NHL	Durvalumab dose escalation up to 10 doses + JCAR014 (CD19-specific 4-1BB-costimulated CAR-T cells)	50	42	NA	NA	NA	Durvalumab dose escalation ongoing
Panayiotidis 2022, [88], Phase 2	55	R/R MCL, WM, MZL	Atezolizumab + obinutuzumab (MCL+WM) or rituximab (MZL)	MCL (*n* = 30): 17 WM (*n* = 4): 0 MZL (*n* = 21): 43	NA	NA	NA	NA	
Sang 2022, [72], Phase II	12	R/R CD30+ lymphoma (9 cHL, 1 angioimmunoblastic T-cell lymphoma (AITL), 2 gray zone lymphoma)	Cohort 1: 10^6/kg of CD30 CAR-Ts Cohort 2: 10^7/kg of CD30 CAR-Ts Cohort 3: 10^7/kg of CD30 CAR-Ts + anti-PD-1 antibody q3wks starting 14 days after CAR-T cell infusion†	92 (Cohort 1&2: 86%; Cohort 3: 100%)	70 (Cohort 1&2: 27%; Cohort 3: 80%)	45	70	21.5	Anti-PD1 treatment not mentioned

* until progression or unacceptable toxicity. † Sequential HSCT was done in part of patients; second infusion of CD30 CAR-Ts allowed if PD after first treatment or after ASCT. *Abbreviations: ASCT,* Autologous stem cell transplantation; *doxorubicin, vinblastine, dacarbazine; CHOP,* cyclophosphamide, *hydroxyadriamycine,* vincristine, prednisone; *CR, complete remission; GVD, gemcitabine, vinorelbine, liposomal doxorubicin; HSCT, Hematopoietic stem cell transplantation; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; N, nivolumab; PD, progressive disease; PR, partial response; q2wks, every two weeks; q3wks, every three weeks; R, rituximab; TAA-Ts, tumor associated antigen specific T cells; TCB, T-cell-engaging bispecific; WM, Waldenström's macroglobulinemia.*

4. Predictive biomarkers of response to ICB in lymphoma

Predictive biomarkers of response to ICBs have been identified in different solid tumors, but our ability to accurately predict response in lymphoma remains suboptimal. Mechanisms of immune evasion may differ from one lymphoma subtype to another. Several biomarkers have been

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investigated in lymphoid malignancies, including PD-L1 H-score, alterations/amplification of the 9p24.1 gene, microsatellite instability (MSI), tumor mutational burden (TMB), density of intra-tumoral CD8+ T lymphocyte infiltrates, genetic alterations in MHC class I and II, and miRNA-21, among others [120].

4.1. Tissue expression and plasma levels of PD-Ls

PD-L1 and PD-L2 expression of TME can be influenced by two main signaling pathways. The extrinsic pathway relies on the release of inflammatory signals (i.e. IFN-γ) by TILs after tumor antigen recognition, consequently upregulating the expression of PD-L1/PD-L2 in tumor cells and TME cells [121]. On the other hand, the intrinsic pathway is mainly driven by genomic alteration of the 9p24.1 gene, EBV infection and activation of the JAK/STAT transcription pathway and will be reviewed below [13,122].

4.1.2. PD-L1 expression

In some solid malignancies, PD-L1 expression (measured by immunohistochemistry; IHC) has been associated with an improved response to PD-1/PD-L1 ICB (i.e. melanoma, non-small cell lung carcinoma (NSCLC) and urothelial carcinoma) [123–125] and worse OS irrespective of ICB exposure [126]. PD-L1 expression is now routinely measured by IHC in several solid tumors [127], however, its discriminative value is likely imperfect as patients with PD-L1–negative tumors may achieve durable responses (ref). Additionally, the PD-L1 positive cut-off threshold remains highly variable depending on tumor type, with different IHC scoring systems used to determine PD-L1 expression in tumors [128]. The main scores used are the combined positive score (CPS) [129], the tumor proportion score (TPS) [130] and the H-score [120] (Supplement Table S1); the latter is the mostly used scoring system in lymphoma [120].

Even though some studies revealed that TME PD-L1 expression correlates with poor prognosis in HL and NHL [123,131], it does not seem to be true for all lymphoma subtypes (i.e. NK/T lymphoma) [133]. Similarly, PD-L1 expression is not a reliable biomarker of response to PD-1/PD-L1 ICB for all lymphoma. For reasons explained below (refer to section), PD-L1 expression correlates to response to anti-PD1 therapy in cHL and some non-GCB DLBCL subtypes, but has no predictive value for other subtypes [132,133]. Similarly, soluble PD-L1 (sPD-L1), corresponding to plasma levels of PD-L1, has been investigated as a potential biomarker with mixed results [134–136].

4.1.2. PD-L2 expression

Prognostic significance of PD-L2 expression in malignant tumors remains controversial [137,138]. Gu and colleagues demonstrated that PD-L2 expression on DLBCL cells was significantly associated with prolonged OS and PFS. Higher ORR to R-CHOP/CHOP were also reported in patients with enhanced expression of PD-L2 in malignant and immune cells [139]. Similarly, Tobin et al. demonstrated that PD-L2 is mostly present in the TME of FL and that a low PD-L2 expression was associated with worse outcome [140].

4.2.9. p24.1 gene alterations

Copy number alterations (CNAs) to chromosome 9p24.1 (i.e. polysomy, copy gain, amplification, rarely translocation) leading to increased expression of PD-1 ligands in cHL, PMBCL and some extranodal large B-cell NHL, are an important mechanism of tumor immune evasion. These alterations have been reported in the majority of cHLs (97%) [139], 63-75% of PMBCL [141,142], over 40% of PTL and roughly 20% of PCNSL [143]. Unlike cHL, there is generally a low incidence (10-27%) of structural variations of PD-L1/PD-L2 in DLBCL [144,145]. The H-score could be used as a surrogate marker of level of 9p24.1 gene alteration and predict response to ICB [146]. cHL patients presenting 9p24.1 CNAs are more likely to present with advanced stage disease and worse prognosis, with significantly shorter PFS (ref). On the other hand, they also tend to benefit from therapy with a PD1 inhibitor [44,139,147]. However, Green et al. (2010) described that Hodgkin Reed-Sternberg cell lines

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harboring low levels of 9p24.1 CNAs still expressed PD-L1, suggesting that PD-L1 expression could be driven by other mechanisms [139]. Although the vast majority of NHL have a considerably low sensitivity to PD-1/PD-L1 ICB, particular subtypes, such as PCNSL, PTL, PMBCL harbor 9p24.1 CNAs conferring them an increased vulnerability to these agents [15,143]. In PMBCL, the magnitude of 9p24.1 CNAs is significantly associated with PD-L1 expression and survival outcome [14].

4.3. Epstein–Barr virus (EBV) and JAK/STAT signaling pathway

In cHL and PMBCL cell lines, Green et al. (2010) observed that broader 9p24.1 amplifications also included the Janus kinase 2 (JAK2) locus located upstream from PD-1 ligand genes [139]. As a consequence, 9p24.1 CNAs directly enhanced the JAK/STAT intrinsic signaling pathway, promoting PD-1 ligand transcription [139]. Additionally, the JAK/STAT signaling pathway can also be activated by various cytokines secreted by cells within the TME (i.e. IFN-γ), leading to PD-L1 upregulation on tumor cells [148]. In solid tumors, e.g. NSCLC and melanoma, the level of mRNA IFN-γ expression has been demonstrated to correlate with PD-1/PD-L1 ICB response [149].

Even though underlying mechanisms have not yet been fully elucidated, recent studies indicate that viruses also use the PD-1 signaling pathway to escape immune detection [150]. Thus, viral infections (i.e. human papillomavirus (HPV), EBV) seem to play a role as potential biomarkers of response to PD-1/PD-L1 ICB in solid tumors [151,152]. Higher immune cell infiltration and PD-1/PD-L1 expression levels have been described in HPV-positive solid tumors (153). Similarly, EBV-positive solid tumors and lymphomas tend to benefit from ICB therapy [154,155]. Expression of EBV latent membrane protein 1 (LMP1) or latent membrane protein 2a (LMP2a) were shown to be sufficient to activate the signaling cascade of the JAK/STAT pathway, leading to PD-L1 overexpression on tumor cells [150]. Expression of EBV has been implicated in approximately 40% of cHLs, 50-70% post-transplant lymphoproliferative disorders (PTLD), more than 95% of endemic Burkitt lymphoma (BL), 20%-30% of sporadic BL, 25%-40% of immunodeficiency-associated BL, EBV-positive DLBCL NOS, as well as most NK/T cell lymphoma [156–159]. In a cohort of 1253 patients with DLBCL, PD-L1 protein expression was significantly associated with EBV positivity in the non-GCB subtype and showed a trend toward inferior OS in these patients [160].

4.4. Tissue tumor mutational burden (TMB) and plasma tumor mutational burden (pTMB)

Based on the concept that higher mutation loads could yield to improved T cell-recognition of tumors via increased neoantigen production, tumor mutational burden (TMB), defined as the number of somatic mutations per megabase (mut/Mb) [161], was investigated as a predictive biomarker of response to PD-1/PD-L1 ICB in several solid malignancies [162–164]. The cut-off of 10 mut/Mb (high load) has recently been approved by the FDA as a perquisite cut-off to treat patients with PD-1/PD-L1 ICB [165], however, this cut-off fails to accurately predict response across different cancer types.

TMB in hematologic malignancies has only been reported in a few patient series, and its relationship to response to PD-1/PD-L1 ICB is not well established. Using a 406-DNA gene panel, Galanina and colleagues showed a median TMB of 1.7mut/Mb across all hematologic malignancies [166]. Applying whole-exome sequencing (WES), Wienand et al. described a median TMB of 7.7 mut/Mb in cHL, although TMB may differ as per EBV status, EBV-negative cHL harboring a higher mutational level, almost similar to NSCLC (median 9.8 mut/Mb) and melanoma (13.5 mt/Mb) TMB [167–169]. Median TMB of PMBCL has been shown to be within the same range as cHL (7.0 mut/Mb) [170]. Using LymphomaScan, a 405-gene panel, Cho et al. (2021) investigated TMB in different NHL (B-cell neoplasms n=243, T- and NK-cell neoplasms n=53, precursor lymphoid neoplasms n=4), reporting single nucleotide variant (SNV) and insertion–deletion mutations (Indels) for each subtype. Overall, they found that B-cell lymphomas had statistically more mutations (24 SNV/Indel) than T- and NK-cell lymphomas (17 SNV/Indel). PMBCL accounted for the highest TMB load (32 SNV/Indel), followed by PCNSL (30 SNV/Indel), DLBCL NOS (23 SNV/Indel), ALK-negative anaplastic large cell lymphoma (ALCL) (23 SNV/Indel), ALK-positive ALCL (14 SNV/Indel), follicular T-cell lymphoma (14 SNV/Indel), and nodal peripheral T-cell lymphoma with TFH phenotype (PTCL TFH) (14.5 SNV/Indel) [171].

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Circulating tumor DNA (ctDNA), sometimes referred to as liquid biopsy, reflects tumor DNA spread within the circulation [172]. Plasma TMB (pTMB) has been investigated in solid tumors and DLBCL as a surrogate to quantify overall tumor burden and mutational load and more accurately capture molecular tumor heterogeneity and clonal evolution [173,174]. To our knowledge, only a limited number of clinical studies have been conducted in hematological malignancies. One study evaluated pTMB in cHL, showing that higher baseline ctDNA and a sharper ctDNA decrease (>40%), significantly correlated with better clinical responses to sintilimab [175]. Another study, reported as an abstract only, compared TMB with pTMB in several NHL subtypes , with a respective median mut/Mb of 8.9 vs 10.0 for DLBCL, 3.5 vs 3.2 for small B cell lymphoma, 2.4 vs 2.1 for PTCL and 5.9 vs 3.2 for NK/T cell lymphoma [176].

4.5. MSI and d-MMR

Microsatellite instability (MSI), caused by deficiency of the DNA mismatch repair (MMR) system, result in a higher mutational load and tumor antigen expression, leading to increased antitumor T cell activation. MSI and MMR status are well-recognized prognostic factors in several solid tumors. The National Cancer Institute recommends a panel of five microsatellite markers for MSI tumor detection (two mononucleotide repeats: BAT-25, BAT-26; three dinucleotide repeats: D2S123, D5S346, D17S250). MSI-high tumors are defined as having instability in two or more of these markers [177]. Like those harboring a high TMB, patients with MSI-high tumors achieve durable responses to ICB [178]. MSI screening is yet recommended in all newly diagnosed colorectal cancers as a biomarker of response ICB [178], as approximately 15 % of colorectal carcinomas are detected as MSI-high [179]. Pembrolizumab and dostarlimab, both anti-PD1antibodies, are now approved by the FDA for the treatment of unselected advanced-stage tumors with MSI/dMMR [127]. Even though MSI-associated hypermutation represents a potential biomarker for the efficacy of PD-1 blockade, it is likely infrequent in lymphoma: reported frequencies are low, occurring in only 0.46%, of cHL, 3.2% of DLBCL and 8% of PMBCL [169,170,180].

4.6. MHC expression

Antigen presentation by major histocompatibility complex (MHC) molecules is an essential step in T-cell recognition and tumor cell eradication, as T cell activation does not occur at the tumor site but in the lymph nodes. MHC I complex, including the beta-2-microglobulin (B2M) subunit, presents tumor-generated peptides at the cell surface, which can be recognized by cytotoxic CD8+ T cells. On the other hand, MHC II complexes present tumor antigens to CD4+ T cells [181]. Acquired mutations in the antigen processing and presentation molecules is a potential mechanism of tumor escape [182]. B2M mutations resulting in decreased MHC I expression is a well-described acquired resistance mechanism to PD-1/PD-L1 ICB in melanoma [183]. By contrast, in a study in cHL, Roemer et al. (2016) discovered that over 75% of patients had decreased or absent expression of B2M/MHCI and MHCII on tumor cells [184]. Nonetheless, patients with cHL are known to have a high response rate to PD-1 ICB. The postulated alternate mechanism triggering response to PD-1/PD-L1 ICB could be MHC class II expression. Indeed, melanoma patients with low or absent B2M/MHCI expression but increased MHCII expression demonstrated higher responses to ICB [185]. This suggests that MHCII expression could be a potential biomarker for PD-1/PD-L1 ICB response, that requires further evaluation.

4.7. Intra-tumoral CD8+ T lymphocyte infiltrate density

Several studies have demonstrated that response to PD-1/PD-L1 ICB seems tightly related to immune cell infiltration. High levels of cytotoxic CD8+ T lymphocytes at the TME have been independently linked to improved outcomes in several solid tumors (cervical cancer [186]) as well as in hematological malignancies (i.e. DLBCL [187], PTL [188], FL [189], MZL [190] and HL [191,192]. The association between tumor CD8+ T lymphocyte infiltration and response to PD-1/PD-L1 ICB has been confirmed for solid tumors by a large metanalysis conducted by Li et al (2021) [193]. Such data have not yet been reported for hematological malignancies.

4.8. MicroRNAs

MicroRNAs (miRNAs) are small sequences of non-coding RNAs acting as gene expression regulators. miRNAs are involved in various physiologic and pathologic processes including immune responses [194]. Numerous miRNAs are recognized as prognostic biomarkers and are investigated as potential therapeutic targets in solid and hematologic tumors [195]. Among all miRNAs, microRNA-21 (miR-21) is one of the most frequently overexpressed miRNAs in solid tumors and B-NHL [196]. High plasma miR-21 levels have been associated with poor prognosis in several B-NHL subtypes (e.g. primary gastrointestinal DLBCL [197], DLBCL [198], Burkitt lymphoma [199], PCNSL [200]). miR-21 depletion may enhances anti-tumor activity through polarization of macrophages into an M1-like phenotype; on the other hand, miR-21 also upregulates PD-L1 expression [201]. Taking advantages of these properties, Xi et al recently showed in a preclinical model a synergetic effect of miR-21-depleting therapy and PD-1 ICB [201].

4.9. Gut microbiome

Recent evidence shows that the biodiversity of the gut microbiome could influence the antitumor activity of PD-1/PD-L1 ICB; this was notably investigated in melanoma [202,203]. Namely, Liu et al. (2021) demonstrated that a favorable gut microbiome characterized by its diversity and the presence of specific bacteria species could influence the innate and adaptive immune system by increasing antigen presentation and augmenting T cell response. On the other hand, antibiotics use may disrupt the gut microbiome and impair cytotoxic T-cell responses against tumor cells [204]. Hwang et al. studied this association in a small retrospective cohort of 62 cHL patients treated with ICB and observed that prior and/or current antibiotherapy were linked to inferior outcomes [205]. Recently, Casadei et al. (2021) prospectively collected feces (at baseline, before each treatment, at response assessment and for grade >2 adverse events) in cHL (n=12) and PMBCL (n=5) patients undergoing PD-1PD-L1 ICB. They reported the results of the first 6 patients (all cHL) showing clear differences in their microbiome, with a depletion of health-promoting microbial components compared to healthy controls [206].

5. Conclusion

PD-1/PD-L1 ICB is now a well-recognized therapy against specific lymphoproliferative disorders such as cHL and PMBCL. Beside those specific indications, PD-1/PD-L1 ICB shows generally disappointing results across all NHL. Some patients with specific NHL subtypes, (e.g. PMBCL, PTL, PCNSL) or particular molecular findings such as in the case we present (a patient with a high TMB), may derive prolonged clinical benefit from these agents. To date, identification of discriminative biomarkers of response to PD-1 / PD-L1 ICB has been very challenging. Increased PD-L1 expression and high TMB and/or MSI are now FDA-approved predictive biomarkers in several solid tumors. In lymphoma, PD-L1 expression is driven by genetic alterations of the 9p24.1 locus, activation of the JAK/STAT signaling pathway and EBV infection. However, its expression is highly variable among lymphoma subtypes and does not always correlate with clinical response to PD-1/PD-L1 ICB. Additionally, the value of a PD-L1 H-score cut-off is currently not fully understood. Although in solid malignancies high TMB and high MSI correlate with increased response to PD-1/PD-L1 ICB, these biomarkers have not been clearly established in hematological malignancies, a setting where further research in this area is urgently needed.

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