



# Novel immunotherapy in follicular lymphoma: a narrative review

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**Abstract:** Follicular lymphoma (FL), a prototypical indolent lymphoma, is characterized by a prolonged survival with multiple relapses and the intermittent need for therapy. Therapeutic advances in the last two decades have contributed significantly to this extended survival. Manipulating various components of the immune system that form an integral part of the tumor microenvironment have been clinically beneficial. Mechanisms by which these immunotherapies work involve either directly targeting the lymphoma cells and using the immune system for effector function, thereby eliminating lymphoma cells, or by targeting the immune system cells to promote anti-tumor surveillance and generate an effective anti-tumor immune response. Newer generation monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), bispecific antibodies, and cellular therapies such as chimeric antigen receptor T-cell (CAR-T) therapy have shown significant efficacy in FL. Also, these non-chemotherapy options boast a relatively favorable, albeit unique, toxicity profile. Patients with poor prognostic factors such as those with progression within 24 months from frontline therapy have an unmet need for newer and efficacious therapies. Bispecifics and cellular therapies such as CAR-T therapy look promising in this regard. However, careful consideration is required to identify the most suitable patients and the timing of each approach, thereby devising combinations that work synergistically and provide durable remissions while minimizing toxicity. This review focuses on novel immunotherapies currently approved or under clinical testing in FL patients.

**Keywords:** Follicular lymphoma (FL); immunotherapy; novel agents

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## Introduction

Significant progress has been made in the understanding of the genetic and molecular features of B-cell non-Hodgkin lymphomas (NHL) in the last two decades. The expanding knowledge of the interactions, composition, and role of various immune and non-immune cells within the lymphoma microenvironment in lymphomagenesis, progression, and survival has generated great interest in targeting and modulating the immune microenvironment. Several promising novel agents have thus been developed and approved for B-cell NHL. These non-chemotherapeutic

drugs harness the immune system by various mechanisms such as direct targeting of the lymphoma cells and engaging the immune system to eliminate the lymphoma cell, or targeting non-lymphoma immune cells in the tumor and promote their anti-tumor function (1-3). Follicular lymphoma (FL), like other B-cell indolent lymphomas, has an average survival of well over ten years (4). Various frontline treatment strategies include watchful waiting, single-agent rituximab, chemoimmunotherapy such as bendamustine and rituximab (BR), R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), and non-chemotherapy regimen such as lenalidomide and rituximab (R2) (5-10).

The treatment choice is individualized and depends on both the patient and disease-related factors and the efficacy and toxicity profile of the drug. Although FL is a very treatable malignancy, the long survival is characterized by multiple relapses necessitating several rounds of treatment. Additionally, a small subset of patients with disease progression within 24 months of chemoimmunotherapy comprises a particularly poor prognostic group that warrants novel treatment strategies (11-13). Therefore, the goal of newer treatment modalities should focus on minimizing both short and long-term toxicities while maintaining efficacy and attempting to achieve a cure. It is in this high-risk population of FL patients where novel immunological agents may be of particular importance.

This review will broadly cover the mechanism and clinical studies of novel agents that utilize the immune system directly or indirectly for an effective anti-tumor response. These include monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs) that deliver cytotoxic payload targeted to the lymphoma cells, and bispecific antibodies that have dual specificity to the tumor and immune cells, bringing them close to each other. Also, antibodies directly targeting the immune effector cells, such as T-cells and macrophages, along with agents that modulate the tumor microenvironment or target the B-cell receptor (BCR) signaling pathways, will be described. Lastly, we will review clinical studies with cellular therapies such as chimeric antigen receptor (CAR) T-cell therapy and adoptive cell therapies in FL. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/aol-20-48>).

### **Monoclonal antibodies and antibody-drug conjugates targeting the malignant B-cell**

Monoclonal antibodies targeting CD20 have changed the treatment paradigm for B-cell NHL. In FL, rituximab is used widely as a single-agent or in combination with chemotherapy. The role of rituximab in FL is well established in the frontline, maintenance, and relapsed settings and will not be discussed here (5,6,8,9,14). Mechanisms by which rituximab exerts its anti-tumor response include complement-mediated cytotoxicity, antibody-dependent cell killing (ADCC), and direct cytotoxicity via apoptosis (15-17). To manage patients who progress after receiving rituximab, subsequent therapies have focused on two strategies. First, target a different epitope on CD20 or modify the Fc portion of the antibody to enhance

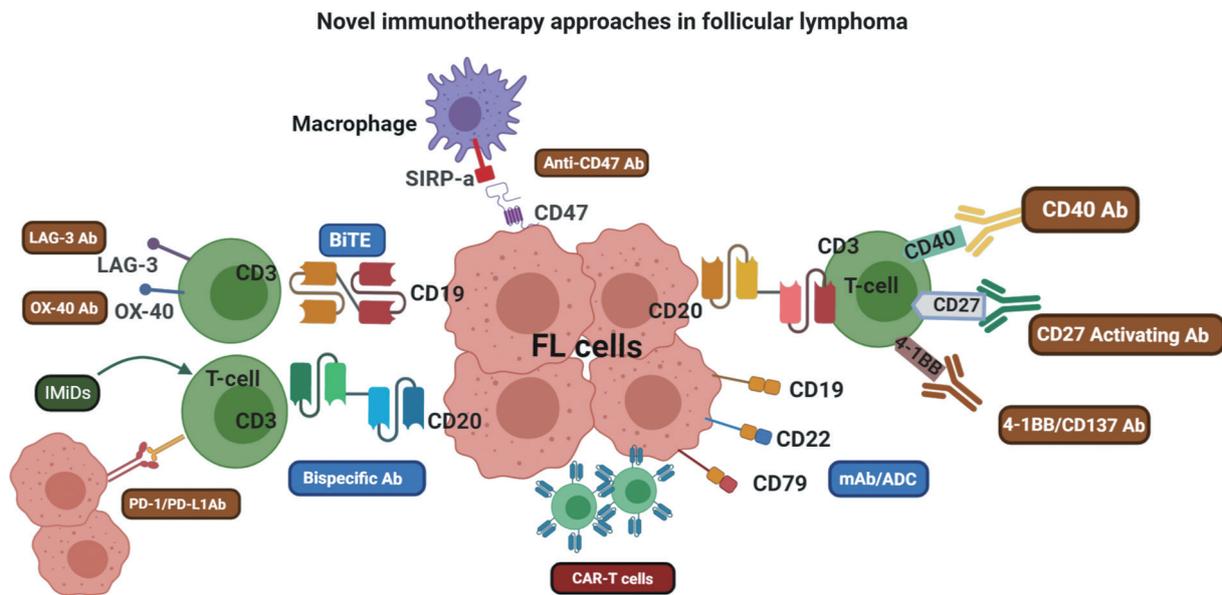
its cell-mediated cytotoxicity. Second, target other B-cell surface antigens such as CD19, CD22, and CD79, which are typically expressed on the FL cell (*Figure 1*).

#### ***CD20 targeting antibodies***

*Obinutuzumab*, a type II glycoengineered IgG1 mAb, shows enhanced ADCC compared to rituximab in preclinical studies (18,19). It is currently FDA approved in both the frontline and relapsed setting in FL based on the results of two phase III trials (GALLIUM and GADOLIN) (20,21). In the GALLIUM study, obinutuzumab and rituximab-based chemoimmunotherapy regimens were compared in the frontline setting. Responding patients were then continued on maintenance therapy for up to 2 years. While there was no improvement in overall survival (OS) between the two arms, the trial was stopped early as it met the primary endpoint of progression-free survival (PFS). There was an absolute difference of 6.7% in the 3-year PFS rate at the interim analysis in favor of obinutuzumab. Grade 3–5 adverse events (AEs) and serious AEs were more frequent in the obinutuzumab arm. The GADOLIN study compared obinutuzumab in combination with bendamustine in rituximab-refractory indolent B-NHL patients (n=396, 81% FL). This trial also showed an improvement in PFS (primary endpoint) at the interim analysis, and obinutuzumab received FDA approval for relapsed/refractory (R/R) FL after a rituximab-containing regimen in 2016. A 2018 update of GADOLIN showed an improvement in OS [hazard ratio (HR), 0.67; 95% CI, 0.47–0.96] for the combination treatment (22). Grade 3–5 AEs were also seen more frequently in the combination arm with extended follow up (median 32 months), 72.5% in bendamustine and obinutuzumab combination compared to 65.5% with bendamustine alone. While these approvals have added to the treatment options in both frontline and R/R FL, some concerns remain regarding lack of OS benefit in the frontline setting and increased risk of AEs and long-term safety, especially with maintenance therapy.

*Ofatumumab*, a fully humanized second generation, type 1 mAb, targets a different CD20 epitope than rituximab. It has been studied both in the frontline and R/R settings in FL in phase I/II trials (23,24). The efficacy and toxicity profile appears to be comparable to the other CD20 targeting mAbs. However, the experience remains limited in FL as obinutuzumab (rather than ofatumumab) was more extensively studied in phase III studies.

*Ublituximab*, another type 1, chimeric, recombinant



**Figure 1** Novel immunotherapy options in Follicular lymphoma. The figure was developed by Arushi Khurana, using BioRender (Toronto, ON, Canada).

IgG1 mAb, targets a unique epitope on CD20 and is also glycoengineered to enhance its affinity for FcγRIIIa variants, thereby enhancing its ADCC effect (25). It has shown single-agent activity of around 40% in the R/R setting when studied in phase I/II trials (26). Currently, combination studies with a phosphatidylinositol 3-kinase (PI3K) inhibitor umbralisib and a Bruton tyrosine kinase (BTK) inhibitor ibrutinib are ongoing, especially in chronic lymphocytic leukemia (CLL) and other indolent B-NHLs (27,28).

### CD19 targeting antibodies

*MOR208 (tafasitamab)* is a novel CD19 targeting humanized Fc engineered mAb with increased affinity for FcγRIIIa on effector cells resulting in enhanced ADCC, antibody-dependent cellular phagocytosis, and apoptosis (29). Single-agent activity in FL was around 30%, with a favorable toxicity profile in the preliminary studies, which makes this drug suitable for testing in combination studies (30). The combination of tafasitamab with lenalidomide was recently approved for R/R diffuse large B-cell lymphoma (DLBCL) based on the phase II L-MIND trial data showing an overall response rate (ORR) of 60%, including 43% patients achieving a complete remission (CR) (31).

*Inebilizumab (MEDI-551)* is also a CD19 targeting humanized mAb with enhanced ADCC in the preclinical

studies (32). Initial trials have been conducted in Japan for dose-finding studies in R/R NHL, where it showed efficacy and favorable toxicity in patients with relapsed or refractory FL and DLBCL (NCT01957579) (33). It has recently been approved in the USA for an autoimmune condition, neuromyelitis optica (34). A phase 1/2 trial (NCT00983619) of inebilizumab alone or in combination with rituximab in FL, CLL, and DLBCL has recently completed recruitment in the US, and the results are currently awaited.

### CD22 targeting antibodies

*Epratuzumab*, a humanized IgG1 mAb, targets CD22 antigen, which is expressed in FL and other B-NHLs. Multiple studies were conducted in the early 2000s evaluating this drug both as monotherapy and in combination with rituximab. Single-agent ORR for epratuzumab was noted to be around 18%, and in combination with rituximab was increased to 55–60% in R/R setting (35–37). The combination was well tolerated with few AEs and drug discontinuations. The ORR was increased to 88% in the frontline setting in FL with a 42% CR rate and a 3-year PFS rate of 60% seen in the CALGB 50701 trial (38). This drug did not move forward in phase III trials due to competing strategies and currently has no ongoing trials in FL.

### *Antibody drug conjugates*

ADCs were developed to improve upon the efficacy of mAbs with the idea of attaching a toxic payload to the mAb and promoting its targeted delivery to the cell of interest. Like mAb, these molecules target cell surface antigens such as CD19, CD22, and CD79 expressed on the B-NHL. The toxic payload can be an anti-mitotic agent such as monomethyl auristatin E (MMAE) or a cytotoxic agent such as a pyrrolobenzodiazepine (PBD) dimer.

*Polatuzumab vedotin* is a CD79b targeting ADC with an MMAE payload. CD79 is an attractive target for B-NHL treatment as it forms an essential component of the BCR signaling and is almost exclusively expressed on the B-cells. It showed promising efficacy as a single agent with ORR up to 47% in indolent NHL. These responses were further improved in combination with rituximab in a phase II study (NCT01691898), where the ORR and CR rates were 70% and 45% in R/R FL, respectively (39). Similar responses were seen in another phase II trial (32 FL patients) combining obinutuzumab with polatuzumab vedotin (ORR, 78%, CR, 30%) (40). The most common grade  $\geq 3$  AEs were neutropenia, and the most common AEs in  $> 20\%$  of patients were fatigue, diarrhea, and nausea. Polatuzumab was combined with BR, and when compared to the BR alone arm, no difference was found in the CR rates or PFS for FL (41). However, these were significantly different in the DLBCL arm, which led to the approval of polatuzumab-BR in R/R DLBCL patients (42). This agent has moved in the frontline setting trials in DLBCL (NCT03274492). Multiple combination studies are also ongoing evaluating polatuzumab vedotin with lenalidomide, atezolizumab (NCT02729896), venetoclax (NCT02611323), and bispecific antibody such as mosunetuzumab (NCT03671018) and glofitamab (NCT03533283) in R/R B-NHL, results for which are currently awaited.

*Loncastuximab tesirine* (ADCT-402) is a CD19 targeting ADC with a PBD dimer payload (43). The phase I study (88 patients) in R/R B-NHL patients (8 FL) showed overall tolerability with most common grade  $\geq 3$  AEs of anemia, thrombocytopenia, and febrile neutropenia, along with fatigue, dyspnea, and liver function test abnormalities (44). Despite small numbers, a response was seen in seven of eight FL patients (87.5%), six of whom achieved a CR. A combination phase I trial of loncastuximab tesirine with an anti-PD-L1 agent durvalumab (NCT03685344) in R/R DLBCL, and FL was recently terminated as no additional activity was evident for the combination *vs.* loncastuximab

alone. Ongoing clinical trials evaluating this agent are being performed in DLBCL and mantle cell lymphoma (MCL).

*Other ADCs:* Other CD19 targeting ADCs previously evaluated are denintuzumab mafodotin (SGN-CD19A) bound to monomethyl auristatin F payload and coltuximab ravtansine (SAR3419) conjugated to potent cytotoxic maytansinoid drug DM4 (45,46). Both the payloads affect microtubule assembly and have ocular side effects (47). Coltuximab ravtansine in the first in human phase I study of 39 patient cohort with R/R B-NHL (44% FL) showed a decrease in tumor size in 74% of patients (48,49). Currently, no ongoing trials are evaluating these two drugs.

Two ADCs targeting CD22 antigen, inotuzumab ozogamicin, and pinatuzumab vedotin have been evaluated in R/R B-NHL, including FL patients. Inotuzumab ozogamicin is an IgG4 anti-CD22mAb with calicheamicin payload, an enediyne antibiotic, and induces DNA damage and cell apoptosis (50). Inotuzumab, when combined with rituximab in a phase I/II trial for R/R B-NHL (119 patients), had an ORR of 87% in the FL cohort (35%) (51). This combination did not show a significant difference when tested in the randomized phase III setting in R/R CD22+ B-NHL (52). Another phase III trial of this agent (NCT00562965) plus rituximab in FL was terminated early due to poor enrollment. Pinatuzumab vedotin, targeting CD22, has the MMAE payload. In the ROMULUS phase II study, R/R FL and DLBCL patients received a combination of rituximab with either pinatuzumab or polatuzumab. The FL patients (n=21) in the pinatuzumab arm, had ORR and CR rates of 62% and 5%, respectively. The most common grade 3–5 AEs were neutropenia and hyperglycemia (39). This drug has not moved forward in trials as polatuzumab vedotin had slightly better outcomes and was preferred.

Other surface antigens currently under investigation are CD37, CD40, CD74, and CD80. The results and toxicity profile of targeting mAbs and completed study results, and ongoing studies are shown in *Tables 1* and *2*.

### **Bispecific antibodies**

A bispecific antibody contains two antigen-binding sites: one directed against a receptor that activates cytotoxic cells and the other against a specific antigen expressed by tumor cells. It is engineered to target both the malignant cell and CD3+ T-cells, bringing them in close proximity for activation of the effector T-cells. It consists of variable domains of two antibodies, one targeting CD3+ cytotoxic T-cells and the other surface antigen such as CD19 or CD20 on the B-NHL

**Table 1** Completed studies with results of novel monoclonal antibodies, and antibody-drug conjugates in follicular lymphoma

Trial	Drug	Target	Phase	Disease setting	Results
NCT01059630 (20) (GADOLIN)	Obinutuzumab + Bendamustine vs. bendamustine	CD20	III	R/R B-iNHL	PFS – median NR vs. 14.9 months
NCT01332968 (21) (GALLIUM)	Obinutuzumab vs. rituximab based chemo	CD20	III	Untreated FL	PFS- 3-year: 80% vs. 73.3%
NCT01647971 (26)	Ublituximab	CD20	I/II	R/R B-NHL or CLL	ORR/CR in FL – 42%/17%
NCT02006485 (27,29)	Ublituximab in combination with umbralisib +/- ibrutinib or bendamustine in patients with B-cell malignancies	CD20	I	R/R B-NHL or CLL	ORR/CR Ublituximab, umbralisib, ibrutinib, 84%/30%; ublituximab, umbralisib, 46%/17%
NCT00553501 (38)	Epratuzumab + rituximab	CD22	II	Untreated FL	ORR/CR – 88.2%/42.4%
NCT01685008 (30)	Tafasitamab	CD19	II	R/R B-NHL	FL- ORR/CR: 29%/9%
NCT00103779 (53)	Dacetuzumab	CD40	I	R/R B-NHL	FL- ORR/CR: 12%/2%
NCT02669017 (44)	Loncastuximab teserine	CD19	I	R/R B-NHL	FL, ORR- 88%
NCT00299494 (51)	Inotuzumab ozogamicin + rituximab	CD22	I/II	R/R B-NHL	FL- ORR/CR: 87%/62%
NCT00868608	Inotuzumab ozogamicin	CD22	II	CD22+ R/R B-iNHL	FL- ORR/CR: 71%/35%
NCT00717925 (54)	Inotuzumab ozogamicin	CD22	I	R/R FL	ORR/CR: 85%/54%
NCT01290549	Polatuzumab vedotin ± rituximab	CD79	I	R/R B-NHL/CLL	Single agent Pola in iNHL ORR/CR: 56%/16%
NCT01691898 (39)	Polatuzumab vedotin + rituximab/ obinutuzumab, pinatuzumab vedotin + rituximab	CD79	I/II	R/R DLBCL, FL	R-Pina 60%/5% R-Pola 70%/45%
NCT00048555 (55)	Galiximab, rituximab	CD80	I/II	R/R FL	ORR/CR: 66%/19%
NCT00575068 (56)	Galiximab	CD80	I/II	R/R FL	ORR/CR: 11%/6%

R/R, relapsed/refractory; NHL, non-Hodgkin lymphoma; iNHL, indolent NHL; HL, Hodgkin lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PR, partial response; SD, stable disease.

cells (57-59). These bispecific antibodies are of various designs, which determines their mechanism of action (60). The majority of bispecific antibodies engage immune cells to destroy tumor cells. One such antibody is blinatumomab, the initial CD19/CD3 bispecific T-cell engager (BiTE) evaluated in R/R B-NHL, showed promising efficacy within the FL cohort (28 patients), with an ORR of 80% and a CR rate of 40% (61). The toxicities, although short-lasting and overall tolerable, were unique such as cytokine release syndrome (CRS) seen in 75% and neurotoxicity in 18% of patients. Phase II (NCT02811679) and phase Ib trials (NCT02961881) are still ongoing in R/R indolent B-NHL.

*Mosunetuzumab*, a CD20/CD3 bispecific antibody, has shown promising efficacy in the heavily pre-treated R/R B-NHL. Data presented at ASH annual meeting in 2019

from the phase I/Ib study included 69 patients with FL, of whom five had received prior chimeric antigen receptor T-cell (CAR-T) therapy. The ORR and CR rates for the indolent NHL group were 64% and 42%, respectively. The CRs were also durable in the indolent NHL subset, with 93% of patients (25/27) who achieved CR remained in remission at data cut off (62). Responses were also noted in patients progressing post-CAR-T therapy. Most of the CRS and neurotoxicity AEs were grades 1–2 (28.4% and 44%, respectively). This data was further updated at ASH 2020 for patients with at least two prior systemic therapies for FL. The ORR was 68% (42/62), with a 50% CR rate. A consistent CR rate (53%) was observed even in patients who progressed within 24 months of front-line therapy. The median duration of response was 20.4 months

**Table 2** Ongoing studies with completion dates of novel monoclonal antibodies, and antibody-drug conjugates in follicular lymphoma

Trial	Drug	Target	Phase	Disease setting	Estimated completion date
NCT04508647	Ublituximab + Umbralisib	CD20	II	Untreated FL and MZL	December 2023
NCT03828448	Ublituximab + Umbralisib	CD20	II	Treatment naïve FL and SLL	February 2023
NCT02793583	Ublituximab + TGR-1202 With or Without Bendamustine and TGR-1202 Alone	CD20	IIb	R/R B-NHL	July 2022
NCT01744912	Ublituximab + lenalidomide	CD20	I/II	R/R B-NHL	Completed, results not available yet
NCT02006485	Ublituximab +TGR-1202, with or without ibrutinib or bendamustine	CD20	I/Ib	R/R B-NHL	Completed, results not available yet
NCT00983619	Inebilizumab ± rituximab	CD19	I/II	R/R B-NHL	Completed, results not available yet
NCT00556699	Dacetuzumab + rituximab	CD40	Ib	R/R FL, MZL	Completed, results not available yet
NCT02257567	Polatuzumab vedotin + Bendamustine + rituximab/obinutuzumab	CD79	Ib/II	R/R DLBCL, FL	October 2021
NCT02600897	Polatuzumab vedotin + obinutuzumab + lenalidomide	CD79	Ib/II	R/R DLBCL, FL	February 2022
NCT02729896	Polatuzumab vedotin + obinutuzumab + atezolizumab	CD79	Ib/II	R/R DLBCL, FL	Completed, results not available yet
NCT02611323	Polatuzumab vedotin + obinutuzumab + venetoclax	CD79	Ib/II	R/R DLBCL, FL	December 2021
NCT03671018	Polatuzumab vedotin + mosunetuzumab	CD79	Ib/II	R/R DLBCL, FL	Jun 2022
NCT01786135	Denintuzumab mafodotin (SGN-CD19A)	CD19	I	R/R B-NHL	Completed, results not available yet
NCT03685344	Loncastuximab Tesirine and Durvalumab	CD19	I	R/R DLBCL, FL, MCL	Terminated early, no additional activity over loncastuximab monotherapy

R/R, relapsed/refractory; NHL, non-Hodgkin lymphoma; iNHL, indolent NHL; HL, Hodgkin lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PR, partial response; SD, stable disease.

(95% CI: 11.7–not reached) for all 42 responders (63). The subcutaneous (SC) administration of this drug as an alternative to minimize CRS risk was evaluated in the phase I/Ib, open-label, multicenter dose-escalation, and expansion study in R/R B-NHL. Five of the 23 patients in this study had R/R FL, with a median of 4 prior lines of therapy in the total cohort. The majority of CRS events were seen in Cycle 1 and were mild, transient, and required minimal intervention. There were no grade  $\geq 3$  CRS events, and less frequent grade 2 CRS events were observed with

SC dosing even at 7-fold higher dose levels versus the IV fixed-dosing group (64). Mosunetuzumab is currently under evaluation in various combination studies (*Table 3*) with agents such as polatuzumab vedotin (NCT03671018), CHOP chemotherapy (NCT03677141), lenalidomide (NCT04246086), and atezolizumab (NCT02500407) in B-NHL, including FL.

*REGN1979 (odronextamab)* is another promising IgG4 CD20/CD3 bispecific antibody in development. Treatment consists of 12 weekly intravenous doses of REGN1979

followed by every 2-week dosing for 12 doses (36 weeks total). Data presented in 2019 from the phase I study included heavily pre-treated patients with B-NHL (25 patients with grade 1–3a FL). An ORR of 95.5% and a CR rate of 77.3% were reported from the 22 evaluable FL patients that received  $\geq 5$  mg of the REGN1979. FL patients treated with  $\geq 80$  mg of this bispecific antibody had 100% ORR. With a median follow-up of 6.8 months in the FL group, the median PFS in the FL cohort was 11.4 months (95% CI, 6.7–not evaluable). At the time of data cutoff, 14/21 responses were ongoing, and 12/17 CRs were maintained (65). This was further updated at ASH 2020 and included 37 patients with FL grade 1–3a. In patients treated with  $\geq 5$  mg of the REGN1979 ( $n=28$ ), the ORR was 92.9%, and CR rate was 75%, with a median duration of response of 7.7 months (66). The most common AEs were fever (80%), and CRS (59.1%); most common grade 3–4 AEs were anemia (22%), lymphopenia (19%), neutropenia (19%) and hypophosphatemia (19%). Most of the neurological events were grade 1–2, and neurological AEs did not cause any treatment discontinuations. REGN1979 is currently in evaluation in R/R B-NHL in combination with cemiplimab (anti-PD-1 mAb, NCT02651662); a global multi-arm trial is under development.

*RO7082859 (glofitamab)*, is a novel T-cell-engaging, bispecific, full-length antibody with a 2:1 molecular configuration that facilitates bivalent binding to CD20 on B-cells and monovalent binding to CD3 on T-cells. Its binding pattern can increase tumor antigen avidity, cause rapid T-cell activation, and enhanced tumor cell killing versus other bispecific formats (67). It is currently under evaluation in a phase I/Ib multicenter, dose-escalation study as a single agent and in combination with obinutuzumab in R/R B-NHL (NCT03075696). Obinutuzumab pre-treatment has been shown to mitigate the risk of CRS with this agent, to allow for rapid step-up dosing (68). Data from the monotherapy dose-escalation arm which had 14 FL patients, showed an ORR in all FL patients of 77%, and 88% in the higher dose cohort (68). The latest data presented at ASH 2020 included 52 patients (24 indolent NHL), with an ORR of 66.7% and 54.2% CR rate in the indolent NHL cohort. The most common AEs in the entire cohort were CRS (63.5%), neutropenia (38.5%), thrombocytopenia, and hypophosphatemia. No treatment discontinuations occurred due to AEs (69). CRS events were only observed in cycles 1 and 2 with a median time to CRS of 14.23 hours after administration of glofitamab and a median duration of 28.7 hours. Tocilizumab was used to

manage CRS for 15.4% of patients. Grade  $\geq 2$  CRS events were reduced in the step-up dosing cohorts compared to the fixed dosing cohorts (36.3% vs. 30.7%).

GEN3013 (*epcoritamab*) is a novel, SC administered CD20/CD3 bispecific antibody studied in an open-label, phase I/II trial (NCT03625037). It is given as an SC 1-mL injection of flat-dose epcoritamab in 28-day cycles (q1w: cycles 1–2; q2w: cycles 3–6; q4w thereafter) until disease progression or unacceptable toxicity. Of the 67 patients enrolled, 12 had FL grade 1–3a, with 4.5 (range, 1–18) median prior lines of therapy. There were no dose-limiting toxicities or febrile neutropenia events and no deaths due to treatment-related AEs. The CRS events were all grade 1–2 (58%) in the entire cohort with no grade  $\geq 3$  events. The most common AEs were pyrexia (70%), local injection-site reaction (48%), and fatigue (45%). The ORR was 100% for the 8 pts with FL receiving epcoritamab  $\geq 0.76$  mg, with 2 pts achieving a CR (PET scans were not mandatory and disease assessment by PET was not available in 4/6 pts who achieved a PR) (70).

Bispecific antibodies provide the advantage of being readily available as off-the-shelf products when compared to autologous CAR-T therapy, which takes a few weeks to manufacture. However, long term data are required for assessing the durability of these agents (Table 3). Additionally, where in the treatment armamentarium these agents will provide the most benefit also remains unclear at this time, given concerns for CD20 antigen escape as a mechanism of resistance in heavily pre-treated patients. Subcutaneous dosing is emerging as the preferred method for its ease of administration and improved safety profile with much fewer grade  $\geq 3$  CRS events making these agents a very attractive therapeutic option.

### CAR-T therapy

CD19 targeting CAR-T therapy has had a significant impact on the outcomes of R/R aggressive B-NHL, with patients achieving durable remissions in an otherwise poor prognostic group of patients (71–74). It is yet to be known whether such durable remissions can be achieved in indolent lymphomas such as FL and its relative efficacy compared to other novel agents available for treatment. The possibility of long term remission also offers the benefit of potentially avoiding exposure to several treatments required with multiple relapses. Younger FL patients progressing within 24 months of initial chemoimmunotherapy (PFS24) is another situation where there is a need for effective

treatments. The toxicities associated with CAR-T therapy are unique such as CRS and neurotoxicity and are more pronounced than those seen with bispecific mAbs. Interim analysis of phase II multicenter trial of axicabtagene ciloleucel (axi-cel), ZUMA-5, enrolled R/R indolent B-NHL patients (FL and MZL). Eighty of the 94 patients were R/R FL patients, the median number of prior therapies was 3, with 66% patients not achieving PFS24 status. Impressive efficacy of CAR-T therapy was seen in this trial with an ORR of 95% and 80% achieving CRs in the FL cohort. The median duration of response was 20.8 months, and the median PFS was 23.5 months. Median OS was not reached in the group. Notable grade  $\geq 3$  AEs were neutropenia (33%), anemia (28%), CRS (11%), and neurotoxicity (19%) (75). Based on this data, an FDA approval application has been submitted for axi-cel in R/R FL.

The phase II ELARA trial of tisagenlecleucel in R/R FL patients was presented at ASH 2020. This trial included 97 patients who received tisagenlecleucel, and 52 patients were evaluable for efficacy with a median follow-up of 9.9 months. The median number of prior lines of therapy was 4 (range, 2–13), including prior autologous transplant in 36%, a FLIPI score  $\geq 3$  in 60%, and 43% required bridging therapy. The ORR was 82.7% (43/52), with a CR rate of 65.4% (34/52) in the intent-to-treat population. For those achieving CR as the best response, the probability of response over six months was 89.7%. The median duration of response, PFS, OS, and time to next lymphoma treatment were not reached. The safety analysis included all 97 patients, of which 68% experienced grade  $\geq 3$  AEs. The CRS rate was 48% for all grades, with no grade  $\geq 3$  events. Any grade neurotoxicity events were noted in 10% of patients, of which 2% were grade  $\geq 3$ . No treatment-related deaths were seen in the trial so far, while 3 patients died from progressive disease (76). Where CAR-T therapy will fit in the treatment landscape for FL patients to ensure maximum benefit is yet to be determined. We anticipate that the coming decade will see a significant upsurge of clinical trials with these cellular therapies to determine their place in the management algorithm of FL treatment.

### Monoclonal antibodies targeting immune cells

Immune cells present within the tumor microenvironment of FL play an important role in lymphomagenesis, cell survival, and progression. One of the mechanisms by which the lymphoma cells evade an antitumor immune surveillance is by the upregulation or overexpression

of immunosuppressive ligands on the tumor cells or on other cells in the tumor microenvironment (3,77,78). Overexpression of programmed death-ligand 1 (PD-L1; CD274) and PD-L2 (CD273) by malignant lymphoma cells is one such mechanism. As T-cells become activated, they express PD-1 to avoid over activation. The immunosuppressive ligands on the lymphoma cells, namely PD-L1 and PD-L2, signal through PD-1 to inhibit T-cell function and promote immune exhaustion, which ultimately results in T-cell apoptosis. Other immune-inhibitory receptors such as T-cell immunoglobulin mucin-3 and lymphocyte-activation gene 3, which are also found to be expressed on the T cells in the microenvironment and are associated with immune exhaustion (79–81). While the FL cells themselves do not overexpress program death-ligand 1 (PD-L1), they can modulate the microenvironment such that intratumoral effector T-cells are exhausted, and macrophages are polarized towards a suppressive environment (79,82–87). Also, the upregulation of PD-1 has been shown on the intratumoral and peripheral blood CD4 and CD8+ T-cells (88,89). Several mAbs targeting PD-1 or its ligand PD-L1, and other checkpoints are under evaluation as monotherapy or in combination in FL are shown in *Table 4*.

### PD-1/PD-L1

*Nivolumab*, a PD-1 blocking mAb, showed ORR up to 40% with a relatively favorable toxicity profile in the initial studies in patients with FL (90). However, these results were not recapitulated in the phase II trial in a larger cohort of R/R FL patients. CheckMate 140 evaluated nivolumab monotherapy efficacy and safety in R/R FL patients who had progressed after at least 2 prior lines of therapy, including a CD20 mAb and an alkylating agent. The ORR (which was the primary endpoint) was 4% (4/92), with a median PFS of 2.2 months (95% CI, 1.9–3.6) (91). In an attempt to improve on these results, the combination of nivolumab with rituximab in a phase II trial for previously untreated FL patients is ongoing (NCT03245021). Other ongoing combination studies include drugs such as lenalidomide (NCT03015896) and copanlisib (NCT04431635).

*Pembrolizumab*, another PD-1 blocking mAb like nivolumab, had disappointing single-agent efficacy with an ORR of 11% based on the partial response in 2 patients and median PFS of 3.4 months (95% CI, 2.1–5.7) in the entire cohort in a phase II trial (96). The combination of pembrolizumab with rituximab appeared more effective in a

**Table 3** Resulted and ongoing studies evaluating BiTEs/bispecifics in follicular lymphoma

Trial	Drug	Target	Phase	Disease setting	Result/completion date
NCT00274742 (61)	Blinatumomab	CD19/CD3	I	R/R B-NHL	FL, ORR- 80%, CR -40%
NCT02811679	Blinatumomab	CD19/CD3	II	R/R B-iNHL	December 2023
NCT02568553	Blinatumomab + lenalidomide	CD19/CD3	I	R/R B-NHL	December 2020
NCT04246086	Mosunetuzumab + Lenalidomide, Glofitamab + lenalidomide or Glofitamab + lenalidomide + obinutuzumab	CD20/CD3	Ib	R/R FL	August 2022
NCT03677141	Mosunetuzumab + CHOP (M-CHOP), or M-CHP-Polatuzumab vedotin	CD20/CD3	Ib/II	R/R B-NHL	June 2022
NCT02500407	Mosunetuzumab ± Atezolizumab	CD20/CD3	I/Ib	R/R B-NHL, CLL	October 2021
NCT02651662	Odronektamab (REGN1979) + cemiplimab	CD20/CD3	I	R/R B-NHL, HL	October 2021
NCT02290951	Odronektamab (REGN1979)	CD20/CD3	I	R/R CD20+ B-cell malignancies	April 2025
NCT03888105	Odronektamab (REGN1979)	CD20/CD3	Open-label	R/R B-NHL	August 2026
NCT03075696	Glofitamab (RO7082859) ± obinutuzumab	CD20/CD3	I	R/R B-NHL	June 2022
NCT03533283	Glofitamab (RO7082859) + atezolizumab or polatuzumab vedotin	CD20/CD3	Ib	R/R B-NHL	August 2021
NCT03467373	Glofitamab (RO7082859) + R-CHOP	CD20/CD3	Ib	R/R B-NHL, Untreated DLBCL	December 2023
NCT04077723	Glofitamab (RO7082859) + RO7227166	CD20/CD3 RO7227166 (CD19, 4-1BB ligand)	I	R/R B-NHL	January 2023
NCT02924402	XmAb13676	CD20/CD3	I	R/R B-NHL, CLL	October 2025

R/R, relapsed/refractory; NHL, non-Hodgkin lymphoma; iNHL, indolent NHL; HL, Hodgkin lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PR, partial response; SD, stable disease.

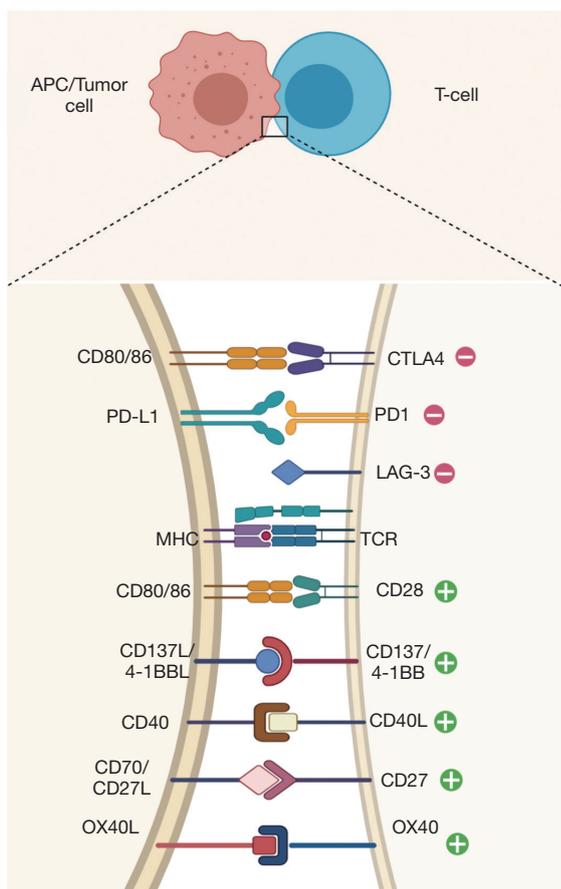
30 patient study with R/R FL with ORR of 64% and a CR rate of 48%, suggesting a possible synergistic effect (93).

Other mAbs targeting the PD-1/PD-L1 pathway have shown similar results as monotherapy. A phase I study of atezolizumab (PD-L1) with 3 patients in the FL cohort had only 1 partial response (97). Higher efficacy was seen with atezolizumab in combination with obinutuzumab (26 FL, ORR 57%) and with both obinutuzumab and lenalidomide in a phase Ib/II study (NCT02631577) (29 patients, ORR 85%) (98,99). Other combination studies are ongoing, combining PD-1/PD-L1 blocking mAbs with ibrutinib,

venetoclax, chemotherapy, histone deacetylase (HDAC) inhibitors, or other immunotherapies (Table 4).

#### **Other costimulatory/checkpoint molecules**

Several other checkpoint molecules and costimulatory molecules are involved in the process of tumor antigen presentation and T-cell activation (Figure 2). Given the low clinical benefit of PD-1/PD-L1 as monotherapy in FL, other molecules and combinations are under investigation as potential targets. CD27 is a costimulatory



**Figure 2** T-cell and tumor cell interaction with various checkpoints/costimulatory molecules. The figure was developed by Arushi Khurana, using BioRender (Toronto, ON, Canada).

molecule on T-cells, and by interacting with its ligand CD70, it promotes T-cell activation. A CD27 agonist mAb varlilumab (CDX-1127) is under investigation in B-NHL and has shown clinical efficacy in early phase trials (6 FL of 25 B-NHL patients) (95). Combination phase II trials of varlilumab with nivolumab and rituximab are ongoing in R/R B-NHL (100,101). 4-1BB (CD137) is another costimulatory molecule present on the CD8+ T-cells which is being explored as a potential target (102). Urelumab, a fully human, CD137 agonist IgG4 mAb, showed increased hepatic toxicities in solid tumors (103,104). In R/R B-cell NHL, the results from two phase I studies (NCT01471210, NCT01775631) of urelumab alone and in combination with rituximab (n=60), showed an ORR and disease control rate in the FL cohort (n=17) of 12% and 35%, respectively (105). Utolimumab, another 4-1BB targeting IgG2 mAb, was studied in combination with rituximab in R/R B-NHL

(33 FL). Within the FL cohort, 24/33 patients were rituximab-refractory; and the ORR in the entire FL cohort and the rituximab refractory cohort was 27% (9/33) and 33% (8/24), respectively (106). Unlike urelumab, no dose-limiting toxicities or hepatic toxicities were seen with this agent. Another costimulatory molecule CD40 was targeted using dacetuzumab, an IgG1 mAb in R/R B-NHL, in a phase I study (53). Monotherapy efficacy of dacetuzumab was not substantial, and a combination study with rituximab in indolent NHL (NCT00556699) is awaiting results.

The results from checkpoint inhibitor or costimulatory agonist mAb trials suggest that the efficacy of monotherapy remains low, and further steps need to be taken to improve outcomes in FL patients. Future strategies will need to include combination studies with agents that show synergy while maintaining a favorable toxicity profile and identifying specific predictive biomarkers associated with these agents to better select patients within the FL subset.

### CD47/SIRP $\alpha$

CD47 and its ligand signal regulatory protein alpha (SIRP $\alpha$ ) are part of the innate immune system and play an important role in the anti-tumor immune response. CD47 is upregulated in B-NHL, including FL, and is responsible for sending a “don’t eat me” signal to the innate immune system cells such as macrophages (107,108). The CD47/SIRP $\alpha$  blocking mAb, Hu5F9-G4 combined with rituximab demonstrated an ORR of 71% and a CR rate of 43% in the FL subset (94). At a median follow-up of 8.1 months in the FL cohort, 91% of patients maintained their response. Another anti-CD47 agent, TTI-621 (SIRP $\alpha$ Fc), consists of the CD47 binding domain of SIRP $\alpha$  linked to the Fc region of human IgG. This agent is designed to engage the Fc $\gamma$  receptors on the macrophages and block the CD47 negative signaling, thereby activating macrophage-mediated phagocytosis (109). It is currently under investigation as monotherapy or in combination with rituximab (NCT02663518) in various lymphoma types, including FL; and results for this subset are awaited (110).

### Immunomodulatory drugs (IMiDs)

The IMiDs deserve a special mention as lenalidomide with rituximab is an approved indication for R/R FL patients. The IMiDs, by binding to cereblon, an E3 ubiquitin ligase, promote degradation of Ikaros and Aiolos transcription regulators of B- and T-cell development (111). This results

**Table 4** Resulted and ongoing studies evaluating checkpoint inhibitors, and costimulatory agonists in follicular lymphoma

Trial	Drug	Target	Phase	Disease setting	Result/completion date
NCT01592370 (90)	Nivolumab	PD-1	I	R/R NHL	FL ORR/CR, 40%/10%
NCT02038946 (91)	Nivolumab	PD-1	II	R/R FL	ORR 4%
NCT02329847 (92)	Nivolumab + ibrutinib	PD-1	I/IIa	R/R NHL, CLL	FL ORR- 33%
NCT03245021, 1st FLOR Study	Nivolumab + rituximab	PD-1	I	Untreated FL	June 2024
NCT04431635	Nivolumab + rituximab + copanlisib	PD-1	Ib	R/R B-iNHL	June 2026
NCT04205409	Nivolumab post CAR-T	PD-1	II	Relapse post CAR-T in hematological malignancies	August 2022
NCT03015896	Nivolumab + lenalidomide	PD-1	I/II	R/R B-NHL, HL	December 2020
NCT02446457 (93)	Pembrolizumab + rituximab ± lenalidomide	PD-1	II	R/R FL	Pembro + rituximab arm: ORR- 80%, CR-60%
NCT02950220	Pembrolizumab + ibrutinib	PD-1	I/Ib	R/R B-NHL	Completed, results not available yet
NCT02677155	Pembrolizumab + sequential intranodal immunotherapy	PD-1	II	Untreated and R/R FL	January 2024
NCT03150329	Pembrolizumab + vorinostat	PD-1	I	R/R DLBCL, FL, HL	July 2020, recruiting status
NCT03498612	Pembrolizumab	PD-1	II	Untreated B-NHL	September 2024
NCT02332980	Pembrolizumab ± ibrutinib or idelalisib	PD-1	II	R/R B-iNHL, CLL	January 2022
NCT01953692 KEYNOTE-013	Pembrolizumab	PD-1	Ib	Advanced hematological malignancies	Completed, results not available for FL
NCT03210662	Pembrolizumab + radiation	PD-1	II	R/R NHL	November 2020
NCT03035331	Pembrolizumab + dendritic cell therapy, cryosurgery	PD-1	I/II	R/R NHL	February 2021
NCT02953509 (94)	Magrolimab (HuF59-G4) + rituximab ± chemotherapy	CD47	Ib/II	R/R B-NHL	FL ORR/CR, 71%/43%
NCT04599634	Magrolimab (HuF59-G4) + venetoclax + obinutuzumab	CD47	I	R/R B-iNHL	June 2025
NCT02663518	TTI-621	CD47	Ia/Ib	R/R hematological malignancies	June 2021
NCT03530683	TTI-622	CD47	Ia/Ib	R/R NHL, HL or myeloma	December 2022
NCT01460134 (95)	Varlilumab	CD27	I	R/R hematological malignancies	FL, ORR 3/6 patients with SD, no PR
NCT03307746	Varlilumab + rituximab	CD27	IIa	R/R B-NHL	September 2022
NCT02927964	SD-101 + ibrutinib + radiation	TLR9	Ib/II	R/R FL	November 2021
NCT03410901	SD-101 + BMS986178 + radiation	TLR9/OX40	I	R/R B-iNHL	October 2020
NCT02061761	BMS-986016 ± nivolumab	LAG-3	I/IIa	R/R B-NHL	January 2021

R/R, relapsed/refractory; NHL, non-Hodgkin lymphoma; iNHL, indolent NHL; HL, Hodgkin lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; PR, partial response; SD, stable disease.

in the stimulation of effector T and NK cells and the improvement of ADCC when combined with rituximab (112). Also, the IMiDs, especially lenalidomide, have been shown to affect the immune cells present in the tumor microenvironment in generating an antitumor response (113,114). It augments the effector function of CD8 T-cells, increases immune synapse formation, and antigen presentation by dendritic cells. It also affects the innate immune system by increasing the NK cell numbers and activity and direct NK cell killing. Lastly, it decreases the pro-inflammatory cytokines such as interleukin (IL)2, IL 6, IL12, and tumor necrosis factor  $\alpha$ , while increasing the anti-inflammatory cytokines such as IL-10.

The phase III RELEVANCE trial showed similar 3-year PFS rate, ORR, and CR rates between R2 and R-chemo arms in newly diagnosed FL, which makes a compelling argument for its use in the upfront setting as a non-chemotherapy regimen (10). In the relapsed setting phase III, the AUGMENT trial compared R2 *vs.* rituximab in marginal zone lymphoma (MZL) and FL (n=147) and met its primary endpoint of improvement in PFS while maintaining an acceptable safety profile (115). Several combination studies are ongoing using lenalidomide in FL to develop effective chemo-free regimens for FL. A newer IMiD currently under investigation is avadomide (CC-122) in B-NHL. In combination with obinutuzumab in a phase I study of R/R B-NHL (53/73 FL), the toxicity profile of avadomide was noted to be manageable, and the combination resulted in an ORR of 76%, with 43% patients achieving CR (116). Efficacy was also noted in rituximab-refractory patients when avadomide was combined with rituximab (117).

### Agents targeting BCR signaling and transduction pathways

BCR pathway is an appealing treatment strategy with multiple available targets from its downstream signaling mechanisms (118-120). These downstream signaling pathways are responsible for B-cell growth, proliferation, and survival and are critical in lymphomagenesis. Several components of the BCR pathway, such as BTK, PI3K already have effective inhibitors with proven benefits in R/R FL, with more agents in development. The inhibition of BCR pathway and off-target activity of BTK and PI3K inhibitors affects multiple components of the tumor microenvironment (77). BTK inhibitors decrease the expression of immunosuppressive markers such as PD-1,

increase the number of CD8 and CD4+ T-cells while also decreasing the fraction of regulatory T-cells, thereby promoting an anti-tumor response (121). The off-target activity of ibrutinib by inhibiting the IL 2 inducible kinase (ITK), promotes a T helper-1 based immune responses with more cytotoxicity than Th-2 based (122). PI3K inhibitors effect on immune cells in the microenvironment is dependant on the isoforms inhibited by the drug. PI3K inhibitors can downregulate the secretion of chemokines such as CXCL-12 and CXCL-13, thereby impairing the chemotaxis and adhesion of the lymphoma cells to the stromal cells, both promoting an anti-tumor response (123). The PI3K $\delta$  inhibition has been shown to impair the function of T-cells, including the T-regulatory cells, which likely resulted in immune-mediated AEs and increased infection rates seen with idelalisib (124). While inhibition of PI3K $\gamma$  isoform polarize tumor-associated macrophages to an anti-inflammatory M1-like state from a protumoral M2 state that restricts tumor expansion (125,126).

### Phosphoinositide 3- Kinase (PI3K) Inhibitors

The PI3K enzymes exist in four different isoforms. Their relative distribution within different tissues helps predict their activity and toxicity profile. While PI3K $\alpha$  and  $\beta$  are present on the majority of the tissues, PI3K $\delta$  and  $\gamma$  are limited predominantly to hematopoietic cells (127-129). Idelalisib, a PI3K $\delta$  inhibitor, received accelerated FDA approval for R/R FL patients after  $\geq 2$  lines of therapy (both rituximab and an alkylating agent) in 2014. This was based on the phase II trial, which included 72 FL patients, with ORR of 57%, CR rate of 6%, and median PFS of 11 months (130). Significant side effects (grade  $\geq 3$ ) with idelalisib included neutropenia, transaminitis, diarrhea, and pneumonia. Despite the side effect profile, the approval of idelalisib was thought to be significant due to a lack of options for treatment of such refractory FL patients. Copanlisib, an intravenous (i.v) pan-PI3K inhibitor, with a predominant effect on PI3K $\alpha$  and  $\delta$  isoforms, received accelerated FDA approval for R/R FL in 2017. In the CHRONOS 1 part B study with 104 FL patients, ORR was 58% with a 14% CR rate. The treatment-related AEs were unique with (all grades) hyperglycemia (49%) and hypertension (29%) owing mostly to inhibition of PI3K $\alpha$  isoform (131). The immune-mediated AEs were much fewer than idelalisib, mostly due to i.v dosing and the effect of hepatic first-pass metabolism. A phase III randomized, double-blind, combination study of rituximab with or

without copanlisib in indolent NHL (n=458) in second-line therapy was recently announced to have met its primary endpoint of PFS (CHRONOS 3) (132). Duvelisib, inhibits both the PI3K $\delta$  and  $\gamma$  and was shown to have an ORR of 42% in R/R FL patients in the DYNAMO study (133). Its side effect profile appeared to be similar to that of idelalisib. Combination trials of duvelisib in FL have been terminated early or withdrawn by the sponsor to focus on studies that can enable the registration of duvelisib (CLL). Umbralisib, a unique PI3K $\delta$  inhibitor with fewer side effects than other PI3K $\delta$  inhibitors, is currently in clinical trials in various combinations. Phase I monotherapy trial (24% FL) showed an ORR of 53%, with 12% CR (134). Multiple combination studies are ongoing in FL with umbralisib.

### ***Bruton Tyrosine Kinase Inhibitors (BTKi)***

BTKi, while having a direct anti-tumoral effect on the survival of the malignant B-cells, also affect the T-cells in the lymphoma microenvironment. They decrease the expression of inhibitory molecules such as PD-1/CTLA-4 while simultaneously enhancing the effector and memory function of T-cells (121). They have also been shown to decrease inflammatory cytokines, reverse T-cell exhaustion, and disrupt the stromal-tumor interactions mediated by chemokines and cell adhesion (135). In addition, BTKi, in combination with PD-L1 blockade has been shown in mouse models to be synergistic (136,137). Single-agent ibrutinib in a phase I study (16/56 FL patients) showed an ORR of 37% with a favorable toxicity profile (138). A similar ORR was seen in a phase 2 study in R/R FL patients (n=40), with a median PFS of 14 months and a 2-year PFS rate of 20.4%. Patients that were rituximab sensitive were noted to have a better response to ibrutinib (139). Monotherapy efficacy of ibrutinib was not considered significant to be further pursued as a single agent in the R/R setting. However, given its effect on the lymphoma microenvironment, multiple combination strategies have been developed and are under investigation. Ibrutinib plus rituximab in treatment-naïve FL patients was investigated in a multicenter phase II study, evaluating two different treatment schedules for the combination. Arm 1 with concurrent administration had an ORR of 85%, with a 35% CR rate, and arm 2 with an 8-week lead-in phase of ibrutinib had an ORR of 75%, with 35% CRs as well (140). The most common grade  $\geq 3$  AEs were rash (10%), fatigue (7%), and fever (10%). A randomized phase III trial (NCT02947347) of rituximab with or without ibrutinib

is ongoing in untreated FL. Another combination of ibrutinib, rituximab, and lenalidomide was explored in the phase I (Alliance A051103) setting in newly diagnosed FL. Although the ORR in the 22 patients was 95% and the 1-year PFS was 80%, this regimen showed a significant rate of dose-limiting rash, with 82% of patients experienced a rash of any grade (36% grade 3) and half of the patients requiring a dose reduction (141). The efficacy was similar to R2 in this setting with significantly more toxicity and dose modifications, and therefore this combination is no longer moving forward in this setting. When combined with BR in a phase 1b study for both previously untreated and R/R B-NHL, the combination was found to be safe and tolerable with a 50% CR rate in the FL cohort (142). There is an ongoing combination study in previously untreated FL, including ibrutinib in combination with either BR or R-CHOP (NCT01974440). Other more specific BTKi such as acalabrutinib, and zanubrutinib while approved for other lymphoma types, are currently under investigation in FL.

### **Conclusions**

The natural history of indolent B-NHL, such as FL, has significantly benefitted from the advances in therapeutics. The treatment options for FL continue to expand with the introduction of novel immunotherapies described in this review. Ongoing studies will further advance the understanding of disease biology, mechanisms of resistance, and the role of microenvironment. However, the challenge is identifying the most strategic ways of combining, sequencing, and predicting the response to these newer therapies while minimizing the toxicities and potentially aiming for a cure. Research is also needed to evaluate the financial and quality of life implications of such newer therapies while making them accessible to those most in need.

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