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Lymphoma (JL Muñoz, Section Editor)

# Novel Therapies for Follicular Lymphoma and Other Indolent Non-Hodgkin Lymphomas

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## Opinion statement

When selecting therapy for patients with indolent non-Hodgkin lymphoma (iNHL) including follicular (FL), marginal zone (MZL), small lymphocytic (SLL), and lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (WM), there are several factors to consider. With a median age around 70 at diagnosis, many patients have accumulated comorbid conditions that may limit treatment options. Although incurable for most, iNHL is a chronic disease with a median overall survival measured in years to decades. This long natural history changes the risk-to-benefit balance with a lower acceptance of toxicity early in the treatment course compared to that of aggressive lymphomas. Despite a recent rapid increase in available therapies, overall progress in iNHL has been slow for several reasons. Initial trials grouped iNHLs together making it challenging to appreciate the differential activity among subtypes. We have not been able to develop prognostic models that maintain validity in the era of chemotherapy-free options. Predictive markers have been elusive and without identified molecular signatures, it is challenging to select and sequence therapy. With these clinical factors in mind, in addition to the heterogeneity among and within iNHLs, I do not have a standard treatment algorithm and feel each patient should

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have an individualized treatment approach. This review focuses on recent updates and controversies in the management of iNHL with a focus on FL and MZL.

## Introduction

The field of lymphoma oncology is becoming increasingly complex as we transition into the personalized medicine era. Not only are more treatment options becoming available, but lymphomas are being further subclassified with nearly 100 subtypes in the most recent World Health Organization classification [1]. One of the main challenges in iNHL is the absence of identified predictive markers to aide in treatment selection and sequencing.

Although chemoimmunotherapy (CIT) remains the preferred frontline option for most patients with FL requiring therapy, there is interest in shifting towards chemotherapy-free approaches. Marginal zone lymphoma subtypes are more variable, with the radiation therapy or rituximab monotherapy as the preferred frontline approach for extranodal (EMZL) and splenic (SMZL), and rituximab monotherapy or CIT the favored approach for treatment-naïve nodal marginal zone (NMZL).

A continued challenge in the frontline treatment of iNHL in patients with iNHL is the lack of predictive and prognostic markers that can identify those at increased risk of poor outcomes. The FL international prognostic index (FLIPI), FLIPI-2, and m7-FLIPI consider clinical and/or molecular features to help risk-stratify patients; however, significant heterogeneity remains among patients in various risk groups and these prognostic scores have different implications if applied to a patient treated with CIT versus a chemotherapy-free approach [2–4]. In the frontline setting, we are still unable to accurately identify patients at increased risk for early relapse, such as progression of disease within 2 years of frontline CIT (POD24), which remains an area of unmet need. Once these patients can be identified prior to starting therapy, novel approaches can be explored in an attempt to change the natural history of disease for these patients. In the relapsed or refractory (R/R) setting, CIT may be appropriate for a minority of patients, but a targeted approach is preferred for most. From June 2020 through March 2021, the Food and Drug Administration (FDA) granted accelerated approval for three new targeted therapies in R/R FL and one for R/R MZL. Chemotherapy-free options in R/R FL now include lenalidomide-based therapy, four different phosphoinositide 3-kinase (PI3K) inhibitors, tazemetostat, and anti-CD19 chimeric antigen receptor T cell (CAR-T) therapy. It has become clear that responses to targeted therapies are different among iNHL subtypes, and options for R/R MZL differ significantly from R/R FL. For example, ibrutinib is active across most iNHL subtypes and FDA-approved for R/R MZL, SLL, WM, and R/R MCL but due to disappointing efficacy is not approved in FL (Table 1, Figure 1).

Autologous and allogeneic stem cell transplantation remain options in select patients with iNHL, but the utilization of these cellular therapies is shifting with the availability of targeted options and CAR-T cell therapy. Many now debate the role of autologous stem cell transplantation in iNHL. Allogeneic stem cell transplantation remains a potentially curative option for select patients, however, is moving later in the treatment landscape due to the growing number of alternative options with favorable toxicity profiles.

# Treatment

## Chemoimmunotherapy

Chemoimmunotherapy remains an important treatment option for patients with iNHL, but use has evolved over the past decade. In the frontline setting,

**Table 1. Targeted therapies in indolent non-Hodgkin lymphomas**

| Agent | Mechanism | Phase | Population | CRR | ORR | Ref |
|---|---|---|---|---|---|---|
| **Lenalidomide** | | | | | | |
| Lenalidomide | Immunomodulatory agent | II | Tx-naïve iNHL + rituximab | 65 | 90 | [16] |
| | | | FL (*n* = 50) | 87 | 98 | |
| | | | MZL (***n*** = 30) | 67 | 90 | |
| | | III | RELEVANCE, R2 vs CIT (*N* = 1030) | | | [17•] |
| | | | FL, R2 (*n* = 513) | 48 | 61 | |
| | | II | Tx-naïve FL, + obinutuzumab | | | [21] |
| | | | FL (***n*** = 90) | | | |
| | | III | AUGMENT | | | [19••] |
| | | | RR iNHL R2 vs R-placebo (***n*** = 358) | 34 | 78 | |
| | | | FL (*n* = 295) | 35 | 80 | |
| | | | MZL(***n*** = 63) | 29 | 65 | |
| | | III | MAGNIFY | | | [20] |
| | | | RR iNHL, R2 (+/- MR), *n* = 370 | | | |
| | | | FL (***n*** = 296) | 46 | 74 | |
| | | | MZL (*n* = 74) | 38 | 65 | |
| | | I/II | R/R iNHL + obinutuzumab (***n*** = 66) | 72 | 98 | [22] |
| **PI3K inhibitors** | | | | | | |
| Idelalisib | PI3K-delta inhibitor, oral | II | RR iNHL | 6 | 57 | [24] |
| (CAL-101, GS-1101) | | | FL (***n*** = 72) | – | 54 | |
| | | | SLL (*n* = 28) | – | 61 | |
| | | | MZL (***n*** = 15) | – | 47 | |
| | | | WM/LPL (*n* = 10) | – | 80 | |
| Duvelisib | PI3K-gamma/delta inhibitor, oral | II | DYNAMO | | | |
| (IPI-145) | | | RR iNHL (***n*** = 129) | 2 | 47 | [25] |
| | | | FL (*n* = 83) | 1 | 42 | |
| | | | SLL (***n*** = 28) | 6 | 39 | |
| | | | MZL (*n* = 18) | 0 | 68 | |
| Umbralisib | PI3K-delta and CK1 inhibitor, oral | II | UNITY-NHL | | | |
| (TGR-1202) | | | RR iNHL | | | [29] |
| | | | FL (***n*** = 117) | 5 | 45 | |
| | | | MZL (*n* = 69) | 16 | 49 | |
| Copanlisib | PI3K-α/δ inhibitor, IV | II | CHRONOS-1 | | | |
| (BAY80-6946) | | | RR iNHL (***n*** = 142) | 12 | 59 | [27] |
| | | | FL (*n* = 104) | 14 | 59 | |
| | | | MZL (***n*** = 23) | 9 | 70 | |
| | | | SLL (*n* = 8) | 0 | 75 | |
| | | | LPL/WM (***n*** = 6) | 0 | 17 | |
| | | III | CHRONOS-3 | | | |

**Table 1** (continued)

| Agent | Mechanism | Phase | Population | CRR | ORR | Ref |
|---|---|---|---|---|---|---|
| | | | RR iNHL, + rituximab (*n* = 307) | 34 | 81 | [31] |
| | | | FL (***n*** = 184) | 37 | 85 | |
| | | | MZL (*n* = 66) | 39 | 76 | |
| | | | SLL (***n*** = 35) | 17 | 77 | |
| | | | LPL/WM (*n* = 22) | 18 | 68 | |
| Parsaclisib | PI3K-δ inhibitor, oral | II | RR FL (***n*** = 106) | 14 | 70 | [32] |
| (IBI-376) | | | RR MZL, BTKi-naive (*n* = 99) | 6 | 54 | [33] |
| **EZH2 inhibitor** | | | | | | |
| Tazemetostat | EZH2 inhibitor, oral | II | RR FL (*n* = 99) | | | [34•] |
| (EPZ-6438) | | | EZH2 wild type(*n* = 54) | 4 | 35 | |
| | | | EZH2 mutant type (***n*** = 45) | 2 | 69 | |
| **BTK inhibitors** | | | | | | |
| Ibrutinib | BTK inhibitor, oral, covalent | II | RR FL (***n*** = 40) | 13 | 37 | [39] |
| (PCI-32765) | | II | RR MZL (*n* = 60) | 3 | 48 | [35••] |
| Zanubrutinib | BTK inhibitor, oral, covalent | II | MAGNOLIA | | | [38] |
| (BGB-3111) | | | RR MZL (*n* = 68) | 15 | 60 | |
| **Bcl2 inhibitors** | | | | | | |
| Venetoclax | Bcl-2 inhibitor, oral | I | RR NHL (*n* = 106) | 13 | 44 | [54] |
| (ABT-199) | | | FL (***n*** = 29) | 14 | 38 | |
| | | | WM (*n* = 4) | 0 | 100 | |
| | | | MZL (***n*** = 3) | 0 | 67 | |
| | | | MCL (*n* = 28) | 21 | 75 | |
| | | Ib/II | RR FL, + ibrutinib (***n*** = 16) | 25 | 69 | [55] |
| **CD-19 CAR-T cell therapy** | | | | | | |
| Axicabtagene | CD19 CAR-T, autologous | II | ZUMA-5 | | | [44•] |
| ciloleucel | | | iNHL (*n* = 104) | 76 | 92 | |
| | | | FL (***n*** = 84) | 80 | 95 | |
| | | | MZL (*n* = 20) | 60 | 85 | |

***Bcl-2*** B-cell lymphoma 2, *BTK* Bruton tyrosine kinase, ***CAR-T*** chimeric antigen receptor T cell, *CIT* chemoimmunotherapy, ***CLL*** chronic lymphocytic leukemia, *CR* complete response, ***EZH2*** enhancer of zeste homolog 2, *FL* follicular lymphoma, ***iNHL*** indolent non-Hodgkin lymphoma, *LPL* lymphoplasmacytic lymphoma, ***MCL*** mantle cell lymphoma, *MZL* marginal zone lymphoma, ***n*** number, *ORR* overall response rate, ***PI3K*** phosphoinositide 3-kinase, *R* rituximab, ***R2*** lenalidomide with rituximab, *Ref* reference, ***RR*** relapsed or refractory, *SLL* small lymphocytic lymphoma, ***Tx*** treatment, *WM* Waldenström Macroglobulinemia

the first challenge is to select the chemotherapy backbone, bendamustine (B) versus cyclophosphamide, vincristine and prednisone with or without doxorubicin (RCHOP/RCVP). The BRIGHT and STiL studies compared rituximab (R) based CIT, BR versus RCHOP/RCVP, in patients with iNHL. STiL, a noninferiority study with progression-free survival (PFS) as the primary endpoint, demonstrated superiority of BR over RCHOP with median PFS of

| FRONTLINE | | | | | | RELAPSED/REFRACTORY | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| FL | MZL | MCL | CLL/SLL | WM | | FL | MZL | MCL | CLL/SLL | WM |
| | | | | | CIT | | | | | |
| N+ | N+ | N+ | | | lenalidomide | + | + | + | | |
| | | | | | idelalisib | | N | | | |
| | | | | | copanlisib | | N | | | |
| | | | | | duvelisib | | N | | | |
| | | | | | umbralisib | | | | | |
| | | | | | tazemetostat | | | | | |
| | | | | +/- | ibrutinib | | | +/- | | |
| | | | | | acalabruinib | | | | | N |
| | | | | | zanubrutinib | | | | N | |
| | | | | | Venetoclax | | | N +/- | | |
| | | | | | CD19 CAR-T | | | | | |

**Fig. 1** FDA-approved and NCCN-recommended indications for CIT, lenalidomide, PI3K inhibitors, tazemetostat, BTK inhibitors, venetoclax and CD19 CAR-T cell therapy in indolent NHL.

69.5 versus 31.2 months respectively (HR 0.58, $p < 0.0001$) and a favorable toxicity profile. Response rates were similar, and there was no difference in overall survival (OS) at 10-year follow-up [5, 6]. BRIGHT, a noninferiority study in patients with iNHL and MCL with a primary endpoint of complete response rate (CRR), showed BR was noninferior to RCHOP/RCVP (CRR 31 versus 25%) with a similar 5-year PFS and OS. Toxicity was different including significantly more rashes and nausea with BR compared to more alopecia, cytopenias, and neuropathy with RCHOP/RCVP [7]. Whether the rate of secondary malignancies is higher with bendamustine compared to CHOP-like regimens remains controversial. In BRIGHT, 19% of patients who received BR developed secondary malignancies versus 11% of those who received RCHOP/RCVP. In STiL, the rates of secondary malignancies at the 36-month and 10-year follow-up time points in both arms were similar. Based on these data, bendamustine has emerged as the favored chemotherapy backbone in patients with treatment-naïve FL and MZL deemed appropriate for CIT. RCHOP is typically reserved for patients with iNHL that have more aggressive features suggestive of transformation, but transformation cannot be proven histologically.

When selecting CIT, the next decision is the choice of CD20 monoclonal antibody (mAb). The GALLIUM study evaluated rituximab with bendamustine, CHOP, or CVP versus the type 2 anti-CD20 mAb obinutuzumab (O) with the same chemotherapy backbones (BO/OCHOP/OCVP) followed by maintenance anti-CD20 mAb in responding patients with treatment-naïve FL or MZL. Obinutuzumab was associated with an improvement in PFS (80 versus 73%, HR 0.66, 95%CI 0.51–0.85) but increased toxicity including infusion reactions, cytopenias, and infections. The rate of grade 3–5 adverse events (AEs) and serious adverse events (SAEs), dose modifications, and discontinuations due to AEs were all higher in the obinutuzumab arm. There was an increased incidence of non-relapse mortality in the obinutuzumab

arm mostly attributed to secondary malignancies and opportunistic infections [8]. When choosing CIT, the frontline setting, my preference is to use rituximab as the anti-CD20 mAb due to the favorable toxicity profile and lower incidence of non-relapse mortality. Although I predominantly use the intravenous (IV) formulation at this time, transitioning to the subcutaneous (SQ) formulation of rituximab may be a more convenient option for select patients that have tolerated IV rituximab well. The SQ rituximab formulation allows for a shorter treatment time but is associated with an increased incidence of injection site reactions, which are usually mild [9]. I feel the combination of prolonged lymphopenia from bendamustine and increased incidence of neutropenia with obinutuzumab may contribute to the increased infectious complications and can occur in all phases of treatment including the maintenance as well as observation periods.

The GADOLIN study compared BO versus bendamustine monotherapy in patients with rituximab-refractory R/R iNHL. The median PFS was not reached for the BO arm, versus 14.9 months for bendamustine alone (HR 0.55, 95%CI 0.40–0.74), with higher rates of grade 3 or higher infusion reactions and neutropenia. Although this does not address the decision to use rituximab versus obinutuzumab in this setting, GADOLIN does demonstrate the benefit of continuing to target CD20 in patients with rituximab-refractory disease [10]. In the R/R setting, for rituximab-refractory or recently exposed patients, my preference is to use obinutuzumab. I am willing to accept a different level of toxicity in rituximab-refractory disease than in the treatment-naïve setting and extrapolating from the treatment-naïve comparative data feel obinutuzumab may provide PFS benefit.

The third debate when using CIT in iNHL is whether to use maintenance. The PRIMA study investigated maintenance rituximab versus observation in patients responding to rituximab CHOP/CVP/FMC. Maintenance significantly improved PFS, median PFS 10.5 versus 4.1 years (HR 0.61, 95%CI 0.52–0.73), but did not affect estimated 10-year OS which was 80% in both arms [11, 12]. The GALLIUM study had similar results, showing a PFS benefit without OS benefit in those receiving maintenance, but the decision to use maintenance was non-random, at the investigator's discretion [8]. Overall, my preference is to use maintenance rituximab in the frontline setting and consider maintenance CD20-mAb therapy in the R/R setting in responding patients, with a very low threshold to discontinue maintenance for toxicity. Considering how rapidly the treatment landscape is changing, and the favorable toxicity profile of CD20-mAb maintenance, I feel a PFS benefit could translate into an OS benefit as an increasing number of novel therapies enter the treatment armamentarium. However, the discussion I have with patients regarding the risk to benefit ratio of maintenance is dynamic. For example, early in the COVID-19 pandemic, I was slightly more hesitant to recommend maintenance and now that we have highly effective vaccinations, the discussion must include possibility of impaired vaccine responsiveness that has been demonstrated in patients treated with CD20 mAb therapies [13].

In summary, CIT with bendamustine or CHOP-like chemotherapy, rituximab, or obinutuzumab immunotherapy, and maintenance or observation post CIT all remain standard of care approaches for symptomatic frontline FL and nodal MZL. Use of single agent rituximab remains common in the

community setting and may be appropriate for older or frail patients. Rituximab is unlikely adequate for bulky disease and is unlikely to clear bone marrow involvement. For patients with FL or nodal MZL, my personal practice typically is to observe until symptomatic by GELF criteria, at which point CIT is my preferred frontline treatment option [14]. The role of CIT in the management of SMZL, EMZL, and other iNHL subtypes remains more variable, especially as novel agents are shifting into the frontline setting, and single agent rituximab is considered standard of care for the frontline treatment of many of these patients.

## Lenalidomide

Lenalidomide is an immunomodulatory agent with several potential mechanisms of action in B-cell lymphoproliferative disorders in part due to inhibitory effects on the E3 ubiquitin ligase, cereblon. In addition to direct cytotoxicity, lenalidomide-induced T cell and NK-cell stimulation may enhance antibody-dependent cellular cytotoxicity, enhance cytotoxic T cell activity, resensitize cells to CD20-mAbs, and synergize with other B-cell receptor targeting agents. Through alteration of inflammatory cytokine production and checkpoint inhibitor expression, disruption of the otherwise protective microenvironment may be an additional mechanism of action in B-NHL [15].

Lenalidomide and rituximab ($R^2$) has been studied across iNHL subtypes in the treatment-naïve and R/R settings. Initial results from a phase 2 study of $R^2$ in patients with treatment-naïve iNHL demonstrated an overall response rate (ORR) of 98% (CR 87%) in 50 patients with FL and ORR of 90% (CR 67%) in 30 patients with MZL [16]. RELEVANCE was a phase 3 study of $R^2$ versus investigators choice of BR or RCHOP/RCVP followed by maintenance rituximab in 1030 patients with treatment-naïve FL. Although this was a negative study, $R^2$ was not superior to CIT in terms of the primary endpoint of CR at 120 weeks (48 versus 53%), efficacy was similar with 3-year PFS 77 versus 78% and 3-year OS of 94 versus 94% for $R^2$ and CIT respectively. Grade ¾ neutropenia, any grade neutropenic fever, nausea, diarrhea, and neuropathy were more common with CIT, while grade ¾ cutaneous toxicity, any grade myalgia, and muscle spasms were higher with $R^2$ [17•]. Due to similar efficacy and a different toxicity profile, $R^2$ is NCCN-recommended as an option for 1L FL (category 2A) and MZL (category 2B) for patients with treatment-naïve iNHL that may benefit from a chemotherapy-free approach, but is not FDA-approved in this setting [18].

AUGMENT was a randomized phase 3 study of $R^2$ versus rituximab plus placebo in 358 patients with R/R grade 1-3a FL (82%) or MZL (18%). All patients were previously exposed to at least 2 doses of rituximab and could not be rituximab-refractory. With a median follow-up of 28.3 months, PFS was 39.4 month for $R^2$ versus 14.1 months for rituximab plus placebo (HR 0.46, 95%CI 0.34–0.62). Key secondary endpoints all significantly favored $R^2$ including time to next treatment, PFS to subsequent anti-lymphoma therapy, and OS in the FL subgroup. As expected, the addition of lenalidomide was associated with increased grade 3 or higher treatment-emergent adverse

events (TEAE), the most common of which were neutropenia and infections [19••]. The phase 3b MAGNIFY study is evaluating 12 months of $R^2$ induction followed by randomization to maintenance with either dose reduced $R^2$ or rituximab monotherapy in 370 patients with R/R iNHL. An interim analysis revealed an ORR of 73% (CR 45%) after 12 months of $R^2$ with no new safety signal [20]. The AUGMENT and MAGNIFY data contributed to the 11/2019 FDA approval of $R^2$ in R/R FL and MZL with at least one prior line of therapy.

There is hope that shifting immunomodulatory agents earlier in the treatment landscape could alter the protective microenvironment, which may change the natural history of FL and potentially improve response to subsequent therapies. $R^2$ has emerged as my favored standard of care approach for most second line FL patients, whether previously treated with CIT or rituximab monotherapy in the 1L setting. For patients that have experienced POD24, $R^2$ remains my preferred regimen unless there is suggestion of transformation to a more aggressive process. For MZL, the sequencing of $R^2$ is less clear due to the more limited data supporting $R^2$ in this setting as well as the availability of other targeted agents, including ibrutinib and umbralisib, approved in the 2L setting and beyond.

In an attempt to improve upon $R^2$, the combination of lenalidomide with obinutuzumab (R-O) is an emerging combination of interest in the treatment-naïve and R/R iNHL settings. In a phase 2 study of R-O in 90 treatment-naïve patients with grade 1-3a FL, the ORR was 98% (CR 94%), 2 year PFS 96%, and 2 year OS 97% [21]. In a phase 1/2 study, R-O also demonstrated promising efficacy in 66 patients with R/R iNHL and median of 2 prior therapies with an ORR of 98% (CR 72%). At a median of 17 months follow-up, the estimated 24-month PFS was 75% and OS 95% [22]. Although not an FDA-approved combination, based on these data, R-O is an NCCN category 2B recommended treatment option for 1L and R/R FL, but is not recommended for MZL [18].

## Phosphoinositide 3-kinase inhibitors

Phosphoinositide 3-kinase is a very appealing target in FL with currently four FDA-approved PI3K inhibitors for FL and one for MZL. Despite several options in this class, use of PI3K inhibitors is limited due to concern regarding the toxicity profiles of these agents. Patients must be monitored for immune-mediated toxicities including pneumonitis, colitis, and hepatitis. Due to the risk of infectious AEs, including opportunistic infections, antiviral and pneumocystis jirovecii pneumonia prophylaxis are considered standard of care.

Idelalisib, the first approved PI3K inhibitor, was studied in a phase 2 trial of 125 patients with R/R FL and a median of 4 prior therapies. The ORR was 57% (CR 6%), median DOR 12.5 months, and median PFS 11 months. Notable grade 3 or higher AEs included diarrhea (13%), elevated ALT (13%), and elevated AST (8%) [23, 24]. Duvelisib is an oral PI3K-delta and gamma inhibitor with FDA-approved indications in R/R FL and chronic lymphocytic leukemia (CLL). The phase 2 DYNAMO study evaluated duvelisib 25 mg

orally BID in 129 patients with R/R FL and a median of 3 prior therapies. The ORR was 47% (CR 2%), median DOR 10 months, and mPFS 9.5 months. Grade 3 or higher AEs included diarrhea (15%), pneumonia (5%), elevated ALT (5%), and elevated AST (3%) [25]. Copanlisib is an intravenous PI3K-delta and alpha inhibitor. CHRONOS-1 evaluated copanlisib 60 mg IV days 1, 8, and 15 of a 28-day cycle in 142 patients with R/R FL and a median of 3 prior therapies. Efficacy was similar to other PI3K inhibitors, ORR 59% (CR 12%), but the toxicity profile was different with grade 3+ infusion-related hypertension (40%) and hyperglycemia (24%) more prominent than grade 3+ diarrhea (8.5%), colitis (1%), elevated AST/ALT (2% each), and non-infectious pneumonitis (1%) [26–28]. These three PI3K inhibitors are FDA-approved as monotherapy in third line or later FL, and NCCN-recommended but not FDA-approved for R/R MZL.

Umbralisib, an oral inhibitor of PI3K-delta and CK1 epsilon, was granted FDA approval in 2/2021 for the treatment of patients with R/R MZL and FL based on the UNITY-NHL study. In this phase 2 study, patients with R/R iNHL including 117 with FL and 69 with MZL received umbralisib 800 mg orally BID until progression or unacceptable toxicity. In the FL cohort, patients had a median of 3 prior therapies and the ORR was 45% (CR 5%), median DOR 11.1 months, and median PFS 10.6 months. For patients with MZL and a median of 2 prior therapies, the ORR was 49% (CR 16%); median DOR and median PFS were not reached. All 11 patients with MZL who achieved CR remain in remission at time of data presentation. Immune-mediated grade 3 or higher AEs included grade 3 or higher diarrhea (10%), elevated AST (7%), elevated ALT (7%), non-infectious pneumonitis (1%), and colitis 2% [29].

PI3K inhibitors have been studied in combination with a variety of other therapies. Several previous studies of a PI3K inhibitor in combination with CIT or other small molecular inhibitors in iNHL, including BR, entospletinib, and venetoclax, were halted due to unacceptable toxicity or desire to focus on registration trials (NCT02576275, NCT02640833) [30]. However, PI3K inhibitors have been successfully combined with rituximab. CHRONOS-3 is a phase 3 study evaluating rituximab plus copanlisib versus rituximab plus placebo in 458 patients with R/R iNHL that were treatment-free and progression free for at least 12 months after the last CD20-mAb containing CIT regimen. With a median of 19.2 months follow-up, PFS was 21.5 months with rituximab and copanlisib versus 13.8 months with rituximab and placebo (HR 0.52, 95%CI 0.39–0.69) and there were no new safety signals [31]. This study does not address whether rituximab with copanlisib provides benefit over copanlisib alone in this patient population.

Due mostly to infectious and immune-mediated toxicities, overall PI3K inhibitors have a reputation of being efficacious but toxic and challenging for patients to tolerate long-term. Moving forward, intermittent dosing schedules may improve toxicity to allow for more widespread use of these agents. One example of this approach is CITADEL, a phase 2 study of the next-generation PI3K-delta inhibitor parsaclisib in iNHL subtypes. Patients received induction parsaclisib 20 mg orally daily for 8 weeks followed by maintenance with either 20 mg orally weekly or 2.5 mg orally daily until progression or unacceptable toxicity. CITADEL-203 includes 106 patients with R/R FL and at least 2 prior lines of therapy, and CITADEL-204 includes 99 BTKi-naïve patients

with R/R MZL and at least 1 prior line of therapy. Dose-reduced daily dosing was selected as the preferred maintenance approach, and those receiving weekly dosing were permitted to cross over. The ORR in FL was 70% (CR 14%), median DOR 15.9 months, and median PFS 15.8 months. For MZL, the ORR was 54% (CR 6%), median DOR 12.0 months, and median PFS 19.4 months. The toxicity profile of parsaclisib was similar to other oral PI3K-delta inhibitors, but with a relatively low rate of elevated AST/ALT (0%/1% in FL and 2%/1% in MZL) [32, 33].

## Enhancer of zeste homolog 2

Enhancer of zeste homolog 2 (EZH2) is an epigenetic regulator central to germinal center B-cell biology. Activating mutations of EZH2 are present in approximately 20% of FL cases, which is felt to be an early event in lymphomagenesis rather than part of clonal evolution. Tazemetostat is an oral, twice daily inhibitor of EZH2 that was FDA approved in 6/2020 for patients with EZH2 mutant (MT) FL and 2 or more prior systemic therapies as well as patient with R/R FL, regardless of EZH2 mutation status or number of prior therapies, if there is no alternative treatment option. In a phase 2 study 99 patients with R/R FL, all grades including grade 3b and transformed FL were treated with tazemetostat 800 mg orally BID until progression, unacceptable toxicity, or withdrawal from study. The OR (CR) rates were 35% (4%) and 69% (2%) for wild type (WT, $n = 54$) and MT ($\boldsymbol{n} = 45$) respectively, with 69% of WT patients and 98% of MT patients demonstrating volumetric tumor reduction. The median DOR was 13 months with a median of 36 months follow-up in the WT cohort and 10.9 months with a median of 22 months follow-up in the MT cohort. Tazemetostat was well tolerated with low rates discontinuation (8%) or dose reduction (9%) due to TEAEs. The most common grade 3 or higher TEAE was anemia (5%) and the most common non-hematologic TEAE was asthenia (3%) [34•]. Given the favorable toxify profile, further studies of tazemetostat in combination with R2 and rituximab in R/R FL are ongoing (NCT04224493, NCT04762160).

## Bruton tyrosine kinase inhibitors

Bruton tyrosine kinase (BTK) is central to B-cell receptor signaling and an important target in in B-cell lymphoproliferative disorders. Ibrutinib was the first in class covalent BTK inhibitor with FDA-approved indications in several subtypes of iNHL including CLL/SLL, MCL, WM, and MZL but ibrutinib is not indicated FL. In a phase 2 study, 63 patients with CD20-mAb exposed R/R MZL with at least 1 prior therapy received ibrutinib 560 mg orally daily until progression or unacceptable toxicity. The ORR was 48% (CR 3%), 78% of patients had volumetric tumor reduction, and the median PFS was 14.2 months. The most common grade 3 or higher AEs were anemia, pneumonia, and fatigue. Discontinuation due to AEs occurred in 10% of patients [35••].

Given the favorable toxicity profile and efficacy, ibrutinib was granted accelerated FDA approval in January 2017 for R/R MZL. Further studies in the frontline setting as monotherapy and in combination with rituximab are ongoing (NCT03697512, NCT04212013).

The activity of zanubrutinib, a next-generation oral covalent BTK inhibitor, has also been preliminarily reported in various B-cell malignancies including MZL [36, 37]. The MAGNOLIA study was a phase 2 study of zanubrutinib 160 mg orally BID in 68 patients with R/R MZL, at least 1 prior line of therapy including anti-CD20 monoclonal antibody therapy, and a median of 2 prior therapies. The ORR was 60% (CR 15%) and at a median of 6.8 months follow-up, the median DOR and median PFS had not been reached. Treatment was well tolerated overall, 1 patient experienced atrial flutter and no patient experienced major hemorrhage or opportunistic infection [38]. Based on these data, zanubrutinib was granted accelerated FDA approval on 9/15/2021 for the treatment of patients with R/R MZL who have received at least 1 prior CD20-mAb based therapy.

The efficacy of BTK inhibition in FL has been disappointing. In a phase 2 study, ibrutinib 560 mg orally daily was evaluated in 40 patients with relapsed/refractory FL. The ORR was 37% (CR 12.5%), median PFS 14 months, and 2-year PFS 20%. The ORR was lower in rituximab-refractory patients compared to rituximab-sensitive patients (ORR 16.7 versus 52.6%). Zero of the 5 patients with CARD11 mutation responded [39]. Ibrutinib was well tolerated overall, but given disappointing activity in FL, further development as a monotherapy was halted and BTK inhibitors are not FDA-approved or NCCN-recommended for use in FL.

Moving forward, it is unclear if we will be able to find a role for BTK inhibitors in the FL treatment landscape. Comparative studies of next-generation covalent BTK inhibitors, such as acalabrutinib and zanubrutinib, compared to ibrutinib in CLL and WM have demonstrated favorable toxicity profiles without differences in efficacy [40, 41]. Of note, switching between covalent BTKi for intolerance is an accepted standard of care, but acalabrutinib and zanubrutinib do not overcome BTKi resistance and should not be used in patients who have progressed on ibrutinib. Several non-covalent BTK inhibitors, designed to overcome covalent BTKi resistance, are also in development across B-cell malignancies with promising early efficacy results in iNHL including pirtobrutinib (LOXO-305) and ARQ 531 [42, 43]. Further data are awaited to determine if these agents will be valuable additions to our treatment armamentarium in iNHL.

## Chimeric antigen receptor T cell therapy and other cellular therapies

There are currently three CD19-directed CAR-T products approved in aggressive lymphomas, including axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel. All three are approved for DLBCL and transformed FL, but lisocabtagene maraleucel is the only product that specifically includes grade 3B FL specifically in the aggressive lymphoma indication. Axicabtagene

ciloleucel is the first and only approved CAR-T product in iNHL to date, with many other constructs under investigation.

ZUMA-5 is a phase 2 study of axicabtagene ciloleucel in patients with iNHL including FL and MZL treated with two or more prior lines of systemic therapy, with prior exposure to both an alkylating agent and CD20-mAb therapy. The primary efficacy analysis was triggered when at least 80 patients with FL had a minimum of 12 months of follow-up. Of the 104 patients evaluable for efficacy, the ORR was 92% (CR 76%) with 16% of patients achieving PR. For the 84 pts with FL, the ORR was 95% (CR 80%) and for the 20 pts with MZL, the ORR 85% (CR 60%). The rate of grade 3 or higher cytokine release syndrome (CRS) was 7% and grade 3 or higher neurological events was 19%. One patient had grade 5 CRS attributed to axicabtagene ciloleucel [44•]. Based on these data, axicabtagene ciloleucel received accelerated FDA approval for patients with FL and at least two prior lines of therapy in 3/2021, and ZUMA-5 enrollment for the MZL cohort is ongoing (NCT03105336).

Longer-term follow-up from CAR-T studies in DLBCL suggest that patients who are in continued complete remission at the 6- to 12-month time point are unlikely to relapse and may be cured. Considering the natural history of R/R DLBCL in the CIT era, surrogate endpoints such as CR at 12 months are clinically relevant in aggressive lymphomas [45]. On the other hand, iNHL is a chronic disease that can relapse after years of remission and therefore these surrogate endpoints are not as convincing clinically. The longest follow-up in FL to date is from a study of tisagenlecleucel in 15 pts with FL with a median of 5 prior therapies. The CRR was 71%, and 89% of responding patients remained in remission at a median of 28.6 months follow-up in the primary analysis. With a median of 49 months follow-up, the median PFS was 32.4 months, median duration of response was not reached (95% CI 9.5mo-NE), and median OS was not reached (27.2mo-NE) [46, 47]. Although the rates of continued CR and PFS at 12 months reported in ZUMA-5 are also encouraging, given the natural history of iNHL, longer follow-up is needed to know if CAR-T may be curative for a proportion of patients with iNHL.

As we continue to explore how best to sequence CAR-T cell therapy for patients with iNHL, we will better understand the effect of prior iNHL therapies, including bendamustine and lenalidomide, on overall T cell fitness. The interaction between Pi3 kinase inhibitors and CAR-T remains unknown, regardless of sequencing, and will need to be studied in a controlled fashion considering the immune-mediated toxicity profile associated with PI3K inhibition. Previously in iNHL, some contended that autologous stem cell transplantation was an underutilized modality that could provide long-term treatment-free benefit for patients with relapsed or refractory iNHL, particularly those with chemotherapy-sensitive high-risk relapse [48, 49]. The availability of CAR-T cell therapy in FL has changed this discussion, and CAR-T may not only replace autologous stem cell transplantation in iNHL but will expand the ability to utilize cellular therapy in patients with iNHL. Compared to autologous stem cell transplantation that has very specific age and fitness requirements, there is no upper age limit for CAR-T cell therapy and the criteria for underlying organ function are more flexible for otherwise fit, well-compensated patients. The role of allogeneic stem cell transplantation in iNHL is further decreasing and will likely be reserved for those that have failed

CAR-T cell therapy. Due to the absence of randomized prospective studies, and the fact that the available data on allogeneic stem cell transplantation does not reflect the current treatment landscape, it has become increasingly challenging to select the subset of iNHL patients that may benefit from this potentially curative option [50–53].

## Emerging therapies

As we further explore the efficacy of targeted therapy in iNHL, we have realized that molecular drivers of disease are poorly understood. For example, considering t(14;18) is the hallmark of FL, activity of the bcl2 inhibitor venetoclax was disappointingly low [54]. Combining well-tolerated, minimally active single agents with non-overlapping mechanisms of action and toxicity, such as venetoclax and ibrutinib, is one method of moving the field forward but is unlikely to convert iNHL from a chronic into a curable group of diseases [55]. Bispecific antibodies, including a number of agents targeting both CD20 and CD3, are in development across iNHL subtypes with promising preliminary results [56–59]. Once we determine how to reliably and reproducibly follow minimal residual disease, risk-adapted consolidative approaches may be an appealing place to develop these bispecific T cell engagers in indolent lymphomas.

## Declarations

**Conflict of Interest**

Lori A. Leslie has received consulting/advisory fees from Bayer, Seattle Genetics, ADC Therapeutics, AbbVie, Janssen, Pharmacyclics, Kite/Gilead, AstraZeneca, and TG Therapeutics, and has received compensation for service on speakers' bureaus from Seattle Genetics, Bristol-Myers Squibb/Celgene, Kite/Gilead, BeiGene, Pharmacyclics/Janssen, AstraZeneca, Epizyme, Karyopharm Therapeutics, and TG Therapeutics.

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