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Overview of Targeted Drugs for Mature B-Cell Non-hodgkin Lymphomas

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The improved knowledge of pathogenetic mechanisms underlying lymphomagenesis and the discovery of the critical role of tumor microenvironments have enabled the design of new drugs against cell targets and pathways. The Food and Drug Administration (FDA) has approved several monoclonal antibodies (mAbs) and small molecule inhibitors (SMIs) for targeted therapy in hematology. This review focuses on the efficacy results of the currently available targeted agents and recaps the main ongoing trials in the setting of mature B-Cell non-Hodgkin lymphomas. The objective is to summarize the different classes of novel agents approved for mature B-cell lymphomas, to describe in synoptic tables the results they achieved and, finally, to draw future scenarios as we glimpse through the ongoing clinical trials. Characteristics and therapeutic efficacy are summarized for the currently approved mAbs [i.e., anti-Cluster of differentiation (CD) mAbs, immune checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, and bispecific antibodies] as well as for SMIs i.e., inhibitors of B-cell receptor signaling, proteasome, mTOR BCL-2 HDAC pathways. The biological disease profiling of B-cell lymphoma subtypes may foster the discovery of innovative drug strategies for improving survival outcome in lymphoid neoplasms, as well as the trade-offs between efficacy and toxicity. The hope for clinical advantages should carefully be coupled with mindful awareness of the potential pitfalls and the occurrence of uneven, sometimes severe, toxicities.

Keywords: anticancer mAbs, tyrosine kinase inhibitors, tailored therapy, personalized medicine, NHL

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INTRODUCTION

Non-Hodgkin lymphomas (NHL) encompass malignant tumors of the lymphoid tissues variously resulting from the clonal growth of B cells, T cells, natural killer cells, or originators of these cells. They derive from cells at varying stages of maturation, and many of the biologic features of these malignant cells reflect their normal counterparts. B cell lymphomas may arise at any stage of normal B cell development, but most are derived from cells that have been exposed to the germinal center reaction (1). The recent World Health Organization (WHO) classification categorizes B-cell lymphomas by morphology, immunophenotype, and genetic findings. These

histological subtypes of B-cell Lymphomas recognized by the WHO present different and somehow specific profiles of clinical aggressiveness and prognosis. Despite, the WHO classification does not explicitly order B-cell lymphomas on the basis of their aggressiveness, also given the significant patient-to-patient variability in the natural history of these neoplasms. Both in real life practice and in the vast majority of clinical trials histological subtypes have been roughly segregated into indolent, aggressive and very aggressive groups, according to their usual clinical behavior. Indolent B-cell lymphomas represent 35 to 40 percent of the non-Hodgkin lymphomas (NHL), and survival is generally measured in years. The most common subtypes include follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), a fraction of mantle cell lymphoma (MCL) cases, extramedullary, nodal and splenic marginal zone lymphoma (MZL), and lymphoplasmacytic lymphoma (LPL) (1, 2). Aggressive subtypes if left untreated survive a few months but if adequately treated may achieve definitive remissions and cure in a significant fraction of patients. The most common subtypes are large B-cell lymphomas, including anaplastic and primary mediastinal lymphoma, and various kinds of diffuse large B cell lymphoma (DLBCL). The highly aggressive subtypes represent about 5 percent of the NHL and survival may be measured in only a few weeks if left untreated. Curing is possible if vigorously treated with high-intensity chemotherapy protocols.

Chemotherapy, radiotherapy, and immunotherapy have been used, alone or in combination, in the last decades to treat B-cell NHL. Therapeutic outcomes may vary according to clinical behavior, whether indolent or aggressive, and patients may suffer various patterns of recurrence requiring subsequent lines of rescue therapies. Dismal prognosis still affects a significant fraction of patients with mature B-cell lymphomas, and new treatment strategies should be conceived to improve both objective response and survival (3–9).

In the last decade, the remarkable and exponential understanding of intracellular processes that are deregulated during lymphomagenesis, such as signal transduction pathways, transcriptional and translational regulation, protein stability and degradation, cell cycle regulation, and mitosis and apoptosis, as well as the study of the microenvironment have led to the discovery and progress of new targeted therapies (10–16).

These novel biological therapies include monoclonal antibodies (mAbs), small molecule inhibitors (SMIs) (i.e., growth factors or their receptors), vaccines, and genetic therapies. They may complement or replace conventional chemotherapies (with their burden of systemic toxicities) ensuring novel mechanisms of "targeted" tumor cell kill and proliferation control while, hopefully, lessening iatrogenic adverse events.

Additionally, the role of the immune system in the pathogenesis and development of hematological neoplasms has long been known, but especially in recent years we have seen a significant change in knowledge in this area, such as new open therapeutic perspectives. Using the immunologic mechanism to treat cancer is an old and well-known concept, and it consists in activating the immune system to hit the tumor rather than directly hitting the cancer cell. This approach represents a real change in the treatment paradigm (3, 8, 11, 14, 17–20). Tumor immunotherapy has undergone a new phase of development, in particular linked to the development of T-cell checkpoint inhibitors and the development of CAR T cell therapy, a personalized treatment involving the use of genetically modified T lymphocytes to attack the cancer cells (21–24).

This review is intended to provide an overview of all Food and Drug Administration (FDA)-approved novel drugs and therapies for "targeting" mature B-cell neoplasms. Immunotherapy agent treatments [i.e., anti-Cluster of differentiation (CD) mAbs, immune checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, and bispecific antibodies] as well as for SMIs (i.e., inhibitors of B-cell receptor signaling, proteasome and mTOR BCL-2 HDAC pathways) are summarized in their mechanisms of action (**Figure 1**)—the results they achieved in mature B-cell lymphomas are described in synoptic tables and the ongoing clinical trials are detailed to draw, at a glance, a glimpse on future scenarios.

METHODS

To assess the actual understanding of targeted drugs for NHL, a search on the Cochrane Library and PubMed were performed crossing the keywords "Targeted Therapy" AND "B-Cell Neoplasm." In the second step "indolent" and "aggressive and very aggressive" were singularly added, limited to the English literature but with no restriction on time. "Monoclonal antibodies" and "Small molecule Inhibitors" restricted the search. The authors examined the titles of the 2090 papers retrieved; 521 of them met the call for monoclonal antibodies while 183 were relevant to SMIs. Most of them were cited in the manuscript.

Papers that did not include anticancer inhibitor series and appeared redundant were excluded. A search for abstracts or full text led to the exclusion of other non-pertinent papers. For studies conducted by the same research institute at different times, the most recent and complete one was included unless different methods, endpoints, or specific issues had been addressed. Papers whose full text or at least abstract were not available were excluded as well. The reference sections of pertinent papers were searched for other relevant articles. Here, we considered novel agents to be the mAbs and SMIs that are in ongoing clinical trials or were in trials that have been completed in the last 2 years.

The Clinicaltrial.gov database was queried regarding the terms of each novel agent and therapy in combination with B-cell lymphoma.

MONOCLONAL ANTIBODIES (mABs)

The therapeutic antibodies targeting cell surface receptors have been employed in the standard care treatments for most cancers, both solid tumors and hematological neoplasms. Therapeutic mABs target specific antigen molecules, such as extracellular growth factors and transmembrane receptors. In some cases, mABs are conjugated with radioisotopes or toxins to allow the specific delivery of these cytotoxic agents to the tumor cell target.

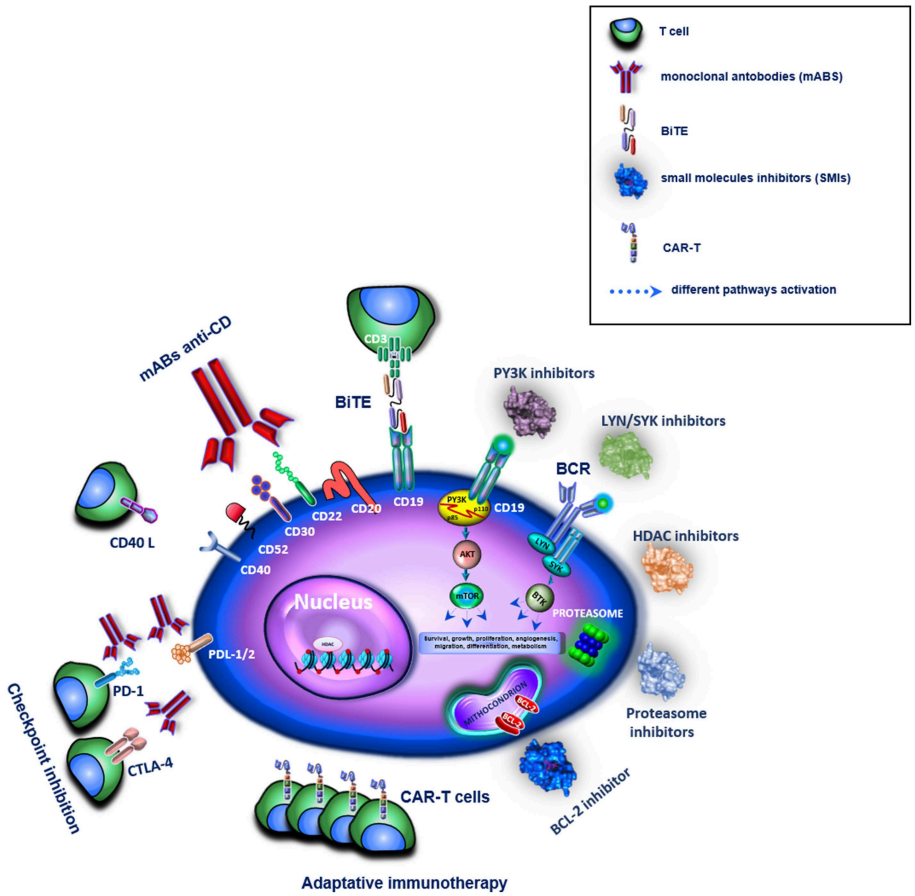

FIGURE 1 | Overview of different target therapies in clinical or pre-clinical use for the treatment of B-cell lymphomas. In the figure these are represented by mABs, BiTE, SMIs, and immune checkpoint inhibitors for an adaptative immunotherapy. The different drugs are shown as family groups based on their different mechanisms of actions.

In general, the mechanisms that allow therapeutic antibodies to inhibit growth or kill cancer cells fall into two categories: immune-mediated mechanisms as antibody-dependent cell cytotoxicity (ADCC), and complementary cytotoxicity (CDC), and mechanisms that interfere with tumorigenesis pathways (e.g., triggering apoptosis, inhibiting cell proliferation or blocking of angiogenesis) (25).

Herein, for the currently approved mAbs for Lymphomas (**Table 1**) we recap in four groups the efficacy of (i) anti-Cluster of differentiation (CD) mAbs; (ii) immune checkpoint inhibitors; (iii) chimeric antigen receptor (CAR) T-cell therapy; and (iv) bispecific antibodies.

Anti-CD mAbs

In this category are the Anti-CD20 Rituximab and the anti-CD52 Alemtuzumab, the forefathers of the mAbs designed for lymphocyte blocking activities. Both are two chimeric (murine-human) antibodies. The success of rituximab has elicited interest in the development of new agents for other surface antigens on malignant B cells. A new generation of anti-CD20 mABs, including ofatumumab, obinutuzumab, and ublituximab, has been designed with features, distinctive from rituximab, that realize an improvement of ADCC and CDC (26).

Alemtuzumab is an anti-CD52 antibody effective in CLL. Currently, it is only accessible on a compassionate use basis (27, 28).

Brentuximab vedotin (SGN-35) is a conjugated antibody consisting of a chimeric monoclonal anti-CD30 antibody linked to the strong microtubule inhibitor monomethyl auristatin E (MMAE). After CD30 binding, SGN-35 is internalized, and the MMAE is released by the action of lysosomal enzymes on the valine-citrulline linker. The antineoplastic mechanism of the brentuximab vedotin exerts is still not entirely clear. Dissemination of MMAE in the tumor microenvironment and cytotoxic effects on "spectator cells" may partly explain its action (29). On 2011, it was approved by the FDA for the treatment of Hodgkin lymphoma (HL) patients, but it may also be adopted in cases of ALK-positive large B-cell lymphoma (LBCL) and Primary Effusion LBCL (30–34).

Camidanlumab Tesirine (ADCT-301) is a pyrrolobenzodiazepine (PBD) Dimer-containing ADC anti-CD25 (the alpha chain of the IL-2 receptor) (35). CD25 is present

TABLE 1 | Targeted drugs for immunotherapy and signal transduction inhibitors (SMIs) with indications for mature B-cell Lymphomas.

Drug class	Drug (brand name)	Target	Indication
IMMUNOTHERAPY (mAbs and CAR-T)			
Anti-CD mAbs	Alemtuzumab (Lemtrada)	CD52	CLL/SLL
	Brentuximab vedotin (Adcetris)	CD30	LBCL-ALK+, DLBCL
	Camidanlumab Tesirine (ADC-301)	CD25	DLBCL
	Dacetuzumab	CD40	B-NHL
	Lucatumumab	CD40	CLL/SLL
	Obinutuzumab (Gazyva)	CD20	B-NHL
	Ofatumumab (Arzerra)	CD20	FL B-NHL
	Polatuzumab Vedotin (DCDS4501A)	CD79b	FL, DLBCL, B-NHL
	Rituximab (Mabthera)	CD20	CLL/SLL, LPL,FL, MZL, MCL, DLBCL, HG-BCL
	Ublituximab (TG-1101)	CD20	B-NHL
Immune Checkpoint inhibitors	Atezolizumab (Tecentriq)	PD-L1	FL DLCBL
	Durvalumab	PD-L1	B-NHL, DLBCL
	Ipilimumab (Yervoy)	CTLA-4	B-NHL, FL
	Nivolumab (Opdivo)	PD-1	DLBCL,FL
	Pembrolizumab (Keytruda)	PD-1	DLBCL
	Pidilizumab (MEDI4736)	PD-1	DLBCL
	Urelumab	CD137	CLL/SLL
Chimeric Antigen receptor (CAR) T-Cell Therapy	Axicabtagene ciloleucel	CAR T-4-1BB	DLBCL
	Tsagenlecleucel (CTL019)	CAR T-4-1BB	HG-BCL
Bispecific antibodies	AFM13	CD30/CD16A	DLBCL
	Blinatumomab (Blincyto)	CD19/CD3	DLBCL
	DART	CD19/CD3	DLBCL
	Mosunetuzumab (BTCT4465A)	CD20/CD3	CLL/SLL, iNHL
SIGNAL TRANSDUCTION PATHWAY INHIBITHORS			
BCR Inhibitors	Acalabrutinib (Calquence)	BTK	CLL/SLL
	Ibrutinib (Imbruvica)	BTK	CLL/SLL, DLBCL, MCL MZL,
	Buparlisib (BKM120)	PI3K	DLBCL, B-NHL
	Copanlisib (Aliqopa)	PI3K γ	DLBCL, MCL
	Idelalisib (Zydelig)	PI3K δ	CLL/SLL, DLBCL, FL
	Cerdulatinib (PRT062070)	SYK JAK 1-2	FL
	Entospletinib (GS-9973)	SYK	CLL/SLL
	Fostamatinib (Tavalisse)	SYK	DLBCL
	TAK659	SYK/FLT3	DLBCL
Proteasome inhibitors	Bortezomib (Velcade)	PIs	FL, MCL, MZL,
	Carfilzomib (Kyprolis)	PIs	B-NHL
	Ixazomib (Ninlaro)	PIs 20S subunit	NHL DLBCL
mTor inhibitors	Everolimus (Afinitor)		CLL/SLL, DLBCL
	Temsirolimus (Torisel)		DLBCL, MCL
BCL2 Inhibitor	Venetoclax (Venclexta)	BH3 domain	DLBCL CLL/SLL
HDAC Inhibitors	CUDC-907	Class I and II+ PI3K	DLBCL
	Mocetinostat (MGCD0103)	Class I and IV	DLBCL, FL
	Panobinostat (Farydak)	Class I, II and IV	DLBCL
	Vorinostat (Zolinza)	Class I and II	FL

B-NHL, B-NHL not otherwise specified; CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia; DLBCL, Diffuse Large B cell Lymphoma; FL, Follicular Lymphoma; HG-BCL, High Grade B-cell lymphoma; iNHL, indolent NHL; LBCL, Large B-cell lymphoma; MCL, Mantle Cell Lymphoma; MZL, Marginal Zone Lymphoma.

on the cell surface in B-cell lymphomas such as DLBCL, further than several T-cell lymphoma subtypes (36, 37).

Dacetuzumab is a monoclonal anti-CD40 antibody. A specific gene signature may be predictive of sensitivity to dacetuzumab in patients with DLBCL. It has shown effectiveness as monotherapy in a phase I study of 50 B-cell NHL patients. Almost 33% of patients had a reduction in tumor bulk with an 8 mg/kg/week dose for 4 weeks. In one case a complete response was observed, and five cases showed partial responses (38, 39).

Lucatumumab is another monoclonal anti-CD40 antibody. In relapsing CLL, results of the phase I reported that the dosages were well-tolerated in a cohort of 26 patients; 1 patient had a partial response, in 17 cases the disease was stable (40, 41).

Obinutuzumab is another humanized anti-CD20-IgG2 class of monoclonal antibody. It retains better ADCC than rituximab, with less CDC than ofatumumab. It has a unique feature in CD20 cross-link, resulting in increased direct cell death. FDA approved obinutuzumab for the treatment of CLL. Also, this mAB has been tested for R/R NHL. A phase III study compared alkylating agent (bendamustine) alone vs. obinutuzumab plus bendamustine followed by maintenance therapy with obinutuzumab in indolent NHL patients refractory to rituximab. The outcomes reported a significantly longer PFS in the of obinutuzumab plus bendamustine arm (24, 42).

Ofatumumab is a human mAb direct against a new CD20 epitope. In preclinical models compared with rituximab, ofatumumab has demonstrated a closer linkage with the B-cell surface and enhanced complement-dependent cytotoxicity (43–45).

Polatuzumab vedotin is a first-in-class anti-CD79b antibody-drug conjugate (ADC) currently being investigated for the treatment of different NHLs (46, 47). CD79b protein is highly specific and expressed in most of B-cell malignancies (48). To date, some ongoing studies are assessing the safety and effectiveness of polatuzumab vedotin for several types of NHL, including trials exploring combinations with obinutuzumab, rituximab, venetoclax, and atezolizumab (46, 47, 49–51).

Rituximab is still the most widely used antibody for treating mature B-cell lymphoma NHL B cells, also including CLL/SLL. Rituximab is an IgG1 chimeric antibody binding to CD20, a B-lymphocyte antigen transmembrane, which is present on the surface of both non-neoplastic (pre, immature, mature, and activated B cells) and malignant B cells (52, 53). The antibody was first approved in 1997 for NHL and subsequently, in 2009, for CLL. After that, rituximab has become an ordinary component of the treatment of FL, DLBCL, and MCL (25).

Ublituximab (TG-1101) targets an exclusive epitope on the CD20 and has been engineered to improve affinity for all variants of FcγRIIIa receptors, with better ADCC than ofatumumab and rituximab (54).

Commonly Anti-CD mAbs Toxicities

Due to the presence of the entire range of murine immunoglobulins (Igs), mAbs retain a high antigenic potential to humans, therefore carrying a risk for hypersensitivity reactions upon parenteral administration. Indeed, infusional reactions take place quite commonly during or after mAbs administration. Tumor lysis syndrome may occur in patients carrying an elevated number of circulating neoplastic cells. Infusion-related adverse events are equally frequent and may be severe as well, seen also with the new-generation anti-CD20 mAbs ofatumumab and obinutuzumab. The toxicity profile of the Brentuximab vedotin is manageable, though the peripheral neuropathy is an important clinical feature hampering prolonged administration of the drug (29). Patients treated with these new drugs often may form anti-mouse immunoglobulin antibodies, which could counteract the therapeutic effect. To limit these adverse effects, the more recently developed chimeric mAbs contain an increased proportion of human Ig components (about 65%) and a reduced portion of murine Ig components while humanized mAbs account for 95% of the human component (55). Their co-administration with vaccines should be avoided.

Immune Checkpoint Inhibitors (ICIs)

Immunotherapy has reformed the treatment of solid tumors and hematological neoplasms over the past decade with numerous agents approved by the FDA in recent years. While various approaches are used to modify the antitumor immunity of the host, perhaps the most commonly studied and used is the checkpoint block (15, 56–59). The motivation for adopting ICIs in the treatment of lymphoma relies on the existence in such malignancies of mechanisms that escape immune surveillance due to genetic variance. These agents may re-educate cells in the microenvironment, restoring chemokine and cytokine signaling as well as expression of checkpoint proteins (56, 60–66). They are able to block the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) pathways. PD-1 is an important receptor of the immune checkpoint expressed on activated T cells (67). In recent years, interest in the inhibition of PD-1 in combination with other therapies has increased in the hope of generating a synergistic anti-tumor effect. CTLA-4 is a co-inhibitory receptor expressed primarily in the cytoplasm of inactive naïve T cells. Upon antigen stimulus, CTLA-4 is mobilized to the T cell surface and binds with its ligands CD86 and CD80, causing down-regulation of T cell activation (68–71).

In lymphomas, blocking the checkpoint and harnessing the immune system as antineoplastic therapy is an active area of clinical study. Monoclonal antibodies directed against PD-1 and CTLA-4 are being designed to reduce the down-regulation of T-cell responses against malignant cells (68). Through diminished inhibitory signals, the immune response is improved and able to destroy the malignant cells. The results of the anti-PD-1/PD-L1 block are very exciting in lymphomas with 9p24.1 aberrations such as LBCL primary mediastinal (PMBCL), primary b-Cell testicular and cerebral lymphomas. Less encouraging results are reported for CLL/SLL and most of DLBCL (72). The currently used immune checkpoint inhibitors are the anti-PD-1 mABs Nivolumab, Pembrolizumab, and Pidilizumab, the anti-PDL-1 mAbs Durvalumab, Urelumab, and Atezolizumab, and the anti-CTLA-4 mAb Ipilimumab (73).

The profile of PD-L1 expression by immunochemistry has been lately proposed to retain prognostic and diagnostic significance (24).

Atezolizumab (MPDL3280A), is a humanized IgG1 anti PD-L1. It is sustained for use against several hematologic malignancies. Still little is known on the expression of CTLA-4 in human tissue. So far it has been reported that CD80 and CD86, physiological ligands for the expression of CTLA-4, can be observed in T-cell lymphoma patients, in the cells of the dendritic system, and in a subgroup of B-cells of the germinal center and B-immunoblasts in lymphomas (74).

Durvalumab (MEDI4736) is a high-affinity human IgG1 mAb that selectively inactivates PD-L1 by binding PD-1 and CD80. It has shown preliminary evidence of antitumor activity across multiple tumor types (68, 75).

Ipilimumab is a wholly humanized IgG1 mAb against the CTLA-4. Ipilimumab plus lenalidomide has been reported as well-tolerated after both autologous and allogeneic stem cell transplantation in a phase 2 study achieving a significant proportion of complete responses (76).

Nivolumab, a completely humanized IgG4 anti-PD-1 mAB, is now approved for melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma. The activity of nivolumab in lymphoid malignancies has also been widely tested (60, 61, 66, 68, 77). Patients with recurrent B-cell NHL were treated at the identical schedule with dose escalation of 1–3 mg/kg of nivolumab. Furthermore, nivolumab as a single agent is undergoing a trial in patients with FL and is currently in phase II studies (NCT02038946). Many ongoing studies also are assessing the effectiveness of nivolumab either in polychemotherapy and/or in combination with other targeted drugs such as ibrutinib (NCT02329847), ipilimumab (NCT01896999), urelumab (NCT02253992), and indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor (NCT02327078). Combinations with ibrutinib or IDO1 are particularly striking in enhancing antitumor T-cell immune responses mechanism (68). Phase 2 trials with nivolumab in patients with DLBCL (CHECKMATE 139, NCT02038933) have mature results. No response was observed in a cohort of MCL patients who receive nivolumab (78).

Pembrolizumab (alias lambrolizumab) is a humanized IgG4 antagonistic anti-PD-1 mAb. The usage of IgG4 restricts Fc receptor engagement; this produces the loss of ADCC activity of PD-1- cells, thus enhancing the antitumor immune response. A correlation with a distinctive genetic signature has been described in large B-cell lymphomas also containing alterations and translocations in the number of copies (i.e., 9p24.1/PD-L1/PD-L2) (72). However, several studies on lambrolizumab, either as a single agent (NCT02576990, NCT02362997, NCT02453594, NCT02684292, NCT02535247) and/or in combination with rituximab (NCT02446457), SMIs such as ibrutinib, idelalisib, and IDO1 (NCT02332980, NCT02178722), or conventional chemotherapy (NCT02541565), are ongoing for DLBCL and PMBCL as well as FL and other B cell lymphomas with indolent behavior (56, 74, 79, 80).

Pidilizumab was the first humanized IgG1 mAb anti PD-1 to be tested in lymphoid malignancies (56, 68, 74). It is noteworthy that CLL/SLL neoplastic cells show weak PD-1 expression (57), and low numbers of lymphocytes infiltrate PD-1 positive tumors (80). There is evidence of PD-L1 and 2 expressions in a subgroup of NHL, making this pathway a promising target (81).

Urelumab is a wholly humanized IgG4 mAb direct against CD137. CD137 (alias 4-1BB or TNFRSF9 receptor) is a member of the growth factor family receptors. CD137 is usually present on the activated T and B cells and monocytes. Although it is not part of the CTLA-4 or PD-1 pathways, its potential to immunostimulatory activities has gained an interest in the clinical development of this mAb. It has been assessed in terms of efficacy and safety in combination with nivolumab and/or rituximab against different subtypes of mature B-cell lymphomas (NCT02253992, NCT02420938) (68).

Immune Checkpoint Inhibitors-Toxicities

ICIs are tempting due to their moderately low toxicity profile. The Phase I study in solid tumors reported that 41% of patients treated with nivolumab had an adverse event, and, of them, only 6% were grade 3 or above. The investigators also reported that 71% of patients who received pembrolizumab had adverse events, with 9.5% grade 3 or higher. The main toxicity profile of CTLA-4 and PD-1 inhibitors is associated with its activity in boosting the immune response. Researches on solid tumors report hepatitis, pneumonia, colitis, thyroiditis, hypophysitis, and other inflammatory reactions. Patients receiving therapies with checkpoint inhibitors should regularly be checked for thyroid function and ACTH/cortisol levels if they experience symptoms such as fatigue or hyponatremia (58, 59, 74).

Chimeric Antigen Receptor (CAR) T-Cell Therapy

It is known that lymphomas are highly susceptible to cellular therapies, including allogeneic stem cell transplantation and the adoptive relocation of specific EBV T cells, which could be seen as the predecessor of the CAR T cells (82). CAR T cells are autologous T lymphocytes genetically modified to bind to specific antigens present on cancer cells. As a result of the binding of CAR T cells to a neoplastic cell, the signaling domains stimulate cytokine secretion, cytolysis of the tumor cell, and T cell proliferation. CAR T cells are created by apheresis of the mononuclear cells from peripheral blood. Successively, the isolated T cells are then transduced *in vitro* with a retroviral or lentiviral vector with a CAR complex including a single-chain variable fragment of antibodies (scFv) or a peptide (21, 22, 24). The later generation (second and third) of CAR cells integrate an additional domain such as CD28 into the construct, which provides a co-stimulator signal. After the expansion of treated T cells, they are ready for infusion into the patient for 1–2 days. Before CAR T cell infusion, patients receive chemotherapy that reduces lymphoma. Ideally, the target antigen of CAR T cells must be absent on healthy cells but present on cancer cells only (24). To date, for hematological malignancies, several CART therapies have received FDA approval. The first was approved was in August 2017 for the treatment of patients aged up to 25 years carrying B-cell precursor acute lymphoblastic leukemia (ALL) to CD19 cell therapy CART-4-1BB (tsagenlecleucel CTL019, Kymriah, Novartis, Basel, Switzerland) (20, 83, 84). In October 2017, the FDA granted regular approval to CD19 CAR T therapy axicabtagene ciloleucel (Yescarta, Kite Pharma, Inc.) for large B-cell lymphoma adult patients relapsed or

refractory after two extra lines of conventional therapy. They include high-grade B-cell lymphoma, DLBCL NOS, PMBCL, and DLBCL arising from FL (82, 85–87). However, despite the early efficacy observed in the procedure of CAR-T in the treatment of CLL, the initial trials in other NHLs were less promising than the response rates observed in patients with ALL. With improved induction chemotherapy, which has been demonstrated to trigger the patient for rapid expansion of T cells to adoptive transfer, CAR T cells are now showing a more likely response. There have been two reports from an ongoing study of CAR T cells carrying CD19 receptor composed of a recognition ectodomain ScFv and stimulant endodomain 4-1BB (CTL019) that demonstrate the effectiveness both in DLBCL and FCL (82). In the DLBCL cohort as part of an ongoing phase II study, 40 cases were evaluable for assessing the response at the time of data blocking (NCT03761056).

The lymphodepletion regimen before CAR T cell infusion is dependent on the organization of the institution. Moreover, the protocols for the design of CAR T cells growing and producing lentivirus or retrovirus for cell transduction also differ between studies. The timing of infusion of CAR T cells either after chemotherapy alone or immediately after autologous transplantation need to be standardized. Additional multicenter studies are needed to optimize CAR T cell protocols.

Two CAR-T therapies targeting CD19 on B cell malignancies, Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel, were both effective against multiply recurrent DLBCL. In ZUMA-1, axi-cel resulted in a median duration of response, PFS and OS of 11, 6, and >27 months, respectively (88). In JULIET, relapse-free survival with tisagenlecleucel 1 year after initial response was 65 percent (89). Both agents are associated with serious complications (e.g., fatal neurologic events and cytokine release syndrome), but no new toxicities were identified with longer follow-up. Axi-cel and tisagenlecleucel are approved for use at certified institutions by the US FDA in adults with RR DLBCL after $\geq$2 lines of systemic therapy.

Several studies report some cases that remain resistant to CAR T cells. The resistance can partly be due to the failure of the CAR T cell to overcome the inhibition created by the neoplastic cells. Therefore, studies are ongoing that combine CAR T cell therapy with inhibitors of the mAB control immune system. One trial being conducted at the University of Pennsylvania is exploring pembrolizumab following CAR T cells (NCT02650999). Another trial at Baylor College of Medicine (Houston, TX, USA) combines ipilimumab with CAR T cells (NCT00586391). An alternative mechanism of CAR T cell deficiency is the absence of perseverance of genetically modified CAR T cells. Research is underway to assess whether cytokine co-administration can improve the clonal expansion of CAR T cells (NCT00968760) (24).

CAR T Cells-Toxicities

Cytokine release syndrome (CRS) is possibly one of the leading adverse events of CAR T cell therapy. CRS is related to an elevated number of different cytokines, comprising interleukin-6 (IL-6) and interferon γ. CRS is shown by cumulative adverse events including fever, hypoxia and hypotension. Also, several blood values are altered, such as elevated C-Reactive Protein (CRP), low fibrinogen and highly elevated ferritin. By CAR T cell therapy, the beginning of symptoms correlates with the expansion of T cells, and it is usually evident within days or a few weeks (23). The percentages and severity of CRS therapy in patients with lymphoma are less recurrent than those with high levels of systemic disease such as ALL. The ability of CAR T cells to cross the blood-brain barrier (BBB) and deliver neurological toxicity to the CNS has been documented. A clinical study detected neurological toxicity with CAR T-cell infusion, 3/20 patients presented neurologic toxicity including delirium and 1/20 encephalopathy. The worst of the neurological adverse events are attenuated by the administration of dexamethasone, which also enters the BBB. Due to the exhaustion of non-malignant CD 19 lymphocytes, B cell aplasia is an additional adverse event. Finally, other major adverse events for patients are opportunistic infections due to hypogammaglobulinemia. Hypogammaglobulinemia has efficaciously contrasted with IV immunoglobulin administration after CAR T cell infusion (24, 90–94).

Bispecific Antibodies

Bispecific antibodies (bs-mAbs) are engineered antibodies able to bind two antibodies in a unique molecule and gain the capacity to target diverse epitopes simultaneously. The Bs-mAbs mechanism is analogous to the CAR-T cells, but unlike the latter, the bs-mAbs are "ready to use" drugs (68, 95–98). The identification of the tumor-specific antigen and straight involving T cells can increase the effectiveness of antibody therapy and minimize the toxicity. A BiTE® (Bispecific T-cell engager) antibody complex consists of a single fusion polypeptide (50–60 kDa) able to link two variable fragments of single chain antibodies (scFv) (99). It carries two specific binding sites, one for a link to specific B cell markers (i.e., CD19) and another that targets a co-stimulator on T cells (i.e., CD3) (24). This simultaneously activity results in T cell activation, proliferation, and T cell-induced target cell lysis (100). Differently to the "living" and self-expandable T cells, bsAbs have a short persistence limit in the patient and low objective in strongly immunosuppressed patients. A fusion of both principles can be the modification of immune or tumor cells to permanently express bispecific molecules (101).

AFM13 is a bi-specific, tetravalent chimeric antibody construct (TandAb) designed to recruit natural killer (NK) cells via CD16A as immune effector cells to CD30-expressing malignancies. AFM13 will be tried in a larger phase II trial in HL (NCT02321592) in a study with CD30-positive cutaneous lymphoma (NCT03192202) and in combination with pembrolizumab (NCT02665650) (98, 102).

Blinatumomab (MT103) is the earliest bispecific construct CD19/CD3 approved by the FDA and the EMA for the cure of R/R ALL. Blinatumomab showed high response rates at very low doses in patients with NHL and ALL B precursor. Blinatumomab contains an anti-CD3 arm and an anti-CD19 arm, allowing the junction of CD3 + T cells with the CD19 + B tumor cells. This mechanism determines the lysis of target cells and resembles T-cell-mediated killing (103, 104).

DART proteins (dual affinity retargeting) with a mechanism similar to BiTE® interact with CD3 and CD19. The DART is a new bispecific antibody engineered to overwhelm the mechanical limits of BiTE® to increase stability. DART is composed of diabody-like molecules that have the heavy variable chain (VH) region linked to the variable light (VL) of the second binder, and the VH of the second variable region linked to the VL of the first (96). Early on, DART was revealed to induce cytotoxicity in *in vitro* experiments, exhibited potent activity in several relevant tumors and showed more power than the BiTE® format (105). DART was also revealed to be reliably more effective in eradicating CD19-positive B cells. Notably, without engagement with targeted CD19-positive cells, no activation of T-cells by the DART molecule was observed. Also, *in vivo* in a xenograft mouse model, a DART molecule targeting CD19 assembled using an exclusive anti-T cell receptor antibody portion showed an activity virtually identical to that of the CD19 x CD3 DART molecule (106, 107). The DART setup is mostly attractive for clinical practice since it has been confirmed to have comparable pharmacokinetics with other mAbs. The earliest study on a DART CD19xCD3 was in patients with R/R NHL (96).

Mosunetuzumab is a full-length bispecific CD20/CD3 antibody that redirects endogenous T-cells to kill neoplastic B-cells by concomitantly binding to CD3 on T cells and CD20 on B cells. An ongoing multicenter Phase I/IB study (NCT02500407) is evaluating mosunetuzumab in R/R B cell NHL patients. The interim analysis shows that mosunetuzumab monotherapy is clinically active in this cohort of NHL, thus it is showing promising and durable efficacy in FCL and DLBCL.

BiTE-Toxicities

Accepting the risk of neurotoxicity and CRS, blinatumomab and other BiTE would be given gradually and with weekly progressive doses (24, 108). A phase I/II study of blinatumomab reported several adverse events including CRS, neurological toxicity (aphasia, ataxia, convulsions, headache, tremor), and leukopenia/neutropenia. Also, in the blinatumomab phase study, $<$10% of NHL patients have been grade 3 CRS or higher. Instead, in the phase II study, "early" prophylactic dexamethasone was used for each initiation, and an increased daily blinatumomab infusion dose for 2 days after the start reported no adverse events with CRS (109).

SMALL MOLECULES INHIBITORS (SMIs)

Although monoclonal antibodies and other immunotherapies have led to dramatic advances in the treatment of lymphoma patients, the parallel development of small molecule inhibitors has been equally exciting. These SMIs have reformed the therapeutic model for different subtypes of NHL. Many SMIs have been approved by the FDA, and others are still under evaluation. Several SMIs are administered orally, are moderately well-tolerated and offer patients unprecedented response rates. Their small size ($\leq$500 Daltons) allows for interchange through the plasma membrane, enabling the interaction with intracellular signaling molecules and the cytoplasmic domain of cell surface receptors. These SMIs inhibit signal transduction pathways by targeting proteins involved in transcriptional/translational regulation, protein stability, cell cycle regulation of mitosis and apoptosis. These new agents are a heterogeneous group of drugs with different mechanisms of action: (i) B cell receptor signaling Inhibitors like TKI, BKI, Aurora Kinase Inhibitors (AKI), and SYK; (ii) proteasome inhibitors and; (iii) HDAC inhibitors **(Table 1)**. The SMIs are not free from toxicity, especially when combined with other drugs. Therefore, we will provide advice on the relevant toxicity profiles, because these promising new treatments could hide pitfalls for the treatment of patients with NHL. In clinical practice, these new agents generate a multifaceted step in pharmacokinetics (PK), which does not encompass broad individual PK variability and unpredictable outcomes according to the pharmacogenetic profile of the patient (e.g., cytochrome P450 enzyme) (10, 17, 110, 111).

B Cell Receptor Signaling Inhibitors

Signaling mediated by B cell receptors (BCR) plays a fundamental role in the expansion of B cell neoplasms. Antigenic stimulation of the BCR extracellular domain starts a signaling cascade accountable for several B cell functions and proliferation. This signal leads to the enrollment of CD79a and CD79b, leading to activation of the spleen tyrosine kinase (SYK) and the LYN kinase. SYK and LYN phosphorylated tyrosine-based immunoreceptor activators activate Bruton tyrosine kinase (BTK) and inositol phosphatidyl three kinase δ (PI3Kδ) (111–115). Inhibitors of BTK, PI3Kδ, and the SYK have been designed to block kinases in this way (17).

BTK Inhibitors

Ibrutinib (PCI-32765) is an irreversible oral inhibitor of BTK that binds the active site cysteine-481 (Cys481) of the BTK enzyme. BTK is mainly expressed on—but not limited to—B cells, and ITK is mainly expressed on T cells (111–113). Though chemoimmunotherapy is the standard of care for patients eligible with CLL, its toxicity and risk of infection exclude its use in frail patients (elderly and those with co-morbidities). Another restriction to the treatment group consists of patients carrying 17p aberrations of the TP53 gene as poorly endowed with ordinary chemoimmunotherapy (116, 117). The combination of ibrutinib with mAbs also led to high response rates, with ORRs of 95% with rituximab, 71–100% with oratituumab, and 88% with ublituximab (118, 119). However, there was abrogation of induced lymphocytosis from therapy although it is not yet clear how meaningfully the combination affects the deepness and duration of the response (DOR) equated only to ibrutinib (17). Ibrutinib has been tried in combination with rituximab, ifosfamide, carboplatin, and etoposide (R-ICE). It is also used, as well as rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP), in the second line rescue therapy for R/R DLBCL patients. Ibrutinib was evaluated in R/R FCL and R/R MCL in several clinical trials as monotherapy and combinations.

The second generation BTK inhibitors include acalabrutinib (ACP-196) and underdevelopment ONO-4059 (GS-4059), BGB-311, and CC-292. **Acalabrutinib** is an irreversible BTK inhibitor with a shorter pharmacokinetics $t_{1/2}$. It does not inhibit EGFR and other TK receptors. In a phase I study, 95% of patients with

R/R CLL carrying the 17p alteration accounted for the median at a follow-up of 14 months. A common adverse event was diarrhea and bleeding, but no atrial fibrillation was reported (120). It is improbable that ACP-196 is effective in patients with ibrutinib resistance (120). But its use in intolerance to ibrutinib patients is now under investigation (NCT02717611). Other second-generation BTK inhibitors have accounted for effectiveness (121–123). It remains to be understood whether these molecules will have a noteworthy effect compared to ibrutinib.

BTK-Toxicities

The most common adverse effects were non-hematologic toxicities, including muscle spasms, nausea, fatigue, diarrhea, skin rash, and arthralgia. Hematologic toxicities were less common and included several grades of neutropenia, thrombocytopenia, and anemia (124).

PI3K Inhibitors

More downstream from BTK is PI3K. Ubiquitous PI3K fits a highly conserved family of kinases with specific tissue isoforms α, β,γ, and δ. The isoform δ is present on leukocytes and is, therefore, a target of interest. The γ isoform has been associated with the growth and signaling of T cells. The inhibition of p110δ has been revealed to reduce the downstream signaling of the BCR, CXC 4 receptor (CXCR4), and 5 (CXCR5) chemokines. In preclinical studies, it resulted in decreased protein kinase B (AKT) activation, a molecular target of rapamycin (mTOR) and other pathways (111). The PI3K inhibitors currently in use and under investigation in lymphomas are Idelalisib, Copanlisib, Buparlisib, and Umbralisib. Overall, PI3K inhibitors seem to have low response rates in patients with R/R DLBCL when used as monotherapy. It should be studied in combination with other new agents with carefulness to minimize latent toxicity (125).

Buparlisib is a strong PI3K oral inhibitor that has confirmed effects in *in vitro* and *in vivo* models of hematologic malignancies (126–128).

Copanlisib is an intravenous class I directed against isoforms PI3K-γ and PI3Kδ (129). To assess the effectiveness of copanlisib in DLBCL, patients were treated with 60 mg (130). Copanlisib was evaluated in both indolent and aggressive lymphomas (130–133).

Idelalisib (CAL-101) is a potent and highly specific inhibitor of the PI3K δ isoform. It is approved for refractory indolent lymphoma (134, 135). Idelalisib has shown activity either as a single agent and/or in combination with mAbs in R/R CLL in FCL and HL (136–142).

Duvalisib is an oral inhibitor of PI3K δ and γ isoforms showing activity in the small non-randomized study of patients with multiply relapsed FL. It is approved by the FDA as a single agent for the treatment of relapsed FL patients who received at least two previous conventional therapies. In this study, CRs are quite uncommon although ∼40% of patients achieve a PR. More recently, a small single-arm multicenter trial (DYNAMO) of duvelisib in multi-relapsed patients with CLL/SLL, MZL, and FL reported response rates over 40 percent with an estimated median duration of response of 9.5 months. CLL/SLL patients had a better outcome than the other subtypes (143). Fatal and/or serious toxicities could be seen, including opportunistic pneumonitis from *P. jirovecii* pneumonia, diarrhea or colitis, and cutaneous reactions.

Umbralisib is the latest oral inhibitor of both PI3Kγ and casein kinase 1ε (CK1ε).

PI3K Inhibitor Toxicities

PI3K inhibitors have a distinctive toxicity profile, including severe diarrhea/colitis. Grade 3 or higher toxicity has been reported with an incidence of around 15%. In addition, opportunistic infections including pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV) have been recognized in patients treated with idelalisib (144–146).

SYK Inhibitors

Other components of BCR signaling are potential targets include LYN and SYK as described above (20). SYK is an SH2 domain-containing tyrosine kinase activity. Constitutive activation by SYK leads the development of NHL. It is noted that DLBCL tissue overexpresses the components of the BCR signaling pathway, including SYK. Inhibition of SYK remains a promising goal, but it should be combined with other drugs to produce lasting and meaningful responses (147).

Cerdulatinib (PRT062070) is an oral kinase dual inhibitor of JAK 1/3 and SYK and has been revealed in *in vitro* experiments to have a specific inhibitory action in a subgroup of B-cell lymphoma cell lines (148). Cerdulatinib inhibited B-cell activation in a murine model of chronic BCR stimulus. In DLBCL cell lines, cerdulatinib induced apoptosis, blocking cell-cycle, BCR and JAK/STAT signaling (149). It has been described as having synergistic action of cerdulatinib and venetoclax in primary a CLL primary cell line (150). Remarkably, cerdulatinib showed better inhibition of cell duplication than ibrutinib in the ibrutinib-resistant CLL cells and BTKC481S-transfected/ibrutinib-resistant lymphoma cells (147, 151, 152). This double SYK/JAK inhibitor was also evaluated in patients with different R/R B Cell malignancies (153, 154).

Entospletinib (GS-9973) is an oral drug that selectively inhibits SYK (155). This 2nd generation molecule showed increased *in vitro* and *in vivo* selectivity for JAK-2, c-KIT, FMS-like tyrosine kinase 3 (FLT 3), VEGFR2, and RET compared to fostamatinib (155). In a multicenter study on subjects with R/R CLL and NHL, entelospletinib showed a promising toxicity profile (147). Moreover, in the latest phase II study entospletinib was shown to have low clinical activity in 39 patients with R/R MCL (147, 156).

Fostamatinib is an oral Syk inhibitor leading to a reduction in cell survival (157). In this light, good preliminary results were obtained from a double-blind, randomized study enrolling patients with R/R DLBCL who were not suitable for HSCT (158–160).

TAK659 is a promising selective, reversible SYK and FLT3 inhibitor demonstrated in both *in vitro* and *in vivo* models (161). Inhibition of SYK remains a promising goal, but it should probably be joined with other antineoplastic drugs to harvest lasting and significant responses (111).

SYK Inhibitors Toxicities

The most frequent toxicities observed with SYK Inhibitors are diarrhea, nausea, hypertension and fatigue. Hematological common adverse events are neutropenia and thrombocytopenia (147).

Proteasome Inhibitors (PIs)

The ubiquitin-proteasome pathway is a multifaceted complex responsible for the regulation of proteins involved in neoplastic activity, such as cyclin-dependent kinases (CDK), BCL-2, and NFκB complex (162, 163). The role of the proteasome is upregulation of these key pathways, making it a promising antineoplastic target (10, 164–168). Finding that PIs lead to cell cycle inhibition and apoptosis in tumor cells has pushed them to be developed as antineoplastic agents. The studies revealed a complex system of ubiquitin ligases and related proteins that orchestrate the delicate balance of longevity of proteins within cancer cells. It is thought that the constellation of proteins whose degradation is inhibited by PI interrupts intracellular processes crucial for the survival of tumor cells. Some examples are (1) cell cycle interruption by inhibiting the degradation of CDK such as p21 and p27; (2) inhibition of the nuclear signal transduction pathway of the κB factor (which typically inhibits apoptosis) through the accumulation of the I-κB inhibitory protein; and (3) promoting apoptosis prolonging the function of the pro-apoptotic members of the Bcl-2 proteins, such as Noxa (10, 164–168).

Bortezomib was the first of this class of drugs to undergo clinical development. The first phase 1 study of hematological malignancies showed signs of activity in multiple myeloma (MM), FCL, MCL, and MALT lymphoma (169, 170). It is FDA approved for use in naive and R/R multiple myeloma (MM).

Bortezomib's success has triggered the evolution of 2nd generation PIs, looking to improve on the activity but to minimize the toxicities (primarily peripheral neuropathy) not only for MM but also as therapeutic alternatives in other diseases, including lymphomas and systemic amyloidosis. The development of **carfilzomib** has shown noteworthy advancement to being effective and less neurotoxic for patients with relapsed or R/R MM who failed ≥1 preceding line of therapy. Unlike carfilzomib, bortezomib has demonstrated irreversible inhibitory kinetics.

Ixazomib is a second-generation inhibitor of the 20S proteasome that is supplied in both IV and oral drug formulations. Ixazomib has shown efficacy in preclinical lymphoma models (171, 172). This PI has a modest single-agent activity, although so far combination with other drugs has not been shown to increase overall results (111, 173).

Proteasome Inhibitors Toxicities

Proteasome Inhibitors showed a significant toxicity profile: serious neurotoxic side effects, cardiovascular and gastrointestinal toxicities, peripheral neuropathy and cytopenias (174–176). Other symptoms include herpetic zoster reactivation lymphopenia, thrombocytopenia, and persistent fatigue. In addition, although rare a minor proportion of subjects showing cardiac failure was recorded with the 1st generation of PIs (177).

Mammalian Target of Rapamycin-mTOR Inhibitors (mTOR)

mTOR is a keyway in the regulation of trans-membrane trafficking, protein degradation, ribosome biogenesis, protein kinase C signaling, and DNA transcription (178, 179). Thus, triggering of the PI3K/AKT pathway and mTOR signaling is essential in lymphomagenesis. Inhibition of this pathway revealed the blocking of cell duplication (180–182).

Everolimus is an oral mTOR inhibitor (183). The primary studies examined this agent in R/R DLBCL, and afterward for R/R CLL/SLL and R/R HL (184–190).

Temsirolimus is an FDA-approved IV mTOR inhibitor in metastatic renal cell carcinoma (191). The EMA in Europe approved Temsirolimus for MCL, too (192), and temsirolimus was also added to the list of rescue regimens for R/R NHL patients (193, 194).

mTOR Inhibitor Toxicities

mTOR inhibitors are attractive agents since they are well-tolerated as single agents and in combination with other drugs. They have also demonstrated synergism with PIs, leading to the study of combination therapy (10). The side effects include a variety of metabolic, hematological, respiratory, renal, and dermatological toxicities. The tolerability scale of mTORIs, even at the same dosage and for the same application, ranges from excellent to debilitating (e.g., buccal aphthous), can sometimes be fatal (pneumonitis) and may occur at different time points (from days to years) after the initiation of rapalog therapy. Surprisingly, the rate of some side effects, such as pneumonitis or mucocutaneous effects, seems to increase with the dosage of the drug, whereas mTOR is inhibited at the nanomolar range by rapalogs. Alternatively, the majority of these side effects are idiosyncratic and unpredictable (195–197).

BCL2 Inhibitor

Several neoplasms seem to be mainly dependent on a specific balance of Bcl-2 family expression for their survival, and Bcl-2 overexpression can lead to both *de novo* and acquired chemoresistance (10). The overexpression of the anti-apoptotic BCL-2 protein is frequent in several NHL subtypes, including 30% of the DLBCL (198–201). Inhibition of BCL-2 has become an important treatment strategy because of increasing apoptosis. BCL2 inhibitors were applied primarily for the treatment of CLL patients (111, 202, 203).

Venetoclax is an oral formulation. In preclinical study, it has been shown to have powerful selective "BH3-mimetic" activity independent of BCR signaling (apoptosis free of p53) (204–207). In xenotransplantation models, venetoclax has shown greater efficacy when combined with chemoimmunotherapy. Despite the recurrent overexpression of BCL2, monocomponent venetoclax did not have an equally robust response as expected in the DLBCL, while it seems to be well-tolerated (206, 208). Forthcoming studies focus on multiple combinations of venetoclax to increase responses. The European Commission of Medicines (EMA) has approved the combination of venetoclax plus rituximab (V + R) for the treatment of R/R CLL patients previously treated by other therapies (209–211). EMA approval

is established on the published results of the Phase 3 MURANO randomized trial (210, 212, 213). This trial compared the BCL2 inhibitor venetoclax administered up to a maximum of 2 years, associated in the first 6 months of R treatment, with the classic chemo-immunotherapy regimen bendamustine and rituximab (BR) administered for six cycles every 4 months (210, 213).

BCL2 Inhibitor Toxicities

Nausea, diarrhea, anemia, lymphopenia, neutropenia, and thrombocytopenia are the most frequent AEs, with a minor—although enough to grab attention—incidence of tumor-lysis syndrome (214–216).

HDAC Inhibitors (HDIs)

Histone deacetylases (HDAC) are enzymes designed against both the histone and non-histone proteins. To date, 18 HDAC enzymes were identified based on their homology with yeast deacetylases. Human HDACs were categorized into four classes: class I includes HDAC 1, 2, 3, and 8, which are located in the nucleus. Class II comprises HDAC 4, 5, 6, 7, 9, and 10, which have a mutable cellular location; class III contains the NAD-dependent yeast homologs, SIRT 1-7, which are not targeted by the currently available HDAC inhibitors (HDACI). Finally, class IV includes HDAC 11 (217, 218). HDIs have been shown to activate cell cycle checkpoints, promote apoptosis, induce cell differentiation, suppress angiogenesis, and improve immune surveillance. HDAC inhibitors (HDI) include a class of synthetic or natural chemical compounds that inhibit the enzymatic activity of HDAC. Several HDIs have been studied in lymphomas, demonstrating only modest clinical benefit, and other HDIs are currently studied in preclinical studies (218, 219).

CUDC-907 is a class I-II oral double-inhibitor of HDAC and PI3K (α, β, γ) enzymes (111, 220, 220–222).

Mocetinostat is an oral HDI that inhibits class I and IV, specifically HDAC isoforms 1, 2, 3, and 11 (223, 224). Mocetinostat was evaluated in a phase II study in R/R DLBCL patients (18, 111, 223–225).

Panobinostat is a potent pan-HDAC inhibitor with low dosage achievement against class I, II, and IV HDAC and is FDA approved for DLBCL (225).

Vorinostat is one of the first HDAC inhibitors with activity against HDAC class I and II. It has synergistic antineoplastic action when combined with topoisomerase II inhibitors (111, 226–228).

HDAC-toxicities

Even though the HDAC family contains several chemical compounds with selectivity for different HDAC isoforms, they unexpectedly have analogous toxicity profiles. Generally, common non-hematologic AEs are diarrhea, nausea, vomiting, fatigue, anorexia, weight loss, and asthenia. Most common hematologic AEs are thrombocytopenia, anemia, and neutropenia (229).

NOVEL AGENTS IN MATURE B-CELL LYMPHOMA SUBTYPES WITH INDOLENT BEHAVIOR

Patients suffering mature B-cell lymphoma with histological subtypes associated with an indolent behavior such as CLL/SLL, FL, MZL, LPL, and a fraction of those with MCL are generally highly responsive to chemotherapy regimens conventionally based on purine analogs, alkylators with or without the inclusion of anthracyclines. However, they remain still incurable and suffer subsequent relapses and a high risk of histological transformation toward a "large cell" histology. Targeted agents have redefined treatment paradigms in this setting of recurrent patients (**Table 2**). Most patients with FL experience serial relapse and will be treated with many available agents at some point during their disease course. A preferred order for their use has not been established. Novel agents such as idelalisib, copanlinib, or duvelisib and radioimmunotherapy may be used for multiply relapsed indolent B cell lymphomas. The efficacy and safety of novel agents may quietly differ among different subtypes. As an example, Ibrutinib, which achieves high response rates in MCL, accounts for only 21 and 38 percent ORRs in patients with R/R FL, respectively. Results in the setting of recurrent patients have prompted some of these agents, targeting either cell surface antigens, intracellular pathways or the microenvironment, as a possible front-line option (**Table 4**).

NOVEL AGENTS IN MATURE B-CELL LYMPHOMA SUBTYPES WITH AGGRESSIVE AND VERY AGGRESSIVE BEHAVIOR

Due to the high failure rate produced by excessive toxicity and low response rates to conventional chemotherapies (or both), subtypes with aggressive behavior such as DLBCL, the majority of MCL, transformed FCL and Burkitt lymphoma still represent a burning problem and an unmet need in the setting of mature-B cell lymphoma.

The myriad of novel agents under development, targeting the new pathways fundamental to aggressive B cell growth is expected to offer added clinical benefit to patients with aggressive B cell NHL. Furthermore, these novel agents characterize sustained advancement in the planning for individualized therapies, as single modality treatment, or combined with chemotherapy or other targeted agents (**Table 3**).

The anti-PD-1 and anti-PD-L1 treatment approaches, coupled with other agents have produced somewhat disappointing results for recurrent DLBCL (74). Currently, inhibition of PD-1/PD-L1 is used in the clinical trial in combination CAR T cell therapy (NCT02926833 and NCT02706405) or recurrence after CAR-T cell therapy (NCT02650999).

CAR T therapies that target CD19 on B cell malignancies were effective against multiply relapsed DLBCL in initial trials and have confirmed their effectiveness at longer-term follow-up.

TABLE 2 | Overview of the efficacy of select novel therapies in Mature B-Cell neoplasms: indolent histology.

	Authors	Drug	Target	Phase	Setting	N° of pts	ORR% (CR %)	PFS% (y)	PFS median (mo.s)	*AEs
CLL/SLL	Byrd et al. (121)	Acalabrutinib	BTK	I	R/R with 17p alteration	61	95%	NR	14.3	Dyarrhea
CLL/SLL	Byrd et al. (121)	Ublintuximab	CD20	II	Naïve. Two arms of 1 g/day and 2 g/day	80	67%	NR	20.3	12% neutropenia in 2 g/day arm
CLL/SLL	Nastoupil et al. (230)	Ublintuximab	CD20	I	Dose escalation. Post-Rituximab. In combination with umbralisib, and ibrutinib	46	84%	NR	NR	24%
CLL/SLL/	Ding et al. (83)	Pembrolizumab	PD-1	II	R/R carrying 17p alteration and IGHV unmutated	16	44%	NR	NR	ND
CLL/SLL	Gopal et al. (139)	Idelalisib	PI3K	II	R/R. In combination to Brivatinib	125	57% (6%)	12% (2 y)	11	ND
CLL/SLL	Liu et al. (147)	Entospletinib	Syk	II	R/R. dosing 1,6 g/daily	41	61%	NR	13.8	ND
CLL/SLL	Seymour et al. (210)	Venetoclax	BCL2	II	R/R. 17p deletion In combination to Rituximab	49	86%	82% (2 y)	NR	67%
CLL/SLL	Jaglosky et al. (119)	Ibrutinib	BTK	1b/II	R/R with 17p deletion. Dosing 420mg/day. In combination to Ofatumumab	71	83% (1.5%)	83% (1 y)	NR	11% led discontinuation
CLL/SLL	Rosenthal et al. (18)	Ibrutinib	BTK	III	R/R. In combination to Bendamustine and Rituximab	ND	93% 40%	96% (1 y)	NR	ND
FL	Younes et al. (231)	Nivolumab	PD1	I	R/R in combination to ibrutinib	40	36%	NR	5	13% anemia
FL	Ganjo et al. (232)	Ocaratuzumab	CD20 FcγRIIIa	I/II	R/R with low affinity genotype FcγRIIIa	50	30%	NR	9.2	ND
FL	Czuczuman et al. (233)	Ofatumumab	CD20	I/II	R/R. Dosing 500 mg/day	27	22%	NR	5.8	Neutropenia
FL	Westin et al. (234)	Pidilizumab	PD1	II.	R/R. Dosing 3 mg/kg IV every 4 weeks. In combination to Rituximab	32	52%	NR	15.4	No AEs grade >2
FL	Westin et al. (234)	Pidilizumab	PD-1	II	R/R combined with Rituximab	29	66%	NR	18.8	No AEs grade >2
FL	Gopal et al. (141)	Idelalisib	PI3Kd	II	R/R. Dosing 150mg twice daily	125	57% (50%)	NR	11	Neutropenia 27%
FL	Bartlett et al. (235)	Ibrutinib	BTK	I	Naïve in combination with Rituximab. Dosing 560mg/day	31	37.5% 12.5%	80.4% (2y)	14	Neutropenia 10%
FL	Davids et al. (236)	Venetoclax	BCL2	I	R/R to Bendamustine Rituximab. Dosing 1.2 g/day	29	38%	NR	11	Neutropenia 11%
MZL	Noy et al. (237)	Ibrutinib	BTK	II	R/R. dosage 560 mg/day	63	48%	NR	14.2	pneumonia 8%
B-NHLnos	Goebler et al. (109)	Blinatumumab	CD3/CD19	I	R/R maximum dose tolerated	35	69%	NR	13,5	ND
B-NHLnos	Ansell et al. (238)	Ipilimumab	CTLA-4	I	R/R. 3 mg/kg/mo.s ×4mo.s	18	11%	NR	16	ND
iNHL	Cheson et al. (45)	Obintuzumab	CD20	III	Randomly comparing to bendamustine in R/R to rituximab	396	NR	NR	22.5	ND

**Grade ≥3 non hematological AEs, only.*

ASCT, Autologous Stem Cell Transplantation; B-NHL, B-NHL not otherwise specified; CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia; DLBCL, Diffuse Large B cell Lymphoma; FL, Follicular Lymphoma; HG-BCL, High Grade B-cell lymphoma; IGHV, Immunoglobulin G Heavy Variable chain; iNHL, indolent NHL; IV, intravenous; LBCL Large B-cell lymphoma; MCL, Mantle Cell Lymphoma; mo.s, months; MZL, Marginal Zone Lymphoma;; ND, Not Documented NR, Not Reached; pts, patients; R/R, Refractory/relapsed; y, years.

TABLE 3 | Novel agents currently under investigation in Mature B-Cell neoplasms: aggressive and very aggressive histology.

Subtype	Author	Drug	Class/target	Phase	Setting	N° of pts	ORR%	PFS % (y)	PFS (mo.s)	*AEs
DLBCL	Ansell et al. (63)	Nivolumab	Anti-PD1	II	R/R Failed to ASCT (87 pts). Ineligible to ASCT (34 pts)	121	10% failed 3% ineligible	NR	Failed 12.2 Ineligible 5.8	24%
DLBCL	Armand et al. (239)	Pidilizumab	Anti-PD1	II	R/R ASCT	66	51%	NR	16	ND
DLBCL	Locke et al. (88)	axicabtagene ciloleucel	CD19	I/II	R/R. 1.0 × 10^6 CAR T cells/Kg	101	83% (58%)	NR	5.9	11%
DLBCL	Shuster et al. (89)	tisagenlecleucel	CD19	II	R/R. 1.0 × 10^7-6.0 × 10^8 CAR T cells	93	52% 40%	35% (1 y)	NR	ND
DLBCL	Viardot et al. (110)	Blinatumumab	CD3-CD19	II	escalation dose 9-28-112 ug/day	17	43%	NR	NR	17% Neurologic
DLBCL	Wang et al. (240)	Ibrutinib	BTK	II	R/R	54	28%	NR	3	ND
DLBCL	Younes et al. (241)	Buparlisib	PIK3	II	R/R	26	11.5%	NR	1.8	Hyperglicemia 11%
DLBCL	Flinn et al. (158)	Fostamatinib	Syk	I/II	Ineligible for ASCT. Dosing 200 mg/day	47	21% (4%)	NR	5.3	ND
DLBCL B-NHL	Rhodes et al. (112)	TAK659	Syk/FLT3	II	R/R	77	27%	NR	NR	ND
DLBCL	Witzens-Harig et al. (194)	Temsirolimus	mTOR	II	In combination with rituximab. Dosing 24, 50, 75, or 100 mg	32	28% (12.5%)	NR	2.6	ND
DLBCL	Rhodes et al. (112)	Vorinostat	HDAC	I/II	In combination to R-CVEP	16	57%	NR	9.2	ND
DLBCL FL	Batlevi et al. (225)	Mocetinostat	HDAC	II	R/R	72	18.9%	NR	2.1	ND
DLBCL	Oki et al. (242)	CUDC-907	HDAC/PIK3	II	R/R (14 of them with Myc altered). with or without Rituximab	37	37% 64% in Myc altered	NR	11.2 13.6 in Myc altered	Neutropenia
HG-BCL	Dryling et al. (131)	Copanlisib	Pl3K-γ and Pl3Kδ	II	CD79b mutations	43	25%	NR	2 m	ND
MCL	Wang et al. (243)	Lenalidomide	Pls	II	R/R to Ibrutinib	58	29%	NR	5	No AEs grade >2
MCL	Younes et al. (241)	Buparlisib	PIK3	II	R/R	22	22.7%	NR	11.3	ND
MCL	Jerkeman et al. (244)	Ibrutinib	BTK	II	R/R in combination to Rituximab and Lenalidomide	50	76%	NR	17.8	Neutropenia 38%, Infection 22%

**Grade ≥3 non-hematological AEs, only.*

ASCT, Autologous Stem Cell Transplantation; B-NHL, B-NHL not otherwise specified; CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia; DLBCL, Diffuse Large B cell Lymphoma; FL, Follicular Lymphoma; HG-BCL, High Grade B-cell lymphoma; IGHV, Immunoglobulin G Heavy Variable chain; iNHL, indolent NHL; IV, intravenous; LBCL Large B-cell lymphoma; MCL, Mantle Cell Lymphoma; mo.s, months; MZL, Marginal Zone Lymphoma;; ND, Not Documented NR, Not Reached; pts, patients; R-CVEP, rituximab, cyclophosphamide, vorinostat, etoposide, and prednisone; R/R, Refractory/relapsed; y, years.

TABLE 4 | Ongoing trials of immunotherapeutic agents in mature B cell neoplasms.

Drug	Target	Histologic subtype	Study phase	Schedule	Setting (planned enrollment)	Current trials
ANTI-CD mAbs						
Camidanlumab Tesirine	CD25	B-NHL	I	Single Agent, Adaptive Dose-Escalation Study	R/R (140 pts).	NCT02432235
Epratuzumab	CD22	HG-BCL	I/II	Randomized: 90Y-Epratuzumab wk 2 3 (days 8 & 15)	R/R (70 pts). Random Veltuzumab vs Epratuzumab	NCT01101581
Obinutuzumab	CD20	B-NHL	II	Randomized: Single Agent vs. O-ICE	R/R (25 pts)	NCT02393157
Ofatumumab	CD20	CLL/SLL	I	Dose finding	R/R (60 pts) In combination to rituximab. In addition to bendamustine	NCT02361346
Polatuzumab Vedotin	CD79b	DLBCL FL	Ib/II	Randomized: Pola+Rituximab vs. pola+Rituximab+Bendamustine	R/R. (314 pts) In combination to rituximab. In addition to bendamustine	NCT02257567
Ublituximab	CD20	B-NHL	I/II	450 mg followed by 600 mg, 900 or 1,200 mg in each cohort	R/R CD20 Directed Antibody Therapy	NCT01647971
IMMUNE CHECKPOINT INHIBITORS						
Atezolizumab	PD-L1	DLCBL	II	18 cycles followed by 12 mos of observation	R/R (114 pts) IPI-score $\geq$ 3 in patients to R/R R-CHOP	NCT03463057
Durvalumab	PD-L1	CLL/SLL	I/II	1,500 mg (IV) infusion on Day 1 of Cycles 1 through 13	R/R. (106 pts) In combination to Bendamustine, Lenalidomide and Rituximab in 4 arms	NCT02733042
Ipilimumab	CTLA-4	DLBCL	Ib/II	Ipilimumab mg/kg nivolumab 3 mg/kg	R/R (13 pts) whom are ineligible for ASCT.	NCT03305445
Nivolumab	PD-1	FL	I	240 mg IV q2-weekly for four cycle	Naive (39 pts).	NCT03245021
Pembrolizumab	PD-1	DLBCL	I/II	200 mg IV infusion (day 1), oral CXD101 20 mg twice daily.	R/R (45 pts). In combination to CXD101 HDAC inhibitor	NCT03873025
Pidilizumab	PD-1	iNHL	I/II	Dose safety	R/R (109 pts). In combination with ibrutinib. Three arms	NCT02401048
(CAR) T-CELL THERAPY						
lisocabtagene maraleucel	CAR-T	HG-BCL	II	Single dose intravenous	R/R (50 pts).	NCT03744676
Axicabtagene ciloleucel	CAR T-4-1BB	DLBCL	II	Single infusion of CAR-T post Fludarabina and cyclophosphamide.	High risk (40 pts).	NCT03761056
Axicabtagene ciloleucel	CAR T-4-1BB	DLBCL	II	single infusion of CAR-T	R/R (350 pts). Randomized vs. standard protocols (i.e., R-ICE)	NCT03391466
BISPECIFIC ANTIBODIES						
Blinatumomab	CD19/CD3	iNHL	II	Dose escalation 9–28 μg/day	R/R (28 pts). Single agent	NCT02811679
Mosunetuzumab (BTCT4465A)	CD20/CD3	iNHL and CLL/SLL	I/Ib	atezolizumab 1200 mg IV infusion in combination with Mosunetuzumab.	R/R (665 pts) in combination to Atezolumab	NCT02500407

ASCT, Autologous Stem Cell Transplantation; B-NHL, B-NHL not otherwise specified; CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia; DLBCL, Diffuse Large B cell Lymphoma; FL, Follicular Lymphoma; HG-BCL, High Grade B-cell lymphoma; IGHV, Immunoglobulin G Heavy Variable chain; iNHL, indolent NHL; IV, intravenous; LBCL Large B-cell lymphoma; MCL, Mantle Cell Lymphoma; mo.s, months; MZL, Marginal Zone Lymphoma; ND, Not Documented NR, Not Reached; pts, patients; R- ICE, rituximab, cyclophosphamide, etoposide; R/R, Refractory/relapsed; y, years.

TABLE 5 | Ongoing trials of signal transduction pathway inhibitors in mature B cell neoplasms.

Drug	Target	Histologic subtype	Study phase	Schedule	Setting (planned enrollment)	Current trials
BCR INHIBITORS						
Acalabrutinib	BTK	HG-BCL	I	IV infusion days 1, 3, 5	R/R (42 pts)	NCT03527147
Ibrutinib	BTK	MCL	III	1 tablet/day	Randomized in combination to Venetoclax (287 pts)	NCT03112174
Ibrutinib	BTK	DLBCL	Ib Dose Finding	1 tablet/day until disease progression	R/R (30 pts) in combination to Rituximab and Venetoclax	NCT03136497
LOXO-305	BTK C481 mutation	CLL/SLL	I/II	25 mg/day	R/R with C481 mutation in *BTK* gene.	NCT03740529
Copanlisib	PI3K	B-NHLnos	Ib/II	Days 1, 8, and 15 of a 28-day cycle	R/R (25 pts)	NCT02342665
Duvelisib	PI3Kδ + γ	CLL/SLL	I/II	Orally twice daily	R/R (47 pts) in combination with Venetoclax	NCT03534323
Idelalisib	PI3K δ	CLL/SLL iNHL	II	1 tablet/day (cycle 21 day)	R/R (68 pts). Combination to Pembrolizumab	NCT02332980
Cerdulatinib (PRT062070)	SYKJAK 1-2	FL, DLBCL	I/IIa	Dose finding	R/R (283 pts)	NCT01994382
TAK659	SYK/FLT3	FL, MZL	I	60–80 mg/day	R/R (47 pts). Single agent	NCT03238651
PROTEASOME INHIBITORS						
Bortezomib	PIs	B-NHLnos	I/II	MTD	R/R (56 pts). Combination to Gemcitabime and Rituximab	NCT00863369
Ixazomib	20S subunit	iNHL	II	once weekly × 4 wk	naïve iNHL (36 pts). In addition to Rituximab sd	NCT02339922
mTor- INHIBITORS						
Temsirolimus	mTor	Lymphoblastic Lymphoma	I	Day 1-8 IV	R/R (30 pts). in combination to Etoposide and Cyclophosphamide	NCT01614197
BCL2 INHIBITOR						
Venetoclax	BH3 domain	DLBCL	Ib	1 tablet/day (cycle 28 day)	R/R (30 pts). In combination with Rituximab with 17p deletion	NCT03136497
HDAC INHIBITORS						
CUDC-907	Class I and II+ PI3K	DLBCL	II	ND	R/R (200 pts) with Myc alteration	NCT02674750
Mocetinostat (MGCD0103)	Class I and IV	DLBCL	II	70 mg/3 times per week on a 28 day	R/R (7 pts) with mutations of Acetyltransferase Genes	NCT02282358
Panobinostat	Class I, II and IV	DLBCL	II	30 mg/day	R/R (42 pts). Randomized with or without Rituximab	NCT01238692
Tazemetostat	EZH2	DLBCL FL	I/II	Dose escalation	Single agent (420 pts)	NCT01897571
Vorinostat	Class I and II	DLBCL, FL	I	Days 1–5 and 8–12. Cycle 21 days	R/R (60 pts). In combination to Pembrolizumab	NCT03150329

ASCT, Autologous Stem Cell Transplantation; B-NHL, B-NHL not otherwise specified; CLL/SLL, Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia; DLBCL, Diffuse Large B cell Lymphoma; FL, Follicular Lymphoma; HG-BCL, High Grade B-cell lymphoma; IGHV, Immunoglobulin G Heavy Variable chain; iNHL, indolent NHL; IV, intravenous; LBCL Large B-cell lymphoma; MCL, Mantle Cell Lymphoma; mo.s, months; MZL, Marginal Zone Lymphoma; ND, Not Documented NR, Not Reached; pts, patients; R-CVEP, rituximab, cyclophosphamide, vorinostat, etoposide, and prednisone; R/R, Refractory/relapsed; y, years; MTD, maximum tolerated dose; wk, week; sd, standard dosage.

CONCLUSION AND FUTURE OUTLOOK

The development of drugs in lymphomas has undergone substantial changes in the last decade. An endeavor is ongoing to change conventional chemotherapy, with more targeted molecules directed against cell complexes and pathways that are explicitly related to lymphomagenesis. An overview of the ongoing trials is finally provided (**Table 4**). While mAbs have been the first trend of targeted therapies, there is now a new generation of biological agents, and more of them with an oral formulation, that takes full advantage of a superior understanding of lymphomagenesis. In addition, they have achieved outstanding results especially in subtypes with indolent behavior. Immune therapy with CIs and other models such as CAR-T cells and bispecific antibodies have shown promising results in mature B-cell lymphomas with aggressive behavior where other targeted agents have unfortunately demonstrated only modest improvements. Combined targeted therapy and chemotherapy will be a promising therapeutic strategy and is currently being exploited in ongoing trials (**Tables 4**, **5**). However, early identification and appropriate management of toxicities should represent a significant issue since important adverse events have been reported, due to both on- and off-target effects, which have already been demonstrated to be unpredictable, leading to the early closure of some studies. Most notably, the occurrence of unforeseen immune events has highlighted the pitfalls of novel drugs emblematically, either as a single agent and/or in combination. Immune/inflammatory toxicities have been reported with checkpoint immunotherapy and combinations of PI3K/SYK inhibitors while hematologic toxicities are pronounced with the BCL-2 inhibitors and standard chemotherapy (245).

With the current knowledge of target therapies, each patient's cancer biology may be driven to the best cancer treatment.

AUTHOR CONTRIBUTIONS

SC and RaD wrote the manuscript. SC, MB, and PR selected bibliography. SC and GR prepared **Figure 1**. PV and SM prepared the **Table 1**. RoD and AP over-reviewed the manuscript.

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