

Review

Upcoming immunotherapeutic combinations for B-cell lymphoma

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Summary

After initial introduction for B-cell lymphomas as adjuvant therapies to established cancer treatments, immune checkpoint inhibitors and other immunotherapies are now integrated in mainstream regimens, both in adult and pediatric patients. We here provide an overview of the current status of combination therapies for B-cell lymphoma, by in-depth analysis of combination therapy trials registered between 2015–2020. Our analysis provides new insight into the rapid evolution in lymphoma treatment, as propelled by new additions to the treatment arsenal. We conclude with prospects on upcoming clinical trials which will likely use systematic testing approaches of more combinations of established chemotherapy regimens with new agents, as well as new combinations of immunotherapy and targeted therapy. Future trials will be set up as basket or umbrella-type trials to facilitate the evaluation of new drugs targeting specific genetic changes in the tumor or associated immune microenvironment. As such, lymphoma patients will benefit by receiving more tailored treatment that is based on synergistic effects of chemotherapy combined with new agents targeting specific aspects of tumor biology and the immune system.

Keywords: hematological cancer, lymphoma, immunotherapy, tumor antigen, checkpoint inhibition

Abbreviations: ABVD: doxorubicin, bleomycin, vincristine, dacarbazine; ADC: antibody-drug conjugate; AVD: doxorubicin, vincristine, dacarbazine; BCL: B-cell lymphoma; BEAM: bendamustine, etoposide, cytarabine, melphalan; BiTE: bispecific T-cell engager; BTK: Bruton's tyrosine kinases; BV: brentuximab-vedotin; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CHP: cyclophosphamide, doxorubicin, prednisone; CLL: chronic lymphocytic leukemia; CNS: central nervous system; CPI: checkpoint inhibitors; CVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone; DHAP: dexamethasone, high-dose cytarabine, cisplatin; DLBCL: diffuse large B-cell lymphoma; FDA: United States Food and Drug Association; GCD: gemcitabine, carboplatin, dexamethasone; G-: obinutuzumab; GDP: gemcitabine, dexamethasone, cisplatin; GemOx: gemcitabine, oxaliplatin; GVD: gemcitabine, vinorelbine, doxorubicin; HGBCL: high-grade B-cell lymphoma; ICE: ifosfamide, carboplatin, etoposide; iNHL: indolent Non-Hodgkin lymphoma; mAb: monoclonal antibody; MCL: mantle cell lymphoma; MGZL: mediastinal grey zone lymphoma; MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma; PCNSL: primary central nervous system lymphoma; PI3K: phosphatidylinositol 3 kinase; PMBCL: primary mediastinal B-cell lymphoma; PV: polatuzumab-vedotin; R-: rituximab; SLL: small lymphocytic lymphoma; r/r: relapsed or refractory; ORR: overall response rate.

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Introduction

Immunotherapy has revolutionized the field of hemato-oncology. Before the recent onset of immunotherapy, the classic triad of anticancer therapy consisted of chemotherapy, radiotherapy, and surgery. Therapeutic effects of these latter approaches were long explained by cancer cell destruction or removal, but it is now evident that immune cells play an important part in the processes of cancer cell identification, killing, and removal [1]. With this realization, newer therapies based on the (re) activation or direction of the immune system have emerged, successfully expanding the therapeutic arsenal of hemato-oncologists. One such example in which anticancer treatment targets tumor cells directly, is the antibody rituximab which targets CD20 expressed at the surface of malignant B-cells. This drug was approved more than 20 years ago and has become a mainstay in the treatment of various CD20+ lymphomas. Other more recent examples of immunotherapy focus on re-enabling the immune system to identify and remove cancer cells, for example, checkpoint inhibitory molecules (i.e. PD1, PD-L1, CTLA-4). Simultaneous with the immunotherapy revolution, promising treatments that are now being investigated are based on targeting cellular changes that are associated with cancer cell biology, such as small molecules that target the phosphatidylinositol 3 kinase (PI3K) signaling pathway (i.e. copanlisib and idelalisib). These targeted therapies are now being discovered at increasing speed, helped by new single-cell genomic approaches providing novel targets [2], and find their way into patient care. Both of these newer types of cancer therapy, immunotherapy, and targeted therapy, are being applied in synergy with established therapeutic regimens for B-cell lymphomas to improve clinical results. We here review new developments of combination treatments for patients with B-cell lymphomas, by studying active clinical trials started in 2015–2020, focusing on combination therapies including immunotherapy. We searched clinicaltrials.gov for trials on B-cell lymphoma and combination therapy and included active and completed trials that started in this time frame, were updated in 2018 or later and explicitly described which combination therapy was tested. In this review, we provide an overview of established immunotherapeutic approaches that we encountered in combination therapies and explain their mechanism of action, in order to give the reader insight into why specific combinations are pursued. For those with a specific interest in pediatrics or geriatrics, we have provided additional supplementary tables with trials focusing on these age categories ([Supplementary Table A](#) and [B](#)).

Immune-based approaches

Checkpoint inhibitors (CPI)

Perhaps the most important development in immunotherapy is the discovery of CPI. It has solidified the potential of mobilizing the immune system as an anticancer approach, both by directly showing antitumor effects but also by opening new possibilities for complementary immunotherapeutic approaches. The first United States Food and Drug Association (FDA)-approved checkpoint inhibitor is ipilimumab, a monoclonal antibody that targets CTLA-4[3]. CTLA-4 inhibits T-cell activation, by the outcompeting stimulatory signaling molecule CD28 expressed on the cell surface of T cells for binding to its ligands CD80 and CD86[4]. By binding to CTLA-4, ipilimumab clears the way for T-cell activation via CD28. The results of targeting CTLA-4 in B-cell lymphomas have been discouraging, which is reflected in the amount of ongoing clinical trials focusing on these CPIs. Only two trials include anti-CTLA-4 in their combination therapy regimen and both in combination with PD-1/PD-L1 CPIs: anti-CTLA-4 CPI tremelimumab is combined with anti-PD-L1 CPI durvalumab (NCT02549651). Ipilimumab is combined with nivolumab in NCT02681302 ([Supplementary Table 1](#)).

T-cell membrane protein PD-1 and its ligands PD-L1 and PD-L2 are a second major target in checkpoint inhibition, with PD-1 being targeted by established CPIs nivolumab and pembrolizumab. The binding of PD-1 to PD-L1 also prevents T-cell activation through the CD28 pathway [5], and can thus contribute to the suppression of an adequate immune response. PD-L1 can be constitutively overexpressed on tumor cells [6], which subsequently limits T-cell activation and could be an obstacle to mount an effective antitumor immune response. Other checkpoint inhibitors targeting PD-1 or PD-L1 that are currently being investigated in combination therapy are atezolizumab, durvalumab, spartalizumab, toripalimab, camrelizumab, cemiplimab, and tislelizumab (combinations shown in [Supplementary Table 1](#)).

Checkpoint inhibitors targeting PD-1/PD-L1 have been very successful in B-cell lymphomas. PD-L1 is overexpressed on a number of lymphoma types, including classical Hodgkin lymphoma (cHL) [7, 8], primary mediastinal large B-cell lymphoma [8, 9], primary central nervous system (CNS) lymphoma and primary testicular lymphoma [10]. An inspiring example of how fundamental research can lead to clinical results, anti-PD-therapy has become a standard treatment option in classical Hodgkin lymphoma. It has booked successes in refractory and relapsed cHL [11, 12]. Conversely,

PD-1 is only rarely overexpressed in diffuse large B cell lymphoma (DLBCL) [13, 14], a type of lymphoma that generally shows a poor response to anti-PD-1 therapy [14]. A small subset of DLBCL shows gene amplification of 9p24.1, which contains the PD-L1 and PD-L2 genes [8, 15]. Associated features are young age, a primary mediastinal B-cell lymphoma (PMBCL)-like gene expression and an activated B-cell (ABC) profile [15], suggesting that this may be a distinct subtype of the DLBCL family, which could be used in clinical practice to identify DLBCL patients that may respond to anti-PD-1 therapy. Although better identification of this subgroup is needed and their response to anti-PD-1 therapy remains unclear, it is an example of how better understanding of the individual tumor characteristics may lead to a more targeted choice of treatment.

Bispecific antibodies and bispecific T-cell engagers (BiTE)

Bispecific antibodies have the advantage of being able to bind to two different antigens. BiTEs are bispecific antibodies that recognize T-cells and cancer cells, thereby facilitating their interaction and subsequent killing of the cancer cell. BiTE blinatumomab recognizes B-cell antigen CD19 and T-cell receptor molecule CD3, and binding of both antigens leads to T-cell activation, which induces apoptosis in the B-cell. It has achieved significant results in the treatment of relapsed or refractory (r/r) B-cell precursor ALL [16], leading to FDA approval in 2018. Although blinatumomab monotherapy in r/r DLBCL and indolent non-Hodgkin lymphoma (iNHL) has been successful [17], it has not yet obtained FDA approval. Blinatumomab is currently being investigated in several combination therapy trials with CPIs or lenalidomide (Supplementary Table 2).

With the success of anti-CD20 therapy, it is not surprising that BiTEs directed at this molecule are being developed. Mosunetuzumab/RO7030816, glofitamab/RO7082859 and REGN1979 are all CD20/CD3 BiTEs. They are combined with chemotherapy, CD20 antibodies, antibody-drug conjugates, or CPIs (Supplementary Table 2). No published studies regarding any of these drugs can be found as of yet. However, Schuster and colleagues did report favorable results in a study with mosunetuzumab (ORR (overall response rate) 43.8% and CR 25%) in r/r DLBCL and (transformed) FL in an abstract presentation [18]. A third CD20/CD3 BiTE, REGN1979 is in a phase I trial with r/r B-NHL patients. Preliminary results were presented at a conference [19], with an ORR of >90% for FL grade 1-3a and limited effects in other B-cell NHL (DLBCL; mantle cell lymphoma (MCL); marginal zone

lymphoma (MZL); other grades of FL). The currently ongoing combination trials are reported in Supplementary Table 3. A surprising combination is that of CD20 BiTEs and CD20 mAbs: a single dose is frequently given before initiating therapy with a CD20 BiTE and some trials administer CD20 BiTEs and mAbs concurrently. We could not identify the rationale behind this approach. BiTEs with other targets (RO7227166: targets CD19 and 4-1BB; AFM13: targets CD30 and CD16A) are also emerging (Supplementary Table 4).

Antibody-drug conjugates (ADC)

ADC are a clever combination to improve drug delivery to target cells, combining the specific targeting of monoclonal antibodies to bring damaging agents in the proximity of the targeted cells. In 2011 brentuximab-vedotin (BV) was approved by the FDA for the treatment of CD30-positive lymphomas. This conjugate consists of an anti-CD30 antibody and monomethyl auristatin E, a drug that interferes with cell division, and is used in the treatment of Hodgkin lymphoma [20, 21]. Treatment with BV induces lasting complete remission in some patients with relapsed or refractory Hodgkin lymphoma, who in earlier days had a poor prognosis [22]. The 16 trials that included BV mostly combine it with chemotherapy or nivolumab (Supplementary Table 5).

Polatuzumab vedotin (PV), targeted at B-cell receptor-associated protein CD79B, initially showed promising results in r/r DLBCL and indolent B-cell NHL [23]. The combination strategy PV, bendamustine, and rituximab in r/r DLBCL [24] was recently shown to be effective and this approach has been approved by the FDA. Another recent phase 1b/2 trial adding PV to R-CHP or G-CHP in untreated DLBCL showed an overall response rate of 89% and will be further assessed in a phase 3 trial [25]. In contrast to BV, it is combined with more diverse drug classes, including CPI and chemotherapy but also immunomodulatory drugs (IMiDs), anti-CD20, BiTEs, and Bcl-2 inhibitors (Supplementary Table 6).

IMiDs

Lenalidomide and pomalidomide belong to the family of IMiDs, a group of drugs with multiple antitumor properties [26]. Notably, they can enhance the proliferation of activated T-cells [27], inhibit proliferation and effects of Tregs [28], and stimulate NK cell activity [29, 30]. Lenalidomide was able to reverse impaired T-cell activation as seen in follicular lymphoma [31]. Considering their immunomodulatory role, IMiDs may prove to be a valuable addition to various combination therapy regimens since combinations of IMiDs may empower

T cell-based immunotherapy. When combined with rituximab, a synergistic antitumor effect was seen in immunodeficient mice [29, 32], in vitro [30], and in a phase III trial with indolent NHL [33]. Clinical trials with lenalidomide monotherapy in r/r B-cell lymphoma (DLBCL, FL grade 3, transformed FL, MCL) also showed reasonable response rates [34, 35]. However, results in DLBCL have been discrepant when it comes to the addition of lenalidomide to standard-of-care R-CHOP, possibly because of the heterogeneity of DLBCL. Gene expression profiling has allowed DLBCL to be divided into two major subgroups, germinal center B-cell (GCB) DLBCL, and non-GCB, of which the activated B-cell type (ABC) is the largest subgroup in non-GCB. Two major trials have explored the benefits of the addition of lenalidomide to R-CHOP therapy, known as R²-CHOP. The ROBUST trial enrolled patients with untreated ABC type DLBCL and did not find a significant difference between R²-CHOP and R-CHOP [36]. The ECOG-ACRIN 1412 trial, which included any type of untreated DLBCL, did find a significant improvement in progression-free survival [37], but not for the ABC subpopulation. This discrepancy between GCB and non-GCB malignancies can also be found with lenalidomide monotherapy, with a better response rate in the non-GCB population [38]. Finally, analysis of gene expression in patients who responded well to R²-CHOP identified a subpopulation with increased activity of pro-inflammatory pathways [39]. R²-CHOP may also reduce CNS relapses in DLBCL, which may be due to the ability of lenalidomide to pass through the CNS barrier [40, 41]. In FL, the phase III RELEVANCE trial investigating lenalidomide/rituximab versus R-CHOP in untreated FL showed favorable results for the lenalidomide/rituximab group [42]. R²-CHOP therapy yielded good response rates in a phase II trial with untreated FL [43]. In conclusion, a wide range of combination regimens with IMiDs are currently being investigated. The combination of IMiDs and anti-CD20 stands out when looking at the combination therapy trials that use IMiDs in their regimen, as the majority combines an IMiD with only anti-CD20 or with anti-CD20 and another treatment type (Supplementary Table 7). A visual summary of now prevalent strategies to mobilize the immune system in hematologic malignancies is presented in Fig. 1.

Tumor-based approaches

As stated, the incomplete elimination of cancer cells leads to the selection of intrinsic traits that builds metabolic vulnerabilities that are now being explored for targeted therapy [44]. In contrast to conventional chemotherapy,

targeted therapy requires a personalized approach to treatment choice since it is often unclear who will benefit from a specific therapy, i.e. which tumor contains a targetable vulnerability. Treatment choice is in principle based on predicting treatment response before administering the drug or drug combination. For example; tamoxifen, one of the oldest hormonal drugs, blocks the effects of estrogen in the breast tissue. It is normally used to treat breast cancer patients that express the estrogen receptor (ER) on malignant cells. However, a recent study shows that among patients with ER-positive tumors, only 39% percent of patients have an active ER signaling pathway and that only these patients benefit from tamoxifen treatment [45]. This example shows that in addition to genetic profiling and measuring target protein expression, tests that assess the activity of signal transduction pathways can be a valuable addition in clinical practice in order to determine the best possible treatment strategy.

Bruton's tyrosine kinase (BTK) inhibitors

In B-cell lymphoma, the B-cell receptor and its signaling pathway play an important role in tumor cell survival. Mutations in this pathway can be found in various B-cell lymphoma types. Several targeted therapies act on key molecules in this cascade, such as BTK and PI3K. BTK inhibitors ibrutinib and acalabrutinib bind BTK irreversibly, leading to apoptosis [46] and egress of lymphoma cells from their protective micro-environment [47]. Over the last decade, BTKs have earned their place in the treatment of hematological malignancies: ibrutinib has been approved by the FDA for CLL, MCL, WM, MZL, and SLL, and last year acalabrutinib was approved for r/r MCL. Furthermore, it has a relatively mild safety profile when compared to other therapeutic modalities. It is also successful in combination with immunotherapeutic approaches. For instance, the combination with rituximab has recently been approved as first line therapy in CLL and SLL after an RCT compared it with rituximab-fludarabine-cyclophosphamide in untreated CLL [48]. This combination has also achieved successes for r/r MCL [49] and Waldenstrom [50]. In primary central nervous system lymphoma (PCNSL) patients, the combination of ibrutinib with rituximab and high-dose MTX was found to be safe in a phase 1b trial [51]. Considering these promising results in a wide range of lymphoma types and in different combinations, it is not surprising that a large number of combination trials including BTK inhibitors are underway: over 70 trials are currently registered in various lymphoma types and in a variety of combinations, including combinations

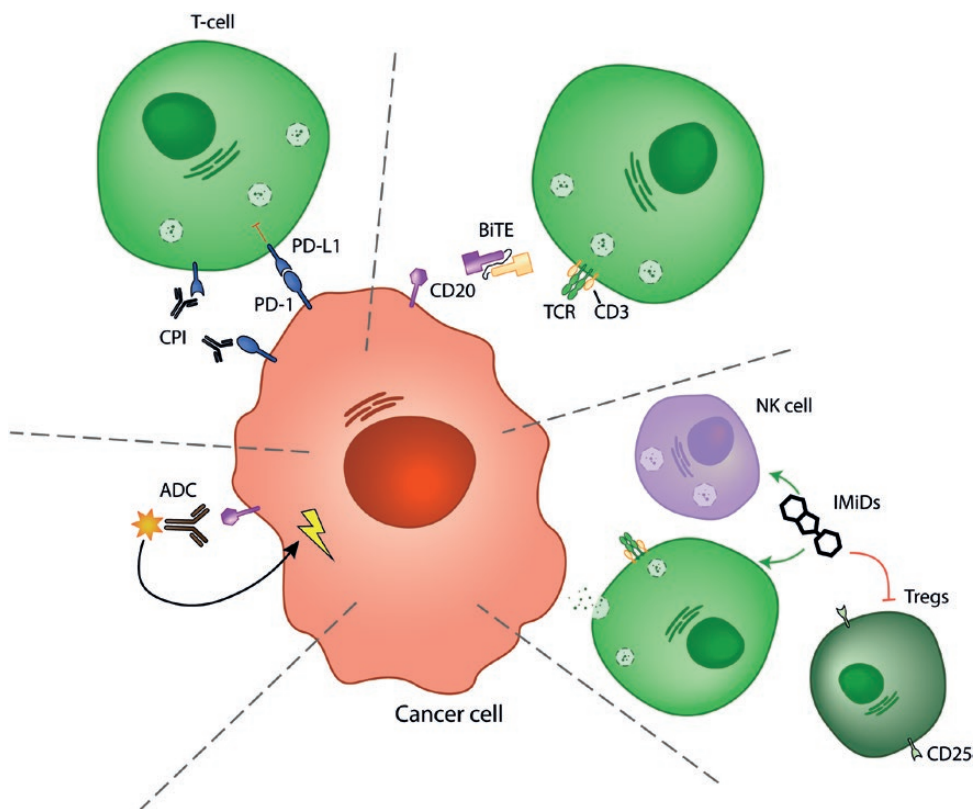


Figure 1 Schematic representation of immunotherapeutic options. Checkpoint inhibitors such as anti-PD-L1 can prevent cancer cells from suppressing T cell reactivity, thereby enhancing the immune response. Bispecific T cell engagers can keep T cells close to cancer cells to allow them to better exert their function. Immunomodulatory drugs stimulate the immune response through various approaches, such as stimulating NK- and T-cells and inhibiting Tregs. Antibody-drug conjugates can carry toxic agents to the proximity of tumor cells. CPI: checkpoint inhibitor; ADC: antibody-drug conjugate; BiTE: bispecific T-cell engagers; TCR: T-cell receptor; NK: natural killer; Treg: T regulatory cell.

with CPIs, rituximab, and rituximab-chemotherapy (Supplementary Table 8).

PI3K inhibitors

PI3 kinases, located downstream of the B-cell receptor, play a central role in cellular signaling and in key processes such as cell proliferation and survival [52]. There are several isoforms, with PI3K δ being specific for B-cells and PI3K γ for T-cells [53]. Idelalisib, specific for PI3K δ , has obtained FDA approval for r/r SLL and r/r FL but also in combination with rituximab for r/r CLL. Other FDA-approved PI3K inhibitors are copanlisib (PI3K α and $-\delta$; for r/r FL) and duvelisib (PI3K γ and $-\delta$; for r/r FL and r/r CLL/SLL). Considering the key role PI3K plays in the B-cell receptor cascade, it is not surprising that combination therapy trials are also investigating applications in other lymphoma types, such as DLBCL and PMBCL (Supplementary Table 9).

BCL-2 inhibitors

The chromosomal translocation t(14;18) is a frequent mutation in follicular lymphoma [54]. This mutation leads to the overexpression of the anti-apoptotic protein BCL-2. An increase in BCL-2 can also be found in MCL and CLL as a result of 13q14 deletion [55, 56]. These discoveries eventually led to the development of BCL-2 inhibitor ABT-199/venetoclax and FDA approval for r/r CLL in 2015, but results in other lymphomas were discouraging. A large number of trials have included a BCL-2 inhibitor, mostly venetoclax, in their combination regimen. The most frequently observed approach is venetoclax added to rituximab and/or chemotherapy, as their primary efficacy may be boosted by the proapoptotic effects of venetoclax. Combinations with other therapies targeted at B-cells (BTK inhibitors, PI3K inhibitors) or, in opposition, checkpoint inhibitors or IMiDs are also frequently found. These studies are not limited to

MCL and FL, but also test the application of venetoclax in other NHLs, including DLBCL (Supplementary Table 10).

Histone deacetylase (HDAC) inhibitors

Histone acetylation is an important epigenetic control system for gene expression: acetylation of DNA allows more gene transcription, deacetylation removes the acetyl group and condenses the DNA, decreasing gene transcription. Essential processes can be influenced through this mechanism, such as the cell cycle, cell proliferation, apoptosis, and MHC expression [57], possibly leading to immunogenic cell death [58]. Mutations in the histone acetylation machinery and deacetylation can be frequently found in lymphoma [59, 60]. Hence, drugs that influence these processes can be a useful tool in lymphoma therapy. The other side of the coin is that they can also be toxic for the immune system depending on the type of HDAC inhibitor and the time of administration [58], which can make the combination of HDAC inhibitors and immunotherapeutic interventions a challenge. Various HDAC inhibitors are FDA-approved for cutaneous T-cell lymphoma and multiple myeloma, but not yet for B-cell lymphoma. Ongoing studies investigating combinations with HDAC inhibitors in B-cell lymphoma are mostly focused on the addition of an HDAC inhibitor to existing treatment regimens. Of the 15 combination trials that we identified, seven used the HDAC inhibitor chidamide, which is approved in China for peripheral T-cell lymphoma but not by the FDA. These trials are mostly a combination of chidamide and chemotherapy and focus on DLBCL, including a phase 3 trial comparing R-CHOP + chidamide and R-CHOP (NCT04231448). The other two chemotherapy trials use vorinostat, with the remaining trials assessing a combination of immunotherapeutic or targeted therapies with HDACi, some of which have not been approved for clinical use at all: abexinostat, CXD101, entinostat, and mocetinostat (Supplementary Table 11).

Proteasome inhibitors

These drugs inhibit the ubiquitin-proteasome pathway which processes the majority of all cellular proteins, including those involved with cell cycle regulation such as factors that mediate cell proliferation and also proapoptotic proteins. The effect of proteasome inhibitors has been well established in multiple myeloma, with bortezomib being the first to receive FDA approval, followed by carfilzomib and ixazomib. Bortezomib is also approved for use in MCL. Over the years, clinical trials with bortezomib and other immunotherapeutic or

targeted therapies in various NHL (DLBCL, FL, MCL, indolent NHL) have been published and showing mild successes, but have not yet lead to FDA approval [61–64]. Looking at the currently ongoing trials, the proteasome inhibitors of interest in B-NHL are bortezomib, carfilzomib, and ixazomib (Supplementary Table 12). A visual summary of the pathways in which the discussed inhibitors can interfere is presented in Fig. 2.

Beyond the scope of cancer and immune cells

Targeted anticancer agents combined with immunotherapy

Multiple targeted anticancer agents, in addition to inhibiting tumor cell growth directly, have been described to modulate immune cell function and activity. These agents therefore have the potential to either enhance or inhibit immunotherapy of cancer. Many of these agents, including EGFR, VEGFR, PDGFR, and Bcr-Abl tyrosine kinase inhibitors, are commonly used for solid tumors or leukemias, but not for lymphomas [65]. However, agents that target the PI3K pathway, as discussed previously, have recently been included in the treatment of lymphoma. In a solid tumor setting, PI3K pathway inhibitors have the capacity to promote T cell activation and inhibit immunosuppressive cell subsets, such as myeloid-derived suppressor cells (MDSC), Tregs and tumor-associated macrophages (TAMs) [66–68], and could therefore enhance the effectiveness of immunotherapy. This view is strengthened by the observation that idelalisib promoted frequent immune-mediated adverse effects in CLL patients [69–71]. Follow-up research showed that Tregs were 13 times more sensitive to inhibition by idelalisib than effector CD8 T cells, possibly explaining the impact of idelalisib on autoimmunity. Combining PI3K inhibitors with immunotherapeutic approaches in lymphoma may therefore be a promising approach. At the moment five different clinical trials that combine PI3K inhibitors with checkpoint inhibition have been started for lymphoma (Supplementary Table 9).

Targeting supporting cells

Besides tumor cells and tumor-reactive immune effector cells, other relevant cell types can play a major role in cancer cell survival, including TAMs and MDSCs [72] as discussed in the previous paragraph, and mesenchymal stromal cells (MSC), through enforcing an immunosuppressive microenvironment [73].

TAMs are frequently found in the tumor microenvironment. While macrophages can express a pro-

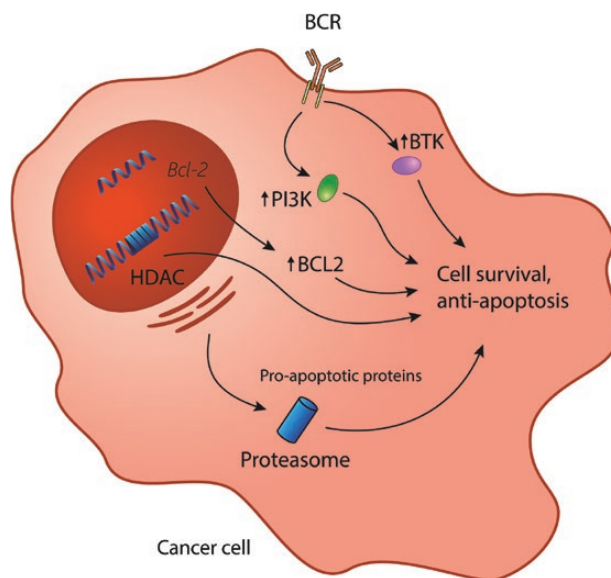


Figure 2 Schematic representation of key pathways that may promote cell survival in B-cell lymphoma. Several pathways that promote cell survival in B-cell lymphoma have been identified: increased expression of kinases PI3K and BTK, downstream of the B-cell receptor and increased BCL-2 expression after chromosomal mutations. HDAC influences gene expression, and dysregulation may promote tumor survival. How HDAC inhibitors work exactly has not been fully elucidated. Chromosomal translocations or mutation may lead to increased expression of BCL-2, which inhibits apoptosis. The proteasome is responsible for the degradation of various proteins, including factors regulating the progression of the cell cycle and pro-apoptotic proteins. Proteasome inhibition leads to apoptosis, possibly due to the increased presence of pro-apoptotic proteins or by toxic stress caused by protein accumulation. HDAC: histone deacetylase; BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; PI3K: phosphoinositide 3-kinase.

anti-inflammatory phenotype [74–76], roughly divided in two types respectively known as M1 and M2, TAMs usually contribute to suppression of the immune response [74]. TAMs can bind to PD-1 and CTLA-4 to block interaction with checkpoint inhibitors. Several strategies to deplete the anti-inflammatory TAMs or reprogram them to pro-inflammatory macrophages are under exploration [77], with TAM-inhibitor JNJ-40346527 being moderately effective in a phase I/IIb trial in relapsed/refractory cHL [78].

MDSCs are a heterogeneous population of hematopoietic cells that have a resemblance to immature-type granulocytes [79]. They suppress T-cells and thereby also contribute to the immunosuppressive microenvironment. An extensive review on MDSCs was recently published, and for details, we refer to this work [80]. In mouse models of pancreatic cancer, immunotherapy combined with anti-MDSC therapy showed significantly improved results [81]. Also in mice, the depletion of MDSCs enhanced the therapeutic effect of checkpoint inhibitors in poorly immunogenic tumors [82]. In rhabdomyosarcoma mouse models, anti-PD-1 therapy was effective when administered shortly after inoculation of tumor cells, but not when anti-PD-1 therapy was delayed, possibly due to rapid proliferation of MDSCs. As such, these

data support that the interference with MDSC localization to the tumor site improves the antitumor effects of late anti-PD-1 administration [83]. Cyclophosphamide, frequently used in the treatment of lymphoma in combination with doxorubicin, vincristine, and prednisolone (CHOP) or in other combinations, can inhibit regulatory cell subsets such as Tregs and MDSC [84–86]. As many as 51 different clinical trials include combinations of immunotherapy with cyclophosphamide (Supplementary Table 13). However, since cyclophosphamide is almost exclusively used in combination with other chemotherapeutic agents it will be difficult to untangle the specific contribution of cyclophosphamide-mediated suppression of MDSC to treatment outcome. Targeted anti-cancer drugs sorafenib and sunitinib, that broadly target protein kinases or receptor tyrosine kinases, respectively, have also been described to inhibit MDSC [87], but are as of yet not included in clinical trials that combine it with immunotherapeutic approaches.

Immunogenic cell death (ICD)

ICD holds the promise for generating an immune response to dying cells in a stimulatory manner that includes uptake of cellular remains by antigen-presenting cells and

effective triggering of adaptive immune cell activation [88]. In the context of immunotherapy, this process offers opportunities: tumor cells loaded with potential antigens discerning them from healthy cells may lead to a broadly carried cancer-specific T-cell response. Additionally, ICD-based approaches may stimulate inflammation and subsequently recruitment and activation of T-cells. Although the role of ICD in anti-cancer responses has been widely studied in solid tumors, it has also been described for B cell lymphomas [89, 90]. Inducers of ICD include radiotherapy and various chemotherapeutics, including oxaliplatin and anthracyclins [91–93].

With this in mind, chemotherapy and radiotherapy may play a new role in future cancer treatment as an adjuvant for immunotherapy [94, 95]. For instance, radiotherapy can enhance the effect of checkpoint inhibitors in melanoma [96–98]. These results may be extrapolated to hematological malignancies, but results so far are limited. Hammerich and colleagues reported increased CD8+ T-cell responses and abscopal effects in iNHL patients when subjected to an ‘in situ vaccine’, consisting of Flt3L, radiotherapy, and a TLR3 agonist [99]. This combination promotes the presence of activated, antigen-presenting dendritic cells in the tumor environment. A follow-up trial adding pembrolizumab to the combination regimen is currently underway (NCT03789097). At the moment only a few trials that combine new therapies and radiotherapy are registered: eight overall, of which five combine checkpoint inhibition with radiotherapy (Supplementary Table 14).

In regard to chemotherapy, cisplatin in combination with radiotherapy enhanced the effects of anti-PD-1 therapy [100]. The anthracyclin doxorubicin is a well-known inducer of ICD and frequently used in the treatment of Hodgkin and non-Hodgkin lymphomas. Combined treatment using doxorubicin and checkpoint inhibitors is described in 19 separate clinical trials in lymphoma patients (Supplementary Table 15). The combination with the abovementioned ICD-inducer oxaliplatin and checkpoint inhibition is less frequent in lymphoma and is described in two clinical trials (Supplementary Table 16).

Future outlook of combination therapy in B-cell lymphoma

The field of cancer therapy is rapidly evolving. New classes of drugs that re-enable the immune system and target essential tumor mechanisms are gaining ground, but their optimal position in therapeutic regimens remains to be determined. Rituximab has made a great addition to established therapies. However, can we say

the same for checkpoint inhibitors and PI3K inhibitors? Or will these interventions take the place of the established drugs? With so many options, determining the best strategy gets harder and harder. On the other hand, established treatments that have proven their efficacy will not be abandoned without strong evidence that a different approach is better. Strategies in testing new combinations in humans mostly comprise the addition of a new drug to an old regimen, or trying a new combination in patients who are ineligible for the standard of care. Neither situation is ideal when it comes to testing completely new combinations, where *ex vivo* or animal studies may be preferable. Therefore the question remains: with all these promising new approaches, how can the new ideal combination therapy that will replace the current first-line therapy be identified as quickly as possible?

In the near future we anticipate the application of more combinations of well-established chemotherapy with new targeted agents. Trials will more often be set up as basket or umbrella trials to facilitate application, testing, or evaluation of new drugs targeting specific genetic changes in the tumor or immune phenomena in the tumor or the patient. These trials allow for rapid testing of new agents in small patient groups, ultimately increasing the availability of new effective treatments for larger patient groups. Since we witness a fast increase of new compounds entering clinical testing this trial design is essential for the fast evaluation of new treatments. In these trials, chemotherapy backbones will be combined with new agents targeting specific aspects of tumor immunology/biology.

New therapies, either immunotherapy-based or a targeted therapy, will steadily increase, added onto existing chemotherapy-based protocols for B-cell lymphomas. To support this statement, we here calculated the relative prevalence of clinical trials registered between 2015–2020, as shown in Fig. 3, that includes (A) rituximab, (B) CPI or (C) CAR T cells (details of all included investigative trials are shown in Supplementary Tables 17, 18 and 19). Of note, CAR (chimeric antigen receptor) T cells, were included as a new therapy that is rapidly emerging; in this therapeutic approach patient T cells are genetically engineered to produce an artificial antigen receptor. We subdivided the trials into multiple groups based on the immunotherapeutic combinations: combinations with chemotherapy, combinations with targeted treatment (including BTK-, PI3K-, HDAC-, BCL-2- or proteasome-inhibitors), combinations with other types of immunotherapy (IMiDs, BITes, ADCs, CPI, CAR T cells, rituximab or other monoclonal antibodies), or a mixture of these types of treatment. We found that for rituximab, combinations of multiple types of treatment

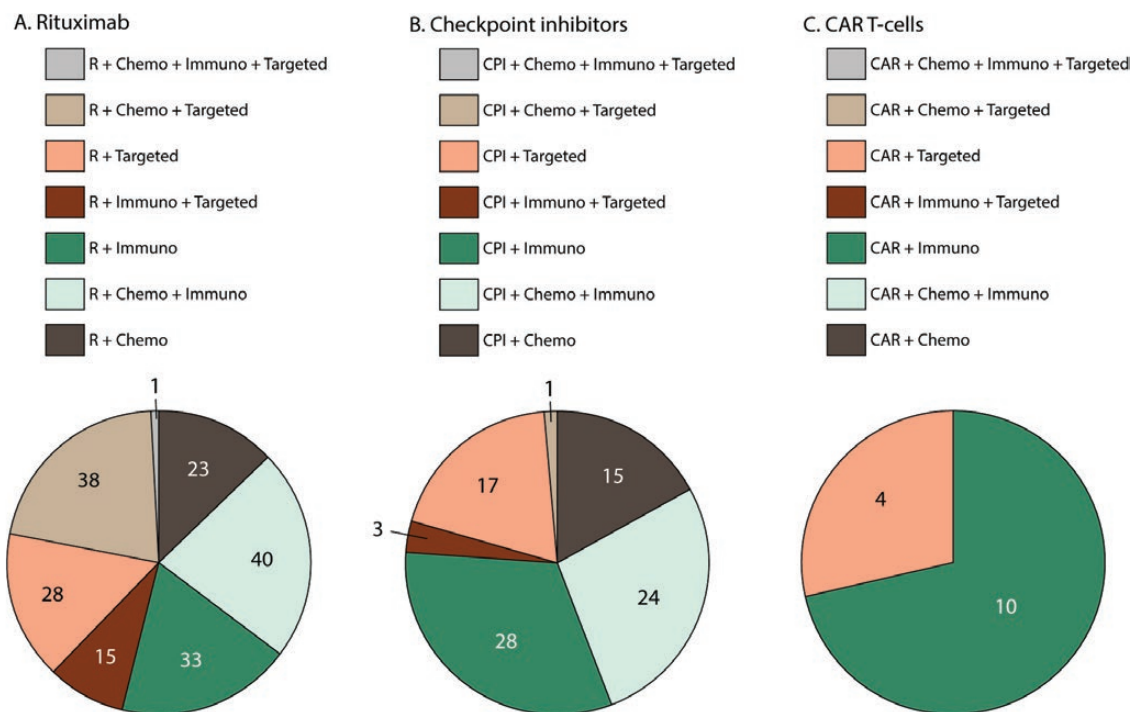


Figure 3 The frequency of combination therapies from three immunotherapeutic perspectives: (a) rituximab (R), (b) checkpoint inhibitors (CPI), (c) chimeric antigen receptor (CAR) T-cells. Frequently encountered therapeutic classes were grouped in chemotherapy, immunotherapy (bispecific antibodies (BiTEs), monoclonal antibodies (mAbs), antigen-drug conjugates (ADCs), immunomodulatory drugs (IMiDs), rituximab, CAR T cells, and checkpoint inhibitors (CPI)) and targeted therapy (BTK-, PI3K-, HDAC-, BCL-2- and proteasome inhibitors). The numbers in the charts represent the number of combinations tested in the included clinical trials.

types were prevalent, with a relatively high proportion of combinations including targeted therapies (82 out of 178 combinations; 46%). For newer types of immunotherapy; CPI and CAR T cells, combinations with other types of immunotherapy were relatively more prevalent (55 out of 88 combinations; 63% and 10 out of 14 trials; 71%, respectively) instead of combinations with targeted therapy (21 out of 88 trials; 24% and 4 out of 14 trials; 29%, respectively).

In the meantime, combinations of newer drugs without rituximab or chemotherapeutics are also being investigated. We found 129 trials that did not include either rituximab or a chemotherapeutic agent. These combinations most usually include a CPI, 63 in total. 14 Include chimeric antigen receptor T-cells, of which five combine CAR-T cells with CPI. The remaining 57, 15% of all combination trials we encountered, combine the newer therapies discussed in the review, leaving out traditional therapies (chemotherapy and rituximab) as well as the revolutionary CPIs and CAR-T cells: BTKs (n = 26), PI3K inhibitors (11), IMiDs (11), BCL-2 inhibitors (10), proteasome inhibitors (7), bispecific antibodies (7), ADCs

(5), HDAC inhibitors (5), monoclonal antibodies (4) and radiotherapy (3). Together these data show that the field is experiencing a surge in studies investigating new combinations in B-cell lymphoma treatment.

Outlook

We have seen an enormous increase in our knowledge on tumor biology and immunology in the past years. Doors have been opened. Immunotherapy has become an essential part of oncological treatment. To design the most efficient treatment for each patient we must invest in better understanding and integration of our knowledge on tumor immunology, focusing on the dynamics of immune interactions and cellular activation. Considering the complexity of host-tumor interactions, combining immunotherapies to create synergistic effects is crucial.

Supplementary material

Supplementary data are available at *Immunotherapy Advances* online.

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Author contributions

P. G.: Conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing – original draft. M. B.: Conceptualization, methodology, funding acquisition, project coordination, supervision, validation, writing – reviewing and editing. V. P. and F. M.-W.: Conceptualization, methodology, funding acquisition, project coordination, supervision, writing – reviewing and editing.

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Conflict of interest

V.P. received royalties payments related to development of venetoclax. P.G., M.B and F.M.W. have no competing interests to report. We have no other industrial links or affiliations we would like to declare.

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Data availability

All data were derived from www.clinicaltrials.gov and are incorporated into the article and its online supplementary material.

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