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The landscape of new drugs in lymphoma

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Abstract

The landscape of drugs for the treatment of lymphoma has become crowded in light of the plethora of new agents, necessitating the efficient prioritization of drugs for expedited development. The number of drugs available, and the fact that many can be given for an extended period of time, has resulted in the emergence of new challenges; these include determining the optimal duration of therapy, and the need to balance costs, benefits, and the risk of late-onset toxicities. Moreover, with the increase in the number of available investigational drugs, the number

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of possible combinations is becoming overwhelming, which necessitates prioritization plans for the selective development of novel combination regimens. In this Review, we describe the mospromising agents in clinical development for the treatment of lymphoma, and provide expert opinion on new strategies that might enable more streamlined drug development. We also address new approaches for patient selection and for incorporating new end points into clinical trials.

Hundreds of new agents are currently being evaluated in preclinical and clinical settings for the treatment of cancer, and the failure rate of drug development processes remains very high[1]. The majority of agents are not successful owing to unacceptable toxicities and/or a lack of antitumour efficacy. Biomarkers to enable selection of patients for a specific therapy and the development of mechanism-based combination regimens are among the strategies that are being deployed to improve the success of drug development. However, drug development, unfortunately, remains a lengthy process that delays the availability of potentially life-saving new drugs. To help overcome these obstacles, innovative clinical trial designs that incorporate robust clinical end points and informative biomarkers are needed.

In recent years, several drugs have received regulatory approval for the treatment of lymphoma, including the antibody-drug conjugate brentuximab vedotin, the novel glycol-engineered anti-CD20 antibody obinutuzumab, the B-cell receptor signalling inhibitor ibrutinib, the PI3K-δ inhibitor idelalisib, and the immunomodulatory drug lenalidomide. Many unapproved targeted drugs have also demonstrated promising efficacy, including the BCL2 inhibitor venetoclax, the second-generation inhibitor of Bruton tyrosine kinase (BTK) acalabrutinib and several antibody-drug conjugates. In addition, various immunotherapies have also demonstrated efficacy in patients with lymphoma, such as mono-specific and bi-specific antibodies, immune-checkpoint inhibitors, and engineered chimeric antigen receptor (CAR) T cells. Thus, the drug landscape for lymphoma has become crowded, necessitating the rational prioritization of the development and selection of combination therapies for these patients. Herein, we provide an overview of the current landscape of drug development in lymphoma, including the mospromising agents currently in clinical testing, and provide expert opinion on new strategies that might enable streamlining of the drug development process.

B-cell receptor signalling inhibitors

Aberrant activation of the B-cell receptor (BCR) signalling pathway is implicated in the pathogenesis and progression of a variety of B-cell malignancies[2]. Novel drugs targeting various components of the BCR signalling pathway have been developed, which target spleen tyrosine kinase (SYK), and subsequently BTK (FIG. 1a).

SYK inhibitors

SYK is a non-receptor tyrosine kinase that is involved in the development of the lymphatic system. Treatment with fostamatinib, a competitive inhibitor of ATP that binds to the SYK catalytic domain (FIG. 1b), demonstrated a 55% response rate in patients with relapsed chronic lymphocytic leukaemia (CLL)[3]. Patients with other B-cell malignancies had a lower response rate to fostamatinib than those with CLL (TABLE 1). These results established the

first proof-of-principle of the therapeutic value of targeting the BCR signalling pathway in patients with B-cell lymphoid malignancies. However, the therapeutic potential of SYK inhibitors has not been fully explored. Accordingly, several selective inhibitors of SYK and dual SYK/Janus kinase (JAK) inhibitors are currently under development as single agents and/or in combination with other agents.

BTK inhibitors

Ibrutinib is a selective and irreversible inhibitor of BTK, which is currently approved by the FDA for the treatment of CLL, mantle-cell lymphoma (MCL), and Waldenstrom macroglobulinaemia[4–7] (TABLE 1). As a single agent, ibrutinib has modest clinical activity in patients with diffuse large B-cell lymphoma (DLBCL) or in those with follicular lymphoma (FL). In patients with relapsed DLBCL, the overall response rate (ORR) was 23%. However, when responses were evaluated based on the cell of origin, 37% of patients with the activated B-cell (ABC) subtype responded compared with 5% of patients with the germinal centre B-cell (GCB) subtype[2]. Accordingly, ibrutinib is being developed in combination with chemotherapy for the treatment of patients with newly diagnosed ABC–DLBCL[8]. Inpatients with relapsed FL, ibrutinib produced an ORR of 28%, reflecting its poor activity in patients with GCB tumours, in which evidence of constitutive BCR signalling is uncommon[9]. Despite the poor activity of ibrutinib in patients with FL relative to its activity in those with other B-cell malignancies, ibrutinib is currently being evaluated as part of novel chemotherapy-free regimens, which include lenalidomide and rituximab, as well as immune-checkpoint inhibitors[10–12]. However, the optimal duration of therapy, the risk:benefit ratio and the costs associated with prolonged drug administration remain to be determined. Future studies should investigate the role of selective treatment withdrawal, or ‘drug holidays’ in patients who achieve a state of negative minimal residual disease state, with retreatment at the time of disease progression to determine if continuous treatment is necessary. Additional studies to assess the optimal use of BTK inhibitors as a monotherapy or in combination with chemoimmunotherapy are currently ongoing. In the majority of patients, the mechanisms of resistance to ibrutinib remain unclear. Although, in a few patients, acquired resistance has been associated with either Cys481Ser (FIG. 1c), or a gain-of-function mutation in PLCγ2 (a signalling molecule downstream of BTK; FIG. 1a)[13]. In Waldenström macroglobulinaemia, primary resistance seems to be related to *CXCR4*^{WHIM} mutations that result in sustained activity of the downstream AKT and ERK enzymes, and escape from ibrutinib-induced apoptosis[14].

Ibrutinib is generally a well-tolerated agent. The most common non-haematological toxicities are gastrointestinal, particularly diarrhoea[15]. Grade 3 and/or 4 neutropenia and thrombocytopenia have been noted in fewer than 10% of patients, most of whom have been heavily pretreated. Petechiae and ecchymoses are also common in these patients, while grade ≥3 bleeding is rare. Ibrutinib also inhibits other kinases that share a homologous Cys481-binding residue, including members of the TEC family, EGFR, and JAK3, which might contribute to the toxicities observed with use of this agent (FIG. 1d)[16–18]. Interestingly, interleukin-2-inducible cell kinase (ITK) inhibition has been shown to induce a favourable antitumour cell response[19]. Most second-generation BTK inhibitors that are currently being developed, such as acalabrutinib and BGB-3111, also bind with Cys489, and

therefore, are unlikely to be significantly more effective than ibrutinib in ibrutinib-resistant patients[20,21]. However, these more-selective inhibitors might be more tolerable than ibrutinib, which could enable prolonged dosing without interruptions or dose reduction. Whether or not these more-selective BTK inhibitors will maintain the antitumour efficacy while reducing the incidence of toxicities is currently unclear. A randomized controlled trial comparing the efficacy of acalabrutinib with ibrutinib in patients with relapsed CLL is designed to address these issues (NCT02477696). Regardless, the approval of several BTK inhibitors is likely to result in healthy competition, which might drive the price down and create a broader opportunity to design novel combination regimens.

PI3K pathway inhibitors

The PI3K pathway is involved in cell growth, survival, and metabolism (FIG. 2). This pathway has been demonstrated to be constitutively active in the majority of patients with B-cell lymphomas. In addition, PI3K isoforms regulate the maturation and development of T cells, macrophages, and dendritic cells, which can affect the tumour microenvironment. Three different classes of PI3K have been identified, but only class I PI3K is being explored as a possible target of cancer therapy. Within class I PI3K class I, there are four isoforms: α, β, γ, and δ (TABLE 1), and multiple pharmacological inhibitors are currently under development with varying levels of selectivity for one or more of these isoforms. Currently idelalisib is the only FDA-approved PI3K inhibitor, which selectively inhibits the δ isoform of PI3K[22]. Idelalisib is approved for the treatment of patients with relapsed CLL, small lymphocytic lymphoma (SLL), or FL. Patients receiving treatment with inhibitors of the PI3K-δ isoform generally have fewer toxicities than those treated with the broader-spectrum PI3K inhibitors, although, idelalisib can result in serious but manageable toxicities, such as diarrhoea or colitis, pneumonitis, and hepatotoxic effects[23]. However, when combined with chemotherapy, idelalisib treatment is associated with an increased risk of serious infection, requiring aggressive monitoring of cytomegalovirus infection status and prophylactic administration of antibiotics to prevent opportunistic infections. Treatment with PI3K α/δ inhibitors is also associated with hyperglycaemia[24]. While data from pre-clinical experiments suggest that broad-spectrum inhibition of PI3K isoforms might enhance the antitumour efficacy of this approach, this observation has not been confirmed in the clinical setting, primarily owing to the added toxicities of broad-spectrum PI3K inhibitors, which preclude optimal dosing.

Most responses achieved with PI3K inhibitors are partial, and so future strategies are focusing on the development of combination regimens based upon the mechanisms of action of each agent, in addition to empirical combinations with existing and effective chemotherapy regimens. Emerging preclinical data suggest that combining PI3K inhibitors with agents that target mTOR, HDAC, BET, BTK, JAK, or BCL2 might be more effective[25–30]. The safety of these novel combinations should be carefully evaluated in phase I clinical trials. Data published in 2015 on the clinical experience with lenalidomide in combination with a PI3K inhibitor indicate that some of these regimens can have unexpected, and severe toxic effects[31]. Furthermore, some of these combinations might be cell-type specific, and will require careful selection of the patient population. For example,

the combination of a PI3K inhibitor with a JAK1 inhibitor demonstrated preferential activity in patients with relapsed Hodgkin lymphoma (HL)[27].

BCL2 inhibitors

Cell survival is regulated by a dynamic balance between proapoptotic and antiapoptotic members of the BCL2 family of proteins (FIG. 3). This family consists of three functional subgroups: firstly, the BCL2-like prosurvival proteins, secondly; the proapoptotic BCL2-associated X (BAX)/BCL2-antagonist/killer (BAK) effector proteins, and thirdly; the proapoptotic BCL2 homology domain 3 (BH3)-only proteins. Disruption of this dynamic process might well lead to tumour development, as well as the induction of chemotherapy resistance. Accordingly, targeting antiapoptotic BCL2 family members is an attractive strategy in broad terms for cancer therapy, and specifically in patients with lymphoma[32].

Navitoclax

This agent is a firsgeneration BH3 mimetic with inhibitory activity against BCL2 family members, including BCL2, BCL-XL, and BCL-W, but not induced myeloid leukaemia cell differentiation protein MCL1 (MCL1). Clinical activity of navitoclax has been demonstrated in patients with CLL and in those with NHL, and this agent is well tolerated, with enhanced efficacy when administered in combination with rituximab. However, application of this agent in the clinic was limited by dose-dependent thrombocytopenia, which is an ‘on-target’ effect mediated via inhibition of BCL-XL[33–35].

Venetoclax

This agent is a BCL2-selective inhibitor with 100-fold affinity for BCL2 compared with BCL-XL, and, consequently, this agent has minimal or no direct effect on platelet counts[36]. The initial clinical experience with venetoclax revealed remarkable activity in patients with relapsed CLL or MCL, with response rates exceeding 70% in cohorts with either of these diseases[37]. In a phase I study in patients with CLL, response rates were unaffected by the presence of the genomic alteration 17pdel, which is generally associated with an inferior prognosis, although only 31 such patients were included in the cohort[37]. Preclinical and *ex vivo* studies using primary patient-derived cells support the existence of a P53-independent mechanism of venetoclax-induced cell death, and data from a large phase II study in patients with relapsed CLL and 17pdel confirmed a high, independently-verified response rate of 79%[37], leading to the regulatory approval of venetoclax by the FDA for this indication. Broader regulatory approval for other forms of CLL might require favourable results from an ongoing randomized controlled trial of venetoclax plus rituximab versus bendamustine plus rituximab (MURANO: NCT02005471). Many novel drug classes are active against CLL and related diseases, although none are currently known to be curative. Therefore, a need exists to determine the optimal sequence of use of these agents, and preliminary data demonstrate that treatment with venetoclax results in a 50% response rate, despite resistance to BCR-signalling inhibitors in some patients, although these data are currently too immature to inform upon the durability of remission[38].

In patients with FL and in those with DLBCL, treatment with venetoclax results in response rates of 38% and 18%, respectively, with a requirement for doses higher than the recommended phase-II dose for patients with CLL of 400 mg (TABLE 1)[39]. In some patients with CLL, venetoclax can result in rapid tumour lysis syndrome. Subsequent studies implemented strict monitoring and treatment of tumour lysis syndrome, in addition to a ramped dose schedule over several weeks, which seems to have mitigated against the risk of clinical tumour lysis syndrome. Venetoclax-based combination regimens are currently under investigation and include combinations with anti-CD20 monoconal antibodies and standard immunochemotherapy regimens (such as rituximab plus bendamustine, and rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone or R-CHOP). Results from preclinical studies indicated that upregulation of MCL1 might be a mechanism of resistance to BCL2 inhibitors, and that the effects of inhibitors of MCL1 might be synergistic with those of venetoclax, thus providing a rationale for future combination strategies[26,40]. Additionally, data from preclinical experiments demonstrated synergistic or additive effects of BTK and PI3K inhibitors, and these combinations are currently being evaluated in phase I/II clinical studies, with a focus on MCL given the strong mechanistic rationale, and high single-agent activity of both drug classes for this indication[41].

JAK/STAT pathway inhibitors

JAKs are a family of non-receptor tyrosine kinases that primarily transduce signals from the cell surface to the nucleus by activating downstream signal transducers and activators of transcription (STATs). The JAK family consists of four members: JAK1, JAK2, JAK3 and TYK2. Following engagement of a cytokine with its receptor, members of the JAK family are phosphorylated, leading to the recruitment, phosphorylation and dimerization of STAT proteins[42]. Subsequently, STATs translocate to the nucleus and bind with DNA to transcribe genes that are involved in cellular proliferation, survival, angiogenesis and immunity. Seven STAT family members have been identified: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6. Data from gene-silencing studies demonstrate that the loss of JAK1, JAK3 and TYK2 result in defective lymphopoiesis, whereas loss of JAK2 leads to impaired erythropoiesis[43].

The JAK/STAT pathway is frequently and aberrantly activated in patients with lymphoma, making it an interesting target of pathway-directed agents. On the basis that activated STAT3 and STAT5 signalling promote the growth and survival of a variety of lymphomas, the novel oral JAK2/receptor-type tyrosine-protein kinase (FLT3) small-molecule inhibitor, pacritinib, was evaluated in patients with relapsed HL and NHL[44]. In total, 34 patients received daily doses of between 100 and 600 mg of this agent. Gastrointestinal toxicities were the commonest toxicities and cytopenias were infrequent. In this study, three patients had partial remissions and 15 others had stable disease, with a total of 17 having tumour reductions ranging from 4% to 70% of the original tumour volume. Two small phase I trials of the JAK1/JAK2 inhibitor ruxolitinib in patients with relapsed DLBCL or peripheral cell lymphoma (PTCL), and in patients with relapsed HL are currently ongoing (NCT01431209 and NCT02164500). The available data provide the proof of principle for therapeutic targeting of the JAK/STAT pathway in patients with lymphoma; however, none of these agents produced sufficient clinical responses to warrant approval for use as a single agent by

regulatory agencies. Instead, these agents might be more suitable for use in combination regimens. In a phase I study, with data published in 2015, patients with relapsed or refractory HL were treated with the PI3Kδ inhibitor INCB040093 alone or in combination with the selective JAK1 inhibitor INCB039110 (REF. 27). Of 11 evaluable patients receiving the PI3Kδ inhibitor, the ORR was 36%, including one complete response. In eight evaluable patients receiving the combination of a PI3Kδ inhibitor plus a JAK1 inhibitor, the overall response rate was 63%, including two complete responses. Owing to the level of interest in JAK inhibitor-based combinations, several companies are currently evaluating the performance of dual inhibitors of SYK and JAK kinases, with some early signs of clinical benefit[45,46]. Additional novel mechanism-based combinations, in addition to the identification of predictive biomarkers, will be essential for the successful development of these agents.

Immunomodulatory drugs

Immunomodulatory drugs enhance the actions of immune-effector cells, repair cell synapses, and improve the ability of the patients' immune system to recognize and kill tumour cells through natural killer (NK)-cell-mediated antibody-dependent cellular cytotoxicity[47]. Lenalidomide, the lead compound in this class of agents, is active in several preclinical models of B-cell malignancies. In the low-grade lymphoma study (NHL-001), investigators reported ORRs of 23%, and median progression-free survival (PFS) duration of 4.4 months in patients with relapsed disease[48]. In a subsequent study in patients with relapsed aggressive lymphoma (NHL-002), 35% of patients responded, with a median PFS duration of 3.6 months[49]. A larger international phase II study (NHL-003) enrolled 217 patients with aggressive NHL (DLBCL, MCL, and grade 3 FL). Results were similar to those of earlier studies, with reported ORRs and PFS durations of 35% and 3.7 months, respectively. In 57 patients with MCL, a 35% ORR was reported, with a median response duration of 16.3 months[50]. A larger single arm phase II trial (MCL-001) enrolled 134 patients, including many who were refractory to bortezomib[51]. The ORR and complete response rates, as determined by independent central review, were 28% and 7.5%, respectively, resulting in the approval of lenalidomide by the FDA as a single agent for relapsed MCL.

Immunomodulatory agents are clearly effective as single agents in various B-cell malignancies, although their true potential might reside in incorporation into novel combination approaches. In a phase II study of lenalidomide and rituximab in patients with untreated FL, the ORR was 98%, with a complete remission rate of 87%[52]. Large phase III studies comparing the efficacy of lenalidomide plus rituximab with that of rituximab plus chemotherapy (RELEVANCE, NCT01476787) and rituximab monotherapy (AUGMENT, NCT01938001) in patients with indolent lymphoma are currently underway. Enhanced activity has also been reported with lenalidomide and rituximab in patients with DLBCL and MCL. In a phase I/II study of the efficacy of lenalidomide and rituximab in patients with relapsed MCL, a 57% ORR and a 36% complete response rate were observed, with a median PFS and OS duration of 11 months and 24 months, respectively[53]. The efficacy of lenalidomide and rituximab was also evaluated in patients with MCL as a frontline treatment

strategy, resulting in an ORR of 84%, with the majority of patients remaining in remission at a median of 24 months of follow-up monitoring[54].

Treatment with the combination of lenalidomide and chemotherapy in patients with aggressive lymphoma has also shown promising results. Initial phase I/II studies conducted at the Mayo Clinic involving R-CHOP plus lenalidomide (R2-CHOP) in patients with untreated, aggressive B-cell lymphoma demonstrated a 98% ORR and a 24-month PFS rate of 59%[55]. Interestingly, the negative influence of a non-GCB phenotype seems to be prevented by the addition of lenalidomide to R-CHOP, compared with historical controls[55]. In the Italian REAL07 study, investigators explored a variation on the lenalidomide, rituximab and CHOP regimen in untreated elderly (age 60–80 years) patients with DLBCL, and observed an ORR of 92% (86% complete response), with a 2-year PFS rate of 80%[56]. Randomized trials formally comparing R-CHOP with or without lenalidomide in patients with DLBCL are currently ongoing. Perhaps the most exciting combinations will emerge from the addition of an immunomodulatory drug to a regimen containing targeted biological agents, in addition to combinations with immune checkpoint inhibitors; however, these trials should be carefully conducted owing to the risks that unforeseen toxicities might emerge.

Immunotherapy

T cells can be involved in an immune response to B-cell lymphoma in various ways: nonspecific activation of T cells can occur with the use of immune checkpoint inhibitors, or in a more-specific fashion either by employing bispecific antibodies/bispecific cell engagers (BiTEs), or by using T cells transduced with a chimeric antigen receptor (CAR) that enables recognition of a B-cell antigen[57].

Immune checkpoint inhibitors

Immune checkpoints regulate the proliferation and activation of cells, and are activated to maintain self-tolerance and prevent autoimmunity (FIG. 4a)[58]. Therefore, expression of immune checkpoint ligands and receptors by tumour cells can enable them to evade cell mediated antitumour immunity[57]. Data from various studies have shown that T cells present within the tumour microenvironment have an exhausted phenotype, and these exhausted cells commonly express immune checkpoint proteins, such as programmed cell death protein 1 (PD-1) and hepatitis A virus cellular receptor 2 (also known as TIM-3), and are unable to proliferate, secrete cytokines, or actively lyse the malignant cells[58–61]. Thus, immune-checkpoint blockade provides a significant opportunity to activate suppressed or exhausted T cells.

Data from studies involving the anti-CTLA-4 antibody, ipilimumab, indicate modest clinical activity in patients with relapsed B-cell NHL and in those with relapsed HL, with a reasonable safety profile[62]. Trials using antibodies that inhibit PD-1, however, showed more-promising clinical activity in patients with relapsed lymphoma, especially in those with HL. An initial study using an anti-PD-1 antibody, pidilizumab, in patients with DLBCL following autologous stem-cell transplantation demonstrated a prolonged PFS duration in patients with relapsed high-risk disease[63]. Furthermore, the ORR in patients who still had measurable disease was approximately 51%. A subsequent trial using pidilizumab in

combination with rituximab in patients with FL revealed an ORR of 65% and a complete response rate of 52%, suggesting that treatment with this combination resulted in a greater level of clinical activity than would be expected with use of rituximab alone[64]. The efficacy of the anti-PD-1 antibodies, nivolumab and pembrolizumab, was evaluated in patients with relapsed B-cell lymphoma, cell lymphoma, or HL (TABLE 1)[65–67]. In patients with relapsed HL that received treatment as part of these phase I trials, both antibodies produced response rates >60%, although the complete response rates were more modest (TABLE 1). A phase II study investigating nivolumab in patients with relapsed HL after autologous stem-cell transplantation and brentuximab vedotin[68] produced a response rate of 66%, which led to FDA approval of nivolumab for this indication in May 2016. A small number of patients with relapsed DLBCL and FL were treated with nivolumab, with response rates approaching 40%[69]. The high response rate observed in patients with HL might be caused by the fact that Reed–Sternberg cells express high levels of programmed cell death 1 ligand 1 PD-L1, and are surrounded by a large number of T cells in the microenvironment. However, whether or not other cells in the microenvironment contribute to anti-tumour activity currently remains unclear. Other studies are currently evaluating the efficacy of various antibodies targeting PD-L1, such as studies involving atezolizumab, with promising early results[70]. The safety and efficacy of antibodies targeting other immune checkpoints, including tumour necrosis factor receptor superfamily member 9 (also known as 4-1BB), such as varlilumab, are currently being examined in a variety of clinical trials.

A variety of studies, designed to assess the efficacy of anti-PD-1 therapy in combination with other checkpoint inhibitors or immunologically active treatment involving combination therapies, are also currently underway. These include combinations of nivolumab with ipilimumab or lirilumab, which target CTLA-4 and inhibitory KIR receptors, respectively[57]. Furthermore, ongoing clinical trials are assessing the combination of urelumab (targeting 4-1BB) with rituximab or pembrolizumab plus rituximab (NCT02446457). Clinical trials investigating the efficacy of nivolumab in combination with urelumab are also ongoing. Another approach would be to combine an immune-checkpoint inhibitor with a small-molecule inhibitor. BTK-inhibition has specifically been studied as these inhibitors might also target interleukin-2-inducible cell kinase, thereby activating T cells and thus promoting a T_H1 response[71]. Trials investigating the efficacy of nivolumab in combination with ibrutinib are also currently underway. Another approach might be to combine immune-checkpoint inhibitors with antibody–drug conjugates or chemotherapy. Several studies are currently testing the effectiveness of anti-PD-1 antibodies in combination with brentuximab vedotin, or in combination with chemotherapy, including a regimen containing doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) for patients with HL and R-CHOP for those with NHL (TABLE 2). Owing to the safety and unique mechanism of action of immunotherapies, their role as maintenance therapies for the eradication of minimal residual disease (MRD) will need to be further explored in future trials.

BITE and bispecific antibodies

The firsin-class BiTE, blinatumomab, has been approved by both the FDA and EMA for the treatment of relapsed and/or refractory B-cell acute lymphoblastic leukaemia (B-ALL). This construct consists of the single-chain variable fragments of murine antibodies recognizing

CD3 and CD19, joined by a linker, which can redirect the T cells directly to the B cells[57]. Most studies with blinatumomab have been performed in patients with B-ALL, firstly in the setting of eradicating MRD and later in patients with relapsed and/or refractory Philadelphia-chromosome-negative B-ALL, in which response rates of 40–50% have been reported. In this patient group, BiTES might be considered a means of enhancing transplantation outcomes. The clinical experience in patients with NHL is limited to two phase I/II studies, in which a total of 100 patients with indolent and aggressive NHL were treated. A higher dose of blinatumomab is needed in these patients than for the treatment of those with ALL. However, the mode of administration, which is via continuous infusion in cycles of 28 days, is a major drawback of treatment with blinatumomab. Furthermore, treatment might be associated with clinically significant cytokine-release syndrome, long-term B-cell depletion and reversible neurotoxicity[57]. Future research should focus on a better understanding of the mechanisms underlying drug-induced toxicities, the management of these toxicities, improving the mode of administration (such as use of subcutaneous administration) and improving the protein structure, in order to enhance the drug half-life.

Chimeric antigen receptor T cells

CARs are composed of a single-chain variable fragment (scFv) derived from a murine or humanized antibody, which functions as the targeting domain. The scFv is attached to an extracellular spacer domain to ensure optimal binding and to the intracellular signalling domain of the cell receptor (TCR; CD3 ζ) to ensure cell activation (FIG. 4b). For optimal cell activation one or two co-stimulatory molecules are added, most often CD28 and/or 4-1BB. The major advantage of CAR-T cells over TCR-transduced T cells is that the recognition of tumour cells is HLA-independent. For this purpose, autologous lymphocyte populations are harvested, stimulated, transduced and expanded, and subsequently re-infused into the patient (adoptive cell transfer). In most trials, patients receive lymphocyte-depleting chemotherapy before infusion of CAR T cells (most often fludarabine and cyclophosphamide)[72]. The efficacy of several CAR cell platforms is currently in clinical trials (TABLE 3)[73]. In patients with B-cell lymphoma, CARs that bind with the CD19 receptor have typically been selected[74]. Trials were conducted in patients with B-ALL, with complete response rates of 67–90% often achieved, with MRD-negative status and responses that often lasted for several years[75]. Results in patients with B-cell NHL and in those with CLL are less impressive compared with those from patients with B-ALL, but remain encouraging. CAR cell therapy is a promising treatment strategy, although several challenges to clinical implementation remain, including toxicities, the routinely successful and timely production of CAR-T cells for patients with aggressive disease, and the durability of responses[76]. Newer versions of CAR-T cells include additional safety measures, such as suicide genes or the expression of cell-surface receptors that can be targeted by monoclonal antibodies. Future directions include rationally-designed combination strategies, and streamlining of production processes to enable an off-the-shelf application strategy.

Antibody-drug conjugates

Antibody–drug conjugates (ADCs) aim to take advantage of the specificity of monoclonal antibodies to deliver potent cytotoxic drugs selectively to antigen-expressing tumour cells.

Current toxic payloads predominantly target DNA, such as pyrrolobenzodiazepine (PBD)[77], or tubulin, such as auristatins (including monomethyl auristatin E/MMAE and MMAF), and maytansinoids (DM1 or DM4) (TABLE 2). Most ADCs that are currently in clinical development in patients with haematological malignancies take advantage of a cleavable linker strategy, with three different types of release mechanism available within this class: firstly, lysosomal protease-sensitive linkers (brentuximab vedotin, polatuzumab vedotin); secondly, acid-sensitive linkers (inotuzumab ozogamicin); and, thirdly glutathione-sensitive linkers (anti-CD19 maytansine conjugate)[78].

In August 2011, the FDA approved brentuximab vedotin, the first agent in this class to be approved for the treatment of HL and systemic anaplastic large-cell lymphoma[79]. Several other ADCs with cleavable linkers are currently under evaluation in phase II studies for various lymphoid malignancies, with promising clinical efficacy (TABLE 2)[80–87]. Critical next steps in the clinical development of ADCs include dose-finding trials and testing of these agents in combination with the conventional firsline and/or salvage chemotherapy regimens, and the identification and characterization of the interactions that lead to unacceptable toxicities. Brentuximab vedotin has been used at 1.2 mg/kg in combination with ABVD, which resulted in excessive pulmonary toxicities, and led to bleomycin being excluded (AVD) in order to reduce the toxic effects of this combination[83]. Brentuximab vedotin, in combination with firsline and second-line regimens, is currently being investigated for the treatment of patients with HL and for those with anaplastic large-cell lymphoma. Other ADCs are also being investigated in combination with chemotherapy regimens, such as R-CHOP and rituximab plus bendamustine. In the future, the identification of additional targets and therapeutic payloads might enable future combinations of ADCs to be assessed and validated.

Epigenetic-modifying drugs

Epigenetic modifications are predominately heritable changes in gene expression that do not involve alterations in DNA sequences. In human cancers, the epigenome is often deregulated and epigenetic alterations, such as DNA methylation and histone modifications, can affect gene expression and lead to the silencing of tumour suppressor genes or to the overexpression of proto-oncogenes. However, unlike genetic mutations, epigenetic changes are reversible, providing exciting potential therapeutic opportunities for cancer therapy.

Bromodomain inhibitors

The bromodomain-containing protein (BRD) and bromodomain and extra-terminal domain protein (BET) group is a subfamily of bromodomain proteins composed of three ubiquitously expressed molecules, BRD4, BRD3 and BRD2, and a fourth testis-specific form, BRDT[88]. These proteins recruit transcription factors to acetylated chromatin and bring the elongation complex close to the promoter, thus triggering gene transcription. The expression of several oncogenes is under epigenetic regulation by BRDs, including c-MYC[89].

OTX015 (MK8628) is an inhibitor of BRD 2, 3 and 4 with notable antiproliferative activity in a large panel of cell lines derived from patients with mature B-cell lymphoid tumours[90].

Data from *in vitro* and *in vivo* experiments show that OTX015 targets NF-KB/TLR/JAK/STAT signalling pathways, genes regulated by MYC and E2F1, and genes related to cell-cycle regulation and chromatin structure[90]. In a phase I trial, OTX015 was given orally to 37 patients (18 with DLBCL, 9 with other lymphomas, and 10 with myeloma)[91]. No dose-limiting toxicities were observed up to a dose of 80 mg once daily. Asymptomatic and rapidly reversible grade 4 thrombocytopenia was the DLT at 40 mg twice daily and 120 mg/day. Overall, 16 patients had grade 3–4 thrombocytopenia and three patients had asymptomatic grade 3–4 neutropenia. Grade 3 non-haematological toxicities included diarrhoea, vomiting, hyperglycaemia, and hypernatraemia. Clinically relevant activity was reported in six patients treated with doses ranging from from 40 to 120 mg per day, including one complete response and one partial response, both in patients with DLBCL who had not responded to three or four prior lines of therapy. Four other patients with lymphoma had minor tumour shrinkage and clinical benefit[91]. In a separate phase I study, the safety and effectiveness of the oral BET inhibitor CPI-0610 was evaluated in 44 patients with relapsed lymphoma[92]. While the treatment was well tolerated, only three patients achieved clinical remissions. The clinical activity observed in these two phase I studies indicates that future strategies should focus on the development of mechanism-based combinations. A better understanding of the mechanisms of resistance to BET inhibitors will also be needed.

EZH2 inhibitors

Histone-lysine *N*-methyltransferase EZH2 (EZH2) is a histone methyltransferase that is responsible for methylation of lysine 27 of histone H3 (H3Lys27), a modification of DNA associated with repressed transcription when trimethylated (H3Lys27me3). Aberrant EZH2 activity, including activating mutations, has been implicated as an oncogenic driver in NHL[93–95]. Data from preclinical experiments have demonstrated the potential therapeutic value of EZH2 inhibitors in lymphoma[96,97]. In a phase I study, the oral EZH2 inhibitor, tazemetostat, was evaluated in 45 patients, including 19 with relapsed lymphoma. Responses were observed in 9 of 15 evaluable patients[98], including those with wild-type *EZH2.* A phase II study is currently enrolling patients to further confirm the clinical activity of tazemetostat in patients with DLBCL and FL (NCT01897571).

Current challenges and future directions

With >600 drugs in clinical or preclinical development for the treatment of cancer, the number of possible combinations is overwhelming, and therefore a prioritization plan for the development of novel combinations should be based upon mechanisms, rather than empiricism[1,99]. Some prioritization can be made on the basis of strong mechanistic and synergistic preclinical data, such as combining a BCL2 inhibitor with an MCL1 inhibitor, or combining a BTK inhibitor with a PI3K inhibitor. However, the prioritization of different drug combinations from each class of targeted agents remains challenging. For example, with more than 10 different PI3K inhibitors and a handful of BTK inhibitors available, investigators and sponsors will need to prioritize the most appropriate PI3K inhibitor and BTK inhibitor for combination, as insufficient resources are available to enable the investigation of all of these different combinations. Although imperfect, a non-biased high-

throughput screening experiment can provide some clues on which combination should receive a higher priority, based on the level of synergistic effects observed on a variety of cell lines (FIG. 5). When a two-drug combination then demonstrates similar levels of synergy, data from subsequent animal studies can further prioritize which combination should be tested first, in terms of optimizing safety. Alternatively, clinical trial designs can be modified to accommodate the testing of different combinations, of a higher priority, within the same clinical trial.

Identification of biomarkers that enable the selection of patients with tumours that harbour the relevant aberrations is an important consideration before the use of targeted therapy. Several randomized studies have been conducted in patients with DLBCL of the ABC subtype, owing to the presence of the relevant oncogenic pathways. Extensive efforts are currently underway to apply genetic sequencing data to link specific genetic alterations to a response or resistance to targeted therapy[100]. Examples include studies of patients with *IDH2* mutations, *CREBBP/EP300* genetic alterations, and *EZH2* mutations. Biomarkers that complement genomic data are also needed, as many patients with lymphoma might not harbour actionable genetic alterations. These include expression of proteins that can be targeted using monoclonal antibodies and antibody–drug conjugates, and intracellular proteins and phosphoproteins, such as MYC, BCL2, and phosphorylated STAT3 and ERK.

In addition to identifying biomarkers that might predict a response to treatment, postreatment bio-markers for the monitoring of MRD can help to identify patients at risk of treatment failure, and could also guide treatment decisions[101]. Apoptosis and necrosis of lymphoma cells leads to the release of circulating tumour DNA (ctDNA) into the blood, which can be detected and quantified using nexgeneration sequencing (NGS) methods[102–104]. VDJ immunoglobulin genes contain unique sequences that are markers of clonality[105], thus, detecting these unique sequences in the serum of patients with lymphoma after the successful completion of firsline therapy might predict impending clinical disease recurrence[106]. Prospective studies are currently being conducted to confirm the potential utility of NGS for the detection of ctDNA-based markers in the clinical setting, and to determine whether eradication of such markers is a relevant goal of curative regimens. If so, the detection of ctDNA at the end of therapy might indicate the need for further therapy, which will be the subject of future novel clinical trial designs. Newer approaches to the detection of ctDNA, such as using deep-sequencing assays (CAPSeq) could improve the sensitivity of immunoglobulin ctDNA, in addition to providing MRD assessment of tumour types that lack clonal VDJ sequences.

Conclusions

The convenience of oral drugs for cancer therapy also creates challenges, including the benefits of prolonged administration, compliance, costs, and late toxicities. The optimal duration of therapy in patients achieving a complete response should be carefully addressed, in addition to the role of retreatment strategies. Finally, in the era of effective and tolerable chronic administration of novel agents, we are witnessing improved PFS durations, even in patients whose treatment response might not meet the definition of ‘response’. Accordingly, patients with ‘minor’ reductions in tumour volume are also deriving benefits from modern

therapies. These observations provide a mandate for the revision of current and traditional response criteria to reflect the true extent of patient benefit, rather than depending on arbitrary cutoffs to define a treatment response. Furthermore, as some new trials are selecting patients based on the presence of genetic bio-markers and not tumour types (so-called basket trials), an accurate assessment of efficacy across tumour types will benefit from a common 'response criteria' definition for lymphoid and solid tumours.

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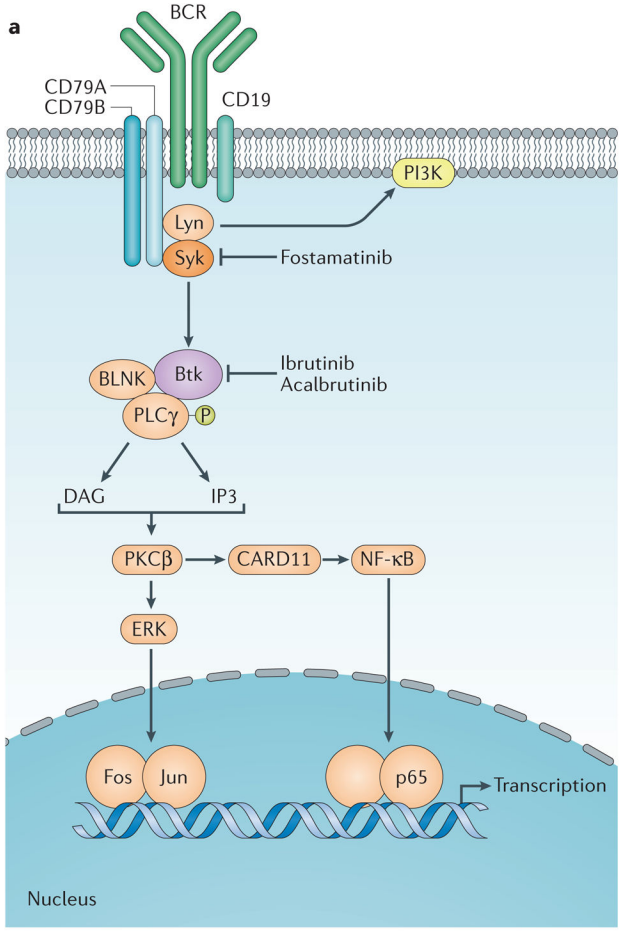
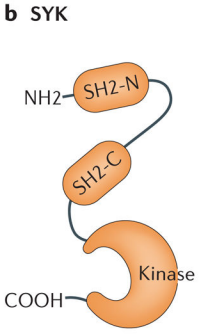
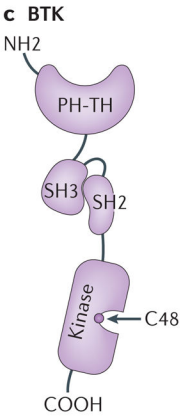
Key points

- The availability of novel small-molecule inhibitors and immunotherapies has changed the landscape of drug development in lymphoma
- The most effective small-molecule inhibitors target B-cell-receptor signalling, PI3K signalling, and the BCL2 protein
- Multiple immunotherapy platforms have demonstrated promising clinical activity, including immune-checkpoint inhibitors, CAR T cells, and bispecific antibodies
- Many companies are developing similar drugs, which inhibit the same target, necessitating a more focused drug development strategy, with prioritization of clinical investigations
- Owing to the high number of drugs in development, the potential number of drug combinations is becoming unmanageable; prioritization should focus on mechanism-based combinations that are potentially safer and more effective







d Kinase targets

Kinase	IC50 (nM)
Btk	0.33
Tec	1.98
Itk	175
Bmx	0.98
Txk	2.27
EGFR	6.18
ErbB2	7.92
ErbB4	2.19
Blk	0.13
JAK3	48

Figure 1. Therapeutic targeting of the B-cell receptor (BCR) signalling pathway in patients with lymphoma

a | BCR signalling pathway. Selective inhibitors for Syk and Btk are either approved by regulatory agencies or are in clinical trials. **b** | SYK structure. SYK is a non-receptor protein-tyrosine kinase containing tandem SRC homology 2 (SH2) domains. SYK inhibitors are able to competitively bind to the ATP-binding pocket of the kinase domain. Most BTK inhibitors bind covalently to cysteine 481 (C481) residues in the BTK active site, **c** | BTK structure. BTK is composed of four major domains: an N-terminal pleckstrin homology (PH) domain, a TEC homology (TH) domain, two SRC homology domains (SH3 followed by SH2), and a C-terminal kinase domain. **d** | A list of kinases that contain a C481 residue in the active kinase site. The IC50 is shown for ibrutinib using a purified kinase assay.

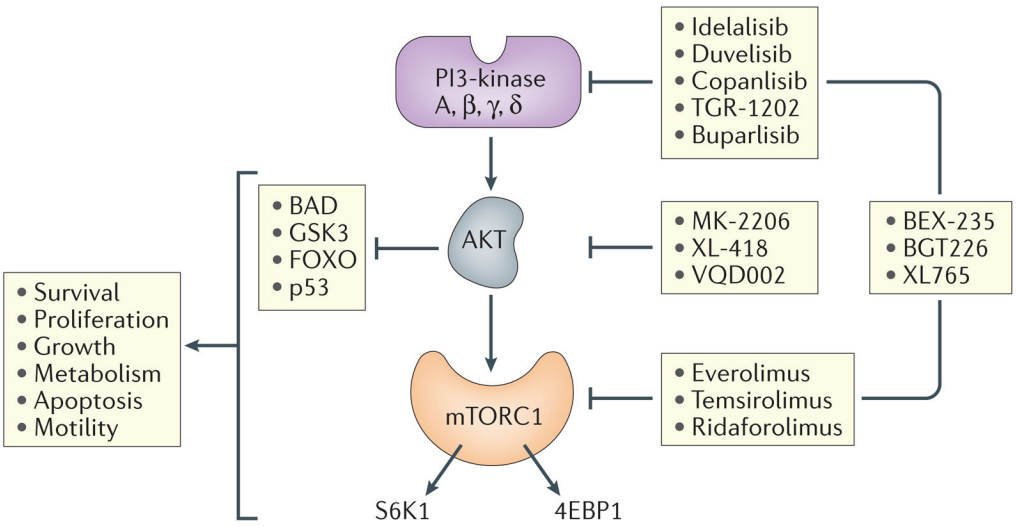


Figure 2. Therapeutic targeting of the PI3K/AKT/mTOR pathway

Several small-molecule inhibitors targeting different nodes in this pathway are under development for the treatment of cancer. Currently, idelalisib, which selectively targets the PI3Kδ isoform, is the only PI3K inhibitor to be approved by regulatory agencies is idelalisib.

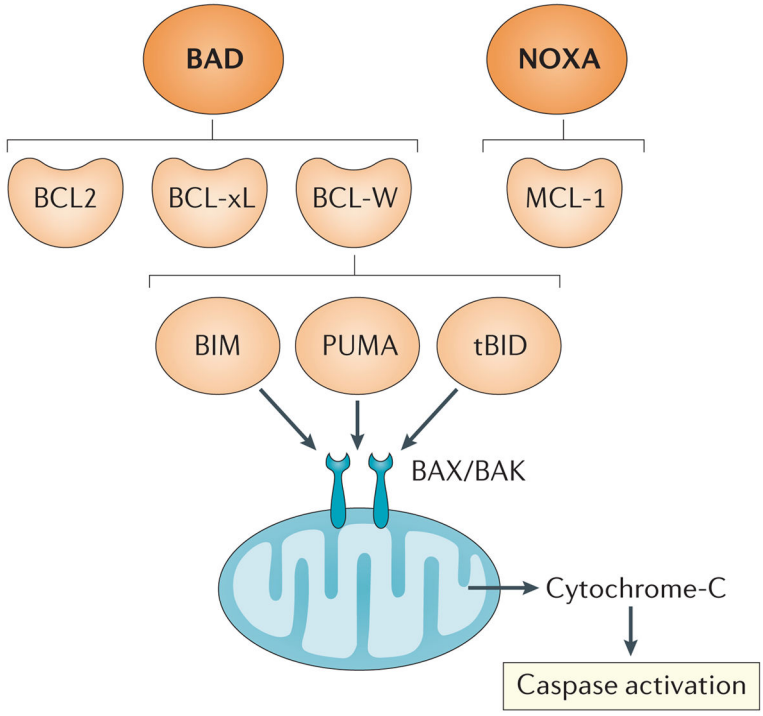


Figure 3. Therapeutic induction of cell death through targeting of the mitochondrial apoptosis pathway

Proteins in the BCL-2 family are classified into pro-survival (orange colour) and pro-apoptotic groups. The pro-apoptotic proteins are further sub-divided into BCL-2 homology 3 (BH3)-only proteins (green colour) and effector proteins (blue colour)

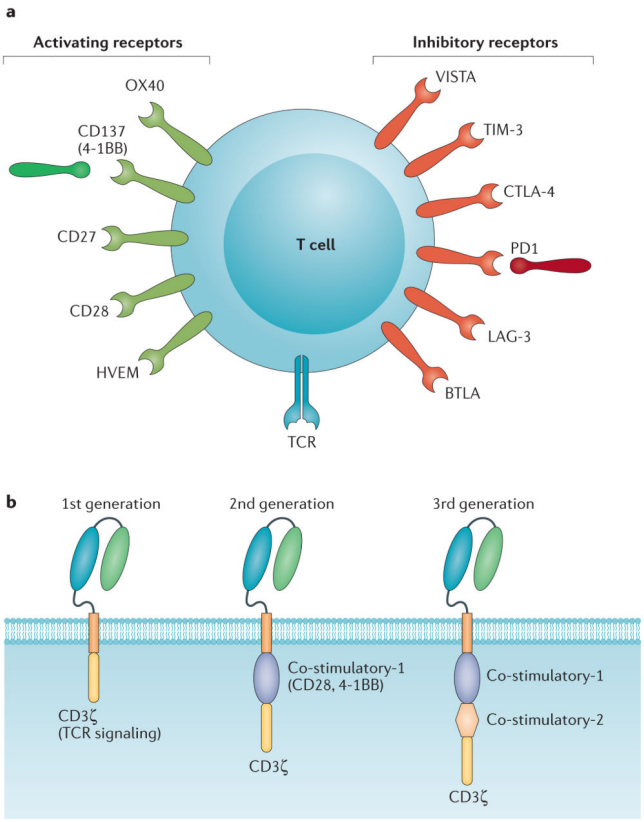


Figure 4. Autologous cell activation strategies

a | T cells can be activated by a set of inhibitory antibodies that target cell-surface receptors that inhibit cell function (redr) or by agonistic antibodies that target cell-surface receptors that regulate cell activation (green). **b** | Autologous T cells can be genetically engineered to express chimeric antigen receptors, which can be selectively activated upon binding with target proteins on cancer cells.

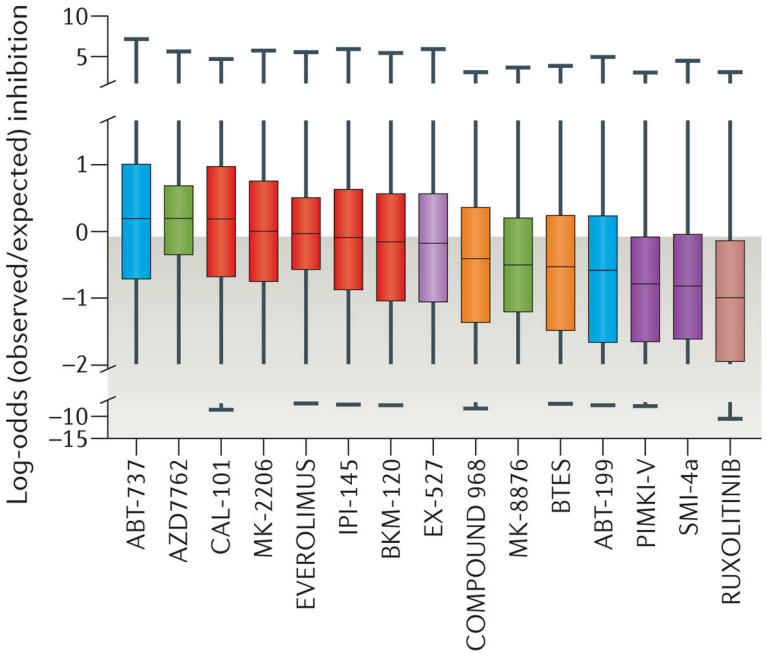


Figure 5. A representative high-throughput screening experiment involving drug combinations with the BET inhibitor JQ1

Each box plot represents data from one combination tested in 12 different lymphoma cell lines using an 8 × 8 viability matrix, with cell viability measured after 72 hours of treatment. The Y axis shows the ratio of expected and observed growth inhibition, on a logarithmic scale. Values above the '0' line indicate additive or synergistic effects. This experiment shows that the BCL2/Bcl-X inhibitor AB737, the checkpoint kinase inhibitor AZD7762, and different PI3K inhibitors (red boxes) have the highest level of synergy when combined with JQ1.

Table 1

Summary of the moseffective agents in patients with relapsed lymphoma

Signalling pathway/mechanism affected	Target	Drug	Response rate (complete + partial)					
			DLBCL	FL	MCL	SLL/CLL	cell	HL
PI3K/AKT/mTOR	mTOR	Everolimus	30%	50%	32%	18%	63%	42%
		Temsirolimus	36%	56%	38%	10%	NA	NA
	AKT	MK2206	0%	25%	9%	50%	0%	20%
	PI3K-6	Idelalisib	NA	57%	40%	72%	NA	12%
		TGR-1202	11%	42%	33%	63%	NA	13%
	PI3K-20	Duvelisib	0%	67%	67%	54%	33%	33%
	PI3K-45	Copanlisib	13%	40%	71%	67%	50%	NA
		Buparlisib	12%	25%	23%	NA	NA	NA
B-cell receptor	SYK	Fostamatinib	22%	10%	11%	55%	0%	NA
	BTK	Ibrutinib	26%	28%	75%	67%	NA	NA
		Acalabrutinib	NA	NA	NA	95%	NA	NA
Apoptosis	BCL2	Venetoclax	15%	28%	75%	77%	NA	NA
Immune checkpoint	PD1	Nivolumab	36%	40%	NA	NA	17%	87%
		Pembrolizumab	NA	NA	NA	NA	NA	66%

CLL, chronic lymphocytic leukaemia; DLBCL, diffuse, large B-cell lymphoma; HL, Hodgkin lymphoma; MCL, mantle-cell lymphoma; mTOR, mechanistic target of rapamycin; NA, not available; PD1, programmed cell death protein 1; SLL, small-lymphocytic lymphoma.

Table 2

Summary of antibody-drug-conjugates results in lymphoma

Drug	Payload	Target	*n*	Dose and schedule	ORR (%) in R/R disease			
					DLBCL	FL	MCL	SLL/CLL
CMC544	Calicheamicin	CD22	79	1.8 mg/m^2	15	68	NA	NA
SAR3419	DM4	CD19	25	55 mg/m^2 qwk	33	29	NA	NA
SAR3419 + rituximab	DM4	CD19	45	55 mg/m^2 + 375 mg/m^2	31 (9)	NA	NA	NA
SGN-CD19A	MMAF	CD19	37	0.5 5mg/kg	30 (16)	NA	NA	NA
Pinatuzumab vedotin	MMAE	CD22	33	2.4 mg/kg q3wk	50 (10)	20	NA	0
Pinatuzumab + rituximab	MMAE	CD22	63	2.4 + 375	57 (24)	62 (10)	NA	NA
Polatuzumab vedotin	MMAE	CD79b	86	2.4 mg/kg q3wk	52 (15)	44 (19)	100 (100)	0
Polatuzumab + rituximab	MMAE	CD79b	59	2.4 mg/kg + 375 q3wk	56 (15)	70 (40)	NA	NA
Brentuximab vedotin	MMAF	CD30	43	1.8 mg/kg q3wk	41	NA	NA	NA

CLL, chronic lymphocytic leukaemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle-cell lymphoma; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; NA, not applicable; ORR; overall response rate; qwk, weekly; q3wk, every 3 weeks; R/R, relapsed and/or refractory disease; SLL, small lymphocytic lymphoma.

Table 3

Summary results of CAR cell studies in patients with lymphoma

Centre	*n*	Conditioning therapy	Infused CAR cell dose	ORR (%)	CR (%)	PR (%)
NCI	4	FLU (25 mg/m^2 × 5 days)/CY (60 mg/kg × 2 days) + iv IL-2 following CAR-cell infusion	0.3 3 × 10^7 CAR T cells/kg	100	0	100
NCI	11	FLU (25 mg/m^2 × 5 days)/CY (60 or 120 mg/kg × 2 days)	1 5 × 10^6 CAR T cells/kg	89	56	33
NCI	9	FLU (30 mg/m^2 × 3 days)/CY (300 mg/m^2 × 3 days)	1 × 10^6 CAR T cells/kg	67	11	56
MSKCC	6	BEAM conditioning and autologous SCT	5 × 10^6 1 × 10^7 CAR T cells/kg	100	100	0
U Penn	23	Variable, including EPOCH, CY, bendamustine, and FLU/CY	3.7 8.9 × 10^6 CAR T cells/kg (median 5.8 × 10^6)	50	38	12
Fred Hutchinson	10	Lymphodepleting chemotherapy	2 × 10^5 or 2 × 10^6 or 2 × 10^7 CAR T cells/kg	67	11	56

BEAM, carmustine, etoposide, cytarabine, melphalan; CAR, chimeric antigen receptor; CR, complete response; CY, cyclophosphamide; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; FLU, fludarabine; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; ORR, overall response rate; PR, partial response; U Penn, University of Pennsylvania.