Immunotherapies shape the treatment landscape for hematologic malignancies

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The treatment landscape for hematologic malignancies is evolving faster than ever before, with a range of available therapeutic options that is now almost as diverse as this group of tumors. Immunotherapy in particular is front and center in the battle to control these diseases. Here, we describe the latest promising developments.

Exploiting T cells

The treatment landscape for hematologic malignancies is diverse, but one particular type of therapy has led the charge in improving patient outcomes. Several features of hematologic malignancies may make them particularly amenable to immunotherapy, including the fact that they are derived from corrupt immune cells and come into constant contact with other immune cells within the hematopoietic environment in which they reside. One of the oldest forms of immunotherapy, hematopoietic stem-cell transplantation (HSCT), remains the only curative option for many patients with hematologic malignancies.[1,2]

Given the central role of T lymphocytes in anti-tumor immunity, research efforts have focused on harnessing their activity for cancer treatment. One example of this is adoptive cellular therapy (ACT), in which T cells are collected from a patient, grown outside the body to increase their number and then reinfused back to the patient. Allogeneic HSCT, in which the stem cells are collected from a matching donor and transplanted into the patient, is a crude example of ACT. The graft-versus-tumor effect is driven by donor cells present in the transplant, but is limited by the development of graft-versus-host disease (GvHD), whereby the donor T cells attack healthy host tissue.

Other types of ACT have been developed in an effort to capitalize on the anti-tumor effects of the patients own T cells and thus avoid the potentially fatal complication of GvHD. Tumor-infiltrating lymphocyte (TIL) therapy was developed to exploit the presence of tumor-specific T cells in the tumor microenvironment. To date, the efficacy of TIL therapy has been predominantly limited to melanoma.[1,3,4]

Most recently, there has been a substantial buzz around the idea of genetically engineering T cells before they are reintroduced into the patient, to increase their anti-tumor efficacy and minimize damage to healthy tissue. This is achieved either by manipulating the antigen binding portion of the T-cell receptor to alter its specificity (TCR T cells) or by generating artificial fusion receptors known as chimeric antigen receptors (CAR T cells; Figure 1). The former is limited by the need for the TCR to be genetically matched to the patient's immune type, whereas the latter is more flexible in this regard and has proved most successful.

CARs are formed by fusing part of the single-chain variable fragment of a monoclonal antibody to part of the TCR and one or more costimulatory molecules. In this way, the T cell is guided to the tumor through antibody recognition of a particular tumor-associated antigen, whereupon its effector functions are activated by engagement of the TCR and costimulatory signal.[5]

Headlining advancements with CAR T cells

CAR T cells directed against the CD19 antigen, found on the surface of many hematologic malignancies, are the most clinically advanced in this rapidly evolving field (Table 1). Durable remissions have been demonstrated in patients with relapsed and refractory hematologic malignancies, including non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and acute lymphoblastic lymphoma (ALL), with efficacy in both the pre- and posttransplant setting and in patients with chemotherapy-refractory disease.[4,5]

CTL019, a CD19-targeted CAR-T cell therapy, also known as tisagenlecleucel-T, has received breakthrough therapy designation from the US Food and Drug Administration (FDA) for the treatment of pediatric and adult patients with relapsed/refractory B-cell ALL and, more recently, for the treatment of

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adult patients with relapsed/refractory diffuse large B cell lymphoma.[6]

It is edging closer to FDA approval for the ALL indication, having been granted priority review in March on the basis of the phase 2 ELIANA trial, in which 50 patients received a single infusion of CTL019. Data presented at the American Society of Hematology annual meeting in December 2016 showed that 82% of patients achieved either complete remission (CR) or CR with incomplete blood count recovery (CRi) 3 months after treatment.[7]

Meanwhile, Kite Pharma has a rolling submission with the FDA for KTE-C19 (axicabtagene ciloleucel) for the treatment of patients with relapsed/refractory B-cell NHL who are ineligible for HSCT. In the ZUMA-1 trial, this therapy demonstrated an overall response rate (ORR) of 71%.[8] Juno Therapeutics is developing several CAR T-cell therapies, including JCAR017, which elicited CR in 60% of patients with relapsed/refractory NHL.[9]

Target antigens other than CD19 are being explored, but these are mostly in the early stages of clinical development. While the focus has predominantly been on the treatment of lymphoma and leukemia, a presentation at the American Society for Clinical Oncology annual meeting in June reported the efficacy of a CAR-T cell therapy targeting the B-cell maturation antigen in patients with multiple myeloma. Results from 19 patients enrolled in an ongoing

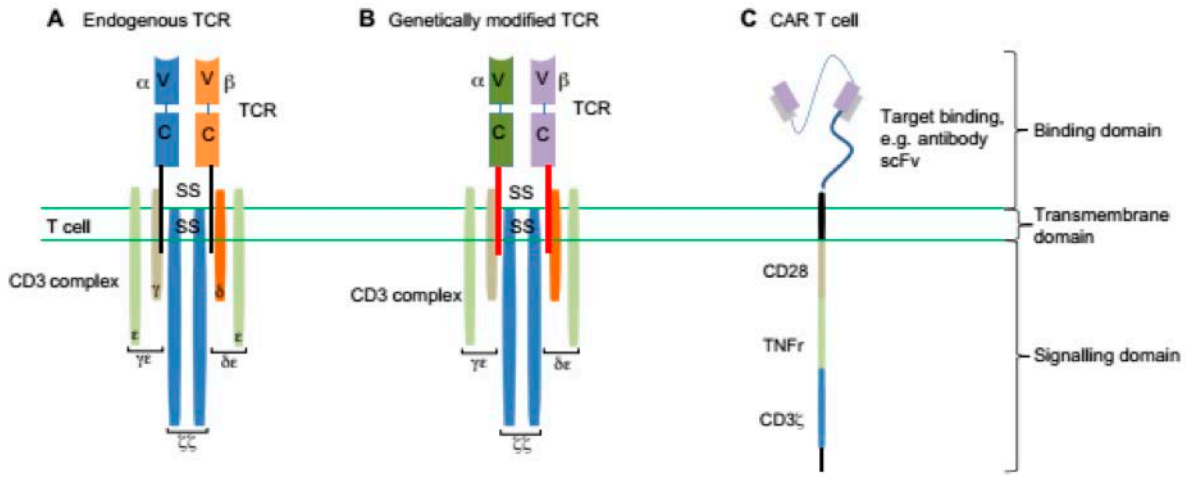

FIGURE 1 Genetically modified T-cell receptors for cancer immunotherapy. T cells can be manipulated to redirect their cytotoxic activity against tumor cells via genetic engineering of the T-cell receptor to improve its specificity and affinity for specific tumor-associated antigens. Reference: Sharpe M et al. Dis Model Mech. 2015;8:337-350. Reproduced under Creative Commons Attribution License.

TABLE 1 CAR T cell therapies in development

Drug	Manufacturer	CAR T-cell target	Most advanced clinical testing (clinicaltrials.gov identifier)
bb2121	Bluebird Bio, Celgene	BCMA	Phase 1 in multiple myeloma (NCT02658929)
UCART19	Cellectis	CD19	Phase 1 in pediatric and adult B-cell ALL (NCT02808442, NCT02746952)
JCAR014	Juno	CD19	Phase 1 in relapsed/refractory B-cell NHL (NCT02706405)
JCAR016	Juno	WT1	Phase 1 in AML, MDS or CML (NCT01640301)
JCAR017	Juno	CD19	Phase 1 in B-cell NHL (NCT02631044)
JCAR018	Juno	CD22	Phase 1 in pediatric ALL and NHL (NCT02315612)
KTE-C19 (axicabtagen ciloleucel)	Kite	CAR T-cells targeting CD19	Phase 2 in NHL, ALL, MCL, and DLBCL (NCT02348216, NCT02614066, NCT02601313, NCT02926833)
CTL019 (tisagenlecleucel-T)	Novartis	CAR T-cells targeting CD19	Phase 3 in ALL (NCT03027739)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BCMA, B-cell maturation antigen; CML, chronic myelogenous leukemia; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; WT1, Wilm's tumor protein

phase 1 trial in China showed that 14 had achieved stringent CR, 1 partial remission (PR) and 4 very good partial remission (VGPR).[10]

Antibodies evolve

Another type of immunotherapy that has revolutionized the treatment of hematologic malignancies is monoclonal antibodies (mAbs), targeting antigens on the surface of malignant B and T cells, in particular CD20. The approval of CD20-targeting mAb rituximab in 1997 was the first coup for the development of immunotherapy for the treatment of hematologic malignancies. It has become part of the standard treatment regimen for B-cell malignancies, including NHL and CLL, in combination with various types of chemotherapy.

Several other CD20-targeting antibodies have been developed (Table 2), some of which work in the same way as rituximab (eg, ofatumumab) and some that have a slightly different mechanism of action (eg, obinutuzumab).[11] Both types of antibody have proved highly effective; ofatumumab is FDA approved for the treatment of advanced CLL and is being evaluated in phase 3 trials in other hematologic malignancies, while obinutuzumab has received regulatory approval for the first-line treatment of CLL, replacing the standard rituximab-containing regimen.[12]

The indications for both drugs were expanded in 2016, ofatumumab to include maintenance therapy and combination therapy with fludarabine and cyclophosphamide for the treatment of CLL and obinutuzumab in combina-

TABLE 2 Clinically significant antibodies

Drug	Manufacturer	Description	FDA approval/ongoing clinical testing and most advanced clinical testing (clinicaltrials.gov identifier)
Rituximab (Rituxan)	Genentech/ Biogen	CD20-targeted mAb	FDA approved as front-line therapy for DLBCL in combination with CHOP and FL in combination with CVP (2006), as 1st- and 2nd- line treatment for CLL in combination with fludarabine and cyclophosphxamide (2010), and as maintenance therapy for FL following rituximab-chemotherapy regimen (2011) *Numerous trials ongoing, mostly as combination therapy*
Ofatumumab (Arzerra)	Novartis	CD20-targeted mAb	FDA approved for relapsed/refractory CLL (2009) and in front-line for CLL in combination with chlorambucil (2014) *Numerous clinical trials ongoing*
Obinutuzumab (Gazyva)	Genentech	CD20-targeted mAb	FDA approved for frontline treatment of CLL in combination with chlorambucil (2013) and for relapsed/refractory FL in combination with bendamustine, followed by obinutuzumab monotherapy (2016) *Numerous clinical trials ongoing*
MOR208	MorphoSys	CD19-targeted mAb	Phase 3 in DLBCL (B-MIND; NCT02763319) Phase 2 in CLL (COSMOS; NCT02639910)
Nivolumab (Opdivo)	Bristol-Myers Squibb	PD-1-targeted mAb	FDA approved for treatment of classic HL that has relapsed after autologous HSCT and posttransplantation brentuximab vedotin (2016) Phase 3 in plasma cell myeloma (CheckMate 602; NCT02726581)
Pembrolizumab (Keytruda)	Merck	PD-1-targeted mAb	Phase 3 in plasma cell myeloma (NCT02579863)
Daratumumab (Darzalex)	Janssen	CD38-targeted mAb	FDA approved as monotherapy (2015) and in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone for treatment of relapsed/refractory multiple myeloma (2016) *Numerous clinical trials ongoing, including phase 3 in treatment-naïve multiple myeloma (NCT02252172)*
Isatuximab	Sanofi	CD38-targeted mAb	Phase 3 in multiple myeloma (ICARIA-MM; NCT02990338)
Elotuzumab (Empliciti)	Bristol-Myers Squibb	CS-1-targeted mAb	FDA approved in combination with lenalidomide and dexamethasone for treatment of relapsed/refractory multiple myeloma (2015) *Numerous clinical trials ongoing*

CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; CLL, chronic lymphocytic leukemia; CVP, cyclophosphamide, vincristine sulfate, and prednisone; DLBCL, diffuse large B cell lymphoma; FDA, (US) Food and Drug Administration; FL, follicular lymphoma; HL, Hodgkin lymphoma; HSCT, hematopoietic stem-cell transplantation; mAb, monoclonal antibody

tion with bendamustine for treating patients with relapsed/refractory follicular lymphoma.

The use of ofatumumab as maintenance therapy is supported by the results of the phase 3 PROLONG study in which 474 patients were randomly assigned to ofatumumab maintenance for 2 years or observation. Over a median follow-up of close to 20 months, ofatumumab-treated patients experienced improved progression-free survival (PFS; median PFS: 29.4 months vs 15.2 months; hazard ratio [HR], 0.50; $P < .0001$).[13] Obinutuzumab's new indication is based on data from the phase 3 GADOLIN trial, in which the obinutuzumab arm showed improved 3-year PFS compared with rituximab.[14]

Until recently, multiple myeloma had proven relatively resistant to mAb therapy, but two new drug targets have dramatically altered the treatment landscape for this type of hematologic malignancy. CD2 subset 1 (CS1), also known as signaling lymphocytic activation molecule 7 (SLAMF7), and CD38 are glycoproteins expressed highly and nearly uniformly on the surface of multiple myeloma cells and only at low levels on other lymphoid and myeloid cells.[15]

Several antibodies directed at these targets are in clinical development, but daratumumab and elotuzumab, targeting CD38 and CS1, respectively, are both newly approved by the FDA for relapsed/refractory disease, daratumumab as monotherapy and elotuzumab in combination with lenalidomide and dexamethasone.

The indication for daratumumab was subsequently expanded to include its use in combination with lenalidomide plus dexamethasone or bortezomib plus dexamethasone. Support for this new indication came from 2 pivotal phase 3 trials. In the CASTOR trial, the combination of daratumumab with bortezomib–dexamethasone reduced the risk of disease progression or death by 61%, compared with bortezomib–dexamethasone alone, whereas daratumumab with lenalidomide–dexamethasone reduced the risk of disease progression or death by 63% in the POLLUX trial.[16,17]

Numerous clinical trials for both drugs are ongoing, including in the front-line setting in multiple myeloma, as well as trials in other types of B-cell malignancy, and several other CD38-targeting mAbs are also in development, including isatuximab, which has reached the phase 3 stage (NCT02990338).

Innovative design

Newer drug designs, which have sought to take mAb therapy to the next level, have also shown significant efficacy in hematologic malignancies. Antibody-drug conjugates (ADCs) combine the cytotoxic efficacy of chemotherapeutic agents with the specificity of a mAb targeting a tumor-specific antigen. This essentially creates a targeted payload that improves upon the efficacy of mAb monotherapy but mitigates some of the side effects of chemotherapy related to their indiscriminate killing of both cancerous and healthy cells.

The development of ADCs has been somewhat of a rollercoaster ride, with the approval and subsequent withdrawal of the first-in-class drug gemtuzumab ozogamicin in 2010, but the field was reinvigorated with the successful development of brentuximab vedotin, which targets the CD30 antigen and is approved for the treatment of multiple different hematologic malignancies, including, most recently, for posttransplant consolidation therapy in patients with Hodgkin lymphoma at high risk of relapse or progression.[18]

Brentuximab vedotin may soon be joined by another FDA-approved ADC, this one targeting CD22. Inotuzumab ozogamicin was recently granted priority review for the treatment of relapsed/refractory ALL. The FDA is reviewing data from the phase 3 INO-VATE study in which inotuzumab ozogamicin reduced the risk of dis-

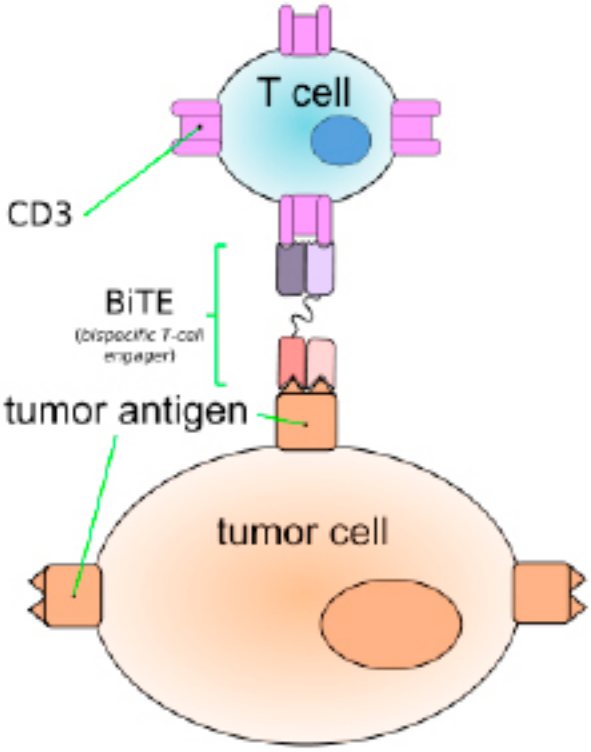

FIGURE 2 Bispecific T-cell engaging (BiTE) antibodies. BiTEs, such as blinatumomab (Blincyto), are designed to target two antigens simultaneously, one specific to the tumor cells and the other to T cells. In this manner they physically link tumor cells with cytotoxic T cells, stimulating T-cell activity and killing the tumor cell. Reproduced with permission: "BiTE antibody 01" by Armin Kübelbeck, available under a Creative Commons Attribution-ShareAlike 3.0 Unported http://commons.wikimedia.org/wiki/File:BiTE_antibody_01.svg. Accessed April 1, 2015.

TABLE 3 Bispecific antibodies and ADCs in development

Drug	Manufacturer	Description	FDA approved/ongoing clinical testing and most advanced clinical testing (clinicaltrials.gov identifier)
Blinatumomab (Blincyto)	Amgen	BiTE targeting CD3 and CD19	FDA approved for Philadelphia chromosome-negative relapsed/refractory B-cell ALL in adult patients (2014) and pediatric patients (2016)
AFM13	Affimed	BiTE targeting CD16A and CD30	Phase 2 in HL (NCT02321592)
MP0250	Molecular Partners	DARPin targeting VEGF and HGF	Phase 2 in multiple myeloma (NCT03136653)
MCLA-117	Merus	BiTE targeting CD3 and Clec12A	Phase 1 in AML (NCT03038230)
AMG330	Amgen	BiTE targeting CD3 and CD33	Phase 1 in AML (NCT02520427)
AMG420/BI836909	Amgen	BiTE targeting CD3 and BCMA	Phase 1 in multiple myeloma (NCT02514239)
AFM11	Affimed	BiTE targeting CD3 and CD19	Phase 1 in B-cell NHL (NCT02106091) and B-cell precursor ALL (NCT02848911)
MGD006	Macrogenics/Servier	DART targeting CD3 and CD123	Phase 1 in AML or MDS (NCT02152956)
Duvortuxizumab (MGD011)	Macrogenics/ Johnson & Johnson	DART targeting CD3 and CD19	Phase 1 in B cell malignancies (NCT02454270)
REGN1979	Regeneron	BiTE targeting CD3 and CD20	Phase 1 in B cell malignancies (NCT02290951) and lymphoma (NCT02651662)
RG7828/BTCT4465A	Roche/Genentech	BiTE targeting CD3 and CD20	Phase 1 in NHL and CLL (NCT02500407)*
XmAb14045	Xencor/Novartis	BiTE targeting CD3 and CD123	Phase 1 in CD123-expressing hematologic malignancies (NCT02730312)
JNJ-63709178	Johnson & Johnson/ Genmab	BiTE targeting CD3 and CD123	Phase 1 in AML (NCT02715011)
Brentuximab vedotin (Adcetris)	Seattle Genetics	CD30-targeting ADC	FDA approved for treatment of relapsed/refractory HL and systemic ALCL (2011) and for post-ASCT consolidation in HL patients at risk of relapse or progression (2015)
Inotuzumab ozogamicin (Besponsa)	Pfizer	CD22-targeting ADC	Phase 3 in ALL (NCT03150693, NCT01564784*)
Polatuzumab vedotin	Genentech/Roche	CD79b-targeting ADC	Phase 1/2 in DLBCL (NCT02611323, NCT02600897)
Denintuzunab mafodotin	Seattle Genetics	CD19-targeting ADC	Phase 2 in DLBCL (NCT02855359, NCT02592876)
RG7986	Genentech/Roche	ADC with undisclosed target	Phase 1 in NHL (NCT02453087)
AGS67E	Agensys/Astellas	CD37-targeting ADC	Phase 1 in lymphoid malignancies (NCT02175433) and AML (NCT02610062)
GSK-2857916	GlaxoSmithKline	BCMA-targeting ADC	Phase 1 in multiple myeloma (NCT02064387)
Naratuximab emtansine	ImmunoGen	CD37-targeting ADC	Phase 2 in NHL (NCT02564744)
Indatuximab ravtansine	Biotest	CD138-targeting ADC	Phase 1/2 in multiple myeloma (NCT01638936)*
AMG224	Amgen	ADC with undisclosed target	Phase 1 in multiple myeloma (NCT02561962)
SGN-CD19B	Seattle Genetics	CD19-targeted ADC	Phase 1 in NHL (NCT02702141)
SGN-CD352A	Seattle Genetics	CD352-targeted ADC	Phase 1 in multiple myeloma (NCT02954796)
SGN123A	Seattle Genetics	CD123-targeted ADC	Phase 1 in AML (NCT02848248)

TABLE 3 continued

Drug	Manufacturer	Description	FDA approved/ongoing clinical testing and most advanced clinical testing (clinicaltrials.gov identifier)
ADCT-301	ADC	CD25-targeted ADC	Phase 1 in AML/ALL (NCT02588092) and NHL (NCT02432235)
ADCT-402	ADC	CD19-targeted ADC	Phase 1 in B-cell NHL (NCT02669017) and ALL (NCT02669264)
IMGN779	ImmunoGen	CD33-targeted ADC	Phase 1 in AML (NCT02674763)
AGS62P1	Agensys/Astellas	FLT3-targeted ADC	Phase 1 in AML (NCT02864290)
Vadastuximab talirin	Seattle Genetics	CD33-targeted ADC	Phase 3 in AML (CASCADE; NCT02785900)

ADC, antibody drug conjugate; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ASCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; BiTE, bispecific T-cell engaging antibody; Clec12A, C-type lectin 12A; CLL, chronic lymphocytic lymphoma; DART, dual affinity retargeting antibody; DLBCL, diffuse large B-cell lymphoma; FDA, (US) Food and Drug Administration; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma

*Trial ongoing but no longer recruiting participants

ease progression or death by 55% compared with standard therapy, and a decision is expected by August.[19] Other ADC targets being investigated in clinical trials include CD138, CD19, and CD33 (Table 3). Meanwhile, a meta-analysis of randomized trials suggested that the withdrawal of gemtuzumab ozogamicin may have been premature, indicating that it does improve long-term overall survival (OS) and reduces the risk of relapse.[20]

Bispecific antibodies are another notable type of innovative design, fusing the single chain variable fragments of two different antibodies together to give a single drug specificity for two different antigens. Among the different types of bispecifics that have been developed, bispecific T-cell engagers (BiTEs) are the most advanced in clinical development (Figure 2). This drug class is distinguished by the fact that one of their targets is the TCR. The second target is a tumor-associated antigen, such as CD19, as in the case of the first FDA-approved member of this drug class, blinatumomab. In this way, BiTEs bind to both T cells and tumor cells and help to physically link the two via the formation of an immunological synapse that allows the T cell to kill the tumor cell.[21]

Blinatumomab was granted accelerated approval in 2014 for the treatment of Philadelphia chromosome-negative B-cell ALL based on findings from a phase 2 trial. Earlier this year, Amgen submitted an application for full regulatory approval on the basis of the follow-up phase 3 TOWER trial, in which the efficacy and safety of blinatumomab in this patient population were confirmed. This study also provided evidence for the efficacy of blinatumomab in patients whose tumors display the Philadelphia chromosome.[22]

Bispecific antibodies that link natural killer (NK) cells to tumor cells, by targeting the NK-cell receptor CD16, known as BiKEs, are also in development in an attempt to harness the power of the innate immune response.

B-cell signaling a ripe target

Beyond immunotherapy, molecularly targeted drugs directed against key drivers of hematologic malignancies are also showing great promise. In particular, the B-cell receptor (BCR) signaling pathway, a central regulator of B-cell function, and its constituent kinases that are frequently dysregulated in B cell malignancies, has emerged as an exciting therapeutic avenue.

A variety of small molecule inhibitors targeting different nodes of the BCR pathway have been developed (Table 4), but the greatest success to date has been achieved with drugs targeting Bruton's tyrosine kinase (BTK). Their clinical development culminated in the approval of ibrutinib for the treatment of patients with mantle cell lymphoma in 2013 and subsequently for patients with CLL, Waldenström macroglobulinemia, and most recently for patients with marginal zone lymphoma.

Briefly, each mature B cell acquires a unique receptor on its surface that is activated upon antigen binding. The signal is propagated downstream of the BCR through a series of kinases, including the LYN, spleen tyrosine kinase (SYK), and BTK kinases, ultimately activating transcriptional programs in the nucleus that regulate B-cell function.[23-25]

More than 100 clinical trials of ibrutinib are ongoing in an effort to further clarify its role in a variety of different disease settings. Furthermore, in an effort to address some of the toxicity concerns with ibrutinib, more specific BTK inhibitors are also being developed.

Other kinases that orchestrate the BCR pathway, including phosphatidylinositol-3-kinase (PI3K) and SYK, are also being targeted. The delta isoform of PI3K is expressed exclusively in hematopoietic cells and a number of PI3K delta inhibitors have been developed. Idelalisib received regulatory approval for the treatment of patients with CLL in combination with rituximab, and for patients with follicular lymphoma and small lymphocytic leukemia.

As with ibrutinib, a plethora of clinical trials are ongoing, however a major setback was suffered in the frontline setting when Gilead Sciences halted 6 clinical trials due to reports of increased rates of adverse events, including deaths.[26] Meanwhile, SYK inhibitors have lagged behind somewhat in their development, but one such offering, entospletinib, is showing promise in patients with AML.[27]

Finally, there has been some success in targeting one of the downstream targets of the BCR signaling pathway, the Bcl2 protein that is involved in the regulation of apoptosis. Venetoclax was approved last year for the treatment of patients with relapsed/refractory CLL in patients who have a chromosome 17p deletion, based on the demonstration of impressive, durable responses.[28]

TABLE 4 Targeting the BCR pathway

Drug	Manufacturer	Description	FDA approved/ongoing clinical testing and most advanced clinical testing (clinicaltrials.gov identifier)
Ibrutinib (Imbruvica	Pharmacyclics/Janssen	BTK inhibitor	FDA approved for the treatment of previously treated patients with MCL (2013), for patients with relapsed/refractory CLL (2014), for patients with Waldenström macroglobulinemia (2015), for patients with previously untreated CLL (2016), and for patients with relapsed/refractory MZL (2017)
Acalabrutinib	Acerta Pharma	BTK inhibitor	Phase 3 in MCL and CLL (NCT02972840, NCT02477696, NCT02970318)
BGB-3111	BeiGene	BTK inhibitor	Phase 3 in Waldenström macroglobulinemia (NCT03053440)
Tirabrutinib (GS-4059)	Gilead Sciences	BTK inhibitor	Phase 2 in CLL (NCT02983617, NCT02968563)
Entospletinib	Gilead Sciences	SYK inhibitor	Phase 2 in CLL and AML (NCT01799889, NCT02983617, NCT02343939)
Cerdulatinib (PRT062070)	Portola Pharmaceuticals	SYK inhibitor	Phase 1/2 in CLL/SLL/NHL (NCT01994382)
Idelalisib (Zydelig)	Gilead Sciences	PI3K inhibitor	Phase 3 in CLL and FL (NCT01659021*, NCT02536300, NCT01569295*)
Duvelisib (IPI-145)	Verastem	PI3K inhibitor	Phase 3 CLL/SLL (NCT02004522*)
TGR-1202	TG Therapeutics	PI3K inhibitor	Phase 3 CLL and DLBCL (NCT02612311, NCT02793583)
Venetoclax (Venclexta)	AbbVie/Genentech	Bcl2 inhibitor	Phase 3 in CLL and AML (NCT02242942*, NCT02756611, NCT03069352*, NCT02993523)

AML, acute myeloid leukemia; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FDA, (US) Food and Drug Administration; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; SLL, small lymphocytic leukemia; SYK, spleen tyrosine kinase

*Trial ongoing, but not recruiting participants

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