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REVIEW ARTICLE

Leveraging the Immunomodulatory Potential of Ibrutinib for Improved Outcomes of T Cell-Mediated Therapies of B Cell Malignancies: A Narrative Review

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Abstract
Standard treatment options for B cell malignancies include immunochemotherapies and/or targeted therapies, which often provide temporary disease remission. However, many patients do not achieve complete remission with these treatments, develop resistance, and eventually experience disease relapse. New immunomodulatory treatments, such as T cell-based therapies, show promise in treating various types of blood cancers, including B cell malignancies. However, their effectiveness is often limited by the immunosuppressive tumor microenvironment and altered function of patient-derived T cells. Ibrutinib, a Bruton tyrosine kinase inhibitor, has been shown to restore immune balance and function in patients with chronic lymphocytic leukemia. Ibrutinib is being studied as adjuvant or combinatorial therapy with chimeric antigen receptor (CAR) T cells or T cell-engaging bispecific antibodies for the treatment of B cell malignancies. Current evidence suggests that ibrutinib could be beneficial when used before, during, or after CAR T cell administration, potentially providing higher complete response rates and reduced toxicity. In conclusion, existing evidence strongly supports the combined use of ibrutinib and T cell therapies. However, additional clinical trials are needed to further validate the effectiveness of this treatment strategy in patients with various B cell malignancies.

1 Introduction

Treatment options for B cell malignancies (BCMs), including chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenström macroglobulinemia, and marginal zone lymphoma, have evolved significantly in recent years, propelled by advancements in targeted therapy, immunotherapy, and precision medicine [1–4]. However, in patients with high-risk disease

Key Points

T cell-based therapies, such as chimeric antigen receptor (CAR) T cell therapy, are effective for B cell malignancies but are limited by the immunosuppressive tumor microenvironment and T cell dysfunction.

Ibrutinib, a Bruton tyrosine kinase inhibitor, has demonstrated the unique ability to restore immune balance via T cell function and mediate functional recovery of the adaptive immune system in patients with B cell malignancies. Through disruption of B cell receptor signaling pathways and T cell immunomodulatory effects, ibrutinib has the potential to enhance CAR T cell function.

Ibrutinib in combination with CAR T cell therapy has shown enhanced efficacy with no detrimental effects on safety. Combination of ibrutinib with T cell-engaging bispecific antibodies has shown promise in preclinical studies, and early clinical studies are ongoing.

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characteristics, relapsed or refractory (R/R) disease, or an aggressive disease transformation (i.e., Richter transformation), treatment options have limited efficacy, and the prognosis remains unfavorable [5, 6].

The advent of T cell–based therapies, such as chimeric antigen receptor (CAR) T cell therapy and T cell–engaging bispecific antibodies (BsAbs), has significantly improved the treatment of hematologic malignancies, with the potential to transform the treatment landscape [7, 8]. Similarly, ibrutinib, a Bruton tyrosine kinase inhibitor (BTKi), emerged as a cornerstone in the treatment of CLL and other BCMs [4, 9]. Recent studies have begun to unravel the potential synergy between these two therapeutic modalities, offering new avenues for enhanced efficacy and improved outcomes in patients with BCM [10–14]. This review examines the rationale, preclinical evidence, and clinical implications of integrating ibrutinib, the first-in-class BTKi, with CAR T cell or BsAbs therapies in the treatment of BCMs. By focusing primarily on studies conducted in CLL to describe the mechanism of T cell dysfunction, we aim to distill key findings that may be generalizable to other BCMs.

2 T Cell Dysfunction in CLL

CLL is characterized by the clonal expansion of B cells [15]. Although a BCM, research over the past 2 decades has shed light on impaired T cell numbers and function in the BCM tumor microenvironment, suggesting the potential involvement of T cells in disease progression and therapeutic responses [16].

T cells, both CD4 and CD8 subsets, generally exhibit protumor functions in CLL [16]. The dysfunctionality of T cells, marked by exhaustion and anergy, contributes to immune evasion and disease progression (Fig. 1) [17]. Prolonged antigen exposure and tumor-induced immune suppression can lead to T cell exhaustion, characterized by upregulation of the inhibitory receptor programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) [17–21]. Although PD-1+ T cells are increased in CLL and CD8 T cells showed functional defects in proliferation and cytotoxicity, no overall functional impairment of cytokine production by T cells was observed, distinguishing this state from true T cell exhaustion as observed in chronic viral infections [17].

Impaired T cell cytotoxicity and effector functions in CLL can compromise immune surveillance mechanisms and promote an immunosuppressive environment, allowing the survival and proliferation of malignant B cells [22, 23]. Dysregulated T cell effector function is apparent by changes in cytokine production, proliferation, and activation [24]. It is also evident in CLL that, T cells skew toward more differentiated effector memory T phenotypes as opposed to naive cells, which might have detrimental effects on the capacity to fight infections and impact treatments that involve activation of the immune system [16, 18]. Moreover, cellular communication between T cells and B cells is impaired in CLL as the process of immune synapse formation is affected [25].

Another hallmark of T cell dysfunction in CLL is the inversion of the CD4:CD8 T cell ratio, with a relative decrease in CD4 T cells compared with CD8 T cells [26]. Importantly, inverted CD4:CD8 ratios have been associated with a shorter time to first treatment and overall survival [19, 27].

Furthermore, the immunosuppressive microenvironment in CLL, driven in part by overabundant regulatory T (T_{reg}) cells in peripheral blood and lymphoid tissues, further impedes effective antitumor immunity [28–32]. The expansion of T_{reg} cells may result from tumor-derived factors, cytokine-mediated signals, and dysregulated interactions within the tumor microenvironment. Alterations of T_{reg} cells include increased expression of PD-1 and CTLA-4, as well as an increased capacity to produce the immunosuppressive cytokines interleukin-10 (IL-10) and transforming growth factor β [21, 29, 33]. Similar to T_{reg} cells, irregularities in IL-17–secreting T cells (T helper [T_h]17), including cell count and altered phenotype, have been reported in CLL [34, 35]. While the exact role of T_h17 cells in CLL is not fully understood, their proinflammatory cytokine production may indirectly promote an immunosuppressive environment, while their cytotoxic activity may conversely have antitumor effects [35]. Notably, research on autoimmune diseases found that perturbances in T_{reg}:T_h17 ratios play a pathologic role in immunity, which is also observed in patients with CLL [34, 36, 37]. While T_h17 cells possess immune stimulatory characteristics, in healthy individuals, this action is balanced through the immunosuppressive activities of T_{reg} cells, ensuring immune homeostasis [38]. Therefore, an observed imbalance in CLL may contribute to an altered immune landscape, potentially promoting tumor evasion and progression or even autoimmunity [35].

Additionally, CLL is characterized by a shift in T_h cell polarization from a T_h1 to a T_h2 phenotype among CD4 T cell-derived T_h cells [39]. Interferon-gamma– and tumor necrosis factor-alpha–producing T_h1 cells are key components in orchestrating cellular immunity, while T_h2 cells secrete a variety of cytokines (IL-4, IL-5, IL-10, and IL-13) that promote humoral immune responses. A skew toward the T_h2 phenotype can lead to inhibition of effective antitumor responses and promote CLL B cell proliferation [40].

Lastly, CLL is associated with alterations in the T cell receptor (TCR) repertoire, characterized by clonal expansions and oligoclonal patterns [41–44]. This skewed distribution of T cell clones may result from chronic antigenic

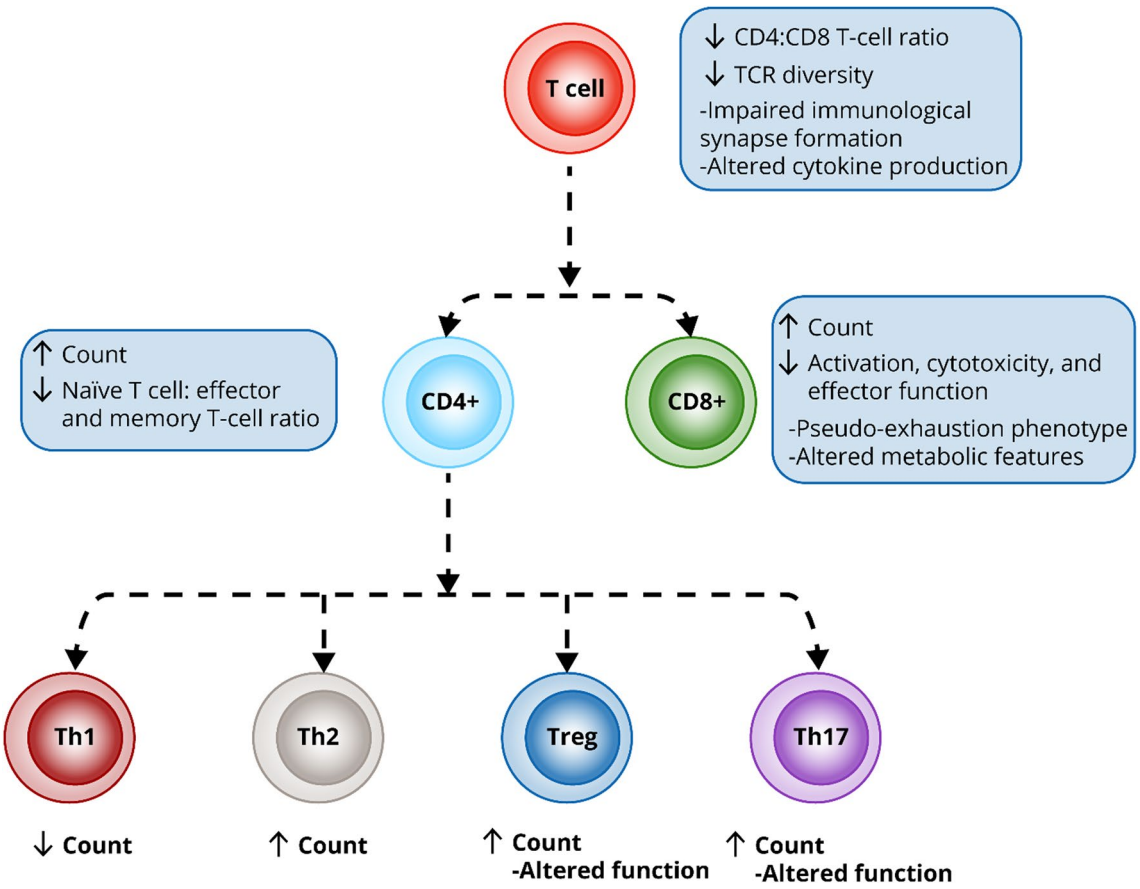

Fig. 1 T cell dysfunction in patients with CLL. CLL and other B cell malignancies affect different T cell subpopulations in multiple ways, including cell counts, function, activation, and differentiation. *CLL* chronic lymphocytic leukemia, *CD* cluster of differentiation, *TCR* T cell receptor, *Th* T helper, T_{reg} regulatory T cell

stimulation by leukemia cells, leading to the emergence of dysfunctional T cell subsets with limited diversity and specificity [41, 44–47]. In addition, disease stage, previous chemotherapy treatments, and the emergence of Richter transformation correlate with a more profound impairment of the TCR repertoire [41, 48, 49].

Therefore, functional changes within the T cell compartment observed in CLL and other BCMs may offer insight into the mechanisms of disease progression and therapeutic responses. T cell dysfunction, characterized by exhaustion, anergy, and altered subset distribution, facilitates immune evasion and tumor proliferation. Additionally, dysregulated cytokine production, impaired cellular communication, and skewed TCR repertoire may further contribute to the immunosuppressive environment in BCMs. Understanding these complex dynamics not only enhances our comprehension of BCM pathogenesis, but also holds promise for developing targeted therapeutic interventions aimed at restoring T cell functionality and improving clinical outcomes.

3 Effects of Ibrutinib on Endogenous T Cells

Ibrutinib revolutionized the treatment landscape of CLL, offering long-term clinical and survival benefits superior to chemotherapy and chemoimmunotherapy [50–53]. Remarkably, unlike chemotherapy and chemoimmunotherapy, first-line ibrutinib treatment is associated with survival rates that are similar to those seen in the age-matched general population [54]. Beyond its direct effects on B cell receptor signaling pathways, accumulating evidence suggests that ibrutinib exerts profound immunomodulatory effects, particularly on T cell function, shaping the immune microenvironment in CLL. Importantly, ibrutinib affects various cellular functions beyond those driven by the B cell receptors [55]. The effect of ibrutinib on T cells can be mediated directly via its BTKi activity [56]; IL-2−inducible T cell kinase inhibitor (ITKi) activity [57, 58]; and crosstalk with other immune cells, such as B cells, or other components of the tumor microenvironment (Fig. 2) [59]. Within the tumor microenvironment, the expansion of myeloid-derived suppressor cells (MDSCs), which are at least partially Bruton tyrosine

kinase (BTK) dependent, has also been associated with loss of immune effector cell function and reduced effectiveness of immune-based cancer therapies [60]. Thus, MDSCs are another promising therapeutic target. The results of studies demonstrate that ibrutinib has the potential to modulate MDSC function and development, highlighting yet another mechanism by which ibrutinib may enhance T cell function [61].

One of the unique therapeutic effects of ibrutinib in patients with CLL is its ability to restore T cell numbers and function [62, 63]. Long-term ibrutinib treatment results in elimination of CLL cells, as well as normalization of cell counts of different T cell subpopulations, natural killer cells, MDSCs, and circulating monocytes [63]. In addition to immune cell repopulation, ibrutinib mediates functional recovery of the T cell compartment of the adaptive immune system [62].

Preclinical studies have demonstrated that ibrutinib alleviates T cell dysfunction by reversing T cell exhaustion and promoting antitumor immunity. Specifically, ibrutinib has been shown to restore the balance of CD4:CD8 and T_h1:T_h2 cell ratios [57, 58, 64, 65], as well as T_{reg} cell numbers and function [59]. Ibrutinib also plays a role in reversing the overexpression of PD-1 and CTLA-4 [59, 66, 67], and reducing T cell exhaustion [66, 68].

Clinical observations corroborate these preclinical findings. A study analyzing samples from patients in the E1912 study, characterizing the longitudinal effects on T cells of first-line treatments with ibrutinib-rituximab or fludarabine, cyclophosphamide, and rituximab (FCR) in patients with CLL, underscores the enhanced cytotoxic potential of T cells during ibrutinib-rituximab therapy, driven in part by an augmented formation of CD8 T cell lytic synapses after ibrutinib-rituximab treatment but not after FCR treatment [69]. The same study showed that the expression of immune checkpoint molecules, such as PD-1 and programmed death-ligand 1 (PD-L1), was associated with minimal residual disease (MRD) status, suggesting their potential as predictive

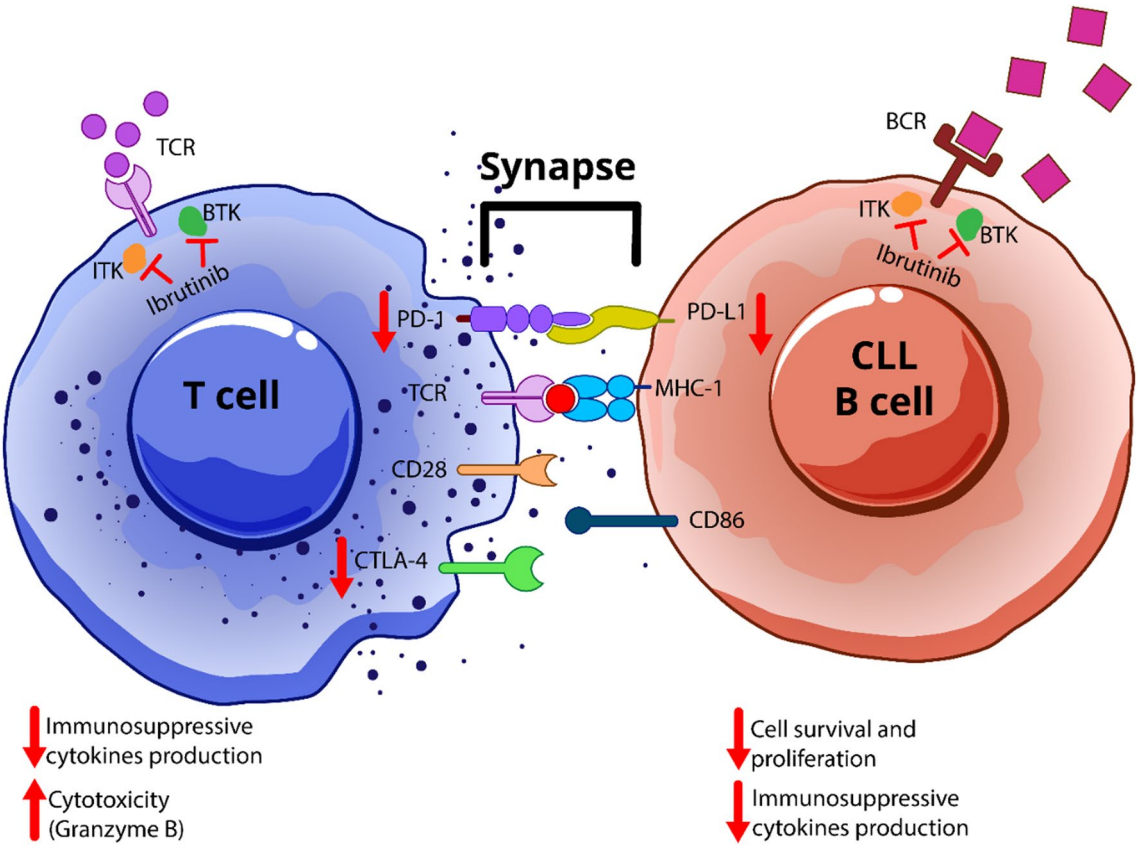

Fig. 2 Ibrutinib-mediated inhibition of BTK- and ITK-dependent signaling pathways in T cells and its cross-talk with CLL B cells. Ibrutinib works by inhibiting BTK and ITK signaling in T cells. This inhibition results in enhanced cytotoxicity through Granzyme B and leads to the downregulation of immunosuppressive cytokines and immune checkpoint proteins such as PD-1 and CTLA-4. In CLL B cells, ibrutinib not only suppresses cell survival and proliferation, but also mediates the downregulation of immunosuppressive cytokines and PD-L1. *BCR* B cell receptor, *BTK* Bruton tyrosine kinase, *CD* cluster of differentiation, *CLL* chronic lymphocytic leukemia, *CTLA-4* cytotoxic T lymphocyte-associated protein 4, *ITK*, interleukin-2–inducible T cell kinase, *MHC-1* major histocompatibility complex-1, *PD-1* programmed cell death protein 1, *PD-L1* programmed death-ligand 1, *TCR* T cell receptor

markers in the context of ibrutinib-based therapies [69]. Additionally, correlative analyses between ibrutinib treatment and clinical outcomes revealed a significant decrease in the T_h2:T_h1 ratio among patients achieving complete remission, indicating a potential mechanistic link between T cell polarization and treatment response [64]. In another phase 2 investigator-initiated study, ibrutinib exerted multiple antitumor effects, such as reduction of T_h17 counts, normalization of T cell PD-1 expression, and modulation of the tumor microenvironment via cytokine and chemokine expression [67].

Ibrutinib treatment of CLL in the R/R setting has been shown to broaden the TCR repertoire diversity, correlating with favorable treatment response and lower infection-related adverse events [42]. Conversely, first-line ibrutinib treatment of CLL was shown to increase TCR repertoire clonality, suggesting different mechanisms between the R/R and first-line settings [43].

Studies looking at global gene expression within the T cell compartment in CLL confirm a general notion of an immunosuppressive and exhausted phenotype of T cells and reversal of this phenotype with ibrutinib treatment. In a mouse model, RNA sequencing confirmed that ibrutinib directly reduced the T cell exhaustion-related transcriptional profile [68]. Importantly, using BTK-deficient mice, the effect of ibrutinib was shown to be independent of BTK expression, suggesting mechanisms mediated by other targets, which possibly include inducible T cell kinase (ITK) [68]. Single-cell RNA sequencing studies addressing T cell phenotypes in patients with CLL demonstrate the effect of ibrutinib treatment on T cells, with more substantial downregulation of genes important for immune cell activation such as CD28, JUN, and ZAP70 in CD8 versus CD4 cells [70]. Interestingly, the differences in expression of checkpoint molecules and immune-suppressive genes were observed in T cells from patients who were sensitive versus resistant to ibrutinib, suggesting the reversal of immunosuppression as an important biomarker of treatment response [71].

While the effects of ibrutinib are primarily mediated via BTK-dependent pathways, studies have also demonstrated that the ITK pathway in T cells, which regulates the T_h1:T_h2 cell balance, is inhibited by ibrutinib [9, 57, 58]. Moreover, genetic- or ibrutinib-mediated inhibition of ITK has been shown to regulate T_h17 and T_{reg} cell differentiation in vitro [72]. The reduction in the T_{reg}:CD4 T cell ratio in the blood of patients treated with ibrutinib, but not acalabrutinib, further supports the notion of an ITK-dependent mechanism of T cell modulation [59]. Additionally, preclinical studies demonstrate that ibrutinib can prevent the exhaustion of cytotoxic CD8 T cells independent of BTK inhibition [68]. Notably, ITK inhibition is a unique characteristic of ibrutinib among all BTKis, which likely underlies its distinct immunomodulatory action [73, 74].

In summary, the intricate interplay between ibrutinib, T cells, and CLL cells underscores the multifaceted mechanisms underlying CLL pathogenesis and treatment response.

4 CAR T Cells in B Cell Malignancies

Other BCMs are often associated with impaired intrinsic T cell activity. Thus, the T cell immune response can still be leveraged as a potential therapeutic approach against these malignancies.

CAR T cell therapy involves genetic engineering of patients' T cells to express synthetic receptors targeting tumor-associated antigens, thereby enabling specific recognition and elimination of malignant B cells [8].

Encouraging results with CAR T cell therapy have been observed in patients with a myriad of BCMs. Thus far, second-generation CD19-targeted CAR T cells have shown less efficacy in CLL than in other BCMs. CAR T cells induced complete responses (CRs) in 21–29% of patients with CLL, and those who achieved a CR were unlikely to relapse [75–77]. Recently, lisocabtagene maraleucel received accelerated approval for treatment of R/R CLL based on the results of the TRANSCEND CLL 004 trial [78]. In this study, the CR rate was 18%, and those with a CR showed durable responses consistent with previous reports [79]. Importantly, the patient population consisted of heavily pretreated individuals with extremely limited therapeutic options and required failure of previous BTKi therapy for enrollment.

CD19-directed CAR T cell therapies appear more effective in other BCMs than CLL, and several CAR T cell therapies have already been approved by the US Food and Drug Administration (FDA): brexucabtagene autoleucel and lisocabtagene maraleucel for R/R MCL; lisocabtagene maraleucel, tisagenlecleucel, and axicabtagene ciloleucel for R/R DLBCL; tisagenlecleucel, lisocabtagene maraleucel, and axicabtagene ciloleucel for R/R FL; and the aforementioned lisocabtagene maraleucel for R/R CLL/small lymphocytic lymphoma (SLL) [78, 80–82]. The 3-year follow-up data from the pivotal ZUMA-2 phase 2 trial (brexucabtagene autoleucel) showed a CR rate of 68% in patients with R/R MCL after failure of at least 2 prior lines of therapy, including a BTKi [83]. Recent updates of the TRANSCEND NHL 001 study of lisocabtagene maraleucel in patients with heavily pretreated MCL, including those with a high-risk disease, reported a CR rate of 72% with acceptable toxicity [84]. Early data on CAR T cell (tisagenlecleucel) efficacy in R/R DLBCL reported a CR rate of 43% [85]. In two pivotal studies in patients with R/R DLBCL (ZUMA-1 [axicabtagene ciloleucel] and JULIET [tisagenlecleucel]), 58% and 39% of patients, respectively, achieved

CR [86, 87]. Similarly, in the TRANSCEND NHL 001 study (lisocabtagene maraleucel) in patients with R/R DLBCL, the CR rate was 53% at 2 years of follow-up [88]. Moreover, CAR T cell efficacy and safety has been evaluated in three clinical trials (ZUMA-7, TRANSFORM, and BELINDA) as a second-line therapy for patients with transplant-eligible DLBCL, resulting in approvals of axicabtagene ciloleucel and lisocabtagene maraleucel for this indication [89]. In one of the first studies of tisagenlecleucel in R/R FL, the CR rate was 71% [85], and more recent studies with a long-term follow-up (ZUMA-5 [axicabtagene ciloleucel], TRANSCEND FL [lisocabtagene maraleucel], and ELARA [tisagenlecleucel]) confirmed the depth and durability of the responses; CR rates were 79, 94, and 68%, respectively [89–92]. Together with favorable response rates, the treatment led to durable remissions and MRD negativity, highlighting the curative potential of CAR T cell therapy in selected patient populations.

Despite these promising results, challenges remain in the broader implementation of CAR T cell therapy, with the management of toxicities being a key hurdle [93]. Cytokine release syndrome (CRS) and neurotoxicity represent unique adverse events associated with CAR T cell therapies, necessitating close patient monitoring and supportive care strategies [94]. Other unmet challenges include mitigation of mechanisms of relapse and optimization of patient selection. Approximately half of patients with BCMs treated with commercially available CAR T cell products either have disease that is primarily refractory to CAR T cell therapy from the outset or ultimately relapse after initially responding, with dismal outcomes [95, 96]. The efficacy of CAR T cell therapy in BCMs can be hindered by target antigen loss by tumor cells and/or by CAR T cell hypofunction, including insufficient CAR T cell proliferation along with impaired cytokine secretion and cytotoxicity [93, 97]. Moreover, as discussed earlier in this review, the immunosuppressive microenvironment associated with BCMs may impede T cell infiltration and the antitumor activity of CAR T cells.

5 Bispecific Antibodies in B Cell Malignancies

BsAbs engage both an antigen present on tumor cells and another antigen present on immune cells, such as T cells, thereby inducing targeted cytotoxicity by immune cell activation. Two commonly identified BCM-specific target antigens are CD19 and CD20; CD3 is the most studied T cell-engaging antigen.

In preclinical CLL studies, the CD19/CD3 BsAb blinatumomab demonstrated potent antitumor activity, with a > 90% killing of CLL cells in vitro [98]. Additionally, the preliminary dose-escalation investigation of novel BsAbs in patients with R/R CLL showed clinical activity with a manageable safety profile [99].

In a clinical study of single-agent mosunetuzumab, a CD20/CD3 BsAb, in patients with R/R FL, the CR rate was 48%; in extended follow-up of selected patients, the CR rate increased to 60% [100]. This study led to the approval of mosunetuzumab for the treatment of R/R FL in the European Union and accelerated approval by the FDA in the United States, both in 2022 [101–103].

Glofitamab, a CD20/CD3 BsAb, showed a CR rate of 39% in a phase 1–2 study in patients with R/R DLBCL, which prompted the FDA approval of this BsAb for patients with DLBCL after 2+ previous lines of therapy [104, 105]. Glofitamab was also preliminarily tested in patients with grade 1–3 FL and in those with R/R MCL, resulting in promising CR rates of 48 and 67%, respectively [106, 107]. With a median follow-up of 17.2 months, the updated analysis of the glofitamab study in patients with MCL reported that 60% of CRs were sustained [108].

Recently, epcoritamab, another CD20/CD3 BsAb, gained accelerated approval from the FDA for the treatment of R/R DLBCL and R/R FL, based on the EPCORE NHL-1 trial, in which CR rates of 39 and 68%, respectively, were demonstrated [109–112]. Other BsAbs, such as odronextamab (CD20/CD3) and blinatumomab (CD19/CD3), were evaluated in phase 1 trials in a small number of patients with R/R FL, R/R DLBCL, and R/R MCL, with encouraging results, warranting further efficacy evaluation [113, 114].

Similar to the challenges seen with the implementation of CAR T cell therapies for BCMs, treatment with BsAbs may have unique toxicities such as CRS, treatment resistance, and disease relapse. Additionally, a lack of treatment response may be caused by heterogeneity of tumor cell target antigen expression, an immunosuppressive tumor microenvironment, or suboptimal immunogenic responses toward BsAbs [115, 116]. Addressing these obstacles is critical for realizing the full therapeutic potential of BsAbs in the treatment of BCMs.

6 Ibrutinib and CAR T Cell Therapies

Through its ability to disrupt B cell receptor signaling pathways and to modulate the immune microenvironment by dual BTK and ITK inhibitory activities, ibrutinib treatment sets the stage for optimizing CAR T cell function (Fig. 3).

Several preclinical studies suggested that ibrutinib has the potential to enhance the "fitness" of CAR T cells and to improve their function in a BTKi-independent fashion. One preclinical study demonstrated that ibrutinib can ameliorate CAR T cell exhaustion mediated by tonic CAR signaling, providing persistent antigen-specific stimulation to a higher

degree than zanubrutinib and orelabrutinib [14]. Similarly, another study reported that ibrutinib enhances CAR T cell fitness to a greater extent than acalabrutinib or zanubrutinib by reducing CAR T cell activation-induced cell death, maintaining a naive state, and preventing premature exhaustion [117]. Since zanubrutinib, orelabrutinib, and acalabrutinib all lack ITKi activity, the unique immunomodulatory properties of ibrutinib are ascribed to its ITKi function [73, 74]. Several studies suggest that ibrutinib pretreatment may improve the yield of CAR T cell products derived from patients and have the potential to enhance CAR T cell function [14, 118–121]. Similarly, in a xenograft model, treatment with a BTKi, either ibrutinib or acalabrutinib, during long-term stimulation of anti-CD19 CAR T cell products, has been shown to lead to increased cytokine secretion; T cell activation, proliferation, and survival; and improved CAR T cell-mediated tumor clearance [11]. However, only treatment with ibrutinib, not acalabrutinib, during CAR T cell stimulation resulted in improved T_h1 differentiation, highlighting the unique ITKi-mediated activity of ibrutinib [11]. Additionally, in a study performed on patient samples and cell lines generated from patients with MCL, ibrutinib enhanced cytotoxicity, provided superior disease control, and allowed achievement of long-term remission in a murine model [122]. Further research also demonstrated the efficacy of ibrutinib in reducing the CAR-19 T cell-mediated CRS in a murine model of BCM [123].

Clinical studies (summarized in Table 1) have shown that, among patients who did not initially respond to or whose disease progressed while on prior ibrutinib, the outcomes following CAR T cell therapy tended to be favorable. In TRANSCEND CLL 004, heavily pretreated patients with R/R CLL, all of whom had previously received a BTKi, had a CR rate of 18% after a single dose of lisocabtagene maraleucel [79]. An analysis of TRANSCEND CLL 004, performed on a subset of patients who previously received ibrutinib and who continued ibrutinib post−CAR T cell infusion, showed promising efficacy (CR rate, 47%) with a manageable safety profile in this heavily pretreated population [124]. Similarly, a smaller

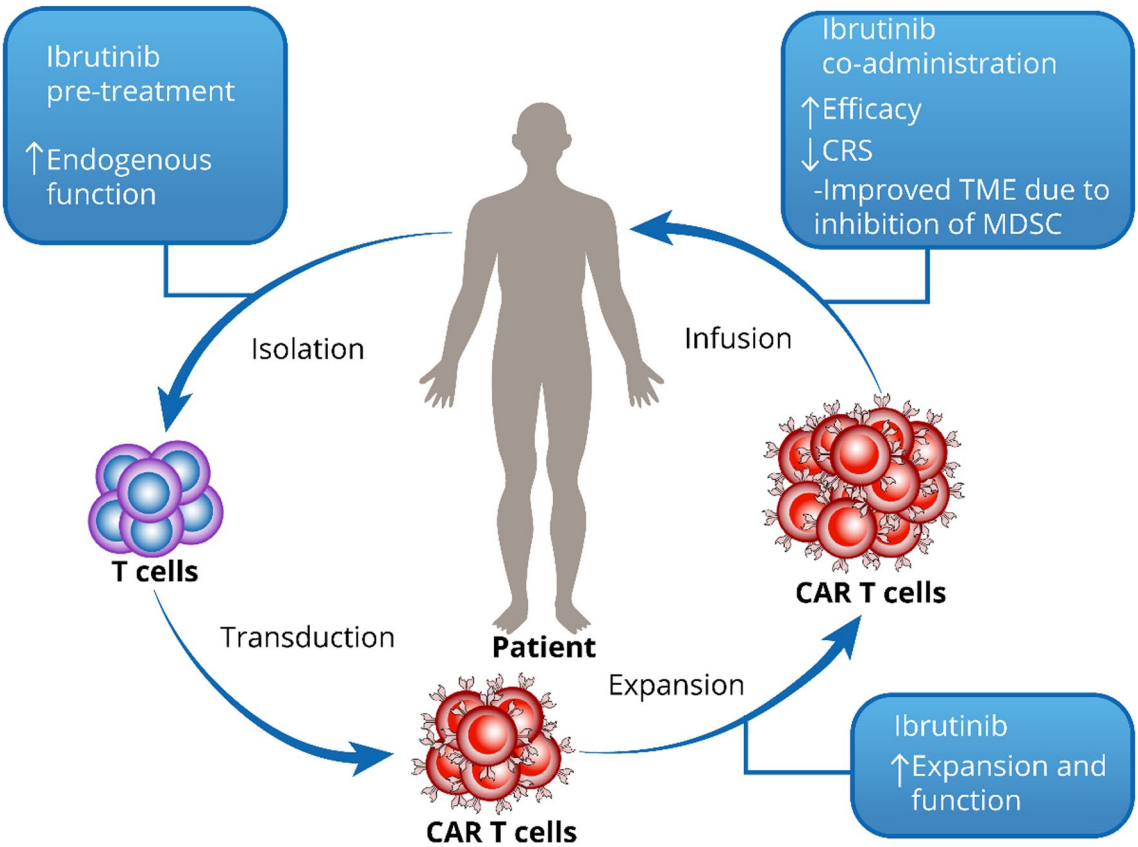

Fig. 3 Multifaceted action of ibrutinib in improving efficacy of CAR T cell therapy in B cell malignancies. Ibrutinib has potential beneficial effects at multiple stages of CAR T cell therapy. The CAR T cell process involves isolation and genetic modification (transduction) of T cells collected from the patient's blood, followed by ex vivo multiplication (expansion). The final cell product is then infused back into the patient. Ibrutinib may be administered prior to isolation, added during ex vivo CAR T cell production, or co-administered during and following the infusion. *CAR* chimeric antigen receptor, *CRS* cytokine release syndrome, *MDSC* myeloid-derived suppressor cells, *TME* tumor microenvironment

observational study showed that CAR T cell therapy is effective (CR rate, 21%) in patients with high-risk R/R CLL after treatment failure with ibrutinib [75]. Results of an observational study conducted in Chinese patients with BCMs showed that pretreatment with ibrutinib improved the outcomes in patients receiving repeated CAR T cell therapy [121]. As such, this study supports the use of ibrutinib as a pretreatment for patients with BCMs [121]. Additionally, in the ZUMA-2 study, patients with R/R MCL who previously received ibrutinib, as opposed to acalabrutinib, had numerically higher CR rates after CAR T cell therapy (prior ibrutinib CR rate, 67%; prior acalabrutinib CR rate, 50%) [83]. Importantly, patients in the prior ibrutinib cohort had a numerically higher 24-month PFS rate, higher peak CAR T cell levels, and peak immunomodulatory and proinflammatory cytokine levels compared with the prior acalabrutinib cohort, although interpretation of these results is limited due to the small number of patients [83]. Several studies have evaluated the impact of administering ibrutinib alongside CAR T cell therapy and found that this treatment sequencing can be beneficial. In a small preliminary study with two nonrandomized arms, patients with R/R DLBCL received either ibrutinib pretreatment or no ibrutinib prior to CAR T cell therapy; patients in both arms received ibrutinib starting at lymphodepletion for up to 24 months post-infusion [125]. The responses (ibrutinib pretreatment: CR in 2 of 4 patients, partial response in 2 of 4 patients; no ibrutinib pretreatment: CR in 2 of 6 patients, partial response in 1 of 6 patients) and tolerability were reported as favorable. Additionally, a nearly twofold increase in the number of viable CAR T cells in the final product after ibrutinib pretreatment versus no pretreatment suggests that ibrutinib plays a potentially beneficial role in CAR T cell manufacturing [125]. In another prospective study, patients with CLL received ibrutinib pretreatment followed by continued ibrutinib during CAR T cell therapy [10]. Patients with concurrent ibrutinib treatment had higher rates of CR (44%) and undetectable MRD (72% of patients) than patients from previous studies without concurrent ibrutinib treatment [10]. Remarkably, in the similarly designed phase 2 TARMAC study, which included patients with R/R MCL, a high CR rate (80%) and a high proportion of flow cytometry-measured undetectable MRD (70% of patients) were reported [126]. In a head-to-head study of CAR T cell therapy, with or without ibrutinib co-treatment in patients with R/R CLL [127], CAR T cell therapy with concurrent ibrutinib was associated with lower CRS severity and more robust CAR T cell expansion compared with CAR T cells alone. However, responses were similar between the two cohorts (ibrutinib CR rate, 72%; no ibrutinib CR rate, 67%) [127]. In a 6-year follow-up of this study, concurrent ibrutinib was associated with a higher median peak of CD4 CAR T cell expansion but had no impact on survival outcomes [128].

Taken together, these data show promise for ibrutinib-CAR T cell combination therapy, enhancing both the quality of the CAR T cell product and improving treatment outcomes in CLL and other BCMs.

7 Ibrutinib and Bispecific Antibodies

As previously discussed in this review, the beneficial effects of ibrutinib on the immunosuppressive tumor microenvironment and T cell function in CLL may improve the anticancer efficacy of BsAbs.

Preclinical studies have demonstrated synergistic effects when combining ibrutinib with BsAbs in CLL models. For example, in vitro ibrutinib co-administration improved killing of CLL cells by a BsAb [98]. Similarly, ibrutinib treatment enhanced the cytotoxic potential of receptor tyrosine kinase-like orphan receptor 1 (ROR1), a BsAb T cell engager in samples from patients with CLL [129]. Mechanistically and irrespective of ITK inhibition, ibrutinib downregulated immunosuppressive features of CLL cells, resulting in enhanced cytotoxicity of T cells [13]. In blood from patients with CLL, epcoritamab induced a higher degree of T cell activation, proliferation, and expression of cytotoxic effectors in T cells from patients receiving ibrutinib than from those who were previously untreated [12]. Moreover, in samples from patients treated with ibrutinib-rituximab in the E1912 trial, glofitamab was shown to revitalize T cell-mediated cytotoxicity in vitro [69].

Clinical trials investigating the combination of ibrutinib and BsAbs in BCMs are scarce; however, several studies are in early stages of enrollment: a phase 2 study of ibrutinib and blinatumomab in R/R B cell acute lymphoblastic leukemia (NCT02997761); a phase 1/2 study of glofitamab plus ibrutinib with obinutuzumab in MCL (NCT06357676); and a phase 1/2 study of epcoritamab in combination with antineoplastic agents, including ibrutinib, in DLBCL, FL, and MCL (NCT05283720).

8 Conclusions

In conclusion, the immunomodulatory effects of ibrutinib on T cell function are a testament to its therapeutic potential in BCMs. Through a coordinated interplay between BTK inhibition and ITK modulation, ibrutinib holds a promising role for restoring immune homeostasis, enhancing antitumor immune responses, and supporting T cell-based immunotherapies in CLL and related B cell disorders.

Table 1 Selected studies on combinatorial use of ibrutinib and CAR T cell therapies in B cell malignancies

Publication	Study	Disease state	Cohorts	CAR T cell therapy	Ibrutinib use	Outcomes	Safety/tolerability
Minson et al. [126]	NCT04234061, TARMAC: open-label, multicenter, single-arm, phase 2 study	R/R MCL	$N = 20$	Tisagenlecleucel (tisa-cel)	50% of patients had previous ibrutinib exposure; all patients were co-treated during CAR T cell therapy	CR rate, 80%; uMRD by flow cytometry, 70%; 12-mo PFS, 75%; 12-mo OS, 100%	CRS, $n = 15$; Grades 1 and 2 CRS, $n = 12$; Grade 3 CRS, $n = 3$; Grades 1 and 2 neurotoxicity, $n = 2$
Siddiqi et al. [79]	NCT03331198, TRANSCEND CLL 004: multicenter, open-label, single-arm, phase 1/2 study	R/R CLL	Heavily pretreated patients, $N = 117$	Lisocabtagene maraleucel (liso-cel)	All patients in the efficacy set previously received and had failure on a BTKi (ibrutinib or acalabrutinib)	*Responses and survival outcomes, n = 49:* CR rate,18% ($n = 9$); ORR, 43% ($n = 21$); uMRD rate in blood, 63% ($n = 31$); uMRD in BM, 59% ($n = 29$); median (IQR) DOR, 35.3 mo (11.0–NR); median (IQR) PFS, 11.9 mo (5.7–26.2); median (IQR) OS, 30.3 (11.2–NR)	*Safety cohort, n = 117:* Grade 3 CRS, $n = 10$; Grade 4 or 5 CRS, $n = 0$; Grade 3 neurotoxicity, $n = 21$; deaths due to CAR T cell therapy, $n = 1$
Liang et al. [128]	NCT01865617: open-label, nonrandomized, single-arm, phase 1/2 study	R/R CLL and Richter transformation	Did not receive concurrent ibrutinib, $n = 30$; received concurrent ibrutinib (started 2 weeks before leukapheresis), $n = 19$	JCAR014	96% of patients had previous intolerance and/or disease progression on ibrutinib	*Responses, n = 47:* ORR, 70% ($n = 33$); CR rate, 6% ($n = 3$); median (95% CI) DOR, 18.9 mo (9.66–55.6) *Survival outcomes, n = 49:* Median (95% CI) PFS, 8.9 mo (3.0–19.9); median (95% CI) OS, 25.0 mo (11.5–62.1)	Deaths on the study, $n = 4$ (non-CAR T cell therapy related)

Table 1 (continued)

Publication	Study	Disease state	Cohorts	CAR T cell therapy	Ibrutinib use	Outcomes	Safety/tolerability
Wang et al. [83]	NCT02601313, ZUMA-2: open-label, multicenter, single-arm, phase 2 study	R/R MCL	Heavily pretreated patients, $N = 68$	Brexucabtagene autoleucel (KTE-X19)	76% of patients ($n = 52$) were previously treated with ibrutinib	*Responses and survival outcomes in all patients, n = 68:* ORR, 91% ($n = 62$); CR rate, 68% ($n = 46$); median (95% CI) DOR, 28.2 mo (13.5–47.1); median (95% CI) PFS, 25.8 mo (9.6–47.6); median (95% CI) OS, 46.6 mo (24.9–NE) *Responses and outcomes in patients with prior ibrutinib, n = 52:* ORR, 92% ($n = 48$); CR rate, 67% ($n = 35$); median (95% CI) DOR, 28.2 mo (10.4–46.7); median (95% CI) PFS, 25.8 mo (9.6–47.6); median (95% CI) OS, 46.4 mo (22.9–NE)	No new CRS events or treatment-related deaths occurred since primary analyses [138]
Gill et al. [10]	Prospective, single-center, phase 2 study	CLL (R/R or receiving first-line ibrutinib)	$N = 19$	Humanized anti-CD19 binding domain T cells	All patients received ibrutinib for ≥ 6 mo, prior to CAR T cell therapy and continued during and after CAR T cell therapy	*Responses:* CR rate at 3 mo, 44% ($n/N = 7/16$); uMRD at 12 mo, 72%; ($n/N = 13/18$) *Survival outcomes:* Median PFS and OS were NR at a median (range) follow-up of 42 mo (17–58)	*Safety cohort, n = 19:* CRS, $n = 18$; neurotoxicity, $n = 5$; treatment-related deaths, $n = 2$

Table 1 (continued)

Publication	Study	Disease state	Cohorts	CAR T cell therapy	Ibrutinib use	Outcomes	Safety/tolerability
Liu et al. [121]	Observational case series	R/R MCL, R/R FL	Heavily pretreated patients, $N = 7$ (R/R MCL, $n = 3$; R/R FL, $n = 4$)	Anti-CD19 CAR T cell (ChiCTR-ONN-16009862)	Ibrutinib salvage therapy after first CAR T cell therapy until disease progression	*Responses after first CAR T cell therapy, n = 7:* CR rate, 0% *Responses after second CAR T cell therapy, n = 7:* CR rate, 86% ($n = 6$)	*Safety cohort, n = 7:* CRS after first CAR T cell therapy, $n = 7$ (all grade 0–2); CRS after second CAR T cell therapy, $n = 7$ (all grade 2–4)
Wang et al. [138]	NCT02601313, ZUMA-2: open-label, multicenter, single-arm, phase 2 study	R/R MCL	Heavily pretreated patients, $N = 68$	Brexucabtagene autoleucel (KTE-X19)	76% of patients ($n = 52$) were previously treated with ibrutinib; 14 patients received bridging therapy with ibrutinib	*Responses and survival outcomes, n = 60:* ORR, 93% (95% CI 84–87); CR rate, 67% (95% CI 53–78); 12-mo PFS, 61%; 12-mo OS, 83%	*Safety cohort, n = 68:* CRS, 91%; grade ≥ 3 CRS, 15%; neurotoxicity, 63%; grade ≥3 neurotoxicity, 31%; serious AEs, 68%; deaths due to CAR T cell therapy, $n = 1$
Gauthier et al. [127]	NCT01865617: open-label, nonrandomized, single-arm, phase 1/2 study	R/R CLL and Richter transformation	Received no concurrent ibrutinib, $n = 30$; received concurrent ibrutinib (started 2 weeks before leukapheresis), $n = 19$	JCAR014	96% of patients had intolerance and/or disease progression on ibrutinib	*Responses in concurrent ibrutinib cohort, n = 18:* ORR, 83% ($n = 15$); uMRD by flow cytometry in BM, 72% ($n = 13$) *Survival outcomes in concurrent ibrutinib cohort, n = 18:* 1-year PFS, 38%; 1-year OS, 64% *Responses in no ibrutinib cohort, n = 18:* ORR, 56% ($n = 10$); uMRD by flow cytometry in BM, 67% ($n = 12$) *Survival outcomes in no ibrutinib cohort, n = 18* 1-year PFS, 50%; 1-year OS, 61%	*Safety in concurrent ibrutinib cohort, n = 19:* grade ≥ 3 CRS, $n = 0$; grade ≥ 3 neurotoxicity, $n = 5$; deaths due to CAR T cell therapy, $n = 0$ *Safety in no ibrutinib cohort, n = 19:* grade ≥ 3 CRS, $n = 2$; grade ≥ 3 neurotoxicity, $n = 7$; deaths due to CAR T cell therapy, $n = 1$

Table 1 (continued)

Publication	Study	Disease state	Cohorts	CAR T cell therapy	Ibrutinib use	Outcomes	Safety/tolerability
Wierda et al. [124]	NCT03331198, TRANSCEND CLL 004: multicenter, open-label, single-arm, phase 1/2 study	R/R CLL	Heavily pretreated patients, $N = 19$	Lisocabtagene maraleucel (liso-cel)	All patients previously received ibrutinib and continued ibrutinib during and after CAR T cell administration	*Responses, n = 19:* ORR, 95% ($n = 18$); CR/CRi, 47% ($n = 9$); uMRD in BM by flow cytometry, 89% ($n = 17$)	CRS, $n = 14$ ($n = 1$ grade 3); neurotoxicity, $n = 6$ ($n = 3$ grade ≥ 3)
Chavez et al. [125]	Multicenter, open-label, phase 1b study	R/R DLBCL	Ibrutinib pretreatment cohort, $n = 4$; no ibrutinib pretreatment cohort, $n = 6$	Tisagenlecleucel (tisa-cel)	All patients received ibrutinib during and following lymphodepletion, CAR T cell infusion, and post-infusion for 24 mo	*Responses in ibrutinib pretreatment cohort, n = 4:* CR, $n = 2$ *Responses in no ibrutinib pretreatment cohort, n = 6:* CR, $n = 2$	*Safety in ibrutinib pretreatment cohort, n = 4:* CRS, $n = 1$; neurotoxicity, $n = 0$ *Safety in no ibrutinib pretreatment cohort, n = 6:* CRS, $n = 5$; neurotoxicity, $n = 1$
Turtle et al. [75]	Open-label, phase 1/2 study	R/R CLL	Heavily pretreated patients, $N = 24$	CD19 CAR T cells	All patients previously received ibrutinib	*Responses and outcomes:* ORR, 74% ($n/N = 14/19$); CR rate, 21% ($n/N = 4/19$); uMRD in BM by flow cytometry, 88% ($n/N = 15/17$); median follow-up, 6.6 mo; median PFS, 8.5 mo; median OS, NR	*Safety cohort, n = 24:* CRS, $n = 20$; grade ≥ 3 CRS, $n = 2$; neurotoxicity, $n = 8$; grade ≥ 3 neurotoxicity, $n = 6$

AE adverse event, *BM* bone marrow, *BTKi* Bruton tyrosine kinase inhibitor, *CAR* chimeric antigen receptor, *CD* cluster of differentiation, *CI* confidence interval, *CLL* chronic lymphocytic leukemia, *CR* complete response, *CRi* complete response with incomplete hematologic recovery, *CRS* cytotoxic release syndrome, *DLBCL* diffuse large B cell lymphoma, *DOR* duration of response, *FL* follicular lymphoma, *IQR* interquartile range, *MCL* mantle cell lymphoma, *mo* months, *NE* not evaluable, *NR* not reached, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *R/R* relapsed/refractory, *uMRD* undetectable minimal residual disease

Combination approaches incorporating ibrutinib with CAR T cell therapy have shown enhanced efficacy and potentiation of antitumor immune responses, with no detrimental effects regarding safety. Similarly, the combination of ibrutinib with BsAbs is a promising therapeutic strategy for BCMs, leveraging the synergistic effects of targeted therapy and immunomodulation.

Subsequent T cell-based therapy may potentially be enhanced by tumor debulking via ibrutinib pretreatment [130]. Prior to starting ibrutinib-venetoclax combination therapy, three cycles of ibrutinib lead-in led to effective tumor debulking and decreased the risk of the tumor lysis syndrome associated with the ibrutinib-venetoclax regimen in first-line treatment of CLL/SLL [130]. While this has not yet been directly studied in combination with T cell-based therapy, tumor debulking in the context of CAR T cell therapy may improve short- and long-term responses and efficacy [131].

Of note, preclinical investigation of ibrutinib in combination with an anti–PD-1 immune checkpoint inhibitor, whose mode of action is partially T cell-mediated, showed synergistic antitumor effects [132]. The combination has also been preliminarily tested in phase 1 and 2 human trials for R/R DLBCL, CLL, FL, MCL, and Richter transformation (NCT02329847, NCT02420912, NCT03153202), yielding promising clinical responses and manageable safety profiles [133–135].

Currently, the enhancement of T_h1 immunity and the regulation of T_h17 and T_{reg} cell differentiation are understood to be dependent on ITK inhibition. The distinctive ability of ibrutinib to inhibit ITK within the T cell compartment sets it apart from other currently available BTKis and may be responsible for its broad immunomodulatory effects.

Challenges remain in the integration of ibrutinib with T-cell–based therapies, such as dosing regimen optimization, timing, overlapping toxicity mitigation, predictive response biomarker identification, and regulatory pathway. Moreover, the emergence of resistance mechanisms, such as immunosuppressive tumor microenvironment, antigen loss or T cell exhaustion, underscore the need for combinatorial approaches to overcome treatment resistance and prolong remission duration.

Although ibrutinib treatment carries some tolerability and safety risks typical of the BTKi drug class, there is a lack of evidence that combinatorial use with CAR T cells or BsAbs leads to exacerbation of any potential adverse events. Additionally, current clinical and real-world evidence studies demonstrate that most ibrutinib-related adverse events can be mitigated with dose modifications [136, 137]. However, to directly address the safety and efficacy concerns and establish the risk–benefit profiles for various combinations of ibrutinib and T cell-based therapies, properly controlled, multi-arm clinical trials should be designed and performed in the future.

Ibrutinib is the first-in-class BTKi approved for the treatment of various BCMs, and thus has the most expansive body of data available regarding combinatorial use of ibrutinib and T cell-mediated therapies versus other BTKis. Moreover, the unique ability of ibrutinib to inhibit IL-2-ITK in addition to BTK drove the specific focus of this review [57]. However, the landscape is rapidly expanding, and several trials of combinations of acalabrutinib, zanubrutinib, orelabrutinib, and pirtobrutinib with T cell-mediated therapies are presently being conducted (NCT04484012, NCT04257578, NCT06553872, NCT05873712, NCT06054776, NCT04186520, NCT05020392, ACTRN12621000507886).

Continued research efforts aimed at elucidating the underlying mechanisms, optimizing treatment protocols, and identifying the patient subsets most likely to benefit will be instrumental in realizing the full clinical potential of this combination therapy. The promising results of small clinical trials cited herein warrant well-powered randomized trials to determine efficacy and safety of ibrutinib administration before apheresis and CAR T cell manufacturing, followed by continued treatment with ibrutinib after CAR T cell infusion in disease-specific cohorts. Correlative studies determining T cell kinase occupancy with pharmacokinetic, single-cell RNA sequencing, MRD, and toxicity data may help elucidate molecular differences in response to BTKis plus CAR T cell therapy and further benefit patients undergoing CAR T cell therapy.

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