



## New actionable targets and investigational drugs in chronic lymphocytic leukemia

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**Summary** The treatment landscape of chronic lymphocytic leukemia (CLL) has shifted from chemotherapy-based approaches to targeted agents in the last decade. However, evolving drug resistance and accumulating toxicity remain challenges that still limit patients' clinical outcomes. Furthermore, currently licensed targeted agents such as inhibitors of Bruton's tyrosine kinase (BTK) and anti-apoptotic protein B-cell lymphoma 2 (BCL2) do not adequately compensate for the poor clinical outcomes associated with high-risk genetics such as TP53 alterations. New insights into disease biology facilitated design and investigation of several new targeted agents with encouraging results in early clinical trials. This short review focuses on novel actionable targets and investigational drugs aimed at circumventing acquired resistance and avoiding accumulating toxicity.

**Keywords** Pirtobrutinib · Umbralisib · Tafasitamab · CAR-T cell immunotherapy · Lisocabtagene maraleucel

### Introduction

The treatment landscape of chronic lymphocytic leukemia (CLL) has undergone profound change in the last decade. From chemotherapy-based regimens accomplishing first overall survival benefits in first-line therapy [1], treatment-associated toxicity and inferior clinical outcomes in patients with high-risk disease biology necessitated alternative treatment approaches with targeted agents. Superior in terms of efficacy and tolerability, inhibitors of Bruton's tyrosine

kinase (BTK) and anti-apoptotic protein B-cell lymphoma 2 (BCL2) entered the arena of CLL therapy in record time and strongly shifted chemoimmunotherapy into the background of commonly accepted treatment algorithms [2–5]. However, acquired resistance and drug-associated toxicity remain a persisting issue with currently licensed CLL therapeutics rendering most patients to several lines of treatment throughout the course of the disease [6, 7]. In particular, high-risk genetics such as unmutated immunoglobulin heavy chain variant region (IGHV) status, TP53 alterations and a complex karyotype continue to pose therapeutic challenges and are associated with a more aggressive course of disease and poor clinical outcomes [3, 4]. New insights into disease biology initiated the investigation of several new potential therapeutic targets with promising results in early clinical trials. This review focuses on novel investigational drugs aimed at circumventing emerging drug-resistance and avoiding accumulating toxicity.

### Reversible Bruton's tyrosine kinase inhibitors

BTK inhibition has proceeded to become an integral part of CLL treatment [8]. Positioned directly downstream of the constitutively activated B-cell receptor in CLL cells, inhibition of BTK hampers multiple cellular processes, including cell proliferation and migration. As such, the malignant cells are deprived from the nourishing stimuli of their local microenvironment and more easily succumb to apoptosis [9]. Nevertheless, minimal residual disease (MRD) frequently persists with monotherapy requiring continuous treatment to allow long-term disease control [10]. Accordingly, acquired resistance commonly evolves and frequently involves gene mutations altering the binding site Cys481 of currently licensed irreversible BTK inhibitors such as ibrutinib and acalabrutinib [11,

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12]. At ASCO 2021, early results of ELEVATE-RR [13], a randomized phase 3 study comparing acalabrutinib ( $n=268$ ) head-to-head with ibrutinib ( $n=265$ ) in relapsed CLL patients harboring either a deletion of 17p or 11q, were presented, meeting its primary endpoint of non-inferiority progression-free survival (PFS, 38.4 months, hazard ratio 1.00) with a median follow-up of 41 months and demonstrating a favorable toxicity profile of acalabrutinib in terms of atrial fibrillation (9% vs. 15.6%), low-grade bleeding events (38% vs. 51.3%) and hypertension (9.4% vs. 23.2%) [13]. Zanubrutinib, another irreversible BTK inhibitor still under investigation in CLL, has also been compared with ibrutinib in the randomized phase 3 trial ALPINE in 415 relapsed CLL patients. With a median follow-up of only 14 months, very early data indicate a PFS benefit with zanubrutinib at 1 year (94.9% vs. 84.0%,  $p=0.0007$ ) and reduced incidence of any grade atrial fibrillation (2.5% vs. 10.1%) [14].

To overcome acquired resistance, reversible BTK inhibitors have been designed to inhibit BTK by non-covalent binding. Following encouraging *in vitro* results demonstrating effective blockade of BTK signaling in ibrutinib-resistant BTK C481S mutants, several compounds have entered early clinical investigation [15–17]. Pirtobrutinib (LOXO-305) is currently among the most promising and highly selective compounds of these non-covalent binding next generation BTK inhibitors [18]. In an ongoing phase 1/2 trial in 323 patients with relapsed/refractory B cell malignancies no dose-limiting toxicity was observed leading to the phase 2 dose of 200 mg daily. The most common adverse events (AE) were fatigue (20%), diarrhea (17%), and contusion (13%). Notably, grade 3/4 atrial fibrillation was not seen. All 170 CLL patients included were previously treated with an irreversible BTK inhibitor and received a median of four preceding lines of treatment. Overall response rate (ORR) was 62% and similar between CLL patients intolerant or resistant to previous covalent BTK inhibition (52% versus 67%) [18].

Taken together, these early data suggest that pirtobrutinib is active and well-tolerated in multiple pretreated CLL patients, including those resistant or intolerant to irreversible BTK inhibitors. Upcoming randomized controlled clinical trials, however, are eagerly awaited to better define the role of this new class of drugs in the treatment landscape of CLL (NCT04666038, NCT04965493).

### Next-generation PI3K inhibitors

Besides chronic activation of BTK, aberrant B-cell receptor stimulation in CLL leads to constitutive PI3K signaling essential for B-cell proliferation and survival [19].

In 2014, the first-in-class inhibitor of the PI3K subunit delta idelalisib was approved for relapsed, refractory CLL patients by the US Food and Drug Admin-

istration (FDA) and the European Medicines Agency (EMA) [20]. However, accumulating immunogenic AE including hepatotoxicity, colitis, and pneumonitis as well as infectious complications, such as pneumocystis jirovecii pneumonia and cytomegalovirus reactivation, resulted in a black box warning and premature discontinuation of multiple ongoing clinical trials [21]. Hence, idelalisib is often reserved for patients resistant or intolerant to inhibitors of BTK and BCL2, but remains an effective treatment option in relapsed/refractory CLL.

Umbralisib is a structurally distinct next-generation PI3K inhibitor with a greater selectivity for the delta subunit. Contrary to idelalisib, umbralisib has not been associated with immunogenic AE. Most common AE were low-grade and included diarrhea (43%), nausea (42%), and fatigue (31%) when used as monotherapy [22]. At ASH 2020, first results from a phase 3 study were presented comparing umbralisib combined with the novel anti-CD20 antibody ublituximab versus chlorambucil and obinutuzumab in 421 CLL patients (untreated  $n=240$ , relapsed/refractory  $n=181$ ) [23]. ORR was significantly higher in the experimental study arm (83.3% vs. 68.7%,  $p<0.001$ ), while the benefit was mainly derived from the previously treated study population (82% vs. 57% ORR), in particular those patients failing previous BTK inhibitor treatment (57% vs. 25% ORR). At a median follow-up of 36.2 months, progression-free survival (PFS) was significantly prolonged with umbralisib and ublituximab versus chemoimmunotherapy, an effect that was consistent in both treatment-naïve and relapsed/refractory CLL patients (38.5 vs. 26.1 months and 19.5 vs. 12.9 months, respectively). Data on MRD monitoring remain to be published. Grade 3/4 AE of interest in both cohorts included neutropenia (30.6% vs. 34.7%), diarrhea (12.1 vs. 2.5%), transaminitis (8.3% vs. 2%), colitis (3.4% vs. 0%) and pneumonitis (2.9% vs. 0%) [23].

Reviewing the feasible toxicity profile and significantly prolonged PFS versus chemoimmunotherapy suggests umbralisib plus ublituximab as a valuable addition to the CLL treatment landscape.

### Anti-CD19 monoclonal antibodies

Tafasitamab is an anti-CD19 monoclonal antibody with encouraging efficacy (ORR 67% according to clinical criteria) and adequate tolerability in a phase I trial with 27 multiple relapsed CLL patients. Most frequent AEs were low-grade infusion-related reactions (IRR) [24]. In 2019, the first results of combination treatment with either the PI3K inhibitor idelalisib ( $n=11$ ) or venetoclax ( $n=11$ ) were reported in CLL patients failing prior BTK therapy. In combination with idelalisib, ORR was 90.9% (CR=9.1%, PR 81.8%), while one out of eight patients assessed for MRD achieved MRD negativity in the bone marrow. Most common AE comprised usually low-grade myelotox-

icity, foremost anemia (55%), IRR, and pyrexia (46% each). Serious AE were reported in 8 patients, including, pulmonary infection (5 patients).

In combination with venetoclax, ORR was 76.9% (CR=23.1%, PR 53.8%), while response was not evaluable in 23.1% of cases. Six out of 7 patients assessed for MRD in the peripheral blood were negative within 7 cycles. Most common AE included myelotoxicity, foremost high-grade neutropenia, and low-grade IRR. Serious AE were reported in 9 patients, including pyrexia ( $n=3$ ) and IRR ( $n=2$ ) [25].

Combination treatment with tafasitamab and lenalidomide was investigated in another phase 2 study in 25 CLL patients (untreated  $n=12$ , relapsed/refractory  $n=13$ ) [26].

Combination treatment yielded an ORR of 67% (1 CR, 7 PR) and 15% (PR only) in treatment-naïve and relapsed/refractory CLL patients, respectively. Grade 3–4AE included pulmonary infections ( $n=4$ ), neutropenia ( $n=3$ ), and IRR ( $n=2$ ) in untreated patients and primarily infections ( $n=7$ ) in relapsed/refractory patients [26]. These early results suggest adequate tolerability and encouraging efficacy of tafasitamab in combination with other targeted agents and warrant further investigation in larger randomized clinical trials.

### CAR-T cell immunotherapy

Chimeric antigen receptor-engineered (CAR)-T cell therapy has emerged as the most complex immunotherapeutic approach in recent years, primarily directed against CD19+ B-cell malignancies [27]. CARs are genetically engineered synthetic constructs transfected into immunocompetent T cells of the patients to recognize a specific antigen on the surface of tumor cells [27]. Several clinical trials have demonstrated efficacy of CD19-directed CART-cell therapy leading to FDA and EMA approval in certain B-cell lymphomas [28, 29]. Early studies in CLL suggested only minor efficacy compared to B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma with low CR rates (20–30%) and limited PFS of 25% at 18 months [30–32], which has been attributed to the disease characteristic exhausted phenotype of CD4+ and CD8+ T cells with low proliferative and cytotoxic capacities [33]. However, preconditioning lymphodepletion with fludarabine and cyclophosphamide as well as pre- and concomitant treatment with ibrutinib may significantly enhance clinical outcomes [32, 34]. Recently, the phase I study TRANSCEND CLL 004 was updated investigating lisocabtagene maraleucel (liso-cel) either alone ( $n=23$ ) or in combination with ibrutinib ( $n=19$ ) in heavily pretreated CLL relapsed/refractory patients [35, 36]. Most patients were defined high-risk with a median of five pretreatments, including ibrutinib in all patients. In the monotherapy cohort, ORR was 82% (CR with or without incomplete count recovery (CRi) 46%; PR 36%) with a median PFS of

18 months. Notably, 75% (15/20) of patients achieved MRD negativity, mostly within 30 days of therapy (60%). Common grade 3/4AE included myelotoxicity, foremost anemia (74%). Cytokine release syndromes were usually low-grade, observed in 74% of patients and generally manageable with corticosteroids and tocilizumab [35]. Of 19 patients beyond 1 month of follow-up in the combination treatment cohort, ORR and CR/CRi were 95% and 47%, respectively. 89% of patients achieved MRD negativity in the peripheral blood as measured by flow cytometry. Common grade 3/4AE included myelotoxicity, foremost neutropenia (89%). Cytokine release syndromes were usually low-grade, observed in 74% of patients and generally manageable with corticosteroids and tocilizumab [36].

In summary, these early results suggest adequate tolerability and favorable efficacy of liso-cel in combination with ibrutinib in highly pretreated CLL patients. Longer follow-up of the monotherapy cohort suggests sustained deep responses at 24 months and no delayed safety signals.

With rapidly growing efficacy data and clinical experience in managing the associated toxicity profile, CAR-T cell therapy may emerge as an increasingly important treatment option for CLL patients with high-risk disease and relapsed/refractory to prior therapy with BTK- and BCL2-inhibitors.

### Conclusion

In recent years, targeted therapies have revolutionized CLL (chronic lymphocytic leukemia) treatment. Foremost, inhibitors of BTK (Bruton's tyrosine kinase) and BCL2 (anti-apoptotic protein B-cell lymphoma 2) such as ibrutinib and venetoclax with or without the addition of an anti-CD20 antibody have become frontline treatment of choice regardless of patient age, comorbidity and most genetic risk factors. However, neither inhibitors of BTK nor BCL2 may overcome the inferior prognosis associated with high-risk genetics such as TP53 dysfunction and unmutated IGHV (immunoglobulin heavy chain variant region) status.

Early clinical trials currently focus on next-generation agents of established drug targets or new actionable targets with encouraging efficacy and safety. Longer follow-up and randomized clinical trials provided, some of these new compounds may indeed serve as a valuable addition to the therapeutic armamentarium in CLL. However, for now CLL remains an incurable disease and the most effective CLL treatment in the clinical and experimental setting may comprise combined therapy rather than monotherapy. Besides looking for effective and well-tolerated novel agents directed against new actionable targets, studies are therefore also warranted to analyze the best combinations and sequences of available drugs to further improve clinical outcomes in a chronic B-cell malignancy commonly requiring multiple retreatments during the course of the disease.

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