Improve the dismal outcomes reported following failure of a Bruton tyrosine kinase inhibitor (BTKi) represents a key challenge for providers caring for patients with mantle cell lymphoma (MCL; Jain et al., 2021; Martin et al., 2016; Rai et al., 2021). Partnering a BTKi alongside venetoclax (Venclexta), lenalidomide (Revlimid), bortezomib (Velcade), and/or an anti-CD20 monoclonal antibody, which have their own known activity in MCL, is a promising strategy (Davids et al., 2017, 2018; Eyre et al., 2018; Goy et al., 2009, 2013, 2015; Le Gouill et al., 2021; Tam et al., 2018, 2020; Trnený et al., 2016; Wang et al., 2012, 2016, 2021a; Witzig et al., 2017; Zinzani et al., 2013). Combination therapy is especially interesting where synergistic activity may exist, which is often listed as the rationale to combine ibrutinib (Imbruvica) with venetoclax (Handunnetti et al., 2019; Jerkeman et al., 2018; Killock, 2018; Le Gouill et al., 2021; Portell et al., 2014; Tam et al., 2020; Wang et al., 2021a). Despite this work to increase the value of the BTKi in relapsed/refractory MCL, the competing interest to incorporate these game-changing agents into front-line therapy could leave providers with fewer options for relapsing patients (ClinicalTrials.gov, 2017, 2021a, b, c). Intriguing new BTKi agents aim to further the responses that are seen by exploiting the B-cell receptor pathway while attempting to address the issue of resistance and continue to improve upon the tolerability of these agents. In addition to the quest for a better BTKi, exploration of new targets is gaining traction in the MCL space.

Key Points

- Outcomes are very poor for patients who progress on BTK inhibitors, leading to the search for alternative options such as BTKi-based combination therapy and other novel agents.
- As APs caring for MCL patients may be the first ones to identify signs of relapse, it is important to be aware of options under investigation.

Both primary and acquired resistance mechanisms have been described with ibrutinib. The most widely discussed include the C481S point mutation in the BTK binding pocket and gain-of-function mutations in PLCG2, but these have been rarely seen in patients with MCL (George et al., 2020). While the underlying causes of ibrutinib
failure in MCL are yet to be fully understood, little benefit is expected by using a second-generation BTKi, acalabrutinib (Calquence) or zanubrutinib (Brukinsa), in cases where patients either fail to respond or progress on ibrutinib. All of these agents inhibit BTK through covalent and irreversible binding; this is thought to result in an incomplete target inhibition at the end of the dosing interval and thereby make patients vulnerable to emerging resistance (Wang et al., 2021b).

**BTK INHIBITORS**

Pirtobrutinib (formerly LOXO-305) is an oral, non-covalent, reversible BTKi with activity in patients with wild-type as well as mutated BTK (Mato et al., 2021; Wang et al., 2021b). The phase I/II BRUIN study included a heavily pretreated population of relapsed/refractory MCL patients, 52 of whom had prior BTKi exposure and were eligible for efficacy assessment (Wang et al., 2021b). An overall response rate (ORR) of 52% was seen in these BTKi-exposed patients. No maximum tolerated dose was determined leading investigators to select 200 mg daily as the optimal dose to move forward in future research based on the efficacy and tolerability data. Adding to the attractiveness of this third-generation BTKi are early signals that pirtobrutinib is associated with low rates and limited severity of many of the problematic BTKi adverse effects, including atrial fibrillation, bleeding, bruising, hypertension, and arthralgias.

**ROR-1 INHIBITORS**

Receptor tyrosine kinase-like orphan receptor 1 (ROR-1) is a transmembrane receptor with a role in embryonic development that, in adults, is expressed exclusively on malignant cells thus reducing the likelihood of toxicity to normal tissues (Chu et al., 2021; Jiang et al., 2021). The antibody-drug conjugate VLS-101 targets ROR-1 and carries a payload of the microtubule inhibitor monomethyl auristatin E (MMAE), building upon work demonstrating specificity and clinical activity of the naked ROR-1 targeted monoclonal antibody cirmtuzumab (Jiang et al., 2020; Lee et al., 2020). In preclinical models, VLS-101 has activity in BTKi, venetoclax, and even CD19 chimeric antigen receptor (CAR) T-cell–resistant MCL (Jiang et al., 2020). Data from the phase I first-in-human study of this agent was presented at the 2020 American Society of Hematology annual meeting showing this to be a well-tolerated and clinically active agent in heavily pretreated patients with MCL (Wang, 2020). Taking into account the clinical activity and predictable adverse effect profile, researchers will continue to evaluate VLS-101 at a dose of 2.5 mg/kg administered intravenously via 30-minute infusion every 3 weeks until progression or unacceptable toxicity. In 15 MCL patients, all of whom previously received a BTKi and discontinued due to progression (87%) or atrial fibrillation (13%), an impressive ORR of 47% and 20% complete response rate were reported from this dose-finding study.

**EXPLOITING THE IMMUNE SYSTEM**

Bispecific antibodies are a branch of immuno-oncology that have piqued the interest of researchers for various lymphoid malignancies. Redirecting T cells to tumor cell surface markers, in this case CD20, harnesses a cytotoxicity mechanism that can produce results in patients even after failure of traditional monoclonal antibodies targeting this prominent feature of B-cell malignancies (van der Horst et al., 2021).

A phase I study of the subcutaneously administered CD20xCD3 bispecific antibody epocitamab found a 50% ORR in the 4 evaluable patients with MCL (Hutchings et al., 2021). Given the limited data, especially in MCL, further study will be required to better understand the potential place in therapy for this agent. On the other hand, brexucabtagene autoleucel is a CAR T-cell therapy that also works through manipulation of the immune system and is already commercially available for MCL (Wang et al., 2020). However, results from the MCL cohort of TRANSCEND-001, evaluating another CAR T-cell product, lisocabtagene maraleucel, have been presented illustrating impressive response rates and low rates of cytokine release syndrome (CRS) and neurotoxicity (Palomba et al., 2020). Building a better CAR T-cell product or advancing bispecific antibodies will rely on the ability for safe administration by reducing the potential for cytokine release syndrome and neurotoxicity in concert with durable clinical efficacy.
The Advanced Practitioner Perspective

Advanced practitioners who manage MCL patients may be the first members of the care team to identify signs concerning for relapse, especially for patients on long-term oral BTKi. Therefore, it is important to be aware of the innovative treatment options coming down the pipeline and understand their potential places in therapy. Sharing the potential benefits and risks along with understanding patient preferences can help in determining the best treatment options, especially in a field where the portfolio of therapies contains both oral and intravenous agents. Other considerations such as tolerability to prior therapies, access, cost, and duration of treatment are key factors to weigh in selecting a best fit for patients with relapsed or refractory MCL.

Disclosure

Dr. Valla has served on the speakers bureau for BeiGene.

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