CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

The Development of BTK Degraders for Patients With Relapsed CLL

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H&O What are Bruton tyrosine kinase (BTK) degraders, and how do they differ from BTK inhibitors?

AD BTK degraders are from a new class of molecules, called proteolysis-targeted chimeras (PROTACS). Instead of blocking BTK function the way BTK inhibitors do, BTK degraders eliminate the entire BTK molecule. They promote degradation of the BTK molecule by binding both the BTK protein and the E3 ligase cereblon (CRBN). Many oncologists are familiar with CRBN because it is a target that is modulated by lenalidomide, which has been used for decades in myeloma and lymphoma.

A single BTK degrader molecule can attack multiple molecules of the BTK. After the degrader processes one molecule, it returns into the circulation and attacks the next one, and so on. As a result, relatively low concentrations of the drug are sufficient to achieve effective BTK degradation.

H&O What needs are BTK inhibitors designed to address?

AD BTK inhibition is effective in lymphoid malignancies, but drug resistance is inevitable over time. This resistance is mediated in part by mutations that arise in *BTK* and prevent the binding of BTK inhibitors. For example, the C481S mutation in *BTK* has been shown to lead to resistance to the first-generation BTK inhibitor ibrutinib (Imbruvica, Pharmacyclics/Janssen). Similar mutations have been discovered that explain resistance to second-generation BTK inhibitors, such as acalabrutinib (Calquence, AstraZeneca) and zanubrutinib (Brukinsa, BeiGene). Now that we have noncovalent BTK inhibitors, such as pirtobrutinib (Jaypirca, Lilly), we have discovered additional BTK mutations that lead to resistance to those drugs.

> I personally have followed patients who have received BTK degraders for close to 3 years without any evidence of disease progression.

What is exciting about BTK degraders is that they can overcome these resistance mutations. Preclinical studies, both in vitro and in vivo, have shown that BTK degraders are able to destroy BTK, regardless of the *BTK* mutations that are present. This finding has been supported by clinical trials showing that patients who become resistant to ibrutinib and other drugs are able to respond to BTK degraders.

H&O What BTK degraders are being developed?

AD The BTK degraders farthest along in development are NX-2127 and NX-5948, which are both from Nurix, and

BGB-16673, which is from BeiGene. All 3 of those agents have clinical data available. Phase 1 trials are recruiting patients for studies of NX-2127 (NCT04830137) and NX-5948 (NCT05131022) in advanced B-cell malignancies, and the phase 1/2 CaDAnCe-101 trial that is looking at the use of BGB-16673 in B-cell malignancies is also recruiting patients (NCT05006716). In addition, ABBV-101 from AbbVie has very strong preclinical data, and a phase 1 clinical trial is currently recruiting patients (NCT05753501).

H&O Could you describe the research that has been done with these agents?

AD Preclinical research has demonstrated that cell lines that have been manipulated to express mutant *BTK* and are resistant to ibrutinib exhibit sensitivity to BTK degraders, both in vitro and in vivo. Now we have phase 1 clinical trial results with several of these BTK degrader molecules, and they do show very impressive efficacy in heavily pretreated patients with B-cell malignancies, especially chronic lymphocytic leukemia (CLL). Response rates with these agents are on the order of 80% to 90%, which is quite impressive for patients who received 4 or 5 prior therapies, including BTK inhibitors and venetoclax (Venclexta, AbbVie/Genentech). Some of the patients also received pirtobrutinib, meaning that they were essentially resistant to all the targeted therapies that we have today. The high response rates are especially impressive when combined with the durability of the responses. Patients remain on these agents for many years, and I personally have followed patients who have received them for close to 3 years without any evidence of disease progression.

> The exciting thing about PROTACs is that they provide the opportunity to target any protein of interest, including oncoproteins, which traditionally have been difficult to target.

What we rarely see with BTK degraders is complete responses; we are far more likely to see deep partial responses. This is consistent with our experience with BTK inhibitors. Over time, however, the responses might deepen to the point of becoming complete responses. Longer follow-up of the studies will be needed to determine if that will happen.

In the first phase 1 clinical trial of BTK degraders to be published, NX-2127 was shown to degrade BTK by more than 80% and clinical responses were seen in 79% of evaluable patients, regardless of the mutant *BTK* genotype.[1]

In the phase 1 CaDAnCe-101 study, which was presented at the 2024 American Society of Hematology (ASH) Annual Meeting, the overall response rate (ORR) among 49 response-evaluable patients who had CLL treated with BGB-16673 was 78%, and the rate of complete response/complete response with incomplete hematologic recovery was 4%.[2] The median time to first response was 2.8 months. Of the 17 patients who remained on treatment for at least 9 months, all had ongoing responses.

In another phase 1 study that was presented at the 2024 ASH Annual Meeting, NX-5948 was shown to produce an ORR of 76.7% among 30 response-evaluable patients with CLL.[3] There were 20 partial responses, 3 partial responses with lymphocytosis, 5 cases of stable disease, and 2 cases of progressive disease. The median duration of safety follow-up was 4.7 months.

BGB-16673 and NX-5948 have both received fast-track designation for use in relapsed or refractory CLL or small lymphocytic leukemia (SLL).

H&O What side effects are seen with BTK degraders?

AD The side effects are in alignment with what we see with BTK inhibitors. We see some bruising and some occasional cytopenias that are very easily managed. We also see general side effects, such as occasional rashes, fatigue, and diarrhea. The drugs are very well tolerated overall, and discontinuation due to adverse events is infrequent. For example, in the CaDAnCe-101 study of BGB-16673, which was presented at the most recent ASH Annual Meeting, the most common grade 3 or higher treatment-emergent adverse events (TEAEs) were neutropenia in 20% of patients and pneumonia in 10% of patients. TEAEs that led to dose reduction occurred in 3 patients (6%).

BTK degraders also help us avoid the adverse events we might see with other CLL treatments. Patients with CLL whose disease has progressed on BTK inhibitors and venetoclax currently have few options. The only approved agent is pirtobrutinib, which is well tolerated. If disease progresses on pirtobrutinib, the only other

option is chimeric antigen receptor (CAR) T-cell therapy. CAR T-cell therapy comes with a risk of multiple serious side effects, including infections, cytokine release syndrome, and neurotoxicity. It also has a high mortality rate. When we look at the treatment options available for patients with double-refractory CLL and compare BTK degraders with CAR T-cell therapy, BTK degraders are better tolerated.

H&O Do BTK degraders cause increases in the lymphocyte count?

AD Yes, we see redistribution lymphocytosis with both BTK degraders and BTK inhibitors. This lymphocytosis happens early and then resolves within months.

H&O What future studies are planned?

AD A phase 3 randomized trial that began in late April is comparing BGB-16673 with the investigator's choice of treatment in patients with relapsed or refractory CLL (NCT06846671).

H&O Is there anything you would like to add?

AD BTK degraders are a novel class of drugs that represent a big step in the fields of molecular pharmacology and lymphoma therapeutics. The exciting thing about PROTACs is that they provide the opportunity to target any protein of interest, including oncoproteins, which traditionally have been difficult to target. The field of PROTACS transcends CLL and lymphoid malignancies as we design new molecules that target important oncoproteins.

Disclosures

Dr Danilov has received consulting fees from AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, Bristol Myers Squibb, Genmab, Janssen, Lilly Oncology, MEI Pharma, Merck, Nurix, Regeneron, and Roche, and has received research funding from AbbVie, AstraZeneca, BeiGene, Genmab, Lilly Oncology, Merck, Nurix, and Regeneron.

References

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