ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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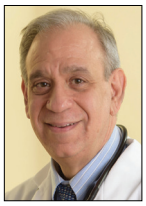
Zandelisib and B-Cell Lymphomas



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H&O How does zandelisib work?

AZ Zandelisib is a phosphoinositide 3-kinase delta (PI3K-δ) inhibitor with a long half-life. PI3K comes in multiple isoforms, including alpha, beta, gamma, and delta, with the delta isoform largely restricted to white cells. PI3K plays an important role in both B-cell biology and T-cell biology, and the toxicity of PI3K inhibition is partly associated with its effect on T cells. Idelalisib (Zydelig, Gilead), a selective PI3K-δ inhibitor, was the first in its class to receive approval. Several other PI3K-δ inhibitors were subsequently approved, though they have since been removed from the market.

H&O How does zandelisib compare with the other PI3K inhibitors?

AZ Umbralisib targets both the delta inhibitor and CK1 epsilon. In clinical trials, umbralisib has had a somewhat better safety profile compared to what has been observed with idelalisib and duvelisib (Copiktra, Secura Bio). Duvelisib targets PI3K-γδ, which we thought would be useful in T-cell lymphomas, but the concentrations needed to hit gamma make it primarily act as a delta inhibitor. Copanlisib (Aliqopa, Bayer) was developed as a PI3K-α/δ inhibitor, but it has pan-PI3K activity. As a result, alpha inhibitors have a different toxicity profile regarding hypertension and hyperglycemia.

Zandelisib is unique among the PI3K-δ inhibitors in that it has a long-half life, which provided a rationale for intermittent dosing. We ultimately came to the conclusion that if you gave the drug for 1 week, modeling predicted 2 weeks of activity on the tumor while also allowing for T-cell recovery. Because of its long half-life, levels of the agent remained above the minimal inhibitory concentration. The long half-life of zandelisib allowed us to explore a modified dose schedule for the purpose of treating patients with B-cell lymphoma. When administered on a continuous daily basis, the side effect profile of zandelisib is not differentiated from that of other PI3K-δ inhibitors, such as duvelisib or idelalisib. The intermittent dosing schedule (continuous for 8 weeks followed by days 1-7 of a 28-day cycle), made possible by its unique pharmacokinetic properties, made it a promising option.

H&O Could you describe your phase 1, 1b, and 2 studies of zandelisib for patients with B-cell lymphoma?

AZ The development of zandelisib for patients with malignancy was informed by a phase 1, first-in-human study in normal volunteers that provided important insights into the pharmacokinetics of the drug. These insights informed the design of the phase 1b dose-escalation trial. The initial cohorts of this study were restricted to patients with chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL) because we already had data regarding response with other agents in the class. This enabled the

dose-escalation trial to focus on determining the optimal biological dose that would achieve a response rate in patients with relapsed or refractory B-cell malignancy, limited to CLL and FL. In the dose-escalation part of the trial, patients received oral zandelisib once daily (60 mg, 120 mg, or 180 mg). The 60-mg dose was further evaluated and showed good activity, but patients experienced toxicities, including transaminitis and immune-mediated diarrhea, that were similar to those with other PI3K-δ inhibitors. Pneumonitis was not seen in the early cohort likely because of the small size of the cohort. Given the toxicity seen with continuous dosing and the long half-life of the drug, we evaluated an intermittent dosing regimen consisting of 2 cycles (56 days) of continuous dosing followed by dosing on day 1 to 7 of each subsequent 28-day schedule. The safety profile with the intermittent dosing schedule was much more favorable than the continuous dosing schedule with maintained efficacy. Fewer than 10% of patients discontinued therapy because of toxicity.

> The FDA recommendation is that this class of drugs needs to be developed based on identifying an optimized biological dose and schedule.

The phase 1b study also further evaluated zandelisib monotherapy or zandelisib with intravenous rituximab (375 mg/m^2) on days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 3 to 6, using a continuous daily schedule or intermittent dosing therapy (days 1-28 of cycles 1-2 and days 1-7 of subsequent cycles), which led to good response rates. No dose-limiting toxicities were observed.

The phase 1b study also included an expansion cohort of zanubrutinib (Brukinsa, BeiGene), a covalent BTK inhibitor, with zandelisib. In the early cohort, this regimen resulted in toxicity, which was overcome by starting the zandelisib on the intermittent dosing schedule without the 2-month continuous dosing lead-in and reduction of zanubrutinib to 80 mg twice a day. The response rates with this combination, which were presented by Dr Jacob Soumerai at the 2022 American Society of Hematology (ASH) symposium, were similar, at approximately 75%, but the complete response rate in MCL was slightly higher (20% vs 35%, respectively). The question of whether zanubrutinib improves efficacy when added to zandelisib would require a prospective randomized trial. The phase 1b study showed excellent activity in patients with CLL, with a response rate close to 100%. However, because CLL's drug development was felt to be a crowded space, the phase 2 study, TIDAL, focused on FL and marginal zone lymphoma (MZL). TIDAL was a phase 2 prospective study for patients with either FL or MZL with at least 2 prior lines of therapy treated with zandelisib monotherapy dosed at 60 mg on an intermittent dosing schedule (two 28-day cycles of continuous dosing, followed by 1 week on and 3 weeks off). The study was conducted during the peak of COVID-19, and some COVID-related deaths occurred, but the efficacy was excellent. In the FL population, the objective response rate was 72% with a complete response rate of 38%. The study recapitulated the data that were seen in the phase 1b study. Responses occurred early, with 87% of responses observed at the end of cycle 2 and 78% of the complete responses observed at the end of cycle 4. The response rate was similar to that seen in the phase 1b portion of the study, and the complete response rate was 35% in patients who had a history of progression of disease within 24 months of prior chemoimmunotherapy (POD24) and received zandelisib as their third-line treatment. The median duration of response was approximately 15 to 18 months, and the median progression-free survival (PFS) was 11.4 months. Unlike chemoimmunotherapy, zandelisib provides activity in POD24. Zandelisib on the intermittent dosing schedule is well-tolerated, which helps patients stay on treatment. The TIDAL trial is being closed, and the results presented at ASH were the final data available.

H&O Have any other studies investigated the use of zandelisib in B-cell lymphomas?

AZ The COASTAL study was a randomized phase 3 study to investigate the safety and efficacy of zandelisib plus rituximab vs standard immunochemotherapy. That trial has been terminated because changes in trial endpoints requested by the FDA made it impractical to continue the study.

H&O With the FDA's Oncology Drug Advisory Committee recommending against accelerated approval for PI3K inhibitors owing to safety and efficacy concerns, what is the registration plan for this agent?

AZ The FDA has taken a relatively extraordinary approach to the PI3K inhibitors, raising concerns about safety signals

arising from some of the studies. Some sponsors never completed their requirements for full registration, leading to provisional or accelerated approvals. For instance, idelalisib received full approval based on a randomized trial in CLL, but the manufacturer never completed any additional phase 3 studies to obtain full approval in FL or MZL. The FDA recommendation is that this class of drugs needs to be developed based on identifying an optimized biological dose and schedule. Zandelisib was developed with these goals in mind prior to the FDA recommendation. We established an optimal biological dose and a schedule that maintained efficacy while reducing toxicity. The TIDAL study was designed to meet all the requirements to get accelerated approval. However, the FDA changed its requirements twice, first by not allowing accelerated approval, and then by requiring the randomized COASTAL study to not only show a difference in PFS, but also an absence of excess deaths due to toxicity. These additional requirements added time to the approval process and made it more difficult to receive approval. Patients with FL have several treatment options with excellent long-term survival; thus, the survival endpoint was not going to be obtained quickly. The additional requirement of showing no excess deaths related to toxicity in addition to the primary endpoint of PFS is unprecedented in the field of lymphoma drug development.

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

AZ The entire development plan for zandelisib included a first-in-human, non-patient, non-malignant pharmacokinetic study, followed by a phase 1b study to establish the dosing schedule. The TIDAL study, which was a phase 2 study in FL and MZL, showed that the drug was active. Despite the positive results from the TIDAL study, the FDA changed its requirement for approval, requiring not only evidence of an improvement in PFS benefit but also enough safety data to demonstrate no adverse effect on OS. Thus, the ongoing phase 3 COASTAL study in patients with third-line and beyond FL and MZL was discontinued.

Disclosures

Dr Zelenetz has served in a consulting role to Genentech/Roche, Gilead Sciences, Celgene, Janssen, Amgen, Novartis, Adaptive Biotechnologies, MorphoSys, AbbVie, AstraZeneca, and MEI Pharma; has received research funding from MEI Pharma, Genentech/Roche, and BeiGene; has received salary support and institutional funding from SPORE; and has served on the data monitoring committee of BeiGene, Bristol Myers Squibb, Celgene, and Juno Pharmaceuticals.

Suggested Readings

Goto H, Izutsu K, Ennishi D, et al. Zandelisib (ME-401) in Japanese patients with relapsed or refractory indolent non-Hodgkin's lymphoma: an open-label, multicenter, dose-escalation phase 1 study. *Int J Hematol*. 2022;116(6):911-921.

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Zelenetz AD, Jurczak W, Ribrag V, et al. Efficacy and safety of zandelisib administered by intermittent dosing (ID) in patients with relapsed or refractory (R/R) follicular lymphoma (FL): primary analysis of the global phase 2 study TIDAL [ASCO abstract 7511] *J Clin Oncol*. 2022;40(16)(suppl).

Zelenetz AD, Jurczak W, Ribrag V, et al. Efficacy and safety of single-agent zandelisib administered by intermittent dosing in patients with relapsed or refractory (R/R) follicular lymphoma (FL): final results of the Tidal phase 2 study [ASH abstract 1563] *Blood*. 2022;140(1)(suppl).