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Duvelisib, a New PI3K Inhibitor for Lymphoid Malignancies



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H&O What type of drug is duvelisib?

NL Duvelisib (Copiktra, Verastem Oncology) is an orally bioavailable, highly selective and potent small-molecule inhibitor of the delta (δ) and gamma (γ) isoforms of phosphoinositide-3 kinase (PI3K). In 2018, the US Food and Drug Administration (FDA) approved duvelisib for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) or follicular lymphoma who have relapsed after 2 prior therapies.

The PI3K family is categorized into 3 different classes (I-III), whose members are further differentiated based on their primary structure and substrate specificity. The most therapeutically relevant are class I, comprised of the PI3K α , β , and δ isoforms; and class II, which includes the PI3K γ isoform. The α and β isoforms are responsible for cellular proliferation and insulin signaling, respectively. Importantly, the PI3K p110 α and β isoforms are expressed ubiquitously, whereas the PI3K p110 δ and γ isoforms are expressed primarily in leukocytes.

Idelalisib (Zydelig, Gilead) was the first PI3K inhibitor approved by the FDA. In 2014, idelalisib, which inhibits PI3K δ , was approved for use in combination with rituximab for the treatment of relapsed CLL and follicular lymphoma. Unfortunately, clinical trials in the frontline setting were halted based on safety concerns. Increased adverse events included infectious and immune-mediated side effects.

Duvelisib targets both the PI3K δ isoform, which is necessary for cell proliferation and survival, and the γ isoform, which is critical for cytokine signaling and proinflammatory responses from the microenvironment.

Unlike other isoforms of PI3K, the δ and γ isoforms are overexpressed primarily in hematologic malignancies and inflammatory and autoimmune diseases. Selective targeting of these PI3K isoforms minimizes the impact of PI3K signaling in normal, non-neoplastic cells, which may result in a more favorable safety profile. The dual inhibition may also provide an advantage over single-isoform selective inhibitors by reducing cell migration, which can disrupt CLL cell homing to the protective microenvironment.

H&O What did early clinical studies suggest about duvelisib?

NL The efficacy and safety profile of duvelisib monotherapy for the treatment of hematologic malignancies was demonstrated in several studies. In a preliminary phase 1 trial from 2013, the safety, maximum tolerated dose, and pharmacodynamics of duvelisib was assessed in 155 patients with hematologic malignancies, 44 of whom had relapsed/refractory CLL. The median age was 67 years in the relapsed/refractory CLL cohort. Among these patients, 33 (75%) had received at least 3 systemic therapies previously, and 14 of 32 patients tested (44%) had a 17p deletion. The dose of duvelisib ranged from 8 mg to 75 mg. Duvelisib had clinical activity in the relapsed/refractory cohort and rapidly caused lymphocytosis; the absolute lymphocyte count returned to baseline within six 28-day cycles. After 2 cycles of duvelisib, lymphadenopathy decreased in 35 (79%) of the patients with relapsed/refractory CLL. Escalation of the duvelisib dose did not increase the severity of the drug's adverse effects. In the initial report from this study, the overall response rate

(ORR) was 52%; 1 patient had a complete remission, and 15 patients had partial remissions.

In a 2018 phase 1 study in patients with advanced hematologic malignancies, clinically meaningful activity was observed in a cohort of patients with relapsed or refractory CLL/SLL, with a 56% ORR and a median progression-free survival (PFS) of 15.7 months. Diarrhea was the most common nonhematologic adverse event (47%). Transaminase elevations were the most frequent laboratory abnormality (30.9%). The most common grade 3 or higher adverse event was neutropenia (44%). Reductions in serine/threonine protein kinase B phosphorylation (p-AKT) and proliferating (Ki67+) CLL cells were seen in patient samples following administration of duvelisib, demonstrating pharmacodynamic evidence of PI3K inhibition. Based on the combined efficacy, safety, pharmacokinetics, and pharmacodynamic data from these phase 1 studies, duvelisib at 25 mg twice daily was selected as a clinically active dose for a phase 3 investigation in CLL/SLL.

H&O What did the phase 3 data show?

NL The encouraging results from early studies resulted in several late-phase trials to further assess the efficacy of duvelisib in patients with CLL. The DUO study was a global, phase 3 randomized study of duvelisib vs ofatumumab (Arzerra, Novartis) monotherapy in patients with relapsed or refractory CLL/SLL. Patients were randomly assigned in a 1:1 ratio to treatment with oral duvelisib at 25 mg twice daily (n=160) or ofatumumab intravenously at the standard dose (n=159). The study met the primary endpoint, improvement in PFS. For all patients, the median PFS was 13.3 months in the duvelisib arm vs 9.9 months in the ofatumumab arm (hazard ratio [HR], 0.52; $P<.0001$). Duvelisib improved PFS in patients with high-risk features, 17p13.1 deletions, and/or *TP53* mutations (HR, 0.40; $P=.0002$). The ORR was 74% with duvelisib vs 45% with ofatumumab ($P<.0001$), and this improvement was observed regardless of the deletion 17p status.

Although these results were encouraging, it should be noted that approximately 78% of patients had discontinued duvelisib 2 to 3 years after initiation of treatment. Discontinuation was attributed to adverse events in 35%, progressive disease in 22%, subject withdrawal in 8%, and death in 8%. Adverse events of grade 3 or higher occurred in 87% of the duvelisib arm and 48% of the ofatumumab arm. In the duvelisib arm, the most common severe adverse events were neutropenia (30%), diarrhea (15%), pneumonia (14%), and anemia (13%). In the ofatumumab arm, only neutropenia (17%) occurred in 10% or more of patients. As previously observed in the phase 1 study, severe immune-related toxicities (grade 3 or higher) were reported in patients treated with duvelisib. In this

phase 3 study, severe immune-related toxicities included colitis (12%) and pneumonitis, alanine transaminase, or aspartate transaminase increase (3% each). These events were managed primarily with dose interruptions. However, 60% of patients with pneumonitis or colitis received corticosteroid therapy, which resolved nearly all cases at the time of data cutoff. None of the events were fatal.

The FDA approval of duvelisib was based on a sub-analysis of patients from the overall DUO population who had received at least 2 prior lines of therapy (n=196). In this subpopulation, the median PFS as assessed by an independent review committee was 16.4 months with duvelisib vs 9.1 months with ofatumumab. The ORR as assessed by independent review was 78% in the duvelisib group vs 39% in the ofatumumab group; all responses were partial.

H&O Has duvelisib been studied in combination with other treatments?

NL Several studies have evaluated duvelisib in combination with other therapies. Davids and colleagues recently reported data from a phase 1b/2 study of duvelisib in combination with fludarabine, cyclophosphamide, and rituximab (FCR) for frontline therapy in younger patients with CLL. Duvelisib was administered for 1 week, then combined with standard FCR for up to six 28-day cycles, then given alone for up to 2 years as maintenance. Thirty-two patients were enrolled in the trial. The phase 2 dose of duvelisib was identified as 25 mg twice daily. Hematologic toxicity was common, and all-grade non-hematologic toxicities included transaminitis (28%), febrile neutropenia (22%), pneumonia (19%), and colitis (6%). The best ORR in the intention-to-treat analysis was 88%, which consisted of complete responses/complete responses with incomplete hematologic recovery in 56% and partial responses in 32%. In the intention-to-treat population, the best rate of undetectable minimal residual disease in the bone marrow was 66%. The primary endpoint of the rate of complete response with undetectable minimal residual disease in the bone marrow at the end of combination treatment was 25%. At 3 years, the rate of PFS was 73%, and the rate of overall survival was 93%.

Of note, the toxicities observed with duvelisib plus FCR were those expected of each treatment. Even with mandatory administration of granulocyte colony-stimulating factor, the rate of febrile neutropenia was 22%. Immune-mediated adverse events were relatively common, and required active management. Grade 3 or higher transaminitis occurred in 28% of patients. Several patients developed diarrhea and colitis, which are known toxicities with PI3K inhibitors. Many of these immune-mediated adverse events responded to drug holds and corticosteroids, but some patients required prolonged intervention

prior to resolution. In addition, infectious complications were common despite mandatory growth factor support and antimicrobial prophylaxis. Reports of opportunistic infections, including *Pneumocystis jirovecii pneumonia* and a case of cytomegalovirus reactivation, highlighted the need for careful management of patients treated with duvelisib plus FCR.

H&O Is duvelisib under study in other settings?

NL As mentioned, duvelisib is approved for CLL and follicular lymphoma. Duvelisib has been explored in combinations with agents such as rituximab and obinutuzumab in untreated patients with follicular lymphoma. A phase 1 trial has also investigated the efficacy of duvelisib in combination with rituximab, with or without bendamustine, in patients with relapsed/refractory lymphoma or CLL.

There are several ongoing studies of duvelisib. The phase 2 PRIMO trial is evaluating the efficacy and safety of duvelisib monotherapy in up to 120 adult patients with relapsed/refractory peripheral T-cell lymphoma. The primary endpoint is ORR, and the secondary endpoints include duration of response and PFS. A phase 1/2 trial is evaluating the efficacy of duvelisib in combination with venetoclax (Venclexta, Genentech/AbbVie) in 47 patients with relapsed/refractory CLL or SLL. A phase 1 trial is evaluating the efficacy of duvelisib in combination with either romidepsin (Istodax, Celgene) or bortezomib in 88 patients with relapsed/refractory T-cell lymphoma. The primary endpoint is the maximum tolerated dose, and the secondary endpoint is ORR.

H&O How will duvelisib fit into the treatment armamentarium for CLL?

NL Although the PI3K inhibitors are certainly active in CLL, there is much therapeutic competition in this space. I do not anticipate that most patients will receive treatment with duvelisib indefinitely, given some of the known adverse events associated with this class of drugs. In addition, Bruton's tyrosine kinase (BTK) inhibitors, such as ibrutinib (Imbruvica, Pharmacyclics/Janssen) and acalabrutinib (Calquence, AstraZeneca), are well-established options for frontline therapy. Venetoclax was also recently approved in combination with obinutuzumab as a time-limited therapy in the frontline setting, as well as in patients who develop relapsed disease after treatment with BTK inhibitors. Therefore, the use of duvelisib—and of PI3K inhibitors in general—will likely remain limited to patients with CLL who have relapsed multiple times. Nonetheless, this class remains an important and potent therapy for CLL. For example, I could reasonably foresee combination strategies with duvelisib that are active and

time-limited to mitigate some of this drug's potential adverse events. Duvelisib could be used in patients with CLL who initially respond favorably to BTK inhibitors, but then become intolerant to treatment. Rather than moving directly to venetoclax, it might be helpful to exploit another agent in the B-cell antigen receptor (BCR) signaling pathway. Positive results have been seen in this setting, as well. Given the ever-evolving therapeutic landscape in CLL, and the activity of duvelisib in a variety of hematologic malignancies, I look forward to emerging data for this agent in combination strategies in the near future.

Disclosure

Dr Lamanna has served on the scientific committee/advisory board of AbbVie, AstraZeneca, BeiGene, Celgene, Genentech, Gilead, and Pharmacyclics/Janssen. She has received research support from AbbVie, AstraZeneca, BeiGene, Genentech, MingSight, Oncternal, TG Therapeutics, and Verastem.

Suggested Readings

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