To the editor:

**Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy**

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Follicular lymphoma (FL) is the most common type of indolent non-Hodgkin lymphoma (NHL), accounting for ~22% of all patients with NHL.1 Several studies identified a high-risk population of patients, comprising ~20% of all patients with NHL, who had FL that progressed within 24 months from initiation of the first-line chemoimmunotherapy and were at increased risk of death.2,4

Idelalisib, a highly selective, orally bioavailable inhibitor of the δ isosform of phosphoinositide 3-kinase δ (p110δ), is indicated in the United States and Europe as monotherapy for relapsed FL.5,6 A phase 2, multicenter, open-label, single-arm study evaluated the efficacy and safety of idelalisib in 125 patients previously treated with first-line chemoimmunotherapy who had relapsed indolent NHL that was refractory to both alkylators and rituximab (NCT01282424).7

The primary efficacy end point was the overall response rate (ORR), assessed using the standard criteria for lymphoma8 by an independent review committee. Key secondary end points included duration of response (DOR), lymph node response rate, overall survival (OS), progression-free survival (PFS), and safety.7 After median duration of treatment with idelalisib monotherapy of 6.6 months, 90% of patients in this study achieved tumor reductions in the size of lymph nodes. The ORR was 57%, with 7 (6%) complete responses and 63/125 (50%) partial responses. The median DOR was 12.5 months and the median PFS was 11 months.7

To examine whether idelalisib improved clinical outcomes in patients with FL experiencing early progressive disease (PD) after initial chemoimmunotherapy, we performed a retrospective post hoc analysis in a subgroup of patients with FL. Histological types of FL permitted in the study included grades 1, 2, and 3A (with specific exclusion of grade 3B). Of the 72 patients with FL,7 46 received first-line chemoimmunotherapy. Nine of these patients had late PD after 24 months from the initiation of treatment, and 37 had early PD within ~24 months from the start of treatment. This high-risk population was well represented in the trial (37/125 [30%]), and all 37 patients received idelalisib treatment (supplemental Figure 1, available on the Blood Web site). A total of 19 (51.4%) of these patients were male and 18 (48.6%) were female; 89.2% had grade 1 or 2 FL, and 56.8% had high-risk Follicular Lymphoma International Prognostic Index9 scores. The majority of patients (21/37 [56.8%]) received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone-based therapies (R-CHOP-like [R-CHOP, R-CHEP, R-CHOJ) as first-line therapy (supplemental Table 1; supplemental Figure 1), and were heavily pretreated, with median number of 3 prior therapies. The median (range) time from the start of first-line therapy to the start of idelalisib treatment was 30.3 (8.9–94.7) months and the mean (standard deviation) intertreatment interval between first- and second-line treatments was 12.5 (6.12) months.

Idelalisib had an acceptable safety profile in patients with early PD. Overall, 34 (91.9%) and 19 (51.4%) early PD patients received oral idelalisib 150 mg twice daily for ≥2 months and ≥6 months, respectively. In total, 13 out of 37 patients (35.1%) and 4 out of 37 patients (10.8%) had to reduce idelalisib dose to 100 mg and 75 mg twice daily, respectively, mostly due to increased levels of alanine aminotransferase and aspartate aminotransferase, followed by diarrhea and neutropenia, consistent with the similar trend observed in the overall study population.7 The most commonly occurring AEs were diarrhea (51.4%), cough (40.5%), pyrexia (35.1%), nausea (32.4%), neutropenia (24.3%), night sweats (24.3%),...
abdominal pain (21.6%), fatigue (21.6%), and upper respiratory tract infection (21.6%) (supplemental Table 2).

Across the studies investigating the effects of idelalisib therapy, commonly reported idelalisib-related serious AEs included pneumonitis and elevated liver transaminases in up to 3% and 13% of patients, respectively.\textsuperscript{7,10,11}

In this study, a total of 19/37 (51.4%) patients experienced serious AEs, mostly pyrexia (18.9%), diarrhea (10.8%), and pneumonia (10.8%) (supplemental Table 3). Among patients with pneumonia, 1 patient each had cytomegalovirus pneumonia, \textit{Streptococcus pneumoniae}, \textit{Staphylococcus aureus} pneumonia, and aspiration pneumonia. Two patients had documented cytomegalovirus colitis. No cases of \textit{Pneumocystis jirovecii} pneumonia were reported. Prophylaxis for \textit{P jirovecii} was not mandated in this study.

The rate of grade $\leq 3$ diarrhea in this study (11%) was comparable to the rates reported in other studies of hematologic malignancies involving
idelalisib (4% to 20%).\textsuperscript{11-13} Among the clinical laboratory abnormalities, grade 3 or 4 elevations of alanine aminotransferase and aspartate aminotransferase levels were reported in 3/37 of patients (8.1%). Seven deaths (18.9%) occurred during the study and long-term follow-up. Three deaths were observed within 30 days of the last dose of drug. Two patients died of pneumonitis and splenic infarction, which were considered likely to be related to idelalisib treatment.

The efficacy results of this post hoc analysis indicate that idelalisib has antitumor activity in high-risk FL patients who relapsed within 24 months following initial chemoimmunotherapy. After a median (range) duration of idelalisib treatment of 8.2 (0.6–29.0) months, 22 out of 37 patients (59.4%) achieved a ≥50% decrease from baseline in the sum of the products of the greatest perpendicular diameters of index lesions following idelalisib treatment, which constitutes a standard criterion for lymphadenopathy response\textsuperscript{8} (Figure 1). The ORR was 21 out of 37 (56.8%), with 5 complete responses (13.5%) and 16 partial responses (43.2%). The response rates were not significantly different between patients with PD ≤ 12 months after initial therapy (ORR = 12/17 [70.6%]) and patients who experienced PD between 12 and 24 months following initial therapy (ORR = 9/20 [45.0%]) (P = .18).

The median DOR for all 37 patients with early PD was 11.8 months (95% confidence interval [CI], 3.8, not reached [NR]). The median (95% CI) PFS was 11.5 (5.5, 19.3; Figure 2A) months overall and 8 (3.9, 27) and 13.6 (3.7, 19.3) months for the subgroups with PD ≤ 12 months and between 12 to 24 months, respectively (hazard ratio, 1.09; 95% CI, 0.46, 2.60; P = .84).

The probability of survival ± standard error following initial progression after first-line chemoimmunotherapy was 79% ± 8% at 60 months. The survival probability ± standard error at 24 months following initiation of idelalisib was 79% ± 7%; the median OS was not reached. The median OS (95% CI) was not reached for patients with PD ≤ 12 months (NR [NR, NR]) and PD between 12 to 24 months (NR [16.6, NR]; hazard ratio, 0.85; 95% CI 0.19–3.79; P = .83; Figure 2B).

When interpreting the promising efficacy results from this analysis, caution should be exercised when comparing these results to registry-based outcomes.\textsuperscript{2} It is likely that patients reported here represent only a subset of patients with treatment failure within 24 months and may not fully reflect the characteristics of this population.

Thus far, these results are the first to describe the efficacy and safety of idelalisib in patients with FL relapsing early following first-line chemoimmunotherapy and suggest that idelalisib, or other therapeutic agents in this class, may provide a viable therapeutic option for patients with double-refractory FL with early relapse after initial therapy. However, given the small sample size and uncontrolled study design, additional prospective studies in this high-risk patient population are warranted.

The online version of this article contains a data supplement.

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