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Management of Relapsed/Refractory Follicular Lymphoma

- How I Treat Relapsed/Refractory Follicular Lymphoma: An Expert Perspective
- Highlights from:

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How I Treat Relapsed/Refractory Follicular Lymphoma

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H&O What are the first-line treatment options for follicular lymphoma?

PM Some patients with newly diagnosed follicular lymphoma do not need treatment at the time of diagnosis.[1] When treatment is indicated, there are several different approaches, depending on a mix of lymphoma-related and patient-related details.[2] The most evaluated treatment in the first-line setting of follicular lymphoma is rituximab, with or without chemotherapy.[3-5] Recently, the monoclonal antibody obinutuzumab was approved in combination with chemotherapy.[6] There may be maintenance therapy after the initial therapy.[7]

H&O How often do patients with follicular lymphoma develop relapsed/refractory disease?

PM Some patients, particularly those with early-stage disease, might be cured with existing therapies. Additionally, some patients might remain in remission for a long period without clinical evidence of recurrence. However, most patients with follicular lymphoma will eventually relapse.

H&O What are the second-line treatment options, and how effective are they?

PM There are at least as many options for the second-line setting as for the first-line. After relapse or progression, the first question is whether treatment is required.[8] Very often, the answer is no, and asymptomatic patients with slowly progressive disease can be observed, just as they may have been when the lymphoma was originally diagnosed.

Among patients who do have indications for therapy, the first question is whether the follicular lymphoma is transformed or still indolent. Transformed disease requires treatment that is more intense. If the follicular lymphoma is not transformed, then it is necessary to devise a treatment plan based, again, on several lymphoma-related and patient-related factors. In the relapsed/refractory setting, there are additional data to consider: the patient's previous therapy and response.

Options include single-agent rituximab and rituximab plus chemotherapy.[9] In addition, the US Food and Drug Administration (FDA) has approved several regimens for relapsed/refractory follicular lymphoma. Bendamustine, with or without obinutuzumab, is approved for patients with rituximab-refractory follicular lymphoma.[10,11] Ibritumomab tiuxetan is also approved for previously treated indolent lymphoma, but it is seldom used.[12] More intensive options include autologous stem cell transplant,[4] particularly for patients who relapsed very early after first-line immunochemotherapy.

H&O Do patients in need of third-line treatment pose any particular challenges?

PM There are challenges in treating these patients, although they do not necessarily reflect the line of therapy. A patient who has received 2 prior lines of therapy may have accumulated some treatment-related toxicity and may have a more resistant tumor. There are several different scenarios in this setting. For example, a patient might receive treatment with rituximab and remain in remission for 5 years, and then receive an additional course of rituximab that leads to another 5-year remission. This case obviously differs from a patient who relapses quickly after 2 lines of therapy. In the third-line setting, there is the potential for a more treatment-resistant tumor. Patients in need of third-line treatment may be older and have more comorbid conditions than a newly diagnosed patient.

H&O What are the third-line treatment approaches, and is there a standard of care?

PM Options used in the first-line and second-line setting can also be used in the third-line setting. In addition, the FDA has approved 2 agents specifically for third-line treatment: the phosphoinositide 3 (PI3)-kinase inhibitors copanlisib and idelalisib.[13,14] There is no standard of care. The treatment choices are based on the particular patient scenario. All of these options have reasonable roles, depending on the context.

H&O Do data support the use of ibrutinib in follicular lymphoma?

PM Ibrutinib is not approved by the FDA for follicular lymphoma, so any use would be off-label. Currently, the evidence for ibrutinib, particularly as monotherapy, in follicular lymphoma is not very strong. Clinical trials suggested that ibrutinib works 20% to 30% of the time.[15] The duration of response was fair. I do not use ibrutinib frequently in patients with follicular lymphoma.

Ibrutinib may have activity in combination with other drugs in relapsed/refractory follicular lymphoma. The phase 3 SELENE trial (A Phase III Study of Ibrutinib in Combination With Either Bendamustine and Rituximab [BR] or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone [R-CHOP] in Patients With Previously Treated Follicular Lymphoma or Marginal Zone Lymphoma) is combining chemotherapy and rituximab, with or without ibrutinib.[16] This trial may lead to a new approval for ibrutinib and change practice patterns.

H&O How do the goals of therapy differ in certain settings?

PM It is important to define the goal of third-line treatment. In approximately 80% of patients with follicular lymphoma, longevity is comparable with that seen in people without the disease. Some of these patients may die from lymphoma or related complications, but their life is not necessarily shortened by the disease. In these cases, the goal of every line of therapy should be to maintain quality of life by minimizing interference from symptoms of lymphoma and side effects of therapy.

In 20% of patients with follicular lymphoma, the disease will significantly shorten life. For these patients, it may be necessary to consider treatments that are more intense and/or associated with more significant side effects. The goal is to help patients live longer, and the best therapy is debatable. A randomized, phase 3 intergroup trial in higher-risk follicular lymphoma is comparing 3 arms: chemotherapy, an immunomodulatory drug plus an anti-CD20 agent, and a PI3-kinase inhibitor plus an anti-CD20 agent.[17]

H&O When a patient has received 2 prior lines of an anti-CD20 therapy and develops relapsed/refractory disease, is it time to change to a therapy with a different mechanism of action?

PM My initial answer is yes. There are, however, some controversial data suggesting that obinutuzumab can work in patients who are refractory to rituximab.[18] Under some circumstances, it might be reasonable to treat a patient who is refractory to rituximab with obinutuzumab plus bendamustine. Patients who are refractory to anti-CD20 therapy and chemotherapy will probably require treatment with therapies that have different mechanisms of action. For example, the PI3-kinase inhibitors have been effective in early trials.[19]

H&O What is unique about the PI3-kinase inhibitor copanlisib?

PM Copanlisib is approved by the FDA for the treatment of patients with follicular lymphoma that has relapsed after 2 prior lines of therapy or is refractory to 2 prior lines of therapy.[13] Copanlisib differs from the other PI3-kinase inhibitors in several ways. For example, copanlisib inhibits both the alpha and delta isoforms, whereas the others are specific to delta. Copanlisib is administered weekly by intravenous infusion, and the others are administered orally. Outside of a phase 3 trial, it is hard to compare the efficacy of different PI3-kinase inhibitors. However, it is clear that the side effect profile of copanlisib is unique. The alpha inhibition can result in hyperglycemia and hypertension. The pharmacokinetic properties may result in lower rates of autoimmune or inflammatory issues.

H&O What did the CHRONOS-1 trial show?

PM The open-label, multicenter, international phase 2 CHRONOS-1 trial (Open-Label, Uncontrolled Phase II Trial of Intravenous PI3K Inhibitor BAY80-6946 in Patients With Relapsed, Indolent or Aggressive Non-Hodgkin's Lymphomas) evaluated copanlisib in patients with indolent non-Hodgkin lymphoma (NHL) that had relapsed following 2 prior lines of therapy (including rituximab).[20] The study enrolled approximately 140 patients. Most patients had follicular lymphoma, and 60% were refractory to their previous line of therapy. Copanlisib was clearly active. The response rate was approximately 60%, and the median progression-free survival was about 1 year. Alpha inhibition can result in transient hyperglycemia and hypertension, and these adverse events were among the most common in the study. In addition, there were some serious adverse events, including infection. Approximately 16% of patients stopped copanlisib owing to adverse events.

H&O How do you view the efficacy data for copanlisib as a single agent for relapsed follicular lymphoma?

PM Copanlisib clearly has activity as a single agent in this patient population. This population was heavily pretreated, and most patients were refractory to their prior line of therapy. The response rate and progression-free survival were sufficient for FDA approval.[13] Outside of a

phase 3 trial, it is hard to know how copanlisib compares with other agents.

H&O How is copanlisib administered?

PM Unlike other medications currently in development, copanlisib is administered by intravenous infusion once weekly. The dosing schedule is 3 weeks on followed by 1 week off. At a time when many new drugs are administered orally, it will be interesting to see if the intravenous dosing improves or reduces effective drug delivery in a real-world setting.

H&O Are the adverse events manageable?

PM The FDA label lists the adverse events and describes how to manage them. I mentioned hyperglycemia, which peaks about 5 to 8 hours after infusion, and hypertension. The FDA label states that a patient's levels of serum glucose and blood pressure should be under control before initiation of copanlisib. If this is done, then patients are unlikely to develop post-treatment hyperglycemia or hypertension. Patients are probably at higher risk of overtreatment than undertreatment. If a patient's glucose level is normal when starting copanlisib, any rise should be transient and will resolve with adequate fluid intake and urination. Similarly, if a patient starts treatment with normal blood pressure, then hypertension should resolve quickly. In other words, patients should take their usual antihypertensive medications on the day of the infusion.

With any PI3-kinase inhibitor, there is some risk for inflammatory or autoimmune reactions, such as liver enzyme abnormalities, pneumonitis, and colitis. Copanlisib appears to be associated with a relatively low rate of these reactions, but patients should be carefully monitored for them. If any of these events occur, copanlisib should be stopped. Patients receiving treatment with PI3-kinase inhibitors may be at risk for infection because of the intensity of their prior therapies, as well as the PI3-kinase inhibition itself. The infections might be severe and can be uncommon; they include *Pneumocystis* pneumonia. It is reasonable to consider use of prophylaxis to avoid opportunistic infections.

H&O What has been learned from follow-up analyses of the CHRONOS-1 trial, as presented at the 2017 ASH meeting?

PM Analyses of the CHRONOS-1 trial presented at the 2017 American Society of Hematology (ASH) meeting were helpful in that they confirmed the efficacy and side effect profile.[21,22] There were no new side effects of particular concern. Autoimmune reactions, which might be expected to arise with longer treatment, were not significantly more common than suggested by early data. Efficacy was similar with longer follow-up. The duration of response decreased slightly with longer-term follow-up, which is common.

H&O Are there any other ongoing studies of copanlisib?

PM There are several other CHRONOS trials. CHRONOS-3 is a phase 3 study evaluating copanlisib in combination with rituximab in relapsed, indolent NHL.[23] The phase 3 CHRONOS-4 trial is evaluating copanlisib in combination with standard immunochemotherapy in relapsed, indolent NHL.[24] These multiple CHRONOS studies will provide more randomized data about copanlisib, which is ultimately the best way to learn about the efficacy and adverse events related to a particular drug.

H&O Do you have any other suggestions for the clinical use of copanlisib?

PM In general, we should aim to practice evidence-based medicine. Copanlisib is approved by the FDA for the third-line treatment of follicular lymphoma. It should be used on-label, and monitored according to the label directions. This approach should lead to results that are similar to those seen in clinical trials.

Disclosure

Dr Martin has consulted for Bayer, Gilead, Acerta, Janssen, Roche, Seattle Genetics, and Kite.

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Highlights in Follicular Lymphoma From the 2017 American Society of Hematology Annual Meeting and Exposition

Commentary by Peter Martin, MD, MS

Updated Safety and Efficacy From the Copanlisib CHRONOS-1 Trial in Patients With Relapsed or Refractory Indolent B-Cell Lymphoma: Low Incidence of Late-Onset Severe Toxicities

This updated analysis of the phase 2 CHRONOS-1 study (Open-Label, Uncontrolled Phase II Trial of Intravenous PI3K Inhibitor BAY80-6946 in Patients With Relapsed, Indolent or Aggressive Non-Hodgkin's Lymphomas) indicated that with 8 additional months of follow-up since the primary analysis, copanlisib continued to demonstrate strong efficacy and manageable toxicity in patients with relapsed or refractory indolent B-cell lymphoma.[1,2] Independent radiologic review assessed the objective response rate.[3]

The study enrolled 142 patients with relapsed or refractory disease after at least 2 prior lines of treatment. Copanlisib was administered at a fixed dose of 60 mg. Among these patients, 104 had follicular lymphoma, 23 had marginal zone lymphoma (MZL), 8 had small lymphocytic lymphoma, and 6 had lymphoplasmacytoid/Waldenström macroglobulinemia. The median duration of treatment was 26 weeks (range, 1-139 weeks) in this updated follow-up vs 22 weeks (range, 1-105 weeks) in the primary analysis.[1,2]

The objective response rate was 58.5% overall (n=83; 95% CI, 49.9-66.7) and 57.7% in patients with follicular lymphoma (n=60; 95% CI, 47.6-67.3). Complete responses occurred in 14.1% of patients overall (n=20) and 16.4% of patients with follicular lymphoma (n=17). The median duration of response was 12.2 months (range, 0.03-28.1 months) vs 22.6 months (range, 0-22.6 months) in the primary analysis.[1,2] Rates of median progression-free survival were similar with both analyses, at 11.3 months (range, 0.03-30.0 months) at follow-up and 11.2 months (range, 0.2-24.0 months) in the primary analysis (Figure 1).[1,2] The median overall survival had not been reached.[1]

The most common all-grade treatment-emergent adverse events (AEs) were transient hyperglycemia (49.3%) and transient hypertension (29.6%).[1] These

rates were similar to those reported in the primary analysis.[2] Serious AEs occurred in 52.1% of patients (n=74) in the follow-up analysis vs 50.0% of patients (n=71) in the primary analysis. However, few serious AEs occurred in more than 3 patients each.[1,2] Similarly, grade 3/4 treatment-emergent AEs remained primarily unchanged from the primary analysis, even with the longer follow-up. The individual grade 3/4 treatment-emergent AEs that increased did so by only 1 patient.[1,2] The authors concluded that the promising efficacy and manageable safety support the use of copanlisib in this patient population.

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Commentary: This updated analysis of the CHRONOS-1 trial included data for 8 more months of follow-up. There were no new side effects of concern. Rates of all-grade treatment-emergent AEs were similar to those reported in the primary analysis. Although rates of autoimmune reactions might have been expected to increase, they were not more common than in the earlier analysis. Efficacy was also similar. The duration of response decreased slightly, which would be expected because more patients relapse as time goes on.

High Complete Response Rates With Pembrolizumab in Combination With Rituximab in Patients With Relapsed Follicular Lymphoma: Results of an Open-Label, Phase 2 Study

The combination of pembrolizumab with rituximab in patients with relapsed follicular lymphoma showed clinically meaningful efficacy and a tolerable safety profile in a phase 2 trial.[1] Pembrolizumab and rituximab could act synergistically in follicular lymphoma by activating both innate and adaptive immune responses.[2]

Thirty patients with grade 1 to 3a follicular lymphoma that had relapsed after at least 1 prior line of therapy and was sensitive to rituximab were treated with rituximab and pembrolizumab for up to 16 cycles. The response assessment was performed with the Lugano classification.[3] The patients' median age was 64 years (range, 43-84 years).

The median follow-up was 13.8 months. The overall response rate (ORR) was 67%, and the complete response rate was 50% (Figure 2). The median progression-free survival was 11.4 months (range, 8.25 months to not reached). The median duration of response was 14.1 months (range, 11 months to not reached). No deaths occurred.

An analysis of 19 tumors indicated that programmed death ligand 1 (PD-L1) expression levels were not associated with response to therapy (P=.71). An analysis of immune cell gene signatures in 18 patients indicated an association between the CD8-positive T-effector score and a complete response. Among patients with high levels of CD8 T-effector cells, 67% experienced a complete

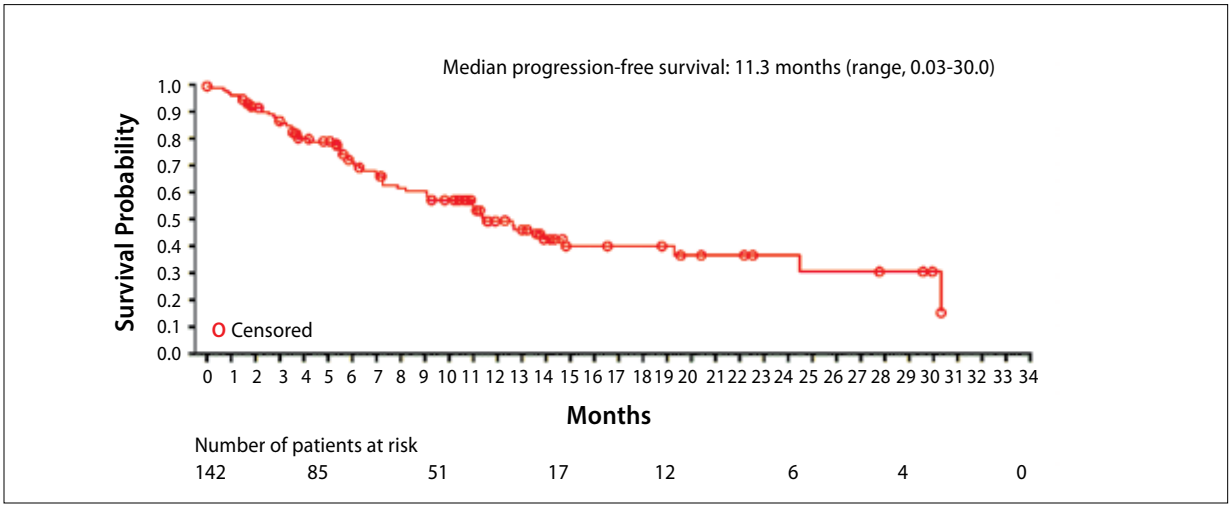

Figure 1. Median progression-free survival in a follow-up analysis of the phase 2 CHRONOS-1 study, which evaluated copanlisib in patients with relapsed or refractory indolent B-cell lymphoma. CHRONOS-1, Open-Label, Uncontrolled Phase II Trial of Intravenous PI3K Inhibitor BAY80-6946 in Patients With Relapsed, Indolent or Aggressive Non-Hodgkin's Lymphomas. Adapted from Dreyling M et al. ASH abstract 2777. *Blood*. 2017;130(suppl 1).[1]

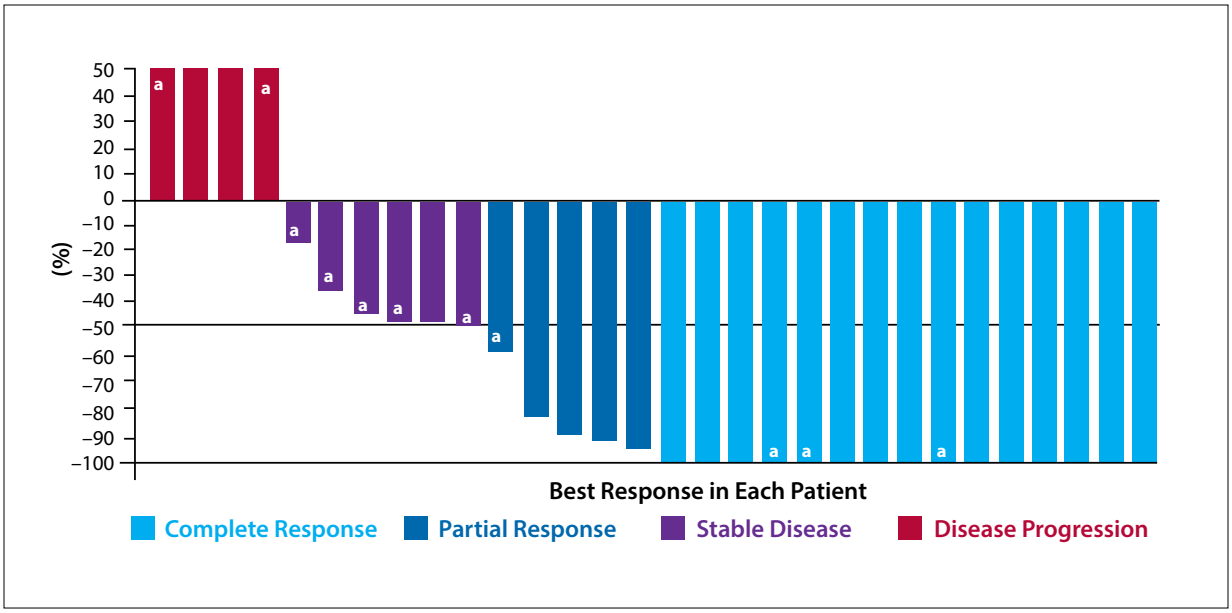

Figure 2. Responses among patients with relapsed follicular lymphoma who received pembrolizumab plus rituximab. [a]Patients with an early relapse (<24 months) after frontline treatment. Adapted from Nastoupil L et al. ASH abstract 414. *Blood*. 2017;130(suppl 1).[1]

response. Among those with low levels, the complete response rate was 25%. Peripheral blood interferon gamma gene signatures were associated with a percent change in tumor size in response to treatment with pembrolizumab and rituximab in both a 10-gene panel (*P*=.016) and a 28-gene panel (*P*=.023). This correlation must be prospectively validated in a larger study.

All-cause grade 3/4 AEs were diarrhea (3%), transaminitis (3%), and nausea/vomiting (7%). Immune-related AEs occurring in more than 1 patient included diarrhea (grade 1/2, n=11; grade 3, n=1), transaminitis (grade 1, n=7), pneumonitis (grade 2, n=2), hypothyroidism (grade 1, n=2), and rash (grade 1/2, n=7). Six patients discontinued therapy, all because of immune-related AEs.

Commentary: This study is interesting, in that follicular lymphoma would seemingly be an ideal target for immunotherapy. It is a slow-growing lymphoma that can spontaneously regress for reasons likely related to anti-tumor immune effects. Occasionally, there are spontaneous responses. The thought would be that a therapy that interacts with the immune system would work well in follicular lymphoma. Interestingly, pembrolizumab and other PD-1 inhibitors do not seem to work well in indolent non-Hodgkin lymphoma. This study evaluated whether combining pembrolizumab with rituximab might improve outcome, which is an interesting hypothesis. The challenge is in distinguishing the benefits of rituximab from those resulting from the synergy between rituximab and pembrolizumab. The results from this phase 2 trial are mainly hypothesis-generating, but they are relatively promising.

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Pharmacodynamic Study of Copanlisib in Patients With Non-Hodgkin's Lymphoma and Advanced Solid Tumors: Confirmation of On-Target PI3K Inhibitory Activity

This phase 1 study assessed dose-dependent pharmacodynamics of copanlisib on plasma exposure in patients with non-Hodgkin lymphoma (NHL) or solid tumors, demonstrating dose-dependent, on-target pharmacodynamics and a manageable safety profile.[1] Inhibition of the phosphoinositide 3 (PI3)-kinase can be therapeutically efficacious for relapsed or refractory B-cell lymphomas. Copanlisib is a pan-class 1 PI3-kinase inhibitor that

predominantly inhibits PI3-kinase alpha and PI3-kinase delta and has previously demonstrated efficacy in NHL.[2] Patients with NHL (n=33) had received at least 1 prior chemoimmunotherapy or immunotherapy, and those with solid tumors (n=30) had advanced and/or refractory disease. All patients had tumors with a *PIK3CA* or *PTEN* alteration of at least 30%.

A total of 63 patients were treated with copanlisib at a dose of either 0.4 mg/kg or 0.8 mg/kg. The researchers assessed pharmacodynamics via biomarkers related to PI3-kinase signaling, including pAKT in platelet-rich plasma and the pS6 ribosomal protein Ser235/236 in paired tumor tissues. Treatment with copanlisib resulted in a decrease of 50% or higher in pAKT in platelet-rich plasma during the initial 2 cycles of therapy, with a sustained response for 24 hours after administration of the drug. Paired tumor biopsies from baseline and at day 15 showed greater inhibition of pAKT and pS6 ribosomal protein at the dose of 0.8 mg/kg (n=16) vs 0.4 mg/kg (n=14; *P*=.05). Plasma exposure to copanlisib increased according to dose (Figure 3).

In the cohort of patients with NHL, 2 patients (6.1%) had a complete response. Both of these patients had received 0.8 mg/kg of copanlisib. Among the 5 patients with NHL who experienced a partial response (15.2%), 4 had received the higher dose of copanlisib. Nine patients with NHL were not assessed or not evaluable. In the cohort of patients with solid tumors, 1 patient (3.3%), who was treated with the higher dose, experienced a partial response.

All-grade treatment-emergent AEs occurred in 59 patients (93.7%). The most common of these events were hyperglycemia (50.8%), hypertension (42.9%), nausea (38.1%), fatigue (38.1%), diarrhea (33.3%), and anemia (28.6%).

The authors concluded that this pharmacodynamic analysis indicated on-target modulation by copanlisib and showed dose-dependency of pharmacodynamic measurements. The higher dose of 0.8 mg/kg was more efficacious than the lower dose.

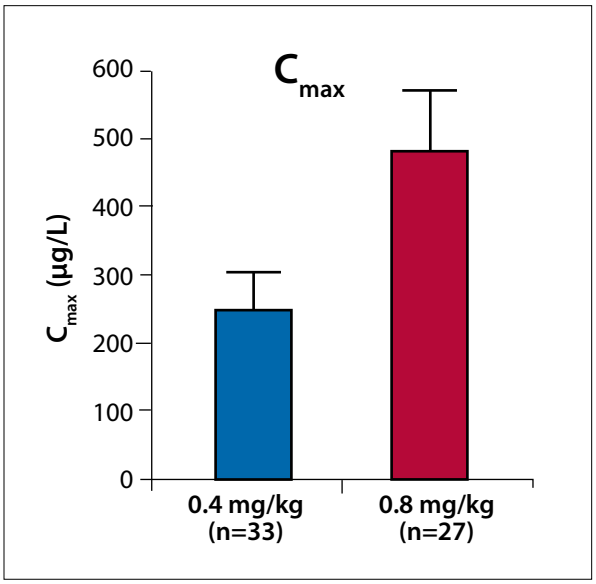

Figure 3. C_{max} plasma exposure of copanlisib after the first infusion on cycle 1, day 1. Adapted from Morschhauser F et al. ASH abstract 1256. *Blood*. 2017;130(suppl 1).[1]

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Commentary: Some have suggested that intermittent delta isoform inhibition might reduce the incidence of inflammatory side effects relative to that seen with more continuous inhibition. The pharmacokinetics of copanlisib are intermittent rather than sustained in delta isoform inhibition, allowing some periodic remittance of the PI3-kinase inhibition. This should reduce the incidence of the inflammatory side effects that are seen with more sustained PI3-kinase inhibition. The pharmacokinetics of copanlisib may allow it to be administered intermittently. It is not so much the target, but rather the intermittent administration, that changes the side effect profile.

Pooled Safety Analysis From Phase 1 and 2 Studies for Patients With Relapsed Indolent Non-Hodgkin's Lymphoma Treated With Intravenous Copanlisib

Dr Pier Luigi Zinzani and colleagues presented a pooled safety analysis from four phase 1 and phase 2 trials of copanlisib monotherapy in 168 patients with indolent NHL.[1-5] In these trials, copanlisib was administered intermittently instead of continuously. All patients had previously received rituximab, and 99.4% had received prior alkylating agents. The median number of prior lines of therapy was 3 (range, 1-10). The median duration of treatment was 22 weeks (range, 1-206 weeks).

Dose reductions, interruptions, or delays occurred in 76.2% of patients (Figure 4). Dose modifications owing to treatment-emergent AEs occurred in 68.5% of patients, with a typical incidence ranging from 10% to 30% per cycle. Discontinuation of copanlisib owing to treatment-emergent AEs occurred in 24.4% of patients

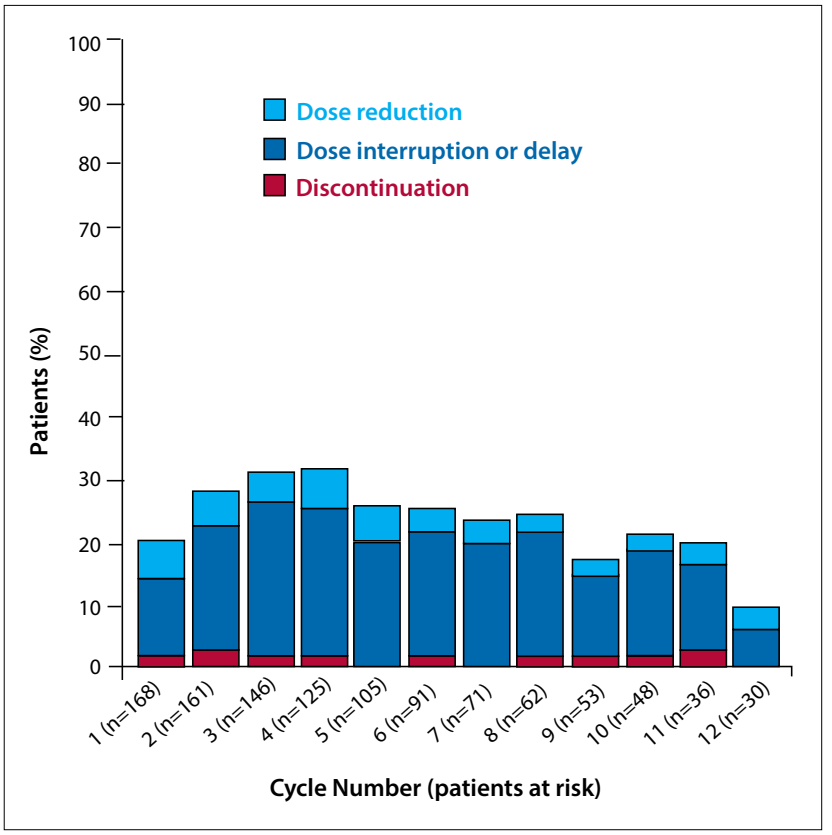

Figure 4. Dose reductions, interruptions, delays, or discontinuations in a pooled safety analysis of phase 1 and 2 trials evaluating copanlisib monotherapy in patients with indolent non-Hodgkin lymphoma. Adapted from Zinzani PL et al. ASH abstract 4042. *Blood.* 2017;130(suppl 1).[1]

(n=41), with an incidence of approximately 2% to 3% per cycle and an even distribution across treatment cycles. All-grade treatment-emergent AEs occurred in 98.8% of patients (n=166), the most common of which were hyperglycemia (50.6%), diarrhea (35.7%), and hypertension (34.5%). The most common grade 3 treatment-emergent AEs were hyperglycemia (31.5%), hypertension (26.8%), and neutropenia (8.3%). The most common grade 4 treatment-emergent AEs were neutropenia (11.9%) and hyperglycemia (6.0%). Grade 3/4 hyperglycemia and grade 3 hypertension were typically infusion-related, transient, and asymptomatic. Serious treatment-emergent AEs occurred in 48.2% of patients (n=81). Treatment-emergent AEs were more common and severe in the first treatment cycle. The prevalence of treatment-emergent AEs remained fairly constant throughout the period of observation, suggesting that copanlisib is not associated with late-onset or cumulative toxicities.

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2. Patnaik A, Appleman LJ, Tolcher AW, et al. First-in-human phase I study of copanlisib (BAY 80-6946), an intravenous pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-Hodgkin's lymphomas. *Ann Oncol.* 2016;27(10):1928-1940.
3. Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol.* 2017;35(35):3898-3905.
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5. Morschhauser F, Awada A, Machiels JP, et al. Pharmacodynamic study of copanlisib in patients with non-Hodgkin's lymphoma and advanced solid tumors: confirmation of on-target PI3K inhibitory activity [ASH abstract 1256]. *Blood.* 2017;130(suppl 1).

Commentary: This pooled safety analysis focused on trials in which copanlisib was administered intermittently instead of continuously. The safety profile of intermittent copanlisib appeared tolerable—and is in some ways better than continuous inhibitors—although the hyperglycemia and hypertension require some attention.

Results From a Phase 1/2 Study of INCB050465, a Potent and Highly Selective PI3Kδ Inhibitor, in Patients With Relapsed or Refractory B-Cell Malignancies

Dr Andres Forero-Torres and colleagues presented results of the dose-escalation and monotherapy expansion cohorts of the phase 1/2 CITADEL-101 trial of INCB050465 and itacitinib in patients with previously treated B-cell malignancies.[1] Results indicated a tolerable

safety profile and suggested clinical efficacy.[1] This analysis evaluated 72 patients with baseline tumor subtypes of NHL, Hodgkin lymphoma, chronic lymphocytic leukemia, and Waldenström macroglobulinemia. The NHL subtypes were diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, mantle cell lymphoma, and MZL. Forty-three patients had received 3 or more prior systemic regimens. The patients' median age was 66 years (range, 30-89 years).

The protocol began with a single-patient cohort receiving 5 mg of INCB050465 once daily. Next was a 3-plus-3 design, with doses of 10 mg/day to 45 mg/day. An evaluation of pharmacokinetics/pharmacodynamics led to expansion of the 20-mg once daily and 30-mg once daily cohorts. The treatment schedule was modified to once weekly dosing after week 9. The median duration of exposure was 16.4 weeks (range, 1-85.7 weeks).

Response was evaluable in 69 patients (96%). Objective responses occurred at all doses, except 5 mg daily. Objective response rates were 53% in NHL, 33% in chronic lymphocytic leukemia, 20% in Hodgkin lymphoma, and not evaluable in Waldenström macroglobulinemia. Among patients with NHL, 93% of the responses occurred by the first evaluation at week 9.

No dose-limiting toxicities were reported. Discontinuation of therapy occurred in 76% of patients, most frequently owing to disease progression (40%) and treatment-emergent AEs (19%). Treatment-emergent AEs also resulted in dose interruption (42%) and dose reduction (6%). Among the 16 patients with NHL who received once-weekly dosing, none discontinued therapy based on treatment-emergent AEs. The most common non-hematologic, all-grade, treatment-emergent AEs were nausea (36%) and diarrhea/colitis (36%). Grade 3/4 hematologic treatment-emergent AEs included neutropenia (grade 3, 14%; grade 4, 6%) and thrombocytopenia (grade 3, 4%; grade 4, 6%). All-grade serious treatment-emergent AEs occurred in 40% of patients, and included diarrhea/colitis (11%).

The authors concluded that INCB050465 demonstrated a manageable safety profile in patients with relapsed or refractory B-cell malignancies. Clinical efficacy was promising, particularly in patients with NHL. Responses were rapid, deep, and durable.

Reference

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Commentary: This trial evaluated the PI3-kinase delta inhibitor INCB050465. An interesting aspect of this trial is that treatment began with a daily dose, and then switched to weekly dosing after 9 weeks. The hypothesis is that it may be possible to maintain efficacy with less frequent dosing, which could reduce side effects and keep patients safely on treatment for longer durations. The clinical efficacy was promising, particularly in patients with indolent NHL.

Efficacy of Copanlisib Monotherapy in Patients With Relapsed or Refractory Marginal Zone Lymphoma: Subset Analysis From the CHRONOS-1 Trial

Dr Martin Dreyling and colleagues presented updated efficacy results on the subset of patients with MZL enrolled in the phase 2 CHRONOS-1 trial.[1,2] Among the 142 patients enrolled in CHRONOS-1, 16.2% had MZL. Their median age was 69 years (range, 39-81 years), and their median prior lines of therapy was 3. The objective response rate was assessed via independent radiologic review after at least 4 treatment cycles.[3]

Most patients in this subset had nodal MZL (65.2%), and 4 patients each (17.4%) had mucosa-associated lymphoid tissue lymphoma or splenic MZL. Patients received a median of 5.8 cycles of therapy, with a median duration of treatment of 23 weeks (range, 1-138 weeks). Dose interruptions or delays occurred in 91.3%, and dose modifications were reported in 95.7%.

The objective response rate was 69.6%. Complete responses occurred in 13.0% of patients, all of whom had splenic MZL. Among the patients with nodal MZL, 80.0% experienced an objective tumor response (Figure 5). At the time of data cut-off, the median duration of response had not been reached (range, 1-23.9 months). Responses appeared rapid and durable, and 73.9% of patients experienced a reduction in the target lesion from baseline. This reduction was at least 50% in 60.9%. Responses at 9 months were estimated in 85.0% of patients.

Across the overall CHRONOS-1 study population, at least 1 treatment-emergent AE occurred in 98.6% of patients, and 52.1% of patients experienced at least 1 serious treatment-emergent AE. The most common all-grade treatment-emergent AEs were hyperglycemia (50.7%), diarrhea (33.8%), decreased neutrophil count (31.7%), fatigue (31.0%), and hypertension (30.3%). The authors concluded that these results indicate promising efficacy for copanlisib monotherapy in patients with relapsed or refractory MZL. Responses were rapid and durable, and the overall safety profile was manageable.

References

1. Dreyling M, Panayiotidis P, Egyed M, et al. Efficacy of copanlisib monotherapy in patients with relapsed or refractory marginal zone lymphoma: subset analysis from the CHRONOS-1 trial [ASH abstract 4053]. *Blood*. 2017;130(suppl 1).

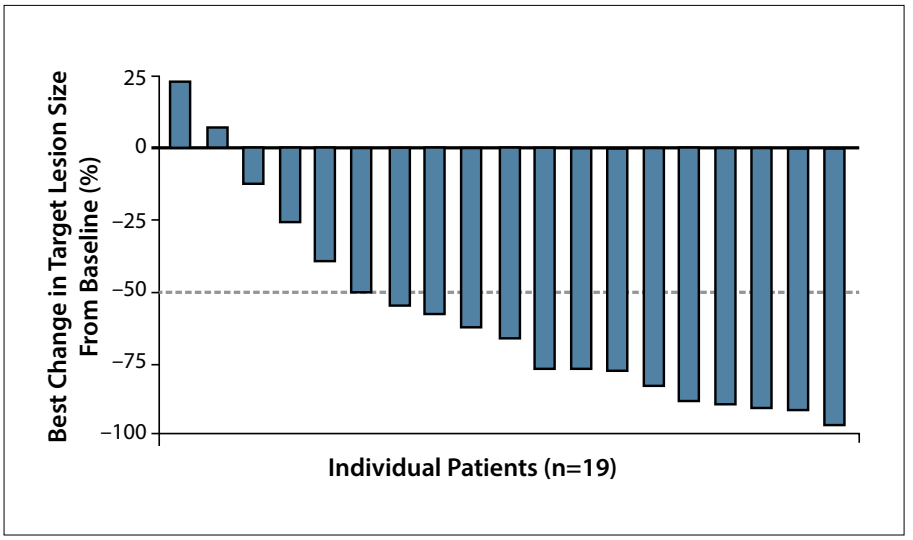

Figure 5. Percent best change from baseline in target lesion size among patients with marginal zone lymphoma treated with copanlisib in the CHRONOS-1 trial. CHRONOS-1, Open-Label, Uncontrolled Phase II Trial of Intravenous PI3K Inhibitor BAY80-6946 in Patients With Relapsed, Indolent or Aggressive Non-Hodgkin's Lymphomas. Adapted from Dreyling M et al. ASH abstract 4053. *Blood*. 2017;130(suppl 1).[1]

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Commentary: PI3-kinase inhibitors have activity in MZL, as was shown in this trial. It is expected that PI3-kinase inhibitors would be effective in this setting. The results from this trial are encouraging. The challenge is to obtain FDA approval of a drug specifically for MZL.

CC-122, a Novel Cereblon Modulating Agent, in Combination With Obinutuzumab in Patients With Relapsed and Refractory B-Cell Non-Hodgkin Lymphoma

Dr Jean-Marie Michot presented updated safety and efficacy results for a phase 1 trial of obinutuzumab combined with CC-122 in patients with relapsed/refractory B-cell NHL.[1] Data were gathered from an additional 12 months of follow-up. Preliminary results from this trial showed promising efficacy in patients with relapsed/refractory B-cell NHL.[2] The study evaluated 44 patients with relapsed/refractory NHL: 19 patients with DLBCL, 24 with follicular lymphoma, and 1 with MZL.[1] CC-122 was administered in escalated oral doses, and the intravenous dose of obinutuzumab was fixed at 1000 mg. The median duration of treatment was 23.6 weeks (range, 3.4-87.0 weeks).

The ORR across cohorts was 68%, and the complete response rate was 27%. Among all patients, the median progression-free survival was 11.3 months. In patients with DLBCL, the ORR was 47% and the complete response rate was 11%. In patients with follicular lymphoma/MZL, the ORR was 84% and the complete response rate was 40%. At 12 months, rates of overall response, complete response, and progression-free survival did not differ among patients with follicular lymphoma that had relapsed early or that was refractory to both rituximab and chemotherapy as compared with the rest of the cohort.

Dose reductions of CC-122, which occurred in 32% of patients, were all owing to AEs. Dose interruptions occurred in 84% of patients, mostly owing to AEs. Dose-limiting toxicities consisted of 1 case of grade 4 neutropenia and another of grade 5 tumor flares. The most common grade 3/4 treatment-emergent AEs were neutropenia (55%) and thrombocytopenia (26%).

References

1. Michot JM, Bouabdalla R, Doorduijn JK, et al. CC-122, a novel cereblon modulating agent, in combination with obinutuzumab (GA101) in patients with relapsed and refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) [ASH abstract 411]. *Blood*. 2017;130(suppl 1).
2. Michot JM, Doorduijn JK, Bouabdallah R, et al. A phase 1b study of CC-122 in combination with obinutuzumab (GA101) in relapsed or refractory diffuse large B-cell lymphoma and indolent non-Hodgkin lymphoma [ASH abstract 4199]. *Blood*. 2016;128(suppl 1).

Commentary: There are other mechanisms of action that clearly have activity in follicular lymphoma, beyond anti-CD20, cytotoxic chemotherapy, and PI3-kinase inhibition. Immunomodulatory drugs (IMiDs), such as lenalidomide, target cereblon and have activity in follicular lymphoma. In the future, it is possible that lenalidomide will be FDA-approved for the treatment of follicular lymphoma. CC-122, which more specifically targets cereblon, may be another option. It is not yet known how CC-122 differs from IMiDs. In early clinical trials, CC-122 had activity in patients with non-Hodgkin lymphomas, as expected.


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