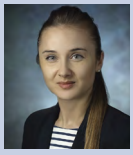
Relapsed/Refractory Multiple Myeloma, DLBCL, and CLL: 2023 ASCO Annual Meeting Highlights for the Advanced Practitioner



Oxana Megherea, PharmD, BCOP, of the Hospital of the University of Pennsylvania, discusses the MonumenTAL-1 study of talquetamab in relapsed/refractory multiple myeloma. She also summarizes a subgroup analysis of elderly patients enrolled in the phase III POLARIX study and results of a phase III study of ibrutinib, obinutuzumab, and venetoclax vs. ibrutinib plus obinutuzumab (IO) for treatment-naive older patients with chronic lymphocytic leukemia.

Abstract 8036

Phase II Results of MonumenTAL-1: Talquetamab for Relapsed/Refractory Multiple Myeloma

By JADPRO Staff

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Updated results from the pivotal phase I/II MonumenTAL-1 study of the investigational bispecific antibody talquetamab for patients with relapsed/refractory multiple myeloma (RRMM) revealed improved clinical outcomes and increased response rates in patients with RRMM treated with talquetamab—a GPRC5D × CD3 bispecific antibody.

A total of 339 patients with relapsed or refractory multiple myeloma were recruited for the study. Patients were intolerant to or progressed on established therapies (phase I) or had ≥ 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody. 288 patients received talquetamab 0.4 mg/kg weekly (n = 143) or 0.8 mg/kg of talquetamab biweekly (n = 145) with step-up doses. 51 patients who had received prior T-cell redirection therapy were randomly assigned to receive either dose.

Results

The overall response rates to treatment with talquetamab were 74%, 73%, and 63% for the once- and twice-weekly talquetamab-treated groups and the T-cell redirection therapy groups, respectively. These observed rates were also consistent across all treatment subgroups. Furthermore, the median progression-free survival was 7.5 months in

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the once-weekly talquetamab cohort, 11.9 months in the twice-weekly talquetamab cohort, and 5.1 months in the T-cell redirection therapy cohort, according to the investigators.

Adverse Events

Treatment-related adverse events included cytokine release syndrome (79% for once-weekly talquetamab vs. 75% for twice-weekly talquetamab vs. 77% for T-cell redirection therapy), dysgeusia (50% vs. 48% vs. 61%), nail-related conditions (54% vs. 53% vs. 61%), and skin-related conditions (56% vs. 71% vs. 69%). Rates of infection were 58%, 65%, and 71% with low rates of opportunistic infections, respectively. There were no talquetamab-related deaths.

Conclusion

"Pivotal phase II talquetamab data showed > 70% overall response rate in heavily pretreated patients with RRMM. High response rates were also seen in patients with prior T-cell redirection therapy. The safety profile was clinically manageable with low rates of high-grade infections and talquetamab discontinuations," said Carolina Schinke, MD, Associate Professor of Medicine at the Myeloma Center at the University of Arkansas for Medical Sciences and principal investigator.

The Advanced Practitioner Perspective

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Talquetamab is a bispecific antibody targeting CD3 and GPRC5D, redirecting T cells to mediate the killing of GPRC5D-expressing multiple myeloma cells. The current abstract reports on the use of talquetamab in patients with relapsed/refractory multiple myeloma after three or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Patients received talquetamab 0.4 mg/kg subcutaneously once per week or 0.8 mg/kg subcutaneously every other week with an initial step-up dose schedule to mitigate the risk of cytokine release syndrome (CRS). Patients had a median number of prior lines of therapy of five to six regimens, with approximately three quarters of patients having triple-class refractory disease and one third of patients having penta-drug refractory disease. The overall response rate (ORR) was 74% in the weekly dosing cohort and 73% in the every other week dosing cohort, with a median progression-free survival of 7.5 and 11.9 months for the weekly and the every other week dosing cohorts, respectively.

With several T-cell redirecting therapies currently approved in the multiple myeloma space, the role of talquetamab in patients with prior T-cell redirecting therapy is an active area of interest. The investigators report on a cohort of 51 patients with a history of prior T-cell redirecting therapies. Seventy-one percent of these patients received a prior chimeric antigen receptor (CAR) T-cell therapy, 35% of patients received a bispecific antibody, and 6% of patients received both. The ORR in this patient cohort was 63%, and the median progression-free survival at the time of this report was 5.1 months, highlighting the activity of talquetamab in this patient population. Treatment-emergent adverse effects in the entire cohort of patients included CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), skin and nail-related adverse effects, and infections.

Implications for the Advanced Practitioner

Talquetamab has demonstrated encouraging results, inducing deep and durable responses in heavily pretreated multiple myeloma patients, including patients with a history of prior T-cell redirecting therapy. The drug is an off-the-shelf product, allowing for prompt initiation of therapy, and has a manageable toxicity profile. An initial step-up dosing schedule is required to mitigate the risk of CRS, as well as its administration in centers with the necessary expertise to administer the drug and manage CRS and ICANS. Based on the experience with currently approved T-cell redirecting agents in this space, a significant collaborative effort among members of the health-care team will be necessary to ensure proper training and education on administration, toxicity monitoring, and management.

Infectious risk with talquetamab warrants consideration. A report on infections occurring in patients treated with talquetamab was presented at the meeting, suggesting that infections occurred less frequently in patients treated with talquetamab compared with patients treated with B-cell maturation antigen (BCMA)-targeted T-cell–based therapies currently approved for multiple myeloma, with low rates of grade 3 and 4 infections and most infectious episodes occurring within the first 100 days of treatment with the drug. As investigative efforts on the use of talquetamab alone or in combination with other agents continue, an evaluation of the infectious risk with the agent will be paramount to ensure the implementation of adequate supportive care measures to mitigate the risk of infections.

Disclosure: Dr. Megherea has no conflicts of interest to disclose.

Abstract 7518

Subgroup Analysis of Elderly Patients With Diffuse Large B-Cell Lymphoma in the Phase III POLARIX Study

By JADPRO Staff

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In a phase III study, researchers explored the efficacy and safety of polatuzumab vedotin (Polivy) combined with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) compared with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in elderly patients (aged ≥ 70 years) with previously untreated diffuse large B-cell lymphoma (DLBCL). The study, presented at the 2023 ASCO Annual Meeting, aimed to determine the most effective and safe treatment regimen for this population of elderly patients.

The POLARIX study randomized patients with previously untreated DLBCL 1:1 to receive 6 cycles of Pola-R-CHP or R-CHOP, in addition to two cycles of rituximab. 284 patients were analyzed for efficacy, with 141 patients in the Pola-R-CHP arm and 143 patients in the R-CHOP arm. 280 patients were analyzed for safety, with 137 patients in the Pola-R-CHP arm and 143 patients in the R-CHOP arm. The median age was 74 years (range 70–80), and 69.7% had an International Prognostic Index score of 3 to 5. Most patients in either arm received all 6 doses of polatuzumab vedotin or vincristine (88.3% and 91.6% in the Pola-R-CHP and R-CHOP arms, respectively).

Results

At a median follow-up of 24.2 months, the risk of progression, relapse, or death was lower with Pola-R-CHP compared with R-CHOP (hazard ratio, 0.64; 95% confidence interval = 0.41–0.99). Overall survival and disease-free survival results also favored the Pola-R-CHP group. The two treatment regimens showed comparable safety profiles.

Adverse Events

Death by any cause occurred in 14.2% and 19.6% of patients treated with Pola-R-CHP and R-CHOP, respectively. Both groups experienced similar rates of adverse events, including peripheral neuropathy, neutropenia, and infection.

Conclusion

"Pola-R-CHP and R-CHOP demonstrated similar safety profiles in patients aged ≥ 70 years with previously untreated DLBCL," said Bei Hu, MD, of Atrium Health Department of Hematologic Oncology and Cellular Therapy, Lymphoma Section. "The risk-benefit profile favored Pola-R-CHP vs. R-CHOP."

The Advanced Practitioner Perspective

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Polatuzumab vedotin is an antibody-drug conjugate that targets CD79B, which is present on malignant B cells, including diffuse large B-cell lymphoma (DLBCL). In an effort to improve outcomes in newly diagnosed patients with DLBCL, the POLARIX trial evaluated the use of a modified rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen—Pola-R-CHP (replacing vincristine with polatuzumab vedotin)—and compared it with R-CHOP in patients with newly diagnosed intermediate and high-risk DLBCL.

A prior report showed a progression-free survival (PFS) benefit in patients treated with Pola-R-CHP compared with patients treated with R-CHOP that was sustained at a median follow-up of 39.7 months and similar safety profiles for the two regimens. As elderly patients may have a harder time tolerating multidrug regimens, the current report sought to evaluate the efficacy and safety of this intervention in patients aged 70 years or older at enrollment. Patients received 6 cycles of Pola-R-CHP or R-CHOP, followed by 2 cycles of rituximab monotherapy. The primary efficacy endpoint was investigator-assessed PFS.

Two hundred and eighty-four and 280 patients were included in the efficacy and safety analyses, respectively, with baseline characteristics similar in both arms. The median age of the patient cohort was 74 years, and 69.7% of patients had an International Prognostic Index score of 3 to 5. At a median follow-up of 24 months, patients in the Pola-R-CHP arm had a significantly lower risk of progression, relapse, or death compared with patients treated in the R-CHOP arm. The overall survival rates were similar between the groups at the time of this report, 86.2% and 82.8% for Pola-R-CHP and R-CHOP, respectively.

The toxicity profiles were similar between the intervention arms, with similar rates of neutropenia, grade 3 and 4 infections, and peripheral neuropathy. The rates of grade 3 to 4 febrile neutropenia were higher in the intervention arm at 21.2% and 8.4% for Pola-R-CHP and R-CHOP, respectively, however the rate of infection-related deaths was lower in the intervention arm.

Implications for the Advanced Practitioner

Pola-R-CHP is an effective regimen in the older population with newly diagnosed DLBCL. While the rate of febrile neutropenia was higher with Pola-R-CHP, administering granulocyte colony-stimulating factors with each cycle of Pola-R-CHP and initiating patients on antimicrobial prophylaxis per local institutional guidelines may help mitigate the risk of infections and cytopenias with this regimen. Notably, the need for close monitoring for peripheral neuropathy, which may require delays or dose reduction, is important with this regimen despite omitting the neurotoxic agent vincristine, as monomethyl auristatin E, the active payload in polatuzumab vedotin, is a microtubule inhibitor that has been associated with peripheral neuropathy.

Disclosure: Dr. Megherea has no conflicts of interest to disclose.

Abstract 7500

New Findings on CLL, COVID-19, and Treatment With Obinutuzumab Plus Venetoclax

By JADPRO Staff

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The phase III, multicenter Alliance A041702 trial examined initial therapy for older patients with previously untreated chronic lymphocytic leukemia (CLL). The study investigated the regimen of ibrutinib (Imbruvica) plus venetoclax (Venclexta) plus obinutuzumab (Gazyva) compared with the doublet of ibrutinib plus obinutuzumab.

The study is the successor trial to the A041202 study, which demonstrated a superior progression-free survival for either ibrutinib given alone or in combination with rituximab compared with chemoimmunotherapy with bendamustine plus rituximab. Although ibrutinib produces long-term durable remissions for many patients, patients sometimes have difficulties with the indefinite administration of therapy in terms of long-term toxicity and sometimes financial implications of a continuous treatment. Therefore, the purpose of this study was to see whether adding venetoclax to this doublet might allow more patients to have undetectable minimal residual disease and complete responses and thus be able to discontinue therapy.

Patients were randomized to the triplet ibrutinib, venetoclax, obinutuzumab (IVO) or the doublet ibrutinib plus obinutuzumab (IO). After a year of treatment, all patients underwent a response evaluation. Those patients who were on the doublet arm all then continued ibrutinib indefinitely, and the patients on the triplet arm underwent a response-adapted either discontinuation of ibrutinib or continuation of therapy.

The reason the study was presented so early was because it met its futility boundary, meaning that IVO is not superior to IO. However, importantly, the authors suspect that this study may have been confounded somewhat by the COVID-19 pandemic, where the death rate from COVID-19 was higher in patients treated on the triplet arm than those treated on the doublet arm. Outside of this, the toxicity profile between the two regimens were relatively similar. There was a slightly higher risk of hematologic toxicity with the addition of venetoclax, but nonhematologic toxicity in general was fairly similar on the two arms.

Results

The progression-free survival (PFS) at the time of the presentation at 14 months of follow-up was similar between the triplet and the doublet arms, with the PFS trending toward favoring the doublet slightly over the triplet. However, when censoring patients who died of COVID-19, the trend was reversed, where there was a trend toward improved PFS with the triplet vs. the doublet. The authors emphasized the importance of following this study in the long term to see if some patients would benefit from the discontinuation of therapy.

Conclusion

"In addition to long-term follow-up on this study, we are going to continue, in the Alliance for Clinical Trials in Oncology, to investigate frontline therapy for older patients with CLL, with the goal of really trying to determine what is the optimal therapy for this patient group," commented Jennifer A. Woyach, MD, of The Ohio State University Comprehensive Cancer Center.

The Advanced Practitioner Perspective

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The Bruton tyrosine kinase (BTK) inhibitor, ibrutinib, with or without obinutuzumab, is a standard-of-care regimen for newly diagnosed elderly patients with chronic lymphocytic leukemia (CLL). Ibrutinib alone rarely leads to deep remissions, thus requiring the use of continued administration of the drug until progression of disease or intolerance. Continuous drug regimens may be associated with increased side effects, interactions with concomitant medications, high treatment costs, and drug resistance. Combination treatments in this setting is an exciting area of research, with the goal of combining agents to deepen responses and allow for the possibility of fixed-duration treatment in patients with undetectable minimal residual disease (uMRD).

The current study sought to evaluate if the addition of venetoclax, a once-daily, oral inhibitor of B-cell lymphoma-2 (BCL-2), to ibrutinib and obinutuzumab with response-guided discontinuation of ibrutinib confers a progression-free survival (PFS) benefit compared with continuous ibrutinib and obinutuzumab in newly diagnosed elderly patients with CLL. Ibrutinib and obinutuzumab were dosed in standard fashion. Venetoclax was added to ibrutinib and obinutuzumab in the interventional arm on day 1 of cycle 3 to mitigate the risk of tumor lysis syndrome and continued for 12 cycles. After 14 cycles of treatment, all patients underwent disease response assessment, including CT scans and bone marrow biopsy with central MRD assessment by flow cytometry. In patients in the intervention arm that were found to have uMRD, ibrutinib was stopped. All other patients continued on ibrutinib until progression or unacceptable toxicity.

Four hundred and sixty-five patients were evaluated. The median age was 74 years, and Rai stage III to IV was seen in 55% and del17p in 13% of patients. At 14 months of follow-up, the PFS rates in the ibrutinib and obinutuzumab arm were 87.5% and in the venetoclax, ibrutinib, and obinutuzumab arm were 85%, crossing the futility boundary that was predefined for the study. While responses were deeper in the intervention arm, with complete response and uMRD rates at 68.5% vs. 31.3% and 86.8% vs. 33.3%, respectively, the PFS in the venetoclax-containing arm was not impacted by the depth of response at the time of this report. The lack of PFS benefit may have been attributed to an imbalance in the COVID-related deaths in the two treatment arms, with patients in the intervention arm having a higher risk of dying due to COVID compared with patients in the control arm. After censoring for COVID-related deaths, the PFS favored the intervention arm, however, it did not reach statistical significance.

Implications for the Advanced Practitioner

From a safety perspective, the addition of venetoclax to ibrutinib and obinutuzumab resulted in significantly higher rates of grades 3 to 5 hematologic adverse events, while the grades 3 to 5 nonhematologic adverse effects were similar in both treatment arms.

At the time of this report, the addition of venetoclax to ibrutinib and obinutuzumab with response-guided discontinuation of ibrutinib did not confer a PFS benefit, and the current results do not support the use of this regimen in older patients with CLL.

Disclosure: Dr. Megherea has no conflicts of interest to disclose.