2022–2023 Drug Updates in Hematologic Malignancies

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Presenter's disclosures of conflicts of interest are found at the end of this article.

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Abstract

At JADPRO Live 2023 in Orlando, Rebecca L. Rezac, PharmD, BCOP, summarized key information on US Food and Drug Administration approvals from late 2022 to late 2023. Dr. Rezac described indications, mechanisms of action, and monitoring and management of side effects of new therapies for hematologic malignancies.

At the Drug Updates session at JADPRO Live, Rebecca L. Rezac, PharmD, BCOP, a board-certified oncology pharmacist at the University of Colorado Hospital in the UCHealth Blood Disorders and Cell Therapies Center, reviewed recent US Food and Drug Administration (FDA) approvals in hematologic malignancies.

TECLISTAMAB FOR MM

Teclistamab was the first bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager approved for adult patients with relapsed or refractory multiple myeloma who received at least four prior lines of therapy, including at least one proteasome inhibitor, one immunomodulatory drug, and one anti-CD38 monoclonal antibody.

The MajesTEC-1 trial was a phase I/II study in relapsed/refractory multiple myeloma. Just over a quarter of patients had high-risk cytogenetics, the median prior lines of therapy for patients included in the trial was five, and about 30% of patients were penta-refractory to prior therapy. The overall response rate (ORR) was 63%, and the median time to response was 1.2 months. The median duration of response was 18.4 months. Median progression-free survival (PFS) was just over 11 months, and there were 44 patients who were negative for measurable residual disease after therapy.

Dosing, Monitoring, and Adverse Event Management

Teclistamab has a black box warning for cytokine release syndrome (CRS) and neurotoxicity. It is also Risk Evaluation and Mitigation Strategy (REMS) restricted and therefore requires registration of both the pharmacy and the prescriber.

As with other bispecific engagers approved in this space, such as talquetamab and elranatamab, there is a step-up dosing approach. Teclistamab requires admission for the

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step-up dosing and the first full dose. There are two step-up doses required to be given prior to administering the final treatment dose of 1.5 mg/kg. Teclistamab requires premedication with acetaminophen, diphenhydramine, and a corticosteroid for all step-up doses and the first full dose. After the full dose on day seven of cycle 1 is completed, and as long as there are no complications, the patient can be discharged and continue receiving weekly dosing in the outpatient setting.

"If patients experience adverse events, additional days may be required to allow for recovery before the next dose," noted Dr. Rezac.

Patients with CRS may have fever, chills, hypotension, tachycardia, or hypoxia. The majority of CRS cases were grade 1 or 2.

Patients with immune effector cell–associated neurotoxicity syndrome (ICANS) may have neurologic changes, mental status changes, coordination difficulties, headache, or somnolence. All-grade ICANS was reported at 6% of patients.

TALQUETAMAB FOR MM

Talquetamab is approved in the same setting for relapsed/refractory multiple myeloma after four prior lines of therapy. It binds to and engages CD3 but also a new target, GPRC5D, which is expressed on myeloma plasma cells.

"Because of this unique target, it has some unique associated adverse effects in the mouth, skin, and nails," said Dr. Rezac. "Patients can experience taste and nail changes, dry mouth, dry skin or rash, and nail discoloration due to GPRC5D expression on keratinized tissue of the skin and tongue."

The MonumenTAL-1 trial was a phase I/II open-label study looking at relapsed/refractory multiple myeloma. Notably, patients had a similar median prior lines of therapy as seen with teclistamab, which was six. Additionally, 30% of patients were penta-refractory to prior therapy.

The full phase I data has not yet been published, but so far the ORR to the weekly dosing of 0.4 mg/kg is 70%, and the ORR to every-2-weeks dosing at 0.8 mg/kg is 64%.

Dosing, Monitoring, and Adverse Event Management

Talquetamab has a black box warning for CRS and ICANS and is REMS restricted.

There are two options for dosing: weekly at 0.4 mg/kg and biweekly with the dose doubled to 0.8 mg/kg. The differences between these two dosing strategies include an additional step-up dose in the biweekly schedule and different final target doses. As with teclistamab, there is some variation allowable during the step-up dosing phase in how many days are required to separate each dose in order to allow for recovery from adverse events if they occur.

ELRANATAMAB FOR MM

Elranatamab is a bispecific antibody approved for relapsed/refractory multiple myeloma. It engages with CD3 and BCMA.

The MagnetisMM-3 trial was a phase II open-label single-arm trial. Just over a quarter of patients had a high-risk cytogenetic profile and over 40% of patients were penta-refractory to prior therapy. The MagnitisMM-3 study design had two separate cohorts: Cohort A looked at patients who did not have prior BCMA therapy and cohort B looked at patients who had prior BCMA-directed therapy. In cohort A, the ORR was 61% for those patients without prior BCMA-directed treatment.

Complete response was achieved by 35% of patients, and time to response was a median of 1.2 months. In patients who achieved CR or better, just under 90% of those patients were negative for measurable residual disease.

Dosing, Monitoring, and Adverse Event Management

Elranatamab has a black box warning for CRS and ICANS and is REMS restricted.

There are two step-up doses administered on days 1 and 4, with a final treatment dose of 76 mg given on day eight. Doses are administered weekly through week 24 and then biweekly after week 25. Elranatamab requires premedications (acetaminophen, dexamethasone, and diphenhydramine) to be administered 1 hour prior to the first two step-up doses and the final treatment dose. Premedications can be continued for patients who have had a break in therapy for longer than 6 weeks or if they require therapy reinitiation for any reason.

EPCORITAMAB FOR DLBCL

Epcoritamab is one of the bispecific antibodies approved for use in lymphoma patients. It is

approved for relapsed/refractory DLBCL after two or more prior lines of therapy. It binds to CD3 on T cells and CD20 expressed on the lymphoma cell surface.

The EPCORE NHL-1 trial was a phase I/II single-arm study. About 70% of patients had de novo DLBCL and 30% had transformed DLBCL. Just under 40% of patients had four or more prior lines of therapy. Approximately 40% of patients had already received prior chimeric antigen receptor (CAR) T-cell therapy at the time of inclusion in this study. Of those 40% of patients, about 75% had progressed within 6 months of CAR T-cell therapy.

The ORR was 63.1%, and the complete response rate was 38.9%. The median PFS was 4.4 months, and OS has not yet been reached. The duration of response was 12 months, and the time to response with epcoritamab was 1.4 months.

Dosing, Monitoring, and Adverse Event Management

Epcoritamab has a black box warning for CRS and ICANS. It is given by the subcutaneous route. Notably, epcoritamab prescribing information specifies giving prophylaxis for *Pneumocystis jiroveci* pneumonia (PJP) and herpes virus. Epcoritamab requires premedication, specifically prednisolone 100 mg or dexamethasone 15 mg or a steroid equivalent with acetaminophen and diphenhydramine. Premedications are only required for cycle 1 and only continued for patients with grade 2 or 3 CRS with any dose.

Cycles are 28 days in length, with cycle 1 requiring a two-dose step-up dosing schedule prior to the first full treatment dose of 48 mg. For the first full treatment dose, patients are required to be admitted for monitoring. For cycles 2 and 3, there is a dose-dense schedule with weekly dosing. For cycles 4 through 9, dosing is reduced to a biweekly schedule and for cycles 10 and beyond, epcoritamab is given once a month.

GLOFITAMAB FOR DLBCL AND LBCL

Glofitamab is approved for patients with DLBCL in the relapsed/refractory setting, as well as for patients with large B-cell lymphoma arising from follicular lymphoma after two or more lines of therapy. The targets are CD3 receptors on the T-cell surface and CD20 expressed on the lymphoma cell surface.

The study evaluating glofitamab was a phase II single-arm dose expansion cohort study. Patients had relapsed/refractory DLBCL, transformed follicular lymphoma, and high-grade B-cell lymphoma. Thirty percent of patients were refractory to prior CAR T-cell therapy. Approximately 40% of patients achieved a complete response, and the median time to response was 42 days.

Dosing, Monitoring, and Adverse Event Management

Glofitamab has a black box warning for CRS. Other adverse events include ICANS, serious infections, tumor flare, and rash. Glofitamab is given intravenously, which differs from epcoritamab. Required premedications include dexamethasone 20 mg, acetaminophen, and diphenhydramine. In contrast with epcoritamab, the treatment cycles for glofitamab are 21 days in length. For cycle 1 day one, patients do not receive glofitamab and will instead receive obinutuzumab at a dose of 1,000 mg to allow for B-cell depletion, which helps reduce the risk for CRS.

The first step-up dose of 2.5 mg on day eight should be given in the inpatient setting in order to monitor patients for adverse events. Step-up dose two is given on day 15 of cycle 1 and then for cycles 2 through 12. Patients will only receive treatment on day 1 of each cycle at a dose of 30 mg.

Acetaminophen and diphenhydramine are required to be continued throughout the entire treatment duration. Dexamethasone can be removed after cycle 3 for patients who did not experience CRS but should continue to be included as a premedication for patients who had any grade of CRS throughout their initial treatment.

MOSUNETUZUMAB FOR FL

Mosunetuzumab is approved for patients with relapsed/refractory follicular lymphoma after two or more prior lines of therapy. It binds and engages with the CD3 receptor on the T-cell surface and CD20 on the lymphoma cell surface.

Patients in the trial evaluating mosunetuzumab had a median of three prior lines of therapy before inclusion in the study. Just under 50% of these patients had stage four disease. Sixty percent

of patients achieved a complete response, and of those 60% with a CR, 70% were able to maintain their response for at least 18 months. The median PFS was just under 18 months. Overall survival was just under 90 months, and the duration of response was 22.8 months.

Dosing, Monitoring, and Adverse Event Management

Mosunetuzumab has a 21-day treatment cycle length. There are two step-up doses on days 1 and 8, with progression to the full dose of 60 mg on day 15. For cycle three and subsequent dosing, the dose drops back down to 30 mg.

Mosunetuzumab is given for eight cycles. After 8 cycles, patients should be assessed for response. For patients who have a complete response, no further treatment is needed. For patients who have a partial response or maintained stable disease, they can receive an additional nine cycles for a total of 17 cycles of treatment. Mosunetuzumab is given intravenously over four hours in cycle 1, but infusion time can be reduced to 2 hours in cycle two.

Premedications include a corticosteroid, an antihistamine, and an antipyretic. Dr. Rezac discussed infection considerations and what advanced practitioners' particular institutions might want to implement, potentially agent-specific or across the board.

"Our institution decided to go ahead and implement PJP and herpes simplex virus prophylaxis for all patients receiving a bispecific for lymphoma. This way, expectations are clear on which agents need these prophylactic medications implemented," commented Dr. Rezac.

Advanced practitioners should monitor for cytopenias by watching the complete blood count at routine intervals before each dose. There is a risk for tumor flare.

PIRTOBRUTINIB FOR MCL

Pirtobrutinib is approved for patients with relapsed/refractory mantle cell lymphoma after receiving at least two prior systemic therapies, including a BTK inhibitor. It reversibly binds to the ATP binding site of BTK. This prevents malignant B cells from proliferating. Pirtobrutinib maintains efficacy even in patients who have *BTK* C481S mutations.

Its landmark trial is the BRUIN trial, which was a phase I/II single-arm trial. This trial included patients who were 18 years and older with a B-cell malignancy. There were 120 patients with mantle cell lymphoma included in the trial, and their median number of prior lines of therapy was three. The ORR in these patients was 50%, and this included 13% of patients who achieved a complete response and about 38% of patients who achieved a partial response. The median duration of response was 8.3 months at the initial follow-up.

Dosing, Monitoring, and Adverse Event Management

Pirtobrutinib is dosed orally at 200 mg once daily. There are class effects of cardiovascular adverse events with BTK inhibitors, specifically atrial fibrillation and flutter, that advanced practitioners should be aware of. Additionally, there is a risk for second primary malignancies, which could include skin cancer but also other solid tumors. Therefore, it is important for patients to continue monitoring their skin. Other more common adverse events that are possible include myelosuppression, and therefore a risk for bleeding and infection, as well as an increase in serum creatinine.

QUIZARTINIB FOR *FLT3*-ITD+ AML

In the acute myeloid leukemia (AML) space, quizartinib is FDA approved for patients who have newly diagnosed *FLT3* internal tandem duplication (ITD)+ AML. It is used in conjunction with standard 7 + 3 induction chemotherapy and cytarabine consolidation.

Quizartinib binds to the inactive FLT3 receptor and prevents receptor activation and downstream signaling. It differs from other agents already on the market, like midostaurin and gilteritinib, in that these are considered to be type 1 FLT3 inhibitors. Therefore, they have activity both against the FLT3-tyrosine kinase domain and ITD. Quizartinib is a type 2 FLT3 inhibitor, meaning that it only has activity in the setting of FLT3-ITD+ but is considered to be more potent for these patients.

The QuANTUM-First trial was a phase III randomized double-blind placebo-controlled trial. Notably, the majority of patients had intermediate cytogenetic risk.

The OS hazard ratio (HR) was 0.78, and 55% of patients achieved a complete remission. The composite complete remission was 72%. For patients who received quizartinib, this trial reported a duration of complete response of 38.6 months vs. 12.4 months for patients who received placebo. The relapse-free survival HR was 0.61.

Dosing, Monitoring, and Adverse Event Management

During induction and consolidation, the dose remains the same at 35.4 mg once daily. Quizartinib is given on days 8 through 21 of induction for patients who receive 7 + 3, and for patients receiving the more condensed 5 + 2 regimen, they receive quizartinib on days 6 through 19. Cycles are 28 days in length, and patients can receive up to two cycles of quizartinib with induction. For consolidation, patients receive 2 weeks of treatment on days 6 through 19 of a 28-day cycle for up to four cycles. In the maintenance phase, patients are initiated on a dose of 26.5 mg daily for days 1 through 14.

A patient's corrected QT interval (QTc) is taken into consideration. Quizartinib can only be initiated for patients whose QTc is ≤ 450 ms. If QTc remains ≤ 450 ms on day 15, then the dose of quizartinib can be increased to 53 mg. However, if the QTc is above 500 ms, patients should be maintained on the initial maintenance dose of 26.5 mg daily.

Quizartinib has a black box warning for QT prolongation and torsades de pointes, as well as a risk for cardiac arrest. Because of this warning, it is a REMS-restricted drug.

"It is important to monitor patients throughout treatment for electrolyte abnormalities, specifically hypokalemia and hypomagnesemia, and if those are present, to replete patients appropriately," said Dr. Rezac.

It is recommended that patients receive electrocardiograms at baseline and then weekly during the first month after initiation of the drug and then also at any point during escalation. Quizartinib also has drug-drug interactions with strong inhibitors of CYP3A4.

OLUTASIDENIB FOR *IDH1*+ AML

Olutasidenib is FDA-approved for patients with relapsed or refractory AML with an *IDH1* mutation. *IDH1* mutations occur in 7% to 14% of patients with AML. Olutasidenib is a small-molecule IDH1 inhibitor that reduces 2-Hydroxyglutarate production, which allows for restoration of normal cell differentiation.

"It takes a bit longer to have effect, so patients need to have treatment for at least 6 months before they can be appropriately assessed for clinical response to the drug," noted Dr. Rezac.

Approval was based on a phase I/II single-arm trial, in which 35% of patients achieved a complete remission or complete remission with hematologic recovery. The ORR was 48%, with a median duration of response of just under 26 months. Of 86 patients who were transfusion dependent at baseline, 29 achieved transfusion independence. The median overall survival was 11.6 months.

Dosing, Monitoring, and Adverse Event Management

Olutasidenib requires dosing on an empty stomach. It is dosed at 150 mg orally twice daily.

A main safety consideration is the black box warning for differentiation syndrome. Differentiation syndrome occurred in 16% of patients on trial, with 8% of patients reporting grade 3 or 4 differentiation syndrome. If differentiation syndrome is suspected, clinicians should stop olutasidenib and start corticosteroids. A standard steroid treatment recommendation would be dexamethasone 10 mg intravenously every 12 hours. Dexamethasone should be continued for a minimum of 3 days but can be extended for a longer duration in order to allow for the symptoms to resolve.

Olutasidenib can also be associated with noninfectious leukocytosis. Hydroxyurea can be used for cytoreduction in these patients. It is important to monitor hepatic function; there are specific holding parameters based on the grading of hepatotoxicity. Other more common adverse events include GI upset, mucositis, rash, and generalized arthralgia or fevers. ●

Disclosure

The presenter has no relevant financial relationships to disclose.