

# 2018–2019 Drug Updates in Hematologic Malignancies

PRESENTED BY LAUREN HELD, PharmD, BCOP

From Seattle Cancer Care Alliance, Seattle, Washington

Presenter's disclosure of conflicts of interest is found at the end of this article.

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## Abstract

Lauren Held, PharmD, BCOP, updated attendees on the FDA-approved therapies for initial or expanded indications for hematologic malignancies across the past year, as well as their supporting clinical trial data and best practices for safe and effective dosing and administration, drug monitoring, and adverse event management.

**W**ith the number of drug approvals for hematologic malignancies seemingly increasing every year, it's imperative for advanced practitioners to not only stay up to date and informed but to also understand the data supporting the approval of these drugs. At JADPRO Live 2019, Lauren Held, PharmD, BCOP, a clinical pharmacy specialist in hematology from Seattle Cancer Care Alliance, discussed the pharmacology and indications of medications approved from late 2018 to October 2019 for the management of patients with hematologic malignancies. Dr. Held also summarized the pivotal clinical trial data considered by the U.S. Food & Drug Administration (FDA) when approving new oncologic agents and the impact of these agents in advanced practice.

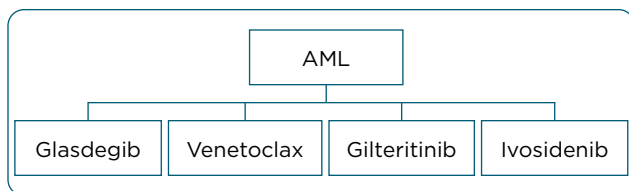
“We're moving away from the large phase III randomized controlled trials, especially with our

acute myeloid leukemia drugs, so it's important to consider the overall side-effect profile, the patient population studies, and the overall clinical efficacy,” said Dr. Held. “All of these factors need to be assessed before giving these drugs to our patients.”

## NEW DRUG APPROVALS AND INDICATIONS IN AML

### Glasdegib for AML (November 2018)

As Dr. Held reported, the sonic hedgehog (Shh) signaling pathway is essential for normal embryonic development and plays a role in adult tissue maintenance, renewal, and regeneration. Glasdegib inhibits smoothed (SMO) involved with downstream signaling effects that lead to cell proliferation and apoptotic suppression. Approval for glasdegib was based on data from a phase II trial of newly diagnosed patients with acute myeloid leukemia (AML) who were randomized to either glasdegib 100 mg daily continuously plus



**Figure 1.** New drug approvals and new indications in acute myeloid leukemia. All are oral therapies.

low-dose cytarabine (20 mg SQ twice daily  $\times$  10 days of each 28-day cycle), or low-dose cytarabine (20 mg SQ twice daily every 28 days).

Data showed a median overall survival with glasdegib plus low-dose cytarabine of 8.3 months vs. 4.3 months with low-dose cytarabine alone (Norsworthy et al., 2019). Complete response rates were 18.2% vs. 2.6% in glasdegib plus low-dose cytarabine vs. low-dose cytarabine, respectively.

Glasdegib is approved for newly diagnosed AML in combination with low dose cytarabine in patients who are older than 75 years of age, or who have comorbidities that preclude the intensive chemotherapy (Figure 1).

#### **Venetoclax for AML (November 2018)**

Venetoclax inhibits B-cell lymphoma-2 (BCL-2) and is approved in combination with azacitidine or decitabine, or low-dose cytarabine in patients at least 75 years old with newly diagnosed AML or who have comorbidities that preclude the use of intensive chemotherapy. At least 30% of patients experienced the following adverse reactions: nausea, diarrhea, cytopenias, constipation, febrile neutropenia, fatigue, vomiting, peripheral edema, pyrexia, pneumonia, dyspnea, hemorrhage, rash, abdominal pain, sepsis, back pain, myalgia, dizziness, cough, oropharyngeal pain, and hypotension.

Approval for venetoclax was based on a non-randomized, open-label phase Ib trial in combination with azacitidine (n = 67) or decitabine (n = 13) in newly diagnosed AML (DiNardo et al., 2019). When venetoclax was combined with azacitidine, 25 patients achieved a complete response (37%), with a median observed time in remission of 5.5 months. In combination with decitabine, 7 patients achieved a complete response (54%), with a median observed time in remission of 4.7 months.

In a non-randomized, open-label phase Ib/II trial in combination with low-dose cytarabine (n

= 61) in newly diagnosed AML, including patients previously exposed to a hypomethylating agent, 13 patients achieved a complete response (21%), with a median observed time in remission of 6 months (Wei et al., 2019).

#### **Gilteritinib for AML (November 2018)**

Gilteritinib is a small molecule that inhibits multiple receptor tyrosine kinases, including cells expressing *FLT3*-ITD and tyrosine kinase mutations (TKD). The former mutation occurs in 25% of cases and confers a poor prognosis, while the latter (*FLT3*-TKD) occurs in 7% to 10% of cases with an unknown prognostic value, said Dr. Held.

Approval for gilteritinib was based on data from the phase III ADMIRAL trial that included 371 patients with relapsed or refractory AML with an *FLT3* mutation. Patients were randomized to receive gilteritinib or salvage chemotherapy. Overall survival was 9.3 months on gilteritinib vs. 5.6 months on chemotherapy (Perl et al., 2017).

#### **Ivosidenib for AML (May 2019)**

Isocitrate dehydrogenase (*IDH*) mutations occur in approximately 20% of patients with AML (6% to 9% of AML cases involve *IDH1* mutations while 8% to 12% of AML cases involve *IDH2*).

As Dr. Held reported, with ivosidenib, an *IDH1* inhibitor, there is a black box warning for differentiation syndrome, which can develop as early as 1 day after the start of therapy and during the first 3 months of treatment. *IDH* differentiation syndrome was seen in 25% of patients with newly diagnosed AML and 19% of patients with relapsed/refractory AML, said Dr. Held, who noted that the treatment is dexamethasone 10 mg IV every 12 hours (or equivalent dose) until improvement and for a minimum of 3 days.

Ivosidenib demonstrated durable remissions in *IDH1* relapsed/refractory AML, with 32.8% of patients (57 of 174) achieving complete remission or complete remission with partial hematologic recovery (DiNardo et al., 2018). Dr. Held noted that an extension of the study enrolled untreated AML patients who were at least 75 years old or with comorbidities (n = 28); 42.9% achieved complete remission while 41.2% who were transfusion dependent became independent of red blood cell and/or platelet transfusions.

An ongoing multicenter phase III trial will determine the benefit of azacitidine with or without ivosideinib, Dr. Held reported.

## LYMPHOMAS AND CLL

### Brentuximab Vedotin for Systemic Anaplastic Large Cell Lymphoma and Peripheral T-Cell Lymphoma (November 2018)

Brentuximab vedotin is a CD30-directed monoclonal antibody conjugated to monomethyl auristatin E (MMAE), which is a microtubule inhibitor. ECHELON-2, a phase III double-blind trial, randomized 452 patients with previously untreated CD30-positive T-cell lymphomas to either brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone (BV + CHP), or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Median progression-free survival was 48.2 months vs. 20.8 months in the brentuximab vedotin and CHOP arms, respectively (Horwitz et al., 2019). Peripheral neuropathy was reported in 52% of patients on the brentuximab vedotin arm and 55% on the CHOP arm (Figure 2).

### Lenalidomide for Follicular Lymphoma and Marginal Zone Lymphoma (May 2019)

As Dr. Held explained, lenalidomide is an immunomodulatory agent (IMiD) with multiple effects on the tumor cell and microenvironment, including downregulation of pro-survival cytokines and increased activation of immune effector cells and costimulatory molecules. In a phase III, multicenter, randomized trial of patients with previously treated follicular lymphoma (FL) or marginal zone lymphoma (MZL), patients receiving lenalidomide had a progression-free survival of 39.5 months vs. 14.1 months in the control arm (Leonard et al., 2019). Progression-free survival was seen in all subgroups except MZL, but the overall response rate for patients with MZL was improved.

### Polatuzumab Vedotin for Diffuse Large B-Cell Lymphoma (June 2019)

Polatuzumab vedotin is a CD79b-directed antibody-drug conjugated to MMAE. In a phase 1b/II study, 80 relapsed/refractory diffuse large B-cell lymphoma transplant-ineligible patients were randomized to receive polatuzumab vedotin plus bendamustine or bendamustine alone (Skrabek et al., 2019). Of the 25 patients who achieved a partial or complete response, 16 patients had response durations of at least 6 months and 12 had response durations of at least 12 months. Median overall survival was 11.8 months in the polatuzumab vedotin arm vs. 4.7 months with bendamustine alone. Median progression-free survival was also improved from 2 months to 6.7 months with the addition of polatuzumab vedotin.

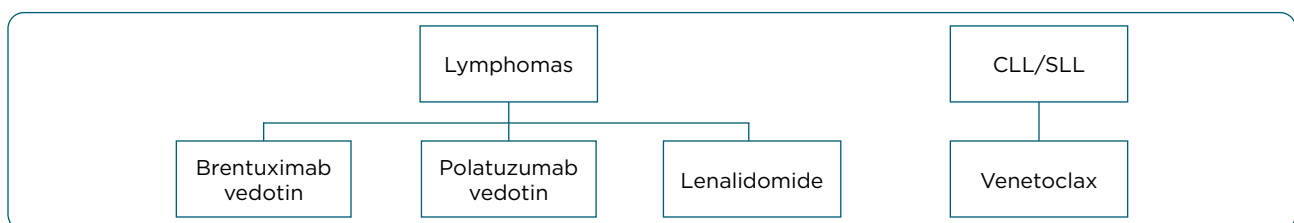
### Venetoclax for CLL/Small Lymphocytic Lymphoma (May 2019)

The approval for venetoclax was expanded to include patients with previously untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with coexisting medical conditions. This indication was based on data from a phase III trial of 432 patients with previously untreated CLL and coexisting conditions who were randomized to obinutuzumab plus venetoclax, or obinutuzumab plus chlorambucil (Fischer et al., 2019). Patients in the venetoclax arm had improved progression-free survival, and this benefit was observed in subgroups with *TP53* deletion, mutation, or both, and in patients with unmutated *IGHV*.

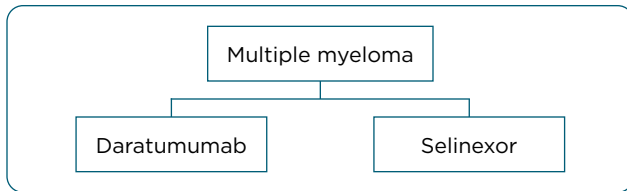
## MULTIPLE MYELOMA

### Selinexor for Multiple Myeloma (July 2019)

Selinexor, an oral selective inhibitor of nuclear export (SINE), blocks exportin 1 (XPO1) and reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and oncogenic



**Figure 2.** New drug approvals and new indications in lymphomas and chronic lymphocytic leukemia and small lymphocytic lymphoma. Lenalidomide and venetoclax are oral agents.



**Figure 3.** New drug approvals and new indications in multiple myeloma. Selinexor is an oral agent.

proteins. As Dr. Held reported, approval of selinexor was based on data from the STORM clinical trial of patients with relapsed/refractory multiple myeloma who had previously received at least three lines of anti-myeloma treatment regimens (Chari et al., 2019). A subgroup analysis of 83 patients whose disease was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab showed an overall response rate of 25.3% with a median time to first response of 4 weeks and a median response duration of 3.8 months (Figure 3).

#### **Daratumumab for Multiple Myeloma (September 2019)**

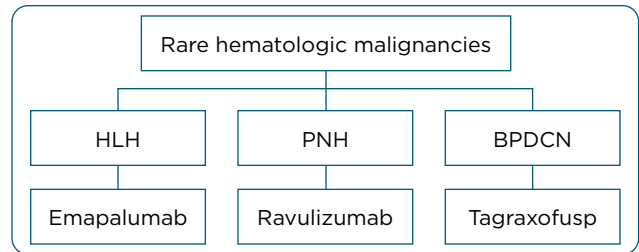
As Dr. Held reported, daratumumab was approved in combination with lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplant. Approval was based on phase III data of 737 newly diagnosed patients with multiple myeloma who were transplant ineligible (Facon et al., 2019). The addition of daratumumab to lenalidomide plus dexamethasone significantly improved progression-free survival and nearly doubled complete response rates.

Daratumumab was also approved in newly diagnosed transplant eligible patients after consolidation at 100 days after autologous transplant based on data from the CASSIOPEIA trial (Moreau et al., 2019). With the addition of daratumumab to bortezomib, thalidomide, and dexamethasone, stringent complete response rates were consistent across all subtypes, with the exception of patients with high-risk cytogenetic profile or International Staging System stage III.

### **RARE HEMATOLOGIC MALIGNANCIES**

#### **Tagraxofusp for Blastic Plasmacytoid Dendritic Cell Neoplasm (December 2018)**

As Dr. Held reported, blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an extremely rare



**Figure 4.** New drug approvals in rare hematologic malignancies/disorders. HLH = hemophagocytic lymphohistiocytosis; PNH = paroxysmal nocturnal hemoglobinuria; BPDCN = blastic plasmacytoid dendritic cell neoplasm.

hematopoietic malignancy that arises from the precursors of myeloid-derived plasmacytoid dendritic cells, and virtually all of these cells express an interleukin 3 receptor, or CD123. Tagraxofusp is a CD123-directed cytotoxin composed of recombinant human interleukin-3 (IL-3) and truncated diphtheria toxin that inhibits protein synthesis and causes cell death in CD123-expressing cells.

Tagraxofusp is indicated in adult and pediatric patients with BPDCN. The first cycle should be administered in the inpatient setting (Pemmaraju et al., 2019). There is a black box warning for capillary leak syndrome, hypersensitivity, and hepatotoxicity, said Dr. Held (Figure 4).

#### **Emapalumab for Hemophagocytic Lymphohistiocytosis (November 2018)**

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory disease that leads to a stimulation of CE8 and macrophages and an overall cytokine storm, which can then lead to tissue destruction. Emapalumab inhibits interferon gamma, which stimulates macrophages and cytokines, and is approved in adult and pediatric patients with primary HLH with refractory, recurrent or progressive disease, or intolerance with conventional HLH therapy (Merli et al., 2019).

#### **Ravulizumab for Paroxysmal Nocturnal Hemoglobinuria (December 2018)**

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematologic disorder manifested by a genetic deficiency in linking complement inhibitors to the blood cell surface (Rother, Rollins, Mojciak, Brodsky, & Bell, 2007). Ravulizumab is a C5 complement inhibitor indicated for the treatment of adult patients with PNH. As Dr. Held reported,

however, there is a black box warning for serious meningococcal infections. Patients should be immunized with the meningococcal vaccine at least 2 weeks prior to the first dose, and if patients are unvaccinated, they should receive 2 weeks of antibiotics with vaccination, said Dr. Held. ●

### Disclosure

Dr. Held has no conflicts of interest to disclose.

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