

2019–2020 Drug Updates in Hematologic Malignancies

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

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Abstract

During JADPRO Live Virtual 2020, Heidi D. Finnes, PharmD, BCOP, FHOPA, discussed the pharmacology and indications of medications approved from late 2019 to late 2020 for the management of patients with hematologic malignancies, reviewed pivotal clinical trial data, and covered the adverse events of these hematologic medications.

From late 2019 to late 2020, the U.S. Food & Drug Administration (FDA) approved a number of medications for the management of patients with hematologic malignancies, including drugs for lymphoma, myeloma, myelodysplastic syndrome, and sickle cell anemia. During JADPRO Live Virtual 2020, Heidi D. Finnes, PharmD, BCOP, FHOPA, of Mayo Clinic, discussed the pharmacology and indications of these recent approvals and reviewed the pivotal clinical trial data considered by the FDA. Dr. Finnes also discussed the impact of these agents on advanced practice.

ZANUBRUTINIB

Zanubrutinib (Brukinsa), a novel, irreversible Bruton tyrosine kinase (BTK) inhibitor, received accelerated FDA approval in November 2019 for adult patients with mantle cell lymphoma who have received at least one prior therapy (Table 1). Ap-

proval was based on overall response data from the phase II, single-arm, open-label BGB-3111-206 trial of relapsed/refractory mantle cell lymphoma patients who received oral zanubrutinib 160 mg twice daily (Song et al., 2020).

In the phase II study, zanubrutinib demonstrated high and durable overall response rates of 84% and complete response rates of 69% in patients with relapsed/refractory mantle cell lymphoma who had received at least one prior therapy.

“When compared with ibrutinib and acalabrutinib, zanubrutinib compares favorably to other BTK inhibitors,” said Dr. Finnes, who also reported a benefit in *TP53*-mutated tumors. “Because zanubrutinib leads to a longer progression-free survival in this particularly challenging subset, I suggest selecting zanubrutinib for patients with *TP53*-mutated mantle cell lymphoma.”

Due to higher complete and sustained occupancy of BTK, zanubrutini-

Table 1. New Drug Approvals From 2019 to 2020

Lymphoma
• Zanubrutinib
• Brexucabtagene autoleucl
• Tafasitamab-cxix
Myeloma
• Isatuximab-lrfc
• Belantamab mafodotin-blmf
Myelodysplastic syndromes
• Decitabine + cedazuridine
• Luspatercept-aamt ^a
Sickle cell anemia
• Crizanlizumab-tmca
• Voxelotor

Note. ^aAlso approved for beta thalassemia in Nov. 2019.

nib also has a lower frequency of grade 3 or greater adverse events such as diarrhea, neutropenia, thrombocytopenia, infection, and hemorrhage. No cases of atrial fibrillation or flutter were reported in this study, said Dr. Finnes.

Warnings and precautions with zanubrutinib include hemorrhage, which can be serious or fatal. Purpura and petechia occur in 50% of patients with 2% incidence of grade 3 or higher bleeding events such as intracranial, gastrointestinal hemorrhage, hematuria, and hemothorax. “As with other BTK inhibitors, it will be important to monitor patients more closely on concurrent antiplatelet or anticoagulant medications,” said Dr. Finnes.

Grade 3 or higher neutropenia occurred in 27% of patients and can increase risk of infection. Grade 3 or higher infections occurred in 23% of patients on zanubrutinib. Practitioners should consider prophylaxis for herpes simplex and pneumocystis, and other infections.

Other warnings occurring in less than 10% of patients include thrombocytopenia (10%), anemia (8%), second primary malignancies (9%), cardiac arrhythmias (2%), and embryo-fetal toxicity.

Zanubrutinib is metabolized by CYP3A4, so dose reductions are listed for concurrent use of moderate or strong CYP3A4 inhibitors and inducers.

BREXUCABTAGENE AUTOLEUCEL

Brexucabtagene autoleucl (Tecartus), an anti-CD19 chimeric antigen receptor (CAR)-T cell immunotherapy, was FDA approved in July 2020 for the treatment of adult patients with relapsed or refractory mantle cell lymphoma based on objective response data from the ZUMA-2 trial (Wang

et al., 2020). Results of the multicenter, phase II study in patients with mantle cell lymphoma who had received up to five prior therapies (including a BTK inhibitor) showed an objective response rate of 93%, including 67% complete response and 27% partial response.

At a median follow-up of 12.3 months, 57% of the 60 patients in the primary efficacy analysis were in remission. At 12 months, the estimated progression-free and overall survival was 61% and 83%, respectively. Grade 3 or higher adverse events included cytopenias, infections, neurologic toxicity, and cytokine release syndrome. Two grade 5 infectious events occurred.

Subgroup analysis showed that progression-free survival at 6 months was consistent among patients with poor prognostic features, including pleomorphic morphologic characteristics, *TP53* mutation, or Ki-56 proliferation index of 50% or higher.

“As with all FDA-approved CAR-T therapies, there is a Risk Evaluation Mitigation Strategy (REMS) program requiring hospitals and those who prescribe brexucabtagene to understand cytokine release syndrome and associated neurologic toxicities and how to manage these symptoms should they arise,” said Dr. Finnes. “Patients should be educated that serious and life-threatening toxicities are possible with this therapy.”

TAFASITAMAB-CXIX

Tafasitamab (Monjuvi), an anti-CD19 monoclonal antibody, received accelerated FDA approval for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma based on overall response rates of the L-MIND trial (Salles et al., 2020). Patients enrolled in the open-label, single arm, phase II study were not eligible for an autologous stem cell transplant, had a poor prognosis, and had received one to three prior therapies, including a CD20-targeted regimen.

A total of 80 patients were included in the analysis, and median follow-up was 17.3 months. The overall response rate was 60%, with 43% of patients having a complete response, and the median time to response was 2 months.

The median duration of response was 21.7 months, median progression-free survival was 12.1 months, and median overall survival was not

reached. The duration of response and overall survival rates at 12 months were 71.6% and 73.7%, respectively. Subgroup analysis showed that patients with one prior line of therapy had better outcomes than those with two or more prior lines. For patients who were refractory to their last therapy, similar overall response rates were observed, said Dr. Finnes.

Warnings and precautions for tafasitamab include infusion-related reactions, which may require rate reductions (6%), myelosuppression, including grade 3 neutropenia in 1 of 4 patients, grade 3 thrombocytopenia in 12%, and anemia in 7%.

“It will be important to monitor for signs and symptoms of infection and consider white blood cell colony-stimulating factors if needed,” said Dr. Finnes. “Tafasitamab may cause fetal B-cell depletion, so effective contraception is required.”

ISATUXIMAB-IRFC

Isatuximab (Sarclisa), an anti-CD38 monoclonal antibody, was FDA approved in March 2020 for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least two prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Isatuximab was approved based on the results of the phase III ICARIA-MM trial, which randomized patients with relapsed and refractory multiple myeloma who had received at least two prior lines of therapy (including lenalidomide and a proteasome inhibitor) to receive isatuximab plus pomalidomide and dexamethasone vs. pomalidomide and dexamethasone alone (Attal et al., 2019).

At a median follow-up of 11.5 months, median progression-free survival was 11.5 months in the isatuximab arm vs. 6.5 months with pomalidomide and dexamethasone alone. The significant progression-free survival benefit of isatuximab translated into all myeloma subgroups, said Dr. Finnes, including patients with poor prognosis, refractory to lenalidomide, a proteasome inhibitor, or both.

Warnings and precautions of isatuximab include neutropenia, which occurs in 96% of patients, with 85% being grade 3 or 4; febrile neutropenia, which occurs in 12% of patients; and infusion reactions, which have been observed in

39% of patients but resolve on the same day. Patients may need prophylactic white blood cell colony-stimulating agents and anti-infective prophylaxis, said Dr. Finnes.

BELANTAMAB MAFODOTIN-BLMF

Belantamab (Blenrep) is an FDA-approved B-cell maturation antigen (BCMA)-directed antibody and microtubule inhibitor drug conjugate for the treatment of adult patients with relapsed/refractory multiple myeloma who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Belantamab mafodotin received accelerated FDA approval based on the response rates of the phase II DREAMM-2 trial, which randomized patients with relapsed or refractory multiple myeloma with disease progression after three or more lines to receive belantamab mafodotin 2.5 or 3.4 mg/kg intravenously every 3 weeks (Lonial et al., 2020).

At data cutoff, 31% of patients in the 2.5 mg/kg cohort vs. 34% in the 3.4 mg/kg cohort achieved an overall response. A very good partial response (VGPR) or better was achieved by 19% and 20% of the 2.5 mg/kg and 3.4 mg/kg cohorts, respectively. At median follow-up of 6.3 and 6.9 months, respectively, median duration of response had not yet been reached.

Adverse events of special interest included thrombocytopenia, infusion-related reactions, and keratopathy. Adverse events leading to dose reduction occurred in 29% of patients in the 2.5 mg/kg cohort vs. 41% in the 3.4 mg/kg cohort.

“Thrombocytopenia and anemia were more common in the 3.4-mg/kg cohort, so 2.5 mg/kg was selected as the dose moving forward,” said Dr. Finnes.

Although belantamab mafodotin may be utilized in patients who are unable to receive CAR-T therapy due to myelosuppression, frailty, or existing neurotoxicity, said Dr. Finnes, the required documentation and rigidity of the REMS program for ocular toxicity monitoring may be burdensome to its widespread use in the community setting.

DECITABINE AND CEDAZURIDINE

Decitabine-cedazuridine (Inqovi) is a combination hypomethylating and cytidine deaminase

inhibitor FDA approved for adult patients with myelodysplastic syndromes. In the phase III ASCERTAIN study, which compared oral decitabine-cedazuridine to IV decitabine, decitabine-cedazuridine achieved an oral/IV area under the curve ratio of 98.9% (Savona et al., 2019).

“This oral product is almost identical to IV decitabine,” said Dr. Finnes. “Phase II studies demonstrated durable clinical responses with a median overall survival of 18.3 months, which was consistent with IV decitabine.”

Although no significant differences in safety signals were observed, Dr. Finnes cautioned that decitabine-cedazuridine causes myelosuppression. Thrombocytopenia occurred in 82%, neutropenia occurred in 73%, anemia occurred in 71%, and febrile neutropenia occurred in 33% of patients.

Complete blood counts should be followed with each cycle, noted Dr. Finnes, and growth factors and anti-infective therapies may be needed as prophylaxis.

“This oral outpatient regimen for patients with myelodysplastic syndromes and chronic myelomonocytic leukemia reduces the need for frequent health-care visits and is very convenient,” she added.

LUSPATERCEPT-AAMT

Luspatercept (Reblozyl) was FDA approved in April 2020 for patients with myelodysplastic syndromes and in November 2019 for patients with beta thalassemia. Luspatercept was approved based on the results of the MEDALIST trial, a double-blind, placebo-controlled, phase III trial of patients with very low-risk or intermediate-risk myelodysplastic syndromes with ring sideroblasts who had been receiving regular red blood cell transfusions (Fenaux et al., 2020).

Transfusion independence for 8 weeks or longer was observed in 38% of patients receiving luspatercept vs. 13% of those receiving placebo, said Dr. Finnes. Luspatercept also had higher transfusion independence in weeks 1 to 24 (28% vs. 8%) and during weeks 1 to 48 (33% vs. 12%).

Common side effects associated with luspatercept included fatigue, diarrhea, asthenia, nausea, and dizziness, but these were manageable, said Dr. Finnes, who noted that trials in eryth-

ropoiesis stimulating-naïve transfusion-dependent patients with low-risk myelodysplastic syndromes are ongoing.

VOXELOTOR

Voxelotor (Oxbryta) is a hemoglobin S polymerization inhibitor that was FDA approved in November 2019 for sickle cell disease in adult and pediatric patients 12 years of age and older (Vichinsky et al., 2019).

Data from a multicenter, phase III, double-blind, randomized, placebo-controlled trial comparing the safety and efficacy of two doses of voxelotor (1,500 mg and 900 mg) administered orally once daily vs. placebo in persons with sickle cell disease showed significantly greater hemoglobin response with voxelotor 1,500 mg once daily compared with placebo (51% vs. 7%, respectively). The absolute change in hemoglobin from baseline to week 24 was 1.1 g/dL in the voxelotor 1,500 mg group vs. 0.1 in the placebo group, which is also a statistically significant figure, said Dr. Finnes. The median increase in hemoglobin among participants receiving voxelotor was also consistent across patient subgroups, including those also receiving hydroxyurea.

The most common adverse events that occurred at any grade during this clinical trial were headache and diarrhea. However, most adverse events in this trial were judged by investigators to be unrelated to the clinical trial drug.

“Voxelotor was well tolerated and will be a new promising sickle cell-modifying agent in our armamentarium,” she observed.

CRIZANLIZUMAB-TMCA

Crizanlizumab (Adakveo) was FDA approved in November 2019 for sickle cell anemia based on the results of the SUSTAIN trial (Ataga et al., 2017). Data from the double-blind, randomized, placebo-controlled, phase II trial in which patients with sickle cell disease received crizanlizumab 2.5 mg/kg vs. crizanlizumab 5 mg/kg or placebo 14 times over 52 weeks showed that crizanlizumab reduced the number of health-care visits for vaso-occlusive crisis annually (median annual rate of 1.63 compared with 2.98 visits, respectively). In addition, 36% of patients did not have a vaso-occlusive crisis during the study, and it delayed

time to first vaso-occlusive crisis (from 1.4 months to 4.1 months). Adverse events were manageable, said Dr. Finnes.

NEW DRUG INDICATIONS

New medications that received indications in 2019 to 2020 include gemtuzumab ozogamicin (Mylotarg) for acute myeloid leukemia, acalabrutinib (Calquence) and ibrutinib (Imbruvica) plus rituximab (Rituxan) for chronic lymphocytic leukemia/small lymphocytic lymphoma, selinexor (Xpovio) and tazemetostat (Tazverik) for lymphoma, and daratumumab hyaluronidase (Darzalex Faspro) for myeloma (Table 2). ●

Disclosure

Dr. Finnes had no conflicts of interest to disclose.

References

- Ataga, K. I., Kutlar, A., Kanter, J., Liles, D., Cancado, R., Friedrichs, J.,...Rother, R. P. (2017). Crizanlizumab for the prevention of pain crises in sickle cell disease. *New England Journal of Medicine*, 376(5), 429–439. <https://doi.org/10.1056/nejmoa1611770>
- Attal, M., Richardson, P. G., Rajkumar, S. V., San-Miguel, J., Beksac, M., Spicka, I.,...Anderson, K. C. (2019). Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): A randomised, multicentre, open-label, phase 3 study. *Lancet*, 394(10214), 2096–2107. [https://doi.org/10.1016/s0140-6736\(19\)32556-5](https://doi.org/10.1016/s0140-6736(19)32556-5)
- Fenaux, P., Platzbecker, U., Mufti, G. J., Garcia-Manero, G., Buckstein, R., Santini, V.,...List, A. F. (2020). Luspatercept in patients with lower-risk myelodysplastic syndromes. *New England Journal of Medicine*, 382(2), 140–151. <https://doi.org/10.1056/NEJMoal908892>
- Lonial, S., Lee, H. C., Badros, A., Trudel, S., Nooka, A. K., Chari, A.,...Usmani, S. Z. (2020). Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): A

Table 2. New Drug Indications From 2019 to 2020

Acute myeloid leukemia
• Gemtuzumab ozogamicin
Chronic lymphocytic leukemia and small lymphocytic lymphoma
• Acalabrutinib
• Ibrutinib + rituximab
Lymphoma
• Selinexor
• Tazemetostat
Myeloma
• Daratumumab hyaluronidase-fihj

two-arm, randomised, open-label, phase 2 study. *Lancet Oncology*, 21(2), 207–221. [https://doi.org/10.1016/s1470-2045\(19\)30788-0](https://doi.org/10.1016/s1470-2045(19)30788-0)

- Salles, G., Duell, J., González Barca, E., Tournilhac, O., Jurczak, W., Liberati, A. M.,...Maddocks, K. (2020). Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): A multicentre, prospective, single-arm, phase 2 study. *Lancet Oncology*, 21(7), 978–988. [https://doi.org/10.1016/s1470-2045\(20\)30225-4](https://doi.org/10.1016/s1470-2045(20)30225-4)
- Savona, M. R., Odenike, O., Amrein, P. C., Steensma, D. P., DeZern, A. E., Michaelis, L. C.,...Garcia-Manero, G. (2019). An oral fixed-dose combination of decitabine and cedazuridine in myelodysplastic syndromes: A multicentre, open-label, dose-escalation, phase 1 study. *Lancet Haematology*, 6(4), e194–e203. [https://doi.org/10.1016/s2352-3026\(19\)30030-4](https://doi.org/10.1016/s2352-3026(19)30030-4)
- Song, Y., Zhou, K., Zou, D., Zhou, J., Hu, J., Yang, H.,...Zhu, J. (2020). Treatment of patients with relapsed or refractory mantle-cell lymphoma with zanubrutinib, a selective inhibitor of bruton's tyrosine kinase. *Clinical Cancer Research*, 26(16), 4216–4224. <https://doi.org/10.1158/1078-0432.ccr-19-3703>
- Vichinsky, E., Hoppe, C. C., Ataga, K. I., Ware, R. E., Nduba, V., El-Beshlawy, A.,...Intondi, A. (2019). A phase 3 randomized trial of voxelotor in sickle cell disease. *New England Journal of Medicine*, 381(6), 509–519. <https://doi.org/10.1056/nejmoa1903212>
- Wang, M., Munoz, J., Goy, A., Locke, F. L., Jacobson, C. A., Hill, B. T.,...Peng, W. (2020). KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *New England Journal of Medicine*, 382(14), 1331–1342. <https://doi.org/10.1056/nejmoa1914347>