

# Updates in the Diffuse Large B-Cell Lymphoma Treatment Landscape

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

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## Abstract

During JADPRO Live Virtual 2021, presenters discussed updates in the treatment of diffuse large B-cell lymphoma (DLBCL), including novel agents and chimeric antigen receptor (CAR) T-cell therapy, and how the treatment and management of patients with DLBCL has been affected by the COVID-19 pandemic.

A number of novel agents have entered the therapeutic arena for diffuse large B-cell lymphoma (DLBCL). Chief among these are antibody-drug conjugates and chimeric antigen therapy (CAR) T-cell therapies. While new treatments are improving survival, the COVID-19 pandemic has added another layer to the management of this challenging patient population. Updates of important clinical trials, along with recommendations keeping DLBCL patients safe in the era of COVID-19, were presented at JADPRO Live Virtual 2021 by Ashley Ames, FNP-BC, and Diane Lee, AGPCNP-BC, both nurse practitioners at Memorial Sloan Kettering Cancer Center in New York, New York.

New and upcoming agents and regimens Ms. Ames and Ms. Lee discussed included the antibody-drug conjugates polatuzumab vedotin (Polivy), naratuximab emtansine, and loncastuximab tesirine (Zyn-

lonta), and the anti-CD19-directed monoclonal antibody tafasitamab (Monjuvi).

## FRONT-LINE STUDIES

“Since 30% to 50% of patients relapse, there is a strong need to improve on front-line therapy options for our newly diagnosed patients, in particular high-risk DLBCL. It’s important for us as advanced practitioners to know that there are ongoing trials for alternative front-line treatment options,” Ms. Lee said.

Polatuzumab vedotin was evaluated in the front-line phase III POLARIX trial of more than 800 newly diagnosed patients with DLBCL (Pelosci, 2021). The study compared front-line polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin and prednisone (R-CHP), vs. standard treatment with rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Updated results presented at the

2021 American Society of Hematology (ASH) Annual Meeting & Exposition showed that the study met its primary endpoint, reducing the risk of progression by 27% (hazard ratio [HR] 0.73;  $p < .02$ ; Tilly et al., 2021).

The results of this “pivotal trial” have the potential to be “transformative,” said Ms. Ames, noting that 40% of patients relapse after disease progression and are in need of better treatments. As polatuzumab vedotin is expected to be approved by the U.S. Food and Drug Administration (FDA), she said that “advanced practitioners should be aware of these findings.”

The anti-CD19–directed monoclonal antibody tafasitamab was evaluated in the open-label randomized multicenter phase Ib First-MIND trial of 66 newly diagnosed patients (Belada et al., 2021). Tafasitamab was added to the standard-of-care regimen of R-CHOP (arm A) or was given with R-CHOP and lenalidomide (arm B). The study excluded patients with double-hit or triple-hit DLBCL and required growth factors and prophylaxis for venous thromboembolism. Tafasitamab and lenalidomide in combination is already FDA-approved for adults with relapsed/refractory DLBCL who are ineligible for autologous stem cell transplant.

Of 60 evaluable patients, 89.7% responded to tafasitamab/R-CHOP and 93.5% responded to tafasitamab/R-CHOP plus lenalidomide. Serious treatment-related adverse events were observed in 42.4% and 51.5%, respectively.

“The data suggest that R-CHOP plus tafasitamab or R-CHOP plus tafasitamab and lenalidomide is tolerable, with toxicities that are similar to those expected with R-CHOP alone or R-CHOP with lenalidomide. Dose intensity for R-CHOP was maintained in both arms,” Ms. Lee reported.

First-MIND formed the basis for the ongoing phase III randomized, double-blind Front-MIND study, which is evaluating tafasitamab plus lenalidomide with R-CHOP vs. R-CHOP alone in newly diagnosed, high/intermediate-risk and high-risk DLBCL patients, with progression-free survival as the primary endpoint (Vitolo et al., 2021). “The combination of R-CHOP and tafasitamab plus lenalidomide may be synergistic against malignant B-cells,” she added.

## STUDIES IN RELAPSED OR REFRACTORY DLBCL

The anti-CD37–directed antibody drug-conjugate naratuximab emtansine is being evaluated in combination with rituximab in an open-label phase II trial of 80 refractory patients (Levy et al., 2021). The overall response rate was 44.7%, with 31.6% of patients achieving a complete response. The toxicities of most concern were grade 3/4 cytopenias, which were manageable with growth factor support and transfusions.

“Naratuximab in combination with rituximab yielded deep and long-lasting responses in patients with relapsed and refractory DLBCL,” Ms. Ames observed. “We feel this is important because a lot of patients will relapse after front-line therapy—or, even more so, after second, third, and fourth lines. Advanced practitioners should be familiar with newer drugs and combinations with drugs we’re already using, and be aware of ongoing clinical trials.”

The CD19-directed antibody-drug conjugate loncastuximab tesirine, also known as lonca, has shown promising single-agent activity in non-Hodgkin lymphoma and was evaluated as monotherapy in the LOTIS-2 study (Caimi et al., 2021). The open-label phase II study enrolled 145 patients with double- and triple-hit disease, transformed lymphoma or primary refractory DLBCL who had received two or more systemic regimens. The primary endpoint, overall response, was achieved by 48.3%, with 35 of the 70 responders achieving a complete response, with no new safety signals observed.

“A subgroup of patients received subsequent consolidative therapies, like stem cell transplant and CAR T-cell therapy, which suggests there is potential for lonca to be a bridge to other treatments,” Dr. Lee said.

The phase III LOTIS-5 trial is currently enrolling 300 patients to evaluate loncastuximab tesirine plus rituximab (lonca-R) vs. the standard immunochemotherapy regimen of rituximab with gemcitabine and oxaliplatin (R-GemOx), in patients with relapsed/refractory DLBCL ineligible for transplant (Hamadani et al., 2021). The population includes patients with transformed lymphoma or high-grade B-cell lymphoma with MYC or BCL2 and/or BCL6 gene rearrangements. The primary endpoint is progression-free survival.

The Pola-R-Len trial is evaluating the novel triplet regimen of polatuzumab vedotin with rituximab and lenalidomide in 57 patients with relapsed/refractory DLBCL (Diefenbach et al., 2021). Patients who respond to induction are receiving a 6-month consolidation treatment with lenalidomide and every-2-month rituximab. The primary endpoints of this study are safety, tolerability, and complete responses by PET (PET-CR) after induction.

In 49 patients receiving the recommended phase II dose of lenalidomide, 36 patients have responded (74%), of whom 17 are complete responses. The PET-CR rate at the end of induction was 29%. Grade 3 and 4 adverse events were seen in 75%, with lenalidomide dose reductions needed in about half the patients and dose interruptions in almost two thirds.

### IMPACT OF RITUXIMAB BIOSIMILARS IN DLBCL

Emerging studies are confirming that rituximab biosimilars have an impact on overall survival that is as good as that of the originator product. In a Dutch-based population study in adults with DLBCL, 3-year overall survival did not differ between patients treated with rituximab biosimilars and those receiving rituximab originators (Brink et al., 2021).

As Ms. Ames noted, The Netherlands was one of the first European countries to implement rituximab biosimilars. By the end of 2018, rituximab biosimilars accounted for 91% of rituximab purchases in that country, yielding a 43% reduction in annual costs.

The study's findings are clearly relevant to the United States, where rituximab biosimilar use has grown. While she pointed out that treatment selection is often dictated by the payors, "It's important to let patients know that there is no difference between the rituximab originator and biosimilars—that their outcomes are similar," Ms. Ames said.

### CAR T-CELL THERAPY

Positive results of the ZUMA-7 trial were recently reported (Ross, 2021) and updated at the 2021 ASH Annual Meeting & Exposition (Locke et al., 2021). ZUMA-7 is a randomized phase III trial evaluating the CAR T-cell therapy axicabtagene ciloleucel (axi-cel) vs. high-dose chemotherapy and stem cell transplant for patients with second-

line relapsed or refractory large B-cell lymphoma. ZUMA-7 demonstrated the superiority of axi-cel, which yielded a median event-free survival of 8.3 months vs. 2.0 months with the standard of care (HR 0.398;  $p < .0001$ ). Objective response rate was also significantly improved, and interim overall survival analysis showed a trend favoring axi-cel.

"The findings have implications for changing practice, once the information is fully published," Ms. Ames said. "For several years, high-dose chemotherapy followed by autologous stem cell rescue was the standard of care for second-line therapy in DLBCL, but the ZUMA-7 data can change that. It shows that CAR T-cell therapy may be much superior to high-dose chemotherapy and transplant, which is associated with significant toxicities and secondary malignancies."

While findings for CAR T-cell therapies are impressive, this approach is not suitable for all patients, and it engenders complete responses in only about 50% of patients: many patients, therefore, need other options. Alternative treatments are available, and their outcomes are essentially as good as those achieved with CAR T-cell therapy, according to a single-center, retrospective, observational study of 215 patients (Sermer et al., 2020). The study compared outcomes from CAR T-cell therapy ( $n = 69$ ) with a historical population treated with other therapies ( $n = 1446$ ), such as small-molecule inhibitors and novel agents in phase I/II trials.

When the comparison was adjusted for unfavorable pretreatment characteristics, the overall response rate remained higher with CAR T-cell therapies but progression-free and overall survival were similar.

### CONSIDERATIONS DURING THE COVID-19 PANDEMIC

Cancer patients are at increased risk for contracting and developing complications from COVID-19 infection, but patients with DLBCL are at higher risk still, since their cancer involves immune cells. Within the DLBCL population, the highest risk is assumed by patients in active treatment, since the standard agent, the anti-CD20 antibody rituximab (Rituxan), can cause acute and prolonged suppression of the humoral immune system. Chemotherapy can also suppress T cells and render patients more susceptible to infection.

“ASH acknowledges that there are certain patient populations that are at higher risk of not developing an adequate immune response to the COVID vaccine, and this includes our DLBCL patient population, especially those receiving B-cell directed therapy, such as the anti-CD20 monoclonal antibody therapy, rituximab,” Ms. Lee said.

While the efficacy of COVID-19 vaccines in the DLBCL population has not been thoroughly studied (trials excluded these patients), ASH and the National Comprehensive Cancer Network (NCCN) have issued guidelines and recommendations regarding vaccination. The NCCN recommends vaccinating patients with hematologic malignancies on active treatment but does not recommend it for patients with neutropenia; vaccinated patients should continue to wear masks and follow social distancing guidelines (NCCN, 2021).

“As we’ve all experienced since the beginning of this COVID pandemic, guidelines are constantly changing, and it is our professional responsibility to remain up to date with them,” Ms. Lee said. ●

## Disclosure

The presenters had no conflicts of interest to disclose.

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