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The latest developments from US FDA drug, biologic, and medical device advisory committee meetings.

Today's Headline: Overwhelming Support for Genentech's Polivy to Treat Untreated DLBCL

March 9, 2023
Meeting Begin Time: 12:00 p.m. | **End Time:** 5:24 p.m.

IN THIS ISSUE

Oncologic Drugs Advisory Committee Meeting

AdComm Profiles and Voting Histories—Drugs/Biologics (IDRAC 175864)

Subject: Supplemental biologics license application (sBLA) 761121/8: Polivy (polatuzumab vedotin-piiq) for injection, submitted by Genentech, Inc, for use in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

Announced in the Federal Register January 26, 2023 (IDRAC 359121) (Volume 88, Number 17)

Decision/Voting

The Oncologic Drugs Advisory Committee (ODAC) voiced near-unanimous support for the benefit-risk profile of Polivy (IDRAC 331167) (polatuzumab vedotin-piiq) for injection, submitted by Genentech, Inc, in a supplemental application to extend the product's indication to treat adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) in combination with R-CHP (rituximab product, cyclophosphamide, doxorubicin, and prednisone). The ODAC focused on efficacy concerns arising from the POLARIX study, but ultimately agreed with the sponsor because the trial met its primary efficacy endpoint.

FDA Question(s) to the Committee	Vote		Comments
	Yes	No	
Given the results of the POLARIX trial, does polatuzumab vedotin-piiq have a favorable benefit-risk in patients with previously untreated LBCL, including DLBCL NOS?	**11**	2	
NOTE: The FDA is not obligated to follow the voting recommendation of the advisory committee, but it may do so once all information is considered.			

POLARIX is an ongoing phase 3 trial evaluating the substitution of vincristine with Polivy in the R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen in participants with previously untreated LBCL, including DLBCL not otherwise specified (NOS). The drug is already on the US market for the treatment of adult patients with relapsed or refractory (R/R) DLBCL NOS, after ≥2 prior therapies, in combination with bendamustine and rituximab.

Opening the discussion, an ODAC member asked what the benefit was of measuring progression-free survival (PFS) in POLARIX. Traditionally, cancer trials use overall survival (OS) as the primary efficacy endpoint, but PFS is used to determine the duration of treatment with additional therapies for recurrent disease. The panelist, referencing his own clinical practice, said that PFS is a good indicator of treatment effectiveness because the longer a patient does not need additional chemotherapy, the better. Another panelist added that

subsequent therapies to treat DLBCL patients (e.g., stem cell transplantation [SCT]), who are not cured by first-line (1L) drugs, are "very toxic" and require hospitalization. He concluded by stating that he did not have any concerns regarding excessive toxicity with Polivy.

Other panelists acknowledged that PFS was a valid endpoint in POLARIX because the R-CHOP regimen already cures approximately (~) 60% of DLBCL patients, and it is difficult to surpass this high level of efficacy with a new drug. Another ODAC member emphasized that more treatment options are needed because certain patients are not eligible for therapies such as SCT due to a number of factors (e.g., preexisting conditions).

One panelist remarked, "I'm usually not a fan of progression-free survival," but added that he would be encouraged if results from POLARIX were considered an "interim" marker of Polivy's efficacy. However, he was "stunned" by the study design because DLBCL diagnosis or disease progression were not "centrally confirmed." He concluded by stating, "My problem is I'm not sure if I trust who progressed and who didn't, and what their base disease was." This member also commented that PFS is a "challenging endpoint to convey to patients" because it does not indicate whether a patient "lived longer or better."

Nearly all panelists agreed that PFS was a valid and clinically meaningful endpoint in POLARIX. But many acknowledged that, even with additional data, it would be difficult to show how PFS translates to OS. Some members questioned the "statistical style" of POLARIX and said that more data would not be meaningful to ascertain OS; however, these data would be beneficial for oncologists and patients because it would convince them to use Polivy in clinical settings.

Panelists who voted in favor of the benefit-risk profile mostly said that the clinical trial met its primary efficacy endpoint and, even though the PFS difference was small, it was statistically significant. One panelist noted that the gain in PFS was meaningful for patients, especially because no major toxicity concerns emerged from POLARIX. The increase in PFS also meant that patients using Polivy for DLBCL would require fewer treatments such as SCT in the future. The R-CHOP control arm experienced more toxicity because those participants ultimately required other treatments (e.g., SCT). Patients choosing Polivy "would be spared more toxic and complicated salvage therapies," another panelist concluded.

The ODAC members who voted against the benefit-risk profile of Polivy said that there was too much uncertainty about the "magnitude and robustness" of the treatment effect, and that POLARIX did not "meet the basics" of a large clinical trial as there was no confirmation of diagnosis or disease progression.

Background Information

At this meeting, the Oncologic Drugs Advisory Committee (ODAC) was convened to review supplemental biologics license application (IDRAC 37905) (sBLA) 761121/8 for Polivy (polatuzumab vedotin-piiq [ATC: L01FX14]) for injection, submitted by Genentech, Inc, for use in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

Polivy, for use in combination with bendamustine hydrochloride and a rituximab product, was granted accelerated approval (IDRAC 37909) in 2019 (see *Regulatory Issues*) for the treatment of adult patients with relapsed or refractory (R/R) DLBCL, not otherwise specified (NOS), after ≥2 prior therapies. A cluster of differentiation 79B (CD79B)-directed antibody-drug conjugate (ADC), Polivy targets and kills dividing B cells but may also destroy healthy B cells in the process.

As shared in the Event Materials (IDRAC 361206), the sponsor noted that DLBCL is the most common form of aggressive lymphoma. It accounts for 30% of all non-Hodgkin lymphoma (NHL) cases, and approximately (~) 27,000 people in the US are diagnosed with DLBCL every year. DLBCL has a poor prognosis that results in death, usually within a year, if left untreated. The FDA stated that "newly diagnosed DLBCL is treated with curative intent," with standard first-line (1L) therapy curing ~60% of all cases.

R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) is the standard of care (SOC) for DLBCL NOS and some other LBCLs in the US. However, ~40% of

patients diagnosed with DLBCL are not cured with 1L treatment and new therapies are needed to address their cancers, the sponsor noted. There is a significant unmet medical need in this patient population and individuals with R/R DLBCL would also benefit from additional chemotherapy options, agreed the FDA and the sponsor.

The discussion at this meeting anchored on issues arising from POLARIX, which was one of 2 phase 3 studies that the sponsor was conducting in DLBCL at the time of accelerated approval in 2019. These studies were intended to fulfill the post-marketing requirement to verify and describe the clinical benefit of Polivy in DLBCL. POLARIX is the sponsor's earliest possibility to fulfill the post-marketing requirement given that it read out in 2021, whereas the second study, POLARGO, is actively enrolling patients and its results are expected in late 2024. It was hypothesized in POLARIX that replacing vincristine in R-CHOP with Polivy would improve the regimen by augmenting efficacy without significantly increasing toxicity for 1L DLBCL patients.

Regarding the sponsor's proposed indication to expand the Polivy label, the FDA expressed concern over the use of "DLBCL" referring to LBCL and encompassing histologies that are distinct from DLBCL (e.g., high-grade BCL [HGBL]). The agency also stated that the relationship between Polivy dose and clinical efficacy in patients with previously untreated DLBCL is "not well-characterized due to the limited dose-finding."

Proposed Indication

- *Polivy (polatuzumab vedotin-piiq) in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients with previously untreated DLBCL.*

Proposed Dose

- *Polivy 1.8 mg/kg administered via intravenous (IV) infusion every 21 days for 6 cycles.*

Regulatory History

February 4, 2011	The FDA indicated to the sponsor that it may proceed with its investigational new drug application (IDRAC 34592) (IND) 109049 for the development of Polivy to treat B-cell malignancies.
December 12, 2016	The FDA granted orphan drug designation (IDRAC 37910) to Polivy for the treatment of DLBCL.
April 3, 2017	The FDA and the sponsor participated in a Type B meeting to discuss the proposed phase 3 study in 1L DLBCL. The sponsor obtained agreement on the design of the study, including the endpoints, target patient population, safety monitoring plan, and statistical analysis proposal [Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products, December-2017 (IDRAC 267090); Guidance Bulletin (IDRAC 268263)].
July 19, 2017	The FDA sent the sponsor a non-hold comment (IDRAC 34592) related to POLARIX regarding the primary progression-free survival (PFS) analysis to follow all patients for ≥24 months.
September 12, 2017	The FDA granted Polivy breakthrough therapy designation (IDRAC 37909) for use in combination with bendamustine and rituximab for the treatment of R/R DLBCL.
December 19, 2018	The FDA accepted BLA 761121 and granted it priority review (IDRAC 37909) for the use of Polivy in combination with bendamustine plus rituximab for the treatment of R/R DLBCL.
June 10, 2019	The FDA granted accelerated approval (IDRAC 37909) to BLA 761121 (IDRAC 297580) for Polivy injection, indicated in combination with bendamustine and a rituximab product for the treatment of adult patients with R/R DLBCL NOS after ≥2 prior therapies.
September 18, 2020	The FDA approved sBLA 761121/3 (IDRAC 331167) for various updates to the Polivy product label including the introduction of a new 30 mg/vial lyophilized product configuration, the addition of a moisture release testing method, and an extension to the storage conditions.
October 1, 2020	The FDA sent the sponsor Type C written feedback (IDRAC 268263)

	regarding the proposed content and format of sBLA 761121/8 to enable regular approval for the proposed indication in 1L DLBCL.
October 12, 2020	The sponsor submitted all versions of the statistical analysis plan (SAP) under IND 109409. The FDA confirmed that the proposed content of SAP version 3 was reasonable.
October 23, 2020 December 8, 2020	Following on the written feedback from October 1, 2020, the FDA and the sponsor communicated to clarify additional topics regarding the sBLA.
January 6, 2021	The FDA confirmed its agreement with the sponsor's final proposal for the content and format of sBLA 761121/8.
September 24, 2021	The FDA and sponsor participated in a Type B pre-sBLA meeting (IDRAC 268263) to discuss results from POLARIX and obtain feedback on the acceptability of the results to form the basis of an sBLA for Polivy in the proposed indication.
December 2, 2021	The sponsor submitted its SAP version 4 to the FDA to introduce a second interim analysis of overall survival (OS) to include in the initial sBLA submission.
April 2, 2023	The Prescription Drug User Fee Act (IDRAC 9046) (PDUFA) target action date for sBLA 761121/8.

Regulatory Issues

Accelerated approval may be granted to a drug on the basis of a surrogate endpoint that is "reasonably likely" to predict clinical benefit for indications where the new product appears to provide a benefit over currently available therapy [Marketing Authorization Procedures: Procedure for Priority Review/Accelerated Approval (IDRAC 37909)]. The accelerated approval pathway is defined in section 506(c) of the Federal Food, Drug, and Cosmetic Act (IDRAC 17027) (FD&C Act), 21 CFR part 314, subpart H (IDRAC 8838), and 21 CFR 601, subpart E (IDRAC 26695). A relevant FDA resource is the Guidance for Industry: Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway (Final), January-2019 (IDRAC 289217) [Guidance Bulletin (IDRAC 177874)].

Benefit-risk assessments are critical to the drug approval process because they help the FDA determine whether the advantages of a product outweigh its adverse effects. The Draft Guidance for Industry: Benefit-Risk Assessment for New Drug and Biological Products, September-2021 (IDRAC 336364) notes that some of the criteria used in the FDA's assessments include therapeutic context, post-marketing studies, uncertainties about safety and efficacy, and the agency's ability to manage risks.

Evaluations of benefits and risks occur during premarket development but do not end at drug approval. The FDA uses post-market evidence such as adverse event (AE) reports and external medical trials for future benefit-risk assessments under section 505(o)(3) of the FD&C Act. The agency has the authority to reexamine the safety profile of an approved drug and modify the current regulations concerning approvals.

The FDA noted in the Event Materials (IDRAC 361206) that many considerations exist when establishing surrogacy of an endpoint. Although PFS has been used to support regular approval in oncology, it requires submission of OS data to support the regulatory decision. Regarding the current sBLA for Polivy, the FDA pointed out that it did not agree with the sponsor that surrogacy of PFS for OS has been established in patients with previously untreated LBCL. An overview of study endpoints for cancer development programs is available in the FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (Final), December-2018 (IDRAC 288210). In this document, PFS is defined as the time from randomization until objective tumor progression or death, whichever occurs first.

In its evaluation of sBLA 761121/8, the FDA summarized that the sponsor seeks traditional approval in the curative-intent setting based on the results of a single clinical study, POLARIX. The agency noted that the only FDA approval for untreated DLBCL in the past 2 decades, rituximab, was based on 3 randomized trials, "each demonstrating a statistically significant prolongation of OS as well as clear improvement in the primary efficacy endpoint." In light of uncertainties with the PFS and OS results, the ODAC was asked at today's meeting to consider whether Polivy has a favorable benefit-risk profile, based on the totality of the data, in patients with LBCL in the 1L setting, including those with DLBCL NOS.

In the FDA's Draft Guidance for Industry: Core Patient-Reported Outcomes in Cancer Clinical Trials, June-2021 (IDRAC 331182), the agency states that sponsors should collect a core set of patient-reported outcomes (PROs) in cancer trials. This guidance provides details on how to collect PROs, their use, and specific considerations for cancer therapy trials that demonstrate an effect on survival, tumor response, and delay in disease progression. The guidance also discusses the importance of frequently conducting PROs, especially during the first ~6 months, which is the time period when many patients experience acute toxicity from chemotherapy. Particular core PROs highlighted by the FDA are disease symptoms, symptomatic AEs, overall side effect impact summary measure, physical function, and role function.

Clinical Issues

The sponsor submitted the results from POLARIX (Study GO39942) to support sBLA 761121/8. POLARIX is an ongoing confirmatory study intended to verify the clinical benefit of Polivy when substituted for vincristine in the R-CHOP regimen as a 1L therapy for LBCL, including DLBCL NOS. It is a multiregional study, with the US as the highest enrolling country. The Event Materials (IDRAC 361206) and Table 1 provide additional details on the study.

Table 1. Polatuzumab Clinical Program

Trial	Design	Regimen	No. Patients	Primary Endpoint
POLARIX	Multicenter, randomized, double-blind, placebo-controlled phase 3 study	1:1 randomization: pola+R-CHP[1] or R-CHOP[2]	879	PFS measured for ≤38 months

Pola+R-CHP = Polivy plus R-CHP (rituximab, cyclophosphamide, doxorubicin, and prednisone).
R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.
PFS = progression-free survival, assessed by using the Lugano response criteria for malignant lymphoma, from randomization to first occurrence of disease progression or relapse, or death from any cause.
[1] Participants in the pola+R-CHP arm received polatuzumab 1.8 mg/kg IV, placebo for vincristine IV, rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, and doxorubicin 50 mg/m^2 IV on day 1 and prednisone 100 mg/day orally on days 1 to 5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m^2 IV was administered as monotherapy in cycles 7 and 8.
[2] Participants in the R-CHOP comparator arm received placebo for polatuzumab, rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, and vincristine 1.4 mg/m^2 IV on day 1 and prednisone 100 mg/day orally on days 1 to 5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m^2 IV was administered as monotherapy in cycles 7 and 8.

The key secondary endpoints in POLARIX were modified event-free survival (EFS), complete response (CR) rate at the end of therapy by blinded independent central review (BICR), and OS.

Safety

The sponsor highlighted the following main points about the safety data from POLARIX:

- The pola+R-CHP arm had comparable treatment discontinuations and interruptions as the R-CHOP arm.
- There was a lower incidence of dose reductions in the pola+R-CHP arm compared to the R-CHOP arm.
- The incidence of grade 5 AEs in POLARIX was comparable between the 2 treatment arms.
- The proportion of participants who experienced serious neutropenia was higher in the pola+R-CHP arm compared to the R-CHOP arm.
- The proportion of subjects who experienced infections and the incidence of grade ≥3 infections were higher in the pola+R-CHP arm compared to the R-CHOP arm.
- There were no fatal neutropenia events, and fatal (grade 5) infections were similar between both arms (1.1% in pola+R-CHP and 1.4% in R-CHOP).
- To address the FDA's concern that myelosuppression may be underestimated in the POLARIX data, the sponsor stated that it conducted an additional analysis; the incidence of neutropenia was comparable between 2 treatment groups.

The FDA agreed that the "overall safety profile of pola+R-CHP was comparable to R-CHOP," but the incidences of infection, febrile neutropenia, nausea, and diarrhea "were at least 5% higher" in participants taking pola+R-CHP. The agency further added that fewer patients in the pola+R-CHP arm resolved their peripheral neuropathy by the cutoff date.

In the event materials, the FDA also commented on the sponsor's use of PRO measures, which were collected at treatment and follow-up visits for participants who did not have disease progression. The agency pointed to various shortcomings, including that the PROs were exploratory and descriptive endpoints without multiplicity adjustment. In its PRO analysis, the FDA focused on tolerability through the month 12 timepoint from the collected PRO data. The agency stated that it disagrees with the sponsor that "no detriment to global quality of life during treatment was observed with pola+R-CHP compared to R-CHOP." Among reasons given for this stance, the FDA pointed out that superiority is not suitable evidence for claims of comparability or similarity between arms.

Efficacy

According to the sponsor, POLARIX met its primary efficacy endpoint and demonstrated a "statistically significant and clinically meaningful improvement of PFS in the pola+R-CHP arm relative to the R-CHOP arm in patients with 1L DLBCL." Genentech explained that the observed PFS hazard ratio (HR) of 0.73 (95% confidence interval [CI]: 0.57, 0.95) meant a reduction to the risk of disease progression, relapse, or death by 27% in the pola+R-CHP arm compared to the R-CHOP arm. Using Kaplan-Meier estimates, the sponsor showed that pola+R-CHP treatment led to more participants who were progression-free at 2 years relative to those in the R-CHOP arm (76.7% versus 70.2%, respectively).

In its review, the FDA did not agree with the sponsor's assessment that the results from POLARIX "clearly demonstrate a positive benefit-risk" profile for the use of Polivy. The agency expressed the following concerns about the study:

- The sponsor's primary efficacy analysis demonstrated a "modest PFS benefit" for pola+R-CHP versus R-CHOP, with an HR of 0.73. The point estimates for 1- and 2-year PFS rates differed by 4.1% and 6.5%, respectively. The agency questioned whether this difference in rates is "clinically meaningful" and asked the ODAC to consider the findings in the context of "other efficacy results, OS results, and toxicity."
- The FDA conducted various sensitivity analyses to evaluate the robustness of POLARIX's PFS result. The largest calculated difference in 2-year PFS was 6.5%, which did not result in a benefit in CR rate or OS, added the agency.
- The final prespecified analysis of OS, with a median follow-up time of 39.7 months, did not demonstrate an improvement in OS for pola+R-CHP (HR = 0.94 [95% CI: 0.67, 1.33]). The FDA noted that " at some early timepoints," the OS rates in the Kaplan-Meier survival curves were lower for the pola+R-CHP arm than the R-CHOP arm.
- The HR for OS in the largest histological subgroup (DLBCL NOS) was 1.02. This led the agency to question the certainty of that subgroup's results.
- Modified EFS was statistically significant in the pola+R-CHP arm (HR = 0.75 [95% CI: 0.58, 0.96; p-value = 0.0244]), but "the treatment effect was modest."
- The difference in CR rate by BICR was not statistically significant in the pola+R-CHP and R-CHOP arms (78.0% versus 74%, respectively; p-value = 0.1557). The investigator-assessed objective response rates (ORRs) were also similar (84.5% versus 80.9%, respectively). The agency cited these results as raising additional uncertainty about the treatment benefit of pola+R-CHP.
- Additional analyses of disease-free survival (DFS) and duration of response (DOR) "suggested modest benefit" with pola+R-CHP.
- The study population was heterogenous because 84% of participants had DLBCL NOS; 11% had either HGBL NOS or HGBL with MYC, BCL2, and/or BCL6 translocations; and 5% had other LGBLs. The FDA stated that "results across all of these endpoints were either marginal or not indicative of a positive treatment effect."

Medical Issues

According to the National Cancer Institute (NCI) and the Lymphoma Research Foundation (LRF), DLBCL refers to several fast-growing B-cell NHLs whose cells look large under microscope. B cells, a type of white blood cell, are responsible for creating antibodies to fight infections. DLBCL is characterized by rapidly growing tumors in the bone marrow, liver, lymph nodes, spleen, or other organs or tissues. Symptoms of DLBCL include, but are not limited to,

fever, night sweats, fatigue, weight loss, and swollen lymph nodes. While DLBCL can develop at any age, it usually occurs in older adults. Most patients are aged >60 years at the time of diagnosis. The Event Materials (IDRAC 361206) state that the clinical course of DLBCL can be debilitating due to symptoms, lymphadenopathy, organ damage, and bone marrow failure that can lead to anemia, infections, and thrombocytopenia.

The LRF notes that DLBCL is the most common type of NHL in the US and worldwide, accounting for ~22% of newly diagnosed cases in the US (>18,000 people every year). "Despite being an aggressive lymphoma, DLBCL is considered potentially curable," the LRF states. As listed by the LRF, the different DLBCL subtypes are as follows:

- **T-cell/histiocyte-rich BCL:** Under microscope, this form of DLBCL appears as a few scattered, large, and atypical B cells in a background of normal T cells and histiocytes.
- **Primary DLBCL of the central nervous system (CNS):** This type of DLBCL originates in the brain or eye. Secondary DLBCLs may develop if the lymphoma moves into the brain or spinal cord at a later time.
- **Primary cutaneous DLBCL, leg type:** This DLBCL type contains large B cells that appear as red or bluish-red tumors. These lymphomas can spread to areas other than the skin and can involve arms, legs, and other body parts.
- **Epstein-Barr virus (EBV)-positive DLBCL in the elderly:** This form of DLBCL occurs in individuals who are aged ≥50 years and test positive for EBV.
- **DLBCL NOS:** This category is reserved for DLBCLs that do not fall into other categories. The LRF notes that ~25-30% of NHL cases diagnosed in adults are NOS, and this percentage is higher in the developing world.

The most common treatment for DLBCL is a combination of rituximab [Rituxan (IDRAC 339983), from Genentech, Inc], cyclophosphamide [e.g., cyclophosphamide (IDRAC 335715), from Ingenus Pharmaceuticals, LLC], doxorubicin [e.g., Doxil (IDRAC 92954), from Pfizer Inc], vincristine [e.g., Marqibo (IDRAC 313408), from Acrotech Biopharma LLC], and prednisone [e.g., Rayos (IDRAC 304454), from Horizon Pharma USA Inc] known as R-CHOP. In most patients, R-CHOP is administered in 21-day cycles for an average of 6 cycles. However, the number of cycles and duration between them depends on a patient's DLBCL disease level. In certain cases, another chemotherapy drug, etoposide, is added to the R-CHOP regimen, resulting in a combination called R-CHOEP. R-EPOCH is a related regimen involving the same drugs, but it is administered as a continuous IV infusion over 4 days.

The sponsor noted in the event materials that after first relapse of DLBCL, 2 second-line (2L) therapies—autologous stem cell transplantation (SCT) and chimeric antigen receptor (CAR)-T products—may provide a second chance of cure, but at a rate lower than 1L therapy. However, a substantial proportion of 2L DLBCL patients are not eligible for those therapies. Furthermore, although CAR-T products and SCT may cure a minority of patients, they are associated with fatal and severe (grade 3-4) AEs. The FDA stated that it agrees with the sponsor's presentation of the treatment landscape for untreated DLBCL NOS. However, it added, "there is no universal standard for previously untreated HGBL, for which more intensive regimens are generally favored in the US because of concerns with inferior outcomes with R-CHOP."

Pharmacology Issues

Polatuzumab vedotin-piiq is a CD79B-directed ADC comprising 3 components: 1) the humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) specific for human CD79B; 2) the small molecule anti-mitotic agent, monomethyl auristatin E (MMAE); and 3) a protease-cleavable linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mc-vc-PAB), that covalently attaches MMAE to the polatuzumab mAb.

As summarized in the Event Materials (IDRAC 361206), the FDA stated that it identified the limited dose exploration and higher rates of select treatment-emergent AEs (TEAEs) with higher exposure to Polivy as issues with the sponsor's submitted pharmacology data to support the 1L DLBCL indication in sBLA 761121/8. The agency expressed the following main concerns:

- The dose exploration of Polivy was limited by the small number of subjects with previously untreated DLBCL who received Polivy doses <1.8 mg/kg.
- The study enrolled very few participants with untreated DLBCL for dosages <1.8 mg/kg administered every 21 days.

- Given the small number of participants, it is difficult to determine any preliminary efficacy or safety difference in lower dosages (e.g., 1.4 mg/kg) when compared to Polivy 1.8 mg/kg administered every 21 days.
- The Polivy monotherapy study (DCS4968g) did not include participants with untreated DLBCL and only included limited dose explorations in R/R DLBCL (4 subjects given 1.8 mg/kg and 8 subjects given doses <1.8 mg/kg).
- The relationships between Polivy dose and clinical efficacy are still not fully characterized in combination with R-CHP for previously untreated DLBCL or as monotherapy for R/R DLBCL.
- Higher rates of febrile neutropenia and infections in participants who received pola+R-CHP were associated with higher antibody-conjugated MMAE (acMMAE) and MMAE exposure.
- Higher acMMAE and MMAE exposure were associated with higher rates of anemia, febrile neutropenia, infection, and thrombocytopenia, all at grade ≥3. Higher MMAE exposure was associated with higher rates of grade ≥3 neutropenia, and higher acMMAE exposure was associated with higher rates of grade ≥2 peripheral neuropathy.
- Higher acMMAE and MMAE exposure were associated with higher rates of TEAEs leading to dose modification.

Market Issues

If approved by the FDA, Polivy (polatuzumab vedotin-piiq) for injection, from Genentech, Inc, would be another option for use in combination with R-CHP (rituximab product, cyclophosphamide, doxorubicin, and prednisone) for the treatment of adult patients with previously untreated DLBCL. As noted, since ~40% of patients are not cured after currently available 1L DLBCL therapy, and R/R disease is common, more options are needed to treat this type of lymphoma. According to the sponsor, POLARIX is the first study in >20 years that shows improved survival over R-CHOP. Additionally, existing treatments (e.g., SCT) for patients whose DLBCL is not cured after 1L therapy typically requires hospitalization.

In the European Union (EU), Polivy received a conditional marketing authorization as a second-line treatment for DLBCL on January 16, 2020 [EMA EPAR EMEA/H/C/004870 Revision 4: POLIVY (polatuzumab vedotin), 08-June-2022 (IDRAC 348405)]. On March 24, 2022, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended Polivy, in combination with R-CHP, in patients with previously untreated DLBCL. In May 2022, the European Commission approved Polivy for that indication.

In the Pipeline

AbbVie Inc, in collaboration with Genmab A/S, is recruiting ~900 participants for a randomized, open-label phase 3 study (EPCORE DLBCL-2) to evaluate the safety and efficacy of epcoritamab—an investigational subcutaneous bispecific antibody—in combination with R-CHOP in subjects with newly diagnosed DLBCL. This trial is comparing the combination of epcoritamab and R-CHOP to R-CHOP alone. Participants receive either subcutaneous epcoritamab combined with IV and oral R-CHOP, followed by epcoritamab in 21-day cycles, or IV and oral R-CHOP followed by IV rituximab in 21-day cycles. The primary outcome measure is the number of participants with PFS with an international prognostic index (IPI) of 3 to 5, measured for ≤46 months. Begun in February 2023, the study is expected to complete in June 2030.

Merck Sharp & Dohme LLC is recruiting ~420 participants for a randomized, multicenter, open-label 2-part phase 2/3 study (MK-2140-003) to evaluate the safety and efficacy of zilovertamab vedotin (zilovertamab) in combination with standard of care (SOC) options for the treatment of R/R DLBCL. Zilovertamab is an ADC containing a mAb-recognizing extracellular receptor tyrosine kinase–like orphan receptor 1 (ROR1) and the anti-microtubule cytotoxin MMAE. Part 1 of the study focuses on dose confirmation through 2 parallel cohorts: 1) zilovertamab plus R-GemOx (rituximab, gemcitabine, and oxaliplatin) and 2) zilovertamab plus bendamustine and rituximab. Part 2 is an efficacy expansion study in which all participants in each cohort will be assigned to 2 treatment groups for the duration of the study. The primary outcome measures are the number of participants who experienced dose-limiting toxicities (DLTs) in part 1; the number of participants who experienced AEs; the number of participants who discontinued treatment due to AEs; and PFS. The study began in January 2022 and is estimated to complete in December 2025.

Additional *Cortellis RI* Resources Briefing Information

Event Materials (IDRAC 361206)

AdComm Bulletin and *FDA Workshop Bulletin* Coverage

Click here for:
Drugs and Biologics FDA Advisory Committees (IDRAC 23827)
Medical Devices and IVDs FDA Advisory Committees (IDRAC 289859)
and
Drugs and Biologics FDA Workshops (IDRAC 40156)*
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**FDA Workshop Bulletins* are added directly to Cortellis.

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Principal Content Editors
Deborah A. Komlos, MS
Jaime Gavazzi
Senior Content Editors
Asher Madan, MBBS
Jennifer Nguyen, PhD

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