

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761121Orig1s000

SUMMARY REVIEW

Summary Review
 (Cross-Discipline Team Leader, Division Director, and
 Office Director Review)

Date	see stamp date
From	R. Angelo de Claro, MD (CDTL) Ann T. Farrell, MD (Division Director) Richard Pazdur (Office Director)
Subject	Summary Review
NDA/BLA # and Supplement#	BLA 761121 Original application (New Molecular Entity)
Applicant	Genentech, Inc.
Dates of Submission	November 21, 2018 December 19, 2018
PDUFA Goal Date	August 19, 2019
Proprietary Name	Polivy
Established or Proper Name	polatuzumab vedotin-piiq
Dosage Form(s)	For injection: 140 mg of polatuzumab vedotin-piiq as a lyophilized powder in a single-dose vial
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed Dosing Regimen(s)	1.8 mg/kg as an intravenous infusion over 90 minutes every 21 days for 6 cycles, in combination with bendamustine (90 mg/m ² /day for 2 days) and rituximab
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	In combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies
Recommended Dosing Regimen(s) (if applicable)	Same as Applicant's proposed dosing regimen

Material Reviewed/Review Discipline	Reviewers
Clinical Review	Yvette Kasamon, M.D. / R. Angelo de Claro, M.D.
Statistical Review	Alexei Ionan, Ph.D. / Jingjing Ye, Ph.D. / Rajeshwari Sridhara, Ph.D.
Clinical Pharmacology Review	Salaheldin Hamed, Ph.D. / Justin Earp, Ph.D. / Xinyuan Zhang, Ph.D. / Yuching Yang, Ph.D. / Lian Ma, Ph.D. / Guoxiang Shen, Ph.D. / Nam Atiqur Rahman, Ph.D.

Material Reviewed/Review Discipline	Reviewers
Pharmacology-Toxicology Review	Ramadevi Gudi, Ph.D. / Natalie Simpson, Ph.D. / Christopher Sheth, Ph.D. / Haleh Saber, Ph.D.
Product Quality Review	Leslie Ann Rivera Rosado, Ph.D. (Application Technical Lead) / refer to CMC review for full list
OSI	Anthony Orenca, M.D.
OSE/DMEPA	Naomi Boston, Pharm.D./ Elizabeth Everhart, R.N. Nicole Garrison, Pharm.D./ Hina Mehta, Pharm.D.
OPDP	Nisha Patel Pharm.D./ Trung-Hieu Tran Pharm.D.
Regulatory Project Manager	Wanda Nguyen, Pharm.D.
Cross-Disciplinary Team Lead	R. Angelo de Claro, M.D.
Division Director (DHP)	Ann Farrell, M.D.
Office Director (OHOP)	Richard Pazdur, M.D.

OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; OPDP, Office of Prescription Drug Promotion; DHP, Division of Hematology Products; OHOP, Office of Hematology and Oncology Products; OCE, Oncology Center of Excellence

1. Benefit-Risk Assessment

The efficacy and safety results from clinical trial GO29365 (NCT02257567) demonstrate substantial evidence of effectiveness and an acceptable benefit-risk profile for polatuzumab vedotin-piiq, in combination with bendamustine and rituximab product, for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies.

All review teams recommend approval.

Accelerated approval is recommended because the efficacy was established based on a response rate endpoint. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

The recommended dosing regimen of polatuzumab vedotin-piiq is 1.8 mg/kg administered as an intravenous infusion every 21 days for 6 cycles in combination with bendamustine and rituximab product. Administer POLIVY, bendamustine, and rituximab product in any order on Day 1 of each cycle. The recommended dose of bendamustine is 90 mg/m²/day on Day 1 and 2 when administered with POLIVY and a rituximab product.

Refer to benefit-risk analysis framework in next page.

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Efficacy: The efficacy of polatuzumab vedotin-piiq (pola) is based on complete response (CR) rate assessed by an independent review committee (IRC), best overall response rate (BOR), and duration of response (DOR) in Study GO29365, which included a randomized, open-label, cohort of 80 patients with relapsed or refractory DLBCL. Patients were randomized 1:1 to receive either pola + bendamustine and rituximab (BR) or BR alone for six 21-day cycles. Eligible patients were not candidates for autologous hematopoietic stem cell transplantation (HSCT) at study entry. The primary endpoint was IRC-assessed CR rate by PET-based criteria at end-of-treatment (EOT). The median number of prior therapies was 2, with 29% receiving one prior therapy, 25% receiving 2 prior therapies, and 46% receiving 3 or more prior therapies. Eighty percent of patients had refractory disease to last therapy.

Patients in the pola +BR arm received a median of 5 cycles, whereas patients in the BR arm received a median of 3 cycles. The difference in exposure was driven by the higher rate of early treatment discontinuation due to inefficacy in the BR arm. At EOT, the FDG-PET CR rate per IRC was 40% with pola + BR vs. 18% with BR. This represented a 22% higher observed CR rate (95% CI: 3, 41) in the pola arm. A best response of CR or PR per IRC was achieved by 63% of the pola + BR arm and 25% of the BR arm, whereas a best response of CR was achieved by 50% and 23%, respectively.

Responses tended to be more durable in the pola + BR arm. Of the 25 responding patients in the pola + BR arm, 16 (64%) had a DOR of ≥ 6 months, and 12 (48%) had a DOR of ≥ 12 months. Of the 10 responding patients in the BR arm, 3 had a DOR lasting ≥ 6 months, and 2 had a DOR lasting ≥ 12 months. Although progression-free survival (PFS) and overall survival (OS) were available in Study GO29365, the small number of events and sample size limit the interpretability of the PFS and OS results.

Safety: In 173 patients with lymphoma treated with pola, bendamustine, and either rituximab or obinutuzumab in Study GO29365, fatal AEs occurred in 4.6% within 90 days of last treatment, with infection as a leading cause. SAEs occurred in 60%, most often from infection. Adverse reactions in $\geq 20\%$ of patients were diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, pyrexia, decreased appetite, anemia, and vomiting.

Benefit/Risk: Pola + BR has an overall favorable benefit/risk in patients with relapsed or refractory DLBCL after at least 2 prior lines of therapy. There were too few patients with one prior line (11 in the pola+BR arm) to inform benefit/risk.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	DLBCL is fatal if not cured. In refractory DLBCL, standard salvage regimens produce ORRs of 20-30%, with <15% CR and an estimated median OS of 6 months.	There is a need for more effective yet tolerable salvage therapies for DLBCL.
Current Treatment Options	Widely used salvage regimens for DLBCL include platinum, etoposide, and/or cytarabine-based combination regimens with rituximab, while less intensive regimens include gemcitabine and bendamustine. Axicabtagene ciloleucel and tisagenlecleucel have regular approval for relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.	Patients with relapsed or refractory DLBCL have unmet medical need. Although axicabtagene ciloleucel and tisagenlecleucel are approved for R/R large B-cell lymphoma, these therapies are not widely available, and have specific requirements for therapy.
Benefit	<ul style="list-style-type: none"> • An open-label phase 2 study (GO29365) randomized 80 patients with DLBCL after at least 1 prior therapy to pola + BR or BR alone for 6 cycles. At EOT, the PET CR rate was 40% with pola + BR vs. 18% with BR. This represented a 22% higher observed CR rate (95% CI: 3, 41) in the experimental arm. • A best response of CR or PR per IRC was achieved by 63% of the pola + BR arm and 25% of the BR arm, whereas a best response of CR was achieved by 50% and 23%, respectively. • Responses tended to be longer in the pola + BR arm. 	Based on CR rate at EOT, BOR, and DOR per IRC in a randomized phase 2 study, pola + BR has clinically meaningful activity in patients with relapsed or refractory DLBCL. Despite the limitations of the study, there is a strong indication of a positive treatment effect with the addition of pola to BR in the intended population.
Risk and Risk Management	<ul style="list-style-type: none"> • In 173 patients with lymphoma treated with pola, bendamustine, and either rituximab or obinutuzumab in Study GO29365, fatal AEs occurred in 4.6% within 90 days of last treatment, with infection as a leading cause. SAEs occurred in 60%, most often from infection. • Adverse reactions in ≥20% were diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, pyrexia, decreased appetite, anemia, and vomiting. 	<ul style="list-style-type: none"> • Pola + BR has an acceptable safety profile in the intended population. • Peripheral neuropathy, infusion-related reaction, myelosuppression, and serious or opportunistic infections should be included in the Warnings and Precautions.

2. Background

On December 19, 2018, Genentech, Inc. (Applicant) submitted a Biologics License Application (BLA) for Polivy. The Applicant proposed the following indication for Polivy: (b) (4)

Polivy (polatuzumab vedotin-piiq), a new molecular entity, is a CD79b-directed antibody-drug conjugate. Other approved antibody-drug conjugates for oncologic indications include brentuximab vedotin, inotuzumab ozogamicin, gemtuzumab ozogamicin, and trastuzumab emtansine.

DLBCL is fatal if not cured. In refractory DLBCL, standard salvage regimens produce ORRs of 20-30%, with <15% CR and an estimated median OS of 6 months. Widely used salvage regimens for DLBCL include platinum, etoposide, and/or cytarabine-based combination regimens with rituximab, while less intensive regimens include gemcitabine and bendamustine. Although axicabtagene ciloleucel and tisagenlecleucel are approved for R/R large B-cell lymphoma, these therapies are not widely available, and have specific requirements for therapy.

The primary basis for the application are the results of clinical trial GO29365 (NCT02257567), an open-label, multicenter clinical trial that included a randomized cohort of 80 patients (polatuzumab+BR vs BR) with relapsed or refractory DLBCL after least one prior regimen. Other cohorts in GO29365 provided supportive evidence of efficacy and safety.

***CDTL Comment:** In the discipline reviews, the review teams used the term “polatuzumab vedotin” to refer to polatuzumab vedotin-piiq. The four-letter suffix was not finalized at the time of review completion of the various review disciplines.*

3. Product Quality

Source: Product Quality Review

Product Quality Team Recommendation: Approval

- General product quality considerations

Polatuzumab vedotin-piiq is a CD79b-targeted antibody-drug conjugate (ADC) that preferentially delivers an anti-mitotic agent (monomethyl auristatin E [MMAE]) to B cells, which results in anti-cancer activity against B-cell malignancies. The polatuzumab vedotin-piiq molecule consists of MMAE covalently attached to a CD79b-directed humanized IgG1 monoclonal antibody (produced in CHO cells) through the protease-cleavable linker maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mc-vc-PAB). The polatuzumab vedotin-piiq manufacturing

process was designed to deliver an average of 3.5 linked MMAE moieties per antibody molecule [drug-to-antibody ratio (DAR) = 3.5].

POLIVY (polatuzumab vedotin-piiq) is provided in single-dose 20 mL vials as a sterile, white to grayish-white lyophilized powder with cake-like appearance and contains no preservatives. It is intended for intravenous infusion after reconstitution with sterile water for injection and dilution in 0.9% sodium chloride solution, 0.45% sodium chloride solution, or 5% dextrose solution. Reconstituted POLIVY contains 20 mg/mL polatuzumab vedotin-piiq in (b) (4) succinate, (b) (4) sucrose, (b) (4) polysorbate 20, pH 5.3.

Fill size and dosage form: 140 mg/vial, for injection

Dating period:

- Drug Product: 24 months at 2-8 °C
- Drug Substance: (b) (4)
- Antibody Intermediate: (b) (4)

The assessment of manufacturing information provided in the application and in the cross-referenced drug master file (DMF) has concluded that the methodologies and processes used for antibody intermediate, vcMMAE intermediate, drug substance, and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The antibody intermediate and drug substance manufacturing processes are robust for removal and control of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

- Facilities review/inspection

All facilities used for the manufacture and quality control testing were found acceptable for the proposed operations.

- Other notable issues: None

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology/ Toxicology Review

Pharmacology/Toxicology Team Recommendation: Approval

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The pharmacology and toxicology studies reviewed included primary pharmacodynamics, genotoxicity, safety pharmacology, repeat dose toxicology, and embryo-fetal developmental toxicity of polatuzumab vedotin-piiq.

Mechanism of Action

Polatuzumab vedotin-piiq binds to human CD79b, is internalized, cleaved by lysosomal proteases, thereby delivering MMAE to malignant B-cells. The released MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.

Pharmacology

In cell-based assays, polatuzumab vedotin-piiq antibody-dependent cell-mediated cytotoxicity (ADCC) was one order of magnitude lower than the positive control (rituximab) and no complement-dependent cytotoxicity (CDC) was observed. Polatuzumab vedotin-piiq demonstrated anti-tumor activity in vitro in CD79b expressing human Burkitt lymphoma (Ramos) cells (IC₅₀ = 0.071 nM) and in vivo in DLBCL and human B-cell lymphoma mouse xenograft models. A single IV dose of 12 mg/kg induced durable complete responses (i.e., no measurable tumor) in 75% of mice in a DLBCL xenograft model. The addition of obinutuzumab or rituximab and bendamustine or CHP [cyclophosphamide (C), doxorubicin (H), prednisone (P)] chemotherapy to 2 mg/kg polatuzumab vedotin-piiq reduced the time to tumor doubling.

Safety pharmacology assessments (neurobehavioral, cardiovascular, and respiratory) that were incorporated into the repeat-dose toxicology studies showed no polatuzumab vedotin-piiq- or surrogate ADC-induced adverse effects in monkeys. MMAE alone did not appreciably inhibit the human ether-à-go-go-related gene (hERG) channel (IC₅₀ > 100 μM) in voltage-clamped human embryonic kidney cells.

Toxicology

In the repeat-dose rat study, polatuzumab vedotin-piiq was administered by intravenous (IV) injection once weekly for 4 weeks at doses of 2, 6, and 10 mg/kg. The adverse effects were observed at all dose levels and included bone marrow hypocellularity with associated hematology effects and liver toxicity, including increased apoptosis/mitoses of hepatocytes, multifocal hepatic necrosis with higher serum liver transaminases, and total bilirubin. Male reproductive organ toxicities included testicular seminiferous tubule degeneration with consequent abnormal lumen contents in the epididymis. Microscopic findings in many tissues were consistent with the known effects of MMAE on inducing mitotic arrest (due to inhibition of tubulin formation), particularly in cells/tissues with a higher background mitotic rate.

In the repeat-dose monkey toxicology study, polatuzumab vedotin-piiq or surrogate ADC were administered once every 3 weeks (Days 1, 22, 43, 64) by IV injection resulting in doses of 1, 3, and 5 mg/kg or 3 and 5 mg/kg, respectively. Toxicities related to polatuzumab vedotin-piiq and surrogate ADC treatment included, reversible dose-dependent bone marrow hypocellularity with corresponding myelosuppression at 3 and 5 mg/kg. The surrogate ADC induced decreases in circulating B-lymphocytes (CD20+) and absence of lymphoid follicular germinal centers in the spleen at 3 and 5 mg/kg, consistent with expected pharmacologic effects. Anti-drug-antibodies to

polatuzumab vedotin-piiq or the surrogate ADC did not appear to impact exposure at any dose level and the toxicokinetic (TK) profiles were similar between ADA-positive and ADA-negative animals.

Acute and longer-term effects of MMAE administration evaluated in rats and cynomolgus monkeys included bone marrow toxicity (characterized by decreased peripheral platelets, red blood cell [RBC] and white blood cell [WBC] parameters, and decreased bone marrow cellularity), liver toxicity (characterized by elevated peripheral liver indices and hepatocellular apoptosis, necrosis, and increased mitosis), and lymphoid organ toxicity (characterized by decreased lymphoid cellularity in the thymus and spleen).

Taken together, the primary polatuzumab vedotin-piiq target organs identified by the repeat-dose toxicity studies were the bone marrow, hematolymphopoietic tissues, liver and the male reproductive organs consistent with the expected activity of MMAE.

- Carcinogenicity

Carcinogenicity studies in animals have not been performed with polatuzumab vedotin-piiq or MMAE and are not warranted for the proposed indication.

- Reproductive toxicology/Embryofetal development study

A designated fertility study was not conducted with polatuzumab vedotin or MMAE and is not needed for the proposed indication. However, results of repeat-dose toxicity studies in rats indicate the potential for polatuzumab vedotin-piiq to impair fertility in males.

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. Based on positive genotoxicity and results of general toxicology studies showing adverse effects on rapidly dividing cells, a dedicated embryofetal developmental (EFD) study with the ADC or the MMAE is not necessary, per recommendations in ICH S9. Despite this, results of EFD studies were submitted. In an embryo-fetal developmental study, pregnant rats were given 2 intravenous doses of 0.2 mg/kg MMAE during the period of organogenesis on gestation Days 6 and 13. MMAE-related toxicities included pre-/post-implantation loss and embryo-fetal lethality (early resorptions, pre-implantation and post-implantation loss, decreased numbers of live fetuses, and malformations). The fetal malformations included protruding tongue, malformed mandible corresponding to agnathia, malrotated limbs, and gastroschisis. These effects were observed at doses below the therapeutic AUC in patients who received the recommended dose of 1.8 mg/kg POLIVY every 21 days.

- Other notable issues: None

5. Clinical Pharmacology

Source: Clinical Pharmacology Review

Clinical Pharmacology Team Recommendation: Approval

- General clinical pharmacology considerations

Absorption

Not applicable, administered by intravenous infusion.

Distribution

The volume of distribution of polatuzumab vedotin-piiq is 3.15 L. The plasma protein binding of MMAE ranges from 71% to 77%.

Elimination

The terminal half-life of polatuzumab vedotin-piiq is approximately 12 days, and the elimination half-life of MMAE is approximately 4 days. The primary route of MMAE elimination is the biliary route.

Metabolism

Polatuzumab vedotin-piiq catabolism has not been studied in humans; however, it is expected to undergo catabolism to small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related catabolites. MMAE is a substrate for CYP3A4.

- Drug-drug interactions

No dedicated clinical drug-drug interaction studies with POLIVY in humans have been conducted.

- Pathway of elimination

Refer to General Clinical Pharmacology considerations.

- Intrinsic factors potentially affecting elimination, Demographic interactions, and Special populations

No dose adjustments are recommended based intrinsic or extrinsic factors. Population PK analysis did not identify differences in polatuzumab vedotin-piiq PK due to age (20 to 89 years), sex, race/ethnicity (Asian and non-Asian), or renal impairment (mild and moderate).

Although patients with mild hepatic impairment had approximately 40% increase in MMAE exposure, no dose adjustment is recommended based on exposure-safety information. The effect of moderate and severe hepatic impairment on safety and PK of polatuzumab vedotin-piiq is unknown.

- Thorough QT study or other QT assessment

The effect of polatuzumab vedotin-piiq (1.8 mg/kg) on the QTc interval was evaluated based on triplicate ECG data from two open-label studies in 209 patients with previously treated B-cell malignancies. The administration of polatuzumab vedotin-piiq did not prolong the mean QTc interval by more than 20 ms from baseline. Small increases in the QTc interval (less than 10 ms) cannot be excluded because these studies did not include placebo arms or positive control arms.

- Other issues:

Immunogenicity. The immunogenicity of polatuzumab vedotin-piiq was determined in 134 patients across all arms of study GO29365; 8 patients (6%) tested positive for antibodies against polatuzumab vedotin-piiq. Across clinical trials, 14/536 (2.6%) tested positive for polatuzumab vedotin-piiq antibodies.

Bridging of formulations. The PK and safety of the lyophilized drug product (to-be-marketed) formulation was characterized in the Arm G (~40 patients) in study GO29365. Population PK analysis indicated that there is no difference in the PK between the lyophilized formulation and the solution formulation used in other clinical studies of polatuzumab vedotin-piiq.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Source: Statistical and Clinical Reviews

Clinical Team Recommendation: Approval
Statistical Team Recommendation: Approval

Statistical Review (Executive Summary)

Polatuzumab vedotin-piiq is a CD79b-directed antibody–drug conjugate and is a new molecular entity (NME). In this application, the Applicant seeks the approval of polatuzumab vedotin-piiq (b) (4)

(b) (4) The BLA application was based on the pivotal Study GO29365, which is an open-label, randomized, multicenter study of polatuzumab vedotin-piiq in combination with bendamustine and a rituximab product (BR) versus BR alone for six 21-day cycles. The primary objective of the study GO29365 was to determine whether the addition of polatuzumab vedotin-piiq to BR improves complete response (CR) rate compared with BR alone in adult patients with DLBCL, not otherwise specified, who have received at least one prior therapy.

The key efficacy results in study GO29365 are summarized below:

- **Major outcome** in Study GO29365 is complete response (CR) rate at primary response assessment. CR rate is 40% (95% CI: 25, 57) in P+BR group and 18% (95% CI: 7, 33) in BR group. The estimated difference in CR rates between P+BR and BR groups is 22% (95% CI: 3, 41). Subgroup analyses and additional sensitivity analyses have not revealed major issues in interpretation of the major outcome analysis.
- **Duration of response** exceeds 12 months in 48% (12/25; P+BR) and 20% (2/10; BR) of patients who achieved a partial response (PR) or CR.
- **Best overall response (BOR)** rate is 62% (95% CI: 46, 77) in P+BR group and 25% (95% CI: 13, 41) in BR group.
- In **lyophilized formulation** of polatuzumab vedotin-piiq in combination with BR single-group cohort, CR rate at primary response assessment is 34% (95% CI: 19, 53) and BOR rate is 47% (95% CI: 29, 65).
- A benefit observed on a CR outcome may not necessarily translate to a **benefit in survival**. No definitive conclusions can be drawn from progression-free survival (PFS) and overall survival (OS) results in Study GO29365 due to limited number of events.

Study GO29365 has demonstrated the benefit of polatuzumab vedotin-piiq in combination with BR over BR alone for the treatment of patients with R/R DLBCL in CR rate and provided supportive evidence in duration of response.

Statistical Conclusion and Recommendations: The efficacy of polatuzumab vedotin-piiq in combination with rituximab and bendamustine (N=40) compared to rituximab and bendamustine alone (N=40) for the treatment of patients with R/R DLBCL has been assessed based on the randomized pivotal Study GO29365. Internal consistency of P+BR favorable efficacy has been demonstrated by i) advantage over BR in the pre-specified major efficacy outcome of complete response rate at the primary response assessment ii) supporting evidence on best overall response rates and the duration of response iii) supporting efficacy evidence on lyophilized formulation of polatuzumab vedotin-piiq from a single-group cohort (N=32).

Clinical Review (Substantial Evidence of Effectiveness)

The efficacy of polatuzumab vedotin-piiq (pola) in combination with BR is based on response rates and duration as determined by an independent review committee (IRC) in a multicenter, open-label clinical trial (Study GO29365). The study randomized 80 patients with relapsed or refractory DLBCL after at least one prior therapy to either pola + BR (N = 40) or BR alone (N = 40) for six cycles. The primary endpoint was complete remission (CR) rate at the end of therapy per IRC. At the end of therapy, the PET CR rate was numerically more than 2-fold higher in the pola + BR arm (40%; 95% CI, 25-57) than in the BR arm (18%; 95% CI, 7-33), representing a 22% higher observed CR rate (95% CI: 3, 41). The best objective response (BOR) rate was likewise more than 2-fold higher in the pola + BR arm (63%, vs. 25% with BR

alone). Of the 25 responding patients in the pola + BR arm, 16 (64%) had a DOR of ≥ 6 months, and 12 (48%) had a DOR of ≥ 12 months. In contrast, of the 10 responding patients in the BR arm, 3 had a DOR lasting ≥ 6 months, and 2 had a DOR lasting ≥ 12 months. Progression-free survival (PFS) and overall survival (OS) also tended to be longer in the pola + BR arm; however, there are multiple limitations with those data, specifically due to small sample size.

Because of the small sample size, the magnitude of the treatment effect with the addition of pola is uncertain. However, the observed differences between arms in depth of response at end of therapy, overall response, and response duration are clinically meaningful. These response data provide substantial evidence of effectiveness and are the basis for the recommended accelerated approval. Because of the paucity of data in patients with one prior therapy, the recommended indication is restricted to patients with relapsed or refractory DLBCL after at least two prior therapies.

Conclusions on the Substantial Evidence of Effectiveness: Efficacy was based on complete response (CR) rate at the end of treatment and DOR (duration of response), as determined by an independent review committee (IRC). These endpoints are acceptable efficacy endpoints for oncology indications. Approval based on a single pivotal trial is supported by internal consistency demonstrated in complete response rate results and supporting evidence of overall response rates and duration of response in the randomized cohort and other single-arm DLBCL cohorts in trial GO29365. Accelerated approval is recommended because the efficacy findings represent endpoints that are reasonably likely to predict clinical benefit.

8. Safety

Source: Clinical Review

Clinical Team Recommendation: Approval

The determination of safety is based on Study GO29365. The primary safety population consisted of patients with DLBCL who received BR with (N = 45) or without (N = 39) polatuzumab vedotin-piiq (pola), including 6 recipients of pola + BR in the phase 1b portion. Patients treated with pola plus BR received a median of 5 cycles, with 49% receiving 6 cycles. Patients treated with BR alone received a median of 3 cycles, with 23% receiving 6 cycles. For increased sensitivity, the analysis was supplemented with data from an expanded safety population, comprised of all recipients of pola or LYO (lyophilized formulation) pola + BR or BG in Study GO29365 (N = 173).

In the primary safety population (N=45), fatal AEs within 90 days of last treatment occurred in 7% of recipients of pola + BR. SAEs occurred in 64% of recipients of pola + BR, most often from infection. SAEs in $\geq 5\%$ included pneumonia (16%), febrile neutropenia (11%), pyrexia (9%), and sepsis (7%). AEs led to dose reduction in 18%, dose interruption in 51%, and permanent discontinuation of all treatment in 31%. The leading AEs resulting in treatment discontinuation were thrombocytopenia (9% of all patients) and neutropenia (7%). The most common ARs ($\geq 20\%$) were neutropenia, thrombocytopenia, anemia, peripheral neuropathy,

fatigue, diarrhea, nausea, pyrexia, decreased appetite, and pneumonia. More than 20% of patients developed grade 3 or 4 neutropenia, leukopenia, or thrombocytopenia, and >10% developed grade 4 neutropenia (13%) or grade 4 thrombocytopenia (11%).

Safety was also evaluated in 173 adult patients with rel/ref FL or DLBCL who received POLIVY (clinical trial or to-be-marketed formulation), bendamustine, and either rituximab or obinutuzumab in Study GO29365, including the 45 patients with DLBCL described above. The overall safety profile in the primary and expanded safety populations was similar. In the expanded safety population, fatal AEs within 90 days of last treatment occurred in 4.6%, with infection as a leading cause. SAEs occurred in 60%, most often from infection. ARs in $\geq 30\%$ of patients were nausea, diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, and pyrexia. Other ARs in $\geq 20\%$ of patients included decreased appetite, anemia, constipation, vomiting, and abdominal pain. Infection-related events in > 10% of patients included upper respiratory tract infection, febrile neutropenia, pneumonia, and herpesvirus infection.

Across all arms of Study GO29365, 8/134 (6%) patients tested positive for antibodies against polatuzumab vedotin-piiq at one or more post-baseline time points. Across clinical trials, 14/536 (2.6%) evaluable POLIVY-treated patients tested positive for such antibodies at one or more post-baseline time points. Due to the limited number of patients with antibodies against polatuzumab vedotin-piiq, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

9. Advisory Committee Meeting

The application was not presented to the Oncologic Drug Advisory Committee or other external consultants, as it did not raise significant efficacy or safety concerns.

10. Pediatrics

Polivy is exempt from pediatric study requirements described in 21 CFR 314.55. FDA granted Orphan Drug Designation for polatuzumab vedotin for the treatment of diffuse large B-cell lymphoma on December 12, 2016.

CDTL Comment: Orphan drug designation occurred prior to finalization of the four-letter suffix (“-piiq”).

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): No issues.
- Exclusivity or Patent Issues of Concern: No issues.
- Financial Disclosures: In accordance with 21 CFR 54.4, the Applicant submitted the required financial disclosure requirement and certification for clinical trial GO29365.
- Other GCP Issues: None

- Office of Scientific Investigation (OSI) Audits: The OSI inspected the Applicant and a single clinical site (#272994) with regard to the randomized phase 2 study in DLBCL (the basis of efficacy in Study GO29365). The clinical review team selected the site because of its relatively high accrual and disclosed financial interests (see Appendix, Section 13.2). The preliminary regulatory compliance classification for both the Applicant and the clinical site was No Action Indicated.
- Other outstanding regulatory issues: None

12. Labeling

Prescribing Information

Refer also to primary discipline reviews and labeling consults (OPDP, DMEPA) for other labeling recommendations. All teams participated in the labeling discussions.

Section	Applicant's Proposed Labeling	Recommended Labeling
Indication	(b) (4)	In combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified after at least two prior therapies (accelerated approval)
Dosage and Administration		<ul style="list-style-type: none"> • Administer infection prophylaxis, including for PJP and herpesvirus • Consider TLS prophylaxis • Revise and expand toxicity management guidelines. <ul style="list-style-type: none"> – Before dose reducing bendamustine for neutropenia, consider GCSF prophylaxis. – Before discontinuing all treatment for neutropenia or thrombocytopenia, consider pola dose reduction. – Add guidelines for IRR
Warnings and Precautions		<ul style="list-style-type: none"> • Add IRR as a warning. • Use all recipients of pola or LYO pola + BR/BG in Study GO29365 (N = 173) as the denominator to inform safety, with more detailed descriptions of toxicity.
Adverse Reactions		<ul style="list-style-type: none"> • In addition to safety based on primary safety population, expand safety characterization to include all recipients of pola or LYO pola + BR/BG. • Use grouped PTs for more sensitive labeling. • Expand reporting of lab abnormalities.

Section	Applicant's Proposed Labeling	Recommended Labeling
Efficacy	(b) (4)	<ul style="list-style-type: none"> • Add pneumonitis as a clinically relevant AR. • Limit efficacy reporting to response (ORR and CR rate) at EOT and BOR per IRC, with a text description of DOR. • Remove (b) (4).

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The review teams determined that a REMS is not needed. Based on the observed safety profile of polatuzumab vedotin-piiq, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The Division recommended issuance of accelerated approval (AA) PMRs to verify clinical benefit. Verification of clinical benefit through either Study GO39942 (POLARIX) or Study MO40598 would be adequate to fulfill the accelerated approval requirement.

AA PMR 1: Complete Study GO39942, a randomized, double-blind, placebo-controlled trial that evaluates polatuzumab vedotin-piiq in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP in patients with previously untreated diffuse large B-cell lymphoma. The primary endpoint would be progression-free survival. Key secondary endpoints would include complete remission rate per independent review committee and overall survival.

AA PMR 2: Complete Study MO40598, a randomized clinical trial that evaluates polatuzumab vedotin-piiq in combination with rituximab, gemcitabine, and oxaliplatin (R-GemOx) versus R-GemOx alone in patients with relapsed or refractory large B-cell lymphoma. The primary endpoint would be overall survival. Key secondary endpoints would include progression-free survival and complete remission rate.

CMC team recommended a PMC for further development of the immunogenicity assay.

PMC: Develop and validate a sensitive assay to evaluate the neutralizing capacity of anti-polatuzumab vedotin-piiq antibodies (ADA) in confirmed ADA-positive patient samples. The assay should be designed to be capable of detecting neutralizing ADA in the presence of polatuzumab vedotin-piiq levels that are expected to be present in patient samples at the time of ADA sample collection. The final report should include the assay validation report and assay standard operating procedure.

Refer to action letter for final wording and milestones for the PMRs and PMC.

14. Recommended Comments to the Applicant

None

15. Division Director Review

I agree with the recommendations of the clinical team. This application for polatuzumab vedotin-piiq for patients with relapsed and refractory diffuse large B-cell lymphoma is recommended for accelerated approval based on an improvement in complete response (CR) rate, assessed by an independent review committee, and supported by analyses of best overall response rate (BOR), and duration of response (DOR) in Study GO29365. At the time of study entry, patients were not candidates for hematopoietic stem cell transplant. The majority of patients had received 2 or more prior therapies. The FDG-PET CR rate per IRC was 40% with pola + BR vs. 18% with BR. This improvement was supported by exploratory analyses of CR by IRC, best response rate by IRC and duration of response data. Infection was the leading non-progression cause of fatal adverse events (AEs) in the clinical trial. Serious AEs occurred in 60%, most often from infection. Adverse reactions in $\geq 20\%$ of patients were diarrhea, neutropenia, peripheral neuropathy, fatigue, thrombocytopenia, pyrexia, decreased appetite, anemia, and vomiting. Given the likely fatal outcome for patients with relapsed and refractory diffuse large B-cell lymphoma, this product used in combination with bendamustine and rituximab has an overall favorable benefit/risk in patients with relapsed or refractory DLBCL after at least 2 prior lines of therapy.

16. Office Director Review

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WANDA D NGUYEN
06/06/2019 12:06:15 PM

ROMEO A DE CLARO
06/06/2019 12:09:23 PM

ANN T FARRELL
06/06/2019 12:49:24 PM

RICHARD PAZDUR
06/06/2019 01:38:40 PM