POLIVY™
polatuzumab vedotin-piiq
INJECTION FOR INTRAVENOUS USE 140MG

POLIVY + bendamustine + a rituximab product (BR)

Dosing and Administration Guide

Indication

POLIVY in combination with bendamustine and a rituximab product is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least 2 prior therapies.

Accelerated approval was granted for this indication based on complete response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Important Safety Information

Serious and sometimes fatal adverse reactions can occur with POLIVY treatment. Peripheral neuropathy, infusion-related reactions, myelosuppression, serious and opportunistic infections, progressive multifocal leukoencephalopathy (PML), tumor lysis syndrome, hepatotoxicity, and embryo-fetal toxicity can occur with POLIVY treatment.

Please see additional Important Safety Information on pages 8-9 as well as full Prescribing Information.

Visit us at POLIVY.com/hcp to learn more

POLIVY is a CD79b-directed antibody-drug conjugate (ADC)

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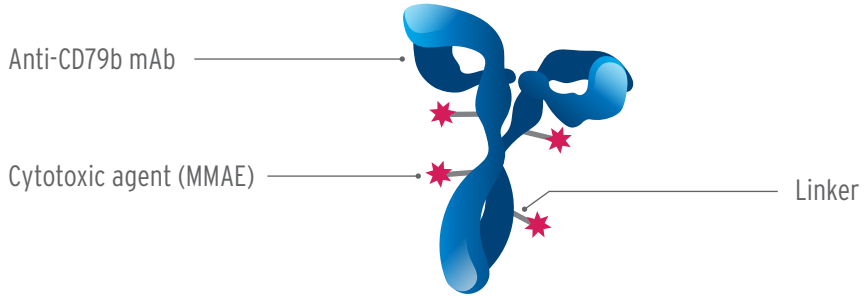
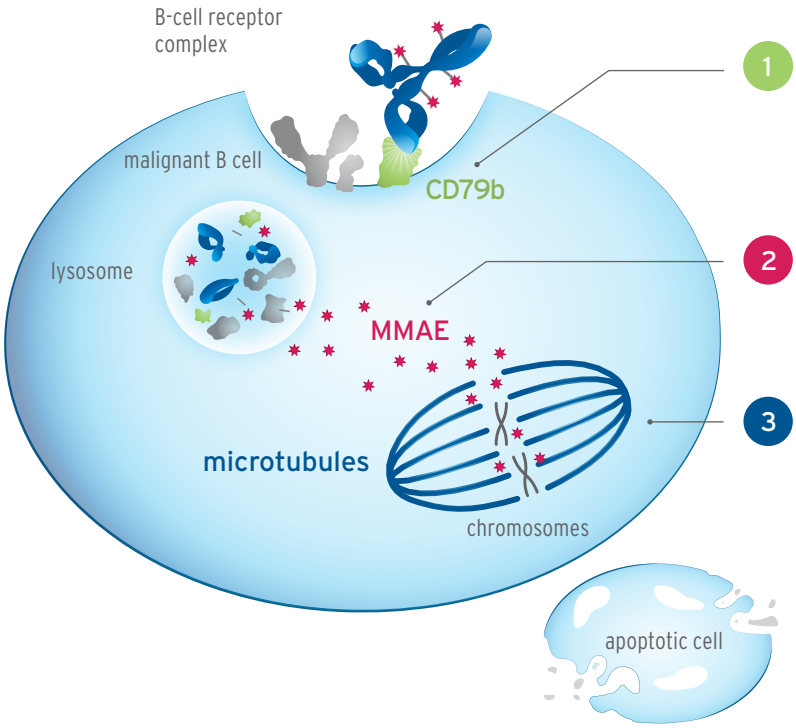
POLIVY is composed of the potent cytotoxin monomethyl auristatin E (MMAE) and a CD79b-targeted monoclonal antibody (mAb)[1]

MMAE is an anti-mitotic agent covalently attached to the antibody via a protease-cleavable linker.



Proposed mechanism of action (MOA)

POLIVY is proposed to deliver the anti-mitotic MMAE to B cells and induce apoptosis.



1 ADC internalization
POLIVY binds to the CD79b portion of the B-cell receptor complex on B cells, triggering internalization of POLIVY and the receptor complex.

2 Cytotoxin delivery
Once internalized, the stable linker is cleaved, releasing MMAE within the B cell.

3 Microtubule disruption and apoptosis induction
MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.

IV=intravenous.

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Dosing and administration

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Dosage forms and strengths[1]

POLIVY for injection is a sterile, preservative-free, white to grayish-white lyophilized powder, which has a cake-like appearance and is supplied in a 140 mg single-dose vial.

Recommended dosing schedule for POLIVY[1]

Day 1

POLIVY
1.8 mg/kg IV

Bendamustine
90 mg/m^2 IV

Rituximab product
375 mg/m^2 IV

Day 2

Bendamustine
90 mg/m^2 IV

Wait 3 weeks
between infusions

Repeat
for a total of
6 cycles

POLIVY, bendamustine, and a rituximab product can be administered in any order on Day 1 of each cycle.

Recommended infusion and monitoring times for POLIVY

1st **90-MINUTE INITIAL IV INFUSION** should be administered while monitoring patients for infusion-related reactions.
90-MINUTE MINIMUM MONITORING for infusion-related reactions following completion of the dose.

2+ **30-MINUTE SUBSEQUENT INFUSIONS** may be administered if the initial infusion was well tolerated. Monitor patients during the infusion.
30-MINUTE MINIMUM MONITORING following completion of these infusions.

Important administration considerations

- POLIVY must be administered using a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2- or 0.22-micron pore size) and a catheter
- Do not mix POLIVY or administer as an infusion with other drugs

POLIVY is typically administered in an outpatient setting, such as an infusion center

Please see Important Safety Information on pages 8-9 as well as full Prescribing Information.

Premedication and drug interactions

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Recommended prophylactic medications[1]

Premedication for potential infusion-related reactions

If the patient was not already premedicated for a rituximab product, be sure to administer an antihistamine and an antipyretic at least 30 to 60 minutes prior to POLIVY.

Prophylaxis for other potential adverse events

- Administer prophylaxis for *Pneumocystis jiroveci* pneumonia and herpesvirus throughout treatment with POLIVY
- Consider prophylactic G-CSF administration for neutropenia
- Administer tumor lysis syndrome prophylaxis for patients at increased risk of tumor lysis syndrome

POLIVY drug interactions

Strong CYP3A inhibitors

- Concomitant use with a strong CYP3A4 inhibitor may increase unconjugated MMAE AUC, which may increase POLIVY toxicities. Monitor patients for signs of toxicity

Strong CYP3A inducers

- Concomitant use with a strong CYP3A4 inducer may decrease unconjugated MMAE AUC

G-CSF=granulocyte colony-stimulating factor; CYP3A=cytochrome P450 family 3 subfamily A; AUC=area under the concentration-time curve.

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Preparing POLIVY for infusion

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Reconstitution of POLIVY[1]

1. CALCULATE

Calculate the dose, the total volume of reconstituted POLIVY solution required, and the number of POLIVY vials needed.

2. RECONSTITUTE

Reconstitute each 140 mg POLIVY vial by using a sterile syringe to slowly inject 7.2 mL of Sterile Water for Injection, USP, to obtain a concentration of 20 mg/mL of POLIVY. Swirl the vial gently until completely dissolved.

Do not shake.

3. INSPECT

The reconstituted solution should appear colorless to slightly brown, clear to slightly opalescent, and free of visible particulates. Discard the reconstituted solution if it is discolored, cloudy, or contains visible particulates.

Do not freeze or expose to direct sunlight.

Dilution of POLIVY

Dilute within 48 hours of reconstitution.

1. WITHDRAW

Determine the volume of 20 mg/mL reconstituted solution needed. Withdraw the reconstituted solution from the POLIVY vial using a sterile syringe. Discard any unused portion left in the vial.

2. DILUTE

Dilute POLIVY to a final concentration of 0.72 to 2.7 mg/mL in an IV infusion bag with a minimum volume of 50 mL containing 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; or 5% Dextrose Injection, USP.

3. MIX & INSPECT

Gently mix the IV infusion bag by slowly inverting the bag.

Do not shake.

Inspect the IV infusion bag for particulates and discard if present.

Storage and Transportation

After reconstitution, discard vial if cumulative storage time prior to dilution exceeds 48 hours

Limit transportation to 30 minutes at 9°C to 25°C or 12 hours at 2°C to 8°C

- Limit agitation of diluted product during preparation and transportation to administration site
- Do not transport diluted product through an automated system

Refer to Section 2.4 of the full Prescribing Information for additional details about storage and transportation

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Dose modifications for management of adverse reactions

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If a patient experiences an infusion reaction or select adverse reaction, adjust treatment as follows:

POLIVY dose modifications for peripheral neuropathy[1]

Severity*	Dose Modification
Grade 2–3 (moderate to severe)	Hold POLIVY dosing until improvement to Grade 1 or lower. If recovered to Grade 1 or lower on or before Day 14, restart POLIVY with the next cycle at a permanently reduced dose of 1.4 mg/kg. If a prior dose reduction to 1.4 mg/kg has occurred, discontinue POLIVY. If not recovered to Grade 1 or lower on or before Day 14, discontinue POLIVY.
Grade 4 (life-threatening)	Discontinue POLIVY.

POLIVY+BR dose modifications for myelosuppression[1]

Severity*†	Dose Modification
Grade 3-4 neutropenia‡ (severe to life-threatening)	Hold all treatment until ANC recovers to >1000/µL. If ANC recovers to >1000/µL on or before Day 7, resume all treatment without any additional dose reductions. Consider G-CSF prophylaxis for subsequent cycles, if not previously given. If ANC recovers to >1000/µL after Day 7: • Restart all treatment. Consider G-CSF prophylaxis for subsequent cycles, if not previously given. If prophylaxis was given, consider dose reduction of bendamustine • If dose reduction of bendamustine has already occurred, consider dose reduction of POLIVY to 1.4 mg/kg
Grade 3-4 thrombocytopenia‡ (severe to life-threatening)	Hold all treatment until platelets recover to >75,000/µL. If platelets recover to >75,000/µL on or before Day 7, resume all treatment without any additional dose reductions. If platelets recover to >75,000/µL after Day 7: • Restart all treatment, with dose reduction of bendamustine • If dose reduction of bendamustine has already occurred, consider dose reduction of POLIVY to 1.4 mg/kg

*Severity grading is based on NCI CTCAE version 4.[2]
†Severity on Day 1 of any cycle.
‡If primary cause is due to lymphoma, dose delay or reduction may not be needed.
ANC=absolute neutrophil count; NCI=National Cancer Institute; CTCAE=Common Terminology Criteria for Adverse Events.

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Dose modifications for management of adverse reactions (cont)

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POLIVY dose modification for infusion-related reactions[1]

Severity*	Dose Modification
Grade 1-3 (mild transient to prolonged reaction)	Interrupt POLIVY infusion and give supportive treatment. For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue POLIVY. For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue POLIVY. Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes. For the next cycle, infuse POLIVY over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles.
Grade 4 (life-threatening)	Stop POLIVY infusion immediately. Give supportive treatment. Permanently discontinue POLIVY.

*Severity grading is based on NCI CTCAE version 4.[2]

Common Terminology Criteria for Adverse Events (CTCAE)[2]

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral neuropathy • Motor • Sensory	Asymptomatic; clinical or diagnostic observations only (motor); intervention not indicated (motor); loss of deep tendon reflexes or paresthesia (sensory)	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated (motor)	Life-threatening consequences; urgent intervention indicated
Myelosuppression • Neutropenia • Thrombocytopenia	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Infusion-related reactions	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated

A semicolon indicates "or" within the description of the grade.
ADL=activities of daily living; NSAIDs=nonsteroidal anti-inflammatory drugs.

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Important Safety Information

Peripheral Neuropathy

POLIVY can cause severe peripheral neuropathy. Peripheral neuropathy occurs as early as the first cycle of treatment and is cumulative. POLIVY may exacerbate preexisting peripheral neuropathy.

In Study GO29365, of 173 patients treated with POLIVY, 40% reported new or worsening peripheral neuropathy, with a median time to onset of 2.1 months. The peripheral neuropathy was Grade 1 in 26% of cases, Grade 2 in 12%, and Grade 3 in 2.3%. Peripheral neuropathy resulted in POLIVY dose reduction in 3% of treated patients, dose delay in 1.2%, and permanent discontinuation in 2.9%. Sixty-five percent of patients reported improvement or resolution of peripheral neuropathy, after a median time to resolution of 1 month, and 48% reported complete resolution.

The peripheral neuropathy is predominantly sensory; however, motor and sensorimotor peripheral neuropathy also occur. Monitor for symptoms of peripheral neuropathy such as hypoesthesia, hyperesthesia, paresthesia, dysesthesia, neuropathic pain, burning sensation, weakness, or gait disturbance. Patients experiencing new or worsening peripheral neuropathy may require a delay, dose reduction, or discontinuation of POLIVY.

Infusion-Related Reactions

POLIVY can cause severe infusion reactions. Delayed infusion-related reactions as late as 24 hours after receiving POLIVY have occurred. With premedication, 7% of patients (12/173) in Study GO29365 reported infusion-related reactions after the administration of POLIVY. The reactions were Grade 1 in 67% of patients, Grade 2 in 25%, and Grade 3 in 8%. Symptoms included fever, chills, flushing, dyspnea, hypotension, facial swelling, and urticaria.

Administer an antihistamine and an antipyretic prior to the administration of POLIVY, and monitor patients closely throughout the infusion. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management.

Myelosuppression

Treatment with POLIVY can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. In patients treated with POLIVY plus bendamustine and a rituximab product (BR) (n=45), 42% received primary prophylaxis with granulocyte colony-stimulating factor. Grade 3 or higher hematologic adverse reactions included neutropenia (42%), thrombocytopenia (40%), anemia (24%), lymphopenia (13%), and febrile neutropenia (11%) (see Adverse Reactions [6.1]). Grade 4 hematologic adverse reactions included neutropenia (24%), thrombocytopenia (16%), lymphopenia (9%), and febrile neutropenia (4.4%). Cytopenias were the most common reason for treatment discontinuation (18% of all patients).

Monitor complete blood counts throughout treatment. Cytopenias may require a delay, dose reduction, or discontinuation of POLIVY. Consider prophylactic granulocyte colony-stimulating factor administration.

Important Safety Information (cont)

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Serious and Opportunistic Infections
Fatal and/or serious infections, including opportunistic infections such as sepsis, pneumonia (including *Pneumocystis jiroveci* and other fungal pneumonia), herpesvirus infection, and cytomegalovirus infection, have occurred in patients treated with POLIVY.

Grade 3 or higher infections occurred in 32% (55/173) of patients treated with POLIVY. Infection-related deaths were reported in 2.9% of patients within 90 days of last treatment.

Closely monitor patients during treatment for signs of infection. Administer prophylaxis for *Pneumocystis jiroveci* pneumonia and herpesvirus.

Progressive Multifocal Leukoencephalopathy (PML)
PML has been reported after treatment with POLIVY (0.6%, 1/173). Monitor for new or worsening neurological, cognitive, or behavioral changes. Hold POLIVY and any concomitant chemotherapy if PML is suspected, and permanently discontinue if the diagnosis is confirmed.

Tumor Lysis Syndrome
POLIVY may cause tumor lysis syndrome. Patients with high tumor burden and rapidly proliferating tumors may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures, including tumor lysis syndrome prophylaxis.

Hepatotoxicity
Serious cases of hepatotoxicity that were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with POLIVY.

In recipients of POLIVY in Study GO29365 (n=173), Grade 3 and 4 transaminase elevations of AST and/or ALT developed in 1.9% and 1.9%, respectively. Laboratory values suggestive of drug-induced liver injury (both an ALT or AST greater than 3 times upper limit of normal [ULN] and total bilirubin greater than 2 times ULN) occurred in 2.3% of patients.

Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk of hepatotoxicity. Monitor liver enzymes and bilirubin level.

Embryo-Fetal Toxicity
Based on the mechanism of action and findings from animal studies, POLIVY can cause fetal harm when administered to a pregnant woman. When administered to rats, the small molecule component of POLIVY, monomethyl auristatin E, caused adverse developmental outcomes, including embryo-fetal mortality and structural abnormalities, at exposures below those occurring clinically at the recommended dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with POLIVY and for at least 3 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with POLIVY and for at least 5 months after the last dose.

The Most Common Adverse Reactions
The most common adverse reactions (≥20%) included neutropenia, thrombocytopenia, anemia, peripheral neuropathy, fatigue, diarrhea, pyrexia, decreased appetite, and pneumonia.

Lactation
Advise women not to breastfeed during treatment with POLIVY and for at least 2 months after the last dose.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see full Prescribing Information for additional Important Safety Information.

Helping patients and the people who support them

We work every day to help people who need our medicines, so they can focus on what matters most. People who take our medicines have several programs and resources available to them:

For people who need help understanding insurance coverage and costs related to Genentech medicines: **Genentech Access Solutions**

For people who have insurance and can't afford their Genentech medicine: **Affordability Options**

For people who do not have insurance coverage or who have concerns about the cost of their Genentech medicine and meet certain eligibility criteria: **Genentech Patient Foundation**

For people who want information and resources about a diagnosis and treatment with a Genentech medicine: **Genentech Patient Education and Treatment Resources**

The Genentech Patient Resource Center can help answer your questions and connect you to an appropriate Genentech patient support service.

Call (877) GENENTECH

Visit Genentech-Access.com/POLIVY

Contact your Genentech representative

to learn more or ask about dosing and administration

Please refer to the full Prescribing Information for patient counseling information.

Please see Important Safety Information on pages 8-9 as well as full Prescribing Information.

References: 1. POLIVY Prescribing Information. South San Francisco, CA: Genentech, Inc.; June 2019. **2.** National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) V4. 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed August 28, 2019.

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