Genentech
A Member of the Roche Group

POLIVY® (polatuzumab vedotin-piiq): Understanding the Data Behind the USPI

This is a medical resource for scientific information and is intended for healthcare providers practicing in the United States.

Current as of Dec 2024

Indications and Usage

POLIVY is a CD79b-directed antibody and microtubule inhibitor conjugate indicated:

- 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), not otherwise specified (NOS) or high-grade B-cell lymphoma (HGBL) and who have an international prognostic index score of 2 or greater
- in combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory DLBCL, NOS, after at least two prior therapies

Please see Important Safety Information throughout and full Prescribing Information provided with this presentation

Please Note: For FDA approved products please consult the product's full prescribing information for a complete discussion of risks and benefits of the product(s) for its approved indication(s).

The information we provide may additionally include relevant references to non-Genentech product information derived from publicly available sources.

POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023.

POLARIX: DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY DESIGN OVERVIEW[1,2]

Patients (N=879)

- Previously untreated DLBCL*
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

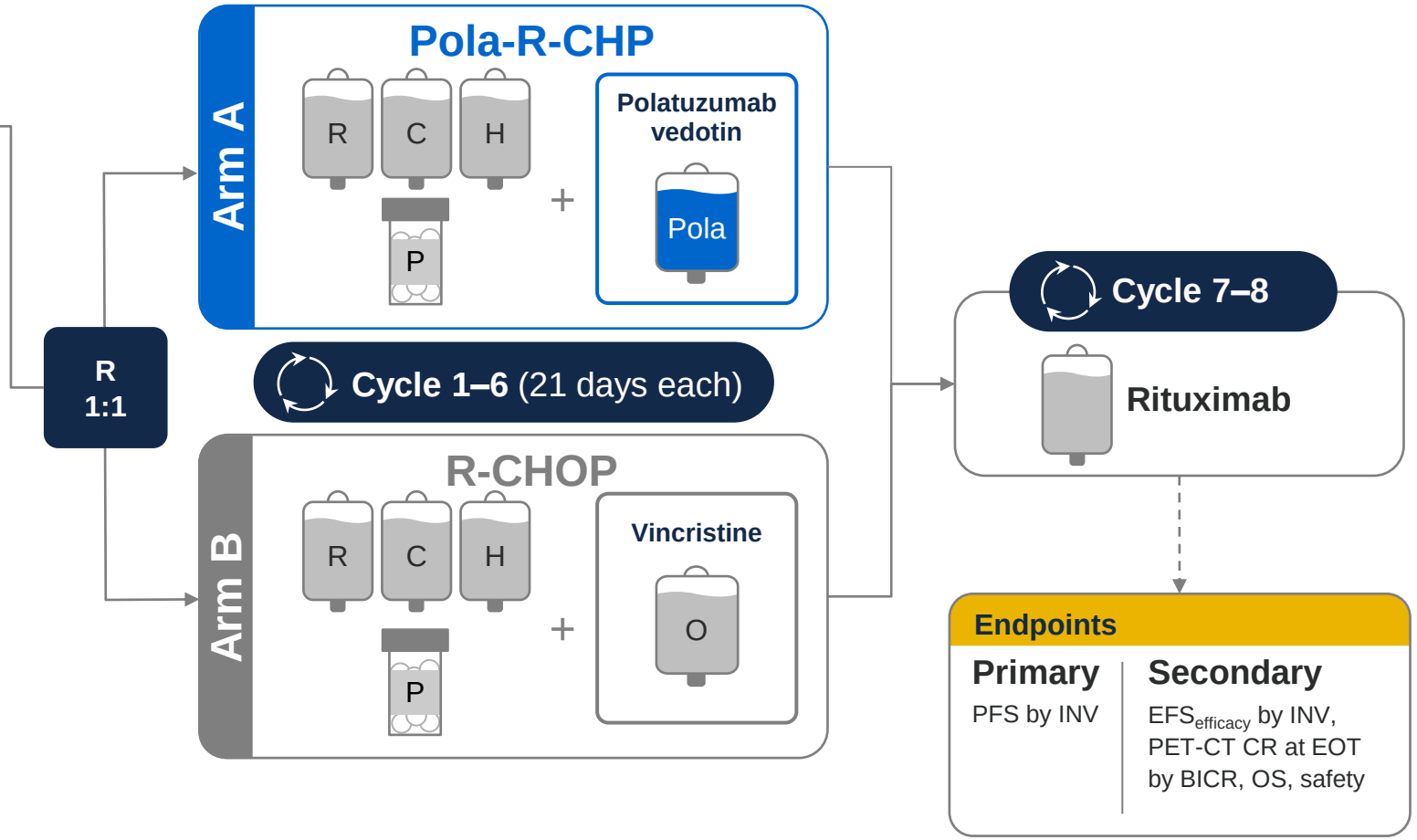
Stratification factors

- IPI score (2 vs 3–5)
- Bulky disease (≥7.5 cm vs absence)
- Geographic region†

Key exclusion factors

- Transformed lymphoma
- Primary mediastinal large B-cell lymphoma
- Known CNS lymphoma
- Grade 2+ peripheral neuropathy

Collaboration with LYSA
NCT03274492



*Previously untreated CD-20 positive DLBCL with diagnoses by 2016 WHO classification of lymphoid neoplasms. †Western Europe, United States, Canada and Australia vs Asia vs Rest of World.
BICR=blinded independent central review; CR=complete response; ECOG PS=Eastern Cooperative Oncology Group performance status; $EFS_{efficacy}$=event-free survival for efficacy causes (time from randomization to the earliest occurrence of disease progression/relapse, death due to any cause, initiation of any non-protocol specified anti-lymphoma treatment, or biopsy-confirmed residual disease after treatment completion); EOT=end of treatment; INV=investigator; IPI=International Prognostic Index; LYSA=Lymphoma Study Association; PET-CT=positron emission tomography and computed tomography; R=randomization; R-CHP=rituximab plus cyclophosphamide, doxorubicin, prednisone; R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone.

1. POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023; 2. Tilly H, et al. N Engl J Med 2022;386(4):351–63.

Differences between POLARIX Clinical Trial ITT Population and the FDA-approved Indication

POLARIX Protocol Inclusion Criteria*	ITT Patient Population by Histology	POLIVY Indication
DLBCL, not otherwise specified (NOS) Including GCB and ABC	DLBCL, not otherwise specified (DLBCL, NOS): 84% Pola-R-CHP: n=373 R-CHOP: n=363	DLBCL, not otherwise specified (DLBCL NOS)
High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (double-hit or triple-hit lymphoma) and High-grade B-cell lymphoma, NOS	High Grade B-cell lymphoma (HGBL): 11% Pola-R-CHP: n=43 R-CHOP: n=50	High Grade B-cell lymphoma (HGBL)
T-cell/histiocyte-rich large B-cell lymphoma	T-cell/histiocyte-rich large B-cell lymphoma: 3% Pola-R-CHP: n=16 R-CHOP: n=12	Not included in indication
Epstein-Barr virus positive DLBCL, NOS	Epstein-Barr virus positive DLBCL, NOS: 2% Pola-R-CHP: n=8 R-CHOP: n=10	Not included in indication
ALK-positive large B-cell lymphoma	None enrolled	Not included in indication
HHV8-positive DLBCL, NOS	None enrolled	Not included in indication

- **The primary and key secondary data, as well as safety information presented in the USPI, are based on the ITT patient population**
- **Data from subgroup analyses for PFS and OS for DLBCL NOS and HGBL were also included in the label**

*Previously untreated CD20-positive DLBCL, including one of these diagnoses by 2016 WHO classification of lymphoid neoplasms.
ITT=intention-to-treat.
1. POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023; 2. Tilly H, et al. N Engl J Med 2022;386(4):351–63.

Primary and Secondary Endpoints: Results and Statistical Considerations

Summary of Efficacy in POLARIX (ITT): §14.1

Outcomes	Pola-R-CHP n=440	R-CHOP n=439
PFS per Investigator[a]		
Number (%) of patients with event	107 (24)	134 (31)
Progression	88	114
Death	19	20
HR (95% CI)	**0.73 (0.57, 0.95)**	
p-value[b]	**0.0177**	
Modified EFS per Investigator[c]		
Number (%) of patients with event	112 (26)	138 (31)
HR (95% CI)	**0.75 (0.58, 0.96)**	
p-value[b]	**p=0.0244**	
Objective Response at EOT[d]		
Objective response rate, % (95% CI)	86 (82, 89)	84 (80, 87)
CR rate, %	78 (74, 82)	74 (70, 78)
Difference in CR rate, % (95% CI)	3.9 (–1.9, 9.7)	
p-value[e]	0.1557	
Overall Survival (final analysis)		
HR (95% CI)	0.94 (0.67, 1.33)	
p-value	p=0.7326	

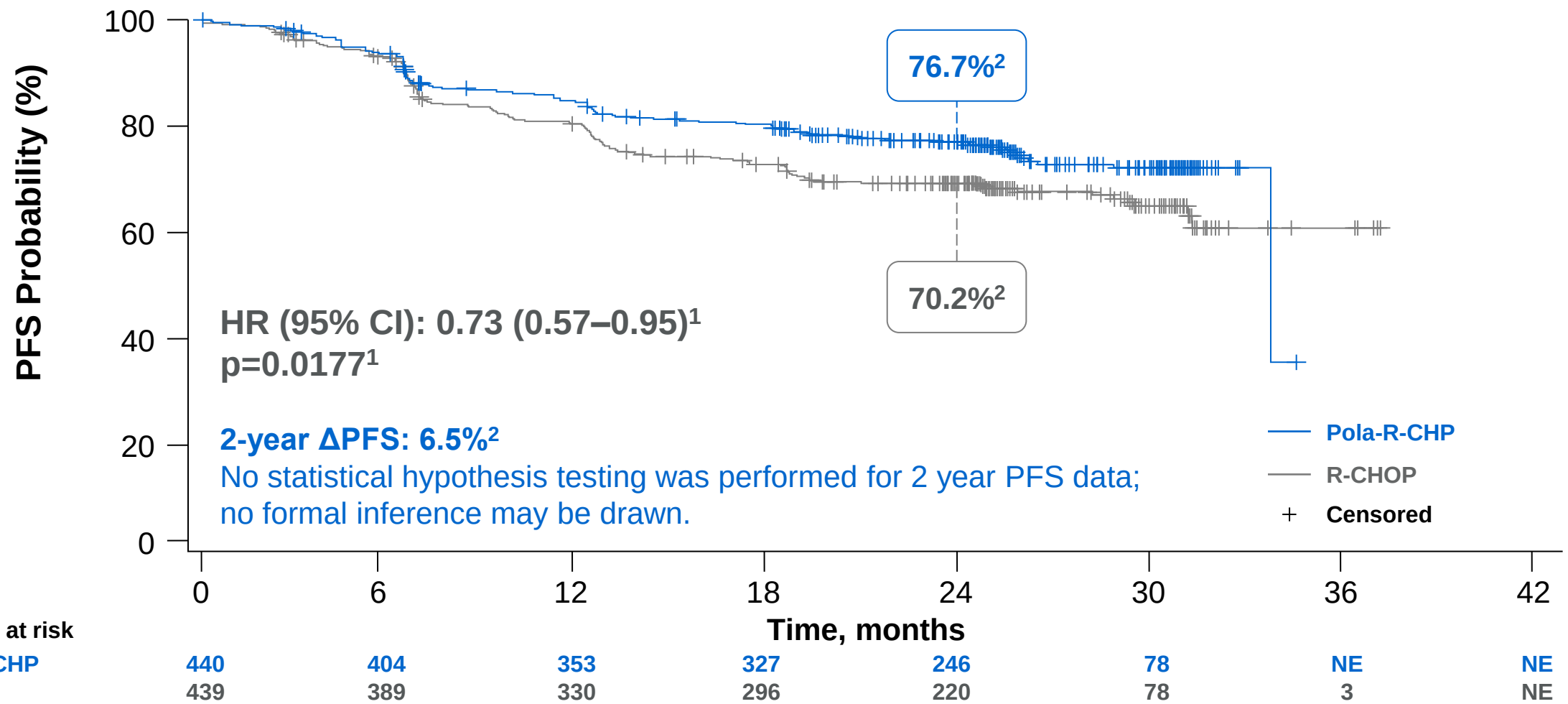
The hierarchical testing order was PFS, modified EFS, then CR rate and overall survival.

[a] Estimated median follow-up for PFS was 24.7 months in both arms combined.
[b] Stratified log-rank test, with a two-sided significance boundary of 0.05. The hierarchical testing order was PFS, modified EFS, then CR rate and overall survival.
[c] Modified EFS was defined as time from randomization to the earliest occurrence of disease progression or relapse, death, an efficacy finding that led to non-protocol specified lymphoma treatment, or biopsy positive for residual disease.
[d] By blinded independent central review, per 2014 Lugano response criteria.
[e] Cochran-Mantel-Haenszel chi-squared test, with a two-sided significance boundary of 0.01.

CI=confidence interval; CR=complete response; EFS=event-free survival efficacy; EOT=end of treatment; HR=hazard ratio; PFS=progression-free survival.

POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023; Tilly H, et al. N Engl J Med 2022;386(4):351–63 [Supplementary material: protocol].

POLARIX Primary Endpoint: PFS by Investigator



Patients at risk

Pola-R-CHP	**440**	**404**	**353**	**327**	**246**	**78**	**NE**	**NE**
R-CHOP	**439**	**389**	**330**	**296**	**220**	**78**	**3**	**NE**

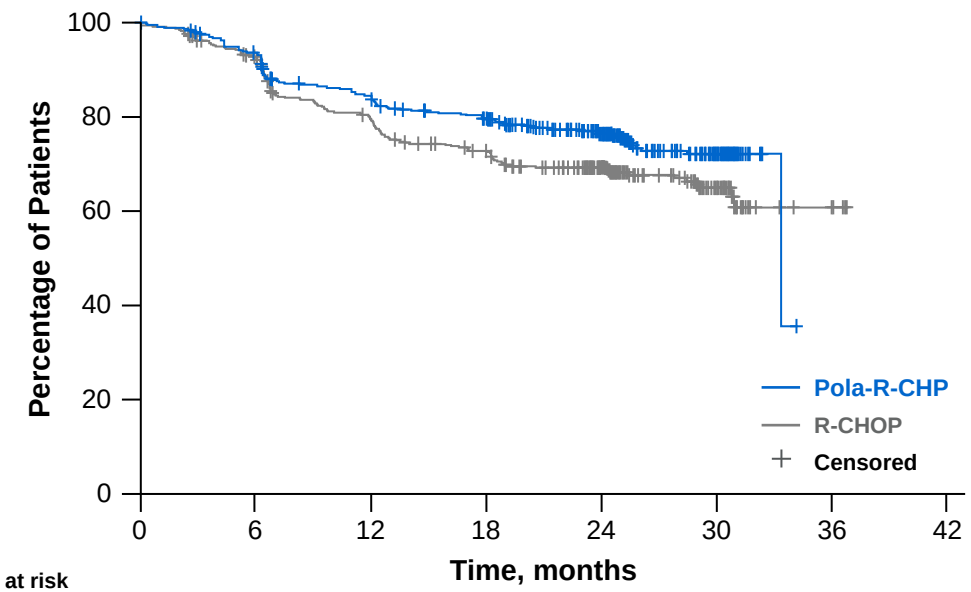
Analysis based on the ITT population. Kaplan–Meier estimate.
CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; NE=not evaluable.

1. POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023; 2. Tilly H, et al. N Engl J Med 2022;386(4):351–63.

POLARIX: Other Endpoints

$EFS_{efficacy}$ *

Outcomes	Pola-R-CHP n=440	R-CHOP n=439
Modified EFS per Investigator[c]		
Number (%) of patients with event	112 (26)	138 (31)
HR (95% CI)	**0.75 (0.58, 0.96)**	
p-value[b]	**0.0244**	



OR at EOT; OS (ITT): §14.1

Outcomes	Pola-R-CHP n=440	R-CHOP n=439
Objective Response at EOT[d]		
Objective response rate, % (95% CI)	86 (82, 89)	84 (80, 87)
CR rate, %	78 (74, 82)	74 (70, 78)
Difference in CR rate, % (95% CI)	3.9 (–1.9, 9.7)	
p-value[e]	0.1557	
Overall Survival (final analysis)		
HR (95% CI)	0.94 (0.67, 1.33)	
p-value	p=0.7326	

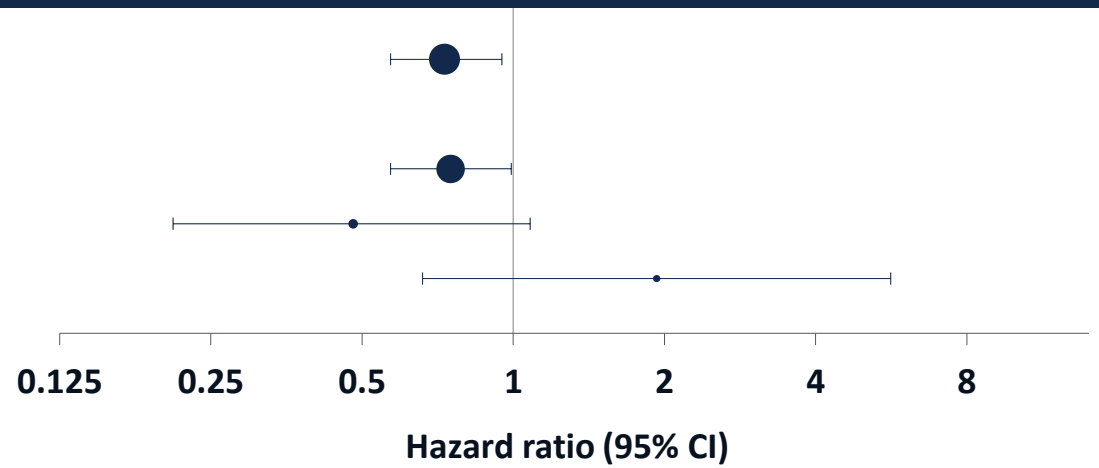
*The $EFS_{efficacy}$ curve is not included in the Polivy prescribing information.

POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023; Tilly H, et al. N Engl J Med 2022;386(4):351–63.

Prespecified Exploratory Subgroup Analyses: PFS

- In a prespecified descriptive analysis of the largest lymphoma subgroup, DLBCL, NOS, the PFS HR was 0.75 (95% CI: 0.57, 0.99). In patients with HGBL, the PFS HR was 0.48 (95% CI: 0.21, 1.08). There were insufficient data to evaluate efficacy in other large B-cell lymphomas

NHL Subtype	Pola-R-CHP* (event/N)	R-CHOP* (event/N)	HR (95% CI)
Overall	440	439	0.73 (0.57–0.95)
DLBCL, NOS	88/373	112/367	0.75 (0.57–0.99)
HGBL NOS, DH/TH	9/43	17/50	0.48 (0.21–1.08)
Other Large B-Cell	10/24	5/22	1.93 (0.66–5.64)

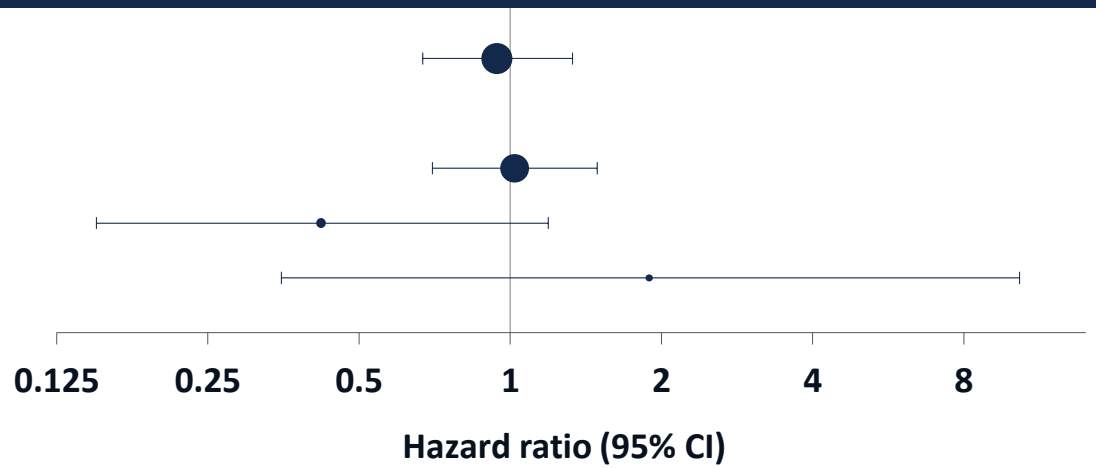


*Pola-R-CHP and R-CHOP arms were well balanced in terms of histology.
The forest plot is not included in the Polivy prescribing information.
POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023; FDA ODAC presentation.

Overall Survival: Prespecified Final Analysis, and Post-hoc Exploratory Subgroup Analyses

- With an estimated median follow-up of 3.3 years, the prespecified final analysis of overall survival (OS) showed no statistically significant difference, with a HR of 0.94 (95% CI: 0.67, 1.33). In a descriptive analysis, the OS HR in patients with DLBCL, NOS was 1.02 (95% CI: 0.70, 1.49). The OS HR in patients with HGBL was 0.42 (95% CI: 0.15, 1.19)

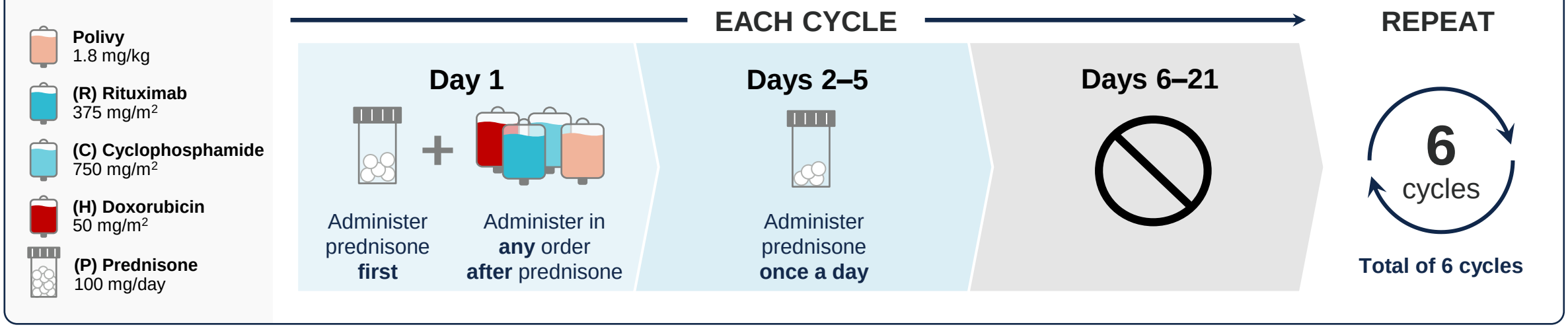
NHL Subtype	Pola-R-CHP* (event/N)	R-CHOP* (event/N)	HR (95% CI)
Overall	440	439	0.94 (0.67–1.33)
DLBCL, NOS	55/373	53/367	1.02 (0.70–1.49)
HGBL NOS, DH/TH	5/43	12/50	0.42 (0.15–1.19)
Other Large B-Cell	4/24	2/22	1.89 (0.35–10.33)



*Pola-R-CHP and R-CHOP arms were well balanced in terms of histology.
The forest plot is not included in the Polivy prescribing information.
POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023; FDA ODAC presentation.

Recommended Dosage For All Indicated Patients

Sequence of Polivy plus R-CHP Administration from the USPI

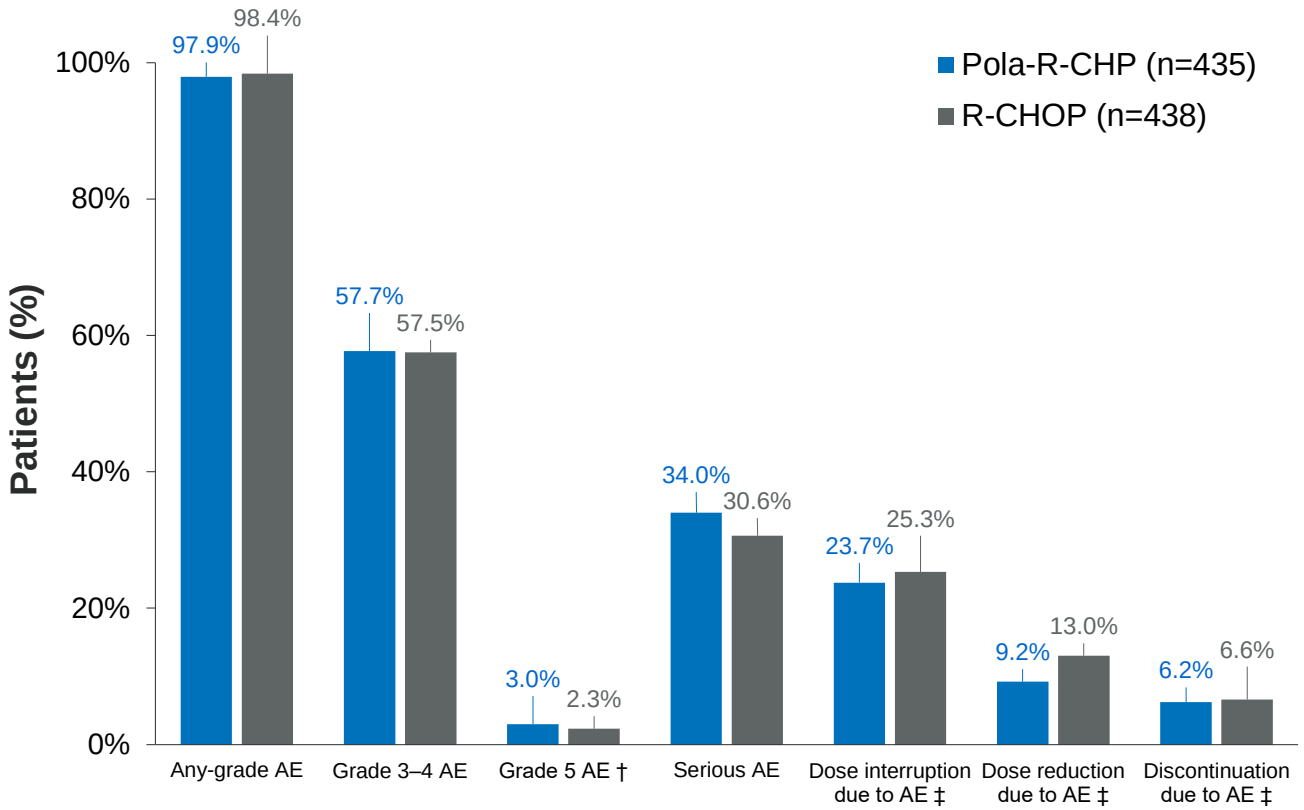


- If a planned dose of Polivy is missed, administer as soon as possible. Adjust the schedule of administration to maintain a 21-day interval between doses.[1]

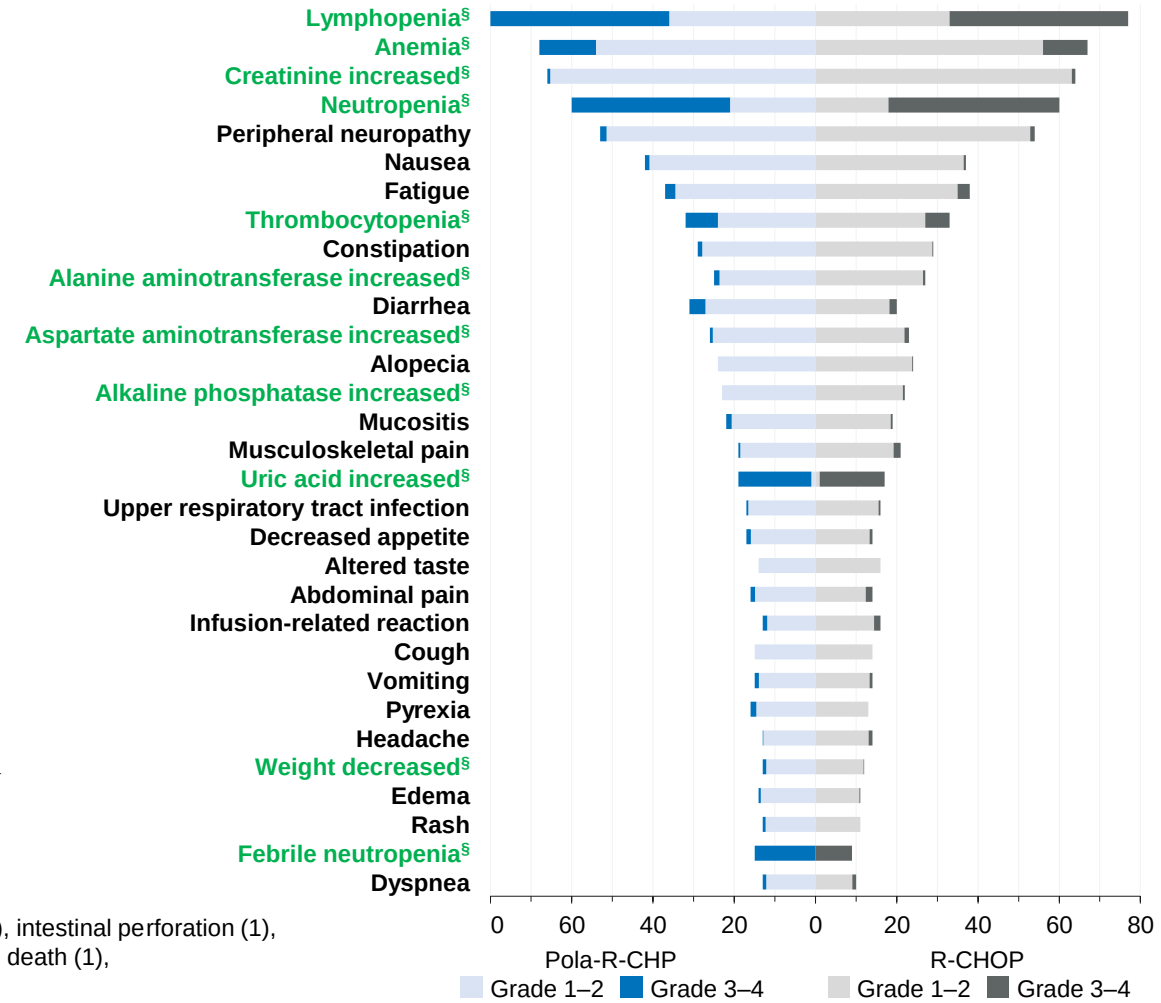
POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023.

Safety Profile in POLARIX

Overall Safety Profile*,1



Select Adverse Reactions Occurring in ≥10% of Patients Treated with POLIVY Plus R-CHP[2]



*Clinical cut-off date: June 28, 2021. Incidence rates may differ from the USPI due to differences in definitions.
†Grade 5 AEs, Pola+R-CHP (13): pneumonia (4), sepsis or septic shock (1), unexplained death (4), cardiac death (1), intestinal perforation (1), acute kidney injury (1), respiratory failure (1); R-CHOP (10): pneumonia (3), sepsis or septic shock (3), unexplained death (1), multiple organ dysfunction syndrome (1), atrioventricular block complete (1), injury (1).
‡Dose interruption, reduction, or discontinuation of any agent.
§Lab abnormalities indicated in green. Laboratory values are based on integrated analysis of laboratory and adverse reaction data. Reported investigations exclude electrolytes.

1. Tilly H, et al. N Engl J Med 2022;386(4):351–63; 2. POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023.

Management of Peripheral Neuropathy

- Table 1 provides management guidelines for peripheral neuropathy in patients receiving Polivy plus R-CHP [see Warnings and Precautions (5.1)].

Adverse reaction	Grade	Dose modification[a]
Peripheral sensory neuropathy	Grade 1	None
	Grade 2	If resolves to Grade 1 or lower before the next scheduled dose, resume at the same dose level. If Gr 2 persists at the next scheduled dose, **reduce one dose level**.
	Grade 3	Withhold until Grade 2 or lower and **reduce one dose level**.
	Grade 4	**Permanently discontinue**.
Peripheral motor neuropathy	Grade 1	None
	Grade 2 or 3	Withhold until Grade 1 or lower and **reduce one dose level**.
	Grade 4	**Permanently discontinue**.

R-CHP should be continued if Polivy is withheld.
If there is concurrent sensory and motor neuropathy, follow the guidance for the most severe neuropathy. If the grade of sensory and motor neuropathy are the same, follow the guidance for motor neuropathy.

[a] Starting dose for Polivy is 1.8 mg/kg. First dose reduction level is 1.4 mg/kg. Second dose reduction level is 1 mg/kg. No further dose reduction is recommended beyond 1 mg/kg. If further reduction needed discontinue Polivy.

Graded using NCI CTCAE version 4.0.

POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023.

Peripheral Neuropathy: Definitions and Grading

Peripheral sensory neuropathy: a disorder characterized by inflammation or degeneration of the peripheral sensory nerves. Damage to sensory nerves can cause:

- Tingling, numbness, or a pins-and-needles feeling in extremities that may spread to limbs
- Inability to feel extremes in temperature
- Inability to feel pain

Peripheral motor neuropathy: A disorder characterized by inflammation or degeneration of the peripheral motor nerves. Damage to motor nerves can cause:

- Weak or achy muscles that may cause patients to lose balance, trip easily, or have impaired manual dexterity i.e., buttoning shirts or opening jars
- Muscles that twitch and cramp, or atrophy
- Swallowing or breathing difficulties

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental activities of daily living	Severe symptoms; limiting self care activities of daily living	Life-threatening consequences; urgent intervention indicated	Death
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental activities of daily living	Severe symptoms; limiting self care activities of daily living; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death

Nerve Problems (Peripheral Neuropathy) and Cancer Treatment - Side Effects – NCI
Common Terminology Criteria for Adverse Events (CTCAE Version 4.0) (nih.gov)
Activities of Daily Living (ADLs): Activities of daily living are activities related to personal care (cms.gov)
POLIVY [prescribing information]. South San Francisco, CA: Genentech, Inc. 2023.

Genentech
A Member of the Roche Group

THANK YOU