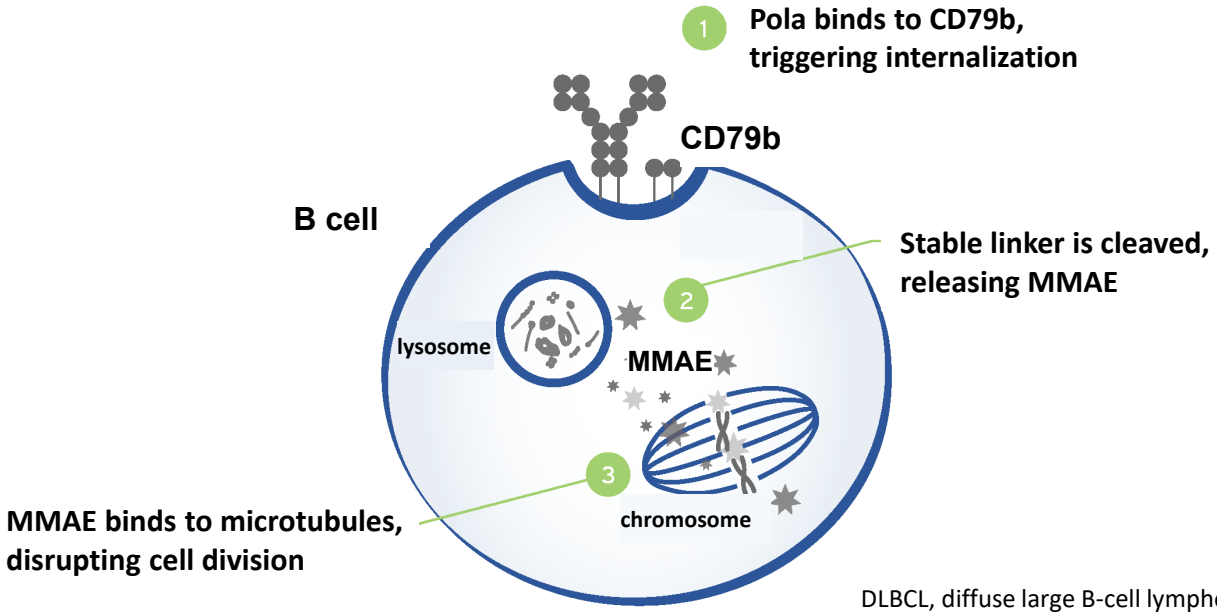
Polatuzumab Vedotin-piiq for First-Line Treatment of Diffuse Large B-cell Lymphoma

FDA Introductory Comments
Oncologic Drugs Advisory Committee Meeting
March 9, 2023

Yvette Kasamon, MD
Clinical Team Leader
Division of Hematologic Malignancies II
Office of Oncologic Diseases

Polatuzumab vedotin-piiq

- Accelerated approval 6/2019: in combination with bendamustine and a rituximab product for adult patients with relapsed or refractory DLBCL, not otherwise specified, after at least two prior therapies



DLBCL, diffuse large B-cell lymphoma; Pola, polatuzumab vedotin; MMAE, monomethyl auristatin
Source: Modification of Applicant's figure

Post-marketing requirement

- Study GO39942 (POLARIX): randomized, double-blind, placebo-controlled trial of pola+R-CHP vs R-CHOP in untreated DLBCL

Pola+R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Evidentiary criteria for approval

- Safety
  - Sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in proposed labeling

Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics

Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drugs and Biological Products

Evidentiary criteria for approval

- Safety
  - Sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in proposed labeling
- Substantial evidence of effectiveness
  - Based on adequate and well-controlled investigations
  - The drug will have the effect it purports or is represented to have under the conditions of use represented in proposed labeling
  - For a single randomized trial to support an application, results must be sufficiently robust and compelling

Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics

Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drugs and Biological Products

Treatment landscape: newly diagnosed DLBCL

- Heterogeneous category
- R-CHOP is the usual standard
- Rituximab in first-line DLBCL: 3 RCTs with OS advantage

	Study 1 (n=632)		Study 2 (n=399)		Study 3 (n=823)	
	R-CHOP	CHOP	R-CHOP	CHOP	R-chemo	Chemo
HR for OS	0.72		0.69		0.40	
OS at 2 years*	74%	63%	69%	58%	95%	86%

*Kaplan-Meier estimate

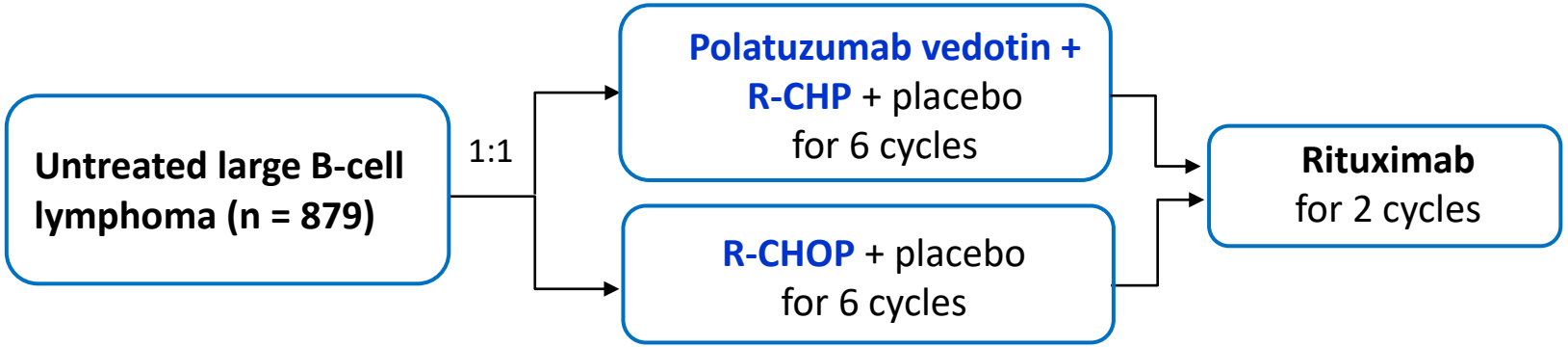
Source: USPI

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RCT, randomized controlled trial; OS, overall survival; R-chemo, rituximab + chemotherapy; HR, hazard ratio; USPI, U.S. prescribing information

POLARIX

Applicant's proposed indication: Polatuzumab vedotin in combination with R-CHP is indicated for the treatment of adult patients with previously untreated DLBCL

Regimen: Substitution of vincristine with polatuzumab vedotin in R-CHOP



Primary endpoint: PFS
Key secondary: modified EFS, CR rate, OS

R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PFS, progression-free survival; EFS, event-free survival; CR, complete remission

POLARIX

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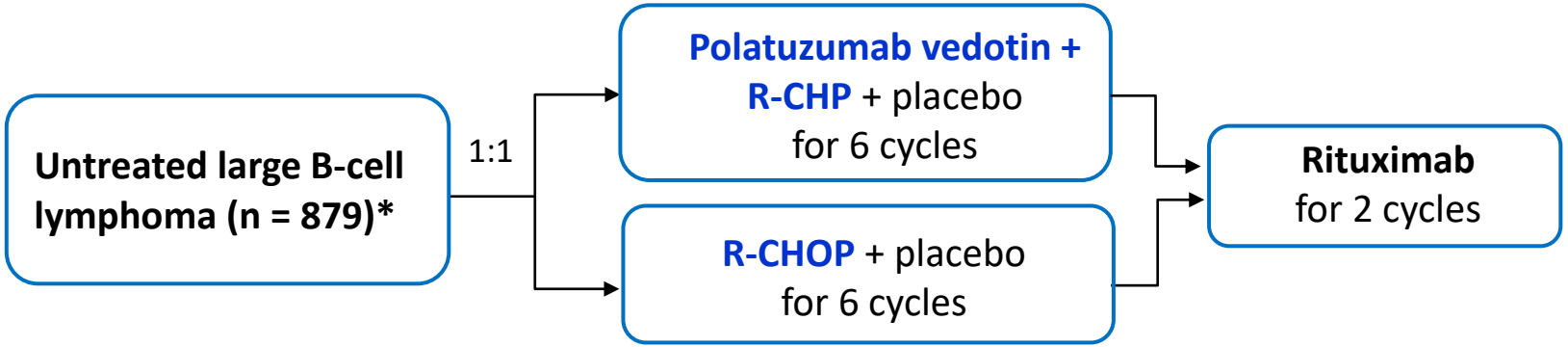

Primary endpoint: PFS
Key secondary: modified EFS, CR rate, OS

* Includes DLBCL NOS (84%), HGBL (11%), and other large B-cell lymphomas (5%)

R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; PFS, progression-free survival; EFS, event-free survival; CR, complete remission; NOS, not otherwise specified; HGBL, high-grade B-cell lymphoma

Main topics

1. Modest PFS benefit of pola+R-CHP
2. OS results
3. Other efficacy endpoints
4. Heterogeneity of study population

Main topics

1. **Modest PFS benefit of pola+R-CHP**
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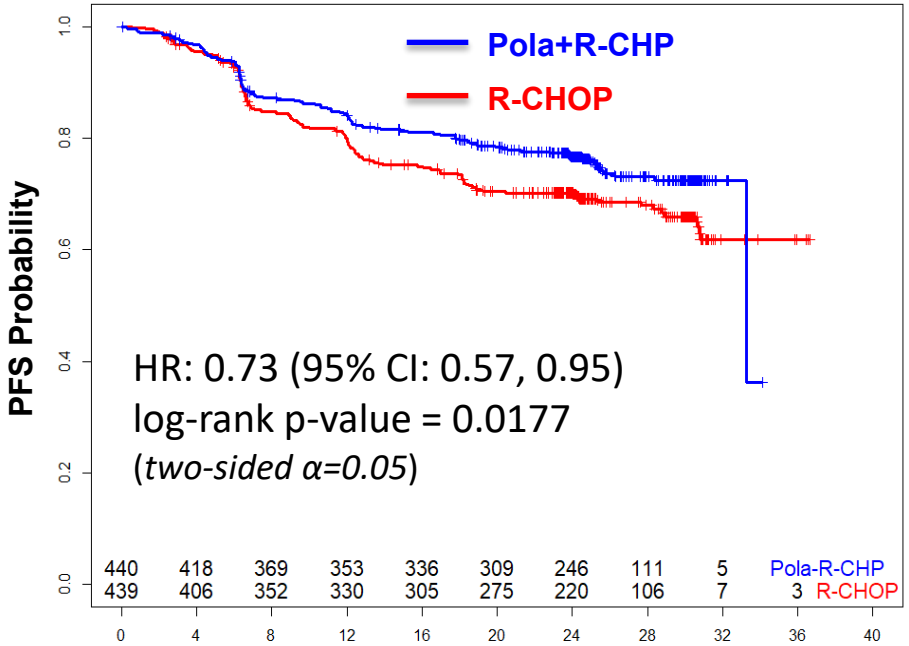
Modest PFS benefit of pola+R-CHP

Applicant's primary analysis



	Pola+R-CHP (N=440)	R-CHOP (N=439)	Difference
1 year	83.9%	79.8%	4.1%
2 years	76.7%	70.2%	6.5%

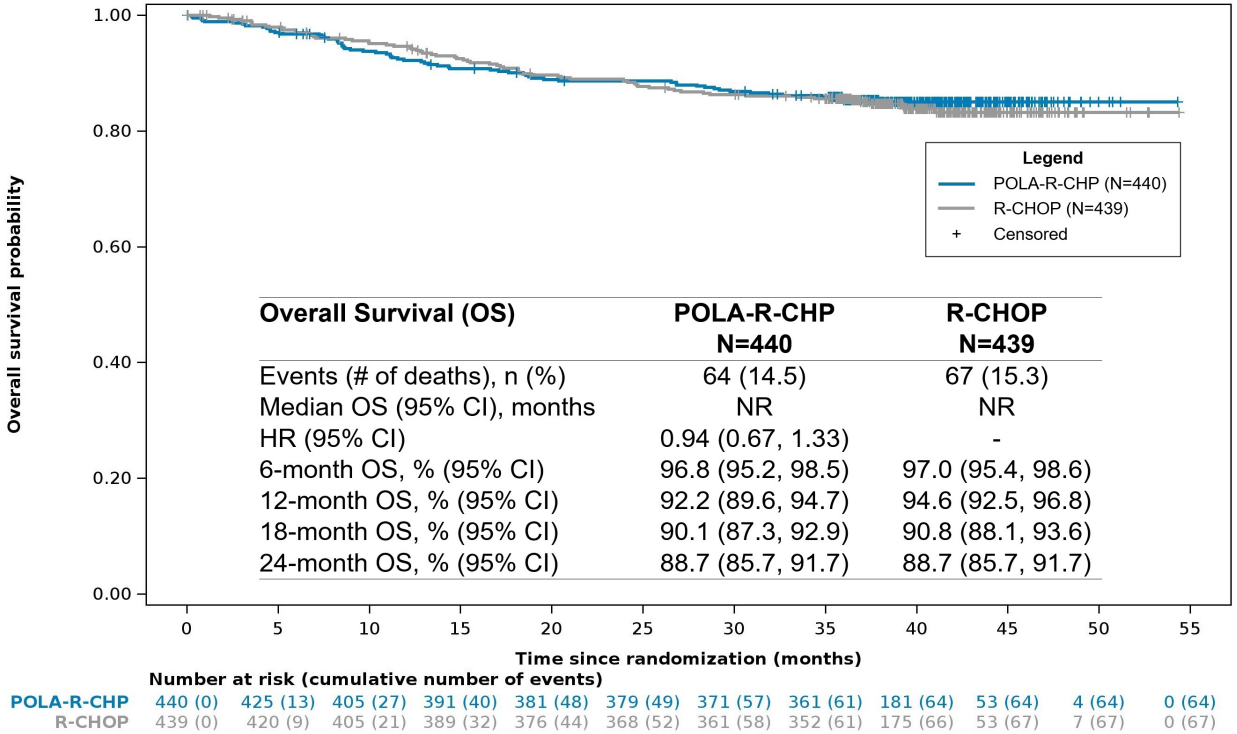
Uncertain contribution of pola to the overall regimen

CI, confidence interval; pola, polatuzumab vedotin

Main topics

1. Modest PFS benefit of pola+R-CHP
2. **OS results**
3. Other efficacy endpoints
4. Heterogeneity of study population

POLARIX: no improvement in OS



Overall Survival (OS)	POLA-R-CHP N=440	R-CHOP N=439
Events (# of deaths), n (%)	64 (14.5)	67 (15.3)
Median OS (95% CI), months	NR	NR
HR (95% CI)	0.94 (0.67, 1.33)	-
6-month OS, % (95% CI)	96.8 (95.2, 98.5)	97.0 (95.4, 98.6)
12-month OS, % (95% CI)	92.2 (89.6, 94.7)	94.6 (92.5, 96.8)
18-month OS, % (95% CI)	90.1 (87.3, 92.9)	90.8 (88.1, 93.6)
24-month OS, % (95% CI)	88.7 (85.7, 91.7)	88.7 (85.7, 91.7)

Number at risk (cumulative number of events)

POLA-R-CHP	440 (0)	425 (13)	405 (27)	391 (40)	381 (48)	379 (49)	371 (57)	361 (61)	181 (64)	53 (64)	4 (64)	0 (64)
R-CHOP	439 (0)	420 (9)	405 (21)	389 (32)	376 (44)	368 (52)	361 (58)	352 (61)	175 (66)	53 (67)	7 (67)	0 (67)

NR, not reached
Source: FDA analysis

Overall survival

- Key metric of both safety and efficacy
- Trial need not be powered for OS to provide important information
- Critical to the benefit-risk determination

Main topics

1. Modest PFS benefit of pola+R-CHP
2. OS results
3. **Other efficacy endpoints**
4. Heterogeneity of study population

No improvement in response rates

Response per BICR	Pola+R-CHP (N=440)	R-CHOP (N=439)
Overall response rate (95% CI)	**85.5%** (81.8, 88.6)	**83.8%** (80.0, 87.2)
CR rate (95% CI)	**78.0%** (73.8, 81.7)	**74.0%** (69.7, 78.1)
Difference (95% CI)	3.9% (-1.9, 9.7)	
p-value (stratified)	0.1557*	

* alpha allocation = 0.01

BICR, blinded independent central review; CI, confidence interval

Other secondary endpoints: modest differences

Modified EFS

HR 0.75 (95% CI: 0.58, 0.96); p = 0.0244*

2-year difference: 6.2%

* alpha allocation = 0.05

Duration of response

	Pola+R-CHP (N=422)	R-CHOP (N=413)
2-year DOR rate (95% CI)	75.7% (71.0, 80.3)	71.7% (67.1, 76.2)
Difference (95% CI)	4.0% (-2.5, 10.5)	

Disease-free survival

	Pola+R-CHP (N=381)	R-CHOP (N=363)
2-year DFS rate (95% CI)	81.8% (77.4, 86.2)	77.4% (72.7, 82.0)
Difference (95% CI)	4.4% (-1.9, 10.8)	

DOR, disease-free survival; DFS, disease-free survival

Main topics

1. Modest PFS benefit of pola+R-CHP
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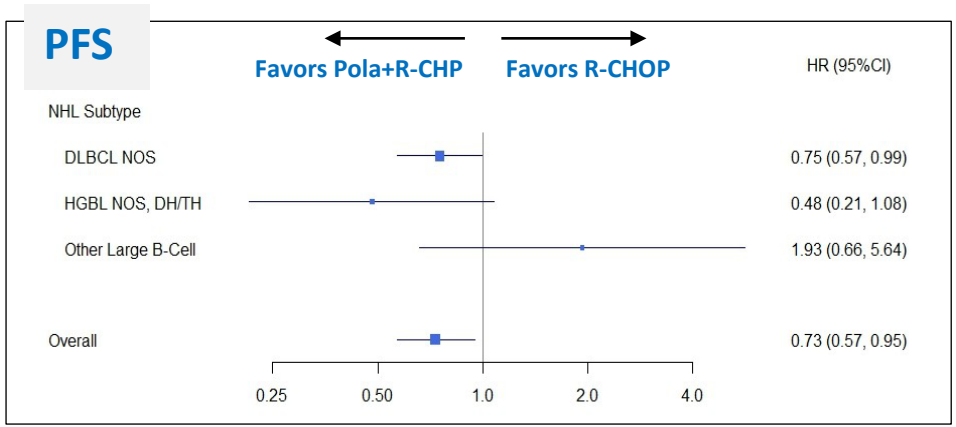
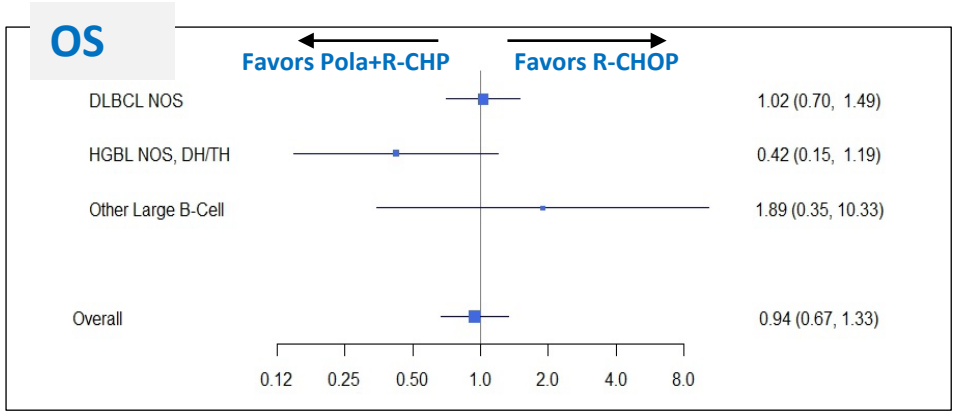
4. **Heterogeneity of study population**

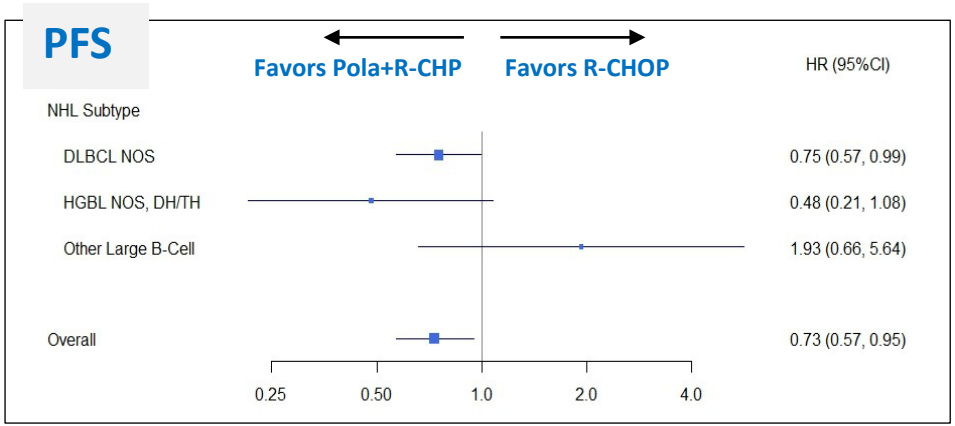
Heterogenous population and outcomes

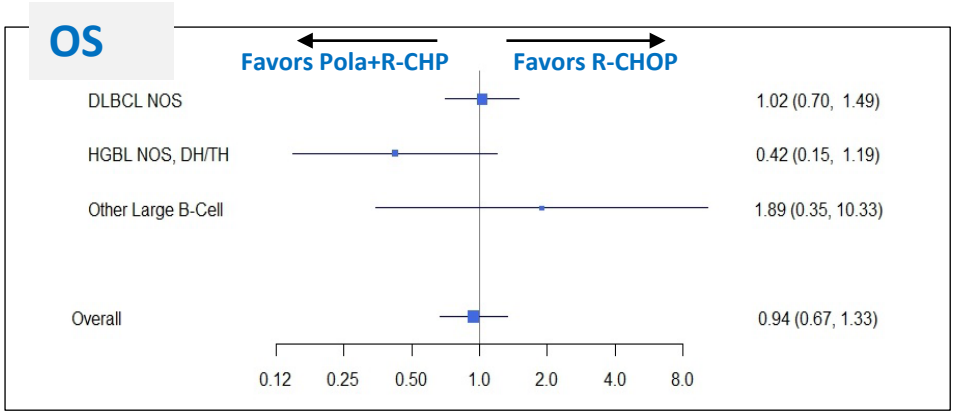




NHL, non-Hodgkin lymphoma; DH/TH, double-hit/triple-hit
Source: FDA review

Heterogenous population and outcomes

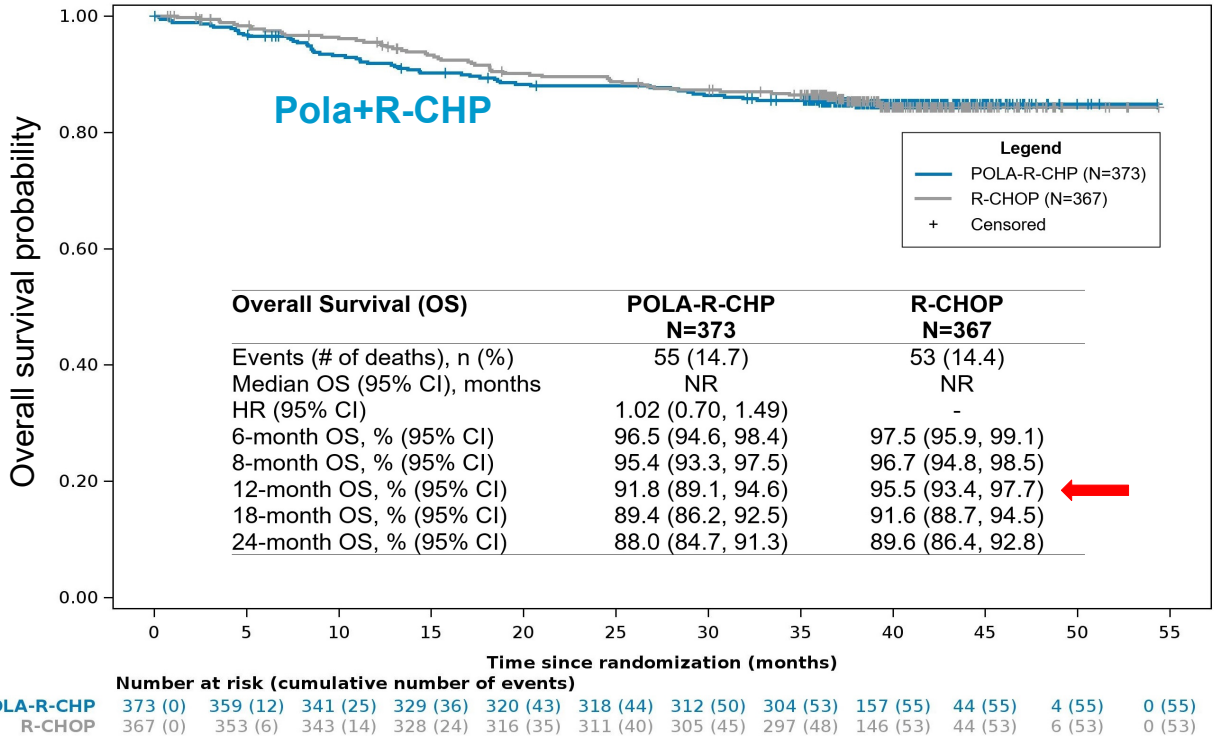




	Pola+R-CHP	R-CHOP
DLBCL NOS (n=740)		
CR rate	76.7%	74.9%
Difference	**1.7%**	
HGBL (n=93)		
CR rate	88.4%	64.0%
Difference	**24.4%**	
Other large B-cell lymphomas (n=46)		
CR rate	79.2%	81.8%
Difference	**-2.7%**	

NHL, non-Hodgkin lymphoma; DH/TH, double-hit/triple-hit
Source: FDA review

Heterogenous outcomes: Overall survival in DLBCL NOS



Overall Survival (OS)	POLA-R-CHP N=373	R-CHOP N=367
Events (# of deaths), n (%)	55 (14.7)	53 (14.4)
Median OS (95% CI), months	NR	NR
HR (95% CI)	1.02 (0.70, 1.49)	-
6-month OS, % (95% CI)	96.5 (94.6, 98.4)	97.5 (95.9, 99.1)
8-month OS, % (95% CI)	95.4 (93.3, 97.5)	96.7 (94.8, 98.5)
12-month OS, % (95% CI)	91.8 (89.1, 94.6)	95.5 (93.4, 97.7)
18-month OS, % (95% CI)	89.4 (86.2, 92.5)	91.6 (88.7, 94.5)
24-month OS, % (95% CI)	88.0 (84.7, 91.3)	89.6 (86.4, 92.8)

NR, not reached
Source: FDA review

Selected safety findings

Outcome	Pola+R-CHP (N=435) %	R-CHOP (N=438) %
SAEs	34	31
Grade ≥ 3 AE	61	60
Fatal AEs	2.8[a]	2.3

[a] 3.0% counting fatal infection after PD
Source: FDA analysis

Selected AEs	Pola+R-CHP (N=435) %		R-CHOP (N=438) %	
	All	Grade 3-4	All	Grade 3-4
Peripheral neuropathy	53[a]	1.6	54[a]	1.1
Neutropenia[b]	60	39	60	42
Febrile neutropenia	14	14	8	8
Infection	50	14	43	11

[a] Resolution: **58%** (pola+R-CHP), **67%** (R-CHOP)
[b] Prophylactic filgrastim was required.
Source: Applicant's analysis

- Generally similar safety profiles and dose intensity
- ≥ 5% higher in pola+R-CHP arm:
  - Febrile neutropenia, infection, nausea, diarrhea
- Myelosuppression likely underestimated

AE, adverse event; SAEs, serious adverse events; PD, progressive disease

Regulatory perspectives

- Modest PFS benefit
- Lack of improvement in OS
- Other secondary endpoints have limitations
- Heterogeneous population and treatment effect
  - May impact generalizability
  - Uncertain OS findings in largest subgroup

Regulatory perspectives

- Modest PFS benefit
- Lack of improvement in OS
- Other secondary endpoints have limitations
- Heterogeneous population and treatment effect
  - May impact generalizability
  - Uncertain OS findings in largest subgroup
- Uncertain benefit-risk of pola+R-CHP in patients with previously untreated LBCL

Discussion topics

- Discuss the benefit-risk profile of pola+R-CHP for the proposed patient population with LBCL, including patients with DLBCL NOS, considering the results of the POLARIX trial.

- Based on the results of the POLARIX trial, specifically the OS results, discuss whether additional follow-up data from POLARIX should be required to inform the benefit-risk of polatuzumab vedotin in patients with LBCL in the frontline setting.

Voting question

- Given the results of the POLARIX trial, does polatuzumab vedotin-piiq have a favorable benefit-risk profile in patients with previously untreated LBCL, including DLBCL NOS?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ADMINISTRATION

Polatuzumab vedotin-piiq
BLA 761121 / Supplement 008

FDA Presentation
Oncologic Drugs Advisory Committee Meeting
March 9, 2023

Maryam S. Yazdy, MD
Division of Hematologic Malignancies II
Office of Oncologic Diseases

FDA Review Team

Division of Hematologic Malignancies II
Nicole Gormley, MD
Yvette Kasamon, MD
Nicholas Richardson, DO, MPH
Maryam S. Yazdy, MD
Bindu Kanapuru, MD
Laura Wall, MS, BSN
Theresa Carioti, MPH

Division of Biometrics IX
Wenjuan Gu, PhD
Lisa Rodriguez, PhD
Yuan Li Shen, PhD
Susan Jin, MS

Office of Oncologic Diseases
Richard Pazdur, MD
Marc R. Theoret, MD
Vishal Bhatnagar, MD

Division of Cancer Pharmacology I
Division of Pharmacometrics
Yue Xiang, PharmD
Robyn Konicki, PharmD
Jiang Liu, PhD
Ruby Leong, PharmD
Olanrewaju Okusanya, PharmD, MS
Brian Booth, PhD

Outline

- Main topics
  - Modest PFS benefit of pola+R-CHP
  - OS results
  - Other efficacy endpoints
  - Heterogeneity of study population

- Other topics: safety, PROs

PFS, progression-free survival; pola+R-CHP, polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; OS, overall survival; PROs, patient-reported outcomes

Applicant's Proposed Indication

Polatuzumab vedotin in combination with R-CHP is indicated for the treatment of adult patients with previously untreated DLBCL*

- *Proposed dosage*: 1.8 mg/kg IV every 21 days for 6 cycles
- *Proposed pathway*: Regular approval

*Includes DLBCL NOS, HGBL (NOS, or with *MYC* and *BCL2* and/or *BCL6* rearrangements), and other large B-cell lymphomas (T-cell/histiocyte-rich LBCL, EBV+ DLBCL, ALK+ LBCL, and HHV8+ DLBCL)

DLBCL, diffuse large B-cell lymphoma; NOS, not otherwise specified; HGBL, high-grade B-cell lymphoma; LBCL, large B-cell lymphoma; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; EBV, Epstein-Barr virus; ALK, anaplastic lymphoma kinase; HHV8, human herpesvirus 8

Polatuzumab Vedotin-piiq: Accelerated Approval in June 2019

Indication: In combination with bendamustine and a rituximab product for the treatment of adult patients with R/R DLBCL, NOS, after at least two prior therapies
Recommended dosage: 1.8 mg/kg IV every 21 days for 6 cycles

R/R, relapsed or refractory

Polatuzumab Vedotin: Accelerated Approval
Pivotal study GO29365

- *de novo* DLBCL, R/R after ≥ 1 prior therapy
- Ineligible for HSCT

1:1

Pola 1.8 mg/kg + BR for 6 cycles
(N = 40)

BR for 6 cycles
(N = 40)

Efficacy per IRC	Pola + BR (N = 40)	BR (N = 40)
Response at End of Therapy		
ORR (95% CI)	45% (29, 62)	18% (7, 33)
CR	40% (25, 57)	18% (7, 33)
Best Overall Response		
ORR (95% CI)	58% (41, 73)	25% (13, 41)
CR	50% (34, 66)	23% (11, 38)
Duration of Response	(from n of 25)	(from n of 10)
≥ 6 months	64%	30%
≥ 12 months	48%	20%

Primary endpoint: CR rate per IRC at end of therapy

BR, bendamustine, rituximab; PN, peripheral neuropathy; HSCT, hematopoietic stem cell transplantation; ORR, objective response rate; CR, complete response; IRC, independent review committee

Source: FDA analysis

Polatuzumab Vedotin in DLBCL: Post-marketing Requirements

- Study GO39942 (POLARIX): randomized, double-blind, placebo-controlled trial of pola+R-CHP vs R-CHOP in previously untreated DLBCL; primary endpoint, PFS

- Study MO40598 (POLARGO): randomized trial of pola+R-GemOx vs R-GemOx in R/R DLBCL; primary endpoint, overall survival
  - Preliminary results expected late 2024

*Verification of clinical benefit through either PMR could be adequate to fulfill the AA requirement.

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; pola+R-GemOx, polatuzumab vedotin, rituximab, gemcitabine, and oxaliplatin; PMR, post-marketing requirement; AA, accelerated approval

Establishing CHOP as SOC for DLBCL

HOP vs CHOP

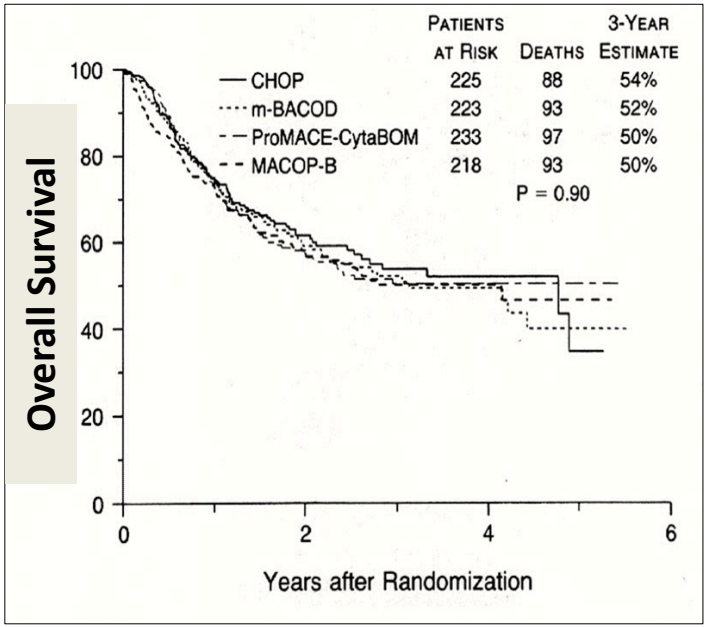
HYDROXYLDAUNOMYCIN (ADRIAMYCIN) COMBINATION CHEMOTHERAPY IN MALIGNANT LYMPHOMA

EUGENE M. MCKELVEY, MD, JEFFREY A. GOTTLIEB, MD, HENRY E. WILSON, MD, ARTHUR HAUT, MD, ROBERT W. TALLEY, MD, RONALD STEPHENS, MD, MONTAGUE LANE, MD, JESS F. GAMBLE, MD, STEPHEN E. JONES, MD, PETRE N. GROZEA, MD, JORDON GUTTERMAN, MD, CHARLES COLTMAN, JR., MD, AND THOMAS E. MOON, PHD

1st generation	2nd generation	3rd generation
MOPP/C-MOPP	COP/BLAM	m-BACOD
BACOP	M-BACOD	ProMACE d1/MOPP d8
CHOP	ProMACE/MOPP	ProMACE-CytaBOM
COMLA		MACOP-B

For information on the regimens, refer to https://www.cancer.gov/about cancer/treatment/drugs

CHOP as SOC

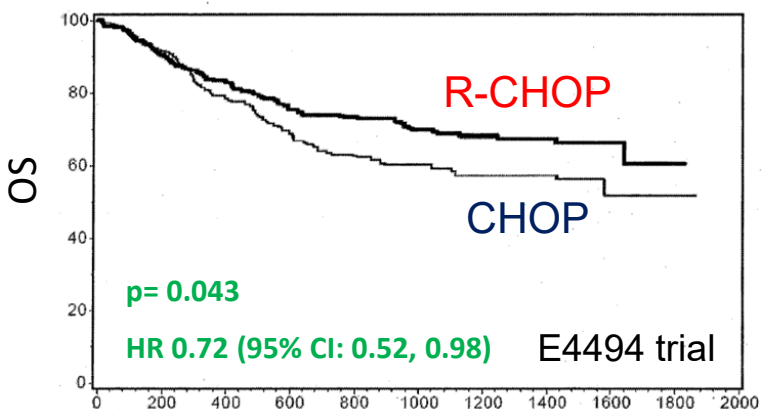


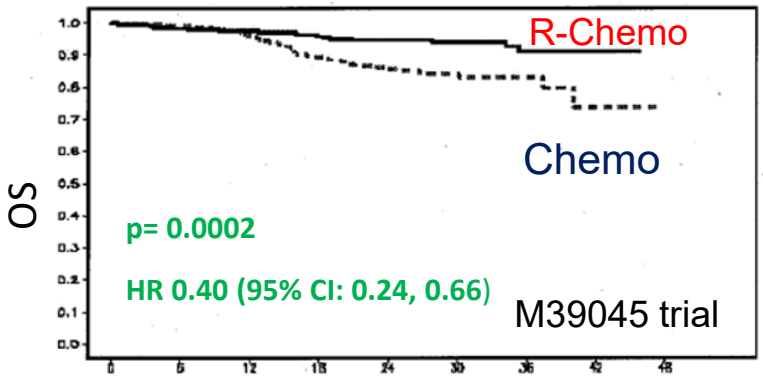
Contribution of effect of vincristine in CHOP was never studied

SOC, standard of care; HOP, doxorubicin, vincristine, and prednisone

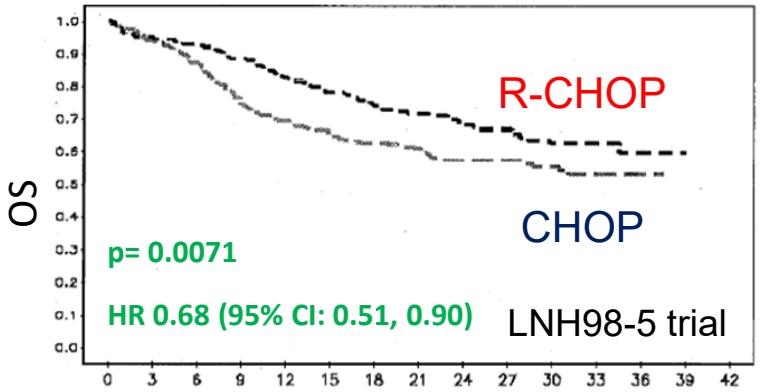
References: McKelvey et al. Cancer 1976;38(4):1484; Fisher et al , N Engl J Med 1993;328(14):1002; Major et al. Clin Adv Hematol Oncol 2021;19(11):698

Approval of Rituximab Based on 3 RCTs Demonstrating Overall Survival Benefit





R-CHOP has been standard of care for previously untreated DLBCL since 2006



RCT, randomized controlled trial; HR, hazard ratio; CI, confidence interval; R-chemo, rituximab + chemotherapy

Source: FDA review

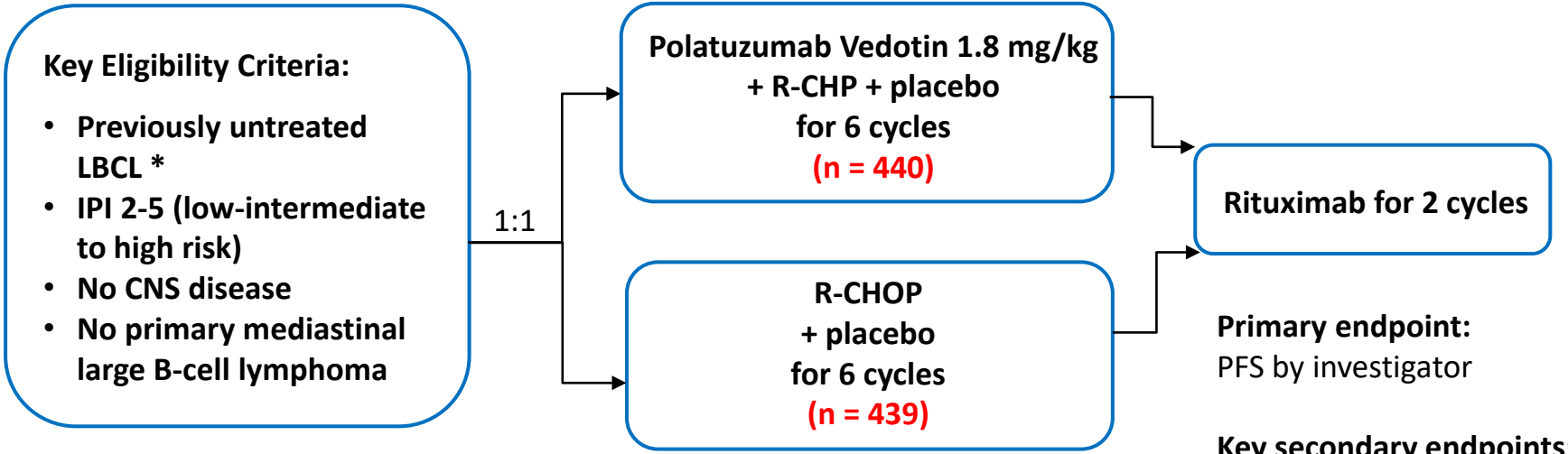
RCTs with Unsuccessful Attempts to Improve R-CHOP

Trial	Experimental arm	N	PFS, experimental vs standard arm	Outcome
PRELUDE[1]	R-CHOP + enzastaurin maintenance	758	70% vs 71% (4 y)	Negative
PILLAR-2[2]	R-CHOP + everolimus maintenance	742	77% vs 78% (3 y)	Negative
CALGB 50303[3]	DA-EPOCH-R	524	79% vs 76% (2 y)	Negative
GOYA[4]	Obinutuzumab-CHOP	1418	70% vs 67% (3 y)	Negative
REMoDL-B[5]	R-CHOP + bortezomib	1128	75% vs 71% (2.5 y)	Negative
PHOENIX[6]	R-CHOP + ibrutinib	838	71% vs 68% (3 y)	Negative
ROBUST[7]	R-CHOP + lenalidomide	570	67% vs 64% (2 y)	Negative

DA-EPOCH-R; dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; y, year

References: [1]Crump et al. J Clin Oncol 2016;34:2484. [2]Witzig et al. Ann Oncol 2018;29(3):707. [3]Bartlett et al. J Clin Oncol 2019; 37(21):1790. [4]Vitolo et al. J Clin Oncol 2017;35(31):3529. [5]Davies et al. Lancet Oncol 2019;20:649. [6]Younes et al. J Clin Oncol 2019;37(15):1285, [7]Nowakowski et al. J Clin Oncol 2021;39:1317.

POLARIX: Double-Blind Substitution Trial



*DLBCL NOS, HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements, HGBL NOS, and other LGBLs (T-cell/histiocyte-rich LBCL, EBV+ DLBCL, ALK+ LBCL, and HHV8+ DLBCL)

IPI, International Prognostic Index; CNS, central nervous system; EFS, event-free survival; LBCL, large B-cell lymphoma

Source: modification of Applicant's schema

Substitution of Vincristine with Polatuzumab Vedotin

Pola+R-CHP	R-CHOP
Rituximab 375 mg/m^2	Rituximab 375 mg/m^2
Cyclophosphamide 750 mg/m^2	Cyclophosphamide 750 mg/m^2
Doxorubicin 50 mg/m^2	Doxorubicin 50 mg/m^2
Placebo	Vincristine 1.4 mg/m^2
Polatuzumab vedotin 1.8 mg/kg	Placebo
Prednisone 100 mg daily D1-5	Prednisone 100 mg daily D1-5

Source: FDA review

Trial Design Considerations

- FDA approves specific drugs and biologics
  - Based on understanding of the treatment effect of the product

- Generally, efficacy can be demonstrated using a superiority or noninferiority (NI) design

- POLARIX was designed as a superiority trial
  - NI design not possible
    - Lack of understanding of vincristine activity
    - Use of PFS as an endpoint

Trial Design Considerations

- With a superiority active control trial, the aim is to show superiority relative to the control

Trial Design Considerations

- With a superiority active control trial, the aim is to show superiority relative to the control

- With a superiority **substitution** trial, the aim is to show superiority relative to the control, in the setting of other agents

- R-CHP+pola versus R-CHP+vincristine
  - Challenging to interpret contribution of effect of pola because the activity of vincristine in the CHOP regimen is unknown

POLARIX Eligibility Criteria: Clarification

Previously untreated patients with CD20+ DLBCL, including the following diagnoses per 2016 WHO classification criteria:	
• DLBCL, NOS including germinal center B-cell (GCB) type or activated B-cell (ABC) type	← DLBCL, NOS
• HGBL, NOS • HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements	← HGBL NOS, DH/TH
• T-cell/histiocyte-rich large B-cell lymphoma • EBV+ DLBCL, NOS • ALK+ large B-cell lymphoma • HHV8+ DLBCL, NOS	← Other LBCL

WHO, World Health Organization; DH/TH, double-hit / triple-hit
Source: FDA review

Heterogenous Patient Population in POLARIX

Lymphoma subgroups	Pola + R-CHP (N=440), %	R-CHOP (N=439), %
DLBCL NOS	85	84
HGBL (NOS or DH/TH)	10	11
Other LBCL*	5	5

* T-cell / histiocyte-rich LBCL or EBV+ DLBCL
Source: FDA review

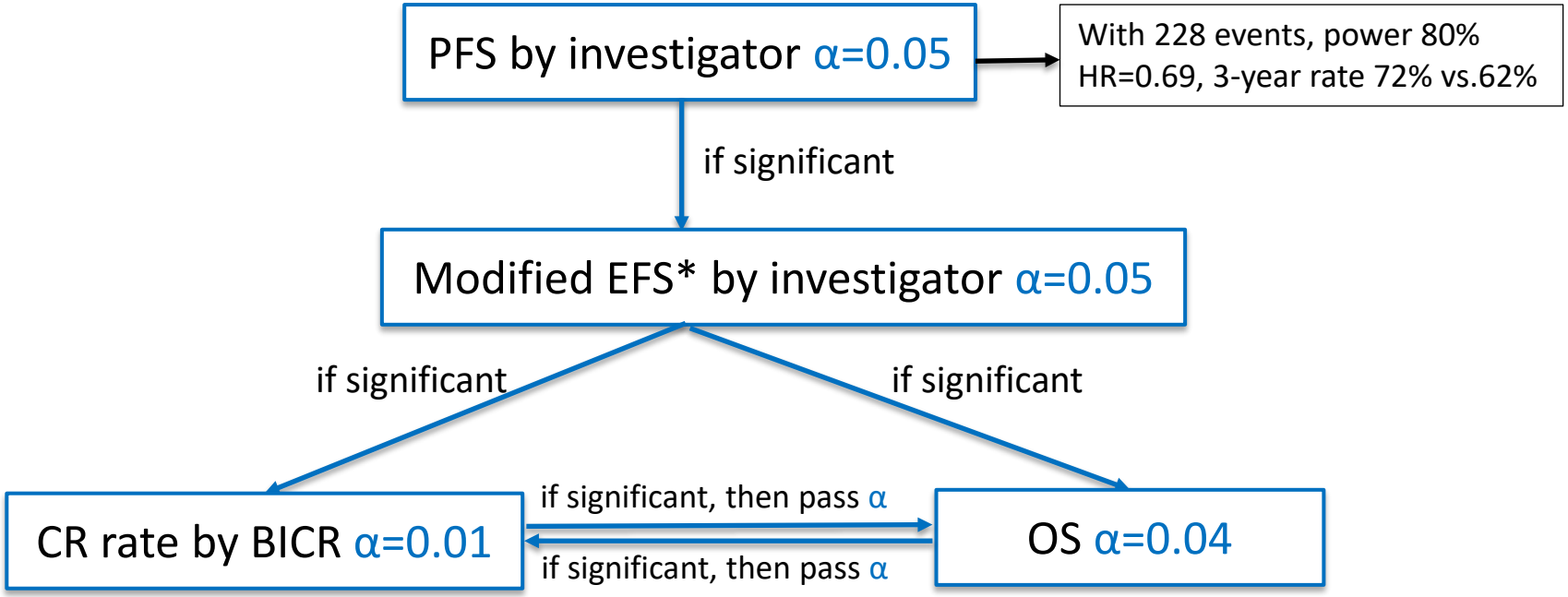
Treatment Guidelines: Newly Diagnosed HGBL with *MYC* and *BCL2* and/or *BCL6* Translocations
Clinical trial is recommended
R-CHOP may be associated with a sub-optimal outcome. – Could be considered for low-risk IPI patients.
Dose-adjusted EPOCH-R
R-HyperCVAD alternating with high-dose methotrexate and cytarabine
R-CODOX-M alternating with R-IVAC
Additional considerations – Central nervous system prophylaxis – Consolidation with autologous SCT can be considered

Source: Modified from NCCN Guidelines, version 2.2023

- Treatment for HGBL may not be generalizable or applicable to a U.S. population
- More intensive chemotherapy backbones favored for HGBL

R-HyperCVAD: rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; R-CODOX-M: rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate; R-IVAC: rituximab, ifosfamide, etoposide, and cytarabine; SCT, stem cell transplantation; NCCN, National Comprehensive Cancer Network

Testing Hierarchy and Alpha Allocation (2-sided)



* Modified EFS (EFS efficacy) defined from randomization to the earliest occurrence of disease progression, relapse, death, initiation of new anti-lymphoma therapy (NALT) for efficacy reasons, or positive biopsy for residual disease.
BICR, blinded independent committee review

Applicant's Primary PFS Analysis

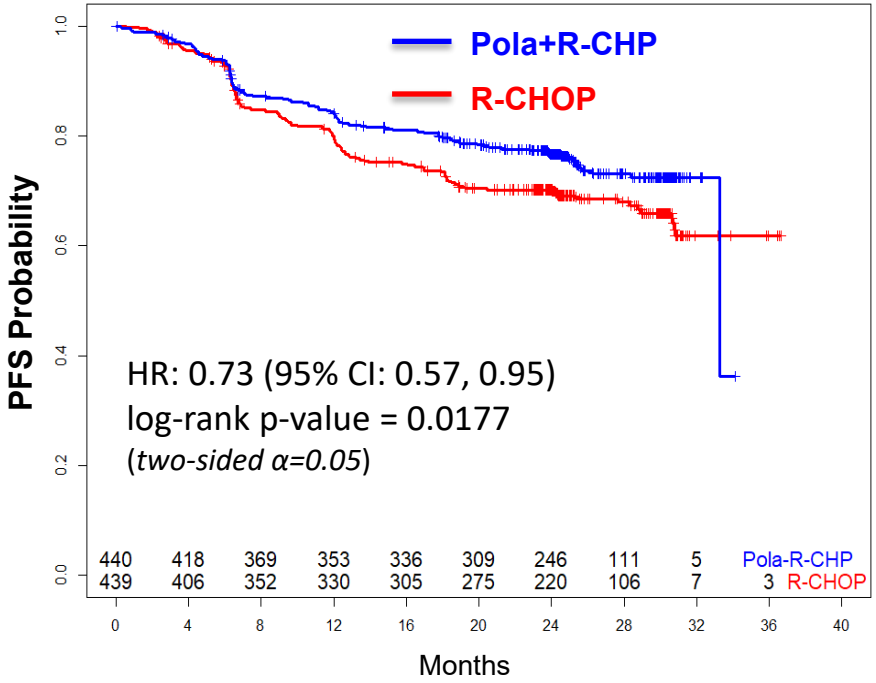
- **PFS definition:** Time from date of randomization until the first occurrence of disease progression, relapse, or death from any cause.
- **New anti-lymphoma treatment (NALT):** includes all non-protocol new treatments for lymphoma
- **Applicant's PFS analysis:** Not censored for NALT or ≥2 missed assessments

Main topics

1. **Modest PFS benefit of pola+R-CHP**
2. OS results
3. Other efficacy endpoints
4. Heterogeneity of study population

Modest PFS Benefit of Pola+R-CHP

Applicant's Primary Analysis



	Pola+R-CHP (N=440)	R-CHOP (N=439)	Difference (95% CI)
1 year	83.9% (80.1, 87.1)	79.8% (75.6, 83.3)	**4.1% (-1.0, 9.3)**
2 years	76.7% (72.3, 80.5)	70.2% (65.5, 74.4)	**6.5%** (0.5, 12.5)

- **Contribution of effect of polatuzumab vedotin?**

Abbreviations: HR, hazard ratio; CI, confidence interval

Source: FDA review

PFS Sensitivity Analyses: Modest Treatment Effect

PFS Analyses by Censoring Rules	Difference in 2-year PFS	HR (95% CI)	p-value
Original Data			
NALT: Not Censor **≥2 Missed Assessments:** Not Censor	6.5%	0.73 (0.57, 0.95)	0.0177
Sensitivity Analyses on Original Data (nominal p-values)			
NALT: Censor **≥2 Missed Assessments:** Not Censor	4.9%	0.77 (0.59, 1.01)	0.0567
NALT: Censor **≥2 Missed Assessments:** Censor	4.9%	0.77 (0.59, 1.01)	0.0541

Source: FDA review and Applicant analysis

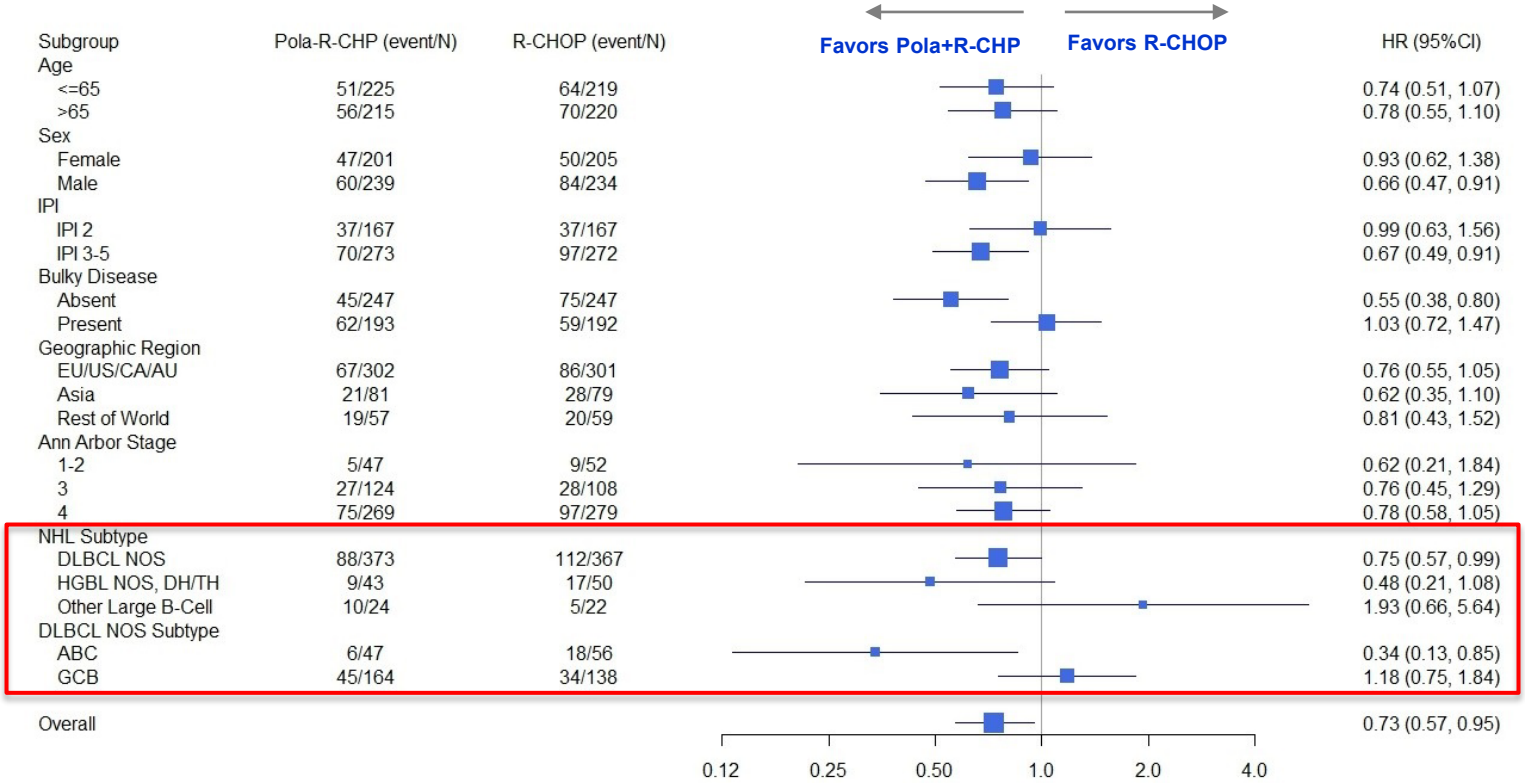
PFS Sensitivity Analyses: Modest Treatment Effect

PFS Analyses by Censoring Rules	Difference in 2-year PFS	HR (95% CI)	Nominal p-value
Sensitivity analyses after recategorizing NALT			
NALT: Censor **≥2 Missed Assessment:** Not Censor	6.1%	0.74 (0.57, 0.96)	0.0251
NALT: Censor **≥2 Missed Assessment:** Censor	5.9%	0.75 (0.57, 0.97)	0.0308

- **IRC assessment of PFS was not available**

Source: FDA review

PFS Subgroup Results



Subgroup	Pola-R-CHP (event/N)	R-CHOP (event/N)	HR (95%CI)
Age			
<=65	51/225	64/219	0.74 (0.51, 1.07)
>65	56/215	70/220	0.78 (0.55, 1.10)
Sex			
Female	47/201	50/205	0.93 (0.62, 1.38)
Male	60/239	84/234	0.66 (0.47, 0.91)
IPI			
IPI 2	37/167	37/167	0.99 (0.63, 1.56)
IPI 3-5	70/273	97/272	0.67 (0.49, 0.91)
Bulky Disease			
Absent	45/247	75/247	0.55 (0.38, 0.80)
Present	62/193	59/192	1.03 (0.72, 1.47)
Geographic Region			
EU/US/CA/AU	67/302	86/301	0.76 (0.55, 1.05)
Asia	21/81	28/79	0.62 (0.35, 1.10)
Rest of World	19/57	20/59	0.81 (0.43, 1.52)
Ann Arbor Stage			
1-2	5/47	9/52	0.62 (0.21, 1.84)
3	27/124	28/108	0.76 (0.45, 1.29)
4	75/269	97/279	0.78 (0.58, 1.05)
NHL Subtype			
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)
DLBCL NOS Subtype			
ABC	6/47	18/56	0.34 (0.13, 0.85)
GCB	45/164	34/138	1.18 (0.75, 1.84)
Overall			0.73 (0.57, 0.95)

Other LBCL: T-cell/histiocyte-rich LBCL and EBV+ DLBCL

Source: FDA analysis

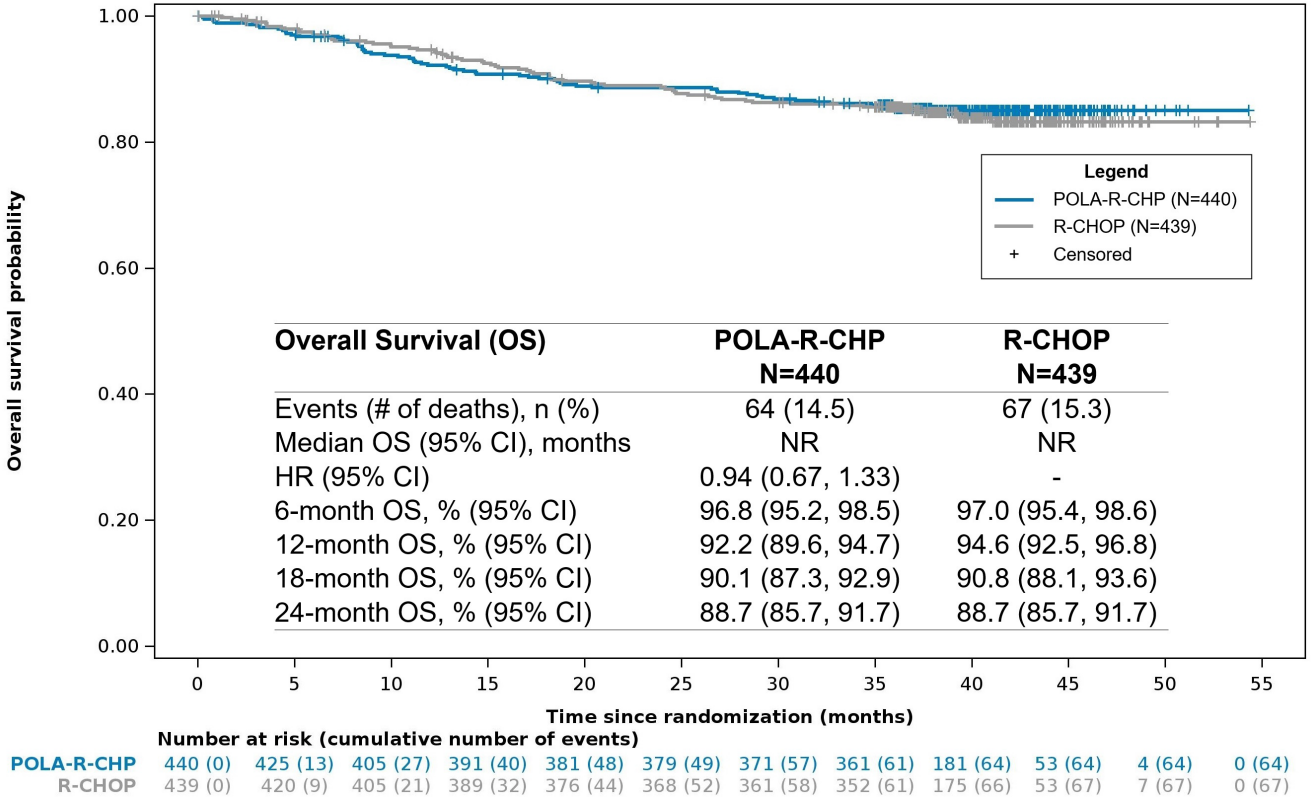
Main topics

1. Modest PFS benefit of pola+R-CHP
2. **OS results**
3. Other efficacy endpoints
4. Heterogeneity of study population

Overall Survival

- Clinically meaningful measure of safety and efficacy
- Inadequate statistical power could limit the ability to detect statistically significant OS improvements
- FDA relies on an OS analysis to inform benefit-risk
- OS plays an important role in the benefit-risk determination in the context of totality of data

Lack of Improvement in OS: Final Analysis

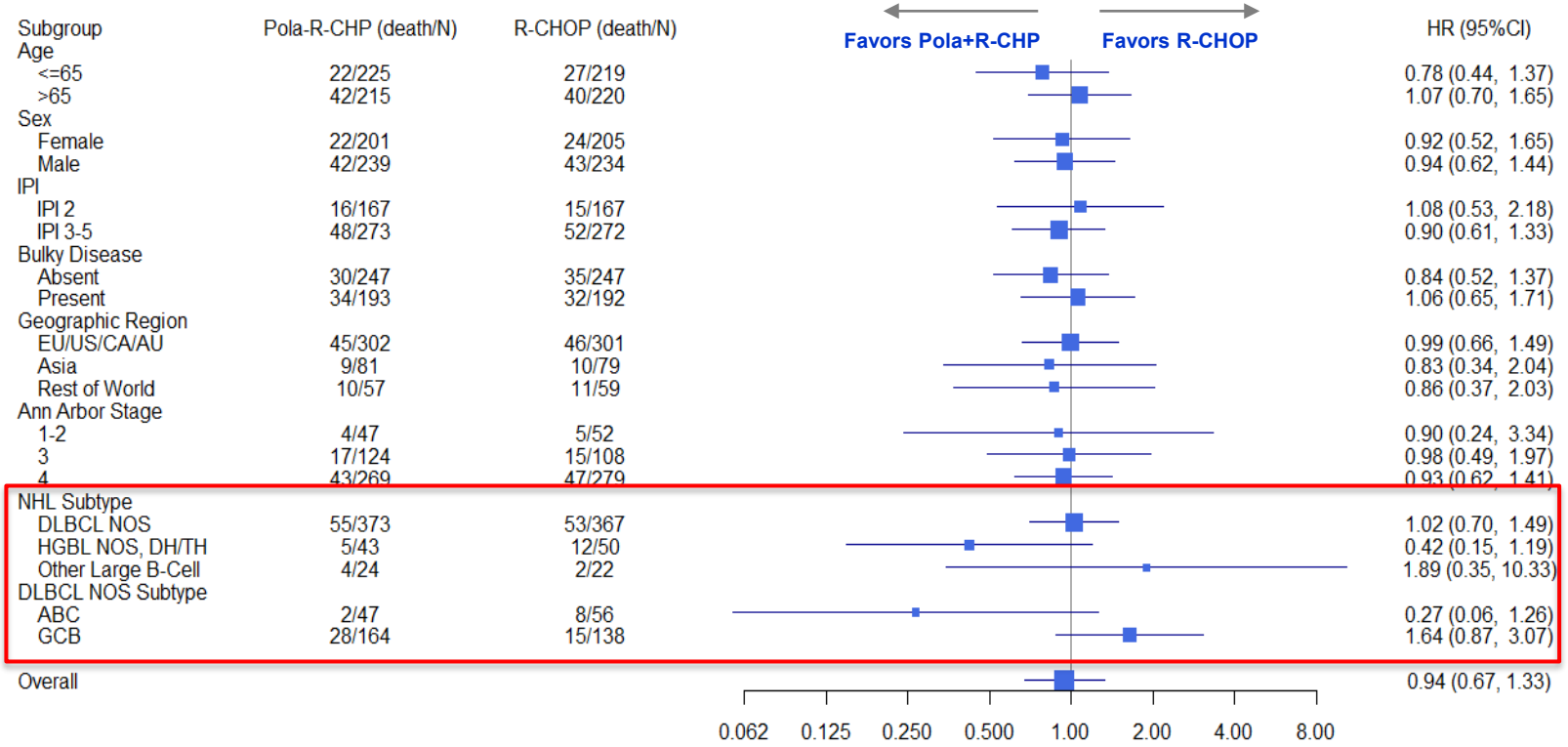


Overall Survival (OS)	POLA-R-CHP N=440	R-CHOP N=439
Events (# of deaths), n (%)	64 (14.5)	67 (15.3)
Median OS (95% CI), months	NR	NR
HR (95% CI)	0.94 (0.67, 1.33)	-
6-month OS, % (95% CI)	96.8 (95.2, 98.5)	97.0 (95.4, 98.6)
12-month OS, % (95% CI)	92.2 (89.6, 94.7)	94.6 (92.5, 96.8)
18-month OS, % (95% CI)	90.1 (87.3, 92.9)	90.8 (88.1, 93.6)
24-month OS, % (95% CI)	88.7 (85.7, 91.7)	88.7 (85.7, 91.7)

Median Follow-up:
39.7 months

NR, not reached
Source: FDA analysis

OS Subgroup Results



Subgroup	Pola-R-CHP (death/N)	R-CHOP (death/N)	HR (95%CI)
Age			
<=65	22/225	27/219	0.78 (0.44, 1.37)
>65	42/215	40/220	1.07 (0.70, 1.65)
Sex			
Female	22/201	24/205	0.92 (0.52, 1.65)
Male	42/239	43/234	0.94 (0.62, 1.44)
IPI			
IPI 2	16/167	15/167	1.08 (0.53, 2.18)
IPI 3-5	48/273	52/272	0.90 (0.61, 1.33)
Bulky Disease			
Absent	30/247	35/247	0.84 (0.52, 1.37)
Present	34/193	32/192	1.06 (0.65, 1.71)
Geographic Region			
EU/US/CA/AU	45/302	46/301	0.99 (0.66, 1.49)
Asia	9/81	10/79	0.83 (0.34, 2.04)
Rest of World	10/57	11/59	0.86 (0.37, 2.03)
Ann Arbor Stage			
1-2	4/47	5/52	0.90 (0.24, 3.34)
3	17/124	15/108	0.98 (0.49, 1.97)
4	43/269	47/279	0.93 (0.62, 1.41)
NHL Subtype			
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)
DLBCL NOS Subtype			
ABC	2/47	8/56	0.27 (0.06, 1.26)
GCB	28/164	15/138	1.64 (0.87, 3.07)
Overall			0.94 (0.67, 1.33)

Source: FDA analysis

Main topics

1. Modest PFS benefit of pola+R-CHP
2. OS results
3. **Other efficacy endpoints**
4. Heterogeneity of study population

Lack of Improvement in Response Rates

Response per IRC ITT population	Pola+R-CHP (N=440)	R-CHOP (N=439)
ORR (95% CI)	**85.5%** (81.8, 88.6)	**83.8%** (80.0, 87.2)
CR rate (95% CI)	**78.0%** (73.8, 81.7)	**74.0%** (69.7, 78.1)
Difference (95% CI)	**3.9% (-1.9, 9.7)**	
p-value (stratified)	**0.1557***	

* alpha allocation = 0.01

No difference

Efficacy claims based on numerically higher CR rate are unsupported

Source: FDA review

Modified EFS Results

	Pola+R-CHP (N=440)	R-CHOP (N=439)
HR (95% CI)	0.75 (0.58, 0.96)	
Stratified p-value	0.0244	
1 year (95% CI)	82.5% (78.9, 86.1)	78.7% (74.8, 82.6)
Difference (95% CI): 3.8% (-1.5, 9.2)		
2 years (95% CI)	75.6% (71.5, 79.7)	69.4% (65.0, 73.8)
Difference (95% CI): 6.2% (0.1, 12.2)		

Limitation

Similar to primary PFS result, the difference is modest (6.2% at 2 years)

Source: FDA review

Other Secondary Endpoints

Duration of response

	Pola + R-CHP (N=422)	R-CHOP (N=413)
Median (95% CI)	30.5 months (30.5, NE)	NE (NE, NE)
2-year DOR rate (95% CI)	75.7% (71.0, 80.3)	71.7% (67.1, 76.2)
Difference (95% CI)	4.0% (-2.5, 10.5)	

Disease-free survival

	Pola + R-CHP (N=381)	R-CHOP (N=363)
Median (95% CI)	30.5 months (30.5, NE)	NE (NE, NE)
2-year DFS rate (95% CI)	81.8% (77.4, 86.2)	77.4% (72.7, 82.0)
Difference (95% CI)	4.4% (-1.9, 10.8)	

Limitations

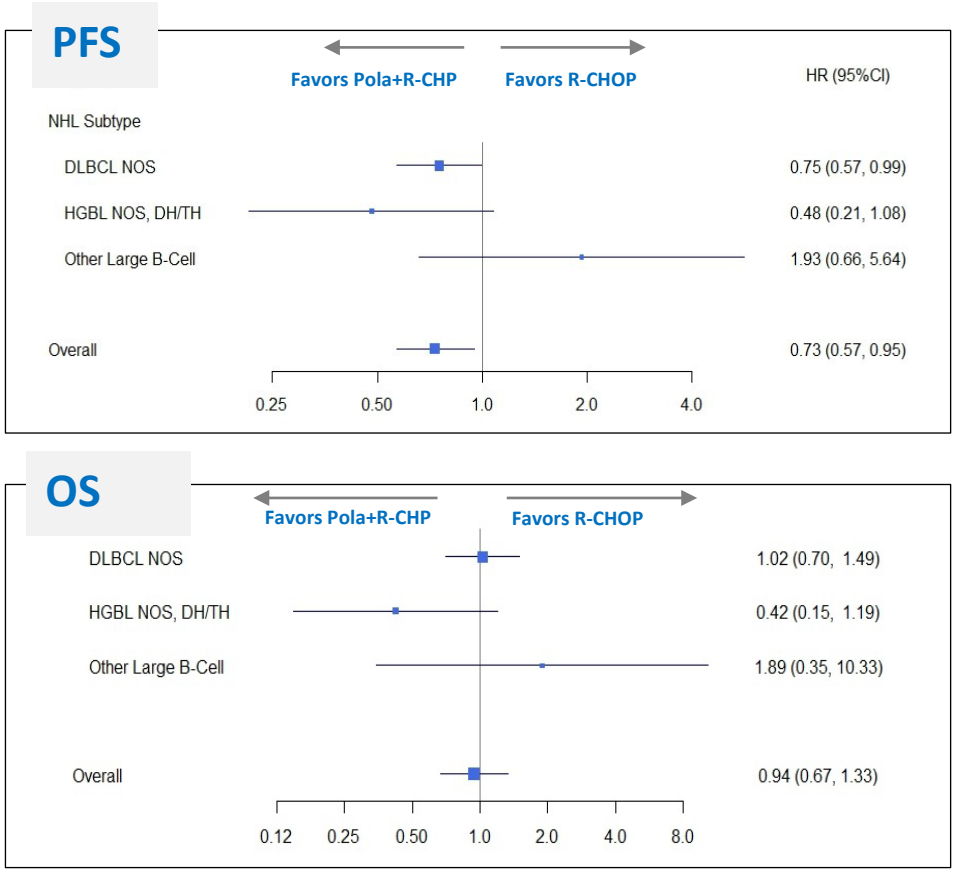
- Results are modest.
- Exploratory; based on non-randomized subsets of patients and not controlled for Type I error rate.
- Applicant's analyses do not censor NALT, which makes it difficult to separate the effect of the investigational drug from the effect of NALT.

DOR, duration of response; DFS, disease-free survival; NE, not estimable
Source: FDA review

Main topics

1. Modest PFS benefit of pola+R-CHP
2. OS results
3. Other efficacy endpoints
4. **Heterogeneity of study population**

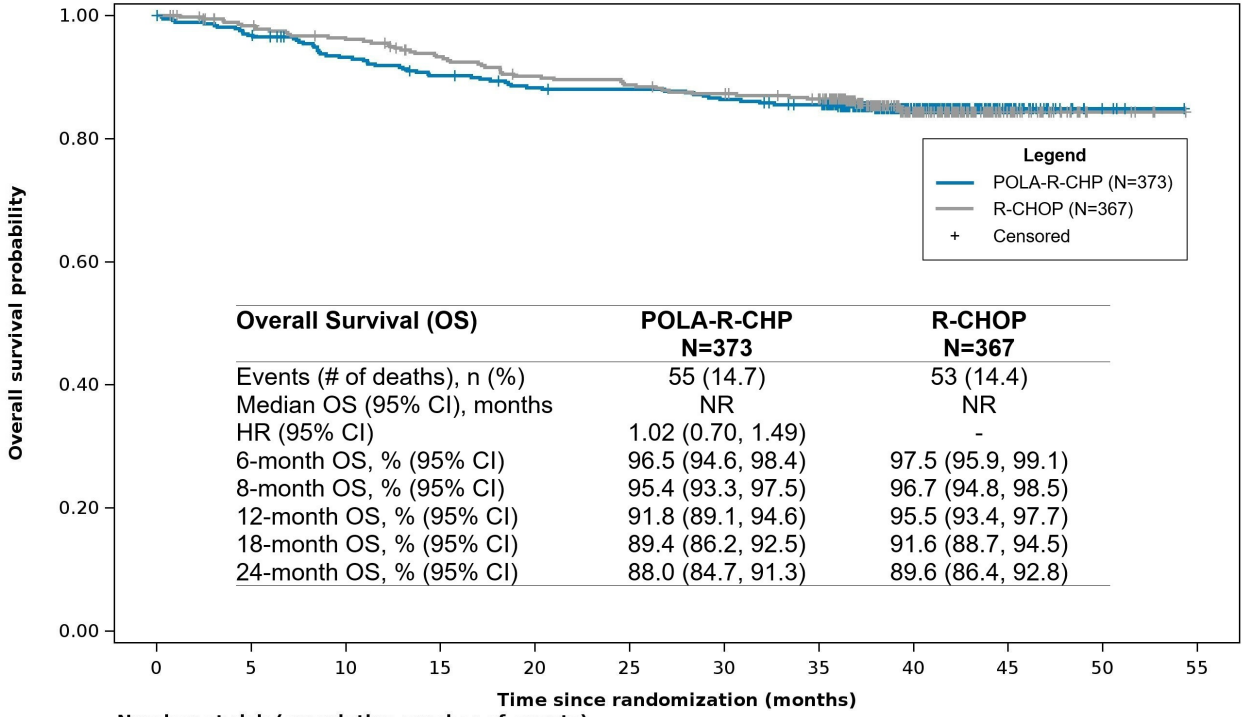
Heterogenous Patient Population and Outcomes



Source: FDA review

Heterogenous Patient Population and Outcomes

OS- DLBCL NOS



Overall Survival (OS)	POLA-R-CHP N=373	R-CHOP N=367
Events (# of deaths), n (%)	55 (14.7)	53 (14.4)
Median OS (95% CI), months	NR	NR
HR (95% CI)	1.02 (0.70, 1.49)	-
6-month OS, % (95% CI)	96.5 (94.6, 98.4)	97.5 (95.9, 99.1)
8-month OS, % (95% CI)	95.4 (93.3, 97.5)	96.7 (94.8, 98.5)
12-month OS, % (95% CI)	91.8 (89.1, 94.6)	95.5 (93.4, 97.7)
18-month OS, % (95% CI)	89.4 (86.2, 92.5)	91.6 (88.7, 94.5)
24-month OS, % (95% CI)	88.0 (84.7, 91.3)	89.6 (86.4, 92.8)

Number at risk (cumulative number of events)

POLA-R-CHP	373 (0)	359 (12)	341 (25)	329 (36)	320 (43)	318 (44)	312 (50)	304 (53)	157 (55)	44 (55)	4 (55)	0 (55)
R-CHOP	367 (0)	353 (6)	343 (14)	328 (24)	316 (35)	311 (40)	305 (45)	297 (48)	146 (53)	44 (53)	6 (53)	0 (53)

Source: FDA review

Heterogenous Patient Population and Outcomes

	Pola+R-CHP	R-CHOP
DLBCL NOS	n= 373	n= 367
PFS HR (95% CI)	0.75 (0.57, 0.99)	
OS HR (95% CI)	1.02 (0.70, 1.49)	
CR rate (95% CI)	76.7%	74.9%
Difference (95% CI)	1.7% (-4.7, 8.2)	
HGBL NOS, DH/TH	n= 43	n= 50
PFS HR (95% CI)	0.48 (0.21, 1.08)	
OS HR (95% CI)	0.42 (0.15, 1.19)	
CR rate (95% CI)	88.4%	64.0%
Difference (95% CI)	24.4% (5.8, 42.9)	
Other LBCL	n= 24	n= 22
PFS HR (95% CI)	1.93 (0.66, 5.64)	
OS HR (95% CI)	1.89 (0.35, 10.33)	
CR rate (95% CI)	79.2%	81.8%
Difference (95% CI)	-2.7% (-28.2, 22.9)	

Source: FDA review

Main Topics: Summary

- Pola+R-CHP
  - Demonstrated modest PFS benefit over R-CHOP
  - Did not improve CR rate
  - Did not improve OS

- The results of other secondary endpoints are modest.

- Heterogeneous treatment effect

Other Topics

1. Safety considerations
2. Inadequate assessment of PROs

Abbreviations: PROs: patient-reported outcomes

Selected Safety Findings

Outcome	Pola+R-CHP (N=435) %	R-CHOP (N=438) %
SAEs	34	31
Grade ≥3 AE	61	60
Fatal AEs	2.8*	2.3

*3.0% if fatal infection after PD is included

Source: FDA analysis

Selected AEs	Pola+R-CHP (n=435) %		R-CHOP (n=438) %	
	All	Grade 3-4	All	Grade 3-4
Neutropenia[a]	60	39	60	42
Peripheral neuropathy	53[b]	1.6	54[b]	1.1
Infection	50	14	43	11
Febrile neutropenia	14	14	8	8

[a] Prophylactic mandatory filgrastim: 90% (pola+R-CHP), 93% (R-CHOP)

[b] **Resolution: 58% (pola+R-CHP), 67% (R-CHOP)**

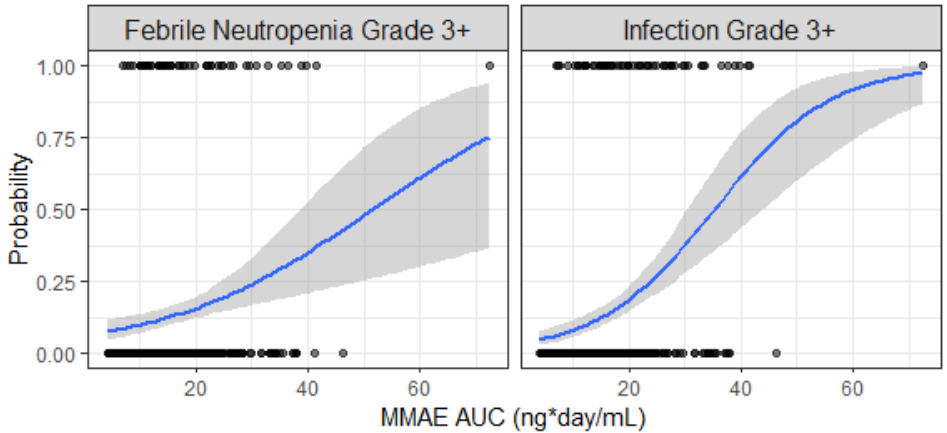
Source: Applicant's analysis

- Incidence of febrile neutropenia, infections, nausea and diarrhea was at least 5% higher in the pola+R-CHP arm
- Underestimated incidence of neutropenia: labs required only at beginning of each cycle
- Uncertainty with impact on myelosuppression

AE, adverse event; SAEs, serious adverse events; PD, progressive disease

Unknown if Lower Doses Could Reduce Toxicity Without Impacting Efficacy

- Uncertain efficacy and safety for doses lower than 1.8 mg/kg Q3W with R-CHP
  - Limited dose-finding in previously untreated DLBCL
- No clear association between polatuzumab vedotin exposure and OS or CR rate in subjects with untreated DLBCL
- Higher rates of **Grade ≥3 febrile neutropenia** and **Grade ≥3 infection** are associated with higher polatuzumab vedotin exposure



Q3W, every 3 weeks;
AUC, area under the concentration-versus-time curve;
MMAE, monomethyl auristatin E
Data shown for Pola+R-CHP arm (n=429) of POLARIX.
Source: FDA analysis

Other Topics

1. Safety considerations
2. Inadequate assessment of PROs

Patient-Reported Outcomes

1- PRO assessment strategies (instruments, assessment frequency, endpoints) were inadequate to measure tolerability.

2- EORTC-QLQ-C30, FACT-LYM, and FACT/GOG-NTX were administered sparsely and no “overall side effect bother” item (FACT GP5).

3- Exploratory endpoints; no anchor-based methods used.

4- Slightly higher patient-reported diarrhea, nausea, and decreased appetite in Pola+R-CHP arm during treatment period.

5- Although there were no major differences observed between arms, FDA disagrees with the Applicant that there was no detriment observed with pola+R-CHP compared to R-CHOP.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire; FACT-LYM, Functional Assessment of Cancer Therapy-Lymphoma Lymphoma Subscale; GOG-NTX, Gynecologic Oncology Group-Neurotoxicity

Conclusions

- **Pola+R-CHP in patients with previously untreated LBCL**
  - Modest PFS benefit
    - 6.5% absolute improvement in PFS at 2 years
  - Lack of improvement in CR rate
  - Lack of an OS benefit

- **Heterogeneity of trial population and outcomes impacts generalizability of the findings**
  - Variable results in DLBCL NOS with concerning OS results

- **Uncertain benefit-risk of pola+R-CHP in patients with previously untreated LBCL, including patients with DLBCL NOS**

Discussion Topics

- Discuss the benefit-risk profile of pola+R-CHP for the proposed patient population with LBCL, including patients with DLBCL NOS, considering the results of the POLARIX trial.

- Based on the results of the POLARIX trial, specifically the OS results, discuss whether additional follow-up data from POLARIX should be required to inform the benefit-risk of polatuzumab vedotin in patients with LBCL in the frontline setting.

Voting Question

- Given the results of the POLARIX trial, does polatuzumab vedotin-piiq have a favorable benefit-risk profile in patients with previously untreated LBCL, including DLBCL NOS?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Back-up Slides

PFS Results Sensitive to Small Change in Events

Scenario	Applicant's Approach	Alternate Approach	Events after Censoring (Pola+R-CHP vs. R-CHOP)
Original Data			
Event after NALT	Event	Censor	7 (1.6%) vs. 16 (3.6%)
Event after ≥2 consecutive missed assessments	Event	Censor	4 (0.9%) vs. 1 (0.2%)
New PFS data (different categorization of NALT)			
Event after NALT	Event	Censor	6 (1.4%) vs. 7 (1.6%)
Event after ≥2 consecutive missed assessments	Event	Censor	4 (0.9%) vs. 1 (0.2%)

- Censoring 23 (2.6%) events caused change of statistical significance