Cause of Death and Prognosis of Patients With Primary Refractory Disease, and Prognosis of Patients Reaching PFS24: Descriptive Analysis of POLARIX

To be presented by Brannon Flores on behalf of the authors

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Summary

Here we provide a **descriptive analysis** of the effects of **primary refractory disease** or **achievement of PFS24** on outcomes of patients with previously untreated DLBCL in the **POLARIX study**

The **risk of death** was **7.4-fold higher in patients** with **primary refractory disease** than in those with non-primary refractory disease

These results show that **Pola-R-CHP reduced the risk** of **primary refractory disease** and **increased** the likelihood of achieving **PFS24** compared with R-CHOP in the 1L DLBCL setting

Pola-R-CHP reduces the risk of a **PFS event** at **24 months** by **25%** versus R-CHOP

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Background

- In the past decade, disease progression has been reported as the main cause of death in patients with diffuse large B-cell lymphoma (DLBCL) who were treated with first-line (1L) rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and progressed within the first 24 months
  - Outcomes in patients with primary refractory disease are particularly poor.[1] Being alive and disease-free at 24 months has been defined as a robust endpoint for disease-related outcomes.[2]
- Since then, newer treatment options, such as polatuzumab vedotin plus bendamustine and rituximab, chimeric antigen receptor T-cell therapy (CAR-T), and tafasitamab plus lenalidomide, have been introduced in the relapsed/refractory setting.
- In the POLARIX study (NCT03274492), polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) demonstrated improved progression-free survival (PFS) versus R-CHOP in 1L DLBCL, with a similar safety profile[3]
  - With longer follow-up of 39.7 months, the PFS benefit with Pola-R-CHP versus R-CHOP was sustained.[4]
- Here, we report an ad hoc analysis of data from POLARIX to evaluate the cause of death and prognosis of patients with primary refractory disease and of patients who were progression free at 24 months (PFS24) after 1L treatment.

Methods

- The data analyzed here are from the POLARIX study (data cut-off June 15, 2022; median follow up: 39.7 months); the methods have previously been described.[3]
- Causes of death were disease progression, adverse events (AE), or other.
- Three patient populations were defined based on response to 1L therapy:
  - Patients who were primary refractory (lack of complete response [CR] or relapse within 12 months after treatment completion)[5,6]
  - Patients who were non-primary refractory (CR and no relapse within 12 months after treatment completion)
  - Patients who achieved PFS24 (no PFS events during the 24 months after treatment initiation).
- Time-to-event data were described using Kaplan–Meier curves and cause-specific cumulative incidence functions.
- Event decomposition was performed using a competing risk approach.[7]
- Baseline risk factors for risk of death during study follow up were analyzed using multivariate Cox regression
  - There was adjustment for treatment effect, age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), geographic region, International Prognostic Index (IPI) score, bulky disease, lactate dehydrogenase (LDH) levels, median time from diagnosis, Ann Arbor stage, extranodal involvement, cell-of-origin subtype, double-expressor lymphoma status, and double-/triple-hit lymphoma status.

Results: Cause of death

- At data cut-off, 14.7% of patients treated with Pola-R-CHP and 15.8% of patients treated with R-CHOP had died; the main cause of death was disease progression (**Table 1**).
- After adjustment for treatment effect, age (continuous), sex (male vs female), ECOG PS (2 vs 0–1), and LDH levels (elevated vs normal) were associated with increased risk of death in the POLARIX study.

Table 1. Cause of death in the POLARIX study (safety-evaluable population)

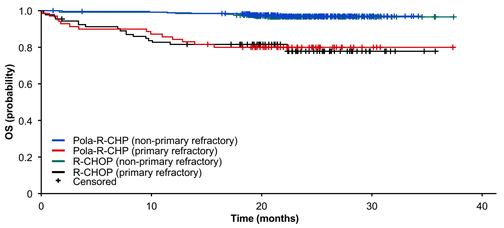
n (%)	Pola-R-CHP (n=435)	R-CHOP (n=438)
Disease progression	34 (7.8)	35 (8.0)
Adverse events*	13 (3.0)	11 (2.5)
Other causes	17 (3.9)	23 (5.3)
DLBCL as a contributing factor	4 (0.9)	5 (1.1)
DLBCL not known to be a contributing factor	13 (3.0)	18 (4.1)

*The most frequent Grade 5 AEs (by preferred term) were pneumonia (Pola-R-CHP, 4 patients [0.9%]; R-CHOP, 3 patients [0.7%]), death (Pola-R-CHP, 4 patients [0.9%]; R-CHOP, 1 patient [0.2%]), and septic shock (Pola-R-CHP, 0 patients; R-CHOP, 2 patients [0.5%]); All other Grade 5 AEs were reported in no more than one patient per treatment arm.

Results: Effect of primary refractory disease on OS

- Based on a landmark analysis, risk of death was 7.4-fold higher in patients with primary refractory disease than in those with non-primary refractory disease (**Figure 1**)
  - Overall survival (OS) hazard ratio (HR): 0.14; 95% confidence interval (CI): 0.07–0.25.

Figure 1. A comparison of OS in patients with primary refractory and non-primary refractory disease*



Number at risk					
Pola-R-CHP (non-primary refractory)	302	296	236	17	0
Pola-R-CHP (primary refractory)	71	62	47	4	0
R-CHOP (non-primary refractory)	270	268	212	18	0
R-CHOP (primary refractory)	94	78	59	6	0

Data were analyzed from the end of treatment, plus 12 months, i.e., 17 months in total.
*Before 17 months, 41 patients had died in the Pola-R-CHP treatment arm and 37 patients had died in the R-CHOP treatment arm.

Results: Subsequent therapy according to refractory status

- At data cut-off, 159 (73.6%) and 67 (11.7%) patients had received a new anti-lymphoma therapy (NALT) in the primary refractory and non-primary refractory populations, respectively (**Table 2**)
  - Patients with primary refractory disease received more intensive regimens such as stem cell transplant (SCT; 19.0%) or CAR-T (10.2%)
  - Patients in the primary refractory population who did not receive a NALT mostly achieved a partial response at the end of treatment.

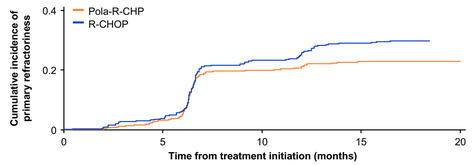
Table 2. Type of NALT received in POLARIX according to primary refractory status

n (%)	Primary refractory n=216	Non-primary refractory n=573
Any	**159 (73.6)**	**67 (11.7)**
Systemic therapy	**133 (61.6)**	**39 (6.8)**
CAR-T	22 (10.2)	3 (0.5)
SCT	41 (19.0)	8 (1.4)
Radiotherapy	**59 (27.3)**	**34 (5.9)**
Unplanned	53 (24.5)	12 (2.1)
Planned	6 (2.8)	22 (3.8)

Results: 1L treatment effect on primary refractory disease

- The cumulative incidence of refractory disease was 22.7% (95% CI: 18.7–26.8) with Pola-R-CHP and 29.7% (95% CI: 25.2–34.1) with R-CHOP (subdistribution HR: 0.75; 95% CI: 0.58–0.99; Gray's test for equality: p=0.0376; **Figure 2**).

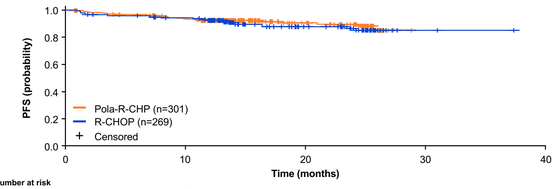
Figure 2. Cumulative incidence of primary refractory disease according to 1L treatment received



Results: 1L treatment effect in patients with non-primary refractory disease

- Patients with non-primary refractory disease had favorable outcomes, regardless of the 1L treatment received (**Figure 3**).
- Overall, 74.2% and 67.9% of patients were non-primary refractory in the Pola-R-CHP and R-CHOP treatment arms, respectively.

Figure 3. PFS in patients with non-primary refractory disease



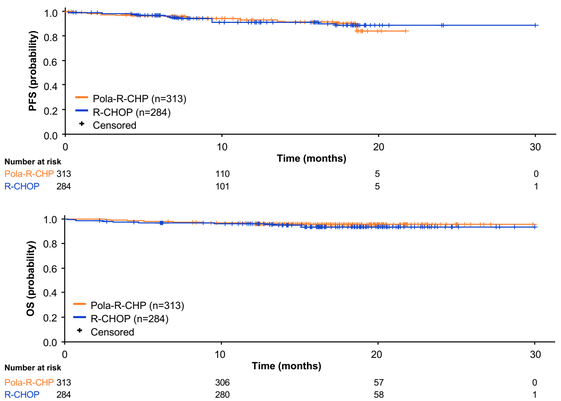
Number at risk					
Pola-R-CHP	301	267	93	0	0
R-CHOP	269	246	83	2	0

Data were analyzed from the end of treatment, plus 12 months, i.e., 17 months in total.

Results: Effect of achievement of PFS24 on efficacy

- Overall, 77.0% of patients were progression free at 24 months with Pola-R-CHP versus 70.4% with R-CHOP (stratified HR: 0.75; 95% CI: 0.57–0.98; **Figure 4**).
- Eighteen months after achieving PFS24:
  - 90.3% and 88.7% of patients in the Pola-R-CHP and R-CHOP arms, respectively, were progression free
  - OS rates were 98.3% and 98.9% with Pola-R-CHP and R-CHOP, respectively.

Figure 4. PFS and OS landmark analysis at 24 months after treatment initiation in patients achieving PFS24



Conclusions

- Despite therapeutic improvements in the relapsed/refractory DLBCL setting, progression remained the main cause of death in patients with previously untreated DLBCL in the POLARIX study
  - Identification of patients with a high risk of death remains a challenge
  - Patients with primary refractory disease still have a high unmet medical need
  - Patients with non-primary refractory disease and those who reached PFS24 appear to show similarly excellent outcomes.
- In 1L DLBCL, Pola-R-CHP reduced the risk of refractory disease and increased the likelihood of achieving PFS24 compared with R-CHOP.
- Together, these results reinforce the value of Pola-R-CHP in 1L DLBCL.

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