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Deciphering the Clinical Benefit of Pola-R-CHP versus R-CHOP in Different Genetic Subtypes Beyond Cell of Origin in the POLARIX Study

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Summary

Pola-R-CHP demonstrated prolonged PFS versus R-CHOP in untreated DLBCL in the POLARIX study

Exploratory subgroup analysis indicated a heightened PFS benefit with Pola-R-CHP in ABC-DLBCL but outcomes across DLBCL molecular subtypes beyond COO are unclear

In DZsig^{Pos} DLBCL (predominantly GCB), a trend of higher 2-year PFS was observed with Pola-R-CHP versus R-CHOP

A trend towards improved PFS in Pola-R-CHP-treated patients was seen in EZB (predominantly GCB) and MCD (predominantly ABC) subtypes

These findings suggest the benefit of Pola-R-CHP transcends COO subtypes; molecular profiling tools beyond COO are necessary to apply precision medicine for DLBCL and sufficiently address the heterogeneity of the disease

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Background

- In the POLARIX study (NCT03274492), polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) demonstrated prolonged progression-free survival (PFS) versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with previously untreated diffuse large B-cell lymphoma (DLBCL)[1]
- In exploratory subgroup analyses of POLARIX, greater PFS improvement was observed in activated B cell-like (ABC) DLBCL with Pola-R-CHP versus R-CHOP, and a trend of inferior PFS with Pola-R-CHP versus R-CHOP was observed in patients with double-hit/triple-hit lymphoma (DHL/THL)[1]
- Certain molecular subtypes of DLBCL beyond cell of origin (COO) classification, such as dark zone signature positive (DZsig^{Pos}), have shown poor prognosis with R-CHOP,[2,3] and outcomes for Pola-R-CHP versus R-CHOP in these subtypes remain unclear
- In this post-hoc exploratory analysis, we explored the prevalence and clinical outcomes of molecularly defined DLBCL subtypes in patients treated with Pola-R-CHP versus R-CHOP in POLARIX

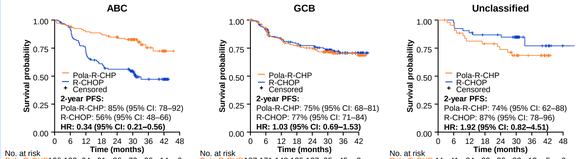
Methods

- The full methodology of POLARIX in patients with untreated DLBCL has been described previously[1]
- All genetic analyses were performed on baseline tumor biopsies. The NanoString Lymph2Cx assay was used to determine COO
  - Fluorescence in situ hybridization (FISH) was used to examine *BCL2*, *MYC*, and *BCL6* rearrangements
- DZsig status was determined from global gene expression patterns (GEP) data measured by RNA sequencing (RNAseq), as previously described[4]
- Using somatic single-nucleotide variants and copy number variation derived from whole exome sequencing (WES), patients were allocated to different genetic subtypes, as defined by the LymphGen classifier
- Multivariable Cox regression was performed to identify relationships between different biomarker subgroups and investigator-assessed PFS. Hazard ratios (HR) were adjusted for International Prognostic Index score (2 vs 3–5) and age (≤60 vs >60 years)
- Due to the exploratory nature of the subtype analyses, all statistics are descriptive, and not controlled for Type I error

Results: Outcomes in COO subgroups

- COO status was determined in 689 patients in POLARIX (ABC-DLBCL, n=235; germinal center B cell [GCB]-DLBCL, n=357; unclassified DLBCL, n=97)
- Based on a data cutoff of June 15, 2022, with a median follow-up of 39.7 months, a PFS difference between treatment groups was observed in ABC-DLBCL, but not in GCB or the unclassified subgroups (**Figure 1**)

Figure 1. Kaplan–Meier Estimates of Investigator-Assessed PFS* by COO Subgroup.



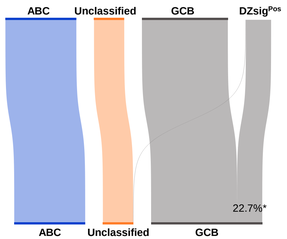
*Investigator-assessed disease progression and disease relapse or death from any cause were counted as events. Tick marks indicate censored data.
ABC, activated B cell; CI confidence interval; COO, cell of origin; GCB, germinal center B cell; HR, hazard ratio; PFS, progression-free survival.

Results: Outcomes in DZsig subgroups

- GEP and COO data were available for 641 patients (Pola-R-CHP, n=318; R-CHOP, n=323)
  - 76 GCB and 1 unclassified tumors were found to be DZSig positive (DZsig^{Pos}; Pola-R-CHP, n=37; R-CHOP, n=40), accounting for 12.0% of all patients (**Figure 2**)
  - 22.7% of GCB were re-classified to DZsig^{Pos}
  - DZsig^{Pos} represent the majority of DHL/THL (18/29 [62%] DHL/THL were DZsig^{Pos})
  - 3 ABC tumors that were DZsig^{Pos} remained to be assigned to the ABC group
- In the R-CHOP arm, patients with DZsig^{Pos} DLBCL experienced shorter PFS versus those with DZsig negative/indeterminate (DZsig$^{Neg/Ind}$) GCB-DLBCL (HR 2.04 [95% CI: 1.08–3.86]; 2-year PFS, 64% [95% CI: 51–81] vs 81% [95% CI: 75–89])
- In the Pola-R-CHP arm, no significant difference in PFS was observed between patients with DZsig^{Pos} DLBCL versus those with DZsig$^{Neg/Ind}$ GCB-DLBCL (HR 0.77 [95% CI: 0.37–1.58]; 2-year PFS, 75% [95% CI: 62–91] vs 75% [95% CI: 68–83])
- A trend of higher 2-year PFS rate was observed in patients with DZsig^{Pos} DLBCL treated with Pola-R-CHP versus R-CHOP, but not in those with DZsig$^{Neg/Ind}$ GCB-DLBCL (**Figure 3**)

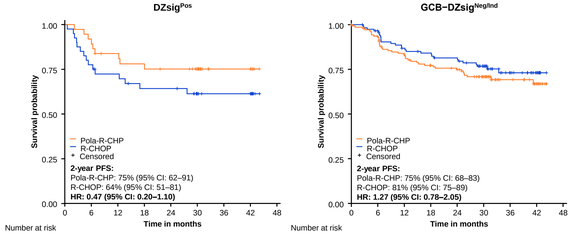
Figure 2. Distribution of DZsig status across COO subgroups in the overall POLARIX population.

Subgroups	Number (%) Total=641
ABC	214 (33.4)
Unclassified	91 (14.2)
GCB	259 (40.4)
DZsig^{Pos}	77 (12.0)



*Proportion of GCB re-classified to DZsig^{Pos}

Figure 3. Kaplan–Meier estimates of investigator-assessed PFS* of DZsig groups by treatment arms.



*Investigator-assessed disease progression and disease relapse or death from any cause were counted as events.
ABC, activated B cell; CI, confidence interval; COO, cell of origin; DZsig, dark zone signature; GCB, germinal center B cell; HR, hazard ratio; PFS, progression-free survival.

Results: Outcomes in genetic subtypes by LymphGen classifier

- Using WES data, somatic variants were identified in 594 patients (Pola-R-CHP, n=292; R-CHOP, n=302), and baseline clinical characteristics were balanced between treatment arms
- GCB-DLBCL was composed predominantly of *EZH2* mutations and *BCL2* translocations (EZB), the undetermined subgroup, and *BCL6* fusions and *NOTCH2* mutated (BN2) subtypes (**Figure 4**)
- In ABC-DLBCL, the *MYD88* and *CD79B*-mutated (MCD) subtype and the undetermined subgroup were the major genetic subtypes (**Figure 4**)
- The EZB and MCD subtypes showed a trend of higher 2-year PFS in the Pola-R-CHP versus R-CHOP arms, but the overall HRs were not significant (**Figure 5**)
- The 2-year PFS rate in patients with the BN2 subtype was numerically lower with Pola-R-CHP versus R-CHOP, however, the overall HR was not significant (**Figure 5**)
  - For the *SGK1* and *TET2* mutations (ST2) and A53 subtypes, the numbers of patients were relatively small (**Figure 5**)
- In the subgroup of patients with an undetermined genetic subtype, a trend of higher 2-year PFS estimates was observed with Pola-R-CHP versus R-CHOP, with a non-significant HR (**Figure 5**)

Figure 4. Distribution of LymphGen subtypes across COO subgroups.

Subtypes	Number (%) total=594
A53	19 (3)
BN2	55 (9)
EZB	142 (24)
MCD	56 (9)
N1	3 (1)
ST2	28 (5)
Genetically composite	19 (3)
Undetermined	272 (46)

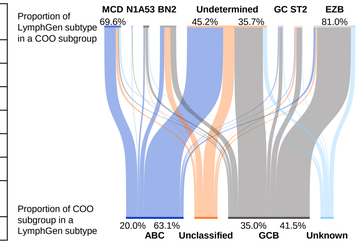
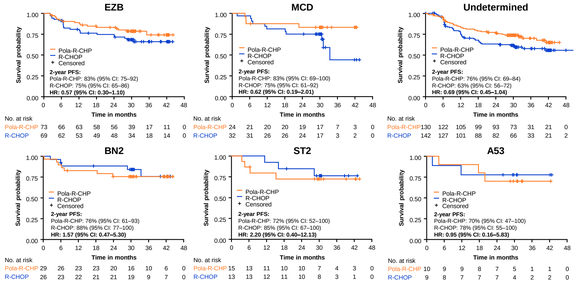


Figure 5. Kaplan–Meier estimates of investigator-assessed PFS across LymphGen subtypes by treatment.



A53, aneuploid with *TP53* inactivation; BN2, *BCL6* fusions and *NOTCH2* mutations; CI, confidence interval; EZB, *EZH2* mutations and *BCL2* translocations; GC, genetically composite; HR, hazard ratio; MCD, *MYD88* and *CD79B* mutations; N1, *NOTCH1* mutations; NR, not reported; PFS, progression-free survival; ST2, *SGK1* and *TET2* mutated.

Conclusions

- Patients with DZsig^{Pos} by RNAseq, and EZB and MCD by LymphGen, had poor outcomes when treated with R-CHOP, validating prior findings[2]
- Patients with DZsig^{Pos} DLBCL who were almost exclusively GCB-DLBCL and represented the majority of high-risk DHL/THL, had a potential better outcome when receiving Pola-R-CHP versus R-CHOP
- LymphGen classification identified EZB, MCD, and undetermined subtypes to have more favorable outcomes with Pola-R-CHP versus R-CHOP; however, these differences were not significant
- These findings suggest that the benefit of Pola-R-CHP transcends COO subtypes; molecular profiling tools beyond COO are necessary to apply precision medicine for DLBCL and sufficiently address the heterogeneity of the disease

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Disclosures

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