ELSEVIER

Blood 142 (2023) 3000–3003

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

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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Introduction: In the POLARIX study, polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) demonstrated prolonged progression-free survival (PFS) vs rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients (pts) with previously untreated diffuse large B-cell lymphoma (DLBCL; NCT03274492; Tilly et al. N Engl J Med 2022); the PFS benefit was sustained with longer follow-up (Herrera et al. Blood 2022). Exploratory analyses demonstrated a trend towards greater PFS improvement in activated B cell-like (ABC) DLBCL with Pola-R-CHP vs R-CHOP (Tilly et al. N Engl J Med 2022). Although not yet available for daily practice, more granular molecular subtypes of DLBCL beyond cell of origin (COO) classification have demonstrated poor prognosis with R-CHOP, including *EZH2* mutations/ *BCL2* translocations (EZB), *MYD88*/ *CD79B*-mutated (MCD; as defined by LymphGen; Wright et al. Cancer Cell 2020), and dark zone gene expression signature (DZsig; Alduaij et al. Blood 2023). Here, in a post hoc exploratory analysis, we investigate the prevalence and clinical outcomes of molecularly defined subtypes of DLBCL in pts treated with Pola-R-CHP vs R-CHOP in POLARIX.
Methods: All genetic analyses were performed on baseline tumor biopsies. Using mutations derived from whole exome sequencing (WES), pts were allocated to different genetic subtypes, as defined by the LymphGen classifier. DZsig status was determined from global gene expression patterns (GEP) as measured by RNAseq, as previously described (Ennishi et al. J Clin Oncol 2019). COO was determined by NanoString. 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.
Results: WES data were available for 594 pts (Pola-R-CHP, n=292; R-CHOP, n=302), and baseline clinical characteristics were balanced between treatment arms. The observed 2-year PFS rates with EZB and MCD subtypes were numerically higher but not statistically significant in the Pola-R-CHP vs R-CHOP arm (**Table**): EZB, 83% (95% confidence interval [CI]: 76-92) vs 75% (95% CI: 65-86), HR 0.61, 95% CI: 0.33-1.13; MCD, 85% (95% CI: 73-98) vs 73% (95% CI: 63-90), HR 0.64, 95% CI: 0.24-1.70. Lower 2-year PFS rates were observed in pts with the *BCL6* fusions and *NOTCH2* mutations (BN2) subtype treated with Pola-R-CHP vs R-CHOP (HR 1.82, 95% CI: 0.46-7.18; **Table**). In the subgroup of pts with an undetermined genetic subtype, 2-year PFS estimates were numerically higher with Pola-R-CHP vs R-CHOP (74% vs 62%, respectively; HR 0.70, 95% CI: 0.46-1.07).

GEP data were available for 665 pts (Pola-R-CHP, n=331; R-CHOP, n=334); 108 (16.2%) were DZsig+ (Pola-R-CHP, n=52; R-CHOP, n=56). Of those who were DZsig+, 103 (95.4%) had germinal center B cell-like (GCB) DLBCL, 3 (2.8%) had ABC DLBCL, and 2 (1.9%) had an unknown COO. In pts who were DZsig+ and had FISH results, 54/86 (62.8%) had *BCL2* translocations, 41/92 (44.6%) had *MYC* translocations, and 6/40 (15%) had *BCL6* translocations (*BCL6* FISH was only done in pts with a *MYC* translocation), resulting in 23/90 (25.6%) pts with double/triple-hit DLBCL. Pts who were DZsig+ were predominantly within the EZB genetic subtype (60.3%). In the R-CHOP arm, pts who were DZsig+ had shorter PFS vs pts who were DZsig− (2-yr PFS: 62% [95% CI: 51-77] vs 73% [95% CI: 68-79], respectively; HR 1.61, 95% CI: 1.02-2.56; **Figure**). In the Pola-R-CHP arm, no significant difference in PFS was observed between pts who were DZsig+ vs DZsig− (2-yr PFS: 77% [95% CI: 66-89] vs 79% [95% CI: 74-84]; HR 0.97, 95% CI: 0.54-1.75). Improved PFS was demonstrated in pts who were DZsig+ and treated with Pola-R-CHP vs R-CHOP (HR 0.47, 95% CI: 0.24-0.95).

Conclusions: In this exploratory biomarker analysis, we recapitulated that pts with molecularly defined DLBCL subtypes, including EZB and MCD by LymphGen and DZsig+ by RNAseq, have poor outcomes with R-CHOP therapy. In pts with the EZB and MCD subtypes, Pola-R-CHP appeared to improve 2-year PFS compared with R-CHOP. Pts with GCB DLBCL who were DZsig+ significantly benefited from Pola-R-CHP vs R-CHOP. In summary, our data indicate that molecular analysis beyond COO leads to identification of distinct molecular subsets of DLBCL that may respond favorably to Pola-R-CHP; future prospective validation is required.

Disclosures Morschhauser: *F. Hoffmann-La Roche Ltd, AbbVie, BMS, Genmab, Gilead, Novartis:* Consultancy; *F. Hoffmann-La Roche Ltd, Gilead, AbbVie:* Membership on an entity's Board of Directors or advisory committees. **Leung:** *Genentech, Inc./F. Hoffmann-La Roche Ltd:* Current Employment, Current equity holder in publicly-traded company. **Raghavan:** *F. 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Hoffmann-La Roche Ltd, BMS, Takeda:* Honoraria. **Herrera:** *BMS:* Consultancy, Other: Travel/Accommodations/Expenses, Research Funding; *Genentech/Roche:* Consultancy, Research Funding; *Merck:* Consultancy, Research Funding; *AbbVie:* Consultancy; *Regeneron:* Consultancy; *Allogene Therapeutics:* Consultancy; *Pfizer:* Consultancy; *Kite, a Gilead Company:* Research Funding; *Genmab:* Consultancy; *Takeda:* Consultancy; *Seattle Genetics:* Consultancy, Research Funding; *Tubulis GmbH:* Consultancy; *Caribou Biosciences:* Consultancy; *Adicet Bio:* Consultancy; *ADC Therapeutics:* Consultancy, Research Funding; *Karyopharm Therapeutics:* Consultancy; *AstraZeneca/MedImmune:* Consultancy; *Gilead Sciences:* Research Funding; *AstraZeneca:* Research Funding. **Sehn:** *Kite/Gilead:* Consultancy; *Merck:* Consultancy; *Seattle Genetics:* Consultancy; *Teva:* Research Funding; *Roche/Genentech:* Research Funding; *Janssen:* Consultancy; *Incyte:* Consultancy; *Genentech/Roche:* Consultancy; *BMS/Celgene:* Consultancy; *BeiGene:* Consultancy; *AstraZeneca:* Consultancy; *Amgen:* Consultancy; *AbbVie:* Consultancy. **Sharman:** *AbbVie, AstraZeneca, BMS, Beigene, Lilly, Genentech, Inc., Genmab:* Consultancy; *Seattle Genetics:* Research Funding; *Merck, Novartis:* Consultancy; *AbbVie, AstraZeneca, BeiGene, BMS, Genentech, Inc., Lilly:* Consultancy. **Flowers:** *CPRIT Scholar in Cancer Research:* Research Funding; *Cancer Prevention and Research Institute of Texas:* Research Funding; *V Foundation:* Research Funding; *National Cancer Institute:* Research Funding; *Eastern Cooperative Oncology Group:* Research Funding; *Burroghs Wellcome Fund:* Research Funding; *Ziopharm:* Research Funding; *Xencor:* Research Funding; *TG Therapeutics:* Research Funding; *Takeda:* Research Funding; *Sanofi:* Research Funding; *Celgene:* Consultancy, Research Funding; *Denovo Biopharma:* Consultancy; *Foresight Diagnostics:* Consultancy, Current holder of *stock options* in a privately-held company; *Genentech Roche:* Consultancy, Research Funding; *Genmab:* Consultancy; *Gilead:* Consultancy, Research Funding; *Karyopharm:* Consultancy; *N-Power Medicine:* Consultancy, Current holder of *stock options* in a privately-held company; *Pharmacyclics Jansen:* Consultancy; *SeaGen:* Consultancy; *Spec-*

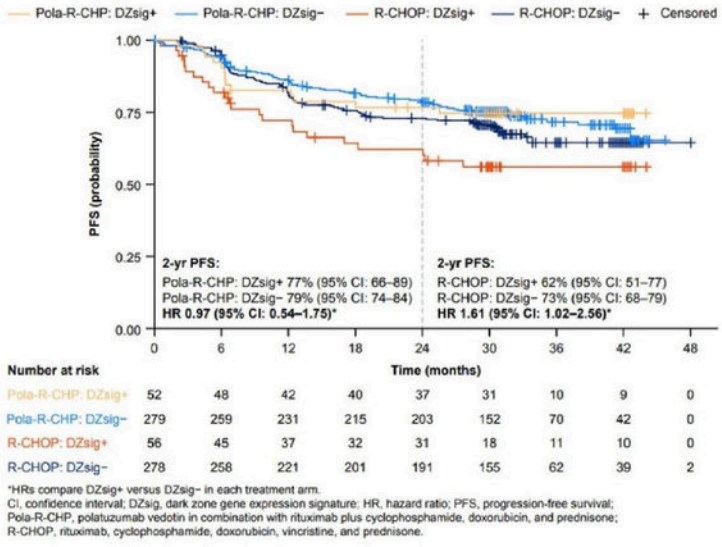
trum: Consultancy; *4D:* Research Funding; *Acerta:* Research Funding; *Adaptimmune:* Research Funding; *Allogene:* Research Funding; *Amgen:* Research Funding; *Cellectis:* Research Funding; *Guardant:* Research Funding; *Iovance:* Research Funding; *Jannsen Pharmaceuticals:* Research Funding; *Kite:* Research Funding; *Morphosys:* Research Funding; *Nektar:* Research Funding; *Novartis:* Research Funding; *Pfizer:* Research Funding; *Pharmacyclics:* Research Funding; *Beigene:* Consultancy; *Bayer:* Consultancy, Research Funding; *Abbvie:* Consultancy, Research Funding. **Trněný:** *Janssen, Gilead Sciences, Takeda, BMS, Amgen, AbbVie, F. Hoffmann-La Roche Ltd, MorphoSys, Novartis:* Honoraria; *Gilead Sciences, Takeda, BMS, F. Hoffmann-La Roche Ltd, Janssen, AbbVie:* Other: Travel, Accommodation, Expenses; *Takeda, BMS, Incyte, AbbVie, Amgen, F. Hoffmann-La Roche Ltd, Gilead Sciences, Janssen, MorphoSys, Novartis, Genmab, SOBI:* Consultancy. **Tilly:** *BMS:* Membership on an entity's Board of Directors or advisory committees; *F. Hoffmann-La Roche Ltd:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *ADC Therapeutics:* Membership on an entity's Board of Directors or advisory committees. **Herbaux:** *AbbVie, F. Hoffmann-La Roche Ltd, AstraZeneca, Janssen:* Consultancy; *AbbVie, F. Hoffmann-La Roche Ltd, AstraZeneca, Janssen:* Honoraria; *AbbVie, Takeda:* Research Funding; *Physician and professor of Hematology at academic center (CHU Montpellier France):* Current Employment. **Tracy:** *F. Hoffmann-La Roche Ltd:* Current equity holder in publicly-traded company; *Genentech, Inc.:* Current Employment. **Bolen:** *F Hoffmann-La Roche Ltd:* Current equity holder in publicly-traded company; *Genentech, Inc.:* Current Employment. **Harris:** *Genentech, Inc.:* Current Employment, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company. **Hirata:** *F. Hoffmann-La Roche Ltd:* Current equity holder in private company; *Genentech, Inc.:* Current Employment. **Lee:** *F. Hoffmann-La Roche Ltd:* Current equity holder in publicly-traded company; *Genentech, Inc.:* Current Employment. **Jiang:** *F. Hoffmann-La Roche Ltd:* Current Employment, Current equity holder in publicly-traded company. **Salles:** *Incyte:* Consultancy; *Nurix:* Consultancy; *AbbVie:* Consultancy, Honoraria; *Novartis:* Consultancy; *Orna:* Consultancy; *Merck:* Consultancy, Honoraria; *ATB Therapeutics:* Consultancy; *Genentech, Inc./F. Hoffmann-La Roche Ltd:* Consultancy, Research Funding; *Debiopharm:* Consultancy; *BeiGene:* Consultancy; *BMS/Celgene:* Consultancy; *Molecular Partners:* Consultancy; *Ipsen:* Consultancy, Research Funding; *Nordic Nanovector:* Consultancy; *Owkin:* Current holder of *stock options* in a privately-held company; *Genmab:* Consultancy; *Loxo/Lilly:* Consultancy; *Kite/Gilead:* Consultancy; *Janssen:* Consultancy, Research Funding; *EPIZYME:* Consultancy.

Table

Subtypes	Prevalence, n (%)		2-yr PFS, % (95% CI)	
	Pola-R-CHP n = 292	R-CHOP n = 302	Pola-R-CHP	R-CHOP
EZB	81 (28)	73 (24)	83 (76–92)	75 (65–86)
MCD	33 (11)	40 (13)	85 (73–98)	75 (63–90)
BN2	27 (9)	26 (9)	78 (63–95)	88 (77–100)
N1	1 (>1)	1 (>1)	NA	NA
ST2	17 (6)	15 (5)	76 (57–100)	86 (69–100)
Genetically composite	10 (3)	13 (4)	50 (27–93)	77 (57–100)
Other	123 (42)	134 (44)	74 (67–82)	62 (54–71)

BN2, BCL6 fusions and NOTCH2 mutations; CI, confidence intervals; EZB, *EZH2* mutations and *BCL2* translocations; MCD, *MYD88*^{L265P} and *CD79B* mutations; NA, not applicable; N1, *NOTCH1* mutations; PFS, progression-free survival; Pola-R-CHP, polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ST2, *SGK1* and *TET2* mutated.

Figure



*HRs compare DZsig+ versus DZsig− in each treatment arm.
CI, confidence interval; DZsig, dark zone gene expression signature; HR, hazard ratio; PFS, progression-free survival; Pola-R-CHP, polatuzumab vedotin in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Figure 1

https://doi.org/10.1182/blood-2023-178623