

## CORRESPONDENCE



## Cell-of-Origin Subtypes and Therapeutic Benefit from Polatuzumab Vedotin

**TO THE EDITOR:** Tilly et al. (Jan. 27 issue)<sup>1</sup> report the results of POLARIX, an important trial of polatuzumab vedotin in patients with previously untreated diffuse large B-cell lymphoma (DLBCL). Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) showed a significant progression-free survival benefit over the standard regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). In so doing, pola-R-CHP represents the first induction regimen of available agents to achieve this feat among randomized, blinded trials in more than 20 years (Fig. 1A), and it recently received Food and Drug Administration (FDA) approval.

Differential efficacy of polatuzumab vedotin against DLBCL subtypes, defined according to cell of origin as germinal-center B cell (GCB) or non-GCB (predominantly activated B cell [ABC]), has been repeatedly observed in clinical studies, consistent with preclinical studies implicating CD79b-dependent vulnerability of ABC DLBCLs.<sup>2,3</sup> We reassessed the benefit–risk profile of polatuzumab vedotin in DLBCL subtypes, considering evidence from early- and late-stage clinical trials and post-marketing reports of polatuzumab vedotin (see the

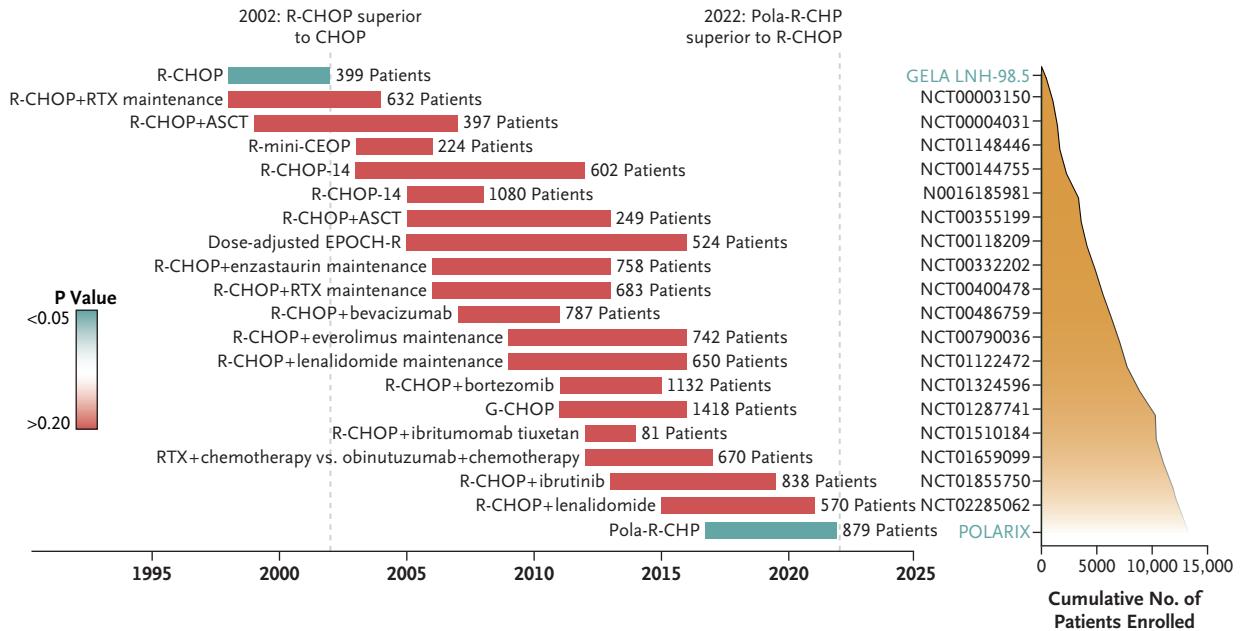
### Figure 1 (facing page). Consistency of Differential Efficacy of Polatuzumab Vedotin in DLBCL Subtypes.

Panel A shows the history of randomized, controlled trials for previously untreated diffuse large B-cell lymphoma (DLBCL) over the past 25 years. On the left, a bar chart shows the start and end dates of each trial, beginning with the trial that led to approval of R-CHOP (rituximab [RTX], cyclophosphamide, doxorubicin, vincristine, and prednisone) and ending with the trial that led to approval of pola-R-CHP (polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone). On the right, a graph shows the cumulative number of patients enrolled in phase 3 randomized, controlled trials during this time frame. ASCT denotes autologous stem-cell transplantation, CEOP cyclophosphamide, etoposide, vincristine, prednisone, and EPOCH-R etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab. As shown in Panel B, the percentages of patients with a response to regimens containing polatuzumab vedotin have been consistently higher among those with activated B-cell (ABC) DLBCL (blue) than among those with germinal-center B-cell (GCB) DLBCL (orange) in phase 1 and 2 and postmarketing (PostMktg) studies ( $P < 0.001$  by Fisher's exact test; 119 total patients, with each box denoting 1 patient). US/CA/EU denotes United States, Canada, and the European Union. References for the five cited trials are provided in the Supplementary Appendix. As shown in Panel C, polatuzumab vedotin plus rituximab produced a greater reduction in tumor size of ABC DLBCLs than GCB DLBCLs ( $P = 0.002$  by Mann–Whitney U test; 22 patients). As shown in Panel D, a phase 2, randomized, controlled trial (GO29265) and a phase 3, randomized, controlled trial (POLARIX) of regimens containing polatuzumab vedotin showed significantly lower hazard ratios (HRs) for disease progression, relapse, or death and for death alone among patients with ABC DLBCL than among those with GCB DLBCL ( $P < 0.001$  for both comparisons; z-test for difference in log hazard ratios). As shown in Panel E, a phase 2, randomized, controlled trial (OPUS) and a phase 3, randomized, controlled trial (CRYSTAL) of cetuximab-containing regimens showed lower hazard ratios for disease progression or death and for death alone among patients with RAS wild-type metastatic colorectal cancer than among those with RAS-mutant disease. Detailed methods are provided in the Supplementary Appendix.

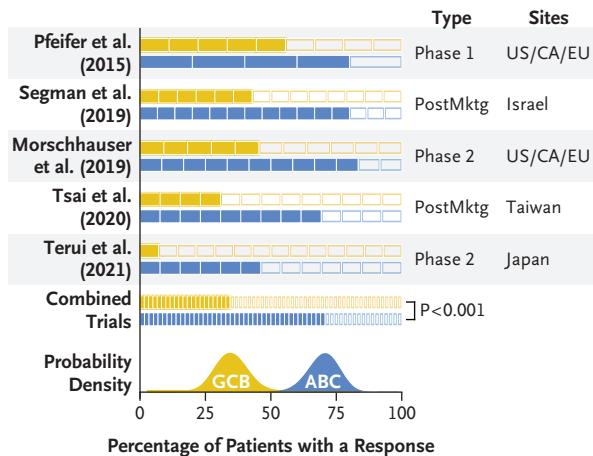
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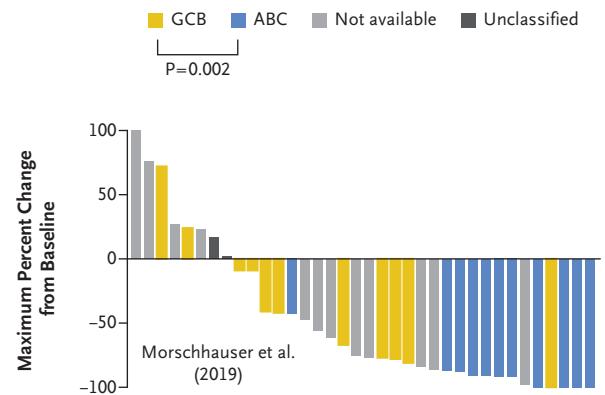
**A Randomized, Controlled Trials for Previously Untreated DLBCL**



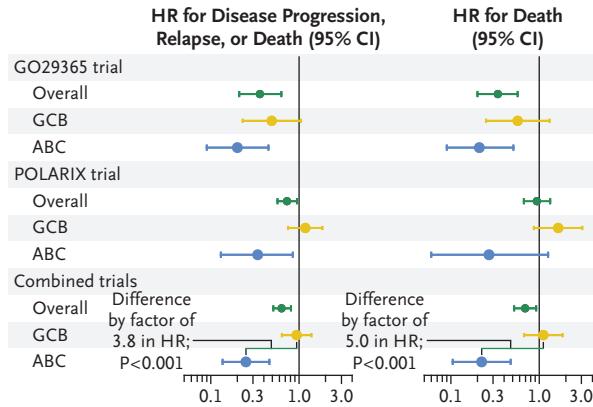
**B Cell of Origin and Response to Polatuzumab Vedotin in DLBCL**



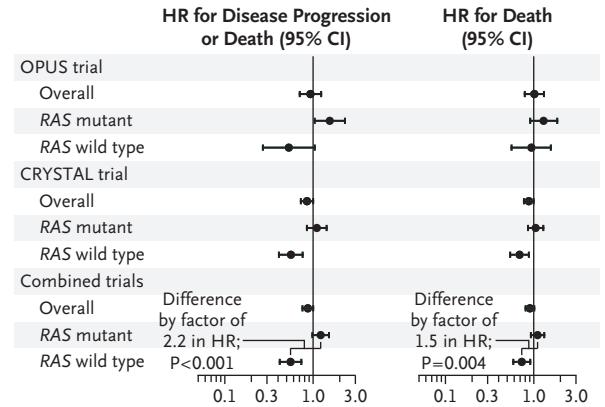
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**D Cell of Origin and Benefit of Polatuzumab Vedotin in DLBCL**



**E RAS and Cetuximab Benefit in Metastatic Colorectal Cancer**



Supplementary Appendix, available with the full text of this letter at NEJM.org). Five studies that were reported before the POLARIX trial, involving patients with relapsed or refractory disease, provide compelling evidence that ABC tumors are more responsive than GCB tumors to regimens containing polatuzumab vedotin ( $P < 0.001$ ) (Fig. 1B and 1C). Thus, unlike chance associations of variable effect size within subgroups defined according to sex or ethnic group, the influence of cell of origin on the efficacy of polatuzumab vedotin is established by multiple previous studies and corroborated by the POLARIX trial.

Data that were presented at the March 9, 2023, meeting of the FDA Oncologic Drugs Advisory Committee showed that ABC tumors in the POLARIX trial benefited profoundly from polatuzumab vedotin: the hazard ratio for disease progression, relapse, or death among patients who received pola-R-CHP as compared with those who received R-CHOP was 0.34 (95% confidence interval [CI], 0.13 to 0.85), and the hazard ratio for death was 0.27 (95% CI, 0.06 to 1.26). GCB tumors showed no significant benefit from polatuzumab vedotin: the hazard ratio for progression, relapse, or death among patients who received pola-R-CHP as compared with those who received R-CHOP was 1.18 (95% CI, 0.75 to 1.84), and the hazard ratio for death was 1.64 (95% CI, 0.87 to 3.07). Considering both the randomized phase 2 GO29365 trial involving patients with relapsed or refractory disease (polatuzumab vedotin plus bendamustine–rituximab vs. bendamustine–rituximab alone) and the randomized phase 3 trial involving previously untreated patients (pola-R-CHP vs. R-CHOP), we found that differential benefits of polatuzumab vedotin according to cell of origin were consistently large and significant (difference by a factor of 3.8 in the hazard ratio for disease progression, relapse, or death and difference by a factor of 5.0 in the hazard ratio for death;  $P < 0.001$  for both comparisons) (Fig. 1D). These large differences surpass the effect of RAS mutations as predictive biomarkers of response to epidermal growth factor receptor antibody in patients with advanced colon cancer (Fig. 1E).<sup>4,5</sup>

These findings indicate that the modest overall benefit with respect to progression-free survival in the POLARIX trial arises from a large

benefit in non-GCB tumors, diluted by no benefit in GCB tumors. Pola-R-CHP appears to be remarkably beneficial for ABC DLBCL. Conversely, GCB DLBCL may more appropriately continue to be treated with R-CHOP, especially given the higher incidence of febrile neutropenia with pola-R-CHP, despite the obligatory use of granulocyte colony-stimulating factor with this regimen, and potential harms suggested by hazard ratios greater than 1 for disease progression, relapse, or death and for death alone. Although the lack of central pathological review in the POLARIX trial left uncertainties in the identification of high-grade B-cell lymphomas, the results support the use of pola-R-CHP for non-GCB tumors (see the Supplementary Appendix). We anticipate that forthcoming research will uncover the mechanistic basis for the differential efficacy of polatuzumab vedotin, which may relate to both ABC-specific vulnerability of CD79b targeting and differential efficacy of the polatuzumab vedotin payload, monomethyl auristatin E. The influence of DLBCL cell of origin on the efficacy of polatuzumab vedotin was established by multiple studies and confirmed by two randomized, controlled trials, which indicates that precision medicine is now warranted in previously untreated DLBCL.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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