Unmet Medical Need in Norwegian Clinical Practice and Cost-Effectiveness Analysis of Polatuzumab in Combination With R-CHP Compared to R-CHOP in Patients With Previously Untreated DLBCL With an IPI Score of Three and Above

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INTRODUCTION

The Phase III GO39942 trial (RCT; POLARIX; NCT03274492) evaluating the efficacy, safety of Polatuzumab (Pola) plus rituximab with , cyclophosphamide, doxorubicin and prednisone (R-CHP) versus rituximab with, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is the first study in 20 years showing significant progression-free survival (PFS) improvement in IPI 2-5 (intermediate-high-risk) previously untreated DLBCL (1).

The greatest unmet need in Norway is for DLBCL patients with high-risk disease ; overall R-CHOP failure rates for patients approach 50% (2-5).

In Norway, medical clinical guidelines recommend that front-line DLBCL patients with IPI 3-5 should be treated with R-CHOP or other R-CHOP-like regimens (6).

MEDICAL NEED IN NORWAY

First line (1L) DLBCL patients in the Nordic countries including Norway are commonly treated with R-CHOP or R-CHOP-like regimens.

For low risk disease IPI 0-1 patients, R-CHOP21 is recommended (6), while selected high risk patients (IPI 3-5) may get more intensified treatments such as R-CHOEP21, R-CHOP14, R-CHOEP14 or R-DA-EPOCH (7). Attenuated R-CHOP is given to fragile high risk patients, who cannot tolerate full dose or intensified regimens. In later lines, eligible patients may be treated with either ASCT, Pola+BR, CAR-Ts or other R-chemotherapies (6).

Based on the results of the POLARIX study IPI 3-5 subgroup analysis (8), treatment with Pola + R-CHP provides significant clinical benefit to patients in this high risk unmet need population. POLARIX also showed statistically significant and clincally meaningful PFS benefit in the overall ITT population. In Norway, guidelines (6) include high intensity regimens for these patients and there is data (20) that suggests that the Pola + R-CHP regimen could provide similar efficacy with better safety and convenience for the patient.

OBJECTIVES

We aim to investigate if the treatment with Pola + R-CHP against R-CHOP is cost-effective in the treatment of high-risk IPI 3-5 1L DLBCL patients based on POLARIX trial. We will also showcase the impact of the addition of high impact subsequent therapy treatments on the incremental cost-utility ratio (ICUR).

METHODS

To conduct the cost-effectiveness analysis we used a 3-state (PFS, progression, death) partitioned survival model, estimating the life year (LY), quality-adjusted life year (QALY), and costs over a lifetime horizon. Safety and efficacy data on PFS, OS, drug utilization, treatment duration, frequency of adverse events (AE) and the proportion of subsequent therapies received were sourced directly from the POLARIX study (8). HRQoL EQ-5D measurements were available from the POLARIX trial (8) , the UK Hematological Malignancy Research Network (HMRN) (9) and from a match-adjusted GOYA (NCT01287741) (10) trial population . Drug costs were sourced from Leggemidelsøk (11), while other cost components were gathered from the DRG Somatikk liste (12) or EnhetskostnaderV1.3 (13) sheets, as available.

The patient cohort of previously untreated DLBCL can be separated into patients experiencing long-term remission and fast/early relapsers. Standard extrapolation methods fail to capture the differences in survival between the cohorts. Hence, cure-mixture modelling was used (14) employing the approach by Fellizzi et al (15). Patients who remain progression-free for ≥ 2 years are considered in long-term remission and revert back to sex- and age matched general population mortality (16,17,18). PFS KM curves from the POLARIX trial in both arms were extended with match-adjusted GOYA data to provide more follow-up for a more accurate estimate of the cure-fraction. This is a conservative approach as it assumes the same efficacy in both treatment arms in PFS after month 42. The time point was chosen as according to Pocock et al (19), where KM survival curve estimates are more robust when there are at least 10-20% of patients at risk. The proportions of subsequent treatment therapies received by patients after progression were taken from the POLARIX trial (8) and adjusted to the expected Norwegian treatment landscape (Table 1) during an advisory board meeting held prior to submission in February 2022. The willigness-to-pay (WTP) for a new intervention is guided by the disease severity, expressed through the calculation of the absolute shortfall (21).

Table 1: Proportions of subsequent treatments from POLARIX for patients in both treatment arms, localized and adapted to Norwegian clinical practice (as per February 2022)

Regimen	Autologous Stem Cell Transplant	Salvage Therapy + R	Chemotherapy	Chemotherapy + R	Pola + BR	Bridgning Therapy + CAR-T
Pola + R-CHP	24%	47%	9%	32%	4%	8%
R-CHOP	24%	44%	10%	19%	16%	11%

RESULTS

Parameterization for PFS with Weibull, log-logistic and generalized gamma did not converge for Pola+R-CHP whereas for R-CHOP parameterization with weibull, log-normal and log-logistic did not converge. Gompertz did not estimate a long-term remission fraction, exponential was chosen as base case. Sinced OS was informed by PFS, the survival distribution for OS will be the same. Exponential did provide a good fit to both arms.

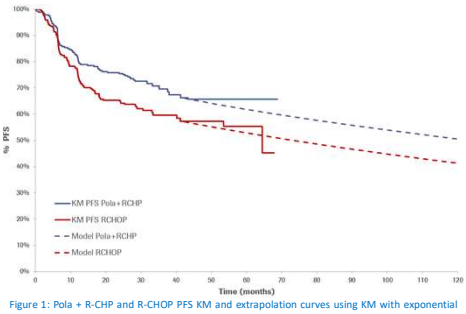

Figure 1: Pola + R-CHP and R-CHOP PFS KM and extrapolation curves using KM with exponential tail, IPI 3-5 POLARIX trial

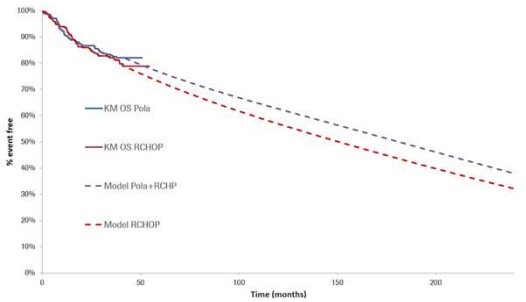

Figure 2: Pola + R-CHP and R-CHOP OS KM and extrapolation curves using KM with exponential tail, IPI 3-5 POLARIX trial

The cost-effectiveness analysis for patients with previously untreated DLBCL with Pola + R-CHP is expected to generate an incremental QALY and LY gain of 0.83 and 0.85 respectively, resulting in an estimated incremental cost-utility ratio (ICUR) of NOK 168,171 per QALY gained based on list prices (AUP ex VAT). The absolute shortfall was calculated at 5.2, resulting in a approximate WTP threshold of NOK 450.000. The primary overall drivers on cost-effectivness were the drug costs, the costs for subsequent therapies (in 2L+) as well as the supportive care costs associated with progression. The cost drivers in the intervention were the drug and supportive care costs, whereas for the comparator the costs were driven by a much larger proportion by the supportive care costs and subsequent therapy costs. Drug costs for R-CHOP were negligible. The recent addition of 2L CAR-T as a treatment alternative favors the intervention because fewer patients experience progression (Table 2). The deterministic sensitivity analysis in Table 2 further informs, that the selection of POLARIX population (ITT or IPI 3-5) for evaluation greatly impacts the ICUR.

Table 2: Deterministic sensitivity analysis

Parameter	Incr. QALYs	Incr. LYs	ICUR
Base-case (IPI 3-5)	0.83	0.85	168,171
ITT population (KM with Gen. Gamma tail)	0.44	0.32	425,861
IPI 3-5 without GOYA extension	0.72	0.67	177,097
Base-case (IPI 3-5) with 2L CAR-T	0.83	0.85	-111,825
ITT population with 2L CAR-T	0.44	0.32	81,912

A Probability sensitivity analysis (PSA) was also conducted, where the vast majority of simulations placed in the NE quadrant of the incremental cost-effectiveness plane, indicating for the intervention to almost always be more costly but also almost always be more effective.

DISCUSSION AND CONCLUSIONS

Following the assumptions made in the base-case analysis, the implementation of Pola + R-CHP for high risk IPI 3-5 1L DLBCL patients is a cost effective use of Norwegian health care resources with an ICUR of NOK 168,171 per QALY gained and is therefore well within the WTP threshold. The intervention is cost-effective in all scenarios (Table 2), including when removing the GOYA KM extension for PFS and also with the analysis carried out on the POLARIX ITT population. In August 2023, CAR-T therapy acheived reimbursement in Norway as a 2L treatment option for patients who progress or relapse <12 months after completion of systemic first-line therapy. The proportion of subsequent treatment therapies was updated beyond what is shown in Table 2 during the assessment process to reflect the anticipated changes in treatment landscape, using local clinical expert input. The cost-effectiveness of Pola+R-CHP in 1L DLBCL IPI 3-5 (and ITT) improved drastically as shown in table 2, as the availability of efficacious but costly treatment alternatives in later lines amplifies the benefits of 1st line interventions that allow more patients to remain progression-free for ≥ 2 years, increasing the probability of long-term survivorship.

The IPI 3-5 patient population is identified as the “high risk” sub-group of 1L DLBCL patients with a high need for a more efficacious alternative to standard of care (SoC) in Norway. The POLARIX subgroup analysis for IPI 3-5 patients suggests that Pola + R-CHP provides a significant clinical benefit in these patients over SoC and the health economic analysis suggests that the regimen in this patient population represents a cost-effective use of Norwegian health care resources at list-price (AUP ex VAT).

REFERENCES

1. Hervé T et al., Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma,. N Engl J Med. 2022; 386:351-363. DOI: 10.1056/NEJMoa2115304 [PubMed] [Google Scholar] 2. Sehn L.H., Berry B., Chhanabhai M. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2007;109(5):1857–1861. [PubMed] [Google Scholar] 3. Ziepert M., Hasenclever D., Kuhnt E. Standard international prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(14):2373–2380. [PubMed] [Google Scholar] 4. Zhou Z., Sehn L.H., Rademaker A.W. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood. 2014;123(6):837–842. [PMC free article] [PubMed] [Google Scholar] 5. Gleeson M., Counsell N., Cunningham D. A comparison of prognostic indices in diffuse large B-cell lymphoma within the UK NCRI R-CHOP 14 versus 21 phase III trial. Blood. 2018;132(Suppl 1):2956. [Google Scholar] 6. Helsedirektoratet, Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling of oppfølging av pasienter med maligne lymfomer. Retrived from Legeforeningen: https://www.legeforeningen.no/contentassets/830ca1e1e1f747ef90df5d0b047ef557/maligne-lymfomer nasjonalt-handlingsprogram-med-retningslinjer-for-diagnostikk-behandling-og-oppfolging.pdf, October the 20th 2023. 7. Pfreundschuh, M. S., Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomized controlled trial (RICOVER-60). The Lancet. Oncology, 1470-2045 [PubMed] [Google Scholar] 8. POLARIX Primary CSR, Report 1106275 (F. Hoffmann-La Roche Ltd 2021). 9. Wang, H., et al., PCN351 - HEALTH-STATE UTILITY VALUES IN DIFFUSE LARGE B-CELL LYMPHOMA., 2018, Value in Health, 21(S3), [S74]. https://doi.org/10.1016/j.jval.2018.09.433. 10. Sehn LH, Martelli M, Trněný M, et al. A randomized, open-label, Phase III study of obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-Cell lymphoma: final analysis of GOYA. J Hematol Oncol. 2020;13(1):71. Published 2020 Jun 6. doi:10.1186/s13045-020-00900-7. [PubMed] [Google Scholar] 11. Statens legemiddelverk, Legemiddelsøk, https://www.legemiddelsok.no/. Accessed 25.10.2023 12. Helsedirektoratet, DRG-systemet, Retrived from: https://www.helsedirektoratet.no/tema/finansiering/innsatsstyrt-finansiering-og-drg-systemet/drg-systemet, Accessed October the 20th 2023. 13. Statens legemiddelverk, Enhetskostnadsdatabase. Retrived from: https://legemiddelverket.no/offentlig-finansiering/metodevurdering-av-legemidler/dokumentasjon-for-metodevurdering/enhetskostnadsdatabase, Accessed October 20th 2023. 14. Rodigo S. Ho and Aino Launonen, Comparison of statistical methods for extrapolating survival in previously untreated diffuse large B-cell lymphoma: Results based on the POLARIX study, J Med Econ. 2023;26:1, 1178-1189 [PubMed] [Google Scholar] 15. Felizzi, F., Paracha, N., Pöhlmann, J., & Ray, J. Mixture Cure Models in Oncology: A Tutorial and Practical Guidance. PharmacoEconomics – open 2021, 5(2), 143–155. https://doi.org/10.1007/s41669-021-00260-z [PubMed] 16. Maurer MJ et al., Progression-free survival at 24 months (PFS24) and subsequent outcome for patients with diffuse large B-cell lymphoma (DLBCL) enrolled on randomized clinical trials. Annals of oncology. 2018;29(8), 1822–1827. https://doi.org/10.1093/annonc/mdy203 [PubMed] 17. Qian Shi et al., Progression-Free Survival as a Surrogate End Point for Overall Survival in First-Line Diffuse Large B-Cell Lymphoma: An Individual Patient-Level Analysis of Multiple Randomized Trials (SEAL). J Clin Oncol. 2018;36(25), 2593–2602. https://doi.org/10.1200/JCO.2018.77.91249 [PubMed] 18. Jakobsen et al., Minimal Loss of Lifetime for Patients With Diffuse Large B-Cell Lymphoma in Remission and Event Free 24 Months After Treatment: A Danish Population-Based Study. J Clin Oncol. 2017;35(7), 778–784. https://doi.org/10.1200/JCO.2016.70.0765 [PubMed] 19. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet. 2002;359(9318):1686-1689. doi:10.1016/S0140-6736(02)08594-X [PubMed] 20. Lenz G., Tilly H, Ziepert M., et al., Pola-R-CHP vs. R-CHOEP in young patients with high-risk diffuse large B-cell lymphoma. ICML June 13-17, 2023. P308 21. Statenslegemiddelverk, Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals, https://www.legemiddelverket.no/globalassets/documents/english/public-funding-and-pricing/documentation-for-sta/guidelines-18.10.2021.pdf (Accessed 30 October 2023).

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