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**Introduction:** Rituximab (R) and lenalidomide ($R^2$) is a highly effective therapy for frontline and relapsed/refractory (R/R) follicular lymphoma (FL) (Fowler 2018, Leonard 2019) and is the standard comparator and backbone therapy in ongoing randomized trials for relapsed FL. The efficacy of $R^2$ in relapsed FL was largely defined by AUGMENT (Leonard 2019) which excluded R refractory patients, in contrast to the current phase 3 studies. Because of limited randomized data on the efficacy of $R^2$ in R-refractory FL (Andorsky 2019) we performed a meta-analysis of FL-specific data to assess the progression free survival (PFS) and response rates of len+anti-CD20 based regimens. We also estimated the OR, CR and PFS rates for R2+X (X = systemic agent).

**Methods:** We searched MEDLINE, EMBASE and ClinicalTrials.gov using keywords "lymphoma" and "lenalidomide" from database inception to Dec. 12, 2025. Clinical trials and observational studies evaluating len with an anti-CD20 mAb (with or without another agent) were potentially eligible, including abstracts. Primary endpoints were overall (OR) and complete response (CR) rates by end of induction, and progression free survival (PFS). A mixed-effects model was used to calculate pooled OR and CR, 1-year PFS estimates and 95% confidence intervals. Study heterogeneity was assessed with the $I^2$ statistic. Patients were pooled according to treatment setting (frontline vs. R/R) and therapy ($R^2$ vs. "$R^2$+X"); a separate analysis of studies that included R-refractory patients was also done.

**Results:** Our search yielded 6627 unique abstracts; 36 met inclusion criteria and were included in the final analysis (15 abstracts, 21 manuscripts). In the pooled analysis of frontline studies, the OR rate for $R^2$ was 85.0% (76.2–95.0, $n$ = 814) compared to 96.1% (93.2–99.1, $n$ = 203) for $R^2$+X, and CR rates were 64.6% (51.4–81.1, $n$ = 1076) and 81.6% (74.3–89.6, $n$ = 211). In the R/R setting, OR rate was 79.9% (74.1–86.1, $n$ = 1090) with $R^2$ and 84% (77.2–91.3, $n$ = 632) with $R^2$ +X, and CR rates were 40.2% (33.1–49.0, $n$ = 1159) and 52% (40.2–67.7, $n$ = 632). Analysis of studies including R-refractory patients showed OR and CR rates of 79.6% (71.9–88.1, $n$ = 852) and 44.2% (36.2–54, $n$ = 921) for $R^2$, and 83.3% (75.5–92.0) and 60.3% (50.0–72.7) for $R^2$+X ($n$ = 577). Pooled 1-year PFS estimates for frontline therapy were 83.5% (73.74–94.59, $n$ = 309) for $R^2$ and 92.5% (81.31–100.00, $n$ = 90) for $R^2$+X. For R/R patients, corresponding estimates were 59% (47.44–74.18) and 44.5% (28.19–70.37). Inter-study heterogeneity was high ($I^2$ > 60%) in most analyses.

**Conclusions:** Our FL-specific meta-analysis demonstrates that the cumulative OR, CR and PFS for R/R FL patients are lower than observed in AUGMENT. Furthermore, our results support the addition of an agent to $R^2$ to improve efficacy, possibly with the greatest benefit observed in R-refractory patients. High inter-study heterogeneity was observed as expected with varying $R^2$ dosing schedules, $R^2$ combinations, sample sizes and trial design.

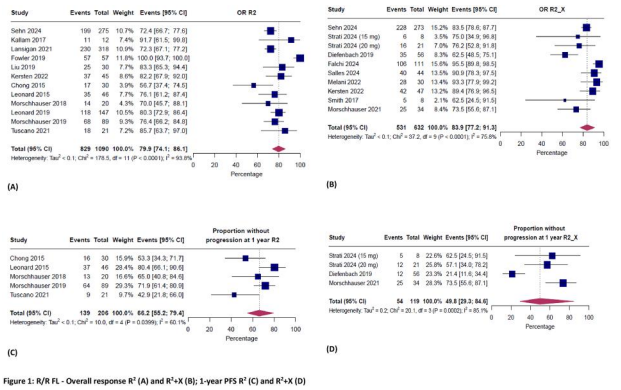


Figure 1: R/R FL - Overall response $R^2$ (A) and $R^2$+X (B); 1-year PFS $R^2$ (C) and $R^2$+X (D)

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## 580 | CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF HIGH-GRADE B-CELL LYMPHOMAS TRANSFORMED FROM INDOLENT LYMPHOMAS IN HIV-NEGATIVE AND HIV-POSITIVE PATIENTS

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**Introduction:** Limited and fragmentary literature suggest a different prognosis and molecular profile of high-grade B-cell lymphoma not otherwise specified (HGBCL-NOS), double-hit MYC-BCL2 lymphoma (DHL-BCL2), and DHL MYC-BCL6 (DHL-BCL6). A few studies suggest that a variable proportion of these lymphomas arise in patients priorly affected by indolent lymphomas. However, the prognosis and characteristics of transformed HGBCL (tHGBCL) was a matter of a few reports. Herein, we report a retrospective multicenter study where tHGBCLs were reviewed to better establish clinical pathological findings of this interesting neoplasm.

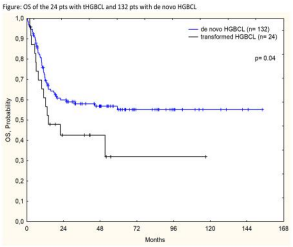
**Methods:** adults (18–75 years) with HGBCL-NOS, DHL-BCL2, and DHL-BCL6 diagnosed between 2010 and 2024 in six Italian Cancer Centers were reviewed. Diagnosis was performed by local expert pathologists and reclassified according to ICC/WHO5 classifications. All cases were assessed with FISH for MYC, BCL-2, and BCL-6.

**Results:** 156 pts with complete pathology, FISH, and clinical data were analyzed: 57 (37%) pts had DHL-BCL2, 21 (13%) had DHL-BCL6, and 78 (50%) had HGBCL-NOS. 28 (18%) pts had HIV infection. Twenty-four (15%) tHGBCL were recorded: 17 (71%) were DHL-BCL2, 1 (4%) was DHL-BCL6, and 6 (25%) were HGBCL-NOS. There was a single tHGBCL diagnosed in HIV-positive pts; 73% of transformations occurred after follicular lymphoma. tHGBCL was significantly correlated to lymphoma entity, bcl-2 immunostaining, Ki67 score, and HIV infection (Table), whereas no correlations with Hans algorithm and other clinical features were detected. Twenty-five pts (3 tHGBCL) were treated with RCHOP and 131 (21 tHGBCL) with intensified regimens. At a median follow-up of 48 months (IQR 26–71), 18 (75%) tHGBCL pts experienced a PFS event: 13 had chemorefractory disease, two died of toxicity, and three experienced relapse after initial response; all events but two occurred in the first 9 months from diagnosis. Fourteen (58%) tHGBCL pts died due to lymphoma ($n = 11$) or infections ($n = 3$). The overall prognosis of tHGBCL was significantly poorer in comparison with de novo HGBCL (Figure), with a 5-year OS of 32% (95% CI: 7–61) and 57% (95% CI: 54–60), respectively ($p = 0.04$). This was in line with a significantly poorer survival recorded for pts with DHL-BCL2 in comparison with DHL-BCL6 and HGBCL-NOS, with a 5-year OS of 36% (95% CI: 21–51), 79% (95% CI: 78–80), and 58% (95% CI: 55–61), respectively ($p = 0.01$). In multivariate analysis, age, PS, and tHGBCL were independently associated with PFS and OS.

**Conclusions:** Near 15% of HGBCL are diagnosed in pts with a history of indolent lymphoma. tHGBCL carries often MYC and BCL2 rearrangements, whereas involvement of BCL6 is uncommon. Whereas clinically undistinguishable from other HGBCLs, the transformed form is associated with poor prognosis, even when treated with intensified chemotherapy regimens.

Table: Distribution of pathological and clinical findings. Spearman correlation test

| Variable | | tHGBCL (n= 24) | *De novo* HGBCL (n= 132) | P |
|---|---|---|---|---|
| Median age (range) | | 60 (45-73) | 61 (22-75) | NS |
| Male gender | | 16 (66%) | 83 (63%) | NS |
| Lymphoma entity | | | | 0.0007 |
| | DHL-BCL2 | 17 (71%) | 40 (30%) | |
| | DHL-BCL6 | 1 (4%) | 20 (15%) | |
| | HGBCL-NOS | 6 (25%) | 72 (55%) | |
| Immunostaining | | | | |
| | CD10 | 19 (79%) | 97 (73%) | NS |
| | Bcl-6 | 17 (71%) | 107 (81%) | NS |
| | MUM-1 | 7 (29%) | 36/83 (43%) | NS |
| | Bcl-2 | 22 (92%) | 81/123 (66%) | 0.01 |
| Germinal center phenotype (Hans) | | 21 (88%) | 101/121 (83%) | NS |
| | Ki67 ≥80% | 16 (67%) | 103/124 (83%) | 0.05 |
| ECOG-PS >1 | | 9 (38%) | 52 (39%) | NS |
| Advanced stage (Ann Arbor III-IV) | | 23 (96%) | 109 (83%) | NS |
| Extranodal disease | | 17 (71%) | 70/124 (56%) | NS |
| CNS involvement | | 3 (13%) | 12 (9%) | NS |
| High LDH serum level | | 21 (88%) | 107 (81%) | NS |
| Bulky disease | | 14 (58%) | 53 (40%) | NS |
| HIV seropositivity | | 1 ( 4%) | 27 (20%) | 0.05 |




**Keywords:** aggressive B-cell non-Hodgkin lymphoma

No potential sources of conflict of interest.

## 581 | THE BURDEN OF RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA IN ENGLAND: A RETROSPECTIVE ANALYSIS OF REAL-WORD TREATMENT PATTERNS AND OUTCOMES

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**Introduction:** Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma. Disease progression after first-line (1L) therapy is common, however, there is currently no standard treatment (tx) for relapsed or refractory (R/R) FL in England. Therefore, we aimed to describe real-world (rw) tx patterns, outcomes, and healthcare resource utilisation (HCRU) in adult patients (pts) with R/R FL in England.

**Methods:** This retrospective, observational study analysed data from the Cancer Analysis System database (National Health Service England). Eligible pts were aged ≥ 18 years at initial diagnosis of FL (grade 1, 2, or 3A) from 1 January 2014 to 31 December 2021 and had received ≥ 2 lines of therapy (LOT), including tx with an anti-CD20 antibody (rituximab or obinutuzumab). Pts were excluded if they had a record of transformation or CNS metastases or received tx as part of a clinical study. Outcomes included overall survival (OS), time-to-next tx, and rw progression-free survival (PFS). Outcomes were stratified by tx group and by progression of disease within 24 months (mo) from initiation of 1L therapy (POD24). Disease progression was inferred by a record of a subsequent LOT. HCRU rates (inpatient admissions, outpatient and specialist visits, and disease monitoring) were measured in rate per person per year (PPPY) and reported for the overall cohort and stratified by record of a subsequent LOT.

**Results:** The study included 1313 pts with R/R FL from a total 17,068 pts with FL. Median (interquartile range [IQR]) age at