Title: Comparison of immunohistochemistry and gene expression profiling subtyping for diffuse large B-cell lymphoma in the phase III clinical trial of R-CHOP ± ibrutinib

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Summary

We assessed the concordance between immunohistochemistry **(IHC)** and gene expression profiling (GEP) for determining diffuse large B-cell lymphoma (DLBCL) cell of origin (COO) in the phase III PHOENIX trial of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with or without ibrutinib. Among 910/1114 screened patients with non-germinal centre B-cell–like (non-GCB) DLBCL by **IHC**, the concordance with GEP for non-GCB calls was 82·7%, with 691 (75·9%) identified as activated B-cell–like (ABC), and 62 (6·8%) as unclassified. Among 746/837 enrolled patients with verified non-GCB DLBCL by **IHC**, the concordance with GEP was 82·**8**%, with 567 (76·0%) identified as ABC and 51 (6·8%) unclassified; survival outcomes were similar regardless of COO or treatment, whereas among patients with ABC DLBCL <60 years, the overall and event-free survival were substantially better with ibrutinib *versus* placebo plus R-CHOP (hazard ratio [HR] 0·365, 95% confidence interval [CI] 0·147-0·909, $P = 0·0305$; HR 0·561, 95% CI 0·326-0·967, $P = 0·0348$, respectively). **IHC** and GEP showed high concordance and consistent survival outcomes among tested patients, indicating centralized **IHC** may be used to **enrich populations for response to ibrutinib plus R-CHOP.**

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma, representing approximately 40% of lymphoma cases worldwide.[1] It can be classified into distinct molecular subtypes based on the cell of origin (COO).[2] Gene expression profiling (GEP) methods classify DLBCL into germinal centre B cell–like (GCB), activated B cell–like (ABC) and unclassified groups.[2,3] Immunohistochemistry **(IHC)-**based methods are widely used and provide an approximation of GEP by dichotomizing DLBCL into GCB and non-GCB subtypes. In **IHC** analysis by the "Hans" algorithm, a non-GCB classification requires negative stains for CD10 **(MME)** and BCL-6, or a positive stain for MUM1 **(IRF4)** if the BCL-6 stain is positive.[4] More recently, four prominent genetic subtypes in DLBCL designated *MCD, BN2, N1* and *EZB* have been identified.[5] Additional genetic analysis identified five DLBCL subsets, which generally overlapped with the aforementioned subtypes and included ABC DLBCL subsets of extrafollicular/marginal zone origin; two subsets of GCB DLBCL; and an ABC/GCB-independent group.[6] Nevertheless, all these recently identified subtypes are generally segregated into one of three GEP defined groups, highlighting the persistent clinical relevance of COO classification.

Many common genetic aberrations in GCB DLBCL were not reported in ABC DLBCL.[7] In clinical studies, patients with ABC DLBCL showed poorer outcomes than those with GCB DLBCL with standard front-line DLBCL treatment rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).[8] **In more** recent phase I and II **trials**, novel agents like ibrutinib (a Bruton's tyrosine kinase inhibitor) or lenalidomide (an immunomodulatory drug) **demonstrated** preferential activity in patients with relapsed/refractory ABC DLBCL or in previously untreated patients with non-GCB DLBCL, respectively, *versus*

those with GCB DLBCL.[9,10] These data **support** the predictive significance of DLBCL subtyping, necessitating the development of rapid and accurate COO identification methods.

Microarray-based GEP was developed to subtype DLBCL COO.[11] GEP is not routinely used in the clinical setting due to cost and technical issues, including a slow turnaround time of 2–3 weeks.[2,7,12] Therefore, **IHC** remains widely adopted in clinical practice, although inter-laboratory variance limits **comparison** across sites,[13,14] **warranting the use of more reliable centralized assays**. **Despite** the development of multiple **IHC** assays using different combinations of protein markers,[13] the Hans method is most widely used in diagnostic clinical laboratories because of its simplicity and validated prognostic value.[4,12] Several recently emerged simplified GEP-based methods can reproduce the original comprehensive microarray-based classification, which include the Lymphoma Subtyping Test (LST) assay (NanoString, Seattle, WA, USA) and the next-generation sequencing–**based** EdgeSeq DLBCL Cell-of-Origin Assay (HTG Molecular Diagnostics, Tucson, AZ, USA).[12] Given these options, the optimal assay for selecting patients with poor prognosis DLBCL for clinical trials remains undetermined.

PHOENIX (NCT01855750) was a randomized, placebo-controlled phase III trial **comparing** the efficacy and safety of ibrutinib plus R-CHOP and placebo plus R-CHOP in previously untreated patients with **IHC**-selected non-GCB DLBCL.[15] The trial did not meet its primary endpoint: the addition of ibrutinib to R-CHOP did not improve event-free survival (EFS) in the intent-to-treat (ITT) or ABC (by GEP) population.[15] In **an** exploratory analysis, an improvement in EFS, progression-free survival (PFS) and overall survival (OS) with ibrutinib plus R-CHOP was observed in patients <60 years, but not in those ≥60 years, likely because of increased toxicity in the older population limiting completion of treatment.[15] The current prespecified analysis aims to assess the concordance between **IHC** and GEP by HTG EdgeSeq

DLBCL Cell-of-Origin Assay for COO subtyping, both performed by central laboratory, and to investigate patient outcomes with COO GEP, which was tested following non-GCB selection by **IHC**, in the PHOENIX trial.

Materials and methods

Trial design and patients

A detailed methodology for this trial is published elsewhere.[15] Briefly, patients ≥18 years who had previously untreated non-GCB DLBCL (*n* = 838) based on **centralized IHC** results at screening were randomly assigned at a 1:1 ratio to receive ibrutinib (560 mg daily) plus R-CHOP or placebo plus R-CHOP for 6 or 8 cycles per local guidelines. The primary endpoint was investigator-assessed EFS in the ITT or ABC (by GEP) population. Secondary endpoints included PFS, complete response rate and OS in the ITT population.[15]

Cell of origin analysis and concordance evaluation

COO analysis was performed as stated in the Supplementary Information. Concordance between **IHC** and GEP assays was estimated with reference to **IHC** data, as described in the Supplementary Information.

Validation of GEP prognostic value and prediction of treatment effect

The prognostic value of the GEP assay was assessed using probability scores derived from the expression levels of COO signature genes, housekeeping markers, and positive controls[16] using methods previously described, as stated in the Supplementary Information.

Survival outcomes analysis

Survival outcomes were estimated by Kaplan–Meier analysis with log-rank *P* value**, as described in the Supplementary Information.** The hazard ratios (HRs) and their Wald's confidence intervals (CIs) were estimated using Cox proportional hazards regression modelling.

Results

Trial samples

Of 1490 patients screened, valid **IHC** results were obtained from 1338 (89·8%) tissue samples and showed 268 GCB and 1070 non-GCB cases. These samples were further tested by GEP with 1114 samples (83·3%) yielding valid GEP results. **Fig S1 shows the percentage and concordance of screened and enrolled IHC-selected patients in each GEP subpopulation.**

Concordance in screened patients

Of 1114 screened samples with evaluable results for both **IHC** and GEP, 910 were identified as non-GCB by **IHC**. Among these, 691 (75·9%) were identified as ABC, 62 (6·8%) unclassified and 157 (17·3%) GCB by GEP. These results led to a concordance of 82·7% (95% CI 80·2-85·1) for non-GCB calls between **IHC** and GEP (Table I). Of the 204 samples identified by **IHC** as GCB, 145, 49 and 10 were called GCB, ABC and unclassified by GEP, respectively, leading to a concordance of 71·1% (95% CI 64·5-76·9) for GCB calls between assays (Table I). The overall concordance between the assays was 80·6% (95% CI 78·2-82·8) (Table I).

Concordance in enrolled patients

The PHOENIX trial enrolled 838 patients with non-GCB DLBCL, among whom one actually was GCB by **IHC** during further verification.[15] Among 837 enrolled patients with non-GCB

IHC-verified subtype, 746 (89·1%) samples were evaluable by GEP **(Table II)**. All **GEP**-evaluable **samples** were CD10-negative because of the non-GCB pre-selection by **IHC**. Of these, 128 (17·2%), 567 (76·0%) and 51 (6·8%) were identified as CD10-negative GCB, ABC and unclassified by GEP, respectively (Fig 1). This led to a non-GCB concordance of 82·**8**%.

Of non-GCB **IHC**-selected samples evaluable by GEP, 301 were from patients <60 years and 445 were from those ≥60 years. Among patients <60 years, the number of CD10-negative GCB, ABC and unclassified by GEP samples was 70, 205 and 26, respectively (Fig **S2A**), leading to a non-GCB concordance of 76·7%. In patients ≥60 years, the number of CD10-negative GCB, ABC and unclassified by GEP samples was 58, 362 and 25, respectively (Fig **S2B**), resulting in a non-GCB concordance of 86·8%.

OS comparison

In the ITT population, OS was similar between treatment arms regardless of ABC (HR 1·035, 95% CI 0·706-1·518, $P = 0·8584$) or CD10-negative GCB (HR 1·027, 95% CI 0·382-2·759, $P = 0·9585$) subpopulations (Fig 2A). There was a non-significant trend towards better OS for CD10-negative GCB *versus* ABC **subpopulation** in both the ibrutinib plus R-CHOP ($P = 0·2532$) and placebo plus R-CHOP ($P = 0·2183$) arms (Fig **2A**). In patients <60 years, OS was significantly better in the ibrutinib plus R-CHOP *versus* placebo plus R-CHOP arm in the ABC subpopulation (HR 0·365, 95% CI 0·147-0·909, $P = 0·0305$) but was similar between arms in the CD10-negative GCB subpopulation (HR 0·266, 95% CI 0·031-2·281, $P = 0·2272$) (Fig **2B**). However, within each treatment arm, as expected, patients in the CD10-negative GCB subpopulation showed a non-significant trend for better OS than those in the ABC subpopulation (ibrutinib plus

R-CHOP [*P* = 0·4906]; placebo plus R-CHOP [*P* = 0·4163]), but the between-subpopulation difference appeared to be more pronounced with placebo plus R-CHOP.

Within-arm EFS comparison by GEP subpopulations

In an exploratory analysis, EFS for CD10-negative GCB, ABC and unclassified subpopulations by GEP was compared within each treatment arm in the ITT population and by the **60-year** age cut-off (Fig 3). In the placebo plus R-CHOP arm, although statistically non-significant (*P* = 0·5319) among the GEP CD10-negative GCB, ABC and unclassified subpopulations, there was a trend towards better EFS in patients with CD10-negative GCB ***versus*** ABC DLBCL in the ITT population (Fig 3A); the difference was more pronounced in patients <60 years (*P* = 0·4115) (Fig 3B). While also statistically non-significant in the **GEP** subpopulations, in the ibrutinib plus R-CHOP arm, the difference in EFS between the CD10-negative GCB and ABC subpopulations were less pronounced *versus* the placebo plus R-CHOP arm for both the ITT population (*P* = 0·6338) and patients **<60 years (*P* = 0·6902) (Fig 3C–D). Specifically, beyond 24 months in the ABC and CD10-negative GCB subpopulations, there was little progression in the ibrutinib plus R-CHOP arm, while progression was seen in the placebo plus R-CHOP arm in the ITT population (Fig 3A–3C) and in patients <60 years (Fig 3B–3D).**

Within GEP subpopulation EFS comparison by treatment arms

In the ITT population, EFS was similar between arms among patients with ABC (HR 0·937, 95% CI 0·697-1·259, *P* = 0·6637) or CD10-negative GCB DLBCL (HR 0·916, 95% CI 0·452-1·856, *P* = 0·8081) by GEP (Fig S3).

Among patients <**60 years, EFS was** significantly better in the ibrutinib plus R-CHOP *versus* placebo plus R-CHOP arm among patients with ABC DLBCL (HR 0·561, 95% CI 0·326-

0·967, *P* = 0·0348) (Fig **S4A). While this was not significant in the CD10-negative GCB subpopulation (HR 0·644, 95% CI 0·223-1·858, *P* = 0·4119), the numbers were small; beyond 2 years, there was little progression with ibrutinib plus R-CHOP, unlike with placebo plus R-CHOP (Fig S4B).**

Among patients ≥60 years, EFS was similar between treatment arms in both the ABC (HR 1·188, 95% CI 0·822-1·715, *P* = 0·3583) and CD10-negative GCB (HR 1·279, 95% CI 0·480-3·408, *P* = 0·6217) subpopulations (Fig S5)**, although patient numbers were small in the latter.**

Validation of prognostic value and prediction of treatment effect

Assessment of the prognostic value of the GEP assay and correlation of the predetermined cut-off with treatment effect prediction included 559 patients (total samples: 419 ABC, 41 unclassified, 99 CD10-negative GCB). The mean GCB probability scores in all patients were 0·103, 0·494 and 0·811 for the ABC, unclassified and CD10-negative GCB by GEP subpopulations, respectively; similar results were obtained for the separate treatment arms (Table SI). The GEP assay's prognostic value was confirmed by showing the likelihood of patient survival increased proportionately with the CD10-negative GCB probability score. A higher score was associated with longer survival in the placebo plus R-CHOP arm; this non-significant trend was less clear for the ibrutinib plus R-CHOP arm (Figs S6–S8). Lowering the cut-off of the CD10-negative GCB score did not significantly alter the outcomes (Table SII; Fig S9).

Discussion

In all screened patients, the concordance between **IHC** and GEP for non-GCB calls was high (82·7%). The overall concordance (proportion of patients of non-GCB or GCB concordance in

relation to patients with test results from both GEP and IHC assays) between the assays in screened patients was 80·6%. In enrolled patients with non-GCB DLBCL, concordance was also high (82·7%) in the ITT population, but greater for patients ≥60 years (86·8%) than those <60 years (76·7%). These results were generally consistent with the reported overall concordance between the Hans-based **IHC method** and the DNA microarray-based GEP, LST and EdgeSeq COO **assays** (79·6%, 80·0% and 78·1%, respectively).[12]

Validation of the GEP method showed a higher score was associated with longer survival for the placebo plus R-CHOP arm; this **non-significant** trend was less defined for the ibrutinib plus R-CHOP arm. Lowering the cut-off of the CD10-negative GCB score did not significantly alter the HR for the between-arm comparison (Supplementary Table SII; Fig S9).

Studies have shown patients with distinctive DLBCL subtypes respond differently to chemotherapy or chemoimmunotherapy regimens.[8,9] R-CHOP was associated with poorer outcomes in non-GCB or ABC than GCB DLBCL.[8,9] With this regimen, patients with GCB DLBCL **showed** a higher probability of PFS and OS *versus* those with ABC DLBCL.[8] Similarly, patients with non-GCB DLBCL treated with R-CHOP reportedly had an inferior 2-year PFS and OS *versus* patients with GCB DLBCL.[9]

In **interpreting the data, we should consider the small sample size. However,** in our analysis, patients <60 years in the ABC subpopulation showed significantly better OS and EFS with ibrutinib plus R-CHOP *versus* placebo plus R-CHOP. Supporting our findings, ibrutinib demonstrated preferential activity in ABC *versus* GCB **(by GEP)** DLBCL in a phase I/II trial,[10] with **objective** responses in 37% of patients with ABC DLBCL ***versus*** 5% with GCB DLBCL, despite the small sample size ($N = 80$). **Recent DLBCL genetic classifications** [5,6,17] **have**

suggested a molecular basis for the increased activity of B-cell receptor (BCR) inhibitors in ABC and unclassified (or non-GCB) DLBCL. The exact molecular definitions are not established but it is apparent the activity of these compounds may span multiple genetic subtypes, suggesting a continued role for COO in DLBCL prognostication. Also, in the enrolled patients of this study, the GCB subpopulation by GEP was CD10 negative because of the non-GCB preselection by **IHC**. Although the clinical features of CD10-negative *versus* CD10-positive GCB DLBCL have not been well studied, it is possible CD10-negative GCB DLBCL by GEP may identify or enrich a genetic GCB DLBCL subtype with higher sensitivity to **BCR** inhibitors than CD10-positive GCB disease, which constitutes the majority of GCB DLBCL tumours. **Until these** GCB **subtypes are better** characterized, the generalizability of the results should be interpreted with these considerations.

Nonetheless, in the overall population, survival outcomes were similar regardless of COO or treatment. In the ITT population, although there was a non-significant trend towards better survival in patients with CD10-negative GCB DLBCL ***versus*** ABC DLBCL in both treatment arms, the differences between subpopulations were smaller with ibrutinib plus R-CHOP than placebo plus R-CHOP. Consistently, there was a non-significant trend towards a higher EFS rate beyond 2 years of study in the ibrutinib plus R-CHOP *versus* the placebo plus R-CHOP arm **among patients with CD10-negative GCB DLBCL, implying some clinical benefit, although numbers were small, especially in patients <60 years.**

The overall similar survival outcomes in this analysis are consistent with the high concordance between IHC and GEP, which continues to highlight the clinical relevance of COO classification and the use of centralized **IHC** to select patients with an inferior prognosis or enrich **BCR-inhibitor sensitive** populations in future clinical trials. Ongoing trials are

investigating the impact of COO subtyping on treatment efficacy in previously untreated or relapsed/refractory DLBCL.[18-21]

Determining the utility of IHC as a surrogate for GEP profiling is important because the time and infrastructure required for GEP are challenging for the real-time management of patients with DLBCL. **These** results show that centralized **IHC** is sufficiently concordant with GEP in our study**, as both represent complex molecular entities**. Therefore, centralized diagnostic assays such as **IHC** could serve as **a reasonable** surrogate for GEP methods **to enrich populations for response to ibrutinib plus R-CHOP.**

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Conflicts-of-interest disclosure

S. B.: Janssen employment and stock ownership from Johnson & Johnson, Gilead Sciences, Celgene, Vertex, and AbbVie; S.W., C.M., M.S., J.C., S.M.S, S.S, and J.V.: Janssen employment and stock ownership from Johnson & Johnson; B.H. and J.G.: of Janssen employment; L.H.S: honoraria from Amgen, Apobiologix, AbbVie, Celgene, Gilead Sciences, Janssen-Ortho, Karyopharm Therapeutics, Kite Pharma, Lundbeck, Merck, Roche/Genentech, Seattle Genetics, Takeda Pharmaceuticals, TEVA Pharmaceuticals Industries, and TG Therapeutics, research funding from Roche/Genentech, consulting or an advisory role with Karyopharm Therapeutics, Kite Pharma, Merck, Takeda Pharmaceuticals, TEVA Pharmaceuticals Industries, and TG Therapeutics; P.J.: reports honoraria from Bristol Myers Squibb, Takeda, Novartis, Celgene, Janssen, Epizyme, Boehringer Ingelheim, Kite, Genmab, and Incyte, research funding from Epizyme and Janssen, and consulting or advisory role with Janssen; P.L.Z.: advisory roles for Verastem, Janssen, Takeda, TG Therapeutics, Bristol Myers Squibb, Roche, Gilead, Novartis, and Celltrion; W.W and L.S.: have no competing interests.

Author contributions

S.B., S.W., C.M., S.S.: study conceptualization and design, data collection, and data review, analysis and interpretation. B.H., M.S., L.H.S., L.S.: data review, analysis and interpretation. P.J.: study conceptualization, provision of study material or patients, and data collection,

analysis, and interpretation. P.L.Z.: data collection and assembly. J. C. and S.M.S: study conduct and data analysis. J.G.: data review and editing. J.V.: study conceptualization and design and investigation. W.W.: study conceptualization, investigation, and data analysis. All authors reviewed/edited and approved the manuscript for submission.

Supporting information

Additional information may be found online in the Supporting Information section at the end of the article.

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Table I. Concordance between **IHC** and GEP in screened patients ($N = 1114$).

		GEP assay, *n* (%)			
		ABC	Unclassified	GCB	Total
IHC assay, *n* (%)	Non-GCB	691 (75·9)	62 (6·8)	157 (17·3)	910 (100·0)
	GCB	49 (24·0)	10 (4·9)	145 (71·1)	204 (100·0)
Non-GCB concordance, % (95% CI) = 82·7 (80·2-85·1)*					
GCB concordance, % (95% CI) = 71·1 (64·5-76·9)*					
Overall concordance, % (95% CI) = 691 + 62 + 145 / 1114 = 80·6 (78·2-82·8)*					

*95% CI based on score method.

ABC, activated B-cell–like; CI, confidence interval; GCB, germinal centre B-cell–like; GEP, gene expression profiling; **IHC, immunohistochemistry**.

Table II. Concordance between IHC and GEP in GEP-evaluable enrolled patients (*N* = 746).

		GEP assay, *n* (%)			
		ABC	**Unclassified**	**GCB**	**Total**
IHC assay, *n* (%)	**Non-GCB**	**567 (76·0)**	**51 (6·8)**	**128 (17·2)**	**746 (100·0)**
Non-GCB concordance, % (95% CI) = 82·8 (80.0-85.4)*					

***95% CI based on score method.**

ABC, activated B-cell–like; CI, confidence interval; GCB, germinal centre B-cell–like; GEP, gene expression profiling; IHC, immunohistochemistry.

Figure Legends

Fig 1. IHC-selected patients in each GEP COO category in enrolled patients. The proportion of patients in the CD10-negative GCB, ABC and UNC subpopulations assessed by GEP are described. ABC, activated B-cell–like; CD10- GCB, CD10-negative GCB; COO, cell of origin; GCB, germinal centre B-cell–like; GEP, gene expression profiling**; IHC, immunohistochemistry;** UNC, unclassified.

Fig 2. OS by GEP subpopulations **in (A) ITT population and (B) patients aged <60 years**. The OS is described in both CD10-negative GCB and ABC subpopulations for patients treated with either placebo plus R-CHOP or ibrutinib plus R-CHOP. **P* values are from an exploratory analysis. ABC, activated B-cell–like; CD10- GCB, CD10-negative GCB; CI, confidence interval; GCB, germinal centre B-cell–like; GEP, gene expression profiling; HR, hazard ratio; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Fig 3. EFS by GEP subpopulations within each treatment arm. (A) Shows EFS in the ITT population by CD10-negative GCB, ABC and UNC subpopulations in the placebo plus R-CHOP arm. (B) Shows EFS in patients aged <60 years by CD10-negative GCB, ABC and UNC subpopulations in the placebo plus R-CHOP arm. (C) Shows EFS in the ITT population by CD10-GCB, ABC and UNC subpopulations in the ibrutinib plus R-CHOP arm. (D) Shows EFS in patients aged <60 years by CD10-negative GCB, ABC and UNC subpopulations in the ibrutinib plus R-CHOP arm. ABC, activated B-cell–like; CD10- GCB, CD10-negative GCB; CI, confidence interval; EFS, event-free survival; GCB, germinal centre B-cell–like; GEP, gene

expression profiling; ITT, intent to treat; NE, not evaluable; NR, not reached; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; UNC, unclassified.

Figures

Fig 1

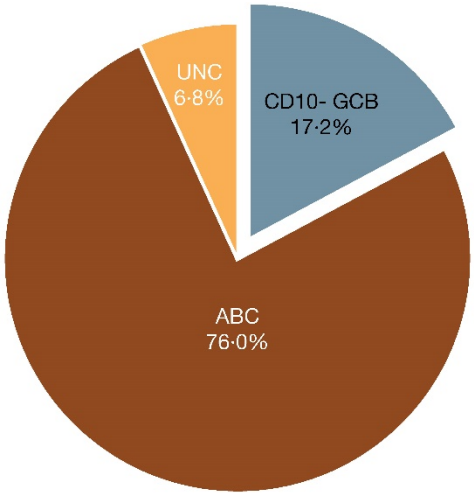
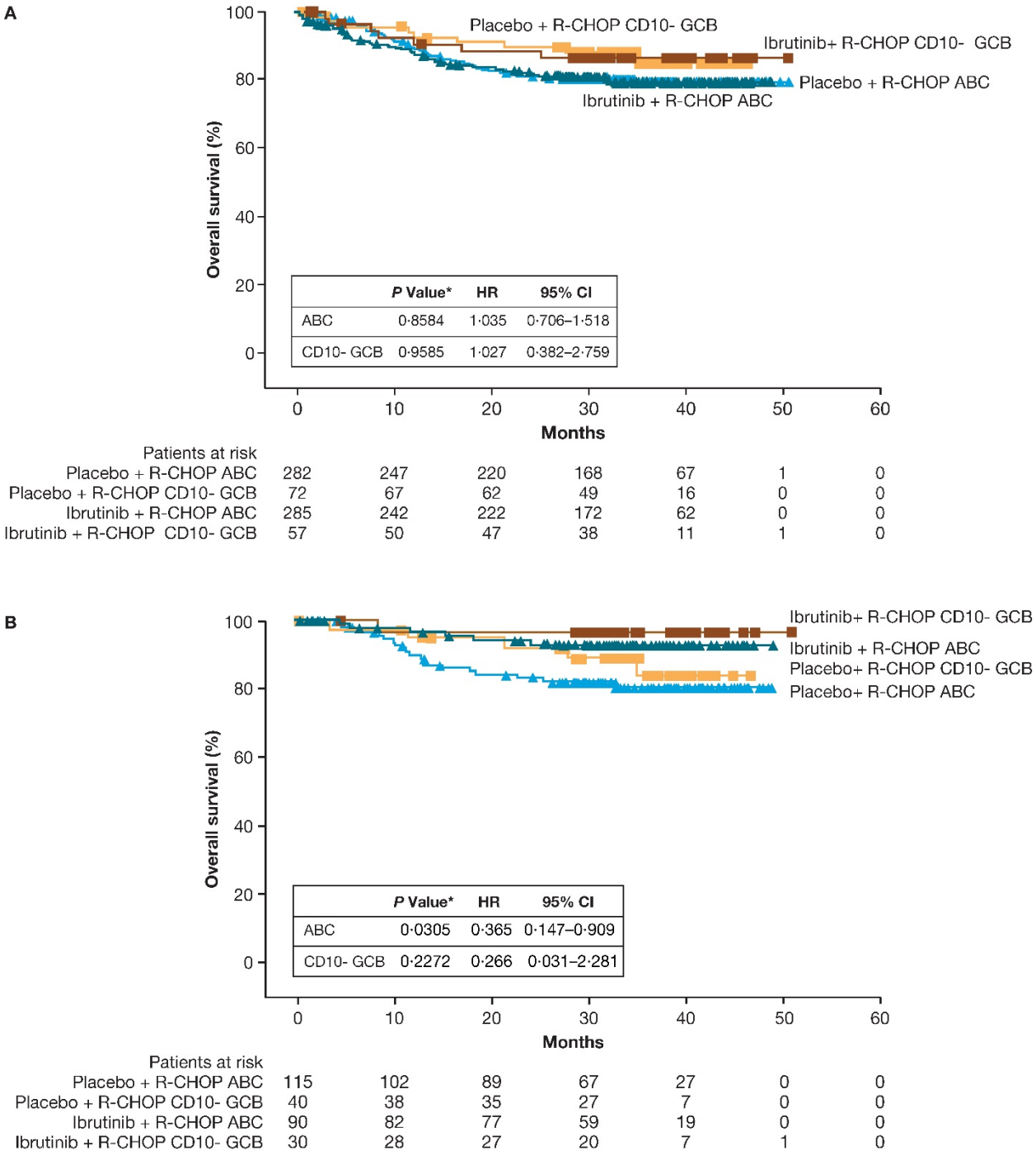
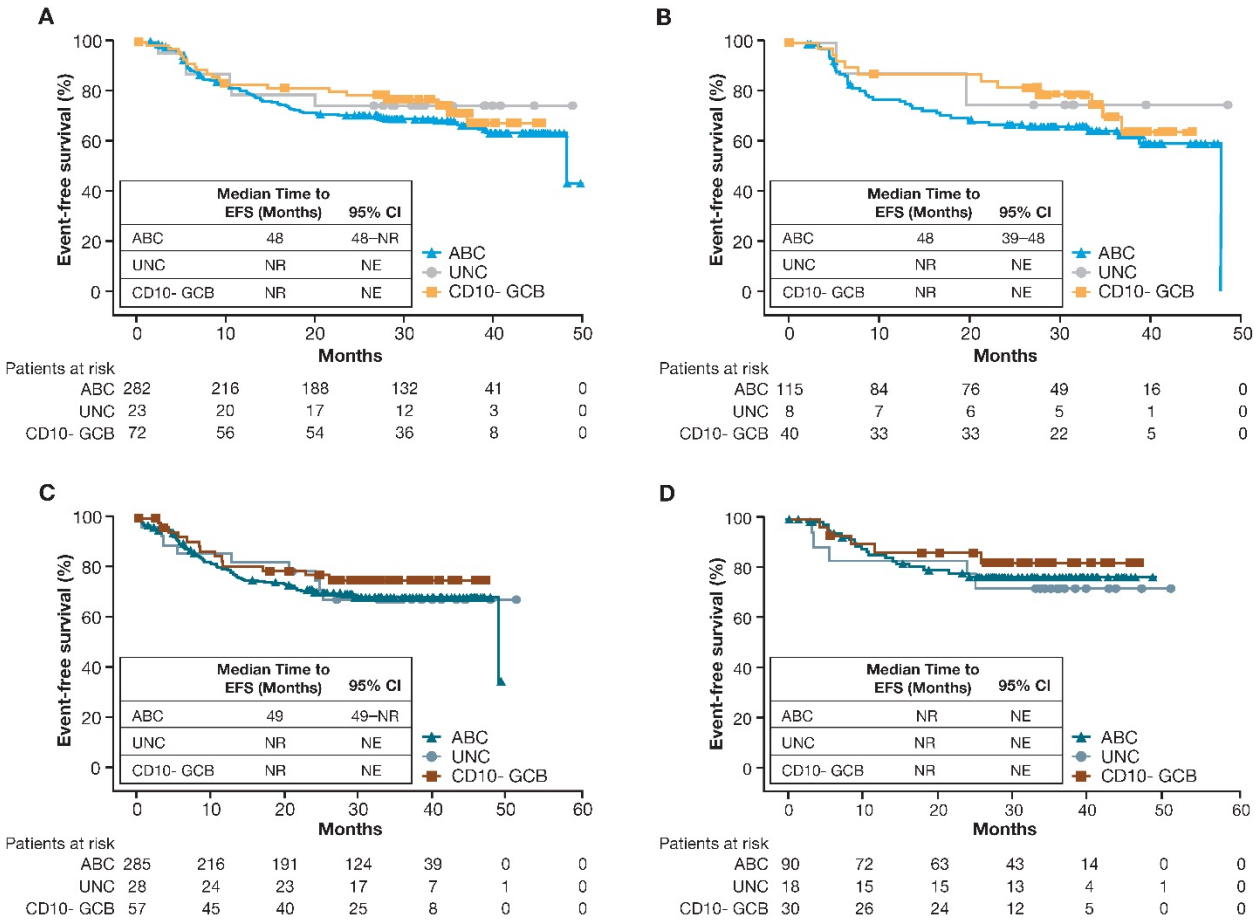


Fig 2


A
Placebo + R-CHOP CD10- GCB
Ibrutinib+ R-CHOP CD10- GCB
Placebo + R-CHOP ABC
Ibrutinib + R-CHOP ABC
Overall survival (%)
100
80
60
40
20
0
P Value* HR 95% CI
ABC 0·8584 1·035 0·706–1·518
CD10- GCB 0·9585 1·027 0·382–2·759
0 10 20 30 40 50 60
Months
Patients at risk
Placebo + R-CHOP ABC 282 247 220 168 67 1 0
Placebo + R-CHOP CD10- GCB 72 67 62 49 16 0 0
Ibrutinib + R-CHOP ABC 285 242 222 172 62 0 0
Ibrutinib + R-CHOP CD10- GCB 57 50 47 38 11 1 0
B
Ibrutinib+ R-CHOP CD10- GCB
Ibrutinib + R-CHOP ABC
Placebo+ R-CHOP CD10- GCB
Placebo+ R-CHOP ABC
Overall survival (%)
100
80
60
40
20
0
P Value* HR 95% CI
ABC 0·0305 0·365 0·147–0·909
CD10- GCB 0·2272 0·266 0·031–2·281
0 10 20 30 40 50 60
Months
Patients at risk
Placebo + R-CHOP ABC 115 102 89 67 27 0 0
Placebo + R-CHOP CD10- GCB 40 38 35 27 7 0 0
Ibrutinib + R-CHOP ABC 90 82 77 59 19 0 0
Ibrutinib + R-CHOP CD10- GCB 30 28 27 20 7 1 0

1 **Fig 3**


A
Event-free survival (%)
100
80
60
40
20
0
Median Time to EFS (Months) 95% CI
ABC 48 48–NR
UNC NR NE
CD10- GCB NR NE
ABC
UNC
CD10- GCB
0 10 20 30 40 50
Months
Patients at risk
ABC 282 216 188 132 41 0
UNC 23 20 17 12 3 0
CD10- GCB 72 56 54 36 8 0
B
Event-free survival (%)
Median Time to EFS (Months) 95% CI
ABC 48 39–48
UNC NR NE
CD10- GCB NR NE
ABC
UNC
CD10- GCB
0 10 20 30 40 50
Months
Patients at risk
ABC 115 84 76 49 16 0
UNC 8 7 6 5 1 0
CD10- GCB 40 33 33 22 5 0
C
Event-free survival (%)
Median Time to EFS (Months) 95% CI
ABC 49 49–NR
UNC NR NE
CD10- GCB NR NE
ABC
UNC
CD10- GCB
0 10 20 30 40 50 60
Months
Patients at risk
ABC 285 216 191 124 39 0 0
UNC 28 24 23 17 7 1 0
CD10- GCB 57 45 40 25 8 0 0
D
Event-free survival (%)
Median Time to EFS (Months) 95% CI
ABC NR NE
UNC NR NE
CD10- GCB NR NE
ABC
UNC
CD10- GCB
0 10 20 30 40 50 60
Months
Patients at risk
ABC 90 72 63 43 14 0 0
UNC 18 15 15 13 4 1 0
CD10- GCB 30 26 24 12 5 0 0

2

3