clinical trial updates

Differential Efficacy From the Addition of Bortezomib to R-CHOP in Diffuse Large B-Cell Lymphoma According to the Molecular Subgroup in the REMoDL-B Study With a 5-Year Follow-Up

Andrew J. Davies, PhD[1]; Sharon Barrans, PhD[2]; Louise Stanton, MSc[3]; Josh Caddy, BSc[3]; Sam Wilding, MSc[3]; Geoff Saunders, BSc[3]; Christoph Mamot, MD[4]; Urban Novak, MD[5]; Andrew McMillan, MD[6]; Paul Fields, MD[7]; Graham P. Collins, MD[8]; Richard Stephens, MA[9]; Francesco Cucco, PhD[10]; Chulin Sha, PhD[11]; Moniek van Hoppe, PhD[2]; Reuben Tooze, PhD[12]; John R. Davies, PhD[11]; Gareth Griffiths, PhD[3]; Anna Schuh, MD[13]; Catherine Burton, MD[2]; David R. Westhead, PhD[11]; Ming-Qing Du, PhD[10]; and Peter W.M. Johnson, MD[1]

abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

The REMoDL-B phase III adaptive trial compared rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) versus R-CHOP + bortezomib (RB-CHOP) in patients with diffuse large B-cell lymphoma (DLBCL), stratified by molecular subtype. Primary analysis at a median follow-up of 30 months found no effect of bortezomib on progression-free survival (PFS) or overall survival (OS). Retrospective analysis using a gene expression–based classifier identified a molecular high-grade (MHG) group with worse outcomes. We present an updated analysis for patients successfully classified by the gene expression profile (GEP). Eligible patients were age older than 18 years with untreated DLBCL, fit enough for full-dose chemotherapy, and with adequate biopsies for GEP. Of 1,077 patients registered, 801 were identified with Activated B-Cell (ABC), Germinal Center B-cell, or MHG lymphoma. At a median follow-up of 64 months, there was no overall benefit of bortezomib on PFS or OS (5-year PFS hazard ratio [HR], 0.81; $P = .085$; OS HR, 0.86; $P = .32$). However, improved PFS and OS were seen in ABC lymphomas after RB-CHOP: 5-year OS 67% with R-CHOP versus 80% with RB-CHOP (HR, 0.58; 95% CI, 0.35 to 0.95; $P = .032$). Five-year PFS was higher in MHG lymphomas: 29% versus 55% (HR, 0.46; 95% CI, 0.26 to 0.84). Patients with ABC and MHG DLBCL may benefit from the addition of bortezomib to R-CHOP in initial therapy.

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INTRODUCTION

Molecular heterogeneity is a recognized feature of diffuse large B-cell lymphoma (DLBCL), with varying outcomes among karyotypic, genomic, and transcriptomic subtypes.[1-4] Clinical trials have tested whether additional targeted therapies might improve outcomes, by modulating aberrant intracellular pathways in malignant B cells.[5-7] The REMoDL-B trial compared rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) versus R-CHOP + bortezomib (RB-CHOP) in patients with newly diagnosed DLBCL. Primary analysis at a median follow-up of 30 months found no difference in progression-free survival (PFS) between the two treatment arms (hazard ratio [HR], 0.86; 95% CI, 0.65 to 1.13).[8] Subsequent analysis of biopsies using a gene expression–based classifier identified a more aggressive subtype (molecular high-grade [MHG]) characterized by a proliferative phenotype closely related to centroblasts, which showed a trend toward therapeutic benefit from bortezomib (PFS HR, 0.58; 95% CI, 0.31 to 1.07).[9]

This article updates the trial results after the full 5-year follow-up of all patients whose lymphomas were successfully classified by gene expression profile (GEP).

METHODS

Details of the REMoDL-B design and primary analysis have been published.[8] REMoDL-B was an open-label randomized phase III adaptive trial, which recruited from centers in the United Kingdom and Switzerland. Participants had DLBCL with sufficient diagnostic material from initial biopsies for GEP and pathology review; were age 18 years or older; had an Eastern Cooperative Oncology Group performance status of ≤2; bulky stage I or stage II–IV disease; measurable disease, and cardiac, lung, renal, and liver function sufficient to tolerate full-dose chemotherapy.

ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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TABLE 1. Baseline Characteristics of the Participants by Treatment Group

Characteristic	R-CHOP[a] (n = 407)	RB-CHOP (n = 394)
Age, years, median (range)	65 (24-86)	63 (20-84)
Sex, No. (%)		
Male	229 (56.3)	216 (54.8)
Female	178 (43.7)	178 (45.2)
ECOG performance status,[b] No. (%)		
0	219 (55.9)	192 (50.8)
1	125 (31.9)	141 (37.3)
2	48 (12.2)	45 (11.9)
Missing	15 (3.7)	16 (4.1)
Bone marrow involvement,[c] No. (%)		
Yes	67 (16.7)	45 (11.7)
No	334 (83.3)	339 (88.3)
Missing	6 (8.2)	10 (18.2)
Serum LDH level, No. (%)		
>ULN	195 (58.7)	191 (61.2)
≤ULN	137 (41.3)	121 (38.8)
Missing	75 (18.4)	82 (20.8)
IPI score,[d] No. (%)		
Low (0-1)	110 (27.0)	106 (26.9)
Low intermediate (2)	101 (24.8)	105 (26.6)
High intermediate (3)	125 (30.7)	114 (28.9)
High (4-5)	71 (17.4)	69 (17.5)
Stage, No. (%)		
I	11 (2.7)	13 (3.3)
II	119 (29.4)	114 (29.1)
III	117 (28.9)	128 (32.7)
IV	158 (39.0)	137 (34.9)
Missing	2 (0.5)	2 (0.5)
Bulk >10 cm, No. (%)		
Yes	111 (27.5)	120 (31.1)
No	293 (72.5)	266 (68.9)
Missing	3 (0.7)	8 (2.0)
Maximum tumor diameter, cm, No. (%)		
0-5	182 (45.0)	164 (42.5)
>5-10	111 (27.5)	102 (26.4)
>10	111 (27.5)	120 (31.1)
Missing	3 (0.7)	8 (2.0)
Molecular phenotype[a]		
ABC	125 (30.7)	124 (31.5)
GCB	240 (59.0)	229 (58.1)
MHG	42 (10.3)	41 (10.4)

Abbreviations: ABC, activated B cell; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MHG, molecular high grade; RB-CHOP, rituximab, bortezomib, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; ULN, upper limit of normal.

[a]Includes eight nonrandomized patients who were able to be retrospectively classified (see the Methods section).

[b]See Appendix 3 in protocol for the ECOG, Performance Status descriptions.

[c]Denominator is the number of patients with bone marrow involvement.

[d]See Appendix 4 in protocol for the IPI, Score descriptions.

All patients received R-CHOP for one cycle and were randomly assigned to R-CHOP or R-CHOP + bortezomib for cycles 2-6, stratified by International Prognostic Index (IPI) and cell of origin (COO), determined by GEP. Biopsies were analyzed by fluorescence in situ hybridization for *MYC*, *BCL2*, and *BCL6* rearrangements and by targeted genomic analysis using enrichment of 70 genes recurrently mutated in lymphomas by customized HaloPlex HS probe library (Agilent Technologies, Santa Clara, CA).

Whole-genome GEP was performed on mRNA extracted from diagnostic tissue by Illumina DASL array (Cambridge, UK). Classification in the trial was by DLBCL automatic classifier[10] in real time. Biopsies were categorized as activated B-cell (ABC), germinal center B-cell (GCB), or unclassifiable—the MHG group was not characterized at initial implementation. The COO classification was also analyzed retrospectively, with improved data normalization over the complete trial data set to classify patients as ABC, GCB, MHG, or unclassifiable. The analysis of results with extended follow-up prespecified these subgroups, for consistency with the previous paper identifying the MHG group.[9] All patients were followed for 5 years after treatment ended. This trial is registered with ClinicalTrials.gov identifier: NCT01324596.

The primary end point was PFS. The sample size calculation of the trial has been previously reported.[1] All analyses followed a prespecified statistical analysis plan. Time-to-event analyses by trial arm were summarized using the Kaplan-Meier method and Cox regression modeling (including IPI and where applicable COO), both overall and within the subgroups. 95% confidence intervals for HR for the treatment effect were estimated from the Cox model and a two-sided P value of $<$ .05 used to define statistical significance. To assess for differences in treatment effect by subgroups, heterogeneity and interaction tests were performed. No adjustment for multiple testing was performed. We used Stata statistical software v17 and SAS v9.4 (College Station, TX) for all analyses.

RESULTS

Survival Outcomes According to Molecular Subtype

In the trial, 1,129 patients were registered between June 2011 and June 2015. Of these, 1,077 underwent GEP, with 801 retrospectively classified as ABC, GCB, or MHG. 407 were randomly assigned to R-CHOP, and 394 to RB-CHOP, an increase of 82 from the 719 classified prospectively for random assignment as ABC or GCB. Seventy-eight of 199 biopsies assessed as unclassifiable at random assignment could be allocated to ABC, GCB, or MHG. Five of 719 allocated to ABC or GCB prospectively could not be classified retrospectively. Eight of 15 who had initially unsuccessful GEP could be allocated as ABC, GCB, or MHG. One GCB patient randomly assigned to RB-CHOP had not provided data for primary analysis but provided data for the long-term follow-up. Full details of prospective and retrospective classifications are provided in the Data Supplement (online only).[9]

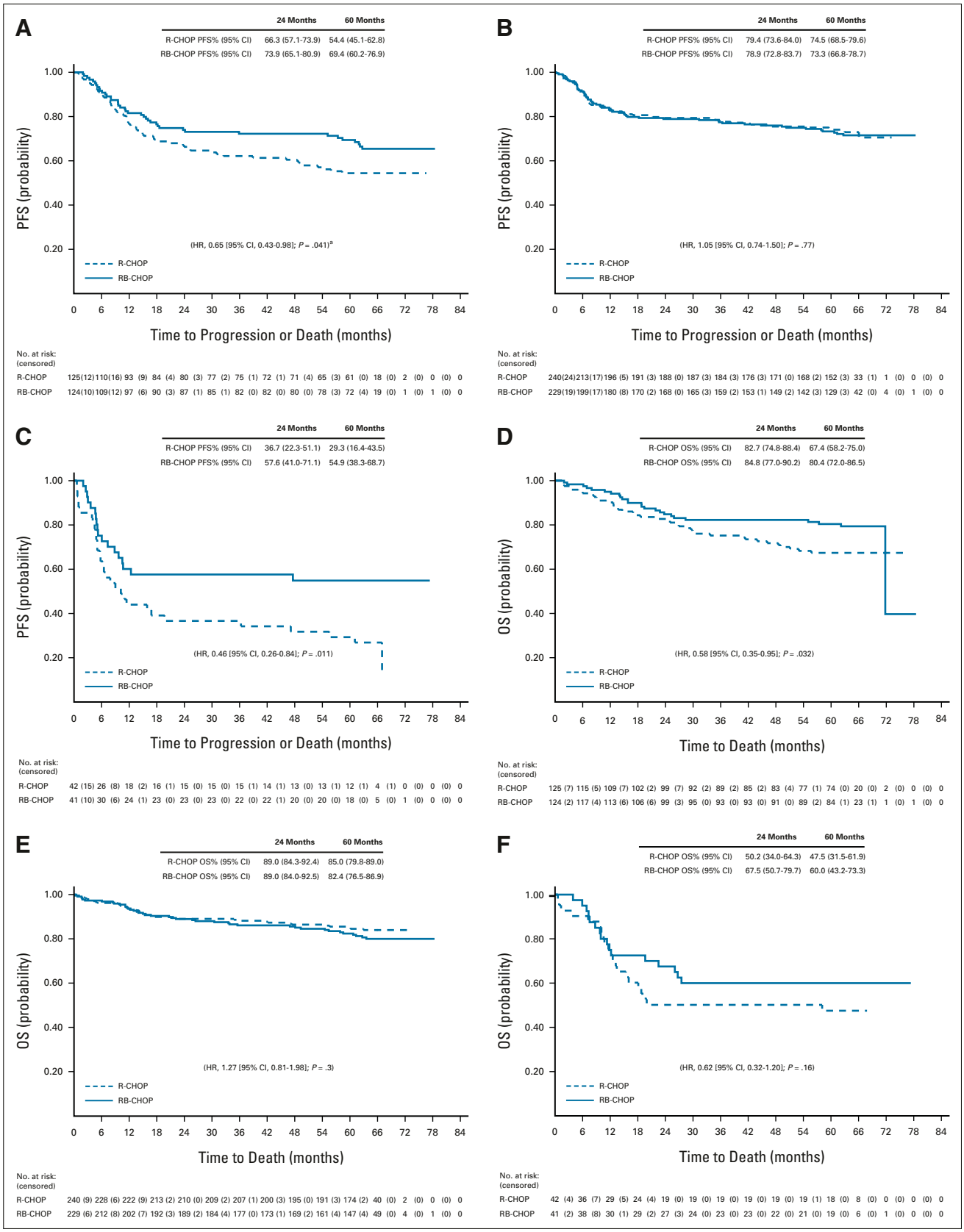

FIG 1. PFS and OS by arm and molecular profile group. (A) PFS of ABC patients, (B) PFS of GCB patients, (C) PFS of MHG patients, (D) OS of ABC patients, (E) OS of GCB patients, and (F) OS of MHG patients. HRs presented in this figure are from the Cox regression model adjusted for IPI score (low 0-1, intermediate 2-3, and high 4-5 used for analysis). [a]There was some evidence of nonproportional hazards for the high (continued on following page)

FIG 1. (Continued). IPI group adjusted for within this Cox model. Therefore, a restricted mean survival time regression analysis was also performed adjusting for IPI. The estimated RMST for RB-CHOP from this was 45.9 months and 39.4 months for R-CHOP (RMST difference of 5.9 months; 95% CI, 0.1 to 11.8; $P = .0463$). ABC, activated B-cell; GCB, germinal center B-cell; HR, hazard ratio; IPI, international prognostic index; MHG, molecular high grade; OS, overall survival; PFS, progression-free survival; RB-CHOP, rituximab, bortezomib, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; RMST, restricted mean survival time.

Baseline characteristics of the patients were well-balanced (Table 1).

At a median follow-up of 64 months for survivors, there was no overall benefit of bortezomib in PFS or OS among all the successfully classified patients (Data Supplement).

Improved PFS was seen with bortezomib in MHG and ABC lymphomas. With additional follow-up, 95 patients with ABC lymphoma have progressed or died, an increase of 22 (13 after R-CHOP and nine after RB-CHOP) from the previous report, resulting in a 60-month PFS of 54.4% (95% CI, 45.1 to 62.8) after R-CHOP versus 69.4% (95% CI, 60.2 to 76.9) after RB-CHOP (HR, 0.65; 95% CI, 0.43 to 0.98; Fig 1A). Six patients with MHG lymphomas have progressed since the previous analysis (five after R-CHOP and one after RB-CHOP), leading to a 60-month PFS of 29.3% (95% CI, 16.4 to 43.5) after R-CHOP versus 54.9% (95% CI, 38.3 to 68.7) after RB-CHOP (HR, 0.46; 95% CI, 0.26 to 0.84; Fig 1C).

A 60-month OS advantage was seen in the ABC group. Sixty-four of 249 patients with ABC lymphomas have died (21 more than the previous analysis: 15 after R-CHOP and six after RB-CHOP, Data Supplement), leading to a 60-month OS of 67.4% (95% CI, 58.2 to 75.0) after R-CHOP versus 80.4% (95% CI, 72.0 to 86.5) after RB-CHOP (HR, 0.58; 95% CI, 0.35 to 0.95; Fig 1D). Thirty-seven of 83 patients with MHG lymphomas have died (four more, two on each arm), leading to a 60-month OS of 47.5% (95% CI, 31.5 to 61.9) after R-CHOP versus 60.0% (95% CI, 43.2 to 73.3) after RB-CHOP (HR, 0.62; 95% CI, 0.32 to 1.20; Fig 1F).

No PFS or OS difference was observed in the GCB group according to the treatment arm (Figs 1B and 1E). There was a small increase in lymphoma-related deaths in the group treated with RB-CHOP (27 [21.8%] *v* 18 [14.4%]; Data Supplement).

Subgroups characterized by double-hit cytogenetics, with *MYC* and *BCL2* translocation, and by high levels of *MYC*

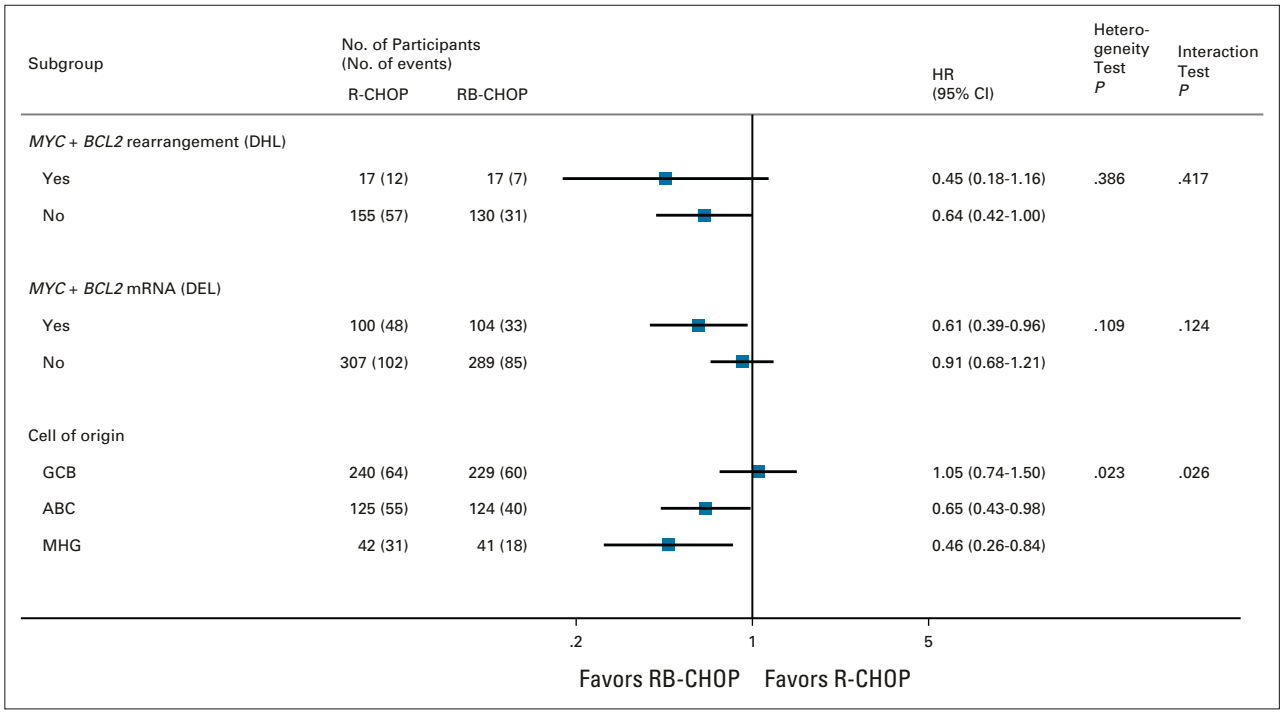

FIG 2. Forest plot of HRs on the basis of PFS for participants at high risk and with different molecular subtypes of disease, by treatment group (all patients who were successfully retrospectively classified, n = 801). Data are for all randomly assigned participants who were successfully retrospectively classified. HRs and *P* values are effect estimates from a multivariable model adjusted for IPI score. ABC, activated B-cell; DEL, dual-expressor lymphoma; DHL, double-hit lymphoma; GCB, germinal center B-cell; HR, hazard ratio; IPI, international prognostic index; MHG, molecular high-grade; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; RB-CHOP, rituximab, bortezomib, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

and *BCL2* mRNA showed similar PFS results to those previously reported (Fig 2). Those with high *MYC* and *BCL2* mRNA show an increase in PFS with RB-CHOP (HR, 0.61; 95% CI, 0.39 to 0.96). Four hundred patients could be retrospectively analyzed using the LymphGen algorithm[11] although 179 (45%) of these could not be classified (Data Supplement). There was no clear difference in outcomes by treatment arm in any LymphGen subgroup (Data Supplement).

Adverse Events and Second Cancers

Adverse events were similar to those reported previously.[8] The addition of bortezomib was well-tolerated (Data Supplement). RB-CHOP was not associated with increased hematologic toxicity, and 398 (87.1%) of 459 participants assigned to RB-CHOP completed six cycles of treatment. Neuropathy of any grade was more common after RB-CHOP, but grade 3 or worse neuropathy was reported in 17 (3.8%) patients who were given RB-CHOP versus 10 (2.2%) who were given R-CHOP. Serious adverse events occurred in 190 (42.5%) patients who were given R-CHOP, including five treatment-related deaths, and 225 (50.7%) who were given RB-CHOP, including four treatment-related deaths.

Of 1,041 patients included in safety analyses, there were 20 second cancers reported, 14 after R-CHOP (2.3%) and six after RB-CHOP (1.4%; see the Data Supplement).

DISCUSSION

This study confirms that different molecular subtypes of DLBCL exhibit different responses to bortezomib when given in combination with R-CHOP and specifically that the ABC and MHG subtypes show improvements in PFS after the addition of bortezomib, which is also reflected in improved OS for the ABC group (60-month PFS difference 15%; OS difference 13%). Conversely, no such effect was seen in the GCB group. Targeting of constitutive NFkB pathway activation provides a potential explanation for the effect of bortezomib in ABC-DLBCL. However, this mechanism is unlikely to explain the effect in MHG. An alternate explanation for the therapeutic effect across these disparate subtypes may lie in *MYC*-driven proteotoxic stress, rendering cells sensitive to bortezomib-mediated proteasome inhibition.

This is one of the largest studies conducted in DLBCL using GEP in real time for stratified random assignment. However, the proportion of MHG lymphoma in DLBCL is relatively small (approximately 10%), with the result that even in this trial, only 83 cases were identified, limiting the ability to detect important differences in survival.

With mature follow-up, this study suggests a benefit from the addition of bortezomib to R-CHOP for ABC and MHG subtypes of DLBCL. Ideally, this should be confirmed in a prospective trial, with a more potent proteasome inhibitor carrying less risk of additive neurotoxicity.

AFFILIATIONS

[1]School of Cancer Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom
[2]Haematological Malignancy Diagnostic Service, Leeds Cancer Centre, Leeds Teaching Hospitals, Leeds, United Kingdom
[3]Southampton Clinical Trials Unit, University of Southampton, Southampton, United Kingdom
[4]Cantonal Hospital Aarau, Aarau, Switzerland
[5]Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[6]Department of Haematology, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom
[7]Department of Haematology, Guy's and St Thomas's Hospitals NHS Trust, Kings Health Partners, London, United Kingdom
[8]Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford, United Kingdom
[9]National Cancer Research Institute Consumer Forum, London, United Kingdom
[10]Department of Pathology, University of Cambridge, Cambridge, United Kingdom
[11]School of Molecular and Cellular Biology, Faculty of Biological Sciences, University of Leeds, Leeds, United Kingdom
[12]Section of Experimental Haematology, University of Leeds, Leeds, United Kingdom
[13]Department of Oncology, University of Oxford, Oxford, United Kingdom

CORRESPONDING AUTHOR

Peter W.M. Johnson, MD, Cancer Immunology, Building MP217, Southampton General Hospital, Southampton SO16 6YD, United Kingdom; Twitter: @pwmjohnson; e-mail: johnsonp@soton.ac.uk.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Individual participant data will be made available, including data dictionaries, for approved data sharing requests. Individual participant data will be shared that underlie the results reported in this article, after deidentification and normalization of information (text, tables, figures, and appendices). The statistical analysis plan will be provided upon request. Anonymized data will be available beginning 3 months after and

ending 5 years after publication of this article to researchers who provide a completed Data Sharing Agreement that describes a methodologically sound proposal for the purpose of the approved proposal. Proposals should be directed to ctu@soton.ac.uk. Data will be shared once all relevant parties approve and sign the Data Sharing Agreement. Data sharing requests are available for 5 years via the Southampton Clinical Trials Unit website.

AUTHOR CONTRIBUTIONS

Conception and design: Andrew J. Davies, Louise Stanton, Richard Stephens, Peter W.M. Johnson
Financial support: Ming-Qing Du
Administrative support: Josh Caddy
Provision of study materials or patients: Andrew J. Davies, Urban Novak, Graham P. Collins, Peter W.M. Johnson
Collection and assembly of data: Andrew J. Davies, Sharon Barrans, Louise Stanton, Josh Caddy, Christoph Mamot, Andrew McMillan, Graham P. Collins, Moniek van Hoppe, Catherine Burton, Ming-Qing Du, Peter W.M. Johnson
Data analysis and interpretation: Andrew J. Davies, Louise Stanton, Sam Wilding, Geoff Saunders, Urban Novak, Andrew McMillan, Paul Fields, Graham P. Collins, Francesco Cucco, Chulin Sha, Reuben Tooze, John R. Davies, Gareth Griffiths, Anna Schuh, David R. Westhead, Ming-Qing Du, Peter W.M. Johnson
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Andrew J. Davies
Honoraria: Gilead Sciences, Kite, a Gilead company, AbbVie, Incyte, Roche, Celgene/Bristol Myers Squibb, Genmab, AstraZeneca
Consulting or Advisory Role: Gilead Sciences, Roche, Acerta Pharma, Kite, a Gilead company, Janssen, Celgene, Regeneron, AbbVie
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Travel, Accommodations, Expenses: Roche

Urban Novak
Consulting or Advisory Role: Roche, Gilead Sciences, Celgene, Takeda, AstraZeneca
Travel, Accommodations, Expenses: Celgene, Takeda, Amgen, Roche

Andrew McMillan
Honoraria: Roche/Genentech, Amgen, Protherics, Takeda
Consulting or Advisory Role: Amgen
Speakers' Bureau: Roche/Genentech
Research Funding: Pfizer, Roche/Genentech (Inst)
Travel, Accommodations, Expenses: Takeda
Uncompensated Relationships: Kite/Gilead
Uncompensated Relationships: Novartis

Graham P. Collins
Honoraria: Roche, Takeda, Gilead Sciences, Pfizer, Novartis, Daiichi Sankyo, Incyte, Celleron Therapeutics, MSD Oncology, BeiGene, ADC Therapeutics, AstraZeneca
Consulting or Advisory Role: Roche, Takeda, Incyte, Pfizer, MSD, Celgene, BeiGene, Daiichi Sankyo, Celleron Therapeutics, ADC Therapeutics
Speakers' Bureau: Roche, Takeda, Novartis, Gilead Sciences
Research Funding: MSD Oncology (Inst), Celgene (Inst), BMS (Inst), Amgen (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Roche, Takeda

Moniek van Hoppe
Employment: Leeds Teaching Hospitals NHS Trust

Reuben Tooze
Honoraria: Roche, Celgene
Consulting or Advisory Role: Medicxi
Research Funding: UCB
Travel, Accommodations, Expenses: Celgene

Gareth Griffiths
Honoraria: AstraZeneca, AbbVie
Research Funding: AstraZeneca (Inst), Astex Pharmaceuticals (Inst), Bristol Myers Squibb (Inst), Jansen-Cilag (Inst), Novartis (Inst), Roche (Inst), HeartFlow (Inst), BioNTech (Inst), GlaxoSmithKline (Inst), HeartFlow (Inst)

Anna Schuh
Stock and Other Ownership Interests: Illumina, SERENOx
Consulting or Advisory Role: AbbVie, Roche, Janssen, AstraZeneca
Research Funding: Johnson & Johnson, Illumina (Inst), Oxford Nanopore Technologies (Inst)
Travel, Accommodations, Expenses: AbbVie, Janssen Oncology

Catherine Burton
Honoraria: Takeda, Roche
Consulting or Advisory Role: Celgene, Bristol Myers Squibb
Speakers' Bureau: Roche, Celgene
Travel, Accommodations, Expenses: Takeda Science Foundation

Ming-Qing Du
Employment: GlaxoSmithKline

Peter W.M. Johnson
Honoraria: Epizyme, InCyte
Consulting or Advisory Role: Epizyme
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