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Ibrutinib- and bortezomib-extended R-CHOP induction in elderly higher-risk patients newly diagnosed with diffuse large B-cell lymphoma – first analysis of toxicity and efficacy signals

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Abstract

Diffuse large-cell B-cell lymphoma (DLBCL) is the most common lymphoid malignancy. About 30-40% of the patients will not be cured by standard Rituximab (R)-CHOP-like immune-chemotherapy, and many of them experience relapse and eventually succumb to their disease. Enhancing first-line efficacy in patients at higher risk, among them many elderly, is key to improve long-term outcomes. Numerous attempts to combine R-CHOP with targeted agents failed in large randomized phase III trials. The addition of Ibrutinib enhanced survival in younger patients, but increased toxicity across all age groups, especially in the elderly. Older DLBCL patients impose particular challenges, since they often present with more advanced disease, and exhibit treatment-relevant comorbidities. ImbruVeRCHOP trial aims at identifying patients who need that benefit from rationally augmented first-line regimens without experiencing overt toxicity and detecting their molecular signatures of response. This first analysis presents encouraging feasibility, safety, and preliminary response data in elderly high-risk DLBCL patients.

Keywords

Lymphoma and Hodgkin disease; biomarker; diffuse large B-cell lymphoma; novel study design; prediction; targeted therapy.

Introduction

About one-third of the patients diagnosed with diffuse large B-cell lymphoma (DLBCL) is refractory to or will relapse after standard Rituximab (R) plus CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) induction, and many of the failing patients do not lastingly benefit from modern next-line treatments [1–3]. Over the last decades, alternative regimens, and, in particular, 'R-CHOP plus X' extensions lined up to outperform the standard of care – either in so-called 'all-comer' settings of nonselected newly diagnosed patients, or predetermined subgroups, often defined by the presumed cell-of-origin (COO), that is, the germinal center B-cell (GCB)- or the activated B-cell (ABC)-subtype, with the latter known to experience inferior long-term outcome to R-CHOP [4]. Despite promising signals from relapsed or refractory (R/R) settings or earlier-phase first-line studies, numerous randomized phase III trials aiming to improve R-CHOP efficacy by additional or alternative therapeutic agents – namely the more intense B-ALL/NHL 2002 GMALL protocol, the anti-CD20 antibody Obinutuzumab, the chemotherapeutic agent Etoposide, the vascular endothelial growth factor (VEGF) inhibitor Bevacizumab, the immunomodulatory drug Lenalidomide, the proteasome blocker Bortezomib or the Bruton's Tyrosine Kinase (BTK) inhibitor Ibrutinib – produced negative results [5–12]. While the Bortezomib extension failed to prolong progression-free survival (PFS) in the REMoDL-B trial [7], R-CHOP plus Ibrutinib produced

significantly superior PFS and overall survival (OS) in patients younger than 60 years according to a post-hoc age group analysis in the PHOENIX study [12]. The trial formally failed because of overt toxicity, potentially due to a relatively high daily Ibrutinib dose, and poor R-CHOP dose adherence across all age groups, particularly in the elderly subpopulation. Notably, prophylactic co-therapeutics were not mandatory, and their limited use especially in older patients might explain to some extent these mixed results in PHOENIX. Moreover, although set out as a 'Non-GCB' trial, transcriptome-based re-evaluation of the immunohistochemically obtained COO status leading to a substantial re-classification of participating patients as GCB unveiled that the Ibrutinib benefit seen in the younger population was largely independent of the COO subtype [12].

The lasting efficacy of targeted therapeutics is often hindered by rapidly emerging signaling-specific resistance mechanisms. Combination therapies that inhibit two mediators in a linear fashion, as exploited, for instance, with the BRAF/MEK double blockade in melanoma [13], might counter this problem. We reasoned that a proximal/distal co-targeting strategy at the B-cell receptor (BCR)/NF-jB cascade, considered a key survival backbone of DLBCL [14], may be a promising addition to R-CHOP induction, especially if flanked with a strategy to identify molecular markers of response. With this intent, we launched the ImbruVeRCHOP phase I/II trial – Ibrutinib (Imbruvica®), Bortezomib (Velcade®) plus R-CHOP – and report here a first interim analysis, indicating that this extended regimen can be safely administered to an elderly patient population with very encouraging early signals of lasting lymphoma control.

Materials and methods

Trial design and treatment

The ImbruVeRCHOP trial exploits a four-modality regimen consisting of a signaling inhibitor (i.e. Ibrutinib), a biological (i.e. Bortezomib), an immune therapeutic (i.e. Rituximab), and conventional chemotherapy (i.e. CHOP). The innovative design not only refers to the first-in-human proximal (i.e. at the BTK) and distal (i.e. at the IjBa-degrading proteasome) co-targeting of the BCR/NF-jB-pathway with two different small compounds in addition to the R-CHOP backbone, but also to the in-depth molecular characterization of the lymphoma prior to, acutely under first-time drug encounter in the cycle (C) one (C1), and, in case of a residual mass that is technically well accessible for computed tomography (CT)- or ultrasound-guided rebiopsy, once again at the time of interim CT imaging prior to C3. CT imaging was selected as a response assessment because of its universal availability at all trial sites at the time of protocol approval. Moreover, flanking blood-based liquid biopsies provide additional genomic and proteomic information in the course of therapy [15]. The primary endpoint is the 2-year PFS. Secondary endpoints include the predictive power of COO subtypes, assessment of minimal residual disease by plasma-based circulating tumor DNA (ctDNA) over time, and multi-omics-retrieved gene signatures that discriminate responders from non-responders in this study. Moreover, mice harboring xenografts derived from study-enrolled patients exposed to a combination or singular components of the ImbruVeRCHOP drug regimen allow further functional and molecular analyses of effector mechanisms, for example, cellular senescence. The trial is designed as a multi-center, single-arm, open-label phase I/II study, and actively recruits patients in Germany and Austria. ImbruVeRCHOP is registered under EudraCT number 2015-003429-32 and the ClinicalTrials.gov identifier NCT03129828.

The treatment protocol specifically consists of a 4-day pre-phase with Prednisone, followed by six 21-day cycles of standard immune-chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, Prednisone, and the anti-CD20 antibody Rituximab. In addition, patients receive Bortezomib (1.3mg/m2 s.c., on d3 and 8 in C1 and d1 and d8 in C2–6) and Ibrutinib (420mg daily p.o. from C1–6, starting on day 6 in C1), plus two additional cycles of Rituximab as inaugurated by the RICOVER-60 trial for this age group [16] (Figure 1(A)). Quadruple prophylaxis consisting of highly recommended antibiotic, antiviral, as well as Pneumocystis jirovecii prophylaxes, and mandatory G-CSF growth factor support accompanies the specific anti-lymphoma regime. Of note, according to the initial study protocol, Ibrutinib was dosed at 560mg daily, and applied as such to eight patients, before it was amended to 420mg as a company-requested safety precaution based on data from the PHOENIX trial and a potential link to fungal infections in other settings when administered in combination with high-dose corticosteroids. After the safety run-in phase I of the trial was completed with the first 13 patients enrolled, and no signs of overt toxicity or inadequate efficacy were observed, the Data and Safety Monitoring Board (DSMB) recommended in 2019 continuation of the trial in its phase II segment.

Patients

By the end of August 2020, a total of 19 untreated ndDLBCL patients has been enrolled (Figure 1(B)). Key

eligibility criteria were age 61–80 years, an unfavorable risk profile according to the International Prognostic Index score (IPI ≥ 2) as well as a good performance status (ECOG) 0–2. Patients with lymphoma involvement of the central nervous system or preexisting polyneuropathy > grade 1 were not eligible. The full listing of inclusion and exclusion criteria can be found in the study registration and trial protocol respectively [15]. The sex distribution is balanced, and about two thirds presented with stage III/IV disease. One of the 19 patients dropped out to receive further treatment elsewhere because of relocation. Two patients were just enrolled and started treatment shortly before the data cut for this analysis, hence, no interim staging data of those two are available at this time point. Per protocol safety evaluation is based on specified clinical assessments including physical examination, laboratory tests, and functional diagnostics prior to, during, and after treatment at determined time points. Documentation and reporting of Adverse Events (AE), Serious Adverse Events (SAE), and Suspected Unexpected Serious Adverse Reactions (SUSAR) is carried out according to International Conference on Harmonization – Good Clinical Practice guidelines (IHC-GCP). Adverse Events are categorized and graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Statistical analysis

We defined the efficacy of the ImbruVeRCHOP regimen to be considered unacceptable if ☐60% of the patients are progression-free at 2 years. This mark was chosen based on the outcome of comparable elderly DLBCL patient populations treated with R-CHOP in two large randomized phase III trials (the RICOVER-60 trial of the German study group DSHNHL [16], and the LNH98-5 trial conducted by the French study group GELA [17]), and a trial design used in an explorative early-phase Bortezomib-R-CHOP trial of similar size [18]. Patients prematurely dropping out of the study (e.g. due to intolerable toxicities) will be followed for the status of the primary endpoint and included in the analyses if they completed at least the first cycle. Survival analyses will be depicted as Swimmer Plot (and with more patients enrolled and longer follow-up in Kaplan–Meier curves), and statistical analyses to identify differences between relevant subgroups will be performed using the Log-Rank/Mantel-Cox test. The adverse reactions are listed in groups, separately for hematological and non-hematological toxicities, according to their severity and frequency.

Results

Safety

Of the 19 patients enrolled at the time of data collection, 16 were evaluable for safety analysis. Hematologic and non-hematologic toxicities are listed by severity grade 3 and above, according to CTCAE (Table 1). In total, 55 grade 3 adverse events and 17 grade 4 adverse events occurred. The percentage of the total number of adverse events is indicated for each toxicity. Most common were lowered hematologic parameters. Hyperuricemia was the sole nonhematologic grade 3 side effect that occurred with more than 3 events; no grade 4 non-hematologic toxicities were noted.
Anticipated toxicities in the combination of Ibrutinib and Bortezomib with R-CHOP were atrial fibrillation (AF), peripheral polyneuropathy (PNP), and bleeding events. However, these toxicity events occurred much less frequently than observed in comparable age groups diagnosed with chronic lymphocytic leukemia or multiple myeloma, and being treated with Ibrutinib or Bortezomib, respectively [19,20]). Atrial fibrillation occurred in only 2 of 16 patients, and no bleeding events of grade 3 or greater were seen. For the two AF patients, electrical cardioversion was successful, and temporary anticoagulation was initiated. Ibrutinib administration was paused in one AF patient, and in the second patient, AF occurred 1 month after the last dose, thus, no dose reduction with Ibrutinib was necessary. PNP was observed in 3 of 16 patients, which led to dose reductions of Bortezomib in two cases. In one patient, Bortezomib was paused because of thrombocytopenia and later applied at a lowered dose. Ibrutinib dosing was reduced or temporarily paused in a total of six patients in response to thrombocytopenia, pleural effusion, after a fall incident, dizziness, nausea, ecchymoses, and a rash (see Table 2). Overall, dose reductions were rarely needed, and followed a hierarchical algorithm to preserve, if anyhow possible, full dosing of the R-CHP standard of care. Hematological impairment primarily prompted Ibrutinib dose adaptation, while polyneuropathic affection triggered a dose reduction of Vincristine alone or in conjunction with Bortezomib. As a per-protocol safety precaution, Ibrutinib treatment was short-time-interrupted in all patients who received a re-biopsy in cycle 3, for minor procedures and when prophylactic CNS treatment with Methotrexate was administered (i.e. 3 days prior to and 3 days after the intervention). One grade 5 toxicity occurred due to pneumonia. This patient achieved a complete remission, which was ongoing at the last follow-up visit 26months after the end of therapy. One month later, the patient was hospitalized because of pneumonia. A therapy-associated acute myeloid leukemia (tAML) was diagnosed, from which this patient died in the course of treatment.

Two SUSAR were reported, one of them reflecting an unconfirmed potential colon perforation with no need of surgical intervention and full recovery of the abdominal symptoms, the other a pleural effusion. Importantly, treatment adherence was very high among the 16 evaluable patients, with no component of the regimen being dosed less than 96% of the per-protocol-planned dose.

<u>Treatment responses</u>

Of the 19 patients enrolled at the time of data collection, 16 were evaluable for response analysis with a median follow-up of 13months (range 0–31 months). Eight patients achieved a complete remission (CR) and eight patients a partial remission (PR) as their best response according to CT-based revised response criteria for malignant lymphoma [21]. At the end of treatment (EOT), six patients were in CR and nine patients in PR, accounting for 15/16 or 94% overall response rate (ORR) at EOT. Three PR patients converted later to a CR according to radiologic response criteria during follow-up – presumably explained by the progressive resolution of an associated immune infiltration at non-active residual lymphoma sites. All but one (i.e. 8/9) patients with a CR and all but one (i.e. 6/7) patients with a PR as their best response remain in these respective categories in ongoing remissions [21] (see Figure 2). Two patients experienced a disease recurrence. So far, two patients have died; one due to complications under lymphoma salvage therapy, the other while undergoing anti-leukemia therapy after being diagnosed with tAML. One patient was subjected to second-line salvage immune-chemotherapy followed by high-dose chemotherapy with autologous stem cell support and remains in remission ever since.

Discussion

According to this interim analysis, the extension of standard-dose R-CHOP by the novel combination of two additional agents, Ibrutinib and Bortezomib, appeared to be feasible for elderly DLBCL patients being at an increased risk of poor lymphoma long-term control (IPI ≥ 2). With a median follow-up of 13 months and based on 16 DLBCL patients included in this analysis, the ImbruVeRCHOP regimen not only presents with a quite moderate toxicity profile but also an excellent ORR of currently 94% at EOT. This ORR compares favorably to historic trials such as the '6x R-CHOP + 2x R' arm of the RICOVER-60 phase III trial for a similar elderly age group with an ORR of 84% [16] or a Bortezomib-R-CHOP phase II trial which included patients from 18 to 80 years of age and reported an ORR of 88% [18]. Notably, nearly all CR/PR patients of the ImbruVeRCHOP cohort remain in ongoing remissions. Since the ImbruVeRCHOP trial was set out to address response according to the revised response criteria for malignant lymphoma from 2007 by CT scan only [21], no metabolic assessment by positron emission tomography (PET) is carried out as a mandatory component of the study protocol. With this in mind, the high fraction of patients in durable PR – and unknown metabolic response state – underscores further the profound disease control beyond CR patients achieved by this novel regimen. If PET scanning would have been a compulsory component of the protocol, the CR rate would most likely be higher than concluded from sole CT assessment.
Up to date, evidence for more intense protocols and targeted treatment additions remains inconclusive. Current phase III trials failed to improve the survival of the entire study population by adding either Ibrutinib or Bortezomib to the R-CHOP backbone. In the PHOENIX trial, the R-CHOP plus Ibrutinib arm produced significantly superior PFS and OS in patients younger than 60 years of age, whereas patients above 60 missed realizing an Ibrutinib benefit [12]. Less stringent North American guidelines regarding anti-infective prophylaxes in the elderly compared to Europe [22] might have contributed to poor R-CHOP dose adherence and the inability to receive at least 6 cycles of R-CHOP especially in the Ibrutinib arm, actually dropping below 75% of the planned R-CHOP medication [12], which, as shown in other contexts, is associated with decreased survival [23–25]. Consistent with our findings, several trials demonstrated that patients within the range of 61–80 years may indeed tolerate a fully dosed R-CHOP induction with excellent results (GELA LNH-98-5 [17], RICOVER-60 [2], UK NCRI RCHOP14v21 [26]). An elderly-selective combined analysis across the two latter trials further backed our approach to treating patients up to 80 years of age with a classic R-CHOP regimen [27]. Due to limited additional and rather modest overlapping side effects, even an Ibrutinib/Bortezomib-extended version thereof may not produce critical additional toxicity, if consistently administered with anti-infective quadruple prophylaxis. Likewise, rapid lymphoma control may also reduce the risk of subsequent infectious complications in such an intrinsically more vulnerable patient population.
We purposely opened the ImbruVeRCHOP trial to all-comers, independent of the lymphoma COO assignation, whose underlying immunohistochemical algorithm is somewhat error-prone, and even its transcriptome-based re-assessment failed to mark the ABC-subtype as an exclusive responder subgroup in the PHOENIX trial. Moreover, patients with a Myc/Bcl2 doube-expessor lymphoma seemed to particularly benefit from the addition of Ibrutinib in the PHOENIX trial [28], thereby further underscoring the complex relationship between certain risk profiles and susceptibility to novel targeted approaches. Given the durable

responses observed across virtually all ImbruVeRCHOP participants presented in this interim analysis, we feel that our all-comer strategy is adequate and that molecular characteristics of benefitting patients are unlikely to primarily follow stratifiers such as the COO, which, at best, reflect biological vulnerabilities and the susceptibility of specific drug targets only indirectly.

In addition to the clinical parameters, it is worth noting that the molecular characteristics of DLBCL in elderly patients may be differently distributed or fundamentally differ from this disease in younger patients [29,30], as immune effector networks and other treatment-relevant host functions vary by age as well. Recently presented novel genomic DLBCL subsets might predict outcome more precisely and likely imply subgroup-differential treatment strategies, but such correlative evidence remains to be obtained, especially in prospective studies [31,32]. For this reason, the ImbruVeRCHOP trial includes patients in an unbiased manner and seeks to molecularly scrutinize patient individual responsiveness by up to two additional re-biopsies of their lymphoma (plus liquid biopsies) under treatment.

This innovative and informative ImbruVeRCHOP re-biopsy approach is further matched by a real-world comparator DLBCL patient cohort receiving standard R-CHOP. Based on this strategy, we seek not only to demonstrate the safety and efficacy of the Ibrutinib/Bortezomib extension to R-CHOP for elderly DLBCL patients at enhanced risk but to identify a molecular stratified that predicts benefit from such intensification in a personalized manner.

Conclusion

Overall, the ImbruVeRCHOP trial offers a double, proximal, and distal BCR/NF-jB-targeting extension by adding Ibrutinib and Bortezomib to the current R-CHOP standard treatment. This interim analysis of the ImbruVeRCHOP cohort presents an excellent response rate and durable remissions with a moderate toxicity profile. The data indicate that such extended protocol is safe and feasible in elderly DLBCL patients with a higher risk profile.

Ethical approval

Leading ethics commission: Ethics commission of the state of Berlin, Landesamt für Gesundheit und Soziales, application number: 16/0338-EK10, positive vote on 09/02/2017. Registered: EudraCT number 2015-003429-32 (31/07/2015), ClinicalTrials.gov identifier NCT03129828 (24/04/2017).

Consent to participate

Informed consent was obtained from each subject, and all procedures were performed in accordance with the Helsinki Declaration.

Consent for publication

The study participants agreed to the publication of the results along with the study enrollment.

Author contributions

The authors were involved in all content and editorial matters and were engaged in all phases of manuscript preparation and have accepted the final version. In addition, the individual authors have made the following contributions. S.D.: coordinating investigator, preparation and realization of the trial, training of the participating study centers, protocol writing, submission to authorities, contract work, local investigator, analysis of the trial results and the accompanying translational program, writing of the manuscript. A.B.: preparation of the trial, submission to authorities. I.-K.N.: local investigator, support in project preparation and realization, contribution of expertise. J.K.: protocol writing, preparation of the trial. M.F.: preparation of the trial and submission to authorities, local investigator. U.Ke., C.B., A.H., J.D., M.J., S.M., R.M., U.Kr., L.B.: local investigator, proofreading of the manuscript. C.A.S.: representative of the sponsor, principal investigator/LKP, national coordinator, preparation and supervision of the trial, submission to authorities, protocol writing, analysis of the trial results and the accompanying translational program, writing of the manuscript.

Disclosure statement

S.D., A.B., M.F., J.K., J.H., C.T., C.B., A.H., J.D., M.J., S.M., U.Kr., I.-K.N., and L.B. had no financial relationships with Janssen-Cilag during the 36 months prior to publication. R.M. participated in an Advisory board with Janssen-Cilag during the 36 months prior to publication. U.Ke. reports personal fees from

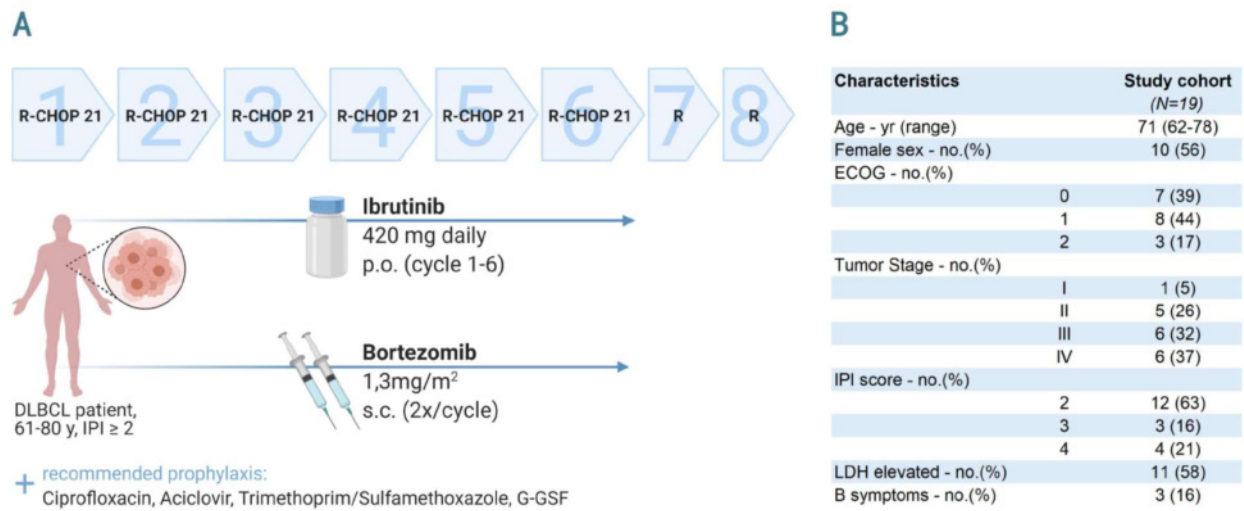## ORCID

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Ibrutinib- and bortezomib-extended R-CHOP induction in elderly higher-risk patients newly diagnosed with diffuse large B-cell lymphoma – first analysis of toxicity and efficacy signals

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R-CHOP 21 R-CHOP 21 R-CHOP 21 R-CHOP 21 R-CHOP 21 R-CHOP 21 R R

Ibrutinib
420 mg daily
p.o. (cycle 1-6)

Bortezomib
1,3mg/m² s.c. (2x/cycle)

DLBCL patient,
61-80 y, IPI ≥ 2

+ recommended prophylaxis:
Ciprofloxacin, Aciclovir, Trimethoprim/Sulfamethoxazole, G-GSF

B

Characteristics		Study cohort (N=19)
Age - yr (range)		71 (62-78)
Female sex - no.(%)		10 (56)
ECOG - no.(%)		
	0	7 (39)
	1	8 (44)
	2	3 (17)
Tumor Stage - no.(%)		
	I	1 (5)
	II	5 (26)
	III	6 (32)
	IV	6 (37)
IPI score - no.(%)		
	2	12 (63)
	3	3 (16)
	4	4 (21)
LDH elevated - no.(%)		11 (58)
B symptoms - no.(%)		3 (16)

(A) Treatment schedule of the drugs administered over time. Patients receive six 21-day cycles of Cyclophosphamide, Doxorubicin, Vincristine, Prednisone and Rituximab plus Bortezomib (1.3 mg/m² s.c., on d3 and 8 in C1 and d1 and d8 in C2-6) and Ibrutinib (420 mg daily p.o. from C1-6, starting on day 6 in C1). Cycle 7 and 8 are Rituximab only.
(B) Patient characteristics.

Abbreviations: ECOG: Eastern Cooperative Oncology Group (performance status), IPI: International Prognostic Index, LDH: lactate dehydrogenase.

Figure 1. Treatment schedule and patient characteristics. (A) Treatment schedule of the drugs administered over time. Patients receive six 21-day cycles of Cyclophosphamide, Doxorubicin, Vincristine, Prednisone and Rituximab plus Bortezomib (1.3 mg/m2 s.c., on d3 and 8 in C1 and d1 and d8 in C2-6) and Ibrutinib (420mg daily p.o. from C1-6, starting on day 6 in C1). Cycle 7 and 8 are Rituximab only. (B) Patient characteristics. Abbreviations. ECOG: Eastern Cooperative Oncology Group (performance status); IPI: International Prognostic Index; LDH: lactate dehydrogenase. The illustration was created with *BioRender.com*

Tumor Response of Study Patients by Month

Legend:
→ Ongoing treatment
● Complete Remission (CR)
◆ Partial Remission (PR)
▲ Progression
▲ Death
○ Trial Discontinuation

X-axis: Months (0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39)
Y-axis: Number of Patients (1–19)
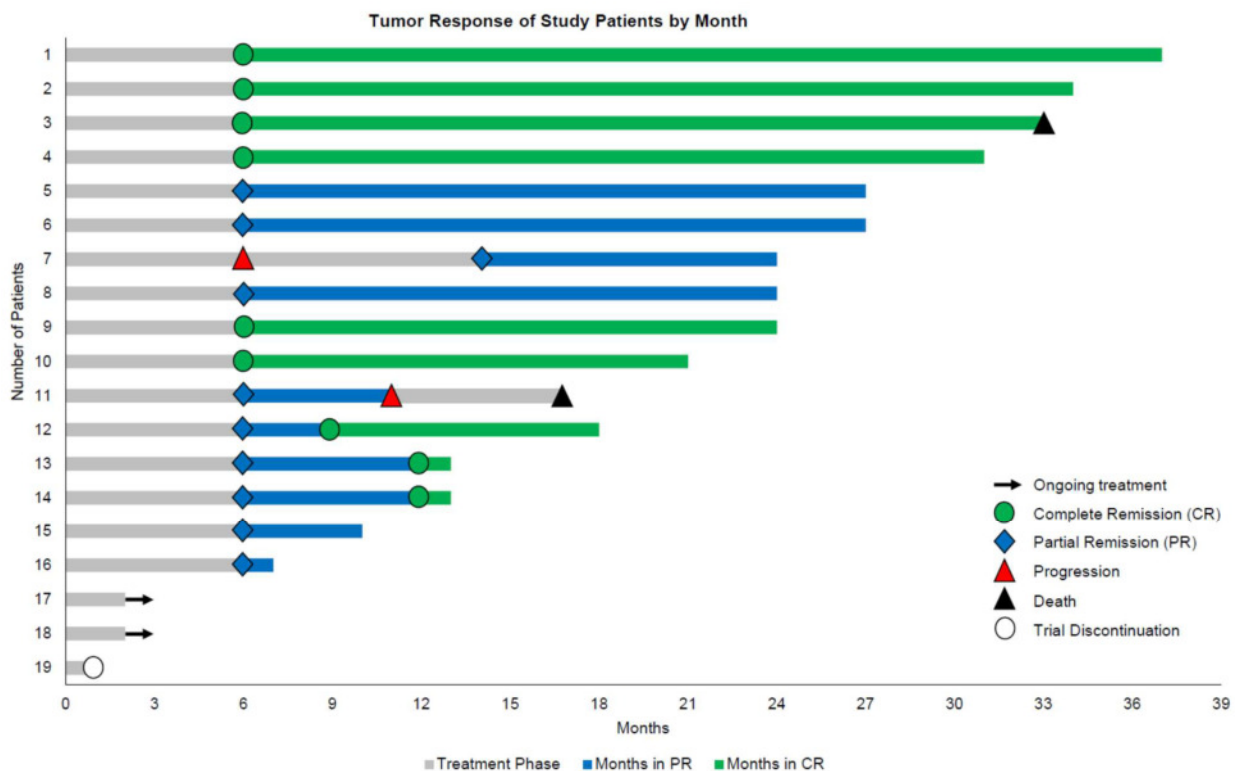
■ Treatment Phase ■ Months in PR ■ Months in CR

Figure 2. Tumor responses of study patients by month (swimmer plot). Abbreviations. CR: complete remission; PR: partial remission.

Table 1: Toxicity - Adverse Events (AE) Grade 3-5 and Serious Adverse Events (SAE)

	Adverse Events			Serious Adverse Events
	Grade 3	Grade 4	Grade 5	
	no. of events (%)			
Hematologic event				
Platelet count decreased	5 (7%)	7 (10%)	0	1 (1%)
Neutrophil count decreased	6 (8%)	5 (7%)	0	0
Lymphopenia	13 (18%)	3 (4%)	0	0
White-cell count decreased	4 (5%)	2 (3%)	0	0
Anemia	5 (7%)	0	0	0
Non-hematologic event				
Atrial fibrillation	2 (3%)	0	0	2 (3%)
Pneumonia	1 (1%)	0	1 (1%)	2 (3%)
Nausea	1 (1%)	0	0	1 (1%)
Urinary retention	1 (1%)	0	0	1 (1%)
Febrile neutropenia	1 (1%)	0	0	1 (1%)
Severe Pain	1 (1%)	0	0	1 (1%)
Suspected colonic perforation	0	0	0	1 (1%)
Fever	0	0	0	1 (1%)
Lymphoma relapse	0	0	0	1 (1%)
Pleural effusion	0	0	0	1 (1%)
Hyperuricemia	4 (5%)	0	0	0
Hypokalemia	3 (4%)	0	0	0
Clostridium difficile gastroenteritis	1 (1%)	0	0	0
Hyperglycemia	1 (1%)	0	0	0
Delayed MTX elimination	1 (1%)	0	0	0
Fatigue	1 (1%)	0	0	0
Urinary infection	1 (1%)	0	0	0
Hypertension	1 (1%)	0	0	0
Peripheral sensory neuropathy	1 (1%)	0	0	0
Syncope	1 (1%)	0	0	0
Sum of events, worst grade	55	17	1	13

Table 1 shows the number of Adverse Events (AE) Grade 3-5 and Serious Adverse Events (SAE) separated by hematologic and non-heamtologic cause.

Table 2: Dose reductions

Medication	no. of patients	Reason for dose reduction (in no. of patients)
Ibrutinib	6	Thrombocytopenia (2), pleural effusion (1), fall incident (1), dizziness (1), rash (1), ecchymoses (1), nausea (1)
Bortezomib	2	Polyneuropathy (2), thrombocytopenia (1)
Rituximab	0	
Cyclophosphamide	0	
Doxorubicin	0	
Vincristine	2	Polyneuropathy (2)
Prednisone	0	

Table 2 decribes the reasons for dose reductions in every case for a specific drug administered in the trial as well. Not included in this table are the planned pauses in medication for biopsies, small procesdures and administration of high-dose methotrexate as a CNS prophylaxis.

Abbreviations: central nervous system (CNS)