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RESEARCH ARTICLE

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Patient-reported outcomes in patients with relapsed or refractory follicular lymphoma treated with zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy: results from the ROSEWOOD trial

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ABSTRACT

Objective: We report patient-reported outcomes (PROs) measuring health-related quality of life (HRQoL) from the ROSEWOOD trial (NCT03332017), which demonstrated superior efficacy and a manageable safety profile with zanubrutinib plus obinutuzumab (ZO) versus obinutuzumab (O) in patients with heavily pretreated relapsed/refractory follicular lymphoma (R/R FL).

Methods: PROs were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and EQ-5D-5L questionnaires at baseline and subsequently every 12 weeks. All QLQ-C30 domains and EQ-5D-5L visual analog scale (VAS) scores were analyzed descriptively. At the key clinical timepoints (weeks 12 and 24), a mixed model for repeated measures (MMRM) analysis was used to evaluate the key PRO endpoints, including global health status, physical and role functioning, and symptoms of fatigue, pain, diarrhea, and nausea/vomiting. Clinically meaningful change was defined as $a \geq 5$-point mean difference from baseline and between the ZO and O arms.

Results: Patients were randomized to ZO ($n = 145$) or O ($n = 72$). By week 48, descriptive analysis results indicated that patients in the ZO arm demonstrated improved outcomes in role functioning and fatigue and nausea/vomiting symptoms, compared with those in the O arm. Both groups experienced improvements in pain symptoms. EQ-5D-5L VAS scores showed no observable differences between treatment arms through week 48. MMRM analysis revealed that the global health status/quality of life of patients treated with ZO improved, as did fatigue, at week 12. At week 24, patients in the ZO arm experienced a clinically meaningful improvement in role functioning, pain, and fatigue.

Conclusions: In patients with R/R FL, ZO was associated with improved PROs compared with O. These findings suggest that zanubrutinib contributed clinically meaningful benefits to patient HRQoL when added to obinutuzumab.

Trial registration: The ROSEWOOD trial is registered on ClinicalTrials.gov (BGB-3111-212; ClinicalTrials.gov identifier: NCT03332017).

PLAIN LANGUAGE SUMMARY

Follicular lymphoma (or FL) is a common blood cancer where abnormal white blood cells form lumps in organs and glands in the body that normally help fight infection (lymph nodes). Zanubrutinib selectively blocks Bruton tyrosine kinase, which can prevent cancer cells growing and lead to their death. Obinutuzumab binds to a protein called CD20 on cancer cells, facilitating their removal using the body's natural defense system. Previous results from the ROSEWOOD trial showed that zanubrutinib plus obinutuzumab had improved cancer-fighting effects versus obinutuzumab alone, with manageable side effects in patients whose cancer returned after treatment or when treatment had failed. This study examined how these two cancer treatments impacted the patients' wellbeing and day-to-day functioning as reported directly by them (patient-reported outcomes). Researchers found that by week 48 of the trial, patients who received zanubrutinib plus obinutuzumab found it easier to manage daily activities (role functioning) and had fewer symptoms of feeling exhausted all the time (fatigue) and nausea/vomiting versus those who received obinutuzumab alone. Further analysis showed that

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the patients who received zanubrutinib plus obinutuzumab had noticeable improvements from the start of treatment in role functioning, pain, and fatigue versus patients receiving obinutuzumab alone at week 24 of the trial. In conclusion, this study showed that zanubrutinib plus obinutuzumab was associated with improved patient-reported outcomes versus obinutuzumab alone in patients with relapsed or refractory FL.

Introduction

Follicular lymphoma (FL) is the second most commonly diagnosed non-Hodgkin lymphoma subtype worldwide[1], with ~14,000 cases diagnosed in the United States (US) in 2016, and has become increasingly prevalent due to the indolent nature of the disease[2]. Only 10–15% of patients present with apparent early-stage FL; the majority of patients are diagnosed with more advanced disease that may manifest itself through symptoms such as fatigue and weight loss[3,4]. The occurrence of these disease-related symptoms can also significantly impact health-related quality of life (HRQoL)[4]. There is considerable heterogeneity within the disease and among patients, with those who have not had an event within 2 years of immunochemotherapy having a similar survival as the general population[5], and fewer than half of patients receiving first-line therapy progressing to second-line therapy[6,7]. However, the clinical course of FL in patients who experience a relapse is typically one of serial relapses, with successive treatment regimens resulting in progressively shorter disease-control intervals and refractory disease[8]. Importantly, patients with FL who have relapsed are more likely to experience worse HRQoL than those newly diagnosed[4]. In addition, cumulative treatment-related toxicity can also lead to early treatment discontinuation and a negative impact on HRQoL. Although the median survival for patients diagnosed with FL is approaching 20 years, for most patients it remains incurable[9].

Obinutuzumab, the second-generation anti-CD20 monoclonal antibody, in combination with bendamustine, is approved for patients with relapsed or refractory (R/R) FL, following treatment with a rituximab-containing regimen[10]. Additionally, obinutuzumab monotherapy has demonstrated activity in patients with R/R FL[11]. Based on efficacy outcomes from recent clinical trials, a number of targeted therapies, including axicabtagene ciloleucel, lenalidomide, tazemetostat, and mosunetuzumab, have been approved as therapeutic options in this patient population; however, these new therapies have limited data on durable disease control and are associated with considerable toxicities for patients[12–16].

Zanubrutinib is a potent and highly selective next-generation Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize off-target effects[17]. The ROSEWOOD trial (BGB-3111-212; NCT03332017) is an open-label, multicenter, randomized phase 2 study that compared the efficacy and safety of zanubrutinib plus obinutuzumab (ZO) versus obinutuzumab (O) monotherapy in adult patients with heavily pretreated R/R FL[18]. At a median follow-up of 20.2 months, treatment with this combination demonstrated superior efficacy (overall response rate: 69% for ZO versus 46% for O; complete response rate: 39% versus 19%, respectively) and a manageable safety profile[18]. Based on these data, the European Commission has approved the combination of ZO for the treatment of adult patients with R/R FL following at least 2 prior systemic therapies[19]. Additionally, the US Food and Drug Administration granted accelerated approval for use of the combination in this setting[20]. This analysis evaluated patient-reported outcomes (PROs) in patients who received ZO or O in the ROSEWOOD trial.

Methods

The detailed methodology for the global ROSEWOOD trial is available in the published literature[18], with pertinent details summarized below.

Study design and patients

Patients were randomized 2:1 to receive ZO or O monotherapy. Zanubrutinib 160 mg was orally administered twice daily; O 1,000 mg was administered intravenously on days 1, 8, and 15 of cycle 1 (28 days per treatment cycle), day 1 of cycles 2 to 6, and then once every 8 weeks for up to 20 total infusions (2-year maintenance). The drugs were administered until progressive disease or unacceptable toxicity. Randomization was stratified by the number of prior lines of therapy, rituximab-refractory status, and geographic region. Eligible patients were at least 18 years of age and had measurable grade 1–3 A FL based on the World Health Organization's 2008 classification without transformation to aggressive B-cell lymphoma, received $\geq$2 prior systemic therapies for FL (including an anti-CD20 antibody and an alkylating agent), had an Eastern Cooperative Oncology Group performance status of 0–2, and had adequate organ function. Exclusion criteria included prior treatment with a BTK inhibitor.

This trial was approved by the Institutional Review Board or Independent Ethics Committee at each study site and conducted in accordance with applicable regulatory requirements, the principles of the Declaration of Helsinki, and Good Clinical Practice guidelines of the International Conference on Harmonization. A list of all sites that enrolled patients in the study is included in the Supplement. All patients provided written informed consent before trial enrollment.

Patient-reported outcome measures

PROs were prespecified secondary endpoints in the trial and were assessed for all patients using 2 validated instruments: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30)[21] and EQ-5D-5L[22].

Table 1. Demographics and baseline disease characteristics (ITT population).

Parameter	ZO ($n = 145$)	O ($n = 72$)
Age (years), median (range)	63.0 (31–84)	65.5 (32–88)
Geographic region		
Mainland China	21 (14.5)	12 (16.7)
Rest of the world	124 (85.5)	60 (83.3)
ECOG performance status ≥1	59 (40.6)	41 (57.0)
FLIPI score ≥3	77 (53.1)	37 (51.4)
Ann Arbor stage III–IV	119 (82.1)	60 (83.3)
Bulky disease (≥7 cm)	23 (15.9)	12 (16.7)
High LDH level (>ULN)	49 (33.8)	29 (40.3)
High tumor burden per GELF criteria	83 (57.2)	40 (55.6)
Number of prior lines of therapy, median (range)	3 (2–11)	3 (2–9)
Rituximab-refractory disease	78 (53.8)	36 (50.0)
Refractory disease to most recent line of therapy	47 (32.4)	29 (40.3)
Progressive disease ≤24 months after starting first-line therapy	50 (34.5)	30 (41.7)
Prior therapy		
Immunochemotherapy	143 (98.6)	71 (98.6)
Anthracyclines	118 (81.4)	57 (79.2)
Cyclophosphamide	136 (93.8)	68 (94.4)
Bendamustine	79 (54.5)	40 (55.6)

Abbreviations. ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; ITT, intent-to-treat; LDH, lactate dehydrogenase; O, obinutuzumab; ULN, upper limit of normal; ZO, zanubrutinib plus obinutuzumab.
Note. Date are n (%) unless otherwise indicated.

Table 2. Mean PRO endpoint and EQ-5D-5L VAS scores at baseline (ITT population).

	ZO ($n = 145$)	O ($n = 72$)
EORTC QLQ-C30 domains		
GHS/QoL	69.4 (21.8)	68.9 (20.2)
Physical functioning	81.7 (19.6)	78.4 (22.1)
Role functioning	78.1 (26.2)	79.2 (29.7)
Fatigue symptoms	30.0 (22.6)	30.1 (24.6)
Pain symptoms	19.5 (24.5)	19.6 (24.8)
Nausea/Vomiting symptoms	4.6 (10.7)	2.7 (9.4)
Diarrhea symptoms	8.7 (19.0)	10.9 (22.0)
EQ-5D-5L VAS	74.4 (19.3)	74.1 (17.7)

Abbreviations. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; GHS/QoL, global health status/quality of life; ITT, intent-to-treat; O, obinutuzumab; PRO, patient-reported outcome; VAS, visual analog scale; ZO, zanubrutinib plus obinutuzumab.
Note. Data are presented as mean (SD).

The QLQ-C30 evaluates the overall HRQoL in cancer patients, with a recall period of 7 days. The key PRO endpoints, defined as the most relevant disease-/treatment-related scales selected from QLQ-C30, comprised the 2-item global health status/quality of life (GHS/QoL) scale, 2 functional scales (physical functioning [5 items] and role functioning [2 items]), and 3 symptom scales (fatigue [3 items], nausea/vomiting [2 items], and diarrhea [1 item]); these domains were aligned with the most relevant manifestations of FL disease and treatment-related symptoms. The items of the GHS/QoL were assessed using a numeric rating scale from 1 to 7, with anchors at 'very poor' and 'excellent,' while other items were rated on a Likert scale from 1 to 4, ranging from 'not at all' to 'very much.' Higher scores on the GHS/QoL and functioning scales and lower scores on the symptom scales reflect improved HRQoL. The EQ-5D-5L provides a generic measure of overall health status and includes a visual analog scale (VAS) where patients rate their general health 'today' on a scale from 0 ('the worst health you can imagine') to 100 ('the best health you can imagine').

Patients completed both PRO assessments at baseline (day 1 of cycle 1; i.e. before the first study drug dose) and then every 12 weeks for 2 years (48 weeks), every 24 weeks for the next 2 years, and then annually until disease progression, death, or withdrawal of consent, regardless of study treatment discontinuation. PRO assessments at weeks 12, 24, 36, and 48 were selected to describe the short- and longer-term effects of treatments. Patients completed the questionnaires prior to the administration of any study drug.

Statistical analyses

The patient population for the HRQoL evaluation included all patients who were randomized, received at least 1 dose of study drug, and completed the questionnaires at baseline and each post-baseline assessment. Compliance rates were determined by dividing the number of patients who completed a questionnaire by the number of patients still receiving treatment at each visit in each arm. The scoring procedures for the EORTC QLQ-C30 were conducted in accordance with the EORTC scoring manual[23]. Descriptive analysis of scores and changes from baseline for all QLQ-C30 domains and the EQ-5D-5L VAS was conducted using means and standard deviations (SDs).

A linear mixed model for repeated measures (MMRM) was used for comparing the key PRO endpoints between treatment arms at 2 predefined key clinical timepoints (weeks 12 and 24). Per protocol, the unstructured covariance matrix model included repeated measurements of PRO endpoint scale scores at baseline, week 12, and week 24 as the dependent variable, with treatment arm, time-point (as a categorical variable), the interaction between treatment arm and time-point, and randomization stratification factors (number of prior lines of therapy [2–3 versus >3] and rituximab-refractory status [yes versus no]) as covariates. Changes from baseline in QLQ-C30 domain scores for each treatment arm, along with differences between treatments, were estimated, based on least square (LS) means change (95% CI) and LS means change difference (95% CI). *P*-values were

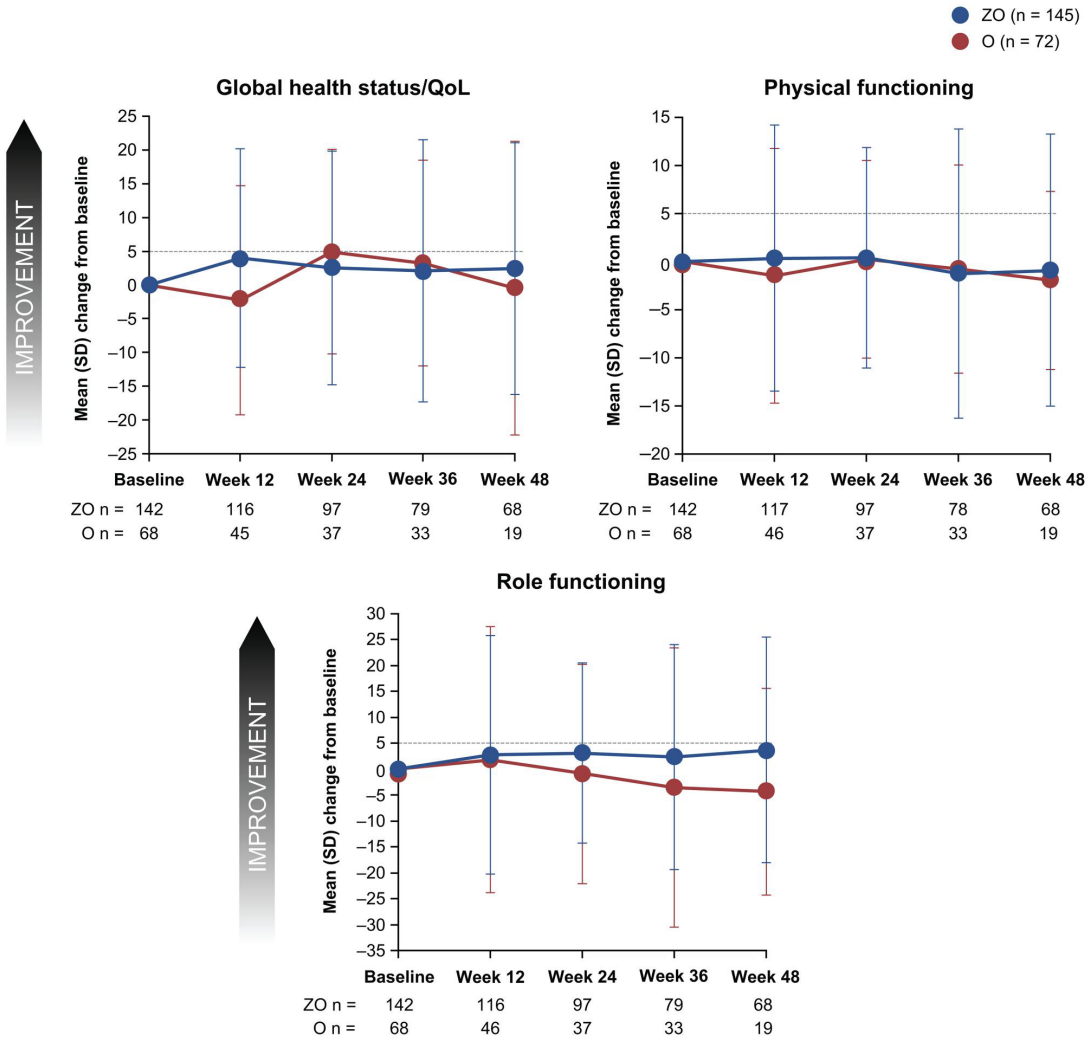

Figure 1. Mean change from baseline in EORTC QLQ-C30 GHS/QoL and functional domain scores through week 48 by treatment.
Abbreviations. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; GHS/QoL, global health status/quality of life; O, obinutuzumab; SD, standard deviation; ZO, zanubrutinib plus obinutuzumab.
Note. Only patients with data at both baseline and each post-baseline visit were included in the summary statistics for change from baseline.

2-sided and nominal without multiple adjustment as the analysis was not powered to determine statistical significance. Clinically meaningful change was defined as $a \geq 5$-point mean change from baseline and mean difference between treatment arms. All analyses were conducted using a data cutoff date of June 25, 2022. Clinically meaningful change in PROs pertains to improvement from baseline within each treatment arm, focusing on the differences between treatment arms rather than individual patients.

Results

The intent-to-treat (ITT) population consisted of 217 patients from 127 sites in 17 countries/regions. Patients were randomized to receive ZO ($n = 145$) or O ($n = 72$). Baseline demographics and disease characteristics were well balanced between the treatment arms (Table 1). Median age was 64 years; approximately half of the patients (53%) had a high (≥3) FL International Prognostic Index score at screening and 83% presented with Ann Arbor stage III–IV disease. The median number of prior lines of therapy was 3 (27% of patients had received >3 previous lines of therapy) and 37% had progressed within 24 months of commencing first-line therapy. Detailed information on the baseline demographic and clinical characteristics of the ITT population has been published[18].

The median (range) duration of study treatment was 12.2 (0.5–44.1) months in the ZO arm and 6.5 (0.1–28.7) months in the O arm; the median (range) number of O infusions was 11 (3–20) and 9 (3–20), respectively.

At baseline, the QLQ-C30 and EQ-5D-5L VAS scores were all balanced between treatment arms (Table 2). At each

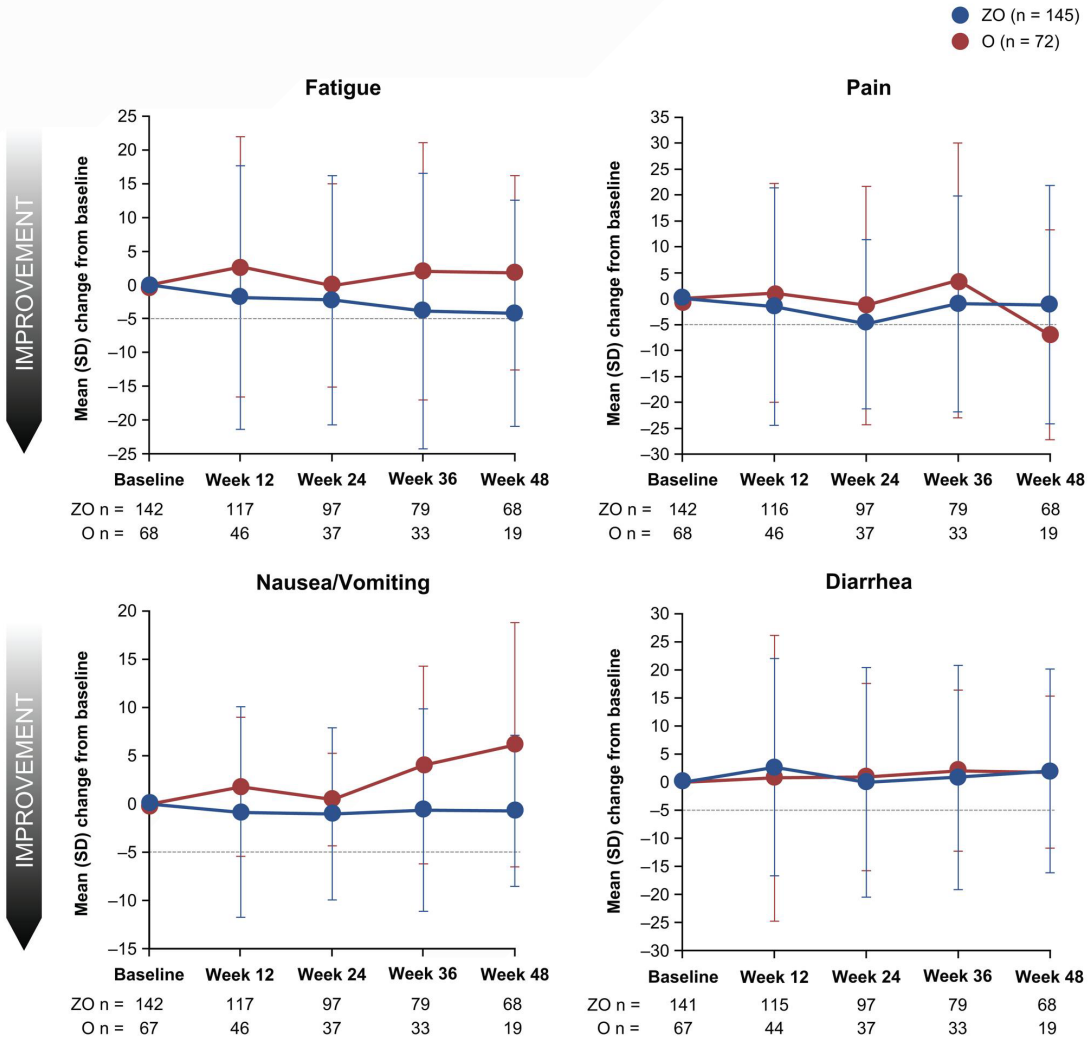

Figure 2. Mean change from baseline in EORTC QLQ-C30 symptom domain scores through week 48 by treatment.
Abbreviations. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; O, obinutuzumab; SD, standard deviation; ZO, zanubrutinib plus obinutuzumab.
Note. Only patients with data at both baseline and each post-baseline visit were included in the summary statistics for change from baseline.

assessment visit, compliance rates for the PROs were high (≥77%) and consistent across the treatment arms (Table S1).

Descriptive analysis

EORTC QLQ-C30

Mean changes from baseline through week 48 in the key PRO endpoints are shown in Figures 1 and 2. Patients in the ZO arm showed improvements in GHS/QoL scores at week 12 (mean change from baseline: 4.0 [SD: 16.2]), whereas patients in the O arm showed improvements in GHS/QoL scores at week 24 (mean change from baseline: 5.0 [SD: 15.1]; Table S2). Physical functioning scores were maintained from baseline and were similar for both treatment arms through week 48 (Table S3). Compared with the O arm, patients in the ZO arm had consistently more improvements in role functioning scores across prespecified timepoints (e.g. mean change from baseline at week 48: 3.7 [SD: 21.7]; Table S4).

Patients in the ZO arm had consistently more improvements in fatigue symptom scores across prespecified timepoints (e.g. mean change from baseline at week 48: −4.2 [SD: 16.7]; Table S5) compared with the O arm. Patients treated with ZO had improvements in pain symptom scores by week 24 (mean change from baseline: −5.0 [SD: 16.3]), whereas those treated with O showed improvements by week 48 (mean change from baseline: −7.0 [SD: 20.3]; Table S6). Nausea/vomiting symptom scores were maintained in the ZO arm, whereas they consistently worsened in the O arm by week 48 (mean change from baseline: 6.1 [SD: 12.7];

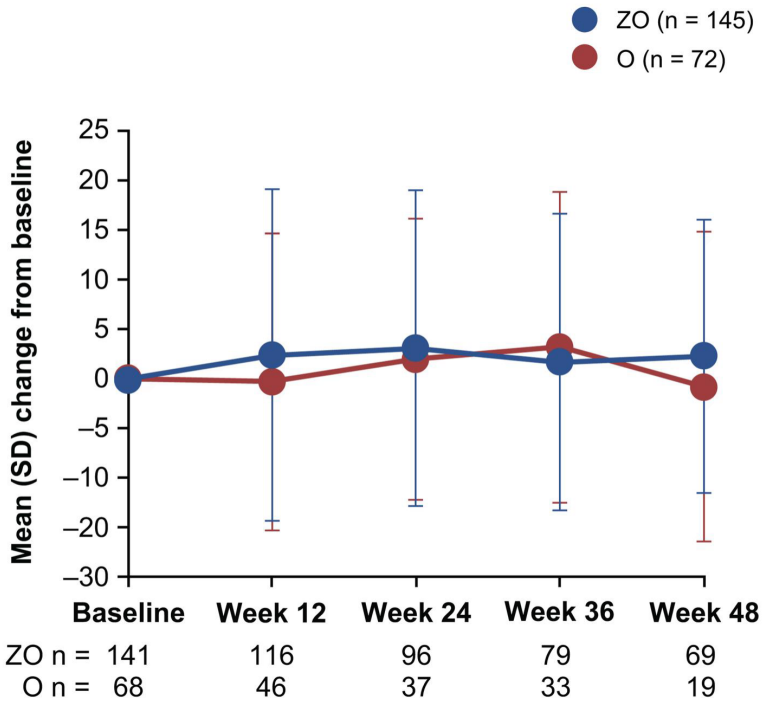

Figure 3. Mean change from baseline in EQ-5D-5L VAS scores through week 48 by treatment.
Abbreviations. O, obinutuzumab; SD, standard deviation; VAS, visual analog scale; ZO, zanubrutinib plus obinutuzumab.
Note. Only patients with data at both baseline and each post-baseline visit were included in the summary statistics for change from baseline. *P* positive values denote improvement.

Table S7). Diarrhea symptom scores were maintained from baseline in both treatment arms through week 48 (Table S8).

EQ-5D-5L VAS

Mean scores from the EQ-5D-5L VAS showed no meaningful change from baseline between treatment arms from week 12 through week 48 (Figure 3 and Table S9).

MMRM analysis

Changes in the PRO endpoint scores from baseline based on the MMRM analysis are shown in Figure 4. Overall, patients receiving ZO experienced greater GHS/QoL, functional, and symptomatic improvements than patients receiving O alone. At week 12, the differences between cohorts were clinically meaningful for GHS/QoL (LS mean difference: 6.4 [95% CI: 0.6, 12.3], $p = 0.0302$) and fatigue symptoms (LS mean difference: −4.6 [95% CI: −11.1, 1.9], $p = 0.1614$). At week 24, these differences were clinically meaningful for role functioning (LS mean difference: 5.6 [95% CI: −2.3, 13.5], $p = 0.1637$) and symptoms of fatigue (LS mean difference: −4.7 [95% CI: −11.6, 2.2], $p = 0.1817$) and pain (LS mean difference: −4.9 [95% CI: −12.6, 2.8], $p = 0.2148$).

Discussion

In the phase 2 ROSEWOOD trial, patients with R/R FL who were treated with ZO showed improved HRQoL outcomes compared with those receiving O. Descriptive analyses over a 48-week period showed that the PRO endpoints did not worsen from baseline to week 48 in patients treated with ZO; however, patients treated with O worsened on all HRQoL domains except for pain symptoms. Patients treated with the combination regimen had particularly larger decreases in symptoms of fatigue and nausea/vomiting as well as higher improvements in role functioning. Furthermore, the EQ-5D-5L VAS scores showed no meaningful change from baseline between treatment arms from week 12 through week 48.

The MMRM analysis results using the most relevant disease- or treatment-related measures further demonstrated that differences in improvement were clinically meaningful for both GHS/QoL and fatigue at week 12 in patients treated with ZO compared with those treated with O. Additionally, at week 24, differences in improvement among patients treated with ZO versus O were clinically meaningful for role functioning and symptoms of fatigue and pain. The overall stability and observed improvement in PRO outcomes in patients treated with ZO compared with those treated with O alone were likely due to the improved disease control with the addition of zanubrutinib[18].

The current study is one of the first to examine the impact of a BTK inhibitor in combination with obinutuzumab in heavily pretreated patients with R/R FL. The phase 3 GALLIUM study in patients with advanced FL treated with obinutuzumab- or rituximab-based chemotherapy in the first line setting reported similar HRQoL improvements in both treatment arms over the course of treatment[24]. PRO scores

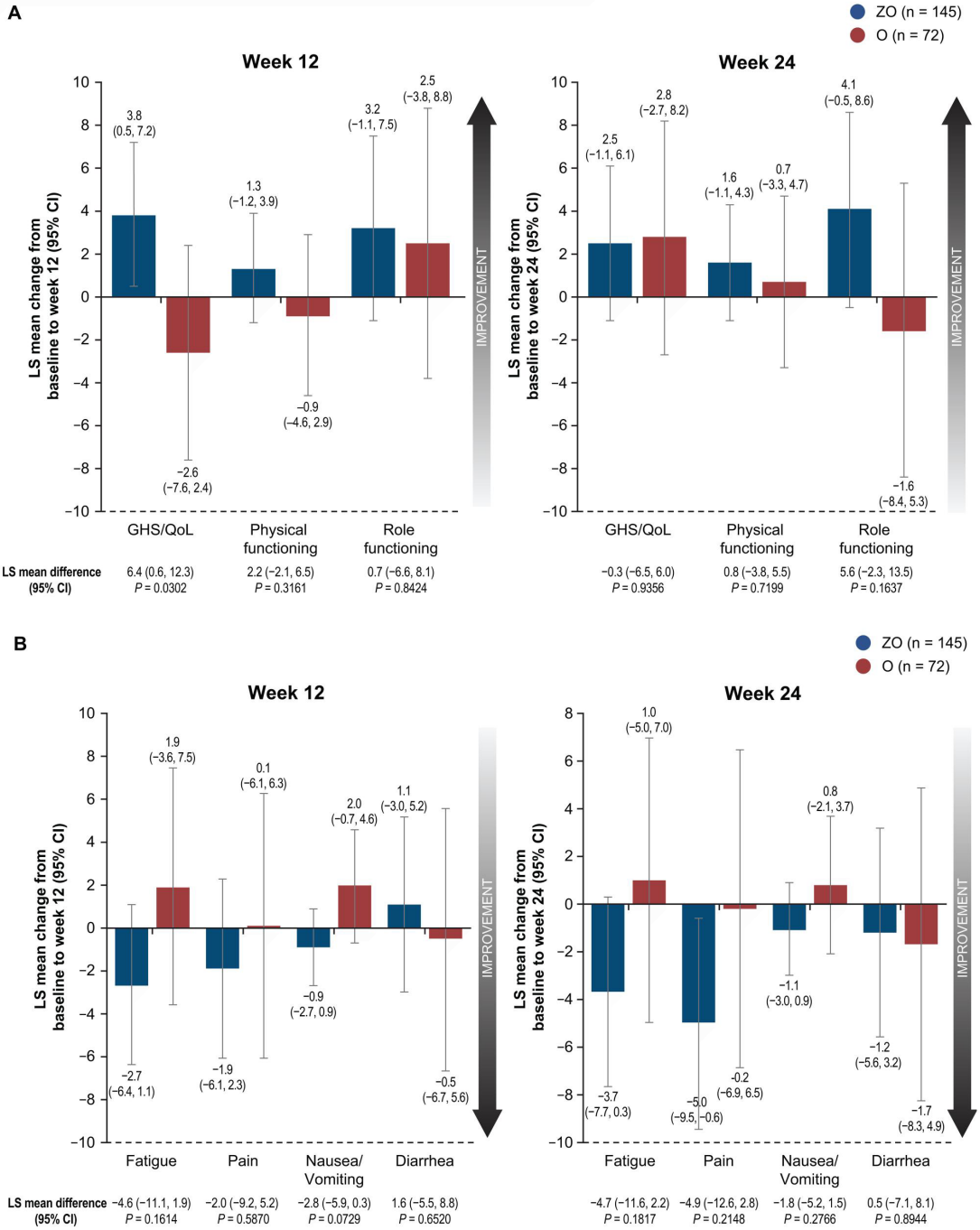

Figure 4. MMRM analysis of EOTRC QLQ-C30 (A) GHS/QoL and functional domain scores and (B) symptom domain scores by treatment.
Abbreviations. CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; GHS/QoL, global health status/quality of life; LS, least square; MMRM, mixed model for repeated measures; O, obinutuzumab; ZO, zanubrutinib plus obinutuzumab.
Note. Only patients with data at both baseline and each post-baseline visit were included in the LS mean difference summary statistics.

were similar regardless of the treatment or treatment-related adverse events. In the phase 3 GADOLIN study of patients with rituximab-refractory indolent non-Hodgkin lymphoma, a higher proportion of patients in the obinutuzumab plus bendamustine arm reported clinically meaningful improvements in HRQoL and delayed time to worsening than those in the bendamustine alone arm[25]. In both studies, HRQoL was assessed *via* Functional Assessment of Cancer

Treatment-Lymphoma questionnaire that incorporated well-being and lymphoma-specific subscales. In contrast, the EORTC instruments used in the current study allowed the delineation of specific domains and symptoms, and thus a more robust analysis of PRO outcomes.

A limitation of the current study was that the PRO data were analyzed separately from other clinical outcomes. Future analyses will examine the association between the patient-reported symptoms and clinical outcomes. In addition, exploring how PROs differ based on sex and regional/ethnic factors could offer significant insights. Future studies should integrate statistical modeling to explore the relationships among the differences in PRO endpoints.

The ROSEWOOD patient population was high risk, with over a third of the patients having progressed within 24 months of first-line chemoimmunotherapy and refractory to their most recent line of therapy prior to joining the trial. Despite this, ZO demonstrated meaningful efficacy and a manageable safety profile[18]. The improved HRQoL seen in patients treated with ZO is consistent with this profile and suggests that when disease is better controlled with a tolerable treatment, key PRO domains are improved.

Conclusions

These findings, along with the primary clinical outcomes, suggest that ZO for treatment of patients with R/R FL is associated with greater clinical benefits and better HRQoL than treatment with O in the ROSEWOOD trial. Such clinically meaningful benefits support the use of ZO as a deliverable, tolerable, and effective combination therapy for patients with R/R FL.

Transparency

Declaration of funding

This study was funded by BeiGene, Ltd.

Declaration of financial/other relationships

JT received research funding from BeiGene, Bristol Myers Squibb, Cellectar, Janssen, and Roche. PLZ has served in a consulting or advisory role for ADC Therapeutics, AstraZeneca, BeiGene, Bristol Myers Squibb, Celltrion, EUSA Pharma, Gilead Sciences, Incyte, Janssen-Cilag, Kyowa Kirin, MSD, Novartis, Roche, Sandoz, Secura Bio, SERVIER, Takeda, and TG Therapeutics; and has served on speaker's bureau for AstraZeneca, BeiGene, Bristol Myers Squibb, Celltrion, EUSA Pharma, Gilead Sciences, Incyte, Janssen-Cilag, Kyowa Kirin, MSD, Novartis, Roche, SERVIER, and Takeda. YS has nothing to disclose. RD is an employee of BeiGene and may own company stock/stock options from Bristol Myers Squibb/Celgene/and BeiGene. JM has received research funding from BeiGene. ACDO has served in a consulting or advisory role for Alexion and Janssen; and received travel funds from Janssen. SEA has served in a consulting or advisory role for Amgen, BeiGene, Bristol Myers Squibb, Genentech/Roche, Janssen, Novartis, Paladin Labs, and Pfizer; and has received research funding from Novartis. CRF has served in a consulting or advisory role for AbbVie, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb/Celgene, Celgene, Curio Science, Denovo Bipharma, Epizyme, Foresight Diagnostics, Genentech/Roche, Genmab, Gilead Sciences, Karyopharm Therapeutics, MorphoSys, Pharmacyclics/Janssen, Seagen, and Spectrum Pharmaceuticals; may own company stock/stock options from Foresight Diagnostics and NPower; and received research funding from 4D Pharma, AbbVie, Acerta Pharma, Adaptimmune, Alimera Sciences, Amgen, Bayer, Celgene, Cellectis, EMD Serono, Genentech/Roche, Gilead Sciences, Guardant Health, Iovance Biotherapeutics, Janssen Oncology, Kite/Gilead, Millennium Pharmaceuticals, MorphoSys, Nektar, Novartis, Pfizer, Pharmacyclics, Sanofi, Takeda, TG Therapeutics, Xencor, and ZIOPHARM Oncology. PK, EI, RK, and GB are employees of BeiGene and may hold stock or other ownership. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Authors' contributions

JT, PLZ, YS, RD, EI, RK, JM, ACDO, SEA, CRF, and GB were responsible for study design and data collection. All authors were responsible for data interpretation and reviewing and approving drafts of the manuscript. PK and GB were responsible for data analysis.

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Data availability statement

BeiGene voluntarily shares anonymous data on completed studies responsibly and provides qualified scientific and medical researchers access to anonymous data and supporting clinical trial documentation for clinical trials in dossiers for medicines and indications after submission and approval in the US, China, and Europe. Clinical trials supporting subsequent local approvals, new indications, or combination products are eligible for sharing once corresponding regulatory approvals are achieved. BeiGene shares data only when permitted by applicable data privacy and security laws and regulations. In addition, data can only be shared when it is feasible to do so without compromising the privacy of study participants. Qualified researchers may submit data requests/research proposals for BeiGene review and consideration through BeiGene's Clinical Trial Webpage at https://www.beigene.com/our–science–and–medicines/our–clinical–trials/.

Ethics statement

This trial was approved by the Institutional Review Board or Independent Ethics Committee at each study site and conducted in accordance with applicable regulatory requirements, the principles of the Declaration of Helsinki, and Good Clinical Practice guidelines of the International Conference on Harmonization. A list of all sites that enrolled patients in the study is included in the Supplement. All patients provided written informed consent before trial enrollment.

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