REGULAR ARTICLE

blood advances

Phase 3 SELENE study: ibrutinib plus BR/R-CHOP in previously treated patients with follicular or marginal zone lymphoma

Loretta J. Nastoupil,[1] Georg Hess,[2] Miguel A. Pavlovsky,[3] Iwona Danielewicz,[4] Jane Freeman,[5] Alejandro Martin García-Sancho,[6] Valeria Glazunova,[7] Andrew Grigg,[8] Jing-Zhou Hou,[9] Ann Janssens,[10] Seok Jin Kim,[11] Zvenyslava Masliak,[12] Pam McKay,[13] Francesco Merli,[14] Wataru Munakata,[15] Hirokazu Nagai,[16] Muhit Özcan,[17] Meir Preis,[18] Tingyu Wang,[19,20] Melissa Rowe,[21] Monelle Tamegnon,[22] Rui Qin,[22] Todd Henninger,[22] Madeliene Curtis,[21] Donne Bennett Caces,[22] Catherine Thieblemont,[23,*] and Gilles Salles[24,*]

[1]Department of Lymphoma-Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Hematology Department, Johannes Gutenberg-Universität Mainz, Mainz, Germany; [3]Department of Hematology, Fundaleu, Buenos Aires, Argentina; [4]Department of Clinical Oncology, Maritime Hospital in Gdynia, Gdynia, Poland; [5]Northern Haematology and Oncology Arm, Sydney Adventist Hospital, Sydney, NSW, Australia; [6]Department of Hematology, Hospital Universitario de Salamanca, Centro de Investigación Biomédica en Red Cáncer, Centro de Investigación del Cáncer de Salamanca-Instituto Universitario de Biología Molecular y Celular del Cáncer, Salamanca, Spain; [7]SP Botkin City Clinical Hospital, Moscow, Russia; [8]Department of Clinical Haematology, Austin Hospital, Melbourne, VIC, Australia; [9]University of Pittsburgh Medical Center, Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA; [10]Department of Hematology, Universitair Ziekenhuis Leuven, Leuven, Belgium; [11]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [12]Institute of Blood Pathology and Transfusion Medicine, Lviv, Ukraine; [13]The Beatson West of Scotland Cancer Centre, Glasgow, Scotland; [14]Hematology, Azienda Unità Sanitaria Locale - Istituti di Ricovero e Cura a Carattere Scientifico di Reggio Emilia, Reggio Emilia, Italy; [15]Department of Hematology, National Cancer Center Hospital, Tokyo, Japan; [16]Department of Hematology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan; [17]Department of Hematology, Ankara University School of Medicine, Ankara, Turkey; [18]Institute of Hematology, Lady Davis Carmel Medical Center, Haifa, Israel; [19]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; [20]Tianjin Institutes of Health Science, Tianjin, China; [21]Janssen Research & Development, High Wycombe, United Kingdom; [22]Janssen Research & Development, Raritan, NJ; [23]Hemato-Oncology Department, Hôpital Saint-Louis, Paris, France; and [24]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Key Points

- SELENE is a phase 3, placebo-controlled trial evaluating ibrutinib or placebo added to BR/R-CHOP for patients with R/R FL or MZL.
- The addition of ibrutinib to BR or R-CHOP did not significantly improve the PFS.

The phase 3 SELENE study evaluated ibrutinib + chemoimmunotherapy (CIT; bendamustine and rituximab [BR]; or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) for patients with relapsed/refractory (R/R) follicular lymphoma (FL) or marginal zone lymphoma (MZL). Adult patients who had received ≥1 prior line of CIT were randomized 1:1 to oral ibrutinib (560 mg) or placebo daily, plus 6 cycles of BR/R-CHOP. The primary end point was investigator-assessed progression-free survival (PFS). Overall, 403 patients were randomized to ibrutinib + CIT (n = 202) or placebo + CIT (n = 201). Most patients received BR (90.3%) and had FL (86.1%). With a median follow-up of 84 months, median PFS was 40.5 months in the ibrutinib + CIT arm and 23.8 months in the placebo + CIT arm (hazard ratio [HR], 0.806; 95% confidence interval [CI], 0.626-1.037; P = .0922). Median overall survival was not reached in either arm (HR, 0.980; 95% CI, 0.686-1.400). Grade ≥3 treatment-emergent adverse events (TEAEs) were reported in 85.6% and 75.4% of patients in the ibrutinib + CIT and placebo + CIT arms, respectively. In each arm, 13 patients had TEAEs leading to death. The addition of ibrutinib to CIT did not significantly improve PFS compared with placebo + CIT. The safety profile was consistent with known profiles of ibrutinib and CIT. This trial was registered at www.clinicaltrials.gov as #NCT01974440.

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*C.T. and G.S. contributed equally to this work.

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency.

Qualified researchers may request access to the study data through the Yale Open Data Access Project site at http://yoda.yale.edu.

The full-text version of this article contains a data supplement.

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Introduction

Follicular lymphoma (FL) and marginal zone lymphoma (MZL) account for ~20% and 12% of all non-Hodgkin lymphomas (NHLs), respectively.[1] Most patients with FL or MZL present with advanced-stage disease, which is considered incurable with standard therapy and requires lifelong disease management.[2,3] Although survival outcomes among patients with FL and MZL have improved with the refinement of chemotherapy regimens and introduction of anti-CD20 antibodies such as rituximab, disease relapse is common, resulting in substantial morbidity and poor health-related quality of life.[3,4]

Chemoimmunotherapy (CIT) regimens, incorporating chemotherapy and anti-CD20 antibodies, are a mainstay of treatment for patients with relapsed or refractory (R/R) NHL, with 2 of the most common regimens being bendamustine plus rituximab (BR) and rituximab cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[5] The clinical use of BR and R-CHOP in R/R FL and MZL is recommended in international clinical practice guidelines,[6-8] and these regimens are widely used in clinical practice.[5]

Prognosis after relapse varies among patients and disease histologies; however, duration of response (DOR), progression-free survival (PFS), and overall survival (OS) outcomes have all been shown to decline with repeated lines of therapy, and some patients develop disease that is resistant to subsequent treatment.[5,9-14] Therefore, there remains a need for more effective therapies that can reverse or mitigate these trends by providing durable clinical benefit with minimal added toxicities.

Ibrutinib is a once-daily oral inhibitor of Bruton tyrosine kinase (BTK) that has previously shown activity and tolerability as monotherapy for patients with R/R FL, with an overall response rate (ORR) of 21% and DOR of 19.4 months.[15] For patients with R/R MZL, ibrutinib monotherapy resulted in an ORR of 58%, median DOR of 27.6 months, and median PFS of 15.7 months.[16] In both studies, the most common grade ≥3 adverse events (AEs; occurring in >5% of patients) were anemia, pneumonia, and fatigue. Grade ≥3 neutropenia was also reported in >5% of patients with R/R FL.[15] Additionally, the combination of ibrutinib plus BR had a promising toxicity profile in a phase 1/1b study of patients with untreated and R/R NHL,[17] suggesting that combining ibrutinib with CIT may be a tolerable and effective therapeutic approach for patients with indolent NHL.

The phase 3 SELENE study was designed to provide efficacy and safety data for ibrutinib plus either BR or R-CHOP for patients with R/R FL or MZL who had received prior treatment with an anti-CD20–containing CIT regimen and to determine whether the treatment combination is associated with prolonged PFS compared with BR or R-CHOP plus placebo.

Methods

Patients

Patients were eligible if they were aged ≥18 years and had a histologically confirmed diagnosis of FL (grade 1, 2, or 3a) or MZL (splenic, nodal, or extranodal), R/R disease after ≥1 prior treatment with an anti-CD20–containing CIT regimen, ≥1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma,[18] Eastern Cooperative Oncology Group performance status of 0 or 1, and laboratory values within protocol-defined parameters. Additional eligibility criteria are provided in the supplemental Methods.

Study design and treatment

SELENE was a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study (NCT01974440). After eligibility confirmation, patients were stratified based on backbone CIT regimen (BR vs R-CHOP), R/R disease, FL or MZL, and number of prior lines of therapy (1 vs >1). Patients were randomized 1:1 to placebo or ibrutinib 560 mg administered orally once daily until progressive disease (PD), unacceptable toxicity, or study end, whichever occurred first. All patients received background therapy with either BR or R-CHOP, selected by the investigator before randomization based on prior treatment history and cardiac function. BR comprised IV bendamustine 90 mg/m^2 on days 1 and 2 of cycles 1 to 6, plus rituximab 375 mg/m^2 on day 1 of cycles 1 to 6 (28-day cycles), whereas R-CHOP comprised IV rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (maximum dose of 2 mg) on day 1 of cycles 1 to 6 and prednisone 100 mg orally on days 1 to 5 of cycles 1 to 6 (21-day cycles). Supportive care, including the use of prophylactic anti-infective agents, was administered at the discretion of the investigator.

The study was performed in accordance with the protocol, current International Conference on Harmonization guidelines on Good Clinical Practice, and applicable regulatory and country-specific requirements. Before the start of the study, the protocol and associated materials were fully approved by an independent ethics committee or institutional review board, and all patients provided written, informed consent.

End points and assessments

The study population and characteristics, efficacy, and patient-reported outcomes data were assessed in the intention-to-treat population, comprising all randomized patients. The primary end point was investigator-assessed PFS, which was defined as the duration from the date of randomization to the date of PD or death, whichever occurred first. Data of patients who were progression-free and alive or had unknown status were censored at the last tumor assessment. Secondary end points included OS (measured from the date of randomization to the date of death); the rate of complete response (CR) and the ORR (proportion of patients who achieved a complete or partial response); DOR (duration from the date of initial documentation of a response to the date of first documented evidence of PD); time to worsening of functional assessment of cancer therapy–lymphoma (FACT-Lym) scores (defined as the time from randomization to the first 5-point decrease from baseline score); and safety. The safety population included all patients receiving ≥1 dose of any study treatment. AEs were reported by the investigator and classified by National Cancer Institute Common Terminology Criteria for AEs version 4.03.

Statistical analyses

The study was designed to achieve a hazard ratio (HR) of 0.70 in PFS for ibrutinib plus BR/R-CHOP (ibrutinib + CIT) vs placebo plus BR/R-CHOP (placebo + CIT) for at least 80% power, with a 2-sided significance level of 5%. The O'Brien–Fleming boundaries

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were used for a superiority test of efficacy in an interim and primary analysis, when ~151 and ~252 cases of PFS had been observed, respectively. The significance boundary for superiority in the primary analysis was $P < .0476$. Demographics, baseline characteristics, and safety were summarized using descriptive statistics and categorical variables using frequency tabulations. Time-to-event end points using an HR with 2-sided 95% confidence intervals [CIs] were estimated using the Kaplan-Meier method, stratified log-rank test for treatment efficacy, and Cox proportional hazards model. Binary end points were summarized in frequency and percent based on the arm, with a stratified Cochran-Mantel-Haenszel test to evaluate treatment efficacy. All *P* values besides those for the primary end point were nominal.

Results

Patients and treatment

Between 28 March 2014 and 5 November 2015, 403 patients were randomized to treatment with ibrutinib + CIT (n = 202) or placebo + CIT (n = 201); 1 patient in the ibrutinib + CIT arm and 2 in the placebo + CIT arm never received treatment and were excluded from the safety population (Figure 1). PD was the most frequent reason for treatment discontinuation in both arms (Figure 1). No patients in either treatment arm discontinued ibrutinib or placebo because of a COVID-19–related AE.

Baseline demographics and disease characteristics are summarized in Table 1. Most patients (77.2%) had relapsed disease, and 90.3% of patients were treated with BR as backbone therapy. Of patients treated with BR, 85.1% in the placebo + CIT arm and 77.5% in the ibrutinib + CIT arm received the full 6 cycles. The median time from the end of the prior line of therapy to randomization was 14.2 months for the ibrutinib + CIT arm and 11.6 months for the placebo + CIT arm. Prior treatments are summarized in Table 2.

Efficacy

The median follow-up of the study was 84 months. In the ibrutinib + CIT arm, 119 patients (58.9%) had a PFS event vs 134 patients (66.7%) in the placebo + CIT arm. Most events (97 in the ibrutinib + CIT arm and 119 in the placebo + CIT arm) were because of PD. Six patients from each group reported transformation to diffuse large B-cell lymphoma. Median PFS was 40.5 months in the ibrutinib + CIT arm vs 23.8 months in the placebo + CIT arm (HR, 0.81; 95% CI, 0.63-1.04; $P = .0922$; Figure 2A). Although a positive trend favoring the ibrutinib + CIT arm was observed for PFS up to ~36 months, the *P* value efficacy boundary of .0476 was not crossed; therefore, the primary end point was not met. PFS with ibrutinib + CIT was consistent across subgroups (Figure 2B).

In a post hoc landmark analysis evaluating baseline disease characteristics for patients with a PFS ≤ 12 months vs > 12 months, patients with a PFS ≤ 12 months in both arms had a shorter median time from initial diagnosis to randomization; had received a median of 2 prior lines of therapy (vs 1 for patients with a PFS > 12 months); were more likely to have refractory disease, bulky disease, extranodal disease with bone marrow involvement, and higher risk PRIMA scores; and were more likely to have progressed within 24 months of first CIT (POD24; supplemental Table 1).

ORR and CR rates were similar between treatment arms (Table 3). However, the DOR among patients treated with ibrutinib + CIT was 44.3 months (95% CI, 32.89-60.02) compared with 21.7 months (95% CI, 17.61-32.36) in the placebo + CIT arm (supplemental Figure 1).The OS was similar between treatment arms (HR, 0.98; 95% CI, 0.69-1.40; $P = .9115$). The median OS was not reached in either arm. Estimated 7-year OS rates were 67.4% and 68.3% in the ibrutinib + CIT and placebo + CIT arms, respectively (Figure 3). Exploratory analysis showed that median time to next treatment was not reached in either arm.

A prespecified analysis of the 347 patients with FL showed that median PFS was 38.4 months (95% CI, 24.18-49.35) in the ibrutinib + CIT arm and 20.6 months (95% CI, 18.69-27.24) in the placebo + CIT arm (HR, 0.81; 95% CI, 0.63-1.05; $P = .118$; supplemental Figure 2). Other results from the FL subgroup were similar to those of the intention-to-treat population and are not presented. In a prespecified analysis of the 56 patients with MZL, the median PFS was prolonged in both arms (not reached in the ibrutinib + CIT arm [95% CI, 49.25 to not evaluable] vs 91.6 months

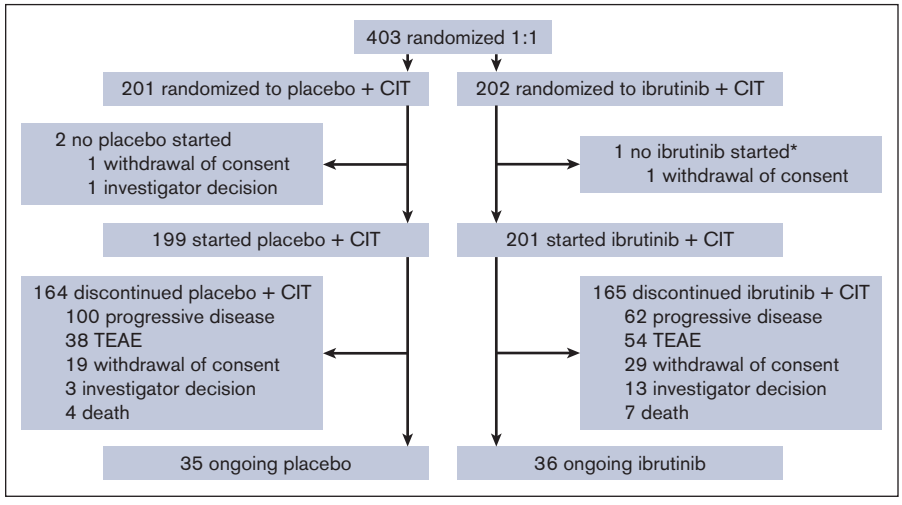


Figure 1. CONSORT diagram. An asterisk (*) indicates patients who received 1 dose of CIT.

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Table 1. Baseline demographics and disease characteristics

Characteristic	Ibrutinib + CIT (n = 202)	Placebo + CIT (n = 201)
Median age, y (range)	59.5 (22-87)	59 (30-86)
≥65	74 (36.6)	72 (35.8)
<65	128 (63.4)	129 (64.2)
Sex, n (%)		
Male	113 (55.9)	99 (49.3)
Female	89 (44.1)	102 (50.7)
ECOG PS, n (%)		
0	132 (65.3)	125 (62.2)
1 or 2	70 (34.7)	76 (37.8)
FL, n (%)	174 (86.1)	173 (86.1)
Grade 1 or 2	146 (72.3)	142 (70.6)
Grade 3a	28 (13.9)	31 (15.4)
MZL, n (%)	28 (13.9)	28 (13.9)
Splenic	1 (0.5)	4 (2.0)
Nodal	10 (5.0)	18 (9.0)
Extranodal	17 (8.4)	6 (3.0)
Gastric	5 (2.5)	2 (1.0)
Median time since diagnosis, mo (range)	45.8 (3.2-270.0)	42.9 (5.1-313.0)
Prior LOT, n (%)		
1	108 (53.5)	112 (55.7)
>1	94 (46.5)	89 (44.3)
Median time from end of prior LOT to randomization, mo (range)	23.5 (0.8-124.5)	20.2 (0.5-114.1)
Disease type, n (%)		
Refractory	49 (24.3)	43 (21.4)
Relapsed	153 (75.7)	158 (78.6)
Extranodal	121 (59.9)	117 (58.2)
Bone marrow involvement	78 (38.6)	77 (38.3)
PRIMA PI, n (%)		
High risk	54 (26.9)	46 (23.2)
Medium risk	43 (21.4)	41 (20.7)
Low risk	104 (51.7)	111 (56.1)
POD24, n (%)		
≤24 mo	101 (50.2)	118 (58.7)
>24 mo	100 (49.8)	83 (41.3)
Backbone CIT (BR/R-CHOP) received during study, n (%)		
BR	182 (90.1)	182 (90.5)
R-CHOP	20 (9.9)	19 (9.5)

ECOG PS, Eastern Cooperative Oncology Group performance status; LOT, line of therapy; PRIMA PI, PRIMA prognostic index.

[95% CI, 9.23 to not evaluable] in the placebo + CIT arm; HR, 0.72; 95% CI, 0.31-1.68; $P = .451$). Similar ORR and CR rates were observed among patients with MZL in the ibrutinib + CIT and placebo + CIT arms (89.3% vs 82.1% and 64.3% vs 60.7%, respectively; supplemental Table 2). For patients with MZL, the median DOR was not reached in the ibrutinib + CIT arm and was 89.2 months in the placebo + CIT arm; the 7-year OS rates were 76.6% in the ibrutinib + CIT arm and 68.5% in the placebo + CIT arm.

Safety

Median duration of exposure was 14.5 months (range, 0.1-96.0 months) for ibrutinib + CIT and 18.0 months (range, 0.3-95.6 months) for placebo + CIT. Safety data are summarized in Table 4. The percentage of patients with grade ≥3 treatment-emergent AEs (TEAEs) (85.6% vs 75.4%), serious TEAEs (55.7% vs 37.2%), TEAEs leading to dose reduction of ibrutinib or placebo (20.4% vs 10.6%), and TEAEs leading to discontinuation

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Table 2. Types of treatments used as prior lines before study entry

Type of treatments used as prior lines before study entry, n (%)	First line (n = 403)	Second line (n = 183)	Third line (n = 85)	Later lines (n = 75)
Anthracycline based	222 (55.1)	34 (18.6)	12 (14.1)	8 (10.7)
Alkylator based	134 (33.3)	40 (21.9)	21 (24.7)	28 (37.3)
Bendamustine	23	15	7	5
Fludarabine based	12 (3.0)	18 (9.8)	7 (8.2)	8 (10.7)
Anti-CD20 monotherapy	11 (2.7)	34 (18.6)	16 (18.8)	16 (21.3)
Standard salvage*	1 (0.2)	28 (15.3)	8 (9.4)	8 (10.7)
Other	19 (4.7)	29 (15.8)	21 (24.7)	7 (9.3)

Prior maintenance rituximab (any line) was administered to 164 (40%) patients; prior high-dose chemotherapy + autologous stem cell transplant (any line) was administered to 23 (5.7%) patients.

*Salvage therapy includes ifosphamide, carboplatin, etoposide; dexamethasone, cytarabine, cisplatin; and etoposide, cisplatin, cytarabine, prednisone; with or without rituximab.

(30.8% vs 18.6%) were higher in the ibrutinib + CIT arm than in the placebo + CIT arm. A similar pattern was observed when comparing safety data during the first 6 months (corresponding to the CIT + ibrutinib/placebo combination period) vs >6 months to 8 years (corresponding to ibrutinib/placebo monotherapy period; supplemental Table 3). TEAEs leading to death were balanced between the arms (13 patients [6.5%] per arm). TEAEs leading to death in the ibrutinib + CIT arm comprised pneumonia in 3 patients and *Aspergillus* infection, nocardiosis, sepsis, septic shock, lung cancer, bladder cancer, ovarian cancer, cardiac failure, hypotension, and ischemic stroke in 1 patient each. TEAEs leading to death in the placebo + CIT arm comprised cardiac arrest in 2 patients; and pneumonia, pneumocystis pneumonia, staphylococcal sepsis, encephalitis, lung cancer, hypopharyngeal cancer, nasal cavity cancer, acute myeloid leukemia, small intestine obstruction, failure to thrive, and respiratory failure in 1 patient each.

The most common TEAEs of any grade, occurring in ≥20% of patients treated with ibrutinib + CIT, were diarrhea, nausea, neutropenia, fatigue, rash, pyrexia, vomiting, cough, anemia, upper respiratory tract infection, thrombocytopenia, and decreased appetite (supplemental Table 4). Of these, diarrhea, nausea, and rash occurred at a >10% greater frequency in the ibrutinib + CIT arm vs the placebo + CIT arm (51.2% vs 34.7%, 51.2% vs 39.7%, and 34.3% vs 16.6%, respectively). Grade ≥3 thrombocytopenia and anemia were reported more frequently in the ibrutinib + CIT arm than in the placebo + CIT arm (10.0% vs 5.0% and 11.4% vs 4.0%, respectively). Rates of grade ≥3 neutropenia were similar in both arms (30.8% vs 31.2%). Overall, TEAEs leading to discontinuation of treatment (ibrutinib or placebo) were reported in 62 patients (30.8%) in the ibrutinib + CIT arm and 37 patients (18.6%) in the placebo + CIT arm. Neutropenia led to treatment discontinuation in 7 patients (3.5%) in the ibrutinib + CIT arm and 3 patients (1.5%) in the placebo + CIT arm. Of the TEAEs of clinical interest for BTK inhibitors, atrial fibrillation was reported in 6.5% of the patients in the ibrutinib + CIT arm and 2.0% of the patients in the placebo + CIT arm. Hypertension was reported in 9.5% of the patients in the ibrutinib + CIT arm and 9.0% of the patients in the placebo + CIT arm and diarrhea in 51.2% and 34.7%, major hemorrhage in 3.0% and 1.0%, and arthralgia in 13.9% and 18.1% of the patients, respectively. New malignancies occurring during or after treatment were reported in 14.9% and 13.1% of the patients in the ibrutinib + CIT and placebo + CIT arms, respectively.

Safety data for the subgroups of patients with FL or MZL according to the treatment arm are summarized in supplemental Table 5. The median duration of exposure for patients with MZL was 28.62 months (range, 0.1-96.0 months) for ibrutinib + CIT and 29.32 months (range, 0.7-94.0 months) for placebo + CIT. Rates of treatment-related serious TEAEs (12 patients [42.9%] in the ibrutinib + CIT arm compared with 8 patients [28.6%] in the placebo + CIT arm) and TEAEs leading to dose reduction (8 patients [28.6%] compared with 3 [10.7%] in the ibrutinib + CIT and placebo + CIT arms, respectively) were higher among patients with MZL receiving ibrutinib + CIT than among those receiving placebo + CIT. TEAEs leading to the discontinuation of ibrutinib or placebo in patients with MZL were balanced between the 2 arms (8 [28.6%] and 7 [25.0%], respectively). Seven of 28 patients with MZL receiving ibrutinib + CIT had COVID-19–related TEAEs, and 2 of these patients had COVID-19–related serious TEAEs. Three patients in the ibrutinib + CIT arm (preferred terms: bladder cancer, hypotension, and pneumonia) and 2 patients in the placebo + CIT arm (preferred terms: failure to thrive and small intestinal obstruction) experienced TEAEs leading to death. The most common TEAEs of any grade, occurring in ≥20% of patients with MZL treated with ibrutinib + CIT are summarized in supplemental Table 6.

Patient-reported outcomes

The median time to worsening in FACT-Lym Subscale scores was 24.8 months in the ibrutinib + CIT arm, and 37.0 months in the placebo + CIT arm (HR, 1.27; 95% CI, 0.98-1.64; $P = .0728$; supplemental Figure 3A). Throughout the study, there was a general improvement in the mean FACT-Lym Subscale scores at most time points in both arms (supplemental Figure 3B).

Discussion

In this large, randomized, phase 3 study of patients with R/R FL or MZL who had all received prior treatment with an anti-CD20–containing CIT regimen, the addition of ibrutinib to CIT did not significantly improve PFS compared with placebo + CIT. Although the primary end point of the study was not met, a numerical improvement in the median PFS of 16.7 months was observed, suggesting that continued exposure to ibrutinib provided additional activity beyond the completion of CIT in this setting. The median

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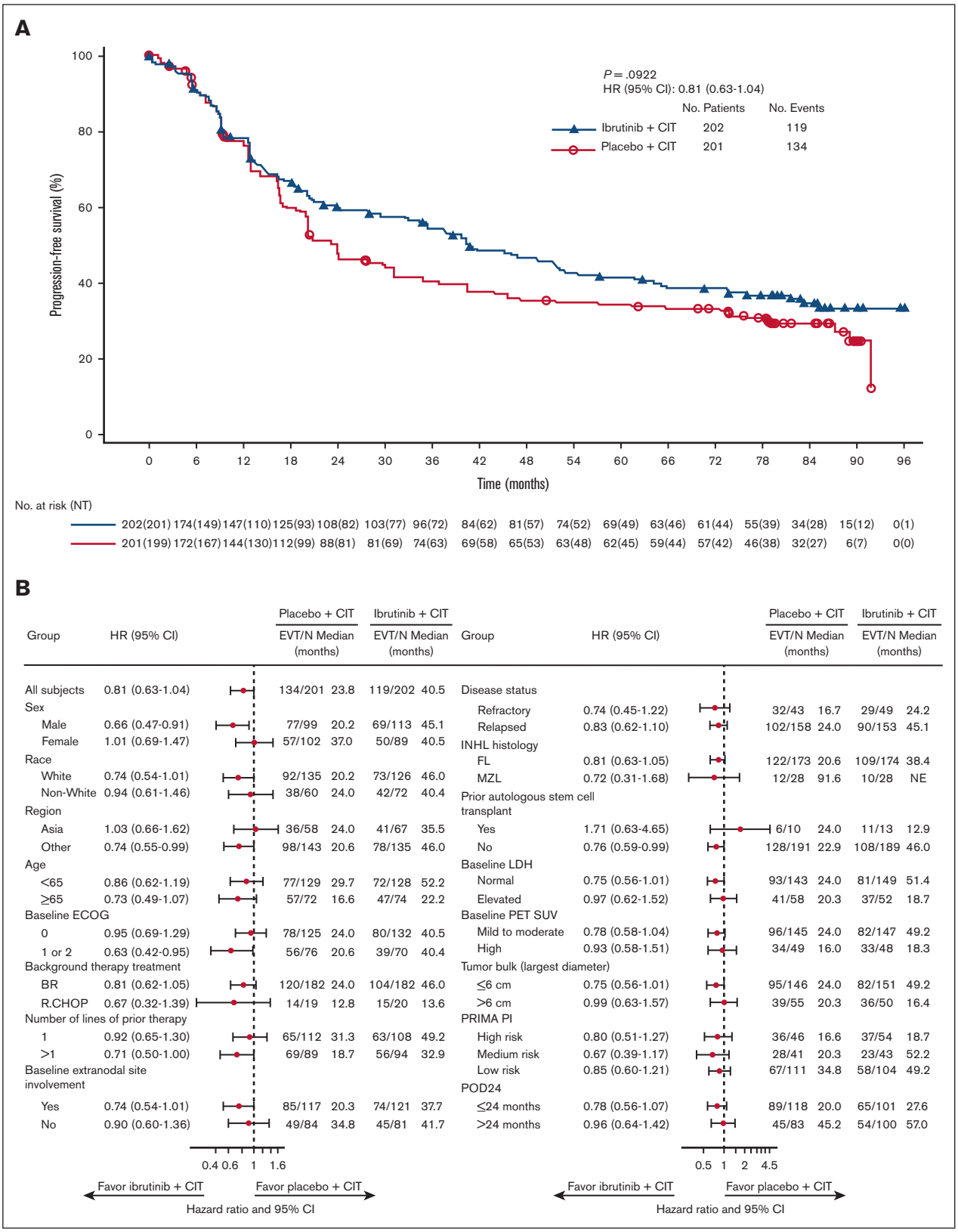


Figure 2. Progression-free survival. (A) Investigator-assessed PFS. (B) PFS as per the subgroup. ECOG PS, Eastern Cooperative Oncology Group performance status; EVT, event; INHL, indolent NHL; LDH, lactate dehydrogenase; NT, number treated; PET SUV, positron emission tomography standardized uptake value (mild to moderate, SUV < 13; high, SUV ≥ 13); PRIMA PI, PRIMA prognostic index.

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Table 3. Response analysis among the intention-to-treat population

Response, n (%)	Ibrutinib + CIT (n = 202)	Placebo + CIT (n = 201)
ORR	185 (91.6)	182 (90.5)
Best response		
CR	111 (55.0)	101 (50.2)
PR	74 (36.6)	81 (40.3)
SD	5 (2.5)	11 (5.5)
PD	4 (2.0)	2 (1.0)
Unknown	8 (4.0)	6 (3.0)

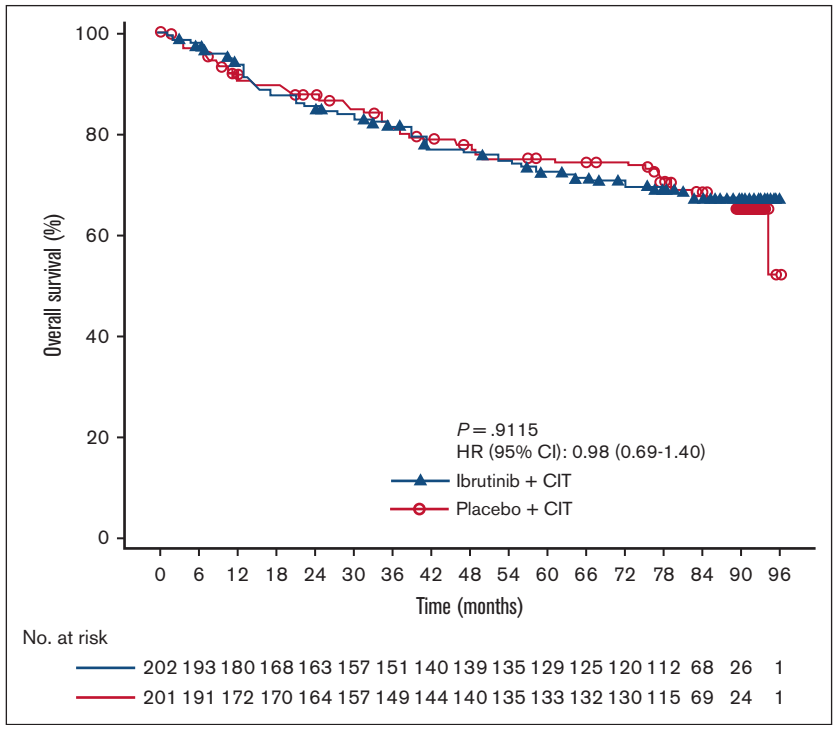
PR, partial response; SD, stable disease.

OS was not reached, which is perhaps unsurprising given the indolent nature of FL and MZL.

The prespecified PFS analysis for the study with the Cox proportional hazards model assumed that the HR is constant over time. However, the PFS Kaplan-Meier curves demonstrated that the treatment effect was variable over time. This may explain why the log-rank test for PFS was not statistically significant despite the observed improvement in the median PFS (ie, 16.8-month difference in the median PFS observed between the control and experimental arm), surpassing the original assumption that informed the study hypothesis (ie, 8.6-month difference in median PFS assumed during study design). In the first 12 to 15 months, there was no difference between treatment arms, but thereafter the curves separated. A post hoc analysis comparing patients with a PFS $\leq$ 12 months vs $>$ 12 months identified several baseline characteristics potentially associated with a worse PFS. For example, more patients with a PFS $\leq$ 12 months in both arms presented with a higher burden of disease and were reported to have had PD within 24 months after their first CIT treatment (POD24), an established risk factor for poor survival.[19] The baseline characteristics of patients with a PFS $>$ 12 months were mostly similar between treatment arms, with more extranodal disease in the ibrutinib + CIT arm (8.8%) than in the placebo + CIT arm (2.1%). The varied treatment effect over time may reflect the heterogeneity of the patient population enrolled in the study. Additional studies, particularly correlative studies are needed to confirm whether there are subgroups of patients with FL/MZL or disease biology that identify those who could benefit from extended treatment with ibrutinib after CIT.

The SELENE study is, to our knowledge, the first randomized, controlled trial of patients with R/R FL and MZL that has CIT as an active comparator for patients who have all had prior exposure to an anti-CD20–containing CIT. Because nearly all patients with indolent NHL receive anti-CD20 therapy as part of their first-line treatment regimen (with or without chemotherapy or another agent),[6,7,20] the patient population recruited to SELENE is highly representative of patients encountered in clinical practice. Before the SELENE study, there were limited data on outcomes with CIT in this patient population. The median PFS of 23.8 months for placebo + CIT observed in this study, to our knowledge, provides the first true understanding of the efficacy of CIT (mainly BR) in this CIT pretreated R/R population. The median PFS of 40.5 months observed with ibrutinib + CIT is a reasonable outcome in the context of other published phase 3 studies in R/R FL and MZL, in which median PFS ranged between 21.5 and 39.4 months.[21-23] In the AUGMENT study, the combination of lenalidomide plus rituximab had a median PFS of 39.4 months in a patient population in which 28% had not received a prior rituximab-containing CIT

Figure 3. OS (intention-to-treat analysis).



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Table 4. **Summary of safety among all patients who received at least 1 dose of study treatment**

Event, n (%)	Ibrutinib + CIT (n = 201)	Placebo + CIT (n = 199)
TEAE	199 (99.0)	197 (99.0)
COVID-19 related	12 (6.0)	3 (1.5)
Treatment related	187 (93.0)	160 (80.4)
TEAE leading to death	13 (6.5)	13 (6.5)
Grade ≥3 TEAE	172 (85.6)	150 (75.4)
Serious TEAE	112 (55.7)	74 (37.2)
COVID-19 related	3 (1.5)	0
Treatment related	70 (34.8)	36 (18.1)
TEAE leading to dose reduction of Ibr or Pbo	41 (20.4)	21 (10.6)
TEAE leading to discontinuation of Ibr or Pbo	62 (30.8)	37 (18.6)

Intestine obstruction, failure to thrive, and respiratory failure in 1 patient each.
Ibr, ibrutinib; Pbo, placebo.

regimen and 16% were rituximab naive.[21] In the CHRONOS-3 study, the combination of copanlisib and rituximab had a median PFS of 25.8 months[22]; in the GADOLIN study, obinutuzumab and bendamustine had a median PFS of 25.8 months for patients who were rituximab refractory.[23]

In a prespecified analysis of the subset of patients with R/R MZL, the median PFS was not reached in the ibrutinib + CIT arm and was longer than anticipated. In the AUGMENT and CHRONOS-3 studies, a median PFS of 20.2 months and 22.1 months, respectively, was observed for patients with R/R MZL.[21,24] Although there was a numerical trend in PFS favoring ibrutinib + CIT, the study was not adequately powered to allow for a formal statistical comparison, given the small number of patients with MZL.

The overall safety profile of ibrutinib + CIT was consistent with the established safety profiles of both ibrutinib and BR/R-CHOP. With a median follow-up of ~7 years, no new safety signals were identified for ibrutinib for patients with FL or MZL. As expected, however, the addition of ibrutinib to CIT resulted in additive toxicity. Among all patients, there was a higher incidence of grade ≥3 TEAEs, serious TEAEs, and TEAEs leading to discontinuation among patients receiving ibrutinib + CIT than among those receiving placebo + CIT. The number of TEAEs leading to death was balanced in both arms. For the small cohort of patients with MZL, the absolute numbers of patients who had grade ≥3 AEs and serious TEAEs were similar in both treatment arms. In terms of AEs associated with BTK inhibitors, the incidence of atrial fibrillation was expectedly higher in the ibrutinib + CIT arm but consistent with the rate previously reported in studies of ibrutinib monotherapy.[15,16] Atrial fibrillation events were generally low grade and manageable, and none led to treatment discontinuation. The incidence of treatment-emergent hypertension was balanced between the treatment arms.

In this large, randomized, phase 3 SELENE study, the addition of ibrutinib to CIT for patients with R/R FL or MZL did not significantly improve PFS. The data provide useful information on the efficacy and safety of BR/R-CHOP for patients previously treated with a CIT regimen, including those with refractory disease, and provide additional understanding about the use of BTK inhibitors in R/R FL or MZL that may inform future studies.

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Authorship

Contribution: T.W., V.G., I.D., and J.F. performed investigation; C.T., H.N., W.M., and F.M. provided resources; A.M.G.-S., Z.M., S.J.K., and M.Ö. performed investigation and provided resources; M.P. and G.H. performed investigation and data curation and provided resources; R.Q. was responsible for methodology, software, formal analysis, and visualization; M.C. was responsible for conceptualization, methodology, validation, formal analysis, visualization, supervision, and project administration, performed investigation and data curation, provided resources, and wrote the original draft; M.R. was responsible for formal analysis, investigation, visualization, and project administration and wrote the original draft; T.H. was responsible for conceptualization, methodology, validation, formal analysis, investigation, visualization, supervision, and project administration; D.B.C. was responsible for conceptualization, methodology, formal analysis, investigation, visualization, supervision, and project administration and wrote the original draft; M.T. was responsible for methodology, validation, and formal analysis; P.M. was responsible for investigation and supervision; J.-Z.H. provided resources and was responsible for data curation and project administration; L.J.N. was responsible for investigation and supervision, provided resources, and wrote the original draft; A.J. performed investigation, provided resources, and was responsible for data curation and project administration; G.S. was responsible for conceptualization, methodology, investigation, and supervision; A.G. was responsible for investigation and project administration and provided resources; M.A.P. was responsible for conceptualization,

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methodology, validation, formal analysis, investigation, and data curation; and all authors reviewed and edited the manuscript.

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ORCID profiles: L.J.N., 0000-0001-6071-8610; G.H., 0000-0002-9282-5688; M.A.P., 0000-0003-4561-3153; A.M.G.-S., 0000-0001-6330-1028; A.J., 0000-0002-1812-412X; P.M., 0000-0002-3959-9730; F.M., 0000-0002-0979-7883; W.M., 0000-0002-4679-0656; M.Ö., 0000-0002-1326-1918; G.S., 0000-0002-9541-8666.

Correspondence: Loretta J. Nastoupil, Department of Lymphoma-Myeloma, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; email: lnastoupil@mdanderson.org.

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