Chemotherapy-free combination of ibrutinib and obinutuzumab for untreated advanced follicular lymphoma: results of a phase II study from the German Lymphoma Alliance

Christian Schmidt,[1*] Gabriel Scheubeck,[1*] Vindi Jurinovic,[1*] Martin Sökler,[2,3] Roswitha Forstpointner,[1] Christian Buske,[4] Andreas Viardot,[4] Ulrich Keller,[5,6] Ullrich Graeven,[7] Reinhard Marks,[8] Mathias Hänel,[9] Rüdiger Liersch,[10] Jan Dürig,[11] Christiane Pott,[12] Eva Hoster,[1,13] Michael Unterhalt[1] and Wolfgang Hiddemann[1] on behalf of the German Lymphoma Alliance (GLA)

[1]Department of Medicine III, University Hospital, LMU Munich, Munich, Germany; [2]Department of Medicine II, University Hospital Tübingen, Tübingen, Germany; [3]Department of Oncology and Hematology, Spital Thun, Thun, Switzerland; [4]Department of Medicine III, University Hospital Ulm, Ulm, Germany; [5]Department of Internal Medicine III, Klinikum Rechts der Isar der TU München, Munich, Germany; [6]Department of Hematology and Oncology, Charité University Hospital, Campus Benjamin Franklin, Berlin, Germany; [7]Department of Hematology, Oncology, Gastroenterology, Kliniken Maria Hilf GmbH, Mönchengladbach, Germany; [8]Department of Medicine I, University Hospital Freiburg, Freiburg, Germany; [9]Department of Medicine III, Klinikum Chemnitz GmbH, Chemitz, Germany; [10]GEHO, Practice for Hematology and Medical Oncology, Münster, Germany; [11]Department of Hematology, University Hospital Essen, Essen, Germany; [12]Department of Medicine II, University Hospital Schleswig-Holstein, Kiel, Germany and [13]Institute for Medical Information Processing, Biometry, and Epidemiology, LMU Munich, Munich, Germany

CS, GS and VJ contributed equally as first authors.

Correspondence: C. Schmidt
Christian_Schmidt@med.uni-muenchen.de

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Abstract

Immunochemotherapy induces long-term responses in patients with follicular lymphoma. However, the toxicity of chemotherapy remains a relevant challenge. The Bruton tyrosine kinase inhibitor ibrutinib has shown significant activity in patients with indolent B-cell lymphoma. Combining ibrutinib with obinutuzumab may, therefore, be an attractive chemotherapy-free option. We conducted a prospective, single-arm, multicenter phase II trial to evaluate the chemotherapy-free regimen of obinutuzumab plus ibrutinib in patients with previously untreated advanced-stage follicular lymphoma. Patients received six 21-day cycles of ibrutinib and obinutuzumab for induction and 12 additional 2-month cycles for maintenance. The primary endpoint was 1-year progression-free survival (PFS). The study was powered to detect an improvement of 10% over the 1-year PFS of 85%. Ninety-eight patients were enrolled in the trial. The median follow-up was 5.5 years. After induction, five patients (5%) had a complete response and 82 (85%) had a partial response. The 1-year PFS was 80%, missing the prospected improvement of a 1-year PFS of 85% (P=0.93). The median PFS was 4.5 years; median duration of response and overall survival were not reached. The most common adverse events of grade 3/4 were neutropenia, lung infection, hypertension, fatigue, rash and thrombocytopenia. The trial of a chemotherapy-free regimen of obinutuzumab and ibrutinib in follicular lymphoma patients failed to demonstrate a 10% improvement in the primary efficacy endpoint. However, the combination produced durable and deep responses and had an acceptable safety profile. Trial registration, EudraCT-Number: 2014-005164-15.

Introduction

Follicular lymphoma (FL) is one of the most frequent nodal indolent lymphomas, accounting for approximately 20% of all non-Hodgkin lymphomas worldwide. The clinical course is characterized by a slow progression over years, with regular relapses despite good response to initial treatment. Immunochemotherapy combining an anti-CD20

antibody (rituximab or obinutuzumab) with chemotherapy backbones such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, prednisone) or bendamustine followed by 2 years of rituximab or obinutuzumab maintenance is considered the standard of care for patients with advanced-stage FL. While such treatments can achieve long-term remissions of more than 10 years, chemotherapeutic combinations induce severe immunosuppression, reduce bone marrow stem cell reserves and have the potential to induce secondary malignancies. Moreover, these regimens set high demands on the treatment logistics for both physicians and their patients.

Minimal residual disease (MRD) has been established as an independent prognostic marker in FL. Achieving MRD negativity after immunochemotherapy predicts prolonged disease control.[1-3]

In recent years a number of new agents have been developed which target biological alterations in lymphoma cells and are easy and safe to use. Ibrutinib, a first-in-class, potent Bruton tyrosine kinase (BTK) inhibitor, is one of these agents and has demonstrated significant activity in patients with indolent non-Hodgkin lymphoma in phase I and II studies.[4-6] Notably, two recent studies investigated the combination of rituximab and ibrutinib, documenting promising response rates.[7,8] However, limitations such as investigation of the potentially less potent CD20 antibody rituximab, limited follow-up time and sample availability for MRD analysis underscore the need for further research to refine treatment strategies and optimize long-term outcomes. It, therefore, appeared attractive to combine ibrutinib with an anti-CD20 antibody and to evaluate the activity of such a chemotherapy-free combination. Anticipating a positive result of the GALLIUM trial, obinutuzumab was chosen as the anti-CD20 antibody.[9]

The German Lymphoma Alliance therefore initiated the phase II ALTERNATIVE trial to assess the efficacy and safety of the chemotherapy-free combination of obinutuzumab plus ibrutinib in patients with previously untreated advanced FL. The primary endpoint of this trial was 1-year progression-free survival (PFS). The results were intended to support the decision of whether it would or would not be worthwhile testing this chemotherapy-free treatment in a confirmatory phase III trial.

Methods

Study design and patients

ALTERNATIVE was a prospective, single-arm, multicenter, national phase II study. Eligible patients were ≥18 years of age and had a previously untreated histologically confirmed FL grade 1, 2 or 3A and advanced-stage disease (stage III/IV or stage II not suitable for radiotherapy, or stage II with bulky disease [nodal or extranodal mass > 7 cm]), at least one bi-dimensionally measurable lesion >2 cm, an Eastern Cooperative Oncology Group performance status of 0 to 2 and adequate hematologic function. Biopsy samples were centrally reviewed to confirm the diagnosis. All patients were in need of treatment on the basis of having bulky disease, B-symptoms, hematopoietic insufficiency with granulocyte counts <1.5×10^9/L, hemoglobin levels <100 g/L and platelet counts <100×10^9/L, compressive syndrome, or pleural/peritoneal effusion caused by lymphoma or symptomatic extranodal manifestations. Before initiation, the study was approved by the responsible ethics committee. All patients provided written informed consent.

Treatment

The study treatment comprised an induction with six 21-day cycles of ibrutinib plus obinutuzumab, followed by 12 additional 2-month cycles of ibrutinib plus obinutuzumab maintenance in patients with at least partial remission (PR) at the end of induction. Ibrutinib was administered once daily orally at a dose of 560 mg until the end of maintenance treatment. Obinutuzumab, at a dose of 1,000 mg, was delivered by intravenous infusion on days 1, 8 and 15 of the first cycle and on day 1 of subsequent cycles.

In patients in clinical remission who were MRD-positive at the end of maintenance treatment, single-agent ibrutinib treatment was continued at a dose of 560 mg for another 12 months (extended maintenance).

Study endpoints

The primary endpoint was the percentage of patients alive without progression at 1 year after registration (1-year PFS). The 1-year PFS was chosen in order to assess the efficacy of the treatment in a timely manner of 2 years (1 year of recruitment plus 1 year of follow-up). The primary outcome was evaluated in an intention-to-treat way, so that only patients without observed progression or death during the first year but with missing staging results were excluded from the analysis, ignoring other protocol violations. Secondary endpoints included PFS (as a time-to-event variable), overall survival (OS), duration of response, complete response (CR) and overall response rate at the end of induction, 1 year after the start of treatment and after the end of maintenance treatment, safety and percentage of MRD-negative patients after the end of induction and maintenance. PFS was defined as the time from registration to lymphoma progression or death from any cause. Patients alive and without documented progression were censored at the time of last contact. OS was calculated from time of registration to death. Patients without an event were censored at the time of last contact. For patients with CR or PR at the end of induction, duration of response was calculated as the time from the end of induction to progression or death from any cause. All secondary variables were evaluated in the intention-to-treat population of all registered patients. Safety was evaluated in all patients

who started treatment with obinutuzumab or ibrutinib.
Responses were assessed by the investigators according to the Revised Response Criteria for Malignant Lymphoma[10] and included physical examinations, computed tomography/magnetic resonance imaging scans, blood tests, laboratory results and bone marrow examinations.
Efficacy evaluations including computed tomography imaging (magnetic resonance imaging if computed tomography was contradicted) were performed after six cycles of induction treatment and every 6 months thereafter until clinical progression. If bone marrow involvement was detected at screening, a bone marrow aspirate for BCL2/IgH (MRD) was required at the end of induction and maintenance for all responders (CR/PR). If no involvement was found, these assessments at 6 and 30 months were optional but strongly recommended for MRD evaluation and potential post-maintenance treatment in MRD-positive patients.
In addition, MRD was assessed on peripheral blood and/or bone marrow samples collected before the start of treatment and at months 3, 6, 9, 12, 18, 24 and 30. Diagnostic peripheral blood and bone marrow samples were initially screened by consensus polymerase chain reaction using Biomed 2 primers[11] to detect a t(14;18) translocation and/or clonal immunoglobulin heavy chain (IgH) rearrangement. In patients with a detectable t(14;18) translocation, real-time quantitative (RQ)-PCR targeting t(14;18) was used to quantify MRD at a sensitivity level of 10^{-5}. In t(14;18)-negative patients, allele-specific primers matching the junctional region of rearranged IgH genes were designed and allele-specific RQ-PCR was conducted to quantify MRD at a comparable sensitivity level.
MRD status in a sample was classified as positive (including low-level positivity below the quantifiable range) or negative. If a patient had MRD values for both peripheral blood and bone marrow, the MRD value was considered positive if either of the two values was positive, and negative if no value was positive and at least one was negative (pooled analysis). MRD analyses were continued every 6 months until clinical progression or until the end of the study.

Sample size and statistical analysis

The study was powered to detect an improvement of 10% in 1-year PFS for the combination of obinutuzumab and ibrutinib as compared to a 1-year PFS of 85% for chemotherapy without antibody treatment in the GLSG2000 trial,[12] estimated from our own updated data. On this basis, a one-sided binomial test with a one-sided significance level of 0.05 was applied to test the primary outcome. All secondary endpoints were evaluated in a hypothesis-generating manner with 95% confidence intervals (95% CI) provided for numeric estimates. For time-to-event data, Kaplan-Meier estimates were calculated with the 95% CI estimated at yearly intervals.

Results

Patients' and treatment characteristics

A total of 98 patients were enrolled into the trial between April 1, 2016 and May 8, 2017. One patient did not start study treatment because of a second diagnosis of Hodgkin lymphoma; one did not have evaluable staging after 1 year and one patient withdrew from the trial after the induction treatment (Figure 1). Sixty patients (61%) finished the full 24 months of maintenance treatment.
The median age of patients in the intention-to-treat population of all registered patients was 59 years (range, 29-81). Fifty-nine (60%) patients were male, 88 (90%) had stage III

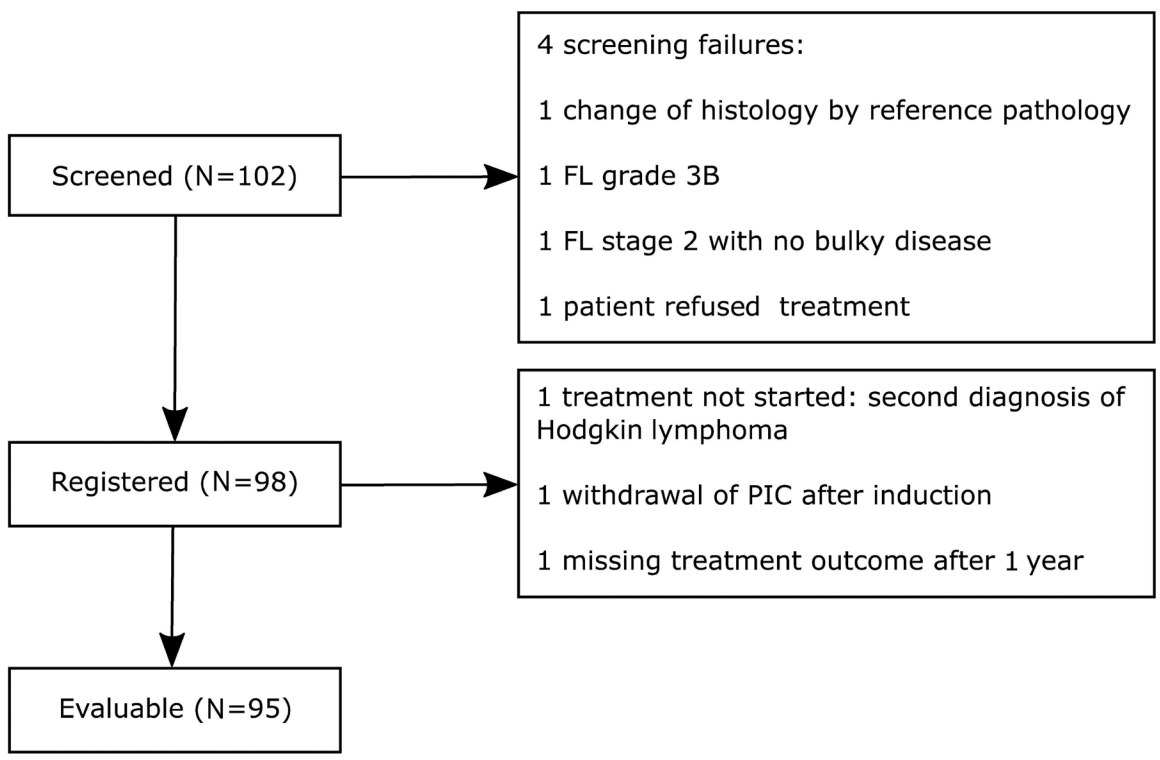

Figure 1. Primary analysis population. FL: follicular lymphoma; PIC: patient's informed consent.

or IV disease and 40 (41%) had a high-risk Follicular Lymphoma International Prognostic Index (FLIPI) score. The main characteristics of the patients are summarized in Table 1.

Efficacy

Primary outcome

After a median follow-up time of 5.5 years, 95 patients were evaluable for 1-year PFS. Five patients had progression of disease during induction treatment, two of whom died within 1 year of registration. Thirteen further patients progressed after induction but within 1 year of registration. One patient died within a year of registration following a PR. Hence, 76 (80%) patients survived without progression for at least 1 year, clearly not supporting our hypothesis of improved 1-year PFS over the 85% observed with the standard antibody-free chemotherapy (P=0.93).

Secondary outcomes

After induction treatment, five patients (5% of 97 evaluable patients) had a CR (95% CI: 2-12), 82 (85%) a PR, five (5%) had stable disease and five (5%) had progression of disease. After 1 year, the CR rate rose to 12% (11 of 95 evaluable patients, 95% CI: 7-20), 63 patients (66%) had a PR, three (3%) had stable disease and 18 (19%) had progression of disease. Thus, overall response rates were 90% (87/97, 95% CI: 82-94) at the end of induction and 78% (74/95, 95% CI: 69-85) after 1 year. Three patients (3%) died within a year of registration, two of whom had previous progression of disease.

When analyzed as a time-to-event variable, the the PFS at 1 year was 83% (95% CI: 76-91), and dropped to 70% after 2 years (95% CI: 61-80) and 63% after 3 years (95% CI: 54-74). The 1-, 2- and 3-year OS were 97% (95% CI: 93-100), 96% (95% CI: 92-100) and 94% (95% CI: 89-99), respectively. The rate of progression of disease within 24 months was 29% (28/95).

After 5.5 years, the median PFS was 4.5 years, while the median OS was not reached. Estimates of PFS and OS are shown in Figure 2. Of note, the 1-year PFS estimated by the Kaplan-Meier method was slightly higher than the estimate for the primary, binary outcome because a time window of 2 weeks was accepted for the binary 1-year PFS status. The estimated binary probability of 80% was comparable to the Kaplan-Meier PFS estimate of 80% 2 weeks after month 12 (Figure 2).

Of 87 patients who had a response after induction, 86% (95% CI: 79-94) had an ongoing response after 1 year, 73% (64-83) after 2 years and 66% (57-77) after 3 years (Figure 2). The median duration of response was not reached.

At the time of data cut-off, a total of 50 (51%) patients had experienced progression of disease. In six patients (6%) the FL had transformed into aggressive B-cell lymphoma. Salvage therapy was started in 70% (35/50) of the patients with progressive disease. Immunochemotherapy was the most frequently used salvage regime (62%), followed by high-dose chemotherapy with autologous stem cell transplantation (ASCT) and radiotherapy in 11% each. Among patients with evaluable staging after salvage therapy, ten had CR (20%) and six had PR (50%),

Table 1. Demographic and disease characteristics of the patients at baseline (intention-to-treat population).

Variable	N evaluable	Value	N (%)
Age	98	>60 years	44 (45)
Sex	98	Male	59 (60)
Histology	98	FL grade 1 FL grade 2 FL grade 3A Hodgkin lymphoma	24 (24) 59 (60) 14 (14) 1 (1)
Quality of histology	98	Confirmed by reference Only local pathology	93 (95) 5 (5)
Ann Arbor stage	98	I II III IV	1 (1) 9 (9) 34 (35) 54 (55)
LDH	98	Above upper normal limit	34 (35)
Hemoglobin	98	<12 g/dL	14 (14)
Involved nodal areas	98	>4	42 (43)
FLIPI risk factors*	98	0 1 2 3 4 5	4 (4) 14 (14) 40 (41) 27 (28) 11 (11) 2 (2)
FLIPI group†	98	Low Intermediate High	18 (18) 40 (41) 40 (41)
ECOG‡	97	0 1 2	71 (73) 25 (26) 1 (1)
B-symptoms	98	Present	41 (42)
Fever	98	Present	2 (2)
Loss of weight	98	Present	25 (26)
Night sweats	98	Present	28 (29)

*Follicular Lymphoma International Prognostic Index (FLIPI) risk factors are hemoglobin level <12 g/dL, more than four nodal areas (with the exception of spleen), age older than 60 years, lactate dehydrogenase level above the upper limit of normal, and Ann Arbor stage III or IV disease. †FLIPI group: the FLIPI score indicates low (0 or 1), intermediate (2), or high (3 to 5) risk on the basis of a scoring system that gives one point for each risk factor. ‡Eastern Cooperative Oncology Group performance status. 0: fully active, able to carry out all pre-disease activities without restriction; 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours. FL: follicular lymphoma; LDH: lactate dehydrogenase; ECOG: Eastern Cooperative Oncology Group.

resulting in an overall response rate of 60%. The 1- and 2-year overall survival rates of progressed patients from the time of disease progression were 85% (95% CI: 73.5-98.1%) and 78% (95% CI: 64.5-93.9%), respectively (*Online Supplementary Figure S1*).

Minimal residual disease

A baseline sample for MRD marker screening was available for 97 patients, but only 68 (70%) had a detectable marker. At baseline, 65 patients of these patients were positive for MRD with the MRD value in the quantitative range, and three were positive but below the quantitative range. MRD at the end of induction was evaluable for 66 patients (40 bone marrow samples, 65 peripheral blood samples), 19 (29%) were MRD-positive (pooled analysis). Among them, 16 had PR, two had stable disease, and one had disease progression. Of the 47 MRD-negative patients (71%), 44 had CR or PR, and one had stable disease. Despite negative MRD, two patients experienced disease progression. Complete molecular remission was achieved in 51 patients (78%) in peripheral blood and 24 (60%) in bone marrow. At 1 year, MRD was evaluable in 49 patients (15 bone marrow, 46 peripheral blood); nine (18%) were MRD-positive, including eight who were also positive at end of induction. Again, two MRD-negative patients had disease progression. Of 60 patients who completed the last maintenance visit (C18D1), 41 had an MRD value at the end of maintenance. Three patients (9%) were MRD-positive at the end of maintenance and started extended maintenance. For 26 patients with a baseline MRD sample who did not complete maintenance, MRD at end of maintenance was estimated from the nearest available measurement. Of 17 patients assessed, ten (59%) were MRD-positive. In total, 58 patients had an MRD result at end of maintenance, with 13 (22%) being MRD-positive.

MRD positivity at end of induction was significantly associated with shorter PFS in patients with CR, PR, or stable disease (hazard ratio [HR]=3.94, 95% CI: 1.91-8.11, P=0.00020) (Figure 3A). The effect was more pronounced in peripheral blood (HR=5.96, 95% CI: 2.74- 12.94, P=6.5x10^{-6}) (Figure 3B) than in bone marrow (HR=3.21, 95% CI: 1.30-7.87, P=0.011) (Figure 3C).

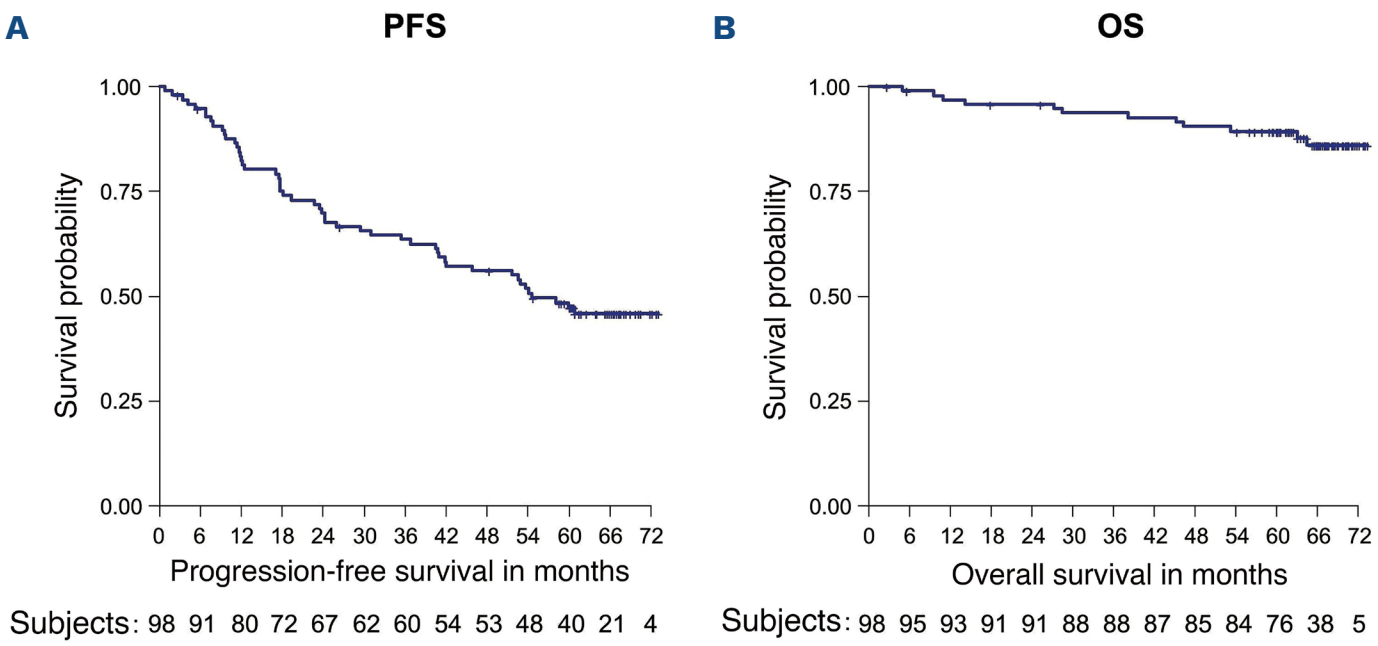

Figure 2. Progression-free survival, overall survival and duration of response among patients with advanced-stage follicular lymphoma treated with obinutuzumab and ibrutinib. (A, B) Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) among 98 patients who were included in the primary efficacy analysis. (C) Kaplan-Meier estimate of the duration of response among the 87 patients of the primary efficacy analysis who had a response. PFS: progression-free survival; OS: overall survival; DoR: duration of response.

Safety

All 97 patients who started treatment had at least one adverse event (AE). During induction treatment, 46 (47%) patients had an AE of grade 3 or 4, with the most common AE reported being neutropenia (7 AE in 7 [7%] patients), hypertension (4 AE in 4 [4%] patients), thrombocytopenia (4 AE in 4 [4%] patients), lymphocytopenia (3 AE in 3 [3%] patients), rash, dyspnea and atrial fibrillation (2 AE in 2 [2%] patients each). No toxicity-related death was reported during induction treatment.

Eighty-six patients started maintenance treatment. During maintenance, 44 patients had an AE of grade 3 or 4, one patient died because of an AE (grade 5 event). The most common AE of grade 3/4 during maintenance were lung infection (7 AE in 5 [5%] patients), fatigue (5 AE in 5 [5%] patients), neutropenia (5 AE in 3 [3%] patients), hypertension (4 AE in 4 [4%] patients) and sepsis (4 AE in 2 [2%] patients).

In the follow-up period, lung infection was the most common AE of grade 3/4 occurring in three patients (3%). There were 15 more AE of grade 3/4, which all occurred in one patient each. Three patients had a grade 5 event (sepsis, aspiration with hypoxia and ventricular fibrillation, and esophageal adenocarcinoma).

Overall, the most common AE of grade 3/4 were neutropenia (12 AE in 10 [10%] patients), lung infection (11 AE in 9 [9%] patients), hypertension (8 AE in 7 [7%] patients), fatigue, rash and thrombocytopenia (5 AE in 5 [5%] patients each). Five cases (5%) of secondary malignancy occurred, none of which seemed to be related to either obinutuzumab or ibrutinib. Table 2 lists all grade 3-5 AE reported in more than one patient.

Discussion

In the search for an alternative chemotherapy-free approach, the current ALTERNATIVE study explored the combination of obinutuzumab and ibrutinib as first-line therapy for patients with advanced stage FL in a prospective, sin-

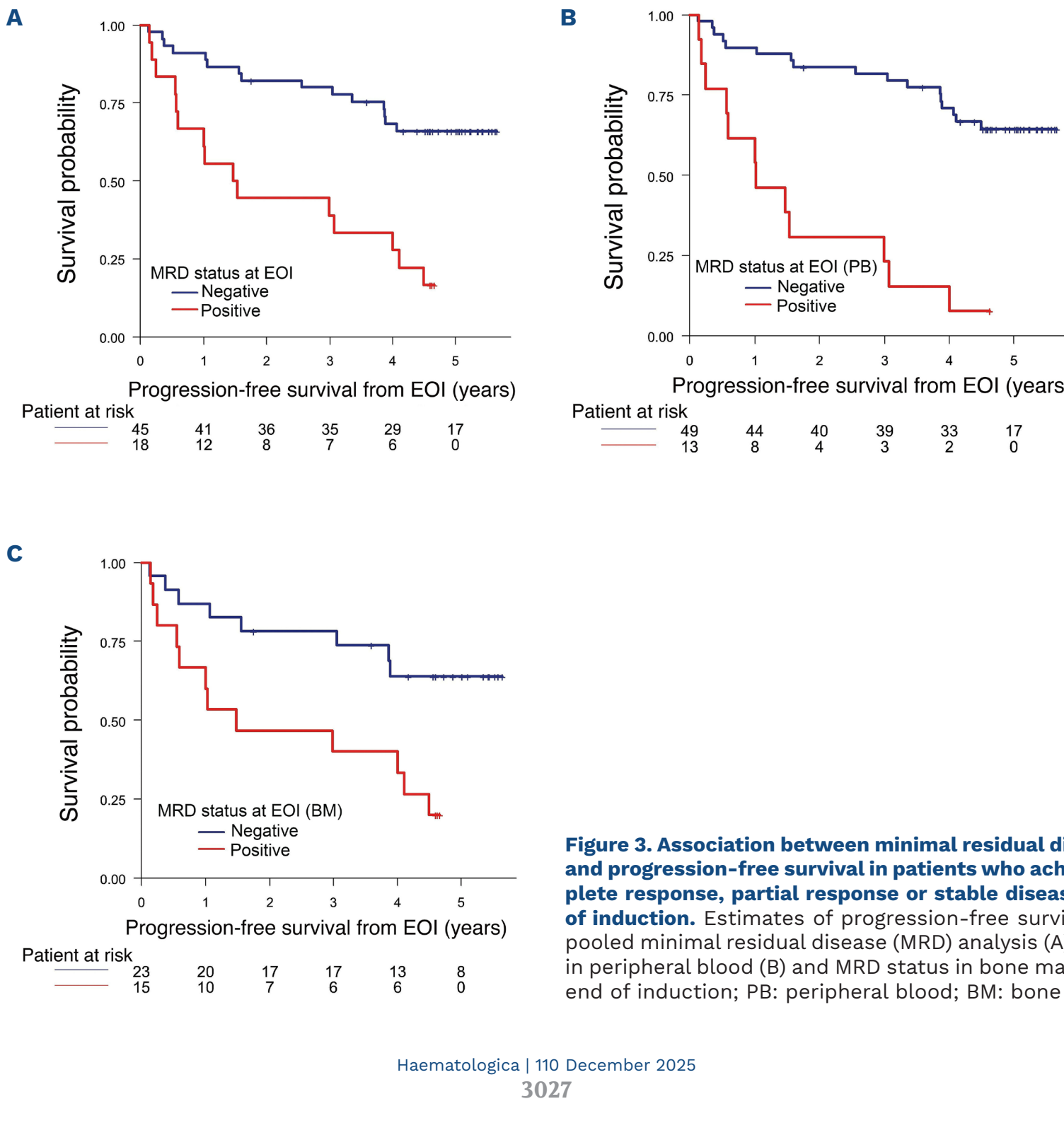

Figure 3. Association between minimal residual disease status and progression-free survival in patients who achieved a complete response, partial response or stable disease at the end of induction. Estimates of progression-free survival based on pooled minimal residual disease (MRD) analysis (A), MRD status in peripheral blood (B) and MRD status in bone marrow (C). EOI: end of induction; PB: peripheral blood; BM: bone marrow.

Table 2. Grade 3-5 adverse events by system organ class category.

SOC/Adverse event	Induction phase N* (%)	Maintenance phase N (%)	Follow-up N (%)	Total N (%)
Blood and lymphatic system disorders	15 (15)	5 (6)	0 (0)	19 (20)
Neutropenia	7 (7)	3 (3)	0 (0)	10 (10)
Thrombocytopenia	4 (4)	1 (1)	0 (0)	5 (5)
Lymphocytopenia	3 (3)	0 (0)	0 (0)	3 (3)
Leukopenia	1 (1)	1 (1)	0 (0)	2 (2)
Other	2 (2)	0 (0)	0 (0)	2 (2)
Cardiac disorders	3 (3)	2 (2)	1 (1)	5 (5)
Atrial fibrillation	2 (2)	1 (1)	1 (1)	4 (4)
Other	1 (1)	1 (1)	0 (0)	2 (2)
Ear and labyrinth disorders	0 (0)	1 (1)	0 (0)	1 (1)
Eye disorders	0 (0)	3 (3)	0 (0)	3 (3)
Gastrointestinal disorders	1 (1)	5 (6)	2 (2)	8 (8)
Abdominal pain	0 (0)	1 (1)	1 (1)	2 (2)
Diarrhea	1 (1)	1 (1)	0 (0)	2 (2)
Gastritis	0 (0)	1 (1)	1 (1)	2 (2)
Other	0 (0)	2 (2)	1 (1)	3 (3)
General disorders and administration site conditions	2 (2)	8 (9)	0 (0)	9 (9)
Fatigue	0 (0)	5 (6)	0 (0)	5 (5)
Fever	0 (0)	2 (2)	0 (0)	2 (2)
Other	2 (2)	2 (2)	0 (0)	4 (4)
Hepatobiliary disorders	0 (0)	2 (2)	1 (1)	3 (3)
Immune system disorders	2 (2)	1 (1)	0 (0)	3 (3)
Infections and infestations	5 (2)	16 (19)	7 (7)	27 (28)
Lung infection	0 (0)	6 (7)	2 (2)	8 (8)
Upper respiratory infection	0 (0)	4 (5)	1 (1)	5 (5)
Sepsis	0 (0)	2 (2)	1 (1)	3 (3)
Other	1 (1)	1 (1)	0 (0)	2 (2)
Herpes dermatitis	0 (0)	1 (1)	0 (0)	1 (1)
Sinusitis fungal	0 (0)	1 (1)	0 (0)	1 (1)
Bacteremia	1 (1)	0 (0)	0 (0)	1 (1)
Gastroenteritis	0 (0)	1 (1)	0 (0)	1 (1)
Corona virus infection	0 (0)	0 (0)	1 (1)	1 (1)
Vulval abscess	1 (1)	0 (0)	0 (0)	1 (1)
Severe acute respiratory syndrome	0 (0)	0 (0)	1 (1)	1 (1)
Diverticulitis	0 (0)	0 (0)	1 (1)	1 (1)
Escherichia infection	0 (0)	1 (1)	0 (0)	1 (1)
Febrile infection	1 (1)	0 (0)	0 (0)	1 (1)
Otitis media	0 (0)	1 (1)	0 (0)	1 (1)
Urinary tract infection	0 (0)	1 (1)	0 (0)	1 (1)
Sinusitis	1 (1)	0 (0)	0 (0)	1 (1)
Injury, poisoning and procedural complications	1 (1)	3 (3)	0 (0)	4 (4)
Investigations	8 (8)	5 (6)	0 (0)	13 (13)
GGT increased	1 (1)	1 (1)	0 (0)	2 (2)
Other	8 (8)	4 (5)	0 (0)	12 (12)
Metabolism and nutrition disorders	1 (1)	3 (3)	1 (1)	5 (5)
Musculoskeletal and connective tissue disorders	3 (3)	5 (6)	0 (0)	7 (7)
Spinal pain	0 (0)	2 (2)	0 (0)	2 (2)
Muscle cramp	1 (1)	1 (1)	0 (0)	2 (2)
Other	2 (2)	2 (2)	0 (0)	3 (3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	3 (3)	1 (1)	4 (4)
Nervous system disorders	2 (2)	1 (1)	0 (0)	3 (3)
Headache	1 (1)	1 (1)	0 (0)	2 (2)
Other	1 (1)	0 (0)	0 (0)	1 (1)

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SOC/Adverse event	Induction phase N* (%)	Maintenance phase N (%)	Follow-up N (%)	Total N (%)
Psychiatric disorders	1 (1)	1 (1)	0 (0)	2 (2)
Renal and urinary disorders Acute kidney injury Other	1 (1) 0 (0) 1 (1)	2 (2) 2 (2) 0 (0)	1 (1) 0 (0) 1 (1)	4 (4) 2 (2) 2 (2)
Reproductive system and breast disorders	1 (1)	0 (0)	1 (1)	2 (2)
Respiratory, thoracic and mediastinal disorders Dyspnea Other	4 (4) 2 (2) 2 (2)	3 (3) 0 (0) 3 (3)	1 (1) 0 (0) 1 (1)	6 (6) 2 (2) 5 (5)
Skin and subcutaneous tissue disorders Rash Other	2 (2) 2 (2) 0 (0)	4 (5) 3 (3) 1 (1)	0 (0) 0 (0) 0 (0)	6 (6) 5 (5) 1 (1)
Vascular disorders Hypertension Other	4 (4) 4 (4) 0 (0)	4 (5) 4 (5) 1 (1)	0 (0) 0 (0) 0 (0)	7 (7) 7 (7) 1 (1)

Only the adverse events reported in more than one patient are displayed by name. All adverse events are displayed for the system organ classification “Infections and infestations”. *N: number of patients with at least one specified adverse event. SOC: system organ class category.

gle-arm, multicenter, phase II study. In spite of promising results from phase I studies demonstrating significant anti-lymphoma activity of ibrutinib,[4,5] the current trial failed to meet the prospected primary endpoint of improving the 1-year PFS of 85% achieved with chemotherapy alone by at least 10%.[13] Our findings can be contextualized within previous research, including the studies by Fowler *et al*.[7] and Østenstad *et al*.,[8] which evaluated rituximab and ibrutinib in similar patient cohorts. While Fowler *et al*.[7] observed comparable overall response rate and PFS data, our study adds to this knowledge by longer follow-up and more detailed MRD assessment. The combination of ibrutinib with obinutuzumab resulted in a higher 3-year PFS compared to its combination with rituximab, which Østenstad *et al*.[8] reported to be 45%. Furthermore, PFS was inferior to the results of phase III studies with chemotherapy together with obinutuzumab. The 3-year PFS of obinutuzumab plus ibrutinib was 63% while obinutuzumab plus chemotherapy achieved a 3-year PFS of 80% in the GALLIUM trial.[14]

In contrast to these rather disappointing results, the recent RELEVANCE phase III study demonstrated a comparable efficacy of the chemotherapy-free combination of rituximab and lenalidomide compared to conventional immunochemotherapy in previously untreated FL patients with fewer episodes of febrile neutropenia.[15] The 3-year OS of 94% in our study is in line with data from the GALLIUM trial with an OS rate of 92% at 3 years[14] and from the rituximab-chemotherapy group of the RELEVANCE trial with an OS rate of 94% at 3 years.[15]

Assessment of MRD revealed that 70% of patients with an evaluable MRD marker turned negative after induction in the pooled peripheral blood/bone marrow analysis. The rate of complete molecular response is inferior compared to that achieved with rituximab and chemotherapy (77%) and rituximab and lenalidomide (90%) in the RELEVANCE trial.[16] As reported by others, MRD negativity was associated with a longer PFS while MRD positivity predicted a poorer outcome.[2,17] The poor prognostic value of MRD positivity was stronger in the peripheral blood compared to bone marrow, suggesting that persistence of molecular disease in peripheral blood is an even stronger negative predictor of outcome.

The safety analysis revealed expected AE consistent with the known safety profiles of the study drugs. During induction therapy, the most common grade 3 or 4 AE were hematologic toxicity. There were no fatal AE. During maintenance treatment, pneumonia and fatigue were the most common grade 3/4 events and three events were fatal.

The most common grade 3/4 AE during the trial were pneumonia, neutropenia and thrombocytopenia. Serious AE appeared in 52 patients (53%), which is in line with the findings of a previous study investigating ibrutinib as monotherapy in relapsed or refractory FL patients in whom 48% had serious AE.[18]

Even though the prospected endpoint in the ALTERNATIVE trial was not achieved, the combination of ibrutinib and obinutuzumab is a chemotherapy-free regimen that is capable of producing durable responses and MRD negativity in previously untreated FL patients. Gopal *et al*. reported that regulatory T cells were downregulated only in patients responding to ibrutinib while the Th1-promoting cytokines interleukin-12 and interferon-γ were significantly increased.[18] This suggests that a response to ibrutinib might be linked to the inhibitor’s T-cell immunomodulatory effects. While BTK inhibitors exhibit immunomodulatory effects that enhance T-cell activity, potential drawbacks must also

be considered. Da Roit *et al*. reported that ibrutinib can negatively affect the efficacy of anti-CD20 therapies by inhibiting key cell-mediated immune mechanisms.[20] Their study demonstrated that ibrutinib suppresses natural killer cell activation, antibody-dependent cellular cytotoxicity, and macrophage- and neutrophil-mediated phagocytosis, which are critical pathways for the antitumor activity of anti-CD20 antibodies such as obinutuzumab.

Characterizing patients with durable responses to ibrutinib more deeply might, therefore, enable identification of a subgroup of patients who might benefit from treatment with a BTK inhibitor.

Given the lack of clear superiority of obinutuzumab plus ibrutinib over standard immunochemotherapy, the findings of the ALTERNATIVE trial do not support the immediate adoption of the combination as a new standard-of-care regimen for untreated FL. However, this combination was demonstrated to induce MRD negativity and durable responses in a subgroup of patients, suggesting that further research - potentially in a biomarker-selected population - may refine the role of chemotherapy-free approaches in this disease. Future studies should focus on identifying subgroups of patients who may benefit most from targeted therapy combinations.

Disclosures

No conflicts of interest to disclose.

Contributions

CS, WH and MU conceived the trial. VJ, EH and MU performed the formal analysis. CS, GS and VJ assembled data and wrote the original draft of the paper. EH and WH reviewed and edited the paper. CS, GS, MS, RF, CB, AV, UK, UG, RM, MH, RL and JD collected clinical data. CP performed the MRD analysis. All authors approved the final version of the manuscript and are accountable for all aspects of the work.

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Data-sharing statement

The data generated and analyzed during this study are available from the corresponding author on reasonable request.

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