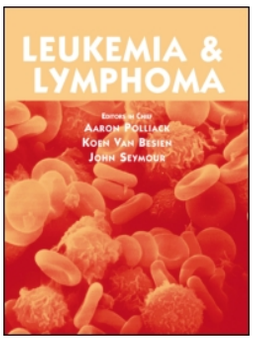

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Phase III, randomized study of ofatumumab versus physicians' choice of therapy and standard versus extended-length ofatumumab in patients with bulky fludarabine-refractory chronic lymphocytic leukemia

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ABSTRACT

We report results of a randomized, phase III study of ofatumumab versus physicians' choice treatment in patients with bulky fludarabine-refractory chronic lymphocytic leukemia and explore extended versus standard-length ofatumumab treatment. Patients (79 ofatumumab, 43 physicians' choice) completed a median 6 (ofatumumab) or 3 (physicians' choice) months' therapy. Ofatumumab-treated patients with stable disease or better were randomized (2:1) to 6 months' extended ofatumumab treatment or observation. Although the study did not meet the primary endpoint of progression-free survival (PFS) by independent review committee (ofatumumab: 5.4 months, physicians' choice: 3.6 months; $p = 0.27$), median PFS by investigators was significantly longer for ofatumumab versus physicians' choice (7.0 versus 4.5 months; $p = 0.003$) as was time to next therapy (median 11.5 versus 6.5 months; $p = 0.0004$). PFS and time to next therapy were significantly longer with ofatumumab extended treatment than observation ($p = 0.026$ and $p = 0.002$, respectively; $n = 37$). The adverse-event profile of long-term ofatumumab administration showed no unexpected findings (Clinicaltrials.gov identifier: NCT01313689).

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Introduction

Ofatumumab, an anti-CD20 human monoclonal antibody, is approved for patients with double-refractory (DR) CLL who are refractory to both fludarabine and alemtuzumab. Patients with bulky (lymphadenopathy >5 cm) fludarabine-refractory (BFR) CLL also had a high unmet medical need because available treatment options such as alemtuzumab appear to be less effective, with response rates ranging from 8% to 12%,[1–3] and are associated with increased toxicity.[4] In the retrospective study from 2007 by Tam et al. [5] examining salvage therapies for refractory CLL, the response rate for BFR CLL patients was 26%, and none of the patients responded to monotherapy with monoclonal antibodies. The median time to treatment failure was 2–3 months, with an overall survival (OS) of 14 months.[5] The recently available small therapeutic molecules ibrutinib and idelalisib have changed this perspective for patients with refractory CLL, even though not all patients respond and relapses continue to occur.[6–9] Thus, development of new drugs, as well as optimizing the use of existing therapies, remains an important issue.

In a previous non-randomized study (Hx-CD20-406), single-agent ofatumumab was administered over 24 weeks to patients with CLL who were either refractory to both fludarabine and alemtuzumab (DR, $n = 95$) or

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who were refractory to fludarabine and were considered ineligible for alemtuzumab treatment due to bulky lymphadenopathy (BFR, $n = 112$). The overall response rate (ORR) was 47% (49% DR, 43% BFR), median progression-free survival (PFS) was 5.5 months (4.6 months DR, 5.5 months BFR), and median OS was 17.3 months (13.9 months DR, 17.4 months BFR). The treatment was well tolerated, with no unexpected toxicities, but relapses tended to occur rapidly after the ofatumumab treatment period.[10]

The present study, OMB114242, an open-label, randomized, phase III study of ofatumumab versus physicians' choice (PC) therapy, was conducted in patients with BFR CLL to verify in a randomized setting whether ofatumumab is effective but also, through a second randomization after 24 weeks, to compare extended ofatumumab treatment (up to a total of 12 months) versus no further treatment (observation after week 24). PC therapy was considered an appropriate comparator at the time of initiation of this study, given that no consensus existed around standard-of-care treatment for this difficult-to-treat population.

Materials and methods

Patients

Eligible patients were ≥18 years old, had a diagnosis of BFR CLL based on the modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL)-updated National Cancer Institute – Working Group (NCI-WG) guidelines,[11] had bulky lymphadenopathy (at least one lymph node >5 cm, determined by physical assessment), were refractory to fludarabine (either no response to ≥2 cycles of a fludarabine-containing regimen, or PR or better lasting <6 months after ≥2 cycles of a fludarabine-containing regimen [11]), had active disease requiring therapy,[11] had at least 2 prior therapies for CLL, and had Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.[12]

Exclusion criteria included prior allogeneic stem cell transplantation, prior autologous stem cell transplantation within 6 months of randomization, known transformation of CLL, prolymphocytic leukemia (PLL), CNS involvement of CLL, or active autoimmune hemolytic anemia (AIHA) requiring treatment except if associated with active CLL.

Study design and treatment

This study was an open-label, 2-arm, randomized, phase III study of ofatumumab or PC treatment in patients with BFR CLL. Patients were randomized 2:1 to receive the approved standard length of ofatumumab or PC treatment for up to 24 weeks (6 months). Ofatumumab treatment consisted of eight weekly infusions followed by four monthly infusions (dose 1: 300 mg; dose 2–12: 2000 mg). PC treatment was non-ofatumumab-containing therapy, including treatments approved for CLL and all well-established standards of care, for up to 6 months. Patients in the ofatumumab arm who did not have disease progression after 6 months of treatment, as assessed by the investigator, were eligible for a second 2:1 randomization to receive either six additional infusions (2000 mg every 4 weeks) (ofatumumab extended) or no further treatment (observation). Patients in the PC arm who developed progressive disease (PD) could receive ofatumumab salvage therapy for up to 12 months.

The trial was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines, and its protocol and conduct were approved by the ethics committee for each participating center. Written informed consent was obtained from each subject. The study, initiated on 28 April 2011, is registered at clinicaltrials.gov (NCT01313689).

Efficacy evaluations

The primary endpoint was progression-free survival (PFS), defined as the time from randomization to the date of PD or death due to any cause. For patients who did not progress or die, PFS was censored at the time of last follow-up. PD was determined by an Independent Review Committee (IRC), using the 2008 update of the NCI-WG CLL guidelines.[11]

Secondary endpoints were investigator assessment of PFS, overall response rate (ORR) assessed by the IRC and investigators (percentage of patients achieving either complete response [CR] or a partial response [PR]), OS (time from randomization to death due to any cause), and time to next therapy for CLL (TNT; time from randomization until start of next-line treatment).

Investigators conducted clinical assessments and response evaluations were based on blood counts, constitutional symptoms, and physical examination of lymph nodes, spleen, and liver. The investigators did not use results of any CT scans to make their response assessments in the study. The IRC used the same data for constitutional symptoms, physical examination, use of concomitant blood products and central laboratory data of blood counts, and bone marrow analysis in their response assessments. The IRC also conducted a sensitivity analysis whereby physical examination of lymph node, liver, and spleen size was replaced with CT assessments. CT scans were performed at screening, at

least 2 months after best response for CR and PR, and after disease progression.

Patient-reported outcome assessments were performed at baseline, every 3 months throughout active therapy, during follow-up, and after disease progression was determined. Three domains of the QLQ-CLL16 were pre-specified: fatigue, treatment side effects, and disease effects. Differences were assessed using mixed-model repeated measurement for data up to week 24.

Safety evaluations

Safety assessments included monitoring and recording of all adverse events (AEs), serious AEs (SAEs), and evaluation of AEs of special interest, such as cytopenias and autoimmune hematologic complications.

Statistical analysis

The intent-to-treat (ITT) population included all patients randomized at the first randomization. The safety population included all patients who received at least one dose of study drug.

A total of 120 patients were planned for enrollment to observe 95 events of PD or death. Approximately 95 events were needed to achieve at least 90% power to demonstrate a treatment-arm difference in median PFS of 3 months in the primary comparison (ofatumumab versus PC arm, 6 months versus 3 months) at a 2-sided alpha level of 5%.

The PFS (IRC and investigator assessments), as well as OS and TNT, was compared using stratified log-rank tests. ORR was compared using conditional logistic regression analysis. AEs and clinical safety endpoints were reported using descriptive statistics.

Role of the funding source

This study was sponsored by GlaxoSmithKline and Genmab; ofatumumab is an asset of Novartis AG as of 2 March 2015. GlaxoSmithKline and Genmab provided the drug and worked closely together with the investigators in the development of study design and interpretation of the data. GlaxoSmithKline and Genmab funded the study and were also responsible for collection and analysis of the data. Of the sponsor, only Chai-Ni Chang had access to the raw data after the official treatment unblinding.

Results

Patients and treatment

One hundred twenty-two patients underwent the first randomization to receive ofatumumab ($n = 79$) or PC ($n = 43$) (Figure 1) at 41 centers in 14 countries. The clinical characteristics are shown in Table 1. Median ages were 61.5 and 63 years, and median numbers of prior regimens were 4 and 3, respectively. A 17p deletion was found in 20% of all patients.

Overall, patients received a median of six treatment cycles (12 infusions; 6 months of therapy) in the ofatumumab arm, with patients who underwent the second randomization receiving a median of 12 cycles (18 infusions; 12 months of therapy) in the ofatumumab-extended arm ($n = 24$) and a median of six cycles (12 infusions) in the observation arm ($n = 13$).

In the PC arm, patients received a median of three treatment cycles. PC therapies and cycle duration varied, with 44% of patients receiving <3 cycles and 56% receiving 3–6 cycles. The most common treatment regimens in the PC arm were classified as alkylator-based combination regimens (28%) or alemtuzumab-based monotherapy or combination therapies with corticosteroids (26%). While 16 patients in the PC arm received a rituximab-containing chemotherapy regimen, only two received single-agent rituximab. Further details of the PC treatments are given in Table 2. Of the 43 patients randomized to the PC arm, 22 received ofatumumab salvage therapy after PD.

Prophylactic antibiotics or anti-viral therapy were administered to 66% of all patients; the proportion of patients who received prophylaxis was generally comparable among treatment arms and across the different antibiotic types. Aciclovir (44%), trimethoprim (43%), and sulfamethoxazole (40%) were the most common prophylactic agents received. Granulocyte colony-stimulating factor (G-CSF) was administered to 29% of patients in the OFA arm, 37% in the PC arm, 38% in the OFA-extended arm, and 8% in the observation arm. Erythropoiesis-stimulating agents were only given to three patients in the OFA arm and four patients in the PC arm. The median time to first dose of G-CSF was 22 d in the OFA versus 8 d in the PC arm, likely due to the use of combination chemotherapy in the PC arm.

The median treatment duration was 161 d (5.4 months) for the ofatumumab arm and 64 d (2.1 months) for the PC arm. The median duration of follow-up was 362 d (12 months) in the ofatumumab arm and 149 d (5.0 months) in the PC arm. Patients in the PC arm who received ofatumumab salvage therapy at progression were not included in the PC group follow-up, contributing to the large difference in the follow-up time between the two arms.

The duration in the study for the ofatumumab treatment arm included data from subjects who were randomized to the second randomization if they did not

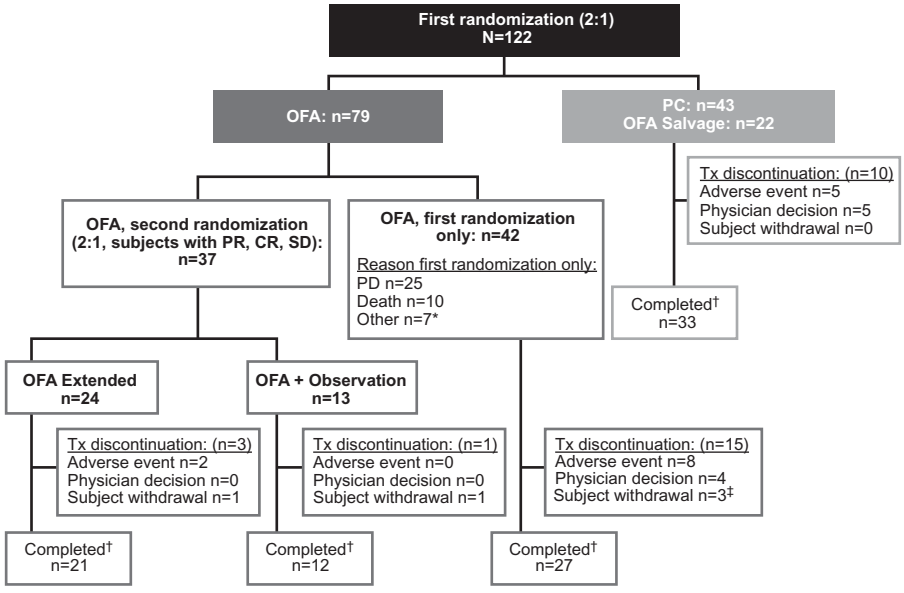

Figure 1. CONSORT diagram: phase III study of ofatumumab versus PC and standard versus extended-length ofatumumab treatment in patients with BFR CLL. BFR, bulky fludarabine-refractory; CLL, chronic lymphocytic leukemia; CR, complete response; OFA, ofatumumab; PC, physicians' choice; PD, progressive disease; PR, partial response; SD, stable disease; Tx, treatment. *For two patients the investigator suspected PD and started new treatment, and five patients were withdrawn. †Patients who completed treatment and entered follow-up for progression, or patients with PD or death. ‡Excludes one patient who was documented as "protocol completed" and withdrew consent due to disease progression.

have PD at the end of the first randomization. Therefore, the longer duration in this arm was due to the days after the second randomization.

For the PC treatment arm, the duration in the study included data from subjects who entered the PC arm at the first randomization; however, if they entered the ofatumumab salvage therapy arm, the duration after ofatumumab salvage was NOT counted. That is, for subjects in the PC arm who received ofatumumab salvage therapy, duration in the study was defined as days from randomization to the start of ofatumumab treatment.

Efficacy

The primary endpoint of IRC-assessed median PFS was 5.4 months in the ofatumumab arm compared with 3.6 months in the PC arm ($p = 0.27$) (Figure 2A). In contrast, a sensitivity analysis of investigator-assessed PFS demonstrated significantly longer median PFS in the ofatumumab arm compared with the PC arm (7.0 versus 4.5 months, $p = 0.003$) (Figure 2B).

The IRC-assessed overall response rate (ORR) was higher in the ofatumumab arm (38% versus 16%, $p = 0.019$). Investigator-assessed ORR was 49% in the ofatumumab arm compared with 37% in the PC arm ($p = 0.42$). Patients in the ofatumumab arm had significantly longer TNT (median 11.5 versus 6.5 months, $p = 0.0004$) (Figure 3A). The median overall survival was 19.2 months with ofatumumab versus 14.5 months with PC ($p = 0.13$) (Figure 3B). Subgroup analysis of IRC-assessed PFS by demographics and baseline characteristics, including in patients with 17p and 11q deletions, is displayed in Figure 4. Patients with 17p– in the ofatumumab arm had a median PFS of 4.3 months compared with 3.5 months for patients with 17p– in the PC arm (HR = 0.71; 95% CI: 0.26–1.92).

An ad hoc analysis was performed to investigate the impact of the number of prior therapies (1–2 versus $\geq$3) on the IRC-assessed PFS. Twenty-one (27%) patients in the ofatumumab arm received 1–2 prior therapies compared with 14 (33%) patients in the PC arm. There were 58 (73%) patients in the ofatumumab arm and 29 (67%) patients in the PC arm who received $\geq$3 prior therapies. The median PFS for patients with 1–2 prior therapies were 5.4 and 5.3 months for ofatumumab and PC arms, respectively. The median PFS was similar in both arms; however, it should be noted that sample size was small and any difference between the arms would, therefore, be unlikely to be apparent. The median PFS for patients with $\geq$3 prior therapies were 4.9 and 3.5 months for the ofatumumab and PC arms, respectively.

The second randomization of patients in the ofatumumab arm who had SD, PR, or CR after 24 weeks of ofatumumab treatment, to either ofatumumab extended treatment or observation, was based on the investigator's response assessment, and therefore, investigator-

Table 1. Demographic and baseline disease characteristics.

	Ofatumumab[a] (*n*=79)	PC[b] (*n* = 43)
Age, years		
Median (min–max)	61.5 (46–82)	63.0 (40–76)
≥65 years, *n* (%)	33 (42)	19 (44)
≥75 years, *n* (%)	9 (12)	3 (7)
Sex, n (%)		
Male	55 (70)	29 (67)
Female	24 (30)	14 (33)
Modified Rai stage, n (%)		
Low risk (Stage 0)	0	0
Intermediate risk (Stages I and II)	33 (42)	18 (42)
High risk (Stages III and IV)	43 (54)	24 (56)
Binet stage, n (%)		
A	6 (8)	3 (7)
B	34 (43)	15 (35)
C	38 (48)	25 (58)
Chromosomal aberrations[c], n (%)		
17p deletion	15 (19)	9 (21)
11q deletion	21 (27)	12 (28)
12q trisomy	7 (9)	5 (12)
13q deletion	37 (47)	18 (42)
No abnormalities found	23	14
ECOG performance status, n (%)		
0, 1	70 (89)	38 (88)
2	9 (11)	5 (12)
Prior anti-cancer therapy		
Number of prior therapies (min–max)	4 (2–16)	3 (2–11)
Type, *n* (%)		
Fludarabine-based[d]	79 (100)	43 (100)
Alkylator-based	44 (56)	19 (44)
Bendamustine-based[e]	24 (30)	18 (42)
Monoclonal antibodies		
Alemtuzumab-based	12 (15)	7 (16)
Rituximab-based	8 (10)	11 (26)
Glucocorticoid-based	2 (3)	1 (2)
Small molecule targeted therapy	1 (1)	1 (2)

ECOG, Eastern Cooperative Oncology Group; PC, physicians' choice.
[a]Ofatumumab includes all patients assigned to ofatumumab at the first randomization, including *n* = 37 patients who underwent a second randomization to either ofatumumab extended treatment for an additional 24 weeks (*n* = 24) or observation (*n* = 13).
[b]PC includes all patients assigned to PC at the first randomization, including *n* = 22 patients who received ofatumumab salvage after PD.
[c]The TP53 mutation test was not available/performed in this study.
[d]Includes FCR (28 [35%] patients in the ofatumumab arm and 18 [42%] patients in the PC arm).

assessed PFS, TNT, and OS are presented in the following paragraph with time starting from the second randomization.

Extending ofatumumab treatment was associated with an improvement in PFS from time of second randomization (*n* = 24; median 5.6 months), compared with observation (*n* = 13; median 3.5 months; *p* = 0.026) (Figure 5A). TNT was also significantly longer in the ofatumumab extended treatment arm than in the observation arm (median 9.2 versus 2.8 months, *p* = 0.002) (Figure 5B). The median OS times from second randomization were 25.4 months and 17.8 months, respectively (*p* = 0.65; data not shown). Patients in the PC arm who had PD and started ofatumumab salvage (*n* = 22) achieved an ORR of 50% and a median PFS of 5.4 months.

Table 2. Treatment regimens administered in the PC arm.

Treatment regimen	PC (*n* = 43)
Alemtuzumab-based therapy, *n* (%)	11 (26)
Combination therapy[a]	5 (12)
Monotherapy	6 (14)
Alkylator-based therapy, *n* (%)	12 (28)
Combination therapy	12 (28)
Monotherapy	0
Bendamustine-based therapy, *n* (%)	5 (12)
Combination therapy	4 (9)
Monotherapy	1 (2)
Chlorambucil-based therapy, *n* (%)	4 (9)
Combination therapy	3 (7)
Monotherapy	1 (2)
Fludarabine-based therapy, *n* (%)	6 (14)
Combination therapy	5 (12)
Monotherapy	1 (2)
Glucocorticoid-based therapy, *n* (%)	3 (7)
Combination therapy	0
Monotherapy	3 (7)
Rituximab-based therapy ± prednisone therapy	2 (5)
Combination therapy	2 (5)
Monotherapy	0

PC, physicians' choice.
Patients in the PC treatment arm could have received more than 1 study drug. Treatment regimens in the PC arm were classified using a hierarchical order (for example, regimens containing fludarabine and alemtuzumab were classified as alemtuzumab-based therapy rather than fludarabine-based therapy).

A significant difference was observed for the patient-reported outcome of fatigue, as demonstrated by a change from baseline between the arms up to week 24, with patients on ofatumumab showing less fatigue (*p* = 0.008). No significant differences were observed between arms in treatment side effects (*p* = 0.15) or in patient-reported disease effects (*p* = 0.83).

Safety

Ninety percent of patients in the ofatumumab arm and 79% of patients in the PC arm had at least 1 AE up to 60 d after last dose; 50% and 51% of patients, respectively, had serious AEs (SAEs). The most common AEs (≥15% in either arm) were neutropenia (26% in ofatumumab, 28% in PC), pneumonia (17% versus 19%), and anemia (9% versus 19%). The most common ≥ grade 3 reported AEs are shown in Table 3.

Infusion reactions occurred in 42% of patients in the ofatumumab arm and in 26% of patients in the PC arm. In the ofatumumab arm, 5% of patients had an infusion reaction that was ≥ grade 3 (none were fatal).

The proportions of patients with infection AEs were similar in the ofatumumab and PC arms (59% versus 56%). SAEs of infections occurred in 32% of patients in the ofatumumab arm and in 28% of patients in the PC arm. Infection SAEs were primarily pneumonia (12% ofatumumab, 14% PC). In addition, there were

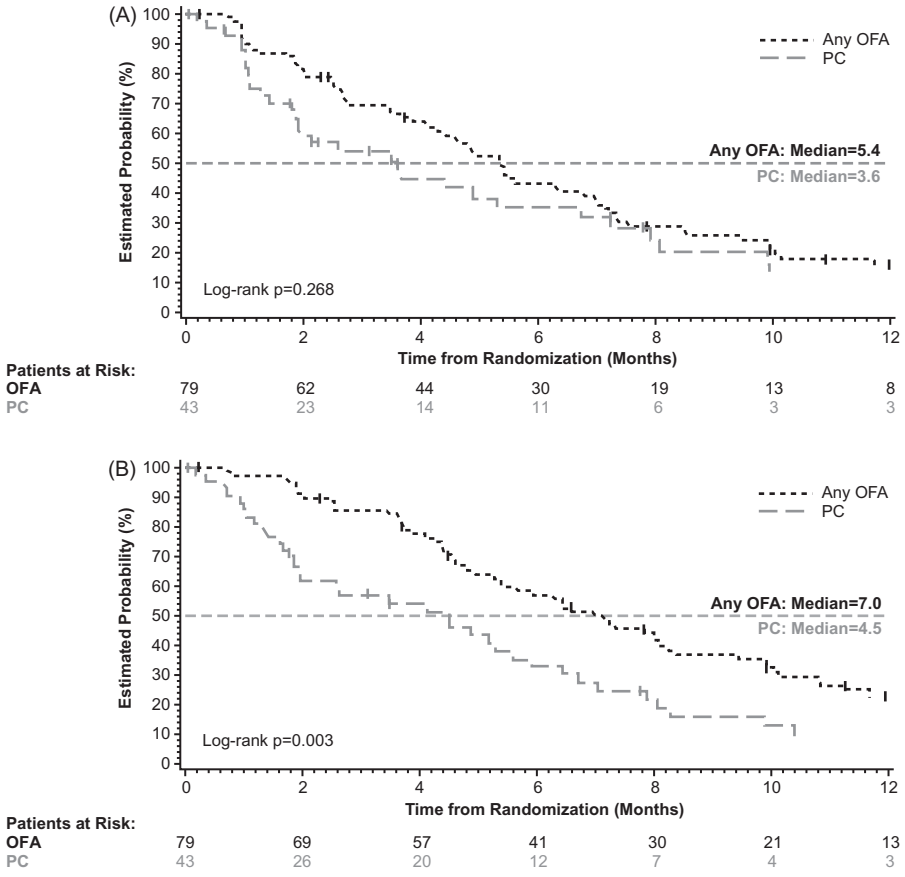

Figure 2. (A) Kaplan–Meier estimates of IRC-assessed PFS in patients treated with OFA ($n = 79$) or PC ($n = 43$). PFS defined as time from first randomization until disease progression or death. (B) Kaplan–Meier estimates of investigator-assessed PFS in patients treated with OFA ($n = 79$) or PC ($n = 43$). IRC, independent review committee; OFA, ofatumumab; PFS, progression-free survival; PC, physicians' choice.

six patients (14%) with SAEs of sepsis in the PC arm, and one patient (1%) in the ofatumumab arm. Fatal SAEs of infections occurred in 5% and 7% of patients, respectively.

Overall, 63 deaths were reported in either the ofatumumab arm (36/78, 46%) or the PC arm (27/43, 63%). Of the 36 deaths in the ofatumumab arm, 24 occurred prior to the second randomization; 16 of these were assessed as disease-related by investigators and eight were due to SAEs of which two were considered related to ofatumumab treatment (one cardiac failure and one renal failure). Four deaths occurred after ofatumumab-extended treatment; two were assessed as disease-related by investigators and two were due to SAEs, of which one was considered related to ofatumumab treatment (multi-organ failure). A further four deaths occurred after randomization to the observation group; two were disease-related and two were due to SAEs, of which one was considered related to ofatumumab treatment (progressive multifocal leukoencelopathy). Of the 27 deaths in the PC arm, 13 occurred in patients who did not receive ofatumumab salvage therapy, and 14 of the deaths occurred during or after ofatumumab salvage therapy. The majority of all deaths (40/63) were judged by investigator as disease-related (ofatumumab 30%, PC 37%). Overall, 36 of the 63 deaths (ofatumumab 27%, PC 35%) occurred more than 60 d after the last dose of study drug.

Discussion

Results from this study show some degree of activity for ofatumumab monotherapy in patients with BFR CLL. Although the study did not meet the primary endpoint of demonstrating statistically significant superior PFS as assessed by the IRC, the PFS assessed by the investigators was significant. The sample size estimation for this study was based on assumptions for median PFS of 6 months in the ofatumumab arm (for patients receiving 24 weeks of ofatumumab treatment) and of 3 months in the PC arm. The 3-month PFS assumption for the PC arm was based on retrospective data in patients with BFR CLL from a single-center study.[5] The actual median PFS observed in the PC arm of the present study OMB114242 (3.6 months) was

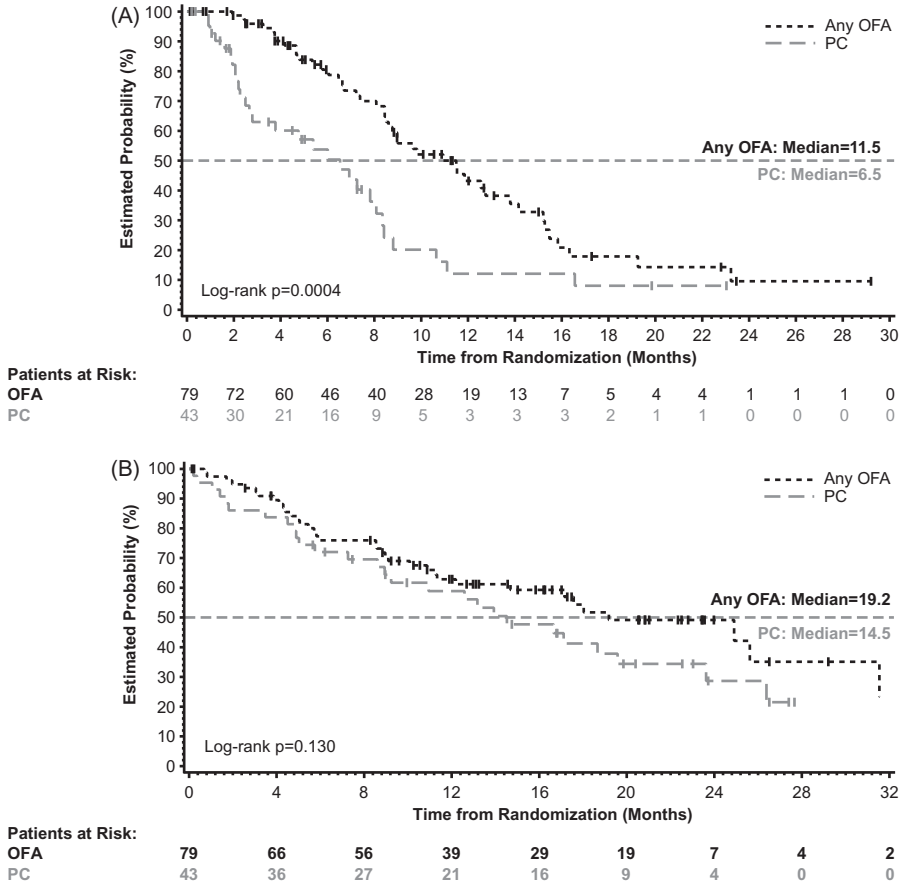

Figure 3. (A) Kaplan–Meier estimates of TNT in patients treated with OFA ($n = 79$) or PC ($n = 43$). TNT defined as time from first randomization until start of next-line treatment. **(B)** Kaplan–Meier estimates of OS in patients treated with OFA ($n = 79$) or PC ($n = 43$). OFA, ofatumumab; OS, overall survival; PC, physicians' choice; TNT, time to next therapy.

somewhat higher than expected from the Tam et al. [5] study. Most patients in the PC arm received rituximab-, alemtuzumab-, alkylator-, or fludarabine-based therapies also available in the Tam et al. [5] study, therefore, it appeared less likely that patients in our study were receiving more effective treatment options. In contrast, retrospective data in strictly consecutive BFR patients from a geographically well-defined region without external referrals [13] showed a different outcome with a median time to treatment failure of 5.3 months. The median IRC-assessed PFS of 5.4 months in the ofatumumab arm of study OMB114242 was consistent with the median IRC-assessed PFS of 5.5 months in the BFR population of the non-randomized study Hx-CD20-406.[10]

In study OMB114242, a PFS difference between the ofatumumab and PC arms (7.0 versus 4.5 months, $p = 0.003$) was evident only in the sensitivity analysis of investigator-assessed PFS. The discordance between IRC- and investigator-assessments of PD for analysis of PFS may have been caused in part by investigators' possibly exercising prospective *clinical judgment*, whereas the IRC strictly adhered to the IWCLL updated NCI-WG guidelines [11] when assessing progression retrospectively. Such discordances between IRC- and investigator-based assessments have been reported previously in other studies,[14] and as such, raise the question of whether the use of an IRC for the primary endpoint is mandatory or not; examples of both principles exist in recent phase III (first-line) trials in CLL.[15,16] Given that the criteria for PD are fulfilled when a slight increase in lymphocytosis or lymphadenopathy occurs, it may be argued that TNT should also be considered in phase III trials. Even though this endpoint is more dependent on the investigator's subjective assessment, it may also be clinically more relevant for patients. In our study, median TNT was significantly longer with ofatumumab than with PC (median 11.5 versus 6.5 months, $p = 0.0004$).

The median OS in the ofatumumab arm was 19.2 months compared with 14.5 months in the PC arm, but the difference was not significant. The patient-reported outcome of fatigue improved during ofatumumab therapy but worsened during PC therapy; the difference was significant at the end of the 24-week treatment period.

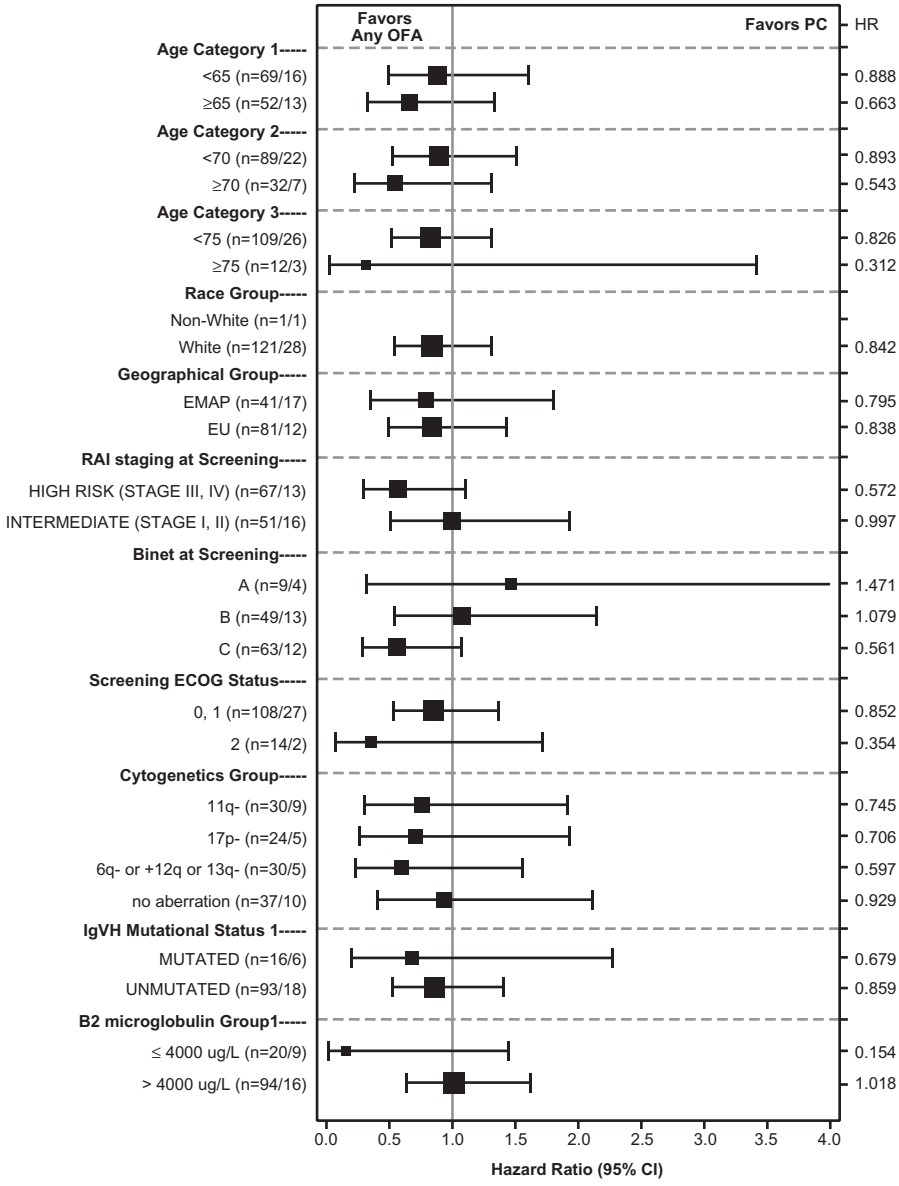

Figure 4. Forest plot of hazard ratios and 95% CIs for IRC-assessed PFS by demographics, baseline characteristics, and prognostic factors. PFS defined as time from first randomization until disease progression or death. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EMAP, emerging markets Asia-Pacific; EU, European Union; HR, hazard ratio; IgVH, immunoglobulin heavy chain variable region; IRC, independent review committee; OFA, ofatumumab; PC, physicians' choice; PFS, progression-free survival.

Notably, there was a significantly longer median PFS in patients who underwent the second randomization to receive extended ofatumumab treatment versus those in the observation group who received the approved, standard length of ofatumumab treatment. Median TNT was also significantly longer with extended ofatumumab, suggesting that long-term maintenance with ofatumumab should be explored further, which is also supported by a recently reported phase III trial that specifically addresses ofatumumab maintenance therapy,[17] as well as other recent CD20 monoclonal antibody maintenance studies.[18,19]

New options for relapsed or refractory CLL patients have been provided by the recently available kinase inhibitors ibrutinib and idelalisib.[6,9] However, it is important to note that these agents are not curative and are taken continuously until progression, and not all patients respond. The risk, rate, and reason for relapse are unknown.[8] While ofatumumab monotherapy was inferior to continuous ibrutinib treatment in a recent comparative study,[7] it still offers a possible therapeutic option for patients who relapse after treatment with kinase inhibitors. Given the relatively long PFS observed in this study with extended ofatumumab, and the

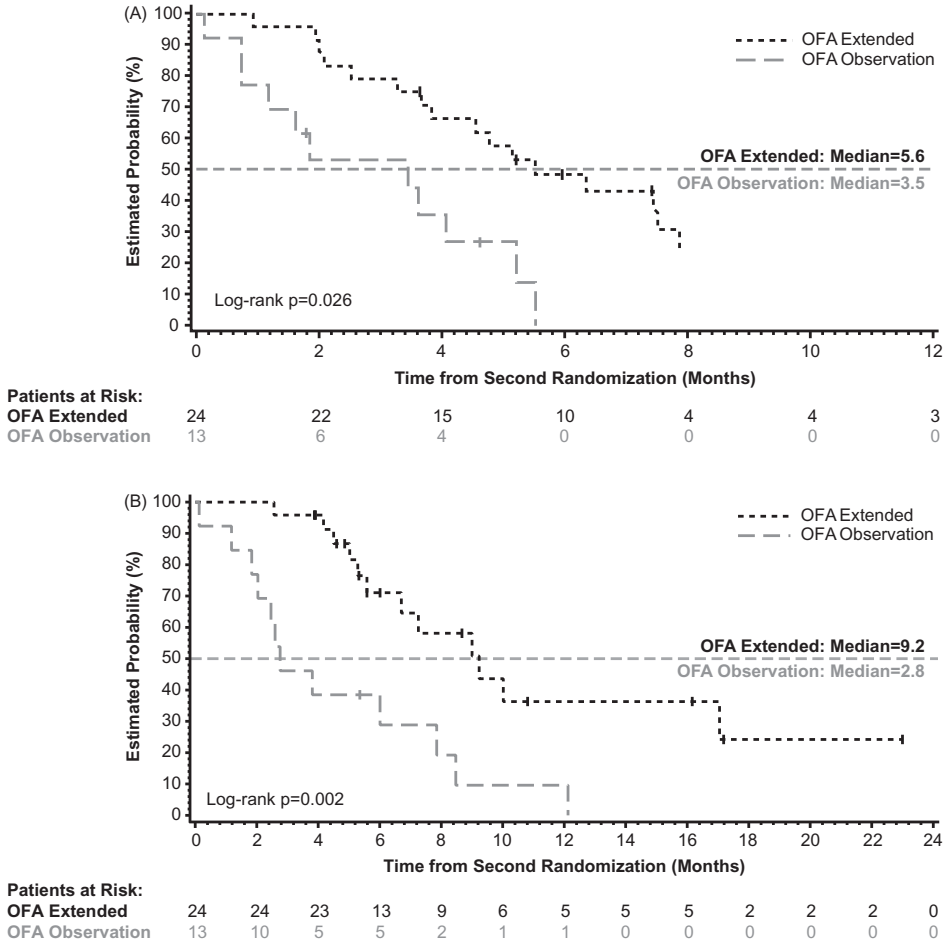

Figure 5. (A) Kaplan–Meier estimates of investigator-assessed PFS in patients assigned at the second randomization to OFA extended treatment ($n = 24$) or observation ($n = 13$). PFS defined as time from second randomization until disease progression or death. (B) Kaplan–Meier estimates of TNT in patients assigned at the second randomization to OFA extended treatment ($n = 24$) or observation ($n = 13$). TNT defined as time from first randomization until start of next-line treatment. IRC, independent review committee; OFA, ofatumumab; PC, physicians' choice; PFS, progression-free survival; TNT, time to next therapy.

Table 3. Most common (≥5%) grade 3 or higher adverse events[a].

MedDRA preferred term	Ofatumumab (n=78)	PC (n=43)
Any AEs, *n* (%)	48 (62)	24 (56)
Neutropenia	19 (24)	12 (28)
Pneumonia	10 (13)	4 (9)
Thrombocytopenia	6 (8)	4 (9)
Anemia	6 (8)	7 (16)
Sepsis	1 (1)	6 (14)
Autoimmune hemolytic anemia	0	2 (5)
Leukopenia	1 (1)	2 (5)
Hyperglycemia	0	2 (5)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PC, physicians' choice.

current difference in drug costs between ibrutinib and ofatumumab, a head-to-head cost-effectiveness study of long-term ofatumumab induction + maintenance versus long-term ibrutinib may be considered.

Ofatumumab in this study showed an AE profile that was consistent with the established safety profile of ofatumumab and other anti-CD20-based therapies. Overall, no new safety signals were detected with extended ofatumumab treatment.

Further studies are warranted on ofatumumab as long-term maintenance, in combination with bendamustine as initial therapy for patients with co-morbidities,[20] as well as in combination with small molecule-targeted therapeutics.

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