

# A phase 3, randomized study of ofatumumab combined with bendamustine in rituximab-refractory iNHL (COMPLEMENT A + B study)

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## Introduction

Non-Hodgkin lymphoma (NHL) is one of the most common haematologic malignancies worldwide, with an estimated 77 240 new cases and 19 940 deaths in 2020 in the USA.<sup>1,2</sup> Indolent NHL (iNHL) is a heterogeneous subgroup that accounts for almost 40% of NHL cases, of which follicular

## Summary

The standard of care for indolent non-Hodgkin lymphoma (iNHL) is rituximab, an anti-CD20 antibody, with/without chemotherapy. However, multiple relapses are common in these patients. This phase 3, randomized study compared outcomes of a combination of ofatumumab (a second-generation anti-CD20 antibody) and bendamustine, with bendamustine alone in patients unresponsive to prior rituximab-based treatment. Overall, 346 patients were randomized to receive either the combination or bendamustine alone. Bendamustine was given for  $\leq 8$  cycles and ofatumumab for  $\leq 12$  cycles. The primary end-point was progression-free survival (PFS) after 215 protocol-defined events assessed by independent review committee (IRC). Median IRC-assessed PFS was 16.7 and 13.8 months in the combination and monotherapy arms respectively [hazard ratio (HR) = 0.82;  $P = 0.1390$ ]. Median overall survival (OS) was 58.2 and 51.8 months in the combination and monotherapy arms respectively (HR = 0.89,  $P = 0.4968$ ). The safety profile was consistent with previous reports. Overall, 73% and 80% of patients in the combination and monotherapy arms, respectively, experienced a  $\geq$  grade 3 adverse event. The study did not meet its primary end-point. No significant improvement in PFS and OS was seen with the combination of ofatumumab and bendamustine as compared with bendamustine alone in rituximab-refractory iNHL (NCT01077518).

**Keywords:** anti-CD20, ofatumumab, rituximab, bendamustine, rituximab-refractory indolent non-Hodgkin lymphoma.

lymphoma (FL) is the most common.<sup>3,4</sup> Despite the many treatment options available for the majority of patients, iNHL remains an incurable disease.

Since the introduction of rituximab, improved outcomes in subjects with iNHL have been observed.<sup>5,6</sup> Rituximab has been shown to be effective as a single agent,<sup>7</sup> and also to improve progression-free (PFS) and overall survival (OS)

when given<sup>8</sup> in combination with chemotherapy regimens including cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)<sup>9</sup>, cyclophosphamide, vincristine and prednisone (R-CVP)<sup>10</sup>, fludarabine<sup>11</sup>, and bendamustine<sup>4,12,13</sup> to patients with previously untreated and relapsed/refractory iNHL.<sup>14</sup> Based on encouraging results observed in multiple clinical trials, rituximab-based chemo-immunotherapy has become the standard of care for patients with advanced-stage, high tumour burden iNHL.<sup>15</sup>

Despite favourable up-front response rates with rituximab in combination with chemotherapy, multiple relapses with progressively shorter remission periods are common, and the disease may eventually become unresponsive to rituximab-based treatment.<sup>8,14</sup> Approximately 20% of patients experience progression within two years of inducing chemo-immunotherapy have poor OS, and have been prioritized for clinical trials by the US National Clinical Trials Network.<sup>16,17</sup> Due to repeated exposure to rituximab, the risk for acquired resistance increases, and there is an unmet medical need for an effective and safe therapeutic option for this patient population.<sup>18</sup> Although, stem cell transplantation is a potential curative option, the challenges and risks involved with transplantation limit its use in elderly patients with co-morbidities.<sup>19</sup>

Bendamustine is approved in the USA and Europe for the treatment of iNHL that has progressed during or within six months of treatment with rituximab or rituximab-containing regimen.<sup>20,21</sup> Rituximab in combination with bendamustine is established in the treatment of front-line and relapsed/refractory iNHL.<sup>4,12,21,22</sup> Ofatumumab is a type I human monoclonal antibody (mAb) that binds to an epitope on the small and large loops of CD20, which is distinct from the binding site of rituximab.<sup>23</sup> Single-agent ofatumumab has been approved for the treatment of fludarabine and alemtuzumab-refractory chronic lymphocytic leukaemia (CLL) and has shown positive results in the maintenance setting after at least two lines of treatment, in combination with cyclophosphamide and fludarabine for relapsed CLL, and in combination with chlorambucil for up-front treatment of patients with CLL deemed unfit for fludarabine.<sup>24,25</sup> Previous phase 1/2 and phase 3 trials of ofatumumab have demonstrated clinical activity in patients with relapsed/refractory iNHL with an acceptable safety profile.<sup>18,23</sup>

The complement A + B study evaluated the hypothesis that the addition of ofatumumab to bendamustine might provide additional clinical benefit to patients with iNHL who had failed to respond or progressed following rituximab-containing regimen.

## Methods

### *Study design and patient population*

COMPLEMENT A + B was a phase 3, open-label, randomized, multicentre, international study. Patients at least

18 years of age with CD20<sup>+</sup> iNHL, which included small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma and Grades 1–3A FL based on the World Health Organization guidelines, were eligible for the study. Enrolled patients were unresponsive to rituximab, which was defined as either stable disease (SD) after or progressive disease (PD) during or within six months of rituximab-containing treatment. Patients had an Eastern Cooperative Oncology Group performance status of 0–2 and a life expectancy of  $\geq 6$  months. Key exclusion criteria included prior autologous or allogeneic stem cell transplant in the past six months; treatment with any monoclonal antibody (mAb; other than anti-CD20) within three months of randomization; treatment with bendamustine within the past one year not resulting in at least a partial response (PR) lasting for  $\geq 6$  months; chronic or current active infectious disease; clinically significant cardiac, cerebrovascular, hepatic disease; and/or screening laboratory abnormalities [neutrophils  $< 1.5 \times 10^9/l$ , platelets  $< 100 \times 10^9/l$ , creatinine  $> 1.5$  times upper limit of normal (ULN), total bilirubin  $> 1.5$  times ULN, and/or transaminases  $> 2$  times ULN]. All patients were required to provide written informed consent to participate in the study.

Patients were stratified based on prior exposure to bendamustine and the type of prior rituximab therapy (monotherapy or in combination with chemotherapy), and were subsequently randomized 1:1 to receive either the combination of ofatumumab and bendamustine or bendamustine alone. Bendamustine (90 mg/m<sup>2</sup> in the combination arm and 120 mg/m<sup>2</sup> in the monotherapy arm) was given for up to eight cycles on days 1 and 2, every 21 days. In the combination arm, ofatumumab (1 000 mg) was given on day 1 of each cycle of bendamustine until eight cycles and subsequently every 28 days until 12 doses were completed. The decision to add four additional treatments with ofatumumab following completion of combination cycles was based on data with rituximab demonstrating enhanced response with prolonged administration<sup>26–28</sup> as well as the data from the CLL Study NCT00349349.<sup>29</sup> For patients in the bendamustine arm, if deemed appropriate by the investigator, ofatumumab monotherapy was allowed within 120 days of independent review committee (IRC)-confirmed PD. In these patients, 1 000 mg of ofatumumab was given, followed by 2 000 mg once a week for three weeks and then 2 000 mg monthly for eight months. The study was conducted in accordance with Good Clinical Practice guidelines and the guiding principles of the Declaration of Helsinki. The protocol was reviewed by an Independent Review Board at each participating Centre (clinicaltrials.gov identifier NCT01077518).

### *Study assessments*

The primary end-point was progression-free survival (PFS), defined as the time interval from randomization until disease

progression or death as per IRC. The secondary end-points were PFS in patients with FL, overall response rate (ORR), time to response (TTR), duration of response, time to progression and time to next therapy in all patients and in patients with FL.

The response assessments, complete response (CR), PR, SD and PD, were based on criteria defined in the Revised Response Criteria for Malignant Lymphoma guidelines.<sup>30</sup> Lymphoma symptoms and contrast-enhanced computed tomography scans of the thorax, abdomen and pelvis (and neck, if palpable disease at baseline) were used to determine response assessments on days 84, 168 and 252, then quarterly until 18 months and yearly until 54 months. A repeat bone marrow examination to confirm CR was required within eight weeks from onset of CR if there was disease involvement in the bone marrow at baseline. All adverse events (AEs) and serious AEs (SAEs), regardless of the relationship to study drug, were collected from the first dose of treatment until 60 days after the last treatment. SAEs continued to be reported from 61 days after the last dose until the end of the follow-up period or until subsequent anti-lymphoma therapy initiated.

### Statistical analysis

Interim and futility analyses and Independent Data Monitoring Committee (IDMC) review were performed when approximately two-thirds (or 180) of the initial total 259 IRC events had occurred. Due to the length of the study, the drop-out rate was higher than the protocol assumed (21% vs 12% respectively). As such, the protocol was amended to revise the number of PFS events required for the primary analysis to approximately 215. Since, during the interim analysis, 180 PFS events were observed by the IRC, the final boundary for PFS in terms of the *P* value scale was calculated as a two-sided 0.0482 using EAST v6.4.<sup>31</sup>

The secondary end-points, PFS in patients with FL, ORR and OS in all patients and in patients with FL were to be tested sequentially only if the previous end-point was statistically significant. Survival distributions were estimated using the Kaplan–Meier (KM) curves, which were compared using a stratified log-rank test. Analytical results included estimation of HRs along with 95% confidence intervals (CIs) and associated probabilities for the effect of treatment, stratification factors and the covariates.

## Results

### Patients

Between September 2010 and May 2016, 346 patients were enrolled and randomized at 85 centres across 15 countries. Of these patients, 43% (*n* = 149) received rituximab monotherapy as their qualifying treatment regimen and 57% (*n* = 197) received rituximab in combination with

chemotherapy. The median number of prior rituximab-containing regimens was 1 and only 10% of patients (*n* = 33) enrolled on the study had prior exposure to bendamustine. The baseline characteristics were well-balanced between the two arms (Table I). The median age of patients was 62 years; 59% were males; and 67% of patients had FL, 14% SLL and 11% MZL at initial diagnosis. Ann Arbor staging IV was common and reported for 65% of patients.

### Patient disposition

The median treatment duration was 260 (1–367) days with combination and 135 (2–250) days with bendamustine. After a median duration of follow-up of 61.1 months, 58% and 65% of patients completed treatment with ofatumumab and bendamustine, respectively, in the combination arm, whereas 43% completed treatment in the bendamustine arm (Fig 1). Thirty patients in the bendamustine arm were treated in the optional ofatumumab arm after disease progression. In the combination arm, 94%, 81% and 59% completed three, six and 12 cycles of treatment, respectively, whereas with monotherapy, 91% and 65% completed three and six cycles respectively. Seventeen percent of patients in the ofatumumab and bendamustine arm and 10% of patients in the bendamustine arm discontinued the study treatment due to disease progression. Adverse events were the main reason for premature discontinuation for all treatments in the study.

### Efficacy

The primary end-point of efficacy, PFS, was conducted after 217 PFS events as assessed by an IRC were reached. The primary end-point, analyzed using a log-rank test stratified by the type of last prior rituximab therapy and prior exposure to bendamustine, was not statistically significantly different between the treatment arms (*P* = 0.1390, 2-sided). There were 105 (61%) and 112 (65%) PFS events in the combination and monotherapy arms respectively. The median PFS was 16.7 months with ofatumumab and bendamustine vs 13.8 months with bendamustine [HR 0.82 (95% CI 0.62, 1.07; Fig 2A)]. The estimated PFS rates at 12 months were 59.6% and 55.1% for the combination and monotherapy arms respectively.

The secondary end-points for the study were not tested, as the primary end-point was not statistically significant. In the subset of patients with FL, there were 73 (61%) events in the combination arm with a median PFS of 16.6 months, and 75 (63%) events in the monotherapy arm with a median PFS of 12.1 months [HR 0.76 (95% CI 0.55, 1.06; Fig 2B)]. In this subset, the estimated PFS rates at 12 months were 60.1% and 50.8% for the combination and monotherapy arms respectively. Within 24 months, 51% and 58% of patients progressed in the combination and monotherapy arms respectively. The subgroup results were consistent with observations from the overall population as demonstrated by the

Table I. Patient characteristics.

Parameter	Ofatumumab + bendamustine	Bendamustine	Total
Age (years), <i>n</i> (%)	( <i>n</i> = 171)	( <i>n</i> = 171)	( <i>n</i> = 342)
18–64	94 (55)	100 (58)	194 (57)
65–74	52 (30)	46 (27)	98 (29)
≥75	25 (15)	25 (15)	50 (15)
Median (min, max)	63 (29, 83)	62 (21, 87)	62 (21,87)
Sex, <i>n</i> (%)	<i>n</i> = 172	<i>n</i> = 174	<i>n</i> = 346
Female	70 (41)	73 (42)	143 (41)
Male	102 (59)	101 (58)	203 (59)
Ethnicity, <i>n</i> (%)	<i>n</i> = 172	<i>n</i> = 174	<i>n</i> = 346
Hispanic or Latino	5 (3)	11 (6)	16 (5)
Others	167 (97)	163 (94)	330 (95)
Histology at initial diagnosis, <i>n</i> (%)	<i>n</i> = 173	<i>n</i> = 173	<i>n</i> = 346
FL	118 (68)	115 (66)	233 (67)
SLL	28 (16)	21 (12)	49 (14)
MZL	19 (11)	18 (10)	37 (11)
Others	8 (5)	18 (10)	26 (8)
Ann arbor staging at screening, <i>n</i> (%)	<i>n</i> = 173	<i>n</i> = 173	<i>n</i> = 346
I	10 (6)	4 (2)	14 (4)
II	17 (10)	26 (10)	33 (9)
III	30 (17)	40 (23)	70 (20)
IV	113 (65)	110 (64)	223 (65)
Missing	3 (2)	3 (2)	6 (2)
Number of prior rituximab therapies median (min, max)	1 (1, 6)	2 (1, 9)	1 (1, 9)
Prior anti-cancer therapies, <i>n</i> (%) <sup>*,†</sup>	<i>n</i> = 172	<i>n</i> = 174	<i>n</i> = 346
Fludarabine-based	14 (8)	11 (6)	25 (7)
Bendamustine-based	10 (6)	13 (7)	23 (7)
Alkylator-based <sup>‡</sup>	96 (56)	104 (60)	200 (58)
Rituximab-based	1 (1)	0 (0)	1 (1)
Glucocorticoid	54 (31)	48 (28)	102 (29)

FL, follicular lymphoma; SLL, small lymphocytic lymphoma; MZL, marginal zone lymphoma.

\*One patient with more than one anti-cancer therapy has been counted under both treatment categories.

<sup>†</sup>Data are based on the electronic case report form (eCRF) database.

<sup>‡</sup>Alkylator-based therapies also include patients treated with prior bendamustine.

fact that the 95% CI included one for most subgroups tested. The exceptions were age < 65 years (*n* = 195, HR = 0.64, 95% CIs: 0.45, 0.92) and low FLIPI-1 scores (*n* = 193, HR = 0.68, 95% CIs: 0.46, 0.98; Fig 3).

The IRC-assessed ORR was similar in both arms. With combination, the ORR (95% CI) was 73% (66%, 80%), with 21% of patients achieving CR, 53% PR and 13% SD. With bendamustine monotherapy, the ORR (95% CI) was 75% (67%, 81%), with 17% achieving CR, 58% PR and 9% SD. There was a difference in ORR of −1.2% (−10.4%, 8.1%) between the two arms. Similar results were observed in patients with FL. The ORR in the combination and monotherapy arms was 77% (68%, 84%) and 76% (67%, 83%), respectively, with a difference in ORR of 1.0% (−9.8%, 11.8%). In these patients, 24% had CR, 53% had PR and 12% had SD with the combination, while in the monotherapy arm, 20% had CR, 55% had PR and 6% had SD. For the 30 patients in the bendamustine arm who received optional ofatumumab following disease progression, the ORR at one month was 17% (6%, 35%). There was no

difference in the KM estimates of TTR in either treatment arm, in all patients or in patients with FL [2.9 months each, 95% CI (2.8, 2.9)]. The KM estimates of the duration of response (DOR, 95% CI) for all patients were 17.7 months (13.0, 22.6) in the combination arm and 14.5 months (10.8, 16.8) with monotherapy. Similarly, in patients with FL, the DoRs (95% CI) were 16.4 months (11.5, 20.5) and 11.2 months (8.6, 16.4) in the combination and monotherapy arms respectively.

### Survival

Median OS was 58.2 months vs 51.8 months with combination and monotherapy respectively [HR 0.89, 95% CI (0.63, 1.25); *P* = 0.4968; Fig 4A, B]. The frequencies of deaths and on-treatment deaths were similar in both arms. Overall, 38% of patients died in the combination arm, of which 7% were on-treatment deaths. Among patients treated with bendamustine, 41% died, with 9% on-treatment deaths. The main cause of death was the primary disease for both on-treatment

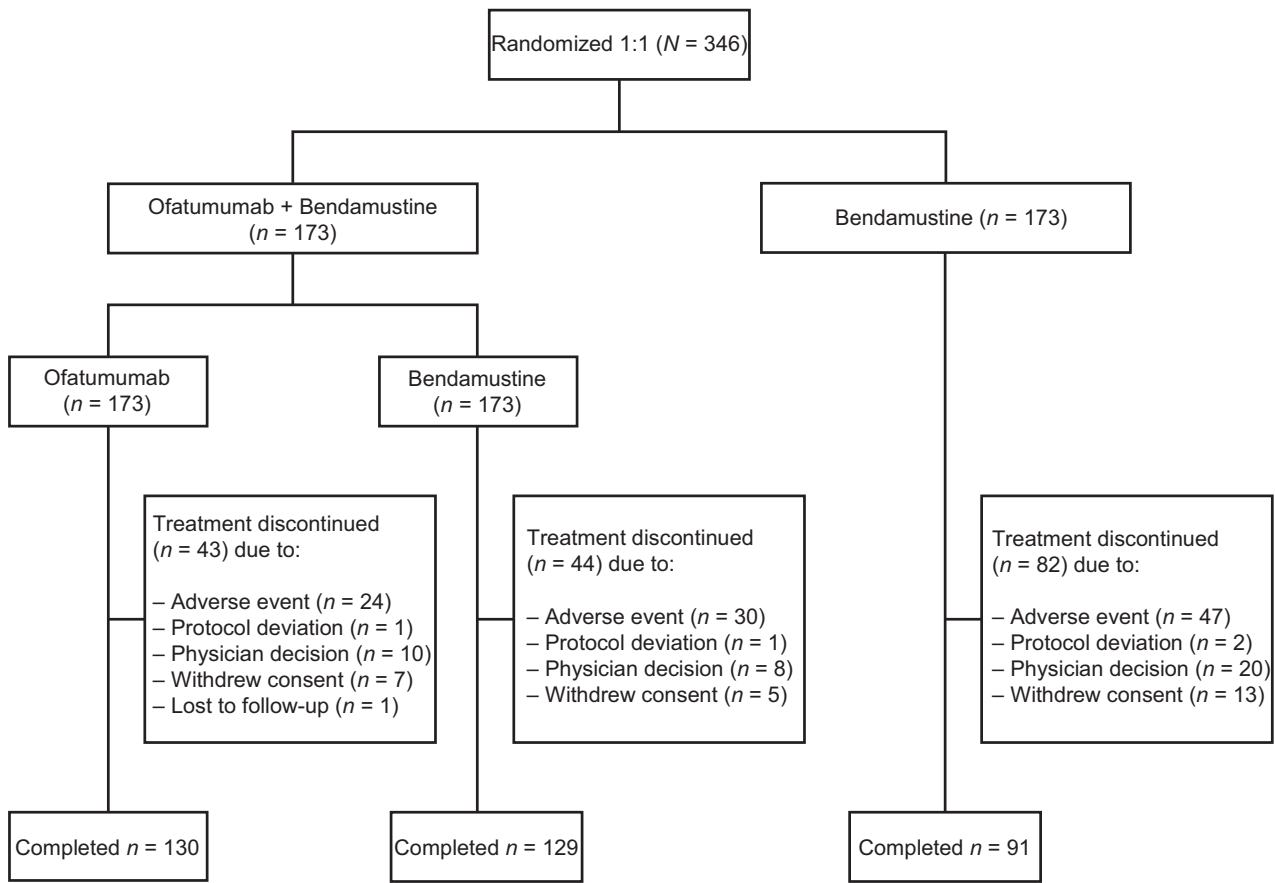


Fig 1. CONSORT diagram.

deaths and deaths during the study; 20% of deaths during the study and 2% of deaths during treatment in the combination arm and 15% and 5%, respectively, in the monotherapy arm were due to the disease under study (Table II).

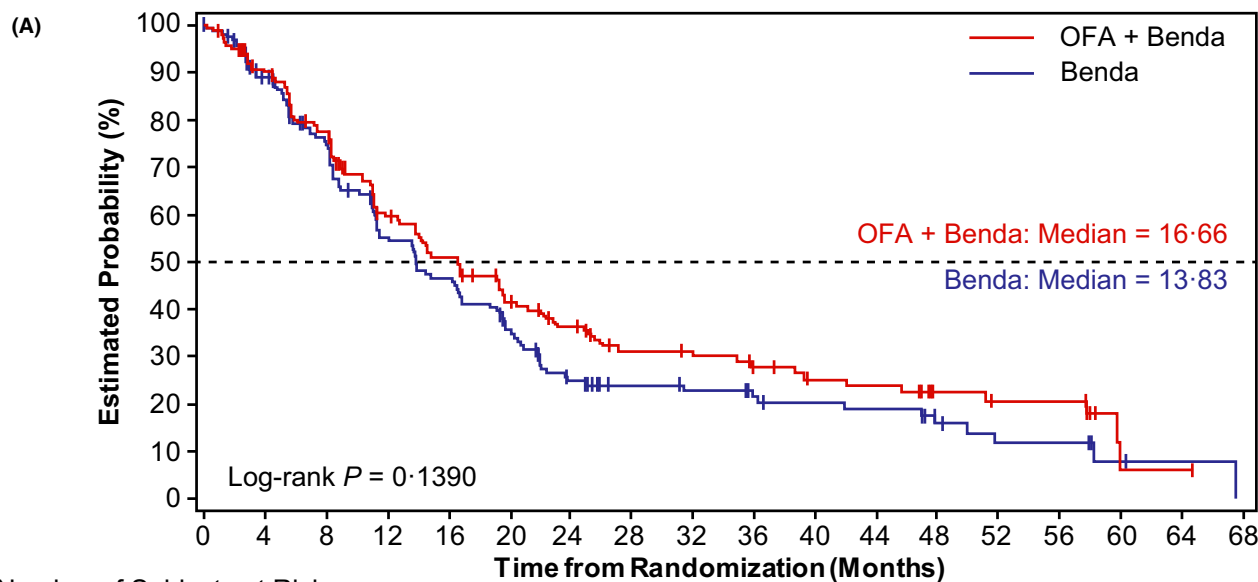
### Safety

During the study, 96% of patients in the combination arm and 99% in the monotherapy arm reported at least one AE of which 84% and 93%, respectively, were related to the study drug. Overall, 73% of patients in the combination arm and 80% in the monotherapy arm experienced a  $\geq$ grade 3 AE, of which 64% and 68% respectively were related to study treatment. Serious AEs were observed in 42% and 49% of patients, in the combination and monotherapy arm respectively; and in 22% and 30% of the patients, these SAEs were due to the study drug (Table III). The most common AEs ( $>1\%$  in each arm) resulting in permanent discontinuation of study drug in the combination and monotherapy arm respectively were neutropenia (6% each), thrombocytopenia (2% vs 6%), anaemia ( $<1\%$  vs 2%) and leukopenia (2% vs none). Drug-related AEs observed frequently in the combination and monotherapy treatment groups were nausea (34%

and 54%), neutropenia (37% and 44%) and fatigue (20% and 31%) respectively. The duration (in days) from start of treatment to first occurrence of AE has been summarized in Table IV.

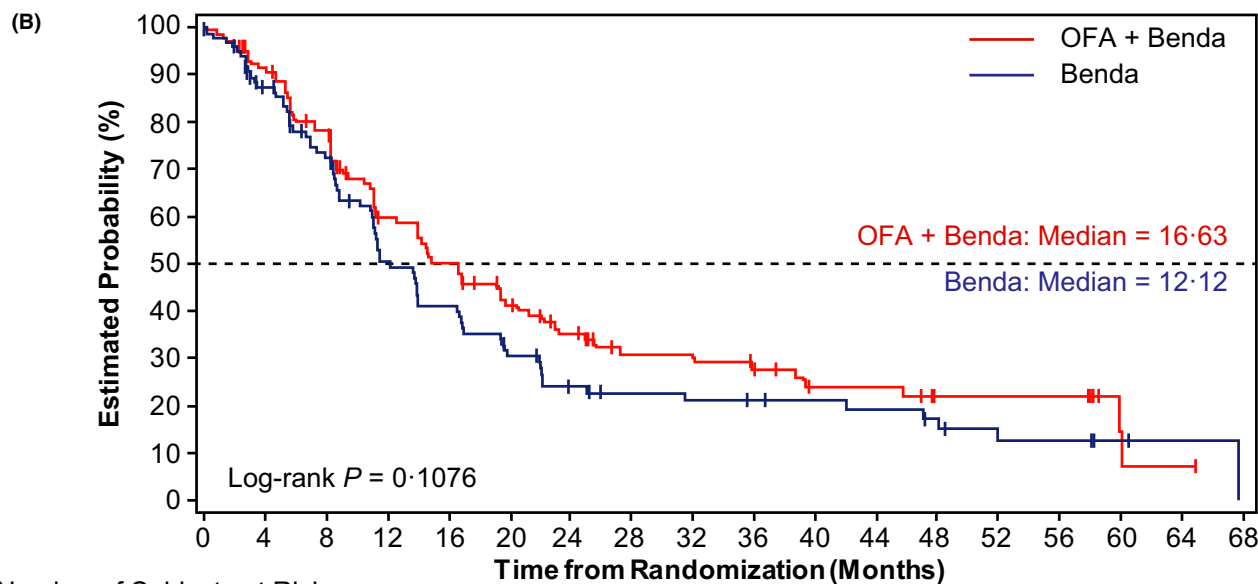
### Discussion

COMPLEMENT A + B evaluated whether the combination of ofatumumab and bendamustine improved outcomes as compared to bendamustine alone in patients refractory to a prior rituximab-based therapy. The primary end-point, PFS, evaluated at 217 events was not statistically significantly different between the two treatment groups. These results were contrary to those observed in the GADOLIN study, which evaluated the combination of obinutuzumab and bendamustine in patients with rituximab-refractory iNHL. Results of the updated GADOLIN study demonstrated a significantly longer PFS with the combination compared to bendamustine alone (25.8 months vs 14.1 months, HR = 0.57;  $P < 0.001$ ), and subsequently demonstrated an OS benefit for the combination as compared to bendamustine alone (OS events: 25.5% vs 34.9%, HR = 0.67;  $P = 0.027$ ) in line with its primary analysis.<sup>32,33</sup> The



Number of Subjects at Risk:

OFA + Benda	173	142	114	78	66	51	41	29	28	23	19	18	11	9	9	1	1	0
Benda	173	130	102	71	60	44	29	22	20	17	15	14	9	6	6	2	1	0



Number of Subjects at Risk:

OFA + Benda	120	99	80	56	47	36	28	20	20	16	12	12	7	7	7	1	1	0
Benda	119	86	65	43	35	25	18	14	13	12	11	10	7	5	5	2	1	0

Fig 2. Kaplan–Meier estimates of IRC-assessed progression-free survival (PFS). The vertical axis represents the estimated rates of PFS. The number of patients at risk at each point is provided below in the table. (A) In the intent-to-treat population. (B) In patients with follicular lymphoma. OFA, ofatumumab; Benda, bendamustine. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

difference in outcomes observed in our study *versus* GADOLIN may be due to several reasons.

Firstly, patients who received combination therapy in our study received only four additional monthly doses of ofatumumab as compared to those in the combination arm of the GADOLIN study who were treated with obinutuzumab for up to two years following completion of the bendamustine-

containing cycles. Although the impact of maintenance therapy with anti-CD20 antibodies remains debated, studies in both treatment-naïve and relapsed patients have demonstrated longer PFS but not OS with prolonged maintenance therapy.<sup>7,34–36</sup> In the GADOLIN study, the PFS curves for obinutuzumab and bendamustine *versus* bendamustine alone appear to separate after six months suggesting that the true

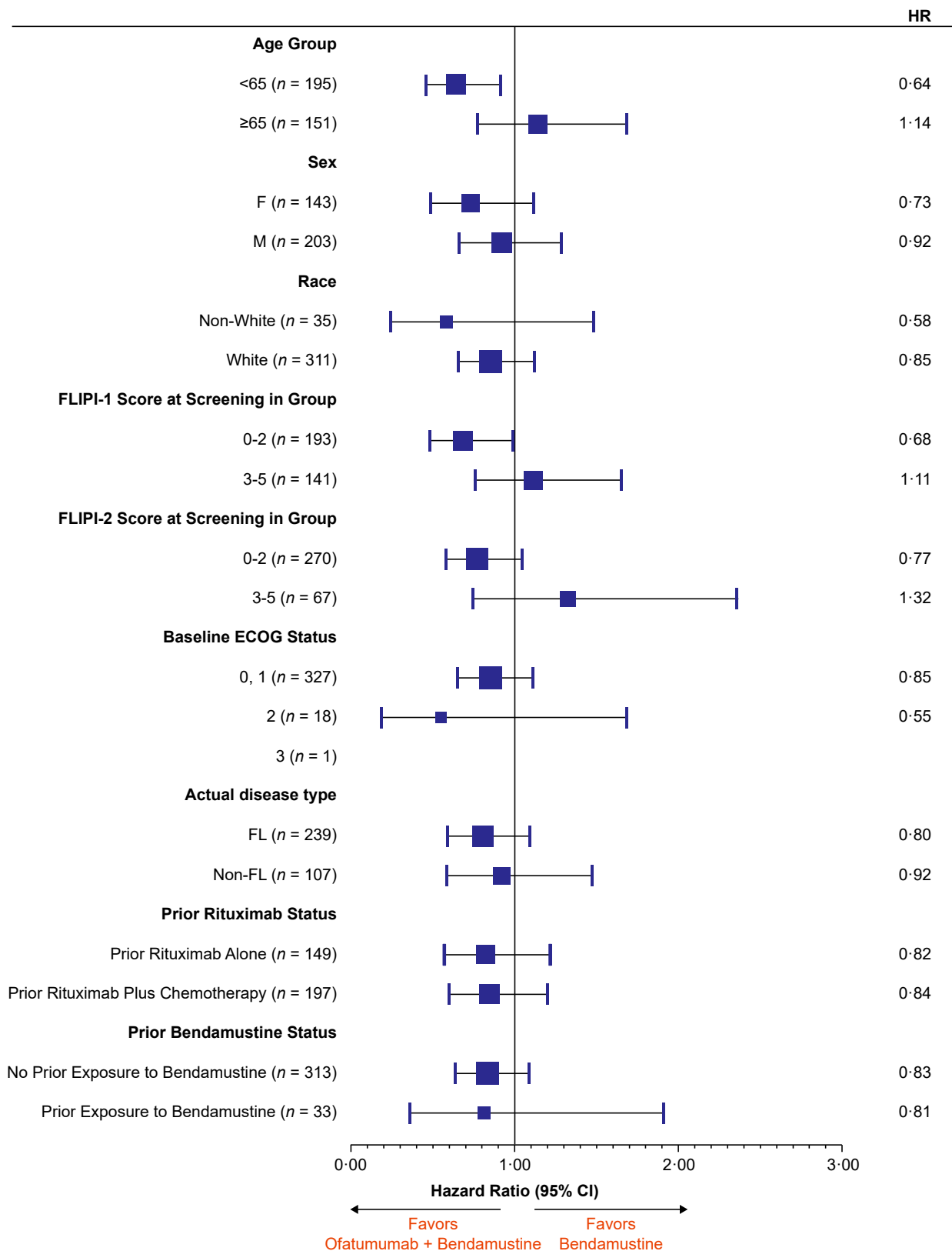
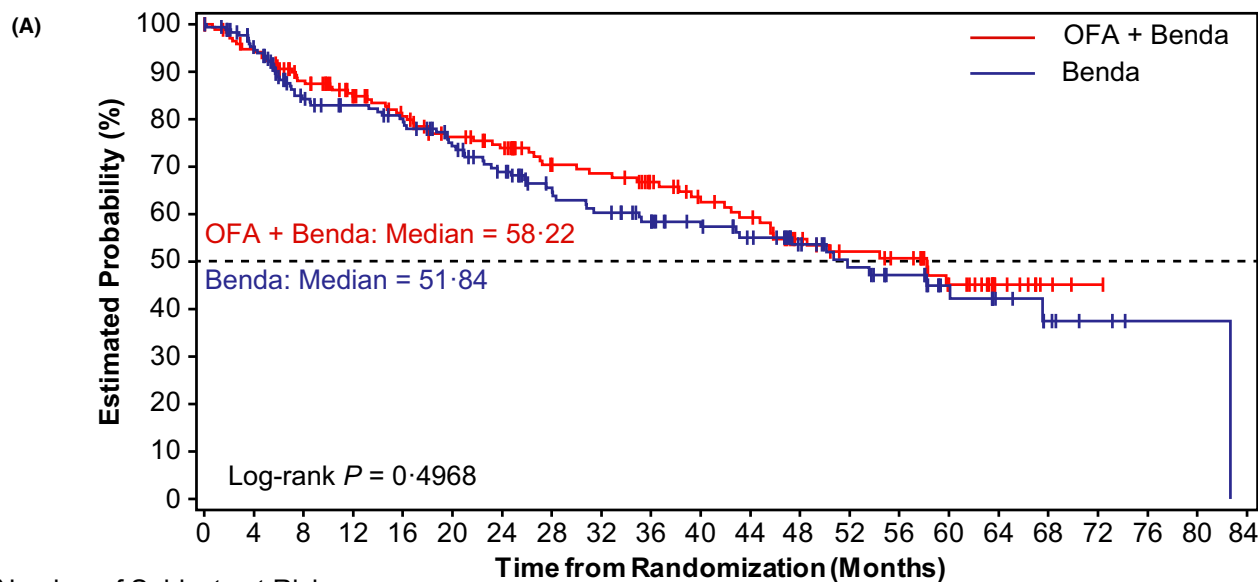
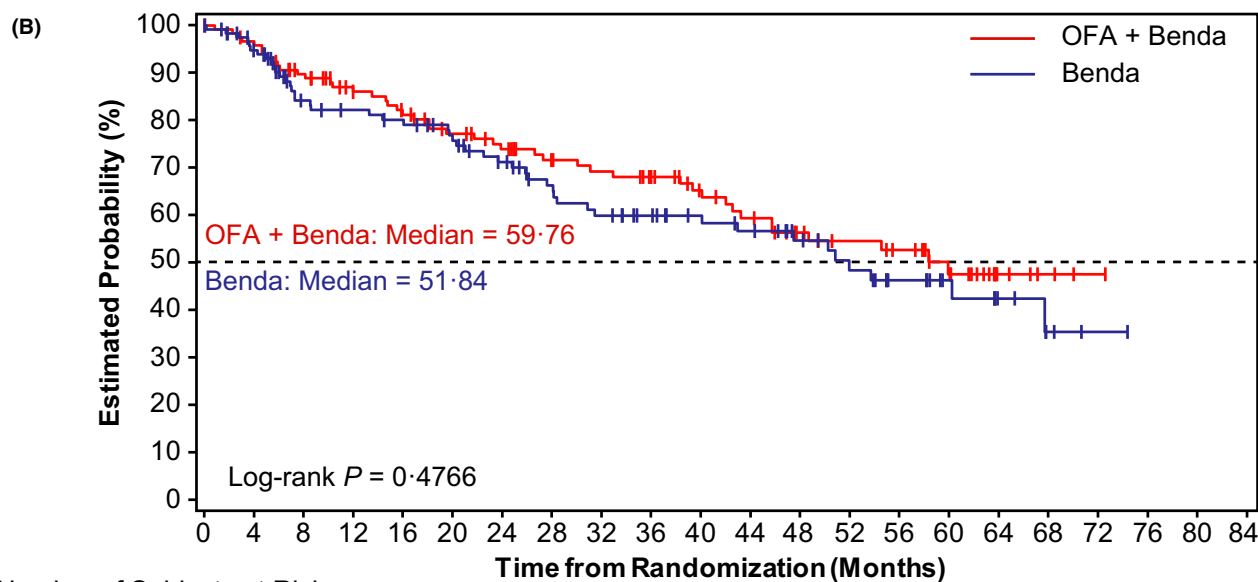


Fig 3. Forest plot for subgroup analysis [age, sex, race, Follicular Lymphoma International Prognostic Index-1 (FLIPI-1), FLIPI-2, Eastern Cooperative Oncology Group (ECOG), disease type, prior rituximab status and prior bendamustine status] of progression-free survival. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



Number of Subjects at Risk:

OFA + Benda	173	160	142	126	113	102	95	79	76	67	58	54	43	37	34	22	9	3	1	0	0	0
Benda	173	155	126	119	113	100	88	75	69	62	54	47	37	30	24	16	10	6	3	1	1	0



Number of Subjects at Risk:

OFA + Benda	120	113	101	89	83	75	69	61	58	52	44	40	33	29	26	16	6	3	1	0	0	0
Benda	119	106	83	79	76	69	61	52	47	42	37	34	28	23	17	12	7	3	1	0	0	0

Fig 4. Kaplan–Meier estimates of overall survival (OS). The vertical axis represents the estimated rates of OS. The number of patients at risk at each point is provided below in the table in the intent-to-treat (ITT) population. (A) In the ITT population. (B) In patients with follicular lymphoma. OFA, ofatumumab; Benda, bendamustine. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

effect of obinutuzumab was potentially a result of the prolonged maintenance phase.<sup>33</sup> Therefore, it is possible that with a longer maintenance phase, a similar result would have been observed with ofatumumab. Secondly, the differences in the results from the two studies could be attributed to the differences in patient population and the underlying sub-type of iNHL.<sup>33</sup> Thirdly, it is also possible that the different

mechanisms of action (MOA) of ofatumumab, a type I anti-CD20 monoclonal antibody and obinutuzumab, a type II anti-CD20 monoclonal antibody, may have played a role in the discrepant study outcomes. In preclinical studies, ofatumumab has been shown to cause clustering of CD20 on the cell surface, induce complement-dependent cytotoxicity (CDC) by engaging the complement component 1q (C1q),



Table II. Summary of on-treatment deaths.

	Ofatumumab + bendamustine (n = 172)				Bendamustine (n = 170)			
	FL	MZL	Other	Total	FL	MZL	Other	Total
Died, n (%)	8 (5)	1 (<1)	3 (2)	12 (7)	9 (5)	3 (2)	3 (2)	15 (9)
Primary cause of death, n (%)								
Acute myocardial infarction	0	0	0	0	1 (<1)	0	0	1 (<1)
Adenocarcinoma	1 (<1)	0	0	1 (<1)	0	0	0	0
Cardiopulmonary arrest	1 (<1%)	0	0	1 (<1)	0	0	0	0
Disease under study	0	1 (<1)	2 (1)	3 (2)	6 (4)	1 (<1)	2 (1)	9 (5)
Failure to thrive	1 (<1)	0	0	1 (<1)	0	0	0	0
Renal failure not related study medication	0	0	0	0	1 (<1)	0	0	1 (<1)
Rupture of aneurysma abdominalis	1 (<1)	0	0	1 (<1)	0	0	0	0
SAE not related to IP	0	0	1 (<1)	1 (<1)	0	0	0	0
SAE not related to study medication	0	0	0	0	0	0	1 (<1)	1 (<1)
SAE possibly related to study medication	2 (1)	0	0	2 (1)	1 (<1)	1 (<1)	0	2 (1)
SAE related to prior anthracycline induced cardiac toxicity	1 (<1)	0	0	1 (<1)	0	0	0	0
Septic shock	1 (<1)	0	0	1 (<1)	0	0	0	0
Worsening of general conditions	0	0	0	0	0	1 (<1)	0	1 (<1)

FL, follicular lymphoma; IP, investigational procedure; MZL, marginal zone lymphoma; SAE, serious adverse events.

Table III. Adverse events,  $\geq$ Grade 3 adverse events and serious adverse events irrespective of relation to study drug.

Preferred term, n (%)	Ofatumumab + bendamustine (n = 172)	Bendamustine (n = 170)
AEs (>25% of patients)		
Any event	165 (96)	169 (99)
Nausea	62 (36)	95 (56)
Neutropenia	66 (38)	78 (46)
Fatigue	42 (24)	59 (35)
Anaemia	31 (18)	54 (32)
Pyrexia	35 (20)	47 (28)
Thrombocytopenia	30 (17)	49 (29)
Decreased appetite	24 (14)	45 (26)
$\geq$ Grade 3 AEs ( $\geq$ 5% of patients)		
Any event	126 (73)	136 (80)
Neutropenia	61 (35)	70 (41)
Anaemia	13 (8)	25 (15)
Leukopenia	16 (9)	13 (8)
Thrombocytopenia	9 (5)	32 (19)
Neutrophil count decreased	11 (6)	12 (7)
Febrile neutropenia	12 (7)	7 (4)
Fatigue	6 (3)	13 (8)
Pneumonia	9 (5)	11 (6)
Lymphopenia	10 (6)	9 (5)
Serious AEs ( $\geq$ 5% of patients)		
Any event	72 (42)	84 (49)
Pneumonia	10 (6)	14 (8)
Anaemia	2 (1)	10 (6)
Pyrexia	7 (4)	9 (5)
Febrile neutropenia	8 (5)	5 (3)
Neutropenia	6 (3)	8 (5)

AEs, adverse events; SAEs, serious adverse events.

Table IV. Summary of duration (in days) from treatment start to first occurrence of adverse event by treatment.

Preferred term, n (%)	Ofatumumab + bendamustine (n = 172)	Bendamustine (n = 170)
AEs (>25% of patients), median days		
Anaemia	65	72
Decreased appetite	37	23
Fatigue	41	23
Nausea	4	3
Neutropenia	63	45
Pyrexia	54	45
Thrombocytopenia	83	44

AEs, adverse events.

and induce antibody-dependent cellular cytotoxicity (ADCC), but not directly trigger apoptosis.<sup>37-39</sup> Instead, obinutuzumab's MOA is through directly inducing apoptosis and ADCC with decreased CDC.<sup>40</sup> The safety profile for ofatumumab in this study was consistent with prior experience from other studies and remains acceptable.<sup>41</sup> There were no new safety signals identified.

There are some limitations to our study. The single-agent bendamustine dose of 120 mg/m<sup>2</sup> has been associated with higher toxicity and may have contributed to the higher rates of treatment discontinuations as well as  $\geq$ grade 3 infections in the monotherapy arm; we chose this dose as it was FDA-approved, and a similar dose to what was used for single-agent bendamustine in the GADOLIN trial. The median number of prior rituximab-containing regimens was only one (1-8), and the median time since diagnosis was very

short (2-7 years). Both suggest that patients were exposed to first-line therapy for a short period of time prior to entering our study, and patients may not have received optimal treatment with rituximab prior to being judged refractory as only three cycles of combination therapy or four infusions of rituximab monotherapy were required for study enrollment. However, this also suggests a significant number of patients enrolled in our study may have had early disease progression after initial chemo-immunotherapy.<sup>16</sup> Unfortunately, we are not able to determine the exact number of these patients due to limitations in data acquisition.

In summary, combining ofatumumab and bendamustine did not show any significant improvement in the PFS when compared with bendamustine alone in patients with iNHL who were unresponsive to prior rituximab-based therapy. These findings are in contrast to the GADOLIN study, which showed that obinutuzumab in combination with bendamustine significantly improved the clinical outcomes compared to bendamustine alone in patients with rituximab-refractory iNHL. The difference in the outcome could be due to multiple factors including duration of maintenance therapy, and a difference in the MOA of the anti-CD20 antibodies.

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## Conflicts of interest

MJR reports receiving honoraria from Celgene, Amgen, Astellas, Eisai, Gilead, Janssen, Mundipharma, Roche and Symbio; fees for Advisory Board from Amgen, Gilead, Janssen, Mundipharma and Roche; research funding from Mundipharma and Roche; AJ reports receiving consultancy fees from Janssen, Abbvie, Amgen and Roche; fees for Speaker's Bureau Janssen, Abbvie, Sanofi-Genzyme, Amgen and Roche; fees for Advisory Board from Abbvie, Roche and Novartis; DM reports receiving honoraria from Roche, Lundbeck, Amgen, Gilead, Seattle Genetics, Janssen and Abbvie; JWF reports receiving honoraria from Bayer; DMD reports honoraria for Advisory Board from Roche, Amgen, Gilead, Lundbeck, Seattle Genetics, Janssen and Abbvie; JD, JL and NL are employees of Novartis; MI is an employee of Novartis and holds equity ownership in Novartis; MK and JZ have no financial relationships to disclose.

## Author contributions

MJR has contributed to the conception and design, enrolled patients, and has collected and interpreted data. JWF has

contributed to the conception and design, and interpretation. AJ, DMcD, M-KK and JMZ have enrolled patients, contributed to data collection, conduct of the study and the interpretation of the data. JD and MI have contributed to conception, design, data interpretation and conduct of the study. JL has contributed to data collection, interpretation and conduct of the study. All the authors have critically reviewed and approved the manuscript.

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