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Letter
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Obinutuzumab Can Be Administered as a 90-minute Short Duration Infusion in Patients With Previously Untreated Follicular Lymphoma: GAZELLE End of Induction Analysis

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For patients with follicular lymphoma (FL) requiring treatment, survival advantages have been shown with the addition of anti-CD20 monoclonal antibodies (mAbs) to conventional chemotherapy regimens versus chemotherapy alone for first-line treatment.[1] Rituximab was the first anti-CD20 agent approved for FL treatment, and obinutuzumab is a type II anti-CD20 mAb with a distinct mode of action versus rituximab.[2–4] In the phase III GALLIUM trial, obinutuzumab plus chemotherapy demonstrated improved progression-free survival versus rituximab plus chemotherapy in patients with previously untreated, advanced FL.[5–7]

Obinutuzumab is currently administered by intravenous (IV) infusion over 3–4 hours. Previous studies found rituximab was well tolerated as a shorter 90-minute infusion by patients who did not experience grade ≥3 infusion-related reactions (IRRs) after the first standard-rate infusion.[8] A 90-minute short duration infusion (SDI) of obinutuzumab may offer the potential to reduce time and resources required to administer treatment, providing time and cost savings for both patients and healthcare settings.

GAZELLE (NCT03817853) was an international, open-label, multicenter, single-arm, phase IV study investigating the safety and efficacy of a 90-minute SDI of obinutuzumab as induction (with chemotherapy) and maintenance (as monotherapy) in patients with previously untreated, advanced FL. Here, we report the primary results from GAZELLE, focusing on the induction phase of treatment.

All enrolled patients had histologically documented CD20+ FL (grade 1–3a), Eastern Cooperative Oncology Group performance status 0–2, and advanced disease (stage III or IV, or stage II with bulky disease). During the induction phase, IV obinutuzumab (1000 mg) was administered on days (D) 1, 8, and 15 of cycle (C) 1, and on D1 thereafter, plus chemotherapy selected by the investigator for 6–8 cycles (bendamustine; cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]; or cyclophosphamide, vincristine, and prednisone [CVP]; Suppl. Methods). Obinutuzumab was administered at the standard infusion rate in C1. Patients without a grade ≥3 IRR in C1 received obinutuzumab as a 90-minute SDI (or <110 min) from C2 onwards (including in the maintenance phase). IRRs were defined as any events that occurred during or within 24 hours from the end of study treatment infusion and were judged by an investigator as related to the infusion of study treatment components. Patients with grade ≥3 IRR in C1 received obinutuzumab at the standard infusion rate in C2, and obinutuzumab SDI from C3 onwards if no grade ≥3 IRRs occurred in C2. Patients with a second grade ≥3 IRR or a grade 4 IRR (regardless of infusion rate) discontinued obinutuzumab.

The primary end point was the incidence of grade ≥3 IRRs during C2 (severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0). Secondary safety end points included the incidence, nature, and severity of all-causality adverse events (AEs), and the incidence, timing, and duration of IRRs (any grade). Investigator-assessed objective response rate (ORR) at the end of induction (EOI) according to the site-specific guidelines[9–11] was a key secondary end point. Patient-reported outcomes (MD Anderson Symptom Inventory [MDASI] scores[12]) and provider-reported outcomes were exploratory end points. For data sharing information, see Suppl. Methods.

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At data cutoff (December 3, 2020), 114 patients were enrolled from 32 centers across 7 countries. A total of 113 patients started induction therapy and comprised the overall population. Fourteen patients from this population were subsequently excluded, leaving 99 patients in the SDI population (Suppl. Figure S1). Baseline patient and disease characteristics are summarized in Suppl. Table S1. Obinutuzumab-bendamustine (45.1% of patients) was the most common treatment regimen, followed by obinutuzumab-CHOP (38.1%); 16.8% of patients received obinutuzumab-CVP.

During the induction phase, the overall median cumulative obinutuzumab dose was 8000 mg (range, 80–10,000 mg). At C1D1 and C1D8, the proportion of patients with low obinutuzumab dose intensity (<90%) was 2.7% and 1.8%, respectively (no low dose intensity occurred after C1D8). During the induction phase, 46 patients (40.7%) had ≥1 obinutuzumab infusion modification (Suppl. Table S2). Most infusion modifications were reported during C1 and due to AEs. Infusion interruption was the most common modification. For details of premedication administration and chemotherapy exposure, see Suppl. Results.

The median obinutuzumab SDI duration in each cycle of C2–C8 was 95.0–98.0 minutes (Figure 1). Obinutuzumab infusion duration during this part of the induction period was ≤110 minutes in >90% of patients.

Almost all patients (99.1%) experienced AEs of any grade (all causality) during the induction period (Suppl. Table S3). Grade ≥3 AEs and serious AEs (SAEs) were reported in 69.0% and 18.6% of patients, respectively. The most common grade ≥3 AEs were neutropenia (49.6%), leukopenia (11.5%), and lymphopenia (10.6%); SAEs experienced by ≥2 patients were febrile neutropenia (4.4%), pneumonia (2.7%), and neutropenia (1.8%). Infections and infestations were reported for 45 of 113 patients (39.8%; 64 events), with grade ≥3 infections or infestations reported for 10 of 113 patients (8.8%; 14 events).

No patients experienced a grade ≥3 IRR with obinutuzumab SDI in C2 (primary end point; Figure 2). IRRs were reported in 71 of 113 patients (62.8%), with most occurring on C1D1. Grade 3 IRRs were reported in 7 of 113 patients (6.2%) during the study; no grade 4 or grade 5 IRRs were reported. Of the 99 patients in the SDI population who received obinutuzumab SDI in C2, 10 (10.1%) experienced an IRR (grade 1, 8.1%; grade 2, 2.0%). In subsequent cycles, only 1 patient experienced a grade ≥3 IRR with obinutuzumab SDI (grade 3 hypertension in C5, which resolved on the same day).

The most common IRR symptoms at any infusion rate in the overall population were nausea (23.0%), pyrexia (11.5%), and chills (10.6%). Most patients who experienced an IRR during C1 and C2 recovered/resolved their IRR. One patient discontinued the study due to an IRR during C1, and no patients discontinued due to an IRR in C2 or later (overall population).

Of 113 patients in the overall population, 104 had an available response assessment at EOI. The ORR was 86.7% (98/113), including 67.3% of patients with a complete response ([CR], 76/113) and 19.5% (22/113) with a partial response. Six patients (5.3%) had progressive disease. Data were missing for the remaining 9 of 113 patients (8.0%), who were counted as nonresponders. In a subgroup of patients with fluorodeoxyglucose positron emission tomography scans evaluated by Lugano 2014 criteria[9] (n = 57), the ORR at EOI was 96.5% (55/57; CR, 80.7% [46/57]; Suppl. Table S4).

Mean MDASI scores were low at baseline and remained stable from baseline to EOI (Suppl. Figure S2), with a mean change in symptom severity score of −0.1 (SD, 1.4) and mean change in interference score of −0.4 (SD, 2.4). Mean MDASI scores did not differ between risk subgroups (data not shown).

For the administration of obinutuzumab as an SDI compared with the standard-rate infusion, staff time savings of ≥1 hour were reported for 58 of 64 nurse evaluators (90.6%) and 44 of 51 (86.3%) physician evaluators, with a ≥4-hour time saving reported for 8 of 51 (15.7%) physicians. Compared with the standard-rate infusion, obinutuzumab SDI was considered much more convenient to administer by 42 of 64 nurse evaluators (65.6%) and 42 of 51 physician evaluators (82.4%) and was preferred by 59 of 62 nurses (95.2%) and 50 of 51 physicians (98.0%); reasons for this preference included patient and clinic/staff time savings.

In summary, this study found that obinutuzumab administered as an SDI in C2 and beyond was well tolerated with no new safety signals, in patients with previously untreated, advanced FL. These results were consistent with previous studies showing the tolerability of obinutuzumab SDI in patients with diffuse large B-cell lymphoma[13] and support the feasibility of obinutuzumab SDI delivery, as has been previously reported for rituximab.[8,14]

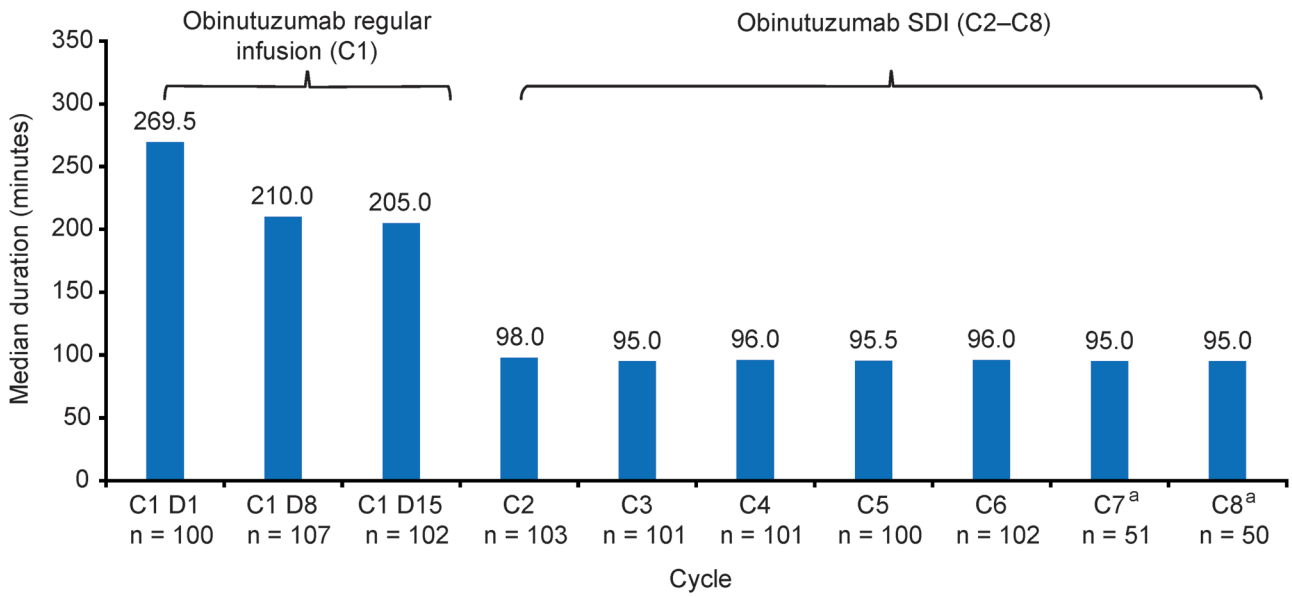

Figure 1. Median duration of obinutuzumab infusion by cycle during induction (overall population). [a]Cycles 7 and 8 only included patients who received CVP. C = cycle; CVP = cyclophosphamide, vincristine, and prednisone; D = day; SDI = short duration infusion.

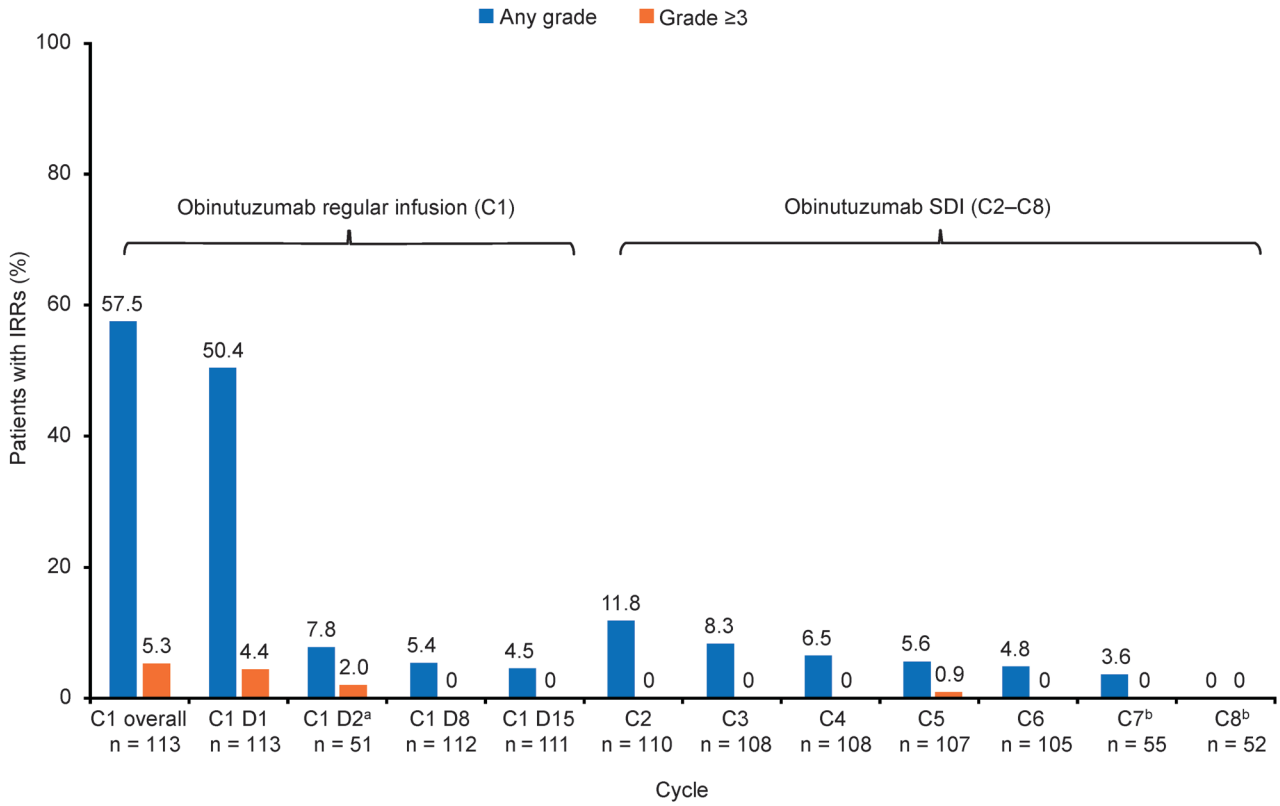

Figure 2. Incidence of IRRs by cycle and grade (overall population). [a]The C1D2 time point only included patients treated with bendamustine. [b]Cycles 7 and 8 only included patients who received CVP. C = cycle; CVP = cyclophosphamide, vincristine, and prednisone; D = day; IRR = infusion-related reaction; SDI = short duration infusion.

The higher frequency of IRRs observed with obinutuzumab- versus rituximab-chemotherapy in the GALLIUM trial[5–7] did not appear to be a limitation for obinutuzumab SDI in this study.

The EOI ORR from this study (86.7%) was in line with that reported in the GALLIUM trial (88.5%) using a standard 3- to 4-hour obinutuzumab infusion (~195 min).[5] These results highlight that responses were essentially the same with SDI administration of obinutuzumab compared to the standard-rate infusion, regardless of infusion time.

Additionally, obinutuzumab SDI demonstrated a minimal impact on patient quality of life, with relatively stable MDASI scores throughout the induction period, as well as the potential for time and cost savings. Time savings of ≥1 hour compared with the standard-rate infusion were reported by >85% of nurses and physicians, with a ≥4-hour time saving reported by 16% of physicians. The reporting of time savings of ≥4 hours, when the standard infusion rate for obinutuzumab is 3–4 hours, suggested that evaluations were based on the entire time patients were in the clinic, rather than just the infusion time. SDI administration was preferred by the majority (>95%) of healthcare providers, mainly due to the time savings for both healthcare staff and patients.

Study limitations include the single-arm study design, lack of pharmacokinetic data, and relatively small number of patients, although the number of patients enrolled was in accordance with the planned sample size.

In conclusion, our results suggest that obinutuzumab SDI is likely to improve the convenience for patients with FL and efficiency for infusion facilities, without compromising safety or efficacy.

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AUTHOR CONTRIBUTIONS

Study design: MAC, TAB, JPS, DK, SP, and JP. Study conduct: MAC, JPS, EV, JP, and KH. Recruitment and follow-up of patients: MAC, JAPB, TI, KI, AS, JPS, EV, KH, and LMF. Data collection: MAC, KI, JPS, EV, and KH. Data analysis: MAC, JAPB, JPS, DK, SP, JP, and KH. Data interpretation: MAC, TAB, JPS, DK, SP, EV, PT, JP, and KH.

DATA AVAILABILITY

Data availability information is included in the supplemental digital content.

DISCLOSURES

MAC reports a consultancy role with Beigene, EUSA Pharma, Celgene-BMS, Kite-Gilead, Janssen, Incyte, Karyopharm, Kyowa, Novartis, F. Hoffmann-La Roche Ltd., Sanofi, and Takeda, and honoraria from EUSA Pharma, Celgene-BMS, Kite-Gilead, Janssen, Kyowa, F. Hoffmann-La Roche Ltd., Sandoz, and Takeda. TAB reports a leadership role and is a stockholder of Nucleix and Empyrean Medical Systems, honoraria from Genentech, Inc., F. Hoffmann-La Roche Ltd., Abivax, and Precisa, a consulting or advisory role with Genentech, Inc. and F. Hoffmann-La Roche Ltd., patents, royalties, and other intellectual property with MD Anderson Cancer Center, and travel, accommodations, and expenses from Genentech, Inc. JAPB, LMF, and TI, report no conflicts. KI reports honoraria from Chugai Pharmaceutical, AbbVie, AstraZeneca, Daiichi Sankyo, Genmab, Kyowa Kirin, Novartis, Ono Pharmaceutical, Symbio, and Takeda and research funding from Chugai Pharmaceutical and Eisai. AS reports a consultancy role with Janssen, EUSA Pharma, BMS, Celgene, and Beigene, research funding from AbbVie, and a speaker's bureau role for Janssen, BMS, and Celgene. JPS owns stock options with Centessa Pharmaceuticals, consultancy with AbbVie, AstraZeneca, Beigene, Bristol Myers Squibb, Lilly, Pharmacyclics, TG Therapeutics and

Genentech, Inc., and membership on board of directors or advisory committees for Centessa Pharmaceuticals. DK reports employment with F. Hoffmann-La Roche Ltd and Celegene, and is a stockholder of F. Hoffmann-La Roche Ltd. JP reports employment with F. Hoffmann-La Roche Ltd and is a stockholder of F. Hoffmann-La Roche Ltd. SP reports employment with F. Hoffmann-La Roche Ltd. EV reports employment with IQVIA. PT reports employment with Genentech, Inc. and is a stockholder of F. Hoffmann-La Roche Ltd. KH reports employment with University of Cologne, a consultancy role with F. Hoffmann-La Roche Ltd., research funding from F. Hoffmann-La Roche Ltd., Celgene, BMS, and Janssen, honoraria from F. Hoffmann-La Roche Ltd., Servier, Gilead, Celgene, BMS, and EUSA Pharma, a speaker's bureau role for F. Hoffmann-La Roche Ltd., Servier, Celgene, BMS, and EUSA Pharma, membership on an entity's Board of Directors or advisory committees for F. Hoffmann-La Roche Ltd., Hexal, Novartis, Gilead, and Incyte.

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