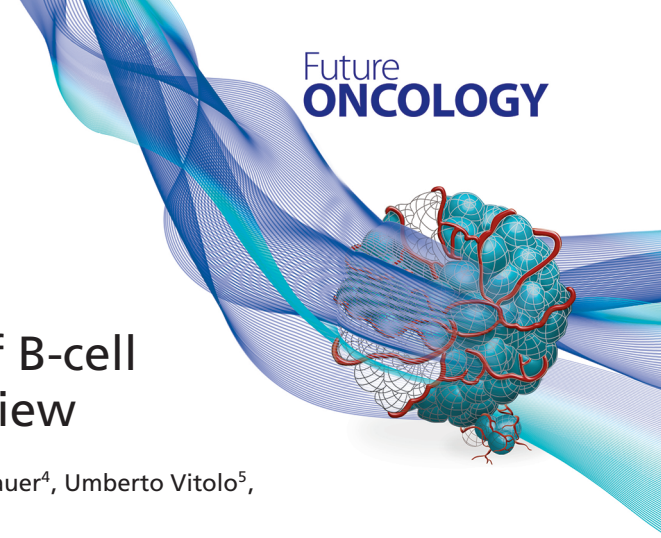
Drug Evaluation

Future ONCOLOGY



Obinutuzumab in the treatment of B-cell malignancies: a comprehensive review

Andrew Davies*[,1], Arnon P Kater[2], Jeff P Sharman[3], Stephan Stilgenbauer[4], Umberto Vitolo[5], Christian Klein[6], Joana Parreira[7] & Gilles Salles[8]

[1]Cancer Research UK Centre, University of Southampton, Southampton, UK
[2]Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands
[3]Willamette Valley Cancer Institute & Research Center & US Oncology, Eugene, OR 97401, USA
[4]Comprehensive Cancer Center Ulm, Early Clinical Trials Unit (ECTU), Ulm, & Division of CLL, Department of Internal Medicine III, Ulm University, Ulm, Germany
[5]Medical Oncology, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy
[6]Roche Innovation Center Zurich, Schlieren, Switzerland
[7]F. Hoffmann-La Roche Ltd, Basel, Switzerland
[8]Memorial Sloan Kettering Cancer Center, Department of Medicine, NY 10021, USA
*Author for correspondence: Tel.: +44 238 120 6184; a.davies@soton.ac.uk

The type II anti-CD20 antibody obinutuzumab has structural and mechanistic features that distinguish it from the first anti-CD20 antibody, rituximab, which have translated into improved efficacy in phase III trials in indolent non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL). These gains have been shown through improvements in, and/or increased durability of, tumor response, and increases in progression-free survival in patients with CLL or follicular lymphoma (FL). Ongoing research is focusing on the use of biomarkers and the development of chemotherapy-free regimens involving obinutuzumab. phase II trials of such treatment regimens have shown promise for CLL, FL and mantle cell lymphoma, while phase III trials have highlighted obinutuzumab as the antibody partner of choice for novel agents in first-line CLL treatment.

First draft submitted: 2 February 2022; Accepted for publication: 23 June 2022; Published online: 20 July 2022

Keywords: anti-CD20 • antibody • B-cell malignancies • CLL • DLBCL • FL • obinutuzumab

B cells are a key component of the adaptive humoral immune system and mediate the production of antibodies directed against invasive pathogens. CD20 is a 33–37 kDa non-glycosylated phosphoprotein that is expressed on the surface of B-cell precursors and mature undifferentiated B cells [1]. The biological function of CD20 in B cells remains unclear, but it may be involved in B-cell receptor activation and Ca^{2+} transport [2]. Functional studies have suggested that CD20 is required for efficient receptor signaling in B cells (reviewed by Pavlasova and Mraz [3]). Crucially, CD20 is found in 95% of B-cell malignancies [4], diseases that include lymphocytic leukemias and B-cell lymphomas. Chronic lymphocytic leukemia (CLL) is frequently a slowly progressing disease that mainly affects older adults and is the most common form of leukemia in western countries [5]. Lymphomas are hematologic malignancies that arise mainly from mature T or B cells in secondary lymphoid tissue, notably the lymph nodes [6,7]. They are subdivided based on cellular characterization into Hodgkin lymphoma and non-Hodgkin lymphoma (NHL), with NHL accounting for approximately 90% of cases [7]. Follicular lymphoma (FL) and marginal zone lymphoma (MZL) are indolent B-cell NHLs, while diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma and mantle cell lymphoma (MCL) are more aggressive and faster-growing [7].

Rituximab & the era of targeted therapy

The outlook for patients with B-cell NHL improved markedly in the late 1990s following the introduction of targeted therapy with the CD20-directed monoclonal antibody (mAb) rituximab [8,9]. This agent engages Fc receptors on immune effectors, such as natural killer cells and macrophages, and mediates complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity/phagocytosis (ADCC/ADCP) as a main

Future Medicine

mechanism of action. It also has direct antiproliferative and pro-apoptotic effects [10]. Recent studies have shown that two rituximab Fab domains bind to a single CD20 dimer. The resulting well-ordered assemblies are thought to be highly efficient at recruiting complement, thereby encouraging CDC [11].

Early trials of rituximab focused on monotherapy in patients with relapsed or refractory (R/R) CD20-positive low-grade FL, resulting in a 48% response rate [9]. phase III research focused on the addition of rituximab to chemotherapy in previously untreated patients. Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapy (R-CHOP) resulted in significantly increased overall response (OR) compared with CHOP alone (76 vs 63%; p = 0.005) and significantly greater overall survival (OS) at 2 years (70 vs 57%; p = 0.007) in older patients with previously untreated DLBCL [12]. In previously untreated FL, rituximab plus cyclophosphamide, vincristine and prednisone resulted in significant improvements in response rates and survival outcomes [13]. In the PRIMA study, rituximab maintenance for 2 years after an initial response to chemoimmunotherapy was shown to provide a progression-free survival (PFS) benefit over 9 years of follow-up in patients with FL [14]. In the CLL8 study, in patients with treatment-naive CLL, the addition of rituximab to fludarabine plus cyclophosphamide (FC) significantly increased PFS and OS compared with FC alone [15].

Treatment resistance & rationale for the development of obinutuzumab

Despite the advance provided by rituximab, many patients still relapse after an initial response to rituximab-based treatment or have disease that is rituximab-refractory [16]. The mechanisms underlying treatment failure after rituximab are not fully understood but may include resistance to CDC or failure of cells to undergo apoptosis [17,18]. Loss of CD20 via 'shaving' has also been postulated, whereby complexes between type I mAbs, such as rituximab, and CD20 are removed by trogocytosis, a process through which lymphocytes conjugated to antigen-presenting cells extract surface molecules from these cells and express them on their own surface [19]. Modulation via internalization and degradation of the type I mAb-CD20 complex may also take place, restricting the engagement of effector cells and reducing the half-life of the anti-CD20 mAb [20].

The challenges posed by treatment relapse and resistance to rituximab, together with improvements in understanding of the biology and mechanisms of action of anti-CD20 mAbs, have led to the development of novel agents with potential mechanistic and treatment advantages over rituximab. One such agent is the humanized and glycoengineered, type II anti-CD20 mAb, obinutuzumab (GA101). Type I mAbs such as rituximab rely primarily on CDC (through clustering of CD20 in lipid rafts) and ADCC for their effects, whereas type II mAbs such as obinutuzumab have enhanced direct cell death effects and reduced CDC, but with retained or enhanced ADCC/ADCP activity [21,22].

Structure & mode of action of obinutuzumab

Obinutuzumab is distinguished by its Fc domain, which is modified by glycoengineering to enhance ADCC and ADCP relative to rituximab (Figure 1) [20,23,24]. Obinutuzumab lacks a fucose residue from immunoglobin (Ig) G oligosaccharides in its Fc region, which enhances its affinity for FcγRIIIa receptors on immune effector cells [23,25]. The CD20 binding sites of obinutuzumab and rituximab also differ [22,26]. This leads to differences in CD20 complex associations and membrane compartmentalization, and these conformational differences are associated with the distinct cellular responses to type I (rituximab) and type II (obinutuzumab) mAbs. Recently, structural studies have confirmed the suggested binding mode for obinutuzumab as opposed to rituximab and ofatumumab (type I mAbs) [27].

Unlike type I mAbs, only a single type II mAb binds to each CD20 dimer; these do not form lipid rafts with FcγRIIb receptors and subsequent internalization of CD20 [11,22]. As CDC depends on translocation of CD20 onto lipid rafts [28] it is not a significant mechanism by which obinutuzumab induces cell death [28]. Obinutuzumab has shown greater B-cell depletion than rituximab, experimentally in blood from healthy human donors and *in vitro* CLL models [23,29], as well as dose-dependent and superior *in vivo* efficacy in xenograft models compared with rituximab and ofatumumab at saturating doses of up to 30 mg/kg [23,24].

Dosing considerations

The dosage of rituximab is 375 mg/m^2 administered on day 1 of each cycle of chemotherapy for up to eight infusions in DLBCL, or once on the day prior to initiation of FC followed by 500 mg/m^2 on day 1 of cycles 2–6 in CLL [30]. The higher dose of 500 mg/m^2 was adopted following investigation of the dose–response relationship of rituximab monotherapy in CLL, but escalation trials in DLBCL did not yield significant results

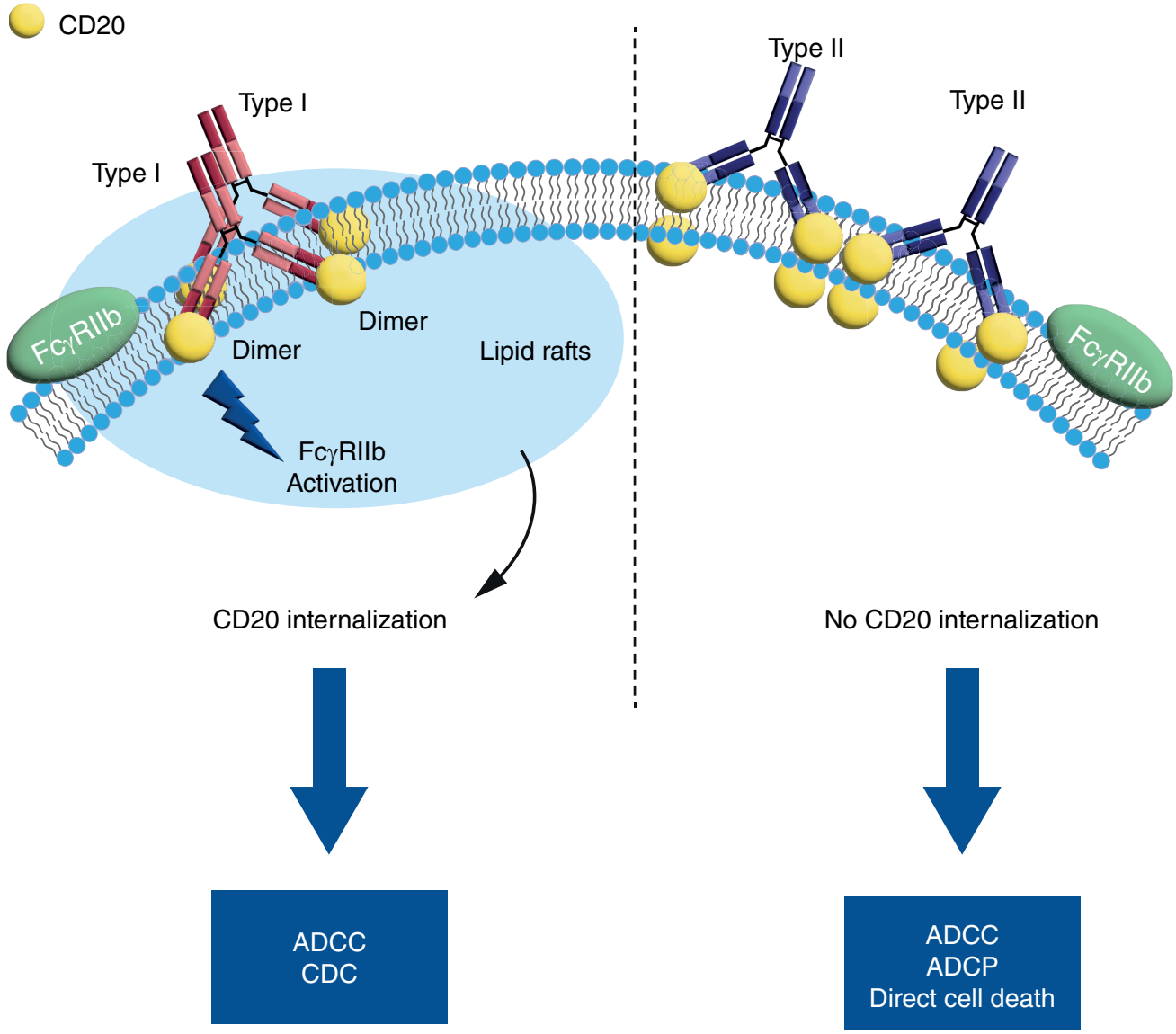


Figure 1. Mechanism of action of type I and type II anti-CD20 monoclonal antibodies.
Adapted from [22,25] with permission from Taylor & Francis Group.
ADCC: Antibody-dependent cell-mediated cytotoxicity; ADCP: Antibody-dependent cell-mediated phagocytosis; CDC: Complement-dependent cytotoxicity.

when compared with historical data [31]. Pharmacokinetic modeling has also suggested a potential PFS benefit with higher (1500 mg/m^2) doses of rituximab when administered as a monotherapy or as part of the R-CHOP regimen, but this model was limited by the inclusion of data from only patients with FL and lacked information to validate doses higher than 375 mg/m^2 [32]. In a simulation of fixed-dose intravenous (i.v.) monoclonal antibodies, including rituximab, inter-subject exposure variability was not increased relative to body size-based dosing [33]. A fixed dose of 1400 mg rituximab, administered subcutaneously, was assessed in the phase III SABRINA study (NCT01200758), and demonstrated similar efficacy and safety profiles to rituximab i.v. [34].

Obinutuzumab is given at a fixed dose of 1000 mg, determined by data from early phase clinical trials. Flat dosing of obinutuzumab was considered more convenient, and pharmacokinetic modeling suggested that additional doses of obinutuzumab on days 8 and 15 of cycle 1 would be needed to overcome target-mediated clearance and achieve and maintain a steady state of drug early on and for as long as possible during treatment [35–38].

The use of different doses in clinical trials of obinutuzumab and rituximab, such as the CLL11 and GALLIUM studies, has attracted criticism regarding the ability to make true efficacy comparisons between the two agents [39]. However, studies show no advantage to using higher doses of rituximab [40,41], despite initial suggestions from phase II dose-escalation data obtained in a small number of patients [42]. Furthermore, modeling studies indicate that the improved antitumor activity of obinutuzumab relative to rituximab is not a dose effect, i.e. the activity of the fixed dosing regimen of obinutuzumab is not equivalent to a dosage of rituximab in excess of 375 mg/m^2 [43,44].

Early-phase development of obinutuzumab

Obinutuzumab development was supported by the findings of phase I and II studies in patients with B-cell NHL or CLL. The multicenter phase Ib/II GAUGUIN trial (NCT00517530) of obinutuzumab monotherapy showed promising activity and favorable safety and tolerability across a range of R/R B-cell malignancies, including FL, DLBCL, MCL and CLL, and consolidated the place of the 1000 mg fixed dose [35,36,45]. Promising activity of obinutuzumab 1000 mg weekly for 4 weeks, followed by maintenance for up to 2 years, was also reported in the phase I/II GAUSS trial (NCT00576758) in patients with relapsed indolent NHL [38].

Results of studies of obinutuzumab plus chemotherapy showed similar promise. All rituximab-refractory patients with FL (n = 14) responded to induction treatment in the phase Ib GAUDI study (NCT00825149) of obinutuzumab plus CHOP (G-CHOP) or FC (G-FC) [46]. In addition, G-CHOP conferred OR and complete response (CR) rates of 82 and 55%, respectively, in the first-line GATHER study (NCT01414855) in patients with advanced DLBCL [47]. Manageable toxicity and good activity in patients with previously untreated CLL were also shown in the phase II GAGE monotherapy trial (NCT01414205) and the phase Ib GALTON study (NCT01300247) of G-FC or obinutuzumab plus bendamustine (G-Benda) [48].

Obinutuzumab in chronic lymphocytic leukemia

Monotherapy & chemoimmunotherapy

Obinutuzumab has been investigated in CLL in combination with available treatment options, including chemotherapy agents such as chlorambucil (Clb; Table 1). In the phase III CLL11 study (NCT01010061), 781 patients with CLL and a score exceeding 6 on the Cumulative Illness Rating Scale or an estimated creatinine clearance of 30–69 mL/min were randomized to receive first-line Clb alone, rituximab (375 mg/m^2) plus Clb (R-Clb), or obinutuzumab (1000 mg) plus Clb (G-Clb) for six 28-day cycles [49,50]. G-Clb was associated with a significantly increased PFS versus Clb alone (Figure 2) [49,50]. Patients receiving G-Clb, but not R-Clb, also showed significantly longer OS versus Clb alone [49]. G-Clb was associated with significantly longer PFS than R-Clb (hazard ratio [HR]: 0.39; 95% CI: 0.31–0.49; $p < 0.001$), and with a greater tumor CR rate (21 vs 7%, respectively) [49,50]. Furthermore, minimal residual disease (MRD) negativity at end of treatment (EOT) in bone marrow (BM; 19.5 vs 2.6%; $p < 0.001$) and PB (37.7 vs 3.3%; $p < 0.001$) was achieved in significantly higher proportions of patients in the G-Clb arm than with R-Clb, respectively [49]. In the final analysis (median additional follow-up of ~2 years), an OS benefit was observed for G-Clb versus R-Clb (HR: 0.76; 95% CI: 0.60–0.97; p = 0.02), with 2- and 5-year survival rates of 91 versus 84% and 66 versus 57% for G-Clb versus R-Clb, respectively. The PFS benefit was maintained at the final analysis (HR: 0.49; 95% CI: 0.41–0.58; $p < 0.0001$; Figure 2) [50].

As one of the primary sources of safety data for obinutuzumab treatment in CLL, the CLL11 study documented that the incidence of grade 3 or 4 neutropenia was highest with G-Clb and was lowest with Clb alone [49]. In the G-Clb group, grade 3 or 4 infusion-related reactions (IRRs) occurred in 20% of patients during the first infusion of obinutuzumab, but there were no grade 3 or 4 reactions during subsequent obinutuzumab infusions. Rates of grade ≥3 infection were similar (11–14%) across treatments [49].

At the request of regulatory authorities following the approval of obinutuzumab for CLL, the phase IIIb GREEN study (NCT01905943) was initiated to evaluate the safety of obinutuzumab alone or with chemotherapy in patients with previously untreated or R/R CLL [51,52]. Chemotherapy allocation occurred by line of therapy and patient fitness [51,52]. Among 971 patients treated with an obinutuzumab regimen, grade ≥3 IRRs occurred in 19.4% of previously untreated patients and in 19.6% of R/R patients; IRRs were largely restricted to the first infusion and did not result in any deaths [52]. As a secondary end point, efficacy of the different treatment combinations was evaluated, with best overall response (BOR) rates found to be high in all groups, ranging from 77.8% and 60.0% in previously untreated and R/R patients treated with obinutuzumab monotherapy, to 96.1 and 97.5% in previously untreated and R/R patients treated with G-FC, respectively [52]. Subgroup analyses also confirmed

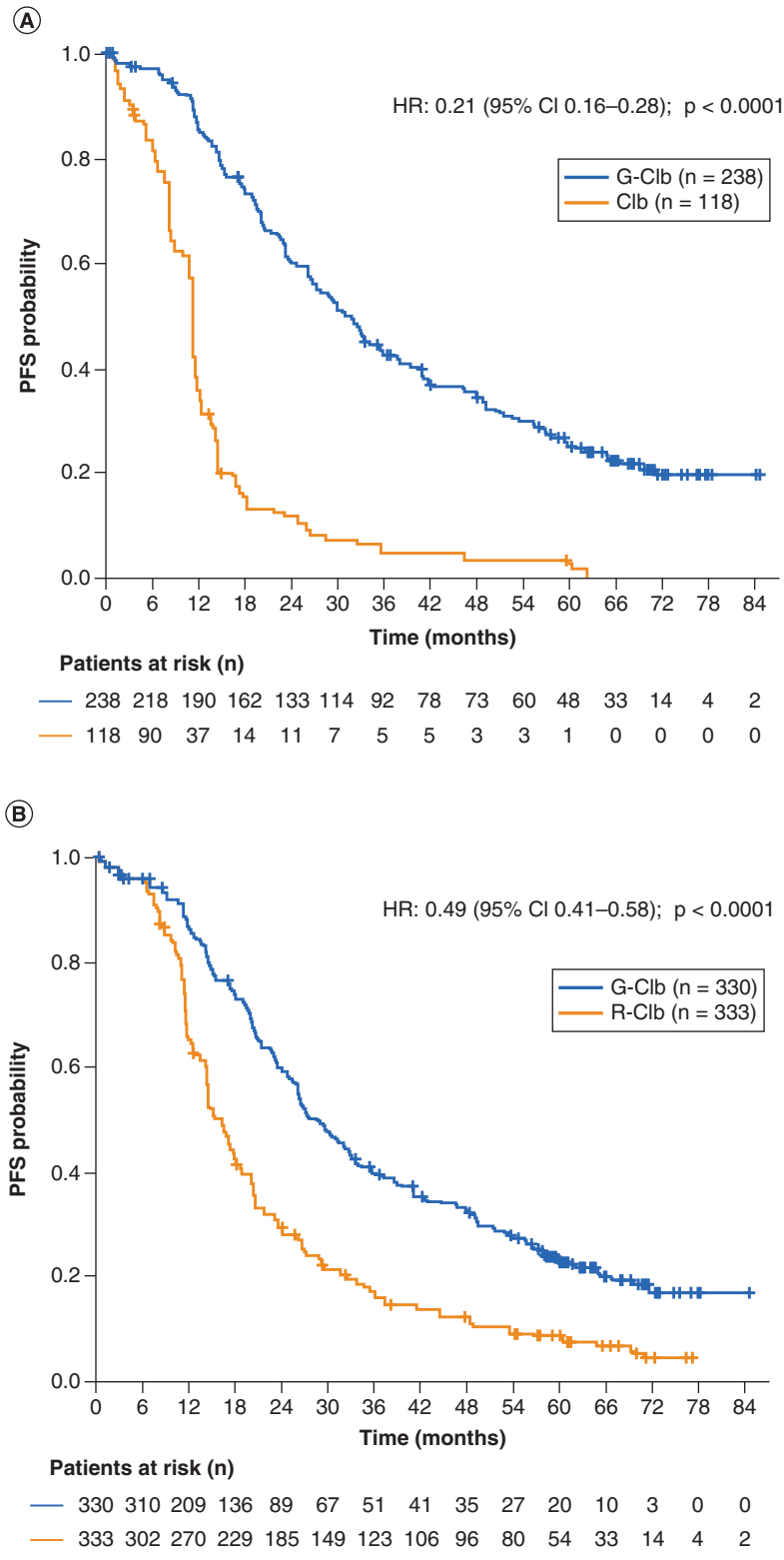


Figure 2. Progression-free survival with obinutuzumab-chlorambucil versus chlorambucil, andobinutuzumab-chlorambucil versus rituximab-chlorambucil, in the phase III CLL11 study in patients with previously untreated chronic lymphocytic leukemia. (A) G-Clb versus Clb. **(B)** G-Clb versus R-Clb.
Clb: Chlorambucil; CLL: Chronic lymphocytic leukemia; G: Obinutuzumab; HR: Hazard ratio; PFS: Progression-free survival; R: Rituximab.

Table 1. Key clinical trials of obinutuzumab in patients with chronic lymphocytic leukemia.

Trial	Tumor response rates	Survival and other time-to-event end points (medians unless stated otherwise)	Ref.
Chemoimmunotherapy as 1L therapy			
– CLL11; NCT01010061; phase III			[49,50]
Primary analysis			[49]
Clb, n = 118†	31.4% OR (all PR)	PFS 11.1 mo	
G-Clb, n = 238†	77.3% (CR 22.3%) p < 0.001 vs Clb or R-Clb‡	PFS 26.7 mo HR: 0.18; p < 0.001 vs Clb HR: 0.39; p < 0.001 vs R-Clb‡ OS NR HR: 0.41; p = 0.002 vs Clb NS vs R-Clb‡	
R-Clb, n = 233†	65.7% (CR 7.3%) p < 0.001 vs Clb	PFS 16.3 mo HR: 0.44; p < 0.001 vs Clb OS NR NS vs Clb	
Final analysis			[50]
Clb, n = 118†	N/A	PFS 11.1 mo TTNT 15.1 mo OS 66.7 mo	
G-Clb, n = 238†	N/A	PFS 31.1 mo HR: 0.21; p < 0.0001 vs Clb HR: 0.49; p < 0.0001 vs R-Clb‡ TTNT 55.7 mo HR: 0.25; p < 0.0001 vs Clb HR: 0.58; p < 0.0001 vs R-Clb‡ OS NR HR: 0.68; p = 0.0196 vs Clb HR: 0.76; p = 0.0245 vs R-Clb‡	
R-Clb, n = 330†	N/A	PFS 15.7 mo TTNT 34.9 mo OS 73.1 mo	
Chemoimmunotherapy in 1L or R/R disease			
– GREEN; NCT01905943; phase IIIb			[51,52]
Primary analysis			[51]
G, n = 127§	1L OR 63.5% (CR 20.6%) R/R OR 42.2% (CR 4.7%)	N/A	
G-FC, n = 193§	1L OR 89.5% (CR 46.4%) R/R OR 82.5% (CR 22.5%)	N/A	
G-Clb, n = 114§	1L OR 82.4% (CR 16.2%) R/R OR 54.3% (CR 6.5%)	N/A	
G-Benda, n = 538§	1L OR 81.8% (CR 35.7%) R/R OR 72.8% (CR 19.9%)	N/A	
Final analysis			[52]
G, n = 128§	1L CR 50.8% R/R CR 27.7%	1L PFS 30.2 mo R/R PFS 17.6 mo 1L 4-yr OS 0.83 (95% CI: 0.67–0.91) R/R 4-yr OS 0.59 (95% CI: 0.43–0.71) 1L TTNT NR R/R TTNT 22.5 mo	

†Clb: Clb 0.5 mg/kg d1, d15 × 6 q28d; G-Clb: G 1000 mg d1–2, d8, d15, then d1 c2–6 + Clb; R-Clb: R 375 mg/m^2 d1 c1, then 500 mg/m^2 d1 c2–6 + Clb.
‡G-Clb n = 333; R-Clb n = 330 (n = 329 for tumor response rates).
§G: 1000 mg d1, d8, d15 c1, then d1 c2–6 q28d; G-FC: G + FC 25/250 mg/m^2 intravenously or 40/250 mg/m^2 orally d1–3 c1–6 q28d; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–6 q28d; G-Benda: G + Benda 70 mg/m^2 R/R or 90 mg/m^2 1L q28d.
¶G-Ven: G 1000 mg d1–2, d8, d15 c1, then d1 c2–6 q28d + VEN 400 mg daily after ramp-up × 12c; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–12 q28d.
#G-Ibr: G 1000 mg d1–2, d8, d15 c1, then d1 c2–6 q28d + Ibr 420 mg daily continuously; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–12 q28d.
††G-ACA: G 1000 mg d1–2, d8, d15 c2, then d1 c3–7 q28d + ACA 100 mg twice-daily continuously; ACA: 100 mg twice-daily continuously; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–6 q28d.
1L: First line; ACA: Acalabrutinib; Benda: Bendamustine; BOR: Best overall response; c: Cycle; Clb: Chlorambucil; CLL: Chronic lymphocytic leukemia; CR: Complete response; d: Day; FC: Fludarabine plus cyclophosphamide; G: Obinutuzumab; HR: Hazard ratio; Ibr: Ibrutinib; mo: Month; N/A: Not available; NR: Not reached; NS: Nonsignificant; OR: Overall response; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; q28d: Every 28 days; R: Rituximab; R/R: Relapsed/refractory; TTNT: Time to next treatment; TTNTD: Time to next antileukemic treatment or death; VEN: Venetoclax; yr: Year.

Table 1. Key clinical trials of obinutuzumab in patients with chronic lymphocytic leukemia (cont.).

Trial	Tumor response rates	Survival and other time-to-event end points (medians unless stated otherwise)	Ref.
G-FC, n = 193[§]	1L CR 68.6% R/R CR 60.0%	1L PFS NR R/R PFS 24.8 mo 1L 4-yr OS 0.94 (95% CI: 0.89–0.97) R/R 4-yr OS 0.70 (95% CI: 0.53–0.82) 1L TTNT NR R/R TTNT 32.6 mo	
G-Clb, n = 114[§]	1L CR 61.8% R/R CR 32.6%	1L PFS 31.8 mo R/R PFS 14.1 mo 1L 4-yr OS 0.67 (95% CI: 0.53–0.79) R/R 4-yr OS 0.54 (95% CI: 0.37–0.69) 1L TTNT 53.7 mo R/R TTNT 20.4 mo	
G-Benda, n = 537[§]	1L CR 62.5% R/R CR 45.3%	1L PFS 58.0 mo R/R PFS 28.6 mo 1L 4-yr OS 0.85 (95% CI: 0.81–0.89) R/R 4-yr OS 0.68 (95% CI: 0.60–0.75) 1L TTNT NR R/R TTNT 38.3 mo	
Combinations with novel agents			
– CLL14; NCT02242942; phase III			[53,54]
Primary analysis			[53]
G-Ven n = 216 1L[¶]	OR 84.7% (CR 49.5%) $p < 0.001$ vs G-Clb	30 events at 28.1 mo HR: 0.35; $p < 0.001$ vs G-Clb 24-mo PFS 88.2% (95% CI: 83.7–92.6%)	
G-Clb, n = 216 1L[¶]	OR 71.3% (CR 23.1%)	77 events at 28.1 mo 24-mo PFS 64.1% (95% CI: 57.4–70.8%)	
Updated analysis			[54]
G-Ven, n = 216 1L[¶]	N/A	PFS NR HR: 0.31; $p < 0.0001$ vs G-Clb 36-mo PFS 81.9% (95% CI: 76.5–87.3%) TTNTD NR HR: 0.51 vs G-Clb OS NR HR: 1.03; p = 0.92 vs G-Clb	
G-Clb, n = 216 1L[¶]	N/A	PFS 35.6 mo 36-mo PFS 49.5% (95% CI: 42.4–56.6%) TTNTD NR OS NR	
– iLLUMINATE; NCT02264574; phase III			[55]
G-Ibr, n = 113 1L[#]	OR 88% (CR 19%)	PFS NR HR: 0.23; $p < 0.0001$ vs G-Clb 30-mo PFS 79% (95% CI: 70–85%) OS NR 30-mo OS 86% (95% CI: 77–91%)	
G-Clb n = 116 1L[#]	OR 73% (CR 8%)	PFS 19.0 mo 30-mo PFS 31% (95% CI: 23–40%) OS NR 30-mo OS 85% (95% CI: 77–90%)	

[†]Clb: Clb 0.5 mg/kg d1, d15 × 6 q28d; G-Clb: G 1000 mg d1–2, d8, d15, then d1 c2–6 + Clb; R-Clb: R 375 mg/m^2 d1 c1, then 500 mg/m^2 d1 c2–6 + Clb.
[‡]G-Clb n = 333; R-Clb n = 330 (n = 329 for tumor response rates).
[§]G: 1000 mg d1, d8, d15 c1, then d1 c2–6 q28d; G-FC: G + FC 25/250 mg/m^2 intravenously or 40/250 mg/m^2 orally d1–3 c1–6 q28d; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–6 q28d; G-Benda: G + Benda 70 mg/m^2 R/R or 90 mg/m^2 1L q28d.
[¶]G-Ven: G 1000 mg d1–2, d8, d15 c1, then d1 c2–6 q28d + VEN 400 mg daily after ramp-up × 12c; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–12 q28d.
[#]G-Ibr: G 1000 mg d1–2, d8, d15 c1, then d1 c2–6 q28d + Ibr 420 mg daily continuously; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–12 q28d.
[††]G-ACA: G 1000 mg d1–2, d8, d15 c2, then d1 c3–7 q28d + ACA 100 mg twice-daily continuously; ACA: 100 mg twice-daily continuously; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–6 q28d.
1L: First line; ACA: Acalabrutinib; Benda: Bendamustine; BOR: Best overall response; c: Cycle; Clb: Chlorambucil; CLL: Chronic lymphocytic leukemia; CR: Complete response; d: Day; FC: Fludarabine plus cyclophosphamide; G: Obinutuzumab; HR: Hazard ratio; Ibr: Ibrutinib; mo: Month; N/A: Not available; NR: Not reached; NS: Nonsignificant; OR: Overall response; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; q28d: Every 28 days; R: Rituximab; R/R: Relapsed/refractory; TTNT: Time to next treatment; TTNTD: Time to next antileukemic treatment or death; VEN: Venetoclax; yr: Year.

Table 1. Key clinical trials of obinutuzumab in patients with chronic lymphocytic leukemia (cont.).

Trial	Tumor response rates	Survival and other time-to-event end points (medians unless stated otherwise)	Ref.
– ELEVATE-TN; NCT02475681; phase III			[56,57]
Interim analysis			[56]
G-ACA, n = 179 1L††	BOR 94% (CR 13%)	PFS NR HR: 0.10; p < 0.0001 vs G-Clb 24-mo PFS 93% (95% CI: 87–96%) OS NR HR: 0.47; p = 0.0577 vs G-Clb	
ACA, n = 179 1L††	BOR 86% (CR 1%)	PFS NR HR: 0.2; p < 0.0001 vs G-Clb 24-mo PFS 87% (95% CI: 81–92%) OS NR HR: 0.60; p = 0.1556 vs G-Clb	
G-Clb, n = 177 1L††	BOR 79% (CR 5%)	PFS 22.6 mo 24-mo PFS 47% (95% CI: 39–55%) OS NR	
Updated analysis			[56,58]
G-ACA, n = 179 1L††	OR 96.1% (CR 30.7%)	PFS NR p < 0.0001 vs G-Clb 48-mo PFS 87% OS NR p = 0.0604 vs G-Clb 48-mo OS 93%	
ACA, n = 179 1L††	OR 89.9% (CR 11.2%)	PFS NR p < 0.0001 vs G-Clb 48-mo PFS 78% OS NR 48-mo OS 88%	
G-Clb, n = 177 1L††	OR 82.5% (CR 13.0%)	PFS 27.8 mo 48-mo PFS 25% OS NR 48-mo OS 88%	

†Clb: Clb 0.5 mg/kg d1, d15 × 6 q28d; G-Clb: G 1000 mg d1–2, d8, d15, then d1 c2–6 + Clb; R-Clb: R 375 mg/m^2 d1 c1, then 500 mg/m^2 d1 c2–6 + Clb.
‡G-Clb n = 333; R-Clb n = 330 (n = 329 for tumor response rates).
§G: 1000 mg d1, d8, d15 c1, then d1 c2–6 q28d; G-FC: G + FC 25/250 mg/m^2 intravenously or 40/250 mg/m^2 orally d1–3 c1–6 q28d; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–6 q28d; G-Benda: G + Benda 70 mg/m^2 R/R or 90 mg/m^2 1L q28d.
¶G-Ven: G 1000 mg d1–2, d8, d15 c1, then d1 c2–6 q28d + VEN 400 mg daily after ramp-up × 12c; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–12 q28d.
#G-Ibr: G 1000 mg d1–2, d8, d15 c1, then d1 c2–6 q28d + Ibr 420 mg daily continuously; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–12 q28d.
††G-ACA: G 1000 mg d1–2, d8, d15 c2, then d1 c3–7 q28d + ACA 100 mg twice-daily continuously; ACA: 100 mg twice-daily continuously; G-Clb: G + Clb 0.5 mg/kg d1 + d15 c1–6 q28d.
1L: First line; ACA: Acalabrutinib; Benda: Bendamustine; BOR: Best overall response; c: Cycle; Clb: Chlorambucil; CLL: Chronic lymphocytic leukemia; CR: Complete response; d: Day; FC: Fludarabine plus cyclophosphamide; G: Obinutuzumab; HR: Hazard ratio; Ibr: Ibrutinib; mo: Month; N/A: Not available; NR: Not reached; NS: Nonsignificant; OR: Overall response; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; q28d: Every 28 days; R: Rituximab; R/R: Relapsed/refractory; TTNT: Time to next treatment; TTNTD: Time to next antileukemic treatment or death; VEN: Venetoclax; yr: Year.

that obinutuzumab plus chemotherapy is efficacious in specific subgroups, for example, patients with mutated immunoglobulin heavy chain gene (IGHV) and non-del(17p)/del(11q) [52].

Obinutuzumab has also been investigated in combination with bendamustine in previously untreated patients with CLL. In the single-arm phase II GIBB study (NCT02320487) in 102 patients with previously untreated CLL who received up to six cycles of G-Benda, an OR rate of 89% (50% CR) was reported [59]. Median PFS was 35.5 months, while median OS was not reached after a median follow-up of 34.3 months. MRD-negativity at the clinical response assessment was achieved for 33/74 (45%) and 30/51 (59%) evaluable patients in PB and BM, respectively [59].

Combinations with novel agents

Ongoing research focuses on the application of targeted therapy to maximize tumor responses and survival, while minimizing adverse events (AEs) and patient discomfort. Therefore, some combinations discussed in this manuscript are investigational only and currently off-label. Anti-CD20 agent combinations with novel therapies are now used in an effort to provide effective treatment options by targeting multiple cellular mechanisms, while reducing reliance on, and avoiding some of the toxicity associated with, chemotherapy. In addition, DNA-damaging agents such as

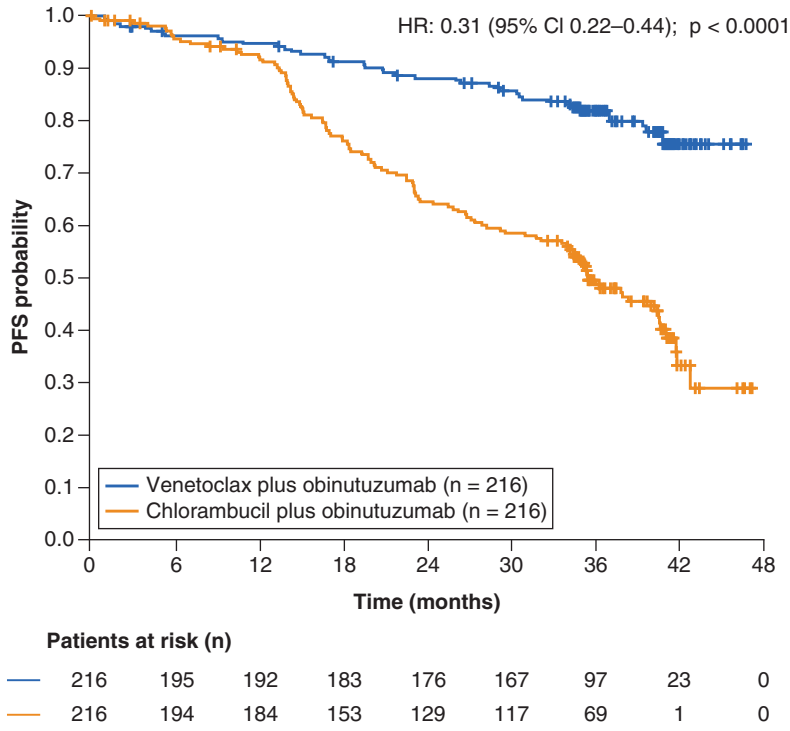


Figure 3. Progression-free survival with obinutuzumab-venetoclax versus obinutuzumab-chlorambucil in the phase III CLL14 study in patients with previously untreated chronic lymphocytic leukemia.
HR: Hazard ratio; PFS: Progression-free survival.

cytotoxic chemotherapies can cause CLL cells to accumulate adverse biological features and develop resistance to therapies after disease progression [60], underlining the need for alternative approaches.

The feasibility of chemotherapy-free combination treatment was originally shown in the phase III MURANO study (NCT02005471) in patients with R/R CLL who received rituximab plus either the *Bcl-2* inhibitor venetoclax (R-Ven) or bendamustine [61]. Patients receiving the targeted therapy combination achieved significantly longer PFS (HR: 0.16; 95% CI: 0.12–0.23; $p < 0.001$) and OS (HR: 0.50; 95% CI: 0.30–0.85; $p = 0.0093$), and higher rates of undetectable MRD, than those receiving chemoimmunotherapy [62].

The combination of obinutuzumab with venetoclax (G-Ven) was compared with G-Clb in the phase III CLL14 study (NCT02242942) in 432 patients with previously untreated CLL and comorbidities [53]. After a median follow-up of 28.1 months, PFS was significantly improved with G-Ven versus G-Clb, with 30/216 and 77/216 patients experiencing PFS events, respectively (HR: 0.35; 95% CI: 0.23–0.53; $p < 0.0001$) [53]. The PFS rate at 2 years was significantly higher with G-Ven versus G-Clb (88.2 vs 64.1%; $p < 0.001$); median PFS was not reached in either arm at 2 years [53]. A significantly longer PFS was also observed with G-Ven compared with G-Clb after a median follow-up of 39.6 months (HR: 0.31; 95% CI: 0.22–0.44; $p < 0.0001$; Figure 3) [54]. Significantly higher proportions of patients also achieved MRD-negativity at EOT in the intent-to-treat population with G-Ven versus G-Clb in PB (75.5 vs 35.2%, respectively; $p < 0.001$) and BM (56.9 vs 17.1%, respectively; $p < 0.001$) [53]. The toxicity profile observed for G-Clb was similar in severity to that of G-Ven, with implemented safety measures effectively mitigating the risk of tumor lysis syndrome [53].

In CLL14, G-Clb demonstrated favorable efficacy in comparison with that previously observed for this combination in the CLL11 study, with a median PFS of 31.1 months observed for patients treated with G-Clb in CLL11 [50]. Approximately 49 and 60% of patients were event free at 30 months in CLL11 and CLL14, respectively [49,50,53]. The improvement in survival observed in CLL14 is most likely due to patients receiving 12 cycles of G-Clb in this study versus the 6 cycles received in CLL11 [49,50,53].

Improved efficacy was also demonstrated in two trials in patients with previously untreated CLL, in which obinutuzumab was combined with a Bruton's tyrosine kinase (BTK) inhibitor rather than with Clb [55,56]. In iLLUMINATE (phase III; NCT02264574), PFS was significantly longer for patients treated with ibrutinib plus

obinutuzumab (G-Ibr) than with G-Clb (HR: 0.23; 95% CI: 0.15–0.37; p < 0.0001) [55]. MRD status was evaluated in responding patients after the start of study treatment, and 35% of evaluable G-Ibr-treated patients and 25% of G-Clb-treated patients had undetectable MRD in BM or PB. The added contribution of G-Ibr to the overall outcome was limited by the absence of a single-agent ibrutinib group to allow for a head-to-head comparison with G-Ibr [55].

The phase III GAIA study (CLL13) evaluated three venetoclax plus CD20 antibody-based regimens (R-Ven, G-Ven, and obinutuzumab, ibrutinib plus venetoclax) versus standard chemoimmunotherapy in fit patients with previously untreated CLL without *TP53* mutation/deletion [63]. At month 15, the rate of undetectable MRD was significantly higher with G-Ven compared with chemoimmunotherapy: 86.5% (97.5% CI: 80.6–91.1) versus 52.0% (97.5% CI: 44.4–59.5; p < 0.0001), respectively. The undetectable MRD rate for obinutuzumab, ibrutinib plus venetoclax was also higher (92.2%; 97.5% CI: 87.3–95.7) compared with chemoimmunotherapy (p < 0.0001), while the difference observed with R-Ven versus chemoimmunotherapy was not significant (57.0%, 97.5% CI: 49.5–64.2; p = 0.317) [64]. The median MRD level at month 9 was lower in the chemoimmunotherapy, G-Ven, and obinutuzumab, ibrutinib plus venetoclax (all 1×10^{-5}) arms compared with the R-Ven (2×10^{-5}) arm [64]. CR rates at month 15 for chemoimmunotherapy, R-Ven, G-Ven, and obinutuzumab, ibrutinib plus venetoclax were 31.0, 49.4, 56.8 and 61.9%, respectively. All treatment arms demonstrated a tolerable safety profile in this fit population [64].

Similarly, in ELEVATE-TN (phase III; NCT02475681), both acalabrutinib plus obinutuzumab (G-acalabrutinib) and acalabrutinib monotherapy led to longer PFS compared with G-Clb. Notably, the HR for G-acalabrutinib versus G-Clb (HR: 0.10; 95% CI: 0.06–0.17; p < 0.0001) was lower than that for acalabrutinib monotherapy versus G-Clb (HR: 0.20; 95% CI: 0.13–0.30; p < 0.0001) [56]. This trend was replicated in the OS data: the HR for G-acalabrutinib versus G-Clb was 0.47 (95% CI: 0.21–1.06; p = 0.06) while the HR for acalabrutinib monotherapy versus G-Clb was 0.60 (95% CI: 0.28–1.27; p = 0.16) [56]. At a 4-year update with a median follow-up of 46.9 months, median PFS was not reached with G-acalabrutinib or acalabrutinib, versus 27.8 months with G-Clb [57,58]. Of note, early suggestions of antagonism of anti-CD20-induced ADCC by ibrutinib have not been demonstrated in clinical practice [65]. Rates of undetectable MRD were similar for G-acalabrutinib and G-Clb in PB (49 vs 61%, respectively) and BM (26 vs 22%, respectively) [56]. Furthermore, a *post-hoc* analysis demonstrated a PFS benefit with the addition of obinutuzumab to acalabrutinib, with an HR for PFS between G-acalabrutinib and acalabrutinib monotherapy of 0.49 (95% CI: 0.26–0.95) [56].

The benefit of adding obinutuzumab to a BTK inhibitor in ELEVATE-TN contrasts with findings from randomized trials showing no survival or response advantage of adding rituximab to ibrutinib in patients with CLL [66,67]. The addition of rituximab to ibrutinib (R-Ibr) demonstrated minimal improvement for patients with CLL in a phase II study of 208 patients (NCT02007044) [67]. PFS estimates were 86.9% (95% CI: 77.3–92.6) and 86.0% (95% CI: 76.6–91.1) for patients receiving R-Ibr and ibrutinib, respectively, after 36 months, but MRD was significantly reduced with R-Ibr after 12 months (16% reduction [95% CI: 9.6–22.4]; p < 0.0001) and 24 months (7.6% reduction [95% CI: 1.3–13.9]; p = 0.0180) versus monotherapy [67].

Many other combinations have also been evaluated – and continue to be assessed. In a phase II study (NCT02427451) the combination of obinutuzumab, ibrutinib and venetoclax demonstrated ORRs of 84% and 88% in patients with treatment-naive and R/R CLL, respectively [68]. In this study, 67% of treatment-naive patients and 50% of R/R patients had undetectable MRD in PB and BM two months after the completion of treatment, and median PFS was not reached at 24.2 months and 21.5 months, respectively [68]. The combination of obinutuzumab, ibrutinib and venetoclax has also shown to be effective in patients with previously untreated high-risk CLL in a phase II study, with a CR rate of 58.5% (CLL2-GIVe; NCT02758665) [69]. Obinutuzumab has also shown efficacy when administered as induction therapy in combination with ibrutinib after two courses of bendamustine (47.5% of 61 patients had undetectable MRD) in the exploratory phase II CLL2-BIG trial (NCT02345863) [70]. Results from the phase II CLL2-BAG trial (NCT02401503), in which obinutuzumab was given with venetoclax after two courses of bendamustine, also demonstrate high response rates (OR rate 95%; 95% CI: 87–99) and acceptable safety profiles across treatment-naive and R/R patients with CLL [71]. In the phase II CLL2-BCG trial (NCT02445131), two courses of bendamustine followed by obinutuzumab plus idelalisib achieved clinical responses in patients with CLL (OR rate 80% and 85% in the full analysis set and per protocol population, respectively) [72]. However, due to the toxicity profile of idelalisib, alternative treatment combinations may be preferred [72]. An ongoing phase II trial (AVO; NCT03580928), demonstrated that acalabrutinib, venetoclax, and obinutuzumab is active and tolerated in patients with previously untreated CLL; after a median follow-up of 27.6 months the CR rate was 38%, with

undetectable MRD in the BM [73]. Furthermore, the combination of zanubrutinib, obinutuzumab, and venetoclax was well tolerated and met its primary end point, with 89% of previously untreated patients with CLL reaching undetectable MRD in a phase II trial (NCT03824483) [74].

Baseline prognostic markers & surrogate outcome markers

Efforts to explore potential baseline prognostic markers and surrogate outcome markers to guide therapy and clinical trial design in CLL are ongoing. MRD at the EOT has been identified as a potential surrogate marker for clinical outcomes. Important baseline prognostic markers include del(17p), del(11q), unmutated IGHV and mutated *NOTCH1* and *TP53*.

Multiple studies have demonstrated that post-induction MRD levels are independently associated with PFS in young, fit patients with CLL [75,76]. MRD analysis in CLL11 also showed this to be the case in older, less fit patients with comorbidities who were treated less intensively [77]. Median PFS in patients with undetectable MRD in PB at the EOT was 56.4 months, compared with 13.9 months for MRD-positive patients [77].

In an exploratory biomarker analysis from the GREEN study, PFS was longer across treatment groups in patients with mutated IGHV, del(13q) or trisomy 12, whereas worse PFS outcomes were reported in patients with del(11q), del(17q) or unmutated IGHV [52].

The PFS benefit seen in the overall study population with G-Ven in CLL14 was maintained in high-risk patients with *TP53* deletion or mutation, or both, and those with unmutated IGHV [53]. In a study of the prognostic value of genetic markers in CLL14, a multivariate analysis identified that del(17p), del(11q), unmutated IGHV and mutated *TP53*, *BIRC3* and *SF3B1* were independently associated with PFS with G-Clb; for G-Ven, however, only del(17p) was significantly prognostic [72]. In one genetic analysis of CLL14, del(17p) and mutated *TP53* were the only markers impacting PFS in both G-Ven-treated and G-Clb-treated patients. Patients with unmutated IGHV, del(17p), del(11q), mutated *TP53*, *BIRC3*, *NOTCH1* and *ATM*, receiving G-Clb, had lower response rates, as well as shorter PFS and lower rates of MRD-negativity than patients without these markers; multivariate analyses identified del(17p) as the only significant prognostic factor for patients receiving G-Ven [70]. PFS was improved with G-Ven in comparison with G-Clb across all clinical and biological risk groups [54].

In iLLUMINATE, PFS benefit with G-Ibr versus G-Clb was noteworthy in the high-risk group of 148 patients with del(17p) or *TP53* mutation, del(11q), or unmutated IGHV (median PFS not reached vs 14.7 months; HR: 0.15; 95% CI: 0.09–0.27; $p < 0.0001$) [55]. Median PFS durations in the high-risk and overall populations with G-Ibr were similar at 30 months [55]. In ELEVATE-TN, estimated 24-month PFS was consistently improved with G-acalabrutinib and acalabrutinib monotherapy versus G-Clb; this remained the case in patients with unmutated IGHV (G-acalabrutinib 91% [95% CI: 83–95%] in 103 patients; G-Clb 31% [95% CI: 22–40%] in 116 patients) and patients with del(17)(p13.1) (G-acalabrutinib 88% [95% CI: 61–97%] in 17 patients; G-Clb 22% [95% CI: 5–45%] in 16 patients) [56]. At the 4-year update, median PFS was not reached in patients with unmutated IGHV treated with G-acalabrutinib versus 22.2 months with G-Clb (both $p < 0.0001$) [57]. In patients with del(17)(p13.1), median PFS was not reached with G-acalabrutinib versus 17.7 months for G-Clb ($p < 0.005$) [57].

Obinutuzumab in follicular lymphoma

Chemoimmunotherapy

In the phase III GALLIUM trial (NCT01332968), obinutuzumab plus chemotherapy (CHOP, bendamustine or cyclophosphamide, vincristine and prednisone [CVP]) was compared with rituximab plus chemotherapy in 1202 patients with previously untreated advanced FL (Table 2) [44]. Patients with a response at the end of induction (EOI) received maintenance therapy with the same anti-CD20 mAb for up to 2 additional years or until disease progression. At the primary analysis, after a median follow-up of 34.5 months, the risk of progression, relapse or death with obinutuzumab-based therapy was significantly lower than with rituximab-based therapy (HR: 0.66; 95% CI: 0.51–0.85; $p = 0.001$) [44]. Estimated 3-year PFS rates were 80.0% with obinutuzumab plus chemotherapy versus 73.3% with rituximab plus chemotherapy [44]. Other time-to-event end points were consistent with this investigator-assessed PFS, with event-free survival (EFS) and time to next treatment (TTNT) both significantly longer in the obinutuzumab arm, although there was no significant between-group difference in OS [44]. This lack of OS benefit was not unexpected in light of the variety of effective salvage therapies available, and given that the study was not powered to demonstrate a difference in OS [78]. These trends in PFS and other time-to-event end points were retained after additional follow-up, with patients demonstrating an improved 5-year PFS with obinutuzumab plus chemotherapy compared with rituximab plus chemotherapy (HR: 0.76; 95% CI: 0.62–0.92;

Table 2. Key clinical trials of obinutuzumab in patients with follicular lymphoma.

Trial	Tumor response rates	Survival and other time-to-event end points (medians unless stated otherwise)	Ref.
Chemoimmunotherapy in 1L disease			
– GALLIUM; NCT01332968; phase III			[44,79]
Primary analysis			[44]
G-CHOP, CVP or Benda, n = 601[†]	EOI OR 88.5% (CR 19.5%) NS vs R	3-yr PFS 80.0% (95% CI: 75.9–83.6%) HR: 0.66; p = 0.001 vs R 3-yr OS 94.0% (95% CI: 91.6–95.7%) HR: 0.75; p = 0.21 vs R 3-yr TTNT 87.1% (95% CI: 84.0–89.6%) HR: 0.68; p = 0.009 vs R	
R-CHOP, CVP or Benda, n = 601[†]	EOI OR 86.9% (CR 23.8%)	3-yr PFS 73.3% (95% CI: 68.8–77.2%) 3-yr OS 92.1% (95% CI: 89.5–94.1%) 3-yr TTNT 81.2% (95% CI: 77.6–84.2%)	
Updated analysis			[79]
G-CHOP, CVP or Benda, n = 601[†]	N/A	5-yr PFS 70.5% (95% CI: 66.4–74.1%) HR: 0.76; p = 0.0043 vs R 5-yr OS 90.2% (95% CI: 87.5–92.4%) HR: 0.87; p = 0.41 vs R 5-yr TTNT 79.7% (95% CI: 76.1–82.7%) HR: 0.72; p = 0.0039 vs R	
R-CHOP, CVP or Benda, n = 601[†]	N/A	5-yr PFS 63.2% (95% CI: 59.0–67.1%) 5-yr OS 89.4% (95% CI: 86.6–91.6%) 5-yr TTNT 72.9% (95% CI: 69.1–76.4%)	
Chemoimmunotherapy in R/R disease			
– GADOLIN; NCT01059630; phase III			[82,83]
Primary analysis			[82]
Benda, n = 202 R-refractory (166 FL)[‡]	BOR 77% (CR 17%) EOI OR 63% (CR 12%)	PFS 14.9 mo EFS 13.7 mo TTNT 21.6 mo OS NR	
G-Benda, n = 194 R-refractory (155 FL)[‡]	BOR 79% (17% CR) EOI OR 69% (11% CR)	PFS NR HR: 0.55; p = 0.0001 vs Benda EFS 26.8 mo HR: 0.57; p = 0.0001 vs Benda TTNT NR HR: 0.65 vs Benda OS NR HR: 0.82; p = 0.40 vs Benda	
Final analysis			[83]
Benda, n = 209 R-refractory (171 FL)[‡]	N/A	PFS 14.1 mo OS NE TTNT 19.4 mo	
G-Benda, n = 204 R-refractory (164 FL)[‡]	N/A	PFS 25.8 mo HR: 0.57; p < 0.001 vs Benda OS NE HR: 0.67; p = 0.0269 vs Benda TTNT 40.8 mo HR: 0.60 vs Benda	
Combinations with novel agents			
– GALEN; NCT01582776; phase I			[84]
G-LEN, n = 89 R/R[§]	EOI OR 79% (38% CR)	2-yr EFS 62% (95% CI: 51–72%) 2-yr PFS 65% (95% CI: 54–74%) 2-yr DOR 70% (95% CI: 57–79%) 2-yr OS 87% (95% CI: 78–93%)	
– GALEN; NCT01582776; phase II			[85]
G-LEN, n = 100 1L[§]	EOI OR 92% (CR 47%)	3-yr PFS 82% 3-yr OS 94%	

[†]G-CHOP, CVP or Benda: CHOP, CVP or Benda + G 1000 mg d1, d8, d15, then d1 c2–6 or 8 (CTX-dependent) q28d, then every 2 months if response for ≤2 yr; R-CHOP, CVP or BEN: CHOP, CVP or Benda + R 375 mg/m^2 d1 c1–6 or 8 (CTX-dependent) q28d, then every 2 months if response for ≤2 yr.
[‡]Benda: 120 mg/m^2 d1, d2 c1–6 q28d; G-Benda: Benda 90 mg/m^2 d1, d2 c1–6 + G 1000 mg d1, d8, d15 c1, then d1 c2–6, q28d then every 2 months for 2 yrs or until response.
[§]G-LEN: G 1000 mg d1, d8, d15 c1, then d1 c2–6 + LEN 20 mg d1–21 c1, then d2–22 c2–6 q28d, then LEN 10 mg d2–22 q28d + G 1000 mg d1 every 56 days for 1 yr, then G 1000 mg every 56 days for 1 yr.
1L: First-line; Benda: Bendamustine; BOR: Best overall response; c: Cycle; CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisone; CR: Complete response; CTX: Chemotherapy; CVP: Cyclophosphamide, vincristine and prednisone; d: Day; DOR: Duration of response; EFS: Event-free survival; EOI: End of induction; FL: Follicular lymphoma; G: Obinutuzumab; HR: Hazard ratio; LEN: Lenalidomide; mo: Month; N/A: Not available; NE: Not estimated; NR: Not reached; NS: Nonsignificant; OR: Overall response; OS: Overall survival; PFS: Progression-free survival; q28d: every 28 days; R: Rituximab; R/R: Relapsed/refractory; TTNT: Time to next treatment; yr: Year.

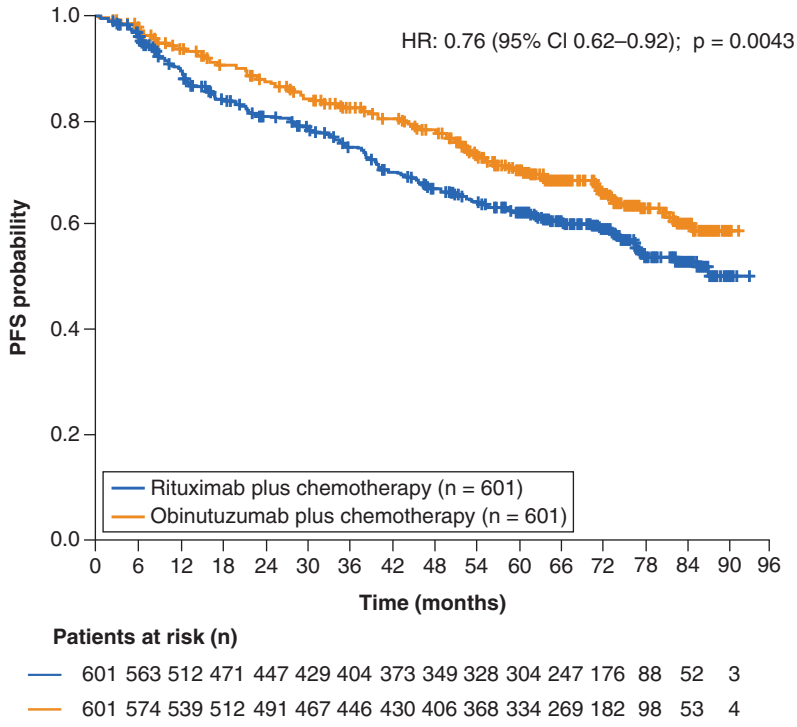


Figure 4. Progression-free survival with rituximab-chemotherapy versus obinutuzumab-chemotherapy in the phase III GALLIUM study in patients with previously untreated advanced follicular lymphoma.
HR: Hazard ratio; PFS: Progression-free surviva.

p = 0.0043; Figure 4) [79]. It was also shown that obinutuzumab-based therapy was associated with greater MRD-negativity at EOI than rituximab-based therapy in 696 patients with available PB or BM samples (92 vs 85%; p = 0.0041) [80]. Notably, in a GALLIUM exploratory analysis, fewer early disease progression events occurred with obinutuzumab versus rituximab (average risk reduction of 46.0%) [81].

The phase III GADOLIN trial (NCT01059630) evaluated G-Benda in patients with rituximab-refractory indolent NHL. Patients (n = 396) received bendamustine either as monotherapy or with obinutuzumab as induction therapy, followed by 2 years of obinutuzumab maintenance [82]. In the FL cohort, which made up 81% of the population, PFS was significantly longer in patients who received G-Benda than those who received bendamustine alone (HR: 0.55; 95% CI: 0.40–0.74; p = 0.0001) [82]. OS was also significantly extended with obinutuzumab and was maintained with long-term follow-up [83,86]. The PFS benefit was reflected by other end points, including EFS and TTNT. In a sub-analysis of the GADOLIN study, MRD at EOI was evaluated for FL patients with a detectable clonal marker (t[14;18] translocation and/or Ig heavy or light chain rearrangement) at baseline [87]. At EOI, MRD-negativity rates were 86% for G-Benda versus 55% for bendamustine monotherapy (p = 0.0002), and MRD-negativity was maintained for longer in patients receiving obinutuzumab maintenance [87].

Grade ≥3 AEs and serious AEs were more frequent in the obinutuzumab arm in GALLIUM, but these were generally manageable, and rates of fatal AEs were similar in the two treatment arms [44]. The most common AEs were IRRs and these were reported more frequently with obinutuzumab than rituximab (59.3 vs 48.9%; p < 0.001), but most IRRs were grade 1–2 and typically occurred during the first infusion [44]. The higher rate of IRRs observed with obinutuzumab may be due to quantitative differences in cytokine release induced by obinutuzumab in comparison with rituximab [88]. All-grade nausea (47% in both groups) and neutropenia (obinutuzumab 49%, rituximab 44%) were also frequently reported [44]. Infection rates were comparable between the obinutuzumab group (20.0% grade ≥3 AEs; 18.2% serious AEs [n = 595]) and rituximab group (15.6% grade ≥3 AEs; 14.4% serious AEs [n = 597]) [44]; reductions from baseline in IgA, IgG and IgM were also comparable between obinutuzumab and rituximab [89]. Grade ≥3 and serious AEs were more frequent in the obinutuzumab arm than in the rituximab arm in GADOLIN. The most common grade ≥3 AEs in the obinutuzumab arm were neutropenia, thrombocytopenia, anemia and IRRs [82]. Overall, toxicity associated with obinutuzumab-based therapies was manageable in both

studies, and AE profiles were consistent with the known safety profiles of obinutuzumab and the other study medications.

Clinical trials with rapid infusion rituximab have demonstrated benefits in convenience for patients and efficiency for infusion facilities [90,91]. In the open-label phase IV GAZELLE study (NCT03817853) of a 90-min short duration infusion (SDI) of obinutuzumab from cycle 2 onwards in patients with previously untreated advanced FL, no grade 3 IRRs were observed in cycle 2, and only one grade 3 IRR was reported in subsequent cycles [92]. No new safety signals were reported with obinutuzumab SDI and response rates were consistent with previous studies [92].

Concerns have been raised that patients treated with anti-CD20 chemoimmunotherapy may experience more severe COVID-19 infection and decreased efficiency of the COVID-19 vaccination [93,94]. In a recent case report, a patient with FL experienced a prolonged COVID-19 infection associated with anti-CD20-mediated B-cell depletion following two cycles of obinutuzumab in combination with bendamustine [93]; however, these results are of an isolated event. In addition, the effectiveness of the COVID-19 vaccination is currently unknown in patients receiving obinutuzumab and studies are ongoing to further the understanding in that area [95,96]. Additional research and specific guidelines to manage infection control under these circumstances are needed.

Combinations with novel agents

Investigations of chemotherapy-free treatment options using obinutuzumab plus other targeted therapies are underway for FL (as for CLL, with the same rationale), including the InHarmony program of early phase clinical studies investigating obinutuzumab in combination with drugs with differing mechanisms of action. Such combinations include lenalidomide, atezolizumab, venetoclax and polatuzumab vedotin [97].

Good clinical activity has been reported with obinutuzumab plus lenalidomide, an immunomodulator with direct antiproliferative activity that enhances T-cell and natural killer cell function and improves ADCC and ADCP. Phase I/II data from 66 patients with relapsed indolent NHL who received the investigational combination of obinutuzumab plus lenalidomide (G-Len) demonstrated an OR rate of 98% (CR 72%) and an estimated 24-month PFS of 73% (Table 2) [85]. G-Len was also evaluated in the phase II GALEN trial (NCT01582776) [84]. A total of 89 patients with R/R FL received G-Len induction therapy, followed by 1 year of G-Len maintenance therapy and then 1 year of obinutuzumab maintenance [84]. The primary end point of OR rate at EOI was 79%, with 38% CR [84]. The most common AEs were asthenia (61%), neutropenia (43%) and bronchitis (41%); neutropenia was the most common grade $\geq$3 toxicity [84].

In the first-line setting, the G-Len regimen has been investigated in a phase II study in 100 patients with advanced FL requiring systemic therapy [98]. The OR rate according to the International Working Group 1999 response criteria (primary end point) was 92% (47% CR, including unconfirmed CR) [98]. In a further study of G-Len in 90 patients with previously untreated advanced FL with high tumor burden (NCT02871219), the 2-year PFS rate was 96%, with an OR rate of 98% (85 CR, 1 PR) [99]. Toxicities were manageable, with no unexpected safety signals. There were no deaths at the time of reporting; 11 patients (12%) discontinued therapy due to AEs (upper respiratory infection in five patients) [99]. A phase Ib/II trial (NCT02600897) also demonstrated promising response rates with polatuzumab vedotin plus G-Len (Pola-G-Len) in patients with R/R FL, and the safety profile was consistent with known profiles of the individual drugs [100].

Prognostic value of MRD response

The prognostic value of MRD status at EOI was investigated in the GALLIUM trial. MRD status was evaluated in PB and BM at mid-induction (MI; cycle 4, day 1) in PB, at EOI in PB and BM, and at 6-monthly intervals during maintenance or follow-up in PB up to 24 months post-EOI or treatment discontinuation [101]. In all MRD-evaluable patients, those who were MRD-negative at EOI had longer PFS than those who were MRD-positive at EOI (HR: 0.38; 95% CI: 0.26–0.56; $p < 0.0001$), irrespective of treatment [101]. In GADOLIN, 86% of patients receiving G-Benda were MRD-negative at EOI compared with 55% of patients receiving bendamustine alone ($p = 0.0002$) [87]. Patients who were MRD-negative at EOI had improved PFS (HR: 0.33; 95% CI: 0.19–0.56; $p < 0.0001$) and OS (HR: 0.39; 95% CI: 0.19–0.78; $p = 0.008$) compared with those who remained MRD-positive, and MRD-negative status was maintained for longer in patients who received obinutuzumab maintenance compared with those who did not [87].

Obinutuzumab in aggressive B-cell lymphoma, specifically DLBCL

Obinutuzumab has also been investigated in the setting of aggressive NHL (Table 3). The randomized phase III

Table 3. Key clinical trials of obinutuzumab in patients with aggressive non-Hodgkin lymphoma.

Trial	Tumor response rates	Survival and other time-to-event end points (medians unless stated otherwise)	Ref.
Chemoimmunotherapy in 1L advanced DLBCL			
– GOYA; NCT01287741; phase III			[102,103]
Primary analysis			[102,103]
G-CHOP, n = 706†	ETR 77.4% (CR 56.7%)	3-yr PFS 69.6% HR: 0.92; p = 0.386 vs R 3-yr OS 81.2% (95% CI: 77.9–84.1%) HR: 1.0; NS vs R 3-yr EFS 69.9% (95% CI: 66.2–73.2%) HR: 0.92; NS vs R	
R-CHOP, n = 712†	ETR 77.9% (CR 59.5%)	3-yr PFS 66.9% 3-yr OS 81.4% (95% CI: 78.1–84.3%) 3-yr EFS 66.5% (95% CI: 62.7–70.1%)	
Final analysis			[103]
G-CHOP, n = 704†	ETR 77.1% (CR 56.5%)‡	5-yr PFS 63.8% (95% CI: 59.3–68.0%) HR: 0.94; NS vs R 5-yr OS 77.0% (95% CI: 73.3–80.3%) HR: 1.02; NS vs R 5-yr EFS 60.6% (95% CI: 56.3–64.6%) HR: 0.95; NS vs R	
R-CHOP, n = 710†	ETR 77.6% (CR 59.1%)‡	5-yr PFS 62.6% (95% CI: 58.1–66.8%) 5-yr OS 77.7% (95% CI: 74.1–80.9%) 5-yr EFS 58.9% (95% 54.5–63.1%)	
Combinations with novel agents			
– GALEN; NCT01582776; phase II			[104]
G-LEN, n = 71 R/R DLBCL§	OR 35.2% (CR 18.3%)	PFS 4.1 mo OS 10.6 mo	
G-LEN, n = 13 R/R MCL§	OR 46.2% (CR 15.4%)	PFS 5.8 mo OS NR	

†G-CHOP: CHOP + G 1000 mg d1, d8, d15, then d1 c2–8; R-CHOP: CHOP + R 375 mg/m^2 d1 c1–8.
‡Results according to PET–computed tomography; computed tomography alone was also reported, with similar results.
§G-LEN: G 1000 mg d1, d8, d15 c1, then d1 c2–6 + LEN 20 mg d1–21 c1, then d2–22 c2–6 q28d, then LEN 10 mg d2–22 q28d + G 1000 mg d1 q56d for 1 yr, then G 1000 mg q56d for 1 yr.
¶G-Atezo: G 1000 mg d1, d8, d15 c1, then d1 c2–8 q3wk + Atezo 1.2 g q3wk + VEN 800 mg/d for 24 c.
1L: First-line; Atezo: Atezolizumab; c: Cycle; CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisone; CR: Complete response; d: Day; DLBCL: Diffuse large B-cell lymphoma; EFS: Event-free survival; ETR: Response at end of treatment; G: Obinutuzumab; HR: Hazard ratio; LEN: Lenalidomide; MCL: Mantle cell lymphoma; mo: Month; N/A: Not available; NR: Not reached; NS: Nonsignificant; OR: Overall response; OS: Overall survival; PFS: Progression-free survival; q28d: Every 28 days; q56d: Every 56 days; q3wk: Every 3 weeks; R: Rituximab; R/R: relapsed/refractory disease; yr: Year.

GOYA trial (NCT01287741) compared G-CHOP with R-CHOP in 1418 patients with previously untreated advanced DLBCL [102]. The primary end point was investigator-assessed PFS, and after a median observation time of 29 months, the number of events in the intent-to-treat population, was similar for G-CHOP (201; 28.5%) and R-CHOP (215; 30.2%), with a stratified HR of 0.92 (95% CI: 0.76–1.11; p = 0.39) [102]. Estimated 3-year PFS rates were 69.6 and 66.9%, respectively [102]. Frequently documented AEs, such as neutropenia, nausea and constipation, were seen at similar rates in both groups, while IRRs were more common in the obinutuzumab arm compared with the rituximab arm (36.1 vs 23.5%) [102]. The results of the final analysis, published after a median follow-up of 47.7 months, were consistent with the primary analysis (HR: 0.94; 95% CI: 0.78–1.12; p = 0.48; Figure 5) [103].

The randomized phase III GAINED trial (NCT01659099) compared obinutuzumab with rituximab, both combined with chemotherapy, in 670 transplant-eligible patients with previously untreated DLBCL. The primary end point, EFS, demonstrated that 2-year EFS was similar in the obinutuzumab and rituximab groups (59.8 vs 56.6%; p = 0.123; HR: 0.88) [105]. The 2-year PFS in the entire cohort was 83.1% (95% CI: 80–85.8) [105]. The study concluded that obinutuzumab does not provide any significant additional tumor control in newly diagnosed transplant-eligible DLBCL patients compared with rituximab.

Combinations with novel agents

The combination of obinutuzumab with novel agents has also been investigated in DLBCL, specifically additional chemotherapy-free treatment alternatives (Table 3). The GALEN trial investigated the combination of G-Len and

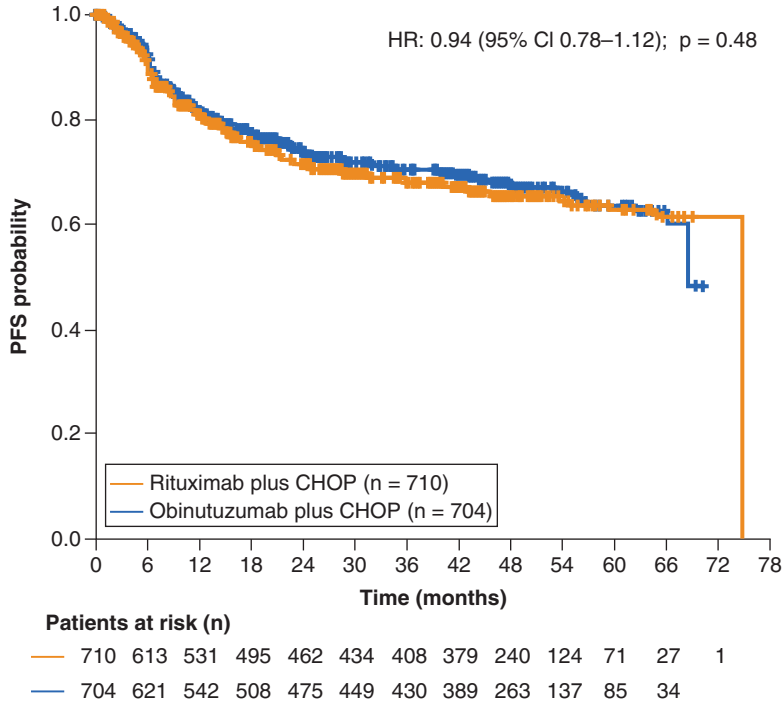


Figure 5. Progression-free survival with rituximab-cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapyversus obinutuzumab-cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapyin the phase III GOYA study in patients with previously untreated diffuse large B-cell lymphoma.
CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapy; HR: Hazard ratio; PFS: Progression-free survival.

included 84 patients with R/R aggressive NHL (71 DLBCL and 13 MCL) [104]. OR rate at EOI was 36.5% across all patients; the primary end point of OR rate after six cycles (based on 95% power to detect an OR increase from 28 to 48% at EOI) was not met [104]. A cell-of-origin (COO) subgroup analysis showed a tendency toward better efficacy in activated B-cell (ABC)-DLBCL over germinal center B-cell (GCB)-DLBCL (OR: 44.4 vs 23.1%; median OS: 27 months vs 7.9 months) [104].

Additional research is also ongoing to evaluate the use of a single dose of obinutuzumab prior to treatment with glofitamab to mitigate the risk of cytokine release syndrome associated with CD20xCD3 bispecific antibodies [106–108]. Obinutuzumab pre-treatment was used in a phase I trial (NCT03075696) of glofitamab, a CD20-T-cell-engaging bispecific antibody, in 73 patients with R/R DLBCL. Patients received 1000 mg obinutuzumab 7 days before their first dose of glofitamab. Glofitamab showed favorable activity, with durable responses and a manageable safety profile [108]. At glofitamab doses ≥10 mg, OR and CR rates were 55.3 and 42.1%, respectively [107].

Biomarkers

Although the GOYA study did not demonstrate an overall superiority with obinutuzumab versus rituximab, an effort was carried out to evaluate if obinutuzumab could provide a clinical benefit to some subgroups of patients with DLBCL. A prospective COO subgroup analysis was performed, where a trend toward PFS benefit was observed for obinutuzumab in patients with GCB-DLBCL (HR: 0.72; 95% CI: 0.51–1.03) [102]. This COO subtype shares more biological similarity with FL than with the ABC or unclassified subtypes [109]. The superiority of obinutuzumab-based therapies over rituximab-based regimens in FL may provide some explanation for the observed difference in efficacy.

In addition to COO data, investigators sought information relating to somatic mutations in patients from the GOYA study. Targeted DNA next-generation sequencing (NGS) in tissue biopsies from GOYA participants showed *Bcl-2* alterations to be strongly associated with reduced PFS (HR: 2.6; 95% CI: 1.6–4.2) when multivariate Cox regression was used to evaluate the prognostic effect of individual genomic changes [110]. Of 102 patients with *Bcl-2*

translocations, 90% had GCB-DLBCL. *Bcl-2* alterations were also significantly correlated with mRNA and *Bcl-2* protein expression [110].

Other potential biomarkers include baseline natural killer cell levels in PB (lower levels being associated with reduced PFS in GALLIUM and GOYA) [111]. Circulating tumor DNA-based NGS of pre-treatment plasma samples from patients with DLBCL has also been described [112–115]. This approach employs a single method to determine nucleotide variants, insertions and deletions and fusions, and to relate these to other baseline variables, including tumor burden and COO data, to improve prognostic stratification and potentially permit personalized risk-adapted therapy in patients with DLBCL [110–113].

Obinutuzumab investigation in additional indications

Marginal zone lymphoma

The phase III GALLIUM trial enrolled a subset of 195 patients with MZL (66 nodal; 61 extranodal; 68 splenic) to investigate consistency of treatment effects with those seen in the FL cohort [116]. There was no PFS difference for obinutuzumab plus chemotherapy versus rituximab plus chemotherapy (HR: 0.82; 95% CI: 0.45–1.46; 3-year PFS: 75 vs 78%, respectively), while there were higher frequencies of grade 3–5 AEs (82.2 vs 77.4%), serious AEs (64.4 vs 51.6%) and fatal AEs (11.9 vs 6.5%) in the obinutuzumab arm versus the rituximab arm, respectively. However, it should be noted that at baseline extranodal involvement, bulky disease and B-symptoms were more common in patients treated with obinutuzumab plus chemotherapy than with rituximab plus chemotherapy, which may have impacted the rates of AEs observed. Furthermore, these findings are limited in part by the small patient population enrolled in this sub-analysis; 99 patients received obinutuzumab plus chemotherapy and 96 patients received rituximab plus chemotherapy [116].

Mantle cell lymphoma

Activity of G-Len was observed in 13 patients with R/R MCL participating in the phase II GALEN trial previously described (Table 3) [104]. A further phase II trial, LYMA-101 (NCT02896582), is investigating obinutuzumab plus high-dose dexamethasone, cytarabine and cisplatin followed by autologous stem cell transplantation plus obinutuzumab maintenance in 86 young (<66 years old) untreated patients with MCL, eligible for intensive therapy [117]. The primary end point of this study was met; 75.0% of 73 patients with available data achieved MRD-negativity in BM after induction, and PFS and OS were 93.4 and 96.0%, respectively, after 1 year [117,118]. Promising activity and tolerability have also been reported in both R/R and previously untreated MCL in the phase I/II OAsIs trial (NCT02558816), evaluating combination therapy with G-Ibr plus venetoclax [119]. In terms of MRD status, MRD clearance was seen in 71.5% of relapsed, and in 100% of untreated, MRD-evaluable patients (n = 12) at the end of cycle 3 [119].

Conclusion

Obinutuzumab was developed as part of an effort to address the need for anti-CD20 mAbs with superior activity over rituximab. Research has shown that the type II mechanism of action of obinutuzumab translates into improved outcomes in patients with CLL and FL. These improvements have been mainly in terms of PFS and MRD response, although significantly extended OS has also been reported in patients with CLL after extended follow-up, and in patients with R/R FL. Obinutuzumab plus chemotherapy with obinutuzumab maintenance has also been shown, in an exploratory analysis of the GALLIUM study, to reduce the risk of early progression in patients with previously untreated FL, which may help to improve outcomes among this patient group. Ongoing research is focusing on the development of chemotherapy-free treatments based on obinutuzumab combined with novel agents aimed at different targets. Recent studies have demonstrated the efficacy of chemotherapy-free obinutuzumab-based regimens for the treatment of patients with CLL, including in combination with the BTK inhibitors ibrutinib, acalabrutinib and zanubrutinib [55,56,74]. Investigators are also making progress with identifying prognostic and/or predictive biomarkers that may enable them to optimize and individualize therapy [120]. With the evolving treatment landscape, namely in CLL and R/R NHL, it may be relevant to further explore combining obinutuzumab with new agents, including T cell-engaging bispecific antibodies.

Future perspective

Over the next 5–10 years, research in the field of B-cell malignancies is likely to continue to focus on the development of chemotherapy-free treatment regimens combining anti-CD20 therapies with novel targeted agents, with more

of these regimens likely to enter clinical practice. These regimens are likely to maximize tumor response and patient survival, while minimizing adverse events and patient discomfort. With the evolving treatment landscape in CLL and NHL, this may involve combining obinutuzumab with agents, such as T cell-engaging bispecific antibodies, leveraging immune-based therapeutic approaches. Further progress is also likely to be made in the identification of prognostic and/or predictive biomarkers that enable physicians to optimize and individualize therapy.

Executive summary

- Obinutuzumab is a humanized and glycoengineered, type II anti-CD20 monoclonal antibody.
- Obinutuzumab has demonstrated favorable efficacy and tolerability across a range of B-cell malignancies, including chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL).

Obinutuzumab in CLL

- Obinutuzumab with chemotherapy has improved outcomes for patients with CLL. In the phase III CLL11 study, obinutuzumab plus chlorambucil (Clb) improved survival outcomes compared with both Clb alone and rituximab plus Clb for patients with previously untreated CLL. Preliminary data indicate deeper responses with obinutuzumab compared with rituximab, when combined with venetoclax. The combination of obinutuzumab, venetoclax and ibrutinib has also shown activity in fit patients with previously untreated CLL, in the CLL13 study.
- There is a lack of pivotal data with combinations of obinutuzumab and novel agents; current research is focusing on the use of baseline prognostic markers and surrogate outcome markers to guide therapy and clinical trial design.
- To date, obinutuzumab has demonstrated efficacy in combination with a range of targeted agents, including venetoclax, Bruton's tyrosine kinase inhibitors, and combinations of these agents.

Obinutuzumab in FL

- Obinutuzumab has also improved outcomes for patients with FL. In the phase III GALLIUM trial, progression-free survival (PFS) was improved with obinutuzumab plus chemotherapy in comparison with rituximab plus chemotherapy in patients with previously untreated FL.
- Studies of obinutuzumab in combination with other targeted therapies are underway, with obinutuzumab plus lenalidomide demonstrating promising clinical activity in both previously untreated patients, and those with relapsed/refractory disease.
- In the phase IV GAZELLE study, a short duration infusion of obinutuzumab has demonstrated response rates at end of induction comparable to previous studies, with no new safety signals.

Obinutuzumab in aggressive B-cell lymphoma, specifically diffuse large B-cell lymphoma

- The safety and efficacy of obinutuzumab plus chemotherapy has also been investigated in diffuse large B-cell lymphoma, however no significant improvement in PFS, or event-free survival, was observed with obinutuzumab plus chemotherapy compared with rituximab plus chemotherapy in patients with previously untreated diffuse large B-cell lymphoma in the phase III GOYA or GAINED trials, respectively.

Obinutuzumab in additional indications

- A subset analysis of the phase III GALLIUM trial demonstrated no PFS difference for obinutuzumab plus chemotherapy versus rituximab plus chemotherapy in patients with marginal zone lymphoma.
- Obinutuzumab plus lenalidomide has demonstrated activity in a subset of patients with relapsed/refractory mantle cell lymphoma in the phase II GALEN trial. The combination of obinutuzumab plus venetoclax and ibrutinib has also shown promising activity in a first line setting.

Conclusion

- Since its development, obinutuzumab has significantly improved outcomes for patients with CLL and FL.
- Research is ongoing to develop chemotherapy-free treatment regimens based on obinutuzumab.

Financial & competing interests disclosure

A Davies declares Celgene (Research Funding, Advisory Board, Honorarium, Other: travel to scientific conferences); Roche (Advisory Board, Honorarium, Research Support, Other: travel to scientific conferences); Gilead/Kite Pharma (Advisory Boards, Honorarium, Research Support); Takeda (Advisory Boards, Honorarium, Research Support); Janssen (Honorarium, Research Support); Kayropharma (Advisory Board, Research Support); Acerta Pharma (Research Support, Honorarium); AstraZeneca (Research Support, Honorarium); ADC Therapeutics (Research Support, Honorarium); Incyte (Advisory Board attendance, Honorarium); VelosBio (Advisory Board attendance, Honorarium). AP Kater declares personal fees and research support from Genentech, Roche, and AbbVie; Research Support from Janssen; Consultancy fees from AbbVie, Genentech, Roche, BMS, Astra Zeneca, Janssen, and Lava; Teaching Support from AbbVie. JP Sharman declares personal fees from AbbVie, Acerta Pharma (a member of the AstraZeneca Group), AstraZeneca, Genentech, Pharmacyclics, Sunesis, and TG Therapeutics. S Stilgenbauer declares Advisory Board fees, Research Support, Travel Support, and Speaker fees from AbbVie, Amgen, AstraZeneca, BeiGene, BMS, Celgene, Gilead, GSK, Roche,

Janssen, Novartis, Sunesis. U Vitolo declares Roche (Honorarium, Advisory role, Speakers' bureau); Janssen (Honorarium, Advisory role, Speakers' bureau); Celgene (Honorarium, Advisory role, Speakers' bureau, Research Support); Mundipharma (Honorarium, Speakers' bureau). C Klein declares employment, patents & royalties and stock ownership with Roche. J Parreira declares employment, honorarium and stock ownership with Roche. G Salles research was funded in part through the NIH/NCI Cancer Center support grant P30 CA008748; G Salles declares consulting fees from Morphosys, Incyte, Novartis, Epizyme; honorarium from Abbvie, BMS/Celgene, Epizyme, Janssen, Regeneron, Bayer; Advisory Board fees from Beigene, Epizyme, Genentech/Roche, Genmab, Janssen, Incyte, Gilead/Kite, Miltenyi, Morphosys, Novartis, Velosbio, Takeda, Rapt, Loxo. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Third-party medical writing assistance, under the direction of the authors was provided by A Lynch and E Lynch of Ashfield MedComms, an Inizio company, and was funded by F Hoffmann-La Roche Ltd.

References

Papers of special note have been highlighted as: •• of considerable interest

1. Tedder TF, Klejman G, Schlossman SF, Saito H. Structure of the gene encoding the human B lymphocyte differentiation antigen CD20 (B1). *J. Immunol.* 142(7), 2560–2568 (1989).
2. Polyak MJ, Li H, Shariat N, Deans JP. CD20 homo-oligomers physically associate with the B cell antigen receptor. Dissociation upon receptor engagement and recruitment of phosphoproteins and calmodulin-binding proteins. *J. Biological Chem.* 283(27), 18545–18552 (2008).
3. Pavlasova G, Mraz M. The regulation and function of CD20: an "enigma" of B-cell biology and targeted therapy. *Haematologica* 105(6), 1494–1506 (2020).
4. Davis TA, Czerwinski DK, Levy R. Therapy of B-cell lymphoma with anti-CD20 antibodies can result in the loss of CD20 antigen expression. *Clin. Cancer Res.* 5(3), 611–615 (1999).
5. Eichhorst B, Robak T, Montserrat E *et al.* Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 26(Suppl. 5), v78–84 (2015).
6. Swerdlow SH, Campo E, Harris NL *et al. WHO classification of tumours of haematopoietic and lymphoid tissues*. IARC, Lyon, France (2017).
7. Zappasodi R, de Braud F, Di Nicola M. Lymphoma immunotherapy: current status. *Front. Immunol.* 6, 448 (2015).
8. Maloney DG, Grillo-Lopez AJ, White CA *et al.* IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood* 90(6), 2188–2195 (1997).
9. McLaughlin P, Grillo-Lopez AJ, Link BK *et al.* Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J. Clin. Oncol.* 16(8), 2825–2833 (1998).
10. Boross P, Leusen JH. Mechanisms of action of CD20 antibodies. *Am. J. Cancer Res.* 2(6), 676–690 (2012).
11. Rougé L, Chiang N, Steffek M *et al.* Structure of CD20 in complex with the therapeutic monoclonal antibody rituximab. *Science* 367(6483), 1224–1230 (2020).
12. Coiffier B, Lepage E, Briere J *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N. Engl. J. Med.* 346(4), 235–242 (2002).
13. Marcus R, Imrie K, Solal-Celigny P *et al.* Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J. Clin. Oncol.* 26(28), 4579–4586 (2008).
14. Bachy E, Seymour JF, Feugier P *et al.* Sustained progression-free survival benefit of rituximab maintenance in patients with follicular lymphoma: long-term results of the PRIMA study. *J. Clin. Oncol.* 37(31), 2815–2824 (2019).
15. Hallek M, Fischer K, Fingerle-Rowson G *et al.* Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase III trial. *Lancet* 376(9747), 1164–1174 (2010).
16. Chao MP. Treatment challenges in the management of relapsed or refractory non-Hodgkin's lymphoma - novel and emerging therapies. *Cancer Manag. Res.* 5, 251–269 (2013).
17. Takei K, Yamazaki T, Sawada U, Ishizuka H, Aizawa S. Analysis of changes in CD20, CD55, and CD59 expression on established rituximab-resistant B-lymphoma cell lines. *Leuk. Res.* 30(5), 625–631 (2006).
18. Jazirehi AR, Vega MI, Bonavida B. Development of rituximab-resistant lymphoma clones with altered cell signaling and cross-resistance to chemotherapy. *Cancer Res.* 67(3), 1270–1281 (2007).

19. Beum PV, Kennedy AD, Williams ME, Lindorfer MA, Taylor RP. The shaving reaction: rituximab/CD20 complexes are removed from mantle cell lymphoma and chronic lymphocytic leukemia cells by THP-1 monocytes. *J. Immunol. (Baltimore, MD.: 1950)* 176(4), 2600–2609 (2006).
20. Beers SA, French RR, Chan HT *et al.* Antigenic modulation limits the efficacy of anti-CD20 antibodies: implications for antibody selection. *Blood* 115(25), 5191–5201 (2010).
21. Robak T, Robak E. New anti-CD20 monoclonal antibodies for the treatment of B-cell lymphoid malignancies. *BioDrugs* 25(1), 13–25 (2011).
22. Klein C, Lammens A, Schafer W *et al.* Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties. *MAbs* 5(1), 22–33 (2013).
23. Mössner E, Brünker P, Moser S *et al.* Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood* 115(22), 4393–4402 (2010).

•• **A preclinical study describing the development of obinutuzumab, an anti-CD20 monoclonal antibody with increased direct and immune effector cell-mediated cytotoxicity against B cells in comparison with rituximab.**

24. Herter S, Herting F, Mundigl O *et al.* Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab *in vitro* and in xenograft models. *Mol. Cancer Ther.* 12(10), 2031–2042 (2013).
25. Goede V, Klein C, Stilgenbauer S. Obinutuzumab (GA101) for the treatment of chronic lymphocytic leukemia and other B-cell non-Hodgkin's lymphomas: a glycoengineered type II CD20 antibody. *Oncol. Res. Treat.* 38(4), 185–192 (2015).
26. Niederfellner G, Lammens A, Mundigl O *et al.* Epitope characterization and crystal structure of GA101 provide insights into the molecular basis for type I/II distinction of CD20 antibodies. *Blood* 118(2), 358–367 (2011).
27. Kumar A, Planchais C, Fronzes R, Mouquet H, Reyes N. Binding mechanisms of therapeutic antibodies to human CD20. *Science* 369(6505), 793–799 (2020).
28. Cragg MS, Glennie MJ. Antibody specificity controls *in vivo* effector mechanisms of anti-CD20 reagents. *Blood* 103(7), 2738–2743 (2004).
29. Patz M, Isaeva P, Forcob N *et al.* Comparison of the *in vitro* effects of the anti-CD20 antibodies rituximab and GA101 on chronic lymphocytic leukaemia cells. *Br. J. Haematol.* 152(3), 295–306 (2011).
30. Rituximab Highlights of Prescribing Information. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf (Accessed September 2021) (2021).
31. Freeman CL, Sehn LH. A tale of two antibodies: obinutuzumab versus rituximab. *Br. J. Haematol.* 182(1), 29–45 (2018).
32. Ternant D, Cartron G, Hénin E, Tod M, Girard P, Paintaud G. Model-based design of rituximab dosage optimization in follicular non-Hodgkin's lymphoma. *Br. J. Clin. Pharmacol.* 73(4), 597–605 (2012).
33. Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. *J. Clin. Pharmacol.* 49(9), 1012–1024 (2009).
34. Davies A, Merli F, Mihaljević B *et al.* Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase III trial. *Lancet Haematol.* 4(6), e272–e282 (2017).
35. Morschhauser FA, Cartron G, Thieblemont C *et al.* Obinutuzumab (GA101) monotherapy in relapsed/refractory diffuse large B-cell lymphoma or mantle-cell lymphoma: results from the phase II GAUGUIN study. *J. Clin. Oncol.* 31(23), 2912–2919 (2013).
36. Salles G, Morschhauser F, Lamy T *et al.* Phase I study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. *Blood* 119(22), 5126–5132 (2012).
37. Sehn LH, Assouline SE, Stewart DA *et al.* A phase I study of obinutuzumab induction followed by 2 years of maintenance in patients with relapsed CD20-positive B-cell malignancies. *Blood* 119(22), 5118–5125 (2012).
38. Sehn LH, Goy A, Offner FC *et al.* Randomized phase II trial comparing obinutuzumab (GA101) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: final analysis of the GAUSS study. *J. Clin. Oncol.* 33(30), 3467–3474 (2015).
39. Pierpont TM, Limper CB, Richards KL. Past, present, and future of rituximab-the world's first oncology monoclonal antibody therapy. *Front. Oncol.* 8, 163 (2018).
40. Friedrichs B, Nickelsen M, Ziepert M *et al.* Doubling rituximab in high-risk patients with aggressive B-cell lymphoma -results of the DENSE-R-MegaCHOEP trial. *Br. J. Haematol.* 184(5), 760–768 (2019).
41. Lugtenburg P, de Nully Brown P, van der Holt B *et al.* Randomized phase III study on the effect of early intensification of rituximab in combination with 2-weekly CHOP chemotherapy followed by rituximab or no maintenance in patients with diffuse large B-cell lymphoma: results from a HOVON-Nordic Lymphoma Group study. *J. Clin. Oncol.* 34(Suppl.), abstr 7504 (2016).
42. O'Brien SM, Kantarjian H, Thomas DA *et al.* Rituximab dose-escalation trial in chronic lymphocytic leukemia. *J. Clin. Oncol.* 19(8), 2165–2170 (2001).
43. Kamisoglu K, Phipps A, Jamois C *et al.* Greater efficacy and potency of obinutuzumab compared with rituximab in chronic lymphocytic leukemia patients confirmed by a semi-mechanistic pharmacokinetic/pharmacodynamic model. *Blood* 130(Suppl. 1), 1267 (2017).

44. Marcus R, Davies A, Ando K *et al.* Obinutuzumab for the first-line treatment of follicular lymphoma. *N. Engl. J. Med.* 377(14), 1331–1344 (2017).

•• **A planned interim analysis of the phase III GALLIUM study, in which progression-free survival was significantly improved with obinutuzumab plus chemotherapy in comparison with rituximab plus chemotherapy in patients with previously untreated advanced-stage follicular lymphoma.**

45. Cartron G, de Guibert S, Dilhuydy MS *et al.* Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase I/2 GAUGUIN study. *Blood* 124(14), 2196–2202 (2014).

46. Radford J, Davies A, Cartron G *et al.* Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). *Blood* 122(7), 1137–1143 (2013).

47. Sharman JP, Forero-Torres A, Costa LJ *et al.* Obinutuzumab plus CHOP is effective and has a tolerable safety profile in previously untreated, advanced diffuse large B-cell lymphoma: the phase II GATHER study. *Leukemia Lymphoma* 60(4), 894–903 (2019).

48. Brown JR, O'Brien S, Kingsley CD *et al.* Obinutuzumab plus fludarabine/cyclophosphamide or bendamustine in the initial therapy of CLL patients: the phase Ib GALTON trial. *Blood* 125(18), 2779–2785 (2015).

49. Goede V, Fischer K, Busch R *et al.* Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N. Engl. J. Med.* 370(12), 1101–1110 (2014).

•• **The primary analysis of the phase III CLL11 study of obinutuzumab plus chlorambucil versus rituximab plus chlorambucil in patients with previously untreated chronic lymphocytic leukemia. This study demonstrated that obinutuzumab was superior to rituximab when combined with chlorambucil in this patient group.**

50. Goede V, Fischer K, Dyer MJ *et al.* Overall survival benefit of obinutuzumab over rituximab when combined with chlorambucil in patients with chronic lymphocytic leukemia and comorbidities: final survival analysis of the CLL11 study. *EHA Library* 215923, abstract S151 (2018).

51. Leblond V, Aktan M, Ferra Coll CM *et al.* Safety of obinutuzumab alone or combined with chemotherapy for previously untreated or relapsed/refractory chronic lymphocytic leukemia in the phase IIIb GREEN study. *Haematologica* 103(11), 1889–1898 (2018).

52. Stilgenbauer S, Bosch F, Ilhan O *et al.* Safety and efficacy of obinutuzumab alone or with chemotherapy in previously untreated or relapsed/refractory chronic lymphocytic leukaemia patients: final analysis of the phase IIIb GREEN study. *Br. J. Haematol.* 192(2), 325–338 (2021).

53. Fischer K, Al-Sawaf O, Bahlo J *et al.* Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N. Engl. J. Med.* 380(23), 2225–2236 (2019).

•• **A phase III study demonstrating improved progression-free survival with the chemotherapy-free regimen of venetoclax plus obinutuzumab, in comparison with chlorambucil plus obinutuzumab, in patients with previously untreated chronic lymphocytic leukemia and coexisting conditions.**

54. Al-Sawaf O, Zhang C, Tandon M *et al.* Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase III trial. *Lancet Oncol.* 21(9), 1188–1200 (2020).

55. Moreno C, Greil R, Demirkan F *et al.* Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase III trial. *Lancet Oncol.* 20(1), 43–56 (2019).

•• **A phase III study investigating the safety and efficacy of the chemotherapy-free regimen of ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in patients with previously untreated chronic lymphocytic leukemia. This study demonstrated that ibrutinib plus obinutuzumab is an efficacious treatment option in this patient setting.**

56. Sharman JP, Egyed M, Jurczak W *et al.* Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase III trial. *Lancet* 395(10232), 1278–1291 (2020).

•• **This phase III study compared the efficacy of acalabrutinib with or without obinutuzumab against obinutuzumab plus chlorambucil in patients with previously untreated chronic lymphocytic leukemia, and demonstrated improved progression-free survival with acalabrutinib plus obinutuzumab in comparison with both acalabrutinib alone and obinutuzumab plus chlorambucil.**

57. Sharman JP, Egyed M, Jurczak W *et al.* Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: elevate-TN four-year follow up. *J. Clin. Oncol.* 39(Suppl. 15), 7509–7509 (2021).

58. Sharman JP, Egyed M, Jurczak W *et al.* Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. *Leukemia*, (2022).

59. Sharman JP, Burke JM, Yimer HA *et al.* Final results from the multicenter, open-label, phase II GIBB study of obinutuzumab+bendamustine in previously untreated patients with chronic lymphocytic leukemia. *Blood* 134(Suppl. 1), 4317 (2019).

60. Tam CS, Stilgenbauer S. How best to manage patients with chronic lymphocytic leuekmia with 17p deletion and/or TP53 mutation? *Leukemia Lymphoma* 56(3), 587–593 (2015).

61. Seymour JF, Kipps TJ, Eichhorst B *et al.* Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N. Engl. J. Med.* 378(12), 1107–1120 (2018).
62. Kater AP, Seymour JF, Hillmen P *et al.* Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs suvival: post-treatment follow-up of the MURANO phase III study. *J. Clin. Oncol.* 37(4), 269–277 (2019).
63. Eichhorst B, Niemann C, Kater AP *et al.* A randomized phase III study of venetoclax-based time-limited combination treatments (RVe, GVe, GIVe) vs standard chemoimmunotherapy (CIT: FCR/BR) in frontline Chronic Lymphocytic Leukemia (CLL) of fit patients: first co-primary endpoint analysis of the international intergroup GAIA (CLL13) trial. *AsH Online Program*. Available at: https://ash.confex.com/ash/2021/webprogram/Paper146161.html (Accessed January 2022) (2021).
64. Fürstenau M, Schilhabel A, Robrecht S *et al.* High resolution assessment of Minimal Residual Disease (MRD) By Next-Generation Sequencing (NGS) and high-sensitivity Flow Cytometry (hsFCM) in the phase III GAIA (CLL13) trial. *AsH Online Program.*, Available at: https://ash.confex.com/ash/2021/webprogram/Paper147729.html (Accessed January 2022) (2021).
65. Kohrt HE, Sagiv-Barfi I, Rafiq S *et al.* Ibrutinib antagonizes rituximab-dependent NK cell-mediated cytotoxicity. *Blood* 123(12), 1957–1960 (2014).
66. Woyach JA, Ruppert AS, Heerema NA *et al.* Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N. Engl. J. Med.* 379(26), 2517–2528 (2018).
67. Burger JA, Sivina M, Jain N *et al.* Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. *Blood* 133(10), 1011–1019 (2019).
68. Rogers KA, Huang Y, Ruppert AS *et al.* Phase II study of combination obinutuzumab, ibrutinib, and venetoclax in treatment-naïve and relapsed or refractory chronic lymphocytic leukemia. *J. Clin. Oncol.* 38(31), 3626–3637 (2020).
69. Huber H, Edenhofer S, von Tresckow J *et al.* Phase II study of obinutuzumab (GA-101), ibrutinib and venetoclax (CLL2-GIVe) in patients with untreated high-risk chronic lymphocytic leukemia. *Blood*, (2021).
70. von Tresckow J, Cramer P, Bahlo J *et al.* CLL2-BIG: sequential treatment with bendamustine, ibrutinib and obinutuzumab (GA101) in chronic lymphocytic leukemia. *Leukemia* 33(5), 1161–1172 (2019).
71. Cramer P, von Tresckow J, Bahlo J *et al.* Bendamustine followed by obinutuzumab and venetoclax in chronic lymphocytic leukaemia (CLL2-BAG): primary endpoint analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol.* 19(9), 1215–1228 (2018).
72. Cramer P, Von Tresckow J, Fink AM *et al.* Bendamustine followed by obinutuzumab and idelalisib in patients with chronic lymphocytic leukemia (CLL): CLL2-BCG trial of the German CLL Study Group (GCLLSG). *AsH Online Program*, 1316 (2020).
73. Davids MS, Lampson BL, Tyekucheva S *et al.* Acalabrutinib, venetoclax, and obinutuzumab as frontline treatment for chronic lymphocytic leukaemia: a single-arm, open-label, phase 2 study. *Lancet Oncol.* 22(10), 1391–1402 (2021).
74. Soumerai JD, Mato AR, Dogan A *et al.* Zanubrutinib, obinutuzumab, and venetoclax with minimal residual disease-driven discontinuation in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: a multicentre, single-arm, phase II trial. *Lancet Haematol.* 8(12), e879–e890 (2021).
75. Bottcher S, Ritgen M, Fischer K *et al.* Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. *J. Clin. Oncol.* 30(9), 980–988 (2012).
76. Kwok M, Rawstron AC, Varghese A *et al.* Minimal residual disease is an independent predictor for 10-year survival in CLL. *Blood* 128(24), 2770–2773 (2016).
77. Langerak AW, Ritgen M, Goede V *et al.* Prognostic value of MRD in CLL patients with comorbidities receiving chlorambucil plus obinutuzumab or rituximab. *Blood* 133(5), 494–497 (2019).
78. Bachy E, Rufibach K, Parreira J, Launonen A, Nielsen T, Hackshaw A. Phase III clinical trials in first-line follicular lymphoma: a review of their design and interpretation. *Adv. Ther.* 38(7), 3489–3505 (2021).
79. Townsend W, Buske C, Cartron G *et al.* Comparison of efficacy and safety with obinutuzumab plus chemotherapy versus rituximab plus chemotherapy in patients with previously untreated follicular lymphoma: updated results from the phase III GALLIUM study. *J. Clin. Oncol.* 38(Suppl. 15), 8023–8023 (2020).
80. Pott C, Hoster E, Kehden B *et al.* Minimal residual disease in patients with follicular lymphoma treated with obinutuzumab or rituximab as first-line induction immunochemotherapy and maintenance in the phase III GALLIUM study. *Blood* 128(22), 613 (2016).
81. Seymour JF, Marcus R, Davies A *et al.* Association of early disease progression and very poor survival in the GALLIUM study in follicular lymphoma: benefit of obinutuzumab in reducing the rate of early progression. *Haematologica* 104(6), 1202–1208 (2019).

•• **This study assessed the impact of early disease progression on overall survival in previously untreated patients with follicular lymphoma enrolled in the GALLIUM study. This analysis identified an association between early progression (progression of disease within 24 months) and poor prognosis, along with a marked reduction in the rate of early disease progression events with obinutuzumab plus chemotherapy in comparison with rituximab plus chemotherapy.**

82. Sehn LH, Chua N, Mayer J *et al.* Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase III trial. *Lancet Oncol.* 17(8), 1081–1093 (2016).

83. Sehn LH, Trněný M, Bouabdallah K *et al.* Sustained overall survival benefit of obinutuzumab plus bendamustine followed by obinutuzumab maintenance compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin Lymphoma: final results of the Gadolin study. *Blood* 134(Suppl. 1), 2822–2822 (2019).

84. Morschhauser F, Le Gouill S, Feugier P, Bailly S, Nicolas-Virelizier E, Bijou F. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. *Lancet Haematol.* 6, e429–e437 (2019).

85. Fowler NH, Nastoupil LJ, Chin C *et al.* A phase I/II study of lenalidomide plus obinutuzumab in relapsed indolent lymphoma. *Blood* 134(Suppl. 1), 348 (2019).

86. Cheson BD, Chua N, Mayer J *et al.* Overall survival benefit in patients with rituximab-refractory indolent non-Hodgkin lymphoma who received obinutuzumab plus bendamustine induction and obinutuzumab maintenance in the GADOLIN study. *J. Clin. Oncol.* 36(22), 2259–2266 (2018).

87. Pott C, Sehn LH, Belada D *et al.* MRD response in relapsed/refractory FL after obinutuzumab plus bendamustine or bendamustine alone in the GADOLIN trial. *Leukemia* 34(2), 522–532 (2020).

88. Freeman CL, Morschhauser F, Sehn L *et al.* Cytokine release in patients with CLL treated with obinutuzumab and possible relationship with infusion-related reactions. *Blood* 126(24), 2646–2649 (2015).

89. Hiddemann W, Barbui AM, Canales MA *et al.* Immunochemotherapy with obinutuzumab or rituximab for previously untreated follicular lymphoma in the GALLIUM study: influence of chemotherapy on efficacy and safety. *J. Clin. Oncol.* 36(23), 2395–2404 (2018).

•• **This report focusses on the impact of the chemotherapy backbone on the efficacy and safety of obinutuzumab plus chemotherapy versus rituximab plus chemotherapy in the phase III GALLIUM study. Progression-free survival was shown to be improved with obinutuzumab plus chemotherapy irrespective of chemotherapy backbone.**

90. Sehn LH, Donaldson J, Filewich A *et al.* Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. *Blood* 109(10), 4171–4173 (2007).

91. Tuthill M, Crook T, Corbet T, King J, Webb A. Rapid infusion of rituximab over 60 min. *Eur. J. Haematol.* 82(4), 322–325 (2009).

92. Hübel K, Buchholz TA, Izutsu K *et al.* Obinutuzumab can be administered as a 90-minute short-duration infusion (SDI) in patients with previously untreated follicular lymphoma: GAZELLE end of induction analysis. *Hematological Oncol.* 39(S2), (2021).

93. Kos I, Balensiefer B, Roth S *et al.* Prolonged course of COVID-19-associated pneumonia in a B-cell depleted patient after rituximab. *Front. Oncol.* 10, 1578 (2020).

94. Baker D, Roberts CAK, Pryce G *et al.* COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. *Clin. Exp. Immunol.* 202(2), 149–161 (2020).

95. Herishanu Y, Avivi I, Aharon A *et al.* Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood* 137(23), 3165–3173 (2021).

96. Marchesi F, Pimpinelli F, Giannarelli D *et al.* Impact of anti-CD20 monoclonal antibodies on serologic response to BNT162b2 vaccine in B-cell Non-Hodgkin's lymphomas. *Leukemia* 36(2), 588–590 (2022).

97. Hernandez J, Nielsen T, Klein C, Wenger M. Obinutuzumab for the treatment of non-Hodgkin lymphomas. Available at: www.nature.com/articles/d42473-018-00278-8 (Accessed September 2021) (2021).

98. Bachy E, Houot R, Feugier P *et al.* Obinutuzumab plus lenalidomide (GALEN) in advanced, previously untreated follicular lymphoma in need of systemic therapy. *Blood* 139(15), 2338–2346 (2021).

99. Nastoupil LJ, Westin JR, Hagemeister FB *et al.* Results of a phase II study of obinutuzumab in combination with lenalidomide in previously untreated, high tumor burden follicular lymphoma (FL). *Blood* 134(Suppl. 1), 125 (2019).

100. Diefenbach C, Kahl B, Banerjee L *et al.* Polatuzumab vedotin (Pola) + obinutuzumab (G) and lenalidomide (Len) in patients (pts) with relapsed/refractory (R/R) follicular lymphoma (FL): interim analysis of a phase Ib/II trial. *J. Clin. Oncol.* 37(Suppl. 15), 7505–7505 (2019).

101. Pott C, Hoster E, Kehden B *et al.* Minimal residual disease response at end of induction and during maintenance correlates with updated outcome in the phase III GALLIUM study of obinutuzumab- or rituximab-based immunochemotherapy in previously untreated follicular lymphoma patients. *Blood* 132(Suppl. 1), 396 (2018).

102. Vitolo U, Trněný M, Belada D *et al.* Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. *J. Clin. Oncol.* 35(31), 3529–3537 (2017).

•• **This manuscript reports the results of the phase III GOYA study, in which no significant improvement in progression-free survival was observed with obinutuzumab plus chemotherapy in comparison with rituximab plus chemotherapy in previously untreated patients with diffuse large B-cell lymphoma.**

103. Sehn LH, Martelli M, Trněný M *et al.* A randomized, open-label, phase III study of obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma: final analysis of GOYA. *J. Hematol. Oncol.* 13(1), 71 (2020).

104. Houot R, Cartron G, Bijou F *et al.* Obinutuzumab plus lenalidomide (GALEN) for the treatment of relapse/refractory aggressive lymphoma: a phase II LYSA study. *Leukemia* 33(3), 776–780 (2019).
105. Le Gouill S, Ghesquières H, Oberic L *et al.* Obinutuzumab vs rituximab for advanced DLBCL: a PET-guided and randomized phase III study by LYSA. *Blood* 137(17), 2307–2320 (2021).
106. Bacac M, Colombetti S, Herter S *et al.* CD20-TCB with obinutuzumab pretreatment as next-generation treatment of hematologic malignancies. *Clin. Cancer Res.* 24(19), 4785–4797 (2018).
107. Morschhauser F, Carlo-Stella C, Offner F *et al.* Dual CD20-targeted therapy with concurrent CD20-TCB and obinutuzumab shows highly promising clinical activity and manageable safety in relapsed or refractory B-cell non-hodgkin lymphoma: preliminary results from a phase Ib trial. *Blood* 134(Suppl. 1), 1584–1584 (2019).
108. Hutchings M, Morschhauser F, Iacoboni G *et al.* Glofitamab, a novel, bivalent CD20-targeting T-cell–engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. *J. Clin. Oncol.* 29(18), 1959–1970 (2021).
109. Pon JR, Marra MA. Clinical impact of molecular features in diffuse large B-cell lymphoma and follicular lymphoma. *Blood* 127(2), 181–186 (2016).
110. Bolen CR, Klanova M, Trneny M *et al.* Prognostic impact of somatic mutations in diffuse large B-cell lymphoma and relationship to cell-of-origin: data from the phase III GOYA study. *Haematologica* 105(9), 2298–2307 (2019).
111. Klanova M, Oestergaard MZ, Trněný M *et al.* Prognostic impact of natural killer cell count in follicular lymphoma and diffuse large B-cell lymphoma patients treated with immunochemotherapy. *Clin. Cancer Res.* 25(15), 4634–4643 (2019).
112. Tabari E, Lovejoy AF, Lin H *et al.* Molecular characteristics and disease burden metrics determined by next-generation sequencing on circulating tumor DNA correlate with progression free survival in previously untreated diffuse large B-cell lymphoma. *Blood* 134(Suppl. 1), 490 (2019).
113. Tabari E, Lovejoy AF, Lin H *et al.* Genetically defined subtypes of DLBCL from targeted panel on plasma match previously described tumor tissue subtypes. EHA25. Available at: https://library.ehaweb.org/eha/2020/eha25th/293781/ehsan.tabari.genetically.defined.subtypes.of.dlbcl.from.targeted.panel.on.html (Accessed October 2021) (2020).
114. Kim EC, Fan J, Bolen CR *et al.* Recapitulation of prognostic mutational subtyping utilizing F1H in GOYA and CAVALLI and the potential to highlight benefit of targeted therapy in *de novo* DLBCL. *Blood* 134(Suppl. 1), 2788–2788 (2019).
115. Raval A, Tracy S, Ray J *et al.* Risk profiling of first-line DLBCL patients by measuring circulating tumor DNA. EHA25. Available at: https://library.ehaweb.org/eha/2020/eha25th/293704/aparna.raval.risk.profiling.of.first-line.dlbcl.patients.by.measuring.html?f=listing%3D3%2Abrowseby%3D8%2Asortby%3D1%2Amedia%3D1 (Accessed October 2021) (2020).
116. Herold M, Hoster E, Janssens A *et al.* Immunochemotherapy with obinutuzumab or rituximab in a subset of patients in the randomised GALLIUM trial with previously untreated marginal zone lymphoma (MZL). *Hematol. Oncol.* 35(S2), 146–147 (2017).
117. Le Gouill S, Beldi-Ferchiou A, Cacheux V *et al.* Obinutuzumab plus DHAP followed by autologous stem cell transplantation (ASCT) plus obinutuzumab maintenance provides a high MRD response rate in untreated MCL patients. Results of LYMA-101 trial, a LYSA Group study. *Hem. Oncol.* 37(S2), 44–45 (2019).
118. Le Gouill S, Beldi-Ferchiou A, Alcantara M *et al.* Molecular response after obinutuzumab plus high-dose cytarabine induction for transplant-eligible patients with untreated mantle cell lymphoma (LyMa-101): a phase 2 trial of the LYSA group. *Lancet Haematol.* 7(11), e798–e807 (2020).
119. Le Gouill S, Morschhauser F, Chiron D *et al.* Ibrutinib, obinutuzumab, and venetoclax in relapsed and untreated patients with mantle cell lymphoma: a phase I/2 trial. *Blood* 137(7), 877–887 (2021).
120. Ballman KV. Biomarker: predictive or prognostic? *J. Clin. Oncol.* 33(33), 3968–3971 (2015).