HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 12, 2820–2841
https://doi.org/10.1080/21645515.2018.1508624

Taylor & Francis
Taylor & Francis Group

PRODUCT REVIEW

Anti-CD20 monoclonal antibodies: reviewing a revolution

J. M. L. Casan[a], J. Wong[a], M. J. Northcott[b,c], and S. Opat[a,c]

[a]Haematology Department, Monash Health, Melbourne Australia; [b]Rheumatology Department, Monash Health, Melbourne, Australia; [c]School of Clinical Sciences, Monash University, Melbourne, Australia

ABSTRACT

Since the inception of rituximab in the 1990s, anti-CD20 monoclonal antibodies have revolutionised the treatment of B cell hematological malignancies and have become a cornerstone of modern gold-standard practice. Additionally, the potent efficacy of these agents in depleting the B cell compartment has been used in the management of a broad array of autoimmune diseases. Multiple iterations of these agents have been investigated and are routinely used in clinical practice. In this review, we will discuss the physiology of CD20 and its attractiveness as a therapeutic target, as well as the pharmacology, pre-clinical and clinical data for the major anti-CD20 monoclonal antibodies: rituximab, obinutuzumab and ofatumumab.

ARTICLE HISTORY
Received 18 June 2018
Revised 14 July 2018
Accepted 2 August 2018

KEYWORDS
Monoclonal antibody; CD20; rituximab; obinutuzumab; immunotherapy; lymphoma

Introduction

Few recent medical advances rival the development of monoclonal antibodies against CD20 in terms of impact on treatment paradigms. Since the FDA approval of rituximab in 1997, anti-CD20 therapy has defined a new epoch, particularly in the management of B cell malignancies, such that the term "pre-rituximab era" and "rituximab era" are common place in the vernacular of hematology and oncology. Although the precise physiological role of CD20 remains incompletely defined, it is clear that targeting this molecule is a highly effective means of depleting the B cell compartment, and thus it has become a cornerstone of the management B cell lymphoma. Beyond malignant disease, anti-CD20 therapies play an important role in the treatment of inflammatory and autoimmune diseases. This review will seek to explore the physiological and pathophysiological underpinnings of CD20 monoclonal antibodies (mAbs), the history of their development, their pharmacological properties and the difference between various iterations of anti-CD20 agents. Focusing on malignant conditions, the review will then summarise the extant scientific evidence for the role of these drugs in the management of various diseases. Though a multitude of CD20 mAbs have been produced and utilised to various extents, this review will focus on the dominant agents, rituximab, obinutuzumab and ofatumumab.

CD20 in health and disease

CD20 is a non-glycosylated surface phosphoprotein that is found on most healthy and malignant B cells.[1] Although CD20 is not expressed on precursor B cells, it appears early in the B cell maturation pathway, but is ultimately lost from fully differentiated plasma cells.[2] A member of the membrane spanning 4-A protein family, the CD20 molecule includes two extracellular loops (a large loop and a small loop) within which the epitope binding sites for the anti-CD20 mAbs are located.[3] The natural ligand of CD20 continues to elude detection, however its association with the B cell receptor (BCR) complex suggests a role in BCR signalling. Evidence suggesting structural similarities with known ion channels lead to the supposition that CD20 was involved in calcium flux, and indeed, subsequent studies of cell lines transfected with CD20 revealed increased ion shift when compared to untransfected cells; the increased conductance being abrogated by the addition of a calcium chelator.[4–6] For many years, the function of CD20 in normal immune physiology remained abstruse, though some data have demonstrated a role in the generation of maximal humoral responses. CD20 deficiency in mice and humans has been shown to cause modest quantitative deficiencies in antibody production and germinal centre formation, though data are somewhat inconsistent and a thorough model of the mechanistic details remains incomplete.[7,8]

CD20's attractiveness as a therapeutic target is underpinned by several properties related to its structure and expression. Clearly, the conservation of CD20 expression in virtually all mature B cell lymphoid malignancies is chief amongst its allures as a treatment target.[9] Its distinct absence from pre-B hematopoietic stem cells and terminally differentiated plasma cells limits off target toxicity, and conserves the stem cell pool, which is important for B cell regeneration following therapy.[10] CD20 undergoes little post-translational structural modification, thereby maintaining predictable binding epitopes, and the absence of a natural ligand means mAbs have no known endogenous binding competitors.[11] CD20 is not normally shed from the cell surface, nor does it internalise upon ligand binding.[12] Importantly, the degree of expression

CONTACT J. M. L. Casan joshua.casan@gmail.com; Joshua.casan@monashhealth.org Monash Haematology, level 4, 246 Clayton Rd, Clayton, VIC 3168, Australia

of CD20 on cancerous B cells compared to normal B cells is also relatively constant,[13] and this feature in conjunction with the close proximity of CD20's extracellular epitope components to the cell membrane also enhance its appeal as a therapeutic target, particularly in relation to complement-mediated killing and antibody-dependent cellular cytotoxicity (ADCC).[14] Few antigens boast such a panoply of characteristics favourable to antibody binding.

Mechanism of action of CD20 mAbs

CD20 mAbs are postulated to destroy B cells via several distinct mechanisms, with observable differences between the various mAbs that can be explained by examination of their structural variations and the resultant differences in CD20 binding. Broadly, mAbs targeting CD20 can be subclassified into two major categories: type 1 and type 2, determined by their relative ability to induce the redistribution of CD20 into lipid rafts within the plasma membrane.[15] Found inside the bilayer of cellular membranes, lipid rafts are defined as heterogenous, small and dynamic lipid-protein microdomains that serve as platforms for signal transduction. Lipid rafts facilitate cellular processes via colocalization of receptors and effector molecules; this has been shown to be important in BCR signalling.[16] Such translocation of CD20 (caused by type 1 mAbs but not type 2) has been demonstrated to have significant implications for mAb effector functions. Beyond differences in the mode of cell killing, the subtypes also display variable susceptibilities to mechanisms of mAb resistance. Type 1 antibodies bind twice as many molecules per target cell when compared to type 2 mAbs, but this increased density appears to make them more vulnerable to internalisation and therefore to proteolytic degradation and downregulation of CD20 expression, so called "antigen modulation".[17] It is important to appreciate that such subtle differences in structure, or even the spatial configuration in which the antibodies bind to CD20,[18] can potentially exert pronounced differences in mAb activity and target cell response, with implications for clinical outcomes and decision making. We will therefore discuss the critical mechanisms of anti-CD20 mAb action.

Complement dependent cytotoxicity

Originally thought to be the predominant mechanism of anti-tumour activity, rituximab was demonstrated to bind C1q, leading to complement pathway activation and complement-dependent cytotoxicity (CDC). This manifests as enhanced phagocytosis via opsonisation, cell-busting membrane attack complex formation, and upregulated recruitment of other immune effector cells.[11]

Type 1 antibodies, such as rituximab and ofatumumab, are more effective in activating the classical complement cascade by virtue of their ability to redistribute CD20 into lipid rafts.[19] However, superior complement activation may be at least partially explained by the arrangement of Type 1 CD20 mAbs on the surface of the target cell. Tight clustering of mAbs allows for better interaction with C1q, which requires at least double-headed binding for activation.[20] Ofatumumab demonstrates even more potent stimulation of the complement pathway than its fellow type 1 mAb rituximab, and this is thought to be related to the finding that ofatumumab binds to both extracellular loops of CD20, achieving a closer proximity to the cell surface membrane.[21] This is likely critical to optimising the Fc:Fc interactions that benefit the recruitment of effector molecules such as C1q.[21] Further evidence for the importance of structural antibody configuration in complement activation comes from a study demonstrating the formation of IgG hexamers between neighboring Fc regions, maximising interactivity with C1q.[11] This finding prompted engineered mutational modification of mAbs to induce hexameric formation on target cells to enhance complement activation.[11] Such modifications may also serve to augment the limited CDC of type 2 mAbs, at least in in vitro models.[22] However, what remains to be proven, is whether such antibody upgrades will deliver superior efficacy and clinical outcomes.

Fcγ receptor mediated effects

Expressed on many immune cells including neutrophils, natural killer (NK) cells and macrophages, Fcγ receptors interact with IgG antibodies, and are the key mediator by which antibodies trigger cellular immune responses. NK cells are powerful effector cells and following stimulation via FcγRIIIa, attack opsonized targets by releasing cytolytic compounds like granzyme B and perforin in a process known as antibody-dependent cell-mediated cytotoxicity (ADCC).[23] Additionally, once opsonized, signaling through FcγR on macrophages, neutrophils and monocytes stimulates engulfment and ultimately destruction of the target cell following fusion of the phagosome with the effector cell's lysosome, a process that has come to be known as antibody-dependent cell-mediated phagocytosis (ADCP).[24] In addition to ADCC and ADCP, type 1 CD20 mAbs can produce a form of caspase-dependent apoptotic direct cell death, resultant from a phenomenon termed "hypercrosslinking".[25–27] A further form of direct killing that is also caused by hypercrosslinking but appears to be caspase-independent and related to extracellular calcium influx and reactive oxygen species generation has also been described.[28] Although the relative importance of the various FcγR dependent pathways on in vivo mAb efficacy remain unclear, the centrality of FcγR-mediated mechanisms to CD20 mAb function has been demonstrated in numerous studies. Both ADCC and ADCP activity were nullified in genetically modified mice with absent or dysfunctional FcγR signaling, and target cell killing was enhanced in mice with FcγR signaling inhibitors knocked out.[29,30] In humans, some clinical trials have revealed the presence of an FcγR polymorphism that confers increased binding affinity to IgG to be correlated with improved clinical response to mAb therapy,[3132,33] although this finding has not been consistently reproduced in other studies.[33]

Cellular vaccine effect

In addition to the aforementioned modes of CD20 mAb activity, there are data that suggest these agents are capable

of inducing long term changes in specific immunity by promoting antigen presentation and thereby activation of effector T cells directed against tumour antigens. This mechanism of action may explain the delayed responses that have been observed in some patients with lymphoproliferative disorders, and can occur despite clearance of the mAb.[32] While there are limited data from human studies to support this concept, it has been shown that follicular lymphoma idiotype-specific T cells are increased in patients following treatment with rituximab.[34] There is also growing evidence of the importance of T cell responses as mediators of tumour cell killing with mAbs in animal models.[32,35]

Controversies and future directions

Though our understanding has improved considerably, the differences between *in vitro* versus *in vivo* effector functions, as well as physiologic differences between murine and human models confound interpretation.[11,36,37] Adding further complexity are findings that support interactions between both antagonistic and synergistic effector pathways. Specifically, complement activation can enhance FcγR-mediated cellular killing via anaphylatoxin generation,[38] but conversely, some studies have demonstrated that complement fixation may reduce ADCC. It has been shown that increased deposition of C3b can mitigate NK cell activity, and that depleting C3 using cobra venom factor can abrogate this inhibitory effect.[39,40] Additionally, a C1qa polymorphism that reduces C1q levels, has been correlated with superior responsiveness to rituximab in follicular lymphoma patients.[41] These findings have led many to question the relative impact of complement to therapeutic efficacy in vivo, despite strong evidence of its role in vitro, but the truth may simply be more complex and nuanced than current data can reveal.

As our understanding of the numerous effector pathways continues to grow, there is burgeoning interest in methods to modulate the characteristics of new anti-CD20 mAbs, aiming to enhance both complement-mediated and FcγR-mediated killing. Obinutuzumab is an example of such efforts, having been de-fucosylated based on data demonstrating that this modification greatly augments IgG1 affinity for CD16a Fc receptor.[42] While further exploration of potential molecular modifications is beyond the scope of this article (and has been reviewed recently by Kellner et al[37]), these developments offer promise for overcoming resistance to extant mAbs, but many are yet to prove their efficacy in the clinical arena.

Rituximab

In 1997, intravenous rituximab was the first monoclonal antibody therapy approved for cancer treatment by the FDA, its European sanction following the year after. Rituximab's inception was a herald of a new era of "biological" therapeutics that have transformed modern hematology and oncology practice and have become an essential cornerstone in the management of many cancers.[43] Rituximab is a chimeric human/murine IgG kappa immunoglobulin, with murine 2B8 light and heavy chain variable region sequences combined with human kappa and IgG1 constant region sequences.[44] The origins of rituximab can be traced to the original Nobel prize-winning development of hybridoma technology, which enabled production of clonal antibodies from a single B cell. Therapeutic applications of these antibodies were first tested in the 1980, and work by the Nadler and Levy groups proved that antibody therapies were highly active against lymphoma cells.[45,46] These early efforts with patient-specific antibodies that were unsuitable for commercialization, were contemporaneous with other work exploring the expression of cell surface antigens using monoclonal antibodies. In 1987 Press et al tested a murine monoclonal antibody with specificity for the antigen that would later be renamed CD20, and demonstrated the mAb's ability to deplete malignant B-cells from patients with refractory B-cell lymphomas with impressive, albeit ephemeral, clinical responses.[47] However, murine antibodies are immunogenic in humans, and thus survive only briefly in vivo; they also have a reduced capacity for complement fixation and weakened ADCC.[48] The advent of recombinant DNA technology allowed these shortcomings to be overcome through the production of a murine-human chimeric mAb against CD20.[49] In 1994 Reff et al reported on the activity of another chimeric CD20 mAb, IDEC-C2B8, that was able to stimulate complement and antibody-dependent cytolysis of human B cell-lymphoma cells lines in vitro, and could deplete 95% of bone marrow and lymph node B cells from macaques with minimal toxicity.[44] 3 years later, rituximab became the fourth monoclonal antibody approved by the FDA, and the first for treatment of a malignancy. Approval from European regulators followed in 1998.

Despite the array of clinical studies utilizing rituximab (outlined in the following section), some aspects of its use remain uncertain. The complex pharmacokinetics of rituximab have been explored but clinical use of the drug has not necessarily been optimized as a result. Rituximab disposition shows a non-linear, 2-exponential decay pattern with an elimination half-life of approximately 3 weeks; the antibody being cleared rapidly from the circulation by target binding, and more slowly by catabolism.[50] The pivotal initial study of rituximab that justified its regulatory approval used a 375mg/m^2 dose.[51] Modern dosing is still based on this initial trial although a number of factors have been shown to alter the pharmacokinetics of rituximab. Tumour burden has been shown relate inversely to circulating concentrations of rituximab, which is significant as circulating rituximab levels have been correlated with patient response.[52–54] Specifically, maintain trough levels of rituximab above 25mcg/ml appears to be an important threshold concentration for optimal patient response.[52] This "tumour sink" phenomenon can also vary with the type of disease, for example, clearance of rituximab has been shown to be significantly accelerated in patients with chronic lymphocytic leukemia (CLL) compared to non-Hodgkin lymphoma (NHL), likely because of the higher number of malignant cells present in CLL.[55] As logically follows, the clearance of rituximab tends to reduce in line with disease burden through progressive therapeutic cycles, and this could have significant implications for dosing.[54] A further important contributor to rituximab pharmacokinetics is gender, and several studies have shown that the elimination half-life is

longer in female patients.[56,57] The resultant increased drug exposure is thought to underpin the gender difference in outcomes shown in the RICOVER-60 trial, in which female gender correlated with superior progression-free survival (PFS).[56] A similar outcome was found in the CORAL trial, in which women attained superior event-free survival (EFS) compared to men.[58] To address this, the SEXIE-R-CHOP trial administered a higher dose of rituximab (500mg/m^2) to elderly men, whilst maintaining traditional dosing for women.[59] In this study, rituximab trough levels, overall survival (OS) and PFS were no different between men and women, and no excess toxicity for the higher dose of rituximab was documented; suggesting that perhaps pharmacokinetic-considered dosing could abrogate gender differential outcomes shown in other studies.[59]

A further development is the advent of subcutaneously administered rituximab,which reduces the demand on healthcare resources and can potentially improve access to treatment, especially in resource-limited settings, while also improving the patient's experience and quality of life. The subcutaneous preparation contains human recombinant DNA-derived hyaluronidase which breaks down the subcutaneous matrix enabling larger proteins such as immunoglobulin to be absorbed[60,61] Preclinical studies in xenograft and animal models showed the subcutaneous formulation to have equivalence in therapeutic efficacy and pharmacokinetics.[61,62] Thereafter, trials to demonstrate safety and pharmacokinetic equivalence were undertaken in patients with CLL, follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL).[63–65] These studies consistently demonstrated the non-inferiority of the subcutaneous formulation for maintaining adequate trough levels of rituximab. Clinical efficacy and safety were confirmed by several large phase III trials, including the MabEASE, SABRINA and SAWYER studies, which demonstrated no difference in clinical outcomes between intravenous and subcutaneous routes of rituximab administration.[65–67] Safety findings appeared comparable as well, and no unexpected safety signals have been generated. However, the subcutaneous formulation has been associated with a slightly increased risk of administration reactions in some trials, as well as local injection site reactions, but these seem to be generally mild and easily managed.[60] Examination of the patient experience has generally favored subcutaneous rituximab, which is associated with a much lower median administration time than intravenous (6 minutes vs 170–240 minutes).[68]

Indolent hematological malignancies

Follicular lymphoma

Rituximab's initial regulatory approval was predicated on early studies demonstrating efficacy in relapsed/refractory low grade lymphoma, in which rituximab monotherapy produced overall response rates (ORRs) in the order of 38–57%.[51,69–72] More contemporary phase III studies have now indisputably established the activity of rituximab monotherapy in both the upfront and relapsed settings.

The establishment of rituximab's activity as a single agent in FL, logically prompted investigation of its effect when combined with conventional chemotherapy drugs. That rituximab enhances outcomes for FL patients receiving chemotherapy has been conclusively established through many studies, including a plethora of randomised controlled trials (RCTs) that have examined the use of rituximab as therapy for both upfront and relapsed disease and in combination with a variety of different chemotherapy backbones. A detailed analysis of each of these trials is beyond the scope of this article, and the trials have been summarized in Table 1.[73–76]

In addition to its utility in both induction and salvage therapy for FL, rituximab has also been established as useful for maintenance therapy, prolonging time to next treatment and enhancing PFS outcomes. However, studies have not consistently demonstrated an OS benefit, and use of maintenance is associated with a modest increase in the risk of infection.

The largest study to investigate rituximab maintenance in frontline FL management was the "Primary Rituximab and Maintenance" (PRIMA) trial, a phase III study of 1019 patients with advanced FL, who were randomised to 8-weekly rituximab maintenance (375mg/m^2) for 2 years or to observation alone.[77,78] This occurred after induction treatment with a physician's choice rituximab-containing regimen, including R-CVP, R-CHOP and R-FCM. In the most recent release of data from this trial with a median of 9 years of follow-up, median PFS in those receiving maintenance was 10.49 years compared to 4.06 years for observation, with this benefit extending to all subgroups of patients who achieved at least a partial response to induction (although statistically significance was not recached for those treated with R-CVP). OS at 10 years, was however, identical at 80% in each arm.

The RESORT study, run by the Eastern Cooperative Oncology Group (ECOG) compared rituximab maintenance to a re-treatment strategy in patients with low tumour burden (by GELF criteria), untreated FL.[79] The primary endpoint of this study was time to treatment failure, and ultimately no difference in this metric was demonstrable between the two groups. 3-year freedom from cytotoxic therapy was better in the maintenance group (95% vs 84%), but the median number of rituximab doses was far greater in the maintenance arm (18 vs 4). The efficacy of maintenance therapy following treatment for relapsed disease has also been studied by several groups, and the largest trial performed by van Oers and colleagues showed that the 334 patients who received maintenance (3 monthly rituximab at 375mg/m^2 for 2 years) benefited from greater median PFS (3.7 years vs 1.3 years), which was observed in patients who were treated with either CHOP or R-CHOP.[76,80] Those who received R-CHOP induction had a median PFS of 4.4 years with maintenance and 1.9 years with observation alone. However, once again, even a long-term follow-up study did not show a statistically significant benefit for OS, with a 5 year OS of 74.3% in the maintenance arm vs 64.7% in the observation arm ($p = 0.07$).[80] Given the equivocal impact of maintenance therapy on OS, Vidal et al undertook, and recently updated, a meta-analysis that pooled individual patient data from seven maintenance trials.[81] This analysis does in fact show a benefit in OS, but this was limited to patients receiving maintenance following treatment for relapsed disease or for those who had not received rituximab during their induction regimen (hazard ratio [HR] 0.79, 95%

Table 1. Major trials of rituximab in Follicular lymphoma.

	Reference	Line of therapy	No of patients	Regimen	ORR	CR	Outcome	OS
GLLSG	Hiddemann et al	1L	428	R-CHOP vs CHOP	96% vs 90%	20% vs 17%	TF (median observation time 18 months): 12.6% vs 29.8%	Deaths: 2.7% vs 8.3%
East German Study Group	Herold et al	1L	201	R-MCP vs MCP	92% vs 75%	50% vs 25%	PFS: NR vs 28.8 months EFS: NR vs 26 months mFU 47 months	4-yr: 87% vs 74%
	Marcus et al	1L	321	R-CVP vs CVP	81% vs 57%	41% vs 10%		4-yr: 83% vs 77%
GELA-GOELAMS FL2000	Salles et al Bachy et al	1L	358	R-CHVP + INF vs CHVP + INF	81% vs 72%	51% vs 39%	EFS: 5.5 yrs vs 2.8 yrs 5-yr EFS:53% vs 37% 8-yr EFS: 44% vs 28% mFU: 5 and 8.3 yrs	5-yr: 84% vs 79% 8-yr: 79% vs 70%
FOLL05	Federico et al.	1L	504	R-CVP vs R-CHOP vs R-FM	88% vs 93% vs 91%	67% vs 73% vs 72%	3-yr PFS: 52% vs 68% vs 63%, HR 0.64, R-CHOP vs R-CVP, HR 0.66, R-FM vs R-CVP 3-yr TF: 46% vs 62% vs 59%, HR 0.62, R-CHOP vs R-CVP, HR 0.63, R-FM vs R-CVP mFU: 34 months	3-yr: 95% (all patients)
	Rummel et al	1L	514 (420 NHL inc 279 FL, 94 MCL)	R-benda vs R-CHOP	93% vs 91%	40% vs 30%	PFS: 69.5 months vs 31.2 months (HR 0.58) mFU: 45 months	Deaths: 16.5% vs 17.8%
EORTC 20981	van Oers et al	R/R	465	R-CHOP vs CHOP	85.1% vs 72.3%	29.5% vs 15.6%	PFS: 33.1 months vs 20.2 months (HR 0.65) mFU: 39.4 months	3-year: 82.5% vs 71.9% (HR 0.74)
PRIMA	Salles et al	1L (maintenance)	1018	R maintenance vs observation			3-yr PFS: 74.9% vs 57.6% 6-yr PFS: 59.2% vs 42.7%	87.4% vs 88.7%
RESORT	Hochster et al	1L	228	R maintenance vs retreatment			Time to treatment failure – ND 3-yr freedom from cytotoxic therapy	95% vs 84%

1L firstline, aNHL aggressive non-Hodgkin lymphoma, *Chl* chlorambucil, *CLL* chronic lymphocytic leukemia, *CR* complete response, *DLBCL* diffuse large B-cell lymphoma, *EFS* event-free survival, *FL* follicular lymphoma, *G* obinutuzumab (GA101), *HR* hazard ratio, *iNHL* indolent non-Hodgkin lymphoma, *MCL* mantle cell lymphoma, *mDOR* median duration of response, *mFU* median follow-up, *mOS* median overall survival, *mPFS* median progression-free survival, *mTTNT* median time to next treatment, MZL marginal zone lymphoma, *NHL* non-Hodgkin lymphoma, *NR* not reported, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *R* rituximab, *R/R* relapsed/refractory, *SD* stable disease, *SLL* small lymphocytic lymphoma, *TF* treatment failure

CI 0.66–0.96). However, the study also enumerates the price of maintenance in terms of infection risk, with grade 3 or 4 infections being significantly more frequent in those receiving maintenance (relative risk [RR] 1.67, 95% CI 1.4–2.0). This risk when considered in conjunction with the unclear effect on OS, the cost of providing ongoing rituximab and the absence of data showing improved quality-of-life has led a minority of experts to question the virtue of maintenance therapy, particularly after induction with rituximab-containing therapy.

Chronic lymphocytic leukemia (CLL)

Several phase I/II studies published at the beginning of the century generated substantial interested in a potential role for rituximab in CLL, demonstrating both efficacy and safety in this population when used as a single agent or when combined with other CLL-active therapies.[82–85] However the evidentiary foundations for rituximab in CLL were two large RCTs that tested rituximab in addition to fludarabine and cyclophosphamide (FCR) against FC alone. The CLL-8 study was the first randomised trial exploring FCR vs FC in 817 treatment naïve CLL patients.[86] At 3 years, PFS was significantly better for FCR (PFS, 65% vs 45%). Additionally, FCR bested FC in terms of OS (HR 0.67, P = 0.012), and ORR and CR rate (P < 0.0001). Recipients of FCR were more likely to experience grade 3 or 4 neutropenia and leukopenia (P < 0.001), but no difference in other toxicities, including severe infections was detected. A recent update of these data reveals an even greater benefit to rituximab with prolonged follow-up, as patients treated with FCR enjoyed almost double the length of PFS compared to FC recipients (56.8 months vs 32.9 months), as well as greater median OS (FCR: not reached, FC 86 months).[87] Follow up studies also demonstrated striking results for a subset of patients with favourable disease characteristics (absence of del17p, mutated immunoglobulin heavy chain variable region), many of which achieved extremely durable remissions from FCR.[87,88]

However, CLL is a disease of older adults with a median age at presentation of 72 years and the use of FC-chemotherapy backbone in younger patients was associated with a 3–5% treatment related mortality.[86,89] The CLL11 study examined the use of CD20 monoclonal antibodies in combination with chlorambucil which is better tolerated in older patients. In this study (which also examined obinutuzumab), the addition of rituximab to chlorambucil was associated with a 56% reduction in the risk of progression or death (HR: 0.44; 95% CI: 0.34;0.56; p < 0.0001) and prolonged OS (HR: 0.60, 95% CI: 0.38;0.94; p = 0.0242 PFS 16.3 vs 11.1 months compared with treatment with Clb alone.[90,91]

The REACH trial investigated the same question as CLL-8, but compared the two treatments in CLL patients who had received prior therapies.[92] 552 patients were randomised to FCR or FC and those getting FCR had a 10-month improvement in median PFS compared with FC (30.6 months vs 20.6 months; HR 0.65, P < 0.001). Although no significant difference was seen in OS, ORR and CR rates were better for FCR, and duration of follow up (median of 25 months) was perhaps too short to establish meaningful survival outcomes

in an indolent disease as fewer than 10% of patients died during this period.[92] Thereafter, rituximab was shown to be effective in CLL when combined with other chemotherapy partners including bendamustine and chlorambucil,[89,93,94] and at least at present, rituximab continues to be a cornerstone of CLL treatment in modern practice. The emergence of new targeted therapies in CLL such as inhibitors of Bruton's tyrosine kinase (BTK), BCL2 and PI3K may be the herald of another revolution in CLL care, and the potential synergy with CD20 mAbs is the subject of a number of clinical trials currently in progress.

Aggressive hematological malignancies

Diffuse large B cell lymphoma

Rituximab is considered the standard of care for patients receiving treatment for new diagnoses of DLBCL, as well as in combination salvage regimens for relapsed disease.[95] Vose et al published the first Phase II data establishing efficacy and safety for rituximab in untreated DLBCL in 2001, demonstrating an ORR of 94% (61% CR).[96] Several landmark randomised trials followed on from this study, beginning with studies of elderly patients with DLBCL, in which participants were randomised to R-CHOP or CHOP alone.[97,98] The French GELA group published the first randomised trial of patients aged 60–80 and showed the superiority of the addition of rituximab in terms of CR rate (76% vs 63%), 2-year event free survival (EFS, defined as disease progression, new treatment or death from any cause) (57% vs 38%) and 2 year OS (70% vs 57%).[97] A longer term (median of 5 years) follow-up report from this cohort continued to affirm the benefits of rituximab, showing median EFS to be 3.8 years in the R-CHOP arm against 1.1 years in the CHOP group.[99] At 10 years, those who had rituximab continued to demonstrate a survival advantage (OS 44% vs 28%).[100] Perhaps more meaningful, particularly in an elderly study population, the 5-year median PFS and OS remained in favor of rituximab: 54% vs 30%, and 58% vs 45%.[99] A second phase III randomised trial also demonstrated outcome benefits for elderly patients receiving rituximab, and interestingly demonstrated no benefit of post induction rituximab maintenance therapy for those in the R-CHOP cohort.[98] The pivotal MINT trial helped to shift the paradigm for younger patients with favorable disease characteristics, randomizing patients aged 18–60 (median age 47) and aaIPI of 0 or 1 to CHOP-like chemotherapy with or without the addition of rituximab.[101] Whilst this study was limited to patients with favorable prognostic features, a clear benefit for rituximab-containing therapy was evident in 3-year EFS (79% vs 59%), PFS (85% vs 68%) and OS (93% vs 84%).[101] A follow-up study again demonstrated that this benefit was sustained in the longer term, with a 6-year OS rate of 90% vs 80%.[102]

The evidence for rituximab in patients with relapsed/refractory DLBCL is less robust than in the upfront setting, particularly because randomised trials are few, and include a low proportion of patients with previous rituximab exposure. Given the near universal adoption of up-front rituximab in the modern era, the benefit of this agent in the relapsed setting is less certain. A HOVON group trial of 239 patients with relapsed aggressive B-cell lymphomas randomised patients to chemotherapy with dexamethasone, high-dose cytarabine and cisplatin (DHAP) and etoposide, ifosfamide and methotrexate (VIM), delivered as DHAP-VIM-DHAP, with or without rituximab.[103] Approximately 90% of patients in both arms had DLBCL. The results favored the addition of rituximab in terms of failure-free survival (FFS) at 24 months (50% vs 24%), PFS at 24 months (52% vs 31%), with cox-regression showing an OS benefit at the same time point (HR 0.60 [95%CI 0.41–0.89 vs 0.76 [0.52–1.10]). However, of the 225 patients evaluable for analysis, only 4% had ever been exposed to rituximab previously, significantly reducing the applicability of these findings to modern practice.[103] There have been no other randomised trials that directly compare rituximab-containing regimens to chemotherapy-only regimens, but several studies of salvage combinations that include the CD20 mAbs have outcomes that compare favorably against historical control data; thereby allowing more relapsed/refractory patients to proceed to autologous stem cell transplant.[104,105]

Burkitt lymphoma

In the management of Burkitt lymphoma (BL), a number of prospective but uncontrolled trials have examined incorporating rituximab into conventional chemotherapy regimens, and have consistently impressive outcomes, suggesting an advantage was derived from the addition of the mAb.[106–109] Ribrag and colleagues subsequently published the only randomised controlled trial of rituximab in BL, recruiting 260 HIV negative BL patients from French centers and randomly assigning them to a dose-dense chemotherapy regimen with or without added rituximab.[110] At a median follow-up of 38 months, the outcomes were significantly better for patients who were treated with rituximab; 3-year EFS was 75% vs 62% and 3-year OS was 83% vs 70%. This translates to EFS and OS hazard ratios of 0·59 (95% CI 0·38–0·94) and 0·51 (0·30–0·86) respectively. Importantly, safety outcomes were not significantly different between the rituximab and no rituximab groups, with similar rates of infectious and hematological toxicity and there was no increase in deaths from treatment toxicity amongst those treated with rituximab.[110]

B-cell acute lymphoblastic leukemia

CD20 is expressed in approximately 30%–40% of B-cell acute lymphoblastic leukemia (B-ALL), and unsurprisingly there has been significant interest in the potential utility of anti-CD20 mAbs in these cases.[111,112] Thomas et al studied 216 patients with Philadelphia chromosome negative (Ph-) pre B-ALL, who received two doses of rituximab to complement a Hyper-CVAD chemotherapy backbone, and found improved OS at 3 years compared to historical controls, most evident in those under 60 years of age (3 year OS 71% vs 47%).[113] A further non-randomised study from the GMALL group also demonstrated a benefit in 263 patients receiving induction chemotherapy with added rituximab over historical outcomes, showing higher CR rates and improved 5-year OS for both standard and high-risk patients.[114] However, the veracity of conclusions based on comparison to historical data is far from ideal. Consequently, the GRALL-

2005 study, undertaken from 2006 to 2014, is the only randomised trial of rituximab in the CD20+ (>20% by immunohistochemistry) Ph-ve B-ALL setting.[115] 209 patients were randomised and the 105 patients in the rituximab arm received 16–18 doses of rituximab (375mg/m^2) across induction, consolidation and maintenance phases of therapy. The primary endpoint, EFS, was significantly superior for the rituximab group at 2 years (65% vs 52%), predominantly due to a reduced rate of relapse (18% vs 30.5%). However, these benefits were not shown to translate into increased rate of CR, minimal residual disease (MRD) negativity or evidence of enhanced OS.[115]

Obinutuzumab

Obinutuzumab is a fully humanized, de-fucosylated IgG1 type 2 monoclonal antibody against CD20. Obinutuzumab recognizes a unique, exposed epitope of CD20 and has a modified elbow-hinge amino acid sequence (substitution of leucine by valine) compared to type 1 agents, resulting in spatial alterations to the CD20-mAb assembly complex on B-cells. De-fucosylation of the Fc region enhances its binding affinity to the FcγRIII receptor leading to increased direct cell death induction and enhanced ADCC and ADCP compared to rituximab. Conversely, CDC is reduced (up to 100-fold compared to type 1 antibodies), as type 2 antibodies do not localize the antibody-antigen complex into lipid rafts. However, this has the effect of reducing FcγrIIb-mediated CD20 internalization, leading to increased binding capacity and perhaps reducing the risk of antigen modulation.[116]

In preclinical studies, obinutuzumab caused increased depletion of normal B-cells from the blood of healthy volunteers compared to rituximab,[117] as well as increased depletion of malignant B-cells from the blood of patients with CLL.[118] Obinutuzumab has demonstrated improved efficacy compared to rituximab in human lymphoma xenograft models, inducing complete tumour regression in an aggressive DLBCL model while rituximab only inhibited further growth. Superiority of obinutuzumab has also been reported in similar xenograft models of advanced mantle cell lymphoma and rituximab-refractory DLBCL.[116,117,119]

Obinutuzumab was the first cancer drug to receive FDA approval with the breakthrough therapy designation on November 1, 2013, for the treatment of previously untreated CLL. Breakthrough therapy–designated drugs must show a substantial improvement of outcomes over current therapies according to the FDA Safety and Innovation Act enacted in 2012. Obinutuzumab was subsequently licensed in Europe in July 2014 following the first published data from the phase III CLL11 trial, in combination with chlorambucil for the treatment of adult patients with previously untreated CLL and comorbidities, unsuitable for full dose fludarabine-based therapy. This study also identified the issue of obinutuzumab infusion-related reaction (IRR), occurring mainly with the first dose of administration. While there were no IRR-related deaths, IRR of grade 3 or more occurred in 20% of patients with 7% withdrawal due to adverse event (AE) compared to rates of 4% and <1% respectively in the rituximab plus chlorambucil arm.[91]

Obinutuzumab has since been studied extensively across a range of B cell malignancies (see Table 2).

Indolent hematological malignancies

Indolent NHL

Single agent obinutuzumab was initially evaluated in pretreated patients with indolent NHL, aggressive NHL and CLL in the multicentre phase I-II GAUGUIN study. The phase I stage aimed to investigate the safety and tolerability of escalating doses of obinutuzumab monotherapy and 21 patients with relapsed/refractory indolent NHL were enrolled. The overall response rate (ORR) at end of treatment was 33%; responses were only obtained in the follicular lymphoma (FL) patients, resulting in an ORR of 54% in this subgroup (31% CR).[120] Based on the phase I results, two dosing regimens (400/400mg and 1600/800mg) were compared in the phase II stage which enrolled 40 patients with relapsed/refractory indolent NHL, most with FL. 90% had stage 3–4 disease and 55% were refractory to prior rituximab therapy. End of treatment ORR in rituximab-refractory group was 8% in the low dose arm and 50% in the high dose arm, with 2 CRs in the high dose arm.[121] Subsequently, 175 patients with relapsed indolent NHL (149 patients with FL) were randomly assigned to induction followed by maintenance therapy with either single-agent obinutuzumab or rituximab. The investigator-assessed ORR was higher with obinutuzumab compared with rituximab (43.2 vs 35.6% in the overall population, 43.2 vs 38.7% in patients with FL). There was no difference in the secondary endpoint of PFS, although the trial was not powered for this outcome.[122] These early phase trials established the acceptable safety profile and tolerability of obinutuzumab. IRRs were the most common adverse events, nearly all of which were grade 1–2 in severity.

Dose-finding studies such as GAUGUIN demonstrated that plasma concentrations increased more rapidly upon administration of a 1600/800mg dose than with lower doses, leading to a steady state indicative of CD20 target saturation. Pharmacokinetic modelling showed that 1000mg on days 1, 8 and 15 of cycle 1 could achieve similar exposures.[123] A simplified fixed dose schedule of obinutuzumab 1000mg on days 1, 8 and 15 of the first 21-day cycle and day 1 of subsequent 21-day cycles was selected to achieve adequate exposure levels in subsequent phase II and III trials. Pharmacokinetic studies showed that the flat-dose schedule rapidly achieved CD20 target saturation and serum drug concentrations were maintained at the therapeutic level throughout the treatment course.[124]

Based on rituximab-based combination regimens, obinutuzumab was evaluated in combination with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or FC (fludarabine, cyclophosphamide) in patients with relapsed/refractory FL in the phase 1b GAUDI study. There were no dose-limiting toxicities (DLT) or unexpected AEs. This study was the first to demonstrate the benefit of obinutuzumab-based therapy in rituximab-refractory disease.[125] Obinutuzumab in combination with CHOP or bendamustine

Table 2. Trials of obinutuzumab.

	Phase	Reference	Population		No of patients	Regimen	ORR	CR	PR	Other
GAUGUIN	Phase I	Salles et al	Relapsed/refractory NHL	34	13 FL, 4 MCL, 1 DLBCL, 3 others	G 50/100–1200/2000mg	43%	5	4	
	Phase II	Salles et al	Relapsed/refractory iNHL	40	18 (14 FL, 4 others)	G 400/400mg	26% (5/14)	11% (2)	22% (4)	mPFS 6 months
					22 (20 FL, 2 others)	G 1600/800mg	60% (12/20)	23% (5)	41% (9)	mPFS 11.9 months
	Phase II	Morschhauser et al	Relapsed/refractory aNHL	40	21 (10 DLBCL, 11 MCL)	G 400/400mg	24%	15% (3)	10% (2)	mPFS 2.6 months
					19 (15 DLBCL, 4 MCL)	G 1600/800mg	37%	16% (3)	21% (4)	mPFS 2.7 months
	Phase I	Cartron et al	Relapsed/refractory CLL	13		G 400/800 – 1200/2000mg	62% (8)		62% (8)	mPFS NR, mDOR 10.5 months
	Phase II	Cartron et al	Relapsed/refractory CLL	20		G 1000/1000mg	30% (6)	5% (1)	25% (5)	mPFS 10.7 months, mDOR 8.9 months
GAUSS	Phase I	Sehn et al	Relapsed/refractory NHL	22	Including 5 CLL, 2 SLL	G 200-2000mg then G maintenance			23%	
	Phase II	Sehn et al	Relapsed/refractory iNHL	175	74 FL, 14 others	G 1000mg weekly x 4 then G maintenance	64%	38% (28)	26% (19)	mPFS 17.6 months
					75 FL, 12 others	R 375mg/m2 weekly x 4 then R maintenance	49%	27% (20)	23% (17)	mPFS 25.4 months
Japanese study	Phase I	Ogura et al	Relapsed/refractory iNHL	12	8 FL, 2 SLL, 1 MZL, 1 other	G 200/400 – 1200/2000mg	58%	17% (2)	42% (5)	
GALTON	Phase Ib	Brown et al	Untreated CLL	41	21	G 1000mg + FC	62%	24% (5)	38% (8)	No relapses or deaths after mFU 20.7 months
					20	G 1000mg + Bendamustine	90%	45% (9)	45% (9)	No relapses or deaths after mFU 23.5 months
GAGE	Phase II	Byrd et al	Symptomatic, untreated CLL	80	41	G 1000mg	49%	5% (2)	44% (18)	PFS (18 months) 59%
					39	G 2000mg	67%	20% (8)	46% (18)	PFS (18 months) 83%
CLL11	Phase III	Goede et al	Untreated CLL in elderly/ comorbidities	781		Chl 0.5mg/kg D1 + 15 x 6 cycles alone or with G 1000mg x 6 cycles or with R 375/500mg/m2 x 6 cycles				G-Chl vs Chl: mPFS 29.9 vs 11.1 months, HR 0.18, $p < 0.001$, mOS NR vs NR G-Chl vs R-Chl: mPFS 29.2 vs 15.4 months, HR 0.40, $p < 0.001$, mOS NR vs NR, mTTNT 42.7 vs 32.7 months, HR 0.54, $p < 0.001$
GAUDI	Phase Ib	Radford et al	R/R FL	56	14	CHOP-21 x 6–8 cycles + G 400/400mg	93%	14% (2)	79% (11)	
					14	CHOP-21 x 6–8 cycles + G 1600/ 800mg	100%	64% (9)	36% (5)	
					14	FC x 4–6 cycles + G 400/400mg	100%	79% (11)	21% (3)	
					14	FC x 4–6 cycles + G 1600/800mg	86%	21% (3)	64% (9)	
		Dyer et al	Untreated FL	81	40	CHOP-21 x 6–8 cycles + G 1000mg then G maintenance		70%		PFS (32 months) 84%
					41	Bendamustine 90mg/m2 x 4–6 cycles + G 1000mg then G maintenance		61%		PFS (32 months) 92%
GATHER	Phase II	Zelenetz et al	Untreated advanced DLBCL	80		CHOP-21 x 6 cycles + G 1000mg	83%	55% (44)	28% (22)	
GADOLIN	Phase III	Sehn et al	Rituximab-refractory iNHL		198	Bendamustine 120mg/m2 x 6 cycles	63%	12% (23)		mPFS 15 months, deaths 41
					194	Bendamustine 90mg/m2 x 4–6 cycles + G 1000mg then G maintenance	69%	11% (21)		mPFS NR, deaths 34
GALLIUM	Phase III	Marcus et al	Untreated iNHL (FL and MZL)	1202	601	CHOP-21 x 6 cycles or CVP x 8 cycles or Bendamustine x 6 cycles + G 1000mg then G maintenance	88.5% (532)	19.5% (117)		mPFS 3-yr: 80% vs 73%, mFU 34.5 months, HR 0.66 (95% CI 0.51–0.85); $p = 0.001$
					601	CHOP-21 x 6 cycles or CVP x 8 cycles or Bendamustine x 6 cycles + R 375mg/m2 then R maintenance	86.9% (522)	23.8% (143)		
GOYA	Phase III	Vitolo et al	Untreated DLBCL	1418	706	CHOP-21 x 6–8 cycles + G 1000mg	77% (518)	57% (379)		mPFS 3-yr: 70% vs 67%, mFU 29 months, HR 0.92 (95% CI 0.76 to 1.11); $p = 0.3868$
					712	CHOP-21 x 6–8 cycles + R 375mg/m2	78% (518)	59% (396)		
GREEN	Phase IIIb	Stilgenbauer et al	Untreated and R/R CLL		158	Bendamustine x 6 cycles + G 1000mg	78.5% (124)	32% (51)	46% (73)	mPFS NR (med observation time of 11.2 months)

1L firstline, aNHL aggressive non-Hodgkin lymphoma, *Chl* chlorambucil, *CLL* chronic lymphocytic leukemia, *CR* complete response, *DLBCL* diffuse large B-cell lymphoma, *EFS* event-free survival, *FL* follicular lymphoma, *G* obinutuzumab (GA101), *HR* hazard ratio, *iNHL* indolent non-Hodgkin lymphoma, *MCL* mantle cell lymphoma, *mDOR* median duration of response, *mFU* median follow-up, *mOS* median overall survival, *mPFS* median progression-free survival, *mTTNT* median time to next treatment, MZL marginal zone lymphoma, *NHL* non-Hodgkin lymphoma, *NR* not reported, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *R* rituximab, *R/R* relapsed/refractory, *SD* stable disease, *SLL* small lymphocytic lymphoma, *TF* treatment failure

was also evaluated in 81 treatment-naïve FL patients; patients with an end-of treatment response were eligible for obinutuzumab maintenance therapy for 2 years or until disease progression. IRRs were once again the most common AE (58%) with the majority being grade 1/2. Grade 3/4 neutropenia was the most common hematologic AE (36% during induction and 7% during maintenance). ORR at the end of induction was 94% with CR rate of 36%. Estimated 3-yr PFS was 90% in the obinutuzumab plus bendamustine group and 84% in the obinutuzumab plus CHOP group.[126]

The GADOLIN trial was the first randomized phase III study to demonstrate the efficacy of an alternative anti-CD20 monoclonal antibody in rituximab refractory indolent NHL. Obinutuzumab plus bendamustine (G-B) followed by obinutuzumab maintenance was compared to single-agent bendamustine induction in patients who had been either refractory to a rituximab-containing regimen or had experienced progression during or within 6 months of receiving rituximab. Most patients had FL and were refractory to chemoimmunotherapy; 72–78% had intermediate or high risk FLIPI. In the primary analysis, the median PFS was longer in the G-B arm (not reached) than in the bendamustine monotherapy arm (14.9 months) as assessed by independent review committee with a 45% reduction in risk of progression or death. Updated results with 17 more patients and an additional 10 months of follow-up demonstrated superior median PFS in the FL cohort of 25 months in the G-B arm compared to 14 months in the bendamustine arm; median OS had not been reached in the G-B arm at the time of updated analysis compared to 54 months. Toxicities were manageable and comparable between both groups.[127,128] Following the results of the primary analysis, the FDA granted approval in 2016 for the use of obinutuzumab (in combination with bendamustine) for treatment of relapsed or refractory FL following a rituximab-containing regimen.

In the phase III GALLIUM trial, patients with untreated indolent NHL (FL or marginal zone lymphoma) were randomly assigned to receive obinutuzumab or rituximab as part of induction chemoimmunotherapy in combination with CHOP, CVP or bendamustine, followed by maintenance for two years with the same anti-CD20 monoclonal antibody. In the 1202 patients with FL, median investigator-assessed 3-year PFS was 80% with obinutuzumab compared to 73% with rituximab, producing a clinically meaningful reduction in the risk of progression by 34%. The time to next treatment also favoured the obinutuzumab arm. There was no difference in OS at 3 years however it will be several more years before the OS data is mature given the long natural history of FL. Adverse events mostly related to cytopenias and IRRs, and grade 3–5 AEs were slightly more frequent in the obinutuzumab arm, although the incidence of treatment discontinuation was relatively similar between arms.[129] The GALLIUM data support the use of obinutuzumab-based regimens as frontline therapy for FL. However given a median PFS of 10 years or more with rituximab based induction and maintenance, it remains uncertain whether obinutuzumab is best used in the frontline or relapsed and refractory setting.

CLL

Thirteen patients with relapsed/refractory CLL were given single-agent obinutuzumab (ranging from 400-1200mg) in the initial phase I dose-escalation stage of the GAUGUIN study. Obinutuzumab was subsequently administered at a fixed dose of 1000mg to 20 relapsed/refractory CLL patients in the phase II stage. Interestingly, the end-of-treatment ORR in the phase I cohort was 62%, but only 15% in the phase II cohort (best overall response 62% vs. 30%). The authors postulated that this may be related to higher baseline tumour burden in the fixed-dose group, resulting in lower exposure to treatment.[130]

The GALTON study evaluated obinutuzumab in combination with chemotherapy of the investigator's choice (either fludarabine/cyclophosphamide or bendamustine) given to 41 treatment-naïve CLL patients. The ORR was higher in the bendamustine arm (G-B, 90%) compared to the FC arm (G-FC, 62%), as was the CR rate (20% compared to 10%). Toxicity was manageable, with IRRs being the most common AE (88%, grade 3–4 20%) and grade 3–4 neutropenia in 48% with G-FC and 55% with G-B.[131]

Goede and colleagues from the German CLL Study Group (GCLLSG) published the first phase III clinical trial data for obinutuzumab in 2014 from the pivotal CLL11 trial, which sought to establish the role of obinutuzumab as part of frontline treatment for CLL in patients with significant comorbidities (defined as a Cumulative Index Rating Scale score > 6 and/or an estimated creatinine clearance of 30–69 ml/min). At the time of study initiation, the standard of care for this patient group was largely undefined with chlorambucil monotherapy established as the comparator based on the GCLLSG CLL5 study.[132] The median age of patients was 73 years with most having more than three comorbidities. The first stage of the trial demonstrated the superiority of chlorambucil with either rituximab or obinutuzumab over chlorambucil alone. Patients receiving chlorambucil monotherapy who progressed during or after treatment (n = 30) were permitted to cross over to the G-Clb group. Following accrual of additional patients, the second stage directly compared R-Clb (330 patients) with G-Clb (total of 333 patients). Treatment was administered every 28-days for six cycles.

Both antibody-containing combinations significantly improved PFS compared to chlorambucil alone. However G-Clb demonstrated a superior median PFS (26.7 vs. 15.2 months), CR rate (21% vs. 7%), and rates of MRD negativity in both peripheral blood and bone marrow in comparison to R-Clb.[90] AEs were more frequent with G-Clb, with IRRs being the most common (20% grade 3 or greater) mainly occurring with the first infusion. While neutropenia was more frequent, rates of infections were not increased.[133] Additionally, a recently presented update of this trial, encompassing an additional 2 years of follow-up has demonstrated a significant OS benefit for patients treated with G-Clb compared to those receiving R-Clb (median OS not reached vs 73.1months, HR 0.76, 95% CI 0.60–0.97, p = 0.0245).[134]

Higher rates of IRR have been consistently reported with obinutuzumab compared to rituximab. The higher affinity of obinutuzumab for FcγRIII leads to stronger FcγR activation and faster recruitment and activation of immune effector cells,

particularly in the peripheral blood, causing strong cytokine release. Immediate and marked release of IL-6 and IL-8 with the first infusion is accompanied by rapid, profound depletion of circulating B-cells and disappearance of NK cells from blood.[135] Preliminary data indicate correlation between CD20 surface expression on CLL cells, FcrγRIII polymorphisms, and risk of developing any grade of IRR with first infusion of rituximab or obinutuzumab. Trisomy 12 is associated with higher levels of CD20 expression and was found to be a risk factor for occurrence of IRR.[136]

The GREEN study, an open-label, multicentre phase IIIb safety trial, enrolled both fit and unfit patients with previously untreated and relapsed/refractory CLL to receive obinutuzumab alone or in combination with chemotherapy (FC, bendamustine, or chlorambucil). The study aimed to reduce IRRs on the first day of administration by using a lower dose and slower infusion rate; in contrast to CLL11, the first dose was split (25mg on day 1 at 12.5mg/hour and 975mg on day 2). Although preliminary safety data indicated a safety profile similar to previous studies, with more manageable IRRs, later analysis did not show any substantial reduction in the incidence of IRRs compared to CLL11.[137,138]

Building on the CLL11 trial which established G-Clb as the standard of care for older comorbid patients, the combination of obinutuzumab and venetoclax was evaluated in the CLL14 study in comparison to G-Clb. Data from the run-in phase demonstrated an ORR of 100% in 13 patients who completed therapy (median age of 75 years). This cohort included 2 patients with 17p deletion. After the fixed duration treatment of 12 cycles with median follow-up of 29.6 months, 80.2% were progression-free and 92.3% were still alive. 92% achieved MRD negativity in peripheral blood within 3 months of completion of 12 month therapy; at 18 months of follow-up, 64% remained MRD negative.[139] Analysis of the randomized phase, which subsequently recruited 432 patients, is currently awaited. This combination is also undergoing study in the CLL2-BAG trial (NCT02401503), which is evaluating a sequential regimen of bendamustine debulking followed by induction with obinutuzumab and venetoclax and maintenance for up to 24 months, in both treatment-naïve and pre-treated CLL patients.[140] Other combinations currently under investigation in phase II trials include obinutuzumab and idelalisib in the CLL2-BCG trial (NCT02445131) and obinutuzumab and ibrutinib in the CLL2-BIG trial (NCT02345863).[140]

Aggressive B-cell lymphomas

The rationale for investigating obinutuzumab in aggressive lymphoma was based on the GAUGUIN study which included 40 patients with relapsed/refractory DLBCL (25) and MCL (15); 63% were rituximab-refractory. Five out of 25 rituximab-refractory patients had objective responses to induction with single agent obinutuzumab with the majority occurring in the high dose arm.[141] The combination of obinutuzumab with CHOP chemotherapy (G-CHOP) in the frontline was first evaluated in the phase II GATHER study. Obinutuzumab dosing was based on early PK studies and designed to achieve saturation of CD20 binding during the first cycle. An ORR of 83% was documented with a CR rate of 55%.[142] However, the subsequent phase 3 GOYA trial that included 1418 patients failed to demonstrate the superiority of G-CHOP over R-CHOP. The primary end-point of investigator-assessed PFS was not met with 66% in R-CHOP arm and 69% in G-CHOP arm being progression free after a median follow-up of 29 months (HR 0.92 (0.76, 1.11), p = 0.3868). Grade 3/4 AEs and fatal AEs were more common in the G-CHOP group, as were treatment discontinuations, dose reductions, and dose interruptions due to AEs.[143]

Ofatumumab

Ofatumumab is a fully humanised type 1 monoclonal antibody against CD20, binding to an epitope that incorporates components of both the small extracellular loop and the N-terminal region of the large extracellular loop.[21] Ofatumumab shows tighter binding to CD20 than rituximab as well as a slower dissociation rate with a half-life of three hours. While ofatumumab is a type 1 antibody, it does not induce apoptotic B cell death upon binding as rituximab does.[144] Ofatumumab's structural characteristics enable to bind to CD20 at closer proximity to the cell membrane surface in comparison to rituximab.[144] This feature in addition to more avid binding to C1q and a seemingly reduced impact of complement regulatory proteins, contribute to ofatumumab's superior CDC compared with rituximab.[145] Regarding ADCC, most data demonstrate relative equivalence between rituximab and ofatumumab, though some studies suggest that ofatumumab displays greater efficacy in this modality also.-[146,147] Preclinical studies of ofatumumab demonstrated superior *in vitro* activity in comparison to rituximab providing justification for further clinical trials.[146,148]

Indolent hematological malignancies

Follicular lymphoma

The first study of ofatumumab in FL reported single-agent activity in 40 patients with relapsed/refractory, grade 1/2 FL. Patients received four weekly doses of either 300mg, 500mg, 700mg or 1000mg with response rates of 63%, 33%, 20% and 50% at the respective doses. 15 of the patients had been previously exposed to rituximab, and of these, 64% showed a response, including 3 out 4 patients that were judged to be rituximab refractory. The median time to progression (TTP) was 8.8 months and the median duration of response was 29.9 months.[149] Based on this demonstration of ofatumumab's activity, a subsequent trial was undertaken in 116 rituximab refractory FL patients, in which patients received 8 weekly treatments of ofatumumab, with 300mg in cycle one, followed by random allocation to 500mg or 1000mg in subsequent cycles.[150] 86% of these patients had advanced stage disease, and approximately half were high risk according to the FL international prognostic index (FLIPI). Ofatumumab once again proved to be exceedingly well tolerated, however its efficacy as a single agent in this trial was at best modest, with an overall response rate (ORR) of 11% and no significant difference between dosing levels. The median progression free survival (PFS) proved only to be 5.8 months. Ofatumumab at

500mg or 1000mg was subsequently tested in the upfront setting in FL grades 1–3 and was delivered in combination with CHOP chemotherapy for six cycles.[151] 29 patients were treated in each dose group, with an ORR in the 500mg group of 90% with 24% complete response (CR); in the 1000mg group the ORR was 100% with 38% in CR. Curiously, the CR rate was greatest (76%) in those with high risk FLIPI scores, but limited follow-up precludes determination as to whether this translates into a survival benefit. Overall, these results were considered comparable to pre-existing data for rituximab in combination with both bendamustine and CHOP.[74,152]

CLL

The utility of single agent ofatumumab in relapsed/refractory CLL was demonstrated in a study of 33 heavily pretreated patients. Each patient received four doses of ofatumumab administered weekly, at one of three escalating dose regimens. At the highest dose level (500mg for one week, followed by 3 x 2000mg), the ORR was 50%, although no patient achieved a CR. Therapy was well tolerated, however 51% of patients developed an infection, with the vast majority being either grade 1 or 2.[153] Based on these initial data, a larger phase II trial of ofatumumab monotherapy was conducted in 138 patients with either alemtuzumab and fludarabine refractory or bulky fludarabine refractory disease, in which participants were treated over 24 weeks with initial 8 weekly doses of ofatumumab, consolidated with 4 monthly infusions.[154] The ORR in the alemtuzumab and fludarabine refractory group and the bulky fludarabine refractory group was 58% and 47% respectively. With median PFS of 5.7 and 5.9 months, and OS of 15.4 and 13.7 months respectively. The results of this trial prompted the FDA and the European Medicines agency (EMA) to approve the use of ofatumumab in fludarabine and alemtuzumab refractory cases in 2009 and 2010 respectively.[155]

Investigators have subsequently examined single agent ofatumumab as the comparator for ibrutinib in phase 3 studies of CLL with ibrutinib demonstrating superiority in regard to PFS (8.1 months vs not reached), and 12-month OS (81% vs 90%) and ORR (4.1% vs 42.6%) with a comparable rate of serious adverse events (SAEs).[156] The notably lower response rate in ofatumumab arm when compared to previous studies was attributed to the use of CT guided response assessment, which was not included in the landmark study.

The GIMEMA group explored ofatumumab in combination with bendamustine in refractory CLL, yielding an ORR of 72.3% with 17% of patients achieving CR.[157] The PFS and OS at a median follow-up of 24.2 months were 49.6% and 83.6% respectively. Although significant myelosuppression was common (grade 3 or 4 neutropenia occurred in 61.7% of patients) this did not translate into a high rate of serious infections (grade 3 or 4 infections occurred in 6% of patients). The COMPLEMENT-2 trial recently reported the efficacy of ofatumumab with fludarabine and cyclophosphamide (FC) in comparison to FC alone in the relapsed setting. Patients who received ofatumumab had greater PFS (28.9 months vs 18.8 months) and ORR (84% vs 68%), though no statistically significant increase in OS was observed (56.4 months vs 45.8 months, 95%CI 0.56–1.09).[158]

Further studies of ofatumumab in combination with novel agents have demonstrated efficacy with lenalidomide,[159] ibrutinib,[160] and idelalisib.[161] However, the latter combination was associated with increased rates of serious infections and death.

Frontline studies of single-agent ofatumumab in CLL have confirmed activity, but CR rates were low (~2.5%), suggesting that it may be better used in combination.[162] Induction therapy with fludarabine, cyclophosphamide and ofatumumab (FCO) has been investigated by Weirda et al in a randomised trial.[163] 61 patients were treated in two dosing cohorts; both groups received standard FC plus ofatumumab 300mg (first dose), thereafter the dose of ofatumumab varied; group A received 500mg and group B received 1000mg for the remaining 5 cycles. The ORR and CR rate were 77% and 32% in group A and 73% and 50% in group B, respectively.[155] FCO was tolerated well, with the most frequent AE being grade 1 or 2 infusion reactions. Grade 3 or 4 neutropenia did occur in 48%, but only 8% of patients suffered grade 3 or 4 infections. For those patients deemed unsuitable for fludarabine-based therapy, ofatumumab was investigated in combination with chlorambucil in the COMPLEMENT-1 study.[164] Patients were randomised to chlorambucil and ofatumumab or chlorambucil alone. The ORR and CR rate for the dual therapy arm were 82% and 12%, respectively, as opposed to 69% and 1% for chlorambucil monotherapy. Median PFS was significantly greater for those who received ofatumumab (22.4 vs 13.1 months). OS was not reached for either group at the time of follow-up and the frequency of severe infections was similar between the two arms.[164] These data led both the FDA and EMA to approve the use of this combination as upfront management of patients unfit for fludarabine-based induction regimens.

Another potential role for ofatumumab is as maintenance therapy for those who had a complete or partial response following second or third line CLL therapy. This application was studied in the PROLONG trial, in which patients were treated with 8-weekly ofatumumab (1000mg) for up to 2 years and compared to observation alone.[165] Median PFS was longer for the maintenance cohort (29.4 vs 15.2 months), though no difference in OS was evident. Both PFS and time to next treatment declined rapidly after discontinuation of ofatumumab, perhaps suggesting the possibility of further benefit with more prolonged maintenance. However, again in the era of novel therapies and novel drug combinations, the role of this drug at all stages of CLL management remains uncertain.

Aggressive hematological malignancies

There is a relative paucity of data on ofatumumab in aggressive hematological malignancy. A study of ofatumumab in a group of heavily pre-treated patients with DLBCL relapsing post, or ineligible for autologous stem cell transplant, achieved a meagre ORR of 14% and median PFS of 2.6 months.[166] A subsequent phase II trial of ofatumumab in combination with ICE or DHAP as second line treatment in relapsed DLBCL, (mirroring the CORAL study which examined the same agents in combination with rituximab) demonstrated a similar ORR of 61% with a CR rate of 30% to the rituximab based

studies.[167,168] The ORCHARRD study sought to directly compare ofatumumab versus rituximab in conjunction with DHAP as induction pre-autograft in patients with relapsed or refractory DLBCL. Response rates with O-DHAP and R-DHAP were similar (38% vs 42%), as were the proportion that could proceed to transplant (33% vs 37%), PFS at 2 years (24% vs 26%) and OS at 2 years (41% vs 38%).[169]

Rituximab in autoimmune diseases

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune condition characterised by inflammatory arthritis affecting multiple joints of the body. In the absence of treatment, RA commonly leads to pain, loss of function and premature mortality in affected individuals.[170] However, the prognosis of rheumatoid arthritis has drastically improved in recent decades due to the introduction of biologic therapies targeting specific components of pathogenesis, including tumour necrosis factor (TNF) inhibition and B cell depletion amongst several other targets. Biologic agents are typically used in conjunction with more traditional synthetic disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate.[170]

The pathogenesis of RA is complex, and the precise contribution of B lymphocytes to RA pathogenesis is not well defined. B cells have several potential roles, including acting as antigen presenting cells, activating T lymphocytes, secretion of proinflammatory cytokines such as TNF and the production of rheumatoid factor and other autoantibodies.[171] However, the strongest evidence for the role of B lymphocytes in RA pathogenesis comes from several trials of rituximab, which report successful control of disease activity following B lymphocyte depletion.

The first randomised control trial (RCT) of rituximab in RA, published in 2004, involved 161 patients with active RA, and compared two doses of 1000mg rituximab either as a single agent or in combination with methotrexate or cyclophosphamide, with methotrexate alone.[172] The primary outcome was the American College of Rheumatology (ACR) response criteria, which is a composite measure including patient and physician assessments, pain scales, functional questionnaires and acute phase reactants. All treatment protocols containing rituximab showed superiority to methotrexate alone at 24 weeks, with the rituximab/methotrexate and rituximab/cyclophosphamide combination groups showing superiority out to 48 weeks. Further studies, designed predominantly to identify optimal dosing regimens, have repeatedly confirmed these results.[173,174]

Rituximab efficacy has now been well established in patients not previously exposed to other biologic agents such as TNF inhibitors,[173] as well as those patients who have previously failed these therapies.[175,176] Beyond clinical symptoms, imaging studies have also reported reduction of joint damage in patients treated with rituximab.[177,178] Currently, rituximab is typically prescribed for RA patients who have had inadequate responses to synthetic DMARDs and TNF inhibitors. It is generally prescribed in combination with methotrexate therapy, with large registries suggesting better response rates with combination therapy compared to rituximab monotherapy.[179] It is overall well tolerated, with infection rates and adverse events similar to many other commonly prescribed biologic agents in RA patients.[180]

ANCA associated vasculitis

The anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides include granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg Strauss). These are rare conditions in which autoimmune mediated small vessel inflammation and necrosis occurs in one or multiple organs, often leading to rapid organ failure and death without treatment. For many years, the mainstay of induction therapy for these diseases has been cyclophosphamide, with chronic exposure leading to an array of unwanted side effects including infertility and bladder malignancy.[181,182]

Like RA, the aetiology and pathogenesis of ANCA associated vasculitis is complex and poorly defined. However, evidence suggests B lymphocytes are involved in the process. Active B lymphocytes are present in the blood of patients with GPA in greater quantities than in healthy individuals.[183] Cyclophosphamide, a drug known to be successful in the treatment of ANCA associated vasculitis, has been shown to have an inhibitory influence on B cell activation and function.[184–186]

In 2010, on a background of several positive uncontrolled studies, an RCT comparing rituximab therapy with cyclophosphamide in the 197 patients with either GPA or MPA showed that rituximab was non-inferior to cyclophosphamide as an induction agent, with superiority suggested in patients with relapsing disease.[184] A more recent RCT has also reported that rituximab has efficacy as a maintenance agent above that of the traditionally used DMARD azathioprine.[187]

Rituximab is now commonly used in the management of GPA and MPA, particularly in younger patients who wish to preserve fertility, with cost being the limiting factor to access for all patients. An RCT of the efficacy of rituximab in EGPA is currently underway.

Other autoimmune conditions

Despite a lack of RCT evidence, there are several other autoimmune conditions in which off-label rituximab is used in some circumstances.

Rituximab has been trialled in systemic lupus erythematosus (SLE), an autoimmune condition characterised by multi-organ inflammation, polyclonal B cell activation and the presence of multiple autoantibodies.[188] Despite the role of B cells in the pathophysiology of this illness, two RCTs assessing both renal and non-renal SLE failed to show benefit of rituximab above that of standard therapy.[189,190] However, there are case reports and case series suggesting efficacy in a subset of patients with SLE,[191] and rituximab is sometimes prescribed in patients who have failed more mainstream therapies.

Similarly, despite positive uncontrolled study reports, an RCT evaluating the efficacy of rituximab as a second line therapy in adult immune thrombocytopenic purpura (ITP) also failed to show benefit over placebo in patients previously treated with corticosteroids.[192] However, there was a trend towards benefit with higher response rates that did not reach statistical significance in this study. Additionally, Tran et al published a relatively large prospective trial of 122 patients with chronic, relapsed or refractory ITP showed an ORR of 44% with excellent safety outcomes.[193]

Other autoimmune conditions with uncontrolled case report or case series data suggesting benefit of rituximab include anti-phospholipid syndrome,[194] blistering diseases of the skin such as pemphigus and pemphigoid,[195,196] myasthenia gravis,[197] neuromyelitis optica[198] and the inflammatory myopathies.[199] Within the realm of hematology, similarly limited evidence exists in supporting the use of rituximab either alone or in combination with other immunosuppressants in acquired hemophilia,[200,201] autoimmune hemolytic anaemia (including a small randomised controlled trial),[202–204] and thrombotic thrombocytopenic purpura.[205–207] Further controlled trials are required to more definitively establish efficacy in these conditions, although the rarity of several of these diseases poses a significant challenge to trial recruitment.

Other anti-CD20 mAbs in autoimmune disease

Numerous trials utilising new generation anti-CD20 mAbs have been undertaken or remain ongoing in autoimmune disease. These agents include ofatumumab, obinutuzumab, ocrelizumab and veltuzumab. Some of these drugs have demonstrated safety and efficacy in these settings, though an exploration of these data is beyond the scope of this article and has been recently reviewed by Du and colleagues.[208] Nonetheless it is important to note that there are no published data comparing these agents to rituximab directly, hence it is difficult to determine where these mAbs may be most usefully deployed in clinical practice, and the advantages of these drugs over rituximab remain to proven.

Anti-drug antibodies

Monoclonal antibodies can be immunogenic and provoke the formation of anti-drug antibodies (ADAs). ADAs can affect the pharmacokinetic, efficacy and toxicity profile of mAbs, but there is considerable variability between different drugs. As these agents have evolved from murine to chimeric to humanised and fully human iterations, there has been a reduction in the frequency of ADAs detected.[209] Nonetheless, ADAs may still form in up to 26.3% of patients treated with fully human mAbs.[210] The presence and impact of ADAs have not been routinely reported in large clincal trials of CD20 mAbs, and data correlating ADAs with patient outcomes is extremely scarce. A recent review by van Brummelen that examined data from EMA and FDA drug reports, showed that ADAs formed in 1–2% of patients treated with rituximab, 6% of patients receiving obinutuzumab, but no data were available for ofatumumab.[210] Interestingly, there are no data that show the presence of ADAs significantly impacts efficacy, toxicity or pharmacokinetics in the anti-CD20 agents in the setting of cancer treatment.[210] A recent study of 339 patients with multiple sclerosis (MS) treated with rituximab showed a much higher rate of ADA formation, occurring in 37% of relapsing-remitting MS patients and 26% of progessive MS patients. However, although the presence of ADAs was associated with incomplete B cell depletion, no relationship could be established with adverse events or patient outcomes.[211] Accordingly, it remains unclear how important an issue ADAs are for anti-CD20 mAbs, and further study is required to clarifiy the significance of this phenomenon.

Conclusion

Extensive though this review may be, it cannot provide a panoptical analysis of all scientific and clinical data for all anti-CD20 mAbs. However, the profound and revolutionary impact of these agents on modern medical therapeutics is surely undisputed. The prospect of an ongoing role for CD20 mAbs is relatively assured in the short-term, and new developments in this arena abound. Modern pharmaceutical engineering methods are achieving impressive and targeted modulation of mAb properties that may augment their clinical efficacy and safety, and lead to new generations of CD20 targeted drugs.[11] Indeed, a variety of other anti-CD20 mAbs not discussed in this article have been trialled in numerous diseases. Novel therapy combinations also offer potential synergistic benefits to overcome resistant disease or improve response rates. An intriguing development, beyond the scope of our article, is the production of so-called "biosimilars" in the wake of patent expirations. These copies of the aforementioned mAbs represent a chance for a larger number of patients to access these therapies that can be prohibitively expensive in resource-limited settings, but also pose difficulties in the critical task of establishing therapeutic equivalence.-[212] While work continues to decipher the remaining mysteries of CD20 physiology and the mechanisms of action of the mAbs, the potential applications of targeting this antigen may yet to be fully realised and will hopefully continue the revolution sparked by rituximab's emergence, now over twenty years ago.

Abbreviations

aaIPI	age-adjusted international prognostic index
ACR	American College of Rheumatology
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
AE	adverse event
ANCA	anti-neutrophil cytoplasmic antibody
B-ALL	B-cell acute lymphoblastic leukemia
BCR	B-cell receptor
BL	Burkitt lymphoma
BTK	Bruton tyrosine kinase
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CI	confidence interval
Clb	chlorambucil
CLL	chronic lymphocytic leukemia
CR	complete response

CVP	cyclophosphamide, vincristine, prednisone
DHAP	dexamethasone, high-dose cytarabine and cisplatin
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMAR	Ddisease modifying anti-rheumatic drug
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EGPA	eosinophilic granulomatosis with polyangiitis
EMA	European Medicines Agency
FC	fludarabine and cyclophosphamide
FCM	fludarabine, cyclophosphamide and mitoxantrone
FCO	fludarabine, cyclophosphamide and ofatumumab
FCR	fludarabine, cyclophosphamide and rituximab
FCO	fludarabine, cyclophosphamide and ofatumumab
FDA	Food and Drug Administration
FFS	failure-free survival
FL	follicular lymphoma
FLIPI	follicular lymphoma international prognostic index
G	obinutuzumab (GA-101)
GELF	Groupe d'Etude des Lymphomes Folliculaires
GPA	granulomatosis with polyangiitis
HIV	human immunodeficiency virus
HR	hazard ratio
IRR	infusion-related reaction
ITP	immune thrombocytopenic purpura
mAb	monoclonal antibody
MCL	mantle cell lymphoma
MPA	microscopic polyangiitis
MRD	minimal residual disease
MS	multiple sclerosis
NHL	non-Hodgkin lymphoma
NK	natural killer
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
Ph-	Philadelphia chromosome negative
R	rituximab
RA	rheumatoid arthritis
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SLE	systemic lupus erythematosus
TNF	tumour necrosis factor
TTP	time to progression
VIM	etoposide, ifosfamide and methotrexate

Dislcosure of potential conflicts of interest

In accordance with Taylor & Francis policy and our ethical obligations as researchers, we report that Prof Opat:

(1) Consulted for Roche, Janssen, Celgene, Takeda, Novartis, Abbvie, Gilead, Bristol-Myers Squib, Merck, Sanofi, Mundipharma
(2) Received honoraria from Roche, Janssen, Celgene, Takeda, Novartis, Abbvie, Gilead, Mundipharma
(3) Received clinical trial support from Roche, Janssen, Celgene, Takeda, Novartis, Abbvie, Gilead, Beigene, Merck
(4) Received travel support from Roche, Brisol-Myers Squibb

We have disclosed those interests fully to Taylor & Francis, and have in place an approved plan for managing any potential conflicts arising from that involvement.

The remaining authors have no potential conflict of interest to report.

References

1. Cragg MS, Walshe CA, Ivanov AO, Glennie MJ. The biology of CD20 and its potential as a target for mAb therapy. In: B cell trophic factors and B cell antagonism in autoimmune disease. Basel: KARGER. 2004. p. 140–174.
2. Leandro MJ. B-cell subpopulations in humans and their differential susceptibility to depletion with anti-CD20 monoclonal antibodies. Arthritis Res Ther. 2013;15:S3. doi:10.1186/ar3908.
3. Oldham RJ, Cleary KLS, Cragg MS. CD20 and its antibodies: past, present, and future. For Immunopathol Dis Therap. 2014;5:7–23. doi:10.1615/ForumImmunDisTher.2015014073.
4. Bubien JK. Transfection of the CD20 cell surface molecule into ectopic cell types generates a Ca2+ conductance found constitutively in B lymphocytes. J Cell Biol. 1993;121:1121–1132. doi:10.1083/jcb.121.5.1121.
5. Walshe CA, Beers SA, French RR, Chan CHT, Johnson PW, Packham GK, Glennie MJ, Cragg MS. Induction of cytosolic calcium flux by CD20 is dependent upon B Cell antigen receptor signaling. J Biol Chem. 2008;283:16971–16984. doi:10.1074/jbc.M708459200.
6. Polyak MJ, Li H, Shariat N, Deans JP. CD20 homo-oligomers physically associate with the B cell antigen receptor. J Biol Chem. 2008;283:18545–18552. doi:10.1074/jbc.M800784200.
7. Morsy DED, Sanyal R, Zaiss AK, Deo R, Muruve DA, Deans JP. Reduced T-dependent humoral immunity in CD20-deficient mice. J Immunol. 2013;191:3112–3118. doi:10.4049/jimmunol.1202098.
8. Kuijpers TW, Bende RJ, Baars PA, Grummels A, Derks IAM, Dolman KM, Beaumont T, Tedder TF, van Noesel CJM, Eldering E, et al. CD20 deficiency in humans results in impaired T cell-independent antibody responses. J Clin Invest. 2010;120:214–222. doi:10.1172/JCI40231.
9. Nadler LM, Ritz J, Hardy R, Pesando JM, Schlossman SF, Stashenko P. A unique cell surface antigen identifying lymphoid malignancies of B cell origin. J Clin Invest. 1981;67:134–140. doi:10.1172/JCI110005.
10. Cragg MS, Walshe CA, Ivanov AO, Glennie MJ. The biology of CD20 and its potential as a target for mAb therapy. Curr Dir Autoimmun. 8;2005:140–174.
11. Marshall MJE, Stopforth RJ, Cragg MS. Therapeutic antibodies: what have we learnt from targeting CD20 and where are we going? Front Immunol. 2017;8:1327–1422. doi:10.3389/fimmu.2017.01245.
12. Einfeld DA, Brown JP, Valentine MA, Clark EA, Ledbetter JA. Molecular cloning of the human B cell CD20 receptor predicts a hydrophobic protein with multiple transmembrane domains. EMBO J. 7;1988:711–717.
13. Ginaldi L, de Martinis M, Matutes E, Farahat N, Morilla R, Catovsky D. Levels of expression of CD19 and CD20 in chronic B cell leukaemias. J Clin Pathol. 51;1998:364–369.
14. Cleary KLS, Chan HTC, James S, Glennie MJ, Cragg MS. Antibody distance from the cell membrane regulates antibody effector mechanisms. J Immunol. 2017;198:3999–4011. doi:10.4049/jimmunol.1601473.
15. Deans JP, Robbins SM, Polyak MJ, Savage JA. Rapid redistribution of CD20 to a low density detergent-insoluble membrane compartment. J Biol Chem. 1998;273:344–348. doi:10.1074/jbc.273.1.344.
16. Pike LJ. Rafts defined: a report on the Keystone symposium on lipid rafts and cell function. J Lipid Res. 2006;47:1597–1598. doi:10.1194/jlr.M600040-JLR200.
17. Beers SA, French RR, Chan HTC, Lim SH, Jarrett TC, Vidal RM, Wijayaweera SS, Dixon SV, Kim H, Cox KL, et al. Antigenic modulation limits the efficacy of anti-CD20 antibodies: implications for antibody selection. Blood. 2010;115:5191–5201. doi:10.1182/blood-2009-12-255992.
18. Niederfellner G, Lammens A, Mundigl O, Georges GJ, Schaefer W, Schwaiger M, Franke A, Wiechmann K, Jenewein S, Slootstra JW, et al. Epitope characterization and crystal structure of GA101 provide insights into the molecular basis for type I/II distinction of CD20

antibodies. Blood. 2011;118:358–367. doi:10.1182/blood-2011-02-334870.
19. Cragg MS, Morgan SM, Chan HTC, Morgan BP, Filatov AV, Johnson PWM, French RR, Glennie MJ. Complement-mediated lysis by anti-CD20 mAb correlates with segregation into lipid rafts. Blood. 2003;101:1045–1052. doi:10.1182/blood-2002-06-1761.
20. Golan MD, Burger R, Loos M. Conformational changes in C1q after binding to immune complexes: detection of neoantigens with monoclonal antibodies. J Immunol. 129;1982:445–447.
21. Teeling JL, Mackus WJM, Wiegman LJJM, van den Brakel JHN, Beers SA, French RR, van Meerten T, Ebeling S, Vink T, Slootstra JW, et al. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. J Immunol. 2006;177:362–371. doi:10.4049/jimmunol.177.1.362.
22. de Jong RN, Beurskens FJ, Verploegen S, Strumane K, van Kampen MD, Voorhorst M, Horstman W, Engelberts PJ, Oostindie SC, Wang G, et al. A novel platform for the potentiation of therapeutic antibodies based on antigen-dependent formation of IgG hexamers at the cell surface. PLoS Biol. 2016;14:e1002344. doi:10.1371/journal.pbio.1002344.
23. Pross HF, Maroun JA. The standardization of NK cell assays for use in studies of biological response modifiers. J Immunol Methods. 1984;68:235–249. doi:10.1016/0022-1759(84)90154-6.
24. Gül N, van Egmond M. Antibody-dependent phagocytosis of tumor cells by macrophages: a potent effector mechanism of monoclonal antibody therapy of cancer. Cancer Res. 2015;75:5008–5013. doi:10.1158/0008-5472.CAN-14-3569.
25. Ghetie MA, Bright H, Vitetta ES. Homodimers but not monomers of Rituxan (chimeric anti-CD20) induce apoptosis in human B-lymphoma cells and synergize with a chemotherapeutic agent and an immunotoxin. Blood. 97;2001:1392–1398.
26. Glennie MJ, French RR, Cragg MS, Taylor RP. Mechanisms of killing by anti-CD20 monoclonal antibodies. Mol Immunol. 2007;44:3823–3837. doi:10.1016/j.molimm.2007.06.151.
27. Janas E, Priest R, Wilde JI, White JH, Malhotra R. Rituxan (anti-CD20 antibody)-induced translocation of CD20 into lipid rafts is crucial for calcium influx and apoptosis. Clin Exp Immunol. 2005;139:439–446. doi:10.1111/j.1365-2249.2005.02720.x.
28. Bellosillo B, Villamor N, Lopez-Guillermo A, Marcé S, Esteve J, Campo E, Colomer D, Montserrat E. Complement-mediated cell death induced by rituximab in B-cell lymphoproliferative disorders is mediated in vitro by a caspase-independent mechanism involving the generation of reactive oxygen species. Blood. 98;2001:2771–2777.
29. Clynes RA, Towers TL, Presta LG, Ravetch JV. Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. Nat Med. 2000;6:443–446. doi:10.1038/74704.
30. de Haij S, Jansen JHM, Boross P, Beurskens FJ, Bakema JE, Bos DL, Martens A, Verbeek JS, Parren PWHI, van de Winkel JGJ, et al. In vivo cytotoxicity of type I CD20 antibodies critically depends on Fc receptor ITAM signaling. Cancer Res. 2010;70:3209–3217. doi:10.1158/0008-5472.CAN-09-4109.
31. Cartron G, Dacheux L, Salles G, Solal-Celigny P, Bardos P, Colombat P, Watier H. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcgammaRIIIa gene. Blood. 2002;99:754–758. doi:10.1182/blood.V99.3.754.
32. Abès R, Gélizé E, Fridman WH, Teillaud J-L. Long-lasting anti-tumor protection by anti-CD20 antibody through cellular immune response. Blood. 2010;116:926–934. doi:10.1182/blood-2009-10-248609.
33. Ghesquières H, Cartron G, Seymour JF, Delfau-Larue M-H, Offner F, Soubeyran P, Perrot A, Brice P, Bouabdallah R, Sonet A, et al. Clinical outcome of patients with follicular lymphoma receiving chemoimmunotherapy in the PRIMA study is not affected by FCGR3A and FCGR2A polymorphisms. Blood. 2012;120:2650–2657. doi:10.1182/blood-2012-05-431825.
34. Hilchey SP, Hyrien O, Mosmann TR, Livingstone AM, Friedberg JW, Young F, Fisher RI, Kelleher RJ, Bankert RB, Bernstein SH. Rituximab immunotherapy results in the induction of a lymphoma idiotype-specific T-cell response in patients with follicular lymphoma: support for a "vaccinal effect" of rituximab. Blood. 2009;113:3809–3812. doi:10.1182/blood-2008-03-146472.
35. Ren Z, Guo J, Liao J, Luan Y, Liu Z, Sun Z, Liu X, Liang Y, Peng H, Fu Y-X. CTLA-4 limits anti-CD20-mediated tumor regression. Clin Cancer Res. 2017;23:193–203. doi:10.1158/1078-0432.CCR-16-0040.
36. Beers SA, Chan CHT, French RR, Cragg MS, Glennie MJ. CD20 as a target for therapeutic type I and II monoclonal antibodies. Semin Hematol. 2010;47:107–114. doi:10.1053/j.seminhematol.2010.01.001.
37. Kellner C, Otte A, Cappuzzello E, Klausz K, Peipp M. Modulating cytotoxic effector functions by Fc engineering to improve cancer therapy. Transfus Med Hemother. 2017;44:327–336. doi:10.1159/000479980.
38. Gelderman KA, Tomlinson S, Ross GD, Gorter A. Complement function in mAb-mediated cancer immunotherapy. Trends Immunol. 2004;25:158–164. doi:10.1016/j.it.2004.01.008.
39. Wang S-Y, Racila E, Taylor RP, Weiner GJ. NK-cell activation and antibody-dependent cellular cytotoxicity induced by rituximab-coated target cells is inhibited by the C3b component of complement. Blood. 2008;111:1456–1463. doi:10.1182/blood-2007-02-074716.
40. Wang S-Y, Veeramani S, Racila E, Cagley J, Fritzinger DC, Vogel C-W, St John W, Weiner GJ. Depletion of the C3 component of complement enhances the ability of rituximab-coated target cells to activate human NK cells and improves the efficacy of monoclonal antibody therapy in an in vivo model. Blood. 2009;114:5322–5330. doi:10.1182/blood-2009-04-215525.
41. Racila E, Link BK, Weng W-K, Witzig TE, Ansell S, Maurer MJ, Huang J, Dahle C, Halwani A, Levy R, et al. A polymorphism in the complement component C1qA correlates with prolonged response following rituximab therapy of follicular lymphoma. Clin Cancer Res. 2008;14:6697–6703. doi:10.1158/1078-0432.CCR-08-0745.
42. Shields RL, Lai J, Keck R, O'Connell LY, Hong K, Meng YG, Weikert SHA, Presta LG. Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human Fcgamma RIII and antibody-dependent cellular toxicity. J Biol Chem. 2002;277:26733–26740. doi:10.1074/jbc.M202069200.
43. Smolewski P, Robak T. The preclinical discovery of rituximab for the treatment of non-Hodgkin's lymphoma. Expert Opin Drug Discov. 2015;10:doi:10.1517/17460441.2015.1045295.
44. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, Newman RA, Hanna N, Anderson DR. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood. 83;1994:435–445.
45. Nadler LM, Stashenko P, Hardy R, Kaplan WD, Button LN, Kufe DW, Antman KH, Schlossman SF. Serotherapy of a patient with a monoclonal antibody directed against a human lymphoma-associated antigen. Cancer Res. 40;1980:3147–3154.
46. Miller RA, Maloney DG, Warnke R, Levy R. Treatment of B-cell lymphoma with monoclonal anti-idiotype antibody. N Engl J Med. 1982;306:517–522. doi:10.1056/NEJM198203043060906.
47. Press OW, Appelbaum F, Ledbetter JA, Martin PJ, Zarling J, Kidd P, Thomas ED. Monoclonal antibody 1F5 (anti-CD20) serotherapy of human B cell lymphomas. Blood. 69;1987:584–591.
48. Waldmann TA. Immunotherapy: past, present and future. Nat Med. 2003;9:269–277. doi:10.1038/nm0303-269.
49. Liu AY, Robinson RR, Murray ED, Ledbetter JA, Hellström I, Hellström KE. Production of a mouse-human chimeric monoclonal antibody to CD20 with potent Fc-dependent biologic activity. J Immunol. 139;1987:3521–3526.
50. Golay J, Semenzato G, Rambaldi A, Foà R, Gaidano G, Gamba E, Pane F, Pinto A, Specchia G, Zaja F, et al. Lessons for the clinic from rituximab pharmacokinetics and pharmacodynamics. mAbs. 2013;5:826–837. doi:10.4161/mabs.22965.
51. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, Heyman MR, Bence-Bruckler I, White CA, Cabanillas F, 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. 1998;16:2825–2833. doi:10.1200/JCO.1998.16.8.2825.
52. Berinstein NL, Grillo-López AJ, White CA, Bence-Bruckler I, Maloney D, Czuczman M, Green D, Rosenberg J, McLaughlin P, Shen D. Association of serum Rituximab (IDEC-C2B8) concentration and anti-tumor response in the treatment of recurrent low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol. 1998;9:995–1001. doi:10.1023/A:1008416911099.
53. Rozman S, Grabnar I, Novaković S, Mrhar A, Jezeršek Novaković B. Population pharmacokinetics of rituximab in patients with diffuse large B-cell lymphoma and association with clinical outcome. Br J Clin Pharmacol. 2017;83:1782–1790. doi:10.1111/bcp.v83.8.
54. Yin A, Li J, Hurst D, Visich J. Population pharmacokinetics (PK) and association of PK and clinical outcomes of rituximab in patients with non-Hodgkin's lymphoma. J Clin Oncol. 2010;28:e13108–e131088. doi:10.1200/jco.2010.28.15_suppl.e13108.
55. Li J, Zhi J, Wenger M, Valente N, Dmoszynska A, Robak T, Mangat R, Joshi A, Visich J. Population pharmacokinetics of rituximab in patients with chronic lymphocytic leukemia. J Clin Pharmacol. 2012;52:1918–1926. doi:10.1177/0091270011430506.
56. Müller C, Murawski N, Wiesen MHJ, Held G, Poeschel V, Zeynalova S, Wenger M, Nickenig C, Peter N, Lengfelder E, et al. The role of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. Blood. 2012;119:3276–3284. doi:10.1182/blood-2011-10-388512.
57. Jäger U, Fridrik M, Zeitlinger M, Heintel D, Hopfinger G, Burgstaller S, Mannhalter C, Oberaigner W, Porpaczy E, Skrabs C, et al. Rituximab serum concentrations during immuno-chemotherapy of follicular lymphoma correlate with patient gender, bone marrow infiltration and clinical response. Haematologica. 2012;97:1431–1438. doi:10.3324/haematol.2011.059246.
58. Gisselbrecht C, Schmitz N, Mounier N, Singh Gill D, Linch DC, Trneny M, Bosly A, Milpied NJ, Radford J, Ketterer N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. J Clin Oncol. 2012;30:4462–4469. doi:10.1200/JCO.2012.41.9416.
59. Pfreundschuh M, Held G, Zeynalova S, Zwick C, Haenel M, Truemper L, Dreyling MH, Dierlamm J, Loeffler M, Schmitz N, et al. Increased rituximab (R) doses and effect on risk of elderly male patients with aggressive CD20+ B-cell lymphomas: results from the SEXIE-R-CHOP-14 trial of the DSHNHL. J Clin Oncol. 2014;32:8501–8511. doi:10.1200/JCO.2013.54.6911.
60. Davies A, Berge C, Boehnke A, Dadabhoy A, Lugtenburg P, Rule S, Rummel M, McIntyre C, Smith R, Badoux X. Subcutaneous rituximab for the treatment of B-cell hematologic malignancies: a review of the scientific rationale and clinical development. Adv Ther. 2017;34:2210–2231. doi:10.1007/s12325-017-0610-z.
61. Mao C-P, Brovarney MR, Dabbagh K, Birnböck HF, Richter WF, Del Nagro CJ. Subcutaneous versus intravenous administration of rituximab: pharmacokinetics, CD20 target coverage and B-cell depletion in cynomolgus monkeys. PLoS ONE. 2013;8:e80533. doi:10.1371/journal.pone.0080533.
62. Bittner B, Richter WF, Hourcade-Potelleret F, Herting F, Schmidt J. Non-clinical pharmacokinetic/pharmacodynamic and early clinical studies supporting development of a novel subcutaneous formulation for the monoclonal antibody rituximab. Drug Res (Stuttg). 2014;64:569–575. doi:10.1055/s-00023610.
63. Salar A, Avivi I, Bittner B, Bouabdallah R, Brewster M, Catalani O, Follows G, Haynes A, Hourcade-Potelleret F, Janikova A, et al. Comparison of subcutaneous versus intravenous administration of rituximab as maintenance treatment for follicular lymphoma: results from a two-stage, phase IB study. J Clin Oncol. 2014;32:1782–1791. doi:10.1200/JCO.2013.54.6911.
64. Davies A, Merli F, Mihaljević B, Siritanaratkul N, Solal-Céligny P, Barrett M, Berge C, Bittner B, Boehnke A, McIntyre C, et al. Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): stage 1 analysis of a randomised phase 3 study. Lancet Oncol. 2014;15:343–352. doi:10.1016/S1470-2045(13)70510-2.
65. Assouline S, Buccheri V, Delmer A, Gaidano G, Trneny M, Berthillon N, Brewster M, Catalani O, Li S, McIntyre C, et al. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukaemia (SAWYER): a phase 1b, open-label, randomised controlled non-inferiority trial. Lancet Haematol. 2016;3:e128–38. doi:10.1016/S2352-3026(16)00004-1.
66. Davies A, Merli F, Mihaljević B, Mercadal S, Siritanaratkul N, Solal-Celigny P, Boehnke A, Berge C, Genevray M, Zharkov A, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. Lancet Haematol. 2017;4:e272–82. doi:10.1016/S2352-3026(17)30078-9.
67. Lugtenburg P, Avivi I, Berenschot H, Ilhan O, Marolleau J-P, Nagler A, Rueda A, Tani M, Turgut M, Osborne S, et al. Efficacy and safety of subcutaneous and intravenous rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in first-line diffuse large B-cell lymphoma: the randomized MabEase study. Haematologica. 2017;102:1913–1922. doi:10.3324/haematol.2016.158808.
68. Rummel M, Kim TM, Aversa F, Brugger W, Capochiani E, Plenteda C, Re F, Trask P, Osborne S, Smith R, et al. Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab). Ann Oncol. 2017;28:836–842. doi:10.1093/annonc/mdx075.
69. Feuring-Buske M, Kneba M, Unterhalt M, Engert A, Gramatzki M, Hiller E, Trümper L, Brugger W, Ostermann H, Atzpodien J, et al. IDEC-C2B8 (Rituximab) anti-CD20 antibody treatment in relapsed advanced-stage follicular lymphomas: results of a phase-II study of the German Low-Grade Lymphoma Study Group. Ann Hematol. 2000;79:493–500. doi:10.1007/s002770000163.
70. Foran JM, Gupta RK, Cunningham D, Popescu RA, Goldstone AH, Sweetenham JW, Pettengell R, Johnson PW, Bessell E, Hancock B, et al. A UK multicentre phase II study of rituximab (chimaeric anti-CD20 monoclonal antibody) in patients with follicular lymphoma, with PCR monitoring of molecular response. Br J Haematol. 2000;109:81–88. doi:10.1046/j.1365-2141.2000.01965.x.
71. Davis TA, White CA, Grillo-López AJ, Velásquez WS, Link B, Maloney DG, Dillman RO, Williams ME, Mohrbacher A, Weaver R, et al. Single-agent monoclonal antibody efficacy in bulky Non-Hodgkin's Lymphoma: results of a phase II trial of rituximab. J Clin Oncol. 1999;17:1851–1861. doi:10.1200/JCO.1999.17.6.1851.
72. Piro LD, White CA, Grillo-López AJ, Janakiraman N, Saven A, Beck TM, Varns C, Shuey S, Czuczman M, Lynch JW, et al. Extended Rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol. 1999;10:655–661. doi:10.1023/A:1008389119525.
73. Marcus R, Imrie K, Solal-Celigny P, Catalano JV, Dmoszynska A, Raposo JC, Offner FC, Gomez-Codina J, Belch A, Cunningham D, 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. 2008;26:4579–4586. doi:10.1200/JCO.2007.15.2777.
74. Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, Reiser M, Metzner B, Harder H, Hegewisch-Becker S, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2005;106:3725–3732. doi:10.1182/blood-2004-04-1622.
75. Bachy E, Houot R, Morschhauser F, Sonet A, Brice P, Belhadj K, Cartron G, Audhuy B, Fermé C, Feugier P, et al. Long-term follow up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. Haematologica. 2013;98:1107–1114. doi:10.3324/haematol.2012.082412.

76. van Oers MHJ, Klasa R, Marcus RE, Wolf M, Kimby E, Gascoyne RD, Jack A, van't Veer M, Vranovsky A, Holte H, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial. Blood. 2006;108:3295–3301. doi:10.1182/blood-2006-03-013334.
77. Salles G, Seymour JF, Offner F, López-Guillermo A, Belada D, Xerri L, Feugier P, Bouabdallah R, Catalano JV, Brice P, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet. 2011;377:42–51. doi:10.1016/S0140-6736(10)62175-7.
78. Salles GA, Seymour JF, Feugier P, Offner F, López-Guillermo A, Belada D, Xerri L, Bouabdallah R, Catalano J, Brice P, et al. Long term follow-up of the PRIMA study: half of patients receiving rituximab maintenance remain progression free at 10 years. Blood. 2017;130:486–496.
79. Kahl BS, Hong F, Williams ME, Gascoyne RD, Wagner LI, Krauss JC, Habermann TM, Swinnen LJ, Schuster SJ, Peterson CG, et al. Rituximab extended schedule or re-treatment trial for low-tumor burden follicular lymphoma: eastern cooperative oncology group protocol e4402. J Clin Oncol. 2014;32:3096–3102. doi:10.1200/JCO.2013.54.6911.
80. van Oers MHJ, van Glabbeke M, Giurgea L, Klasa R, Marcus RE, Wolf M, Kimby E, van t Veer M, Vranovsky A, Holte H, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol. 2010;28:2853–2858. doi:10.1200/JCO.2009.26.5827.
81. Vidal L, Gafter-Gvili A, Salles G, Bousseta S, Oberman B, Rubin C, van Oers MHJ, Fortpied C, Ghielmini M, Pettengell R, et al. Rituximab maintenance improves overall survival of patients with follicular lymphoma-Individual patient data meta-analysis. Eur J Cancer. 2017;76:216–225. doi:10.1016/j.ejca.2017.01.021.
82. Keating MJ, O'Brien S, Albitar M, Lerner S, Plunkett W, Giles F, Andreeff M, Cortes J, Faderl S, Thomas D, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol. 2005;23:4079–4088. doi:10.1200/JCO.2005.12.051.
83. Schulz H, Klein SK, Rehwald U, Reiser M, Hinke A, Knauf W-U, Aulitzky W-E, Hensel M, Herold M, Huhn D, et al. Phase 2 study of a combined immunochemotherapy using rituximab and fludarabine in patients with chronic lymphocytic leukemia. Blood. 2002;100:3115–3120. doi:10.1182/blood-2002-03-0706.
84. O'Brien SM, Kantarjian H, Thomas DA, Giles FJ, Freireich EJ, Cortes J, Lerner S, Keating MJ. Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol. 2001;19:2165–2170. doi:10.1200/JCO.2001.19.10.2674.
85. Wierda W, O'Brien S, Wen S, Faderl S, Garcia-Manero G, Thomas D, Do K-A, Cortes J, Koller C, Beran M, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol. 2005;23:4070–4078. doi:10.1200/JCO.2005.12.516.
86. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, Hensel M, Hopfinger G, Hess G, von Grünhagen U, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376:1164–1174. doi:10.1016/S0140-6736(10)61381-5.
87. Fischer K, Bahlo J, Fink AM, Goede V, Herling CD, Cramer P, Langerbeins P, Tresckow von J, Engelke A, Maurer C, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016;127:208–215. doi:10.1182/blood-2015-06-651125.
88. Thompson PA, Tam CS, O'Brien SM, Wierda WG, Stingo F, Plunkett W, Smith SC, Kantarjian HM, Freireich EJ, Keating MJ. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood. 2016;127:303–309. doi:10.1182/blood-2015-09-667675.
89. Eichhorst B, Fink AM, Bahlo J, Busch R, Kovacs G, Maurer C, Lange E, Köppler H, Kiehl M, Sökler M, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016;17:928–942. doi:10.1016/S1470-2045(16)30051-1.
90. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, Chagorova T, de la Serna J, Dilhuydy M-S, Illmer T, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014;370:1101–1110. doi:10.1056/NEJMoa1313984.
91. Goede V, Fischer K, Engelke A, Schlag R, Lepretre S, Montero LFC, Montillo M, Fegan C, Asikanius E, Humphrey K, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. Leukemia. 2015 2013 28:3;29:1602–1604. doi:10.1038/leu.2014.245.
92. Robak T, Dmoszynska A, Solal-Celigny P, Warzocha K, Loscertales J, Catalano J, Afanasiev BV, Larratt L, Geisler CH, Montillo M, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2010;28:1756–1765. doi:10.1200/JCO.2009.26.4556.
93. Fischer K, Cramer P, Busch R, Stilgenbauer S, Bahlo J, Schweighofer CD, Böttcher S, Staib P, Kiehl M, Eckart MJ, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2011;29:3559–3566. doi:10.1200/JCO.2010.33.8061.
94. Hillmen P, Gribben JG, Follows GA, Milligan D, Sayala HA, Moreton P, Oscier DG, Dearden CE, Kennedy DB, Pettitt AR, et al. Rituximab plus chlorambucil as first-line treatment for chronic lymphocytic leukemia: final analysis of an open-label phase II study. J Clin Oncol. 2014;32:1236–1241. doi:10.1200/JCO.2013.54.6911.
95. Tilly H, Gomes Da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, Walewski J, André M, Johnson PW, Pfreundschuh M, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v116–25. doi:10.1093/annonc/mdv383.
96. Vose JM, Link BK, Grossbard ML, Czuczman M, Grillo-Lopez A, Gilman P, Lowe A, Kunkel LA, Fisher RI. Phase II study of rituximab in combination with chop chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2001;19:389–397. doi:10.1200/JCO.2001.19.10.2674.
97. Coiffier B, Lepage E, Brière J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, van den Neste E, Salles G, Gaulard P, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235–242. doi:10.1056/NEJMoa011795.
98. Habermann TM, Weller EA, Morrison VA, Gascoyne RD, Cassileth PA, Cohn JB, Dakhil SR, Woda B, Fisher RI, Peterson BA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol. 2006;24:3121–3127. doi:10.1200/JCO.2005.05.1003.
99. Feugier P, van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Fermé C, Christian B, Lepage E, Tilly H, Morschhauser F, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d"Etude des Lymphomes de l"Adulte. J Clin Oncol. 2005;23:4117–4126. doi:10.1200/JCO.2005.09.131.
100. Coiffier B, Thieblemont C, van den Neste E, Lepeu G, Plantier I, Castaigne S, Lefort S, Marit G, Macro M, Sebban C, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe

d"Etudes des Lymphomes de l"Adulte. Blood. 2010;116:2040–2045. doi:10.1182/blood-2010-03-276246.
101. Pfreundschuh M, Trümper L, Osterborg A, Pettengell R, Trneny M, Imrie K, Ma D, Gill D, Walewski J, Zinzani P-L, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol. 2006;7:379–391. doi:10.1016/S1470-2045(06)70664-7.
102. Pfreundschuh M, Kuhnt E, Trümper L, Osterborg A, Trneny M, Shepherd L, Gill DS, Walewski J, Pettengell R, Jaeger U, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol. 2011;12:1013–1022. doi:10.1016/S1470-2045(11)70150-4.
103. Vellenga E, van Putten WLJ, Van 't Veer MB, Zijlstra JM, Fibbe WE, van Oers MHJ, Verdonck LF, Wijermans PW, van Imhoff GW, Lugtenburg PJ, et al. Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL: a prospective randomized HOVON trial. Blood. 2008;111:537–543. doi:10.1182/blood-2007-08-108415.
104. Zelenetz AD, Hamlin P, Kewalramani T, Yahalom J, Nimer S, Moskowitz CH. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Ann Oncol. 2003;14(Suppl 1):i5–10. doi:10.1093/annonc/mdg702.
105. Kewalramani T, Zelenetz AD, Nimer SD, Portlock C, Straus D, Noy A, O'Connor O, Filippa DA, Teruya-Feldstein J, Gencarelli A, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2004;103:3684–3688. doi:10.1182/blood-2003-11-3911.
106. Corazzelli G, Frigeri F, Russo F, Frairia C, Arcamone M, Esposito G, de Chiara A, Morelli E, Capobianco G, Becchimanzi C, et al. RD-CODOX-M/IVAC with rituximab and intrathecal liposomal cytarabine in adult Burkitt lymphoma and "unclassifiable" highly aggressive B-cell lymphoma. Br J Haematol. 2012;156:234–244. doi:10.1111/j.1365-2141.2011.08947.x.
107. Rizzieri DA, Johnson JL, Byrd JC, Lozanski G, Blum KA, Powell BL, Shea TC, Nattam S, Hoke E, Cheson BD, et al. Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002. Br J Haematol. 2014;165:102–111. doi:10.1111/bjh.12736.
108. Evens AM, Carson KR, Kolesar J, Nabhan C, Helenowski I, Islam N, Jovanovic B, Barr PM, Caimi PF, Gregory SA, et al. A multicenter phase II study incorporating high-dose rituximab and liposomal doxorubicin into the CODOX-M/IVAC regimen for untreated Burkitt's lymphoma. Ann Oncol. 2013;24:3076–3081. doi:10.1093/annonc/mdt414.
109. Ribera J-M, García O, Grande C, Esteve J, Oriol A, Bergua J, González-Campos J, Vall-Llovera F, Tormo M, Hernández-Rivas J-M, et al. Dose-intensive chemotherapy including rituximab in Burkitt's leukemia or lymphoma regardless of human immunodeficiency virus infection status: final results of a phase 2 study (Burkimab). Cancer. 2013;119:1660–1668. doi:10.1002/cncr.27918.
110. Ribrag V, Koscielny S, Bosq J, Leguay T, Casasnovas O, Fornecker L-M, Recher C, Ghesquières H, Morschhauser F, Girault S, et al. Rituximab and dose-dense chemotherapy for adults with Burkitt's lymphoma: a randomised, controlled, open-label, phase 3 trial. Lancet. 2016;387:2402–2411. doi:10.1016/S0140-6736(15)01317-3.
111. Raponi S, de Propris MS, Intoppa S, Milani ML, Vitale A, Elia L, Perbellini O, Pizzolo G, Foà R, Guarini A. Flow cytometric study of potential target antigens (CD19, CD20, CD22, CD33) for antibody-based immunotherapy in acute lymphoblastic leukemia: analysis of 552 cases. Leuk Lymphoma. 2011;52:1098–1107. doi:10.3109/10428194.2010.535182.
112. Thomas DA, O'Brien S, Jorgensen JL, Cortes J, Faderl S, Garcia-Manero G, Verstovsek S, Koller C, Pierce S, Huh Y, et al. Prognostic significance of CD20 expression in adults with de novo precursor B-lineage acute lymphoblastic leukemia. Blood. 2009;113:6330–6337. doi:10.1182/blood-2008-03-146472.
113. Thomas DA, O'Brien S, Faderl S, Garcia-Manero G, Ferrajoli A, Wierda W, Ravandi F, Verstovsek S, Jorgensen JL, Bueso-Ramos C, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. J Clin Oncol. 2010;28:3880–3889. doi:10.1200/JCO.2009.26.9456.
114. Hoelzer D, Huettmann A, Kaul F, Irmer S, Jaekel N, Mohren M, Lipp T, Wedelin K, de Valle F, Schmid M, et al. Immunochemotherapy with rituximab improves molecular CR rate and outcome in CD20+ B-lineage standard and high risk patients; results of 263 CD20+ patients studied prospectively in GMALL study 07/2003. Blood. 2010;116:170.
115. Maury S, Chevret S, Thomas X, Heim D, Leguay T, Huguet F, Chevallier P, Hunault M, Boissel N, Escoffre-Barbe M, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. N Engl J Med. 2016;375:1044–1053. doi:10.1056/NEJMoa1605085.
116. Herter S, Herting F, Mundigl O, Waldhauer I, Weinzierl T, Fauti T, Muth G, Ziegler-Landesberger D, van Puijenbroek E, Lang S, 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. 2013;12:2031–2042. doi:10.1158/1535-7163.MCT-12-1016-T.
117. Mössner E, Brünker P, Moser S, Püntener U, Schmidt C, Herter S, Grau R, Gerdes C, Nopora A, van Puijenbroek E, 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. 2010;115:4393–4402. doi:10.1182/blood-2009-12-255992.
118. Patz M, Isaeva P, Forcob N, Müller B, Frenzel LP, Wendtner C-M, Klein C, Umana P, Hallek M, Krause G. Comparison of the in vitro effects of the anti-CD20 antibodies rituximab and GA101 on chronic lymphocytic leukaemia cells. Br J Haematol. 2010;152:295–306. doi:10.1111/j.1365-2141.2010.08444.x.
119. Herting F, Friess T, Bader S, Muth G, Hölzlwimmer G, Rieder N, Umana P, Klein C. Enhanced anti-tumor activity of the glycoengineered type II CD20 antibody obinutuzumab (GA101) in combination with chemotherapy in xenograft models of human lymphoma. Leuk Lymphoma. 2014;55:2151–5160. doi:10.3109/10428194.2013.856008.
120. Salles G, Morschhauser F, Lamy T, Milpied N, Thieblemont C, Tilly H, Bieska G, Asikanius E, Carlile D, Birkett J, et al. Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. Blood. 2012;119:5126–5132. doi:10.1182/blood-2011-10-388512.
121. Salles GA, Morschhauser F, Solal-Celigny P, Thieblemont C, Lamy T, Tilly H, Gyan E, Lei G, Wenger M, Wassner-Fritsch E, et al. Obinutuzumab (GA101) in patients with relapsed/refractory indolent non-hodgkin lymphoma: results from the phase II GAUGUIN study. J Clin Oncol. 2013;31:2920–2926. doi:10.1200/JCO.2013.49.0219.
122. Sehn LH, Goy A, Offner FC, Martinelli G, Caballero MD, Gadeberg O, Baetz T, Zelenetz AD, Gaidano G, Fayad LE, 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. 2015;33:3467–3474. doi:10.1200/JCO.2014.59.2139.
123. Cartron G, Hourcade-Potelleret F, Morschhauser F, Salles G, Wenger M, Truppel-Hartmann A, Carlile DJ. Rationale for optimal obinutuzumab/GA101 dosing regimen in B-cell non-Hodgkin lymphoma. Haematologica. 2016;101:226–234. doi:10.3324/haematol.2016.143271.
124. Gibiansky E, Gibiansky L, Carlile DJ, Jamois C, Buchheit V, Frey N. Population Pharmacokinetics of Obinutuzumab (GA101) in

Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin's Lymphoma and Exposure–response in CLL. CPT. 3;2014:e144–11.
125. Radford J, Davies A, Cartron G, Morschhauser F, Salles G, Marcus R, Wenger M, Lei G, Wassner-Fritsch E, Vitolo U. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). Blood. 2013;122:1137–1143. doi:10.1182/blood-2012-12-471029.
126. Grigg A, Dyer MJS, Díaz MG, Dreyling M, Rule S, Lei G, Knapp A, Wassner-Fritsch E, Marlton P. Safety and efficacy of obinutuzumab with CHOP or bendamustine in previously untreated follicular lymphoma. Haematologica. 2017;102:765–772. doi:10.3324/haematol.2016.158808.
127. Sehn LH, Chua N, Mayer J, Dueck G, Trneny M, Bouabdallah K, Fowler N, Delwail V, Press O, Salles G, 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 3 trial. Lancet Oncol. 2016;17:1081–1093. doi:10.1016/S1470-2045(16)30097-3.
128. Cheson BD, Chua N, Mayer J, Dueck G, Trneny M, Bouabdallah K, Fowler N, Delwail V, Press O, Salles G, 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. 2018;JCO.2017.76:365–410.
129. Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C, Phillips E, Sangha R, Schlag R, Seymour JF, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med. 2017;377:1331–1344. doi:10.1056/NEJMoa1614598.
130. Cartron G, de Guibert S, Dilhuydy M-S, Morschhauser F, Leblond V, Dupuis J, Mahe B, Bouabdallah R, Lei G, Wenger M, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. Blood. 2014;124:2196–2202. doi:10.1182/blood-2014-07-586610.
131. Brown JR, O'Brien S, Kingsley CD, Eradat H, Pagel JM, Lymp J, Hirata J, Kipps TJ. Obinutuzumab plus fludarabine/cyclophosphamide or bendamustine in the initial therapy of CLL patients: the phase 1b GALTON trial. Blood. 2015;125:2779–2785. doi:10.1182/blood-2014-07-591040.
132. Goede V, Fischer K, Busch R, Jaeger U, Dilhuydy M-S, Wickham N, de Guibert S, Ritgen M, Langerak AW, Bieska G, et al. Chemoimmunotherapy with GA101 plus chlorambucil in patients with chronic lymphocytic leukemia and comorbidity: results of the CLL11 (BO21004) safety run-in. Leukemia. 2013 2013 28:3;27:1172–1174. doi:10.1038/leu.2012.252.
133. Golay J, Da Roit F, Bologna L, Ferrara C, Leusen JH, Rambaldi A, Klein C, Introna M. Glycoengineered CD20 antibody obinutuzumab activates neutrophils and mediates phagocytosis through CD16B more efficiently than rituximab. Blood. 2013;122:3482–3491. doi:10.1182/blood-2012-12-471029.
134. Goede V, Fischer K, Dyer MJS, Muller L, Smolej L, Di Bernado MC, Knapp A, Nielsen T, Hallek M. 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. Stockholm. 2018.
135. Freeman CL, Morschhauser F, Sehn L, Dixon M, Houghton R, Lamy T, Fingerle-Rowson G, Wassner-Fritsch E, Gribben JG, Hallek M, et al. Cytokine release in patients with CLL treated with obinutuzumab and possible relationship with infusion-related reactions. Blood. 2015;126:2646–2649. doi:10.1182/blood-2015-09-670802.
136. Freeman CL, Dixon M, Houghton R, Kreuzer K-A, Fingerle-Rowson G, Herling M, Humphrey K, Böttcher S, de Costa CS, Iglesias V, et al. Role of CD20 expression and other pre-treatment risk factors in the development of infusion-related reactions in patients with CLL treated with obinutuzumab. Leukemia. 2016 2013 28:3;30:1763–1766. doi:10.1038/leu.2016.124.
137. Bosch F, Illmer T, Turgut M, Cortelezzi A, Lasserre SF, Truppel-Hartmann A, Leblond V, Foà R, Stilgenbauer S. Preliminary safety results from the phase IIIb GREEN study of obinutuzumab (GA101) alone or in combination with chemotherapy for previously untreated or relapsed/refractory Chronic Lymphocytic Leukemia (CLL). Blood. 124;2014:3345.
138. Stilgenbauer S, Leblond V, Foà R, Böttcher S, Ilhan O, Knauf W, Mikuskova E, Renner C, Tausch E, Woszczyk D, et al. Obinutuzumab plus bendamustine in previously untreated patients with CLL: a subgroup analysis of the GREEN study. Leukemia. 2013 28:3 2018;26:15.
139. Fischer K, Al-Sawaf O, Fink AM, Dixon M, Bahlo J, Warburton S, Kipps TJ, Weinkove R, Robinson S, Seiler T, et al. Venetoclax and obinutuzumab in chronic lymphocytic leukemia. Blood. 2017;129:2702–2705. doi:10.1182/blood-2017-01-761973.
140. Cramer P, Tresckow von J, Bahlo J, Engelke A, Langerbeins P, Fink AM, Fischer K, Wendtner C-M, Kreuzer K-A, Stilgenbauer S, et al. CLL2-BXX Phase II trials: sequential, targeted treatment for eradication of minimal residual disease in chronic lymphocytic leukemia. Fut Oncol. 2018;14:499–513. doi:10.2217/fon-2017-0442.
141. Morschhauser FA, Cartron G, Thieblemont C, Solal-Celigny P, Haioun C, Bouabdallah R, Feugier P, Bouabdallah K, Asikanius E, Lei G, 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. 2013;31:2912–2919. doi:10.1200/JCO.2013.49.0219.
142. Mobasher M, Costa LJ, Flinn I, Flowers CR, Kaminski MS, Sandmann T, Trunzer K, Vignal C, Forero-Torres A. Safety and efficacy of obinutuzumab (GA101) plus CHOP chemotherapy in first-line advanced diffuse large B-cell lymphoma: results from the phase 2 gather study (GAO4915g). Blood. 2013;122:1820. doi:10.1182/blood-2012-12-471029.
143. Vitolo U, Trneny M, Belada D, Burke JM, Carella AM, Chua N, Abrisqueta P, Demeter J, Flinn I, Hong X, et al. Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. J Clin Oncol. 2017;35:3529–3537. doi:10.1200/JCO.2017.73.3402.
144. Teeling JL, French RR, Cragg MS, van den Brakel J, Pluyter M, Huang H, Chan C, Parren PWHI, Hack CE, Dechant M, et al. Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. Blood. 2004;104:1793–1800. doi:10.1182/blood-2003-11-3979.
145. Bologna L, Gotti E, Da Roit F, Intermesoli T, Rambaldi A, Introna M, Golay J. Ofatumumab is more efficient than rituximab in lysing B chronic lymphocytic leukemia cells in whole blood and in combination with chemotherapy. J Immunol. 2013;190:231–239. doi:10.4049/jimmunol.1202645.
146. Li B, Shi S, Qian W, Zhao L, Zhang D, Hou S, Zheng L, Dai J, Zhao J, Wang H, et al. Development of novel tetravalent anti-CD20 antibodies with potent antitumor activity. Cancer Res. 2008;68:2400–2408. doi:10.1158/0008-5472.CAN-07-6663.
147. Craigen JL, Mackus WJM, Engleberts P, Miller SR, Speller S, Chamberlain LC, Davis BG, McHugh SM, Bullmore E, Cox CJ, et al. Ofatumumab, a human mab targeting a membrane-proximal small-loop epitope on CD20, induces potent NK cell-mediated ADCC. Blood. 2009;114:1725–1735. doi:10.1182/blood-2009-04-215525.
148. Cillessen SAGM, Mackus WJM, Castricum KCM, Vos W, Kortman PC, van de Winkel JGJ, Parren PWHI, Meijer CJLM, Oudejans JJ. Intr. by Ole Baadsgaard. Chemotherapy-refractory Diffuse Large B-Cell Lymphomas (DLBCL) are effectively killed by Ofatumumab-induced complement-mediated cytoxicity. Blood. 110;2007:2346–2356.
149. Hagenbeek A, Gadeberg O, Johnson P, Pedersen LM, Walewski J, Hellmann A, Link BK, Robak T, Wojtukiewicz M, Pfreundschuh M, et al. First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. Blood. 2008;111:5486–5495. doi:10.1182/blood-2007-10-117671.
150. Czuczman MS, Fayad L, Delwail V, Cartron G, Jacobsen E, Kuliczkowski K, Link BK, Pinter-Brown L, Radford J, Hellmann A, et al. Ofatumumab monotherapy in rituximab-refractory

follicular lymphoma: results from a multicenter study. Blood. 2012;119:3698–3704. doi:10.1182/blood-2011-10-388512.
151. Czuczman MS, Hess G, Gadeberg OV, Pedersen LM, Goldstein N, Gupta I, Jewell RC, Lin TS, Lisby S, Strange C, et al. Chemoimmunotherapy with ofatumumab in combination with CHOP in previously untreated follicular lymphoma. Br J Haematol. 2012;157:438–445. doi:10.1111/j.1365-2141.2012.09086.x.
152. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, Grünhagen von U, Losem C, Kofahl-Krause D, Heil G, Welslau M, Balser C, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381:1203–1210. doi:10.1016/S0140-6736(12)61763-2.
153. Coiffier B, Lepretre S, Pedersen LM, Gadeberg O, Fredriksen H, van Oers MHJ, Wooldridge J, Kloczko J, Holowiecki J, Hellmann A, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood. 2008;111:1094–1100. doi:10.1182/blood-2007-09-111781.
154. Wierda WG, Kipps TJ, Mayer J, Stilgenbauer S, Williams CD, Hellmann A, Robak T, Furman RR, Hillmen P, Trneny M, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol. 2010;28:1749–1755. doi:10.1200/JCO.2009.25.3187.
155. Laurenti L, Innocenti I, Autore F, Sica S, Efremov D. New developments in the management of chronic lymphocytic leukemia: role of ofatumumab. OTT. 2016:421–429. doi:10.2147/OTT.
156. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371:213–223. doi:10.1056/NEJMoa1410490.
157. Cortelezzi A, Sciumè M, Liberati AM, Vincenti D, Cuneo A, Reda G, Laurenti L, Zaja F, Marasca R, Chiarenza A, et al. Bendamustine in combination with Ofatumumab in relapsed or refractory chronic lymphocytic leukemia: a GIMEMA multicenter phase II trial. Leukemia. 2014 2013 28:3;28:642–648. doi:10.1038/leu.2014.105.
158. Robak T, Warzocha K, Govind Babu K, Kulyaba Y, Kuliczkowski K, Abdulkadyrov K, Loscertales J, Kryachok I, Kłoczko J, Rekhtman G, et al. Ofatumumab plus fludarabine and cyclophosphamide in relapsed chronic lymphocytic leukemia: results from the COMPLEMENT 2 trial. Leuk Lymphoma. 2017;58:1084–1093. doi:10.1080/10428194.2016.1233536.
159. Costa LJ, Fanning SR, Stephenson J, Afrin LB, Kistner-Griffin E, Bentz TA, Stuart RK. Sequential ofatumumab and lenalidomide for the treatment of relapsed and refractory chronic lymphocytic leukemia and small lymphocytic lymphoma. Leuk Lymphoma. 2015;56:645–649. doi:10.3109/10428194.2014.905773.
160. Jaglowski SM, Jones JA, Nagar V, Flynn JM, Andritsos LA, Maddocks KJ, Woyach JA, Blum KA, Grever MR, Smucker K, et al. Safety and activity of BTK inhibitor ibrutinib combined with ofatumumab in chronic lymphocytic leukemia: a phase 1b/2 study. Blood. 2015;126:842–850. doi:10.1182/blood-2014-12-617522.
161. Jones JA, Robak T, Brown JR, Awan FT, Badoux X, Coutre S, Loscertales J, Taylor K, Vandenberghe E, Wach M, et al. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. Lancet Haematol. 2017;4:e114–26. doi:10.1016/S2352-3026(17)30019-4.
162. Flinn IW, Ruppert AS, Harwin W, Waterhouse D, Papish S, Jones JA, Hainsworth J, Byrd JC. A phase II study of two dose levels of ofatumumab induction followed by maintenance therapy in symptomatic, previously untreated chronic lymphocytic leukemia. Am J Hematol. 2016;91:1020–1025. doi:10.1002/ajh.v91.10.
163. Wierda WG, Kipps TJ, Dürig J, Griskevicius L, Stilgenbauer S, Mayer J, Smolej L, Hess G, Griniute R, Hernandez-Ilizaliturri FJ, et al. Chemoimmunotherapy with O-FC in previously untreated patients with chronic lymphocytic leukemia. Blood. 2011;117:6450–6458. doi:10.1182/blood-2010-12-323980.
164. Hillmen P, Robak T, Janssens A, Babu KG, Kloczko J, Grosicki S, Doubek M, Panagiotidis P, Kimby E, Schuh A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. Lancet. 2015;385:1873–1883. doi:10.1016/S0140-6736(15)60027-7.
165. van Oers MHJ, Kuliczkowski K, Smolej L, Petrini M, Offner F, Grosicki S, Levin M-D, Gupta I, Phillips J, Williams V, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. Lancet Oncol. 2015;16:1370–1379. doi:10.1016/S1470-2045(15)00143-6.
166. Coiffier B, Radford J, Bosly A, Martinelli G, Verhoef G, Barca G, Davies A, Decaudin D, Gallop-Evans E, Padmanabhan-Iyer S, et al. A multicentre, phase II trial of ofatumumab monotherapy in relapsed/progressive diffuse large B-cell lymphoma. Br J Haematol. 2013;163:334–342. doi:10.1111/bjh.12537.
167. Matasar MJ, Czuczman MS, Rodriguez MA, Fennessy M, Shea TC, Spitzer G, Lossos IS, Kharfan-Dabaja MA, Joyce R, Fayad L, et al. Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. Blood. 2013;122:499–506. doi:10.1182/blood-2012-12-471029.
168. Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, Bosly A, Ketterer N, Shpilberg O, Hagberg H, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28:4184–4190. doi:10.1200/JCO.2010.28.1618.
169. van Imhoff GW, McMillan A, Matasar MJ, Radford J, Ardeshna KM, Kuliczkowski K, Kim W, Hong X, Goerloev JS, Davies A, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: the ORCHARRD study. J Clin Oncol. 2017;35:544–551. doi:10.1200/JCO.2016.69.0198.
170. Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. Lancet. 2010;376:1094–1108. doi:10.1016/S0140-6736(10)60826-4.
171. Bugatti S, Codullo V, Caporali R, Montecucco C. B cells in rheumatoid arthritis. Autoimmun Rev. 2007;7:137–142. doi:10.1016/j.autrev.2007.02.017.
172. Edwards JCW, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM, Shaw T. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350:2572–2581. doi:10.1056/NEJMoa032534.
173. Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ, Latinis K, Abud-Mendoza C, Szczepanski LJ, Roschmann RA, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis. 2010;69:1629–1635.
174. Rubbert-Roth A, Tak PP, Zerbini C, Tremblay J-L, Carreño L, Armstrong G, Collinson N, Shaw TM. MIRROR trial investigators. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a phase III randomized study (MIRROR). Rheumatology (Oxford). 2010;49:1683–1693. doi:10.1093/rheumatology/keq116.
175. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, Keystone EC, Loveless JE, Burmester G-R, Cravets MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54:2793–2806. doi:10.1002/art.22025.
176. Haraoui B, Bokarewa M, Kallmeyer I, Bykerk VP. RESET investigators. Safety and effectiveness of rituximab in patients with rheumatoid arthritis following an inadequate response to 1 prior

tumor necrosis factor inhibitor: the RESET trial. J Rheumatol. 2011;38:2548–2556. doi:10.3899/jrheum.100724.
177. Cohen SB, Keystone E, Genovese MC, Emery P, Peterfy C, Tak PP, Cravets M, Shaw T, Hagerty D. Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate. Ann Rheum Dis. 2010;69:1158–1161. doi:10.1136/ard.2009.119222.
178. Tak PP, Rigby WF, Rubbert-Roth A, Peterfy CG, van Vollenhoven RF, Stohl W, Hessey E, Chen A, Tyrrell H, Shaw TM, et al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. Ann Rheum Dis. 2011;70:39–46. doi:10.1136/ard.2010.139832.
179. Chatzidionysiou K, Lie E, Nasonov E, Lukina G, Hetland ML, Tarp U, van Riel PLCM, Nordström DC, Gomez-Reino J, Pavelka K, et al. Effectiveness of disease-modifying antirheumatic drug co-therapy with methotrexate and leflunomide in rituximab-treated rheumatoid arthritis patients: results of a 1-year follow-up study from the CERERRA collaboration. Ann Rheum Dis. 2012;71:374–377. doi:10.1136/annrheumdis-2011-200003.
180. Ramiro S, Sepriano A, Chatzidionysiou K, Nam JL, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, Bijlsma JW, Burmester GR, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2017;76:1101–1136. doi:10.1136/annrheumdis-2016-210708.
181. Talar-Williams C, Hijazi YM, Walther MM, Linehan WM, Hallahan CW, Lubensky I, Kerr GS, Hoffman GS, Fauci AS, Sneller MC. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. Ann Intern Med. 1996;124:477–484. doi:10.7326/0003-4819-124-5-199603010-00003.
182. Huong DLT, Amoura Z, Duhaut P, Sbai A, Costedoat N, Wechsler B, Piette J-C. Risk of ovarian failure and fertility after intravenous cyclophosphamide. A study in 84 patients. J Rheumatol. 29;2002:2571–2576.
183. Popa ER, Stegeman CA, Bos NA, Kallenberg CG, Tervaert JW, Differential B. T-cell activation in Wegener's granulomatosis. J Allergy Clin Immunol. 1999;103:885–894. doi:10.1016/S0091-6749(99)70434-3.
184. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CGM, St Clair EW, Turkiewicz A, Tchao NK, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221–232. doi:10.1056/NEJMoa1011205.
185. Stevenson HC, Fauci AS. Activation of human B lymphocytes. XII. Differential effects of in vitro cyclophosphamide on human lymphocyte subpopulations involved in B-cell activation. Immunology. 39;1980:391–397.
186. Cupps TR, Edgar LC, Fauci AS. Suppression of human B lymphocyte function by cyclophosphamide. J Immunol. 128;1982:2453–2457.
187. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O, Cohen P, Maurier F, Decaux O, Ninet J, Gobert P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371:1771–1780. doi:10.1056/NEJMoa1410490.
188. Bengtsson AA, Rönnblom L. Systemic lupus erythematosus: still a challenge for physicians. J Intern Med. 2017;281:52–64. doi:10.1111/joim.12529.
189. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, Maciuca R, Zhang D, Garg JP, Brunetta P, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study. Arthritis Rheum. 2012;64:1215–1226. doi:10.1002/art.34359.
190. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, Utset TO, Gordon C, Isenberg DA, Hsieh H-J, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum. 2010;62:222–233. doi:10.1002/art.27631.
191. Iwata S, Saito K, Hirata S, Ohkubo N, Nakayamada S, Nakano K, Hanami K, Kubo S, Miyagawa I, Yoshikawa M, et al. Efficacy and safety of anti-CD20 antibody rituximab for patients with refractory systemic lupus erythematosus. Lupus. 2018;27:802–811. doi:10.1177/0961203317749047.
192. Ghanima W, Khelif A, Waage A, Michel M, Tjønnfjord GE, Romdhan NB, Kahrs J, Darne B, Holme PA. RITP study group. Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2015;385:1653–1661. doi:10.1016/S0140-6736(14)61495-1.
193. Tran H, Brighton T, Grigg A, McRae S, Dixon J, Thurley D, Gandhi MK, Truman M, Marlton P, Catalano J. A multi-centre, single-arm, open-label study evaluating the safety and efficacy of fixed dose rituximab in patients with refractory, relapsed or chronic idiopathic thrombocytopenic purpura (R-ITP1000 study). Br J Haematol. 2014;167:243–251. doi:10.1111/bjh.2014.167.issue-2.
194. Erkan D, Aguiar CL, Andrade D, Cohen H, Cuadrado MJ, Danowski A, Levy RA, Ortel TL, Rahman A, Salmon JE, et al. 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. Autoimmun Rev. 2014;13:685–696. doi:10.1016/j.autrev.2014.01.053.
195. Wang -H-H, Liu C-W, Li Y-C, Huang Y-C. Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. Acta Derm Venereol. 2015;95:928–932. doi:10.2340/00015555-2116.
196. Le Roux-Villet C, Prost-Squarcioni C, Alexandre M, Caux F, Pascal F, Doan S, Brette M-D, Soued I, Gabison É, Aucouturier F, et al. Rituximab for patients with refractory mucous membrane pemphigoid. Arch Dermatol. 2011;147:843–849. doi:10.1001/archdermatol.2010.303.
197. Iorio R, Damato V, Alboini PE, Evoli A. Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis. J Neurol. 2015;262:1115–1119. doi:10.1007/s00415-015-7653-3.
198. Collongues N, Brassat D, Maillart E, Labauge P, Ouallet JC, Carra-Dalliere C, Moreau T, Bourre B, Papeix C, Brochet B, et al. Efficacy of rituximab in refractory neuromyelitis optica. Mult Scler. 2016;22:955–959. doi:10.1177/1352458515602337.
199. Fasano S, Gordon P, Hajji R, Loyo E, Isenberg DA. Rituximab in the treatment of inflammatory myopathies: a review. Rheumatology (Oxford). 2017;56:26–36. doi:10.1093/rheumatology/kew146.
200. Franchini M. Rituximab in the treatment of adult acquired hemophilia A: a systematic review. Crit Rev Oncol Hematol. 2007;63:47–52. doi:10.1016/j.critrevonc.2006.11.004.
201. Boles JC, Key NS, Kasthuri R, Ma AD. Single-center experience with rituximab as first-line immunosuppression for acquired hemophilia. J Thromb Haemost. 2011;9:1429–1431. doi:10.1111/j.1538-7836.2011.04345.x.
202. Birgens H, Frederiksen H, Hasselbalch HC, Rasmussen IH, Nielsen OJ, Kjeldsen L, Larsen H, Mourits-Andersen T, Plesner T, Rønnov-Jessen D, et al. A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia. Br J Haematol. 2013;163:393–399. doi:10.1111/bjh.12541.
203. Laribi K, Bolle D, Ghnaya H, Sandu A, Besançon A, Denizon N, Truong C, Pineau-Vincent F, de Materre AB. Rituximab is an effective and safe treatment of relapse in elderly patients with resistant warm AIHA. Ann Hematol. 2016;95:765–769. doi:10.1007/s00277-016-2605-2.
204. Rodrigo C, Rajapakse S, Gooneratne L. Rituximab in the treatment of autoimmune haemolytic anaemia. Br J Clin Pharmacol. 2015;79:709–719. doi:10.1111/bcp.12498.
205. Westwood J-P, Thomas M, Alwan F, McDonald V, Benjamin S, Lester WA, Lowe GC, Dutt T, Hill QA, Scully M.

Rituximab prophylaxis to prevent thrombotic thrombocytopenic purpura relapse: outcome and evaluation of dosing regimens. Blood Adv. 2017;1:1159–1166. doi:10.1182/bloodadvances.2017008268.
206. Scully M, McDonald V, Cavenagh J, Hunt BJ, Longair I, Cohen H, Machin SJ. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood. 2011;118:1746–1753. doi:10.1182/blood-2011-02-334870.
207. Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Rituximab reduces risk for relapse in patients with thrombotic thrombocytopenic purpura. Blood. 2016;127:3092–3094. doi:10.1182/blood-2016-03-703827.
208. Du FH, Mills EA, Mao-Draayer Y. Next-generation anti-CD20 monoclonal antibodies in autoimmune disease treatment. Autoimmun Highlights. 2017;8:1–12. doi:10.1007/s13317-017-0100-y.
209. Hwang WYK, Foote J. Immunogenicity of engineered antibodies. Methods. 2005;36:3–10. doi:10.1016/j.ymeth.2005.01.001.
210. van Brummelen EMJ, Ros W, Wolbink G, Beijnen JH, Schellens JHM. Antidrug antibody formation in oncology: clinical relevance and challenges. Oncologist. 2016;21:1260–1268. doi:10.1634/theoncologist.2015-0336.
211. Dunn N, Juto A, Ryner M, Manouchehrinia A, Piccoli L, Fink K, Piehl F, Fogdell-Hahn A. Rituximab in multiple sclerosis: frequency and clinical relevance of anti-drug antibodies. Mult Scler. 90;2017:1352458517720044.
212. Rioufol C, Salles G. Biosimilar monoclonal antibodies in lymphoma: a critical appraisal. Expert Rev Anticancer Ther. 2015;15:569–578. doi:10.1586/14737140.2015.1028919.