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Role of Rituximab and Rituximab Biosimilars in Diffuse Large B-Cell Lymphoma

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Abstract

Diffuse large B-cell lymphoma (DLBCL), an aggressive non–Hodgkin lymphoma (NHL), is the most-common subtype of NHL. DLBCL can be classified into at least 3 major immunologically distinct types, which contributes to considerable variation in disease prognosis and response to treatment. DLBCL potentially is curable, even when diagnosed at advanced stages. The current standard of care for most patients with untreated or relapsed/refractory DLBCL is chemoimmunotherapy containing rituximab, an anti-CD20 monoclonal antibody. With advanced understanding of the molecular mechanisms involved in the pathogenesis of DLBCL and specific signaling pathways that are activated in different subtypes, potential new therapeutic targets have been identified, some of which are at the late stages of clinical development. This review summarizes the critical role of rituximab in the current standard of care treatment for DLBCL and discusses why rituximab is likely to remain an important component of treatment options for DLBCL in the foreseeable future. In addition, current and emerging therapeutic agents, including potential benefits of rituximab biosimilars, for patients with DLBCL are discussed. The advent of rituximab biosimilars may facilitate accessibility of rituximab-based chemotherapies to patients with DLBCL and has potential cost-saving benefits for healthcare systems globally.

Keywords

Anti-CD20 monoclonal antibody; Chemoimmunotherapy; DLBCL; Non–Hodgkin lymphoma; R-CHOP

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Introduction

Non–Hodgkin lymphoma (NHL) is the seventh most common cancer in the United States, with an estimated 71,850 new cases and 19,790 deaths occurring in 2015.[1] Worldwide, NHL will be diagnosed in approximately 414,772 individuals and be responsible for an estimated 215,074 deaths.[2] NHL is slightly more prevalent in men than in women, and the probability of developing NHL increases with age, from 0.3% and 0.2% in men and women, respectively, at age less than 49 years to 1.8% and 1.4%, respectively, at age 70 years and older.[1] The most common histologic subtype of NHL is diffuse large B-cell lymphoma (DLBCL),[3–5] which is an aggressive, fast-growing lymphoma, unlike indolent subtypes such as follicular, marginal zone, and small lymphocytic lymphomas. DLBCL is morphologically, genetically, and clinically heterogeneous, but on the basis of gene expression profiling and immunohistochemical analysis, DLBCL can be classified into at least 3 major immunologically distinct types—germinal center B-cell, activated B-cell, and primary mediastinal B-cell—that contribute to considerable variation in disease prognosis and response to treatment.[6,7]

DLBCL potentially is curable, particularly when diagnosed at an early stage. This NHL subtype is chemosensitive, and combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been the well-established standard treatment since the 1970s. The introduction of rituximab, an anti-CD20 monoclonal antibody, in combination with chemotherapy regimens, has drastically improved disease outcomes, changing the therapeutic landscape for DLBCL.[8–10] According to the Surveillance, Epidemiology, and End Results analysis of the data between 2004 and 2010, the 5-year relative survival by stage at diagnosis is estimated at 81.6% for the localized disease compared with 61.6% for the distant disease.

Rituximab is a chimeric type I monoclonal antibody directed to CD20, which is present predominantly on the surface of normal B cells and in most lymphomas. Although the exact mechanisms of action of rituximab are unclear, they likely include complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity, and direct induction of apoptosis.[11–13] Rituximab (Rituxan, Genentech, South San Francisco, CA)[14] was first approved by the US Food and Drug Administration (FDA) for treatment of relapsed or refractory low-grade or follicular lymphoma (FL) NHL in 1997 and licensed as MabThera (Roche, Basel, Switzerland)[15] in 1998 by the European Medicines Agency (EMA). In 2006, after demonstration of improved efficacy outcomes associated with the combination treatment in clinical trials, the FDA granted approval of rituximab in combination with CHOP or other anthracycline-based chemotherapy for first-line treatment of DLBCL.[16] Although there are patients with DLBCL who are refractory to or relapse after rituximab-based chemoimmunotherapy, most patients benefit from treatment. Indeed, it is also considered the standard of care to combine rituximab with second or subsequent lines of chemotherapies for relapsed/refractory CD20+ DLBCL.

This review summarizes the critical role of rituximab in the current treatment of DLBCL and discusses why rituximab is likely to remain an important component of treatment options for DLBCL in the foreseeable future.

Discussion

Development of Rituximab Chemoimmunotherapy in DLBCL

The clinical benefit of adding rituximab to the chemotherapy regimen versus chemotherapy alone was demonstrated in several pivotal clinical trials. The randomized phase III trial conducted by the Group d'Etude des Lymphomes de l'Adulte in elderly (aged 60–80 years) patients with previously untreated DLBCL showed a significantly higher complete response rate (76% vs. 63%; $P = .005$) and longer event-free (not reached vs. 13 months; $P < .001$) and overall ($P = .007$) survival with, respectively, rituximab plus CHOP (R-CHOP) versus CHOP alone.[17] In an open-label, randomized phase III trial in patients aged ≥ 60 years with untreated DLBCL in the United States, R-CHOP resulted in a substantially improved 3-year failure-free survival versus CHOP alone (53% vs. 46%, $P = .04$).[18] The combination of rituximab and CHOP-like chemotherapy was further evaluated in the MabThera International Trial in a population of younger (aged 18–60 years), treatment-naïve patients who had a more favorable prognosis of DLBCL.[19] The results confirmed the superiority of rituximab plus CHOP-like chemotherapy versus chemotherapy alone in younger patients, with higher 3-year event-free (79% vs. 59%; $P < .0001$) and overall (93% vs. 84%; $P = .0001$) survival rates. The addition of rituximab to chemotherapy was generally well tolerated and did not lead to any significant increases in clinically relevant toxicities, such as infection, or raise new safety concerns.[17–19] Rituximab-related infusion reactions were reported, but usually resolved after slowing or stopping the infusion. The follow-up reports from these trials indicated that the beneficial effects of R-CHOP over CHOP-like chemotherapy alone in DLBCL, respectively, were sustained over a longer term in older patients (eg, median event-free survival: 3.8 vs. 1.1 years; $P = .00002$[20] or 10-year progression-free survival: 36.5% vs. 20.1%[21]) and in younger patients (6-year event-free survival: 74.3% vs. 55.8%; $P < .0001$[22]).

Standard CHOP chemotherapy is administered every 3 weeks, that is, 21 days (CHOP21). When compared with CHOP21 plus rituximab (R-CHOP21), the dose-dense R-CHOP regimen administered every 2 weeks (R-CHOP14) did not increase the 2-year overall survival rate (82.7% vs. 80.8% for R-CHOP21, $P = .3763$) or progression-free survival rate (75.4% vs. 74.8% for R-CHOP21; $P = .5907$) in patients of all ages with untreated DLBCL, leading to the conclusion that R-CHOP21 should remain the standard regimen.[23] Similar results were reported in another randomized phase III trial of R-CHOP21 versus R-CHOP14 in older patients (aged 60–80 years).[24] In the MabThera International Trial, adding etoposide to CHOP was found to achieve a significantly higher 3-year event-free survival than CHOP alone, but the difference was nullified in the presence of rituximab.[19] Other regimens, such as a dose-intensive chemotherapy consisting of doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone combined with rituximab or a dose-adjusted infusional CHOP plus etoposide in combination with rituximab demonstrated efficacy in previously untreated younger patients with DLBCL.[25,26] In a randomized phase III trial in elderly patients (median age, 83 years; range, 80–95) with untreated DLBCL, a reduced dose of CHOP with rituximab (R-miniCHOP) was efficacious and safe.[27] Salvage regimens consisting of rituximab with various combinations of chemotherapeutic agents (eg, ifosfamide, etoposide, and platinum, infusional ifosfamide, etoposide, and platinum plus dexamethasone [DICE],

and bortezomib [a proteasome inhibitor] or dexamethasone, cytarabine, and cisplatin [DHAP]) showed some efficacy in patients with relapsed or refractory DLBCL.[28,29]

The subcutaneous formulation of rituximab (MabThera) was approved by the European Commission for FL (with chemotherapy for treatment-naïve or relapsed/refractory FL or as maintenance therapy in patients who respond to induction therapy) and CD20+ DLBCL (in combination with CHOP) in 2014, on the basis of noninferiority of the pharmacokinetic profile and lack of safety concerns with subcutaneous compared with intravenous rituximab.[30] Safety of switching rituximab from intravenous (375 mg/m^2) to subcutaneous (1400 mg) administration during first-line treatment is being evaluated in patients with DLBCL or FL in a single-arm, open-label phase IIIb trial (NCT01987505), as well as in combination with chemotherapy in a randomized, phase IIIb trial (NCT01649856).

Current Recommended Treatment Options for DLBCL

The treatment strategy for DLBCL depends on the clinical stage, age, and prognosis of patients. Staging is established using the Ann Arbor staging system (I to IV). Prognostic assessments at initial diagnosis commonly are based on the International Prognostic Index (IPI) and age-adjusted IPI,[31] which were developed in the pre-rituximab era, or its adaptation, National Comprehensive Cancer Network (NCCN)-IPI,[32] which was formulated with the database in the rituximab era. The classification for various risk groups according to each of these indices is shown in Table 1.

The guidelines on recommended treatment options for DLBCL from NCCN[7] and the European Society for Medical Oncology[33,34] are summarized in Table 2. In both of these guidelines, chemoimmunotherapy consisting of rituximab plus CHOP or similar chemotherapeutic agents is a recommended treatment option for first-line and relapsed/refractory DLBCL that remains CD20+. Maintenance therapy with rituximab after R-CHOP currently is not recommended by either guideline because of the seemingly lack of evidence for additional benefit.[18,35] There are some minor differences that exist between the 2 guidelines, including the use of involved field radiotherapy in patients at low risk and the use of [^{18}F] deoxyglucose positron emission tomography scan for interim staging.

Although the majority of patients benefit from rituximab-based chemoimmunotherapy, there is a medical need for more effective therapy for relapsed/refractory DLBCL and for patients at high risk, including those with “double hit” (*MYC* and *BCL2* or *MYC* and *BCL6* rearrangements) and “triple hit” (*MYC*, *BLC2*, and *BCL6* translocation) disease.[36]

New Therapeutic Agents in the Late Stages of Clinical Development for DLBCL

Gene-expression profiling facilitated understanding of molecular mechanisms involved in the pathogenesis of DLBCL and specific signaling pathways that are activated in different subtypes, leading to identification of scores of potential new therapeutic targets.[37–42] After the success of rituximab in treatment of DLBCL and other NHL subtypes, several emerging monoclonal antibodies targeting CD20 and other B-cell–specific surface markers, such as CD19 and CD22,[40,41,43,44] have been developed. In the current article, we focus on the new anti-CD20 antibodies that are in the late stages of clinical development for treatment of DLBCL.

Obinutuzumab (GA101, RO5072759) is a humanized, type II anti-CD20 monoclonal antibody with reputedly higher direct and immune effector-mediated cell death compared with rituximab.[45] Obinutuzumab was initially approved, in combination with chlorambucil, for the treatment of patients with treatment-naïve chronic lymphocytic leukemia (CLL) in 2013 in the United States (as Gazyva) and in 2014 in the European Union (as Gazyvaro). In an open-label, single-arm phase II trial, obinutuzumab plus CHOP resulted in an objective response rate of 83%, including a 55% complete response, and with no new specific safety concerns, in patients with previously untreated DLBCL.[46] Head-to-head comparisons between obinutuzumab and rituximab, in combination with CHOP or doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone, for untreated DLBCL are currently ongoing in an open-label, randomized phase III trial (NCT01287741; GOYA) or at the stage of recruiting younger patients (aged ≤ 60 years) in another randomized phase III trial (NCT01659099; GAINED). The efficacy of obinutuzumab plus DHAP is being investigated in relapsed or refractory DLBCL in an open-label, single-arm phase II trial (NCT02374424; GIOTTO).

Ofatumumab is a human type I anti-CD20 monoclonal antibody, with higher complement-mediated cytotoxicity than rituximab.[47] Marketed as Arzerra, it was first approved as second-line treatment for CLL in the United States in 2009 and the European Union in 2010, and in 2014 it was approved in combination with chlorambucil for treatment of patients with CLL not suitable for fludarabine-based chemotherapy. On the basis of the promising results of a phase II trial,[48] a randomized phase III trial was conducted to compare ofatumumab with rituximab in combination with salvage DHAP chemotherapy in refractory or relapsed DLBCL; however, the study did not meet the primary end point of prolonged progression-free survival, and no major differences were observed in secondary efficacy end points or clinically relevant toxicities.[49] In some phase II trials, ofatumumab monotherapy showed clinical benefits and tolerability in patients with relapsed or refractory DLBCL,[50] and, in combination with a reduced dose of CHOP, ofatumumab appeared efficacious and safe in patients aged > 80 years who had untreated DLBCL.[51] A small phase II trial is evaluating ofatumumab combined with bendamustine in elderly patients with newly diagnosed DLBCL (NCT01626352).

Role of Rituximab Biosimilars in Future Treatment of DLBCL

A wide variety of monoclonal antibodies targeting CD20 and other B-cell surface antigens and novel molecularly targeted agents are being intensively investigated, although few have reached the late stages of clinical development. Rituximab-based chemoimmunotherapy likely is to remain a mainstay of treatment for DLBCL for the foreseeable future. The composition of matter patent covering rituximab in Europe (MabThera) expired in 2013 and its counterpart in the United States (Rituxan) will expire in 2018. Furthermore, rituximab is not yet widely accessible to patients in some countries. For example, a survey of 450 hematologists and oncologists in the United States, Mexico, Turkey, Russia, and Brazil found that more than 50% of the physicians in countries outside the United States viewed rituximab as not easily accessible and would increase its use if a more affordable alternative became available for treatment of NHL, including DLBCL.[52] In many Asian countries, where a significant disparity also exists in available healthcare resources and limited

access to new drugs, the guidelines for recommended management of NHL are resource-stratified.[53] A wider availability of rituximab would be expected to lead to improved treatment because rituximab inaccessibility has been reported as the adverse prognostic factor for progression-free survival among some Thai patients with DLBCL.[54] Likewise, in Africa, programs of both pediatric and adult oncohematology would benefit from access to rituximab added to chemotherapy.[55] With rituximab continuing to play a key role in treatment of DLBCL and other NHL subtypes, the introduction of rituximab biosimilars has the potential to expand access to this important treatment option.

Biosimilars refer to biologic products that are highly similar to the approved reference (also referred to as innovator or originator) product such that no clinically meaningful differences exist between the reference and biosimilar products in terms of purity, safety, and efficacy. Biosimilars, like the reference biologic product, are highly complex molecules that are produced in living organisms and purified through extensive purification procedures. To facilitate timely assessment and approval of biosimilars, several guidelines to demonstrate biosimilarity have been established by the EMA,[56] FDA,[57] and World Health Organization,[58] as well as regulatory agencies from several other countries. Since the first biosimilar product Omnitrope (the growth hormone somatropin) was approved by the EMA in 2006, an increasing number of biosimilars have entered the market, and their use has grown globally. In March 2015, Zarxio (filgrastim-sndz) became the first biosimilar product approved in the United States through the biosimilar approval pathway under the US Biologics Price Competition Innovation Act of 2009.[59]

To obtain regulatory approval, it is necessary to demonstrate structural and functional similarities, as well as clinical efficacy and safety (including immunogenicity), of the rituximab biosimilar to the reference rituximab.[57] However, the rituximab biosimilar does not have to show efficacy to the reference rituximab in each of its approved disease subtypes if extrapolation of clinical data for one indication to another can be scientifically justified and any differences, if found, can be addressed in “the context of the totality of supporting evidence.”[57] To date, no rituximab biosimilar has been approved through this approval pathway by the FDA or, through a similar pathway, the EMA (where the rituximab patent has already expired) or any other internationally recognized regulatory agency. However, there are a number of rituximab biosimilars in development in anticipation for increased demands with the rituximab US patent expiry.[60] Rituximab biosimilars that are under clinical evaluations for DLBCL or FL, registered at ClinicalTrials.gov or Clinicaltrialsregister.eu, are listed in Table 3. Although it is potentially more challenging to demonstrate the biosimilarity of larger and more complicated biologics (eg, monoclonal antibodies[61,62]) compared with smaller biologics (eg, growth factors), the first monoclonal antibody biosimilars (to infliximab) were approved by the EMA in 2013. It is likely that rituximab biosimilars will be considered for approval globally over the next few years, which is expected to improve accessibility of rituximab-based chemoimmunotherapies to patients with DLBCL and has potential cost-saving benefits for healthcare systems.

Conclusions

DLBCL, an aggressive NHL, is the most common subtype of NHL. Chemoimmunotherapy consisting of CHOP and other standard chemotherapies in combination with rituximab is the treatment option for first-line and relapsed/refractory CD20+ DLBCL recommended by the NCCN and the European Society for Medical Oncology guidelines. Although new anti-CD20 monoclonal antibodies and other molecularly targeted novel agents are being evaluated for treatment of DLBCL, particularly for relapsed or refractory disease and patients with high risk, rituximab is expected to remain an important component of DLBCL therapy in the foreseeable future. With the rituximab patent expiry, a number of rituximab biosimilars are under intensive clinical development. The advent of rituximab biosimilars likely would facilitate expanded access to the rituximab-based standard of care chemoimmunotherapy for treatment of patients with DLBCL.

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Table 1

International Prognostic Index for Aggressive NHL or DLBCL

	IPI[31]	Age-adjusted IPI[31] ≤60 years	NCCN-IPI[32]
Risk factors used (No. point allotted)			
Age >60 years	+ (1)	-	−
Age, years	-	-	+
>40-≤60			(1)
>60-<75			(2)
≥75			(3)
Ann Arbor stage III/IV	+ (1)	+ (1)	+ (1)
ECOG performance status 2–4	+ (1)	+ (1)	+ (1)
Serum LDH, more than normal	+ (1)	+ (1)	−
Serum LDH, normalized	-	-	+
>1-≤3			(1)
>3			(2)
Extranodal involvement >1 site	+ (1)	-	+ (1)
Risk group, no. points			
Low	0 or 1	0	0–1
Low intermediate	2	1	2–3
High intermediate	3	2	4–5
High	4 or 5	3	>6

Abbreviations: DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LDH = lactate dehydrogenase; NCCN = National Comprehensive Cancer Network; NHL = none–Hodgkin lymphoma.

Table 2

Summary of Treatment Recommendations for DLBCL

NCCN Guidelines[7]			ESMO Guidelines[33,34]		
Classification		**Treatment Options**	**Classification**		**Treatment Options**
Ann Arbor stage I *or* II	Nonbulky	• R-CHOP[a] x 3 cycles + IFRT *or* • R-CHOP[a] x 6 cycles ± IFRT • IFRT for noncandidates for chemotherapy	Young	IPI low risk with no bulk	• R-CHOP21 x 6 cycles
	Bulky	• R-CHOP[a] x 6 cycles ± locoregional Rt		IPI low risk with bulk *or* low-intermediate risk	• R-ACVBP with sequential consolidation *or* • R-CHOP21 x 6 cycles + IFRT on bulk
Ann Arbor stage III *or* IV		• Clinical trials *or* • R-CHOP21 • Alternatives: DA-EPOCH + R *or* dose-dense R-CHOP14		IPI intermediate-high risk *or* high risk	• R-CHOP21 x 8 cycles *or* R-CHOP14 x 6 with 8 cycles R • More intensive regimens: R-CHOEP14 x 6 cycles *or* R-ACVBP + HDCT with ASCT *or* R-dose-dense (R-CHOP14—like) + R-HDCT with ASCT
For >80 year with comorbidities		• R-miniCHOP	Elderly	>60 year, healthy	• R-CHOP21 x 8 cycles • (R-CHOP21 x 6 cycles for IPI low risk) *or* • R-CHOP14 x 6 with 8 cycles R
For very frail *or* with poor LVF		• R-CEPP • R-CDOP • R-CNOP • DA-EPOCH + R • R-CEOP		>80 year without cardiac dysfunction	• Attenuated regimen: R-miniCHOP21 x 6 cycles
				Unfit/frail *or* >60 year with cardiac dysfunction	• R-C(X)OP21 x 6 cycles *or* • Palliative care
Relapse/refractory	Intend to proceed to high-dose therapy	Second-line and subsequent: • DHAP ± R • ESHAP ± R • GDP ± R • GemOx ± R • ICE ± R • MINE ± R	First relapse/ progress	Eligible to transplant	•Salvage regimen with platinum-based chemotherapy regimens (ie, R-DHAP, R-IcE) • R-HDCT with ASCT for chemosensitive patients • Allogeneic transplantation for relapsed after R-HDCT with ASCT *or* with poor risk at relapse
	Noncandidates for high-dose therapy	Clinical trial *or* second and subsequent lines: • Bendamustine ± R • Brentuximab vedotin (for CD30+ disease) • CEPP ± R • CEOP ± R • DA-EPOCH ± R • GDP ± R • GemOx ± R • Lenalidomide ± R • R *or* • Palliative RT *or* • Best supportive care		Not eligible to transplant	•Platinum and/*or* gemcitabine-based regimens *or* • Clinical trials with novel drugs
			>2 relapse/ progress	Eligible to transplant	• Allogeneic transplantation *or* • Clinical trials with novel drugs

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NCCN Guidelines[7]			ESMO Guidelines[33,34]		
Classification		**Treatment Options**	**Classification**		**Treatment Options**
			Not eligible to transplant		• Clinical trials with novel drugs *or* • Palliative care

Abbreviations: ACVBP = doxorubicin, vindesine, cyclophosphamide, bleomycin, and prednisolone; ASCT = autologous stem cell transplantation; CDOP = cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone; CEOP = cyclophosphamide, etoposide, vincristine, and prednisone; CEPP = cyclophosphamide, etoposide, prednisone, and procarbazine; CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP14=cyclophosphamide, doxorubicin, vincristine, and prednisone dosed for 14 days; CHOP21 = cyclophosphamide, doxorubicin, vincristine, and prednisone dosed for 21 days; CNOP = cyclophosphamide, mitoxantrone, vincristine, and prednisone; DA-EPOCH = dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DHAP=dexamethasone, cisplatin, cytarabine; DLBCL=diffuse large B-cell lymphoma, ESHAP=etoposide, methylprednisolone, cytarabine, and cisplatin; ESMO = European Society for Medical Oncology; GDP = gemcitabine, dexamethasone, and cisplatin/carboplatin; GemOX = gemcitabine and oxaliplatin; HDCT = high-dose chemotherapy; ICE = ifosfamide, carboplatin, and etoposide; IFRT = involved-field radiation therapy; IPI = International Prognostic Index; LVF = left-ventricular function; MINE = mesna, ifosfamide, mitoxantrone, and etoposide; NCCN= National Comprehensive Cancer Network; R= rituximab; R-miniCHOP = rituximab plus reduced dose cyclophosphamide, doxorubicin, vincristine, and prednisone; RT = radiation therapy; X = doxorubicin substitution with etoposide, liposomal doxorubicin, others.

[a]For patients who are intolerant to anthracyclines, alternative chemoimmunotherapies include R-CEPP, R-CDOP, R-CNOP, DA-EPOCH plus rituximab, and R-CEOP, which are also recommended first-line therapy for patients with poor left ventricular function or very frail patients.

Table 3

Rituximab Biosimilars at the Late Stages of Clinical Development for DLBCL and FL

Agent/Company	Indication	Development Stage/Comparison	Comparison	Outcomes
CMAB304 (Retuxira)/ Shanghai CP Guojian Pharmaceutical, Shanghai, China	DLBCL	Randomized, open-label phase III (NCT01459887)	CHOP + CMAB304 vs CHOP followed by CMAB304	Status: Completed PCD: December 2010 Primary end point: ORR Secondary end point: EFS No results have been reported.
RTXM83/mAbxience SA, Madrid, Spain	First-line DLBCL	Randomized, double-blind phase III (NCT02268045)	RTXM83 + CHOP vs rituximab + CHOP	Status: recruiting patients Estimated PCD: May 2016 Primary end point: RR Secondary end points: EFS, safety, PK, PD, immunogenicity
MabionCD20/ MABION SA, Kutno, Poland	DLBCL	Randomized, double-blind phase III (EudraCT2013-005506-56)	MabionCD20 vs rituximab	Status: ongoing Estimated trial duration: 1 year 6 mo Primary end point: PK Secondary end point: PK Objective: demonstrate high level of biosimilarity
PF-05280586/Pfizer Inc, New York, NY	First-line FL	Randomized, double-blind phase III (NCT02213263; EudraCT2014-000132-41)	PF-05280586 vs rituximab	Status: recruiting patients Estimated PCD: November 2016 Primary end point: ORR Secondary end points: TTF, PFS, complete remission rate, OS, duration of response, C_{max}, C_{min}, safety, ADA
CT-10/CeNtrion Inc, Incheon, South Korea	First-line FL	Randomized, double-blind phase I/III (NCT02162771; EudraCT2013-004493-96)	CT-10 + CVP vs rituximab + CVP	Status: recruiting patients Estimated PCD: February 2017 Primary end point: PK (AUC_{tau}, C_{maxss}) Secondary end point: ORR
GP2013/HEXAL AG, Holzkirchen, Germany	First-line FL	Randomized, double-blind phase III (NCT01419665; EudraCT2010-019522-13)	GP2013 vs rituximab	Status: active, not recruiting Estimated PCD: December 2017 Primary end point: ORR Secondary end point: % of patients with AEs
MK-8808/Merck Sharp & Dohme, Kenilworth, NJ	CD20+ FL	Open-label, single arm phase I (NCT01370694)	MK-8808 + CVP, followed by MK-8808 maintenance	Status: completed PCD: December 2014 Primary end point: AE Secondary end points: PK, clinical response
BI695500/Boehringer Ingelheim, Ingelheim, Germany	First-line FL	Randomized, double-blind phase I (NCT01950273)	BI695500 vs rituximab	Status: recruiting patients Estimated PCD: December 2015 Primary end point: AUC Secondary end points: AE, PK, PD (CD19+ B-cells), tumor response
ABP 798/Amgen Inc, Thousand Oaks, CA	CD20+ B-cell NHL	Randomized, double-blind phase I/III (EudraCT2013-005542-11)	ABP 798 vs rituximab	Status: ongoing Estimated trial duration: 2 year, 4 mo Primary end point: ORR risk difference Secondary end points: safety, PK, PD, ADA, PFS, OS

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; AUC = area under the concentrationetime curve; AUCtau = area under the concentrationetime curve at steady-state; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; Cmax = maximum observed concentration; Cmaxss = maximum concentration at steady-state; Cmin = minimum observed concentration; CVP = cyclophosphamide, vincristine, and prednisone; DLBCL = diffuse large B-cell lymphoma; EFS = event-free survival; FL = follicular lymphoma; NHL = NoneHodgkin lymphoma; ORR = overall or objective response rate; OS = overall survival; PCD = primary completion date; PD = pharmacodynamics; PFS = progression-free survival; PK = pharmacokinetics; RR = response rate; TTF = time to treatment failure.