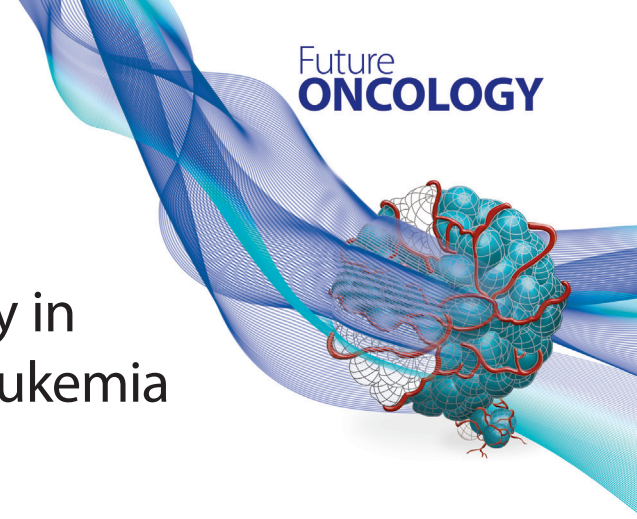
DRUG EVALUATION



Ofatumumab as front-line therapy in untreated chronic lymphocytic leukemia

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ABSTRACT: Ofatumumab is a fully human IgG1 type I anti-CD20 monoclonal antibody that binds to both the small and large loop of the membrane antigen CD20. Much of its therapeutic efficacy is derived through complement-dependent cytotoxicity, although it also appears to operate via induction of caspase-dependent apoptosis and shows potent antibody-dependent cellular phagocytosis. CD20 is an important but sometimes difficult antigen to effectively target in chronic lymphocytic leukemia (CLL) secondary to its overall dim expression in CLL cells. Currently, ofatumumab is approved in the USA and EU for fludarabine- and alemtuzumab-refractory CLL patients. However, the experience with ofatumumab in untreated CLL patients is mounting and shows competitive response and survival rates with an acceptable adverse event profile. Herein, we outline the efficacy and toxicities of ofatumumab alone and in combination for the front-line treatment of CLL.

KEYWORDS
• chronic lymphocytic leukemia • immunotherapy • monoclonal antibodies • ofatumumab • untreated

Chronic lymphocytic leukemia (CLL) is characterized by proliferation and accumulation of malignant mature monoclonal B lymphocytes. CLL is the most common chronic leukemia diagnosed in adults in western countries. As of 2010, the prevalence of CLL in the USA was estimated at approximately 120,000 individuals. In the USA, 15,680 new cases of CLL were diagnosed in 2013, 9720 in men and 5960 in women for a men-to-women ratio of 1.6:1. Additionally, 4580 deaths from CLL have been estimated in the USA in 2013, with 2750 deaths in men and 1830 in women [1]. The median age at CLL diagnosis is 72 years, and the incidence increases with age. Other factors associated with an increased risk of CLL are a family history of hematologic malignancy [2,3], and possibly red blood cell transfusions [4].

The clinical course of CLL is variable but typically characterized by a chronic, indolent course that can progress for years to decades. A large proportion of patients will be asymptomatic and diagnosed incidentally while undergoing routine physical examination. Symptoms associated with CLL progression are varied and may include fever, night sweats and unintentional weight loss (i.e., B symptoms), but also lymphadenopathy, hepatosplenomegaly, and fatigue, infections and bleeding associated with decreased production of normal blood cell components or autoimmune processes.

The diagnosis of CLL is established by the presence of B-cell lymphocytosis >5000 cells/μl in peripheral blood for longer than 3 months. The characteristic immunophenotype of CLL cells shows a coexpression of the T-cell antigen CD5 along with the B-cell antigens CD19, CD20 (dim) and in most cases CD23. Monoclonality can be determined by immunoglobulin light chain restriction, cytogenetic abnormalities and/or immunoglobulin gene rearrangements. The prognosis of CLL relies on the clinical stage at presentation (e.g., early stage has a survival

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of >10 years while advanced stage of <3 years) and cytogenetic abnormalities (e.g., 17p deletions are associated with worse survival rates), among other factors.

Given the chronicity and incurability of CLL, it is a standard approach to delay therapy until patients are symptomatic from the disease; hence, most of the patients do not need therapy at the time of diagnosis. Once initiated, the main objective of CLL therapy is to improve symptoms and quality of life. New chemoimmunotherapy combinations have shown progression-free survival (PFS) and even overall survival (OS) benefit in younger patients [5], in particular those individuals who attained low levels of minimal residual disease [6]. Despite these important advances there still remains no current curative therapy for CLL. Survival benefits are less clear in older patients who cannot tolerate the side effects of chemoimmunotherapy.

Overview of the market

A series of drugs are currently US FDA-approved for the treatment of CLL. Chlorambucil (Leukeran®; CHL), fludarabine (Fludara®), alemtuzumab (Campath®), bendamustine (Treanda®), ofatumumab (Arzerra®) and ibrutinib (Imbruvica™) have been approved as single-agent therapies. CHL is an alkylating agent that has shown to induce responses lasting from 1 to 2 years in patients with CLL. Fludarabine, alemtuzumab and bendamustine were approved based on randomized controlled trials (RCTs) showing higher response rates and longer PFS than CHL [7–9]. Fludarabine is an antimetabolite agent that has been associated with higher rates of severe infections and neutropenia. Alemtuzumab, an anti-CD52 monoclonal antibody (mAb), has shown efficacy in high-risk patients carrying 17p deletions, but it is associated with profound immunosuppression, an increased rate of cytomegalovirus reactivation and presence of cytopenias [7,10]. Bendamustine, an alkylator, has an acceptable toxicity profile although with potential long-term stem cell-damaging effects. Based on a multicenter open label Phase Ib–II study, ibrutinib was recently approved by the FDA for single- agent use in relapsed and refractory CLL. Ibrutinib is an oral BTK inhibitor that has induced responses in 71% of patients with relapsed/refractory CLL; the most common adverse events (AEs) were transient diarrhea, fatigue and upper respiratory infections. Importantly, ibrutinib has shown single-agent activity in patients with 11q and 17p deletions [11].

The combination of the antimetabolite fludarabine, the alkylator cyclophosphamide (Cytoxan®) and the chimeric anti-CD20 mAb rituximab (Rituxan®; FCR) has been approved as combination therapy in untreated and previously treated patients with CLL. FCR has shown in two separate RCTs, one in untreated and one in previously treated patients, to be superior to fludarabine plus cyclophosphamide (FC) by significantly prolonging PFS [5,12]. However, the rates of AEs such as neutropenia, febrile neutropenia, thrombocytopenia, hypotension, hepatitis B and pancytopenia were higher in patients who received FCR compared with FC. Furthermore, the patients included in these studies were younger than the general population diagnosed with CLL. Recently, the combination of obinutuzumab (Gazyva®), a glycoengineered type II anti-CD20 mAb, and CHL has been approved for the front-line treatment of CLL patients based on an RCT in which the combination showed higher response rates and longer PFS than patients treated with CHL alone [13]. The most common AEs associated with the combination were infusion reactions, thrombocytopenia, neutropenia, musculoskeletal pain and fever.

Newer agents that have shown efficacy and that are likely to be approved in CLL are lenalidomide (Revlimid®) and idelalisib (formerly GS-1101 and CAL-101), among others. Lenalidomide is an oral immunomodulator that in a Phase II study has shown to induce responses in 47% of relapsed/refractory CLL patients with neutropenia, thrombocytopenia and flare reaction as the most common AEs [14]. Idelalisib is an oral PI3K inhibitor that is associated with 56% response rate in relapsed/refractory CLL patients; the most common AEs are liver enzyme elevation, pneumonia, diarrhea and fever. Like ibrutinib, idelalisib has shown efficacy against patients with high-risk cytogenetic anomalies [15].

Ofatumumab

CD20 represents an ideal target for mAb directed therapy as it is not expressed on stem cells, is present on most B-cell malignancies and blockade does not result in irreparable side effects. Functionally, CD20 is thought to augment calcium signals delivered via the B-cell receptor during mature and immature B-cell antigen recognition [16]. In CLL, however, CD20 expression is dim, which contributes to

the limited efficacy of rituximab monotherapy in both the front-line and relapsed/refractory settings [17–19]. Moreover, in CLL patients during the initial rituximab infusion there is a rapid clearance of $C20^+$ cells. Postinfusion a significant number of B cells return to circulation but are now $CD20^-$ [20]. This phenomenon, termed antigenic modulation, is a process in which constant tumor epitope targeting by mAbs leads to loss of surface antigen thereby decreasing rituximab efficacy. In CLL cells, the rituximab:CD20 complex is shaved from the B cell by monocytes present within the reticuloendothelial system thereby creating this antigenic modulation [21].

Rituximab attachment to CD20 relocates CD20 to already existing detergent insoluble lipid rafts present within the plasma membrane. The ability to redistribute CD20 in this manner is characteristic of type I anti-CD20 mAbs and is thought to be the rationale behind the ability of type I mAbs to activate complement and induce complement-dependent cytotoxicity (CDC) [22]. Type II mAbs, of which tositumomab (Bexxar®) was the first studied and obinutuzumab (Gazyva®) the most recently clinically applied, are ineffective in complement activation. Instead their mechanism of action appears to be more associated with induction of direct cell death in a caspase-independent manner [23]. Interestingly, type I mAbs also appear to have some direct cell death through mAb crosslinking via caspase-mediated apoptosis [16,24]. However, the contribution of direct cell death to efficacy is decidedly less than that of type II mAbs. Previously type I and II mAbs have been reported to be equally effective at antibody-dependent cellular cytotoxicity (ADCC) [16]. Recently however *in vitro* data have shown that newer glycoengineered type II mAbs such as obinutuzumab have greater ADCC than type I mAbs [25,26].

In order to more effectively target B-cell expression of CD20, newer anti-CD20 mAbs with increased potency have been developed. Ofatumumab is a fully human IgG1 anti-CD20 mAb created from transgenic mice. Ofatumumab is a type I mAb that has demonstrated similar ADCC but greater CDC in CLL cell lines when compared with rituximab [26,27]. Ofatumumab has been approved by the FDA for the treatment of fludarabine- and alemtuzumab-refractory CLL patients (double refractory; DR), a patient population that typically has survival times of less than a year. The approval of ofatumumab was based on a prospective single-arm open-label Phase II trial that showed an investigator-determined overall response rate (ORR) of 42% in DR CLL patients [28].

Pharmacodynamics

Ofatumumab binds directly to the small and large loop of CD20 [29] with a slower off-rate than rituximab [27]. The molecule's Fab domain binds with B-cell surface CD20 while the Fc domain mediates immune cell effector function [28]. Drug infusion leads to an initial decrease in the absolute lymphocyte count, complement levels and surface expression of CD20 by CLL cells. Over time, lymphocyte numbers and complement levels return toward normal while CLL CD20 positivity continues to decrease [30]. Given the type I nature of ofatumumab, its clinical efficacy is mainly through CDC with some contribution from ADCC and possibly additional efficacy via apoptosis. Ofatumumab induces greater cell lysis than rituximab through increased CDC activity, primarily through greater activation of the classical complement pathway [31,32]. When compared with rituximab, the CDC activity of ofatumumab is augmented by the drug's ability to more efficiently utilize available complement; a nontrivial finding when taking into account the often low complement availability within the blood of CLL patients [33]. Ofatumumab is also able to induce similar ADCC as that seen with rituximab but more potent antibody-dependent cellular phagocytosis (ADCP) and greater direct cell killing than rituximab in CLL cells [26]. Despite the contributions to CLL cell death from these other modalities, the primary therapeutic effect of ofatumumab still appears to be through CDC [31]. Although CDC is effective in cell killing, CLL cells use complement destruction regulators such as the inhibitory cell surface proteins CD55/CD59 and soluble complement factor H to evade complement-mediated destruction thereby producing ofatumumab resistance [34].

Pharmacokinetics & metabolism

Patients reliably reach therapeutic levels of ofatumumab after the first infusion and see their serum levels rise with repeat infusions. Furthermore, the effect is long lived with patients showing evidence of circulating ofatumumab up to 7 months from their last infusion [35]. In the clinical trial setting, ofatumumab has a linear clearance rate of 7.5 ml/h, a half-life of 21.8 days and a steady-state volume of

distribution of 5.3 l, values that are similar to those seen with other monoclonal IgG antibodies. Target-mediated clearance of ofatumumab increases overall clearance and decreases overall half-life from the linear values and is dependent on the number of malignant circulating B cells [35,36]; more robust responses are seen in patients with lower clearance rates of the drug and higher serum antibody concentrations [35]. No dosage adjustments are required for body weight, age, sex or creatinine clearance. Drug elimination is dependent on target binding as ofatumumab is cleared more rapidly from circulation during initial administrations as there is a plethora of B cells with associated CD20 expression that serve as an intravascular drug sink [28].

Clinical efficacy

• Phase I/II

The first reported clinical trial of ofatumumab was an open-label multicenter study that examined its safety and activity in relapsed/refractory CLL patients. Thirty-three patients in total divided into three cohorts were enrolled and given escalating doses of ofatumumab following a Fibonacci 3 + 3 design. Importantly, the maximum tolerated dose was not reached in this study. In the highest dose cohort (n = 27) that received an initial infusion of 500 mg followed by three subsequent infusions of 2000 mg, the ORR was 50%. Responses, however, tended to be short lived with this dosing schema as the median PFS was only 106 days [37].

A large international open-label Phase II study demonstrated the efficacy of single-agent ofatumumab in CLL patients refractory to fludarabine and alemtuzumab (DR; n = 59) or CLL patients with bulky disease refractory to fludarabine (BF; n = 79) using a slightly different dosing schema from its predecessor. Here, patients were given 8 weekly infusions followed by 4 monthly infusions over a 24-week time period starting with 300 mg in dose 1 then escalating to 2000 mg for doses 2–12. The ORR, as determined by an independent review committee, for DR and BF was 58 and 47%, respectively. The median PFS was approximately 6 months in each group with an OS of nearly 14 months in the DR group and over 15 months in BF patients. Responses tend to occur shortly after initiation of therapy at a median of 1.8 months [38].

Ofatumumab monotherapy in the front-line setting has been examined. Flinn and colleagues enrolled 77 patients with newly diagnosed CLL that required treatment in an open-label Phase II trial. Patients were either over the age of 65 or younger than 65 but declined fludarabine-based treatment. Ofatumumab was given weekly for 8 weeks with an initial dose of 300 mg followed by either 2000 mg (cohort 1) or 1000 mg (cohort 2) on weeks 2–8. Patients who responded or had no evidence of disease progression received ofatumumab maintenance for 2 years. The ORR for cohort 1 and 2 was 55 and 36%, respectively. The PFS at 15 months for cohort 1 was 74% while that for cohort 2 has yet to be reported [39].

The initial study to combine ofatumumab with chemotherapy for frontline induction in untreated CLL was conducted by Wierda and colleagues as an open-label Phase II study that utilized ofatumumab given at either 500-mg or 1000-mg doses with cyclophosphamide and fludarabine for six cycles (FCO). In a relatively young patient population (median age: 56 years), the ORR and complete response (CR) rates were 77 and 32%, and 73 and 50% for the 500-mg and 1000-mg cohorts, respectively. The combined ORR and CR of both dose cohorts was 75 and 41%. Although the CR rate as similar to previous chemoimmunotherapy trials, the ORR was lower, which the authors attributed to a higher-risk profile patient population [40].

More recently, Shanafelt and colleagues conducted an open-label Phase II study in untreated patients that combined ofatumumab with pentostatin and cyclophosphamide (PCO) for six cycles of chemoimmunotherapy. Of the 48 patients enrolled, 46 responded (96% ORR) with 22 patients (46%) attaining a CR. Compared to the results of a historical cohort that received pentostatin, cyclophosphamide and rituximab (PCR), PCO had a longer time to retreatment; at 24 months 86% of patients were free of retreatment with PCO while 68% of patients treated with PCR were free of retreatment at 24 months [41]. A similar Phase II study of PCO front-line therapy in CLL was conducted by in 49 patients from 12 Italian centers. In a patient population with a median age of 73 years, the ORR was 94% with 41% of patients attaining CR or CR with incomplete marrow recovery. The authors concluded that the efficacy of ofatumumab-based chemoimmunotherapy compares favorably to rituximab-based chemoimmunotherapy with an improved side-effect profile [42]. It should be emphasized that this analysis represents a comparison of

patients treated on sequential Phase II trials rather than being a randomized comparison.

An intriguing prospect for CLL treatment is the role of early treatment in patients with early-stage disease but with poor prognostic features such as 17p or 11q deletions. In a single-center open-label Phase II study, 25 patients with Rai Stage 0, I or II disease with high-risk features have been enrolled with 18 patients evaluable for response. Responses were as follows: six CR (33%), three (17%) nodular partial response (PR), three (17%) PR and six (33%) with stable disease. Three patients progressed on ofatumumab monotherapy at 18.8, 14.1 and 3.2 months, respectively. Further conclusions have not been made due to short follow-up, however early findings suggest that ofatumumab in early-stage CLL may delay time to first chemoimmunotherapy [43]. Further enrollment to this study and maturation of the data should provide a more comprehensive answer to this question.

• Phase III

A front-line open-label, randomized Phase III study compares CHL alone versus CHL plus ofatumumab (CHL+O). This study examined an older patient population with a median age of 69 years and randomized 447 patients from 16 countries. CHL+O showed a significantly longer PFS of over 22 months compared with 13 months for CHL alone with an additional superior CR rate of 12% compared with 1%. Thus far, the study has not matured enough to report median OS. AEs grade ≥3 were observed in 50% of patients with CHL+O and 43% of CHL patients with the most common grade ≥3 AE being neutropenia (CHL+O: 26%; CHL: 14%). No difference in grade ≥3 infections and no fatal infusion-related reactions were seen suggesting a favorable side-effect profile [44]. A summary of all studies that deliver ofatumumab either as monotherapy or combined with chemotherapy for the first-line treatment of CLL is present in **Table 1**.

Safety & tolerability

• Single agent

Ofatumumab monotherapy is well tolerated in heavily pretreated patient populations. The most common overall AEs are infusion-related events that typically occur within the first hours after starting the infusion. These reactions include transient rigors, fevers, fatigue, rash and diaphoresis, and tend to decrease with subsequent infusions [37,40]. The most common grade ≥3 AEs were infections, seen in 8–12% of patients, and neutropenia (6–14% of patients) [38]. A list of the AEs associated with ofatumumab therapy can be found in [45].

• In combination

In the abovementioned study of PCO, 77% of patients completed the intended six cycles of therapy. The most common AE was neutropenia, which was grade 3 in 15% of patients and grade 4 in 8% of patients. Moreover, the overall degree of grade ≥3 neutropenia with PCO (23%) [41] compares favorably to that typically seen with PCR (34%) [46]. In both the PCO and PCR studies, growth factor support was administered. Interestingly, grade ≥3 neutropenia with the FCO regimen was noted in 35–60% of patients depending on which ofatumumab dose was used. The rate of infection, however, was similar to that seen with ofatumumab monotherapy at 3–13% [40].

Overall, the primary toxicities of infection and neutropenia correlate with number of total treatments and current disease status, as heavily pretreated patients with relatively refractory disease will be at high risk for neutropenia and infections by virtue of their CLL in and of itself, and secondary to decreased bone marrow reserve and immunosuppression.

Postmarketing surveillance

One retrospective study has examined the use of ofatumumab monotherapy outside of the clinical trial setting throughout 25 European centers. A total of 103 heavily pretreated patients with a median age of 64 years were included for evaluation of response and safety. In this real-world setting, the ORR was 23% with a PFS and OS of 5 and 12 months, respectively. The most common grade ≥3 AEs were infections (36%), neutropenia (19%) and thrombocytopenia (12%). Hematological toxicities increased as the number of prior therapies increased. Importantly, the main causes of death were disease progression (61%) and infection (28%) suggesting the overall poor prognosis inherent to the study population [47].

Regulatory affairs

Ofatumumab is currently approved in the USA and the EU for the treatment of CLL patients with fludarabine- and alemtuzumab-refractory disease.

Table 1. Clinical trials reported to date to use ofatumumab alone or in combination with chemotherapy as first-line treatment in chronic lymphocytic leukemia.

Trial	Phase	Patients (n)	Median age (years)	Overall response rate (%)	Median PFS (months)	Ref.
O	Phase II	Cohort 1: 44 Cohort 2: 33	Cohort 1: 69 Cohort 2: 75	Cohort 1: 55 Cohort 2: 36	NR	[39]
O	Phase II	25	59	66	NR	[43]
FCO	Phase II	61	56	75	NR	[40]
PCO	Phase II	48	65	96	NR	[41]
PCO	Phase II	49	73	94	NR	[42]
CHL+O vs CHL	Phase III	447	69	CHL+O: 82 CHL: 69	CHL+O: 22 CHL: 13	[44]

CHL: Chlorambucil; FCO: Fludarabine plus cyclophosphamide plus ofatumumab; NR: Not reported; O: Ofatumumab; PCO: Pentostatin plus cyclophosphamide plus ofatumumab; PFS: Progression-free survival.

Conclusion

The landscape of CLL therapy is changing at a rapid pace. The advent of anti-CD20 mAbs certainly has changed the way we treat CLL and has provided patients with response and survival benefits. Ofatumumab, specifically, has shown to be effective in the relapsed/refractory setting, and there is mounting evidence that it is also effective and well tolerated in previously untreated patients with CLL. Preclinically, ofatumumab has shown to be a more potent anti-CD20 agent with distinct features of those of rituximab. Direct clinical comparisons between ofatumumab and rituximab, however, are lacking and unlikely to be undertaken.

There are data, however, showing that ofatumumab is associated with competitive response and survival rates when compared with historical studies undertaken with rituximab. The ORR to eight cycles of single-agent rituximab in untreated CLL patients has been reported at 58% [19] with a median PFS of 19 months. The combination of FCR induced ORR of 95%, CR rates of 44% and a median PFS of 59 months [5]. Similarly, the PCR regimen showed ORR of 91%, CR of 41% and a median PFS of 33 months [46]. Besides efficacy, ofatumumab might also be associated with a better AEs profile than rituximab. Ofatumumab alone or in combination seems to be associated with lower rates of infusion-related reactions as well as cytopenias and infectious complications.

The median age at CLL diagnosis is 72 years; however, most of the studies evaluating therapy for CLL include younger patients who are more likely to tolerate more intensive and toxic regimens. Hence, of interest are the results of the combination of ofatumumab and CHL in older CLL patients. In this study, the CR rate was 12% with a median PFS of approximately 2 years [44]. Such combination might become a standard of care in elderly patients or patients with comorbidities who will not be able to tolerate fludarabine or pentostatin-based regimens. Certainly, additional studies need to focus on populations more closely reflecting real-life scenarios.

The future of CLL therapy will likely be impacted by the advent of novel nonchemotherapeutic agents. The new generation glycoengineered anti-CD20 mAb obinutuzumab is showing efficacy in patients with CLL and has recently been approved to treat patients with previously untreated CLL in combination with CHL. Novel agents targeting pathways related with B-cell receptor signaling are of great interest. Agents such as the BTK inhibitor ibrutinib and the PI3K inhibitor idelalisib have shown efficacy and safety as single agents or in combination with anti-CD20 mAbs even in high-risk CLL patients (e.g., 17p deletion), who typically have lower response and survival rates when treated with immunochemotherapy. The oral administration makes these agents highly desirable and paradigm changing in a population of patients in which maintaining an acceptable quality of life is paramount.

The future development of ofatumumab in CLL would focus on its rational combination with oral agents such as ibrutinib and idelalisib, and such studies are ongoing in patients with relapsed/refractory disease. Such combinations should be studied in older patients or patients with comorbidities who are less likely to tolerate and/or benefit from chemoimmunotherapy. The role of ofatumumab in the management of untreated CLL patients is still to be defined.

Information resources

Website: www.arzerra.com

Company review disclosure

In addition to the peer-review process, with the author(s) consent, the manufacturer of the product(s) discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made at the discretion of the author(s) and based on scientific or editorial merit only.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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EXECUTIVE SUMMARY

Mechanisms of action

- Ofatumumab is a fully human type I anti-CD20 monoclonal antibody that activates host immune system function via complement-dependent and antibody-dependent cellular toxicity mechanisms. There may also be some contribution from direct cell death via apoptosis.

Pharmacokinetic properties

- Distribution: ofatumumab is distributed throughout the body with a steady-state volume of distribution of 5.3 l. Following administration it persists within the circulation as evident by a half-life of nearly 24 days.
- Elimination: highly dependent on the number of target B cells present. A high tumor burden with large numbers of B cells results in more rapid elimination.

Clinical efficacy

- Single agent: 55% overall response rate in untreated chronic lymphocytic leukemia (CLL).
- Fludarabine plus cyclophosphamide plus ofatumumab (FCO) regimen: 75% overall response rate, 41% complete response rate in untreated CLL.
- Pentostatin plus cyclophosphamide plus ofatumumab (PCO) regimen (USA): 96% overall response rate, 46% complete response rate in untreated CLL.
- PCO regimen (Italy): 94% overall response rate, 41% complete response rate in untreated CLL.

Safety & tolerability

- Adverse events: >10%, infusion-related reactions, fatigue, rash, nausea, diarrhea, neutropenia, anemia, infection, pneumonia, cough, dyspnea, bronchitis; 1–10%, edema, hypertension, hypotension, tachycardia, chills, insomnia, headache, urticaria, sepsis, herpes zoster, back pain, muscle spasm, sinusitis; <1% (important or life-threatening), angina pectoris, bacteremia, hemolytic anemia, hepatitis B (new onset or reactivation), hypoxia, interstitial pulmonary disease (infectious), intestinal obstruction, peritonitis, progressive multifocal leukoencephalopathy, sepsis neutropenic, septic shock, thrombocytopenia.

Drug interactions

- Enhancement of toxic effect of immunosuppresants and other monoclonal antibodies: abciximab, Bacillus Calmette–Guérin (BCG), belimumab, denosumab, *Echinacea*, natalizumab, pimecrolimus, sipuleucel-T, tacrolimus, tofacitinib, trastuzumab and live vaccines.
- Other interactions: digoxin, leflunomide and roflumilast.
- Possible diminished effect of inactivated vaccines.

Dosage & administration

- Initial dose: 300 mg iv. week 1, followed 1 week later by 2000 mg iv. once weekly for 7 doses (doses 2–8), followed 4 weeks later by 2000 mg iv. once every 4 weeks for 4 doses (doses 9–12); for a total of 12 doses.
- Premedicate with acetaminophen, an antihistamine, and a corticosteroid 30–120 min prior to treatment.

References

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

1 The Leukemia & Lymphoma Society. Facts 2013. www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdf

2 Chatterjee N, Hartge P, Cerhan JR *et al.* Risk of non-Hodgkin's lymphoma and family history of lymphatic, hematologic, and other cancers. *Cancer Epidemiol. Biomarkers Prev.* 13, 1415–1421 (2004).

3 Mensah FK, Willett EV, Ansell P *et al.* Non-Hodgkin's lymphoma and family history of hematologic malignancy. *Am. J. Epidemiol.* 165, 126–133 (2007).

4 Castillo JJ, Dalia S, Pascual SK. Association between red blood cell transfusions and development of non-Hodgkin lymphoma: a meta-analysis of observational studies. *Blood* 116, 2897–2907 (2010).

5 Hallek M, Fischer K, Fingerle-Rowson G *et al.* Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, Phase 3 trial. *Lancet* 376, 1164–1174 (2010).

•• **First study in chronic lymphocytic leukemia (CLL) to show a benefit of one regimen (fludarabine plus cyclophosphamide plus rituximab [FCR]) over the other (fludarabine plus cyclophosphamide [FC]) in terms of overall survival.**

6 Bottcher S, Ritgen M, Fischer K *et al.* Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. *J. Clin. Oncol.* 30, 980–988 (2012).

• **Subset analysis of the GCLLSG CLL8 trial showing benefit of minimal residual disease in terms of progression-free and overall survival.**

7 Hillmen P, Skotnicki AB, Robak T *et al.* Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J. Clin. Oncol.* 25, 5616–5623 (2007).

8 Knauf WU, Lissichkov T, Aldaoud A *et al.* Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J. Clin. Oncol.* 27, 4378–4384 (2009).

9 Rai KR, Peterson BL, Appelbaum FR *et al.* Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N. Engl. J. Med.* 343, 1750–1757 (2000).

10 Stilgenbauer S, Zenz T, Winkler D *et al.* Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. *J. Clin. Oncol.* 27, 3994–4001 (2009).

11 Byrd JC, Furman RR, Coutre SE *et al.* Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N. Engl. J. Med.* 369, 32–42 (2013).

12 Robak T, Dmoszynska A, Solal-Celigny P *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.* 28, 1756–1765 (2010).

13 Goede V, Fischer K, Humphrey K *et al.* Obinutuzumab (GA101) plus chlorambucil (Clb) or rituximab (R) plus Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and preexisting medical conditions (comorbidities): final stage 1 results of the CLL11 (BO21004) Phase III trial. *ASCO Meeting Abstracts* 31, 7004 (2013).

14 Chanan-Khan A, Miller KC, Musial L *et al.* Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a Phase II study. *J. Clin. Oncol.* 24, 5343–5349 (2006).

15 Furman RR, Sharman JP, Coutre SE *et al.* Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N. Engl. J. Med.* 370(11), 997–1007 (2014).

16 Beers SA, Chan CHT, French RR *et al.* CD20 as a target for therapeutic type I and II monoclonal antibodies. *Semin. Hematol.* 47, 107–114 (2010).

17 Golay J, Lazzari M, Facchinetti V *et al.* CD20 levels determine the *in vitro* susceptibility to rituximab and complement of B-cell chronic lymphocytic leukemia: further regulation by CD55 and CD59. *Blood* 98, 3383–3389 (2001).

18 Huhn D, von Schilling C, Wilhelm M *et al.* Rituximab therapy of patients with B-cell chronic lymphocytic leukemia. *Blood* 98, 1326–1331 (2001).

19 Hainsworth JD, Litchy S, Barton JH *et al.* Single-Agent Rituximab as First-Line and Maintenance Treatment for Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma: a Phase II Trial of the Minnie Pearl Cancer Research Network. *J. Clin. Oncol.* 21, 1746–1751 (2003).

20 Kennedy AD, Beum PV, Solga MD *et al.* Rituximab Infusion promotes rapid complement depletion and acute CD20 loss in chronic lymphocytic leukemia. *J. Immunol.* 172, 3280–3288 (2004).

21 Beum PV, Kennedy AD, Williams ME *et al.* The shaving reaction: rituximab/CD20 complexes are removed from mantle cell lymphoma and chronic lymphocytic leukemia cells by THP-1 monocytes. *J. Immunol.* 176, 2600–2609 (2006).

22 Cragg MS, Morgan SM, Chan HT *et al.* Complement-mediated lysis by anti-CD20 mAb correlates with segregation into lipid rafts. *Blood* 101, 1045–1052 (2003).

23 Chan HTC, Hughes D, French RR *et al.* CD20-induced lymphoma cell death is independent of both caspases and its redistribution into Triton X-100 insoluble membrane rafts. *Cancer Res.* 63, 5480–5489 (2003).

24 Byrd JC, Kitada S, Flinn IW *et al.* The mechanism of tumor cell clearance by rituximab *in vivo* in patients with B-cell chronic lymphocytic leukemia: evidence of caspase activation and apoptosis induction. *Blood* 99, 1038–1043 (2002).

25 Herter S, Herting F, Mundigl O *et al.* Preclinical activity of the Type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab *in vitro* and in xenograft models. *Mol. Cancer Ther.* 12, 2031–2042 (2013).

26 Rafiq S, Butchar JP, Cheney C *et al.* Comparative assessment of clinically utilized CD20-directed antibodies in chronic lymphocytic leukemia cells reveals divergent NK cell, monocyte, and macrophage properties. *J. Immunol.* 190, 2702–2711 (2013).

• **Mechanistic study of ofatumumab compared with obinutuzumab and rituximab in CLL cells.**

27 Teeling JL, French RR, Cragg MS *et al.* Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. *Blood* 104, 1793–1800 (2004).

•• **Initial work that chronicles the discovery of ofatumumab and describes the increased complement-depedent cytotoxicity seen in ofatumumab compared with rituxumab.**

28 Lemery SJ, Zhang J, Rothmann MD *et al.* U.S. Food and Drug Administration approval: ofatumumab for the treatment of

patients with chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab. *Clin. Cancer Res.* 16, 4331–4338 (2010).

29 Teeling JL, Mackus WJ, Wiegman LJ *et al.* The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. *J. Immunol.* 177, 362–371 (2006).

30 Baig NA, Taylor RP, Lindorfer MA *et al.* Induced resistance to ofatumumab-mediated cell clearance mechanisms, including complement-dependent cytotoxicity, in chronic lymphocytic leukemia. *J. Immunol.* 192, 1620–1629 (2014).

31 Bologna L, Gotti E, Da Roit F *et al.* Ofatumumab is more efficient than rituximab in lysing B chronic lymphocytic leukemia cells in whole blood and in combination with chemotherapy. *J. Immunol.* 190, 231–239 (2013).

• ***In vitro* data that focus in on superiority of ofatumumab over rituximab in terms of tumor cell lysis in CLL.**

32 Pawluczkowycz AW, Beurskens FJ, Beum PV *et al.* Binding of submaximal C1q promotes complement-dependent cytotoxicity (CDC) of B cells opsonized with anti-CD20 mAbs ofatumumab (OFA) or rituximab (RTX): considerably higher levels of CDC are induced by OFA than by RTX. *J. Immunol.* 183, 749–758 (2009).

33 Okroj M, Eriksson I, Osterborg A, Blom AM. Killing of CLL and NHL cells by rituximab and ofatumumab under limited availability of complement. *Med. Oncol.* 30, 759 (2013).

34 Hörl S, Banki Z, Huber G *et al.* Complement factor H-derived short consensus repeat 18–20 enhanced complement-dependent cytotoxicity of ofatumumab on chronic lymphocytic leukemia cells. *Haematologica* 98, 1939–1947 (2013).

35 Coiffier B, Losic N, Rønn BB *et al.* Pharmacokinetics and pharmacokinetic/pharmacodynamic associations of ofatumumab, a human monoclonal CD20 antibody, in patients with relapsed or refractory chronic lymphocytic leukaemia: a Phase 1–2 study. *Br. J. Haematol.* 150, 58–71 (2010).

36 Struemper H, Sale M, Patel BR *et al.* Population pharmacokinetics of ofatumumab in patients with chronic lymphocytic leukemia, follicular lymphoma, and rheumatoid arthritis. *J. Clin. Pharmacol.* doi:10.1002/jcph.268 (2014) (Epub ahead of print).

37 Coiffier B, Lepretre S, Pedersen LM *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* 111, 1094–1100 (2008).

38 Wierda WG, Kipps TJ, Mayer J *et al.* Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *J. Clin. Oncol.* 28, 1749–1755 (2010).

•• **Initial study that led to ofatumumab monotherapy approval in fludarabine-refractory patients.**

39 Flinn IW, Harwin WN, Ward P *et al.* Phase II trial of ofatumumab (OFA) for older patients and patients who refuse fludarabine-based regimens with previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Presented at: *54th ASH Annual Meeting and Exposition*. Atlanta, GA, USA, 8–11 December 2012 (Abstract 719).

40 Wierda WG, Kipps TJ, Dürig J *et al.* Chemoimmunotherapy with O-FC in previously untreated patients with chronic lymphocytic leukemia. *Blood* 117, 6450–6458 (2011).

41 Shanafelt T, Lanasa MC, Call TG *et al.* Ofatumumab-based chemoimmunotherapy is effective and well tolerated in patients with previously untreated chronic lymphocytic leukemia (CLL). *Cancer* 119, 3788–3796 (2013).

• **Phase II data using ofatumumab in combination with chemotherapy with excellent overall response rates and acceptable side-effect profiles.**

42 Montillo M, Rossi D, Motta M *et al.* A Phase II multi-center trial of pentostatin plus cyclophosphamide with ofatumumab (PCO) In older previously untreated chronic lymphocytic leukemia (CLL) patients. Presented at: *55th ASH Annual Meeting and Exposition*. New Orleans, LA, USA, 7–10 December 2013 (Abstract 4177).

43 Keating MJ, Ferrajoli A, Konopleva M *et al.* Early ofatumumab treatment for high-risk, treatment-naive patients with chronic lymphocytic leukemia. Presented at: *55th ASH Annual Meeting and Exposition*, New Orleans, LA, USA 7–10 December 2013 (Abstract 5307).

44 Hillmen P, Robak T, Janssens A *et al.* Ofatumumab + chlorambucil versus chlorambucil alone in patients with untreated chronic lymphocytic leukemia (CLL): results of the Phase III study complement 1 (OMB110911). Presented at: *55th ASH Annual Meeting and Exposition*. New Orleans, LA, USA, 7–10 December 2013 (Abstract 528).

45 UpToDate: Ofatumumab: drug information. www.uptodate.com/contents/ofatumumab-drug-information?source=see_link

46 Kay NE, Geyer SM, Call TG *et al.* Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. *Blood* 109, 405–411 (2007).

47 Moreno C, Montillo M, Panayiotis P *et al.* A multicenter, Phase IV observational study of ofatumumab in chronic lymphocytic leukemia (CLL): a European Research Initiative On CLL (ERIC) study. *Blood* 122(21), Abstract 1645 (2013).