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Obinutuzumab for chronic lymphocytic leukemia: promise of the first treatment approved with breakthrough therapy designation

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Abstract

Obinutuzumab (also known as GA101, afutuzumab, Gazyva) is a humanized, glycoengineered type II monoclonal antibody targeted against CD20. The US Food and Drug Administration has approved obinutuzumab for use with chlorambucil in patients with previously untreated chronic lymphocytic leukemia. The drug is the first treatment to receive approval under the agency's breakthrough therapy designation, a program intended to facilitate and expedite the review and development of therapies for serious and life-threatening conditions. In preclinical studies, obinutuzumab has showed superior efficacy, as compared with rituximab, by inducing direct cell death and increased antibody-dependent cellular cytotoxicity activity with less complement-dependent cytotoxicity. Regulatory approval of obinutuzumab is based on a phase III (CLL11) study that demonstrated improved outcomes with a combination of obinutuzumab with chlorambucil in previously untreated patients with chronic lymphocytic leukemia and comorbidities. Obinutuzumab plus chlorambucil induced deeper and longer remissions than rituximab plus chlorambucil combination as evidenced by prolongation of progression-free survival and higher complete response and molecular response rates. Marketing applications for obinutuzumab have also been submitted to other regulatory authorities including the European Medicines Agency.

Keywords

Chronic Lymphocytic Leukemia, Obinutuzumab, Anti-CD20, Breakthrough therapy Designation

Introduction

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in elderly people and is the most common leukemia in the western world with an annual incidence of 4.2/100,000 population.[1] The incidence increases to >30/100 000 per year at an age of more than 80 years. The median age at diagnosis is 72 years. About 10% of CLL patients are reported to be younger than 55 years of age. On 1 November 2013, the US Food and Drug Administration (FDA) granted approval to obinutuzumab, a CD20-directed cytolytic antibody, for use in combination with chlorambucil for treating patients with previously untreated CLL.[2] Obinutuzumab is unique because it is the first drug approved with the FDA's breakthrough therapy designation, since the administrative agency began using that designation in 2012 as per the requirements in the Food and Drug Administration Safety and Innovation Act (FDA SIA).

Breakthrough therapy designation

Breakthrough Therapy designation aims to expedite the development of drugs for serious or life-threatening conditions. The criteria for this designation require preliminary clinical evidence that demonstrates the new

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drug having substantial improvement on one or more clinically significant endpoints over available therapy. Determination of whether the advantage over existing therapy is substantial is a matter of judgment and depends upon both the magnitude of the therapeutic effect, including its duration, and the clinical importance of the observed outcomes. In general, the preliminary clinical evidence should show a definite advantage over the available therapy. What differentiates the breakthrough therapy designation from other FDA approaches to expedited drug development including fast track designation, priority review and accelerated approval—all of which have been in place for more than 20 years—is the requirement of preliminary clinical data demonstrating an exceptional benefit. Sponsor can request for breakthrough designation as early as the time of Investigational New Drug application (IND) submission and ideally prior to the end-of-Phase 2 meeting. The FDA has 60 days to respond to such requests. For breakthrough therapies, senior managers and experienced review staff at FDA are expected to work closely with sponsors to help design and conduct of an efficient drug development program. This may include alternative trial designs and other efficient ways of gathering non-clinical and clinical data that accelerate drug approval and minimize the number of patients exposed to potentially less efficacious treatments.[3]

Similar to US, the EU has created programs intended to facilitate and expedite development and review of new drugs. These include the accelerated assessment and conditional marketing authorization programs. 'Accelerated assessment' procedure can be requested for medicinal products considered to be of major interest from the point of view of public health and therapeutic innovation. If accepted, the timeframe for assessment is reduced from 210 to 150 days.[4] A 'conditional marketing authorization' may be granted to new drugs belonging to select categories, even though they are supported by less than comprehensive clinical data. However, they are required to satisfy certain criteria – fulfill unmet clinical needs, have a positive risk-benefit balance, there is a likelihood that comprehensive clinical data will be provided and benefits of immediate availability outweighs risks that additional robust data are still required. Conditional approvals are subject to review on an annual basis.[5] In contrast to US regulatory provisions, no equivalent 'breakthrough therapy designation' development pathway exists in EU. Absence of a counterpart in Europe may make the breakthrough therapy designation less attractive for sponsors since their investigational products may still be required to undergo the traditional drug development pathway in Europe.[6] An existing initiative of USFDA and EMA to provide 'parallel scientific advice' can serve to bridge this gap between existing regulations regarding the development of breakthrough therapies. This program provides a platform for sponsors to engage with these regulatory authorities and receive key fundamental inputs on drug development program early in the lifecycle of a new product. Sponsors are expected to benefit from a deeper understanding of regulatory expectations of the two agencies and can avoid unnecessary replication of testing. Parallel scientific advice program focuses primarily on critical breakthrough drugs and significant safety issues concerning products belonging to following clusters of interest: Oncology, pediatric medicines, vaccines and orphan drugs, nanotechnology, advanced therapies, pharmacogenomics and blood products.[7]

Mechanism of action of obinutuzumab

Obinutuzumab (GA-101) is a fully humanized, type II anti-CD20 mAb, whose Fc region has been glycoengineered by reduction in fucose content, resulting in enhanced antibody dependent cellular cytotoxicity (ADCC) activity and induction of direct cell death compared with type I monoclonal antibodies. In addition, type II antibodies do not stabilize CD20 in lipid rafts and thus exhibit reduced complement binding and weak complement-dependent cytotoxicity (CDC) activity. Compared with rituximab, obinutuzumab has demonstrated superior activity in whole blood B-cell depletion assays, in mouse xenograft models of human lymphoma resulting in complete tumor remission and improved survival, and in depleting B-cells in lymphoid tissue in nonhuman primates.[8] Although obinutuzumab recognizes an epitope overlapping with that of rituximab, it binds CD20 in a completely different orientation and at a wider elbow angle than type I antibodies, which might be responsible for its distinct cellular effects.[9]

Clinical efficacy

The approval of obinutuzumab was based on evaluation of a randomized, controlled, open-label, multicenter study (Phase III CLL11 trial) conducted at 155 centers in 24 countries.[10] This was a three-arm, two-stage study that included previously untreated CLL patients with comorbidities (Figure 1). Patients were treated with chlorambucil control (Arm 1), obinutuzumab in combination with chlorambucil (Arm 2) or rituximab in combination with chlorambucil (Arm 3). Stage 1 of the trial comprised 590 patients and compared Arm 1 vs. Arm 2 (Stage 1a) and Arm 1 vs. Arm 3 (Stage 1b). An additional 190 patients were enrolled into stage 2, which was a direct head-to-head comparison of Arm2 vs. Arm 3.

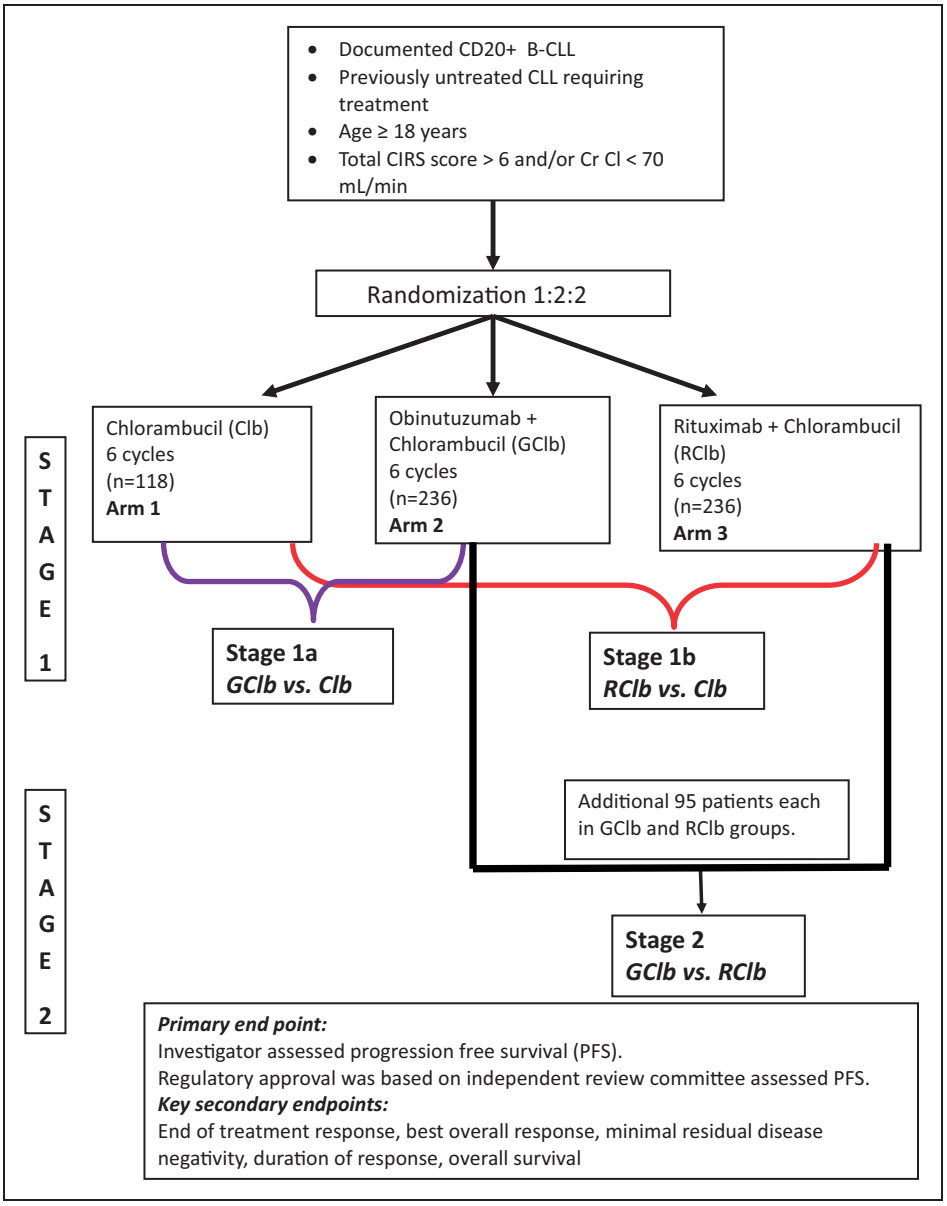

Figure 1. Study design of CL11 trial. CIRS: cumulative illness rating scale; Cr Cl: creatinine clearance.

Table 1. Cumulative Illness Rating Scale (CIRS).

The Cumulative Illness Rating Scale (CIRS) uses a scoring system that includes 14 organ system domains and a severity score for each domain. Each system has a severity ranging from 0 to 4, which are added to create a total score ranging from 0–56. Higher scores indicate worse health status. Within each organ system if two or more illnesses are present, the illness with the highest severity is evaluated.

Organ systems
Cardiac, Hypertension, Vascular, Respiratory, Eye/Ear/Nose/Throat/Larynx, Upper GI, Lower GI, Hepatic, Renal, Genitourinary, Musculoskeletal, Neurological, Endocrine/Metabolic, Psychiatric/Behavioural.

Each organ system is rated as follows:
0 = None; no illness/impairment of the organ system
1 = Mild; impairment of organ system does not interfere with normal activity and may or may not require treatment, excellent prognosis.
2 = Moderate; impairment of organ system interferes with normal activity and requires treatment, good prognosis
3 = Severe; impairment of organ system is disabling and requires urgent treatment, unclear prognosis
4= Extremely Severe; impairment of organ system is life threatening and requires emergency treatment, adverse prognosis.

Obinutuzumab was approved by FDA on the basis of data from stage 1a of the trial. The study subjects received 1000 mg of obinutuzumab intravenous infusion on days 1, 8 and 15 of the first cycle, followed by treatment on the first day of five subsequent cycles (total of six cycles, each lasting 28 days). To minimize the risk of infusion-related reactions and on the recommendation of the Data Safety Monitoring Board (DSMB), a protocol amendment was introduced. Following this, the first infusion of obinutuzumab was to be given over two days; 100 mg on Day 1 and 900 mg on Day 2. Chlorambucil was given orally at 0.5 mg/kg on Day 1 and Day 15 of all treatment cycles. Median age of the trial participants was 73 years (range 39–88 years); 39% patients in Arm 1 and 47% patients in Arm 2 had both a total cumulative illness rating scale (CIRS) > 6 (see supplementary appendix) and creatinine clearance <70 ml/min. Based on MedRA, the most frequent comorbidities seen in at least 30% ITT population were vascular disorders, cardiac disorders, gastrointestinal disorders, metabolism and nutrition disorders, renal and urinary disorders and musculoskeletal and connective tissue disorders.[10] Eighty-one percent of patients treated with obinutuzumab in combination with chlorambucil received all treatment cycles compared to 67% of patients in the chlorambucil alone arm.

The independent review committee-assessed median progression free survival (PFS) in the obinutuzumab plus chlorambucil arm was 23.0 months versus 11.1 months in the chlorambucil-alone arm (hazard ratio [HR] 0.16 [95% CI: 0.11, 0.24], $p < 0.0001$). At one year, 36% of patients in the Arm I and 83% of patients in the Arm 2 were progression-free. The best overall response rate was 75.9% in the obinutuzumab plus chlorambucil arm vs. 32.1% in chlorambucil alone arm. The median duration of response was 15.2 months in the former group and 3.5 months in the latter (HR 0.10 [95% CI: 0.05, 0.20], $p < 0.0001$).[10]

Data comparing Arm 2 vs. Arm 3 of trial CLL11 were not available at the time of approval. Recently these results were presented at 2013 American Society of Hematology (ASH) annual meeting.[11] In the final stage 2 analysis, patients in the obinutuzumab plus chlorambucil arm achieved a median PFS of 26.7 months that was significantly longer as compared to 15.2 months for those in the rituximab plus chlorambucil arm (HR 0.39, [95%CI 0.31, 0.49], $p < 0.0001$). A comparison of data from the two treatment arms revealed higher overall response rate (78% compared with 65%) in obinutuzumab arm and more than tenfold higher percentage of patients achieving minimal residual disease (MRD) negativity (29.4% compared with 2.5%) at end of treatment. Although minimal residual disease quantification has been suggested to be a useful predictor of overall survival in CLL patients,[11] an improved overall survival benefit was not noted for obinutuzumab plus chlorambucil over rituximab plus chlorambucil (HR 0.66 [95% CI: 0.41, 1.06], $p = 0.09$).

Clinical safety

The most common adverse reactions with obinutuzumab in combination with chlorambucil were infusion-related reactions, neutropenia, thrombocytopenia, leukopenia and anemia. The incidence of infusion reactions was 69% with the first infusion of obinutuzumab, of which 21% were grade 3/4 adverse events. The incidence of reactions with successive infusions was 3% with the second dose and <1% thereafter. No serious infusion-related events were reported beyond the first dose infusion.[12] The findings on infusion-related adverse events were corroborated by safety results from stage 2 of the study. Grade 3/4 adverse events occurred in 20% patients in obinutuzumab plus chlorambucil arm versus 4% of rituximab plus chlorambucil arm patients. Approximately 13% of obinutuzumab recipients tested positive for anti-obinutuzumab antibodies at one or more time points. However, their neutralizing activity and clinical significance is not known.[12]

The drug is approved with a boxed warning about Hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML), either of which may be fatal. It is recommended to screen all patients for HBV infection before initiating treatment and to monitor HBV-positive patients during and after treatment with this drug. PML is suspected in any patient presenting with new onset or changes to prior neurologic manifestations. Development of PML in obinutuzumab-treated patients warrants discontinuation of this drug as well as stoppage/dose reduction of any concomitant chemotherapy or immunosuppressive therapy.[12]

Pharmacokinetics

The elimination behavior of obinutuzumab is complex, comprising a linear clearance pathway and a time-dependent non-linear clearance pathway. As treatment progresses, the impact of the time-dependent pathway reduces in a manner suggesting target-mediated disposition. Based on population pharmacokinetic studies, geometric mean (CV%) obinutuzumab clearance and half-life at steady-state are approximately 0.09 (46%) L/day and 28.4 (43%) days, respectively. Mild or moderate renal impairment does not affect obinutuzumab exposure. There are insufficient data available to determine the effect of severe renal impairment or hepatic impairment on obinutuzumab pharmacokinetics. No

treatment modifications are expected in these populations as monoclonal antibodies are generally metabolized by ubiquitous proteolytic enzymes.[13]

Cost considerations

The cost of entire course of therapy (six cycles) with obinutuzumab (Gazyva) is $49536 (average wholesale price), while that for rituximab (Rituxan) is $47750.[14] A study evaluating cost-effectiveness of obinutuzumab therapy in combination with chlorambucil in CLL patients found that obinutuzumab plus chlorambucil showed a cost per quality-adjusted life-year (QALY) in the base case analysis of £18,000 to £19,000 when compared to chlorambucil monotherapy and £29,000 to £32,000 when compared to rituximab plus chlorambucil.[15] However, the study was based on patient data from CL11 trial and applied a range of price assumptions of similarly innovative cancer therapies. While the authors concluded that obinutuzumab might be a potential cost-effective therapy in comparison to the current standard of care therapy, a further analysis of emerging data from the real world use of obinutuzumab will be needed to substantiate these findings.

Current status

Obinutuzumab is indicated, in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia. The dosing regimen for obinutuzumab is based on a 28-day treatment cycle. During Cycle 1, patients receive a 100-mg dose on Day 1, a 900-mg dose on Day 2 and 1000-mg on days 8 and 15. Cycles 2–6 each consist of 1000 mg on Day 1. It should be diluted into 0.9% sodium chloride and administered only as an intravenous infusion and never as an intravenous push or bolus. Clinicians should consider withholding antihypertensive drug therapy for 12 hours prior to and during the infusion and for the first hour after administration of obinutuzumab. It is recommended to premedicate patients with intravenous glucocorticoid, paracetamol and an anti-histamine to minimize the risk of infusion-related reactions.[12]

Conclusions

Obinutuzumab plus chlorambucil was superior to rituximab plus chlorambucil in elderly chronic lymphocytic leukemia (CLL) patients with comorbidities, with an acceptable safety profile, based on the findings of phase III CLL11 trial. The novel agent in combination with chlorambucil led to a prolongation of progression-free survival and improved complete response rates and minimal residual disease–negativity status. For more than a decade, rituximab has remained supreme as the monoclonal antibody specifically targeting CD20 expressed on B cells. This activity has led to a role for rituximab in a range of B-cell lymphomas and leukemias. Obinutuzumab, the new molecule, appears promising and has the potential to eventually replace rituximab for the treatment of CLL patients. However, further clinical trial data will be needed to clearly define the role and provide reassurance on safety and efficacy of obinutuzumab. Worldwide, obinutuzumab is undergoing phase III evaluations for non-Hodgkin's lymphoma and particularly diffuse large B-cell lymphoma.

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Conflicts of interest

None declared.

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