**A 5-year follow-up of untreated patients with CLL treated with ofatumumab and chlorambucil: Final analysis of the COMPLEMENT 1 phase 3 trial**

Fritz Offner1, Tadeusz Robak2, Ann Janssens3, K. Govind Babu4, Janusz Kloczko5, Sebastian Grosicki6, Jiri Mayer7, Panagiotis Panagiotidis8, Anna Schuh9, Andrew Pettitt10, Marco Montillo11, Olena Werner12, Ghislaine Vincent13, Sadhvi Khanna13, Peter Hillmen14

**Affiliations:**1Department of Hematology, University Hospital Ghent, Gent, Belgium; 2Department of Haematology, Medical University of Lodz, Lodz, Poland; 3Universitaire Ziekenhuizen Leuven, Leuven, Belgium; 4Department of Medical Oncology, Kidwai Memorial Institute of Oncology, HCG Hospitals, Bangalore, India; 5Department of Hematology, Medical University of Bialystok, Bialystok, Poland; 6Medical University of Silesia, Katowice, Poland; 7Department of Internal Medicine, Haematology and Oncology, Masaryk University Hospital Brno, Brno, Czech Republic; 8National and Kapodistrian University of Athens Medical School, Haematology Department, Department of Internal Medicine University of Athens, Laikon General Hospital, Athens, Greece; 9Department of Oncology, University of Oxford, Oxford, UK; 10University of Liverpool, Liverpool, UK; 11Department of Haematology, Niguarda Cancer Center, Niguarda Hospital, Milan, Italy; 12Novartis Pharma AG, Basel, Switzerland; 13Novartis Pharma S.A.S, Paris, France; 14Department of Haematology, St James’s University Hospital, Leeds, UK

**Corresponding author:**

Prof. Fritz Offner

Head of Department of Hematology

University Hospital Ghent

10 Corneel Heymanslaan

B 9000 Gent, Belgium

Fritz.Offner@UGent.be

Tel: +3293322132

**Summary**

The COMPLEMENT 1 trial investigated the efficacy and safety of ofatumumab+chlorambucil with chlorambucil monotherapy in patients with previously untreated CLL. On long-term follow-up there was an estimated 12% (not significant) and 39% risk reduction in OS and PFS, respectively, in the chemoimmunotherapy arm vs the chemotherapy arm. High rate (61%) of treatment with next-line therapies in both the treatment arms may dilute any potential OS difference and confound the interpretation of the OS results. Addition of ofatumumab to chlorambucil demonstrated clinical benefit and tolerability as a frontline treatment option in patients unfit for fludarabine-containing therapy, with no new safety concerns.

Keywords: Ofatumumab, chlorambucil, COMPLEMENT 1, anti-CD20 monoclonal antibodies, chronic lymphocytic leukaemia

**Short title:** Ofatumumab in untreated patients with CLL

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia, with a heterogeneous disease course and a varying 5-year overall survival (OS) rate of 23%‑93% (Parikh 2018). Treatment with fludarabine, cyclophosphamide, and rituximab (FCR) is the first-line treatment option in fit patients with CLL; however, in elderly patients with CLL, FCR treatment is too toxic and chlorambucil (CHL) remains the treatment of choice but with limited efficacy (Eichhorst*, et al* 2009). The backbone of the treatment landscape for CLL thus shifted rapidly in recent years from chlorambucil to chlorambucil plus anti-CD20 monoclonal antibodies (mAbs) to Btk-inhibitors or combinations of anti-CD20 mAbs and bcl-2 inhibitors (Burger*, et al* 2019, Kater*, et al* 2019). At the start of this study, CHL combinations with different anti-CD20 mAbs were set up to compare to CHL monotherapy. Rituximab and obinutuzumab resulted in improved progression-free survival (PFS), higher response rates, and OS in elderly or unfit patients with CLL having comorbidities (Evers*, et al* 2018, Foa*, et al* 2014, Goede*, et al* 2015, Goede*, et al* 2014, Hillmen*, et al* 2014, Laurenti*, et al* 2013) with many studies successfully exploring them in combination with various chemotherapeutic agents.

The COMPLEMENT 1 trial ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) [NCT00748189]) investigated the efficacy and safety of ofatumumab+CHL compared with CHL monotherapy in patients with previously untreated CLL for whom fludarabine-based treatment regimens were inappropriate. In the published 2015 primary analysis (PA) (Hillmen*, et al* 2015), there was a 43% reduction in the risk of PFS event (hazard ratio [HR]=0.57 (95% confidence interval [CI]: 0.45, 0.72); p<0.0001) with median PFS of 22.4 months in the chemoimmunotherapy arm vs 13.1 months in the chemotherapy arm (improvement in median PFS of 71%). Patients who received ofatumumab+CHL reported a longer time to next therapy, along with higher overall response and complete response rates. At a median follow-up of 28.9 months, the OS was not reached (NR) in either of the study arms. Ofatumumab+CHL was well tolerated as frontline therapy in patients with CLL unfit for fludarabine‑containing therapy (Hillmen*, et al* 2015). In the present analysis, we discuss the 5-year follow‑up and final analyses of OS, investigator-assessed PFS, and cumulative safety.

Adult patients of any age with untreated CLL were stratified by age (<65 vs ≥65 years), Binet stage (A vs B vs C), and Eastern Cooperative Oncology Group performance status (0-1 vs 2) and randomized (1:1) to receive either ofatumumab(cycle 1: 300 mg day 1, 1000 mg day 8; subsequent cycles 2-12: 1000 mg day 1)+CHL (10 mg/m2, days 1-7 for 1 to 12 cycles of 28 days each) or CHL alone (10 mg/m2, days 1-7 for 1 to 12 cycles of 28 days each). Treatment was administered for a minimum of 3 cycles, until best response, or ≤12 cycles. Patients were subsequently followed up for disease status 1 month post-treatment and then every 3 months for up to 5 years after the last dose. Patients who experienced progressive disease or started subsequent CLL therapy were followed every 6 months for up to 5 years after the last dose. PFS and OS was estimated using the Kaplan-Meier method, and survival curves were compared using a stratified log-rank test. The p-values reported from log-rank test are nominal p-values, not adjusted for multiplicity.

Of 447 patients in the study cohort, 221 were randomized to the ofatumumab+CHL arm and 226 to the CHL arm. Patient and disease characteristics were well balanced between the two treatment arms, and, overall, 74% of patients completed the treatment phase. Overall, 183 patients (41%) died, 245 (55%) withdrew from the study, and 19 (4%) patients completed the 5-year follow-up.

In the final analysis, the OS events (defined as death due to any cause during the study) for the ofatumumab+CHL vs CHL arm was 38% vs 44%, respectively. The final analysis of OS resulted in an estimated 12% risk reduction in the risk of death in the chemoimmunotherapy vs the CHL monotherapy arm (HR=0.88; 95% CI: 0.65, 1.17; p=0.363). The final median OS was not estimable (NE) in the chemoimmunotherapy and was 84.67 months in the CHL arm (**Figure 1A**). The estimated OS rate at 5 years was 68.5% in the chemoimmunotherapy arm vs 65.7% in the chemotherapy arm. The overall trend observed in the final analysis was similar to that reported in the PA. The median PFS was 23.39 vs 14.72 months in the chemoimmunotherapy vs chemotherapy arm, which was consistent with that observed in the PA. Update on investigator-assessed PFS showed an estimated 39% risk reduction in the ofatumumab+CHL arm over the CHL alone arm (HR=0.61; 95% CI: 0.49, 0.76; p<0.001) (**Figure 1B**).

Overall, 96% of patients in the ofatumumab+CHL arm vs 90% of patients in the CHL arm had adverse events (AEs). The incidences of grade ≥3 AEs and serious AEs (SAEs) were 64% and 45%, respectively, in the chemoimmunotherapy arm vs 48% and 37%, respectively, in the chemotherapy arm. The most common grade ≥3 AEs (≥5% in either arm) in the ofatumumab+CHL vs CHL alone arm were neutropenia (26% vs 15%), thrombocytopenia (5% vs 10%), pneumonia (9% vs 5%), and anemia (5% each). Drug-related AEs were consistent with those observed in the PA (**Table 1**). SAEs related to study treatment (≥2%) in the ofatumumab+CHL vs CHL arm were neutropenia (3% vs 1%), febrile neutropenia (2% each), and pneumonia (2% each). From the safety population (n=444) a total of 39% and 44% of patients died in the ofatumumab+CHL and CHL arms, respectively. Five on-treatment deaths were reported in both arms; 3 (1%) and 2 (<1%) deaths in the ofatumumab+CHL and CHL alone arms, respectively, occurred within >30 to ≤60 days of the last dose and 76 (35%) and 92 (41%) deaths, respectively, occurred >60 days after the last dose.

 Following discontinuation, a greater proportion of patients in the chemotherapy arm (66%) vs the chemoimmunotherapy arm (56%) received post-treatment anticancer therapy, which was started earlier in the monotherapy arm compared with the ofatumumab+CHL arm (median: 485.5 vs 743 days, respectively); rituximab as monotherapy or in combination with chemotherapy was the most common anticancer therapy in both arms (CHL, 44%; ofatumumab+CHL, 40%).

In the updated survival analysis of the CLL11 study, the median OS was significantly improved in the obinutuzumab+CHL arm as compared with the CHL arm (NR vs 58.5 months; HR=0.62; p=0.0167), along with improved median PFS (31.1 vs 11.1 months; HR=0.20; p<0.0001) (Goede*, et al* 2015). In the same study, the obinutuzumab+CHL combination was also superior to the rituximab+CHL combination, with a superior updated median PFS (28.7 vs 15.7 months, respectively; HR=0.46; p<0.0001) and a trend benefit in OS over the combination of rituximab+CHL (HR=0.77; p=0.0932). Addition of both the mAbs, i.e., ofatumumab and obinutuzumab, reported significantly improved PFS over CHL alone (Goede*, et al* 2015, Hillmen*, et al* 2015).

Although it is difficult to compare between trials, it is notable that the PFS and OS of patients treated with CHL alone was substantially worse in the CLL11 trial compared to COMPLEMENT-1 (Goede*, et al* 2015, Hillmen*, et al* 2015). This raises the possibility that the beneficial effect of adding different anti-CD20 antibodies to CHL might depend on the CHL regimen used (10 mg/m2 days 1-7 repeated every 28 days in COMPLEMENT-1 versus 0.5 mg/kg on day 1 and 15 repeated every 14 days in CLL11). In keeping with this idea, patients who received frontline rituximab+CHL (10 mg/m2 days 1-7 repeated every 28 days) in the phase 3b MABLE study achieved a median PFS of 30 months – substantially better than that observed with rituximab+CHL in CLL11 and similar to that obtained with obinutuzumab+CHL in CLL11 or ofatumumab+CHL in COMPLEMENT-1 (Goede*, et al* 2015, Hillmen*, et al* 2015, Michallet*, et al* 2018)

 The updated safety data by Goede et al. (2015) reported no new safety signals and in the MABLE study the most commonly reported AE was neutropenia (Goede*, et al* 2015, Michallet*, et al* 2018). The frequency of neutropenia in our study (26%) was comparatively lower not only to the MABLE study (49%) but also to that reported in the PA by Goede et al. (2014) in the obinutuzumab+CHL arm (35%) and similar to that of the rituximab+CHL arm (27%); thereby, supporting the safety of ofatumumab+CHL in line with other anti-CD20 mAbs.

Other reports with small sample sizes also support the overall efficacy for use of chemoimmunotherapy regimens. Rituximab+CHL as a frontline treatment option showed a median PFS of 23.5 months, with a median OS of NR; neutropenia and lymphopenia being the most frequent grade 3/4 AEs (Hillmen*, et al* 2014). In elderly unfit patients who received rituximab+CHL, the median PFS reached at a median time of 29 months and the OS rate was 78% at a median follow-up of 30 months with neutropenia being the most common grade 3-4 AE (Laurenti*, et al* 2013). A retrospective data analysis of obinutuzumab with CHL from the Polish Adult Leukemia Group reported a median PFS of NR at a median follow-up of 18 months (Dlugosz-Danecka*, et al* 2018). On comparing the median PFS of anti-CD20 mAbs with CHL, ofatumumab was similar and that of obinutuzumab was better than rituximab with neutropenia being the most common grade 3-4 AE (Goede*, et al* 2015, Hillmen*, et al* 2014). These findings support the use of anti-CD20 mAbs with CHL for better outcomes in elderly unfit patients and as a frontline treatment option in patients with CLL.

In conclusion, the long-term follow-up of the COMPLEMENT 1 study supports the results of the PA, with an estimated 12% and 39% risk reduction in OS and investigator-assessed PFS, respectively, in the chemoimmunotherapy arm vs the chemotherapy arm although the OS results remain confounded by the use of next line therapies. Addition of ofatumumab to CHL demonstrated clinical benefit and tolerability as a frontline treatment option in patients unfit for fludarabine-containing therapy, with no new safety concerns.

**Authors’ Disclosure of Potential Conflicts of InteresT**

FO, AJ, KGB, JK, and SG have nothing to disclose. TR received research funding from Novartis, MJ received research funding from Novartis and GSK and accepted travel from Novartis. PP received honoraria from Novartis, GSK, Roche, Gilead, Abbvie and Janssen; research funding from Novartis, GSK, and Roche; expert testimony to Roche and Abbvie; accepted travel from Novartis, Genesis, Abbvie, and Roche, AS received honoraria from Gilead, Janssen, Abbvie, Acerta, Astra Zeneca, and Roche; consulting and advisory role for Roche, Abbvie, Janssen, and Gilead; research funding from Janssen and Gilead; travel from Roche, Abbvie, Janssen and Gilead. AP received research funding from Celgene, Gilead, GSK, Napp and Roch; speaker fees from Gilead and hospitality from Celgene and Gilead. Peter Hillmen is on advisory boards of Janssen, Acerta, Abbvie, and Gilead; speaker’s fee from Janssen, Acerta, and Abbvie; research funding from Janssen, Roche, Gilead and Abbvie; travel from Janssen and Abbvie. TS, GV are employed by and hold stock or other ownership of Novartis. OW is employed by Novartis. All potential conflict of interest have been disclosed.

**AUTHOR CONTRIBUTIONS**

Data analysis and interpretation were performed by FO, TR, OW, GV, SK, and PH. Collection and assembly of data were performed by FO, TR, AJ, KGB, JK, SG, JM, PP, AS, AP, MM, GV, OW, SK, and PH. Concept and design were undertaken by FO and PH. FO, TR, AJ, KGB, JK, SG, JM, PP, AS, AP, MM, GV, OW, SK, and PH contributed to manuscript writing. All authors contributed to final approval of the manuscript and are accountable for all aspects of the work.

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**Table I. Grade 3, 4, and 5 AEs (≥5% in any group) and drug-related grade 3, 4, and 5 AEs by preferred term (≥2% in any group)**

|  |  |  |
| --- | --- | --- |
| **Preferred Term** | **OFA+CHL****(N=217)** | **CHL****(N=227)** |
| **Grade 3** | **Grade 4** | **Grade 5** | **Grade 3** | **Grade 4** | **Grade 5** |
| Grade 3, 4, and 5 AEs (≥5%), n (%) |
| Neutropenia | 32 (15%) | 25 (12%) | 0 | 16 (7%) | 17 (7%) | 0 |
| Thrombocytopenia | 8 (4%) | 2 (<1%) | 0 | 16 (7%) | 7 (3%) | 0 |
| Pneumonia | 13 (6%) | 2 (<1%) | 4 (2%) | 7 (3%) | 2 (<1%) | 3 (1%) |
| Drug-related grade 3, 4, and 5 AEs (≥2%), n (%) |
| **Any event** | **59 (27%)** | **35 (16%)** | **3 (1%)** | **38 (17%)** | **26 (11%)** | **2 (<1%)** |
| Neutropenia | 31 (14%) | 23 (11%) | 0 | 14 (6%) | 15 (7%) | 0 |
| Thrombocytopenia | 7 (3%) | 2 (<1%) | 0 | 12 (5%) | 6 (3%) | 0 |
| Anemia | 4 (2%) | 3 (1%) | 0 | 7 (3%) | 2 (<1%) | 0 |
| Febrile neutropenia | 2 (<1%) | 1 (<1%) | 0 | 1 (<1%) | 4 (2%) | 0 |
| Leukopenia | 5 (2%) | 1 (<1%) | 0 | 1 (<1%) | 0 | 0 |
| Rash | 4 (2%) | 0 | 0 | 0 | 0 | 0 |

CHL, chlorambucil; OFA, ofatumumab

**Figure legend:**

**Figure 1 A) Kaplan-Meier overall survival curve and B) Kaplan-Meier investigator-assessed progression-free survival curve**

CHL, chlorambucil; CI, confidence interval; OFA, ofatumumab