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To the editor:

Venetoclax and obinutuzumab in chronic lymphocytic leukemia

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In chronic lymphocytic leukemia (CLL), the median age at diagnosis is 72 years, and most patients requiring therapy have coexisting medical conditions. Venetoclax is a potent BH3-mimetic compound that selectively antagonizes BCL-2 and has shown efficacy as monotherapy and with rituximab in patients with relapsed/refractory CLL.[1-4] Obinutuzumab has also demonstrated impressive clinical activity in CLL as a single agent and in combination.[5,6] First results from an ongoing phase 1b trial with both compounds suggest a venetoclax dose of 400 mg.[7] In the phase 3 CLL14 trial, patients with previously untreated CLL and coexisting medical conditions as assessed by a cumulative illness rating scale (CIRS) total score >6 and/or an estimated creatinine clearance <70 mL/min were randomized to receive either 6 cycles of chlorambucil plus obinutuzumab plus 6 cycles of chlorambucil or 6 cycles of venetoclax plus obinutuzumab plus 6 cycles of venetoclax (NCT02242942). Here, we report the safety and efficacy results of the run-in phase of the CLL14 trial.

Between December 2014 and April 2015, 13 previously untreated patients with CLL from Australia, Canada, Germany, New Zealand, the United States, and Spain were enrolled to receive the combination of obinutuzumab and venetoclax. At baseline, the patients had a median age of 75 years (range, 59-88 years), a median creatinine clearance of 57.6 mL/min, and a median CIRS score of 8 (Table 1). Obinutuzumab was administered IV as follows: 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8 and day 15 of cycle 1, and subsequently 1000 mg on day 1 for cycles 2 to 6. Daily oral doses of venetoclax were gradually ramped up each week, starting with 20 mg on day 22 of cycle 1 and then increased to 50 mg, 100 mg, 200 mg, and 400 mg daily, which was continued through to cycle 12.

At data cutoff, all patients had completed 12 months of therapy with the exception of 2 patients: 1 patient developed a grade 4 infusion-related reaction (IRR) during the first dose of obinutuzumab and was withdrawn from the study according to protocol requirements; the second patient discontinued at cycle 8 due to the patient's wish. All patients experienced at least 1 adverse event (AE), and 10 patients (83.3%) had at least 1 grade 3/4 AE (Table 2). Seven patients (58.3%) had grade 3/4 neutropenia, and among these patients, 5 were treated successfully with granulocyte colony-stimulating factor and 3 events (25.0%) of grade 3/4 febrile neutropenia occurred. Reported infections (in 8 patients [66.7%]) were mostly mild, except for 2 grade 3/4 infections (16.7%) (1 case each of influenza and respiratory tract infection). No fatal AEs were reported. Two patients (16.7%) experienced laboratory tumor lysis syndrome (TLS); 1 event occurred during venetoclax ramp up to 200 mg at cycle 2 and the other event on the first day of cycle 1 after the 100-mg infusion of obinutuzumab. Both events were grade 3 with no evidence of clinical TLS in either patient; they were managed by IV fluids (1.5-2 L) and in 1 case by administration of sodium polystyrene sulfonate for treatment of hyperkalemia and resolved without sequelae. No clinical TLS events were reported. IRRs occurred in 9 patients (75.0%) during the first obinutuzumab administration.

Rapid reduction in the peripheral lymphocyte count was observed in all patients within the first cycle of obinutuzumab (supplemental Figure 1, available on the *Blood* Web site). Overall response rate 3 months after the end of treatment was 100%. Complete responses according to International Workshop on Chronic Lymphocytic Leukemia guidelines were achieved in 7 of 12 patients (58%), including 1 patient with incomplete bone marrow (BM) recovery due to a hemoglobin value of 10.2 g/dL. Five patients were reported with a partial response, 3 of whom had a normalization of blood count and resolved lymphadenopathy but did not consent to BM biopsy and were therefore graded as partial response. Two patients had residual lymph nodes of 18 mm and 16 mm. All patients showed reduction of lymphadenopathy (supplemental Figure 2). At cycle 7, 10 of 11 patients with available minimal residual disease (MRD) peripheral blood (PB) samples were MRD negative ($<10^{-4}$), and 1 patient was assessed as intermediate ($\geq 10^{-4}$ $<10^{-2}$). At cycles 9 and 12, all patients with available MRD data were assessed as MRD negative in the PB, and at final staging (3 months after the end of treatment), 11 of 12 patients were MRD negative in the PB and 1 was assessed as intermediate (supplemental Table 1). At cycle 9, BM aspirates from 5 patients were available, and of those, 3 were MRD negative, 1 was intermediate, and 1 was positive ($\geq 10^{-2}$) (supplemental Table 1). At final staging, BM

Table 1. Patient baseline characteristics (N = 13)*

Demographic and baseline characteristics	Total
Sex	
Male	8 (61.5)
Female	5 (38.5)
Age (y)	
Median (range)	75.0 (59–88)
≥70	11 (84.6)
Binet stage	
A	2 (15.4)
B	3 (23.1)
C	8 (61.5)
CIRS score (total)	
Median (range)	8 (6–14)
>6	10 (76.9)
Cardiac scale score >0	6 (46.2)
Hypertension scale score >0	7 (53.8)
Vascular scale score >0	7 (53.8)
Respiratory scale score >0	9 (69.2)
Eye, ear, nose, throat, larynx scale score >0	6 (46.2)
Upper gastrointestinal scale score >0	4 (30.8)
Lower gastrointestinal scale score >0	5 (38.5)
Hepatic scale score >0	1 (7.7)
Renal scale score >0	5 (38.5)
Other genitourinary scale score >0	7 (53.8)
Musculoskeletal-integumentary scale score >0	8 (61.5)
Neurological scale score >0	3 (23.1)
Endocrine-metabolic scale score >0	8 (61.5)
Psychiatric-behavioral scale score >0	2 (15.4)
CrCl* (mL/min)	
Median (range)	57.6 (30.3-108.2)
<70	10 (76.9)
Cytogenetic subgroup (hierarchical order) (n = 8)	
del(17p)	2 (25.0)
del(11q)	2 (25.0)
Trisomy 12	1 (12.5)
Not del(17p)/del(11q)/trisomy 12/del(13q)	0 (0.0)
del(13q)	3 (37.5)
Missing sample	5 (41.7)
***TP53* mutational status (n = 8)**	
Mutated	2 (25.0)
Not mutated	6 (75.0)
Missing sample	5 (41.7)
***TP53* deleted and/or mutated (n = 8)**	
Yes	2 (25.0)
None	6 (75.0)
Missing sample	5 (41.7)
***IGHV* mutational status (n = 7)**	
Mutated	1 (14.3)
Unmutated	6 (85.7)
Missing sample	5 (41.7)
Sample not evaluable	1 (7.7)

Values represent number (percentage) of patients unless otherwise indicated.
CrCl, creatinine clearance.
*One patient developed a grade 4 IRR during the first dose of obinutuzumab and was withdrawn from the study according to protocol requirements.

aspirates of 7 patients were available, and of those, 5 were MRD negative and 2 were intermediate. One of 7 patients was assessed negative in PB and intermediate in BM at final staging. At a median follow-up of 15 months, there were no events of progressive disease or deaths.

Our results demonstrated that venetoclax could be safely combined with obinutuzumab, even in patients with comorbidities and at increased risk of TLS due to renal impairment. The occurrence of TLS in venetoclax-treated patients has been reported in previous studies, including 2 fatal events, and warrants careful monitoring.[2] In our study, firstly, the individual risk for TLS was assessed prior to treatment administration based on lymphocyte count and lymph node mass. Secondly, patients received hydration with at least 1.5 to 2 L and allopurinol as prophylaxis, and patients at high risk of TLS and with high uric acid levels also received rasburicase prophylactically. Thirdly, the combination treatment was initiated with obinutuzumab followed by a gradual venetoclax dose ramp up over 5 weeks. Following this strategy, no clinical TLS event was observed in this study and 2 laboratory TLS events occurred; further treatment and observation is warranted in the main phase to assess TLS frequency in this patient population.

The frequency of neutropenia (66.7%) and febrile neutropenia (25%) was comparable to other venetoclax-based treatments,[2,4] where neutropenia rates of 45% to 55% and neutropenic fever rates of 6% to 12% were observed. The rates of neutropenia with chlorambucil plus obinutuzumab were lower (eg, in CLL11),[8] indicating that BCL-2 inhibition might induce clinically relevant cytopenias. This aspect needs to be carefully evaluated in the main phase of CLL14 and future trials utilizing BCL-2 inhibition.

Efficacy results for venetoclax and obinutuzumab demonstrate an increased response rate with an overall response rate of 100% and a 92% MRD negativity rate in PB 3 months after treatment completion. Given the limited number of available BM samples and a few discordances observed between MRD levels assessed in PB and BM, further follow-up is needed to evaluate the depth of response.[9-11]

A phase 1b study showed good safety and efficacy of venetoclax plus rituximab in 49 patients with relapsed/refractory CLL.[4] Our data suggest that venetoclax and obinutuzumab can be safely administered in previously untreated CLL patients of advanced age with coexisting medical conditions. The regimen induces high rates of overall response, though the small patient population should be taken into account. Longer follow-up and a larger patient population will determine whether these responses remain durable. The randomized phase of the CLL14 (BO25323) study was opened in August 2015 and completed recruitment of 432 patients in August 2016.

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Contribution: K.F., O.A.-S., B.E., S.S., and M.H. designed the research, collected, analyzed and interpreted the data, and wrote the paper; A.-M.F. and S.B. collected, analyzed, and interpreted the data and wrote the paper; M.D. and S.W. analyzed data; J.B. and C.-M.W. analyzed and interpreted the data and wrote the paper; K.H. analyzed and interpreted the data; R.H. reviewed and approved the paper; E.T. collected the data and wrote the paper; L.F. and M.M. interpreted the data.; A.W.L., J.J.M.v.D., and M.R. collected and analyzed the data. V.G. designed the research and wrote the paper. T.J.K., R.W., S.R., T.S. S.O., C.O., and J.L. provided patients. All authors critically reviewed the paper and approved the final version.

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Table 2. Adverse events

Safety	Total
Total no. of AEs*	236
Patients receiving obinutuzumab and venetoclax with ≥1 AE	12 (100.0)
Total no. of grade 3/4 AEs	30
Patients receiving obinutuzumab and venetoclax with ≥1 grade 3-4 AE	10 (83.3)
Patients receiving obinutuzumab and venetoclax (n)	12
Neutropenia	
Any grade	8 (66.7)
Grade 3-4	7 (58.3)
Febrile neutropenia	
Any grade	3 (25.0)
Grade 3-4	3 (25.0)
Infections	
Any grade	8 (66.7)†
Grade 3-4	2 (16.7)‡
Bradycardia	
Any grade	1 (8.3)
Grade 3-4	1 (8.3)
Diarrhea	
Any grade	6 (50.0)
Grade 3-4	1 (8.3)
Hyperglycemia	
Any grade	2 (16.7)
Grade 3-4	1 (8.3)
IRR	
Any grade	9 (75.0)
Grade 3-4	1 (8.3)
Leukopenia	
Any grade	1 (8.3)
Grade 3-4	1 (8.3)
Myocardial infarction	
Any grade	1 (8.3)
Grade 3-4	1 (8.3)
Presyncope	
Any grade	2 (16.7)
Grade 3-4	1 (8.3)
Pyrexia	
Any grade	4 (33.3)
Grade 3-4	1 (8.3)
Syncope	
Any grade	2 (16.7)
Grade 3-4	2 (16.7)
Thrombocytopenia	
Any grade	2 (16.7)
Grade 3-4	2 (16.7)
Laboratory TLS	
Any grade	2 (16.7)
Grade 3-4	2 (16.7)
Transaminases increased	
Any grade	2 (16.7)
Grade 3-4	1 (8.3)
Pruritus	
Any grade	7 (58.3)
Grade 3-4	0 (0.0)
Cough	
Any grade	6 (50.0)
Grade 3-4	0 (0.0)
Constipation	
Any grade	5 (41.7)
Grade 3-4	0 (0.0)
Hyperkalemia	
Any grade	5 (41.7)
Grade 3-4	0 (0.0)
Dizziness	
Any grade	4 (33.3)
Grade 3-4	0 (0.0)
Nausea	
Any grade	4 (33.3)
Grade 3-4	0 (0.0)
Back pain	
Any grade	3 (25.0)
Grade 3-4	0 (0.0)
Fatigue	
Any grade	3 (25.0)
Grade 3-4	0 (0.0)
Headache	
Any grade	3 (25.0)
Grade 3-4	0 (0.0)
Vomiting	
Any grade	3 (25.0)
Grade 3-4	0 (0.0)

Values represent number (percentage) of patients unless otherwise indicated.

*This table includes all grade 3-4 AEs regardless of frequency and AEs of any grade observed in at least 3 patients.

†Including 2 cases of influenza infections, 2 upper respiratory tract infections, 1 respiratory infection, 1 urinary tract infection, 1 case of bronchitis, 1 case of cystitis, 1 ear infection, 1 eye infection, 1 localized infection, 1 case of oral herpes, 1 case of paronychia, 1 case of pneumonia, 1 case of rhinitis, and 1 skin infection.

‡Including 1 case of influenza and 1 respiratory tract infection.

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To the editor:

FNDC3B is another novel partner fused to RARA in the t(3;17)(q26;q21) variant of acute promyelocytic leukemia

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Acute promyelocytic leukemia (APL) is characterized by the promyelocytic leukemia-retinoic acid receptor α (*PML-RARA*) fusion. In rare instances, *RARA* is fused to other partners, which dictate sensitivity to targeted therapies. Chen et al previously reported in *Blood* a novel *TBLR1-RARA* fusion, which is all-*trans*-retinoic acid (ATRA)-insensitive in vivo, in a t(3;17)(q26;q21)-harboring APL.[1,2] Here, we report another new *RARA* fusion resulting from the same translocation in a variant APL patient.

The patient was a 36-year-old man who presented with fatigue, dyspnea, and easy bruising for 2 weeks. Complete blood count revealed a hemoglobin level of 5.4 g/dL, platelet count of 41×10^9/L, and white blood cell count of 3.6×10^9/L with 60% hypergranular blasts. Clotting profile showed a decreased fibrinogen level and prolonged prothrombin time but normal activated partial thromboplastin time. Bone marrow (BM) examination showed 68% of blasts with morphology similar to those in peripheral smear (Figure 1A). The blasts were positive for myeloperoxidase, CD13, CD15, CD33, and CD117 but negative for CD34 and HLA-DR by flow cytometry. A diagnosis of APL was suggested and ATRA (45 mg/m^2 per day) was initiated while awaiting molecular findings. On day 4 of ATRA therapy, the patient developed differentiation syndrome (DS) with fluid retention and pleural effusions. Steroids and diuretics were started, and the 7 + 3 induction chemotherapy was commenced with cytarabine (200 mg/m^2) and daunorubicin (60 mg/m^2). A morphological complete remission was confirmed at day 30.

Reverse transcription–polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH) failed to detect *PML-RARA* in the diagnostic BM. However, FISH indicated 72% of cells with split *RARA* signals, suggesting a variant *RARA* translocation. Karyotype and metaphase FISH studies revealed 45,X,-Y,t(3;17)(q26;q21)[8]/46,XY [5] (Figure 1B-C) but the expected *TBLR1-RARA* fusion previously identified in t(3;17) was absent. No mutations in *FLT3*, *NPM1*, *CEBPA*, *DNMT3A*, *RUNX1*, *K/NRAS*, *WT1*, or *IDH1/2* were detected. Using 5′-rapid amplification of complementary DNA ends, we found that *RARA* was fused to another 3q26 gene called fibronectin type III (FN3) domain containing 3B (*FNDC3B*) in our patient. Subsequent RT-PCR confirmed the fusion between exon 24 of *FNDC3B* and exon 3 of *RARA* (Figure 1D), which is involved in all other *RARA* fusions. FNDC3B was originally identified as an adipocyte differentiation factor.[3] It contains 9 FN3 domains, which are implicated in protein interactions. The full-length *FNDC3B-RARA* transcript is predicted to encode a 1461-amino acid protein, containing 8 FN3 domains of FNDC3B as well as the DNA-binding and ligand-binding domain of RARA (Figure 1E). Two reciprocal *RARA-FNDC3B* transcripts were also detected. The major transcript involves an in-frame fusion between *RARA* exon 2 and *FNDC3B* exon 25, whereas the minor transcript involves an out-of-frame fusion between the same *RARA* exon and *FNDC3B* exon 26 (Figure 1D). These transcripts are expected to generate 205- and 111-amino acid proteins, respectively (Figure 1E). Both *FNDC3B-RARA* and *RARA-FNDC3B* fusions were undetected after the patient