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Letters to Blood

TO THE EDITOR:

Durable remissions with obinutuzumab-based chemoimmunotherapy: long-term follow-up of the phase 1b GALTON trial in CLL

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GALTON was an open-label, parallel-arm, nonrandomized, multicenter, phase 1b study to investigate the safety and preliminary efficacy of either obinutuzumab (G) plus fludarabine/cyclophosphamide (FC; G-FC) or obinutuzumab plus bendamustine (B; G-B) as frontline therapy in chronic lymphocytic leukemia (CLL). Initial results of this study have been previously reported[1]; here, we report the final study results.

Enrolled patients met the International Workshop on Chronic Lymphocytic Leukemia 2008 criteria for therapy and were considered fit for chemoimmunotherapy by the investigators. Each center selected 1 treatment arm for all of its patients. Details of treatment administration and end points have been published previously.[1] Evaluation of B-cell depletion, defined as $<0.07 \times 10^9$ $CD19^+$ cells per liter, was a planned component of this protocol. Minimal residual disease (MRD) was measured in peripheral blood using 4-color flow cytometry and the ClonoSEQ immunoglobulin next-generation sequencing assay[2-4] in a single-center exploratory analysis. In accordance with the generally accepted definition, undetectable MRD as measured by flow cytometry was defined as <1 CLL cell per 10 000 leukocytes.[5]

Forty-one patients were enrolled: 21 in the G-FC arm and 20 in the G-B arm. Median age was 60 years (range, 25-80 years), and approximately one-third of patients had advanced Rai stage III/IV disease. An unmutated immunoglobulin heavy chain variable region gene (*IGHV*) was seen in 45% of patients tested (17 of 38); the G-FC arm had 1 patient with del(17p) and 4 with del(11q), whereas the G-B arm had 2 patients with del(11q). Median time from diagnosis to study therapy was 24 and 32 months in the G-FC and G-B arms, respectively.

As previously reported,[1] the primary analysis of the GALTON study showed that G-FC and G-B had manageable toxicity, with infusion-related reactions being the most common adverse event (AE) (88%; grade 3-4, 20%). Grade 3-4 neutropenia was reported in 48% and 55% of patients in the G-FC and G-B arms, respectively. The objective response rate was 62% (13 of 21) in the G-FC arm and 90% (18 of 20) in the G-B arm. The objective response rate in the G-FC arm likely does not reflect the true activity of the regimen as it is based on an intent-to-treat analysis, including 3 patients who did not reach their initial response evaluation, 3 patients who did not have the full protocol-required response evaluation, and 1 patient whose response evaluation was outside of the protocol-required window and was therefore disallowed. At the time of data cutoff for the primary analysis (median follow-up 20.7 and 23.5 months in the G-FC and G-B cohorts, respectively), no patients had relapsed or died.

In this final analysis, median observation time was 40.4 months (range, 17.6-43.6 months; clinical cutoff date, 8 December 2015), representing an additional 2 years beyond the previous report. Thirty-five of the 41 enrolled patients (85.4%) completed the study (G-FC arm, 17 of 21 [81.0%]; G-B arm, 18 of 20 [90.0%]), and 31 (75.6%) completed study treatment (G-FC arm, 14 of 21 [66.7%]; G-B arm, 17 of 20 [85.0%]). Seven of 21 patients (33.3%) in the G-FC arm and 2 of 20 patients (10.0%) in the G-B arm discontinued study treatment due to an AE; discontinuations were predominantly due to cytopenia, along with 1 case of grade 3-4 transaminitis in the G-FC arm after the first 100-mg dose of obinutuzumab. During the posttreatment reporting period, 10 of 41 patients (24.4%) experienced at least 1 grade 3-5 AE (G-FC arm, 2 of 21 [9.5%]; G-B arm, 8 of 20 [40.0%]; Table 1). In the same period, 7 additional serious AEs were reported in 4 patients, all in the G-B arm, including 1 pneumonitis and respiratory failure grade 5 (as noted later in this letter), 1 leukopenia and neutropenia grade 4, 1 small cell lung cancer and pneumothorax grade 4, and 1 melanoma. During the follow-up period, 6 patients had at least 1 grade 3-5 AE of neutropenia (G-FC arm, 2 of 21 [9.5%]; G-B arm, 4 of 20 [20.0%]; Table 1).

At the time of data cutoff, only 4 progression-free survival (PFS) or overall survival events had been observed and median PFS and overall survival were not reached. Thirty-seven patients were alive in follow-up: 18 in the G-FC arm (2 lost to follow-up) and 19 in the G-B arm. One patient per arm was deceased due to an AE: unreported cause of death in 1 patient with unresolved grade 4 pancytopenia in the G-FC arm, who underwent allogeneic stem cell transplantation (SCT) >15 months after completing trial

Table 1. Grade 3-5 AEs during the follow-up period of the GALTON trial

AE*	During follow-up period, n (%)			Overall, n (%)†		
	G-FC, n = 21	G-B, n = 20	All patients, N = 41	G-FC, n = 21	G-B, n = 20	All patients, N = 41
Total no. of patients with at least 1 event	2 (9.5)	8 (40.0)	10 (24.4)	15 (71.4)	18 (90.0)	33 (80.5)
Febrile neutropenia	2 (9.5)	1 (5.0)	3 (7.3)	4 (19.0)	2 (10.0)	6 (14.6)
Neutropenia	0	3 (15.0)	3 (7.3)	5 (23.8)	10 (50.0)	15 (36.6)
Leukopenia	0	1 (5.0)	1 (2.4)	0	1 (5.0)	1 (2.4)
Thrombocytopenia	0	1 (5.0)	1 (2.4)	3 (14.3)	3 (15.0)	6 (14.6)
Dyspnea	0	1 (5.0)	1 (2.4)	0	1 (5.0)	1 (2.4)
Pneumonitis	0	1 (5.0)	1 (2.4)	0	1 (5.0)	1 (2.4)
Pneumothorax	0	1 (5.0)	1 (2.4)	0	1 (5.0)	1 (2.4)
Respiratory failure	0	1 (5.0)	1 (2.4)	0	1 (5.0)	1 (2.4)
Small cell lung cancer	0	1 (5.0)	1 (2.4)	0	1 (5.0)	1 (2.4)
Melanoma	0	1 (5.0)	1 (2.4)	0	1 (5.0)	1 (2.4)
Chills	0	1 (5.0)	1 (2.4)	0	1 (5.0)	1 (2.4)
Skin infection	0	1 (5.0)	1 (2.4)	0	1 (5.0)	1 (2.4)
Syncope	0	1 (5.0)	1 (2.4)	0	1 (5.0)	1 (2.4)
Intermittent claudication	0	1 (5.0)	1 (2.4)	0	1 (5.0)	1 (2.4)

The follow-up period was 36 months. One case each of myelodysplastic syndrome and of Richter transformation were noted after the planned follow-up of the trial.

*Multiple occurrences of the same AE in an individual are only counted once.

†Including only those grade 3-5 AEs with an incidence rate of at least 5%.

therapy and died 11 months after SCT, and 1 pneumonitis with respiratory failure in the G-B arm; neither death was considered to be related to study treatment. One event of progressive disease was seen in each arm. Thus, at the end of the study, 95% of patients were alive and 90% of patients had not experienced a PFS event.

Following the last cycle of therapy, 39 of 41 patients (95.1%) were B-cell–depleted ($<0.07 \times 10^9$/L): 19 of 21 (90.5%) in the G-FC arm (1 patient did not have B-cell depletion, and the second was not evaluable due to an absence of data) and 20 of 20 in the G-B arm. Within 6 to 12 months of study follow-up, very few patients had recovered from B-cell depletion (2 of 19 patients [10.5%] in the G-FC arm and 0 of 20 in the G-B arm). At 36 months, 9 of 19 patients (47.3%) in the G-FC arm had achieved B-cell recovery, 3 of 19 patients (15.8%) were still B-cell–depleted, and 7 of 19 patients (36.8%) were not evaluable. In the G-B arm, 6 of 20 patients (30%) had achieved B-cell recovery, 1 patient was still B-cell–depleted, and 13 of 20 patients (65%) were not evaluable.

At posttherapy restaging, attempts to perform bone marrow MRD testing were limited by too few cells to achieve 10^{-4} sensitivity. Furthermore, as false-negative results are common after therapy with an anti-CD20 antibody, the value of these results was unclear. Between 6 and 14 months after therapy, when this concern persists but is lessening, 9 patients in the G-FC arm were tested for MRD by 4-color flow cytometry in peripheral blood, and all had undetectable MRD (patients in the G-B arm were not tested). With the caveat of small patient numbers and inevitable differences in patient populations across studies, these results suggest that G-FC may clear residual disease more effectively than rituximab plus FC, given that previous studies of rituximab plus FC showed an undetectable MRD rate of ≤45%.[6,7] Eight of the patients with undetectable MRD from the current analysis were also tested with the clonoSEQ assay. The 4 patients who had undetectable MRD in both assays remain in remission, whereas 2 of the 4 who were positive only by clonoSEQ analysis died after the protocol follow-up period: 1 of pneumonia in the setting of Richter transformation and the other from complications related to myelodysplastic syndrome. The relationship of those events to the clonoSEQ positivity is unclear. One other patient who was positive by clonoSEQ underwent previously planned allogeneic SCT and remains in remission. These data are consistent with the notion that flow cytometry is less sensitive than the clonoSEQ assay for detecting MRD, as noted in prior studies.[8,9]

We conclude that obinutuzumab with either fludarabine/cyclophosphamide or bendamustine results in excellent long-term disease control in this patient population, largely without

del(17p).[10-13] These regimens were well tolerated with AEs similar to those of comparable chemoimmunotherapy regimens using rituximab. Most evaluable patients had B-cell recovery by 36 months. These data support moving forward with these regimens in subsequent trials, which are currently ongoing.[14-16]

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Authorship

Contribution: S.O., J.H., and T.J.K. designed the study; J.R.B., S.O., C.D.K., H.E., J.M.P., and T.J.K. enrolled patients; T.M. provided statistical analysis; J.R.B., R.M.-Z., and T.J.K. analyzed and interpreted data; J.R.B. wrote the first draft of the manuscript with assistance from R.M.-Z. and T.M.; J.R.B., S.O., C.D.K., H.E., J.M.P., J.H., R.M.-Z., T.M., and T.J.K. reviewed and commented on the manuscript; and all authors had access to the study data and made a substantial contribution to the study, interpreted data, reviewed the manuscript, and approved the final version of the manuscript.

Conflict-of-interest disclosure: J.R.B. has served as a consultant for Abbvie, Acerta, Beigene, Genentech/Roche, Gilead, Juno/Celgene, Kite, Loxo, Novartis, Pfizer, Pharmacyclics, Sunesis, TG Therapeutics, and Verastem; received honoraria from Janssen and Teva; received research funding from Gilead, Loxo, Sun, and Verastem; and served on data safety monitoring committees for Morphosys and Invectys. S.O. has served as a consultant for Abbvie, Alexion, Amgen, Astellas, Celgene, GlaxoSmithKline, Janssen Oncology, Aptose Biosciences Inc, and Vaniam Group LLC; received research funding from Kite, Regeneron, and Acerta; and served as a consultant for, and received research funding from, Gilead, Pharmacyclics, TG Therapeutics, Pfizer, and Sunesis. T.J.K. has received research funding from, served as a consultant for, and received honoraria from F. Hoffmann-La Roche. C.D.K. has received honoraria from Genentech. H.E. has served as a consultant for F. Hoffmann-La Roche and Genentech and has received honoraria from F. Hoffmann-La Roche. J.M.P. has received research funding from Genentech. J.H. is an employee of Genentech, and owns stock in F. Hoffmann-La Roche. R.M.-Z. and T.M. are employees of F. Hoffmann-La Roche.

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