To the editor:

Rituximab maintenance obviates the poor prognosis associated with circulating lymphoma cells in patients with follicular lymphoma

Follicular lymphoma is typically a disseminated disease with frequent bone marrow infiltration at the time of diagnosis,[1] but only a few patients manifest detectable circulating peripheral blood lymphoma cells (CLC).[2-5] We recently described the poor prognosis of patients with follicular lymphoma presenting with this feature. The present report evaluates the effect of rituximab maintenance on the outcome of such patients.

At Primary Rituximab and Maintenance (PRIMA) study (NCT00140582)[6] entry, 92 patients were identified with CLC assessed by local laboratories and documented in case reports forms, with a mean lymphoma cell count of 14.4×10^9/L (median, 2×10^9/L; range, 0.1 - 176×10^9/L). These patients with CLC were significantly younger and presented more frequently with advanced-stage disease, extranodal involvement, anemia, and high serum levels of lactate dehydrogenase or β_2-microglobulin than those without CLC (each $P < .05$; data not shown). Response rates at the end of rituximab chemotherapy induction were similar in patients with and without CLC (complete response/complete response unconfirmed [CR/CRu], 68.5% and 64.9%, and partial response [PR], 25% and 25%, respectively).[7] Considering all patients from randomization (13 patients with CLC failed to reach randomization), progression-free survival (PFS) and time to next lymphoma treatment (TTNT) both were shorter in patients with CLC (respectively, 36.8 months vs not reached [log-rank $P = .0003$] and 45.6 months vs not reached [$P = .0005$]). However, a striking difference was observed between the 2 PRIMA study groups. In patients from the observation group, the presence of CLC at study entry was associated with a significantly reduced PFS (median, 22 months vs 54 months for patients without CLC; $P < .0001$; Figure 1A) and TTNT (median, 30 months vs not reached; $P < .0001$); whereas in the rituximab maintenance group, PFS and TTNT for patients with or without CLC did not significantly differ ($P = .3$ and .9, respectively; Figure 1B). A trend for a shorter overall survival for patients with CLC was also observed in the observation group ($P = .07$; hazard ratio [HR], 2.4; 95% confidence interval [CI], 0.9 - 6.34), but not in the maintenance group ($P = .61$; HR, 0.7; 95% CI, 0.16 - 2.9). Only 5 of 44 patients with CLC experiencing disease progression presented with CLC again at that time, as assessed at local laboratories. Of note, the PFS for patients without CLC according to the randomization group remained highly significant ($P < .0001$; HR, 0.615; 95% CI, 0.49 - 0.77), indicating that rituximab maintenance benefit was not restricted to patients with CLC.

These results indicate that 2-year rituximab maintenance is able to obviate the poor prognosis associated with CLC but also raise several questions. Despite similar CR/CRu rates, shorter PFS estimates in the observation group for patients with CLC demonstrate the persistence of residual lymphoma cells responsible for early progression. Monitoring minimal residual disease at the end of induction, using quantitative methods, could be valuable in this context.[8] Moreover, it may be hypothesized that different mechanisms of action of the antibody, including induction of immune specific mechanisms,[9] may account for the clinical efficacy of rituximab maintenance against the pool of these residual lymphoma cells. Overall, achieving a sustained control of tumor cells in these patients with high circulating tumor burden at diagnosis appears to require a prolonged treatment, even if an apparent CR is achieved after induction.

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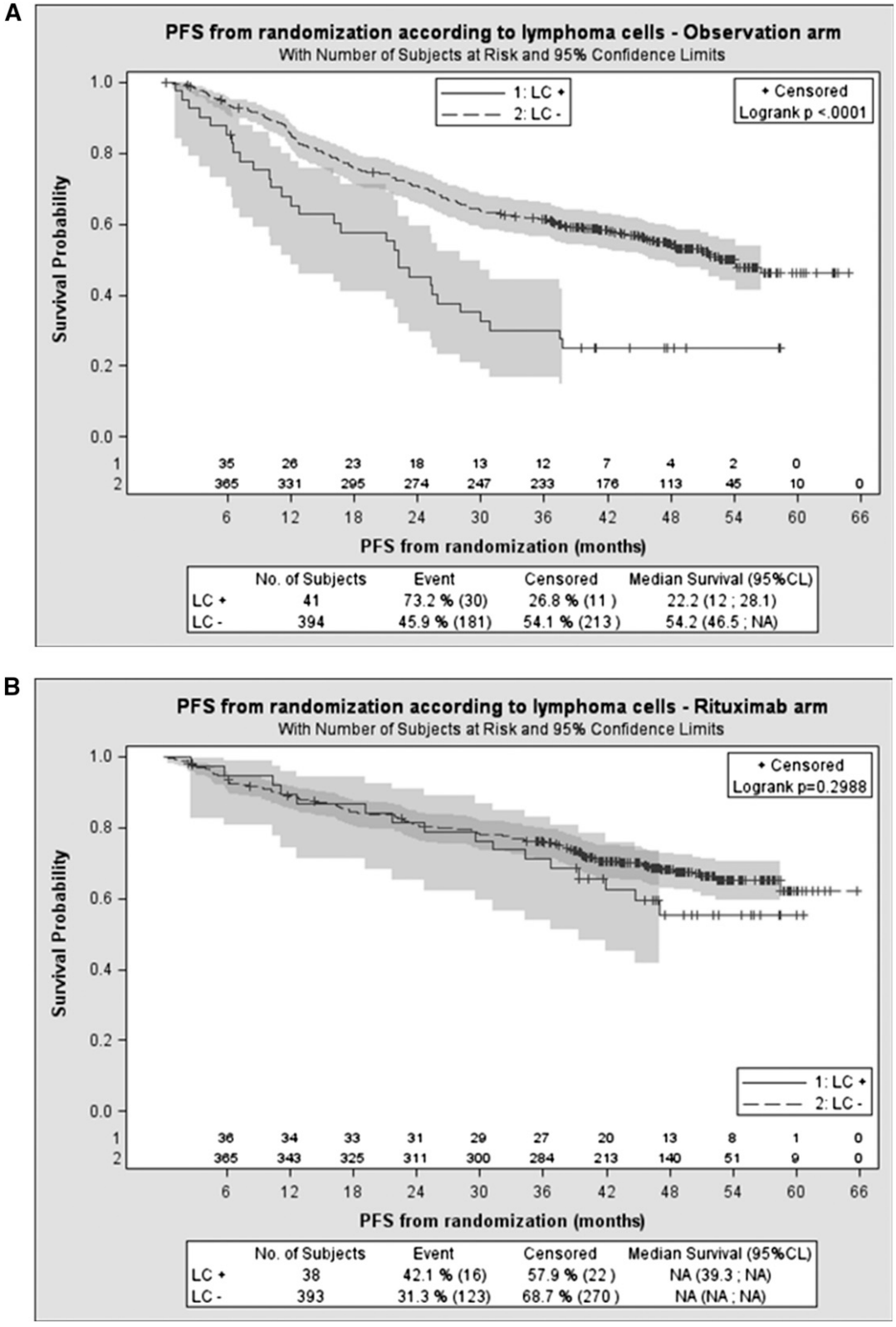

Figure 1. PRIMA study: PFS according to CLC and maintenance group. (A) Patients with follicular lymphoma and leukemic cells (CLC) treated without rituximab maintenance after induction regimen presented a worse PFS than patients with follicular lymphoma without CLC who were treated without rituximab maintenance. $LC^{+/-}$, presence/absence of circulating lymphoma cells. (B) With rituximab maintenance therapy, patients with and without CLC presented similar PFS.

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Contribution: C.S. and G.S. designed and performed research, analyzed data, and wrote the paper; J.F.S, C.F., D.C., H.G., S.L., R.D., L.M.P., C.M., M.G.S., C.C.-C., and M.M. performed research and contributed data ; and all authors edited and approved the manuscript.

Conflict-of-interest disclosure: C.S. and M.G.S. received honoraria from Roche. R.D. received honorarium and travel support from Roche. G.S. participated on Roche advisory boards, and received honoraria and research support from Roche. The remaining authors declare no competing financial interests.

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To the editor:

PLZF staining identifies peripheral T-cell lymphomas derived from innate-like T-cells with TRAV1-2-TRAJ33 TCR-α rearrangement

Peripheral T-cell lymphomas (PTCL) are uncommon and account for <10% of all non-Hodgkin lymphomas.[1] The most common category of PTCL is "not otherwise specified" (PTCL-NOS), reflecting the lack of specific parameters to define PTCL subsets in a biologically relevant way.[2] Although it is recognized that PTCL arise from both adaptive and innate lymphoid cells, the precise cell of origin for most PTCL cases remains unknown. Classically, γδ T-cell and true natural killer (NK) cell lymphomas are thought to arise from innate cells.[3] However, there are rare subsets of αβ T-cell populations, such as NK T-cells and mucosal-associated invariant T-cells (MAIT) that do not have described malignant counterparts. These cells have limited α chain diversity and demonstrate an innate-like behavior by rapidly producing cytokines in response to antigen presentation by non-classical major histocompatibility complex class I molecules, even without previous priming.[4] These cells require the promyelocytic leukemia zinc finger (PLZF) transcription factor for development and maturation. Therefore, we determined if PLZF expression could identify PTCL derived from innate-like T-cells by performing immunohistochemistry with an anti-PLZF antibody on a tissue microarray generated using biopsies from 26 PTCL-NOS, 11 anaplastic large cell lymphomas (ALCL), anaplastic lymphoma kinase $(ALK)^-$, and 13 ALCL, ALK^+. Only rare positive cells were identified in normal tonsil, lymph node, and thymus (not shown). In contrast, the intestinal mucosa, which is normally enriched in $PLZF^+$ innate like T-cells, showed expression in 8% to 10% of lymphocytes (not shown). Using a cutoff of >20% of lymphoma cells with nuclear staining for PLZF, 2 of 26 PTCL-NOS cases were scored as positive (Figure 1A-D), but no ALCL, ALK^+ or ALCL, ALK^- lymphomas met this criterion (Figure 1E-F). Because the innate-like T-cells are defined by the invariant T-cell receptor (TCR)-α rearrangements, we next performed polymerase chain reaction followed by Sanger sequencing to determine the identity of the TCR-α V-J rearrangements. Both PLZF-positive cases showed the TRAV1-2-TRAJ33 TCR-α rearrangement (Vα1-2-Jα33) characteristic of MAITs.[5] No amplification was observed for the TRAV10-TRAJ18 rearrangement seen in NKT cells. Patient 1 presented with large bowel involvement and retroperitoneal lymphadenopathy and patient 2 with generalized lymphadenopathy. Bone marrow was involved in both patients. Both cases expressed CD2, CD3, CD4, and CD5. CD7 and partial CD30 expression was observed in case 1, whereas these antigens were not expressed in case 2.

In contrast to precursor T-lymphoblastic lymphoma/leukemia, PLZF expression is rare in PTCL with only one other positive case reported in the literature.[6] To our knowledge, this is the first report to demonstrate PTCL arising from MAITs, based on both PLZF staining and the Vα1-2-Jα33 gene rearrangement. Although rare, these cases likely represent a biologically unique group of PTCL that may be clinically relevant. It is well-known that innate T-cells are highly resistant to xenobiotics due to high expression of the transporter adenosine triphosphate-binding cassette B1 (ABCB1). Prospective evaluation for PLZF expression will be useful in identifying patients who will benefit from therapy targeting this pathway of drug resistance.

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