this is a hypothesis that has yet to be proven, but it remains a viable potential explanation for the immunologic changes we observed.

Psomas et al also highlight the different conclusions reached by our trials regarding the effects of maraviroc intensification on changes in T-cell activation and monocyte activation. As discussed in our recent paper,[1] we agree that technical issues and differences in patient populations may have contributed to the reductions in T-cell activation observed in several uncontrolled trials of maraviroc intensification.[2-4] Psomas et al discount the possibility that increased adherence to the background antiretroviral therapy regimen could have contributed to the decreased T-cell activation levels or plasma 16S ribosomal DNA levels observed in their study because levels did not significantly change between enrollment and the start of study medication, but adherence typically improves when trial subjects start taking a study medication, particularly when they know that pills are being counted. This appeared to be the case in the placebo arms of our trial and another recent placebo-controlled treatment intensification study.[1,5] This is one of the reasons why double-blind randomized placebo-controlled trials are the gold standard for evidence in clinical research. We agree that further research will be necessary to understand many of the unexpected effects of maraviroc intensification on the immune system in treated HIV infection, but strongly suggest that this work be conducted in the context of adequately powered randomized controlled trials so that observed effects can be clearly attributed to the intervention.

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To the editor:

MYD88 (L265P) mutation is an independent risk factor for progression in patients with IgM monoclonal gammopathy of undetermined significance

MYD88 (L265P) is a recurrent somatic mutation in Waldenström macroglobulinemia (WM).[1-4] By means of allele-specific polymerase chain reaction (AS-PCR), the *MYD88* mutation is detectable in almost all patients with WM and in roughly half the patients with IgM monoclonal gammopathy of undetermined significance (IgM-MGUS).[2,3,5]

IgM-MGUS patients have a probability of progression to WM or to other lymphoproliferative disorders (LPD) of ~1.5% per year, and the initial concentration of the serum monoclonal (M) protein is the main predictor of progression.[6]

In a case-control study of 77 IgM-MGUS patients, we previously demonstrated that the *MYD88* mutation was associated with higher disease burden and with a higher risk of progression to WM or to other LPD.[2]

We have now analyzed by AS-PCR bone marrow samples, collected at the time of diagnosis, of 136 consecutive IgM-MGUS patients, with the aim to confirm the prognostic role of the *MYD88* mutation in a longitudinal study and to evaluate the effect of the *MYD88* mutation and of the other potential risk factors in multivariate analysis.

Genomic DNA was extracted from bone marrow mononuclear cells (n = 92) or archival Giemsa-stained slides (n = 44). AS-PCR was performed as previously described.[2] Sensitivity of AS-PCR was 0.1%. Cumulative probability of progression was calculated using the Kaplan-Meier product-limit method. The effects of potential risk factors on progression rates were examined in a Cox proportional hazards model.

The *MYD88* (L265P) mutation was detected in 71 of 136 patients (52%). Patients were followed for a total of 469 person-years (median, 34 months). During follow-up, 11 of them (8%) progressed to WM (n = 9) or to marginal zone lymphoma (n = 2). Eight of 9 patients who progressed to WM and 1 of 2 patients who progressed to marginal zone lymphoma carried the *MYD88* (L265P) mutation at the time of diagnosis of IgM-MGUS. The other 2 patients were *MYD88* wild type at diagnosis as well as at progression.

In a competing-risk model considering death for any cause as a competing event, the 5- and 10-year cumulative incidence of progression was respectively 15% and 45% in patients with the *MYD88* mutation compared with 2% and 14% in patients with *MYD88* wild

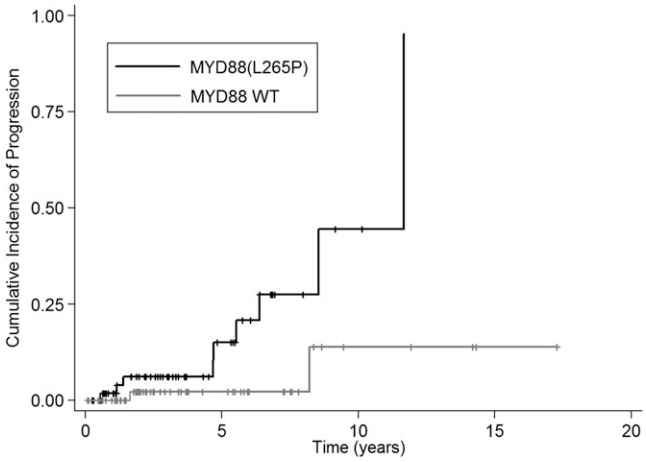

Figure 1. Cumulative probability of progression to WM or to other LPDs in patients with IgM-MGUS according to their *MYD88* mutational status.

type ($P = .027$) (Figure 1). In multivariate analysis, the *MYD88* mutation and the concentration of the serum M protein were independent prognostic factors for progression, with a hazard ratio of 5.45 ($P = .04$) and 3.96 ($P < .001$), respectively.

We constructed a risk-stratification model incorporating the *MYD88* mutational status and the concentration of the serum M protein, using a cutoff level of 1.5 g/dL. Forty-seven patients (36%) had none of the risk factors, 64 (48%) had 1 risk factor, and 21 (16%) had both risk factors.

The 5- and 10-year progression rates were respectively 1% and 12% for patients with none or 1 risk factor, compared with 31% and 60% for patients with 2 risk factors ($P = .007$).

These findings indicate that the *MYD88* (L265P) mutation is an independent predictor of progression of IgM-MGUS to WM or to other LPD, irrespective of the concentration of the M protein. The presence of both *MYD88* mutation and a serum M protein >1.5 g/dL at diagnosis identifies a subset of IgM-MGUS patients at high risk of progression.

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Contribution: M.V., L.A. and M.C. designed the research; S.Z. developed the allele-specific PCR and did molecular investigations; E.B. and M.P. reviewed histological diagnosis; S.R., S.M., M.G. and L.P. collected clinical data; and C.P. performed statistical analysis.

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