Response to the comment: "Identifying potential factors of variable response to mogamulizumab in adult T-cell leukemia/lymphoma between Japanese and other populations"

As Janakiram and Miljkovic describe in their comment,[1] the dosing schedules were different between our study[2] and that reported by Ishida *et al*.[3] In our study patients were given mogamulizumab weekly for the first 5 weeks and then biweekly while patients in the study by Ishida *et al*. were treated weekly for 8 weeks. However, the exposure to the drug in both trials during the first 8 weeks of dosing were similar based upon half-life and pharmacokinetic data, suggesting that under-dosing is not a reason for a difference in the outcomes of the trial. In addition, in our trial, a large proportion of patients were not able to complete more than one planned 28-day cycle (65% received ≤1 cycle), further supporting our attribution of the difference in response rates to baseline differences in the populations of patients enrolled (especially our enrollment of patients with refractory disease and a high proportion with Eastern Cancer Oncology Performance Status score of 2) rather than to dosing regimen.

As mentioned by Janakiram and Miljkovic, it has been shown in preclinical studies that CCR4 expression may be decreased with prior exposure to histone deacetylase inhibitors. In our trial, three patients randomized to mogamulizumab had previously been treated with a histone deacetylase inhibitor. One of the three was a patient with an acute subtype of disease who had been previously exposed to belinostat (remote prior therapy) and who ultimately received just one cycle of mogamulizumab, with no response to therapy. The two other patients received romidepsin as immediate prior therapy. The first had an acute subtype, received two cycles of treatment and had an unconfirmed partial response to therapy. The second had a chronic, unfavorable subtype of disease, experienced a confirmed partial response and completed 21 cycles of treatment. There were additional pertinent findings in the MAVORIC trial (mogamulizumab *versus* vorinostat in cutaneous T-cell lymphoma). In a *post-hoc* analysis of the data, the effect of prior therapy on the efficacy of mogamulizumab was investigated. There were 16 patients who had received romidepsin immediately prior to mogamulizumab therapy; their confirmed overall reponse rate to mogamulizumab was 38%, higher than the response rate of 28% to mogamulizumab in the intention-to-treat analysis. In patients randomized to vorinostat who crossed over to mogamulizumab after progression or intolerance, the confirmed overall response rate was 30%, again similar to the 28% response rate seen for all patients randomized to mogamulizumab.[4] These findings suggest that if there is a decrease in CCR4 expression due to exposure to a histone deacetylase inhibitor, this decrease does not have a clinically meaningful impact on the efficacy of mogamulizumab.

In summary, we believe that the response rate in our study was not as high as that observed in the Japanese study, most likely due to the refractory and aggressive nature of the disease of the patients enrolled, rather than because of any difference in dosing between studies or adverse influence of type of prior treatments administered.

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