# RESPONSE TO LETTER

## Response to "The Role of FcRn in the Pharmacokinetics of Biologics in Patients with Multiple Myeloma"

Xu Steven Xu[1], Jordan M. Schecter[1], Richard Jansson[2] and Xiaoyu Yan[1]

**To the Editor:** Daratumumab, a therapeutic immunoglobulin G (IgG) 1κ monoclonal antibody, targets CD38 for the treatment of multiple myeloma. In our article, we reported that daratumumab exhibited time-dependent and concentration-dependent pharmacokinetics (PK) consistent with target-mediated drug disposition, based on data from studies of daratumumab as a monotherapy.[1] Jacobs and Mould[2] posit that saturation of the neonatal Fc-receptor (FcRn) contributes to the nonlinear PK of daratumumab. We agree that interactions between FcRn, IgG M-protein, and daratumumab are likely to influence daratumumab PK.

When recycled, IgG proteins are protected from degradation by FcRn.[3] Daratumumab and IgG-type M-protein may compete for FcRn and, thus, in the presence of IgG M-protein, daratumumab (or other therapeutic IgGs) may have a shorter half-life. Jacobs and Mould[2] present modeling data suggesting that, to offset this effect, the daratumumab dose should be increased from 16 mg/kg to 30 mg/kg in patients with ≥60 mg/L of IgG M-protein. Similarly, our modeling data demonstrate that daratumumab concentrations in non-IgG patients are ~50% (95% confidence interval (CI) = 38–60%) higher than in IgG patients.[4] However, current data do not support adjustment of daratumumab dose based on IgG status. First, despite lower concentrations of daratumumab in IgG patients, efficacy data indicate that overall response rates among patients receiving daratumumab 16 mg/kg are similar between IgG and non-IgG patients (32.0%; 95% CI = 22.5–43.3 vs. 30.3%; 95% CI = 21.0–41.4, respectively). Even among patients with baseline levels of IgG M-protein ≥30 mg/mL, overall response rate was similar to that of non-IgG patients. Second, preliminary data from an ongoing study suggest that higher doses increased exposure in IgG patients but did not increase target saturation (which was maximized at 16 mg/kg) or improve efficacy. Modeling data estimate that IgG patients have lower thresholds of effective concentration (half-maximal effective concentration) than non-IgG patients. Finally, current data demonstrated similar safety profiles in IgG and non-IgG patients at 16 mg/kg.[4] Increasing daratumumab doses would increase peak concentrations, with unknown effects on the safety of daratumumab.

Jacobs and Mould[2] note that, as patients respond to daratumumab and IgG M-protein levels decrease, dose adjustment may be possible given the decreasing clearance over time. This idea is consistent with our observations and a report by Liu *et al.*[5] on clearance of nivolumab. For daratumumab, weekly dosing overcame the initial high clearance, establishing efficacious concentrations. Every 2 weeks or monthly dosing schedules were sufficient to maintain target saturation, thus reducing the risk of disease progression.[1]

Potential effects of FcRn and IgG M-protein on the PK and efficacy of therapeutic antibodies for the treatment of multiple myeloma should be investigated as this therapeutic class becomes more prevalent.

### CONFLICT OF INTEREST

The authors declared no conflict of interest.

### DISCLOSURE

All authors are employees of Janssen Research & Development, LLC and hold stock in Johnson & Johnson.



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[1]Janssen Research & Development, LLC, Raritan, New Jersey, USA; [2]Janssen Research & Development, LLC, Spring House, Pennsylvania, USA. Correspondence: XS Xu (sxu26@its.jnj.com)

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