Is Bodyweight-Based Dosing Truly Better Than Flat Dosing for Panitumumab? [Letter]

Dear editor

With great interest we read the paper by Liao et al in which they compared a 2-weekly bodyweight-based (6 mg/kg) and fixed (480 mg) administration of panitumumab, a monoclonal antibody (Mab) binding the EGFR receptor. The authors used a population pharmacokinetics model to simulate pharmacokinetics of 1200 virtual individuals for each strategy. The observed interpatient variability in mean simulated AUC (CVAUCmean) was compared and was 34% (fixed dosing) versus 29% (bodyweight-based dosing). Based on this, the authors concluded for panitumumab that “body weight-based approach is the recommended patient dosing strategy”.

Previously, we assessed feasibility of fixed dosing as an alternative strategy for thirteen Mabs including panitumumab. We concluded that fixed dosing is a more rational approach as pharmacodynamics (efficacy and toxicity) of antagonistic Mabs are not concentration-related at concentrations exceeding the minimum target inhibitory concentration (ICmin). For panitumumab, the estimated threshold is 3.83 μg/mL. The authors compared the CV AUCmean of both dosing strategies. However, because of the ICmin trough levels (Cmin) would be a better parameter for assessing efficacy of panitumumab. Although the observed Cmin after bodyweight-based dosing is reported (Figure 1 and Discussion), we miss report of simulated Cmin of the fixed dosing schedule. As the lowest interquartile AUC after fixed and bodyweight-based dosing of panitumumab is comparable (987 versus 908 μg*d/mL, respectively, in Table 2), it is likely that Cmin of the both strategies is comparable (~20–30 μg/mL and >ICmin) and, therefore, both strategies have equivalent efficacy.

The reported difference in CVAUCmean for both dosing strategies is mainly caused by the higher exposure of panitumumab in patients with a low bodyweight after fixed dosing (Figure 2). This results in a difference between the highest interquartile AUC after fixed and bodyweight-based dosing (1582 versus 1254 μg*d/mL, respectively in Table 2). However, this is clinically irrelevant as for panitumumab (like most Mabs in oncology), an exposure-toxicity relationship is absent. Although increased incidence of skin toxicity has been reported with increasing doses, this is related to the EGFR inhibition and reaches a plateau at doses of ≥2.5 mg/kg. As onset of ≥grade 2 toxicity is related to better survival and is a result of target inhibition, it even may be evaluated as biomarker for efficacy. In fact, the manufacturer reports that doses up to 12 mg/kg have been used and that the safety profile was consistent with the recommended dose. Since
an exposure-toxicity relationship is absent in the tested dose range, the interpatient variability of Mabs is of less concern as long as $C_{\text{min}}$ stays above $IC_{\text{min}}$.

In conclusion, both fixed and bodyweight-based dosing give an exposure that is far above $IC_{\text{min}}$ and therefore give similar clinical benefit and risks. Therefore, we argue that for panitumumab – as for most Mabs in oncology – no dosing strategy is to be preferred over the other. If one should be preferred, it should be the fixed dosing strategy for several reasons.\textsuperscript{2,5} This is in accordance with the recently FDA and EMA approved fixed doses of nivolumab and pembrolizumab.

**Disclosure**
The authors declare no conflicts of interest in this communication.

**References**