

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

This article was published in the following Dove Press journal:  
*Clinical Pharmacology: Advances and Applications*

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## 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.<sup>1</sup> 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 ( $CV_{AUC\text{mean}}$ ) 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.<sup>2</sup> 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 ( $IC_{\min}$ ).<sup>2</sup> For panitumumab, the estimated threshold is 3.83  $\mu\text{g/mL}$ .<sup>1</sup> The authors compared the  $CV_{AUC\text{mean}}$  of both dosing strategies.<sup>1</sup> However, because of the  $IC_{\min}$ , trough levels ( $C_{\min}$ ) would be a better parameter for assessing efficacy of panitumumab. Although the observed  $C_{\min}$  after bodyweight-based dosing is reported (Figure 1 and Discussion)<sup>1</sup>, we miss report of simulated  $C_{\min}$  of the fixed dosing schedule. As the lowest interquartile AUC after fixed and bodyweight-based dosing of panitumumab is comparable (987 versus 908  $\mu\text{g}\cdot\text{d}/\text{mL}$ , respectively, in Table 2)<sup>1</sup>, it is likely that  $C_{\min}$  of the both strategies is comparable ( $\sim 20\text{--}30 \mu\text{g/mL}$  and  $\gg IC_{\min}$ ) and, therefore, both strategies have equivalent efficacy.

The reported difference in  $CV_{AUC\text{mean}}$  for both dosing strategies is mainly caused by the higher exposure of panitumumab in patients with a low bodyweight after fixed dosing (Figure 2)<sup>1</sup>. This results in a difference between the highest interquartile AUC after fixed and bodyweight-based dosing (1582 versus 1254  $\mu\text{g}\cdot\text{d}/\text{mL}$ , respectively in Table 2)<sup>1</sup>. However, this is clinically irrelevant as for panitumumab (like most Mabs in oncology), an exposure-toxicity relationship is absent.<sup>2,3</sup> 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  $\geq 2.5 \text{ mg/kg}$ .<sup>3,4</sup> As onset of  $\geq$  grade 2 toxicity is related to better survival and is a result of target inhibition, it even may be evaluated as biomarker for efficacy.<sup>3</sup> 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.<sup>4</sup> Since

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an exposure-toxicity relationship is absent in the tested dose range, the interpatient variability of Mabs is of less concern as long as  $C_{\min}$  stays above  $IC_{\min}$ .

In conclusion, both fixed and bodyweight-based dosing give an exposure that is far above  $IC_{\min}$  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.<sup>2,5</sup> 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.

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