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Letter to the Editor

Letter to the Editor: Exposure–response or clearance–response relationship in immune checkpoint therapy?—A comment on 'correlation between nivolumab exposure and treatment outcomes in non-small-cell lung cancer' by Basak et al

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Dear Editor,

In their manuscript, 'Correlation between nivolumab exposure and treatment outcomes in non-small-cell lung cancer', Basak et al [1] hypothesise that patients who were treated with nivolumab and exhibited stable disease and progressive disease would have benefited from an increased systemic exposure and propose that a higher dose of nivolumab should be considered for those patients. They arrive at this conclusion after evaluation of pharmacokinetic and outcome data in patients with non–small-cell lung cancer who all received a dose of 3 mg/kg, where some patients with higher trough concentrations experience a survival benefit. The use of 'exposure–response' relationship, although technically accurate, may be misleading, given that other recent data within the literature demonstrate the breakdown of already modest exposure–response relationships observed within a single dose level of immune checkpoint inhibitors when evaluating exposure–response relationships across multiple dose levels [2,3].

In a traditional exposure–response relationship, when poor response is associated with low drug exposure, compensating with a higher dose and subsequent higher exposure should prove beneficial. Similar to what Basak et al [1] observed, Agrawal *et al.* also observed modest exposure–response relationships when looking within either the 1-mg/kg or the 10-mg/kg dose levels of nivolumab that were evaluated in their study [3]. Similarly, Turner et al evaluated response to the programmed cell death protein 1 (PD-1)–targeted immune checkpoint inhibitor, pembrolizumab, at 2 and 10 mg/kg doses and also observed exposure–response trends within each dose level. However, these exposure–response relationships were diminished when looking across the 10-fold or 5-fold dose ranges in the two studies [2,3].

Agrawal et al [3] reported no difference in response to nivolumab when 1 and 10 mg/kg doses were compared. Similarly, Turner et al observed a flat dose–response

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Table 1
Exposure–response relationship of two nivolumab dose levels in hypothetical patients with high versus. low drug clearance (CL). PD, progressive disease; PR, partial response; CR, complete response; AUC, area under the nivolumab concentration vs. time curve.

CL (L/day)	Dose (mg)	AUC (mg/L*day)	Response	Dose (mg)	AUC (mg/L*day)	Response
0.15	70	467	PR	700	4667	CR
0.45	70	156	PD	700	1556	PD

curve and no relationship between pembrolizumab exposure, as represented by area under the concentration vs. time curve (AUC), and overall survival across the two dose levels of 2 and 10 mg/kg [2]. In these studies, there was no improvement in survival between the two dose levels across all patients despite a ten-fold or five-fold increase in exposure, respectively. Collectively, these data indicate that a subset of patient tumours will not respond to immune checkpoint therapy, regardless of dose or exposure. The bright side, however, is that the remainder of patients' tumours will respond, and as Basak et al have suggested, there is an opportunity to increase the dose and likely improve response in those patients. So, how do we know which patient's tumours will respond to immune checkpoint therapy?

The studies conducted by Turner et al and Agrawal et al revealed a peculiar finding—that despite a lack of response relationship to drug exposure or dose, when response was evaluated against clearance, it was discovered that patients with lower baseline clearance, irrespective of dose or exposure, exhibited improved overall survival. Notably, it is only possible to interrogate this separation of exposure–response from clearance–response in studies considering multiple dose levels. As Basak *et al.* evaluated only a single dose level, clearance (CL) and exposure in their study are perfectly correlated (CL = Dose/AUC), making it impossible to uncouple AUC response from CL–response relationships, as was achieved in the studies conducted by Turner et al [2] and Agrawal et al [3]. This suggests the possibility that what Basak et al observed was not, in fact, an exposure–response relationship, but rather a CL–response relationship. For clarity, Table 1 presents a hypothetical scenario that demonstrates this conundrum. A 70-kg patient with low clearance (0.15 L/day) responds to nivolumab treatment at both dose levels (1 and 10 mg/kg), whereas a second patient with higher clearance (0.45 L/day) fails to respond at the same dose levels, although the exposure within the second patient at the higher dose is 3.3-fold greater than the exposure in the first patient at the lower dose. Furthermore, the patient with the responsive tumour (and lower CL) may experience an improved response with the higher dose level.

We agree with Basak et al that there is a chance to improve response to nivolumab by increasing dose, but only in a subset of patients. Because exposure was not strongly associated with outcomes in either of the studies conducted by Turner et al or Agrawal et al, the observed clearance–response relationship is likely a surrogate for other factors that are influencing the sensitivity of some patients' diseases to immune checkpoint therapy. The study by Turner et al offers some hints as to how we may determine that subset of patients—by assessing the presence of cachexia, which causes increased catabolism and protein turnover, which may in turn translate to high therapeutic antibody clearance. Moreover, elevated interleukin-6 levels and subsequent glucocorticoid overload may promote glucocorticoid-mediated immunosuppression and explain lack of response to immune checkpoint inhibitors in patients with high baseline clearance regardless of the dose [4,5]. Further investigation is warranted to determine if we can use clearance and other markers of cachexia to identify those patients who are most likely to respond to higher doses of nivolumab or other immune checkpoint inhibitor therapy.

Conflict of interest statement

None declared.

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