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ORIGINAL ARTICLE

# Pretreatment albumin is a prognostic and predictive biomarker for response to atezolizumab across solid tumors

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## Abstract

**Objectives.** Reliable predictive biomarkers for response to immune checkpoint inhibition (ICI) are lacking. Pretreatment serum albumin, a known prognostic and predictive factor in ICI-treated patients, has been proposed as a potential pharmacokinetic surrogate marker for anti-PD1/PD-L1 antibodies, as it shares a homeostatic pathway with IgG. However, this hypothesis is currently based on theoretical considerations and limited evidence from retrospective data. Therefore, we comprehensively investigated the prognostic and predictive value of pretreatment albumin and its relationship with anti-PD-L1 IgG levels. **Methods.** We analysed pretreatment albumin and atezolizumab serum levels and clinical response in four trials (IMvigor210, IMvigor211, IMmotion151 and OAK) of patients with metastatic lung-, renal- or urothelial cancer who received atezolizumab alone or in combination. **Results.** A total of 3391 patients were analysed. Correlation between serum albumin and atezolizumab levels was weak (Pearson's coefficient 0.23). We found a strong prognostic value for pretreatment serum albumin across all trials. Both atezolizumab serum levels and serum albumin were independently correlated with overall survival. Importantly, in the three randomised phase III clinical trials, the survival benefit for immunotherapy compared with the active comparator arm was limited to patients with pretreatment serum albumin $> 35$ g $L^{-1}$. **Conclusion.** Our data do not support the hypothesis that albumin serves as a surrogate for atezolizumab pharmacokinetics. However, we show that albumin on its own exerts strong prognostic value for patients treated with immunotherapy. As benefit from immunotherapy was limited to patients with normal/elevated serum albumin levels, baseline albumin could potentially be used as a predictive marker for immune checkpoint inhibition.

**Keywords:** albumin, biomarkers, immunotherapy, NSCLC, RCC, UC

## INTRODUCTION

Recently, Ming Zheng proposed serum albumin as a pharmacokinetic surrogate marker for therapeutic antibody turnover and outcome prediction in patients treated with anti-PD-1/PD-L1 immune checkpoint inhibitors (ICI).[1] He showed a prognostic and predictive value for serum albumin in a retrospective, ICI-treated single-centre pan-cancer cohort ($n$ = 1479). As IgG and albumin share a common recycling pathway *via* the neonatal Fc receptor (FcRn), serum albumin could serve as simple pharmacokinetic surrogate marker for anti-PD-1/PD-L1 antibody turnover. Consequently, he suggested that pretreatment hypoalbuminemia is associated with reduced ICI efficacy because of higher IgG clearance and shorter plasma half-life.

The association between high serum albumin levels and reduced plasma half-life of therapeutic antibodies has been described.[2] In addition, other studies have established a correlation between therapeutic antibody levels and prognosis in ICI-treated cancer patients.[3] Therefore, pretreatment serum albumin potentially represents an easy-to-implement tool for indirect monitoring of therapeutic anti-PD-1/PD-L1 antibody levels *via* simple, inexpensive and widely available measurement of serum albumin concentration.

However, his hypothesis is currently based on an analysis of a retrospective pan-cancer dataset. Furthermore, albumin is associated with survival in many cancer entities independently of immunotherapy and also in nononcological diseases.[4] Besides its well-established prognostic value, albumin has also been shown in large cohorts to be predictive in anti-PD-1/anti-PD-L1 immunotherapy.[5,6] While Ming Zhang provides compelling evidence validating a prognostic value of baseline albumin in ICI-treated cancer patients, he did not provide data supporting his core hypothesis: a correlation between serum albumin and atezolizumab pharmacokinetics.

Therefore, in this study we tested the hypothesis based on the data of a single-arm phase II (IMvigor210[7]) and three randomised phase III clinical trials (OAK,[8] IMvigor211[9] and IMmotion151[10]), comprising a total of 3391 patients with metastatic urothelial carcinoma (mUC), renal cell carcinoma (RCC) and non-small cell lung cancer (NSCLC), treated with the anti-PD-L1 IgG antibody atezolizumab. We provide evidence for a strong prognostic value of pretreatment serum albumin but only a weak correlation with atezolizumab concentration. Furthermore, we demonstrate that patients with hypoalbuminemia are less likely to benefit from ICI compared with chemotherapy.

## RESULTS

A total of 3391 patients from four different phase II/III trials were evaluated in this study (Table 1). The absolute atezolizumab concentration in the blood on Day 1 of Cycle 2 showed a weak correlation with pretreatment serum albumin levels across all trials (Pearson correlation coefficient 0.23 (OAK, IMvigor210/211)–0.26 (IMmotion151), $P < 0.001$, Figure 1). Of note, in the IMmotion151 trial albumin weakly correlated with bevacizumab concentration as well, although correlation was slightly stronger than with atezolizumab concentration (correlation coefficient 0.32).

The prognostic value for pretreatment serum albumin levels was validated in the IMvigor210/211, IMmotion151 and OAK trials: As an albumin concentration of 35 g $L^{-1}$ was the lower limit of the reference range in all trials, it was used as the cut-off for our investigation. Other studies have shown prognostic value of albumin concentration well above 35 g $L^{-1}$.[4] We therefore investigated the prognostic relevance of albumin in 3 g $L^{-1}$ increments as well as continuously in Cox regression. There was a concentration-dependent prognostic value for albumin across all trials (Supplementary table 1 and Supplementary figure 1).

Overall survival (OS) was improved for patients with albumin > 35 g $L^{-1}$ in all trials with hazard ratios (HR) between 0.26 (IMmotion) and 0.58 (IMvigor210; Table 1, Figure 2). Albumin and atezolizumab concentrations were independently associated with OS (Supplementary table 2). The concordance index was higher for albumin (0.72 ± 0.025) than that for atezolizumab concentration (0.69 ± 0.028).

Next, we tested whether pretreatment albumin had an impact on outcome in the randomised treatment arms. Strikingly, OS benefit from atezolizumab when compared to chemotherapy was limited to patients with baseline albumin levels > 35 g $L^{-1}$ (Figure 3). In IMmotion151, there

**Table 1.** Prognostic value of baseline albumin and atezolizumab concentration before second application in the four analysed trials

| Trial | OAK | IMvigor210 | IMvigor211 | IMmotion151 |
|---|---|---|---|---|
| NCT | NCT02008227 | NCT02108652 | NCT02302807 | NCT02420821 |
| Cancer type | NSCLC | UC | UC | RCC |
| Phase | III | II | III | III |
| Treatment arms | Atezolizumab *vs* docetaxel | Atezolizumab (single arm) | Atezolizumab *vs* chemotherapy | Atezolizumab + bevacizumab *vs* sunitinib |
| No. of patients | 1158 | 428 | 899 | 906 |
| No. of patients (atezolizumab pharmacokinetic data available) | 486 | 346 | 345 | 409 |
| Median baseline albumin concentration (g $L^{-1}$) | 40 | 39 | 40 | 42 |
| Median atezolizumab concentration before 2 infusions (mg $L^{-1}$) | 81.45 | 72.15 | 71.10 | 82.35 |
| Median cleared atezolizumab fraction | 79.02% | 79.69% | 80.09% | 77.15% |
| Correlation coefficient (albumin and atezolizumab concentration) | 0.23 | 0.23 | 0.23 | 0.26 |
| *P*-value correlation (albumin and atezolizumab concentration) | < 0.001 | < 0.001 | < 0.001 | < 0.001 |
| Correlation coefficient (albumin and cleared atezolizumab fraction) | 0.16 | 0.19 | 0.21 | |
| *P*-value correlation (albumin and cleared atezolizumab fraction) | < 0.001 | < 0.001 | < 0.001 | |
| HR albumin ≤ 35 g $L^{-1}$ *vs* > 35 g $L^{-1}$ | 0.57 | 0.58 | 0.51 | 0.26 |
| *P*-value ≤ 35 g $L^{-1}$ *vs* > 35 g $L^{-1}$ | < 0.001 | < 0.001 | < 0.001 | < 0.001 |
| HR atezolizumab concentration ≤ median *vs* > median | 0.61 | 0.65 | 0.72 | 0.36 |
| *P*-value atezolizumab concentration ≤ median *vs* > median | < 0.001 | < 0.001 | 0.005 | < 0.001 |
| HR immunotherapy *vs* comparator, albumin ≤ 35 g $L^{-1}$ | 0.83 | – | 0.9 | 1.05 |
| *P*-value immunotherapy *vs* comparator[a], albumin ≤ 35 g $L^{-1}$ | 0.2 | – | 0.5 | 0.9 |
| HR immunotherapy *vs* comparator, albumin > 35 g $L^{-1}$ | 0.75 | – | 0.77 | 0.76 |
| *P*-value immunotherapy *vs* comparator[a], albumin > 35 g $L^{-1}$ | < 0.001 | – | 0.002 | 0.063 |

[a]In the OAK and IMvigor trials, atezolizumab was compared with chemotherapy; in the IMmotion151 trial, atezolizumab and bevacizumab were compared with sunitinib.

was a trend towards a benefit for atezolizumab + bevacizumab *vs* sunitinib in patients with albumin > 35 g $L^{-1}$ and in the subgroup of patients with baseline serum albumin > 40 mg $L^{-1}$, atezolizumab + bevacizumab was associated with significantly prolonged survival compared with sunitinib (HR 0.67, $P = 0.041$).

## DISCUSSION

We found a weak correlation between albumin and atezolizumab serum levels in four different clinical trials. This result strongly opposes the idea that serum albumin could be used as a surrogate marker for the pharmacokinetics of atezolizumab (or more generally for IgG monoclonal antibodies). The fact that the correlation between atezolizumab concentration and serum albumin is weak, and albumin as well as atezolizumab concentrations independently correlate with survival, suggests that the proposed pharmacokinetic effect cannot explain the prognostic value. Although a common mechanism (*e.g.* FcRn) could influence albumin and atezolizumab turnover, our data do not support albumin as a marker for atezolizumab pharmacokinetics. However, in three different phase III studies we demonstrated that especially patients with a high pretreatment albumin level benefit from immunotherapy so that the broadly available serum albumin might be used as a simple predictive parameter in routine clinical practice or

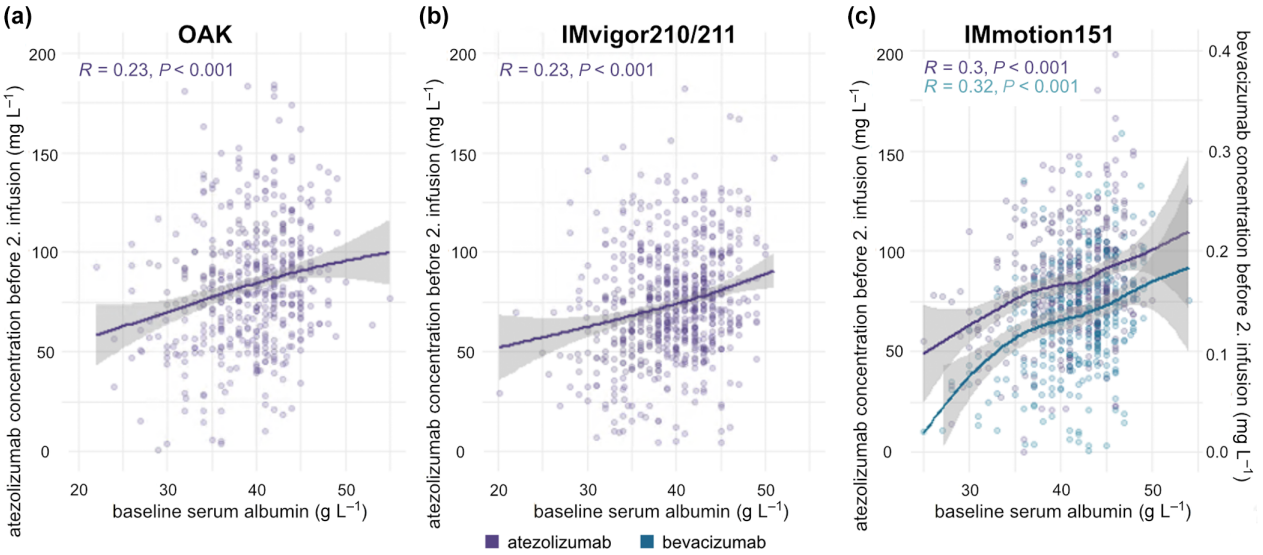


**Figure 1.** Weak correlation between baseline albumin and atezolizumab concentration before the second dose in all three atezolizumab monotherapy trials. **(a, b)** In the OAK trial (NSCLC), as well as the IMvigor 210 and 211 trials (UC) there was a weak correlation between serum albumin levels at baseline and serum atezolizumab levels before the second dose (Pearson's correlation coefficient 0.23, $P < 0.001$). **(c)** In the IMmotion151 trial (RCC), atezolizumab was administered in combination with bevacizumab. Correlation with serum albumin was slightly stronger for bevacizumab (Pearson's correlation coefficient 0.32) than that for atezolizumab (0.3).

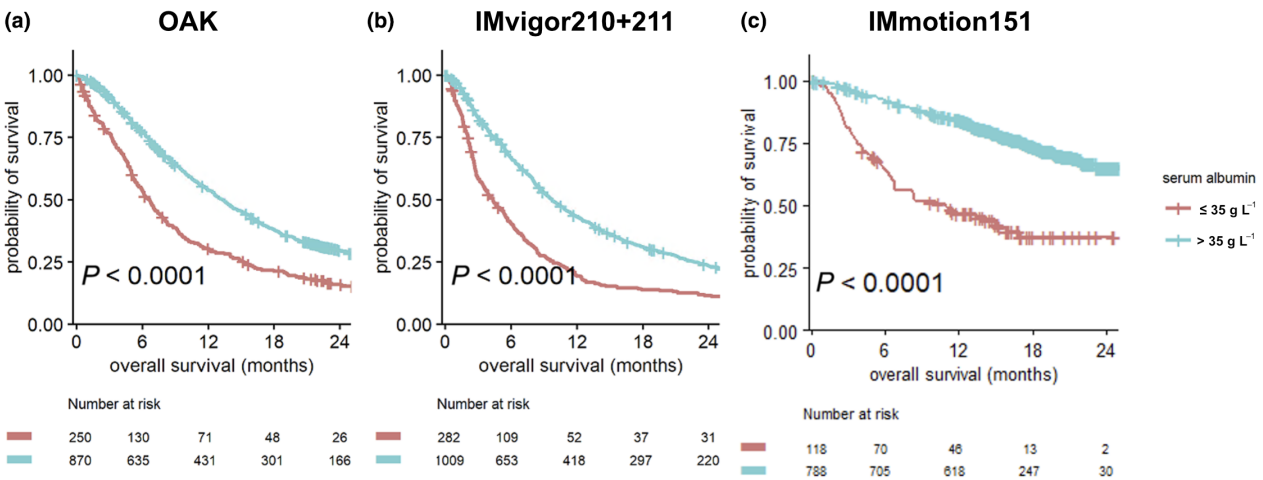


**Figure 2.** Low baseline albumin is associated with unfavorable outcomes. Serum albumin below 35 g $L^{-1}$ was associated with significantly reduced overall survival in NSCLC (OAK) **(a)**, UC (IMvigor210/11) **(b)** and RCC (Immotion151) **(c)**, and for the phase III clinical trials, both treatment arms were pooled. In all trials, log-rank *P*-values were < 0.0001.

in future clinical trials testing immunotherapy regimen.

We were able to independently verify that baseline albumin is prognostic in ICI-treated patients with RCC, mUC and NSCLC. Albumin is known to be prognostic in a variety of cancers and even nonmalignant diseases.[4] The reason is not fully understood but albumin has been suggested as a surrogate for disease severity in general and in patients with cancer could also be a measure of chronic inflammation and cachexia. In combination with inflammatory biomarkers like C-reactive protein (CRP), albumin has a strong prognostic value.[11,12] The CRP/albumin ratio or composite scores like the (modified) Glasgow Prognostic Score have also been shown to be prognostic in a wide range of cancers.[13–16]

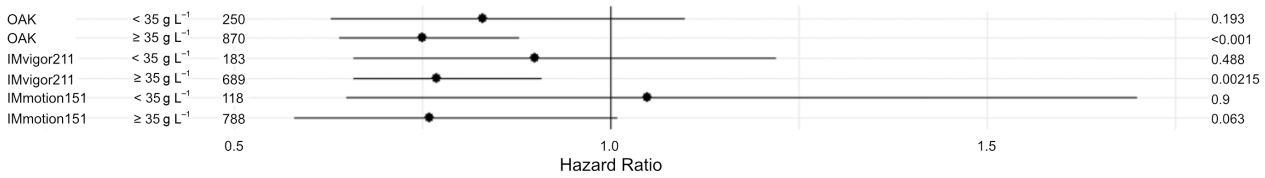


**Figure 3.** Benefit from ICI is limited to patients with normal or high baseline albumin. Forest plot of hazard ratio for atezolizumab (OAK, IMvigor210/211) or atezolizumab + bevacizumab (IMmotion151) *vs* chemotherapy (OAK, Imvigor210/211) or sunitinib (IMmotion151) in baseline albumin subgroups. A significant survival benefit for atezolizumab is only present in patients with baseline albumin ≥ 35 g $L^{-1}$. In the IMmotion151 trail, neither group shows significant superiority for atezolizumab + bevacizumab; however, there is a trend favoring the combination in patients with albumin ≥ 35 g $L^{-1}$.

Clearance of the anti-PD-1 antibody nivolumab decreases over time. This decrease has been shown to be more pronounced in patients responding to therapy.[17] This has led to the hypothesis that lower drug clearance (and therefore higher drug exposure) might be a result of therapy response, and not the cause.[18] This is corroborated by the finding that pembrolizumab clearance is correlated with survival in both 2 mg $kg^{-1}$ and 10 mg $kg^{-1}$ exposure groups, even though there was no survival difference between the treatment groups.[19] A correlation between bevacizumab clearance and serum albumin has been shown previously. However, the albumin cut-off has been very low (< 29 g $L^{-1}$) and only a 20% increase in clearance has been observed.[20] Our data show a weak albeit significant correlation between bevacizumab concentration and albumin that is stronger than the correlation with atezolizumab. Whether these differences are because of statistical or biological variance or specific properties of each monoclonal antibody warrants further investigation. A different study found a relationship between serum albumin, infliximab concentration and response rate in the setting of ulcerative colitis.[2] Whether these findings are informative in the setting of cancer immunotherapy is questionable, as causality in the dose–response relationship is not established in ICI.

As the correlation between atezolizumab clearance and serum albumin levels across four clinical trials is weak, FcRn expression alone seems unlikely to explain the differences in survival. We therefore do not consider the evidence, convincing that hypoalbuminemia in patients with cancer reflects differences in FcRn-mediated catabolism and can serve as a surrogate marker for IgG metabolism. Thus, there needs to be a different explanation for the predictive power of albumin. We suggest that albumin is a surrogate marker for the patient's general health condition. Given that, ICIs harness the patient's own immune system to fight tumor cells a metabolic imbalance caused by chronic inflammation (*e.g.* because of the tumor or co-occurring disease) could impair antitumor immune responses. This could explain why in patients with hypoalbuminemia (*i.e.* strong metabolic imbalance), ICI is less effective than chemotherapy, which directly kills tumor cells. This idea is further supported by the finding that tumor-induced cytokines (in particular IL-6) can inhibit hepatic ketogenesis and the resulting metabolic stress increases plasma corticosteroid levels which inhibit immunotherapy in mice.[21] Our findings are also consistent with previous reports that cancer cachexia is prognostic only in ICI-treated patients but not in chemo-ICI combination treatment.[22]

A possible factor driving the prognostic value of albumin is cancer-induced inflammation and cachexia. There is a significant negative correlation between albumin and CRP (correlation coefficient − 0.46 in the pooled OAK and IMvigor trials), suggesting that hypoalbuminemia in cancer patients occurs in the context of chronic inflammation. Cachexia is increasingly recognised as an inflammatory condition.[11] We show for the first time in a large, prospective, multicentre, multicancer dataset that patients with low albumin levels do not profit from immunotherapy as compared to chemotherapy. This finding should be prospectively validated, as albumin might serve as a predictive biomarker for ICI.

Based on our findings, we believe that albumin could serve as a cost-effective, easy-to-measure and implement predictive biomarker in cancer immunotherapy. To support this idea, pretreatment and on-treatment albumin should be evaluated in prospective ICI trials in future.

## METHODS

Data from four phase II/III trials were accessed *via* the vivli.org platform (IMvigor210, OAK, IMvigor211, IMmotion151). As a result of differences in patient prognosis and characteristics in the different trials (mUC *vs* RCC *vs* NSCLC), analysis was performed in each trial individually. All laboratory values were measured at the screening visit.

Survival analyses were performed using Kaplan–Meier plots and log-rank tests as well as uni- and multivariate Cox regression. Correlation analysis was performed using Pearson's correlation coefficient. Statistical significance was defined to be $P$-values $< 0.05$.

All study protocols were approved by independent ethics committees for each site (listed in the appendix of the original publications). An Independent Review Panel (IRP), including ethics, and the data provider Roche approved our *post hoc* analysis (request ID #7797 and #7164). Data analysis was performed using R Studio (v.1.4).

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## AUTHOR CONTRIBUTIONS

**Jonas Saal:** Conceptualization; formal analysis; investigation; methodology; visualization; writing – original draft; writing – review and editing. **Jörg Ellinger:** Project administration; resources; writing – review and editing. **Manuel Ritter:** Project administration; resources; writing – review and editing. **Peter Brossart:** Project administration; resources; writing – review and editing. **Michael Hölzel:** Conceptualization; funding acquisition; project administration; resources; supervision; writing – review and editing. **Niklas Klümper:** Conceptualization; funding acquisition; investigation; methodology; supervision; writing – original draft; writing – review and editing. **Tobias Bald:** Conceptualization; funding acquisition; project administration; resources; supervision; writing – original draft; writing – review and editing.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Patient-level data have been made available through Vivli but remain property of Roche. The authors do not have permission to share data; however, data access will be provided by Roche *via* vivli.org upon reasonable request.

## FUNDING INFORMATION

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## REFERENCES

1. Zheng M. Serum albumin: A pharmacokinetic marker for optimizing treatment outcome of immune checkpoint blockade. *J Immunother Cancer* 2022; **10**: e005670.
2. Fasanmade AA, Adedokun OJ, Olson A, Strauss R, Davis HM. Serum albumin concentration: A predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. *Int J Clin Pharmacol Ther* 2010; **48**: 297–308.
3. Koguchi Y, Redmond WL. A novel class of on-treatment cancer immunotherapy biomarker: Trough levels of antibody therapeutics in peripheral blood. *Immunol Invest* 2022; **51**: 2159–2175.
4. Levitt DG, Levitt MD. Human serum albumin homeostasis: A new look at the roles of synthesis, catabolism, renal and gastrointestinal excretion, and the clinical value of serum albumin measurements. *Int J Gen Med* 2016; **9**: 229–255.
5. Chowell D, Yoo S-K, Valero C *et al*. Improved prediction of immune checkpoint blockade efficacy across multiple cancer types. *Nat Biotechnol* 2022; **40**: 499–506.
6. Yoo S-K, Chowell D, Valero C, Morris LGT, Chan TA. Pre-treatment serum albumin and mutational burden as biomarkers of response to immune checkpoint blockade. *NPJ Precis Oncol* 2022; **6**: 23.
7. Balar AV, Galsky MD, Rosenberg JE *et al*. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: A single-arm, multicentre, phase 2 trial. *Lancet* 2017; **389**: 67–76.
8. Rittmeyer A, Barlesi F, Waterkamp D *et al*. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; **389**: 255–265.
9. Powles T, Durán I, Heijden MS v d *et al*. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): A multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2018; **391**: 748–757.
10. Rini BI, Powles T, Atkins MB *et al*. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): A multicentre, open-label, phase 3, randomised controlled trial. *Lancet* 2019; **393**: 2404–2415.
11. McGovern J, Dolan RD, Skipworth RJ, Laird BJ, McMillan DC. Cancer cachexia: A nutritional or a systemic inflammatory syndrome? *Brit J Cancer* 2022; **127**: 379–382.

12. Hacker UT, Hasenclever D, Baber R *et al*. Modified Glasgow prognostic score (mGPS) is correlated with sarcopenia and dominates the prognostic role of baseline body composition parameters in advanced gastric and esophagogastric junction cancer patients undergoing first-line treatment from the phase III EXPAND trial. *Ann Oncol* 2022; **33**: 685–692.
13. Proctor MJ, Morrison DS, Talwar D *et al*. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: A Glasgow inflammation outcome study. *Brit J Cancer* 2011; **104**: 726–734.
14. Saal J, Bald T, Hölzel M *et al*. In the phase 3 IMmotion151 trial of metastatic renal cell carcinoma the easy-to-implement modified Glasgow prognostic score predicts outcome more accurately than the IMDC score. *Ann Oncol* 2022; **33**: 982–984.
15. Brown JT, Liu Y, Shabto JM *et al*. Baseline modified Glasgow prognostic score associated with survival in metastatic urothelial carcinoma treated with immune checkpoint inhibitors. *Oncologia* 2021; **26**: 397–405.
16. Park JE, Chung KS, Song JH *et al*. The C-reactive protein/albumin ratio as a predictor of mortality in critically ill patients. *J Clin Med* 2018; **7**: 333.
17. Liu C, Yu J, Li H *et al*. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. *Clin Pharmacol Ther* 2017; **101**: 657–666.
18. Liu X, Guo C, Tou F *et al*. Association of PD-L1 expression status with the efficacy of PD-1/PD-L1 inhibitors and overall survival in solid tumours: A systematic review and meta-analysis. *Int J Cancer* 2020; **147**: 116–127.
19. Turner D, Kondic AG, Anderson KM *et al*. Pembrolizumab exposure-response assessments challenged by association of cancer cachexia and catabolic clearance. *Clin Cancer Res* 2018; **24**: 5841–5849.
20. Lu J-F, Bruno R, Eppler S, Novotny W, Lum B, Gaudreault J. Clinical pharmacokinetics of bevacizumab in patients with solid tumors. *Cancer Chemother Pharmacol* 2008; **62**: 779–786.
21. Flint TR, Janowitz T, Connell CM *et al*. Tumor-induced IL-6 reprograms host metabolism to suppress anti-tumor immunity. *Cell Metab* 2016; **24**: 672–684.
22. Fujii H, Araki A, Iihara H *et al*. Cancer cachexia as a determinant of efficacy of first-line pembrolizumab in patients with advanced non-small cell lung cancer. *Mol Clin Oncol* 2022; **16**: 91.

## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.