Unraveling the complexity of therapeutic drug monitoring for monoclonal antibody therapies to individualize dose in oncology

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INVITED REVIEW

Unraveling the complexity of therapeutic drug monitoring for monoclonal antibody therapies to individualize dose in oncology

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Abstract

Monoclonal antibodies (Mabs) have become key drugs in cancer treatment, either as targeted therapies or more recently as immune checkpoint inhibitors (ICIs). The fact that only some patients benefit from these drugs poses the usual question in the field of onco-hematology: that of the benefit of individual dosing and the potential of therapeutic drug monitoring (TDM) to carry out this individualization. However, Mabs present unique pharmacological characteristics for TDM, and the pharmacokinetic–pharmacodynamic relationship observed should be interpreted differently than that observed for conventional drugs and small molecules. This pharmacology practice review has been summarized from a public debate between the authors at the International TDM and Clinical Toxicology meeting in Banff, 2020, regarding the potential roles of TDM in the Mab/ICI setting.

1 | INTRODUCTION

Immune checkpoint inhibitors (ICIs) have been considered as game-changing drugs in oncology because significant clinical responses have been seen for many patients with tumors with once dismal prognosis such as metastatic melanoma or advanced nonsmall cell lung cancer. However, as of today, ICIs lead to actual sustained efficacy (i.e., meaningful prolonged survival) only in a small number of cancer diseases, with 5-year survival reaching 30%–40% at best. From a global point of view, this relative lack of sustained efficacy of ICIs concerns practitioners and health authorities especially with respect to the extremely high cost of those drugs.[1] This is particularly as the likely beneficiaries of the drug can be difficult to predict, and both responders and non-respond develop toxicities which require additional clinical resources. The fact that a robust and fully validated biomarker is unavailable with ICIs [2] calls for the development of upfront strategies to anticipate potential lack of efficacy or unsustainable toxicities. Among the various possibilities, measuring drug concentrations in patients once administration has begun, a strategy best known as Therapeutic Drug Monitoring (TDM), is a simple and convenient way to build the initial research into dose optimization for patients, postmonoclonal antibody (Mab) registration. Indeed, all the pharmacology, regardless of the drug and mechanism of action, is driven by versions of the Hill equation, where (drug) response is sigmoidally related to input (dose).[3] Countless

neurology, immunosuppressive, antibiotic, or antiviral drugs are monitored, and dose changed on an individual basis to ensure that drug exposures are maintained in the therapeutic window for optimum patient care. As of today, to what extent this simple and convenient strategy could provide similar valuable information with ICIs remains to be fully evaluated. This manuscript reviews the currently known benefits and complexities of such a proposal and offers research solutions to help develop the knowledge in this area.

2 | EVIDENCE FOR TDM OF MABS IN ONCOLOGY

2.1 | General rules for utility of TDM

TDM is usually required when a drug shows a narrow therapeutic window, a wide interpatient variability in its pharmacokinetic (PK) parameters, making dose–exposure relationships erratic. TDM is practiced regularly when treating a serious disease, particularly when factors that affect drug clearance (such as changing organ function) are variable. Virtually all anticancer agents meet these requirements and therefore should be subjected to TDM in routine care.[3] Beyond checking that drug concentrations are in the range of plasma concentrations associated with clinical efficacy and acceptable toxicities, TDM is the cornerstone of adaptive dosing strategies, such as those using Bayesian estimates to identify individual PK parameters to propose tailored dosing next. As such, developing TDM at the bedside is completely aligned with a general practice to set up Precision Medicine in oncology.[4] However, to date, implementing TDM in oncology with adaptive dosing strategies is restricted to a couple of canonical cytotoxics such as methotrexate (MTX), busulfan, or platinum derivatives[5] due predominantly to a number of issues around the service funding and dosing advice support. Regarding oral targeted therapies, tight exposure–relationships have been demonstrated with imatinib[6] and sunitinib,[7] to name a few, and TDM is increasingly considered as a convenient tool to monitor adherence, check drug concentrations and further customize dosing if required.[5]

2.2 | Specific issues for TDM with therapeutic Mabs

Implementing TDM with therapeutic Mabs has been long hampered by bioanalytical difficulties in quantifying Mabs in plasma. However, several studies have suggested exposure–effect relationships with several first-in-class drugs such as bevacizumab,[8] cetuximab,[9] or trastuzumab.[10] To what extent those exposure-effect relationships could be blurred by confounding factors such as target-mediated drug disposition (TMDD) remains an ongoing research question. Unlike for small molecules, no studies evaluating the clinical benefits of tailored, TDM-based adaptive dosing with Mabs have been published yet, despite many studies examining differing dosage regimens. For instance, a randomized clinical study has recently evaluated to what extent dose intensification with trastuzumab would result in improved efficacy in digestive cancer patients.[11] No significant difference was found, but the very design of this study was not to test the relevance of TDM plus customized, adaptive dosing strategies—it was rather a matter of testing two fixed-dosing after patient randomization, regardless of their initial drug exposure concentrations. Similar lack of dose–effect relationships has been previously found with imatinib in GIST patients.[12] It was initially assumed that PK and consequently dosing were not actionable items, until weak dose–exposure relationships with imatinib demonstrated poor correlation observed between dosing and efficacy.[13] Imatinib now has routine TDM as part of practice. As such it is a paradigmatic example of how and why TDM should be performed.[14]

Such discrepancy between lack of dose–effect correlation and proven exposure–effect relationships has similarly been found with the monoclonal antibody anti-CTLA4, ipilimumab. Differences in ipilimumab dosing did not change survival in metastatic melanoma patients, whereas trough concentrations did,[15] supporting the call for personalized dosing, due to interpatient variability of PK parameters with standard dosing. It is now clear that numerous factors can impact the PK of anticancer agents with flat dosing. This is particularly so as most patients with cancers are frequently frail and old with multiple comorbidities. These affect liver and renal functions and potentially affecting drug clearance. Polypharmacy increases the risk of drug–drug interactions, in addition to genetic polymorphisms on genes coding for either liver enzymes or drug transport proteins.[5] In distinction, sources for PK variability with Mabs are only starting to be understood but are expected to include, beyond TMDD, comorbidities such as cachexia with subsequent change in albumin serum concentrations or genetic polymorphisms affecting the FCGRT gene coding for the neonatal Fc receptor (FcRn or Brambell receptor)[16]; inflammation is also known to reduce protein anabolism. This supports the critical research to be undertaken around monitoring of plasma concentrations.

Thus, because of this PK variability, TDM (i.e., checking that drug exposure is likely to yield efficacy) should be considered as a critical step in the new era of precision medicine in oncology to ensure the drug dose is right. For many drugs (e.g., 5FU), genetic tests for tumor, metabolic, or other polymorphisms can be the first step if genetic information is known to be prognostic for choice of drug. Both can help to detect patients with inadequate drug exposure concentrations that are either unlikely to respond or likely to experience severe treatment-related toxicities—making this strategy cost-effective, in addition to improving the efficacy/toxicity balance of anticancer treatments.[17]

3 | EVIDENCE AGAINST TDM FOR MABS IN ONCOLOGY

3.1 | Drug characteristics to predict usual clinical utility of TDM may not apply to Mabs

As with other cancer drug TDM, the following characteristics are of importance for assessment of the utility of a specific Mab[18,19]:

- A relationship between concentration and effect must be present for the drug (at the registered dose range or below)
- No clear relationship between drug dose and effect
- High interindividual variability in PK that leads to a wide range in exposure
- The dose cannot be optimized by clinical observation alone.
- A narrow therapeutic window
- Reliable bioanalytical assays available.

However, for Mabs, these data were frequently not provided in the registration dossier.

3.2 | Clear differences in drug characteristics for Mabs compared to small molecules

3.2.1 | Sparse concentration effect data

For several Mabs in hemato-oncology apparent concentration effect relationships have been identified (alemtuzumab,[20] trastuzumab,[10] ipilimumab[21]). For nivolumab[22] and pembrolizumab[23] an exposure–response relationship in the currently used dose range is uncommon. However, the pharmacological rationale for the approved clinical dose range is unclear. For example, at much lower doses there is an exposure–response relationship. It is possible however that apparent concentration effect relationship is an artifact caused by influential covariates that are more pronounced in patients with more advanced disease.[24]

3.2.2 | PK of Mabs in oncology is complex

It is also subject to target-mediated drug position and time-varying drug clearance. Interindividual variability in PK parameters for clearance and distribution volumes ranges between 15% and 50% though, and as exposure is often associated with efficacy and toxicity, this may warrant treatment individualization. In general Mab PK can be influenced by the following covariates: bodyweight, gender, and disease variables such as tumor burden, target expression, and target in circulation. For some Mabs albumin and alkaline phosphatase[25] concentration are important.

3.2.3 | Exposure-response relationships related to clinical outcome are not fully characterized

For several ICIs, exposure–response relationships related to clinical outcome have been identified but not fully characterized.[23] Because of the complex PK and pharmacodynamics of Mabs, there is not a clear relationship between the dose and the effect. With conventional anticancer therapies, dose–effect relationships mostly had a sigmoid-shaped curve. In contrast, for the newer monoclonal antibodies, the ICIs seem to have a flat or almost flat dose response curve in the investigated and registered dose concentrations. Among other assumptions, this could be due to the Sponsor suggested starting dose being at the top of the sigmoid curve, higher than the usual recommended ED50 starting dose. Further, in oncology clinical observation only can lead to unnoticed therapy failure or severe toxicity, so the frequency of inappropriate dosing is unknown (Figure 1).

3.2.4 | Large therapeutic window

While for the majority of Mabs high concentrations are not associated with clinical toxicity. (ipilimumab is an exception), poor cost-effectiveness (unnecessary drug expenses caused by over exposure, or costs of toxicity, mostly associated with monoclonal antibodies) is common. For example, nivolumab and pembrolizumab costs per patients are estimated at around 50,000 euro per patient per year, ipilimumab around 34,000 Euro.[26] Several years ago, Ratain et al. published "Time is money: optimizing the schedule of nivolumab".[27] Since nivolumab clearance decreases after drug initiation in patients that show good response, personalizing the dose interval was shown to potentially lead to healthcare saving. For pharmaceutical companies there is no incentive to investigate lower dose regimens or regimens with longer dose intervals since most Mabs are currently still reimbursed per vial. So the higher the dose, the higher the reimbursement to the Sponsor. Interestingly, the dosing intervals of both nivolumab and pembrolizumab have changed since their first registration for patient and physician convenience. Where nivolumab was dosed at 3 mg/kg once every 2 weeks, currently, the options are a fixed dose 240 mg once every 2 weeks or 480 mg once every 4 weeks. These different regimens were not tested in randomized controlled clinical trials but in silico trials only by means of population PK/PD modeling techniques.[28,29] The same applies to pembrolizumab where 2 mg/kg every 3 weeks was the original dose regimen; in current clinical practice pembrolizumab is dosed once every 6 weeks. Because of linear drug clearance at higher drug concentrations, higher doses with longer intervals lead to approximately 20% lower trough concentrations. Because of the flat exposure–response curve at the current dose region, no differences in clinical efficacy are found; thus, already 20% of the total ICI costs could have been saved. Looking in more detail to the most widely used ICIs, nivolumab and pembrolizumab raise questions why current dose regimens are so high. Nivolumab showed activity and maximum receptor occupancy at doses as low as 0.1 mg/kg every 2 week in a phase 1 trial.[30] While the current dose recommandation is 240 mg every 2 weeks or 480 mg every 4 weeks. In addition, pembrolizumab phase I study showed maximum effect on lymphocyte stimulation at doses as low as >1 mg/kg,[31] while the current dose is 200 mg once per 3 weeks or 400 mg once per 6 weeks. This gives the strong impression of unnecessary overdosing of these Mabs which leads to financial toxicity. Several research groups have been encouraged by these data to investigate new dosing regimens that can save healthcare costs as can be seen in clinical trials.gov (ClinicalTrials.gov NCT04295863). Clinical trials are currently ongoing looking for longer dose intervals

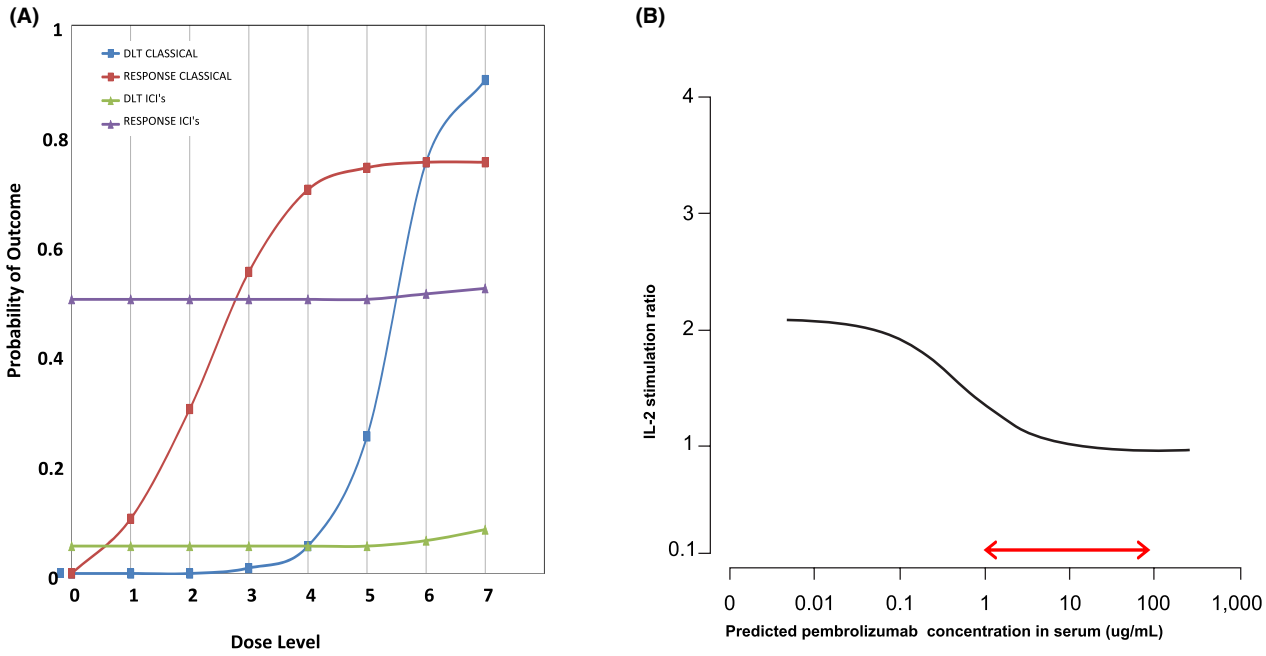

FIGURE 1 (A) Assumptions of dose finding designs for classical oncology drugs and immune checkpoint inhibitors (ICIs). (B) Population-predicted (solid line) programmed death 1 (PD-1) receptor modulation as a function of pembrolizumab exposure under the registered dose range. Adapted from Patnaik, et al[31]

with lower dosages or even shorter treatment periods which are expected to lead to similar efficacy. More scrutiny of the original dose–response work (if it exists) should be undertaken.

3.2.5 | Cost effectiveness of TDM – factors other than drug cost

While currently most compounds are still bought on a per vial basis (not per total treatment cost per year regardless of total dose), the cost effectiveness of testing to change the dose is unclear. However, prolonging the dosing interval may well be.[17,32,33] In fact, Seruda et al. showed that incorporation of TDM of nivolumab in clinical practice could help to maintain a therapeutic drug concentration with lower or less frequent dosses adding a financial benefit, without decreasing clinical efficacy.[32]

4 | FUTURE SOLUTIONS TO TAILOR TDM USE TO IMPROVE PATIENT CARE

4.1 | PK variability as biomarker for therapy success

Change in Mab (and ICI) clearance could be a potential biomarker for good objective response. While it is a significant clinical and cost problem that only 40% in melanoma and 26.1% in lung cancer respond to these expensive therapies,[34] theoretically there may be biomarkers to help predict upfront or in an early phase that patients will respond. In several studies a clear correlation is shown between decline in clearance over time and response to treatment. TDM and more specifically the degree of intrapatient variability in clearance could thus potentially be used as an early marker for therapy success. Most likely patients with low intrapatient variability in PK are also at risk of low response.[10]

4.2 | Options to improve cost effectiveness

Dose individualization by means of TDM could be a method to save healthcare costs when combined with model informed precision dosing to assure personalized dosing intervals. ICIs are increasingly likely to be combined with other conventional therapies for different combination. This will increase the total healthcare cost worldwide, particularly if the added adverse event costs are included, although improved efficacy would improve the effectiveness. Reduction of the dose individualized per patient is less favorable for the patient since the dosing frequency is then not reduced, so reduction of dosing frequency seems the most practical and most patient friendly option. A combination of much lower flat dosing with TDM as a safeguard of underdosing might also be beneficial. Furthermore, new findings indicate that 2 years of full treatment most likely is not required to maintain the initiated immune response to the tumor. Several clinical trials investigate of treatment can be stopped earlier without loss of efficacy.

(https://www.trialregister.nl/trial/7293;https://www.clinicaltrials.gov/ct2/show/NCT04462406?term=Safe+Stop&draw=2&rank=4).

4.3 | Improve the reliability of bioanalytical assays

One of the prerequisites for TDM is access to a validated and standardized bioanalytical assay. Measuring the functionally active ICI concentration is often a challenge, since mAbs in serum or plasma can be in complex with either the target antigen or HAHAs. Serum measurements of ICIs have so far been largely performed by means of electrochemiluminescence immunoassays (ECLIAs) or enzyme-linked immunosorbent assays (ELISAs). Other LC/MS-based options buttom up approaches are also rapidly emerging.[35]

4.4 | Using TDM in an "ad hoc" not "routine" manner

While TDM of Mabs might not seem useful for every situation, there are situations wherein TDM can be a useful tool to reduce Mab costs. There are however some important consideration before choosing applying TDM of Mabs in oncology and more specifically ICIs:

- Serum clearance of Mab is higher in patients with advanced disease (multiple explanations)
- Time-dependent clearance gives opportunities for TDM especially in responding patients
- Time-dependent clearance might be useful as biomarker for therapy success
- Patients with advanced disease have higher clearance but have also less chance to benefit
- Mab clearance changes when patient is improving (40% change during treatment shown for nivolumab)
- TDM of Mabs could improve cost effectiveness

4.5 | *Improving the translatability of data into practice.*

One of the outstanding issues for TDM implementation of monoclonal antibodies is the lack of knowledge of PK–pharmacodynamic relationships of mAbs in actual clinical practice and populations.

Relationships between PK parameters and PD endpoints have been reported for numerous mAbs used as anticancer drugs. For example, with targeted therapies, the team at the "Centre Hospitalier Universitaire" in Tours (France) compared progression-free survival (PFS) and PK parameters of cetuximab (an anti-EGFR) in 96 metastatic colorectal cancer patients.[36] By defining two subgroups according to either their cetuximab clearance (CL) or their residual concentrations (Cmin) at Day 14, they observed significantly better PFS in those with lower CL or higher Cmin. With checkpoint inhibitors, Erasmus University Medical Center researchers observed that nivolumab (an anti-PD1) plasma exposure was significantly different in advanced nonsmall-cell lung cancer (NSCLC) patients with partial response, no change, or progressive disease treated.[37] Those with better outcome (partial response) had significantly higher nivolumab plasma concentrations cycle after cycle. These correlations were observed in standard use of these drugs (i.e., postregistration). Since mAb dose was the same (250 mg/m^2 weekly for cetuximab, 3 mg/kg Q2W for nivolumab), both teams concluded that PK interpatient variability—particularly that corresponding to CL—had an impact on antitumoral efficacy. In other words, treatment failure would be linked (at least partially) to too low mAb plasma concentrations associated with high CL values. There would thus be a rationale to implement TDM of these drugs enable dose increase in patients with insufficient plasma drug exposure. However, in the case of Mabs, several arguments suggest alternative interpretations of these PK-PD correlations that do not support implementing TDM.

4.6 | Data accumulated during Mab clinical development do not consistency support causal correlation between plasma concentrations and outcome

If the relationship between mAb plasma concentrations and their efficacy were causal, similar observations would have been made from the beginning of their clinical development, and particularly during phase 1 dose-escalation studies. Indeed, the wide range of administered dose has been associated with a wider range of plasma exposure among patients than those observed during routine practice where a unique dose is used. Actually, a flat exposure–response relationship over a wide range of dosing has been observed for Mab, particularly for checkpoint inhibitors.[38] The only noteworthy exception is ipilumumab for which relationships have been observed between steady-state trough concentration and either the probability of a grade 3 or more immune-related adverse event or tumor response to treatment of advanced melanoma.[15] The flat exposure–response for all other drugs, associated with the fact that most of the phase 1 trials, was stopped without achieving the maximum tolerated dose, did help promoters of these clinical trials to choose their recommended doses.

Nevertheless, the most convincing work to demonstrate the noncausal nature of correlations retrospectively observed between C_{min} and PD is the prospective study with pembrolizumab (an anti-PD1) in treating melanoma and lung cancer.[24] Two dose levels (2 and 10 mg/kg) were given, and survival was compared between two extreme quartiles of patients defined according to their pembrolizumab CL (Figure 2). For each subgroup, the patients with highest CL (corresponding to those with lowest pembrolizumab plasma concentrations) had significantly lower survival probability. Kaplan–Meier plots for each dose concentration and each disease were similar to those showing better survival of colorectal cancer patients with high cetuximab concentrations. However, the major result was that the plots of both dose levels were actually superimposed. Thus, had the outcome been dependent on pembrolizumab concentrations, the plots corresponding to the 10 mg/m^2 dose would have been associated with better survival probability than those corresponding to 2 mg/m^2. All of these results pointed to the hypothesis that patients

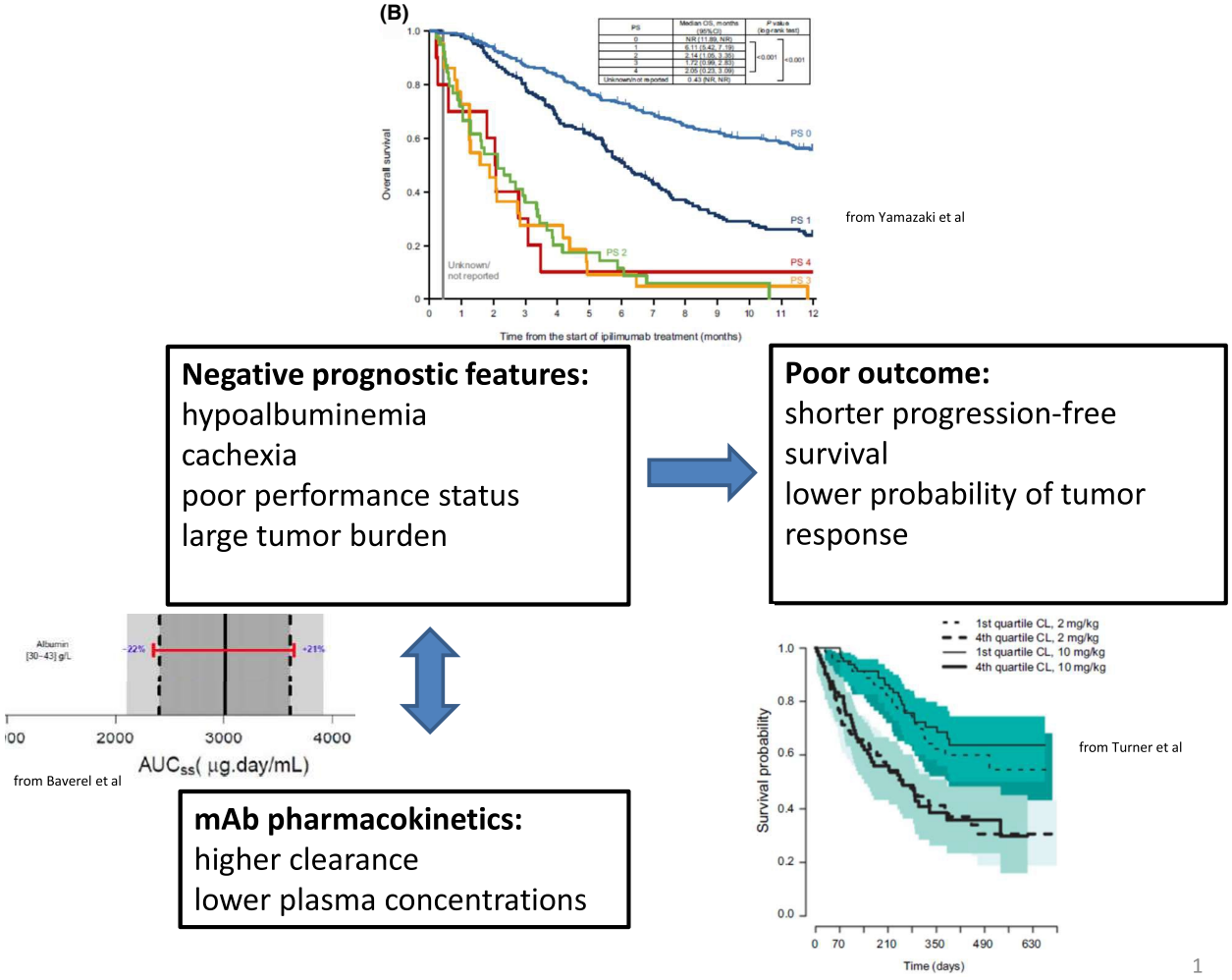

FIGURE 2 Direct impact of the negative prognostic features on monoclonal antibody treatment (illustrated by overall survival by performance status of melanoma patients treated by ipilumumab[58]) and link between these features and mAb PK (illustrated by the lower plasma exposure of durvalumab in patients with hypoalbuminemia[39]) explains the noncausal correlation between mAb PK and outcome (as demonstrated for pembrolizumab given at two dose concentrations[24])

with higher Mab CL values are those who also simultaneously present other characteristics responsible of their relatively insensitive to the antitumoral effects of these Mabs.

4.7 | PK variables misinterpreted as mAb efficacy

Population PK analysis of data accumulated during the clinical drug development of Mabs has shown that serum albumin is a covariate significantly correlated with Mab CL; that is, the lower the albuminemia, the higher the CL. For example, for durvalumab (an anti PD-L1), CL decreases by 3.5% per unit of serum albumin concentration (g/L). It is well known that hypoalbuminemia reflects a nutritional risk, cachexia, increased catabolic activity, and systemic inflammation.[39] Albuminemia is independently associated with survival in various cancers, such as colon cancer.[40] These characteristics (nutritional risk, cachexia) of poor prognosis are most likely associated with lower survival probability. Patients with hypoalbuminemia are probably those with malnutrition and/or cachexia, and we know in oncology that these patients have increased protein catabolism and are also those with the lowest probability of efficacy of any anticancer treatment (Figure 2). Moreover, hypoalbuminemia may be due to inflammation and may therefore be correlated with a high tumor burden in patients with solid tumors.

Our own PK/PD results of cetuximab, in treating advanced head-and-neck cancers, confirmed that patient characteristics, such as poor performance status and large tumor size, are likely to be confounding factors associated with lower cetuximab plasma exposure and worsened PFS.[41] An additional proof of the impact of the disease on Mab PK in oncology (rather than the inverse relationship) is the intrapatient variation of CL cycle after cycle. For example, for nivolumab regardless of its indication (NSCLC, renal cell carcinoma or melanoma),[42] in patients with complete response (CR)—observed antitumoral effect—nivolumab CL tends to decrease. In patients with progressive disease, however, no significant change of nivolumab CL was seen over time. In patients

responding to therapy, decreased inflammation and lessened cachexia is associated with both serum albumin and mAb plasma concentration increase. These changes do not correspond to a decrease in target-mediated CL by tumor cells (corresponding to TMDD) but rather to a nonspecific decrease in IgG catabolism. Indeed, among plasma proteins, both albumin and IgG have the longest half-lives given their affinity for the FcRn receptor in a noncompetitive manner.[43] FcRn protects both albumin and IgG from reticuloendothelial intracellular degradation and recycles them back into the blood stream. Serum albumin concentrations are supposed to reflect the abundance and efficacy of FcRn. Moreover, it should be noted that TMDD does not substantially contribute to the PK of check-point-inhibitors. Indeed, they are administered at doses where TMDD is fully saturated, with their CL corresponding mainly to nonspecific (Fc-mediated) routes. This represents a second argument indicating that the observed decrease of Mab CL in patients responding to immunotherapy does not correspond to a decrease in TMDD.

4.8 | Requirement for alternative dosing strategies for monoclonal antibodies

Although most Mabs are doses based on bodyweight (according to their EMA and FDA approved label), over the last years there is an increasing interest in alternative dosing strategies.[44,45] Based on PK and PD properties, a fixed dose is a more rational, way of Mab dosing.[46] Moreover, a fixed dosing strategy results in decreased medication errors and drug spillage can be reduced.[45,47]

The rationale of fixed dosing is best explained by imagining the body as a barrel, which reflects the volume of distribution of Mabs (Figure 3). Due to their size and hydrophilicity, the volume of distribution of Mabs is limited to the blood compartment and extracellular volume.[48] The Mabs bind to receptors at the outside of the cell membrane, both on tumor tissue and healthy tissue.[45] When the Mab is administered, it will bind to the available receptors. However, since Mabs in oncology are dosed far above doses that result in complete receptor occupancy, nonreceptor bound Mabs remain in the blood compartment and extracellular volume (i.e. "the barrel"; see Figure 3). Although the bodyweight of individuals changes the individual volume of distribution, the change in volume of distribution ("the barrel") is less than proportional compared to bodyweight.[45] Therefore, the barrel of an individual is always filled at therapeutic doses of Mabs in oncology, despite differences in bodyweight. This "barrel" simplification also explains the wide therapeutic window of Mabs in oncology: As the administered dose is far above the minimal dose for complete receptor occupancy (i.e., already overdosed), increased doses do not lead to more effects (both in terms of efficacy and adverse effects). Moreover, this also leads to absence of dose–effect and dose–toxicity relations above the minimal dose for complete receptor occupancy.[45,46,49]

Another important aspect to consider is the clearance of the Mabs and factors that can influence that. Clearance of Mabs is determined by two pathways: binding to the target and a more general clearance route of IgG-like antibodies called proteolytic catabolism.[45,48] Target binding—and the subsequent internalization and degradation of the Mab—is a fast elimination route, which is saturated at therapeutic doses of Mabs. Within the therapeutic range, the general proteolytic catabolism is of much more relevance as it is nonsaturable. This slow and linear clearance route takes mainly place in skin, liver, gut, and muscle tissue.[50] Proteolytic catabolism is weight dependent, and bodyweight is therefore taken into account to estimate individual clearance in in population based PK models. Within these models, a factor is used to describe the effect of bodyweight on clearance.[45] This factor is an exponent between 0 and 1, with 0 meaning effect on bodyweight and 1 meaning a linear effect of bodyweight on clearance. Effects of this exponent on exposure (in terms of area under the plasma concentration- time curve; AUC) after fixed and bodyweight based dosing of Mabs were simulated by Wang at al.[49] These simulations showed that bodyweight has little to moderate effect on clearance of most Mabs and that differences in exposure between bodyweight based dosing and fixed dosing are

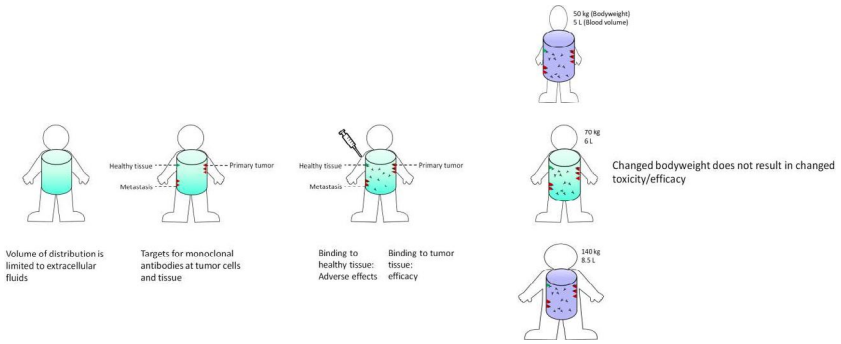

FIGURE 3 General rationale for fixed dosing: the volume of distribution is presented as a barrel that, after administration, is filled with monoclonal antibodies. Within the therapeutic range of monoclonal antibodies, the barrel is filled with such an amount that all binding targets are occupied and most of the monoclonal antibodies are floating through the barrel. Patients with a higher bodyweight have a higher volume of distribution (i.e., a larger barrel). However, as the increase in volume of distribution is nonlinear with the increase in bodyweight, still all binding targets are occupied and antibodies are floating in the barrel. As a result, the change in bodyweight does not result in changed toxicity or efficacy after fixed dosing

usually within 20%. Moreover, deviations between light and heavy subpopulations are less than 40%. Since Mabs in oncology are usually overdosed, this deviation between subpopulations is clinically not relevant.[45]

For a long time pertuzumab was the only Mab in oncology for which it was considered rational to administer a fixed dose during drug development.[45,51] However, times are changing and fixed dosing strategies of Mabs are increasingly accepted. A subcutaneous formulation of trastuzumab was developed as fixed dose, while the original intravenous formulation is dosed on bodyweight [52] and competent authorities like the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved fixed doses of pembrolizumab, nivolumab, durvalumab and avelumab based on population based simulations after initial approval of bodyweight based-dosing schedules.[16,53] Moreover, fixed dosing schedules are also used for initial approval of new drugs like atezolizumab, tremelimumab and cemiplimab.[16,53] However, this does not mean that dosing of Mabs cannot be further optimized. Also for older drugs like trastuzumab, bevacizumab, and panitumumab, the fixed dose approach could be rational and cost-effective.[45,49,54] Moreover, generally accepted fixed dosing strategies can be further optimized for the convenience of patients and treatment costs.

An important aspect to consider to optimize the dosing strategy is the average bodyweight of the patient population. If the fixed dose is not based on average bodyweight of the population, the fixed dose approach might be rational but not cost-effective.[45] The EMA and FDA approved that fixed dose of pembrolizumab is an example of a rational fixed dose that has not taken into account the average bodyweight of the population and therefore is not reducing treatment costs. The approved 200 mg dose is based on a similar population exposure as the initially approve 2 mg/kg dose, but treatment costs for a 70 kg patient would increase from €3758 per cycle to €5368 when a fixed dose is applied (3 week cycles of 2 mg/kg vs. 200 mg, respectively).[16] Based on an average population weight of 70–75 kg, a 150 mg dose would be much more in line with the initially approved 2 mg/kg dose. This is also reflected by the population exposure of fixed doses of pembrolizumab: median exposures relative to mg/kg dosing were −4.6% and +27.1% for 150 and 200 mg fixed dosing, respectively.[33] If a fixed dose of 150 mg pembrolizumab is selected, drug-related treatment costs are significantly reduced.[54,55]

The wide therapeutic window and linear PK of Mabs within the therapeutic range give possibilities for other dosing schedules. For several Mabs, already multiple dosing intervals are used (e.g., 2- and 4-week intervals for nivolumab and 3- and 6-week intervals for pembrolizumab).[16] Due to the linear PK, dosing intervals can be doubled if administered doses are doubled without having lower through concentrations.[16] Due to the absence of exposure–toxicity relationships for most Mabs, dose doubling comes without additional adverse effects, and thus, this strategy can be followed for most Mabs. This makes it possible reduce hospital visits and to align Mab administration with current chemotherapy schedules.[16,56,57]

Overall, it can be concluded that there is a strong rationale or fixed dosing of Mabs. When a fixed dose is based both on achieving minimal plasma concentrations for target inhibition and on average bodyweight of the population, a fixed dose can result in costs reductions, flexibility in dosing schedules, and medication error reductions.

5 | CONCLUSION

ICIs have contributed to improve the response of some tumors such as lung and skin cancer, but the vast majority of cancer patients show little meaningful clinical benefit such as remission or prolonged survival. Because of the lack of validated biomarker, to what extent TDM plus tailored dosing could be a key clinical intervention to improve the efficacy of ICIs remains to be fully evaluated. As for any other drug, PK/PD relationships have been demonstrated with ICIs; however, with respect to the current flat-dosing administration, it is clear that the concentrations of circulating drug in patients largely exceed the threshold required to ensure target engagement, thus lessening the actual impact of PK variability on the clinical outcome. However, from a cost-effectiveness perspective, TDM could help to customize the scheduling, rather than the dosing, that is, by simulating the time by which the patient will reach the trough concentrations associated with efficacy. This could help avoiding over-treating patients, thus reducing drug cost eventually. Randomized prospective trials are awaited to confirm that TDM plus PK modeling and simulation could be part of precision medicine in the era of immunotherapy.

ETHICS STATEMENT

The authors ensure that they have written entirely this original work.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The work does not include data except those corresponding to referenced articles.

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