Clinical and Translational Oncology
https://doi.org/10.1007/s12094-021-02563-3

REVIEW ARTICLE

Dosage of anti-PD-1 monoclonal antibodies: a cardinal open question

M. Sureda[1] · E. Calvo[2] · J. J. Mata[1] · V. Escudero-Ortiz[1] · E. Martinez-Navarro[1] · A. Catalán[1] · J. Rebollo[1]

Received: 11 December 2020 / Accepted: 28 January 2021

Abstract
Discovery and clinical development of monoclonal antibodies with the ability to interfere in the regulation of the immune response have significantly changed the landscape of oncology in recent years. Among the active agents licensed by the regulatory agencies, nivolumab and pembrolizumab are paradigmatic as the most relevant ones according to the magnitude of available data derived from the extensive preclinical and clinical experience. Although in both cases the respective data sheets indicate well-defined dosage regimens, a review of the literature permits to verify the existence of many issues still unresolved about dosing the two agents, so it must be considered an open question of potentially important consequences, in which to work to improve the effectiveness and efficiency of use.

Keywords Immunotherapy · Nivolumab · Pembrolizumab · Personalized dosage

Introduction

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4, CD152) and the programmed cell death 1/programmed cell death ligand 1 (PD-1, CD279/PD-L1, CD274) axis are the best-known checkpoints of the immune system at this moment. Both are negative regulatory checkpoints, interfering with T-cell function. Several monoclonal antibodies (mAbs) that block them have been developed in recent years, with the aim of enhancing immune system activity as immunotherapy against different tumors. Ipilimumab (anti-CTLA-4), nivolumab, pembrolizumab and cemiplimab (anti-PD-1), atezolizumab, durvalumab and avelumab (anti-PD-L1) have been approved by the regulatory agencies based on the positive results of different clinical trials, both in tumors classically classified as responders to immunotherapy and non-responders, and in metastatic and adjuvant setting [1]. The possibilities of combination with other antitumoral agents in addition to clinical trials currently underway exploring new indications, with new agents and multiple combinations between them permit to foresee a promising landscape in this therapeutic field.

Unlike other classes of cancer treatments that act directly on the tumor, cancer immunotherapy first acts via the immune system. This translates into responses in longitudinal tumor size data that may differ from those classically observed with chemotherapy or radiotherapy [2]. In the same direction, immune checkpoint inhibitors (ICIs) do not exert a direct effect on the tumor cells, but they act by predisposing them to the of effector cells of the immune system. In addition, the efficacy and safety profiles of ICIs might be completely different from those of agonistic ones [3]. Isotype of IgGs can have a remarkable impact on bioactivity, being IgG1 e IgG3 more prone to cause antibody-dependent cell-mediated cytotoxicity (ADCC) and IgG4 more efficient in the activation of the alternative complement pathway [3].

Nivolumab and pembrolizumab are the approved agents with the greatest preclinical and clinical experience available so far. Nivolumab is a human IgG4 mAb that binds with high affinity and specificity to PD-1 and blocks its interaction with PD-L1 and PD-L2 (PDCD1LG2), its natural ligands. The constant region of the heavy chain of nivolumab contains an engineered hinge region mutation (S228P) [4]. This mutation has been designed to prevent exchange of Fab' with endogenous IgG4, retaining the low affinity for activating Fc receptors characteristic of wild-type IgG4 antibodies and the minimized both cellular and complement-mediated cytolytic functions [5]. Pembrolizumab is a highly selective,

✉ M. Sureda
manuel.sureda@quironsalud.es

[1] Plataforma de Oncología, Hospital Quironsalud Torrevieja, C/Partida de la Loma s/n, 03184 Torrevieja, Alicante, Spain

[2] START Madrid-Centro Integral Oncológico Clara Campal, Hospital Universitario HM Sanchinarro, Madrid, Spain

Published online: 13 February 2021

humanized anti-PD-1 mAb IgG4/kappa that blocks the interaction of PD-1 with PD-L1 and PD-L2 [6].

We have selected the most relevant literature on the dosing of the two referred agents. An initial search on PubMed for "nivolumab" or "pembrolizumab" or "immune checkpoint inhibitors" and "pharmacokinetics" and/or "pharmacodynamics" until October 2020 was done. In view of the large number of publications available, we decided to pay special attention to the data published by the teams developing preclinical and clinical aspects in the manufacturer laboratories (nivolumab, Bristol-Myers Squibb, Princeton, NJ, USA; pembrolizumab, Merck & Co., Inc, Kenilworth, NJ, USA). A critical analysis of the reviewed works on pharmacokinetics (PK), pharmacodynamics (PD), clinical results, pharmacoeconomics and other related areas, reveals many issues still unresolved, so the adequate dosage has to be considered an open question, with a wide margin for improvement in the efficacy and efficiency of the use of both drugs. In addition, possibly, this concept might be applied to other ICIs targeting PD-L1 and above. The present work has sought to expose the situation from different perspectives and to propose some way of broadening the knowledge that might contribute to the aforementioned improvement.

PD-1/PD-L1 axis constitutes an attractive therapeutic target because PD-1 is only expressed on T cells that are responding to antigen [7]. However, it is a very complex control mechanism. After its manipulation paradoxical responses and sometimes accelerated progression of the disease can be observed [8].

PD-1 is not expressed by naive T lymphocytes, but becomes expressed on all T cells during initial antigen-mediated activation through the T-cell receptor (TCR). When the activating agent is cleared PD-1 expression levels decrease on responding T lymphocytes. If the antigen is not cleared (cancer, chronic infections), PD-1 expression can remain high and sustained. Although TCR engagement constitutes the most important regulator of PD-1 expression, other TCR-independent mechanisms can regulate it too [7].

Usually a significant correlation between expression of PD-L1, T-lymphocytes infiltration and interferon gamma (IFNγ) in the tumor microenvironment (TME) is observed in human tumors [9]. PD-L1 expression can be heterogeneous within the tumor, between primary tumor and metastasis and between different metastases. It is also inducible and can vary rapidly over time in response to cytokines in the TME [3, 10].

The optimal cut-off point of PD-L1 expression in several tumors remains to be defined to adjust the prediction of the response to its blockade with mAb. The most common expression values considered for defining positivity have been 1%, 5% and 50%, but different methods have been reported to quantify it: stained tumor cells/total tumor cells, all stained cells (tumoral and immunological ones)/total cells and others. The relationship between expression and response is continuous in general (more expression, better response) but not always, making difficult to stablish concrete reference points. The complexity of the TME and the potential effect of previous treatments may contribute to the inconsistencies observed between PD-L1 expression and the response after anti-PD-1 administration [10]. Inhibitory mechanisms within the TME including local concentrations of certain cytokines (IL10, TGFβ), the influence of additional checkpoints (TIM3, LAG3) and the presence of metabolic enzymes (IDO, arginase), can generate a highly immunosuppressive environment and thus abrogate the function of specific T lymphocytes in the context of PD-1 blockade [11].

Other immunologically related parameters analyzed in different studies like total mutational burden have shown value as predictors of response to ICIs, independent of PD-L1 expression in multivariate analysis [10].

Pharmacokinetics of anti-PD-1 mAbs

PK properties of mAbs differ markedly from non-mAb drugs, a fact that may have important clinical implications. mAbs are administered intravenously, intramuscularly or subcutaneously. Oral route is excluded by molecular size, hydrophilicity and gastric degradation. The distribution in the tissue is slow due to the molecular size, and the volumes of distribution are generally low. mAbs are metabolized into peptides and amino acids in different tissues, by circulating phagocytic cells or cleared from bloodstream by their target cells containing antigens. Antibodies and endogenous immunoglobulins are protected from degradation by binding to protective receptors as the neonatal Fc receptor (FcRn), which explains their long elimination half-life (up to 4 weeks).

mAbs are agents with high molecular weight, prolonged half-life and little or no renal and hepatic metabolism. Most of them present both linear and non-linear PK components. The linear component is attributed to the clearance mediated by the Fc portion, while the non-linear one is attributed to the epitope binding [2].

Pharmacokinetics of nivolumab

According to the data sheet, nivolumab PK is linear in the dose range of 0.1–10 mg/kg. Geometric mean of clearance (CL), terminal half-life, and mean exposure at steady state at 3 mg/kg every 2 weeks were 7.9 mL/h, 25.0 days and 86.6 µg/mL, respectively. The metabolic pathway of nivolumab has not been completely characterized. Nivolumab is expected to degrade into small peptides and aminoacids via catabolic pathways as endogenous IgGs.

In special populations, the PK of nivolumab has shown no differences in CL according to age, sex, race, type of solid tumor, tumor size, and liver functional status. Lee et al. [12] reported that the PK parameters of nivolumab between different geographical areas (Korea, Japan and USA) overlapped and showed similar distributions. ECOG status, basal glomerular filtration rate (GFR), albumin, body weight and mild hepatic impairment have shown an effect on nivolumab CL but it has not been clinically significant. Nivolumab CL increases with the increase in body weight and decreases over time of continuous treatment. The dosage based on body weight generated a uniform minimum concentration (C_{min}) in steady state over a wide range of weights (34–162 kg) [13].

Pharmacokinetics of pembrolizumab

According to the corresponding data sheet, pembrolizumab is administered intravenously, so it has an immediate and complete bioavailability. It presents a limited extravascular distribution and its volume of distribution in steady state is small (approximately 8.1 L, CV: 22%). As expected, pembrolizumab does not bind to plasma proteins in a specific way. It is catabolized by nonspecific pathways and metabolism does not contribute to its elimination. Pembrolizumab CL is 0.2 L/day (CV: 41%) with a terminal half-life of 26 days (CV: 43%). After repeated administration, pembrolizumab CL was independent of time and systemic accumulation was 2.1 times higher when administered every 3 weeks. In addition, CL values did not show significant differences between the different tumors studied, supporting the idea of a homogeneous PK among them. Concentrations of pembrolizumab near steady state were reached at 18 weeks (mean C_{min} at 18 weeks was approximately 22 µg/mL, at a dose of 2 mg/kg every 3 weeks) [13, 14].

Populational pharmacokinetics of nivolumab and pembrolizumab

Elassaiss et al. [15] reported the results of modeling based on PK data both from the KEYNOTE-001 trial and 14,000 simulations. It showed that pembrolizumab PK was non-linear below 0.3 mg/kg every 3 weeks and linear between 0.3 and 10 mg/kg every 2 or 3 weeks, interval that includes the doses commonly used in clinic.

In the case of nivolumab, analysis of dose proportionality during base-model development indicated that models describing the elimination of the drug by a non-linear model incorporating a Michaelis–Menten elimination term representing elimination by binding to the epitope did not improve the quality of the model compared to the consideration of linear elimination alone [16]. This model was used for the clinical development of nivolumab and was modified to reflect the time-varying CL [16].

In the final model, nivolumab CL decreases over time, with a mean maximal reduction from baseline values around 24%. After an intravenous injection, nivolumab experienced a biphasic elimination, with a rapid distribution phase with a geometric mean terminal half-life of 32 h followed by a slow elimination phase with a geometric mean terminal half-life of 25 days at steady state [16].

Although there is no clear understanding about the variation of nivolumab CL over time, it has been speculated that might be associated with the improvement of the disease and the consequent decrease in the associated cachexia. Low serum albumin is an indicator of cachexia level and hypermetabolic state, caused by accelerated protein turnover in these patients (not due to a decrease in synthesis). Its association with the increase of nivolumab CL is known and, therefore, the normalization of CL could be associated with the improvement in the disease situation. In fact, CL in patients with PS > 0 appeared to be 19% higher than in patients with PS = 0 [16]. In parallel, it has been also associated to a lesser disposal of ligand due to the reduction of the tumor size.

Pharmacodynamics of anti-PD-1 mAb

The search and subsequent use of predictive biomarkers constitutes one of the greatest challenges both in therapeutic development and clinical practice in oncology [17]. In the case of anti-PD-1 mAbs, it is unknown what is the minimum degree of modulation of the receptor that has to be reached for obtaining a response and for how long [3].

In patients with different types of solid and hematological tumors, high levels of PD-1 have been detected in circulating and tumor infiltrating lymphocytes, including T lymphocytes specific for tumor antigens, perhaps due to chronic antigenic stimulation [11].

Despite their low frequency in circulation, CD8+ PD-1+ populations (but not CD8+ PD-1− ones) contained T cells that recognized specific neoantigens of the patient [18].

At 24 h after administering a first dose of nivolumab of 10 mg/kg, there was a decrease in the total number of lymphocytes and CD3+, CD4+ and CD8+ subpopulations, followed by an increase from days 2 to 29 and a further decrease from days 29 to 85. These data permitted to speculate that anti-PD-1 could cause redistribution of lymphocyte subpopulations from the blood to the tumor and tissue sites [4].

In a PD study of nivolumab on peripheral blood CD3+ lymphocytes, the average occupancy of the PD-1 molecules was above 70% more than 2 months after a

single dose of 0.3, 1, 3 or 10 mg/kg, without significant differences related to the dose administered [4, 10]. In patients affected by solid tumors, more than 70% of the PD-1 molecules in the circulating T cells were occupied by nivolumab for more than 2 months after a single intravenous injection of doses between 0.3 and 10 mg/kg [19].

After nivolumab administration, PD-1 occupancy was independent of the dose, with a plateau observed approximately 57 days after one infusion. With undetectable serum levels (< 1.2 µg/mL), sufficient concentration persisted to maintain plateau occupancy. Occupancy decayed after 85 days [4].

No significant changes were observed in the biomarkers studied at any of the dose levels of nivolumab tested (0.3, 2, and 10 mg/kg) [20].

At doses below 1 mg/kg of pembrolizumab, the likelihood of achieving saturation by binding to the epitope decreased considerably, while at a dose of 2 mg/kg every 3 weeks or higher increased significantly [15].

Nivolumab PK in a dose range between 0.1 and 20 mg/kg showed to be linear. As with pembrolizumab, according to the current available clinical efficacy data, no relationship was found between exposure and efficacy in the dose range between 0.1 and 10 mg/kg every 2 weeks used in clinical trials. Target occupancy in circulating T cells was dose-independent through an interval of up to 30 times in a phase I study that recruited patients with several different diagnoses. After stopping the treatment, saturation of the receptor was maintained for several months. Data suggested that even at the 10 mg/kg dose, it was not possible to achieve 100% receptor occupancy [20] and for both pembrolizumab [21] and nivolumab [4], a concentration of 10 µg/mL was required to reach 90% of the maximum achievable receptor occupancy [20].

Cytokine production has been used as a method of measuring response to anti-PD-1 mAb. In mixed lymphocyte reactions, the cytokines monitored to measure T-cell response in culture was different for the two mAb and, therefore, not directly comparable: IFNγ production from CD4+ T lymphocytes for nivolumab and that of interleukin 2 (IL2) from the Jurkat cell line for pembrolizumab. Specifically, nivolumab at a concentration range between 0.05 and 50 µg/mL, increased the concentration of IFNγ between 1000 and 4000 pg/mL, while pembrolizumab, at a concentration range between 0.0149 and 149 µg/mL, produced increments in the IL2 concentration of 1500–2500 pg/mL [22].

IL2 was also used as a circulating biomarker to find a pembrolizumab dosing scheme with clinical efficacy. Notably, the results obtained based in the biomarker were consistent with those obtained following different approaches based on models [17].

Exposures equal or superior to that of 2 mg/kg also ensured that maximal epitope binding was achieved as reported in the first PK/PD report of a clinical biomarker in the KEYNOTE-001 study (release of IL2), which demonstrated a saturation response at 1 mg/kg [15].

A PK/PD evaluation was performed to establish a relationship between plasma concentration of pembrolizumab and modulation of the PD-1 receptor using ex vivo stimulation of IL2 as a clinical biomarker. This evaluation was done during a phase I trial in which patients with several different diagnoses were recruited. The results showed a complete peripheral blockade of the receptor at a dose of 1 mg/kg, with no significant differences between the doses of 1, 3, and 10 mg/kg [20].

Exposure–efficacy and exposure–toxicity relationships of nivolumab and pembrolizumab

Immunotherapies have unique properties in terms of response, relapse, and resistance patterns that distinguish them from other systemic therapies. In addition, dose–response and dose–toxicity relationships are not typically direct or proportional to the dose as in the case of most cytotoxic chemotherapy or targeted therapies [23]. Different doses of mAbs do not have a direct relationship with efficacy and toxicity. In practice, the exposure–efficacy (EE) and exposure–toxicity (ET) relationships with mAb anti-PD-1 have not been clearly determined [2]. Therefore, the definition of a minimum immunologically active dose should be proposed and actively sought [3].

PK and PD are especially relevant for agents that do not show a linear dose–response relationship, for example to determine the optimal biological dose (OBD) for targeted therapies. Further studies are necessary for determining, by analogy with OBD, if an optimal immunological dose (OID) based on PK and PD data could be used for immunomodulatory mAbs [3].

In the case of pembrolizumab, different studies aimed at establishing a minimum effective dose. De Greef et al. [24] specifically stated the appropriate dose range for research in clinical studies as reported by the minimum effective dose estimates. According to this approach, a semimechanistic model that included biological and physiological data key in the response (such as the distribution of the mAb in the tumor tissue and the effect of PD-1 inhibition on tumor growth) was developed. Subsequently, the model was adapted for the prediction of the expected clinical responses, focused on determining the lowest doses that had a high probability of achieving maximum efficacy. The integrated use of clinical data including PD occupancy of receptor and translational data extrapolated from animal data resulted in

a regimen of 1–2 mg/kg administered every 3 weeks as the lowest dose with optimal probability of maximizing clinical efficacy. The potential for decreased efficacy was established for doses below 1 mg/kg [6].

The results of all exposure-tumor size evaluations indicated a flat exposure–response relationship for pembrolizumab in the dose range between 2 mg/kg every 3 weeks and 10 mg/kg every 2 weeks, confirming that the maximum response was practically reached at 2 mg/kg every 3 weeks [24].

Chaterjee et al. [25] concluded that pembrolizumab exposure had no significant clinical impact on response rates. Analyzing the question from different strategies, they observed that the exposure to pembrolizumab was not a significant predictor of the tumor response in size, showing that the plateau of the maximum response was found in the evaluated dose interval (2 and 10 mg/kg every 3 weeks).

The results of these model-based analyses indicated a prolonged response in many patients, but with wide interpatient variability in the evolution of tumor burden over time. The search for covariates for both models showed that baseline disease severity (eg tumor size during screening) was related to the magnitude of the decrease in tumor size, whereas the relationship between changes in tumor size and exposure over a range of up to five times the dose was not statistically significant [25].

Wang et al. [19] described the exposure–response relationship of nivolumab in advanced melanoma, showing that exposure to the drug (in the range of 0.1–10 mg/kg every 2 weeks) represented by the concentration over the time after the first dose was not a significant factor in predicting overall survival (OS), response rate or toxicity.

Recapitulating multiple previous analyses, Agrawal et al. [26] concluded that 3 mg/kg every 2 weeks constituted a unified dose with optimized efficacy in melanoma, renal carcinoma, and NSCLC. Regarding the nature, frequency, and severity of treatment-related AEs, they were similar throughout all dose levels and types of tumors studied. The likelihood of AEs that led to the interruption of treatment appeared to be lower in doses of 1 mg/kg or less than in 3 and 10 mg/kg.

Duration of the treatment

The question about the optimal dose definition and therapeutic scheme of the anti-PD-1 mAbs is closely related to the duration of the treatment. It has not yet been determined under what circumstances the antitumor immunity cycle is perpetuated in absence of serum drug levels or simply maintained through effective serum levels [2].

For other drugs widely used in cancer immunotherapy such as high-dose IL2 or ipilimumab, schemes with predetermined dosage and duration of treatment have been clearly defined. Both can produce long lasting responses in melanoma, with a flattening of the overall survival curve towards 2–3 years [27]. However, optimal sequence, duration of treatment, and possibility of re-treating patients previously exposed to nivolumab or pembrolizumab have yet to be defined [10].

When the patterns of response to anti-PD-1 mAb are analyzed, four groups of patients can be distinguished, without clear characteristics that a priori can permit to predict whether they will fit into one or another. The first group is formed by patients that respond quickly, reaching a complete response (CR) and around 90% maintain the CR after stopping the drug (both for toxicity and clinical or personal decision). Those in the second group show long lasting stable disease (SD) or partial response (PR), requiring continuous administration of the active agent for maintaining the response. In the third group, the patients show tumor progression and the treatment is changed, as is usual in other anticancer therapies. Finally, the fourth group is constituted by patients that experience an acceleration of the course of their disease as a consequence of the therapy.

Regarding the first group, Kushalani et al. [27] recommended the interruption of anti-PD-1 treatment in patients in CR who had received at least 6 months of treatment. In the case of the second group, the preliminary results of the CheckMate-153 study in NSCLC, evaluating duration of treatment with nivolumab in patients with PR or SD, suggested that it could be detrimental to interrupt the administration of nivolumab after 1 year of treatment due to a disease-free survival at 1 year significantly lower (40% vs. 65%, HR 0.42, 95% CI 0.25–0.71) and a non-statistically significant tendency to a lower 1-year OS (81% vs. 88%) compared to maintaining treatment until progression [28]. Regarding the fourth group, the need to find predictive factors to avoid treatment clearly detrimental and contrary to the patient's interests is evident [8].

Many relevant data are known in this setting. In a study conducted in melanoma patients treated with pembrolizumab to whom the possibility of stopping treatment after reaching a CR was given, a disease-free survival (DFS) rate at 24 months from the CR of 90.9% was found in all patients with CR (105) and of 89.9% in the 67 patients with CR who did not continue pembrolizumab and CR was maintained without additional doses of pembrolizumab in 91% during a median of 22 months. Only four patients relapsed after drug was interrupted and three of them returned to respond when it was restarted. The CR rate was higher in patients without previous treatment and in those older than 65 years [28].

CheckMate-067, a study that included melanoma patients comparing treatment with nivolumab vs nivolumab plus ipilimumab vs ipilimumab, showed a 3-year OS rate of 67% in patients who stopped treatment in the combination arm for toxicity. Patients with LDH greater than two times the upper

limit or with PD-L1 expression < 1% seemed to benefit more from the combination than from nivolumab as monotherapy [27].

The long lasting CR observed after stopping ICIs was not previously observed with targeted therapies, modality in which the treatment is prolonged indefinitely or until toxicity or progression [29, 30]. The reported data showed that a period of attenuated treatment could be adequate to elicit a long lasting immune response with relevant clinical benefit [27].

Discussion

As indicated above, a review of the literature shows many unresolved questions about the dosing of nivolumab and pembrolizumab, although the respective data sheets have defined dosage regimens of both agents.

Significant and similar clinical efficacy has been observed in a wide dose range (> 1 log), both with nivolumab and with pembrolizumab, without reaching and determining the MTD for both, permitting to classify them as agents with wide therapeutic index. Their PK characteristics have been defined quite accurately, considering different factors that might have a decisive influence on PK of both. However, the influence of most of these factors has not been shown to be relevant in the clinical setting. Currently, fixed-dose schedules, not dependent on body weight, have been proposed and accepted by regulatory agencies for nivolumab and pembrolizumab in view of the results of in silico studies. When evaluating opportunities to improve the conditions of use, both for patients and for healthcare providers, it was found that the unified fixed dose reduced pharmacy management, preparation time, optimized the use of commercial vials without waste of drug and also reduced the patient's time in the hospital, improving his/her quality of life [14, 31]. In addition, calculation error rate from mg/kg are avoided.

In any case, accepting the evident benefits of fixed dose schemes, several questions remain to be resolved. For pembrolizumab, a fixed dose of 200 mg every 3 weeks was postulated when it had been previously found that a fixed dose of 154 mg every 3 weeks caused a steady-state AUC exposure almost identical to that indicated in the data sheet of 2 mg/kg every 3 weeks. An adaptation to 154 mg would imply a reduction greater than 20% of the dose, with the consequent pharmacoeconomic impact, without diminishing the expectations of response in the light of the known data [14].

Fessas et al. [22] reported a detailed analysis of basic and preliminary clinical aspects of the two agents. They found that nivolumab and pembrolizumab were essentially identical except for the variable regions that bind to the epitope. They concluded that both drugs could be interchangeable and that the differences in the results of the clinical trials between nivolumab and pembrolizumab were more likely to be independent of the drugs than dependent on them. In fact, the combined results of pembrolizumab and nivolumab indicated that the initial development strategies followed by both companies resulted in very accurate translational predictions and analyzes of plasma concentration data obtained from almost 2000 patients treated with nivolumab or pembrolizumab shown similar PK properties [17].

In view of previous data, it seems reasonable to evaluate nivolumab at the dose of 2 mg/kg every 3 weeks or even doses around 1.5 mg/kg every 3 weeks for both agents. This also applies to the fixed-dose schemes, for which a strategy based on multiples of the dose and dosing intervals per body weight has been developed. Some groups have postulated a hybrid strategy, administering weight-based dose and capping it when the flat dose is attained [32], but considering the half-life of both agents, it might be possible to decrease the total dose or prolong administration intervals. As proposed by Ratain and Goldstein [33], it is plausible and testable that less frequent dosing will not only reduce costs, but also improve the safety of ICIs.

There is a recognized need for new predictive markers. Any single biomarker does not perfectly discriminate between responders and non-responders as of now. Combinations of biomarkers that best captures the dynamic interaction between the tumor and the immune cells in TME should be developed [34].

Agrawal et al. [26] relativized the value of peripheral PD markers as occupancy of PD-1, considering that would not give meaningful information for dose selection, because peripheral PD-1 would be saturated at relatively low exposures, corresponding to doses of nivolumab of 0.3 mg/kg every 2 weeks. However, they recognized that the possible usefulness of peripheral PD-1 occupancy data was affected by the limited understanding of the relationship between peripheral and intratumoral occupation and the immunomodulatory activity in the TME.

Different studies reported PK/PD relationships in mAbs used in the treatment of solid and hematological tumors, suggesting the benefit of therapeutic drug monitoring (TDM) of these treatments in routine clinical practice [35–37]. TDM has been considered advantageous for drugs that have a large interindividual variability in exposure with relatively low intraindividual variation, significant EE relationship, a narrow therapeutic window, and availability of a validated bioanalytical assay [38]. Nevertheless, TDM could also represent a useful tool to individualize dosing and optimize the treatment for those drugs with a wide therapeutic window and high cost [39].

The available studies suggest that ICIs have an acceptable safety profile even in non-candidate populations according to common clinical trial criteria, with the exception of the use in recipients of transplantation of solid

organs [40] and allogeneic transplantation of hematopoietic progenitors [11]. In cases such as transplants, clinical problems found in combination treatments, or those raised by patients with variables not considered in clinical trials but widely spread in the "real world" (as patients with previous immunodeficiencies [41, 42]) and considering the cost of immunomodulatory drugs and the problem of reimbursement by health systems or insurance companies, TDM could become an essential tool [3, 43]. In addition to the "problematic" cases, incorporation of the TDM of nivolumab and pembrolizumab in routine clinical practice could help to maintain a therapeutic serum concentration with lower or less frequent doses, adding a financial benefit, without decreasing clinical efficacy. Peer et al. have recently reviewed this subject [44].

TDM as an element of therapeutic personalization has already shown remarkable benefits in the adjustment of doses of other chronic treatments with mAbs such as infliximab, where they are part of the usual clinical practice. In addition, considering the heterogeneity of the responses observed and the wide ranges of doses capable of inducing response, it is mandatory to continue to work in the discovery and integration of PD biomarkers of easy determination as can be the PD-1 occupancy, that, in addition to TDM determinations can offer a personalized effective use of anti-PD-1, in line with the goal of a OBD or OID.

In those cases in which MTD has not been determined, or a saturation phenomenon has been observed in PK and PD parameters, a dose recommendation based on PK/PD should be favored, potentially in the form of a fixed dose [3].

The decision about the duration of the treatment probably needs to be evaluated in a personalized way, incorporating data from new studies and the clinical course of the patient. The pharmacoeconomic implications of a limited but effective schedule of anti-PD-1 in melanoma are profound and go far beyond the costs of the drug and its administration. In a disease where improvements in OS have been remarkable, efforts to return survivors to the workplace should not be underestimated [27]. Costs make effective dose de-escalation in cancer care an area to be mandatorily explored [33]. Green et al. have reviewed the issue and possible strategies to do it [45].

Despite the high degree of development achieved with anti-PD-1 mAb therapy, additional integrated efficacy and safety assessments are needed to plan clinical dosing and design of the trials and to help early identification of combination treatments potentially effective and safe. There is an open field for equivalence studies, comparisons of different doses, schemes, duration of therapy and alternative and easier administration routes as the subcutaneous one to optimize the administrations required by each patient to achieve an optimal immunostimulatory effect.

Conclusions

Current data contribute to confirm former suspects about the possibilities of exploring new scenarios to improve and personalize dosage of nivolumab and pembrolizumab, based in the absence of proven and consistent correlation between exposure and response or toxicity at clinically tested doses, even if in this case data are not uniform, mainly in EE relationship field. Variations in both exposure and individual response may allow further treatment optimization in individual patients and address the significant healthcare costs associated with use of anti-PD-1 agents.

TDM and pharmacodynamic biomarkers should contribute to the proposed individualization and optimization dosage of both agents, not only by financial concerns but also for improving QoL and clinical management aspects. We propose a dynamic dosing schedule integrating TDM, PK/PD and clinical response and toxicity data for achieving the maximal benefit in each patient to substitute the current one-size-fits-all.

Acknowledgements N/A.

Author contributions MS has conceived the work and drafted the paper. EC has made substantial contributions to the design of the work and drafted the paper. JJM has substantively contributed to the design. VE-O has made substantial contributions to the design of the work and drafted the paper. EM-N has substantively revised the work. AC has substantively revised the work. JR has made substantial contributions and drafted the paper. All authors have approved the submitted version and are personally accountable for the author's own contributions and they ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Funding N/A.

Compliance with ethical standards

Conflict of interest Manuel Sureda has received travel grants from Bristol Myers and MSD. Juan José Mata has received travel grants from Bristol Myers. The other authors have no conflicts of interest to disclose.

References

1. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol. 2016;39:98–106.
2. Lee L, Gupta M, Sahasranaman S. Immune checkpoint inhibitors: an introduction to the next-generation cancer immunotherapy. J Clin Pharmacol. 2016;56:157–69.
3. Postel-Vinay S, Aspeslagh S, Lanoy E, Robert C, Soria JC, Marabelle A. Challenges of phase 1 clinical trials evaluating immune checkpoint-targeted antibodies. Ann Oncol. 2016;27:214–24.

4. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28:3167–75.
5. Wang C, Thudium KB, Han M, et al. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. Cancer Immunol Res. 2014;2:846–56.
6. Lindauer A, Valiathan CR, Mehta K, et al. Translational pharmacokinetic/pharmacodynamic modeling of tumor growth inhibition supports dose-range selection of the anti-PD-1 antibody pembrolizumab. CPT Pharmacomet Syst Pharmacol. 2017;6:11–20.
7. Sharpe AH, Pauken KE. The diverse functions of the PD1 inhibitory pathway. Nat Rev Immunol. 2018;18:153–67.
8. Kato S, Goodman A, Walavalkar V, Barkauskas DA, Sharabi A, Kurzrock R. Hyperprogressors after immunotherapy: analysis of genomic alterations associated with accelerated growth rate. Clin Cancer Res. 2017;23:4242–50.
9. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015;27:450–61.
10. Wong AC, Ma B. An update on the pharmacodynamics, pharmacokinetics, safety and clinical efficacy of nivolumab in the treatment of solid cancers. Expert Opin Drug Metab Toxicol. 2016;12:1255–61.
11. Balar AV, Weber JS. PD-1 and PD-L1 antibodies in cancer: current status and future directions. Cancer Immunol Immunother. 2017;66:551–64.
12. Lee KW, Lee DH, Kang JH, et al. Phase I pharmacokinetic study of nivolumab in Korean patients with advanced solid tumors. Oncologist. 2018;23:155-e17.
13. Desnoyer A, Broutin S, Delahousse J, Maritaz C, Blondel L, Mir O, Chaput N, Paci A. Pharmacokinetic/pharmacodynamic relationship of therapeutic monoclonal antibodies used in oncology: part 2, immune checkpoint inhibitor antibodies. Eur J Cancer. 2020;128:119–28.
14. Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. J Immunother Cancer. 2017;5:43.
15. Elassaiss-Schaap J, Rossenu S, Lindauer A, et al. Using model-based "learn and confirm" to reveal the pharmacokinetics-pharmacodynamics relationship of pembrolizumab in the KEYNOTE-001 trial. CPT Pharmacomet Syst Pharmacol. 2017;6:21–8.
16. Bajaj G, Wang X, Agrawal S, Gupta M, Roy A, Feng Y. Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors. CPT Pharmacomet Syst Pharmacol. 2017;6:58–66.
17. Garrido MJ, Berraondo P, Trocóniz IF. Commentary on pharmacometrics for immunotherapy. CPT Pharmacomet Syst Pharmacol. 2017;6:8–10.
18. Gros A, Parkhurst MR, Tran E, et al. Prospective identification of neoantigen-specific lymphocytes in the peripheral blood of melanoma patients. Nat Med. 2016;22:433–8.
19. Wang X, Feng Y, Bajaj G, et al. Quantitative characterization of the exposure-response relationship for cancer immunotherapy: a case study of nivolumab in patients with advanced melanoma. CPT Pharmacomet Syst Pharmacol. 2017;6:40–4.
20. Ogungbenro K, Patel A, Duncombe R, Nuttall R, Clark J, Lorigan P. Dose rationalization of pembrolizumab and nivolumab using pharmacokinetic modeling and simulation and cost analysis. Clin Pharmacol Ther. 2018;103:582–90.
21. Patnaik A, Kang SP, Rasco D, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. Clin Cancer Res. 2015;21:4286–93.
22. Fessas P, Lee H, Ikemizu S, Janowitz T. A molecular and preclinical comparison of the PD-1-targeted T-cell checkpoint inhibitors nivolumab and pembrolizumab. Semin Oncol. 2017;44:136–40.
23. Siu LL, Ivy SP, Dixon EL, Gravell AE, Reeves SA, Rosner GL. Challenges and opportunities in adapting clinical trial design for immunotherapies. Clin Cancer Res. 2017;23:4950–8.
24. de Greef R, Elassaiss-Schaap J, Chatterjee M, et al. Pembrolizumab: role of modeling and simulation in bringing a novel immunotherapy to patients with melanoma. CPT Pharmacomet Syst Pharmacol. 2017;6:5–7.
25. Chatterjee MS, Elassaiss-Schaap J, Lindauer A, et al. Population pharmacokinetic/pharmacodynamic modeling of tumor size dynamics in pembrolizumab-treated advanced melanoma. CPT Pharmacomet Syst Pharmacol. 2017;6:29–39.
26. Agrawal S, Feng Y, Roy A, Kollia G, Lestini B. Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. J Immunother Cancer. 2016;4:72.
27. Khushalani NI. Duration of anti-programmed death-1 therapy in advanced melanoma: how much of a good thing is enough? J Clin Oncol. 2018;36:1649–53.
28. Salati M, Baldessari C, Cerbelli B, Botticelli A. Nivolumab in pretreated non-small cell lung cancer: continuing the immunolution. Transl Lung Cancer Res. 2018;7(Suppl 2):S91–4.
29. Robert C, Ribas A, Hamid O, et al. Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. J Clin Oncol. 2018;36:1668–74.
30. Hamid O, Robert C, Daud A, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol. 2019;30:582–8.
31. Zhao X, Suryawanshi S, Hruska M, et al. Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. Ann Oncol. 2017;28:2002–8.
32. de Lemos ML, Kung C, Waignein S. Efficacy of nivolumab four-weekly dosing schedule based on body weight. J Oncol Pharm Pract. 2019;25:961–3.
33. Ratain MJ, Goldstein DA. Time is money: optimizing the scheduling of nivolumab. J Clin Oncol. 2018. https://doi.org/10.1200/JCO.18.00045 (**Epub ahead of print**).
34. Fujii T, Naing A, Rolfo C, Hajjar J. Biomarkers of response to immune checkpoint blockade in cancer treatment. Crit Rev Oncol Hematol. 2018;130:108–20.
35. Puszkiel A, Noé G, Boudou-Rouquette P, et al. Development and validation of an ELISA method for the quantification of nivolumab in plasma from non-small-cell lung cancer patients. J Pharm Biomed Anal. 2017;139:30–6.
36. Basak E, Wijkhuis A, Mathijssen R, Koolen S, Scheurs M. Development of an ELISA to measure nivolumab and pembrolizumab serum concentrations. Ther Drug Monit. 2018;40:596–601.
37. Irie K, Okada A, Yamasaki Y, et al. An LC-MS/MS method for absolute quantification of nivolumab in human plasma: application to clinical therapeutic drug monitoring. Ther Drug Monit. 2018;40:716–24.
38. Centanni M, Moes D, Trocóniz I, Ciccolini J, van Hasselt J. Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. Clin Pharmacokinet. 2019;58:835–57.
39. Sureda M, Mata JJ, Catalán A, Escudero V, Martínez-Navarro E, Rebollo J. Therapeutic drug monitoring of nivolumab in routine clinical practice. A pilot study. Farm Hosp. 2020;44:81–6.
40. Gormley NJ, Pazdur R. Immunotherapy combinations in multiple myeloma- known unknowns. N Engl J Med. 2018;379:1791–5.
41. Hajjar J. Cancer immunotherapy for the immunosuppressed: Dissecting the conundrum of safety and efficacy. J Immunother Precis Oncol. 2019;2:53–4.
42. Shah M, Jizzini MN, Majzoub IE, Qdaisat A, Reyes-Gibby CC, Yeung SC. Safety of immune checkpoint blockade in

patients with cancer and preexisting autoimmune diseases and/or chronic inflammatory disorders. J Immunother Precis Oncol. 2019;2:59–64.
43. Johnson DB, Sullivan RJ, Menzies AM. Immune checkpoint inhibitors in challenging populations. Cancer. 2017;123:1904–11.
44. Peer C, Goldstein D, Goodell J, Nguyen R, Figg R, Ratain M. Opportunities for using in silico-based extended dosing regimens for monoclonal antibody immune checkpoint inhibitors. Br J Clin Pharmacol. 2020;86:1769–77.
45. Green A, Ohn J, Bach P. Review of current policy strategies to reduce US cancer drug costs. J Clin Oncol. 2019. https://doi.org/10.1200/JCO.19.01628 (**Epub ahead of print**).