COMMENTARY

Commentary on Pharmacometrics for Immunotherapy

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This commentary provides an overview of recent examples of pharmacometrics applied during the clinical development of two antagonists of the programmed-death 1 (PD-1) cell surface receptor, pembrolizumab and nivolumab. Despite the remarkable achievements obtained in predicting the correct dosing schedule from different quantitative approaches, data indicated a great degree of heterogeneity in tumor response. To achieve therapeutic goals the search for predictive biomarkers associated with a lack of response and mechanism-based combination studies are warranted.

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BACKGROUND

Evidence in support of the relevant role of the immune system in the control and eradication of cancer has been growing over the last decade, leading to a revolution in oncology with the introduction of monoclonal antibodies (mAbs) targeting several negative immune checkpoints.1 In fact, the possibility of cure appears to be attainable even for tumors associated with very poor prognosis such as metastatic melanoma and non-small cell lung cancer.

The current issue of CPT: Pharmacometrics & Systems Pharmacology focuses on the application of population pharmacokinetic/pharmacodynamics (popPKPD) to the clinical development of two new immune-modulatory agents acting as antagonists of the PD-1 cell surface receptor, pembrolizumab (Merck, Darmstadt, Germany) and nivolumab (Bristol-Myers Squibb, Princeton, NJ).

In this commentary, we provide first a brief overview of the cancer immunity cycle that might help to understand the corresponding immune mechanisms and the variability in drug response, followed by a summary of the main results emerging from the popPKPD analyses of pembrolizumab and nivolumab. Finally, we discuss some of the current challenges facing immuno-oncology (IO).

BASIC PRINCIPLES IN IMMUNE-RESPONSE APPLIED TO TUMOR TREATMENT

The crosstalk between the immune system and tumors can be described by the cancer-immunity cycle, as shown in Figure 1 and summarized in the following four steps2:

1. Antigen recognition. The antitumor immune responses are initiated by alarm signals that activate local dendritic cells (DCs) capturing tumor antigens (Ags), released by the damaged tumor tissue.
2. Antigen presentation and signal modulation. Mature DCs migrate to the lymph nodes and present Ags to cytotoxic CD8+ T lymphocytes or T-helper CD4+ T cells. This signal is modulated by a variety of positive (i.e., CD28 or CD137) and negative (i.e., PD-1 or CTLA-4) costimulatory molecules and the production of certain cytokines (such as interleukin 12 (IL12)/interferon alpha (IFNα)).
3. Immune response. A successful antitumor immune response will be made up of the coordinated activity of T-helper CD4+ cells, B-cells, cytotoxic CD8+ T lymphocytes, natural killer cells, and M-1 macrophages. These effector cells must reach the malignant tissue and kill the target cells. The presence of tumor-infiltrating lymphocytes (TILs) is associated with tumor immune response.
4. Immune resistance. To achieve efficient tumor response, the effector cells must overcome the different immunosuppressive mechanisms present in the tumor microenvironment. For example, the blockage of PD-1 will hamper the binding to its main ligand, PD-L1, a molecule overexpressed in a variety of solid tumor cells, with one of its known main actions being the abolition of antitumor immune responses.

Based on the summary above, a combination of several biomarkers, for example, PD-L1 protein expression, circulating IL12, and TILs, might be considered as an alternative to gather mechanism-based information regarding variability in response, and to detect at an early stage the presence of nonresponders. In line with this, PD-L1 protein expression has been proposed as a useful biomarker for anti-PD-1/anti-PD-L1 mAbs, since higher response rates are observed in patients with PD-L1-positive tumors.3

INPUT AND HIGHLIGHTS

After reviewing the studies in this issue,4–10 the reader will be able to see that several state-of-the-art pharmacometrics procedures have been applied to this new class of compounds: physiologically based pharmacokinetics applied to mAbs, systems pharmacology (SP) approaches combining in vitro binding results with literature data for translational purposes, mechanistic tumor growth inhibition models, and drug exposure–time-to-event relationships.

Among all the published articles in this issue, there are two that deserve special attention. First, Elassais-Schaap et al. applied the learn and confirm paradigm, based on modeling and simulation (M&S), to improve clinical trial design for a large cohort of patients using limited PK and PD information.4 The search for and subsequent use of predictive biomarkers is a major challenge in oncology.

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drug development and clinical practice. M&S efforts using longitudinal biomarker data gathered at early phases during treatment might help to optimize the dosing schedule, manage toxicity, identify nonresponders, and anticipate progression of the disease. In the above-mentioned article, IL2 was the circulating biomarker used to propose the dosing schedule for clinical efficacy. Remarkably, the biomarker-related results were in accordance with those obtained following different model-based approaches.5,6 These findings are encouraging and point to IL2 as one of the potential markers to be evaluated in future IO trials.

Second, and given the large uncertainty associated with the early phases of clinical development of first-in-class molecules, Lindauer et al. illustrate the SP-like pathway to follow.5 In their study, empirical PK information gathered from drug in plasma profiles was linked with a general physiologically based PK model for antibodies; then, predicted drug concentrations in the interstitial space bind to the PD-1 target as described in an in vitro model, and finally, tumor growth reduction was related to the degree of target inhibition. Results from that SP modeling exercise were translated to the human scenario taking into account biological uncertainty, using human parameters when possible or allometric scaling otherwise, or keeping mice parameters. Finally, dose–response predictions for different growing tumors (from slow to fast) were obtained.

The results from that translational exercise were supported by those extracted from the longitudinal analysis of tumor size,6 where it was observed that drug exposure (obtained in the dose range between 2–10 mg/kg every 3 weeks for the case of pembrolizumab) did not correlate with tumor response, suggesting saturation in the exposure–response relationship. Interestingly, the report by Wang et al., describing the exposure vs. response relationship for nivolumab in patients with advanced melanoma, shows that drug exposure (in the range of 0.1–10 mg/kg every 2 weeks), represented by time-averaged concentration after the first dose, was not a significant factor in predicting different types of responses such as overall survival, RECIST objective response, and toxicity.7 The combined results of pembrolizumab and nivolumab indicate that the early development strategies followed by both companies provided highly accurate translational predictions.

The analysis of plasma concentration data obtained from nearly 2,000 patients treated with pembrolizumab or nivolumab demonstrated similar PK properties for both agents.8,9 Covariates selected during the model-building process did not show clinical relevance. It is worth noting that tumor burden for both drugs, and PD-1 expression for nivolumab, were selected as statistically significant covariates. One intriguing result for nivolumab is its time-variant clearance.9 Time-varying clearance may actually be present for other mAbs too, but time-varying factors are rarely...
evaluated. The immunogenicity of neither drug was shown to affect drug disposition in a relevant manner.

**CURRENT CHALLENGES IN IMMUNO-ONCOLOGY**

One of the aspects that currently remains to be solved, or at least, to be minimized in IO, is the presence of patients who do not respond to treatment. This aspect of the therapy is reflected in the outcome of the population analysis of tumor size dynamics in pembrolizumab-treated advanced melanoma.\(^6\) Tumor size–time profiles showed a great degree of heterogeneity, as described using a mixture modeling approach, differentiating between fast progression, and slow and fast responders. These results, obtained during the clinical development of pembrolizumab, revealed the need to continue basic and drug research to elucidate the mechanism(s) by which tumors in certain patients are not capable of triggering the required immune response or escape immune system control.

In that respect, combination therapies and predictive biomarker discovery will play a fundamental role in improving the outcome of IO. Given, at least in the case of the drug-combination arena, the high number of possibilities to explore, well-planned mechanism-based-oriented animal research is crucial. We anticipate that, if the objective is related to dose finding (as in the examples provided in the current issue), preclinical models such as syngeneic tumors implanted in mice, focusing just on the dynamics of tumor growth might be useful and sufficient. However, such studies will not be able to shed any light on the mechanisms responsible for the great heterogeneity in response.

In conclusion, pharmacometric and systems pharmacology approaches have been successfully applied to establish the dose regimens for pembrolizumab and nivolumab in melanoma and non-small cell lung cancer. These promising results open the field to the new challenge in IO of detecting nonresponders early and finding an alternative treatment, likely a combination therapy. To achieve that therapeutic goal the search for predictive biomarkers and development of mechanism-based study designs are warranted.

**Conflict of Interest/Disclosure.** The authors declare no conflicts of interest.

**Author Contributions.** M.J.G., P.B., and I.F.T. contributed to article writing, organization, and literature search.

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