Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 5–7; doi:10.1002/psp4.12131


PERSPECTIVE

# Pembrolizumab: Role of Modeling and Simulation in Bringing a Novel Immunotherapy to Patients With Melanoma

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**Recently, immunotherapy has yielded promising results in several cancer types. Contrary to the established classical chemotherapy-dosing paradigm, a maximum tolerated dose approach does not always produce better clinical outcomes for novel targeted therapies, as their efficacy is frequently robust at pharmacologically active doses below the maximum tolerated dose. Integrated safety and efficacy assessments are needed to inform clinical dose and trial design, and to support an early identification of potentially safe and efficacious combination treatments.**
*CPT Pharmacometrics Syst. Pharmacol.* (2017) **6**, 5–7; doi:10.1002/psp4.12131; published online 21 September 2016.

The field of pharmacometrics builds upon the pharmacology and disease knowledge to develop an integrated mathematical representation of drug response. This ability to integrate data and information using a structured approach brings considerable advantage in a small, fast-moving oncology program with challenges coming from data imbalances, sparseness of data, heterogeneity of data and response, and multiple sources of variability. Conceptually and practically, the use of modeling and simulation enables more efficient development of targeted therapies in oncology and aids in bringing these promising treatments to patients.[1,2]

## PEMBROLIZUMAB IN MELANOMA: CLINICAL OVERVIEW

Pembrolizumab, a recently introduced immunotherapy, is a potent and highly selective humanized immunoglobulin G4 kappa monoclonal antibody directed to the programmed death 1 (PD-1) receptor and is designed to block the interaction between the receptor and its ligands, programmed death ligand-1 and programmed death ligand-2.[3] The PD-1 pathway represents a major immune switch that tumor cells use to counteract antitumor T-cell activity. When this pathway is blocked on T cells, antitumor activity is reactivated.[4] Given that programmed death ligand-1 is expressed on melanoma tumor cells,[5] the initial clinical development of anti-PD-1 treatment focused on that indication.

Clinical development and initial registration of pembrolizumab was largely built upon a single clinical trial: KEYNOTE-001 (Clinicaltrials.gov identifier, NCT01295827), which was an international, open-label, multicohort, phase Ib study of the safety and efficacy of pembrolizumab. After an initial dose escalation in patients with various solid tumors, treatment of patients with advanced melanoma was initiated. Early efficacy and safety results indicated a favorable benefit-risk profile that led to the decision to seek fast-track development for regulatory submission at a time when little dose ranging had been conducted in the program.[6–8] The single expanded phase I study ($N = 411$)[9] would eventually form the basis of the initial approval of pembrolizumab in the United States for the treatment of unresectable or metastatic melanoma. Modeling and simulation were key components supporting the dose setting and characterization of the clinical pharmacology of pembrolizumab for the US label in lieu of extensive dose-finding and dedicated clinical pharmacology studies, which could have slowed the program or been challenging to implement. A summary of these activities is provided herein, and a visual overview of the applied modeling and simulation strategy is presented in **Figure 1**. More detailed reports on the different components of this strategy can be found elsewhere in this issue.[10–13]

## DOSE SETTING FOR EFFICACY STUDIES

As initial clinical evidence indicated promising efficacy for pembrolizumab, a focused clinical development plan was begun. At the time of planning for the pivotal assessments of clinical efficacy and safety, three key questions were identified that would be primarily addressed through pharmacometric efforts. (1) What is the appropriate dose range for investigation in the clinical studies as informed by estimates of minimal effective dose? (2) What is the appropriate dosage regimen balancing benefits and risks to inform the dosage and administration section of the label? (3) What is the impact of intrinsic and extrinsic factors on exposure and do these effects require any guidance around dose adjustment in subpopulations?

Two complementary modeling and simulation approaches were developed to inform the question around dose ranges for clinical investigation. The first utilized exploratory *ex vivo*

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Received 23 March 2016; accepted 29 August 2016; published online on 21 September 2016. doi:10.1002/psp4.12131

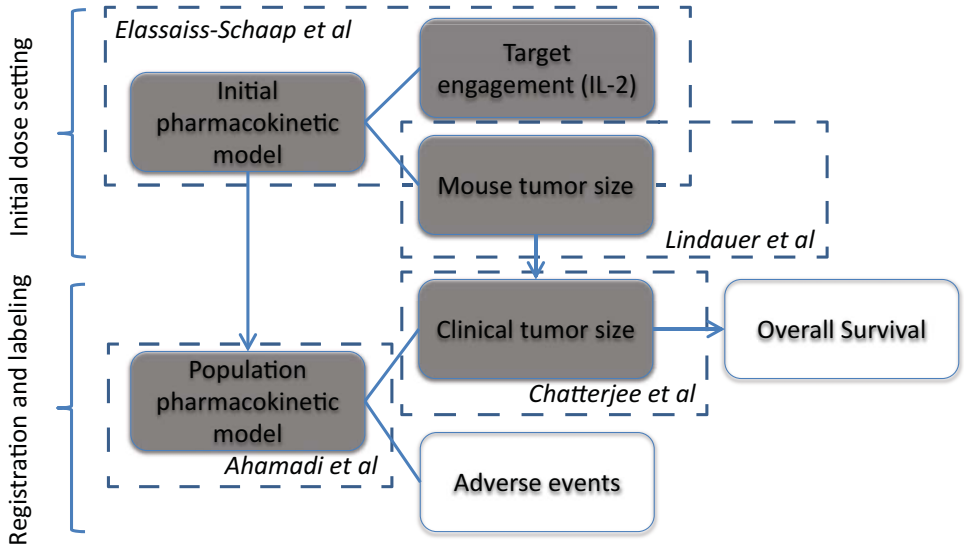


**Figure 1** Pembrolizumab modeling and simulation strategy in melanoma. Various analyses inform and support dose selection, registration, and the label for pembrolizumab.[10–13]

peripheral blood mononuclear cell biomarker and pharmacokinetic (PK) data obtained in the initial cohorts of the clinical study, as described by Elassaiss-Schaap *et al.*[13]. A critical aspect of this approach was the inclusion of a dedicated intrapatient dose-escalation cohort to strengthen the empirical PK-pharmacodynamic analysis. An understanding of the pembrolizumab concentrations and doses at which maximal target engagement was achieved helped to define the lower end of the dose range to be tested in the pivotal efficacy and safety cohorts.

The second analysis to support the minimal effective dose used a translational PK-pharmacodynamic modeling approach, based on integration of available preclinical PK data, PD-1 receptor occupancy, antitumor efficacy data from a syngeneic mouse model, human tumor growth kinetics, and early clinical PK data (Lindauer *et al.*[12]). In this approach, a semimechanistic model capturing key physiologic and biological features of response (such as antibody distribution to tumor tissue and effect of PD-1 inhibition on tumor growth) was developed. Subsequently, the model was adapted for prediction of expected clinical responses, with a focus on determining the lowest doses that have a high probability of achieving maximal efficacy.

The *ex vivo* approach was based on clinical data but required assumptions regarding the link between peripheral blood mononuclear cell target engagement and efficacy, whereas the translational PK-pharmacodynamic approach based in part on animal data relied on a physiology-based interspecies extrapolation. Despite these differences, the two methods converged on a similar answer of a regimen of 1–2 mg/kg administered every 3 weeks as the lowest dose with high optimal likelihood of maximizing clinical efficacy. The potential for lesser efficacy was predicted at doses below 1 mg/kg. Thus, a dosage regimen of 2 mg/kg every 3 weeks was brought forward into the pivotal cohorts of the KEYNOTE-001 trial, along with the previously planned higher-dosage regimens of 10 mg/kg every 3 weeks and 10 mg/kg every 2 weeks, to inform the dose selection for registration.

## MODEL-BASED SUPPORT FOR REGISTRATION AND LABELING

The initial submission of pembrolizumab for the treatment of advanced melanoma relied on the data from a single clinical study. Therefore, the focus of clinical pharmacology characterization was on model-based approaches that could leverage sparse PK, safety, and efficacy data. The foundation for the resulting model framework was provided by a population PK analysis (Ahamadi *et al.*[11]); the latest and most mature version of the population PK model will be continually refined. Furthermore, the analysis was central to the assessment of the impact of key patient covariates on pembrolizumab exposure. In fact, all statements in the special populations sections of the clinical pharmacology portion of the US label are supported by the results of the population PK analysis. Given this critical role, special attention was given to robustly evaluate the ability of the model to pick up covariate effects through extensive simulations and reestimations under a variety of scenarios. Additionally, the population PK analysis produced individual pembrolizumab exposure estimates that were included in exposure–response relationships for efficacy and safety to support both the proposed dose regimen and the therapeutic window for pembrolizumab.

For all melanoma submissions to date, overall survival data were not sufficiently mature to establish robust exposure–response relationships. Therefore, exposure–efficacy evaluations supporting pembrolizumab dose selection centered on tumor size kinetics (longitudinal scans captured by the sum of longest dimensions of the target tumor lesions). As treatment with immunotherapy can result in a wide array of tumor growth characteristics atypical for

traditional cytotoxic or other targeted therapies, development of a tailored tumor size model was required. As described by Chatterjee *et al.*,[14] two approaches were explored that were found to have much commonality and successfully implemented at different stages in the program. The results of all exposure–tumor size assessments indicated a flat exposure–response relationship for tumor size response for pembrolizumab across the 2 mg/kg every 3 weeks to 10 mg/kg every 2 weeks dosage range, indicating that a near-maximal response was achieved at 2 mg/kg every 3 weeks.

In addition to efficacy exposure-response, an exposure-response assessment for safety was performed, focusing on specific categories of adverse events, with an emphasis on immune-related adverse events. Logistic regression and time-to-event approaches were utilized to assess the potential dependence of the occurrence of these adverse events on pembrolizumab exposure. The results of these studies will be reported separately, but overall, these assessments also indicated a flat exposure-response relationship. Collectively, the efficacy and safety exposure–response analyses provided strong support for pembrolizumab 2 mg/kg every 3 weeks as the proposed dosage for the treatment of patients with unresectable or metastatic melanoma.

## CONCLUSION

An integrated set of modeling and simulation evaluations was successfully applied during the clinical development and registration of pembrolizumab, a breakthrough therapy for cancer. In the absence of dedicated clinical studies, the analyses support the dose selection and characterization of critical elements of the compound's clinical pharmacology profile. As such, the work was instrumental in rapidly bringing this treatment at an optimized dosage regimen to patients with advanced melanoma.

**Acknowledgments.** Medical writing and editorial support in the preparation of this manuscript was provided by Tricia Brown, MS, and Melanie Leiby, PhD (ApotheCom, Yardley, PA) and was funded by Merck & Co., Inc. (Kenilworth, NJ).

**Author Contributions.** All authors were involved in the writing and review of the manuscript.

**Conflict of Interest.** All authors are employees of the stated companies. R.dG. reports personal fees received from Merck & Co., Inc., during the conduct of the study. J.E.-S. reports personal fees received from Merck & Co., Inc., during the conduct of the study and after leaving Merck started an independent consultancy company as indicated in the affiliations. M.C. has nothing additional to disclose. D.T. has nothing additional to disclose. M.A. has nothing additional to disclose. M.F. has nothing additional to disclose. D.C. holds stock in Merck & Co., Inc. D.dA. has nothing additional to disclose. A.G.K. has nothing additional to disclose. J.S. reports financial activity with Merck & Co., Inc., outside of the submitted work.

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