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.

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
peripheral blood mononuclear cell biomarker and pharmaco-
kine (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 intra-
patient dose-escalation cohort to strengthen the empirical PK-
pharmacodynamic analysis. An understanding of the pembro-
lizumab 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 physiolog-
ic and biological features of response (such as antibody dis-
tribution 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 effi-
cacy. 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 cen-
tral to the assessment of the impact of key patient covari-
ates on pembrolizumab exposure. In fact, all statements in
the special populations sections of the clinical pharmacolo-
gy 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 simul-
ations and reestimations under a variety of scenarios. Addi-
tionally, 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 therapeu-
tic window for pembrolizumab.

For all melanoma submissions to date, overall survival
data were not sufficiently mature to establish robust
exposure–response relationships. Therefore, exposure–effi-
cacy 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
of a tailored tumor size model was required. As described by Chatterjee et al.,\textsuperscript{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.

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