Model-Based Study Design Revealing the PKPD Relationship of Pembrolizumab in the KEYNOTE-001 Melanoma Trial

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Objectives: Evaluation of PKPD properties played an important role in the early clinical development of pembrolizumab. Analysis of data from a traditional 3+3 dose-escalation design in KEYNOTE-001 revealed several critical uncertainties in PKPD properties. A trial design able to clarify these properties needed to be quickly developed, executed, and analyzed to provide an early assessment of potential pembrolizumab dose regimens to be tested for clinical efficacy.

Methods: A model-based approach was implemented to design and evaluate a robust follow-up study. Intensive multidisciplinary consultation rounds led to the establishment of a paradigm (template) of fast, within-patient dose escalation to minimize patients’ exposure to potentially ineffective concentrations.

14,000 virtual trials (leveraging this within-patient dose escalation) were stochastically generated (Figure) using that clinically acceptable design template, wide dose-ranges, and wide PKPD-parameter-ranges that included estimates from previous data. Designs were evaluated (using simulated data) for ability to correctly identify parameters.

Results: Design optimizations led to a clinical study with three dose levels per subject, extending the dose range by 200-fold. Modeling of the data resulting from execution of that design demonstrated that pembrolizumab pharmacokinetics are nonlinear at <0.3 mg/kg every 3 weeks (Q3W), but linear in the clinical dose range. Saturation of \textit{ex vivo} target engagement in blood began at ≥1 mg/kg Q3W, and a steady-state dose of 2 mg/kg Q3W was needed to reach 95% target engagement, supporting examination of 2 mg/kg Q3W in ongoing trials in melanoma and other advanced cancers.

Conclusions: Multidisciplinary collaboration and modeling and simulation enabled rapid design of an efficient clinical study with desired properties. Model-based analysis of that study’s data successfully contributed to choosing the pembrolizumab dose to test for clinical efficacy: 2 mg/kg Q3W.

References:
1. J. Ellassiass-Schaap, et al., Using model-based "Learn and Confirm" to reveal the PKPD relationship of pembrolizumab in KEYNOTE-001 melanoma trial, CPT-PSP, accepted.