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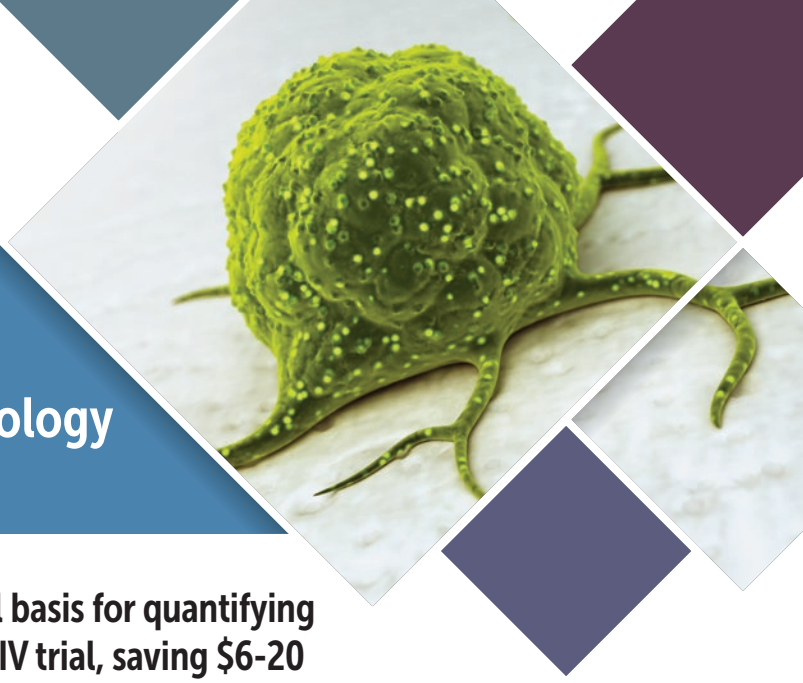

Modeling and Simulation Supports Post-approval Commitment in Oncology

Modeling strategy provided sponsor with rational basis for quantifying efficacy benefit of approved dose to avoid Phase IV trial, saving $6-20 million and redirecting resources toward other programs

Background

A global biopharmaceutical company was seeking to fulfill a post-approval commitment to regulatory authorities for its currently approved oncology drug. Regulatory approval in the given indication was based on results of a pivotal Phase III study to evaluate safety and efficacy of the drug in combination with another agent as a first-line treatment. Dose selection for the pivotal trial was based on Phase II results of the drug as a single-agent, second-line treatment.

Challenge

While the safety profile of the approved dose was not in question, the regulatory authorities noted that lower dose levels were not tested in the proposed indication and requested further investigation as a post-approval commitment. As the sponsor refined its strategy, it became critical to provide a quantitative basis for the approved, higher dose and to establish a comprehensive picture of the drug's efficacy profile at intermediate doses in a first-line setting.

Solution

With support from Certara, the sponsor developed a plan to use modeling and simulation to describe the anti-tumor dose-effect relationship of the drug and explore the efficacy benefit of the higher dose, based on the available data. Certara developed a predictive model for the time course of tumor size measurements (Claret el al, JCO 2009) for the drug and its combination therapy agent, based on the combined Phase II/III study data.

The tumor growth inhibition model was then used to simulate expected dose response in tumor shrinkage over time and across response categories (consistent with published response evaluation rules for cancer patients, see www.recist.com) in first-line patients treated by the drug and its combination agent across a range of relevant doses. The simulations included different scenarios

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Benefit

Avoided spending $6-20 million and 18-24 months for a new trial. safety liability.

that accounted for different dose modification histories observed from the two different studies and patient populations, representing first-line and second-line patients.

Benefit

The model-based approach and simulations offered compelling evidence to demonstrate predicted improvements in the proportion of responders overall response rate (ORR) and corresponding reductions in the proportion of patients with progressive disease at the currently approved dose versus lower, intermediate doses. Based on the weight of the model-based approach, the regulatory authorities accepted the sponsor's modeling and simulation results to meet the post-approval commitment.

Impact

Acceptance of the model-based approach by regulatory authorities enabled the sponsor to avoid further direct investment of $6-20 million and 18-24 months for a new trial (comparable in size and complexity to another Phase II study, eg, three arms and several hundred subjects) that would have been required to demonstrate the efficacy benefits of the originally approved higher dose.[1] In addition to the direct cost savings, the sponsor was able to direct valuable resources to other clinical programs in their portfolio. The modeling and simulation strategy helped the sponsor establish a rigorous, quantitative picture of the drug's efficacy profile to justify dose selection and support productive interactions with regulatory authorities.

References

1. Average Phase IV per patient clinical trial costs in oncology from Cutting Edge Information, 2008. Mean out-of-pocket clinical period costs for Phase II investigational compounds. DiMasi, Hansen, Grabowski. The Price of Innovation: New Estimates of Drug Development Costs. Data used for estimates published in PAREXEL's R&D Statistical Sourcebook, 2009/2010.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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