

Biosimulation Supports Label Claims for New Combination Treatment for Oncology

Certara leverages its modeling and simulation technology to facilitate regulatory approval for a targeted treatment for melanoma

Background

A hallmark of cancer is the abnormal activation of cellular signaling pathways. The RAS/RAF/MEK/ERK cell signaling pathway normally regulates cell proliferation, survival, migration, cell cycle regulation, and angiogenesis.¹ Cancer cells frequently express genetic mutations that cause dysregulation of this signaling pathway. Vemurafenib is a small molecular inhibitor of B-RAF. In 2011, the Food and Drug Administration (FDA) approved Genentech's Zelboraf® (vemurafenib) for patients with metastatic or unresectable melanoma whose tumors also express the gene mutation B-RAF V600E.²

Challenge

Cancer cells have a remarkable ability to become resistant to targeted therapies. Combining two or more therapies that target different parts of a cellular signaling pathway can help to address this challenge.

Cobimetinib is a small molecule inhibitor of MEK, which is in the same signaling pathway as B-RAF. *In vitro* data suggests that this drug is metabolized by CYP3A and UGT2B7.³ In a phase III study of patients with B-RAF V600 mutation-positive unresectable or metastatic melanoma, the combination of cobimetinib and vemurafenib significantly improved progression-free survival (PFS) compared to vemurafenib alone.⁴

To gain approval for this drug combination, the sponsor needed to understand the pharmacokinetics (PK) and exposure-response relationship of cobimetinib and vemurafenib to develop an optimal dosing strategy. They also needed to determine whether patients with certain other clinical complications, such as eliminating organ impairment, might require dose adjustment. Another crucial step was to assess whether co-administration of drugs that modulate the activity of the major enzyme responsible for the metabolic elimination of the drug (CYP3A), such as vemurafenib, might cause clinically significant drug-drug interactions (DDIs).

Challenge

Genentech sought approval for a novel combination treatment for patients with metastatic melanoma who possess a specific genetic mutation.

Solution

The sponsor leveraged both Certara's Simcyp Simulator as well as support from Certara Strategic Consulting scientists to characterize cobimetinib's pharmacokinetic-response relationship, and potential DDIs.

Benefit

The physiologically-based pharmacokinetic (PBPK)-response, systemic drug concentration-QT, and PopPK models helped guide the recommended safe and efficacious dose for all patients.

To characterize the PK of cobimetinib, blood samples were collected from three clinical studies. The patients in these studies all had solid tumor types, the majority being melanoma. The study protocols called for cobimetinib to be administered orally, once daily on a 28-day dosing cycle, either as a single agent or in combination with vemurafenib. In all three studies, serial and sparse plasma samples were collected to capture PK after the first dose and at steady state.

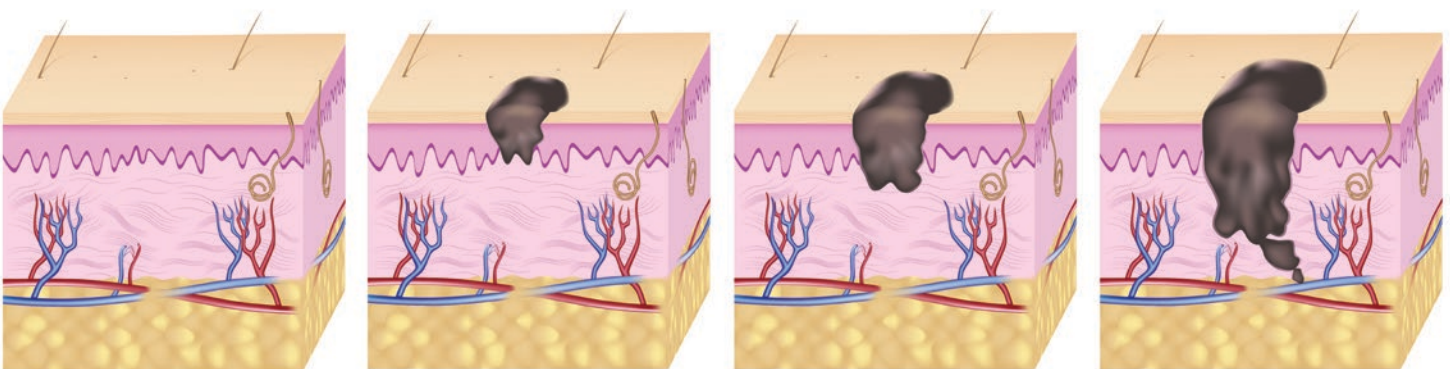
For PK analysis, Certara Strategic Consulting (CSC) scientists developed a population pharmacokinetics (PopPK) model using a non-linear mixed-effects modeling approach.⁵ A linear, two-compartment model with first-order absorption, lag time, and first-order elimination adequately described the PK of cobimetinib.

The PK data after single dose and at steady-state allowed characterization of drug accumulation and estimation of the elimination half-life of cobimetinib. Apparent clearance was shown to decrease with age and the central volume of distribution was shown to increase with body weight. Age and body weight did not, however, measurably impact cobimetinib steady-state exposure.

Likewise, cobimetinib PK, including steady-state exposure, did not appear to be influenced by gender, renal function, Eastern Cooperative Oncology Group (ECOG) score, hepatic function, race, region, or cancer type (melanoma vs. non-melanoma). Co-administration of vemurafenib with cobimetinib did not result in a clinically significant DDI.

CSC scientists also worked with the sponsor to define the exposure-response relationships for cobimetinib in combination with vemurafenib. They conducted exposure-response analysis on data from a Phase III study of cobimetinib in combination with vemurafenib in BRAF V600E mutation-positive patients.⁶ To determine if this drug combination could cause cardiotoxicity, concentration-QT analysis was performed.⁶

The Stages of Malignant Melanoma



For the doses studied, no clinically significant changes were seen in the cobimetinib exposure-response relationship following concomitant administration of cobimetinib and vemurafenib for any of the selected clinical efficacy or safety endpoints. Co-administration of cobimetinib and vemurafenib did not show further increases in QTcF prolongation as compared to when vemurafenib was administered alone.

The sponsor conducted a limited number of clinical DDI studies in healthy subjects. Co-administration of itraconazole, a strong CYP3A inhibitor, with cobimetinib caused a significant increase in cobimetinib exposure. The sponsor used these clinical studies along with cobimetinib *in vitro* data to build and verify a physiologically-based pharmacokinetic (PBPK) model using Certara's Simcyp Simulator.^{7,8} This model was then used to predict the magnitude of potential change in cobimetinib exposure in the presence of various other CYP3A inhibitors and inducers.

Benefit

The PopPK model adequately described cobimetinib's PK. None of the clinically relevant demographic, physiological or pathophysiological patient characteristics appeared to significantly impact steady-state drug exposure. Exposure-response analysis and concentration-QT analysis also provided evidence showing that the proposed dosing regimen was safe and effective with no need for dose adjustments in the broader patient population.

The combined evidence from clinical and virtual PBPK DDI studies helped inform the drug label for cobimetinib, which advises against concurrent use of both strong or moderate CYP3A inhibitors and strong or moderate CYP3A inducers. In the event that a patient needs to take a moderate CYP3A inhibitor for short-term use, the drug label provides guidance on how to adjust the dose to maintain a safe level of exposure. In total, the Simcyp Simulator was used to provide insight into 16 potential DDIs, without a need to perform those specific clinical studies.

Impact

In November 2015, the FDA approved Cotellic (cobimetinib) for use in combination with vemurafenib to treat advanced melanoma that has B-RAF V600E or V600K mutations.⁹ Cotellic was reviewed under the FDA's priority review program. This program allows an expedited six-month review of drugs with the potential to significantly improve the treatment of a serious condition. Cotellic also was designated an orphan drug. This designation provides incentives such as tax credits, user fee waivers, and extended exclusivity to encourage the development of drugs for rare diseases.

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