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CASE STUDY

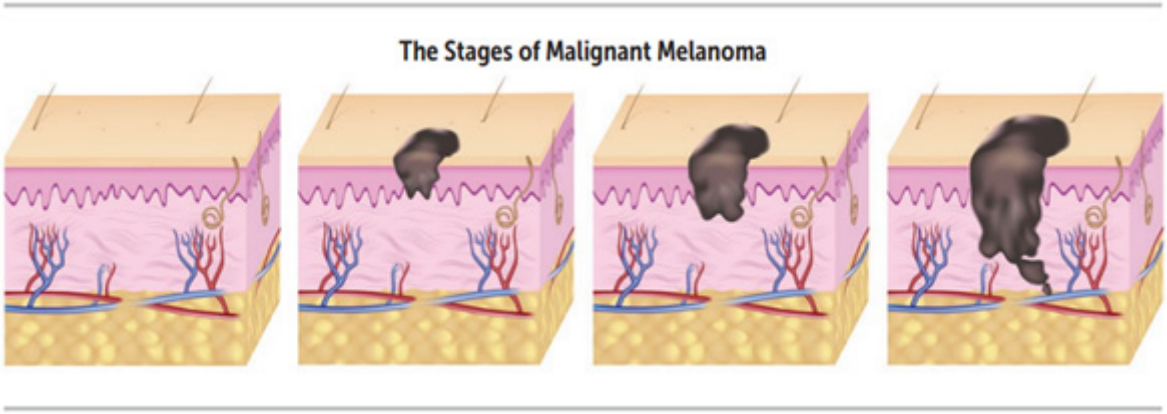
BIOSIMULATION SUPPORTS LABEL CLAIMS FOR A COMBINATION ONCOLOGY TREATMENT

Genentech's Zelboraf® (vemurafenib) is a small molecule B-RAF inhibitor and is FDA-approved to treat patients with metastatic or unresectable melanoma whose tumors express the B-RAF V600E mutation. To reduce the likelihood of cancer cells becoming drug resistant, Genentech wanted to combine vemurafenib with cobimetinib, a small molecule MEK inhibitor that targeted a different part of the cell signaling pathway.

A Phase 3 study of patients with B-RAF V600 mutation-positive unresectable or metastatic melanoma showed that combining cobimetinib and vemurafenib significantly improved progression-free survival compared with vemurafenib alone.

Genentech needed to characterize the pharmacokinetics (PK) and exposure-response relationship of cobimetinib and vemurafenib to optimize dosing. It also needed to assess whether co-administration of the drugs could cause a clinically significant CYP3A-mediated drug-drug interaction (DDI).

A population PK model was developed to characterize cobimetinib's PK. Then an exposure-response analysis was conducted using data from another Phase 3 study of cobimetinib with vemurafenib in BRAF V600E mutation-positive patients. A concentration-QT analysis was also performed to determine whether the drug combination could cause cardiotoxicity. This modeling showed that administration of cobimetinib with vemurafenib did not produce any clinically significant changes in the safety or efficacy endpoints.



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A few clinical DDI studies were conducted with healthy volunteers. Co-administration of itraconazole (a strong CYP3A inhibitor) with cobimetinib produced a significant increase in cobimetinib exposure. These clinical results were used, together with cobimetinib in vitro data, to build and verify a Simcyp Simulator physiologically-based PK (PBPK) model. That model was used to predict the potential changes in cobimetinib exposure in the presence of other CYP3A inhibitors and inducers. In fact, it provided insight into 16 potential DDIs without needing to perform clinical studies. It was also used to determine the optimal dosing for different patient groups. The cobimetinib label advises against concurrent use of strong or moderate CYP3A inhibitors and strong or moderate CYP3A inducers.

The PBPK model built in the Simcyp Simulator provided insight into 16 potential DDIs without needing to perform clinical studies.

Headquartered in New York, Intercept Pharmaceuticals is a biopharmaceutical company focused on the development and commercialization of novel therapeutics to treat progressive non-viral liver diseases, including PBC and nonalcoholic steatohepatitis (NASH). Founded in 2002, Intercept has operations in the United States, Europe, and Canada.

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