Pharmacokinetics and Pharmacodynamics of AV-203, a Humanized anti-ERBB3 Antibody

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Abstract:

ERBB3 is widely expressed in human carcinomas, and its overexpression is associated with poor prognosis in patients with various carcinomas, (i.e., breast, ovarian, prostate, colorectal, pancreatic, gastric, and head and neck cancers). The presence of ERBB3 correlates with local to distant metastasis in lung, gastric, and colorectal cancers as well as bone invasion in prostate cancer. Activation of ERBB3 is also implicated in the development of resistance to current cancer treatments. Due to its lack of kinase activity, the activation of the ERBB3 receptor is dependent on heterodimerization with active receptor tyrosine kinases (RTKs). The recruitment of ERBB3 into active, heterodimer complexes is mediated by its ligand Neuroginulin-1 (Nrg-1) or by amplified, over expressed RTKs in a ligand independent manner. Therefore, ERBB3 can crosstalk with most major receptors involved in cancer development and maintenance such as epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and c-MET.

AV-203 is a potent, humanized anti-ERBB3 antibody that inhibits both ligand-dependent and independent activation of ERBB3 both in vitro and in vivo. Pharmacokinetics (PK) and pharmacodynamics (PD) of AV-203 were characterized in mice using the A549 non-small cell lung cancer xenograft. AV-203 administered in mice demonstrated acceptable pharmacokinetics supporting preclinical efficacy studies. AV-203 administered IV in A549 non-small cell lung cancer xenograft bearing mice had lower serum AUC than naïve mice, demonstrating that the presence of human ERBB3 may alter the PK parameters of AV-203. In evaluating pharmacodynamics in mice, AV-203 was able to down regulate total ERBB3 and ERBB3 signaling in A549 tumors in a time-dependent manner. Inhibition of ERBB3 signaling correlated with significant dose-dependent tumor growth inhibition in this model. Dose scheduling studies with the constant AV-203 dose of 2.5 mg/kg revealed that the most efficacious schedule is the more frequent dosing at QD. In comparing the total dose of 10 mg/kg per 14 day cycle, at varying dose per injection and frequency, AV-203 resulted in significant tumor growth inhibition at all dose schedules. These data conclude that the efficacy of AV-203 is driven by total drug exposure and that AV-203 is not dependent on Cmax, for its anti-tumor activity.

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AV-203 exhibited acceptable pharmacokinetics in mice supporting preclinical efficacy studies dosing at twice weekly. Tumor-bearing mice had lower serum AUC, shorter t1/2, and faster CL than naïve mice, suggesting the presence of the target human ERBB3 may increase the CL of AV-203.

AV-203 at 2.5 mg/kg, at varying frequency resulted in the most efficacious being the most frequently dosed at QD.

AV-203 at 10 mg/kg, total dose, per 14 day cycle, at varying dose per injection and varying frequency resulted in similar tumor growth inhibition at all dose schedules. Combined, this data suggested that anti-tumor activity of AV-203 depends on total drug exposure and not on Cmax.

AV-203 down regulates total ERBB3 and pERBB3 signaling in A549 tumors in a time-dependent manner, after a single 20 mg/kg dose.

AV-203 down regulates pAKT signaling in A549 tumors in a time-dependent manner, after a single 20 mg/kg dose.

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