AV-203, a Humanized ERBB3 Inhibitory Antibody Inhibits Ligand-Dependent and Ligand-Independent ERBB3 Signaling in vitro and in vivo

Sylvie Vincent, Christina Fleet, Steven Bottega, Donna McIntosh, William Winston, Ting Chen, Steven Tyler, Kristan Meetze, Solly Weiler, Jeno Gyuris

AVEO Pharmaceuticals, 75 Sidney St, Cambridge, MA, USA

**Summary**

AV-203 is a potent humanized ERBB3 inhibitory antibody that neutralizes NRG1 binding and promotes the downregulation of the ERBB3 pathway.

AV-203 inhibits RTK overexpression-dependent and ligand-induced activation of ERBB3.

AV-203 inhibits cell proliferation in response to NRG1.

**ERBB3 Pathway Activation**

**Ligand-Dependent Activation**

**Proliferation**

**Activation by RTK Overexpression**

**Survival**

**ERBB3**

**ErbB2**

**ErbB3**

**ErbB4**

**Ligand-Dependent**

**Activation by RTK Overexpression**

**Survival**

**Protein Expression**

**Staining**

**AV-203 Inhibition of RTK Dependent Signaling**

AV-203 inhibits EGFR- and NRG1/HER2-dependent ERBB3 signaling in NCI/ADR-res ovarian cancer cells.

**AV-203 Inhibition of Ligand-Dependent Signaling**

AV-203 inhibits ERBB3-dependent signaling in NCI/ADR-res ovarian cancer cells.

**AV-203 Anti-Tumor Activity in RTK Amplified and Non-Amplified Tumors**

AV-203 inhibits tumor growth of HER2 overexpressing MDA-MB-453 xenografts.

**AV-203 Inhibition of NRG1 Dependent Signaling**

AV-203 inhibits phosphorylation of ERBB3 and AKT in exponentially growing HER2-positive MDA-MB-453 breast cancer cells.

**AV-203 Inhibition of NRG1 Dependent Proliferation**

AV-203 inhibits HER2-dependent proliferation of MCF7 breast cancer cells.

**HER2/ERBB3 Dimer Inhibition**

AV-203 can inhibit NRG1-induced ERBB3-HER2 heterodimer formation in MCF7 breast cancer cells.

**AV-203 Inhibition of NRG1 Binding to rhERBB3-ECD-Fc**

AV-203 inhibits binding of NRG1 to human ERBB3.

**AV-203 Binding Specificity**

AV-203 binds specifically to human ERBB3 but not murine ERBB3.

**AV-203, a member of the EGFR receptor tyrosine kinase (RTK) family, has been implicated in tumor progression and as a path for resistance to standard of care therapies and RTK inhibitor (TKI) drug treatment. Despite its weak kinase activity, ERBB3 is of particular interest due to its ability to heterodimerize with pro-oncogenic RTK partners, such as HER2, EGFR, and MET.**

Activation of ERBB3 leads to potent activation of the PI3K pathway. We have developed AV-203, a humanized immunoglobulin G1/kappa antibody with potent inhibitory activity against RTK-dependent and ligand-induced activation of ERBB3.

AV-203 specifically binds with high affinity to human ERBB3 and to cynomolgus monkey ERBB3 but not to mouse, allowing for toxicological assessment. AV-203 potently inhibits the binding of the ERBB3 ligand Neuregulin (NRG1/HRG) to ERBB3 and to toxicological assessment.

AV-203 is capable of down-regulating ERBB3 receptor in vitro and in vivo. Lastly, AV-203 inhibits tumor growth in a broad spectrum of xenograft models with and without RTK amplifications, such as the pancreatic cancer (BXPC3) or HER2 overexpressing MDA-MB-453 breast cancer cell line, MCF7, and of a BaF3 cell line engineered to overexpress ERBB3 and HER2 (BaF3-ERBB3/HER2). AV-203 is a potent humanized ERBB3 inhibitory antibody that neutralizes NRG1 binding and promotes the downregulation of the ERBB3 pathway.

**Kinetic Values of AV-203 Binding to Human ERBB3-ECD**

AV-203 binds to monomeric human ERBB3 with high affinity (Ka=4.0E+7 M⁻¹) at 37°C.

AV-203 binds to human and cynomolgus ERBB3 but not murine ERBB3.

**Average Affinity (KD)**

**nM**

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<th>Temp.</th>
<th>n</th>
<th>Kd Average (nM)</th>
<th>KD Average (nM)</th>
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**AV-203 Binding Specificity**

AV-203 binds specifically to ERBB3 but not murine ERBB3.

**AV-203 also exhibits significant tumor growth inhibition of breast, lung, kidney, head and neck, pancreatic, and ovarian xenografts.**