Structural characterization of a potent humanized anti-CD38 antibody in phase I

F. Vallée\textsuperscript{1}, S. Pouzieux\textsuperscript{1}, A. Rak\textsuperscript{1}, F. Michoux\textsuperscript{1}, M. Wetzel\textsuperscript{1}, J. Deckert\textsuperscript{2}, A. Kannt\textsuperscript{2}, V. Blanc\textsuperscript{1}, V. Mikol\textsuperscript{1}

\textsuperscript{1}Sanofi Research et development, Vitry sur Seine, France, \textsuperscript{2}Sanofi Research and development, Frankfurt am main, Germany, \textsuperscript{3}Immunogen, Inc., Waltham, MA, USA

CD38 is a type II transmembrane glycoprotein with both ADP-riboosyl cyclase and glycohydrolase activities. CD38 is highly expressed at the surface of malignant plasma cells of multiple myeloma. SAR650984 is a humanized IgG1 antibody targeting CD38 in early clinical development that is acting through several potential mechanisms including ADCC, CDC and pro-apoptotic activity. Here we report further preclinical characterization of SAR650984 with a high resolution structure of Fab-SAR650984 in complex with CD38 allowing an epitope mapping. The crystal structure of SAR650984-Fab/huCD38 complex shows that SAR650984 neither blocks the access nor alters the configuration of the ADPRC catalytic site of CD38 although in vitro assays have demonstrated that SAR650984 behaves as a strong inhibitor of the ADPRC activity of CD38. These results suggest that SAR650984 is likely an allosteric antagonist of CD38 that alters the dynamics of enzyme upon binding.

\cite{Deckert2014} Deckert et al (July 1, 2014), Clinical Cancer Research 10.1158/1078-0432.CCR-14-0695, \cite{Wetzel2013} Wetzel et al; AACR2013 #4736, \cite{Wetzel2013} Wetzel et al; IMW2013 #P228

Keywords: CD38, anti-CD38 antibody, myeloma