AVELUMAB INTERNALIZATION AND LYSOSOMAL DEGRADATION BY CIRCULATING IMMUNE CELLS IN HUMAN IS MEDIATED BY BOTH FC GAMMA RECEPTOR (FCGR) AND PD-L1 BINDING

1Hulin Jin*, 2Vittorio D’Ursio, 3Berend Neuteboom, 2Sean McKenna, 2Rene Schwickhardt, 2Alec Gross, 2Yaes Fomekong Nanfack, 1Lars Toleikis, 1Markus Fluck, 1Juergen Scheuenpflug, 2Ti Cai, 1Merck KGaA, Darmstadt, Germany, Darmstadt, Germany; 1EMO Serono Research and Development Institute, Inc., Billerica, MA, USA; a business of Merck KGaA, Darmstadt, Germany, Billerica, MA, USA

Background Receptor-mediated endocytosis results in antibody recycling (via endosomes) or degradation (in lysosomes). Avelumab is a human anti–PD-L1 antibody, with wild type (WT) IgG1 isotype and effector function, approved for treating certain cancers. Here, we report the mechanism of avelumab internalization and association with pharmacokinetic (PK) properties.

Methods A flow cytometry-based antibody internalization assay using pH-sensitive fluorescent dye was applied to directly monitor antibody internalization and lysosomal degradation in healthy donor blood. Avelumab, a WT IgG1 with full FcgR binding capability, its FcgR binding-deficient variant (N297A amino acid substitution), and a PD-L1 binding-deficient R99K variant were compared. Internalization of avelumab/variants was also compared with another anti–PD-L1 antibody with the same Fab domain as atezolizumab (containing N297A replacement) and its WT IgG1 variant. The two WT IgG1 antibodies showed clearly different internalization ratios, indicating that the PD-L1 binding epitope may influence either their internalization or fate after internalization. However, N297A variants of both antibodies showed strong reduction in internalization, indicating the main receptor mediating the internalization is FcgR. Similar results were observed using whole blood from cynomolgus monkeys. Conducting the internalization experiment in the presence of competing soluble FcgRs, showed soluble CD64 significantly reduced internalization of avelumab. Serum concentration profiles after IV dosing in cynomolgus monkeys showed the R99K variant had the longest half-life, followed closely by the N297A variant. In comparison, avelumab showed the shortest half-life in vivo.

Conclusions These findings indicate that the major mechanism of avelumab internalization by circulating immune cells in human blood is through FcgR binding, in synergy with PD-L1 binding, and suggest that these mechanisms have a major impact on antibody PK properties. These results will support optimization of future therapeutic antibody development.

Ethics Approval This study was approved by the Vanderbilt Institutional Review Board.

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CHECKPOINT BLOCKADE THERAPY FOR BRAIN-METASTATIC NON-SMALL CELL LUNG CANCER: A COMPARATIVE EFFECTIVENESS ANALYSIS OF NATIONAL DATA

1Nayan Lamba, 3Bryan Iorgulescu*, 1Harvard Medical School, Boston, MA, USA; 2Dana-Farber Cancer Institute, Boston, MA, USA

Background Management of advanced non-small cell lung carcinoma (NSCLC) has been transformed by PD-1/PD-L1 immune checkpoint inhibitors (ICI), with FDA approvals in 2015 (second-line) and 2016 (first-line). Despite ~40% of NSCLC patients developing brain metastases, these patients were disproportionately excluded from the pioneering ICI trials. Thus herein we evaluate the overall survival (OS) associated with ICI in NSCLC brain metastases nationally.

Methods Patients newly-diagnosed with stage 4 NSCLC, including brain metastases, from 2010–2016 were identified from the National Cancer Database (comprising >70% of all newly-diagnosed cancers in the U.S.) Landmark survival analysis was used to address immortal time bias. Post-approval, median time from diagnosis to ICI was 58 days, and this timepoint was selected for all landmark survival analyses (OS estimated by Kaplan-Meier technique, and compared by log-rank test and multivariable Cox regression) and for multivariable logistic regression to identify predictors of ICI utilization.

Results 50,858 patients presented with advanced NSCLC that involved the brain: representing 27.6% of all newly-diagnosed stage 4 cases. Following initial FDA approvals in 2015, ICI use in brain metastasis patients rose from 7.2% in 2015 to 12.7% in 2016. OS for NSCLC brain metastasis patients