(28.2%). Of these, 167 patients (43.2%) developed chronic irAEs; 82 (49.1%) were symptomatic, 55 (32.9%) required glucocorticoids, and most were grade 1–2 (96.4%). Endocrinopathies (73/88, 83.0%) arthritis (22/45, 48.9%), xerostomia (9/17, 52.9%), neurotoxicities (8/8, 100.0%), and ocular events (5/8, 63.0%) were likely to become chronic events. In contrast, colitis (6/44, 13.6%), hepatitis (4/25, 16.0%), pneumonitis (6/18, 33.3%) were less likely to become chronic. Overall, the most common chronic irAEs were hypothyroidism (14.0%), dermatitis/pruritis (6.6%) arthralgias (5.7%), adrenal insufficiency (3.1%), and xerostomia (2.3%). Age (p=0.67), gender (p=0.31), time of onset of acute irAEs (p=0.95), and initial need for glucocorticoids (p=0.15) were not associated with chronicity. Only 24 (14.4%) of chronic irAEs ultimately resolved during the median 529-day follow-up. In particular, endocrinopathies (100%) arthralgias (100%) ocular events (100%), xerostomia (88.9%), and cutaneous events (89.5%) had high rates of persistence at last follow-up.

Conclusions Chronic irAEs to anti-PD-1 were more common than previously recognized and frequently persisted even with prolonged follow-up, although most were low-grade. The risks of chronic toxic effects should be integrated into treatment decision making.

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

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

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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 an amino acid sequence identical to atezolizumab (IgG1 with N297A substitution) and its WT IgG1 Fc-restored variant. In vivo PK studies in cynomolgus monkeys were performed after a single intravenous (IV) bolus injection of 5 mg/kg. Serum concentrations were measured by immunoassay.

Results Compared with avelumab, the FcgR binding-deficient N297A variant showed significantly reduced internalization. PD-L1 binding–deficient R99K variant showed a reduced internalization ratio as well, although to a lesser extent, particularly in granulocytes. These data indicate that both FcgR and PD-L1 binding contribute to avelumab internalization, with FcgR binding playing the major role. To test this hypothesis, we compared the internalization of avelumab and its N297A variant with an internally generated antibody that has 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 The study was conducted according to the principles of the Declaration of Helsinki. All volunteers provided written informed consent. Protocol approval was obtained from independent review boards or ethics committees at each site.

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

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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