stroke, sepsis, medications, seizures), 4 for primary central nervous system malignancy, and 6 for CD related to new or worsening brain metastases. Six had CD possibly related to IO (table 1). Most had also received chemotherapy either concurrently or prior to starting IO, but two patients had only ever received IO cancer therapy. Four of the six had documented MMSE or neuropsychological testing. On careful chart review, no alternative diagnosis was identified as clearly causal for the change in cognition.

Abstract 192 Table 1 Patient Characteristics

PATIENT AGE/SEX	CANCER TYPE	IO/ #INFUSIONS	PRIOR CHEMO	CLINICAL COURSE
54 M	Nasopharyngeal	Pembrolizumab, 47	5-FU, cisplatin	After 43 cycles of IO, patient reported progressive short-term memory loss, inattention, slowed information processing, speech, language, and executive function changes worsening over 6 months. Confirmed by formal neuropsychological testing
69 F	Non-small cell lung	Nivolumab, 15 Pembrolizumab, 18	carboplatin/pemetrexed EC1456 gemcitabine/vinorelbine	After 14 cycles pembrolizumab (and 1 year after 15 cycles nivolumab) patient reported memory loss and word finding difficulties worsening over 6 months. Confirmed with formal neuropsychological testing
77 M	Non-small cell lung	Pembrolizumab, 11	Carboplatin/paclitaxel	Patient with dementia had worsening dementia after 6 cycles IO, confirmed on MMSE (15 to 10 to 8)
85 M	Melanoma	Nivolumab, 9	-	Patient with dementia had worsening dementia after 9 cycles IO, confirmed on MMSE (13 to 11)
67 F	Non-small cell lung	Pembrolizumab, 2	-	Patient had an episode of encephalopathy without identified cause and skin rash following second dose of IO, which was then discontinued
75 M	Non-small cell lung	Nivolumab, 9	Carboplatin/gemcitabine Docetaxel	After 9 cycles of IO (with docetaxel 1st 6 cycles), patient reported memory loss first attributed to metabolic causes. This was again noticed in throughout 2017 with unclear cause, patient refused formal testing

Conclusions Patients receiving IO cancer therapy do report CD, which has not been broadly described. Though our data is corollary, it opens the question as to whether prospective pre- and post-treatment cognitive monitoring may identify more patients with neurocognitive symptoms related to immunotherapy. Future research is needed to report incidence of potential IO-related CD and to develop preventative or therapeutic strategies.

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193 DIFFERENCES IN THYROID IMMUNE-RELATED ADVERSE EVENTS BETWEEN LUNG CANCER TYPES, A RETROSPECTIVE ANALYSIS

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Background Immune modulation of the PD-1/PD-L1 pathway is a promising treatment of various malignancies however, alteration of the pathway is known to cause many immune related adverse events (irAEs) including thyroid dysfunction. Whether the frequency of thyroid irAEs differ between lung cancer types has not yet been studied.

Methods A total of three hundred twenty-nine lung cancer patients treated with immunotherapy at East Carolina University between April 2014 and July 2019 were included in a retrospective cohort analysis. Baseline TSH and TSH at each treatment cycle were recorded along with the type of lung cancer, specific agent used, timing of thyroid dysfunction and need for levothyroxine replacement. The frequency of thyroid irAEs as defined by TSH < 0.4 or > 4.0 and its relationship with lung cancer types were analyzed using chi square tests and logistic regression.

Results Of the three hundred twenty-nine patients; 54.4% had adenocarcinoma, 31.6% had squamous cell carcinoma, 11.3% had small cell carcinoma and 2.7% had poorly differentiated lung cancer. Overall, 135 patients (41.0%) developed thyroid irAEs (table 1). Pearson's chi square test was used to compare the frequencies of thyroid irAEs for each type of lung cancer against all other lung cancer types. Patients with squamous cell carcinoma developed significantly less thyroid irAEs (32.7%), compared to all other lung cancers (44.9%), X2 (1, N = 329) = 4.4, p = 0.037. Conversely, patients with lung cancer types other than squamous cell carcinoma were more likely to develop thyroid irAEs, OR = 1.68 (95% CI: 1.03 – 2.73).

Abstract 193 Table 1 Frequency of lung cancer type and thyroid dysfunction within each group

Type of Cancer (N=329)	Patients With Each Cancer Type	Patients With Thyroid Dysfunction Within Each Cancer Type (N=135)
Adenocarcinoma	179(54.4%)	81(42.3%)
Squamous Cell Carcinoma	104(31.6%)	34(32.7%)
Small Cell Carcinoma	37(11.3%)	17(46.0%)
Poorly Differentiated	9(2.7%)	3(33.3%)

Conclusions Thyroid irAEs occurred significantly less frequently in patients with squamous cell carcinoma than those with other lung cancer types. This analysis may allow clinicians to better identify patients more likely to develop irAE thyroid dysfunction based on lung cancer type.

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194 A MULTICENTER CHARACTERIZATION OF CHRONIC TOXICITIES FOLLOWING ADJUVANT ANTI-PD-1 THERAPY FOR HIGH RISK RESECTED MELANOMA

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Background Anti-programmed death-1 (anti-PD-1) therapies have improved long-term survival across many advanced cancers. However, chronic immune-related adverse events (irAEs) are not well-defined. We sought to determine the incidence, time-course, spectrum, and predictors of chronic irAEs arising from adjuvant anti-PD-1.

Methods In this retrospective cohort, we analyzed patients from 8 academic medical centers with stage III-IV melanoma treated with anti-PD-1 in the adjuvant setting. Acute and chronic (persisting at least 3 months after therapy cessation) irAEs were characterized by type, time-course, management, and incidence.

Results Among 387 patients, most were male (60.7%) with a median age of 63 years, had cutaneous primaries (85.8%), BRAF/NRAS WT (51.2%), and resected stage IIIb (33.1%) or IIIc (39.5%) melanomas. Median overall survival and relapse-free survival (RFS) were not reached. 359 patients (93.0%) were alive at median follow-up of 529 days. Patients with acute ($p<0.009$) or chronic ($p<0.001$) irAEs had superior RFS compared with patients lacking irAEs. Treatment was discontinued for therapy completion (50.0%), irAEs (25.3%), and disease progression (20.9%). 267 patients (69.0%) had any acute irAE, including 19.5% (n=52) with grade 3–5 events. Acute irAEs were most commonly dermatitis/pruritis (25.8%), thyroiditis/hypothyroid (16.3%), arthralgias (10.6%), colitis/diarrhea (9.8%) and required glucocorticoids in 109 patients

(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