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Associations between immune checkpoint inhibitor response, immune-related adverse events, and steroid use in RADIOHEAD: a prospective pan-tumor cohort study

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ABSTRACT

Background Immune checkpoint inhibitors (ICIs) have led to enduring responses in subsets of patients with cancer. However, these responses carry the risk of immune-related adverse events (irAEs), which can diminish the overall benefit of ICI treatment. While associations between irAE development and overall survival have been increasingly documented, there is a need for further understanding of these connections in large prospective real-world cohorts.

Methods The Resistance Drivers for Immuno-Oncology Patients Interrogated by Harmonized Molecular Datasets (RADIOHEAD) study, a pan-tumor, prospective cohort of 1,070 individuals undergoing standard of care first-line ICI treatment, aims to identify factors driving irAEs and clinical response. Clinical data and longitudinal blood samples were collected prospectively at multiple time points from 49 community-based oncology clinics across the USA. Structured, harmonized clinical data underwent unbiased statistical analysis to uncover predictors of real-world overall survival (rwOS) and risk factors for irAEs.

Results Across 1,070 participants' treatment courses, RADIOHEAD accumulated over 4,500 clinical data points. Patients experiencing any irAE (25.4%, n=272) exhibited significantly improved rwOS in the pan-tumor cohort (n=1,028, HR=0.41, 95% CI=(0.31, 0.55)). This association persisted when adjusting for age and metastatic disease in multivariate time-dependent Cox proportional hazard analysis, and was consistent across major tumor subtypes, including lung cancer and melanoma. Skin and endocrine irAEs of any grade were strongly associated with improved rwOS (Cox proportional hazard analysis, skin, p=2.03e−05; endocrine, p=0.0006). In this real-world cohort, the irAE rate appeared lower than those reported in clinical trials. Patients receiving corticosteroids prior to initiation of ICI treatment had significantly worse survival outcomes than non-users (HR 1.37, p=0.0054), with a stronger association with systemic steroid use (HR 1.75, p=0.0022). The risk of irAE was increased by exposure to combination immunotherapy relative to monotherapy (OR 4.17, p=2.8e−7), zoster vaccine (OR 2.4, p=5.2e−05), and decreased by prior chemotherapy (OR 1.69, p=0.0005).

Conclusion The RADIOHEAD cohort is a well-powered, real-world cohort that clearly demonstrates the association between irAE development with improved response and baseline steroid use with worse response to ICI treatment after adjustment for survival bias.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies of immune-related adverse events (irAEs) and survival following immune checkpoint inhibitors (ICIs), have largely been based in clinical trials or of a retrospective nature. These studies suggest a link between irAEs and improved survival with ICIs, but real-world, large-scale data on this association is limited.

WHAT THIS STUDY ADDS

⇒ This study, using data from the Resistance Drivers for Immuno-Oncology Patients Interrogated by Harmonized Molecular Datasets (RADIOHEAD) cohort, confirms the link between irAEs and better survival outcomes, shows worse responses to ICIs in patients on baseline steroids, and reports a novel association between the zoster vaccine and irAEs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study establishes the RADIOHEAD cohort as a key resource for understanding irAEs and response to ICI therapy, guiding future research and precision medicine strategies, and potentially influencing clinical practices for managing irAEs.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by inducing

durable responses in select cancer patient populations. However, this therapeutic advancement is accompanied by the risk of immune-related adverse events (irAEs), which have the potential to cause significant morbidity and mortality, offsetting the overall benefit of ICI therapy.[1–3]

While associations between the frequency of irAEs and immunotherapy treatment response have been observed in clinical trial settings and retrospective studies, conflicting evidence exists with initial associations varying by irAE type.[4–6] Many studies later found that this link weakened when accounting for survival bias, as patients needed to survive and continue treatment long enough to develop an irAE.[7] Our understanding of ICI efficacy, irAE incidence and their relationship with therapeutic response in real-world, standard of care settings remains limited. Additionally, ICI treatment in standard of care cohorts, characterized by broad inclusion criteria and minimal exclusion criteria, has been increasingly met with a disconnect between clinical use and benefit.[8 9] This highlights the need for prospective studies in the real-world setting to bridge the gap between research findings and clinical practice.

To address these knowledge gaps and to elucidate the clinical and molecular drivers of ICI-induced irAEs and treatment response, a real-world cohort of patients with cancer receiving first-line ICI therapy as standard of care was established, paired with prospective, longitudinal sample collection. Named Resistance Drivers for Immuno-Oncology Patients Interrogated by Harmonized Molecular Datasets (RADIOHEAD), this pan-tumor cohort comprises 1,070 individuals undergoing standard of care first-line ICI treatment.

In this report, we present the demographics and clinical characteristics of the RADIOHEAD cohort. Through comprehensive statistical analyses, we identify associations between clinical risk factors and real-world overall survival (rwOS) and irAEs. Results from this study will provide insights into the clinical outcomes of ICI therapy in real-world settings, ultimately informing future treatment strategies and improving cancer patient care.

METHODS

Patient identification

Following informed consent, subjects were enrolled from 49 community oncology clinics (online supplemental table 1) across the USA from May 2018 to May 2022. Patients with solid cancers and who were naïve to ICIs were eligible to participate. A cohort of over 1,000 subjects receiving standard of care therapy was deemed adequate to capture rare irAEs.

Data and sample collection

To capture a comprehensive profile of each patient, we prospectively collected blood samples at pretreatment, prior to cycle 3 (3–6 weeks after treatment initiation), and 6-month and 12-month time points together with clinical features recorded via case report forms and electronic medical records. If patients experienced irAEs, additional sample and clinical data collections were made if possible at the time of irAE, and then at 4–6 weeks, 6 months, and 12 months after irAE onset. Clinical data collected included basic demographic information, past medical history, medication use, vaccinations and prior cancer therapy alongside longitudinal data specific to their cancer treatment, such as cancer stage, presence of metastases, and treatment changes. Tissue-specific irAEs, such as rash, hypothyroidism, and colitis, were noted with details including treatment and grade at multiple study time points. Data were collected by research coordinators at each site and entered into a study-wide REDCap (Research Electronic Data Capture)[10] database.

Clinical data quality control and harmonization

Clinical data and annotations were systematically reviewed to identify probable erroneous data points, for example, infeasible dates and inconsistent responses in intentionally redundant fields. Flagged data points were subsequently reviewed and reconciled with sites. Data was de-identified and transacted into an in-house integrated datomic database, part of a suite of tools called the Cancer Data and Evidence Library (CANDEL) which enable storage, harmonization, and query of clinical and molecular data.[11] Data was mapped to standard ontologies or CANDEL-specific entities, and study time points were transformed to be relative to study or therapy start. Pre-existing conditions and irAEs, which were recorded as a combination of free and structured responses, were mapped to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms using a combination of manual lookups and Biomedical Ontology's BioPortal REST API. We employed a multistage quality control procedure for patient inclusion, first excluding individuals who did not have sufficient evidence of being on an immunotherapy treatment regimen or who were not immunotherapy-naive prior to study, and second those who were on study for less than 30 days.

For statistical analyses of survival, data was truncated at 15 months to reduce potential non-systematic bias from individuals involved in an extension study where select subjects, particularly those with irAEs, were followed for longer periods of time. Calculation of rwOS was performed by using reported ICI treatment start date and either the date of death or the last date of contact with the patient. For survival analyses, patients who exited the study on hospice were grouped with patients who had died on study. Patients included in survival analyses were required to be on a regimen that included programmed death (ligand) 1 (PD-(L)1) and have a reported rwOS of at least 30 days. It was possible for patients to have had previous anticancer treatments that were not ICIs prior to study enrollment.

For statistical analyses of irAEs, MedDRA[12] preferred terms were grouped into MedDRA System Organ Classes which were reviewed by a clinician and recategorized

where necessary so that each term contributed to a unique class (online supplemental table 2). Corticosteroids were designated as systemic, non-systemic, or unclear according to their route of administration. Oral medications were assigned to the systemic category, while inhaled and topical corticosteroids comprised the non-systemic category. Medications that can span multiple routes of administration were categorized as unclear if clarification was not included in the patient's original medication record. Clarifying terms include qualifiers such as "Spray", "Inhaler", "Powder", and "Ointment".

Statistical analysis

Demographics of the cohort including age, sex, treatment type, cancer type and stage, were described using count and percent. Prior to statistical analysis, we confirmed that study center was not significantly associated with irAE status or survival through χ^2 tests. As appropriate, comparisons between irAE groups used χ^2 tests unless cell sizes were ever less than 5 (in which case Fisher's exact tests were used) for testing associations between categorical variables. Student's t-test was used for testing associations between categorical and continuous variables. Alpha levels were set to 0.05.

We also ran exploratory multi-phenotype association studies to identify relationships between clinical variables, survival, and irAE features. To classify irAE features, we considered multiple levels of binning including (1) any irAE, (2) irAE grade (all vs severe (grade 3 or 4)), (3) irAEs in a broad organ class, such as endocrine and skin, and (4) specific irAE, such as hypothyroidism and rash. The R survival package (V.3.6–4, Therneau 2024) was used to perform univariate Cox regression using rwOS as the outcome and clinical variables, including irAE status, as predictors. To account for survival bias (that perhaps the association between irAEs and rwOS is caused by patients living long enough to develop an irAE), these same associations were also tested using a time-dependent Cox proportional hazard analysis. Time-dependent Cox analysis allows variables to change over time and is able to address survival bias. Associations between irAE outcomes and clinical variables were assessed using logistic regression models. A minimum of five or more patients was required per category for each clinical variable. Analyses were performed in the pan-tumor cohort as well as the two largest tumor-specific subcohorts: lung cancer and melanoma. Ad hoc analyses were performed to ensure trends were maintained when adjusting for age.

RESULTS

Patient demographics

The final RADIOHEAD cohort consists of 1,070 ICI-naive patients with cancer treated in a standard of care community hospital setting (table 1). Initially, 1,254 subjects were consented, 1,212 had at least one sample collected, and 1,070 were included in the final analysis following exclusions for registration errors (such as enrollment when they had been on prior ICIs), less than 30 days of clinical follow-up (such as death prior to ICI initiation), missing critical treatment or cancer data. The median age was 69 (IQR 62–77) with full range from 25 to 89 years old and 56.3% of patients were male. Consistent with standard of care treatment regimens, PD-(L)1 inhibitors (nivolumab, pembrolizumab, cemiplimab, atezolizumab, durvalumab, and avelumab) were the most used form of ICI, comprising 91.6% of the cohort (with 67.0% receiving ICI alone, 22.4% receiving ICI and chemotherapy, and 2.1% administered ICI alongside other anticancer agents). The remaining 8.4% were patients administered PD-(L)1 and CTLA-4 inhibitor (ipilimumab) in combination. Within this pan-cancer cohort, non-small cell lung cancer (NSCLC) was the most common form of cancer (37.2%), followed by melanoma (12.0%), renal cell cancer (8.8%) and urothelial cancer (8.3%). Most patients were being treated for either stage III (24.0%) or stage IV (68.7%) cancer. Patients were predominantly white (90.7%) and non-Hispanic (90.6%) and were collected broadly across the USA but with more representation from the Northeast (47.3%) and Midwest (36.0%) than the South (14.2%) or West (2.5%).[13]

ICI efficacy

Consistent with previous reports in clinical trial data,[14] ICI-treated patients with melanoma displayed significantly improved survival compared to patients with NSCLC or individuals with other cancer types (online supplemental figure 1). At 15 months of follow-up, 61% of patients were alive, 33% were dead, 2% were enrolled in hospice, and 3.9% were lost to follow-up. Therefore, survival analyses were limited to the 1,028 subjects that were known to be alive, dead or entered in hospice.

ICI toxicity

We next examined the real-world occurrence of irAEs (table 2). Skin and subcutaneous tissue disorders were the predominant irAE (26.5%, n=111), followed by endocrine disorders (22.9%, n=96), gastrointestinal disorders (16.0%, n=67), and respiratory, thoracic and mediastinal disorders (11.0%, n=46) (figure 1A). The most common organ-specific irAEs were rash (8.9%, n=95), thyroid dysfunction (6.2%, n=66) and diarrhea/colitis (4.8%, n=51). Diarrhea/colitis, hepatitis, and pneumonitis had the highest incidence of severe (grade III–IV) irAEs (figure 1B). Most patients experiencing irAEs reported only one (17.9% of overall cohort, n=191), fewer had two irAEs (5.4%, n=58) and 2% (n=23) of patients had three or more irAEs. Most of the patients who developed irAEs did so in the first 3 months (n=176 of 272 total patients with irAEs) (online supplemental figure 2).

Relationship between irAEs and rwOS

Given previous reports that suggest an association between improved survival outcomes and irAE incidence, we sought to identify whether rwOS varied by irAE development. Improved rwOS was observed in patients who

Table 1 Characteristics of patients included in the RADIOHEAD cohort

Pretreatment characteristic	Full cohort, No. (%)	Any irAE incidence (Grade I–IV), No. (%)	Severe irAE incidence (Grade III–IV), No. (%)
All subjects, No. (%)	1070	272 (25.4)	65 (6.1)
Age, years, median (IQR)	69 (62–77)	68 (61–76)	67 (62–77)
Sex, No. (%)			
Female	468 (43.7)	119 (25.4)	27 (5.8)
Male	602 (56.3)	153 (25.4)	38 (6.3)
ICI treatment groups, No. (%)			
Anti-PD-(L)1 antibody	980 (91.6)	223 (22.8)	49 (5)
Anti-PD-(L)1 and anti-CTLA-4 combination	90 (8.4)	49 (54.4)	16 (17.8)
ICI combinations, No. (%)			
Anti-PD-(L)1 monotherapy	717 (67)	173 (24.1)	37 (5.2)
Anti-PD-(L)1 combined with chemotherapy	240 (22.4)	41 (17.1)	10 (4.2)
Anti-PD-(L)1 other combination*	23 (2.1)	9 (39.1)	2 (8.7)
Anti-PD-(L)1 and anti-CTLA-4 combination	87 (8.1)	49 (56.3)	16 (18.4)
Anti-PD-(L)1 and anti-CTLA-4 with chemotherapy	3 (0.3)	0 (0)	0 (0)
Cancer type, No. (%)			
Non-small cell lung cancer (NSCLC)	398 (37.2)	94 (23.6)	23 (5.8)
Melanoma	128 (12)	56 (43.8)	15 (11.7)
Renal cell carcinoma (RCC)	94 (8.8)	31 (33)	8 (8.5)
Urothelial carcinoma (UC)	89 (8.3)	19 (21.3)	3 (3.4)
Small cell lung cancer	68 (6.4)	12 (17.6)	3 (4.4)
Head and neck squamous cell cancer (HNSCC)	58 (5.4)	10 (17.2)	2 (3.4)
Gastroesophageal cancer	36 (3.4)	5 (13.9)	1 (2.8)
Hepatocellular carcinoma	36 (3.4)	6 (16.7)	1 (2.8)
Breast cancer	26 (2.4)	7 (26.9)	3 (11.5)
Colorectal cancer	24 (2.2)	2 (8.3)	0 (0)
Endometrial cancer	23 (2.1)	4 (17.4)	0 (0)
Prostate cancer	17 (1.6)	5 (29.4)	2 (11.8)
Non-melanoma skin cancer	10 (0.9)	4 (40)	0 (0)
Lymphoma	9 (0.8)	3 (33.3)	0 (0)
Merkel cell carcinoma (MCC)	7 (0.7)	2 (28.6)	2 (28.6)
Cervical cancer	6 (0.6)	1 (16.7)	0 (0)
Other	41 (3.8)	11 (26.8)	2 (4.9)
Cancer stage, No. (%)			
0	6 (0.6)	1 (16.7)	1 (16.7)
I	28 (2.6)	5 (17.9)	0 (0)
II	40 (3.7)	13 (32.5)	5 (12.5)
III	257 (24)	81 (31.5)	18 (7)
IV	735 (68.7)	170 (23.1)	40 (5.4)
Unknown	4 (0.4)	2 (50)	1 (25)
Clinical site region, No. (%)			
Midwest	385 (36)	108 (28.1)	32 (8.3)
Northeast	506 (47.3)	113 (22.3)	24 (4.7)
South	152 (14.2)	40 (26.3)	7 (4.6)
West	27 (2.5)	11 (40.7)	2 (7.4)

Continued

Table 1 Continued

Pretreatment characteristic	Full cohort, No. (%)	Any irAE incidence (Grade I–IV), No. (%)	Severe irAE incidence (Grade III–IV), No. (%)
Race (NIH categories), No. (%)			
White	970 (90.7)	257 (26.5)	61 (6.3)
Black	57 (5.3)	6 (10.5)	2 (3.5)
Asian	23 (2.1)	5 (21.7)	0 (0)
American Indian/Alaskan Native	3 (0.3)	1 (33.3)	0 (0)
Hawaiian/Pacific Islander	3 (0.3)	0 (0)	0 (0)
Other	14 (1.3)	3 (21.4)	2 (14.3)
Ethnicity, No. (%)			
Hispanic	54 (5)	13 (24.1)	2 (3.7)
Non-Hispanic	969 (90.6)	241 (24.9)	58 (6)
Unknown	47 (4.4)	18 (38.3)	5 (10.6)
Corticosteroid use within 30 days, No. (%)			
Any corticosteroid			
Yes	308 (28.8)	68 (22.1)	19 (6.2)
No	762 (71.2)	204 (26.8)	46 (6)
If yes, route of administration			
Systemic	69 (6.4)	13 (18.8)	4 (5.8)
Non-systemic	134 (12.5)	29 (21.6)	9 (6.7)
Unclear	182 (17.0)	41 (22.5)	11 (6.0)
Vaccination history, No. (%)			
Pneumococcal vaccine, ever			
Yes	368 (34.4)	105 (28.5)	20 (5.4)
No	400 (37.4)	86 (21.5)	21 (5.3)
Unknown	302 (28.2)	81 (26.8)	24 (7.9)
Zoster vaccine, ever			
Yes	151 (14.1)	60 (39.7)	12 (7.9)
No	525 (49.1)	114 (21.7)	26 (5)
Unknown	394 (36.8)	98 (24.9)	27 (6.9)
Influenza vaccine within 1 year			
Yes	536 (50.1)	145 (27.1)	29 (5.4)
No	293 (27.4)	60 (20.5)	15 (5.1)
Unknown	241 (22.5)	67 (27.8)	21 (8.7)
Antibiotic use, No. (%)			
Any antibiotics within 30 days			
Yes	121 (11.3)	38 (31.4)	6 (5)
No	949 (88.7)	234 (24.7)	59 (6.2)
Any antibiotics within 1 year			
Yes	381 (35.6)	99 (26)	19 (5)
No	496 (46.4)	117 (23.6)	27 (5.4)
Unknown	193 (18)	56 (29)	19 (9.8)

*Other combination category includes TKIs, anti-VEGF, and other targeted treatments.
ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; NIH, National Institute for Health; PD-(L)1, programmed death (ligand) 1; RADIOHEAD, Resistance Drivers for Immuno-Oncology Patients Interrogated by Harmonized Molecular Datasets; TKIs, tyrosine kinase inhibitors.

Table 2 Observed irAEs in the RADIOHEAD cohort study

Pretreatment characteristic	N	irAE groups by disorder organ and disease type, No. (% of N)																
		GI	Renal and urinary	Endocrine	MSK and conn tissue	Blood and lymph system	Nervous system	Resp, thor, and mediastinal	Skin and subcut tissue	Cardiac	Eye	Metabolism and nutrition	Hepatobiliary	Immune system	Infusion related Rxn	Gen disorders and admin site	Infections and Infestations	Vascular
All subjects	1070	55 (5.1)	6 (0.6)	76 (7.1)	16 (1.5)	3 (0.3)	5 (0.5)	46 (4.3)	100 (9.3)	4 (0.4)	4 (0.4)	3 (0.3)	32 (3)	1 (0.1)	5 (0.5)	10 (0.9)	4 (0.4)	1 (0.1)
Subjects with 1+ irAE (Grade I–IV)	272	55 (20.2)	6 (2.2)	76 (27.9)	16 (5.9)	3 (1.1)	5 (1.8)	46 (16.9)	100 (36.8)	4 (1.5)	4 (1.5)	3 (1.1)	32 (11.8)	1 (0.4)	5 (1.8)	10 (3.7)	4 (1.5)	1 (0.4)
Non-severe irAE(s) only (Grade I–II)	207	34 (16.4)	4 (1.9)	60 (29)	11 (5.3)	3 (1.4)	3 (1.4)	35 (16.9)	86 (41.5)	2 (1)	2 (1)	3 (1.4)	14 (6.8)	1 (0.5)	5 (2.4)	4 (1.9)	2 (1)	1 (0.5)
Severe irAE(s) only (Grade III–IV)	65	21 (32.3)	2 (3.1)	16 (24.6)	5 (7.7)	0 (0)	2 (3.1)	11 (16.9)	14 (21.5)	2 (3.1)	2 (3.1)	NA (NA)	18 (27.7)	0 (0)	0 (0)	6 (9.2)	2 (3.1)	0 (0)
Sex																		
Female	468	30 (6.4)	3 (0.6)	36 (7.7)	2 (0.4)	1 (0.2)	2 (0.4)	16 (3.4)	41 (8.8)	0 (0)	1 (0.2)	1 (0.2)	17 (3.6)	0 (0)	3 (0.6)	2 (0.4)	4 (0.9)	1 (0.2)
Male	602	25 (4.2)	3 (0.5)	40 (6.6)	14 (2.3)	2 (0.3)	3 (0.5)	30 (5)	59 (9.8)	4 (0.7)	3 (0.5)	2 (0.3)	15 (2.5)	1 (0.2)	2 (0.3)	8 (1.3)	0 (0)	0 (0)
ICI treatment groups																		
Anti-PD-(L)1 antibody	980	43 (4.4)	5 (0.5)	60 (6.1)	16 (1.6)	3 (0.3)	3 (0.3)	42 (4.3)	81 (8.3)	3 (0.3)	3 (0.3)	3 (0.3)	20 (2)	1 (0.1)	5 (0.5)	8 (0.8)	4 (0.4)	1 (0.1)
Anti-PD-(L)1 and anti-CTLA-4 combo	90	12 (13.3)	1 (1.1)	16 (17.8)	0 (0)	0 (0)	2 (2.2)	4 (4.4)	19 (21.1)	1 (1.1)	1 (1.1)	0 (0)	12 (13.3)	0 (0)	0 (0)	2 (2.2)	0 (0)	0 (0)
ICI combinations																		
Anti-PD-(L)1 monotherapy	717	33 (4.6)	4 (0.6)	45 (6.3)	14 (2)	2 (0.3)	3 (0.4)	36 (5)	67 (9.3)	3 (0.4)	2 (0.3)	2 (0.3)	12 (1.7)	1 (0.1)	4 (0.6)	4 (0.6)	2 (0.3)	0 (0)
Anti-PD-(L)1 combined with chemo	240	6 (2.5)	1 (0.4)	11 (4.6)	2 (0.8)	1 (0.4)	0 (0)	5 (2.1)	13 (5.4)	0 (0)	1 (0.4)	1 (0.4)	6 (2.5)	0 (0)	0 (0)	3 (1.3)	2 (0.8)	1 (0.4)
Anti-PD-(L)1 other combination	23	4 (17.4)	0 (0)	4 (17.4)	0 (0)	0 (0)	0 (0)	1 (4.3)	1 (4.3)	0 (0)	0 (0)	0 (0)	2 (8.7)	0 (0)	1 (4.3)	1 (4.3)	0 (0)	0 (0)
Anti-PD-(L)1 and anti-CTLA-4 combo	87	12 (13.8)	1 (1.1)	16 (18.4)	0 (0)	0 (0)	2 (2.3)	4 (4.6)	19 (21.8)	1 (1.1)	1 (1.1)	0 (0)	12 (13.8)	0 (0)	0 (0)	2 (2.3)	0 (0)	0 (0)
Anti-PD-(L)1 and anti-CTLA-4 with chemo	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cancer type																		
Non-small cell lung cancer	398	17 (4.3)	3 (0.8)	22 (5.5)	6 (1.5)	1 (0.3)	0 (0)	26 (6.5)	32 (8)	2 (0.5)	1 (0.3)	1 (0.3)	5 (1.3)	1 (0.3)	0 (0)	3 (0.8)	1 (0.3)	1 (0.3)
Melanoma	128	14 (10.9)	1 (0.8)	19 (14.8)	3 (2.3)	1 (0.8)	2 (1.6)	4 (3.1)	24 (18.8)	0 (0)	1 (0.8)	1 (0.8)	12 (9.4)	0 (0)	0 (0)	1 (0.8)	1 (0.8)	0 (0)

Continued

Table 2 Continued

Pretreatment characteristic	N	irAE groups by disorder organ and disease type, No. (% of N)																
		GI	Renal and urinary	Endocrine	MSK and conn tissue	Blood and lymph system	Nervous system	Resp, thor, and mediastinal	Skin and subcut tissue	Cardiac	Eye	Metabolism and nutrition	Hepatobiliary	Immune system	Infusion related Rxn	Gen disorders and admin site	Infections and Infestations	Vascular
Renal cell carcinoma	94	5 (5.3)	1 (1.1)	11 (11.7)	1 (1.1)	0 (0)	1 (1.1)	1 (1.1)	13 (13.8)	1 (1.1)	0 (0)	0 (0)	5 (5.3)	0 (0)	2 (2.1)	1 (1.1)	0 (0)	0 (0)
Urothelial carcinoma	89	2 (2.2)	0 (0)	6 (6.7)	2 (2.2)	0 (0)	1 (1.1)	2 (2.2)	11 (12.4)	0 (0)	1 (1.1)	0 (0)	2 (2.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Small cell lung cancer	68	5 (7.4)	0 (0)	4 (5.9)	0 (0)	1 (1.5)	0 (0)	2 (2.9)	4 (5.9)	0 (0)	1 (1.5)	1 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Head and neck squamous cell cancer	58	1 (1.7)	1 (1.7)	5 (8.6)	0 (0)	0 (0)	0 (0)	1 (1.7)	5 (8.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastroesophageal cancer	36	0 (0)	0 (0)	0 (0)	2 (5.6)	0 (0)	0 (0)	0 (0)	2 (5.6)	0 (0)	0 (0)	0 (0)	1 (2.8)	0 (0)	0 (0)	1 (2.8)	0 (0)	0 (0)
Hepatocellular carcinoma	36	0 (0)	0 (0)	0 (0)	2 (5.6)	0 (0)	0 (0)	1 (2.8)	2 (5.6)	1 (2.8)	0 (0)	0 (0)	1 (2.8)	0 (0)	1 (2.8)	0 (0)	0 (0)	0 (0)
Breast cancer	26	1 (3.8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.8)	1 (3.8)	1 (3.8)	0 (0)	0 (0)	0 (0)	3 (11.5)	0 (0)	0 (0)	1 (3.8)	2 (7.7)	0 (0)
Colorectal cancer	24	1 (4.2)	0 (0)	1 (4.2)	0 (0)	0 (0)	0 (0)	1 (4.2)	1 (4.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Endometrial cancer	23	3 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (8.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Prostate cancer	17	1 (5.9)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (5.9)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (5.9)	0 (0)	0 (0)	2 (11.8)	0 (0)	0 (0)
Non-melanoma skin cancer	10	1 (10)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	2 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
Lymphoma	9	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11.1)	1 (11.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11.1)	0 (0)	0 (0)
Merkel cell carcinoma	7	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cervical cancer	6	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	41	3 (7.3)	0 (0)	5 (12.2)	0 (0)	0 (0)	0 (0)	0 (0)	3 (7.3)	0 (0)	0 (0)	0 (0)	2 (4.9)	0 (0)	1 (2.4)	0 (0)	0 (0)	0 (0)
Cancer stage																		
0	6	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
I	28	1 (3.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.6)	1 (3.6)	0 (0)	0 (0)	0 (0)	1 (3.6)	0 (0)	0 (0)	1 (3.6)	0 (0)	0 (0)
II	40	1 (2.5)	0 (0)	4 (10)	2 (5)	0 (0)	1 (2.5)	3 (7.5)	5 (12.5)	0 (0)	0 (0)	0 (0)	4 (10)	0 (0)	0 (0)	1 (2.5)	1 (2.5)	0 (0)
III	257	16 (6.2)	1 (0.4)	23 (8.9)	8 (3.1)	2 (0.8)	0 (0)	20 (7.8)	28 (10.9)	0 (0)	0 (0)	2 (0.8)	9 (3.5)	0 (0)	0 (0)	2 (0.8)	3 (1.2)	1 (0.4)
IV	735	36 (4.9)	5 (0.7)	48 (6.5)	6 (0.8)	1 (0.1)	4 (0.5)	21 (2.9)	64 (8.7)	4 (0.5)	4 (0.5)	1 (0.1)	18 (2.4)	1 (0.1)	5 (0.7)	6 (0.8)	0 (0)	0 (0)
Unknown	4	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Clinical site region																		
Midwest	385	21 (5.5)	3 (0.8)	34 (8.8)	7 (1.8)	3 (0.8)	1 (0.3)	17 (4.4)	35 (9.1)	0 (0)	2 (0.5)	2 (0.5)	17 (4.4)	0 (0)	0 (0)	8 (2.1)	2 (0.5)	0 (0)

Continued

Table 2 Continued

Pretreatment characteristic	N	irAE groups by disorder organ and disease type, No. (% of N)																
		GI	Renal and urinary	Endocrine	MSK and conn tissue	Blood and lymph system	Nervous system	Resp, thor, and mediastinal	Skin and subcut tissue	Cardiac	Eye	Metabolism and nutrition	Hepatobiliary	Immune system	Infusion related Rxn	Gen disorders and admin site	Infections and Infestations	Vascular
Northeast	506	24 (4.7)	1 (0.2)	28 (5.5)	4 (0.8)	0 (0)	3 (0.6)	18 (3.6)	39 (7.7)	2 (0.4)	2 (0.4)	0 (0)	11 (2.2)	1 (0.2)	5 (1)	2 (0.4)	0 (0)	0 (0)
South	152	6 (3.9)	2 (1.3)	12 (7.9)	4 (2.6)	0 (0)	0 (0)	8 (5.3)	21 (13.8)	2 (1.3)	0 (0)	1 (0.7)	3 (2)	0 (0)	0 (0)	0 (0)	1 (0.7)	1 (0.7)
West	27	4 (14.8)	0 (0)	2 (7.4)	1 (3.7)	0 (0)	1 (3.7)	3 (11.1)	5 (18.5)	0 (0)	0 (0)	0 (0)	1 (3.7)	0 (0)	0 (0)	0 (0)	1 (3.7)	0 (0)
Race (NIH categories)																		
White	970	54 (5.6)	5 (0.5)	74 (7.6)	16 (1.6)	2 (0.2)	5 (0.5)	44 (4.5)	95 (9.8)	4 (0.4)	3 (0.3)	2 (0.2)	31 (3.2)	1 (0.1)	3 (0.3)	10 (1)	4 (0.4)	1 (0.1)
Black	57	1 (1.8)	1 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)	2 (3.5)	0 (0)	1 (1.8)	0 (0)	1 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asian	23	0 (0)	0 (0)	2 (8.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (8.7)	0 (0)	0 (0)	0 (0)
American Indian/ Alaskan Native	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hawaiian/Pacific Islander	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	14	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.1)	0 (0)	1 (7.1)	1 (7.1)	0 (0)	0 (0)	1 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethnicity																		
Hispanic	54	1 (1.9)	1 (1.9)	4 (7.4)	0 (0)	0 (0)	0 (0)	2 (3.7)	8 (14.8)	1 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.9)	1 (1.9)
Non-Hispanic	969	52(5.4)	4 (0.4)	67 (6.9)	15 (1.5)	2 (0.2)	5 (0.5)	39 (4)	86 (8.9)	2 (0.2)	4 (0.4)	2 (0.2)	31 (3.2)	1 (0.1)	5 (0.5)	9 (0.9)	2 (0.2)	0 (0)
Unknown	47	2 (4.3)	1 (2.1)	5 (10.6)	1 (2.1)	1 (2.1)	0 (0)	5 (10.6)	6 (12.8)	1 (2.1)	0 (0)	1 (2.1)	1 (2.1)	0 (0)	0 (0)	1 (2.1)	1 (2.1)	0 (0)
Corticosteroid use within 30 days																		
Any corticosteroid																		
Yes	308	17 (5.5)	1 (0.3)	18 (5.8)	3 (1)	1 (0.3)	1 (0.3)	14 (4.5)	24 (7.8)	0 (0)	1 (0.3)	1 (0.3)	11 (3.6)	0 (0)	1 (0.3)	3 (1)	0 (0)	0 (0)
No	762	38 (5)	5 (0.7)	58 (7.6)	13 (1.7)	2 (0.3)	4 (0.5)	32 (4.2)	76 (10)	0 (0)	3 (0.4)	2 (0.3)	21 (2.8)	0 (0)	4 (0.5)	7 (0.9)	0 (0)	0 (0)
If yes, route of administration																		
Systemic or unclear	216	11 (5.1)	1 (0.5)	14 (6.5)	3 (1.4)	0 (0)	0 (0)	11 (5.1)	20 (9.3)	0 (0)	1 (0.5)	1 (0.5)	6 (2.8)	0 (0)	1 (0.5)	2 (0.9)	0 (0)	0 (0)
Non-systemic	134	9 (6.7)	0 (0)	7 (5.2)	0 (0)	1 (0.8)	1 (0.8)	5 (3.8)	10 (7.6)	0 (0)	1 (0.8)	1 (0.8)	5 (3.8)	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)
Vaccination history																		
Pneumococcal vaccine, ever																		
Yes	368	12 (3.3)	3 (0.8)	29 (7.9)	5 (1.4)	1 (0.3)	3 (0.8)	19 (5.2)	42 (11.4)	3 (0.8)	0 (0)	0 (0)	11 (3)	1 (0.3)	3 (0.8)	4 (1.1)	1 (0.3)	1 (0.3)
No	400	20 (5)	2 (0.5)	17 (4.3)	4 (1)	2 (0.5)	1 (0.3)	18 (4.5)	30 (7.5)	0 (0)	3 (0.8)	1 (0.3)	13 (3.3)	0 (0)	1 (0.3)	4 (1)	2 (0.5)	0 (0)
Unknown	302	23 (7.6)	1 (0.3)	30 (9.9)	7 (2.3)	0 (0)	1 (0.3)	9 (3)	28 (9.3)	1 (0.3)	1 (0.3)	2 (0.7)	8 (2.6)	0 (0)	1 (0.3)	2 (0.7)	1 (0.3)	0 (0)

Continued

Table 2 Continued

Pretreatment characteristic	N	irAE groups by disorder organ and disease type, No. (% of N)															
		GI	Renal and urinary	Endocrine	MSK and conn tissue	Blood and lymph system	Nervous system	Resp, thor, and mediastinal	Skin and subcut tissue	Cardiac	Eye	Metabolism and nutrition	Hepatobiliary	Immune system	Infusion related Rxn	Gen disorders and admin site	Infections and Infestations	Vascular
Zoster vaccine, ever																		
Yes	151	10 (6.6)	1 (0.7)	17 (11.3)	4 (2.6)	1 (0.7)	2 (1.3)	13 (8.6)	20 (13.2)	3 (2)	0 (0)	0 (0)	7 (4.6)	0 (0)	1 (0.7)	1 (0.7)	0 (0)	0 (0)
No	525	21 (4)	4 (0.8)	27 (5.1)	5 (1)	2 (0.4)	1 (0.2)	21 (4)	41 (7.8)	0 (0)	3 (0.6)	1 (0.2)	16 (3)	1 (0.2)	3 (0.6)	5 (1)	3 (0.6)	1 (0.2)
Unknown	394	24 (6.1)	1 (0.3)	32 (8.1)	7 (1.8)	0 (0)	2 (0.5)	12 (3)	39 (9.9)	1 (0.3)	1 (0.3)	2 (0.5)	9 (2.3)	0 (0)	1 (0.3)	4 (1)	1 (0.3)	0 (0)
Influenza vaccine within 1 year																		
Yes	536	25 (4.7)	5 (0.9)	36 (6.7)	8 (1.5)	1 (0.2)	3 (0.6)	23 (4.3)	60 (11.2)	3 (0.6)	1 (0.2)	0 (0)	17 (3.2)	1 (0.2)	3 (0.6)	7 (1.3)	3 (0.6)	0 (0)
No	293	11 (3.8)	0 (0)	14 (4.8)	2 (0.7)	2 (0.7)	1 (0.3)	14 (4.8)	19 (6.5)	0 (0)	2 (0.7)	1 (0.3)	6 (2)	0 (0)	1 (0.3)	2 (0.7)	0 (0)	1 (0.3)
Unknown	241	19 (7.9)	1 (0.4)	26 (10.8)	6 (2.5)	0 (0)	1 (0.4)	9 (3.7)	21 (8.7)	1 (0.4)	1 (0.4)	2 (0.8)	9 (3.7)	0 (0)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0)
Antibiotic use																		
Any antibiotics within 30 days																		
Yes	121	4 (3.3)	1 (0.8)	11 (9.1)	1 (0.8)	1 (0.8)	0 (0)	9 (7.4)	13 (10.7)	0 (0)	0 (0)	1 (0.8)	5 (4.1)	0 (0)	1 (0.8)	4 (3.3)	2 (1.7)	0 (0)
No	949	51 (5.4)	5 (0.5)	65 (6.8)	15 (1.6)	2 (0.2)	0 (0)	37 (3.9)	87 (9.2)	0 (0)	0 (0)	2 (0.2)	27 (2.8)	0 (0)	4 (0.4)	6 (0.6)	2 (0.2)	0 (0)
Any antibiotics within 1 year																		
Yes	381	16 (4.2)	2 (0.5)	29 (7.6)	8 (2.1)	1 (0.3)	1 (0.3)	22 (5.8)	32 (8.4)	0 (0)	2 (0.5)	0 (0)	9 (2.4)	0 (0)	2 (0.5)	7 (1.8)	2 (0.5)	0 (0)
No	496	26 (5.2)	3 (0.6)	31 (6.3)	2 (0.4)	1 (0.2)	3 (0.6)	14 (2.8)	50 (10.1)	3 (0.6)	1 (0.2)	1 (0.2)	14 (2.8)	0 (0)	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Unknown	193	13 (6.7)	1 (0.5)	16 (8.3)	6 (3.1)	1 (0.5)	1 (0.5)	10 (5.2)	18 (9.3)	1 (0.5)	1 (0.5)	2 (1)	9 (4.7)	1 (0.5)	1 (0.5)	2 (1)	1 (0.5)	0 (0)

admin, administration; conn, connective; GI, gastrointestinal; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; MSK, musculoskeletal; NIH, National Institute for Health; PD-(L)1, programmed death (ligand) 1; RADIOHEAD, Resistance Drivers for Immuno-Oncology Patients Interrogated by Harmonized Molecular Datasets; resp, respiratory; Rxn, reaction; subcut, subcutaneous; thor, thoracic.

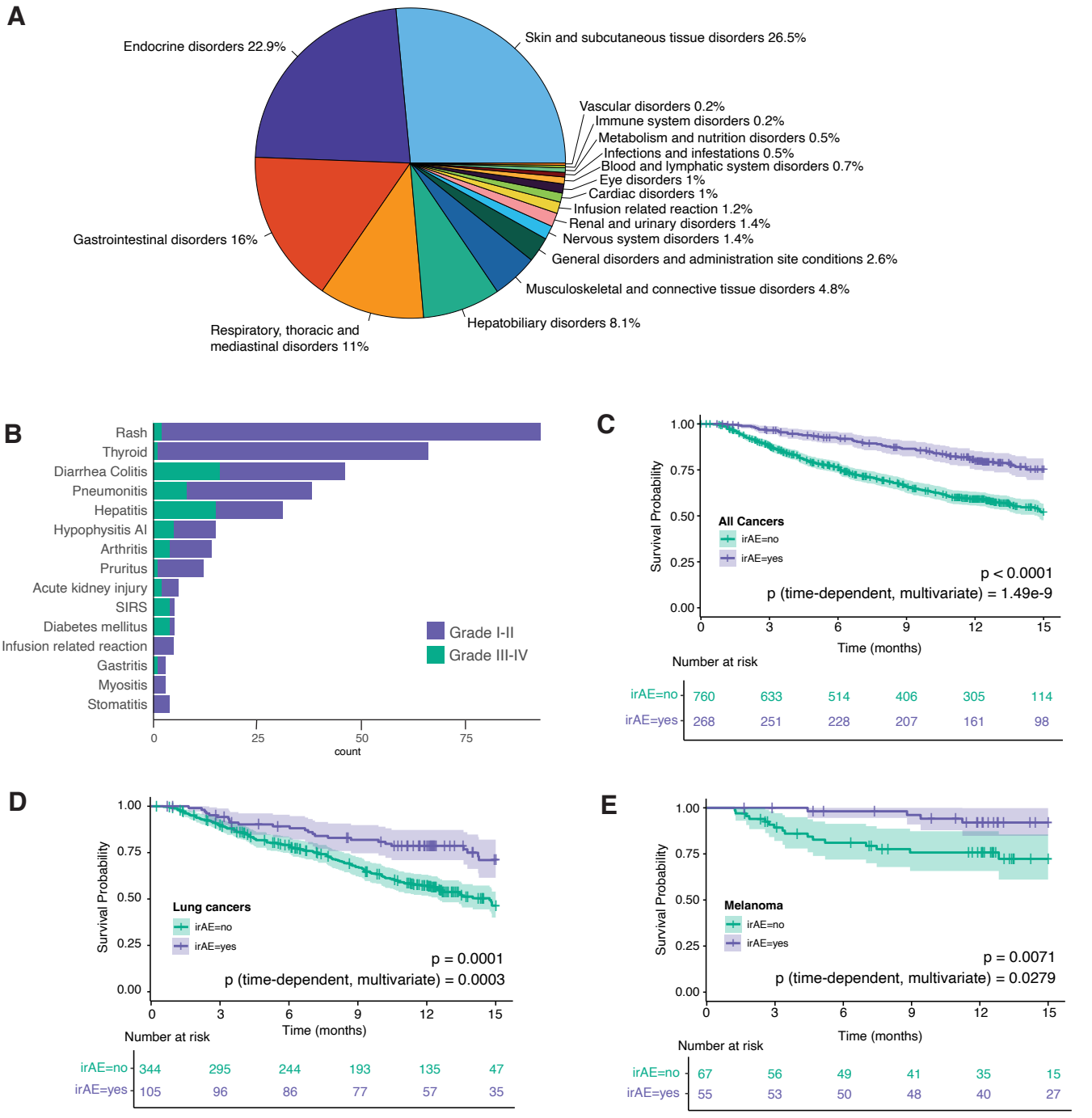

Figure 1 Immune-related adverse events and impact on survival outcome. (A) Distribution of observed irAEs; (B) Most frequently observed irAEs; (C) Kaplan-Meier survival analysis of all patients in the RADIOHEAD cohort with confirmed alive or dead (including hospice) status for any irAE incidence. Statistical significance for this association is shown for both a Cox proportional hazards model adjusted for age (p) and time-dependent Cox proportional hazard model adjusting for age and metastatic disease (p(time dependent)); (D) Kaplan-Meier survival analysis of patients with lung cancer (NSCLC and SCLC) with confirmed alive or dead (including hospice) status for any irAE incidence. Again, significance from both analytic approaches is shown; (E) Kaplan-Meier survival analysis of patients with melanoma with confirmed alive or dead (including hospice) status for any irAE incidence. Again, significance from both analytic approaches is shown. AI, adrenal insufficiency; IrAE; immune-related adverse event; NSCLC, non-small cell lung cancer; RADIOHEAD, Resistance Drivers for Immuno-Oncology Patients Interrogated by Harmonized Molecular Datasets; SCLC, small cell lung cancer; SIRS, systemic inflammatory response syndrome.

developed any irAE in the pan-cancer cohort (n=1,028, HR=0.41, 95% CI=(0.31, 0.55)) (figure 1C). The association between irAE and survival was maintained when adjusting for age, sex, and metastatic disease even in multivariate time-dependent Cox proportional hazard analysis (p=1.49e-9) that accounts for survival time bias. This was similarly observed in the tumor-specific subcohorts for lung cancers (n=449, HR 0.45, p=0.0001) and melanoma (n=122, HR 0.25, p=0.0071) (figure 1D,E).

Clinical characteristics associated with rwOS

To identify additional risk factors between clinical variables and rwOS, a univariate multiple phenotype association study was conducted, with adjustment for age (figure 2A). Development of any skin and subcutaneous tissue irAE (HR 0.24, p=2.41e-6) and endocrine irAE (HR 0.33, p=0.0001), driven by thyroid irAEs (HR 0.38, p=0.001), was associated with improved rwOS (figure 2B,C). The association between these organ-specific irAEs and survival was maintained in a multivariate time-dependent Cox proportional hazard analysis (skin, p=4.26e-6; endocrine, p=8.70e-5).

Patients who reported taking any form of corticosteroids at baseline (n=298/1028), prior to initiating ICI treatment, had significantly reduced survival than those who did not (HR 1.37, p=0.0054). This association was more pronounced in patients taking systemic steroids (n=68/1028, HR 1.75, p=0.0022), and was not observed in individuals receiving non-systemic corticosteroids only (n=87/1028, HR 1.16, p=0.44) (figure 2D). Of the 272 subjects who developed an irAE, 68 were on any baseline steroids and there was no association observed between steroid use and irAE risk (p=0.13). The association between baseline steroid use and rwOS persisted after adjustment for the development of any irAE (systemic corticosteroids HR 1.66, p=0.0056, any corticosteroids HR 1.32, p=0.014)

Clinical characteristics associated with risk of irAEs

Clinical variables were also assessed for potential association with the development of any or severe grade III–IV irAEs (figure 3). Using logistic regression, adjusting for age at time of ICI treatment, a decreased risk of any grade of irAE was observed in patients receiving PD-(L)1 inhibitors alone compared with CTLA-4/PD-(L)1 inhibitors in combination (OR 0.24, p=2.8e-7). Similarly, the risk of severe irAEs was also significantly decreased following exposure to PD-(L)1 inhibitor monotherapy compared with combination CTLA-4/PD-(L)1 inhibitors (OR 0.24, p=6.99e-4). This was consistent with outcomes from clinical trials that compare single-agent and combination treatment.[5]

Use of chemotherapy prior to or along with ICIs is indicated in only a subset of cancers. Within the RADIOHEAD cohort, lung cancer (NSCLC and SCLC) was the predominant cancer with prior treatment with chemotherapy (124 with prior chemotherapy, 238 without prior chemotherapy) and/or being treated with concurrent chemotherapy and ICI therapy (163 received conventional chemotherapy with anti-PD-(L)1, 258 anti-PD-(L)1 monotherapy and 41 combination anti-CTLA-4/PD-(L)1). Within patients with lung cancer, ICI with concurrent chemotherapy was associated with decreased risk of irAE (OR 0.49, unadjusted p value=0.005). Concurrent chemotherapy is indicated in advanced lung cancer, and once adjusted for stage, there was no association with overall survival (unadjusted p value=0.31). We also identified that prior treatment with chemotherapy across all cancer types reduced the risk of any irAE (OR 0.59, p=0.0005, pB=0.043[i]), with severe irAEs showing a consistent but non-significant trend (OR 0.49, p=0.17). Prior chemotherapy within the lung cancer-specific subcohort was not associated with irAE risk (p=0.86 for any irAEs, p=0.86 for severe irAEs). There was no definite association between prior chemotherapy and response. Within the overall cohort, after adjustment for stage, prior chemotherapy was associated with rwOS but did not pass multiple comparison correction (HR 1.26, unadjusted p 0.024, pB=1.0). Within the lung cancer cohort, after adjustment for stage, prior chemotherapy was not associated with rwOS (unadjusted p 0.91, pB=1.0).

Increased risk of any irAE was associated with previous exposure to the zoster vaccine (OR 2.4, p=5.2e-5, pB=0.0044). Despite this association with any irAEs, severe irAE was not associated with zoster vaccination. In those who received a zoster vaccination, 39.7% developed an irAE, compared with 21.7% developing an irAE if not vaccinated (table 1).

There was no association between the development of any or severe irAEs and sex, region in which clinical care was performed, vaccination against pneumococcus, or influenza within the last year, baseline corticosteroid use, antibiotic exposure within 30 days of ICI initiation, or other reported comorbidities.

DISCUSSION

To our knowledge, this is the first large-scale, prospective real-world study of standard of care, first-line ICI treatment with broad collection of clinical features paired with robust longitudinal blood sampling of patients with cancer. In this initial analysis, we aimed to identify the complex connectivity between reported patient demographics and therapeutic response in the RADIOHEAD cohort. As this cohort is drawn from community centers across the USA and the eligibility criteria were broader than for clinical trials, it is generalizable to most Americans. While this study is limited by variably sized groups for each cancer type, lower than expected irAE rates and some missing data around vaccination status, this work will be critical to future applications of the prospectively collected longitudinal samples. Consistent with cancer

[i]Bonferroni-corrected p-value

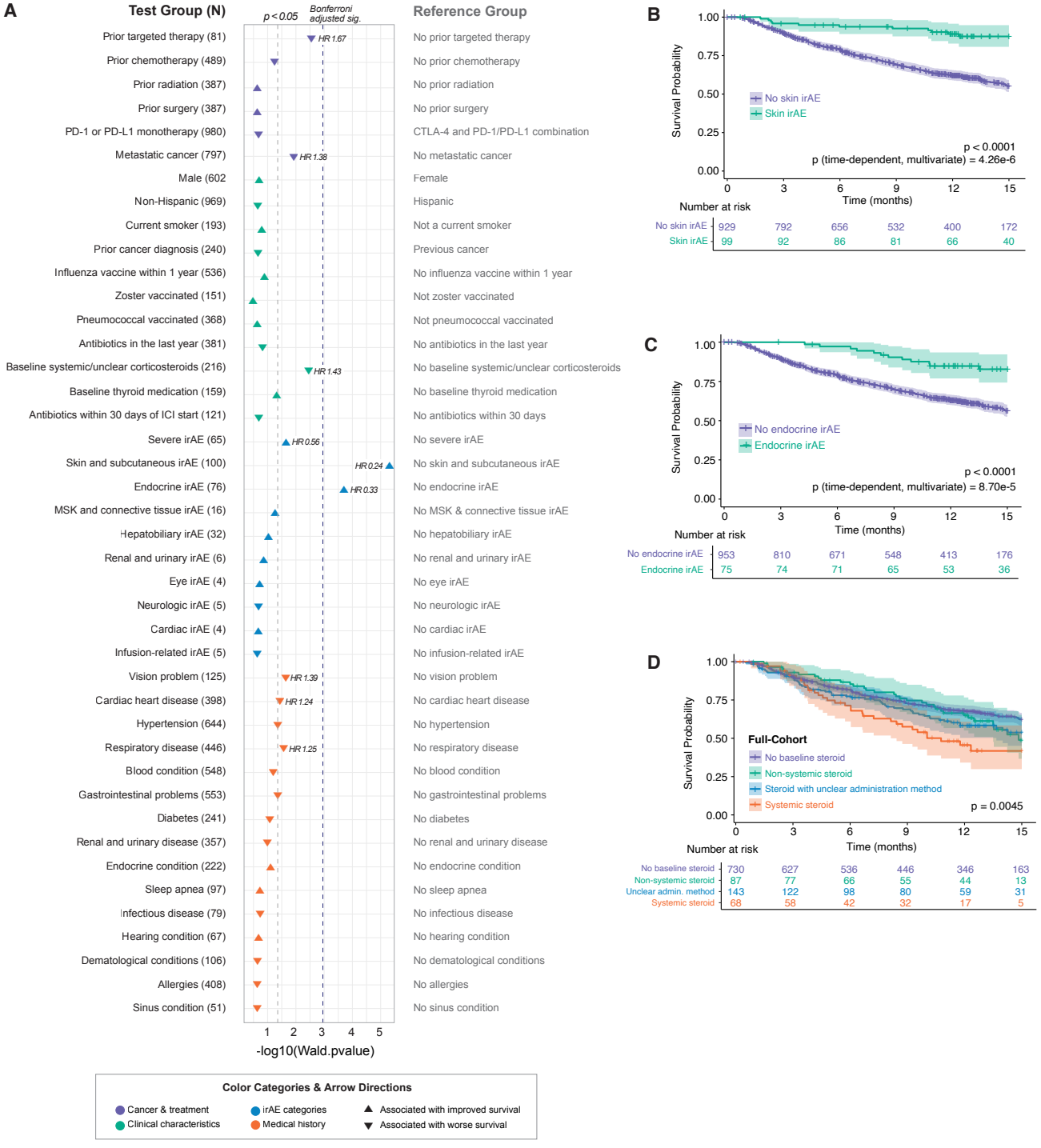

Figure 2 Univariate risk analysis for survival outcomes. (A) Univariate Cox survival graph for age-adjusted clinical risk factors, directionality of the arrow indicates association with either improved or worse survival. HRs are provided for variables if nominally significant (p<0.05 prior to adjustment for multiple comparisons, gray dashed line) or significant after adjusting for multiple comparisons (Bonferroni adjusted, purple dashed line); (B) Kaplan-Meier survival analysis of all patients for any skin or subcutaneous tissue irAE incidence. As in figure 1, statistical significance for this association is shown for both a Cox proportional hazards model adjusted for age (p) and time-dependent Cox proportional hazard model adjusting for age and metastatic disease (p(time dependent)); (C) Kaplan-Meier survival analysis of all patients for any endocrine irAE incidence. Again, significance from both analytic approaches is shown; (D) Kaplan-Meier survival analysis of all patients for baseline corticosteroid use and route of administration. Time-dependent Cox proportional hazards not done as the use of the steroid preceded ICI initiation. ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; MSK, musculoskeletal; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

Figure 3 Univariate risk analysis for irAE occurrences. Univariate predictors of any irAE incidence (pink arrow) and any severe Grade III–IV irAE (purple arrow); directionality of the arrow indicates association with higher or lower risk of irAE. ORs are provided for variables if nominally significant (p<0.05 prior to adjustment, gray dashed line) or significant after adjusting for multiple comparisons (Bonferroni adjusted, purple dashed line). IrAE, immune-related adverse event; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

frequency and FDA-approved clinical indications, NSCLC was the most frequent cancer receiving ICI treatment followed by melanoma. Single-agent PD-(L)1 inhibitors were the most common form of ICI administered. We also see confirmation of the known natural history of disease and ICI efficacy, with survival differing by cancer type, with better survival outcomes in melanoma than patients with NSCLC.[14]

The association between improved antitumor immunity and irAE incidence has been increasingly suggested,[7 15 16] which we clearly demonstrate in this well-powered RADIOHEAD cohort with appropriate statistical methods to account for survival bias. Additionally, we further identified that organ-specific irAEs of the skin and endocrine organs were particularly associated with improved therapeutic response. For both skin and endocrine irAEs, the need for ICI discontinuation is often limited, and the treatment options rely primarily on topical immunosuppressants and replacement hormones, respectively. This contrasts with irAEs affecting other organs or tissue sites, in which there may be a greater need for administration of systemic corticosteroids. While systemic corticosteroids have been suggested by some to not impact ICI treatment outcomes, this may not adequately account for the survival advantage that the indication for which they are being received provides. This form of confounding by indication is challenging to avoid, but there are examples that show the potential that corticosteroids attenuate the antitumor immunity. In individuals developing ICI-induced hypophysitis, significantly worse survival outcomes were observed for patients receiving high concentrations of corticosteroids compared with individuals receiving them in a physiological range.[17]

In the RADIOHEAD cohort, pretreatment exposure to systemic corticosteroids led to worse survival outcomes which has been established in multiple other smaller studies without affecting rates of irAEs.[18 19] Further study should be undertaken to address if switching patients to steroid-sparing immunomodulatory agents prior to ICI initiation would improve their response and survival without affecting the underlying disease requiring the steroid and irAEs.

Aside from corticosteroid exposure, prior studies have also demonstrated associations between baseline antibiotic use and worsened overall survival,[18–21] which RADIOHEAD did not replicate. Baseline antibiotic use within the last 30 days was relatively low (11.3%), and we did see a similar trend to prior studies, although it was not significant (HR 1.12, p=0.5).

Overall, there were lower rates of irAEs in this standard of care patient population than what is generally reported for clinical trials and retrospective studies, particularly from academic centers.[5 22 23] This highlights the importance of the RADIOHEAD cohort to help identify challenges with irAE diagnosis in the community hospital setting. While the top five most common irAEs in this cohort, rash, thyroid dysfunction, colitis/diarrhea, pneumonitis and hepatitis align with the top five irAEs in other cohorts, the rates across all types are lower.[5 22 23] Differences in rates of severe irAEs were smaller, but the number of subjects with severe irAEs is also lower. This lower rate was apparent even for irAEs where extraction should be well defined, such as for thyroid dysfunction where both laboratory changes and medication initiation are performed for all but grade 1 disease, compared with other irAEs where lower grades may be monitored rather than intervened on which could lead to lower identification by chart extractors. Possible reasons for these lower irAE rates include that these patients have had fewer prior treatments, including tyrosine kinase inhibitor use which has been seen to increase rates of irAEs,[24 25] less frequent clinical visits or lab testing, or differing risk patterns and potential exposure to immunosuppressive medications in these standard of care patients than clinical trial patients leading to an increase in under-reporting. It is unclear whether this is due to under-reporting, and potentially inadequate diagnosis through reduced involvement of subspecialties in the community hospital setting, or if in fact there are lower rates in community settings than in trial settings. If the latter is true, ICI safety profiles should be revisited in this context. The lower than anticipated irAE rates did decrease the power of this study, particularly for rare irAEs.

Despite these lower irAE rates, we were able to identify risk factors for irAEs. As previously well established, rates are higher with combination immunotherapy compared with anti-PD-(L)1 monotherapy.[2 26] Interestingly, both prior use of chemotherapy and concurrent use of chemotherapy in patients with lung cancer were associated with decreased risk of irAE. Given the decrease in immune cells from conventional chemotherapy, there is a potential mechanistic rationale that this could be related to a decrease in the presence of autoreactive T cells. Chemotherapy has also been used in some cases to reset the immune system and reduce inflammation in patients with autoimmune disease, including scleroderma, systemic lupus erythematosus, and certain types of arthritis. Most clinical trials have largely assessed standard of care chemotherapy alone to chemoimmunotherapy with the absence of an immunotherapy alone arm, which has led to limited information relating to differences in the irAE profile with and without chemotherapy. Retrospective analyses have identified increased irAEs and treatment discontinuation in lung cancer when ICI is combined with chemotherapy in some[27 28] but not all cohorts.[29] Additionally, a clinical trial using first-line tremelimumab (anti-CTLA-4), durvalumab (anti-PD-L1), and chemotherapy versus durvalumab and chemotherapy in metastatic NSCLC revealed comparative frequency and severity of treatment-related adverse events and similar rates of treatment discontinuation.[30] This may indicate that chemotherapy has the potential to modify the adverse event profile and even restrain the increase in adverse events usually associated with multiple lines of immunotherapy.[2 26] Alternatively, the rationale for treating a patient with chemoimmunotherapy, such

as tumor type (low tumor mutation burden, low PD-L1 expression) and/or patient status (high disease burden requiring rapid response), may also select for patients that are less likely to respond to ICI treatment, which may also be indicative of reduced risk for irAEs. This suggests the need for greater interrogation of the impact of chemotherapy on both ICI-induced irAE frequency and type to determine whether it impacts certain irAEs, particularly those that are autoimmune in nature, preferentially.

We found an association between prior zoster vaccine and development of any irAE, but not severe irAEs. There was no association between prior zoster vaccine and overall survival despite this association with irAE (p=0.38). A limitation of this finding is that the rate of zoster vaccination in this population was only 14.1%, and status was unknown for 36.8% of the cohort. The rates of irAEs in this group with unknown vaccination status were between the irAE rate in the unvaccinated and vaccinated cohort, potentially suggesting a mixed group. Prior literature has largely reported a lack of associations between irAEs and inactivated vaccines,[31] COVID-19 vaccination,[32 33] or seasonal influenza vaccines.[34–39] There is a rare association of Guillain-Barré Syndrome, an autoimmune disease, with zoster vaccine and perhaps this link could help explain, in part, the irAE association[40] but further study is warranted. In the USA, the commonly used Shingrix vaccine is a recombinant, inactivated vaccine which replaced the prior vaccine, Zostavax, a live-attenuated vaccine, in 2017. In 2021, at the tail end of this study, the FDA expanded the indication for the Shingrix vaccine to include adults undergoing conventional chemotherapy due to immunosuppression. Patients were not asked which vaccine type they had received, which limits the ability to hypothesize on mechanism. That said, live vaccines could increase broader adaptive immunity with more chance for cross-reactivity with self.[41] The recombinant vaccine combines a varicella-zoster virus (VZV) antigen glycoprotein with an immune-stimulating adjuvant that increases interferon gamma release by natural killer cells and both $CD4^+$ and $CD8^+$ T cells. There has been no increased risk of autoimmune disease with this adjuvant,[42] but there is also evidence of both T cell-mediated and humoral immune responses to the recombinant vaccine for at least 9 years postvaccination. While the timing of the vaccination relative to ICI start is not available, there was no association between zoster vaccination and chemotherapy (p=0.35) or zoster vaccination and cancer type (p=0.42). Intriguingly, there is evidence for an association between seasonal influenza vaccine and improved overall survival in the existing literature, however, we did not find this for the zoster vaccine[39] and did not show this association with the seasonal influenza vaccine within the RADIOHEAD cohort.

In conclusion, results from this large, real-world cohort study of standard of care patients definitively identify previously suggested variables associated with ICI response and novel risk factors which may impact patient care. Clinical risk factors that enhance treatment selectivity by incorporating both treatment response and irAE risk are essential to deepen our understanding of ICI efficacy. Many of the studies to investigate this have employed small cohort or retrospective analyses, that have not been tailored towards capturing broad clinical features alongside opportunities to probe molecular mechanisms for clinical outcomes. RADIOHEAD was designed to be able to answer both questions simultaneously. In the future, the potential for molecular and immune profiling of samples collected in the RADIOHEAD cohort provides an opportunity to elucidate the potential mechanistic link between irAE and clinical response to ICI, as well as identify clinically actionable mechanisms for immunotherapy resistance via integrated analyses of multiomic datasets to be generated from longitudinal patient samples.

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Contributors ZQ, AL, SIL, EY, SS, and MZHF curated the clinical data. ZQ, SIL, and AL conducted statistical analyses, interpreted the results, and contributed to drafting the manuscript. SIL, LJP, SB, and JEC supervised the research team and coordinated project activities, while NLB, SSM, SB, KCH, JAB, and MSA developed the study methodology and oversaw project planning. LHB, JEC, JAB, and MSA provided supervision, interpreted statistical results, and secured financial support for the project. ACCT and CS contributed to data analysis, manuscript revisions, and drafting. AY developed the study methodology and contributed to both statistical interpretation and manuscript preparation. All authors reviewed and edited the manuscript for intellectual content. ZQ is the guarantor.

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Competing interests ZQ has consulted for Sanofi and Novartis. MSA owns stock in Merck and Medtronic. SIL owns stock in AbbVie. LHB has served on advisory boards for Calidi Biotherapeutics, Western Oncolytics/Kalivir, Torque Therapeutics/Repertoire, Pyxis, CytomX, Roche-Genentech (Biomarkers Roundtable), Khloris, Takeda Oncology, Adaptimmune, RAPT, and DCPrime. LHB holds stocks or shares in Repertoire, Pyxis, RAPT, and CytomX.

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