# Multi-organ immune-related adverse events from immune checkpoint inhibitors and their downstream implications: a retrospective multicohort study

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## Summary

**Background** Understanding co-occurrence patterns and prognostic implications of immune-related adverse events is crucial for immunotherapy management. However, previous studies have been limited by sample size and generalisability. In this study, we leveraged a multi-institutional cohort and a population-level database to investigate co-occurrence patterns of and survival outcomes after multi-organ immune-related adverse events among recipients of immune checkpoint inhibitors.

**Methods** In this retrospective study, we identified individuals who received immune checkpoint inhibitors between May 31, 2015, and June 29, 2022, from the Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute (Boston, MA, USA; MGBD cohort), and between April 30, 2010, and Oct 11, 2021, from the independent US population-based TriNetX network. We identified recipients from all datasets using medication codes and names of seven common immune checkpoint inhibitors, and patients were excluded from our analysis if they had incomplete information (eg, diagnosis and medication records) or if they initiated immune checkpoint inhibitor therapy after Oct 11, 2021. Eligible patients from the MGBD cohort were then propensity score matched with recipients of immune checkpoint inhibitors from the TriNetX database (1:2) based on demographic, cancer, and immune checkpoint inhibitor characteristics to facilitate cohort comparability. We applied immune-related adverse event identification rules to identify patients who did and did not have immune-related adverse events in the matched cohorts. To reduce the likelihood of false positives, patients diagnosed with suspected immune-related adverse events within 3 months after chemotherapy were excluded. We performed pairwise correlation analyses, non-negative matrix factorisation, and hierarchical clustering to identify co-occurrence patterns in the MGBD cohort. We conducted landmark overall survival analyses for patient clusters based on predominant immune-related adverse event factors and calculated accompanying hazard ratios (HRs) and 95% CIs, focusing on the 6-month landmark time for primary analyses. We validated our findings using the TriNetX cohort.

**Findings** We identified 15 246 recipients of immune checkpoint inhibitors from MGBD and 50 503 from TriNetX, of whom 13 086 from MGBD and 26 172 from TriNetX were included in our propensity score-matched cohort. Median follow-up durations were 317 days (IQR 113–712) in patients from MGBD and 249 days (91–616) in patients from TriNetX. After applying immune-related adverse event identification rules, 8704 recipients of immune checkpoint inhibitors were retained from MGBD, of whom 3284 (37·7%) had and 5420 (62·3%) did not have immune-related adverse events, and 18 162 recipients were retained from TriNetX, of whom 5538 (30·5%) had and 12 624 (69·5%) did not have immune-related adverse events. In both cohorts, positive pairwise correlations of immune-related adverse events were commonly observed. Co-occurring immune-related adverse events were decomposed into seven factors across organs, revealing seven distinct patient clusters (endocrine, cutaneous, respiratory, gastrointestinal, hepatic, musculoskeletal, and neurological). In the MGBD cohort, the patient clusters that predominantly had endocrine (HR 0·53 [95% CI 0·40–0·70], p<0·0001) and cutaneous (0·61 [0·46–0·81], p=0·0007) immune-related adverse events had favourable overall survival outcomes at the 6-month landmark timepoint, while the other clusters either had unfavourable (respiratory: 1·60 [1·25–2·03], p=0·0001) or neutral survival outcomes (gastrointestinal: 0·86 [0·67–1·10], p=0·23; musculoskeletal: 0·97 [0·78–1·21], p=0·78; hepatic: 1·20 [0·91–1·59], p=0·19; and neurological: 1·30 [0·97–1·74], p=0·074). Similar results were found in the TriNetX cohort (endocrine: HR 0·75 [95% CI 0·60–0·93], p=0·0078; cutaneous: 0·62 [0·48–0·82], p=0·0007; respiratory: 1·21 [1·00–1·46], p=0·044), except for the neurological cluster having unfavourable (rather than neutral) survival outcomes (1·30 [1·06–1·59], p=0·013).

**Interpretation** Reliably identifying the immune-related adverse event cluster to which a patient belongs can provide valuable clinical information for prognosticating outcomes of immunotherapy. These insights can be leveraged to counsel patients on the clinical impact of their individual constellation of immune-related adverse events and ultimately develop more personalised surveillance and mitigation strategies.

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## Introduction

Immune checkpoint inhibitors are monoclonal antibodies that bind to PD-1, PD-L1, or CTLA-4 and have revolutionised cancer care. However, activating the immune system through immune checkpoint inhibitors can result in a high burden of side-effects, known as immune-related adverse events, which can become chronic and even life-threatening. Up to 70% of patients undergoing immune checkpoint inhibitor therapy can have immune-related adverse events.[1] These adverse events can occur in one or multiple organs and vary in timing from weeks to months after initiation of immunotherapy.[1–3] Managing multiple immune-related adverse events poses substantial challenges to medical oncologists due to their diverse and complex nature and often requires a multidisciplinary care approach.[4–6] However, the specific co-occurrence patterns of immune-related adverse events across multiple organs and their prognostic implications remain understudied.

Although an improved understanding of immune-related adverse event co-occurrence is necessary to improve clinical care for patients who have these side-effects, it might also be valuable for prognosticating outcomes of immunotherapy. For example, several individual immune-related adverse events, notably cutaneous[7,8] and endocrine[9] events, have been associated with improved overall survival. However, despite observing that these events frequently co-occur with adverse events in other organ systems,[10,11] data on how the co-occurrence of immune-related adverse events ultimately affects the outcome of immunotherapy have been conflicting.[12] In one retrospective study of 628 patients with melanoma, lung, gastrointestinal, head or neck, and other cancer types, those who developed multiple cutaneous immune-related adverse events had increased progression-free survival, but not overall survival, compared with patients who developed a single cutaneous immune-related adverse event.[13] Other retrospective studies have suggested that patients with multiple immune-related adverse events had improved overall survival when compared with patients treated with immune checkpoint inhibitors with one or no immune-related adverse events,[5,6,14] whereas one multi-centre study found that patients with multi-organ immune-related adverse events had worse overall survival if one of the events was myocarditis compared with patients treated with immune checkpoint inhibitors who only developed myocarditis.[15]

### Research in context

#### Evidence before this study

We searched PubMed for articles published between Jan 1, 2018, and May 1, 2023. We searched for reviews and systematic surveys with the terms "immune-related adverse event" in their titles and all articles that contained "immune-related adverse event" in their keywords in conjunction with "multi", "multiple", "multisystem", or "multiorgan" in their titles. We identified 34 publications from our search. In the setting of immune checkpoint inhibitor therapy, immune-related adverse events occur frequently. These events can affect one or more organs and have been associated with improved overall survival, particularly among patients with cutaneous immune-related adverse events. Several studies suggested that, compared with patients who did not develop or who only developed one immune-related adverse event, patients who developed multiple events in the setting of treatment with immune checkpoint inhibitors had improved overall survival. Other studies suggested that patients treated with immune checkpoint inhibitors who developed myocarditis in conjunction with other immune-related adverse events had worse overall survival than those who only developed myocarditis. However, little is known about the specific co-occurrence patterns of immune-related adverse events across organs and how these patterns differentially influence immune checkpoint inhibitor outcomes.

#### Added value of this study

Previous studies have been primarily limited to single institutions or small cohorts, raising concerns about generalisability. In this study we leveraged a multi-institutional cohort and compared results obtained with data from a population-level cohort to identify patterns of immune-related adverse event co-occurrence. We did this using robust matrix factorisation and clustering approaches and investigated downstream survival outcomes among recipients of immune checkpoint inhibitors who had multi-organ immune-related adverse events.

#### Implications of all the available evidence

Our findings offer oncologists important prognostic insights that can greatly aid in counselling and managing patients with immune-related adverse events. Additionally, these data can enable the identification of patients who might be at an increased risk of unfavourable clinical outcomes, allowing for more personalised patient counselling, and ultimately leading to improved patient outcomes. Furthermore, these findings contribute to a deeper understanding of the potential biological mechanisms underlying immune-related adverse events across various organs.

The co-occurrence patterns of immune-related adverse events across multiple organs and their implications for patient survival need to be better understood. The few previous studies on this topic have focused on single institutions[16] and pairwise analyses.[4,11] However, large datasets and computational approaches that can capture correlations across complex data are necessary to identify meaningful co-occurrence patterns and their implications on subsequent outcomes. In this study, we used a multi-institutional cohort and latent factorisation and clustering approaches to investigate co-occurrence patterns and subsequent outcomes associated with multi-organ immune-related adverse events among recipients of immune checkpoint inhibitors for treatment of cancer. To ensure the robustness of our findings, we validated our results using an independent population-level database.

## Methods

### Study design and patients

In this retrospective study, we identified patients who had received immune checkpoint inhibitors between May 31, 2015, and June 29, 2022, from the Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute (Boston, MA, USA; MGBD cohort), and between April 30, 2010, and Oct 11, 2021, from the independent US population-based TriNetX network. The patients from MGBD were primarily based in the Boston area of the USA, whereas the TriNetX data were derived from health-care organisations across the USA and did not include patients from MGBD because these institutions had not contributed data to TriNetX.

Recipients of immune checkpoint inhibitors were identified from MGBD and TriNetX using the medication codes and names of seven immune checkpoint inhibitors (appendix p 3). The Enterprise Data Warehouse and the Research Patient Data Registry are two clinical databases at MGBD. The Enterprise Data Warehouse includes detailed immune checkpoint inhibitor records, which was used to identify patients treated by immune checkpoint inhibitors. The Research Patient Data Registry gathers medical records from hospital systems and has several modules, including demographics, encounters, diagnoses, medications, and others. We requested demographic, diagnosis, and medication data for all recipients of immune checkpoint inhibitors identified. Patients were excluded from our analysis if they had incomplete data (eg, their data on diagnosis or medical history were not available from the Research Patient Data Registry) or if they had initiated immune checkpoint inhibitor therapy after Oct 11, 2021. Patients' demographics, diagnostic codes, and medication records were extracted from TriNetX. Because TriNetX only provides access to structured patient data, direct access to individual patient charts and clinical notes was not available in this cohort, precluding any manual chart review of this cohort. Eligible patients from MGBD were then propensity score matched (1:2) with recipients of immune checkpoint inhibitors from TriNetX. The propensity score was calculated using logistic regression based on patient baseline characteristics (self-reported sex, race, ethnicity, age at initiation of immune checkpoint inhibitor therapy, Charlson comorbidity index, cancer type, cancer stage, immune checkpoint inhibitor type, and pre-immune checkpoint inhibitor treatment) and the year of immune checkpoint inhibitor therapy initiation (definitions are in the appendix [pp 4–5]). Matching details are in the appendix (p 6). The goal of this matching was not for causal effect estimation but to ensure a basic level of similarity between the two cohorts.

The development of immune-related adverse events was the exposure of interest in this study (appendix p 7). We applied immune-related adverse event identification rules, defined using diagnostic codes from the International Classification of Diseases versions 9 and 10 (appendix pp 8–12) and validated by comparison with manual chart review of a randomly selected subset of 200 patients from MGBD (appendix pp 13–14), to identify patients who did and did not experience immune-related adverse events in the matched cohorts. Patients who had diagnoses of suspected immune-related adverse within 3 months after chemotherapy were excluded to isolate the cause of an event more specifically to the immune checkpoint inhibitor therapy and reduce the likelihood of false positives. After identifying immune-related adverse events, the MGBD and TriNetX cohorts were analysed independently. Within each cohort, there was no matching between the group of patients who had immune-related adverse events and those who did not (the reference group).

The Mass General Brigham Institutional Review Board approved the study (protocol #2020P002307). The study meets the criteria of secondary research, and so the requirement for patient consent was waived.

See Online for appendix

### Data extraction

We extracted demographic and clinical characteristics and patient mortality data of the study population (summarised in the appendix pp 4–5). Notably, cancer stage was estimated using secondary malignancy diagnostic codes from the International Classification of Diseases versions 9 and 10 (appendix p 15): with metastatic disease defined as any secondary cancer in distant sites; otherwise, referred to as not metastatic. Cytotoxic chemotherapy and targeted anti-neoplastic therapy (appendix p 16) received before and during immune checkpoint inhibitor therapy were categorised as conventional chemotherapy or targeted therapy. Interruption of immune checkpoint inhibitor therapy was categorised as discontinuation if the patient had received fewer than three cycles of immune checkpoint inhibitor therapy, as interruption if two cycles were missed, and as continuation under any other circumstances.

Since systemic immunosuppression is commonly used in the management of immune-related adverse events

and has been associated with worse outcomes from immunotherapy due to concerns of blunting of the anti-tumour activity of immunotherapy, we sought to investigate the extent to which differences in systemic immunosuppressive therapy use explains the observed overall survival outcomes in our study. Manual chart reviews for a convenience subset (1049 patients) of the MGBD cohort were performed to extract the systemic immunosuppressive therapy start date, status, dosage, and the reason for receipt of systemic immunosuppressive therapy (appendix p 17). Based on the manual process, we established an approach to computationally identify systemic glucocorticoid use, since this is the predominant type of systemic immunosuppression used in patients receiving immunotherapy (appendix pp 18–19).

To explore influence of adverse event severity on overall survival, we also manually evaluated the severity of immune-related adverse events in accordance with the Common Terminology Criteria for Adverse Events (version 5.0) in a randomly selected subset of 100 patients with computational immune-related adverse events from the MGBD cohort (appendix p 14). We could not evaluate severity of immune-related adverse events directly across the entire population in this study because it requires manual chart reviews. We approximated that immune-related adverse event severity by leveraging other extracted features, including systemic immuno-suppressive features and interruption of immune checkpoint inhibitor therapy for presence of high-grade immune-related adverse events.

### Statistical analysis

All statistical analyses were initially conducted in the MGDB cohort with subsequent validation in the TriNetX cohort. Pearson's $\chi^2$ test for categorical variables and Student's *t* test for continuous variables were used to compare baseline characteristics. Concordance, Kappa statistic, and positive predictive value were calculated to compare the computationally derived and manually phenotyped immune-related adverse events among the 200 randomly selected patients from the MGBD cohort. We used a collection of statistical methods, including modified Poisson regression,[17] non-negative matrix factorisation (NMF), and hierarchical clustering to identify co-occurrence and clustering patterns of immune-related adverse events. We performed landmark analyses with Cox proportional hazards regression to assess overall survival outcomes among patient clusters.[18]

To investigate the pairwise co-occurrence of immune-related adverse events, we curated a variable for each organ system, indicating the presence of immune-related adverse events in that specific organ within 2 years after initiation of immune checkpoint inhibitor therapy. We performed modified Poisson regression analyses for each organ pair with the first organ as the dependent variable and the second organ as the independent variable. We also evaluated associations between immune-related adverse events and cancer organ systems using modified Poisson regressions (appendix p 20). We calculated risk ratios (RRs) with 95% CIs and p values, adjusted using the sandwich method.[17]

To identify multi-organ immune-related adverse event co-occurrence and clustering patterns, we performed NMF and hierarchical clustering analyses (appendix pp 21–22). Briefly, we constructed a count matrix representing immune-related adverse events in specific organs, with an upper limit of four immune-related adverse events in the count values to mitigate the potential bias from frequent health-care use. NMF was used to decompose the matrix into two low-rank matrices: one representing the multi-organ immune-related adverse event factors (ie, basis matrix) and the other representing the weights of multi-organ immune-related adverse event factors in each patient (ie, weight matrix). Given the paucity of existing knowledge of factors underlying immune-related adverse events, we adopted the elbow method to determine the number of factors in NMF. In the elbow method, we run a series of NMF experiments with the number of factors ranging from two to eight and chose the value by identifying the elbow point where the cophenetic correlation began to increase at a slower rate. Subsequently, we performed hierarchical clustering on the weight matrix to group patients into clusters.

To investigate associations of patient clusters and overall survival outcomes, we performed landmark analyses, with 6 months after initiation of immune checkpoint inhibitor therapy as the landmark time for our primary analyses, using multivariable Cox proportional hazard regression (appendix pp 21–22). Potential confounding variables (age at initiation of immune checkpoint inhibitor therapy, sex, race, ethnicity, cancer type, cancer stage, Charlson comorbidity index, non-immune checkpoint inhibitor treatment, immune checkpoint inhibitor type, and interruption of immune checkpoint inhibitor therapy; appendix pp 4–5) were included as covariates in the multivariable survival models. Hazard ratios (HRs) with 95% CIs and p values were calculated from the models. Patients were grouped on the basis of immune-related adverse events that developed within the landmark time period to mitigate immortal-time bias using the identified clustering patterns (appendix pp 21–22). The reference group comprised patients who did not experience immune-related adverse events within the landmark time period. Ultimately, we combined patient clusters on the basis of their individual overall survival outcomes into three groups: favourable, unfavourable, and neutral, for further analyses.

To enhance the robustness of our study, we performed sensitivity analyses around the landmark time ranging from 5–12 months after initiation of immune checkpoint inhibitor therapy using the same covariates as in our primary analyses, with proportional hazard assumptions

| | MGBD cohort (N=13 086) | TriNetX cohort (N=26 172) | p value |
|---|---|---|---|
| Sex | | | |
| Female | 6072 (46·4%) | 11 671 (44·6%) | 0·0007 |
| Male | 7014 (53·6%) | 14 501 (55·4%) | .. |
| Race | | | |
| White | 11 791 (90·1%) | 23 534 (89·9%) | 0·13 |
| Black or African American | 364 (2·8%) | 746 (2·9%) | .. |
| Asian | 430 (3·3%) | 787 (3·0%) | .. |
| Other or unavailable | 501 (3·8%) | 1105 (4·2%) | .. |
| Ethnicity | | | |
| Not Hispanic | 11 896 (90·9%) | 23 663 (90·4%) | 0·052 |
| Hispanic | 366 (2·8%) | 849 (3·2%) | .. |
| Unavailable | 824 (6·3%) | 1660 (6·3%) | .. |
| Age at initiation of immune checkpoint inhibitor therapy, years | 66 (57–74) | 66 (58–74) | 0·12 |
| Charlson comorbidity index | | | |
| 0 | 77 (0·6%) | 192 (0·7%) | 0·048 |
| 1–2 | 1661 (12·7%) | 3407 (13·0%) | .. |
| 3–4 | 927 (7·1%) | 1995 (7·6%) | .. |
| ≥5 | 10 421 (79·6%) | 20 578 (78·6%) | .. |
| Cancer type | | | |
| Thoracic | 3325 (25·4%) | 7035 (26·9%) | <0·0001 |
| Male genital or urinary | 1760 (13·4%) | 3813 (14·6%) | .. |
| Digestive | 1626 (12·4%) | 3258 (12·4%) | .. |
| Melanoma | 1318 (10·1%) | 2833 (10·8%) | .. |
| Other skin malignancy | 697 (5·3%) | 1337 (5·1%) | .. |
| Breast | 896 (6·8%) | 1366 (5·2%) | .. |
| Lymphoid or haematopoietic | 713 (5·4%) | 1267 (4·8%) | .. |
| Female genital | 636 (4·9%) | 1153 (4·4%) | .. |
| Brain, nervous, or eye | 552 (4·2%) | 804 (3·1%) | .. |
| Oral, lip, or pharynx | 488 (3·7%) | 1026 (3·9%) | .. |
| Other | 1075 (8·2%) | 2280 (8·7%) | .. |
| (Continued from previous column) | | | |
| Cancer stage | | | |
| Distant metastases | 10 252 (78·3%) | 20 234 (77·3%) | 0·021 |
| No metastases | 2834 (21·7%) | 5938 (22·7%) | .. |
| Previous treatment | | | |
| Conventional chemotherapy | 5637 (43·1%) | 11 645 (44·5%) | 0·0004 |
| Targeted therapy | 1136 (8·7%) | 2437 (9·3%) | .. |
| None | 6313 (48·2%) | 12 090 (46·2%) | .. |
| Immune checkpoint inhibitor type | | | |
| PD-1 | 9905 (75·7%) | 19 951 (76·2%) | 0·34 |
| PD-L1 | 1836 (14·0%) | 3592 (13·7%) | .. |
| CTLA-4 | 142 (1·1%) | 241 (0·9%) | .. |
| Combination† | 1203 (9·2%) | 2388 (9·1%) | .. |
| Year of initiation of immune checkpoint inhibitor | | | |
| Before 2017 | 2147 (16·4%) | 4051 (15·5%) | 0·040 |
| 2017 | 2042 (15·6%) | 3924 (15·0%) | .. |
| 2018 | 2355 (18·0%) | 4689 (17·9%) | .. |
| 2019 | 2386 (18·2%) | 4887 (18·7%) | .. |
| 2020 | 2212 (16·9%) | 4603 (17·6%) | .. |
| 2021 | 1944 (14·9%) | 4018 (15·4%) | .. |
| Duration of immune checkpoint inhibitor therapy, days | 106 (29–316) | 92 (22–279) | <0·0001 |
| Mortality status at end of follow-up | | | |
| Alive | 5728 (43·8%) | 16 151 (61·7%) | <0·0001 |
| Dead | 7358 (56·2%) | 10 021 (38·3%) | .. |
| Duration of follow-up, days | 317 (113–712) | 249 (91–616) | <0·0001 |

Data are n (%) or median (IQR). p values were calculated using Pearson's $\chi^2$ test for categorical variables and Student's *t* test for continuous variables. *Definitions of variables are provided in the appendix (pp 4–5). †Combination of CTLA-4 and PD-1 or PD-L1 inhibitor therapy. MGBD=Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute.

***Table 1:*** **Patient characteristics* of the propensity score-matched MGBD and TriNetX cohorts**

assessed across all landmark timepoints. The 6-month landmark time was chosen for use in our primary models to balance the time by which most immune-related adverse events have already occurred and the proportion of the population who were alive for subsequent survival analyses. We performed sample size calculations to verify that each survival analysis was appropriately powered (appendix p 23).

We performed subanalyses to assess the effect of systemic use of immunosuppressive therapy, time to the first immune-related adverse event, and interruption of immune checkpoint inhibitor therapy among patient clusters on overall survival. We conducted landmark overall survival analyses in which we adjusted for use of systemic glucocorticoids in addition to the covariates in our primary analyses. We also did overall survival analyses for individual cancer subgroups (melanoma, thoracic cancer, and other cancer types included in this study) and for immune checkpoint inhibitor subgroups (PD-1, combination, and other types). The subgroups were chosen on the basis of sample size. In these subgroup analyses, we compared the favourable outcome group with all other patients included in the 6-month landmark analyses to ensure sufficient statistical power. We also conducted NMF and hierarchical clustering analysis specifically for the patients who received the combination of anti-CTLA-4 and anti-PD-1 or anti-PD-L1 therapy (post hoc).

We used a significance threshold of 0·05 for p values. We did analyses using stats 4.3.2, MatchIt 4.3.3, epiR 2.0.74, and sandwich 3.1.0 in R (version 4.3.2) and scikit-learn 0.24.2 and scipy 1.7.3 in Python (version 3.8.18).

| | MGBD (n=3284) | TriNetX (n=5538) |
|---|---|---|
| Endocrine | 1196 (36%) | 2069 (37%) |
| Hypothyroidism | 825 (25%) | 1438 (26%) |
| Adrenal insufficiency | 241 (7%) | 340 (6%) |
| Thyroiditis | 237 (7%) | 442 (8%) |
| Hyperglycaemia | 143 (4%) | 243 (4%) |
| Hypophysitis or polyglandular autoimmune syndrome | 106 (3%) | 111 (2%) |
| Hyperthyroidism | 103 (3%) | 183 (3%) |
| Type 1 diabetes | 57 (2%) | 94 (2%) |
| Cutaneous | 787 (24%) | 1399 (25%) |
| Rash or pruritus | 505 (15%) | 982 (18%) |
| Eczema | 148 (5%) | 222 (4%) |
| Drug hypersensitivity of skin | 110 (3%) | 187 (3%) |
| Mucositis | 80 (2%) | 167 (3%) |
| Xerosis | 57 (2%) | 38 (1%) |
| Psoriasis | 45 (1%) | 47 (1%) |
| Vitiligo | 37 (1%) | 61 (1%) |
| Lichen planus | 22 (1%) | 24 (<1%) |
| Alopecia | 20 (1%) | 33 (1%) |
| Bullous dermatitis | 18 (1%) | 24 (<1%) |
| Erythematous conditions | 14 (<1%) | 24 (<1%) |
| Erythema multiforme or Stevens-Johnson syndrome or toxic epidermal necrolysis | 5 (<1%) | 4 (<1%) |
| Photosensitivity | 3 (<1%) | 6 (<1%) |
| Drug rash with eosinophilia and systemic symptoms | 2 (<1%) | 1 (<1%) |
| Musculoskeletal | 744 (23%) | 1236 (22%) |
| Arthritis | 693 (21%) | 1146 (21%) |
| Arthralgia or myalgias | 88 (3%) | 156 (3%) |
| Gastrointestinal | 743 (23%) | 1138 (21%) |
| Diarrhoea | 536 (16%) | 772 (14%) |
| Inflammatory bowel disease | 333 (10%) | 425 (8%) |
| Gastroduodenitis | 97 (3%) | 96 (2%) |
| Xerostomia | 51 (2%) | 69 (1%) |
| Pancreatitis | 44 (1%) | 72 (1%) |
| Duodenitis | 40 (1%) | 20 (<1%) |
| Microscopic colitis | 21 (1%) | 11 (<1%) |
| (Table 2 continues in next column) | | |

| | MGBD (n=3284) | TriNetX (n=5538) |
|---|---|---|
| (Continued from previous column) | | |
| Neurological | 655 (20%) | 939 (17%) |
| Dysphagia | 377 (11%) | 431 (8%) |
| Neuritis | 178 (5%) | 371 (7%) |
| Disturbance of skin sensation | 92 (3%) | 167 (3%) |
| Encephalomyelitis | 40 (1%) | 43 (1%) |
| Meningitis | 20 (1%) | 18 (<1%) |
| Myasthenia gravis | 15 (<1%) | 15 (<1%) |
| Guillain–Barré syndrome | 6 (<1%) | 6 (<1%) |
| Hepatic | 577 (18%) | 767 (14%) |
| Hepatitis | 542 (17%) | 699 (13%) |
| Inflammatory liver disease | 103 (3%) | 88 (2%) |
| Autoimmune hepatitis | 30 (1%) | 85 (2%) |
| Respiratory | 486 (15%) | 723 (13%) |
| Pneumonitis | 486 (15%) | 723 (13%) |
| Renal | 464 (14%) | 709 (13%) |
| Acute kidney injury | 464 (14%) | 709 (13%) |
| Haematological | 260 (8%) | 503 (9%) |
| Thrombocytopenia | 136 (4%) | 274 (5%) |
| Anaemia | 108 (3%) | 248 (4%) |
| Eosinophilia | 31 (1%) | 17 (<1%) |
| Cardiac | 138 (4%) | 257 (5%) |
| Pericarditis | 88 (3%) | 177 (3%) |
| Myocarditis | 59 (2%) | 89 (2%) |
| Ocular | 90 (3%) | 123 (2%) |
| Conjunctivitis | 35 (1%) | 39 (1%) |
| Diplopia | 35 (1%) | 60 (1%) |
| Uveitis | 25 (1%) | 26 (<1%) |
| Rheumatological | 46 (1%) | 26 (<1%) |
| Polymyalgia rheumatica | 33 (1%) | 18 (<1%) |
| Connective tissue disease | 13 (<1%) | 8 (<1%) |

Data are n (%). The sum of patients with specific immune-related adverse events within each organ system might not be same as the total number of patients with the corresponding organ immune-related adverse events because one patient can develop several immune-related adverse events. MGBD=Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute.

***Table 2:*** **Identified immune-related adverse events in each organ system**

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

We identified 15 246 recipients of immune checkpoint inhibitors from MGBD and 50 503 from TriNetX. From the MGBD cohort, 2160 patients were excluded due to incomplete information or to maintain consistency of the last recruitment date with the TriNetX cohort (appendix p 24). Then, 26 172 recipients of immune checkpoint inhibitors from TriNetX were propensity-score matched (2:1) with the 13 086 immune checkpoint inhibitor recipients from MGBD. Propensity score histograms after matching are in the appendix (p 25). In the matched population, 6072 (46·4%) of 13 086 patients in the MGBD cohort and 11 671 (44·6%) of 26 172 in the TriNetX cohort were female, 7014 (53·6%) and 14 501 (55·4%) were male, 11 791 (90·1%) and 23 534 (89·9%) were White, and median age at initiation of immune checkpoint inhibitor therapy was 66 years (IQR 57–74) and 66 years (58–74; table 1). Median duration of follow-up was 317 days (IQR 113–712) and 249 days (91–616), and mortality rates were 56·2% (7358 of 13 086) and 38·3% (10 021 of 26 172; p<0·0001), in the MGBD and TriNetX matched cohorts respectively (table 1). The censoring proportion at every 6-month interval is shown in the appendix (p 26). Despite significant between-cohort differences in several


| | Cardiac | Cutaneous | Endocrine | Gastrointestinal | Haematological | Hepatic | Musculoskeletal | Neurological | Ocular | Renal | Respiratory | Rheumatological |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cardiac | | 1·91 (1·22–2·99) p=0·0049 | 2·47 (1·72–3·56) p<0·0001 | 2·03 (1·30–3·19) p=0·0020 | 3·38 (1·93–5·90) p<0·0001 | 4·60 (3·16–6·72) p<0·0001 | 2·60 (1·72–3·94) p<0·0001 | 4·50 (3·12–6·51) p<0·0001 | 1·41 (0·35–5·60) p=0·63 | 3·74 (2·43–5·75) p<0·0001 | 3·93 (2·59–5·95) p<0·0001 | NA |
| Cutaneous | 1·79 (1·21–2·63) p=0·0035 | | 3·26 (2·85–3·73) p<0·0001 | 3·15 (2·72–3·66) p<0·0001 | 2·58 (2·04–3·28) p<0·0001 | 2·68 (2·26–3·18) p<0·0001 | 3·13 (2·69–3·63) p<0·0001 | 2·78 (2·36–3·26) p<0·0001 | 4·72 (3·65–6·10) p<0·0001 | 2·53 (2·09–3·05) p<0·0001 | 2·57 (2·14–3·10) p<0·0001 | 2·91 (1·78–4·76) p<0·0001 |
| Endocrine | 2·09 (1·60–2·74) p<0·0001 | 2·92 (2·60–3·27) p<0·0001 | | 3·08 (2·75–3·45) p<0·0001 | 2·61 (2·19–3·12) p<0·0001 | 2·68 (2·35–3·05) p<0·0001 | 2·91 (2·59–3·27) p<0·0001 | 2·72 (2·41–3·08) p<0·0001 | 2·21 (1·61–3·04) p<0·0001 | 2·45 (2·12–2·84) p<0·0001 | 2·08 (1·78–2·43) p<0·0001 | 2·71 (1·85–3·97) p<0·0001 |
| Gastrointestinal | 1·89 (1·28–2·80) p=0·0013 | 3·19 (2·74–3·71) p<0·0001 | 3·52 (3·07–4·04) p<0·0001 | | 3·17 (2·54–3·95) p<0·0001 | 3·65 (3·12–4·27) p<0·0001 | 3·47 (2·99–4·03) p<0·0001 | 2·61 (2·19–3·09) p<0·0001 | 4·03 (2·98–5·44) p<0·0001 | 3·42 (2·88–4·06) p<0·0001 | 1·90 (1·52–2·37) p<0·0001 | 2·31 (1·28–4·16) p=0·0055 |
| Haematological | 3·27 (1·92–5·56) p<0·0001 | 2·89 (2·18–3·83) p<0·0001 | 3·27 (2·55–4·19) p<0·0001 | 3·65 (2·79–4·77) p<0·0001 | | 4·04 (3·06–5·35) p<0·0001 | 2·74 (2·05–3·67) p<0·0001 | 4·35 (3·34–5·67) p<0·0001 | 4·63 (2·70–7·95) p<0·0001 | 6·42 (4·95–8·31) p<0·0001 | 3·73 (2·76–5·05) p<0·0001 | 1·46 (0·37–5·69) p=0·59 |
| Hepatic | 3·89 (2·87–5·26) p<0·0001 | 2·81 (2·34–3·38) p<0·0001 | 3·11 (2·64–3·65) p<0·0001 | 3·87 (3·27–4·58) p<0·0001 | 3·63 (2·85–4·62) p<0·0001 | | 3·33 (2·79–3·97) p<0·0001 | 2·83 (2·33–3·43) p<0·0001 | 3·44 (2·32–5·10) p<0·0001 | 2·69 (2·16–3·36) p<0·0001 | 2·60 (2·09–3·25) p<0·0001 | 0·33 (0·05–2·27) p=0·26 |
| Musculoskeletal | 2·34 (1·65–3·30) p<0·0001 | 3·16 (2·72–3·68) p<0·0001 | 3·29 (2·87–3·78) p<0·0001 | 3·47 (2·99–4·03) p<0·0001 | 2·49 (1·94–3·20) p<0·0001 | 3·18 (2·7–3·75) p<0·0001 | | 2·82 (2·39–3·33) p<0·0001 | 3·19 (2·25–4·53) p<0·0001 | 2·05 (1·65–2·55) p<0·0001 | 2·51 (2·06–3·04) p<0·0001 | 4·67 (3·23–6·74) p<0·0001 |
| Neurological | 3·72 (2·79–4·95) p<0·0001 | 2·86 (2·41–3·39) p<0·0001 | 3·11 (2·67–3·62) p<0·0001 | 2·65 (2·22–3·17) p<0·0001 | 3·76 (3·02–4·68) p<0·0001 | 2·78 (2·30–3·36) p<0·0001 | 2·88 (2·43–3·42) p<0·0001 | | 2·70 (1·78–4·12) p<0·0001 | 2·83 (2·31–3·46) p<0·0001 | 3·56 (2·98–4·27) p<0·0001 | 1·16 (0·45–2·96) p=0·76 |
| Ocular | 1·41 (0·35–5·67) p=0·63 | 7·02 (4·64–10·62) p<0·0001 | 2·69 (1·72–4·21) p<0·0001 | 5·36 (3·48–8·25) p<0·0001 | 5·00 (2·76–9·06) p<0·0001 | 4·02 (2·47–6·57) p<0·0001 | 3·89 (2·45–6·17) p<0·0001 | 3·07 (1·84–5·12) p<0·0001 | | 3·55 (2·06–6·13) p<0·0001 | 1·88 (0·95–3·72) p=0·070 | 6·49 (2·13–19·77) p=0·0010 |
| Renal | 3·39 (2·33–4·93) p<0·0001 | 2·69 (2·18–3·32) p<0·0001 | 2·85 (2·37–3·44) p<0·0001 | 3·74 (3·08–4·54) p<0·0001 | 5·67 (4·53–7·10) p<0·0001 | 2·76 (2·19–3·48) p<0·0001 | 2·13 (1·69–2·69) p<0·0001 | 2·96 (2·38–3·67) p<0·0001 | 3·20 (2·00–5·12) p<0·0001 | | 4·18 (3·39–5·15) p<0·0001 | 2·88 (1·45–5·74) p=0·0026 |
| Respiratory | 3·51 (2·45–5·02) p<0·0001 | 2·74 (2·23–3·36) p<0·0001 | 2·32 (1·91–2·8) p<0·0001 | 1·96 (1·55–2·47) p<0·0001 | 3·48 (2·64–4·57) p<0·0001 | 2·65 (2·11–3·33) p<0·0001 | 2·63 (2·13–3·25) p<0·0001 | 3·77 (3·10–4·57) p<0·0001 | 1·81 (0·97–3·38) p=0·064 | 4·15 (3·37–5·10) p<0·0001 | | 1·17 (0·39–3·50) p=0·78 |
| Rheumatological | NA | 3·55 (1·85–6·83) p=0·0002 | 3·68 (2·03–6·68) p<0·0001 | 2·61 (1·26–5·38) p=0·0096 | 1·48 (0·36–6·06) p=0·59 | 0·31 (0·04–2·27) p=0·25 | 6·88 (3·82–12·37) p<0·0001 | 1·17 (0·42–3·25) p=0·76 | 6·68 (2·11–21·13) p=0·0012 | 3·19 (1·43–7·09) p=0·0045 | 1·18 (0·37–3·79) p=0·78 | |

| | Cardiac | Cutaneous | Endocrine | Gastrointestinal | Haematological | Hepatic | Musculoskeletal | Neurological | Ocular | Renal | Respiratory | Rheumatological |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cardiac | | 22 | 39 | 22 | 13 | 34 | 27 | 37 | 2 | 24 | 26 | 0 |
| Cutaneous | 22 | | 269 | 179 | 58 | 126 | 178 | 145 | 37 | 98 | 104 | 12 |
| Endocrine | 39 | 269 | | 267 | 89 | 191 | 256 | 217 | 27 | 145 | 131 | 17 |
| Gastrointestinal | 22 | 179 | 267 | | 66 | 153 | 182 | 130 | 30 | 120 | 75 | 9 |
| Haematological | 13 | 58 | 89 | 66 | | 58 | 53 | 68 | 12 | 69 | 47 | 2 |
| Hepatic | 34 | 126 | 191 | 153 | 58 | | 137 | 108 | 20 | 76 | 77 | 1 |
| Musculoskeletal | 27 | 178 | 256 | 182 | 53 | 137 | | 139 | 24 | 77 | 96 | 18 |
| Neurological | 37 | 145 | 217 | 130 | 68 | 108 | 139 | | 18 | 90 | 114 | 4 |
| Ocular | 2 | 37 | 27 | 30 | 12 | 20 | 24 | 18 | | 15 | 9 | 3 |
| Renal | 24 | 98 | 145 | 120 | 69 | 76 | 77 | 90 | 15 | | 92 | 7 |
| Respiratory | 26 | 104 | 131 | 75 | 47 | 77 | 96 | 114 | 9 | 92 | | 3 |
| Rheumatological | 0 | 12 | 17 | 9 | 2 | 1 | 18 | 4 | 3 | 7 | 3 | |

(Figure 1 continues on next page)

C

| | Cardiac | Cutaneous | Endocrine | Gastrointestinal | Haematological | Hepatic | Musculoskeletal | Neurological | Ocular | Renal | Respiratory | Rheumatological |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cardiac | | 3·41 (2·56–4·56) p<0·0001 | 3·33 (2·56–4·33) p<0·0001 | 2·36 (1·66–3·35) p<0·0001 | 4·12 (2·79–6·08) p<0·0001 | 6·32 (4·74–8·42) p<0·0001 | 3·90 (2·92–5·21) p<0·0001 | 4·65 (3·46–6·26) p<0·0001 | 5·32 (2·80–10·10) p<0·0001 | 4·81 (3·48–6·64) p<0·0001 | 6·57 (4·92–8·77) p<0·0001 | 5·47 (1·44–20·83) p=0·013 |
| Cutaneous | 2·96 (2·34–3·74) p<0·0001 | | 3·56 (3·21–3·94) p<0·0001 | 4·00 (3·57–4·48) p<0·0001 | 2·64 (2·20–3·18) p<0·0001 | 4·10 (3·61–4·65) p<0·0001 | 3·85 (3·44–4·31) p<0·0001 | 3·37 (2·96–3·83) p<0·0001 | 4·09 (3·13–5·36) p<0·0001 | 2·80 (2·40–3·28) p<0·0001 | 2·30 (1·94–2·73) p<0·0001 | 4·01 (2·25–7·16) p<0·0001 |
| Endocrine | 2·69 (2·22–3·26) p<0·0001 | 3·23 (2·95–3·53) p<0·0001 | | 3·24 (2·94–3·56) p<0·0001 | 2·35 (2·02–2·75) p<0·0001 | 3·29 (2·95–3·66) p<0·0001 | 3·33 (3·04–3·65) p<0·0001 | 2·87 (2·58–3·20) p<0·0001 | 2·60 (1·97–3·43) p<0·0001 | 2·84 (2·52–3·20) p<0·0001 | 2·62 (2·32–2·97) p<0·0001 | 3·39 (2·08–5·52) p<0·0001 |
| Gastrointestinal | 2·21 (1·62–3·02) p<0·0001 | 4·19 (3·72–4·73) p<0·0001 | 3·72 (3·31–4·17) p<0·0001 | | 3·23 (2·68–3·91) p<0·0001 | 3·87 (3·34–4·49) p<0·0001 | 3·95 (3·48–4·49) p<0·0001 | 3·63 (3·15–4·18) p<0·0001 | 4·52 (3·37–6·05) p<0·0001 | 4·23 (3·66–4·90) p<0·0001 | 2·84 (2·39–3·38) p<0·0001 | 3·08 (1·40–6·78) p=0·0053 |
| Haematological | 3·95 (2·74–5·71) p<0·0001 | 2·90 (2·34–3·59) p<0·0001 | 2·71 (2·23–3·29) p<0·0001 | 3·53 (2·85–4·37) p<0·0001 | | 4·16 (3·31–5·24) p<0·0001 | 2·78 (2·22–3·49) p<0·0001 | 4·55 (3·69–5·61) p<0·0001 | 3·89 (2·31–6·55) p<0·0001 | 6·11 (4·97–7·50) p<0·0001 | 3·64 (2·84–4·67) p<0·0001 | 1·39 (0·20–9·51) p=0·74 |
| Hepatic | 5·49 (4·31–6·99) p<0·0001 | 4·64 (4·00–5·38) p<0·0001 | 4·04 (3·50–4·65) p<0·0001 | 4·13 (3·52–4·85) p<0·0001 | 3·97 (3·20–4·94) p<0·0001 | | 3·93 (3·35–4·61) p<0·0001 | 3·54 (2·95–4·24) p<0·0001 | 3·73 (2·45–5·67) p<0·0001 | 3·40 (2·77–4·16) p<0·0001 | 2·93 (2·36–3·63) p<0·0001 | 0·91 (0·13–6·23) p=0·92 |
| Musculoskeletal | 3·37 (2·66–4·26) p<0·0001 | 3·96 (3·52–4·45) p<0·0001 | 3·79 (3·40–4·23) p<0·0001 | 3·89 (3·44–4·40) p<0·0001 | 2·59 (2·12–3·17) p<0·0001 | 3·64 (3·15–4·21) p<0·0001 | | 3·99 (3·51–4·55) p<0·0001 | 3·15 (2·23–4·45) p<0·0001 | 2·94 (2·50–3·47) p<0·0001 | 2·57 (2·16–3·06) p<0·0001 | 7·41 (5·03–10·93) p<0·0001 |
| Neurological | 4·08 (3·18–5·25) p<0·0001 | 3·60 (3·13–4·15) p<0·0001 | 3·30 (2·90–3·77) p<0·0001 | 3·74 (3·23–4·34) p<0·0001 | 4·18 (3·47–5·05) p<0·0001 | 3·45 (2·90–4·11) p<0·0001 | 4·22 (3·67–4·84) p<0·0001 | | 4·84 (3·52–6·65) p<0·0001 | 4·03 (3·40–4·76) p<0·0001 | 3·33 (2·78–3·99) p<0·0001 | 5·24 (2·77–9·90) p<0·0001 |
| Ocular | 5·50 (2·82–10·72) p<0·0001 | 5·36 (3·67–7·82) p<0·0001 | 3·22 (2·19–4·73) p<0·0001 | 5·71 (3·87–8·45) p<0·0001 | 4·15 (2·35–7·32) p<0·0001 | 4·14 (2·55–6·72) p<0·0001 | 3·67 (2·39–5·64) p<0·0001 | 5·92 (3·94–8·88) p<0·0001 | | 2·91 (1·65–5·14) p=0·0002 | 2·13 (1·12–4·06) p=0·021 | NA |
| Renal | 4·39 (3·29–5·84) p<0·0001 | 3·03 (2·54–3·61) p<0·0001 | 3·36 (2·88–3·92) p<0·0001 | 4·61 (3·92–5·42) p<0·0001 | 5·76 (4·76–6·99) p<0·0001 | 3·42 (2·79–4·21) p<0·0001 | 3·13 (2·62–3·75) p<0·0001 | 4·20 (3·51–5·01) p<0·0001 | 2·74 (1·63–4·60) p=0·0001 | | 4·82 (4·01–5·78) p<0·0001 | 5·95 (2·94–12·05) p<0·0001 |
| Respiratory | 5·74 (4·49–7·33) p<0·0001 | 2·43 (2·02–2·93) p<0·0001 | 3·04 (2·60–3·55) p<0·0001 | 2·98 (2·47–3·59) p<0·0001 | 3·53 (2·78–4·47) p<0·0001 | 2·94 (2·37–3·65) p<0·0001 | 2·70 (2·24–3·26) p<0·0001 | 3·43 (2·84–4·15) p<0·0001 | 2·06 (1·13–3·74) p=0·018 | 4·80 (4·00–5·76) p<0·0001 | | 1·93 (0·51–7·34) p=0·33 |
| Rheumatological | 5·81 (1·38–24·44) p=0·016 | 5·33 (2·32–12·23) p<0·0001 | 4·86 (2·21–10·70) p<0·0001 | 3·56 (1·35–9·43) p=0·011 | 1·40 (0·19–10·34) p=0·74 | 0·91 (0·12–6·69) p=0·92 | 13·69 (6·36–29·48) p<0·0001 | 6·76 (2·85–16·03) p<0·0001 | NA | 7·38 (2·97–18·33) p<0·0001 | 2·01 (0·48–8·49) p=0·34 | |

Risk ratio: 0, 2, 4, 6, 8, 10, 12

D

| | Cardiac | Cutaneous | Endocrine | Gastrointestinal | Haematological | Hepatic | Musculoskeletal | Neurological | Ocular | Renal | Respiratory | Rheumatological |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cardiac | | 57 | 77 | 35 | 27 | 56 | 57 | 52 | 9 | 42 | 55 | 2 |
| Cutaneous | 57 | | 439 | 295 | 98 | 214 | 307 | 217 | 38 | 143 | 122 | 8 |
| Endocrine | 77 | 439 | | 368 | 130 | 262 | 405 | 280 | 36 | 214 | 203 | 10 |
| Gastrointestinal | 35 | 295 | 368 | | 96 | 166 | 255 | 188 | 34 | 167 | 120 | 5 |
| Haematological | 27 | 98 | 130 | 96 | | 78 | 85 | 100 | 13 | 100 | 66 | 1 |
| Hepatic | 56 | 214 | 262 | 166 | 78 | | 171 | 124 | 19 | 93 | 83 | 1 |
| Musculoskeletal | 57 | 307 | 405 | 255 | 85 | 171 | | 221 | 26 | 132 | 119 | 13 |
| Neurological | 52 | 217 | 280 | 188 | 100 | 124 | 221 | | 30 | 132 | 114 | 7 |
| Ocular | 9 | 38 | 36 | 34 | 13 | 19 | 26 | 30 | | 13 | 10 | 0 |
| Renal | 42 | 143 | 214 | 167 | 100 | 93 | 132 | 132 | 13 | | 118 | 6 |
| Respiratory | 55 | 122 | 203 | 120 | 66 | 83 | 119 | 114 | 10 | 118 | | 2 |
| Rheumatological | 2 | 8 | 10 | 5 | 1 | 1 | 13 | 7 | 0 | 6 | 2 | |

Number of patients with co-occurring events: 0, 100, 200, 300, 400

demographic and clinical characteristics (sex, Charlson comorbidity index, cancer type, cancer stage, previous treatment, duration of immune checkpoint inhibitor therapy, year of immune checkpoint inhibitor initiation, mortality status, and follow-up duration; table 1), the baseline characteristics of the MGBD cohort were largely consistent with those from the TriNetX cohort.

Concordance results between the computational method and the manual chart review in the MGBD cohort for identifying immune-related adverse events are in the appendix (p 27). For patient-level results, among the 100 randomly sampled patients with computational immune-related adverse events, five patients had no immune-related adverse events; among the 100 randomly sampled patients with no computational immune-related adverse events, 17 patients had immune-related adverse events, leading to a concordance of 89% (178 of 200 patients) and Kappa statistic of 0·78 (95% CI 0·64–0·92). For event-level results, among the 100 randomly sampled patients with computational immune-related adverse events, we identified 381 immune-related adverse events of which 322 were clinically meaningful (grade 2 or worse). Of these 322, 250 were true positives and 54 were false positives, resulting in a concordance of 78% (250 of 322 events) and a positive predictive value of 82% (250 of 304 events). Details of false-positive and false-negative events are in the appendix (pp 28–29).

We applied the immune-related adverse event identification rules for the matched MGBD and TriNetX cohorts. From the two cohorts, 4382 patients and 8010 patients were excluded, respectively, because their suspected immune-related adverse events were diagnosed within 3 months after chemotherapy (appendix p 24). After identifying immune-related adverse events, 8704 patients were retained from MGBD, of whom 3284 (37·7%) had and 5420 (62·3%) did not have immune-related adverse events, and 18 162 patients were retained from TriNetX, of whom 5538 (30·5%) had and 12 624 (69·5%) did not have immune-related adverse events.

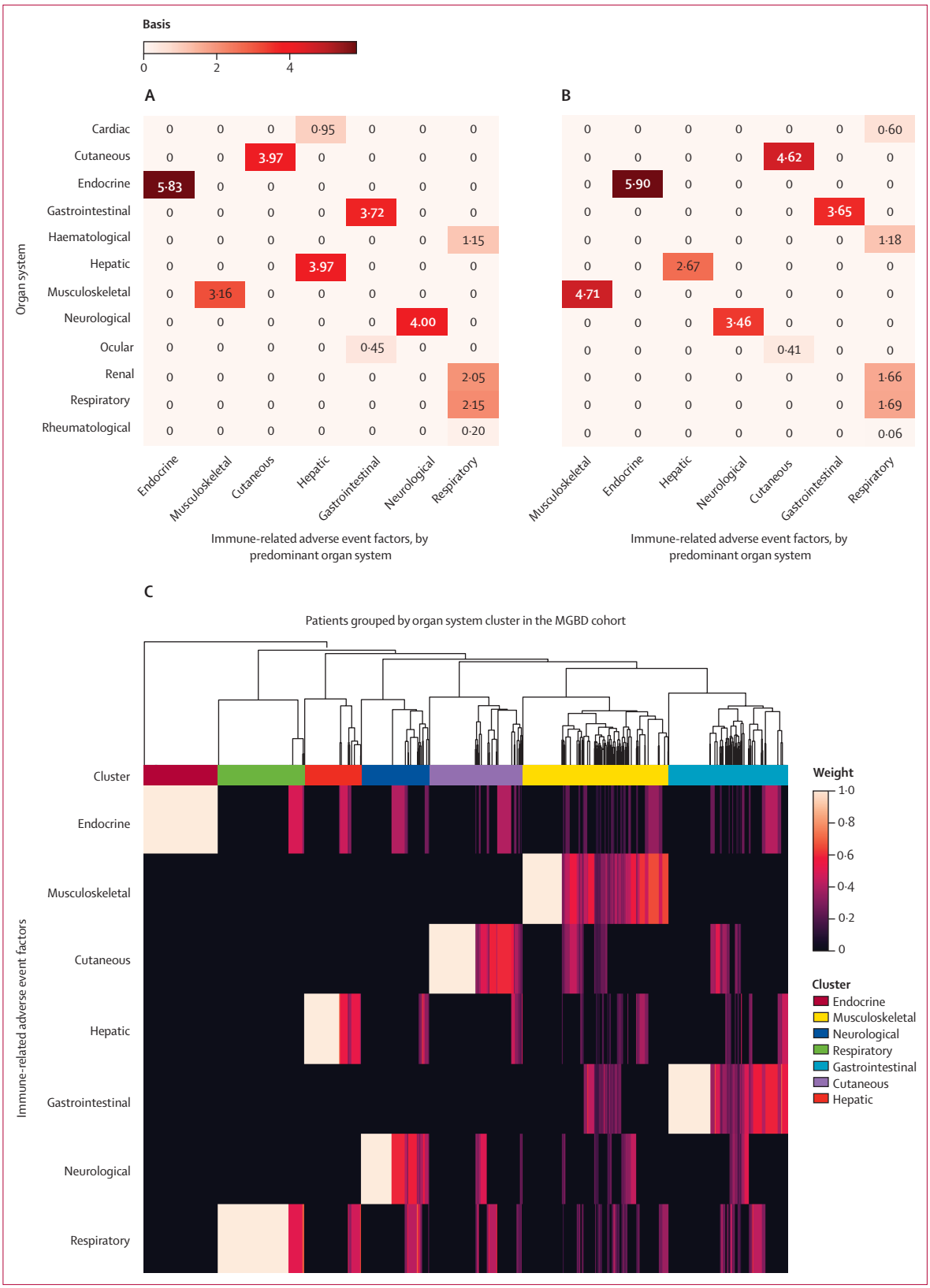
The immune-related adverse events identified in each organ system are shown in table 2. The distribution of immune-related adverse events was generally consistent between the two cohorts. Endocrine immune-related adverse events were the most common in both cohorts, followed by cutaneous events (table 2). Patient characteristics stratified by occurrence of immune-related adverse events are in the appendix (pp 30–33) as well as the pairwise association between immune-related adverse events and cancer organ systems (pp 34–35). For some cancers (thoracic, genitourinary, lymphoid or haematopoietic, non-melanoma skin cancer, and brain, nervous, or eye), the immune-related adverse event organ system was strongly associated with cancer occurring in that same organ system for both cohorts. This association was unclear in melanoma, which seemed to increase the risk of immune-related adverse events in several organ systems, including the skin.

We observed grade 2 or worse immune-related adverse events in 322 (84·5%) of 381 events that occurred in the 100 randomly selected patients with computational immune-related adverse events from the MGBD cohort who were manually chart reviewed. We further estimated the presence of more severe immune-related adverse events using the use of systemic immunosuppressive therapy in the 1049 patient convenience subset (appendix pp 17, 48) and interruption of immune checkpoint inhibitor therapy in the MGBD and TriNetX cohorts (appendix p 55) as proxies for the development of these severe events, which affected a minority of patients. Overall, these results suggest that the modal immune-related adverse event severity in our study was grade 2.

The proportion of patients with immune-related adverse events involving only one organ system or multiple organ systems is shown in the appendix (p 36). Pairwise co-occurrence patterns are shown in figure 1. We observed that pairwise correlations of immune-related adverse events in different organ systems were common for both cohorts. For example, of 817 patients with endocrine immune-related adverse events co-occurring with other organ systems (appendix p 36), 269 (33%) also had cutaneous, 267 (33%) also had gastrointestinal, and 256 (31%) also had musculoskeletal immune-related adverse events (figure 1B). Similar patterns were observed in TriNetX (figure 1D). Cutaneous, endocrine, gastrointestinal, musculoskeletal, and renal immune-related adverse events had significant co-occurrence with all other immune-related adverse event organs evaluated in both cohorts (figure 1A, C). Moreover, in both cohorts, ocular immune-related adverse events commonly co-occurred with cutaneous and gastrointestinal immune-related adverse events (figure 1A, C). Rheumatological immune-related adverse events commonly co-occurred with musculoskeletal immune-related adverse events (figure 1A, C).

***Figure 1:*** **Pairwise co-occurrence patterns of immune-related adverse events in multiple organs**

Adjusted risk ratios and number of patients who developed co-occurring immune-related adverse events in the MGBD (A, B) cohort and TriNetX (C, D) cohort, respectively. NA (not applicable) indicates that no patients developed immune-related adverse events affecting the two specific organ systems (eg, immune-related adverse events affecting ocular and rheumatological organs in the TriNetX cohort). Adjusted risk ratios are presented with 95% CIs in parentheses and p values. Each risk ratio, along with the corresponding 95% CI and p value, was calculated by fitting a Poisson regression model with the row event as the dependent variable and the column event as the independent variable, adjusted by the sandwich method. The risk ratios and 95% CIs (A, C) differ depending on whether the pairwise events are read horizontally or vertically, because the dependent and independent variables were switched in the model. The summation of the numbers in a row for an organ can exceed the total number of patients with immune-related adverse events affecting that organ and other organ systems. The total number of patients with multi-organ immune-related adverse events is presented in the appendix (p 36). MGBD=Massachusetts General Hospital, Brigham and Women's Hospital, Dana-Farber Cancer Institute.




(Figure 2 continues on next page)

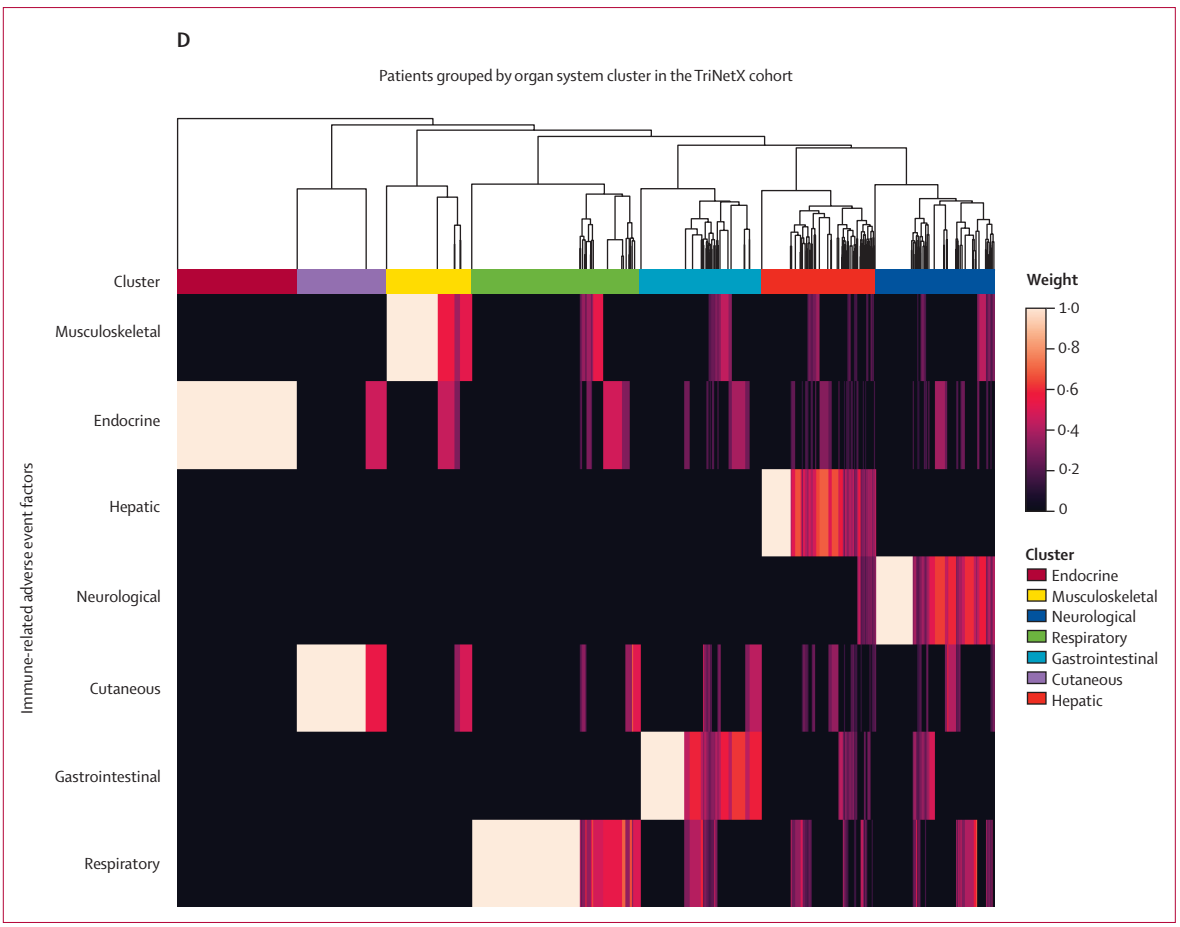
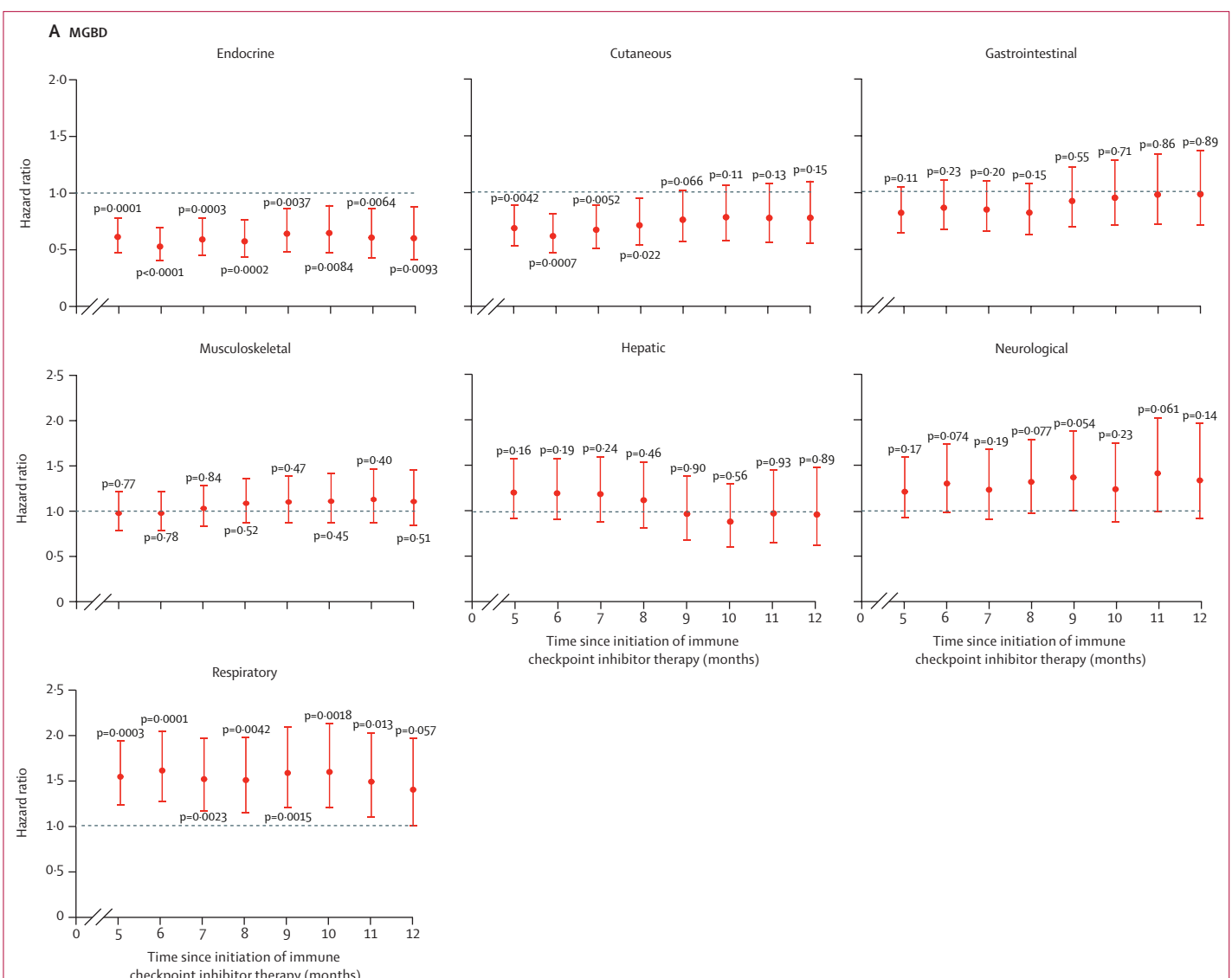



***Figure 2:*** **Co-occurrence patterns using NMF and hierarchical clustering in the MGBD (A, C) and TriNetX (B, D) cohorts**
The two basis matrices for the MGBD (A) and TriNetX (B) cohorts are shown, in which the rows correspond to organ systems, and columns correspond to immune-related adverse event factors, each named by the predominant organ system (eg, the endocrine factor represents the factor predominated by endocrine immune-related adverse events). The two weight matrices for the MGBD (C) and TriNetX (D) cohorts are shown, presenting how patients were clustered with each weight matrix. Patients are represented by columns, and patients from both cohorts were grouped into seven clusters, each predominantly characterised by a single factor. Each cluster was named by the dominant factor (eg, the leftmost cluster on parts C and D was dominated by the endocrine factor that comprised endocrine organ events and, thus, named as the endocrine cluster). MGBD=Massachusetts General Hospital, Brigham and Women's Hospital, Dana-Farber Cancer Institute. NMF=non-negative matrix factorisation.

We adopted NMF and hierarchical clustering to comprehensively assess patterns of all organ-level occurrences of immune-related adverse events, from those affecting a single organ to those involving two or more organs (figure 2). Figures 2A and 2B present the two basis matrices computed using NMF, showing that the presence of immune-related adverse events within 2 years of immune checkpoint inhibitor therapy initiation for each patient could be described by a weighted combination of seven immune-related adverse event factors. These factors were dominated by endocrine, cutaneous, musculoskeletal, hepatic, gastrointestinal, neurological, and respiratory immune-related adverse events. To facilitate interpretation, we named each factor by the predominant organ system in that factor, while the factor should be viewed as a combination of immune-related adverse events in multiple organs if there were more than one non-zero values for the factor. For example, in the MGBD cohort, the respiratory factor comprised respiratory, renal, haematological, and rheumatological immune-related adverse events, whereas the endocrine factor solely comprised endocrine immune-related adverse events (figure 2A). We observed that the respiratory factor was the most complex factor, encompassing immune-related adverse events in more than three organ systems in both cohorts (figure 2A, B). The weights of immune-related adverse event factors in each patient are shown in figure 2C, D. The dendrograms of figure 2C, D show that patients with immune-related adverse events could be categorised into seven clusters, which yielded suitable cluster sizes. These clusters were named according to the predominant immune-related adverse event factors within them. From a clinical perspective, if a patient were to present with a constellation of immune-related adverse events that they have developed to date (eg, within 6 months of initiation of

immune checkpoint inhibitor therapy), this constellation can be mapped onto the NMF and hierarchical clustering diagram to determine the immune-related adverse event cluster this patient belongs to (appendix p 37).

The results of multivariable overall survival analyses by immune-related adverse event clusters at various landmark times are shown in figure 3. For our primary analysis using a 6-month landmark time (table 3), the endocrine cluster and the cutaneous cluster showed favourable survival outcomes across both cohorts by comparison with patients without immune-related adverse events (table 3). The respiratory cluster and the neurological cluster exhibited worse (ie, unfavourable) survival outcomes, although the unfavourable effect of the neurological cluster was only significant in the TriNetX cohort and was not significant in the MGBD cohort. Other clusters did not show differences in survival by comparison to those without immune-related adverse events (ie, neutral survival outcomes). Then we grouped both of the two favourable clusters, the two clusters with a tendency toward unfavourable outcomes, and other neutral clusters for subsequent analyses (appendix p 38). Cox modelling assumptions held for all models, except for a slight violation in the cutaneous cluster model in the TriNetX cohort (appendix p 39). The minimum sample size required for each analysis (appendix p 39) and the reasonably narrow 95% CIs (figure 3) indicated that our models were adequately powered. Additional details of the models and Cox assumption tests for the two clusters with favourable survival outcomes in both cohorts are in the appendix (pp 40–44).




(Figure 3 continues on next page)

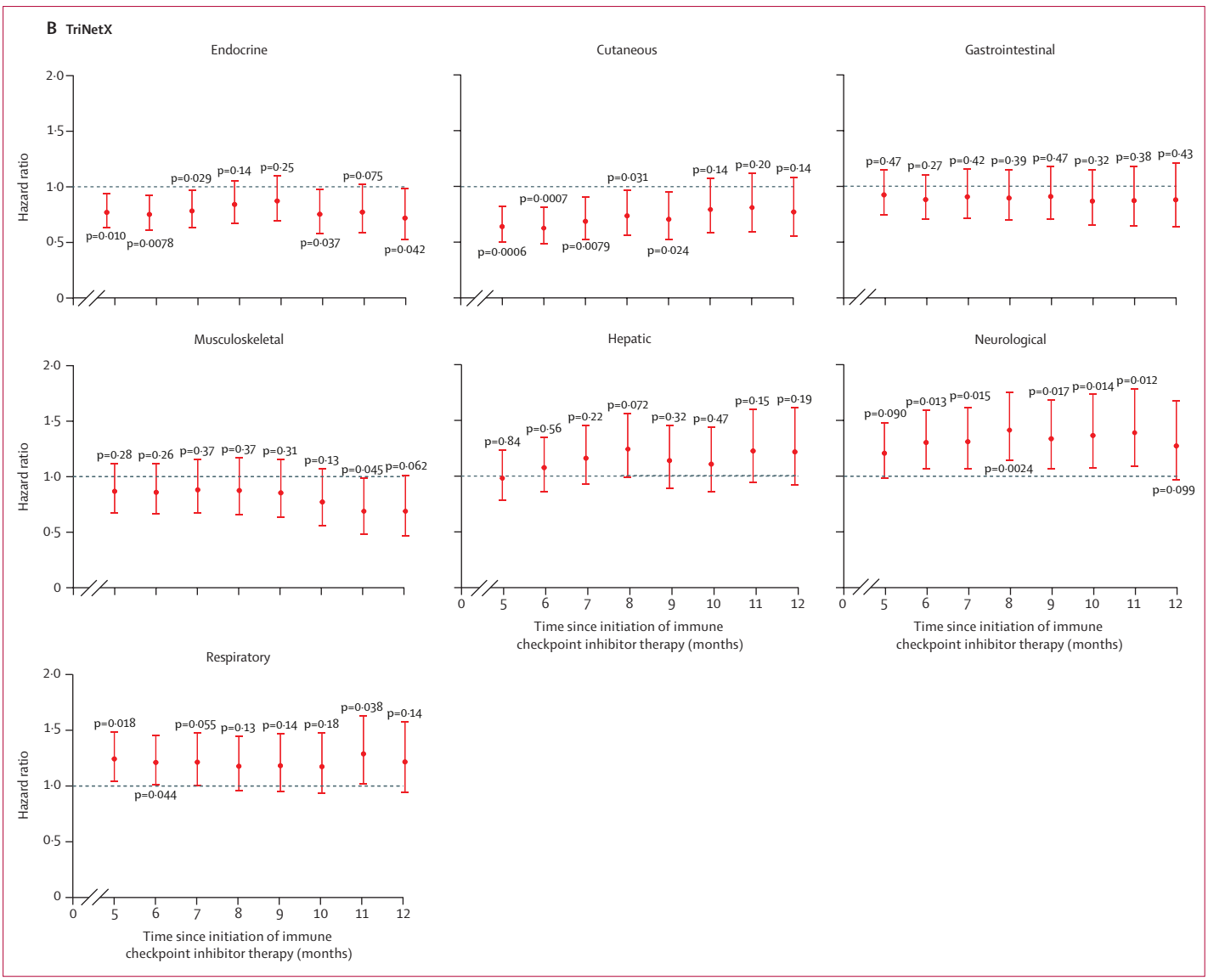



***Figure 3:*** **Landmark overall survival outcomes of patient clusters defined by immune-related adverse event profiles from the MGBD (A) and TriNetX (B) cohorts**
Data are hazard ratios, with error bars showing 95% CIs and p values either above to below each error bar. Separate multivariable Cox proportional hazards models (adjusted for sex, race, ethnicity, age at initiation of immune checkpoint inhibitor therapy, Charlson comorbidity index, cancer type, cancer stage, non-immune checkpoint inhibitor treatment, immune checkpoint inhibitor type, and interruption of immune checkpoint inhibitor therapy) were used at different landmark times. In each analysis, the reference group corresponded to patients who did not have an immune-related adverse event within the landmark time. The reference group was the same across analyses for different clusters at a specific landmark time. MGBD=Massachusetts General Hospital, Brigham and Women's Hospital, Dana-Farber Cancer Institute.

In both cohorts, by comparison with patients without immune-related adverse events, the favourable outcome group consistently showed improved overall survival (appendix p 45), and the unfavourable group exhibited worse prognoses across various landmark timepoints (appendix p 46).

To evaluate the contribution of systemic immunosuppressive therapy to our findings, we manually extracted systemic immunosuppressive therapy data for 1049 recipients of immune checkpoint inhibitors from the MGBD cohort, of whom 713 (68%) remained alive at the 6-month landmark time (appendix p 47). We found that 56 (18%) of 314 patients without immune-related adverse events used systemic immunosuppressive therapy after initiation of immune checkpoint inhibitors, whereas 178 (45%) of 399 patients with immune-related adverse events did so (appendix p 48). The use of systemic immunosuppressive therapy after initiation of immune checkpoint inhibitors significantly differed among the immune-related adverse event clusters, ranging from 11 (21%) of 52 in the endocrine cluster to 59 (66%) of 90 in the gastrointestinal cluster. Overall, endocrine, neurological, and cutaneous clusters had the lowest use of systemic immunosuppression, whereas the

| | Hazard ratio (95% CI) | p value |
|---|---|---|
| **MGBD cohort clusters** | | |
| Endocrine | 0·53 (0·40–0·70) | <0·0001 |
| Cutaneous | 0·61 (0·46–0·81) | 0·0007 |
| Gastrointestinal | 0·86 (0·67–1·10) | 0·23 |
| Musculoskeletal | 0·97 (0·78–1·21) | 0·78 |
| Hepatic | 1·20 (0·91–1·59) | 0·19 |
| Neurological | 1·30 (0·97–1·74) | 0·074 |
| Respiratory | 1·60 (1·25–2·03) | 0·0001 |
| **TriNetX cohort clusters** | | |
| Endocrine | 0·75 (0·60–0·93) | 0·0078 |
| Cutaneous | 0·62 (0·48–0·82) | 0·0007 |
| Gastrointestinal | 0·88 (0·70–1·11) | 0·27 |
| Musculoskeletal | 0·86 (0·66–1·12) | 0·26 |
| Hepatic | 1·07 (0·85–1·35) | 0·56 |
| Neurological | 1·30 (1·06–1·59) | 0·013 |
| Respiratory | 1·21 (1·00–1·46) | 0·044 |

Hazard ratios and corresponding p values were calculated using multivariable Cox proportional hazards models adjusted for age at initiation of immune checkpoint inhibitor therapy, sex, race, ethnicity, cancer type, cancer stage, Charlson comorbidity index, non-immune checkpoint inhibitor treatment, immune checkpoint inhibitor type, and interruption of immune checkpoint inhibitor therapy (definitions are in the appendix [pp 4–5]). For all models, the reference group was the group of patients within that cohort without any immune-related adverse events by the landmark time (6 months). Cox modelling assumptions held for all models, except for a slight violation in the model of the cutaneous cluster for the TriNetX cohort (appendix p 39). MGBD=Massachusetts General Hospital, Brigham and Women's Hospital, and Dana-Farber Cancer Institute. *Each patient cluster was named for the predominant immune-related adverse event factor.

***Table 3:*** **Overall survival outcomes of patient clusters* at the 6-month landmark time**

gastrointestinal and musculoskeletal clusters had the highest use.

In multivariable models adjusting for the computationally extracted systemic immunosuppressive therapy variable (appendix p 49), inpatient systemic glucocorticoid therapy (which was the predominant form of systemic immunosuppression used in this population; appendix p 47) was unfavourably associated with overall survival (appendix pp 50–53). The survival results among different groups remained largely consistent between models without and with adjustment for systemic immunosuppressive therapy (appendix pp 46, 54). Specifically, at the 6-month landmark time, the overall survival association of the favourable group remained significant (MGBD: HR 0·56 [95% CI 0·46–0·69; p<0·0001]; TriNetX: 0·67 [0·56–0·80; p<0·0001]), and the survival association of the unfavourable group became slightly less pronounced but remained significant (MGBD: 1·38 [1·14–1·68; p=0·0012]; TriNetX: 1·16 [1·00–1·34; p=0·048]) after incorporating systemic immunosuppressive therapy as a covariate.

Regarding the time to first immune-related adverse event, despite observed differences among the clusters, the median time to onset of first immune-related adverse event was less than 3 months for all clusters (appendix p 55), with most immune-related adverse events occurring within 6 months after initiation of immune checkpoint inhibitor therapy (appendix pp 30–33). The interruption of immune checkpoint inhibitor therapy, stratified by immune-related adverse event cluster, is presented in the appendix (p 55). In subgroup analyses for individual cancer or immune checkpoint inhibitor type, the favourable survival group consistently had improved overall survival across melanoma, thoracic cancer, and all other cancers (analyses were not performed for all individual cancer categories because the sample sizes were too small in most individual groups to provide sufficient statistical power; appendix p 56) and across anti-PD-1, combination, and all other immune checkpoint inhibitor types (appendix p 57), although the result for the combination therapy group in the MGBD cohort was not significant (p=0·083). NMF and hierarchical clustering results among patients treated with combination therapy, where similar co-occurrence patterns were observed, are shown in the appendix (post-hoc analysis; p 58).

## Discussion

In this retrospective study, we used a multi-institutional cohort from three high-volume academic medical centres and an independent US population-level cohort to investigate co-occurrence patterns of multi-organ immune-related adverse events in patients treated with immune checkpoint inhibitors and their effect on overall survival. Our approach comprehensively evaluated patterns of occurrence of immune-related adverse events, from those affecting single organs to those involving two or more organs. We identified seven patient clusters demonstrating different development patterns of immune-related adverse events and found that, in comparison with patients without immune-related adverse events, patient clusters dominated by endocrine and cutaneous immune-related adverse events were associated with improved survival, while those dominated by respiratory and neurological immune-related adverse events were associated with worse survival outcomes. Our analyses reached similar conclusions across both cohorts, demonstrating their robustness.

These findings validate previous studies identifying improved overall survival among recipients of immune checkpoint inhibitors who experience cutaneous[7,8,19] and endocrine immune-related adverse events.[20] Wan and colleagues have reported that cutaneous immune-related adverse events are most prognostically favourable among recipients of immune checkpoint inhibitors treated for cutaneous squamous cell carcinoma and melanoma.[19] Additionally, two other studies have demonstrated improved overall survival among patients with vitiligo and non-vitiligo cutaneous immune-related adverse events within melanoma and all cancer settings.[7,8] Our findings of improved overall survival in the

cutaneous-predominant immune-related adverse event cluster are consistent with these findings. Furthermore, a 2019 abstract reporting a meta-analysis showed that the development of endocrine immune-related adverse events is associated with improved overall survival in the setting of lung and head and neck cancers, which is also consistent with our findings.[20] However, the differences between immune-related adverse event clusters and survival observed in our study add to the existing literature on multi-organ toxicities,[4–6] which largely reported favourable prognostic associations. We identified that some clusters are prognostically favourable, while others have neutral or potentially harmful effects on survival outcomes. Notably, although valuable in prognosticating overall survival outcomes, these results do not reflect the quality of life burden associated with the development of these toxicities. The reasons our findings might have differed from those of previous studies include the large sample size, increased analytical granularity, and more generalisable populations in our analyses.[5,6,14] Taken together, these results emphasise the clinical importance of identifying co-occurrence patterns of immune-related adverse events and specifically monitoring, diagnosing, and managing cutaneous and endocrine immune-related adverse events, given their correlation with valuable prognostic benefits and potential as biomarkers for immune checkpoint inhibitor therapeutic response.[21] Conversely, identification of patients in unfavourable clusters can be equally valuable. Specifically, this strategy can avoid overtreating patients who are not benefiting from immune checkpoint inhibitor therapy and are therefore only likely to experience the detrimental effect of these adverse events on their quality of life, potentially avoid death due to the adverse events themselves through early identification of susceptible patients, and facilitate earlier consideration of alternative therapeutic regimens.

The improved overall survival among the favourable immune-related adverse event clusters could be partially related to lower use of systemic immunosuppressive therapy after immune checkpoint inhibitor treatment in the endocrine-predominant and cutaneous-predominant clusters than in some other clusters. However, the effect of systemic immunosuppressive therapy on immune checkpoint inhibitor outcomes remains uncertain,[22] with some studies suggesting that these agents contribute to worse survival through blunting the anti-tumour effect of immune checkpoint inhibitors,[23] while others have either not found an association[24] or identified a favourable association postulated to be due to improved efficacy of the immune checkpoint inhibitor through minimising immunotherapy interruption or disruption by rapidly mitigating immune-related adverse events.[25] Our results show that, despite a high frequency of use of systemic immunosuppressive therapy among all clusters, some clusters were associated with improved survival whereas others had similar or slightly worse survival than immune checkpoint inhibitor recipients without immune-related adverse events. This finding suggests that use of systemic immunosuppressive therapy alone does not explain the observed mortality differences between immune-related adverse event clusters in our study. This hypothesis was supported by comparison of the results of our models with and without explicitly adjusting for systemic immunosuppression in multivariable survival analyses, demonstrating that although use of systemic immunosuppressive therapy was independently associated with worse survival, incorporating this variable did not meaningfully alter the associations between individual immune-related adverse event clusters and overall survival. Overall, these findings suggest that other organ-specific mechanisms might be responsible for the observed prognostic differences among immune-related adverse event clusters, including the possibility that some adverse events might contribute directly to mortality.

Furthermore, in pairwise analyses, we observed that most immune-related adverse events tend to co-occur. Notably, ocular immune-related adverse events consistently co-occurred with cutaneous and gastrointestinal immune-related adverse events, a pattern that reflects the biological similarity of the ocular, cutaneous, and gastrointestinal mucosa.[26] Similarly, rheumatological immune-related adverse events co-occurred with musculoskeletal immune-related adverse events, which is indicative of the high overlap between rheumatological and musculoskeletal diseases.[27] Given that endocrine and cutaneous immune-related adverse events are the most easily diagnosed, evaluating immune-related adverse events in other organs for patients with these events is crucial because these patients might benefit from increased early surveillance and targeted or prophylactic intervention.

The limitations of this study include its retrospective design and reliance on ICD codes to identify immune-related adverse events. This method resulted in the inclusion of non-specific diagnoses, such as generalised rash, and prevented direct assessment of severity of immune-related adverse events. Nevertheless, ICD codes have been shown to be valuable in identifying immune-related adverse events in population-level data and enabling urgently needed large-scale analyses of immune checkpoint inhibitor outcomes.[8,28,29] Furthermore, we applied stringent filtering criteria to enhance the specificity of identification of immune-related adverse events, prioritising the inclusion of the most clinically relevant events. We validated our computational immune-related adverse event identification on manually phenotyped events. Despite this rigorous manual validation, a minority of patients were misclassified as false positives or false negatives. Future related studies should also be validated by chart reviews. Additionally, although we mitigated immortal-time bias using landmark analyses, potential selection bias from estimating the correlation between immune-related adverse events

and survival is unavoidable.[30] Furthermore, although systemic glucocorticoids were the predominant immunosuppression agent in our cohorts, a few patients also received treatments with other immunosuppressive agents and were given these in addition to systemic glucocorticoids. As a result, their differential impact on survival could not be deconvoluted in our analyses. Additionally, this study was performed entirely on a US-based population, with a predominantly White cohort of patients. As such the generalisability of our findings to other patient populations might be somewhat limited. Finally, we could not evaluate the effect of LAG-3 inhibitors on our findings because the TriNetX population was followed up until 2021, which was before the approval of this class of immune checkpoint inhibitors. Despite these limitations, this study benefits from validation across two large independent cohorts, novel computational approaches, and a wide range of investigated features, enabling—to our knowledge—the most comprehensive examination of immune-related adverse event co-occurrence and outcomes to date.

#### Contributors

Study concept and design: GW, WC, SK, KR, and YRS. Data collection: SK, GW, WC, KR, NN, BY, HR. Data analysis and interpretation: GW, WC, SK, KR, LZ, MJH, SD, K-HY, WL, AG, NRL, KLR, SGK, and YRS. Drafting of the manuscript: GW, WC, SK, KR, AR, JS, and YRS. Administrative, technical, or material support: YRS. Study supervision: SGK and YRS. GW, WC, SK, and YRS directly accessed and verified the underlying data reported in the manuscript. All authors had access to all the summary data reported in the study. This manuscript was written by the lead investigators and was reviewed and approved for publication by all co-authors.

#### Declaration of interests

YRS is an advisory board member or consultant and has received honoraria from Pfizer, Incyte Corporation, Sanofi, Galderma, Castle Biosciences, and Iovance Biotherapeutics. K-HY has received consulting fees or honoraria from Curatio DL, Cedars-Sinai Medical Center, Mayo Clinic, Roswell Park Comprehensive Cancer Center, Harvard Medical School, Academia Sinica, Taipei Medical University, and Takeda. NRL is a consultant and has received honoraria from Bayer, Seattle Genetics, Sanofi, Silverback, and Synox Therapeutics. All other authors declare no competing interests.

#### Data sharing

All relevant data are available from the corresponding author: Yevgeniy R Semenov. All summary data supporting the findings of this study are available within the Article or its appendix. The patient data generated at Massachusetts General Hospital, Brigham and Women's Hospital, and Data-Farber Cancer Institute for this study can only be shared per specific institutional review board requirements. Upon a request to the corresponding author, a data-sharing agreement can be initiated following institution-specific guidelines. Patient data at the TriNetX network can be accessed following the TriNetX network guidelines.

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#### References

1 Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* 2019; **16:** 563–80.

2 Tang SQ, Tang LL, Mao YP, et al. The pattern of time to onset and resolution of immune-related adverse events caused by immune checkpoint inhibitors in cancer: a pooled analysis of 23 clinical trials and 8,436 patients. *Cancer Res Treat* 2021; **53:** 339–54.

3 Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol* 2021; **39:** 4073–126.

4 Shankar B, Zhang J, Naqash AR, et al. Multisystem immune-related adverse events associated with immune checkpoint inhibitors for treatment of non-small cell lung cancer. *JAMA Oncol* 2020; **6:** 1952–56.

5 Shimozaki K, Sukawa Y, Beppu N, et al. Multiple immune-related adverse events and anti-tumor efficacy: real-world data on various solid tumors. *Cancer Manag Res* 2020; **12:** 4585–93.

6 Kichenadasse G, Miners JO, Mangoni AA, Rowland A, Hopkins AM, Sorich MJ. Multiorgan immune-related adverse events during treatment with atezolizumab. *J Natl Compr Canc Netw* 2020; **18:** 1191–99.

7 Zhang S, Tang K, Wan G, et al. Cutaneous immune-related adverse events are associated with longer overall survival in advanced cancer patients on immune checkpoint inhibitors: a multi-institutional cohort study. *J Am Acad Dermatol* 2023; **88:** 1024–32.

8 Tang K, Seo J, Tiu BC, et al. Association of cutaneous immune-related adverse events with increased survival in patients treated with anti-programmed cell death 1 and anti-programmed cell death ligand 1 therapy. *JAMA Dermatol* 2022; **158:** 189–93.

9 Chieng JHL, Htet ZW, Zhao JJ, et al. Clinical presentation of immune-related endocrine adverse events during immune checkpoint inhibitor treatment. *Cancers (Basel)* 2022; **14:** 2687.

10 Washino S, Takeshita H, Inoue M, et al. Real-world incidence of immune-related adverse events associated with nivolumab plus ipilimumab in patients with advanced renal cell carcinoma: a retrospective observational study. *J Clin Med* 2021; **10:** 4767.

11 Thompson LL, Krasnow NA, Chang MS, et al. Patterns of cutaneous and noncutaneous immune-related adverse events among patients with advanced cancer. *JAMA Dermatol* 2021; **157:** 577–82.

12 Yamada K, Sawada T, Nakamura M, et al. Clinical characteristics of gastrointestinal immune-related adverse events of immune checkpoint inhibitors and their association with survival. *World J Gastroenterol* 2021; **27:** 7190–206.

13 Asdourian MS, Shah N, Jacoby TV, et al. Development of multiple cutaneous immune-related adverse events among cancer patients after immune checkpoint blockade. *J Am Acad Dermatol* 2023; **88:** 485–87.

14 Ricciuti B, Genova C, De Giglio A, et al. Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis. *J Cancer Res Clin Oncol* 2019; **145:** 479–85.

15 Xie X, Wang L, Li Y, et al. Multi-organ immune-related adverse event is a risk factor of immune checkpoint inhibitor-associated myocarditis in cancer patients: a multi-center study. *Front Immunol* 2022; **13:** 879900.

16 Yamaguchi A, Saito Y, Narumi K, et al. Association between skin immune-related adverse events (irAEs) and multisystem irAEs during PD-1/PD-L1 inhibitor monotherapy. *J Cancer Res Clin Oncol* 2023; **149:** 1659–66.

17 Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; **159:** 702–06.

18 Morgan CJ. Landmark analysis: a primer. *J Nucl Cardiol* 2019; **26:** 391–93.

19 Wan G, Khattab S, Leung BW, et al. Cancer type and histology influence cutaneous immunotherapy toxicities: a multi-institutional cohort study. *Br J Dermatol* 2024; published online Feb 15. https://doi.org/10.1093/bjd/ljae053.

20 Gomes-Lima CJ, Kwagyan J, King F, Fernandez SJ, Burman KD, Veytsman I. A comprehensive meta-analysis of endocrine immune-related adverse events of immune checkpoint inhibitors and outcomes in head and neck cancer and lung cancer. *Proc Am Soc Clin Oncol* 2019; **37** (suppl 15)**:** e14096 (abstr).

21 Rosellini M, Marchetti A, Mollica V, Rizzo A, Santoni M, Massari F. Prognostic and predictive biomarkers for immunotherapy in advanced renal cell carcinoma. *Nat Rev Urol* 2023; **20:** 133–57.

22 Goodman RS, Johnson DB, Balko JM. Corticosteroids and cancer immunotherapy. *Clin Cancer Res* 2023; **29:** 2580–87.

23 Faje AT, Lawrence D, Flaherty K, et al. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. *Cancer* 2018; **124:** 3706–14.

24 Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol* 2015; **33:** 3193–98.

25 Riudavets M, Mosquera J, Garcia-Campelo R, et al. Immune-related adverse events and corticosteroid use for cancer-related symptoms are associated with efficacy in patients with non-small cell lung cancer receiving anti-PD-(L)1 blockade agents. *Front Oncol* 2020; **10:** 1677.

26 de Paiva CS, St Leger AJ, Caspi RR. Mucosal immunology of the ocular surface. *Mucosal Immunol* 2022; **15:** 1143–57.

27 Szekanecz Z, McInnes IB, Schett G, Szamosi S, Benkő S, Szűcs G. Autoinflammation and autoimmunity across rheumatic and musculoskeletal diseases. *Nat Rev Rheumatol* 2021; **17:** 585–95.

28 Tiu BC, Zubiri L, Iheke J, et al. Real-world incidence and impact of pneumonitis in patients with lung cancer treated with immune checkpoint inhibitors: a multi-institutional cohort study. *J Immunother Cancer* 2022; **10:** e004670.

29 Kalinich M, Murphy W, Wongvibulsin S, et al. Prediction of severe immune-related adverse events requiring hospital admission in patients on immune checkpoint inhibitors: study of a population level insurance claims database from the USA. *J Immunother Cancer* 2021; **9:** e001935.

30 Hernán MA. The hazards of hazard ratios. *Epidemiology* 2010; **21:** 13–15.