Mortality and immune-related adverse events after immune checkpoint inhibitor initiation for cancer among patients with pre-existing rheumatoid arthritis: A retrospective comparative cohort study

Supplemental material:

Supplemental Table 16. Hazard ratios for mortality after immune checkpoint inhibitor initiation comparing RA cases and matched comparators among only seronegative RA cases and their comparators.

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Supplemental Table 19. Risk of all-grade irAE after immune checkpoint inhibitor initiation only among baseline glucocorticoids users (n=57) and their comparators.

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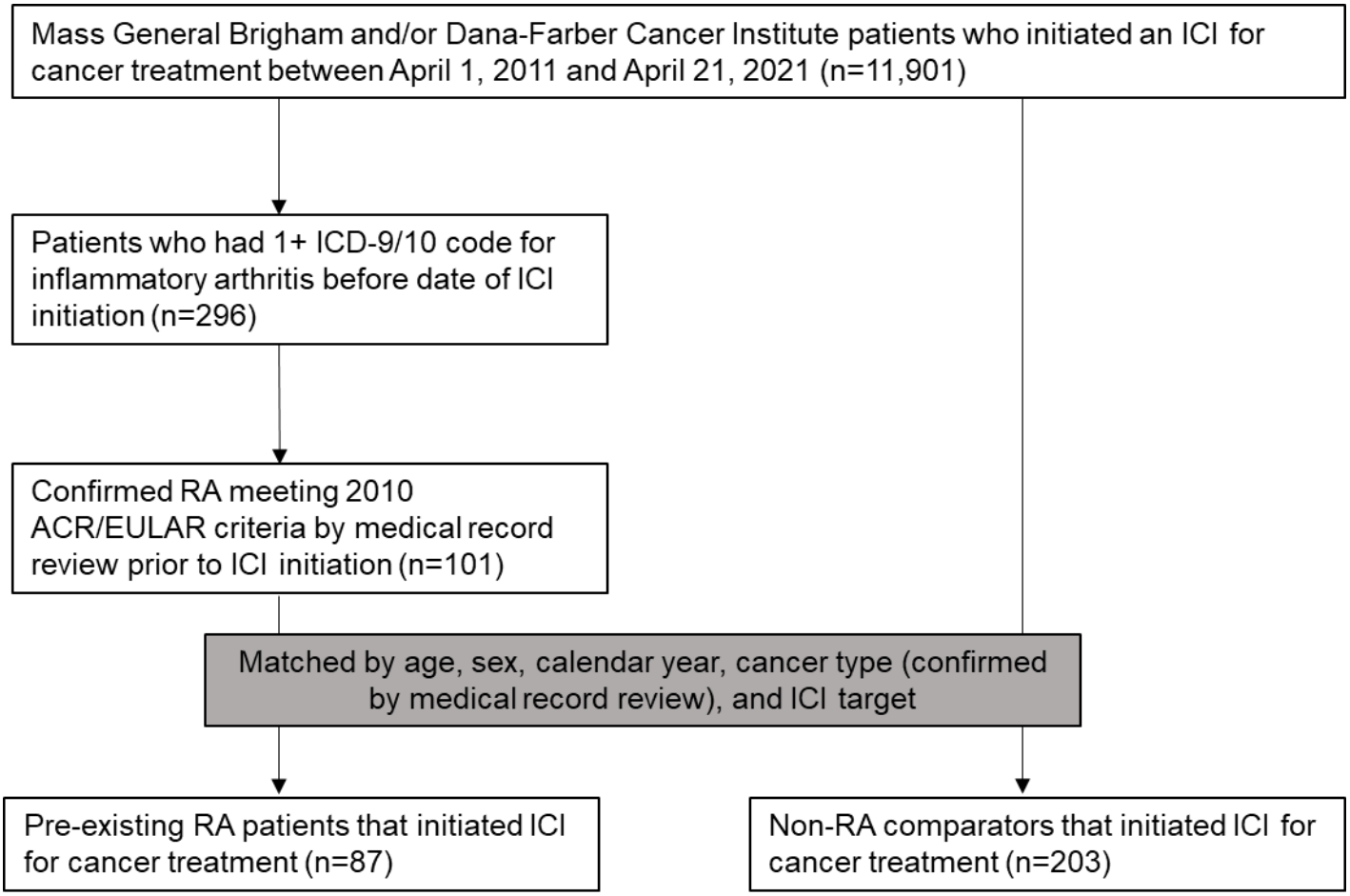
Supplemental Table 30. Risk of grade 3+ irAE after immune checkpoint inhibitor initiation excluding RA and flare and IA, only among females.

Supplemental Figure 1. Flow diagram of analyzed study sample.



Supplemental Table 1. ICD-9 and ICD-10 codes used to identify potential patients with pre-existing rheumatoid arthritis for cases (inflammatory arthritis category) and to exclude pre-existing rheumatic diseases from potential comparators (all categories).

Category	Rheumatic disease (ICD codes)
Inflammatory arthritis	● Rheumatoid arthritis M05% M06% 714% ● Inflammatory arthritis or inflammatory polyarthropathy M06.4 714.89 714.9 ● Juvenile idiopathic arthritis M08.20 714.3 ● Psoriatic arthritis or arthropathic psoriasis L40.50 696.0 ● Ankylosing spondylitis M45.9 720.0
Vasculitis	● ANCA-associated vasculitis: granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis M31.3 M31.7 M30.0 446.0 446.4 446.7 447.6 ● Kawasaki disease M30.3 446.1 ● Takayasu arteritis M31.4 446.7 ● Polyarteritis nodosa M30.0 446.0

	● Giant cell arteritis/polymyalgia rheumatica M31.6 446.5 M35.3 725% ● Behçet's disease M35.2 136.1 ● Unspecified arteritis I77.6 447.6
Other systemic rheumatic diseases	● Systemic lupus erythematosus M32% 710.0 ● Sjögren's syndrome M35.0 710.2 ● Idiopathic inflammatory myositis: dermatomyositis, polymyositis, statin-associated autoimmune myositis, unspecified myositis G72.49 G72.41 M33 710.3 710.4 ● Systemic sclerosis M34.0 M34.1 M34.8% M34.9 710.1 ● CREST syndrome M34.1 710.1 ● Dermatomyositis/polymyositis M33.9 M33.10

M33.2

710.3

710.4

- Mixed connective tissue disease
  M35.1

  710.9

- Antiphospholipid syndrome
  D68.61

  239.81

- Sarcoidosis
  D86.0

  D86.9

  135%

- IgG4-related disease
  M35

- Still's disease
  M08.2

  714.3

- Raynaud's phenomenon
  I73.0

ICD, International Classification of Diseases 9th or 10th revision codes.

*"%" means "wildcard"- any text appearing after the initial string are captured in the coding. For example, M05% includes every sub-classification under M05 (M05.1, M05.2, etc.).

Supplemental Table 2. Duration and number of ICI infusions for pre-existing RA cases and non-RA comparators.

	RA cases	Non-RA comparators	p-value
Median ICI duration, months (IQR)	4 (1, 11)	4 (1, 11)	0.96
Median ICI number (IQR)	6 (2, 13)	5.5 (2, 13)	0.38

Supplemental Table 3. Baseline characteristics of pre-existing RA cases (n=87) and pre-RA cases without matches (n=14) at index date of immune checkpoint inhibitor initiation.

	Pre-existing RA cases in analysis (n=87)	Pre-existing RA cases without matches (n=14)	p-value
Demographics			
Mean age, years (SD)	69.9 (10.6)	71.6 (11.6)	0.58
Female sex, n (%)	52 (59.8%)	11 (78.6%)	0.10
Race, n (%)			
White	81 (93.1%)	14 (100.0%)	0.40
Black	3 (3.5%)	0 (0.0%)	0.64
Asian	1 (1.2%)	0 (0.0%)	0.86
Median calendar year (IQR)	2018 (2017, 2019)	2019.5 (2019, 2020)	0.0063
Lifestyle			
Smoking status, n (%)			
Never	24 (27.6%)	4 (28.6%)	0.99
Past	57 (65.5%)	9 (64.3%)	
Current	6 (6.9%)	1 (7.1%)	
Median pack-years (IQR)	20 (0, 40)	20 (0, 60)	0.77
Median body mass index, kg/m^2 (IQR)	25.8 (22.0, 29.4)	25.4 (23.4, 31.0)	0.36
Comorbidities			
Median CCI (IQR)	8 (6, 9)	9.5 (8, 12)	0.43
Cancer characteristics			
Target of ICI, n (%)			
PD-1	80 (92.0%)	10 (71.4%)	0.037
PD-L1	4 (4.6%)	0 (0.0%)	0.55
CTLA-4	1 (1.2%)	4 (28.6%)	0.0011
Combination	2 (2.3%)	0 (0.0%)	0.74
Type of cancer, n (%)			
Lung	43 (49.4%)	7 (50.0%)	0.97
Non-small cell	41 (47.1%)	0 (0.0%)	0.0003
Small cell	2 (2.3%)	7 (50.0%)	<0.0001
Melanoma	21 (24.1%)	0 (0.0%)	0.029
Genitourinary tract	6 (6.9%)	3 (21.4%)	0.088
Gastrointestinal tract	3 (3.5%)	2 (14.3%)	0.12
Head and neck	4 (4.6%)	0 (0.0%)	0.55
Hematologic	3 (3.5%)	0 (0.0%)	0.64
Brain	2 (2.3%)	0 (0.0%)	0.74
Other**	5 (5.8%)	1 (7.1%)	0.41
Median cancer duration, years (IQR)	0.9 (0.1, 2.4)	0.8 (0.2, 1.1)	0.30
Previous chemotherapy, n (%)	53 (60.9%)	12 (85.7%)	0.0495
Previous hormonal therapy, n (%)	1 (1.2%)	0 (0.0%)	0.86
Previous radiation, n (%)	48 (55.2%)	7 (50.0%)	0.72
Previous stem cell transplant, n (%)	2 (2.3%)	0 (0.0%)	0.74
Previous CAR-T therapy, n (%)	0 (0.0%)	0 (0.0%)	N/A

Previous chemotherapy, hormonal therapy, radiation, stem cell transplant, or CAR-T, n (%)	53 (60.92%)	12 (85.7%)	0.0495

Missing data: race, 2 cases and 7 comparators; BMI, 9 cases and 20 comparators. All other variables had complete data.

*Age, sex, calendar year, ICI target, and cancer type/stage were matching factors.
**Other cancers included neuroendocrine (2 cases and 2 comparators), Merkel cell carcinoma (2 cases and 3 comparators), and mesothelioma (1 case and 1 comparator).

CAR-T, chimeric antigen receptor T cells; CCI, Charlson Comorbidity Index; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; IQR, interquartile range; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RA, rheumatoid arthritis; SD, standard deviation.

Supplemental Table 4. RA characteristics of cases in analysis (n=87) and those without matches (n=14) at index date of immune checkpoint inhibitor initiation.

	Pre-existing RA cases in analysis (n=87)	**Pre-existing RA cases without matches (n=14)**	**p-value**
Median RA duration, years (IQR)	9.4 (4.6, 16.5)	12.5 (6.0, 20.6)	0.43
Seropositive, n (%)	49/71 (69.0%)	10/12 (83.3%)	0.29
Anti-CCP+, n (%)	35/57 (61.4%)	6/10 (60.0%)	0.85
RF+	37/58 (63.8%)	10/10 (100.0%)	0.032
Most recent disease activity, n (%)			
Remission	29/68 (42.6%)	2/10 (20.0%)	0.10
Low	25/68 (36.8%)	7/10 (70.0%)	0.11
Moderate	11/68 (16.2%)	1/10 (10.0%)	0.33
High	3/68 (4.4%)	0/10 (0.0%)	0.64
Glucocorticoid (n, %)	57 (65.5%)	4 (28.6%)	0.0086
Any DMARD (n, %)	40 (46.0%)	5 (35.7%)	0.47
Any csDMARD (n, %)	31 (35.6%)	4 (28.6%)	0.22
Methotrexate (n, %)	19 (21.8%)	3 (21.4%)	0.27
Hydroxychloroquine (n, %)	11 (12.6%)	2 (14.3%)	0.31
Any bDMARD or tsDMARD (n, %)	22 (25.3%)	1 (7.1%)	0.11
TNFi (n, %)	10 (11.5%)	0 (0.0%)	0.21
Interstitial lung disease, n (%)	13 (14.9%)	5 (35.7%)	0.059
Sjogren's syndrome, n (%)	0 (0.0%)	0 (0.0%)	N/A
Rheumatoid vasculitis, n (%)	1 (1.2%)	0 (0.0%)	0.86
Felty's syndrome, n (%)	0 (0.0%)	0 (0.0%)	N/A
Bone erosions or deformities, n (%)	27 (31.0%)	6 (42.9%)	0.38

Missing data: serostatus 16; anti-CCP 30; RF status 29; disease activity 19. All other variables had complete data.

Anti-CCP, anti-cyclic citrullinated peptide; bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; IQR, interquartile range; RA, rheumatoid arthritis; RF, rheumatoid factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug; TNFi, tumor necrosis factor inhibitor.

Supplemental Table 5. Cancer characteristics stratified by index date before 2016 vs. 2016 or later among pre-existing RA cases (n=87).

	Cases before 2016 (n=4)	**Cases 2016 or later (n=83)**	**p-value**
Median cancer duration, years (IQR)	1.33 (0.16, 3.07)	0.92 (0.13, 2.24)	0.77
Previous chemotherapy, n (%)	3 (75.0%)	50 (60.2%)	0.36
Previous hormonal therapy, n (%)	0 (0.0%)	1 (1.2%)	0.95
Previous radiation, n (%)	3 (75.0%)	45 (54.2%)	0.30
Previous stem cell transplant, n (%)	1 (25.0%)	1 (1.2%)	0.089
Previous CAR-T therapy, n (%)	0 (0.0%)	0 (0.0%)	N/A
Previous chemotherapy, hormonal therapy, radiation, stem cell transplant, or CAR-T, n (%)	3 (75.0%)	50 (60.2%)	0.36

Supplemental Table 6. Cancer characteristics stratified by index date before 2016 vs. 2016 or later among non-RA comparators (n=87).

	Comparators before 2016 (n=7)	**Comparators 2016 or later (n=196)**	**p-value**
Median cancer duration, years (IQR)	0.63 (0.10, 6.02)	0.51 (0.13, 1.77)	0.25
Previous chemotherapy, n (%)	3 (42.9%)	88 (44.9%)	0.30
Previous hormonal therapy, n (%)	0 (0.0%)	4 (2.0%)	0.87
Previous radiation, n (%)	3 (42.9%)	68 (34.7%)	0.27
Previous stem cell transplant, n (%)	0 (0.0%)	2 (1.0%)	0.93
Previous CAR-T therapy, n (%)	0 (0.0%)	1 (0.5%)	0.97
Previous chemotherapy, hormonal therapy, radiation, stem cell transplant, or CAR-T, n (%)	3 (42.9%)	91 (46.4%)	0.29

Supplemental Table 7. Hazard ratios for mortality after immune checkpoint inhibitor initiation, comparing pre-existing RA cases (n=87) and matched non-RA comparators, index date before 2016 (n=203).

	Deaths	Person-months	Incidence rate (95%CI) per 1000 person-months	Unadjusted HR (95%CI)	Multivariable* HR (95%CI)
Pre-existing RA cases	3	154.70	19.39 (0.00, 41.34)	1.20 (0.29, 4.96)	1.16 (0.17, 7.96)
Matched comparators	3	292.93	10.24 (0.00, 21.83)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, sex, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson Comorbidity Index.

CAR-T, chimeric antigen receptor T cells; CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor.

Supplemental Table 8. Hazard ratios for mortality after immune checkpoint inhibitor initiation, comparing pre-existing RA cases (n=87) and matched non-RA comparators, index date 2016 or later (n=203).

	Deaths	Person-months	Incidence rate (95%CI) per 1000 person-months	Unadjusted HR (95%CI)	Multivariable* HR (95%CI)
Pre-existing RA cases	57	1,453.97	39.20 (29.03, 49.38)	1.21 (0.89, 1.66)	1.16 (0.85, 1.58)
Matched comparators	124	4,245.07	29.21 (24.07, 34.35)	1.0 (Ref)	1.0 (Ref)

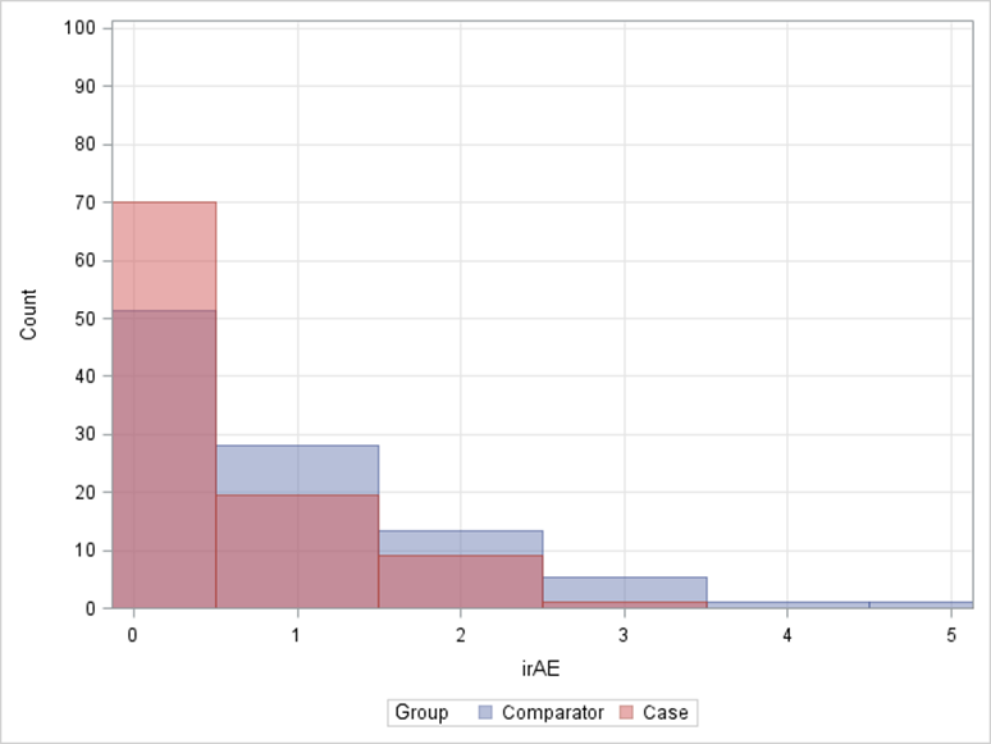
*In addition to matching factors of age, sex, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson Comorbidity Index.

CAR-T, chimeric antigen receptor T cells; CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor.

Supplemental Table 9. Glucocorticoid and DMARD use at any time after index date of ICI initiation.

DMARD	All RA cases (n=87)	Non-RA comparators (n=203)	p-value
Glucocorticoids (n, %)	62 (71.3%)	94 (46.3%)	<0.0001
DMARD (n, %)	38 (43.7%)	14 (6.9%)	<0.0001
csDMARD (n, %)	33 (37.9%)	9 (4.4%)	<0.0001
azathioprine (n, %)	0 (0.0%)	1 (0.5%)	0.70
methotrexate (n, %)	17 (19.5%)	5 (2.5%)	<0.0001
leflunomide (n, %)	3 (3.5%)	0 (0.0%)	0.026
mycophenolic acid (n, %)	0 (0.0%)	0 (0.0%)	N/A
mycophenolate mofetil (n, %)	1 (1.2%)	0 (0.0%)	0.30
sulfasalazine (n, %)	3 (3.5%)	1 (0.5%)	0.075
hydroxychloroquine (n, %)	16 (18.4%)	3 (1.5%)	<0.0001
tsDMARD (n, %)	1 (1.2%)	0 (0.0%)	0.30
tofacitinib (n, %)	1 (1.2%)	0 (0.0%)	0.30
baricitinib (n, %)	0 (0.0%)	0 (0.0%)	N/A
upadicitinib (n, %)	0 (0.0%)	0 (0.0%)	N/A
bDMARD (n, %)	8 (9.2%)	7 (3.5%)	0.043
rituximab (n, %)	4 (4.6%)	3 (1.5%)	0.10
abatacept (n, %)	0 (0.0%)	0 (0.0%)	N/A
Anakinra (n, %)	0 (0.0%)	0 (0.0%)	N/A
TNFi (n, %)	4 (4.6%)	4 (2.0%)	0.14
infliximab (n, %)	2 (2.3%)	4 (2.0%)	0.33
etanercept (n, %)	2 (2.3%)	0 (0.0%)	0.089
adalimumab (n, %)	0 (0.0%)	0 (0.0%)	N/A
certolizumab (n, %)	0 (0.0%)	0 (0.0%)	N/A
golimumab (n, %)	0 (0.0%)	0 (0.0%)	N/A
IL-6i (n, %)	1 (1.2%)	0 (0.0%)	0.30
tocilizumab (n, %)	1 (1.2%)	0 (0.0%)	0.30
sarilumab (n, %)	0 (0.0%)	0 (0.0%)	N/A

Supplemental Figure 2. Histogram comparing number of all-grade irAE for pre-existing RA cases and non-RA comparators after excluding RA flares for cases and IA events for comparators.



Supplemental Table 10. Hazard ratios for mortality after immune checkpoint inhibitor initiation by baseline factors.

	Deaths	Person-Months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted HR (95%CI)	Multivariable* HR (95%CI)
Age (per year)	187	6,146.67	30.42 (26.06, 34.78)	1.02 (1.00, 1.03)	1.02 (1.00, 1.04)
Sex					
Male	72	2,503.33	28.76 (22.12, 35.41)	0.96 (0.72, 1.30)	1.31 (0.91, 1.87)
Female	115	3,643.33	31.56 (25.80, 37.33)	1.0 (Ref)	1.0 (Ref)
Cancer type					
Lung	108	2,996.63	36.04 (29.24, 42.84)	1.0 (Ref)	1.0 (Ref)
Melanoma	29	2,175.13	13.33 (8.48, 18.19)	0.42 (0.28, 0.64)	0.45 (0.27, 0.75)
Other	50	974.9	51.29 (37.07, 65.50)	1.31 (0.94, 1.82)	1.28 (0.85, 1.92)
Smoking Pack years (per unit)	187	6,146.67	30.42 (26.06, 34.78)	1.01 (1.00, 1.01)	1.00 (1.00, 1.01)
Cancer duration (per year)	187	6,146.67	30.42 (26.06, 34.78)	1.00 (0.93, 1.08)	0.99 (0.90, 1.10)
Previous cancer treatment					
No	75	3,397.1	22.08 (17.08, 27.07)	1.0 (Ref)	1.0 (Ref)
Yes	112	2,749.57	40.73 (33.19, 48.28)	1.74 (1.30, 2.34)	1.39 (0.97, 1.97)
Continuous CCI (per unit)	187	6,146.67	30.42 (26.06, 34.78)	1.06 (1.02, 1.09)	1.05 (1.01, 1.09)

*Adjusted for all listed variables in the rows.

Supplemental Table 11. Hazard ratios for mortality after immune checkpoint inhibitor initiation comparing RA cases and matched comparators among only males.

	Deaths	Person-Months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted HR (95%CI)	Multivariable* HR (95%CI)
RA cases	23	720.87	31.91 (18.87, 44.95)	1.15 (0.70, 1.88)	1.11 (0.67, 1.84)
Matched comparators	49	1,782.47	27.49 (19.79, 35.19)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 12. Hazard ratios for mortality after immune checkpoint inhibitor initiation comparing RA cases and matched comparators among only females.

	Deaths	Person-Months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted HR (95%CI)	Multivariable* HR (95%CI)
RA cases	37	887.8	41.68 (28.25, 55.10)	1.29 (0.88, 1.88)	1.19 (0.80, 1.78)
Matched comparators	78	2,755.53	28.31 (22.02, 34.59)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 13. Hazard ratios for mortality after immune checkpoint inhibitor initiation comparing RA cases and matched comparators among only lung cancer.

	Deaths	Person-Months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted HR (95%CI)	Multivariable* HR (95%CI)
RA cases	33	688.1	47.96 (31.60, 64.32)	1.31 (0.88, 1.95)	1.22 (0.81, 1.84)
Matched comparators	75	2,308.53	32.49 (25.14, 39.84)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, sex, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 14. Hazard ratios for mortality after immune checkpoint inhibitor initiation comparing RA cases and matched comparators among only melanoma.

	Deaths	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted HR (95%CI)	Multivariable* HR (95%CI)
RA cases	10	556.43	17.97 (6.83, 29.11)	1.47 (0.70, 3.10)	2.12 (0.88, 5.07)
Matched comparators	19	1,618.7	11.74 (6.46, 17.02)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, sex, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 15. Hazard ratios for mortality after immune checkpoint inhibitor initiation comparing RA cases and matched comparators among only seropositive RA cases and their comparators.

	Deaths	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted HR (95%CI)	Multivariable* HR (95%CI)
RA cases	35	872.63	40.11 (26.82, 53.40)	1.15 (0.77, 1.72)	1.03 (0.70, 1.50)
Matched comparators	83	2,462.43	33.71 (26.45, 40.96)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, sex, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 16. Hazard ratios for mortality after immune checkpoint inhibitor initiation comparing RA cases and matched comparators among only seronegative RA cases and their comparators.

	Deaths	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted HR (95%CI)	Multivariable* HR (95%CI)
RA cases	14	543.5	25.76 (12.27, 39.25)	1.05 (0.58, 1.91)	1.04 (0.55, 1.98)
Matched comparators	25	1,056.47	23.66 (14.39, 32.94)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, sex, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 17. Hazard ratios for mortality after immune checkpoint inhibitor initiation comparing RA cases and matched comparators only among baseline glucocorticoids users (n=57) and their comparators.

	Deaths	Person-Months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted HR (95%CI)	Multivariable* HR (95%CI)
RA cases	43	904.60	47.53 (33.33, 61.74)	1.33 (0.93, 1.90)	1.16 (0.81, 1.67)
Matched comparators	88	2,903.70	30.31 (23.97, 36.64)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 18. Hazard ratios for mortality after immune checkpoint inhibitor initiation comparing RA cases and matched comparators only among baseline non-glucocorticoids users (n=30) and their comparators.

	Deaths	Person-Months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted HR (95%CI)	Multivariable* HR (95%CI)
RA cases	17	704.07	24.15 (12.67, 35.62)	1.02 (0.58, 1.80)	1.03 (0.57, 1.88)
Matched comparators	39	1,634.3	23.86 (16.37, 31.35)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 19. Risk of all-grade irAE after immune checkpoint inhibitor initiation only among baseline glucocorticoids users (n=57) and their comparators.

	All-grade irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	21	193.93	108.28 (61.97, 154.60)	1.86 (1.07, 3.25)	2.19 (1.22, 3.95)	2.02 (1.15, 3.54)	2.38 (1.31, 4.31)
Matched comparators	36	901.53	39.93 (26.89, 52.98)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 20. Risk of all-grade irAE after immune checkpoint inhibitor initiation only among baseline non-glucocorticoids users (n=30) and their comparators.

	All-grade irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	16	325.07	49.22 (25.10, 73.34)	1.04 (0.57, 1.88)	1.17 (0.62, 2.19)	1.08 (0.60, 1.95)	1.22 (0.65, 2.28)
Matched comparators	37	893.10	41.43 (28.08, 54.78)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 21. Risk of all-grade irAE after immune checkpoint inhibitor initiation only among RA cases with moderate/high disease activity (n=14) as baseline (and their comparators).

	All-grade irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	9	22.30	403.59 (139.91, 667.26)	2.56 (1.02, 6.43)	3.73 (1.17, 11.87)	3.69 (1.40, 9.72)	7.95 (2.30, 27.50)
Matched comparators	13	279.53	46.51 (21.23, 71.79)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 22. Risk of all-grade irAE after immune checkpoint inhibitor initiation only among RA cases with remission/low disease activity (n=54) as baseline (and their comparators).

	All-grade irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	37	373.70	99.01 (67.11, 130.91)	1.91 (1.25, 2.92)	1.97 (1.29, 3.02)	1.97 (1.28, 3.04)	2.12 (1.38, 3.26)
Matched comparators	62	1,377.67	45.00 (33.80, 56.21)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 23. Risk of all-grade irAE after immune checkpoint inhibitor initiation only among males.

	All-grade irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	24	277.6	86.46 (51.87, 121.04)	2.08 (1.23, 3.52)	2.78 (1.57, 4.93)	2.34 (1.39, 3.96)	3.06 (1.68, 5.55)
Matched comparators	37	1,183.03	31.28 (21.20, 41.35)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 24. Risk of all-grade irAE after immune checkpoint inhibitor initiation only among females.

	All-grade irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	29	305.73	94.85 (60.33, 129.38)	1.39 (0.87, 2.21)	1.56 (0.97, 2.52)	1.60 (1.00, 2.56)	1.82 (1.13, 2.94)
Matched comparators	62	1,291.83	47.99 (36.05, 59.94)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 25. Risk of grade 3+ irAE after immune checkpoint inhibitor initiation only among males.

	Grade 3+ irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	7	587.03	11.92 (3.09, 20.76)	0.91 (0.38, 2.22)	1.23 (0.45, 3.36)	1.00 (0.41, 2.45)	1.47 (0.51, 4.27)
Matched comparators	18	1,504.4	11.96 (6.44, 17.49)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 26. Risk of grade 3+ irAE after immune checkpoint inhibitor initiation only among females.

	Grade 3+ irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	5	807.43	6.19 (0.76, 11.62)	0.99 (0.35, 2.82)	1.39 (0.46, 4.18)	1.01 (0.36, 2.88)	1.49 (0.50, 4.47)
Matched comparators	12	2,536.77	4.73 (2.05, 7.41)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 27. Risk of all-grade irAE after immune checkpoint inhibitor initiation excluding RA and flare and IA, only among males.

	All-grade irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	14	403.1	34.73 (16.54, 52.92)	0.88 (0.47, 1.67)	1.01 (0.53, 1.95)	0.99 (0.52, 1.88)	1.08 (0.55, 2.11)
Matched comparators	37	1,187.23	31.16 (21.12, 41.21)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 28. Risk of all-grade irAE after immune checkpoint inhibitor initiation excluding RA and flare and IA, only among females.

	All-grade irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	12	638.93	18.78 (8.15, 29.41)	0.39 (0.21, 0.74)	0.47 (0.24, 0.93)	0.40 (0.21, 0.76)	0.49 (0.25, 0.97)
Matched comparators	62	1,296.37	47.83 (35.92, 59.73)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 29. Risk of grade 3+ irAE after immune checkpoint inhibitor initiation excluding RA and flare and IA, only among males.

	Grade 3+ irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	6	598.5	10.03 (2.00, 18.05)	0.76 (0.30, 1.94)	0.94 (0.35, 2.55)	0.83 (0.32, 2.15)	1.07 (0.37, 3.09)
Matched comparators	18	1,504.4	11.96 (6.44, 17.49)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.

Supplemental Table 30. Risk of grade 3+ irAE after immune checkpoint inhibitor initiation excluding RA and flare and IA, only among females.

	Grade 3+ irAE cases	Person-months	Incidence rate (per 1000 person-months) and 95%CI	Unadjusted Cox HR (95%CI)	Adjusted Cox HR (95%CI)	Unadjusted competing risk sdHR (95%CI)	Adjusted competing risk sdHR (95%CI)
RA cases	5	807.43	6.19 (0.76, 11.62)	0.99 (0.35, 2.82)	1.39 (0.46, 4.18)	1.01 (0.36, 2.88)	1.49 (0.50, 4.47)
Matched comparators	12	2,536.77	4.73 (2.05, 7.41)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

*In addition to matching factors of age, calendar year, cancer type, target of ICI, adjusted for smoking pack-years, cancer duration, previous chemotherapy or hormonal therapy, previous radiation, previous stem cell transplant/CAR-T, and continuous Charlson comorbidity index.