Supplementary Table S1. Validated candidate algorithms for cutaneous malignant melanoma and non-melanoma skin cancer.

Algorithms	PPV (95% CI)
Cutaneous malignant melanoma	
≥2 ICD-9 diagnosis codes for melanoma separated by 0 to 60 days.	82% (69.2-90.2%)
>1 ICD-9 diagnosis code for melanoma AND >1 CPT procedure code for excision of malignant lesion occurring 0 to 60 days after diagnosis code	78% (64.8-87.3%)
Any single ICD-9 diagnosis code for melanoma	42% (29.4-55.8%)
Nonmelanoma skin cancer	
>1 ICD-9 diagnosis code for NMSC AND >1 CPT procedure for NMSC excision, destruction, or chemosurgery occurring 0-60 days after diagnosis code	84% (71.5-91.7%)

CPT: Current Procedural Terminology; ICD-9: International Classification of Diseases-Ninth Edition; NMSC: non-melanoma skin cancer; PPV: positive predictive value.

Supplementary Table S2. ICD diagnosis codes and HCPCS codes to define cutaneous malignant melanoma and NMSC.

Condition	Definition
Malignant melanoma	ICD-9: 172.* ICD-10: C43.*, D03.*
NMSC including carcinoma *in situ*	ICD-9: 173.*, 232.* ICD-10: C44.* D04.*
Basal cell carcinoma	ICD-9: 173.*1 ICD-10: C44.*1
Squamous cell carcinoma	ICD-9: 173.*2 ICD-10: C44.*2
Procedure codes for NMSC	HCPCS: 11600, 11601, 11602, 11603, 11604,11605, 11606, 11620, 11621, 11622, 11623, 11624, 11626, 11640, 11641, 11642, 11643, 11644, 11646, 17260, 17261, 17262, 17263, 17264, 17266, 17270, 17271, 17272, 17273, 17274, 17276, 17280, 17281, 17282, 17283, 17284, 17286, 17236, 17311, 17312, 17313, 17314, 17315

HCPCS: Healthcare Common Procedure Coding System; ICD: International Classification of Diseases; NMSC: non-melanoma skin cancer.

Supplementary Table S3. Selected patient characteristics in 356 days prior to cohort entry before 1:1 PS matching.

Patient characteristics	Methotrexate (n=38,842)		Hydroxychloroquine (n=25,291)		Abs. Std. Diff.
Demographic					
Age, years, mean (SD)	73.59	(6.27)	73.75	(6.46)	0.026
Female	29,361	(75.6%)	20,202	(79.9%)	0.103
Region					0.072
Northeast	5,868	(15.1%)	4,395	(17.4%)	
South	16,842	(43.4%)	10,952	(43.3%)	
North central	9,727	(25.0%)	6,174	(24.4%)	
West	6,314	(16.3%)	3,731	(14.8%)	
Unknown	91	(0.2%)	39	(0.2%)	
Race					0.051
White	32,038	(82.5%)	21,315	(84.3%)	
Black	4,419	(11.4%)	2,576	(10.2%)	
Asian	770	(2.0%)	469	(1.9%)	
Hispanic	1,245	(3.2%)	747	(3.0%)	
Native American	370	(1.0%)	184	(0.7%)	
Comorbidities					
Actinic keratosis	2,323	(6.0%)	1,757	(6.9%)	0.039
Atopic dermatitis/contact dermatitis	105	(0.3%)	82	(0.3%)	0.01
Psoriasis	138	(0.4%)	66	(0.3%)	0.017
Alopecia areata	38	(0.1%)	30	(0.1%)	0.006
Vitiligo	48	(0.1%)	44	(0.2%)	0.013
Burn/sunburn	141	(0.4%)	99	(0.4%)	0.005
Chronic ulcer	1,582	(4.1%)	1,075	(4.3%)	0.009
Hypertension	30,565	(78.7%)	20,274	(80.2%)	0.036
Hyperlipidaemia	26,759	(68.9%)	18,125	(71.7%)	0.061
Diabetes	11,738	(30.2%)	7,479	(29.6%)	0.014
Combined comorbidity score, mean (SD)	1.09	(2.00)	1.25	(2.12)	0.077
Claims-based frailty index, mean (SD)	0.15	(0.04)	0.15	(0.05)	0.057
Medications					
Amiodarone	414	(1.1%)	279	(1.1%)	0.004
First-generation macrolide	642	(1.7%)	438	(1.7%)	0.006
Second-generation macrolide	7,635	(19.7%)	5,655	(22.4%)	0.066
Tetracycline	3,096	(8.0%)	2,397	(9.5%)	0.053
Antiplatelet agents	3,602	(9.3%)	2,301	(9.1%)	0.006
Anticoagulant	3,453	(8.9%)	2,350	(9.3%)	0.014
NSAIDs and Coxibs	18,509	(47.7%)	11,663	(46.1%)	0.031
ACE inhibitor	12,726	(32.8%)	8,126	(32.1%)	0.014
ARBs	8,248	(21.2%)	5,795	(22.9%)	0.04
Beta blockers	14,815	(38.1%)	9,995	(39.5%)	0.028
Calcium channel blocker	11,029	(28.4%)	7,618	(30.1%)	0.038
Loop diuretics	7,187	(18.5%)	4,941	(19.5%)	0.026
Thiazides	12,982	(33.4%)	8,561	(33.8%)	0.009
Insulin	2,302	(5.9%)	1,512	(6.0%)	0.002
Non-insulin diabetes medications	7,464	(19.2%)	4,523	(17.9%)	0.034
Statins	17,987	(46.3%)	12,304	(48.6%)	0.047
Antidepressants	11,067	(28.5%)	8,343	(33.0%)	0.098
Opioids	24,832	(63.9%)	16,109	(63.7%)	0.005
Antipsychotics	843	(2.2%)	605	(2.4%)	0.015
Anticonvulsants	7,011	(18.1%)	5,497	(21.7%)	0.092
Any oral steroid use	27,311	(70.3%)	16,190	(64.0%)	0.134
Recent oral steroid use*	22,801	(58.7%)	12,331	(48.8%)	0.2
Cumulative prednisone-equivalent milligrams, mean (SD)	566.25	(1,459.03)	457.84	(822.68)	0.092
Procedures/Healthcare utilisation					
Procedures on benign/premalignant lesions	2,815	(7.2%)	2,187	(8.6%)	0.052
Dermatologist visit	4,266	(11.0%)	3,514	(13.9%)	0.088
Rheumatologist visit	29,253	(75.3%)	20,071	(79.4%)	0.097
Emergency room visit	13,028	(33.5%)	8,596	(34.0%)	0.009
Recent hospitalisation*	1,735	(4.5%)	1,075	(4.3%)	0.011

*Recent: 60 days prior to (including) the index date.
Abs. Std. Diff.: absolute standardised difference; ACE: angiotensin converting enzyme; ARBs: angiotensin II receptor blockers; Coxibs: selective cyclo-oxygenase 2 inhibitors; HCQ: hydroxychloroquine; n: number; NSAIDs: non-steroidal anti-inflammatory drugs; NUVB: narrow-band ultraviolet B; PDT: photodynamic therapy; PS: propensity score; SD: standard deviation; TIA: transient ischaemic attack.

Supplementary Table S4. Incidence rates and hazard ratios (95% CI) for primary outcome in the 1:1 PS matched cohort for subgroups

	Methotrexate					Hydroxychloroquine				
	n. of events	PY	IR/1,000 PY	RD/1,000 PY (95% CI)	HR (95% CI)	n. of events	PY	IR/1,000 PY	RD/1,000 PY (95% CI)	HR (95% CI)
Male	258	5,948	43.38	2.01 (-5.64,9.67)	1.03 (0.86, 1.24)	215	5,198	41.36	Ref	Ref
Female	462	21,811	21.18	0.82 (-1.97, 3.61)	1.03 (0.90, 1.17)	393	19,300	20.36	Ref	Ref
Steroid use	479	18,138	26.41	0.01 (-3.45,3.48)	0.99 (0.86, 1.12)	416	15,760	26.40	Ref	Ref
No steroid use	204	9,818	20.78	-1.64 (-5.90, 2.61)	0.92 (0.75, 1.12)	194	8,653	22.42	Ref	Ref
NSAID use	334	13,361	25.00	2.23 (-1.62, 6.07)	1.07 (0.91, 1.26)	261	11,461	22.77	Ref	Ref
No NSAID use	375	14,411	26.02	-0.77 (-4.64, 3.10)	0.96 (0.83, 1.11)	343	12,801	26.79	Ref	Ref
White	712	24,235	29.38	1.22 (-1.90, 4.33)	1.03 (0.93, 1.15)	603	21,413	28.16	Ref	Ref
Non-white	*	3,660	1.91	-0.03 (-2.13, 2.07)	0.89 (0.30, 2.66)	*	3,096	1.94	Ref	Ref

CI: confidence interval; HR: hazard ratio; IR: incidence rate; n: number; NSAIDs: non-steroidal anti-inflammatory drugs; PY: person-year; RD; rate difference.
* Data suppressed due to low number of events.

Supplementary Table S5. Sensitivity analysis in the 1:1 PS matched cohort using 90-day latency period.
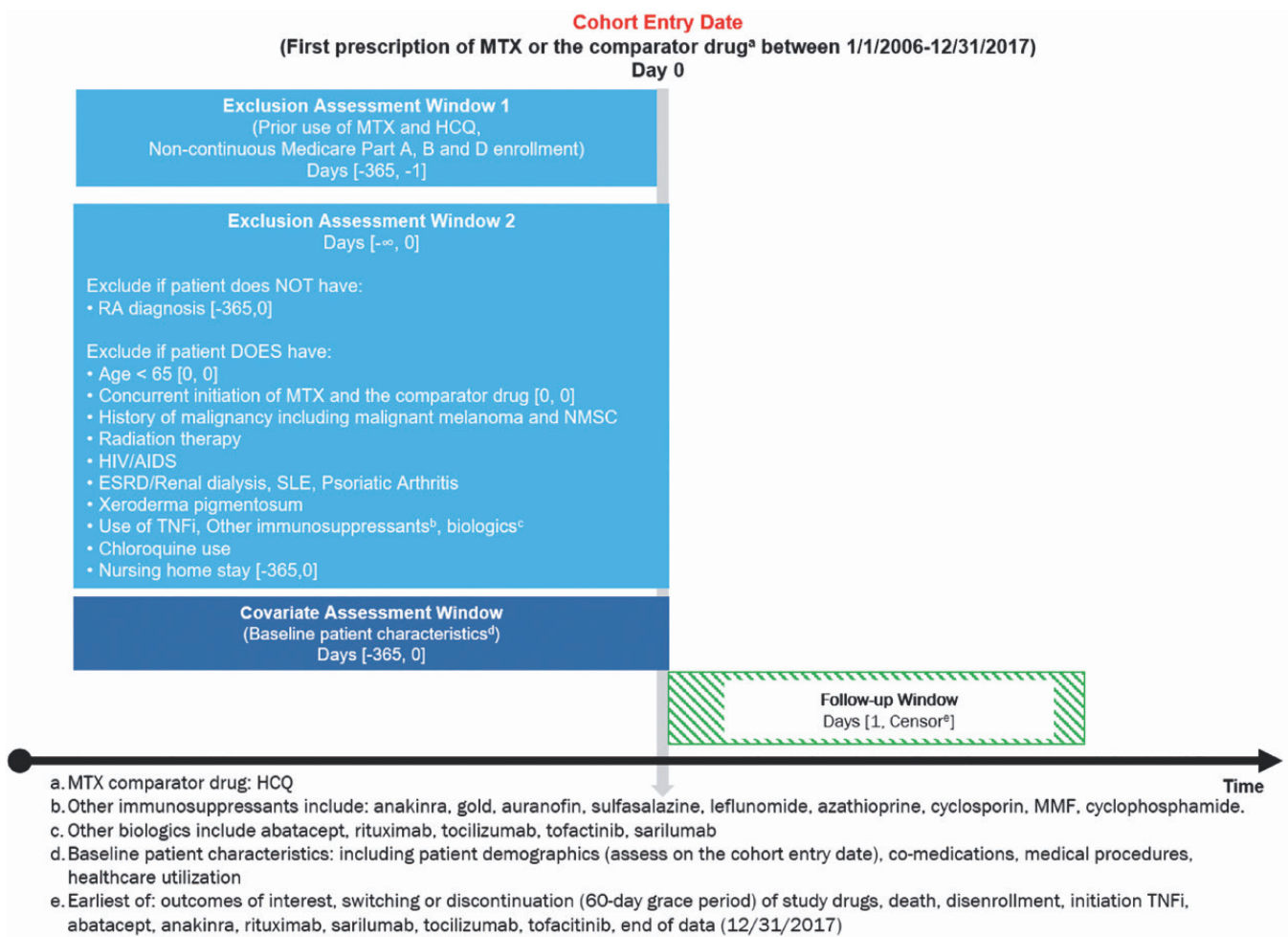
	Methotrexate					Hydroxychloroquine				
	n. of events	PY	IR/1,000 PY	RD/1,000 PY (95% CI)	HR (95% CI)	n. of events	PY	IR/1,000 PY	RD/1,000 PY (95% CI)	HR (95% CI)
Primary outcome										
Malignant melanoma and NMSC	580	19,877	29.18	1.01 (-2.35, 4.36)	1.03 (0.92, 1.16)	544	19,310	28.17	Ref	Ref
Secondary outcomes										
Malignant melanoma	35	20,872	1.68	0.49 (-0.24, 1.22)	1.40 (0.83, 2.36)	24	20,183	1.19	Ref	Ref
NMSC	560	19,904	28.14	0.55 (-2.75, 3.85)	1.02 (0.90, 1.15)	533	19,323	27.58	Ref	Ref
BCC	207	20,538	10.08	2.56 (0.74, 4.39)	1.33 (1.08, 1.64)	150	19,955	7.52	Ref	Ref
SCC	115	20,704	5.55	-1.61 (-3.17, -0.06)	0.76 (0.60, 0.98)	143	19,948	7.17	Ref	Ref

CI: confidence interval; HR: hazard ratio; IR: incidence rate; n: number; NSAIDs: non-steroidal anti-inflammatory drugs; PY: person-year; RD; rate difference.

Supplementary Table S6. Number of events and incidence rates for primary outcome stratified by follow-up time and hazard ratio in a 1:1 PS-matched cohort.

	Methotrexate					Hydroxychloroquine				
Follow-up time (Days)	Number of patients (%)	Number of events	PY	IR/1,000 PY	HR (95% CI)	Number of patients (%)	Number of events	PY	IR/1,000 PY	HR (95% CI)
0-365	17,853 (72.64)	330	7,142.92	46.20	1.07 (0.91, 1.25)	16,749 (68.15)	293	7,063.06	41.48	Ref
366-730	3,266 (13.29)	179	5,361.01	33.39	1.03 (0.83, 1.28)	3,753 (15.27)	148	4,637.10	31.92	Ref
731 +	3,458 (14.07)	219	15,276.07	14.34	1.03 (0.84, 1.25)	4,075 (16.58)	179	12,900.15	13.88	Ref

IR: incidence rate; PS: propensity score; PY: person-year.

Cohort Entry Date
(First prescription of MTX or the comparator drug[a] between 1/1/2006-12/31/2017)
Day 0

Exclusion Assessment Window 1
(Prior use of MTX and HCQ,
Non-continuous Medicare Part A, B and D enrollment)
Days [-365, -1]

Exclusion Assessment Window 2
Days [-∞, 0]

Exclude if patient does NOT have:
• RA diagnosis [-365,0]

Exclude if patient DOES have:
• Age < 65 [0, 0]
• Concurrent initiation of MTX and the comparator drug [0, 0]
• History of malignancy including malignant melanoma and NMSC
• Radiation therapy
• HIV/AIDS
• ESRD/Renal dialysis, SLE, Psoriatic Arthritis
• Xeroderma pigmentosum
• Use of TNFi, Other immunosuppressants[b], biologics[c]
• Chloroquine use
• Nursing home stay [-365,0]

Covariate Assessment Window
(Baseline patient characteristics[d])
Days [-365, 0]

Follow-up Window
Days [1, Censor[e]]

Time

a. MTX comparator drug: HCQ
b. Other immunosuppressants include: anakinra, gold, auranofin, sulfasalazine, leflunomide, azathioprine, cyclosporin, MMF, cyclophosphamide.
c. Other biologics include abatacept, rituximab, tocilizumab, tofactinib, sarilumab
d. Baseline patient characteristics: including patient demographics (assess on the cohort entry date), co-medications, medical procedures, healthcare utilization
e. Earliest of: outcomes of interest, switching or discontinuation (60-day grace period) of study drugs, death, disenrollment, initiation TNFi, abatacept, anakinra, rituximab, sarilumab, tocilizumab, tofacitinib, end of data (12/31/2017)

Supplementary Fig. S1. Study design diagram.
ESRD: end stage renal disease; HCQ: hydroxychloroquine; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome; MTX: methotrexate; NMSC: non-melanoma skin cancer; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; TNFi: tumour necrosis factor inhibitors.