Safety of TofAcitinib in Routine Care Patients With Rheumatoid Arthritis (STAR-RA) – Cancer Endpoints

June 8, 2021

NCT04798287

1. Comparison Details

a. Intended aim(s)

- To compare the risk of composite cancer outcomes, between patients treated with tofacitinib and patients treated with TNF inhibitors (TNFi) for rheumatoid arthritis (RA) among, 1) "real world evidence (RWE)" cohorts including routine care patient population from the US and, 2) "Randomized controlled trial (RCT) DUPLICATE" cohorts including routine care patient population who meet inclusion and exclusion criteria of the *Safety Study Of Tofacitinib Versus Tumor Necrosis Factor (TNF) Inhibitor In Subjects With Rheumatoid Arthritis* ("ORAL Surveillance", NCT02092467) clinical trial.

- To examine the risk of common solid cancers (lung, colorectal, breast, prostate), hematological cancers, and non-melanoma skin cancer as separated endpoints when comparing tofacitinib with TNFi in patients with RA among, 1) "real world evidence (RWE)" cohort including routine care patient population from the US and, 2) "Randomized controlled trial (RCT) DUPLICATE" cohort including routine care patient population who meet inclusion and exclusion criteria of the *Safety Study Of Tofacitinib Versus Tumor Necrosis Factor (TNF) Inhibitor In Subjects With Rheumatoid Arthritis* ("ORAL Surveillance", NCT02092467) clinical trial.

b. Primary endpoint

- Composite all site cancer outcomes excluding non-melanoma skin cancer (NMSC).

2. Person responsible for implementation of analysis in Aetion

Hemin Lee, MD, MPH will implement the study design and analysis in the Aetion Evidence Platform. She is not responsible for the validity of the design and analytic choices. All implementation steps will be recorded and the implementation history will be archived in the platform. Propensity score (PS) fine stratification weighting will be implemented using SAS statistical software (SAS Institute, Cary, NC).

3. Data Source(s)

US MarketScan, 2012-2018
Optum, 2012-2020
Medicare Claims Database, 2012-2017

4. Study Design Diagrams

Figure 1. Inclusion and Exclusion Criteria for RWE and RCT Duplicate Cohorts

Real World Evidence Cohorts

Inclusion Criteria

- Patients treated with tofacitinib or TNF inhibitors in MarketScan (2012-2018), Optum (2012-2020), and Medicare fee-for-service (Parts A, B and D; 2012-2017)
- At least 365 days of continuous enrollment in health plan prior to and including cohort entry date
- At least 2 RA codes between 7 and 365 days apart

Exclusion Criteria

- No index drug in the 365 day prior to cohort entry (prevalent users)
- < 18 years of age (Optum, MarketScan), < 65 (Medicare)
- Missing data on age or gender
- Nursing home or hospice admission
- Diagnosis of malignant cancer prior to cohort entry date
- TNFi users with prior prescriptions of JAK inhibitors (tofacitinib, upadacitinib, or baricitinib)
- TNFi users initiating with multiple TNFi on same date
- Tofacitinib users with prior prescriptions of baricitinib, upadacitinib
- Tofacitinib users initiating treatment with tofacitinib and baricitinib (or upadacitinib) on same day

RCT-Duplicate Cohorts

Additional Inclusion Criteria

- Patients with at least one prescription of methotrexate
- Patients with at least one cardiovascular risk factor (including smoking, hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, family history of ischemic heart disease)

Additional Exclusion Criteria

- < 50 years of age (Optum, MarketScan), < 65 (Medicare)
- Patients recently hospitalized with infections
- Pregnant patients

Figure 2: Study Design for RWE Cohorts

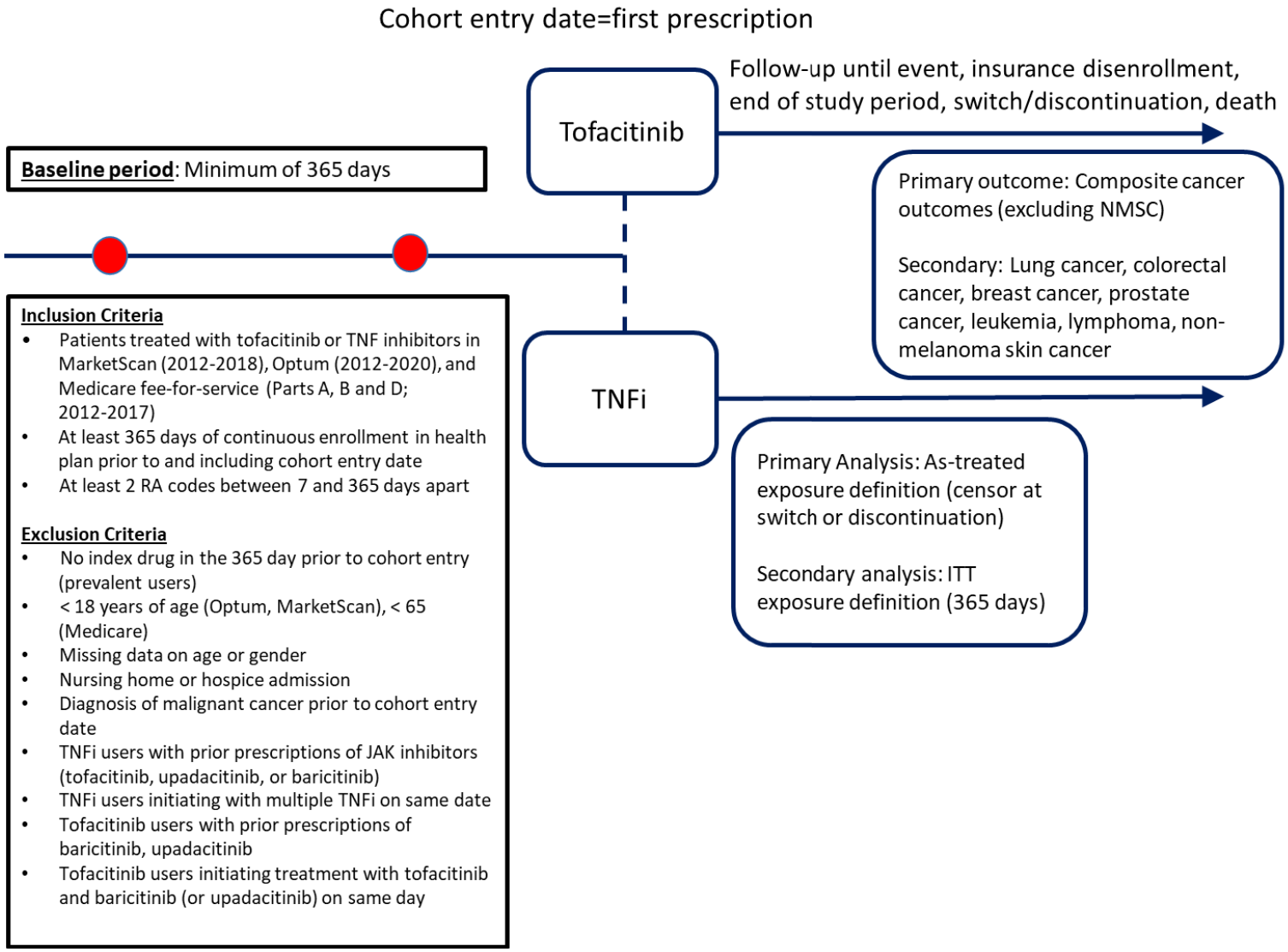


Figure 3: Study Design for RCT-Duplicate Cohorts

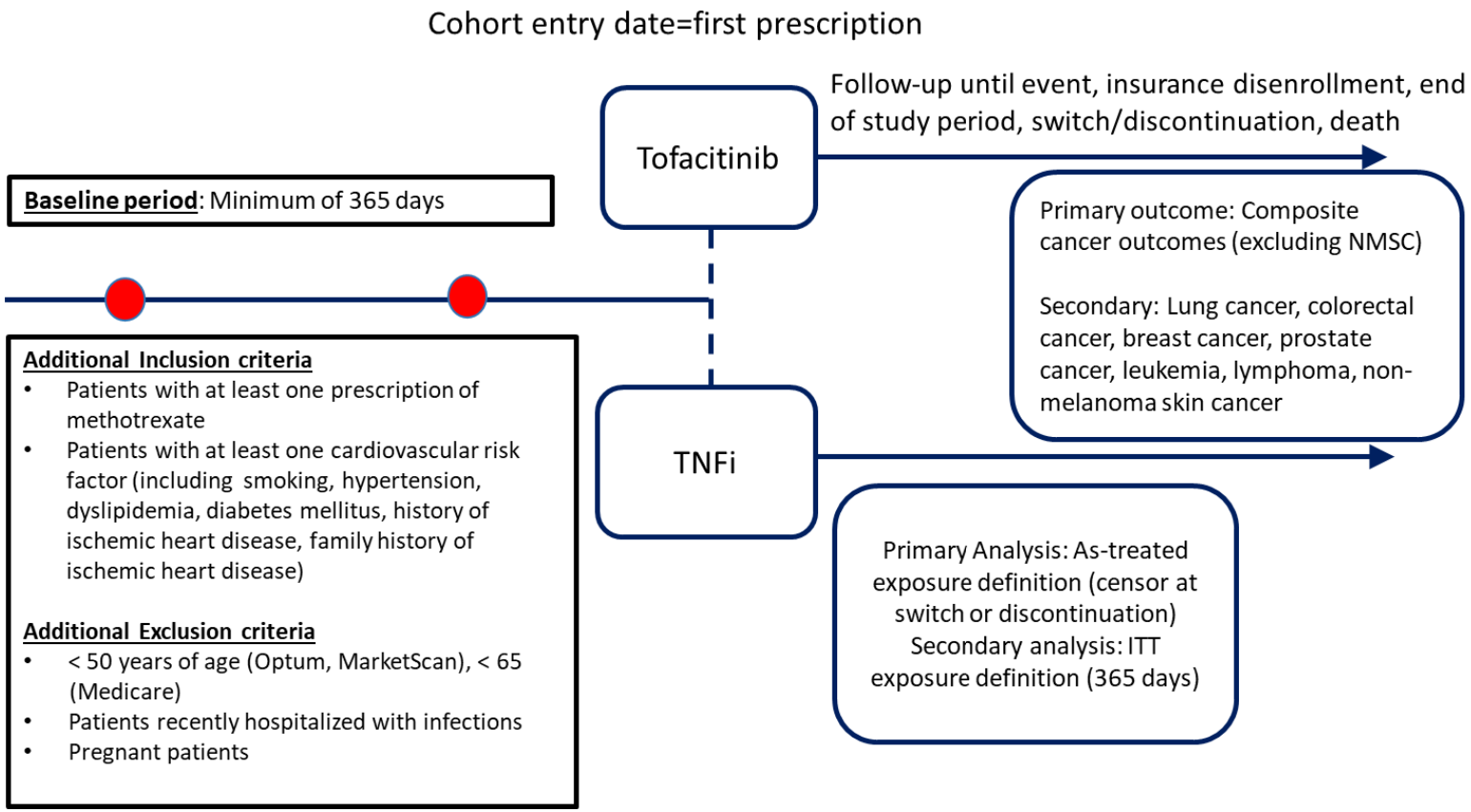
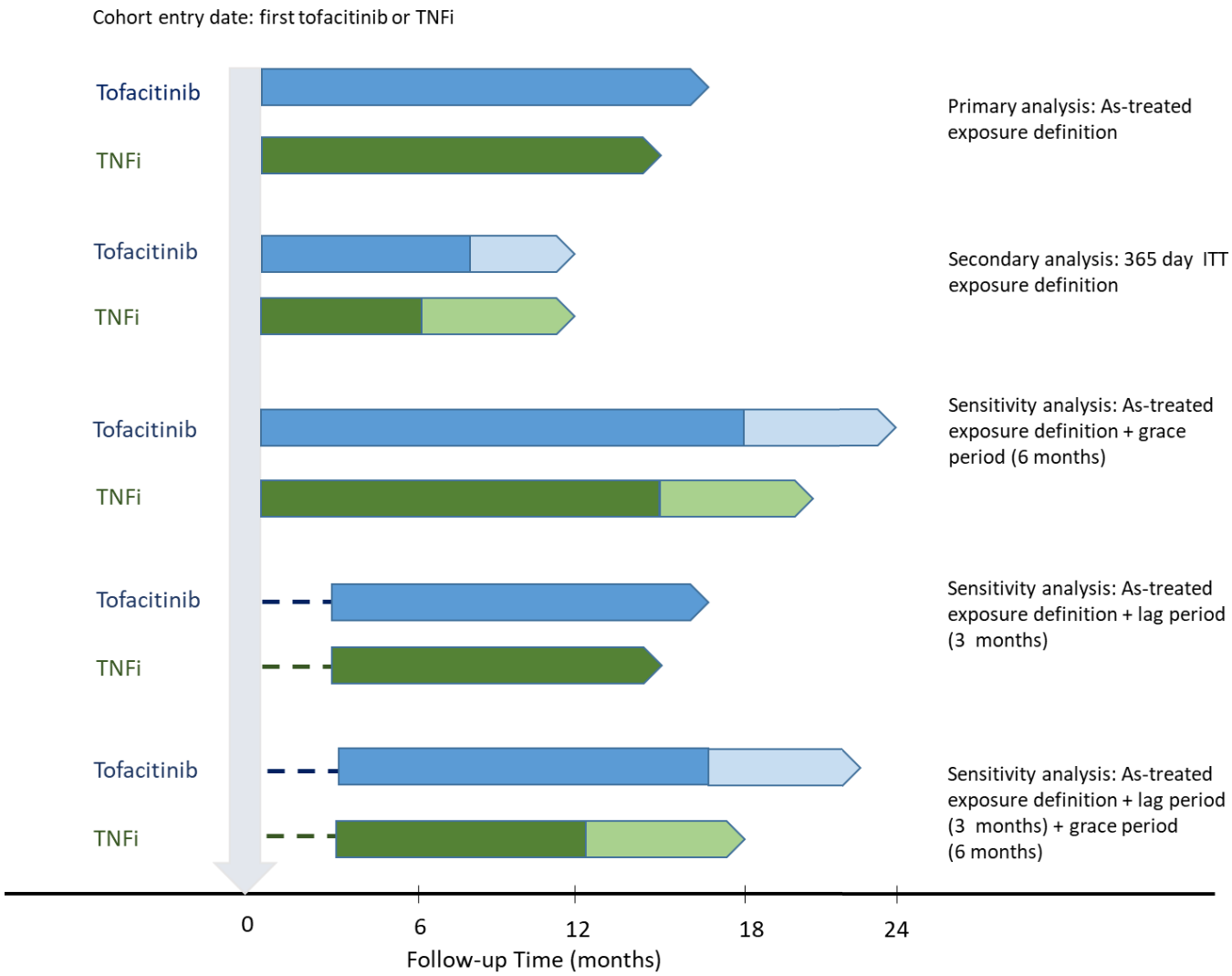


Figure 4: Exposure Definitions for RCT-Duplicate and RWE Cohorts



5. Cohort Identification

a. Cohort Summary

This study will employ an active comparator, new user observational cohort study design comparing initiators of tofacitinib to tumor necrosis factor inhibitors (infliximab, adalimumab, certolizumab pegol, etanercept, and golimumab).[1] The patients will be required to have continuous enrollment in their health plan during the baseline period of 365 days before initiation of tofacitinib or TNFi (cohort entry date). Follow-up begins the day after drug initiation.

There will be two independent study populations:

1) Real-World Evidence (RWE) cohorts: This study population will reflect the patients diagnosed with RA who are routinely treated and managed in setting of clinical practice.

2) RCT-duplicate cohorts: This study population will emulate "the Safety Study Of Tofacitinib Versus Tumor Necrosis Factor (TNF) Inhibitor In Subjects With Rheumatoid Arthritis" clinical trial ("ORAL Surveillance", **NCT02092467**). The inclusion and exclusion criteria of this RCT will be applied to this study population.

b. Inclusion and Exclusion Criteria Common to RWE and RCT-duplicate Cohorts

Cohort entry date:
- First TNFi or tofacitinib dispensation/administration date

Inclusion criteria
- Patients treated with tofacitinib or TNF inhibitors in IBM MarketScan (2012-2018), Optum (2012-2020), and Medicare fee-for-service (Parts A, B and D; 2012-2017)
- A minimum of 365 days of continuous enrollment in health plan prior to (and including) the cohort entry date
- Two diagnosis codes for RA in 365 days baseline period (diagnosis codes between 7 and 365 days apart)

Exclusion criteria

- Index drug in 365 days prior to cohort entry (prevalent users)
- Missing data on age or gender
- Admission to nursing facility or hospice on or prior to cohort entry date (ever look-back)
- Diagnosis of malignant cancer prior to cohort entry date (ever look-back period)
- TNFi users with history of any Janus kinase (JAK) inhibitors (tofacitinib, upadacitinib, or baricitinib) (ever look-back period)
- TNFi users initiating with more than one TNFi on same date
- Tofacitinib users with a prescription of baricitinib, upadacitinib (ever look-back period)
- Tofacitinib users initiating treatment on multiple JAK inhibitors on same day (tofacitinib and baricitinib, tofacitinib and upadacitinib)

c. Exclusion criteria specific to RWE cohorts

- Patients less than 18 years of age (MarketScan and Optum) and 65 years of age (Medicare) at cohort entry

d. Inclusion criteria specific to RCT-duplicate cohorts

- Patients with at least one methotrexate dispensation (six months look-back period)
- Patients with at least one cardiovascular risk factor (including smoking, hypertension, dyslipidemia, diabetes mellitus, history of ischemic heart disease, family history of ischemic heart disease) (one-year look-back period)

e. Exclusion criteria specific to RCT-duplicate cohorts

- Patients less than 50 years of age (MarketScan and Optum) and 65 years of age (Medicare) at cohort entry
- Patients recently hospitalized with infections (30-day look-back period)
- Pregnant patients (one year look-back period)

6. Variables

a. Exposure-related variables:

Study drug:
The study exposure of interest is initiation of tofacitinib

Comparator:
Initiators of tofacitinib will be compared to initiators of TNFi (infliximab, adalimumab, certolizumab pegol, etanercept, and golimumab)

b. Covariates (assessed during 365 day baseline period, unless otherwise specified):

Demographics and Lifestyle Factors	
Age on the cohort entry date	Calendar year of cohort entry
Gender	Obesity
Race	Smoking
Rheumatoid arthritis related factors	
csDMARDs use (methotrexate, hydroxychloroquine, leflunomide, sulfasalazine)	Number of distinct csDMARDs
Glucocorticoids use (365 day baseline, within 60 days of baseline, cumulative dose)	Number of distinct bDMARDs
CVD factors	
Atrial Fibrillation	Coronary Artery Disease
Type 2 Diabetes	Heart Failure
Stroke or transient ischemic attack	Hypertension
Hyperlipidemia	Peripheral vascular disease
Venous thromboembolism	

Comorbid conditions	
Chronic liver disease	Inflammatory bowel disease
Chronic kidney disease (stage 3+)	Psoriasis
Chronic obstructive pulmonary disease	Combined comorbidity index
	Frailty score
Comedication use	
Antidepressant drugs (including serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants)	Antihypertensive drugs (including angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, beta blockers, calcium channel blockers, diuretics, nitrates)
Non-steroidal anti-inflammatory drugs	Lipid lowering drugs (Statins and non-statins)
Selective Cox-2 inhibitors	Anti-arrhythmic drugs
Opioids	Anticoagulants
COPD drugs (bronchodilators, inhaled corticosteroids)	Antiplatelets (including acetylsalicylic acid)
Other hormonal agents/HRT	Non-insulin diabetes medications
	Insulin
Markers for healthy behavior, frailty, healthcare use	
Number of C-reactive protein tests ordered	Echocardiogram
Number of serum creatinine tests ordered	Cardiac stress test
Number of lipid tests	Colonoscopy
Number of outpatient visits	Flu Shot
Number of primary care physician visits	Mammography
Number of rheumatologist visits	Pap smear
Number of emergency department visits	Pneumococcal vaccine
Number of hospitalizations (any, recent)	PSA test
Number of hospital days	Total distinct brand drugs used
Cardiologist visits	Total distinct generic drugs used
Electrocardiogram	Number of unique prescription medications

7. Outcome variables and study follow-up:

- **Primary outcome**: Composite cancer outcome consisting of development of any new malignancies (excluding NMSC) defined by a validated claims-based algorithm using two inpatient or outpatient ICD-9 or ICD-10 diagnosis codes of the same type of malignancy within 60 days. All carcinoma in situs will be excluded.[2,3]

- Secondary outcomes: Using two inpatient or outpatient ICD-9 or ICD-10 diagnosis codes for same type of malignancy within 60 days individually for lung cancer, colorectal cancer, breast cancer, prostate cancer, lymphatic/hematopoietic tissue cancers, lymphoma, leukemia, and non-melanoma skin cancer. Non-melanoma skin cancer will also be identified by using one inpatient or outpatient ICD-9 or ICD-10 code combined with one procedure code within 60 days of diagnosis.

Outcome	Codes	Care Setting	Position
All cancers excluding NMSC	ICD-9 DX: 140.x-149.x, 150.x-159.x, 160.x-165.x, 170.x-172.x,174.x-176.x, 179.x-189.x, 190.x-199.x, 200.x-208.x ICD10 DX: C00.x-C96.x (excluding C44.x), C7A.x, C7B.x, D45	Inpatient/outpatient	Primary/secondary
Lymphatic/hematopoietic tissue cancers	ICD-9 DX: 200.x-208.x ICD10 DX: C81.x- C95.x	Inpatient/outpatient	Primary/secondary
Lung cancer	ICD-9 DX: 162.x ICD-10 DX: C33.x, C34.x	Inpatient/outpatient	Primary/secondary
Colorectal cancer	ICD-9 DX: 153.x, 154.0, 154.1, 154.8 ICD-10 DX: C18.x, C19.x, C20.x	Inpatient/outpatient	Primary/secondary

Breast cancer	ICD-9 DX: 174.x, 175.x ICD-10 DX: C50.x	Inpatient/outpatient	Primary/secondary
Prostate Cancer	ICD-9 DX: 185.x ICD-10 DX: C61.x	Inpatient/outpatient	Primary/secondary
Lymphoma	ICD-9 DX: 200.x, 201.x, 202.x ICD-10 DX: C81.x, C82.x, C83.x, C84.x, C85.x, C86.x, C88.x	Inpatient/outpatient	Primary/secondary
Leukemia	ICD-9 DX: 204.x-208.x ICD-10 DX: C91.x, C92.x, C93.x, C94.x, C95.x	Inpatient/outpatient	Primary/secondary
Non-melanoma skin cancer	ICD-9 DX: 173.x ICD-10 DX: C44.x CPT-4 codes (0-60 days after the diagnosis code): 11600,11601,11602,11603,11604, 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, 17311,17312,17313,17314, 17315	Inpatient/outpatient	Primary/secondary

8. Study Follow-up Period:

For the primary analysis, we will implement an ***as-treated*** exposure definition. Follow-up will start the day after initiation of tofacitinib and TNFi and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest
- The date of end of enrollment in the database
- End of the study period
- Date of treatment switch or drug discontinuation, defined as the date of the last continuous treatment episode of the index drug plus a defined grace period (i.e., discontinuation defined after 60 days of no prescription refills for the index exposure after the days supply end for the most recent dispensing)
- Death

For secondary analysis, we will implement an *intention-to-treat* exposure definition. Follow-up will start the day after initiation of tofacitinib and TNFi and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest
- The date of end of enrollment in the database
- End of the study period
- Death
- 365 days after the cohort entry date

9. Propensity score fine stratification analysis

We will use a propensity-score (PS)-based approach to account for measured confounding in this study.[4] The PS will be calculated as the predicted probability of initiating the exposure of interest (i.e., tofacitinib) conditional on baseline covariates using multivariable logistic regression constructed separately in each data source.[5] On average, patients with similar PSs have similar distribution of potential confounders used to estimate the PS. We will trim non-overlapping regions of the propensity score distributions.[5] Subsequently, we will use PS fine stratification weighting to achieve covariate balance between treatment groups.[6] We will create 50 PS strata, based on the distribution of PS in tofacitinib-treated patients. A weight of one will be assigned to tofacitinib users and TNF inhibitor initiators will be weighted proportional to the distribution of tofacitinib initiators in the PS stratum into which they fell to achieve covariate balance ($\mathbf{N_{exposed\ in\ PS\ stratum\ i}/\ N_{total}}$)/ ($\mathbf{N_{reference\ in\ PS\ stratum\ i}/N_{total\ reference}}$).[6] This weighting strategy estimates the average treatment effect on the treated (ATT).[6]

We will report multiple diagnostics for PS analysis in this protocol. First, the PS distribution overlap will be provided between two groups before weighting.[6] The balance in each individual covariate between two treatment groups will also be reported before and after weighting using standardized differences.[7,8] Distribution of PS weights will be assessed and truncation strategies will be considered if necessary.

10. Statistical analysis plans

Descriptive statistics, including frequencies and proportions for categorical variables and mean, median, standard deviation (SD), interquartile range (IQR), and range (minimum, maximum) for continuous variables, will be used to summarize baseline characteristics for each study cohort. Standardized differences will be used to compare characteristics before and after PS fine stratification weighting.[7,8] Crude incidence rates and corresponding 95% confidence intervals (CI) will be reported for each study outcome. The primary analysis will consist of Cox proportional hazards model weighted using PS fine stratification weights and using an *as-treated* exposure definition. This model will generate weighted hazard ratio and 95% confidence interval when comparing tofacitinib with TNFi. We will also report difference in rates when comparing tofacitinib with TNFi and corresponding 95% CI in the weighted population. Results will be reported independently for each database. Effect estimates will also be pooled across three databases using fixed effects model.

We will also report cumulative incidence and the corresponding 95% CI independently for all outcomes and each study group by time since treatment initiation. Secondary analysis will also be conducted by cumulative duration of use, which will be ascertained by adding the days of supply for use of tofacitinib and TNFi in a time-dependent manner until end of follow-up. We will compare less than one year of cumulative use of tofacitinib with less than one year of use of TNFi and at least one year of cumulative use for tofacitinib with at least one-year of use of TNFi. Pre-specified subgroup analysis will be

conducted based on age (≤65 and > 65) and sex. Secondary analysis will be conducted by using an *intention-to-treat* exposure definition whereby patients will be censored 365 days after initiation of treatment with tofacitinib or TNF inhibitors. We will also conduct propensity score matching where each patient initiating tofacitinib will be matched with those initiating TNFi using nearest neighbor greedy matching without replacement using a caliper of 0.025 on the natural scale of the PS (1:1 matching).[5,9] Standardized differences will be used to compare characteristics before and after matching. In addition, we will examine the risk of cancer outcomes by stratifying by number of previous prescriptions of biological DMARDs (no previous prescriptions of bDMARDs vs ≥1 prescription of bDMARDs).

Sensitivity analysis will be conducted by restricting the TNFi comparator group to only adalimumab and etanercept users and by using herpes zoster as a positive control outcome.[10] In addition, sensitivity analyses will be conducted by lagging exposure by three months after treatment initiation to account for latency of treatment effect and exclude prevalent cases of cancer and by extending the grace period after treatment discontinuation to six months to account for the potential carryover effect of the treatments on cancer outcomes.

11. References

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