THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Original Research

Association between baseline cardiovascular risk and incidence rates of major adverse cardiovascular events and malignancies in patients with psoriatic arthritis and psoriasis receiving tofacitinib

Ther Adv Musculoskelet Dis

2023, Vol. 15: 1–17

DOI: 10.1177/1759720X221149965

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Abstract

Background: Tofacitinib is a Janus kinase inhibitor for the treatment of psoriatic arthritis (PsA) and has been investigated for psoriasis (PsO).

Objectives: This *post hoc* analysis examined baseline cardiovascular (CV) disease risk and its association with the occurrence of major adverse cardiovascular events (MACE) and malignancies in tofacitinib-treated patients with PsA and PsO.

Design: Included three phase III/long-term extension (LTE) PsA trials and seven phase II/phase III/LTE PsO trials of patients receiving ⩾1 dose of tofacitinib.

Methods: Incidence rates (IRs: patients with events/100 patient-years) for MACE and malignancies (excluding non-melanoma skin cancer) were determined in subgroups according to history of atherosclerotic CV disease (ASCVD), baseline 10-year risk of ASCVD (in patients without history of ASCVD), and baseline metabolic syndrome (MetS).

Results: For patients with PsA ($N = 783$) and PsO ($N = 3663$), respectively, tofacitinib exposure was 2038 and 8950 patient-years (median duration: 3.0 and 2.4 years), and 40.9% and 32.7% had MetS. Excluding missing CV risk profile data, 51/773 (6.6%) and 144/3629 (4.0%) patients had history of ASCVD, and in patients without history of ASCVD, around 20.0% had intermediate/high baseline 10-year ASCVD risk. For PsA and PsO, IRs of MACE were greatest in those with history of ASCVD or high baseline 10-year ASCVD risk. For PsA, five of six patients with MACE had baseline MetS. Malignancy IRs in patients with PsA were greatest in those with intermediate/high baseline 10-year ASCVD risk. Of these, eight of nine patients with malignancies had baseline MetS. In the PsO cohort, IR of malignancies was notably greater with high *versus* low/borderline/intermediate baseline 10-year ASCVD risk.

Conclusion: In tofacitinib-treated patients with PsA/PsO, increased ASCVD risk and baseline MetS were associated with higher IRs for MACE and malignancies. Our results support assessing CV risk in patients with PsA/PsO and suggest enhanced cancer monitoring in those with increased ASCVD risk.

Registration (ClinicalTrials.gov): NCT01877668/NCT01882439/NCT01976364/NCT00678210/NCT01710046/NCT01241591/NCT01186744/NCT01276639/NCT01309737/NCT01163253

Keywords: cardiovascular risk, MACE, malignancies, psoriasis, psoriatic arthritis, tofacitinib

Received: 22 August 2022; revised manuscript accepted: 20 December 2022.

Plain Language Summary

People who have psoriatic arthritis or psoriasis may have more heart-related problems and cancer if they have a higher risk of cardiovascular disease: A study in people with psoriatic arthritis or psoriasis receiving tofacitinib

Why was this study done?

- People with psoriatic arthritis (PsA) and psoriasis (PsO) are more likely than the general population to have a disease affecting the heart and blood vessels [cardiovascular (CV) disease].
- People who are more likely to have CV disease may also be more likely to have certain types of cancer.
- Tofacitinib is a medicine to treat people with PsA and has been tested in people with PsO.
- We wanted to know if the risk of CV disease affects the number of heart-related problems (including heart attack, stroke, or death) and cancer in people with PsA and PsO.

What did the researchers do?

- We used results from 10 clinical trials.
- In these trials, people with PsA and PsO were taking tofacitinib 5 or 10 mg twice a day.
- After the trials had ended, we measured people's risk of CV disease using a risk calculator. This risk calculator showed if they had a low, borderline, intermediate, or high risk of CV disease over the next 10 years. We also checked if they had had CV disease before treatment.
- We checked if people had a group of conditions linked to CV disease: diabetes, high blood pressure, and obesity.
- We counted the cases of heart-related problems and cancer in people once they started taking tofacitinib.

What did the researchers find?

In people with PsA and PsO taking tofacitinib:

- There were more cases of heart-related problems and cancer in people who had intermediate or high risk of CV disease.
- There were more cases of heart-related problems in people who had had CV disease before.
- More people with diabetes, high blood pressure, and obesity had heart-related problems and cancer than people without those conditions.

What do the findings mean?

- It is important to measure risk and assess history of CV disease in people with PsA and PsO, including those taking tofacitinib.
- We should test for cancer in people with high risk of CV disease.

Infographic

Association between baseline cardiovascular risk and incidence rates of major adverse cardiovascular events and malignancies in patients with psoriatic arthritis and psoriasis receiving tofacitinib

LE Kristensen, B Strober, D Poddubnyy, YY Leung, H Jo, K Kwok, I Vranic, DL Fleishaker, L Fallon, A Yndestad, DD Gladman

Tofacitinib is a JAK inhibitor for the treatment of PsA, and has been investigated for PsO

Post hoc analysis: Three Phase 3/LTE PsA trials and seven Phase 2/Phase 3/LTE PsO trials of patients receiving ≥1 dose of **tofacitinib**

Incidence of MACE and malignancies (excl NMSC) were assessed by HxASCVD and 10-year risk of ASCVD, per the ASCVD-PCE calculator, and baseline MetS

PsA cohort (*N*=783)

HxASCVD: 6.6%*

No HxASCVD by 10-year risk of MACE category*:
- **High:** 4.3%
- **Intermediate:** 14.9%
- **Borderline:** 11.4%
- **Low:** 62.9%

MetS: 40.9%
Tofacitinib exposure: 2038 PY
*Excl missing CV risk profile data

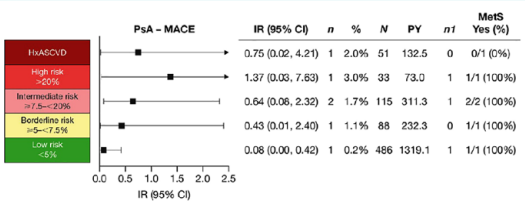
PsO cohort (*N*=3663)

HxASCVD: 4.0%*

No HxASCVD by 10-year risk of MACE category:
- **High:** 4.7%
- **Intermediate:** 19.1%
- **Borderline:** 10.8%
- **Low:** 61.4%

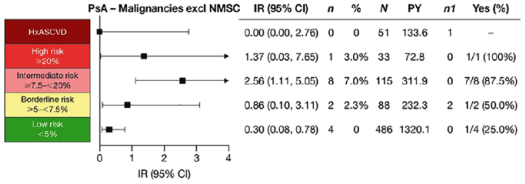
MetS: 32.7%
Tofacitinib exposure: 8950 PY
*Excl missing CV risk profile data

PsA: IR of MACE and malignancies (excl NMSC)



PsA – MACE	IR (95% CI)	*n*	%	*N*	PY	*n1*	MetS Yes (%)
HxASCVD	0.75 (0.02, 4.21)	1	2.0%	51	132.5	0	0/1 (0%)
High risk ≥20%	1.37 (0.03, 7.63)	1	3.0%	33	73.0	1	1/1 (100%)
Intermediate risk ≥7.5–<20%	0.64 (0.08, 2.32)	2	1.7%	115	311.3	1	2/2 (100%)
Borderline risk ≥5–<7.5%	0.43 (0.01, 2.40)	1	1.1%	88	232.3	0	1/1 (100%)
Low risk <5%	0.08 (0.00, 0.42)	1	0.2%	486	1319.1	1	1/1 (100%)

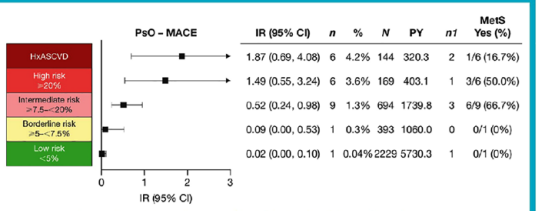
5 of the **6** patients with MACE had baseline MetS



PsA – Malignancies excl NMSC	IR (95% CI)	*n*	%	*N*	PY	*n1*	MetS Yes (%)
HxASCVD	0.00 (0.00, 2.76)	0	0	51	133.6	1	–
High risk ≥20%	1.37 (0.03, 7.65)	1	3.0%	33	72.8	0	1/1 (100%)
Intermediate risk ≥7.5–<20%	2.56 (1.11, 5.05)	8	7.0%	115	311.9	0	7/8 (87.5%)
Borderline risk ≥5–<7.5%	0.86 (0.10, 3.11)	2	2.3%	88	232.3	2	1/2 (50.0%)
Low risk <5%	0.30 (0.08, 0.78)	4	0	486	1320.1	0	1/4 (25.0%)

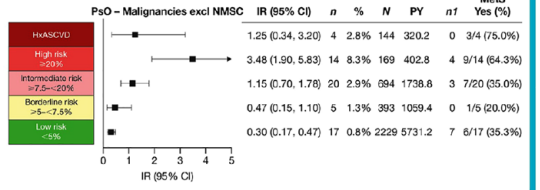
10 of the **15** patients with malignancies had baseline MetS

PsO: IR of MACE and malignancies (excl NMSC)



PsO – MACE	IR (95% CI)	*n*	%	*N*	PY	*n1*	MetS Yes (%)
HxASCVD	1.87 (0.69, 4.08)	6	4.2%	144	320.3	2	1/6 (16.7%)
High risk ≥20%	1.49 (0.55, 3.24)	6	3.6%	169	403.1	1	3/6 (50.0%)
Intermediate risk ≥7.5–<20%	0.52 (0.24, 0.98)	9	1.3%	694	1739.8	3	6/9 (66.7%)
Borderline risk ≥5–<7.5%	0.09 (0.00, 0.53)	1	0.3%	393	1060.0	0	0/1 (0%)
Low risk <5%	0.02 (0.00, 0.10)	1	0.04%	2229	5730.3	1	0/1 (0%)

10 of the **23** patients with MACE had baseline MetS



PsO – Malignancies excl NMSC	IR (95% CI)	*n*	%	*N*	PY	*n1*	MetS Yes (%)
HxASCVD	1.25 (0.34, 3.20)	4	2.8%	144	320.2	0	3/4 (75.0%)
High risk ≥20%	3.48 (1.90, 5.83)	14	8.3%	169	402.8	4	9/14 (64.3%)
Intermediate risk ≥7.5–<20%	1.15 (0.70, 1.78)	20	2.9%	694	1738.8	3	7/20 (35.0%)
Borderline risk ≥5–<7.5%	0.47 (0.15, 1.10)	5	1.3%	393	1059.4	0	1/5 (20.0%)
Low risk <5%	0.30 (0.17, 0.47)	17	0.8%	2229	5731.2	7	6/17 (35.3%)

26 of the **60** patients with malignancies had baseline MetS

In the PsA and PsO cohorts:
- IRs of MACE were greatest in patients with HxASCVD or high baseline 10-year ASCVD risk
- IRs of malignances in patients without HxASCVD were greatest in those with intermediate/high baseline 10-year ASCVD risk

Conclusions

- As expected, in tofacitinib-treated patients with PsA and PsO, increased ASCVD risk and baseline MetS were associated with higher IRs for MACE and malignancies
- Our results support assessing CV risk in patients with PsA and PsO, and suggest enhanced cancer monitoring in those with increased ASCVD risk

Additional information This is an infographic abstract of the original article published in *Therapeutic Advances in Musculoskeletal Disease*
This study was sponsored by Pfizer. Writing support for this summary was provided by Justine Juana, CMC Connect, a division of IPG Health Medical Communications, and was funded by Pfizer
ASCVD: atherosclerotic CV disease; CI, confidence interval; CV, cardiovascular; excl, excluding; HxASCVD, history of ASCVD; IR, incidence rate (patients with first events per 100 PY); JAK, Janus kinase; LTE, long-term extension; MACE, major adverse CV events; MetS, metabolic syndrome; *n*, number of patients with events; *n1*, number of patients with events outside the 28-day risk period; *N*, number of evaluable patients; NMSC, non-melanoma skin cancer; PCE, pooled cohort equations; PsA, psoriatic arthritis; PsO, psoriasis; PY, patient-years

Introduction

Psoriasis (PsO) is a chronic inflammatory skin disease that most commonly presents with psoriatic plaques.[1] Approximately 30% of patients with PsO have psoriatic arthritis (PsA),[2,3] an inflammatory arthritis with several dermatological and musculoskeletal manifestations.[4] Both diseases substantially impact health-related quality of life and the functional capacity of patients.[3,5,6]

Patients with PsA and PsO are more likely to have traditional cardiovascular (CV) disease risk factors than the general population.[7–9] Increased CV disease risk in these patients is thought to be caused by a combination of systemic inflammation and modifiable traditional CV risk factors.[7,8] PsA and PsO are both also associated with a high prevalence of metabolic syndrome (MetS).[7,8] MetS is an important comorbidity in PsA,[10] associated with more severe disease and poor response to therapy.[7] Obesity potentiates MetS and worsens CV risk in PsO.[8]

A possible link between PsO and malignancies has also been investigated, but this association remains debatable.[11] Patients with PsO have been reported to have a slightly increased risk of keratinocyte cancer [i.e. non-melanoma skin cancer (NMSC)] and lymphoma, but data on malignancies in patients with PsA were limited.[11] Another study in patients with PsA and PsO did not find evidence of a higher malignancy rate *versus* the general population overall, although incidence of skin cancer was comparatively higher.[12] There appears to be considerable overlap in risk factors for common types of cancer (e.g. lung cancer, breast cancer, colon cancer) and CV disease,[13] and a recent study found a strong association between 10-year risk of atherosclerotic CV disease (ASCVD) and cancer risk in the general population.[14]

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of PsA, which has also been investigated for PsO. The efficacy and safety of tofacitinib 5 mg twice daily (BID; recommended dosage)[15,16] and 10 mg BID has been demonstrated in two phase III randomized controlled trials (RCTs) of patients with active PsA,[17,18] and those dosages were investigated in an open-label, long-term extension (LTE) study.[19] In addition, tofacitinib has been investigated in patients with moderate-to-severe chronic plaque PsO. While only approved for the treatment of PsO in Russia, the efficacy and safety of tofacitinib 5 and 10 mg BID in patients with PsO was reported in phase II[20,21] and global phase III[22–25] trials, and in an LTE study.[26]

ORAL Surveillance, a post-authorization safety study, evaluated the risk of adjudicated major adverse cardiovascular events (MACE) and malignancies with tofacitinib *versus* tumor necrosis factor inhibitors (TNFis) in patients with rheumatoid arthritis (RA) aged ⩾50 years and with ⩾1 additional CV risk factor.[27] For combined tofacitinib doses (5 and 10 mg BID) *versus* TNFi, non-inferiority was not shown for either adjudicated MACE or malignancies (excluding NMSC).[27] In addition, in this CV risk-enriched RA population, the risk of MACE and malignancies was increased with tofacitinib *versus* TNFis.[27,28]

This *post hoc* analysis of phase II, phase III, and LTE clinical trials examined baseline history of ASCVD, 10-year risk of ASCVD, presence of MetS, and association with MACE and malignancies (excluding NMSC) in patients with PsA and PsO receiving tofacitinib.

Methods

Study design and patients

Post hoc analyses evaluated patients with PsA and PsO treated with tofacitinib in randomized clinical trials. The PsA cohort was pooled from three phase III (NCT01877668; NCT01882439) and open-label LTE (NCT01976364) trials. The PsO cohort was pooled from seven phase II (NCT00678210; NCT01710046), phase III (NCT01241591; NCT01186744; NCT01276639; NCT01309737), and LTE (NCT01163253) trials. Both cohorts included all patients receiving at least one dose of tofacitinib. Full details of each individual study have been published previously, with brief details noted in Table S1.

Adult patients (⩾18 years of age) were included, with patients in the PsA trials receiving tofacitinib (5 or 10 mg BID) in combination with background conventional synthetic disease-modifying drugs (csDMARDs), and patients in the PsO trials receiving tofacitinib as monotherapy (2, 5, 10, or 15 mg BID). In the LTE studies, the tofacitinib dose could be switched for efficacy or safety reasons. Consequently, because patients could change dose during the LTE, this analysis used an 'average dosing algorithm', in which patients were assigned to average tofacitinib 5 or 10 mg

BID if their average total daily dose (i.e. the sum of all doses received divided by the number of days of treatment over the entire study duration for each patient) was <15 mg (i.e. 'average tofacitinib 5 mg BID') or ⩾15 mg ('average tofacitinib 10 mg BID'), respectively.

Final data for the PsA cohort are from 31 July 2019, and for the PsO cohort, are from 18 August 2016 because the PsO clinical trial program was terminated when the objectives of characterizing long-term safety and tolerability were met. All of the trials included were approved by the relevant Ethics Committees or Institutional Review Boards. All patients provided written, informed consent to participate.

Evaluation of history of ASCVD, baseline risk of ASCVD, and presence of MetS

History of ASCVD was defined as at least one of the occurrence of coronary artery disease (CAD; e.g. myocardial infarction or stable angina pectoris), cerebrovascular disease (CeVD; e.g. stroke or transient ischemic disease), or peripheral artery disease (PAD; e.g. peripheral artery thrombosis or intermittent claudication). History of CAD, CeVD, or PAD was identified in patients' general medical histories through Medical Dictionary for Regulatory Activities preferred terms reflecting prior/ongoing events, procedures, or diagnoses with these conditions.

In patients with no history of ASCVD, baseline 10-year risk of events associated with ASCVD was determined using the ASCVD-pooled cohort equation (ASCVD-PCE) calculator, which takes into account factors including age, sex, race, smoking status, systolic blood pressure, anti-hypertensive treatment, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and diabetes mellitus.[29] Based on risk scores, and as suggested by the American College of Cardiology/American Heart Association, patients were assigned to one of the following risk categories: high (⩾20% 10-year risk), intermediate (⩾7.5–<20%), borderline (⩾5–<7.5%), or low (<5%).[30] Note that the ASCVD-PCE calculator was originally validated for patients 40–79 years of age, but here, was applied on patients <40 years of age and also on patients of racial/ethnic groups or from geographical regions where it is not explicitly validated.[29]

MetS status at baseline was defined as present if at least three of the following five criteria were met: hypertension (systolic blood pressure ⩾130 mmHg and/or diastolic blood pressure ⩾85 mmHg and/or concomitant anti-hypertensive medication), raised triglycerides (TG; ⩾150 mg/dl/1.7 mmol/l and/or concomitant TG-lowering medication), reduced HDL-C (<40 mg/dl/1.0 mmol/l in males; <50 mg/dl/1.3 mmol/l in females), high waist circumference (population- and country-specific definitions), or high fasting glucose levels (⩾100 mg/dl and/or concomitant anti-diabetic medication).[31]

Assessment of incidence of MACE and malignancies

In patients, in both the PsA and PsO cohorts, the number of patients with MACE (defined as a composite of myocardial infarction, stroke, and CV deaths) and malignancies (excluding NMSC) is presented according to history of ASCVD, 10-year ASCVD risk categories, and presence of baseline MetS.

In the 12-month, phase III, tofacitinib PsA study, OPAL Broaden,[17] with an active comparator [adalimumab 40 mg subcutaneously every 2 weeks (Q2W)], the number of adalimumab-treated patients with MACE and malignancies at month 12 was also assessed. This study was not designed as a head-to-head comparison of tofacitinib and adalimumab.

A sensitivity analysis that evaluated the incidence of MACE and malignancies in the PsA and PsO cohorts stratified by age group (<40 *versus* ⩾40 years) is presented according to history of ASCVD and 10-year ASCVD risk categories.

Statistical analyses

MACE and malignancies (excluding NMSC) were counted within the predefined risk period, based on the 28-day on-treatment time, defined as time from first study dose to last study dose +28 days or to last contact date (if a patient died, last contact date was the death date), whichever was earliest. Per protocol, a patient experiencing serious adverse events, such as a MACE or malignancy event, was required to discontinue the study drug and the study.

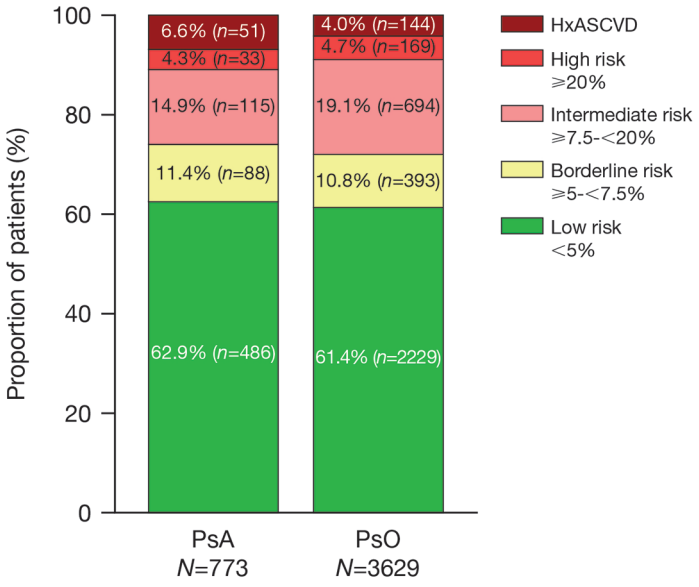


Figure 1. Baseline CV risk profile of PsA and PsO cohorts.
Patients without HxASCVD were categorized according to their 10-year risk of ASCVD, per the ASCVD-PCE risk calculator.[29] ASCVD was defined as any of CAD, CeVD, or PAD. Patients with no 10-year ASCVD risk score due to missing data were not included (PsA, $n=10$; PsO, $n=34$).
ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CeVD, cerebrovascular disease; CV, cardiovascular; Hx, history; *N*, total number of patients in the cohort; PAD, peripheral artery disease; PCE, pooled cohort equations; PsA, psoriatic arthritis; PsO, psoriasis.

Patients without events were censored at the end of the risk period. Crude incidence rates (IRs) were expressed as the number of patients with first events per 100 patient-years (PY), along with two-sided 95% confidence intervals (CIs) using the exact Poisson method.[32]

Results

For a brief summary, please refer to the Infographic.

Patients

A total of 783 patients with PsA and 3663 patients with PsO received ⩾1 dose of tofacitinib. As reported previously,[33] the total tofacitinib exposure (PY) and median (range) length of exposure for the PsA cohort were 2038 PY, with a median exposure of 3.0 (>0–4.8) years; for the PsO cohort, it was 8950 PY, with a median exposure of 2.4 (>0–5.7) years. When analyzed by average tofacitinib dose, 458 and 325 patients in the PsA cohort and 920 and 2743 patients in the PsO cohort were in the average 5 or 10 mg BID dose groups, respectively. The median (interquartile range) dose in the average 5 and 10 mg BID dose groups was 10.0 mg (10.0–12.3 mg) and 18.3 mg (16.7–19.4 mg) for the PsA cohort, and 10.5 mg (10.0–12.9 mg) and 19.5 mg (17.9–20.0 mg) for the PsO cohort, respectively.

CV risk profile was determined in 773 patients with PsA and 3629 patients with PsO. In the PsA cohort, 51/773 (6.6%) patients had a history of ASCVD, a greater proportion than in the PsO cohort, with 144/3629 (4.0%) patients (Figure 1). Similarly, proportionally more patients in the PsA cohort had MetS at baseline [320/783 patients (40.9%); tofacitinib 5 mg BID: 190/458 (41.5%); tofacitinib 10 mg BID: 130/325 (40.0%)] than in the PsO cohort [1197/3663 patients (32.7%); tofacitinib 5 mg BID: 311/920 (33.8%); tofacitinib 10 mg BID: 886/2743 (32.3%)]. In patients without a history of ASCVD, around 20% had intermediate or high baseline 10-year ASCVD risk. Similar trends were seen when patients were analyzed by average dose group (Figure S1).

Table 1 summarizes CV risk factors and concomitant treatments for all patients receiving tofacitinib without a history of ASCVD by 10-year ASCVD risk category and patients with a history of ASCVD. In the PsA and PsO cohorts, ASCVD risk increased with age, and higher risk was associated with being male, having a body mass index ⩾ 30 kg/m^2 or having a history of diabetes, hypertension, or hyperlipidemia. Certain concomitant medications were being used more frequently in higher-risk groups. Baseline characteristics for the average tofacitinib dose groups are presented in Tables S2 and S3.

Tofacitinib in PsA: MACE and association with baseline CV risk

In the PsA cohort, the IR (95% CI) for MACE in the all-tofacitinib group was 0.29 (0.11, 0.62).[33] Table S4 describes MACE that occurred in tofacitinib-treated patients during ($n=6$) or outside ($n=3$) of the 28-day risk period, including their baseline clinical characteristics and concomitant treatment. MACE IR (95% CI) was 0.48 (0.10, 1.42) in patients with PsA that received tofacitinib 5 mg BID throughout this study (i.e. constant tofacitinib 5 mg BID; $n=3$, $N=348$, 618.9 PY). In the phase III study OPAL Broaden,[17] one MACE occurred in a patient initially receiving placebo and then switching to tofacitinib 5 mg BID at month 3 [IR (95% CI): 0.79

Table 1. Baseline demographics and characteristics for all patients receiving tofacitinib with a history of ASCVD or by 10-year ASCVD risk category for the (a) PsA and (b) PsO cohorts.

(a) PsA cohort						
Characteristic	**Overall (*N* = 783)**	**Low (<5%) (*N* = 486)**	**Borderline (≥5–<7.5%) (*N* = 88)**	**Intermediate (≥7.5–<20%) (*N* = 115)**	**High (≥20%) (*N* = 33)**	**HxASCVD (*N* = 51)**
Age, years						
Mean (SD)	48.7 (12.0)	43.1 (10.2)	53.8 (8.7)	59.0 (7.5)	66.5 (5.6)	58.1 (7.5)
Median (range)	50.0 (18–78)	43.0 (18–65)	55.0 (23–67)	59.0 (37–74)	67.0 (54–78)	58.0 (44–71)
≥50 at baseline, *n* (%)	398 (50.8)	145 (29.8)	69 (78.4)	103 (89.6)	33 (100.0)	43 (84.3)
Male, *n* (%)	355 (45.3)	177 (36.4)	37 (42.0)	79 (68.7)	25 (75.8)	31 (60.8)
BMI (kg/m^2)						
Mean (SD)	29.6 (6.0)	28.7 (6.1)	31.2 (6.3)	30.8 (5.2)	31.9 (5.7)	31.2 (5.8)
≥30, *n* (%)	333 (42.5)	175 (36.0)	47 (53.4)	58 (50.4)	20 (60.6)	28 (54.9)
CRP > 2.87 mg/liter[a], *n* (%)	486 (62.1)	306 (63.0)	59 (67.0)	71 (61.7)	22 (66.7)	24 (47.1)
Smoking status, *n* (%)						
Never smoked	485 (61.9)	331 (68.1)	46 (52.3)	55 (47.8)	15 (45.5)	29 (56.9)
Smoker	140 (17.9)	68 (14.0)	24 (27.3)	33 (28.7)	6 (18.2)	9 (17.6)
Ex-smoker	158 (20.2)	87 (17.9)	18 (20.5)	27 (23.5)	12 (36.4)	13 (25.5)
History of diabetes, *n* (%)	107 (13.7)	33 (6.8)	13 (14.8)	26 (22.6)	19 (57.6)	14 (27.5)
History of hypertension, *n* (%)	306 (39.1)	112 (23.0)	43 (48.9)	74 (64.3)	29 (87.9)	43 (84.3)
History of hyperlipidemia, *n* (%)	167 (21.3)	56 (11.5)	29 (33.0)	34 (29.6)	14 (42.4)	31 (60.8)
History of VTE, *n* (%)	10 (1.3)	3 (0.6)	2 (2.3)	2 (1.7)	0	3 (5.9)
Prior therapy, *n* (%)						
csDMARD (non-MTX)	370 (47.3)	216 (44.4)	48 (54.5)	55 (47.8)	16 (48.5)	29 (56.9)
TNFi	377 (48.1)	222 (45.7)	42 (47.7)	62 (53.9)	19 (57.6)	28 (54.9)
Concomitant medications[b], *n* (%)						
MTX	725 (92.6)	458 (94.2)	78 (88.6)	109 (94.8)	28 (84.8)	44 (86.3)
Oral corticosteroids	171 (21.8)	119 (24.5)	15 (17.0)	23 (20.0)	6 (18.2)	7 (13.7)
Anticoagulants	68 (8.7)	7 (1.4)	8 (9.1)	15 (13.0)	7 (21.2)	29 (56.9)
Antiplatelets (including aspirin)	54 (6.9)	5 (1.0)	6 (6.8)	9 (7.8)	6 (18.2)	27 (52.9)
Statins	100 (12.8)	23 (4.7)	19 (21.6)	23 (20.0)	13 (39.4)	21 (41.2)
Oral contraceptives/HRT	72 (9.2)	63 (13.0)	6 (6.8)	0	1 (3.0)	2 (3.9)

(Continued)

Table 1. (Continued)

(b) PsO cohorts						
Characteristic	**Overall (*N* = 3663)**	**Low (<5%) (*N* = 2229)**	**Borderline (⩾5–<7.5%) (*N* = 393)**	**Intermediate (⩾7.5–<20%) (*N* = 694)**	**High (⩾20%) (*N* = 169)**	**HxASCVD (*N* = 144)**
Age, years						
Mean (SD)	44.8 (12.9)	38.5 (10.1)	50.2 (8.5)	55.2 (9.4)	62.1 (10.9)	57.2 (11.2)
Median (range)	45.0 (18–82)	38.0 (18–67)	51.0 (18–67)	56.0 (19–75)	64.0 (19–82)	58.0 (21–79)
⩾50 at baseline, *n* (%)	1401 (38.2)	349 (15.7)	227 (57.8)	542 (78.1)	156 (92.3)	113 (78.5)
Male, *n* (%)	2546 (69.5)	1423 (63.8)	277 (70.5)	578 (83.3)	141 (83.4)	108 (75.0)
BMI (kg/m^2)						
Mean (SD)	29.9 (6.7)	29.0 (6.8)	31.0 (6.6)	30.9 (6.2)	32.5 (5.9)	31.1 (6.3)
⩾30, *n* (%)	1544 (42.2)	805 (36.1)	190 (48.3)	348 (50.1)	114 (67.5)	72 (50.0)
CRP > 2.87 mg/liter[a], *n* (%)	1497(40.9)	820 (36.8)	169 (43.0)	331 (47.7)	89 (52.7)	73 (50.7)
Smoking status, *n* (%)						
Never smoked	1412 (38.5)	1027 (46.1)	118 (30.0)	170 (24.5)	38 (22.5)	43 (29.9)
Smoker	1380 (37.7)	711 (31.9)	187 (47.6)	342 (49.3)	88 (52.1)	40 (27.8)
Ex-smoker	871 (23.8)	491 (22.0)	88 (22.4)	182 (26.2)	43 (25.4)	61 (42.4)
History of diabetes, *n* (%)	499 (13.6)	103 (4.6)	52 (13.2)	182 (26.2)	106 (62.7)	54 (37.5)
History of hypertension, *n* (%)	814 (22.2)	256 (11.5)	113 (28.8)	242 (34.9)	107 (63.3)	86 (59.7)
History of hyperlipidemia, *n* (%)	861 (23.5)	311 (14.0)	112 (28.5)	259 (37.3)	86 (50.9)	86 (59.7)
History of VTE, *n* (%)	11 (0.3)	7 (0.3)	1 (0.3)	1 (0.1)	0	2 (1.4)
Prior therapy, *n* (%)						
csDMARD (non-MTX)	390 (10.6)	243 (10.9)	47 (12.0)	68 (9.8)	13 (7.7)	19 (13.2)
TNFi	580 (15.8)	337 (15.1)	71 (18.1)	109 (15.7)	31 (18.3)	27 (18.8)
Concomitant medications[b], *n* (%)						
MTX	1157 (31.6)	710 (31.9)	129 (32.8)	222 (32.0)	43 (25.4)	49 (34.0)
Oral corticosteroids[c]	N/A	N/A	N/A	N/A	N/A	N/A
Anticoagulants	263 (7.2)	47 (2.1)	24 (6.1)	67 (9.7)	44 (26.0)	77 (53.5)
Antiplatelets (including aspirin)	272 (7.4)	59 (2.6)	27 (6.9)	65 (9.4)	45 (26.6)	72 (50.0)
Statins	487 (13.3)	148 (6.6)	62 (15.8)	148 (21.3)	60 (35.5)	64 (44.4)
Oral contraceptives/HRT	261 (7.1)	225 (10.1)	11 (2.8)	15 (2.2)	2 (1.2)	6 (4.2)

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; CeVD, cerebrovascular disease; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HRT, hormone replacement therapy; Hx, history; MTX, methotrexate; *N*, number of patients in each category (note that *N* varies for some variables); *n*, number of patients with each characteristic; N/A, not applicable; PAD, peripheral artery disease; PCE, pooled cohort equations; PsA, psoriatic arthritis; PsO, psoriasis; SD, standard deviation; TNFi, tumor necrosis factor inhibitor; VTE, venous thromboembolism.
Patients without HxASCVD were categorized according to their 10-year risk of ASCVD, per the ASCVD-PCE risk calculator.[29] ASCVD was defined as any of CAD, CeVD, or PAD.
[a]Indicates values above the upper limit of normal for the general population.
[b]Baseline (day 1).
[c]Concomitant corticosteroid use was not permitted in the PsO studies.

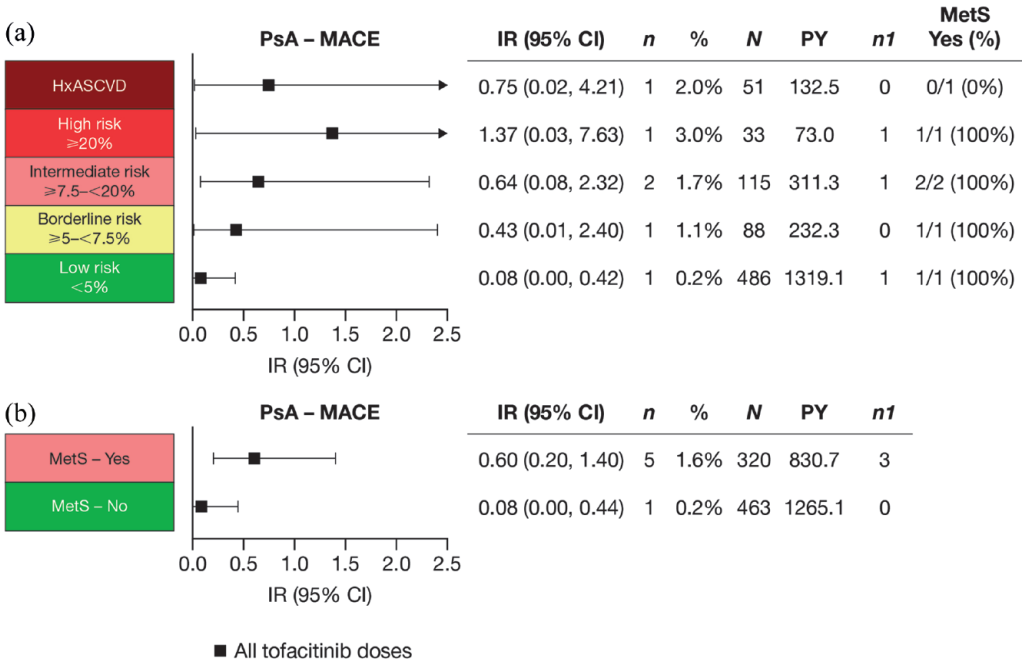


Figure 2. MACE by baseline CV risk profile in all patients receiving tofacitinib in the PsA cohort. (a) MACE IRs by CV risk categories in all patients receiving ⩾1 tofacitinib dose. Patients without HxASCVD were categorized according to their 10-year risk of MACE, per the ASCVD-PCE risk calculator.[29] IRs were expressed as number of patients with first events per 100 PY. (b) MACE IRs by baseline MetS status in all patients receiving ⩾1 tofacitinib dose. IRs were expressed as the number of patients with first events per 100 PY (safety analysis set).
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; Hx, history; IR, incidence rate; MACE, major adverse cardiovascular events; MetS, metabolic syndrome; *N*, number of patients; *n*, number of patients with first event within the risk period (up to 28 days beyond last dose); *n*1, number of patients with events outside the 28-day risk period; PCE, pooled cohort equations; PsA, psoriatic arthritis; PY, patient years.

(0.02, 4.38); $N=159$; 127.3 PY], and one occurred with adalimumab Q2W [IR (95% CI): 1.08 (0.03, 6.03); $N=106$; 92.5 PY].

Patients with PsA who at baseline had a low (i.e. <5%) 10-year risk of ASCVD had lower MACE IRs (95% CI) [0.08 (0.00, 0.42)] than patients in the other CV risk categories (Figure 2(a)). The highest MACE IR [1.37 (0.03, 7.63)] was in patients with a high (i.e. ⩾20%) 10-year risk of ASCVD, followed by those with a history of ASCVD [0.75 (0.02, 4.21)] (Figure 2(a)). MACE IRs for the average tofacitinib dose groups are displayed in Figure S2(a). Because of the relatively low number of MACE, patients, and PY, the 95% CIs for the different CV risk categories were all wide and overlapping, meaning all differences were numerical only, and data should be interpreted with caution.

Although the patients with PsA who had MetS at baseline had numerically higher IRs than those who did not, the 95% CIs were overlapping, likely due to the small number of events (Figure 2(b)). Notably, five of six (83.3%) MACE occurred in patients who at baseline had MetS. MACE IRs by MetS status at baseline for the average tofacitinib dose groups are shown in Figure S2(b).

Tofacitinib in PsA: malignancies (excluding NMSC) and association with baseline CV risk

Malignancy (excluding NMSC) IR (95% CI) in the all-tofacitinib group was 0.71 (0.40, 1.18) in the PsA cohort.[33] Table S5 describes malignancies (excluding NMSC) that occurred in tofacitinib-treated patients during ($n=15$) or outside ($n=3$) of the 28-day risk period, including their baseline clinical characteristics and concomitant treatment. In patients with PsA who received tofacitinib 5 mg BID throughout the study (i.e. constant tofacitinib 5 mg BID), IRs were [1.13 (0.45, 2.33; $n=7$; $N=348$; 619.8 PY)]. In OPAL Broaden,[17] three malignancies occurred with tofacitinib 5 mg BID [IR (95% CI): 2.36 (0.49, 6.91); $N=159$; 126.9 PY], and none were

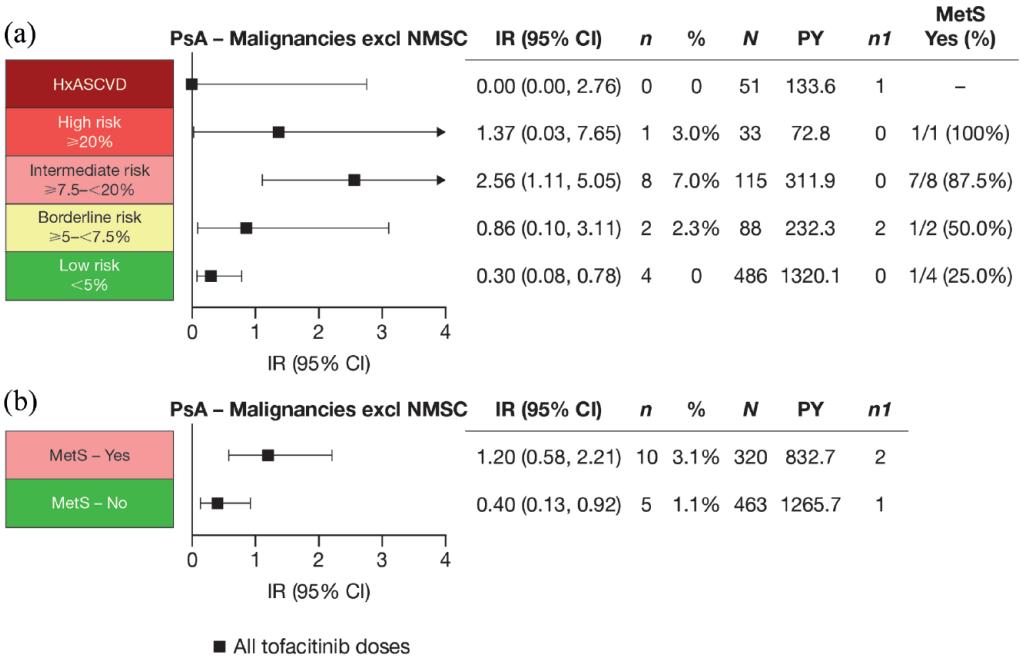


Figure 3. Malignancies (excluding NMSC) by baseline CV risk profile in all patients treated with tofacitinib in the PsA cohort. (a) Malignancy (excluding NMSC) IRs by CV risk categories in all patients receiving ⩾1 tofacitinib dose. Patients without HxASCVD were categorized according to their 10-year risk of MACE, per the ASCVD-PCE risk calculator.[29] IRs were expressed as the number of patients with first events per 100 PY. (b) Malignancy (excluding NMSC) IRs by baseline MetS status in all patients receiving ⩾1 tofacitinib dose. IRs were expressed as the number of patients with first events per 100 PY (safety analysis set).
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; Hx, history; IR, incidence rate; MACE, major adverse cardiovascular events; MetS, metabolic syndrome; *N*, number of patients; *n*, number of patients with first event within the risk period (up to 28 days beyond last dose); *n*1, number of patients with events outside the 28-day risk period; NMSC, non-melanoma skin cancer; PCE, pooled cohort equations; PsA, psoriatic arthritis; PY, patient years.

reported with adalimumab [0.00 (0.00, 3.98); *N* = 106; 92.6 PY].

Patients with PsA and a baseline intermediate (i.e. ⩾7.5–<20%) 10-year risk of ASCVD generally had the highest incidence of malignancies [IR: 2.56 (1.11, 5.05)] and when compared with patients with low 10-year risk of ASCVD [0.30 (0.08, 0.78)], had non-overlapping 95% CIs (Figure 3(a)). No patients with history of ASCVD reported malignancies within the 28-day risk period (Figure 3(a)).

In patients with PsA who had MetS at baseline, malignancy IRs were numerically higher (overlapping 95% CIs) *versus* those who did not have baseline MetS (Figure 3(b)). Of the nine patients with malignancies in the intermediate and high 10-year ASCVD risk categories, eight (88.9%) had MetS at baseline (Figure 3(a)). Malignancy IRs by MetS status at baseline for the average tofacitinib dose groups are shown in Figure S3(b).

In general, IRs for malignancies in the different CV risk categories were numerically higher in patients receiving average tofacitinib 5 mg BID, when compared with average tofacitinib 10 mg BID (Figure S3(a)).

Tofacitinib in PsO: MACE and malignancies (excluding NMSC) and their association with baseline CV risk

IR (95% CI) for MACE in the all-tofacitinib group in the PsO cohort was 0.25 (0.16, 0.37).[33] MACE IRs were highest in patients with a history of ASCVD [1.87 (0.69, 4.08)] or high 10-year risk of ASCVD at baseline [1.49 (0.55, 3.24)] (Figure 4(a)). MACE IRs were markedly lower in patients with low 10-year risk of ASCVD at baseline [0.02 (0, 0.10)], with 95% CIs not overlapping with those of patients with a history of ASCVD, or at least intermediate 10-year risk of ASCVD (Figure 4(a)). There was a numerical difference in MACE IRs by MetS status at baseline, but the 95% CIs were overlapping

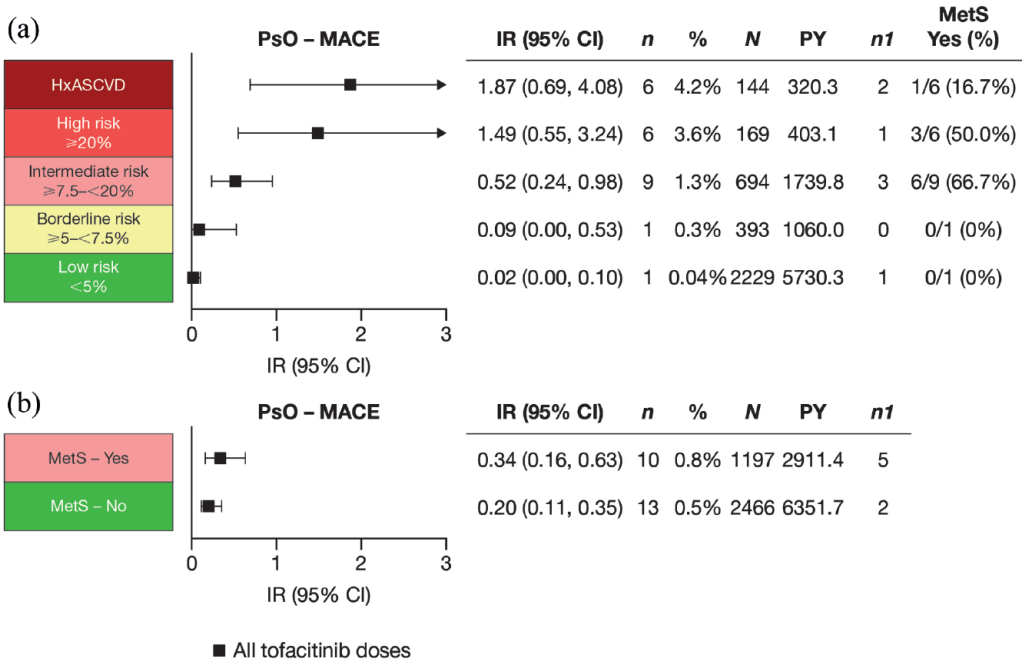


Figure 4. MACE by baseline CV risk profile in all patients receiving tofacitinib in the PsO cohort. (a) MACE IRs by CV risk categories in all patients receiving ⩾1 tofacitinib dose. Patients without HxASCVD were categorized according to their 10-year risk of MACE, per the ASCVD-PCE risk calculator.[29] IRs were expressed as the number of patients with first events per 100 PY. (b) MACE IRs by baseline MetS status in all patients receiving ⩾1 tofacitinib dose. IRs were expressed as number of patients with first events per 100 PY (safety analysis set).
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; Hx, history; IR, incidence rate; MACE, major adverse cardiovascular events; MetS, metabolic syndrome; *N*, number of patients; *n*, number of patients with first event within the risk period (up to 28 days beyond last dose); *n*1, number of patients with events outside the 28-day risk period; PCE, pooled cohort equations; PsO, psoriasis; PY, patient years.

(Figure 4(b)). MACE IRs for the average tofacitinib dose groups by baseline CV risk categories and MetS status are displayed in Figure S4. Notably, these indicated numerically higher risk (overlapping 95% CIs) of MACE in patients with PsO in the average tofacitinib 5 mg BID group compared with the average tofacitinib 10 mg BID group, particularly in patients with PsO with a history of ASCVD or MetS at baseline.

IR (95% CI) for malignancies (excluding NMSC) in the all-tofacitinib group in the PsO cohort was 0.65 (0.49, 0.83).[33] Patients with high 10-year risk of ASCVD at baseline had the highest IR for malignancies [3.48 (1.90, 5.83)], with non-overlapping 95% CIs when compared with any of the CV risk categories, except history of ASCVD (Figure 5(a)). As with MACE, malignancy (excluding NMSC) IRs were numerically different by MetS status at baseline, but with overlapping 95% CIs (Figure 5(b)). Figure S5 shows malignancy IRs for the average tofacitinib dose groups by baseline CV risk categories and MetS status. IRs were similar for patients receiving tofacitinib 5 mg BID (overlapping 95% CIs), but for patients receiving tofacitinib 10 mg BID, IR was higher (non-overlapping 95% CIs) for patients with high baseline 10-year ASCVD risk *versus* patients with intermediate, borderline, or low 10-year ASCVD risk. In patients with MetS at baseline, malignancy IRs were higher (non-overlapping 95% CIs) in the average tofacitinib 5 mg BID group compared with the average tofacitinib 10 mg BID group.

Sensitivity analysis by age group: MACE and malignancies (excluding NMSC) and their association with baseline CV risk in the PsA and PsO cohorts

The sensitivity analysis that stratified patients by age group demonstrated that including patients

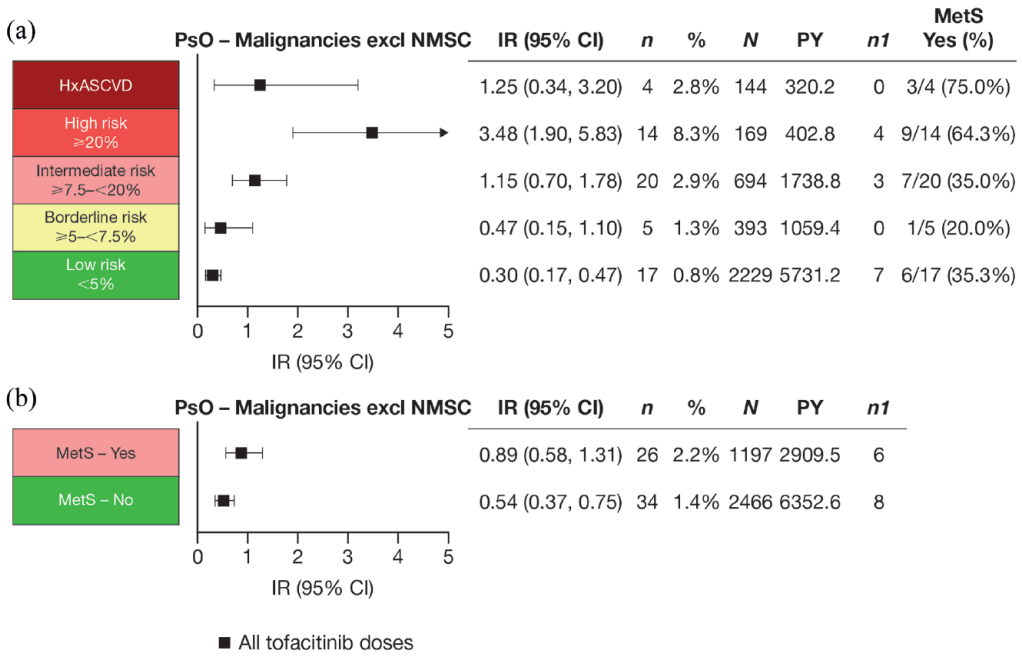


Figure 5. Malignancies (excluding NMSC) by baseline CV risk profile in all patients treated with tofacitinib in the PsO cohort. (a) Malignancy (excluding NMSC) IRs by CV risk categories in all patients receiving ⩾1 tofacitinib dose. Patients without HxASCVD were categorized according to their 10-year risk of MACE, per the ASCVD-PCE risk calculator.[29] IRs were expressed as the number of patients with first events per 100 PY. (b) Malignancy (excluding NMSC) IRs by baseline MetS status in all patients receiving ⩾1 tofacitinib dose. IRs were expressed as the number of patients with first events per 100 PY (safety analysis set).
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; Hx, history; IR, incidence rate; MACE, major adverse cardiovascular events; MetS, metabolic syndrome; *N*, number of patients; *n*, number of patients with first event within the risk period (up to 28 days beyond last dose); *n*1, number of patients with events outside the 28-day risk period; NMSC, non-melanoma skin cancer; PCE, pooled cohort equations; PsO, psoriasis; PY, patient years.

aged <40 years had little impact on the IRs in the different 10-year ASCVD risk categories, for both MACE and malignancies (excluding NMSC) in the PsA and PsO cohorts (Table S6).

Discussion

This *post hoc* analysis of patients receiving tofacitinib in the PsA and PsO clinical trial programs evaluated baseline CV risk and the potential association with MACE and malignancy events. The majority of patients in the clinical trials (>70%) were at low or borderline risk of CV events, and 4.0–6.6% had a previous history of ASCVD. For all patients who received tofacitinib in the PsA and PsO cohorts, there were indications of a relationship between MACE and malignancy events, and higher 10-year ASCVD risk.

The overall IRs for MACE in the PsA and PsO cohorts were 0.29 and 0.25 per 100 PY,[33] respectively. These were similar to the rates reported in integrated analyses of clinical trials of biologic disease-modifying antirheumatic drugs (bDMARDs), such as certolizumab pegol (0.54/100 PY in PsA and 0.27/100 PY in PsO),[34] secukinumab (0.4/100 PY in both PsA and PsO),[35] and ixekizumab (0.5/100 PY in both PsA and PsO),[36] the JAK inhibitor upadacitinib (15 mg QD; 0.3/100 PY in PsA),[37] and to the rates with a variety of bDMARDs and non-biologic agents in PsO, based on observational studies (0.36/100 PY).[38]

The MACE data from this analysis should be interpreted in context of the background CV risk of the population studied. Importantly, the PsA and PsO patients included in these analyses were not enriched on CV risk as was the case with RA patients included in ORAL Surveillance,[27] with the proportions of RA patients with a history of ASCVD (14.7%)[28] differing substantially from the proportions of patients with a history of ASCVD here (PsA: 6.6%; PsO: 4.0%). There

may also be differences in background CV risk associated with RA *versus* PsA and PsO.[39,40] Consequently, the MACE IRs in the overall populations were lower than those observed with tofacitinib in ORAL Surveillance.[27] However, patients with PsA and PsO are more likely than the general population to have traditional CV risk factors, including MetS, and as previously noted, have a higher risk of MACE.[7,8] The European Alliance of Associations for Rheumatology (EULAR) and the American Academy of Dermatology (AAD) recommend that patients with PsA and PsO have their risk of CV disease assessed regularly, using validated risk prediction tools.[41,42] Still, the majority of the patients included in this analysis (>70%) were at low or borderline 10-year risk of MACE. Furthermore, ~10% of patients with PsA or PsO in the tofacitinib clinical studies included here, already had ASCVD, or were at high 10-year risk of having a MACE. Although there were relatively few MACE overall in the tofacitinib PsA and PsO programs, our analysis found that the majority occurred in the 26–28% of patients with a history of ASCVD, or at least at an intermediate 10-year risk of ASCVD [PsA: 4 (66.7%) of 6 MACE; PsO: 21 (91.3%) of 23 MACE]. Particularly in PsA, patients with MetS at baseline, a CV risk-enhancing factor, had higher MACE IRs than patients without MetS [5 (83.3%) of 6 MACE in PsA occurred in patients with baseline MetS]. Notably, concomitant use of statins and antiplatelet medications were low in patients with 10-year ASCVD risk ⩾7.5%, despite treatment guidelines and high occurrence of CV risk factors in the PsA and PsO cohorts. Our findings emphasize the importance of regular assessment and management of CV risk in patients with PsA and PsO.

The overall IRs for malignancies in the PsA and PsO cohorts were 0.71 and 0.65 per 100 PY, respectively, and were in line with those observed with tofacitinib in other clinical trials.[33] They were also similar to those seen in the literature for adalimumab (0.2/100 PY in PsA, 0.5/100 PY in PsO),[43] secukinumab (1.0/100 PY in PsA and 0.9/100 PY in PsO),[35] ixekizumab (⩽0.5/100 PY in both PsA and PsO),[36] and upadacitinib (15 mg QD; 0.7/100 PY in PsA).[37]

CV disease and cancer share non-modifiable and modifiable risk factors, such as age, smoking, diabetes mellitus, and hypertension, and patients with CV disease are at higher risk of developing many cancers, and vice versa.[13,44] Higher ASCVD-PCE risk scores have also been associated with higher rates of incident CV disease and cancer.[45] CV risk assessment using risk prediction calculators has been suggested as a tool to inform personalized cancer screening strategies.[13] Our novel findings presented here support the association between CV risk factors and the risk of cancer. Malignancy events in the PsA and PsO cohorts were highest in those with intermediate and high 10-year ASCVD risk [PsA: 9 (60.0%) of 15 malignancies; PsO: 34 (56.7%) of 60 malignancies] and an association with baseline MetS was observed, mainly in PsA [PsA: 10 (66.7%) of 15 malignancies; PsO: 26 (43.3%) of 60 malignancies]. The overall mean age in the PsA and PsO cohorts was 48.7 and 44.8, respectively. Furthermore, and in contrast with the PsA cohort, the majority of patients in the PsO cohort were either current or ex-smokers.

Notably, a numerically higher IR for malignancies (excluding NMSC) was generally observed for patients in the average tofacitinib 5 mg BID dose group, when compared with the average 10 mg BID dose group in the PsA and PsO cohorts. In the PsO cohort, the same finding was observed for MACE. This may be explained, in part, by better control of inflammation for patients in the average tofacitinib 10 mg BID dose group, as they would have spent more time on this dose. However, these numerical differences should be interpreted with caution, due to the very small number of events reported in each average dose group and the overlapping 95% CIs.

The number of MACE and malignancy events reported in the tofacitinib PsA studies (including OPAL Broaden) in this analysis was in proportion with those reported previously for adalimumab in OPAL Broaden,[17] when considering the longer follow-up time for tofacitinib in this analysis. In this analysis, 6 MACE events and 15 malignancy events were reported for tofacitinib in studies lasting ⩽36 months. In OPAL Broaden,[17] the limited number of MACE and malignancy events was comparable between tofacitinib (1 MACE and 3 malignancies) and adalimumab (1 MACE) over 12 months.

The major strength of this *post hoc* analysis was the ability to provide further insight into the CV risk profile of tofacitinib-treated patients with PsA and PsO, and association with MACE and malignancies in clinical trial settings. We did this

by applying a validated risk prediction tool (ASCVD-PCE) in line with the recommendations of EULAR and AAD,[41,42] and current guidelines on CV disease prevention in the general population.[30] As ASCVD-PCE was validated with data from a US population aged 40–79 years,[29] applying the calculator on younger patients, and patients from racial/ethnic groups or from geographical regions where it is not explicitly validated, could result in inadvertently low or high predicted CV risk. Therefore, a sensitivity analysis was performed with stratified patients by age group (<40 *versus* ⩾40 years) and demonstrated that including patients < 40 years of age in this analysis had little impact on the results. Limitations of this analysis included that overall, the numbers of MACE and malignancy events in the PsO and, in particular, the PsA tofacitinib trials, were low for consideration in subgroup analysis. Therefore, some of the subgroups were small in terms of number of patients and events across each subgroup category, and thus, results should be interpreted cautiously. The follow-up time in the studies included in this analysis (median exposure 3.0 and 2.4 years for the PsA and PsO cohorts, respectively) was also relatively short for the assessment of safety outcomes, and particularly for the assessment of malignancies. Finally, due to the absence of an active control in the PsA and PsO tofacitinib cohorts, any relative differences could not be ascertained.

Conclusion

In conclusion, baseline 10-year ASCVD risk and MetS are, as may be expected, potentially associated with the incidence of both MACE and malignancies in patients receiving tofacitinib in the PsA and PsO clinical trial programs, although the incidence of MACE and malignancy events was low overall. Our results confirm the importance of assessment of CV risk and adequate prevention in patients with PsA and PsO and suggest enhanced cancer monitoring in patients with significant 10-year ASCVD risk.

Declarations

Ethics approval and consent to participate

All of the trials included were approved by the relevant Ethics Committees and Institutional Review Boards. All patients provided written, informed consent to participate.

Consent for publication

Not applicable.

Author contributions

Lars E. Kristensen: Conceptualization; Writing – review & editing.

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Ying-Ying Leung: Conceptualization; Writing – review & editing.

Hyejin Jo: Formal analysis; Writing – review & editing.

Kenneth Kwok: Conceptualization; Formal analysis; Writing – review & editing.

Ivana Vranic: Writing – review & editing.

Dona L. Fleishaker: Conceptualization; Formal analysis; Writing – review & editing.

Lara Fallon: Conceptualization; Writing – review & editing.

Arne Yndestad: Conceptualization; Formal analysis; Writing – review & editing.

Dafna D. Gladman: Conceptualization; Writing – review & editing.

Acknowledgments

The authors thank all patients and study investigators involved in the studies included in this manuscript. This study was sponsored by Pfizer. Medical writing support, under the direction of the authors, was provided by Kimberley Haines, MSc, and administrative support was provided by Nicole Hunchar, CMC Connect, a division of IPG Health Medical Communications, funded by Pfizer, New York, NY, USA, in accordance with Good Publication Practice (GPP 2022) guidelines (*Ann Intern Med* 2022; 175: 1298–304).

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was sponsored by Pfizer.

Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: L.E.K. has received grant/research support from Biogen, Janssen, Novartis, and UCB, and has received speaker's fees from AbbVie, Amgen, Biogen, BMS, Eli Lilly, Janssen, MSD, Novartis,

Pfizer Inc, and UCB. B.S. has acted as a consultant for AbbVie, Almirall, Alumis, Amgen, Arcutis, Arena, Aristea, Asana, Boehringer Ingelheim, Bristol Myers Squibb, Connect Biopharma, CorEvitas Psoriasis Registry, Dermavant, Eli Lilly, EPI Health, Evelo Biosciences, Immunic Therapeutics, Janssen, Leo, Maruho, Meiji Seika Pharma, Mindera Health, Novartis, Ono, Pfizer Inc, Regeneron, Sanofi-Genzyme, Sun Pharma, UCB Pharma, Union Therapeutics, Ventyxbio, and vTv Therapeutics; has received speaker's fees from AbbVie, Eli Lilly, Incyte, Janssen, Regeneron, and Sanofi-Genzyme; has received grants from AbbVie, Cara, CorEvitas Psoriasis Registry, Dermavant, Dermira, and Novartis; is a shareholder of Connect Biopharma and Mindera Health; and has received honoraria from the *Journal of Psoriasis and Psoriatic Arthritis*. D.P. has acted as a consultant for AbbVie, Biocad, Gilead Sciences, GlaxoSmithKline, Eli Lilly, MSD, Novartis, Pfizer Inc, Samsung Bioepis, and UCB; has received grant/research support from AbbVie, Eli Lilly, MSD, Novartis, and Pfizer Inc; and has received speaker's fees from AbbVie, Bristol Myers Squibb, Eli Lilly, MSD, Novartis, Pfizer Inc, and UCB. Y-Y.L. has acted as a consultant for AbbVie, Eli Lilly, Janssen, Novartis, and Pfizer Inc. H.J. is an employee of Syneos Health, which was a paid contractor to Pfizer in connection with the development of this manuscript. K.K., I.V., D.L.F., L.F., and A.Y. are employees and shareholders of Pfizer Inc. D.D.G. has acted as a consultant for AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, Gilead Sciences, Janssen, Novartis, Pfizer Inc, and UCB, and has received grants from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, Pfizer Inc, and UCB.

Availability of data and materials

On request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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Supplemental material

Supplemental material for this article is available online.

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