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Tofacitinib for the Treatment of Ulcerative Colitis: Analysis of Nonmelanoma Skin Cancer Rates From the Ulcerative Colitis Clinical Program

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Background: Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). We present integrated analyses of nonmelanoma skin cancer (NMSC) incidence in the tofacitinib UC clinical program.

Methods: Nonmelanoma skin cancer events were evaluated from 3 randomized, placebo-controlled studies: 2 identical, 8-week induction studies (NCT01465763, NCT01458951), a 52-week maintenance study (NCT01458574), and an open-label, long-term extension study (NCT01470612). Cohorts analyzed were: Induction, Maintenance, and Overall (patients receiving ≥1 dose of tofacitinib 5 mg or 10 mg twice daily [BID]). An independent adjudication committee reviewed potential NMSC. Proportions and incidence rates (IRs; unique patients with events per 100 patient-years of exposure) for NMSC were evaluated. A Cox proportional hazards model was used for risk factor analysis.

Results: Nonmelanoma skin cancer was evaluated for 1124 patients (2576.4 patient-years of tofacitinib exposure; ≤6.8 years' treatment). In the Induction Cohort, NMSC IR was 0.00 for placebo and 1.26 for 10 mg BID. Nonmelanoma skin cancer IR was 0.97 for placebo, 0.00 for 5 mg BID and 1.91 for 10 mg BID in the Maintenance Cohort, and 0.73 (n = 19) in the Overall Cohort. No NMSC was metastatic or led to discontinuation. In the Overall Cohort, Cox regression identified prior NMSC (hazard ratio [HR], 9.09; $P = 0.0001$), tumor necrosis factor inhibitor (TNFi) failure (3.32; $P = 0.0363$), and age (HR per 10-year increase, 2.03; $P = 0.0004$) as significant independent NMSC risk factors.

Conclusions: For patients receiving tofacitinib, NMSC occurred infrequently. Older age, prior NMSC, and TNFi failure, which are previously reported NMSC risk factors in patients with UC, were associated with increased NMSC risk.

Key Words: nonmelanoma skin cancer, tofacitinib, ulcerative colitis

Introduction

Rates of nonmelanoma skin cancer (NMSC) are on the rise, with an estimated 3.3 million people treated for NMSC in the United States in 2012.[1] Based on US claims data, the incidence rate (IR) of NMSC in the general population is 78 cases per 10,000 person-years.[2] A global systematic review reported wide variation in IRs of NMSC, with the highest rates in Australia (>100 cases per 10,000 person-years for basal cell carcinoma [BCC]) and the lowest rates in parts of Africa (<0.1 cases per 10,000 person-years for BCC).[3] Nonmelanoma skin cancer risk factors include cumulative sun and ultraviolet (UV) light exposure, White race, and immunosuppressive medications.[4]

Patients with inflammatory bowel disease (IBD), including ulcerative colitis (UC), have been shown to be at increased risk of developing NMSC,[4–6] attributed to the use of immunosuppressant medications such as thiopurines and/or tumor necrosis factor inhibitors (TNFi).[7–9] Nonmelanoma skin cancer risk in patients with IBD naïve to thiopurines is similar to the risk in the general population.[7] Abbas et al showed that NMSC IR per 100 patient-years (PY) increased with cumulative years of thiopurine use, with an IR of 1.36 for 5 years of use, vs an IR of 0.37 for no prior thiopurine use.[8] A cohort study of 19,486 patients with IBD showed that both current and past thiopurine exposure significantly increased NMSC risk, with hazard ratios (HRs) of 5.9 (95% confidence interval [CI], 2.1–16.4; $P = 0.0006$) and 3.9 (95% CI, 1.3–12.1; $P = 0.02$) for ongoing and past thiopurine exposure, respectively.[7] Furthermore, NMSC risk increases with age in patients with IBD, with IRs per 100 PY of 0, 0.06, and 0.08 for thiopurine-naïve patients <50, 50–65, and >65 years of age, respectively.[7] Similarly, a higher risk for developing NMSC has been observed for patients with IBD receiving TNFi, both as a monotherapy ($P = 0.036$) and in combination with a

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thiopurine ($P < 0.001$), by a proportional reporting ratio metric analysis.[9]

Nonmelanoma skin cancer risk is also higher in patients with a previous history of NMSC. A meta-analysis of subsequent NMSC in patients with previous NMSC history showed that the cumulative risk of developing a second squamous cell carcinoma (SCC) or a second BCC within 3 years was approximately 18% and 44%, respectively.[10]

Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of UC. The efficacy and safety of tofacitinib in adults with moderate to severe UC has been evaluated in clinical trials, including a phase 2 induction study,[11] 2 phase 3 induction studies,[12] a phase 3 maintenance study,[12] and an open-label, long-term extension (OLE) study.[13] As tofacitinib is an immune modulator, and patients with UC are at increased risk of developing NMSC,[4–6] it is important to evaluate and report on the NMSC risk in patients with UC receiving tofacitinib. Within this safety population, a blinded committee adjudicated NMSC events in the phase 3 studies only. Here, we present an integrated analysis of the adjudicated NMSC events in the tofacitinib clinical program for patients with moderate to severe UC.

MATERIALS AND METHODS

Patients

In the tofacitinib UC clinical program, summaries of safety data were analyzed from 3 randomized, placebo-controlled studies (OCTAVE Induction 1 and 2, NCT01465763 and NCT01458951; OCTAVE Sustain, NCT01458574) and an open-label study (OCTAVE Open, NCT01470612) that was ongoing at the time of this analysis. All studies are registered on ClinicalTrials.gov. A total of 1124 patients with moderate to severe UC (moderate or severe disease defined by a total Mayo score of ≥6, with a rectal bleeding score of ≥1, and an endoscopic subscore of ≥2 on the Mayo score) received ≥1 dose of tofacitinib 5 mg or 10 mg twice daily (BID) from the 4 induction, maintenance, and OLE studies.

The adjudicated NMSC analysis comprised 2 identical, 8-week, phase 3 induction studies (OCTAVE Induction 1 and 2)[12] of patients with moderate to severe UC and prior failure or intolerance to treatment with corticosteroids, immunomodulators, and/or the TNFi infliximab and adalimumab (Fig. 1). Additional NMSC analysis involved OCTAVE Sustain,[12] a 52-week, phase 3, randomized, double-blind maintenance study of clinical responders from OCTAVE Induction 1 and 2. Clinical responders were patients whose total Mayo scores decreased from induction study baseline by ≥3 points and ≥30%, accompanied by decreases in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding score ≤1. OCTAVE Open,[13] an OLE study of patients (n = 944) without clinical response in OCTAVE Induction 1 and 2 or patients who completed or demonstrated treatment failure in OCTAVE Sustain, was also included in the NMSC safety analysis. Patient demographics and characteristics data included all phase 3 studies for which NMSC cases were adjudicated.

Nonmelanoma skin cancer events reported in this manuscript were based on adjudication. Adjudicated NMSC events include reported adverse events (AEs) and also any biopsies associated with that event. The calculation of NMSC IR does not include patients in the phase 2 induction study (NCT00787202)[11] because adjudication of potential malignancy cases was not performed. Safety evaluations were conducted for the phase 2 induction study and did not show any AEs in the standardized Medical Dictionary for Regulatory Activities (MedDRA; version 19.0) Neoplasms (including cyst) system organ class.

Malignancy Adjudication Committee

Biopsies of all potentially malignant tumors were submitted for blinded central over-read of histopathology and independent adjudication. An independent, external, blinded malignancy adjudication committee (MAC) reviewed all potential NMSC events in all phase 3 studies and the OLE study. The MAC was established to increase the objectivity of interpretations and better control variability. The MAC included a panel of board-certified, practicing medical oncologists to evaluate and classify potential malignancy cases using a prespecified, consistent set of criteria within the UC clinical program and across the various indications of the entire tofacitinib program. The MAC reviewed all AEs and serious AEs (SAEs) coded to the malignant tumor standardized MedDRA query, events submitted for central histopathology review as potential malignancies, and any additional cases nominated by investigators or the study sponsor for review.

Malignancies, including NMSCs, were identified based on all available data in the study database related to the potential malignancy cases, including output from the central histology review, where available. The reporting of all events began at the time the patient provided informed consent through 28 days after the last study dose, or for SAEs until an ongoing event resolved, or, additionally, at any time after the last dose if a causal relationship to study medication was suspected by the investigator. Additional details of adjudication criteria are included in the supplementary data. Screening skin examination for NMSC by dermatologists was not part of any study protocol. At study screening, history of prior NMSC was ascertained from medical records and patient interviews as part of the patients' medical history.

Review of AEs

Adverse events in the UC clinical program were coded using MedDRA version 19.0 for the Induction and Maintenance Cohorts, and MedDRA version 19.1 for the Overall Cohort. Serious adverse events were defined as any events that resulted in death, were life-threatening, resulted in a persistent or significant disability or incapacity, required patient hospitalization or prolongation of existing hospitalization, resulted in a congenital anomaly or birth defect, or were considered an important medical event. Only SAEs reported after the first dose of study treatment (ie, treatment-emergent) through 28 days after the last study dose are presented.

Cohort Analysis

Three cohorts of patients were evaluated for adjudicated NMSC events: the Induction, Maintenance, and Overall Cohorts (Fig. 1). The Induction Cohort included the 2 phase 3 induction studies; the Maintenance Cohort included the phase 3 maintenance study; and the Overall Cohort included patients receiving ≥1 dose of tofacitinib 5 mg or 10 mg BID in the phase 3 and OLE studies.

In the Overall Cohort, a supplemental analysis for the total tofacitinib population ("Tofacitinib All") stratified patients

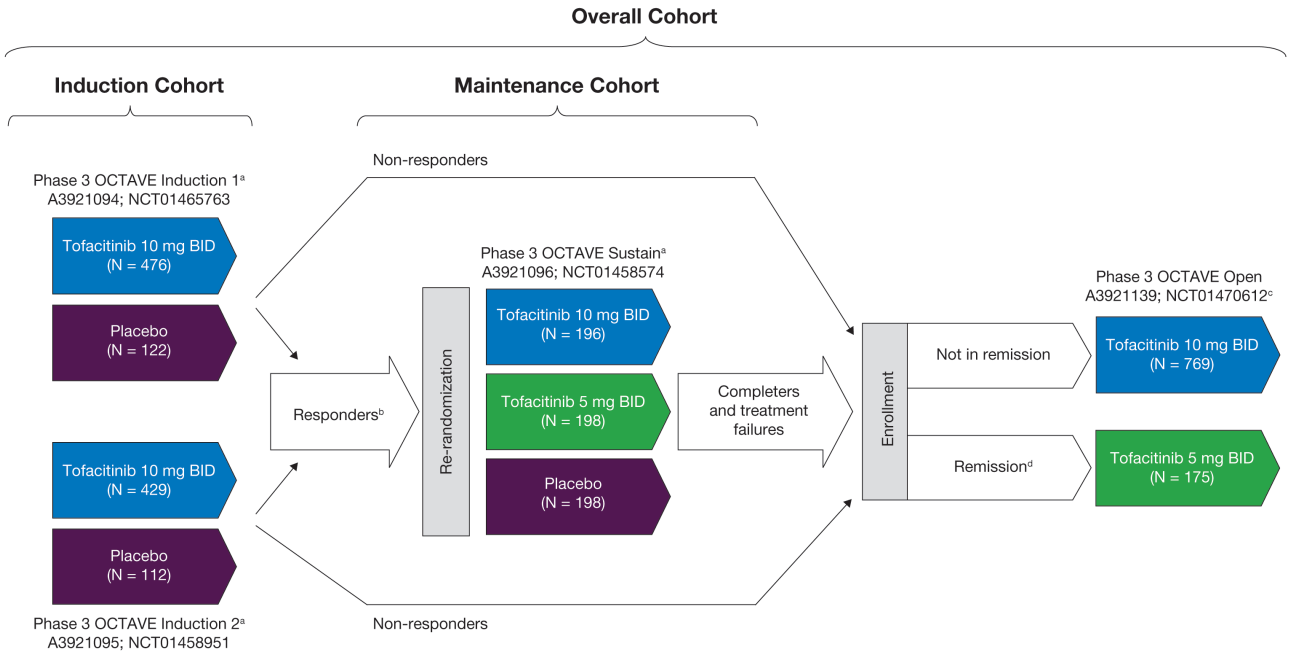

Figure 1. Overview of the tofacitinib UC phase 3 clinical program, analyzed for adjudication of NMSC events. Abbreviations: N, number of patients in each treatment group included in the cohort analysis. [a]Final complete efficacy assessment at week 8/52. Treatment continued up to week 9/53. [b]Clinical response in OCTAVE Induction 1 and 2 was defined as a decrease from induction study baseline total Mayo score of ≥3 points and ≥30%, plus a decrease in rectal bleeding subscore of >1 point or an absolute rectal bleeding subscore of 0 or 1. [c]Study A3921139 (OCTAVE Open) was ongoing at the time of this analysis. [d]Remission was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0. Adapted from Winthrop KL, et al. Inflamm Bowel Dis 2018; 24: 2258–65 (in accordance with the CC BY-NC licence).

by predominant dose (PD) of tofacitinib. A PD of tofacitinib 5 mg BID was determined as an average daily dose <15 mg, whereas a PD of tofacitinib 10 mg BID was determined as an average daily dose ≥15 mg.

Statistical Analysis

Proportions and IRs (unique patients with events per 100 PY of exposure) for NMSC were evaluated. Exact Poisson (adjusted for PY) 95% CIs are provided for the crude IR. The change in NMSC IR over time was assessed for each individual 6-month time interval from 0 to >30 months.

Cox proportional regression models were used to assess the association of various demographic and clinical factors with NMSC events. The Overall Cohort, which included all patients exposed to tofacitinib in the UC clinical program who were adjudicated for NMSC, and excluded any time periods and events experienced while patients were receiving placebo, was used to evaluate risk factors for NMSC. Potential risk factors included age (stratified by <30 years, 30 to <40 years, 40 to <50 years, and ≥50 years, and by 10-year increase for Cox analysis), sex, disease duration (by median), oral corticosteroid use at baseline, prior NMSC, race (White/Black/Asian/other), previous exposure to immunosuppressants (yes/no categories), and previous exposure to, or failure of, TNFi (yes/no categories). Immunosuppressants include nonbiologic agents such as azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, and tacrolimus. Prior TNFi exposure was defined as any prior treatment with TNFi. Prior TNFi failure was determined by investigators and did not specify a minimum dose or treatment duration with TNFi. Additional potential NMSC risk factors that were included in Cox univariate analysis are described in the supplementary data.

For baseline characteristics, the modeling approach first applied univariate models to identify individual risk factors with a statistically significant relationship to each AE. Univariate Cox values were reported in a descriptive manner; no adjustment for multiplicity was applied to the univariate results. A stepwise model was then used, which limited the number of significant associations reported by considering all univariate factors with $P < 0.1$, but including only those with $P < 0.05$ in the final model. At each step, the most significant remaining predictor was added if the lower P value threshold was met. Using this approach, univariate factors, which correlated to items already in the model, were unlikely to be added to the model.

Separate univariate models using time-varying covariates evaluated factors that could change during the study, including postbaseline confirmed low absolute lymphocyte count (ALC; $<1 \times 10^9$/l), low absolute neutrophil count ($<1.5 \times 10^9$/l), and oral corticosteroid dose (prednisone equivalent) in the Overall Cohort. Subgroup analysis was used to identify potential risk factors that could predispose patients to NMSC, including age, prior NMSC, race, geographic location, prior exposure to immunosuppressants, and prior exposure to TNFi.

For the Overall Cohort, the results presented here are based on average dose; patients were classified according to the average dose they took during their entire tofacitinib exposure period. Therefore, no censoring was applied when patients moved from one tofacitinib dose to another. In the Overall Cohort, data are shown from the OLE study, as of May 2019.

Contextualization using Independent

Administrative Data from the Healthcare Insurance Truven MarketScan database in the United States were used for contextualization of the analysis. As of 2015, the MarketScan

claims database contains data on 50 million considered lives. For the purposes of comparison to the tofacitinib studies, a comparator cohort of patients was derived that met the key selection criteria for the tofacitinib phase 3 studies, and consisted of a general adult population of patients (≥18 years of age) with moderate to severe UC. In this cohort, UC was defined as having ≥2 diagnosis codes (International Classification of Diseases, Ninth Revision [ICD-9]) on record in the Truven database between October 01, 2010, and September 30, 2015. At least 12 months of database enrollment before index date, with less than a 30-day gap, was required to enable analysis of patient and disease characteristics that may be important modulators of the relationship of UC with disease outcomes.

At least 1 of the 2 required diagnoses had to have been made by a gastroenterologist. If ICD-9 codes were assigned on different days, codes did not have to be identical for the patients to qualify. The purpose of the "trial-criteria" cohort was to mimic the population in the tofacitinib global phase 3 UC studies for contextualization of the data source, although the Truven population comprised patients from the United States only. Data are shown for the new-use drug-exposure subcohort, in which patients were defined as naïve to the drug or drug class prior to exposure, and measured in the 12 months prior to index date and preceding time (if available). Incidence rate (reported as per 100 PY) was defined as the number of patients with events divided by the sum of the durations of exposures of the patients, from index date to censoring date, during the risk period. Additional details of the Truven methods are shown in the Supplementary Data.

Ethical Considerations

These studies were approved by the institutional review board or independent ethics committee for each center and were conducted in accordance with the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines.

RESULTS

Patients Included for Overall Safety Analysis

A total of 1124 patients were included in the Overall Cohort for integrated safety analysis from phase 3 studies including the OLE study, comprising all patients receiving ≥1 dose of tofacitinib (Table 1). Patient demographics and baseline characteristics, including mean total Mayo score and disease duration, were generally similar among groups within each cohort. This analysis only considers adjudicated NMSC cases from the phase 3 studies. Additional details of all malignancies excluding NMSC are reported in Lichtenstein et al.[14]

Adjudicated NMSC Events

A total of 1124 patients in the Overall Cohort were evaluated for adjudicated NMSC events, equating to 2576.4 PY of tofacitinib exposure in the Overall Cohort and up to 6.8 years of treatment (Fig. 2). The Overall Cohort included all patients receiving ≥1 dose of tofacitinib from phase 3 studies including the OLE study, but did not include patients from the phase 2 induction study as no adjudication took place; although no malignancies (including NMSC) were reported in the phase 2 study.

In the Induction Cohort, there were no placebo-treated patients with NMSC (IR 0.00). Nonmelanoma skin cancer occurred in 2 patients (0.2%) in the tofacitinib 10 mg BID group (IR 1.26): 1 patient had SCC and 1 patient had BCC. In the Maintenance Cohort, NMSC occurred in 1 patient receiving placebo (IR 0.97; the patient had BCC and had previously received tofacitinib in induction) and in 3 patients receiving tofacitinib 10 mg BID (IR 1.91; 2 patients had SCC, and 1 patient had BCC; Fig. 2).

In the Overall Cohort, 51 adjudicated NMSC events were reported in 19 unique patients. Of the 19 patients, 10 (52.6%) reported SCC, and 14 (73.7%) reported BCC; 5 patients (26.3%) reported both BCC and SCC events (Fig. 2). Most of the NMSC events were mild in severity, and most had resolved. Five patients had NMSC events that were classified as SAEs.

When stratified by PD, among the 19 patients who reported NMSC events, 16 (84.2%) were in the PD 10 mg BID group (IR 0.82; 95% CI, 0.47–1.34), and 3 (15.8%) were in the PD 5 mg BID group (IR 0.45; 95% CI, 0.09–1.30).

All NMSC events were reported within the treatment period; all patients continued receiving study treatment, and none were metastatic.

Prior NMSC History and Immunosuppressant or TNFi Treatment Exposure

Of the 19 patients who reported NMSC events, almost all had prior immunosuppressant exposure (18 patients; 94.7%) or TNFi exposure (15 patients; 78.9%). All 15 patients with prior TNFi exposure were also patients with prior TNFi failure. Seven (36.8%) of the 19 patients with NMSC had prior history of NMSC. A high proportion of patients with NMSC events were White (17 patients; 89.5%); race data were unavailable for 1 patient. Of the 10 patients who presented with SCC, 6 had prior history of NMSC, 9 were White (race data were unavailable for 1 patient), all had prior exposure to immunosuppressants, and 8 had prior exposure to TNFi. Of the 14 patients reporting a BCC event, 5 had prior NMSC history, and 13 were White. Further details of the patient demographics and treatment history for the NMSC cases, including the anatomical location of the NMSCs, are listed in Supplementary Table 1.

NMSC Risk Factor Analysis and Hazard Modeling for the Overall Cohort

In the Overall Cohort, significantly higher IRs were observed for those patients with prior history of NMSC vs those without (Fig. 3). Higher IRs were also observed for patients 40 to 50 years of age and ≥50 years of age, vs those <40 years of age. Patients with prior TNFi or immunosuppressant exposure showed a trend for higher IRs for all NMSC, compared with those without (Fig. 3). Patients in the North American region showed numerically higher IRs compared with those from other geographic locations. In the Overall Cohort, there were no patients listed as Black or Asian with NMSC; however, for context, the majority (79.8%) of the general patient population was White.

Univariate Cox regression identified prior NMSC, older age (≥65 vs <65 years of age; per 10-year increase; and continuous), and prior TNFi failure as significant risk factors for NMSC (all $P < 0.01$; Table 2). Geographic region, longer disease duration, prior TNFi exposure, smoking history, and lower baseline ALC were also identified as significant risk factors (all $P \leq 0.05$). However, known NMSC risk factors

including prior immunosuppressant exposure and White race were not found to be significant risk factors in this analysis.

Cox regression after stepwise selection identified prior NMSC (P = 0.0001), age (P = 0.0004), and prior TNFi failure (P = 0.0363) as significant risk factors for development of NMSC (Table 2).

NMSC IRs Through 30 Months

The incidence of NMSC events was analyzed by 6-month intervals over the total treatment duration for all patients receiving tofacitinib in the phase 3 OCTAVE UC studies (Fig. 4). These data show that rates of NMSC were generally low throughout 30 months, with overlapping 95% CIs at all time points. The IR for NMSC was similar for the interval of >30 months' treatment compared with the rate for the 0–6 months' treatment interval, and the IRs were generally similar to the IRs observed in the rheumatoid arthritis (RA) clinical program for tofacitinib.

NMSC Rates for Tofacitinib vs Comparator Treatment

To provide context, NMSC IRs for the Tofacitinib All group in the Overall Cohort of the UC clinical program were presented alongside those of the RA,[15] psoriatic arthritis (PsA),[16] and psoriasis (PsO)[17] clinical programs for tofacitinib and also a Truven cohort for patients receiving TNFi (alone or combined), azathioprine, or 6-mercaptopurine (Fig. 5). In the Truven cohort "Any TNFi" included all patients who received TNFi alone or with immunosuppressive agents. These data show that NMSC IRs in the global Overall Cohort of the tofacitinib UC clinical program were generally numerically lower than those reported for biologic agents (alone or combined) and azathioprine or 6-mercaptopurine in patients with UC in the US Truven comparison cohort.

Discussion

This integrated analysis of the tofacitinib UC clinical program showed that NMSC events were relatively infrequent in patients with moderate to severe UC receiving tofacitinib. As with previous studies of patients with UC, increasing age, prior NMSC history, and prior TNFi failure were identified as significant NMSC risk factors in this analysis.[18, 19]

Immunosuppressant treatments are a mainstay of UC therapy; however, several of these agents have photosensitizing properties, which accelerate the phototoxic process in the skin, potentially resulting in malignancies.[20] Several studies have evaluated the mechanism for increased risk of NMSC following immunosuppressant treatment. The thiopurine azathioprine is believed to cause accumulation of 6-thioguanine in patients' DNA, which, unlike normal DNA, absorbs UVA radiation.[21] When cells with an accumulation of 6-thioguanine are exposed to UVA radiation, reactive oxygen species are generated, which can lead to oxidative stress and mutagenesis in DNA, potentially leading to malignancies.[21] Photosensitizing agents such as methotrexate and thiopurines may potentially increase the risk of subsequent NMSC in patients with a history of previous SCC or BCC.[20] The effect of TNFi exposure on NMSC risk has not been fully explored in patients with UC; however, in patients with IBD, TNFi exposure alone may be associated with a moderate increase in NMSC risk, which seems to be further increased when combined with thiopurines.[9] A recent meta-analysis of RA studies suggested that patients with RA are at an increased risk of SCC when treated with TNFi,[22] whereas an earlier analysis of NMSC in the current tofacitinib UC clinical program revealed prior TNFi failure to be a significant independent risk factor.[19]

The data reported here show that few NMSC events occurred in any study, and all patients continued receiving study treatment. No NMSC was metastatic or led to discontinuation. Subsequently, the low number of events in the Maintenance Cohort (3 in the tofacitinib 10 mg BID group and 1 in the placebo group) preclude wider comparisons with other cohorts. In the Overall Cohort, the majority (84.2%) of patients who had NMSC were receiving the PD 10 mg BID dose; however due to study design, there were more patients assigned to the PD 10 mg BID dose than the PD of 5 mg BID dose. Dose dependency of NMSC IR could not be concluded from the UC data presented here, as dose changes were permitted.

Cells in BCC resemble epidermal basal cells; BCC is typically less aggressive than SCC, which is characterized by atypical proliferation of invasive squamous cells with the potential to metastasize.[23] It has been hypothesized that immunosuppression increases the risk of SCC relative to BCC.[24] Singh et al have previously shown that patients with IBD have an increased risk of BCC, with the majority (86%) of the 237 patients with NMSC studied having BCC.[5] This study also showed a slightly higher HR relative to controls for BCC (1.09; 95% CI, 0.88–1.35) than SCC (0.75; 95% CI, 0.43–1.30) in patients with UC. For patients with UC receiving immunosuppressant medication, there was a significant and strong association with SCC (HR relative to controls 4.44; 95% CI, 1.16–16.92) but not BCC (HR relative to controls 1.07; 95% CI, 0.52–2.21).[5] In contrast, we observed similar frequencies of BCC and SCC in patients with NMSC in our analysis. There were 14 (73.7%; IR 0.53) patients with BCC and 10 (52.6%; IR 0.38) patients with SCC; 5 (26.3%) patients had both BCC and SCC.

Cox stepwise regression analysis selected prior NMSC, prior TNFi failure, and increasing age as significant independent NMSC risk factors. Prior NMSC and increasing age are known risk factors for the development of NMSC[10] and are consistent with previously published analyses for increasing NMSC risk in patients with IBD.[18] A prior history of NMSC is an important risk factor for NMSC development; of the patients with SCC, over half had prior NMSC history, whereas with BCC, approximately one-third of patients had NMSC history, 4 of whom also reported an SCC. Prior TNFi failure was identified as a risk factor for NMSC in an earlier analysis of NMSC in the current tofacitinib UC clinical program.[19] Although TNFi failure and TNFi exposure were both significantly associated with NMSC risk in the univariate analysis, TNFi exposure was eliminated from the final multivariable model following stepwise selection due to correlation with TNFi failure; TNFi failure therefore acted as a marker for TNFi exposure, a known risk factor for NMSC.[9] Prior TNFi failure was determined by investigators and did not specify a minimum dose or treatment duration with TNFi, whereas prior exposure was defined as any prior treatment with TNFi. Prior TNFi failure may not necessarily be a risk in itself but rather may identify patients with a more aggressive course of disease, greater systemic inflammation, and extended prior

Table 1. Demographics and Baseline Characteristics for All Patients in the Tofacitinib Phase 3 UC Clinical Program Following Study Drug Exposure in the Induction, Maintenance, and Overall Cohorts

	Induction Cohort (Phase 3)		Maintenance Cohort (Phase 3)				Overall Cohort (Phase 3, OLE)
	Placebo (N = 234)	Tofacitinib 10 mg BID (N = 905)	Placebo (N = 198)	Tofacitinib 5 mg BID (N = 198)	Tofacitinib 10 mg BID (N = 196)	Tofacitinib All doses (N = 394)	Tofacitinib All doses (N = 1124)j
Total PY of exposure	38.2	151.2	100.4	146.2	154.3	300.5	2576.4
Age (years), mean (range)	41.1 (18–81)	41.2 (18–80)	43.4 (19–80)	41.9 (18–79)	43.0 (18–79)	42.5 (18–79)	41.2 (18–81)
Female, n (%)	102 (43.6)	369 (40.8)	82 (41.4)	95 (48.0)	86 (43.9)	181 (45.9)	466 (41.5)
Race, n (%)							
White	186 (79.5)	726 (80.2)	155 (78.3)	164 (82.8)	153 (78.1)	317 (80.5)	897 (79.8)
Black	3 (1.3)	6 (0.7)	3 (1.5)	2 (1.0)	0 (0.0)	2 (0.5)	10 (0.9)
Asian	28 (12.0)	114 (12.6)	26 (13.1)	23 (11.6)	25 (12.8)	48 (12.2)	144 (12.8)
Other	7 (3.0)	33 (3.6)	9 (4.5)	5 (2.5)	9 (4.6)	14 (3.6)	39 (3.5)
Geographic region, n (%)							
Asia	26 (11.1)	95 (10.5)	20 (10.1)	22 (11.1)	21 (10.7)	43 (10.9)	123 (10.9)
Eastern Europe	67 (28.6)	260 (28.7)	57 (28.8)	66 (33.3)	63 (32.1)	129 (32.7)	319 (28.4)
North America	53 (22.6)	187 (20.7)	45 (22.7)	39 (19.7)	44 (22.4)	83 (21.1)	241 (21.4)
Western Europe	68 (29.1)	274 (30.3)	55 (27.8)	47 (23.7)	57 (29.1)	104 (26.4)	337 (30.0)
Rest of the World	20 (8.5)	89 (9.8)	21 (10.6)	24 (12.1)	11 (5.6)	35 (8.9)	104 (9.3)
Duration of UC (years), mean (range)	8.1 (0.4–36.2)	8.1 (0.3–42.5)	8.8 (0.6–42.7)	8.3 (0.6–40.3)	8.7 (0.6–35.7)	8.5 (0.6–40.3)	8.2 (0.4–42.5)
Extent of disease, n (%)[a,b]							
Proctosigmoiditis	35 (15.0)[g]	132 (14.6)[g]	21 (10.6)[g]	28 (14.3)[g]	33 (16.9)[g]	61 (15.6)[g]	163 (14.5)[g]
Left-sided colitis	76 (32.6)[g]	307 (34.0)[g]	68 (34.3)[g]	66 (33.7)[g]	60 (30.8)[g]	126 (32.2)[g]	380 (33.9)[g]
Extensive/pancolitis	122 (52.4)[g]	463 (51.3)[g]	108 (54.5)[g]	102 (52.0)[g]	102 (52.3)[g]	204 (52.2)[g]	577 (51.5)[g]
Mean total Mayo score (SD)	9.0 (1.5)[h]	9.0 (1.4)[h]	3.3 (1.8)	3.3 (1.8)	3.4 (1.8)	3.4 (1.8)	8.6 (2.0)[h]
Median CRP, mg/l (range)	4.7 (0.1–205.1)[i]	4.6 (0.1–208.4)[i]	1.0 (0.1–45.0)	0.7 (0.1–33.7)	0.9 (0.1–74.3)	0.7 (0.1–74.3)	4.5 (0.1–208.4)[i]
Prior TNFi failure, n (%)[b,c]	124 (53.0)	465 (51.4)	89 (44.9)	83 (41.9)	92 (46.9)	175 (44.4)	583 (51.9)
Prior TNFi exposure, n (%)[b,d]	130 (55.6)	488 (53.9)	92 (46.5)	90 (45.5)	100 (51.0)	190 (48.2)	612 (54.4)
Prior immunosuppressant exposure, n (%)[b,e]	160 (68.4)	683 (75.5)	134 (67.7)	149 (75.3)	144 (73.5)	293 (74.4)	838 (74.6)
Immunosuppressant exposure within 8 weeks before baseline, n (%)[b,e]	56 (23.9)	259 (28.6)	44 (22.2)	45 (22.7)	56 (28.6)	101 (25.6)	313 (27.8)
Oral corticosteroid use at baseline, n (%)[f]	113 (48.3)	412 (45.5)	100 (50.5)	101 (51.0)	86 (43.9)	187 (47.5)	505 (44.9)
Mean oral corticosteroid daily dose at baseline – prednisone equivalent, mg/day (SD)[f]	16.5 (6.0)	16.1 (6.4)	15.9 (6.2)	14.9 (6.2)	14.5 (5.9)	14.7 (6.1)	16.0 (6.3)

Abbreviations: CRP, C-reactive protein; N, number of patients in the treatment group; n, number of unique patients with characteristic; P, phase.
[a]Included one patient with proctitis who received tofacitinib in OCTAVE Induction and placebo in OCTAVE Sustain, and was enrolled as a protocol deviation.
[b]Data were collected at the start of the phase 3 induction studies.
[c]Prior TNFi failure was determined by investigators and did not specify a minimum dose or treatment duration with TNFi.
[d]Prior TNFi exposure was defined as any prior treatment with TNFi.
[e]Immunosuppressants include nonbiologic agents such as azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, and tacrolimus.
[f]Based on prednisone-equivalent total daily dose, and excludes medications such as budesonide and beclomethasone.
[g]Induction Cohort: placebo N = 233, tofacitinib 5 mg BID N = 903; Maintenance Cohort: placebo N = 198, tofacitinib 5 mg BID N = 196, tofacitinib 10 mg BID N = 195, Tofacitinib All n = 391; Overall Cohort: N = 1121.
[h]Induction Cohort: placebo N = 233, tofacitinib 5 mg BID N = 903; Overall Cohort: N = 1122.
[i]Induction Cohort: placebo N = 233, tofacitinib 5 mg bid N = 891; Overall Cohort: N = 1106.
[j]All patients who received tofacitinib 5 mg or 10 mg BID in phase 3 trials (OCTAVE Induction 1 and 2, OCTAVE Sustain, and OCTAVE Open).

exposure to immunosuppressants and steroids—details not captured in this study.

Univariate analysis selected prior NMSC, prior TNFi failure, and increasing age, in addition to disease duration, North American location, ex-smoker status, baseline ALC, and prior TNFi exposure, as significant risk factors. However, the univariate and stepwise regression analyses did not identify other widely reported risk factors for NMSC, such as prior immunosuppressant exposure or White race, although these risk factors did show a trend of higher IR in a subgroup analysis of patients with NMSC. Additionally, of the total 612 patients with TNFi exposure, 597 patients did not report NMSC. The small patient numbers in some subpopulations and the few reported NMSC cases, and the fact that the majority of patients were White (79.8%) or had prior immunosuppressant exposure (74.6%), may have impacted the analysis in this model. Additionally, there may be confounding factors with prior NMSC history.

The IR of NMSC in the UC Tofacitinib All group in the Overall Cohort was generally similar to those reported for the RA, PsA, and PsO programs (all exposure) with tofacitinib.[15–17, 25] In the RA program, in a population of 6194 patients across combined phase 1, 2, 3, and long-term extension studies (19,406 PY of exposure; March 2015 data cutoff), the NMSC IR was 0.6 per 100 PY (95% CI, 0.5–0.7).[25] In RA, the IR generally remained stable across time intervals at approximately 0.41 to 0.89 per 100 PY through up to 84 months of tofacitinib treatment (analyses based on the August 2013 data cutoff).[15] Similarly, for PsA in a study population of 783 patients (776 PY of exposure; May 2016 data cutoff), the NMSC IR was 0.51 per 100 PY (95% CI, 0.14–1.30).[16] The NMSC IR for Tofacitinib All doses for patients with PsO was 0.71 per 100 PY (95% CI, 0.43–1.10) for 1807 patients (2704.75 PY of exposure; April 2014 data cutoff).[17] In the data shown here for UC (May 2019 data cutoff), the interval IRs through >30 months fluctuated, with IRs ranging from 0 to 2.1, and with wide and overlapping 95% CIs. As there were few NMSC events reported, and there was a smaller patient population in this analysis, particularly compared with the RA program, this limits meaningful comparison between the NMSC IRs in the different clinical programs.

Occurrences of NMSC during clinical trials of biologic therapies for patients with UC were relatively infrequent, and IRs were not reported in these trials.[26–31] Therefore, for contextualization purposes, the global IRs for patients with UC in this analysis are shown alongside the NMSC IR for patients with UC in external observational data from the US Truven analysis who received any TNFi, azathioprine, or 6-mercaptopurine.[32, 33] These data show that NMSC IRs in the UC tofacitinib Overall Cohort were generally numerically lower than those reported for TNFi, either alone or in combination, and azathioprine or 6-mercaptopurine in patients with UC in the Truven comparison cohort. However, these comparisons should be treated with caution, given the limitations of comparing clinical trial data with data from a claims database. Differences in the methods of identification of

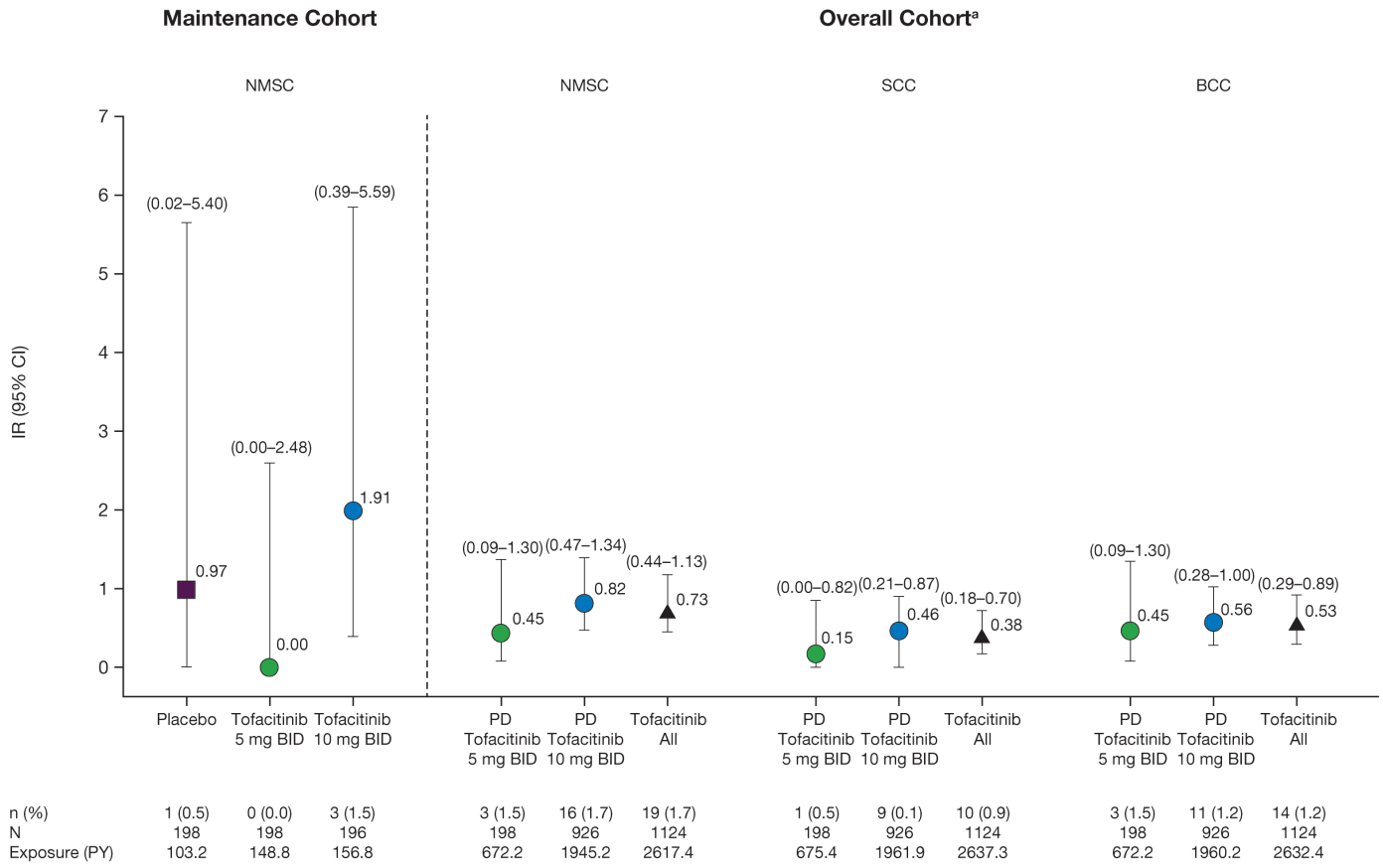

Figure 2. Proportions and IRs of NMSC in the Maintenance Cohort and of NMSC, SCC, and BCC in the Overall Cohort. Abbreviations: N, number of patients randomized and treated; n, number of patients with event. [a]Overall Cohort for adjudicated NMSC, SCC, and BCC; includes phase 3 and OLE studies only.

NMSC events in clinical trials vs claims data should be considered. In addition, despite the application of selection criteria to the claims database simulating similar populations in clinical trials, specific factors such as prior immunomodulator use may not be captured as accurately in the claims data.

There are several limitations for this analysis. Analysis of NMSC event rates in the Induction Cohort should be interpreted with caution, due to the relatively short duration of exposure in this cohort. An important consideration is that NMSC cases were adjudicated in the studies included for analysis, but no dermatological screening took place at baseline. As such, it is not possible to conclusively determine how many NMSCs were preexistent and how many were of new onset since initiation of the study drug. In terms of comparison of NMSC IRs with other treatments, though the Truven comparison cohort serves as an important contextualization tool, comparisons with phase 3 trial data should be made with consideration of differences in population characteristics, including the global vs US populations, the capturing of events, and the limited number of events in the tofacitinib UC clinical program. For example, there was a lack of specific demographic information in the Truven population, such as details of race and prior and concomitant immunosuppressive treatments received alongside TNFi or azathioprine/6-mercaptopurine. Additionally, since Truven is a claims database, there is a potential for misclassification of NMSC. This may affect the NMSC IR presented and confound comparison between different treatments, as this might not only compare modes of action, but also treatment strategies. Over 70% of patients in the Overall Cohort had immunosuppressant exposure, which has been shown to have a lasting impact on NMSC risk, and may affect the analysis of data. Duration of exposure to thiopurines data was not available for the patients analyzed; therefore, it was not possible to further stratify the effect of prior immunosuppressant exposure on NMSC risk.

In conclusion, NMSC events were relatively infrequent in patients with UC receiving tofacitinib across the clinical program. Incidence rates of NMSC for tofacitinib-treated patients in the Overall Cohort were generally similar to the general population,[2] numerically higher than patients with UC naïve to thiopurine treatment, and numerically lower than patients with UC receiving thiopurines beyond their first year of use.[8] Dose dependency of NMSC IR could not be con-

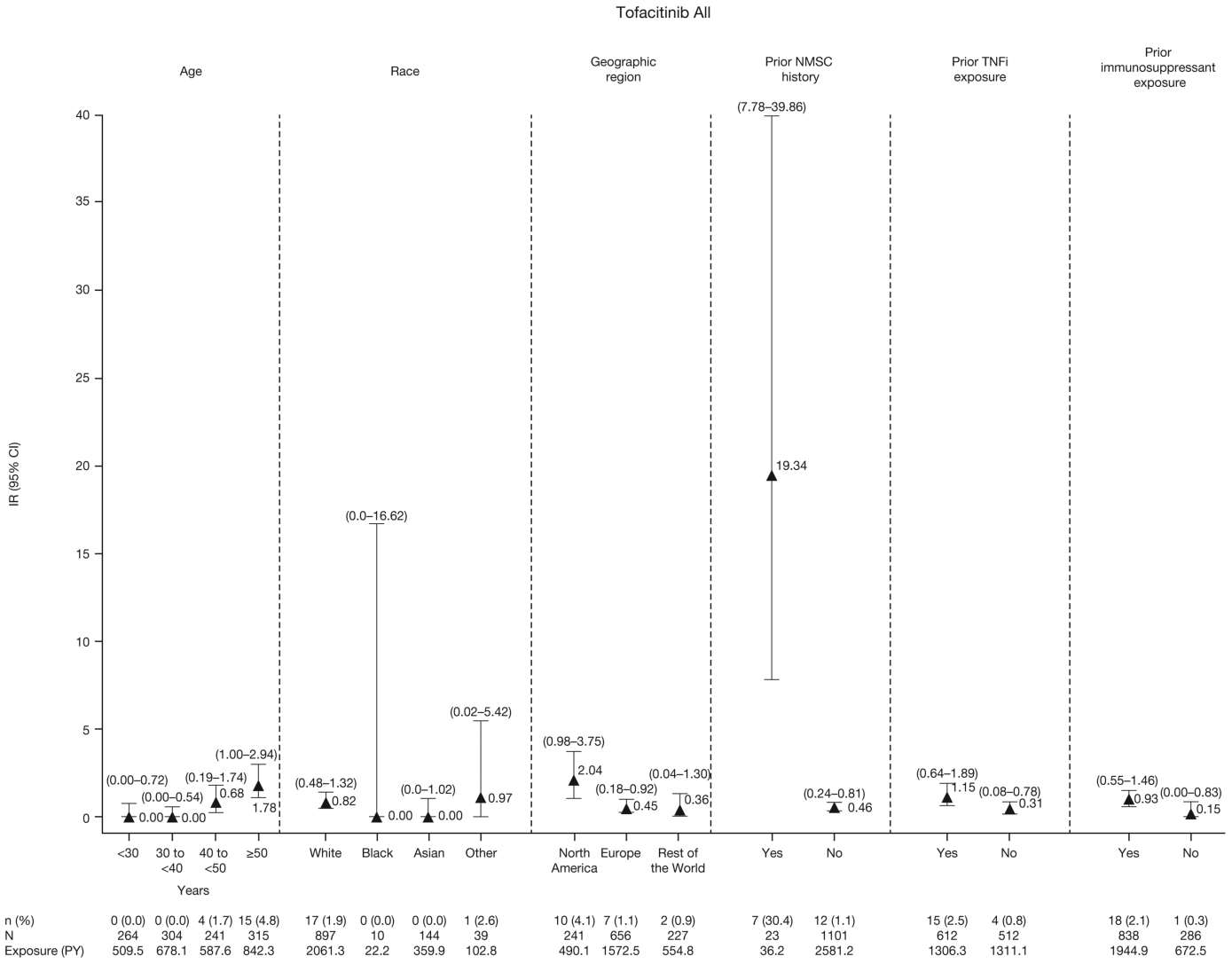

Figure 3. Incidence rates for all NMSC events, by subgroup, in the Overall Cohort (N = 1124). Abbreviations: N, number of patients randomized and treated; n, number of patients with event. For subgroup analysis by race, n = 1 patient with race not specified had NMSC.

Table 2. Cox Univariate and Stepwise Selection Models for Selected Events of Interest for NMSC Risk, in the Overall Cohort (N = 1124)

Parameter	HR	95% CI	*P*
Cox univariate models for selected events of interest			
Prior NMSC	40.73	15.87–104.49	<0.0001
≥65 vs <65 years of age	10.23	4.11–25.43	<0.0001
Age, per 10-year increase	2.76	1.89–4.04	<0.0001
Age, continuous	1.11	1.07–1.15	<0.0001
Region			0.0026[c]
North America vs Europe	4.65	1.77–12.23	
North America vs Other	5.75	1.26–26.24	
Disease duration, per 1-year increase	1.07	1.02–1.11	0.0030
Prior TNFi failure[a]	4.27	1.42–12.87	0.0100
Prior TNFi exposure[b]	3.80	1.26–11.45	0.0179
Smoking history			0.0200[c]
Ex-smoker vs never smoked	4.05	1.52–10.79	
Baseline ALC, continuous	0.47	0.23–0.98	0.0429
Prior immunosuppressant exposure[d]	6.29	0.84–47.12	NS (0.0735)
White race	2.34	0.54–10.11	NS (0.2566)
Weight, ≥90 vs <90 kg	1.95	0.70–5.42	NS (0.1996)
Prior steroid exposure, No vs Yes	2.71	0.90–8.17	NS (0.0770)
Cox regression after stepwise selection for NMSC risk			
Prior NMSC	9.09	2.98–27.73	0.0001
Age, per 10-year increase	2.03	1.37–3.02	0.0004
Prior TNFi failure	3.32	1.08–10.20	0.0363

Abbreviations: ALC, absolute lymphocyte count; HR, hazard ratio; N, number of patients randomized and treated; NS, nonsignificant.
[a]Prior TNFi failure was determined by investigators and did not specify a minimum dose or treatment duration with TNFi.
[b]Prior TNFi exposure was defined as any prior treatment with TNFi.
[c]Overall differences within the parameter; only individual comparisons responsible for driving statistical significance are shown.
[d]Immunosuppressants include nonbiologic agents such as azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, and tacrolimus.
Data show Yes vs No, unless otherwise specified.

cluded from the UC data presented here, as dose changes were permitted during OCTAVE Open. Consistent with previous literature, increasing age, prior NMSC history, and prior TNFi failure were identified as significant NMSC risk factors. Nonmelanoma skin cancer IRs in the UC Overall Cohort were generally similar to those for tofacitinib in the RA clinical program, and generally numerically lower than those reported for patients with UC treated with biologic agents in the Truven comparison cohort.

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DATA SHARING STATEMENT

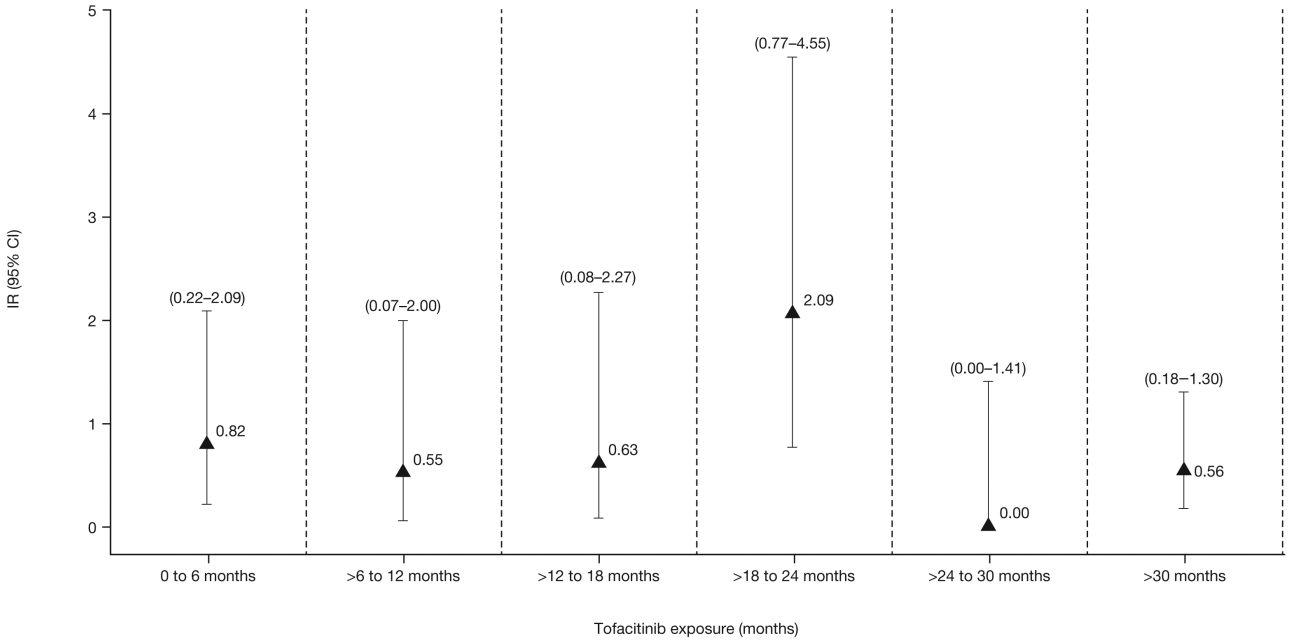
Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Author Contributions

BES, MDL, WR, JP, EVL Jr., CIN, AS, RM, NL, GC, GSF, and CS collected or interpreted data, drafted, and edited the manuscript. RM, NL, GC, GSF, and CS conducted the study/studies. NL, GC, GSF, and CS planned the study/studies. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. Supported by: This work was supported by Pfizer Inc. The clinical trials described in this article were sponsored by Pfizer Inc. Medical writing support was funded by Pfizer Inc.

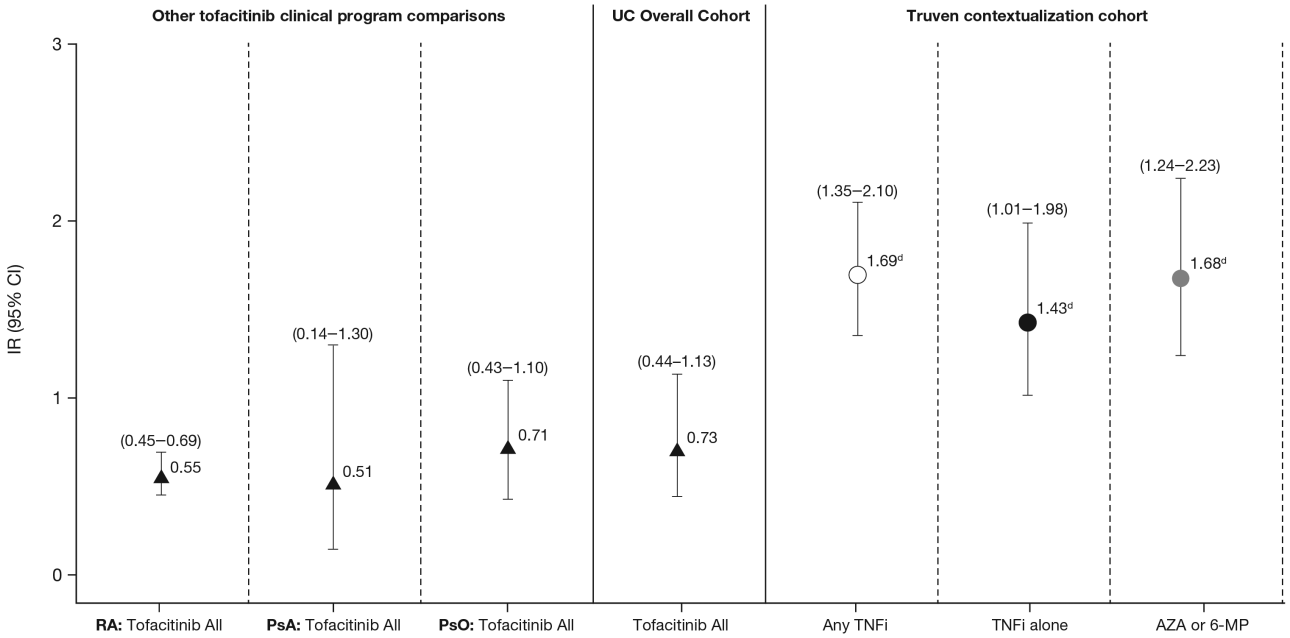
Conflicts of Interest

BES has received consultancy fees from 4D Pharma, AbbVie, Allergan Sales, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Capella Biosciences, Celgene, Eli Lilly, EnGene, Ferring, Gilead, Janssen, Lyndra, MedImmune, Oppilan Pharma, Otsuka, Palatin Technologies, Pfizer Inc, Progenity, Rheos Medicines, Seres Therapeutics, Synergy Pharmaceuticals, Takeda, Target PharmaSolutions, Theravance Biopharma R&D, TiGenix, Vivelix Pharmaceuticals, and WebMD; and has received research funding from Celgene, Janssen, Pfizer Inc, and Takeda. MDL has received consultancy fees from AbbVie, Janssen, Prometheus, Salix, Takeda, Target Pharmasolutions, and UCB; and has received grant support from Pfizer Inc and Takeda. WR has received consultancy fees from Abbott Laboratories, AbbVie, Aesca, Amgen, AM Pharma, AOP Orphan, Arena Pharmaceuticals, Astellas, AstraZeneca, Avaxia, Bioclinica, Biogen IDEC, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Cellerix, Celltrion, Centocor, ChemoCentryx, Covance, Danone Austria, Elan, Eli Lilly, Ernst & Young, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Gilead, Grünenthal, ICON, Index Pharma, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt, Medahead, MedImmune, Millennium, Mitsubishi Tanabe Pharma Corporation, MSD, Nash Pharmaceuticals, Nestlé, Nippon Kayaku, Novartis, Ocera, Otsuka, Parexel, PDL, Periconsulting, Pfizer Inc, Pharmacosmos, Philip Morris Institute, Procter & Gamble, Prometheus, Protagonist, Provention, Robarts Clinical Trials, Roland Berger GmbH, Sandoz, Schering-Plough, Second Genome, Seres Therapeutics, SetPoint Medical, Sigmoid, Takeda, Therakos, Tigenix, UCB,



n (%)	4 (0.4)	2 (0.3)	2 (0.3)	6 (1.0)	0 (0.0)	5 (1.0)
N	1124	784	680	603	546	501
Exposure (PY)	489.9	361.7	318.2	286.8	261.5	899.3

Figure 4. Proportions and IRs (95% CI) of NMSC in the Tofacitinib All group in the Overall Cohort by duration through >30 months. Abbreviations: N, number of patients randomized and treated; n, number of patients with event.



N	6092[a]	783[b]	1807[c]	1124	4420[e]	2785[e]	2650[e]
Exposure (PY)	15,103	776	2704.8	2617.4	4841.9	2580.2	2849.0

Figure 5. Incidence rates (95% CI) for NMSC in the Tofacitinib All group in the UC Overall Cohort, other tofacitinib programs for RA, PsA, and PsO, and the Truven database for any TNFi and azathioprine or 6-mercaptopurine. Abbreviations: AZA, azathioprine; N, number of patients randomized and treated; 6-MP, 6-mercaptopurine. [a]Curtis et al. 2017[15]. [b]Burmester et al. 2017[16]. [c]Papp et al. 2016[17]. [d]IRs for the Truven contextualization cohort are for events per 100 PY. [e]Number of treatment episodes. The study observation period for Truven cohort data was October 1, 2010, to September 30, 2015. "Any TNFi" included all patients who received TNFi alone or with immunosuppressive agents.

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