

# Analysis of non-melanoma skin cancer across the tofacitinib rheumatoid arthritis clinical programme

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## Abstract

### Objective

Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). We evaluated the incidence of non-melanoma skin cancer (NMSC) across the tofacitinib RA development programme.

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### Methods

NMSC events (through August 2013) were identified in patients receiving tofacitinib in two Phase (P)1, eight P2, six P3 and two long-term extension (LTE) studies. In P123 studies, tofacitinib was administered at various doses (1–30 mg twice daily [BID], 20 mg once daily), as monotherapy or with conventional synthetic disease-modifying anti-rheumatic drugs, mainly methotrexate. In LTE studies, patients from qualifying P123 studies received tofacitinib 5 or 10 mg BID. Crude incidence rates (IRs; patients with events/100 patient-years) for first NMSC event were evaluated across doses and over time.

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### Results

In the overall population, comprising data from 18 studies (15,103 patient-years), 83 of 6092 tofacitinib-treated patients had NMSC events. The IR for NMSC (0.55 [95% confidence interval, 0.45–0.69] overall population) was stable up to 84 months of observation. IRs for tofacitinib 5 and 10 mg BID in combined P123 trials were 0.61 (0.34–1.10) and 0.47 (0.24–0.90), respectively. Corresponding IRs for LTE studies were 0.41 (0.26–0.66) and 0.79 (0.60–1.05).

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### Conclusion

The IR for NMSC across the tofacitinib RA clinical development programme was low and remained stable over time. The IR for NMSC in LTE studies was numerically but not significantly higher with tofacitinib 10 versus 5 mg BID; an inverse dose relationship was observed in P123 trials. Longer follow-up is required to confirm these results.

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### Key words

clinical trial, non-melanoma skin cancer, rheumatoid arthritis, tofacitinib

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## Introduction

Certain types of malignancies (lung, skin, lymphoma) are more prevalent in patients with rheumatoid arthritis (RA) than in the general population (1-3). However, the mechanisms underlying this observation are not fully understood. One of the most commonly occurring malignancies associated with immunomodulatory therapy in patients with RA is non-melanoma skin cancer (NMSC) (4). In patients with RA, an elevated risk of NMSC is associated with the use of biologic disease-modifying anti-rheumatic drugs (bDMARDs), including tumour necrosis factor inhibitors (TNFi) (5-9). There is also some evidence that risk of NMSC is further increased when TNFi are administered with methotrexate (MTX) (10, 11). Therefore, it is important that the risk of NMSC should be characterised for immunomodulatory agents used to treat RA.

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA (12). The clinical efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID), with or without background conventional synthetic DMARDs (csDMARDs), have been demonstrated in patients with active moderate to severe RA. These include randomised Phase 2 (13-17) and Phase 3 (18-24) studies of up to 24 months' duration, and open-label, long-term extension (LTE) studies with up to 96 months' observation (25), representing 6092 patients and 15,103 patient-years (pt-yrs) of exposure.

The aim of this analysis was to determine the incidence of NMSC in the tofacitinib RA clinical development programme using pooled data from 6092 patients enrolled in randomised Phase 1, 2, 3 and open-label LTE studies. The effect of tofacitinib dose, time on study drug (over discrete 6-month intervals) and patient factors on the incidence of NMSC were investigated.

## Patients and methods

### Patients

Patients were  $\geq 18$  years of age with active moderate to severe RA, enrolled globally from North America, Europe, Latin America, Asia (including the Pacific Islands) and Australia. Patients

had an inadequate response to MTX (NCT00413660 (15), NCT00976599 (26), NCT00603512 (16), ORAL Scan (20), ORAL Standard (21)), cs-DMARDs or bDMARDs (NCT01484561 (27), NCT00147498 (14), NCT00550-446 (13), NCT00687193 (17), ORAL Solo (19), ORAL Sync (22)) or TNFi (ORAL Step (18)). One Phase 1 study (NCT01262118 (28)) and two Phase 2 studies (NCT01059864 (29) and NCT01359150 (30)) had no eligibility criteria for prior DMARD exposure (*i.e.* any or no prior DMARDs were acceptable). The Phase 3, ORAL Start study (23) was conducted in MTX-naïve patients. Exclusion criteria for all studies prohibited participation of patients with a malignancy or history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell carcinoma (BCC), squamous cell carcinoma (SCC) of the skin or cervical carcinoma in situ. Patients with  $\geq 1$  prior resolved occurrence(s) of NMSC were eligible for inclusion, with no time restriction on the required date for the most recent NMSC prior to trial enrolment.

### Study design

Reports of NMSC were analysed from patients pooled from one open-label and one randomised Phase 1 study (27, 31), eight randomised, double-blind, Phase 2 studies (13-17, 29, 30, 32), six randomised, double-blind, Phase 3 studies (ORAL Scan (20), ORAL Solo (19), ORAL Sync (22), ORAL Standard (21), ORAL Step (18) and ORAL Start (23)) and two open-label LTE studies (ORAL Sequel, NCT00413699 (33) [global] and NCT00661661 [Japan]) of tofacitinib.

In Phase 1, 2 and 3 studies, the dose of tofacitinib and any background DMARDs was required to be stable. Patients in Phase 1 studies received tofacitinib 5 or 10 mg BID for either 72 days or 6 weeks (27, 28). In Phase 2 studies (6 weeks' to 6 months' duration), tofacitinib was administered as 1, 3, 5, 10, 15 or 30 mg BID (20 mg once daily included in one study) either as monotherapy or with background MTX (13-17, 29, 30, 32). In Phase 3 studies, tofacitinib 5 or 10 mg BID was administered as monotherapy (ORAL

Start (23) and ORAL Solo (19)) or with csDMARDs, mainly MTX. Patients enrolled into LTE studies had participated in prior qualifying Phase 1, 2 or 3 studies and initiated treatment with tofacitinib 5 or 10 mg BID (30 August 2013 cut-off date; data collection and analyses ongoing; unlocked database, *i.e.* some values may change for the final, locked study databases). LTE study treatment was initiated with tofacitinib 5 mg BID (patients from Phase 2 studies) or tofacitinib 10 mg BID (patients from Phase 3 studies), with the exception of patients from China and Japan, who initiated treatment with tofacitinib 5 mg BID as per protocol (34). In LTE studies, the tofacitinib dose could be reduced for safety reasons from 10 to 5 mg BID, or temporarily discontinued, at the investigator's discretion, for up to 28 consecutive days for adverse events (AEs) or surgical procedures. In the event of an inadequate response, the dose could be increased from 5 to 10 mg BID at the investigator's discretion. All studies contained a placebo control arm, except ORAL Start (23) (MTX monotherapy comparator arm) and the LTE studies (open label with no active comparator or placebo control arm). In two of the Phase 2 studies (13, 15), patients randomised to tofacitinib 1 or 3 mg BID, 20 mg once daily or placebo, who did not show an adequate response at Week 12, were reassigned to tofacitinib 5 mg BID. Patients randomised to placebo in Phase 3 trials were advanced to tofacitinib 5 or 10 mg BID at Month 3 or 6. Two studies included an adalimumab (ADA) active control arm – 40 mg administered subcutaneously every two weeks as monotherapy (NCT00550446; Phase 2 study (13)) or with background MTX (ORAL Standard (21)).

The studies were conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice Guidelines and relevant local country regulations. The patients provided written, informed consent. The final protocol, amendments and consent documentation were reviewed and approved by the Institutional Review Board and Independent Ethics Committee of the investigational centres.

#### *Identification and classification of NMSC*

NMSC events were identified from investigator-reported AEs, serious AEs and outputs from a central laboratory histology review. Where tissue was available, an over-read process involved a centralised, external, blinded, consensus review of each biopsy performed by  $\geq 2$  independent, board-certified pathologists.

#### *Statistical analyses*

Incidence rates (IR) for the first NMSC event occurring after exposure to tofacitinib were calculated across all doses of tofacitinib using combined data for all tofacitinib-treated patients in Phase 1, 2, 3 and LTE studies, and expressed as the number of unique patients with events per 100 pt-yrs of exposure, with 95% confidence intervals (CIs). IRs were calculated from the number of unique patients with an event, divided by the total exposure through the first NMSC event (for patients with events), or to discontinuation or data cut-off date (all other patients). The 95% CIs were based on maximum likelihood estimation, and Exact Poisson adjusted for exposure when IR is zero. Patients with adequately treated or excised non-metastatic BCC or SCC were permitted to remain in the studies. The rate of recurrent or second incident of NMSC was reported descriptively. To evaluate the occurrence of NMSC with continued tofacitinib exposure, IRs were determined for non-overlapping 6-month intervals. Additionally, IRs were calculated for the following datasets: combined Phase 1, 2, 3 and LTE studies (P123LTE); combined Phase 1, 2 and 3 studies (P123); Phase 3 studies only (P3); combined LTE studies (LTE); and LTE study NCT00413699 (LTE1024). LTE1024 was analysed separately from the combined LTE studies, as the combined studies had a higher proportion of Japanese patients who predominantly received tofacitinib 5 mg BID.

#### *Analysis of IRs for NMSC across subgroups*

IRs for NMSC were assessed in patients receiving tofacitinib 5 and 10 mg BID in P123 and P3. LTE and LTE1024

analyses were based on the average total daily dose (TDD) for each patient (*i.e.* sum of all doses received divided by number of days' treatment up to the 2013 cut-off date or discontinuation): patients with a TDD  $\geq 15$  mg were assigned to the 10 mg BID group, while patients with a TDD  $< 15$  mg were assigned to the 5 mg BID group.

IRs for NMSC were analysed for various additional subgroups based on the P123LTE study population, including background therapy (patients who received tofacitinib monotherapy or tofacitinib with background csDMARDs), prior exposure to TNFi and glucocorticoid use at baseline. Additionally, incidence was evaluated according to patient age at baseline ( $\geq 65$  or  $< 65$  years), ethnicity, geographic location and prior history of NMSC.

## **Results**

### *Patients included in the analysis*

Overall, 6092 patients received  $\geq 1$  dose of tofacitinib and were included in the pooled P123LTE population. The mean age of tofacitinib-treated patients at baseline was 52.2 years (range: 18–86) and 82.7% of patients were female (Table I). Five patients (0.1%) had a history of NMSC prior to study enrolment.

Caucasians and Asians represented approximately 60% and 25%, respectively, of the P123LTE population (all tofacitinib doses). The corresponding proportions in the P3 population were approximately 63% and 24%. In the two LTE studies combined, the proportion of Caucasian and Asian patients was similar with tofacitinib 5 mg BID (46.5% and 43.2%, respectively), whereas with tofacitinib 10 mg BID it was 70.4% and 16.5%, respectively.

### *Overall incidence of NMSC in patients receiving tofacitinib*

The combined exposure to tofacitinib in P123LTE was 15,103 pt-yrs. There were 125 occurrences of NMSC events in 83 tofacitinib-treated patients, resulting in an IR for the first NMSC event of 0.55 (95% CI, 0.45–0.69) per 100 pt-yrs (Fig. 1A). Demographics and baseline characteristics for tofacitinib-

**Table I.** Demographics and baseline characteristics for all patients and patients with NMSC following study drug exposure.

All treated patients <i>Patients with NMSC following study drug exposure</i>	P123LTE All tofacitinib (5 and 10 mg BID)	Tofacitinib		P123			P3			LTE	
		5 mg BID	10 mg BID	Placebo	Adalimumab 40 mg q2w	Methotrexate	5 mg BID	10 mg BID	Placebo	5 mg BID	10 mg BID
Number of patients	6092 83	1849 11	2196 9	1130 2	257 2	186 2	1589 10	1611 9	681 2	1448 <sup>y</sup> 17	3394 <sup>y</sup> 50
Mean age in years (SD)	52.2 (11.9) 62.3 (8.6)	52.3 (11.9) 59.9 (5.7)	52.0 (11.8) 64.6 (9.3)	52.2 (12.1) 60.0 (0.0)	52.7 (11.7) 74.0 (0.0)	48.8 (13.3) 60.5 (12.0)	52.5 (11.9) 60.5 (5.7)	51.7 (12.0) 64.6 (9.3)	52.5 (12.0) 60.0 (0.0)	53.3 (11.9) 63.8 (9.7)	53.0 (11.4) 63.2 (8.8)
Gender, % female	82.7 62.7	82.9 27.3	83.5 77.8	81.6 50.0	80.5 50.0	78.0 0.0	82.6 20.0	84.2 77.8	81.2 50.0	83.0 64.7	82.0 66.0
Race, n (%)											
Caucasian	3835 (63.0) 80 (96.4)	1117 (60.4) 11 (100.0)	1394 (63.5) 8 (88.9)	747 (66.1) 1 (50.0)	191 (74.3) 2 (100.0)	127 (68.3) 2 (100.0)	976 (61.4) 10 (100.0)	1007 (62.5) 8 (88.9)	439 (64.5) 1 (50.0)	673 (46.5) 15 (88.2)	2391 (70.4) 50 (100.0)
Black	181 (3.0) –	63 (3.4) –	68 (3.1) –	38 (3.4) –	4 (1.6) –	4 (2.2) –	58 (3.7) –	47 (2.9) –	24 (3.5) –	24 (1.7) –	110 (3.2) –
Asian	1483 (24.3) 1 (1.2)	481 (26.0) –	513 (23.4) –	254 (22.5) 1 (50.0)	33 (12.8) –	33 (17.7) –	395 (24.9) –	377 (23.4) –	166 (24.4) 1 (50.0)	625 (43.2) 1 (5.9)	559 (16.5) –
Hispanic*	49 (0.8) –	15 (0.8) –	0 (0.0) –	15 (1.3) –	0 (0.0) –	0 (0.0) –	NC –	NC –	NC –	14 (1.0) –	0 (0.0) –
Other/unspecified	544 (8.9) 2 (2.4)	173 (9.4) –	221 (10.1) 1 (11.1)	76 (6.7) –	29 (11.3) –	22 (11.8) –	160 (10.1) –	180 (11.2) 1 (11.1)	52 (7.6) –	112 (7.7) 1 (5.9)	334 (9.8) –
Regions, n (%)											
Europe and Canada	1976 (32.4) 16 (19.3)	598 (32.3) 1 (9.1)	668 (30.4) 1 (11.1)	365 (32.3) –	140 (54.5) –	63 (33.9) 1 (50.0)	590 (37.1) 1 (10.0)	594 (36.9) 1 (11.1)	246 (36.1) –	364 (25.1) 3 (17.6)	1342 (39.5) 12 (24.0)
Latin America	952 (15.6) 5 (6.0)	309 (16.7) 0 (0.0)	299 (13.6) 2 (22.2)	162 (14.3) –	31 (12.1) –	33 (17.7) –	259 (16.3) 0 (0.0)	267 (16.6) 2 (22.2)	98 (14.4) –	257 (17.7) 1 (5.9)	505 (14.9) 2 (4.0)
Rest of the world <sup>‡</sup>	1780 (29.2) 21 (25.3)	600 (32.4) 5 (45.5)	648 (29.5) 4 (44.4)	272 (24.1) 1 (50.0)	43 (16.7) 1 (50.0)	67 (36.0) –	438 (27.6) 5 (50.0)	436 (27.1) 4 (44.4)	177 (26.0) 1 (50.0)	623 (43.0) 1 (5.9)	654 (19.3) 13 (26.0)
USA	1384 (22.7) 41 (49.4)	342 (18.5) 5 (45.5)	581 (26.5) 2 (22.2)	331 (29.3) 1 (50.0)	43 (16.7) 1 (50.0)	23 (12.4) 1 (50.0)	302 (19.0) 4 (40.0)	314 (19.5) 2 (22.2)	160 (23.5) 1 (50.0)	204 (14.1) 12 (70.6)	891 (26.3) 23 (46.0)
Prior exposure to bDMARD, n (%)	1278 (21.0) 24 (28.9)	356 (19.3) 3 (27.3)	516 (23.5) 2 (22.2)	343 (30.4) 1 (50.0)	24 (9.3) 0 (0.0)	1 (0.5) 0 (0.0)	322 (20.3) 3 (30.0)	316 (19.6) 2 (22.2)	216 (31.7) 1 (50.0)	175 (12.1) 4 (23.5)	860 (25.3) 17 (34.0)
Patient age <65 years, n (%)	5208 (85.5) 50 (60.2)	1593 (86.2) 10 (90.9)	1879 (85.6) 5 (55.6)	965 (85.4) 2 (100.0)	219 (85.2) 0 (0.0)	166 (89.2) 1 (50.0)	1362 (85.7) 9 (90.0)	1381 (85.7) 5 (55.6)	580 (85.2) 2 (100.0)	1196 (82.6) 8 (47.1)	2876 (84.7) 28 (56.0)

Tofacitinib dose groups in LTE studies were defined according to average TDD.

<sup>y</sup>Two and three patients in the tofacitinib 5 and 10 mg BID groups, respectively, had no demographic data available at the time of the data cut-off.

\*Hispanic ethnicity was not captured as a separate category in Phase 3 studies; any patients of Hispanic ethnicity will be included as 'Other/unspecified'.

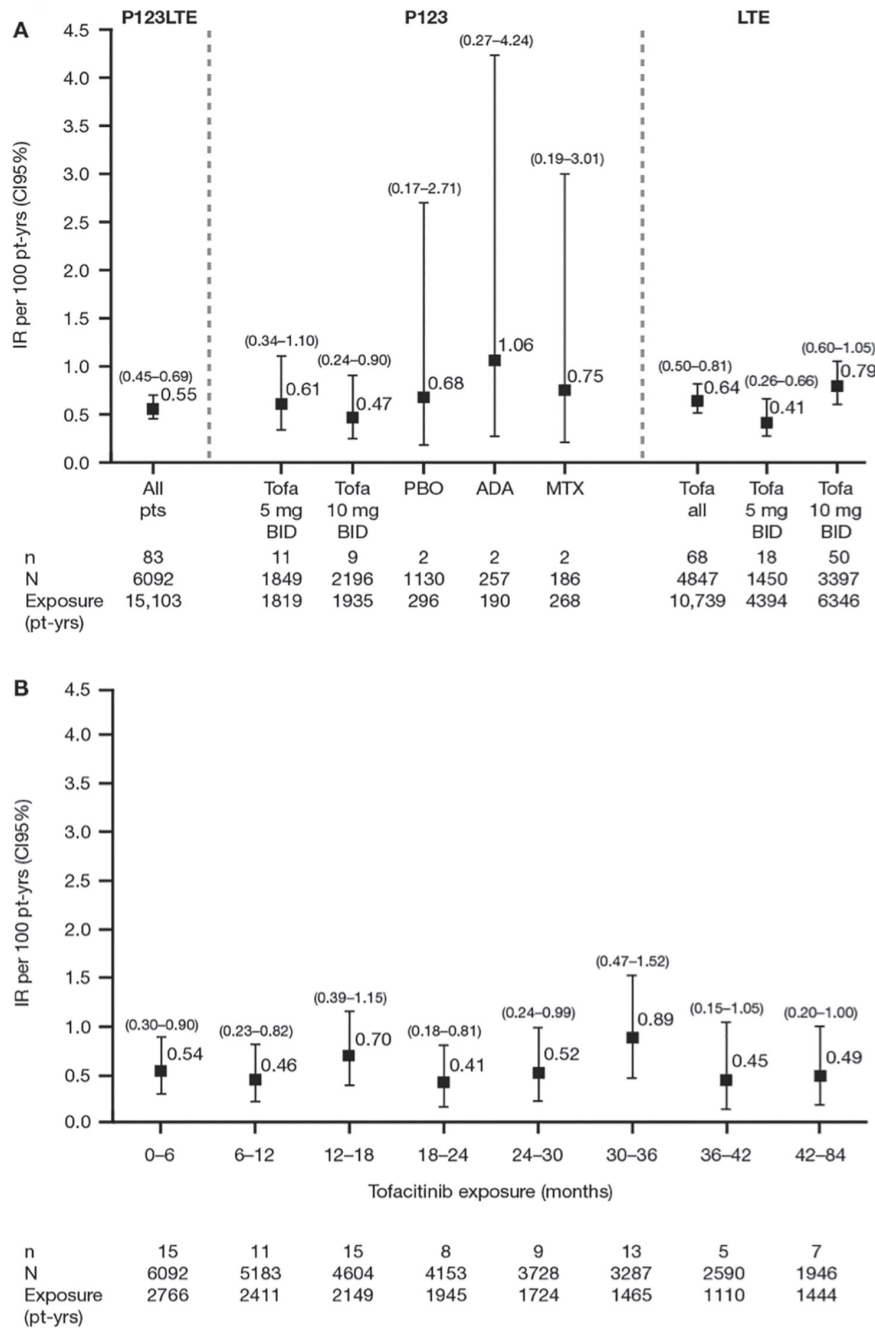
<sup>‡</sup>Rest of the world includes: Australia, China, India, Japan, Korea, Malaysia, New Zealand, Philippines, Taiwan and Thailand. bDMARD: biologic disease-modifying anti-rheumatic drug; BID: twice daily; LTE: long-term extension; NC: not collected, Hispanic patients included in 'Other/unspecified' group; P123: Phase 1, Phase 2 and Phase 3 studies; P3: Phase 3; q2w, once every 2 weeks; SD: standard deviation; TDD: total daily dose.

treated patients with NMSC events are presented in Table I. The median tofacitinib exposure time after the first NMSC event was 441 days (range: 0–2030). There were 71 occurrences of BCC (56.8%) in 52 patients and 51 occurrences of SCC (40.8%) in 39 patients, resulting in a BCC:SCC event ratio of approximately 1.4:1.0. Eleven of the 83 tofacitinib-treated patients with NMSC (13.3%) had both BCC and SCC events. IRs (95% CI) for SCC and BCC were 0.35 (0.26–0.45) and 0.26 (0.19–0.35), respectively. Only

three out of these 83 patients reported 'NMSC other': two patients each with a single event of atypical fibroxanthoma and one patient with a single event of Merkel cell carcinoma. IRs for NMSC in the P123LTE population appeared to be stable over time (Fig. 1B). IRs for NMSC in patients who received placebo, MTX or ADA in the P123 population were comparable with corresponding IRs for tofacitinib (Fig. 1A). However, the exposure to placebo, MTX or ADA was much lower than for tofacitinib.

*Recurring or second NMSC events in patients receiving tofacitinib*

Of the 83 patients with NMSC during the study, 19 (22.9%) had ≥1 further occurrence or a second NMSC event whilst receiving tofacitinib, *i.e.* an additional event occurring at a different time or location. Among these 19 patients who had >1 NMSC event during the tofacitinib exposure period, the majority (n=11) had only two NMSC events in total; six and one patient(s) had three and four NMSC events overall, respectively, and one patient – a



**Fig. 1.** Exposure estimates and crude IRs (with CI95%) for NMSC in patients with RA participating in (A) P123LTE, P123 and LTE studies of tofacitinib, and (B) P123LTE over time.

Of the 83 tofacitinib-treated patients with NMSC, 20 were resident in Australia. Of these, nine patients had BCC as a first event, nine had SCC as a first event and two had ‘NMSC other’. ADA 40 mg was administered every 2 weeks either as monotherapy or with background MTX. Exposure shown is cumulative exposure.

ADA: adalimumab; BCC: basal cell carcinoma; BID: twice daily; CI: confidence interval; IR: incidence rate; LTE: long-term extension; MTX: methotrexate; N: total number of patients exposed to study treatment; n: number of unique patients with events; NMSC: non-melanoma skin cancer; P123: Phase 1, Phase 2 and Phase 3 studies; PBO: placebo; pts: patients; pt-yrs: patient-years; RA: rheumatoid arthritis; SCC: squamous cell carcinoma; Tofa: tofacitinib.

66-year-old Caucasian female from Australia – had a total of 17 NMSC events (further discussion of this patient is included under subgroup analyses). Two of the 19 patients with ≥1 ad-

ditional events had a history of NMSC prior to initiating tofacitinib; patients with a prior history of NMSC are also discussed in more detail under further subgroup analyses.

*Incidence of NMSC according to tofacitinib dose received*

Total exposure (pt-yrs) was similar for tofacitinib 5 and 10 mg BID in P123 (Fig. 1A), but higher in LTE studies for tofacitinib 10 mg BID versus 5 mg BID (Fig. 1A, Table II). In the P3 population, NMSC IRs were similar between tofacitinib dose groups, while in the ongoing, open-label LTE studies, both for LTE1024 and LTE, NMSC IRs were numerically higher with tofacitinib 10 mg BID versus 5 mg BID, although CIs overlapped (Table II).

*Further subgroup analyses*

Among the 83 patients with NMSC events during the study, 78 (94.0%) had no history of NMSC prior to initiating treatment with tofacitinib. The IR (95% CI) for the first NMSC event in this group of patients with no history of NMSC was 0.52 (0.42–0.65).

Five patients who had a history of NMSC accounted for 22 of the 125 (total) NMSC events reported in this analysis. Subsequent to commencing tofacitinib treatment, one patient with a history of NMSC had atypical fibroxanthoma, three patients reported one or two BCC/SCC events each, and one patient – a 66-year-old Caucasian female from Australia – had 10 BCC events and seven SCC events at different locations of the body over the course of a year. The events reported for this patient accounted for 77.3% (17/22) of the NMSC events reported in the five patients with a history of NMSC. Despite experiencing such a high number of NMSC events, this patient completed ORAL Start.

Among the 83 patients with reported NMSC, the most commonly used concomitant medications during the study were anti-inflammatory and anti-rheumatic agents (89.2% [n=74]), which included non-steroidal anti-inflammatory drugs (such as ibuprofen 21.7% [n=18]) and csDMARDs, the most common of which was MTX (60.2% [n=50]).

In the P123LTE overall population, patients who received tofacitinib with background csDMARDs had a numerically higher IR (95% CI) for NMSC than patients who received tofacitinib as monotherapy, although CIs overlapped

**Table II.** Crude incidence rate of NMSC in patients with RA who received tofacitinib.

	P123LTE	P123		P3		Placebo	LTE1024		LTE	
	All tofacitinib (5 and 10 mg BID) n=6092	Tofacitinib 5 mg BID n=1849	Tofacitinib 10 mg BID n=2196	Tofacitinib 5 mg BID n=1589	Tofacitinib 10 mg BID n=1611		Tofacitinib 5 mg BID n=1036	Tofacitinib 10 mg BID n=3325	Tofacitinib 5 mg BID n=1450	Tofacitinib 10 mg BID n=3397
Total exposure, pt-yrs	15,103	1819	1935	1744	1800	203	3248	6135	4394	6346
Patients with event, n	83	11	9	10	9	2	17	50	18	50
IR (CI95%)	0.55 (0.45–0.69)	0.61 (0.34–1.10)	0.47 (0.24–0.90)	0.58 (0.31–1.07)	0.50 (0.26–0.96)	0.99 (0.25–3.95)	0.53 (0.33–0.85)	0.82 (0.62–1.08)	0.41 (0.26–0.66)	0.79 (0.60–1.05)

Data cut-off: 30 August 2013.

BID: twice daily; CI: confidence interval; IR: incidence rate (unique patients with events/100 pt-yrs); LTE: long-term extension; n: total number of patients; NMSC: non-melanoma skin cancer; P123: Phase 1, Phase 2 and Phase 3 studies; P3: Phase 3; pt-yrs: patient-years; RA: rheumatoid arthritis.

(Fig. 2A). The IR for NMSC in patients with prior TNFi exposure was significantly higher than for those who were TNFi-naïve with no overlap of CIs (Fig. 2A). Among patients with glucocorticoid use reported at baseline, the NMSC IR was similar to that for patients with no baseline glucocorticoid use (Fig. 2A).

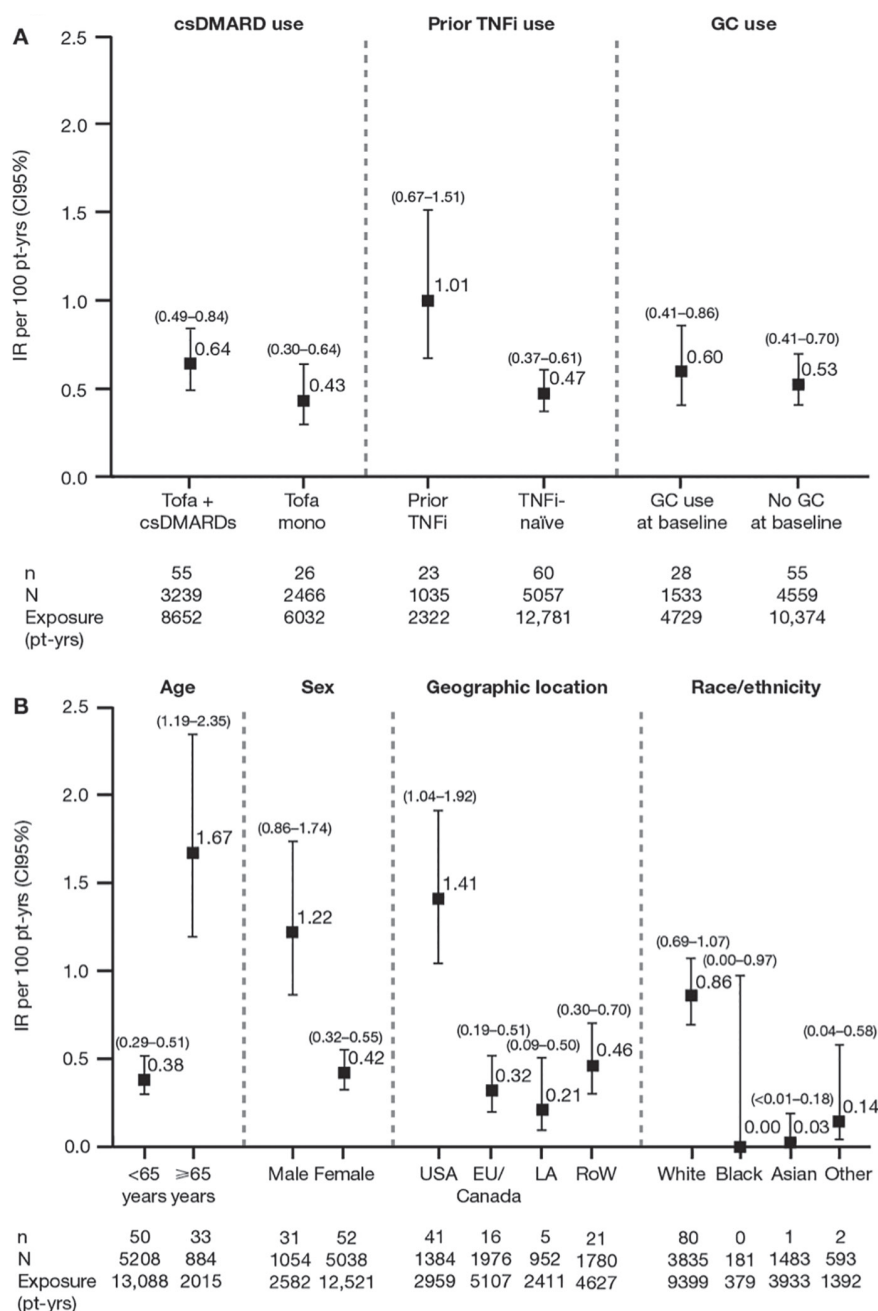
In the pooled P123LTE population, the IR (95% CI) for NMSC was higher among patients ≥65 years of age (1.67 [1.19–2.35]) versus those aged <65 years (0.38 [0.29–0.51]) (Fig. 2B). The NMSC IR was higher in males (1.22 [0.86–1.74]) than in females (0.42 [0.32–0.55]). Patients enrolled at centres in the USA had an NMSC IR of 1.41 (1.04–1.91), which was higher than the rate for patients enrolled in Europe and Canada (0.32 [0.19–0.51]), Latin America (0.21 [0.09–0.50]) and the rest of the world (RoW) (0.46 [0.30–0.70]) (Fig. 2B). RoW contains the Pacific Islands, Australia and Asia: 20 of 21 patients in RoW who had NMSC were Australian and one patient was from Japan. Of the Australian patients, six had BCC, seven had SCC, five had both BCC and SCC, and two patients had ‘NMSC other’ (both atypical fibroxanthoma) as their only NMSC event. The Japanese patient had Merkel cell carcinoma. When the incidence of NMSC was evaluated according to ethnicity, the highest IR was observed in Caucasian patients (0.86 [0.69–1.07]; 9,399 pt-yrs exposure) and the lowest in Black patients (0 [0.0–0.973]; 379 pt-yrs exposure). IRs for Asian patients and other ethnicities were 0.03 (<0.01–0.18 [3933 pt-yrs exposure]) and 0.14 (0.04–0.58 [1392 pt-yrs exposure]), respectively (Fig. 2B).

**Discussion**

In the present analysis, we explored the incidence of NMSC in the global population of patients who received tofacitinib during the RA clinical development programme. Across the tofacitinib RA programme, the IR for NMSC was relatively low and remained stable over time. As of the data cut-off for these analyses (30 August 2013), there were 83 patients with NMSC in tofacitinib RA clinical trials, representing 1.4% of the pooled P123LTE population. The overall IR for NMSC across the tofacitinib RA programme over 15,103 pt-yrs of exposure was consistent with IRs for NMSC in P3 studies of tofacitinib. IRs were similar between tofacitinib 5 and 10 mg BID doses in P3 studies, where randomisation between doses was balanced. In the P123 study population, an inverse dose relationship was observed, with a numerically lower IR for tofacitinib 10 mg BID compared with 5 mg BID. A numerical, but not statistically significant, difference (with overlapping CIs) was observed between IRs for tofacitinib 5 and 10 mg BID in the combined LTE population (majority of patients in LTE were from LTE1024). However, the IRs for NMSC in patients receiving tofacitinib 5 mg BID (0.41 [0.26–0.66]) and 10 mg BID (0.79 [0.60–1.05]) are consistent with published rates for NMSC in patients with RA treated with TNFi and other bDMARDs (range: 0.20–1.45 events per 100 pt-yrs) (5, 9, 35). The IR for NMSC in patients receiving tofacitinib 10 mg BID in the combined LTE population is higher than the overall incidence of NMSC across all studies

(P123LTE; 0.55 [0.45–0.69]). However, it is possible that the IR for NMSC in the LTE 10 mg BID group may have been influenced by the high proportion of Caucasian patients (70.4%) compared with the 5 mg BID group (46.5%), of which 2.9% (98 patients) and 0.1% (one patient) were from Australia. In addition, all Chinese and Japanese patients initiated treatment with tofacitinib 5 mg BID in the LTE study. As observed in the literature (10, 36), and confirmed by this analysis, Asian patients have a lower incidence of NMSC compared with Caucasians, and therefore, this may have introduced an imbalance in the relative baseline risk between the tofacitinib 5 and 10 mg BID groups in the LTE population.

The majority of NMSC events reported in the global tofacitinib RA population were BCC or SCC (97.6%; 122 out of 125 NMSC events), and the ratio of patients with BCC versus those with SCC was 1.4:1.0; some patients had both. The ratio of BCC:SCC events reported in the general population ranged from 1:1– 4:1 (37–39). Both BCC and SCC are treatable with surgery and radiotherapy, and have a low risk of metastasis: BCC <0.5% (40, 41); SCC 2–5% (42). Evaluations of IRs across subgroups of patients suggested an increased likelihood of NMSC in patients who were Caucasian, male, ≥65 years of age (vs. <65 years) or with a history of NMSC. These findings are consistent with results of an observational study of 15,789 patients with RA, from the National Data Bank for Rheumatic Diseases study of the outcomes of RA and osteoarthritis (10). In the present study,



**Fig. 2.** Exposure estimates and crude IRs (with CI95%) for NMSC among tofacitinib-treated patients with RA (P123LTE) according to: (A) concomitant csDMARD use (predominately MTX) versus tofacitinib monotherapy, with/without prior TNFi use and with/without glucocorticoid use at baseline, and (B) selected baseline demographics.

Results from patients who enrolled in the Phase 1, 2 or 3 optional background therapy studies, which allowed both background DMARDs and tofacitinib monotherapy in the same study, are not shown. CI: confidence interval; csDMARD: conventional synthetic disease-modifying antirheumatic drug; EU: Europe; GC: glucocorticoid; IR: incidence rate; LA: Latin America; LTE: long-term extension; mono: monotherapy; MTX: methotrexate; N: total number of patients exposed to study treatment; n: number of unique patients with events; NMSC: non-melanoma skin cancer; P123: Phase 1, Phase 2 and Phase 3 studies; pt-yrs: patient-years; RA: rheumatoid arthritis; RoW: rest of the world; TNFi: tumour necrosis factor inhibitor; Tofa: tofacitinib.

limited conclusions can be drawn from the apparent increase in NMSC IR that was associated with prior TNFi therapy, owing to large differences in cumulative exposure between these two groups

(2322 pt-yrs for prior TNFi; 12,781 pt-yrs for TNFi-naïve). However, the IR for NMSC may also have been influenced by the cumulative effect of different immunosuppressants over time,

including prior TNFi, other bDMARDs and csDMARDs. Nevertheless, our data reflect findings from a US Veterans' Affairs national database, which demonstrated a higher risk of NMSC in patients receiving TNFi therapy versus csDMARDs, with NMSC risk factors of older age, male gender and a history of prior malignancies (8). The rate of occurrence of a second, or more, NMSC event in our analysis (22.9%; 19/83 patients) was slightly higher than in published literature (43), although limited conclusions can be drawn due to low patient numbers.

In the general population, the risk of developing a subsequent skin cancer of a specific type depends on the type of prior NMSC and number of prior skin tumours of that type, with specific follow-up strategies required for patients with BCC and SCC (44). The analysis presented herein revealed that the IR for NMSC was highest in the USA. This may be explained by the fact that Caucasian patients living in geographic locations with year-round high ambient ultraviolet exposure levels are placed at greatest risk of developing NMSC (45). Periodic skin examination is recommended for patients with RA treated with tofacitinib who are at increased risk for skin cancer (46).

Our analysis included data from LTE studies, which may have introduced certain limitations owing to non-randomised assignment of patients to the tofacitinib 5 or 10 mg BID treatment group based on qualifying study enrolment, protocol guidance and investigator discretion. Hence, exposure (pt-yrs) to tofacitinib 10 mg BID was greater than for tofacitinib 5 mg BID in the LTE studies, and some baseline characteristics, such as race, were not distributed evenly between doses, making interpretation of any dose differences uncertain. Similarly, in Phase 2 and 3 studies, exposure to placebo was comparatively low (as per protocol), and for placebo, MTX and ADA, the study population was small compared with pooled tofacitinib; therefore, IR differences between tofacitinib and control arms should be made with caution. Additionally, in the LTE studies, the tofacitinib dose could be modified at the investigator's dis-

cretion based on efficacy and safety outcomes. As such, TDD was used to assign dosing groups in the LTE studies. However, the actual tofacitinib dose received during the LTE study was stable in the majority of patients; approximately 80% of patients did not change dose in the LTE studies.

In conclusion, the IR for NMSC in the global population of patients with RA who received tofacitinib in P123 and LTE studies of the tofacitinib clinical development programme was consistent with published IRs for patients receiving TNFi and other bDMARDs in patients with RA, and remained stable over time. As in the general population, NMSC appeared to be more common in patients who were Caucasian, male,  $\geq 65$  years of age, had previous NMSC or previous exposure to TNFi. As there is a numerical, but not statistically significant, difference of NMSC in LTE with tofacitinib 10 mg BID compared with tofacitinib 5 mg BID, continued longer-term surveillance is necessary to further evaluate any potential risk of developing NMSC during tofacitinib treatment.

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