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EXTENDED REPORT

Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme

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ABSTRACT

Objectives Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). To further assess the potential role of Janus kinase inhibition in the development of malignancies, we performed an integrated analysis of data from the tofacitinib RA clinical development programme.

Methods Malignancy data (up to 10 April 2013) were pooled from six phase II, six Phase III and two long-term extension (LTE) studies involving tofacitinib. In the phase II and III studies, patients with moderate-to-severe RA were randomised to various tofacitinib doses as monotherapy or with background non-biological disease-modifying antirheumatic drugs (DMARDs), mainly methotrexate. The LTE studies (tofacitinib 5 or 10 mg twice daily) enrolled patients from qualifying prior phase I, II and III index studies.

Results Of 5671 tofacitinib-treated patients, 107 developed malignancies (excluding non-melanoma skin cancer (NMSC)). The most common malignancy was lung cancer (n=24) followed by breast cancer (n=19), lymphoma (n=10) and gastric cancer (n=6). The rate of malignancies by 6-month intervals of tofacitinib exposure indicates rates remained stable over time. Standardised incidence ratios (comparison with Surveillance, Epidemiology and End Results) for all malignancies (excluding NMSC) and selected malignancies (lung, breast, lymphoma, NMSC) were within the expected range of patients with moderate-to-severe RA.

Conclusions The overall rates and types of malignancies observed in the tofacitinib clinical programme remained stable over time with increasing tofacitinib exposure.

INTRODUCTION

Chronic inflammation and autoimmune diseases are associated with the development of malignancies.^{1 2} In patients with rheumatoid arthritis (RA), regardless of treatment regimens, some malignancies such as Hodgkin's and non-Hodgkin's lymphoma, leukaemia, myeloma and lung cancer occur more frequently than in the general population.^{1 3} The relationship between malignancies and RA is complex as the immune response and some RA treatments (such as non-steroidal anti-inflammatory drugs and glucocorticoids) can also affect malignancy rates.^{1 4} Furthermore, in addition to the malignancy risk associated with RA, there is also a malignancy risk associated with treatments for chronic inflammation

and autoimmune diseases that involve modulation of the immune system.^{5 6}

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. The efficacy and safety of tofacitinib 5 and 10 mg twice daily has been demonstrated in a variety of patient populations with moderate-to-severe active RA in phase II⁷⁻¹⁰ and phase III¹¹⁻¹⁶ randomised controlled trials, and two long-term extension (LTE) studies.^{17 18}

In the development of immunomodulatory agents with new mechanisms of action such as tofacitinib, there is a particular need for close monitoring of safety events of special interest, including malignancies, to uncover potential adverse drug reactions. Here we report pooled malignancy data from the tofacitinib RA clinical development programme.

METHODS**Patients**

Eligible patients aged ≥ 18 years with active, moderate-to-severe RA were enrolled globally from North America, Europe, Latin America and Asia (see online supplementary appendix for list of countries). Patients were required to have had an inadequate response to methotrexate (MTX) (NCT00413660;¹⁰ NCT00603512;¹⁹ ORAL Scan, NCT00847613;¹⁶ ORAL Standard, NCT00853385¹⁵), non-biological or biological disease-modifying antirheumatic drugs (DMARDs) (NCT00147498;⁷ NCT00550446;⁸ NCT00687193;⁹ ORAL Solo, NCT00814307;¹⁴ ORAL Sync, NCT00856544¹³) or tumour necrosis factor inhibitors (TNFi) (ORAL Step, NCT00960440¹¹). One phase III study (ORAL Start, NCT01039688¹²) included MTX-naïve patients and one phase II study (study NCT01059864²⁰) had no criteria for prior DMARD exposure.

Exclusion criteria were similar across studies; patients with any history of or existing malignancy (other than adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ) were excluded. Patients who developed a malignancy (excepting adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ) were permanently discontinued from the study, but were followed up. Patients who developed non-melanoma skin cancer (NMSC) could remain in the study provided the NMSC was adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or

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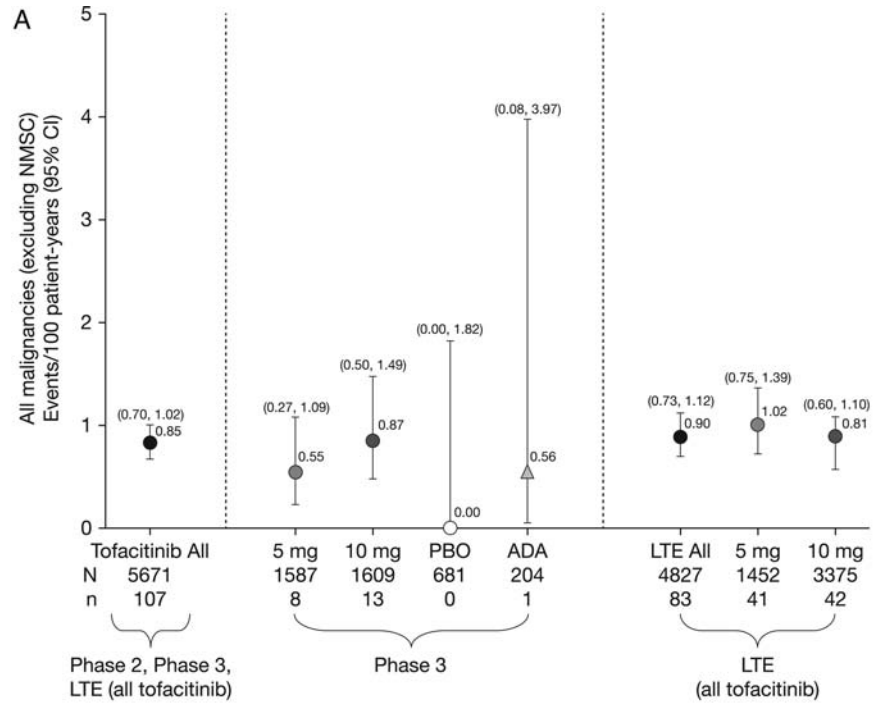
adequately treated cervical carcinoma in situ. Inclusion and exclusion criteria have been reported previously.⁷⁻²⁰

Study design

Patients from six phase II^{7-10 19 20} and six phase III¹¹⁻¹⁶ index studies, and two LTE studies,^{17 18} were included in the pooled

phase II, III and LTE data. The LTE-only analysis comprised patients from two phase I,^{21 22} nine phase II^{7-10 19 20 23-25} and six phase III¹¹⁻¹⁶ studies (see the online supplementary appendix for details on all index studies). The analysis reported here includes all patients with RA exposed to tofacitinib in the clinical development programme. As of April 2013, LTE^{17 18} and ORAL

Figure 1 Incidence rates (and 95% CIs) for (A) all malignancies (excluding non-melanoma skin cancer (NMSC)), including drug exposure data; (B) lung cancer; (C) breast cancer (female patients); (D) NMSC and (E) lymphoma for all active treatments including dose groups. ADA, adalimumab; LTE, long-term extension; N, total number of patients in that group exposed to the study treatment; n, number of unique patients with malignancy event in each treatment group; PBO, placebo.



	Tofacitinib exposure (all doses), patient-years	Tofacitinib exposure (5 mg BID), patient-years	Tofacitinib exposure (10 mg BID), patient-years	Placebo exposure patient-years	Adalimumab exposure patient-years
All Phase 2	187.4	112.2	75.3	63.2	11.2
All Phase 3	3363.3	1464.2	1501.0	202.7	178.9
LTE studies	9195.9	4005.3	5190.6	-	-
All Phase 2/Phase 3/LTE	12664.0	-	-	-	-

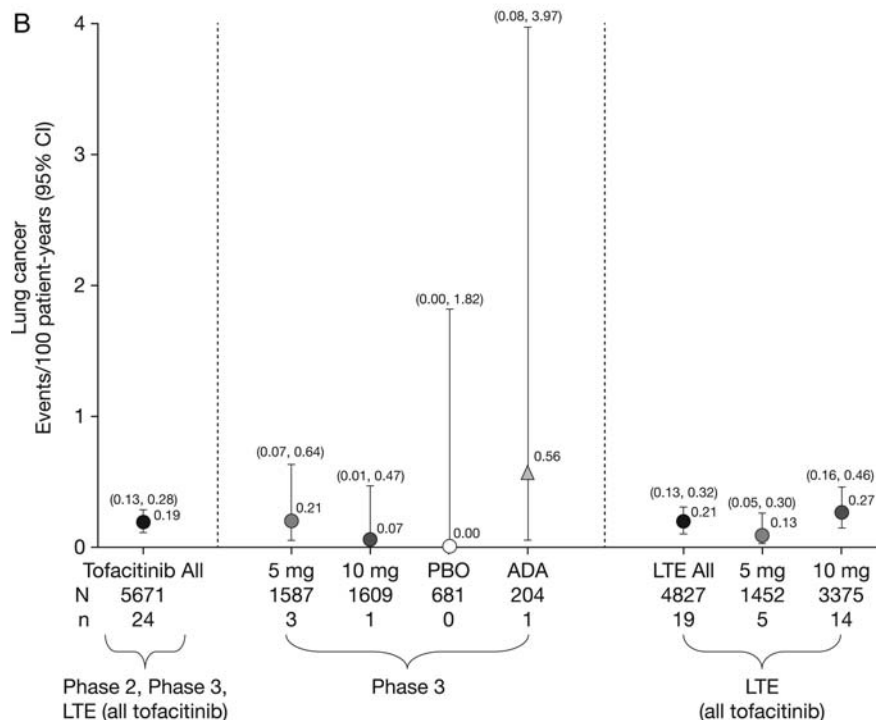
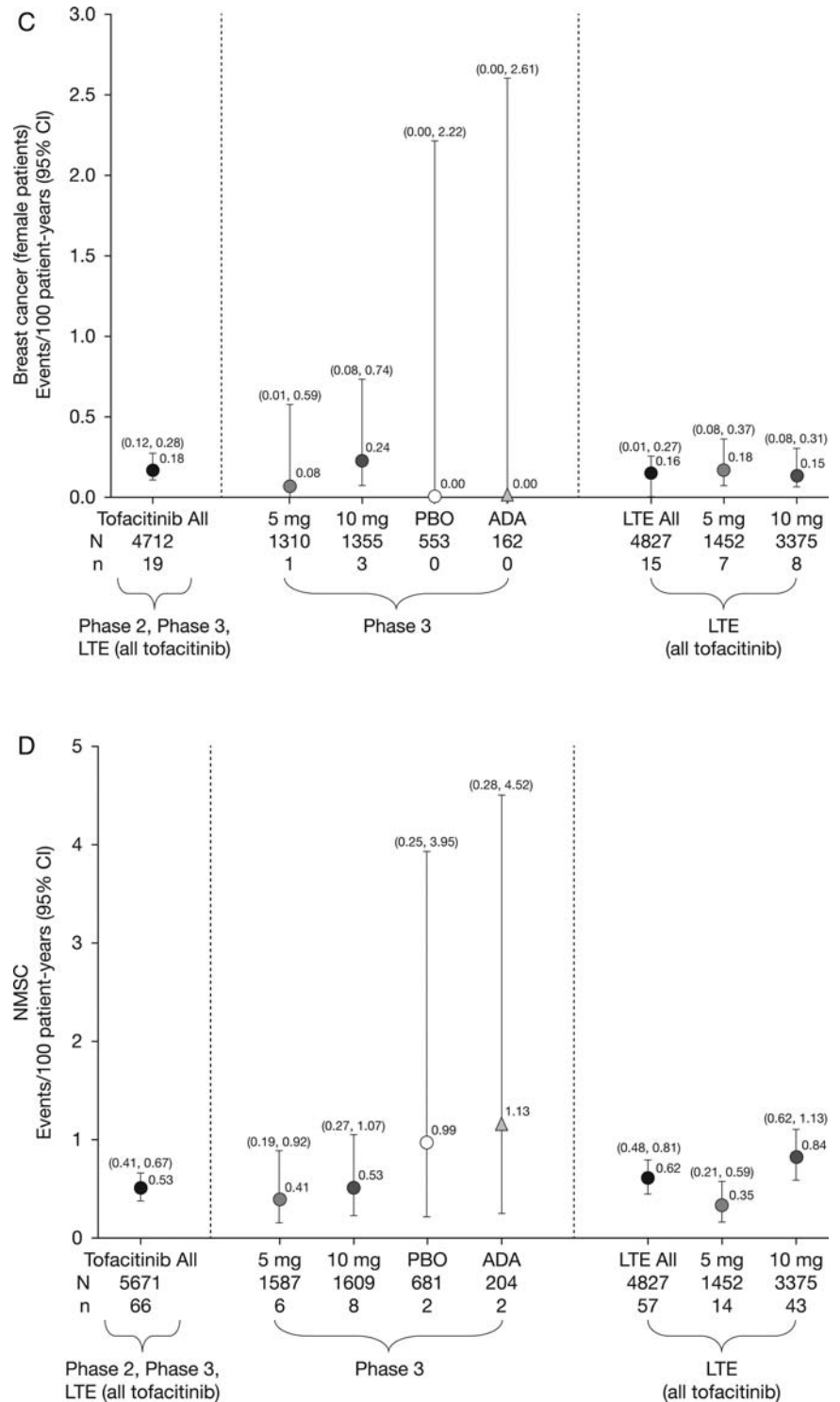


Figure 1 Continued



Start (NCT01039688¹²) data collection and analyses were ongoing, and study databases had not yet been locked. Further details on study design and index studies are given in the online supplementary appendix.

Outcome assessment and adjudication

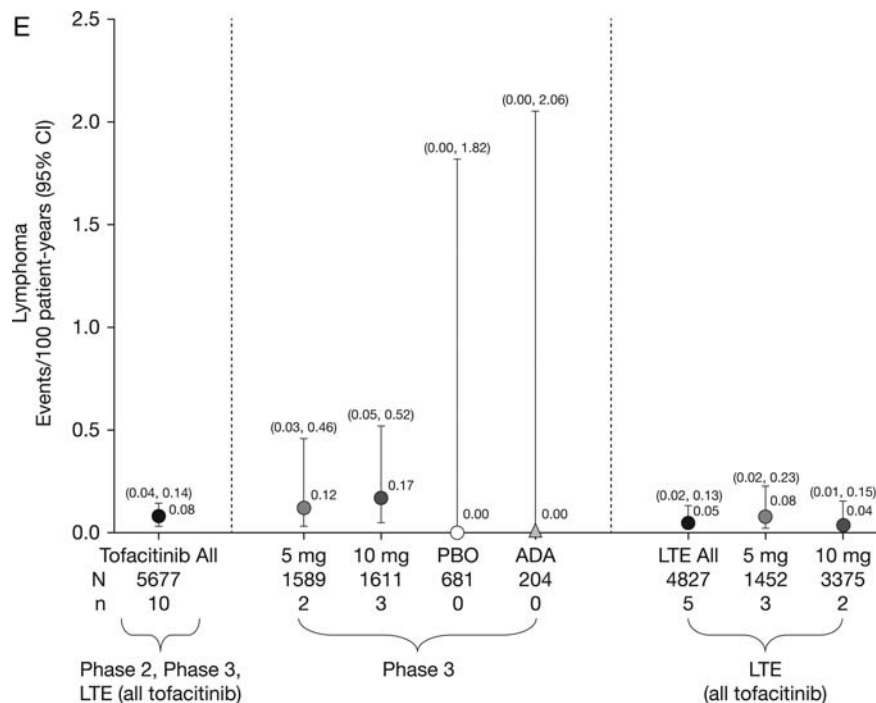
Malignancies were identified and classified by review of investigator-reported adverse events (AEs), serious AEs and from the central laboratory histology review. A malignancy over-read process involved a centralised, external, blinded review of each biopsy case by ≥2 independent, board-certified pathologists. Discordance in opinion between local and central

pathologists was uncommon and resolved by clinical review of all available data; results from both local and central pathologists were reported. Patients who had no biopsy slides available to central reading (25.8%; 335/1299) were reported according to the local pathology report. Patients with no pathology report (1.8%; 23/1299) were classified by malignancy type reported by the study investigator.

Statistical analysis

Malignancies in the tofacitinib clinical programme up to April 2013 were evaluated. For LTE analysis, patients were classified as background DMARDs or monotherapy based on the index

Figure 1 Continued



study. Average total daily dose (TDD) of tofacitinib was calculated by adding all doses received by each patient, and dividing by the number of days a dose was received. The TDD average was used to assign LTE dose: TDD of <15 mg/day was considered 5 mg twice daily, TDD of ≥ 15 mg/day was considered 10 mg twice daily.

Incidence rates (IR) per 100 patient-years (py) of observation for all malignancies (excluding NMSC), lung cancer, breast cancer, lymphoma and NMSC were calculated by exposure and dose. Lung cancer, breast cancer and NMSC were selected as they are the most commonly occurring types; lymphoma was selected due to special interest in associated safety events in RA. IRs were based on number of patients with an event; for those with multiple malignancies, each patient was counted once for all malignancies, and separately for each event. The 95% CIs are based on maximum likelihood estimation, and on Exact Poisson adjusted for exposure time when IR is zero.

Standardised incidence ratios (SIRs) were calculated as the ratio of observed cancers to those expected based on background rates within general population samples; 95% CIs for SIRs were calculated following a Poisson distribution. Expected numbers of cancers for the calculations were based on age-specific and sex-specific rates from the US National Cancer Institute Surveillance and Epidemiology and End Results (SEER) database, 1992–2011.²⁶ The SEER database does not include NMSC or carcinoma in situ of the cervix; therefore, these data were excluded from the tofacitinib data set for the calculation of SIRs only.

RESULTS

Patients

Overall, 5671 patients in tofacitinib treatment groups were included in the analyses; 4204 patients received tofacitinib (across all doses) for >1 year, 3084 >2 years and 1948 >3 years. Total tofacitinib exposure was 12 664 py; overall median exposure was 2.35 years. Drug exposure data for tofacitinib, placebo and adalimumab are presented in figure 1A; baseline demography data are presented in table 1. In phase II and phase III studies, respectively, 657 (47.2%) and 1361 (35.9%) patients

received tofacitinib as monotherapy and 736 (52.8%) and 2435 (64.1%) in combination with non-biological DMARDs.

Observed malignancies

There were 107 tofacitinib-treated patients with malignancies (excluding NMSC); the most common was lung cancer (n=24) followed by breast cancer (n=19), lymphoma (n=10; for completeness, two additional cases are included—see ‘Lymphoma’ section for details) and gastric cancer (n=6). Online supplementary appendix figure S2 lists each malignancy (excluding NMSC) in tofacitinib-treated patients observed per 6-month interval. In the adalimumab treatment group, there was one case of renal cell carcinoma (NCT00550446)⁸ in phase II and one of non-small-cell lung cancer (NSCLC; NCT00853385)¹⁵ in phase III. No malignancies (excluding NMSC) occurred in the phase II or III placebo groups (≤ 6 -month duration). Eight patients receiving tofacitinib 5 mg twice daily, 13 receiving tofacitinib 10 mg twice daily and one each receiving adalimumab and MTX had more than one malignancy; the online supplementary appendix provides details on these and on patients with potential malignancies. IRs for all malignancies and selected malignancies for all active treatments, dose groups and placebo are shown in figure 1.

Overall rates of malignancies were stable over time (figure 2).

All malignancies (excluding NMSC)

In total, 107 of 5671 patients had malignancies (excluding NMSC); the overall IR for all tofacitinib-treated patients in the phase II, III and LTE studies was 0.85 (95% CI 0.70 to 1.02) events per 100 py (figure 1A). Total py exposure for all malignancies (excluding NMSC) is shown in figure 1A. In the phase III populations, malignancy IRs in the monotherapy and combination therapy groups (both doses) were 0.32 (95% CI 0.10 to 0.99) and 0.83 (95% CI 0.53 to 1.28); IRs in the tofacitinib 5 and 10 mg twice daily groups were 0.55 (95% CI 0.27 to 1.09) and 0.87 (95% CI 0.50 to 1.49). There was no association between tofacitinib treatment duration and overall malignancy risk (figure 2A).

Table 1 Baseline demography data by treatment group for patients enrolled in the tofacitinib clinical programme (phase II and III, and LTE studies)

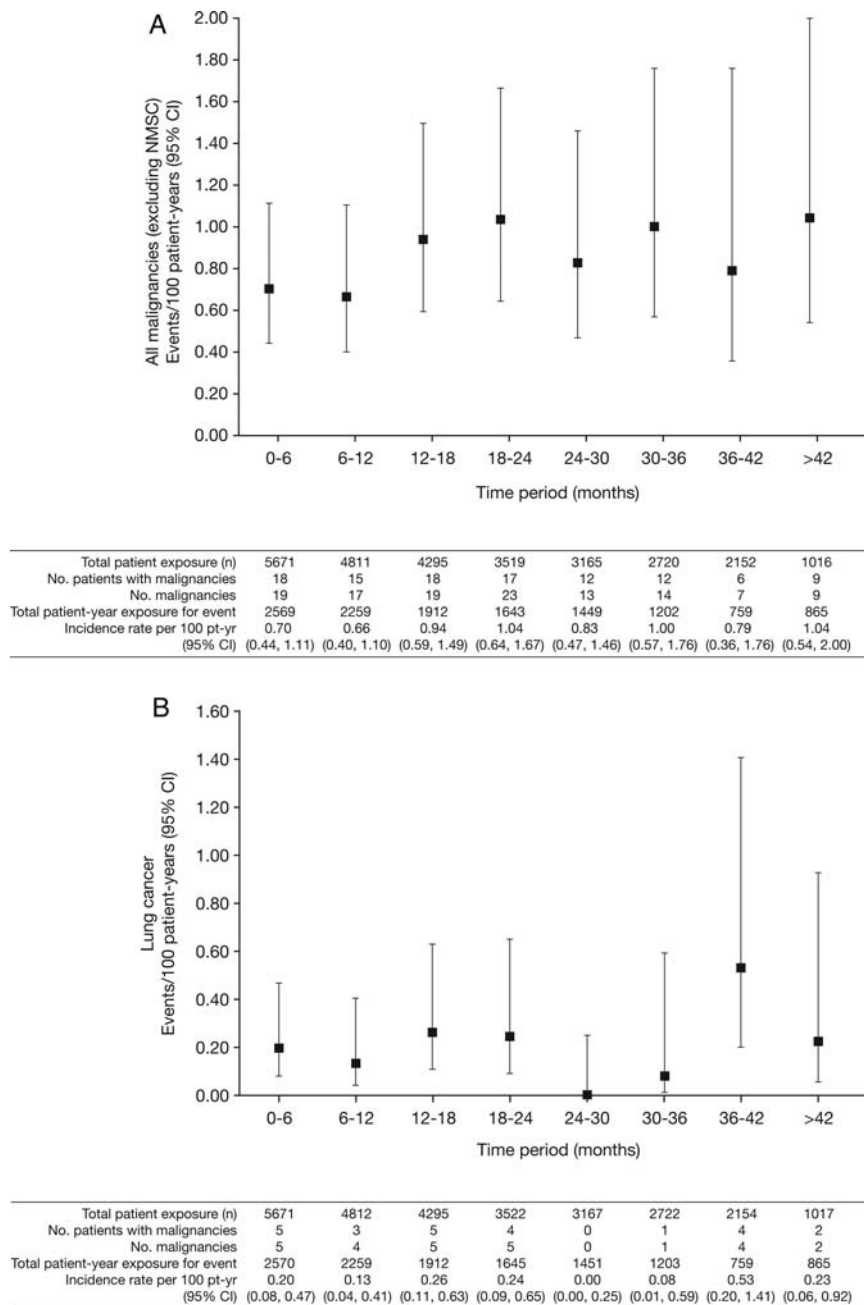
	Phase II studies				Phase III studies*				LTE studies			
	Tofacitinib (all doses)		Placebo		Tofacitinib		Placebo advanced to tofacitinib†		ADA		Tofacitinib	
	n=1393	n=273	n=53	n=1587	5 mg twice daily	10 mg twice daily	5 mg twice daily	10 mg twice daily	n=204	5 mg twice daily	10 mg twice daily	
Mean age (range), years	52.7 (18–83)	52.3 (20–78)	53.5 (18–75)	52.5 (18–86)	51.7 (18–85)	52.8 (18–82)	52.2 (18–80)	52.5 (23–77)	53.1 (18–82)	53.0 (18–86)		
Gender, % female	83.9	84.6	84.9	82.5	84.2	81.0	81.4	79.4	83.2	81.9		
Race, %												
White	55.3	54.2	81.1	61.5	62.5	66.8	62.1	72.5	46.6	70.5		
Black	2.2	2.9	1.9	3.7	2.9	2.3	4.7	1.5	1.7	3.2		
Asian	32.4	31.5	7.5	24.8	23.3	23.6	25.1	14.2	43.1	16.3		
Other	10.1	11.4	9.4	10.0	11.2	7.3	8.0	11.8	7.5	9.5		
Regions, %												
North America	20.6	16.5	24.5	21.1	21.9		25.8	16.7	14.0	28.5		
South America	20.3	19.8	17.0	16.7	17.0		14.4	53.9	17.9	14.7		
Europe	27.2	22.7	50.9	35.0	34.5		33.8	11.8	25.1	37.5		
Asia and Pacific	31.9	41.0	7.5	27.2	26.5		26.0	17.6	43.0	19.3		
No prior exposure to biological DMARD	89.2	89.4	90.6	83.1	84.1		75.3	90.7	N/A	N/A		

* Tofacitinib monotherapy or tofacitinib+MTX or other non-biological DMARD(s).

† Patients randomised to placebo were advanced to tofacitinib at month 3 or month 6.

ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; LTE, long-term extension; MTX, methotrexate; N/A, not available.

Figure 2 Incidence rates (95% CI) per 6-month intervals for (A) all malignancies (excluding non-melanoma skin cancer (NMSC)); (B) lung cancer; (C) breast cancer (female patients); (D) NMSC and (E) age-adjusted and sex-adjusted standardised incidence ratios (95% CI) per 6-month intervals for all malignancies (excluding NMSC). pt-yr, patient-years; SEER, Surveillance Epidemiology and End Result; SIR, standardised incidence ratio as compared with SEER database.



The overall age-adjusted and sex-adjusted SIR for all malignancies (excluding NMSC) versus SEER among tofacitinib-treated patients was 1.17 (95% CI 0.96 to 1.41; table 2). SIRs were stable over time (figure 2E).

Lung cancer

Twenty-four patients (12 men; 12 women) reported lung cancer: most cases were NSCLC; five patients were diagnosed with lung cancer within 6 months of receiving tofacitinib; 14/24 patients were current smokers, 6 were ex-smokers and 4 were non-smokers. The overall (phase II, III and LTE studies) IR in tofacitinib-treated patients was 0.19 (95% CI 0.13 to 0.28) events per 100 py (figure 1B). IRs for lung cancer observed in the phase III and LTE studies are presented in figure 1B. In the phase III studies, the IR for lung cancer in patients receiving tofacitinib 5 and 10 mg monotherapy was 0.00 (95% CI 0.00 to 0.82) and 0.21 (95% CI 0.03 to 1.52), respectively, and was 0.30 (95% CI 0.10 to 0.92) and 0.00 (95% CI 0.00 to 0.36) for patients

receiving 5 and 10 mg tofacitinib in combination with DMARD therapy, respectively. IRs for lung cancer over time are shown in figure 2B. The SIR for lung cancer across phase II, III and LTE studies was 2.19 (95% CI 1.39 to 3.29; table 2).

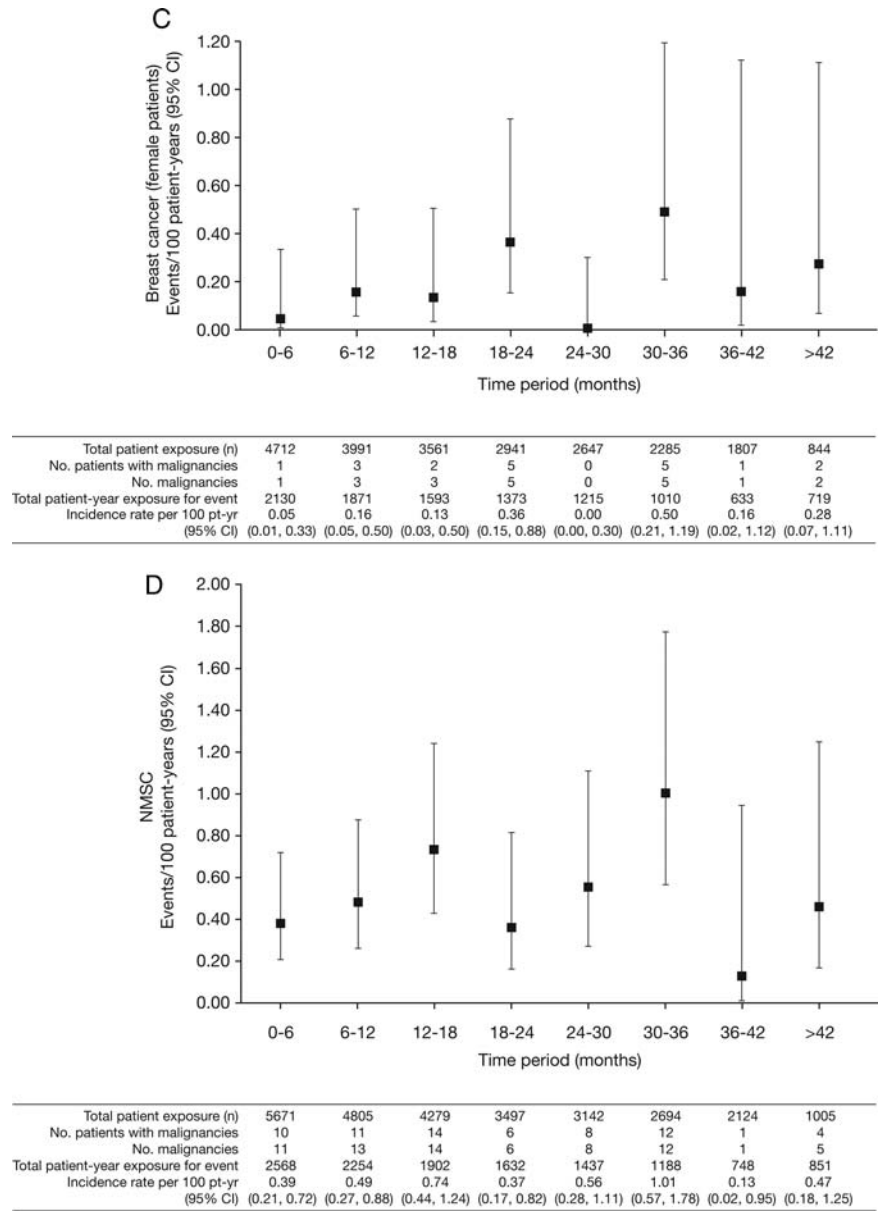
Breast cancer

Nineteen patients (all women) reported breast cancer; the overall (phase II, III and LTE studies) IR was 0.18 events per 100 py (95% CI 0.12 to 0.28) (figure 1C). IRs for breast cancer over time are shown in figure 2C. The SIR for breast cancer across phase II, III and LTE studies was 0.78 (95% CI 0.47 to 1.22; table 2).

Non-melanoma skin cancer

Eighty-two NMSC events were reported in 66/5671 tofacitinib-treated patients; there were 44 cases of basal cell carcinoma (n=39) and 38 cases of squamous cell carcinoma (n=33). The overall (phase II, III and LTE studies) IR was 0.53 events per

Figure 2 Continued



100 py (95% CI 0.41 to 0.67; figure 1D). In the LTE studies, the rates of NMSC were higher in the tofacitinib 10 mg twice daily group versus 5 mg twice daily group (figure 1D). IRs for NMSC over time are shown in figure 2D.

Lymphoma

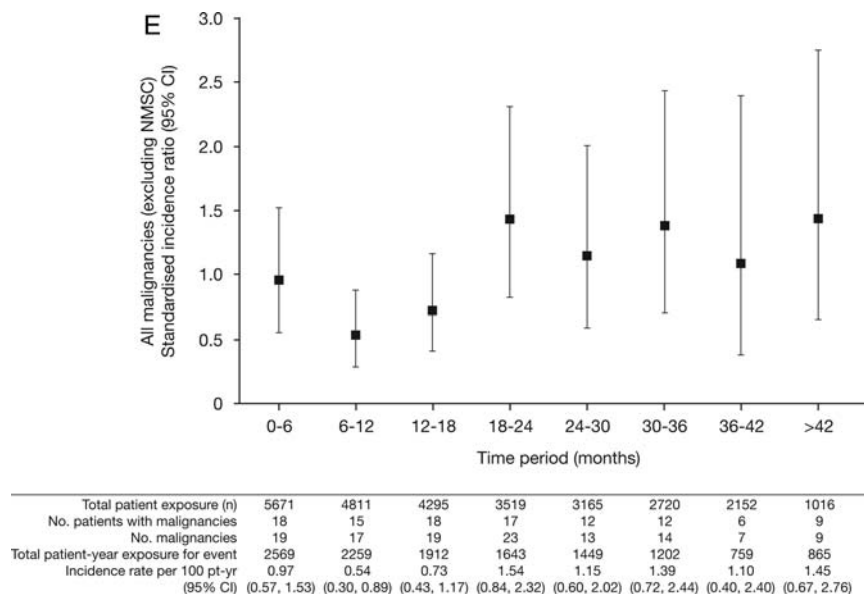
Ten cases (five in the phase III and five in the LTE studies) of lymphoma were reported for patients receiving tofacitinib. There was no apparent pattern of lymphoma occurrence associated with tofacitinib dose or therapy duration. For completeness, 2 of 10 lymphoma cases were included in patients from the second year of the ongoing phase III study NCT01039688 (ORAL Start), with exposure estimates based on randomisation ratios in the ongoing (second year) portion of this study. The overall IR (phase II, III and LTE studies) was 0.08 events per 100 py (95% CI 0.04 to 0.14; figure 1E); estimated total of 13230.87 py. Age-adjusted and sex-adjusted SIR was 2.64 (95% CI 1.27 to 4.86; table 2). Sequential cuts of the tofacitinib clinical programme data were completed from 2011 to 2013 to evaluate SIRs for lymphoma over time (see online supplementary appendix figure S1). Details of the 10 lymphoma cases are

summarised as follows: six patients were treated with chemotherapy; one patient had no treatment information reported; one patient’s lymphoma diagnosis was made through autopsy report (no treatment given); one patient with low-grade non-Hodgkin’s lymphoma refused to be treated with recommended chemotherapy (reported by the investigator to do well without chemotherapy); and one patient had resection of the salivary gland with no chemotherapy or radiotherapy (the patient recovered according to the investigator). The types of lymphoma reported were histopathologically heterogeneous. One case was unequivocally positive for Epstein–Barr virus (EBV), two were equivocal and five were negative. Table 3 and online supplementary appendix present further details.

Deaths due to malignancy

There were 18 deaths due to malignancies in tofacitinib-treated patients. Ten were due to lung cancer (n=3, 5 mg twice daily; n=7, 10 mg twice daily), one each due to breast, colon, gastric, ovarian, gallbladder, hepatic and rectosigmoid cancers (all 5 mg twice daily) and synovial sarcoma (10 mg twice daily).

Figure 2 Continued



DISCUSSION

The overall IRs, SIRs and types of malignancies observed in the tofacitinib clinical programme remained stable over time with increasing tofacitinib exposure (figures 1 and 2 and online supplementary appendix figure 1). SIRs in tofacitinib-treated patients (referent to SEER) (table 2) were within the range expected for patients with moderate-to-severe RA.²⁷⁻⁴¹ In this analysis, the most frequently reported malignancy in tofacitinib-treated patients was lung cancer and, of 24 patients with lung cancer, 20 were current or former smokers. Five patients were diagnosed with lung cancer within 6 months of tofacitinib start. Given the known growth rate of solid tumours, it is highly likely these cancers were pre-existent prior to tofacitinib therapy. The types of lung cancer observed (predominantly NSCLC) were consistent with the demographic characteristics of the patient population.²⁸ Risk factors associated with race may be a consideration for gastric cancer; all five cases occurred in Japan, which has been described as having the highest gastric cancer rates worldwide.⁴²

Context for the data described here may be gained by reviewing results previously reported in the literature: point estimates (IRs: events/100 py) (95% CI) for patients with RA receiving biological DMARDs ranged from 0.61 (0.45 to 0.80) to 1.87 (1.02 to 3.13) for all malignancies (excluding NMSC),²⁷⁻³⁵ 0.05 (0.02 to 0.13) to 0.92 (0.67 to 0.12) for

lymphoma,^{27-31 35 37 38 40} 0.15 (0.08 to 0.27) to 0.23 (0.19 to 0.27) for lung cancer,^{27 28 35} and 0.08 (0.03 to 0.17) to 0.21 (0.17 to 0.26) for breast cancer.^{27 28 34 35} In this report, the corresponding IRs (events/100 py) (95% CI) for tofacitinib were 0.85 (95% CI 0.70 to 1.02) for all malignancies (excluding NMSC), 0.08 (0.04 to 0.14) for lymphoma, 0.19 (0.13 to 0.28) for lung cancer and 0.18 (0.12 to 0.28) for breast cancer. Further discussion on specific outcomes is provided as follows.

Increased risk for NMSC development has been reported in patients with RA, and in patients prescribed TNFi and prednisone;⁴³⁻⁴⁵ two reviews of malignancy in patients receiving TNFi reported 45-102% increased risk of NMSC.^{40 46} In LTE, a higher rate of NMSC was seen in patients treated with tofacitinib 10 mg twice daily than tofacitinib 5 mg twice daily, whereas rates were similar between doses in phase III where randomisation between doses was balanced (figure 1D). The rate of NMSC appeared stable with continued tofacitinib exposure (figure 2D).

Lymphoma is a risk associated with RA and with agents used for RA treatment that affect the immune system. It is unclear whether lymphoma risk is increased further by MTX or TNFi, though some studies have reported that DMARDs were not associated with lymphoma risk.^{47 48} The types of lymphomas reported in the tofacitinib clinical programme were consistent

Table 2 IRs and SIRs for all malignancies (excluding NMSC), lymphoma, lung and breast cancer for tofacitinib-treated patients with RA (across phase II, III and LTE studies)

	IR Events/100 py (95% CI) Tofacitinib N=5671	SIR ^{26*} (95% CI) Tofacitinib N=5671
All malignancies (excluding NMSC)	0.85 (0.70 to 1.02)	1.17 (0.96 to 1.41)
Lymphoma	0.08 (0.04 to 0.14)	2.64 (1.27 to 4.86)
Lung cancer	0.19 (0.13 to 0.28)	2.19 (1.39 to 3.29)
Breast cancer	0.18 (0.12 to 0.28)	0.78 (0.47 to 1.22)

Tofacitinib data up to 10 April 2013.

*SEER database (US General Population), SIR data adjusted for age and sex.

IR, incidence rate; LTE, long-term extension; NMSC, non-melanoma skin cancer; py, patient-years; RA, rheumatoid arthritis; SEER, Surveillance Epidemiology and End Result; SIR, standardised incidence ratio as compared with the SEER database.

Table 3 Summary of lymphoma/lymphoproliferative disorder in phase II, III and LTE studies

Histology	EBV status	Demographics	Onset (days)	Tofacitinib dose*	Location
Large B cell lymphoma	Negative	78-year-old white female	818	5 mg twice daily +MTX	Central nervous system
Lymphoma c/w Hodgkin's	Positive	51-year-old Asian female	227	5 mg twice daily	Abdominal lymph nodes
Low-grade B cell lymphoma	IgG: ± and non-specific EBNA positive	47-year-old Asian female	220	10 mg twice daily +MTX	Thymus
Large B cell lymphoma	EBER positive in rare, scattered mononuclear cells	69-year-old white female	642	10 mg twice daily +MTX	Left breast, mediastinum and left axillary area
Large B cell lymphoma, Burkitt-like	EBER positive in small focus of cells	65-year-old white male	149	10 mg twice daily	Right submandibular gland—right neck
Small B cell lymphocytic lymphoma (mantle cell)	Negative	61-year-old white female	659	5 mg twice daily, 10 mg twice daily†	Tonsil
Non-Hodgkin's lymphoma (DCL lymphoproliferative disorder)	Negative	47-year-old white female	625	10 mg twice daily +MTX	Salivary gland
Low-grade non-Hodgkin's B cell lymphoma (CT guided lung biopsy)	N/A (no EBV report)	65-year-old white female	1621	5 mg twice daily +MTX	Lung
T cell chronic lymphocytic leukaemia	Negative	63-year-old white male	449	5 mg twice daily	Haematological
Non-Hodgkin's lymphoma	N/A (no EBV report)	71-year-old white female	723	5 mg twice daily	Generalised non-Hodgkin's lymphoma affecting bifurcational, para-aortic, peripancreatic and mesenteric lymph nodes, spleen and body of L3

See online supplementary appendix for more details of the lymphoma cases.

*Randomised treatment assignment.

†Patient was receiving 5 mg twice daily at time of event.

DCL, donor cell leukaemia; EBER, Epstein–Barr encoded ribonucleic acid; EBNA, Epstein–Barr nuclear antigen; EBV, Epstein–Barr virus; IgG, immunoglobulin G; LTE, long-term extension; MTX, methotrexate; N/A, not available.

with lymphomas described in the RA and general populations.^{31 49 50} Patients with RA are at increased risk of developing lymphoma than the general population (consistent with the observed age-adjusted and sex-adjusted SIR of 2.64 for tofacitinib)—possibly related to immunosuppressive therapy and RA severity. Some lymphomas in patients with RA arise in B cells in association with latent EBV infection; some lymphomas regress with reduced immunosuppressive therapy.^{35 38 51–53} Baecklund *et al*^{47 48} concluded that high-level RA disease activity coupled with long disease duration is associated with greater lymphoma risk.

EBV staining was positive in one case of lymphoma and equivocal in two of eight lymphomas tested (two from patients receiving tofacitinib monotherapy). Increased risk of EBV-associated lymphoma has been associated with high tofacitinib blood concentrations in renal transplantation studies of tofacitinib, in which patients received tofacitinib in combination with corticosteroids and potent immunosuppressive agents, such as basiliximab and mycophenolate mofetil. Ongoing analysis of LTE studies and postmarketing vigilance will be important to understand whether a relationship exists between tofacitinib and EBV-associated lymphomas in patients with RA.

When evaluating risk of malignancy, factors such as a dose–response relationship and cumulative duration of use may be important. There was no apparent or consistent association between tofacitinib dose and risk of malignancy except for NMSC in the LTE. However, numerically higher rates for all malignancies (excluding NMSC), breast cancer and lymphoma were observed with the higher 10 mg twice daily dose in phase III, but not in LTE (figure 1). Also, we acknowledge that the most susceptible patients at highest risk of cancer who develop a malignancy early are excluded from further trial participation, leading to a less at-risk cohort over time. However, we found that rates were generally stable over time or were even

numerically lower during the first year of exposure (figure 2). This phenomenon has been observed in RA studies with TNFi and other biological DMARDs,^{30 54 55} and it has been suggested that the lower rates might be an effect of recruitment bias of healthier patients.

Study limitations

Our analysis was limited by reliance on randomised, placebo-controlled and LTE trials that reflect a selected patient cohort (here, the exclusion of patients with any previous cancer). While patients' general health was assessed, there were no specific screening procedures that would detect undiagnosed malignancies. Also, patients who developed a malignancy (see Methods section for details) were barred from further trial participation, making analyses of additional risk for second or recurrent malignancies impossible.

Exposure to placebo (266 py) and adalimumab (190 py) was short and yielded imprecise IRs, so comparison to these study arms should be made cautiously. Those data were included in this report mainly for completeness. In LTE, assignment to treatment (tofacitinib 5 or 10 mg twice daily) was not randomised but based on index study enrolment, protocol guidance and investigator discretion. This has resulted in greater length of exposure to tofacitinib 5 mg twice daily, whereas the extent (in py) was greater with tofacitinib 10 mg twice daily, making interpretation of any dose differences uncertain. Also, no formal statistical analysis was performed on the incidence of malignancies between treatment groups, so conclusions are based on descriptive analyses only. Moreover, due to the presumed extended latency periods of some malignancies, patients will continue to require continued observation, beyond the median 2.35 years of exposure to tofacitinib represented in this analysis, and the relationship between greater cumulative duration of tofacitinib use and malignancy warrants further study.

CONCLUSION

The overall rates and types of malignancies observed in the tofacitinib clinical programme remained stable over time with increasing tofacitinib exposure. Continued longer-term surveillance is necessary to further evaluate any potential malignancy risk during tofacitinib treatment.

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Contributors JRC, EBL and IVK contributed to analysis and interpretation of the data, reporting and writing the manuscript. KK was involved in study conception and design, acquisition of data, analysis and interpretation of data, and reviewing the manuscript. JG was involved in data analysis, interpretation, reviewing/editing the manuscript. BB contributed to data interpretation, and manuscript editing/review/approval. KS, LW and RR have contributed to the planning, conduct and reporting of the work described in the manuscript as well as contributed to the planning, authorship and review of the manuscript. All authors approved the final draft of the manuscript for submission.

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Competing interests JRC reports grants and personal fees from Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, outside the submitted work. EBL has acted for a consultant for Pfizer during the conduct of the study; and acted as a consultant for Pfizer outside the submitted work. IVK, KK, JG, BB, KS, LW and RR are employees and shareholders of Pfizer.

Ethics approval The studies were conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice Guidelines, and relevant local country regulations. 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.

Provenance and peer review Not commissioned; externally peer reviewed.

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Online Supplemental Appendix

Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme

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Details on study design

Patients received tofacitinib 1-30 mg BID (20 mg once daily in one study) in Phase 2, and 5 or 10 mg BID in Phase 3, as monotherapy or with background DMARD (mainly MTX). In all Phase 3 studies except one (no placebo arm), patients randomised to placebo advanced to tofacitinib 5 or 10 mg BID at Month 3 or 6. One Phase 2 and one Phase 3 study included an active control arm of adalimumab 40 mg subcutaneously once every 2 weeks. Patients from Phase 2 and 3 studies entering the LTE studies initiated treatment with 5 mg BID or 10 mg BID, respectively. As of April 2013, LTE and ORAL Start (NCT01039688[8]) data collection and analyses were ongoing, and study databases had not yet been locked (ie some values may change for the final, locked study databases). Details on index studies are shown in the following section.

Tofacitinib and background DMARD dosing were required to be stable in index studies. In LTE studies, temporary dose adjustments of tofacitinib and background DMARD were allowed based on the investigator's assessment of efficacy and safety. Patients could receive NSAIDs and low-dose oral glucocorticoids (≤ 10 mg/day) prednisone equivalent, consistent with rheumatology practice worldwide.

The studies were conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice Guidelines, and relevant local country regulations. 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.

Details on index studies

Patients included in the analysis were enrolled from North America, Europe, Latin America and Asia. Actual countries were: Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Croatia, Czech Republic, Denmark, Dominican Republic, Finland, France, Germany, Greece, Hungary, India, Ireland, Italy, Japan, Malaysia, Mexico, New

Zealand, Peru, Philippines, Poland, Republic of Korea, Romania, Russian Federation, Slovakia, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, United Kingdom and Venezuela.

The tofacitinib Phase 2/Phase 3/long-term extension (LTE) analysis included patients from six Phase 2, six Phase 3, and two LTE studies. The Phase 2 randomised controlled trials (RCTs) were of 6-24 weeks' duration; tofacitinib was dosed at 1-30 mg BID (20 mg once daily included in one study) as monotherapy (NCT00147498,[1] NCT00550446,[2] NCT00687193,[3] NCT01059864,[4]) or with background MTX (NCT00413660,[5] NCT00603512,[6]). The six Phase 3 RCTs were of 6-24 months' duration and tofacitinib was dosed 5 or 10 mg BID as monotherapy (ORAL Solo, NCT00814307;[7] ORAL Start [12-month analysis], NCT01039688[8]) or with background MTX (ORAL Scan, NCT00847613;[9] ORAL Step, NCT00960440;[10] ORAL Standard, NCT00853385[11]) or nonbiologic DMARDs (ORAL Sync, NCT00856544[12]). The LTE studies included in this analysis, NCT00413699 (global) and NCT00661661 (Japan)[13], comprised patients from the above index studies.

The LTE-only population and analyses consist of all patients enrolled in the LTE studies, including patients who enrolled from two Phase 1 studies in RA patients (NCT01262118,[14] NCT01484561[18]), nine Phase 2 (the six described above plus NCT01359150,[15] [monotherapy or with background MTX] NCT01164579[19] [monotherapy] and NCT00976599[16] [with background MTX]), and the six Phase 3 index studies above. ORAL Start data was not restricted to 12-month analysis.

One Phase 2 monotherapy study (NCT00550446[2]) and one Phase 3 study (NCT00853385[12]) included an active control arm of adalimumab 40 mg subcutaneously as monotherapy or with background MTX, respectively, every 2 weeks. In all Phase 3 studies, patients randomised to placebo were advanced to tofacitinib 5 or 10 mg BID at Month 3 or 6, except in NCT01039688 (no placebo arm). Patients in Phase 2 studies entering the LTE studies initiated treatment with 5 mg BID, whereas patients from Phase 3 studies (except Chinese and Japanese patients) initiated treatment with 10 mg BID, regardless of prior treatment in the index study.

Patients with more than one malignancy

In patients receiving tofacitinib 5 mg BID, one patient was diagnosed with oesophageal carcinoma and colon carcinoma. Multiple lymph node metastases were detected, and thyroid papillary cancer found from removed lymph nodes. Another patient had prostate cancer and basal cell carcinoma; two patients had simultaneous NMSC events (one with two basal cell carcinoma events and one with two squamous cell carcinoma events); four had more than one non-simultaneous NMSC events (two patients with two basal cell carcinoma events, one patient with two squamous cell carcinoma events, and one with both squamous and basal cell carcinoma events).

In patients receiving tofacitinib 10 mg BID, one patient had melanoma and basal cell carcinoma, and one patient had lung cancer and basal cell carcinoma. One patient had two simultaneous basal cell carcinoma events. Three patients had at least two non-simultaneous basal cell carcinoma events each; one patient had at least two non-simultaneous squamous cell carcinoma events; six patients had both non-simultaneous basal and squamous cell carcinoma events. No apparent trend between multiple events and tofacitinib dose was observed.

One patient receiving adalimumab had both non-simultaneous basal and squamous cell carcinoma events; one patient receiving MTX had two non-simultaneous basal cell carcinoma events.

Patients with potential malignancies

A 75-year-old female receiving tofacitinib 10 mg BID group exhibited a multinodular goitre and subclinical hyperthyroidism. A thyroid biopsy was taken on Study Day 143; local pathological diagnosis reported a hyperplastic nodule with no evidence of malignancy in the sample examined. The central pathology diagnosis was consistent with a neoplasm, although the benign or malignant status was unknown. This was not reported as an adverse event, and concluded unlikely to be a malignancy.

A 58-year-old female receiving tofacitinib 5 mg BID experienced an adverse event of left breast calcifications on Study Day 616. An excisional biopsy revealed dysplasia without evidence of carcinoma in situ from both the local and central laboratory

interpretations. It was concluded that these breast calcifications were likely not a malignancy.

A 51-year-old female receiving tofacitinib 10 mg BID experienced a serious adverse event of ovarian cyst on Study Day 441 and underwent a total hysterectomy and bilateral oophorectomy. Biopsies were reported negative for malignancies by the local pathology report; central pathology diagnosis was mucinous cystic tumour and uncertain of benign or malignant status. It was concluded that this event represented a pre-malignant lesion and not a malignancy at the time of surgical removal.

A 58-year-old female receiving adalimumab 40 mg every 2 weeks developed blood dyscrasia that was considered life-threatening by the investigator on Study Day 208. She experienced soft, black bloody stools, in addition to dizziness and nausea that led to haematemesis. These were attributed to upper gastrointestinal (GI) bleeding, and a complete blood count revealed low platelet and red blood cell levels, and signs of GI bleeding. The patient was diagnosed with myelodysplastic syndrome. Study medication was permanently stopped (last dose was on Study Day 197). The patient was treated with cytarabine and responded very well. The investigator considered that there was a reasonable possibility that the myelodysplastic syndrome was related to study drug; the haematemesis and black bloody stools were considered related to concomitant prednisone.

All four of the above cases were considered equivocal and these were not included in the IRs reported.

Patients with lymphoma

Details of the ten lymphoma cases appear in the main manuscript.

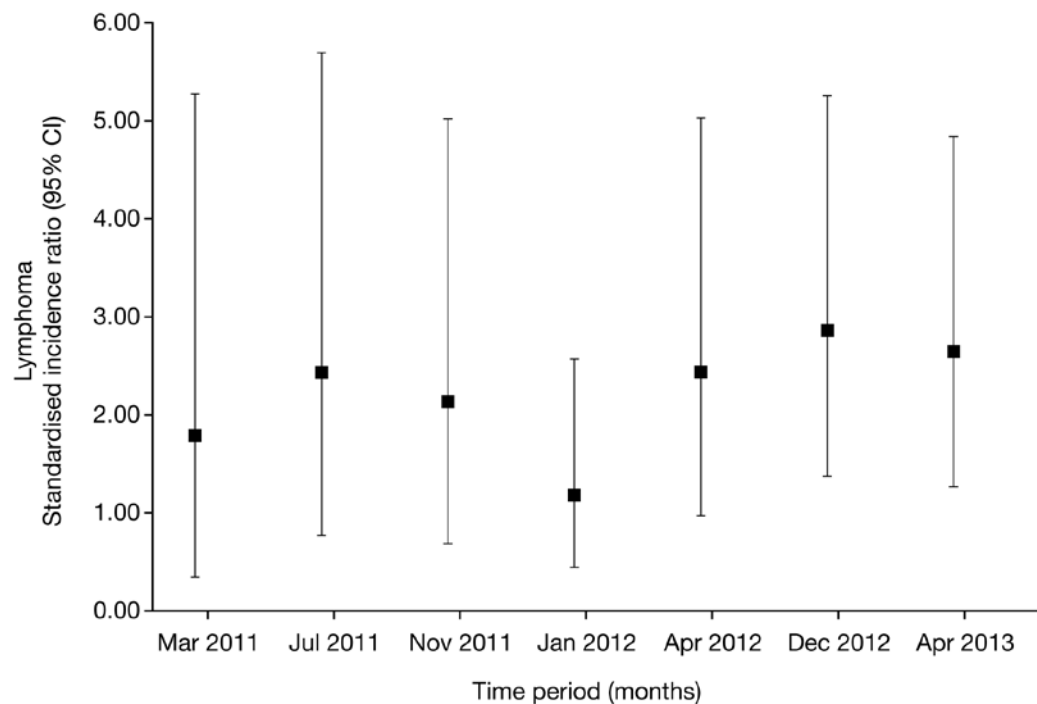
Increased risk of EBV-associated lymphoma has been associated with high tofacitinib blood concentrations in renal transplantation studies of tofacitinib, in which patients received tofacitinib in combination with corticosteroids and potent immunosuppressive agents, such as basiliximab and mycophenolate mofetil.[17]

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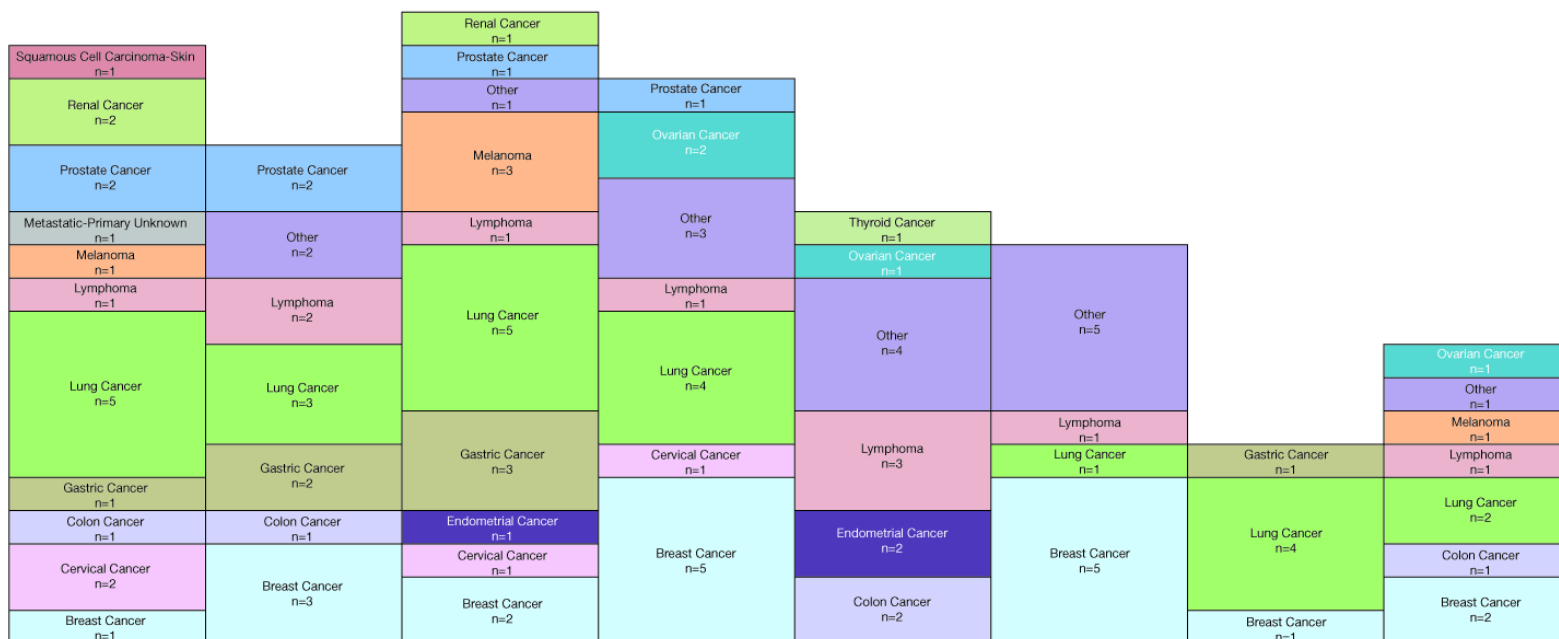
Online Supplemental Appendix Figure 1. Age-and-sex-adjusted standardised incidence ratios (95% CI) (SEER referent) for lymphoma with increasing tofacitinib exposure over time



Patients with events	3	5	5	6	7	10	10
Total patient-year exposure for event	5626	6991	7977	9071	9933	12190	13231
Total patient exposure (n)	4789	5555	5563	5677	5559	5639	5677
Standardised incidence ratio (95% CI)	1.81 (0.37, 5.29)	2.44 (0.79, 5.70)	2.15 (0.70, 5.02)	1.19 (0.44, 2.58)	2.44 (0.98, 5.04)	2.86 (1.37, 5.26)	2.64 (1.27, 4.86)

CI, confidence interval; SEER, Surveillance Epidemiology and End Result

Online Supplemental Appendix Figure 2. Each malignancy (excluding non-melanoma skin cancer)* in tofacitinib-treated patients observed per 6-month intervals†



Time period	0-6 months	6-12 months	12-18 months	18-24 months	24-30 months	30-36 months	36-42 months	>42 months
Total patient exposure (n)	5671	4811	4295	3519	3165	2720	2152	1016
No. patients with malignancies	18	15	18	17	12	12	6	9
No. malignancies	19	17	19	23	13	14	7	9
Total patient-year exposure for event	2569	2259	1912	1643	1449	1202	759	865

*For completeness, two of ten lymphoma cases were included in the figure for patients in the second year of the ongoing Phase 3 study NCT01039688 (ORAL Start), at time periods 12-18 months and 24-30 months, respectively

†Time period >42 months: this time period is open-ended and includes patients with various length of exposure, all >42 months