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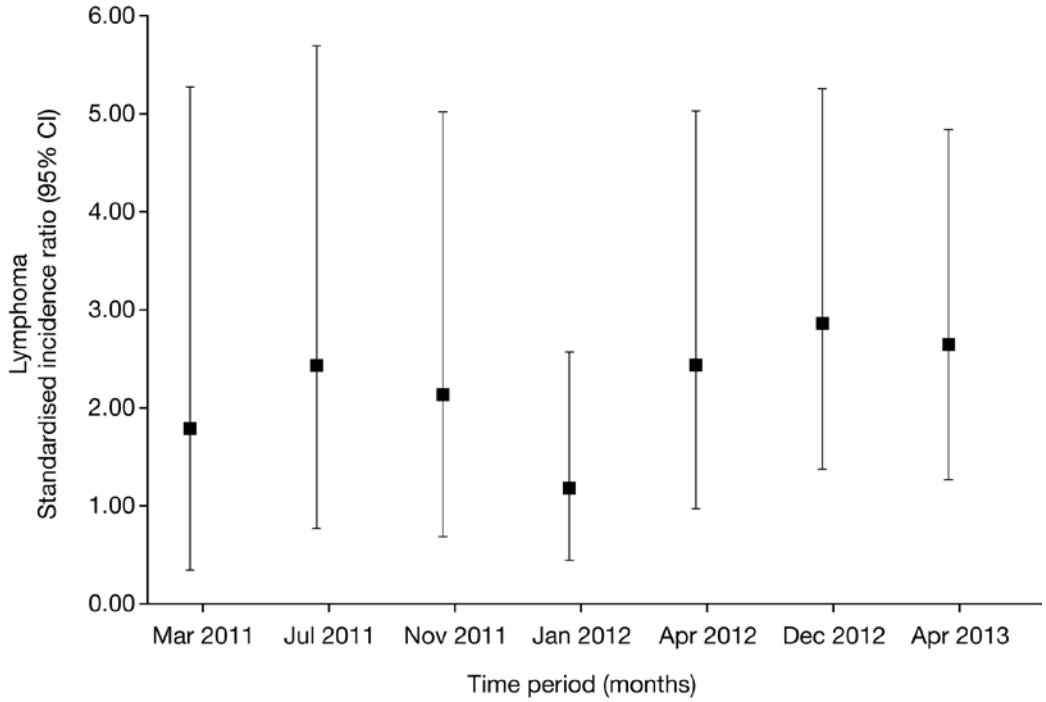
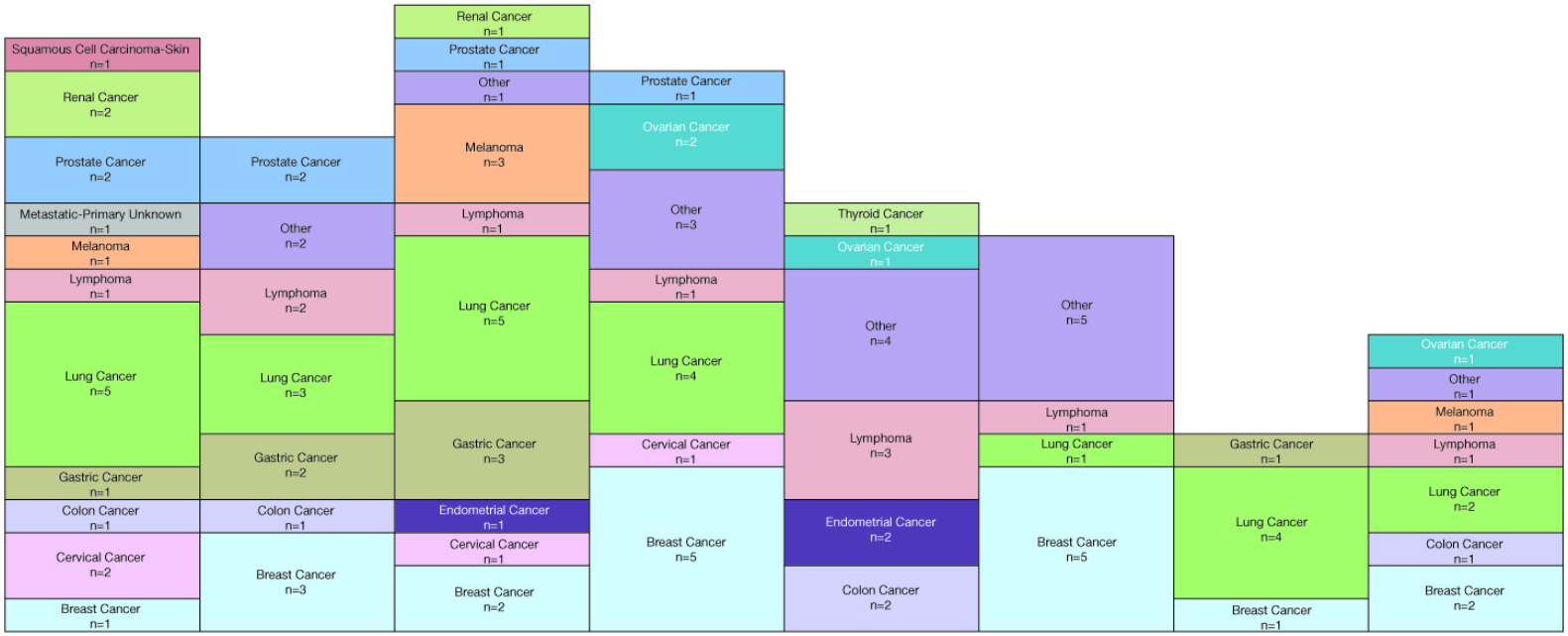
Online Supplemental Appendix Figure 1. Age-and-sex-adjusted standardised incidence ratios (95% CI) (SEER referent) for lymphoma with increasing tofacitinib exposure over time



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