European Crohn's and Colitis Organisation

TOFACITINIB FOR THE TREATMENT OF ULCERATIVE COLITIS: ANALYSIS OF MALIGNANCY RATES FROM THE GLOBAL CLINICAL PROGRAMME

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Background

- Tofacitinib is an oral, small molecule JAK inhibitor that is being investigated for UC
- The safety of tofacitinib for the treatment of moderate to severe UC was evaluated in:
  - An 8-week induction Phase 2 study[1]
    - Not included in analysis; adjudication process used in Phase 3 only
  - Two identical 8-week induction Phase 3 studies[2]
  - A 52-week maintenance Phase 3 study[2]
  - An ongoing, open-label LTE study (OCTAVE Open)[3]

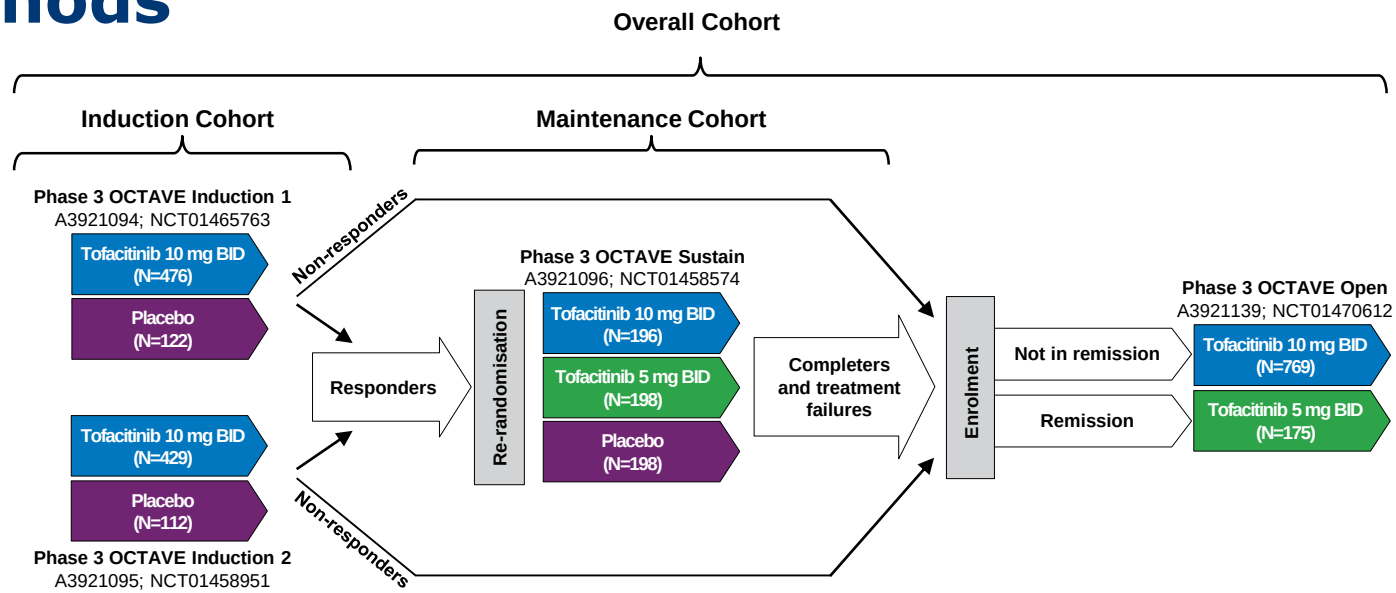
Objective: To describe an integrated analysis of adjudicated malignancies observed in patients with moderately to severely active UC who were treated with tofacitinib

Induction Phase 2 study (NCT00787202); 8-week induction Phase 3 studies (NCT01465763 and NCT01458951); maintenance Phase 3 study (NCT01458574); ongoing, open-label LTE study (OCTAVE Open, NCT01470612)

1. Sandborn WJ et al. N Engl J Med 2012;367:616-624. 2. Sandborn WJ et al. N Engl J Med 2017;376:1723-1736;
3. Lichtenstein GR et al. Am J Gastroenterol 2017;112(S1):Abstract 714

JAK, Janus kinase; LTE, long-term extension; UC, ulcerative colitis

Methods



- All reports of malignancies[a] following ≥1 dose of study treatment are included
- Biopsies of potential malignancies were submitted for blinded, independent central laboratory pathologist over-read
- Proportions and IRs were evaluated for malignancies (excluding NMSC) and NMSC for events occurring <28 days since the last dose of study treatment
- IRs for unique patients with events per 100 patient-years of exposure, with 95% CI computed using an exact method
- Events occurring >28 days after the last dose of study treatment were included as sensitivity analysis for malignancies (excluding NMSC)

Data from the ongoing LTE study are as of 16 December 2016, from the unlocked database
[a]Including carcinoma *in situ,* and other localised malignancies
BID, twice daily; CI, confidence interval; IR, incidence rate; LTE, long-term extension; NMSC, non-melanoma skin cancer

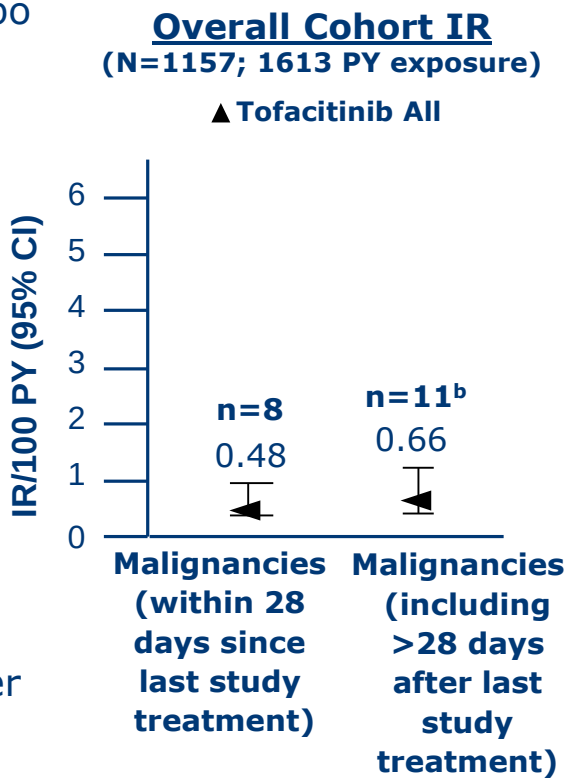
Patient demographics and characteristics

	Induction Cohort		Maintenance Cohort			Overall Cohort
	Placebo (N=282)	Tofacitinib 10 mg BID (N=938)	Placebo (N=198)	Tofacitinib 5 mg BID (N=198)	Tofacitinib 10 mg BID (N=196)	Tofacitinib All (N=1157)
Total PY exposure	44.8	156.2	100.4	146.2	154.3	1612.8
Treatment duration (days), median (range)	62 (7–80)	63 (1–96)	138 (14–382)	364 (22–420)	368 (1–399)	514 (1–1606)
Age (years), mean (range)	41.4 (18–81)	41.3 (18–80)	43.4 (19–80)	41.9 (18–79)	43.0 (18–79)	41.3 (18–81)
Female, %	45.0	40.6	41.4	48.0	43.9	41.3
Duration of UC (years), mean (range)	8.2 (0.4–36.2)	8.2 (0.3–42.5)	8.8 (0.6–42.7)	8.3 (0.6–40.3)	8.7 (0.6–35.7)	8.2 (0.4–42.5)
Prior TNFi treatment, n (%)	130 (55.6)	488 (53.9)	92 (46.5)	90 (45.5)	100 (51.0)	612 (54.4)
Prior immunosuppressant use, n (%)	160 (68.4)	683 (75.5)	134 (67.7)	149 (75.3)	144 (73.5)	838 (74.6)
Smoker status, n (%) Current smoker Never smoked Ex-smoker	 11 (3.9) 195 (69.1) 76 (27.0)	 48 (5.1) 593 (63.2) 296 (31.6)	 12 (6.1) 113 (57.1) 73 (36.9)	 7 (3.5) 142 (71.7) 49 (24.7)	 6 (3.1) 127 (64.8) 63 (32.1)	 59 (5.1) 740 (64.0) 357 (30.9)

Induction Phase 2 study data are included here for the summary of patient demographics and characteristics data, except for prior TNFi or immunosuppressant use, for which data were collected at the start of the Phase 3 Induction studies
BID, twice daily; n, number of unique patients with characteristic; N, number of patients in the treatment group; PY, patient-years; TNFi, tumour necrosis factor inhibitors; UC, ulcerative colitis

Malignancy (excluding NMSC) events

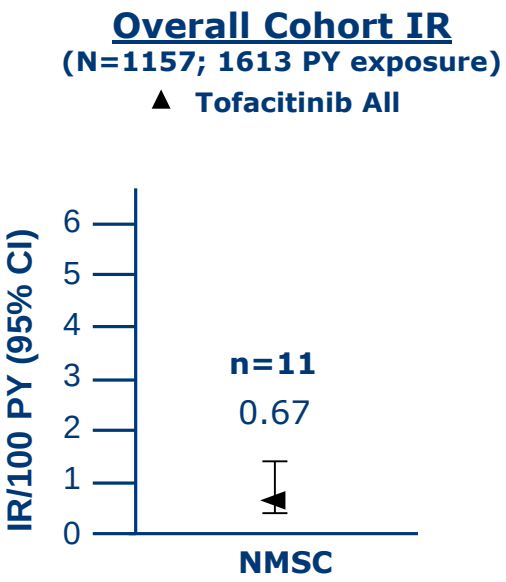
- **Induction Cohort:** No patients with malignancies (excluding NMSC) in either the placebo or tofacitinib 10 mg BID groups
- **Maintenance Cohort:** 1 patient with breast cancer in the placebo group; none in the tofacitinib 5 or 10 mg BID groups
- **Overall Cohort:**
  - 8 patients with malignancies (excluding NMSC) received tofacitinib 10 mg BID
    - >80% patients in the Overall Cohort primarily received tofacitinib 10 mg BID[a]
  - 8 patients with malignancies: cervical cancer, cholangiocarcinoma, cutaneous leiomyosarcoma, EBV-associated lymphoma, essential thrombocythaemia, acute myeloid leukaemia, adenocarcinoma of the colon, and invasive ductal breast carcinoma
  - 3 additional patients with malignancies reported >28 days after the last tofacitinib dose: renal cancer carcinoma, hepatic angiosarcoma and lung cancer



IRs for unique patients with events per 100 PY of exposure
[a]Average daily dose ≥15 mg; [b]11 patients with 12 events: 1 secondary-malignancy liver cancer occurred in a patient with cholangiocarcinoma
BID, twice daily; CI, confidence interval; EBV, Epstein-Barr virus; IR, incidence rate; n, number of unique patients with a particular adverse event; N, number of patients in the treatment group; NMSC, non-melanoma skin cancer; PY, patient-years

NMSC events

- **Induction Cohort:** 2 patients with NMSC in the tofacitinib 10 mg BID group; none in the placebo group
- **Maintenance Cohort:** 3 patients with NMSC in the tofacitinib 10 mg BID group, 1 patient in the placebo group and none in the tofacitinib 5 mg BID group
- **Overall Cohort:** 11 patients with NMSC in the Tofacitinib All group:
  - 7 cases of SCC and 6 cases of BCC occurred
    - 2 patients had both SCC and BCC events
  - 10 of 11 patients had been exposed to azathioprine or 6-mercaptopurine
  - 10 of 11 patients had previously failed treatment with a TNFi
  - 6 patients had previous NMSC, prior to tofacitinib exposure



IRs for unique patients with events per 100 PY of exposure
All NMSC events were diagnosed within the treatment period; none occurred >28 days after last study treatment; all patients continued receiving study treatment
BCC, basal cell carcinoma; BID, twice daily; CI, confidence interval; IR, incidence rate; n, number of unique patients with a particular adverse event; N, number of patients in the treatment group; NMSC, non-melanoma skin cancer; PY, patient-years; SCC, squamous cell carcinoma; TNFI, tumour necrosis factor inhibitor

Limitations

- The Overall Cohort included patients who had switched tofacitinib doses, and so does not provide a clear evaluation of tofacitinib dose dependency with relation to malignancies
  - No dose relationship was observed in the RA programme (>19,000 PY exposure)[1]

Conclusions

- This integrated analysis showed that malignancies occurred infrequently with tofacitinib treatment in the UC clinical programme
- The IRs of malignancies excluding NMSCs, and NMSCs, were similar to those reported for tofacitinib in the RA programme[1] and other tofacitinib clinical programmes,[2–4] and also generally similar for UC patients treated with advanced therapies[5–8]
- An ongoing study comparing the safety of tofacitinib vs TNFi with respect to malignancies will help further characterise this risk[a]

[a]Currently being assessed in RA: Phase 3b/4 randomised safety endpoint study of two doses of tofacitinib in comparison to a TNFi in patients with RA (NCT02092467); malignancies (excluding NMSC) is a primary endpoint

1. Cohen SB et al. Ann Rheum Dis 2017;76:1253-1262; 2. Sandborn WJ et al. J Crohns Colitis 2016;10:PS1(A-1213); 3. Papp KA et al. J Am Acad Dermatol 2016;74:841-850; 4. Wollenhaupt J et al. J Rheumatol 2014;41:837-852; 5. Feagan BG et al. N Engl J Med 2013;398:699-710; 6. Sandborn WJ et al. Gastroenterology 2012;142:257-265; 7. Sandborn WJ et al. Gastroenterology 2014;146:96-109.e1; 8. Colombel JF et al. Gut 2017;66:839-851

IRs, incidence rates; NMSC, non-melanoma skin cancer; PY, patient-years; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor; UC, ulcerative colitis

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