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ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

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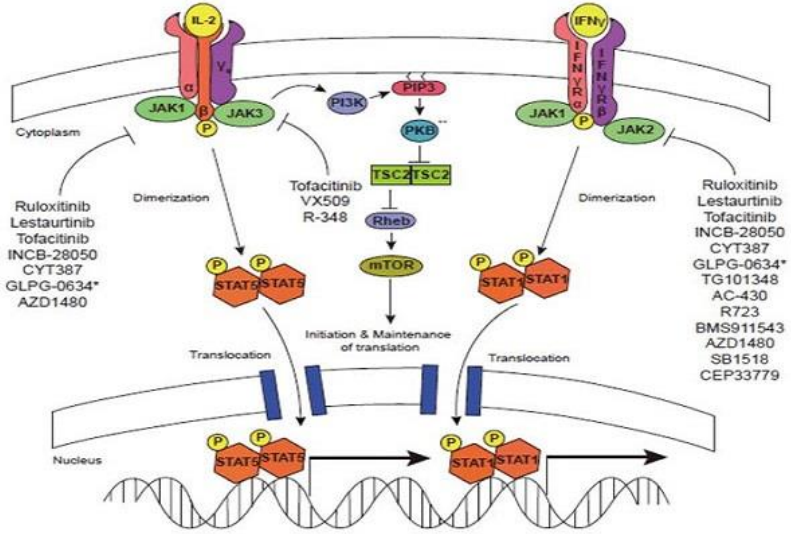
Introduction

- Tofacitinibは，JAK1, JAK3と
軽度JAK2を選択的に阻害し，
関節リウマチの治療に使用される

- 薬剤開発過程で，脂質の上昇，
リンパ腫を含む悪性腫瘍が増加する
可能性が指摘された.
⇒安全性に関するTNF阻害薬との
head-to-head試験が求められた



https://www.clinicaltrialsarena.com/projects/xeljanz-xr-tofacitinib-citrate-modified-release-tablets-for-the-treatment-of-rheumatoid-arthritis/

FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions

Approved uses also being limited to certain patients

- Baricitinib, Upadacitinibは，同様の大規模試験はないが，
  共通したメカニズムを持つことから，Tofacitinibと
  同様のリスクを示す可能性がある．
  ⇒特に有リスク者においては，処方の利点とリスクの評価が必要

- 血液疾患に対して使用されるRuxolitinib, Fedratinib については，
  処方情報の更新はおこなわれなかった．

https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death

1．論文のPICOは何か？

- **P**　50歳以上で，1つ以上の心血管リスク因子
(喫煙者，高血圧，HDL-C<40 mg/dL, 糖尿病，若年の冠動脈疾患の家族歴，関節外病変，冠動脈疾患の既往)を有する，MTX-IRの活動性関節リウマチ患者

1．論文のPICOは何か？

Inclusion criteria

- 研究の内容を了解し，informed consentが得られている
- 50歳以上
- 2010年ACR/EULARのRA分類基準で6点以上を満たし、MTX単剤治療下で中等-重度の関節リウマチ
- 6以上の圧痛/運動時痛のある関節かつ6以上の腫脹関節(28関節中)
- hs-CRP≧0.3 mg/dl
- ACRの1991年改訂Global Functional StatusでClass1-3に該当
    Class1：完全に普段の生活動作を行える
    Class2：趣味の活動には支障がある
    Class3：身辺動作は可能だが，職業や趣味の活動には制限がある

1．論文のPICOは何か？

Inclusion criteria

- スクリーニング時より４ヶ月以上前よりMTX内服中で，Baseline評価前の６週間以上の期間でMTXと葉酸の内服量が一定である
  MTXは不耐または有害事象がある場合には，<15 ㎎/wでよい
  MTX>25 mg/wの増量は不可
  葉酸は5 ㎎/w以上，フォリン酸は2.5 mg/w以上
- １つ以上の心血管リスク因子を有する
- 受診のスケジュール，治療プラン，検査，その他研究プラン等に従うことに同意が得られている
- 研究期間中と最終治療薬内服後28日まで避妊をする
- 検査時の妊娠がないこと
- 活動性結核や不適切な治療が行われた結核がないこと

1．論文のPICOは何か？

Exclusion criteria

- ACRのGlobal Functional StatusのClass IVの患者
- MTXにアレルギーや禁忌がある，重篤な有害事象の既往がある患者
- NYHA class III-IVの心不全があるか，ADAに対して禁忌がある
- 妊娠中，授乳中
- 活動性の感染や特定の感染症(人工関節感染など)の既往がある
- **悪性疾患がある**か**悪性腫瘍の既往**がある(適切に治療された皮膚の基底細胞癌，扁平上皮癌，子宮頸部上皮異形成は除く)
- Hb<9 g/dL，WBC＜3000 /μl，AST/ALT >1.5×ULN, GFR<60 ml/min
- 関節リウマチ，シェーグレン症候群以外の自己免疫疾患がある
- 併用禁止の薬剤を使用している

薬剤に関して

- MTXは臨床的に必要な場合を除き，**用量は維持**する
- 研究期間中**MTX以外のDMARDs(b-DMARDs含む)の使用は不可**
- MTX以外のDMARDs(b-DMARDs含む)の使用歴がある患者は下記の休薬期間を満たせば参加が可能
- ステロイド量は，**PSL≦10 mg/d相当**であれば使用可能
  研究期間中のステロイドの減量は可能

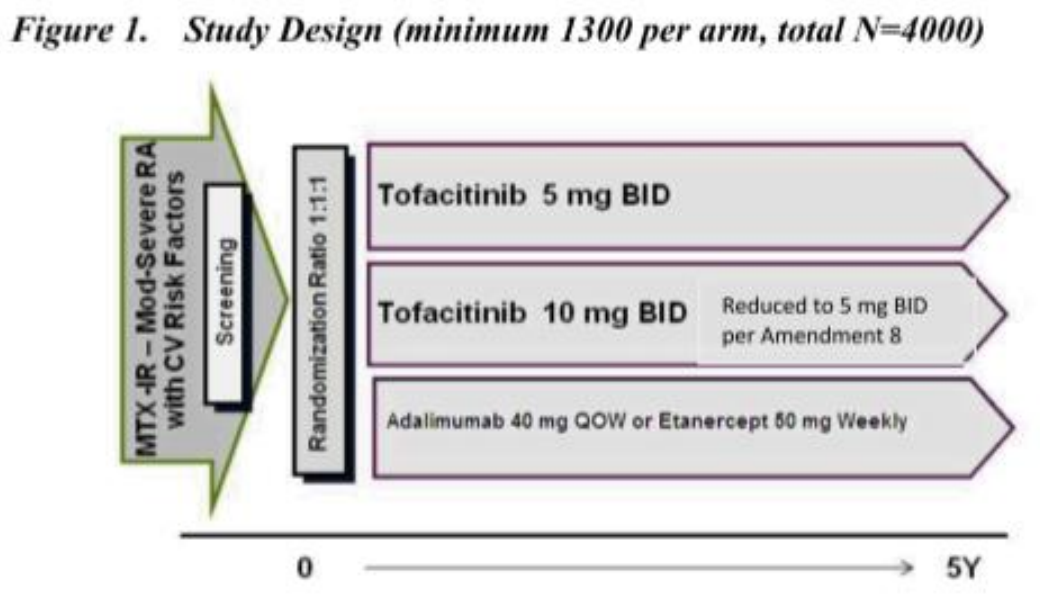
Table 1. DMARDs - Required Washout Period Prior to Randomization Visit

52 weeks	Rituximab (subject must have normal CD 19/20+ counts by FACS analysis)
20 weeks	Gold compounds, including auranofin (Ridaura),and injectable gold (aurothioglucose or aurothiomalate)
12 weeks	Abatacept, certolizumab pegol, leflunomide*, tocilizumab
10 weeks	Golimumab
8 weeks	Infliximab
6 weeks	Adalimumab
4 weeks	Anakinra, azathioprine, cyclosporine, etanercept, minocycline, penicillamine, sulfasalazine, tacrolimus

試薬が製薬会社から提供される試験。一定の休薬期間を設けても患者側にはメリットはある。

1. 論文のPICOは何か？

- **I**　Tofacitinib　5 mg　1日2回
  Tofacitinib 10 mg 1日2回*
- **C**　TNFi(adalimumab) 40mg q2w 皮下注
  Etanercept 50 mg qw(北アメリカ諸国以外)



*: Tofacitinib 10 mg 1日2回は,
安全性の指摘から2019年2月で
5mg 1日2回に減量となる

1. 論文のPICOは何か？

- **O**(safety endpoints)

  Co-Primary safety endpoints

  MACE(心血管死、非致死性の心筋梗塞・脳卒中)、
  悪性腫瘍(メラノーマ以外の皮膚がん)の発症

  Secondary safety endpoints

  日和見感染、肝障害、MACE以外の心血管イベント，
  全有害事象(重症なものを含む)，臨床的に有意な検査異常、
  全死因死亡率、治験薬中止に至った理由

1. 論文のPICOは何か？

- **O**(efficacy endpoints)
    - ベースラインからのΔDAS28-CRP(4), ΔSDAI, ΔCDAI
    - 各ポイントでの寛解達成率
    - 各ポイントでのLDA達成率
    - 各ポイントでのACR20, 50, 70達成率
    - ベースラインからのΔHAQ-DI

2. ランダム割付けされているか？

- ランダム割付け
- 割付け方法
  - 中央割付け
  - 隠蔽化あり

TRIAL DESIGN

ORAL Surveillance was a randomized, open-label, noninferiority, phase 3b–4 safety end-point trial. Patients were randomly assigned in a 1:1:1 ratio, with the use of an automated Web and telephone system, to receive open-label oral tofacitinib at a dose of 5 mg or 10 mg twice daily or a subcutaneous TNF inhibitor (adalimumab at a dose of 40 mg every 2 weeks [in North America, including the United States, Puerto Rico, and Canada] or etanercept at a dose of 50 mg once weekly [in the rest of the world]); background methotrexate

3. Baselineは同等か？

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Safety Analysis Population).*

Characteristic	Tofacitinib, 5 mg Twice Daily (N=1455)	Tofacitinib, 10 mg Twice Daily (N=1456)†	TNF Inhibitor (N=1451)	Total (N=4362)
Age				
Mean — yr	60.8±6.8	61.4±7.1	61.3±7.5	61.2±7.1
≥65 yr — no. (%)	413 (28.4)	478 (32.8)	462 (31.8)	1353 (31.0)
Female sex — no. (%)	1169 (80.3)	1124 (77.2)	1117 (77.0)	3410 (78.2)
Race — no. (%)‡				
White	1128 (77.5)	1126 (77.3)	1099 (75.7)	3353 (76.9)
Black	63 (4.3)	65 (4.5)	83 (5.7)	211 (4.8)
Asian	65 (4.5)	56 (3.8)	55 (3.8)	176 (4.0)
Other	199 (13.7)	209 (14.4)	214 (14.7)	622 (14.3)
Smoking status — no. (%)				
Never smoked	735 (50.5)	752 (51.6)	772 (53.2)	2259 (51.8)
Ever smoked	720 (49.5)	704 (48.4)	679 (46.8)	2103 (48.2)
History of hypertension — no. (%)	955 (65.6)	954 (65.5)	969 (66.8)	2878 (66.0)
History of diabetes mellitus — no. (%)	243 (16.7)	261 (17.9)	255 (17.6)	759 (17.4)
History of venous thromboembolism — no. (%)§	19 (1.3)	33 (2.3)	27 (1.9)	79 (1.8)
History of extraarticular disease — no. (%)¶	532 (36.6)	521 (35.8)	552 (38.0)	1605 (36.8)
History of coronary heart disease — no. (%)	161 (11.1)	172 (11.8)	164 (11.3)	497 (11.4)
Family history of coronary heart disease — no. (%)				
First-degree male relative <55 yr of age	154 (10.6)	132 (9.1)	151 (10.4)	437 (10.0)
First-degree female relative <65 yr of age	115 (7.9)	107 (7.3)	100 (6.9)	322 (7.4)
Fasting HDL cholesterol <40 mg/dl — no. (%)	172 (11.8)	195 (13.4)	173 (11.9)	540 (12.4)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. HDL denotes high-density lipoprotein, and TNF tumor necrosis factor.
† Patients assigned to receive tofacitinib at a dose of 10 mg twice daily who had their dose reduced to 5 mg twice daily or who discontinued the trial drug were counted in the group receiving 10 mg twice daily.
‡ Race was reported by the patient.
§ Venous thromboembolism included deep-vein thrombosis and pulmonary embolism.
¶ Extraarticular disease included nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations, or other clinical features as identified by the site investigator.

Table S2. Additional Patient Demographics and Baseline Disease Characteristics (Safety Analysis Set)

	Tofacitinib 5 mg BID (N=1455)	Tofacitinib 10 mg BID* (N=1456)	TNFi (N=1451)	Total (N=4362)
Age (years), median (range)	60.0 (50.0–86.0)	61.0 (50.0–85.0)	60.0 (50.0–88.0)	60.0 (50.0–88.0)
Duration of RA (years), mean (SD)	10.4 (8.8)	10.2 (9.0)	10.6 (9.3)	10.4 (9.1)
Geographical region, n (%)				
US and Canada	402 (27.6)	409 (28.1)	432 (29.8)	1243 (28.5)
Latin America	385 (26.5)	414 (28.4)	403 (27.8)	1202 (27.6)
Europe	43 (3.0)	56 (3.8)	48 (3.3)	147 (3.4)
Rest of the world	625 (43.0)	577 (39.6)	568 (39.1)	1770 (40.6)
BMI (kg/m^2), mean (SD) [number of patients with missing values]	29.7 (6.5) [7]	29.7 (6.3) [3]	29.8 (6.6) [7]	29.8 (6.5) [17]
BMI ≥30 kg/m^2, n (%)	606 (41.6)	594 (40.8)	617 (42.5)	1817 (41.7)
Concomitant medication use at baseline (day 1), n (%)				
Oral contraceptives or HRT	51 (3.5)	41 (2.8)	45 (3.1)	137 (3.1)
Corticosteroid	836 (57.5)	829 (56.9)	830 (57.2)	2495 (57.2)
Methotrexate	1453 (99.9)	1456 (100.0)	1451 (100.0)	4360 (>99.9)
Aspirin	212 (14.6)	231 (15.9)	224 (15.4)	667 (15.3)
Anticoagulants	47 (3.2)	66 (4.5)	62 (4.3)	175 (4.0)
Antidepressants	218 (15.0)	208 (14.3)	223 (15.4)	649 (14.9)
Methotrexate dose† (mg/week), mean SD [number of patients with missing values]	17.4 (4.4) [21]	17.4 (4.1) [33]	17.3 (4.3) [16]	17.3 (4.3) [70]
Prior medication use, n (%)				
Methotrexate	1455 (100.0)	1456 (100.0)	1451 (100.0)	4362 (100.0)
Nonmethotrexate csDMARDs	421 (28.9)	395 (27.1)	424 (29.2)	1240 (28.4)
bDMARDs	164 (11.3)	138 (9.5)	150 (10.3)	452 (10.4)
TNFi	115 (7.9)	110 (7.6)	105 (7.2)	330 (7.6)
Non-TNFi bDMARDs	71 (4.9)	53 (3.6)	62 (4.3)	186 (4.3)
Number of prior csDMARDs, mean (SD)	1.4 (0.7)	1.4 (0.7)	1.4 (0.7)	1.4 (0.7)
Number of prior bDMARDs,‡ mean (SD)	1.3 (0.6)	1.3 (0.6)	1.2 (0.5)	1.3 (0.6)
Medical history, n (%)				
Depression	176 (12.1)	178 (12.2)	183 (12.6)	537 (12.3)
Myocardial infarction	60 (4.1)	59 (4.1)	48 (3.3)	167 (3.8)
Unstable angina	17 (1.2)	14 (1.0)	7 (0.5)	38 (0.9)
Coronary artery procedures	63 (4.3)	69 (4.7)	63 (4.3)	195 (4.5)
Other coronary heart disease	84 (5.8)	95 (6.5)	101 (7.0)	280 (6.4)
Alcohol use within last 7 days, n (%)	187 (12.9)	193 (13.3)	183 (12.6)	563 (12.9)
Fasting HDL-C (mg/dL), mean (SD)	58.1 (16.8)	57.6 (17.3)	57.9 (16.8)	57.9 (17.0)
Fasting total cholesterol/HDL-C ratio >4, n (%)	433 (29.8)	439 (30.2)	430 (29.6)	1302 (29.8)
CRP >2.87 mg/L, n (%)	1279 (87.9)	1270 (87.2)	1266 (87.3)	3815 (87.5)
SDAI,§ mean (SD) [number of patients with missing values]	41.5 (12.5) [45]	41.5 (12.6) [52]	41.4 (12.5) [65]	41.5 (12.5) [162]
HAQ-DI,¶ mean (SD) [number of patients with missing values]	1.6 (0.6) [11]	1.6 (0.6) [18]	1.6 (0.6) [25]	1.6 (0.6) [54]
TJC28, mean (SD) [number of patients with missing values]	15.7 (6.3) [1]	15.7 (6.4)	15.6 (6.2) [2]	15.7 (6.3) [3]
SJC28, mean (SD) [number of patients with missing values]	11.8 (5.1) [1]	12.0 (5.2)	11.7 (5.0) [2]	11.8 (5.1) [3]
Rheumatoid factor positive, n (%)	1243 (85.4)	1261 (86.6)	1264 (87.1)	3768 (86.4)
Anti-CCP positive, n (%)	1093 (75.1)	1129 (77.5)	1119 (77.1)	3341 (76.6)

- 罹病期間およそ10年程度
- 65歳以上が約3割
- 肥満者が多い
- MTXは平均 17.4mg/w
- ステロイド使用が5割強
- SDAIは平均 41.5程度
- TJC 15.7、SJC 12程度

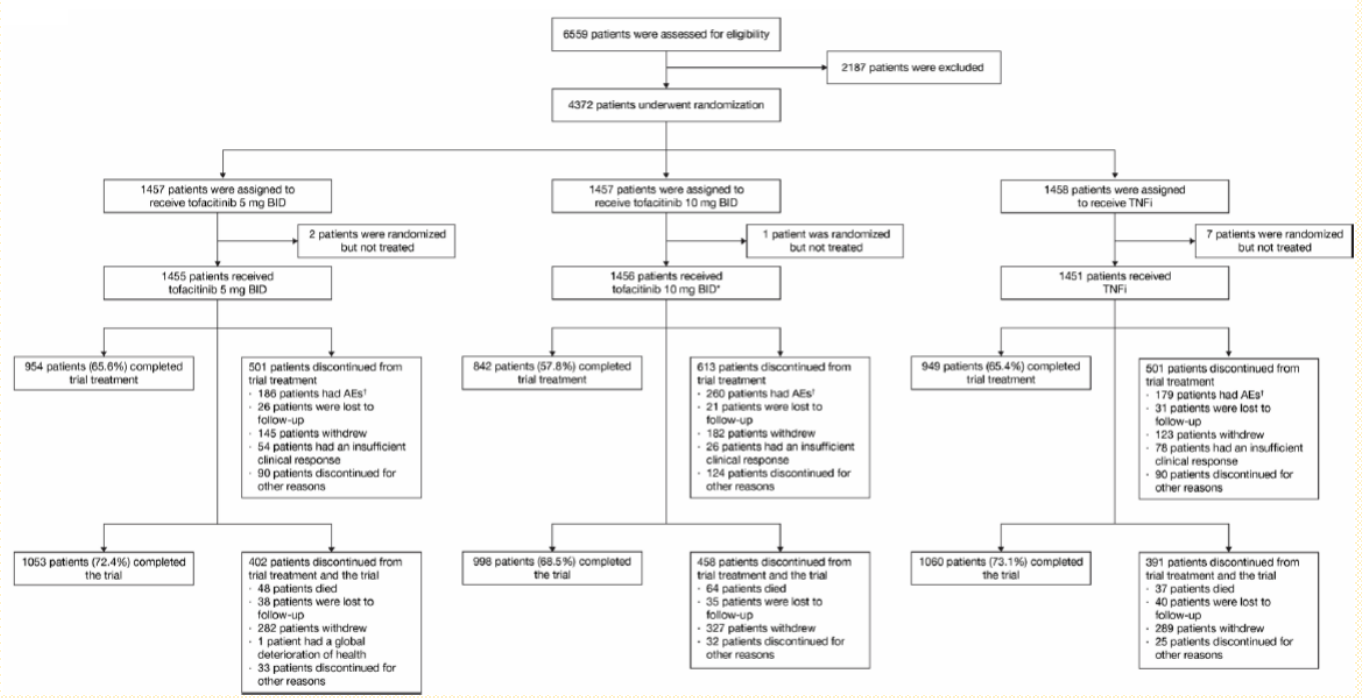
4. 全ての患者の転帰がOutcomeに反映されているか？

4-1. ITT解析か？

Modified ITT解析
(治療を受けなかった例を除外)

4-2. 結果に影響を及ぼすほどの脱落があるか？

最終的には約3割の脱落



5. マスキングされているか？

マスキングされているのはだれか

- 患者
- 介入実施者
- Outcome評価者
  →非盲検化

- データ解析者
  →盲検化？

大規模の多施設研究でもあり、Placebo controlのstudy designには限界もある。

9.5. Data Monitoring Committee

This study will use an external Data Monitoring Committee (DMC).

The DMC will be responsible for ongoing monitoring of safety of subjects in the study in an unblinded manner according to the Charter. All safety data, including potential primary endpoint data will be forwarded to, and reviewed by, the DMC on a regular basis. Based on these reviews, the DMC will have the capacity to make recommendations to Pfizer that might impact the future conduct of the trial. The recommendations made by the DMC to alter the

9.6. Steering Committee

The Steering Committee is a committee established by Pfizer to oversee the conduct of the trial, assess at intervals the progress of a clinical trial (ie, Performance Standards), the aggregate accumulation of primary endpoint events (ie, MACE and malignancies) meeting pre-specified criteria, and the attainment of 1500 subjects completing 3 years in the study. The Steering Committee will recommend to the study team whether to continue, modify or stop a trial, independently from the study team. The Steering Committee will include only non-Pfizer trial experts who are not members of the study team.

The Steering Committee will consider the ongoing accumulation of the adjudicated primary endpoint events and study performance standard metrics and may determine that sufficient events have occurred to assess the primary objectives of the study or that it is not feasible to continue the trial in pursuit of the stated objectives. These determinations by the Steering Committee will be made in accordance with pre-specified rules documented in the Steering Committee Charter and in the Statistical Analysis Plan and following consultations with the US FDA could result in recommendations for changes in study design, including changes in number of subjects studied or duration of study.

The Steering Committee Charter will pre-specify all reviews of the data that will be performed during the conduct of the study and how the data will be evaluated to determine that study completion can be declared.

The Steering Committee will be responsible for blinded review of adjudicated, aggregate primary endpoint data according to its charter.

6. 症例数は十分か？

- 結果に有意差がある
- サンプルサイズは？ー計算されている

症例数：約4000人
(dropoutや追跡不能者を考慮)

イベント発生率
- MACE　：1.0/100 人年
- 悪性腫瘍：1.1/100 人年

Power(ハザード比：1.0と想定)
- MACE　：80%(→65件)
- 悪性腫瘍：90%(→87件)

非劣性マージン：
- ハザード比の95%信頼区間の上限<1.8

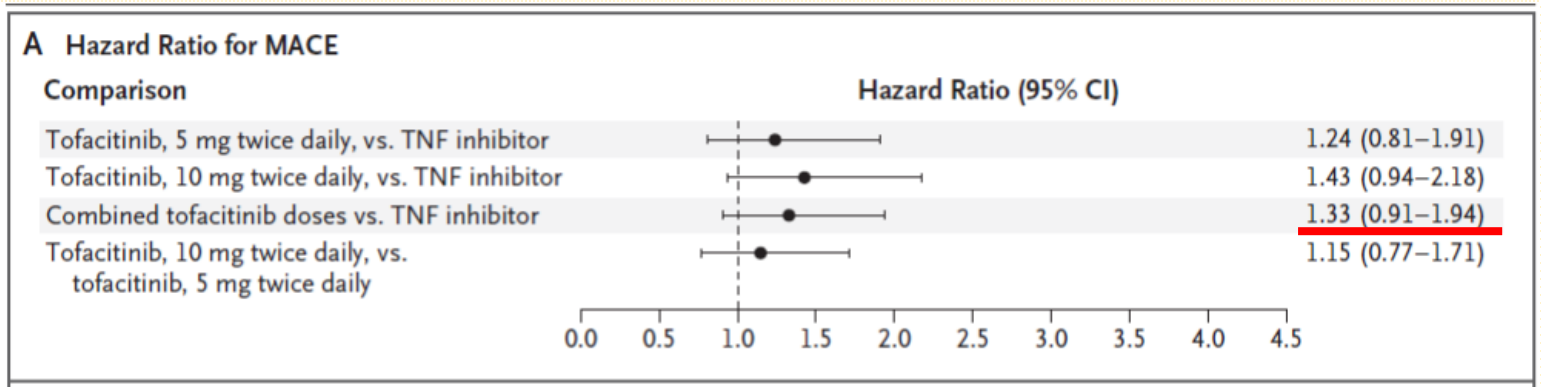
9.1. Sample Size Determination

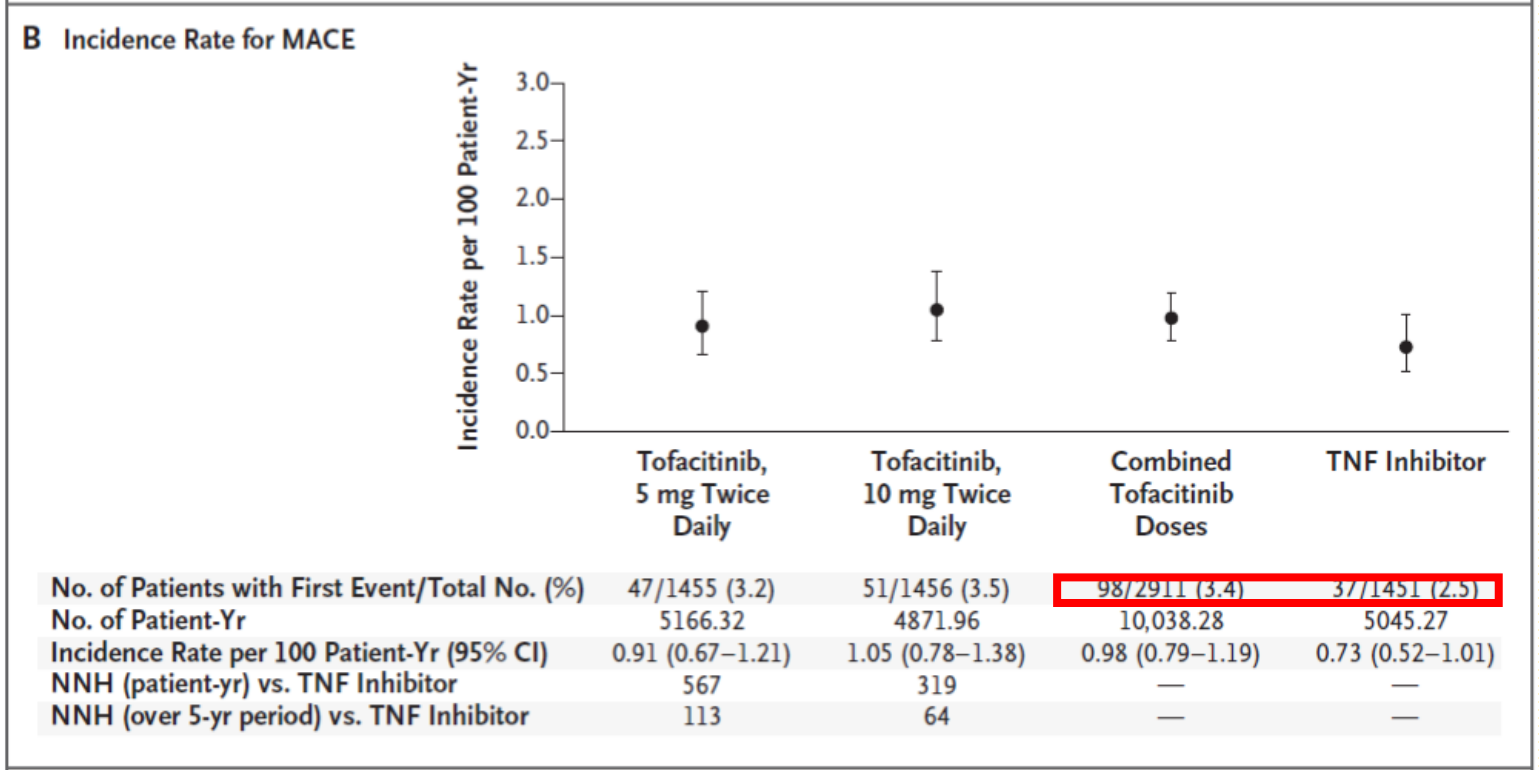
The statistical objectives with respect to the primary safety endpoints, that is, malignancy (excluding non-melanoma skin cancer), and MACE, include drawing inferences with 95% (two-sided) confidence that the hazard ratios of the combined tofacitinib regimens versus the TNFi control regimen are less than 1.8. Assuming that the true hazard ratio is 1.0 the required number of events is 138 for malignancies to achieve 90% power and 103 for MACE to achieve 80% power.

The planned enrollment is approximately 4000 patients within 3 years (1000 in the first year and 1500 per year in the second and third years of recruitment). The assumed 'dropout or Loss to Follow-up' (LTFU) rate for MACE is 10% in the first year, 7% in the second and 5% per year, thereafter. For malignancies, because they will be followed after discontinuation the LTFU rate is assumed to be 5% in the first year, 3.5% in the second year and 2.5% per year thereafter. The assumed event rate for MACE is 1.0 event per hundred patient-years and the assumed rate for malignancy is 1.1 events per hundred patient-years; assumptions are based on results from the CORRONA database,[20] and also based on a meta-analysis of TNF-α inhibitors.[21] Based on those assumptions it is expected that the trial will accrue the desired number of events in approximately 5 years.

Additionally, the statistical objectives with respect to the primary safety endpoints include drawing inferences with 95% (two-sided) confidence that the hazard ratios of the tofacitinib 10 mg regimen to the tofacitinib 5 mg regimen are less than 2.0. Assuming that the true hazard ratio is 1.0 the required number of events is 87 for malignancies to achieve 90% power and 65 for MACE to achieve 80% power. Based on the same assumptions of patient enrollment, LTFU and event rates, the trial is expected to accrue the desired number of events in approximately 5 years.

7. 結果の評価　　MACE





	Tofacitinib, 5 mg Twice Daily	Tofacitinib, 10 mg Twice Daily	Combined Tofacitinib Doses	TNF Inhibitor
No. of Patients with First Event/Total No. (%)	47/1455 (3.2)	51/1456 (3.5)	98/2911 (3.4)	37/1451 (2.5)
No. of Patient-Yr	5166.32	4871.96	10,038.28	5045.27
Incidence Rate per 100 Patient-Yr (95% CI)	0.91 (0.67–1.21)	1.05 (0.78–1.38)	0.98 (0.79–1.19)	0.73 (0.52–1.01)
NNH (patient-yr) vs. TNF Inhibitor	567	319	—	—
NNH (over 5-yr period) vs. TNF Inhibitor	113	64	—	—

Figure 1. Hazard Ratios and Incidence Rates for Adjudicated MACE (Safety Analysis Population, 60-Day On-Treatment Time).

追跡期間：中央値4年

Tofa：3.4%

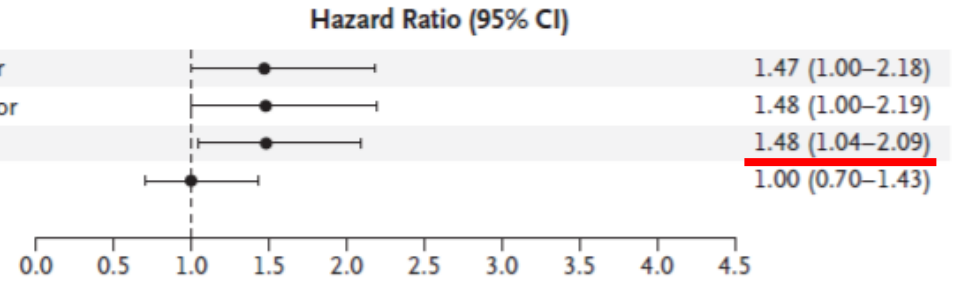
TNFi：2.5%

HR：1.33[0.91-**1.94**]

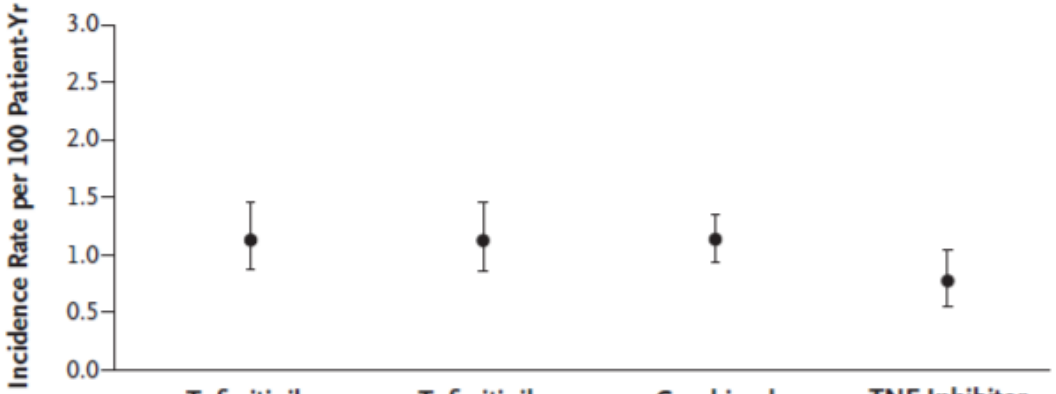
Tofa 5mg vs. 10mgは非劣性

悪性腫瘍

A Hazard Ratio for Cancers, Excluding NMSC



B Incidence Rate for Cancers, Excluding NMSC



	Tofacitinib, 5 mg Twice Daily	Tofacitinib, 10 mg Twice Daily	Combined Tofacitinib Doses	TNF Inhibitor
No. of Patients with First Event/Total No. (%)	62/1455 (4.3)	60/1456 (4.1)	122/2911 (4.2)	42/1451 (2.9)
No. of Patient-Yr	5491.48	5311.71	10,803.19	5482.30
Incidence Rate per 100 Patient-Yr (95% CI)	1.13 (0.87–1.45)	1.13 (0.86–1.45)	1.13 (0.94–1.35)	0.77 (0.55–1.04)
NNH (patient-yr) vs. TNF Inhibitor	276	275	—	—
NNH (over 5-yr period) vs. TNF Inhibitor	55	55	—	—

Figure 2. Hazard Ratios and Incidence Rates for Adjudicated Cancers, Excluding NMSC (Safety Analysis Population, Total-Time Analysis).

追跡期間：中央値4年

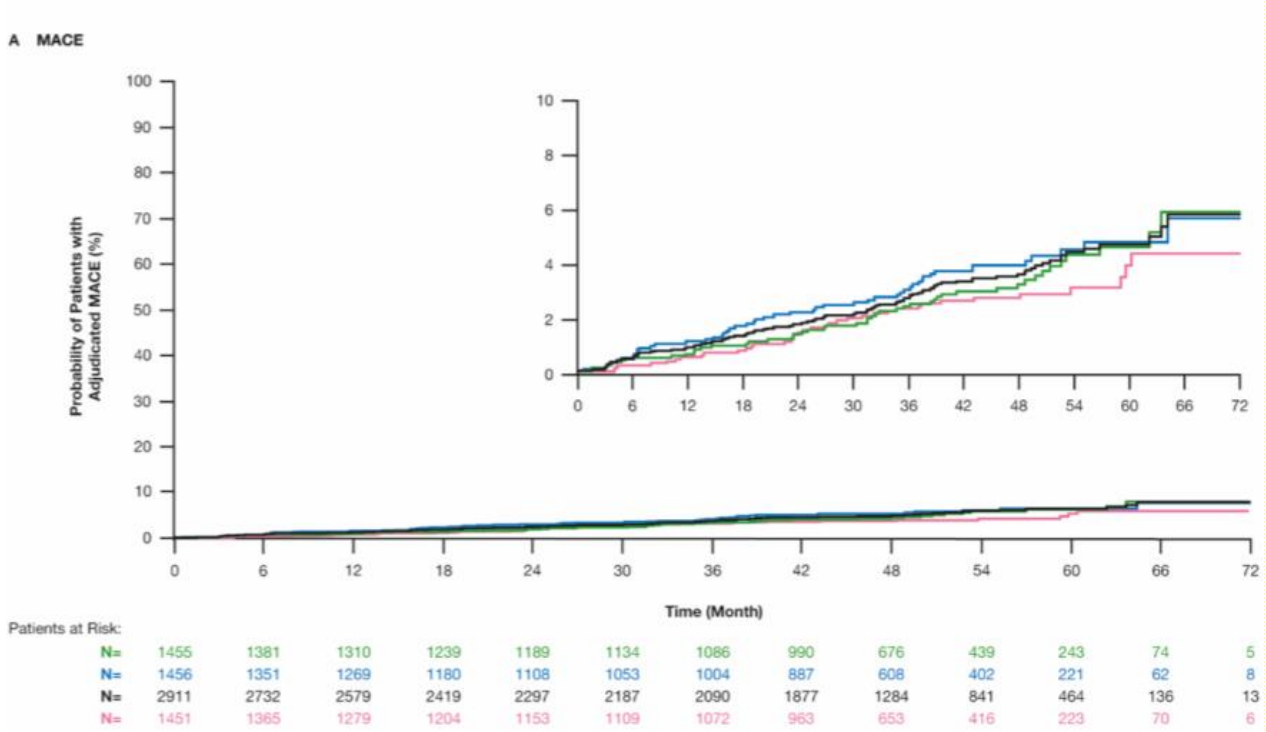
Tofa：4.2%

TNFi：2.9%

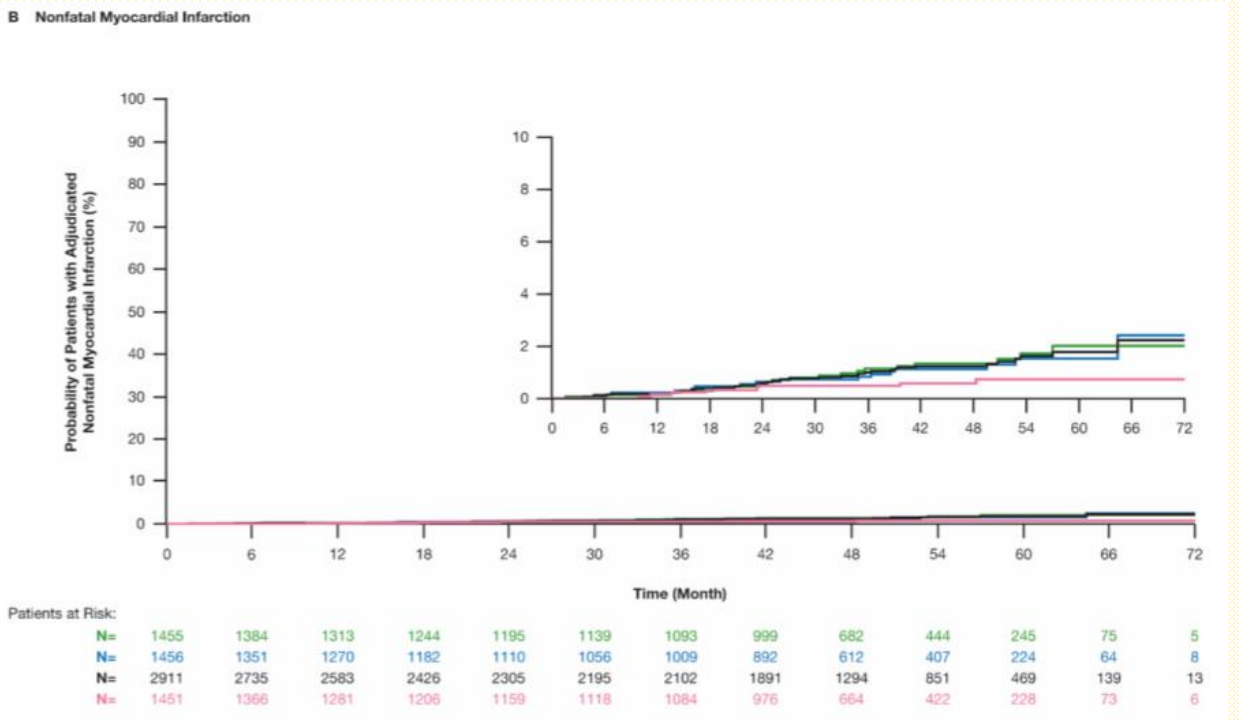
HR：1.48[1.04-**2.09**]

Tofa 5mg vs. 10mgは非劣性

MACE　累積発生率



非致死性心筋梗塞 累積発生率

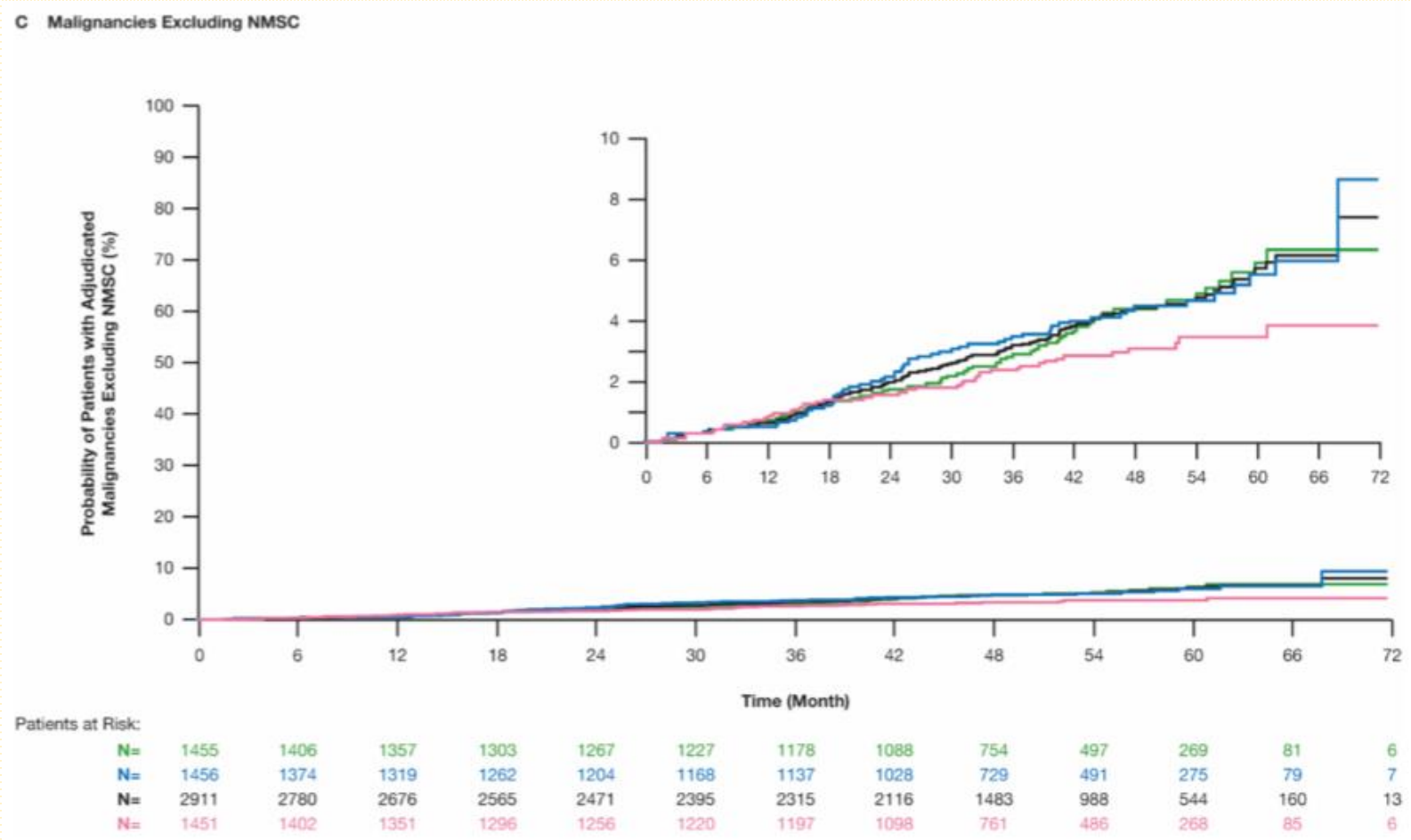


緑：Tofa5mg、青：Tofa10mg、黒：Tofa(5+10mg)、赤：TNF

(5.5年時点)
Tofa(combined dose)：5.8%
TNFi：4.3%

(5.5年時点)
Tofa：2.2%
TNFi：0.7%

悪性腫瘍　累積発生率



(5.5年時点)
Tofa：6.1%,　TNFi：3.8%

有害事象

Table 2. Adverse Events (Safety Analysis Population, 28-Day On-Treatment Time).*

Event	Tofacitinib, 5 mg Twice Daily (N=1455)	Tofacitinib, 10 mg Twice Daily (N=1456)†	TNF Inhibitor (N=1451)
Adverse event — no. (%)	1333 (91.6)	1344 (92.3)	1308 (90.1)
Serious adverse event — no. (%)	351 (24.1)	390 (26.8)	306 (21.1)
Discontinuation of trial treatment due to adverse event — no. (%)			
Permanent discontinuation‡	210 (14.4)	304 (20.9)	210 (14.5)
Temporary discontinuation§	665 (45.7)	736 (50.5)	576 (39.7)
Adverse events of special interest			
Serious infection — no. (%)	141 (9.7)	169 (11.6)	119 (8.2)
Hazard ratio vs. TNF inhibitor (95% CI)	1.17 (0.92–1.50)	1.48 (1.17–1.87)	Referent
Adjudicated opportunistic infection — no. (%)¶	39 (2.7)	44 (3.0)	21 (1.4)
Hazard ratio vs. TNF inhibitor (95% CI)	1.82 (1.07–3.09)	2.17 (1.29–3.66)	Referent
All herpes zoster, serious and nonserious — no. (%)‖	180 (12.4)	178 (12.2)	58 (4.0)
Hazard ratio vs. TNF inhibitor (95% CI)	3.28 (2.44–4.41)	3.39 (2.52–4.55)	Referent
Adjudicated hepatic event — no. (%)	46 (3.2)	72 (4.9)	35 (2.4)
Hazard ratio vs. TNF inhibitor (95% CI)	1.29 (0.83–2.00)	2.14 (1.43–3.21)	Referent
Adjudicated NMSC — no. (%)	31 (2.1)	33 (2.3)	16 (1.1)
Hazard ratio vs. TNF inhibitor (95% CI)	1.90 (1.04–3.47)	2.16 (1.19–3.92)	Referent
Adjudicated pulmonary embolism — no. (%)	9 (0.6)	24 (1.6)	3 (0.2)
Hazard ratio vs. TNF inhibitor (95% CI)	2.93 (0.79–10.83)	8.26 (2.49–27.43)	Referent
Adjudicated DVT — no. (%)	11 (0.8)	15 (1.0)	7 (0.5)
Hazard ratio vs. TNF inhibitor (95% CI)	1.54 (0.60–3.97)	2.21 (0.90–5.43)	Referent
Adjudicated VTE — no. (%)	17 (1.2)	34 (2.3)	10 (0.7)
Hazard ratio vs. TNF inhibitor (95% CI)	1.66 (0.76–3.63)	3.52 (1.74–7.12)	Referent
Adjudicated death from any cause — no. (%)	26 (1.8)	39 (2.7)	17 (1.2)
Hazard ratio vs. TNF inhibitor (95% CI)	1.49 (0.81–2.74)	2.37 (1.34–4.18)	Referent

- 帯状疱疹は、Tofaで多く発症
- Tofaで皮膚がん、塞栓症、全死亡が多く発生

皮膚がん以外の悪性腫瘍

	Tofacitinib 5 mg BID (N=1455)	Tofacitinib 10 mg BID* (N=1456)	Combined Tofacitinib Doses (N=2911)	TNFi (N=1451)
Malignancies excluding NMSC				
Patients with malignancies excluding NMSC, n	62	60	122	42
Patients with a competing risk, n	360	413	773	360
Due to discontinuation from trial	323	360	683	330
Due to death	37	53	90	30
Patients censored, n	1033	983	2016	1049
Subdistribution HR (95% CI) (versus TNFi)	1.47 (1.00 to 2.18)	1.42 (0.96 to 2.11)	1.45 (1.02 to 2.06)	Referent
Subdistribution HR (95% CI) (versus tofacitinib 5 mg BID)	Referent	0.97 (0.68 to 1.38)	–	–

- Tofacitinib 群で**皮膚がん以外の悪性腫瘍も多く**見られた。

有害事象

Table S5. Treatment-Emergent Adverse Events, by System Organ Class and Preferred Term (All Causality) Occurring in ≥3% of Patients

(Safety Analysis Set, 28-Day On-Treatment Time)

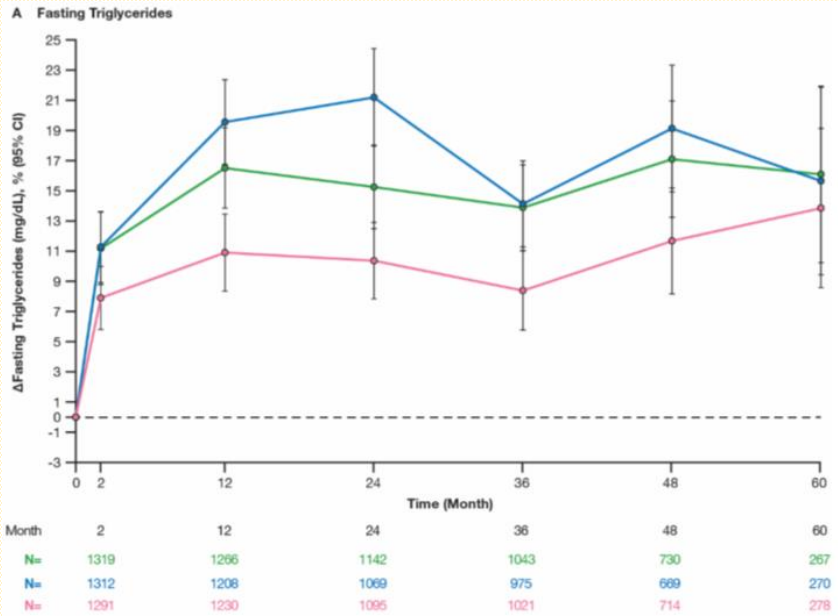
	Tofacitinib 5 mg BID (N=1455)	Tofacitinib 10 mg BID* (N=1456)	TNFi (N=1451)
Infections and infestations, n (%)	1036 (71.2)	1055 (72.5)	930 (64.1)
Bronchitis	222 (15.3)	237 (16.3)	163 (11.2)
Cellulitis	36 (2.5)	32 (2.2)	50 (3.4)
Gastroenteritis	64 (4.4)	79 (5.4)	53 (3.7)
Herpes zoster†	176 (12.1)	167 (11.5)	55 (3.8)
Influenza	90 (6.2)	91 (6.3)	71 (4.9)
Latent tuberculosis	87 (6.0)	67 (4.6)	91 (6.3)
Nasopharyngitis	164 (11.3)	165 (11.3)	158 (10.9)
Pharyngitis	86 (5.9)	79 (5.4)	75 (5.2)
Pneumonia	95 (6.5)	101 (6.9)	78 (5.4)
Respiratory tract infection	43 (3.0)	43 (3.0)	31 (2.1)
Sinusitis	92 (6.3)	79 (5.4)	91 (6.3)
Upper respiratory tract infection	308 (21.2)	312 (21.4)	255 (17.6)
Urinary tract infection	186 (12.8)	221 (15.2)	184 (12.7)

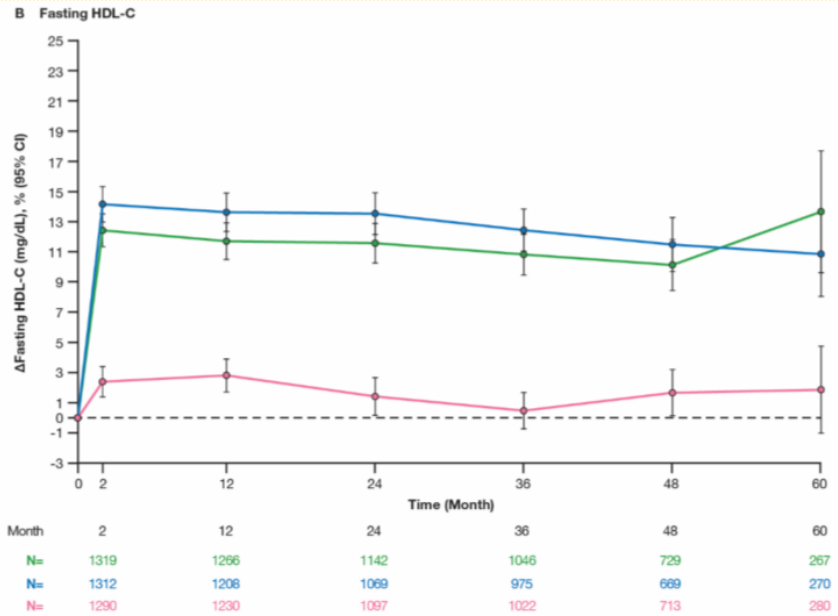
- 有害事象として感染が多く見られた
- 重篤な有害事象として肺炎が最多

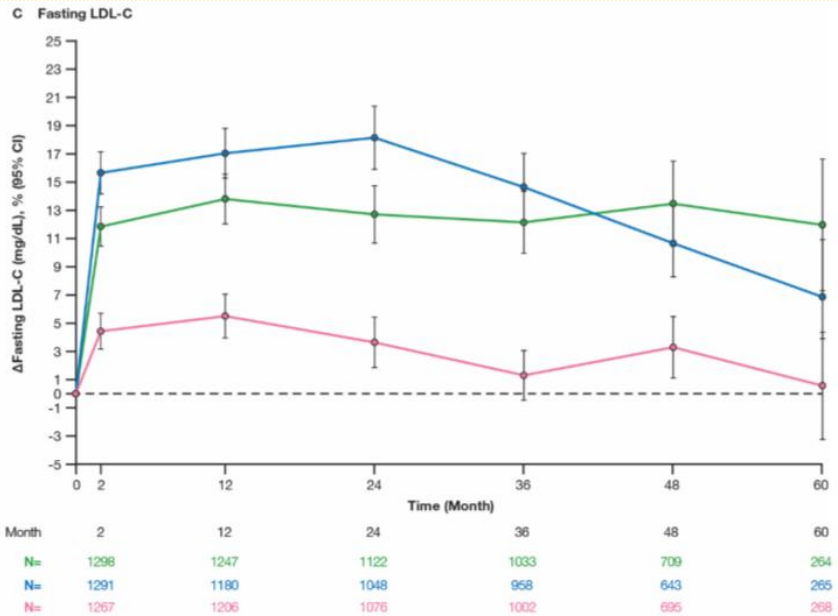
有害事象(全死因死)

	Tofacitinib 5 mg BID (N=1455)		Tofacitinib 10 mg BID* (N=1456)		TNFi (N=1451)	
	n (%)	n1 (%)	n (%)	n1 (%)	n (%)	n1 (%)
Total deaths	26 (1.8)	22 (1.5)	39 (2.7)	27 (1.9)	17 (1.2)	21 (1.5)
Deaths due to infections	4 (0.3)	4 (0.3)	9 (0.6)	7 (0.5)	3 (0.2)	3 (0.2)
Deaths due to cardiovascular events	13 (0.9)	6 (0.4)	20 (1.4)	7 (0.5)	10 (0.7)	5 (0.3)
Deaths due to malignancies	5 (0.3)	5 (0.3)	0	7 (0.5)	1 (0.1)	5 (0.3)
Deaths due to other causes	4 (0.3)	7 (0.5)	10 (0.7)	6 (0.4)	3 (0.2)	8 (0.6)

脂質の推移



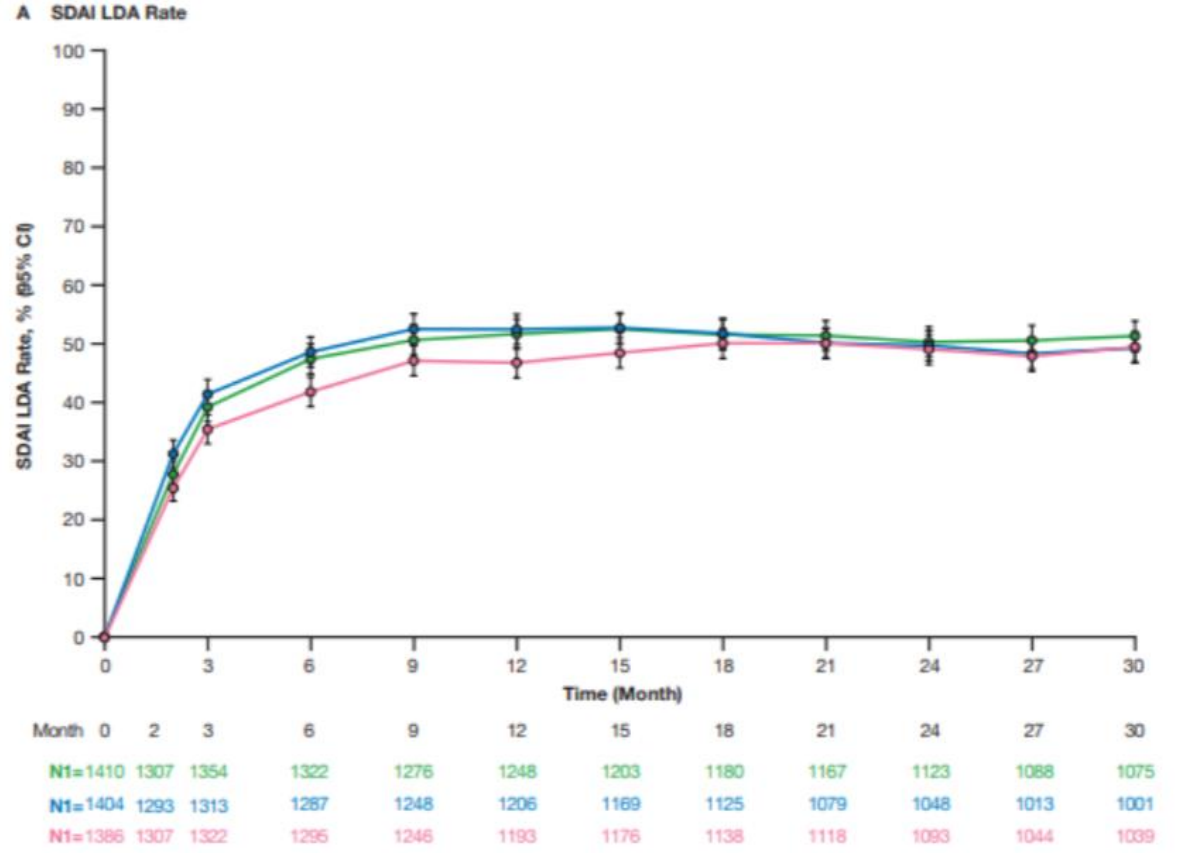


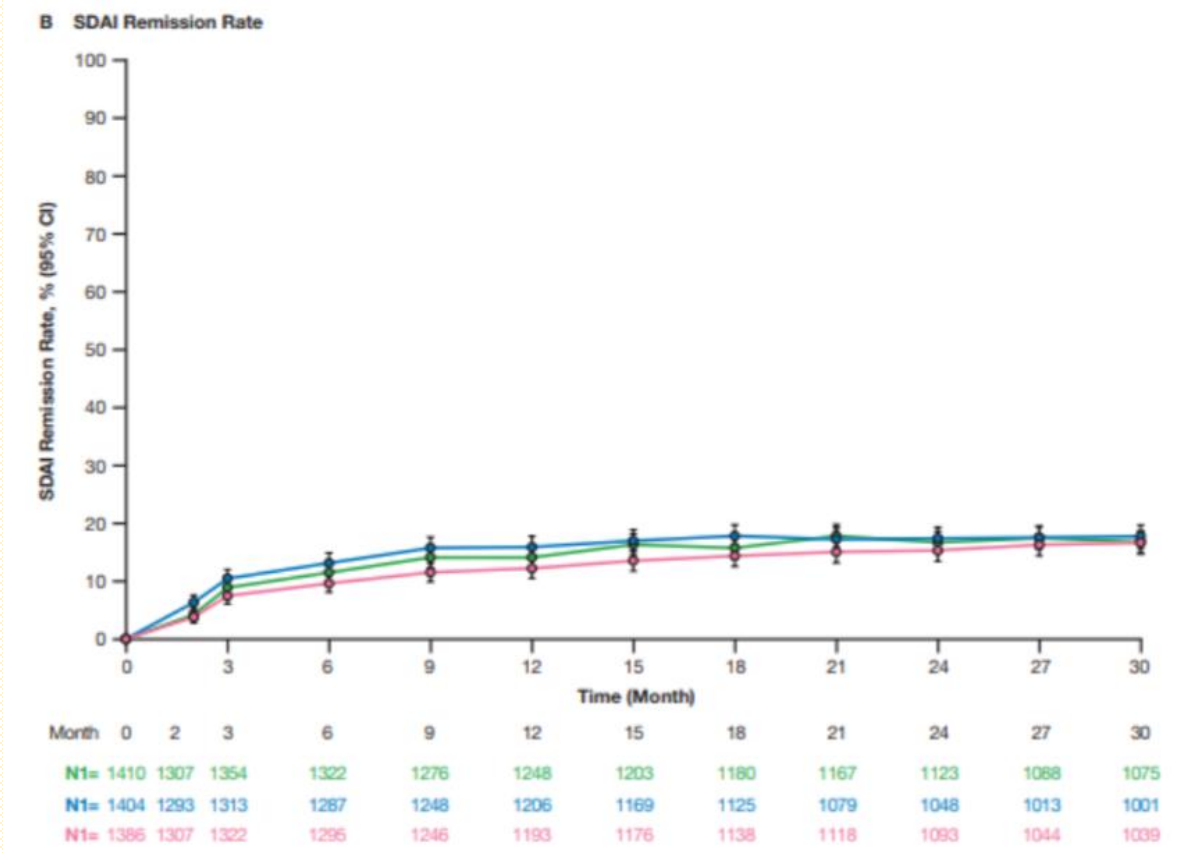


緑：Tofa5mg、青：Tofa10mg、赤：TNF

- Tofacitinib 群でTNFi群と比較して脂質レベルの上昇がみられる

有効性





緑：Tofa5mg、青：Tofa10mg、赤：TNF

有効性については両者に差はなし

Discussion

- 50歳以上の心血管リスクを有する症例において、TNF阻害薬と比較してTofacitinib はMACEや悪性疾患のリスクが高い。
- 全死因死や肺塞栓症が、Tofacitinib 10mg 1日2回内服群で多く発生した。
- 血栓塞栓症リスクの評価にはデータ不十分。他のJAK阻害薬と比べてTofacitinib ではリスクが高いのかも不明である。

この論文の利点・欠点の評価

Positive	Negative
多施設・大規模試験	Funding (結果はNegativeであったが、Pfizerのイメージ向上につながる？)
RCT	Open-label
	脱落者が多い

- 悪性腫瘍については、皮膚がんの発症が多いが、
  皮膚がん以外の悪性腫瘍の発症も多いことが示唆。
- 心血管リスクについては、ステロイド使用等含め
  様々な背景の違いもあり、実臨床で当てはめるには注意が必要。
- トファシチニブの処方にはネガティブな印象を受ける結果。
- 他のJAK阻害薬については評価が待たれる。