Cardiovascular and cancer risk with Tofacitinib in rheumatoid arthritis

Journal club

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OUTLINES

- 01Introduction
- 02.Clinical trial
- 03. Discussion
- 04. Appraisal

Question

- 是否同意有心血管疾病風險以及癌症風險的病人當使用Methotrexate無效後添加JAK inhibitor-Tofacitinib作為其rheumatoid arthritis的治療

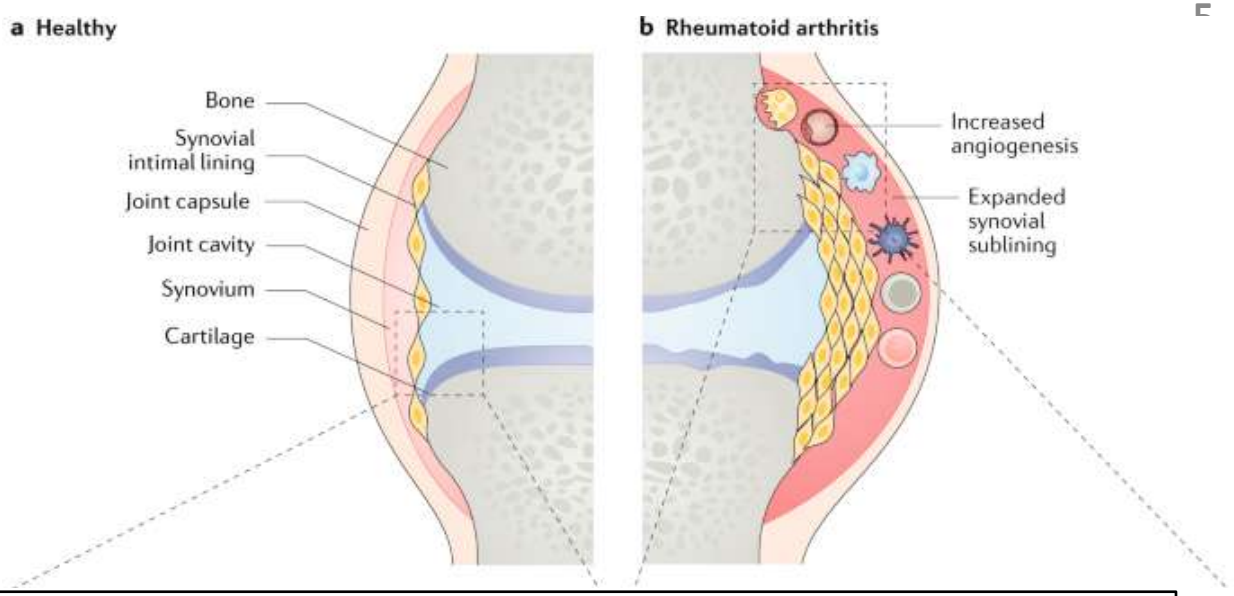
同意

需要更多文獻支持

不同意

01 Introduction

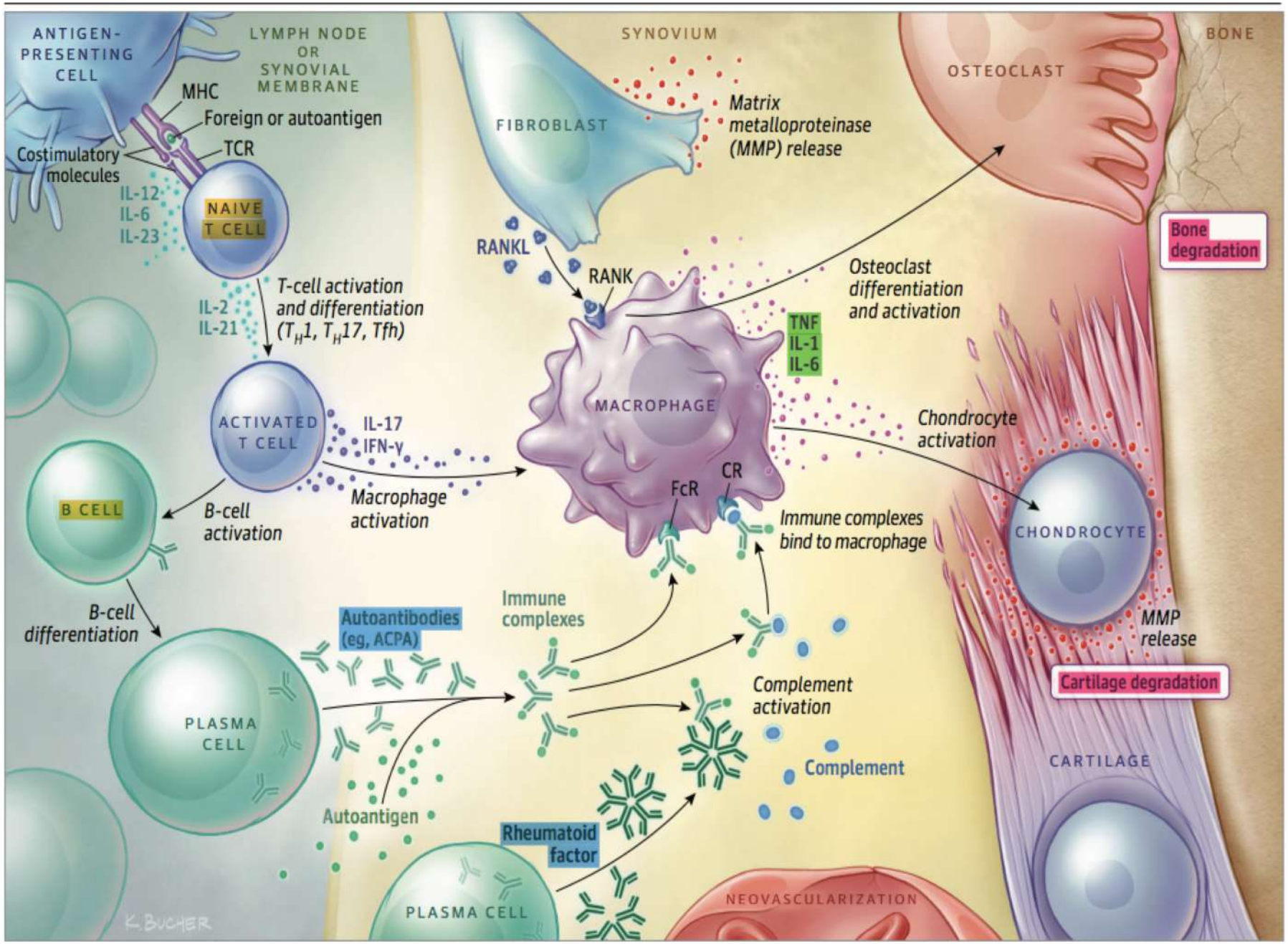
Rheumatoid arthritis



1. A chronic, inflammatory, systemic **autoimmune disorder** characterized by symmetric, erosive synovitis that frequently leads to joint destruction, and disability
2. **Worldwide prevalence** of about 0.24~1%
3. Affects **women** 2 to 3 times more of than men and peak incidence is in **sixth decade**
4. Clinical presentation：
   - presents with pain and swelling in the joints of the hands and feet
   - accompanied by **morning joint stiffness** lasting more than 60 minutes

JAMA October 2, 2018 Volume 320, Number 13

Pathobiology



Diagnosis

ACR/EULAR 2010 classification criteria

Patients who

1. have at least 1 joint with definite clinical synovitis (swelling)
2. with the synovitis not better explained by another disease

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RF：Rheumatoid factors
ACPA：Anti-citrullinated peptide antibodies
CRP：C-reactive protein
ESR：Erythrocyte sedimentation rate

Score ≥6 = Definite RA

	Score
Joint involvement	
=1 large joint	0
>1 large joint	1
1~3 small joint	2
4~10 small joint	3
>10 joints(small joint≥1)	
Serelogy	
Negative **RF** and **ACPA**	0
Low positive RF or ACPA	2
High positive RF or ACPA	3
Duration of symptoms	
<6 weeks	0
≥6 weeks	1
Acute phase reactants	
Normal **CRP** and **ESR**	0
Abnormal CRP and ESR	1

Disease assessment tools

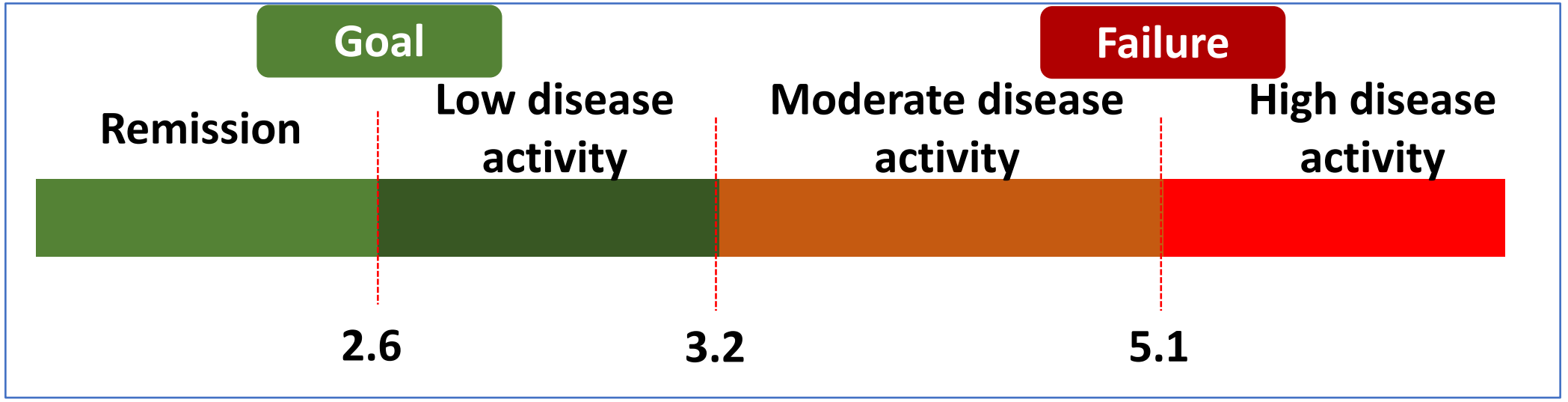
1. DAS28(**Disease activity score in 28 joints**)

   ① TJC28： **Tender** joint count

   ② SJC28：**Swollen** joint count of 28

   ③ Acute phase reactant (ESR or CRP)

   ④ Global health



- **Treatment strategy →"Treat to target"**
  Improved 50% at 3months and achieved target at **6 months**

LANCEt October 22, 2016 Volume 388,

Disease assessment tools

2. SDAI **(simplified disease activity index)**

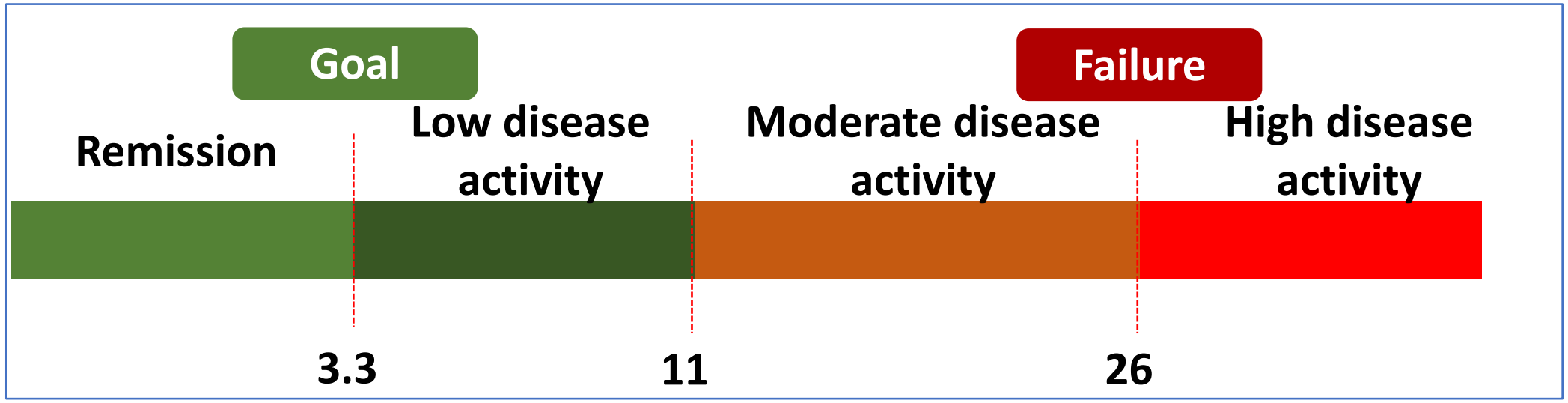
① TJC28： Tender joint count

② SJC28：Swollen joint count of 28

③ Acute phase reactant
CRP(C-creatinine protein)

④ Patient global assessment

⑤ **Physician global assessment**



LANCEt October 22, 2016 Volume 388,

Treatment

Disease modifying anti rheumatic drug

Synthetic

Conventional

Methotrexate
Sulfasalazine
Leflunomide
Azathioprine
Cyclosporine

Targeted

JAK inhibitor

Tofacitinib
Baricitinib
Upadacitinib

Biological

TNF α inhibitor

Etanercept
Infliximab
Adalimumab
Golimumab
Certolizumab-pegal

IL-6 inhibitor

Tocilizumab

Inhibition of T cell co-stimulation

Abatacept

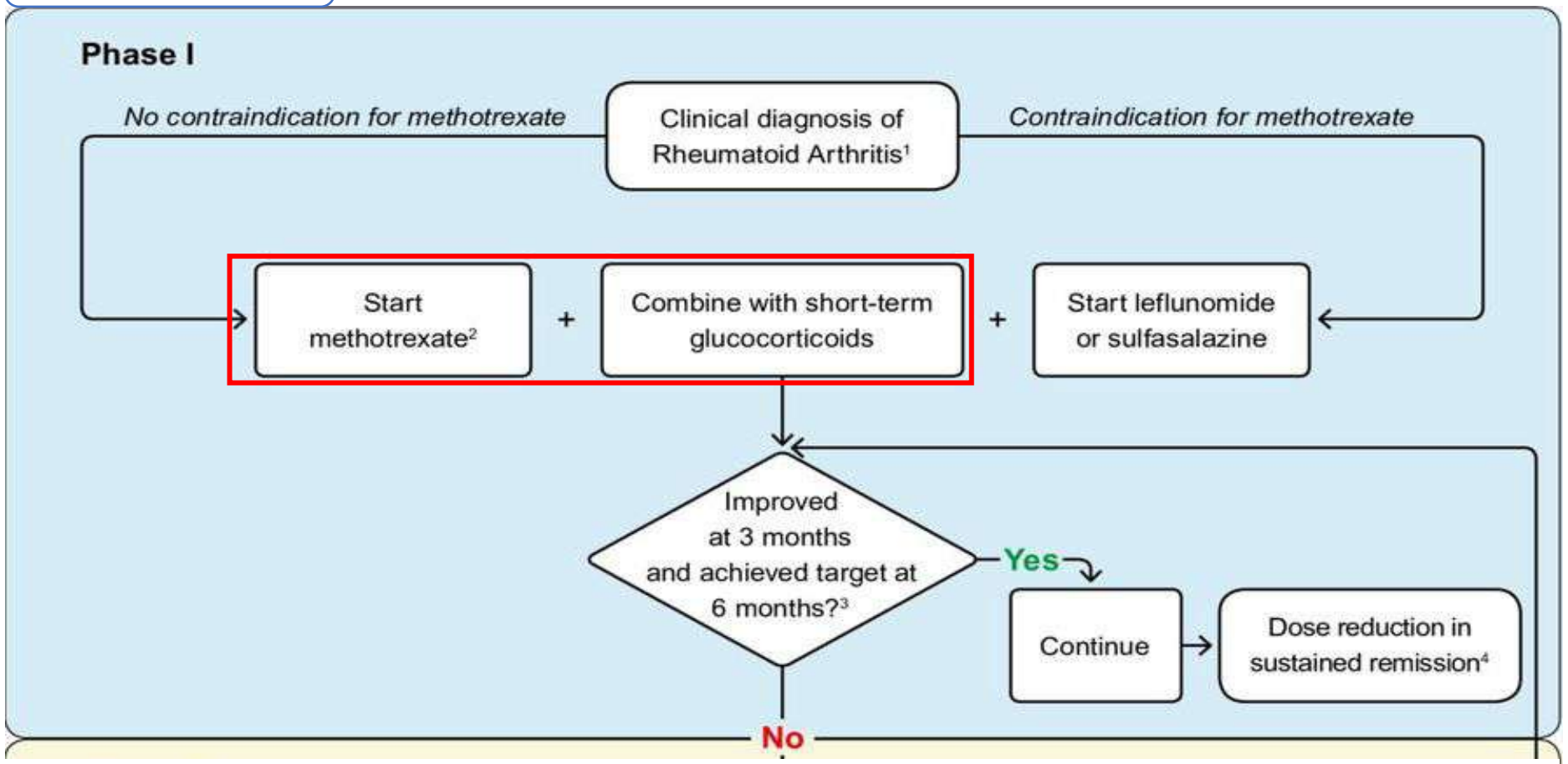
B cell depletion

Rituximab

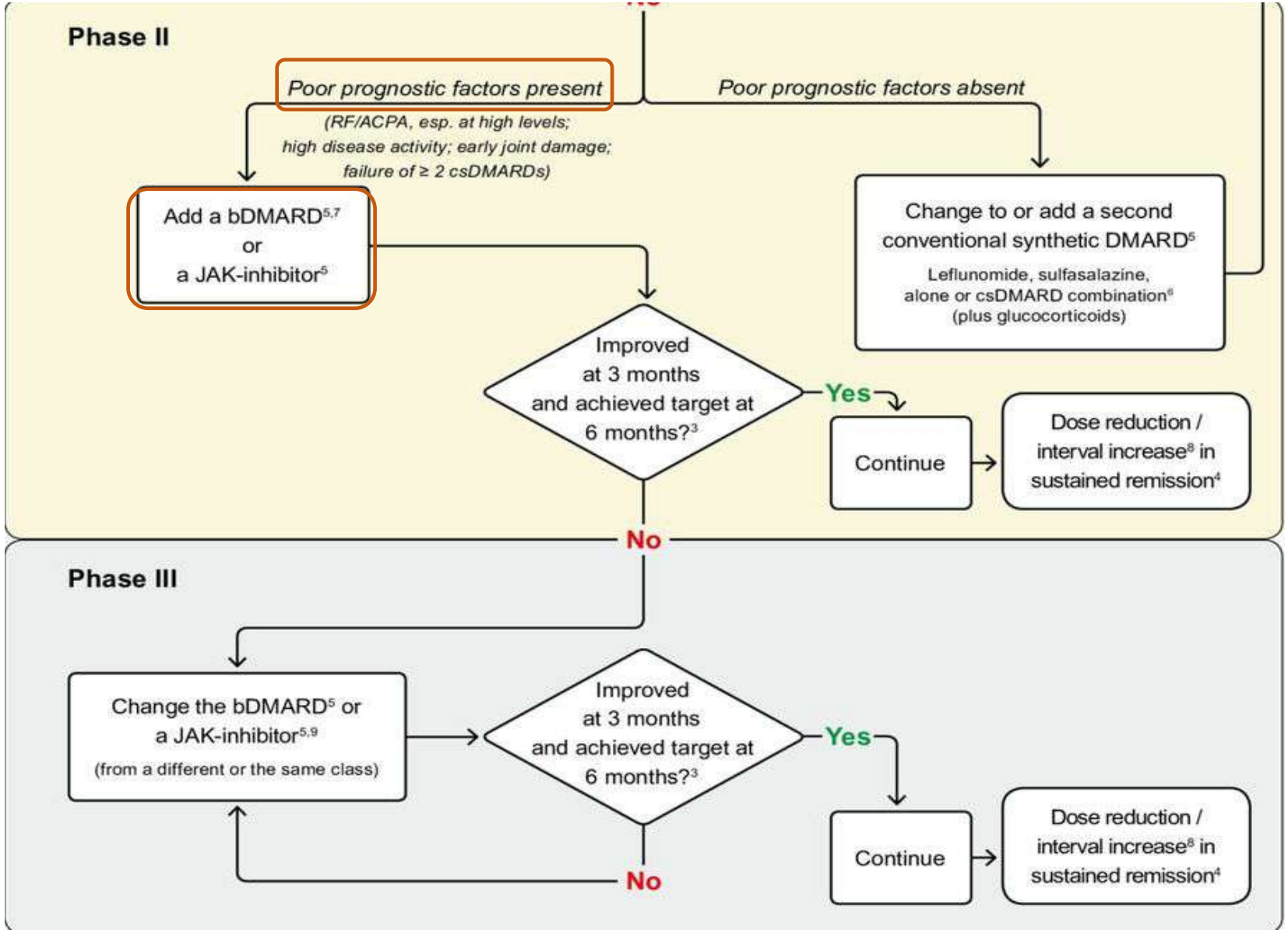
Treatment Algorithm

EULAR 2019 guideline

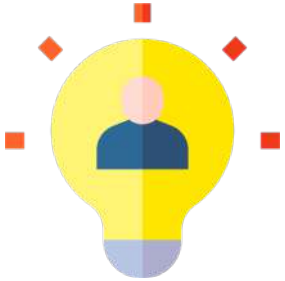
DMARD-naive



Treatment Algorithm



Treatment Algorithm



EULAR 2019 guideline

1. bDMARDs and JAK inhibitor should be **combined with a csDMARD**
2. in patients who cannot use csDMARDs as comedication,
   IL-6 pathway inhibitors or JAK inhibitors may have some advantages compared with other bDMARDs
3. bDMARDs and JAK inhibitor have on average **similar efficacy** and, therefore, no preference can be given to any of these agents for reasons of efficacy
4. Treatment decisions are based on disease activity, **safety issue,** and other patient factors, such as comorbidities.
   (ex：the higher risk of herpes zoster infections on JAK inhibitors)

Treatment

Disease modifying anti rheumatic drug

Synthetic

Conventional

Methotrexate
Sulfasalazine
Leflunomide
Azathioprine
Cyclosporine

Targeted

JAK inhibitor

Tofacitinib
Baricitinib
Upadacitinib

Biological

TNF α inhibitor

Adalimumab
Etanercept
Infliximab
Golimumab
Certolizumab-pegal

IL-6 inhibitor

Tocilizumab

Inhibition of T cell co-stimulation

Abatacept

B cell depletion

Rituximab

Tumor necrosis Factor-α (TNF-α) inhibitors

	Etanercept (Enbrel®)	Infliximab	Adalimumab (Humira®)	Golimumab (Simponi®)	Certolizumab (Cimizia®)
Characteristic	**Fusion protein** of two soluble TNF receptors	Chimeric antibody	Human IG1 antibody	Human antibody	Humanized antibody Fab fragment
Dose& Frequency	50mg SC **QW**	**Loading dose**：3mg/kg IV at 0,2,6 w **Maintenance**：3mg/kg IV Q8W	40mg SC **Q2W**	50 mg SC QM in combination with methotrexate	**Initial dose**：400mg SC **Maintenance**：200mg Q2W or 400mg QM
Monitoring	No routine laboratory monitoring				
Pregnancy	B				

Janus kinase inhibitor (JAK inhibitor)

Drug	Tofacitinib (Xeljanz®)	Upadacitinib (Rinvoq®)	Baricitinib (2mg, 4mg) (Olumiant®)
Mechanism	• JAK1/JAK3 inhibitor (less JAK2/TYk2 inhibitor)	• **Highly selective** JAK 1 inhibitor	• JAK 1/2 inhibitor
Dose& Frequency	• Extended release(ER) ：11 mg QD • **Immediate release(IR) ：5 mg BID**	• 15mg QD	• 4mg QD • 2mg QD in >75y or eGFR Crcl 30~60ml/min
Monitorning	• CBC with differential, creatinine, LFTs (transaminases, albumin, bilirubin) every month for 3 months, then every 3 months; **lipids** 6 to 8 weeks after drug start. →Do not initiate patients with an **absolute lymphocyte count** <500 cells/mm3, **ANC** <1,000 cells/mm3, or **Hb** <8 g/dL		
Pregnancy	C		

Similarities and Differences Among adverse events

JAK inhibitors against TNF α inhibitors

JAK inhibitors

- **Tofacitinib**((10mg/day)
- **Baricitinib**(2mg/day)
- **Upadacitinib**(15mg/day)

TNF α inhibitor

- **Adalimumab** (40mg/q2w)
- **Etanercept** (50mg/q2w)
- **Infliximab** (3-10 mg/kg q2m)
- **Golimumab** (50mg/q1m)
- **Certolizumab-pegal** (200mg/q2w)

Selected Similar adverse events

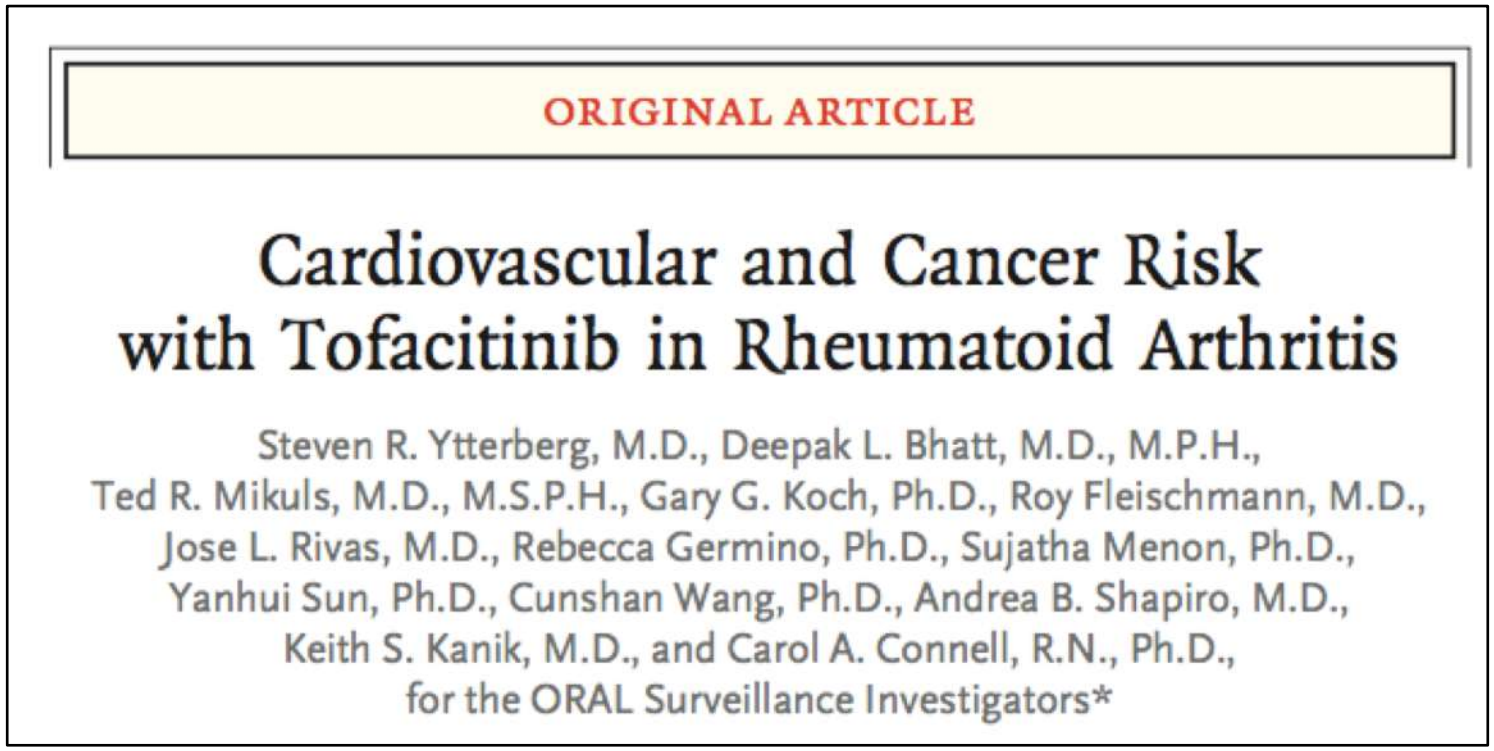
- **Infection(ex：hepatitis B, hepatitis C)**
- **Reactivation of tuberculosis**
- **the risk of malignancy**
- **Cytopenias(including anemias)**

Selected different adverse events

- reactivation of **herpes zoster**
- risk for **dyslipidemia**
  may be risk for other
  cardiovascular events(MACE)

- **exacerbation of heart failure (X：NYHA Fc III/IV)**
- **exacerbation of multiple sclerosis**
- **Hepatoxicity**

Clinical trial



ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

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Keith S. Kanik, M.D., and Carol A. Connell, R.N., Ph.D.,
for the ORAL Surveillance Investigators*

N Engl J Med 2022; 386:316-326
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January 27, 2022

Study objective & Design

Study objective

P **Patient**	Patients with active rheumatoid arthritis despite methotrexate treatment who were **50 years of age or older** and had **at least one additional cardiovascular risk factor.**
I **Intervention**	Tofacitinib at a dose of 5mg , 10mg twice daily.
C **Comparison**	TNF α inhibitor(Adalimumab 40mg SC Q2W or Etanercept 50mg SC QW)
O **Outcome**	**Safety：Major adverse cardiovascular events (MACE) and cancers events** Efficacy：the change of SDAI score

Study design

- Phase 3b/4 **randomized**, parallel arm, **open-label, noninferiority, safety endpoint** study

Patients-Inclusion criteria

Enrolled patients with

1. aged **≥50 years**
2. Active, moderate to severe, rheumatoid arthritis

   (≥ 6 greater on the 2010 ACR/EULAR classification criteria)
3. **Had taken methotrexate continuously** for ≥4 months prior to the screening visit
4. At least one additional **cardiovascular risk factor**
   - current cigarette smoker
   - hypertension
   - high-density lipoprotein cholesterol level of <40 mg per deciliter
   - diabetes mellitus
   - family history of premature coronary heart disease

Patients-Exclusion criteria

Key exclusion criteria

- **Current or previous cancer, except adequately treated non-melanoma skin cancer.**

- **Previously used tofacitinib**
- were being treated with biologic or nonbiologic disease-modifying antirheumatic drugs (DMARDs) other than **methotrexate** or antimalarials (**hydroxychloroquine**)
- **Pregnant females**, breastfeeding females
- Patients who had any of the following **infections**
  - Any infection requiring hospitalization
  - Screened for human immunodeficiency virus (**HIV**) ,**hepatitis B virus infection** **hepatitis C virus infection**
  - Current active **tuberculosis** infection or prior active or latent tuberculosis
- Patients who had **Class III or Class IV heart failure** according to NHYA

Study procedures

Screening From March 2014 through July 2020

- Eligible patients
- Background methotrexate was continued

Randomization in a 1:1:1 ratio

- Tofacitinib 5mg BID PO
- Tofacitinib 10mg BID PO
  - ***Reduced to 5mg BID**
- TNF α inhibitor
  Adalimumab 40mg SC Q2W
  or Etanercept 50mg SC QW

- * In **February 2019**, the tofacitinib dose of **10mg BID was reduced to 5 mg BID** after the data and safety monitoring board noted a **higher frequency of pulmonary embolism**.

- Patients could discontinue the trial drug for **less than 2 months** for safety issue.
- All the patients, including those who permanently discontinued the trial drug, were asked to continue to participate in the trial through its completion

Outcomes assessment

Co-primary end points

1. **Adjudicated MACE**
   - ➢ death from cardiovascular causes
   - ➢ non-fetal myocardial infarction
   - ➢ nonfatal stroke
2. **Cancers (excluding nonmelanoma skin cancer.)**

→

- acute myocardial infarction (MI)
- heart failure
- stroke
- cardiovascular hemorrhage
- other cardiovascular causes: peripheral artery disease.

Secondary end points

- Safety：**Adverse events of special interest**

• Cardiovascular events	• Malignancy events	• Opportunistic infections
• Hepatic events	• Gastrointestinal perforation events	

- Efficacy：
  - change of the **Simplified Disease Activity Index(SDAI) score.** and the **Health Assessment Questionnaire-Disability Index (HAQ-DI) score**.

Statistical analysis

Sample size calculated

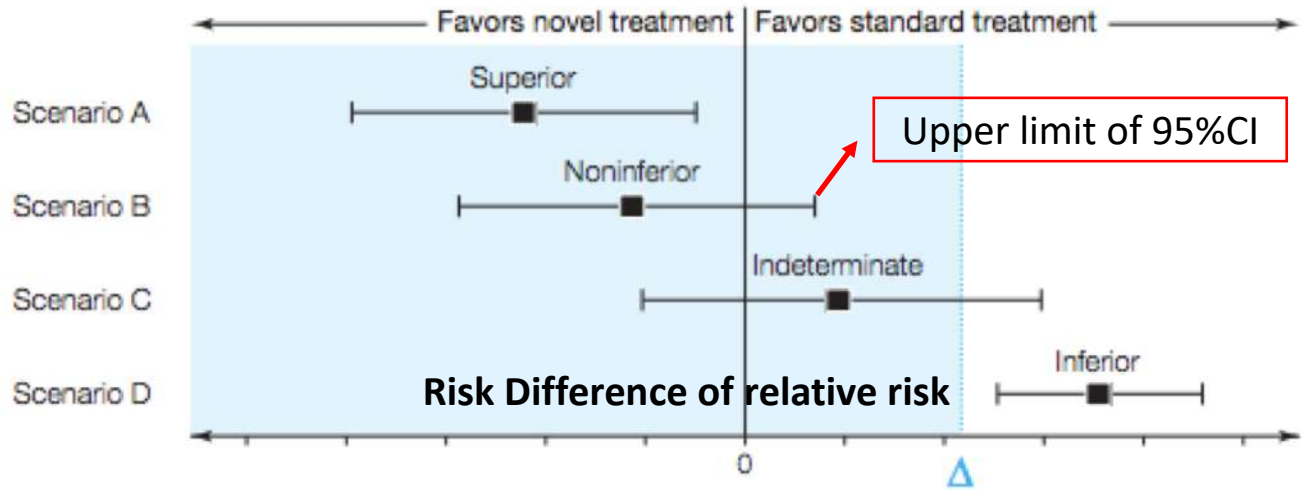
- Calculated that approximately 4000 patients,
  would have 80% power and 90% power to detect a hazard ratio for MACE and Cancers.
- Assuming that the rates were 1.0 and 1.1 events per 100 patient-years
  The estimated trial duration was 5 years.

Hazard ratio

1. Assuming that the true HR rate is 1.0 , with 95% confidence interval

2. **Noninferiority** would be shown

Crude incidence rates



1. Each Tofacitinib vs TNF inhibitor — margin：1.8
2. Tofacitinib 10mgvs Tofacitinib 5mg — margin：2.0

Statistical analysis

Per-protocol analysis

- included all randomized patients from the **safety analysis set**
  with no important protocol deviations that could impact the analysis

Safety analysis set

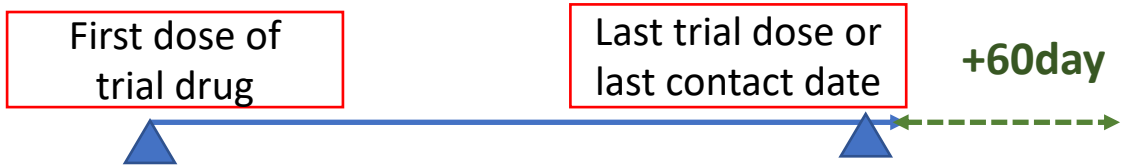
- all subjects who were **randomized** in the study and received
  at least one dose of the randomized investigational drug (tofacitinib or TNFi)

protocol deviation

- Entry into the study by any subject
  who does not meet the study inclusion or exclusion criteria
- failure to take any study medication

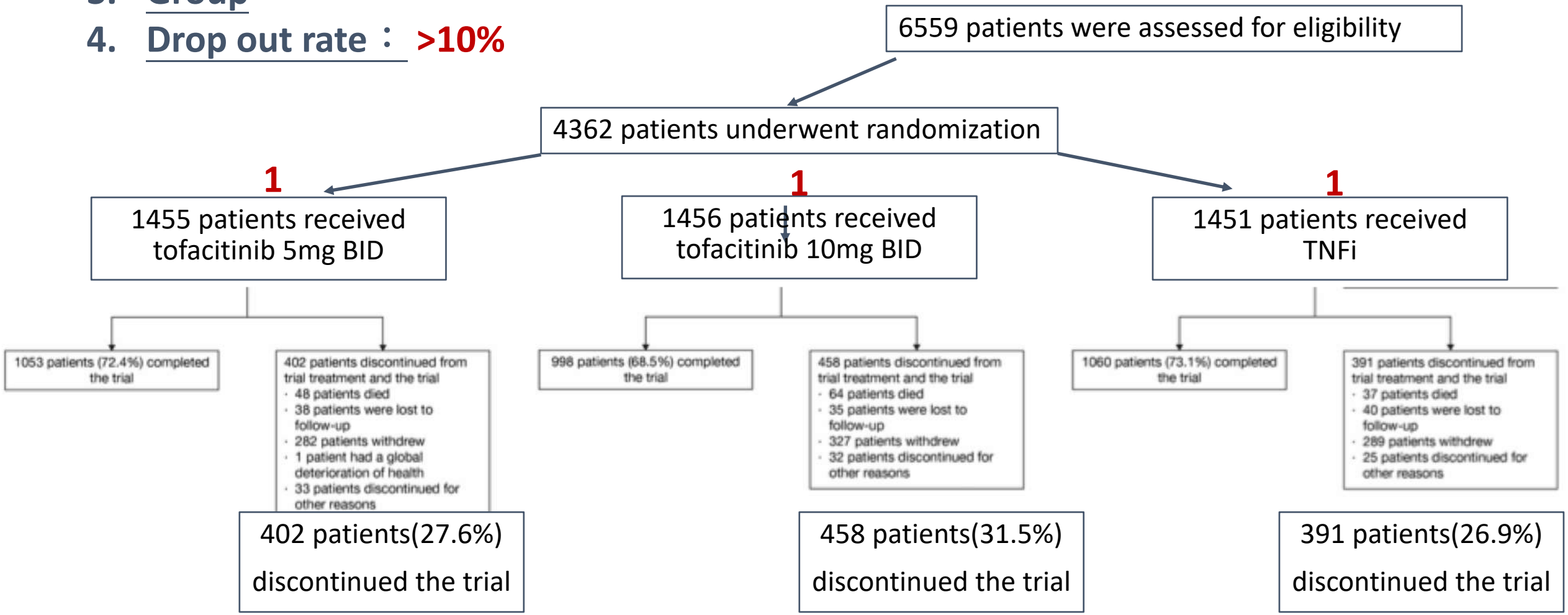
Censoring time

- MACE：60 day on-treatment-time
- Cancer：Total time



Results_Flow of participants

1. **Study period**：From March 2014 through July 2020
2. **Oral surveillance trial**
3. **Group**
4. **Drop out rate**： **>10%**



Results_Flow of participants

1. **Study period**：
   From March 2014 through July 2020
2. **Patient-years of exposure to last trial**
3. **Duration of treatment months**

Table S1. Patient-Years of Exposure and Duration of Treatment (Safety Analysis Set)

	Tofacitinib 5 mg BID (N=1455)	Tofacitinib 10 mg BID* (N=1456)	All tofacitinib doses (N=2911)	TNFi (N=1451)
Patient-years of exposure to last trial treatment†	5073.49	4773.41	9846.89	4940.72
Patient-years of exposure to trial end‡	5551.04	5371.26	10922.31	5526.08
Duration of treatment, months§				
Mean (SD)	41.14 (17.48)	38.53 (18.76)	39.84 (18.17)	40.24 (18.04)
Median (range)	44.68 (0.03–69.82)	42.84 (0.03–71.69)	43.89 (0.03–71.69)	43.96 (0.03–71.13)

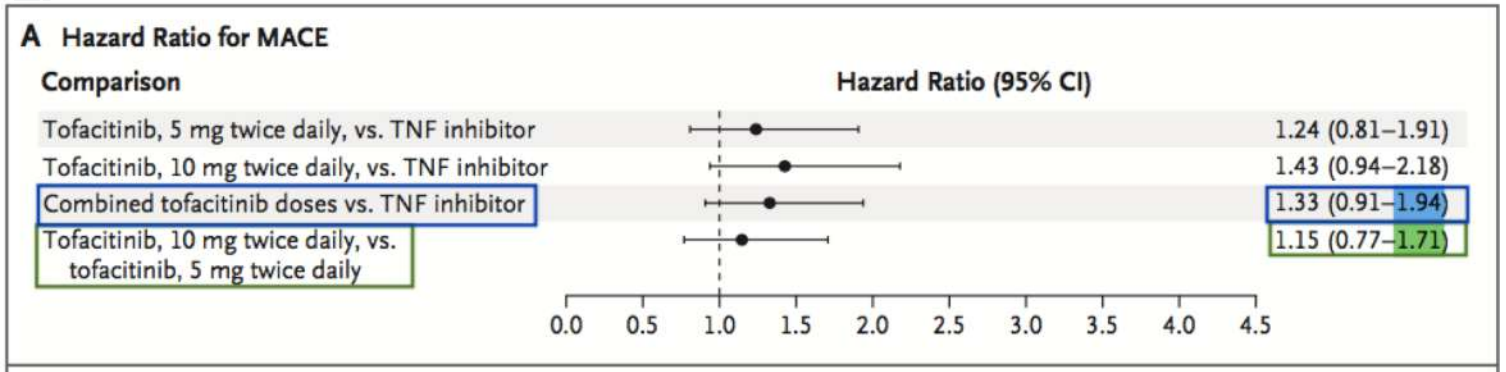
Results-Baseline characteristic

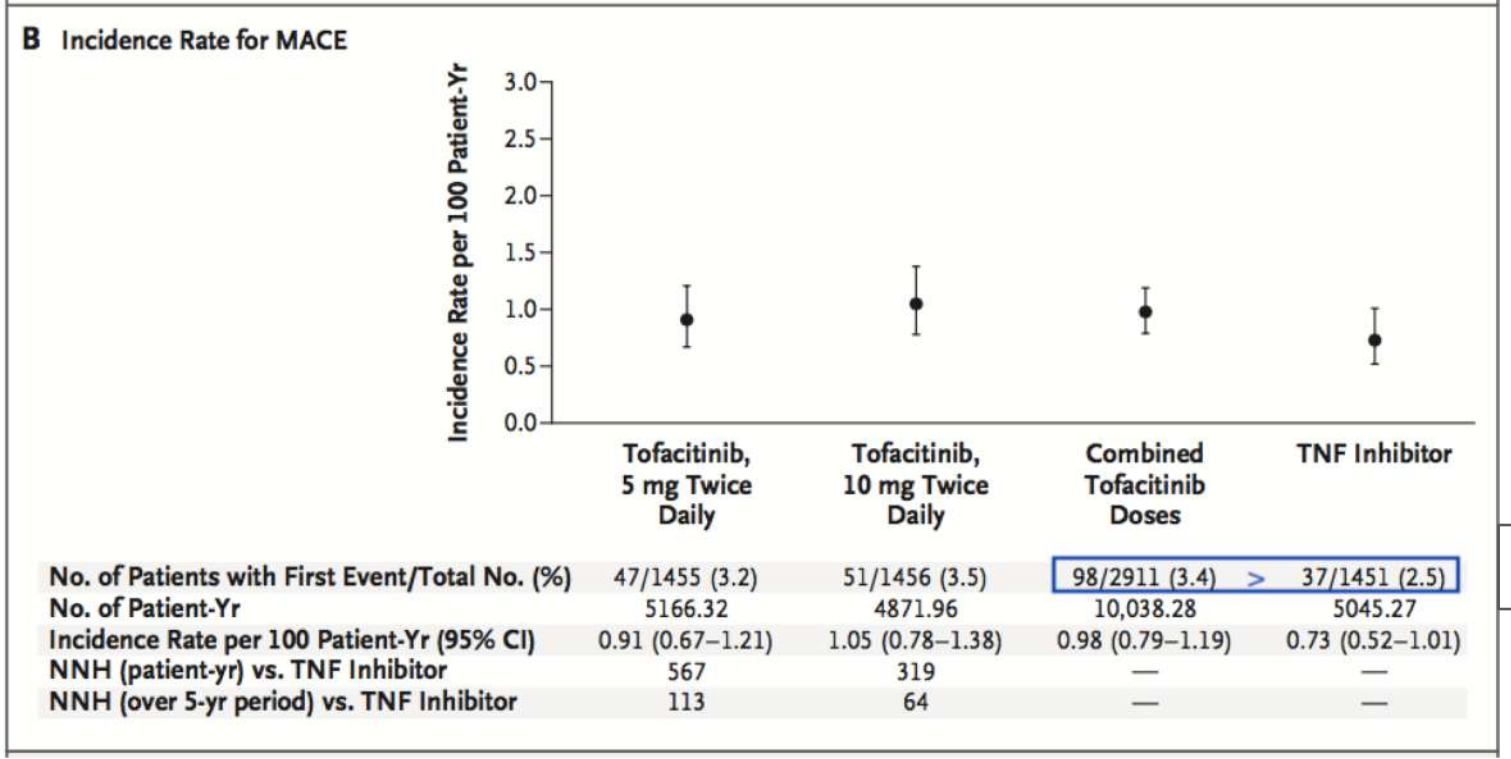
Characteristic	Tofacitinib, 5 mg Twice Daily (N=1455)	Tofacitinib, 10 mg Twice Daily (N=1456)†	TNF Inhibitor (N=1451)	Total (N=4362)
Age				
Mean — yr	60.8±6.8	61.4±7.1	61.3±7.5	61.2±7.1
≥65 yr — no. (%)	413 (28.4)	478 (32.8)	462 (31.8)	1353 (31.0)
Female sex — no. (%)	1169 (80.3)	1124 (77.2)	1117 (77.0)	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)
Duration of RA (years),mean (SD)	10.4(8.8)	10.2(9.0)	10.6(9.3)	**10.4(9.1)**

The baseline characteristic of the patients were similar

Results-main result

Adjudicated MACE (Safety Analysis Population, 60-Day On-Treatment time)





	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	—	—

- **Median follow-up**：4 years
- **Hazard ratio**：**upper boundary of 95%CI**
- **>1.8**：**Noninferiority was not shown**
- **<2.0**：**Noninferiority was shown**

the combined tofacitinib doses are higher

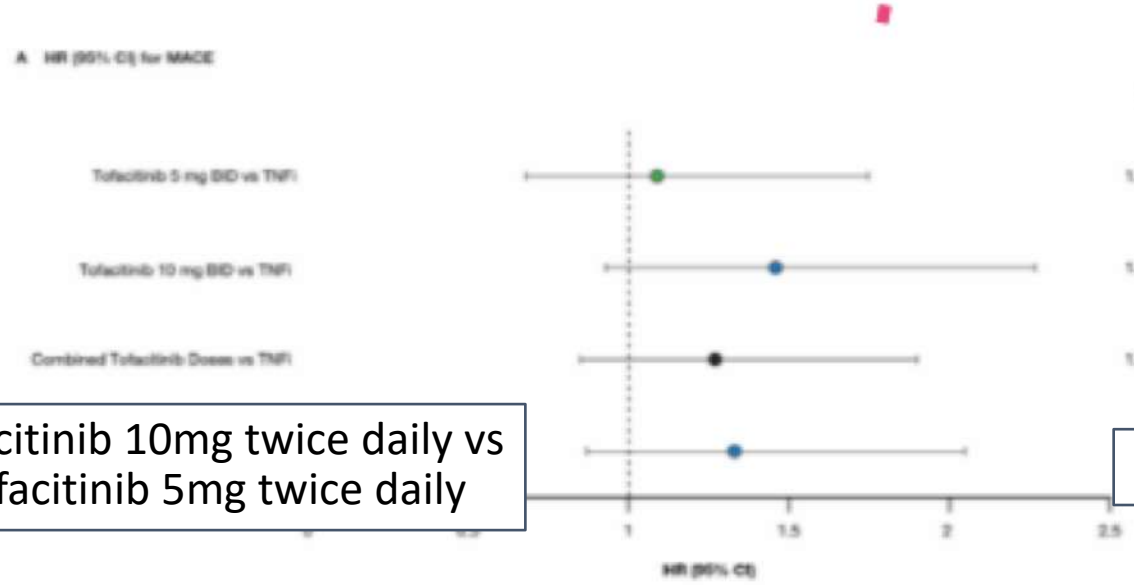
Results-main result

Adjudicated MACE

Sensitivity analysis

(Safety Analysis Population, 60-Day On-Treatment Time Data Cutoff April 22, 2019)

* In **February 2019**, the tofacitinib dose of **10mg BID was reduced to 5 mg BID** after the data and safety monitoring board noted a **higher frequency of pulmonary embolism**.



Tofacitinib 10mg twice daily vs Tofacitinib 5mg twice daily

1.33 (0.87 to **2.05**)

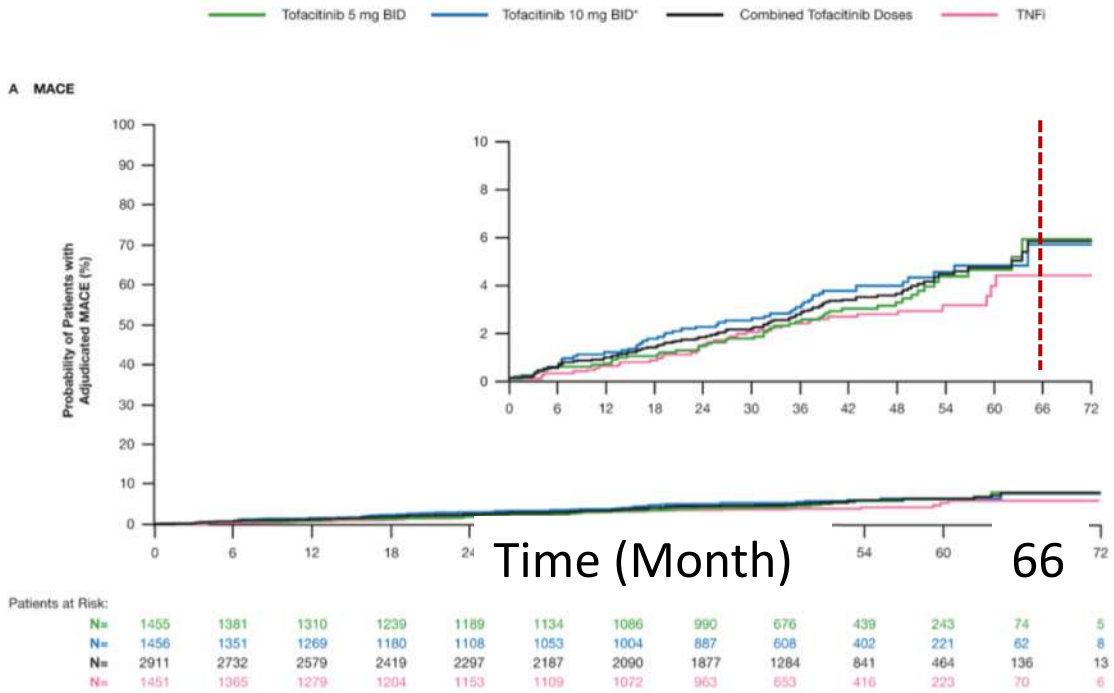
>2.0：Noninferiority was not shown

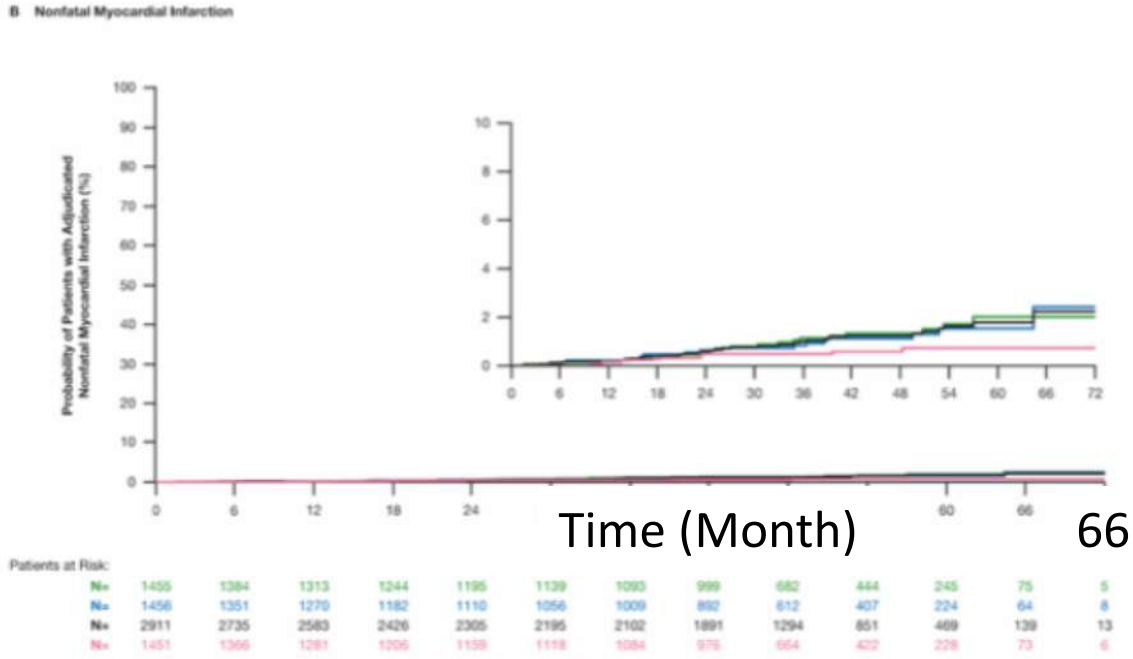
Results-cumulative probability

(a)Adjudicated MACE

(b)Nonfatal myocardial infacrtion

- **Over a period of 5.5 years** ----------→



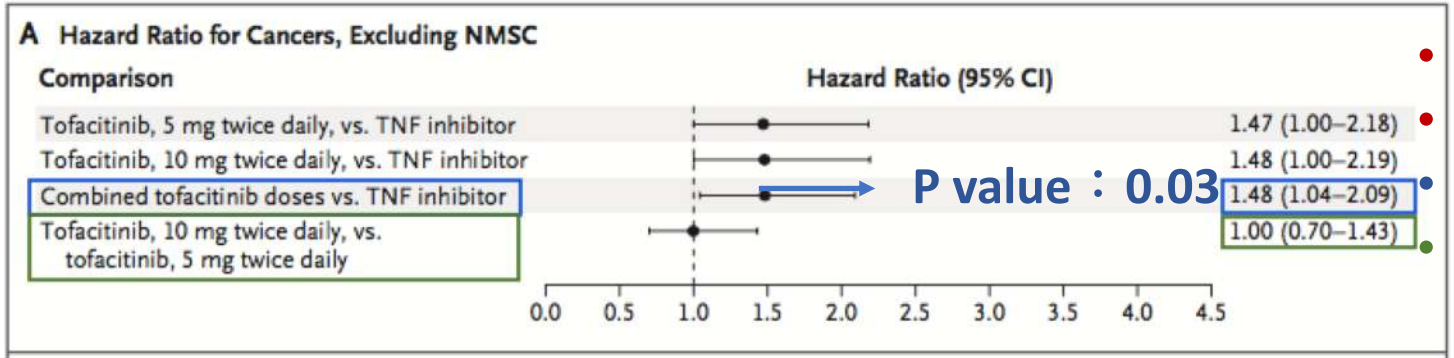


- **Combined Tofacitinib dose：5.8%**
- **TNF inhibitor dose：4.3%**

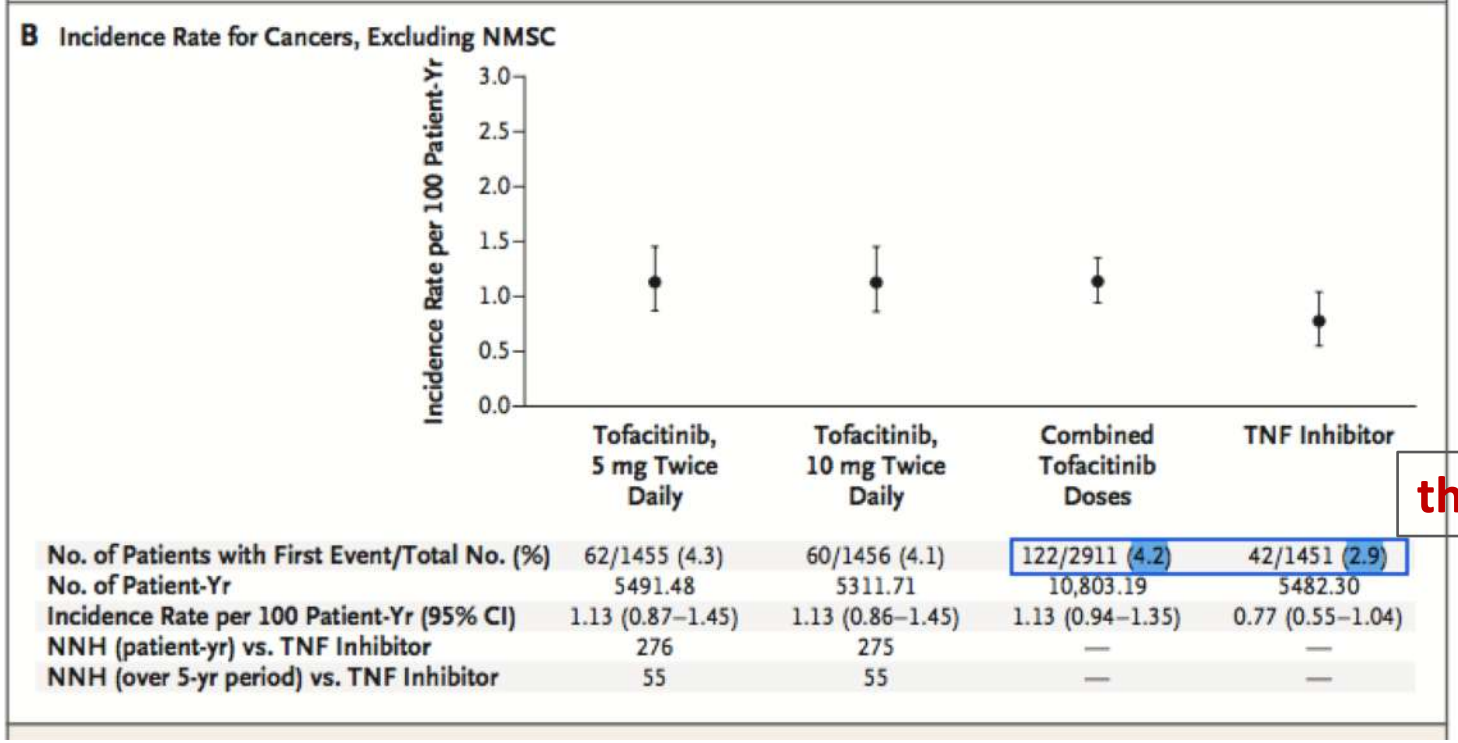
- **Combined Tofacitinib dose：2.2%**
- **TNF inhibitor dose：0.7%**

Results-main result

Adjudicated cancers, Excluding NMSC (Safety Analysis Population, Total-time analysis)



P value：0.03



	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	—	—

- **Median follow-up**：4 years
- **Hazard ratio**：**upper boundary of 95%CI**
- **>1.8**：**Noninferiority was not shown**
- **<2.0**：**Noninferiority was shown**

the combined tofacitinib doses are higher

Results-main result

Adjudicated cancers, Excluding NMSC

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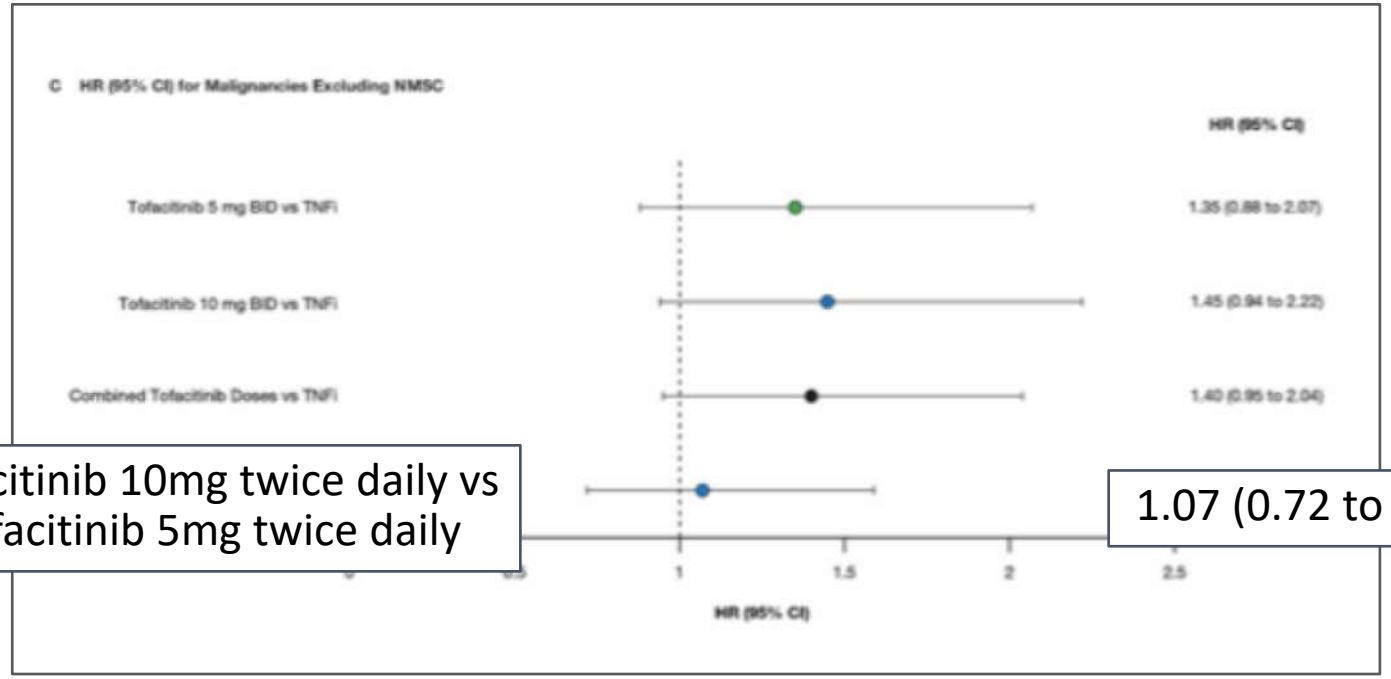
(Safety Analysis Population, Total-time analysis Data Cutoff April 22, 2019)

* In **February 2019**, the tofacitinib dose of **10mg BID was reduced to 5 mg BID** after the data and safety monitoring board noted a **higher frequency of pulmonary embolism**.



Tofacitinib 10mg twice daily vs Tofacitinib 5mg twice daily

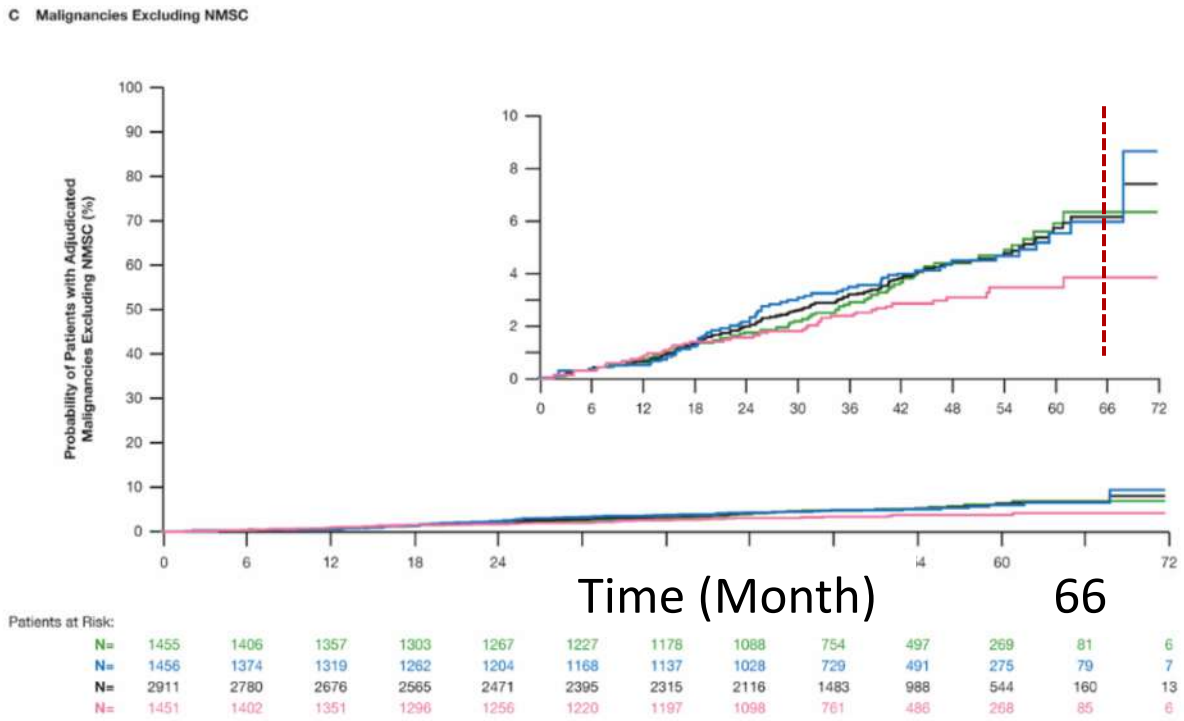
1.07 (0.72 to **1.59**)

<2.0：Noninferiority was shown

Results-cumulative probability

(C) Adjudicated cancers, Excluding NMSC

- **Over a period of 5.5 years** ----------→



- **Combined Tofacitinib dose：6.1%**
- **TNF inhibitor dose：3.8%**

Results – key secondary end points

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)

most common： pneumonia

owing to herpes zoster infection

Results – key secondary end points

Adverse events(Safety Analysis Population, 28-Day on-treatment time)

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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

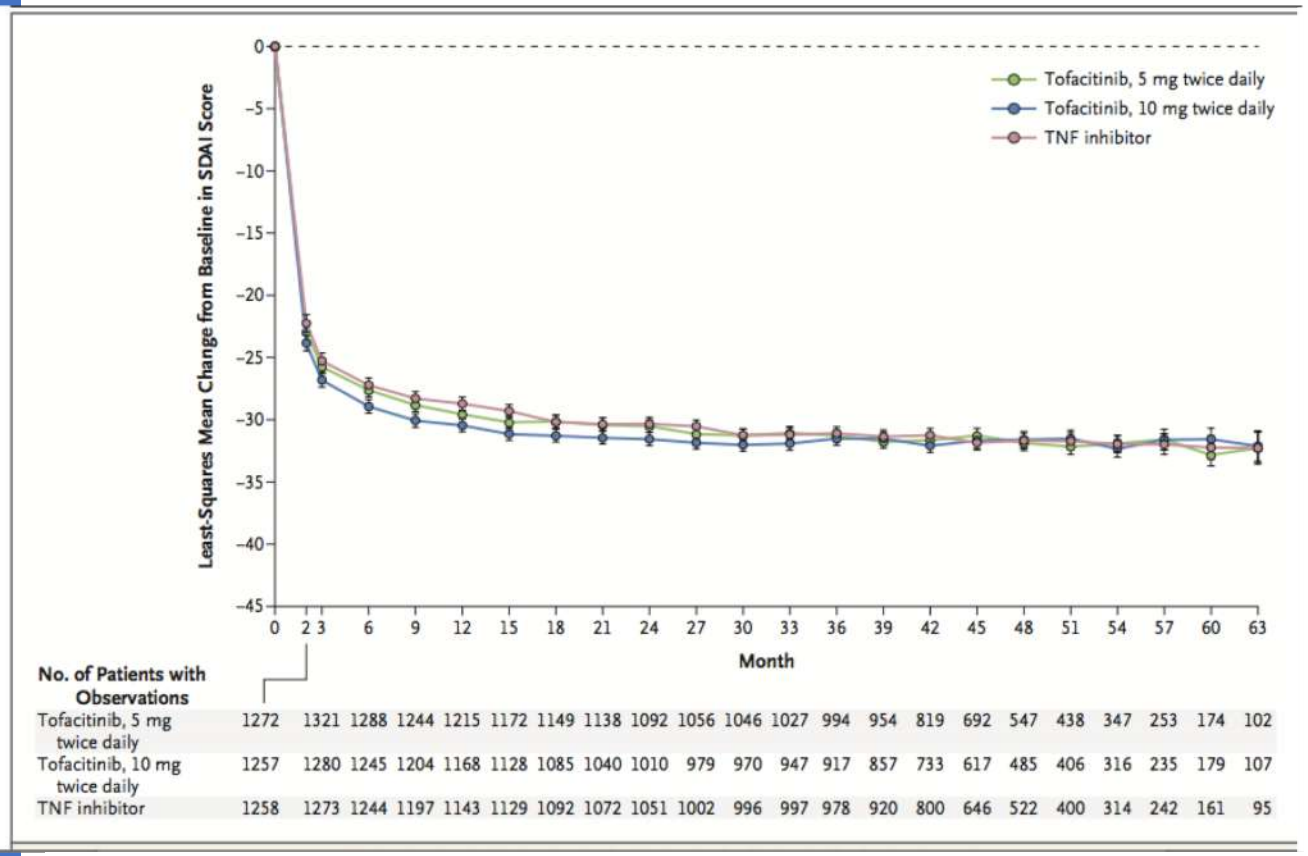
Tofacitinib 10mg BID were higher

- **Serious infection,**
- **Opportunistic infection**
- **Hepatic events**
- **Pulmonary embolism**

  Venous thromboembolism
- **Death**

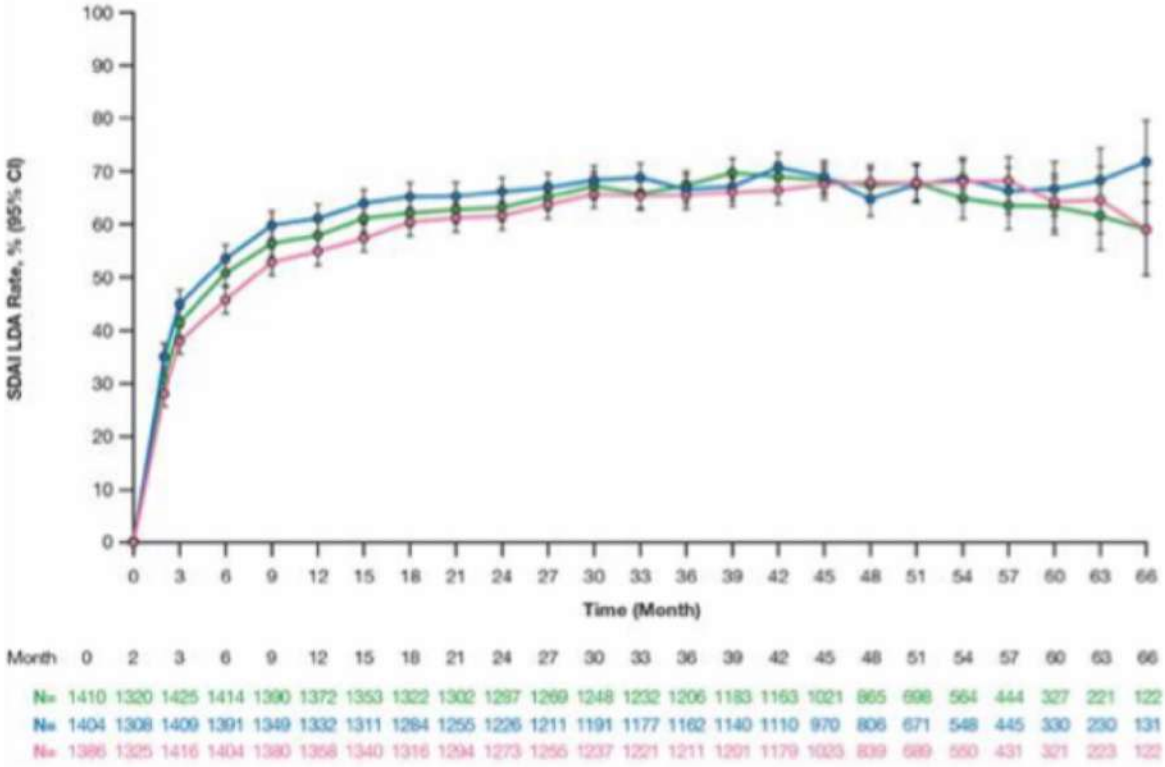
Efficacy endpoints

Change from Baseline in SDAI Score(Full Analysis Population, On-Treatment Time)



No. of Patients with Observations																						
Tofacitinib, 5 mg twice daily	1272	1321	1288	1244	1215	1172	1149	1138	1092	1056	1046	1027	994	954	819	692	547	438	347	253	174	102
Tofacitinib, 10 mg twice daily	1257	1280	1245	1204	1168	1128	1085	1040	1010	979	970	947	917	857	733	617	485	406	316	235	179	107
TNF inhibitor	1258	1273	1244	1197	1143	1129	1092	1072	1051	1002	996	997	978	920	800	646	522	400	314	242	161	95

SDAI LDA Rate



Month	0	2	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66
N=	1410	1320	1425	1414	1390	1372	1353	1322	1302	1297	1269	1248	1232	1206	1183	1163	1021	865	698	564	444	327	221	122
N=	1404	1308	1409	1391	1349	1332	1311	1284	1255	1226	1211	1191	1177	1162	1140	1110	970	806	671	548	445	330	230	131
N=	1386	1325	1416	1404	1380	1358	1340	1316	1294	1273	1256	1237	1221	1211	1201	1179	1023	839	689	550	431	321	223	122

- **Efficacy was similar across treatments,**
  with decreases (improvements) in the SDAI score and increases in the incidence of SDAI-defined low disease activity

03 Discussion

Strength and limitation

Strengths：

- Randomized
- Large patient cohort followed for up to 6 years
- Up to 50% of the patients across treatments were followed for at least **48 months**
- Included patients with rheumatoid arthritis
  who are 50 years of age or older and have at least one additional cardiovascular risk factor.

Limitation：

- Open label design
- High rates of discontinuation of trial treatment
- lack of other control groups
- The use of adalimumab in North American
  and etanercept in the rest of the world
  →It`s also unclear whether the relative risk differed between adalimumab and etanercept.

04 Appraisal

CASP RCT Checklist

Section A：
Is the basic study design valid for a randomized controlled trial?

1 Did the study address a clearly focused research question?

Yes　No　Can`t tell

2 Was the assignment of participants to interventions randomized

Yes　No　Can`t tell

3 Were all the participants who entered the study accounted for at its conclusion

Yes　No　Can`t tell

1

- PICO

Patient	Patients with active rheumatoid arthritis who had **at least one additional cardiovascular risk factor**.
Intervention	Tofacitinib 5mg or 10 mg twice daily.
Comparison	TNF inhibitor
Outcome	Safety of MACE and cancers

2

- Randomized in a 1:1:1 ratio with the use IVRS (an automated web/telephone randomization system provided by the sponsor)

3

- Per-protocol set

Section B：
Was the study methodologically sound

4 Were the participants/ investigators /people analyzing outcome ‘blind’?

Yes No Can`t tell

5 Were the study groups similar at the start of the randomized controlled trial?

Yes No Can`t tell

6 Did each study group receive the same level of care (that is, were they treated equally)?

Yes No Can`t tell

4

- Open label trial.

5

- Table 1

6

- Methotrexate, and hydroxychloroquine were the only concomitant conventional synthetic DMARDs (csDMARDs) allowed at trial entry

Table 1

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 (14.8)	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)
Duration of RA (years),mean (SD)	10.4(8.8)	10.2(9.0)	10.6(9.3)	**10.4(9.1)**

- The demographic and clinical characteristics of the patients
- at baseline were generally similar across the group.

Section B：
Was the study methodologically sound

4 Were the participants/ investigators /people analyzing outcome ‘blind’?

Yes　No　Can`t tell

5 Were the study groups similar at the start of the randomized controlled trial?

Yes　No　Can`t tell

6 Did each study group receive the same level of care (that is, were they treated equally)?

Yes　No　Can`t tell

6

trial entry

- Methotrexate, and hydroxychloroquine were the only concomitant conventional synthetic DMARDs (csDMARDs)

Other treatment

	Tofacitinib 5 mg BID (N=1455)	Tofacitinib 10 mg BID* (N=1456)	TNFi (N=1451)
Oral contraceptives or HRT	51 (3.5)	41 (2.8)	45 (3.1)
Corticosteroid	836 (57.5)	829 (56.9)	830 (57.2)
Methotrexate	1453 (99.9)	1456 (100.0)	1451 (100.0)
Aspirin	212 (14.6)	231 (15.9)	224 (15.4)
Anticoagulants	47 (3.2)	66 (4.5)	62 (4.3)
Antidepressants	218 (15.0)	208 (14.3)	223 (15.4)
	17.4 (4.4) [21]	17.4 (4.1) [33]	17.3 (4.3) [16]

Section C：
What are the results?

7 Were the effects of intervention reported comprehensively

Yes　No　Can`t tell

8 Was the precision of the estimate of the intervention of treatment effected reported

Yes　No　Can`t tell

9 Do the benefits of the experimental intervention outweight the harms and costs

Yes　No　Can`t tell

7 **power**：103 MACE and 138 cancers to achieve **80% and 90% power**

- **Co-primary outcome** were MACE, cancers

➢ **Hazard ratio**
if the **upper limit of the two-sided 95%CI** was less **1.8**

8

	• **95% CI**	• **P-value**
MACE	1.33(0.91-**1.94**)	0.14
Cancer	1.48(1.04-**2.09**)	0.03(P<0.05)

➢ **IRs：Crude incidence rates**
(Patients with first events per 100 patient-years)

	• **95% CI**
MACE	0.98(0.79-1.19)
Cancer	0.73(0.52-1.01)

9

- Benefits：similar efficacy
- **Harms：No inferiority was not shown**

Section D：
Will the results help locally?

10 Can the results be applied to the local population

Yes　No　Can`t tell

11 Wound the experimental intervention provide greater value to the people in your care than any of the existing interventions

Yes　No　Can`t tell

10

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- **Geographic regions and race/ethnicity**
  - RA is most common in Australasian, Western Europe, and North American regions
  - highest rates of RA observed have been in Native Americans

Section D：
Will the results help locally?

10 Can the results be applied to the local population

Yes　　No　　Can`t tell

11 Wound the experimental intervention provide greater value to the people in your care than any of the existing interventions

Yes　　No　　Can`t tell

11

- **Noninferiority was not shown**

Tofacitinib 5mg BID versus TNFi		
	• **95% CI**	• **P-value**
MACE	1.24(0.81-**1.91**)	0.33
Cancer	1.47(1.0-**2.18**)	0.05

- An Increased risk of MACE and cancers with tofacitinib than with a TNF inhibitor **in this patient population**
- Lack other control groups

Take home message

JAK inhibitors

Tofacitinib

Baricitinib

Upadacitinib

FDA box warning

- serious cardiovascular-related events (eg, heart attack, stroke)
- cancer (eg, lymphoma, lung cancer)
- thrombosis, and death

Increase risk!

Recommendation

patients

- current or past smokers
- those with other cardiovascular risk factors
- who develop a malignancy

ensure the benefits outweight risk

Thank you for your listening~~~