ORIGINAL ARTICLE

A Phase 2 Trial of Peresolimab for Adults with Rheumatoid Arthritis

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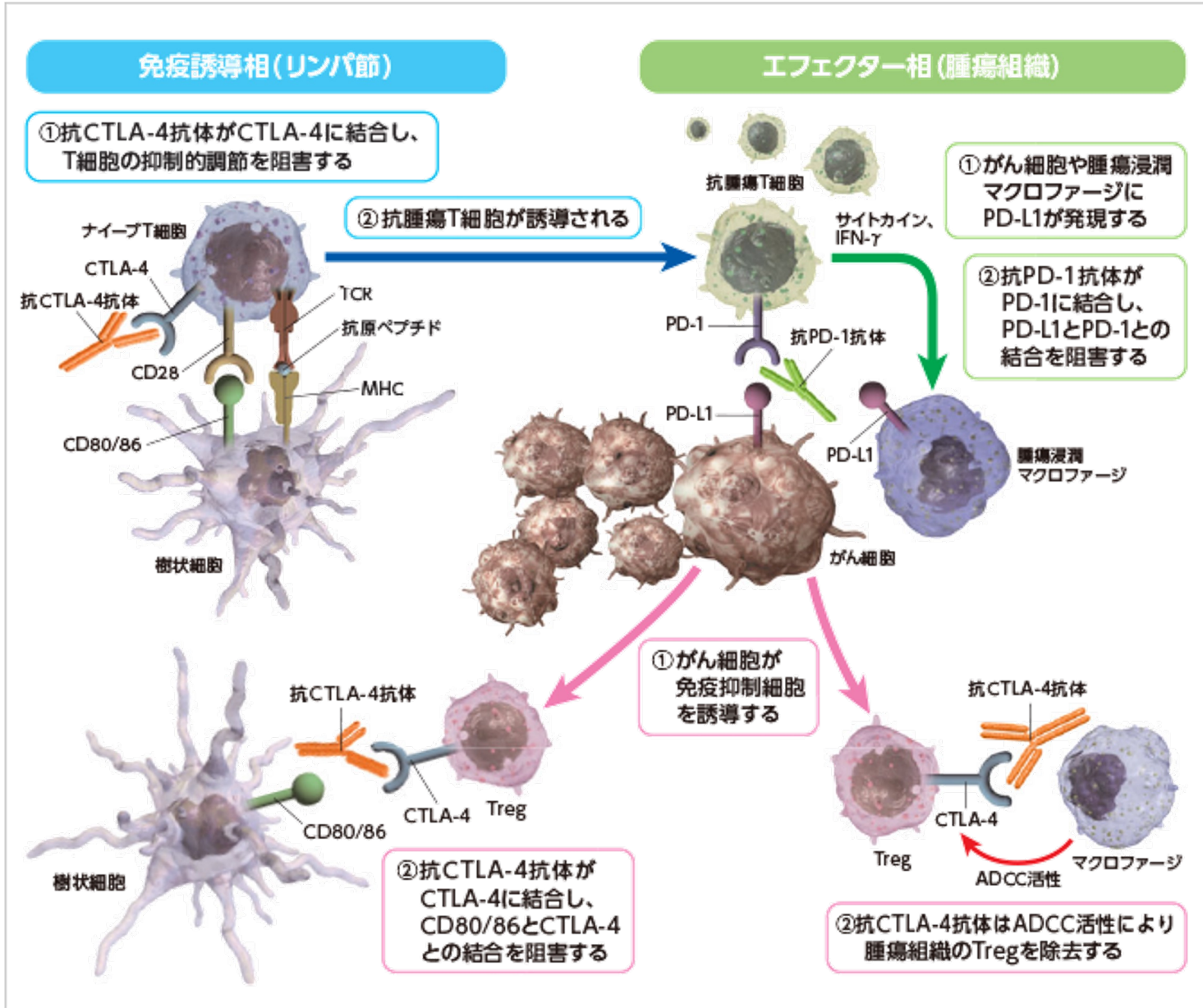
Introduction

- 免疫チェックポイント阻害受容体であるPD-1は末梢性ヘルパーT細胞で多く発現しており，T細胞の活性化を反映していると考えられている
- 滑膜のT細胞ではPD-1発現が亢進しているが，PD-L1とPD-1の結合性が低下することで，免疫応答のダウンレギュレーションが不十分になり，RA発症に関与すると言われている
- PD-1/PD-L1経路を標的とした免疫療法は阻害薬は，種々のがんに有効である一方，免疫反応に関連する有害事象も報告されている
- ヒト化IgG1モノクローナル抗体であるperesolimabはPD-1に結合・活性化して免疫の恒常性を回復させることが想定される



https://www.immunooncology.jp/medical/visualization/vis_05

PICO

- Patient：
  従来の抗リウマチ薬で効果不十分な中等度～重度の成人RA患者
- Intervention：
  peresolimab 700mg i.v. q4weeks
- Comparison：
  placebo or peresolimab 300mg i.v. q4weeks
- Outcome：
  ①12週後のDAS28-CRPの変化量
  ②12週後のACR20/50/70改善率

Patient

- 2010ACR/EULARの分類基準に合致した18歳以上の症例
- 診断時SJC≧6、TJC≧6で活動性滑膜炎が証明されたRA患者
- 少なくとも1つの従来のDMARDsで治療不十分であった症例

＊2種以上のbDMARDs/tsDMARDsに不応であった症例は除外

- MTX(p.o.≦25mg/週・s.c.≦20mg/週)・HCQ≦400mg/日・SASP≦3000mg/日・NSAIDs・PSL≦10mg/日・LEF≦20mg/日の併用可能

Patient

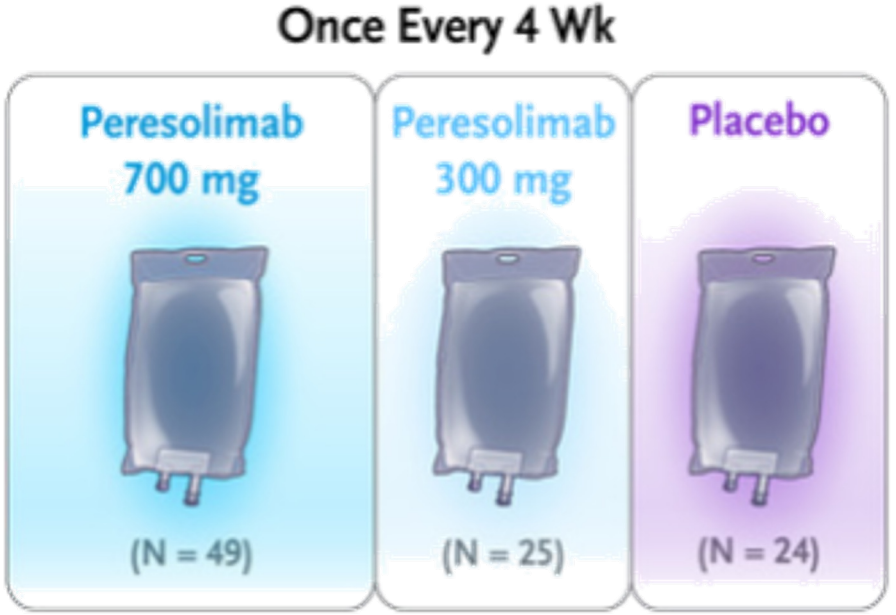
- 女性が8割強
- 年齢51.7±12.6歳
- アジア人は含まず
- RF/ACPA陽性例が9割弱
- 罹病歴10.0±8.0年
- DAS28-CRP5.9±0.8＞4.1

Table 1. Baseline Characteristics.*

Characteristic	Placebo (N=24)	Peresolimab, 300 mg (N=25)	Peresolimab, 700 mg (N=49)
Female sex — no. (%)	19 (79)	20 (80)	43 (88)
Age — yr	55.8±11.1	50.1±15.8	50.5±11.2
Body-mass index†	28.2±4.8	28.2±3.7	29.3±6.8
Race or ethnic group — no. (%)‡			
American Indian or Alaska Native	7 (29)	10 (40)	13 (27)
Black or African American	0	0	2 (4)
White	17 (71)	15 (60)	34 (69)
Seropositivity — no. (%)§			
For anti-CCP antibody or rheumatoid factor	20 (83)	22 (88)	45 (92)
For anti-CCP antibody	19 (79)	22 (88)	42 (86)
For rheumatoid factor	18 (75)	19 (76)	44 (90)
Use of glucocorticoids — no. (%)	14 (58)	15 (60)	30 (61)
Duration of rheumatoid arthritis — yr	10.9±8.4	9.8±8.9	9.7±7.5
DAS28-CRP¶	5.66±0.59	5.91±0.98	6.00±0.87
Tender-joint count among 68 joints — no. of joints	19.0±8.8	22.7±13.7	19.6±8.5
Swollen-joint count among 66 joints — no. of joints	13.7±5.2	18.7±13.3	14.6±5.6
Physician's global assessment of disease activity — mm‖	62.5±16.3	70.2±15.9	67.2±18.4
Patient's global assessment of disease activity — mm‖	69.0±15.8	69.5±15.5	70.8±17.4
Patient's assessment of arthritis pain — mm‖	67.3±18.0	70.4±14.3	72.2±18.1
HAQ-DI score**	1.55±0.56	1.63±0.57	1.66±0.54
High-sensitivity C-reactive protein level — mg/liter††	12.0±12.8	13.3±13.8	16.2±15.0
SF-36‡‡			
Mental component score	50.1±13.0	49.0±9.5	47.1±11.0
Physical component score	32.3±7.0	31.6±7.4	32.5±7.9
Clinical Disease Activity Index score§§	38.3±10.5	43.1±12.8	41.7±13.2
Simplified Disease Activity Index score¶¶	39.4±10.2	44.4±13.4	43.8±13.5
RAMRIS for synovitis‖‖	8.3±4.8	7.7±4.8	8.3±5.3

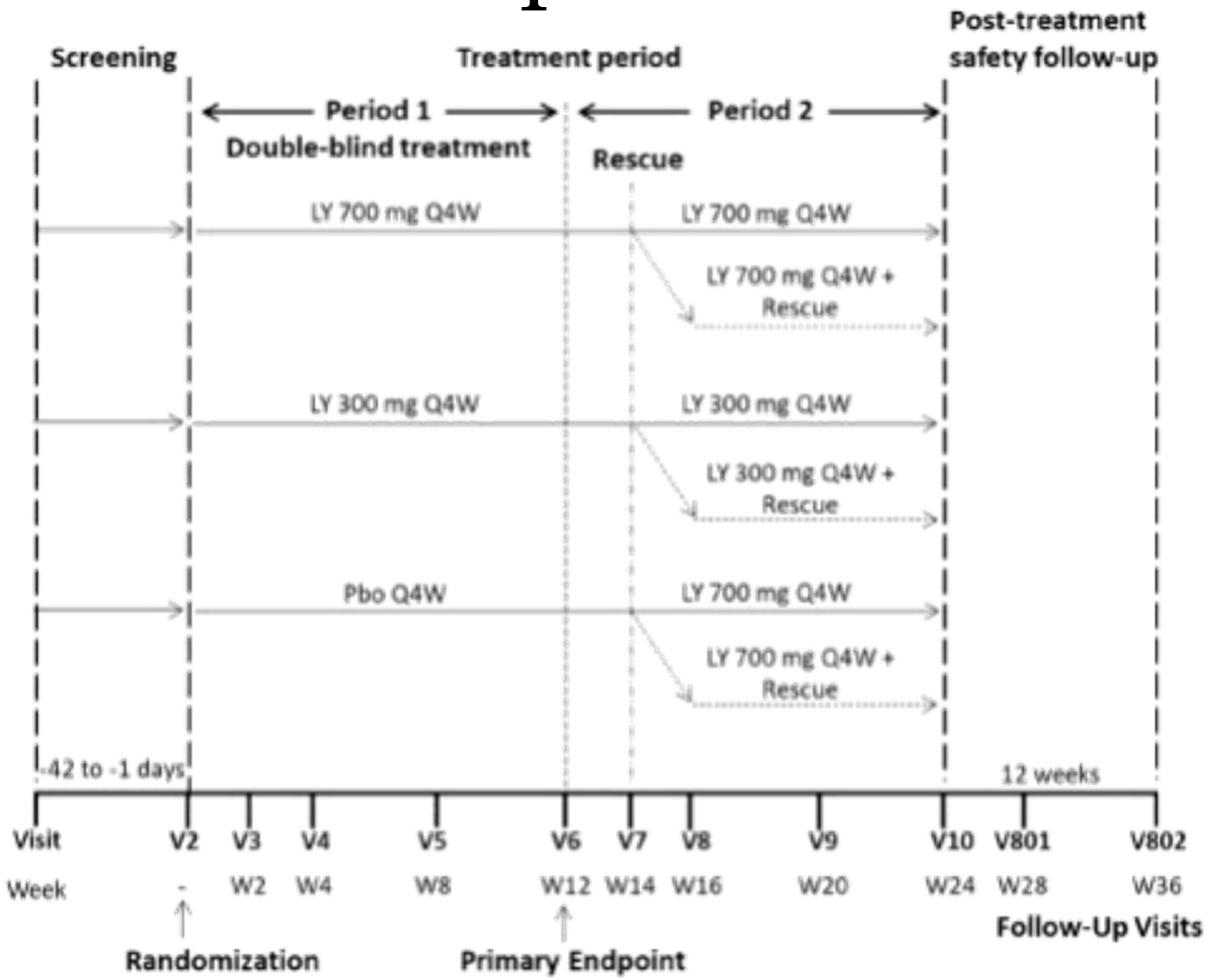
Intervention/Comparison

- double-blind, randomized
  （2:1:1で割り付け）



- 第1期（～12週目）：double-blind期間
- 第2期（～24週目）：14週目に低疾患活動性であるperesolimab群では同量を継続、その他の症例では標準治療へ移行し、36週目までモニター

Intervention/Comparison



Outcome

- DAS28-CRPの12週目のベースラインからの変化量
- ACR20/50/70の12週目の改善率

＊bDMARDs/tsDMARDs使用歴の有無で層別化

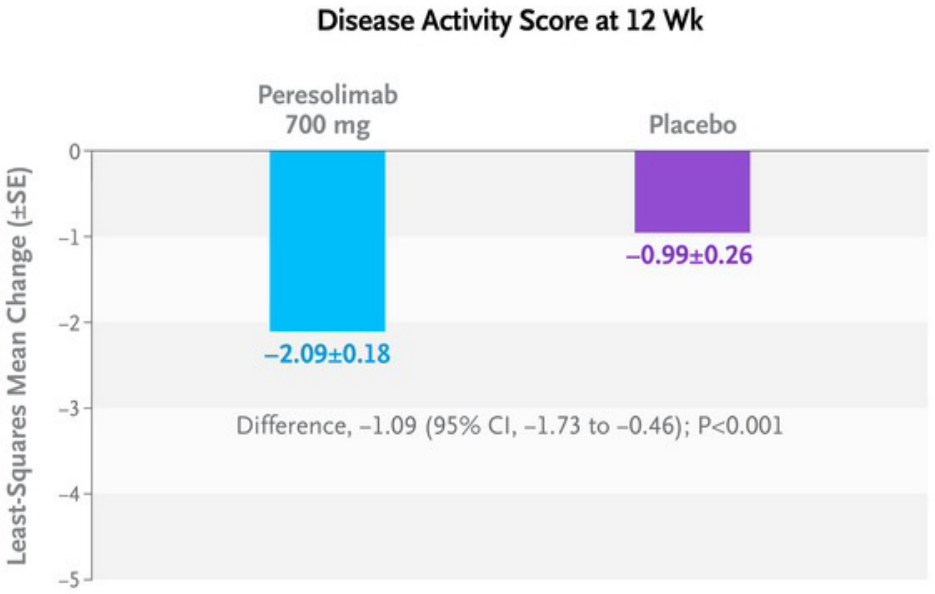
Results

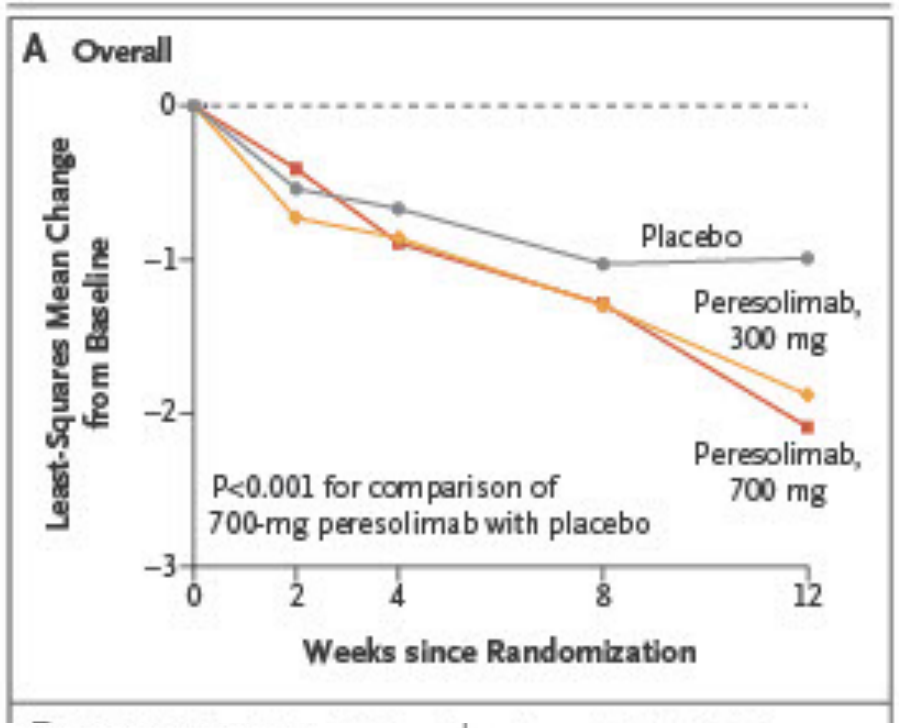
- 12週目のDAS28-CRP変化率はperesolimab 700mg群がplacebo群より有意に大きかった
- ACR20改善率も有意であったが，ACR50/70改善率は有意差なし

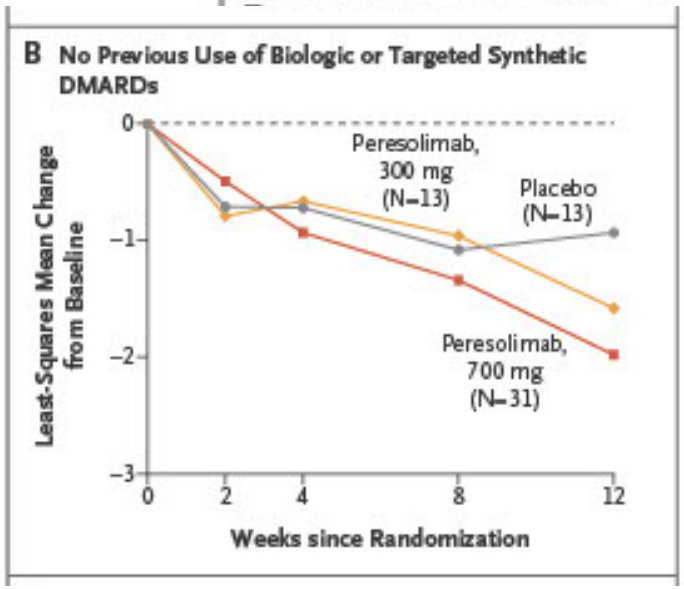
Table 2. Primary and Secondary Efficacy Outcomes at Week 12.*

Outcome	Placebo (N=24)	Peresolimab, 300 mg (N=25)	Peresolimab, 700 mg (N=49)
Primary outcome			
DAS28-CRP			
Change from baseline	−0.99±0.26	−1.88±0.25	−2.09±0.18
Difference in change vs. placebo (95% CI)	—	−0.88 (−1.60 to −0.16)	−1.09 (−1.73 to −0.46)†
Secondary outcomes			
ACR20 response‡			
No. of patients (%)	10 (42)	11 (44)	35 (71)
Least-squares mean difference vs. placebo (95% CI)	—	2.3 (−25.4 to 30.0)	29.8 (6.3 to 53.2)
ACR50 response‡			
No. of patients (%)	5 (21)	5 (20)	19 (39)
Least-squares mean difference vs. placebo (95% CI)	—	−0.8 (−23.4 to 21.7)	17.9 (−3.3 to 39.2)
ACR70 response‡			
No. of patients (%)	4 (17)	1 (4)	10 (20)
Least-squares mean difference vs. placebo (95% CI)	—	−12.7 (−29.4 to 4.1)	3.7 (−15.0 to 22.4)
Tender-joint count for 68 joints			
Change from baseline	−6.89±1.85	−12.08±1.81	−12.33±1.29
Difference in change vs. placebo (95% CI)	—	−5.19 (−10.35 to −0.03)	−5.45 (−9.91 to −0.98)
Swollen-joint count for 66 joints — no. of joints			
Change from baseline	−6.18±1.09	−10.22±1.08	−10.49±0.76
Difference in change vs. placebo (95% CI)	—	−4.04 (−7.12 to −0.96)	−4.31 (−6.94 to −1.67)
Physician's global assessment of disease activity			
Change from baseline	−25.35±5.16	−39.07±5.13	−38.55±3.58
Difference in change vs. placebo (95% CI)	—	−13.72 (−28.23 to 0.80)	−13.20 (−25.68 to −0.72)
Patient's global assessment of disease activity			
Change from baseline	−21.66±5.39	−24.27±5.28	−29.67±3.74
Difference in change vs. placebo (95% CI)	—	−2.60 (−17.62 to 12.41)	−8.01 (−21.05 to 5.03)
Patient's assessment of arthritis pain			
Change from baseline	−17.94±5.10	−23.50±5.00	−31.55±3.54
Difference in change vs. placebo (95% CI)	—	−5.56 (−19.76 to 8.65)	−13.61 (−25.95 to −1.26)
HAQ-DI score			
Change from baseline	−0.41±0.11	−0.35±0.11	−0.42±0.08
Difference in change vs. placebo (95% CI)	—	0.06 (−0.24 to 0.36)	−0.01 (−0.27 to 0.26)
SF-36			
Mental component summary score			
Change from baseline	3.48±1.72	0.55±1.63	4.64±1.17
Difference in change vs. placebo (95% CI)	—	−2.93 (−7.63 to 1.77)	1.15 (−2.95 to 5.26)
Physical component summary score			
Change from baseline	5.01±1.71	7.03±1.63	6.43±1.16
Difference in change vs. placebo (95% CI)	—	2.02 (−2.69 to 6.73)	1.42 (−2.67 to 5.50)
High-sensitivity C-reactive protein level			
Change from baseline	1.34±3.72	−5.26±3.63	−0.66±2.57
Difference in change vs. placebo (95% CI)	—	−6.60 (−16.91 to 3.70)	−2.01 (−10.99 to 6.98)
Clinical Disease Activity Index score			
Change from baseline	−13.75±2.71	−24.06±2.63	−25.51±1.85
Difference in change vs. placebo (95% CI)	—	−10.30 (−17.83 to −2.77)	−11.76 (−18.29 to −5.22)
Simplified Disease Activity Index score			
Change from baseline	−13.80±2.66	−25.06±2.57	−26.90±1.88
Difference in change vs. placebo (95% CI)	—	−11.26 (−18.65 to −3.87)	−13.10 (−19.61 to −6.60)

Results







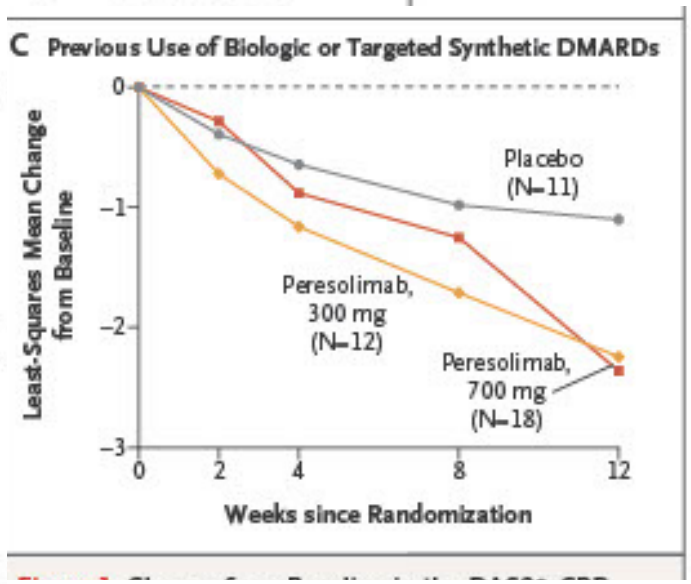


Figure 1. Change from Baseline in the DAS28-CRP Overall and According to DMARD Subgroup.

Results

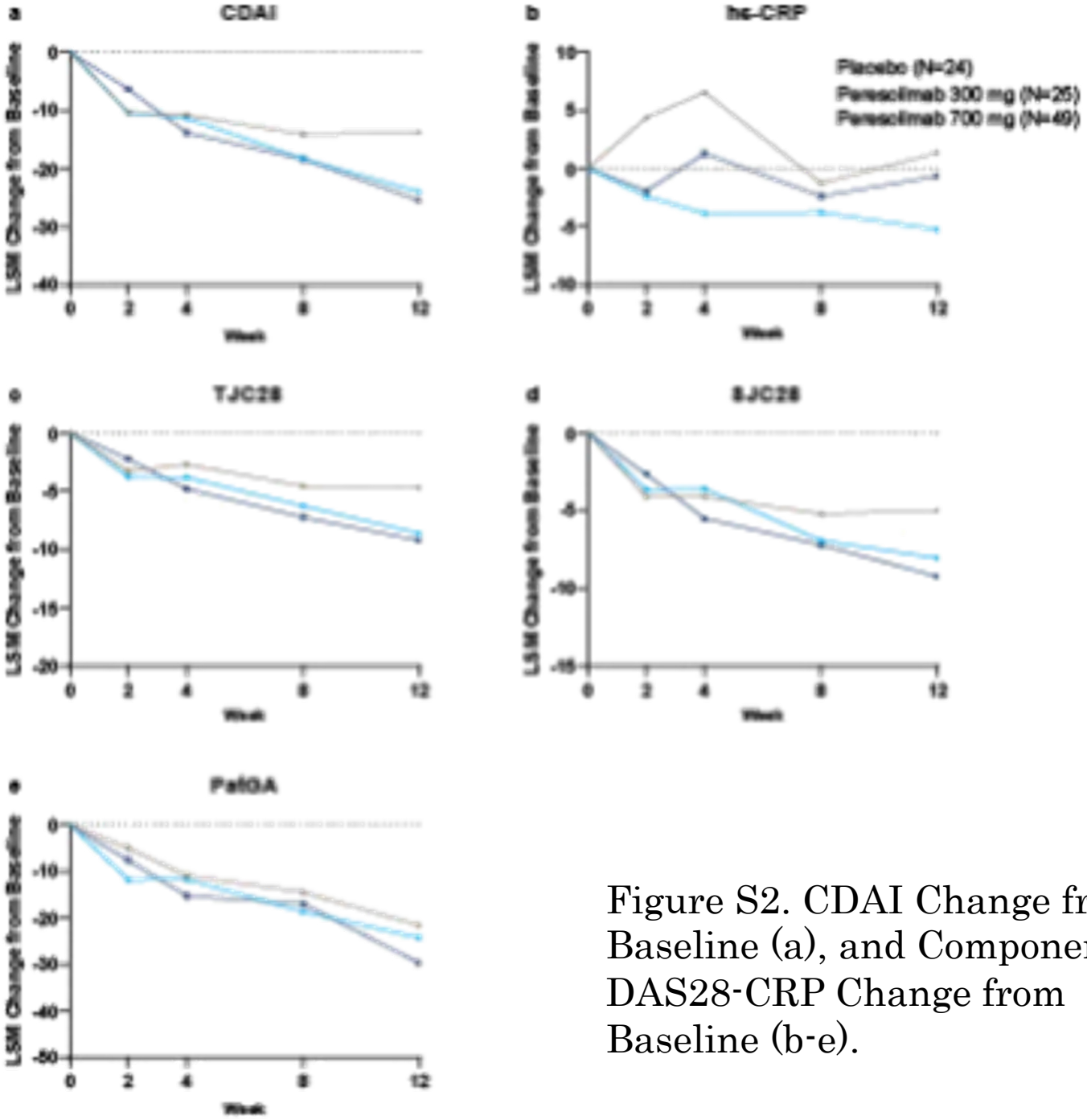


Figure S2. CDAI Change from Baseline (a), and Components of DAS28-CRP Change from Baseline (b-e).

Results

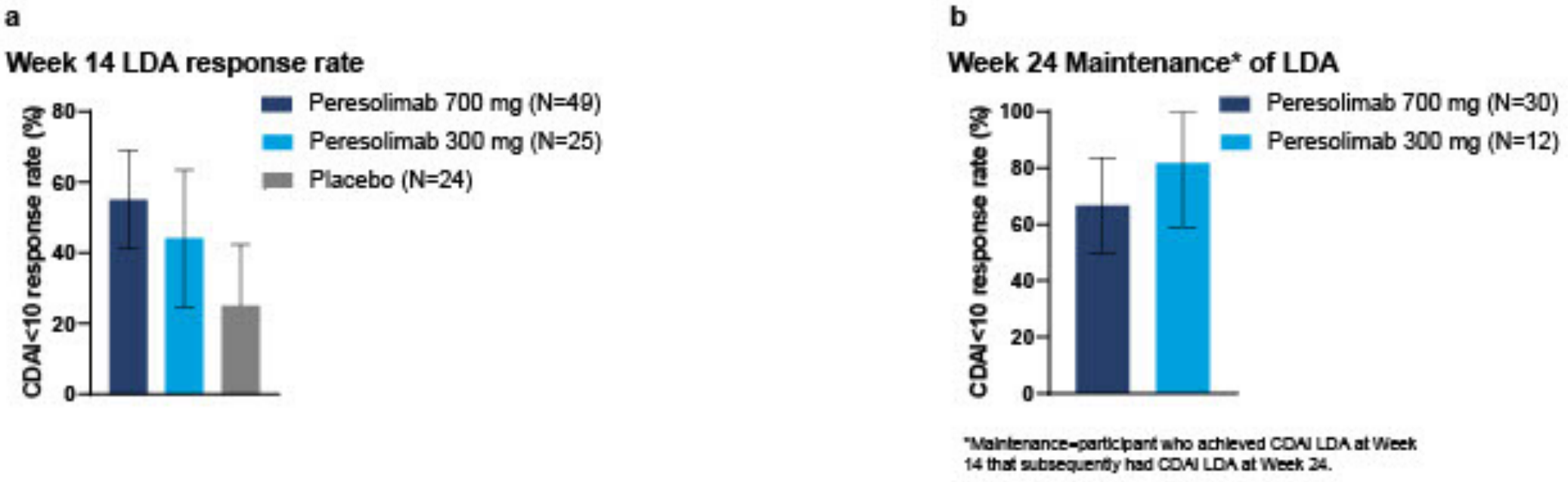


Figure S3. Low Disease Activity (LDA) Response at Week 14 (a), and Proportion of Patients who Achieved LDA at Week 14 and Maintained LDA at Week 24 (b).

Results

- 有害事象：
  治験介入と関連する
  重篤な有害事象や死亡例はなし。

Table 3. Adverse Events between Baseline and Week 12 (Period 1).*

Event	Placebo (N=24)	Peresolimab, 300 mg (N=25)	Peresolimab, 700 mg (N=49)
		no. of patients (%)	
Adverse event during the treatment period			
Overall	9 (38)	8 (32)	14 (29)
According to severity†			
Mild	6 (25)	5 (20)	9 (18)
Moderate	3 (12)	3 (12)	5 (10)
Severe	0	0	0
Serious adverse event	0	0	1 (2)
Discontinuation of placebo or peresolimab because of adverse event	1 (4)	1 (4)	0
Infections and infestations‡	3 (12)	6 (24)	5 (10)
Nasopharyngitis	1 (4)	2 (8)	1 (2)
Coronavirus disease 2019	0	1 (4)	1 (2)
Vulvovaginal candidiasis	0	0	1 (2)§
Gastroenteritis	0	1 (4)	0
Helicobacter infections	0	1 (4)	0
Herpes simplex	1 (4)	0	0
Mastitis	0	1 (4)	0
Rhinitis	0	0	1 (2)
Sinusitis	0	1 (4)	0
Skin bacterial infection	0	1 (4)	0
Tooth abscess	1 (4)	0	0
Upper respiratory tract infection¶	0	0	1 (2)
Upper respiratory tract infection bacterial¶	0	0	1 (2)
Urinary tract infections	0	0	1 (2)
Neoplasma benign, malignant, and unspecified, including cysts and polyps: B-cell lymphoma‡	1 (4)	0	0
Skin and subcutaneous tissue disorders‡	2 (8)	0	2 (4)
Pruritus	1 (4)	0	1 (2)
Dermatitis atopic	0	0	1 (2)
Onycholysis	1 (4)	0	0

Discussion

- 高疾患活動性のRA患者へのperesolimabについての第2a相試験
- 12週目のDAS28-CRP改善率はplaceboよりも有意に大きかった
- ACR20/50/70については，peresolimab 700mg群とplacebo群でのみ奏効率に有意差が見られた
- bDMARDs/tsDMARDs治療歴の有無による層別化では，同様の傾向であった

Limitation

- 試験期間の短さ：有効性，安全性
- サンプル数の少なさ
- 24週目での評価はdouble-blindを解除していることから選択バイアスが生じている可能性

＊悪性腫瘍リスクについての評価が十分でない

臨床への応用

- PD-1経路に作用する新規抗体製剤について，一定の有効性が示唆されるが，特に悪性腫瘍リスクの検討が重要とも想定され，引き続きの追加検討が求められる