①は②のサブ解析

① **Suppression of Serum Interferon-γ Levels as a Potential Measure of Response to Ustekinumab Treatment in Patients With Systemic Lupus Erythematosus**

Cesaroni M et al., Arthritis Rheumatol 2021; 73: 472

***Lancet* 2018; 392: 1330–39**

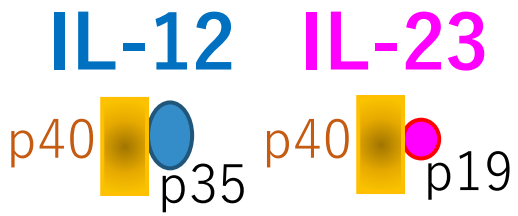
② Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study

Van Vollenhoven RF et al., Lancet 2018; 392: 1330

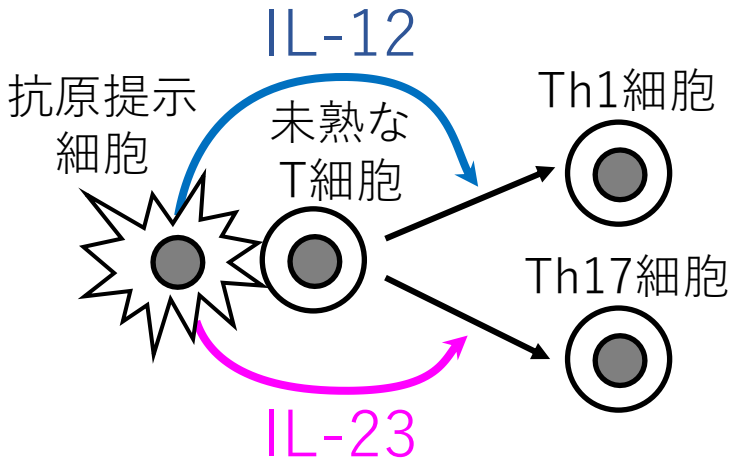
Ustekinumab(ステラーラ®)

抗IL-12/23 p40抗体

適応症
尋常性乾癬及び関節症性乾癬
クローン病/潰瘍性大腸炎



ヘルパーT細胞の分化



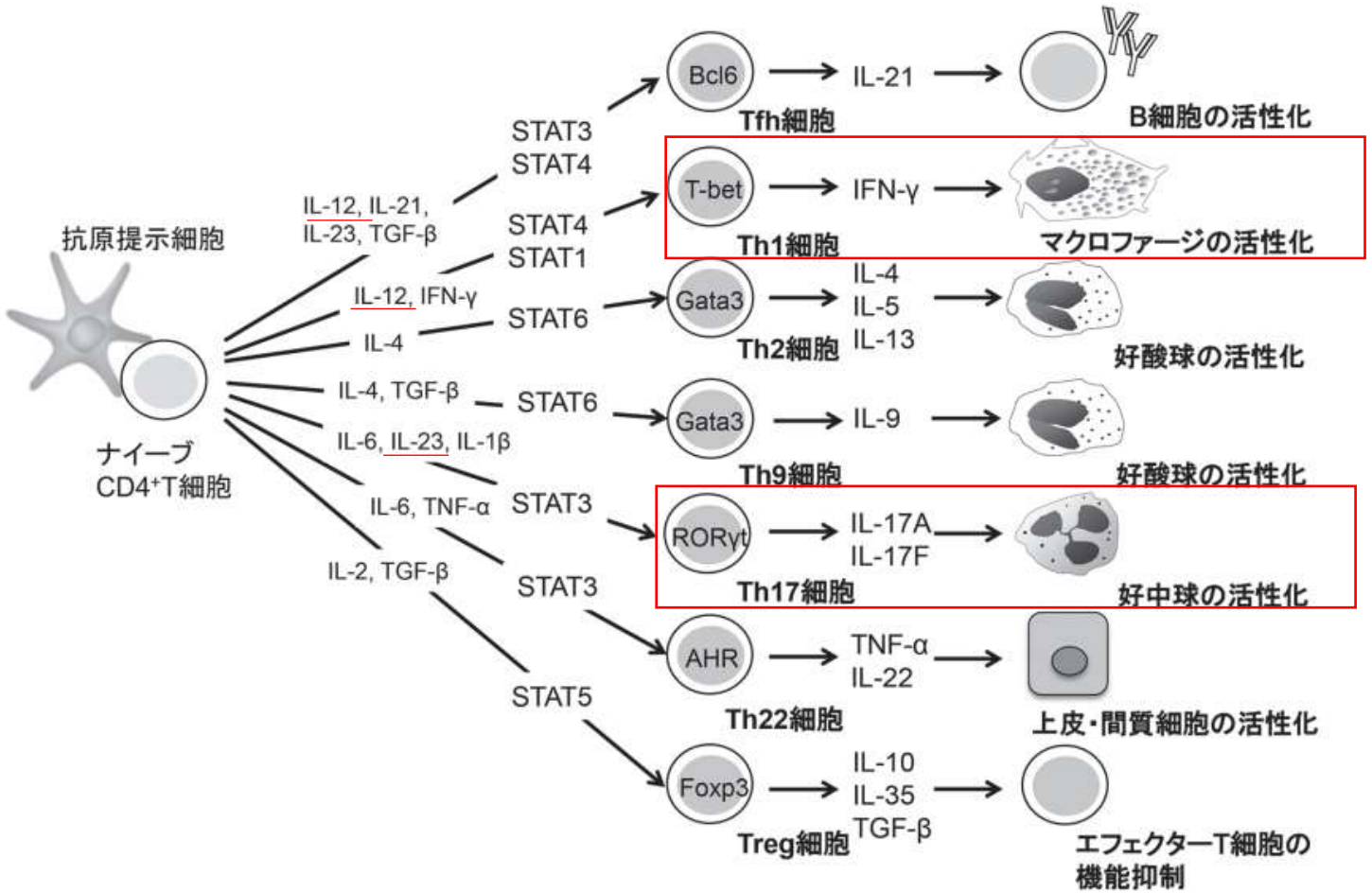
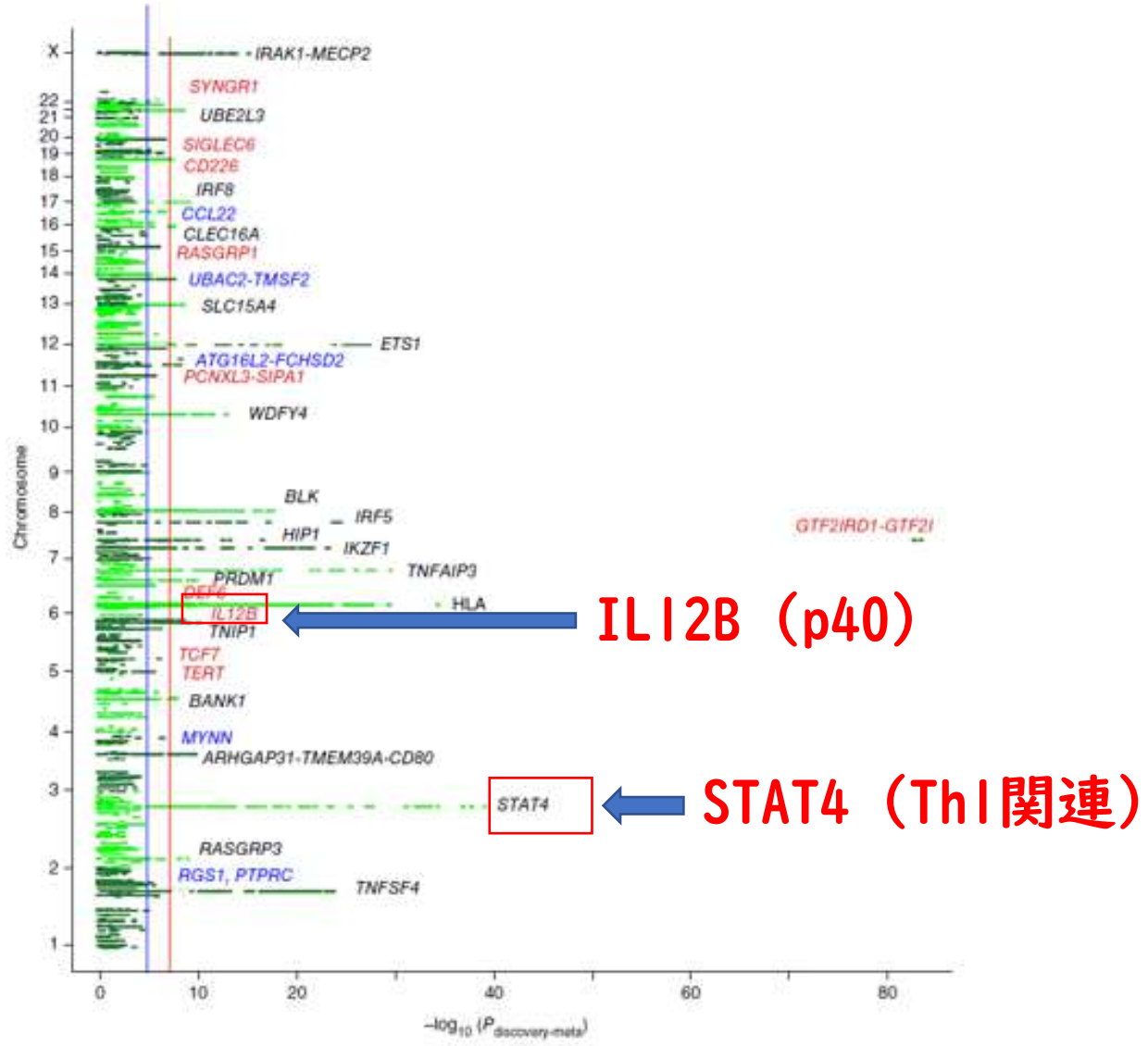


図1　ヒトヘルパーT細胞の分化と機能

中山田真吾、田中良哉 臨床免疫学会雑誌 39巻(1) 1-7, 2016

SLEにおけるIL-12の関与



IL12B（p40）

STAT4（Th1関連）

Sun et al., Nat Genet 2016, 48: 323

SLEにおけるIL-23/IL-17の関与

Th17細胞数上昇、血清IL-17A高値がSLEで認められる	Wong CK, Lupus 2000; 9: 589 Wong CK, Clin Immunol 2008; 127: 385 Vincent FB, Arthritis Re Ther. 2013; 15: R97
IL-17F, IL-21, IL-22のcopy number variationがSLEと関連	Yu B, Arthritis Rheumatol 2011; 63: 3487
SLEにおけるIL-23の重要性	Rana A, Lupus 2012; 21: 1105
IL-23R KO lupus model mouseでLNが抑制	Kyttaris YC J Immunol 2010; 184: 4605

など、多数

② Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study

Van Vollenhoven RF et al., Lancet 2018; 392: 1330

Patients Inclusion/Exclusion Criteria（主なもの）

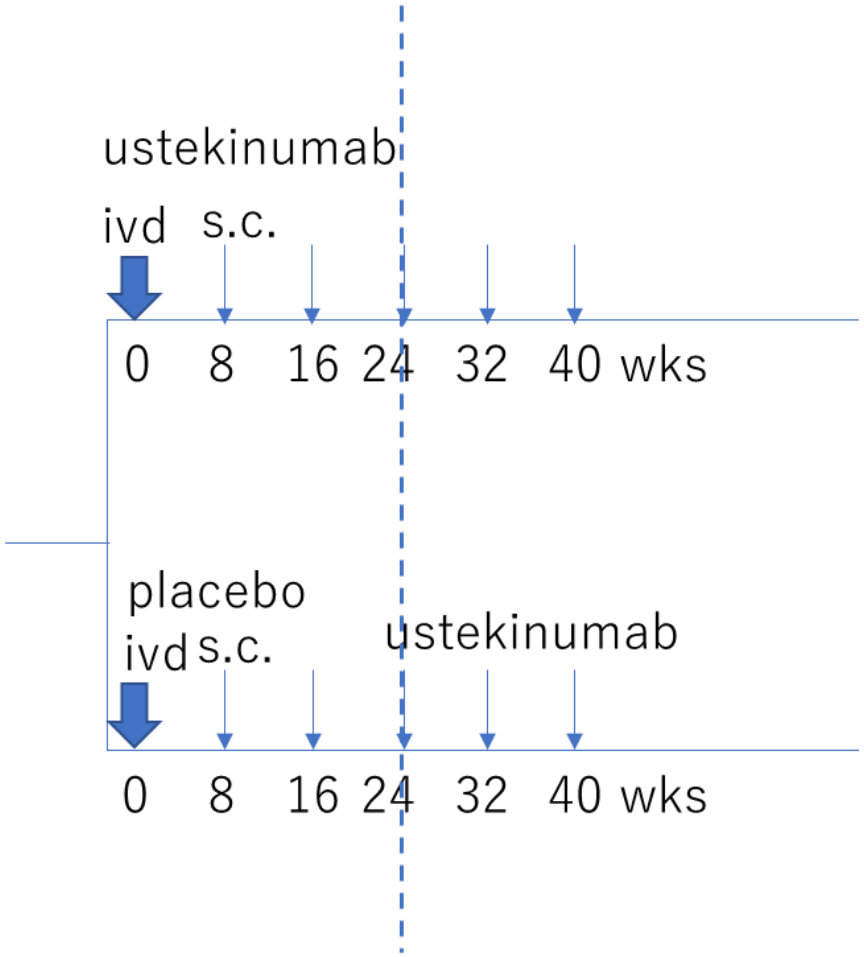
・治験薬開始3ヶ月以上前に2012 SLICC criteriaもしくは自己抗体によってSLEと診断された患者
・スクリーニング時点で少なくとも自己抗体陽性であること
（ANA>1:80 or anti-DNA Ab >75 IU/ml or anti-Sm Ab > 120 aU/ml）
・1 BILAG A or 2 BILAG Bsをスクリーニング時点でもつこと
・SLEDAI-2K ≧ 6 かつ cSLEDAI-2K ≧ 4(スクリーニング時点)
・不安定/進行性SLE患者（eg. Active class III/IV 腎炎、血管炎、CNS症状）は除外

背景治療

・stable doseのステロイド。PSL ≦ 20mg/d (治験薬開始前4週間以上)
・stable dose の免疫抑制薬。MMF≦2g/d、AZA≦2mg/kg/d、MTX ≦25mg/wk(治験薬開始前6週間以上)
・stable doseのHCQ(治験薬開始前8週間以上）。

・PSL 5mg/d以下の増減は許容（wk 0-6)。wk 0-6でPSL増量した場合、 wk 6-12 でPSL 5mg/d以下の減量は許容。
それ以外でのPSL増減はできない。

スタディデザイン



1 endpoint: 24週でのSRI4 達成率

Ustekinumab 初回は体重に応じて260 or 390 or 520mgをivd。
その後は90mg s.c.を8週ごと。

効果判定のOutcome（すべて24wk）

Primary endpoint

SRI-4 response

Secondary endpoints

- SLEDAI-2K改善度
- PGA改善度
- BICLA response

Additional endpoints

- SRI-5
- SRI-6 など

患者背景

	Ustekinumab (n=60)	Placebo (n=42)
Age, years	40·0 (12·0)	42·9 (11·3)
Sex		
Women	58 (97%)	35 (83%)
Men	2 (3%)	7 (17%)
Weight, kg	75·4 (20·6)	74·3 (22·8)
Race		
White	42 (70%)	28 (67%)
Black	4 (7%)	3 (7%)
Asian	8 (13%)	6 (14%)
Other	6 (10%)	5 (12%)
Hispanic ethnicity	20 (33%)	12 (29%)
Disease duration, years	9·7 (8·3)	9·5 (7·2)
SLEDAI-2K	10·6 (3·3)	11·4 (4·5)
≥1 BILAG domain A	27 (45%)	22 (52%)
≥2 BILAG domain B	28 (47%)	16 (38%)
PGA (VAS 0–10 cm)	4·9 (1·6)	4·9 (1·6)
Number of active joints	6·8 (6·3)	7·8 (6·0)
Number of joints with pain	10·5 (7·9)	12·2 (9·2)
Number of joints with swelling	6·7 (6·3)	7·2 (6·0)
≥4 joints with pain and signs of inflammation	39 (65%)	31 (74%)

	Ustekinumab (n=60)	Placebo (n=42)
CLASI activity score	7·2 (6·5)	7·4 (6·4)
CLASI activity score ≥4	37 (62%)	24 (57%)
History of lupus nephritis	9 (15%)	7 (17%)
Anti-nuclear antibodies present	54 (90%)	40 (95%)
Anti-double stranded DNA antibodies present	25 (42%)	18 (43%)
Anti-Smith antibodies present	12 (20%)	10 (24%)
Low C3 concentration	25 (42%)	16 (38%)
Low C4 concentration	16 (27%)	15 (36%)
Type I interferon signature*		
High	37 (63%)	30 (73%)
Low	22 (37%)	11 (27%)
Concomitant immunomodulatory and immunosuppressant medications		
Glucocorticoids	51 (85%)	34 (81%)
Dose, mg per day	9·3 (4·7)	10·5 (5·2)
Antimalarial	44 (73%)	26 (62%)
Mycophenolate mofetil	8 (13%)	7 (17%)
Azathioprine or 6-mercaptopurine	12 (20%)	9 (21%)
Methotrexate	12 (20%)	6 (14%)

Patient flow diagram

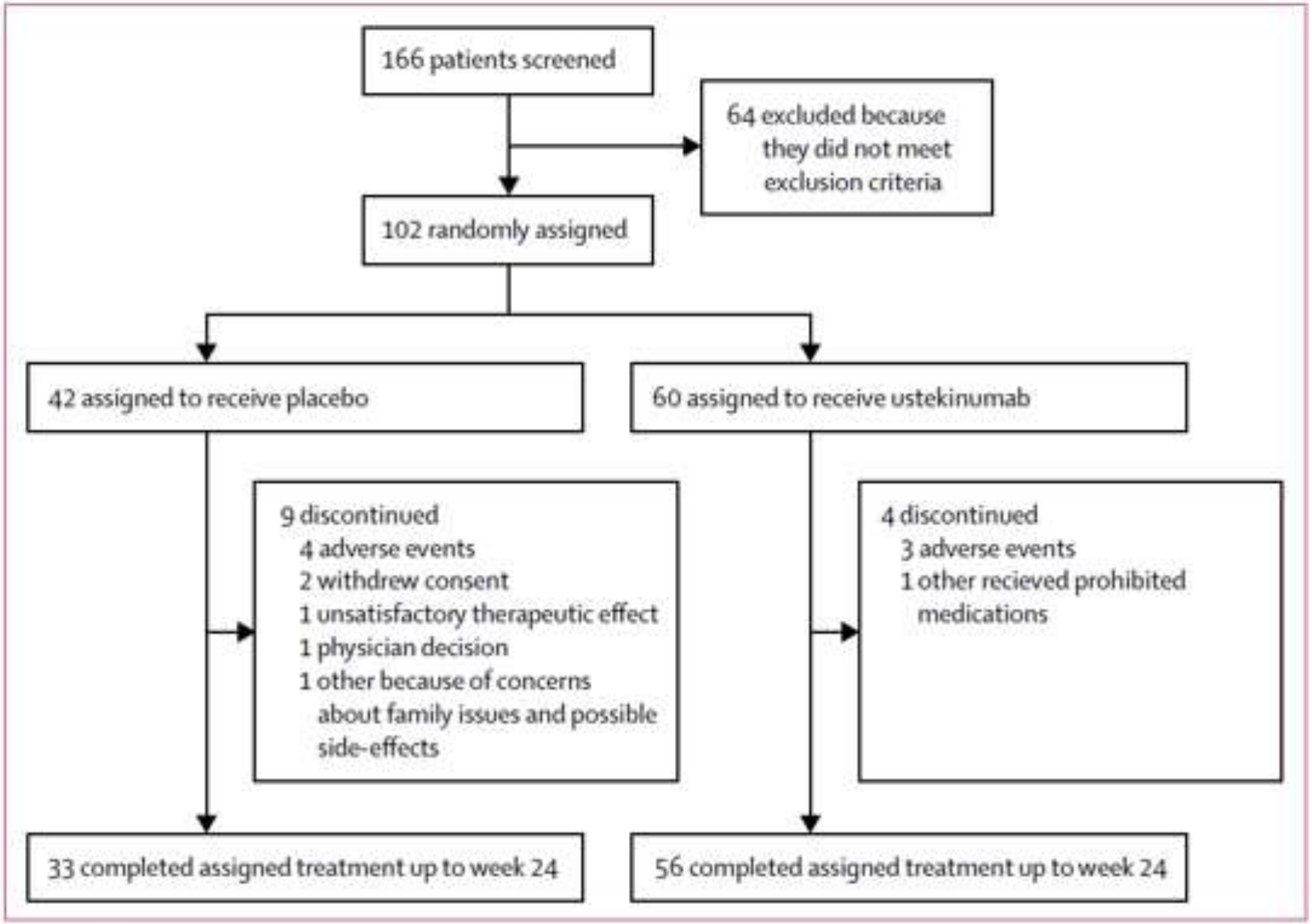
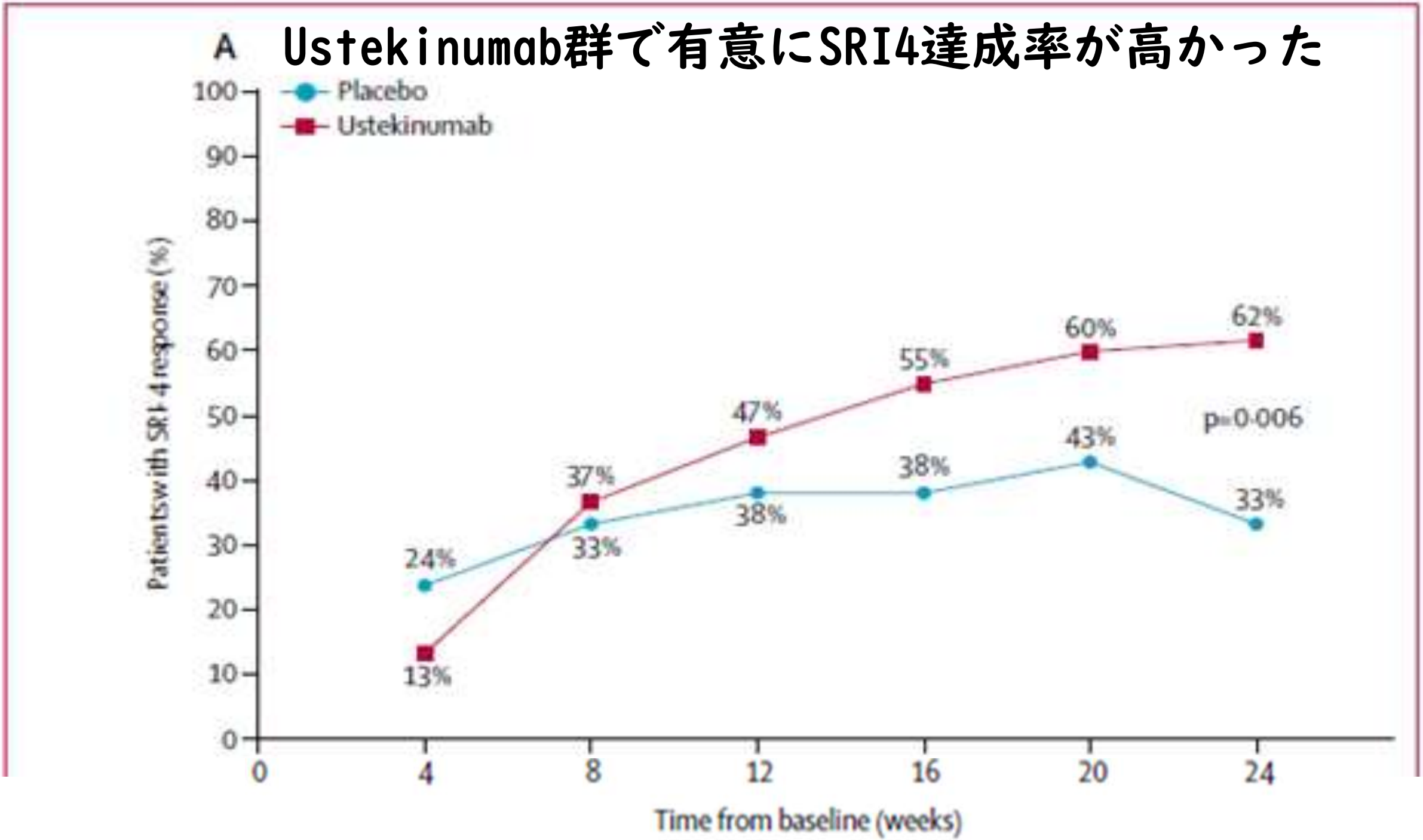


Figure 1: Patient flow diagram

Ustekinumab群で有意にSRI4達成率が高かった

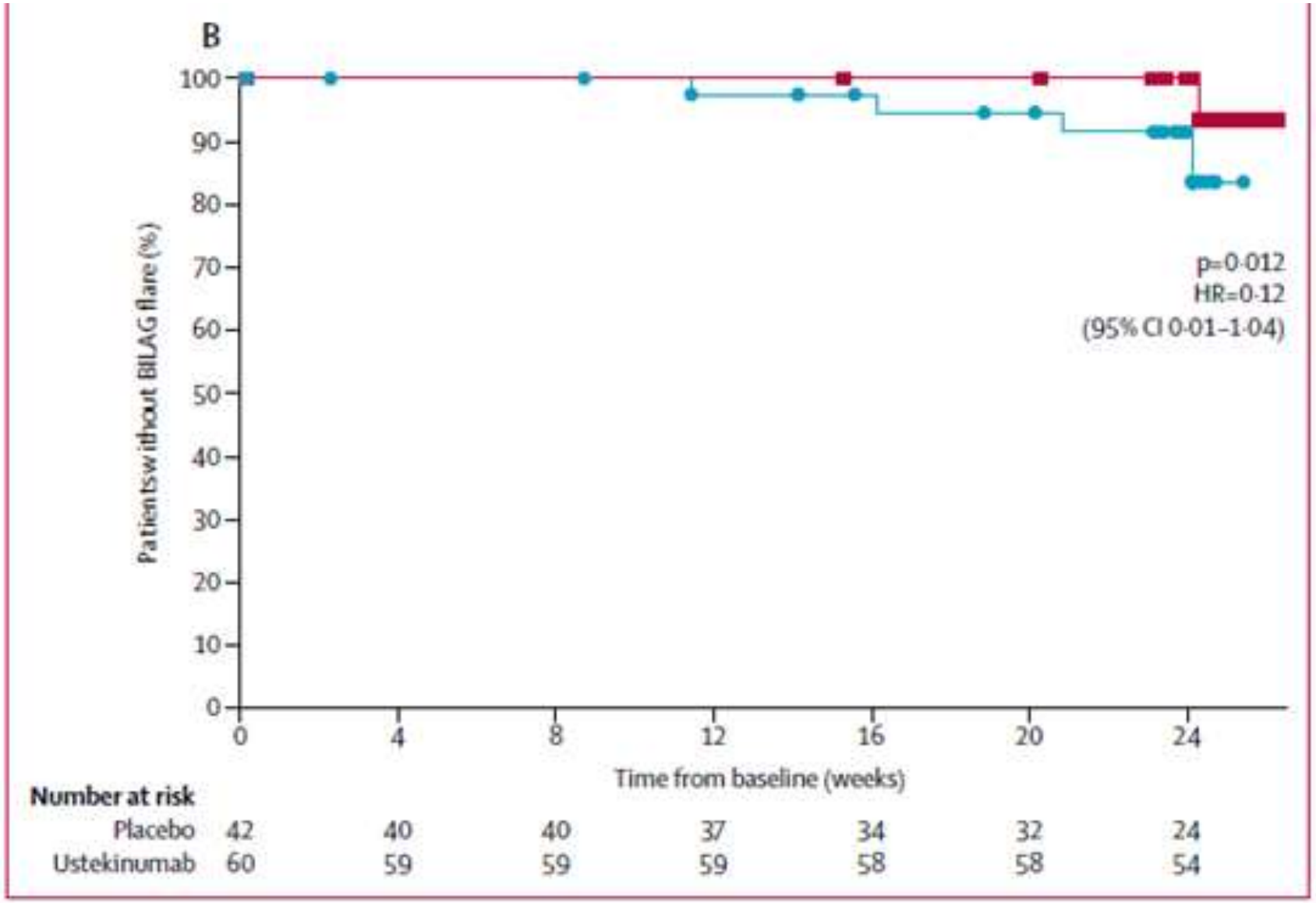


SRI（SLE Responder Index）4

- SLEDAIで4点以上の改善
- PGA(Physician Global Assessment)で0.3以上悪化していないこと（3点満点スケール）
- BILAG-2004の臓器スコアで新しくAが出現していないこと、または2つ以上のBが新たに出現していないこと。

BILAG category
A= 重度の疾患活動性
B= 中等度の疾患活動性
C= 軽度の疾患活動性、安定した軽症
D= 疾患活動性なし（既往あり）
E= 疾患活動性なし（既往なし）

Ustekinumab群で有意に再燃率が低かった



BICLA (BILAG-based Composite Lupus Assessment)

以下をすべて満たす

1）すべてのBILAG A, Bカテゴリーの臓器で1段階以上の改善
2）新規のBILAG Aがない。新規のBILAG Bが2つ以上ない。
3）SLEDAI scoreで悪化がない
4）Physician’s Global Assessmentで10%以上の悪化がない
5）プロトコールにない薬剤の開始がない

BILAG flareの定義：
新規BILAG Aもしくは２つの新規BILAG Bが出現した場合

IFN signatureによらずUstekinumabは有効

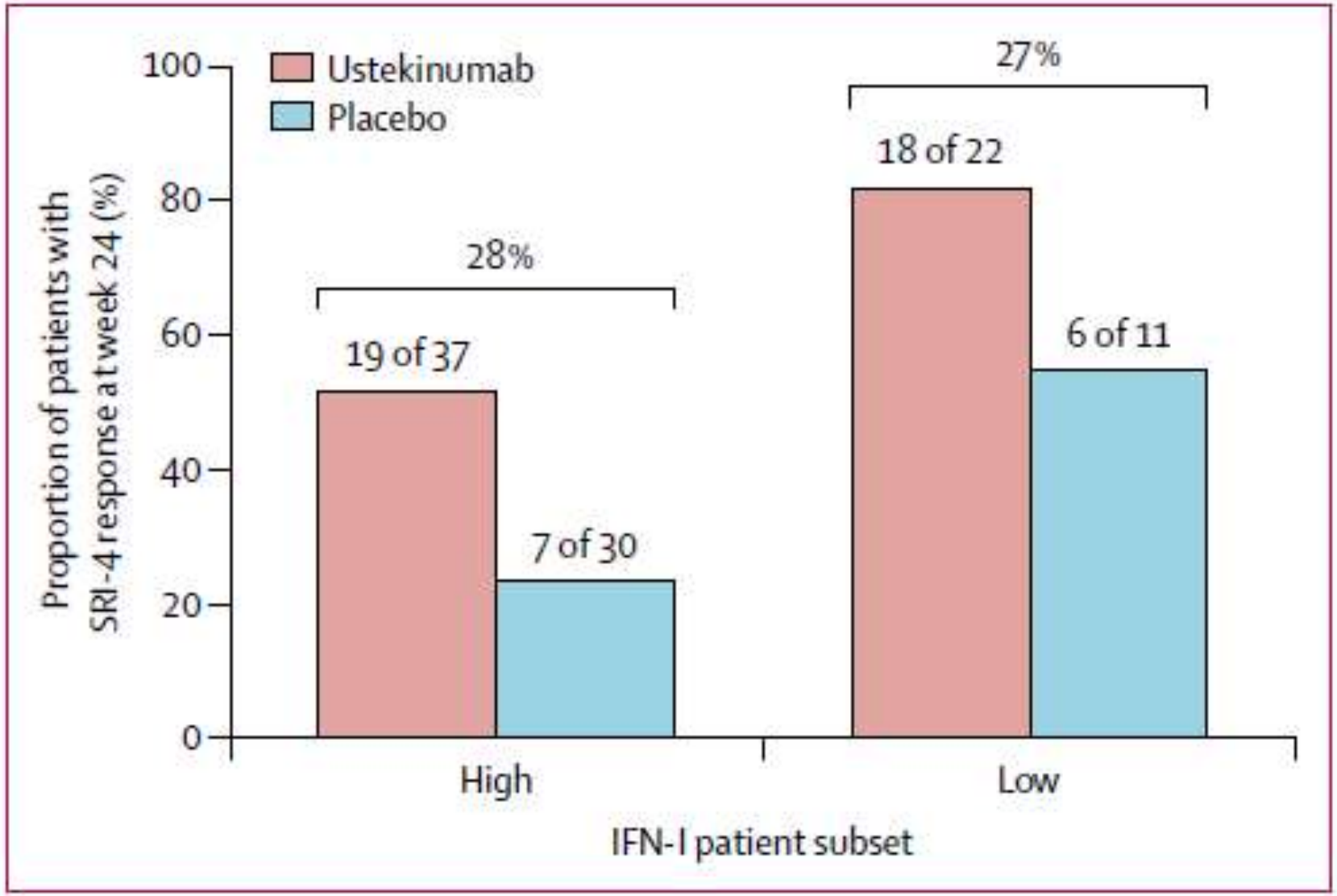


Figure 3: SRI-4 responses in high and low IFN-I patient subsets

有害事象に差はなし

	Ustekinumab (n=60)	Placebo (n=42)
Any adverse event	47 (78%)	28 (67%)
Infections	27 (45%)	21 (50%)
Most common adverse events*		
Urinary tract infection	6 (10%)	5 (12%)
Nasopharyngitis	6 (10%)	3 (7%)
Upper respiratory tract infection	5 (8%)	9 (21%)
Headache	4 (7%)	5 (12%)
Diarrhoea	4 (7%)	0
Worsening of systemic lupus erythematosus	3 (5%)	2 (5%)
Nausea	3 (5%)	2 (5%)
Bronchitis	3 (5%)	0
Pharyngitis	3 (5%)	0
Pharyngotonsillitis	3 (5%)	0
Pyrexia	3 (5%)	1 (2%)
Serious adverse event	5 (8%)	4 (10%)
Serious infections	2 (3%)	0

Data are n (%). No deaths or malignancies were reported in either group. Patients with more than one of the same event were counted once for that event. *Events that occurred in at least 5% of patients in the ustekinumab group.

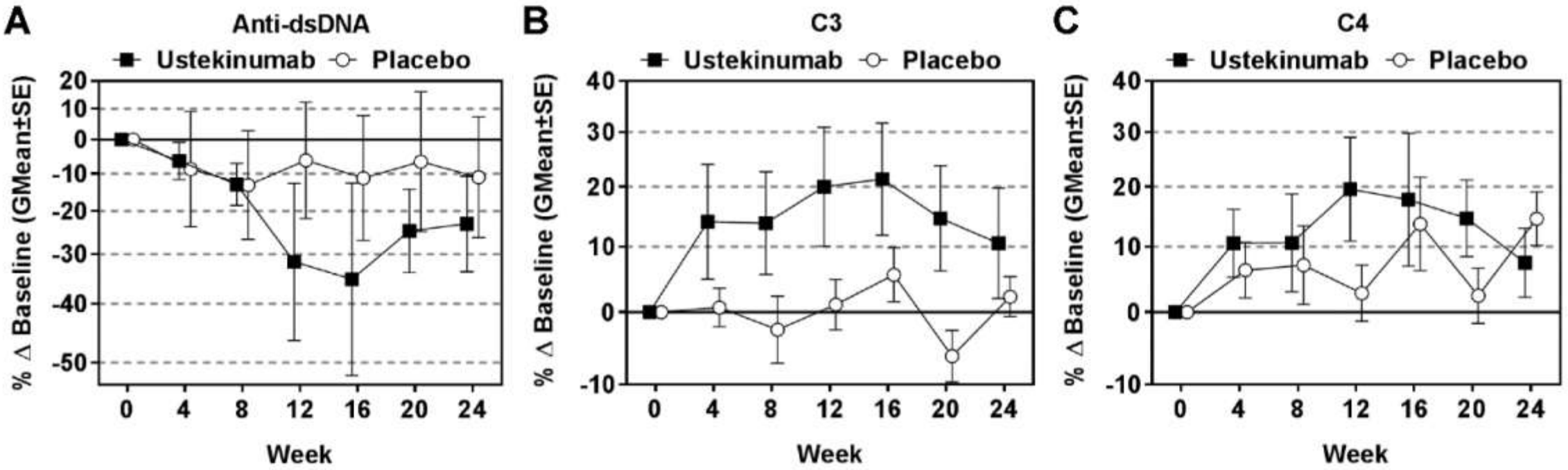
Table 3: Patients with adverse events up to week 24

SRI4，5，6は達成したが、BICLA達成できず

	Ustekinumab (n=60)	Placebo (n=42)	Difference (95% CI)	p value
Primary endpoint				
SRI-4 response	37 (62%)	14 (33%)	28% (10 to 47)	0·006
Main secondary endpoints				
Change from baseline in SLEDAI-2K,	−4·4 (2·9)	−3·8 (5·4)	−0·6 (−2·4 to 1·2)	0·093
Change from baseline in PGA	−2·2 (1·9)	−1·9 (2·2)	−0·2 (−1·1 to 0·6)	0·394*
BICLA response	21 (35%)	14 (33%)	2% (−17 to 20)	0·994*
Additional endpoints				
SRI-5 response	26 (43%)	9 (21%)	22% (4 to 40)	0·022*
SRI-6 response	26 (43%)	8 (19%)	24% (7 to 42)	0·012*
No worsening in BILAG score	29 (48%)	11 (26%)	22% (4 to 41)	0·028*
No worsening in PGA†				
Patients, n/N (%)	51/55 (93%)	29/32 (91%)	2% (−9 to 13)	..
Mean response rate, % (95% CI)	92·4% (81·4 to 97·1)	88·9% (73·4 to 95·9)	..	0·312*
SLEDAI-2K response†				
Patients, n/N (%)	38/53 (72%)	15/31 (48%)	23% (4 to 42)	..
Mean response rate, % (95% CI)	76·8% (76·4 to 77·2)	49·1% (48·2 to 50·0)	..	0·007*

Ustekinumab群でDNA抗体低下、補体上昇がみられた

Supplemental Figure 3. Mean change in anti-double-stranded DNA (dsDNA) autoantibodies (A), Complement C3 (B), and Complement C4 (C) between week 0 and week 24. GMean = geometric mean. SE = standard error.



解説　SLE治験における対象患者と背景治療の比較

	対象SLE	背景治療（PSL）	Outcome
Rituximab (EXPLORER)	重症を除くSLE	PSL max 0.5-1mg/kg, 10wkで10mg以下、52週で5mg以下	52wkでMajor Clinincal Response
Belimumab (BLISS52)	重症を除くSLE	PSL 24wkまで制限なし, 24wkまでにベースの25% or 5mg多い以内に。以後増量不可。	52wkでSRI4
Anifrolumab (TULIP1)	重症を除くSLE	PSL≧10mgはwk 8-40で7.5mg以下に。PSL<10mgでは減量規定なし。	52wkでBICLA
Baricitinib (Phase 2)	関節炎 or 紅斑	PSL≦ 20mgで0-16wkは減量可。16-24wkは増減不可。	24wkで関節炎、紅斑なし
Ustekinumab (Phase 2)	重症を除くSLE	PSL ≦20mgで原則増減不可。Wk0-6で5mg以下の増量可。	24wkでSRI4

①

ここから本日の論文

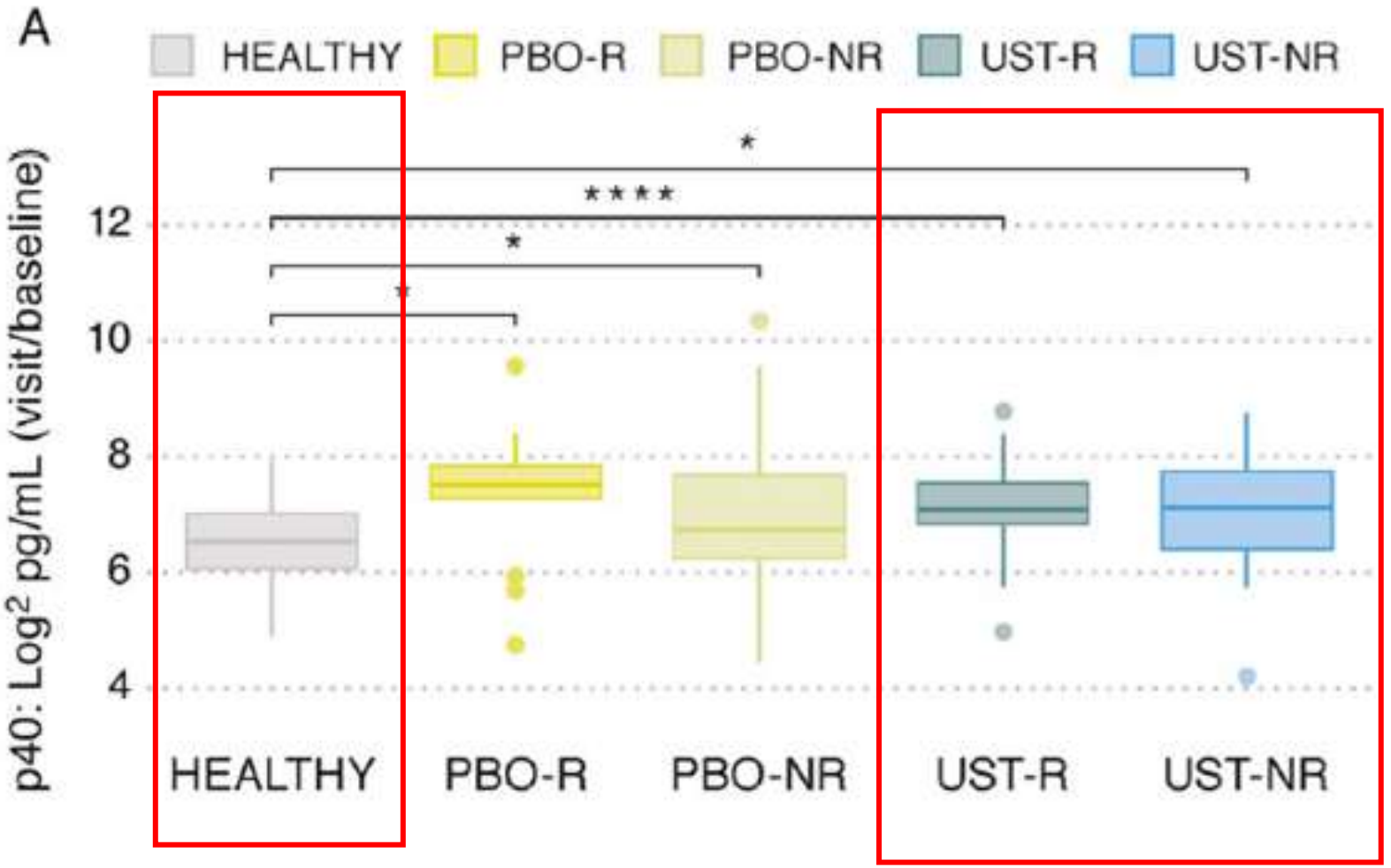
Suppression of Serum Interferon-γ Levels as a Potential Measure of Response to Ustekinumab Treatment in Patients With Systemic Lupus Erythematosus

Cesaroni M et al., Arthritis Rheumatol 2021; 73: 472

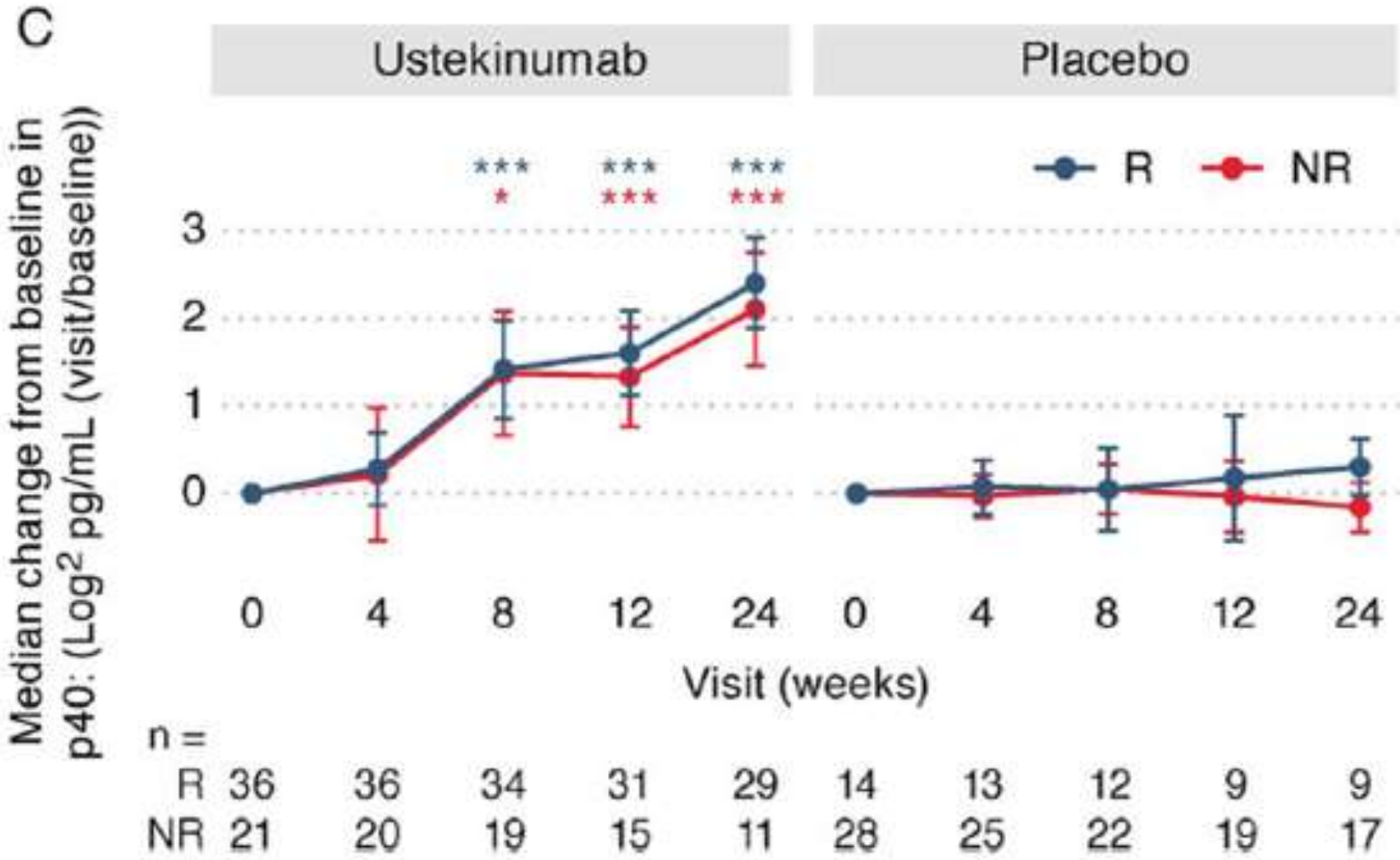
目的：SLEに対するUstekinumab phase 2試験において、
臨床効果と関係するバイオマーカーを探索する。

方法：SRI-4 responderとnon-responder（24wk)における
血清中のp40, IL-23, IFNg, IL-17A, IL-17F, IL-22濃度
を比較

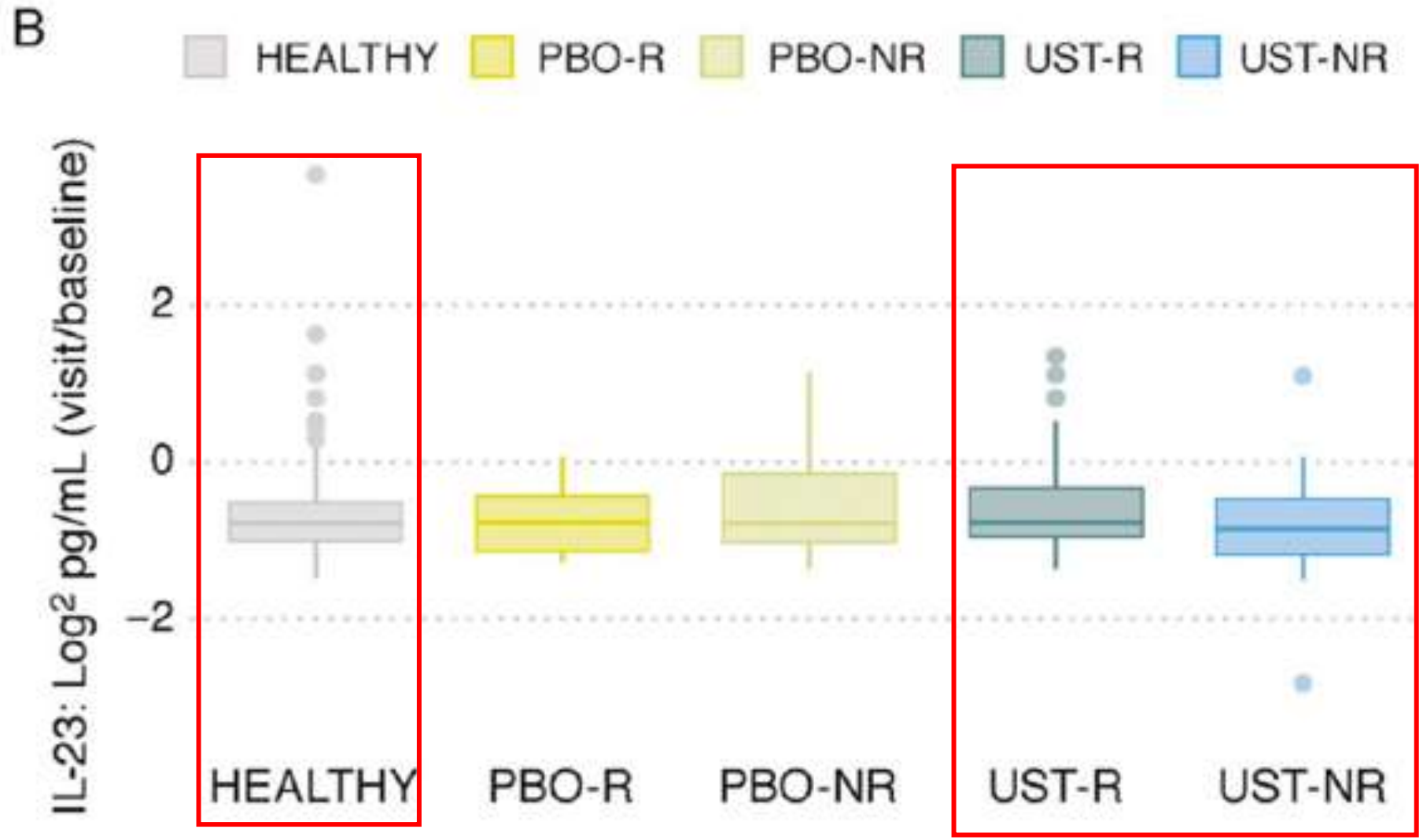
治療前の血中p40濃度でUstekinumab反応性は変わらなかった



Ustekinumab投与で反応性とは無関係にp40は上昇する

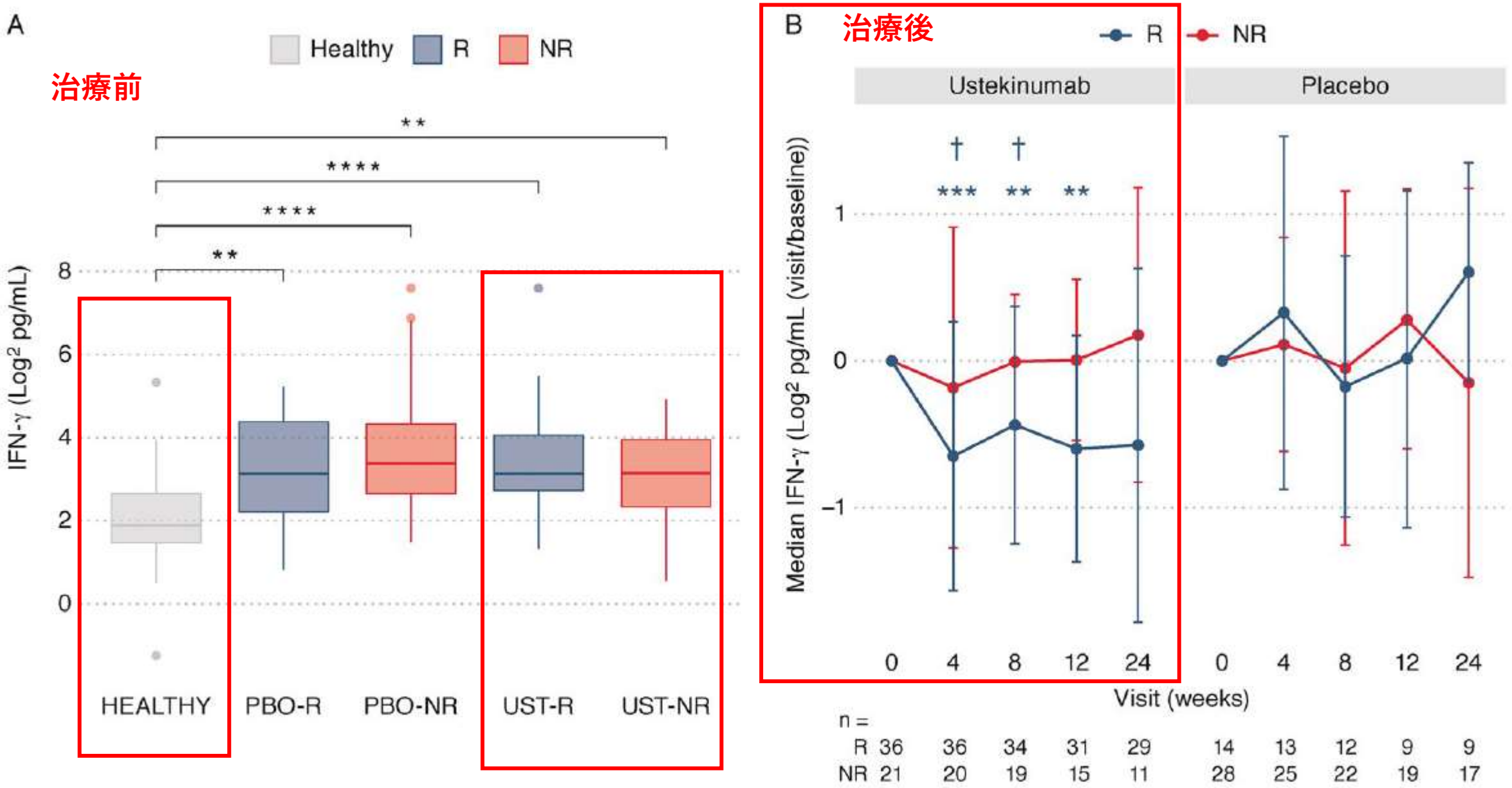


治療前血中IL-23濃度でUstekinumab治療反応性は変わらず

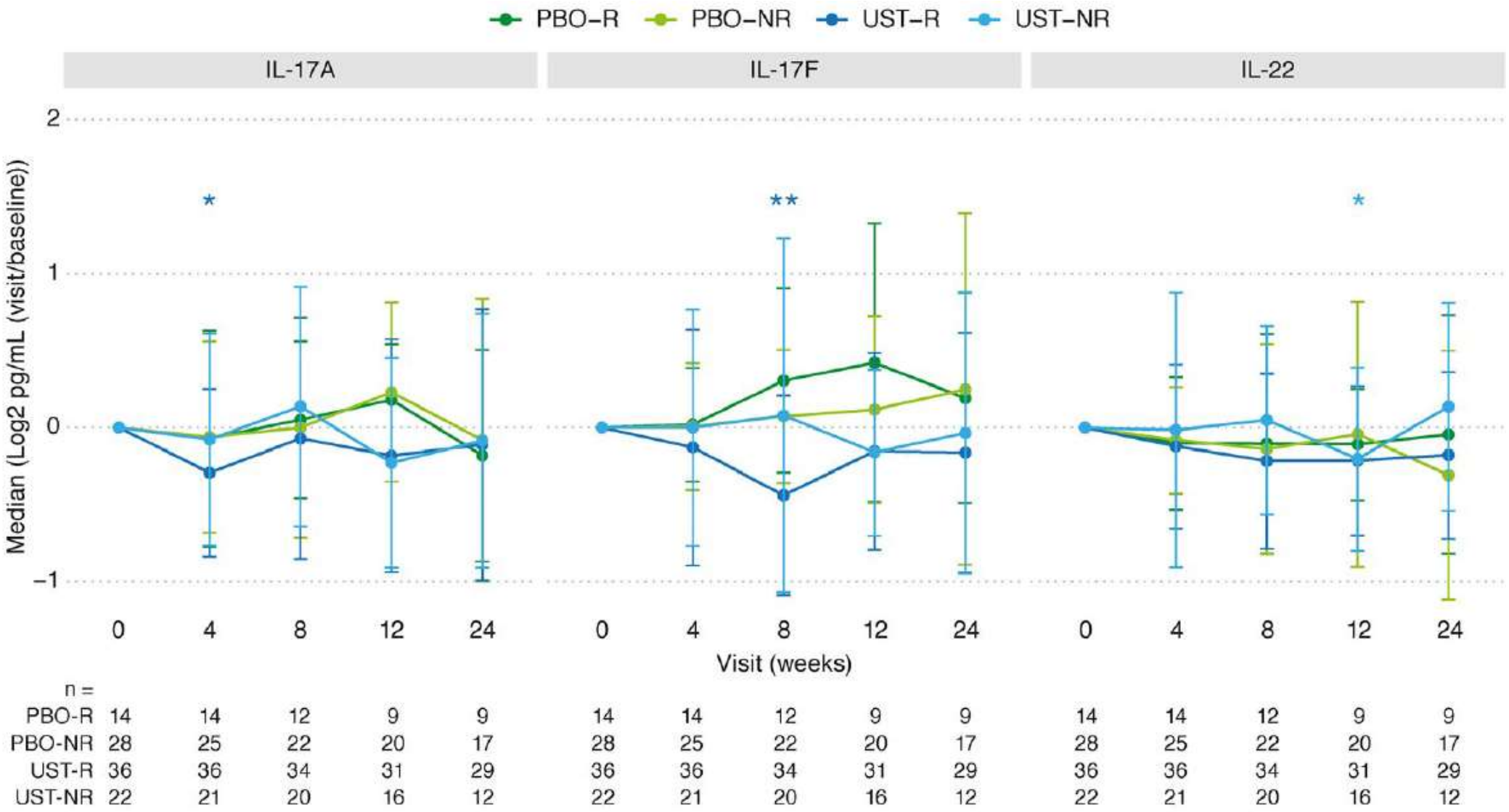


Ustekinumab治療反応性とIL-23は無関係

IFNγが早期から低下する症例がUstekinumab反応例



Ustekinumabレスポンダー、ノンレスポンダーで
IL-17A, IL-17F, IL-22（いずれもTh17が産生）には変化なし



Discussion (1)

Janssen Announces Discontinuation of Phase 3 LOTUS Study Evaluating Ustekinumab in Systemic Lupus Erythematosus

SPRING HOUSE, PENNSYLVANIA, June 26, 2020 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today its decision to discontinue the Phase 3 LOTUS study of STELARA® (ustekinumab) in Systemic Lupus Erythematosus (SLE) due to lack of efficacy in SLE.

About the LOTUS Program

LOTUS is a global, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study of ustekinumab in individuals with active Systemic Lupus Erythematosus. It enrolled 516 patients, including representation from minority populations who are disproportionately impacted by lupus. The Primary Endpoint is the proportion of participants with a composite measure of SRI-4 (Systemic Lupus Responder Index) response at Week 52.
A second Phase 3 study, LOTUS-C, to be conducted in China was planned but will not start given this decision.

SLEがヘテロな疾患であることを物語る？

Discussion (2)

- IFNαや自己抗体上昇前からIFNγの発現が増強するといった報告ある一方、抗IFNγ抗体の治験は無効だった

- IL-23の下流であるIL-17A, F, IL-22は乾癬では高くUstekinumabにより低下するが、SLEではもともと高くなかった

- Limitationとしては局所でのサイトカイン発現の変動はみれておらず、ループス腎炎では局所でIL-23発現が強いとも報告あり