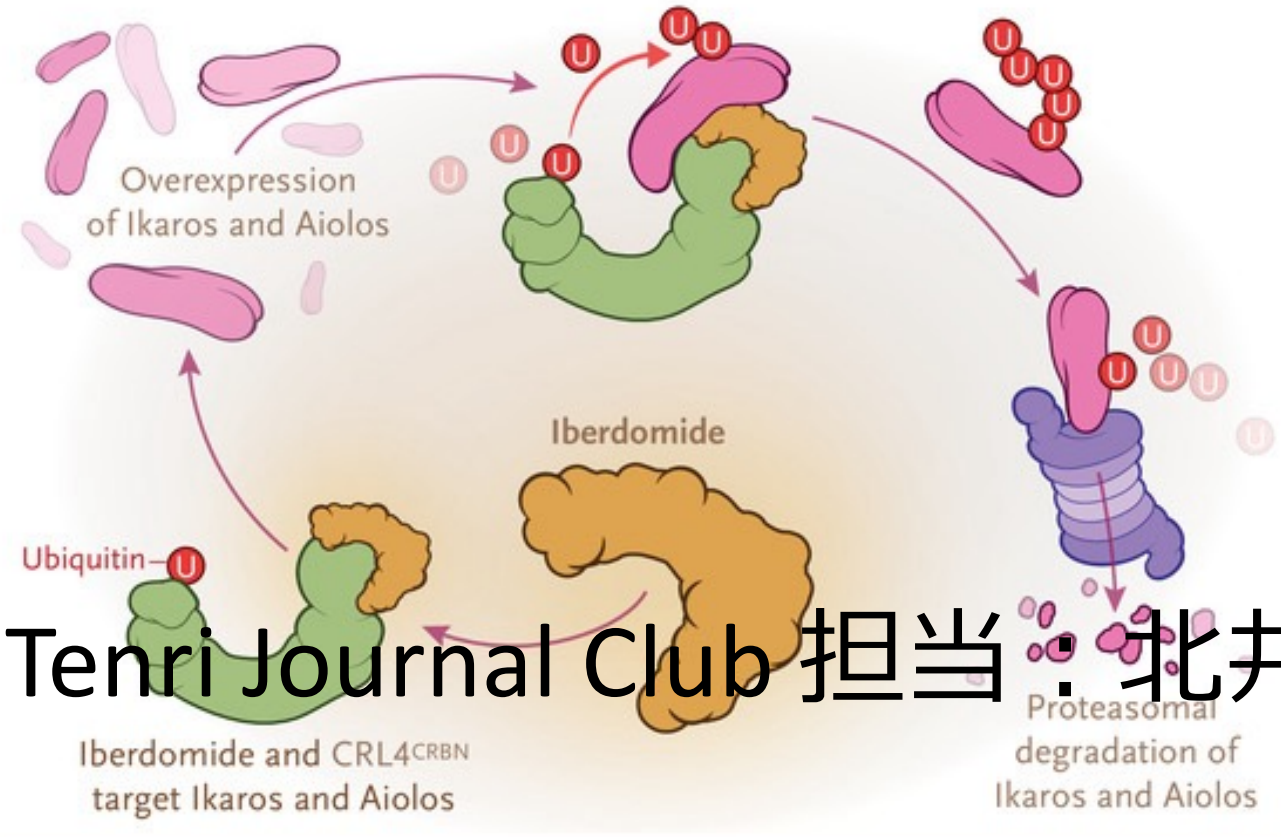
ORIGINAL ARTICLE

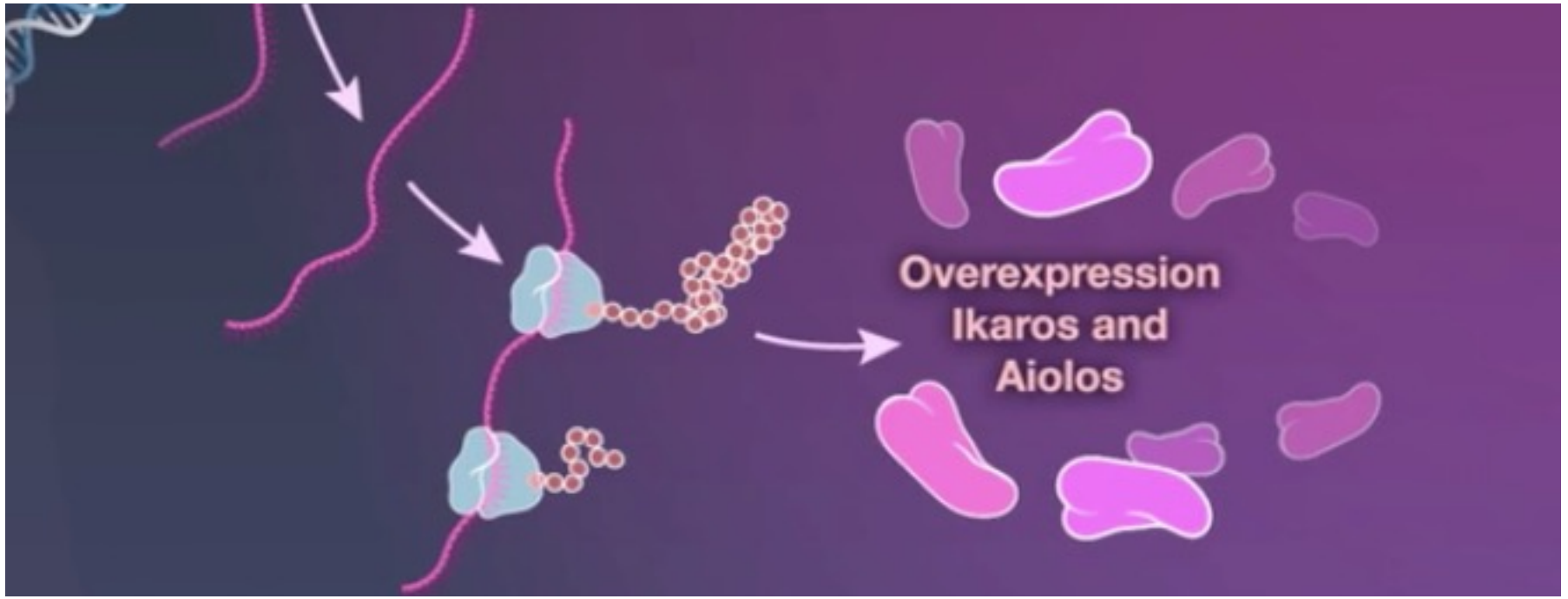
Phase 2 Trial of Iberdomide in Systemic Lupus Erythematosus



R4.4.9 Tenri Journal Club 担当：北井順也

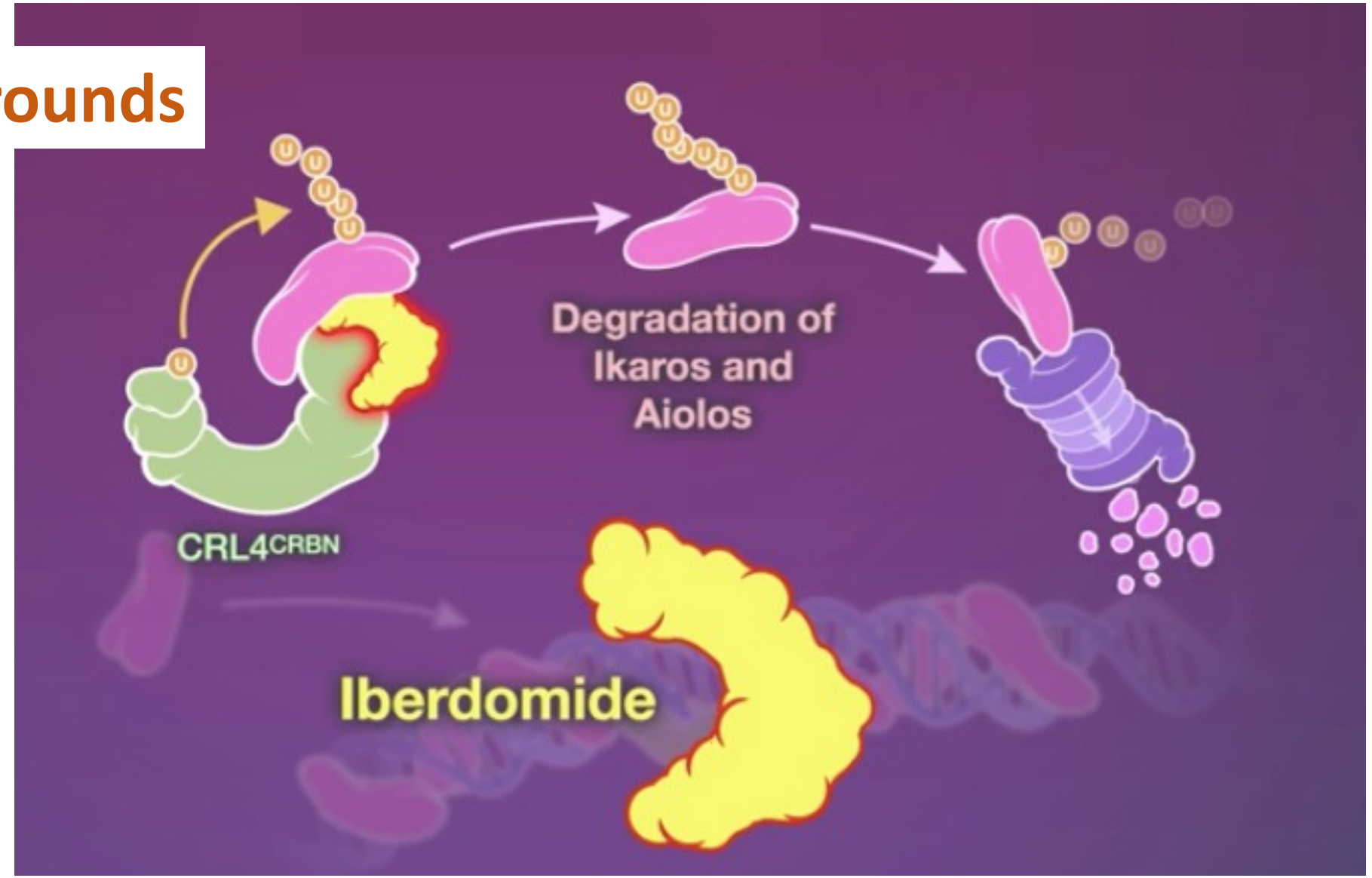
Backgrounds

- Zinc finger転写因子であるIkarosとAiolosは,免疫細胞の発生と恒常性に影響を与え,SLEの遺伝的素因に関与していると考えられている.



- IkarosはB細胞と形質細胞様樹状細胞の発生を誘導し,これらはINF-1を主に産生する. Aiolosは,B細胞の分化をサポートする

Backgrounds

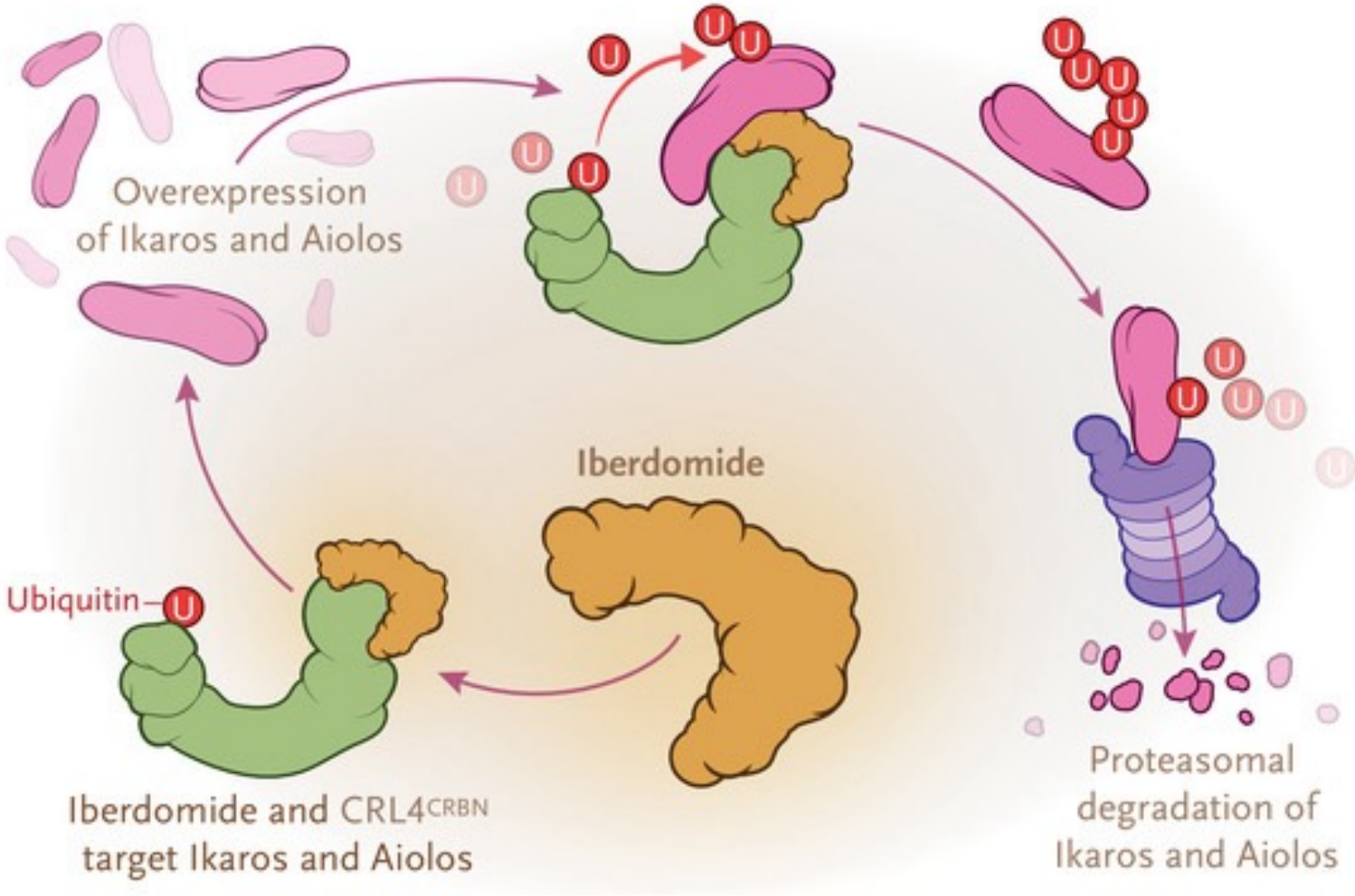


- Iberdomideは, IkarosとAiolosのユビキチン化およびプロテアソーム分解を促進することが知られている.

Backgrounds

- Iberdomideは,IL-2の増加,炎症性cytokineの減少,B細胞分化,自己抗体産生の減少など複数の免疫調節作用を有し,SLE患者を対象とした第2相試験においてIberdomideの効果が認められた.

- 今回の試験では,活動性が高い中等度-重度の SLE 患者を対象とした.



論文のPICO: Pは？

Inclusion criteria

- 18歳以上の男性または女性.スクリーニングの6ヶ月以上前にSLEと診断され, 1997年ACRのSLE分類基準を満たしている.
- SLEDAI 2Kスコアが6点以上, かつSLEDAI 2Kの臨床スコアが4点以上（臨床スコアには, 免疫学的な指標を含む尿や血液の検査結果に起因する点数は含まれない. ループスの神経症状を有する患者は本試験から除外されるため, SLEDAI 2Kスコアの神経症状（1～7項目）はSLEDAI試験参加基準としてカウントされない.
- スクリーニング期間内に中央検査機関で, ANA>40倍・抗Ds-DNA抗体高値・抗Sm抗体高値のうち少なくとも1つ以上が陽性. (スクリーニング段階の過去6ヶ月間またはその間に行われた現地の認定検査機関によるANA検査が陽性であっても, 審査委員会で適正と判断されれば試験への参加は可能.)

論文のPICO: Pは？

Inclusion criteria

- スクリーニング前に, 抗マラリア薬・免疫抑制剤・グルココルチコイドのSLE治療薬の少なくとも1つで治療を受けており、安定した投与量で内服中.
- グルココルチコイドを服用している場合,スクリーニングの少なくとも4週間前からグルココルチコイドを経口内服し,ベースライン検査の2週間以上前からPSL換算で20mg/日以下の安定した投与量を維持している必要あり.
- HCQ,キナクリン,クロロキン,MTX,LEF,SASP,MMF,ミコフェノール酸,AZA,6-メルカプトプリン,Tac,CyAを内服中の場合,被験者はベースライン訪問前に12週間治療を受けていて少なくとも8週間安定投与されている必要がある.
- 試験期間中,免疫抑制剤は1種類のみ使用可能.
- NSAIDsまたは鎮痛剤を常用している患者はスクリーニング検査の2週間前から安定した服用が必要.

論文のPICO: Pは？

Exclusion criteria

- GFR<45mL/min/1.7m^2,またはTP/Crに基づく蛋白尿>2g/日,または判定委員会の見解で導入療法が必要と思われる活動性のループス腎炎を有する患者.
- スクリーニング後6ヶ月以内に,活動性/重症/不安定な精神神経疾患, 心電図でQTc>450ms,B型肝炎またはC型肝炎のいずれか, B型肝炎 or C型肝炎の感染歴が確認されたもの(HBs抗体が単独で陽性の患者は除外しない).
- 先天性・後天性免疫不全症,または感染しやすい基礎疾患を有する患者, あるいはスクリーニング中にHIV感染の検査結果が陽性である患者.
- 細菌・ウイルス・真菌・抗酸菌・その他の感染症（非定型マイコバクテリア症,帯状疱疹を含む）が活動中または再発したことがある患者.

論文のPICO: Pは？

Exclusion criteria

- スクリーニングの4週間以内,スクリーニング期間中,治験薬初回投与までのいずれかで,入院または静注・経口抗菌薬による治療を必要とする重症感染症に罹患した患者.(これらの基準を満たす軽度の感染症患者は,試験参加の承認を得るためにメディカルモニターに相談することができる)
- 潜在性または活動性の結核の既往歴がある.(ただし、地域のガイドラインに従った標準的な治療課程を完了したことを示す記録がある場合を除く)
- 胸部X線写真に異常があり、活動性感染症または悪性腫瘍の可能性がある.(胸部X線写真はベースライン受診前に撮影されるべき)
- 臓器移植（心臓,肺,腎臓,肝臓など）または造血幹細胞・骨髄移植の既往歴.
- 治療済みの基底細胞または扁平上皮の非浸潤性皮膚癌,子宮頸部上皮内悪性腫瘍grade1/2,子宮頸部非浸潤癌を除く悪性腫瘍の既往あり.

論文のPICO: Pは？

Exclusion criteria

- APSの診断または既往歴がある.(LA,抗CL,抗β2-GPIの3つとも陽性の患者、APSと診断されていない抗リン脂質抗体が陽性の患者は力価や抗体陽性数・リスクファクターを元に治験参加可能かを判定委員会で判断、血栓予防を受ける意思がない、動脈または静脈血栓症の既往がある)
- 末梢神経障害の病歴または現在の診断がGrade 2以上, 活動性のぶどう膜炎, 臨床的に重要であると治験担当医師が判断するその他の眼科的所見.
- 線維筋痛症を合併しており,その症状や治療がSLEの病状や活動性の評価に重大な影響を及ぼすと治験責任医師が判断した場合.
- 皮膚筋炎,多発性筋炎,強皮症,関節リウマチ,その他SLE以外の炎症性関節・皮膚疾患またはオーバーラップ症候群を原疾患とする.

論文のPICO: Pは？

Exclusion criteria

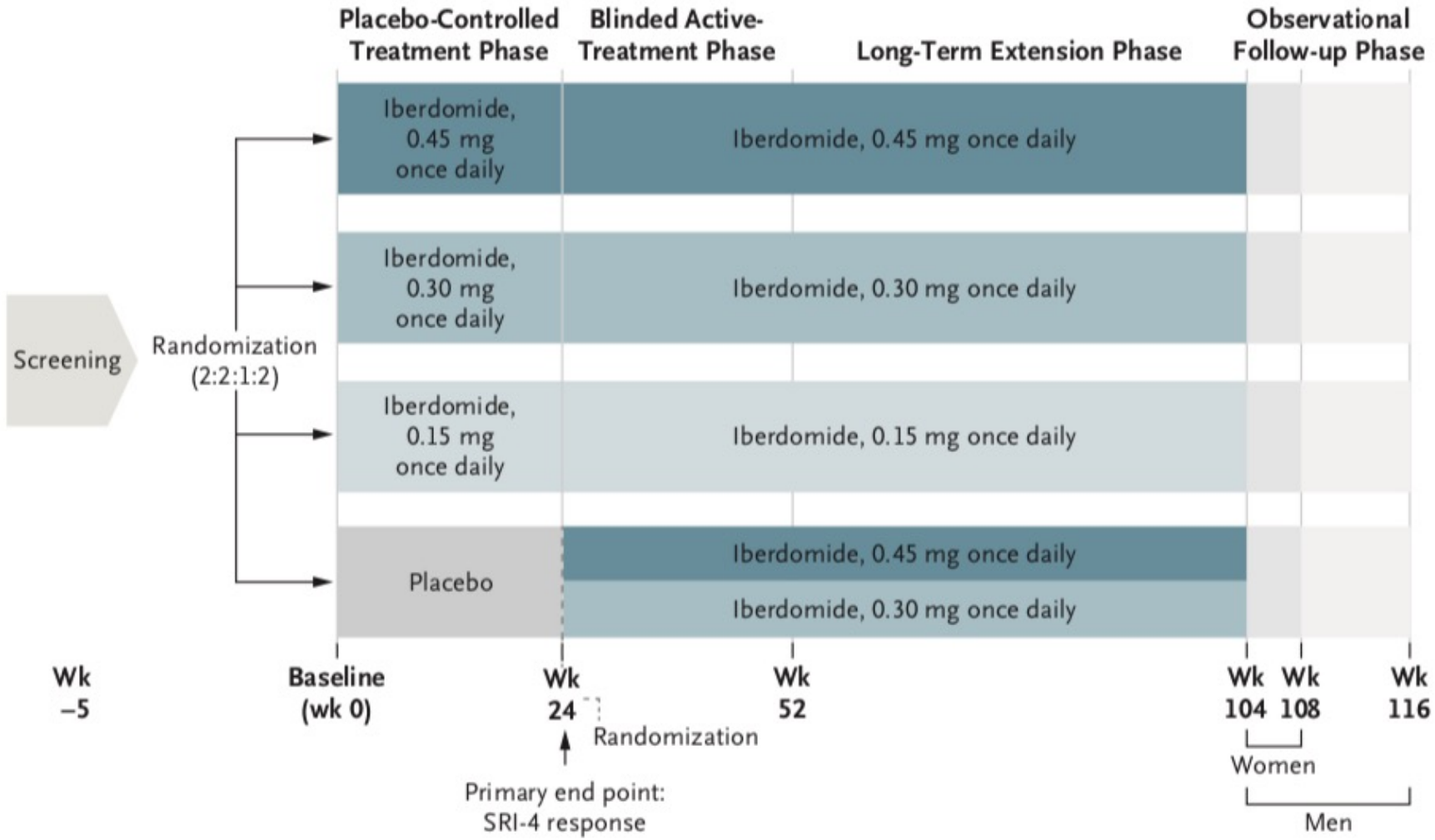
- SLEに起因しない臨床的に重大な,不安定な,コントロールされていない急性あるいは慢性疾患（例：心血管系,肺,血液,消化器,肝,腎,神経,悪性腫瘍,精神,感染症）もしくは検査異常, もしくは予定されている外科処置があり, 医師の判断で患者に過度のリスクを与える可能性がある.
- ベースライン時の来院から6ヶ月以内のCYCの使用,メルファランや他のアルキル化剤の使用,ベースライン訪問前8週間以内のETNの使用,ベースライン訪問前3ヶ月以内のBLMの使用,ベースライン訪問前1年以内のRTXや抗CD22などのB 細胞除去薬の使用,2年以内に他の生物学的製剤または非生物学的製剤の免疫抑制剤の使用.

論文のPICO: Pをまとめると・・・？

- 総じて活動性はそこそこあるが,
  - 重篤な臓器障害（Lupus nephiritis, NPSLEなど含む）はなく、かつ
    入院して集中的な治療が必要な患者ではなさそう....
  - 感染症、悪性腫瘍、APS発症者、オーバーラップ症候群を原疾患とするものは除外されている

論文のPICO: I/Cは？

- Iberdomide 0.45mg 0.30mg 0.15mg,及び placeboの ４群2:2:1:2に割付
- 治験評価者が適応を評価して適宜血栓予防を行った.



論文のPICO: Oは？　Primary endpoint

- 24週時点でのSRI-4 responder

https://gskpro.com/ja-jp/disease-info/sle/score/

論文のPICO: Oは？　Secondary endpoint

- SLEDAI-2Kスコアが4点以上減少
- 皮膚エリテマトーデス病変面積・重症度指数（CLASI）-活動スコア（CLASI-A）が50%以上減少

- 新規でBILAG-2004臓器病変がない
- PGAスコアで0.3点以上の増加なし
- 圧痛/腫脹関節のベースラインからの変化
- PGA/FACIT-fatigueのベースラインからの変化
- PSL換算で10mg以上のグルココルチコイドを内服し,1日10mg未満および7.0mg未満に減量した患者の割合(16週目までに減量し,24週目まで維持)

ランダム割付されているか

s (SLE).[1-3] The zinc finger transcription
Ikaros and Aiolos affect immune-cell
ment and homeostasis[3-5] and are impli-
ı genetic predisposition to SLE.[6-8] Ikaros
development of B cells and plasmacytoid
ic cells, which are major producers of
ıterferon. Aiolos supports B-cell differen-
Messenger RNAs for genes encoding
(*IKZF1*) and Aiolos (*IKZF3*) are overex-
in patients with SLE.[6-8]
lomide is a high-affinity cereblon modu-
at binds to cullin-RING E3 ubiquitin li-
complex,[5] promoting ubiquitination and
omal degradation of Ikaros and Aiolos.[9]
e immunomodulatory effects include in-
levels of interleukin-2 and decreased
f pro-inflammatory cytokines, B-cell dif-
ıtion, and autoantibody production.[4,5] A
a trial of iberdomide in patients with SLE

patients with active, moderate-to-severe SLE.

is
N

METHODS

TRIAL DESIGN

The trial was conducted at 117 sites in the United States, Canada, Europe, South America, Mexico, and Russia from July 6, 2017 through January 21, 2020. Patients with SLE were randomly assigned in a 2:2:1:2 ratio to receive oral iberdomide (at a dose of 0.45, 0.30, or 0.15 mg) or placebo once daily for 24 weeks, along with the continued use of standard-of-care medications (Fig. 1). Stratification factors included the baseline prednisone (equivalent) dose (≥10 mg or <10 mg per day) and the score (≥10 or <10) on the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K, a 24-item weighted score of lupus activity that ranges from 0 to 105,

Placebo-Controlled Blinded Active- Observational

されている

Baselineは同等か？

- SLEの診断からスクリーニングまでの期間にやや差がある.
- ステロイドは約80%,
  HCQは60-80%,
  免疫抑制役薬は約50%程の患者で投与されている.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Iberdomide, 0.45 mg (N=81)	Iberdomide, 0.30 mg (N=82)	Iberdomide, 0.15 mg (N=42)	Placebo (N=83)	Total (N=288)
Age — yr	46.4±11.2	44.7±13.7	43.8±13.0	43.4±13.3	44.7±12.8
Female sex — no. (%)	79 (98)	77 (94)	41 (98)	81 (98)	278 (97)
Race — no. (%)†					
Black	5 (6)	6 (7)	3 (7)	7 (8)	21 (7)
White	60 (74)	59 (72)	29 (69)	60 (72)	208 (72)
Other	16 (20)	17 (21)	10 (24)	16 (19)	59 (20)
Hispanic or Latino ethnic group — no. (%)†	33 (41)	46 (56)	21 (50)	41 (49)	141 (49)
Geographic region — no. (%)					
United States or Canada	18 (22)	20 (24)	9 (21)	16 (19)	63 (22)
Europe	31 (38)	18 (22)	11 (26)	27 (33)	87 (30)
Mexico or South America	29 (36)	39 (48)	20 (48)	35 (42)	123 (43)
Russia	3 (4)	5 (6)	2 (5)	5 (6)	15 (5)
Median time from initial diagnosis of SLE to randomization (range) — yr	9.0 (0.5–31.7)	7.3 (0.5–35.8)	7.3 (0.9–35.7)	5.7 (0.5–35.8)	7.2 (0.5–35.8)
Antinuclear antibody level ≥1:80 — no. (%)	79 (98)	82 (100)	42 (100)	83 (100)	286 (99)
Mean SLEDAI-2K global score‡	9.5±2.8	9.6±2.7	9.5±2.8	9.8±3.6	9.6±3.0
BILAG-2004, 1 A score or >1 B score — no. (%)§	59 (73)	60 (73)	35 (83)	65 (78)	219 (76)
Mean PGA score¶	1.7±0.5	1.7±0.3	1.7±0.4	1.7±0.4	1.7±0.4
Mean CLASI-A activity‖	7.2±7.2	7.1±7.9	7.2±6.1	6.3±6.5	6.9±7.0
Cutaneous lupus subtype — no. (%)					
Acute	38 (47)	43 (52)	30 (71)	50 (60)	161 (56)
Subacute	12 (15)	9 (11)	9 (21)	17 (20)	47 (16)
Chronic	29 (36)	23 (28)	14 (33)	18 (22)	84 (29)
No. of affected joints					
Swollen	5.5±4.0	7.2±6.1	7.2±6.4	6.4±4.7	6.5±5.3
Tender	8.2±5.8	9.8±7.4	8.6±5.9	8.7±6.1	8.9±6.4
High gene signature — no. (%)					
Aiolos	36 (44)	32 (39)	14 (33)	27 (33)	109 (38)
Type I interferon	57 (70)	49 (60)	25 (60)	48 (58)	179 (62)
Ikaros	64 (79)	53 (65)	28 (67)	56 (68)	201 (70)
Elevated anti–double-stranded DNA antibody level — no. (%)	29 (36)	23 (28)	13 (31)	27 (33)	92 (32)
Baseline treatment for SLE — no. (%)					
Any dose of oral glucocorticoid	58 (72)	64 (78)	31 (74)	64 (77)	217 (75)
Oral glucocorticoid ≥10 mg/day	32 (40)	30 (37)	17 (40)	31 (37)	110 (38)
Antimalarial agent	50 (62)	63 (77)	28 (67)	66 (80)	207 (72)
Immunosuppressant agent	37 (46)	36 (44)	22 (52)	34 (41)	129 (45)

ITT解析か？

- 593人が適応評価, 289人が基準を満たした.
- Iberdomide 0.45mg群のうち1人が薬剤内服せず, 最終的には288人に対してmITT解析がなされた.

test with a two-sided significance level of 0.1. The Hochberg procedure was used to adjust for multiplicity in the comparison of iberdomide at a dose of 0.45 or 0.30 mg with placebo for the primary end point, as indicated in the revised statistical analysis plan, which is available with the protocol at NEJM.org. This statistical analysis plan was written before the database had been unlocked. The sample size of the lowest-dose group (0.15 mg) was limited to 40 patients for the estimation of the minimally effective dose.

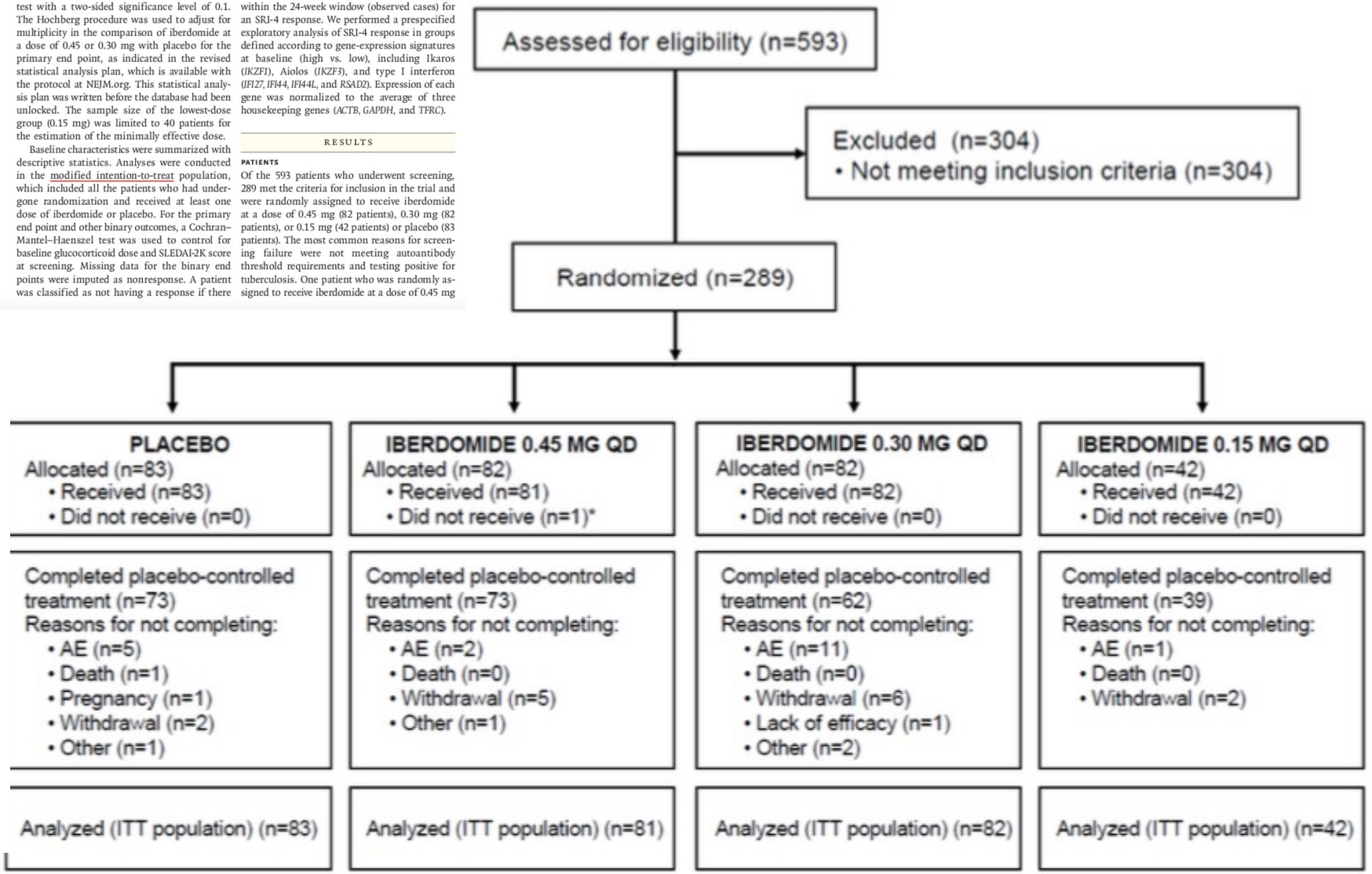
Baseline characteristics were summarized with descriptive statistics. Analyses were conducted in the modified intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of iberdomide or placebo. For the primary end point and other binary outcomes, a Cochran–Mantel–Haenszel test was used to control for baseline glucocorticoid dose and SLEDAI-2K score at screening. Missing data for the binary end points were imputed as nonresponse. A patient was classified as not having a response if there within the 24-week window (observed cases) for an SRI-4 response. We performed a prespecified exploratory analysis of SRI-4 response in groups defined according to gene-expression signatures at baseline (high vs. low), including Ikaros (*IKZF1*), Aiolos (*IKZF3*), and type I interferon (*IFI27*, *IFI44*, *IFI44L*, and *RSAD2*). Expression of each gene was normalized to the average of three housekeeping genes (*ACTB*, *GAPDH*, and *TFRC*).

RESULTS

PATIENTS

Of the 593 patients who underwent screening, 289 met the criteria for inclusion in the trial and were randomly assigned to receive iberdomide at a dose of 0.45 mg (82 patients), 0.30 mg (82 patients), or 0.15 mg (42 patients) or placebo (83 patients). The most common reasons for screening failure were not meeting autoantibody threshold requirements and testing positive for tuberculosis. One patient who was randomly assigned to receive iberdomide at a dose of 0.45 mg

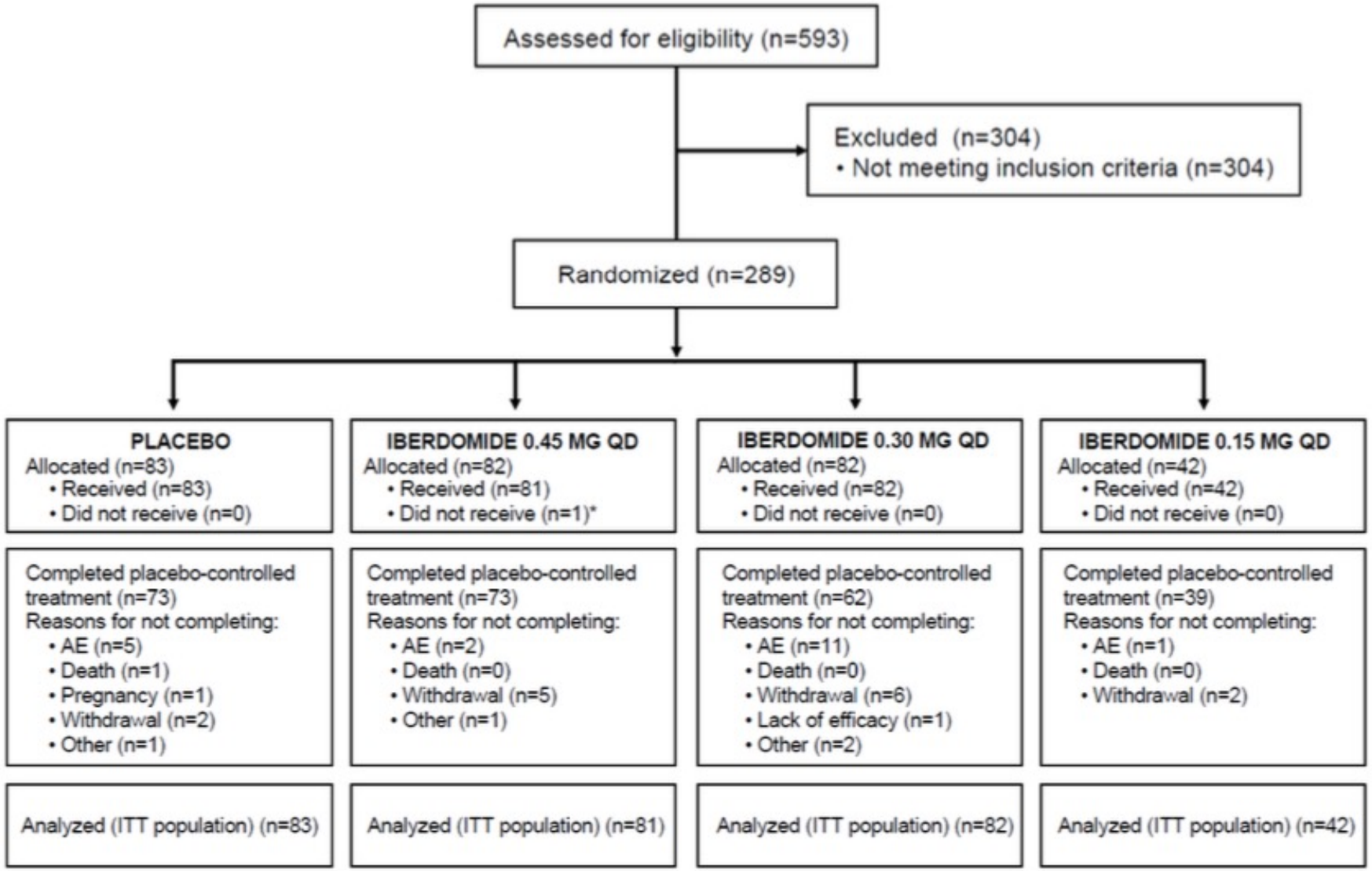
Figure S1. CONSORT Diagram



ITT解析か？

- 288人中247人(86%)が24週の試験を完遂.
- Iberdomide 0.45mg群で73人(90%), 0.30mg群で62人(76%), 0.15mg群で39人(93%), placebo群で73人(88%)
- 0.30mg群で最も多く脱落.

Figure S1. CONSORT Diagram



マスキングされているか

5. マスキング（盲検化）されているか？

マスキング（盲検化）されているのは誰か？

●患者，参加者　●介入（治療）実施者　●Outcome 評価者　●データ解析者

■四重　□三重　□二重　□一重　□盲検なし　□盲検化不可能　□不明

/ULTIPLE INNATE athways is remark- mic lupus erythe- nger transcription ffect immune-cell s[3-5] and are impli- n to SLE.[6-8] Ikaros and plasmacytoid ajor producers of rts B-cell differen- r genes encoding *IKZF3*) are overex- [8]

ity cereblon modu- IG E3 ubiquitin li- ubiquitination and karos and Aiolos.[9]

showed decreased disease activity.[10] In the current phase 2, randomized, placebo-controlled, double-blind trial, we evaluated iberdomide in patients with active, moderate-to-severe SLE.

METHODS

TRIAL DESIGN

The trial was conducted at 117 sites in the United States, Canada, Europe, South America, Mexico, and Russia from July 6, 2017 through January 21, 2020. Patients with SLE were randomly assigned in a 2:2:1:2 ratio to receive oral iberdomide (at a dose of 0.45, 0.30, or 0.15 mg) or placebo once daily for 24 weeks, along with the continued use of standard-of-care medications (Fig. 1). Stratification factors included the

with higher scores indicating greater disease activity). To address the thromboembolic risk associated with cereblon modulators, the patients received at least one form of thromboprophylaxis (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org).

This trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. The protocol, which is available at NEJM.org, was approved by the institutional review board or independent ethics committee at each site and conducted according to applicable laws. All the patients provided written informed consent. An adjudication committee, whose members were unaware of the trial-group assignments, reviewed patient eligibility to participate in the trial and disease scoring throughout the trial. The safety manage-

had severe or unstable neuropsychiatric SLE, an estimated glomerular filtration rate of less than 45 ml per minute per 1.73 m^2, proteinuria greater than 2000 mg per day, nephritis warranting induction treatment, antiphospholipid syndrome, or high-risk antiphospholipid status. The Methods section in the Supplementary Appendix includes detailed eligibility criteria and describes thromboprophylaxis and exclusion criteria, including the concomitant use of certain medications.

END POINTS AND ASSESSMENTS

The primary end point at week 24 was a response on the SLE Responder Index (SRI-4), which was defined as a reduction of at least 4 points in the SLEDAI-2K score, no new disease activity as measured by an A (severe) score or more than one B (moderate) score on the British Isles Lupus Assessment Group (BILAG) 2004 index (BILAG-2004; incorporating 97 items into

results.

9.9.3. Pharmacogenetics Analysis

DNA will be examined for the presence of polymorphisms in or near the genes associated with SLE (including but not limited to the following genes: CC-220 target-related genes CRBN (gene encoding cereblon), CUL4A IKZF1 (gene encoding Ikaros), and IKZF3 (gene encoding Aiolos).

9.9.4. Independent External Data Monitoring Committee

Although Celgene study staff will monitor safety on an ongoing basis throughout the study, formal blinded safety assessments of the relevant study data will be performed by an external independent Data Monitoring Committee (DMC). The DMC will review unblinded data to evaluate safety during the study and data from the interim analysis for futility. The DMC is comprised of independent physician experts and a statistician for whom there is no identified conflict of interest. The DMC will be convened regularly, at least once a year, or ad hoc at the request of the SMT. Recommendations of the DMC based on the overall benefit/risk evaluation may include proceeding with the study per protocol, proceeding with the study with modification, or study suspension. The scope, conduct, membership, processes, and accountabilities of the DMC are specified in the DMC charter.

症例数は十分か？

- Primary endpointに関して,Iberdomide群とplacebo群の間に21点の差を検出する,80%の検出力が得られるようには80人のサンプルが必要と計算.
- 最小有効量を推定するために,最低用量群のサンプルサイズは40人に制限された.

結果の評価

Primary endpoint

Table 2. Primary and Secondary Efficacy End Points at Week 24 in the Intention-to-Treat Population.*

End Point	Iberdomide, 0.45 mg (N=81)	Difference vs. Placebo (95% CI)	P Value	Iberdomide, 0.30 mg (N=82)	Difference vs. Placebo (95% CI)	P Value	Iberdomide, 0.15 mg (N=42)	Difference vs. Placebo (95% CI)	P Value	Placebo (N=83)
		percentage points			*percentage points*			*percentage points*		
Primary end point: SRI-4 response — no./total no. (%)†	44/81 (54)	19.4 (4.1 to 33.4)	0.01	33/82 (40)	5.0 (−9.8 to 19.5)	0.51	20/42 (48)	11.4 (−6.6 to 29.0)	0.21	29/83 (35)

- Iberdomide 0.45mg群で44/81人(54%)
- placebo群で29/83人(35%)

→adjusted difference, 19.4%(95%CI, 4.1 to 33.4; P=0.01)

結果の評価

7. 結果の評価

Primary Oucome

□時間軸に垂直な指標

追跡期間＝（24 週間）

介入群の発生率＝a／(a+b)＝（54）＝EER

対照群の発生率＝c／(c+d)＝（35）＝CER

RR＝EER／CER＝（1.54）

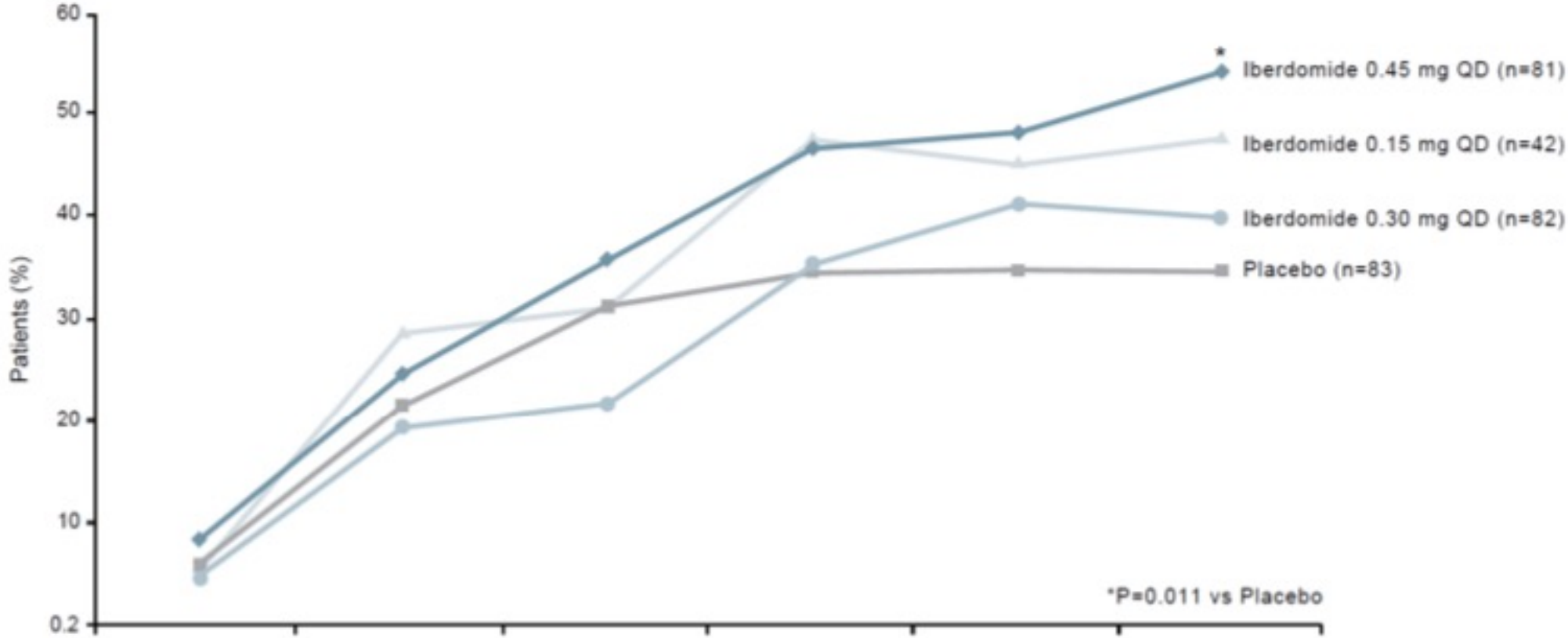
RRR＝1－RR＝（0.54）

ARR＝CER－EER＝（-19）

NNT＝1／ARR＝（5.2）

	Outcome（＋）	Outcome（－）	
介入群	44	37	81
対照群	29	54	83
	73	91	164

Figure S2. Time Course of SRI-4 Response



n/N (%)	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Placebo (N=83)	5/83 (6)	18/83 (22)	26/83 (31)	28/83 (35)	28/83 (35)	28/83 (35)
0.45 mg QD (N=81)	7/81 (9)	20/81 (25)	29/81 (36)	38/81 (47)	39/81 (48)	44/81 (54)
0.30 mg QD (N=82)	4/82 (5)	16/82 (20)	18/82 (22)	29/82 (35)	34/82 (42)	33/82 (40)
0.15 mg QD (N=42)	2/42 (5)	12/42 (29)	13/42 (31)	20/42 (48)	19/42 (45)	20/42 (48)

結果の評価　Secondary endpoint

- SLEDAI-2K 4点以上の改は,iberdomide群がplacebo群より有意に多かった.
- CLASIスコア>10点の患者群でもiberdomide群で有意に改善
- BILAG-2004, PGA, TJC/SJC, FACIT-fatigueスコア, ステロイドの減量で有意差なし.

Secondary end points							
Decrease of ≥4 points from baseline in SLEDAI-2K score — no./total no. (%)	45/81 (56)	19.3 (4.0 to 33.4)	35/82 (43)	6.5 (−8.5 to 21.0)	20/42 (48)	10.3 (−7.7 to 28.0)	30/83 (36)
No new A scores or >1 B score on BILAG-2004 — no./total no. (%)	70/81 (86)	8.0 (−3.9 to 19.7)	59/82 (72)	−5.3 (−18.4 to 8.1)	38/42 (90)	12.4 (−2.7 to 24.1)	65/83 (78)
No significant decrease in PGA score, <0.3 change from baseline — no./total no. (%)	69/81 (85)	6.8 (−5.2 to 18.6)	60/82 (73)	−4.3 (−17.4 to 8.9)	38/42 (90)	12.1 (−3.0 to 23.8)	65/83 (78)
CLASI-50 in subgroup of patients with CLASI score ≥10 at baseline — no./total no. (%)	13/19 (68)	14.2 (−19.5 to 44.5)	8/18 (44)	5.3 (−27.6 to 39.4)	8/11 (73)	24.0 (−12.4 to 53.1)	8/16 (50)
Mean change from baseline in no. of swollen joints in subgroup of patients with ≥2 swollen or tender joints at baseline‡	−6.6±0.3	0.1 (−0.6 to 0.8)	−6.0±0.4	0.7 (−0.1 to 1.6)	−6.0±0.4	0.7 (−0.2 to 1.5)	−6.7±0.3
Mean change from baseline in no. of tender joints in subgroup of patients with ≥2 swollen or tender joints at baseline‡	−7.6±0.5	0.3 (−1.0 to 1.6)	−6.7±0.5	1.3 (0.0 to 2.6)	−6.8±0.6	1.1 (−0.4 to 2.6)	−7.9±0.5
Adjusted mean change from baseline (95% CI) in FACIT-Fatigue score§	5.2 (3.0 to 7.4)	1.4 (−1.6 to 4.4)	3.1 (0.9 to 5.4)	−0.6 (−3.7 to 2.4)	2.7 (−0.3 to 5.6)	−1.1 (−4.7 to 2.5)	3.8 (1.6 to 6.0)
Glucocorticoid dose reduced by wk 16 to <10 mg/day from a dose ≥10 mg/day at baseline — no./total no. (%)	0/32		1/30 (3)	−3.2 (−17.7 to 13.0)	0/17		2/31 (6)

結果の評価

Prespecified Subgroup Analyses According to Biomarkers

- Aiolos/IFN-1遺伝子特性が高い患者群においてSRI-4 responseは高かった.

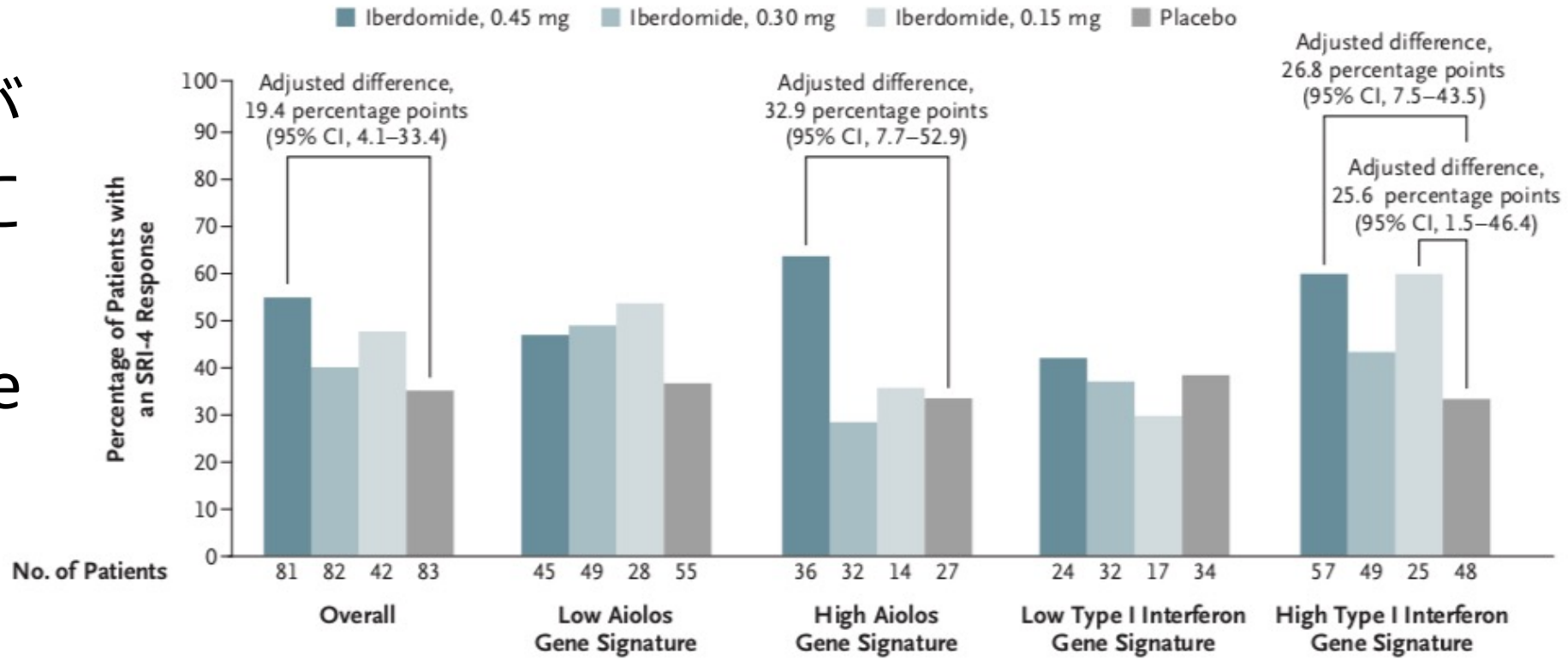


Figure 2. SRI-4 Clinical Response at Week 24 in Patient Subgroups Defined According to Aiolos and Type I Interferon Gene Signature at Baseline.

The percentages of patients with an SRI-4 response are shown. Groups were defined according to the gene-expression signatures at baseline (high vs. low), including Aiolos (*IKZF3*) and type I interferon (*IFI27*, *IFI44*, *IFI44L*, and *RSAD2*). Confidence intervals and secondary end points were not adjusted for multiplicity.

結果の評価

Prespecified Subgroup Analyses According to Biomarkers

- B細胞,樹状細胞はiberdomide群で低い.
- IL-2,Tregはiberdomide群で高い.

Table S5. Summary of Iberdomide Pharmacodynamics

	Iberdomide			Placebo
Biomarker, mean (SE) % change from baseline to week 24	**0.45 mg Once Daily**	**0.3 mg Once Daily**	**0.15 mg Once Daily**	
BLyS-R B cells	-62.0 (5.6)	-42.6 (5.8)	-25.2 (7.3)	-3.7 (7.0)
Switched memory B cells	-54.9 (6.0)	-35.0 (6.5)	-28.6 (8.5)	-14.1 (7.7)
mDC1	-27.0 (8.6)	-8.3 (9.8)	2.6 (12.9)	9.8 (10.2)
pDC	-60.2 (7.5)	-55.6 (7.6)	-36.1 (9.7)	13.7 (8.2)
Type I IFN gene signature	-60.1 (5.5)	-44.8 (5.9)	-46.3 (7.5)	1.3 (5.5)
Regulatory T cells	106.9 (7.7)	68.4 (8.3)	41.9 (9.6)	2.0 (7.1)
IL-2	182.2 (18.7)	129.8 (20.6)	113.2 (25.6)	38.0 (17.7)
Follicular T helper cells	41.0 (7.0)	42.9 (7.0)	28.9 (8.9)	8.4 (6.8)
IL-10	29.7 (8.3)	14.3 (8.7)	1.5 (11.3)	-2.8 (8.0)

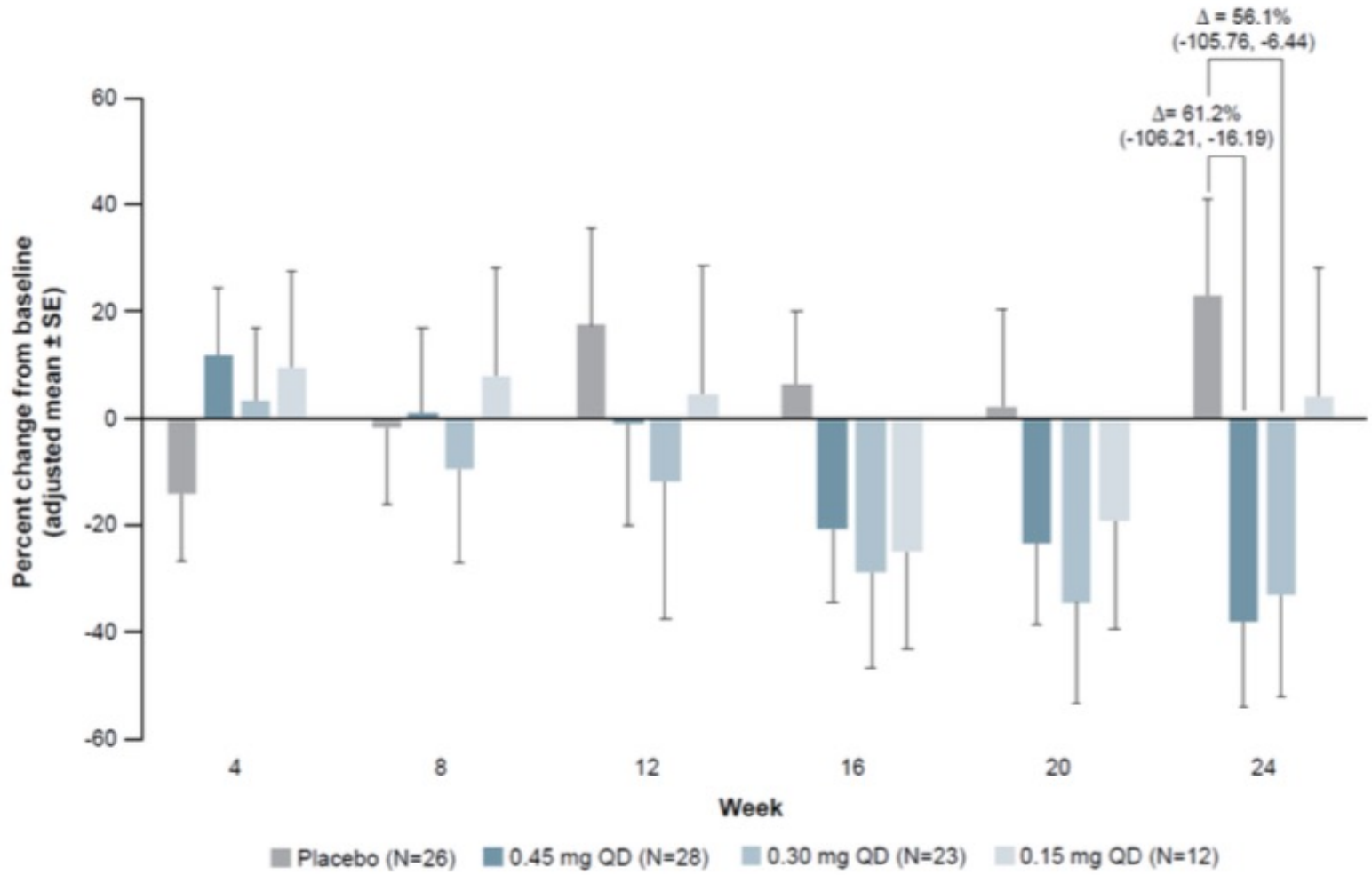
BLyS-R, B lymphocyte stimulator receptor; IFN, interferon; IL, interleukin; mDC, myeloid dendritic cells; pDC, plasmacytoid dendritic cells.

結果の評価

Pharmacodynamic Analyses

- 抗ds-DNA抗体はiberdomide群で低い.

Figure S3. Percent Change From Baseline in Anti-dsDNA Antibodies Over 24 Weeks

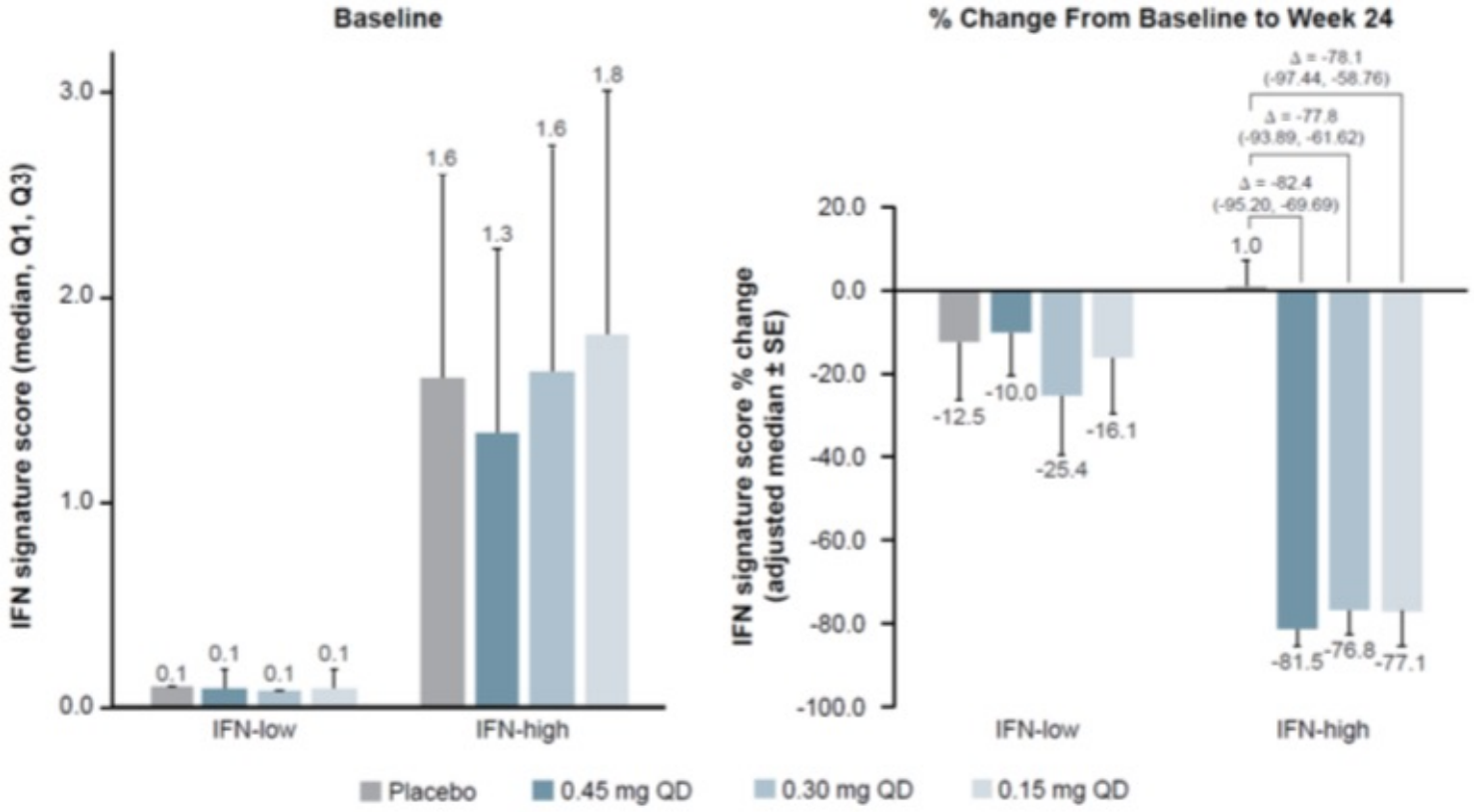


結果の評価

- IFN-1遺伝子特性の減少は，ベースラインでIFN遺伝子特性が高かった患者でのみ観察された

Prespecified Subgroup Analyses According to Biomarkers

Figure S4. Baseline and Percent Change From Baseline in Type I Interferon (IFN) Gene Signature by Baseline Subgroup



IFN gene signature scores in this figure are plotted as antilog values, rather than $\log_2$, to show percent change from baseline.

結果の評価

- Iberdomide
  0.45mg群 63/81人(78%)
  0.30mg群 64/82人(78%)
  0.15mg群 35/42人(74%)
  Placebo群 54/83人(65%)
  で有害事象が発生
- 治験責任医師による
  評価では,ほとんどが
  軽度から中等度

- Iberdomide投与群で
  尿路感染症
  上気道感染症
  好中球減少症
  インフルエンザが高頻度.

Safety

Table 3. Adverse Events during the Intervention Period.

Event	Iberdomide, 0.45 mg (N=81)	Iberdomide, 0.30 mg (N=82)	Iberdomide, 0.15 mg (N=42)	Placebo (N=83)	Iberdomide, Total (N=205)
	number of patients (percent)				
Any adverse event	63 (78)	64 (78)	31 (74)	54 (65)	158 (77)
Any intervention-related adverse event	32 (40)	36 (44)	14 (33)	24 (29)	82 (40)
Any serious adverse event	6 (7)	4 (5)	3 (7)	7 (8)	13 (6)
Any severe adverse event	1 (1)	4 (5)	3 (7)	5 (6)	8 (4)
Any adverse event leading to interruption of intervention	23 (28)	14 (17)	10 (24)	15 (18)	47 (23)
Any adverse event leading to withdrawal of intervention	4 (5)	11 (13)	2 (5)	6 (7)	17 (8)
Death	0	0	0	1 (1)	0
Adverse events with frequency of ≥5%*					
Urinary tract infection	8 (10)	13 (16)	2 (5)	3 (4)	23 (11)
Upper respiratory tract infection	10 (12)	7 (9)	3 (7)	4 (5)	20 (10)
Neutropenia	9 (11)	6 (7)	2 (5)	2 (2)	17 (8)
Influenza	5 (6)	4 (5)	3 (7)	3 (4)	12 (6)
Nasopharyngitis	7 (9)	1 (1)	3 (7)	1 (1)	11 (5)
Leukopenia	5 (6)	3 (4)	1 (2)	1 (1)	9 (4)
Diarrhea	3 (4)	2 (2)	3 (7)	0	8 (4)
Sinusitis	5 (6)	0	1 (2)	1 (1)	6 (3)
Headache	0	0	2 (5)	5 (6)	2 (1)

結果の評価

- 重篤な有害事象はiberdomide群で13/205人(6%) , placebo群7/83(8%)
- placebo群で重篤な有害事象が認められた83例のうち3例(4%)にSLEの再燃が認めらた.

Safety

Serious adverse events					
Any serious adverse event	6 (7)	4 (5)	3 (7)	7 (8)	13 (6)
Chronic obstructive pulmonary disease	1 (1)	0	0	0	1 (<1)
Epistaxis	1 (1)	0	0	0	1 (<1)
Forearm fracture	1 (1)	0	0	0	1 (<1)
Viral gastroenteritis	1 (1)	0	0	0	1 (<1)
Influenza-like illness	1 (1)	0	0	0	1 (<1)
Pneumonia	1 (1)	0	0	0	1 (<1)
Radius fracture	1 (1)	0	0	0	1 (<1)
Acetabulum fracture	0	1 (1)	0	0	1 (<1)
Brain-stem infarction	0	1 (1)	0	0	1 (<1)
Deep-vein thrombosis	0	1 (1)	0	1 (1)	1 (<1)
Hemiparesis	0	1 (1)	0	0	1 (<1)
Hypoxia	0	1 (1)	0	0	1 (<1)
Cardiac tamponade	0	0	1 (2)	0	1 (<1)
Implant site pain	0	0	1 (2)	0	1 (<1)
Leg fracture	0	0	1 (2)	0	1 (<1)
Pericarditis	0	0	1 (2)	0	1 (<1)
SLE flare	0	0	0	3 (4)	0
Diverticular perforation	0	0	0	1 (1)	0
Encephalopathy	0	0	0	1 (1)	0
Endometriosis	0	0	0	1 (1)	0
Laryngeal edema	0	0	0	1 (1)	0
Pulmonary embolism	0	0	0	1 (1)	0
Enterococcal urinary tract infection	0	0	0	1 (1)	0
Escherichia urinary tract infection	0	0	0	1 (1)	0

この論文の利点/欠点

利点

- RCT
- 多施設,global
- 一定の効果あり
- NNT 5は結構良い値

欠点

- ステロイド減らせてない
- 軽症とはいえ感染症は明らかに増えていそう
- Iberdomide0.30mgで離脱が多かった理由が不明確
- 容量依存性に効果が高まったかどうかも不明確