ORIGINAL ARTICLE

Inebilizumab for Treatment of IgG4-Related Disease

J.H. Stone, A. Khosroshahi, W. Zhang, E. Della Torre, K. Okazaki, Y. Tanaka, J.M. Löhr, N. Schleinitz, L. Dong, H. Umehara, M. Lanzillotta, Z.S. Wallace, M. Ebbo, G.J. Webster, F. Martinez Valle, M.K. Nayar, C.A. Perugino, V. Rebours, X. Dong, Y. Wu, Q. Li, N. Rampal, D. Cimbora, and E.L. Culver, for the MITIGATE Trial Investigators*

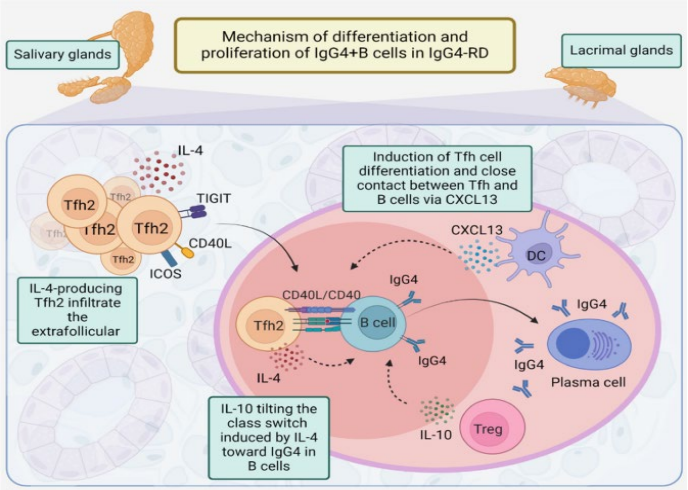
膠原病リウマチ内科　Journal Club（2025/03/04）

井上将

[N Engl J Med. 2024 Nov 14]

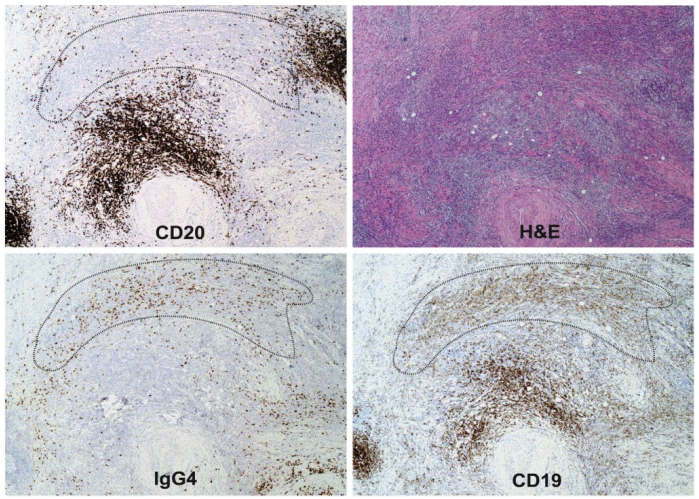
背景

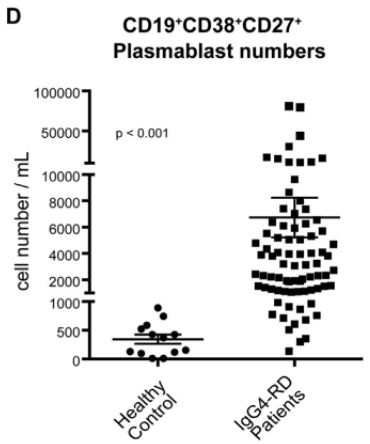
【IgG4関連疾患でのB細胞の関係】



- B細胞は最終的にはIgG4陽性形質細胞に分化する.
- この分化と増殖にはTfh(濾胞性ヘルパーT細胞), 特にTfh2が重要.
- TfhとIL-4などによるクラススイッチで産生されたIgG4自体には, 病原性はないと考えられている.

[Immunol Med. 2025;48(1):11-23]



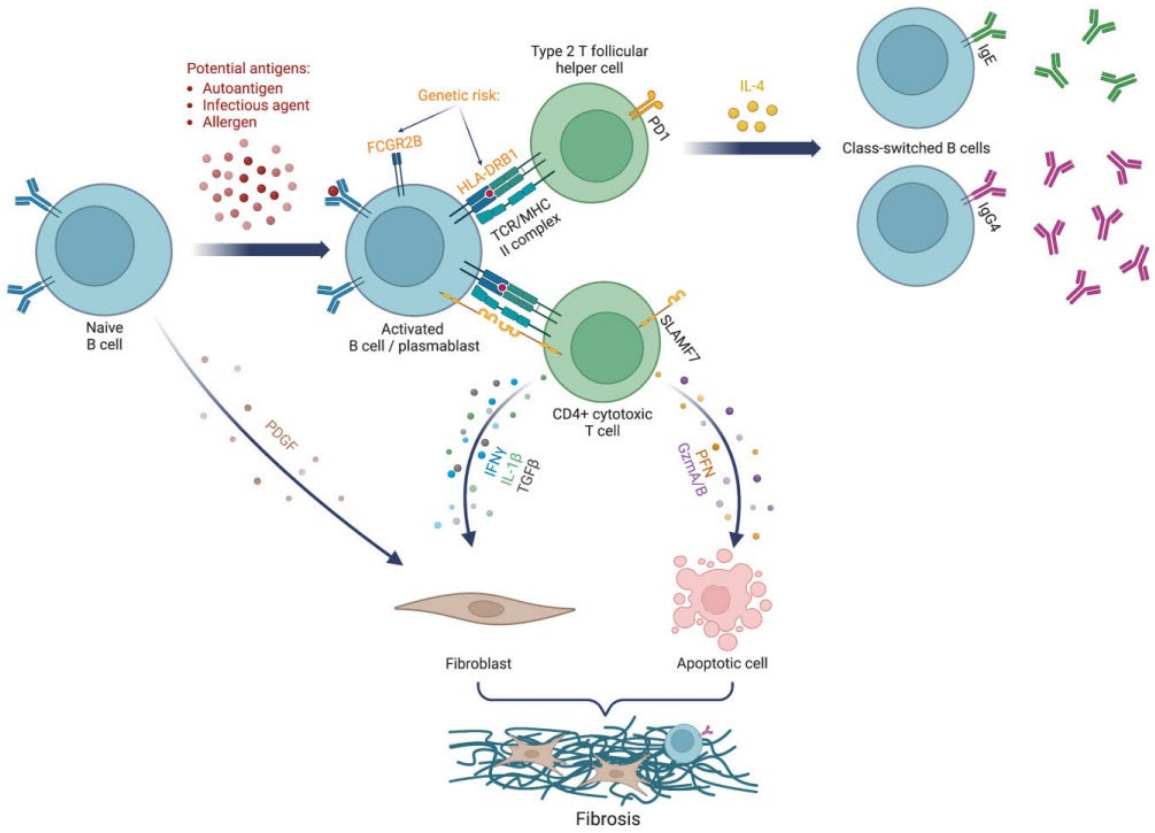


- Plasmablast(CD19+CD27+CD38+)の組織浸潤や末梢血での上昇が知られている(CD20陰性).
- 疾患活動性と相関する

[J Allergy Clin Immunol. 2014;134(3):679-87]

背景

【IgG4関連疾患でのB細胞の関係】

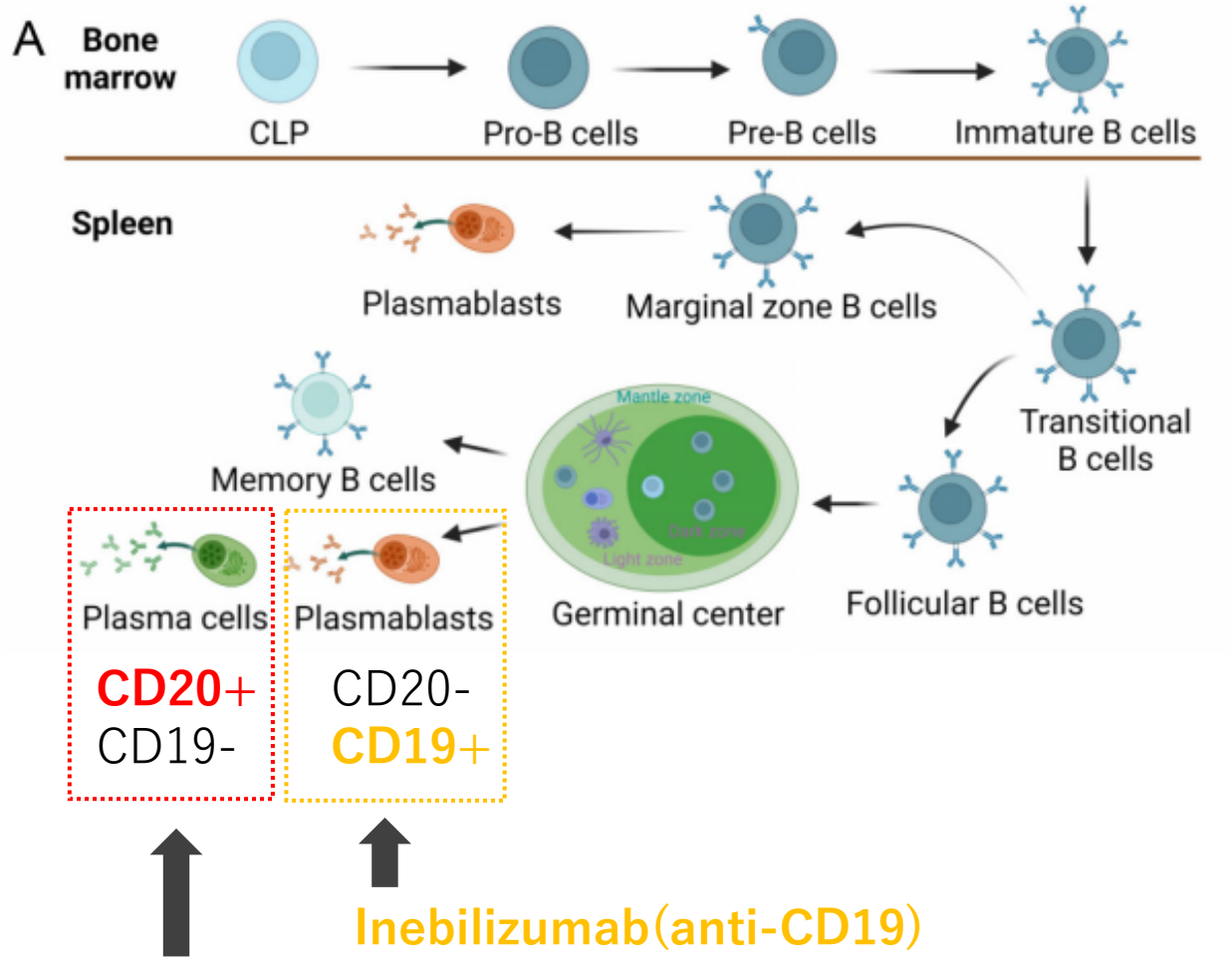


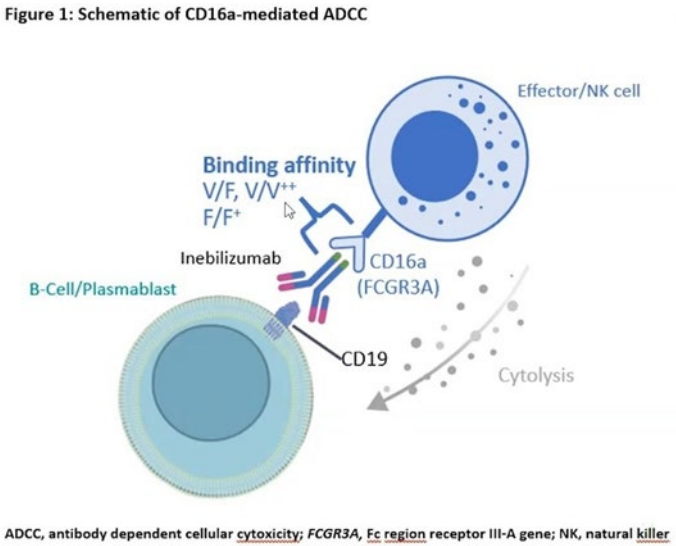
- CD4+ cytotoxic T細胞は, 末梢血で上昇し, 組織浸潤の主要な免疫細胞.
- 治療によって減少し, 障害臓器の数とも相関.
- B細胞自体も, CD4+ cytotoxic T細胞に抗原提示を行い増殖や分化促進させる.
- このCD4+ cytotoxic T細胞は, 細胞障害性のメディエーターを産生し, アポトーシスの促進や線維化を促進させる.
- メモリーB細胞は, 線維化を促進するPDGFBとLOXL2を産生する.

[Rheumatol Adv Pract. 2024;8(2):rkae020]

背景

【InebilizumabとRituximab】





https://www.vjneurology.com/video/hczebyd_wvk-distinctive-attributes-and-efficacy-of-inebilizumab-in-nmosd/より引用

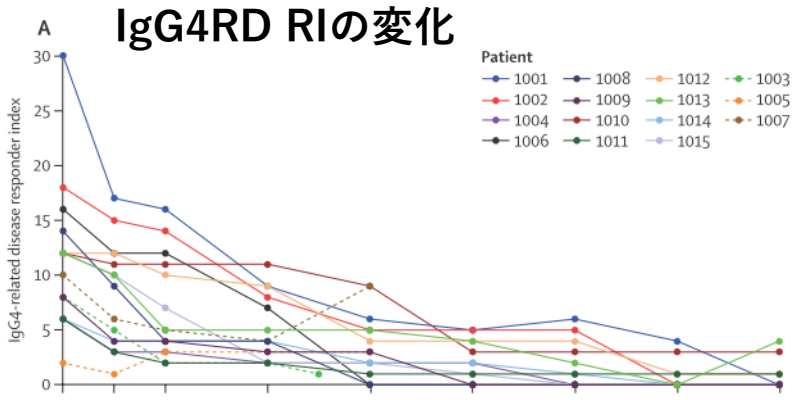
- Inebilizumabは無フコース化したFc領域を持ち, NK細胞などのFCγIIIRaと強力に結合してADCC活性を示す.

[Arthritis Rheumatol. 2023 Mar 10. doi: 10.1002/art.42492. Online ahead of print.]

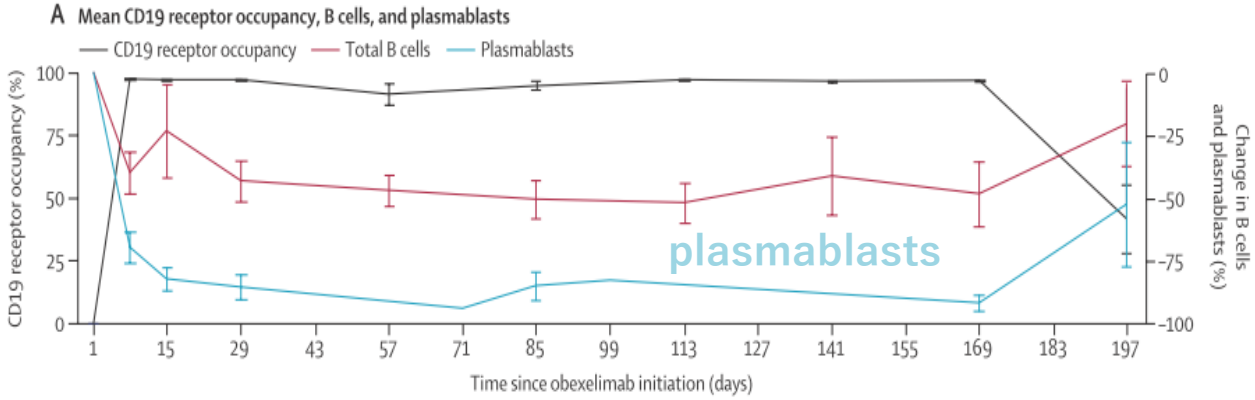
背景

【既報：Obexelimab】

- Obexelimab: CD19とFcγRIIbの両方に結合する非細胞溶解性ヒト化モノクローナル抗体
- open-label, single-arm, single centre, phase 2 pilot trial, n=15



IgG4RD RI≧2改善は12例(80%)達成



投与中, plasmablastsは減少

[Lancet Rheumatol 2023; 5(8): e442–50]

Method: PICO, design

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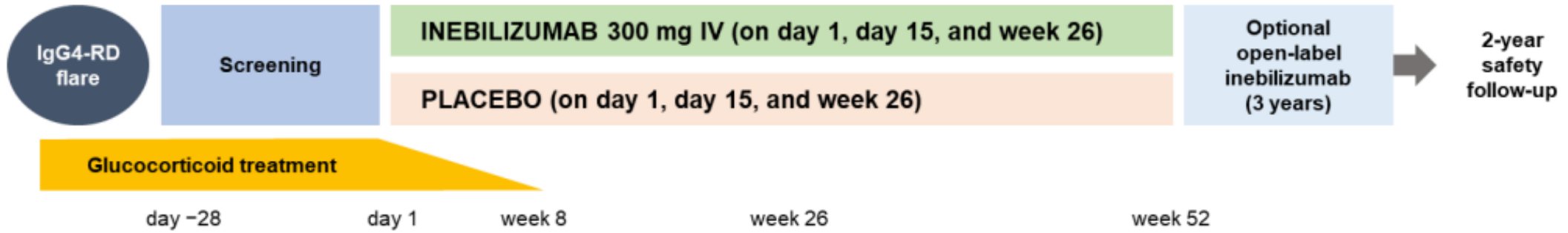
- **P** ２つ以上の臓器障害を持つ, 初発or再燃のIgG4-RD
- **I** Inebilizumab + GC
- **C** PBO + GC
- **O** 再燃までの期間

- phase 3, multicenter, parallel-cohort, double-blind, randomized, placebo-controlled trial
- 22カ国, 2020年9月～2023年4月



Method: design

【ランダム化】

- 初発と再燃で層別化し, 1:1に割り当て.

【GC治療と減量レジメン】

- ランダム化を受ける3〜8週前にGC治療(最大60mg).
- ランダム化の前日に20mgに減量.
- 8週目までに5mgまで減量し, 以降中止.

Table 8 Glucocorticoid Taper Schedule (Randomized-controlled Period)

RCP Week	Oral Prednisone Dose (or Equivalent)
Weeks 1-2	20 mg/day
Weeks 3-4	15 mg/day
Weeks 5-6	10 mg/day
Weeks 7-8	5 mg/day

Method: Inclusion/Exclusion criteria

Inclusion Criteria

- 18歳以上
- 2019 ACR/EULARの分類基準を満たす
- 2つ以上の臓器障害を認める
- GCでの治療が必要

Exclusion Criteria

- 6カ月以内にB細胞除去療法を受けた
- 6カ月以内にベリムマブ, アバタセプト, 生物学的製剤の治療を受けた
- 4週間以内に免疫抑制薬の治療を受けた
- eGFR<30ml/min/1.73 m^2

Method: Endpoint

【Primary endpoint】

- 再燃までの時間

  再燃の定義は, 症状, 身体所見, 血液検査, 病理所見を基にぞれぞれの臓器で定義された.

【Secondary endpoint】

- 再燃率
- 52wまでに再燃なし, GCなしの割合
- 52wまでに再燃なし, 追加治療なし, 疾患活動性なしの割合

例; 大血管の再燃の定義

Aorta and Large Blood Vessels
Symptom(s) or Finding(s)
Symptoms consistent with aorta & large blood vessels flare
Pain, palpable mass
Systemic/constitutional
Other (describe)
None
PE findings consistent with aorta & large blood vessels flare
Palpable arterial mass, especially if pulsatile, or bruit
Other (describe)
None
Imaging of aorta & large blood vessels
Consistent with aneurysm, dissection, thickening/enhancement of vessel wall or other vessel abnormality
Other (describe)
None
Biopsy results consistent with aorta/large blood vessel flare
Biopsy not done, unreadable, or report unavailable
Biopsy consistent with aorta/large blood vessel flare
Biopsy not consistent with aorta/large blood vessel flare

[Rheumatol Ther. 2023;10(6):1795-1808]

Method: Statistics

- プラセボの再燃率が35%と仮定.
- サンプルサイズが160例の場合, 39例の再燃が発生.
- 52週の治療期間中に再燃リスクが 65%に減少したことを検出する90%の検出力が得られる(両側 α レベル 0.05).
- Cox比例ハザードモデルで主要解析を施行(imputationなし).
- 2nd は主要解析で有意差がある場合のみ行われた(multiplicityなし).
- ロジスティック回帰分析と負の二項モデルで施行.

Result

【Baseline】

- Inebilizumab(INE), n=68
- Placebo(PBO), n=67
  - 年齢; INE 58.2歳, PBO 58.2歳
  - 男性; INE 57%, PBO 73%
  - 再発; INE 54%, PBO 54%
  - 初発; INE 46%, PBO 46%

Organ, n (%)*	Placebo (n = 67)	Inebilizumab (n = 68)	Overall (N = 135)
Pancreas	35 (52.2)	35 (51.5)	70 (51.9)
Lymph node(s)	36 (53.7)	31 (45.6)	67 (49.6)
Submandibular gland(s)	29 (43.3)	37 (54.4)	66 (48.9)
Lacrimal glands	22 (32.8)	30 (44.1)	52 (38.5)
Kidney	23 (34.3)	23 (33.8)	46 (34.1)
Bile ducts	25 (37.3)	18 (26.5)	43 (31.9)
Lung	19 (28.4)	16 (23.5)	35 (25.9)

Table 1. Characteristics of the Participants at Baseline (Full Analysis Population).*

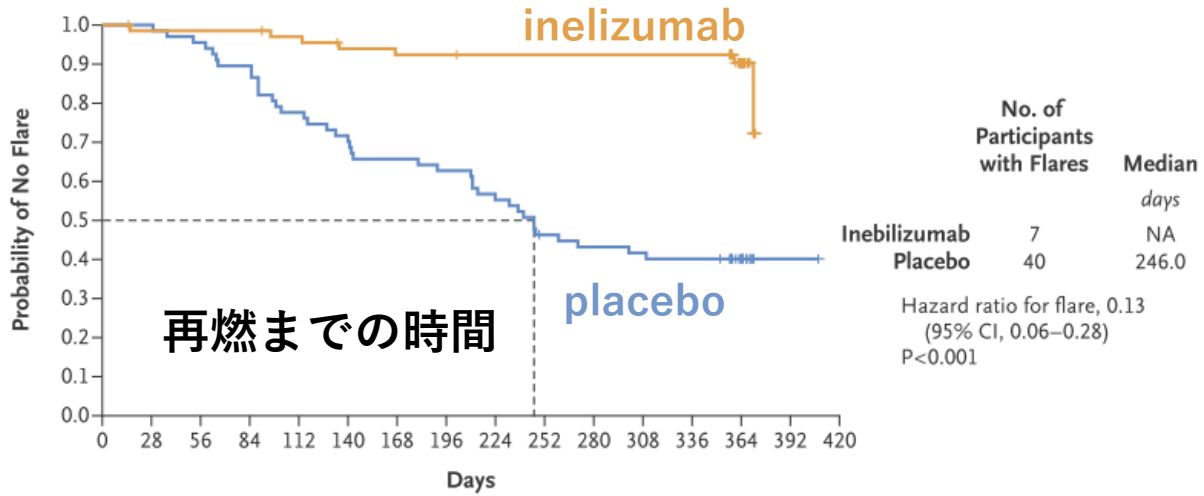
Characteristic	Inebilizumab (N=68)	Placebo (N=67)	Overall (N=135)
Age — yr	58.2±11.5	58.2±12.2	58.2±11.8
Male sex — no. (%)	39 (57)	49 (73)	88 (65)
Race or ethnic group — no. (%)†			
Asian	38 (56)	25 (37)	63 (47)
White	21 (31)	32 (48)	53 (39)
Other	9 (13)	10 (15)	19 (14)
Region — no. (%)‡			
United States	7 (10)	14 (21)	21 (16)
European Union	20 (29)	26 (39)	46 (34)
Asia	34 (50)	18 (27)	52 (38)
IgG4-related disease manifestation			
Recurrent — no. (%)	37 (54)	36 (54)	73 (54)
Newly diagnosed — no. (%)	31 (46)	31 (46)	62 (46)
Disease duration — yr§	2.6±3.7	2.5±3.1	2.6±3.4
Median among patients with recurrent disease (range)	3.6 (0.2–20.5)	3.6 (0.1–12.5)	3.6 (0.1–20.5)
Median among patients with newly diagnosed disease (range)	0.2 (0.1–3.8)	0.1 (0.1–7.3)	0.2 (0.1–7.3)
Median ACR–EULAR score (IQR)¶	38.7 (31.0–46.5)	36.3 (29.2–44.7)	36.7 (30.0–46.2)
No. of organs ever affected by IgG4-related disease — no. of participants (%)‖			
2	15 (22)	7 (10)	22 (16)
3 or 4	24 (35)	34 (51)	58 (43)
>4	29 (43)	26 (39)	55 (41)
Previous surgery or medical procedure, other than biopsy, associated with IgG4-related disease — no. (%)**	14 (21)	19 (28)	33 (24)
Previous treatments for IgG4-related disease — no. (%)			
Immunosuppressants other than glucocorticoids for treatment of disease flare	6 (9)	11 (16)	17 (13)
Maintenance therapy††	11 (16)	12 (18)	23 (17)

Result

【Endpoint】

Table 2. Primary and Key Secondary Efficacy End Points (Full Analysis Population).

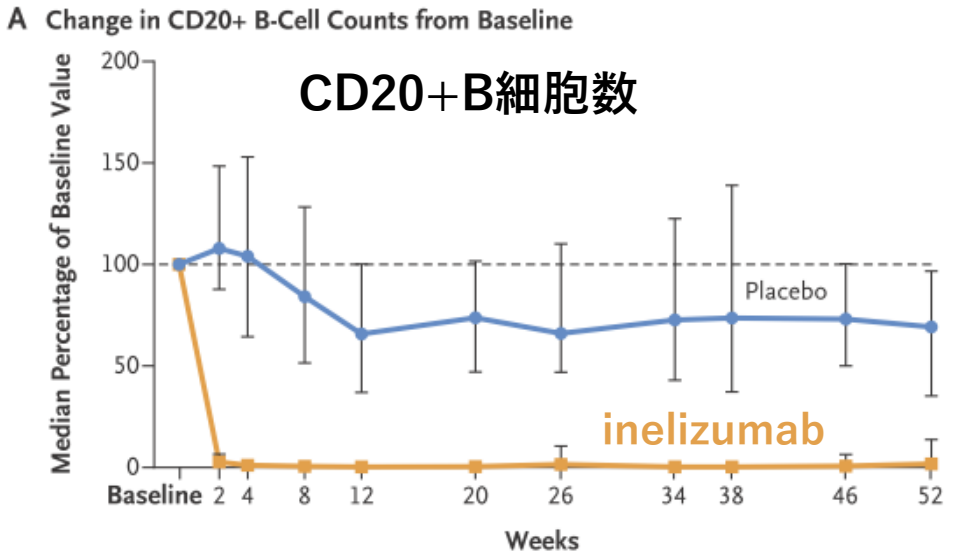
End Point	Inebilizumab (N=68)	Placebo (N=67)	Effect vs. Placebo (95% CI)	P Value
Primary: time to first treated and adjudicated IgG4-related disease flare — no. (%)	7 (10.3)	40 (59.7)	0.13 (0.06–0.28)*	<0.001
Key secondary				
Annualized flare rate: treated and adjudicated IgG4-related disease flares — no. (95% CI)	0.10 (0.05–0.21)	0.71 (0.53–0.94)	0.14 (0.06–0.31)†	<0.001
Flare-free, treatment-free complete remission at wk 52 — no. (%)‡	39 (57.4)	15 (22.4)	4.68 (2.21–9.91)§	<0.001
Flare-free, glucocorticoid-free complete remission at wk 52 — no. (%)¶	40 (58.8)	15 (22.4)	4.96 (2.34–10.52)§	<0.001

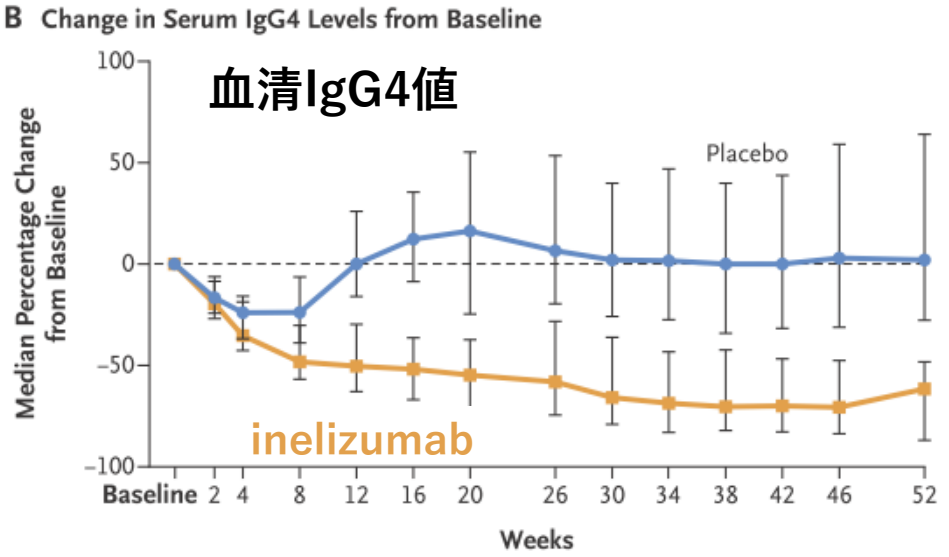


- **INE群**は，再燃を**87%抑制**(HR 0.13, 95%CI 0.06-0.28, p<0.001)
- 再燃; INE群 10.3%, PBO群 59.7%
- **INE群**は，年間の再燃率を**86%減少**
- **INE群**は，再燃なし，GC freeの割合も高い(58.8% vs 22.4%).

Result

【B細胞数と血清IgG4値】





- CD20+ B細胞数はINE投与後から急速に低下
- 血清IgG4値は, INE投与後から急速に低下

Result

【安全性】

	Placebo (n=67)	Inebilizumab (n=68)
Treatment-emergent SAEs	6 (9.0)	12 (17.6)
COVID-19†	0	2 (2.9)
Anal cancer	0	1 (1.5)
Anaphylactic reactions	0	1 (1.5)
Appendicitis	0	1 (1.5)
Deep vein thrombosis	0	1 (1.5)
Diverticulitis	0	1 (1.5)
Femoral neck fracture	0	1 (1.5)
Fibroadenomatoid mastopathy	0	1 (1.5)
Gout	0	1 (1.5)
Hyponatremia	0	1 (1.5)
Pulmonary atypical adenomatous hyperplasia	0	1 (1.5)
Pulmonary embolism	0	1 (1.5)
Acute kidney injury	1 (1.5)	0
Epistaxis	1 (1.5)	0
Coronary artery stenosis	1 (1.5)	0

- Grade 3以上の有害事象; INE群 12例 (18%), PBO群 8例 (12%)
- 重篤な有害事象; INE群 12例(18%), PBO群 6人(9%)
  - COVID-19と血球減少が多い

Table 3. Common Adverse Events Occurring during Treatment Period and Adverse Events of Special Interest (Safety Analysis Population).*

Event	Inebilizumab (N=68)	Placebo (N=67)
	no. of participants (%)	
Event occurring during treatment period†		
Covid-19	16 (24)	13 (19)
Lymphopenia	11 (16)	6 (9)
Urinary tract infection	8 (12)	4 (6)
Headache	6 (9)	7 (10)
Abdominal pain	4 (6)	7 (10)
Arthralgia	4 (6)	7 (10)
Upper respiratory tract infection	4 (6)	8 (12)
Diarrhea	3 (4)	9 (13)
Asthenia	2 (3)	8 (12)
Serious event occurring during treatment period	12 (18)	6 (9)
Event of special interest occurring in ≥1 participant	23 (34)	15 (22)
Cytopenia	17 (25)	9 (13)
Lymphopenia‡	13 (19)	6 (9)
Neutropenia	4 (6)	2 (3)
Anemia§	2 (3)	2 (3)
Cytopenia	1 (1)	0
Leukopenia	1 (1)	1 (1)
Thrombocytopenia¶	1 (1)	2 (3)
Serious or opportunistic infection	6 (9)	2 (3)
Herpes zoster‖	2 (3)	2 (3)
Appendicitis	1 (1)	0
Covid-19**	2 (3)	0
Diverticulitis	1 (1)	0
Infusion-related reaction	3 (4)	5 (7)
Anaphylaxis and serious hypersensitivity reactions	1 (1)	0
Anaphylactic reaction	1 (1)††	0

Discussion

- Inebilizumab(抗CD19モノクローナル抗体)は, IgG4-RDに対して52週間の間に再燃抑制と年間再燃率の低下を示した.
- IgG4-RDの患者全体と類似した参加者が登録され, この結果は一般化が可能.
- 他の免疫抑制薬を併用せずにInelizumabを評価したため, 結果はinelizumabのみに直接起因する. 維持療法での単独療法の有効性の可能性もある.
- NMOSDでのinelizumab投与後4年間では, 感染症の発生率は増加しなかった.

Discussion

【Limitation】

- 小規模な単一の試験.
- ベースラインで再燃の参加者が54%で, その中央値が3.6年のため比較的診断後, 早期の患者が組み入れられた.
- ２つの臓器障害を持つ患者群で評価しており, 単一臓器障害は除外.