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AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Efficacy, Safety, Pharmacokinetics, and Immunogenicity of ABBV-154 in Adults With Glucocorticoid-Dependent Polymyalgia Rheumatica: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial

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Arthritis Rheumatol. 2025 Aug; 77(8): 1041-1051. PMID 39866124

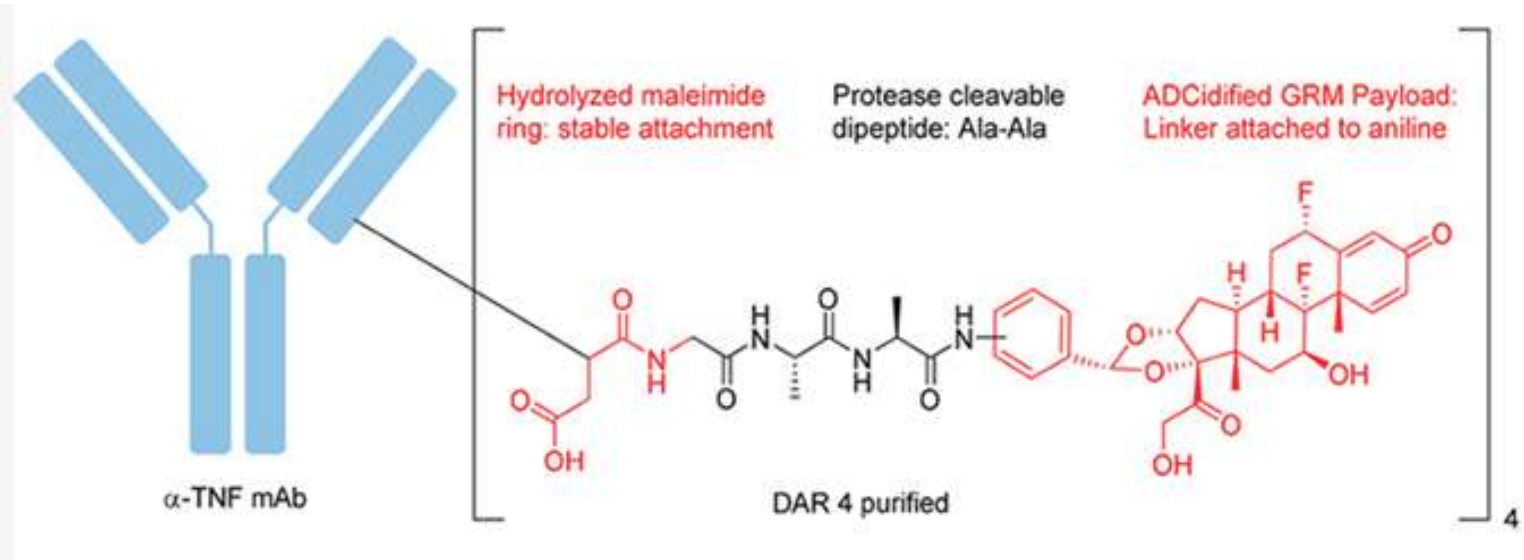
Journal Club 2025/10/14 竹内 遼

ABBV-154: ADAにグルココルチコイド受容体モジュレーターを結合

Journal of Medicinal Chemistry
pubs.acs.org/jmc Featured Article

Design and Development of Glucocorticoid Receptor Modulators as Immunology Antibody–Drug Conjugate Payloads

Adrian D. Hobson,* Michael J. McPherson, Wendy Waegell, Christian A. Goess, Robert H. Stoffel, Xiang Li, Jian Zhou, Zhongyuan Wang, Yajie Yu, Axel Hernandez, Jr., Shaughn H. Bryant, Suzanne L. Mathieu, Agnieszka K. Bischoff, Julia Fitzgibbons, Martyna Pawlikowska, Sujiet Puthenveetil, Ling C. Santora, Lu Wang, Lu Wang, Christopher C. Marvin, Martin E. Hayes, Anurupa Shrestha, Kathy A. Sarris, and Biqin Li



ABBV-154: Adalimumab(抗TNF阻害薬)にGRM(グルココルチコイド受容体モジュレーター)を結合した抗体薬物複合体(ADC)
→GCの有害事象を減少させるように設計

J Med Chem. 2022 Mar 24; 65(6): 4500-4533.

GRM: グルココルチコイド応答配列の転写を抑制し、GCの副作用を抑える

Improved Glucocorticoid Receptor Ligands: Fantastic Beasts, but How to Find Them?

Laura Van Moortel [1,2,3], Kris Gevaert [2,3] and Karolien De Bosscher [1,2,3]*

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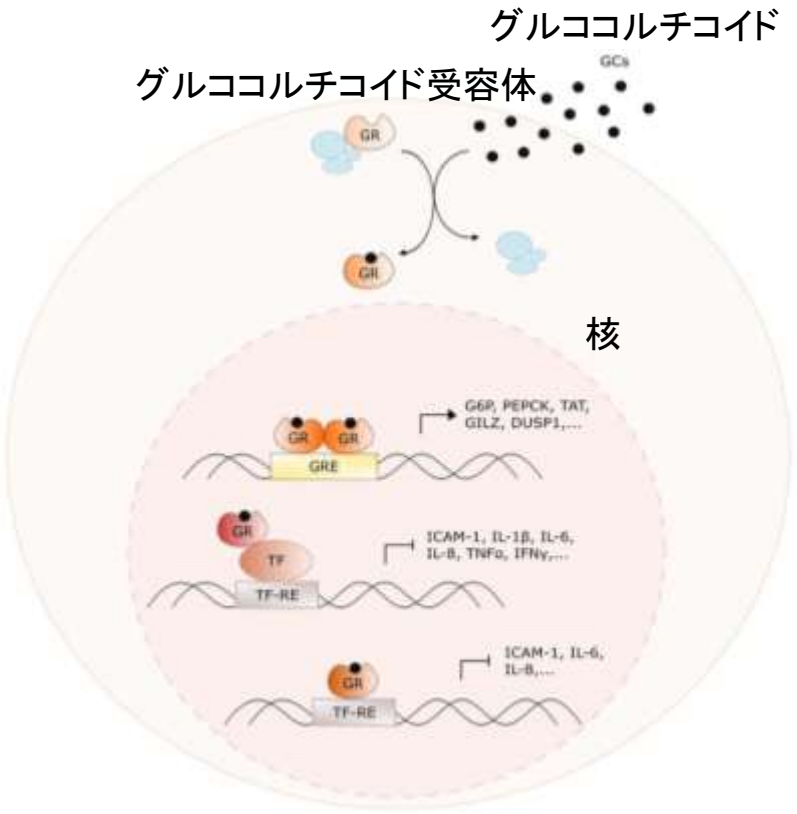
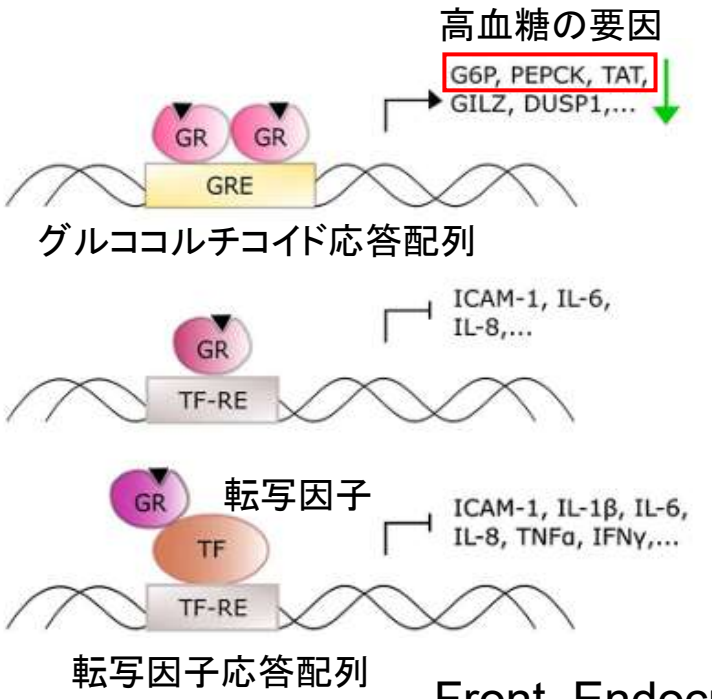




- GRMは核内におけるグルココルチコイド受容体(GR)の二量体を抑制
  →グルココルチコイド応答配列の転写を抑制
  →GCの副作用を抑える
- 単量体のGRがNF−κB、AP−1を抑制し炎症を抑える
  →炎症性抑制効果は不変

Front. Endocrinol. (Lausanne) 2020 Sep 24: 11:559673.

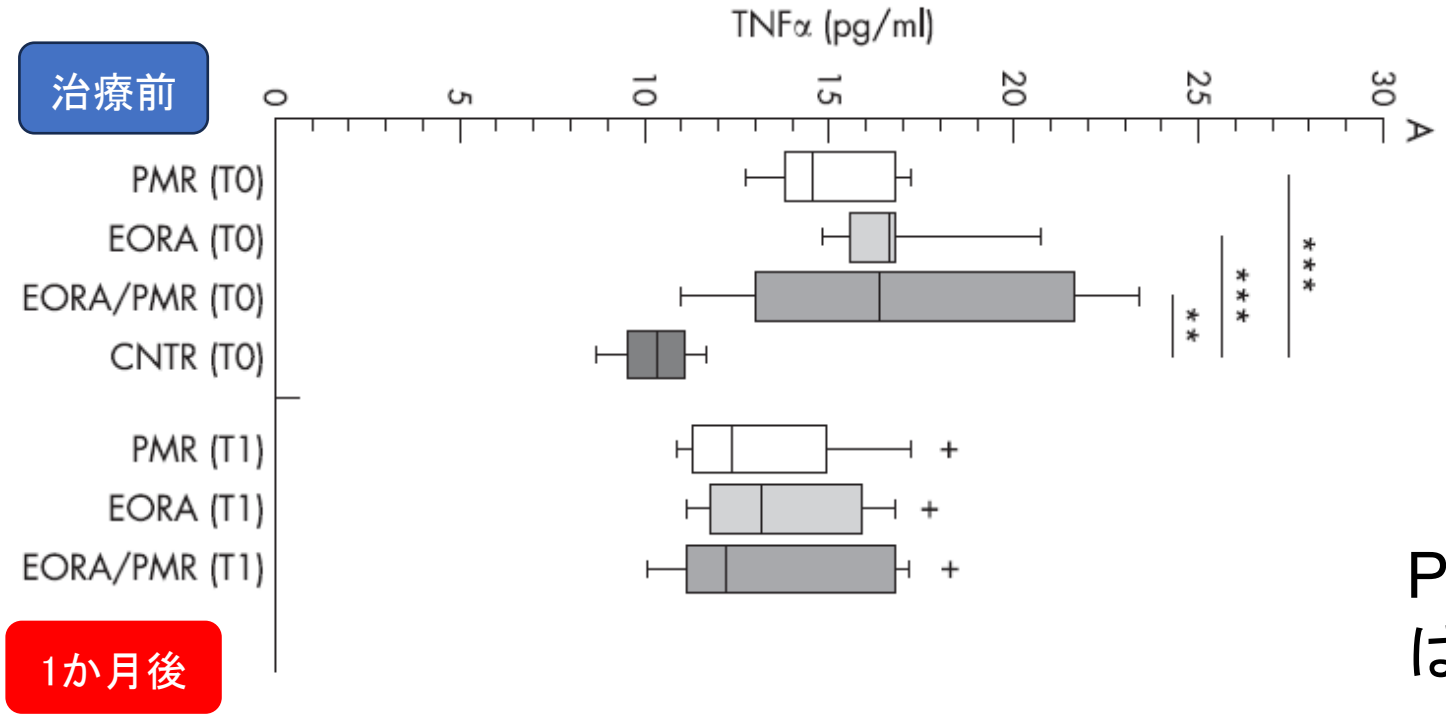
PMR: 血清中のTNFα濃度が高い

EXTENDED REPORT

Serum cytokines and steroidal hormones in polymyalgia rheumatica and elderly-onset rheumatoid arthritis

M Cutolo, C M Montecucco, L Cavagna, R Caporali, S Capellino, P Montagna, L Fazzuoli, B Villaggio, B Seriolo, A Sulli

Ann Rheum Dis 2006;65:1438–1443. doi: 10.1136/ard.2006.051979



PMRはControl群より血清のTNFα濃度は高く、治療により低下

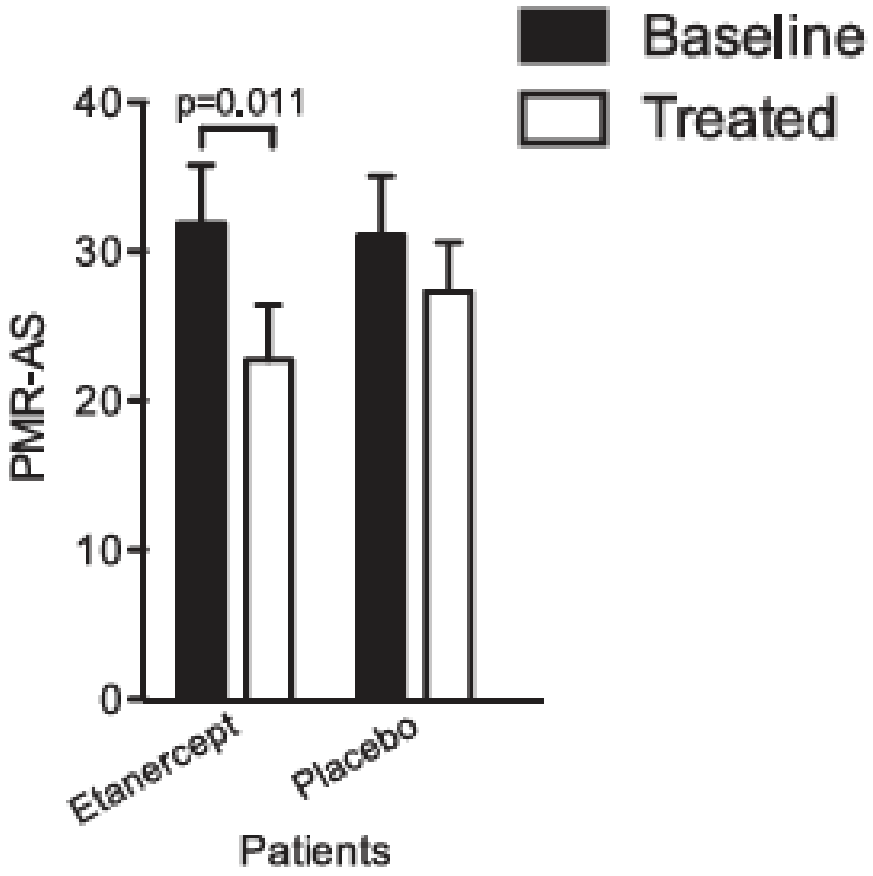
Ann Rheum Dis 2006; 65: 1438-1443.

PMRに対するetanerceptのRCT

RESEARCH ARTICLE Open Access

Effect of etanercept in polymyalgia rheumatica: a randomized controlled trial

Frederik Kreiner*, Henrik Galbo



*PMR-AS=CRP(mg/dL)+ Visual analogue score(VAS) for pain(range 0-10)+VAS for physician's global(range 0-10)+ (duration of morning stiffness in mins) x 0.1+ elevation of upper limbs(range 0-3)

Ann Rheum Dis 2004; 63: 1279-83.

EtanerceptはPMR-ASを24%減少(p=0.011)

Arthritis Res Ther 2010;12(5): R176.

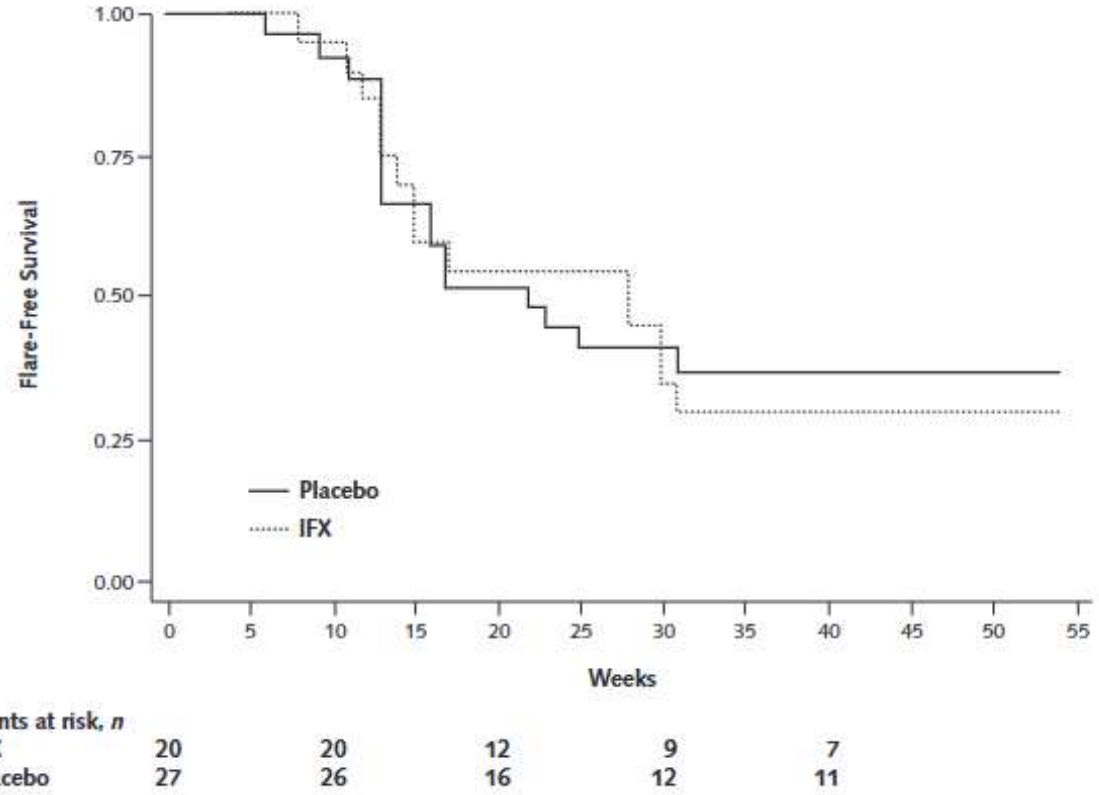
PMRに対するInfliximabのRCT

Annals of Internal Medicine | ARTICLE

Infliximab plus Prednisone or Placebo plus Prednisone for the Initial Treatment of Polymyalgia Rheumatica

A Randomized Trial

Carlo Salvarani, MD; PierLuigi Macchioni, MD; Carlo Manzini, MD; Giuseppe Paolazzi, MD; Aldo Trotta, MD; Paolo Manganelli, MD; Marco Cimmino, MD; Roberto Gerli, MD; Maria Grazia Catanoso, MD; Luigi Boiardi, MD; Fabrizio Cantini, MD; Catherine Klersy, MD; and Gene G. Hunder, MD



52週における再燃していない患者の割合

Infliximab群: 30%

Placebo群: 37%

(p= 0.80)

→有意差なし

Ann Intern Med 2007;146(9):631–639.

Methods

P 2012年ACR/EULAR分類基準を満たす
50歳以上のPMR患者

I ABBV-154+ GC

C GC

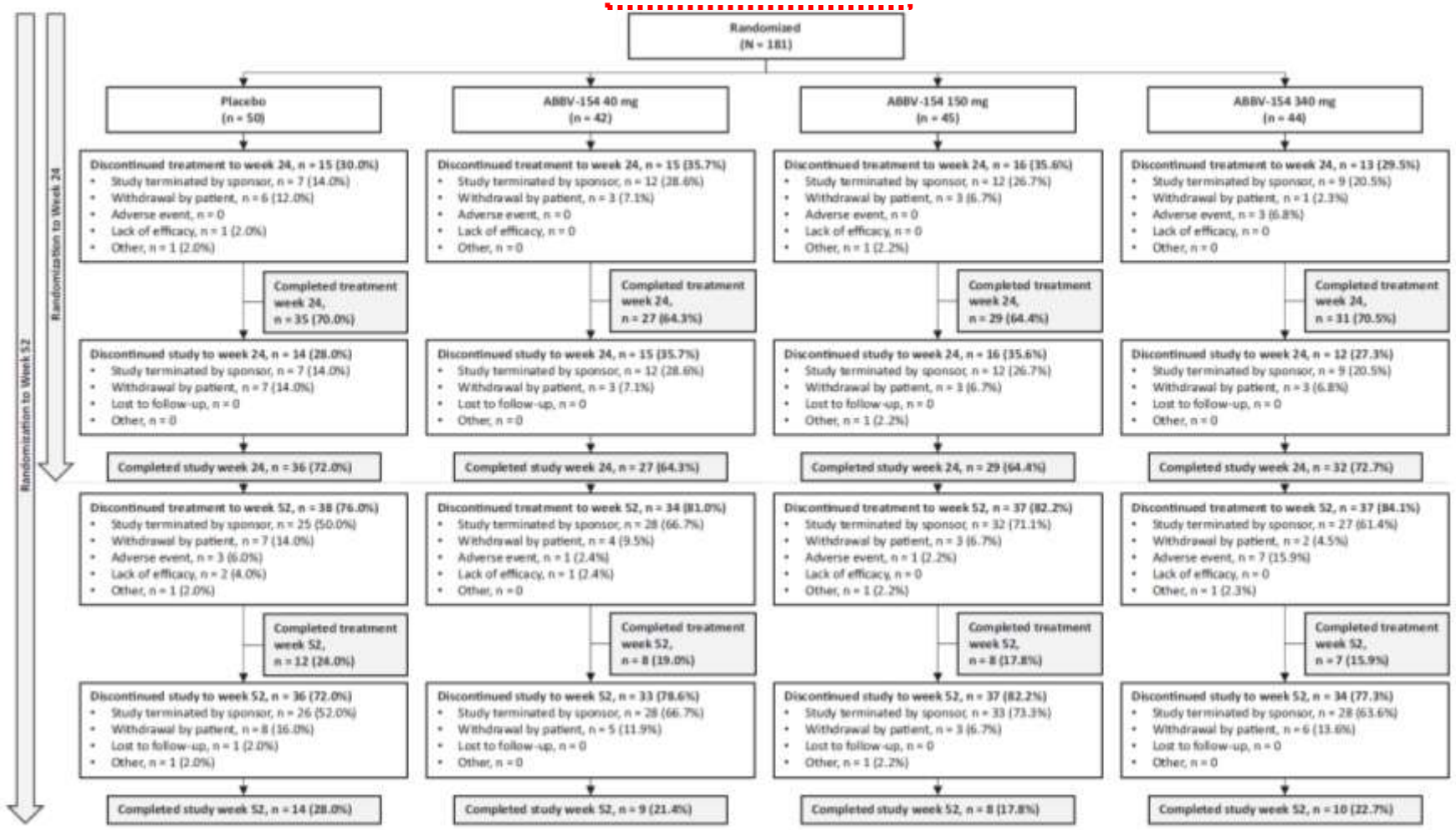
O 再燃までの時間

24週

再燃
PMRの臨床症状、徴候を認め、
GC増加すること

52週

ランダム化



Methods: GC投与量

Supplementary Table 1. Glucocorticoid taper schedule

Dose at	Glucocorticoid (Prednisone/Prednisolone) Dose, mg/day										
Baseline[a]	15	14	13	12	11	10	9	8	7	6	5
Week 1	15	14	13	12	11	10	9	8	7	6	5
Week 2	15	14	13	12	11	10	9	8	7	6	5
Week 3	12	12	12	10	10	9	8	7	6	5	4
Week 4	10	10	10	10	10	9	8	7	6	5	4
Week 5	10	10	10	9	9	8	7	6	5	4	3
Week 6	9	9	9	9	9	8	7	6	5	4	3
Week 7	9	9	9	8	8	7	6	5	4	3	2
Week 8	8	8	8	8	8	7	6	5	4	3	2
Week 9	8	8	8	7	7	6	5	4	3	2	1
Week 10	7	7	7	7	7	6	5	4	3	2	1
Week 11	7	7	7	6	6	5	4	3	2	1	0
Week 12	6	6	6	6	6	5	4	3	2	1	
Week 13	6	6	6	5	5	4	3	2	1	0	
Week 14	5	5	5	5	5	4	3	2	1		
Week 15	5	5	5	4	4	3	2	1	0		
Week 16	4	4	4	4	4	3	2	1			
Week 17	4	4	4	3	3	2	1	0			
Week 18	3	3	3	3	3	2	1				
Week 19	3	3	3	2	2	1	0				
Week 20	2	2	2	2	2	1					
Week 21	2	2	2	1	1	0					
Week 22	1	1	1	1	1						
Week 23	1	1	1	0	0						
Week 24	0	0	0								

[a] At baseline, patients took the same dose of glucocorticoid they had been taking before the baseline visit, rounded up to the nearest 1 mg, to a maximum of 15 mg.

Methods: End Point

Primary End Point:

- PMRの再燃までの時間

Secondary End Point:

- 24週まで再燃しなかった患者の割合
  24週までの平均累積GC量
  24週におけるBaselineからのGC減少量

- NRS、HAQ-DIなどのPRO
- 有害事象など

Methods: Participants

■ 主なInclusion criteria

- 50歳以上
- 2012年ACR/EULARのPMRの分類基準を満たす
- 2回以上再燃をきたしている
- 組み入れ2週間以内に再燃していない

■ Exclusion criteria

- TNF阻害薬の使用歴
- GCA、RA
- 抗CCP抗体陽性

Results: 患者背景

Table 1. Baseline demographics and disease characteristics (full analysis set)*

Characteristic	Placebo (n = 50)	ABBV-154 40 mg (n = 42)	ABBV-154 150 mg (n = 45)	ABBV-154 340 mg (n = 44)
Female, n (%)	33 (66.0)	30 (71.4)	25 (55.6)	29 (65.9)
Age, y, mean ± SD	71.0 ± 7.2	67.5 ± 8.0	69.8 ± 8.3	69.1 ± 6.2
Race, n (%)				
White	42 (84.0)	37 (88.1)	41 (91.1)	39 (88.6)
Asian	8 (16.0)	5 (11.9)	4 (8.9)	5 (11.4)
Hispanic or Latino, n (%)	1 (2.0)	0	2 (4.4)	2 (4.5)
BMI, mean ± SD	28.2 ± 5.5	28.4 ± 5.5	27.9 ± 4.5	29.1 ± 5.1
Duration of PMR, y, median (range)	2.0 (0.2–22.1)	1.2 (0.3–10.5)	1.3 (0.3–11.3)	1.8 (0.3–12.0)
Time since last PMR flare,[a] n (%)	49	40	45	44
≤12 wk	27 (55.1)	23 (57.5)	25 (55.6)	31 (70.5)
>12 wk	22 (44.9)	17 (42.5)	20 (44.4)	13 (29.5)
hsCRP ± mg/L, mean ± SD	8.6 ± 14.4	5.0 ± 8.5	4.4 ± 6.9	5.2 ± 13.0
ESR ± mm/h, mean ± SD	25.1 ± 17.2	22.7 ± 17.6	17.6 ± 14.1	18.9 ± 15.2
Glucocorticoid dose (mg/day),[b] mean ± SD	9.2 (3.8)	9.5 (3.4)	9.1 (3.5)	9.5 (3.3)
Duration of prior glucocorticoid treatment for PMR, n (%)				
≤1 y	16 (32.0)	17 (40.5)	18 (40.0)	19 (43.2)
>1 y	34 (68.0)	25 (59.5)	27 (60.0)	25 (56.8)
Prior bDMARDs and/or csDMARDs, n (%)				
bDMARD[c]	0	1 (2.4)	0	2 (4.5)
csDMARD[d]	16 (32.0)	15 (35.7)	10 (22.2)	17 (38.6)
Pain NRS, mean ± SD; n	3.4 ± 2.6; 49	3.0 ± 2.8	2.9 ± 2.4; 44	3.2 ± 2.7; 43
Stiffness NRS, mean ± SD; n	2.0 ± 1.9; 26	2.3 ± 2.5; 24	3.1 ± 2.0; 29	2.6 ± 2.6; 22
HAQ-DI, mean ± SD; n	0.7 ± 0.6; 49	0.7 ± 0.6; 40	0.6 ± 0.6; 41	0.7 ± 0.6; 41

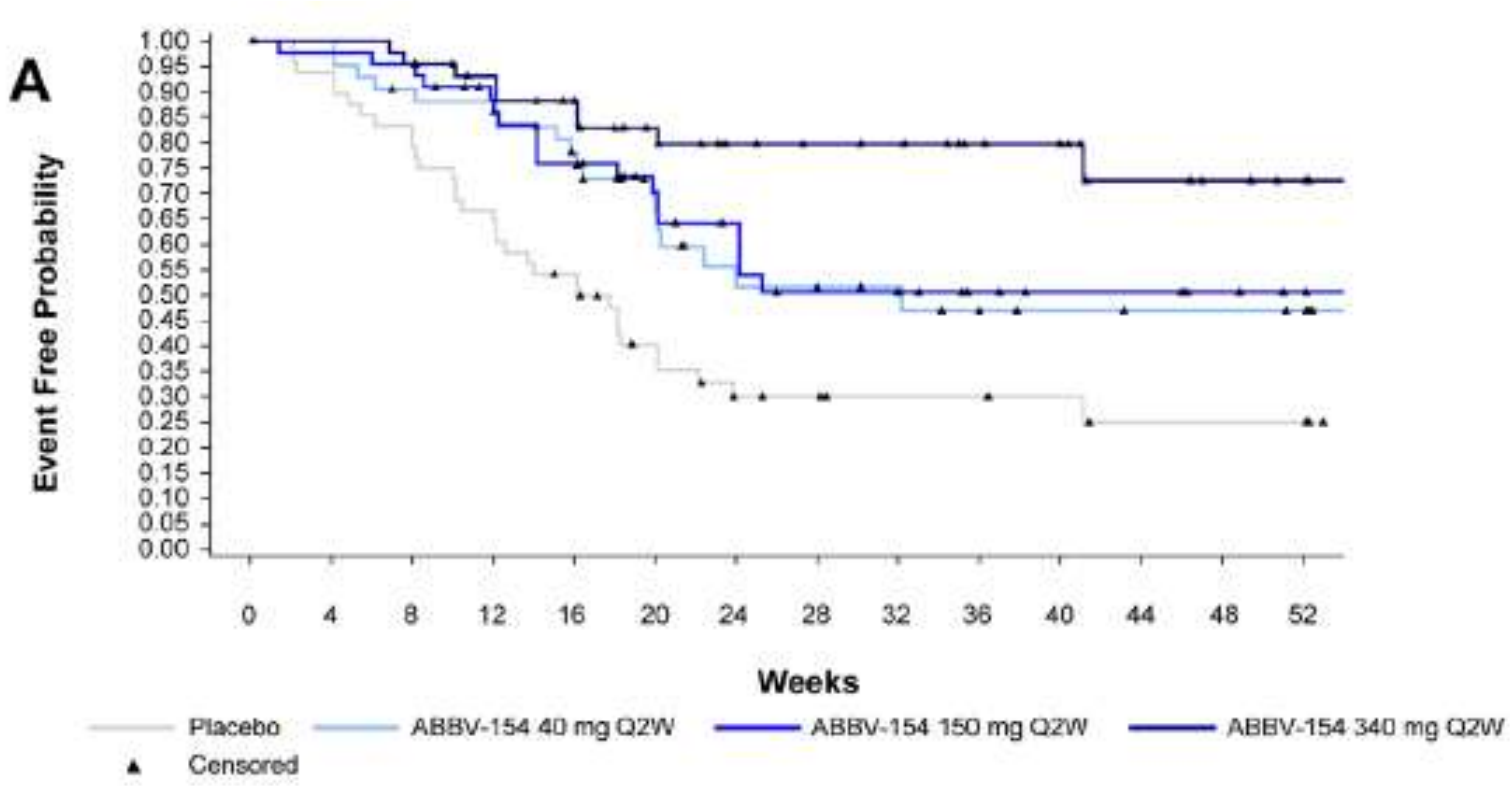
年齢は70歳程度、女性が60%程度

罹患期間は中央値が1～2年

GCは9mg程度内服

csDMARDsを3割程度内服歴あり

Results: Primary End Point

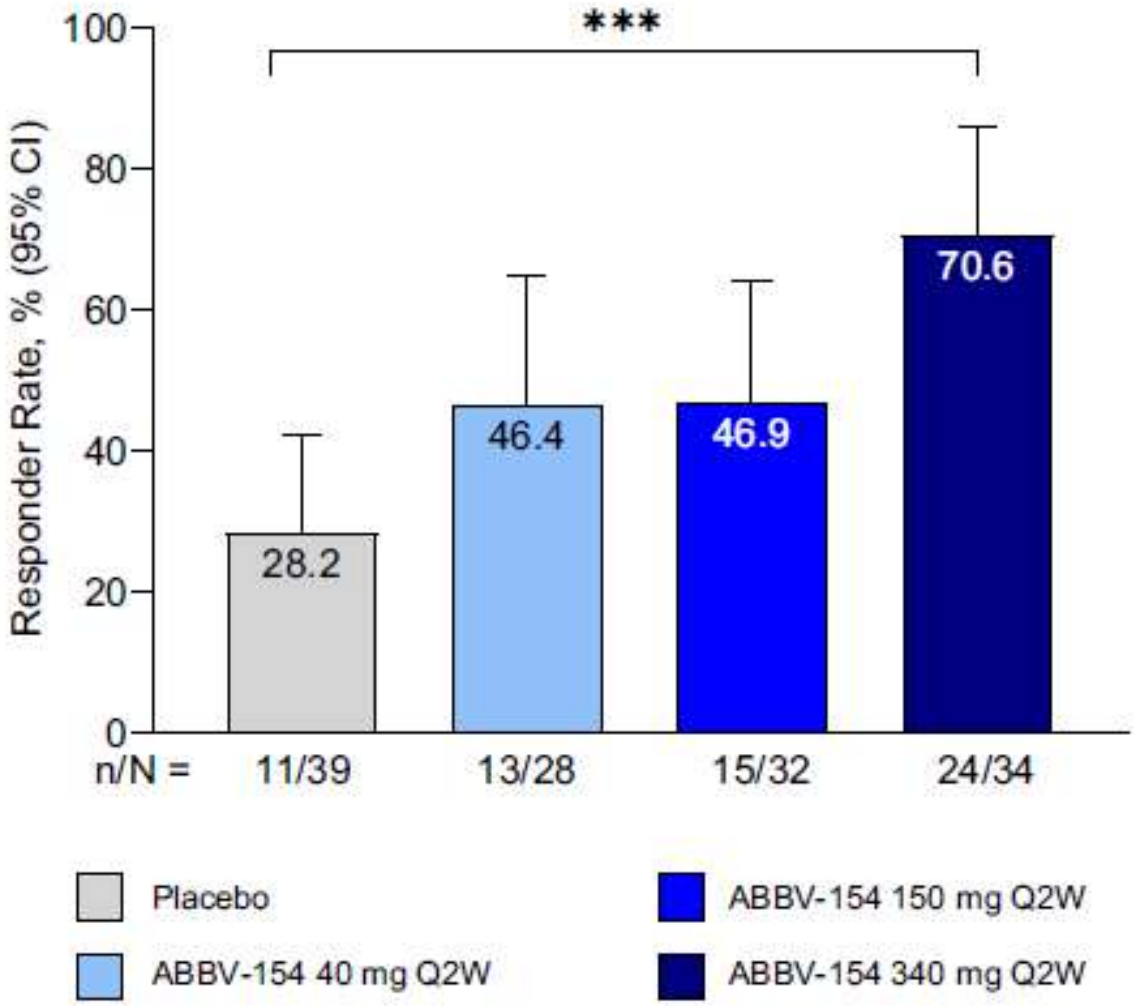


Number of Patients at Risk (With Events)

Placebo	50(0)	45(3)	40(10)	32(17)	25(22)	16(28)	10(32)	9(32)	7(32)	7(32)	6(32)	4(33)	4(33)	4(33)
ABBV-154 40 mg EOW	42(0)	42(0)	37(4)	36(5)	30(9)	21(13)	14(17)	13(17)	11(17)	9(18)	7(18)	6(18)	6(18)	5(18)
ABBV-154 150 mg EOW	45(0)	43(1)	42(2)	36(6)	30(10)	23(12)	19(14)	14(18)	14(18)	10(18)	8(18)	8(18)	6(18)	4(18)
ABBV-154 340 mg EOW	44(0)	44(0)	42(2)	38(3)	34(5)	27(7)	22(8)	20(8)	19(8)	15(8)	14(8)	9(9)	7(9)	5(9)

ABBV-154群はPlacebo群よりもPMRの再燃までの時間が長かった

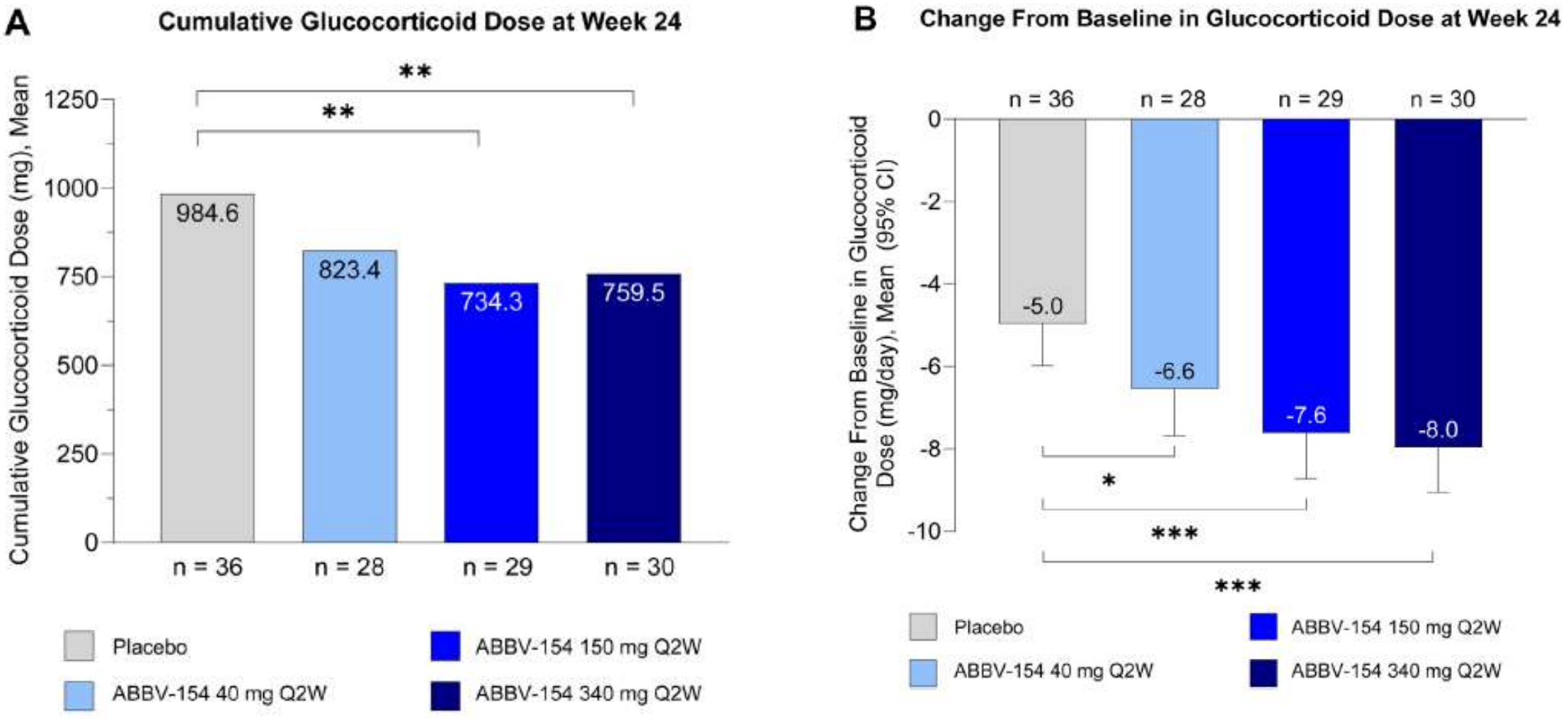
Results: 24週まで再燃しなかった患者の割合



24週まで再燃しなかった患者の割合

- Placebo 28.2%
- ABBV-154 40mg 46.4%
- ABBV-154 150mg 46.9%
- ABBV-154 340mg 70.6%

Results: 24週までのGC累積量、BaselineからのGC減少量



24週までのGC累積量、1日あたりのGC量ともに減少

Results: 有害事象

TEAE, n (%)	Placebo (n = 50)	ABBV-154 40 mg (n = 42)	ABBV-154 150 mg (n = 45)	ABBV-154 340 mg (n = 44)
Safety overview				
Any TEAE	41 (82.0)	32 (76.2)	39 (86.7)	41 (93.2)
COVID-19–related TEAE	9 (18.0)	9 (21.4)	5 (11.1)	7 (15.9)
TEAE with reasonable possibility of being drug related	17 (34.0)	15 (35.7)	21 (46.7)	29 (65.9)
Grade ≥3 TEAE	9 (18.0)	6 (14.3)	7 (15.6)	8 (18.2)
SAE	8 (16.0)	5 (11.9)	8 (17.8)	9 (20.5)
TEAE leading to study drug discontinuation	3 (6.0)	1 (2.4)	1 (2.2)	7 (15.9)
TEAE leading to death	0	0	0	0
Most common TEAEs[a]				
COVID-19	9 (18.0)	9 (21.4)	5 (11.1)	7 (15.9)
Nasopharyngitis	3 (6.0)	4 (9.5)	4 (8.9)	7 (15.9)
Arthralgia	3 (6.0)	4 (9.5)	6 (13.3)	3 (6.8)
Urinary tract infection	5 (10.0)	3 (7.1)	2 (4.4)	7 (15.9)
Headache	2 (4.0)	3 (7.1)	4 (8.9)	4 (9.1)
Fatigue	2 (4.0)	3 (7.1)	4 (8.9)	2 (4.5)
Hypertension	5 (10.0)	1 (2.4)	4 (8.9)	3 (6.8)
Nausea	2 (4.0)	3 (7.1)	2 (4.4)	3 (6.8)
Pneumonia	0	2 (4.8)	1 (2.2)	5 (11.4)
Contusion	0	2 (4.8)	2 (4.4)	3 (6.8)
Diarrhea	4 (8.0)	2 (4.8)	2 (4.4)	3 (6.8)
Injection site erythema	0	2 (4.8)	3 (6.7)	2 (4.5)
Rash	2 (4.0)	2 (4.8)	2 (4.4)	3 (6.8)
Upper respiratory tract infection	2 (4.0)	2 (4.8)	3 (6.7)	2 (4.5)
AEs of special interest				
Serious infections	1 (2.0)	1 (2.4)	3 (6.7)	6 (13.6)
Serious infections excluding COVID-19–related AEs	1 (2.0)	1 (2.4)	3 (6.7)	6 (13.6)
Opportunistic infections	0	0	0	0
Active TB	0	0	0	0
Hypersensitivity reactions	4 (8.0)	4 (9.5)	8 (17.8)	7 (15.9)
Serious allergic reactions	0	0	0	0
Malignancies	0	2 (4.8)	2 (4.4)	2 (4.5)
Malignancies excluding NMSC	0	0	0	2 (4.5)[b]
NMSC	0	2 (4.8)	2 (4.4)	0
Lymphoma	0	0	0	0
Adjudicated systemic glucocorticoid side effects[c]	1 (2.0)	3 (7.1)	1 (2.2)	1 (2.3)
Adrenal insufficiency	0	0	0	0
Iatrogenic Cushing syndrome	0	0	0	1 (2.3)

- ABBV-154群でも有害事象は大きく変化なし
- 重篤な感染症はABBV-154 340mg群で増加

Discussion

- ABBV-154はGC減量できる可能性を示唆
- GC関連の有害事象が減少することが期待されたが、実際には減少しなかった
- 中間解析でABBV-154は既存治療に比べて十分なベネフィットがなかったため、RCTをsponsorが中断

Limitation

- 早期の研究終了によりサンプルサイズが小さく、薬剤投与期間や罹患期間にばらつきがあった
- 第2相試験であり、α= 0.10で両側検定したため、Type Ⅰエラーが増加した可能性
- ADA群との比較ができていないため、グルココルチコイド受容体モジュレーターの効果の有効性、安全性を明確に検討できなかった