New Therapeutic Landscape in IgG4-related Disease

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Northwest Rheumatism Society

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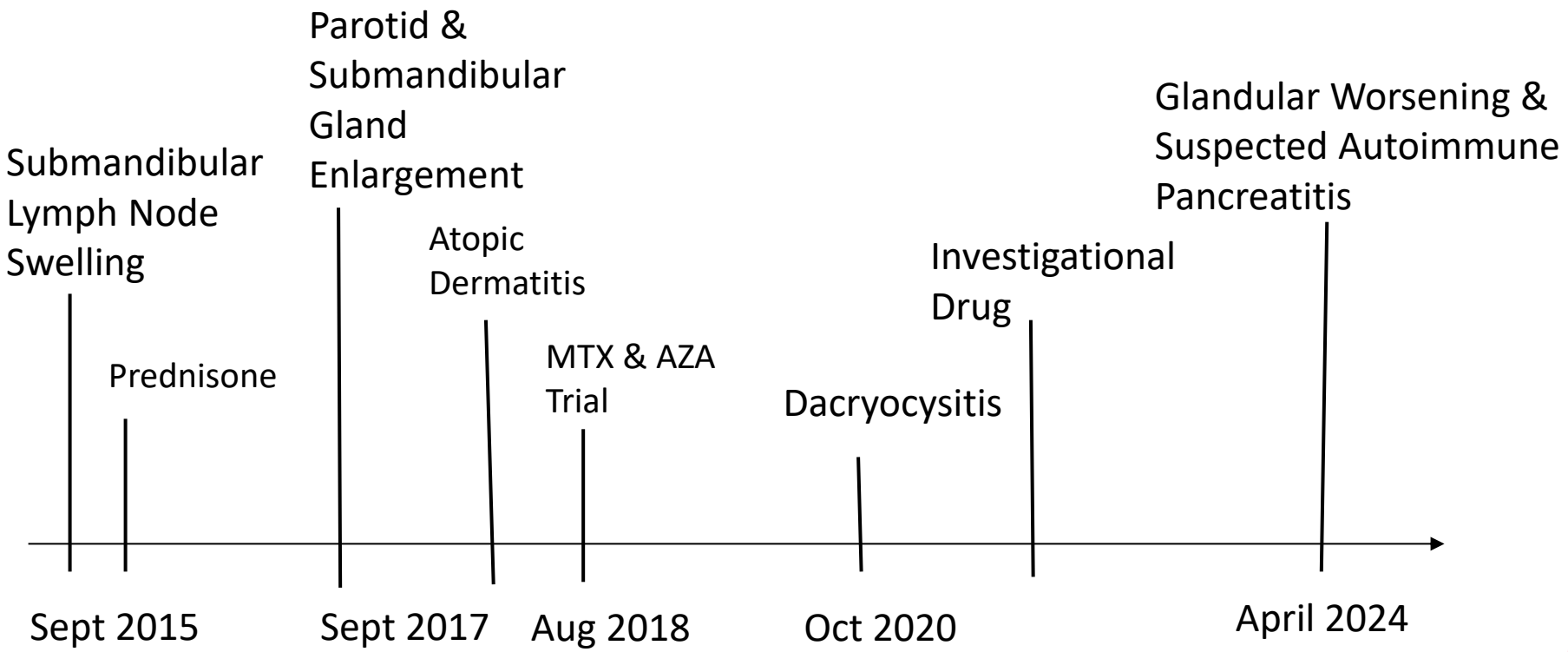
Learning Objectives

- Discuss expert opinion on IgG4-related disease induction therapy
- Explore labeled use in IgG4-related disease
- Examine clinical trial conference data and upcoming developments
- Predict the future of therapeutics in IgG4-related disease

Treatment Case #1

- 74 year old man who initial presented about 10 years ago with submandibular lymph node swelling and parotid enlargement
- An excisional biopsy of the submandibular lymph node showed IgG4-related disease
- His labs and PET scan at the time of presentation showed no extra-glandular involvement
- He now reports worsening glandular swelling with some associated achiness/pressure

Treatment Case #1



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Treatment Case #1: History

Past Medical History
IgG4-related dacryocystic duct stenosis s/p stent June-July 2023
Asthma
Allergic rhinitis
Hyper-CKemia
Coronary artery disease
First degree heart block
GERD
Dermal hypersensitivity rash Dr. De Gannes

Social History
Retired restauranteer. Married. No smoking and occasional drinking.

Medications
Ezetimibe 10 mg daily
Famotidine 20 mg daily
Fluticasone nasal spray PRN sinusitis
Fluticasone inhaler PRN wheezing
Budesonide/Formoterol inhaler
Vitamin D
Desloratidine
Pepcid AC
Clopidogrel

Treatment Case #1: Physical Exam

Notable Findings

New lacrimal gland swelling
Submandibular gland swelling
Submandibular lymph node enlargement
Parotid gland enlargement
No abdominal tenderness

Treatment Case #1: Labs

Basic Labs
6.4/115/231
BUN/Cr/urine ACR WNL
LFTs WNL
Lipase 150 (>75 U/L)

Other Labs
C3 0.96 (>0.87 g/L) /C4 0.22 (>0.19 g/L)

LDH 772 (>618 U/L)

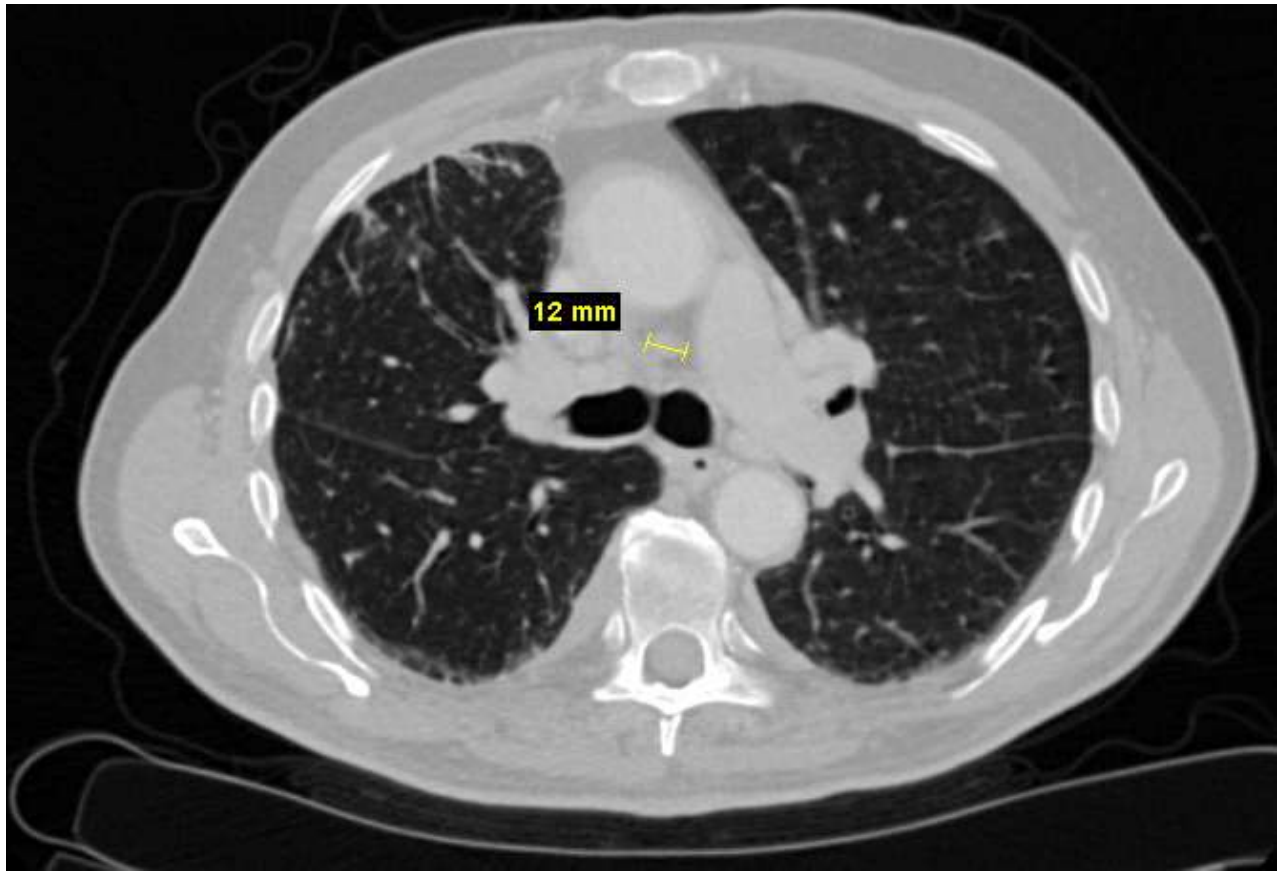
IgG Subclasses
- Current:

6.36 ← 5.55 ← 4.89 (>1.25 g/L)
- Past Peak:

7.1 g/L
- Past Nadir:

2.2 g/L on investigational drug

Treatment Case #1: Radiology



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Treatment Case #1: Recap

- Rising IgG4 level
- Glandular involvement including new dacryoadenitis
- Biochemical but not clinical autoimmune pancreatitis
- Worsening radiographic lymphadenopathy

Is it Joy, Grief or a Mystery?

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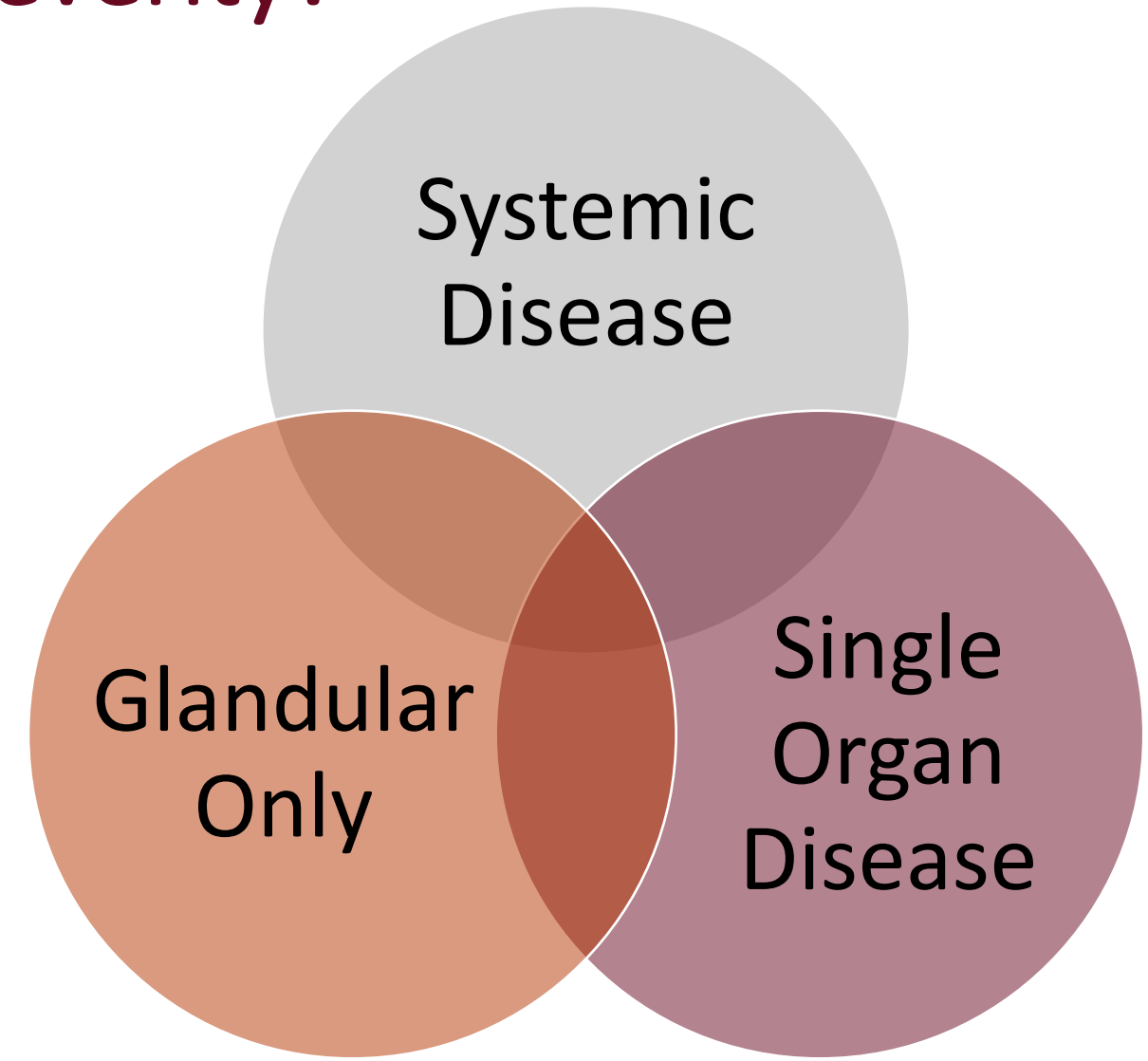
What about severity?



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Treatment Case #1 Options

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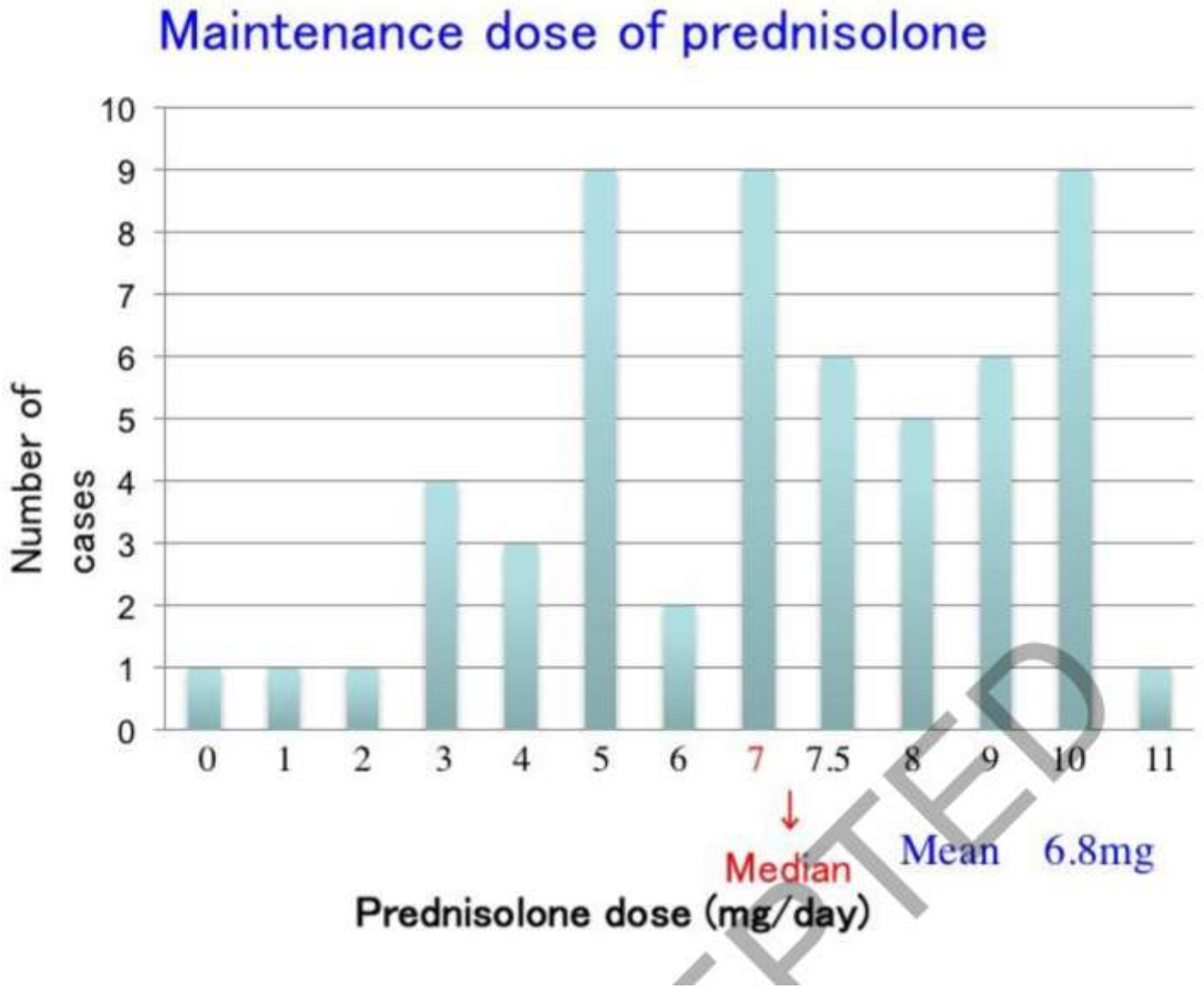
Prednisone



Masaki et al. A multicenter phase II prospective clinical trial of glucocorticoid for patients with untreated IgG4-related disease. Modern Rheum 2017.

Disease Modifying Anti-Rheumatic Drugs

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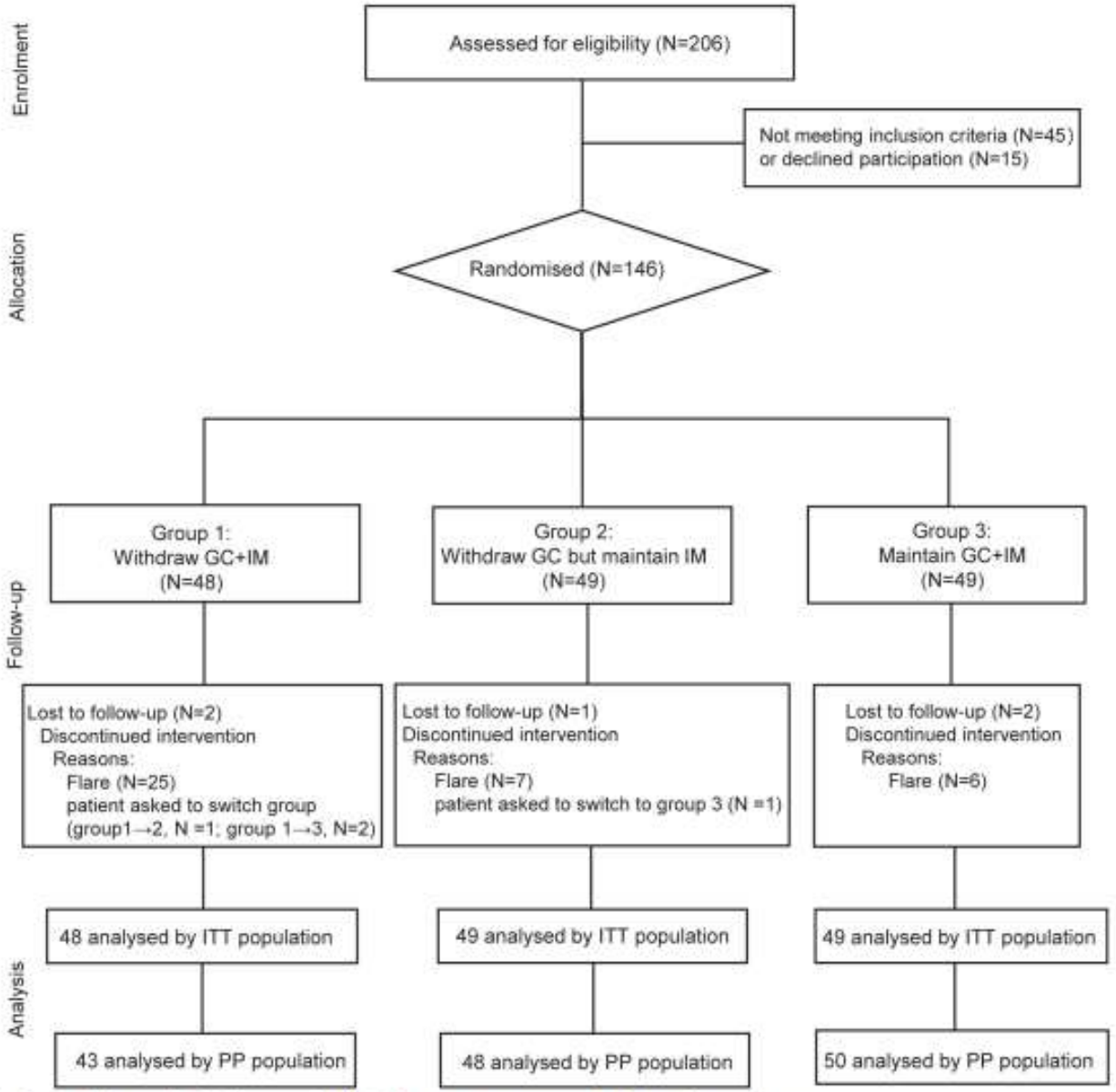

Figure 1 Flowchart of the study. GC, glucocorticoid; IM immunosuppressant; ITT, intention-to-treat.

How are immunosuppressants defined?

- Mycophenolate (~30%)
- Methotrexate (~30%)
- Leflunomide (~15%)
- Azathioprine (<10%)
- Iguratimod (~5%)
- Hydroxychloroquine (~2%)
- Tripterygium glycosides (~2%)
- Cyclophosphamide (Low Dose Oral) (<1%)

Survival Curves to Maintain DMARDs

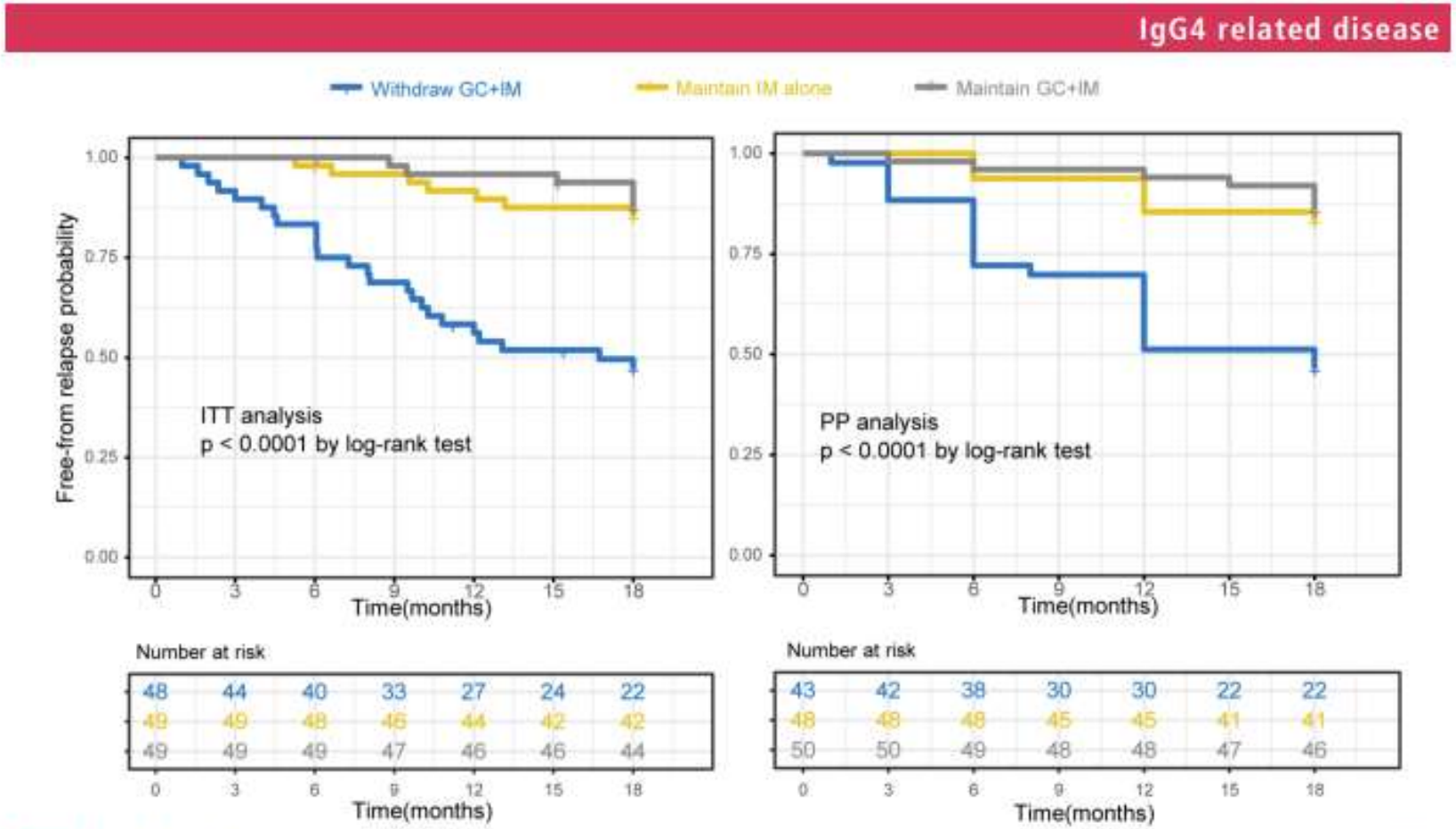

Figure 2 Free-from relapse probability by Kaplan-Meier method of patients from three groups by intention-to-treat (ITT) (left) and per-protocol (PP) analyses (right).

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Mycophenolate

RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/key227

Efficacy and safety of low dose Mycophenolate mofetil treatment for immunoglobulin G4-related disease: a randomized clinical trial

Fei Yunyun[1,*], Peng Yu[1,*], Zhang Panpan[1], Zhang Xia[1], Peng Linyi[1], Zhou Jiaxin[1], Zhang Li[1], Zhang Shangzhu[1], Liu Jinjing[1], Wu Di[1], Lai Yamin[2], Liu Xiaowei[3], Xue Huadan[4], Zhang Xuan[1], Zeng Xiaofeng[1], Zhang Fengchun[1], Zhao Yan[1] and Zhang Wen[1]

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FIG. 1 The CONSORT flow diagram of IgG4-related disease patients

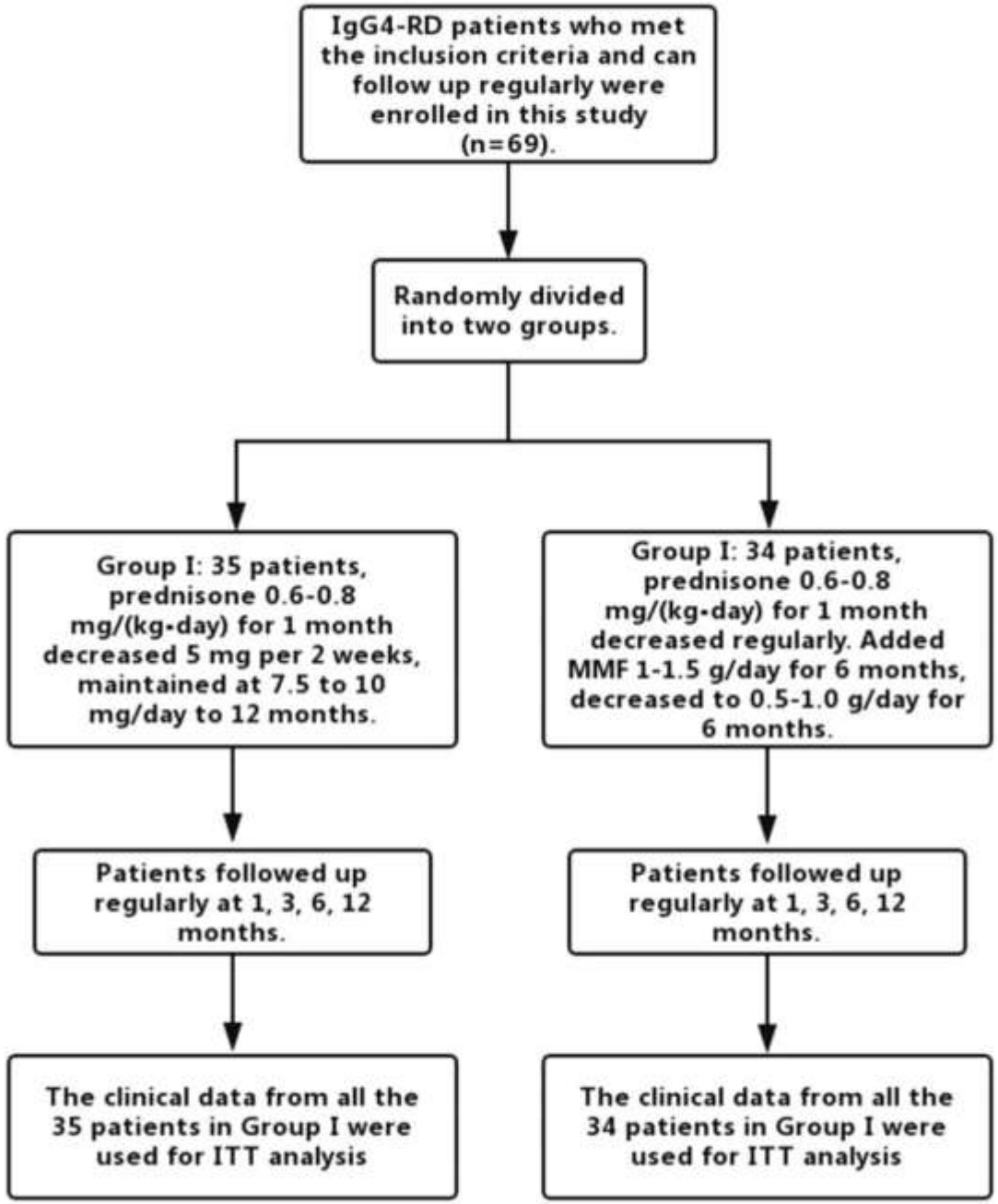
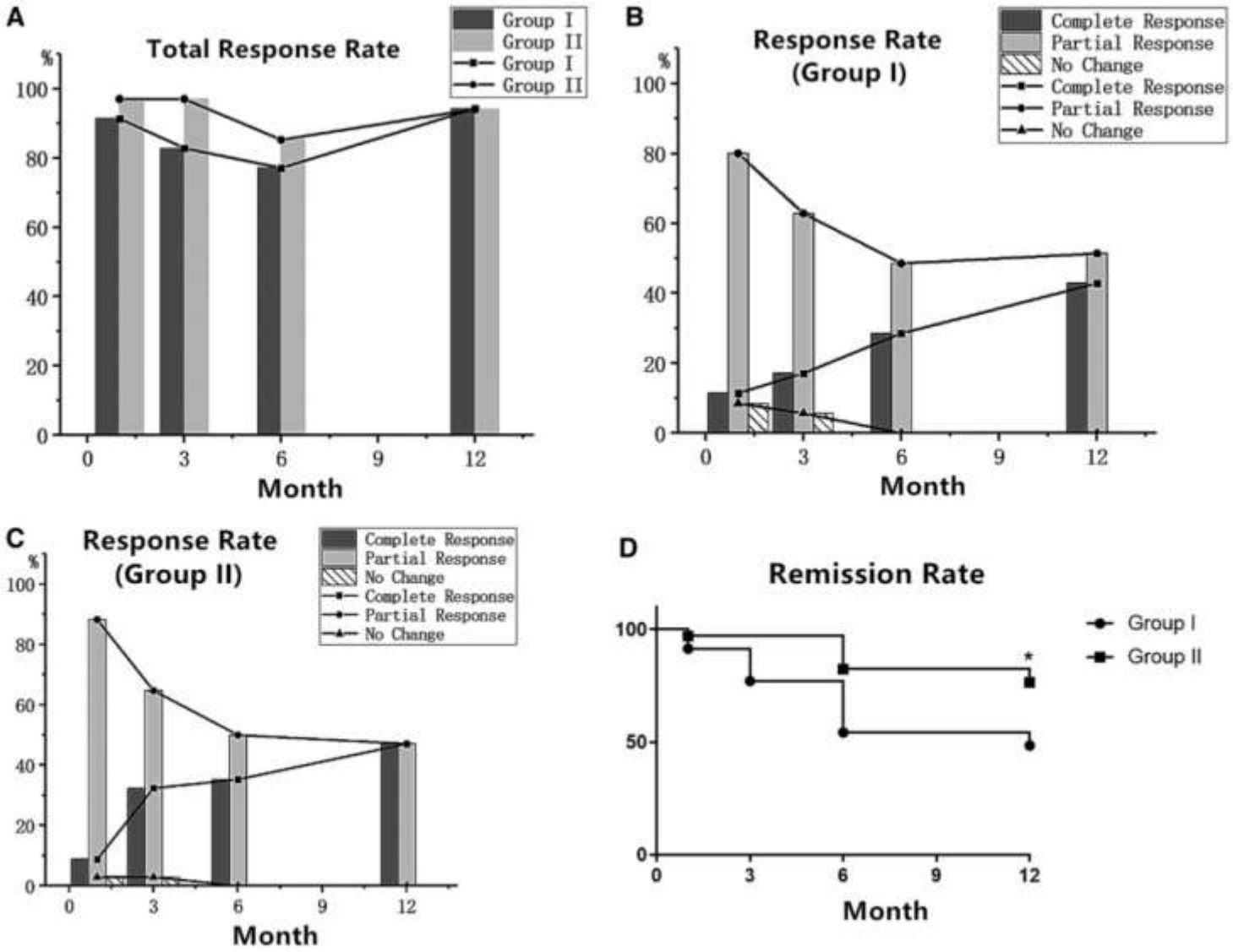


FIG. 2 The response rates and remission rate of Groups I and II

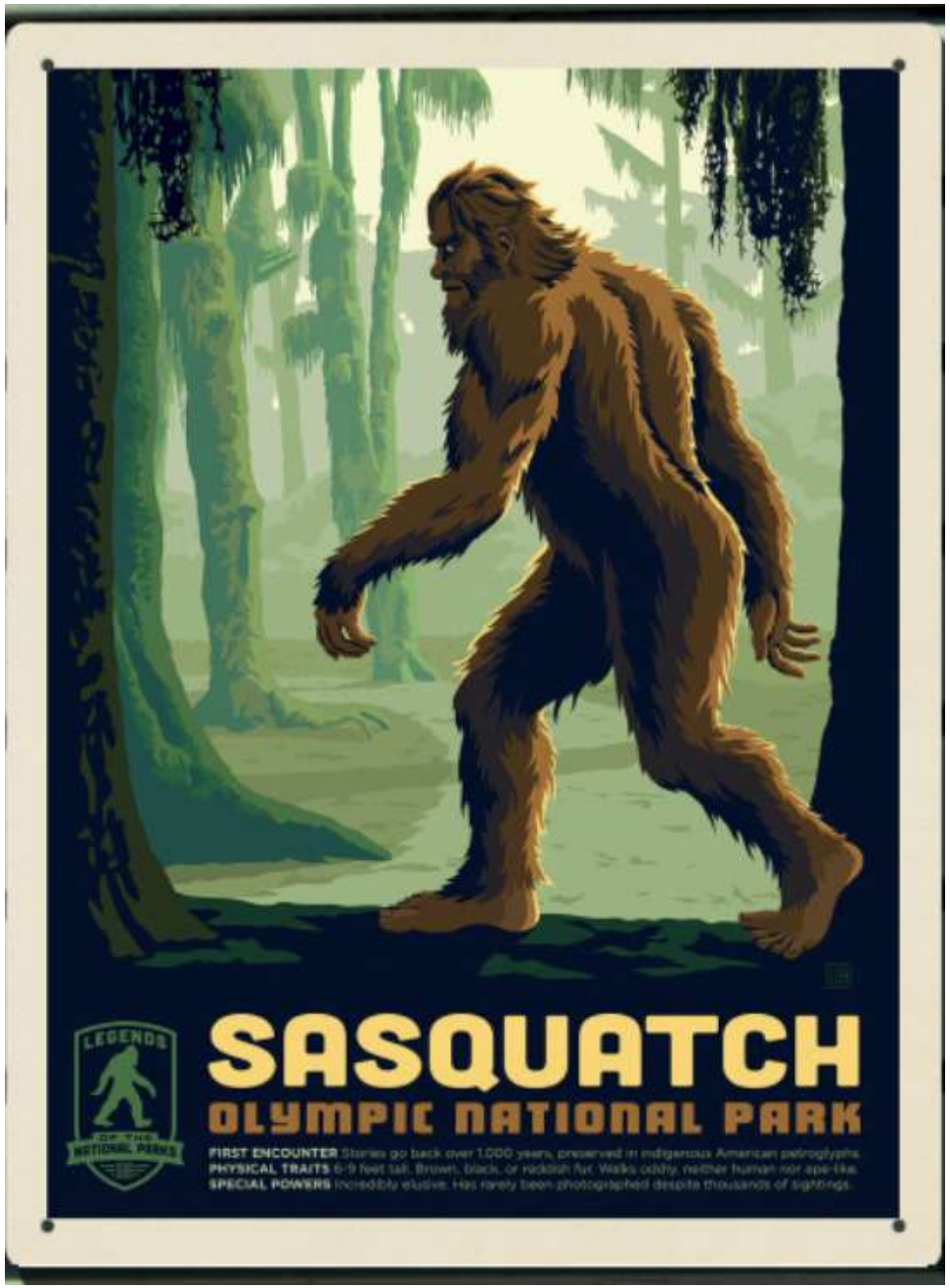


(**A**) The total response rates of the two groups at 1, 3, 6 and 12 months. (**B**) The response rates of patients in Group I at 1, 3, 6 and 12 months. (**C**) The response rates of patients in Group II at 1, 3, 6 and 12 months. (**D**) The persistent remission rates of the two groups at different time points during 1 year.

So What Did I Do with Treatment Case #1?

- None of the above
- Try more prednisone or a DMARD?
- Biologicals?

Sasq’ets
(pronounced *sas-kets*)



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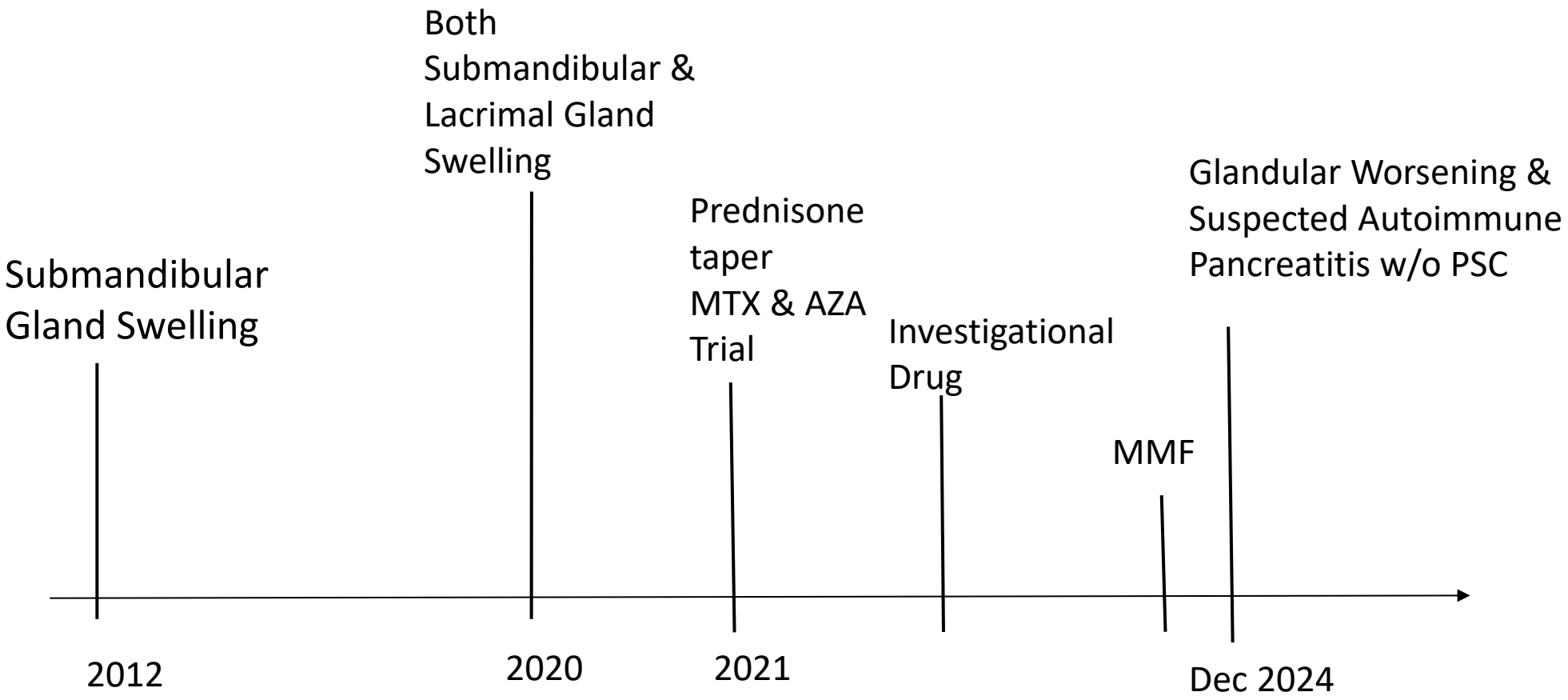
Treatment Case #2

- 59 year old man who initial presented about 10 years ago with submandibular gland swelling with multiple non-diagnostic FNAs
- He had glandular swelling of 3 separate glands (lacrimal, submandibular, parotid glands) plus an IgG4 level of 2.5 g/L to meet ACR/EULAR criteria
- His monitoring labs show obstructive cholangitis and pancreatitis with rising IgG4 level
- At his clinic visit, he reports a 21 pound weight loss, pale stools and dark urine

Treatment Case #2



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Treatment Case #2: History

Past Medical History
Seasonal allergies
BPH
Complex renal cyst 2023
Multiple lipomas

Social History
He is married and has three children. He works as a computer systems consultant. He does not smoke, drink alcohol or use recreational drugs.

Medications
- - OLOPATADINE HCL 0.1 %
- - TAMSULOSIN
- - MYCOPHENOLATE MOFETIL 500 MG BID
- - BILASTINE PRN allergies
- - Budesonide nasal rinses

Treatment Case #2: Physical Exam

Notable Findings:

No visible icterus

Submandibular glands are enlarged

Parotids glands and lacrimal glands are enlarged

Mild epigastric tenderness

Treatment Case #2: Labs

Basic Labs
5.7/143/186
BUN/Cr WNL
Lipase 253 (>75 U/L)
ALT 247 (>50 U/L)
AST 150 (>36 U/L)
Total bilirubin 17 (>17 umol/L)
Alkaline phosphatase 216 (>145 U/L)

Other Labs
C3/C4 WNL
Urine ACR WNL
Gammaglobulin 21 (>14 g/L)

IgG Subclasses
- Current:

7.04 ← 5.53 ← 4.82 (>1.25 g/L)
- Past Peak:

2.8 g/L
- Past Nadir:

1.92 g/L on investigational drug

Treatment Case #2: Radiology

Treatment Case #2: Recap

- Rising IgG4 level
- Radiographic autoimmune pancreatitis
- Endoscopic U/S later shows pancreatic mass with no clear bile duct changes

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Rituximab for IgG4-related disease: a prospective, open-label trial

Mollie N Carruthers,[1] Mark D Topazian,[2] Arezou Khosroshahi,[3] Thomas E Witzig,[4] Zachary S Wallace,[1] Philip A Hart,[2] Vikram Deshpande,[5] Thomas C Smyrk,[6] Suresh Chari,[2] John H Stone[1]

The NEW ENGLAND JOURNAL of MEDICINE

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*

ABSTRACT

Inebilizumab

- CD19 Inhibitor
- 300 mg IV day 1 and 15
- Repeat dosing week 26
- 87% relative risk reduction
- 10X steroid sparing

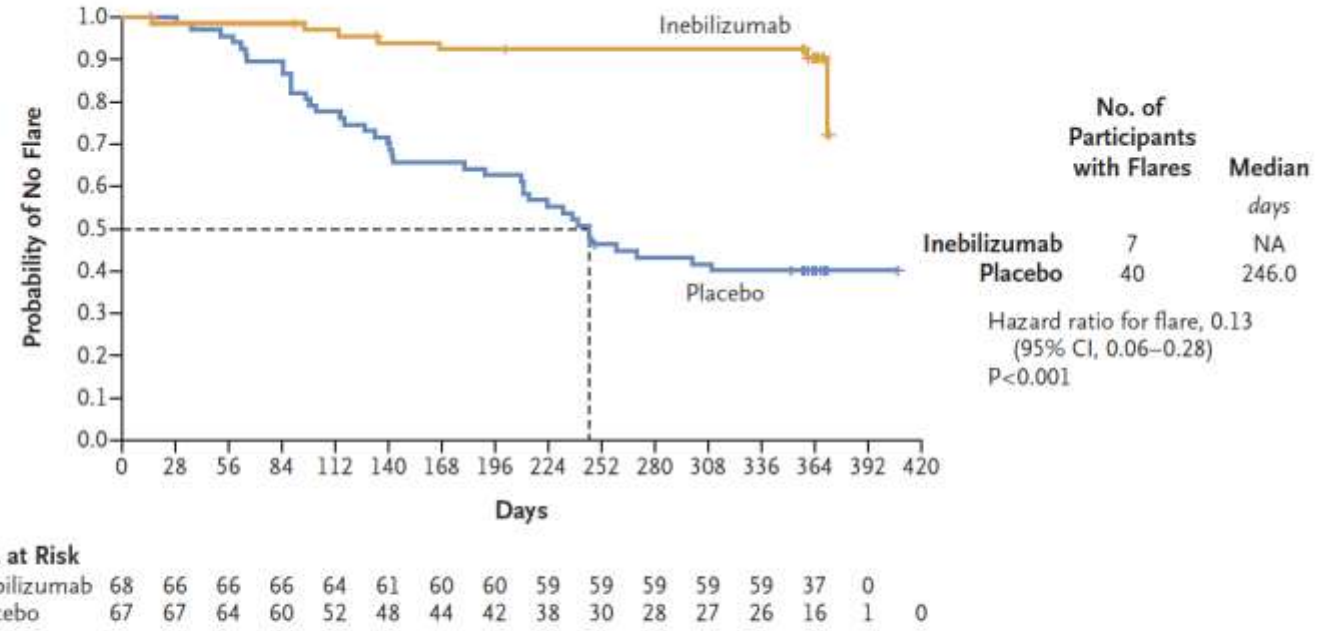

Figure 1. Time to First Treated and Adjudicated IgG4-Related Disease Flare (Full Analysis Population).

The full analysis population included all the participants who underwent randomization and received any dose of inebilizumab or placebo. Tick marks indicate censored data. The dashed lines indicate the median; estimated median time to event in the inebilizumab group could not be determined because less than 50% of the participants had an event by the end of the treatment period. The nominal day-365 visit occurred after day 365 in some participants for safety reasons or owing to the visit window specified in the protocol. CI denotes confidence interval, and NA not available.

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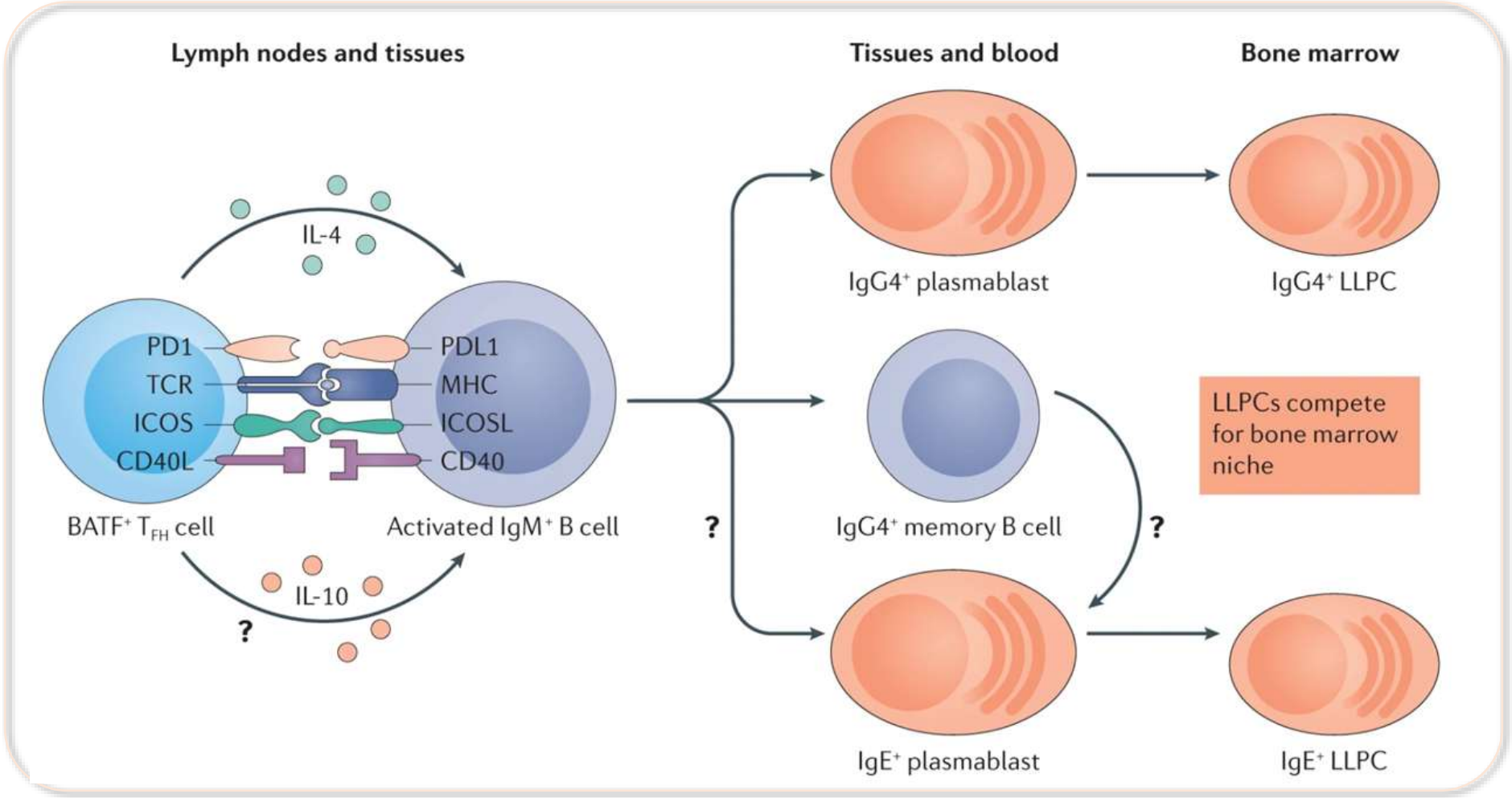
So What Did I Do with Treatment Case #2?

- Off-label rituximab

- Inebilizumab?
  - FDA Approval April 3rd, 2025
  - Health Canada Approval Summer 2025 but not reimbursement

- Other treatments?

IgG4-RD Pathogenesis



Perugino Nat Rev Rheum 2020

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Mechanism of Action

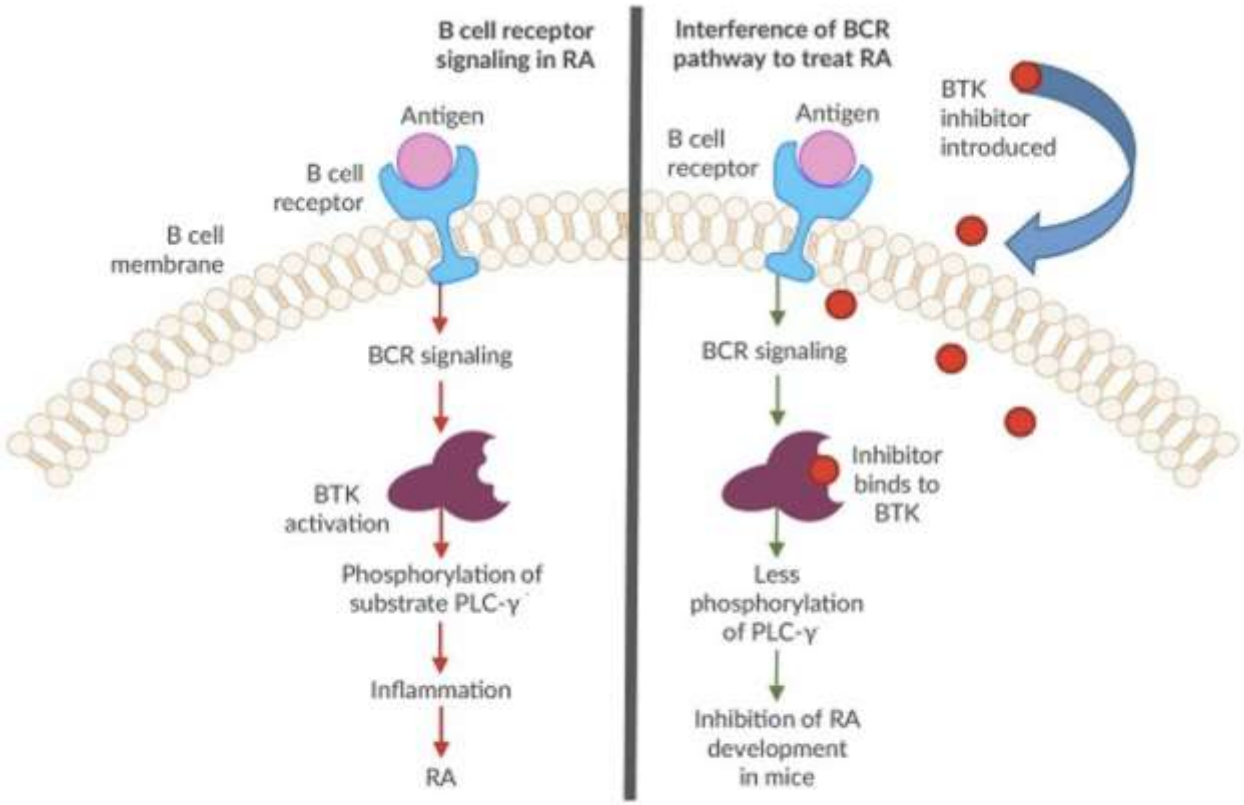


Figure 1 Simplified schematic of the proposed mechanism of BTK inhibition in RA. (Figure modified and used with permission from American Laboratory Products Company. BTK Inhibitors as Cancer Drug Treatments. Available from: https://www.alpco.com/btk-inhibitors-as-cancer-drug-treatments).[44]

Arneson LC, Carroll KJ, Ruderman EM. Bruton's Tyrosine Kinase Inhibition for the Treatment of Rheumatoid Arthritis. Immunotargets Ther. 2021 Aug 28;10:333-342.

Rilzabrutinib in IgG4-RD

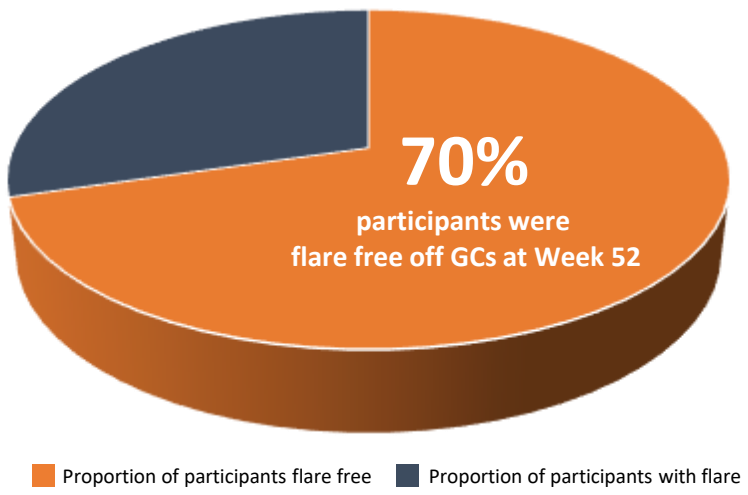
- Phase 2
- Open label
- Oral Bruton Tyrosine Kinase inhibitor given twice daily
- 52 week study
- N=27 patients

Presented by John Stone EULAR 2025, ACR 2025 on behalf of Sanofi

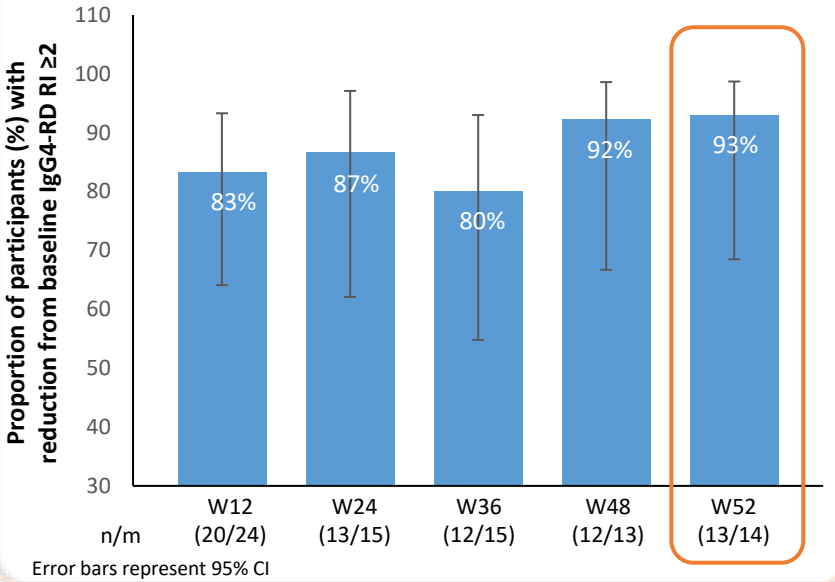
Results

70% of participants treated with Rilzabrutinib were flare free at Week 52

- At week 52, 19 out of 27 (70.4%) [95% CI (0.515, 0.841)] of rilzabrutinib-treated patients were free of disease flare without additional therapy (GCs or immunosuppressants)



At 52 weeks, 92.9% (13/14), [95% CI (0.685, 0.987)] of participants who completed the study experienced a reduction of ≥2 points from their baseline IgG4-RD RI score



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Safety

Summary of adverse events n (%)	Pooled (N = 27)
Participants with at least one TEAE	23 (85.2)
Participants with at least one Serious TEAE	2 (7.4)
Participants with TEAE leading to death	1 (3.7)
Participants with TEAE leading to permanent Study intervention discontinuation*	5 (18.5)
Adverse events in ≥10% of participants	
Diarrhoea	11 (40.7)
COVID-19	5 (18.5)
Dizziness	5 (18.5)
Dry mouth	4 (14.8)
Nausea	4 (14.8)
Haematuria	3 (11.1)
Arthralgia	3 (11.1)

Presented by John Stone EULAR 2025, ACR 2025

Future Directions

- Available Health Canada and Pharmacare approved biologics Canada: None
- Off Label: Rituximab
- Pharmacare possible approval pending: Inebilizumab
- Obexelimab: Phase 3 closed results pending
- Rilzabrutinib: Phase 3 about to start

Acknowledgements

IgG4-related Disease Network

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Dr. Andre Mattman

Dr. Anthony So

Dr. May Kazem

Dr. Jennifer Telford

Dr. Eric Lam

Trainees

Dr. Maddy Beckett

Dr. Derek Chong

Dr. Charles Li

Dr. Aiden Pye

Armaan Jaffer

Daniel Onwuka

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Questions?

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