# New treatment horizons for immunomodulation

Despina Eleftheriou

Professor of paediatric rheumatology

UCL GOS Institute of Child Health

- Disclosures: I am a paediatric rheumatologist!

I love working with neurologists (I always learn a lot!)

# Overview

- Cyclophosphamide/corticosteroids
- Developments in field of novel therapeutics for autoimmunity
- Rheum/general immunomodulation/clinical trial perspective

# Cyclophosphamide

- Concerns about toxicity
- Alternative therapies e.g MMF

CLINICAL SCIENCE

## Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial

Rachel B Jones,[1] Thomas F Hiemstra,[2,3] Jose Ballarin,[4] Daniel Engelbert Blockmans,[5] Paul Brogan,[6,7] Annette Bruchfeld,[8] Maria C Cid,[9] Karen Dahlsveen,[1] Janak de Zoysa,[10,11] Georgína Espigol-Frigolé,[9] Peter Lanyon,[12] Chen Au Peh,[13] Vladimir Tesar,[14] Augusto Vaglio,[15,16] Michael Walsh,[17] Dorothy Walsh,[1] Giles Walters,[18] Lorraine Harper,[19] David Jayne,[1,2] for the European Vasculitis Study Group (EUVAS)

## Results:

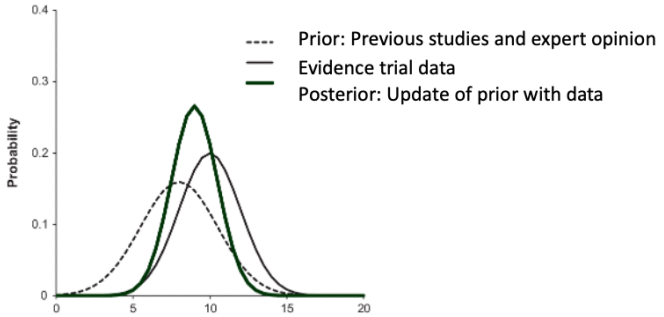
- 140 patients with AAV- non inferiority
- 8 children
- 67% remission rate in MMF group
- 62% in cyclophosphamide group
- MMF safe well tolerated

# Mycophenolate Mofetil (MMF) Versus Cyclophosphamide (CYC) in Childhood Polyarteritis Nodosa: MYPAN trial

Compare the effectiveness of a less toxic treatment (MMF) to standard (more toxic) treatment (cyclophosphamide, CYC)

**Rare diseases:**

- **Sample sizes are often unachievable**
- **Still need randomised data**
- **Bayesian randomised controlled trial**




## Mycophenolate Mofetil Versus Cyclophosphamide for Remission Induction in Childhood Polyarteritis Nodosa: An Open-Label, Randomized, Bayesian Noninferiority Trial

Paul A. Brogan,[1] Barbara Arch,[2] Helen Hickey,[2] Jordi Anton,[3] Este Iglesias,[3] Eileen Baildam,[4] Kamran Mahmood,[4] Gavin Cleary,[4] Elena Moraitis,[5] Charalampia Papadopoulou,[5] Michael W. Beresford,[2] Phil Riley,[6] Selcan Demir,[7] Seza Ozen,[7] Giovanna Culeddu,[8] Dyfrig A. Hughes,[8] Pavla Dolezalova,[9] Lisa V. Hampson,[10] John Whitehead,[10] David Jayne,[11] Nicola Ruperto,[12] Catrin Tudur-Smith,[2] and Despina Eleftheriou[1]

**Results: Combining the prior expert opinion with results posterior estimates of remission:**

- **71% for MMF (90% credibility interval [90% CrI] 51, 83)**
- **75% for CYC (90% CrI 57, 86).**

# Corticosteroids-assessing toxicity

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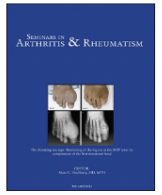
Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit



The pediatric glucocorticoid toxicity index

Paul Brogan [a], Ray Naden [b], Stacy P. Ardoin [c], Jennifer C. Cooper [d], Fabrizio De Benedetti [e], Jean-Francois Dicaire [f], Despina Eleftheriou [a], Brian Feldman [g], Jon Goldin [a], Seth E. Karol [h], Fiona Price-Kuehne [i], David Skuse [a], Constantine A. Stratakis [j], Nicholas Webb [k,l], John H. Stone [a,*]

KD-CAAP

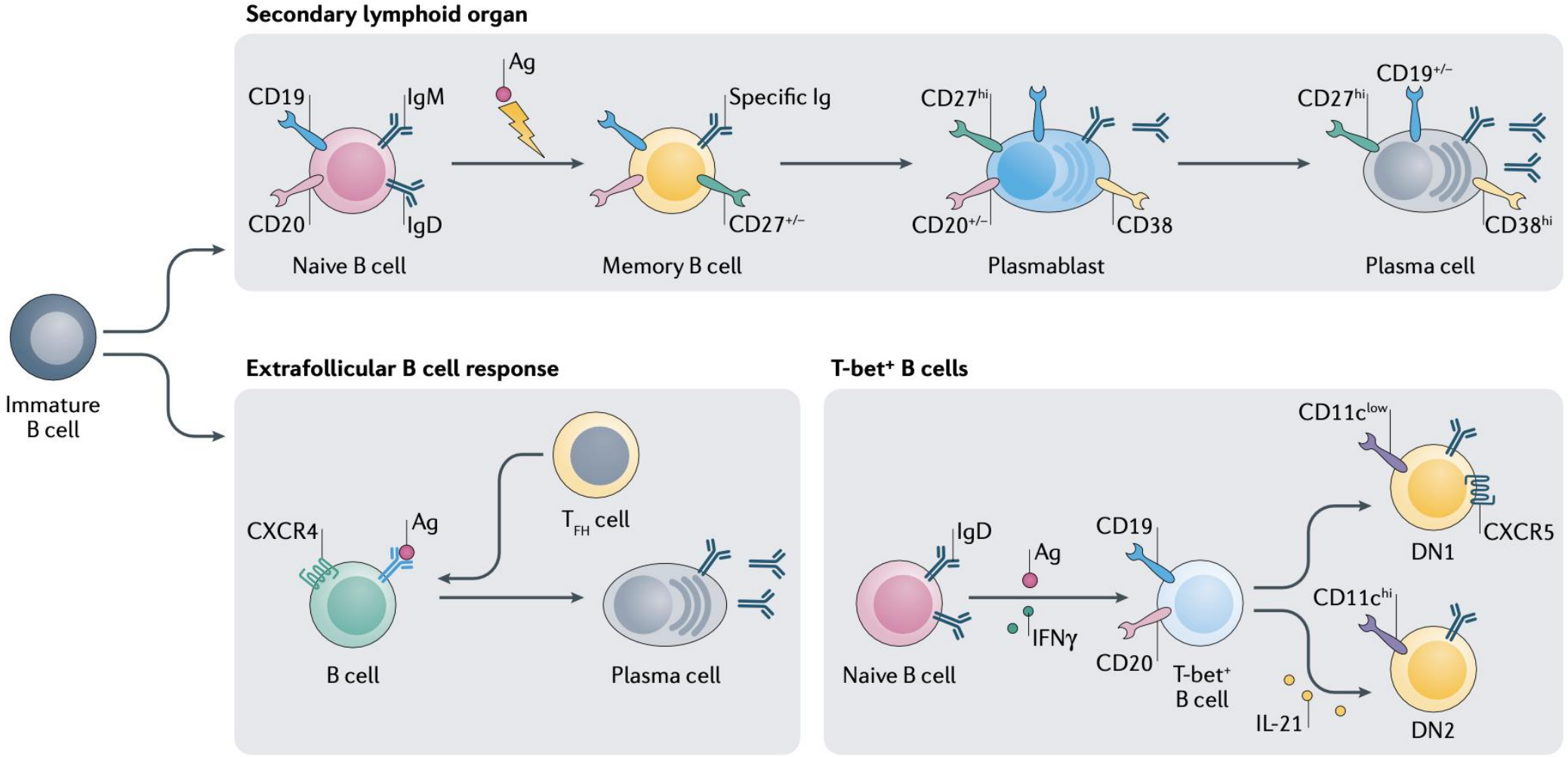
Kawasaki Disease Coronary Artery Aneurysm Prevention trial

http://kdcaap.mrcctu.ucl.ac.uk

- Composite pGTI
  - **Body mass index**
  - **Growth velocity**
  - **Glucose metabolism**
  - **Blood pressure**
  - **Hyperlipidemia**
  - **Bone mineral density**
  - **Steroid myopathy**
  - **Skin glucocorticoid toxicity**
  - **Neuropsychiatric toxicity**
  - **Infections**
- Specific items pGTI

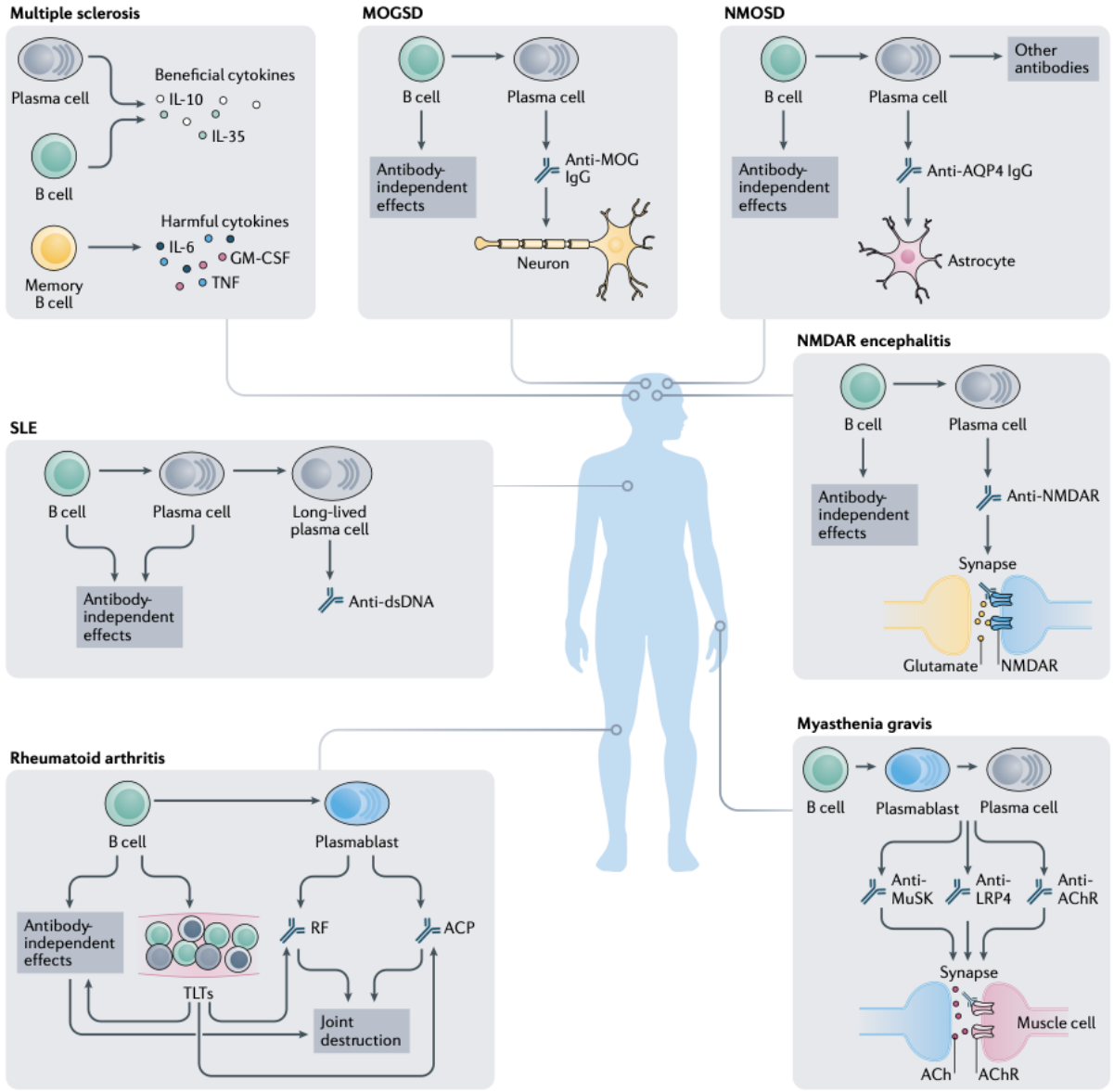
# B cell depleting agents

# B cell biology



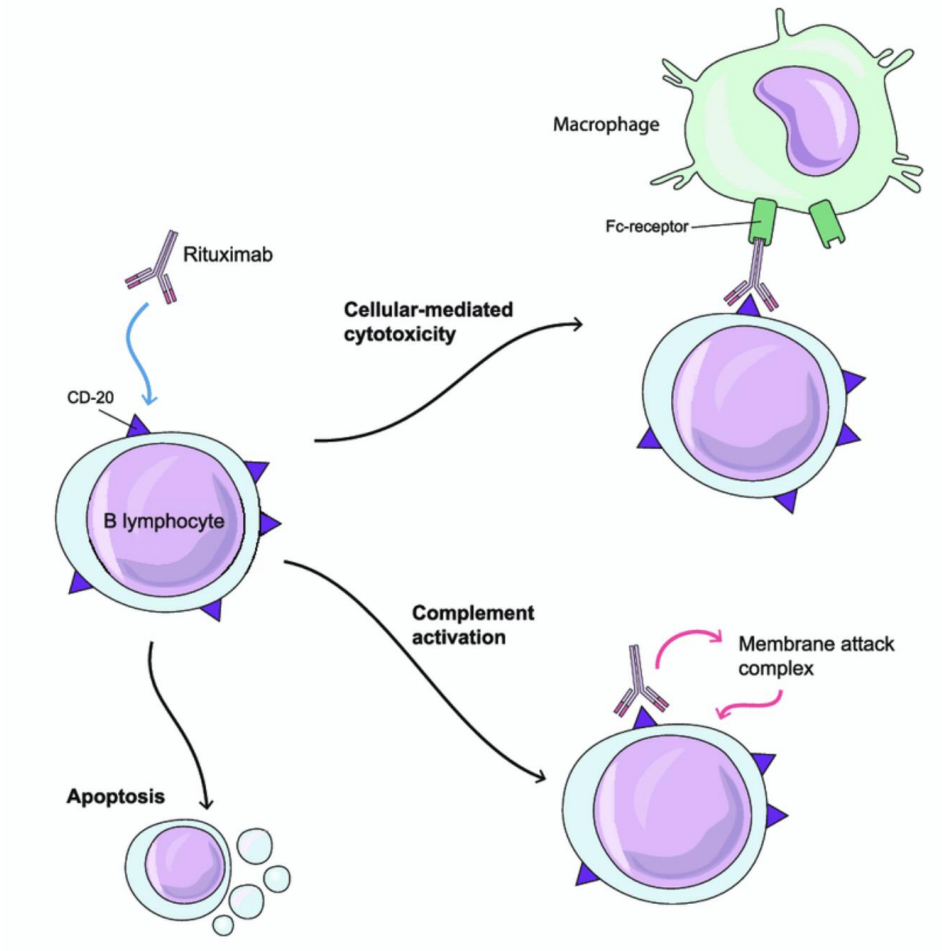

Lee at al, Nature Reviews 2020

# Roles of B cell lineage cells in autoimmune disorders




Lee at al, Nature Reviews 2020

# mAbs targeting CD19 or CD20




Not only antibody mediated
Multiple other pathways targeted

# mAbs targeting CD19 or CD20

| Drug name | Target based technology | Therapeutic indication |
|---|---|---|
| mAbs targeting CD19 or CD20 | | |
| Rituximab | Chimeric anti-CD20 mAb | Relapsing multiple sclerosis |
| | | NMDAR encephalitis |
| | | Systemic lupus erythematosus |
| | | Juvenile dermatomyositis |
| | | ANCA associated vasculitis |
| | | Rheumatoid arthritis |
| Ocrelizumab | Humanized anti-CD20 mAb | Relapsing and progressive multiple sclerosis |
| | | Systemic lupus erythematosus |
| Ofatumumab | Fully humanized anti-CD20 mAb | Relapsing multiple sclerosis |
| | | Pemphigus vulgaris |
| | | Rheumatoid arthritis |

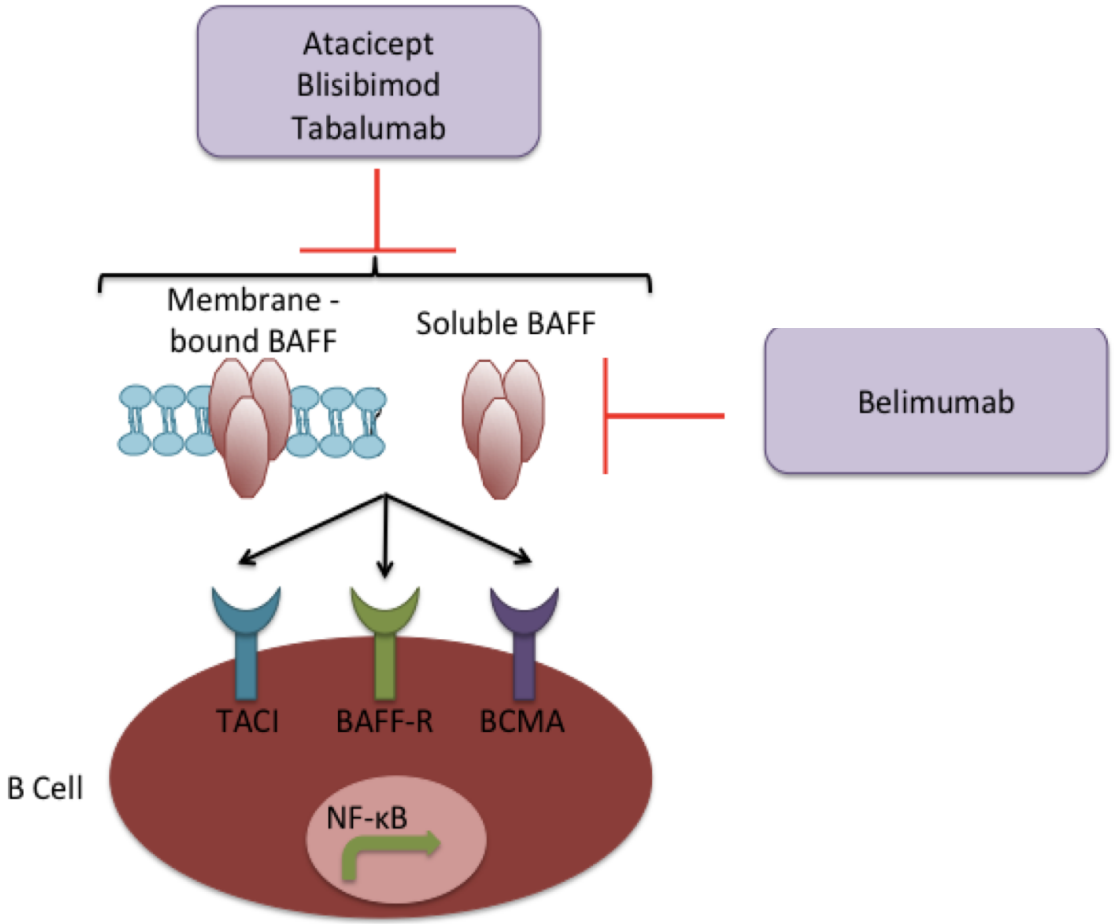
| Drug name | Target based technology | Therapeutic indication |
|---|---|---|
| Ublituximab | Next-generation fully humanized anti-CD20 mAb | Relapsing multiple sclerosis |
| Obinutuzumab | Fully humanized anti-CD20 mAb | Systemic lupus erythematosus |
| Inebilizumab (MEDI-551) | Humanized anti-CD19 mAb | NMOSD |
| | | NMDAR encephalitis |
| | | Relapsing multiple sclerosis |
| Obexelimab (XMAB5871) | Fully humanized anti-CD19 antibody | Systemic lupus erythematosus |
| Belimumab and rituximab combination therapy | Chimeric anti-CD20 and fully humanized anti-BAFF mAbs | Systemic lupus erythematosus |
| | | Lupus nephritis |
| | | Idiopathic thrombocytopenic purpura |

**Rituximab in SLE**

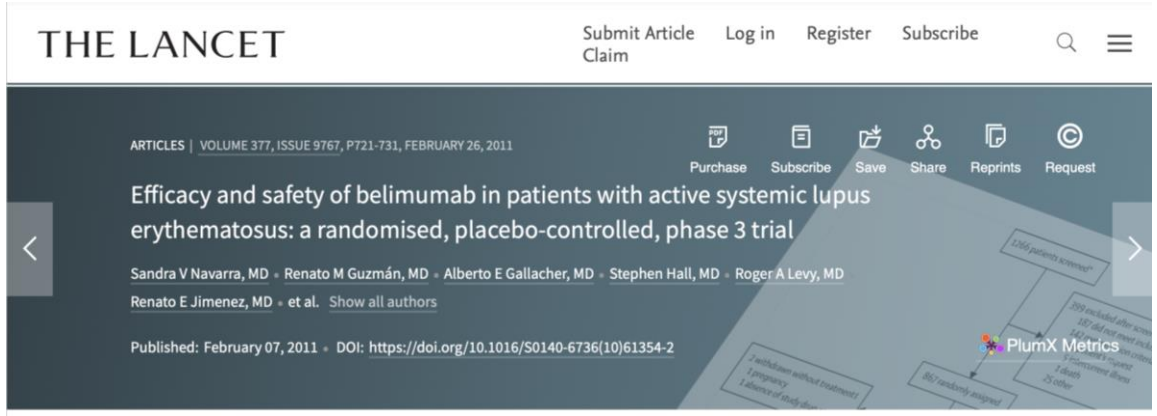
- Merrill *et al*.(EXPLORER)Phase II/III RCT
- Moderate-to-severe
- Primary endpoints:
- a) Major
- b) partial clinical response at 52 weeks

- Primary endpoints not met
- Pre-specified subgroup analysis found better response in blacks and Hispanic group treated with rituximab vs placebo
- Strict definitions for major and partial clinical response
- Amount of background therapy mitigated differences between treatment arms

# B-cell-activating factor of the TNF family (BAFF)



# Belimumab in SLE

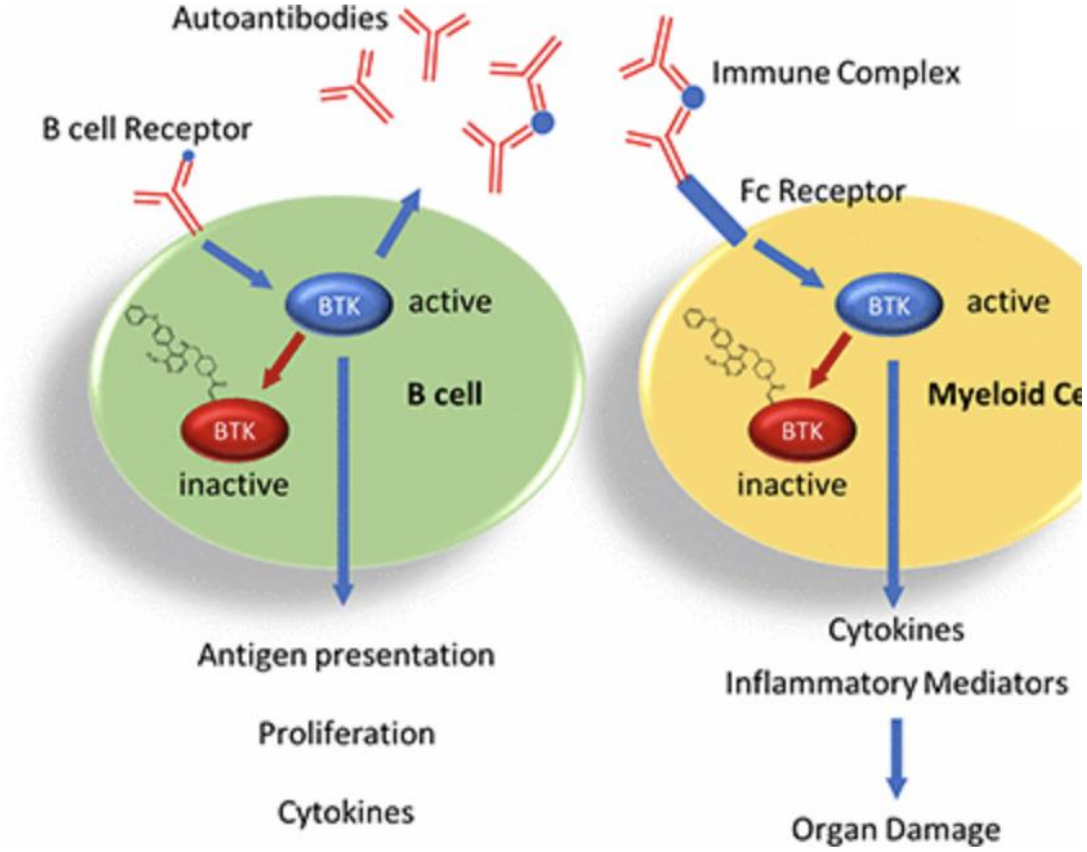



- Randomised 1:1:1 ratio to belimumab 1 mg/kg or 10 mg/kg, or placebo
- 867 patients
- Significantly higher response rates with belimumab 1 mg/kg( p=0·0129) and 10 mg/kg (p=0·0006) than with placebo
- No safety concerns

# B-cell-activating factor of the TNF family (BAFF) inhibitors

| Drug name | Target based technology | Therapeutic indication |
|---|---|---|
| Belimumab | Anti-BAFF mAb | Systemic lupus erythematosus |
| | | Vasculitis |
| | | Sjögren syndrome |
| Ianalumab | Anti-BAFF mAb | Systemic lupus erythematosus |
| | | Sjögren syndrome |
| | | Rheumatoid arthritis |
| Telitacicept (RC18) | TACI–Ig fusion protein | NMOSD |
| | | Rheumatoid arthritis |
| | | Myasthenia gravis |
| | | Multiple sclerosis |
| AMG 570 | Bispecific anti-BAFF peptibody, anti-ICOSL mAb | Systemic lupus erythematosus |
| | | Rheumatoid arthritis |
| Tabalumab | Fully humanized monoclonal antibody against soluble and membrane-bound BAFF | Systemic Lupus Erythematosus |
| Atacicept | Blocks both Blys and APRIL | Systemic lupus erythematosus |
| Blisibimod | Selective BAFF inhibitor | Systemic lupus erythematosus |

# Bruton’s tyrosine kinase (BTK) as a target for autoimmune diseases




Haselmayer et al, J Immunology 2019

# Bruton’s tyrosine kinase (BTK) inhibitors

| Drug name | Target based technology | Therapeutic indication |
|---|---|---|
| Tolebrutinib (SAR442168) | Small molecule | Rheumatoid Arthritis |
| | | Systemic lupus erythematosus |
| | | Relapsing multiple sclerosis |
| | | Secondary progressive multiple sclerosis |
| | | Primary progressive multiple sclerosis |
| | | Systemic lupus erythematosus |
| Evobrutinib | Small molecule | Relapsing multiple sclerosis |

# Other therapies targeting B cells?

# Anti CD19 CAR cell therapies for systemic lupus erythematosus

- In SLE  still several refractory cases
- Deep depletion of CD19+ B cells and plasmablasts in tissues =immune reset
- T cells activated to kill B cells by expressing vector construct encoding CAR for specific antigen on target cells
- Highly effective and robust depletion of target cells in cancer therapy (chronic lymphocytic leukemia, acute lymphoblastic leukemia and B cell non-Hodgkin lymphoma)
- Two preclinical studies in lupus-prone mice supported efficacy of CD19 CAR T cells.
- Tolerability and efficacy of CD19 CAR T cells in a small series of seriously ill and treatment-resistant patients with SLE

Mackensen et al, Nature 2022

# Anti CD19 CAR cell therapies for systemic lupus erythematosus

nature medicine

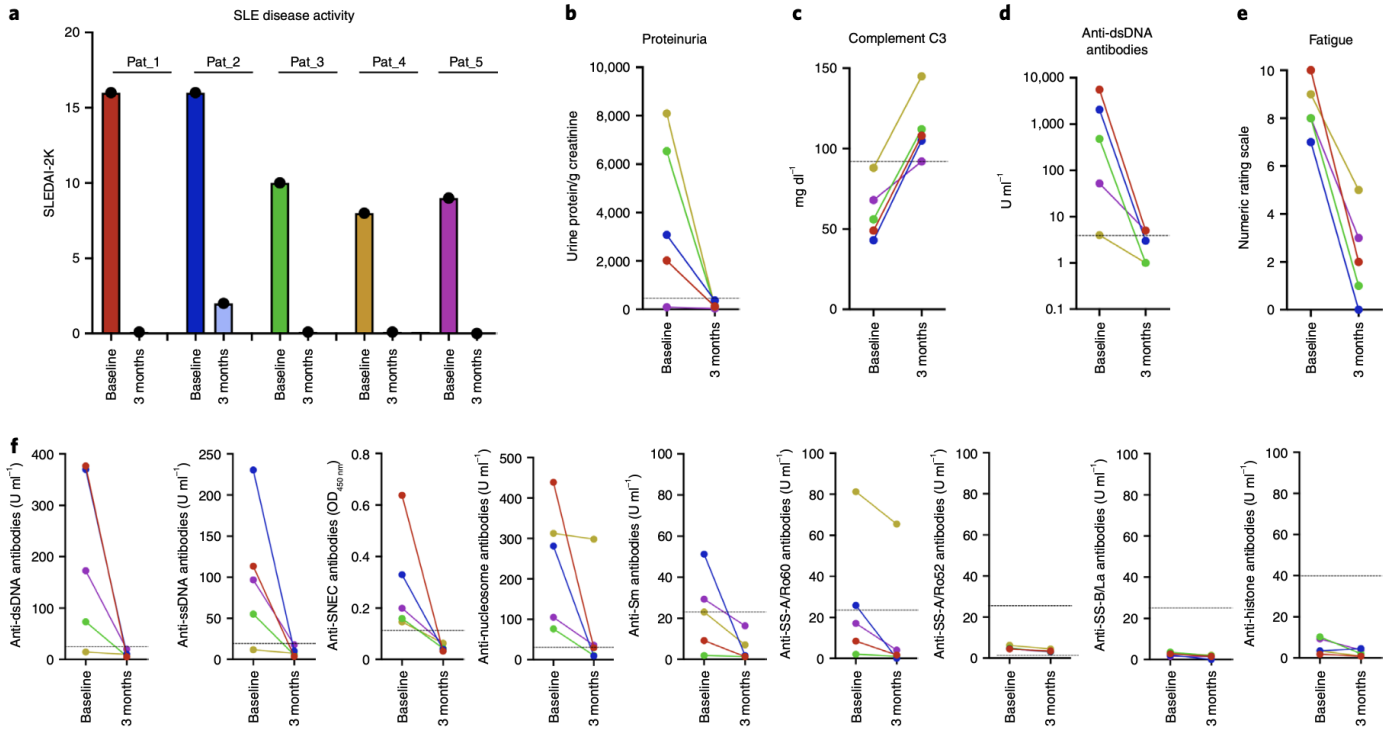
ARTICLES

https://doi.org/10.1038/s41591-022-02017-5

Check for updates

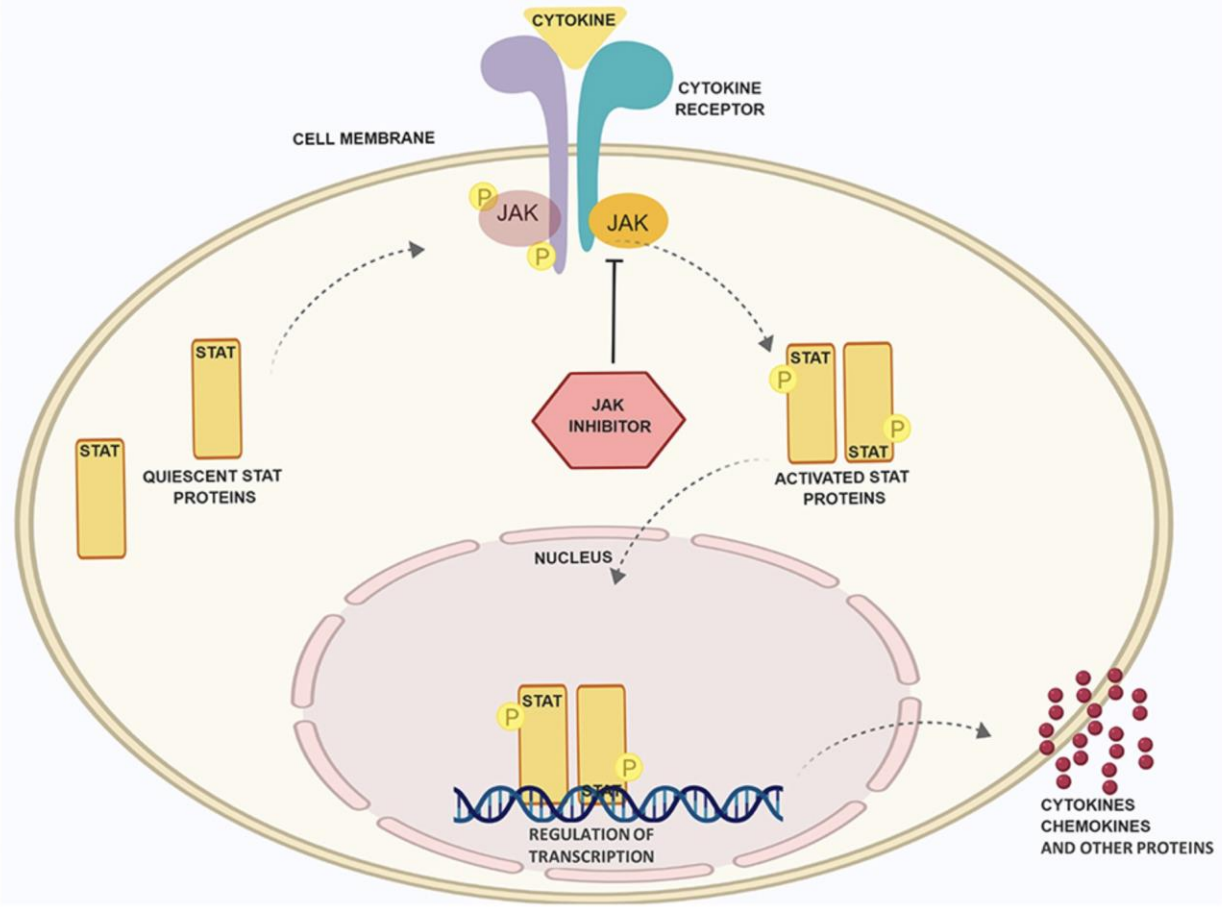
## Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Andreas Mackensen[1,2,8], Fabian Müller[1,2,8], Dimitrios Mougiakakos[1,2,3,8], Sebastian Böltz[2,4], Artur Wilhelm[2,4], Michael Aigner[1,2], Simon Völkl[1,2], David Simon[2,4], Arnd Kleyer[2,4], Luis Munoz[2,4], Sascha Kretschmann[1,2], Soraya Kharboutli[1,2], Regina Gary[1,2], Hannah Reimann[1,2], Wolf Rösler[1,2], Stefan Uderhardt[2,4], Holger Bang[5], Martin Herrmann[2,4], Arif Bülent Ekici[6], Christian Buettner[6], Katharina Maria Habenicht[7], Thomas H. Winkler[7], Gerhard Krönke[2,4,8] and Georg Schett[2,4,8] ✉

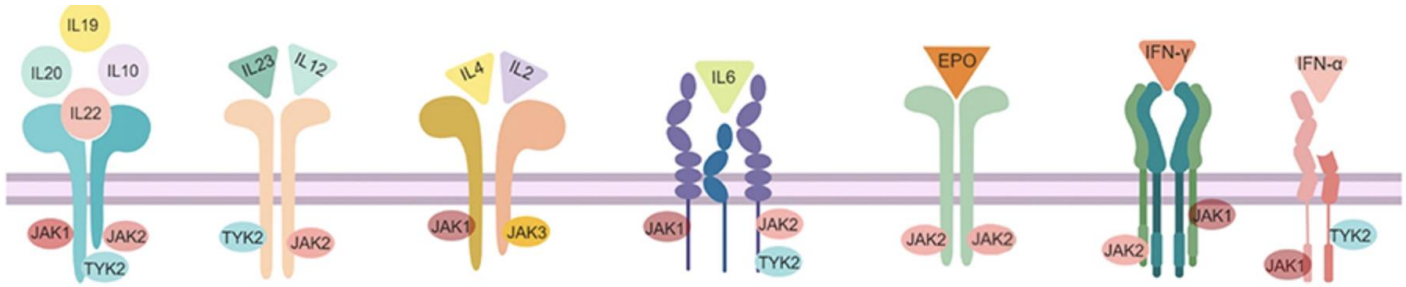


# IFN blockade

# Janus kinase inhibitors: mechanism of action



# Janus kinase inhibitors

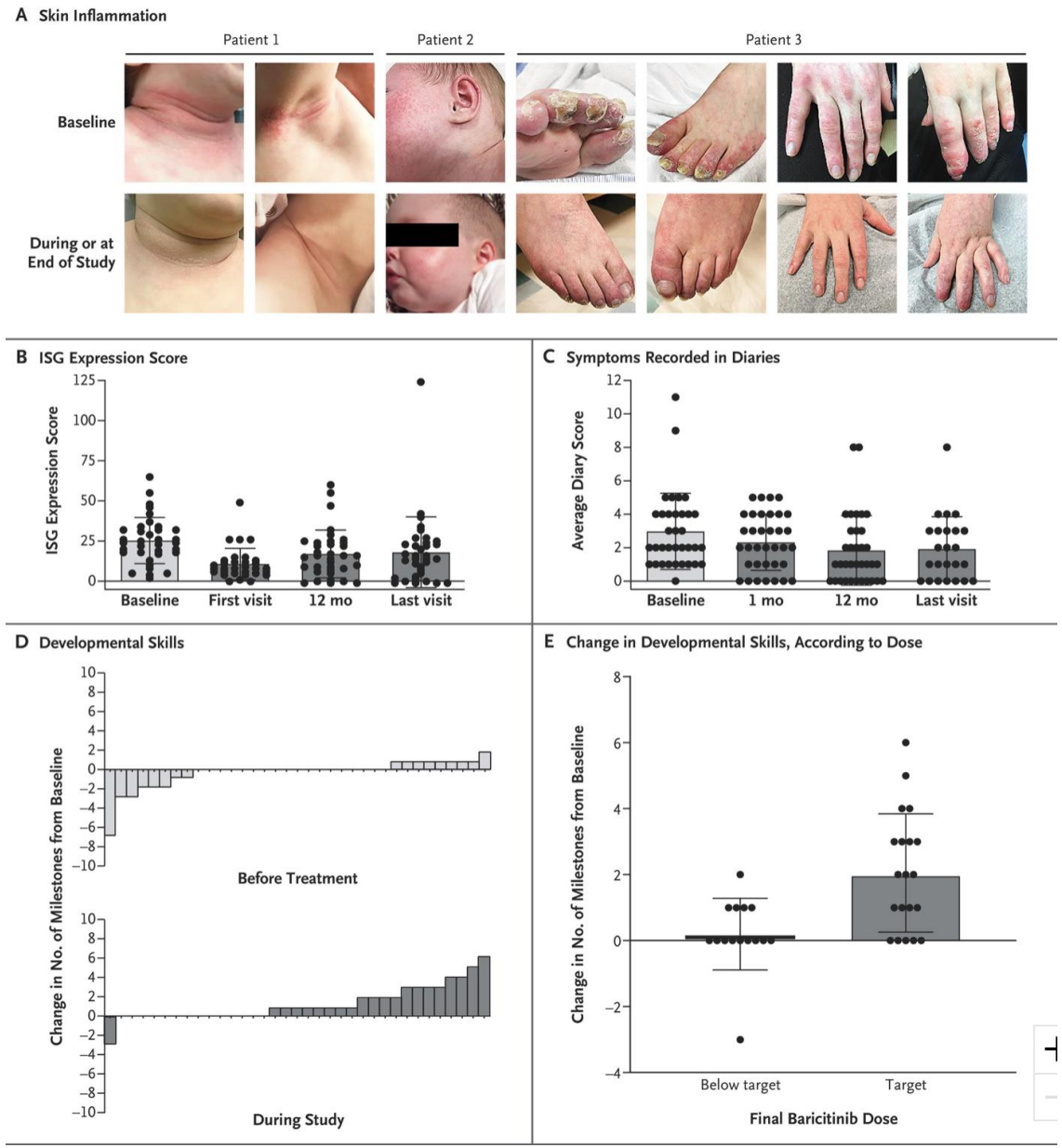



| | IL-10 family receptor | Cytokine sharing the IL -12Rβ1 | Cytokine receptor sharing the γ-chain | Cytokine receptor sharing the gp130 | Homodimeric cytokine receptor | IFN-γ receptor | IFN-α receptor |
|---|---|---|---|---|---|---|---|
| **PAN-JAK INHIBITORS**<br>delgocitinib, peficitinib | + | + | + | + | + | + | + |
| **JAK1 JAK3 INHIBITORS**<br>tofacitinib, ATI-501, ATI-502 | + | - | + | + | - | + | + |
| **JAK1 JAK2 INHIBITORS**<br>baricitinib, CTP-543, upadacitinib, ruxolitinib | + | + | + | + | + | + | + |
| **JAK1 TYK2 INHIBITORS**<br>PF06700841 | + | + | + | + | - | + | + |
| **JAK1 INHIBITORS**<br>itacitinib, PF-04965842, solcitinib, INCB054707, filgotinib | + | - | + | + | - | + | + |
| **JAK2 INHIBITORS**<br>pecritinib, GSK2586184 | + | + | - | + | + | + | - |
| **JAK3 INHIBITORS**<br>PF-06651600 | - | - | + | - | - | - | - |
| **TYK2 INHIBITORS**<br>PF-06835375, BMS986165, PF-06826647 | + | + | - | + | - | - | + |

# JAK inhibition in systemic lupus erythematosus


- 314 patients randomized to: placebo, baricitinib 4 mg, baricitinib 2mg
- 67% on bari 4mg achieved remission at week 24 (OR 1.8 96% CI 1-33) for comparison with placebo

# Janus Kinase Inhibition in the Aicardi–Goutières Syndrome

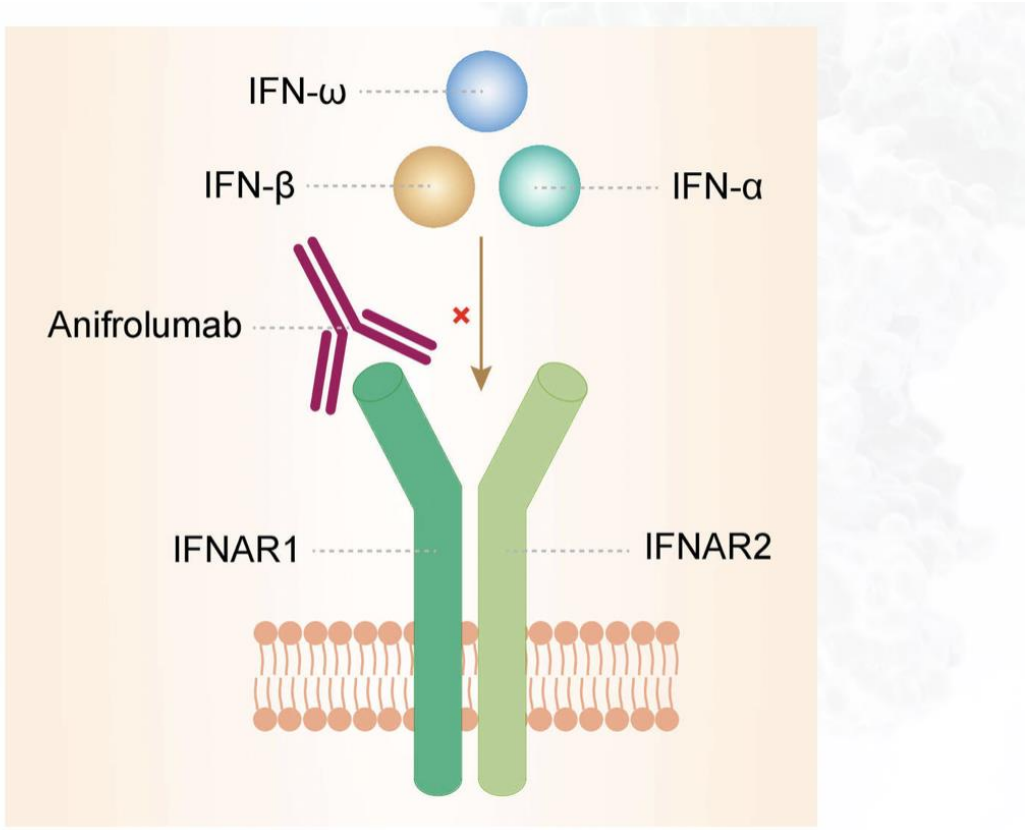



NHS England policy: therapeutic access for monogenic interferonopathies

https://www.england.nhs.uk/publication/baricitinib-for-use-in-monogenic-interferonopathies-adults-and-children-2-years-and-over/

Vanderver et al, NEJM 2020

# Anifrolumab

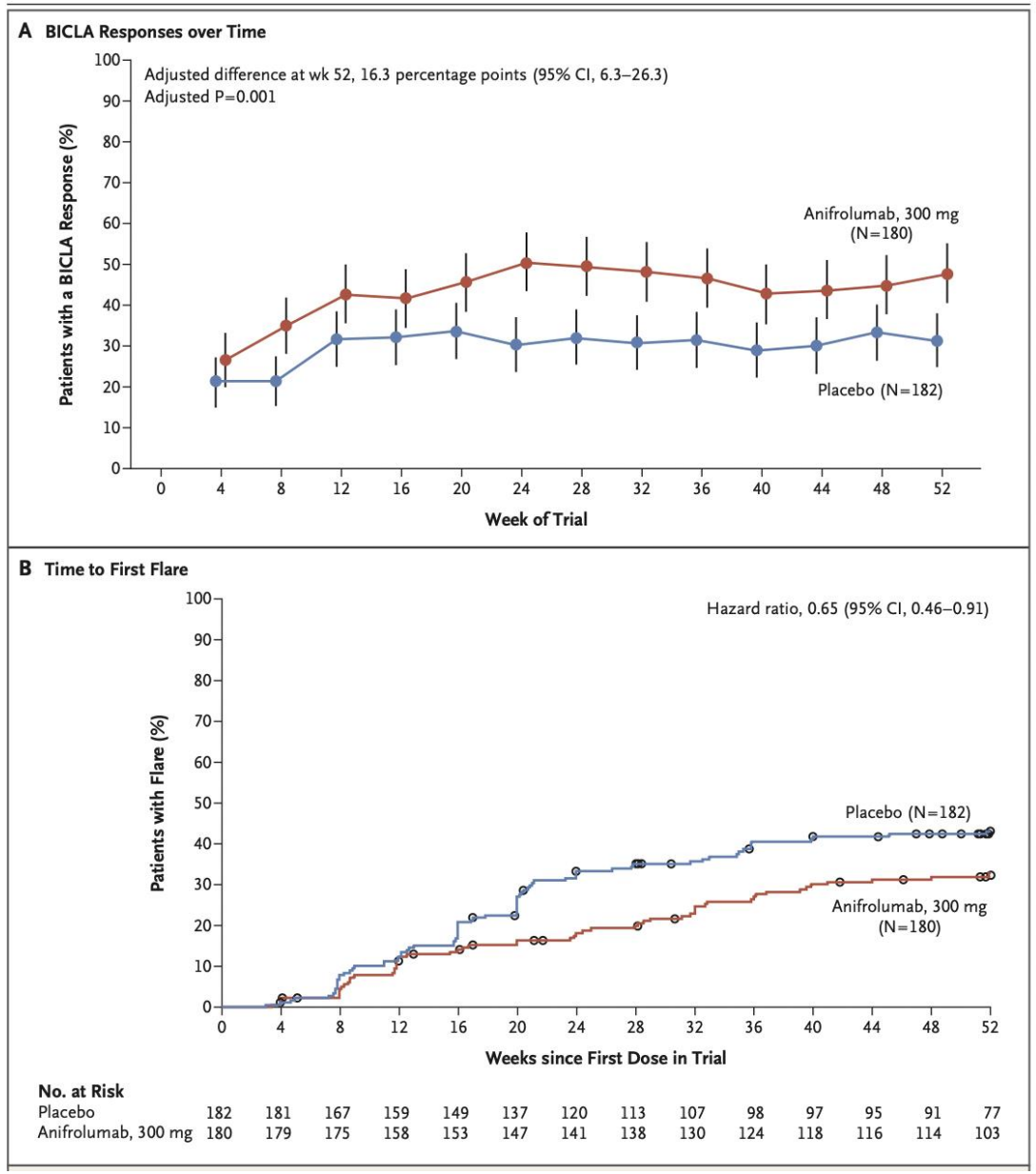


The NEW ENGLAND JOURNAL of MEDICINE

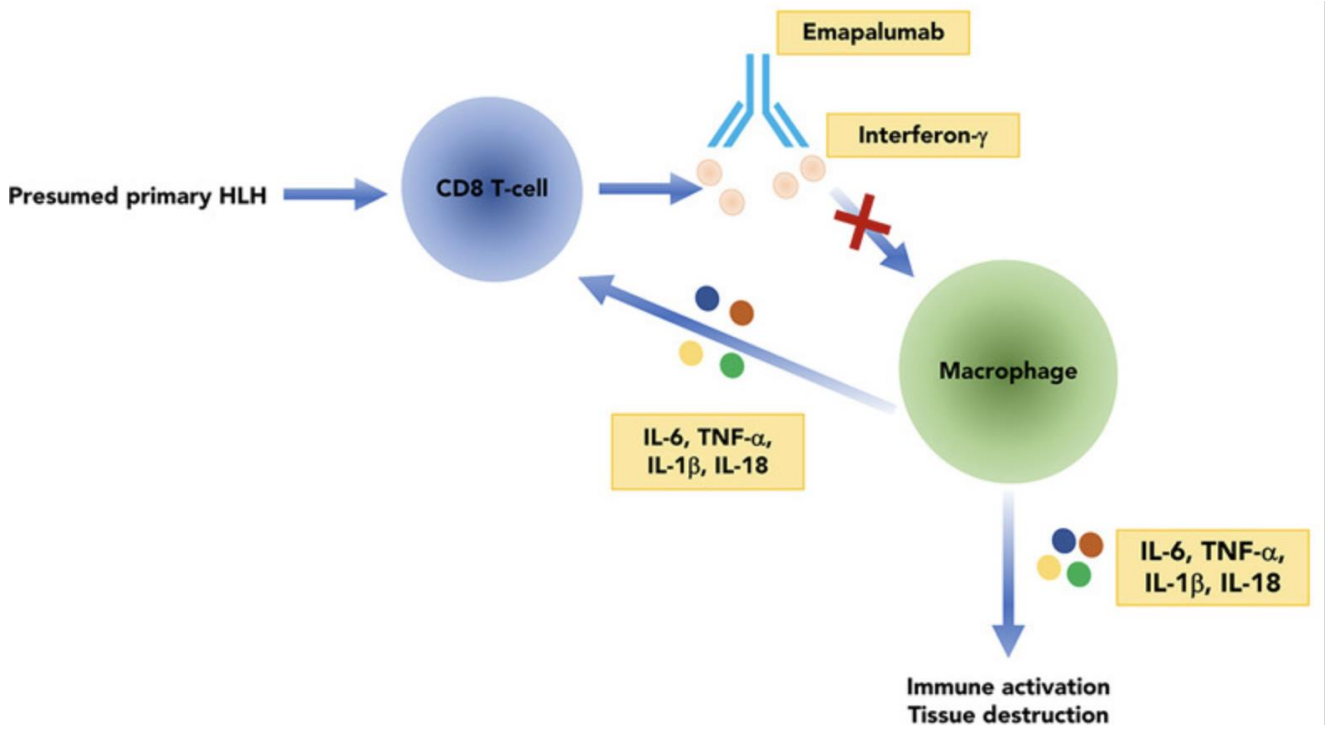
ESTABLISHED IN 1812 JANUARY 16, 2020 VOL. 382 NO. 3

# Trial of Anifrolumab in Active Systemic Lupus Erythematosus

E.F. Morand, R. Furie, Y. Tanaka, I.N. Bruce, A.D. Askanase, C. Richez, S.-C. Bae, P.Z. Brohawn, L. Pineda, A. Berglind, and R. Tummala, for the TULIP-2 Trial Investigators*



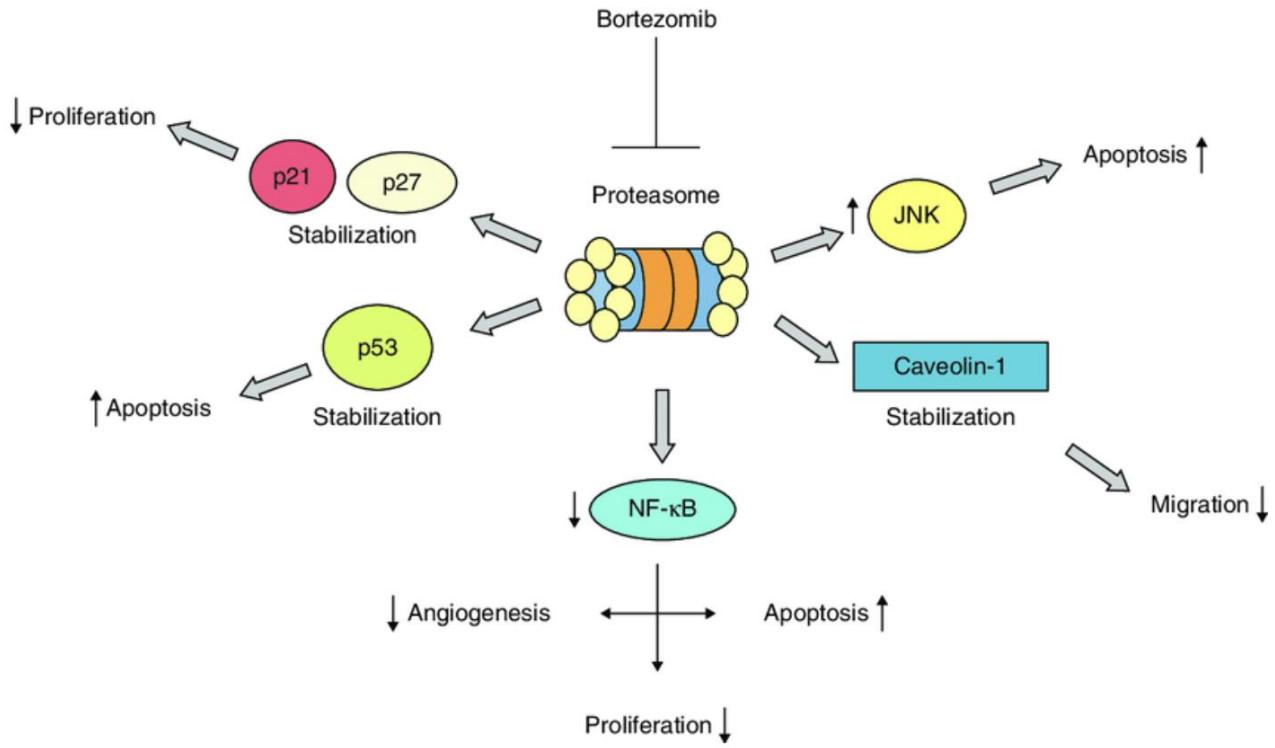
# IFN-γ blockade




FDA approved for primary HLH
Ongoing trial for secondary HLH

Vallurupalli et al, Blood 2019
Locatelli et al, NEJM 2020

# Proteasome inhibitors

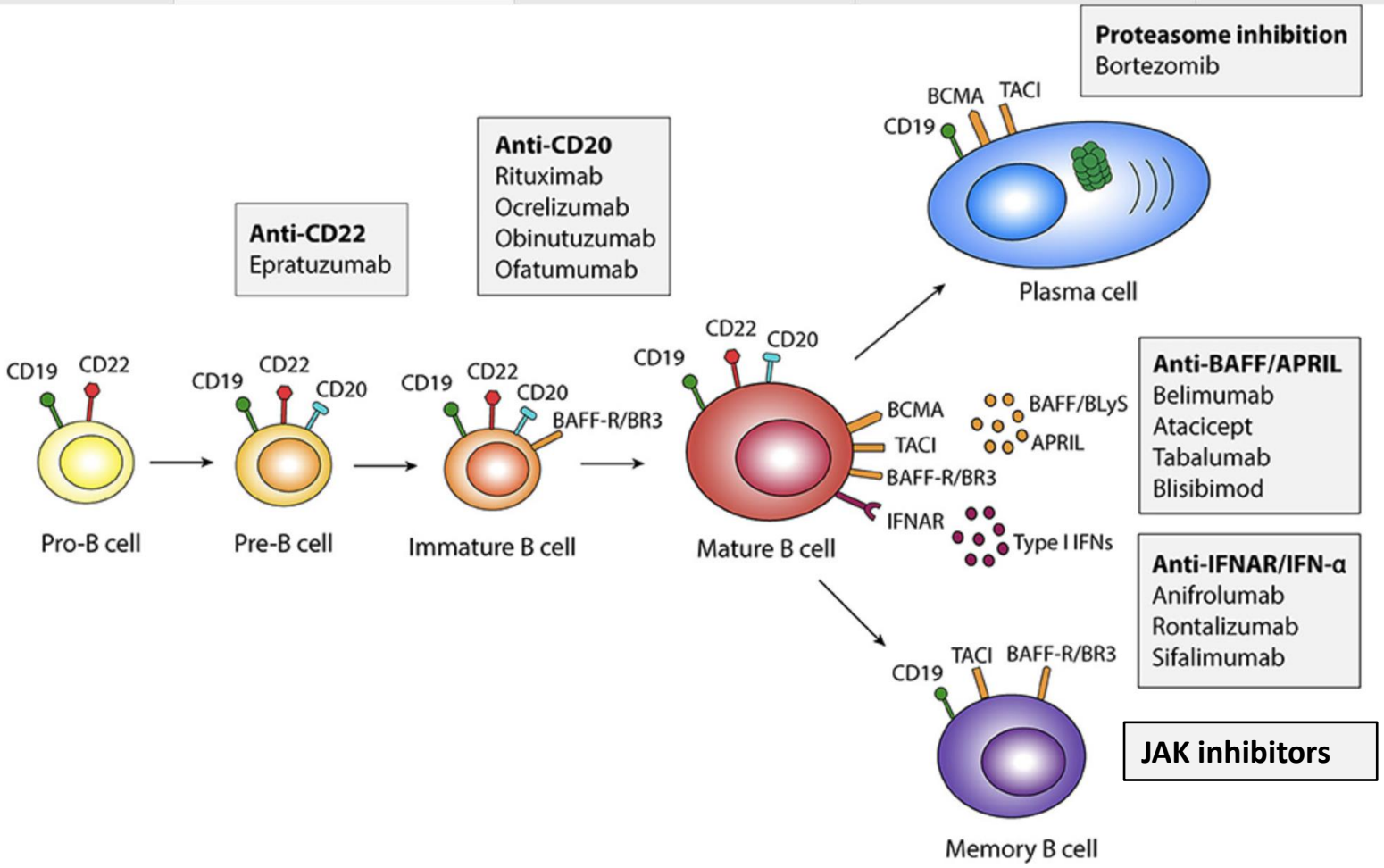



**Clinical Experience of Proteasome Inhibitor Bortezomib Regarding Efficacy and Safety in Severe Systemic Lupus Erythematosus: A Nationwide Study**

*Tomas Walhelm[1], Iva Gunnarsson[2], Rebecca Heijke[3], Dag Leonard[4], Estelle Trysberg[5], Per Eriksson[1,3] and Christopher Sjöwall[1*]*

Russo et al, Adv Therapy 2017

# Summary of pharmaceuticals targets for lupus




Parodis et al, Frontiers Immunology 2020

# Summary

- Several emerging novel therapies
- General thinking paradigm for improving therapies ( rheum experience):
  - Reduce toxicity
  - Understand pathomechanisms
    - Targeted therapies
    - Common mechanisms
  - Robust outcome measures
    - Clinical tools
    - Biomarkers
- Other cytokine/chemokine targeted therapies
- **Treat to target**

# Ongoing challenges

- Therapies for rare diseases
  - Small sample size
  - Robust outcome measures
  - Novel trial design
- Several novel targeted therapies for autoimmune diseases
  - Establish efficacy and safety for specific indications
  - Long term efficacy data
  - Unexpected toxicity
- Access in routine clinical care
  - Costs
  - Age restrictions
- Collaboration (team work!)