



Updates in Rheumatoid Arthritis

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Learning Objectives

- At the conclusion of this session, participants should be able to:
 - Discuss differences between ACR and EULAR treatment recommendations for RA
 - Recognize the structure and function of novel monoclonal antibodies based on new naming conventions
 - Describe new therapeutic targets and new mechanisms of action for compounds in development for RA

Disclosures

- Consultant: AbbVie, Astra Zeneca, Eli Lilly, Janssen, Pfizer, Sanofi, Tonix
- The use of off-label and investigational products will be discussed in this presentation

Outline

- Revised Guidelines for Treatment
- Drug Naming Nomenclature Changes
- New Therapeutics in Development
 - TL1A
 - Nanobodies
 - PAD2/4 (AZD1163)
 - PD1 Agonists
 - CAR-T
 - TCE (BiTE, TriTE)

Revised EULAR Treatment Guidelines

Smolen JS et al, Ann Rheum Dis 2026; 85(6):991-1009



Immediate Start:

Begin DMARD therapy as soon as RA diagnosis is confirmed.



First-Line Therapy:

Use MTX as part of the initial treatment strategy, ideally combined with short-term glucocorticoids tapered quickly. Use LEF or SSZ if MTX not tolerated or contraindicated.



Treat-to-Target Strategy:

Monitor active disease q 1 to 3 months. Adjust or escalate therapy if no improvement by 3 mo or if treatment target (remission or LDA) is not reached by 6 mo.



Adding Advanced Therapies:

If target fails with csDMARDs, add bDMARD. tsDMARDs can also be considered, provided CV and malignancy risks are weighed.



Sequencing After Failure:

If a first biologic/targeted synthetic drug fails, any other bDMARD (same or different class) or tsDMARD recommended.



Tapering in Remission:

If a patient achieves sustained remission, consider tapering DMARDs, but stopping entirely should be approached with caution due to high flare risks.

Comparison of ACR and EULAR Recommendations

Clinical Focus	EULAR Recommendations	ACR Guidelines
Glucocorticoid (Steroid) Bridging	Recommends short-term bridging when initiating/changing conventional DMARDs (rapid taper).	Conditionally recommends against bridging due to toxicity and tapering difficulties.
Initial Failure Options	Prefers a biologic (bDMARD) but permits a JAK inhibitor (tsDMARD) after strict safety checks.	Strongly prefers adding a biologic or JAK inhibitor over moving to conventional triple therapy.
JAK Inhibitor Positioning	Restricts JAK inhibitors behind mandatory MACE, malignancy, and blood clot risk tracking .	Utilizes generalized safety warnings but keeps broader patient demographic choices open.
Comorbid Subpopulations	Uses a general framework meant for all patients, avoiding subpopulation rules.	Provides highly specific algorithms for lung disease, heart failure, and infections.
Remission Tapering Strategy	Cautiously suggests tapering but openly warns against complete cessation due to high flare risks.	Provides an explicit, structured step-down protocol for reducing doses across different drug classes.
Methodological Framework	Rates recommendations based on level of evidence, strength, and expert panel agreement.	Uses the strict, explicit GRADE methodology to directly compare clinical options head-to-head.

EULAR vs ACR Guidelines

Glucocorticoid Divide

- Short term steroid bridge vs prioritize avoiding steroids

Scope vs Streamlining

- Unified algorithm vs highly granular framework with specific recommendations (lung disease, heart failure, etc)

Handling Advanced Drug Failure

- Open ended flexibility (switches within class) vs prefer switching drug classes

Current WHO/INN Naming for Antibody-Based Therapeutics

Structure-based stems replace legacy antibody naming

How Names are Built

Prefix + Infix + Final Stem

Prefix = unique

Infix = target

Suffix = structure

Common Infixes

-ki-	cytokine/cytokine receptor
-li-	immune cell receptor
-sto-	immunostimulatory (ICIs)
-pru-	immunosuppressive
-ta-	tumor/oncology

Final Stems

-tug	unmodified
-bart	engineered
-mig	multispecific
-ment	fragment

Hypothetical “New” Names:

Adalimumab —————> Adakitug

Pembrolizumab —————> Pembrostotug

Certolizumab ~~pegol~~ —————> Certokiment

Peresolimab —————> Perelitug or Pereprutug

—————>

Infix (middle of the name)

- -ki- cytokine/cytokine receptor
- -li- immune cell receptor
- -sto- immunostimulatory (ICIs)
- -pru- immunosuppressive
- -ta- tumor/oncology

Drug Naming Nomenclature Changes

Suffixes

The 4 Modern Antibody Suffix Groups

Group	Suffix	Structural Definition	Examples & Key Formats
Group 1	-tug	Unmodified immunoglobulins: Full-length, monospecific antibodies with unaltered constant regions.	Natural immunoglobulins of any species, classic chimeric, or humanized antibodies.
Group 2	-bart	Engineered immunoglobulins: Full-length, monospecific antibodies containing mutations or artificial modifications.	Antibodies engineered for altered Fc functions, point mutations, or glyco-engineering.
Group 3	-mig	Multi-immunoglobulins: Bispecific, trispecific, or multi-specific formats of any size or sequence length.	BiTEs, BiKEs, TriKEs, and multi-specific nanobody chains.
Group 4	-ment	Monospecific fragments: Any antibody-derived construct that lacks an Fc constant region.	Single monovalent nanobodies (VHH) , Fabs, F(ab') ₂ , and scFvs.

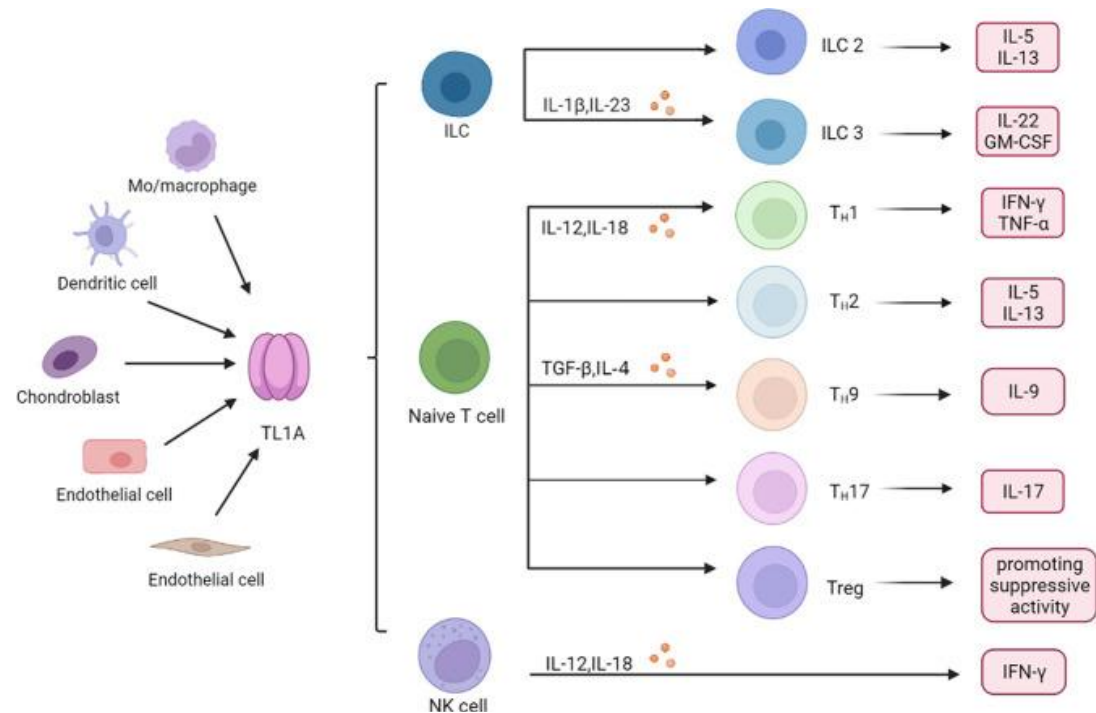
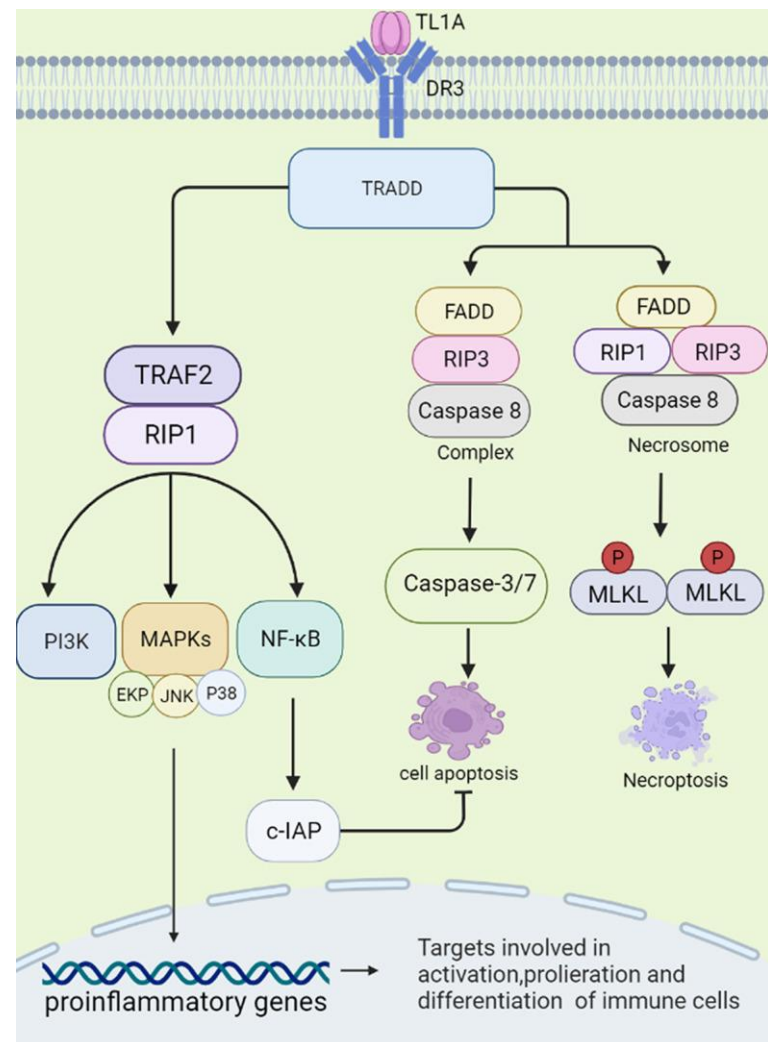
New Therapeutics in Development

- **The Prefix:** A unique, random sound chosen by the manufacturer (e.g., *Ate-*).
- **The Infix:** A syllable identifying the disease target. For immunology/rheumatology, the infix is **-pru-** (immunosuppressive) or **-ki-** (cytokines).
- **The Suffix:** **-bart**, proving it is a structural, artificially engineered

TL1A (TNF-like ligand 1A)

- **The Role of TL1A in Rheumatoid Arthritis**
 - Pro-inflammatory cytokine belonging to the tumor necrosis factor (TNF) superfamily. TL1A is heavily upregulated in **blood and synovial fluid**
- **Dual-Action Damage:**
 - TL1A binds to DR3 receptor, driving a dual wave of destruction: it heavily spikes the production of tissue-destroying cytokines (like TNF-alpha and IL-17) while simultaneously triggering **fibrosis and irreversible cartilage erosion**.
- **Superior Preclinical Performance:**
 - In animal models of arthritis, anti-TL1A antibodies demonstrated efficacy **superior to etanercept** in reducing total joint inflammation and bone erosion

Function and Role of TL1A



Xu WD et al, Front Immunol. 2022;13:891328.

Anti-TL1A MAbs

- **Tulisokibart (MK-7240):**
 - Designed to neutralize both soluble and cell-bound TL1A, binds monomers and trimers. In Phase 2b for RA (NCT07176390)
- **Afimkibart (RG6631):**
 - TL1A blocker that binds trimeric forms only, in Phase 2 in RA (NCT07137598).
- **SPY002:**
 - Next-generation, half-life extended anti-TL1A antibody, binds monomers and trimers. Modified by increasing binding to FcRn. In Phase 2 clinical trials for UC. Basket trial for RA, PsA, SpA underway.
- **Duvakitug:**
 - Targets DR3 binding and spares soluble DcR3 buffer. In Phase 3 for UC. Nothing yet for arthritis
- Tulisokibart¹, Afimkibart², SPY002, and Duvakitug³ have all shown efficacy in ulcerative colitis trials (Phase 3 for Tulisokibart, Phase 2 for amfimkibart, SPY002, duvakitug)

1. Sands BE et al, N Engl J Med 2024; 391:1119-1129. 2. Danese S, et al, Lancet Gastro Hepatol 2025; 10(10):882-895. 3. Reinisch W, Lancet Gastroenterol Hepatol. 2026;11(9):775-785.

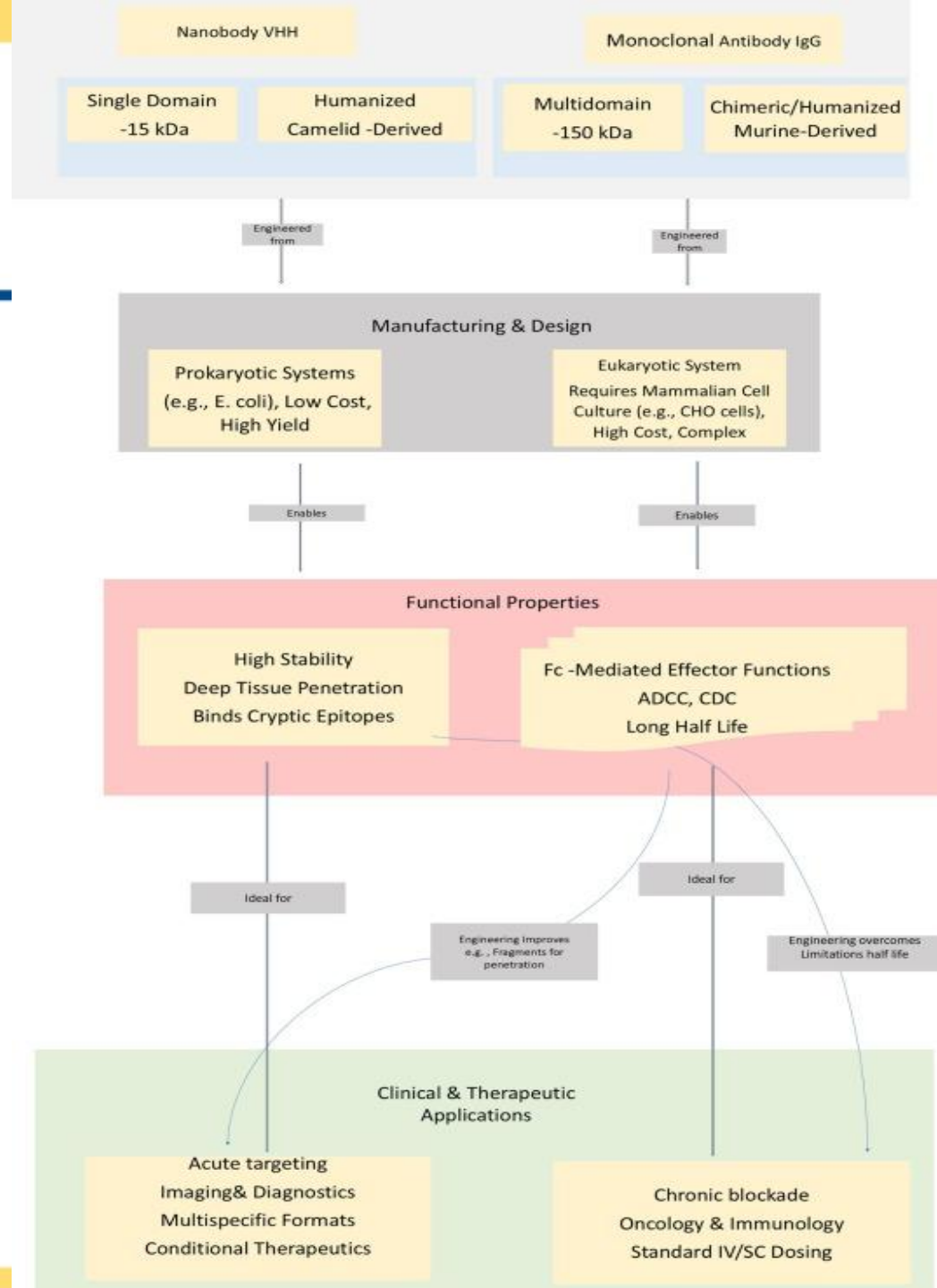
TL1A Compounds in Development

	Tulisokibart			Afimkibart		Duvakitug	
Developer	Merck & its subsidiary Prometheus Biosciences			F. Hoffmann-La Roche		Teva and Sanofi	
Clinical Indications	ILD	IBD	SSc	IBD	MASH	IBD	Asthma
							
	HS	r-axSpA	RA	AD	RA		
							
Furthest clinical trial progress	Phase 3			Phase 3		Phase 3	
Administration route	IV	SC		IV	SC		SC
							
Efficacy	✓			✓		✓	
	IV tulisokibart produced a statistically significant improvement in the primary and most secondary endpoints in UC and CD patients			IV afimkibart produced a statistically significant improvement in the primary endpoint in UC patients		SC duvakitug produced a statistically significant improvement in the primary endpoints in UC and CD patients	
Safety	○			✗		✗	
	No published results for SC tulisokibart			SC afimkibart did not produce a statistically significant improvement in the primary endpoint in UC patients, but the improvement was clinically meaningful		Trial of SC duvakitug for asthma treatment was terminated after meeting futility criteria	
Safety							
	Common adverse events reported include infection (predominantly respiratory and urinary tract infections), worsening or flare of UC/CD, anemia			Common adverse events reported include infection (predominantly respiratory and urinary tract infections), arthralgia, nausea, worsening or flare of UC		Common adverse events reported include respiratory tract infection and anemia	

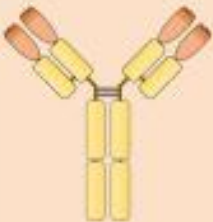
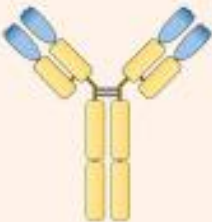
Nanobodies

- Therapeutic proteins derived from single-domain (VHH) fragments of camelid (llama or camel) antibodies
- ~38 kDa vs standard MAb (~150 kDa)
- Deep Synovial Penetration: Hypothesized to penetrate dense, poorly vascularized inflamed joint tissues better than traditional biologics
- Multivalent Customization: Can string multiple nanobodies together to hit different targets at same time

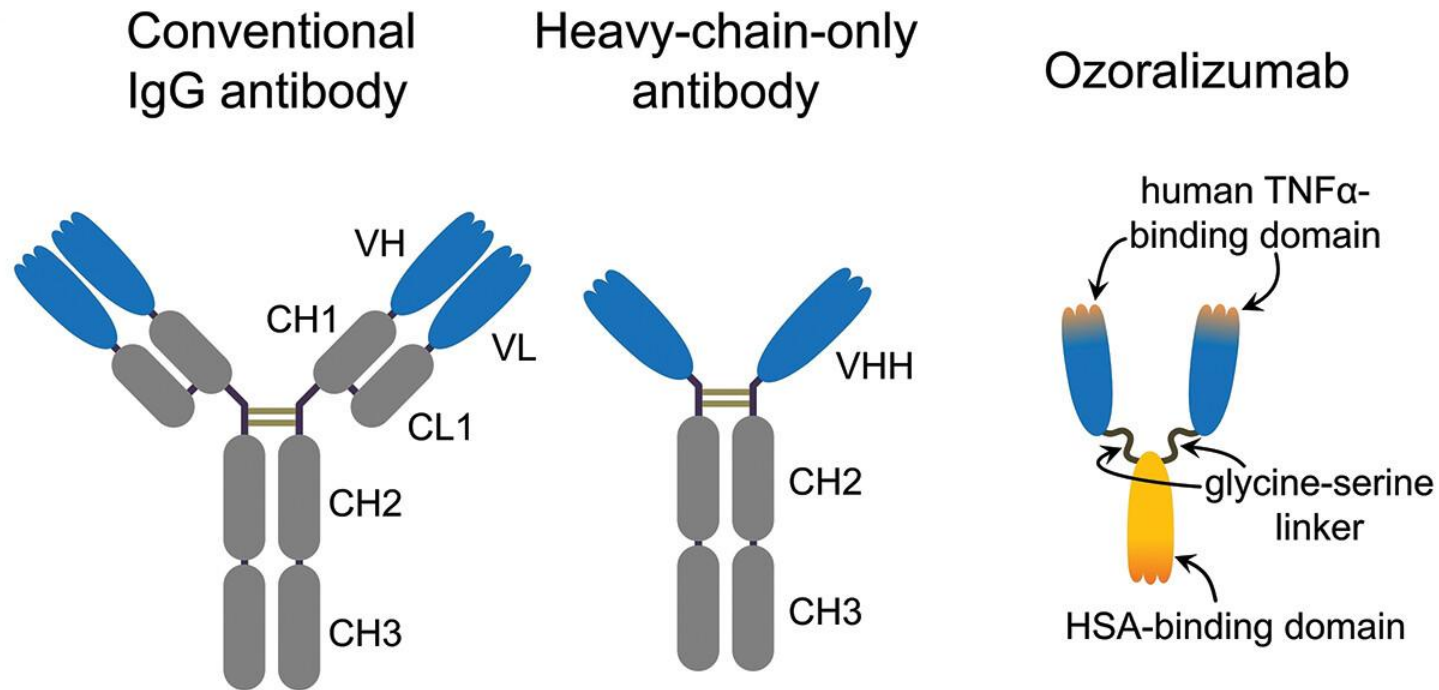
Nanobody vs Traditional MAbs



Comparison of Different TNF blockers

					
Structure	Chimeric antibody	Fully human antibody	Receptor-Fc fusion protein	PEGylated Fab fragment	Humanized VHH antibody
Molecular size	150 kDa	150 kDa	150 kDa	90 kDa	38 kDa
Biological agents	Infliximab	Adalimumab and golimumab	Etanercept	Certolizumab pegol	Ozoralizumab

Structure of Ozoralizumab Nanobody



What would a hypothetical new naming be? Ozora-ki-ment

Nanobodies in Inflammatory Arthritis (xxxx-ki-ment)

- **Ozoralizumab (Nanozora®)** – First Approved RA Nanobody in Japan^{1,2}
- Trivalent, bispecific nanobody that targets **TNF-alpha**
- **Sonelokimab** –Phase 3 ongoing for PsA, Ph 2 published³
- Targets **IL-17A and IL-17F pathways** simultaneously
- **Vobarilizumab (ALX-0061)** – Phase 2b conducted in RA compared with Tocilizumab⁴
- Bispecific nanobody targets **Interleukin-6 Receptor (IL-6R)**

1. Tanaka Y, Mod Rheumatol. 2023 Aug 25;33(5):883-90

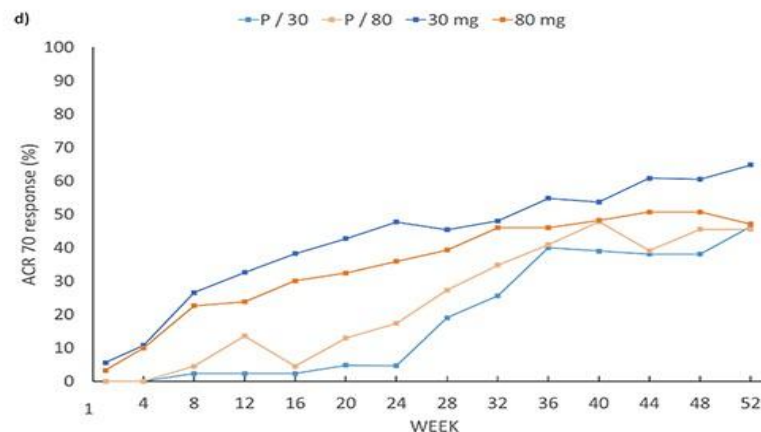
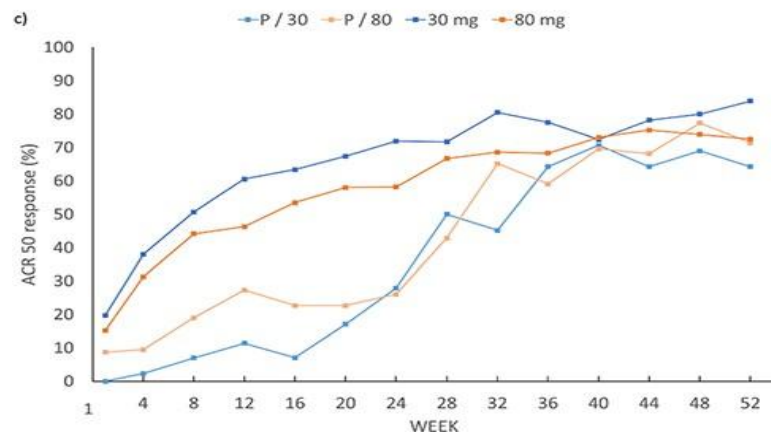
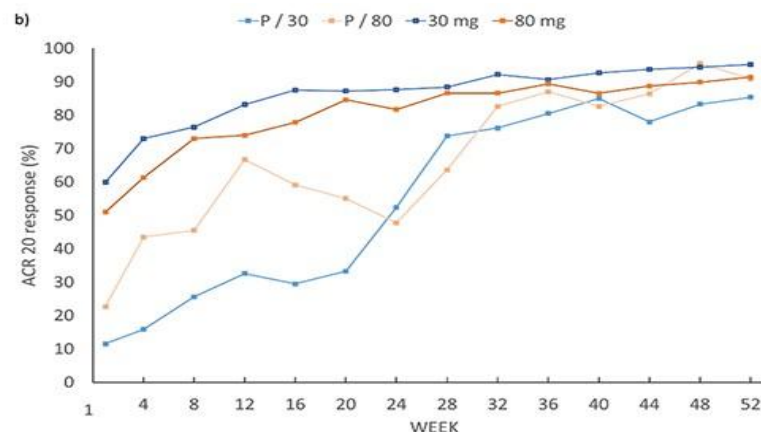
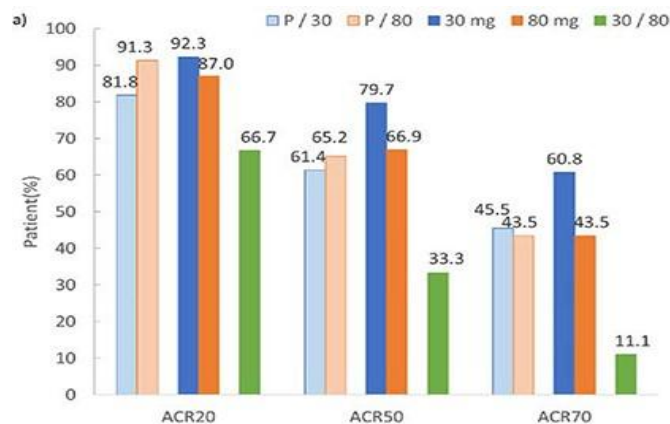
2. Tanaka Y. Mod Rheumatol. 2023 Aug 25;33(5):875-82

3. McInnes IB, Nature Med. 2025; 31:4160-71

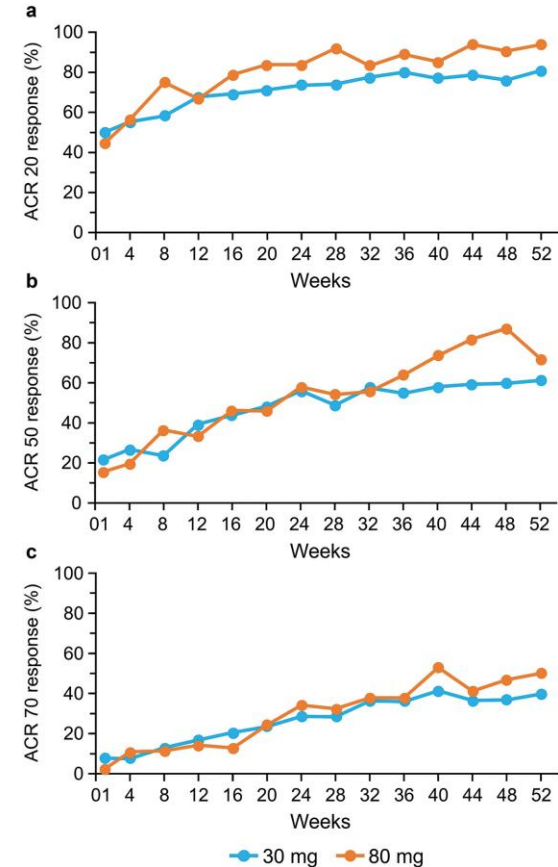
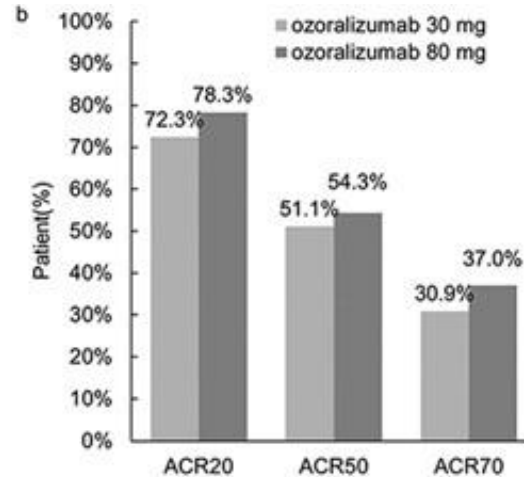
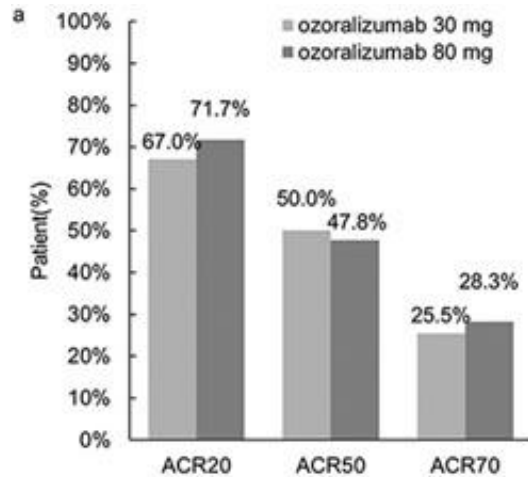
4. Dorner T, Ann Rheum Dis. 2017; 76(Supp 2): 575 (Abstract FRI0239 EULAR)

Ozoralizumab (Ohzora trial, MTX-IR)

Placebo-controlled through 24 weeks, then open label



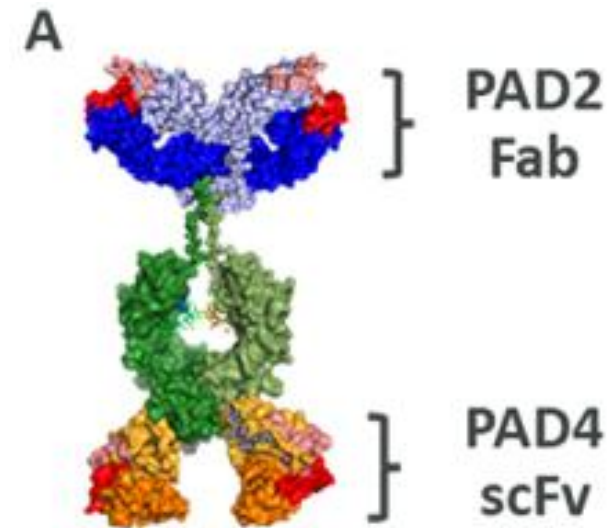
Ozoralizumab (Natsuzora Trial)



Randomized open label, no placebo,
Monotherapy

PAD2/4 (AZD1163) (xxxxxx-li-mig)

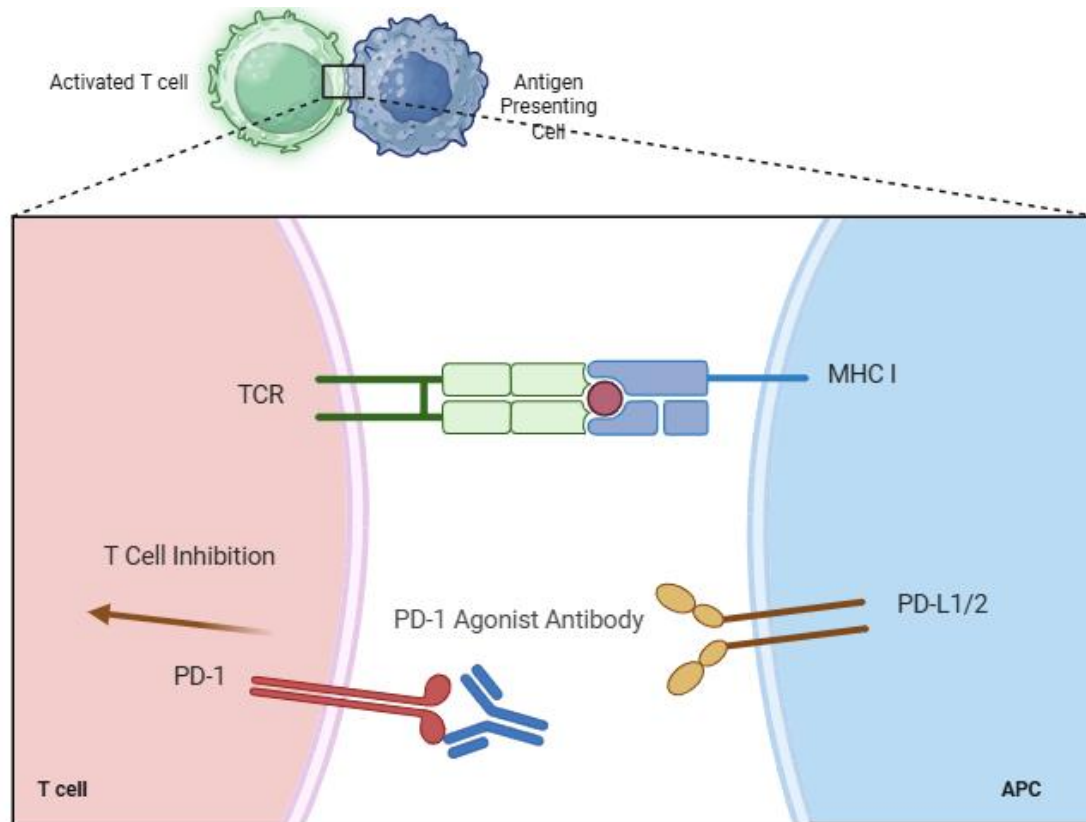
- Bispecific antibody
- Inhibits extracellular PAD2 and PAD4
- Phase 1 reported in healthy volunteers where target was reached and inhibited
- Phase 2 study recruiting (NCT07276581)
- On top of csDMARD or MTX



Sims GP Mabs 2026; 18(1):2657629.

Prothon S, [abstract 1374]. Arthritis Rheumatol. 2025; 77 (suppl 9).ACR 2025

PD-1 Agonists



PD1 Agonists in RA

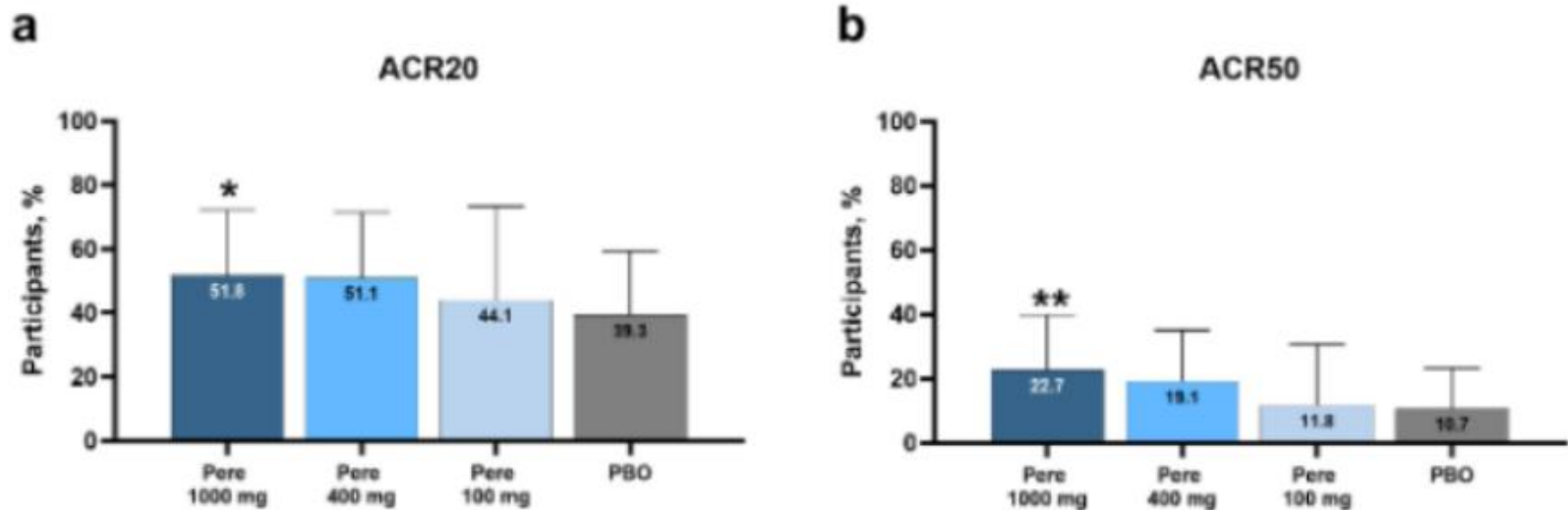
- **Peresolimab**
- Phase IIa—showed some efficacy in RA (Tuttle J, NEJM 2023; 388(30): 1853-62)
- Phase IIb (Resolution, NCT05516758)—terminated due to malignancies (8), possible CV signal, and unimpressive efficacy—Tuttle J, et al, ACR 2025 Abstract 0473
- **Rosnilimab**
- Targets and depletes pathogenic, PD-1-high T cells while hypothesized to simultaneously agonize (stimulate) remaining PD-1+ T cells to restore homeostatic balance.
- Phase IIb RENOIR trial in moderate-to-severe RA (NCT 6041269)
- No malignancies through 38 weeks

Peresolimab (PD1 Agonist)

- Phase IIa—showed some efficacy in RA.
Tuttle NEJM 2023; 388(30): 1853-62
- Phase IIb—Resolution (NCT05516758)—
cancelled due to malignancies (8), possible
CV signal, and unimpressive efficacy—
Tuttle J, et al, ACR 2025 Abstract 0473

Peresolimab Phase IIb

Figure 1. Proportion of participants with ACR20 and ACR50 response at Week 12.



ACR20, American College of Rheumatology 20 response; ACR50, American College of Rheumatology 50 response; PBO, placebo; Pere, peresolimab.

*p value vs PBO <0.05, **p value vs PBO <0.01

Rosnilimab (PD1 Agonist)

- Targets and depletes pathogenic, PD-1-high T cells while hypothesized to simultaneously agonize (stimulate) remaining PD-1+ T cells to restore homeostatic balance.
- Phase IIb RENOIR trial in moderate-to-severe RA (NCT 6041269)
- No malignancies through 38 weeks

Rosnilimab RENOIR Phase II

Graf J, et al [abstract]. *Arthritis Rheumatol.* 2025; 77 (suppl 9). ACR 2025 LB19

Figure 1. Clinical Efficacy Measures

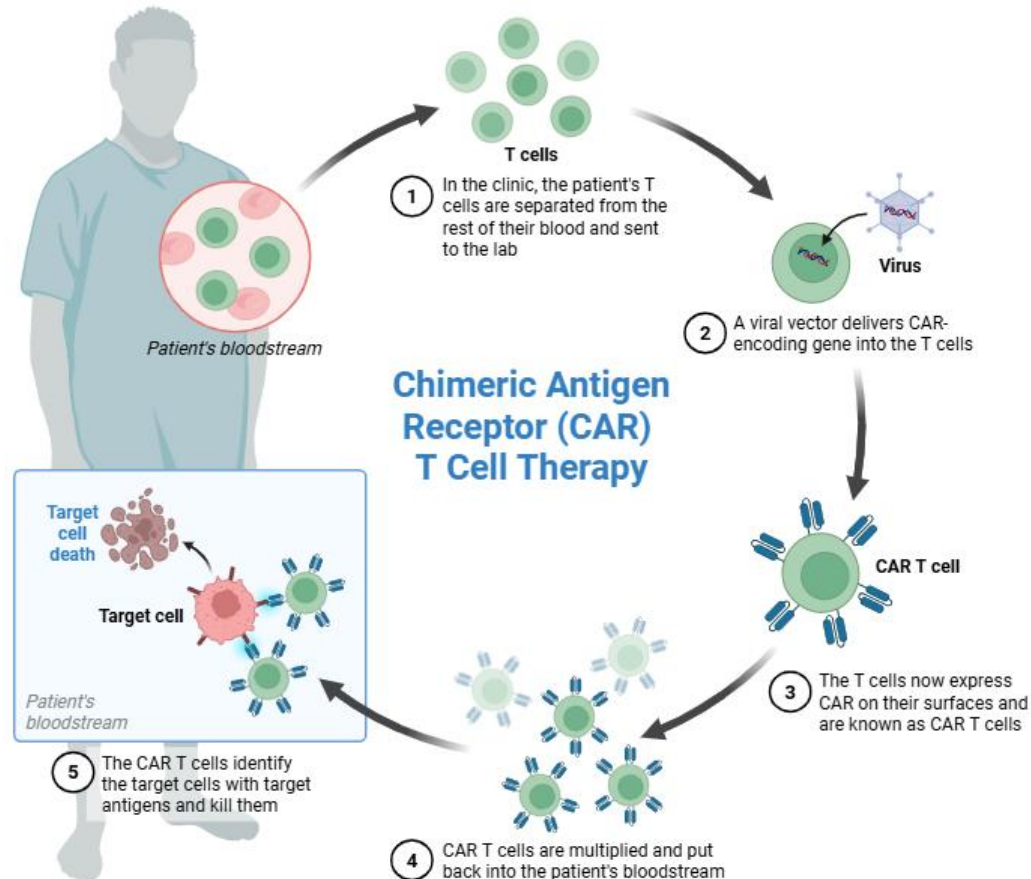
a. Primary and Select Secondary and Exploratory Endpoints at Week 12

	Rosnilimab 100mg Q4W n=106	Rosnilimab 400mg Q4W n=107	Rosnilimab 600mg Q2W n=105	Placebo n=106
Primary Endpoint				
DAS28-CRP at Week 12 (mean change from baseline)	-2.06**	-2.12**	-2.06**	-1.69
Select Secondary Endpoints^ (% of patients)				
ACR20 at Week 12^	68.9*	70.1**	75.2***	52.8
ACR50 at Week 12^	44.3	36.4	46.7*	33.0
Week 28	45.3	48.6	58.1	--
ACR70 at Week 12^	21.7	21.5	21.9	17.9
Week 28	40.6	36.4	44.8	--
CDAI ≤10 (LDA) at Week 12^	46.2*	49.5**	38.1	31.1
Week 28	52.8	54.2	62.9	--
Select Exploratory Endpoints (Mean Change from Baseline)				
DAS28-CRP Week 28	-2.56	-2.48	-2.55	--
hsCRP Week 12	-9.67***	-10.10***	-7.60**	-0.73
Week 28	-7.23	-10.55	-5.98	--
Patient Global Assessment Week 12	-30.1	-30.5	-34.7**	-25.4
Week 28	-37.0	-37.9	-40.1	--
HAQ-DI (range 0-3) Week 12	-0.61	-0.59	-0.60	-0.56
Week 28	-0.78	-0.74	-0.75	--
Pain VAS Week 12	-32.6	-35.3	-39.7**	-29.0
Week 28	-41.2	-43.8	-46.7	--

ITT population; MMRM used for continuous measures at Week 12, MI-LMCF at Week 28, NRI used for dichotomous measures at Week 12 and 28

*P<0.05; **P<0.01; ***P<0.001.

CAR-T Cell Process

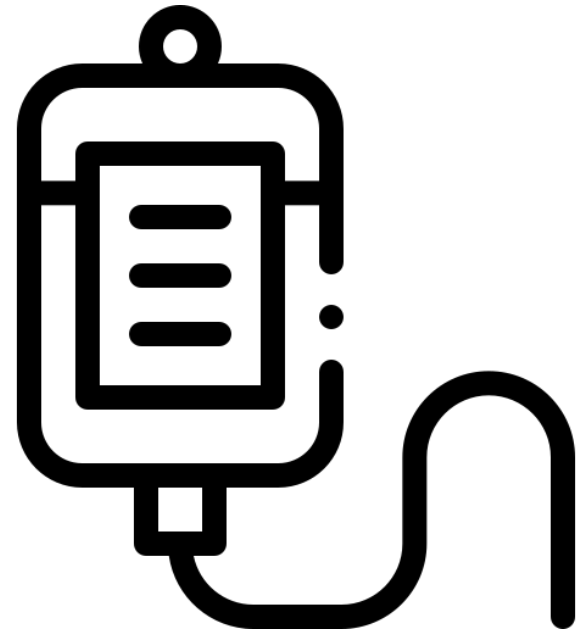


CAR-T Cells--Manufacturing

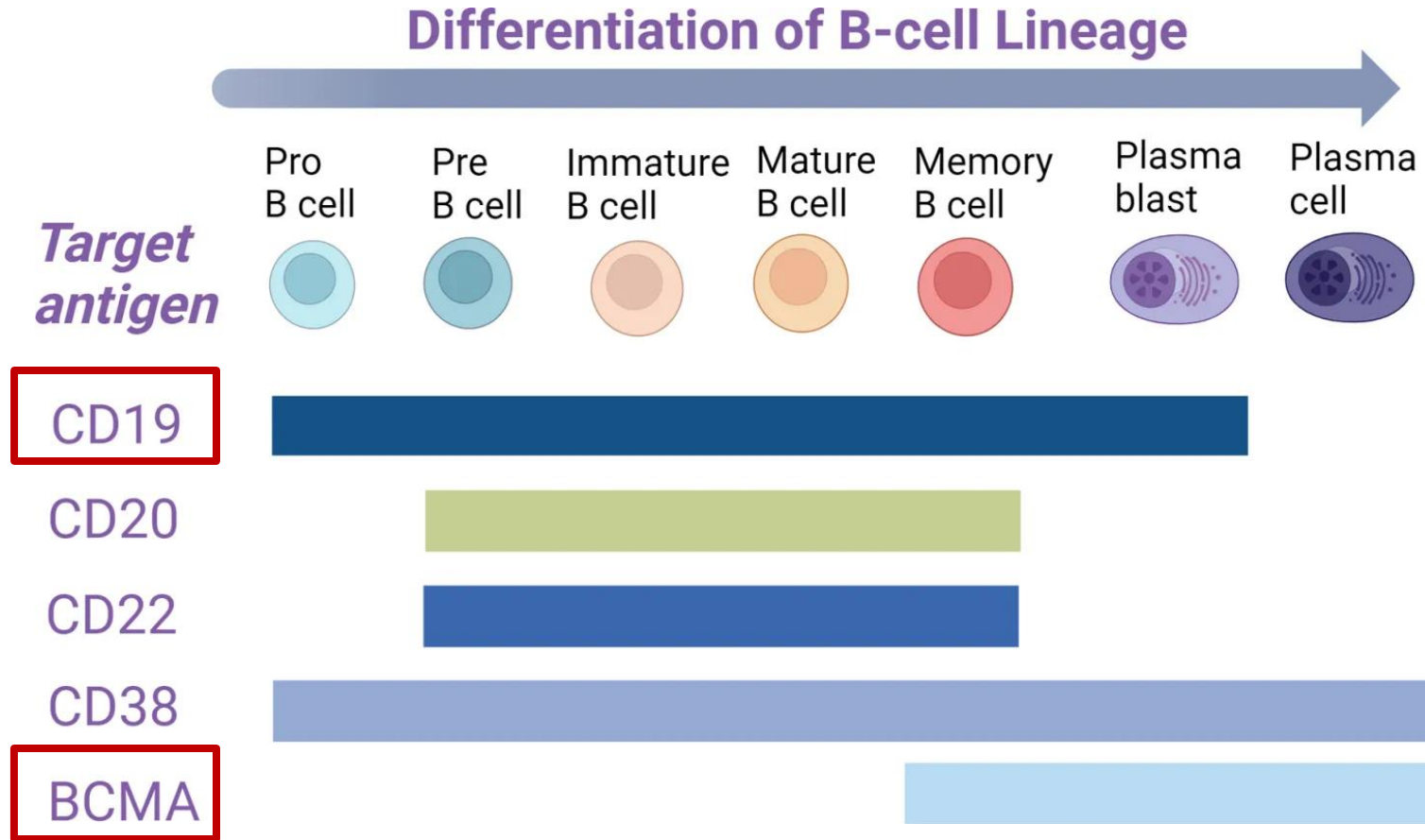
- Viral vectors
 - Permanently splice CAR gene into T cell genome
 - Cells may persist for months or years
- mRNA approaches
 - CAR encoding mRNA via electroporation or lipid nanoparticles
 - CAR expression transient, decrease from dilution and cell division
- mRNA may be especially helpful for BCMA targeting, avoids significant lymphodepletion, reducing risk of CRS and ICANS, potentially allowing for office-based infusions, and potentially less impact on overall Ig levels

“Conditioning” (Immunodepletion) for CAR-T

- Conditioning—intermediate or reduced intensity fludarabine/cyclophosphamide (e.g., 1000 mg/m² over 3 days)
- B cell depletion reconstitution 3-6 months with mostly naïve phenotype, disappearance of pathogenic memory
- Cytokine Release syndrome 15-20%, usually grade 1-2
- ICANS Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) has been lower
- These occur less than in oncology programs possibly due to differences in total number of pathological B cells (higher in heme malignancies)



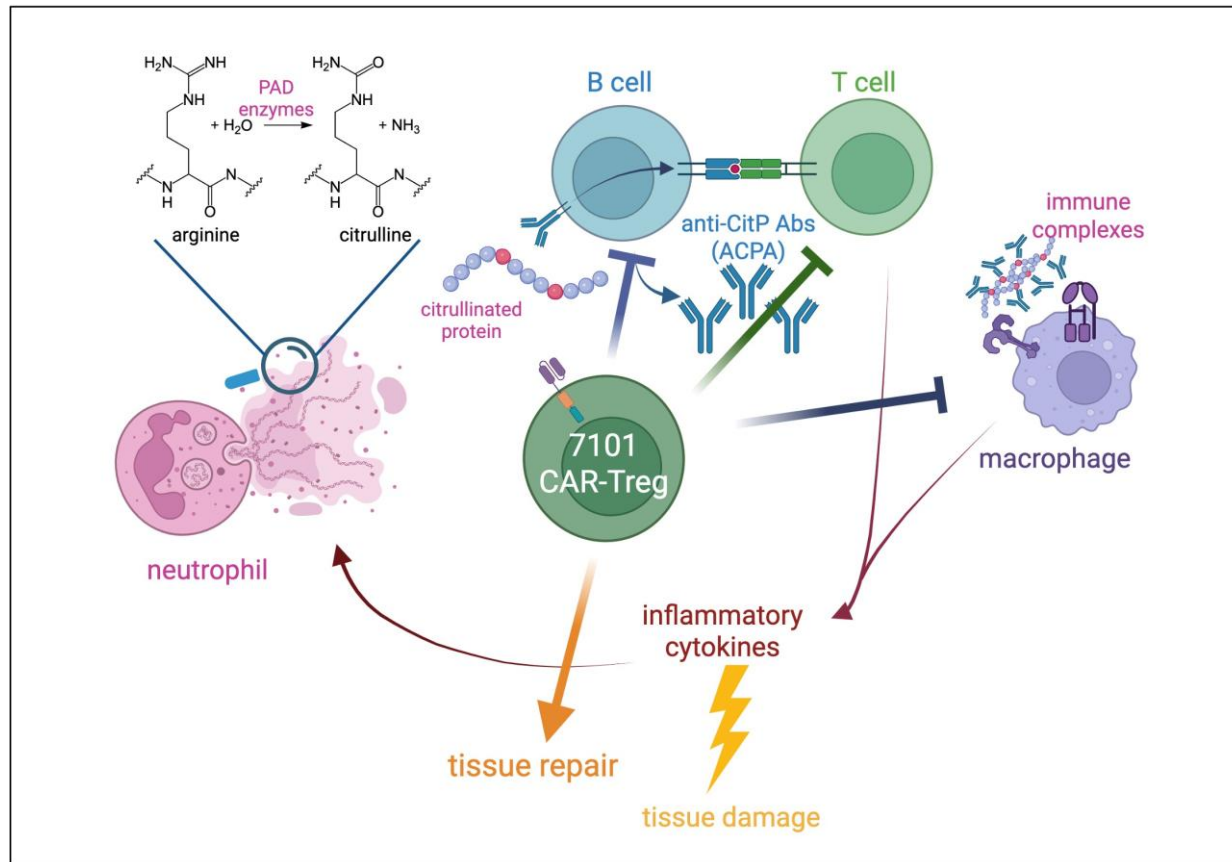
B Cell Lineage Development



CAR-T Targets

- **CD19 (B-Cell Depletion)** Deeply deplete **B cells in the blood and bone marrow**, forcing immune system to rebuild a healthy, naive B-cell population free of autoimmune memory
- **Rapcabtagene autoleucel** in Phase 1/2 trial in RA, **Mivocabtagene autoleucel** presented Phase 1 data at EULAR 2026. **KYV-101** is in Ph 1/2 comparing with Rituxan. CC97540/BMS986353 enrolling across multi-indication rheumatic disease trials
- **BCMA (Plasma Cell Depletion):** Selectively destroy **long-lived plasma cells and plasmablasts** eliminating "factories" producing RA/ACPA
- **HBI0101** (an autologous anti-BCMA retroviral CAR-T cell product) in Ph I trials targeting refractory RA
- **Dual-Targeted (CD19 x BCMA):** Targeting both CD19 and BCMA clears out **early-stage B cells and mature plasma cells**.
- **AZD0120** in phase 1 including RA, **CTA313** and **SCAR02** entering rheumatic trials to optimize complete, system-wide autoantibody
- **4. CAR-Regulatory (CAR-Tregs)** Uses **Regulatory T cells (Tregs)**—uses the body's natural immune brakes. CAR-Tregs are engineered to travel directly to inflamed joint spaces and locally switch off tissue-destroying inflammation.
- **SBT777101** autologous regulatory T-cell product with a CAR designed to bind citrullinated proteins. **QEL-005** targeting Tregs in Phase 1 basket trial including RA

CAR-T Reg for ACPA

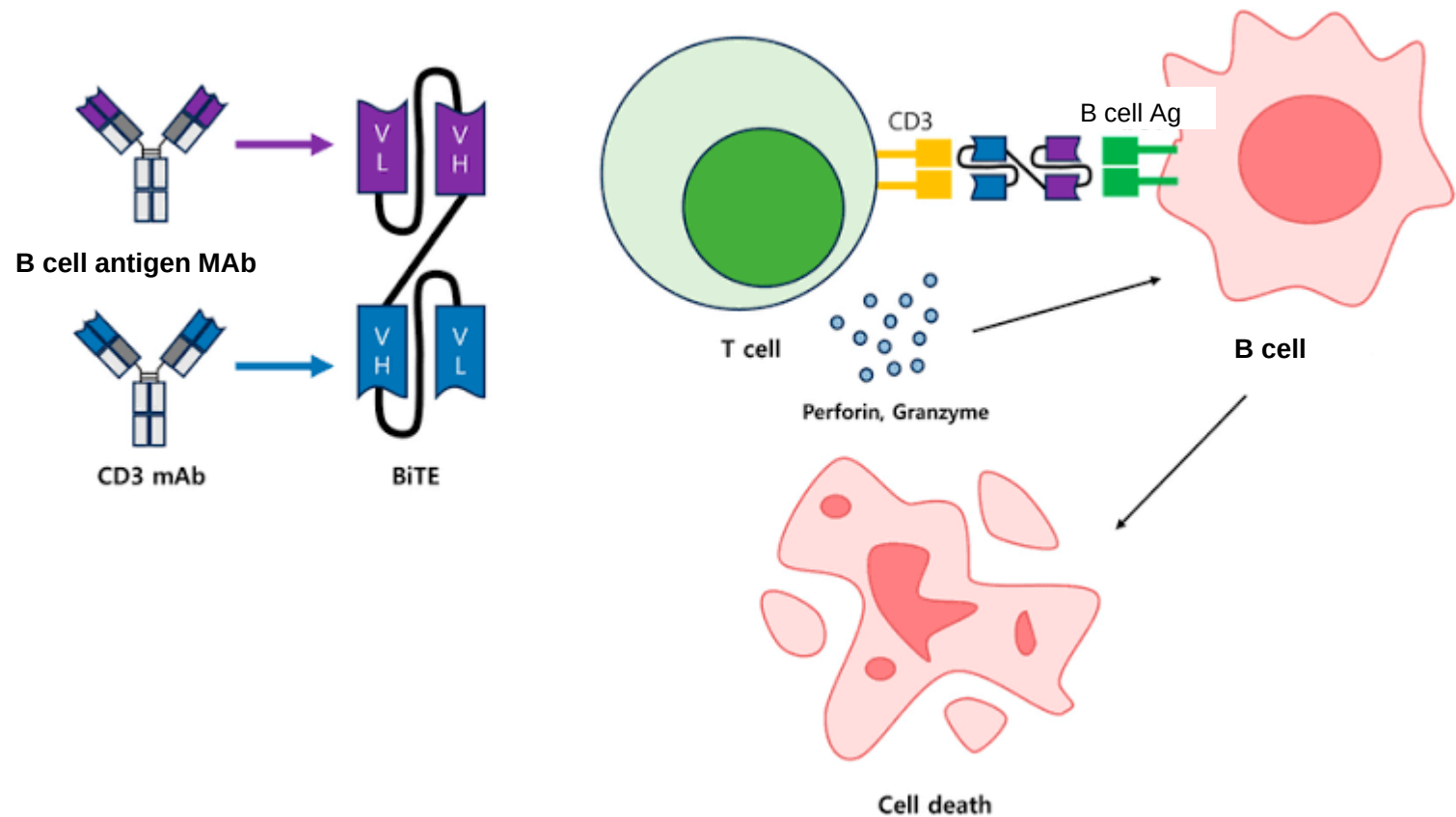


Baxter S, Phase 1b Study of SBT777101, an Engineered CAR-T-Regulatory Cell Product, in Patients With Rheumatoid Arthritis: Interim Demographics and Safety [abstract 0501]. *Arthritis Rheumatol.* 2025; 77 (suppl 9).

T Cell Engagers (TCEs)

- “Off-the-shelf” alternative to personalized CAR-T cell therapies,
- Physically bridge endogenous T cells to specific pathogenic cells (mostly B cells or overactive T cell subsets)
- Induce deep immune depletion and hypothesized immunological “reset”

Bispecific T-Cell Engagers (BiTE)

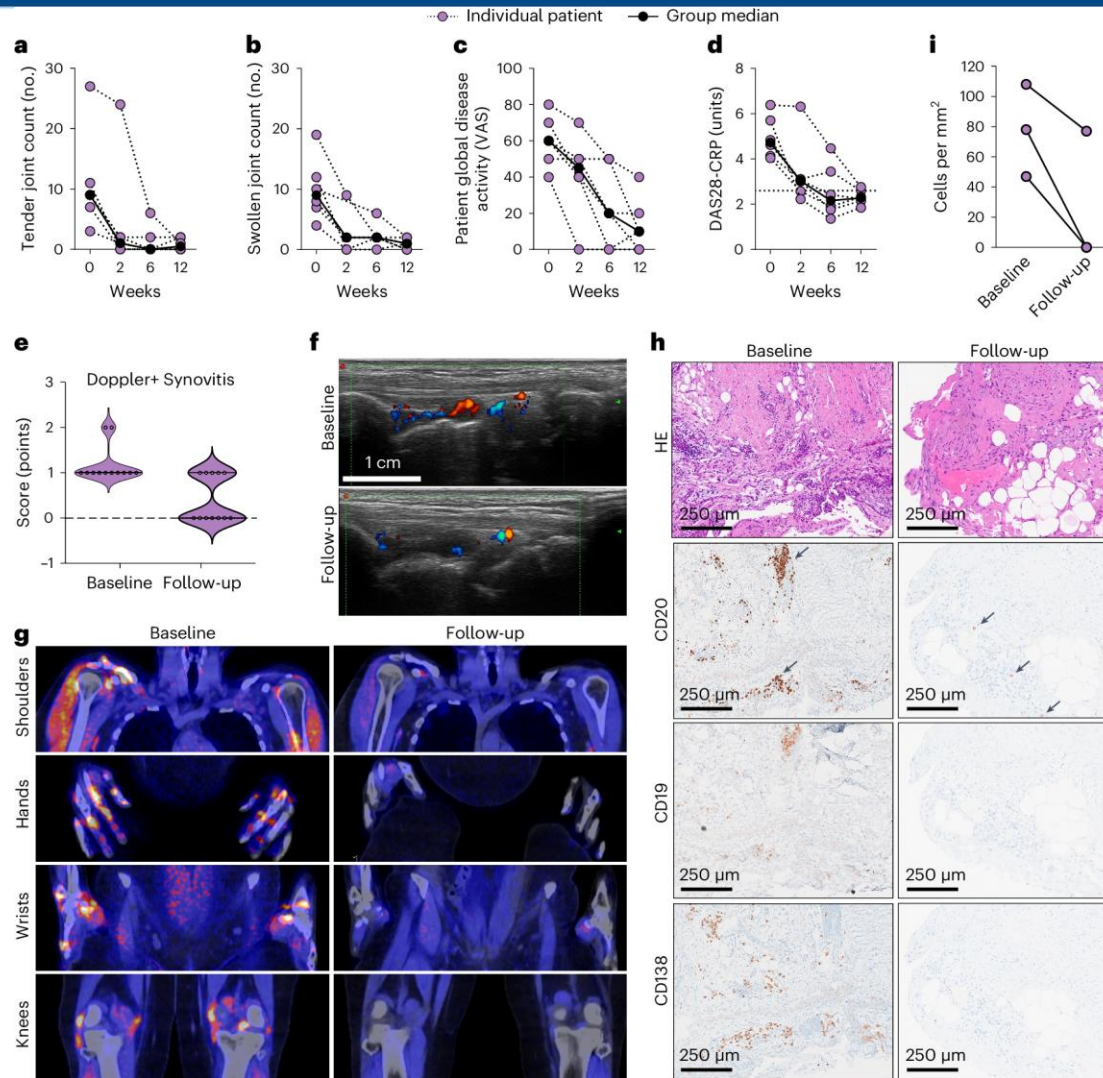


Bispecific TCE's in RA and Autoimmune Diseases

- **Blinatumomab (CD19 x CD3):**
 - Evaluated in refractory RA Ph 1 (Bucci L, Nat Med 2024; 30(6):1593-1601)
 - Rapid B-cell depletion in peripheral blood and inflamed joint tissue, Marked reduction in disease activity, improvements in synovitis (ultrasound and PET-CT), and drop in autoantibodies
 - Phase II platform protocol in progress with a cohort for RA (NCT06570798)
- **Teclistamab (BCMA x CD3):**
 - Exploratory in autoimmune diseases
 - Targets BCMA, depletes mature, long-lived plasma cells
 - Risk of significant hypogammaglobulinemia and infection
 - Long term Ig depletion may lead to need for IVIg

Blinotumumab RA

Bucci L, Nat Med 2024; 30(6):1593-1601



Trispecific T cell Engagers

- **KT501. Teclistamab**

- Designed to bind simultaneously to **CD19, BCMA, and CD3**.
- Dual-targeting CD19 (early B cells) and BCMA (plasmablasts and plasma cells)
- Phase 1 in RA (NCT07234773)
- Data presented for basket trial at EULAR 2026 (OP078), included 2 patients with RA
- CRS in 13/16 patients requiring TCZ
- Hypogammaglobulinemia required IvIg

- **CC312**

- Binds **CD19, CD28, CD3**
- CD28 binding designed to increase **T-cell fitness and survival**.
- Phase 1 including RA (NCT06888960)
- Data presented for lupus nephritis at EULAR 2026 (LB0004)

- **LBL-051**

- Binds **CD19 x BCMA x CD3**.
- Phase 1 in Germany underway

Comparison CAR-T vs BiTE

CAR-T

- Directed to one surface Ag of target cells
- Single IV infusion
- Relatively long duration
- Higher rates of CRS, ICANs, Infection

BiTE

- Two components: One targets pathogenic cell surface antigens, other to T Cell surface CD3/CD8
- Multiple IV/SQ
- Shorter duration
- Lower rates of ICANs, CRS

Immunizations with different B cell Targeting Therapies

CD19

- Most responses maintained (does not take out most plasmablasts or plasma cells)
- Exceptions: S. pneumoniae, H. influenza, B. pertussis
- Delayed response to new vaccines (6 months)

BCMA

- Most vaccine immunity significantly reduced by taking out plasmablasts and plasma cells
- But immediately respond to new vaccinations without having to wait reconstitution
- Total IgG levels reduced
- May require IVIg

What about Seronegative Patients??

- B cell directed therapies tested in seropositive patients
- How do we target the pathogenic cells in seronegative disease?
- Seronegative patients have B cells and plasma cell infiltrates seen in synovial biopsies
- TriTEs are looking to target both B and T cells
- Fibroblast activation protein CAR-T in development, alternative T cell targets to hit infiltrating T cell subsets (CD8 cytotoxic and T peripheral helpers)
- BAITE (Bispecific Autoantigen T cell Engagers) use autoantigen sequence on one arm—but need to find the relevant autoantigen in seronegative disease

Summary

- Treatment guidelines advocate for early DMARD initiation, with bDMARDs or tsDMARDs added on if failure to response and switches between classes if lack or loss of response
- New nomenclature has been developed for monoclonal antibodies that focus on target type and structure
- New therapeutics are in development for RA targeting novel pathways, which will hopefully expand the therapeutic armamentarium
- CAR-T and T Cell Engager therapies are promising new developments for treatment refractory seropositive disease with some concerns regarding short term immunosuppression, acute cytokine mediated reactions, and longer term immunocompetence