# WIN
# WHAT IS NEW
# RHEUMATOLOGY
# 2022


ד"ר יונתן אדל

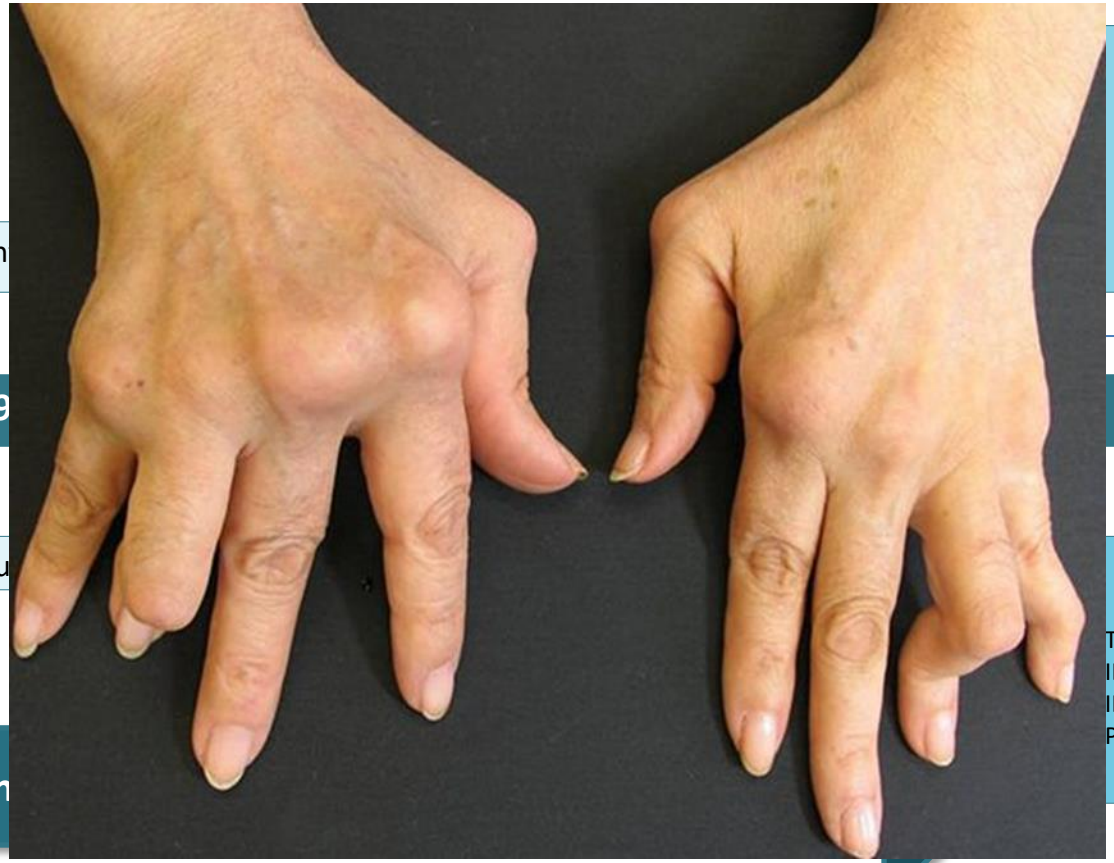
מנהל מחלקה פנימית ב

השרות הראומטולוגי

בית חולים אסותא אשדוד

- RHEUMATOID ARTHRITS
- SYSTEMIC LUPUS ERYTHEMATOSIS
- SYSTEMIC SCLEROSIS
- MYOSITIS
- VEXAS

# RHEUMATOID ARTHRITS



Sulfasalazine
- Second most common DMARD in Europe in 1990s

An

1920s

19

Gold salts

Glu

Therapies for RA h

New agents
- Small molecule drugs:
  - JAK inhibitors

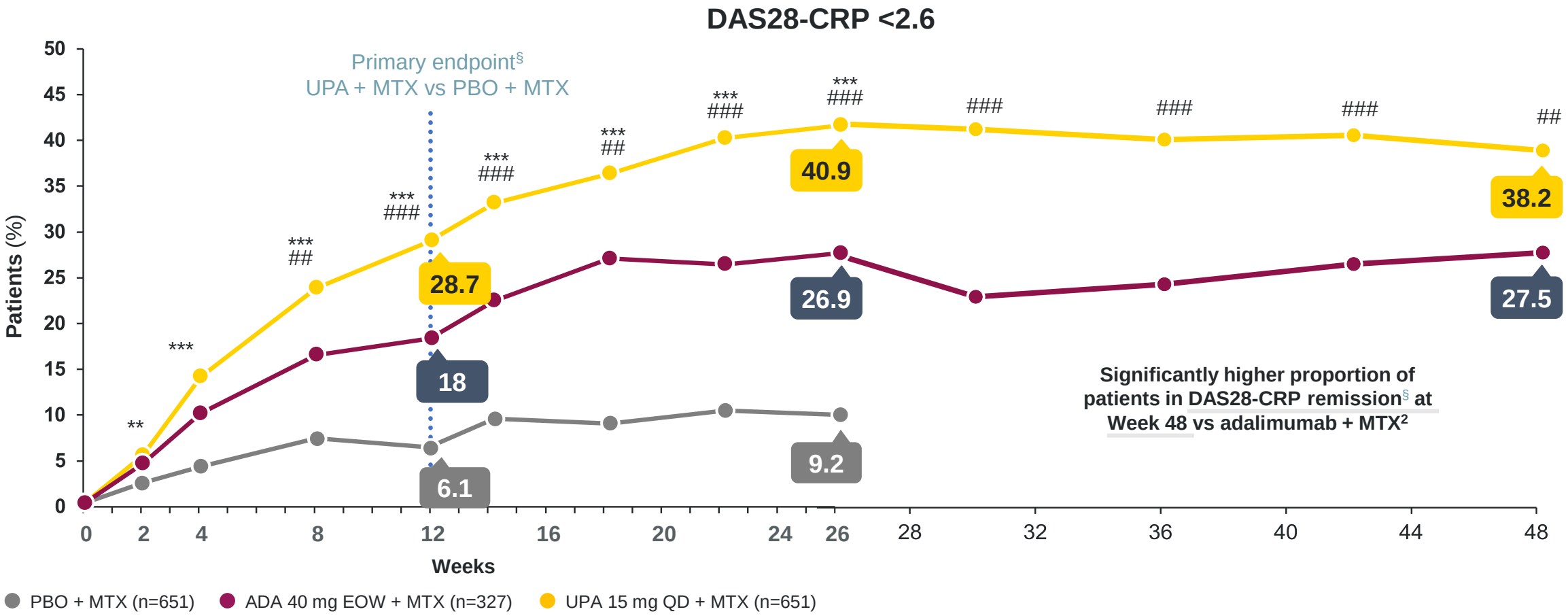
2000s

Biologics
non-TNF inhibitors
T cell co-stimulation
IL-6 inhibitor
IL-1 inhibitor
Protein CD20 inhibitor

*Not indicated for treatment of rheumatoid arthritis.
DMARD, disease modifying antirheumatic drug; IL, interleukin; JAK, Janus kinase; TNF, tumour necrosis factor.

1. Smolen JS, Steiner G. *Nat Rev Drug Discov* 2003;2:473–488; 2. Scott DL, et al. *The Lancet* 2010; 25;376:1094–1108.
3. Weinblatt ME. *Trans Am Clin Climatol Assoc*. 2013;124: 6–25.

# Remission over time (NRI)




**p<0.01, ***p<0.001 UPA + MTX versus PBO + MTX; ##p<0.01, ###p<0.001, UPA + MTX versus ADA + MTX. Primary endpoint compared UPA + MTX with placebo + MTX only. §DAS28 (CRP)<2.6 for upadacitinib + MTX vs adalimumab + MTX at week 12 was a prespecified nonranked, nonmultiplicity controlled endpoint; nominal P-value is provided. Treatment groups are by initial randomization.

Full analysis set.

1. Fleischmann R, et al. Arthritis Rheumatol. 2019;71:1788-1800;
2. Fleischmann R et al. EULAR Congress, Madrid, 12-15 June 2019. Abstract FRI0147]

*Review*

# Janus Kinase Inhibitors Improve Disease Activity and Patient-Reported Outcomes in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis of 24,135 Patients

Lilla Tóth [1,2], Márk F. Juhász [2,3,4], László Szabó [2]
Nelli Farkas [2,9], György Nagy [10,11,12,*,†] and Zsuzs

In comparison to biological disease-modifying antirheumatic drugs, JAK inhibitors show statistical superiority in 13 of the 19 efficacy outcomes.

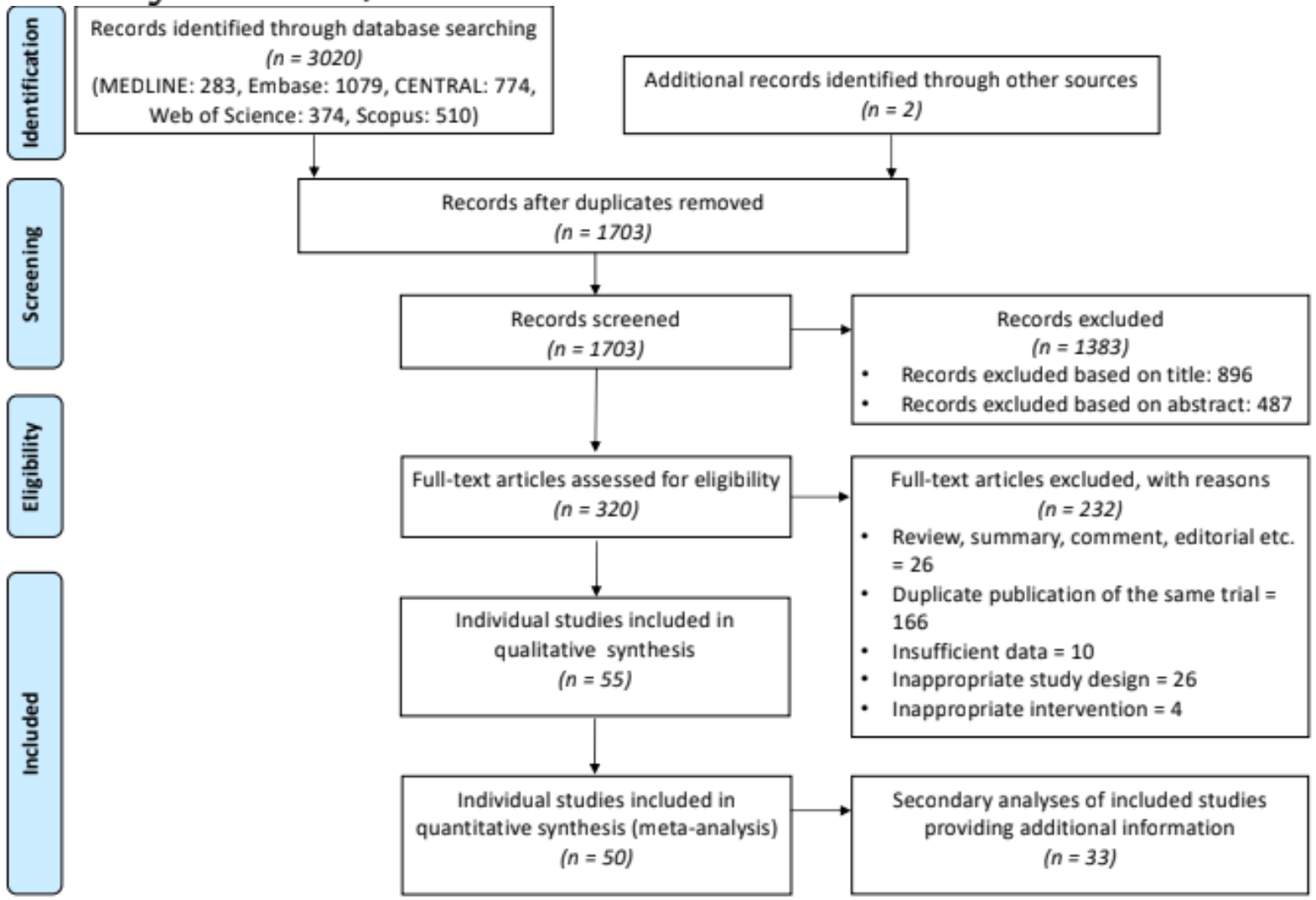



**Figure 1.** Prisma flowchart demonstrating the results of selection process.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H.,
Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D.,
Jose L. Rivas, M.D., Rebecca Germino, Ph.D., Sujatha Menon, Ph.D.,
Yanhui Sun, Ph.D., Cunshan Wang, Ph.D., Andrea B. Shapiro, M.D.,
Keith S. Kanik, M.D., and Carol A. Connell, R.N., Ph.D.,
for the ORAL Surveillance Investigators*

n engl j med 386;4 nejm.org January 27, 2022

- **MACE and cancers** (coprimary end points) occurred **more often** with tofacitinib than with a TNF inhibitor in this trial that included patients with rheumatoid arthritis who were **50 years of age or older and had at least one additional cardiovascular risk factor**.
- Adjudicated **opportunistic infections (including herpes zoster**), all herpes zoster (nonserious and serious), occurred **more often** with both tofacitinib doses than with a TNF inhibitor.
- The incidences of **death** from any cause and of **pulmonary embolism** were **higher** with tofacitinib at a dose of **10 mg** twice daily than with a TNF inhibitor, which led to the switch in the tofacitinib dose from 10 twice daily to 5 mg twice daily during the trial.

# Upadacitinib

| E/100 PY (95% CI)* | RA<br>UPA 15 mg QD N=3209 | RA<br>ADA 40 mg EOW N=579 | RA<br>MTX N=314 |
|---|---|---|---|
| Exposure | | | |
| Total, PY | 7023.8 | 1051.8 | 637.4 |
| Median (min, max), weeks | 136 (0, 232) | 118 (2, 231) | 144 (1, 221) |
| | | | |
| Any AE | 230.7 (227.2, 234.3) | 216.6 (207.8, 225.7) | 227.8 (216.2, 239.8) |
| Any serious AE | 13.0 (12.2, 13.9) | 13.3 (11.2, 15.7) | 10.4 (8.0, 13.2) |
| MACE | 0.4 (0.3, 0.6) | 0.3 (0.1, 0.8) | 0.3 (0.0, 1.1) |
| Malignancy | 0.8 (0.6, 1.1) | 0.8 (0.3, 1.5) | 0.9 (0.3, 2.0) |
| Deaths‡ | 0.4 (0.3, 0.6) | 0.9 (0.4, 1.6) | 0.5 (0.1, 1,4) |

# Baricitinib

| Maximum exposure[a] | 9.3 years[4,6]<br>All-BARI RA N=3770; PYE=14,744.4 |
|---|---|
| **Death, IR/100 PY** | 0.6 |
| **Malignancy, IR/100 PY** | |
| Malignancy excluding NMSC | 0.9 |
| Lymphoma | 0.1 |
| NMSC | 0.3 |
| **Infection, IR/100 PY** | |
| Serious infection | 2.6 |
| Herpes zoster | 3.0 |
| Tuberculosis | 0.1 |
| OI including MD HZ | - |
| OI not including MD HZ | - |
| **MACE, IR/100 PY** | 0.5 |
| Age ≥50 years with ≥1 CV risk factor | 0.77 |
| **DVT/PE, IR/100 PY** | 0.5 |
| DVT | 0.4 |
| PE | 0.3 |
| **GI perforation, IR/100 PY** | 0.06 |
| **Permanent DC due to AE, EAIR** | 4.7 |

Burmester GR et al.
ACR 2021. Poster 1691.

# SLE nephritis

## ESRD in Hopkins Lupus Cohort

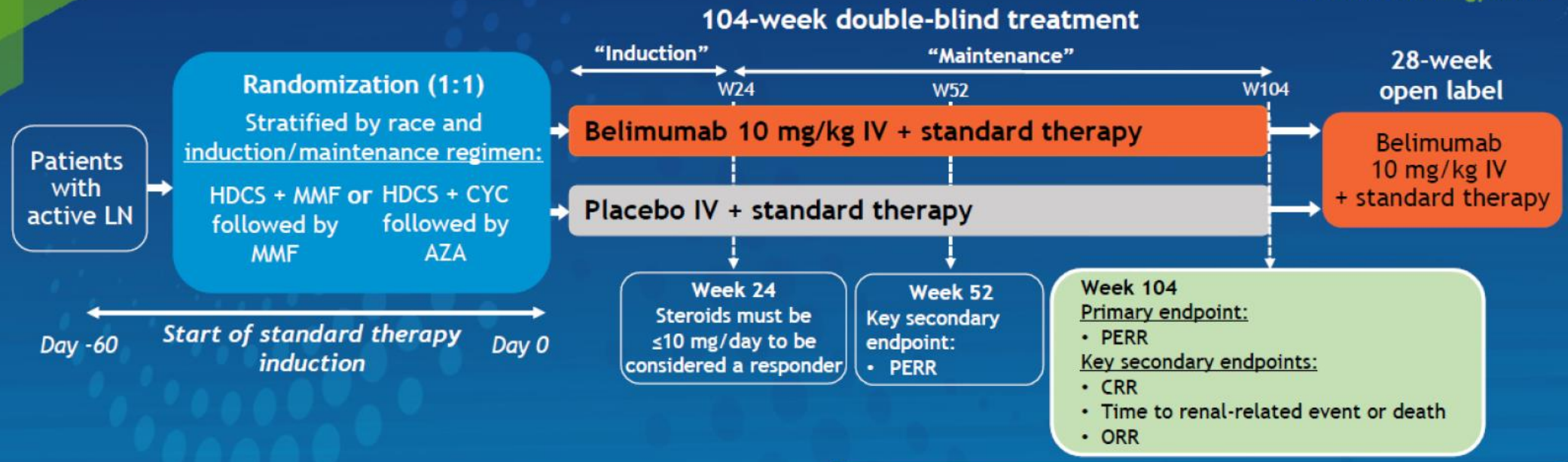
- Among those who satisfy the ACR-11 definition of renal disease within 1 year of SLE diagnosis, the risk of renal failure within 20 years is 20%.
- Risks are higher among men, African Americans, those diagnosed at a young age, and among those with immunologic markers such as low complement and anti-dsDNA.
- Among the immunologic markers, low C3 is the strongest predictor

Petri M, Magder LS, Barr E. *J Rheumatol*. pii: jrheum.191094, 2020.

# STUDY DESIGN

BLISS-LN: Phase 3, randomized, double-blind, placebo-controlled study

ACR Convergence
Where Rheumatology Meets




**Key eligibility criteria:**

- Age ≥18 years
- Screening uPCR ≥1
- Recent renal biopsy LN (Class III, IV, V or III+V or IV+V)

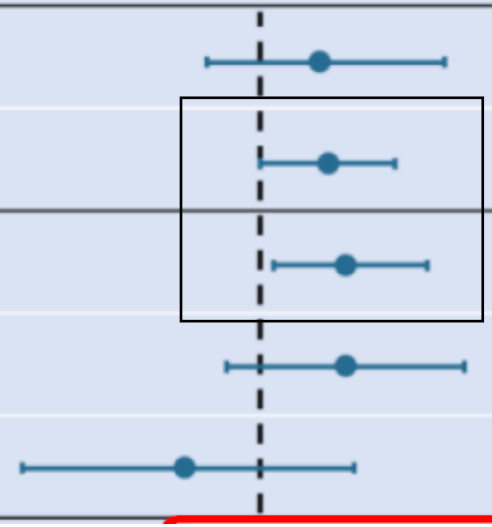
**Other endpoints:**

- Time to first severe SFI flare
- SLEDAI-S2K score <4 at Week 104
- Prednisone dose ≤7.5 mg/day at Week 104
- Prednisone dose ≤5 mg/day at Week 104
- Change from baseline in biomarkers (anti-dsDNA, anti-C1q, C3, C4)
- Safety

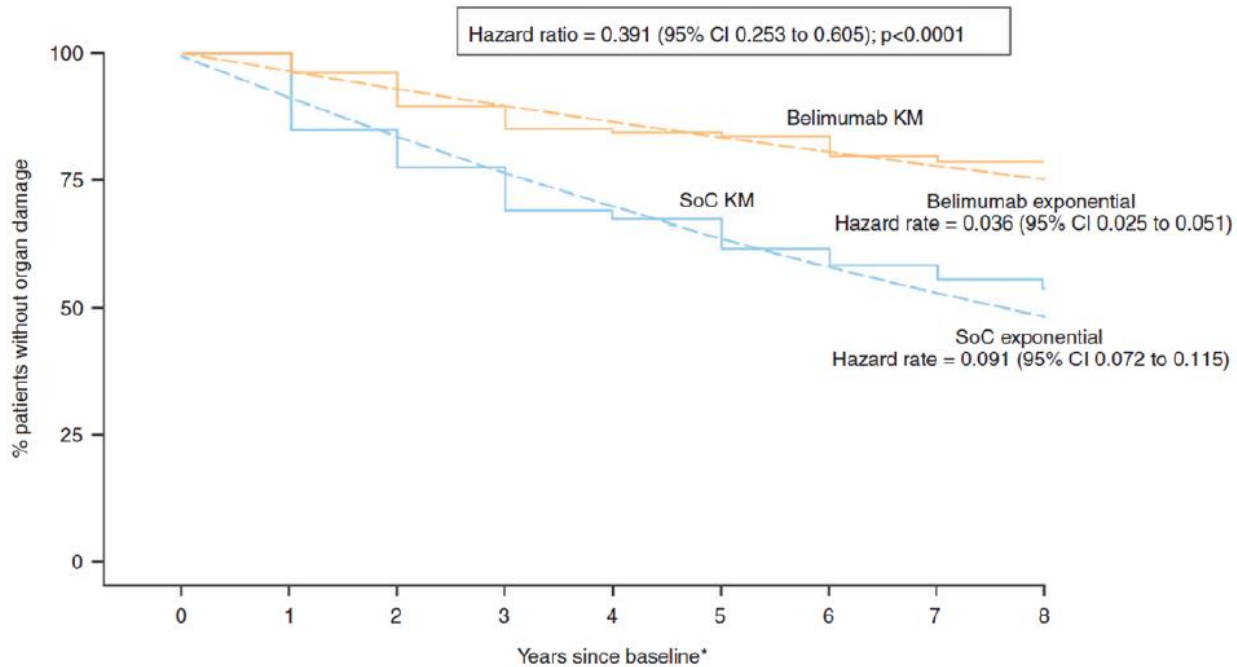
Anti-ds-DNA, anti-double-stranded DNA; AZA, azathioprine; C3/C4, complement 3/4; CRR, complete renal response; CYC, cyclophosphamide; HDCS, high-dose corticosteroids; MMF, mycophenolate mofetil; ORR, ordinal renal response; PERR, primary efficacy renal response; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SFI, SELENA-SLEDAI Flare Index uPCR, urinary protein:creatinine ratio; W, week

Presented at ACR Convergence 2020, November 5-9, 2020. Abstract #1441.

| | | | Responders , n (%) | | Treatment difference (%) | | OR (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|
| | | | Placebo n=223 | Belimumab 10 mg/kg IV n=223 | | *Favors placebo* *Favors belimumab* | | |
| PERR* | Treatment regimen | **CYC/AZA** PBO, n=59; BEL, n=59 | 16 (27.1) | 20 (33.9) | 6.8 | | 1.5 (0.7, 3.5) | 0.3272 |
| | | **MMF** PBO, n=164; BEL, n=164 | 56 (34.1) | 76 (46.3) | 12.2 | | 1.6 (1.0, 2.5) | 0.0501 |
| | LN class | **Class III or IV** PBO, n=132; BEL, n=126 | 42 (31.8) | 60 (47.6) | 15.8 | | 1.8 (1.1, 3.1) | 0.0250 |
| | | **Class III+V or IV+V** PBO, n=55; BEL, n=61 | 15 (27.3) | 23 (37.7) | 10.4 | | 1.8 (0.8, 4.0) | 0.1796 |
| | | **Pure Class V** PBO, n=36; BEL, n=36 | 15 (41.7) | 13 (36.1) | -5.6 | | 0.6 (0.2, 1.9) | 0.4196 |



# Belimumab: Longer Time to Organ Damage Progression




Total number of patients at risk at each time point

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Belimumab | 179 | 166 | 137 | 121 | 112 | 88 | 65 | 31 | 0 |
| SoC | 179 | 135 | 111 | 83 | 71 | 57 | 44 | 30 | 28 |

Urowitz MB, et al. Ann Rheum Dis 2019;78:372-379.

ORIGINAL ARTICLE

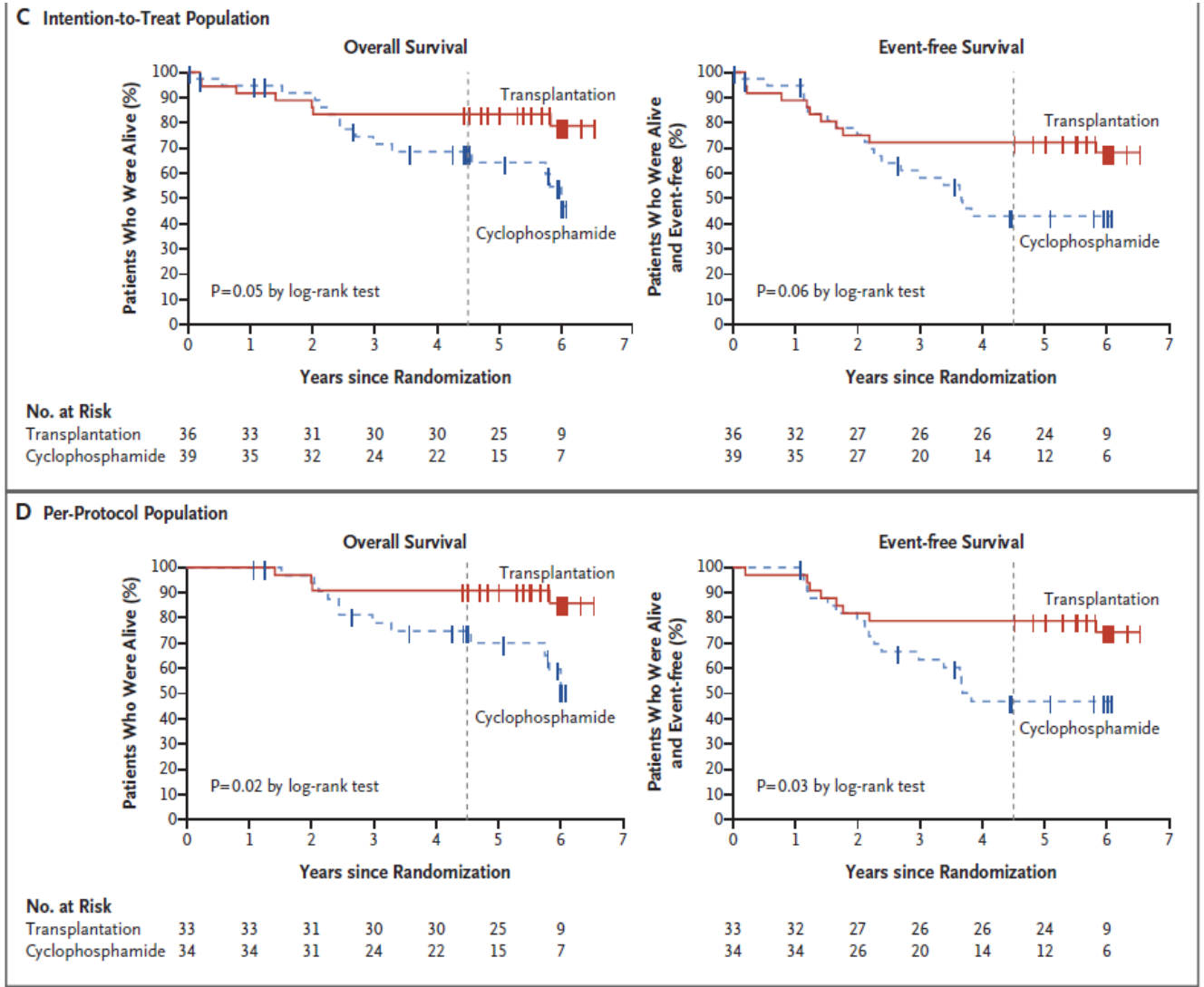
# Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma

- **Participants**:

Adults with scleroderma
for 5 years or less

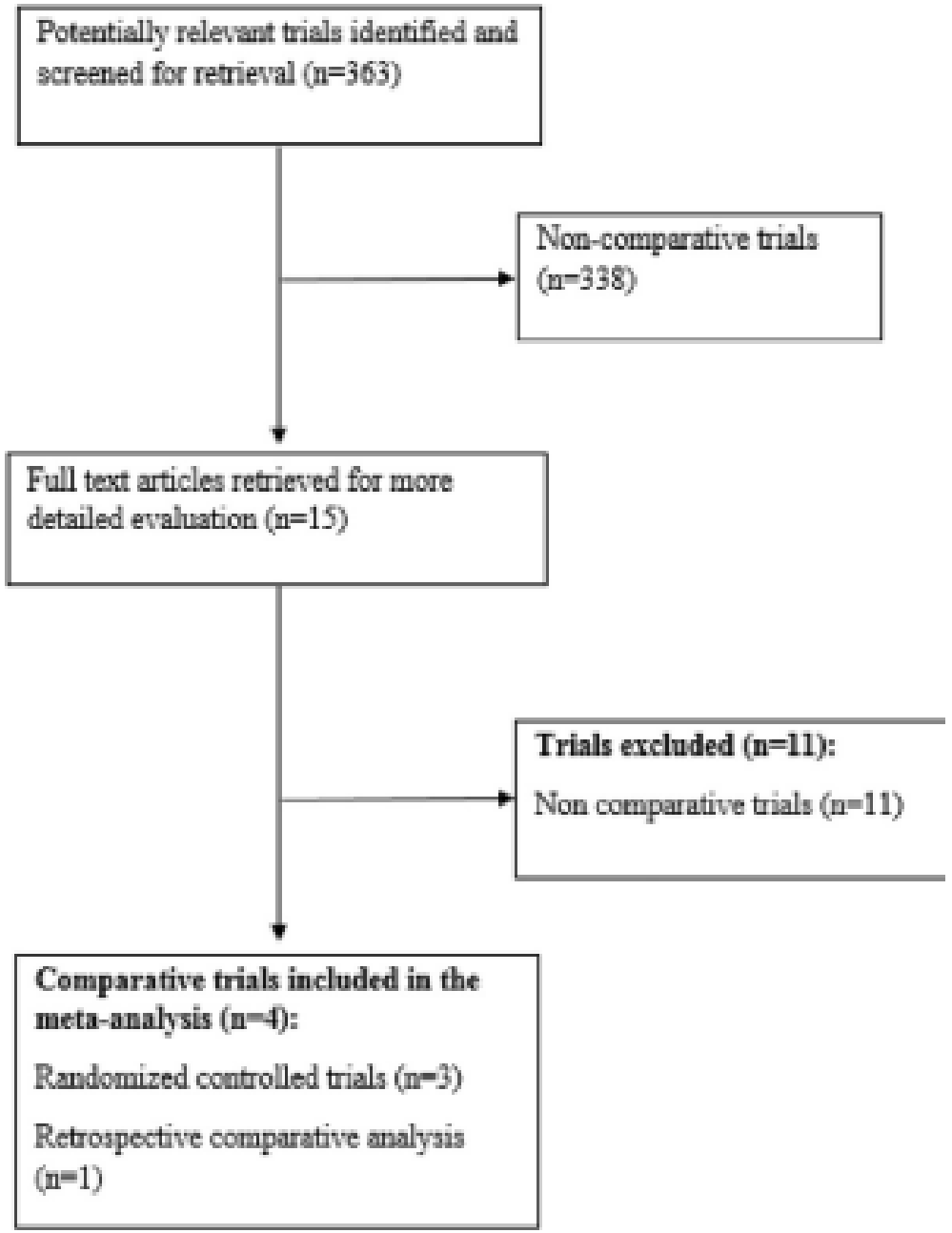
  - Pulmonary involvement required active interstitial lung disease plus either a **(FVC) or a (DLco) of less than 70%** of the predicted value.
  - **Renal involvement** required previous scleroderma-related renal disease.

- **Key exclusion criteria were**:
  - active **gastric antral vascular ectasia**,
  - **DLco of less than 40%** of the predicted value
  - **FVC of less than 45%** of the predicted value
  - **ejection fraction of less than 50%**,
  - **creatinine clearance of less than 40 ml**



# Autologous Hematopoietic Stem Cell Transplantation for Systemic Sclerosis: A Systematic Review and Meta-Analysis

Roni Shouval [1,2,3,†,*], Nadav Furie [3,4,†], Pia Raanani [3,5], Arnon Nagler [1,3], Anat Gafter-Gvili [3,5,6]



# Results

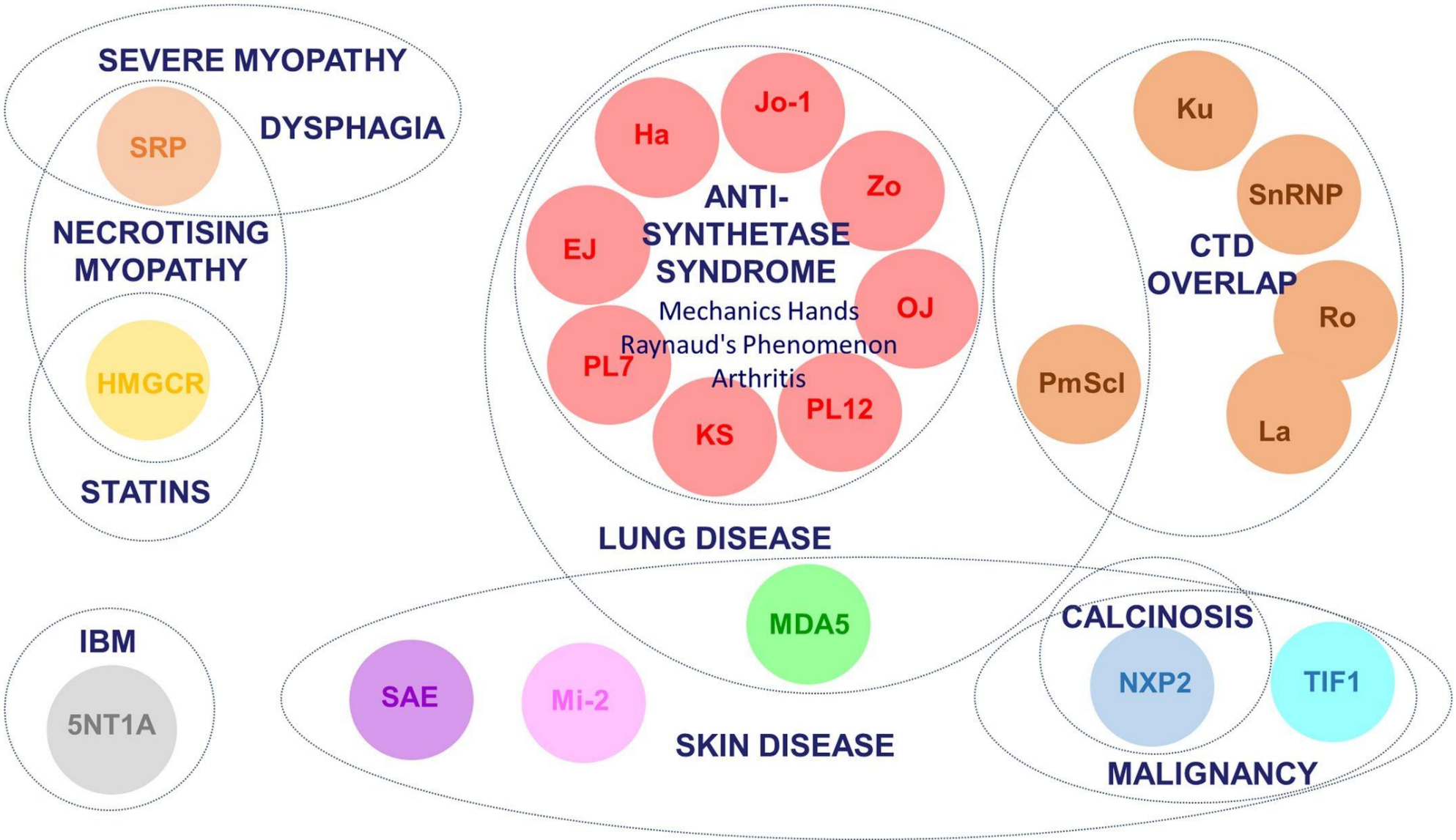
- AHSCT reduced all-cause mortality (risk ratio [RR], .5 [95% confidence interval, .33 to .75])
- improved:
  - skin thickness (modified Rodnan skin score mean difference [MD], 10.62 [95% CI, −14.21 to 7.03])
  - forced vital capacity (MD, 9.58 [95% CI, 3.89 to 15.18]),
  - total lung capacity (MD, 6.36 [95% CI, 1.23 to 11.49]),
  - quality of life (physical 36-Item Short Form Health Survey [MD,6.99 (95% CI, 2.79 to 11.18)]).

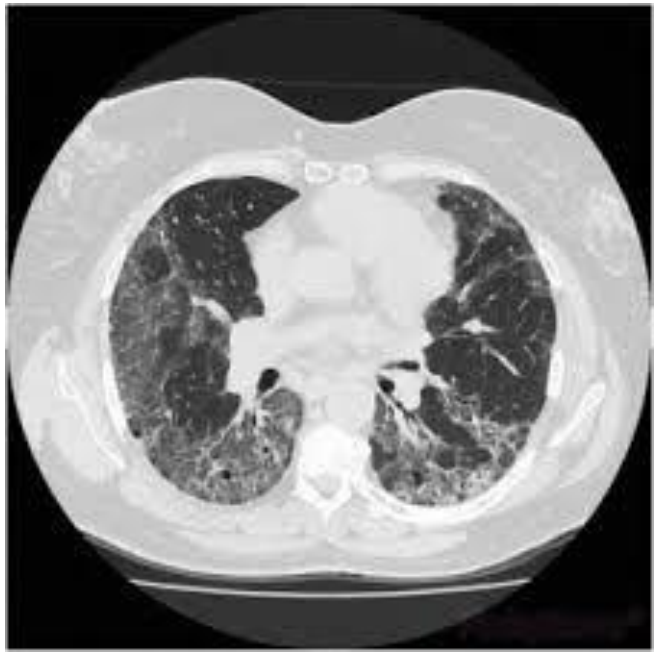
- Treatment-related mortality considerably varied between trials but was overall higher with AHSCT (RR, 9.00 [95% CI, 1.57 to 51.69]).

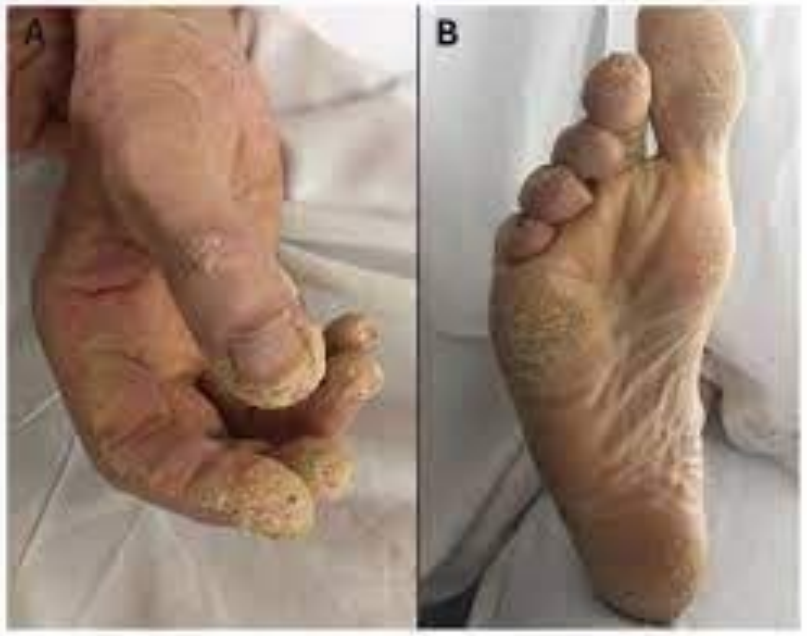
- The risk of bias for studies included in the analysis was low.

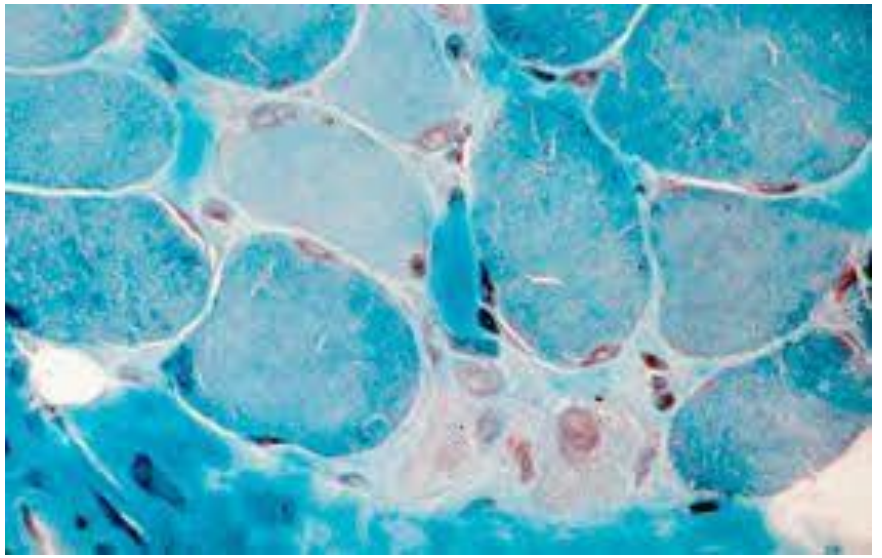
- Overall, AHSCT reduces the risk of all-cause mortality and has properties of a disease-modifying anti-
- rheumatic treatment in SSc.

# myositis


SEVERE MYOPATHY
DYSPHAGIA
SRP
NECROTISING MYOPATHY
HMGCR
STATINS
IBM
5NT1A
Jo-1
Ha
Zo
EJ
ANTI-SYNTHETASE SYNDROME
Mechanics Hands
Raynaud's Phenomenon
Arthritis
OJ
PL7
PL12
KS
LUNG DISEASE
Ku
SnRNP
CTD OVERLAP
Ro
PmScl
La
MDA5
SAE
Mi-2
SKIN DISEASE
CALCINOSIS
NXP2
TIF1
MALIGNANCY




A
B



# VEXAS Syndrome:

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

- The **VEXAS** syndrome is an adult-onset autoinflammatory disease affecting **men over 50**, caused by a mutation in the UBA1 gene.
- **V**acuoles, **E**1 enzyme, **X**-linked, **A**utoinflammatory, **S**omatic.
- The syndrome was first reported in a paper in The New England Journal of Medicine in October 2020.
- A clinical syndrome of **adult-onset** autoinflammatory disorders associated with somatic mutations affecting methionine-41 (p.Met41) in UBA1, the major E1 enzyme that initiates ubiquitylation.

# Clinical Features of VEXAS Syndrome

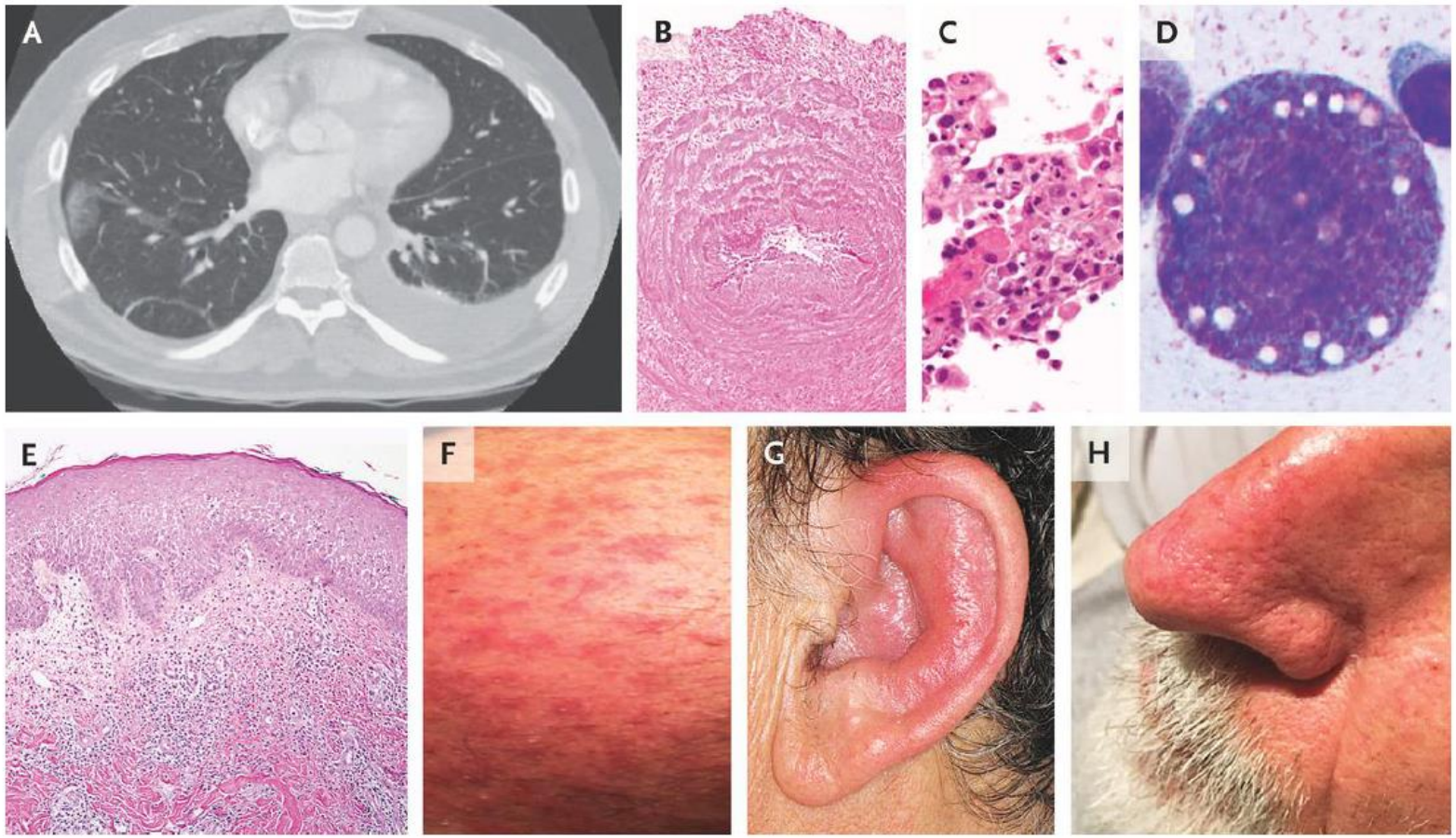
**Inflammatory features**

- Fever
- Skin involvement
- Chondritis
- Arthritis
- Vasculitis
- Pulmonary infiltrates
- Eye inflammatory disease

**Hematologic features**

- Macrocytic anemia
- Thrombocytopenia
- Myelodysplastic syndrome
- Bone marrow vacuoles
- Venous thrombosis
- Monoclonal gammopathy

# Clinical Manifestations of the VEXAS Syndrome.



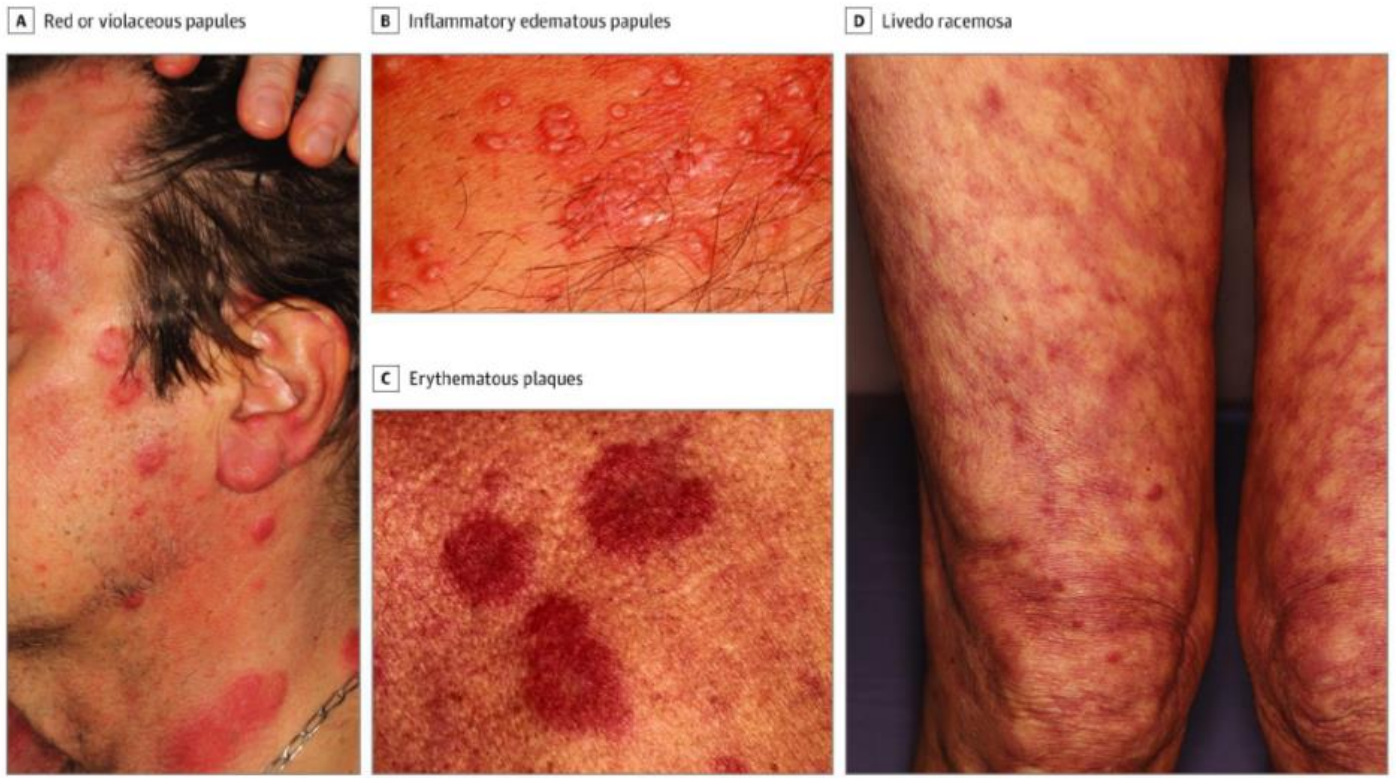

Lung involvement included pulmonary infiltrates and pleural effusions (**Panel A**), vasculitis of medium-sized bronchial arteries (**Panel B**), and neutrophilic alveolitis (**Panel C**). Characteristic vacuoles were present in myeloid precursor cells from bone marrow aspirates (**Panel D**). Cutaneous manifestations included neutrophilic dermatosis with small- to medium-vessel vasculitis (**Panel E**) and tender plaques (**Panel F**). Cartilaginous involvement included auricular chondritis (**Panel G**) and nasal chondritis (**Panel H**), which were sometimes associated with periorbital inflammation. Hematoxylin and eosin staining was used in Panels B, C, and E,

DB Beck et al. N Engl J Med 2020;383:2628-2638.

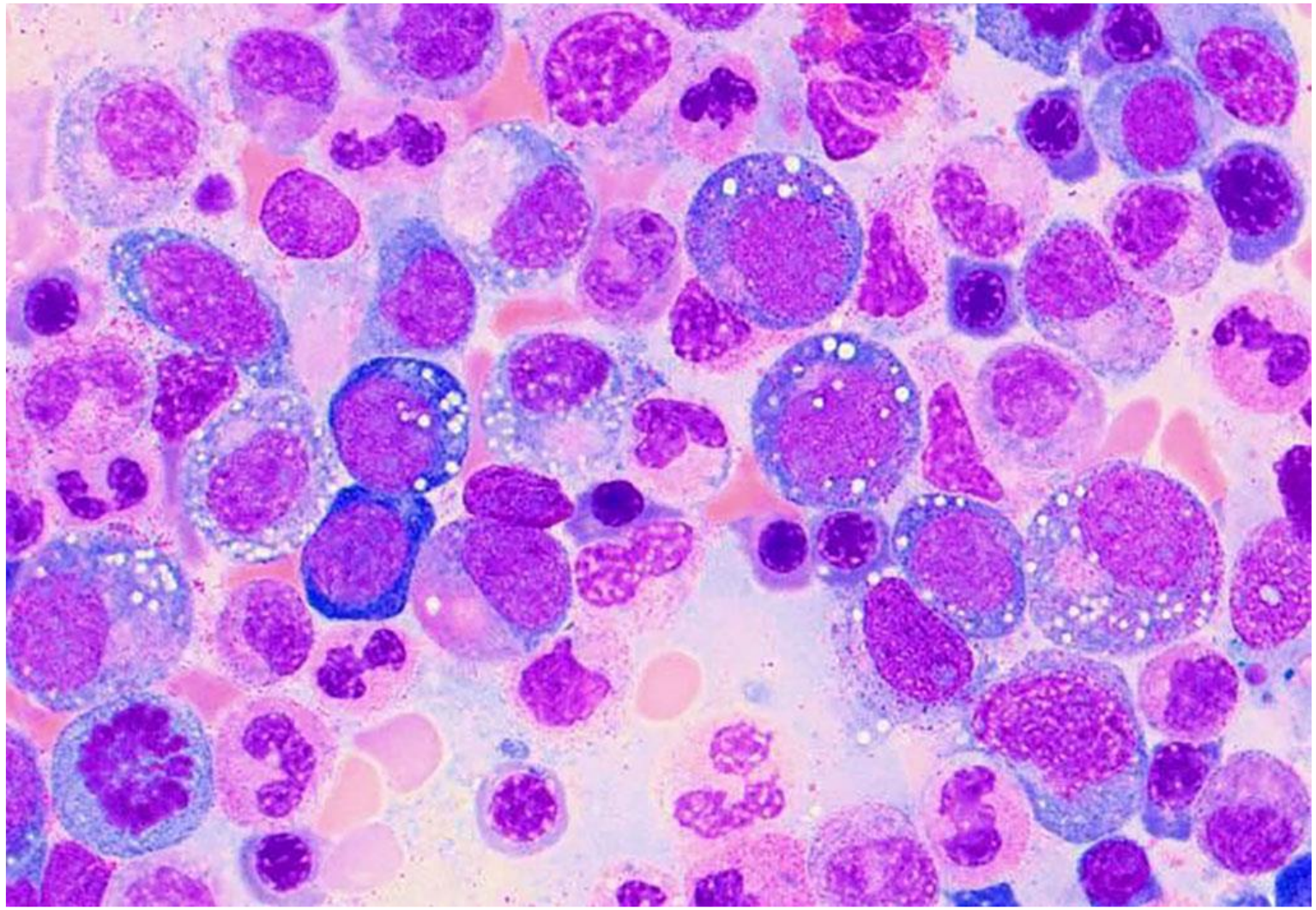
JAMA Network™

From: **UBA1 Variations in Neutrophilic Dermatosis Skin Lesions of Patients With VEXAS Syndrome**

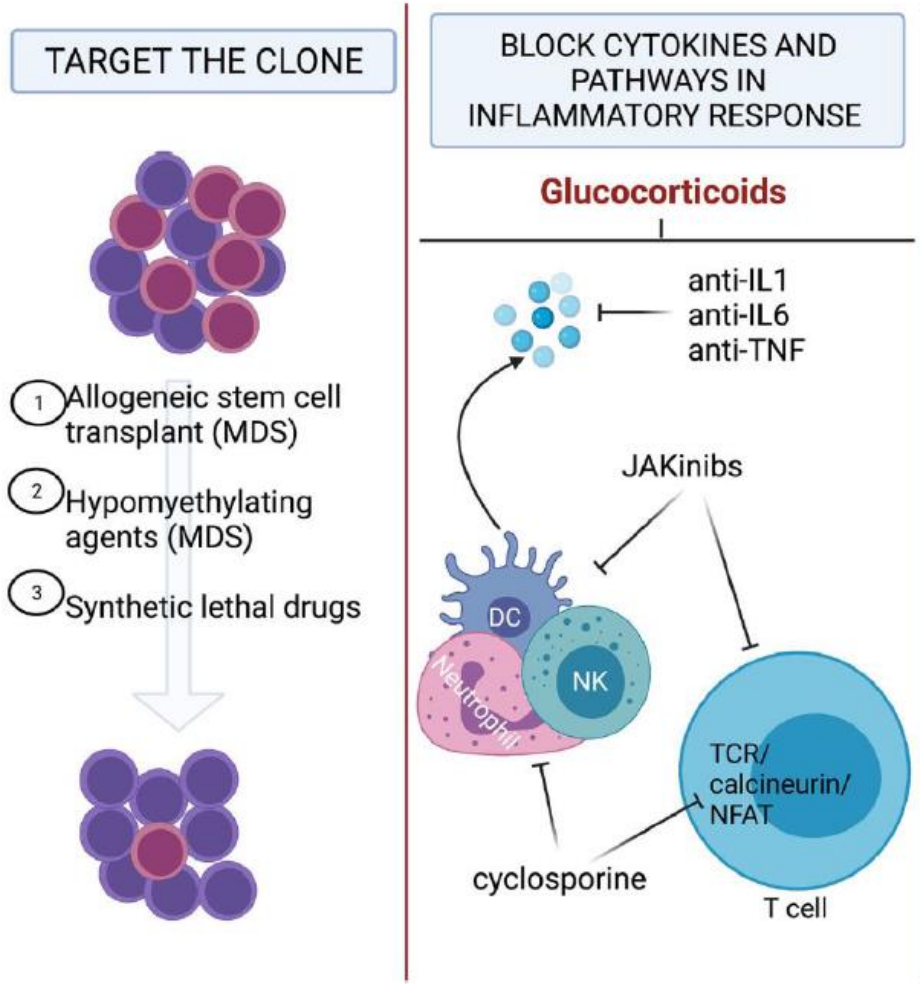
JAMA Dermatol. Published online September 08, 2021. doi:10.1001/jamadermatol.2021.3344




Clinical Presentations of Skin Lesions in Patients With VEXAS Syndrome Skin lesions in patients with a diagnosis of Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic (VEXAS) syndrome included tender red or violaceous papules (A), inflammatory edematous papules on the neck and the trunk (B), firm erythematous purpuric or pigmented infiltrated plaques and nodules (C), and livedo racemosa (D).



# Therapeutic options in VEXAS syndrome




*M. Heiblig, B.A. Patel and E.M. Groarke et al. / Seminars in Hematology 58 (2021) 239–246*