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GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, Best Western Hotel Madison

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VEXAS SYNDROME

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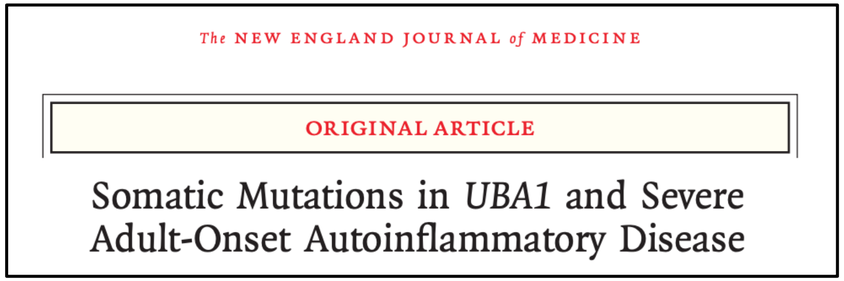
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
GSK			x				

What is VEXAS syndrome?

- A disease identified in 2020 and caused by **somatic alterations in the UBA1 gene (ubiquitylation)**



- Consequence: recalcitrant **inflammatory state**, with **hematologic disturbances**
- UBA1 gene on the **X chromosome** (Xp.11.23): **men** are more affected than women
- In people > 50 years old, the prevalence is **1 in 4'000 men,** and **1 in 26'000 women**
- Symptomatic onset more commonly **from 50 to 65 years** but reports have predominantly ranged **from 40 to 85 years**

Beck DB, et al. N Engl J Med (2020); Koster MJ, et al. Am J Hematol (2024)

What does VEXAS stand for?

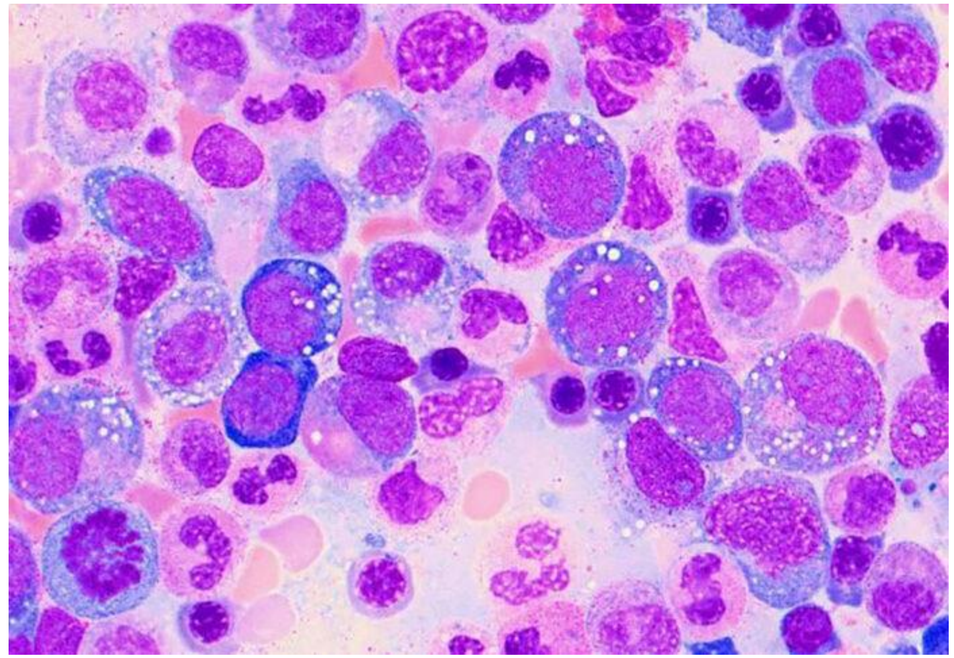
V **V**acuoles are often seen in cells identified in bone marrow biopsies

E **E1** ubiquitin activating enzyme, encoded by the *UBA1* gene which is mutated in patients

X the *UBA1* gene is located on the **X** chromosome

A patients have **A**utoinflammation

S the mutations are **S**omatic (not inherited)



Beck DB, et al. N Engl J Med (2020)

EXPERT REVIEW OF HEMATOLOGY
2025, VOL. 18, NO. 7, 509–519
https://doi.org/10.1080/17474086.2025.2508505

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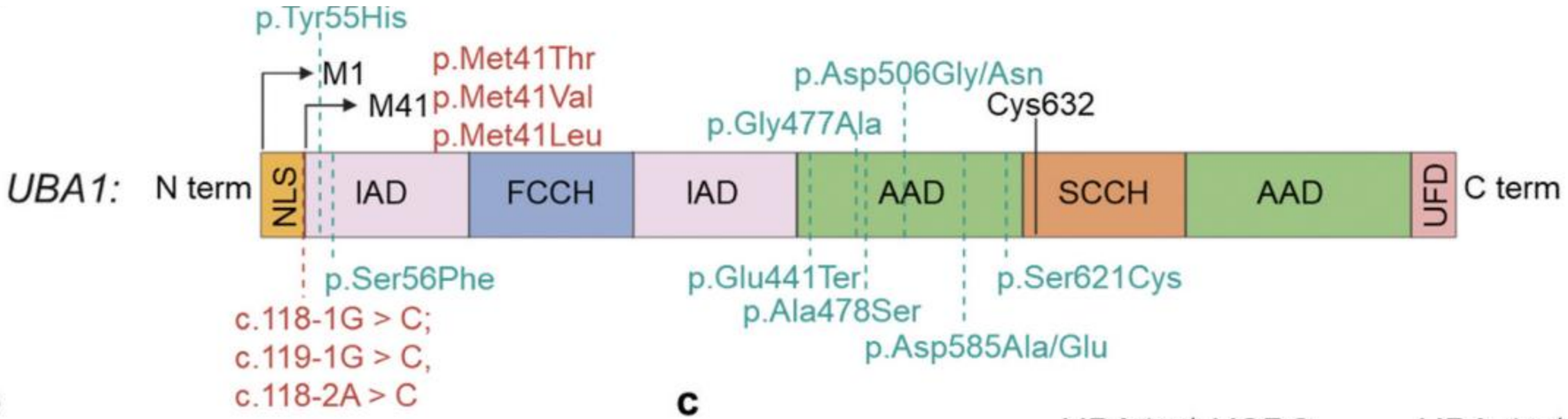
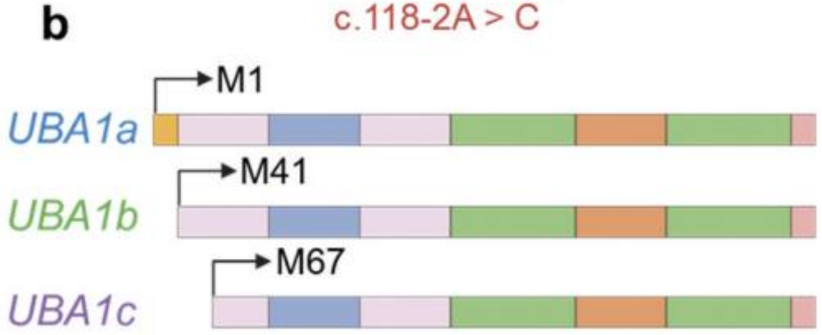
REVIEW

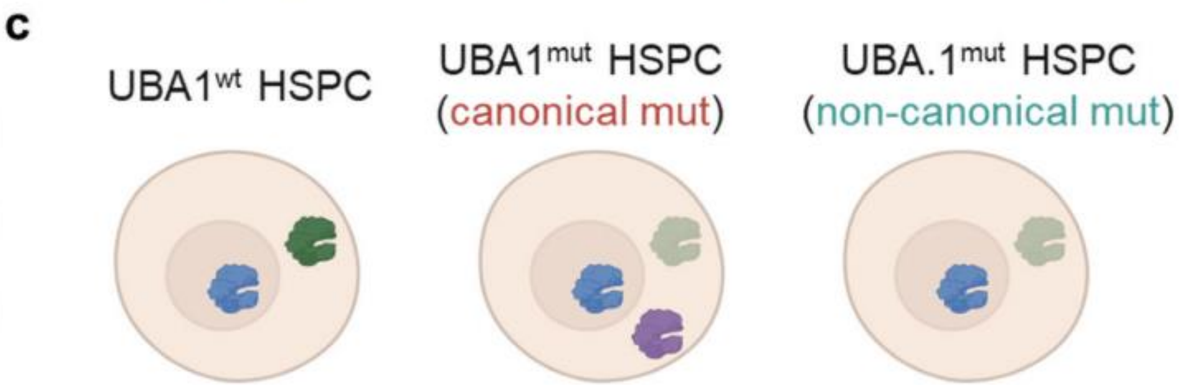
OPEN ACCESS Check for updates

Clonal hematopoiesis meets an autoinflammatory disease: the new paradigm of VEXAS syndrome

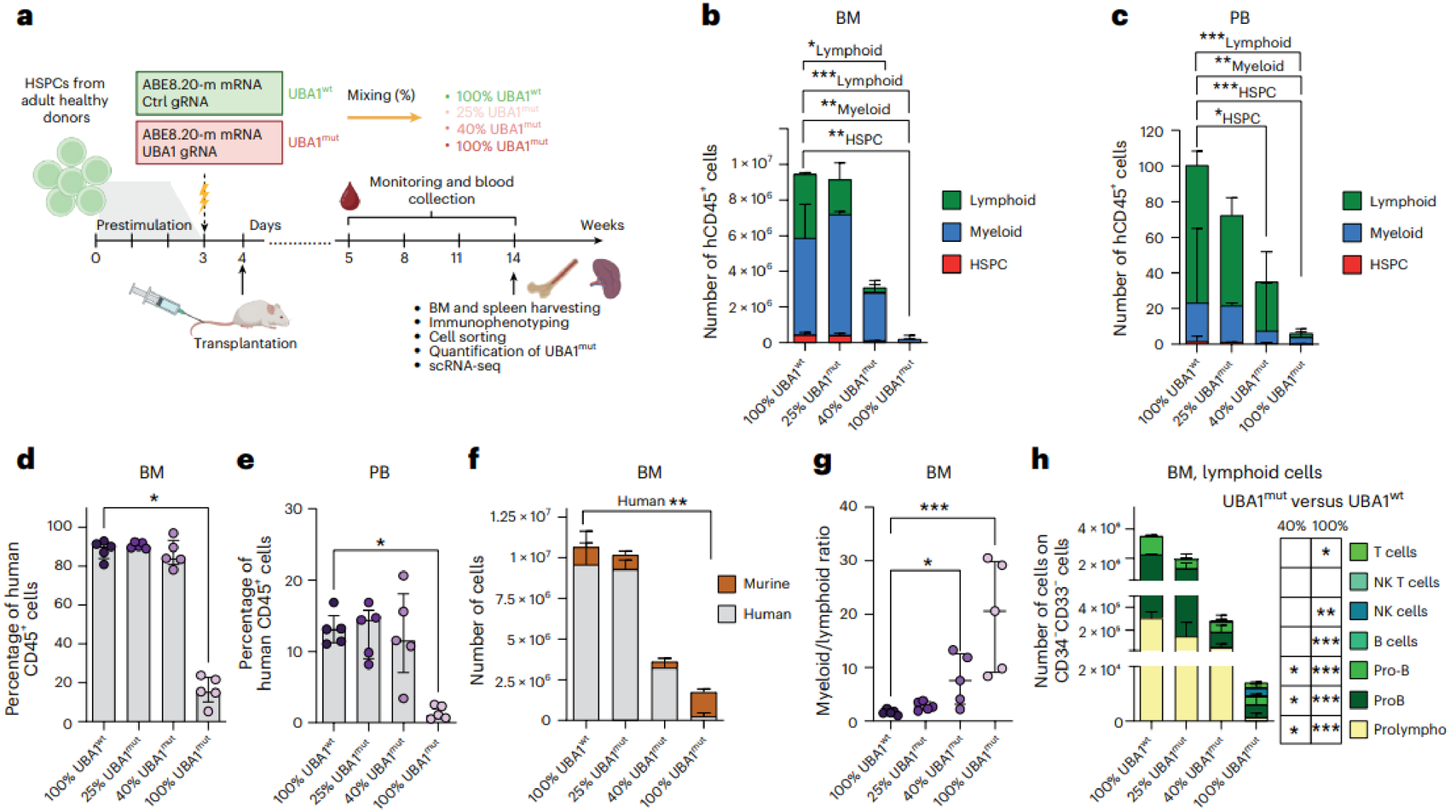
Martina Fiumara [a,b*], Raffaella Molteni[b,c*], Gianluca Scorpio[d], Alessandro Tomelleri[e], Gregorio Maria Bergonzi [d], Samuele Ferrari[a,b], Marco Matucci-Cerinic[b,c], Simone Cenci[b,c], Lorenzo Dagna[b,e], Fabio Ciceri[b,d], Elisa Diral[d] and Corrado Campochiaro [b,e]



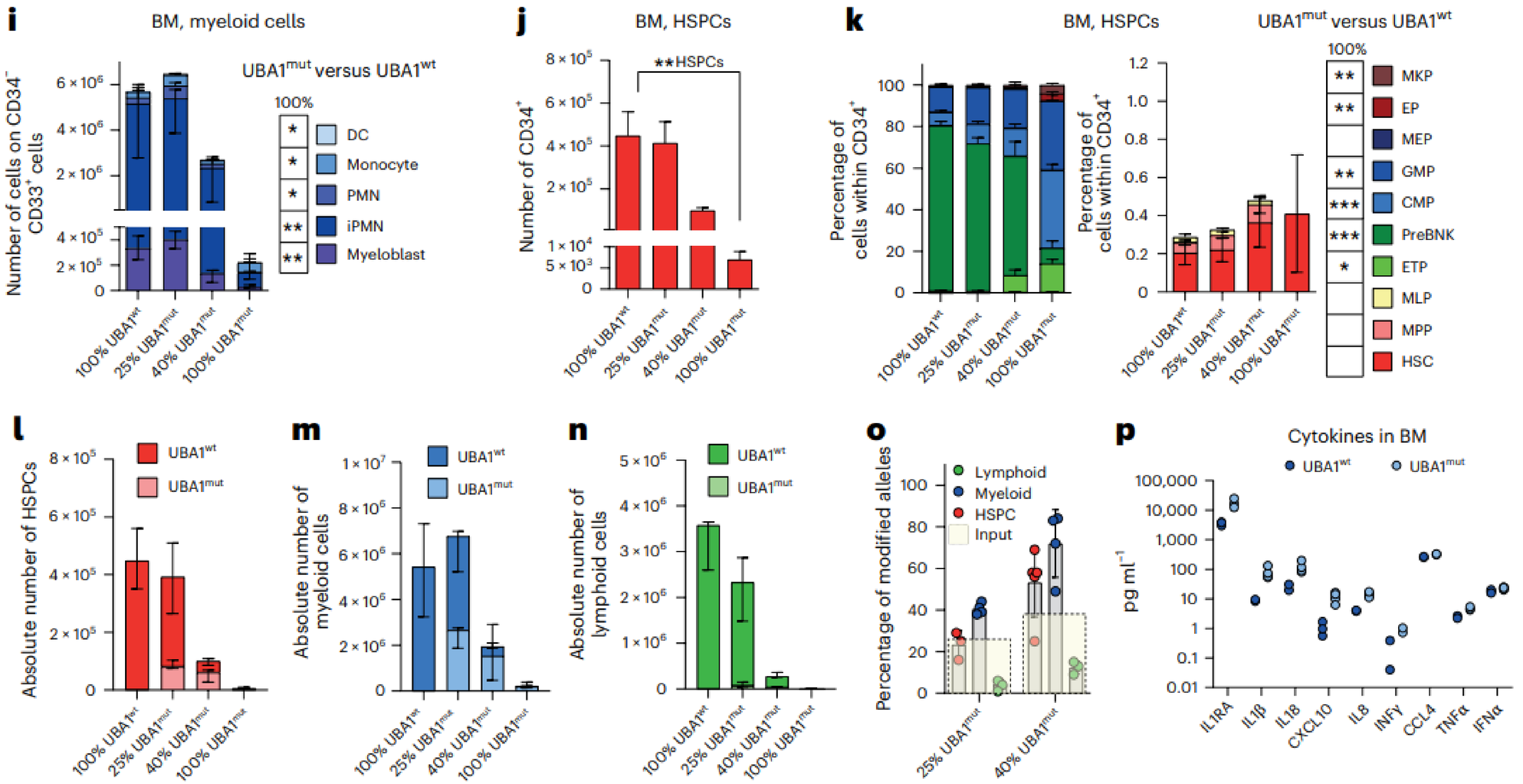




VEXAS pathophysiology



Molteni R, et al. Nature Medicine (2025)



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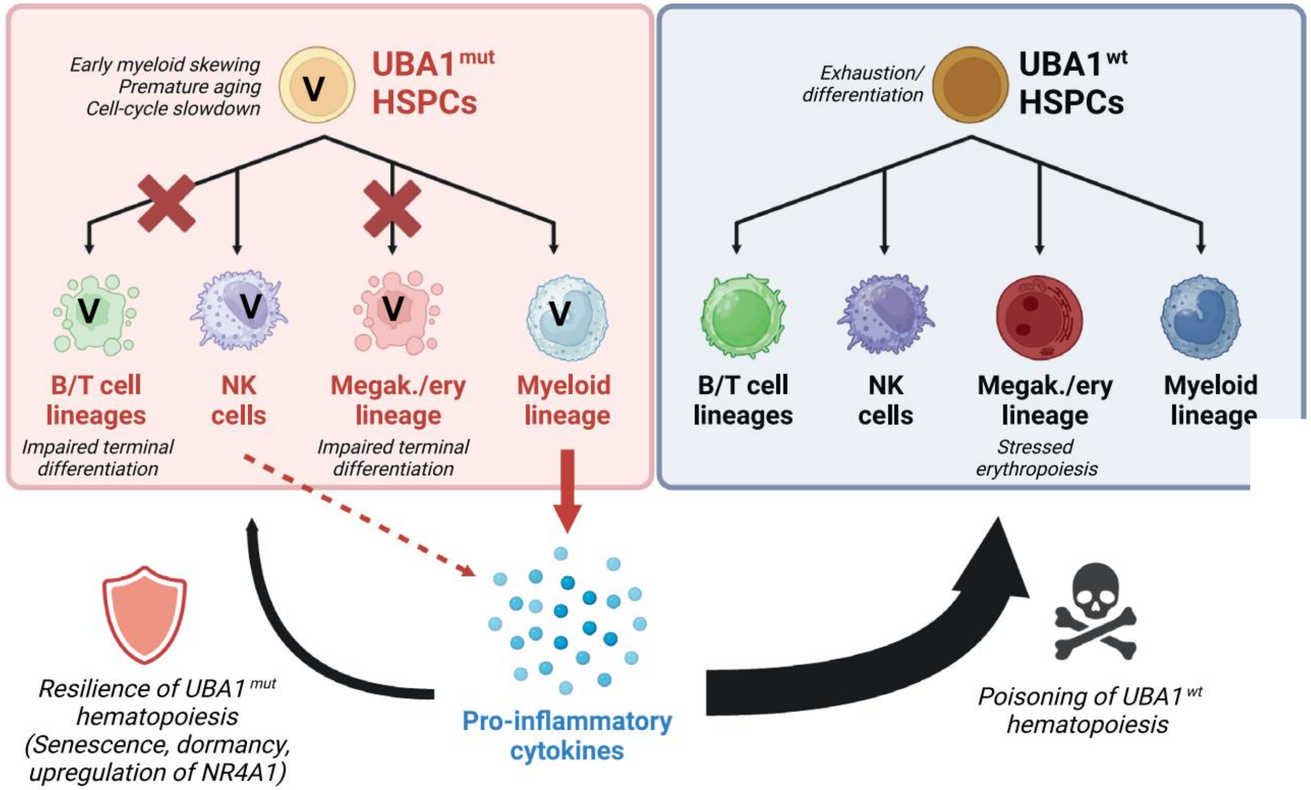
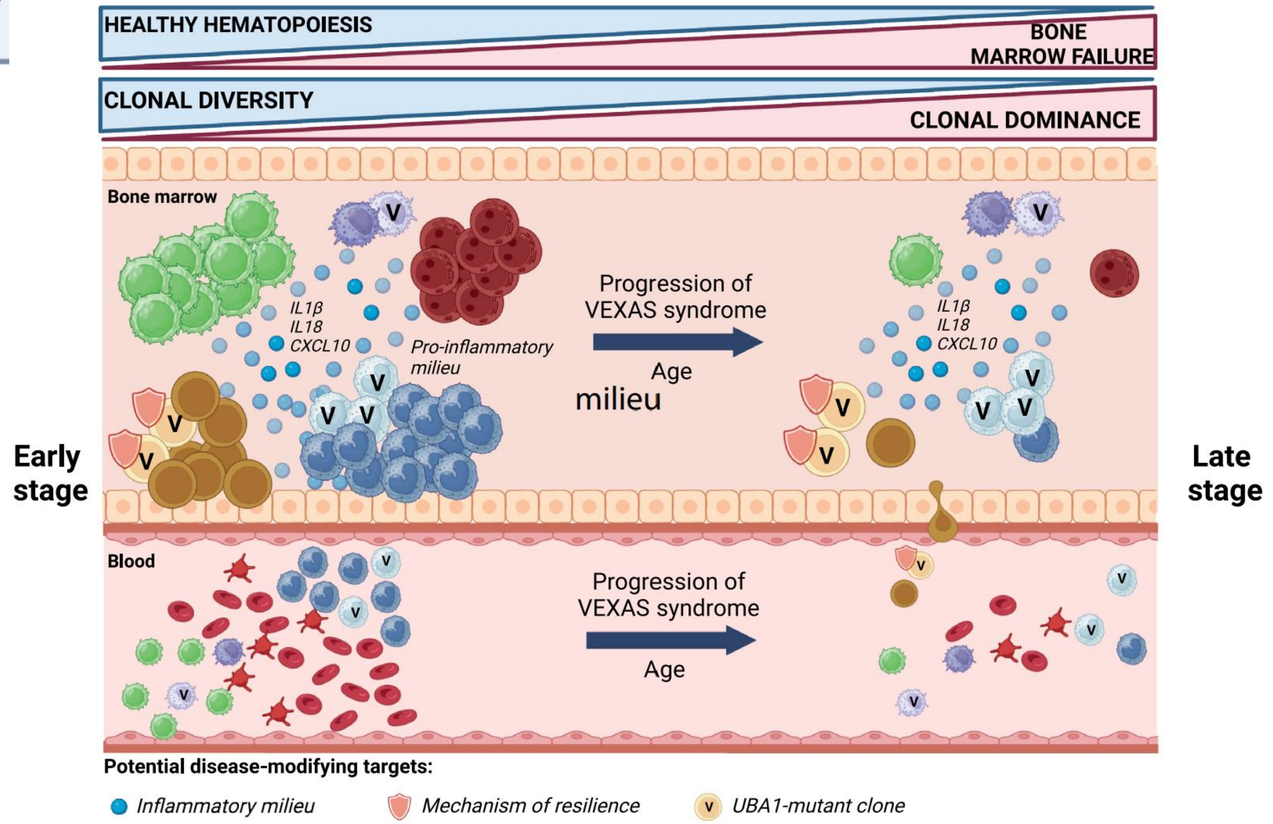
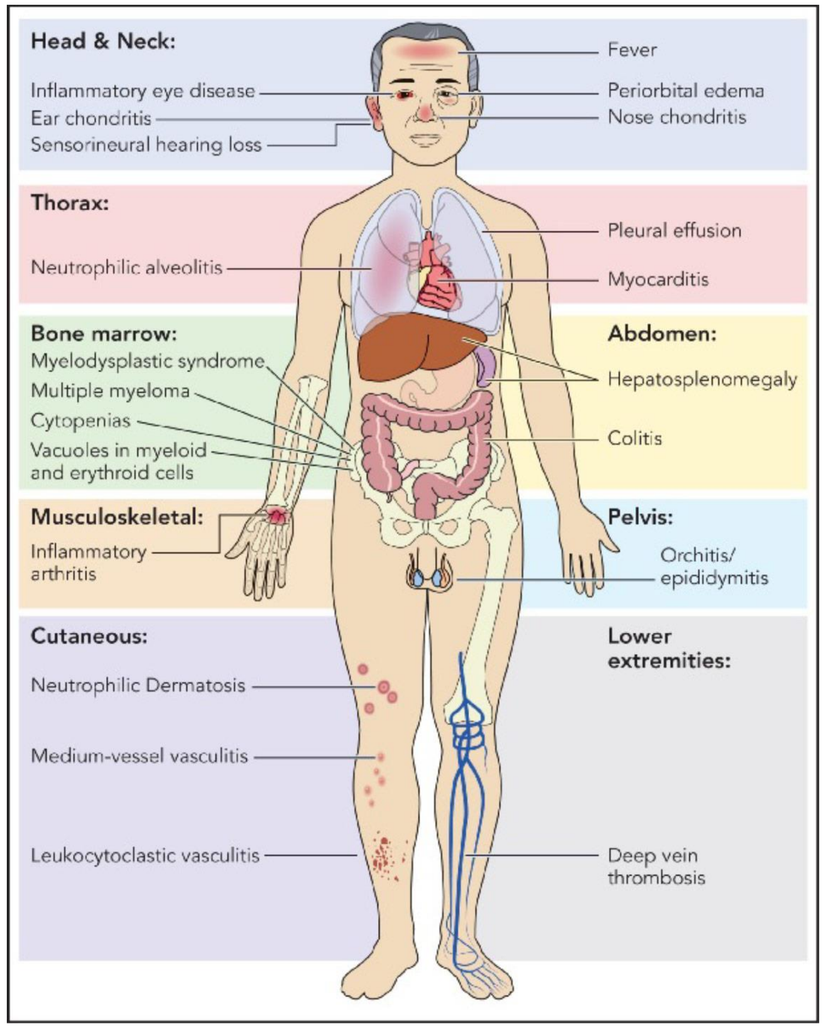




Molteni R, et al. Nature Medicine (2025)

Inflammatory and Hematologic disorder



http://www.niams.nih.gov/labs/grayson-lab/vexas

Constitutional & articular manifestations

- **Fever** is one of the most common features (**64-100%** of patients) →prompt **responsiveness to glucocorticoids**
- Blood tests invariably show elevation of **C-reactive protein** and **erythrocyte sedimentation rate**
- Oligo/poly-articular **inflammatory arthritis** is not a common finding (**<10%** of patients)

Koster MJ, et al. Am J Hematol (2024)

Cutaneous manifestations

- Very common: > 80% of patients

- Wide spectrum of findings:
- tender erythematous papules or plaques
- purpura/cutaneous vasculitis
- livaedo reticularis or racemosa
- injection-site reactions (anakinra)
- pustules, vesicles or bullae

- Lesions mostly found on the trunk and limbs

- Pathological features: mainly **neutrophilic dermatosis**

- Sequencing analysis of paired bone marrow samples & skin lesion biopsies of 8 patients identified **the same loss-of-function *UBA1* variation in both samples** for all patients

Zakine E, et al. JAMA Dermatol (2021)
Georgin-Lavialle S, et al. Br J Dermatol (2022)

Zakine E, et al. JAMA Dermatol (2021)
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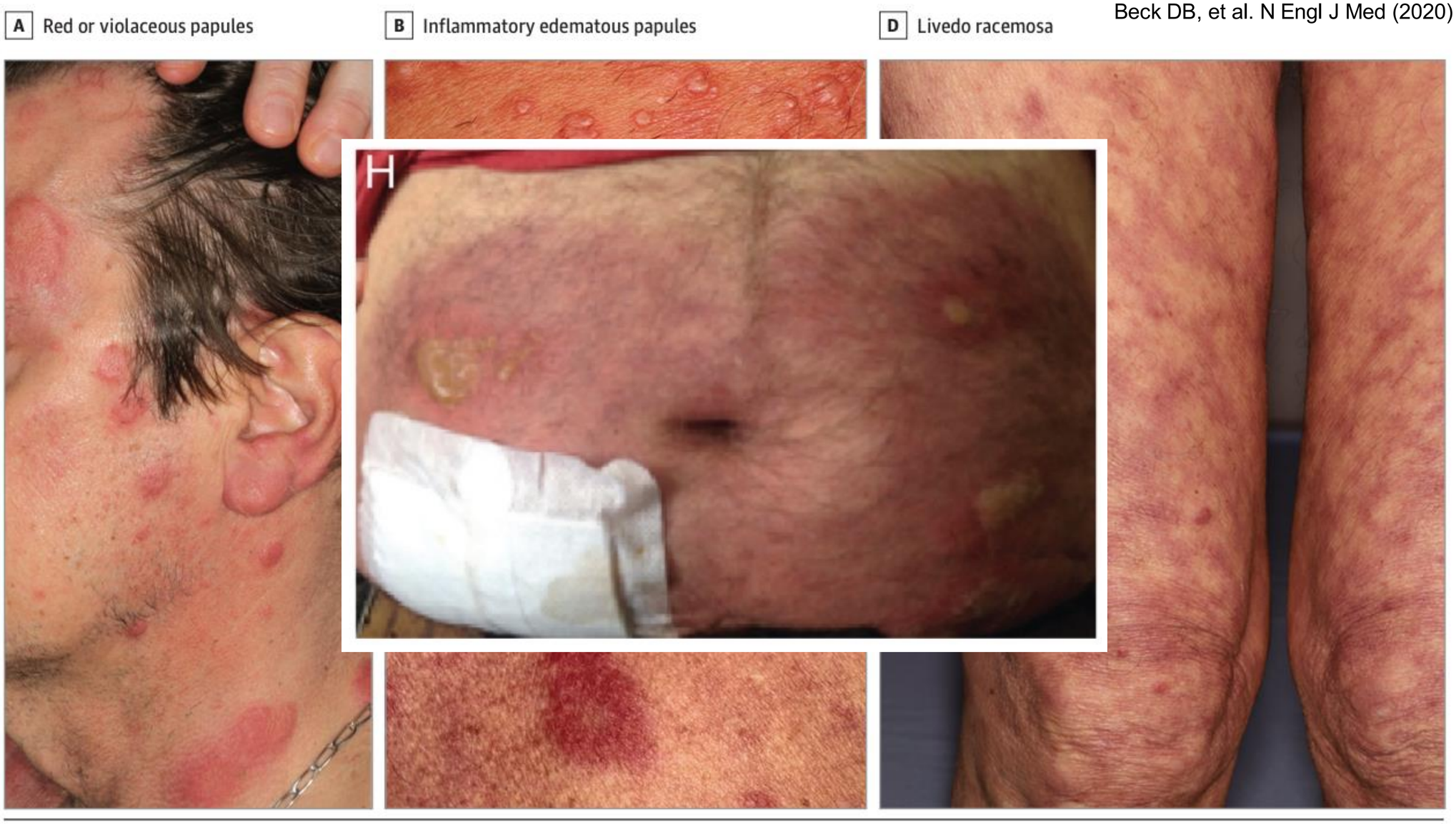
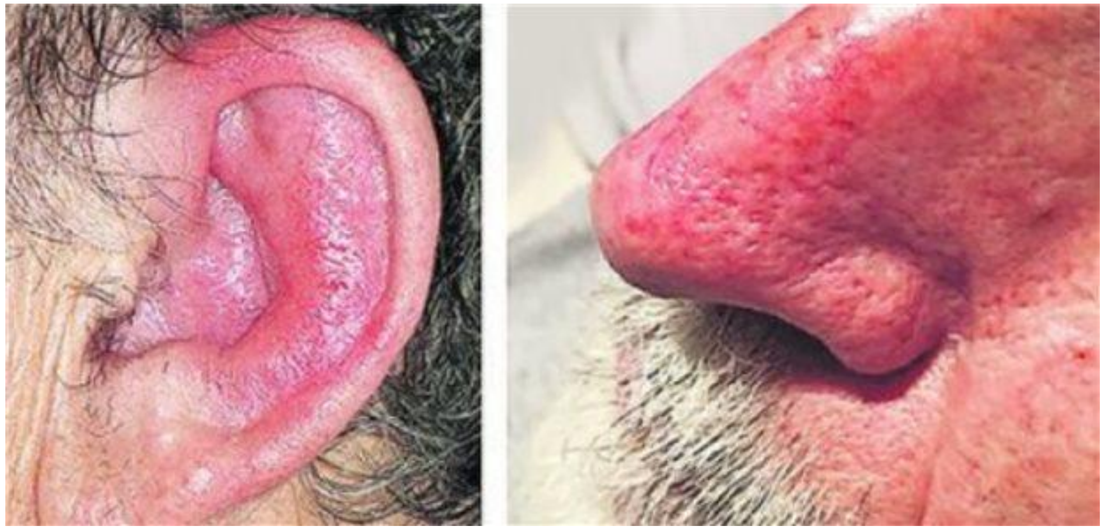


Head & neck manifestations

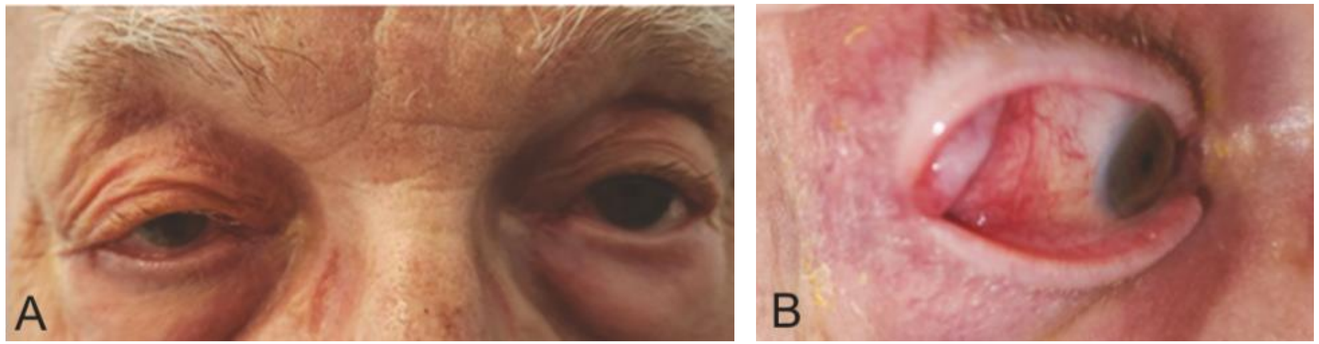
Chondritis 40-60% of patients

Mostly **auricular** and **nasal**



Orbital / peri-orbital oedema

- More often **unilateral**
- Often with **dacryoadenitis,** extra-ocular muscle **myositis**
- Approximately 10-30% of patients



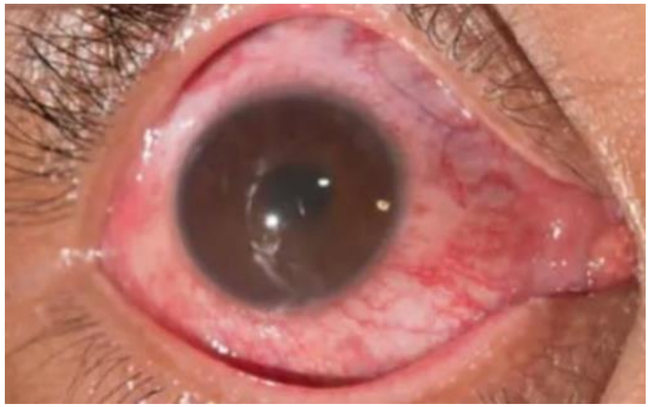
Vitale A, et al. Semin Arthritis Rheum (2024)
Abumanhal M, et al. Eye (2024)
Khitri M-Y, et al. RMD Open (2022)
Ferrada M, et al. Arthritis Rheumatol (2021)

Head & neck manifestations

Eye inflammation

- Episcleritis
- Anterior uveitis
- Iritis
- Scleritis
- Blepharitis

(all < 10%)



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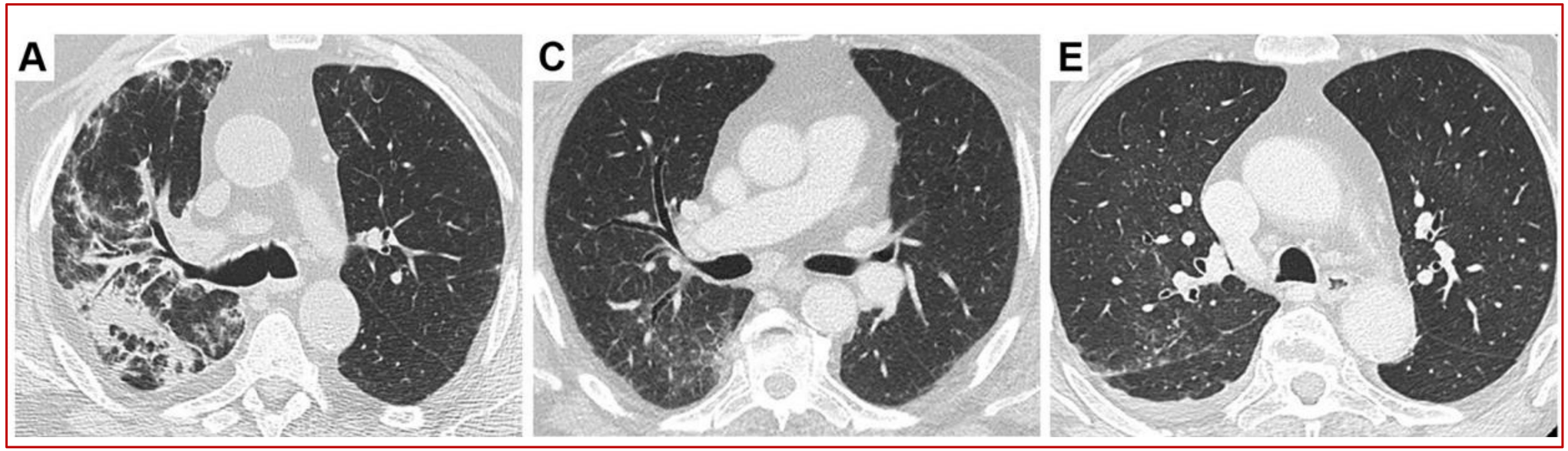
Khitri M-Y, et al. RMD Open (2022)
Ferrada M, et al. Arthritis Rheumatol (2021)

Pulmonary manifestations

- Lung involvement is often **clinically silent**; **<** 50% of patients complain of **dyspnea and cough**

- Lung involvement is **frequent (CT scans: abnormal lung findings in 70%–100% of patients)**

- Radiographic findings include **ground-glass opacities** (87%), **mediastinal lymphadenopathies** (58%), **pleural effusions** (53%), and **lung nodules** (27%)



Casal Moura M, et al. Respir Med (2023)
Borie R, et al. Chest (2023)

Vascular manifestations

Venous thrombosis

- In approximately **40-50%** of patients
- Dysregulation between coagulant and anticoagulant factors induced by **inflammation**
- **Risk factors**: cardiac and pulmonary manifestations
- Treatment with (prolonged) **anticoagulation** is indicated but **inflammatory control** is necessary in preventing recurrences
- **Not** associated with poorer overall survival

(not clear if higher risk of arterial thrombosis)

Vasculitis

- Large (GCA-like), medium (PAN-like), and small vessels (AAV-like) vasculitis: VEXAS is a **variable-vessel vasculitis**
- Presentation and treatment response are **not typical for classical presentations** of primary vasculitides. E.g.:
  - Higher density of infiltrating neutrophils in temporal arteritis (≠ GCA)
  - Mesenteric arteritis never reported (≠ PAN)
- Involvement of **more than one vessel size** in the same patient is frequent

AAV, ANCA-associated vasculitis
GCA, giant cell arteritis
PAN, polyarteritis nodosa

Watanabe R, et al. Front Med (2022)
Kusne Y, et al. Blood (2024)

Other manifestations

Renal involvement

- **25% of patients** from a monocentric cohort (Mayo clinic) of 81 patients had acute kidney injury
- Most patients had **recurrent episodes**
- **Kidney biopsies**: plasma cell-rich interstitial nephritis (n=3), neutrophilic-rich interstitial inflammation (n=1), leukocytoclastic peritubular capillaritis (n=1), acute tubular injury (n=1)

Myocarditis and pericarditis

- Not common (<10%) and **poorly described**

Gastrointestinal involvement

- Not common (<10%) and **poorly described**
- Main symptoms: abdominal pain, diarrhoea, gastrointestinal bleeding with ulcerative lesions

Neuropathic involvement

- Not common (<10%) and **poorly described**
- Main manifestations: sensory neuropathy, multiple mononeuropathy
- One case of chronic inflammatory demyelinating polyradiculoneuropathy reported

Bert-Marcaz C, et al. J Neurol Neurosurg Psychiatry (2021)
Georgin-Lavialle S, et al. Br J Dermatol (2022)
Kalantari K, et al. Rheumatology (2024)

Hemato findings: Macrocytic anemia

- **Very common (>90% of cases)**

- **Typical presentation:** mean Haemoglobin **10.1** (9-11.5) g/dl, mean MCV **101** (94.8-106.75) fL

- **VEXAS Syndrome causes erythroblastopenia**

→ Erythropoiesis is rescued by clones unmutated for UBA1

36 Vexas Syndrome Is a New Cause of p53-Mediated Erythroblastopenia **ASH 2024**

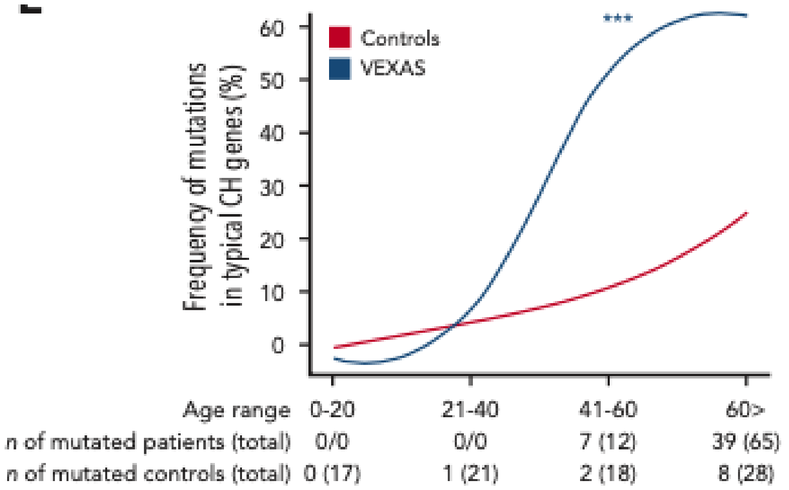
Program: Oral and Poster Abstracts
Type: Oral
Session: 508. Bone Marrow Failure: Acquired: Biological Findings Associated with the Pathophysiology and Outcomes of Aplastic Anemia and PNH
Hematology Disease Topics & Pathways:
Fundamental Science, Research, Acquired Marrow Failure Syndromes, Translational Research, Bone Marrow Failure Syndromes, Genetic Disorders, Diseases

- **Bone marrow evaluation is needed to assess potential underlying myeloid conditions**

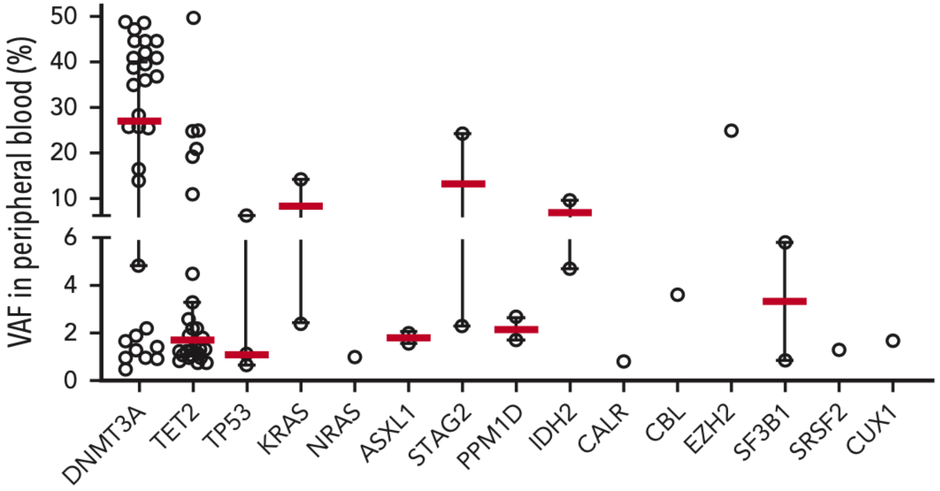
Ferrada et al., Blood, 2022; Mekinian et al., Leukemia, 2022; Georgin-Lavialle et al., BJD, 2022

Cytopenias in VEXAS – Clonal hematopoiesis (CH)

- **CH mutations occurs in up to 60% of pts**
  → Significantly higher frequency than healthy controls

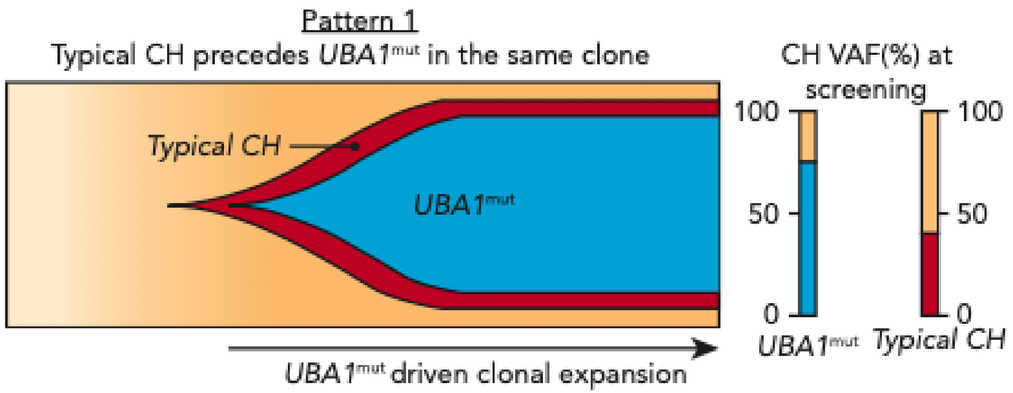


- **Most frequent mutations:**
  - **DNMT3A** (median VAF 27%)
  - **TET2** (median VAF 1.5%)

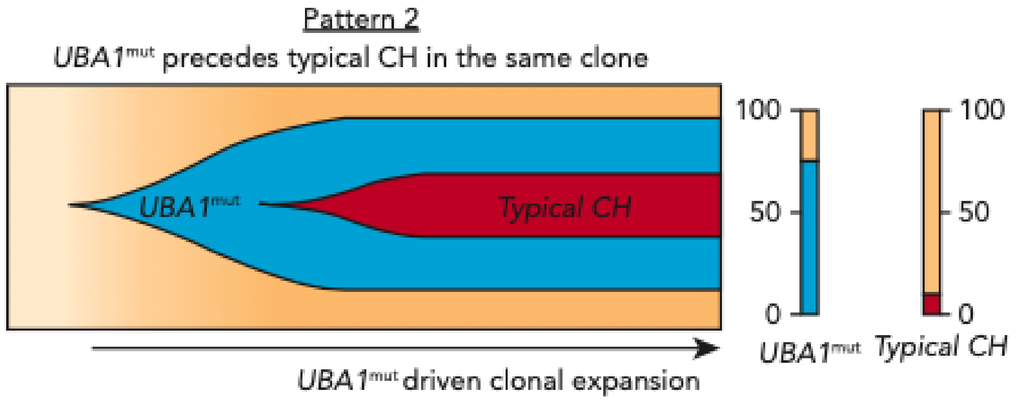


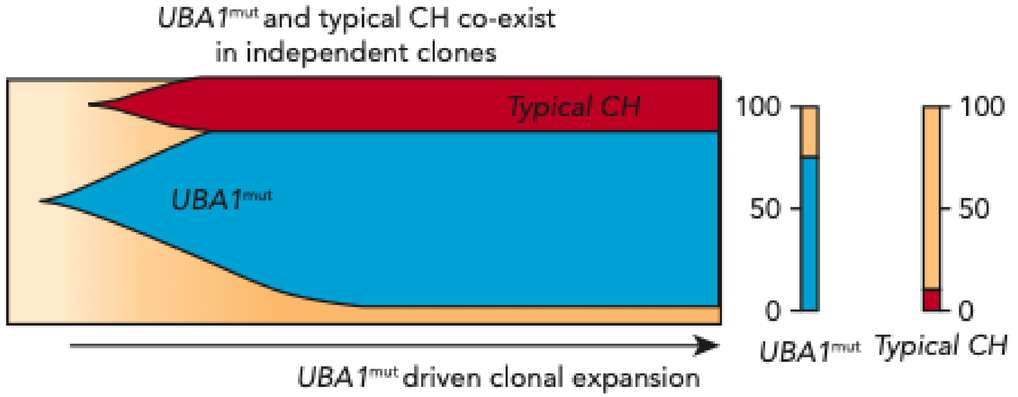
Gutierrez-Rodrigues et al., Blood, 2023

Typical CH **precedes** UBA1mut selection in a clone (**pattern 1**)



Typical CH occurs as a UBA1mut **subclone** or in **independent clones** (**pattern 2**)





Gutierrez-Rodrigues et al., Blood 2023

Classification of cytopenias in VEXAS

Cytopenias w/o CH → **typical VEXAS alterations**

Cytopenias with CH, w/o criteria of MDS **-> CCUS**

Cytopenias with CH and MDS morphological features **-> MDS**

Other findings: cytopenia in CMML, MPNs and AML

Khoury, Leukemia 2022; Diral, Front Immunol 2024; Beck, Jama 2023

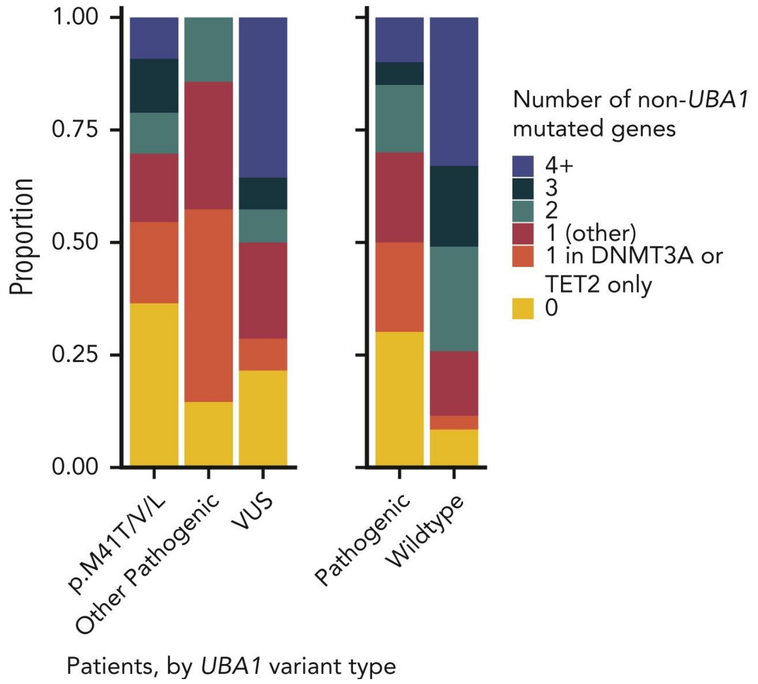
MDS in VEXAS

- **Quite common in VEXAS Syndrome (25-55%)**

- **Characteristics of UBA1mut MDS:**
  - WHO 2016: MDS-SLD or MDS-MLD
  - Low to Intermediate IPSS-R
  - Very Low to Low IPSS-M
  - Low blasts count (<5% in BM)
  - Low risk cytogenetics (normal karyotype)

- **Only one additional mutation in up to 75% of cases**

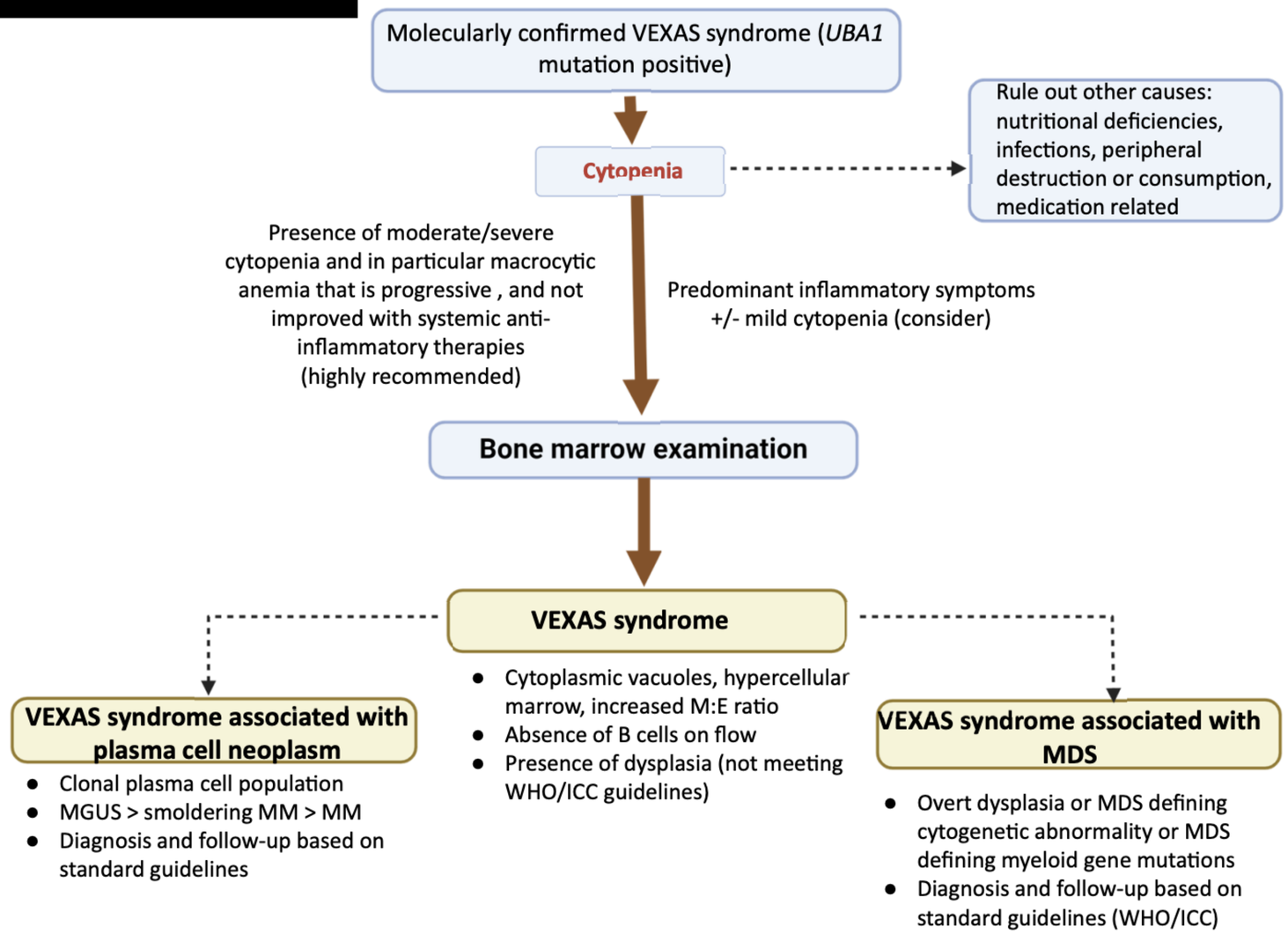
- **Very rare transformation into AML**



IPSS-M cohort:
UBA1mut in 1% of MDS
UBA1mut is more frequent (7%) in MDS with few or no mutations in myeloid driver genes

Ferrada et al., Blood, 2022; Mekenian et al., Leukemia, 2022; Georgin-Lavialle et al., BJD, 2022; Sirenko et al., Blood, 2024

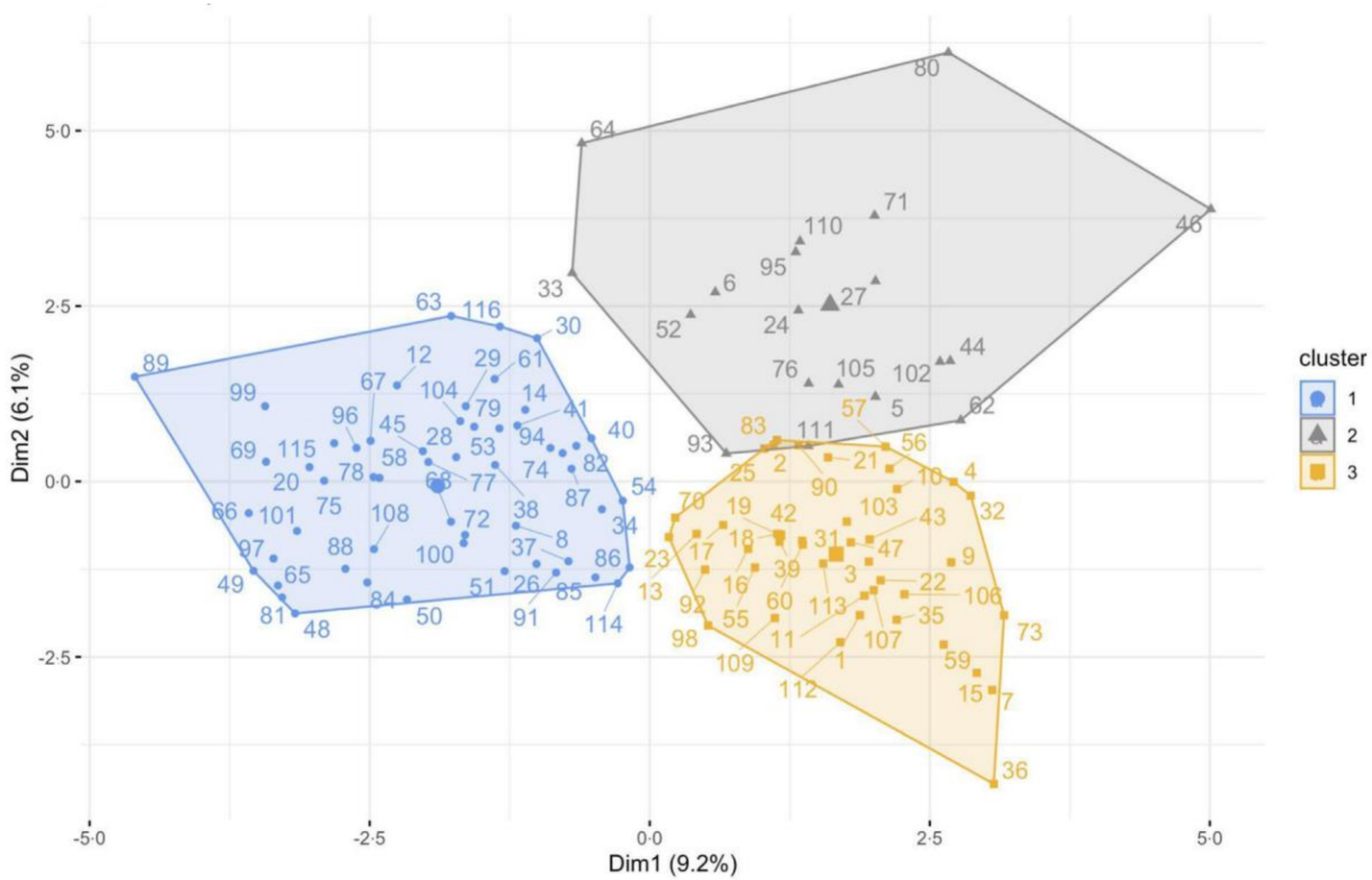
Approach to Hematological Diagnoses in VEXAS



Melkinian A et al, Arthritis Rheumatol 2026

Disease clusters

Unsupervised hierarchical analysis of 116 patients from a multicenter French cohort



Georgin-Lavialle S, et al. Br J Dermatol (2022)

Disease clusters

Cluster 1

- Associated with **p.Met41Leu**
- **Mild/moderate** disease
- **Low** frequency of
  - constitutional symptoms
  - lung and lymph node involvement
  - venous thromboembolism

Cluster 2

- Associated with **p.Met41Val**
- **Associated** with
  - chondritis
  - cardiac involvement
  - MDS
  - MGUS
  - thrombocytopenia

MDS, myelodysplastic syndrome

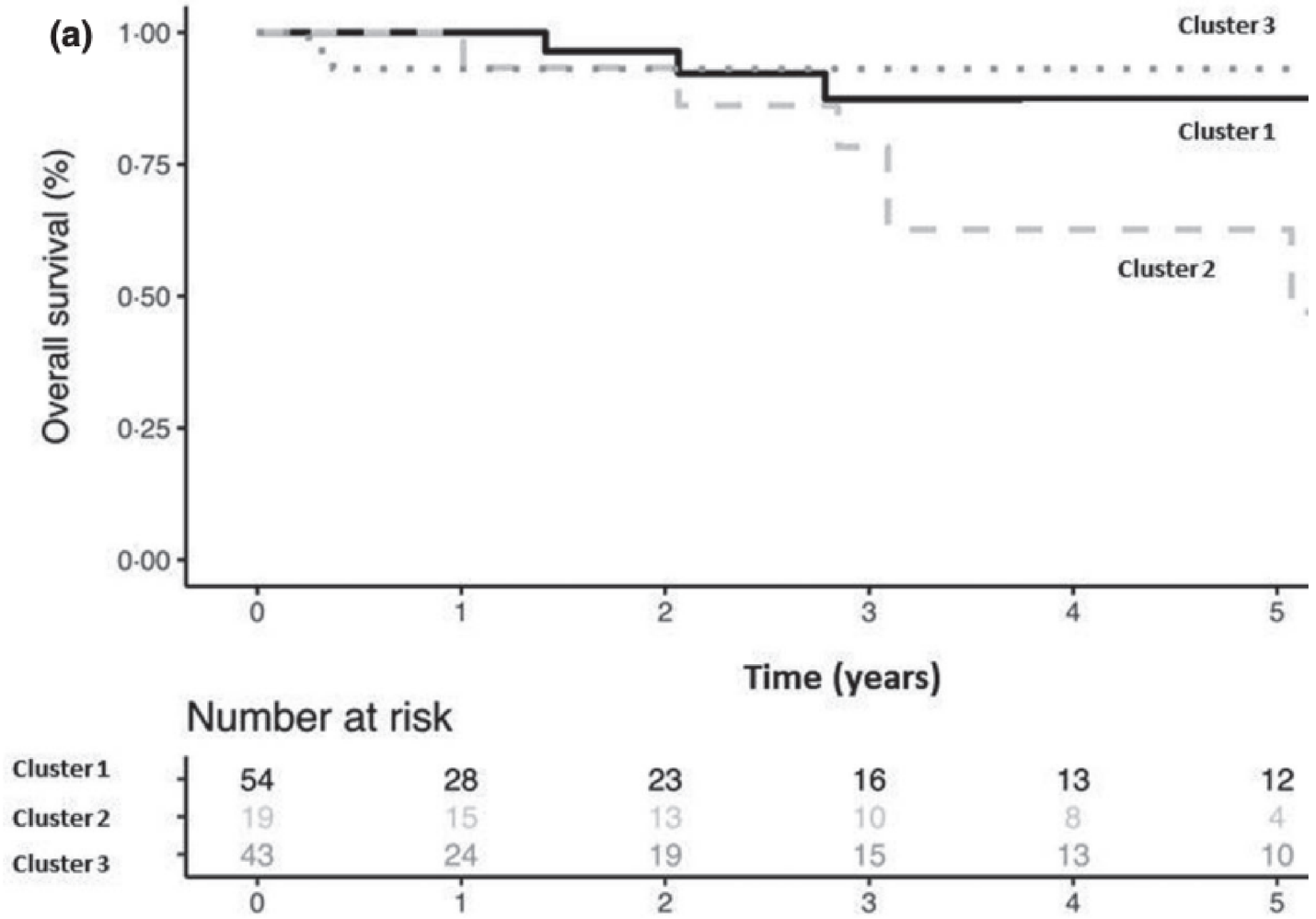
MGUS, monoclonal gammopathy of undetermined significance

Cluster 3

- **Advanced age**
- **Associated** with:
  - weight loss
  - cutaneous vasculitis
  - higher CRP
- **Low** frequency of
  - chondritis

Georgin-Lavialle S, et al. Br J Dermatol (2022)

Disease clusters



The **5-year probability of survival** was:

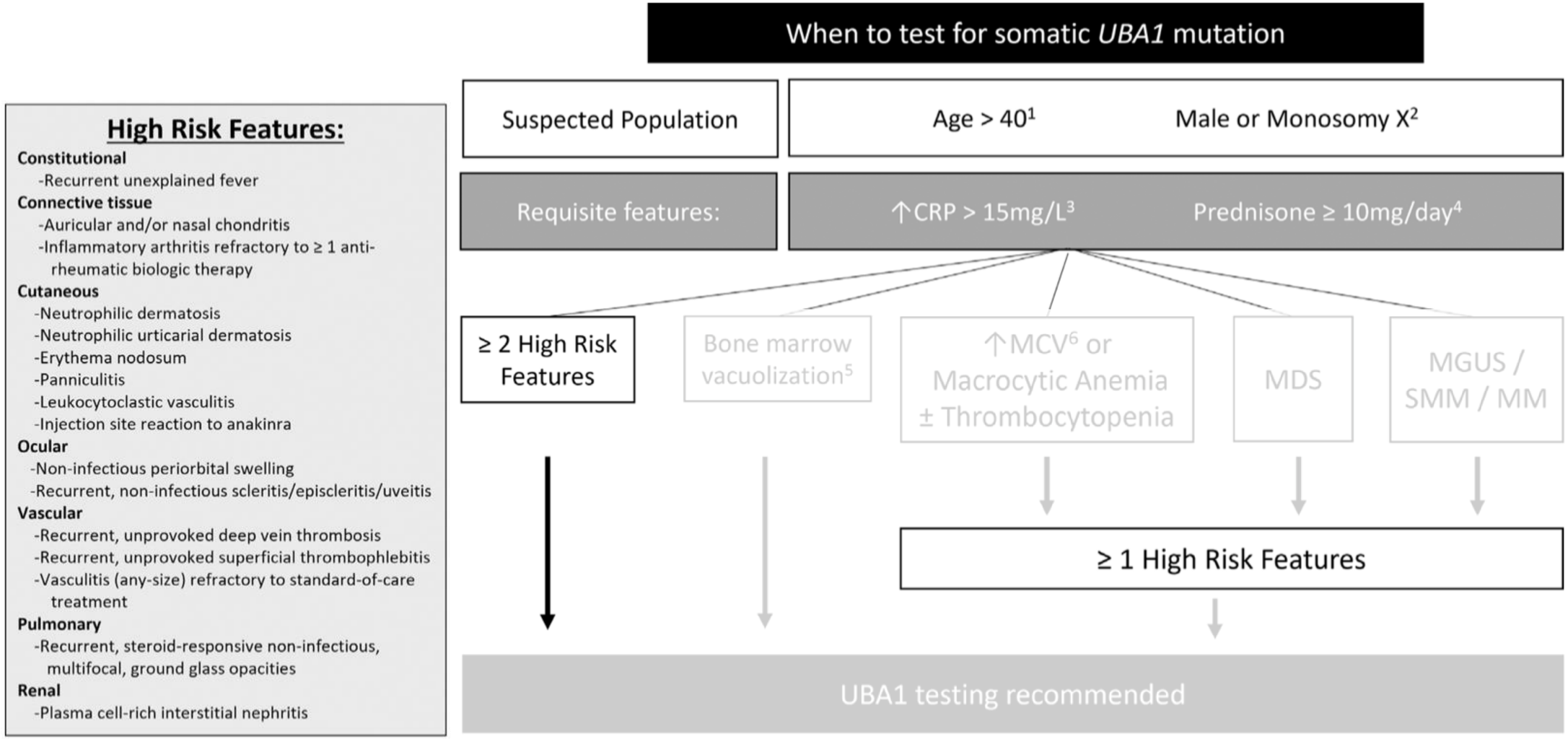
- 84.2% in cluster 1
- 50.5% in cluster 2
- 89.6% in cluster 3

Georgin-Lavialle S, et al. Br J Dermatol (2022)

When to test for somatic *UBA1* mutation

CRP, C-reactive protein; MCV, mean corpuscular volume; MDS, Myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.
(1) Only one case of VEXAS under the age of 40 yrs has been reported to date (2) Rare reports of women cases with Monosomy X have been reported. Testing for VEXAS in women without monosomy X and in patients < 40 yrs should be based on high clinical suspicion. (3) ≥ 2 occurrences of C-reactive protein (CRP) ≥ 15 mg/L; (4) Glucocorticoid dependency with ≥ 10 mg/day oral prednisone (or equivalent) for inflammatory syndrome symptomatic control; (5) Cytoplasmic vacuolization in erythroid and/or myeloid precursors for which copper deficiency, zinc toxicity, or alcohol abuse are not suspected as contributory causes; (6) MCV ≥ 98 femtoliter on one or more occasions without associated folate or vitamin B12 deficiency

Koster MJ, et al. Am J Hematol (2024)



CRP, C-reactive protein; MCV, mean corpuscular volume; MDS, Myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.
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Koster MJ, et al. Am J Hematol (2024)

High Risk Features:

Constitutional
- -Recurrent unexplained fever

Connective tissue
- -Auricular and/or nasal chondritis
- -Inflammatory arthritis refractory to ≥ 1 anti-rheumatic biologic therapy

Cutaneous
- -Neutrophilic dermatosis
- -Neutrophilic urticarial dermatosis
- -Erythema nodosum
- -Panniculitis
- -Leukocytoclastic vasculitis
- -Injection site reaction to anakinra

Ocular
- -Non-infectious periorbital swelling
- -Recurrent, non-infectious scleritis/episcleritis/uveitis

Vascular
- -Recurrent, unprovoked deep vein thrombosis
- -Recurrent, unprovoked superficial thrombophlebitis
- -Vasculitis (any-size) refractory to standard-of-care treatment

Pulmonary
- -Recurrent, steroid-responsive non-infectious, multifocal, ground glass opacities

Renal
- -Plasma cell-rich interstitial nephritis

Koster MJ, et al. Am J Hematol (2024)

Diagnostic strategies

* Sanger

* NGS UBA1 gene

(atypical mutations)

Journal of Clinical Immunology (2025) 45:138
https://doi.org/10.1007/s10875-025-01932-9

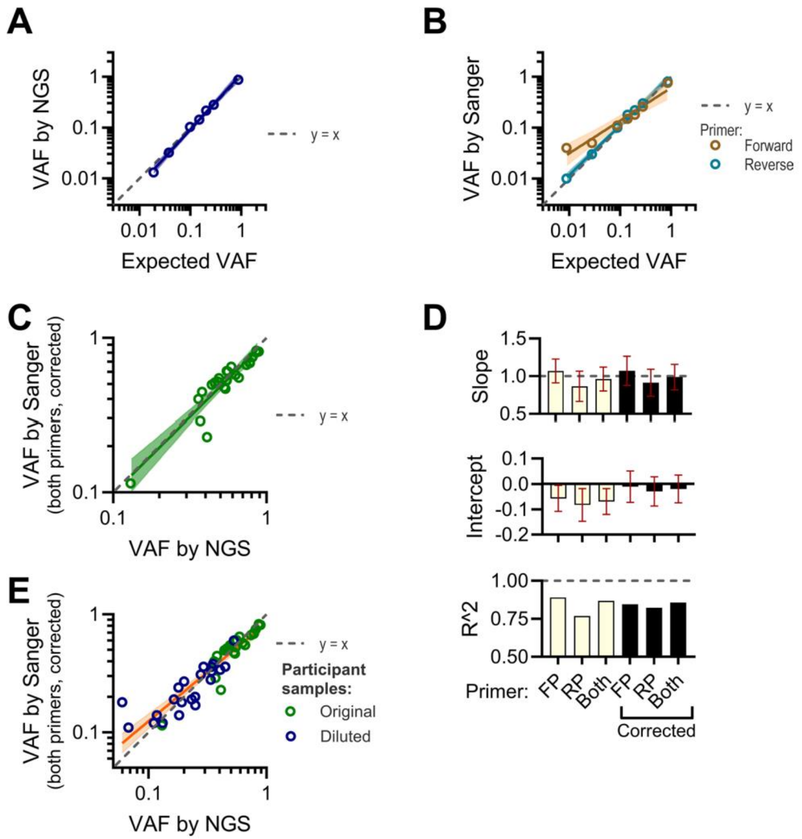
RESEARCH

Diagnostic and Monitoring Strategies for VEXAS Syndrome: Evaluating Sanger Sequencing, NGS, and the SWIM-Score

Lasse von Bornemann Fløe[1] · Kirstine Overgaard Dyrmose[1] · Camilla Darum Sørensen[1] · Maja Nørgaard[1] · Fie Kirstine Udby Pedersen[2] · Johan Vad-Nielsen[2] · Michael Knudsen[2] · Mette Christiansen[2] · Marie Bill[3,5] · Mads Nyhuus Bendix Rasch[4] · Ellen Margrethe Hauge[4,5] · Anne Troldborg[4,5,6] · Nicklas Heine Staunstrup[1] · Jens Magnus Bernth Jensen[1,2]

Cohort n = 104 patients → using Sanger sequencing, 12 patients with mutations in the UBA1 gene were identified. NGS analysis performed on the same patients did not identify any additional VEXAS cases beyond those detected by the Sanger test.

Molecular monitoring strategies → longitudinal tracking of the mutant clone



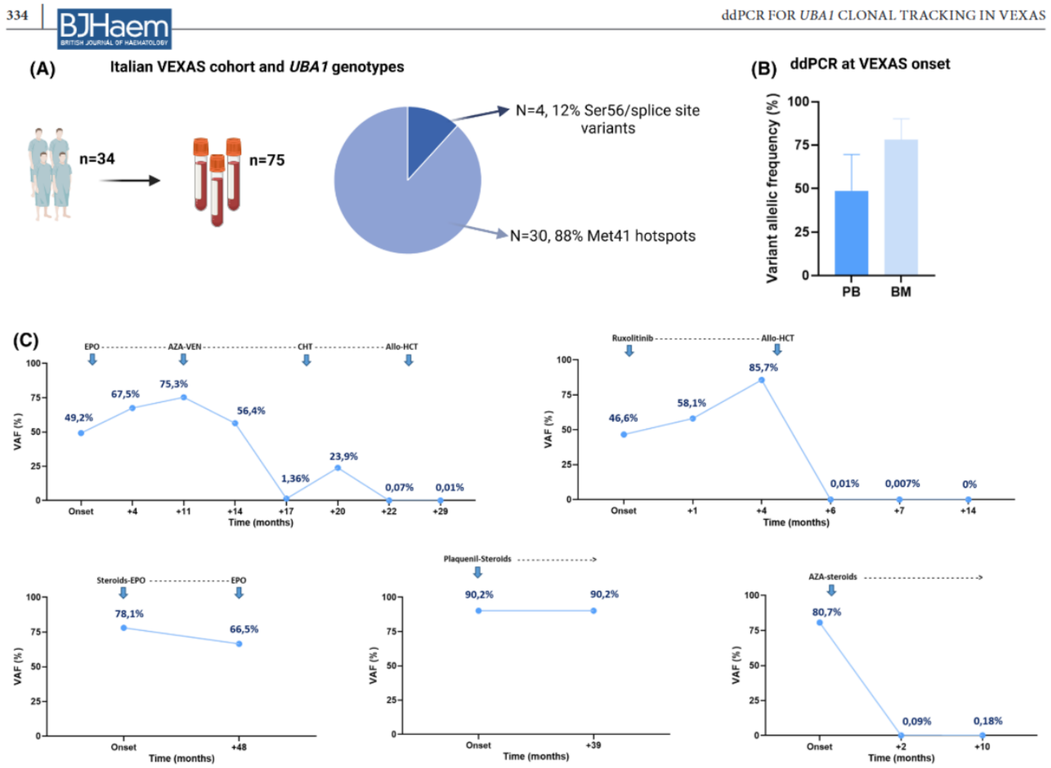


FIGURE 2 Study cohort characteristics and *UBA1* clonal dynamics upon different therapeutics. In the figure, panel (A) describes the Italian study cohort. In panel (B), a bar graph illustrates differences in variant allelic frequency (VAF, *y* axis) in samples collected from peripheral blood and bone marrow. In panel (C), the graphs show the clonal dynamics of the *UBA1* gene in exemplificative patients undergoing different treatment approaches. Dashed line means continuation of the drug. allo-HCT, allogeneic haematopoietic cell transplant; AZA, azacitidine; CHT, chemotherapy; CsA, ciclosporin A; EPO, erythropoietin stimulating agents. [Colour figure can be viewed at wileyonlinelibrary.com]

Sanger sequencing accurately quantified UBA1 VAFs ranging from 0.1 to 0.9.
NGS sensitivity 1%

ddPCR – validation for disease monitoring during follow-up, with quantification of UBA1 VAFs at a sensitivity of 10^{-2}

von Bornemann Fløe, Journal of Clinical Immunology 2025

Treatment of VEXAS syndrome – Therapeutic goals

Control of Inflammation

Reduction of fever, skin and cartilage involvement

Decrease in inflammatory markers (CRP, ESR)

Steroid-Sparing Strategy

Minimize long-term GCs exposure

Introduce targeted or immunosuppressive therapies

Hematologic Improvement

Correction of anemia and cytopenias

Reduction in transfusion dependance

Monitor bone marrow function

Prevention of Complications

Reduce risk of thrombosis, infections, organ damage

Clonal Disease Control

Stabilization or reduction of **UBA1-mutant clone (VAF)**

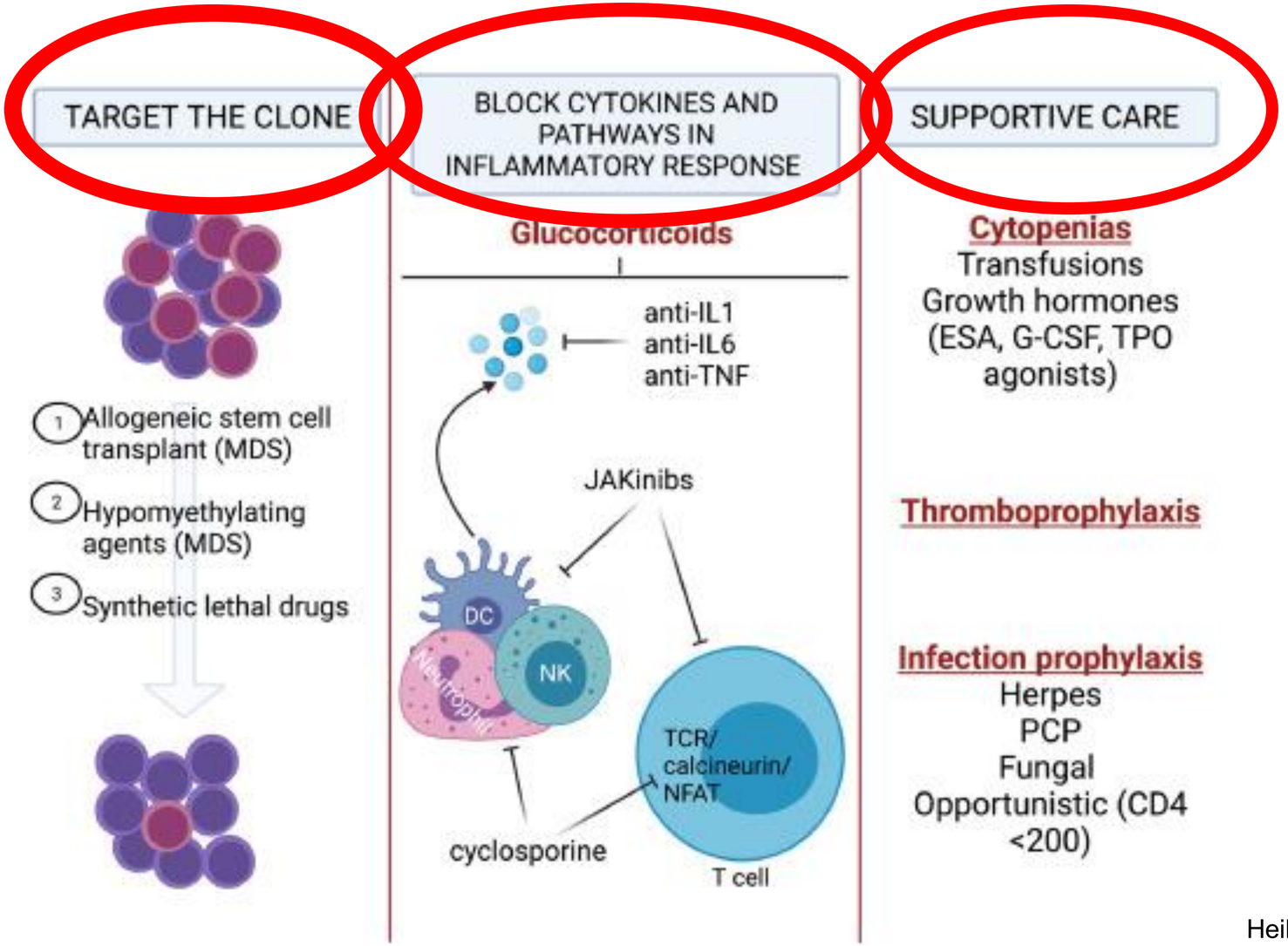
Prevent clonal progression or evolution

Sustained clinical remission

Possible curative approach?

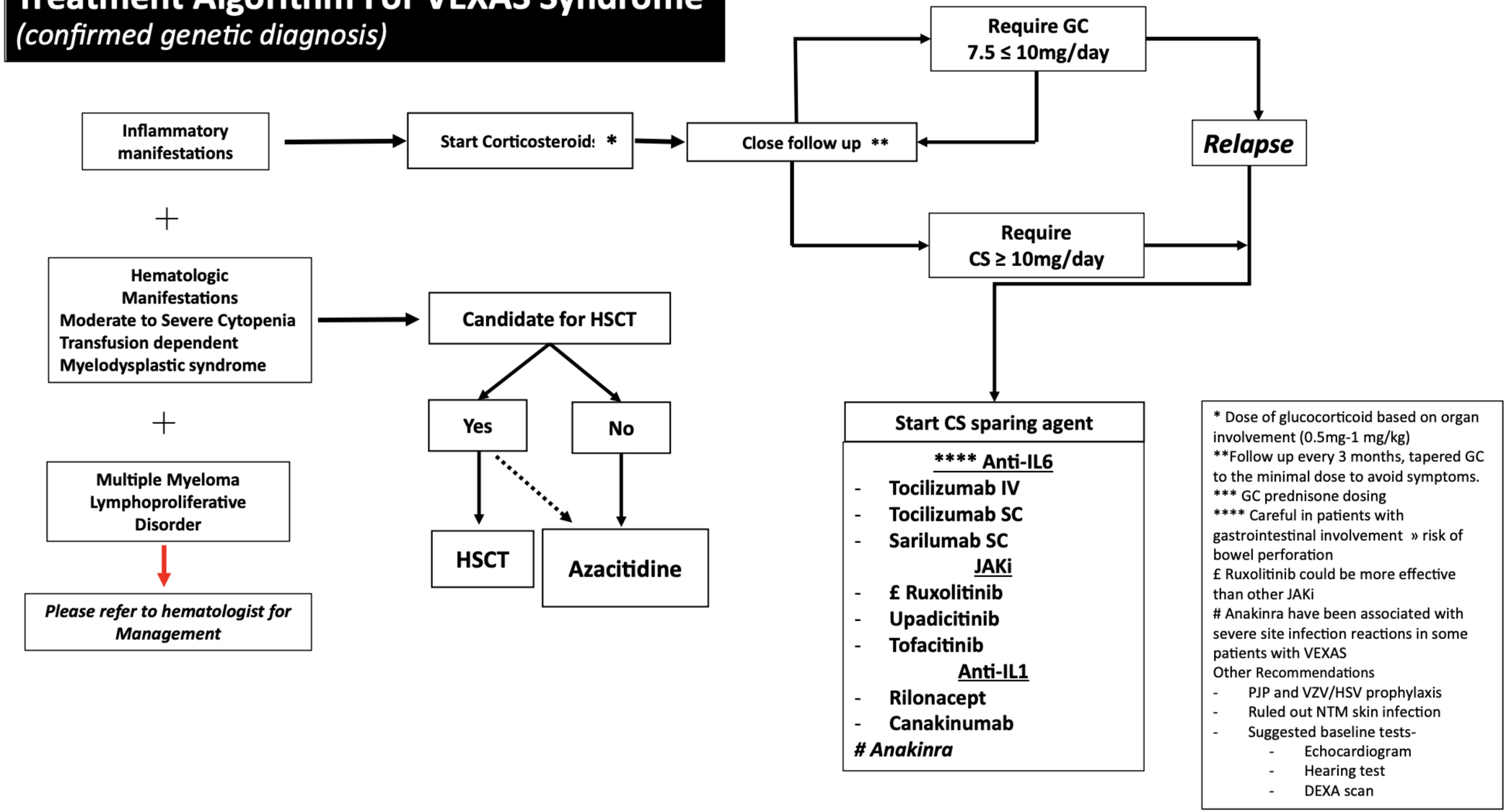
Physician opinion

Treatment of VEXAS syndrome



Heiblig et al. Seminars in Hematology 2021

Treatment Algorithm For VEXAS Syndrome
(confirmed genetic diagnosis)



Melkinian A et

Where do we start?

Glucocorticoids

Minimum of 15–20 mg/day

→ Less aggressive or mild cutaneous features 5–10 mg/day
→ More severe presentations 30–50 mg/day
→ Long-term toxicity

Steroid-sparing agents (csDMARDs)

Methotrexate → Ineffective and may worsen cytopenias
Mycophenolate → Ineffective
Azathioprine → Ineffective and highly NOT recommended → can propagate clonal transformation
Hydroxychloroquine → Ineffective
Cyclosporine A → Partially effective, used in combination with anti-IL-1

Physician opinion

HSR First Experience - rheumatology

	Age, years	Clinical characteristics at presentation	Markers of inflammation at presentation	Previous therapy, reason for stopping	Combination therapy, agent (dosage)	Markers of inflammation	
						At start of combination therapy	At last evaluation
Patient 1	70	Fever, skin lesions, lung involvement, arthritis	ESR 120 mm/hour, CRP 120 mg/liter, ferritin 1,638 ng/ml	ANK, adverse event; CNK, ineffectiveness	ANK (100 mg/day), CsA (200 mg/day), pred. (30 mg/day)	ESR 59 mm/hour, CRP 92 mg/liter, ferritin 623 ng/ml	ESR 20 mm/hour, CRP 1.3 mg/liter, ferritin 445 ng/ml
Patient 2	69	Fever, skin lesions, lung involvement, polychondritis, arthritis, aphthosis	ESR 117 mm/hour, CRP 161 mg/liter, ferritin 1,484 ng/ml	ANK, adverse event; TCZ, neutropenia	CNK (300 mg every 5 weeks), CsA (300 mg/day), pred. (15 mg/day)	ESR 99 mm/hour, CRP 26 mg/liter, ferritin 526 ng/ml	ESR 51 mm/hour, CRP 2.8 mg/liter, ferritin 430 ng/ml
Patient 3	68	Fever, arthritis, skin lesions, polychondritis, lung involvement, orbital pseudotumor	ESR 120 mm/hour, CRP 202 mg/liter, ferritin 1,680 ng/ml	MTX, ineffectiveness; TCZ, neutropenia; TOFA, ineffectiveness	ANK (100 mg/day), CsA (200 mg/day), pred. (20 mg/day)	ESR 42 mm/hour, CRP 31 mg/liter, ferritin 980 ng/ml	ESR 29 mm/hour, CRP 0.8 mg/liter, ferritin 380 ng/ml

* VEXAS = vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ANK = anakinra; CNK = canakinumab; CsA = cyclosporin A; pred. = prednisone; TCZ = tocilizumab; MTX = methotrexate; TOFA = tofacitinib.

Campochiaro C et al. Arthritis & Rheumatology 2022

Anti-IL-6 Strategies

Patient ID	RP13	RP15	RP16
Sex	Male	Male	Male
Age of onset (years)	66.3	73.5	66.6
Time form onset to VEXAS diagnosis (months)	3	2	30
UBA1 variants p.Met41	c.122T>C: p.Met41Thr	c.122T>C: p.Met41Thr	c.121A>C: p.Met41Leu
UBA1 variant fractional abundance*	22.4 %	68.8 %	87.1 %
Clinical findings	High-grade fever, skin rash, RP, scleritis, peritonitis, pericarditis, meningitis	High-grade fever, skin rash, RP, macrocytic anaemia	High-grade fever, skin rash, GCA, RP, MDS, DVT, scleritis, airway involvement
Treatments before TCZ	PSL	PSL, MTX	PSL, AZP, colchicine
Concomitant treatments with TCZ	PSL	PSL	PSL, colchicine
Symptoms existed at TCZ induction‡	High-grade fever, myalgia, headache	Low-grade fever	High-grade fever, skin rash, RBC and PLT transfusion dependence
PSL dose at diagnosis of VEXAS syndrome	30 mg	50 mg	50 mg
PSL dose before TCZ administration	9 mg	22.5 mg	30 mg
PSL dose at last visit	3 mg	13.5 mg	30 mg
Hb level before TCZ administration	119 g/L	118 g/L	†74 g/L
Hb level at last visit	116 g/L	121 g/L	†91 g/L
Adverse events over 4 months	Herpes zoster	None	Herpes zoster, drug eruption
Symptoms existed after 4 months	None	None	Arthritis, RBC transfusion dependence, fever, skin rash, pulmonary infiltration
Serum IL-6 levels before TCZ	10.49 pg/mL	693.33 pg/mL	22.13 pg/mL
Observation period after TCZ	8 months	5 months	5 months

Kirino Y et al. ARD 2021

JAK-inhibitors

Retrospective multicenter study:

- **Ruxolitinib (n=12)**
- **Tofacitinib (n=11)**
- **Baricitinib (n=4)**
- **Upadacitinib (n=3)**

Ruxolitinib showed superior clinic

- **67% response at 1 month**
- **83% response at 3 months**
- **87% response at 6 months**

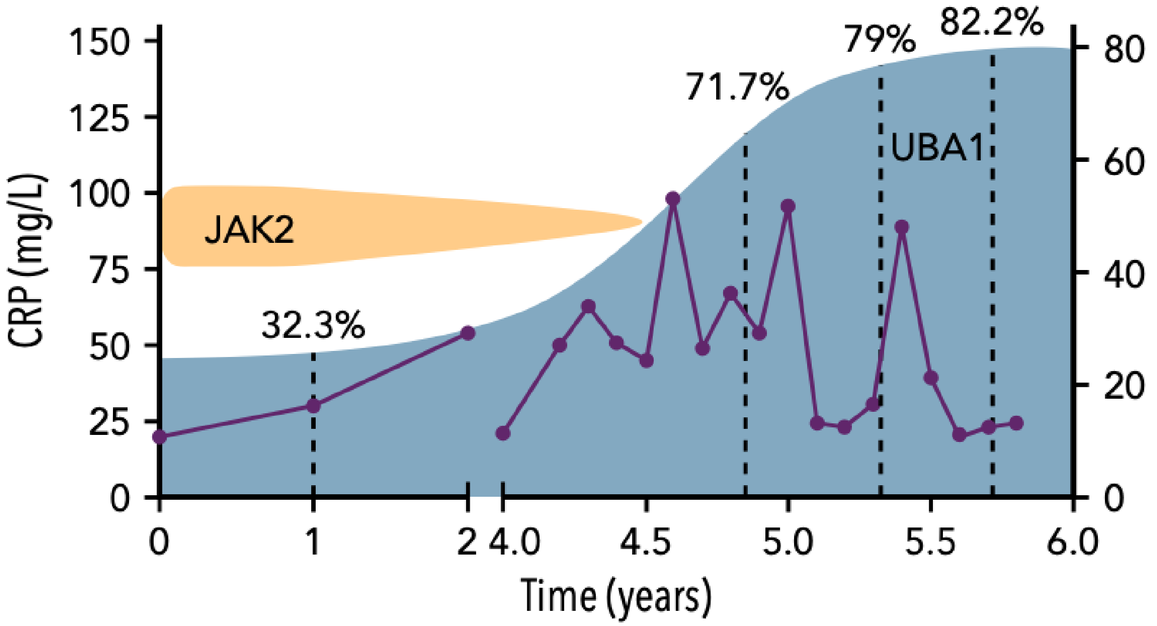
Hematologic Response:

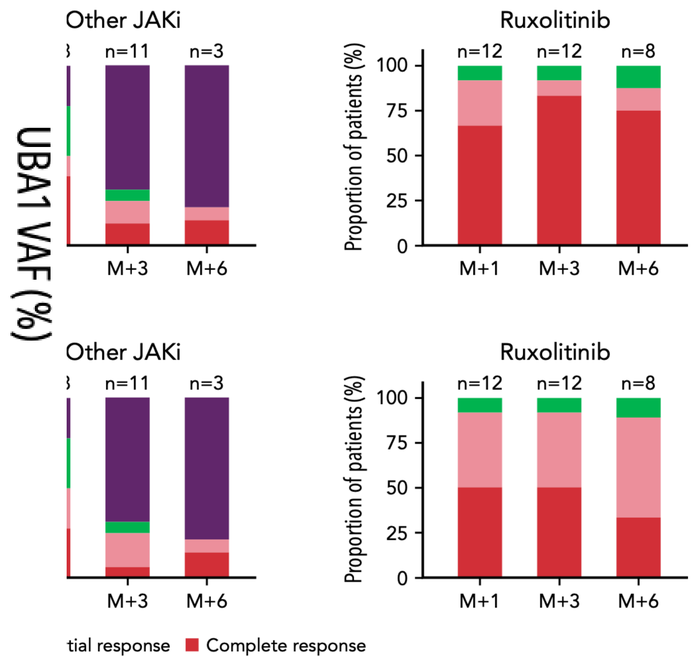
•Patients on Ruxolitinib significan

- **Hemoglobin levels (+10.9 g**
- **Platelet counts (P=0.028)**

Adverse Events:

- **Infections (36.7% of patien**
- **Thromboembolic complica**





Clonal Expansion: Ruxolitinib appears to suppress symptoms but may not cure the underlying hematologic disorder (UBA1 mutation).

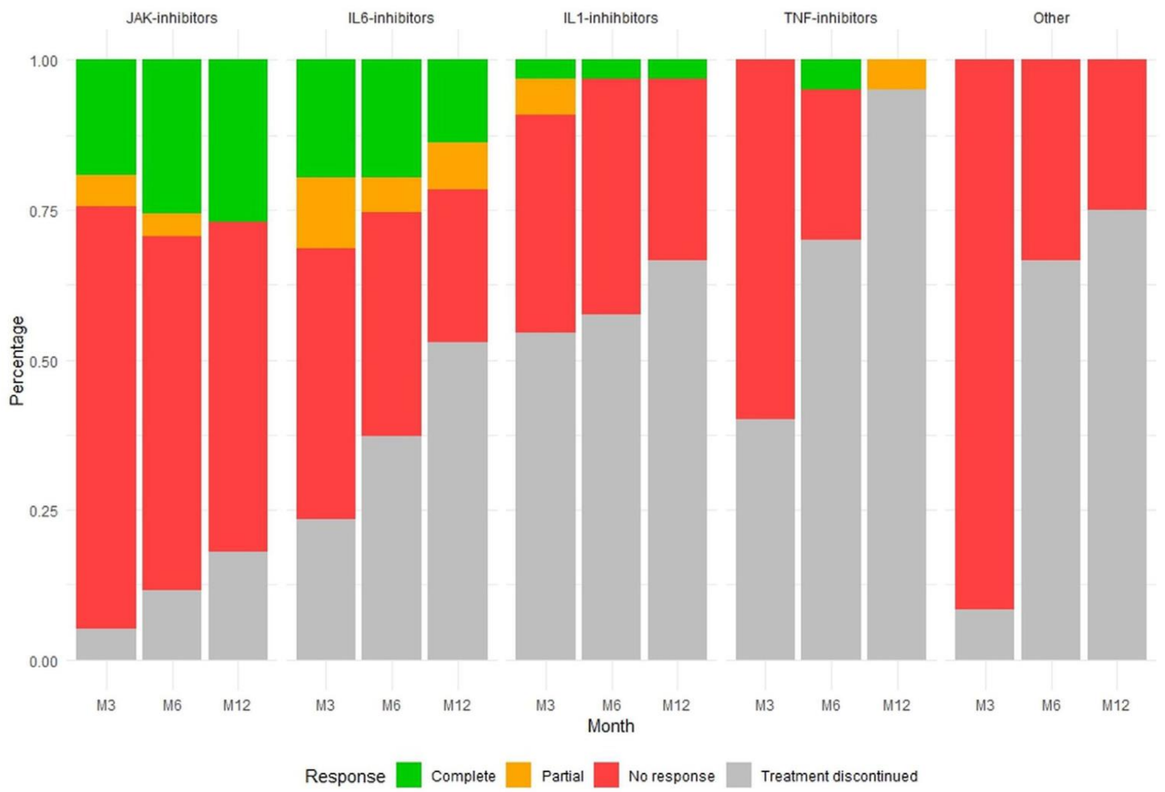
Heiblig M, et al. Blood 2022

Efficacy of anti-inflammatory treatments

Population: 110 VEXAS patients treated with at least one targeted therapy

Targeted Therapies Tested:
- **JAK inhibitors (JAKi)** – 40% of cases.
- **IL-6 inhibitors** – 26% of cases.
- **IL-1 inhibitors** – 17% of cases.
- **TNF-α blockers** – 10% of cases.
- **Other therapies** – 6% of cases (RTX, SEC)

Findings at 6 Months:
- **JAK inhibitors**: 30% response (complete or partial).
- **IL-6 inhibitors**: 26% response.
- **IL-1 inhibitors**: 9% response.
- **TNF-α blockers**: 0% response.
- **Other therapies**: 0% response



Complete response: clinical remission + CRP ≤10mg/L + PDN ≤10mg/day
Partial response: clinical remission + 50% reduction in CRP and PDN daily dose

Hadjadj J, et al. Efficacy and safety of targeted therapies in VEXAS syndrome: retrospective study from the FRENVEX. Ann Rheum Dis 2024

Safety of anti-inflammatory treatments - 1

High Risk of Infections
Data from the French VEXAS registry involving 74 patients and 133 serious infections.
•Common sites of infection:

- Lungs (59%)
- Skin (10%)
- Urinary Tract (9%)

Pathogens Identified:

- **Bacterial (52%)**: *Legionella pneumophila*, *Pseudomonas aeruginosa*.
- **Viral (30%)**: SARS-CoV-2, *Varicella Zoster*.
- **Fungal (15%)**: *Pneumocystis jirovecii*, *Aspergillus spp.*

Impact of Therapies:

- **JAK inhibitors** significantly associated with a higher risk of serious infections (3.84-fold increase).
- **Azacitidine** linked to higher rates of **fungal infections**.
- **Steroid dependency** and long-term use increased infection risk.

Key Findings:

- **Older age** (>75 years), **p.Met41Val mutation**, and use of **JAK inhibitors** are independent risk factors for serious infections.
- Possible **intrinsic immunodeficiency** in VEXAS syndrome.
- Careful management with **anti-infective prophylaxis** is crucial, especially when using JAK inhibitors.

De Valence B et al. Ann Rheum Dis. 2024

Safety of anti-inflammatory treatments - 2

Adverse Events (AEs)

- **JAK inhibitors** 46%

Infections, cytopenias, thrombosis

- **IL-6 inhibitors** 63%

Infections, cytopenia, local reactions

- **IL-1 inhibitors** 58%

Severe local/systemic reactions

- **TNF-α blockers** 50%

Cause, n (%)	Overall (n=194)	JAKi (n=78)	IL-6i (n=51)	IL-1i (n=33)	TNF-αi (n=20)	Others (n=12)
Discontinuation	114 (54)	22 (28)	35 (69)	26 (79)	20 (100)	11 (92)
Primary failure	62 (54)	9 (43)	16 (46)	14 (54)	14 (74)	9 (82)
Loss of efficacy	9 (8)	3 (14)	4 (11)	1 (4)	1 (5)	0 (0)
Serious adverse event	27 (24)	4 (19)	11 (31)	9 (35)	3 (16)	0 (0)
Death	10 (9)	4 (19)	3 (9)	2 (8)	1 (5)	0 (0)
Other	4 (4)	1 (5)	1 (3)	0 (0)	0 (0)	2 (18)

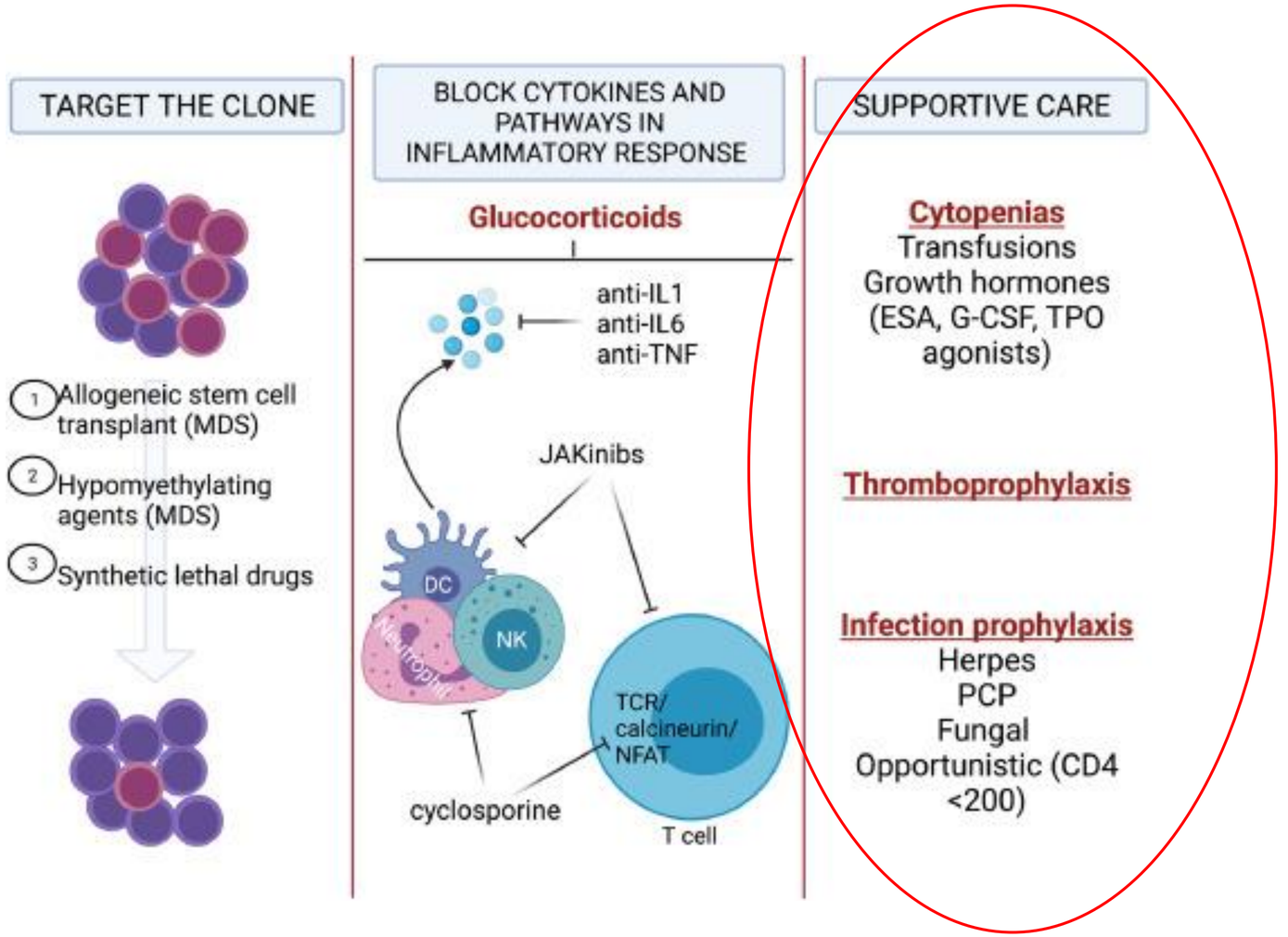
IL, interleukin; JAKi, Janus kinase inhibitor; TNF-i, tumour necrosis factor inhibitor.

Variable, n (%)	Overall (n=194)	JAKi (n=78)	IL-6i (n=51)	Anti-IL-1i (n=33)	Anti-TNF-αi (n=20)	Others (n=12)
Any adverse event	103 (53)	36 (46)	32 (63)	19 (58)	10 (50)	6 (50)
Infection	46 (24)	18 (23)	15 (29)	1 (3)	6 (30)	6 (50)
Cytopenia	36 (19)	18 (23)	15 (29)	3 (9)	0 (0)	0 (0)
Thrombosis	14 (7)	5 (6)	6 (12)	0 (0)	3 (15)	0 (0)
Cardiovascular	8 (4)	4 (5)	3 (6)	1 (3)	0 (0)	0 (0)
Cancer	2 (1)	1 (1)	0 (0)	0 (0)	1 (5)	0 (0)
Hepatitis	3 (2)	0 (0)	3 (6)	0 (0)	0 (0)	0 (0)
Minor reaction at site of injection	8 (4)	–	1 (2)	6 (18)	1 (5)	0 (0)
Major reaction at site of injection	9 (5)	–	1 (2)	7 (21)	1 (5)	0 (0)
Minor systemic reaction after treatment	14 (7)	3 (4)	3 (6)	4 (12)	2 (10)	2 (17)
Major systemic reaction after treatment	3 (2)	0 (0)	2 (4)	0 (0)	1 (5)	0 (0)

JAK inhibitors (Ruxolitinib) highest efficacy in controlling VEXAS symptoms, including steroid-sparing effects
IL-6 inhibitors reasonable alternative for patients who cannot tolerate JAK inhibitors.
IL-1 inhibitors and TNF-α blockers showed limited effectiveness and higher rates of treatment discontinuation.

De Valence B et al. Ann Rheum Dis. 2024

Treatment approaches in VEXAS syndrome



Maël Heiblig et al. Seminars in Hematology 2021

Thrombocytopenia

- Inflammatory component: improvement with the use of corticosteroids and/or anti-inflammatory agents
- Possible treatment with TPO agents? Currently no data are available in VEXAS – data from lower risk MDS

Consider thromboembolic risk in VEXAS

Eltrombopag for Low-Risk Myelodysplastic Syndromes With Thrombocytopenia: Interim Results of a Phase II, Randomized, Placebo-Controlled Clinical Trial (EQOL-MDS)

Oliva, J Clin Oncol 2023

Neutropenia

Increased risk of infections

→ Consider G-CSF in cases of severe infections

Monocytopenia and lymphopenia

Increased risk of infections (Atypical infections)

→ **Anti microbial prophylaxis**

Heiblig, Seminars in Hematology 2021

Treatment of Anemia

Anemia is associated with impaired QoL

- ***Inflammatory component:*** improvement with steroids or anti-inflammatory agents

  ❗ Certain medications may worsen anemia (es. JAK-i)

- ***Transfusions:*** Personalized transfusion support based on symptoms and comorbidities is recommended to improve quality of life

Jansen, Br J Haematol 2003; Carson Ann Intern Med 2012

ESA and Luspatercept in VEXAS

2674 Clinical Efficacy of Erythroid Stimulating Agent (ESA) and Luspatercept (LUSPA) in Vexas Syndrome with or without Myelodysplastic Syndrome (MDS) : A Multicenter Retrospective Study By the Frenvex Group

Program: Oral and Poster Abstracts
Session: 503. Clonal Hematopoiesis, Aging, and Inflammation: Poster II

Sunday, December 8, 2024, 6:00 PM-8:00 PM

ASH 2024
82% concomitant MDS, 83.8% IPSS-M lower risk

Mael Heiblig, MD, PhD[1*], *Vincent Jachiet*[2*], *Jerome Hadjadj, MD, PhD*[3,4*], *Lin Pierre Zhao, MD, PhD*[5*], *Thibault Comont*[6*], *HervÃ© Lobbes*[7*], *Valentin Lacombe*[8*], *Anne Blandine Boutin*[9*], *Joris Galland*[10*], *Yesim Dargaud, MD, PhD*[11], *Benjamin Terrier, MD, PhD*[12*], *Sophie Georgin-Lavialle*[13*], *Pierre Fenaux, MD*[14,15,16] *and Arsene Mekinian, MD, PhD*[2*]

ESA n = 45
NTD 31% – LTD 16%– HTB 29%
HI-E 38% at 16 w (NTD 43.7%) – favorable impact of ANC and alternative UBA1 mutations (no prognostic role TB and EPO levels)
Median DOR 35.2 mo

Luspa n = 8 (ESA failure), HI-E 50%, DOR > 10 mo

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY
British Society for Haematology
Listening • Learning • Leading

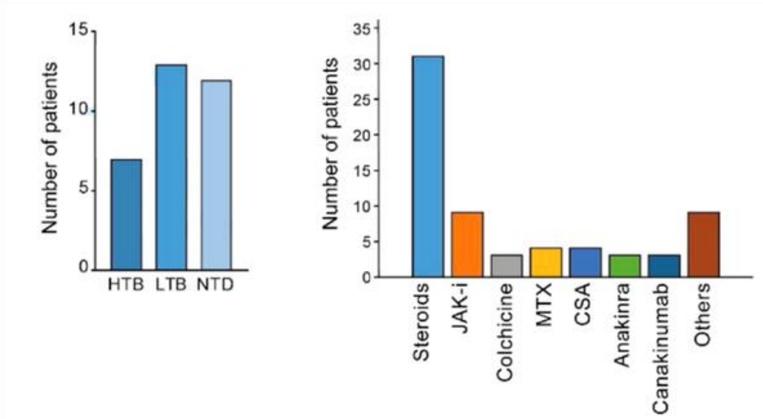
RESEARCH LETTER | Open Access

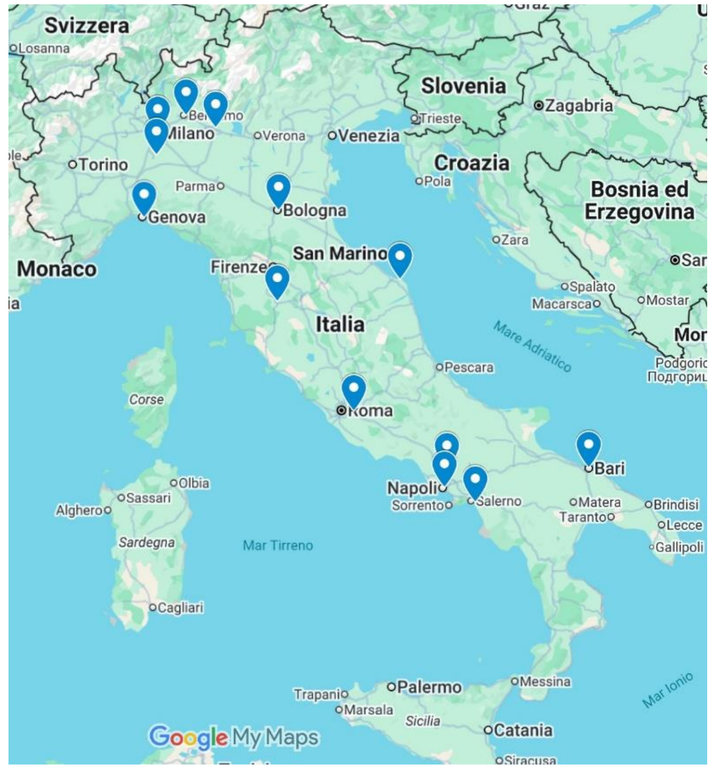
Erythroid-stimulating agents in VEXAS syndrome: A retrospective study from an Italian multicentre cohort

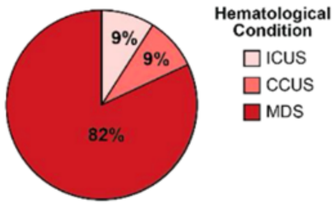
E. Diral, C. Campochiaro, G. Furnari, F. Moretti, J. Ferrari, C. Elena, G. Battipaglia, S. Barbato, A. Vitale, M. Frigeni, F. Crisafulli, M. Frassi, C. Papayannidis, A. D. Romagnoli, C. Cattaneo ... See all authors

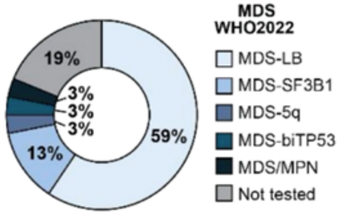
First published: 13 May 2025 | https://doi.org/10.1111/bjh.20157 | Citations: 2

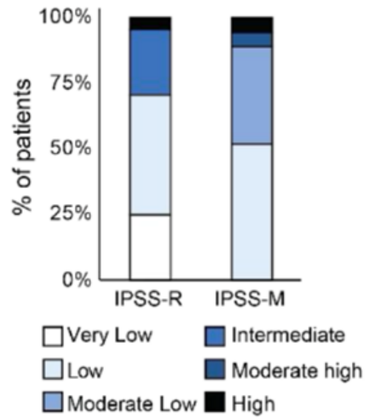
Study population	*n* = 32
Age, median (IQR)	66 (64–73)
Male sex, *n* (%)	32 (100)
Clinical manifestations, *n* (%)	
Constitutional symptoms	22 (69)
Cutaneous	21 (66)
Osteoarticular	17 (53)
Ocular	9 (28)
Pulmonary	7 (22)
Vasculitis	7 (22)
Chondritis	5 (16)
Haemoglobin (g/dL), median (IQR)	9.2 (8.25–9.65)
MCV (fL), median (IQR)	104.8 (99.5–109.6)
Platelets ($\times 10^9$/L), median (IQR)	140 (92–217.5)
Neutrophils ($\times 10^9$/L), median (IQR)	2.17 (1.05–3.5)
C-reactive protein (mg/L), median (IQR)	15.8 (7.6–53)
Endogenous EPO (mU/mL), median (IQR)	124 (57.4–201)
Not available, *n* (%)	10 (31)

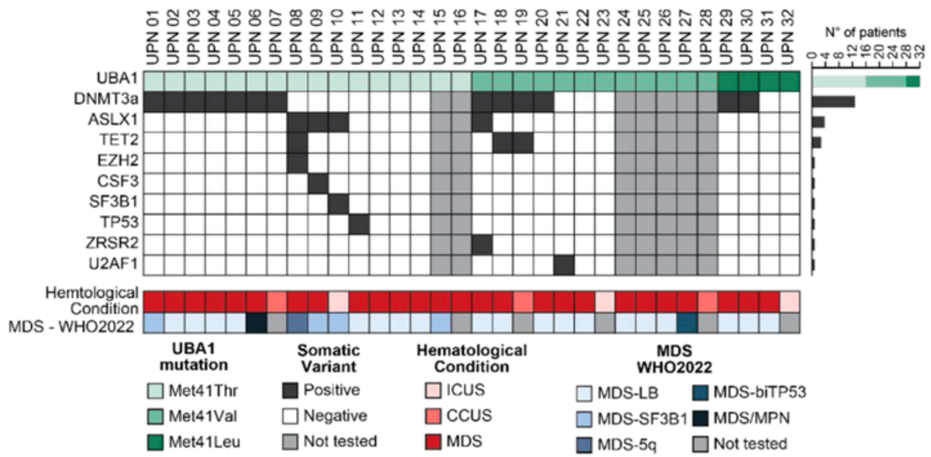












No correlation with:
- MDS vs no MDS
- IPSS-R/IPSS-M risk categories;
- Baseline Hb levels
- Transfusion dependence;
- UBA1 clone size
- Baseline CRP levels

Efficacy

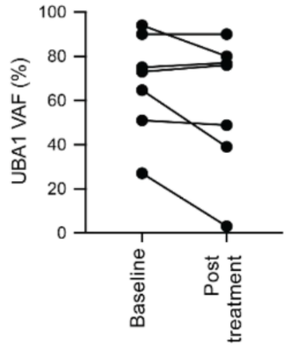
HI-E was achieved in 59% of patients

In multivariate analysis, only lower EPO levels correlated with response [OR 0.985 (95%CI=0.972 – 0.999), p=0.033].

Median duration of response: 13 months.

6 responders (31%) lost response after a median of 14 months.

UBA1 VAF remained stable compared to baseline



Diral E et al, BJH 2025

Safety

During ESAs treatment, only 4 patients experienced DVT (21%).

Thrombosis, *n* (%)	19 (59)
Before VEXAS diagnosis	12 (63)
After VEXAS diagnosis	7 (37)
Thrombosis correlation with ESA, *n* (%)	
Prior to ESA start	12 (63)
During ESA treatment	4 (21)
After ESA discontinuation	3 (16)

Outcomes

With a median follow up of 22.8 months, 24 patients were still alive (75%).

7/8 deaths occurred in patients who either lost or never achieved a response, and were transfusion-dependent at the time of ESAs discontinuation.

ESAs are effective and safe in VEXAS patients.

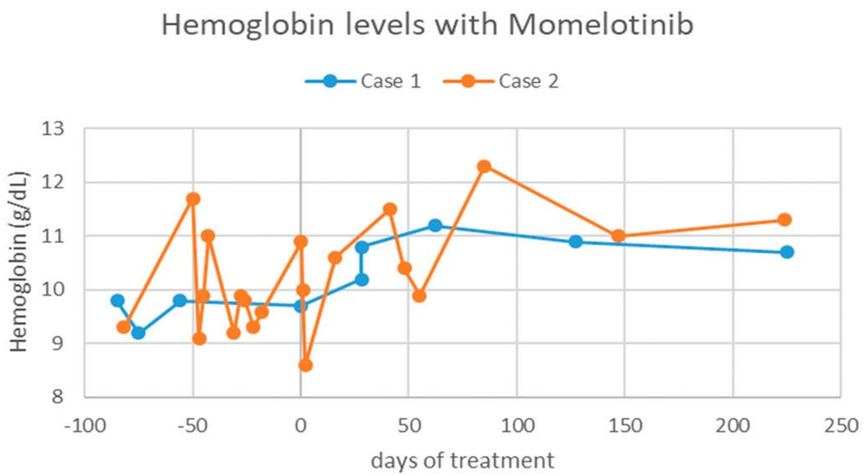
Diral E et al, BJH 2025

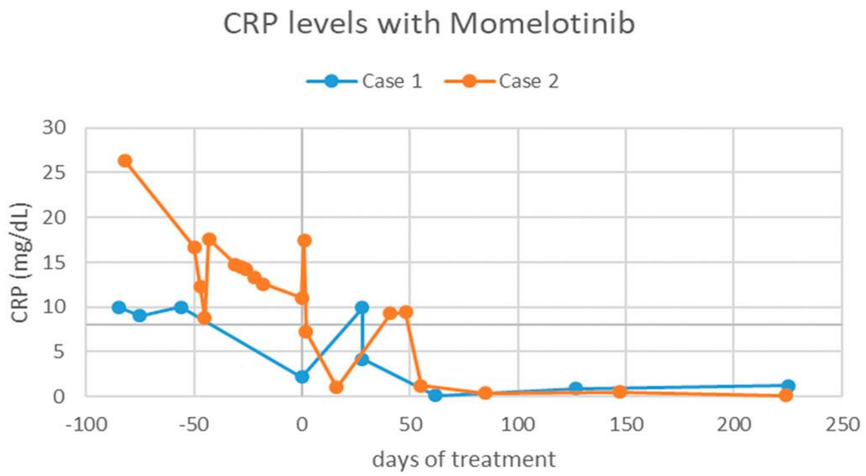
CASE REPORT | Open Access

Momelotinib Is Effective in Treatment for VEXAS Syndrome: Two Cases Within the AGMT Austrian Myeloid Registry

Dominik Kiem, Michael Leisch, Ildiko Toth, Marie-Christina Mayer, Lisa Pleyer, Richard Greil, Alexander Egle, Thomas Melchardt

First published: 29 June 2025 | https://doi.org/10.1111/ejh.14445



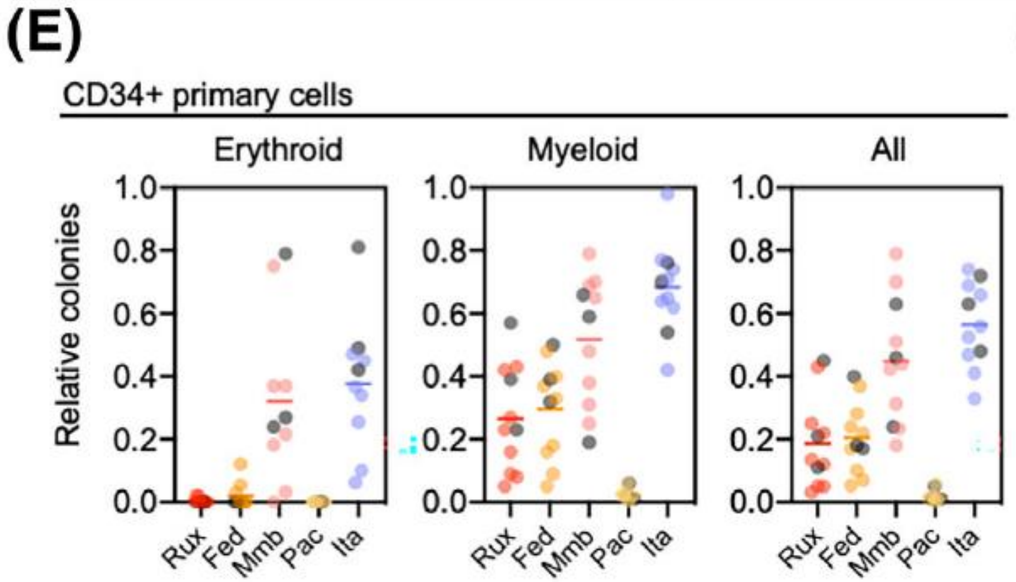


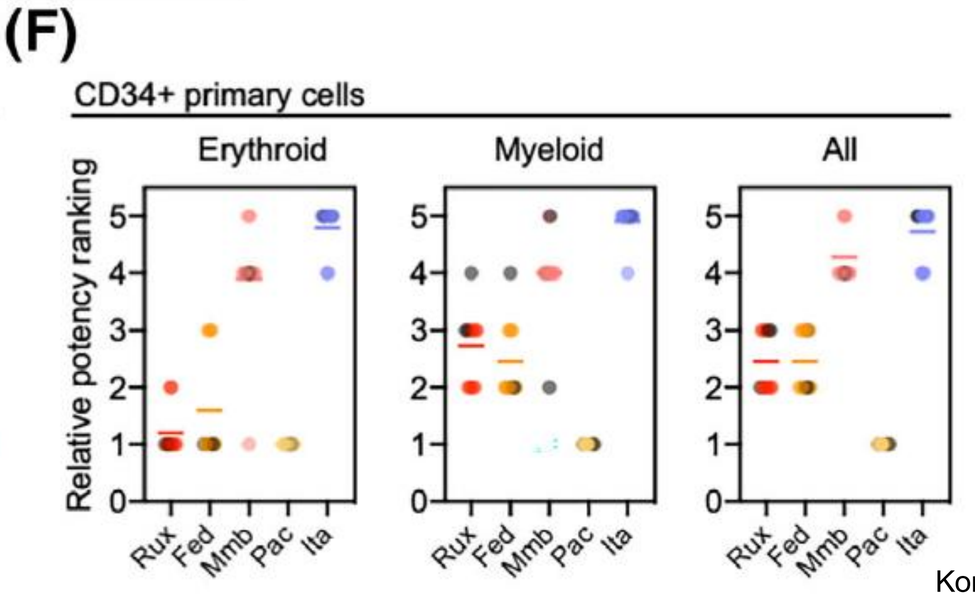
JAK2: hematopoiesis

Inhibitor	Targets JAK2	Additional target(s)
Ruxolitinib	Yes	JAK1
Fedratinib	Yes	FLT3
Momelotinib	Yes	JAK1, ACVR1, IKBKE, TBK1
Pacritinib	Yes	FLT3, IRAK1, CSF1R
Itacitinib	No	JAK1

JAK1: inflammation (IFNγ)

ACVR1: hepcidin production (liver), inhibition of iron absorption (BMP6)
IKBKE, TBK1: innate immunity (IFN type I)





Kong et al. (2023) DOI: 10.1002/ajh.26935

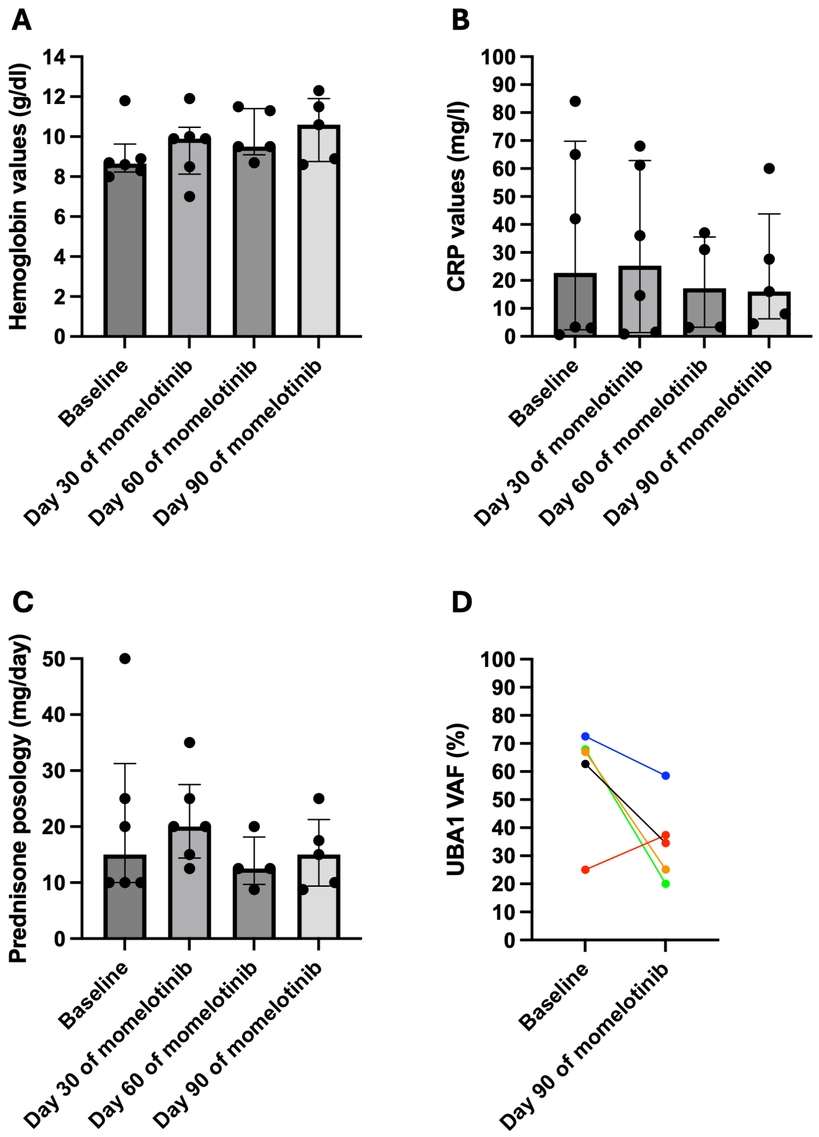
Median age at diagnosis	
Years (IQR)	67 (66-70)
Type of UBA1 mutation, N (%)	
Met41Val	3/6 (50%)
Met41Leu	2/6 (33%)
Splice site mutation ex3	1/6 (17%)
Concomitant MDS	
N (%)	6/6 (100%) – lower risk in all cases
Median glucocorticoid dose	
Mg/die (IQR)	15 (10-23.75)
Number of previous therapies	
Median (IQR)	2.5 (1.75 – 3.25)
Previous JAKi	
N (%)	4/6 (67%)
Concomitant ESA treatment at baseline	
N (%)	4/6 (67%)
Median ESA (epoetin alfa) dosage	
UI/w (IQR)	40.000 (40-50.000)

HSR experience with momelotinib

N = 6 patients with no other available treatment

Off label use Authorized by Rare Disease Center (Mario Negri)

2026 EHA abstract



Initial MMB dose = 200 mg daily.

Reduction/discontinuation:
1 pt MMB discontinued by day 30 for subjective intolerance
1 dose reduction (100 mg daily) for DDIs interactions with concomitant medications.

Infections:
3/6 pts experienced respiratory tract infections requiring admission in two cases.

Thrombosis: no.

Disease flares:
1 pt by day 30 requiring GCs increase

2026 EHA abstract

MMB seems to be safe (no Major infections, no thrombosis)

Possibility of ameliorating Hb levels

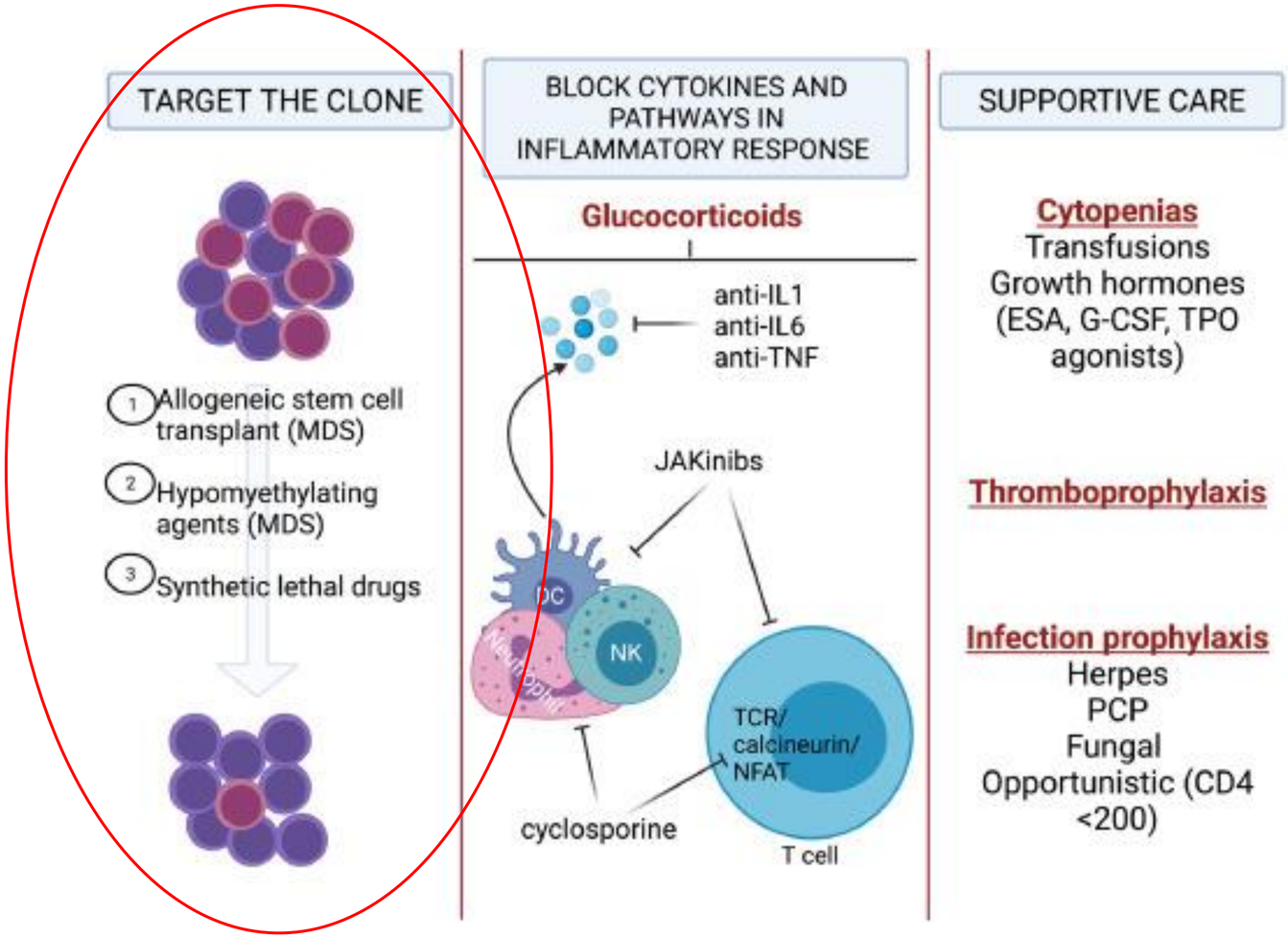
Good control of inflammation (only 1 disease flare, reduction in CRP levels and GCs at 3 months)

Longer follow up needed (further GCs decrease at six months, maintenance of response, confirm the reduction of UBA1 VAF)

Physician opinion

Materiale Formativo/di Aggiornamento Scientifico ad esclusivo uso interno

Treatment approaches in VEXAS syndrome



Maël Heiblig et al. Seminars in Hematology 2021

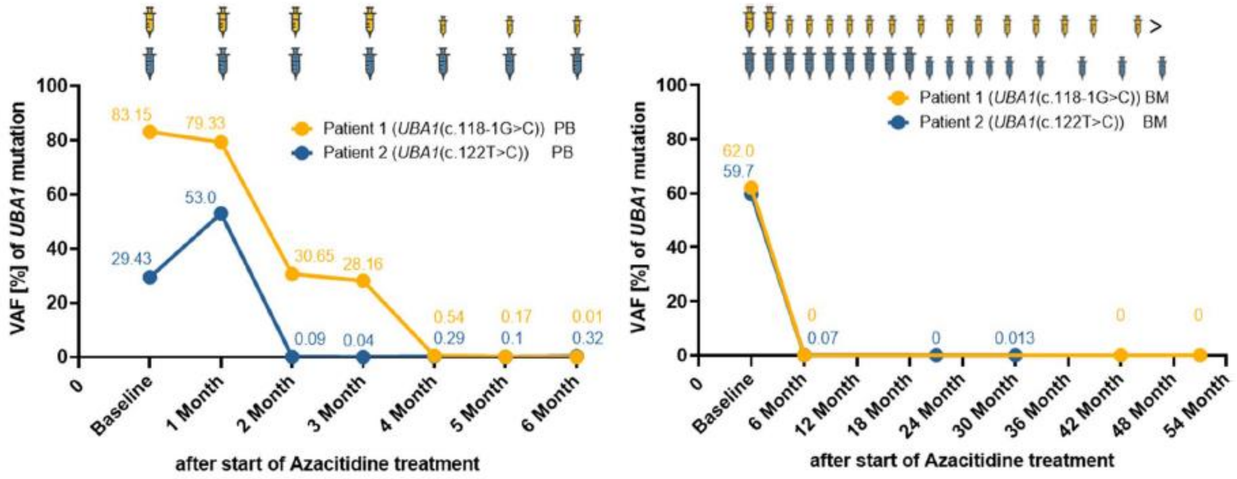
Treatment with 5-azacytidine

Reference	N of pts	Type of cytopenia	Previous treatments	Response to azacytidine	N° of cycles, FUP
Kataoka et al, Int J Hematol 2023	1	MDS	GC and colchicine	SD hemato; response on inflammation (GC 10 mg/d)	6 cycles – no data on FUP
Escoda et al, Rev Neurol 2022	1	MDS	GC and IVIG	Hemato and inflammatory response	***6 + 6 cyles of 5-aza***
Mekinian et al, Leuk 2022	12	MDS	GC and median n° IST = 2	59% response – reduction/STOP GC	Usually > 6 cycles – OS 1y 82%, median OS not reached
Manzoni et al, Clin Hematol Int 2022	1	MDS	None	Treated with aza for MDS-MLD → transfusion independency	2017 to 2021 → Lost response and died 6 months later
Cordts et al, Rheumatology 2022	1	MDS	GC and 2 lines of IST	Trasfusion independency, response on inflammation (GC < 10 mg/d)	3 cycles – no data on FUP
Raaijmakers et al, Hemasphere 2021	3	MDS/CCUS (1/2)	GC and median n° IST = 3	66% response (GC < 10 mg/d)	Median n° of cycles = 3 – 100% OS at last FUP
Comont et al, Br J Hematol 2022	57	MDS/no MDS (50/7)	GC and median n° IST = 2	76% response (100% in pts w/o MDS)	Median n° of cycles = 11 – 72% OS after 29 months FUP
Estes et al, Cureus 2023	1	MDS	GC and 3 lines of IST	No response	NA data on n° cycles and FUP
Johansen et al, Rheumatology 2023	1	NA	GC and 5 lines of IST	Complete response (GC < 10 mg/d)	9 cycles – alive 10 months after 5-aza discontinuation
Sockel et al, Ann Hematol 2024	2	MDS	GC and 3 lines of IST	100% complete response (GC < 10 mg/d)	2019 – 2023 – 100% OS at last FUP
Trikha et al, Haematologica 2024	11 (data on 4 pts)	MDS 4/4	GC and 1 line of IST	100% complete response (GC < 10 mg/d)	Median n° of cycles = 11 - 100% OS at 3 year FUP
Pereira de Costa et al, Front Immunology 2024	1	ICUS	GC and ruxolitinib	Complete response	9 cycles – alive at last FUP
Aalbers et al, Hemasphere 2024	6	MDS/ICUS (4/2)	GC and median n° IST = 2	83% complete response	Median n° of cycles = 5 – for 3 patients, median FUP of 31 months

Data on UBA 1 clone monitoring

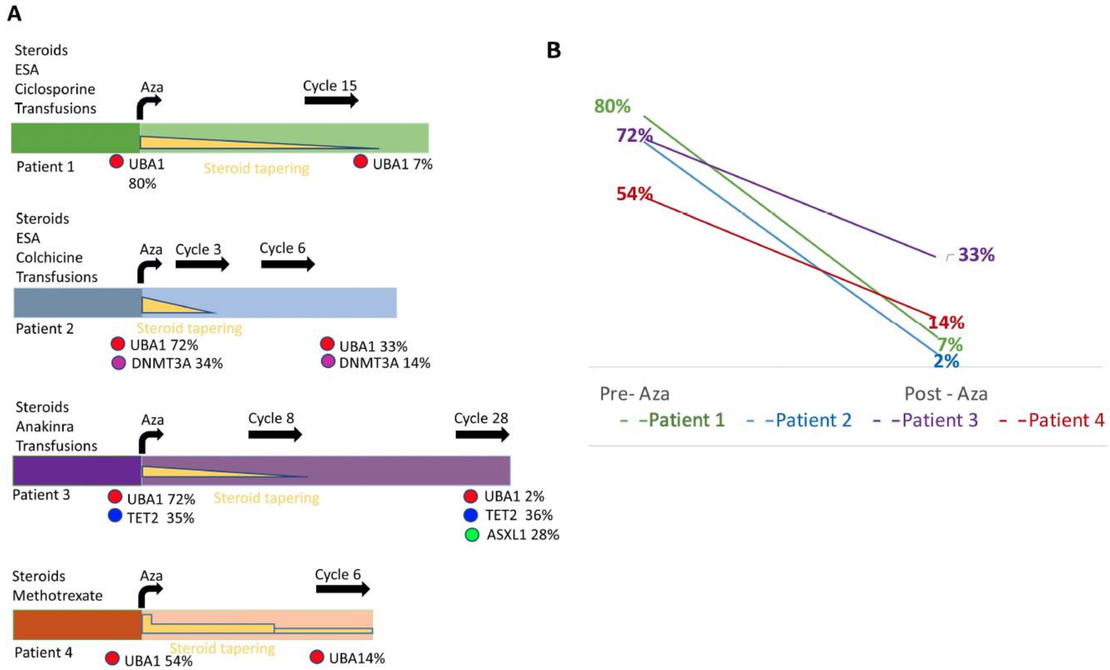
Reference	N of pts	
Manzoni et al, Clin Hematol Int 2022	1	Loss of response to 5-aza due to increase in UBA1 VAF
Raaijmakers et al, Hemasphere 2021	3	2/3 patients with sustained suppression of UBA1 clone at 4,5 years from 5-aza discontinuation
Comont et al, Br J Hematol 2022	57	Data on UBA1 monitoring in 6 responders: negativization in 4/6 pts, significant decrease in 2/6 pts
Johansen et al, Rheumatology 2023	1	Negative UBA1 10 months after 5-aza discontinuation
Sockel et al, Ann Hematol 2024	2	Negative UBA1 at 6 and 21 months from 5-aza start → persistently negative UBA1 at 54 months FUP
Trikha et al, Haematologica 2024	11 (data on 4 pts)	Reduction in UBA 1 VAF
Pereira de Costa et al, Front Immunology 2024	1	Negative UBA1 after 9 cycles of 5-aza
Aalbers et al, Hemasphere 2024	6	5 responding patients UBA 1 < 5% («genetic response») – maintained during follow up

High percentage of genetic response – significant decrease in VAF / negativization of UBA1

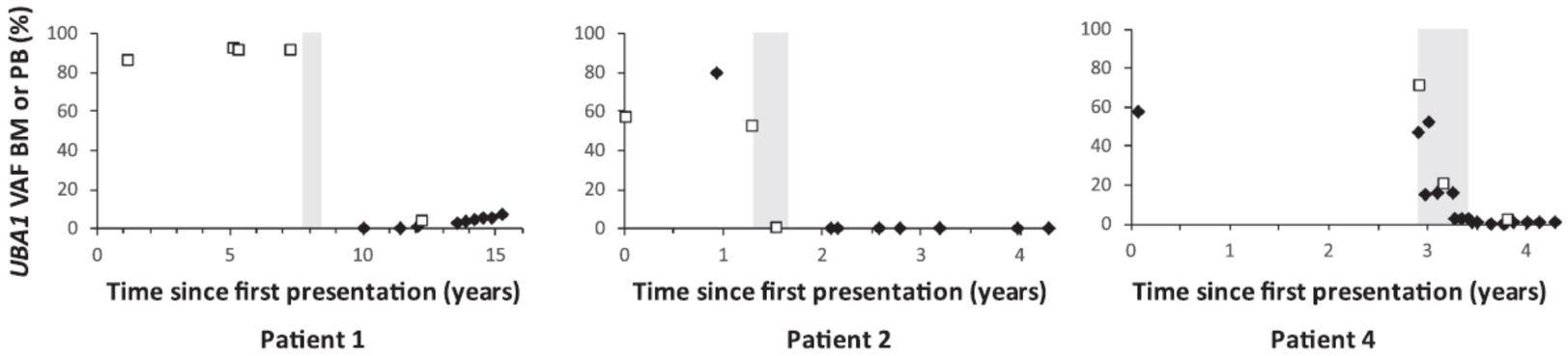


	Baseline	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month	21 Month	30 Month	35 Month	42 Month	51 Month
Patient 1 PB	83.2	79.3	30.7	28.2	0.54	0.17	0.01	-	-	-	-	0
Patient 1 BM	62	-	-	-	-	-	0	-	-	-	0	0
Patient 2 PB	29.4	53.0	0.09	0.04	0.29	0.01	0.32	-	-	0	-	-
Patient 2 BM	59.7	-	-	-	-	-	0.07	0	0.013	-	-	-

Sockel et al, Ann Hematol 2024



Trikha et al, Haematologica 2024



Aalbers et al, Hemasphere 2024

blood® Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Efficacy and safety of azacitidine for VEXAS syndrome: a large-scale retrospective study from FRENVEX

Vincent Jachiet,[1] Olivier Kosmider,[2,*] Maxime Beydon,[3,*] Jérôme Hadjadj,[1] Lin-Pierre Zhao,[4] Vincent Grobost,[5] Valentin Lacombe,[6] Guillaume Le Guenno,[5] Yann Nguyen,[7] Jean-Benoît Arlet,[8] Jérémie Dion,[9] Maël Heiblig,[10] Alice Garnier,[11] Maxime Samson,[12] Achille Aouba,[13] Sylvain Thépot,[14] Sophie Dimicoli-Salazar,[15] Fabien Dutasta,[16] Benoît Faucher,[17] Estibaliz Lazaro,[18] Véronique Morel,[19] Antoine Néel,[20] Roderau Outh,[21] Holy Bezanahary,[22] Julien Rossignol,[23] Anne-Sophie Alary,[24] Audrey Bidet,[25] Pauline Blateau,[26] Anne Bouvier,[27] Guilaine Boursier,[28] Matthieu Decamp,[29] Benjamin Lebecque,[30] Yannick Le Bris,[31] Pierre Sujobert,[32] Alice Marceau-Renaut,[33] Cédric Pastoret,[34] David Rizzo,[35] Nathalie Boiret-Dupré,[30] Lara Boucher,[2] Stéphanie Dulucq,[25] Franck Genevieve,[27] Cassandra Jadeau,[35] Pierre Lemaire,[36] Romain Vazquez,[2] Jean-Baptiste Rieu,[37] Olivier Fain,[1] Sophie Georgin-Lavialle,[38] Lucie Rigolot,[37] Lise Larcher,[36] Pierre Hirsch,[39] Benjamin Terrier,[40] Pierre Fenaux,[4,†] Arsène Mékinian,[1,†] and Thibault Comont,[9] on behalf of FRENVEX

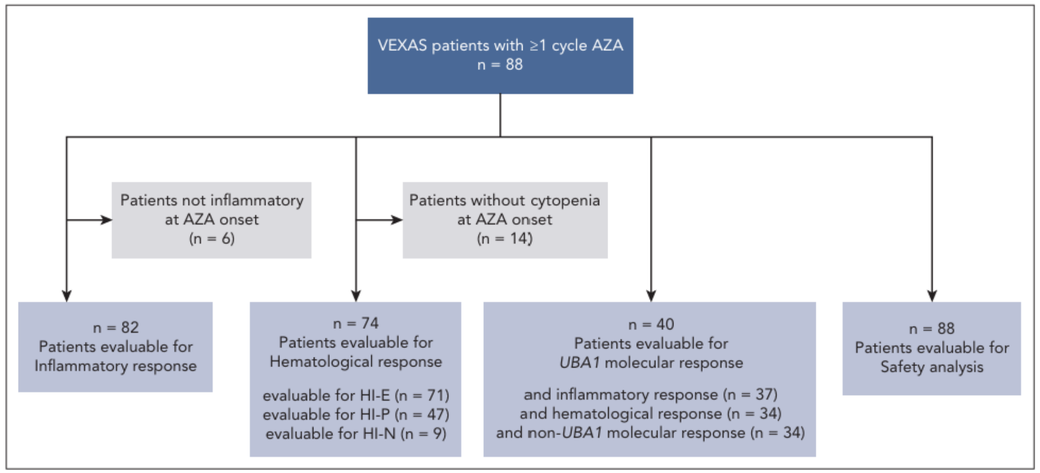


Figure 1. Study flowchart. Flowchart illustrating the number of patients evaluable for inflammatory, hematological, and molecular (*UBA1* and non-*UBA1*) responses, as well as safety analysis. Cytopenia is defined as anemia (hemoglobin of <10 g/dL), neutropenia (absolute neutrophil count of <1 × 10^9/L), or thrombocytopenia (platelet count of <100 × 10^9/L).

Table 1. Baseline characteristics of patients with VEXAS syndrome treated with AZA

Characteristic	Overall (N = 88)	MDS (n = 70)	Non-MDS (n = 18)	*P* value
Male sex	87 (99)	69 (99)	(100)	>.99
Age at first VEXAS syndrome manifestation, y	67.4 (51.3-85.6)	66.7 (51.3-85.6)	69.0 (57.1-81.6)	.22
Age at AZA onset, y	71.5 (54.5-86.5)	71.3 (54.5-86.5)	72.2 (60.6-86.0)	.28
Delay from first symptoms to AZA onset, y	2.7 (0.2-15.5)	2.2 (0.2-15.5)	3.2 (0.7-7.3)	.50
Type of *UBA1* mutation				.49
c.122T>C (p.Met41Thr)	36 (41)	31 (44)	5 (28)	
c.121A>G (p.Met41Val)	24 (27)	18 (26)	6 (33)	
c.121A>C (p.Met41Leu)	19 (22)	15 (21)	4 (22)	
Other*	9 (10)	6 (9)	3 (17)	
UBA1 VAF, %†	67 (20-100)	66 (20-100)	72 (30-90)	.61
Clinically active disease at AZA onset	79 (90)	63 (90)	16 (89)	>.99
Clinical manifestations before AZA onset				
Skin lesions	75 (85)	58 (83)	17 (94)	.29
Fever	67 (76)	51 (73)	16 (89)	.22
Musculoskeletal involvement	62 (70)	50 (71)	12 (67)	.69
Thrombosis	56 (64)	47 (67)	9 (50)	.18
Chondritis	54 (61)	40 (57)	14 (78)	.11
Ocular involvement	49 (56)	38 (54)	11 (61)	.60
Lung involvement	36 (41)	27 (39)	9 (50)	.38
Laboratory tests at AZA onset				
Hemoglobin, g/dL	8.8 (5.2-14.7)	8.8 (5.2-14.0)	8.7 (5.7-14.7)	.69
Platelets, ×10^9/L	94 (5-440)	90 (5-440)	108 (10-260)	.80
Neutrophils, ×10^9/L	2.7 (0.3-32.0)	2.7 (0.3-32.0)	2.8 (0.8-11.0)	.86
CRP‡	52 (1-411)	53 (2-411)	46 (1-150)	.30
RBC transfusion dependence	46 (52)	39 (56)	7 (39)	.22
Low transfusion burden	10 (11)	10 (14)	0 (0)	
High transfusion burden	36 (41)	29 (41)	7 (39)	
Bone marrow features				
Dysplasia	68 (77)	70 (100)	0 (0)	<.001
Bone marrow blasts (%)	2.0 (0.0-10.0)	2.0 (0.0-10.0)	0.0 (0.0-3.0)	<.001
Vacuoles§	67 (99)	52 (98)	15 (100)	>.99
Cytogenetics, abnormal karyotype‖	23 (26)	19 (28)	4 (22)	.77

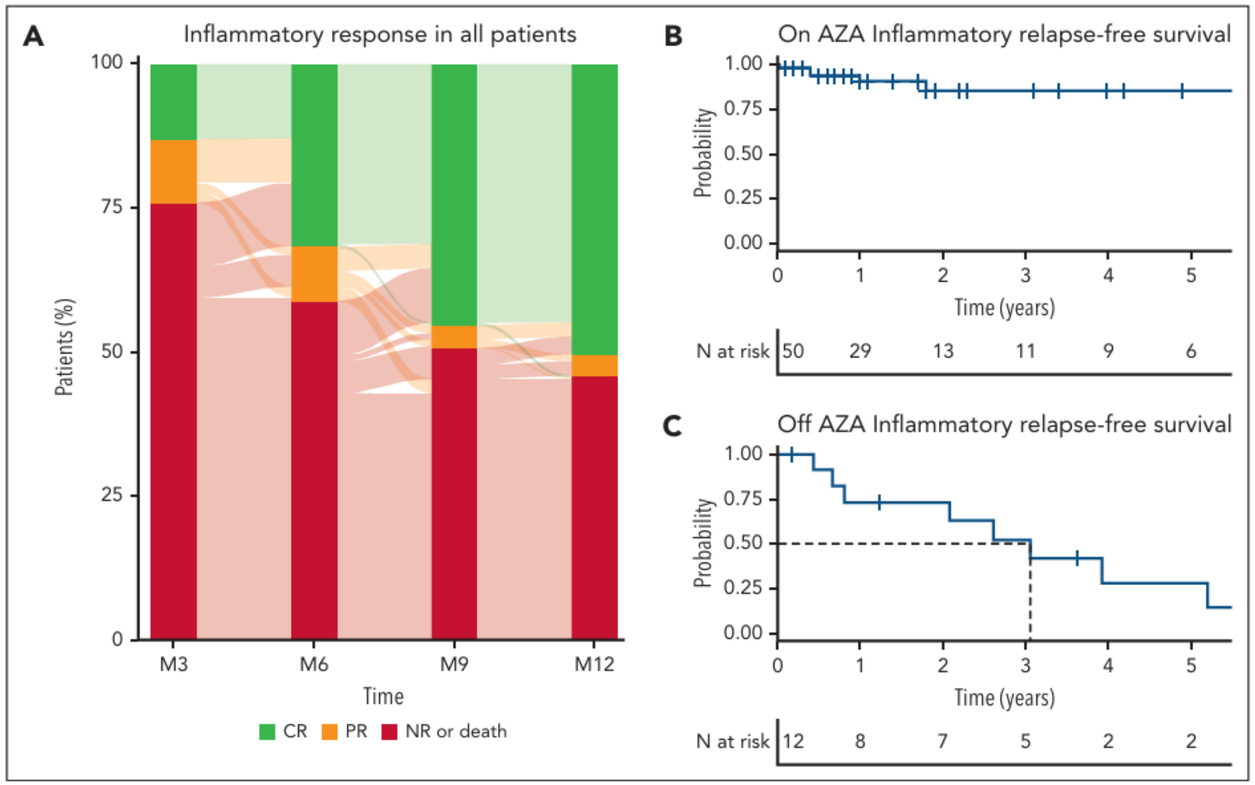


Figure 2. Inflammatory response over time in patients with VEXAS syndrome treated with AZA. (A) Sankey plot showing the distribution and evolution of inflammatory response categories over time at months 3 (M3), 6 (M6), 9 (M9), and 12 (M12). Categories include complete response (CR) in green, partial response (PR) in orange, and nonresponse (NR) or AZA stopped for failure or death in red. (B) Kaplan-Meier curve showing inflammatory relapse-free survival (RFS) in patients who achieved an inflammatory response and remained on AZA therapy (n = 50). The curve starts at the time of achieving an inflammatory response. The 5-year RFS was 85% (95% CI, 73-99). The number at risk is displayed below the x-axis. (C) Kaplan-Meier curve showing RFS after AZA discontinuation in patients who achieved an inflammatory response (n = 12). The curve starts at the time of AZA discontinuation. The dashed line indicates a median RFS of 3.1 years (95% CI, 2.1-5.2) after AZA discontinuation. The number at risk is displayed below the x-axis.

Table 2. Hematological responses in patients with VEXAS syndrome treated with AZA

Response	Overall	MDS	Non-MDS	*P* value
Overall hematological response	51/74 (69%)	41/60 (68%)	10/14 (71%)	>.99
Erythroid response				
HI-E achieved	49/71 (69%)	39/57 (68%)	10/14 (71%)	>.99
Among NTD patients at AZA onset	18/25 (72%)	12/18 (67%)	6/7 (86%)	.63
Among LTB patients at AZA onset	4/10 (40%)	4/10 (40%)	0/0 (0%)	>.99
Among HTB patients at AZA onset*	27/36 (75%)	23/29 (79%)	4/7 (57%)	.33
RBC transfusion independence achieved†	30/46 (65%)	26/39 (67%)	4/7 (57%)	.68
Platelet response				
HI-P achieved	36/47 (77%)	32/40 (80%)	4/7 (57%)	.33
Neutrophil response				
HI-N achieved	7/9 (78%)	6/8 (75%)	1/1 (100%)	>.99

Jachiet et al, Blood 2025

Figure 3. Baseline and follow-up *UBA1* VAF according to inflammatory response. Baseline and follow-up *UBA1* VAF (%) in patients categorized by their inflammatory response: NR (red), PR (orange), and CR (green). Solid lines represent patients with a *UBA1* VAF reduction of <25%, whereas dashed lines indicate reductions of ≥25%. CR, complete response; NR, nonresponse; PR, partial response.

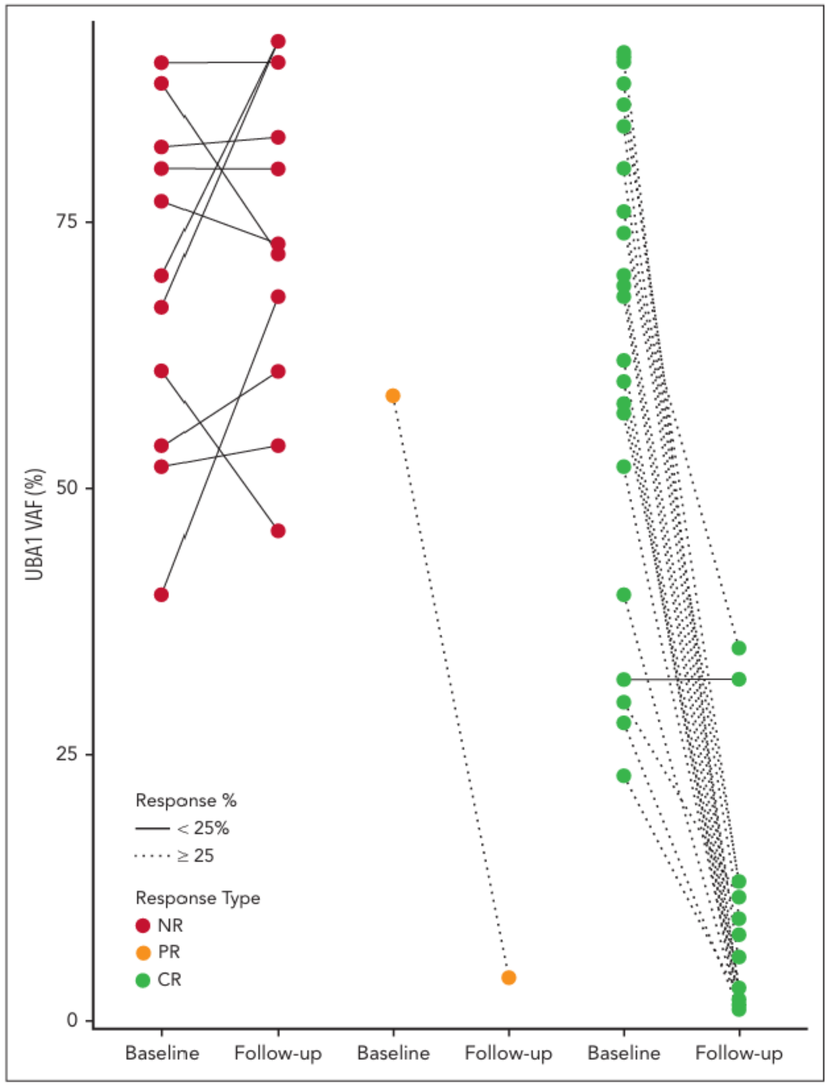


Table 3. ADRs in patients with VEXAS syndrome treated with AZA

Event	n (%) or median (range)
Total ADRs	107
Patient with at least 1 ADR	53/88 (60%)
Number of ADRs per patient	1.0 (1.0-7.0)
Infectious ADRs	56
Patients with infectious ADR	30/88 (34%)
Number of infectious ADRs per patient	1.0 (1.0-5.0)
Cure of first infectious ADR	
Within 1-12 cycles	48/56 (86%)
including 1-3 cycles	34/56 (61%)
After 12 cycles	8/56 (14%)
Infection type	
Not documented	7/56 (13%)
Documented	49/56 (88%)
Bacterial	38/49 (78%)
Viral	7/49 (14%)
Fungal	4/49 (8%)
Infection site	
Pulmonary	21 (38%)
Digestive	11 (20%)
Bacteremia	9 (16%)
Urinary	6 (11%)
Cutaneous	3 (5%)
Other sites*	6 (11%)
Patient condition at time of infection	
Neutrophil count of $<0.5 \times 10^9$/L	10/56 (18%)
Glucocorticoids at >10 mg/d	49/56 (88%)
Clinically active disease	43/56 (77%)
Noninfectious ADRs	51
Patients with noninfectious ADRs	36/88 (41%)
Number of noninfectious ADRs per patient	1.0 (1.0-4.0)
Cytopenia	43/51 (84%)
Neutropenia	25/43 (58%)
Anemia	11/43 (26%)
Thrombocytopenia	7/43 (16%)
Immunoallergic†	3/51 (6%)
Other‡	5/51 (10%)

Jachiet et al, Blood 2025

HSR experience with 5-aza

5-aza treatment (n = 5)

- 1 discontinuation for hypersensitivity pneumonia, actually patient treated with PDN/ruxo/ESA
- 1 discontinuation for diagnosis of solid tumor
- 1 discontinuation for genetic response (off treatments)
- 2 ongoing treatments

Alive: 9/12 pts – no 5-aza related deaths

2016	2017	2018	2019	2021
STEROIDS	ANAKINRA + steroids	TOCILIZUMAB ↓ CANAKINUMAB+ steroids	CANAKINUMAB + CYCLOSPORINE A + steroids + ESA	Diagnosis of VEXAS SYNDROME UBA1 Met41Thr
Onset of inflammatory symptoms	Steroid dependence	Shift to TCZ due to skin reaction Shift to CNK due to neutropenia	Persistent inflammatory symptoms & Low risk MDS diagnosis (IPSS-R)	Persistent inflammatory reactivations Loss of response to ESA

- ✓ Severe transfusion dependent anemia
- ✓ Worsening thrombocytopenia
- ✓ Severe iron overload
- ✓ Frequent inflammatory events and steroid dependence
- ✓ Dyspnea
- ✓ Decreased QoL

Ruxolitinib start in Feb 2023

Maximum dosage 25 mg/day

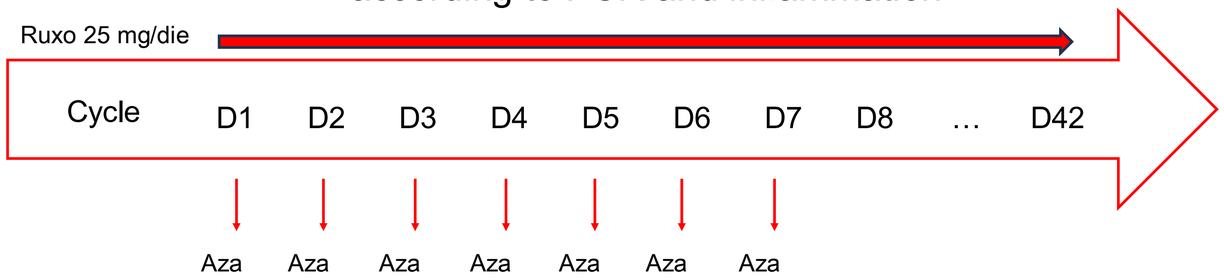
↓

- ✓ Increased PLT counts
- ✓ Biochemical and clinical complete response of inflammation
- ✓ Steroid dose reduction

But

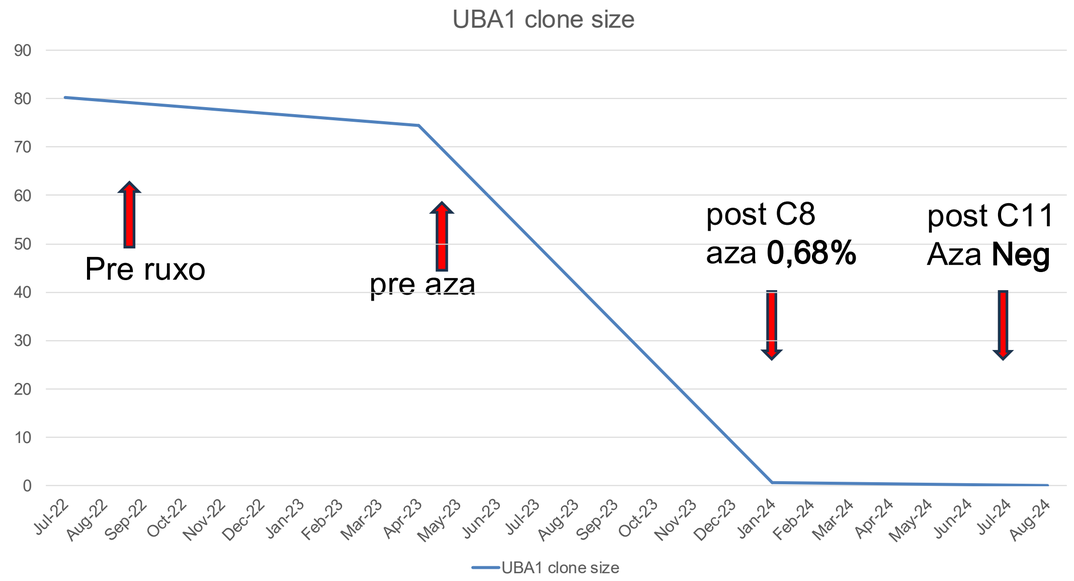
Persistence of transfusion dependent anemia

Ruxo and steroid reductions
according to PCR and inflammation



5-azacitidine start in June 2023

(in association with RUXO and steroids)



September 2024 11 cycles of 5-azacitidine

- ✓ STOP ruxo and steroids
- ✓ PLT > 100.000/mmc
- ✓ Normal Hb levels, transfusion independence from 4° cycle
- ✓ Phlebotomy for iron overload (severe allergic reaction to deferasirox, deferoxamina not available)
- ✓ Better quality of life

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RESEARCH LETTER

Safety and effectiveness of the combination of 5-azacitidine and ruxolitinib in VEXAS syndrome: A single-centre experience

This article relates to:

Gregorio Maria Bergonzi, Enrico Cozzo, Alessandro Tomelleri, Costanza Piccolo, Gianluca Scorpio, Carmelo Gurnari, Francesca Romano, Marco Matucci-Cerinic, Lorenzo Dagna ... See all authors

First published: 14 December 2025 | https://doi.org/10.1111/bjh.70285 | VIEW METRICS

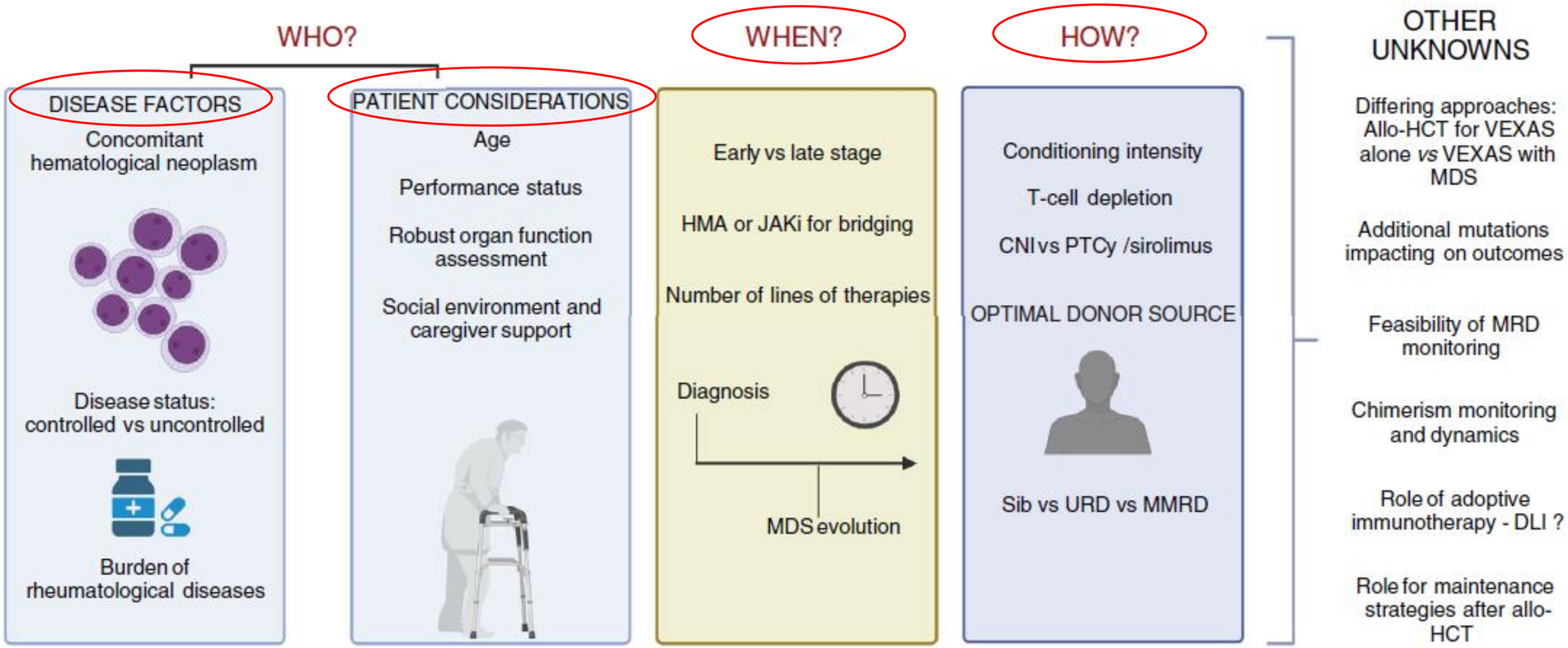
Allogeneic Stem Cell Transplantation in VEXAS

Reference	N of pts	Age	Myeloid malignancy	Median n° of previous IST lines	Conditioning regimens	Donor type	GVHD prophylaxis
Gurnari C et al, Blood Adv 2024	19	Median age 59 y	MDS 12/19 MPN 1/19 «ICUS» 6/19	5	RIC 74% MAC 26%	MRD (3) MUD (12) MMRD (3) MMUD (1)	PT Cy (6), ATG (11) or CAM (2) + CSA/MTX (7) or MMF (5) Ex vivo TCRαβ/CD19 depleted graft (1)
Mangaonkar AA et al, Transplantation Cell Therapy 2024	10	Median age 63 y	NA	NA	Flu/Mel (7) Flu/Bu (2) Bu/Flu/TT (1) (RIC)	MUD (5) MRD (4) Haplo (1)	PTCy/Tac/MMF (9) Tac/MTX (1)
Al Hakim A et al, Br J Haematol 2022	4	Mean age 60 y	MDS 2/4 «ICUS» 2/4	3	Flu/Bu/TT (1) Flu/Mel/CAM (1) Flu/Treo/CAM (1) Flu/Bu/ATG (1)	MRD (1) MUD (2) MMRD (1)	CSA/Tac/MMF (1) CSA (1) CSA/MMF/Alemtuzumab (1) ATG/CSA (1)
Van Leeuwen Kerkhoff N et al, Br J Haematol 2022	1	51 y	«ICUS»	4	ATG/Flu/TT/Mel (MAC)	MMUD 9/10	MMF, GC
Loschi M et al, Bone Marrow Transplant 2022	1	70 y	MDS	10	Bu/Flu (RIC)	MMUD	PT-Cy, CSA, MMF
Diarra et al, Blood Adv 2022	6	Mean age 55 y	MDS 5/6 MPN 1/6	6	Bu/Flu/ATG (2/6) Bu/Flu (2/6) TT/Bu/Flu (1/6) (RIC)	MUD (4) MRD (2)	CSA/MMF (1), CSA/MTX (3), CSA/MMF/PT-Cy (2)

Allogeneic Stem Cell Transplantation in VEXAS

Reference	N of pts	Toxicity	Acute/chronic GVHD	Response
Gurnari C et al, Blood Adv 2024	19	Severe bacterial infection (n = 3) and CNS toxicity (n = 1)	Grade II-IV acute GVHD (5) Chronic extensive GVHD (4)	Alive 15/19 (3 deaths for infections) 2y-OS: 74.2%, TRM: 25.8%; 94% full donor chimerism; Complete remission. UBA1: negative in 6 pts.
Mangaonkar AA et al, Am J Hematol 2023	10	Infections (6)	Late acute skin GVHD (n=2, grade 3 in 1, none with gut/liver or chronic GVHD)	Alive 10/10 5/10 pts with FUP > 12 months: complete remission. UBA1: negative in 4/10 pts
Al-Hakim A et al, Br J Haematol 2022	4	Bacterial infections (2) EBV reactivation (1)	aGVHD (2)	Alive 2/4 (2 death for infections) UBA1 status: NA
Van Leeuwen Kerkhoff N et al, Br J Haematol 2022	1	Mucositis, CMV colitis	No	Alive 100% donor chimerism UBA 1: negative.
Loschi M et al, Bone Marrow Transplant 2022	1	Left wrist swelling, cause unknown	aGVHD max G3 skin and G1 GI → GC and ruxo	Alive Complete remission UBA1: negative
Diarra et al, Blood Adv 2022	6	Bacterial infections 4/6 Viral infections 1/6 (BKV, CMV)	3/6 pts aGVHD 2/6 cGVHD	Alive 5/6 Complete remission 5/5 alive pts

How to choose allo-SCT in VEXAS patients



Gurnari et al, Bone Marrow Transplantation (2022)

Conclusions

Lack of Standardized Treatment Protocols

- **No consensus** on best therapeutic strategy.
- Treatment varies widely across centers, with different combinations of immunosuppressive drugs

Balance between High Risk of infection and necessity of dealing with systemic inflammation

Never forget about supportive treatments !!!

The complexity of VEXAS syndrome demands a multidisciplinary approach

- SAVE the DATE!!!
- 3rd International VEXAS Workshop San Raffaele
- 24th and 25th September 2026

VEXAS

Thank you all

for your attention

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