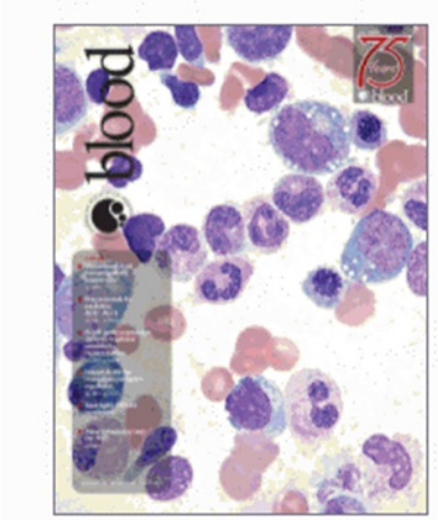


VEXAS syndrome: state of the art and the value of quality of life assessment

Carmelo Gurnari, M.D. Ph.D.

Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy

Translational Hematology and Oncology Research Department of Cleveland Clinic, OH, USA

CMWP MDS subcommittee

carmelogurnari31@gmail.com

@CarmeloGurnari

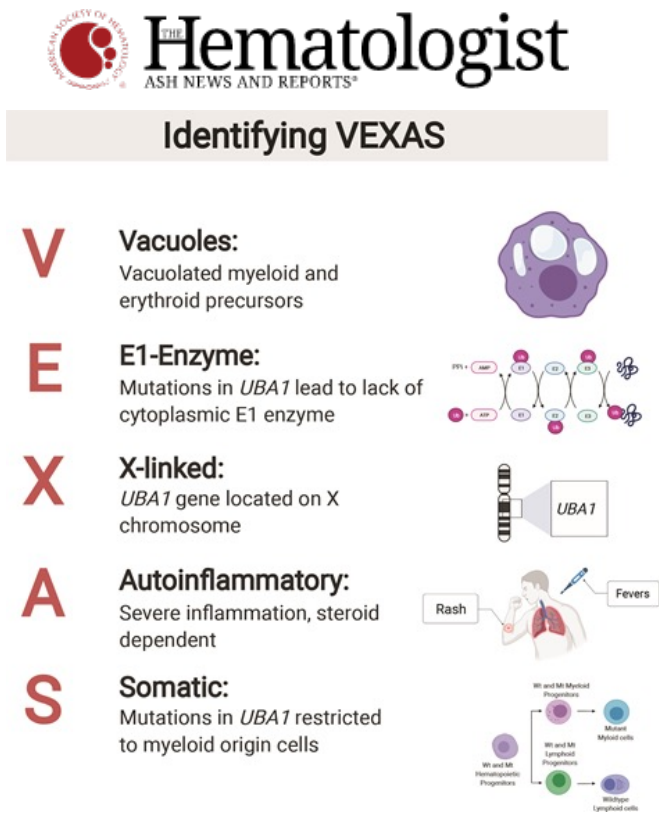
Disclosures

- Sobi, Novartis (Advisory board)
- Genesis Therapeutics (Consultancy)
- Alexion, Novartis (Research grants)

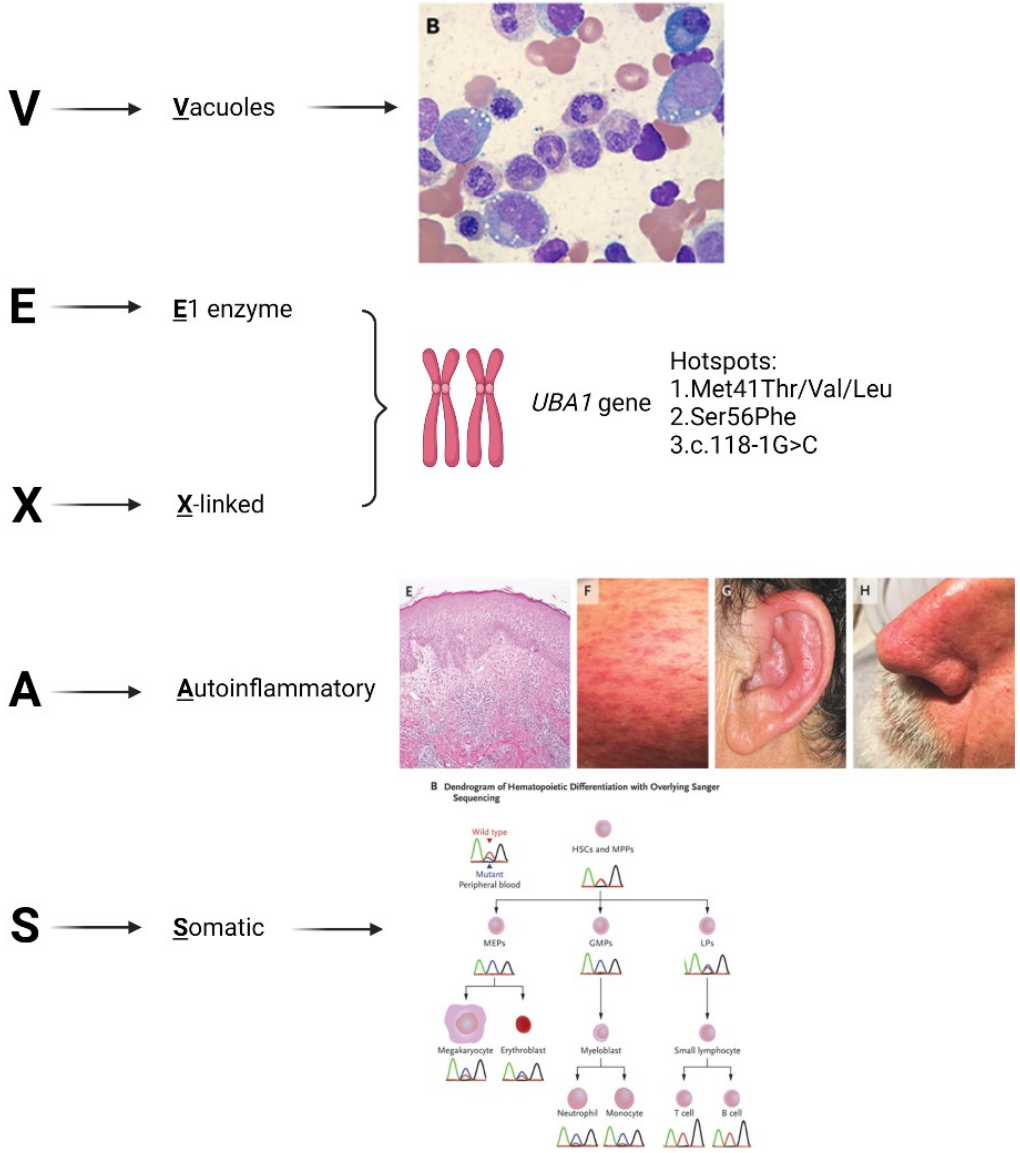
A new syndrome: VEXAS the definition of the acronym

Robert P. Hasserjian, MD, This Year's Best in Hematology Diagnosis: A New Disease Is Discovered

The Hematologist (2022); 19(1)



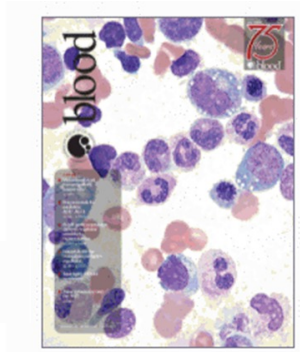
pubMed (9/2025): 557 items in the last 5 years since its discover



Beck et al NEJM 2020; Gurnari et al Blood 2021; Poulter et al Semin Hematol 2021

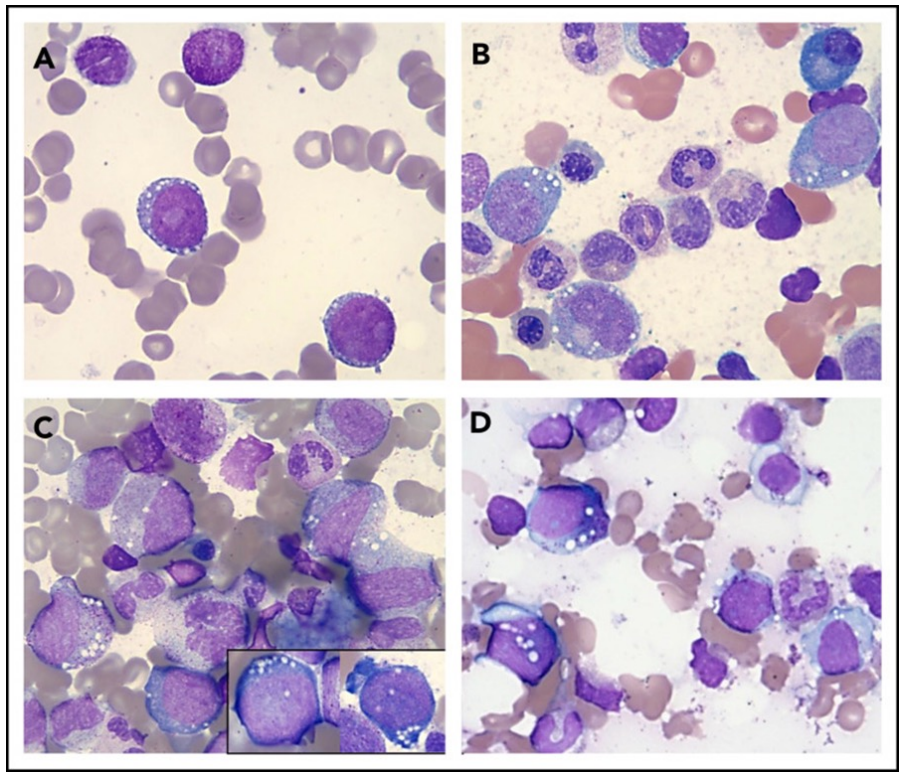
(V)EXAS: The issue of vacuoles (I)

V → Vacuoles →



Volume 137, Issue 26

July 1 2021

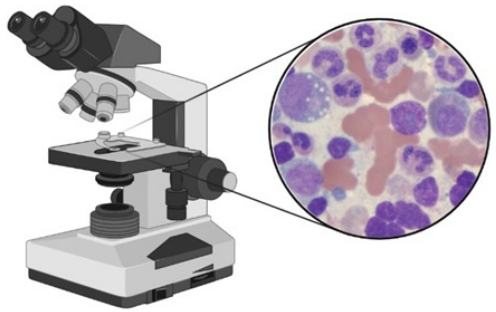


Study design

BM specimens between 2005-2020

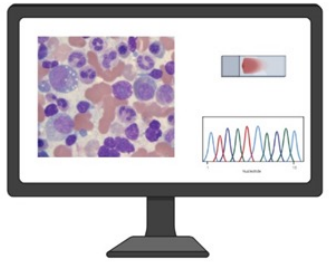
11,772 specimens

MN diagnosis/f-up or cytopenias



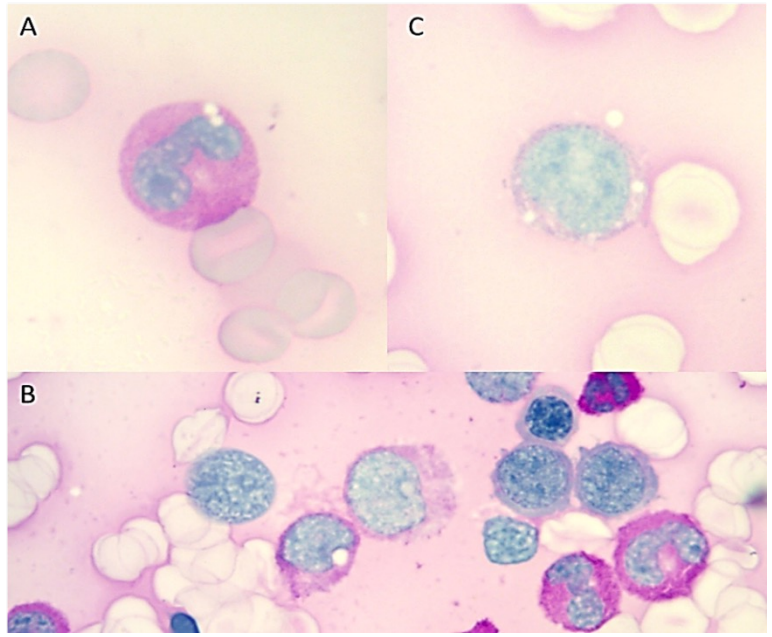
System query for

Presence of vacuoles in HP



24 BM specimens identified

PAS-negative vacuoles



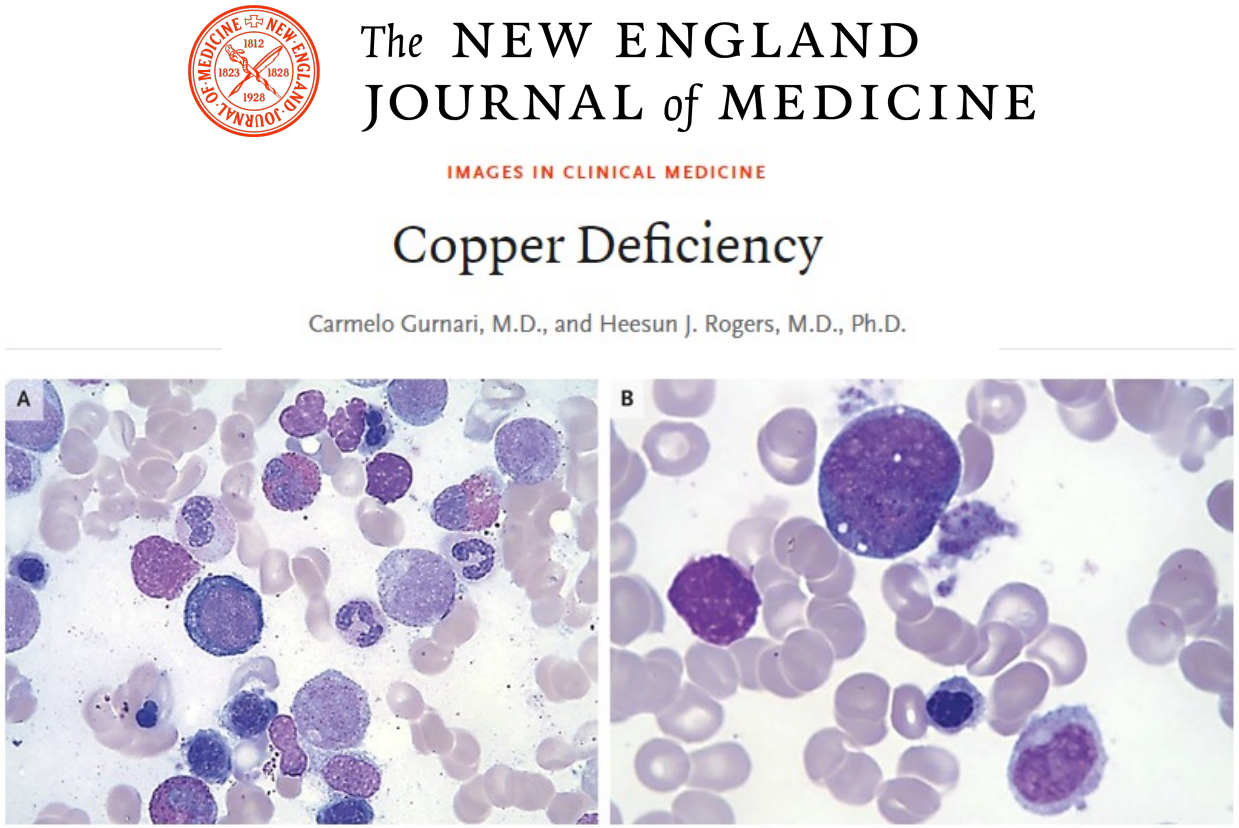
- MDS present in 50% of cases!

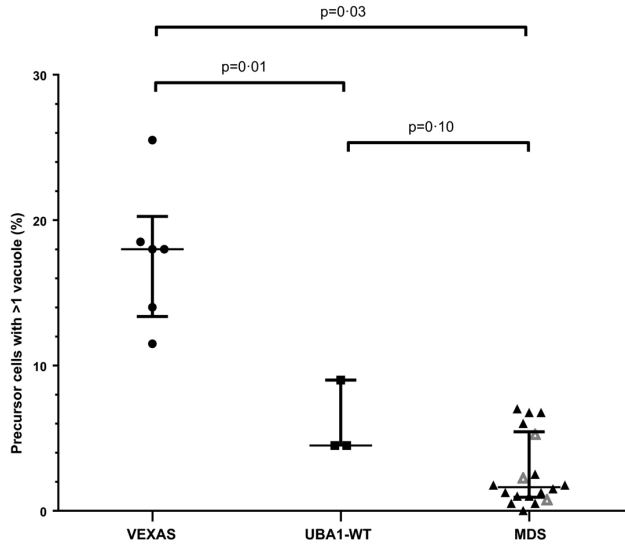
Gurnari C. et al Blood 2021

(V)EXAS: The issue of vacuoles (II)

Causes of vacuolization of HP

Myelodysplastic syndromes
Acute myeloid leukemia
Alcoholic abuse
Pearson disease
Hemophagocytic lymphohistiocytosis
Copper deficiency
Protein-losing enteropathies
Malnourishment
Zinc-toxicity
Bariatric or upper gastrointestinal surgery
VEXAS syndrome





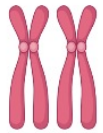
- A threshold of ≥10% of neutrophil precursors with >1 vacuole was associated with the diagnosis of VEXAS syndrome with a sensitivity of 100% and a specificity of 100%.

Gurnari et al Blood 2021; Lacombe et al BJH 2021; Gurnari C & Rogers HJ NEJM 2021

Explaining the acronym…V(EX)A(S)

E → **E**1 enzyme

X → **X**-linked



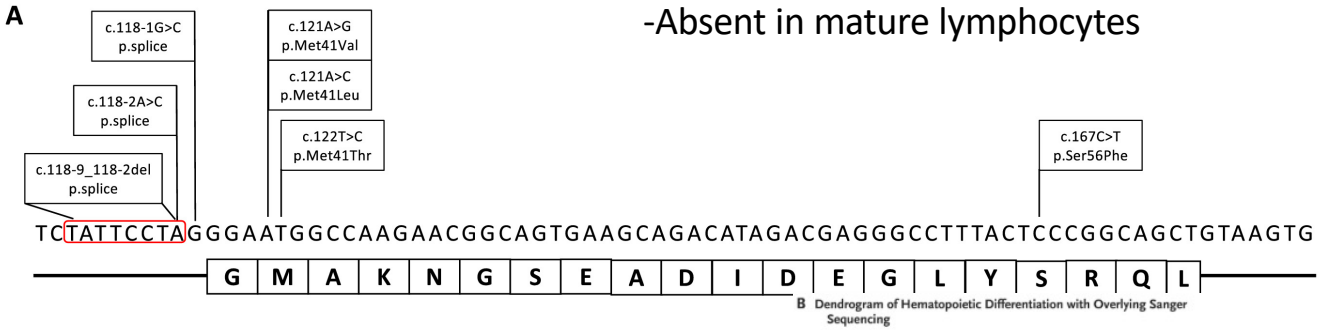
UBA1 gene

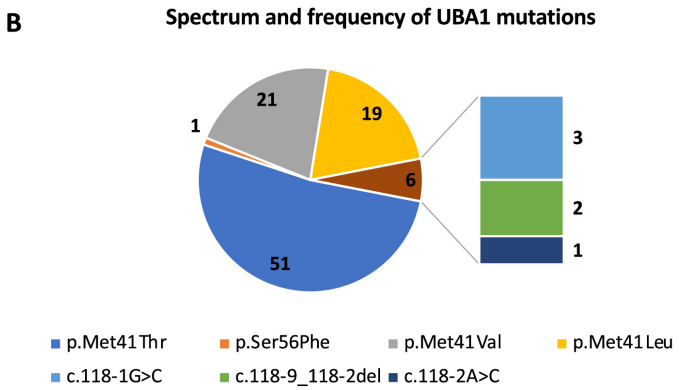
S → **S**omatic

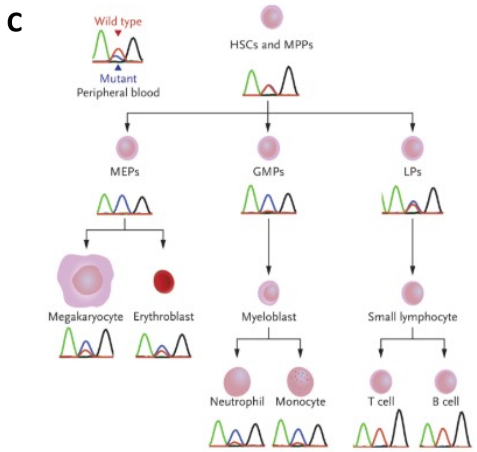
UBA1 **somatic** mutation:
-Major E1 enzyme required for ubiquitin activation
-Mostly with p.Met41Val/Thr/Leu → Loss of function
-Present in HSPCs, restricted to myeloid lineage
-Absent in mature lymphocytes

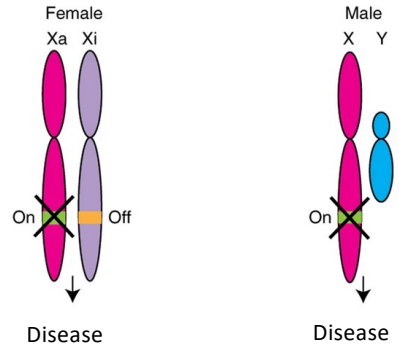
~1%

~ 99%





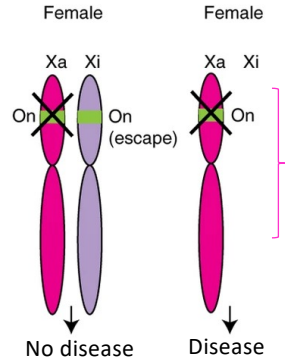




X-inactivation on

e.g., *PIGA*

Equal
M:F ratio



Turner syndrome
Somatic monosomy X
X-skewing

X-inactivation off (escape)

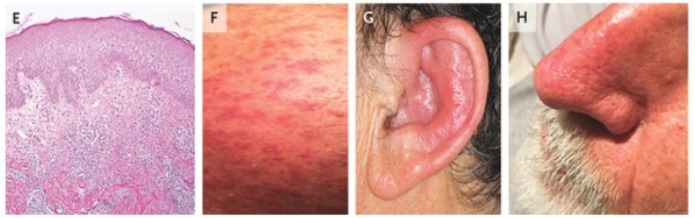
e.g., *UBA1*

Increased
M:F ratio

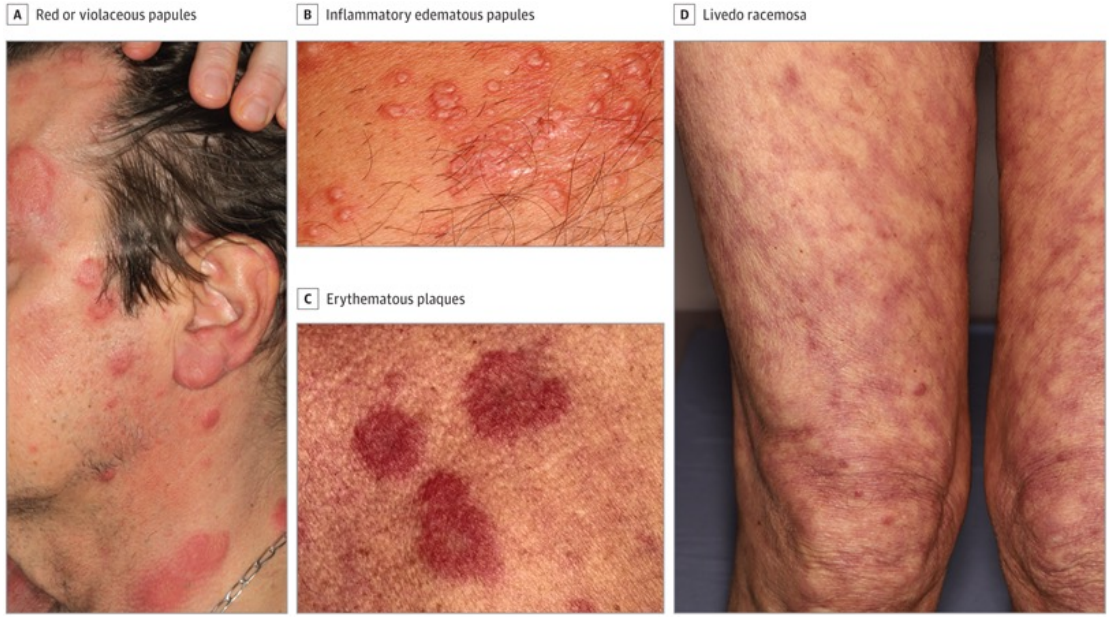
Beck et al NEJM 2020; Poulter et al Blood 2021 & Semin Hematol 2021; Dunford et al Nat Genetics 2016

Explaining the acronym…VEX(A)S

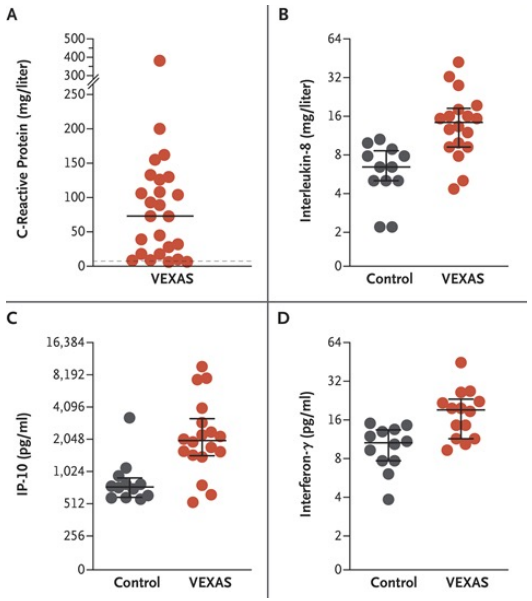
A → **A**utoinflammatory

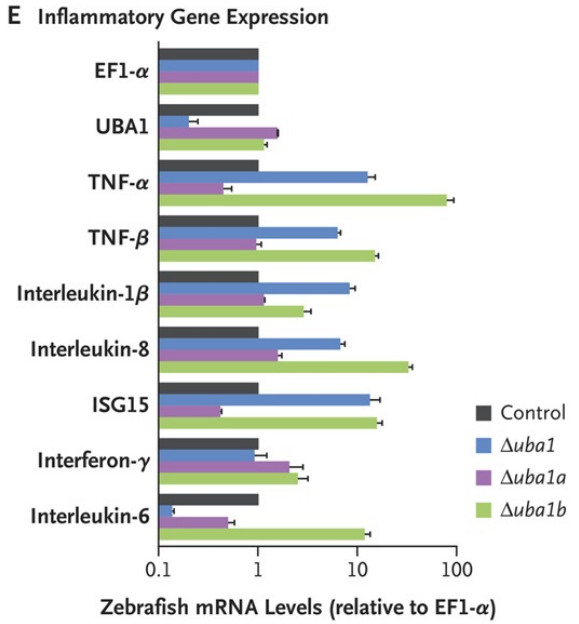


Dermatologic manifestations (~90%)



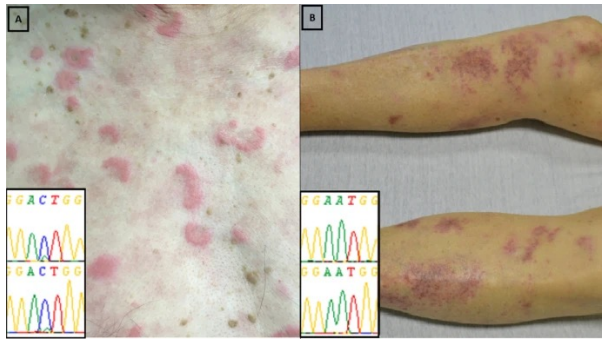
- 8 men
- All with skin involvement
- The skin infiltrate harbored the *UBA1* clonal variant in 100% of cases





- 6 patients
- Various skin manifestations
- Only Sweet syndrome cases harbored *UBA1* variants

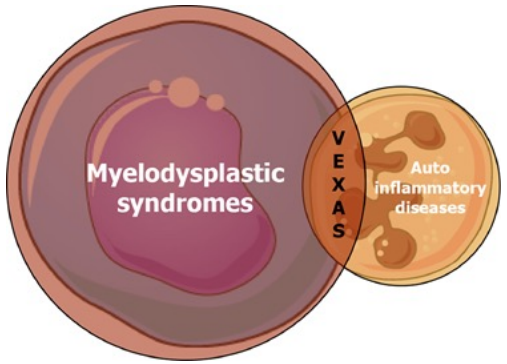
Clonal

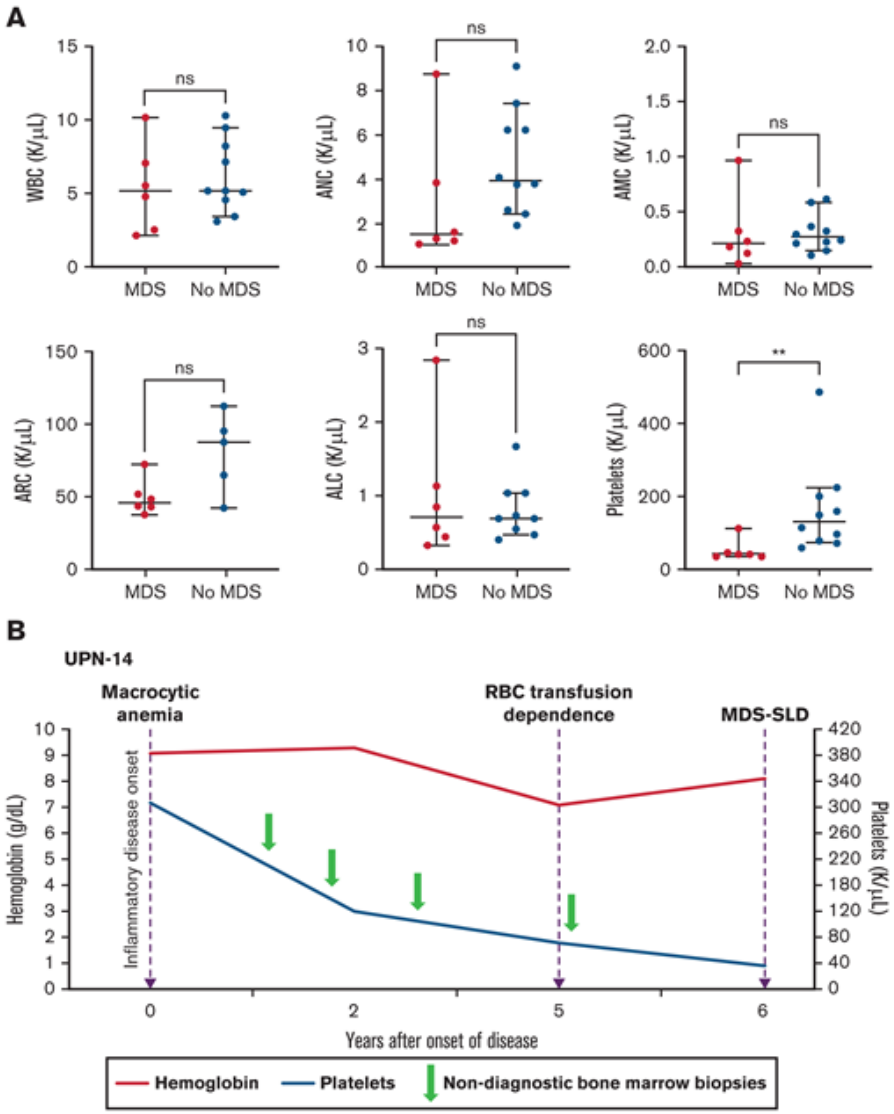


Paraclonal

Beck et al NEJM 2020; Zakine et al Jama Dermatol 2021; Lacombe et al Exp Hematol Oncol 2022

Common Hematological Features





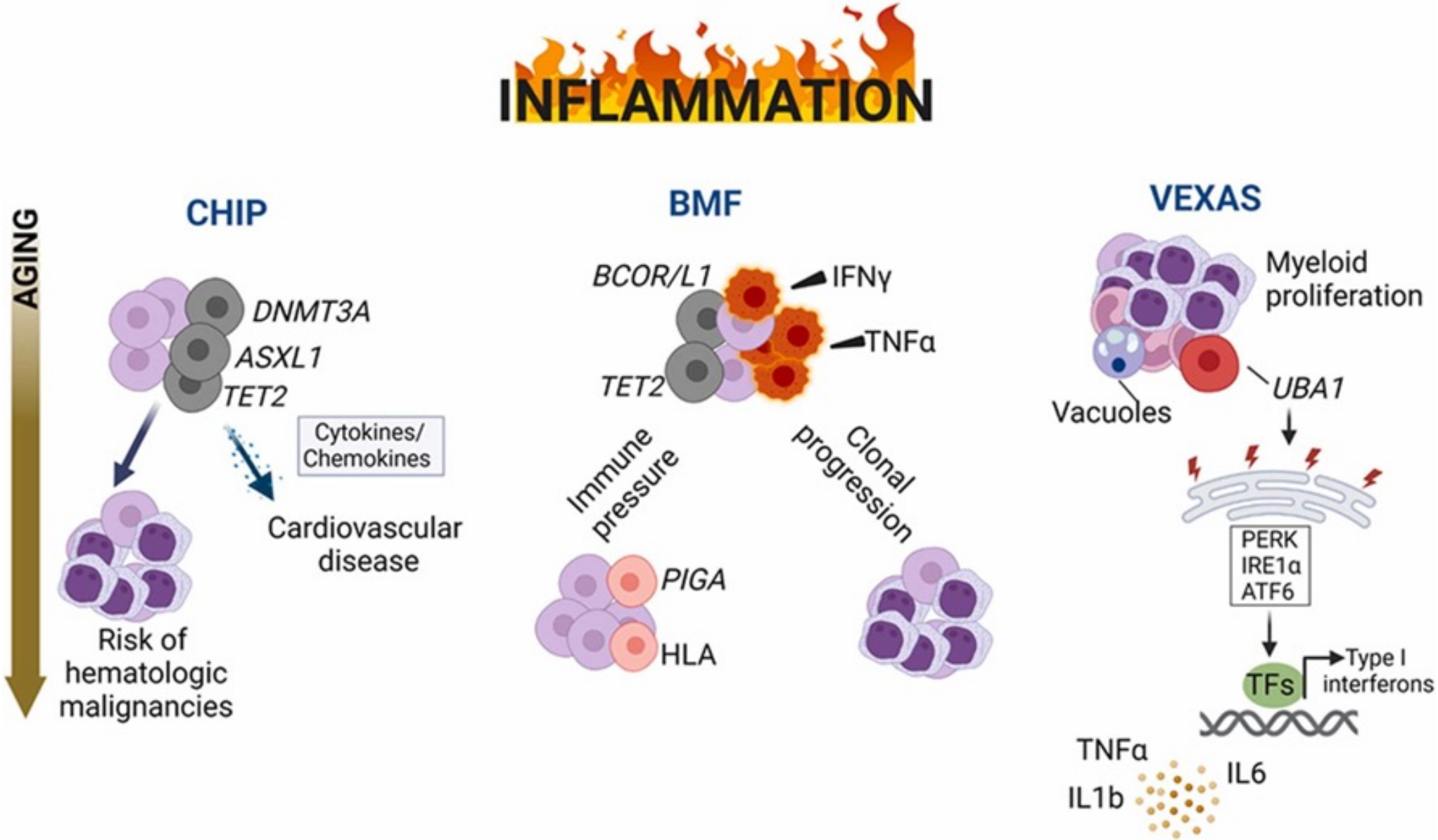
- 16 patients with VEXAS (100% male)
- 100% BM vacuoles
- 100% macrocytic anemia irrespective of overt MDS diagnosis
- Thrombocytopenia and neutropenia more common in MDS
- Lymphopenia (80%)
- MDS typically lower R-IPSS scores (<3.5)
- Plasma cell dyscrasias (25%): 2 MM and 2 MGUS
- Thrombosis (56%) with 60% of events occurring within the first 2 years from disease onset

↓

Increased morbidity and mortality because of VEXAS-associated features

Obiorah et al Blood Adv. 2021; Stubbins et al Haematologica 2021

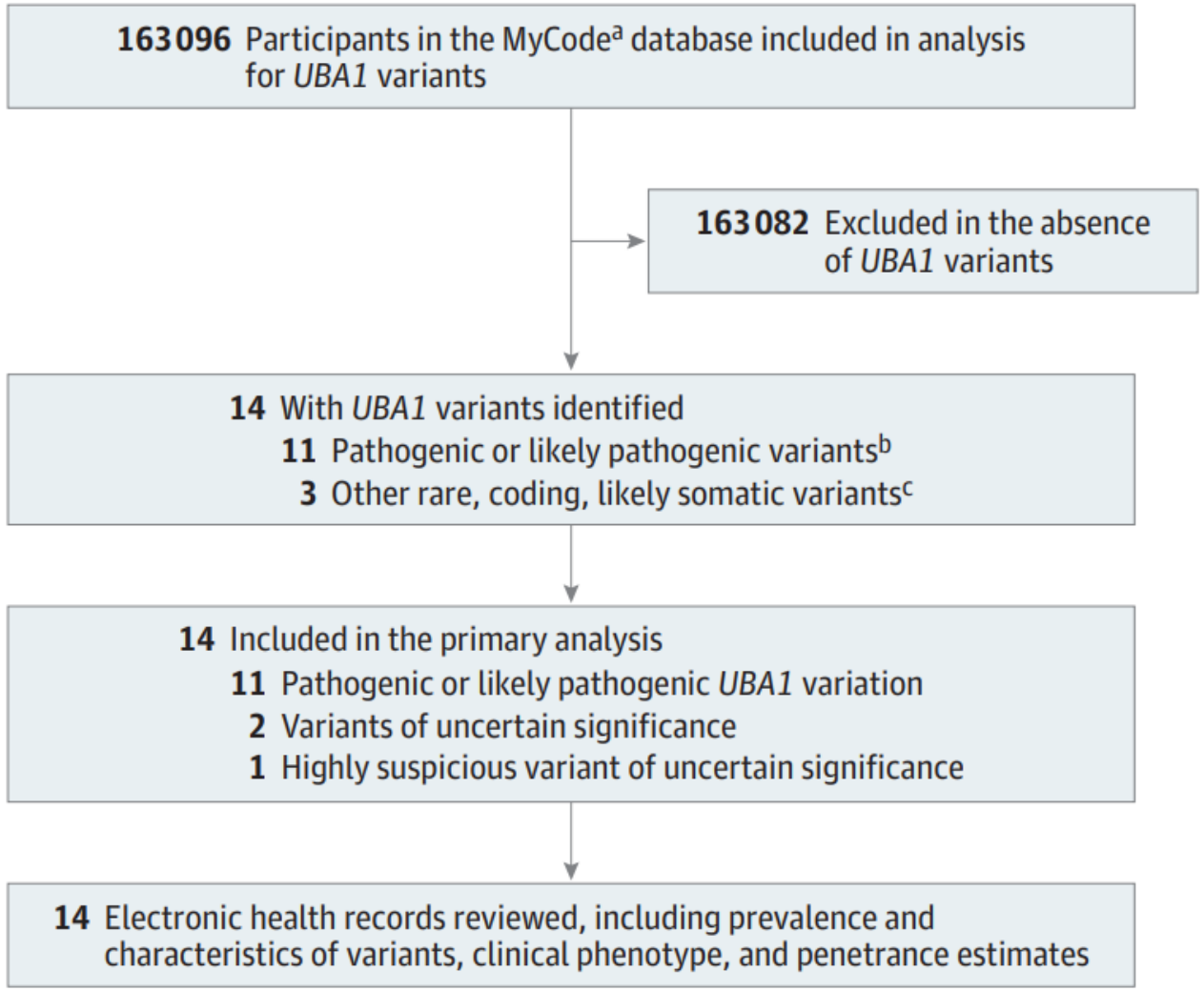
Inflammation is the pivotal player in BMFs, VEXAS, CHIP and MDS



Gurnari & Visconte, Leuk Research 2023

Genetics of VEXAS: prevalence

Figure. Outline of the Study Design



- 163,096 participants (Geisinger MyCode Community Health Initiative)
- HER (electronic health record)
- ~1 in 4,000 men >50 years old
- ~ 6.6 higher probability of mortality vs. age-, sex-, and BMI-matched non-carrier

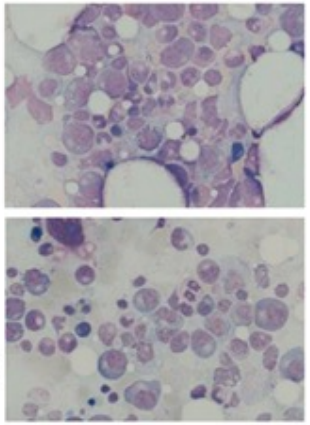
Beck et al, JAMA 2022

MDS and VEXAS: a subtle interface

Context of Research

VEXAS syndrome is a monogenic disease caused by somatic mutations in *UBA1* in hematopoietic cells

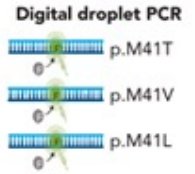
A portion of VEXAS patients meet established diagnostic criteria for MDS



Patients and Methods

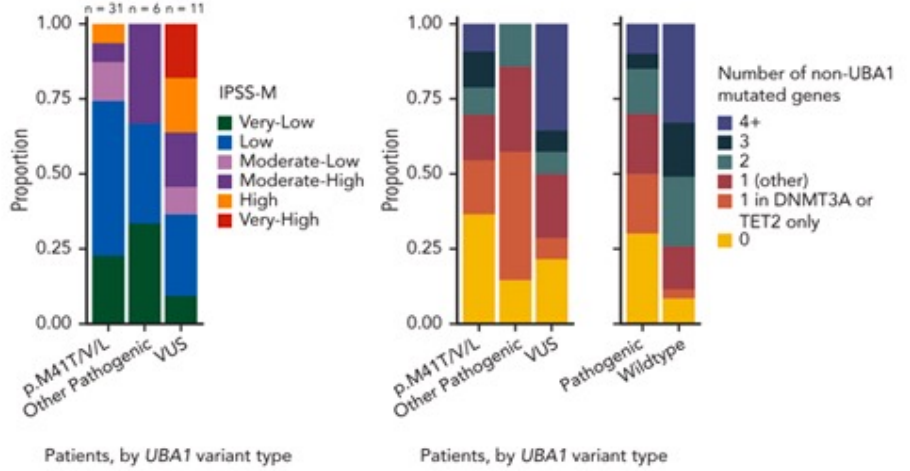
2,198 MDS patients

- *UBA1* ddPCR in 375 patients
- *UBA1* NGS in 2,027 patients
- Correlation with 152 gene myeloid panel and inflammatory clinical presentation

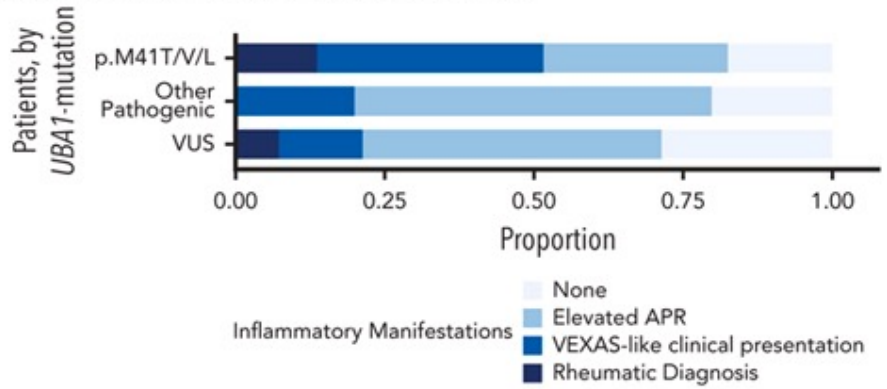


Main Findings

UBA1 mutations enriched in low risk MDS with few mutations



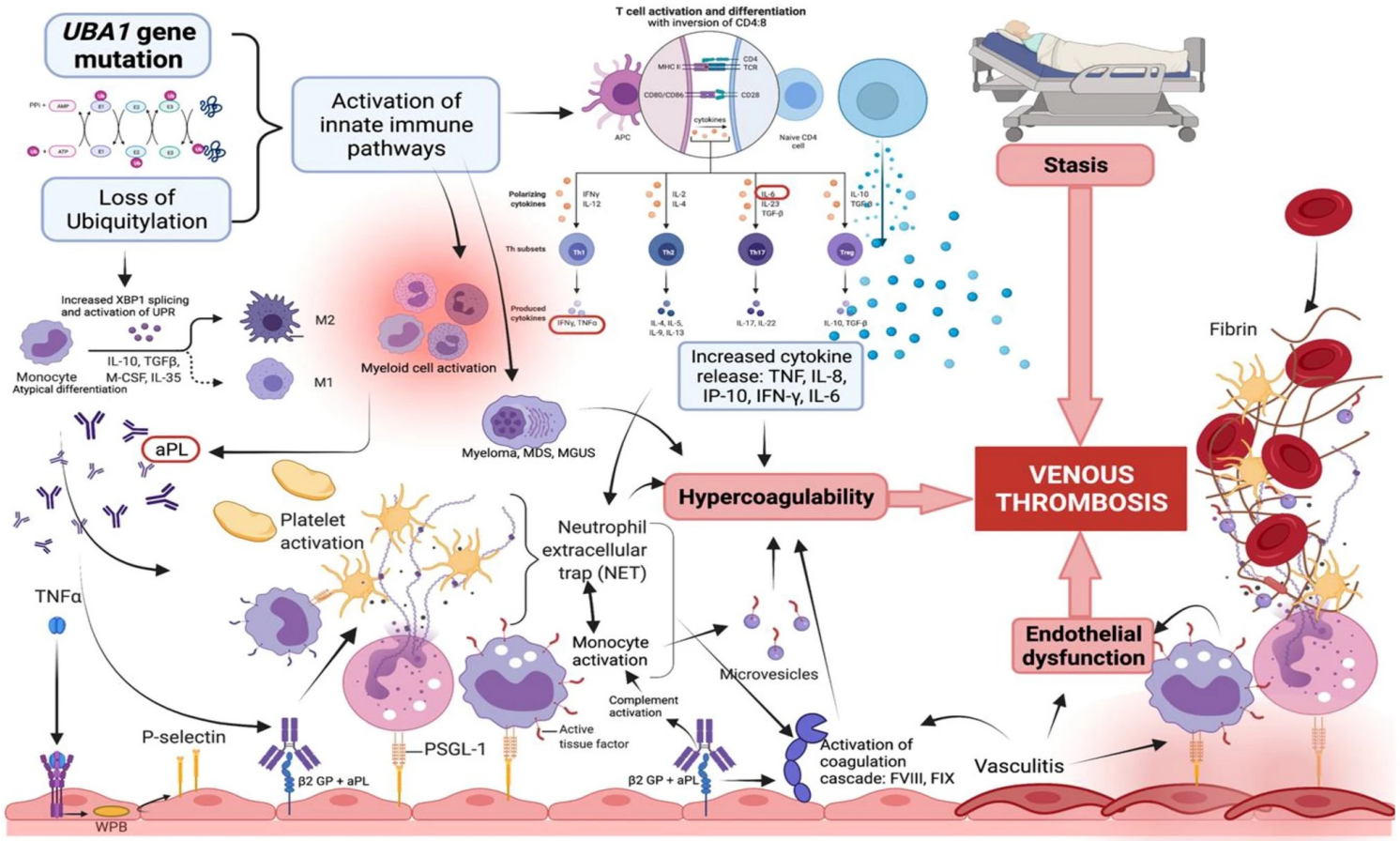
Spectrum of inflammatory clinical presentation in MDS patients with likely/pathogenic *UBA1* mutations



- *UBA1* mutations were identified in 1% of patients with MDS and 7% of patients lacking myeloid mutations or established disease classification.
- Inflammatory clinical presentation and vacuoles were observed in 83% and 71%, respectively, of patients with pathogenic UBA1 mutations.

Sirenko et al Blood 2024

A focus on Thrombotic events



- High thrombotic burden with incidence of venous thromboembolism (36-56%) that is markedly higher than arterial thrombosis (1.6%)
- X-linked somatic mutation in the *UBA1* gene results in decreased ubiquitylation which is a key driver in the development of thrombosis in VEXAS syndrome.
- Chronic cytokine release and inflammation from abnormal crosstalk between the intrinsic effector mechanism of innate immune cells, platelets and endothelium result in dysregulated hemostasis and endothelial dysfunction.
- Further studies are required to uncover the exact mechanisms of thrombogenesis and to evaluate anticoagulation strategies in patients with VEXAS syndrome.

- 44% patients had persistently positive LA and 55% of patients with VTE had positive LA. Other tests for thrombophilia included PNH, antithrombin III activity, and protein C or S activity which were unremarkable

Mon Oo et al Journal of Thrombosis and Thrombolysis 2021; Groarke et al Semin. Hematology 2021

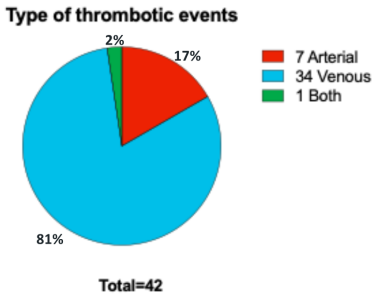
AN ITALIAN CARTOGRAPHY OF VEXAS-RELATED THROMBOSIS: A 218 PATIENT-YEARS ANALYSIS

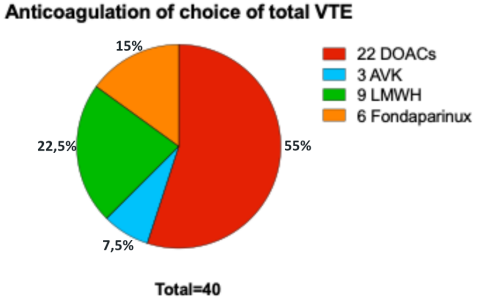
EHA2025 Congress 30th ANNIVERSARY

RESULTS

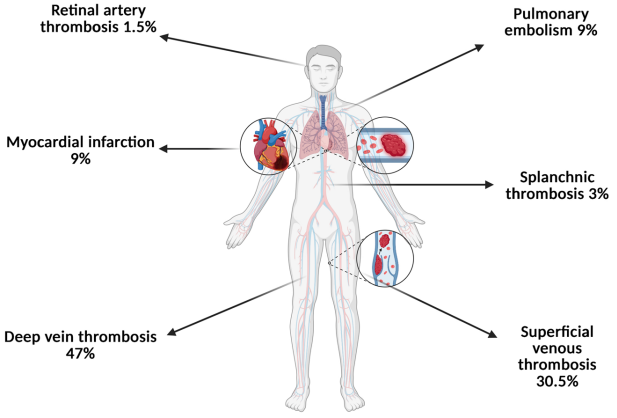
Charachteristics of VEXAS population	Overall (n=85)
Demographics	
Age at diagnosis, median (IQR)	70 (64-75)
Male sex, n (%)	100 (100)
VEXAS phenotype	
Systemic symptoms, n (%)	29 (34)
Skin involvement n (%)	28 (33)
Pulmonary involvement n(%)	9 (11)
Hematological disease	
MGUS, n (%)	31 (36)
MM, n (%)	1 (1)
MDS, n (%)	47 (55)
***UBA1* genotype**	
p.Met41Val (c.121A>G), n (%)	25 (29)
p.Met41Leu (c.121A>C), n (%)	6 (7)
p.Met41Thr (c.122T>C), n (%)	34 (40)
Other, n(%)	20 (24)
Thrombophilic features	
F V Leiden heterozygosis, n (%)	3 (4)
F II G20210A, n (%)	1 (1)
Anti-cardiolipin IgM/IgG, n (%)	5 (6)
Beta2-glycoprotein I IgM/IgG, n (%)	1 (1)
Timing of TE	
Onset, n (%)	28 (67)
On treatment, non responding, n (%)	9 (21)
On treatment, responding, n (%)	2 (5)

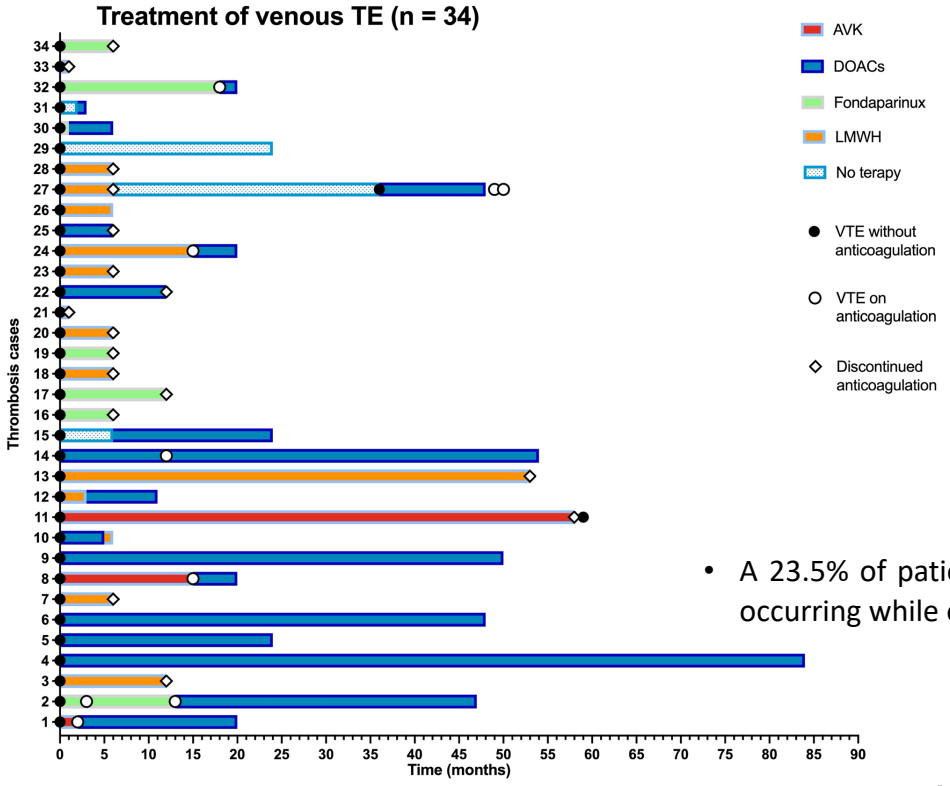
No baseline clinical nor molecular (*UBA1* genotype) characteristic associated with TE occurrence.





50% had TE!





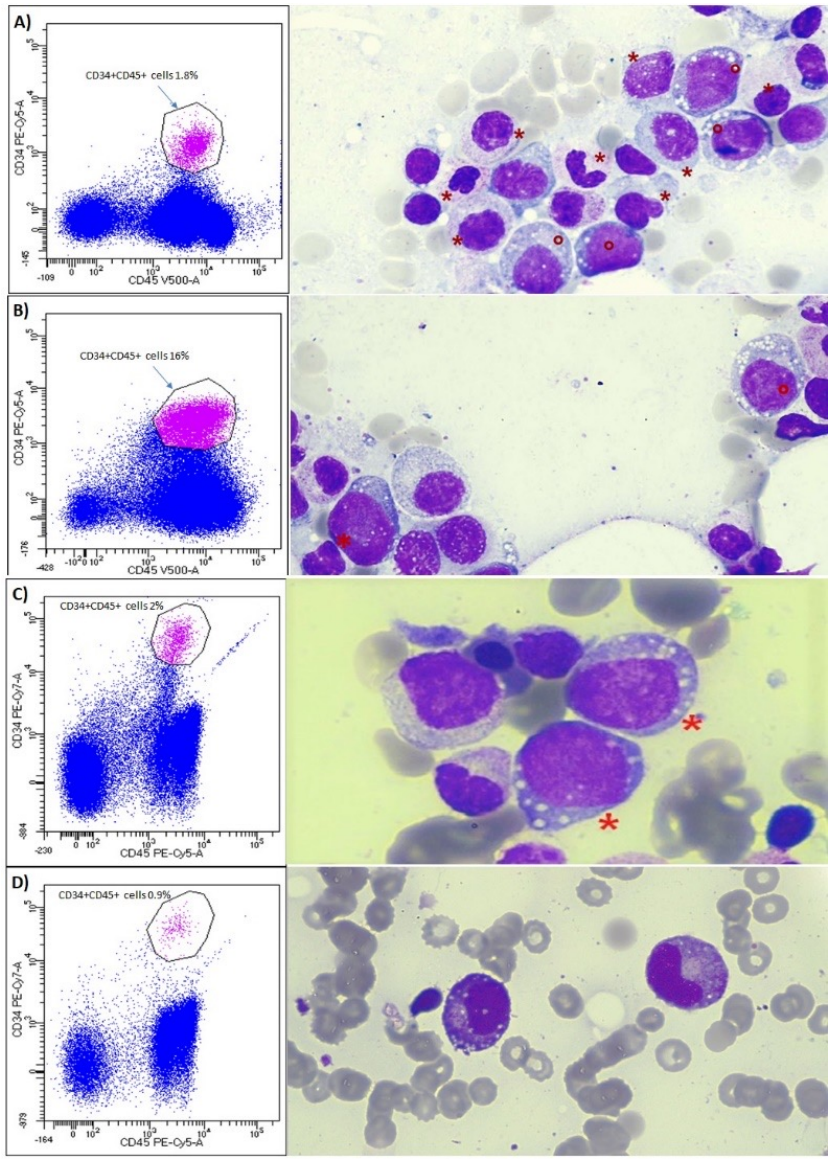
Left: table of characteristics of Italian VEXAS population; *middle:* representation of all reported thrombotic events; *upper right*: on the left a pie-chart of the type of thrombotic events, on the right a pie-chart of anticoagulation of choice of all venous thrombotic events (events that occurred on anticoagulation that didn't modify the therapy were not considered); *lower right*: Swimmer-plot of venous thrombotic events treatment until last follow-up

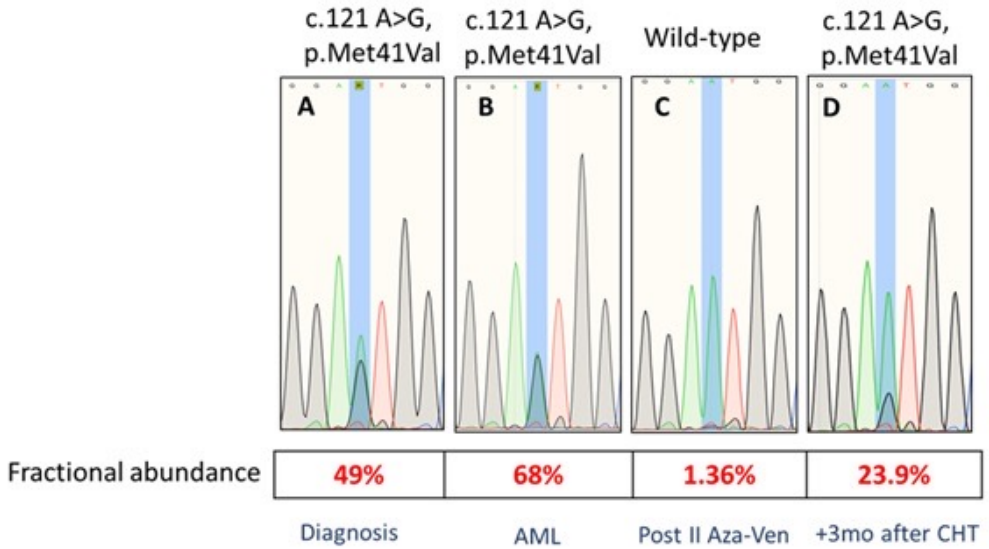
- A 23.5% of patients had >1 TE with 6% occurring while on anti-coagulation

Dr. Giorgia Ranucci

- TE and thrombophilia are common in patients with VEXAS and are not associated with any baseline characteristics, prompting screening early at diagnosis for potential preventive measures is necessary

AML transformation: not impossible!





B

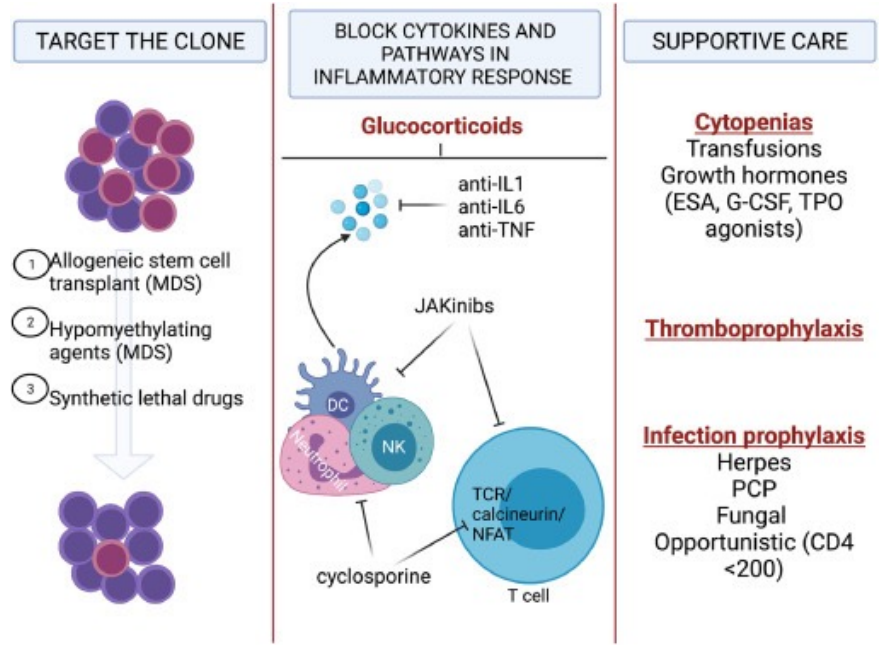
Characteristic (%)	Diagnosis (January 2021)	Follow-up (May 2021)	Evolution to AML (March 2022)	Post I Aza-Ven (May 2022)	Post II Aza-Ven (June 2022)
Blasts in FACS	1.8	0	17	2	0.9
SF3B1, VAF	34	-	34	25.2	35.6
ASXL1, VAF	35	-	35	23.3	35.5
RUNX, VAF	-	-	-	7.8	26.3
UBA-1, VAF	49	67	68	-	1.36

Abbreviations: Met, methionine; Val, valin; AML, acute myeloid leukemia; Aza-Ven, azacytidine venetoclax; mo, months; FACS, fluorescence-activated cell sorting; VAF, variant allele frequency.

Battipaglia et al 2023 Curr Res Transl Med. 2023

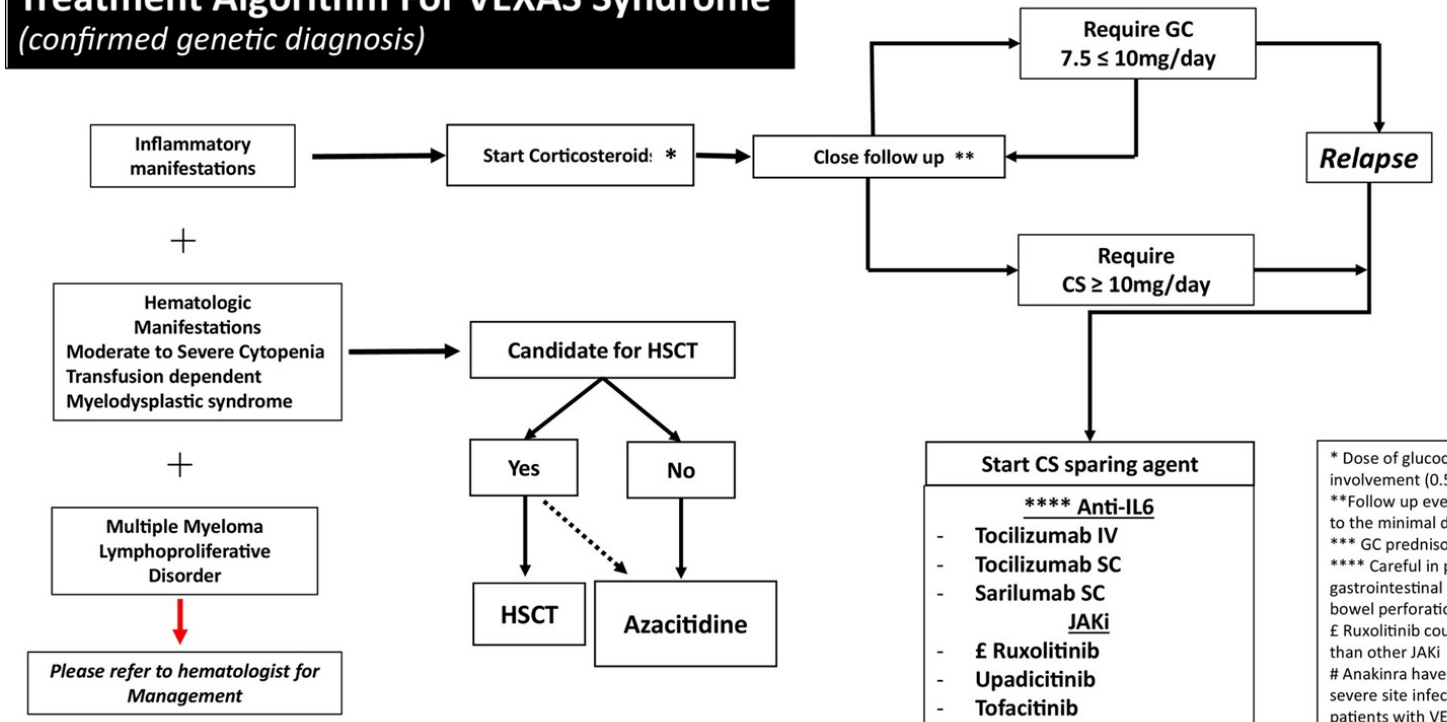
Therapeutic considerations

Possible therapeutic approaches



Treatment Algorithm For VEXAS Syndrome

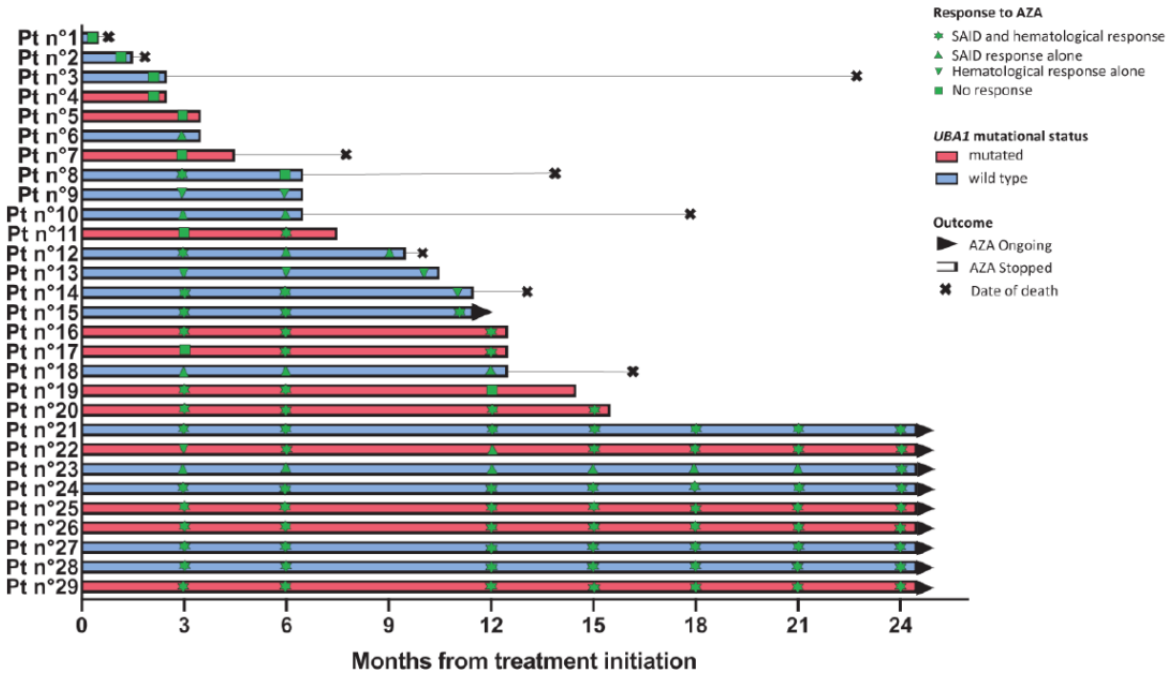
(confirmed genetic diagnosis)



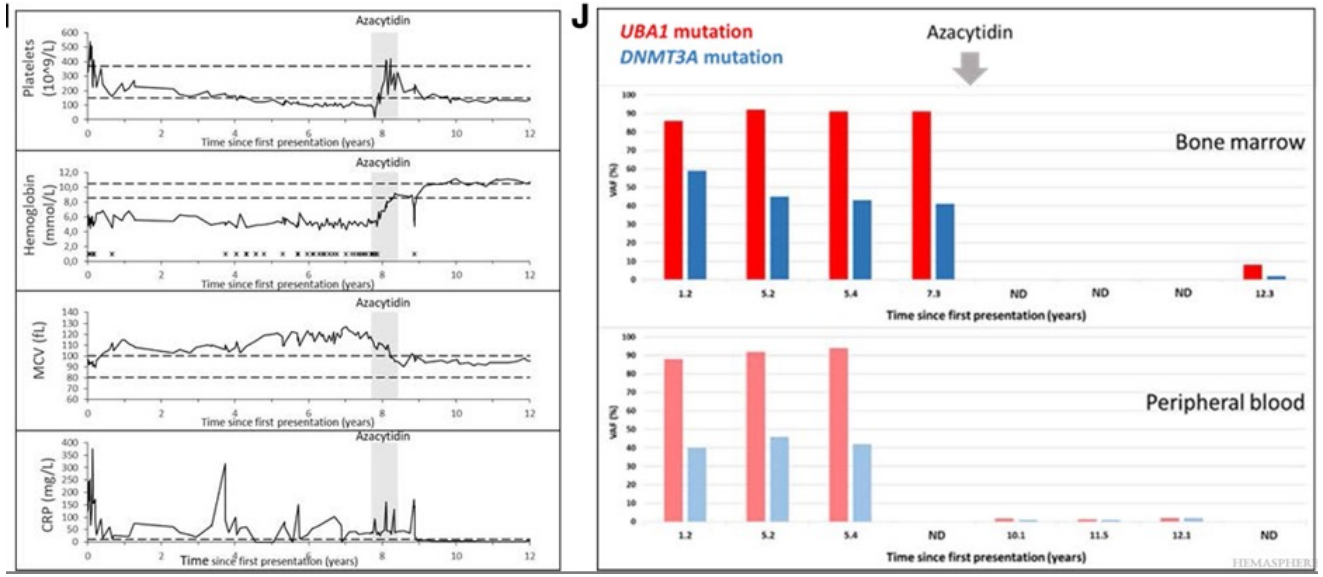
Bourbon et al Blood 2021; Heiblig et al Semin. Hematol 2021; Mekinian et al Arthritis Rheumatol. 2025

MDS/VEXAS clinical dyad: the role of AZA

- AZA treatment led to clinical response in up to 50% ≠ 86% of MDS/SIAD cohorts previously reported (*UBA1* status unknown)
- Best response after a median of 4-6 cycles
- Responders required less steroids treatment



Mutational clearance?

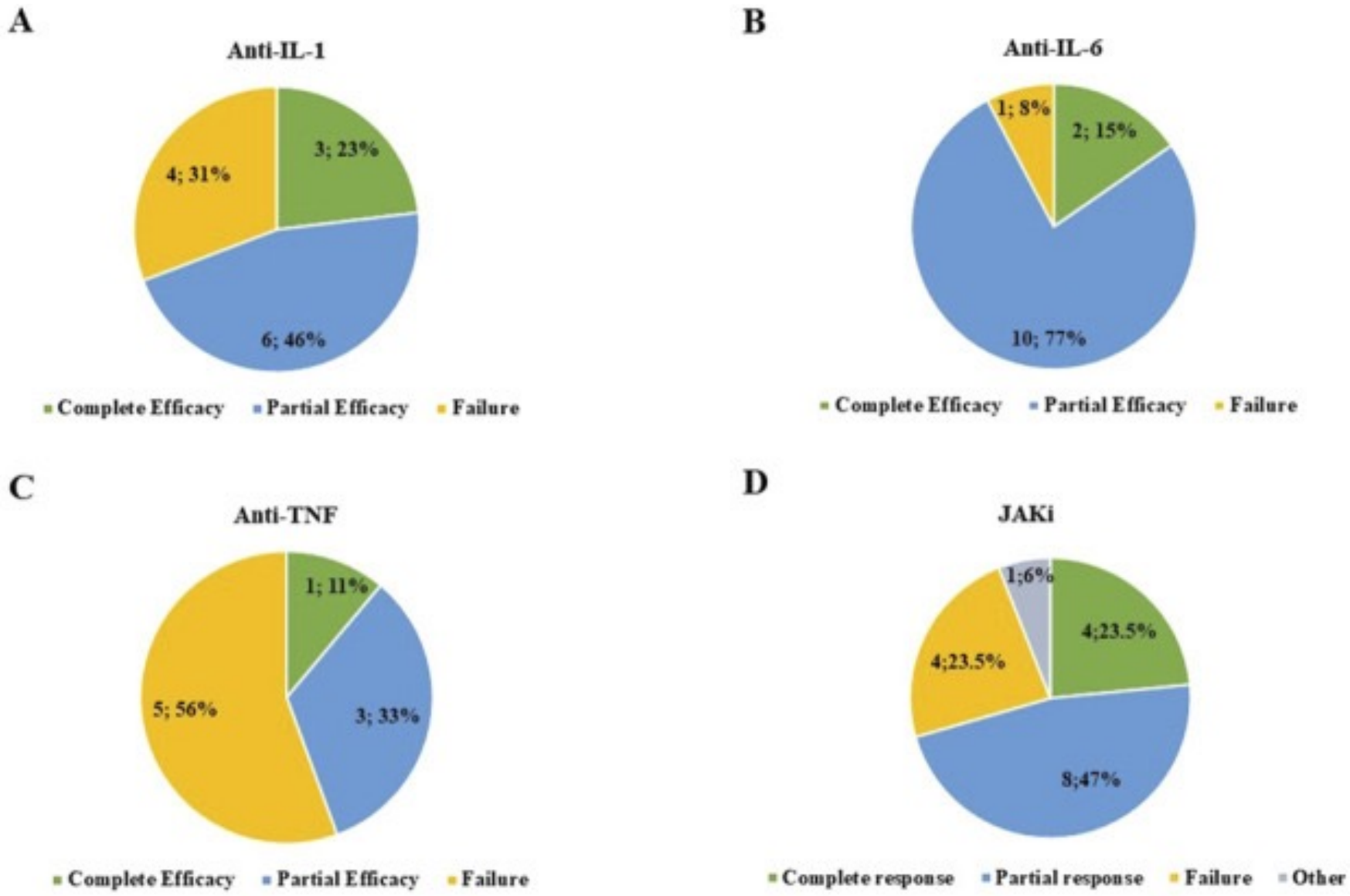


1. AZA stopped because of remitting diverticulitis and a diagnosis of local colorectal adenocarcinoma

2. CR 4.5 years after the last azacitidine administration

Georgin-Lavialle et al BJD 2021; Raaijmakers et al HemaSphere 2021; Comont et al BJH 2021; Mekinian et al Leukemia 2022

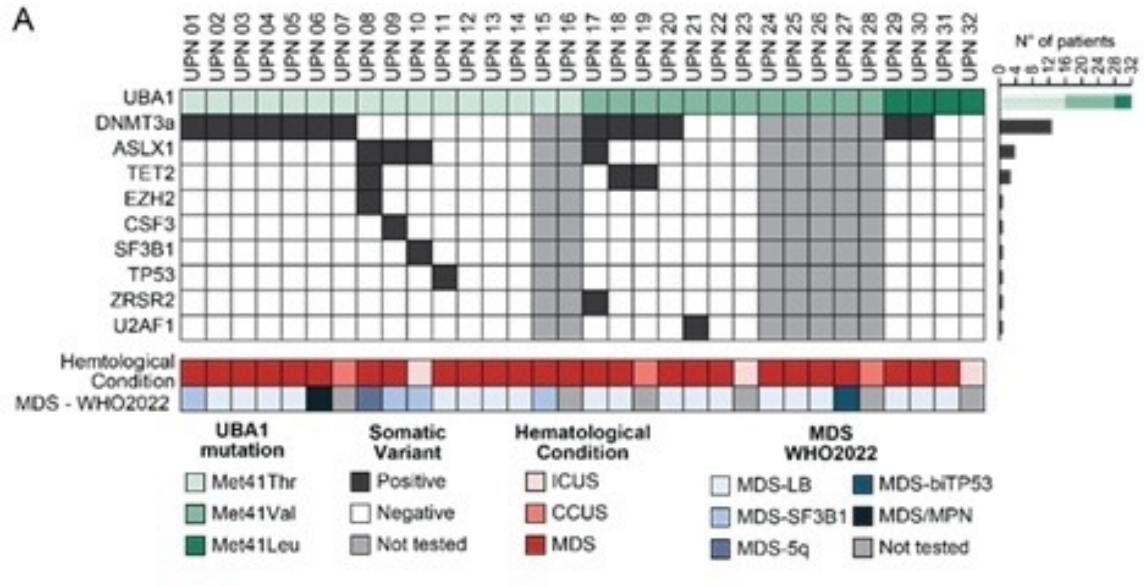
Biotechnological agents and Janus kinase inhibitors in VEXAS syndrome: data from the international AIDA Network VEXAS registry

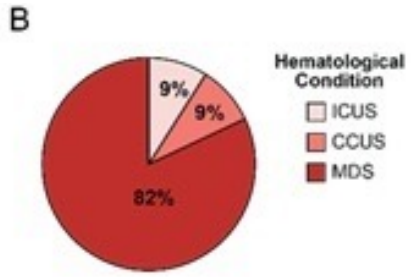


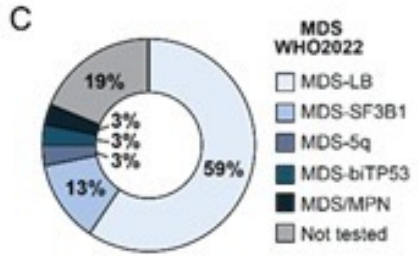
Vitale et al. Front Pharmacol. 2025

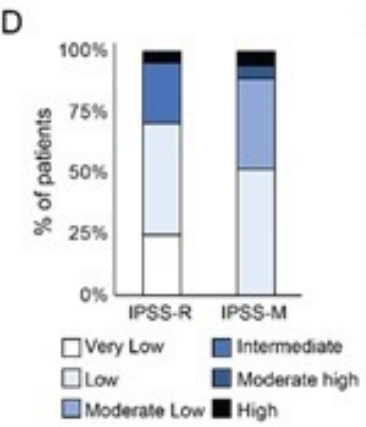
Anemia: ESAs and Luspatercept

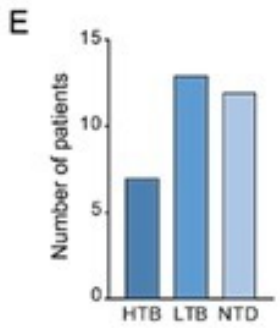
N=32 pts (82% MDS)

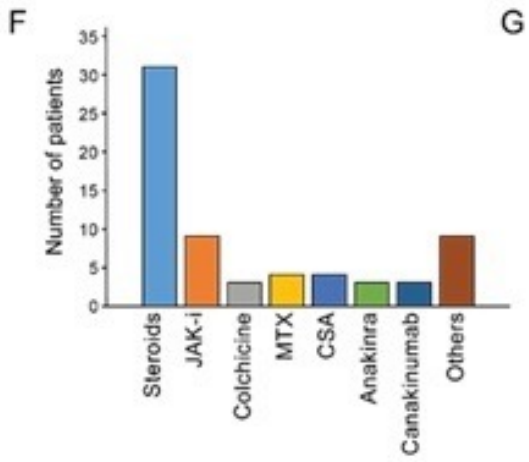


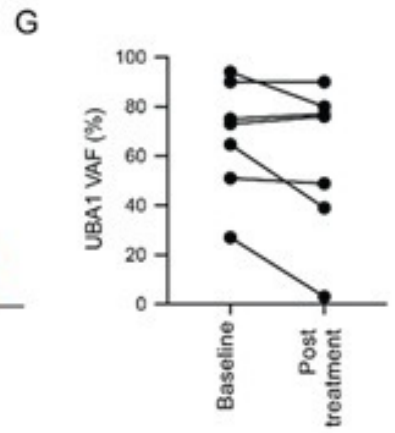












- HI-E was achieved in 19 patients (59%), with all responders obtaining TI
- Median duration of response to ESAs was 13 months

N=45 pts (82% MDS)

HI-E was achieved in 31% at week 16 (44%, 26%, and 23% in NTD, LTB, and HTB, respectively)

N=8 pts treated with Luspatercept

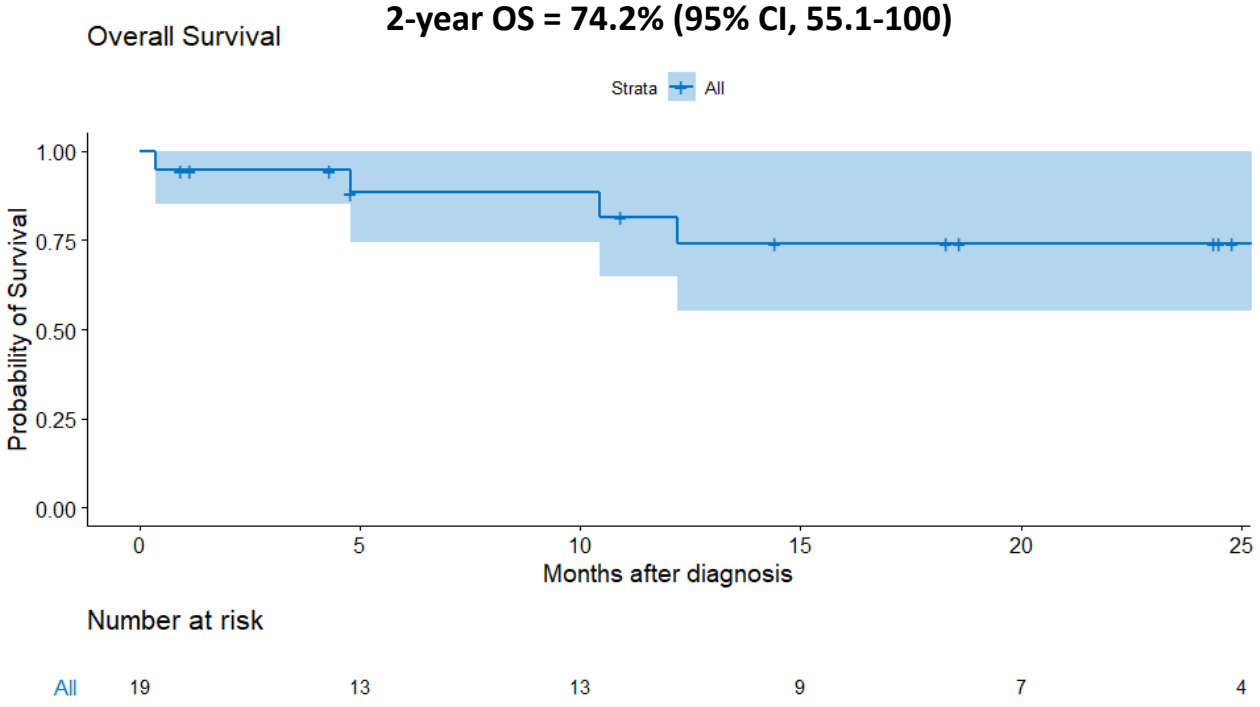
At week 16, 50% reached HI-E, including the NTD and the three LTB, but no HTB patient. Three of the four responders continued LUSPA and were still responders after 15, 16, and 10 months, while the last responders relapsed on anemia and discontinued LUSPA after 6 months.

Diral et al BJH 2025
Heibleig et al HaemaSphere 2025

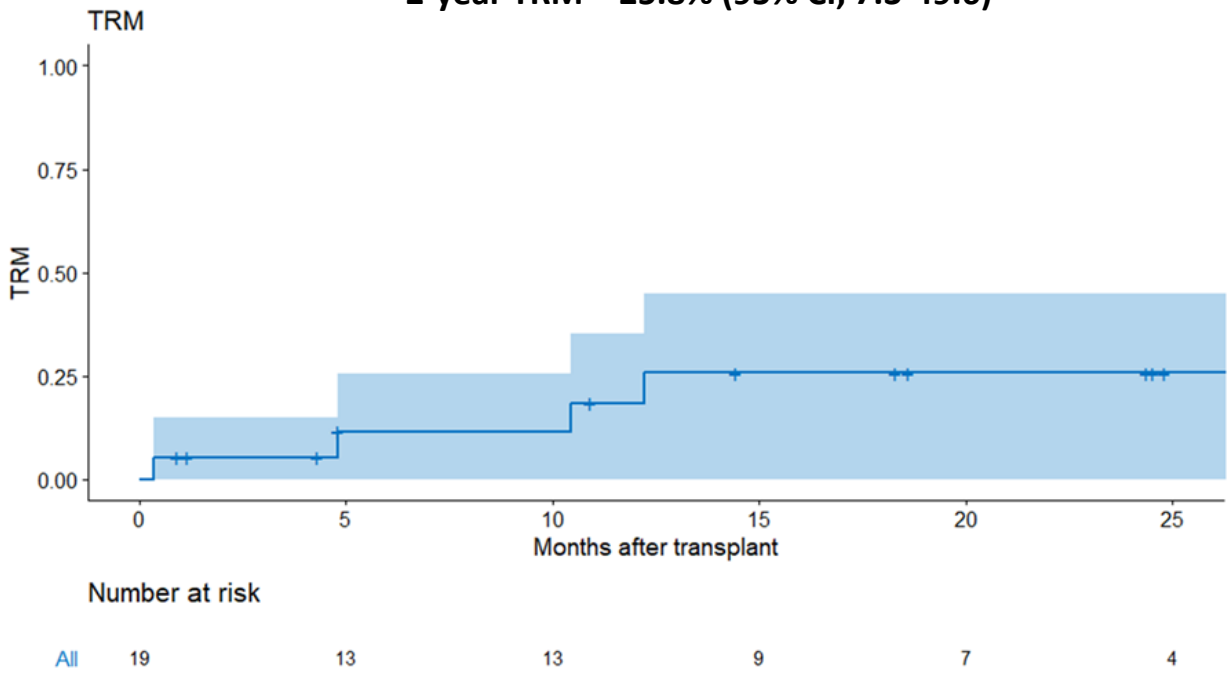
Post-transplant outcomes

- PMN and PLTs engraftment occurred at a median time of 16 (15-20) and 15 (12-24) days from HSCT
- At last follow-up, 94% of patients achieved full donor chimerism
- N=2 cases DLI were given because of an initial (< 6 months) mixed chimeric state
- Grade II-IV acute and chronic GvHD occurred in 26% and 21% of cases
- Median follow-up of 14 months (5-25) from HSCT
- 4 patients died (n=3 bacterial infection and n=1 CNS toxicity).

2-year OS = 74.2% (95% CI, 55.1-100)



2-year TRM = 25.8% (95% CI, 7.3-49.6)



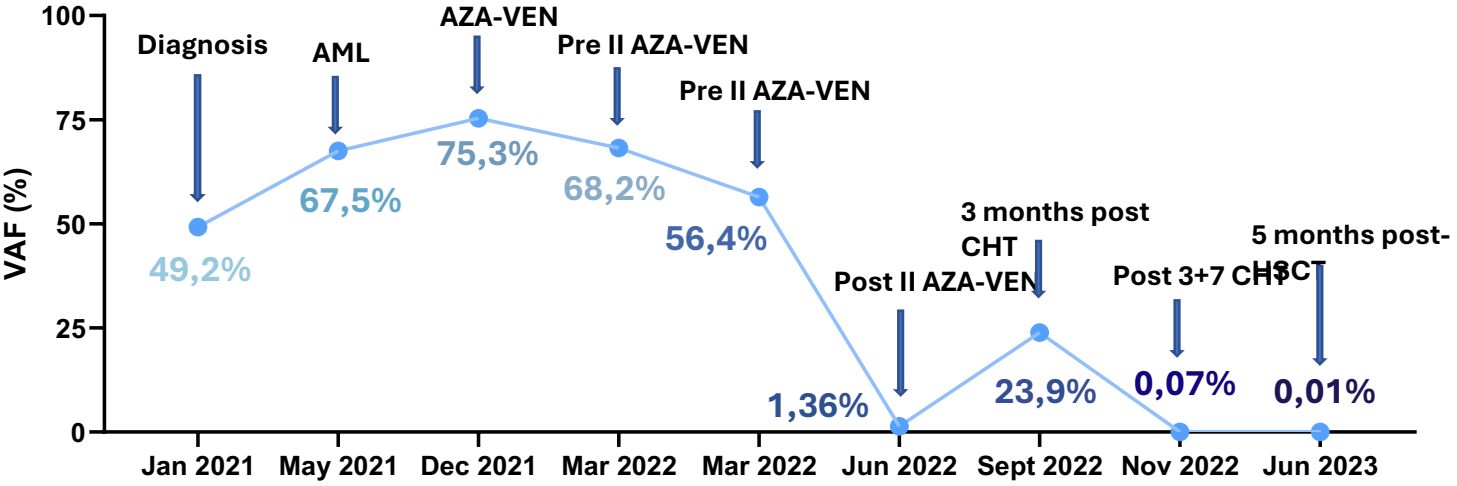
Gurnari C et al Blood Adv 2024

UBA1 clonal dynamics upon different therapeutics

Dr. Francesca Romano

UPN5

(Met41Val)



$$\sum \min\left(\frac{VAFt+1-VAFt}{VAFt}\right)$$

VAFt= baseline
VAFt+10= post-treatment

EPO, steroids, DMARDS

ΔVAF= -9.4% at a median of 36 months

Ruxolitinib

ΔVAF= +61%
n=3 patients at a median of 8 months

Azacitidine

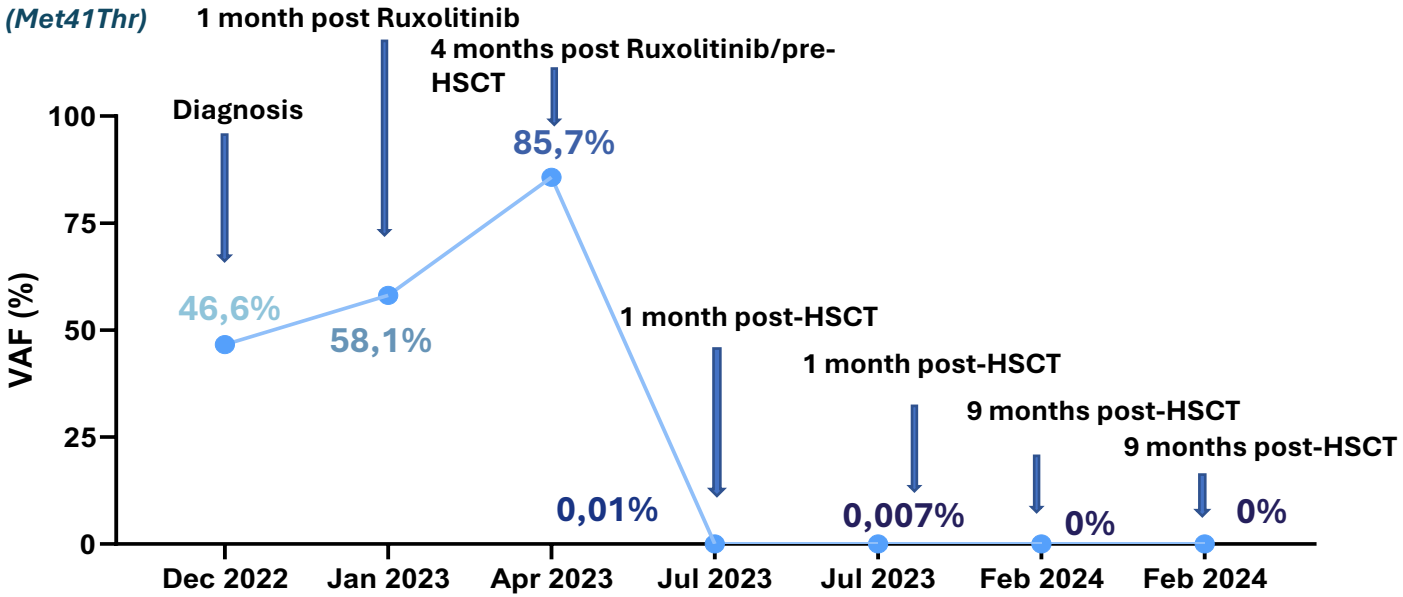
ΔVAF= -97.5%
n=6 patients, median VAF 1.3%, IQR 0.3-4.8 after a median of 8 months

Allo-HCT

Complete eradication
n=5 patients, median of 10 months from transplant

UPN6

(Met41Thr)

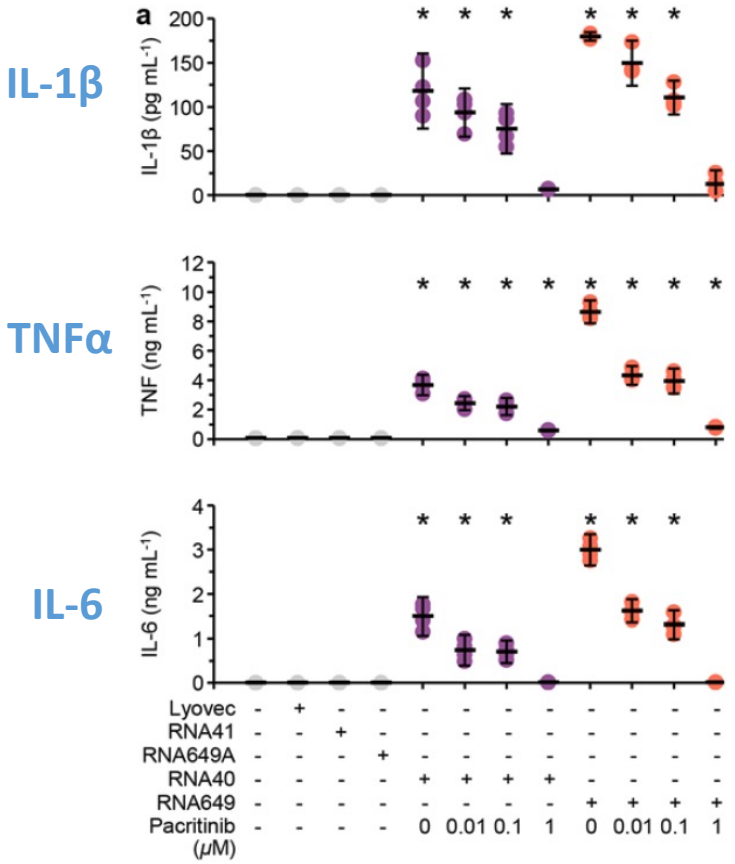


Gurnari et al BJH 2024

Pacritinib targets NFκB-mediated inflammation via IRAK1

Effective cytokine reduction and phenotype reversal in NFκB-driven inflammatory models

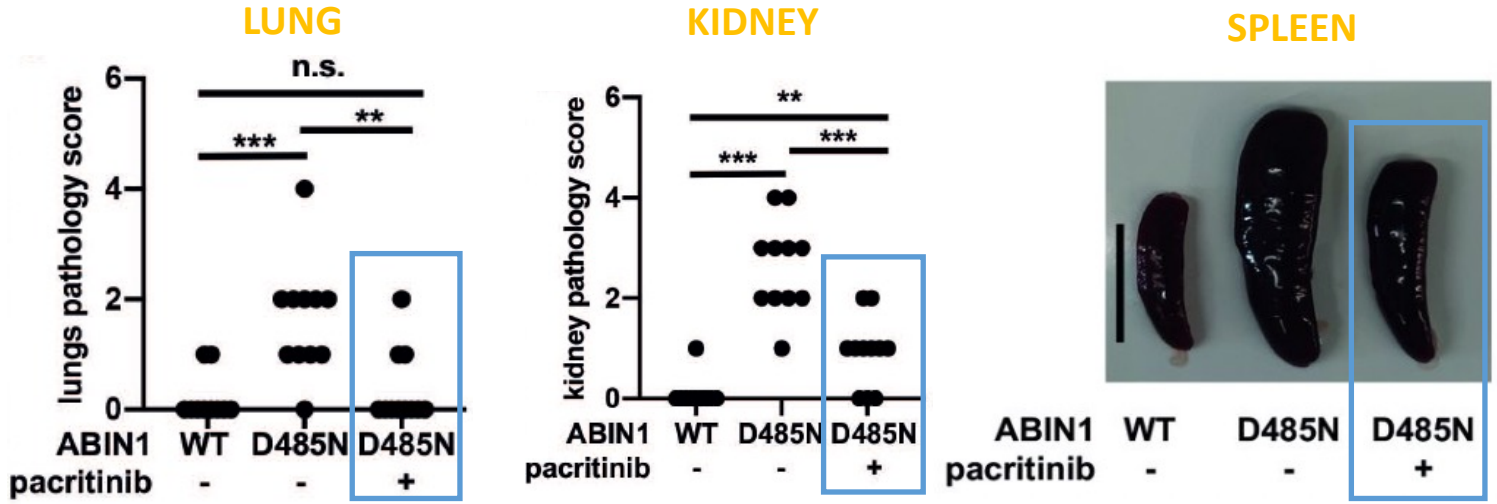
1 PAC leads to dose-dependent decrease in NFκB cytokines in cell culture.[1]



Cells stimulated with ssRNA from SARS-CoV2 (pictured) and HIV1 (not shown) and exposed to increasing concentrations of pacritinib (0, 0.01, 0.1, 1.0 µM).

2 PAC blocks NFκB-mediated inflammation in a murine lupus model.[2]

Pathology: Mice develop lupus due to ABIN1 knockout. ABIN1 is a polyubiquitin binding protein that inhibits NFκB. Knockout of ABIN1 result in inflammation and lupus phenotype.
Data: PAC improved organ pathology, splenomegaly, and dsDNA antibody production



3 **Pacritinib is broadly active against NFκB-associated cytokines and inflammatory pathology**, both *in vitro* and *in vivo*.

ABIN1, A20-binding inhibitor of NF-κB 1; IL, Interleukin; IRAK1, Interleukin-1 receptor-associated kinase 1; NFκB, nuclear factor kappa B; PAC, pacritinib 1. Campbell GR, et al. J Innate Immun. 2023:15:96-106. 2. Petrova T, et al. Lupus Sci Med. 2023;Feb;10(1):e000822.

PAXIS: A randomized, double-blind, placebo-controlled dose-finding phase 2 study (Part 1) followed by an open-label period (Part 2) to assess the efficacy and safety of pacritinib in patients with VEXAS syndrome

GC Escalation and Fixed Taper

Informed consent	Screening & Washout	RAND N=78 1:1:1	Double Blind Treatment Period Day 1 through End of Week 24	Open Label Treatment Period End of Week 24 through End of Week 48	EOT Visit (+7 days of last dose)	Safety Follow-Up (EOT+30)

Key inclusion

- VEXAS syndrome active within prior 6 months
- Stable GC dose 15-45 mg
- Prior therapy washout
- Platelets ≥25 × 10^9/L

Key exclusion

- HMA exposure within prior 6 mo or >4 cycles
- ≥9 RBCs in prior 90 days

PAC 200 mg BID

PAC 100 mg BID + placebo 1 cap. BID

Placebo 2 cap. BID

EOW 12: Open Label Transition
Failure to taper beyond a target GC dose due to Flare

PAC (open label, highest available dose)

PRIMARY ENDPOINT

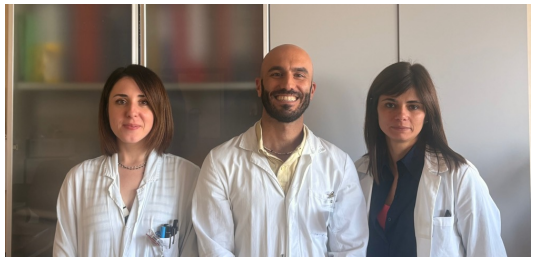
- **Overall Clinical Response**

Flare-free interval lasting ≥8 wks. after successful GC taper, with GC dose ≤10 mg during the entire interval

SECONDARY ENDPOINTS

- Best response
- Number of flare-free days with GC dose <10 mg
- Hematologic improvement
- Change in HRQoL
- PK/PD
- Safety

PAXIS



Dr. Marianna Velocci
Dr. Elisa Meddi

- BID, twice daily; EOT, end of treatment; GC, glucocorticoid; HMA, hypomethylating agent; HRQoL, health-related quality of life; PAC, pacritinib; PD, pharmacodynamic; PK, pharmacokinetic; RBC, red blood cell.

Acknowledgments

The success is the result of a team's efforts!

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

TOR VERGATA
UNIVERSITY OF ROME

EBMT

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carmelogurnari31@gmail.com

@CarmeloGurnari

Cleveland Clinic