Klinikum rechts der Isar
Technische Universität München

VEXAS Syndrom:
Das klinische Chamäleon
Wann daran denken, wie behandeln?

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VEXAS REGISTER

11. Okober 2024
Basel

Interessenkonflikte

- **Consultancy:** BMS, AbbVie, Jazz Pharmaceuticals, Astellas, Otsuka
- **Honoraria:** BMS, AbbVie, Pfizer

Dr. Katja Sockel
Initiatorin des VEXAS Registers Deutschland

VEXAS Syndrome – at the intersection of Hematology, Rheumatology & Dermatology

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

- **VEXAS:** Vacuoloes, E1 Enzyme, X-Linked, Autoinflammatory, Somatic syndrome
- Autoinflammatory disease first described in 2020 (Beck et al, *NEJM 2020*)
- Somatic mutation in *UBA1 (Ubiquitin like modifier activating enzyme),* a gene located on the X chromosome
- Encodes E1 enzyme which intiates protein ubinquitination in the cell

Beck et al, N Engl J Med 2020;383:2628-38

Sequencing Approach Identifies Somatic UBA1 Mutation

Periodic Fever/Systemic Inflammation Database
Undiagnosed Diseases Program

→ Exome Sequencing
2560 Persons

→ Protein Ubiquitylation gene ontology
841 genes

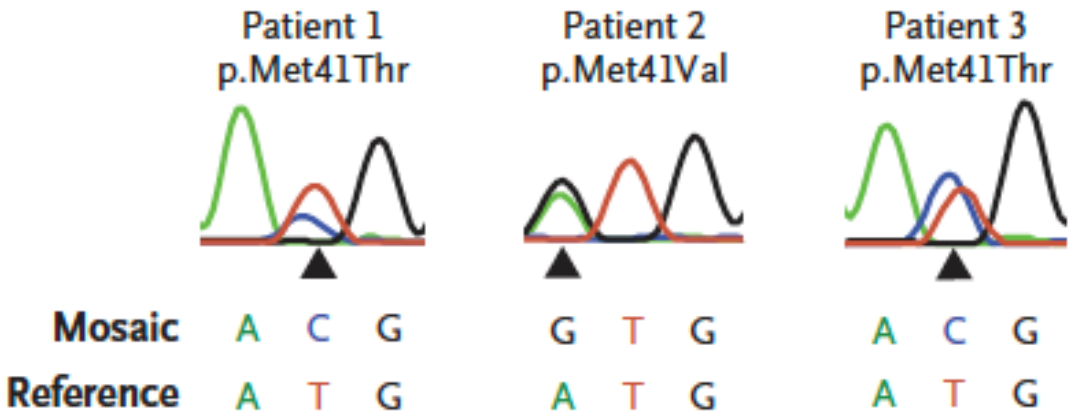
↓

Intolerant to haploinsufficiency
Novel variants
Shared variants

← *UBA1* p.Met41Val/Thr

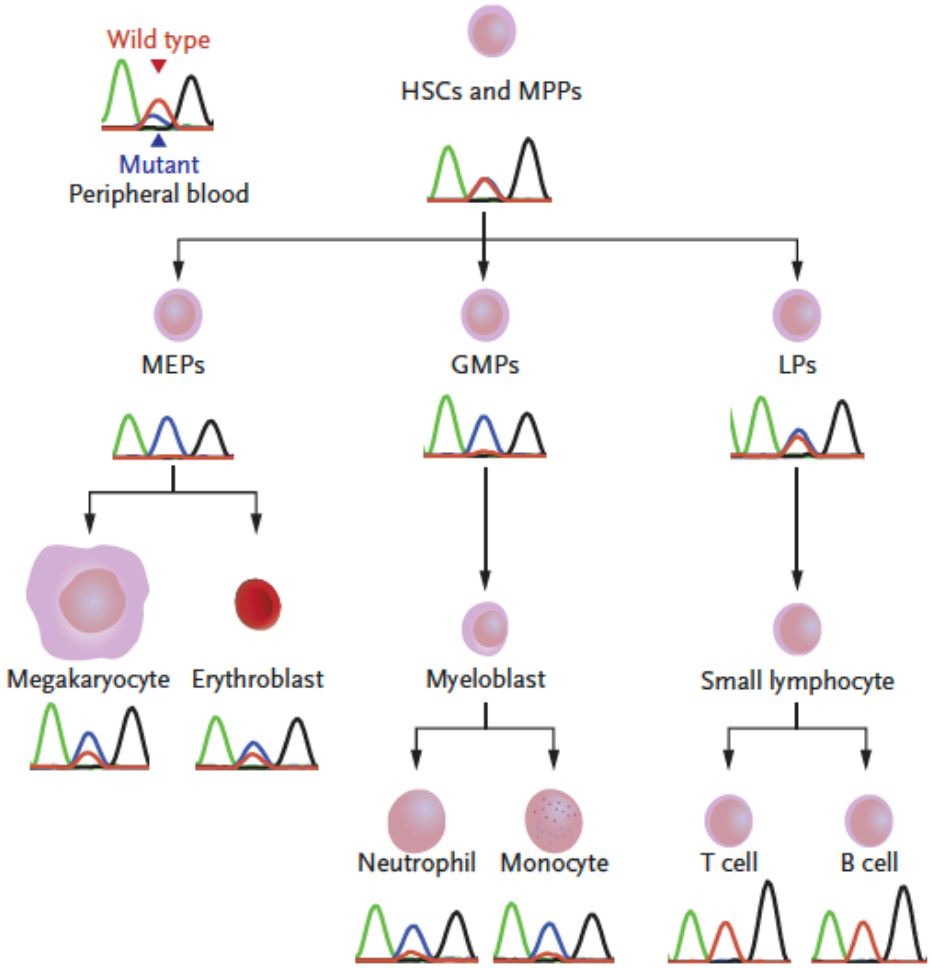
← N = 25

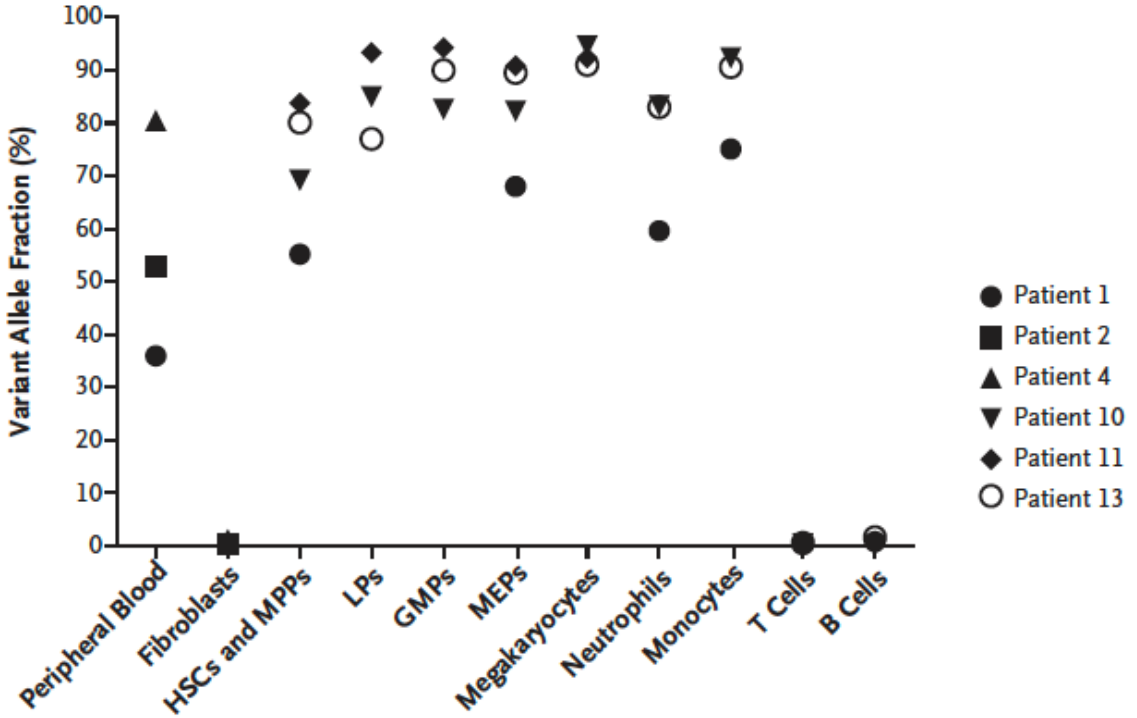
NGS of 22 pts with same clinical phenotype



Beck D et al, N Engl J Med 2020;383:2628-38

UBA1 variants are enriched in hematopoietic progenitors and myeloid cells

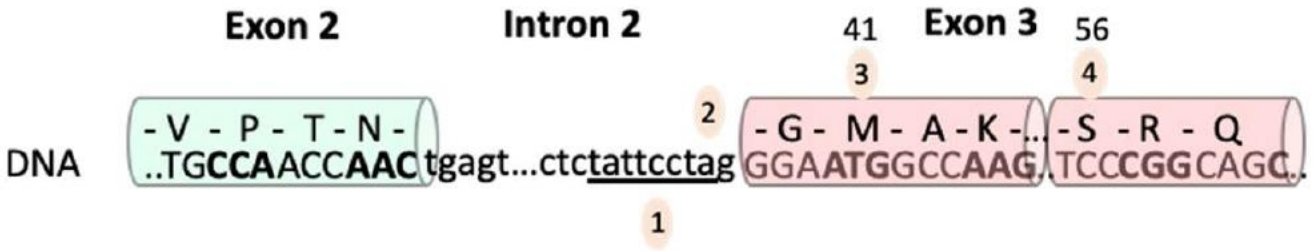




Beck et al, N Engl J Med 2020;383:2628-38

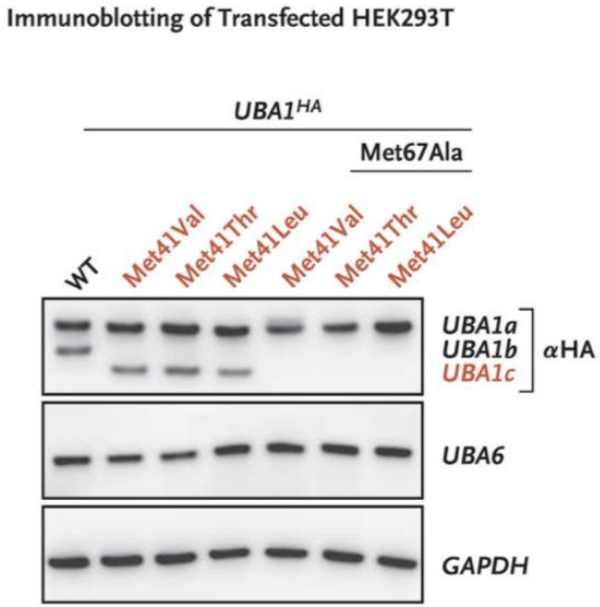
UBA1 Mutations

most commonly in methionine 41 of exon 3



1 Deletion of the site splice : c.118-9_118-2del
2 Point mutation in splice site : c.118-1 et c.118-2
3 Mutation p.Met41
4 Mutation p.Ser56

- p.Met41Thr (c.122 T.C) 45%
- p.Met41Val(c.121 A.G) 30%
- p.Met41Leu (c.121 A.C) 18%
- Splice mutations 7%



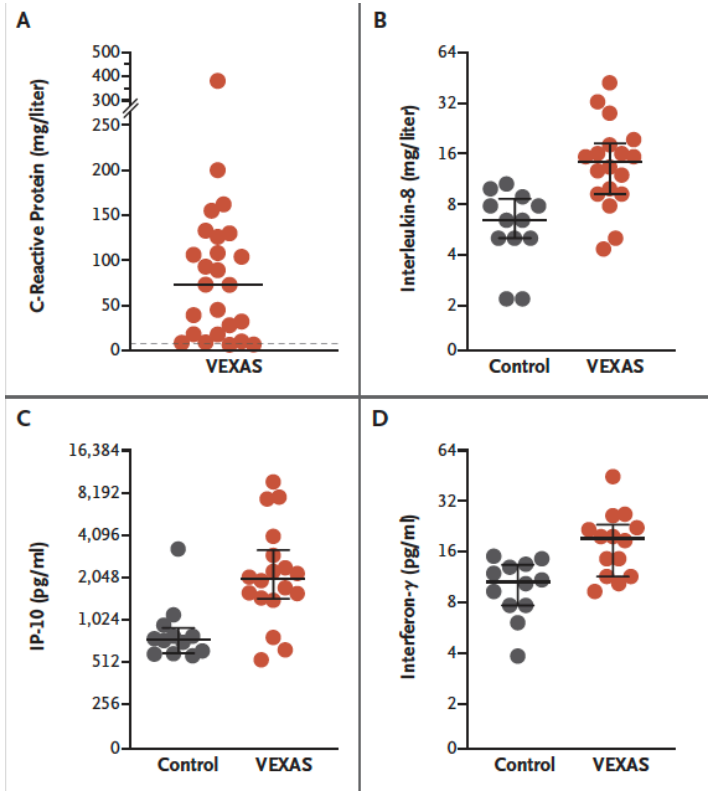
production of catalytically deficient UBA1c

disrupted post-translational protein modification

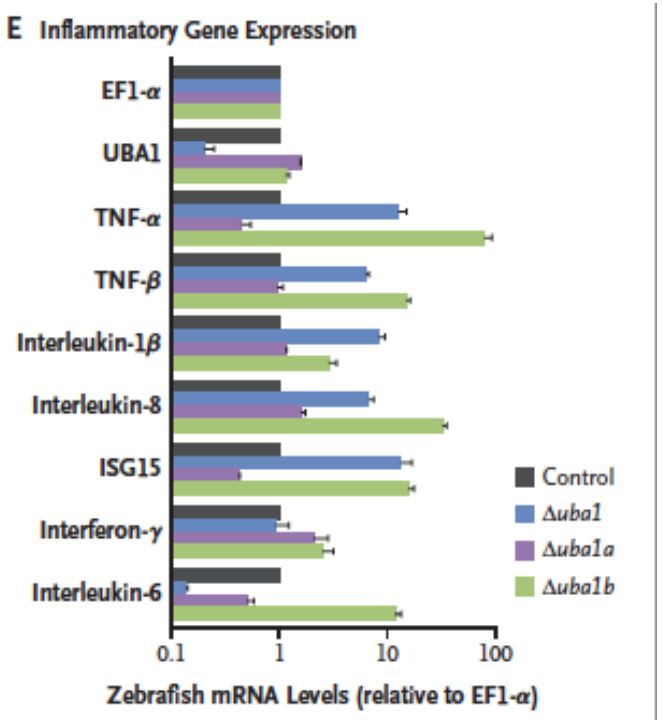
Beck et al, N Engl J Med 2020;383:2628-38, Templé et al, Diagnostics 2022

Link between Clonal Hematopoiesis and Inflammation

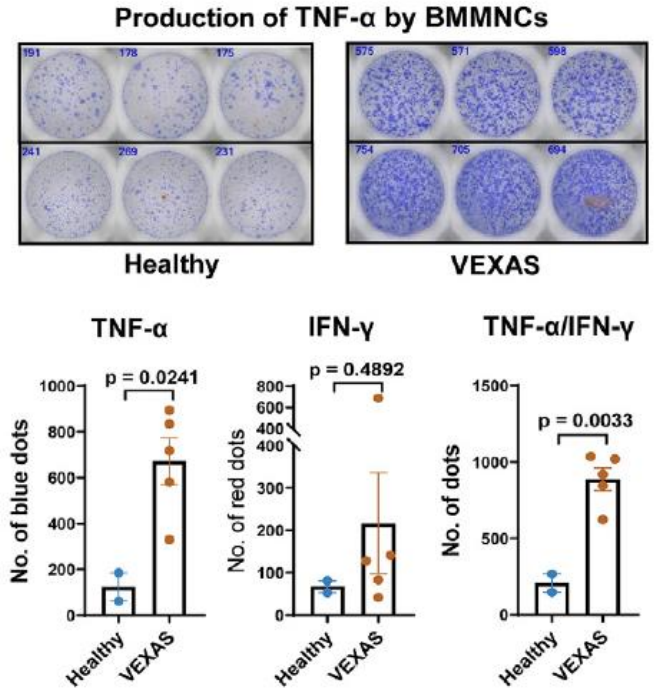
Elevated serum cytokines in VEXAS pts



Gene expression of inflammatory cytokines in gene edited *UBA1* mut zebrafish

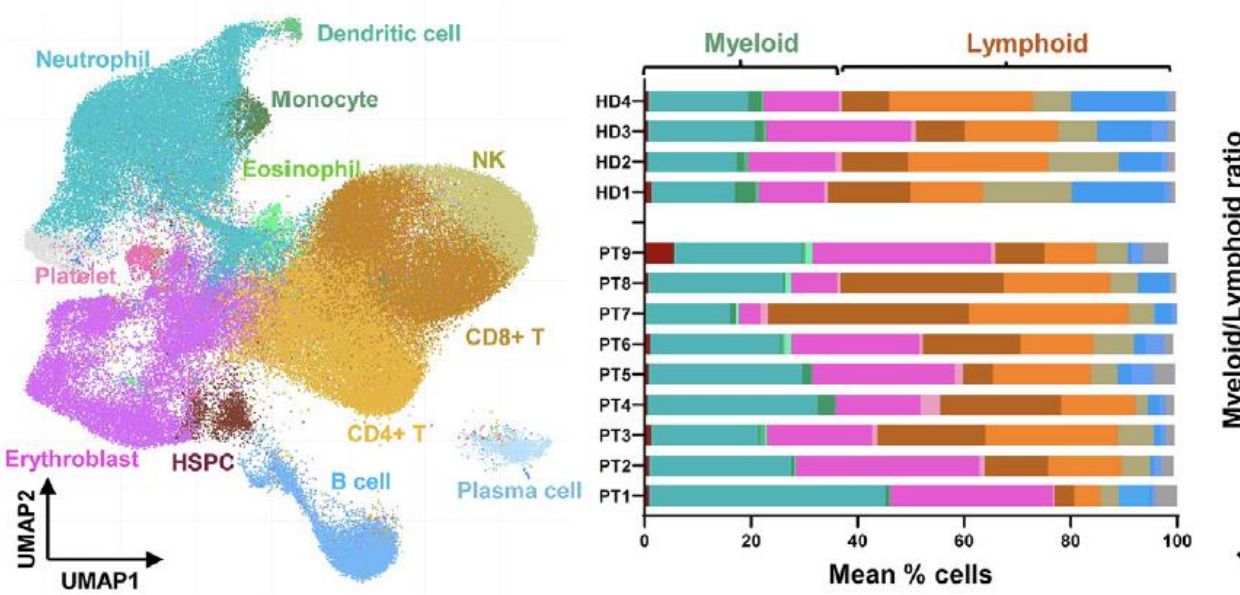


VEXAS BMMNC produce inflammatory cytokines

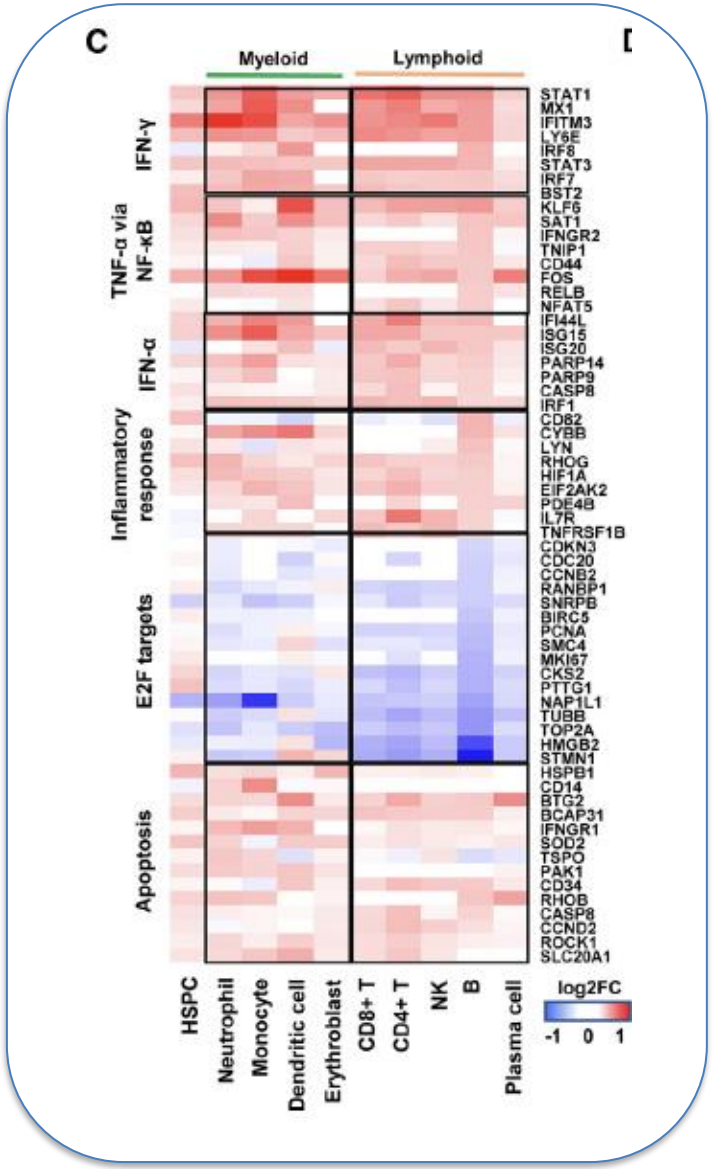


Beck et al, N Engl J Med 2020;383:2628-38 *Wu Z, Gao S et al, Cell Reports Medicine 2023, 4: 101160*

VEXAS HSPC are highly inflamed

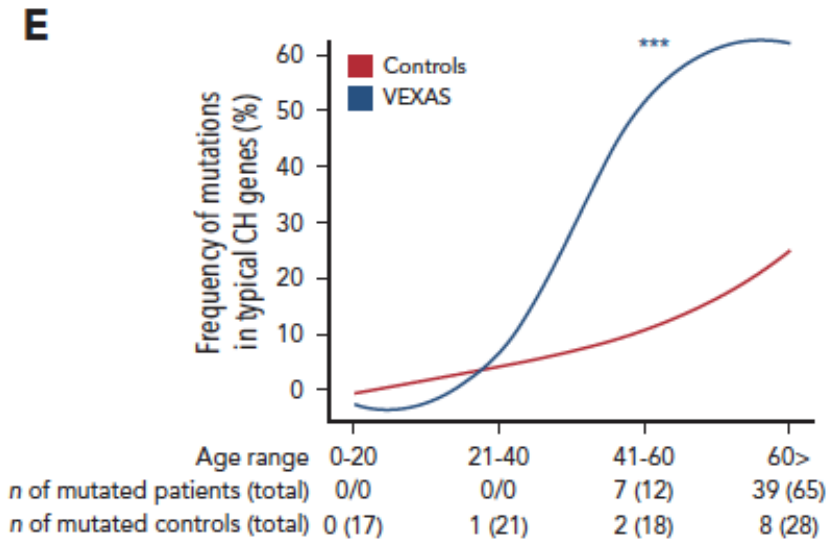


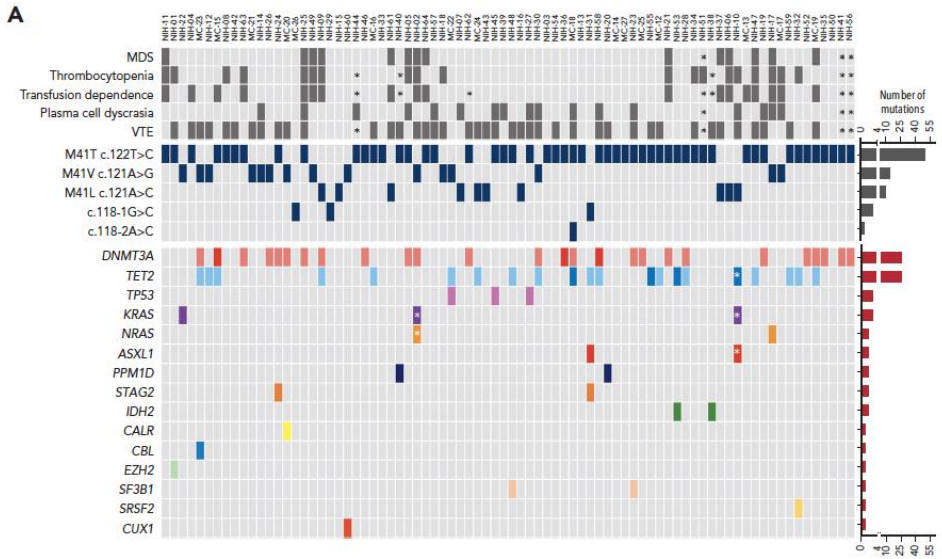
- Inflammation and myeloid dominance originate in hematopoietic stem cells in VEXAS syndrome
- mt*UBA1* myeloid cells upregulate inflammatory pathways compared with wild-type cells
- There are biased granulocytic differentiation and increased proliferation of mt*UBA1* cells

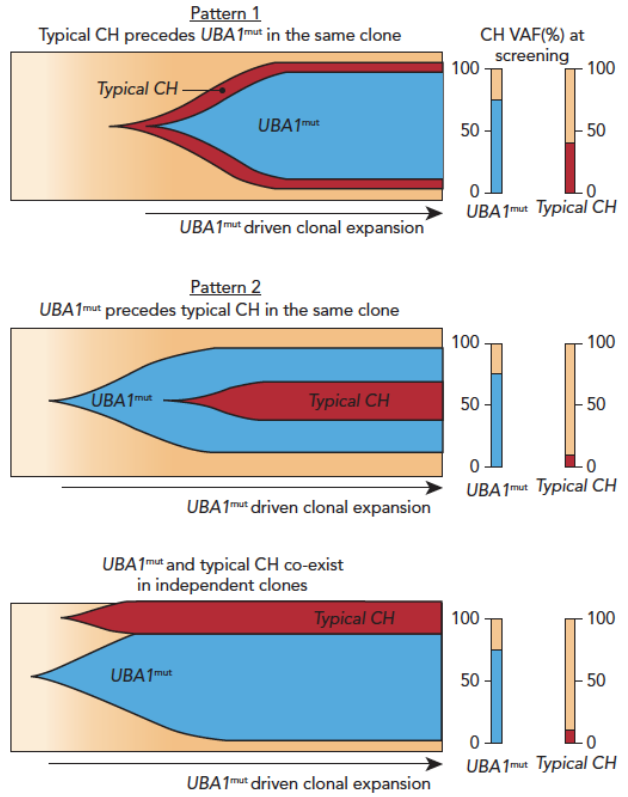


Wu Z, Gao S et al, Cell Reports Medicine 2023, 4: 101160

Clonal Hematopoiesis and VEXAS



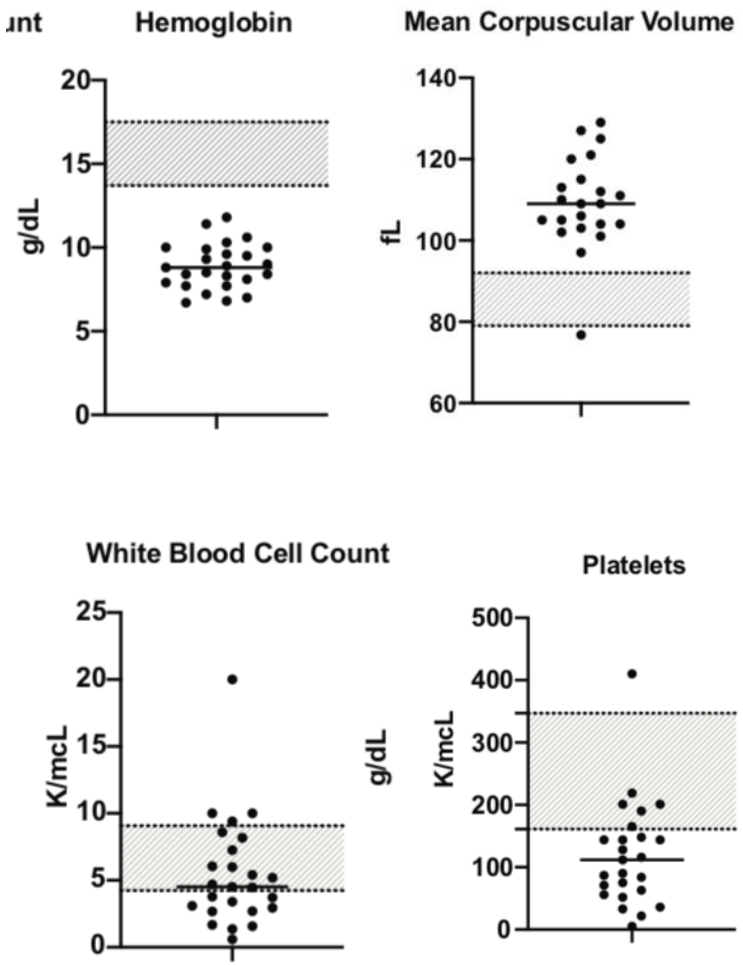




- Patients with VEXAS have enrichment of typical CH mutations
- UBA1 mutations are responsible for myeloid clonal expansion

Guiterrez-Rodrigues F et al, Blood 2023, 142: 244

PB and BM Abnormalities



NIH Cohort

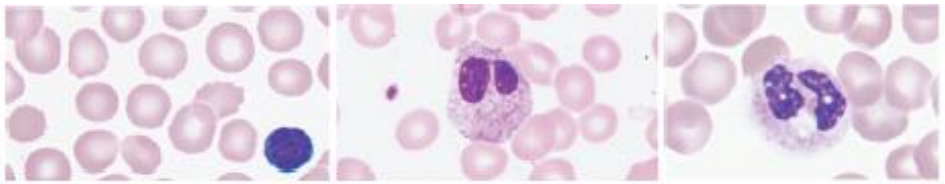
Characteristics	N=14 (%)
Evaluated at NIH after VEXAS diagnosis – no. (%)	9 (64)
Anemia – no. (%)	
Macrocytic anemia	14 (100)
Transfusion dependent	6/9 (67)
Thrombocytopenia – no. (%)	
<100/K	3 (21)
<50/K	6 (43)
Neutropenia – no. (%)	
<1500 per cubic millimeter	1 (7)
Diagnosis of MDS – no. (%)	5 (36)
Vacuoles in bone marrow – no. (%)	
Erythroid precursors	14 (100)
Myeloid precursors	14 (100)
Cellularity – no. (%)	
Normocellular	2 (14)
Hypercellular	12 (86)
Increased M:E ratio (>3:1) – no. (%)	13(93)
Blast percentage	
≥5%	0
>2-<5%	5 (36)
≤2%	9 (64)
Megakaryocyte dysplasia – no. (%)	
<10%	9 (64)
>=10%	5 (36)
Erythroid dysplasia– no. (%)	
<10%	13 (93)
>=10%	1 (7)
Myeloid dysplasia – no. (%)	
<10%	12 (86)
≥10%	2 (14)
Other findings	
Absence of B cell precursors	10/10 (100)
Small clonal B-cell population of undetermined significance	1 (7)
Plasma cell dyscrasia	2 (14)
Myeloid somatic mutations, not including UBA1 – no. (%)	
Yes*	4/9 (44)
No	5/9 (56)

French Cohort

Laboratory data	
Haemoglobin (g dL^{-1})	10·10 (9·00–11·50)
MCV	101 (94·08–106·75)
Platelets (/mm^3)	204 (138·25–260·25)
Leucocytes (/mm^3)	4400 (2972–6222)
Neutrophils (/mm^3)	2600 (1640–4185)
CRP (g L^{-1})	61 (30·00–128)

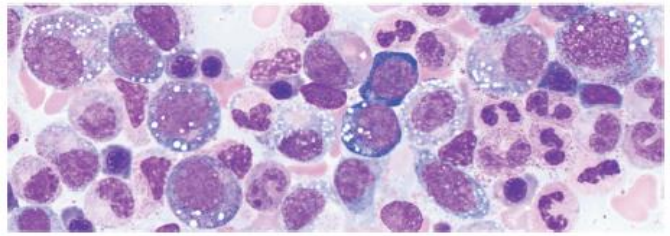
Cytomorphologic Features

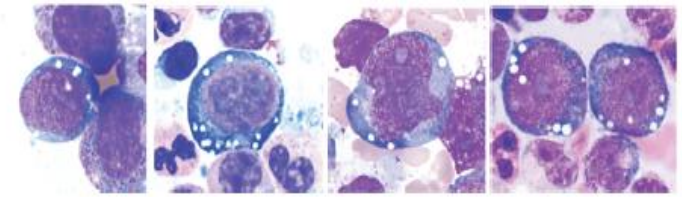
Peripheral Blood

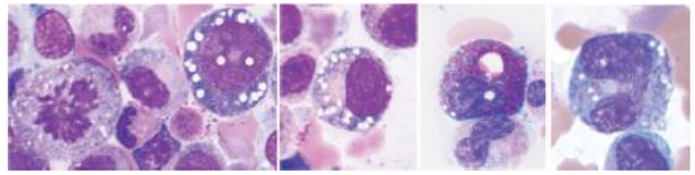


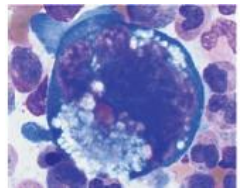
- Macrocytic anemia
- Pelger forms
- Vacuolated neutrophils

Bone Marrow Aspirates



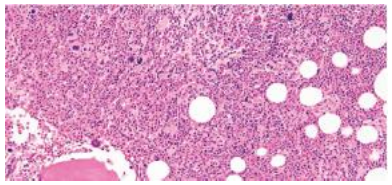






- Vacuolization in myeloid, erythroid precursors and megakaryocytes

BM Histology



Hypercellular BM with G>>E

Proposed scoring:
Medullary cytoplasmic vacuoles (>1/cell) in >10% of neutrophil precursors
+
Clinical context

Obiorah et al, Blood Adv 2021; Lacombe et al, Br J Haematol 2021;Templé et al, Diagnostics 2022

Clinical Manifestations of VEXAS

Table 1. Demographic and Clinical Characteristics of Participants with the VEXAS Syndrome.*

Characteristic	Participants (N=25)
Demographic characteristics	
Male sex — no. (%)	25 (100)
Median age at onset (range) — yr	64 (45–80)
Died before the current study — no. (%)	10 (40)
Genetic characteristics	
Somatic *UBA1* (NM_003334.3) variant (p.Met41) — no. (%)	25 (100)
p.Met41Thr (c.122T→C)	15 (60)
p.Met41Val (c.121A→G)	5 (20)
p.Met41Leu (c.121A→C)	5 (20)
Key clinical features	
Fever — no. (%)	23 (92)
Skin involvement — no. (%)†	22 (88)
Pulmonary infiltrate — no. (%)	18 (72)
Ear and nose chondritis — no. (%)	16 (64)
Venous thromboembolism — no. (%)	11 (44)
Macrocytic anemia — no. (%)	24 (96)
Bone marrow vacuoles — no./total no. (%)	18/18 (100)
Laboratory findings	
Median C-reactive protein (IQR) — mg/liter	73 (18–128)
Median ESR (IQR) — mm/hr	97 (64–124)
Current or past treatment	
Glucocorticoids — no. (%)	25 (100)
Median no. of synthetic DMARDs (IQR)	2 (1–3)
Median no. of biologic or target synthetic DMARDs (IQR)	2 (0.5–3)
Diagnostic or classification criteria that were met — no. (%)	
Relapsing polychondritis	15 (60)
Sweet's syndrome	8 (32)
Myelodysplastic syndrome	6 (24)
Multiple myeloma or monoclonal gammopathy of undetermined significance	5 (20)
Polyarteritis nodosa	3 (12)
Giant-cell arteritis	1 (4)

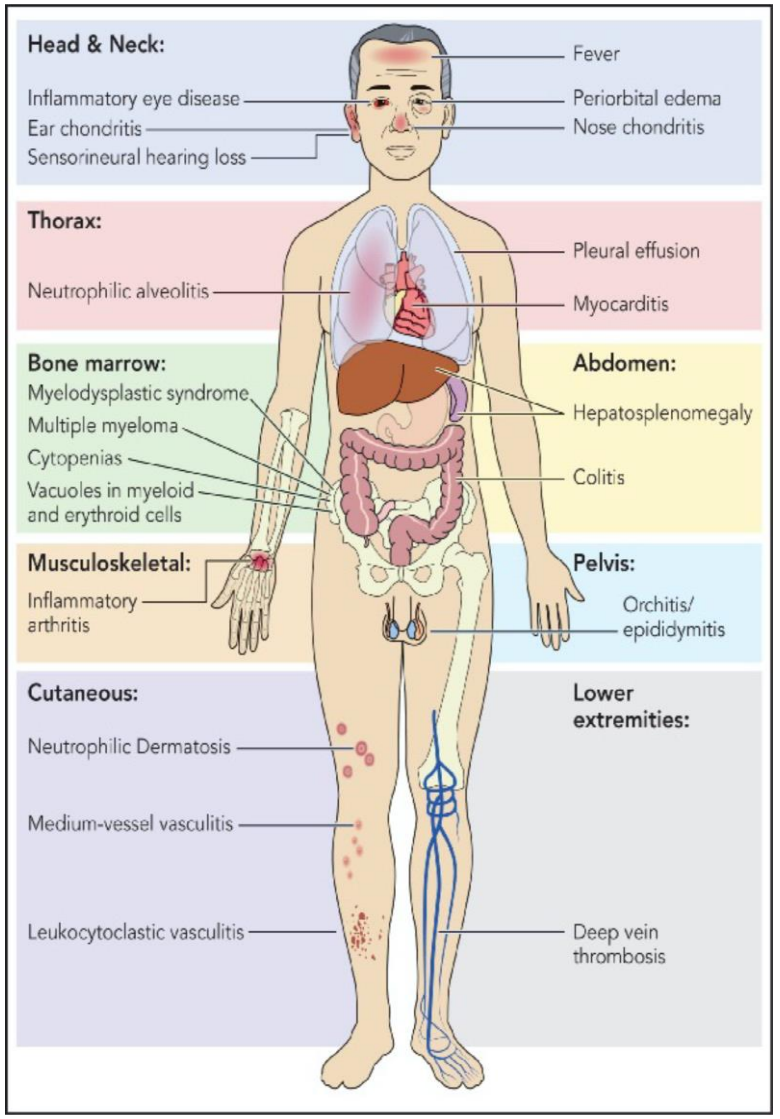
Beck et al, NEJM 2020

Characteristics	All patients (n = 116)
Male sex	111 (95·7)
Age at diagnosis (years)	71·00 (66·25–76·00)
Weight loss	62 (54·5)
Fever	75 (64·6)
Chondritis	42 (36·2)
Auricular chondritis	37 (31·9)
Nasal chondritis	18 (15·5)
Skin lesions	97 (83·6)
Neutrophilic dermatitis	46 (39·6)
Vasculitis	30 (25·9)
Erythema nodosum	15 (12·9)
Urticaria	10 (8·6)
Erythematosus papules	25 (21·5)
Injection-site reactions	9 (7·8)
Periorbital oedema	10 (8·6)
Gastrointestinal tract	16 (13·8)
Abdominal pain	10 (8·6)
Diarrhoea	8 (6·9)
Gastrointestinal bleeding	1 (0·9)
Digestive perforation/obstruction	1 (0·9)
PNS involvement	17 (14·6)
Sensory neuropathy	6 (5·2)
Multiple mononeuropathy	3 (2·6)
Ocular involvement	47 (40·5)
Uveitis	11 (9·5)
Scleritis	10 (8·6)
Episcleritis	14 (12·1)
Orbital mass	4 (3·4)
Heart involvement	13 (11·2)
Pericarditis	5 (4·3)
Myocarditis	3 (2·6)
Lung involvement	57 (49·1)
Pulmonary infiltrates	47 (40·5)
Pleural effusion	11 (9·5)
Arterial involvement	12 (10·3)
Aortitis	2 (1·7)
Aneurysms	4 (3·4)
Lymph node enlargement	40 (34·5)
Cervical	8 (6·9)
Axillary	3 (2·6)
Mediastinal	16 (13·8)
Abdominal	3 (2·6)
Inguinal	3 (2·6)
Spleen/liver enlargements	16 (13·8)/9 (7·8)
Kidney involvement	11 (9·5)
Unprovoked thrombosis	41 (35·3)
Arthralgias	33 (28·4)

Georgin-Lavaille, Br J Dermatol 2022

- Relapsing Polychondritis
- Neutrophilic dermatosis
- Unexplained fever
- Unprovoked thrombosis
- Lung infiltrates
- Macrocytic anemia

- MDS
- MM

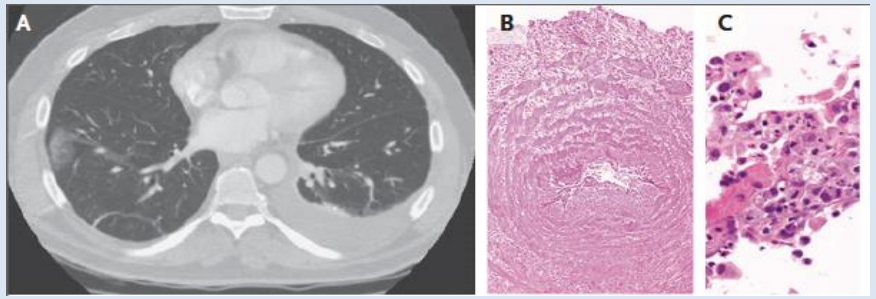


Obiorah et al, Blood Adv 2021

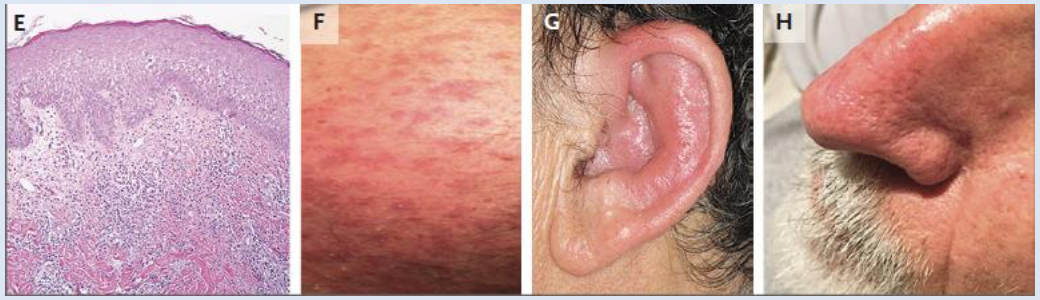
Clinical Manifestations of VEXAS

LUNG

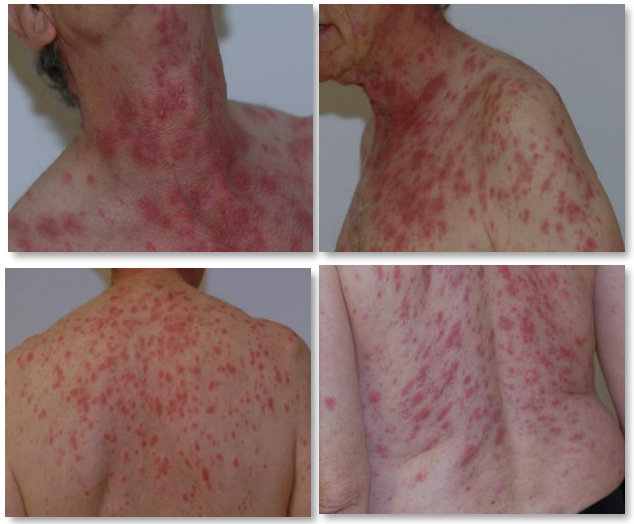
Lung infiltrates Vasculitis Alveolitis

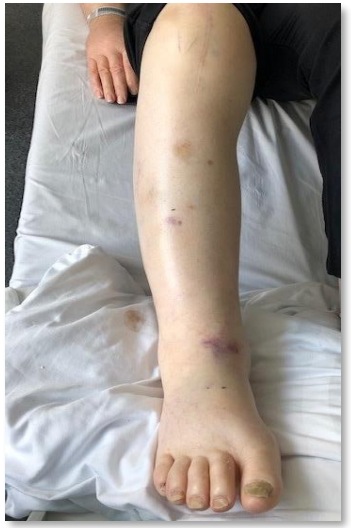


SKIN

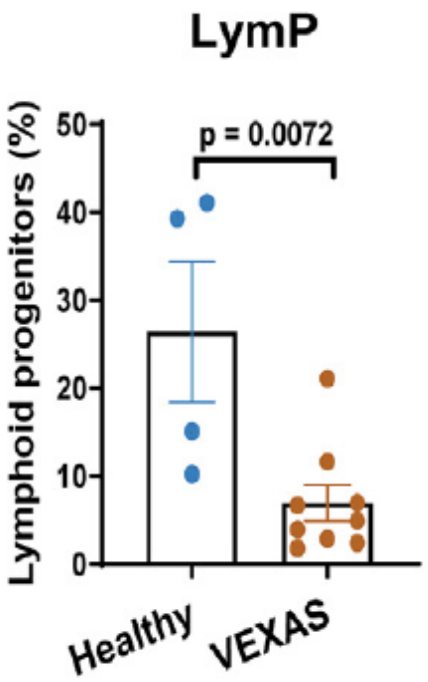


Vasculitis Chondritis





VEXAS patients are at risk for infections



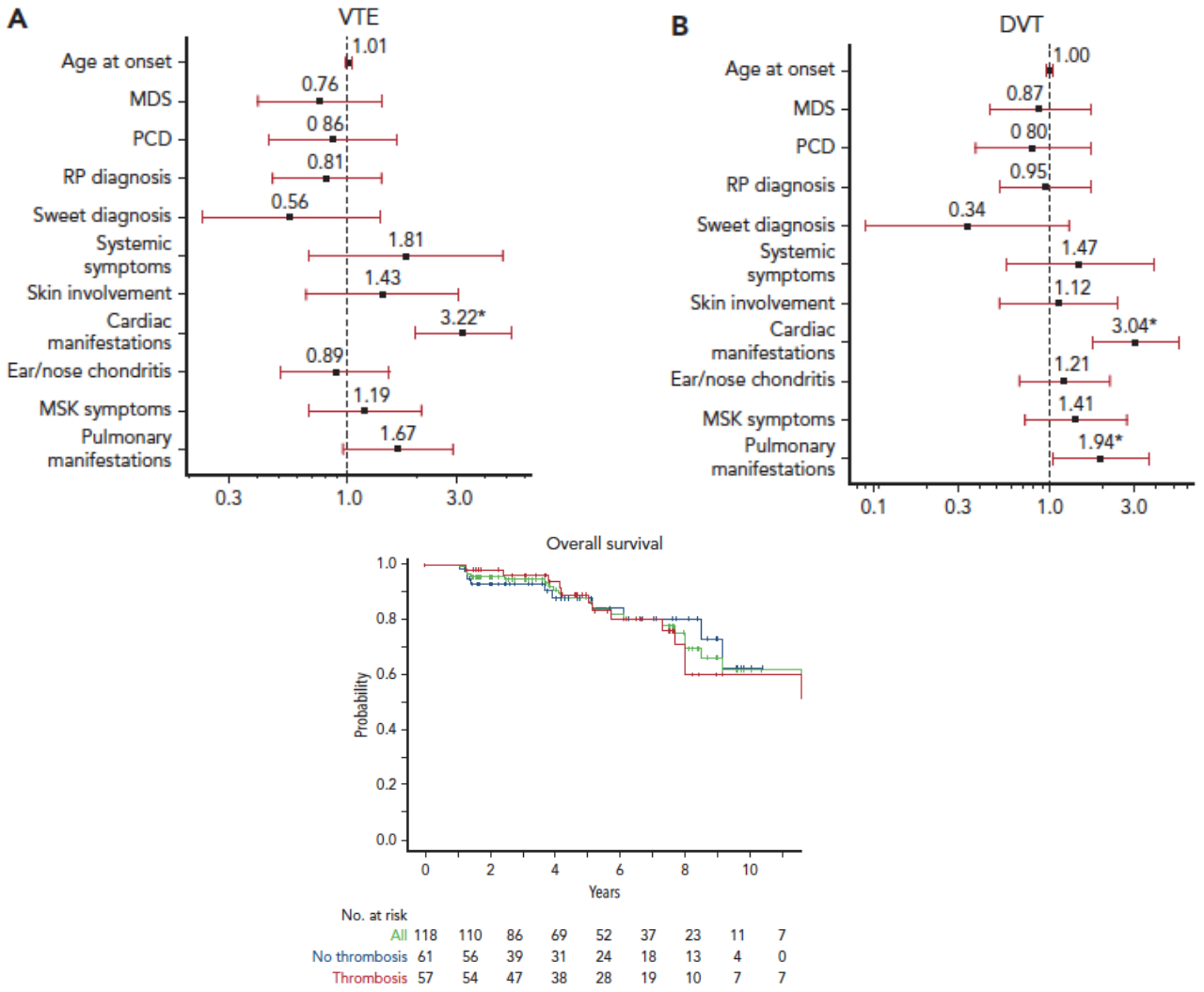
Reduced lymphopoiesis and prolonged steroids

N=94	incidence	risk of death
PJP	6%	HR 72.41 (95% CI, 13.6-533.7)
Herpes (VZV)	15%	OR 12.1 (95% CI, 1.29-114.8)
Mycobact. (NTM)	10%	HR 29.9 (95% CI, 9.5-88.79)

Wu Z, Gao S et al, Cell Reports Medicine 2023, 4: 101160; Czech M et al, Open Forum Infect Dis 2024;11:ofae405

VEXAS patients are at risk for thrombosis

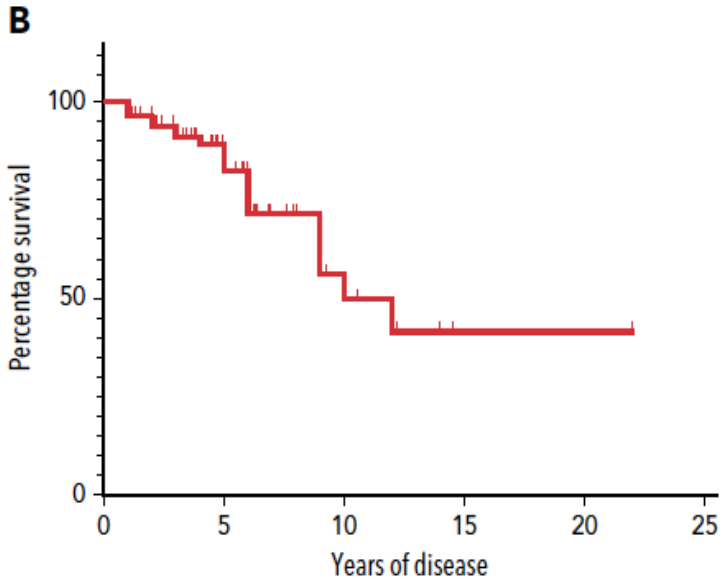
Demographic characteristics	
Male sex, n (%)	119 (100)
Age (y), median (range)	64.5 (39.0-86.0)
Somatic *UBA1* mutations, n (%)	**(n = 117)**
p.Met41Thr	69 (59)
p.Met41Val	27 (23)
p.Met41Leu	16 (14)
Splice motif mutation	5 (4)
Venous thrombotic events	
VTE, n (%)	49 (41)
DVT, n (% of VTE)	41 (84)
Proximal DVT, n (% of VTE)	27 (55)
Distal DVT, n (% of VTE)	12 (24)
PE, n (% of VTE)	17 (35)
Unprovoked event, n (% of VTE)	30 (61)
Recurrent event, n (% of VTE)	20 (41)
Event while on anticoagulation, n (% of VTE)	10 (20)
Arterial thrombotic events	
Any, n (%)	15 (13)
Stroke, n (% of arterial)	5 (33)
MI, n (% of arterial)	7 (47)
Other, n (% of arterial)	3 (27)
Recurrent event, n (% of arterial)	1 (7)



Kusne Y et al, Blood 2024, 143:2190

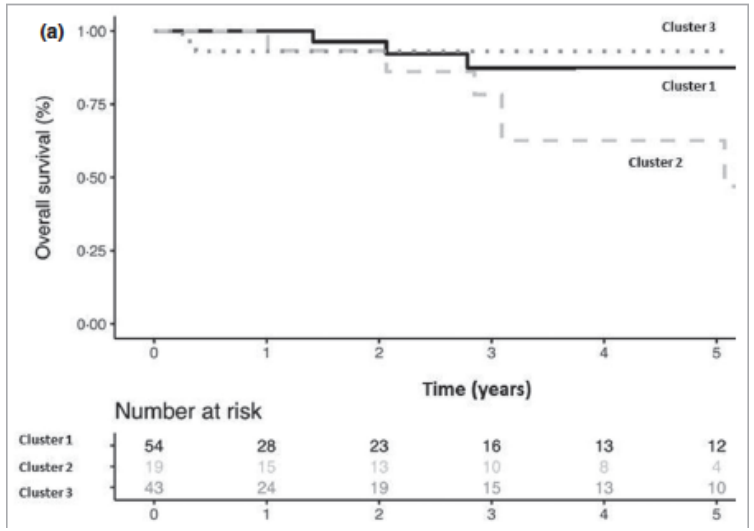
Outcome

Median OS 10y



Ferrada et al, Blood 2022

5y OS 63%



Georgin-Lavialle, Br J Dermatol 2022

Cluster 1: mild disease (47%)
Cluster 2: MDS (16%)
Cluster 3: constitutional symptoms (37%)

Only retrospective data available, VEXAS sometimes diagnosed after death, no long-term follow-up

VEXAS and MDS

Frequent association of MDS with *UBA1* mutation/VEXAS diagnosis

Cohort	Patients, n	macrocytic anemia, n (%)	MDS, n (%)	MM, n (%)
Beck et al	25	24 (96)	6 (24)	5 (20)
Georgin-Lavaille et al	116	116 (100)	58 (50)	12 (10)
Ferrada et al	83	81 (97)	26 (31)	
Obiorah et al	16	16 (100)	6 (38)	2 (12.5)
Bourbon et al	11	7 (64)	6 (55)	
Poulter et al	10	10 (100)	9 (90)	2 (18)
Heiblig et al	30	30 (100)	13 (43)	
Sirenko et al *	40	40 (100)	25 (63)	

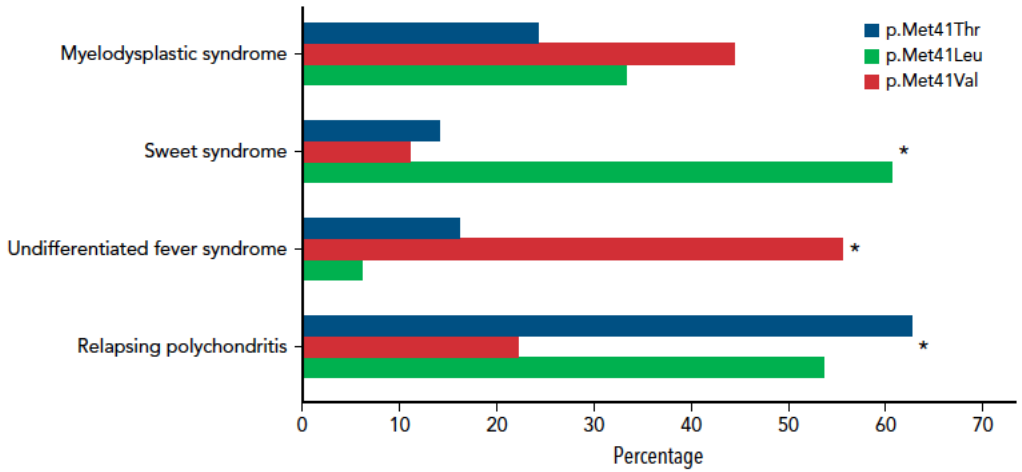
UBA1 mutations need to be considered in the diagnostic workup of MDS

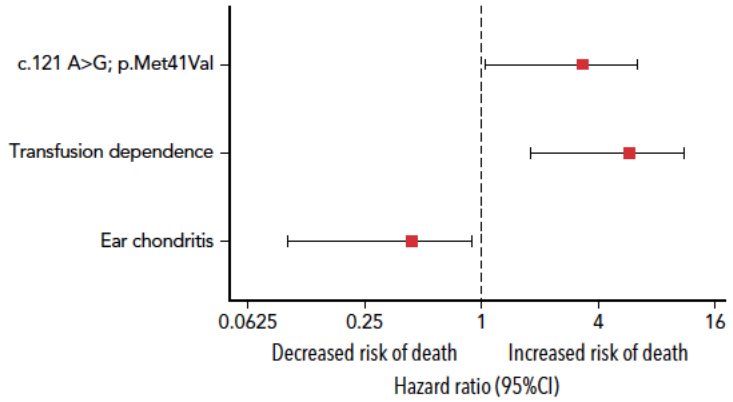
*1% of 2027 MDS pts and 7% of pts w/o clear disease classification

- BM dysplasia present in VEXAS, but >10% only in those that develop MDS
- IPSS-R in VEXAS generally very low/low
- VEXAS patients with MDS have poorer survival rate than VEXAS without MDS

Genotype, Transfusion Dependence and Ear Chondritis are Predictive

	Total cohort (n = 83)	Leu variant (n = 15)	Val variant (n = 18)	Thr variant (n = 50)	*P* value
Demographics					
Age of disease onset median (range)	66 (41-80)	66 (55-74)	65 (50-72)	66 (42-80)	.97
Sex, n (%)	83 (100)	15 (100)	18 (100)	50 (100)	1.00
White, n (%)	83 (100)	15 (100)	18 (100)	50 (100)	1.00
Clinical diagnosis					
Relapsing polychondritis, n (%)	43 (52)	8 (53)	4 (22)	31 (62)	.01
Undifferentiated fever syndrome, n (%)	19 (23)	1 (6)	10 (55)	8 (16)	<.01
Sweet syndrome, n (%)	18 (22)	9 (60)	2 (11)	7 (14)	<.01
MDS, n (%)	26 (31)	5 (33)	8 (44)	13 (26)	.35
Clinical manifestations, n (%)					
Fever	69 (83)	13 (87)	17 (94)	39 (78)	.25
Skin involvement	68 (82)	13 (87)	15 (83)	40 (80)	.82
Arthritis	48 (58)	8 (53)	10 (55)	30 (60)	.87
Pulmonary infiltrates	47 (57)	10 (67)	10 (55)	27 (54)	.67
Ear chondritis	45 (54)	8 (53)	4 (22)	33 (66)	<.01
Unprovoked DVT	34 (41)	9 (60)	6 (33)	19 (38)	.24
Nose chondritis	30 (36)	5 (33)	3 (16)	21 (42)	.13
Periorbital edema	25 (30)	3 (20)	10 (55)	12 (24)	.03
Hearing loss	24 (29)	7 (47)	4 (22)	13 (26)	.25
Ocular inflammation	20 (24)	1 (6)	1 (5)	18 (36)	<.01
Pulmonary embolism	11 (13)	2 (13)	4 (22)	5 (10)	.45
Pleural effusion	11 (13)	2 (13)	4 (22)	5 (10)	.45
Orchitis	10 (12)	0 (0)	4 (22)	6 (12)	.07
Airway chondritis	1 (2)	0 (0)	0 (0)	1 (2)	.60



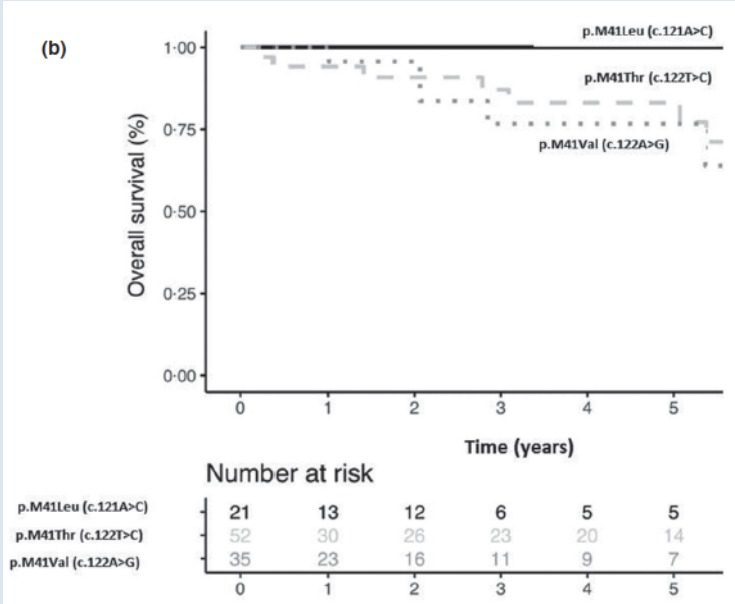


p.Met41Val genotype associated with severe undifferentiated inflammatory syndrome

Ferrada M et al, Blood 2022

Phenotype - Genotype Association with Outcome

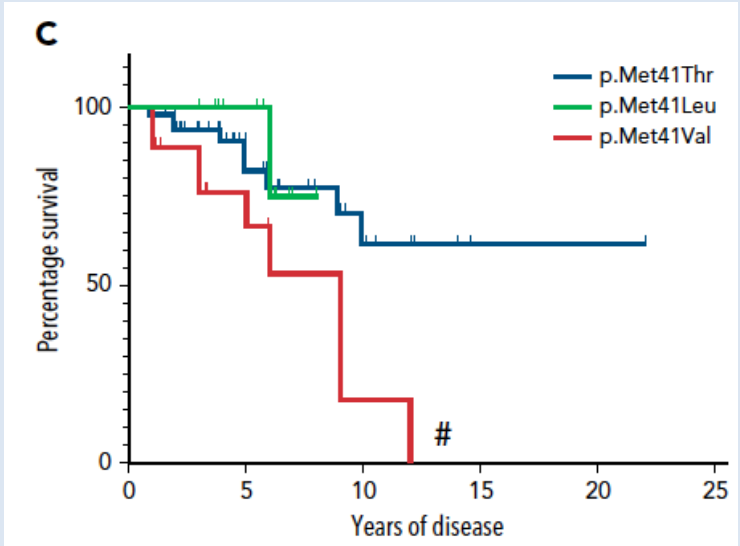
N = 116



French Cohort

Georgin-Lavialle, Br J Dermatol 2022

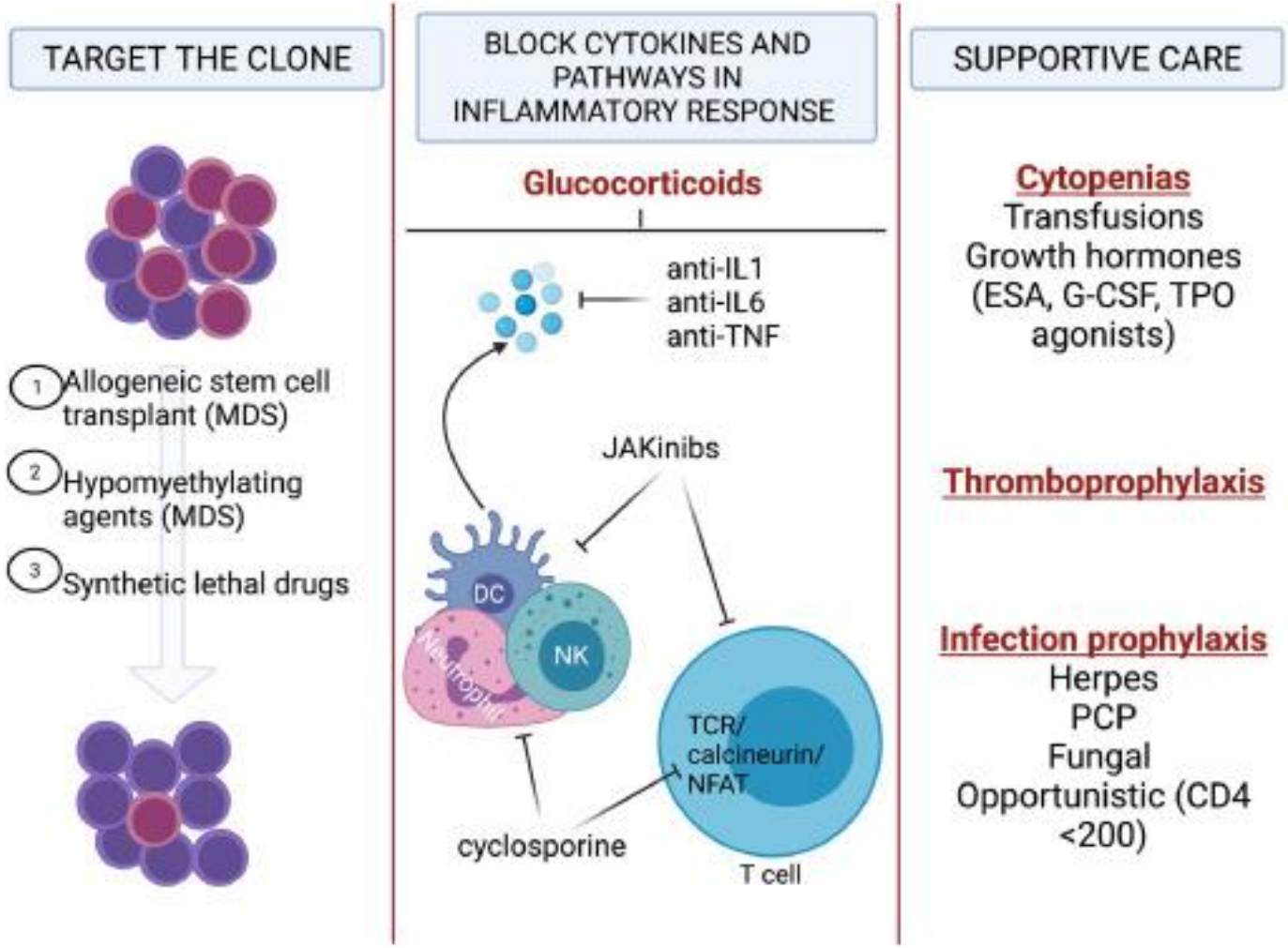
N = 83



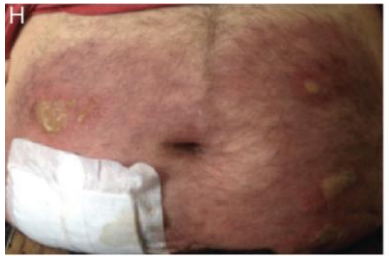
NIH/Leeds Cohort

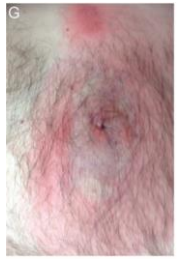
Ferrada et al, Blood 2022

Treatment Options



Cave:
IL-1R Ab (Anakinra) associated with high rate of severe skin reactions (>60%)

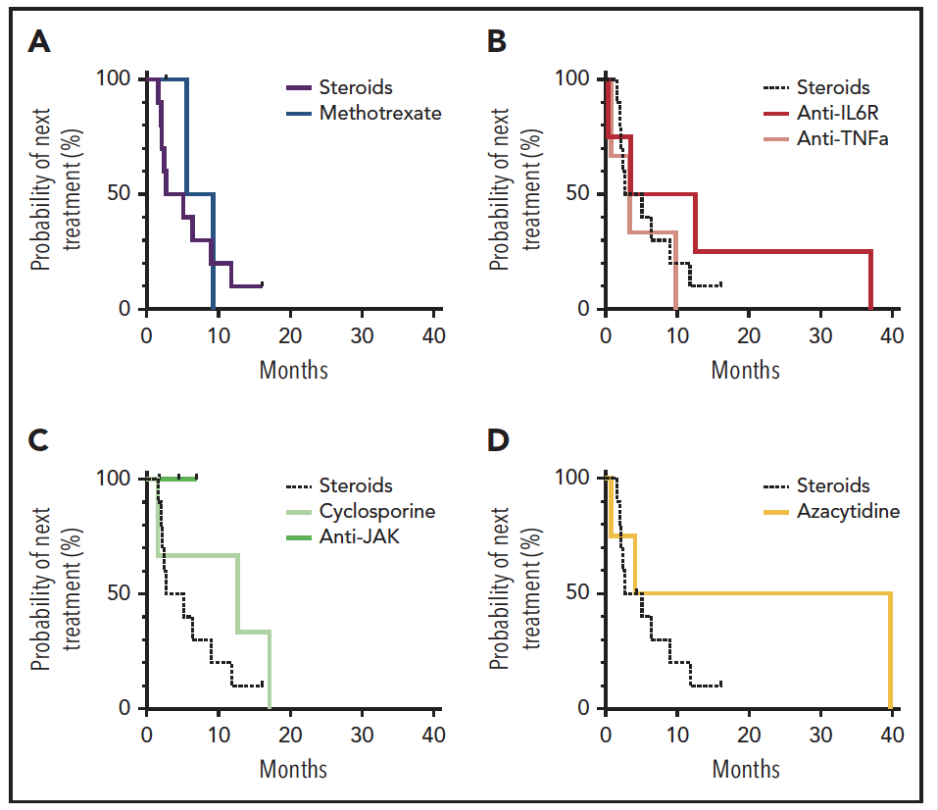




Steroid Sparing Treatments

Various

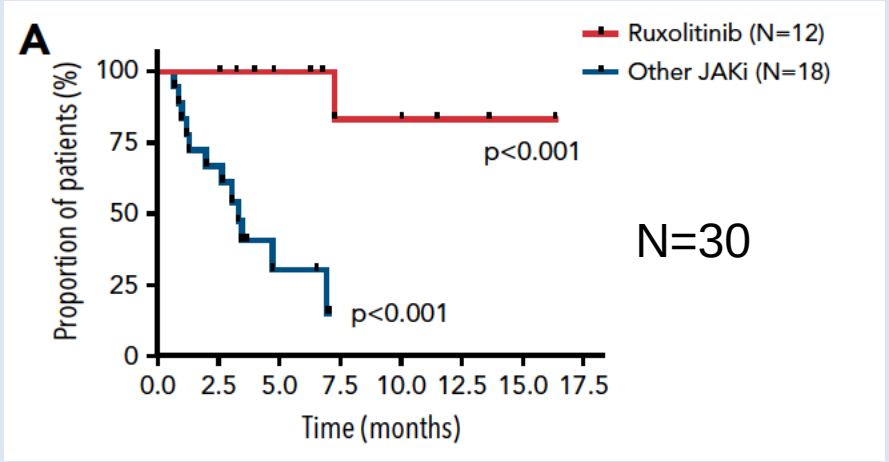
Time to Next Treatment



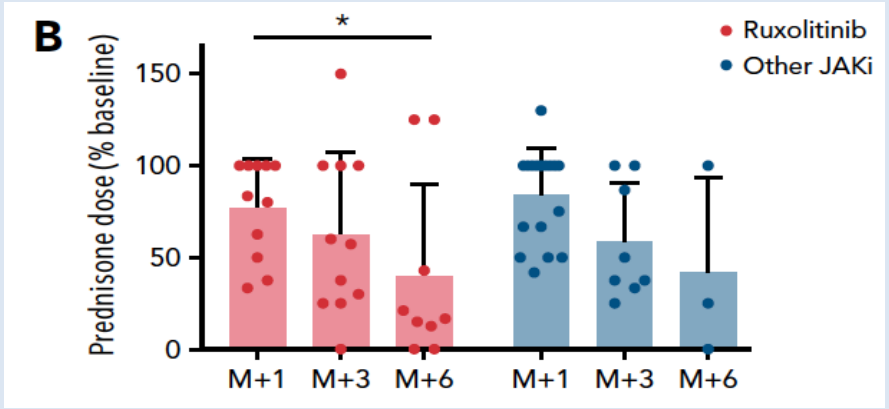
Bourbon et al, Blood 2021

JAK2 Inhibition

Time to Next Treatment



Prednisone dose



Heiblig et al, Blood 2022

AZA for MDS with systemic autoimmune/inflammatory disorder (SAID)

Table 1. Baseline characteristics and comparison between *UBA1*-mutated and -unmutated MDS/CMML patients.

Parameters	All patients ($n = 29$)	*UBA1* mutated ($n = 12$)	*UBA1* unmutated ($n = 17$)	p value
Age, years, median [9]	76 [72–80]	76 [73–78]	76 [72–80]	0.95
Males, *n* (%)	20 (69)	12 (100)	8 (47)	<0.01
WHO 2016 classification, *n* (%)				
MDS-MLD	11 (38)	8 (67)	3 (18)	0.02
MDS-EB 1–2	2 (7)	1 (8)	1 (6)	
MDS-RS	2 (7)	2 (16)	0	
MDS-U	3 (10)	1 (8)	2 (12)	
CMML 1–2	11 (38)	0	11 (65)	<0.01
IPSS-R, *n* (%)				
Very low (≤1.5)	2 (7)	2 (17)	0	
Low (1.5–3)	10 (34)	6 (50)	4 (24)	
Intermediate (3–4.5)	13 (45)	4 (33)	9 (53)	
High (4.5–6)	2 (7)	0	2 (12)	
Very high (>6)	2 (7)	0	2 (12)	
IPSS-R cytogenetic risk, *n* (%)				
Very good	2 (7)	2 (17)	0	
Good	16 (55)	6 (50)	10 (59)	
Intermediate	7 (24)	3 (25)	4 (24)	
Very poor	4 (14)	1 (8)	3 (18)	
Main SAID features, *n* (%)				
Fever	5 (17)	1 (8)	4 (24)	0.62
Skin involvement	14 (48)	5 (42)	9 (53)	1
Lung	4 (14)	2 (17)	2 (12)	0.62
Joint	18 (62)	5 (42)	13 (76)	0.24
Chondritis	6 (21)	4 (33)	2 (12)	0.16
Venous thrombosis	2 (7)	1 (8)	1 (6)	1

multicenter open label phase II trial

- **Inclusion criteria:**
- MDS/CMML
- Age > 18y
- IPSS-R int-2/high
- IPSS-R int-1/low and severe cytopenia
- SAID
- steroid resistant >2 months/>15 mg/d

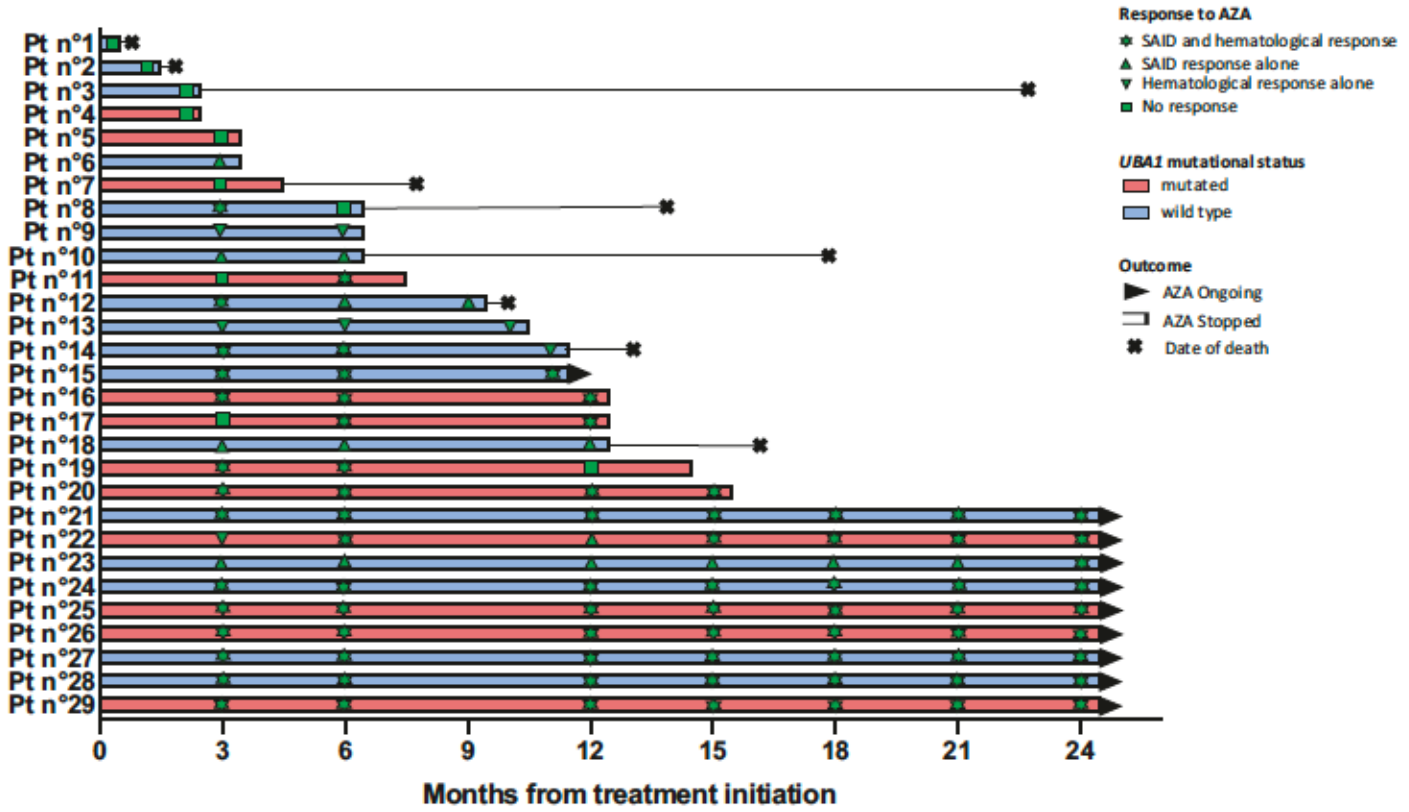
- Retrospective sequencing for *UBA1*

- 52% TET2/IDH mutated

Mekinian et al, Leukemia 2022

Azacitidine in VEXAS with associated MDS

multicenter open label phase II trial



- overall response rate 66% for SAID after 6 cycles
- hematologic improvement in 59%
- steroid sparing effect of AZA
- steroid independence in 84% of responders
- median 16 AZA cycles in responders

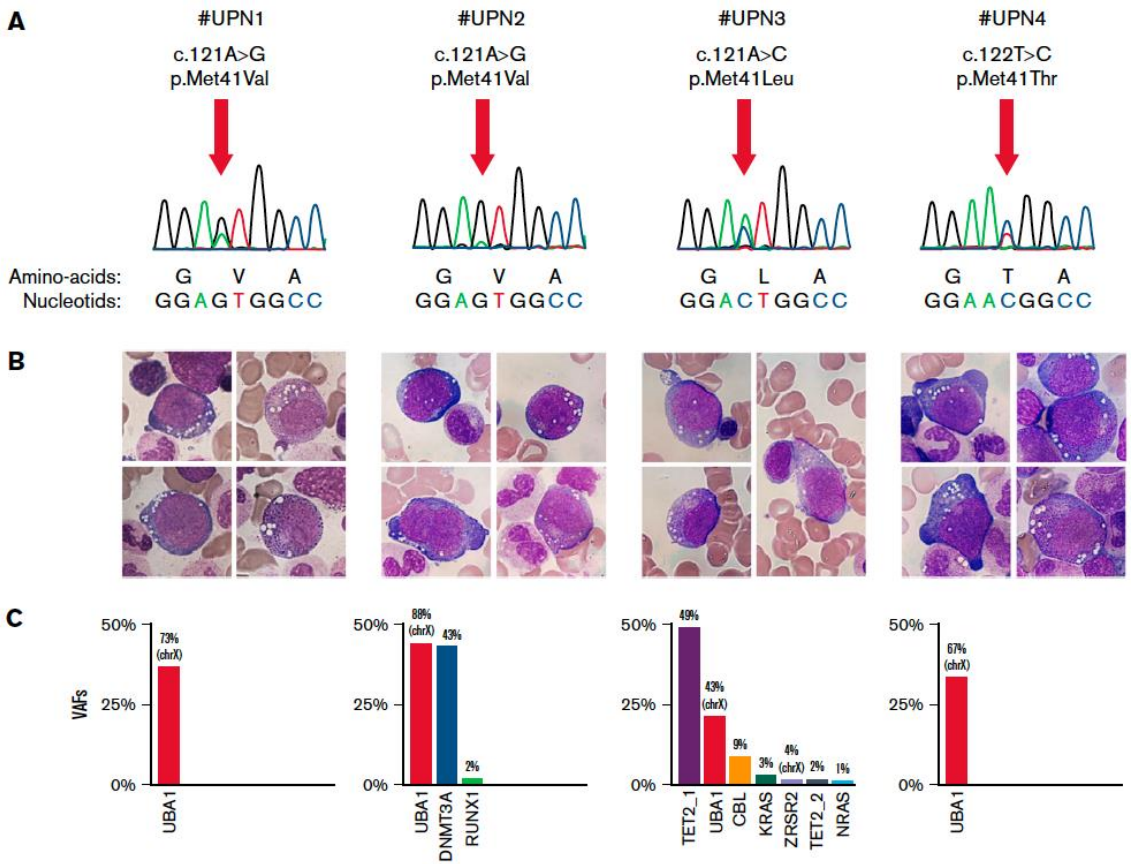
- median OS in *UBA1* mutated MDS NR vs 23 mo in unmutated MDS

Mekinian et al, Leukemia 2022

HMA Therapy: Azacitidine

Pubication	Type of study	Pt characteristics	n, *UBA1* mutated	response rate	median cycle number	Steroid independence	Molecular remission
Mekinian et al, *Leukemia* 2022	prospective phase II trial in MDS	MDS with inflammatory symptoms	12/29	66%	16	83%	n.d.
Comont et al, *Br J Haematol 2022*	retrospective	MDS	11/116	46%		yes	n.d.
Cordts, Götze et al, *Rheumatology 2022*	retrospective	MDS with inflammatory symptoms	1	100%	24	yes	yes
Sockel et al, *Ann Hematol 2024*	retrospective	MDS	2	100%		yes	2/2
Aalbers AM et al, *Hemasphere 2024*	retrospective	4/6 pts with MDS	8	63%	8	yes	yes
Trikha R et al, *Haematoogica 2024*	Prospective phase II trial in MDS/CMML	MDS/CMML	12	75%	>6	yes	in 3/12

Allogeneic Stem Cell Transplantation in VEXAS

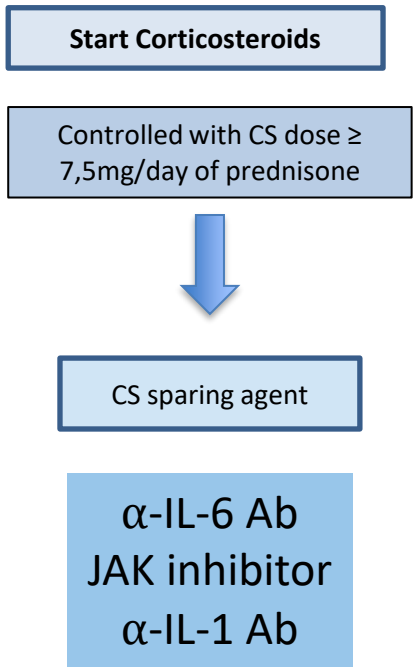


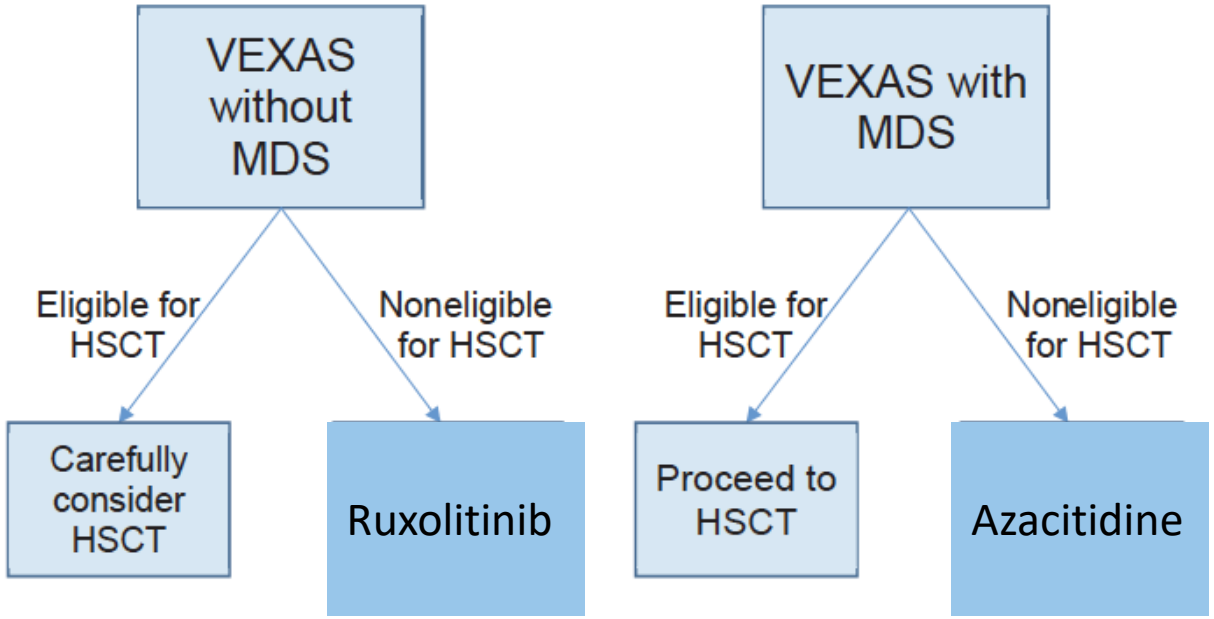
- allo HSCT in 6 VEXAS pts
- all failed multiple prior therapies
- refractory life-threatening autoinflammation (n=3)
- refractory MDS (n=2)
- 3 pts long-term CR at 32, 37 and 38 months
- 2 pts in CR at 3 and 5 months
- 1 death due to infectious complications

- ongoing prospective Phase II trial of allo HSCT for VEXAS (N=37) NCT05027945

Diarra et al, Blood Adv 2021

VEXAS Treatment Algorithm Proposal



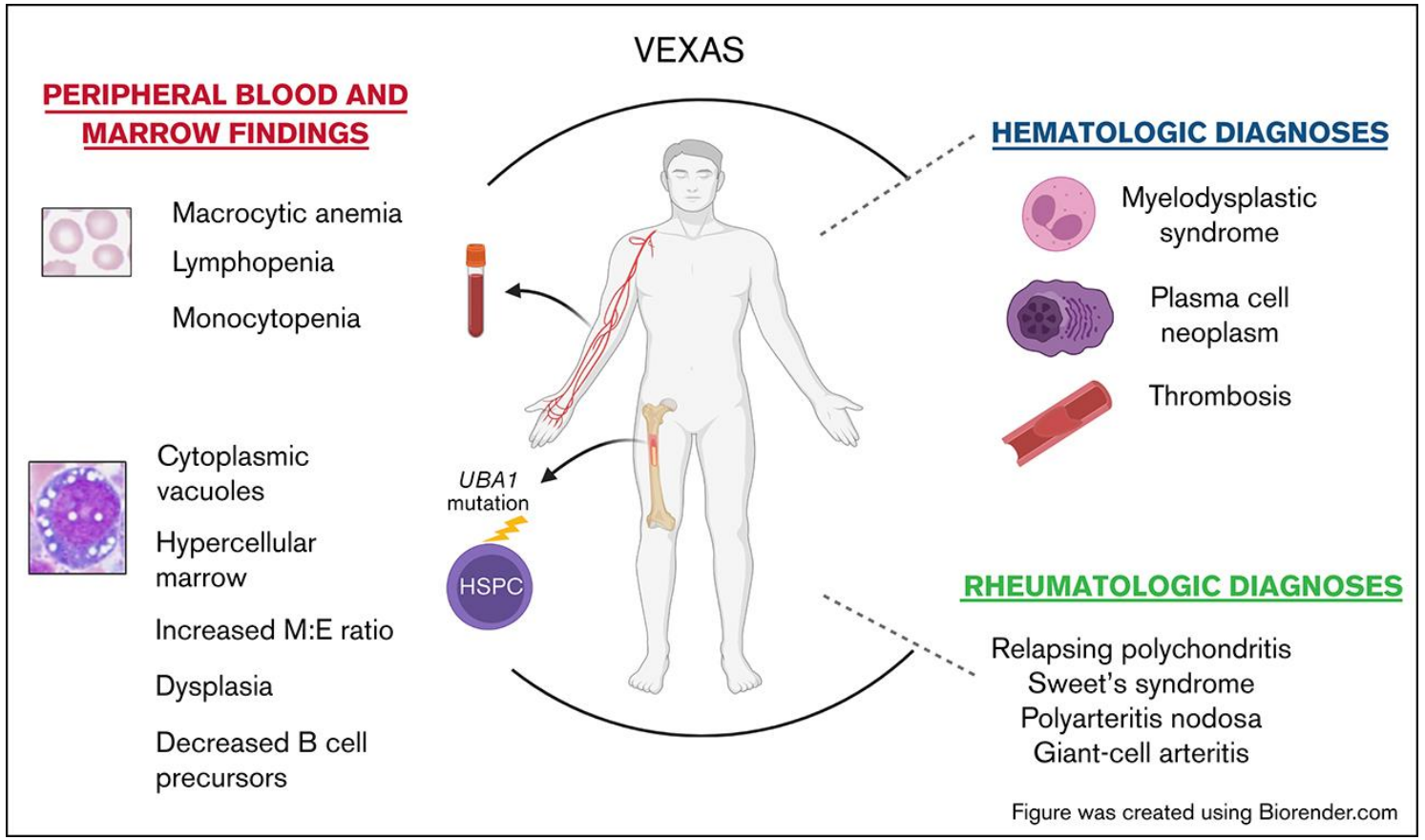


Considerations for allo HSCT:

- genotype (p.Met41Val)
- disease severity
- treatment response
- relapse rate

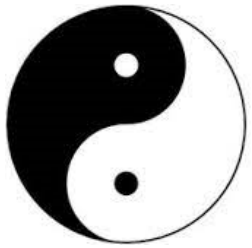
Adapted from Autoimmune Diseases Working Party of the EBMT, 2023

Summary



Myeloid driven inflammation

MDS



Autoimmune disorder

Summary and Outlook

- **Best treatment option remains unclear**
  - VEXAS resistant to classical immunosuppression beyond steroids
  - Allogeneic stem cell transplantation may be curative option in selected patients
  - Ruxolitinib or HMA confer responses in VEXAS with MN
- **VEXAS MDS seems different from more „classical“ MDS in terms of heterogeneity and molecular landscape**
  - Fewer MDS typical co-mutations in VEXAS with MDS
  - VEXAS patients with MDS have poorer survival rate than VEXAS without MDS
  - VEXAS MDS has better outcome on HMA/Ruxolitinib vs MDS without associated VEXAS
- **More functional studies needed to understand underlying pathomechanism**
  - Unclear whether UBA1 mutation is initiating clonal event of MDS or MDS develops due to highly inflammatory microenvironment conducive to clonal selection
  - Larger cohorts and prospective data necessary to understand genotype specific outcomes

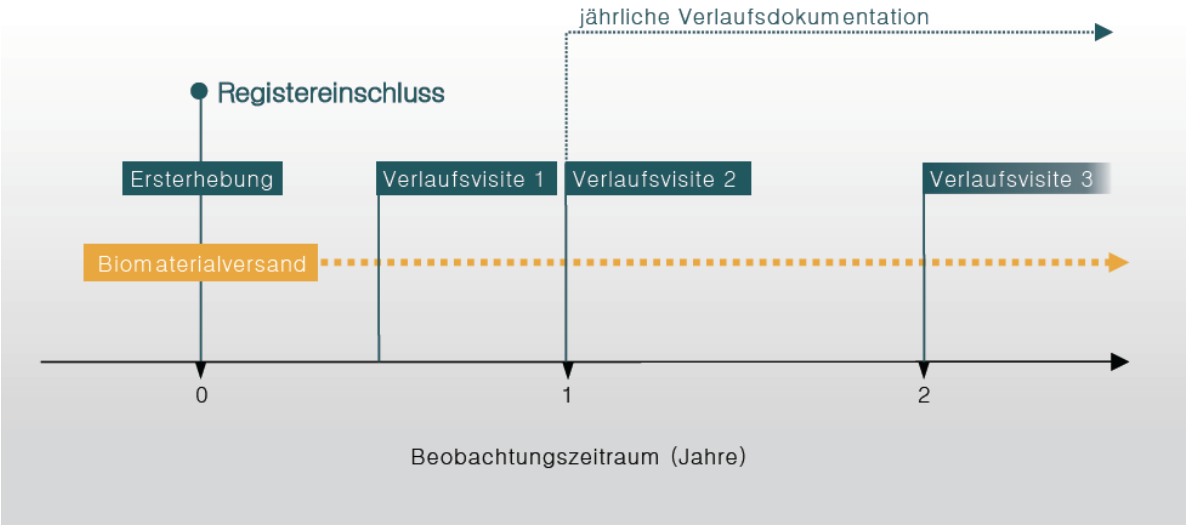
VEXAS-Register

Projektleitung
Dr. med. Katja Sockel
Medizinische Klinik I, Universitätsklinikum Carl Gustav Carus, Dresden

Prof. Dr. med. Katharina Götze
Medizinische Klinik III, TUM Universitätsklinikum, München

Einschlusskriterien

- VEXAS-Syndrom (molekulargenetischer Nachweis einer UBA1-Mutation)
- Patienten ≥ 18 Jahre
- Unterzeichnete Einwilligungs-erklärung Register (+Biobanking)

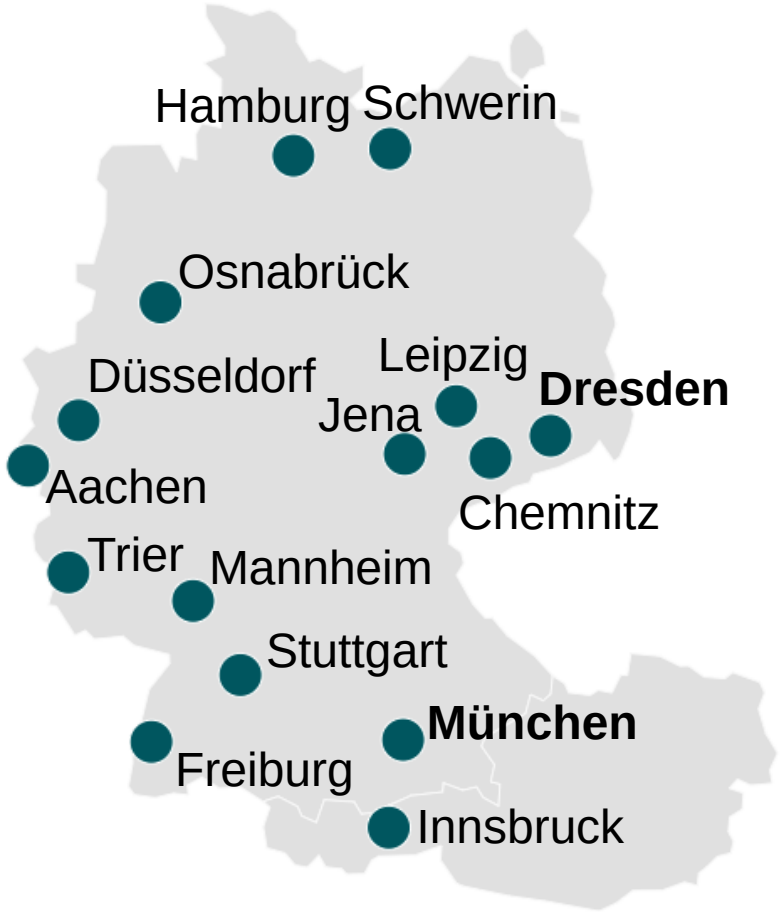


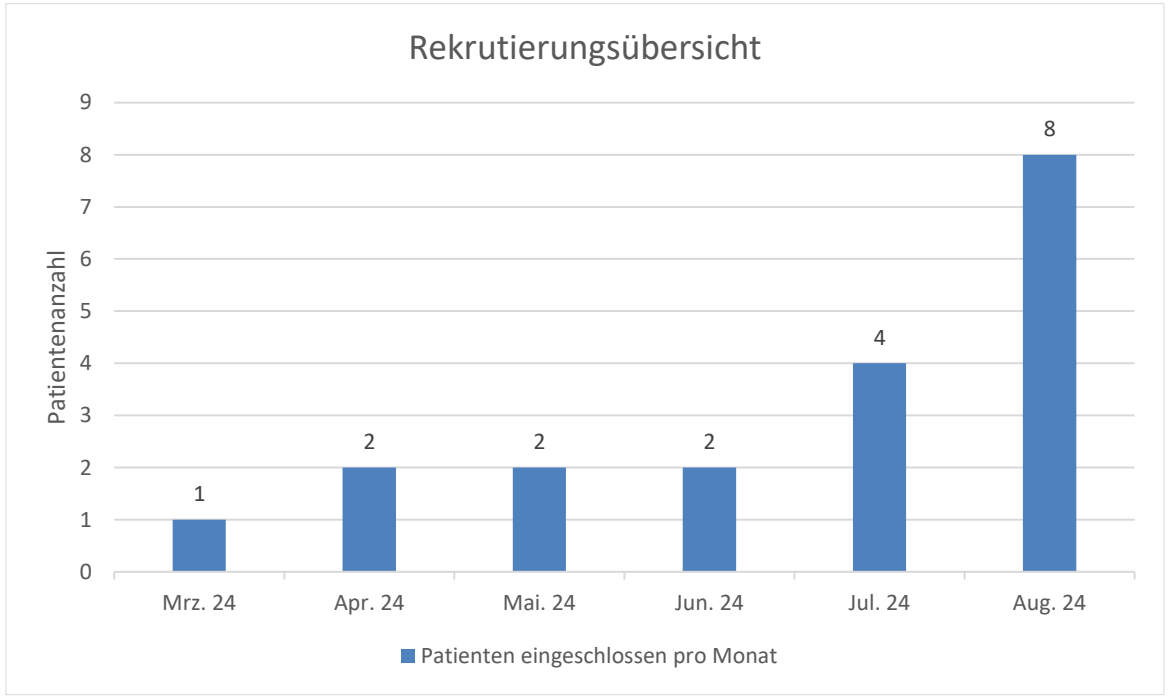
- Dokumentation der Visiten in der REDCap Datenbank
- Ggf. Versand von Biomaterial pro Visite an die BioBank Dresden (Kits für den Versand werden von der Studienzentrale Dresden zur Verfügung gestellt)
- Dokumentationspauschale von 100€ pro Einschluss und 50€ pro Verlaufsvisite

www.vexas.net

Zentren und Rekrutierung

VEXAS REGISTER





- Insgesamt **20** Patienteneinschlüsse seit Registerbeginn März 2024 bis Okt 2024

- Einige Patienten bereits vorangemeldet für Einschluss

Thank you!

Bristol Myers Squibb™
Stiftung Immunonkologie

VEXAS
REGISTER

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D·MDS Deutsche MDS-Studiengruppe

BZKF Bayerisches Zentrum für Krebsforschung

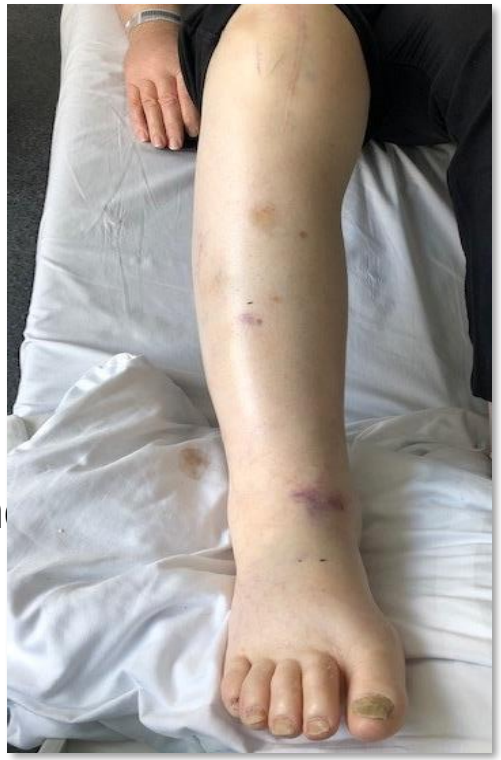
DKTK German Cancer Consortium

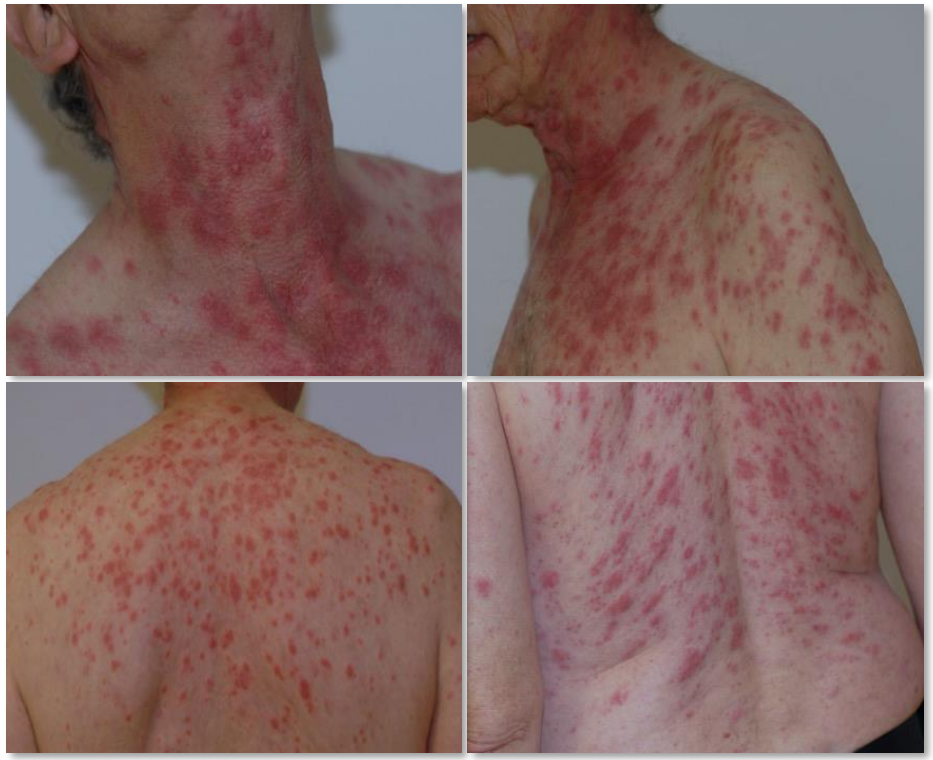
Case report 1

Male patient 71y

- Disseminated skin lesions
- Recurrent fever
- Myalgias and edema
- Macrocytic anemia
- TVT

- Previously diagnosed with pseudolymph
- Multiple immunosuppressive therapies
- Only prednisolone 20 mg/d effective





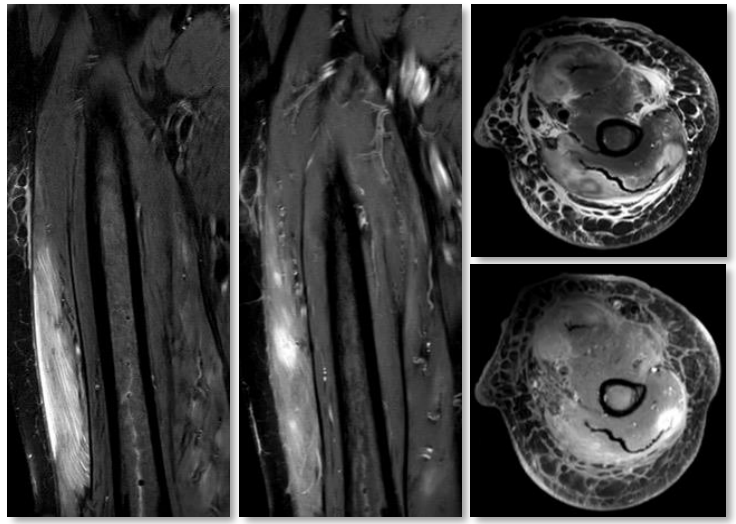
Cordts, Hecker…Götze..et al, Rheumatology 2022

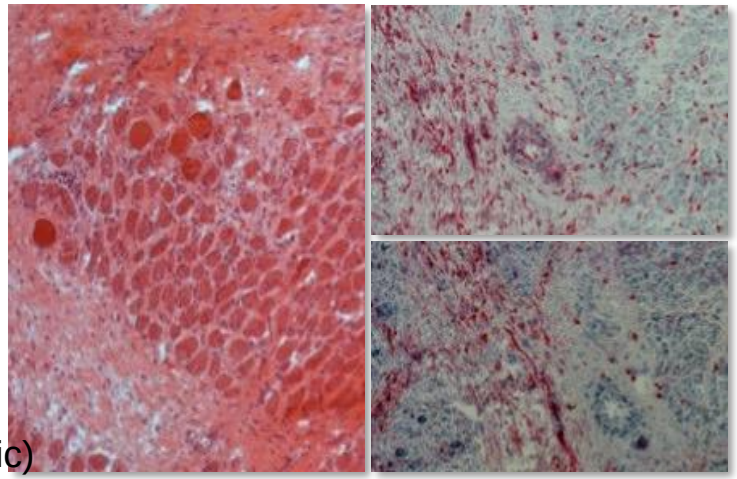
Case report 1

- MRI showed T2 hyeperintensity, contrast enhancement
- Muscle biopsy showed gerenalized active myofasciitis

- BM biopsy:
  - MDS-MLD-RS
  - vacuoles in myeloid cells
  - 46, XY, absence of specific MDS mutations

- **Diagnosis Sweet Syndrome,** malignancy associated





Sequencing for *UBA1* mutation
- c.121A>C, **p.Met41Leu**
- blood: 70%
- muscle: 20%
- B-cells: 0%
- T cells: 20-25%
- neutrophils: 90%

- Diagnosis: VEXAS-Syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic)

Case report 1

Treatment history

- prednisolone effective for skin lesions, edema and fever, no effect on Hb
- Anakinra severe panniculitis and phlegmonitis
- Colchicine no effect, GI symptoms

- Azacytidine clinical benefit, resolution of skin lesions and HI-E, tapering of steroids
  21 cycles of azacytidine in remission for >2 years, normal blood counts

  complete molecular genetic remission (no *UBA1* mutation detectable)

Published VEXAS Cohorts

Male Cases

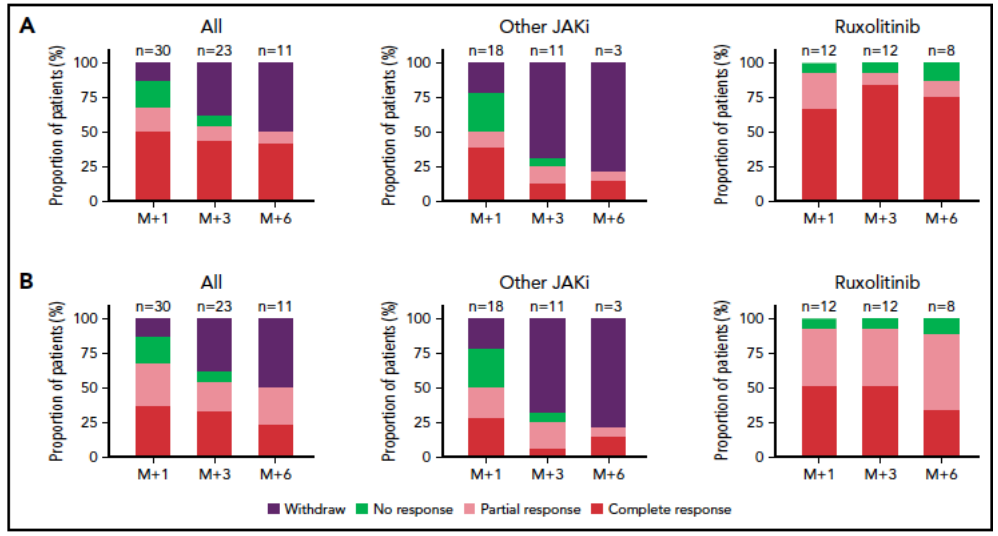
- Initial Cohort (Beck et al, New Engl J 2020) n=25
- Lyon Cohort (Bourbon et al, Blood 2021) n= 19
- Leeds Cohort (Poulter et al, Blood 2021) n= 18
- Multinational Cohort (Ferrada et al, Blood 2022) n=83
- MDS + SAID French Cohort (Mekinian et al, Leukemia 2022) n= 29
- French Cohort (Georgian-Lavialle et al, Br J Dermatol 2022) n= 116
- MLL cohort (Sakuma et al, Leukemia 2023) n=16 $UBA1^{non\text{-}m41}$ variants

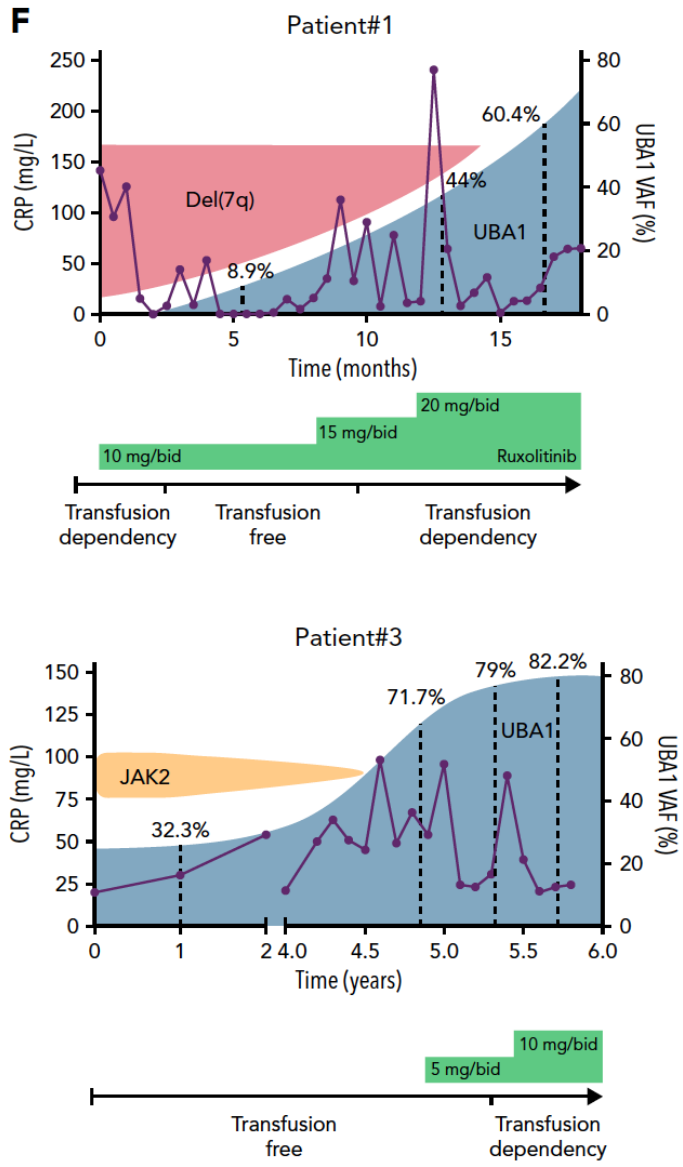
Female cases with monosomy X:

- Arlet et al, N. Engl. J. Med. 2021
- Barba et al , Rheumatology 2021,
- Luquet et al, Int. J. Lab. Hematol. 2021

JAK2 Inhibition for VEXAS: Ruxolinitib vs others

Clinical responses at 1, 3 and 6 months





Heiblig et al, Blood 2022