Syndrome VEXAS

Célestine Simand
Service d'hématologie
Strasbourg

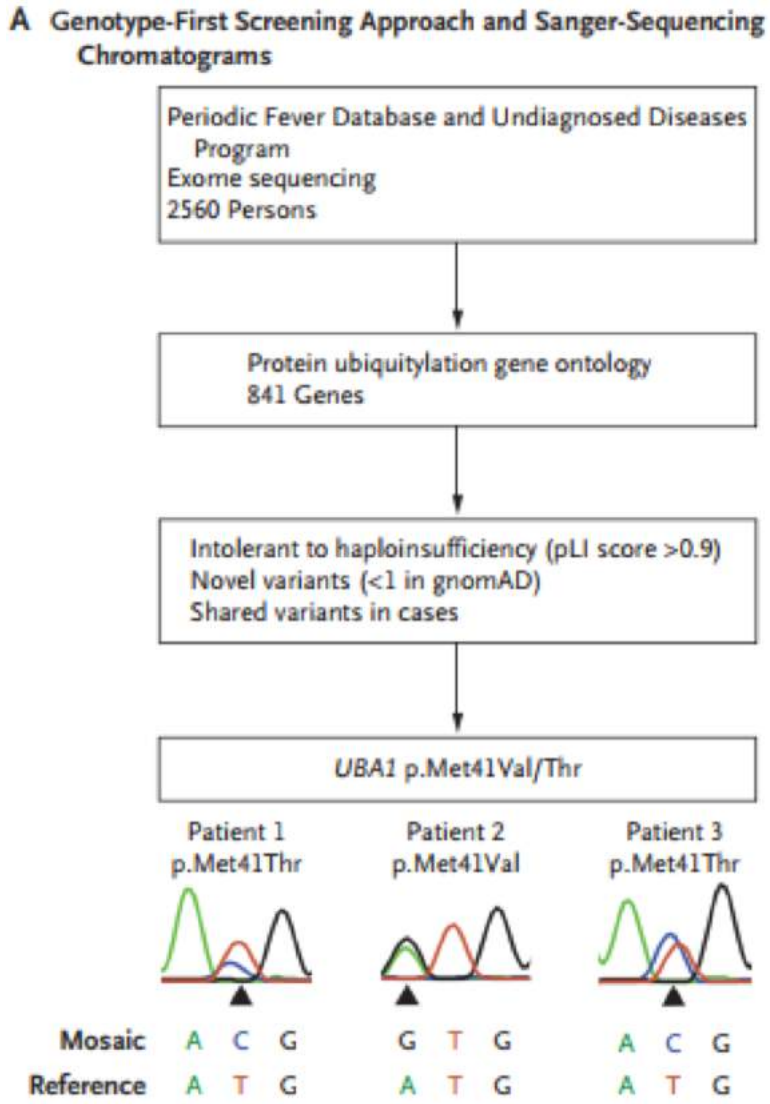
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

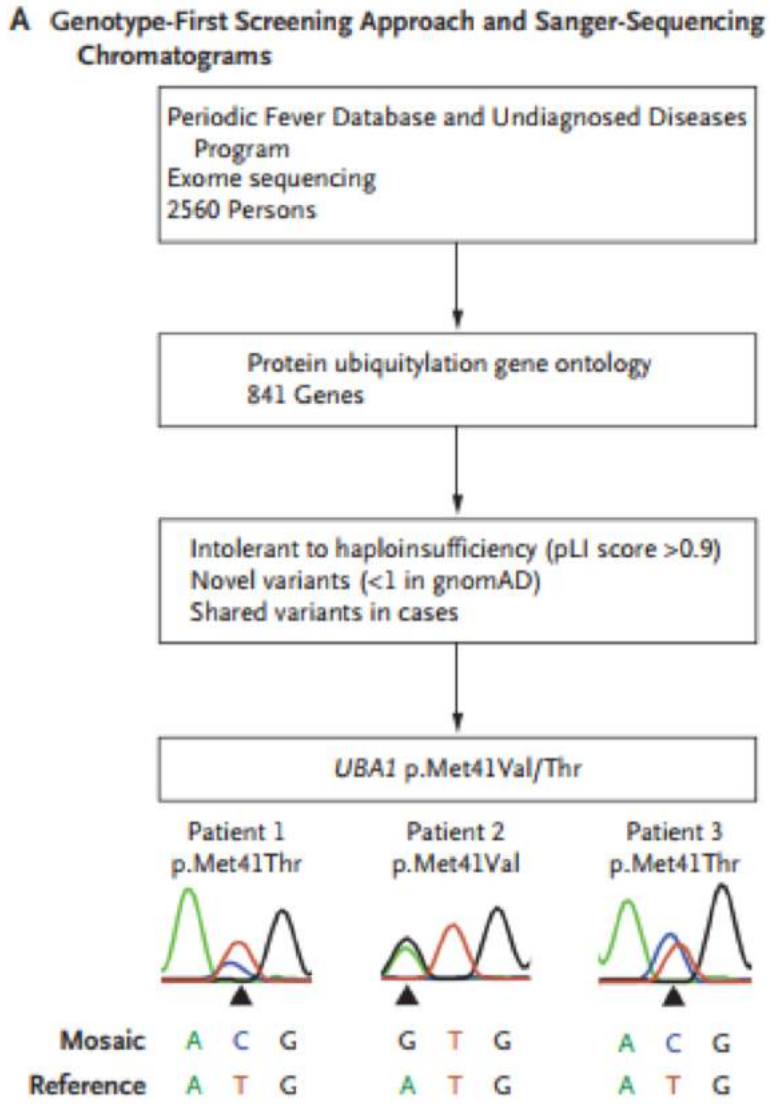
Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

D.B. Beck, M.A. Ferrada, K.A. Sikora, A.K. Ombrello, J.C. Collins, W. Pei, N. Balanda, D.L. Ross, D. Ospina Cardona, Z. Wu, B. Patel, K. Manthiram, E.M. Groarke, F. Gutierrez-Rodrigues, P. Hoffmann, S. Rosenzweig, S. Nakabo, L.W. Dillon, C.S. Hourigan, W.L. Tsai, S. Gupta, C. Carmona-Rivera, A.J. Asmar, L. Xu, H. Oda, W. Goodspeed, K.S. Barron, M. Nehrebecky, A. Jones, R.S. Laird, N. Deuitch, D. Rowczenio, E. Rominger, K.V. Wells, C.-C.R. Lee, W. Wang, M. Trick, J. Mullikin, G. Wigerblad, S. Brooks, S. Dell'Orso, Z. Deng, J.J. Chae, A. Dulau-Florea, M.C.V. Malicdan, D. Novacic, R.A. Colbert, M.J. Kaplan, M. Gadina, S. Savic, H.J. Lachmann, M. Abu-Asab, B.D. Solomon, K. Retterer, W.A. Gahl, S.M. Burgess, I. Aksentijevich, N.S. Young, K.R. Calvo, A. Werner, D.L. Kastner, and P.C. Grayson

ICANS

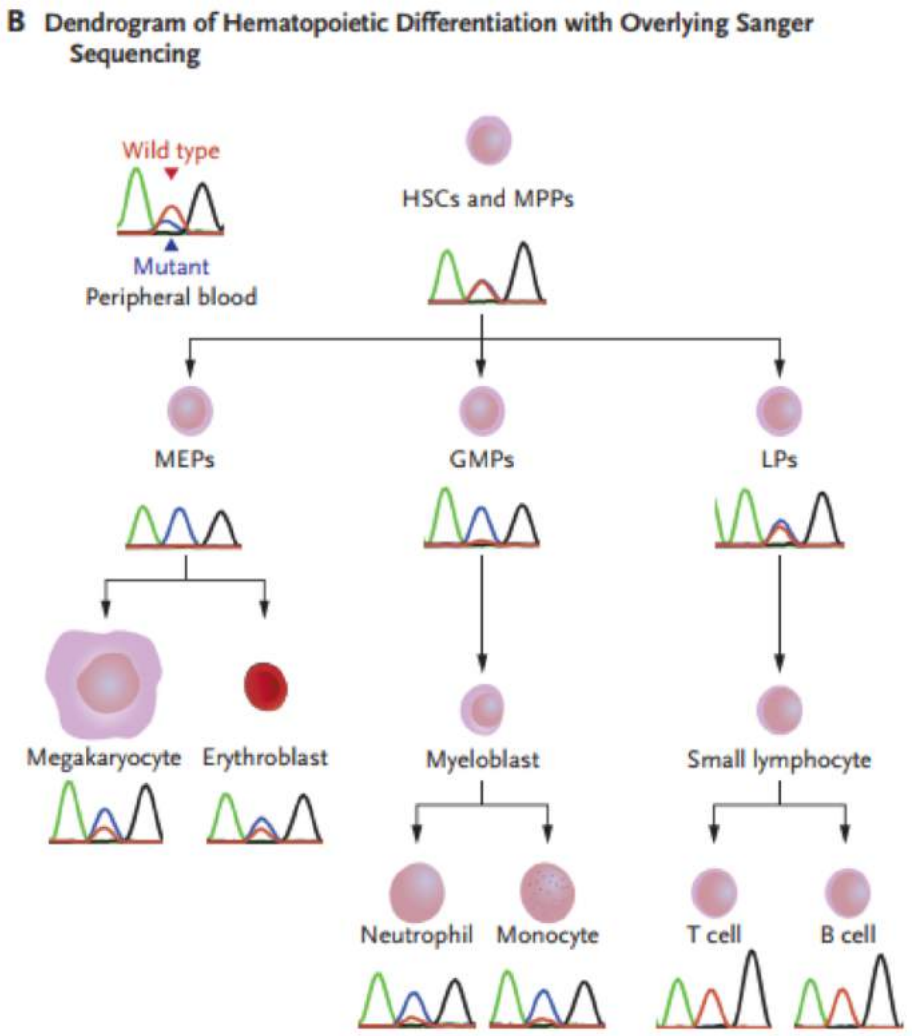


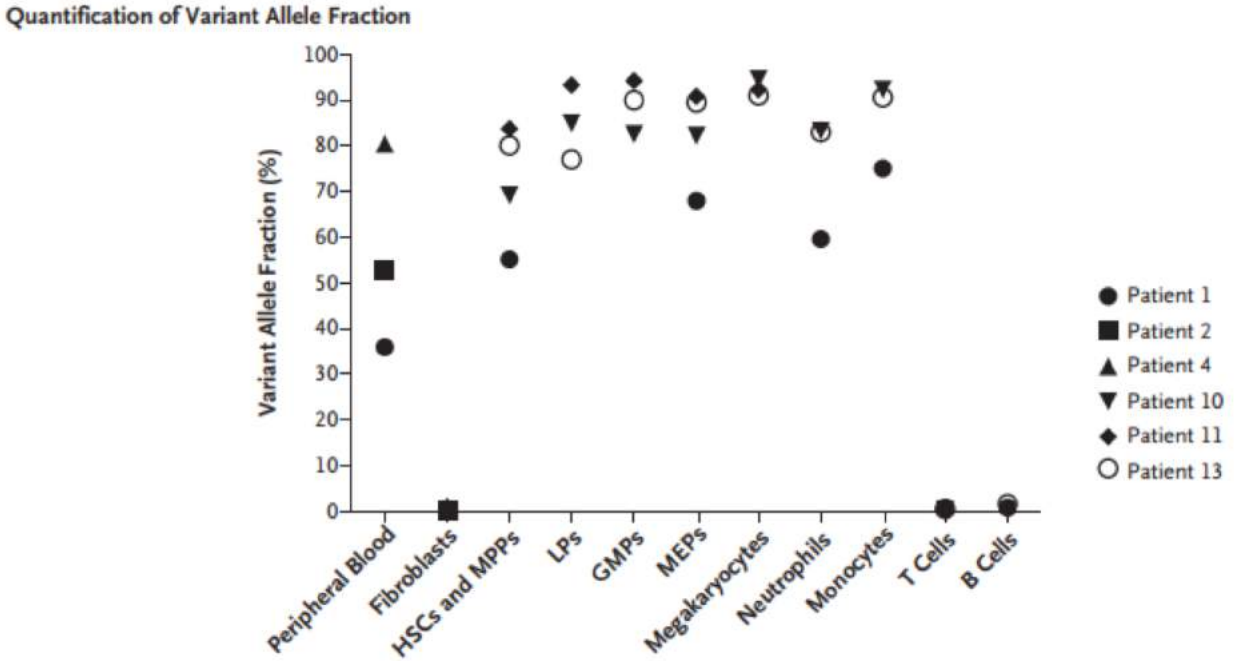
Beck DB et al, N Engl J Med. 2020 December 31; 383(27): 2628–2638



22 patients supplémentaires
avec caractéristiques cliniques identiques

Mosaïcisme





Beck DB et al, N Engl J Med. 2020 December 31; 383(27): 2628–2638

Caractéristiques cliniques

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)

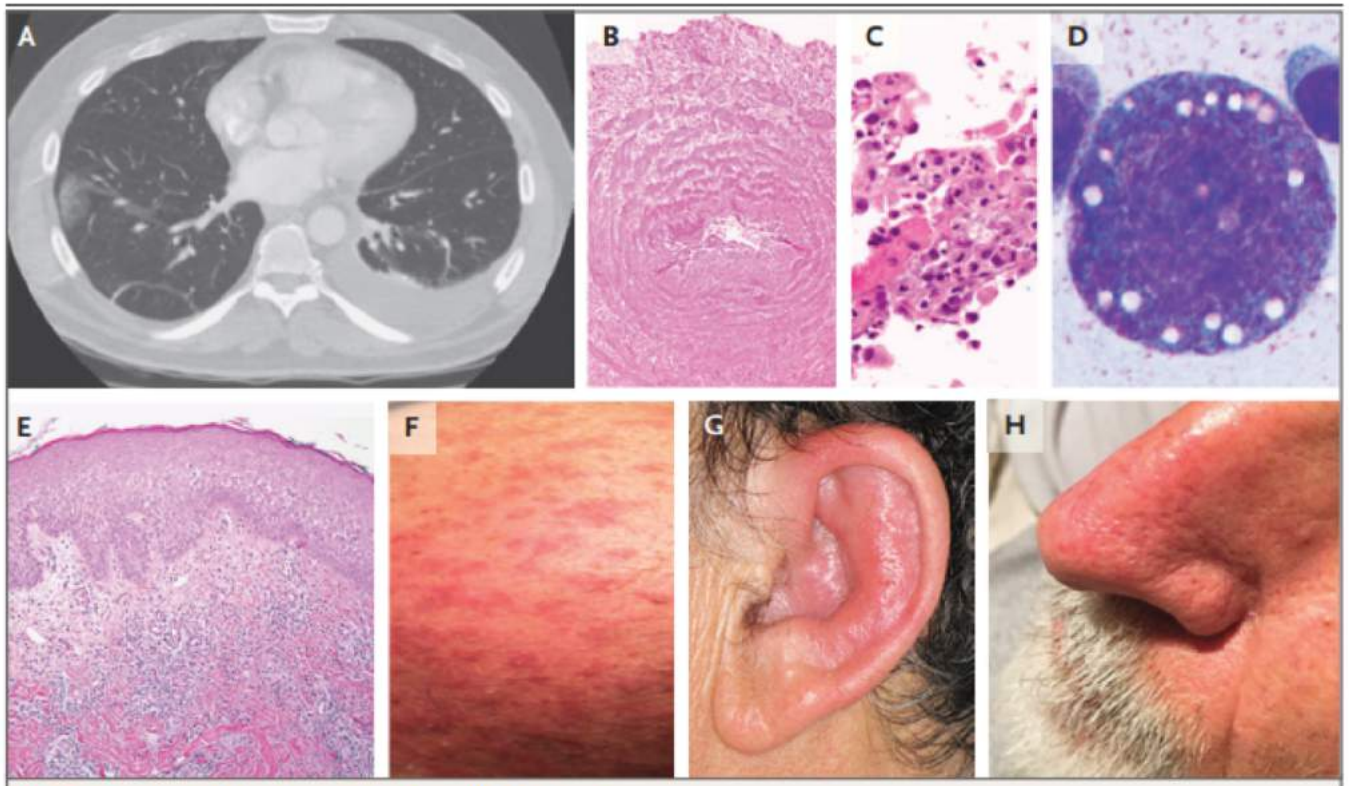


Figure 2. Clinical Manifestations of the VEXAS Syndrome.

Beck DB et al, N Engl J Med. 2020 December 31; 383(27): 2628–2638

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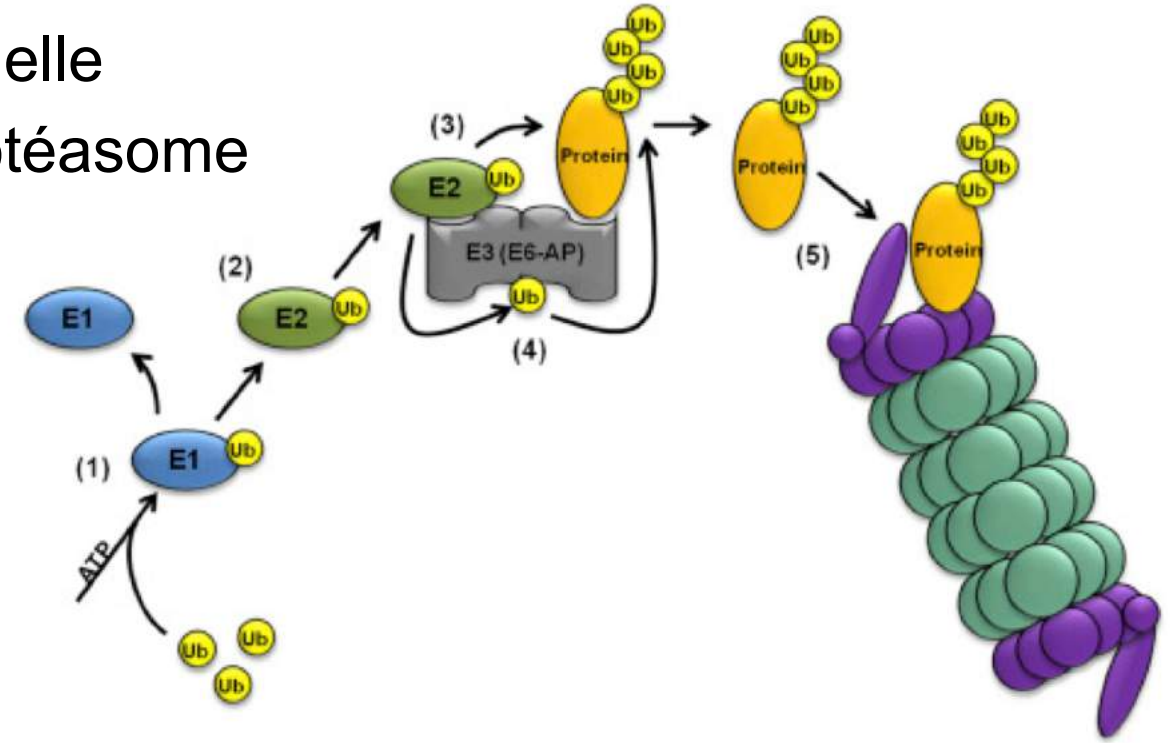
ORIGINAL ARTICLE

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

Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic

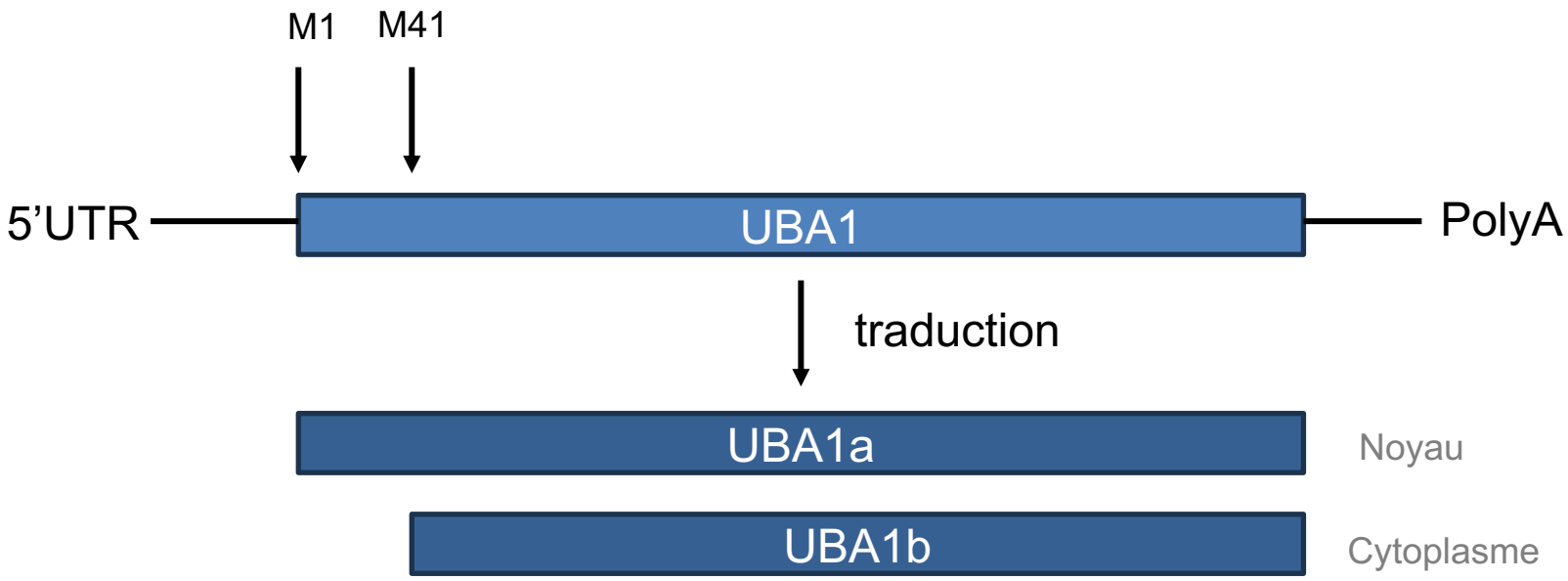
Physiopathologie

- UBA1 = Ubiquitin-like modifier activating enzyme 1
- Chromosome X
- Code pour la principale enzyme E1 chez le mammifère
- Ubiquitination des protéines
  - Modification post traductionnelle
  - Adresse les protéines au protéasome



Kaas GA et al, Learning and Memory: A Comprehensive Reference (Second Edition), 2017

Physiopathologie



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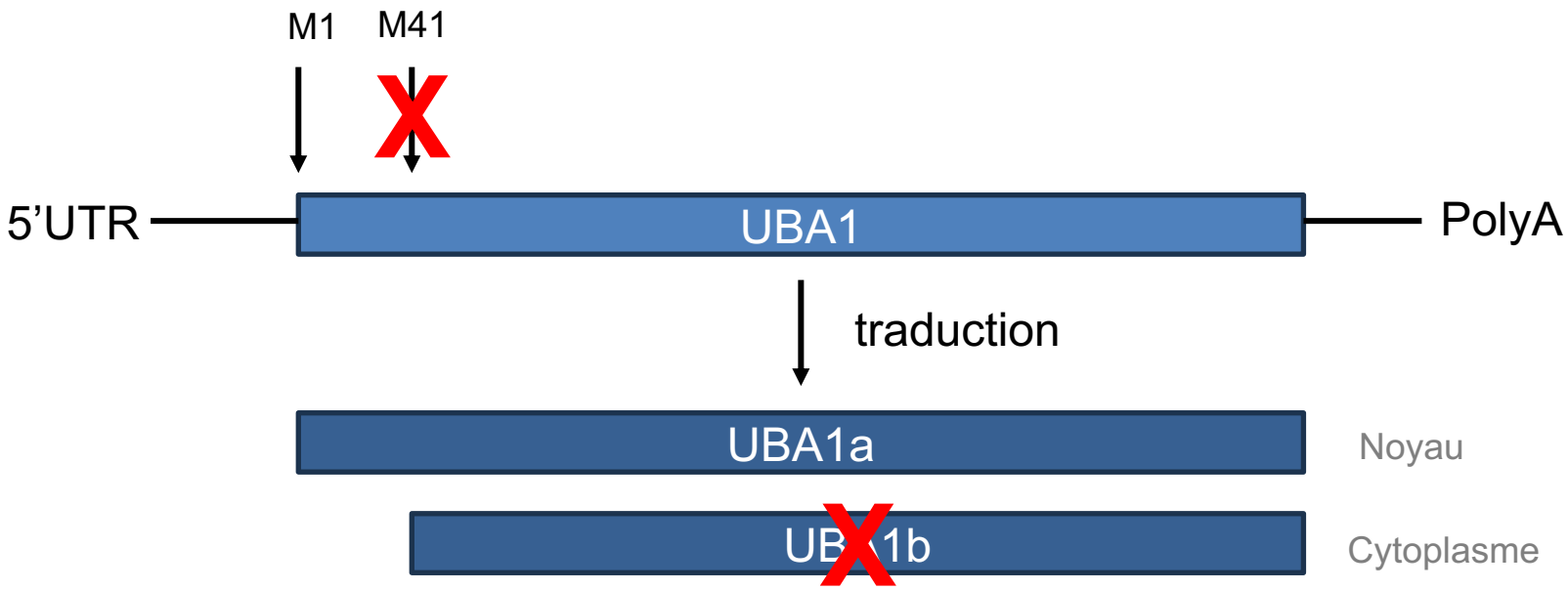
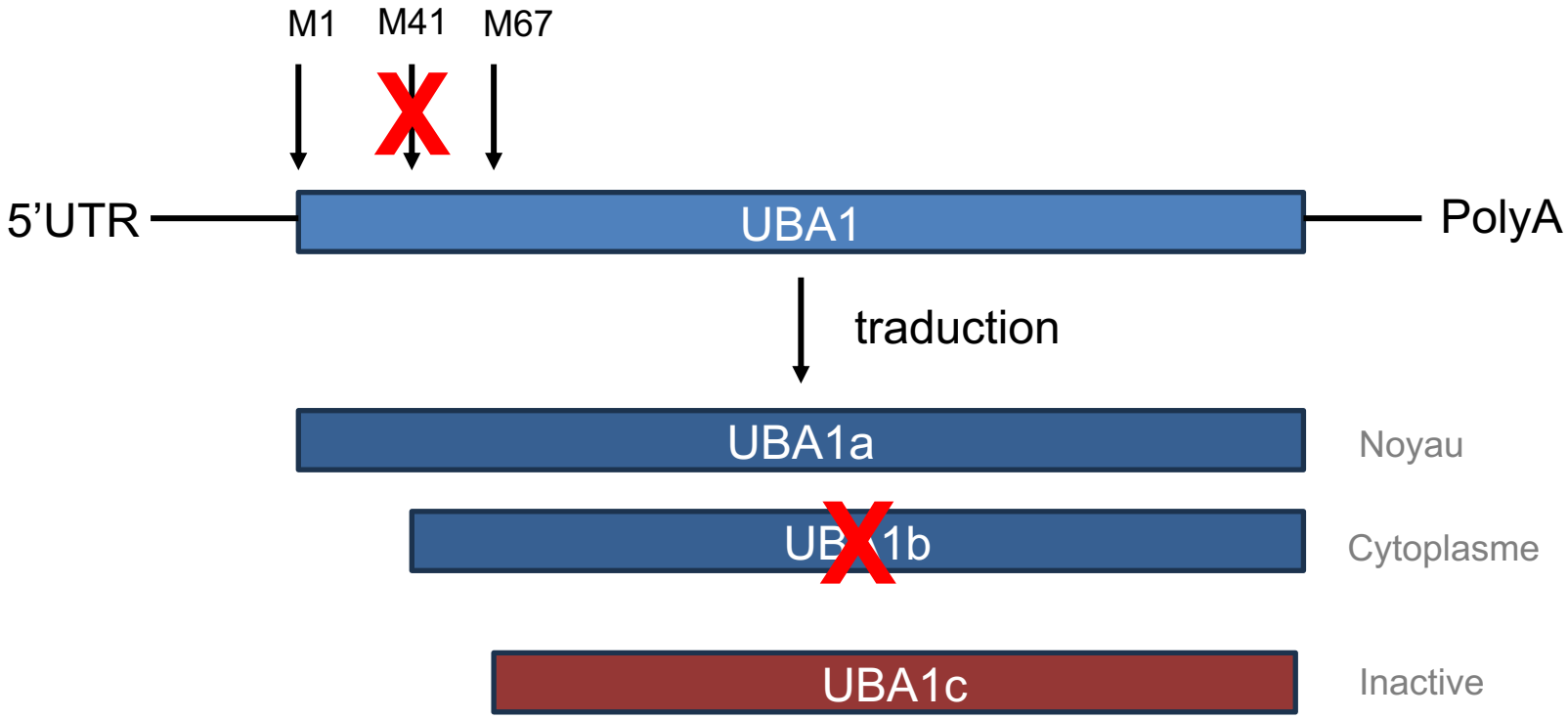
Physiopathologie



Beck DB et al, N Engl J Med. 2020 December 31; 383(27): 2628–2638

Physiopathologie

→ Stress cellulaire



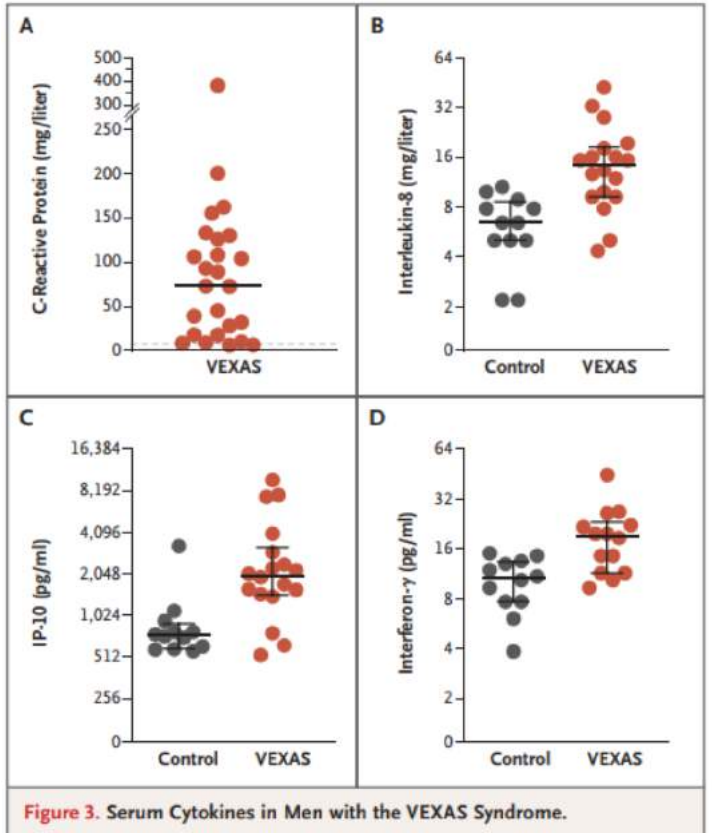
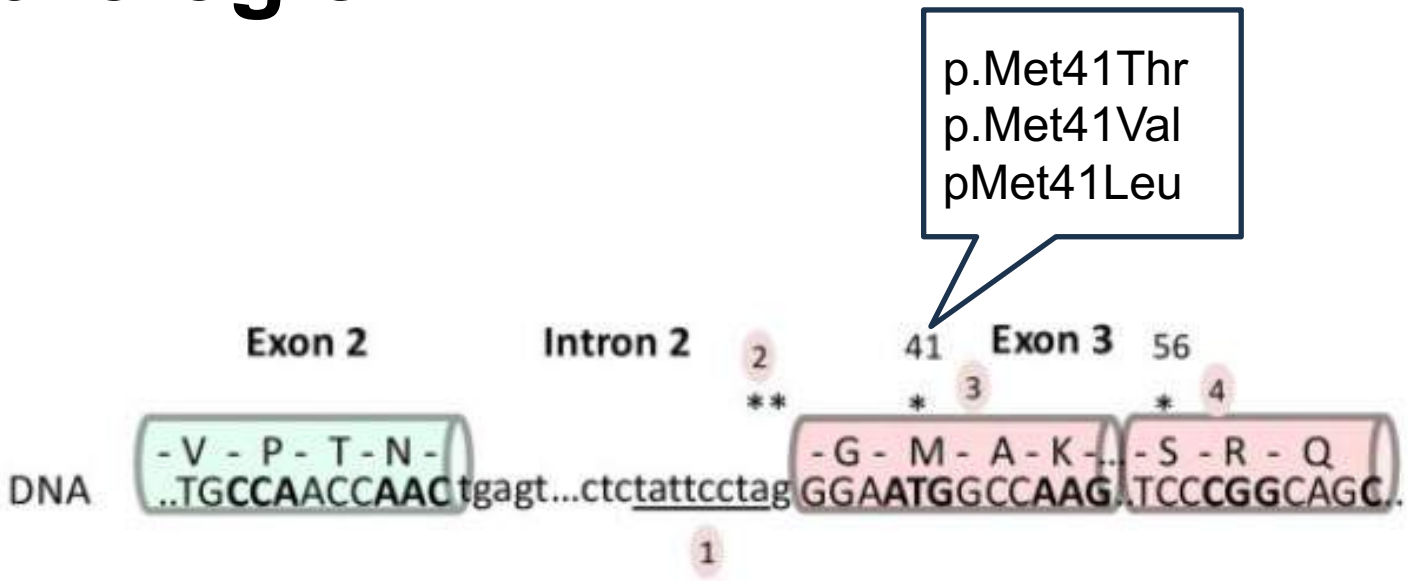


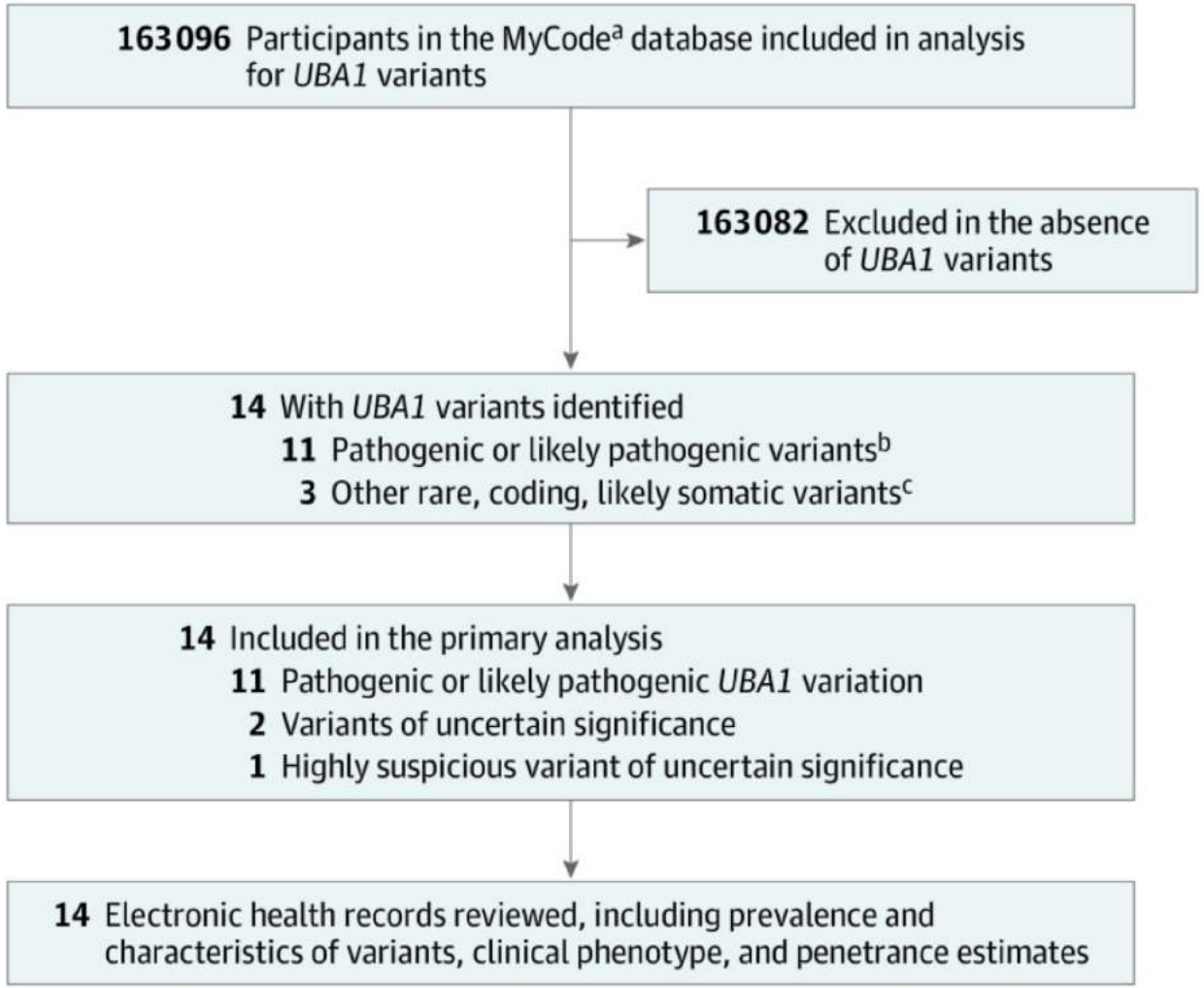
Figure 3. Serum Cytokines in Men with the VEXAS Syndrome.

Beck DB et al, N Engl J Med. 2020 December 31; 383(27): 2628–2638

Physiopathologie



Epidémiologie

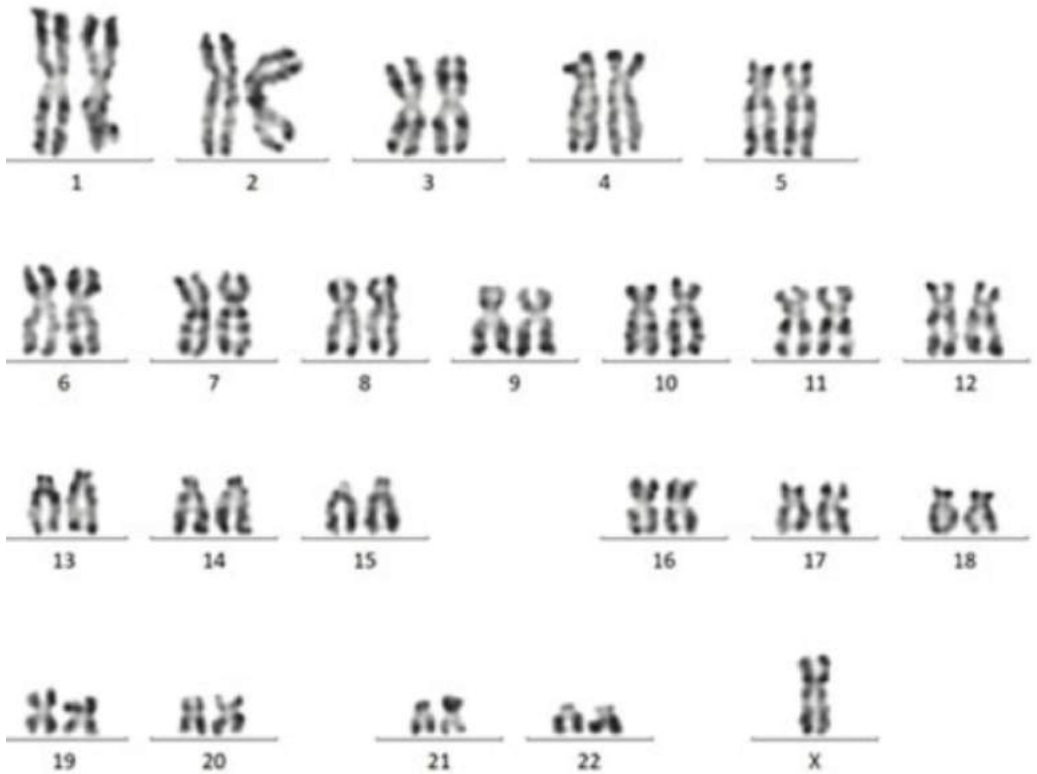


Prévalence estimée
1:13 591

Maladie Behçet 1:10 000

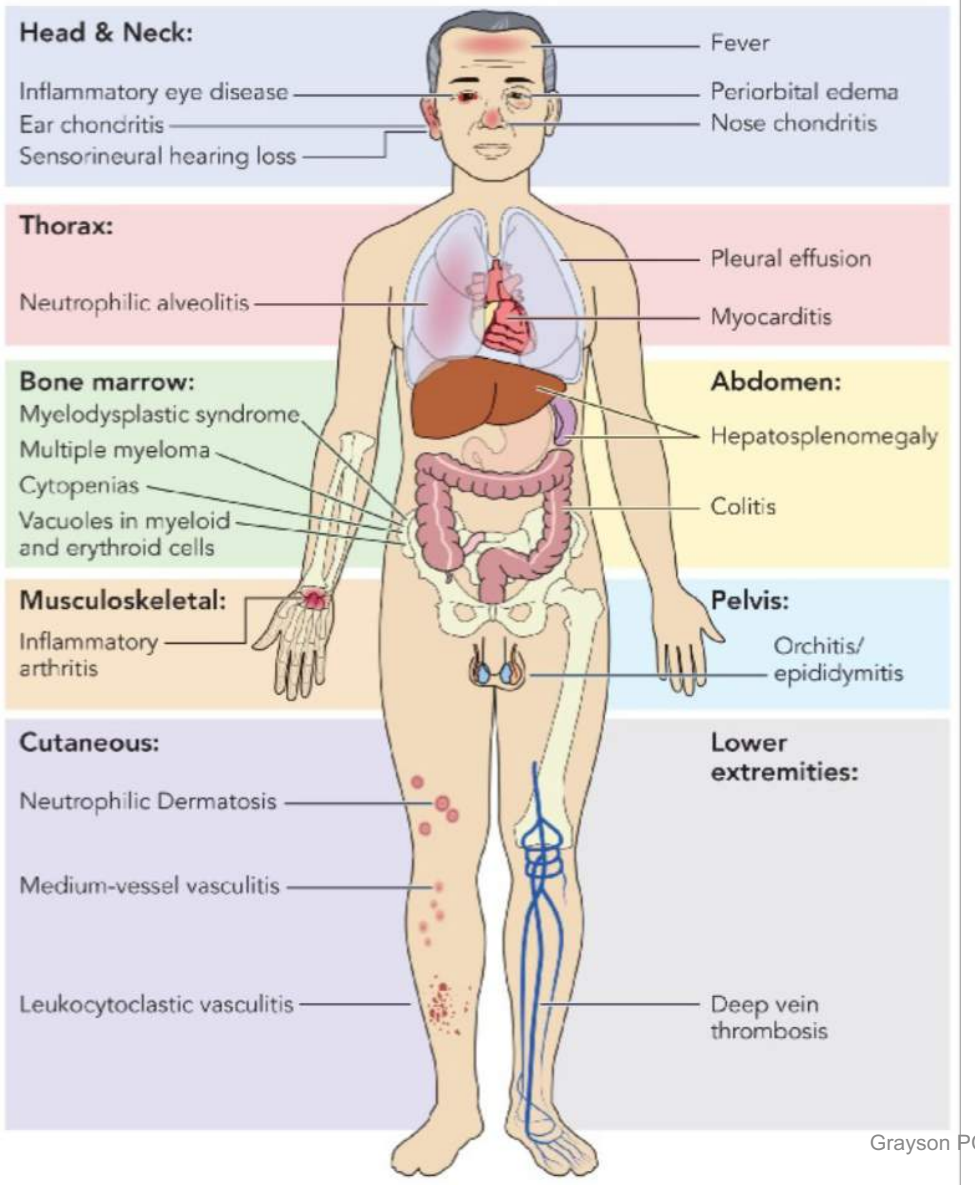
Beck DB, et al. JAMA. 2023 Jan 24;329(4):318-324.

Les femmes aussi…



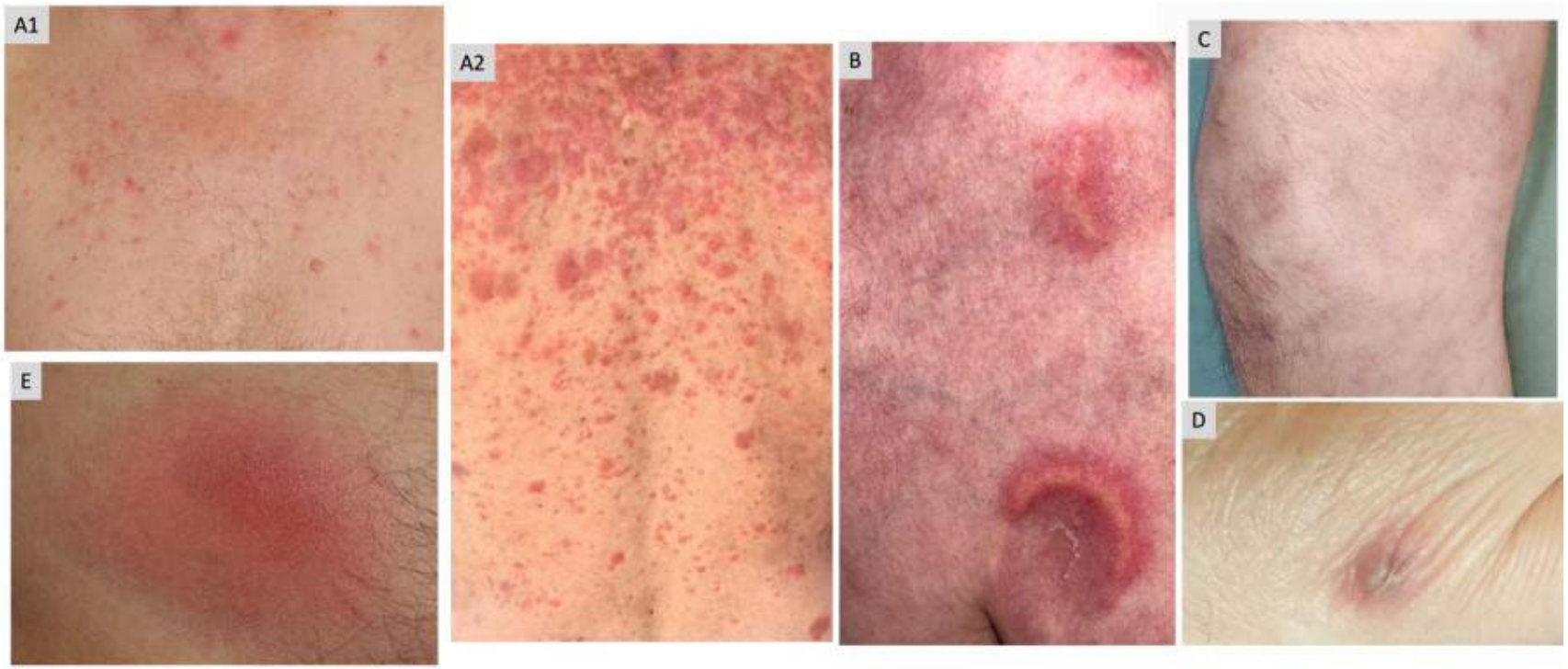
Barba T et al, Rheumatology 2021;60:e402–e403

Phénotype du VEXAS



Grayson PC, Patel BA, Young NS. Blood. 2021 Jul 1;137(26):3591-3594.

Atteintes dermatologiques



Round shaped maculopapules of various sizes (A1-2), arcuate papules (B), livedo (C), pustules (D), and injection-site reactions (E).

Table I. Clinical characteristics of skin involvement ($n = 37$)

Lesion description	
Lesion type	
Maculopapules and nodules	37 (100%)
Pustules	5 (13%)
Vesicles/bullae	4 (11%)
Livedo	6 (16%)
Reticularis	3 (8%)
Racemosa	3 (8%)
Thickness of pattern <1 cm	3 (8%)
Lesion shape	
Round/nummular	36 (97%)
Arcuate/annular	12 (32%)
Lesion color	
Pink	28 (76%)
Red	27 (73%)
Violaceous/purpuric	18 (49%)
Lesion size	
<1 cm	29 (78%)
≥1 cm	29 (78%)
Both	21 (57%)
Number of lesions	
≥10	33 (89%)
<10	4 (11%)
Localization	
Trunk	30 (81%)
Arms	32 (86%)
Legs	31 (84%)
Face	11 (30%)
Pathergy	5 (13%)
Cutaneous symptoms	
Pain	13 (35%)
Pruritus	9 (24%)
Evolution of skin lesions	
Flare/remission periods	30 (81%)
Frequency of flare-ups (times/y, median [IQR])	6 (2-12)
Duration of flare-ups (d, median [IQR])	9.8 (7-10)
Permanent	4 (11%)

Zakine E et al, JAMA Dermatol. 2021 Nov; 157(11): 1–6.
Zakine E et al. J Am Acad Dermatol. 2023 Apr;88(4):917-920.

Atteintes pulmonaires

CT Scan Abnormalities	Initial (n = 45)	Follow-up (n = 81)
Parenchymal disease	45 (100)	73 (90)
Ground-glass opacities	39 (87)	60 (74)
Consolidations	22 (49)	42 (52)
Reticulations	17 (38)	23 (28)
Septal lines	23 (51)	46 (57)
Fibrosis	1 (2)	1 (1)
Nodules	21 (47)	20 (25)
Micronodules	17 (38)	20 (25)
Pleural effusion	24 (53)	37 (46)
Small	23 (96)	28 (34)
Unilateral	14 (58)	21 (26)
Right	9	15
Left	5	6
Pericardial effusion	7 (15)	11 (13)
Mediastinal adenomegaly	26 (58)	53 (65)
< 20 mm	24 (92)	47 (88)
Multiple	19 (73)	35 (66)

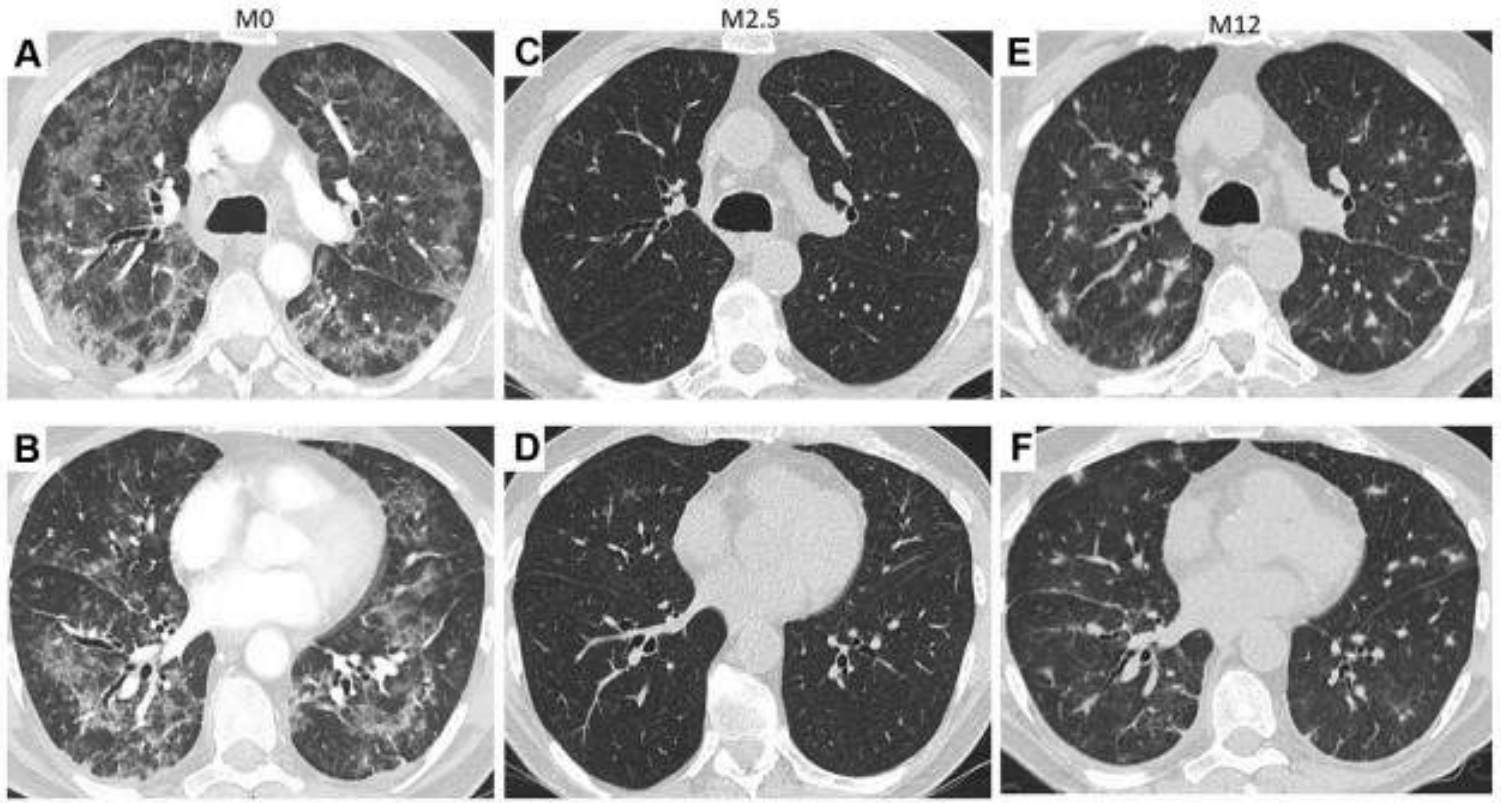
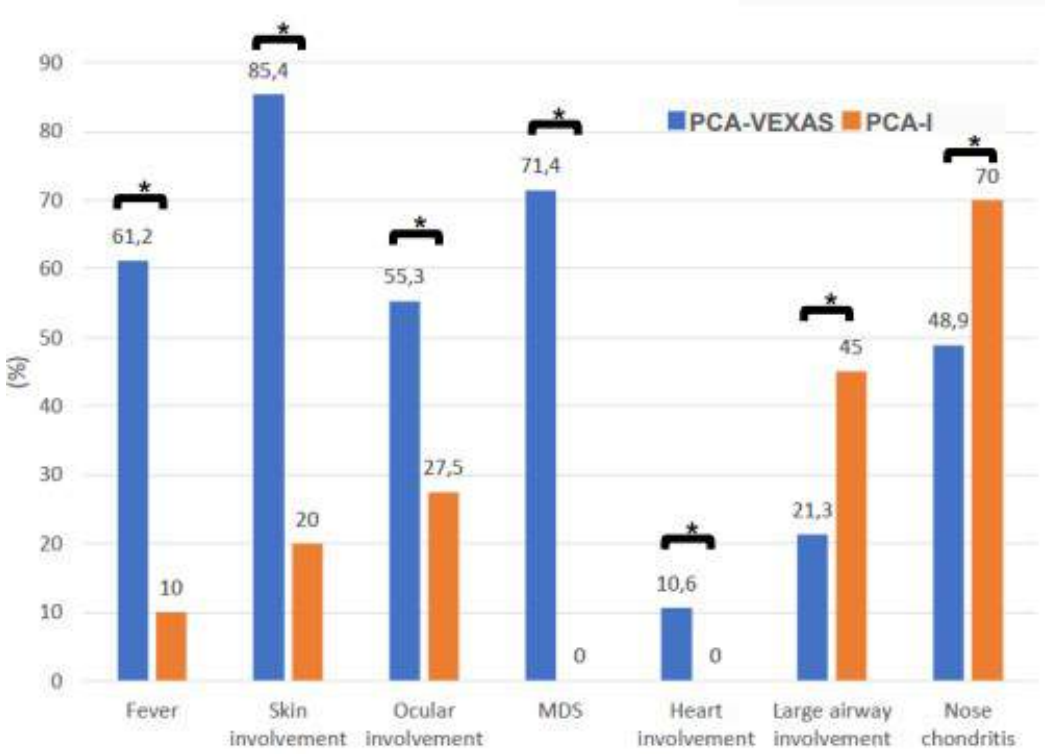


Figure 3 – *A-F, Representative pulmonary CT scans at diagnosis and during follow-up: at diagnosis (A, B); after 2.5 months (C, D) when the vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome was controlled and CT scan findings were normal; and after 12 months during a relapse (E, F).*

Borie R, et al . Chest. 2023 Mar;163(3):575-585.

Polychondrites atrophiantes

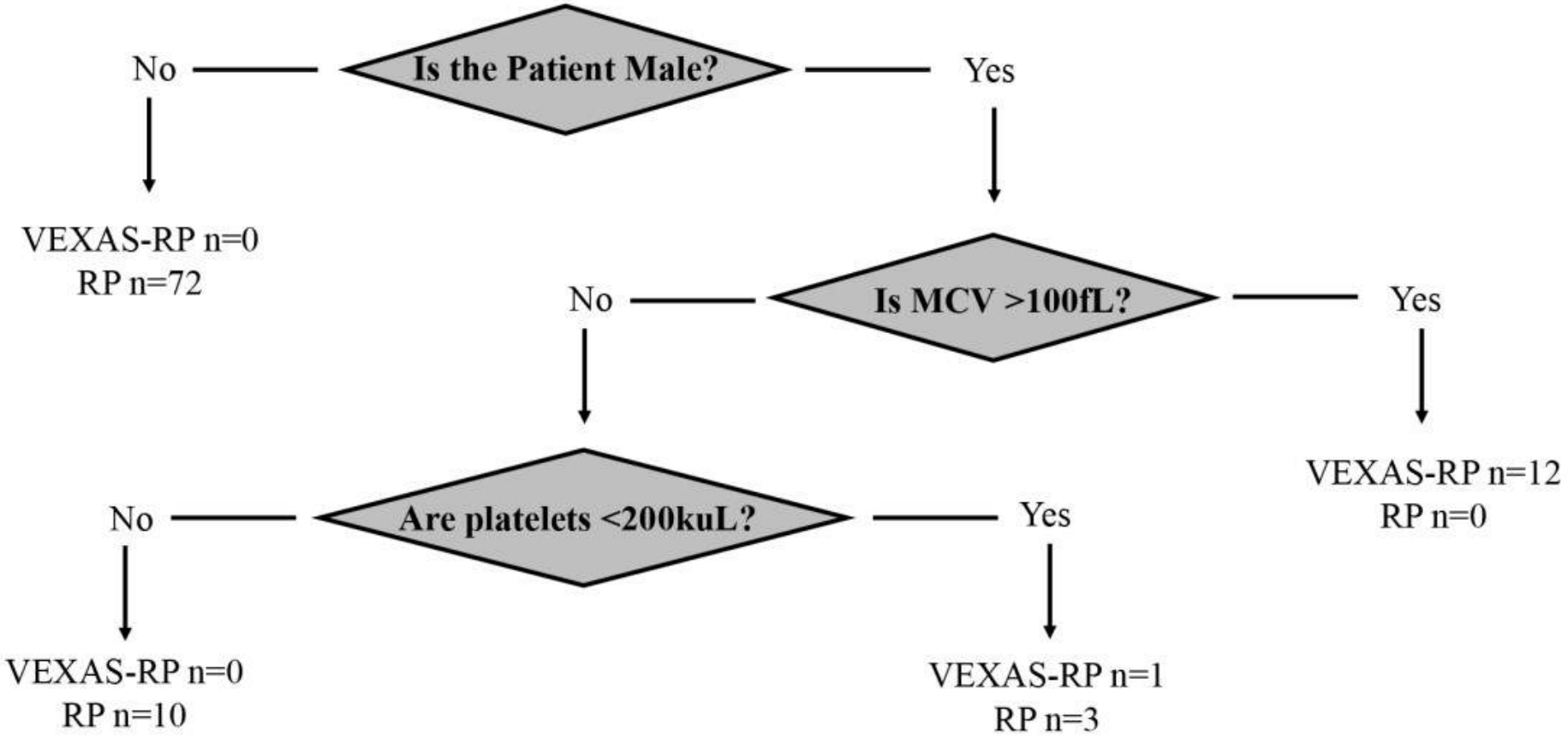
- Comparaison entre PCA idiopathique (n= 40) et PCA liée au VEXAS (n=55)



	I-RP	VEXAS-RP	P value
Male gender (%)	12 (30)	53 (96)	<0.001
Age at diagnosis of RP (median (IQR)) (years)	44(38, 52)	66(61, 72)	<0.001
Laboratory data			
Haemoglobin (median (IQR)) (g/L)	137(130, 140)	103(90, 120)	<0.001
Platelets (median (IQR)) ($10 \times ^{9}$/L)	257(209, 303)	163(115, 236)	<0.001
Neutrophils (median (IQR)) (G/L)	4(3, 5)	2.7(2, 4)	0.018
C-reactive protein (median (IQR)) (mg/L)	10(2, 23)	69(30, 107)	<0.001

Khitri MY, et al. RMD Open. 2022 Jul;8(2):e002255.

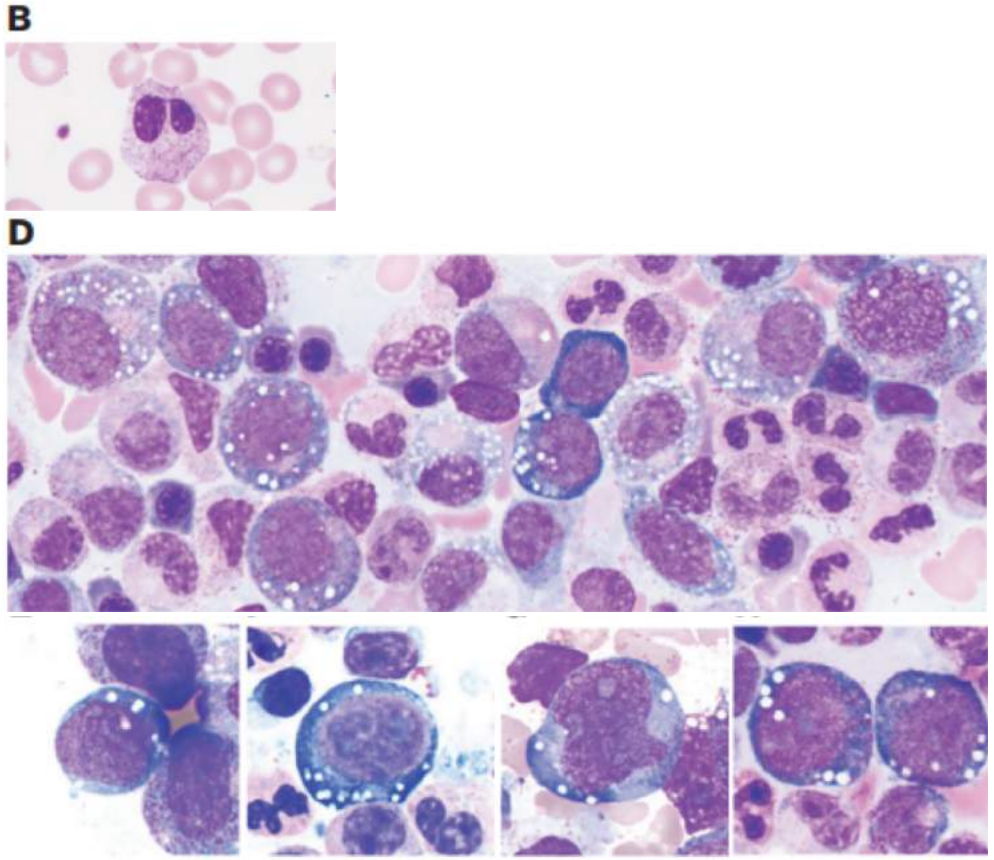
Polychondrites atrophiantes



Ferrada MA et al. Arthritis Rheumatol. 2021 Oct;73(10):1886-1895.

Atteintes hématologiques

Laboratory data	
Hemoglobin (g/dl)	10.10 [9.00, 11.50]
VGM	101 [94.08, 106.75]
Platelets (n/mm3)	204 [138.25, 260.25]
Leucocytes / mm3	4400 [2972 , 6222]
Neutrophils / mm3	2600 [1640 , 4185]
C-reactive protein (g/L)	61 [30.00, 128]



Georgin-Lavialle S, et al. Br J Dermatol. 2022 Mar;186(3):564-574.
Lacombe V et al , Br J Haematol. 2021 Oct;195(2):286-289.
Obiorah IE, et al . Blood Adv. 2021 Aug 24;5(16):3203-3215.

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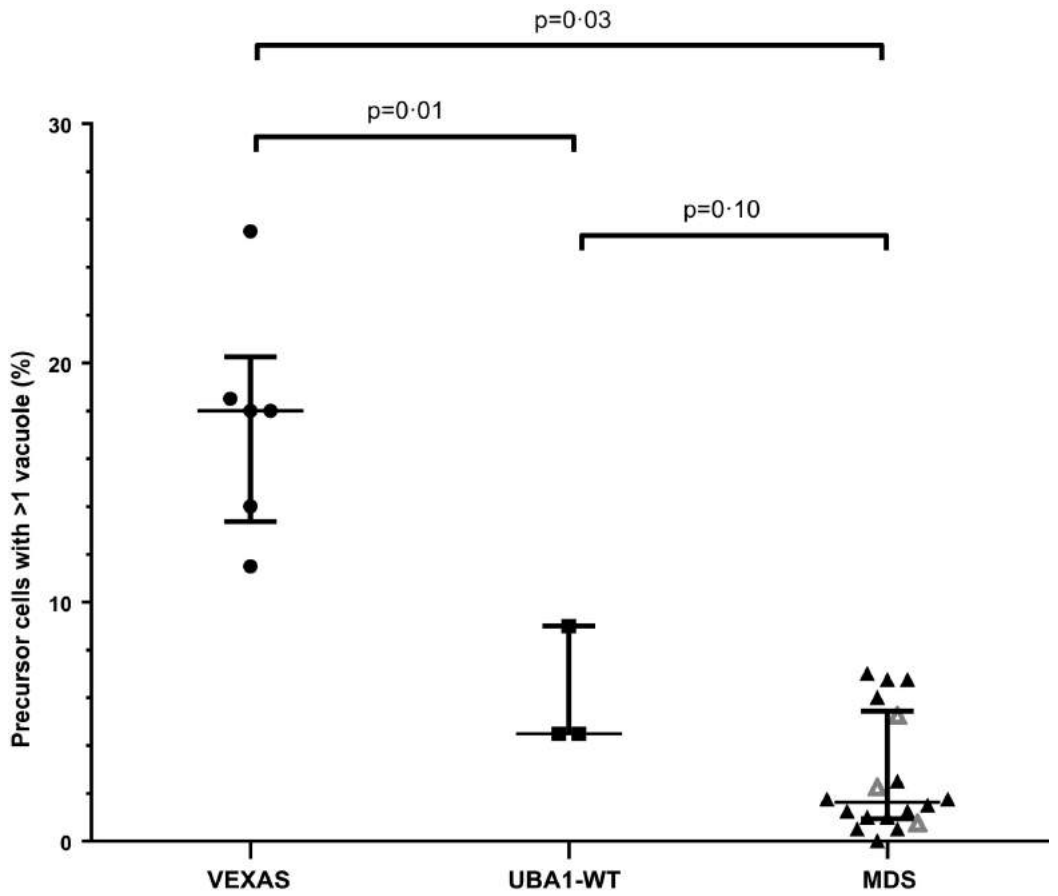

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Obiorah IE, et al . Blood Adv. 2021 Aug 24;5(16):3203-3215.

Atteintes hématologiques: SMD

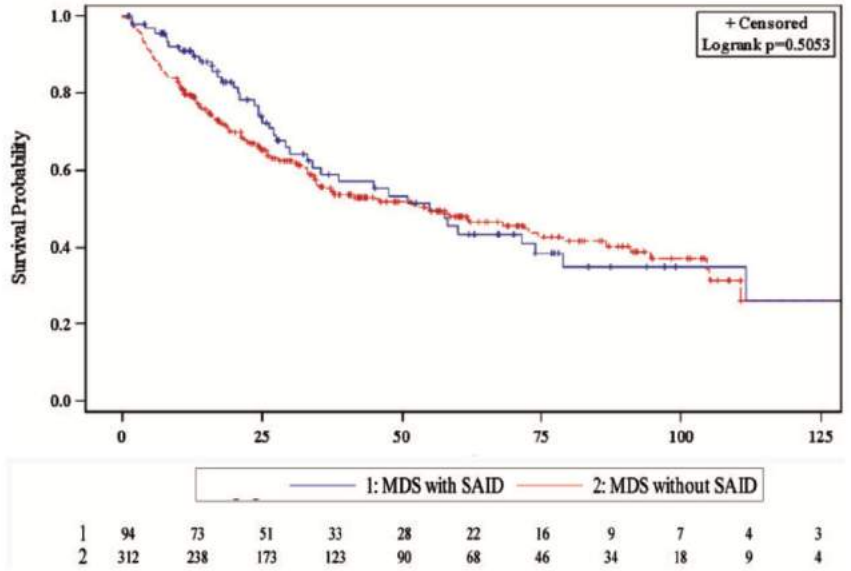
- Fréquence élevée
- 31 à 50% des patients VEXAS ont un SMD
- Survenue tardive

SMD et manifestations auto-inflammatoires

- 25% des SMD avec manifestations auto-inflammatoires

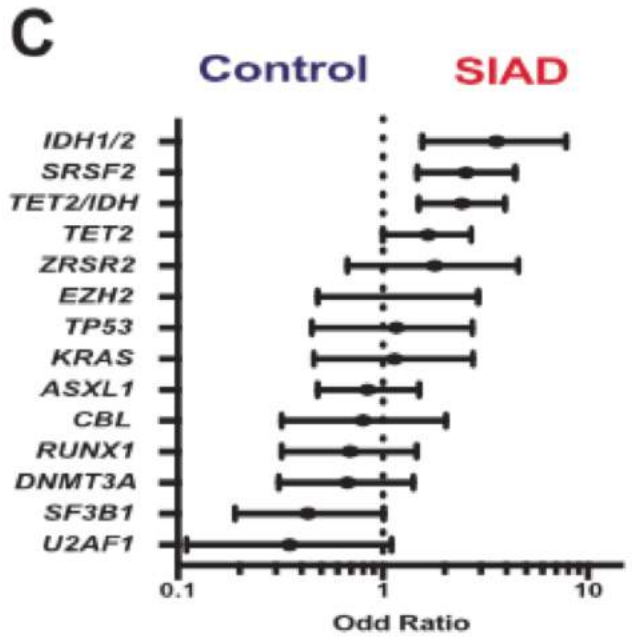
Group	*n* (%) (95% CI)	Type, *n*
Systemic vasculitis	39 (32) (23, 40)	Polyarteritis nodosa, 12 GCA, 9 Behçet's disease, 6 Cryoglobulinaemia, 3 GPA, 1 Unclassified, 8
CTDs	31 (25) (18, 33)	RP, 14 SLE, 8 Primary APS, 4 Myositis, 3 SS, 2
Neutrophilic dermatosis	12 (10) (5, 15)	Aseptic abscesses, 1 Sweet's syndrome, 9 Pyoderma gangrenosum, 2
Inflammatory arthritis	28 (23) (15, 30)	PMR, 10 RA, 4 RS3PO, 4 Undifferentiated, 10
Unclassified	13 (11)	—

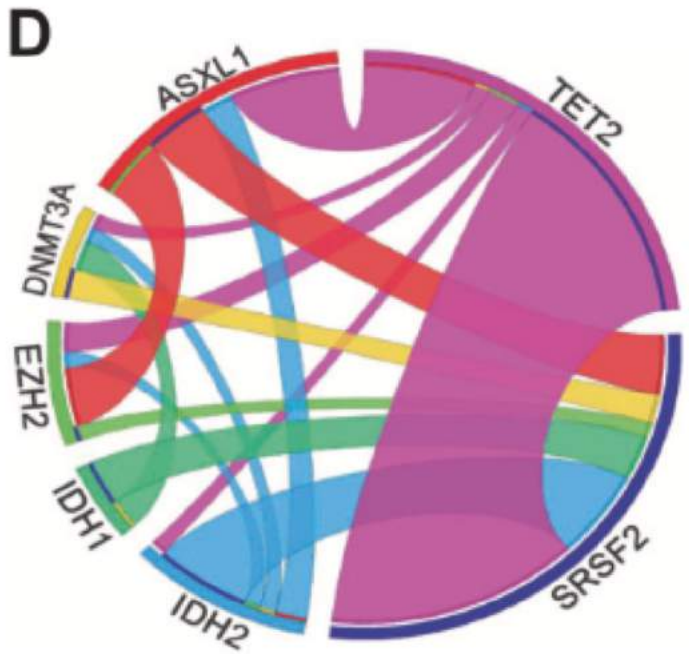
FIG. 2 Overall survival in MDS patients with and without SIADs



Mekinian A et al. Rheumatology (Oxford). 2016 Feb;55(2):291-300.

SMD et manifestations auto-inflammatoires





↓ Treg
Déséquilibre lymphocytes T
↓ Récepteurs du checkpoint

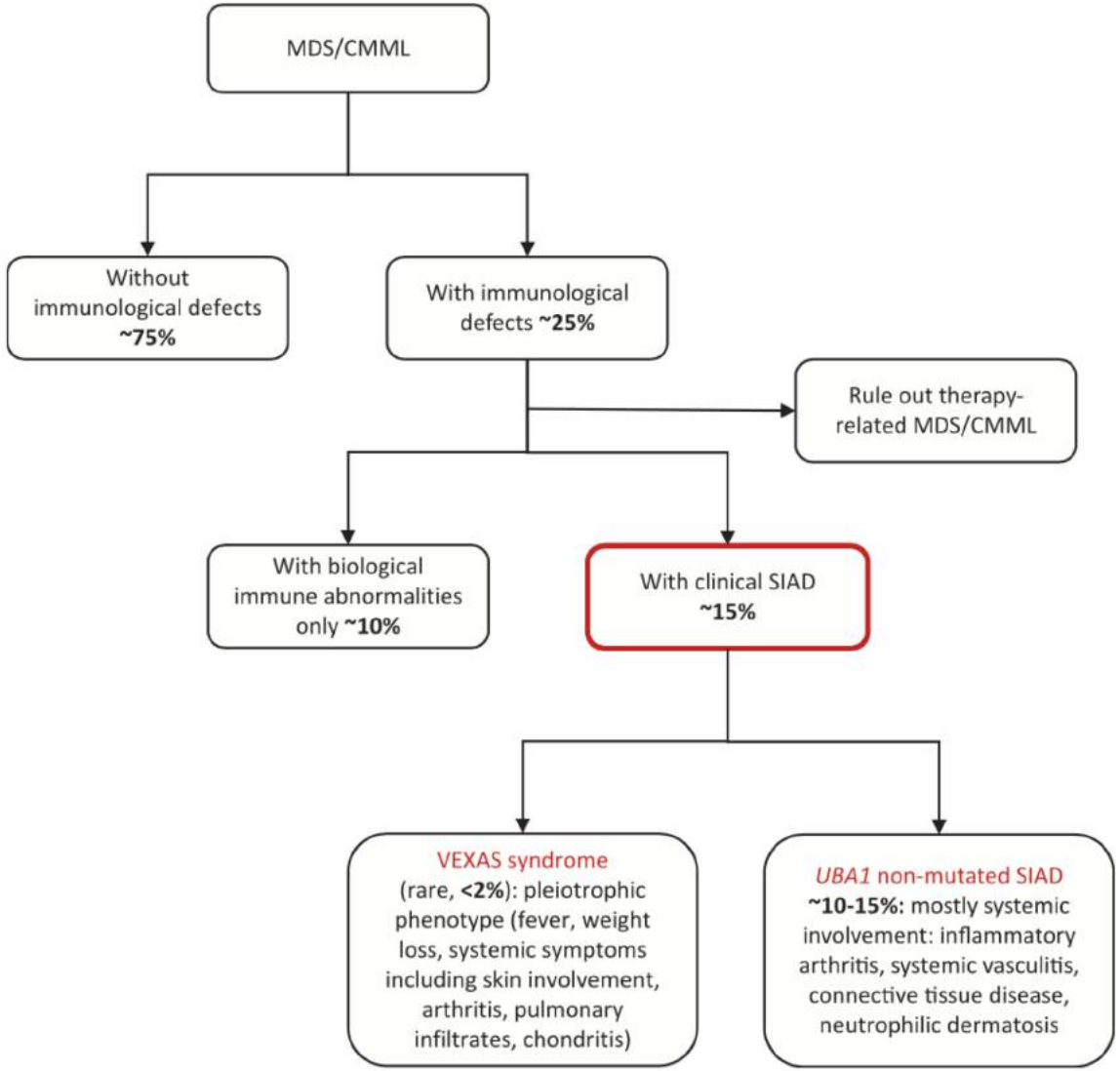
Zhao LP et al. Leukemia. 2021 Sep;35(9):2720-2724.

SMD et manifestations auto-inflammatoires

- Prévalence des mutations *UBA1:*
  - Cohorte de 85 patients SMD avec MAI
  - **12% des patients avec mutation *UBA1***

Zhao LP et al. Leukemia. 2021 Sep;35(9):2731-2733.

SMD et manifestations auto-inflammatoires



Zhao LP et al. Leukemia (2023) 37:1186–1190

VEXAS et SMD

- SMD « atypique »
  - Peu de mutations additionnelles

NGS chez 75 patients (cohorte française):
- 18 patients avec mutation additionnelles (14,9%)
- DNMT3A (9,1%) et TET2 (5%)

Georgin-Lavialle S, et al. Br J Dermatol. 2022 Mar;186(3):564-574

VEXAS et SMD

- SMD « atypique »
  - Peu de mutations additionnelles
  - Caryotype normal

Table I. Baseline patient characteristics.

Chartacteristic	Value
WHO 2016 classification	
MDS single lineage dysplasia, *n* (%)	1 (9)
MDS multiple lineage dysplasia, *n* (%)	6 (55)
MDS EB type 1, *n* (%)	4 (36)
Cytogenetics, *n* (%)	
Normal	8 (73)
-Y	1 (9)
Trisomy 8	2 (18)

Comont T, et al . Br J Haematol. 2022 Feb;196(4):969-974.

VEXAS et SMD

- SMD « atypique »
  - Peu de mutations additionnelles
  - Caryotype normal
  - Faible risque selon R-IPSS

	Total Cohort n=83
R-IPSS Score* *n (%)*	
Very low risk	9 (39)
Low risk	12 (52)
Intermediate risk	0 (0)
High risk	2 (4)
Very high risk	0 (0)

Ferrada M et al.. *Blood*. 2022;140(13):1496-1506

VEXAS et SMD

- SMD « atypique »
  - Peu de mutations additionnelles
  - Caryotype normal
  - Faible risque selon R-IPSS
  - Pas de progression en LAM (1 seul cas décrit)

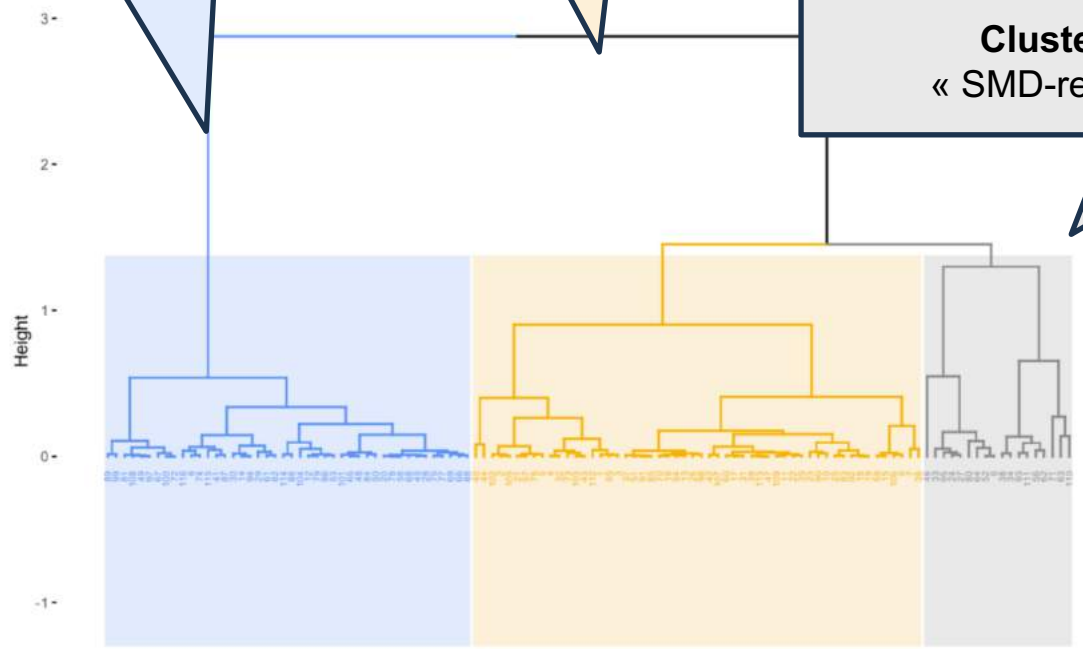
Battipaglia G et al. Curr Res Transl Med 2023;71(2):103386

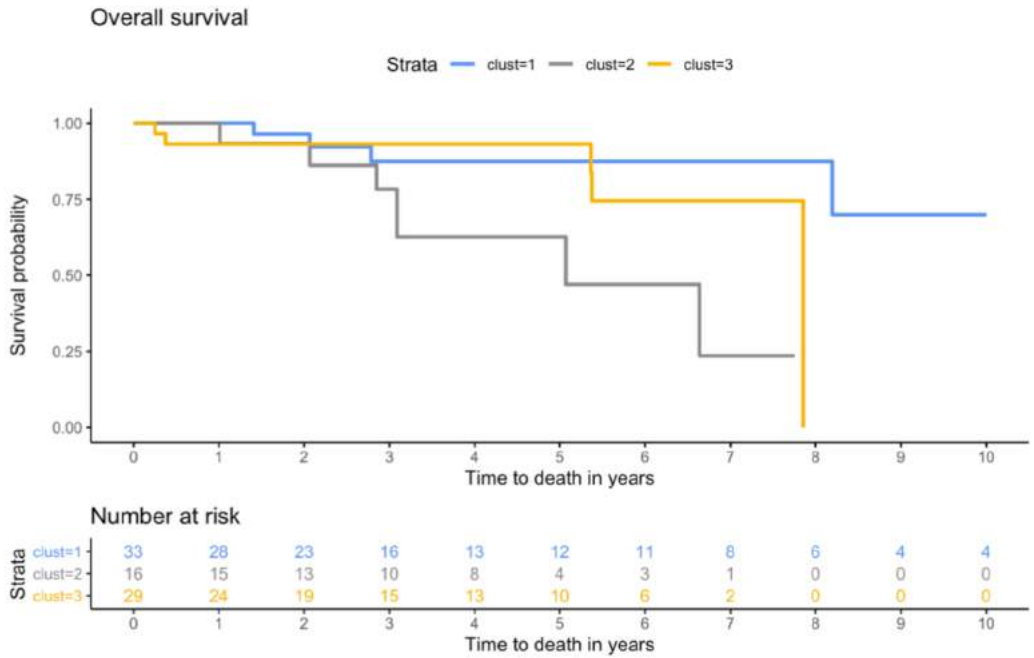
VEXAS et SMD

Cluster 1:
forme modérée

Cluster 3:
forme inflammatoire

Cluster 2:
« SMD-related »

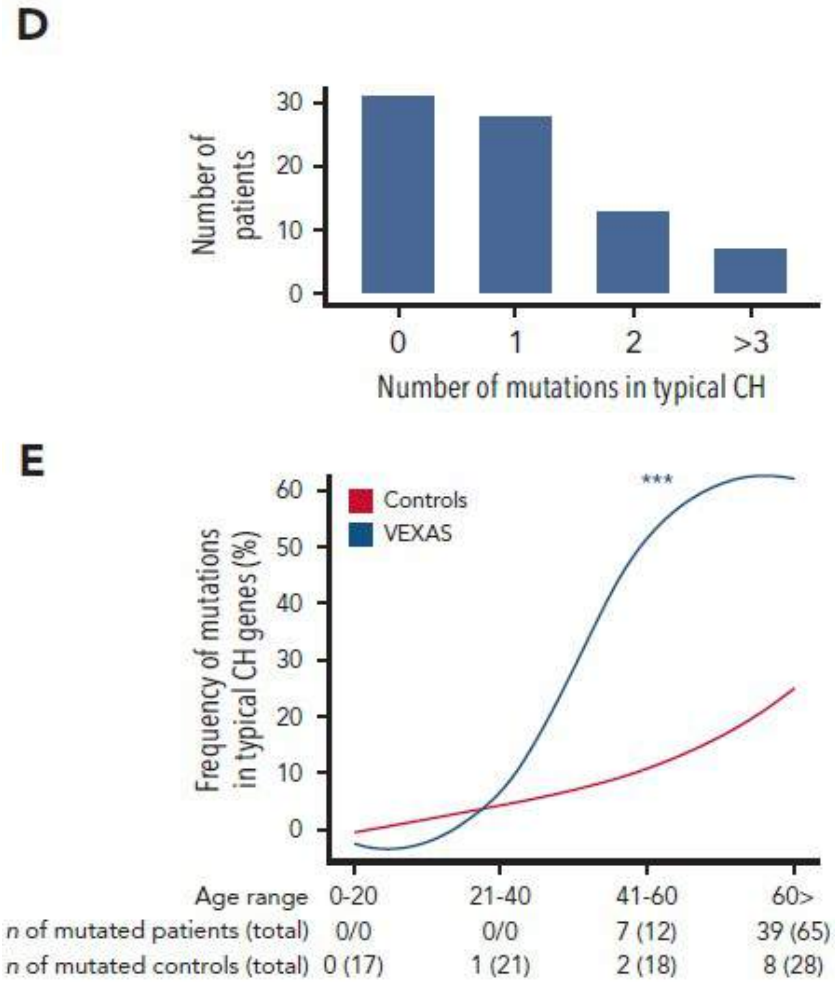




Georgin-Lavialle S,. Br J Dermatol. 2022 Mar;186(3):564-574

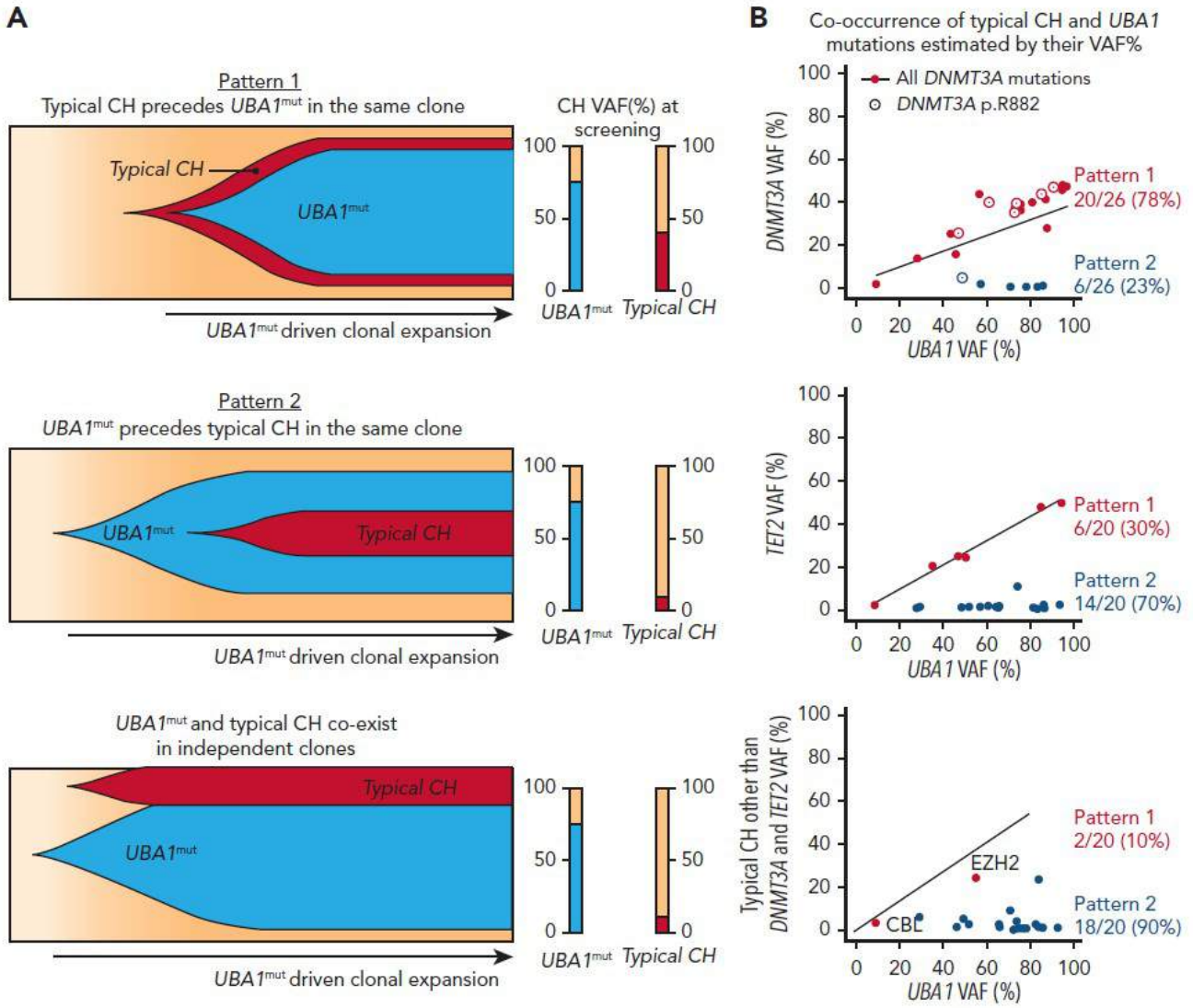
VEXAS et hématopoïèse clonale

n=77



Gutierrez-Rodrigues F, et al . Blood. 2023 Jul 20;142(3):244-259.,

VEXAS et hématopoïèse clonale



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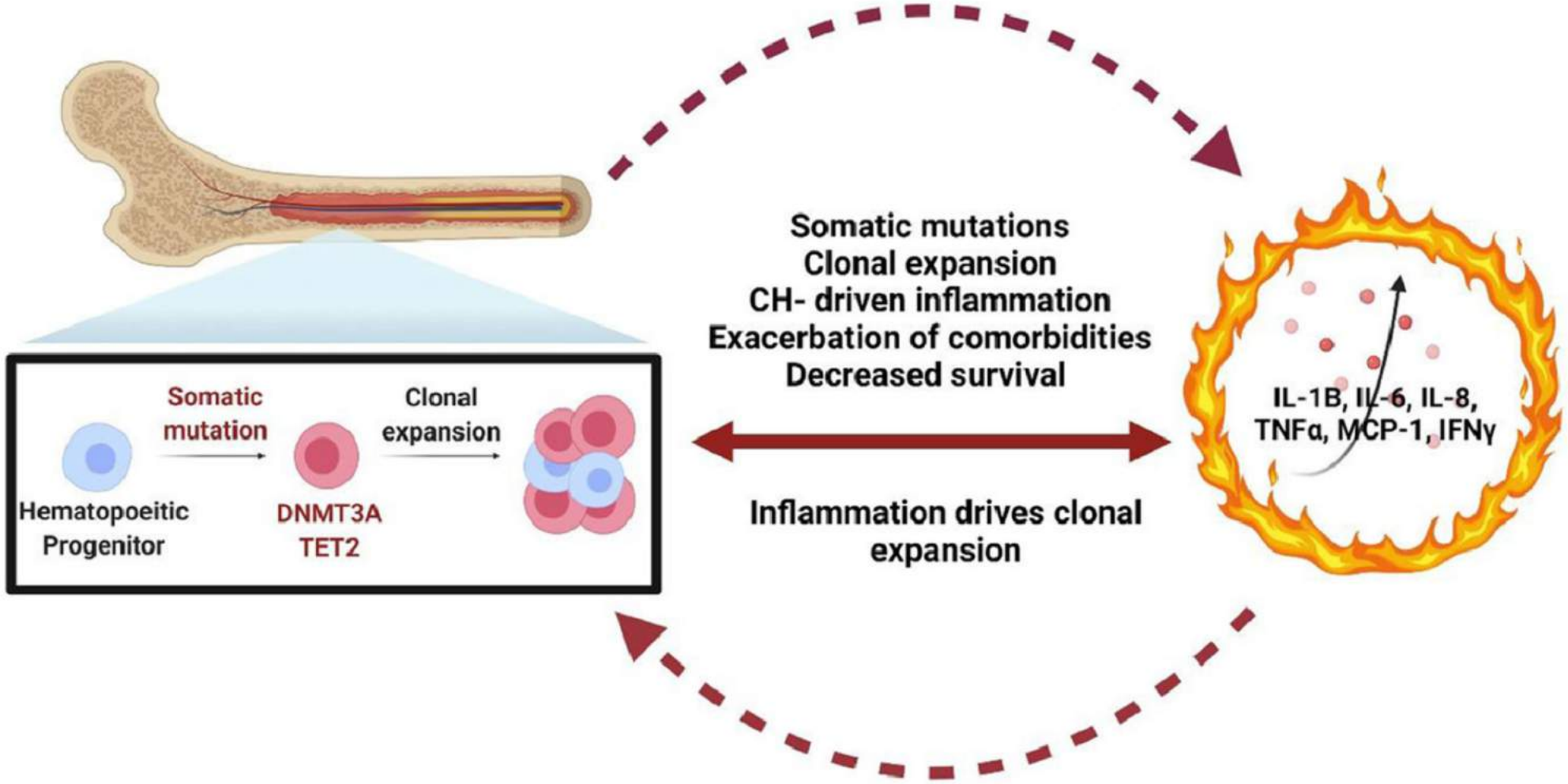
VEXAS et hématopoïèse clonale



Kusne Y et al, Seminars in Hematology, Volume 58, Issue 4, 2021, Pages 226-229,

Relation génotype- phénotype

Table 3. Patients' characteristics according to the type of *UBA1* mutation.

Characteristics	Splice mutations (n=8)	UBA1 p.Met41Leu (c.121A>C) (n=21)	UBA1 p.Met41Thr (c.122T>C) (n=52)	UBA1 p.Met41Val (c.121A>G) (n=35)	p
Sex Male	8 (100.0)	19 (90.5)	51 (98.1)	33 (94.3)	0.452
Age at diagnosis	74.00 [68.00, 76.50]	68.00 [60.00, 72.00]	72.50 [68.75, 77.25]	70.50 [68.00, 74.75]	0.022
Fever	7 (87.5)	4 (19.0)	36 (70.6)	28 (82.4)	<0.001
Weight loss	5 (62.5)	9 (42.9)	28 (54.9)	23 (65.7)	0.396
Chondritis	5 (62.5)	11 (52.4)	21 (40.4)	5 (14.3)	0.006
Skin lesions	7 (87.5)	17 (81.0)	44 (84.6)	29 (82.9)	0.969
Gastrointestinal tract	3 (37.5)	1 (4.8)	6 (11.5)	6 (17.1)	0.123
Peripheral nervous system involvement	2 (25.0)	1 (4.8)	12 (23.1)	2 (5.7)	0.057
Ocular involvement	5 (62.5)	8 (38.1)	24 (46.2)	10 (28.6)	0.220
Heart involvement	2 (25.0)	1 (4.8)	7 (13.5)	3 (8.6)	0.405
Lung involvement	5 (62.5)	2 (9.5)	26 (50.0)	24 (68.6)	<0.001
Lymph nodes	4 (50.0)	3 (14.3)	22 (42.3)	11 (31.4)	0.102
Spleen enlargement	3 (37.5)	3 (14.3)	6 (12.2)	4 (12.9)	0.303
Unprovoked thrombosis	2 (25.0)	6 (28.6)	20 (38.5)	13 (37.1)	0.785
Arthralgias	4 (50.0)	9 (42.9)	10 (19.2)	10 (28.6)	0.105
Infections	4 (50.0)	2 (9.5)	12 (23.1)	7 (20.0)	0.125
Hemoglobin	9.90 [9.45, 10.75]	11.60 [10.05, 13.70]	10.20 [9.15, 11.53]	9.65 [9.00, 10.45]	0.019
VGM	107.45 [105, 113]	102.00 [95.25, 109.58]	100.75 [96, 106]	99.90 [91.42, 103]	0.084
Platelets (n/mm3)	129.00 [90.50, 178]	196.00 [162, 245]	206.00 [127.50, 254.50]	221.00 [149, 268]	0.388
Neutrophils / mm3	800.00 [460, 1180]	735.00 [402.50, 887.50]	910.00 [795, 1345]	1100.00 [650.00, 1327.50]	0.056
C-reactive protein	29 [19, 102]	45 [27.50, 60.50]	50 [29, 104]	131 [79.50, 162]	<0.001
MDS	5 (62.5)	7 (33.3)	22 (42.3)	24 (68.6)	0.031
Relapse	1 (12.5)	1 (4.8)	3 (6.0)	4 (11.4)	0.714
Deaths	1 (12.5)	0 (0.0)	9 (18.0)	8 (22.9)	0.139
Steroid dependence	3 (37.5)	11 (52.4)	24 (48.0)	15 (42.9)	0.853
Follow-up (months)	1.71 [1.02, 2.40]	2.93 [2.39, 6.99]	4.31 [2.26, 6.25]	2.22 [1.39, 4.64]	0.270
VEXAS therapy					0.051
No treatment	0 (0.0)	6 (28.6)	11 (21.2)	9 (25.7)	
Steroids	3 (37.5)	5 (23.8)	13 (25.0)	17 (48.6)	
DMARDs	0 (0.0)	4 (19.0)	8 (15.4)	0 (0.0)	
Biologics	5 (62.5)	6 (28.6)	20 (38.5)	9 (25.7)	

Data are medians with interquartile and number with frequencies.

- Variant Valine:
  - moins de chondrite
  - plus de syndrome inflammatoire
  - plus de SMD
- Variant Leucine:
  - moins d'atteinte pulmonaire

Georgin-Lavialle S,. Br J Dermatol. 2022 Mar;186(3):564-574.

Relation génotype- phénotype

	Total Cohort n=83	*Leucine Variant* n=15	*Valine Variant* n=18	*Threonine Variant* n=50	P value
Demographics					
Age of disease onset *median (range)*	66 (41-80)	66 (55-74)	65 (50-72)	66 (42-80)	0.97
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)	0.01
Undifferentiated Fever Syndrome *n (%)*	19 (23)	1 (6)	10 (55)	8 (16)	<0.01
Sweet syndrome *n (%)*	18 (22)	9 (60)	2 (11)	7 (14)	<0.01
MDS *n (%)*	26 (31)	5 (33)	8 (44)	13 (26)	0.35
Clinical Manifestations *n (%)*					
Fever	69 (83)	13 (87)	17 (94)	39 (78)	0.25
Skin involvement	68 (82)	13 (87)	15 (83)	40 (80)	0.82
Arthritis	48 (58)	8 (53)	10 (55)	30 (60)	0.87
Pulmonary infiltrates	47 (57)	10 (67)	10 (55)	27 (54)	0.67
Ear chondritis	45 (54)	8 (53)	4 (22)	33 (66)	<0.01
Unprovoked DVT	34 (41)	9 (60)	6 (33)	19 (38)	0.24
Nose chondritis	30 (36)	5 (33)	3 (16)	21 (42)	0.13
Periorbital edema	25 (30)	3 (20)	10 (55)	12 (24)	0.03
Hearing loss	24(29)	7 (47)	4 (22)	13 (26)	0.25
Ocular inflammation	20 (24)	1 (6)	1 (5)	18 (36)	<0.01
Pulmonary embolism	11 (13)	2 (13)	4 (22)	5 (10)	0.45
Pleural effusion	11 (13)	2 (13)	4 (22)	5 (10)	0.45
Orchitis	10 (12)	0 (0)	4 (22)	6 (12)	0.07
Airway chondritis	1 (2)	0 (0)	0 (0)	1 (2)	0.60
# of DMARDs, median (IQR)	2 (1-4)	3 (1-5)	2 (1-4)	2 (1-4)	0.62
Hematologic Manifestations					
R-IPSS Score* *n (%)*					
Very low risk	9 (39)	1 (11)	2 (22)	6 (66)	0.72
Low risk	12 (52)	2 (16)	4 (33)	6 (50)	0.77
Intermediate risk	0 (0)	0 (0)	0 (0)	0 (0)	n/a
High risk	2 (4)	0 (0)	1 (50)	1 (50)	0.67
Very high risk	0 (0)	0 (0)	0 (0)	0 (0)	n/a
Macrocytic anemia *n (%)*	81(97)	15 (100)	18 (100)	48 (96)	0.35
Thrombocytopenia *n (%)*	40(83)	7 (47)	8 (44)	25 (50)	0.71
UBA1 Variant Allele Frequency median (IQR)#	75 (57-85)	64 (47-83)	72 (52-86)	76 (69-86)	0.43

- Variant Valine:
  - moins de chondrite
  - plus de syndrome inflammatoire
- Variant Thréonine:
  - plus d'atteinte oculaire
- Variant Leucine:
  - plus de syndrome de Sweet

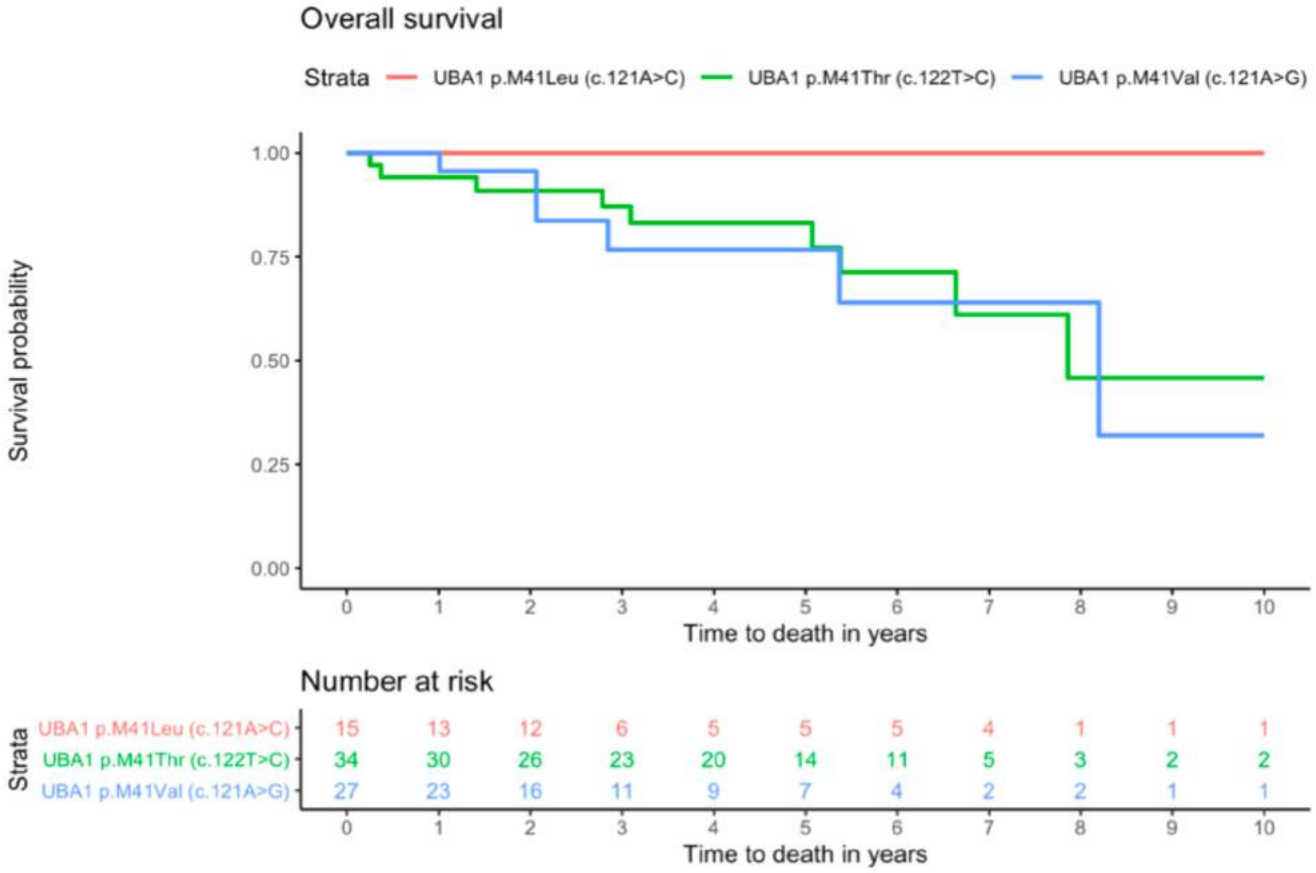
Ferrada M et al.. *Blood*. 2022;140(13):1496-1506

Pronostic

- Mortalité entre 25 et 35% à 5 ans
- Dépendance aux corticoïdes élevée ≈ 45%
- Complications des traitements

Pronostic

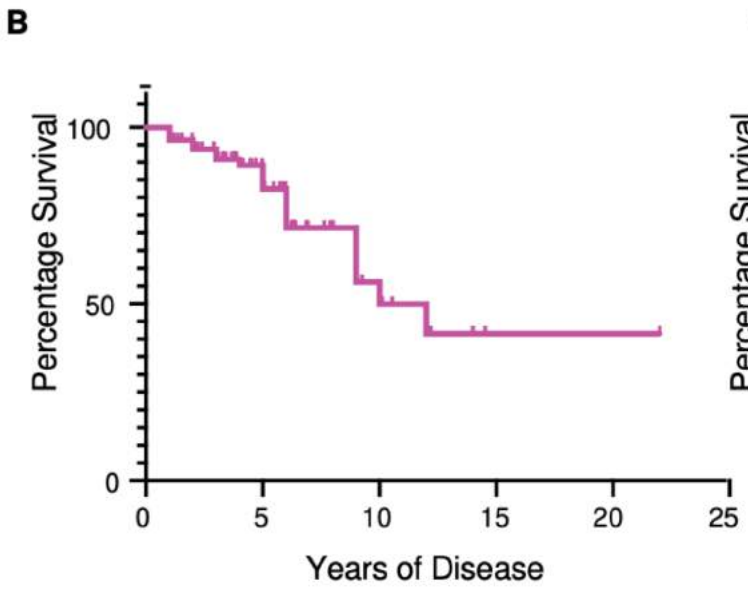
n=116

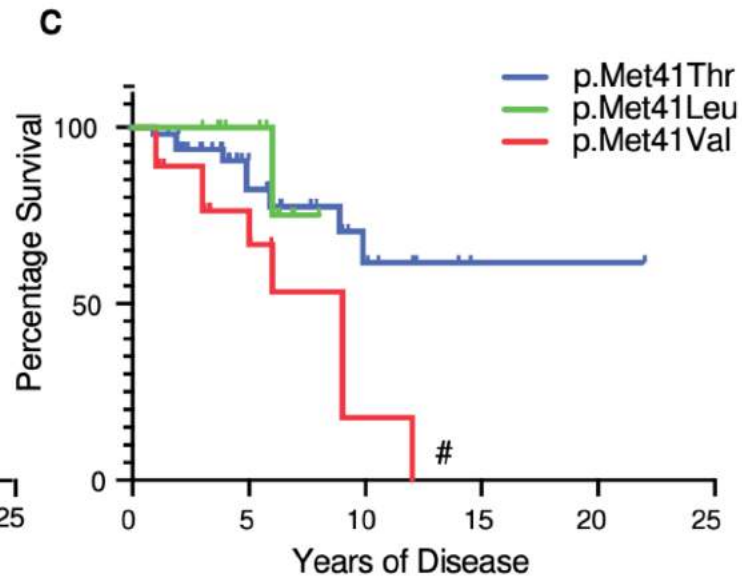


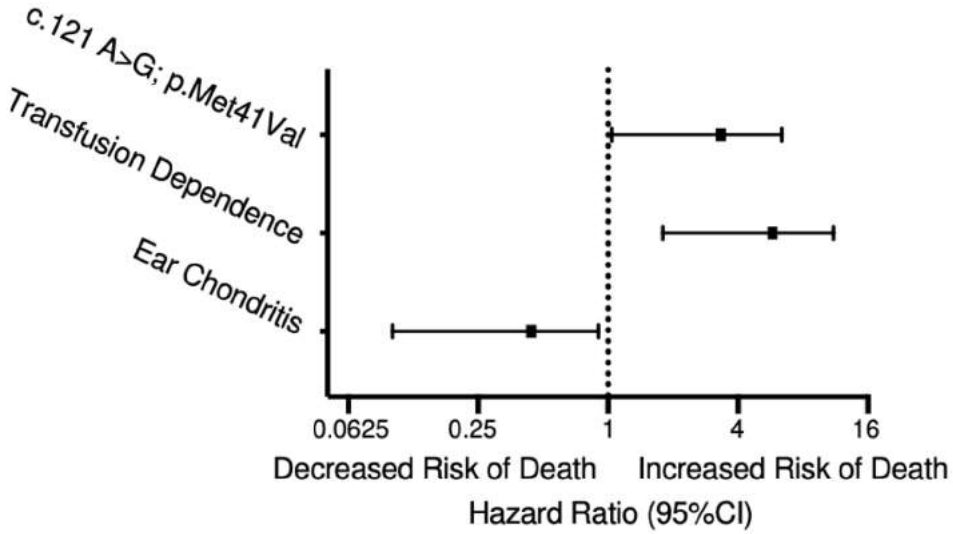
Survie à 5 ans: 63%

Pronostic

n=83



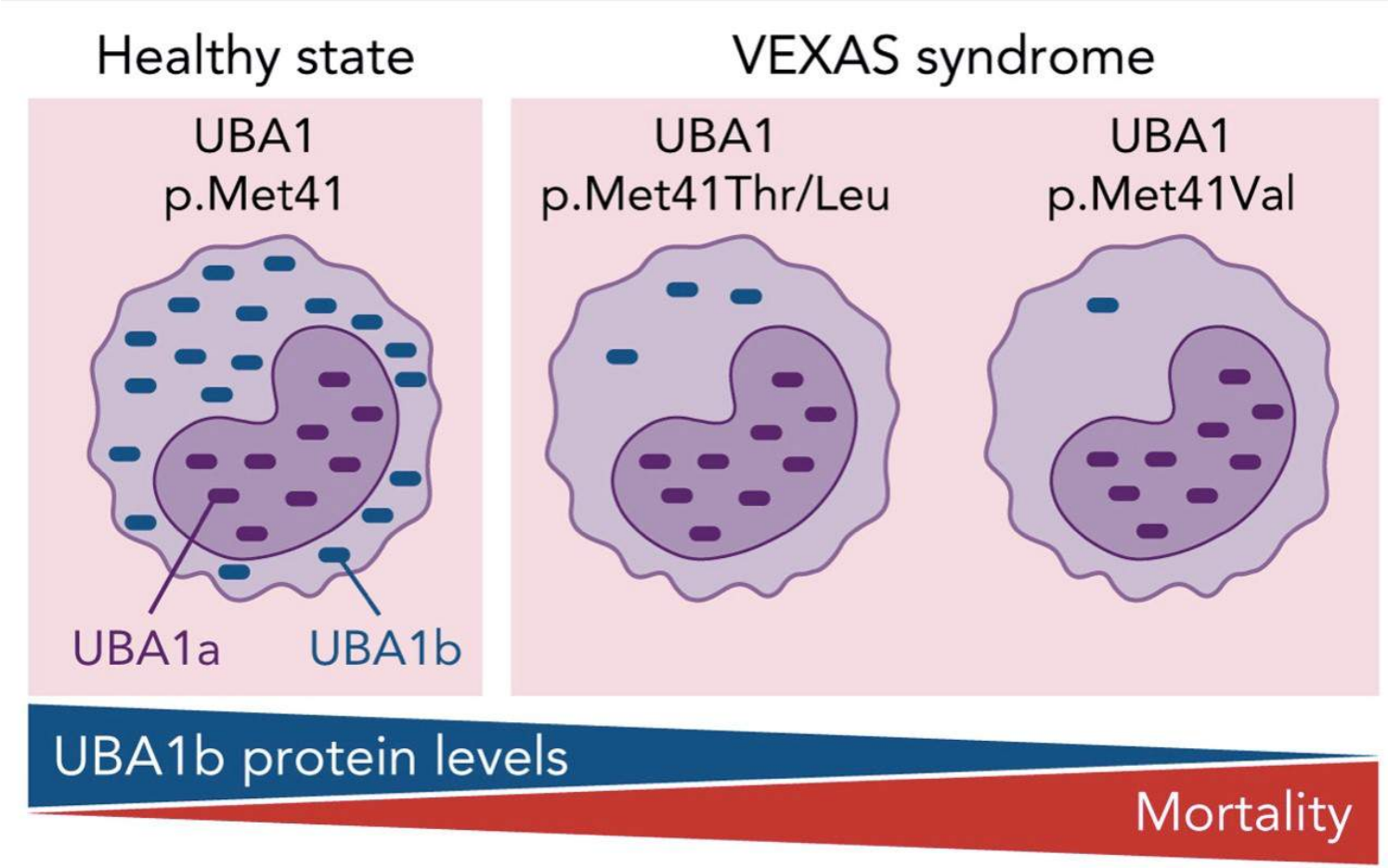




Médiane de survie: 10 ans

Pronostic

n=83



Prise en charge thérapeutique: Objectifs

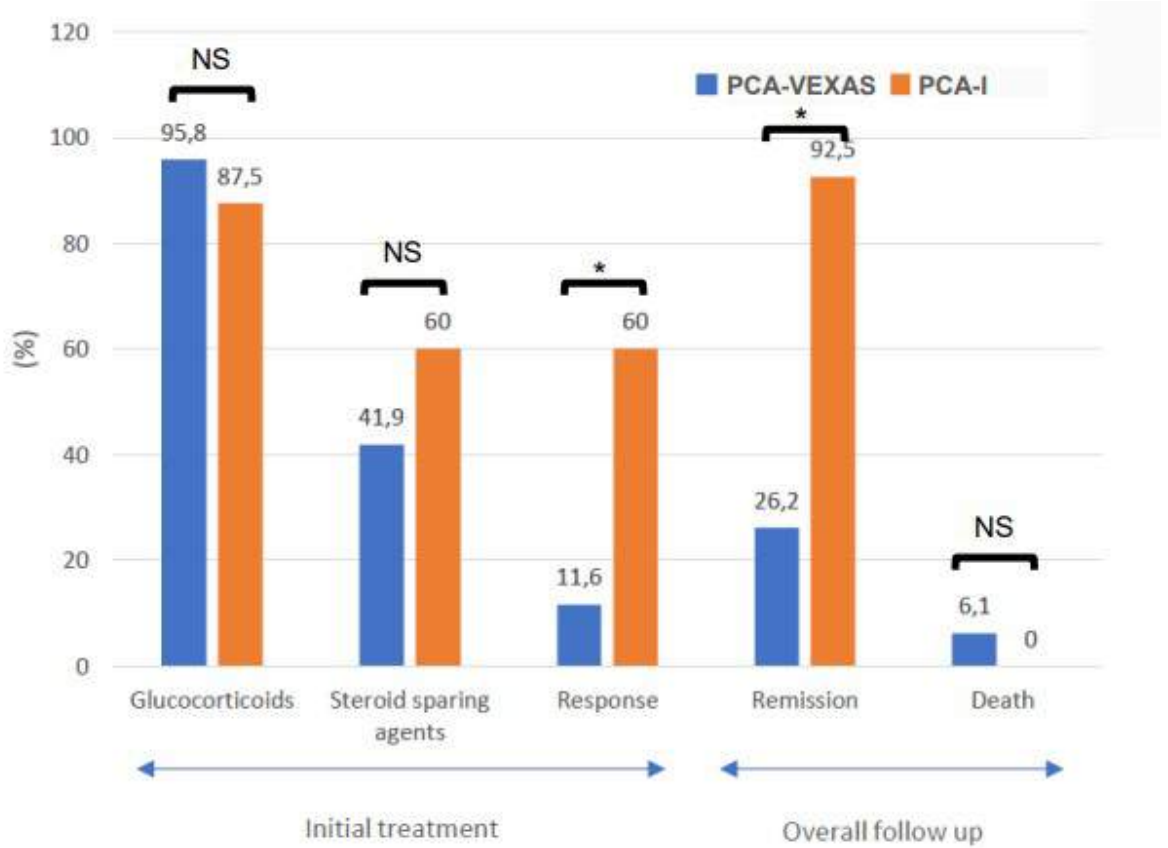
Bloquer l'inflammation
- Corticoïdes
- Autres immunosuppresseurs
- Inhibiteurs JAK

Eradiquer clone UBA1
- Azacitidine
- Allogreffe

Traiter les symptômes
- Thrombose
- Infections
- Anémie

Prise en charge thérapeutique: Corticoïdes

- Traitement de première ligne
- Mais… réponse de courte durée et dépendance
- Dose > 10mg/j eq prednisone



Khitri MY, et al . RMD Open. 2022 Jul;8(2):e002255.

Prise en charge thérapeutique: Autres

Treatment history				
Glucocorticoids, n,N (%)	8/8 (100)	Yes PR‡	Yes PR	8/8
Synthetic DMARDs, n/N	CyS (1/8) NR	None	None	CyS (1/8) NR
	AZA (2/8) NR			AZA (2/8) NR
	MTX (2/8) NR			MTX (2/8) PR (1/1)
	CyC (2/8) NR			MMF (2/8) NR
	MMF (2/8) NR			Dapsone (1/8) NR
	Dapsone (1/8) NR			Leflunomide (1/8) NR
Biological DMARDs, n/N	Tocilizumab (3/4) 2 NR, 1 PR	None	None	Infliximab (1/1) R
	Anakinra (1/4) NR			Anakinra (1/1) R
	Rituximab (1/4) NR			Tocilizumab (1/1) R

Poulter JA, et al. Blood. 2021 Jul 1;137(26):3676-3681.

Prise en charge thérapeutique: Autre

Patient	A	B	C	D	E	F	G	H	I	J	K	L
Treatment												
Glucocorticoids	Prednisone, 60 mg/d, tapering schedule. Methylprednisolone pulse therapy during pulmonary vasculitis flares (3 days, 1000 mg iv)	Methylprednisolone pulse therapy (3 days, 1000 mg iv), tapered to 7,5 mg/d of oral prednisone at best	Prednisone, 60 mg/d, tapering schedule	Prednisone 60 mg/d, tapered to 20 mg/d at best	Prednisone, 60 mg/d, tapered to 5 mg/d at best	Prednisone, 30 mg/d, tapering schedule	Prednisone, 60 mg/d, after tapering multiple flares for which methylprednisolone pulse therapy (3 days, 1000 mg iv)	Prednisone, 60 mg/d, tapering schedule	Prednisone, 60 mg/d, tapering schedule	Prednisolone, 60 mg/d, tapering schedule	Prednisolone, 60 mg/d, tapering schedule	Prednisolone, 60 mg/d, tapering schedule
Methotrexate	—	15 mg/wk, add-on to tocilizumab	—	—	10 mg/wk, discontinued because of side effects	—	15 mg/wk, steroid-sparing agent	25 mg/wk, steroid-sparing agent	—	—	20 mg/wk, steroid-sparing agent	20 mg/wk, steroid-sparing agent
Mycophenolate	—	2 × 1000 mg/d, no response	—	—	—	—	—	—	—	2 × 1000 mg/d	—	—
Azathioprine	—	—	—	—	—		150 mg/d	—	2 mg/kg, initial good response but soon ineffective	150 mg/d	—	—
Cyclo-phosphamide	150 mg/d, partial response	150 mg/d, good response	—	25 mg/d, low dose because of leukopenia	—	—	—	—	—	150 mg/d, 4 mo	—	—
Cyclosporine	—	—	100 mg bid, in combination with steroids partial response	—	5 mg/kg/d, discontinued because of renal toxicity	—	—	—	—	100 mg bid	—	—
Anti–IL-1 therapy	Anakinra, 2 × 100 mg/d sc, lowered to 1 d 100 mg sc owing to neutropenia, good response	Anakinra, 100 mg/d sc, stopped owing to severe local reaction	Anakinra, 100 mg/d sc "on demand"; later 100 mg/d, good response	Anakinra, 100 mg/d sc, discontinued because of disease recurrence	Anakinra, 100 mg/d sc, discontinued owing to subcutaneous infiltrates at injection site. Switch to canakinumab, 300, mg/mo sc; stopped because of disease recurrence	—	Anakinra, 100 mg/d, discontinued owing to persisting skin infiltrates at injection sites, switch to canakinumab, 150 mg/4 wk sc	—	Anakinra, 100 mg/d, discontinue owing to severe skin infiltrates at the injection site, switch to canakinumab, 150 mg/4 wk; reduced to 150 mg/3 wk; variable to good response	—	—	—
Anti–IL-6 therapy	—	Tocilizumab 162 mg/wk sc, partial response	—	Tocilizumab 162 mg/wk sc, response unknown	Tocilizumab 162 mg/wk sc and later iv 8 mg/kg once a mo, partial response	—	—	—	—	Tocilizumab 8 mg/kg/mo iv	Tocilizumab 162mg/wk sc, partial response	Tocilizumab 162mg/wk sc, good response
TNF-α inhibitors	—	—	—	—	—	—	Infliximab	Adalimumab 40 mg/2 wk sc; in combination with	—	Infliximab	—	—

e4.

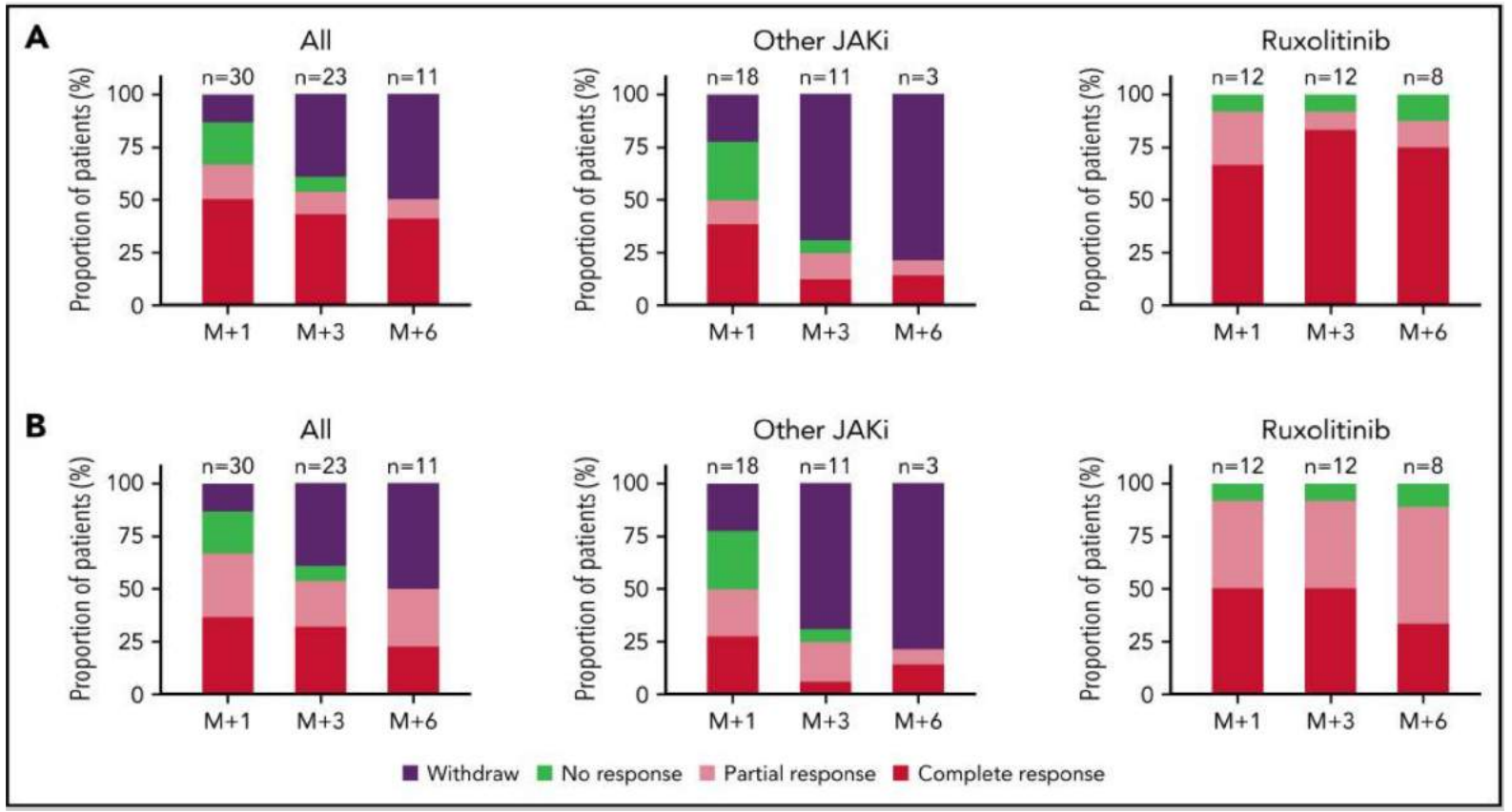
Prise en charge thérapeutique: Tocilizumab

TABLE 3 | Anti-IL-6 inhibitors used in treating VEXAS syndrome.

Target	N	Drug name	Dose	Clinical diagnosis	Clinical indication	Treatment beforeIL-6 inhibitor	Response to IL-6 inhibition	Outcomes	Ref
IL-6R	1	TCZ	10 mg/kg IV every 4 weeks*	PN, RP	Conjunctivitis, chondritis, arthralgia	GC, CY, ANA	Good	Fever resolved and GC could be reduced, but other symptoms remained.	(5)
IL-6R	1	TCZ	Unknown	SpA, IBD, MDS	Macrocytic anemia, Uveitis, chondritis, aphthous colitis, skin involvement	Various synthetic or biologics DMARDs**	Poor	Various synthetic or biologic DMARDs** including TCZ failed to prevent recurrences or to decrease the dose of GC.	(6)
IL-6R	6	TCZ	8 mg/kg IV every 4 weeks or 162 mg SC every week	3 LVV, 1 PN, 2 Unknown	4 macrocytic anemia, 1 pancytopenia, 4 lung and skin lesion, 2 chondritis	Various synthetic or biologics DMARDs**	Partial or good	3 partial responses, 1 good response, 2 unevaluated	(7)
IL-6	1	SLX	Unknown	iMCD, HLH	Normocytic anemia, thrombocytopenia, fever, chondritis, skin lesion	GC, RTX, sirolimus	Good	Fever and skin involvement resolved and less transfusion dependent.	(8)
IL-6R	4	TCZ	Unknown	3 RP, 2 MDS, 1 BD, 1 LVV, 1 PN, 1 RA, 1 Sweet's syndrome	2 macrocytic anemia, 4 skin lesion and arthralgia, 1 lung lesion, 3 chondritis	Various synthetic or biologics DMARDs**	Partial	The median time to next treatment was 8 months for TCZ.	(9)
IL-6R	1	TCZ SAR	Unknown	RP	Fever, myalgia, arthralgia, chondritis, skin lesion	Various synthetic or biologics DMARDs**	Poor	Various synthetic or biologics DMARDs** including IL-6 inhibitors failed.	(10)
IL-6R IL-6	3	2 TCZ 1 SLX	Unknown	2 Sweet's syndrome, 1 MDS, 1 DVT	3 chondritis, 2 lung and lesion, 1 vasculitis	Various synthetic or biologics DMARDs**	Poor	Various synthetic or biologics DMARDs** including IL-6 inhibitors, and IVIG failed, and aHSCT was performed and became CR.	(11)
IL-6R	5	TCZ	Unknown	Unknown	5 macrocytic anemia, 3 chondritis and arthritis, 2 vasculitis, 1 DVT	Various synthetic or biologics DMARDs**	Poor	2 transient and 3 not achieved control of symptoms, and 4 discontinued owing to lack of disease control.	(12)
IL-6R	1	TCZ	Unknown	RA, PsA, AOSD, MDS	Fever, arthritis, pancytopenia, lung and skin lesion, vasculitis	GC, MTX, ADA, ANA, CAN, TOF, IFX, CyA	Partial	Partial response of TCZ, but the steroid dependence was not broken, and various synthetic or biologics DMARDs* were used, but the effect was inadequate. Finally, TCZ and AZA combined therapy was effective.	(13)
IL-6R	1	TCZ	8 mg/kg IV every 4 weeks	RP	Chondritis, lung lesion, macrocytic anemia, thrombocytopenia	GC, MTX	Poor	After TCZ discontinuation, ANA, IFX, and ADA were tried, but all of them were discontinued due to adverse reactions or lack of effect.	(14)
IL-6R	1	TCZ	162 mg SC every week	Sweet's syndrome	Fever, lung and skin lesion,	GC, MTX, MMF	Good	Fever and lung and skin lesion resolved, and GC could be tapered.	(15)

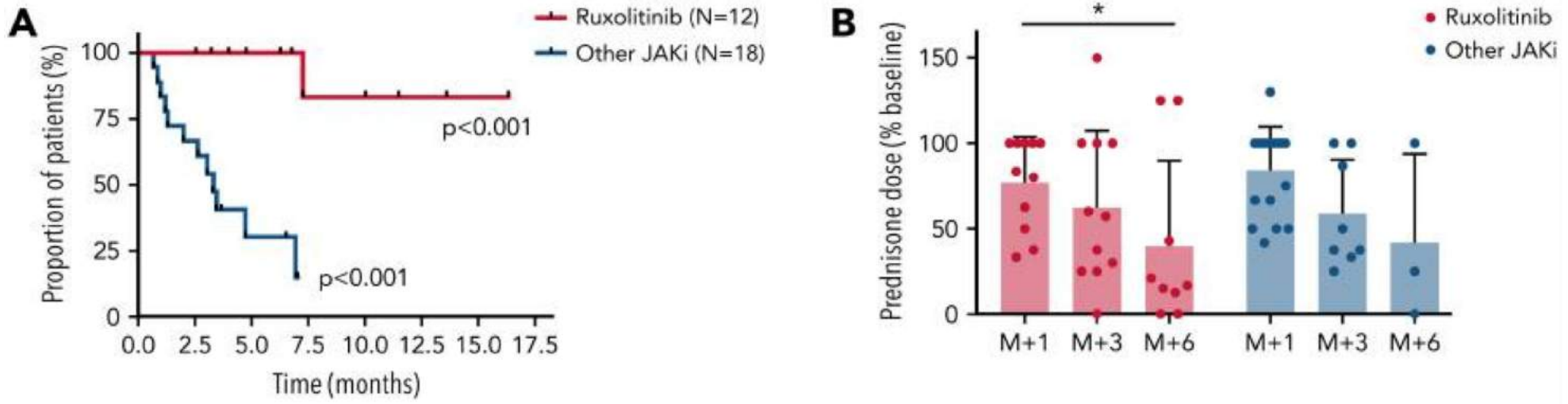
Kunishita Y, et al. Front Immunol. 2022 Jun 13;13:901063. .

Prise en charge thérapeutique: Ruxolitinib



Heiblig M et al. Blood. 2022 Aug 25;140(8):927-931.

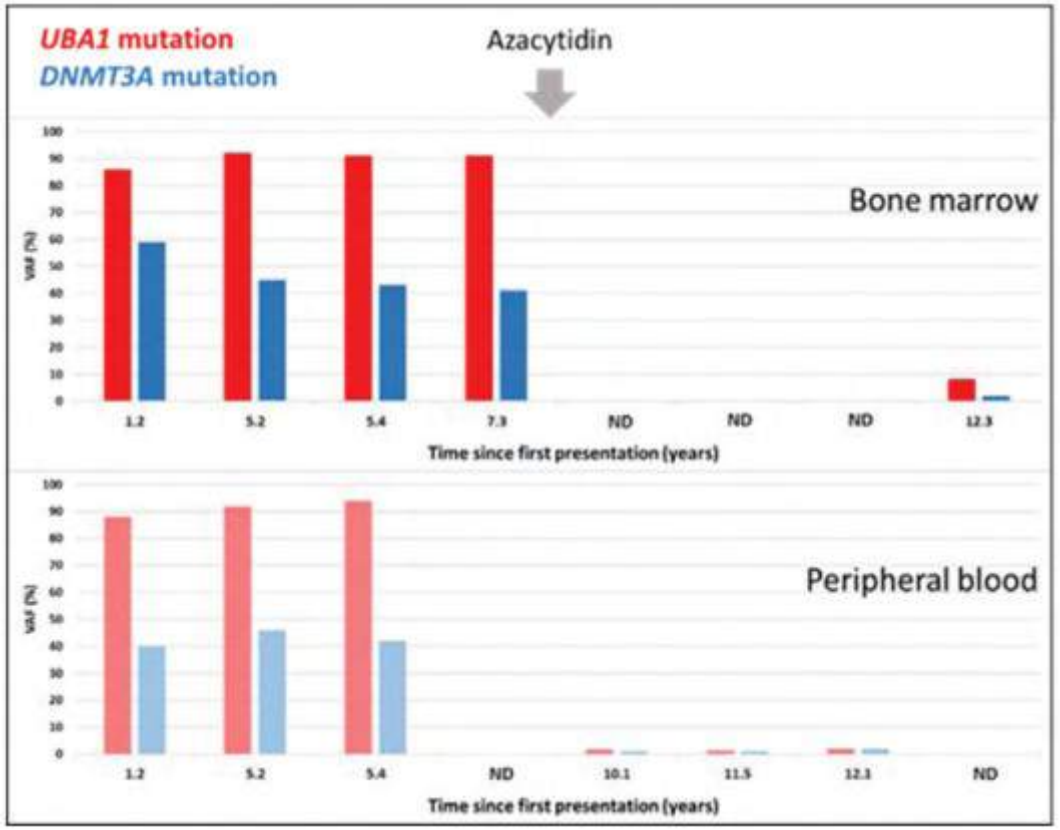
Prise en charge thérapeutique: Ruxolitinib



Heiblig M et al. Blood. 2022 Aug 25;140(8):927-931.

Prise en charge thérapeutique : Azacitidine

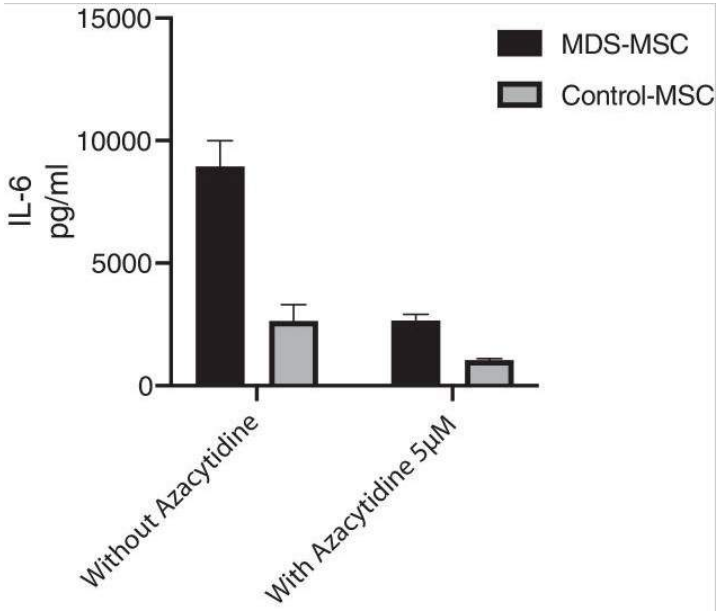
- **Eradication** clone UBA1

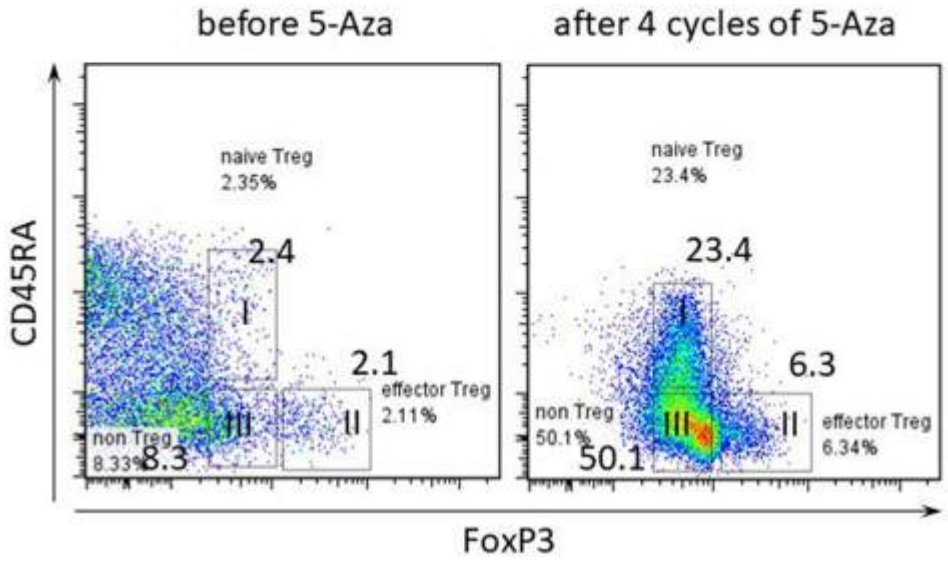


Raaijmakers MHGPet al. Hemasphere. 2021 Nov 17;5(12):e661.

Prise en charge thérapeutique : Azacitidine

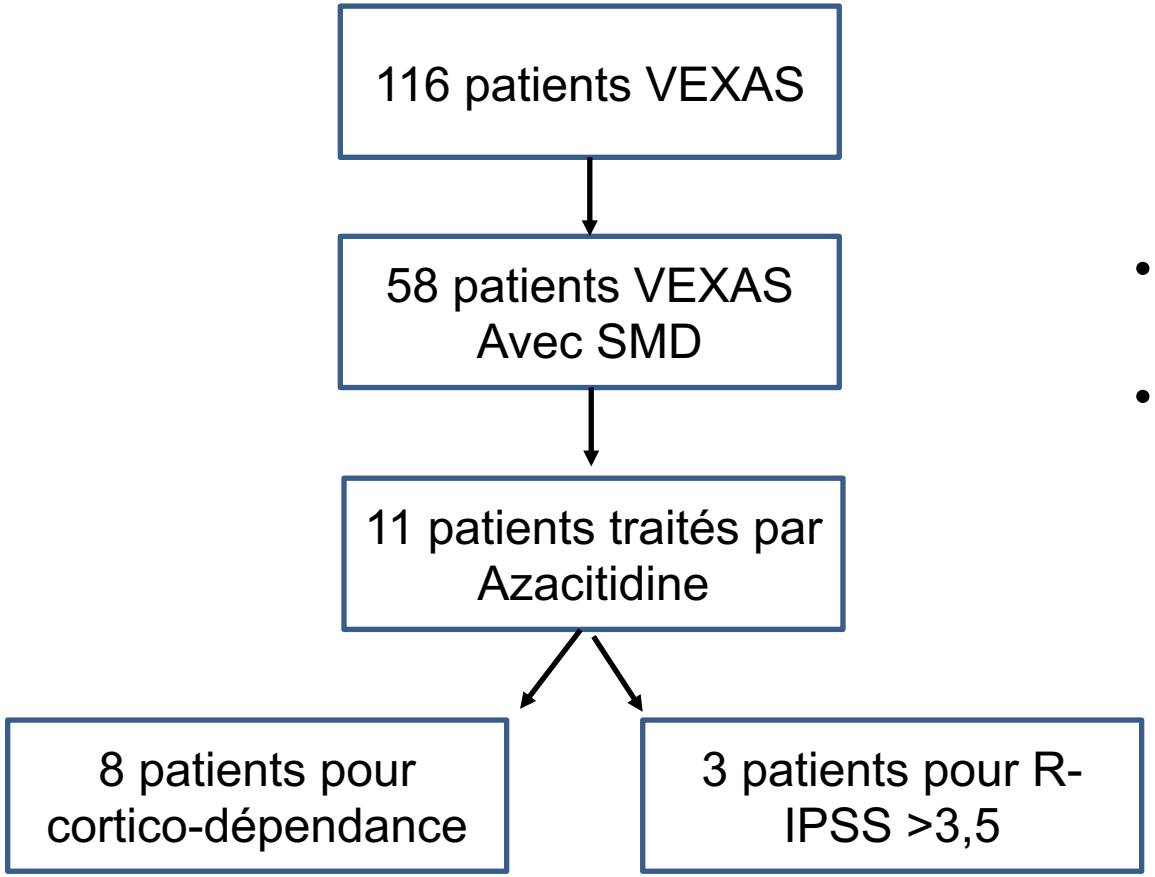
- Effet **immunomodulateur** de l'azacitidine:
  - Modulation de la sécrétion de cytokines inflammatoires
  - Expansion des lymphocytes Treg





Serizawa K et al, Front Oncol. 2018 Jun 5;8:204.
Boada M, et al. Hematol Transfus Cell Ther. 2021 Jan-Mar;43(1):35-42..

Prise en charge thérapeutique : Azacitidine



- Réponse clinique **46%** (réduction stéroïdes)
- Après 4 à 6 cycles

Comont T, et al . Br J Haematol. 2022 Feb;196(4):969-974.

Prise en charge thérapeutique : Azacitidine

- Etude prospective multicentrique

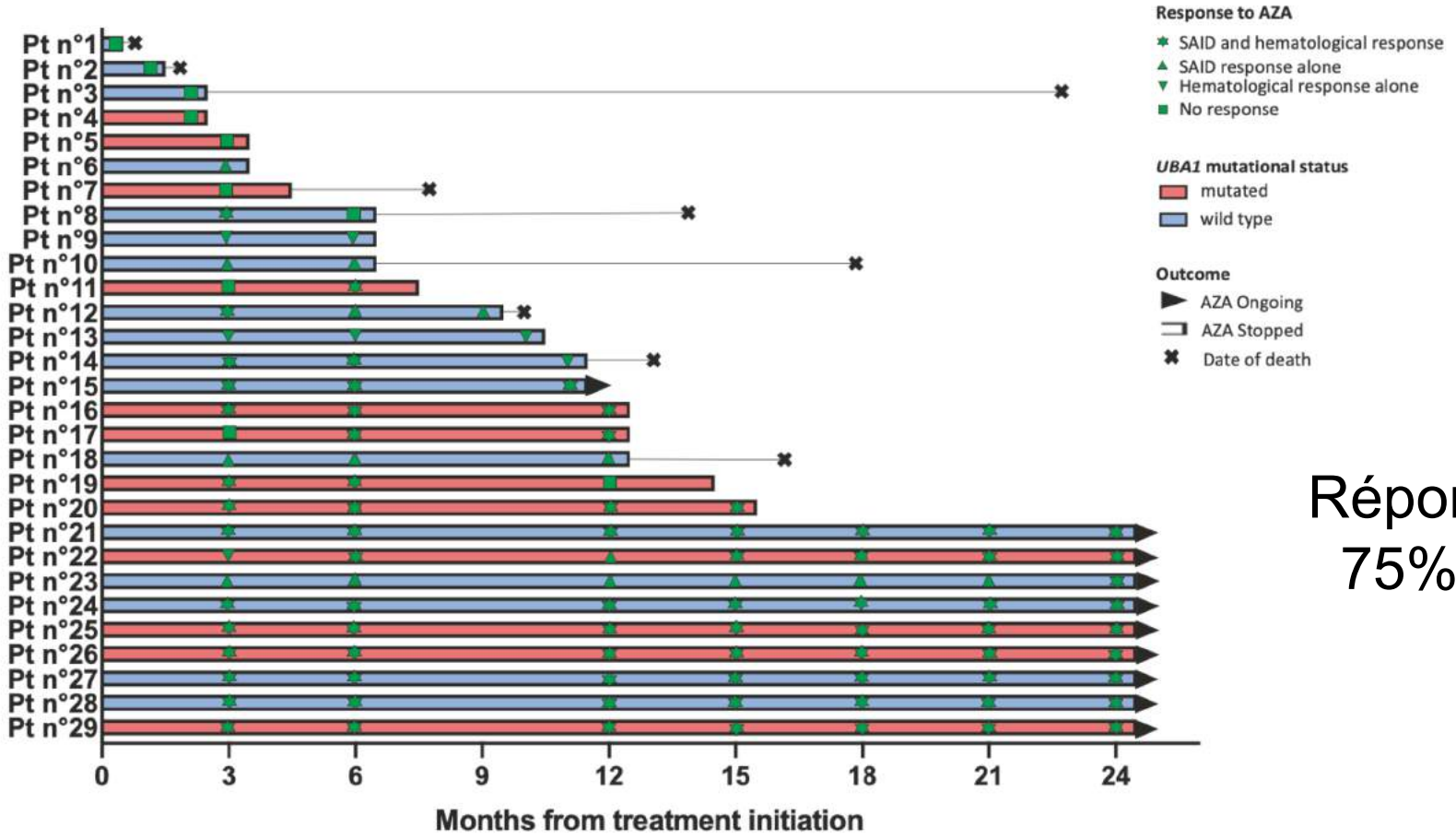
Table 1. Baseline characteristics and comparison between *UBA1*-mutated and -unmutated MDS/CMML patients.

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

Mekinian A, et al. Leukemia. 2022 Nov;36(11):2739-2742.

Prise en charge thérapeutique : Azacitidine

- Etude prospective multicentrique



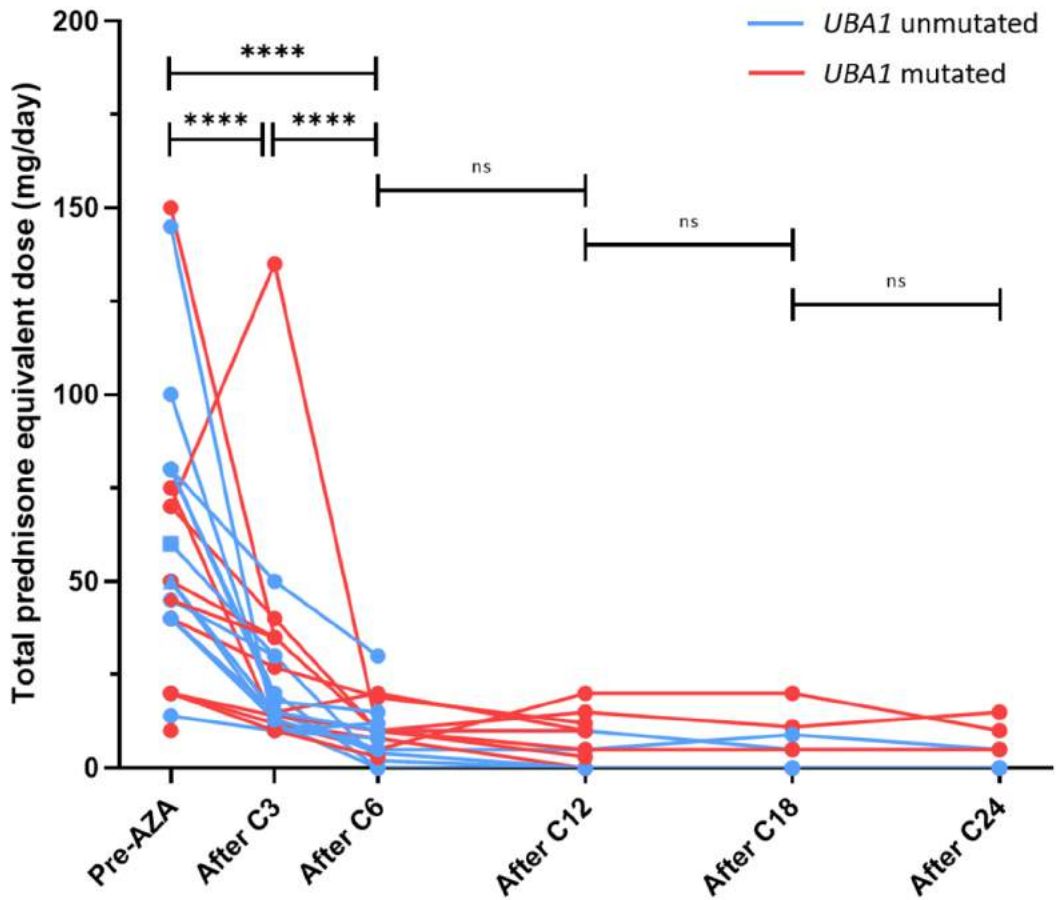
Réponse 66%
75% des patients UBA1

Mekinian A, et al. Leukemia. 2022 Nov;36(11):2739-2742.

Prise en charge thérapeutique : Azacitidine

- Etude prospective multicentrique

Supplementary Figure 2: Daily prednisone equivalent dose evolution concomitant to AZA treatment in the whole cohort. Wilcoxon paired test; ****: p<0.0001



Mekinian A, et al. Leukemia. 2022 Nov;36(11):2739-2742.

Prise en charge thérapeutique : Allogreffe

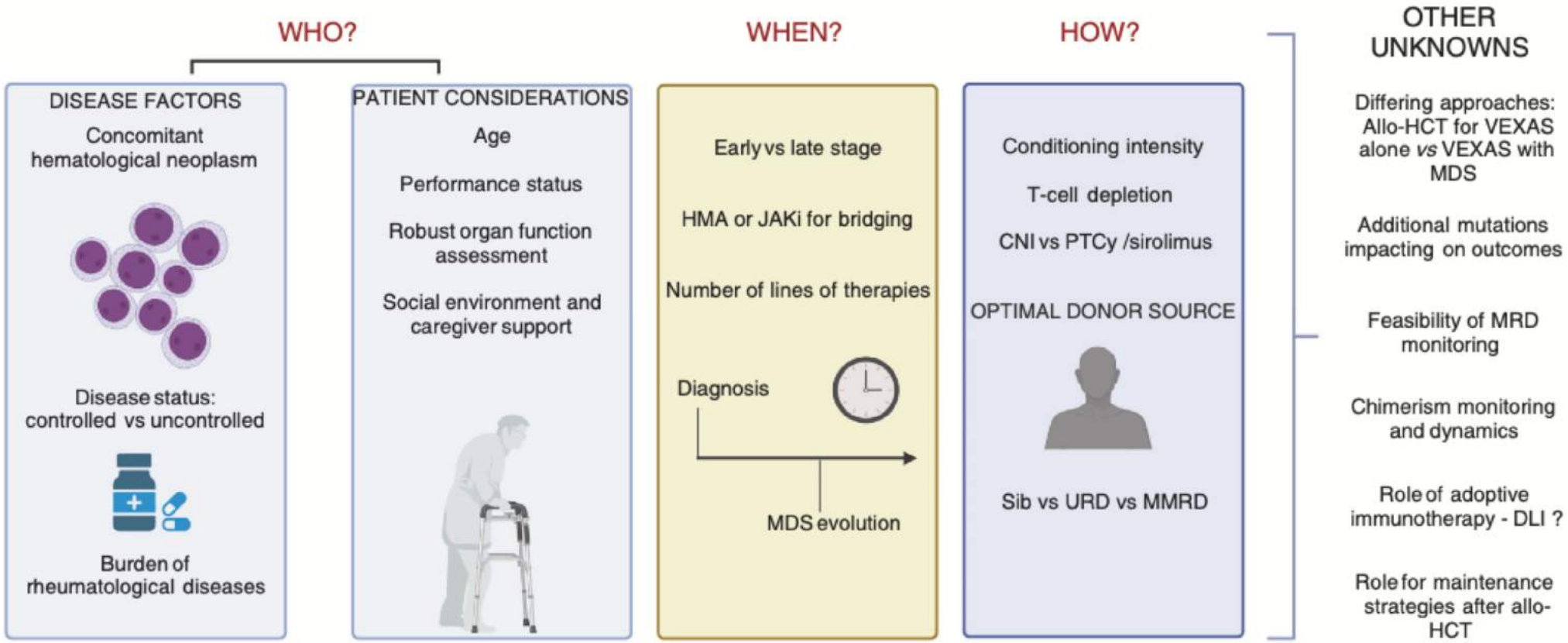
Table 1. Main characteristics of patients with VEXAS undergone HSCT so far described in the literature.

UPN	Age at onset	Concomitant Myeloid disorder	BM vacuoles	VEXAS-features	N. prior lines of therapy	Age at HSCT	Conditioning	Donor	Stem cell source	GvHD prophylaxis	Transplant Complications	Clinical response	Follow-up (months)	Alive	Ref.
1	43	MDS	Present	SS, PN	6	46	FLU, BU, ATG	MUD	PB	CSA, MMF	cGvHD	CR	32	Yes	48/ 49
2	56	MF	Present	SS	8	59	FLU, BU	MRD	BM	CSA, MTX	cGvHD	CR	67	Yes	48
3	63	MDS	Present	SS, PN, chondritis	7	65	FLU, BU	MUD	PB	CSA, MMF, CP	Bacterial infection, BK, CMV reactivation, aGvHD	CR	38	Yes	48
4	48	MDS	Present	SS, chondritis, lung infiltrates, DVT	6	50	FLU, BU, ATG	MUD	PB	CSA, MTX	Bacterial Infection	CR	3	Yes	48
5	56	MDS	NA	chondritis, lung infiltrates	5	58	FLU, BU, TT	MRD	PB	CSA, MMF, CP	Bacterial Infection, aGvHD	CR	5	Yes	48
6	50	MDS	NA	chondritis	4	55	BU, CP, ATG	MUD	PB	CSA, MTX	Bacterial and fungal infections, aGvHD	NA	4	No	48
7	60	MDS	Present	SS, chondritis, SLE	8	70	FLU, BU	MMUD	PB	CSA, MMF, CP	aGvHD	CR	4	Yes	50

MDS Myelodysplastic syndrome, *MF* Primary myelofibrosis, *SS* Sweet Syndrome, *PN* Polyarteritis nodosa, *DVT* Deep vein thrombosis, *FLU* Fludarabine, *BU* Busulfan, *ATG* Antithymocyte globulin, *TT* Thiotepa, *CP* Cyclophosphamide, *MRD* Matched related donor, *MUD* Matched unrelated donor, *MMUD* Mismatched unrelated donor, *PB* Peripheral blood, *BM* Bone marrow, *CR* Complete remission, *CSA* Cyclosporine A, *GC* Glucocorticoids, *aGVHD* Acute graft-versus-host disease, *cGvHD* Chronic graft-versus-host disease, *allo-HSCT* Allogeneic hematopoietic stem cell transplantation, *MMF* Mycophenolate mofetil, *MTX* Methotrexate, *NA* Not available.

Gurnari C et al. Bone Marrow Transplant. 2022 Nov;57(11):1642-1648.

Prise en charge thérapeutique : Allogreffe



Gurnari C et al. Bone Marrow Transplant. 2022 Nov;57(11):1642-1648.

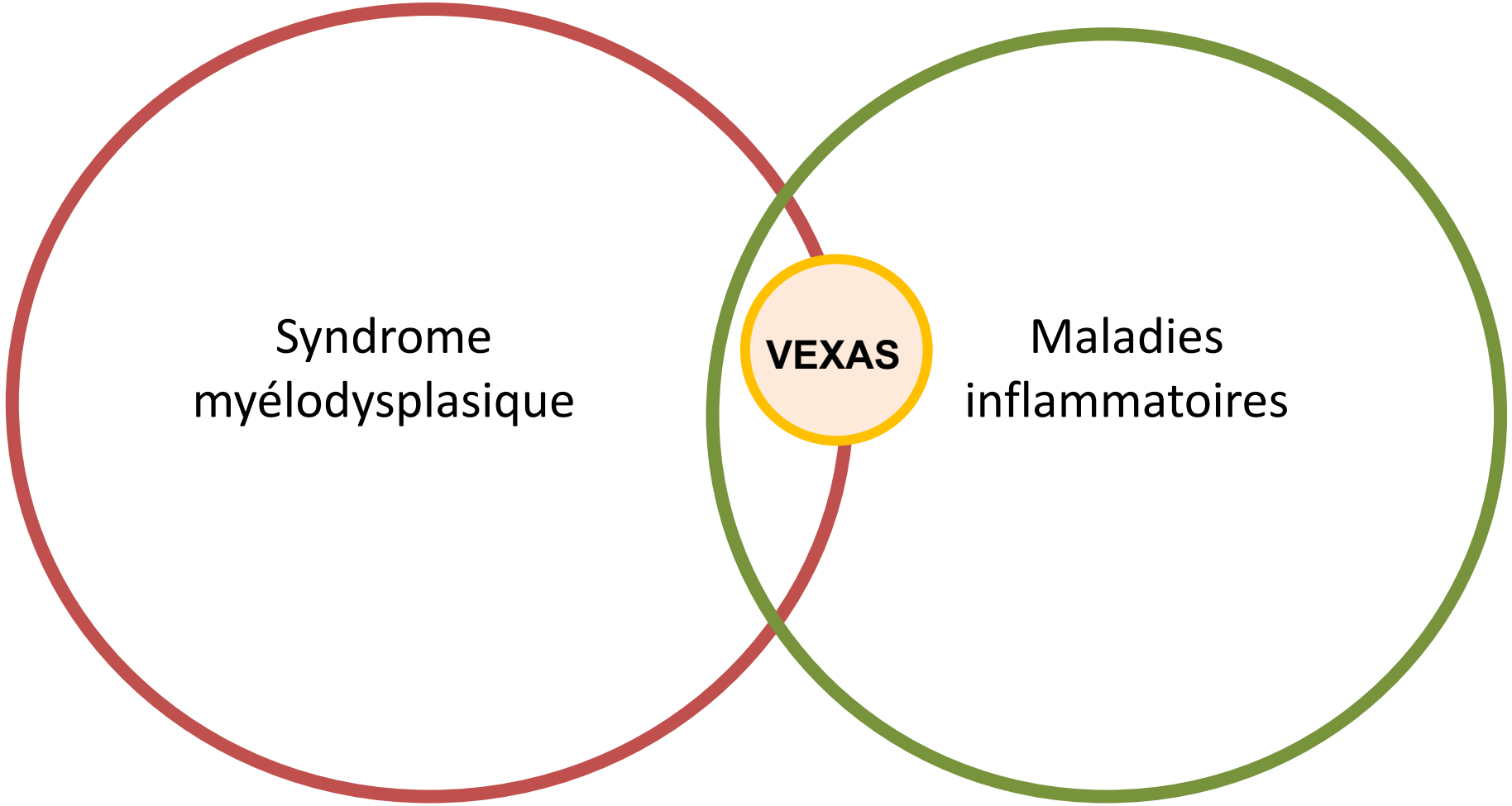
Soins de support

- Cytopénies:
  - Support transfusionnel
  - Traitement chélateur
  - EPO si SMD de faible risque

- TVP:
  - Contrôler l'inflammation
  - Prophylaxie dans les situations de haut risque

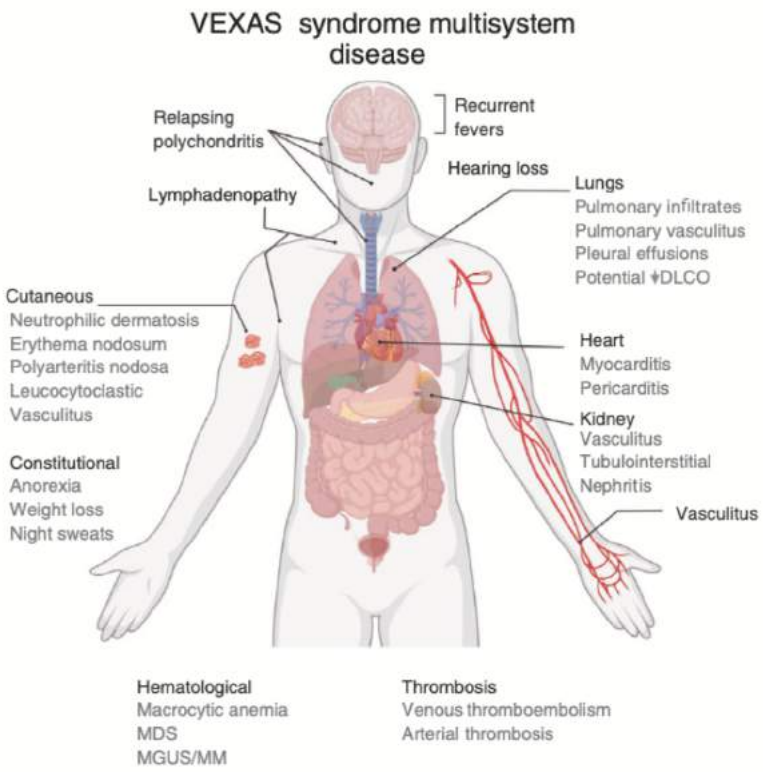
- Prophylaxies:
  - Pneumocystose et VZV recommandées
  - Prophylaxie antifongique à discuter chez les patients neutropéniques

Conclusion

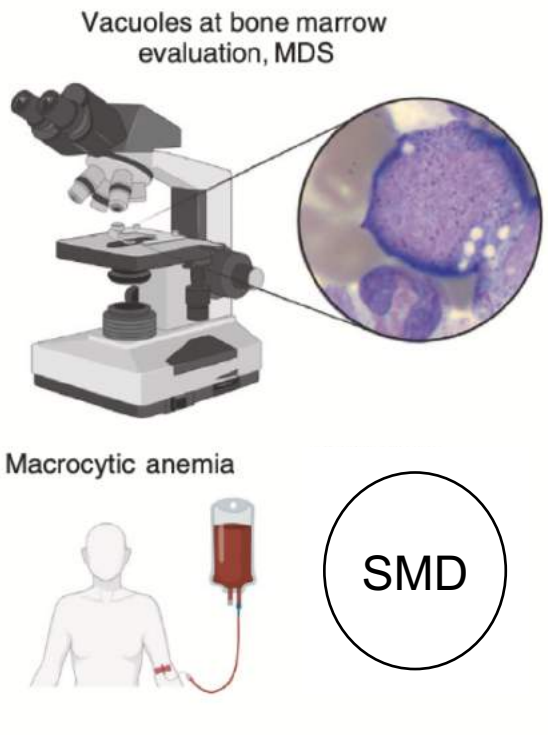

Syndrome
myélodysplasique
VEXAS
Maladies
inflammatoires

Conclusion

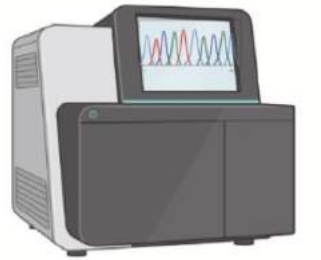
1. Systemic and organ-specific manifestations



2. Hematological features

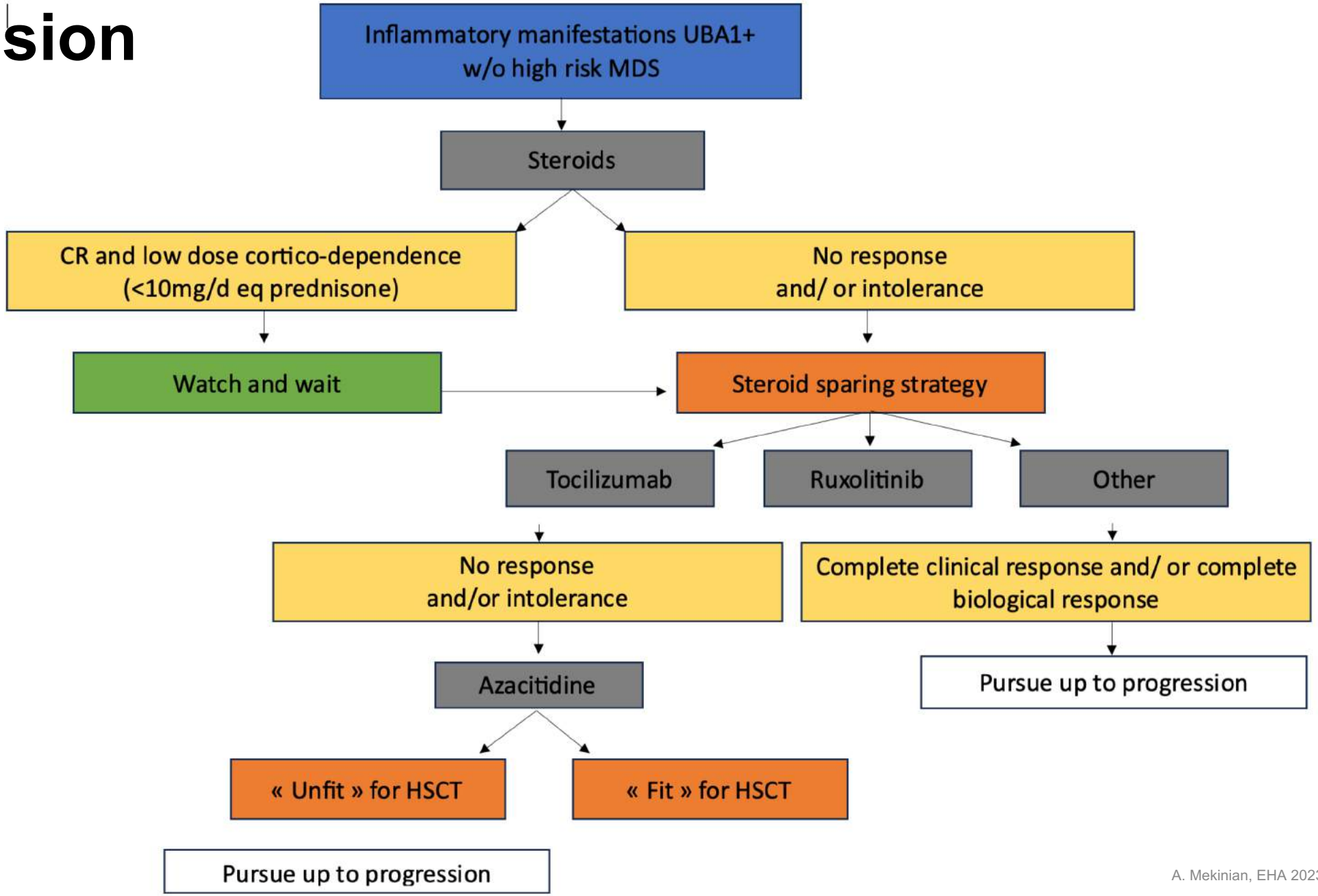


3. VEXAS?

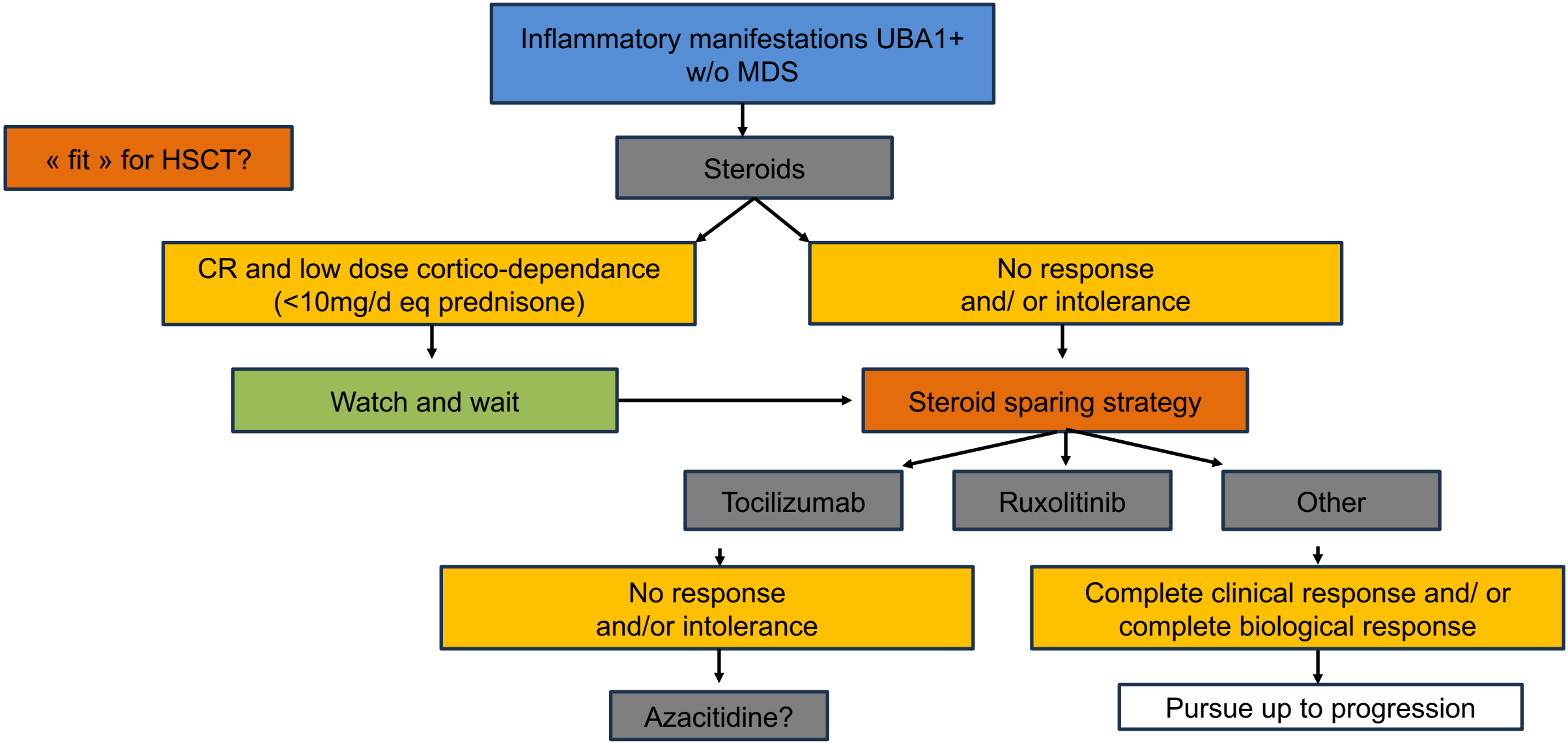


Gurnari C et al. Bone Marrow Transplant. 2022 Nov;57(11):1642-1648.

Conclusion


Inflammatory manifestations UBA1+
w/o high risk MDS
Steroids
CR and low dose cortico-dependence
(<10mg/d eq prednisone)
No response
and/ or intolerance
Watch and wait
Steroid sparing strategy
Tocilizumab
Ruxolitinib
Other
No response
and/or intolerance
Complete clinical response and/ or complete
biological response
Azacitidine
Pursue up to progression
« Unfit » for HSCT
« Fit » for HSCT
Pursue up to progression

Merci!


Inflammatory manifestations UBA1+
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Steroids
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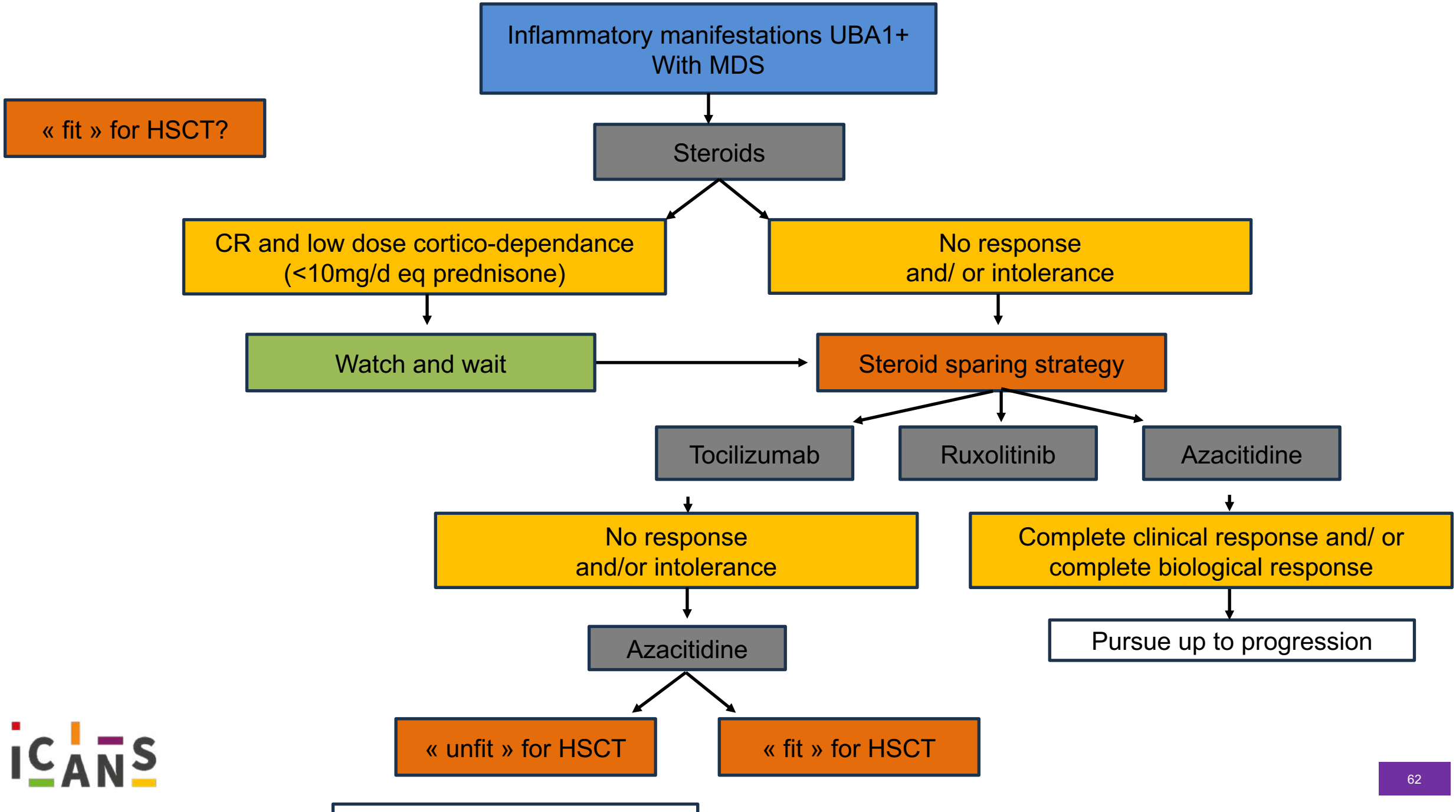
Other
No response
and/or intolerance
Complete clinical response and/ or
complete biological response
Azacitidine?
Pursue up to progression


Inflammatory manifestations UBA1+
With MDS
« fit » for HSCT?
Steroids
CR and low dose cortico-dependance
(<10mg/d eq prednisone)
No response
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Watch and wait
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Complete clinical response and/ or
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Pursue up to progression
« unfit » for HSCT
« fit » for HSCT

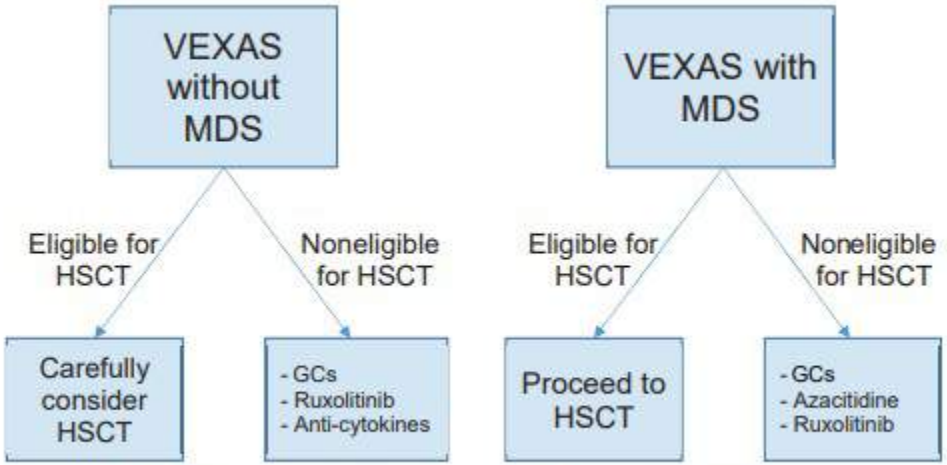

FIG 2. Treatment algorithm we propose for VEXAS according to current evidence.

Méthode d'étude en génétique

	Sanger	NGS panel	NGS WES	NGS WGS
Description	Analyse ciblée d'un gène	Panels de gènes publiés	Tous les gènes (publiés et non publiés)	Tous les gènes (publiés et non publiés) + régions non codantes
Nombre de gènes analysés	Un à quelques	Variable	Tous (sauf certaines régions mal/non séquencées)	Tous
Rapidité d'obtention des résultats	+++	++	-	-
Détection mosaïcisme	+/- (jusqu'à 15%)	+++ (jusqu'à 1%)	+/- (selon profondeur)	+/- (selon profondeur)

Comment rechercher ces mutations ?

Rationnel : ce sont des mutations somatiques hémizygotes

- Sanger = 1ère intention
  - Rentable si le % de mosaïcisme est élevé
  - Rapide, peu coûteux
- NGS panel = 2ème intention
  - Le plus sensible
- NGS Whole exome / NGS Whole genome
  - Sensibilité variable (en général idem Sanger)
  - Long, coûteux