CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, Best Western Hotel Madison

29 maggio 2026

Casi clinici - Sindrome Vexas

Chiara Cattaneo

ASST Spedali Civili di Brescia

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Jazz							Travel Grant

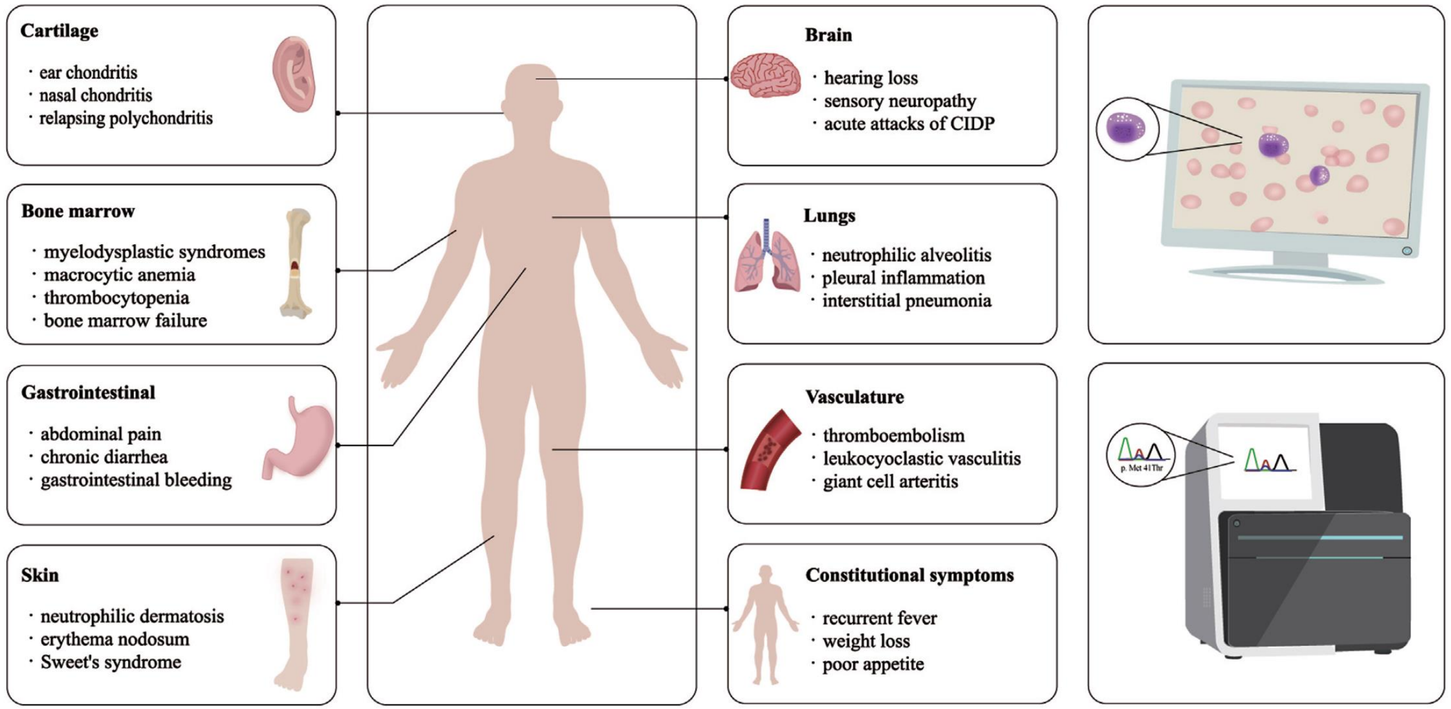
C.F., M, 01/06/1959

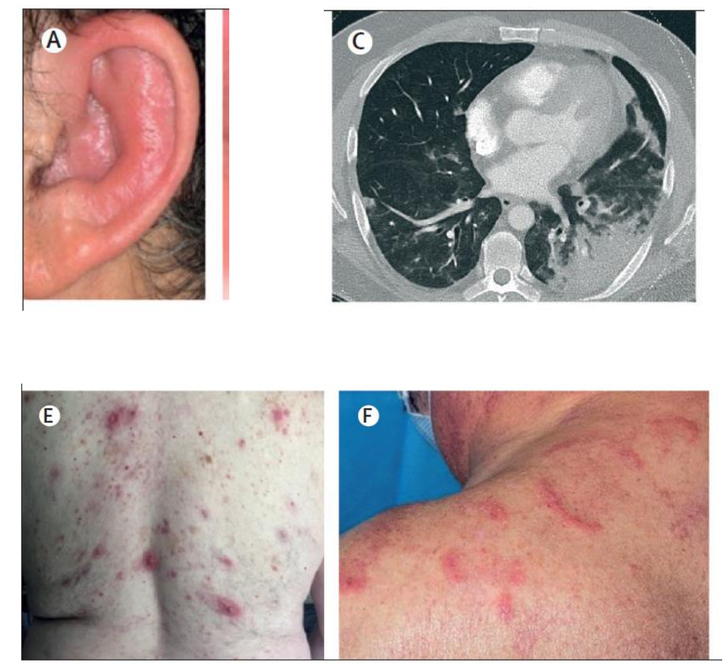
- Da **luglio 2017**: **febbricola ricorrente**, tosse stizzosa, **infiltrati polmonari**, **lesioni cutanee** → ricoveri in Presidi periferici
  - Biopsia cutanea → infiltrato linfocitario T perivascolare
  - Biopsia transbronchiale → minimo, focale infiltrato infiammatorio, modico ispessimento dell'interstizio (polmonite in fase di organizzazione)
  - BOM → «nella norma»

- Giugno 2018 → Ricovero in Medicina Spedali Civili per febbre, dolori ariticolari e piramide nasale → diagnosi di **POLICONDRITE RICORRENTE ASSOCIATA AD AORTITE** (captazioni PET) → follow-up Immunologia

- Hb **10.3** g/dl, MCV **100 fl**, WBC **4.77** x 10^9/l (N 44%), PLT **220** x 10^9/l

Vexas – manifestazioni cliniche





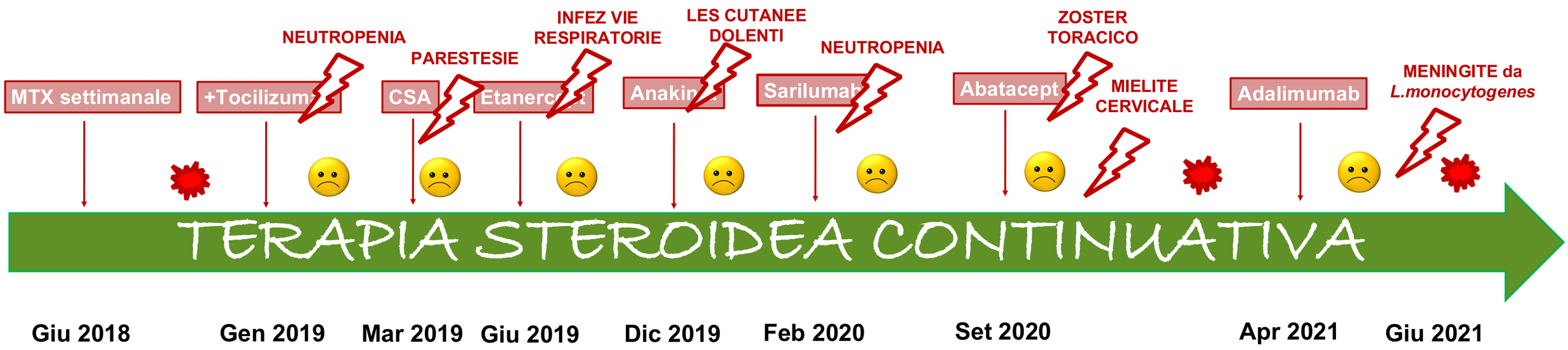
Zhang Glob Med Genet 2023
Groarke Lancet 2026

C.F., M, 01/06/1959

- Ottobre 2019 valutazione ematologica per **a. macrocitica lieve**
  - → mieloaspirato: cellularità aumentata, **non atipie morfologiche**
  - → citogenetica 46, XY
  - → NGS: **DNMT3A**
  - → BOM segnalate note di diseritropoiesi e dismielopoiesi

- *«Prosegue la gestione terapeutica dei colleghi Immunologi ferma restando la nostra collaborazione per il trattamento di citopenie significative»*

C.F. – flowchart terapia



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

28.06.21: diagnosi sdr VEXAS

"We named this disorder the VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome"

Richiesta: **06284707** Del: **28/06/2021** Ore: 08:10

Esame	Risultato	Unità di misura
Campione biologico: Sangue + anticoagulante		
Mutazione somatica UBA1	**Presente**	
Descrizione mutazione (trascritto di riferimento NM_003334):		
c.122T>C, p.(Met41Thr)		

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

Characteristic	Participants (N=25)
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)

C.F., M, 01/06/1959

- Novembre 2021 → rivaluato dagli Immunologi → prosegue steroide con cauto tentativo di riduzione
- 14/3/22 **TVP poplitea dx**

Venous and arterial thrombosis in patients with VEXAS syndrome

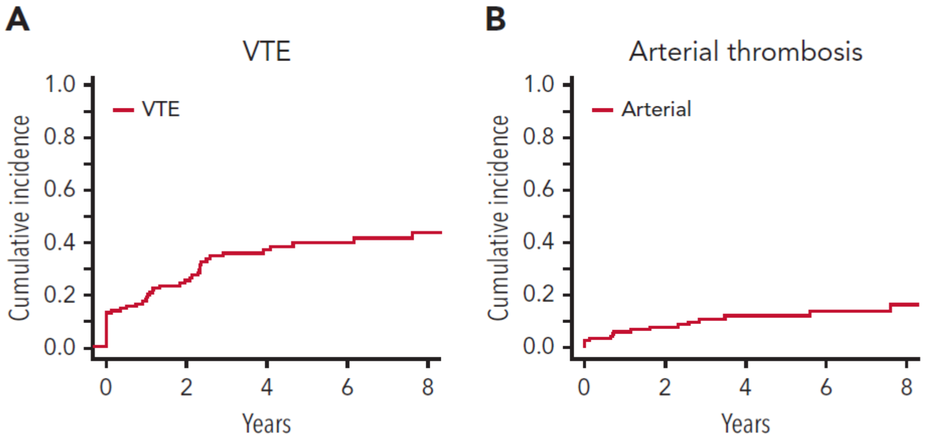
blood® 23 MAY 2024 | VOLUME 143, NUMBER 21

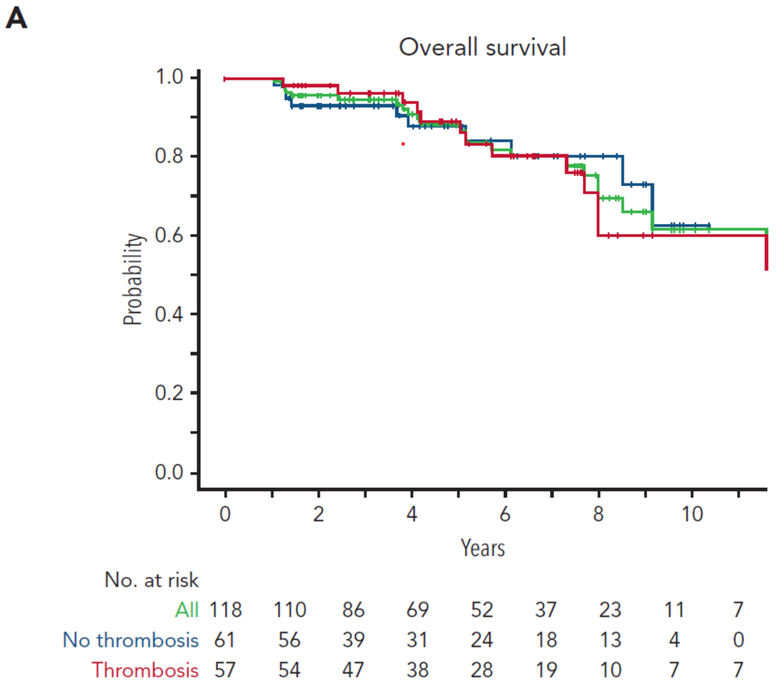
Yael Kusne,[1] Atefeh Ghorbanzadeh,[2] Alina Dulau-Florea,[3] Ruba Shalhoub,[4] Pedro E. Alcedo,[5] Khanh Nghiem,[3] Marcela A. Ferrada,[6] Alexander Hines,[7] Kaitlin A. Quinn,[6] Sumith R. Panicker,[8] Amanda K. Ombrello,[9] Kaaren Reichard,[10] Ivana Darden,[5] Wendy Goodspeed,[6] Jibran Durrani,[5] Lorena Wilson,[9] Horatiu Olteanu,[10] Terra Lasho,[11] Daniel L. Kastner,[9] Kenneth J. Warrington,[12] Abhishek Mangaonkar,[11] Ronald S. Go,[10] Raul C. Braylan,[3] David B. Beck,[8,13] Mrinal M. Patnaik,[11] Neal S. Young,[5] Katherine R. Calvo,[3] Ana I. Casanegra,[2] Peter C. Grayson,[6] Matthew J. Koster,[12] Colin O. Wu,[4] Yogendra Kanthi,[8] Bhavisha A. Patel,[5] Damon E. Houghton,[2,*] and Emma M. Groarke[5,*]

- **Retrospective multicenter study**
- **119 VEXAS patients**
- **Almost two-thirds of VTEs unprovoked**
- **41% recurrent**
- **20% occurring despite anticoagulation**

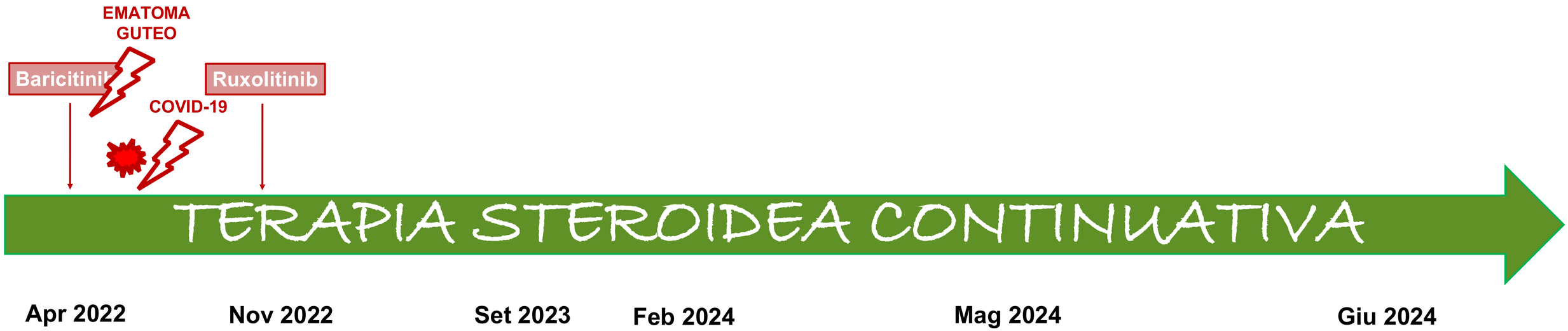
KEY POINTS

- **VTE is common in VEXAS syndrome, occurring in over 40% of patients with frequent recurrences; however, it is not associated with increased mortality.**
- **Given the high risk of VTE, patients with VEXAS syndrome should receive thromboprophylaxis in high-risk settings unless contraindicated.**





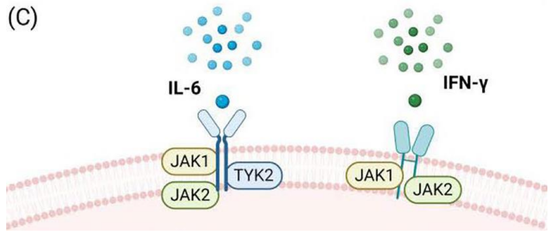
C.F. – flowchart terapia



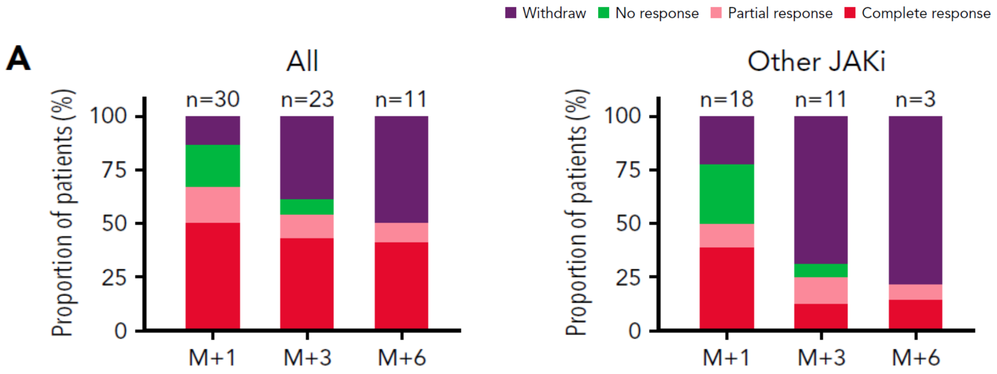
blood® 25 AUGUST 2022 | VOLUME 140, NUMBER 8

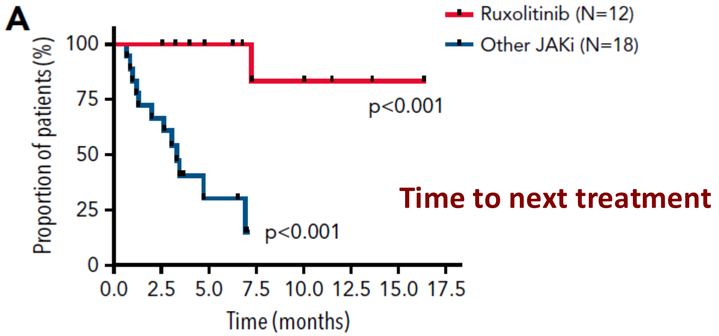
Ruxolitinib is more effective than other JAK inhibitors to treat VEXAS syndrome: a retrospective multicenter study

Maël Heiblig,[1] Marcela A. Ferrada,[2,*] Matthew T. Koster,[3,*] Thomas Barba,[4,*] Mathieu Gerfaud-Valentin,[5] Arsène Mékinian,[6] Henrique Coelho,[7] Gaelle Fossard,[1] Fiorenza Barraco,[1] Lionel Galicier,[8] Boris Bienvenu,[8] Pierre Hirsch,[9] Guillaume Vial,[10] Anne Blandine Boutin,[11] Joris Galland,[12] Guillaume Le Guenno,[13] Adrien Bigot,[14] Kenneth J. Warrington,[3] Tanaz A. Kermani,[15] Peter C. Grayson,[2] Bhavisha A. Patel,[16] David B. Beck,[17,18] Yvan Jamilloux,[5,†] Pierre Fenaux,[19,†] and Pierre Sujobert[20]



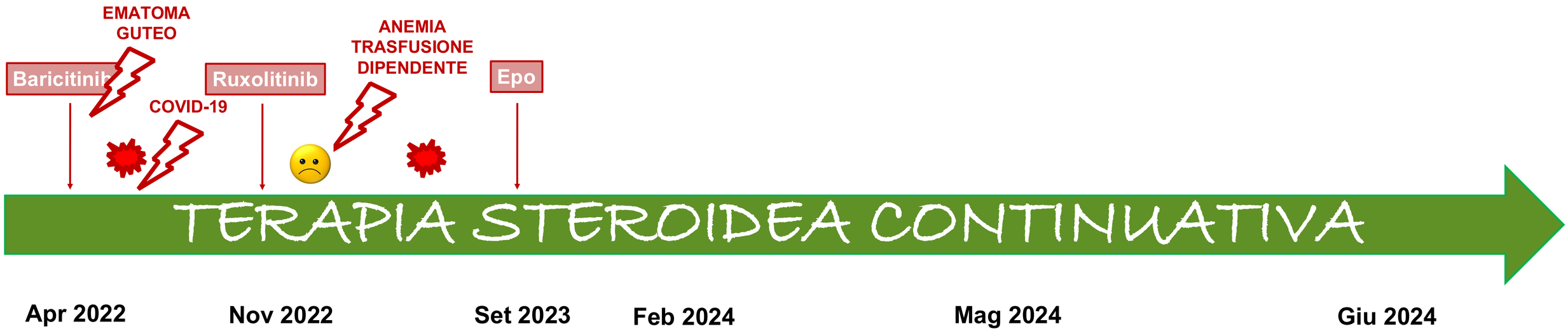
- **Multicenter international retrospective analysis of VEXAS patients treated with different JAKi**
- **30 patients with genetically proven VEXAS syndrome**





Time to next treatment

C.F. – flowchart terapia



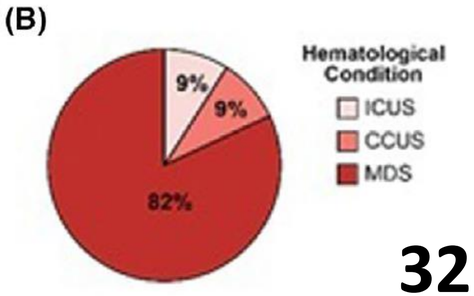
RESEARCH LETTER

BJHaem BRITISH JOURNAL OF HAEMATOLOGY

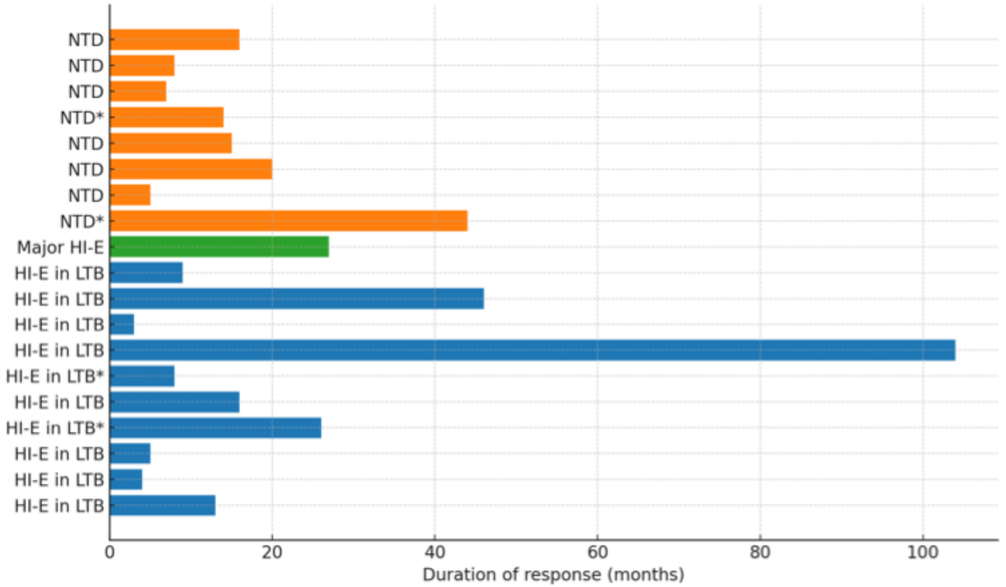
Br J Haematol. 2025;207:273–277.

DIRAL ET AL.

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



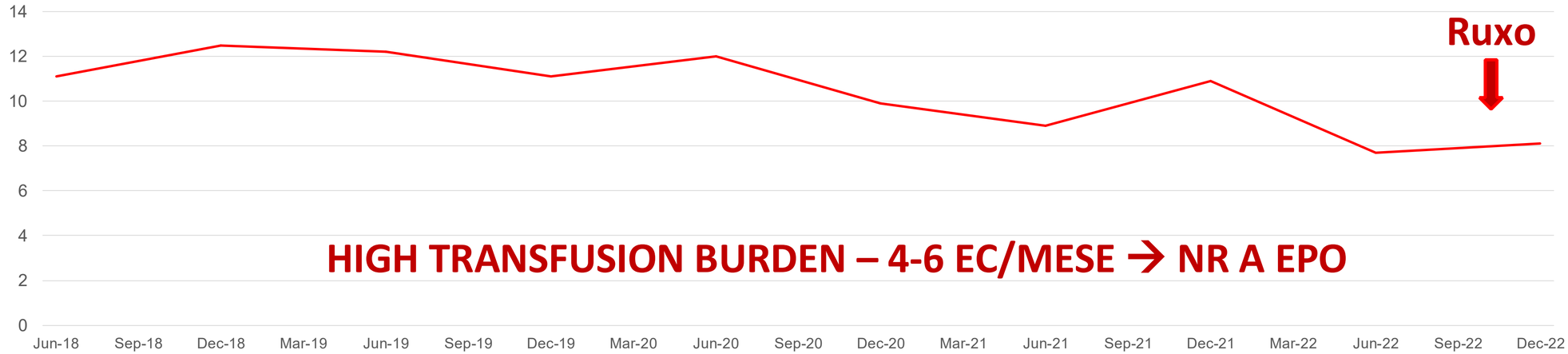
32 pts



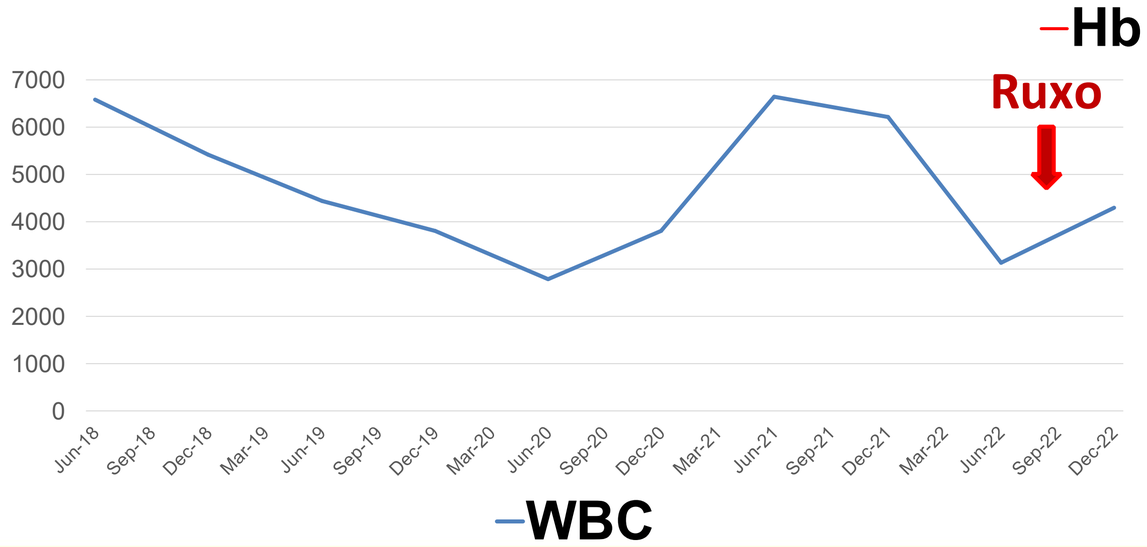
* = patient dead during follow-up

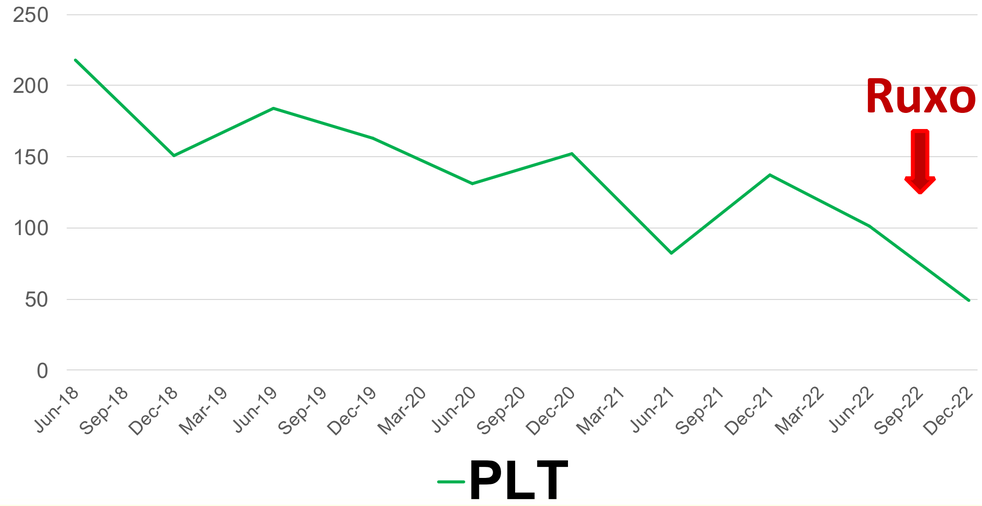
- HI-E in 19 patients (**59%**)→**transfusion independence**
- Responding patients **mostly LTB** (58%) or **non-transfusion dependent** (NTD, 37%)
- **Median duration of response** to ESAs **13 months**
- **Endogenous EPO** associated with the probability of **response to ESAs**

C.F. - variazioni dell'emocromo nel tempo



HIGH TRANSFUSION BURDEN – 4-6 EC/MESE → NR A EPO



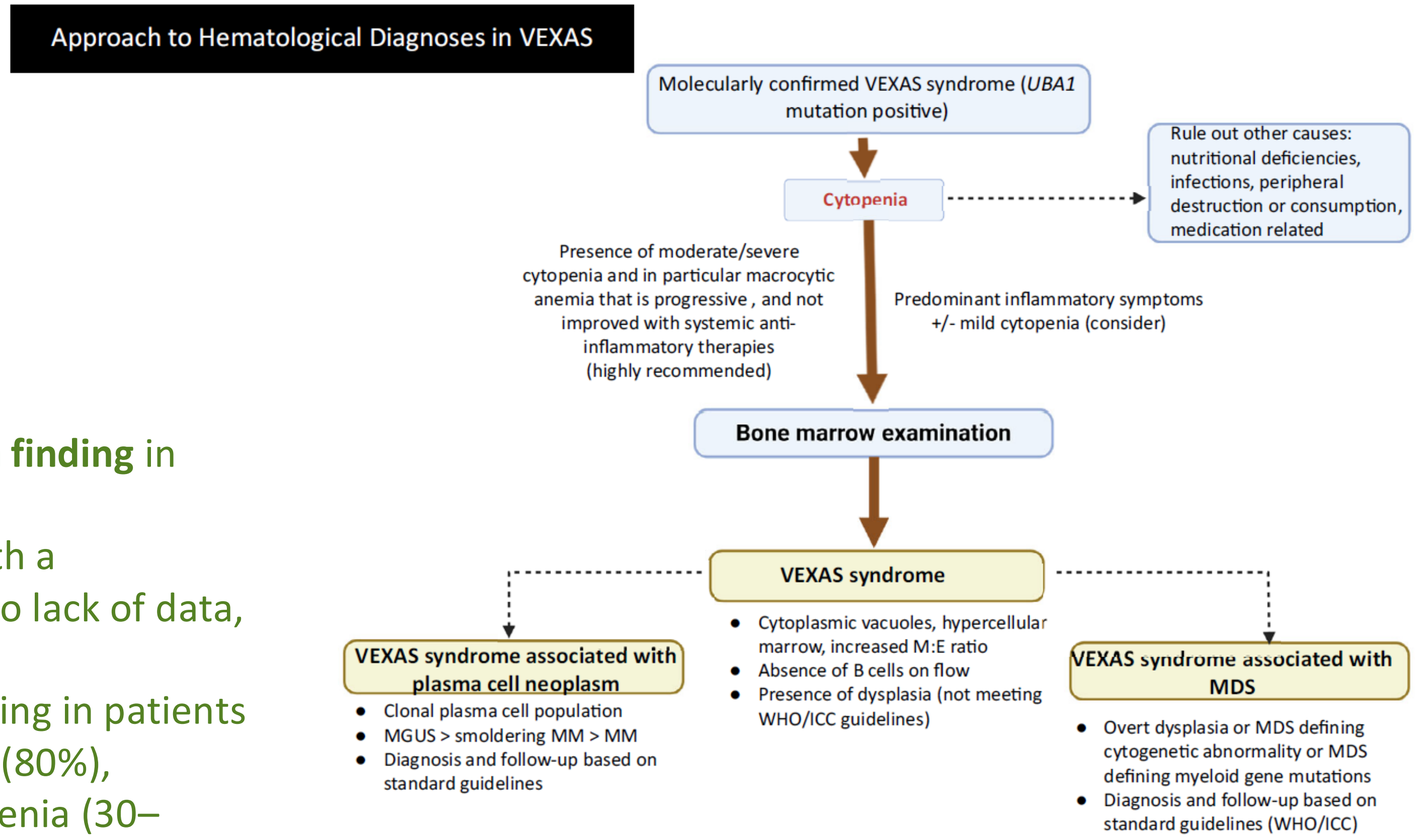


Arthritis & Rheumatology
Vol. 78, No. 3, March 2026, pp 509–522

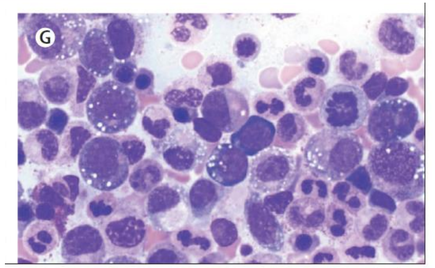
American College of Rheumatology Guidance Statement for Diagnosis and Management of VEXAS Developed by the International VEXAS Working Group Expert Panel

Arsene Mekinian,[1] Sophie Georgin-Lavialle,[2] Marcela A. Ferrada,[3] Sinisa Savic,[4,5] Matthew J. Koster,[6] Olivier Kosmider,[7,8] Thibault Comont,[9] Mael Heiblig,[10] Juan I. Arostegui,[11,12,13] Annmarie Bosco,[14,15,16] Rim Bourguiba,[17,18] Katherine R. Calvo,[19] Catherine Cargo,[20] Chiara Cattaneo,[21] François Chasset,[22] Henrique Coelho,[23] Corrado Campochiaro,[24] Francesca Crisafulli,[21] Stephanie Ducharme-Benard,[25] Raquel Faria,[26,27,28] Franco Franceschini,[29] Micol Frassi,[29] Emma M. Groarke,[30] Carmelo Gurnari,[31,32] Yervand Hakobyan,[33] Yvan Jamilloux,[34] Ciprian Jurcut,[35] Yohei Kirino,[36] Austin Kulasekararaj,[37] Hiroyoshi Kunimoto,[36] Lauren M. Madigan,[38] Heřman F. Mann,[39] Chiara Marvisi,[40,41] Marcin Milchert,[42] Sara Morais,[43] Katja Sockel,[44,45] Francesco Muratore,[41,46] Hideaki Nakajima,[36] Mrinal M. Patnaik,[47] Luísa Regadas,[48] Marie Robin,[49] Abraham Rutgers,[50] Carlo Salvarani,[41,46] Anthony M. Sammel,[16,51] Joerg Seebach,[52] Pierre Sujobert,[53] Alessandro Tomelleri,[24] Geoffrey Urbanski,[54,55] Frédéric Vandergheynst,[56] Romana Vieira,[57] David S. Viswanatha,[58] Ewa Więsik-Szewczyk,[59] Elisa Diral,[60] Benjamin Terrier,[61] Bhavisha A. Patel,[30] Pierre Fenaux,[62] Peter C. Grayson,[63] and David B. Beck,[64,65] on behalf of the International VEXAS working group, and with endorsement of EuroBloodNet, the European Reference Network in Rare Hematological Diseases

- **Cytopenia**, particularly macrocytic anemia, is a **common finding** in VEXAS, **even in the absence of associated MDS**
- **The need for bone marrow examination** in a patient with a molecularly confirmed VEXAS diagnosis is **debated** due to lack of data, especially **in patients without cytopenia**
- **Macrocytosis** is the most common peripheral blood finding in patients with VEXAS, followed by anemia, absolute lymphopenia (80%), moderate thrombocytopenia (30–50%), and monocytopenia (30–50%), whereas **neutrophils are often within normal values**
- We recommend a **baseline bone marrow examination in all patients with cytopenic VEXAS**, **especially before initiating disease-modifying treatments**



Rivalutazioni midollari



Agosto 2021

MIDOLLO Aspirato ☑ Apposizione ☐

Cellularita:	nei limiti
Rapporto L/E:	2/1
Serie Eritropoietica:	maturante
Serie Granulopoietica:	in evoluzione maturativa; presenza di vacuoli nei granulociti neutrofili
Serie Piastrinopoietica:	megacariociti presenti
Linfociti:	6%
Plasmacellule:	
Note:	blasti 2%

Conclusioni:	non chiari elementi a favore di sdr mielodisplastica

Sistema Sanitario Regione Lombardia

Il Medico Esaminatore: cattaneo

Giugno 2023

MIDOLLO Aspirato ☑ Apposizione ☐

Cellularita:	nei limiti
Rapporto L/E:	10/1
Serie Eritropoietica:	molto ridotta
Serie Granulopoietica:	maturante; presente vacuolizzazione
Serie Piastrinopoietica:	megacariociti presenti, spesso microcitici
Linfociti:	4%
Plasmacellule:	
Note:	blasti 2%

Conclusioni:	Marcata ipoplasia della serie eritroide

Sistema Sanitario Regione Lombardia

Il Medico Esaminatore: cattaneo

Febbraio 2024

MIDOLLO Aspirato ☑ Apposizione ☐

Cellularita:	nei limiti
Rapporto L/E:	10/1
Serie Eritropoietica:	marcatamente ipoplasica
Serie Granulopoietica:	maturante, con vacuoli
Serie Piastrinopoietica:	megacariociti molto ridotti
Linfociti:	5%
Plasmacellule:	
Note:	

Conclusioni:	vedi referto, marcata ipoplasia eritroide

Sistema Sanitario Regione Lombardia

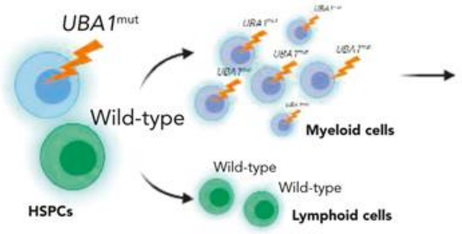
Il Medico Esaminatore: cattaneo

Cariotipo: 46, XY

Non dimostrata displasia → non diagnosi MDS

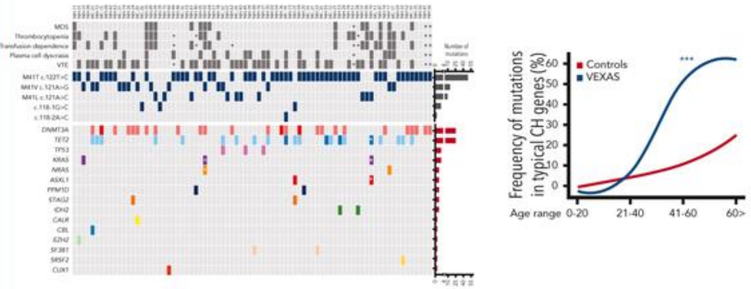
Spectrum of clonal hematopoiesis in VEXAS syndrome

Background: VEXAS is caused by somatic mutations in the *UBA1* gene (*UBA1*^{mut}) and is characterized by heterogeneous systemic auto-inflammation and hematologic manifestations, which may meet criteria for myelodysplastic syndrome or plasma cell dyscrasias.

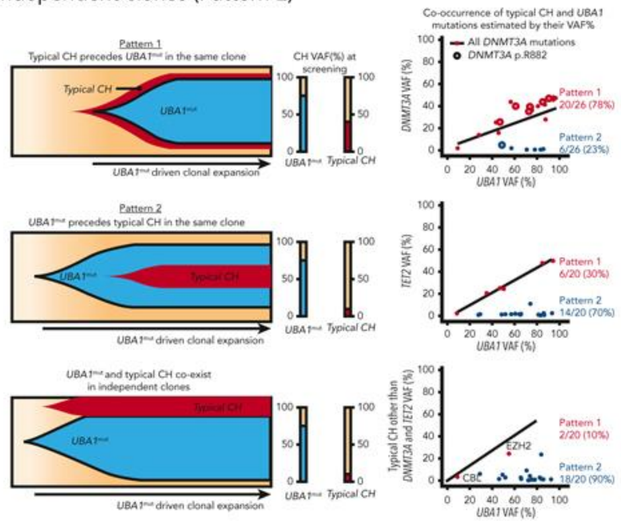


Main characteristics
Systemic inflammation
Venous thromboembolism
Macrocytic anemia
Thrombocytopenia
Myelodysplastic syndrome
Plasma cell dyscrasia

Clonal landscape: VEXAS patients (n = 80) have an enrichment of typical CH mutations concomitant with *UBA1*^{mut}, particularly in *DNMT3A* and *TET2*



Clonal patterns: Based on integrated bulk and scDNA analyses, clonality in VEXAS followed two major patterns: with either typical CH preceding *UBA1*^{mut} selection in a clone (Pattern 1), or occurring as an *UBA1*^{mut} subclone or in independent clones (Pattern 2)



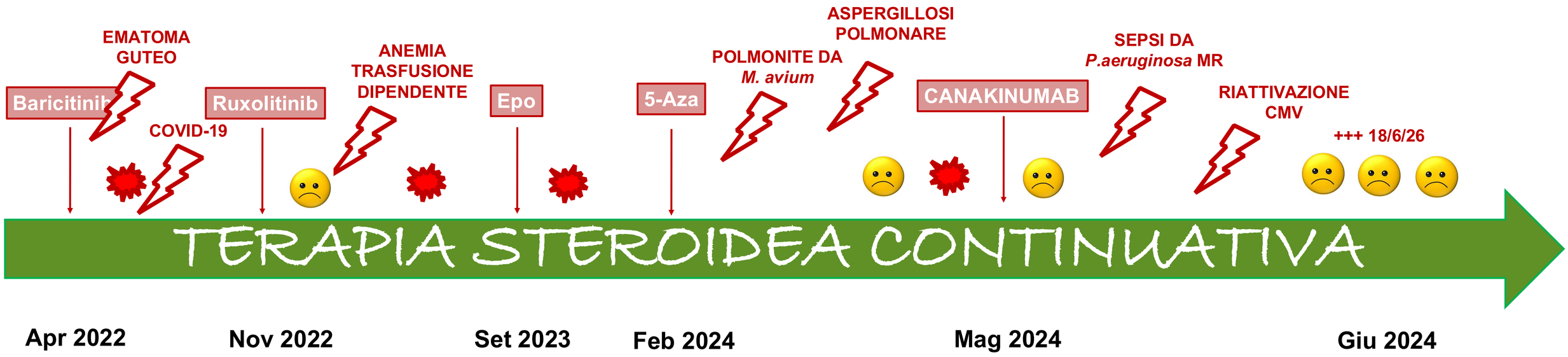
Predictors of MDS: Transfusion-dependent anemia and thrombocytopenia (<100K/µL) but **not typical CH mutations**

Prognostic factors: Transfusion-dependent anemia, thrombocytopenia (<100K/µL), and **typical CH mutations**

UBA^{mut} cells are the main cause of systemic inflammation and bone marrow failure
VEXAS-associated MDS is distinct from classical MDS in its presentation and clinical course

Gutierrez-Rodrigues Blood 2022

C.F. – flowchart terapia



blood® 18 SEPTEMBER 2025 | VOLUME 146, NUMBER 12

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

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

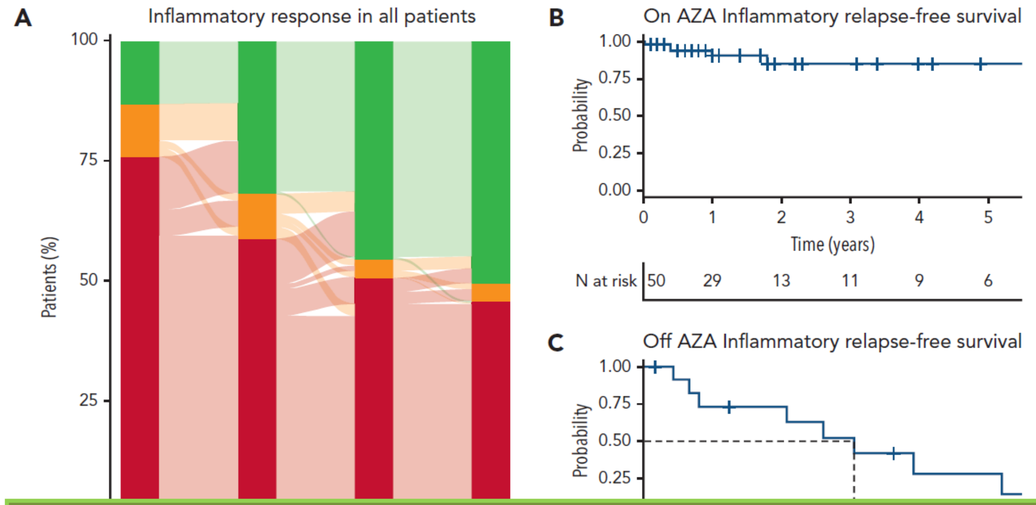
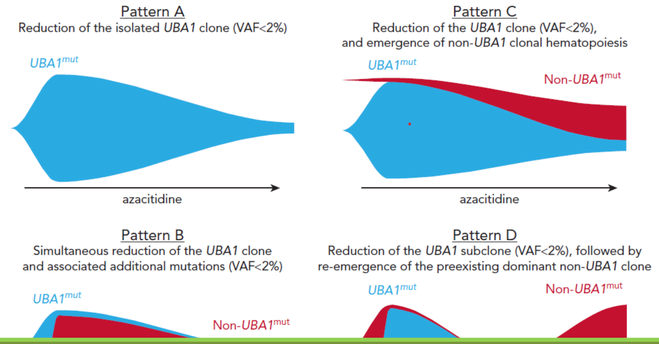


Table 1. Baseline characteristics of patients with VEXAS syndrome treated with AZA

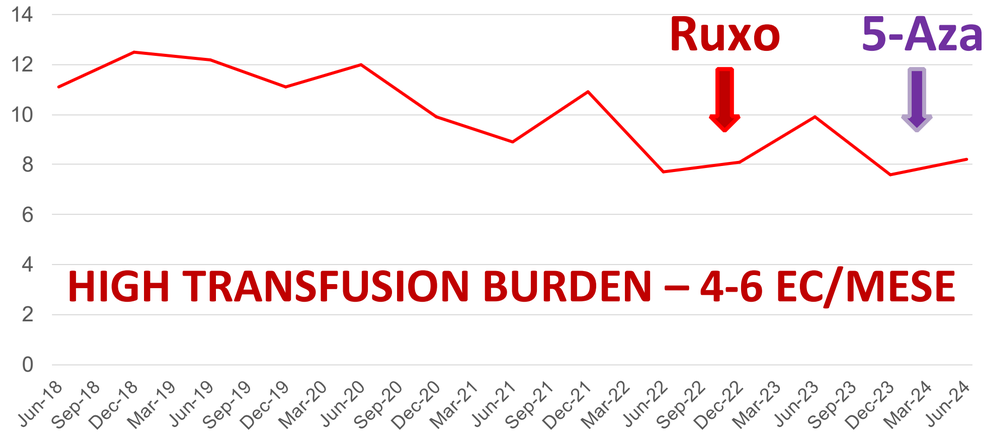
Characteristic	Overall (N = 88)	MDS (n = 70)	Non-MDS (n = 18)
Male sex	87 (99)	69 (99)	(100)
Bone marrow features			
Dysplasia	68 (77)	70 (100)	0 (0)
Bone marrow blasts (%)	2.0 (0.0-10.0)	2.0 (0.0-10.0)	0.0 (0.0-3.0)
Vacuoles§	67 (99)	52 (98)	15 (100)

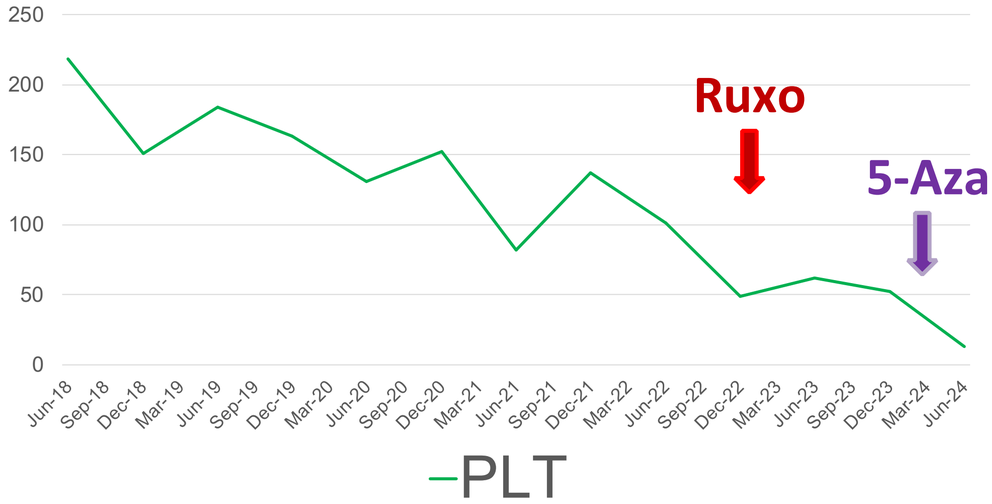
- Inflammatory **response rates** were **41% at 6 months** and **54% at 12 months**, regardless of MDS status
- A total of 50 (61%) patients achieved inflammatory response, with 70% occurring at 6 months, suggesting a **delayed median response**

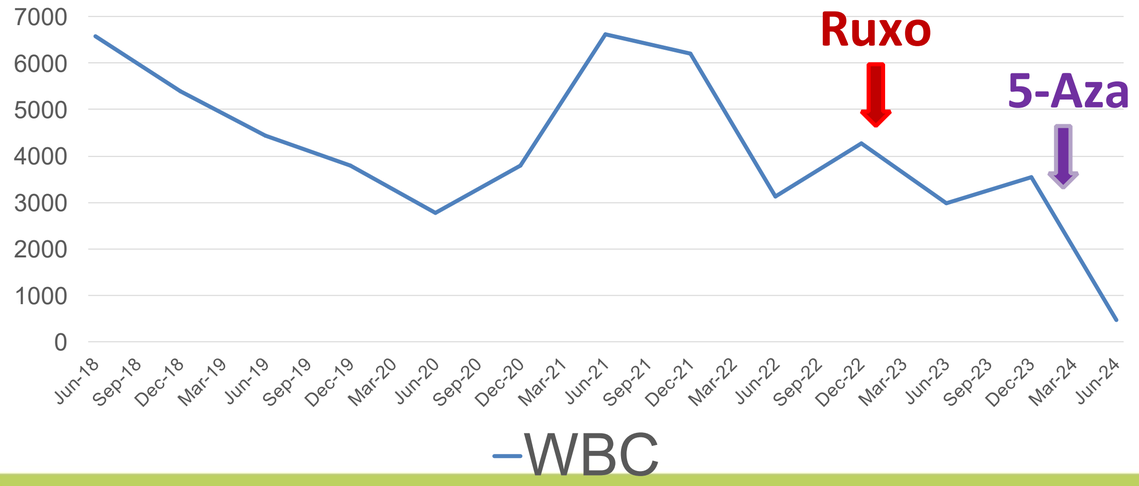


- **Infections (34%) and cytopenias (36%)**
- **Higher than those reported with anti–IL-6 agents (23%) and JAK inhibitors (29%)**

C.F. - variazioni dell'emocromo nel tempo



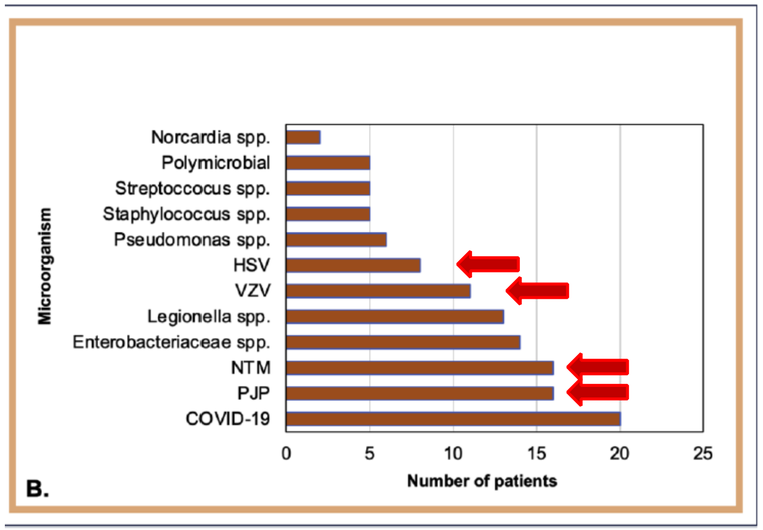




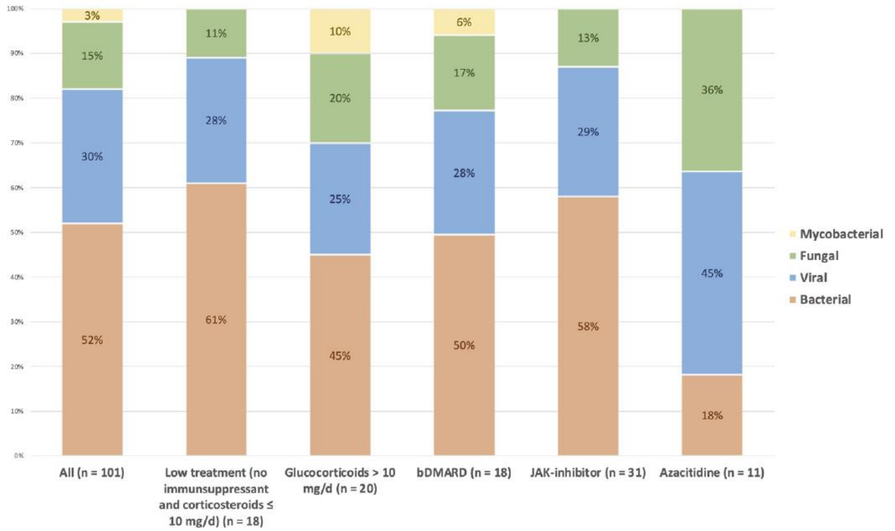
Infections in VEXAS: focus on NTM

Increased risk for infections

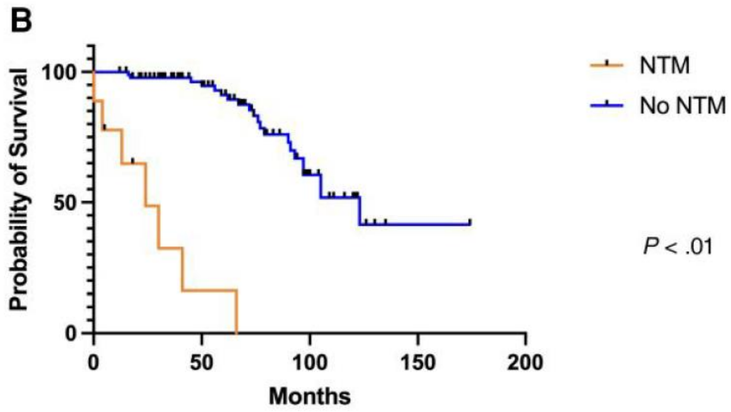
→ advanced age at disease onset
→ necessity for sustained high-dose corticosteroid treatment
→ bone marrow failure
→ imbalance in the ubiquitin proteosome system caused by *UBA1* mutations



Ali & Gurnari Curr Res Trasl Med 2025



De Valence Ann Rheum Dis 2024



Czech Open Forum Infect Dis 2025

Considerazioni

- **Gestione** dei pazienti con VEXAS **complessa**

- **Modulazione della terapia** in base alla **differente penetranza**
  - Dai farmaci modulatori della risposta biologica al trapianto allogenico

- Non sottovalutare il **rischio infettivo**
  - Minimizzare la terapia steroidea
  - Profilassi adeguata (aciclovir, cotrimossazolo)