TEL-AVIV SOURASKY MEDICAL CENTER
ICHILOV
MEDICAL EXCELLENCE AND COMPASSIONATE CARE

TEL AVIV UNIVERSITY אוניברסיטת תל אביב

Inflammatory MDS and JAKi in Rheumatology

MDS and BMF meeting

June 2023

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@talieshua

Agenda

- Hematology-Rheumatology interface
  - Lymphoid and myeloid interface
  - Autoimmunity and autoinflammation
- "Inflammatory MDS"
  - What is inflammatory MDS?
  - Clonal hematopoiesis and inflammation
  - Treatment options for inflammatory MDS
  - VEXAS in Israel and the VEXAS registry
- JAK inhibition in rheumatology
  - ORAL surveillance
  - Thrombotic complications of JAKi in rheumatology vs. in MPD

Take home message

Hematology-Rheumatology interface

Lymphoid and myeloid

Autoimmunity and autoinflammation

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EUROPEAN CONGRESS OF RHEUMATOLOGY

31 MAY – 3 JUNE

Spatial transcriptomics

Practical Skills

Spondyloarthritis across the ages

Clinical Science

Supporting patients in taking active part in their care

Health Professionals in Rheumato...

Talking about Remission

Clinical Science

The brain in RMDs

Challenges in Clinical Practice

The clinic as classroom – teaching and learning with patients

PARE

The Conundrum of diagnosing Axial Spondyloarthritis resolved

Clinical Science

The future perspectives in the treatment of SLE & Sjögren's

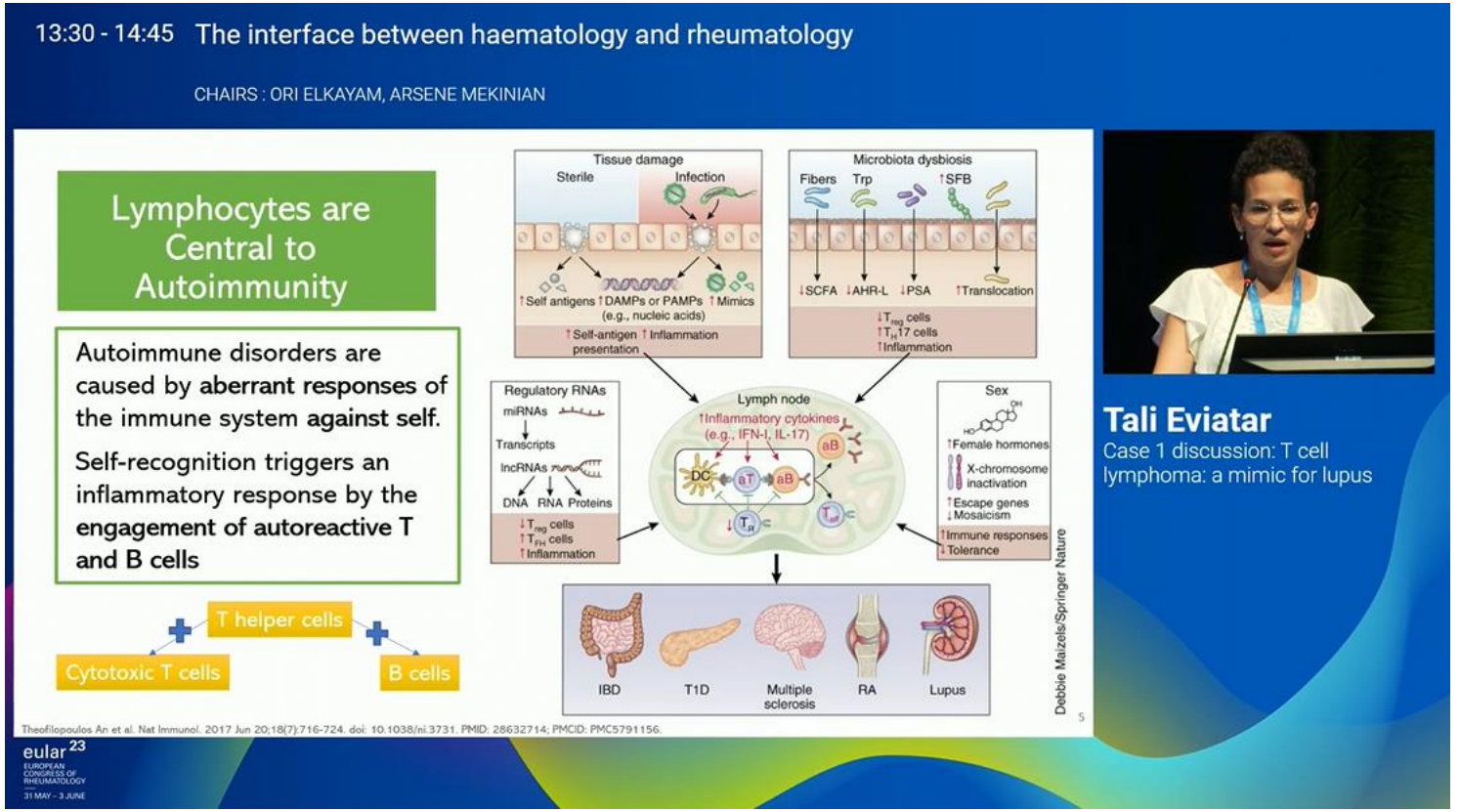
Oral Abstract Presentations

The heart in rheumatology: non-ischemic diseases

Challenges in Clinical Practice

The interface between haematology and rheumatology

Challenges in Clinical Practice



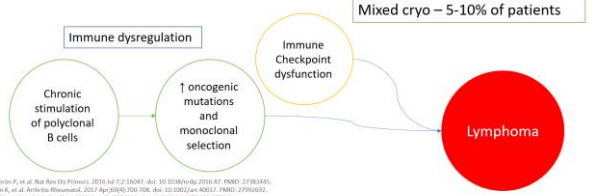
Hematology and rheumatology have a broad interface; diseases, medications and clinical manifestations

Hematology-Rheumatology interface: Connective Tissue Diseases and Lymphomas

Lymphomas In Rheumatology – The Hematology-Rheumatology Interface: **Diseases**

Increased risk of Lymphomas in CTDs

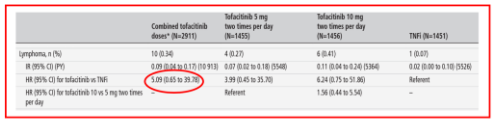
RA – pooled SIR 1.6-2.46
pSjS – pooled SIR 9-44 (~20)
Mixed cryo – 5-10% of patients



Lymphomas In Rheumatology – The Hematology-Rheumatology Interface: **Medications**

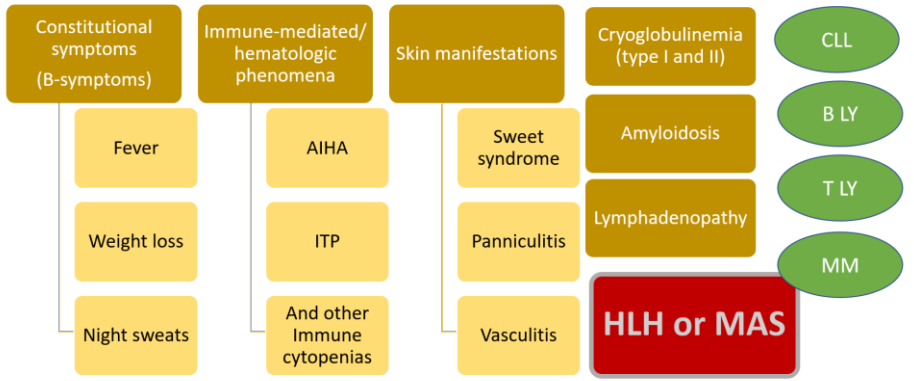
- An increase in Ly risk with TNFi (?)
  - Earlier studies, including RCTs showed an increased risk
  - Most real world studies – no increased risk
- Tofa (JAKi) > TNFi ?

AZA
MTX



	Combined tofacitinib doses* (N=2911)	Tofacitinib 5 mg two times per day (N=1455)	Tofacitinib 10 mg two times per day (N=1456)	TNFi (N=1451)
Lymphoma, n (%)	10 (0.34)	4 (0.27)	6 (0.41)	1 (0.07)
IR (95% CI) (PY)	0.09 (0.04 to 0.17) (10 913)	0.07 (0.02 to 0.18) (5540)	0.11 (0.04 to 0.24) (5364)	0.02 (0.00 to 0.10) (5526)
HR (95% CI) for tofacitinib vs TNFi	5.09 (0.65 to 39.78)	3.99 (0.45 to 35.70)	6.24 (0.75 to 51.86)	Referent
HR (95% CI) for tofacitinib 10 vs 5 mg two times per day	–	Referent	1.56 (0.44 to 5.54)	–

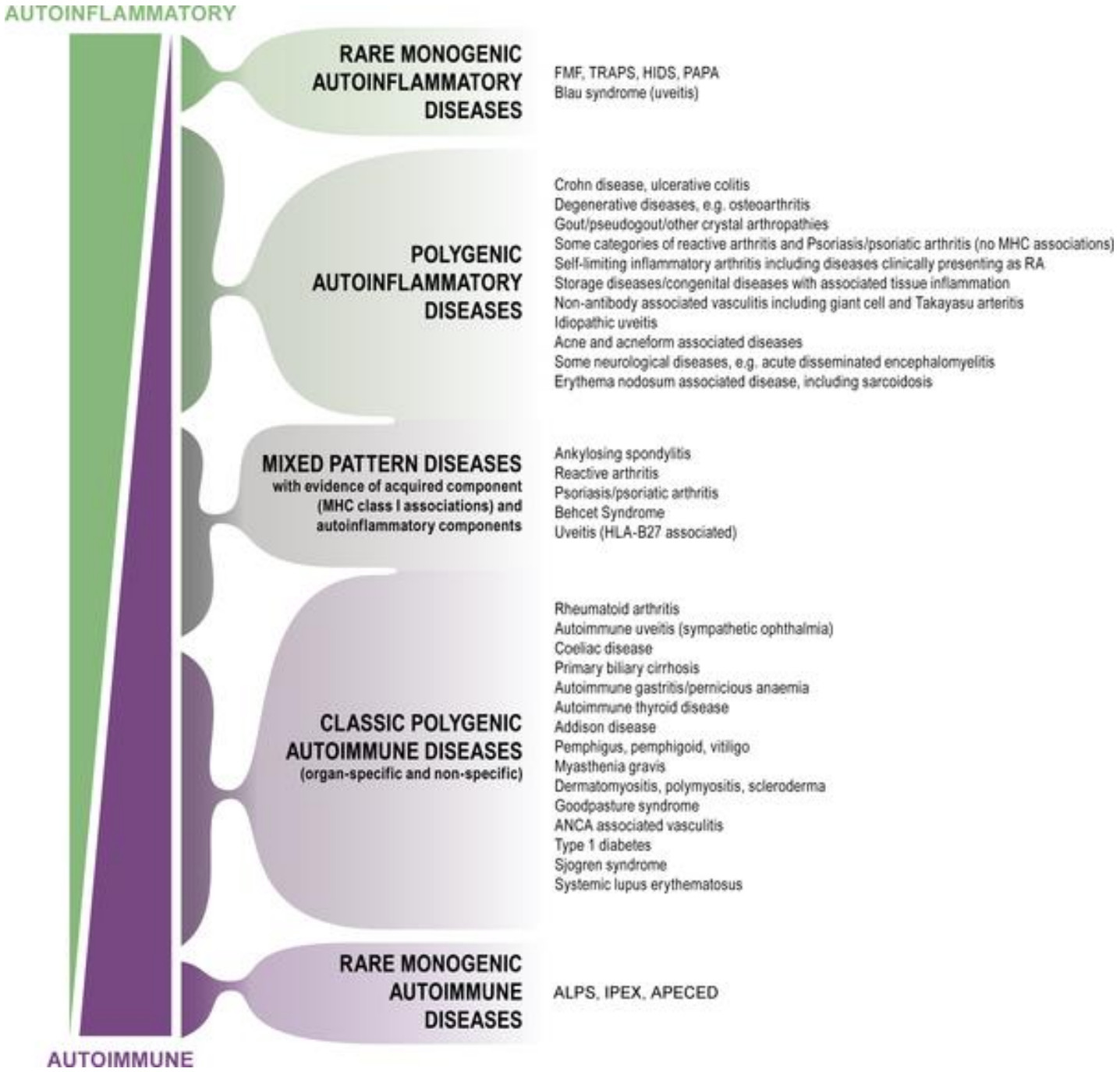
Clinical manifestations of systemic lymphomas may **mimic/overlap** CTD manifestations



Jachiet V, Mekinian A, et al. Leuk Lymphoma. 2018 Jun;59(6):1399-1405.

Adaptive immunity and **Autoimmunity**

Autoimmunity and Autoinflammation



McGonagle D (2006). PLOS Medicine 3(8): e297. https://doi.org/10.1371/journal.pmed.003029

	Autoinflammation	Autoimmunity
Immunological disruption	Innate Immunity	Adaptive immunity
Main cellular involvement	Neutrophils, macrophages	B and T cells
Antibody involvement	Few or no autoantibodies	Autoantibodies present
Clinical features	Recurrent, often seemingly unprovoked attacks	Continuous progression
Conceptual understanding	Tissue-specific factors/danger signals	Breaking of self-tolerance
Main genetic susceptibility	Cytokine and bacterial sensing pathways	MHC class II associations and adaptive response genes
Therapy	Anti-cytokine (IL-1, TNF, IL-6)	Anti-B and T cell
Examples	Monogenic hereditary periodic fevers, polygenic Crohn's disease spondylarthropathies	Monogenic ALPS and IPEX genic RA and SLE

FMF

SLE, CTDs

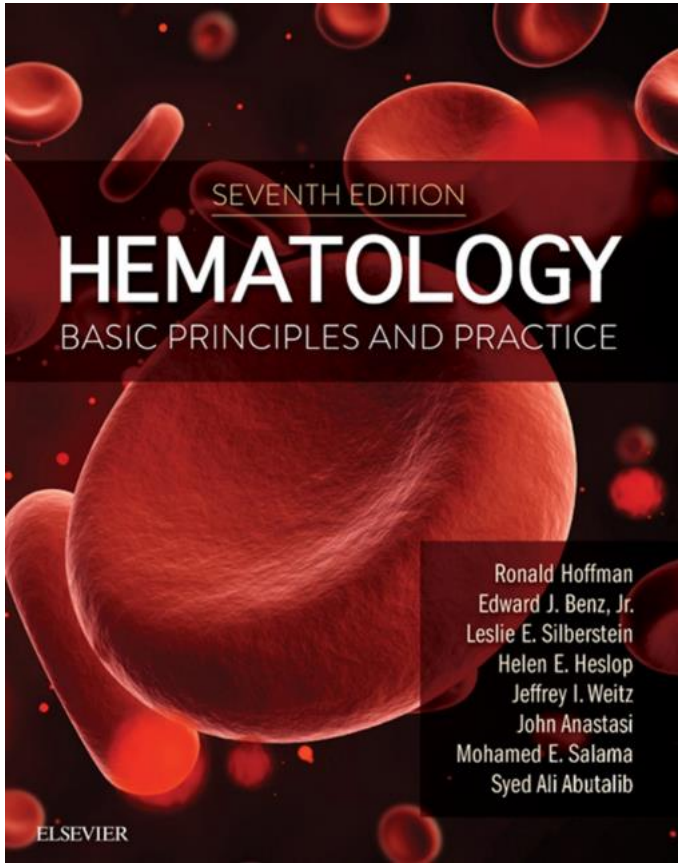
McGonagle D (2006). PLOS Medicine 3(8): e297. https://doi.org/10.1371/journal.pmed.003029

Inflammatory MDS

What is inflammatory MDS?

From bench to bedside and back

Inflammatory MDS



Autoimmune Manifestations

A percentage of patients with MDS may have overlapping immunologic or rheumatologic features to their disease, which may in part arise from the immune dysregulation that occurs during disease pathogenesis.[288] In a few patients, these may be the presenting complaint. Such manifestations can include episodes of seronegative oligoarthritis or polyarthritis,[289] cutaneous vasculitis,[290] polymyositis,[291] or autoimmune peripheral neuropathies. Rare patients can present with a lupus-like syndrome tha[illegible]nclude fever, polyarthralgias, polychondritis, pleuriti[illegible], and cytopenias (including hemolytic anemias)[illegible]e phenomena have also been reported, in[illegible]eous ulcerations, iritis, polymyositis, infla[illegible]ease, and erythrocyte aplasia. Many of these, [illegible]entially paraneoplastic syndromes, respond to the in[illegible]of immunosuppressive agents such as corticosteroids.[292]

Pre-VEXAS

Some reports have additionally documented cases of patients who were diagnosed with rheumatologic conditions only weeks or months before they were found to have MDS, including relapsing polychondritis,[293] polymyalgia rheumatica or temporal arteritis,[294] Raynaud phenomenon, Sjögren syndrome, and autoimmune glomerulonephritis.[295] However, since some of these conditions are relatively common themselves, particularly in older populations, whether they represent a true association with MDS or are merely coincidental occurrences is not entirely clear.

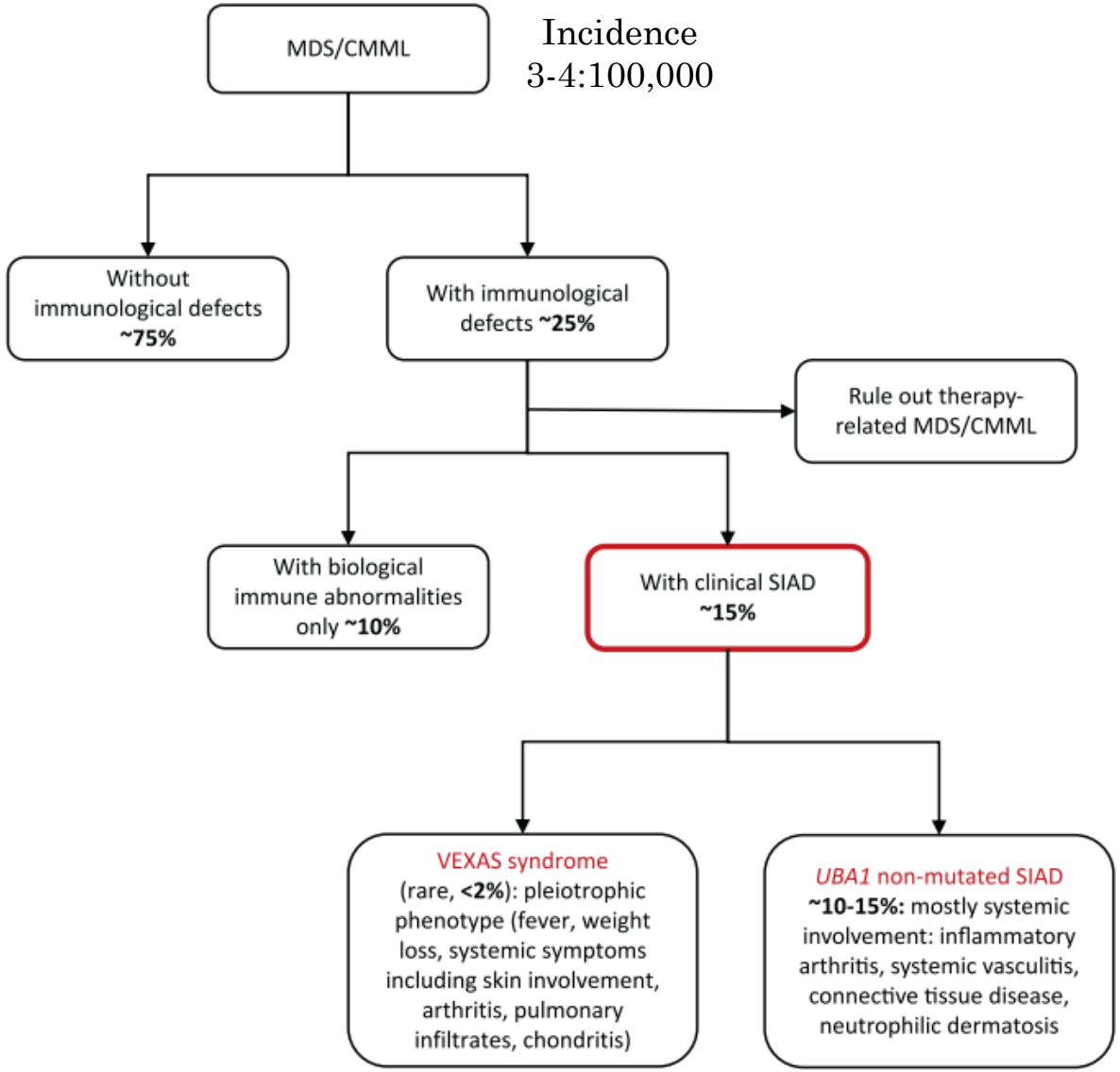
Inflammatory MDS

Inflammatory MDS includes both **UBA1-mutation-associated (VEXAS) and non-UBA1-associated** inflammatory syndromes.

More in **low-risk MDS** (and pre-MDS/CH?) than high-risk MDS

Cytokine profile:
In low-risk MDS– higher TNFα, IFNɣ, IL6

In high-risk MDS – higher IL10.



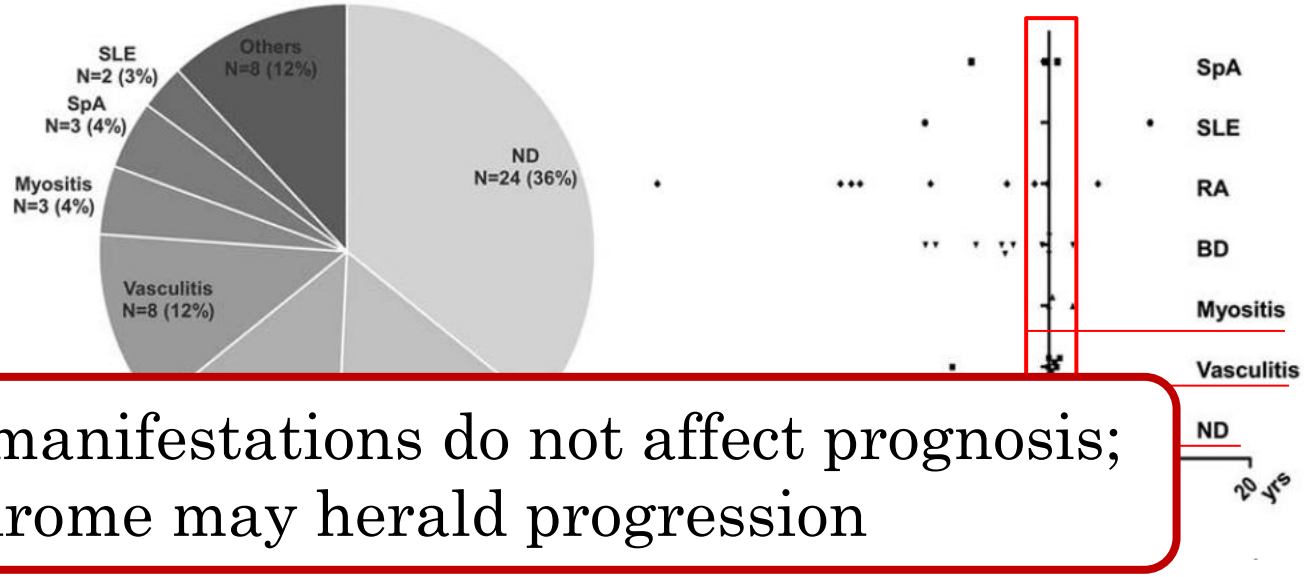
Banerjee T, et al. Blood Rev. 2019 Jul;36:57-69. doi
Zhao LP, et al. Leukemia. 2023 Jun;37(6):1186-1190. doi: 10.1038/s41375-023-01890-4.

Immune/Inflammatory Manifestations of MDS

- Vasculitis – from large "GCA", medium "PAN" to small vessel (skin, GI, etc…)
  - Pseudo-Behcet's-like disease – VVV with predominant intestinal involvement (trisomy 8)
- Arthritis "seronegative RA", "spondyloarthritis", inflammatory arthritis
- Neutrophilic dermatoses – Sweet syndrome and pyoderma gangrenosum
- Connective tissue diseases – SLE, Sjogren's

Characteristics of MDS/CMML-related vasculitis according to MDS/ CMML subtypes.

Characteristics at baseline	Vasculitis-MDS/CMML(n = 70)
Age (years)	71.5 [21–90]
Males (n;%)	49 (70)
Vasculitis before MDS/CMML	31 (44.3)
Time between 2 diagnosis (months)	27 [1 - 120]
Vasculitis after MDS/ CMML	20 (28.5)
Time between 2 diagnosis (months)	6 [1–59]
Type of vasculitis	
Giant cell arteritis (n;%)	24 (34)
Polyarteritis nodosa (n;%)	6 (9)
Behçet / Behçet like disease (n;%)	4 (6) / 7 (10)
Unclassified vasculitis (n;%)	17 (24)
ANCA-associated vasculitis (n;%)	7 (10)
IgA / Cryoglobulinemic vasculitis (n;%)	2 (3) / 3 (4)

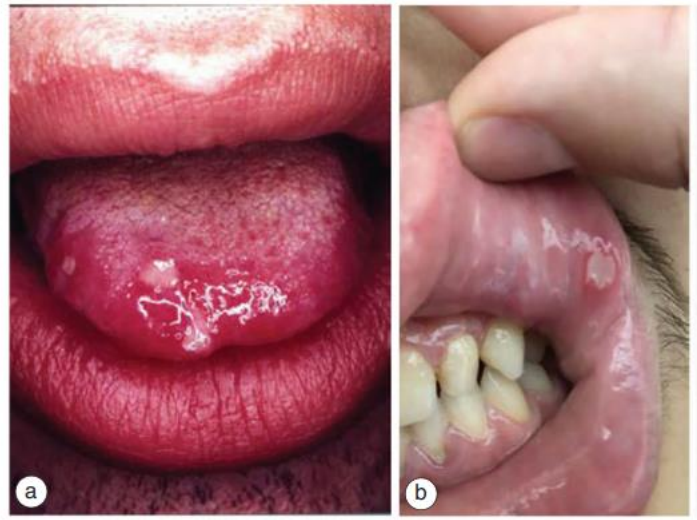


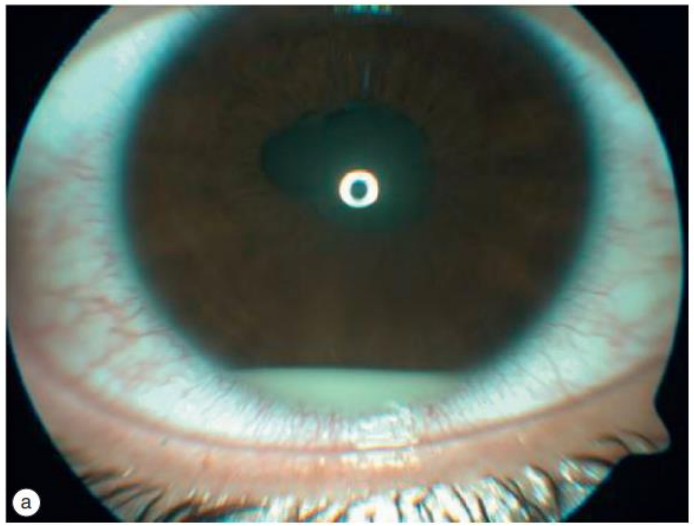
Most inflammatory manifestations do not affect prognosis; Sweet syndrome may herald progression

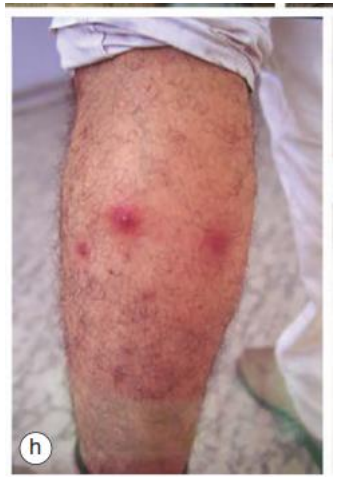
Roupie, A. et al. *Seminars in Arthritis and Rheumatism*, *50*(5), 879–884.
Liu, Z., et al. *Seminars in Arthritis and Rheumatism*, *55*.
Roupie, A. et al. *Autoimmunity Reviews*
Lee, S. et al. *Medicine (United States)*, *95*(13), e3091.

Behcet's disease

- Behcet's disease (BD) is a **variable vessel vasculitis**
  - Oral and genital **ulcers**
  - Neutrophilic **rashes** (EN, papulopustular, etc.)
  - **Uveitis**
  - **Thrombotic** manifestations
- Prevalent in Turkey, far-east, and along silk-road (**HLA-B51**)
- Usually manifests in **adolescents and young adults**
- Haploinsufficiency of A20 – autosomal dominant BD







Behcet's-like syndrome and Trisomy 8

52 patients
Age at BD dx was **45.7±18.6 (4–80)**
Age at MDS dx was 46.9±17.4 (4–76)

39 (**76.5%**) had **trisomy 8**
(7-9% in primary MDS)

GI involvement in 69.2%
(up to 30% in Japan, up to 8% in other regions)
Uveitis in 11.5%

Table III. Clinical presentations of BD associated with MDS involving and not involving trisomy 8.

	BD-MDS with trisomy 8 (n=39)	BD-MDS without trisomy 8 (n=12)	*p*-value
Age at BD diagnosis (years), mean (SD)	45.6 ± 18.9	45.1 ± 18.7	0.94
Age at MDS diagnosis (years), mean (SD)	47.2 ± 17.6	45.4 ± 17.8	0.76
Male (no of patients, (%))	19 (48.7)	7 (58.3)	0.56
Oral ulcers	39 (100)	11 (91.7)	0.23
Genital ulcers	32 (82.1)	8 (66.7)	0.26
Eye lesions	3 (7.7)	3 (25)	0.13
Skin lesions	25 (64.1)	9 (83.3)	0.29
Positive pathergy test	11/17 (64.7)	1/1 (100)	1.00
Arthritis	10 (25.6)	7 (58.3)	0.07
Vascular lesions	6 (15.4)	0 (0)	0.31
GI involvement	29 (74.4)	6 (50)	0.15
Fever	31 (79.5)	4 (33.3)	0.005
HLA-B51	6/21 (28.6)	0	
Fulfillment of Behçet's disease criteria set			
ISG criteria	31 (79.5)	8 (66.7)	0.44
Incomplete Japanese criteria	27 (69.2)	6 (50)	0.23
Complete Japanese criteria	1 (2.6)	2 (16.7)	0.13

Esatoglu SN, et al. Clin Exp Rheumatol. 2015 Nov-Dec;33(6 Suppl 94):S145-51

Trisomy 8 and Other Inflammatory Manifestations

Major **symptomatic relief** when treated with **leukemia-directed therapy** and corticosteroids

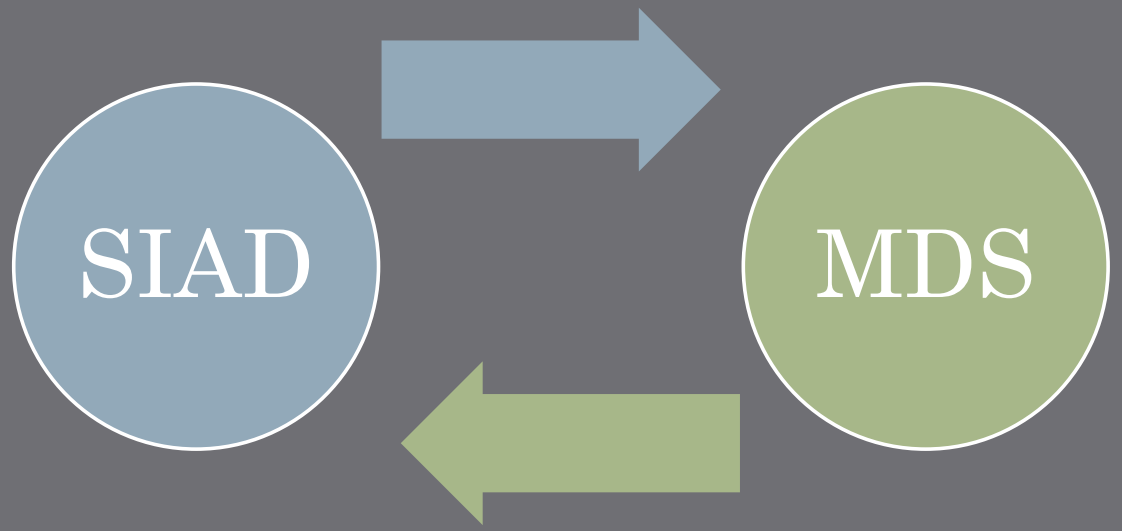
MDS/MPD with trisomy 8	AML with trisomy 8
21 patients with IADs compared to **103** patients without IADs	**3** patients
Behçet's-like disease in 11 (52%) inflammatory arthritis in 4 (19%) Sjögren's syndrome AIHA Aseptic abscess PAN Sweet's syndrome unclassified vasculitis } one patient each	Migratory arthralgias Lymphadenopathy with noncaseating granulomas, Large vessel vasculitis Skin leukocytoclastic vasculitis Myalgias Erythema nodosum

Seven patients receiving azacytidine: **five achieved remission and two partial response**

Buchrits S, et al. Eur J Haematol. 2022 Mar;108(3):199-203. doi: 10.1111/ejh.13725
Wesner N, et al. Eur J Haematol. 2019 Jan;102(1):63-69. doi: 10.1111/ejh.13174.

Systemic inflammation may induce MDS:

1. **Increased risk** of MDS in patients with SIAD
2. **Clonal advantage** of DNMT3a, TET2, etc. clones under an **inflammatory environment**

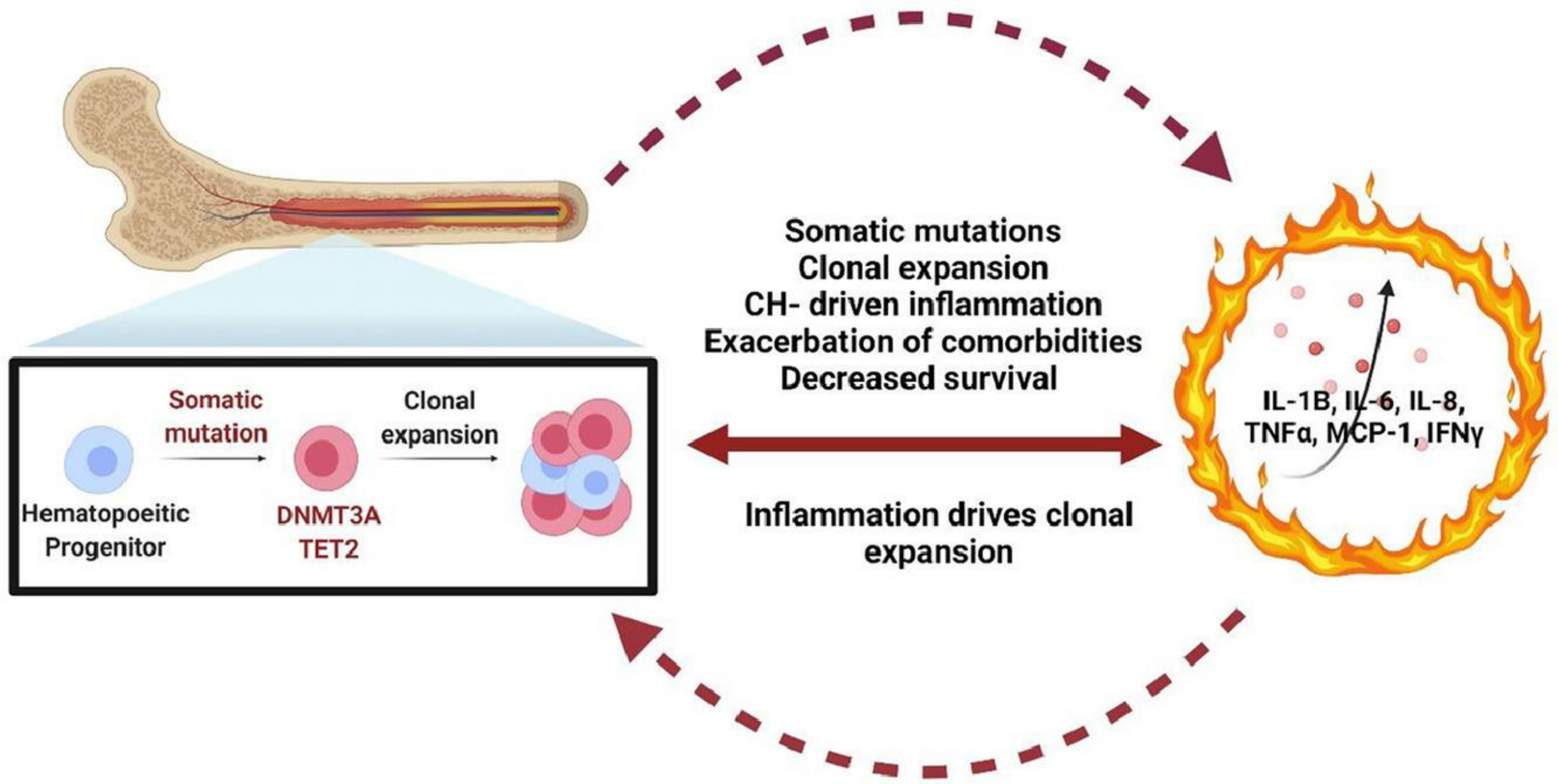


MDS may induce SIAD:

1. **Modulation of T cell repertoire** with increased Th17:regulatory T cell ratio
2. Generation of myeloid cells and lymphocytes with **enhanced proinflammatory characteristics**

Theoretical pathophysiology of inflammatory MDS

Zhao LP, et al. Leukemia. 2023 Jun;37(6):1186-1190. doi: 10.1038/s41375-023-01890-4.
Kusne Y, et al. Semin Hematol. 2021. doi: 10.1053/j.seminhematol.2021.10.004.



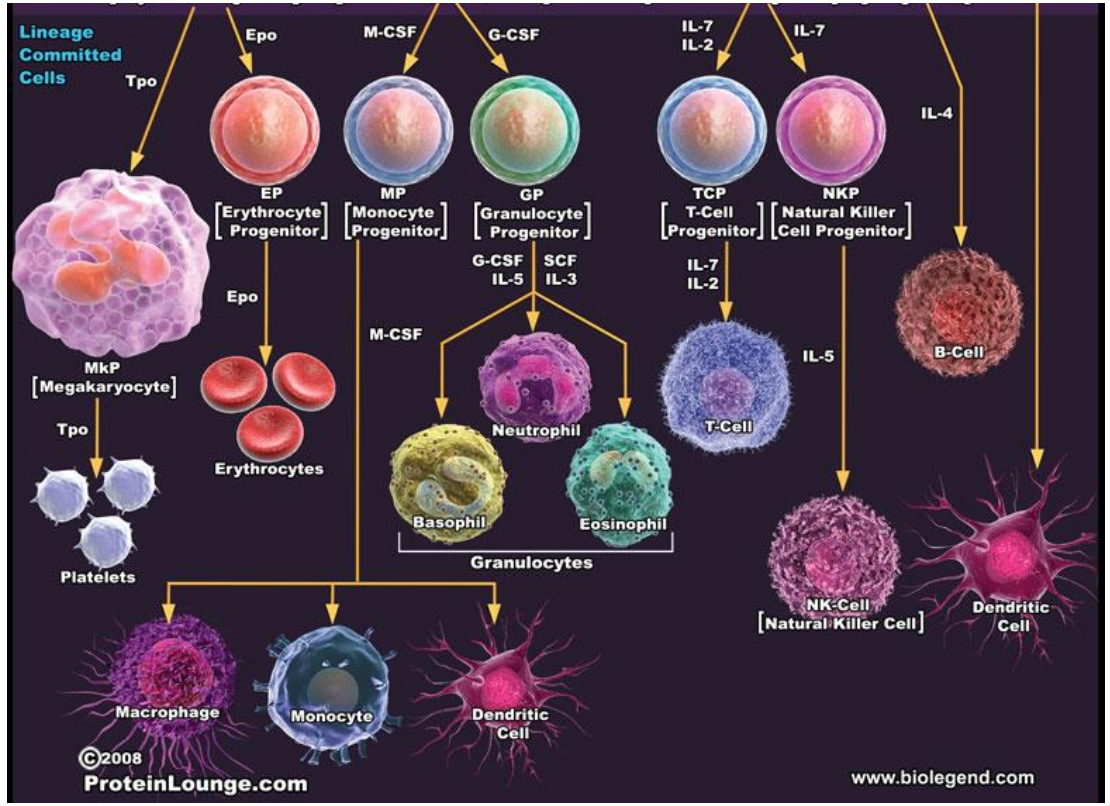
Theoretical pathophysiology of inflammatory MDS

TET2 and inflammation

TET2 plays a role in DNA demethylation.

TET2 loss of function, (MDS ~20%, CMML ~50%), leads to enhanced HSPC self-renewal capacity and a myeloid bias

TET2 inactivation leads to an increase of **tissue-infiltrating macrophages** and **secretion of inflammatory cytokines** (CCL5, CCL22, and NLRP3-dependent IL1ß)

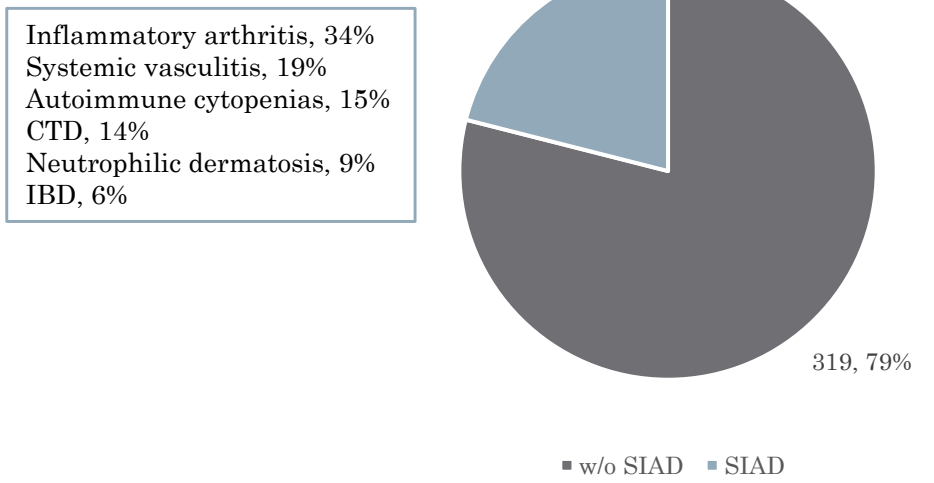


TET2 plays a role in the lymphoid compartment; **maintaining regulatory T cells**, **modulating B germinal center reaction** and **regulating NK** lymphocyte cytotoxicity

Zhao LP, et al. Leukemia. 2023 Jun;37(6):1186-1190.
Banerjee T, et al. Blood Rev. 2019 Jul;36:57-69

TET2 in MDS and inflammation

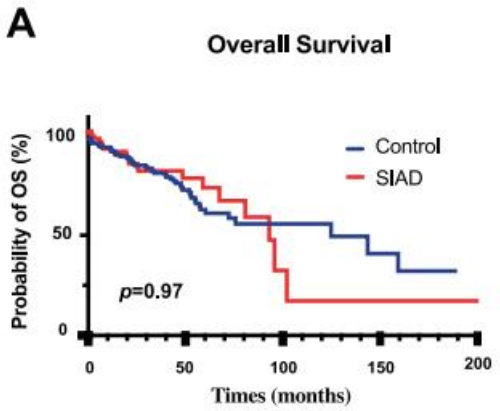
404 patients with MDS/CMML

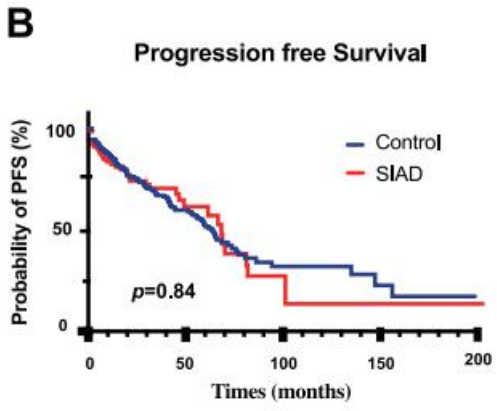


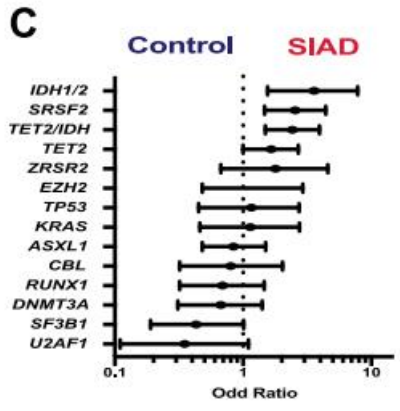
Inflammatory arthritis, 34%
Systemic vasculitis, 19%
Autoimmune cytopenias, 15%
CTD, 14%
Neutrophilic dermatosis, 9%
IBD, 6%

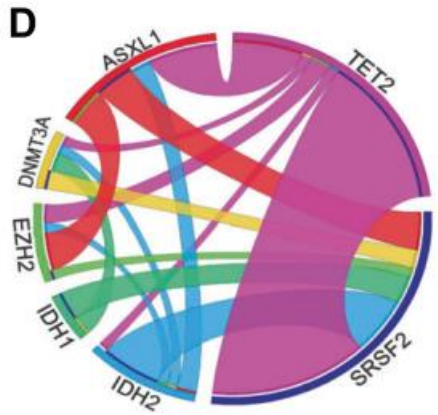
More patients in the SIAD group had low-risk MDS/CMML, p=0.02

TET2 mutations (46% versus 34%, p = 0.04),
IDH1/2 (14% versus 5%, p < 0.01),
and SRSF2 (31% versus 15%, p < 0.01)
were **more prevalent** in **MDS/ CMML patients with SIAD** than MDS/CMML patients without SIAD

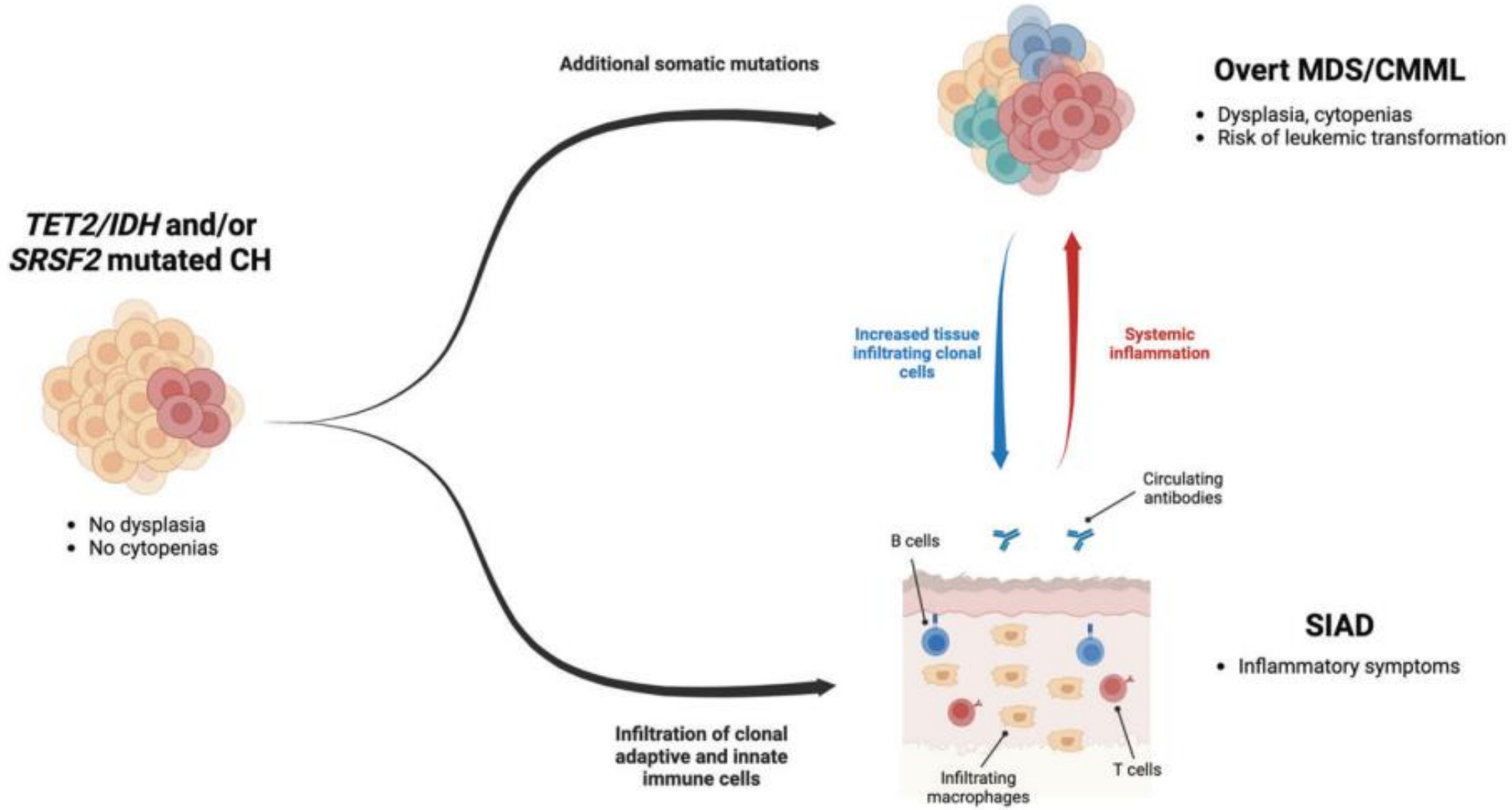








Zhao Lp et al. Leukemia. 2021 Sep;35(9):2720-2724. doi: 10.1038/s41375-021-01152-1..



Proposed model of TET2/IDH mutation and inflammatory MDS

The presence of TET2, IDH1/2, or SRSF2 mutations in the hematopoietic stem and progenitor cells may lead to clonal mutated myeloid and lymphoid committed mature cells, with enhanced inflammatory potential. These cells exacerbate chronic local and systemic inflammation, and in turn facilitate the outgrowth of mutated cells, the acquisition of other somatic events, and promote the transformation to overt MDS/CMML

Zhao LP, et al. Leukemia. 2023 Jun;37(6):1186-1190. doi: 10.1038/s41375-023-01890-4.

Clonal hematopoiesis and inflammation

CH - the detection of **somatic variants** in HSPC (most commonly epigenetic regulators: TET2, DNMT3A, etc.), with the **potential to expand** over time

Received: 8 January 2023 | Revised: 8 March 2023 | Accepted: 15 March 2023

DOI: 10.1002/ajh.26915

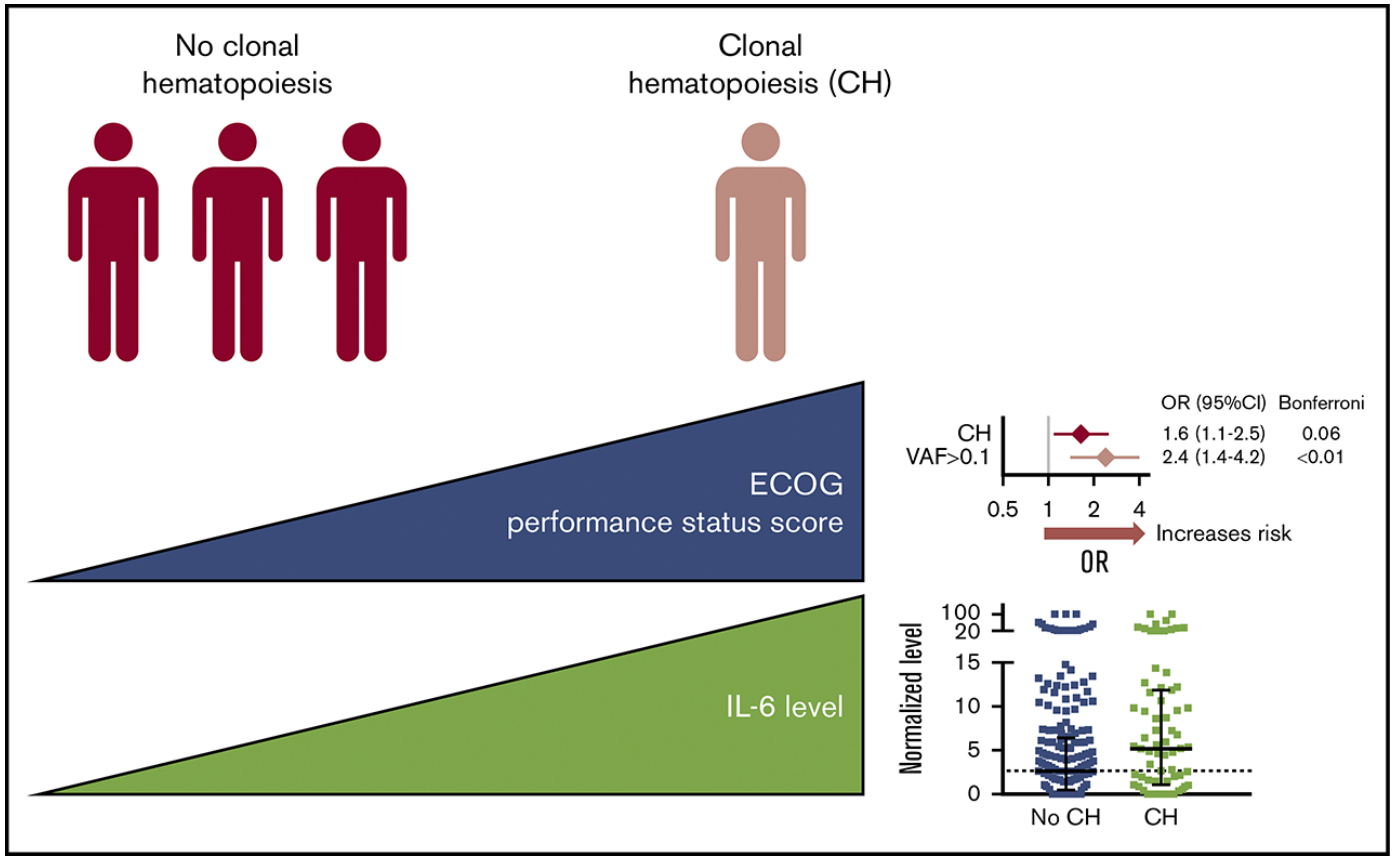
ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES

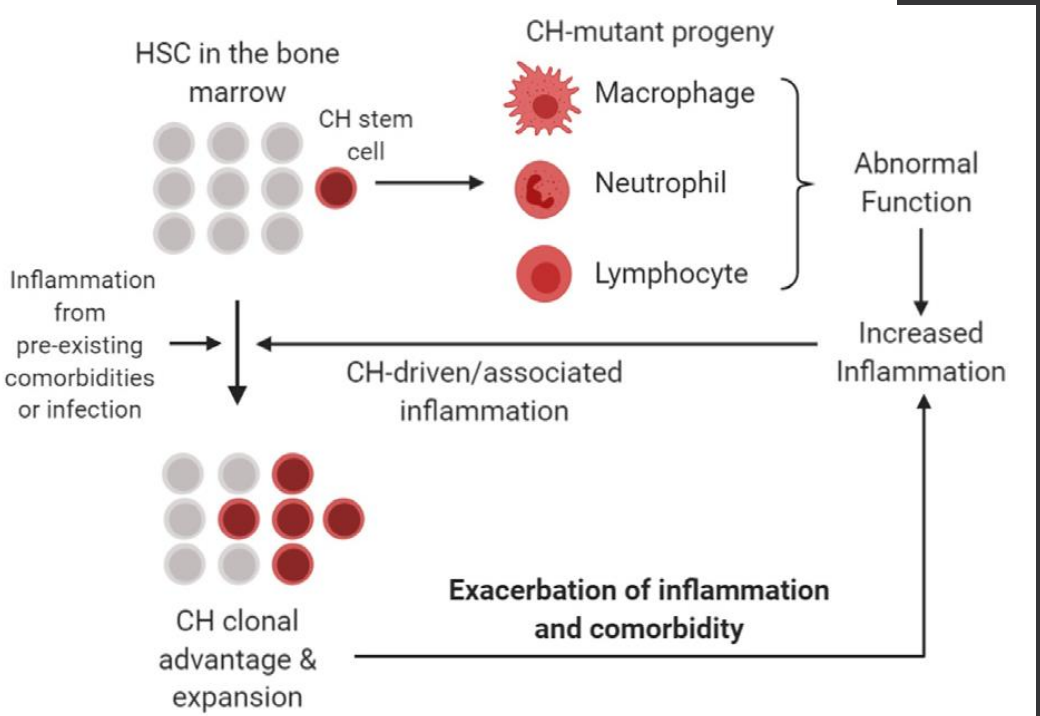
Clonal hematopoiesis of indeterminate potential and clonal cytopenias of undetermined significance: 2023 update on clinical associations and management recommendations

Abhishek A. Mangaonkar | Mrinal M. Patnaik

- **0.5-1%** of individuals with CH will develop **myeloid neoplasms**
- CH prevalence **increases with age**: 9.5% 70–79, 11.7% 80–89, 18.4% ≥90
- CH is associated with increased all-cause **mortality**, cytopenias (CCUS), myeloid neoplasm, cytosis (including monocytosis), and atherosclerotic CVD, ischemic CHF, **VTE**, DM2, COPD, OP, **gout**, and protection against Alzheimer's

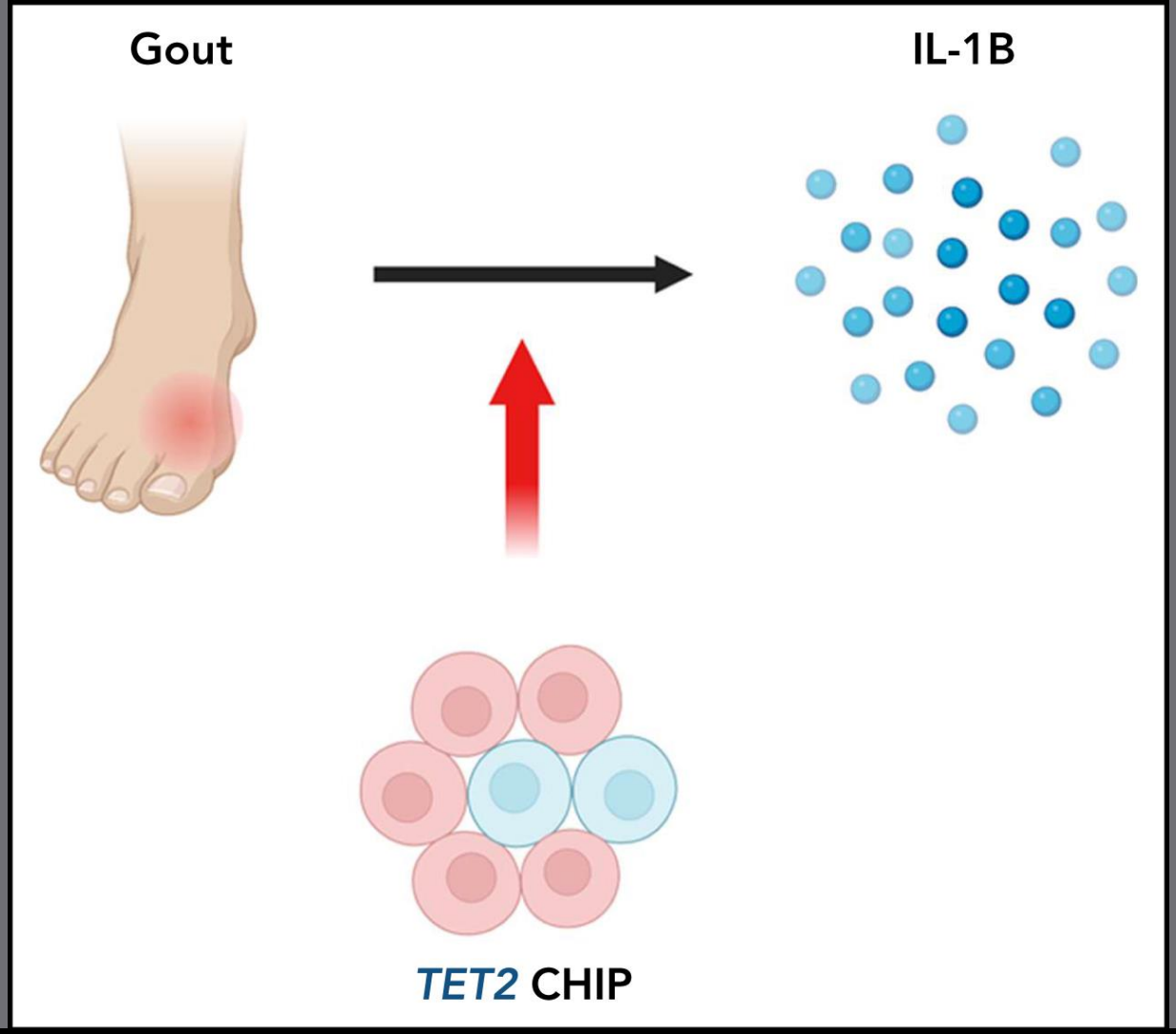
CH is associated with an Inflammatory Cytokine Profile





Normalized **IL-6** values were **twofold higher** in CH compared with people without mutations. **TNFα** was also **increased** in CH compared to controls

Cook EK, et l. Blood Adv. 2019 Aug 27;3(16):2482-2486. doi: 10.1182/bloodadvances.2018024729.
Cook EK, et al. Exp Hematol. 2020 Mar;83:85-94. doi: 10.1016/j.exphem.2020.01.011.



Whole exome sequencing data from **177,824** individuals:

The frequency of gout was **higher among individuals with CHIP** than without CHIP, in a **VAF (dose)-dependent** relationship.

MSU crystals lead to elevated IL-1ß levels in *Tet2* knockout murine models

TET2-mutant Clonal Hematopoiesis And Risk Of Gout

Agrawal M, et al. Blood. 2022 Sep 8;140(10):1094-1103. doi: 10.1182/blood.2022015384.

VEXAS and CH/VEXAS as a CH

- 80 VEXAS patients screened for CH.
- Typical CH mutations **co-occurred in 60%** of patients (mostly DNMT3A and TET2)
- CH mutations were **not associated with inflammatory or hematologic manifestations**.
- Transfusion-dependent anemia, moderate thrombocytopenia, and typical CH mutations, correlated with poor outcomes.
- **In VEXAS, UBA1 cells are the primary cause of systemic inflammation and marrow failure.**

But, isn't UBA1 a CH mutation by itself?

1. VEXAS meets all the defining criteria of MDS (clonality, dysmyelopoiesis, and cytopenias)
2. VEXAS is an example of **clonal hematopoiesis of extra-hematological significance**, which expands the spectrum of CH

Gutierrez-Rodrigues F, et al. Blood. 2023 Apr 21:blood.doi: 10.1182/blood.2022018774.
Sujobert P, et al. Expert Rev Hematol. 2023 May 4:1-5. doi: 10.1080/17474086.2023.2209715.

V H/VEXAS as a CH

TABLE 2 Table showing examples of gene alterations associated with myeloid and lymphoid clonal hematopoiesis (CH).

Myeloid CH	Lymphoid CH
Epigenetic pathway: *DNMT3A, TET2, ASXL1, ASXL2, DNMT3B, IDH1, IDH2, EZH2, SETD2, SUZ12* Splicing pathway: *SF3B1, SRSF2, ZRSR2, U2AF1, SF3A1* Cell signaling: *JAK2, JAK3, MPL, CALR, NOTCH1, NOTCH2, NOTCH3, BRAF, FLT3, CSF1R, CSF3R, EGFR, KIT, MAP2K1, PDGRFA, PIK3CA, RET, SH2B3, STAT3* RAS pathway: *CBL, NRAS, KRAS, PTPN11* Nuclear function/export/ transcription: *RUNX1, CEBPA, MEF2B, GATA1, GATA2, GATA3, NPM1, XPO1, ETV6, RB1* Ubiquitination: *CBLB, UBA1, FBXW7* DNA repair: *FANCL, CHEK2, RAD21* Immune/complement pathway: *CD79B, MYD88, PIGA, TLR2* Tumor suppressor/apoptosis pathway: *TP53, BCOR, BCORL1, PHF6, PTEN* Cohesin complex: *STAG1, STAG2, PDS5B, SMC3* Miscellaneous: *CNOT3, CUX1, CREBBP, CTCF, CTNNB1, EED, EP300, SETBP1, BCL11B, BRCC3, LUC7L2, NT5C2, ATM, PIM1, PRPF40B, RIT1, RPL10, SF1, WHSC1, WT1, SRCAP, GNB1, GNAS*	*DUSP22, MGA, NCOR2, FAT1, ITPKB, Sin3A, KMT2D, ADD2, MYD88, FOXO1, NOTCH1, PAX5, SPEN, NOL9, IRF2BP2, ADGRV1, FAT2, IGLL5, LTB, ZFP36L1, BTG2, VAV1, PTCH1, NFKBIE* (Reference: 20)

1. VEXAS meets all the defining criteria of MDS (clonality, dysmyelopoiesis, and cytopenias)

2. VEXAS is an example of **clonal hematopoiesis of extra-hematological significance**, which expands the spectrum of CH

Gutierrez-Rodrigues F, et al. Blood. 2023 Apr 21:blood.doi: 10.1182/blood.2022018774.
Sujobert P, et al. Expert Rev Hematol. 2023 May 4:1-5. doi: 10.1080/17474086.2023.2209715.

Treatment of inflammatory MDS

Treatment of systemic inflammation

Controlling inflammatory mediators (cells or cytokines)

- csDMARDS:
  MTX, azathioprine, leflunomide, etc.
  (cellular inhibition)

Adaptive immunity (lymphocytes)

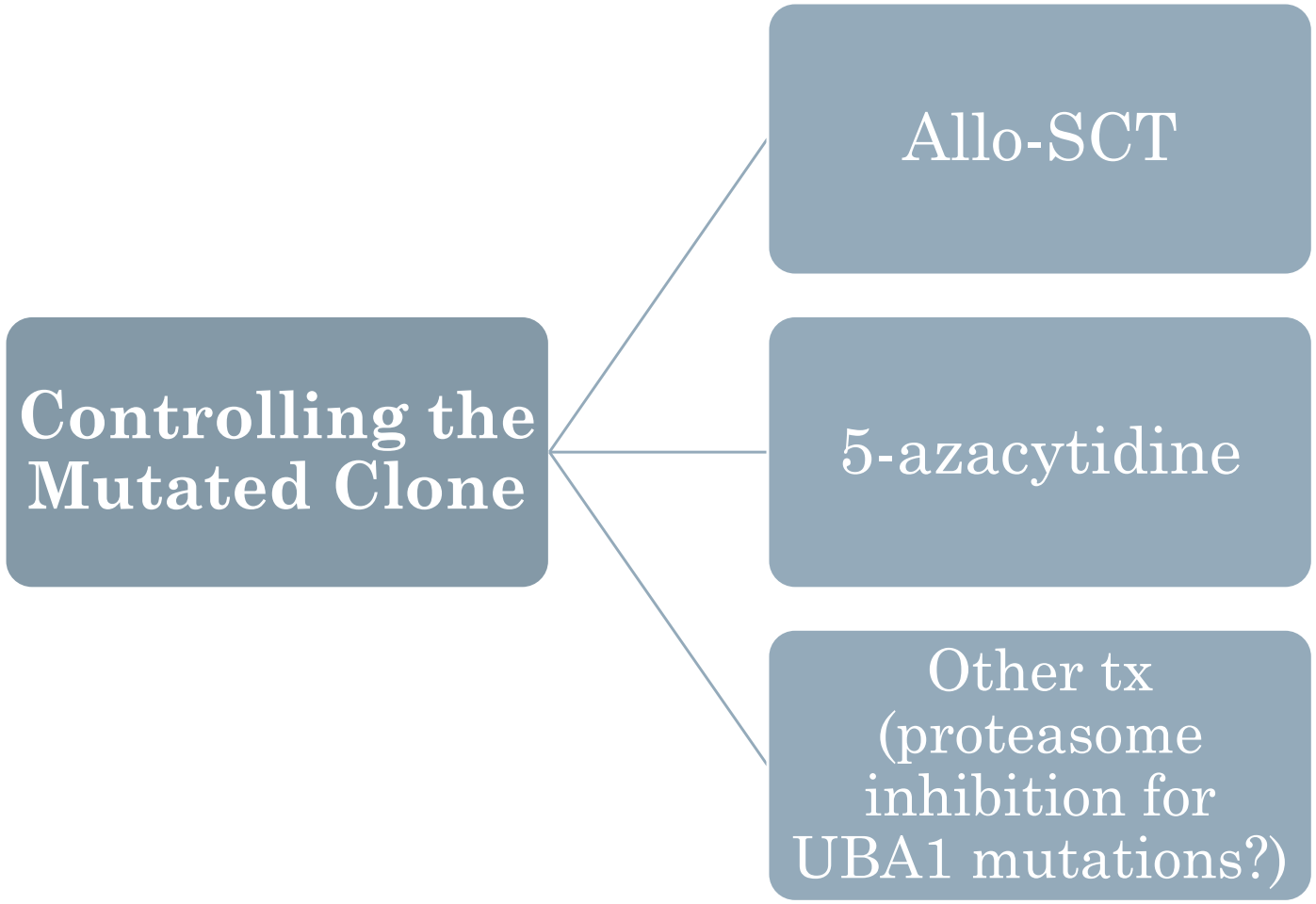
- bDMARDS:
  - Anti CD-20, CTLA4-Ig (cellular inhibition)
  - anti-IL-1, anti-IL-6, anti-TNF, etc. (cytokine inhibition)
- tsDMARDs:
  JAKi (cytokine inhibition)

In inflammatory MDS

Increase in risk of infection

Risk of myelosuppression (accelerate transformation?)

Treatment of the inflammation without addressing the myelodysplastic clone



Treatment of inflammatory MDS

Zhao LP, et al. Leukemia. 2023 Jun;37(6):1186-1190. doi: 10.1038/s41375-023-01890-4.
Lindblad KE, et al. Expert Rev Hematol. 2017 Aug;10(8):745-752. doi: 10.1080/17474086.2017.1346470.
Banerjee T, et al. Blood Rev. 2019 Jul;36:57-69. doi: 10.1016/j.blre.2019.04.004

MYELODYSPLASTIC NEOPLASM

A Phase II prospective trial of azacitidine in steroid-dependent or refractory systemic autoimmune/inflammatory disorders and VEXAS syndrome associated with MDS and CMML

Arsene Mekinian[1,27]✉, Lin Pierre Zhao[2,27], Sylvie Chevret[3], Kristell Desseaux[3], Laurent Pascal[4], Thibaut Comont[5], Alexandre Maria[6], Pierre Peterlin[7], Louis Terriou[8], Maud D'Aveni Piney[9], Marie-Pierre Gourin[10], Norbert Vey[11], Odile Beyne Rauzy[5], Vincent Grobost[12], Holy Bezanahary[13], Sophie Dimicoli-Salazar[14], Anne Banos[15], Stefan Wickenhauser[16], Benoit De Renzis[17], Eric Durot[18], Shanti Natarajan-Amé[19], Laurent Voillat[10], Fatiha Chermat[2], Karine Lemaire[2], Vincent Jachiet[1], Chantal Himberlin[18], Sylvain Thépot[20], Jose Miguel Torregrosa Diaz[21], Laurent Frenzel[22], Emmanuel Gyan[23], Guillaume Denis[24], Pierre Hirsch[25], Olivier Kosmider[26], Lionel Ades[2], Olivier Fain[1] and Pierre Fenaux[2]

Leukemia (2022) 36:2739–2742; https://doi.org/10.1038/s41375-022-01698-8

Prospective open-label single-arm multicenter phase II study of azacytidine in inflammatory MDS

Azacytidine for inflammatory MDS – phase II study

Eligibility criteria:
(1) age ≥18 years,
(2) IPSS-R **intermediate 2 or high**, or IPSS-R **low or intermediate-1 with significant cytopenia**
(3) SAID defined according to usual international criteria
(4) steroid resistance or dependence of SAID - inability to decrease steroids below **15 mg/day** for at least 2 months.

Treatment protocol:

(1) AZA 75 mg/m2 daily for 7 days every 4 weeks for at least **six cycles**

(2) **Prednisone** 1 mg/kg for 1 month, then tapering over 6 months

1

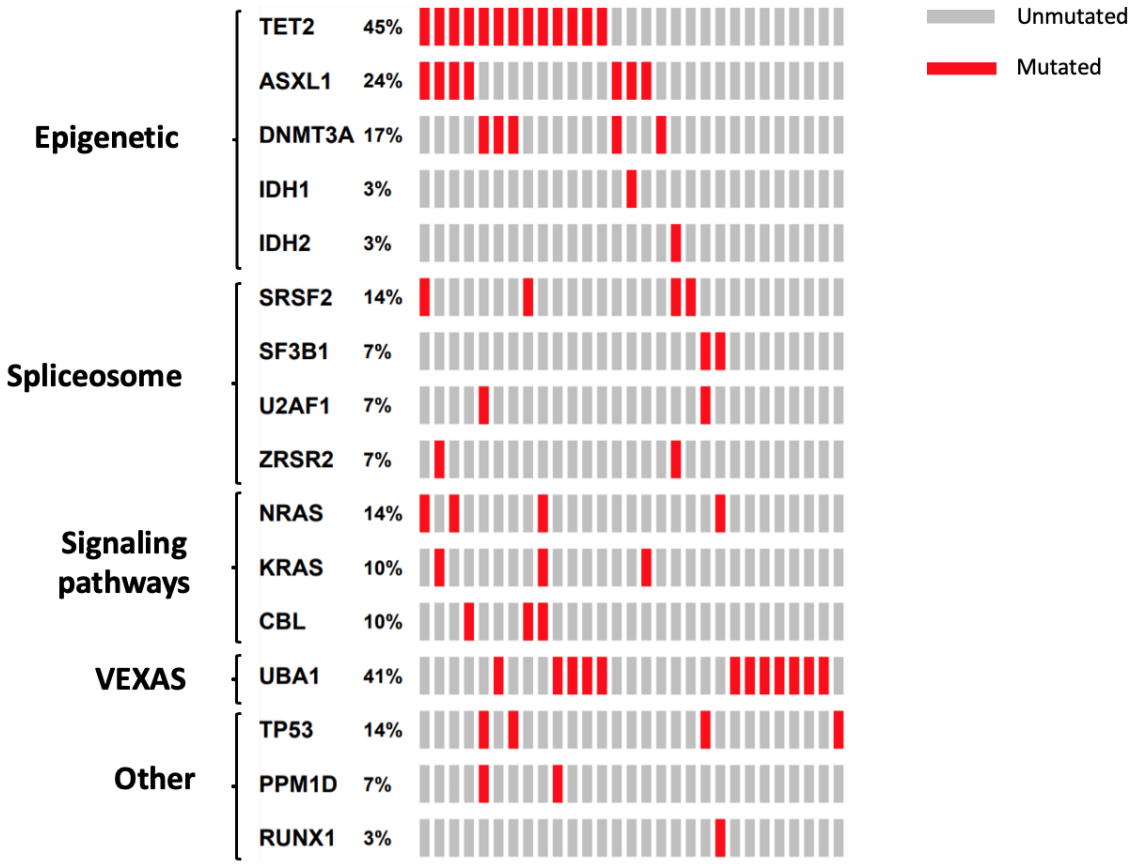
Complete (CR) + partial (PR) responses, after 6 cycles of AZA.
CR/PR – disappearance/50% improvement of both clinical signs and inflammatory/immunological parameters.

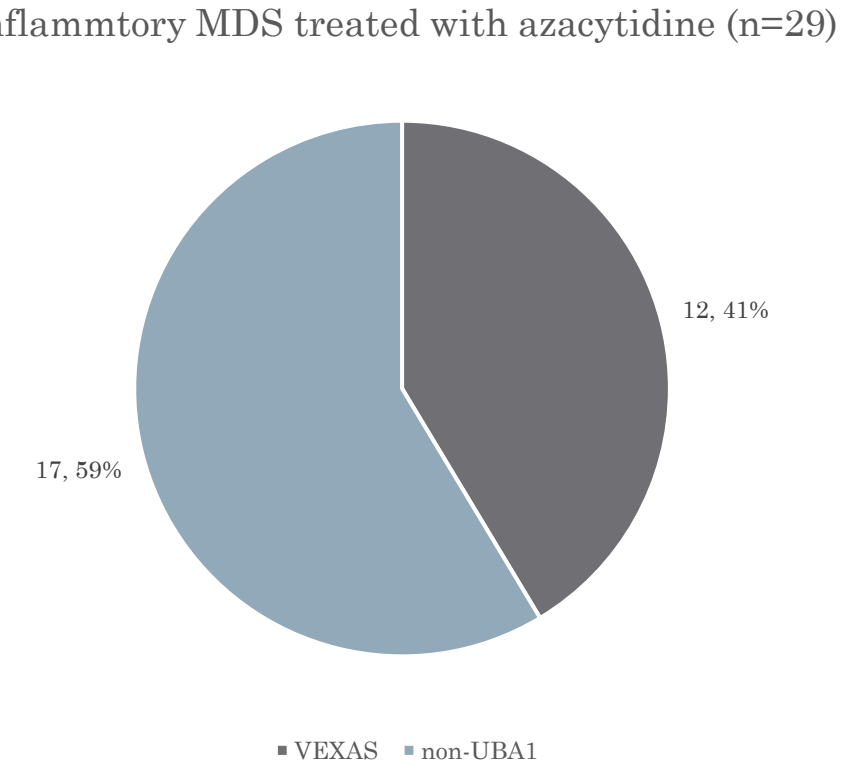
2

MDS/CMML response according to IWG 2006 criteria, response duration, safety, and overall survival.

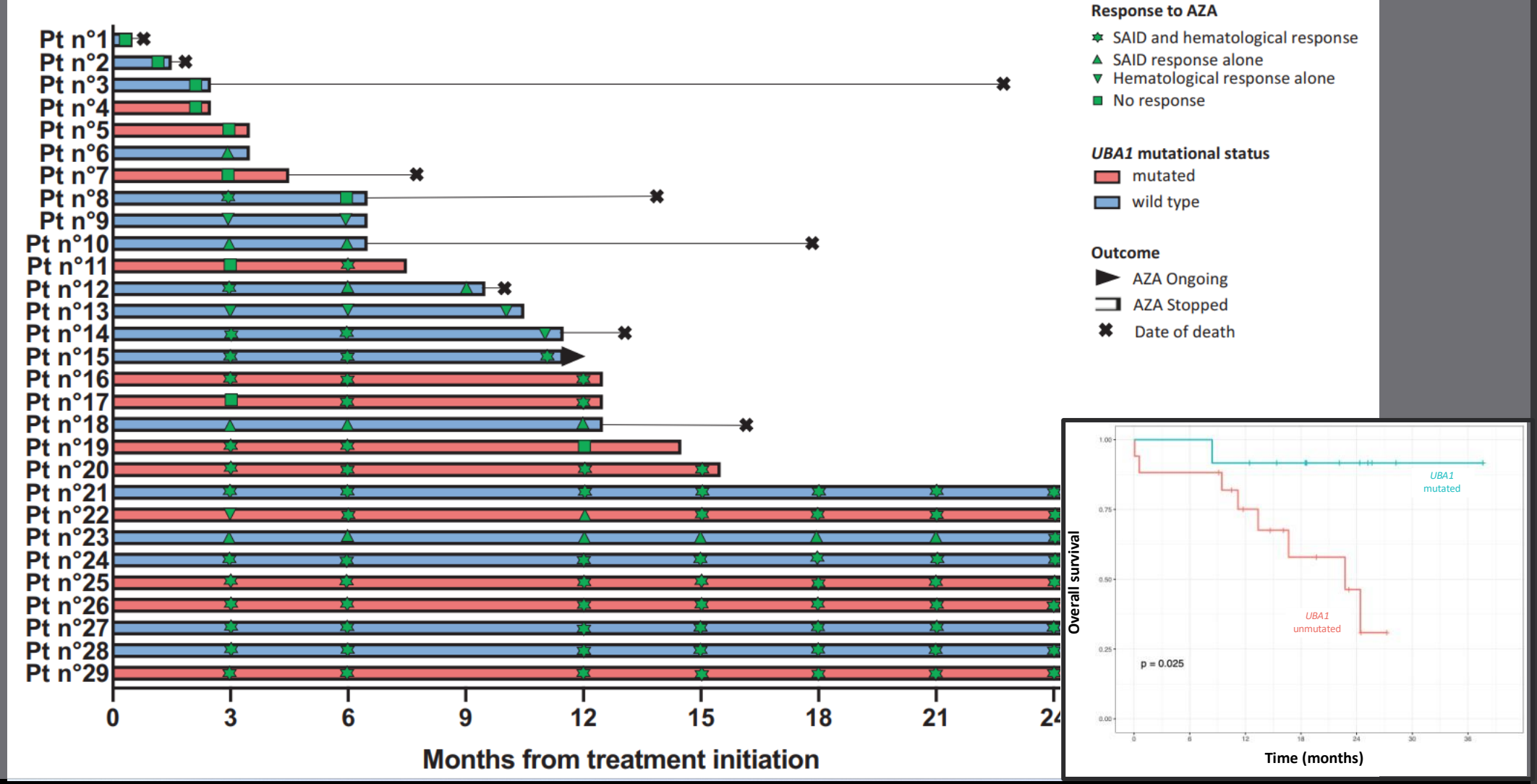
Mekinian, A., et al. *Leukemia* **36**, 2739–2742 (2022). https://doi.org/10.1038/s41375-022-01698-8

Azacytidine for inflammatory MDS – phase II study





Mekinian, A., et al. *Leukemia* **36**, 2739–2742 (2022). https://doi.org/10.1038/s41375-022-01698-8

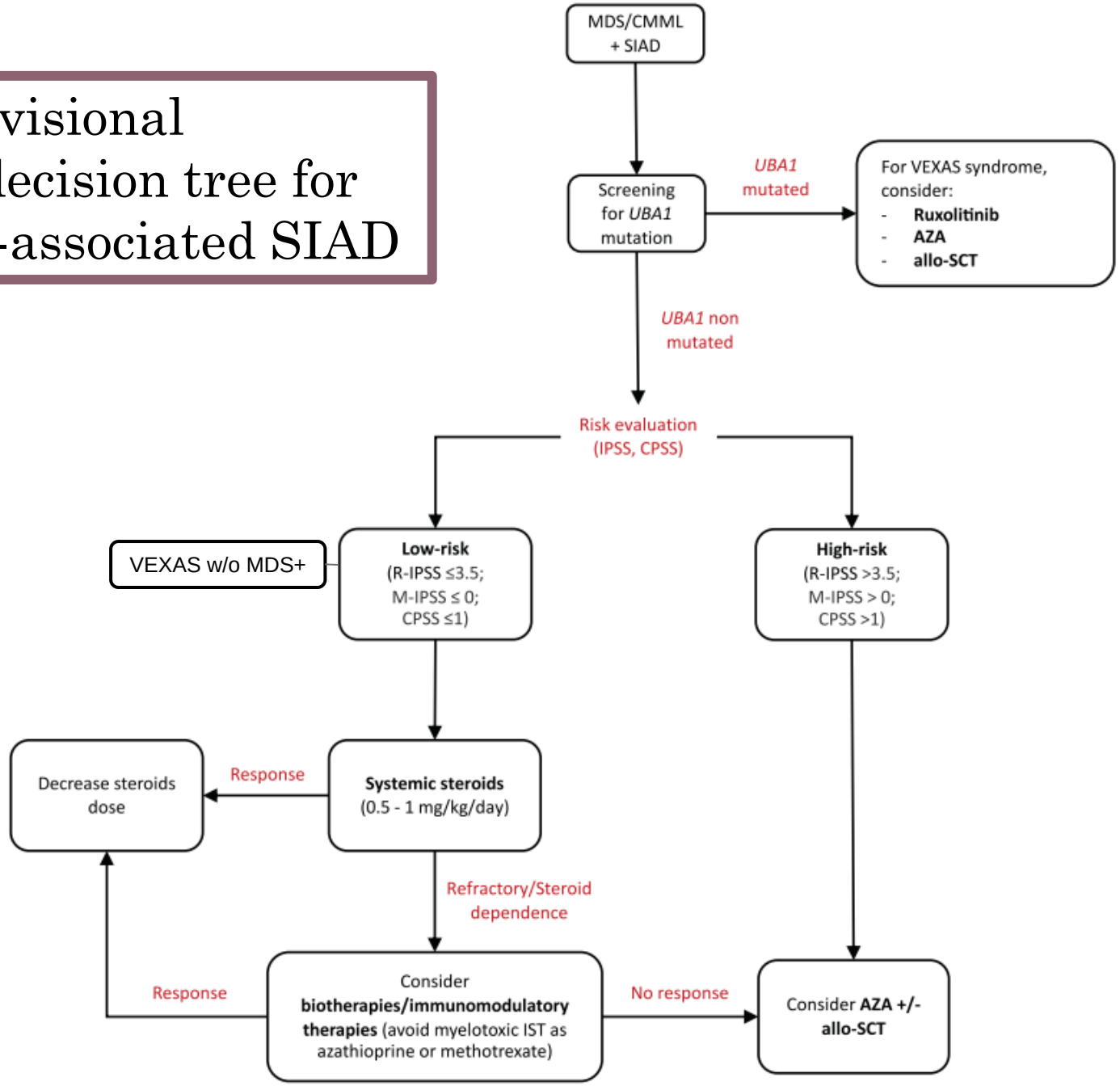


After six cycles, 19 (**66%**) had obtained **SAID response**
16 (84%) achieved steroid independence

17 (**59%**) achieved IWG 2006 **hematological response**,
of whom 15 (88%) also had SAID response

Mekinian, A., et al. *Leukemia* **36**, 2739–2742 (2022). https://doi.org/10.1038/s41375-022-01698-8

Proposed provisional therapeutic decision tree for MDS/CMML-associated SIAD



Zhao LP, et al. Leukemia. 2023 Jun;37(6):1186-1190. doi: 10.1038/s41375-023-01890-4.

VEXAS registry

VEXAS in Israel

The Israeli VEXAS registry

We have a **rare opportunity** to study a “new” disease.
The unmet need in VEXAS is vast

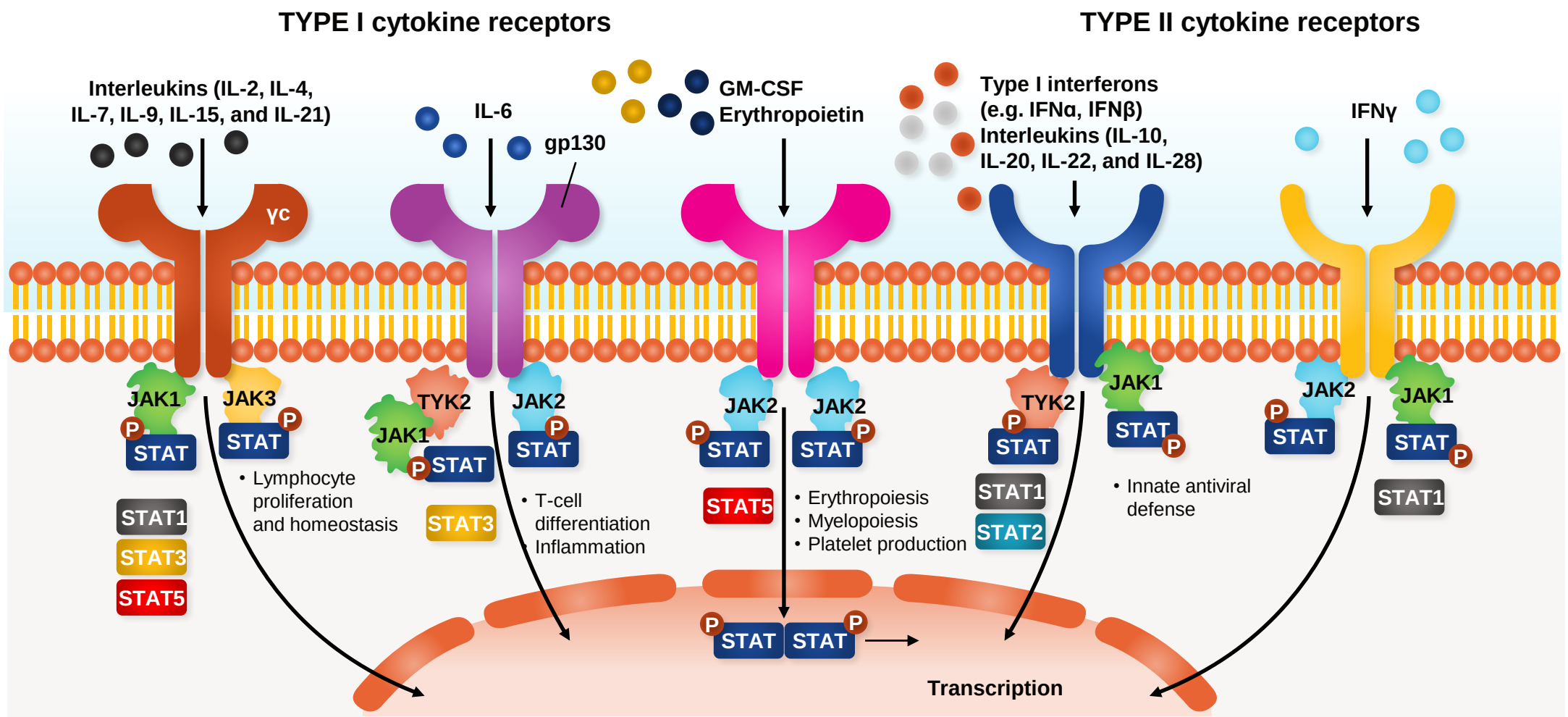
This is an **Israeli Society of Rheumatology** lead collaboration of Israeli medical centers **across disciplines**; **Hematology**, dermatology, ophthalmology, etc.

A **prospective registry** of genetically diagnosed VEXAS patients

Collaborating centers:
Tel Aviv Sourasky
Sheba Tel Hashomer
Beilinson
Haddasah
HaEmek
Soroka
Meir

JAK Inhibitors in Rheumatology

JAKi work across multiple pro-inflammatory JAK–STAT cytokine signalling pathways



1. Westhovens R et al. Ann Rheum Dis 2017;76:998–1008;
2. Winthrop KL et al. Nat Rev Rheumatol 2017;13:234–243

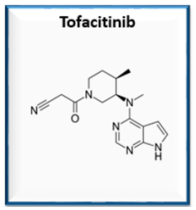
JAK Inhibition in Rheumatology

Indications

Tofacitinib	Baricitinib	Upadacitinib
RA, PsA, PsO, **AS**, UC, COVID-19	**RA**, alopecia areata, COVID-19	**RA, PsA, AxSpA**, UC, atopic dermatitis

Main Ligands Dependent on the JAK Activation Pathway and Adverse Effects That Can Be Expected When Blocking These Enzymes

	Ligands	Expected ("On-Target") Adverse Effects
JAK1	IL-2, IL-4, IL-6, IL-7, IL-9, IL-11, IL-10, IL-15, IFN-α, IFN-β, IFN-γ	Immune suppression, hyperlipidemia
JAK2	EPO, TPO, GM-CSF, IL-3, IL-5, IFN-γ	Anemia, neutropenia, thrombocytopenia
JAK3	IL-2, IL-4, IL-7, IL-9, IL-15	Immune suppression
TYK2	IFN-α, IFN-β, IFN-γ, IL-12	Immune suppression
SYK	Immunoglobulins	Immune suppression

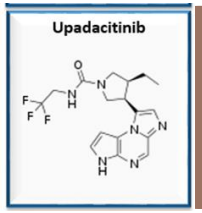


TOFA

- Pan-JAK inhibition
- Dose: 5 mg BID

BARI

- JAK 2,3 inhibition
- Dose: 2/4 mg OD



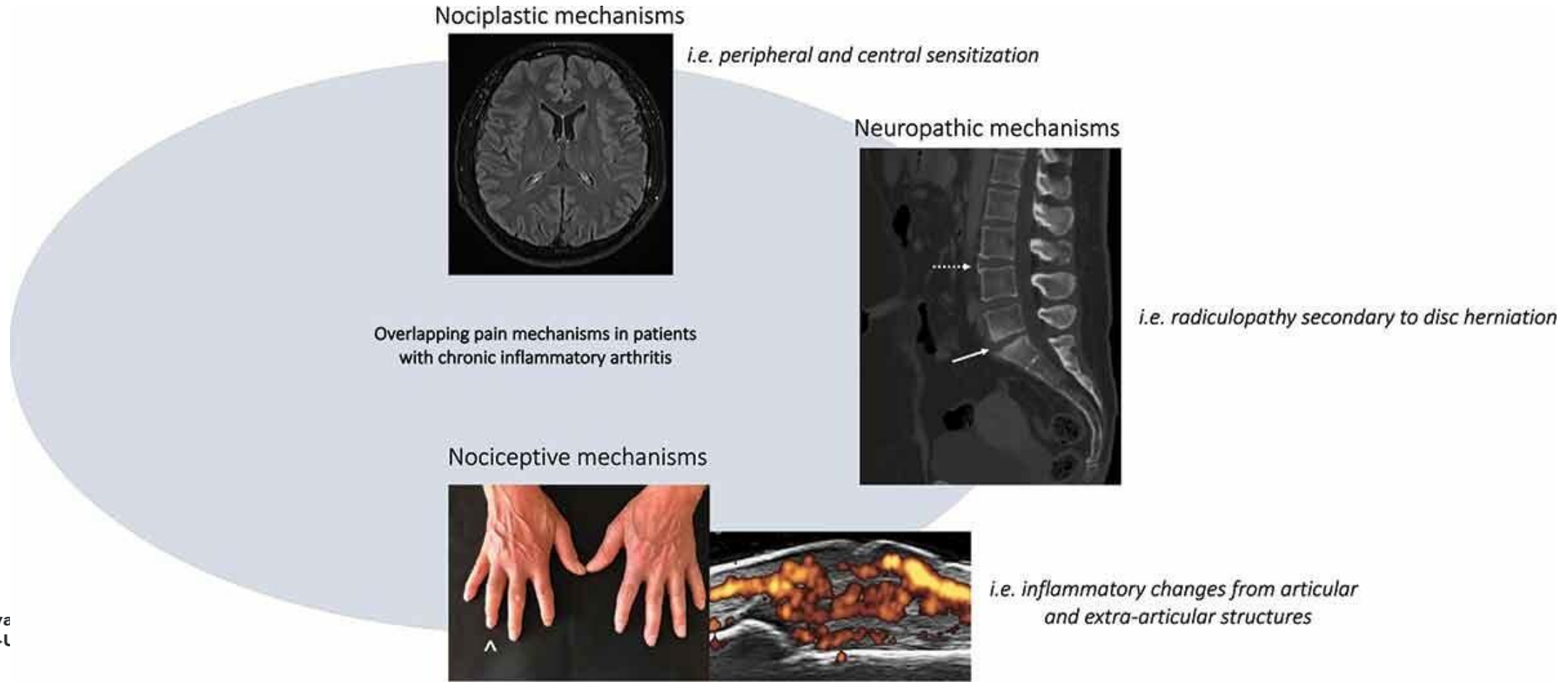
UPA

- JAK 1,3 inhibition
- Dose: 15 mg OD

Off label: dermatomyositis, SLE, other CTDs, interferonopathies (IFN-mediated autoinflammatory diseases)

Hochberg's Rheumatology, 8th ed.; UpToDate
This slide reflects my professional experience

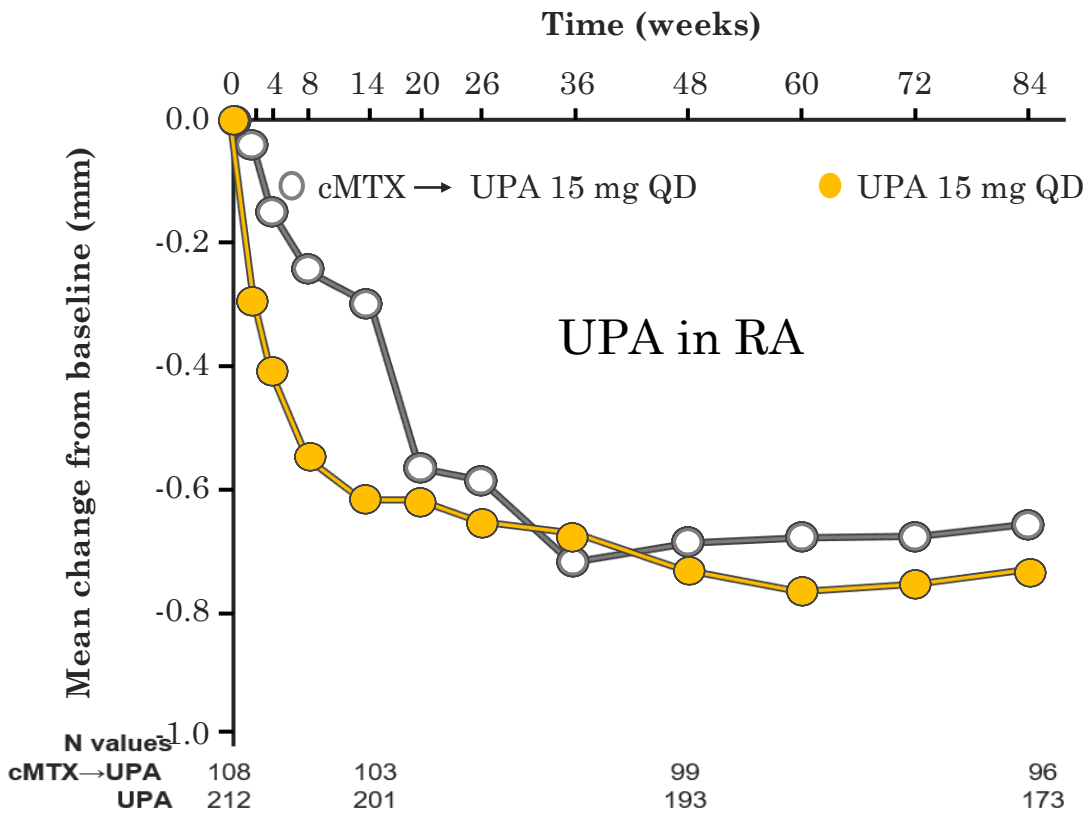
JAKi relieve PAIN fast



Smolen JS et al. EULAR 2019. Poster THU0213. Taylor, P.Cet al. *J. Clin. Med.* **2019**, *8*, 831. https://doi.org/10.3390/jcm8060831

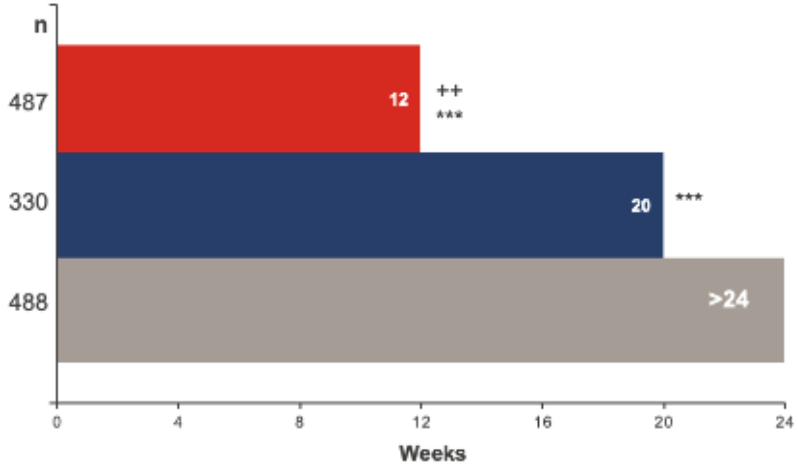
Alciati A, et al. Expert Opin Biol Ther.. doi: 10.1080/14712598.2022.2130243.
Ogdie A, et al. *RMD Open* 2020;**6:**e001042. doi: 10.1136/rmdopen-2019-001042

JAKi relieve PAIN fast

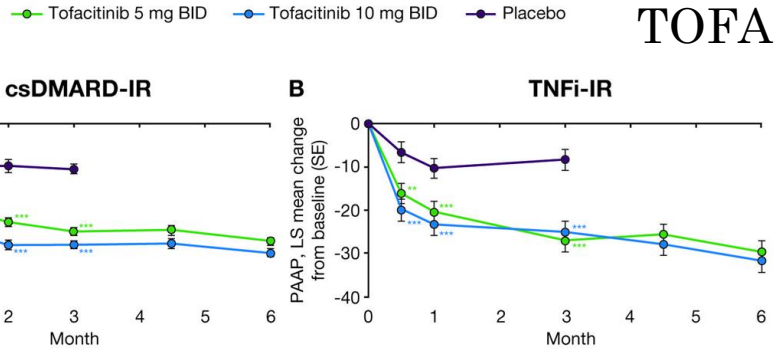


UPA in RA

Median time to>70% improvement of pain



BARI in RA



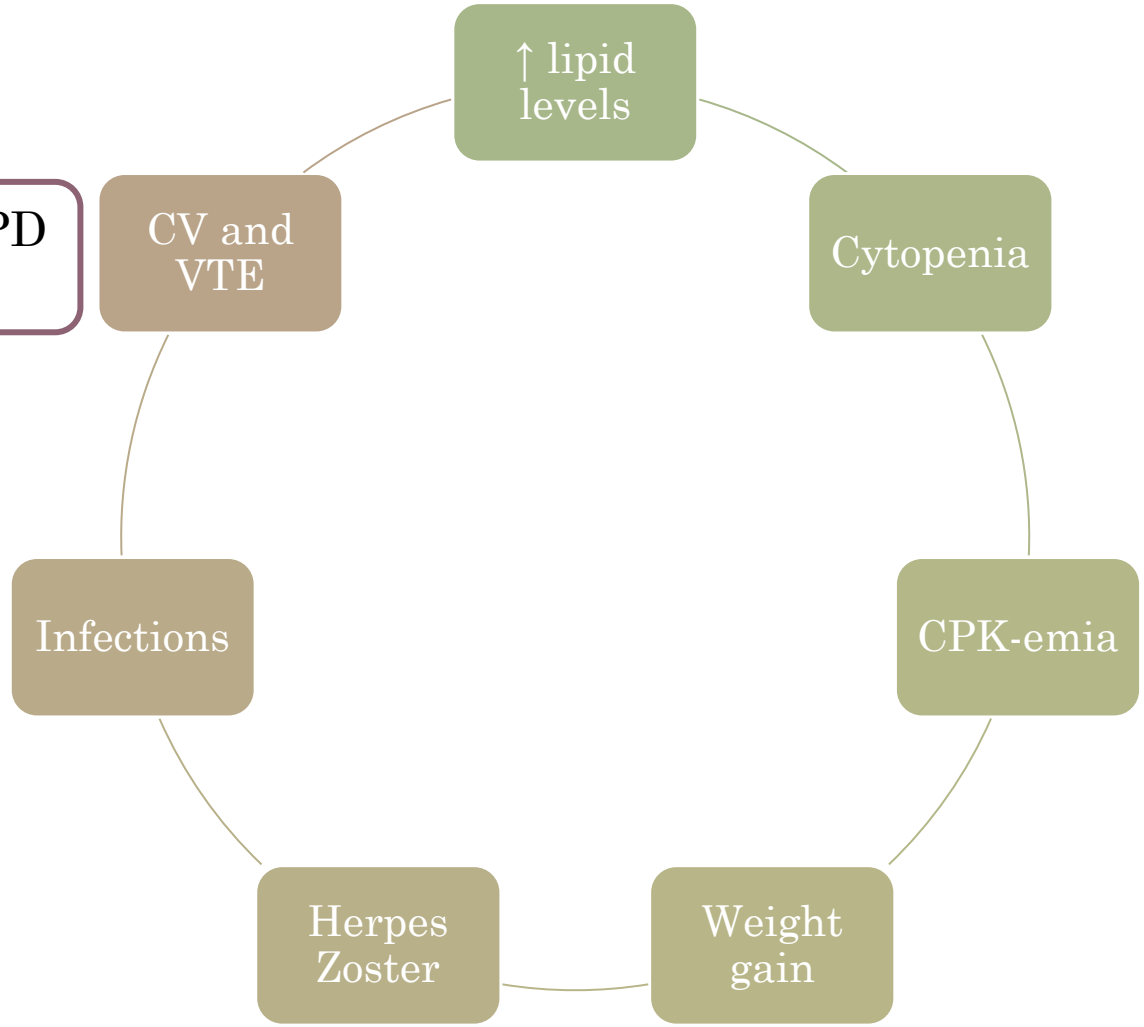
TOFA in RA

Smolen JS et al. EULAR 2019. Poster THU0213. Taylor, P.Cet al. *J. Clin. Med.* **2019**, *8*, 831. https://doi.org/10.3390/jcm8060831

Alciati A, et al. Expert Opin Biol Ther.. doi: 10.1080/14712598.2022.2130243.
Ogdie A, et al. *RMD Open* 2020;**6:**e001042. doi: 10.1136/rmdopen-2019-001042

JAKi – Adverse Effects

VTE risk decreased in MPD with ruxolitinib?



Harrington R, et al. J Inflamm Res. 2020 Sep 14;13:519-531. doi: 10.2147/JIR.S219586.

ORAL SURVEILLANCE
tofacitinib (pan-JAKi) safety study

"During drug development, increases in serum lipid levels and the incidence of cancers, including lymphoma, were observed,[14-16] which prompted the FDA to require a prospective, head-to-head safety trial comparing tofacitinib with TNF inhibitors."

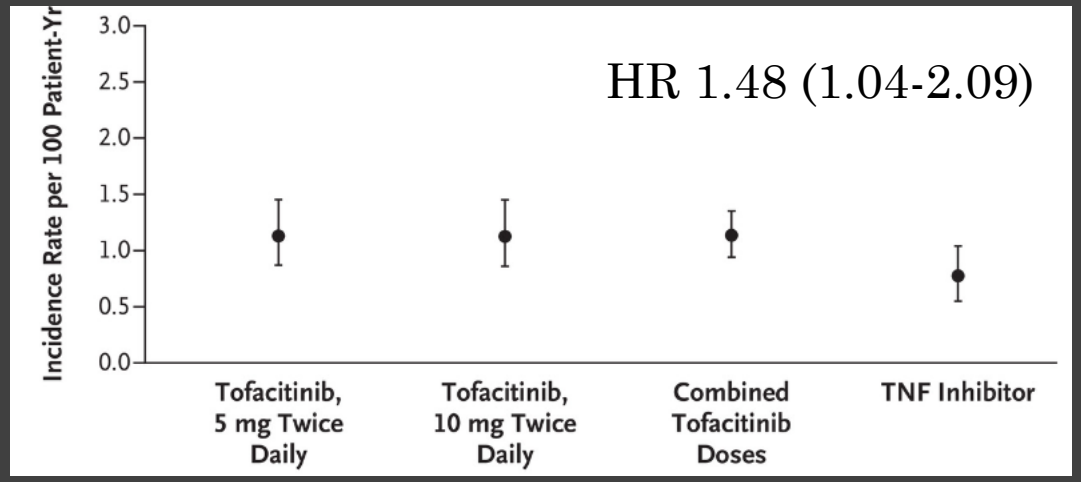
14. Charles-Schoeman C, Fleischmann R, Davignon J, et al. Potential mechanisms leading to the abnormal lipid profile in patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. Arthritis Rheumatol 2015;67:616-625.
15. Charles-Schoeman C, Gonzalez-Gay MA, Kaplan I, et al. Effects of tofacitinib and other DMARDs on lipid profiles in rheumatoid arthritis: implications for the rheumatologist. Semin Arthritis Rheum 2016;46:71-80.
16. Xeljanz (tofacitinib): highlights of prescribing information. New York: Pfizer, 2020 (package insert).

Ytterberg SR, et al. N Engl J Med. 2022 Jan 27;386(4):316-326. doi: 10.1056/NEJMoa2109927.

ORAL SURVEILLANCE

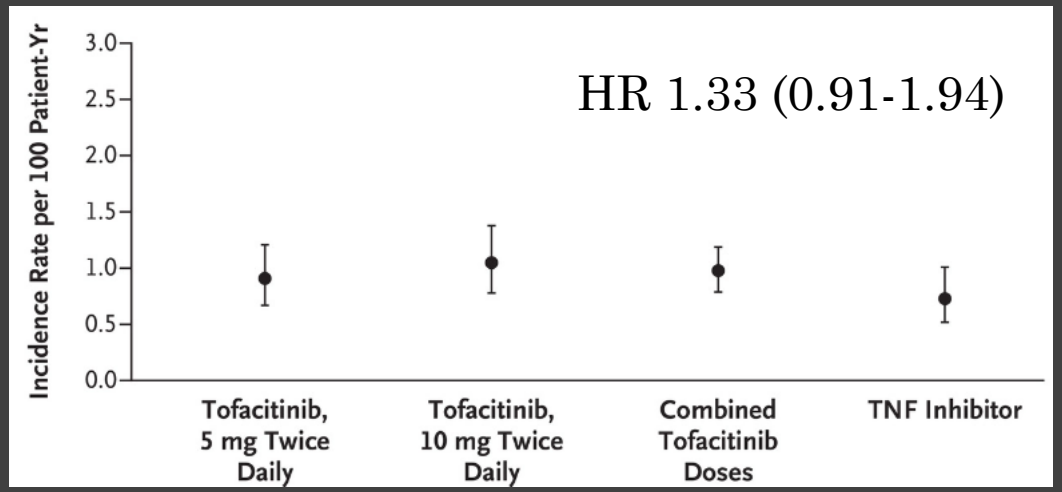
Randomized, open-label trial assessing the **safety** of **TOFA** as compared with a **TNFi** (ADA, ETA) in **RA >50 years+CV** risk factor(s) (n=**4362**)
Coprimary **end points** were **MACE** (death from CV causes, nonfatal MI, or nonfatal stroke) and **cancers**, excluding NMSC

Incidence rates of cancer, excluding NMSC



4.3% 4.1% 4.2.% 2.9%

Incidence rates of MACE

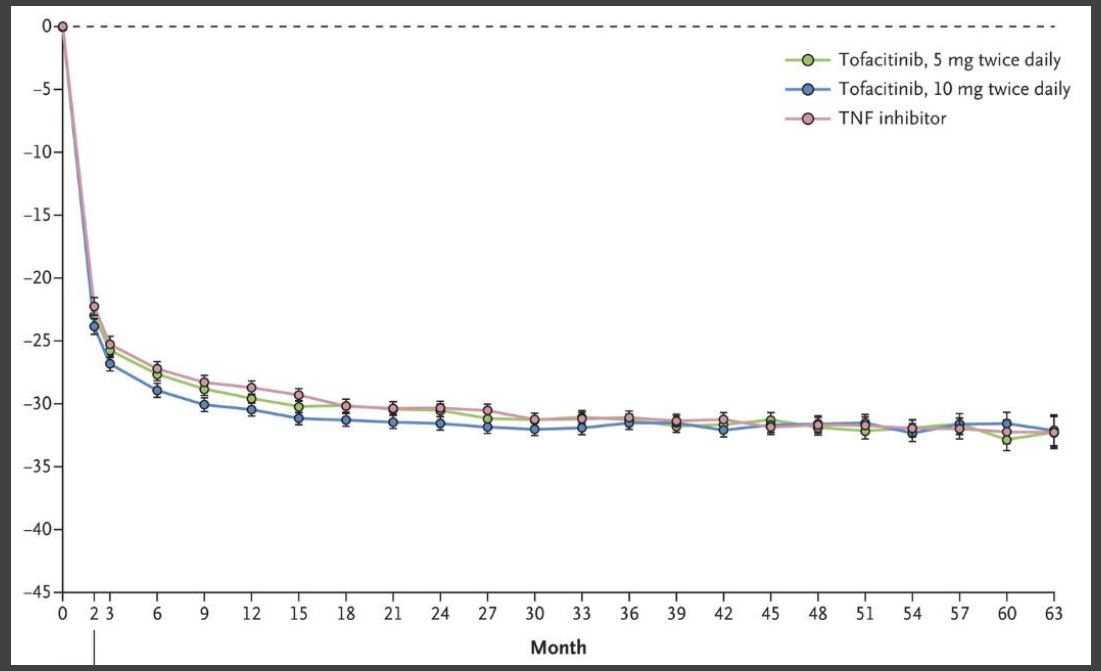


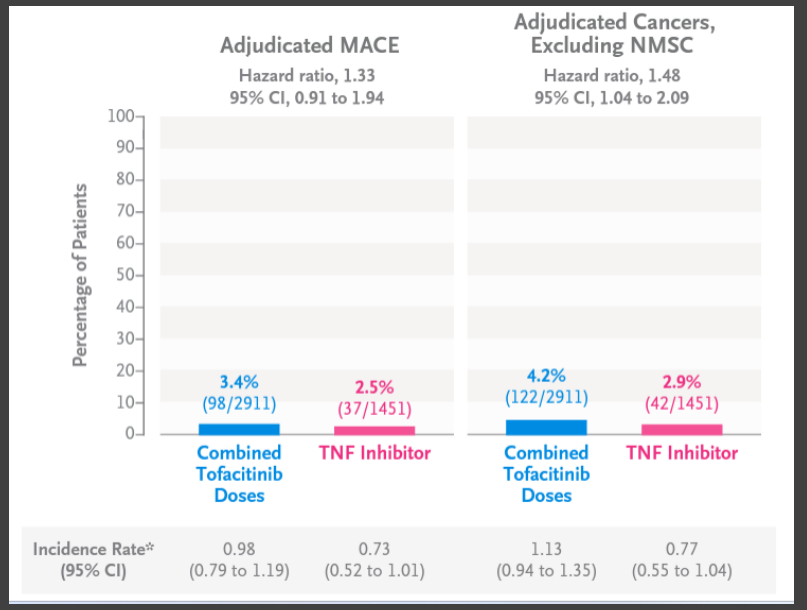
3.2% 3.5% 3.4.% 2.5%

Ytterberg SR, et al. N Engl J Med. 2022 Jan 27;386(4):316-326. doi: 10.1056/NEJMoa2109927.

ORAL SURVEILLANCE

During a follow-up of 4 years, the **incidence of MACE and cancer were higher among TOFA** recipients than among TNFi





Serious infection	HR 1.17 (0.92-1.5)
Opportunistic infection	HR 1.82 (1.07-3.09)
Herpes Zoster	HR 3.28 (2.44-4.41)
VTE	HR 1.66 (0.76-3.63)
Death from any cause	HR 1.49 (0.81-2.74)

Ytterberg SR, et al. N Engl J Med. 2022 Jan 27;386(4):316-326. doi: 10.1056/NEJMoa2109927.

Risk of VTE with tofacitinib

March 2014: Initiation

February 2019: TOFA 10 mg->5 mg

July 2020: End of study

safety monitoring board noted a **higher frequency of PE** among patients receiving TOFA 10 mg BID than those receiving a TNFi and **higher mortality** than TOFA 5 mg and TNFi

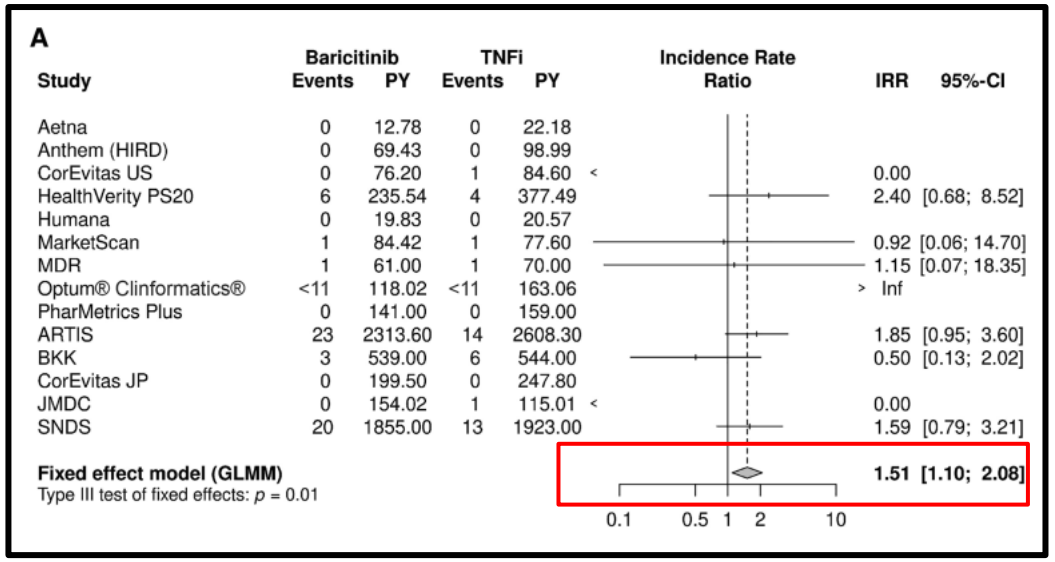
Table 2. Adverse Events (Safety Analysis Population, 28-Day On-Treatment Time).*

Event	Tofacitinib, 5 mg Twice Daily (N=1455)	Tofacitinib, 10 mg Twice Daily (N=1456)†	TNF Inhibitor (N=1451)
Adverse event — no. (%)	1333 (91.6)	1344 (92.3)	1308 (90.1)
Adjudicated pulmonary embolism — no. (%)	9 (0.6)	24 (1.6)	3 (0.2)
Hazard ratio vs. TNF inhibitor (95% CI)	2.93 (0.79–10.83)	8.26 (2.49–27.43)	Referent
Adjudicated DVT — no. (%)	11 (0.8)	15 (1.0)	7 (0.5)
Hazard ratio vs. TNF inhibitor (95% CI)	1.54 (0.60–3.97)	2.21 (0.90–5.43)	Referent
Adjudicated VTE — no. (%)	17 (1.2)	34 (2.3)	10 (0.7)
Hazard ratio vs. TNF inhibitor (95% CI)	1.66 (0.76–3.63)	3.52 (1.74–7.12)	Referent

Ytterberg SR, et al. N Engl J Med. 2022 Jan 27;386(4):316-326. doi: 10.1056/NEJMoa2109927.

Risk of VTE with baricitinib - JAK 2/3 inhibitor

During the 24-week placebo-controlled period of the baricitinib RA clinical program, **a numerical imbalance of VTE between baricitinib 4 mg (6 of 997 patients) and placebo (0 of 1070 patients)** suggested the potential for an increased risk of VTE in baricitinib-treated patients



Meta-analysis of **14 international** registries

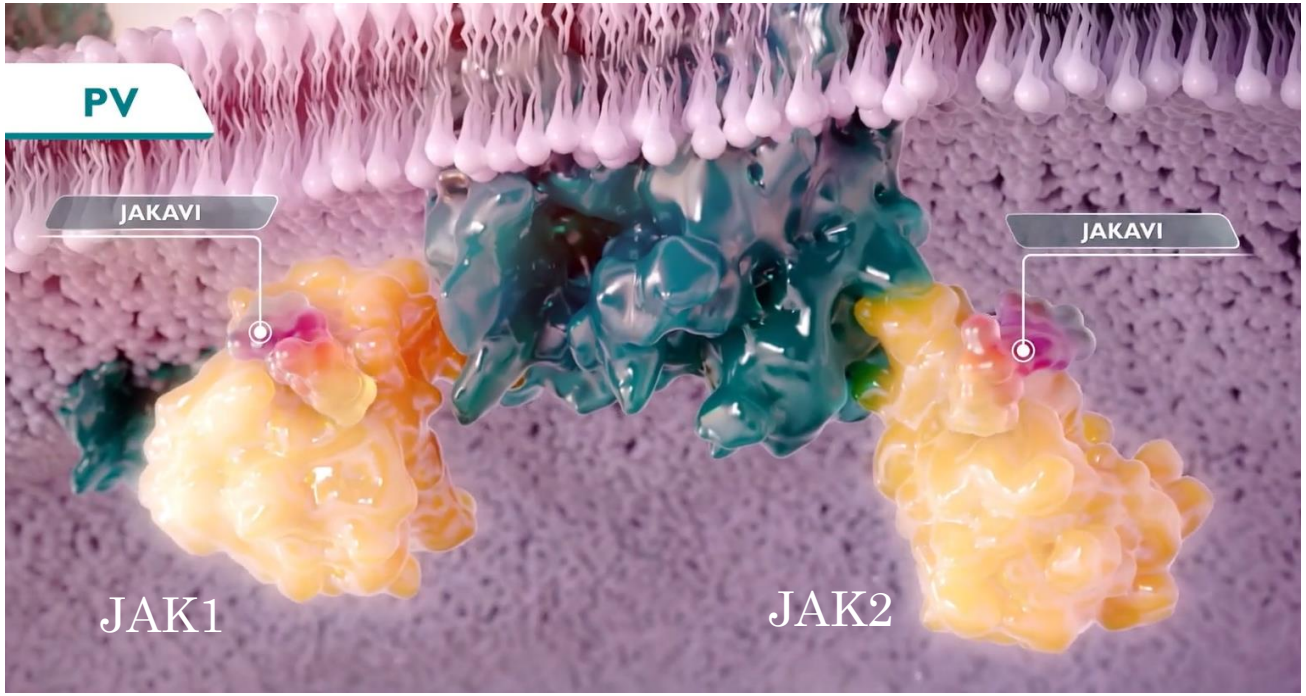
7606 BARI vs. 7606 TNFi matched controls

VTEs: **56 BARI vs. 41 TNFi**

Conclusion: **patients treated with BARI had a 1.5 times higher risk of VTE than patients treated with TNFi**

Salinas CA, et al. 2023 Feb;10(1):201-223. doi: 10.1007/s40744-022-00505-1.

Ruxolitinib – JAK 1/2 inhibitor



Indications: myelofibrosis, polycythemia vera, GVHD, atopic dermatitis, vitiligo
Off-label: alopecia areata, interferonopathies, HLH, VEXAS

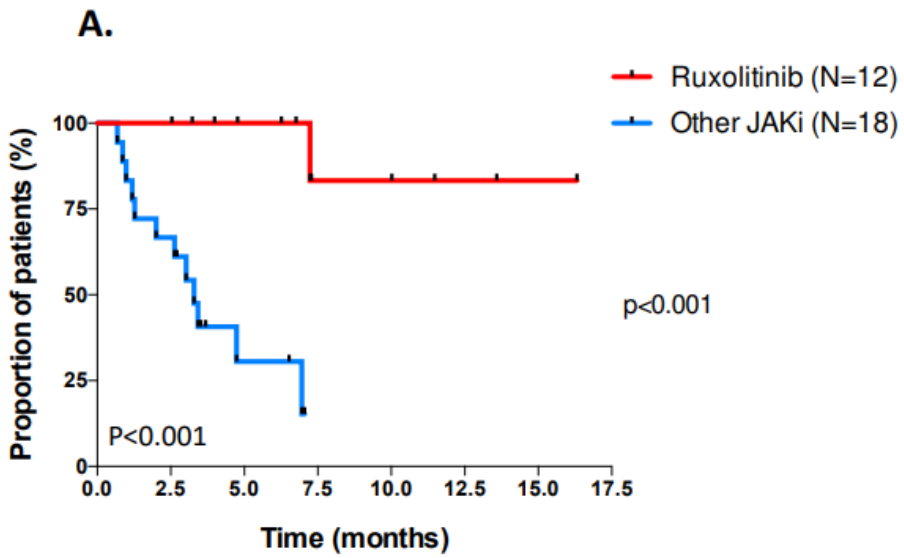
From https://www.jakavi.com/polycythaemia-vera/mechanismofaction

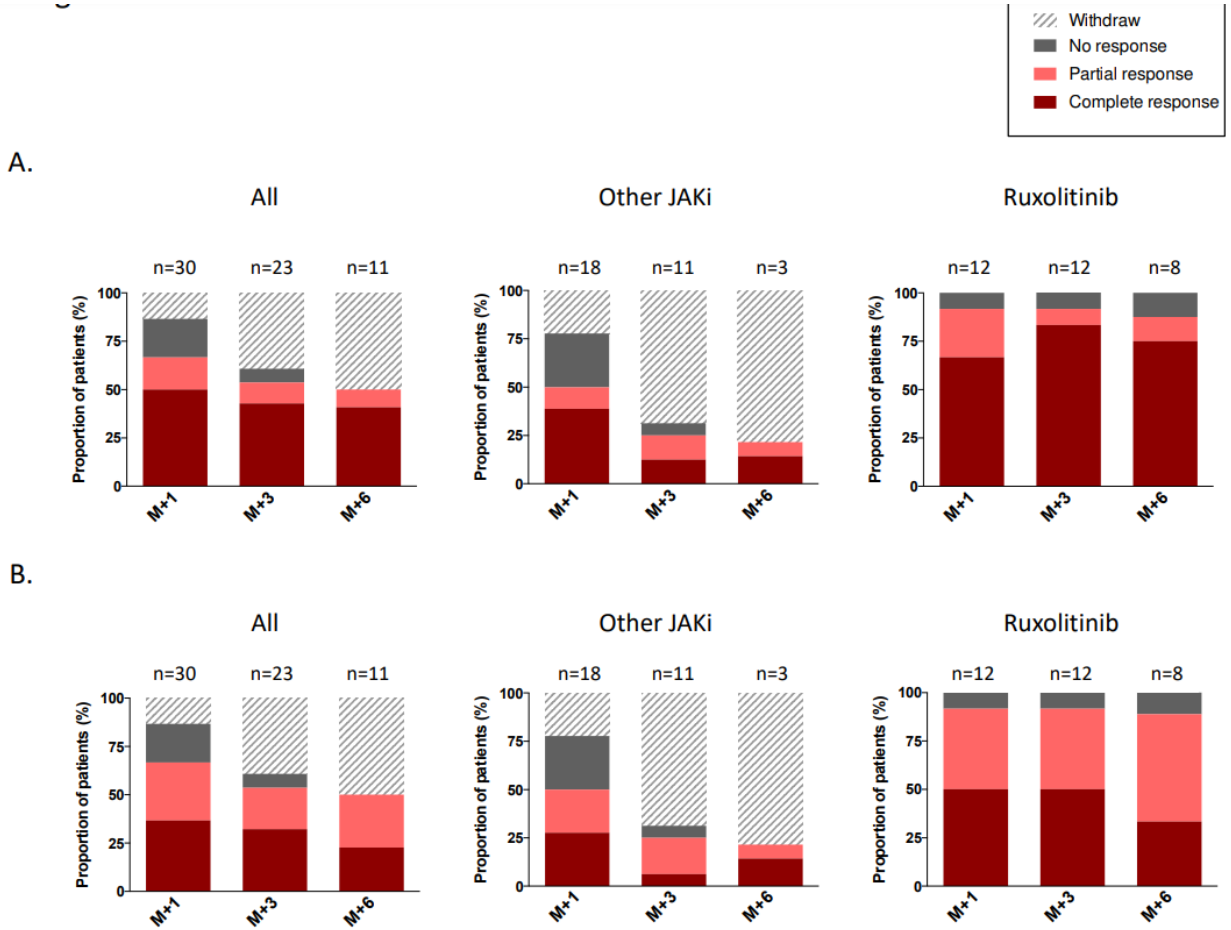
Ruxolitinib in VEXAS

30 patients,
International multicenter

14 with MDS/CMML

After 1 month 50% had a response





Heiblig M, et al. Blood. 2022 May 24:blood. doi: 10.1182/blood.2022016642.

Does Ruxolitinib prevent thrombosis in patients with Polycythemia Vera?

Systematic Review
Articles/EHA/ASH/Additional sources

80 records screened

Metanalysis

15 records included

N= 4
Randomized Clinical Trials included

663 patients

331 Ruxolitinib

vs

332 Best Avalaible Therapy

Median F-up (min-max): 1 year (0.3 -2.6)

Endpoint: thrombosis		
N (%)	16 (4.8%)	22 (6.6%)
Incidence pts-year (95% CI)	3.09% (1.22-4.96)	5. 51 % (3.72-7.30)
RR	**0.56 (p=0.098)**	

Even though not formally confirmed, results suggest an efficacy of Ruxolitinib to prevent thrombosis in patients with PV.

Limitations of this study:
- scarcity of high quality data
- low number of events
- short follow-up duration.

Future clinical trials to confirm that Ruxolitinib has an antithrombotic action are warranted.

(1) RESPONSE
(2) RESPONSE-2
(3) RELIEF
(4) MAJIC

A systematic review and Meta-analysis

The number of thrombotic events reported with ruxolitinib was consistently lower than that with BAT, but, globally, the difference did not reach significance ($P = .098$).

Masciulli A, et al. Blood Adv. 2020. doi: 10.1182/bloodadvances.2019001158.

Original Article

Real-world analysis of main clinical outcomes in patients with polycythemia vera treated with ruxolitinib or best available therapy after developing resistance/intolerance to hydroxyurea

Alberto Alvarez-Larrán, MD [1]; Marta Garrote, MD[1]; Francisca Ferrer-Marín, MD[2]; Manuel Pérez-Encinas, MD[3];

- Retrospective, real-world analysis
- 377 patients from the Spanish Registry of Polycythemia Vera
  - treatment with ruxolitinib (n = 105) or the best available therapy (BAT; n = 272)
- Patients receiving ruxolitinib had a significantly **lower rate of arterial thrombosis** than those on BAT (0.4% vs 2.3% per year; *P* = .03)
- There **were no significant differences** in the rates of **venous thrombosis** (0.8% and 1.1% for ruxolitinib and BAT, respectively; *P* = .7) and **major bleeding** (0.8% and 0.9%, respectively; *P* = .9).
- The results suggest that **ruxolitinib treatment for PV patients** with resistance/intolerance to hydroxyurea **may reduce the incidence of arterial thrombosis**

Alvarez-Larrán A et al. Cancer. 2022 Jul 1;128(13):2441-2448. doi: 10.1002/cncr.34195.

Take home messages

- Myeloid inflammation can be **an inherent manifestation of MDS (or MPD) clones**
- In most inflammatory MDS non-VEXAS cases, inflammatory manifestations **will not affect the prognosis**
- In VEXAS, as in other inflammatory MDS cases (and in the future maybe also inflammatory CH cases?) – **hematologists should be a central part of the medical team**
  - Thought should be given to **treating the myeloid clone and not the inflammatory symptomatology**
- JAK inhibition **adverse event profile may differ** according to specific JAK inhibited and/or disease treated

TEL-AVIV SOURASKY MEDICAL CENTER
ICHILOV
MEDICAL EXCELLENCE AND COMPASSIONATE CARE

Acknowledgements

- Professor Ori Elkayam
- Professor Daphna Paran
- Dr. Michael Zisapel
- Dr. Mor Levi
- VEXAS registry collaborators:
  - Prof. Merav Lidar and Dr. David Uzery, Sheba
  - Prof. Yair Molad and Dr. Ariela Dotrot, Beilenson
  - Dr. Hagit Peleg. Hadassah
  - Prof. Shai Kivity, Meir
  - Dr. Amir Bieber, HaEmek
  - Dr. Iftach Sagy, Soroka

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