

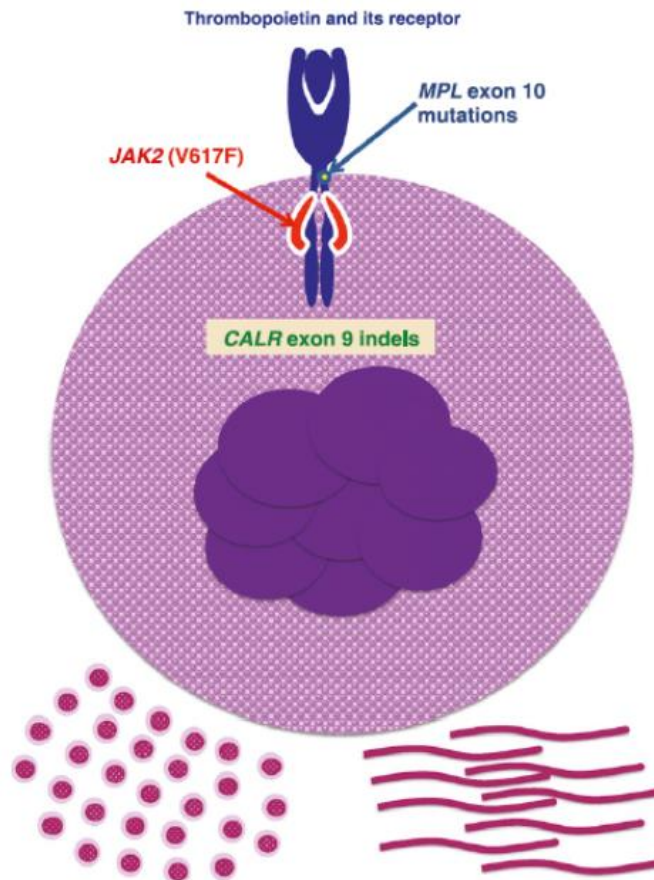
La **DIAGNOSTICA** **EMATOPATOLOGICA** nell'ERA della **MEDICINA** di **PRECISIONE**

PV-like

Giorgio Alberto Croci

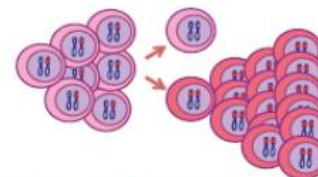
Università di Milano / Fondazione IRCCS Ca' Granda –
Ospedale Maggiore Policlinico, Milano

A Role of megakaryocytes in the pathophysiology of myeloproliferative neoplasms



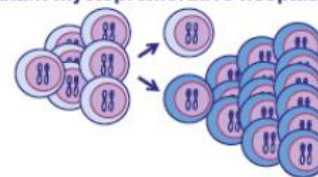
B Patterns of clonal evolution and phenotypic switch in myeloproliferative neoplasms

JAK2 (V617F)-mutant myeloproliferative neoplasms



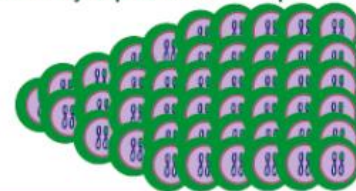
Essential thrombocythemia Polycythemia vera Myelofibrosis

MPL exon 10-mutant myeloproliferative neoplasms



Essential thrombocythemia Myelofibrosis

CALR exon 9-mutant myeloproliferative neoplasms



Essential thrombocythemia Myelofibrosis

Diagnosi MPN



pattern

dati clinico-laboratoristici

+

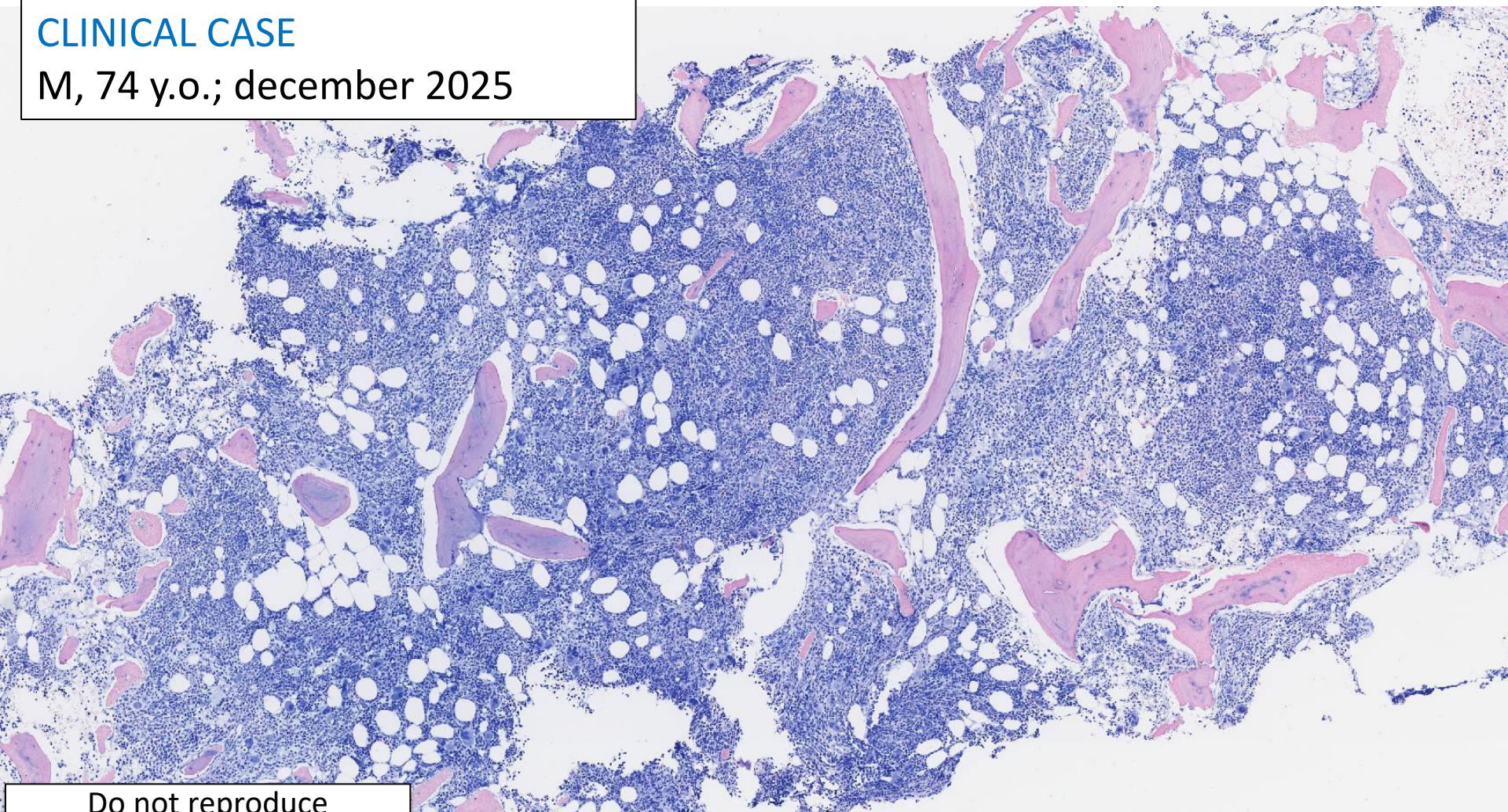
morfologia

+

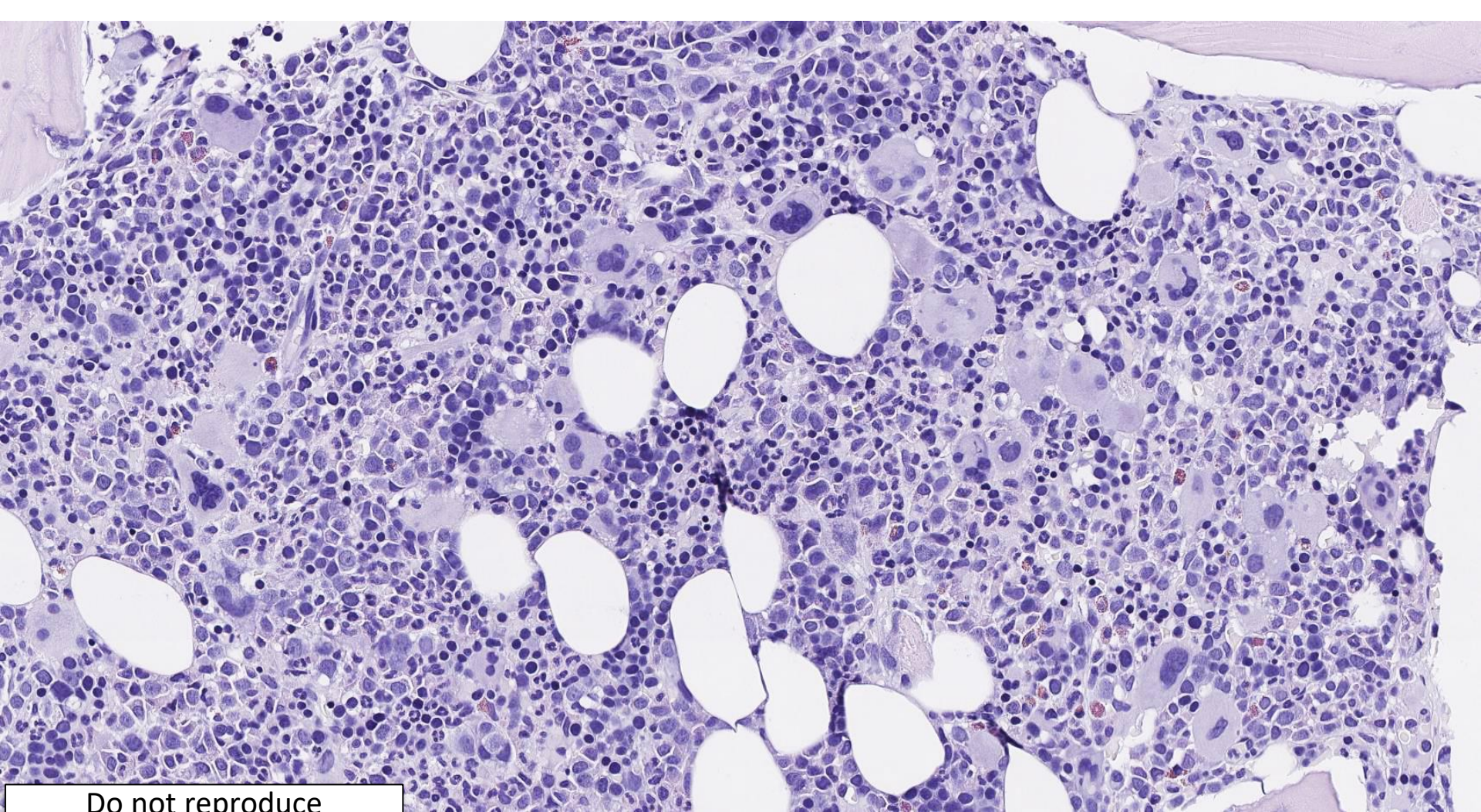
caratteristiche molecolari

CLINICAL CASE

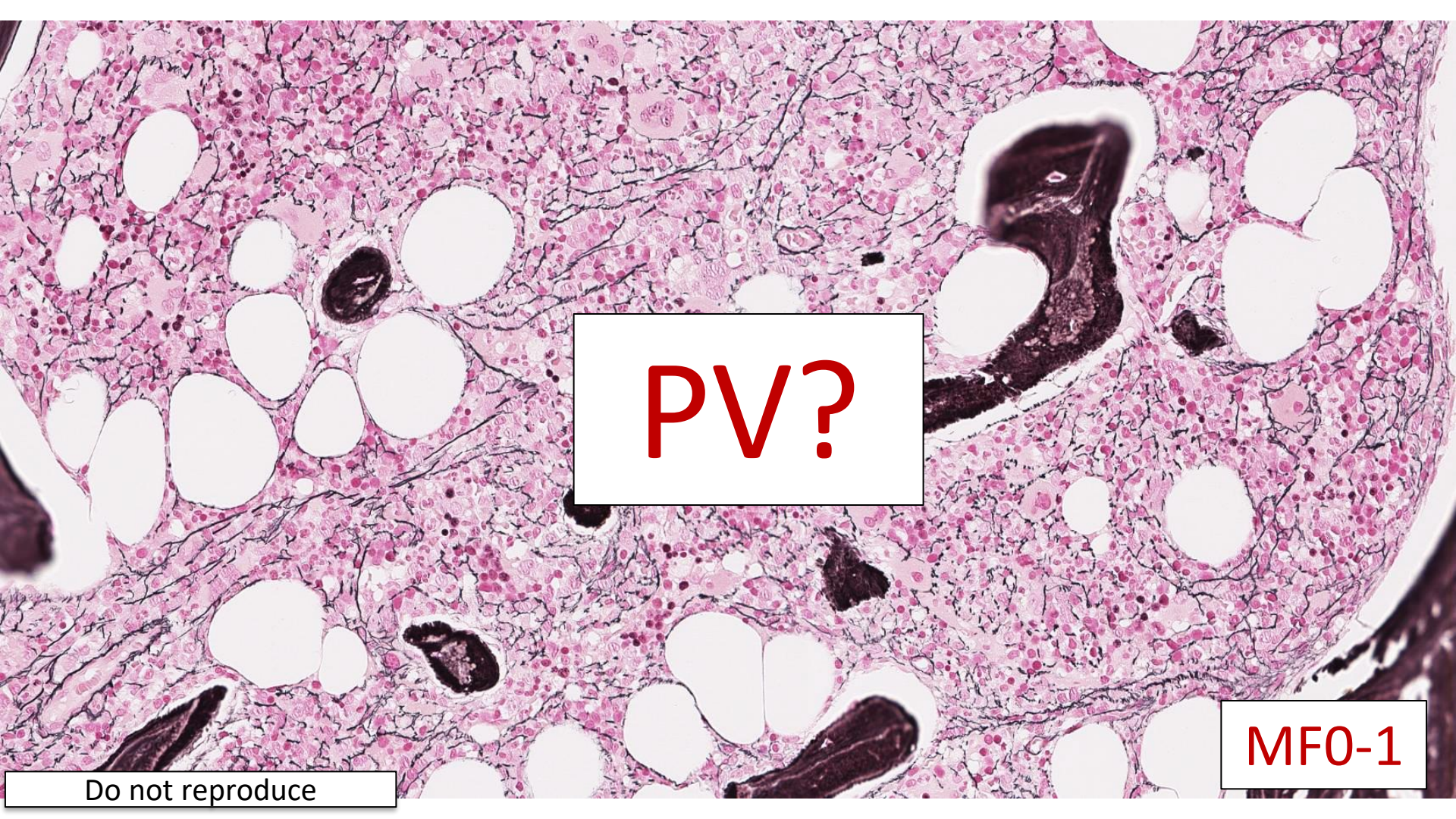
M, 74 y.o.; december 2025



Do not reproduce



Do not reproduce



PV?

Do not reproduce

MFO-1

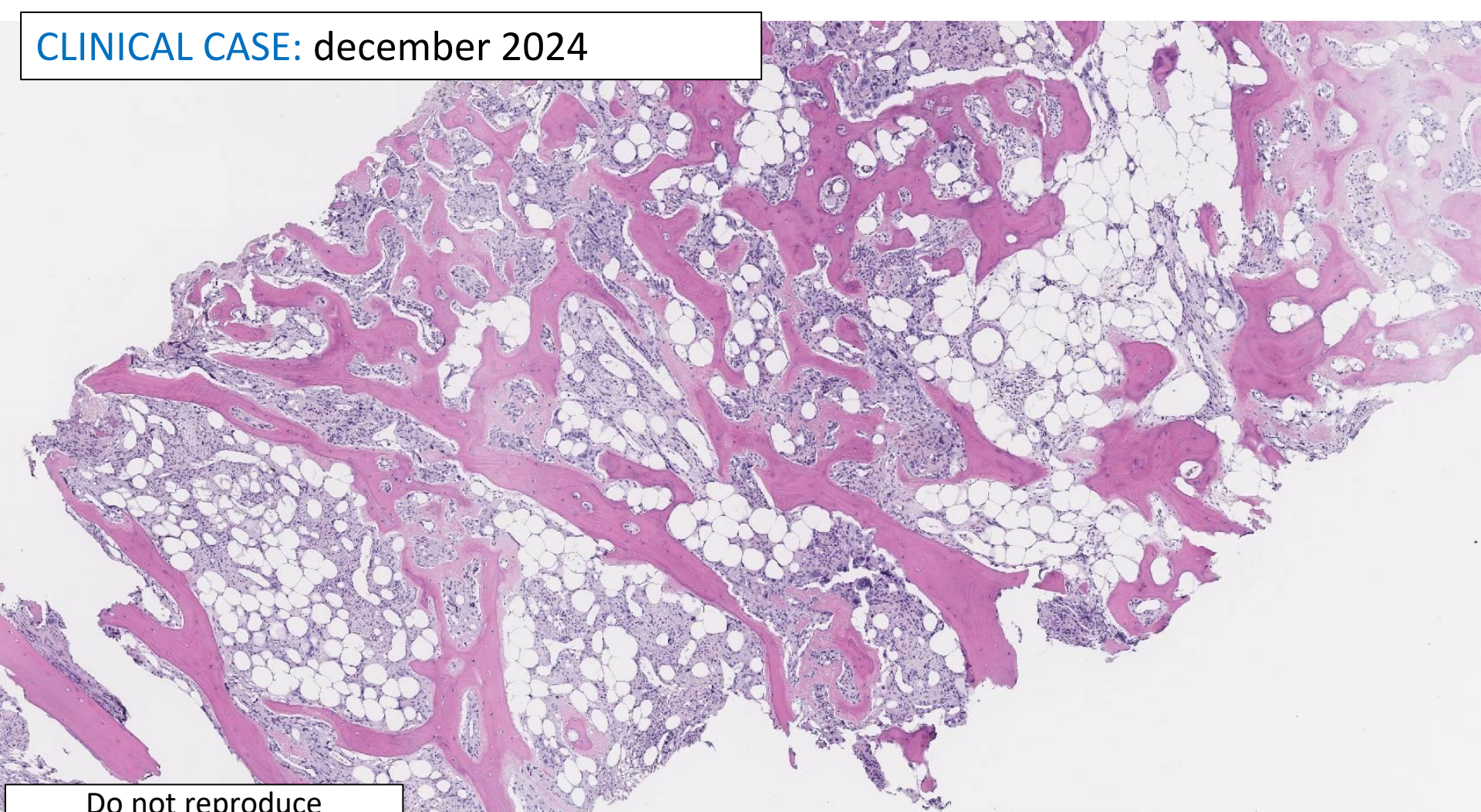
Clinical history

- **essential thrombocytemia** diagnosed in 1998;
- progression to **post-ET myelofibrosis** in 2010; detection of **type 1 CALR mutation** (+ *ASXL1*; karyotype: 46, XY)
- Since 2015, started on hydroxyurea, followed by ruxolitinib for palpable splenomegaly (2021)
- In 2024: good clinical status; Hb 11.5 g/dl, PLT 167,000/mmc, WBC 9,530/mmc; LDH 1429 U/L; palpable splenomegaly (22.9 cm largest diameter; 2,068 mL)



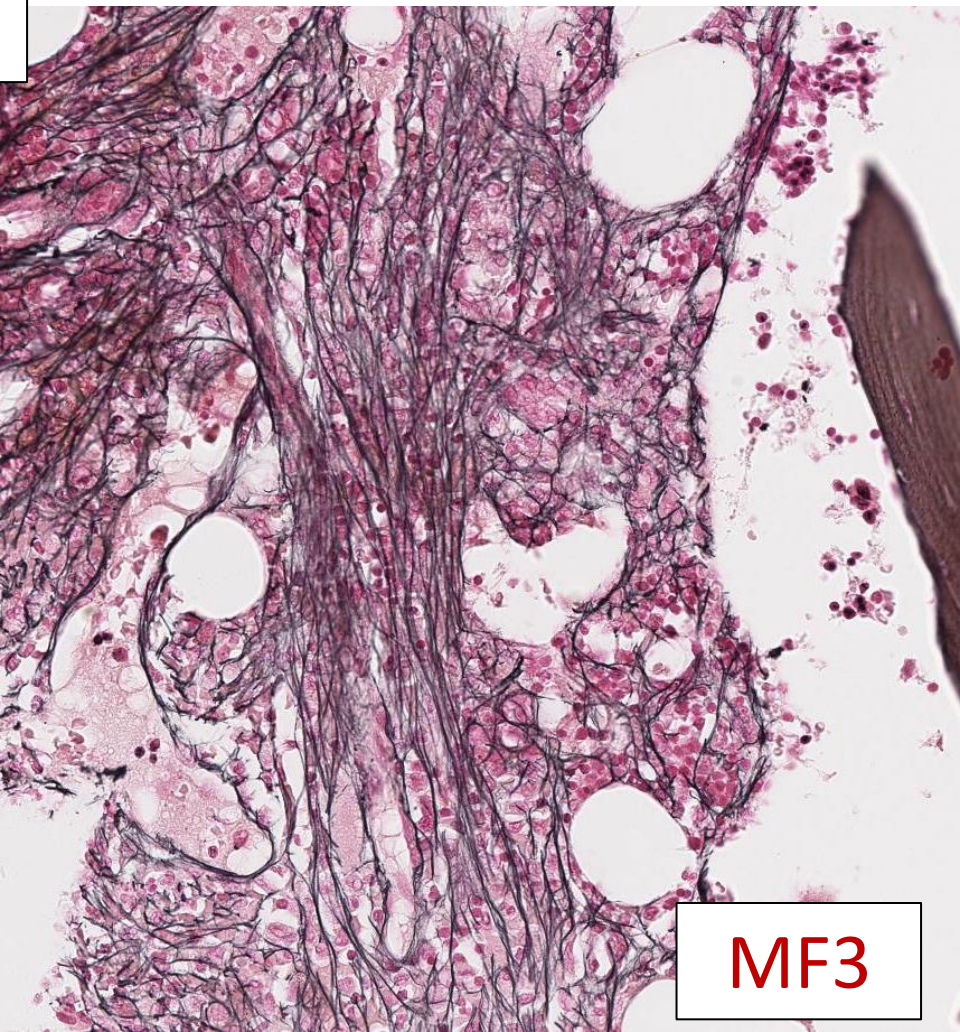
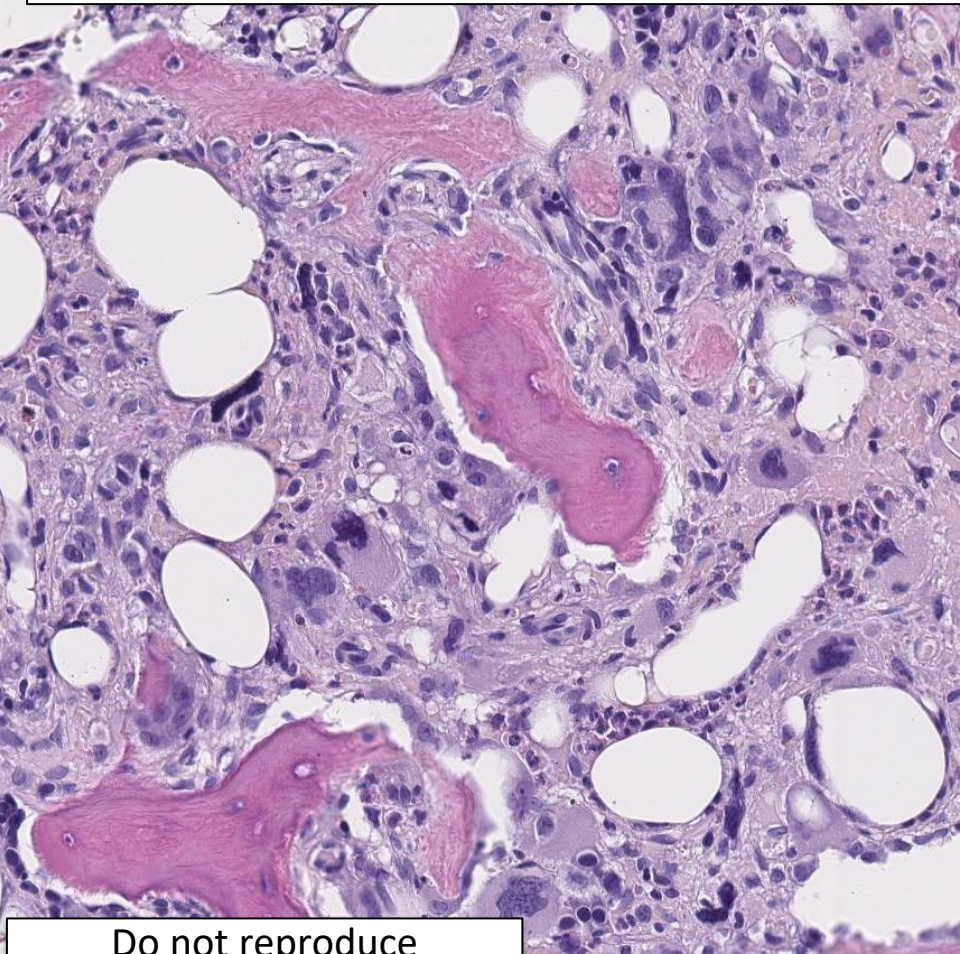
Phase I clinical trial with **anti-CALR antibody** (INCA033989)

CLINICAL CASE: december 2024



Do not reproduce

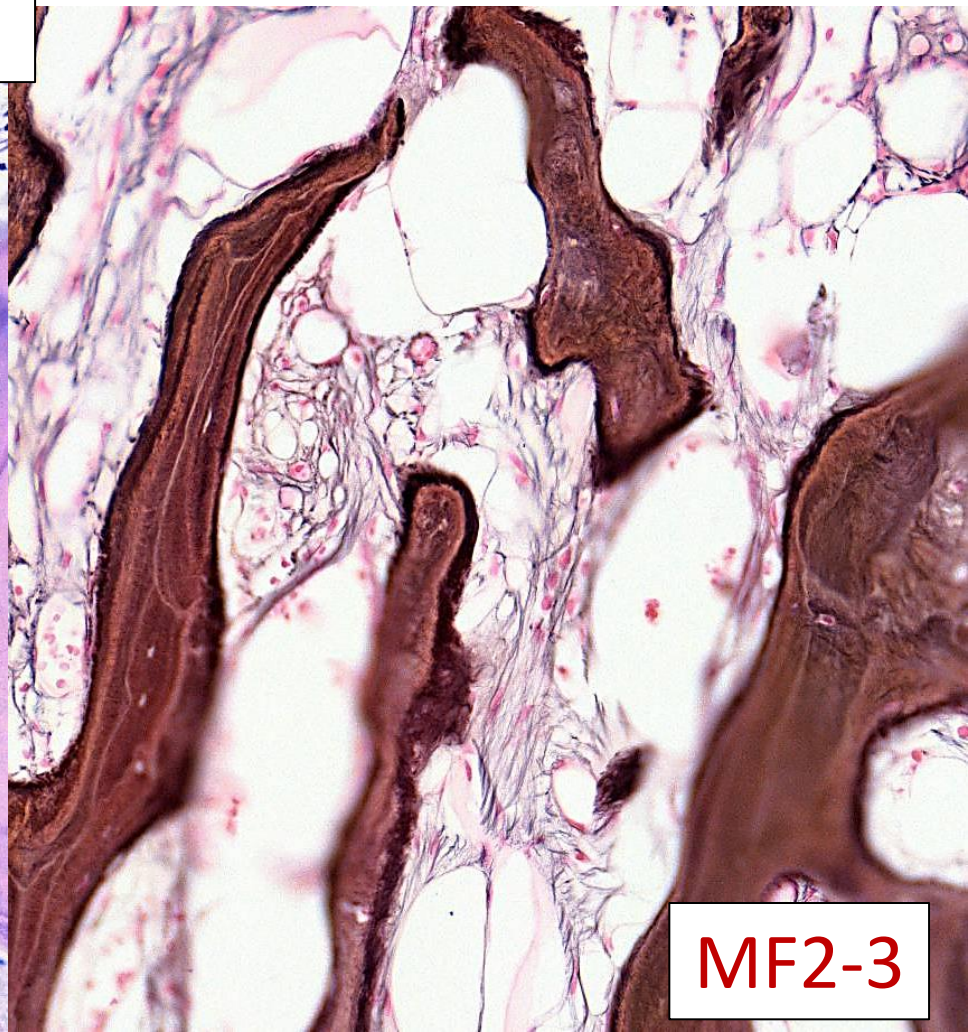
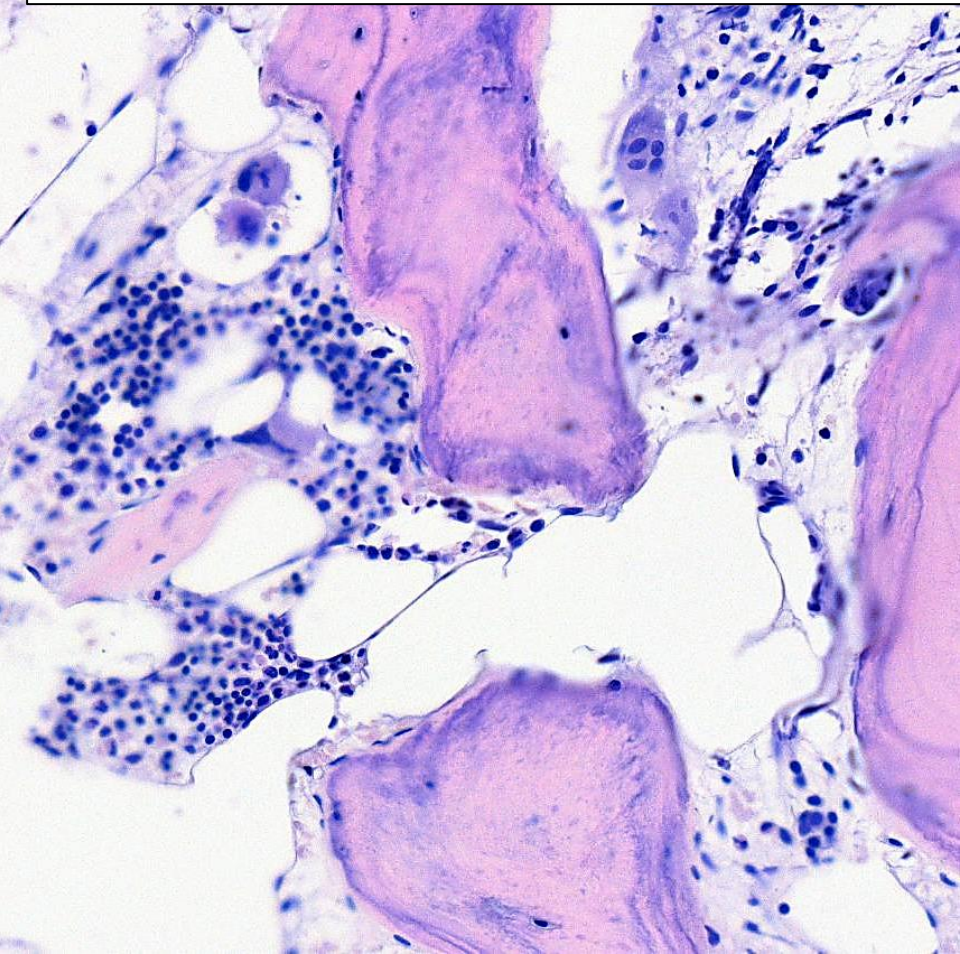
CLINICAL CASE: december 2024



Do not reproduce

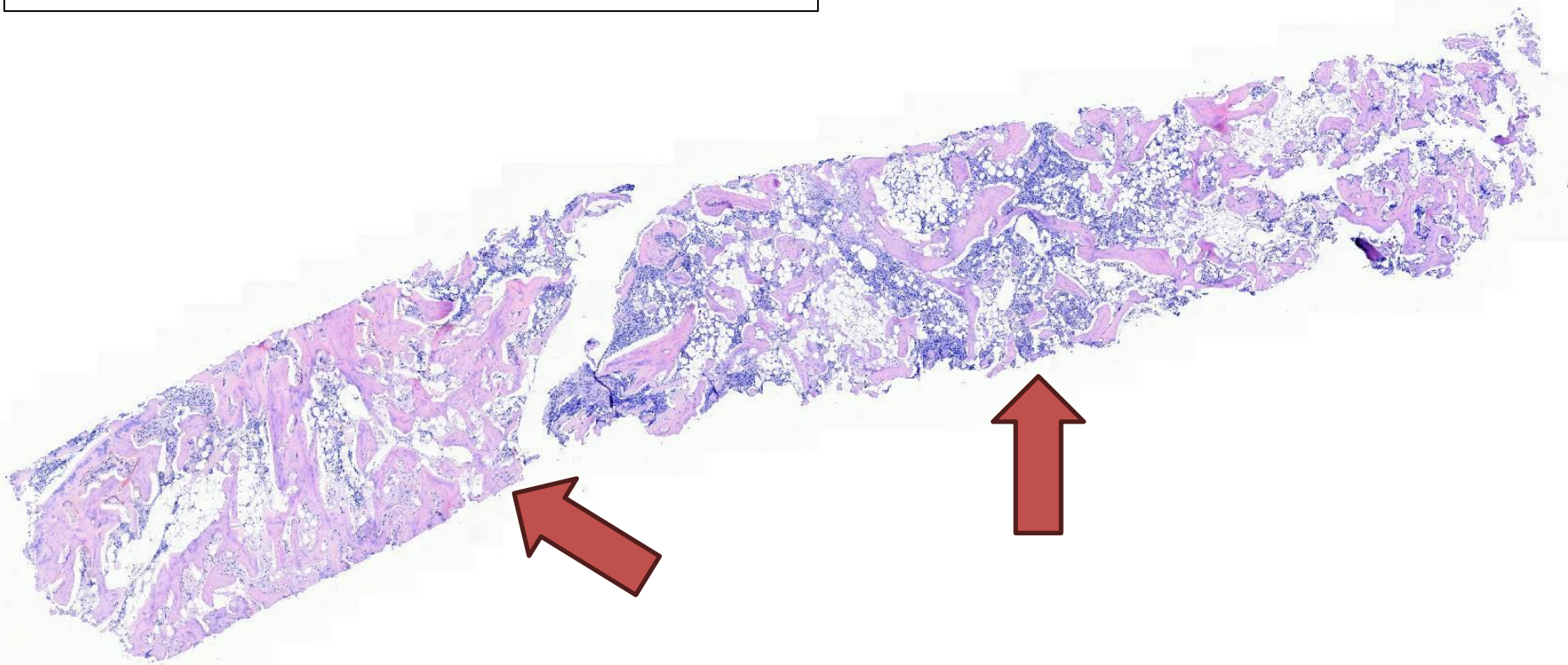
MF3

CLINICAL CASE: april 2025 (+ 4 mo)



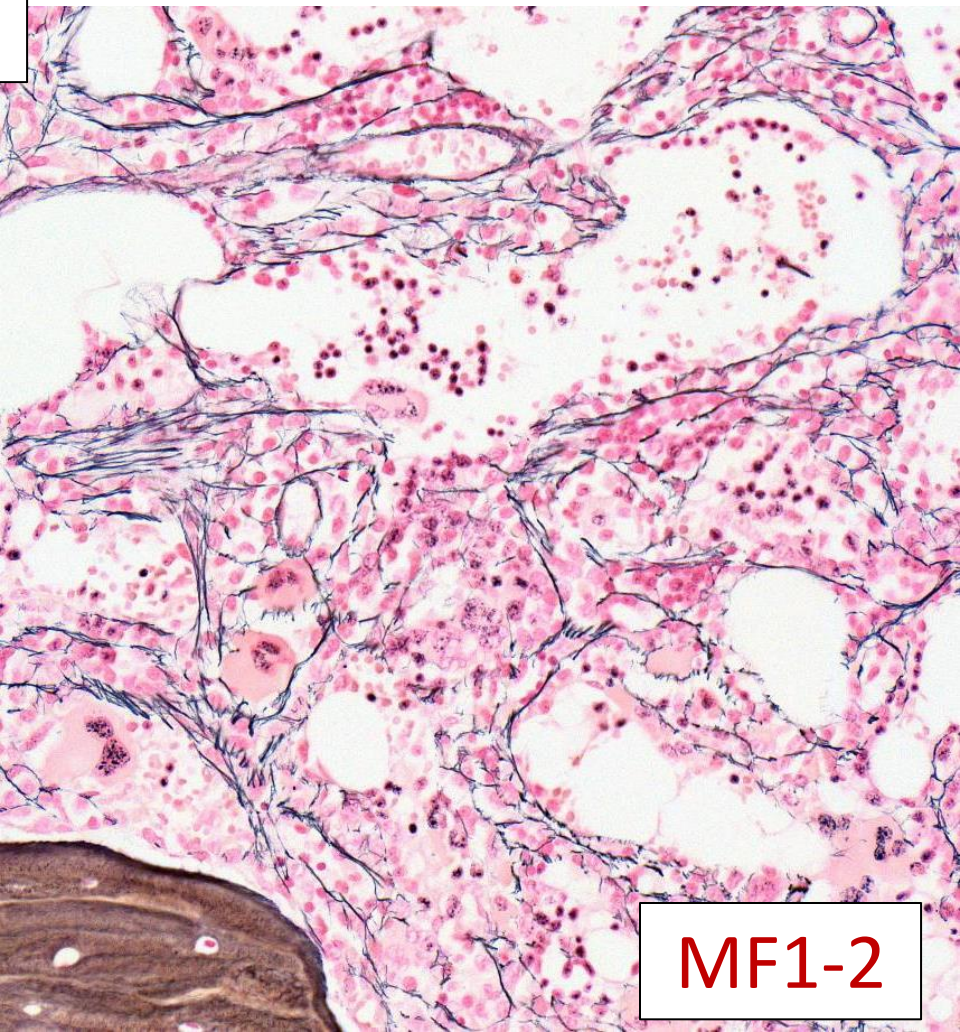
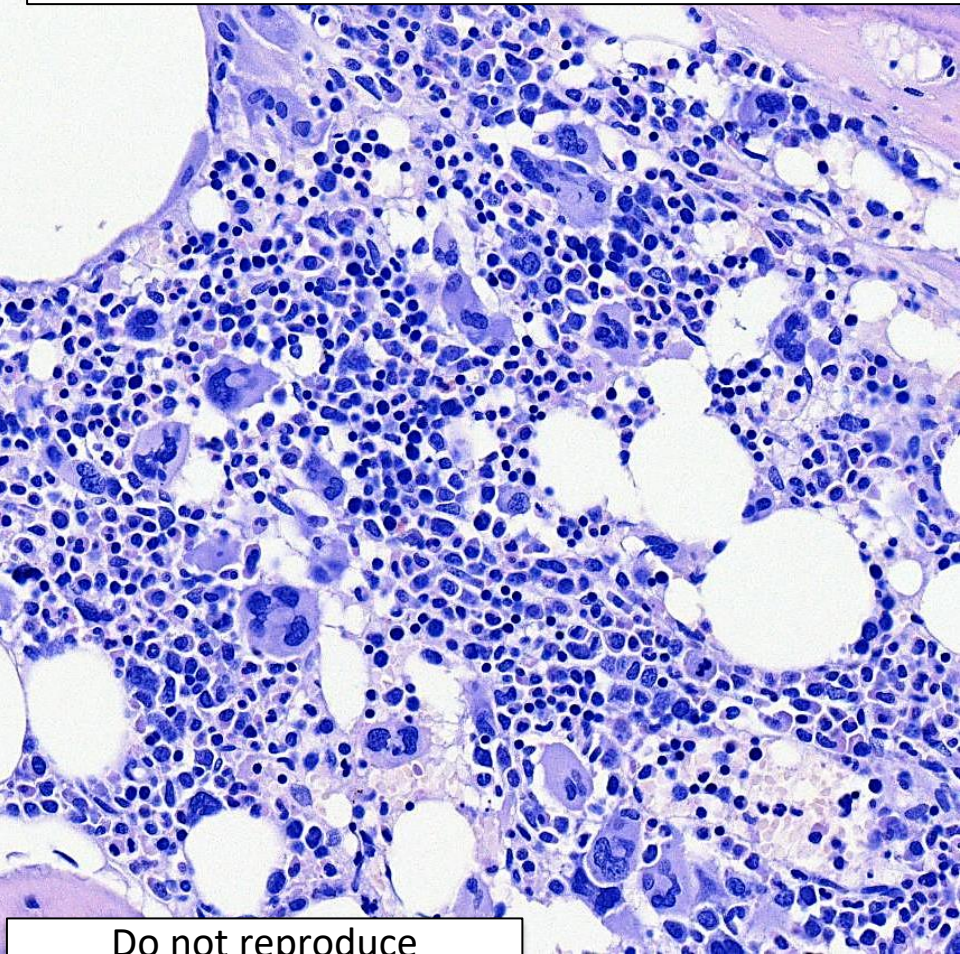
MF2-3

CLINICAL CASE: august 2025 (+ 8 mo)



Do not reproduce

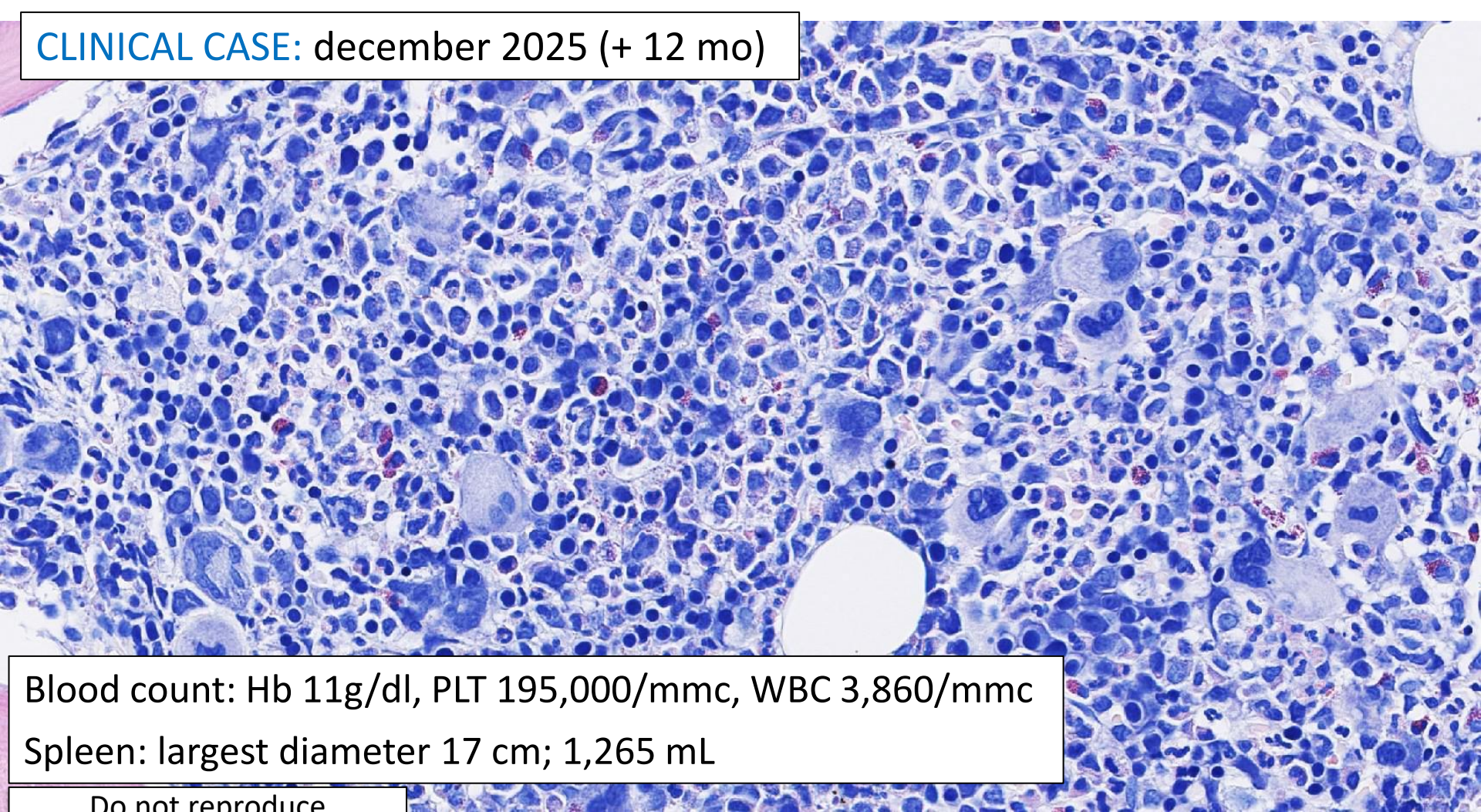
CLINICAL CASE: august 2025 (+ 8 mo)



Do not reproduce

MF1-2

CLINICAL CASE: december 2025 (+ 12 mo)

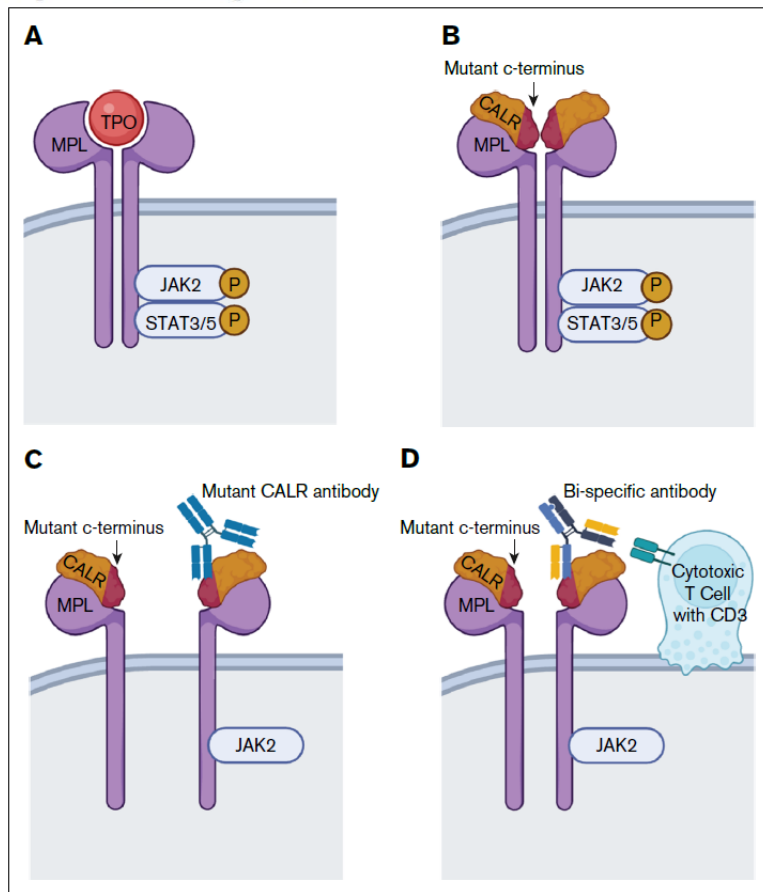


Blood count: Hb 11g/dl, PLT 195,000/mmc, WBC 3,860/mmc

Spleen: largest diameter 17 cm; 1,265 mL

Do not reproduce

Mutant calreticulin-directed immunotherapies in myeloproliferative neoplasms



Joan How,^{1,3} Gabriela S. Hobbs,³ and Ann Mullally^{1,2,4}

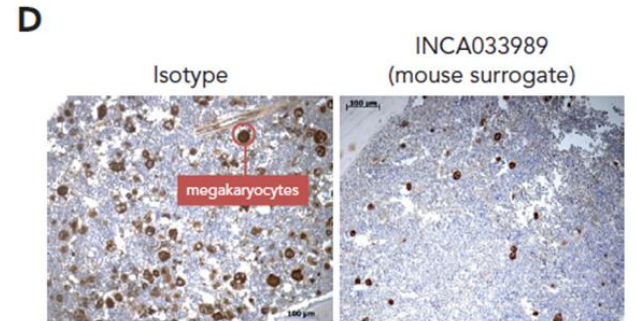
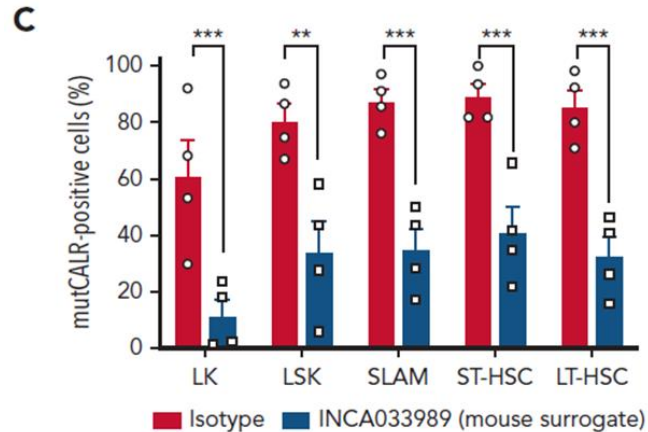
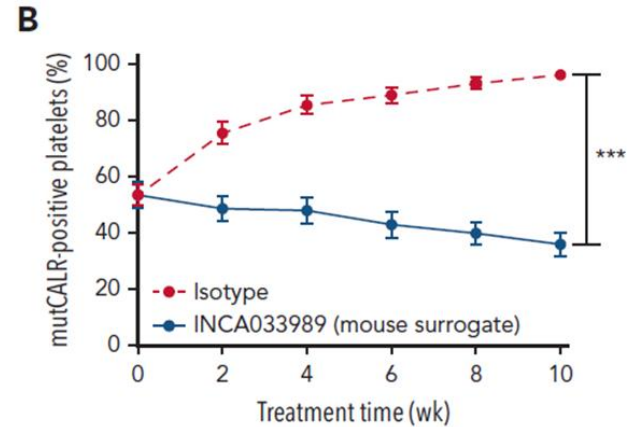
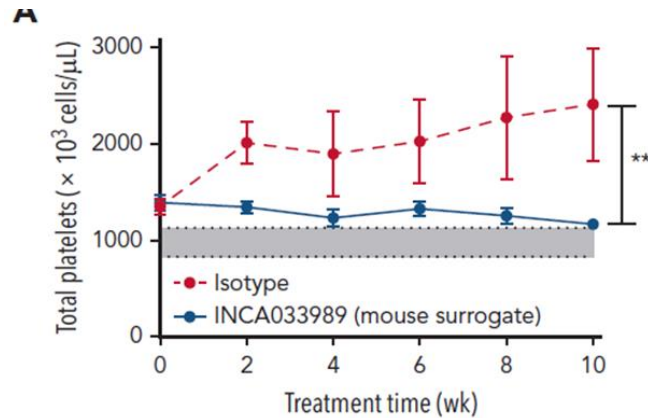
CALR vs JAK2	
ET	
Clinical	Younger, male predominance, lower WBC count, lower Hg/Hct, higher platelets
Thrombosis	Decreased risk
Post-ET MF	Similar to increased
Overall prognosis	Similar
PMF	
Clinical	Younger, lower WBC count, higher Hg/Hct, higher platelets
Thrombosis	Similar, possibly decreased risk
Leukemic transformation	Similar
Overall prognosis	Improved*

Selective targeting of mutated calreticulin by the monoclonal antibody INCA033989 inhibits oncogenic function of MPN



Phase I trial Mouse model

- Platelet reduction
- *CALR*^{mut} clone decrease



CLINICAL CASE: december 2025 (+ 12 mo)

Haematologica 2020
Volume 105(5):1189-1200

Bone marrow niche dysregulation in myeloproliferative neoplasms

blood® 12 MARCH 2026 | VOLUME 147, NUMBER 11

Microenvironmental cell interactions are essential
for sustaining functionality of myelofibrosis
malignant stem cells

HemaSphere. 2025;9:e70185.

Mesenchymal stromal cells from *JAK2*^{V617F}
myeloproliferative neoplasms support healthy and malignant
hematopoiesis in a humanized scaffold model in vivo

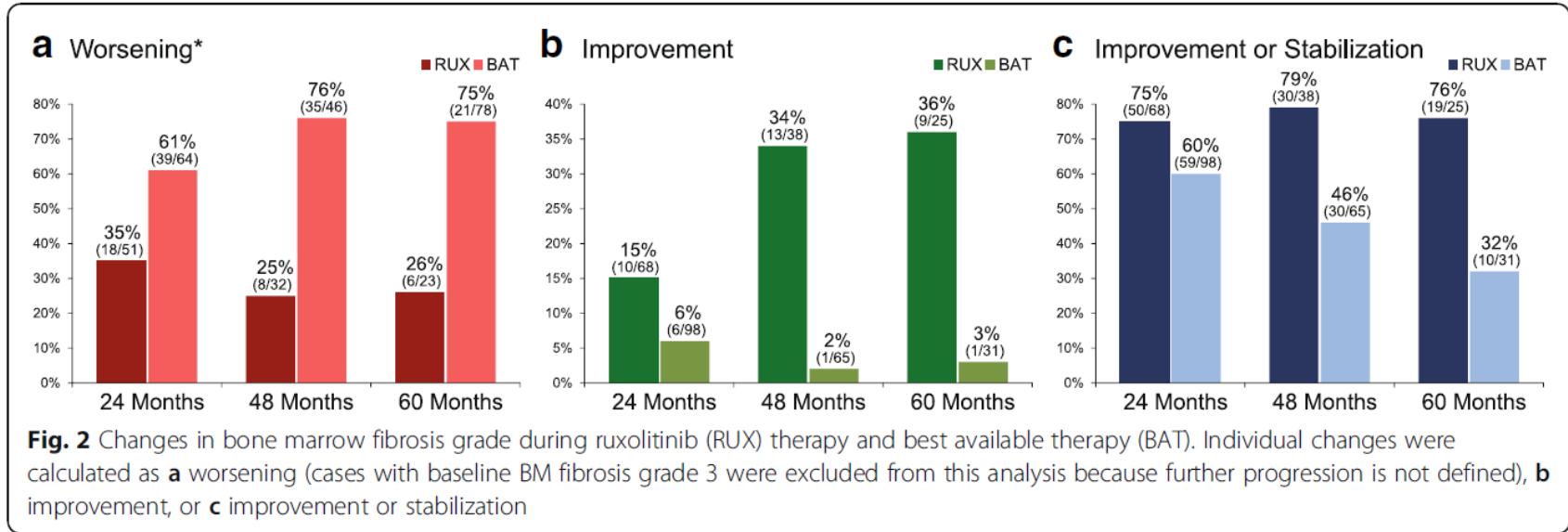
Blood count: Hb 11g/dl, PLT 195,000/mm³, WBC 3,860/mm³
Spleen: largest diameter 17 cm; 1,265 mL

Bone marrow morphological features and therapy in patients with Philadelphia-negative neoplasms

Article Highlights

- Chronic myeloproliferative neoplasms are clonal malignant bone marrow (BM) diseases, arising from a hematopoietic stem cell in which driver mutations constitutively activate the JAK-STAT signalling
- Before the development of JAK2 inhibitors, patients were treated with phlebotomy, hydroxyurea, interferon preparations, anagrelide, and, in more aggressive cases, chemotherapy and transplant.
- Hydroxyurea can reduce BM cellularity, especially of the erythroid and megakaryocyte (MK) lineage but has little influence on fibrotic evolution.
- Interferon therapy can reduce or normalize BM cellularity, improve erythropoiesis, and reduce the MK number and atypia.
- Anagrelide may induce an increase in the MK number of BM, especially immature MKs or precursors, worsen marrow fibrosis and, in some cases, increase the transformation of Essential Thrombocythemia to secondary myelofibrosis.
- Ruxolitinib improves or stabilizes BM fibrosis, especially in Primary Myelofibrosis, and reduces the frequency and dense clustering of MKs.

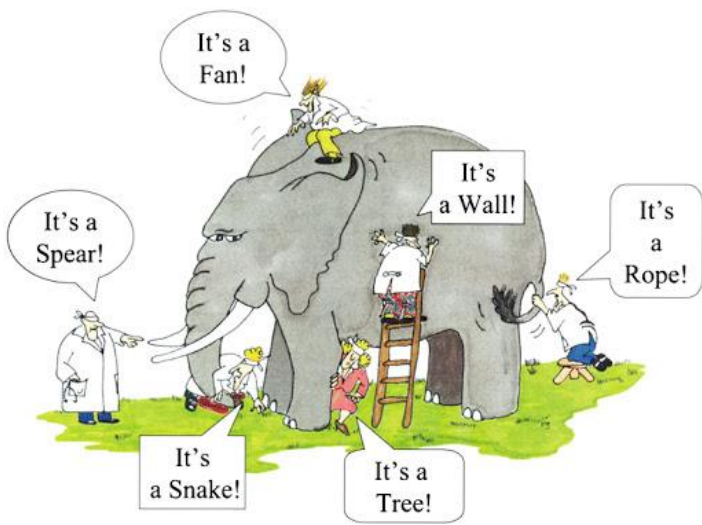
Long-term effects of ruxolitinib versus best available therapy on bone marrow fibrosis in patients with myelofibrosis



- Rux treated pts demonstrated a linear-monotone pattern of change over time in fibrosis
- significant n. of pts revealed a stabilization at 24 months (40/68, 59%), followed by a regression of BM fibrosis thereafter, either at 48 months or 60 months

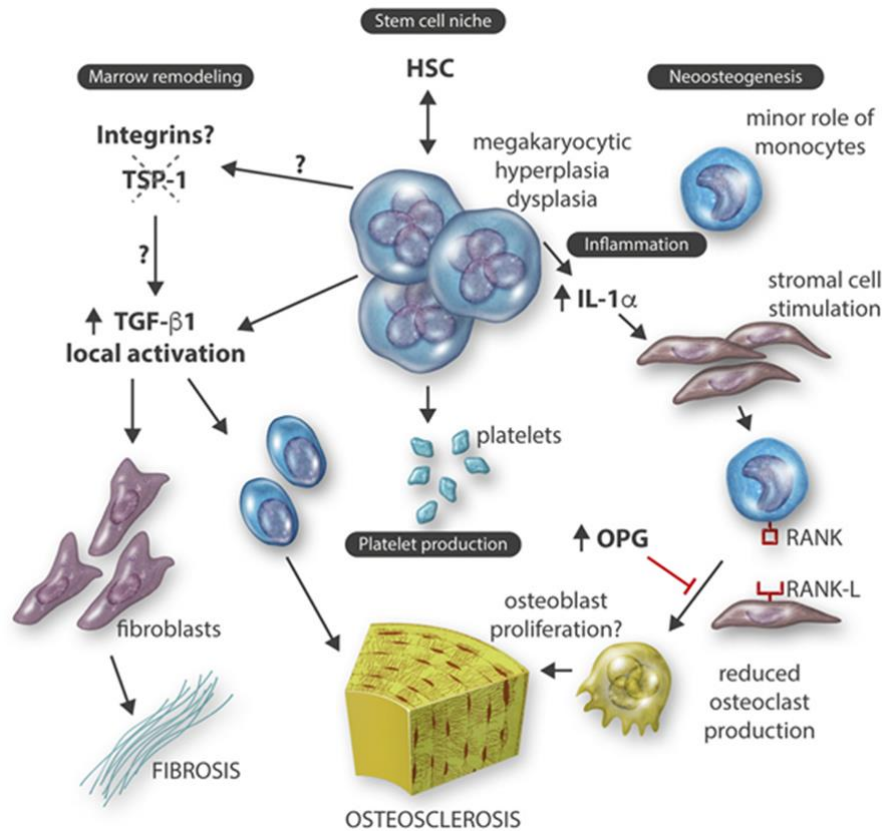
Conclusions

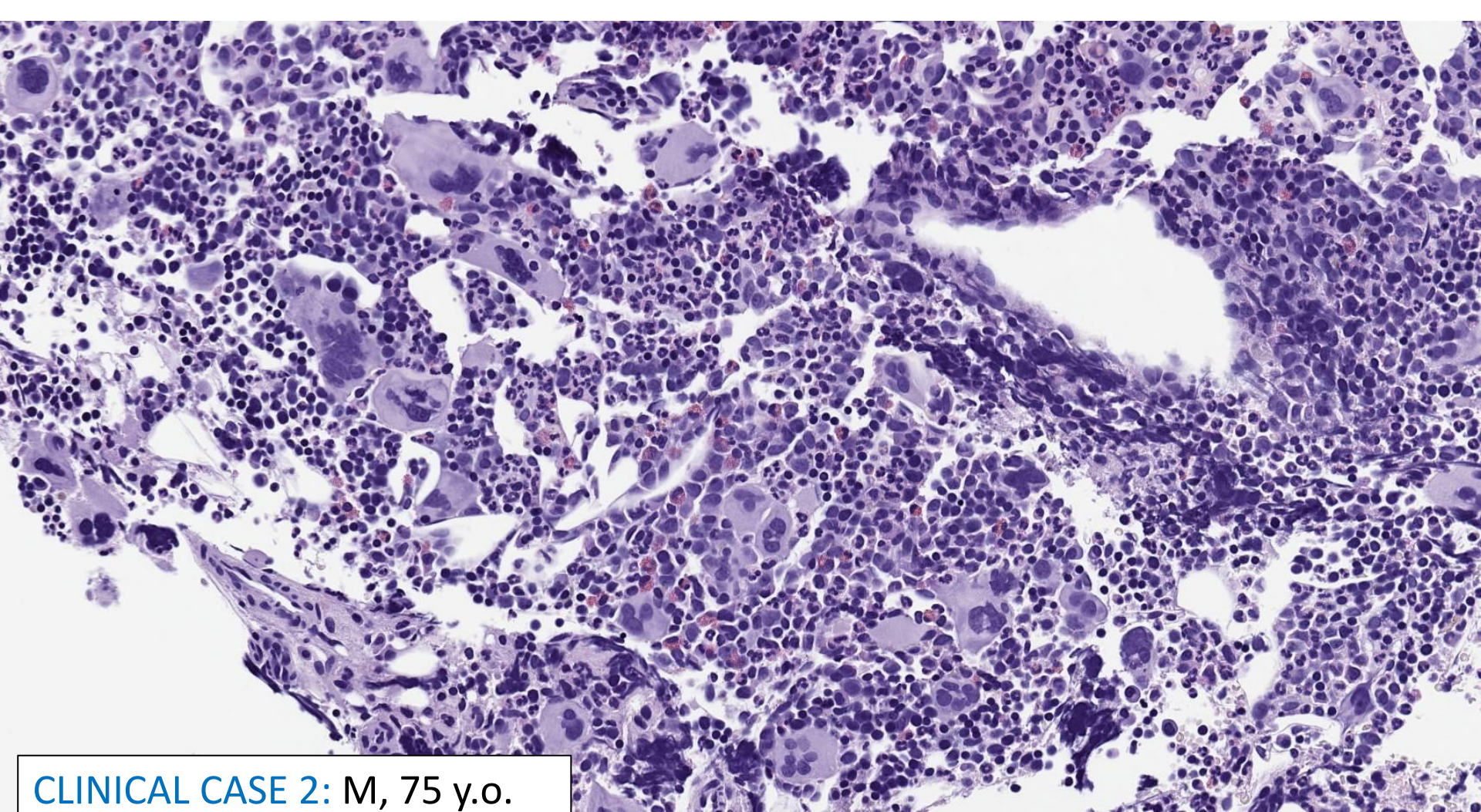
1. Novel morphologic pattern of (novel) therapy-related alterations
2. *Ex adjuvantibus/in vivo* observation of the pivotal role of MK in MPN



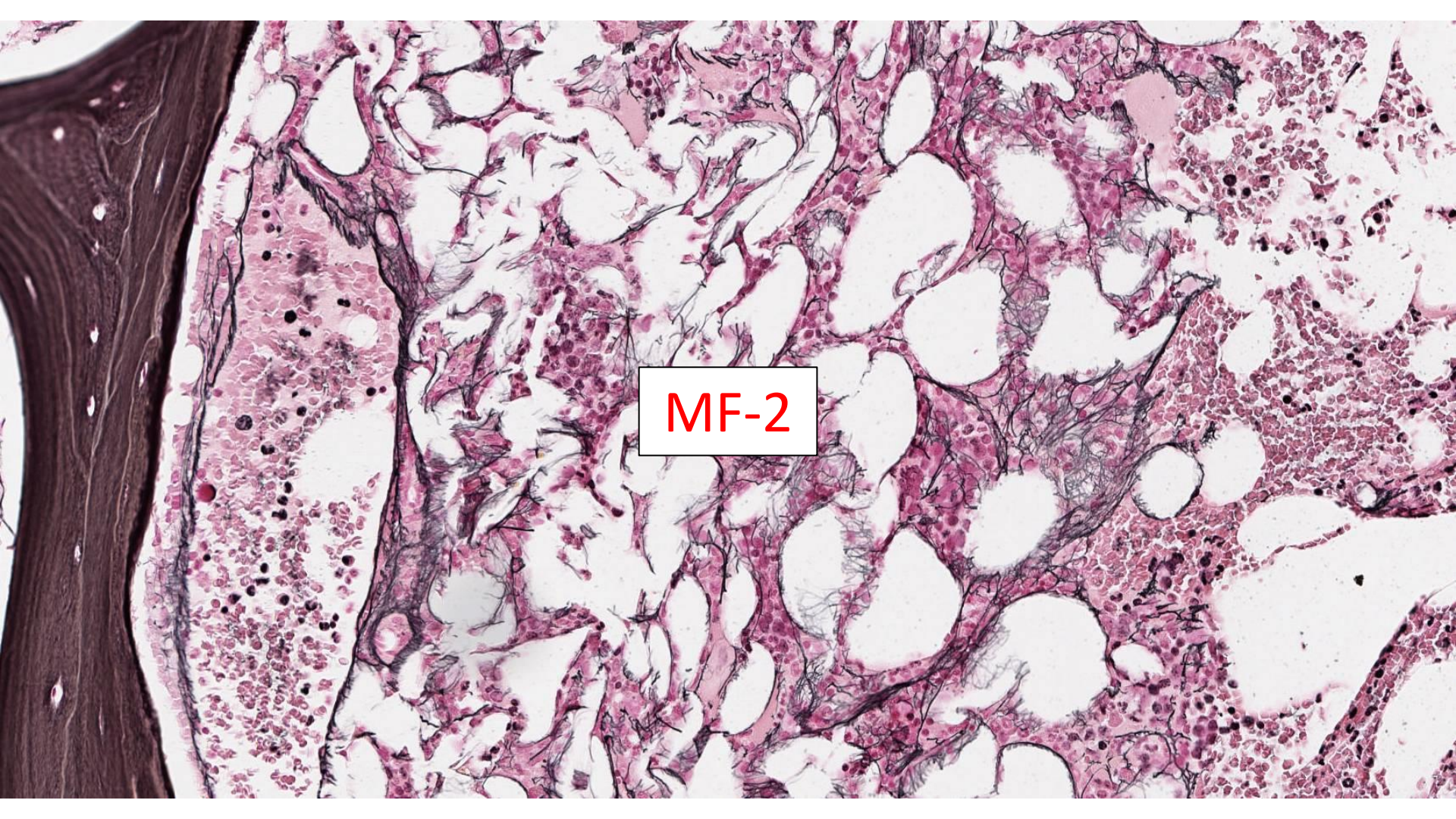
BLOOD, 9 FEBRUARY 2017 • VOLUME 129, NUMBER 6 Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms

William Vainchenker¹⁻³ and Robert Kralovics⁴

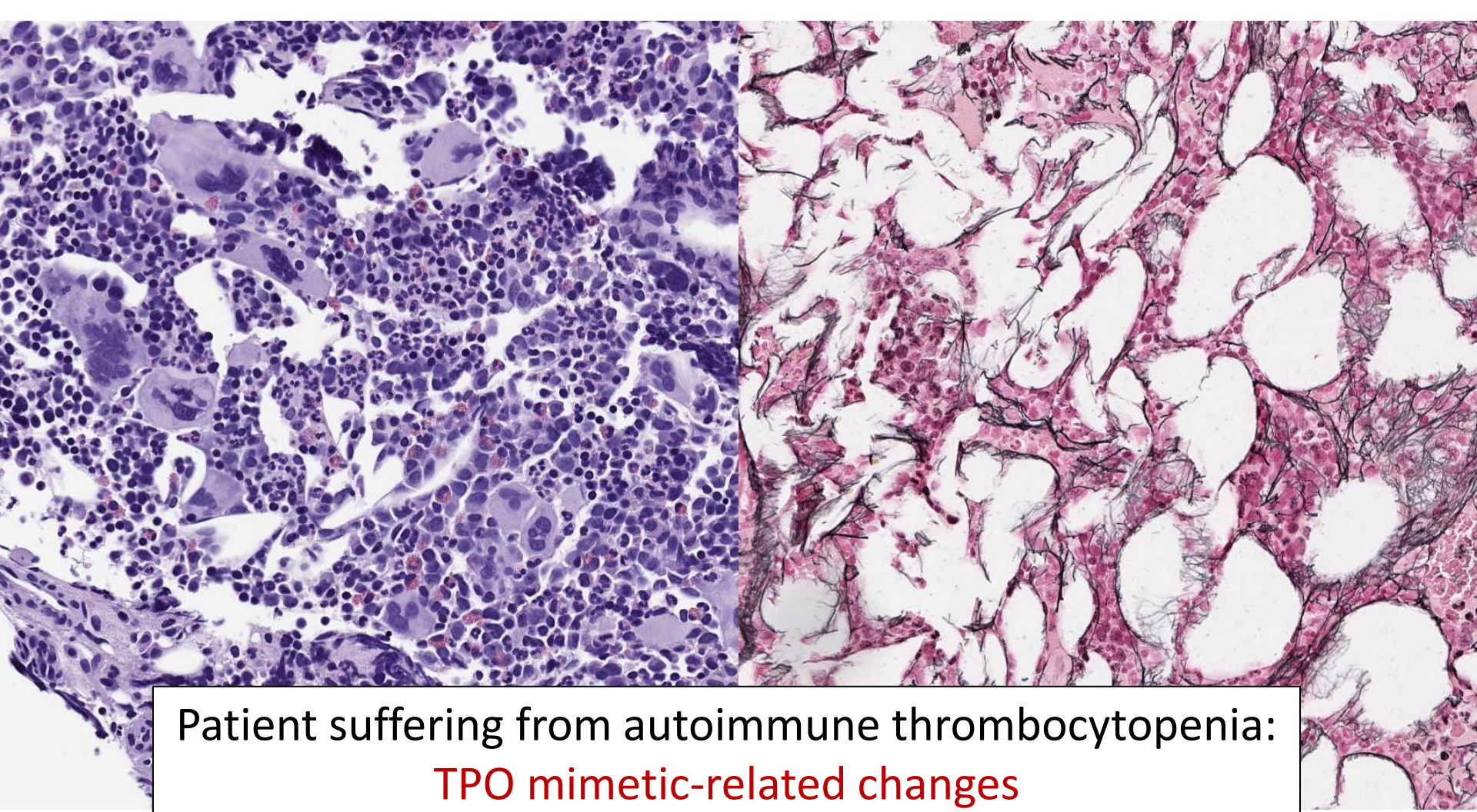




CLINICAL CASE 2: M, 75 y.o.

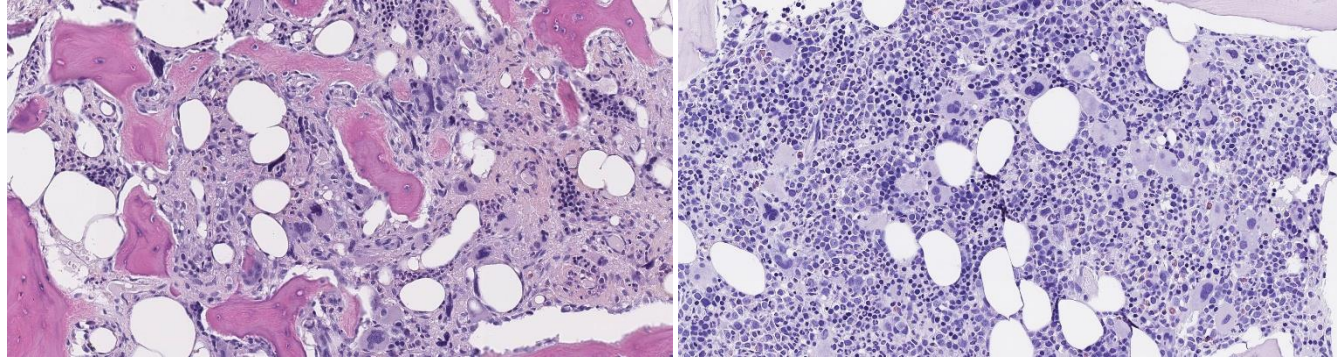


MF-2



Patient suffering from autoimmune thrombocytopenia:
TPO mimetic-related changes

Ringraziamenti



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IRCCS Cà Granda Ospedale Maggiore
Policlinico, Milano

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