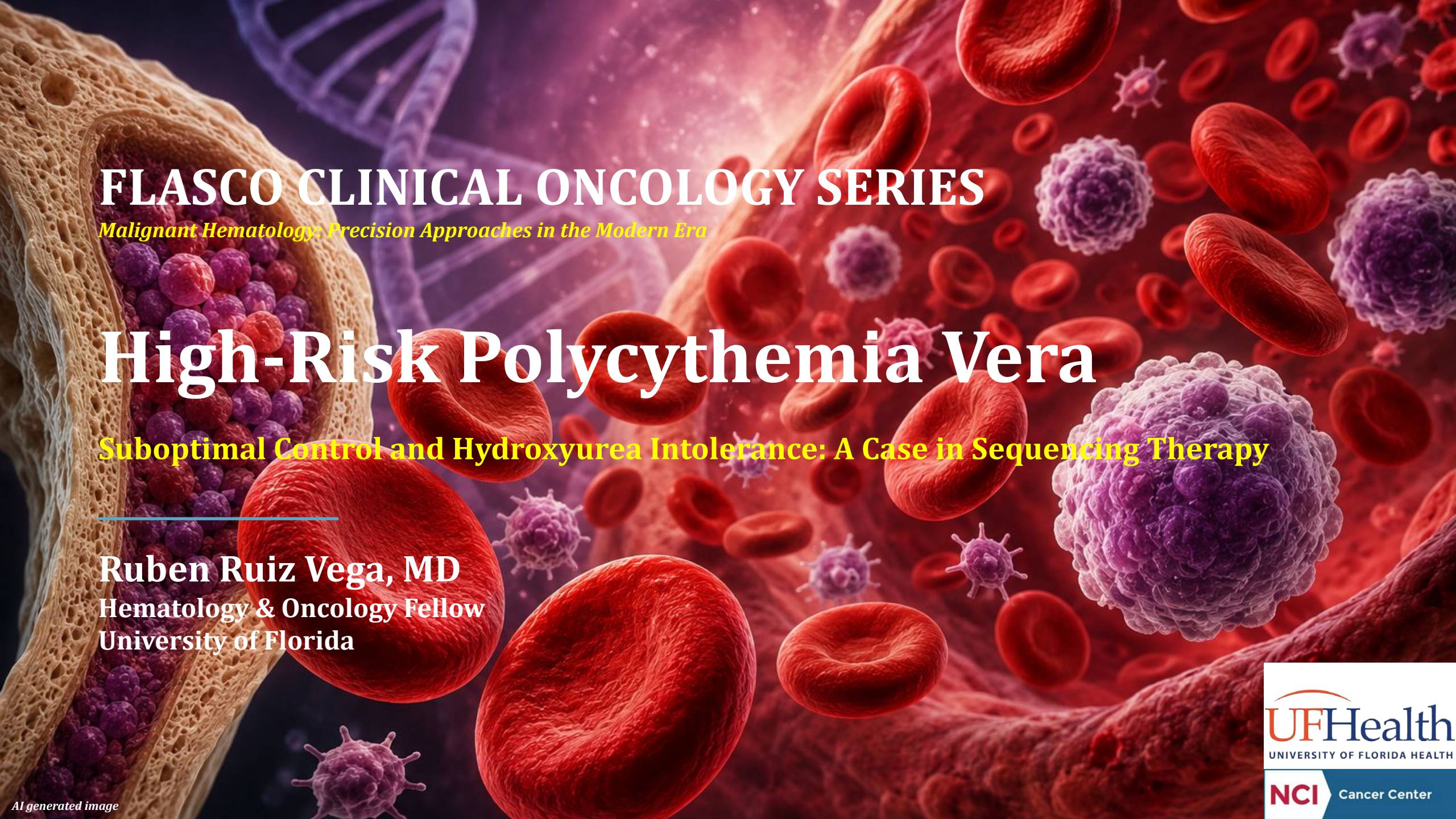




FLASCO CLINICAL ONCOLOGY SERIES

Malignant Hematology: Precision Approaches in the Modern Era

High-Risk Polycythemia Vera

Suboptimal Control and Hydroxyurea Intolerance: A Case in Sequencing Therapy

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JAK2 V617F+ Polycythemia Vera



Demographics

27-year-old male; managed across four institutions (UF, Dana Farber, Mayo, MD Anderson) starting 11/1997



Diagnosis

JAK2 V617F-positive polycythemia vera (11/2020); hallmark erythrocytosis + thrombocytosis



Hematologic Findings

Chronic iron-deficiency anemia; progressive thrombocytosis driving therapy decisions



Lifestyle Factors

Former smoker (quit ~1996); alcohol 1–2x/week; frequent cannabis use (vape/edibles)

KEY QUESTION FOR THE PANEL

In a patient with rising platelet counts, hydroxyurea dose escalation, and eventual intolerance — what is the optimal next-line strategy, and how do we define “treatment failure” in real time?

1996 - 1998

Diagnostic Journey

Incidental erythrocytosis on routine labs led to a two-year diagnostic odyssey before confirmatory red-cell mass testing.

~1996

Incidental Finding

Routine CBC by PCP reveals elevated Hct/platelets; referred to local hematology

11/17/97

Brigham & Women/ Dana Farber's Eval

Hct ~59% and platelets ~500,000; formal work-up for erythrocytosis initiated

11/25/97

UF Health Confirmation

Repeat counts: Hct 57.6%, platelets 548,000 (persistently elevated)

4/14/98

RBC Mass Study

RBC mass 57 mL/kg: grossly elevated, almost 2x normal, confirming true erythrocytosis

5/14/98

Phlebotomy Initiated

Intermittent therapeutic phlebotomy begun; Hct goal <45%, maintained for two decades

Patient reported family history of hepatocellular carcinoma (mother) and a prior 9-year, ~15 cig/day smoking history (quit ~1.5 yrs before 11/97 presentation).

Diagnostic Journey Continued

5/14/98

Phlebotomy Initiated

Intermittent therapeutic **phlebotomy** begun; Hct goal <45%, maintained for two decades

11/23/20

PV diagnosis confirmed

BMBx at UF Health noted **JAK2 c.1849G>T p.V617F** VAF: 47%

7/19/22

Hydroxyurea Initiated

1000 mg daily in the setting of uprending plt count. Previously did not start hydroxyurea as he did not fall into high-risk phenotype

7/2024

Besremi (ropeginterferon alfa-2b-njft) Initiated

Initiated at 50 mcg q2weeks (in combination with hydroxyurea). Dose was increased to 100 mcg q2weeks (maximum: 500 mcg)

4/8/26

Repeat BMBx

JAK2 c.1849G>T p.V617F VAF: 67%

As of 7/23/2026

Besremi stable at **400 mcg q2week**

Besremi up-titrated by 50 mcg every two weeks to reach hematological parameters (hematocrit <45%, platelets <400,000/mm³, and leukocytes <10,000/mm³)

Molecular Profile at Diagnosis

DRIVER MUTATION

JAK2 V617F

47%

Variant Allele Frequency

Cytogenetics: 46,XY[20] — normal
No evidence of leukemia, lymphoma, or
high-grade MDS

Variants of Unknown Significance (VUS)

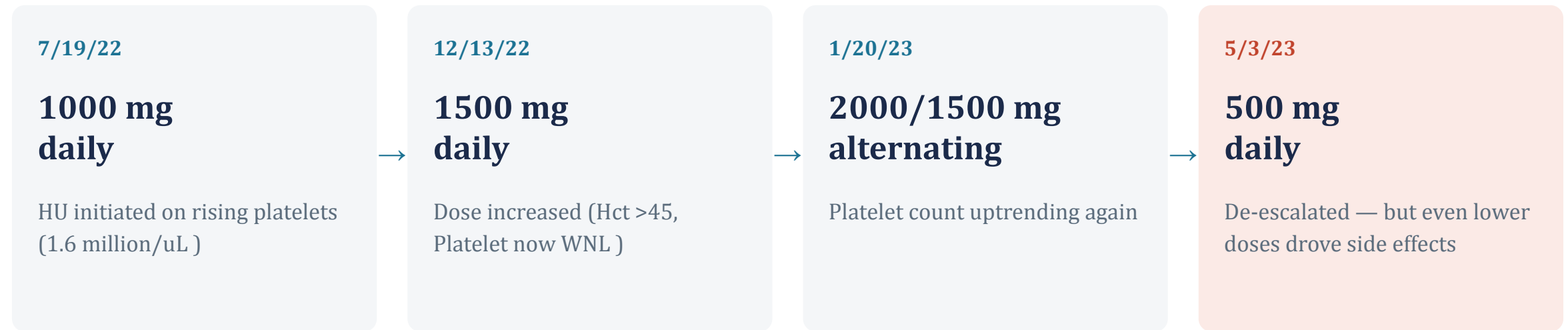
Gene	Variant	VAF
APC	c.7036C>T p.P2346S	44%
FAT1	c.7225G>A p.V2409M	46%
COL4A3	c.1483C>T p.H495Y	10%
NTRK1	c.480C>G p.S160R	37%

VUS require longitudinal tracking — clinical significance for PV progression remains undefined.

Clinical takeaway: at diagnosis, this was a molecularly “clean” JAK2-driven PV — no co-mutations of known prognostic weight.

Hydroxyurea: Escalation, Then Retreat

HU was initiated for a rising platelet count — the patient had not met classic “high-risk” criteria at that point.



INTOLERANCE SIGNALS

High hydroxyurea doses were required just to keep platelets <400K — with facial skin changes, hair loss, and fatigue emerging as dose-limiting toxicities.

3/2/2023 & 10/20/2023

Second Opinion & the Pivot Decision

Mayo Clinic (Dr. Ayalew Tefferi) reviewed the full therapeutic landscape for this young, HU-intolerant patient.

Hydroxyurea

Continued — but already dose-limited by skin toxicity, hair loss and fatigue

Considered

Busulfan

Considered as a cytoreductive alternative

Considered

Ruxolitinib

Not favored for PV in a young patient; splenomegaly not the dominant issue

✗ Deprioritized

Pegylated / Ropeginterferon

Preferred strategy — disease-modifying potential, HU-sparing

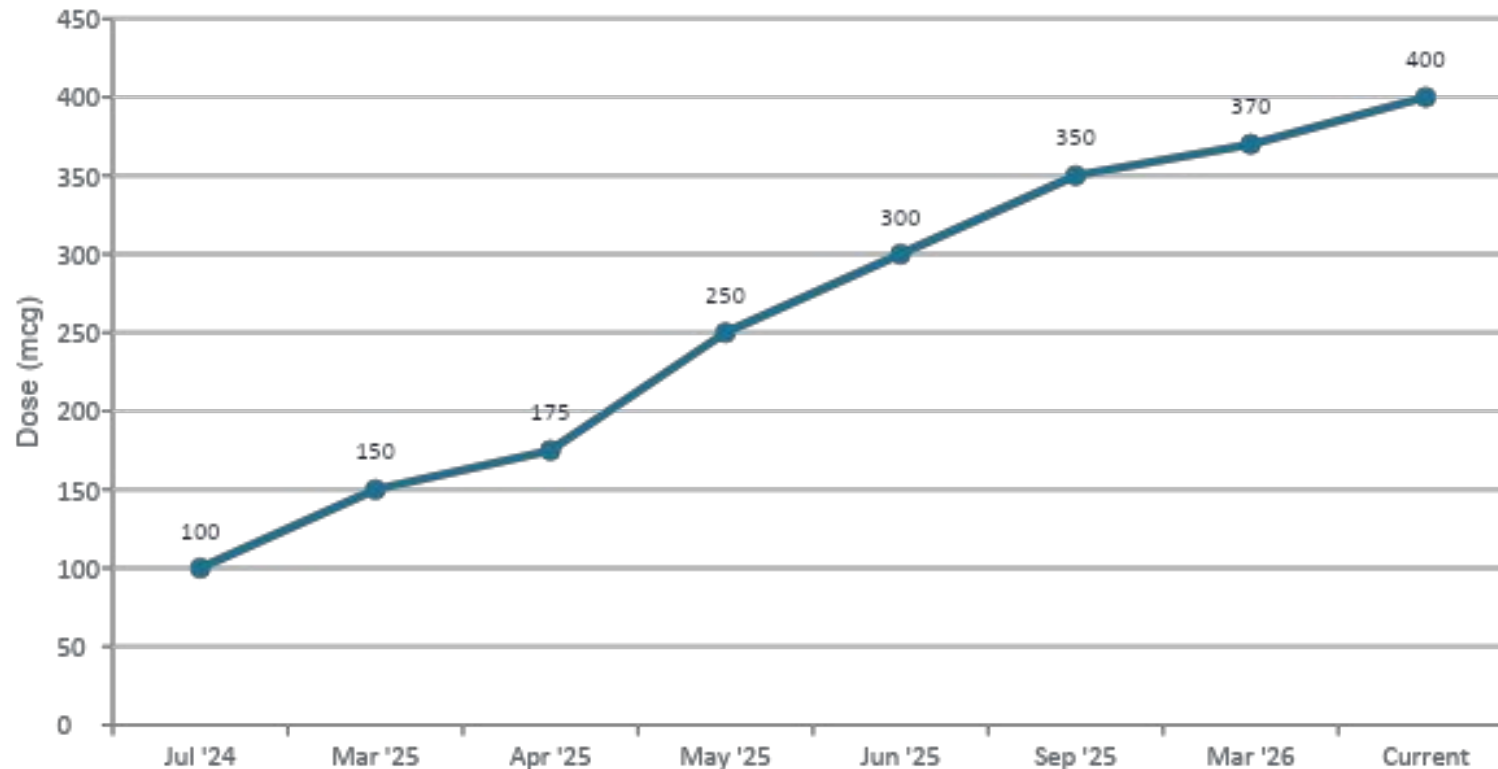
✓ Preferred

10/20/2023 — Dr. Tefferi recommends ropeginterferon alfa-2b-njft (Besremi), directly attributed to HU-related skin changes and hair loss.

7/2024 - PRESENT

Transition to Ropeginterferon: Titration & HU Taper

Gradual biweekly up-titration to hematologic targets (Hct <45%, platelets <400K, WBC <10K), with protocolized HU taper to discontinuation.



9/2025

Hydroxyurea fully discontinued after 20–40% biweekly taper

3/2026

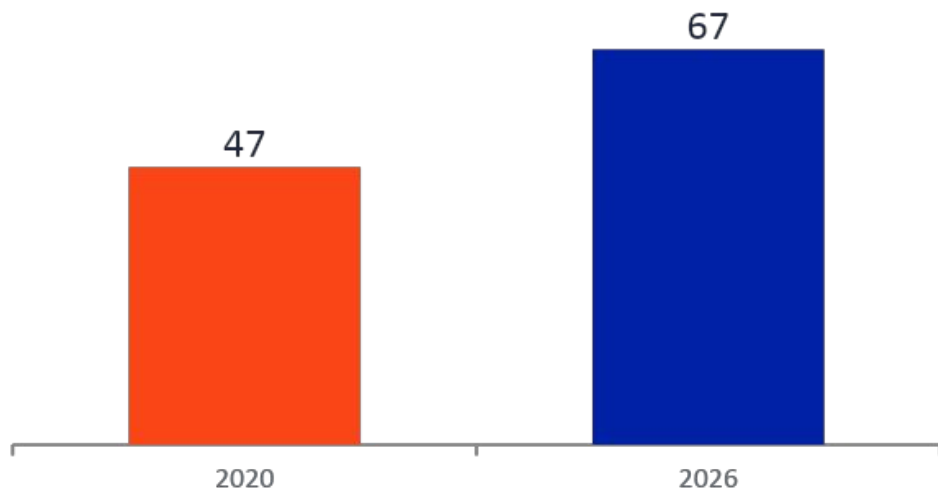
BMBx during dose escalation — see molecular update

Today

Stable maintenance at 400 mcg every 2 weeks

Molecular Evolution Under Therapy

JAK2 V617F Variant Allele Frequency



+20 points despite sustained hematologic response — raises the question of molecular vs. hematologic response discordance.

New on 2026 Marrow

TET2 — likely pathogenic

c.3861dup p.G1288Wfs*12, VAF 2.58% — emerging co-mutation

Moderate reticulin fibrosis (MF-2+)

Hypercellular marrow (80%) with trilineage hematopoiesis

10 additional VUS identified

CIITA, FAT3, FGFR4, IGF2R, INHBA, NFE2, NTRK1, PMS1, RECQL4, STAT5A

Cytogenetics & FISH unchanged

46,XY[20]; negative for *PDGFRB, BCR/ABL1, ETV6* rearrangement

Clinical Response & Current Status

RESPONDING WELL

- **Improved hematologic control** — Condition improved after HU discontinuation and Besremi initiation
- **Reduced phlebotomy burden** — Now reserved only for Hct ≥ 48 –50%, a marked decrease from prior frequency
- **Manageable tolerability** — 2 days of malaise / fogginess post-dose (down from initial 2–3 days of hot flashes and malaise)
- **Subjective well-being** — Patient reports feeling better overall than in years

STILL BEING CHARACTERIZED

- **5-lb weight loss** — With decreased muscle mass over the past year
- **Occasional night sweats** — Attributed by patient to iron deficiency / sleep disturbance
- **Splenomegaly** — 18.6 cm spleen on recent CT; not the dominant clinical driver but warrants monitoring
- **Incidental liver lesion** — Benign-appearing liver spot on recent CT measuring 2.0 cm and 1.3 cm

Open Questions for Panel

1

Rising *JAK2* VAF (47%→67%) plus a new *TET2* subclone despite hematologic response — how should this reshape follow-up and risk assessment?

2

Should ropeginterferon have been considered earlier? How should clinician sequence therapies?

3

How do we define “hydroxyurea intolerance”

4

Does the 18 cm spleen warrant a change in surveillance or treatment intensity?