BOLOGNA
17 FEBBRAIO 2023
NH De La Gare

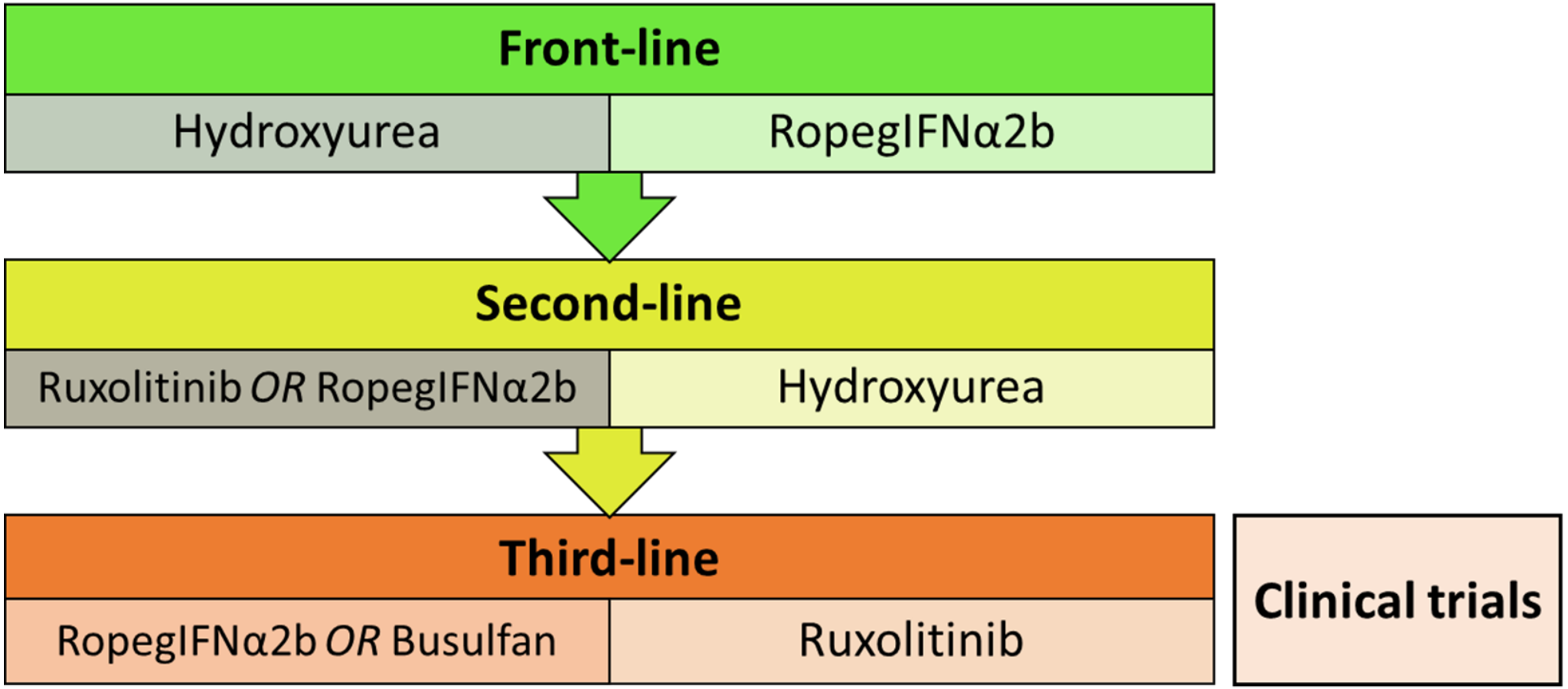
POLICITEMIA VERA NEL 2023:

qualcosa è cambiato

Come riconoscere e gestire il problema della intolleranza a idrossiurea

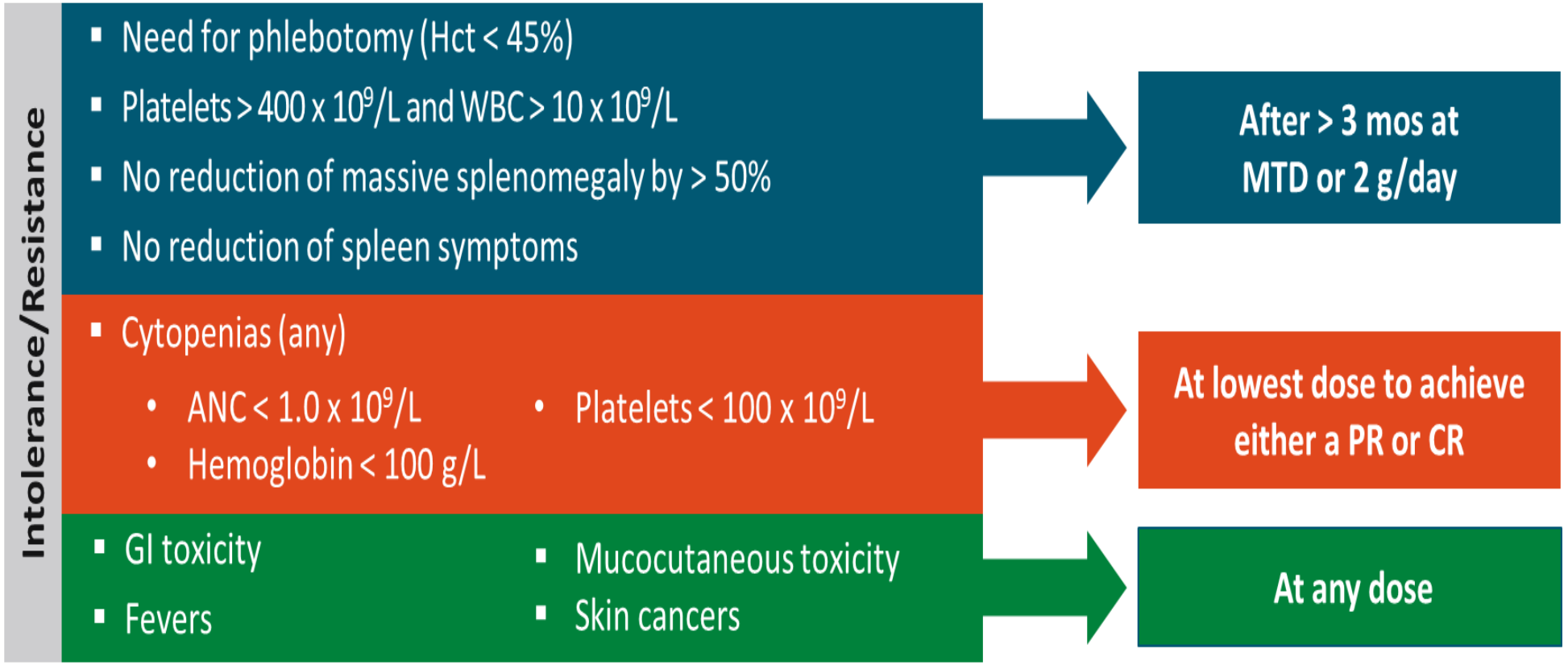
Francesca Palandri

The options of PV therapy in 2022



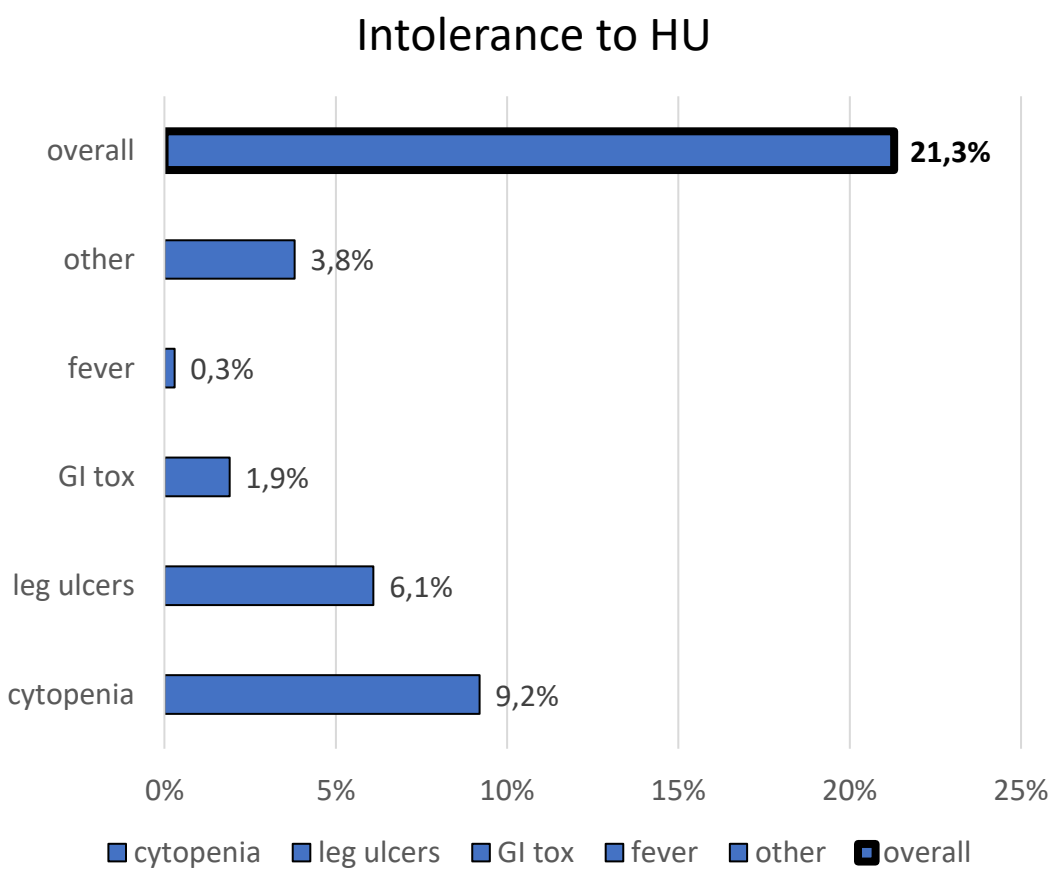
McMullin MF, Br J Haematol. 2019 Jan;184(2):176-191. Spivak JL, Blood. 2019 Jul 25;134(4):341-352; Barbui T, Leukemia. 2018 May;32(5):1057-1069; Vannucchi AM, Haematologica. 2017 Jan;102(1):18-29

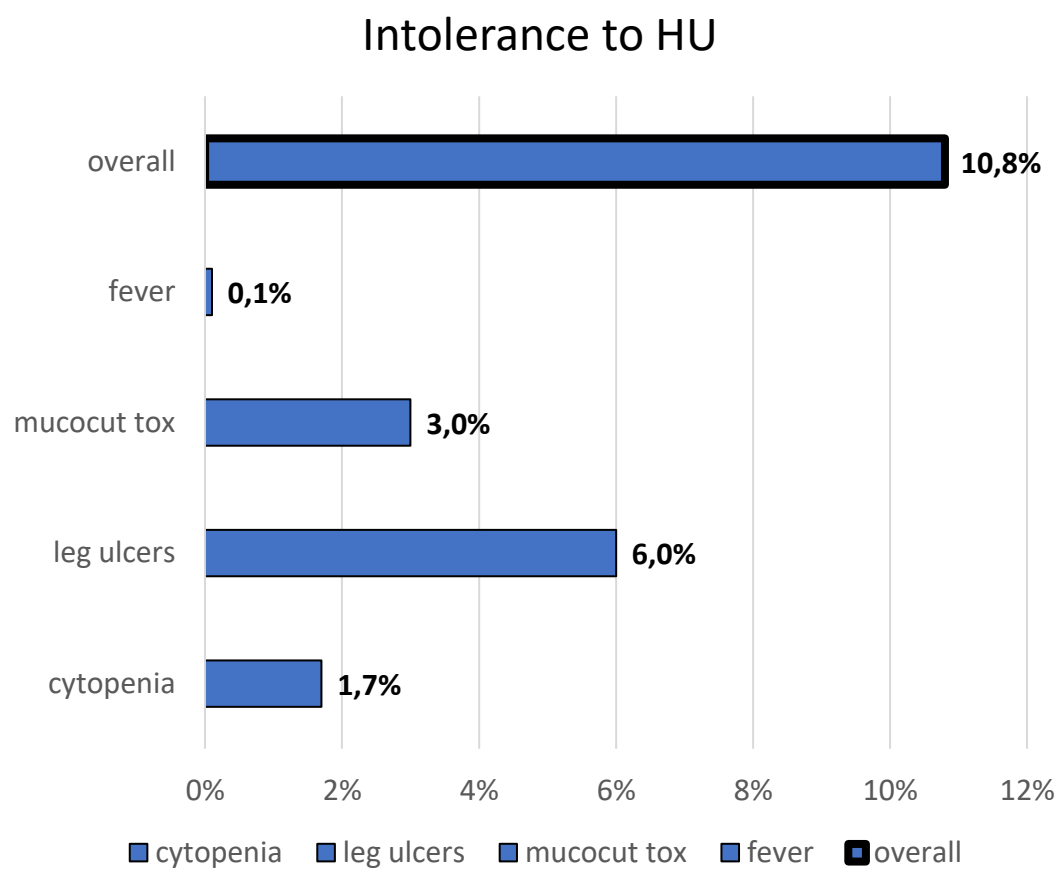
Hydroxyurea in PV –resistance/intolerance



Barosi G, Blood. 2009;113(20):4829-4833

Intolerance to Hydroxyurea affects 15-20% of patients– Spanish registry

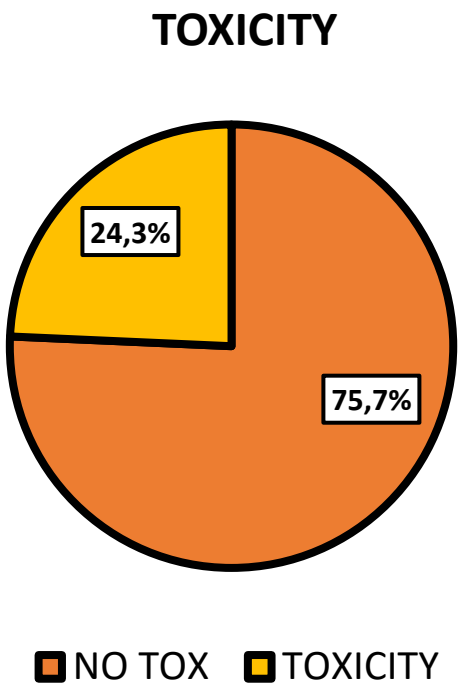




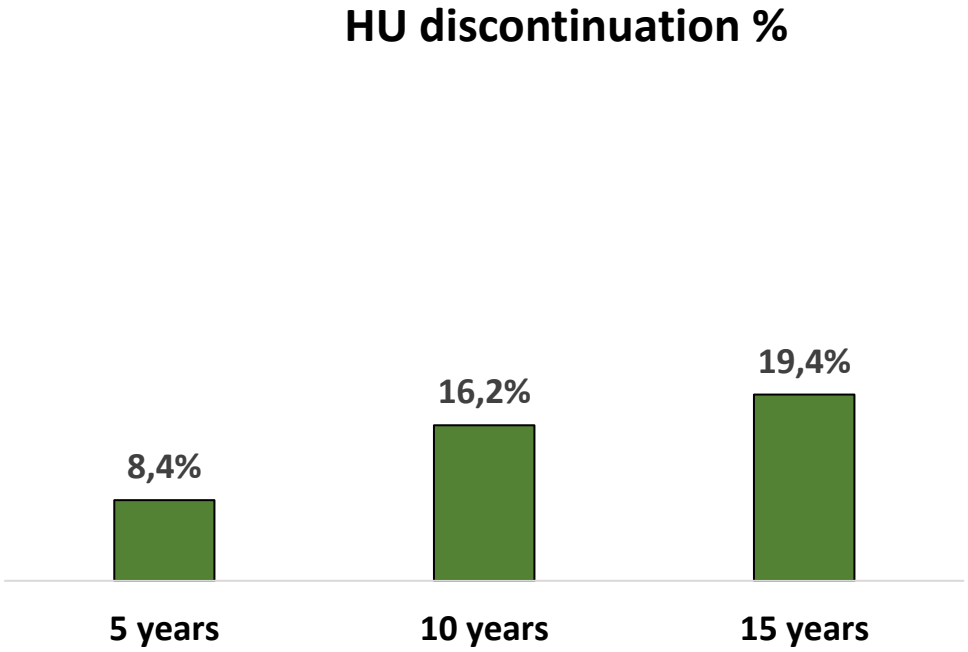
Alvarez-Larrán. Blood. 2012;119:1363; Alvarez-Larran et al; Br J Haematol. 2016 Mar;172(5):786-9

Intolerance to Hydroxyurea affects 15-20% of patients– Italian PV-ARC study

- In the Italian PV-ARC cohort of 506 PV patients treated with HU for ≥12 months, ≥1 HU-related AE occurred in 123 patients (24.3%).



- HU was discontinued by 8.4%, 16.2% and 19.4% at 5, 10 and 15 yrs.
- The overall HU discontinuation rate was 4.1 per 100 pt-yr.

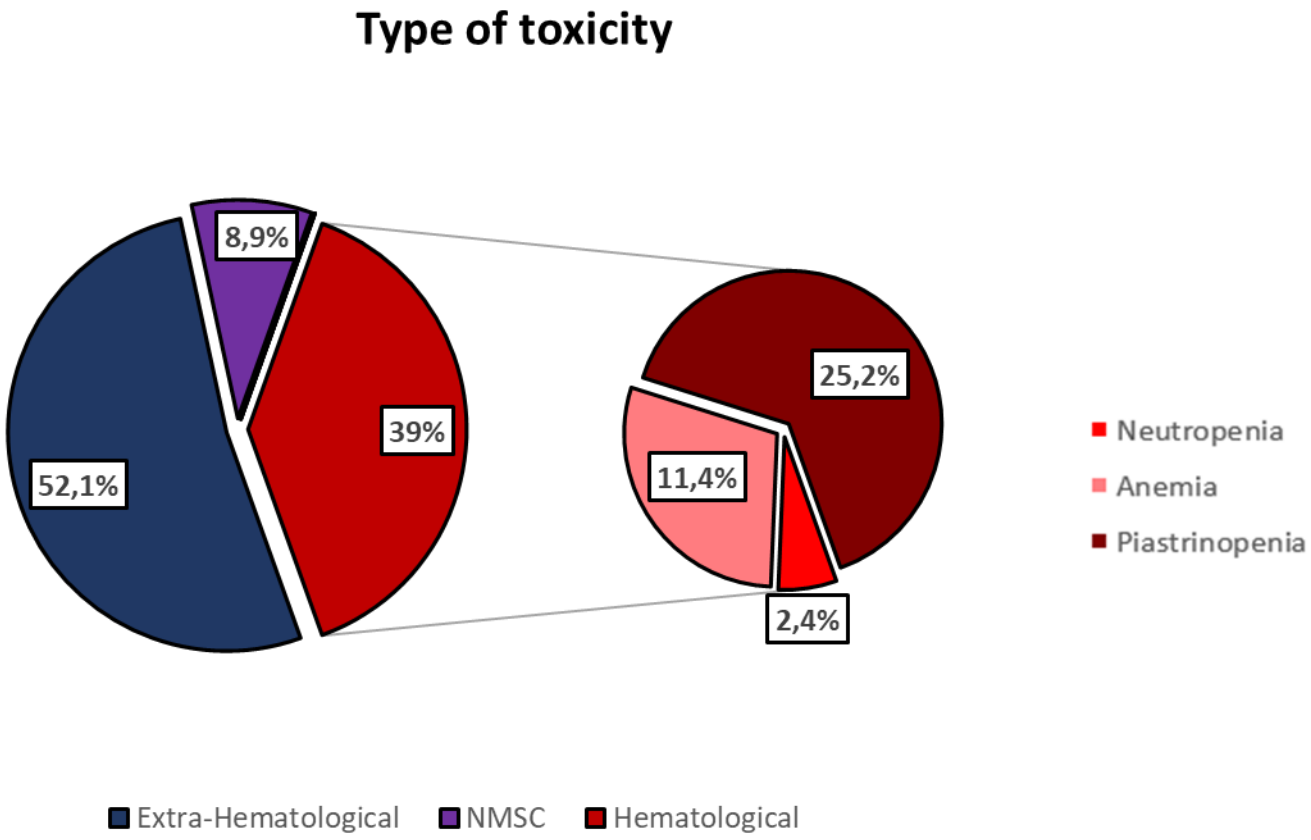


Palandri F et al, SIE 202

Intolerance to Hydroxyurea in PV

CYTOPENIA

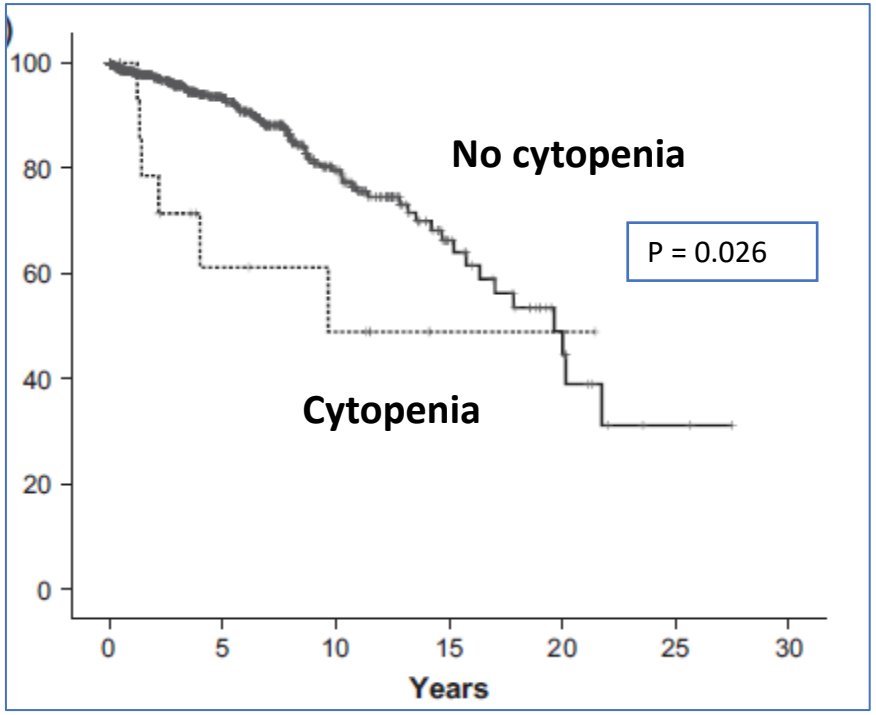
Intolerance to Hydroxyurea – cytopenia in the PV-ARC Italian study

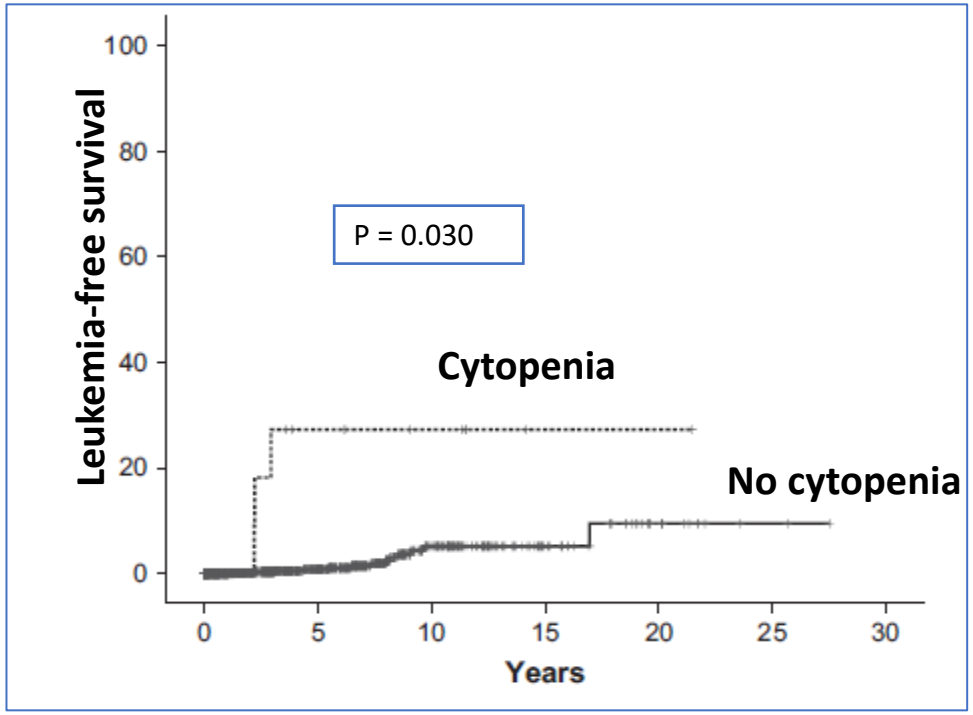


- Overall, **48 out of 506 (9.5%)** patients had a hematological toxicity.
- Hematological toxicity was most frequently thrombocytopenia and anemia.

Palandri F et al, SIE 2021

Cytopenia during Hydroxyurea affects survival and LFS





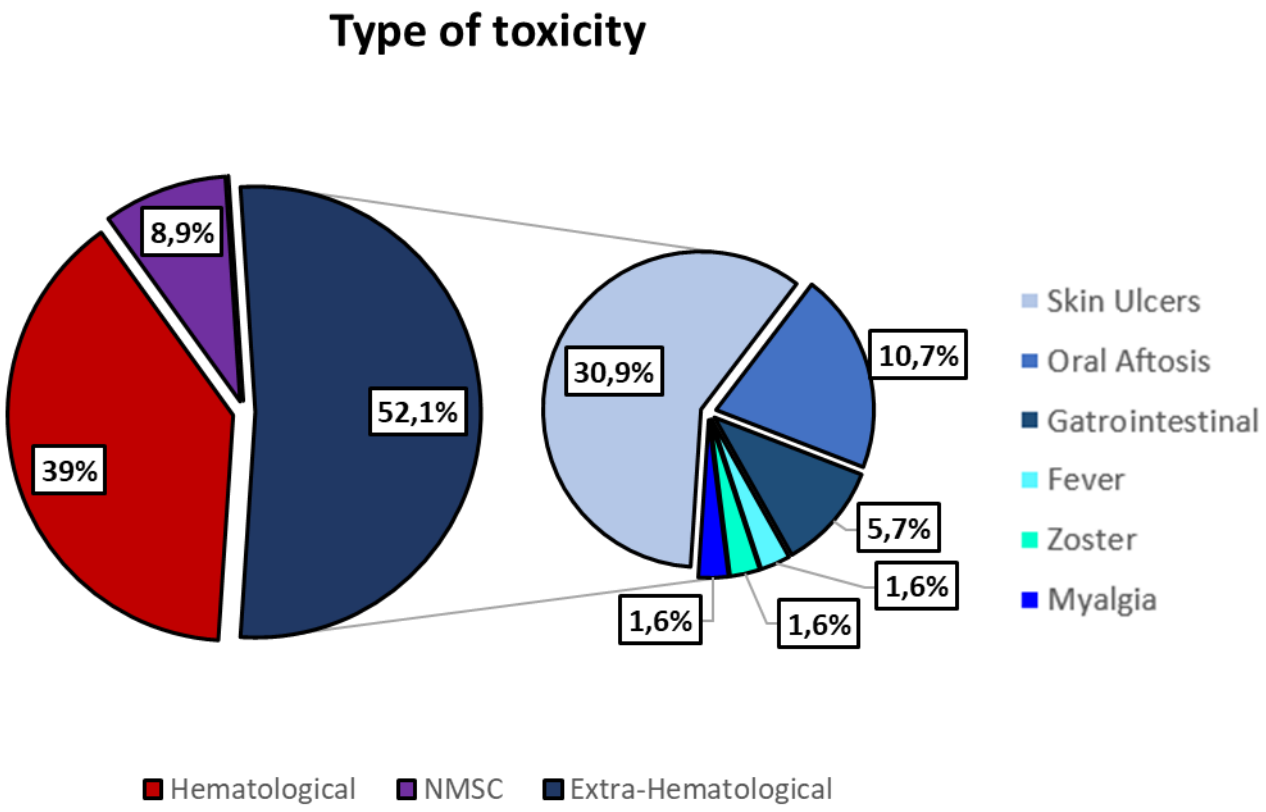
- Retrospective Spanish cohort – 890 patients treated with HU.
- Intolerance to HC was recorded in 96 patients (10.7%). **Cytopenia was observed in 15 patients (1.7%)**

Alvarez-Larran et al; Br J Haematol. 2016 Mar;172(5):786-9

Intolerance to Hydroxyurea in PV

OTHER TOXICITIES

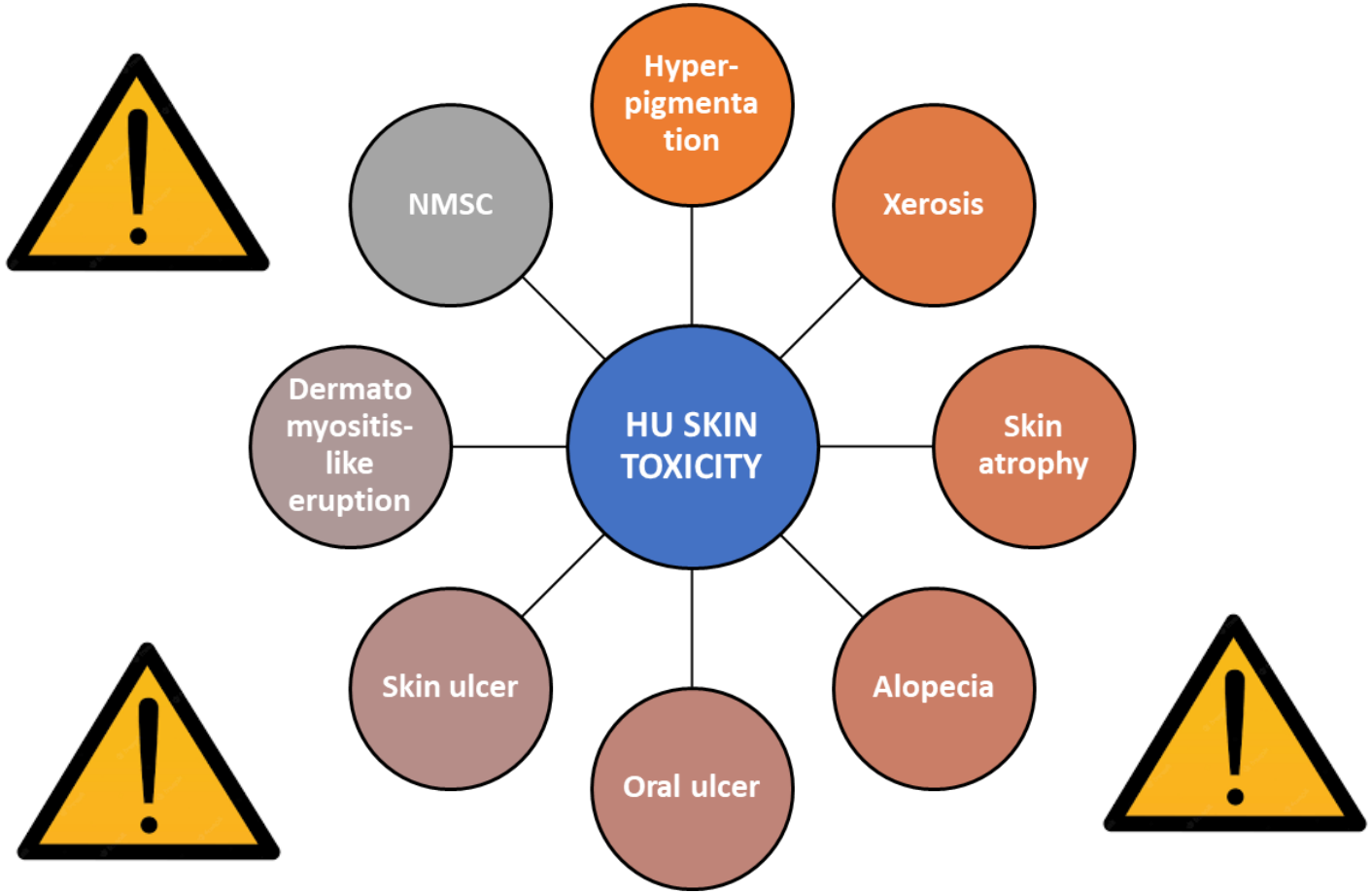
Intolerance to Hydroxyurea – other toxicities in the PV-ARC Italian study



- Overall, **75 out of 506 (14.8%)** patients had a non hematological toxicity.
- Non hematological toxicity was most frequently cutaneous (skin ulcers and oral aftosis), but also gastrointestinal and fever

Palandri F et al, SIE 2021

Hydroxyurea: cutaneous side effects



Bulte, C.A. et al. Int J Dermatol 2020, 60: 810-817.

Hydroxyurea & oral aftosis

Oral stomatitis and ulcerations have been associated with HU.

Occurring in 0.08–5.9% of patients, oral ulcers are associated with pain and burning, occasionally leading to weight loss and tooth decay.

Under reporting?

Reported latency periods range from as early as 7 weeks to several months of HU therapy.

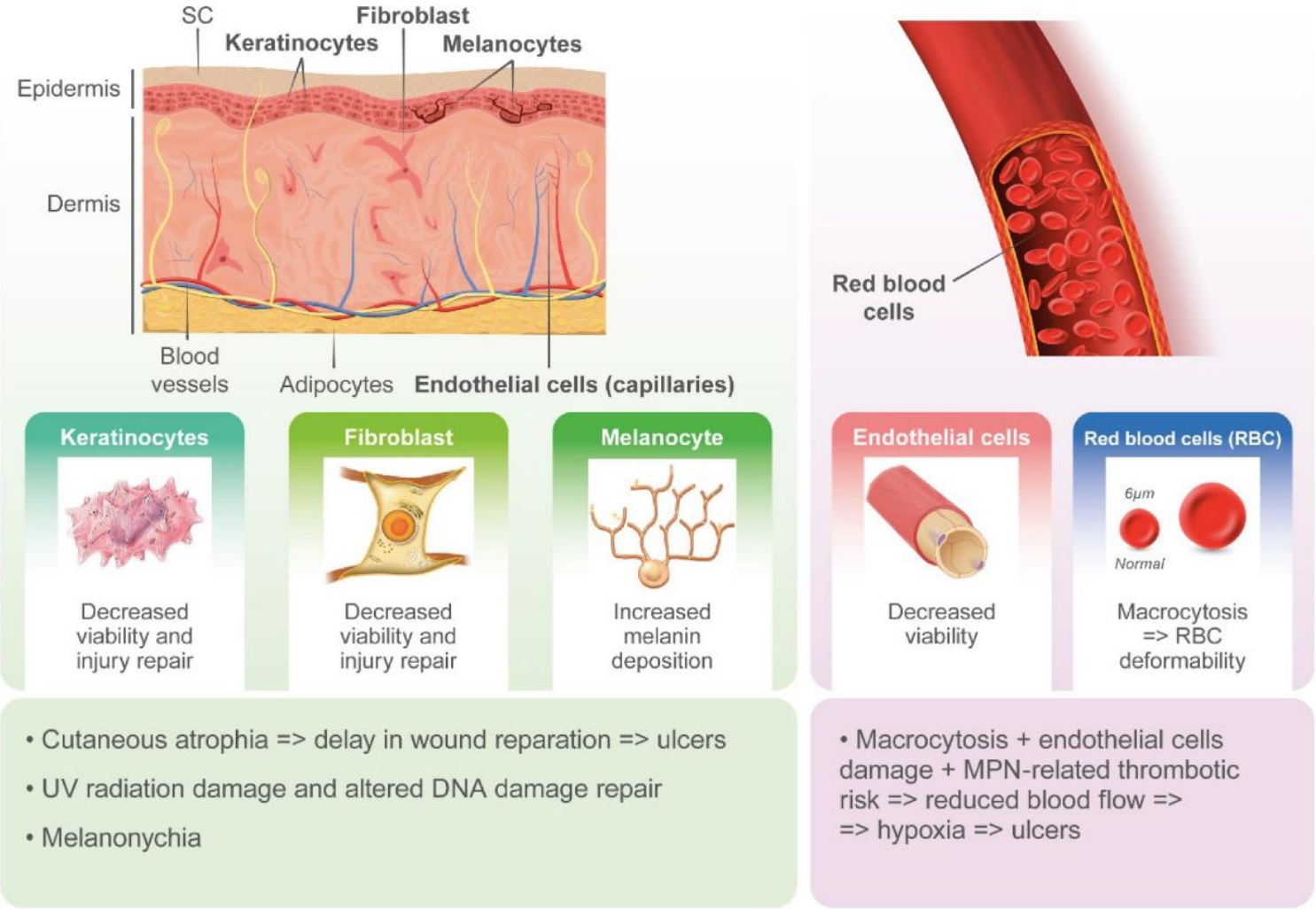
The risk is always there!

Lesions have complete resolution after 1 month of HU termination.

Full recovery requires HU discontinuation!

Bulte, C.A. et al. Int J Dermatol, 60: 810-817.

Pathogenesis of hydroxyurea-induced cutaneous toxicity



- As an antimetabolite, HU has a skin tropism with **reduced cell renewal/proliferation**, resulting in skin atrophia
- The block of skin cells in G1 state induce **higher sensitivity to UVA radiation damage and impaired DNA repair**
- RBC macrocytosis induced by HU also **reduce RBC deformability with endothelial damage** and higher risk of peripheral hypoxia

- All these alterations may result in skin ulcers

Malato A. et al. Int J Mol Sci. 2020 May 30;21(11):3900.

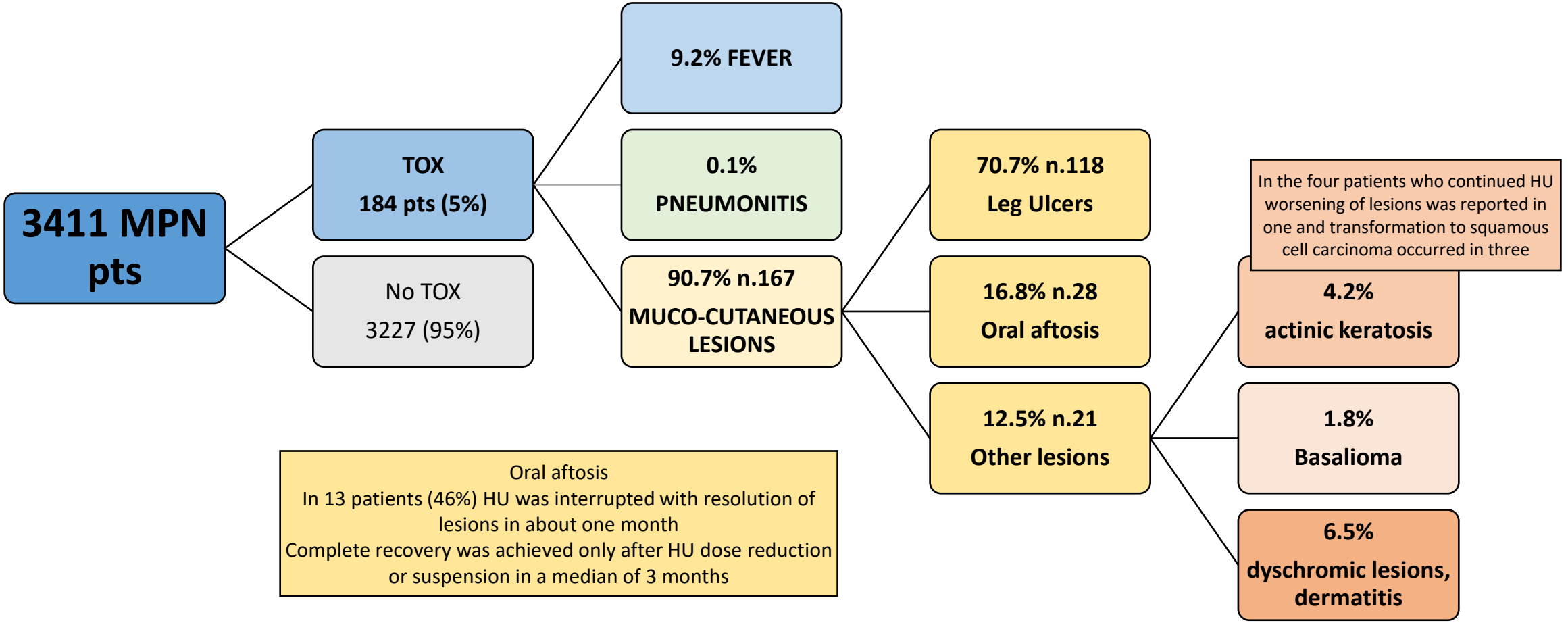
The Mister Hyde Face of a Safe Drug
Mucocutaneous Toxicity of Hydroxyurea in 993 MPN patients

- In a retrospective study from Lazio region including 993 MPN patients, mucocutaneous toxicity was reported in 51 patients (8.3%)
- Skin toxicity occurred after a median period from the initiation of HU treatment of 32.1 months and a mean HU dose of 1085 mg.
- A total of 11 patients (21.6%) of the patients with a muco- cutaneous toxicity and 1.8% of all patients treated with HU developed oral aftosis ulcers.
- 27% of patients had uncomplete resolution of skin toxicity, mainly due to HU continuous therapy

Feature	Oral Aphtosis
No. of patients (%)	11 (21.6)
Mean HU dose, mg	1055
Median time from HU initiation (IR), mo	2.1 (1.6-9.4)
HU modification	
No modification	2
Dose reduction	2
Temporary discontinuation	3
Permanent discontinuation	4
Median toxicity duration (IR), mo	3.3 (0.8-6.6)
Toxicity resolution	
Complete (%)	8 (72.7)
Partial (%)	3 (27.3)

Latagliata R et al. Cancer. 2012 Jan 15;118(2):404-9.

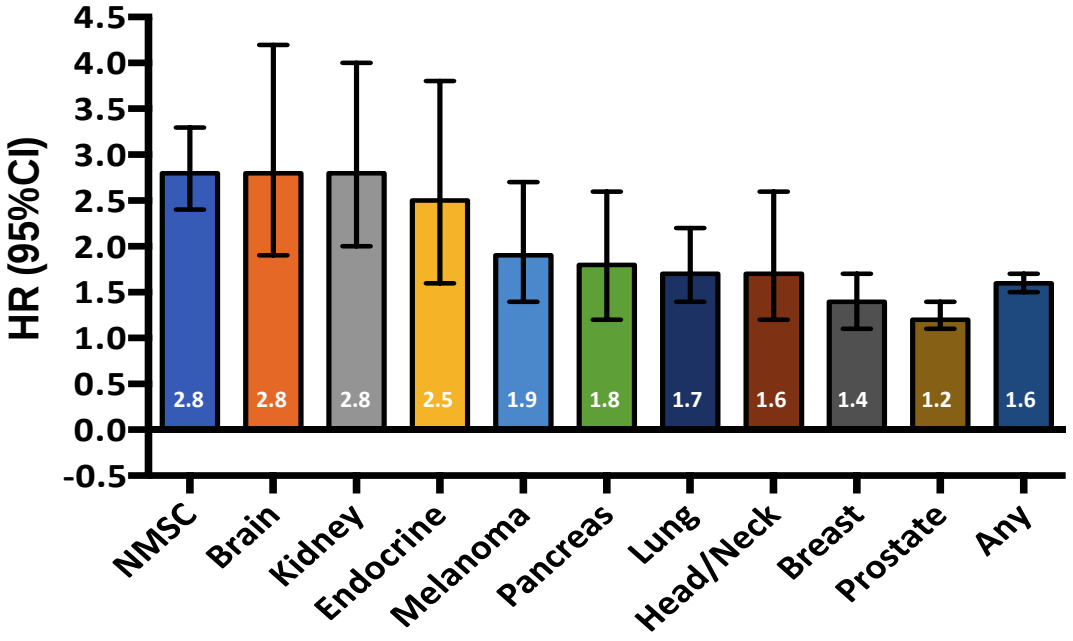
The Mister Hyde Face of a Safe Drug
Hydroxyurea-related toxicity in 3411 MPN patients

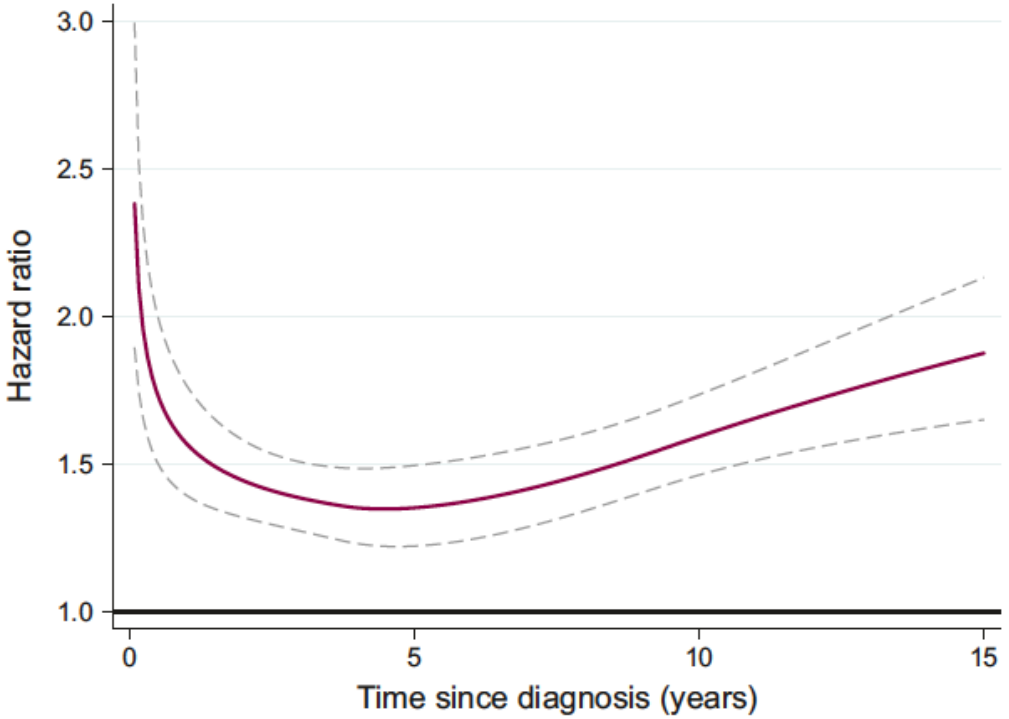


Antonioli E, Am J Hematol. 2012 May;87(5):552-4.

Incidence of second neoplasms in MPNs

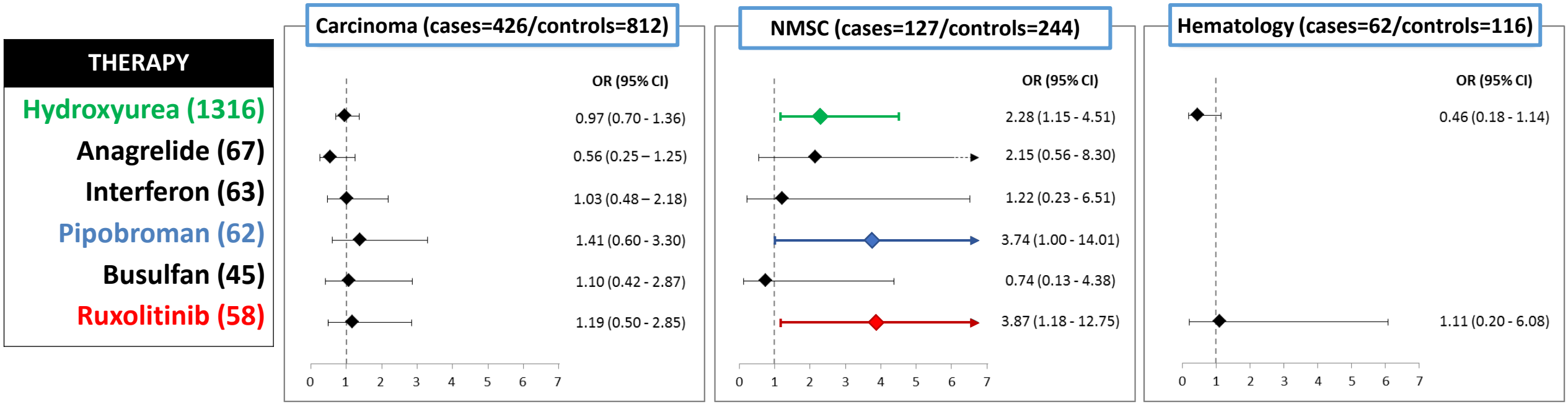
In a Sweedish popoulation-based study on 9379 MPN patients (14.8% MF), diagnosed between 1973 and 2009, an increase of **any nonhematologic cancer** (**HR 1.6**; 95%CI: 1.5-1.7) was observed compared to 35682 matched controls.





Landtblom AR et al. ***Leukemia 2018***;32:2203-2210

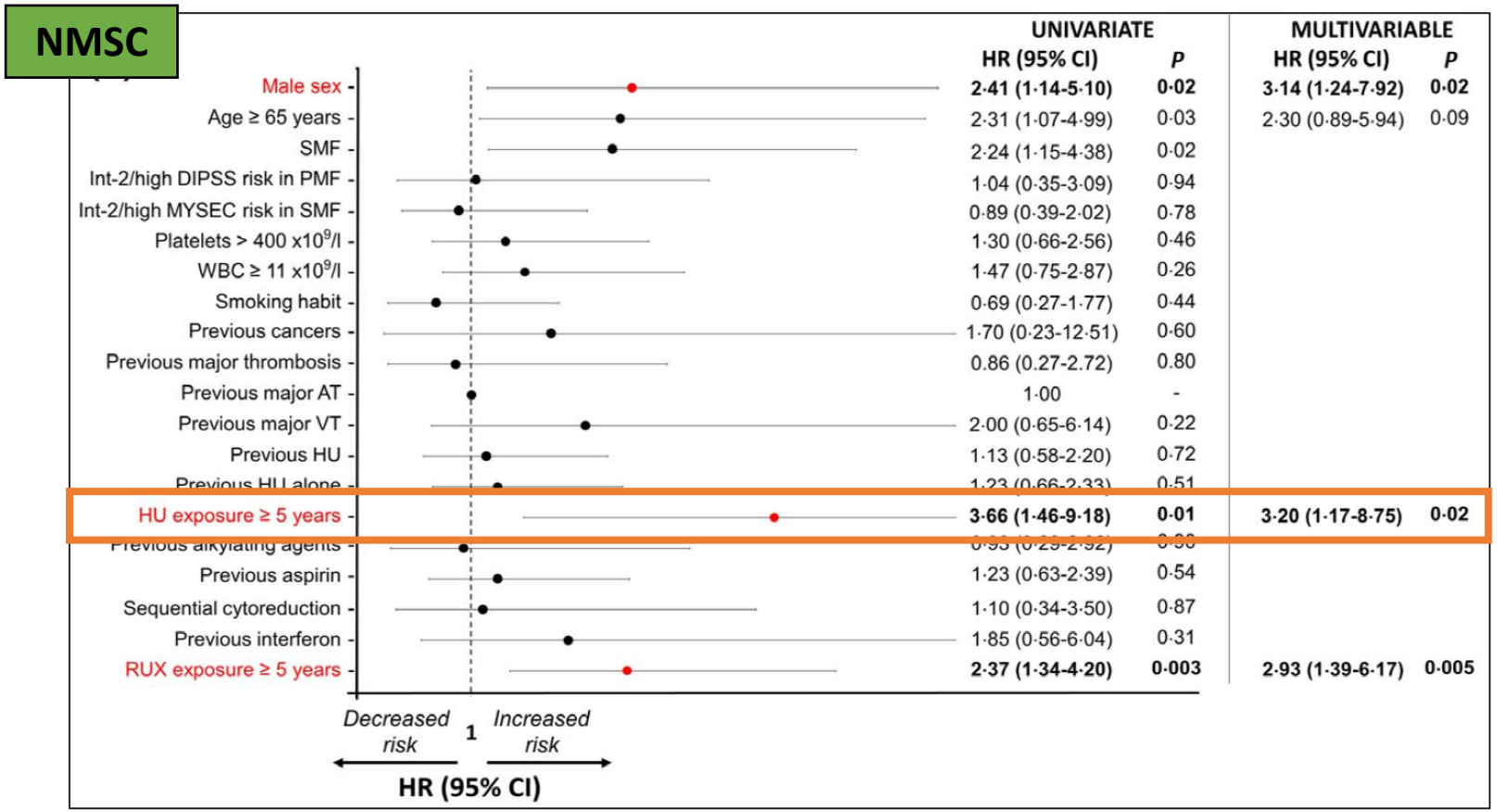
Role of MPN therapy in SPM occurrence
The MPN-K study



- After a median exposure of 3 years, **HU** use was associated with an increase in **non-melanoma skin cancers** (NMSC) (OR 2.28, 95% CI 1.15–4.51).
- Also, **pipobroman** (OR 3.74, 95% CI 1.00–14.01) and **ruxolitinib** (OR 3.87, 95% CI 1.18-12.75) seemed to be associated to a **higher risk of NMSC**

Barbui T et al ***Leukemia 2019***; 33:1996-2005

NMSC in HU and RUX-exposed MF patients

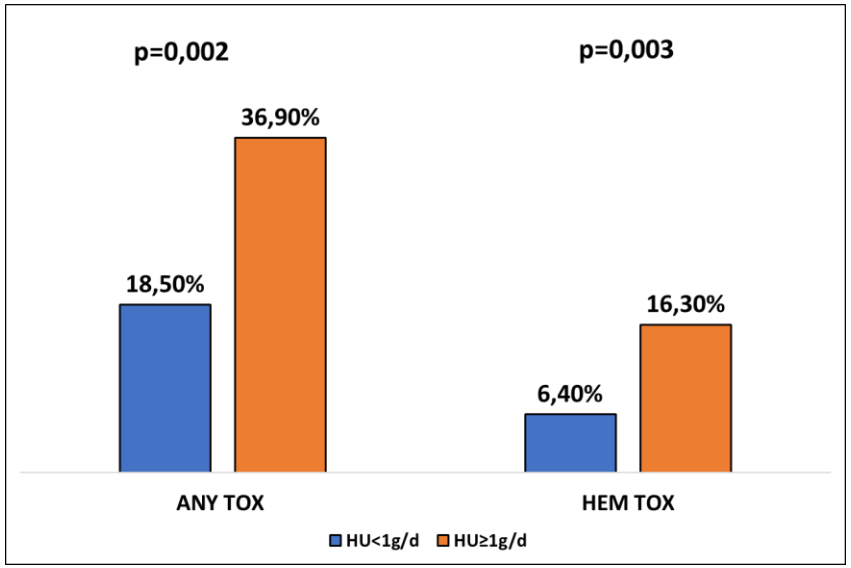


- **In a real-life Italian study, SPMs** occurred in around **10%** of 700 MF patients treated with RUX, their incidence increased over time, and represented the fourth cause of death.
- **NMSCs were the most frequent and were significantly associated with long-term exposure** (≥5 years) to **HU** and **RUX.**

Polverelli N et al, **Br. J. Haematol** (2021), 193: 356-368.

HU dose is associated with toxicity –PV ARC study

- At least one HU-related AE occurred in 123/506 patients (24.3%) and was hematological in 48 patients (9.4%).
- Median HU dose ≥1 g/d was associated with increased incidence of HU-related AEs



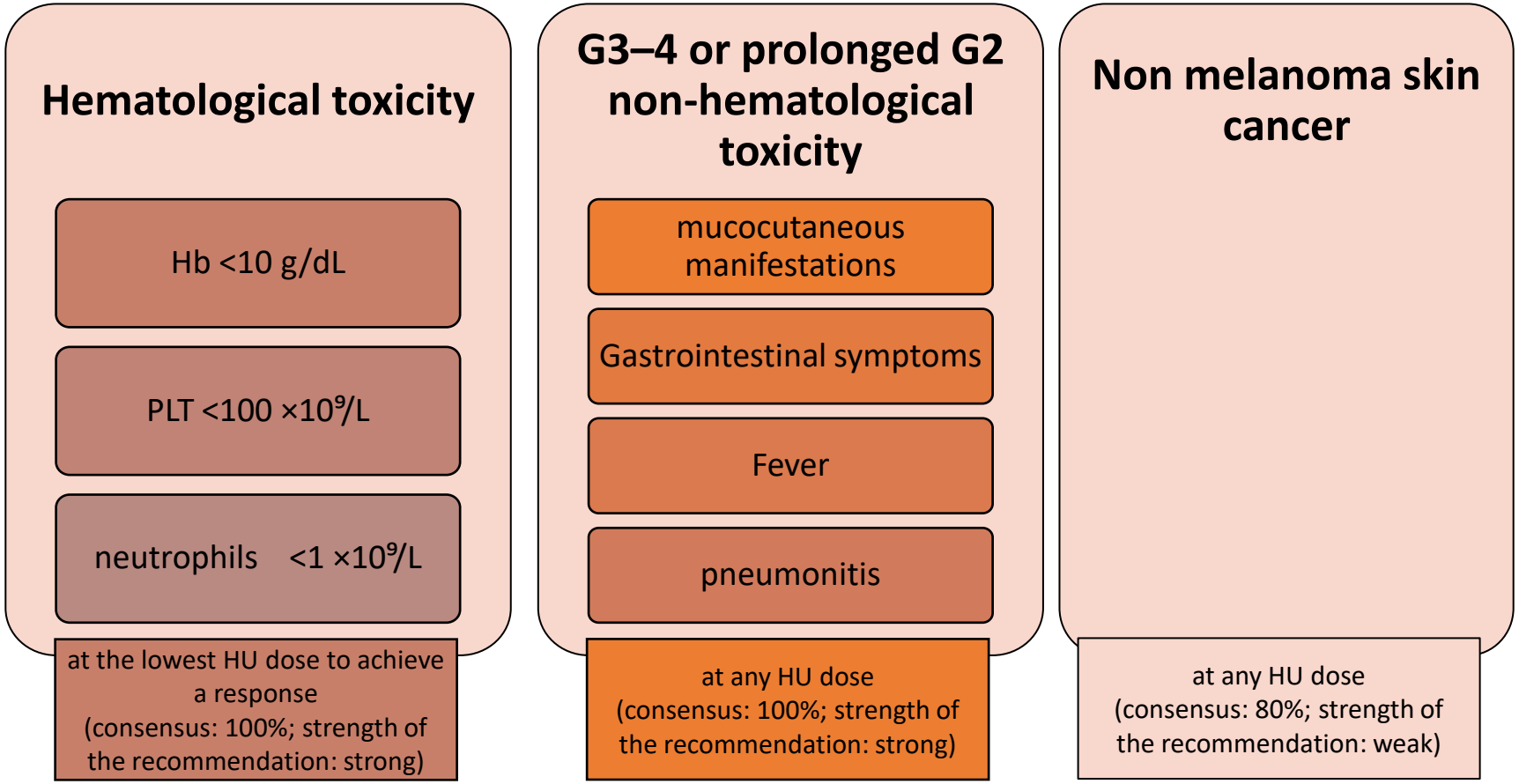
Toxicities	HU < 1g/d (n. 346)		HU ≥ 1g/d (n. 160)		p
	n. (%)	Incidence rate (per 100 patient-years)	n. (%)	Incidence rate (per 100 patient-years)	
Hematological toxicity	22 (6.4%)	1.7	26 (16.3%)	4.0	**0.003**
Anemia	5 (1.5%)	0.4	9 (5.7%)	1.3	**0.03**
Thrombocytopenia	15 (4.3%)	1.2	16 (10%)	2.5	0.09
Neutropenia	2 (0.6%)	0.1	1 (0.6%)	0.2	1.0
Extra-hematological toxicity	42 (12.1%)	3.1	33 (20.6%)	4.7	0.11
Skin ulcers	18 (5.2%)	1.4	20 (12.5%)	2.9	**0.02**
Oral aftosis	9 (2.6%)	0.7	4 (2.5%)	0.6	0.81
GI disturbances	4 (1.1%)	0.3	3 (1.9%)	0.4	0.65
Fever	2 (0.6%)	0.1	0	0	0.43
Myalgia	2 (0.6%)	0.1	0	0	0.43
Zoster reactivations	1 (0.3%)	0.1	1 (0.6%)	0.2	0.69
NMSC	6 (1.7%)	0.4	5 (3.1%)	0.6	0.53
Overall toxicity	64 (18.5%)	4.8	59 (36.9%)	8.7	**0.002**

- Among non hematological adverse events, there was a significant excess of skin ulcers in HU ≥1 g/d
- A total of 11 NMSC occurred during or after HU, with no impact of median HU dose

Suboptimal response (SubOR) included ≥1 of the following criteria after at least 3 months of HU: leukocyte count >10 x10^9/l and platelet count 400 x10^9/l; need for phlebotomy to keep HCT<45%; persistence/occurrence of palpable splenomegaly; failure to completely relieve PV-related symptoms

Palandri F et al, SIE 2021

ELN recommendations for HU switch in intolerant patients



Marchetti M et al, Lancet Haematol . 2022 Apr;9(4):e301-e311.

.

Eight ways to improve management of HU intolerance

Discuss HU-related toxicities before therapy start	• Skin ulcers and oral aftosis can go unrecognized as possible side effects of HU • Early detection may avoid serious complications
Be proactive!	• Early use of antiemetics and anti-diarrotics may reduce discontinuations due to GI toxicity
Low-grade side effects may be burdensome	• Low-grade fevers, hair loss, mouth ulcers are not trivial for patients • If prolonged, they may require HU discontinuation
Hematological monitoring is necessary	• Cytopenia is a frequent HU-related AEs and correlates with worse outcome • Adequate hematological follow-up is required

Palandri F, personal considerations

Eight ways to improve management of HU intolerance

Create a multidisciplinary team	• A skin doctor that is trained on HU lesions may be very helpful • Skin evaluation should be performed once a year
Do not abandon your patient!	• Regular and frequent clinical visits may detect early toxicities
HU discontinuation should not be delayed	• In case of HU-related toxicity which is severe or mild but prolonged, do not delay therapy switch! • Failure to stop HU if dysplastic pre-carcinomatous lesions can favor occurrence of skin cancer
Think fast!	• In case of HU toxicity, type of 2L therapy should be decided asap

Palandri F, personal considerations

BOLOGNA
17 FEBBRAIO 2023
NH De La Gare

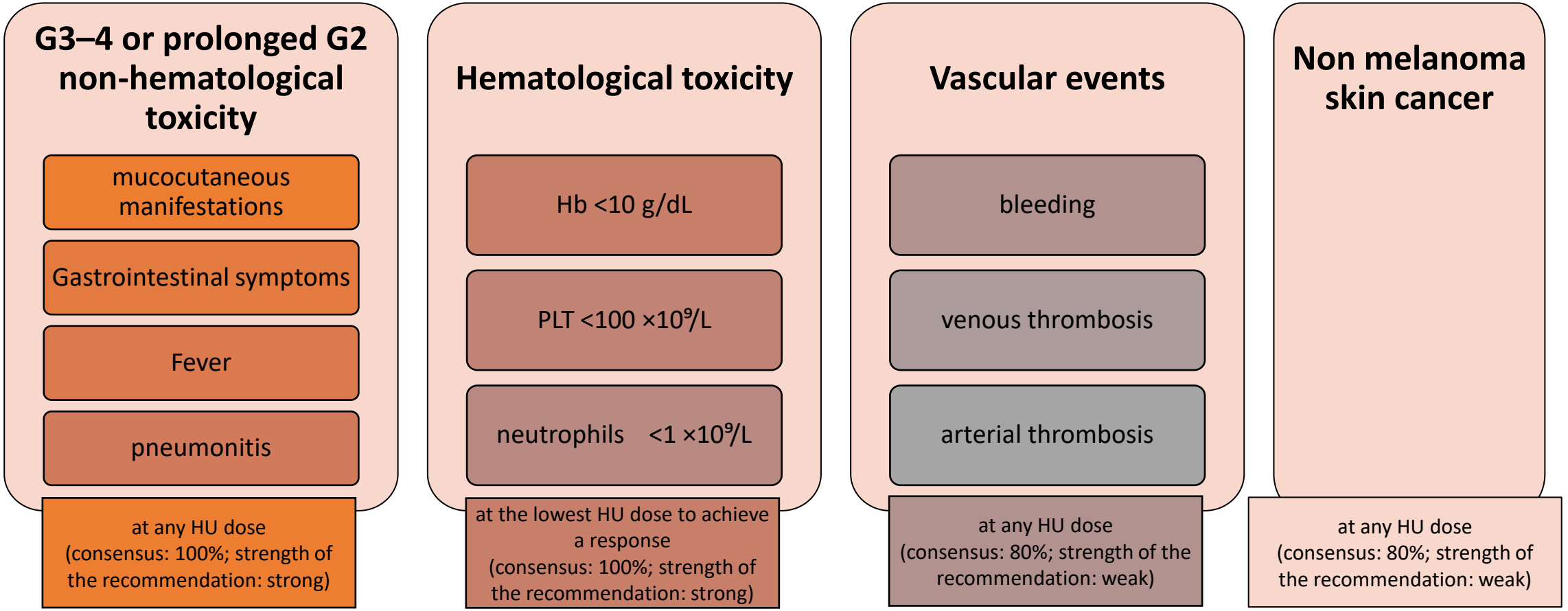
POLICITEMIA VERA NEL 2023:

qualcosa è cambiato

Grazie!

Francesca Palandri

ELN recommendations for HU switch in intolerant patients

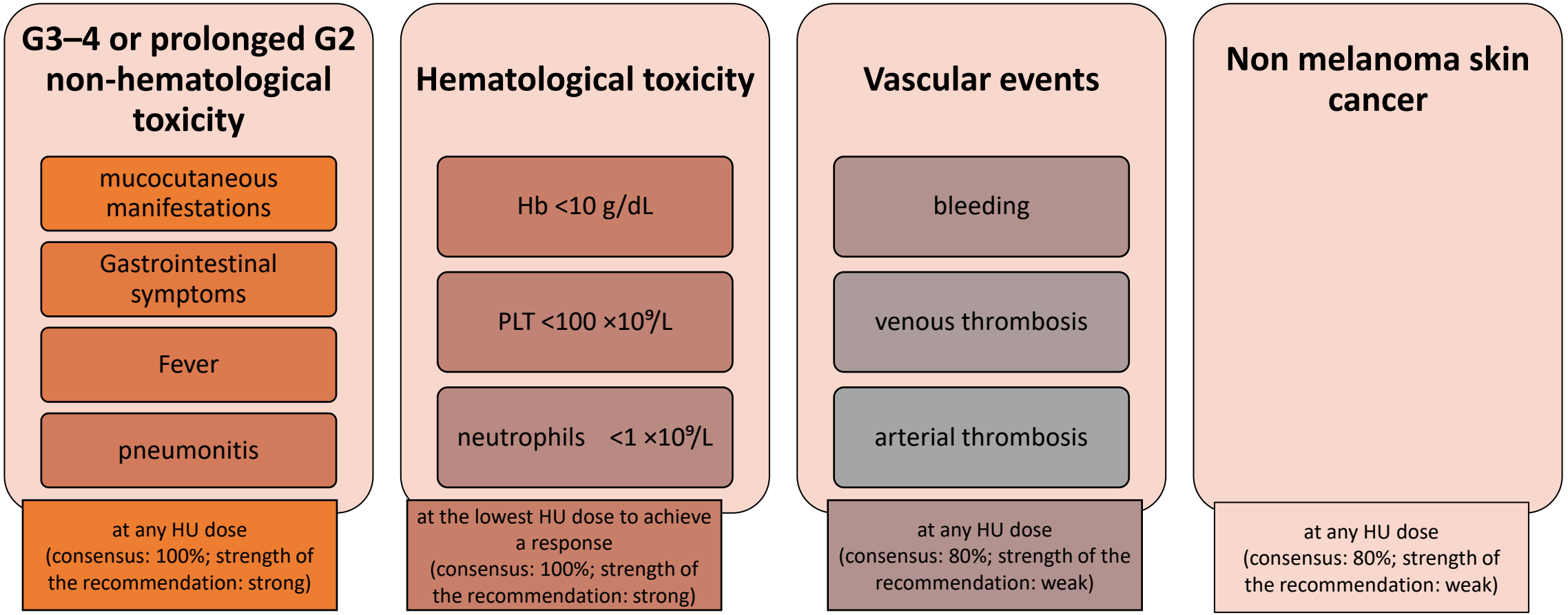


Marchetti M et al, Lancet Haematol . 2022 Apr;9(4):e301-e311.

.

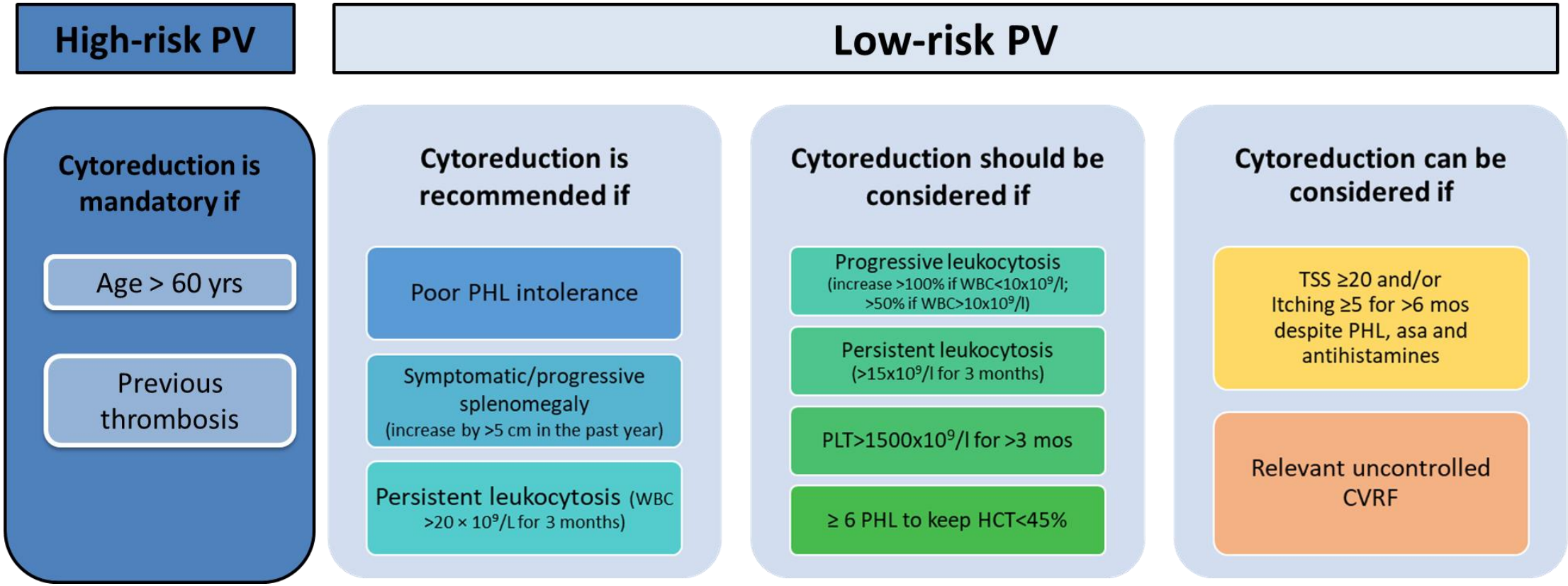
Recommendations for HU switch in intolerant patients

Patients with PV who are receiving hydroxyurea are recommended to change to another cytoreductive drug if they meet at least one of the following criteria:



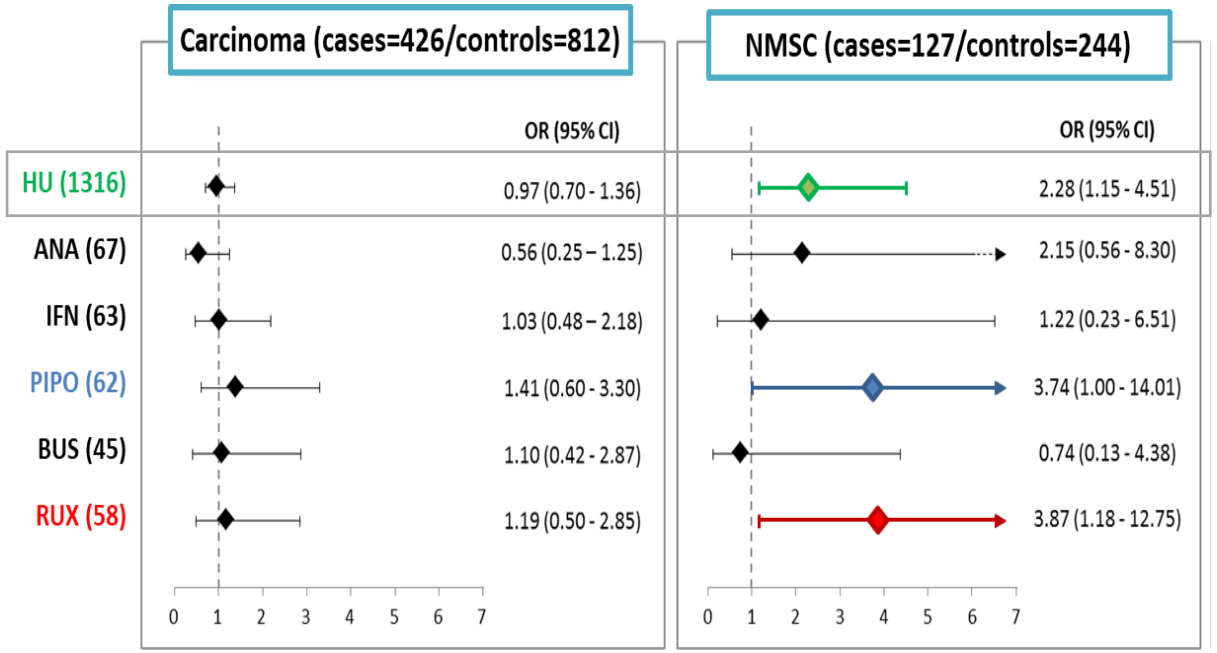
Marchetti M et al, Lancet Haematol . 2022 Apr;9(4):e301-e311.

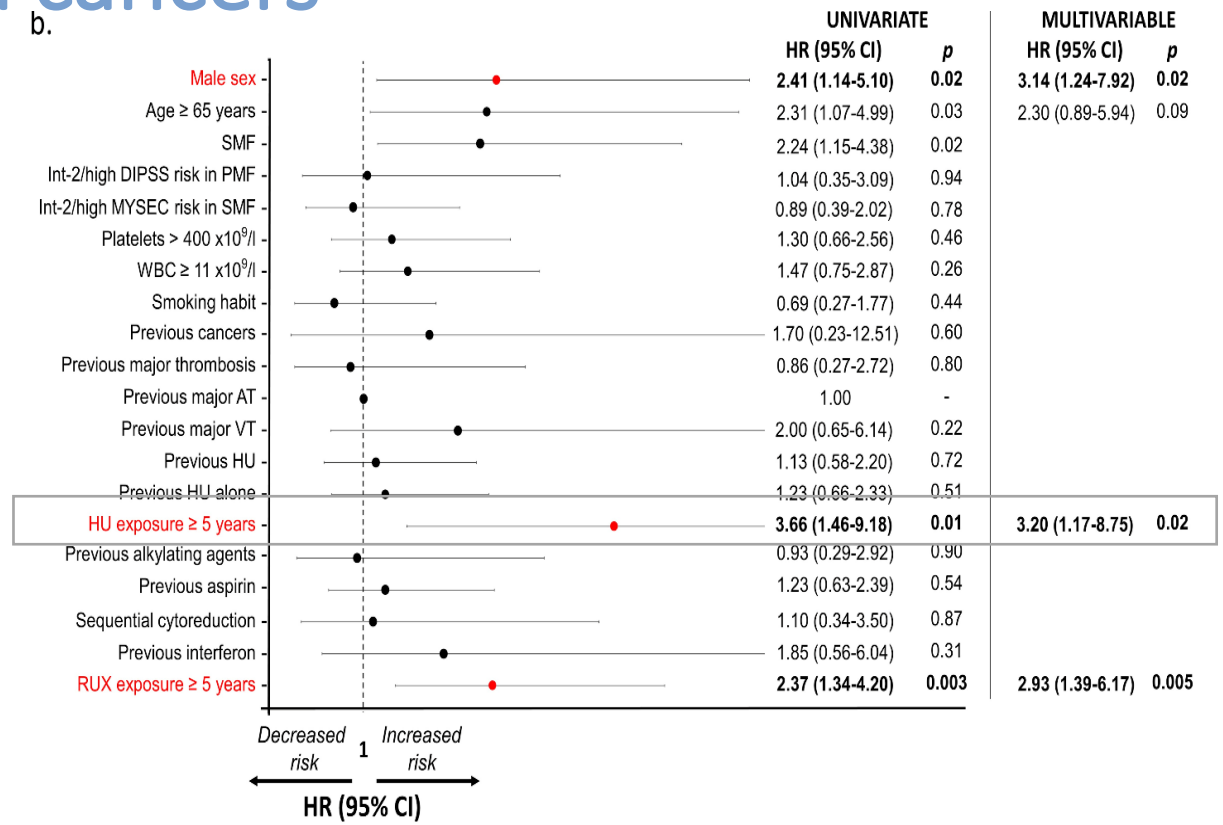
The indications to cytoreductive therapy for PV in 2022



Marchetti M et al, Lancet Haematol . 2022 Apr;9(4):e301-e311

Hydroxyurea & risk of second cancers





A large international nested case-control study (MPN-K) 647 MPN patients with SC, were matched with 1234 MPN controls After a median exposure of 3 years, HU use was associated with an increase in non-melanoma skin cancers

In a retrospective analysis on 700 RUX-treated MF patients, previous exposure to HU > 5 years was associated with an increase in non-melanoma skin cancers but not with second primary malignancies

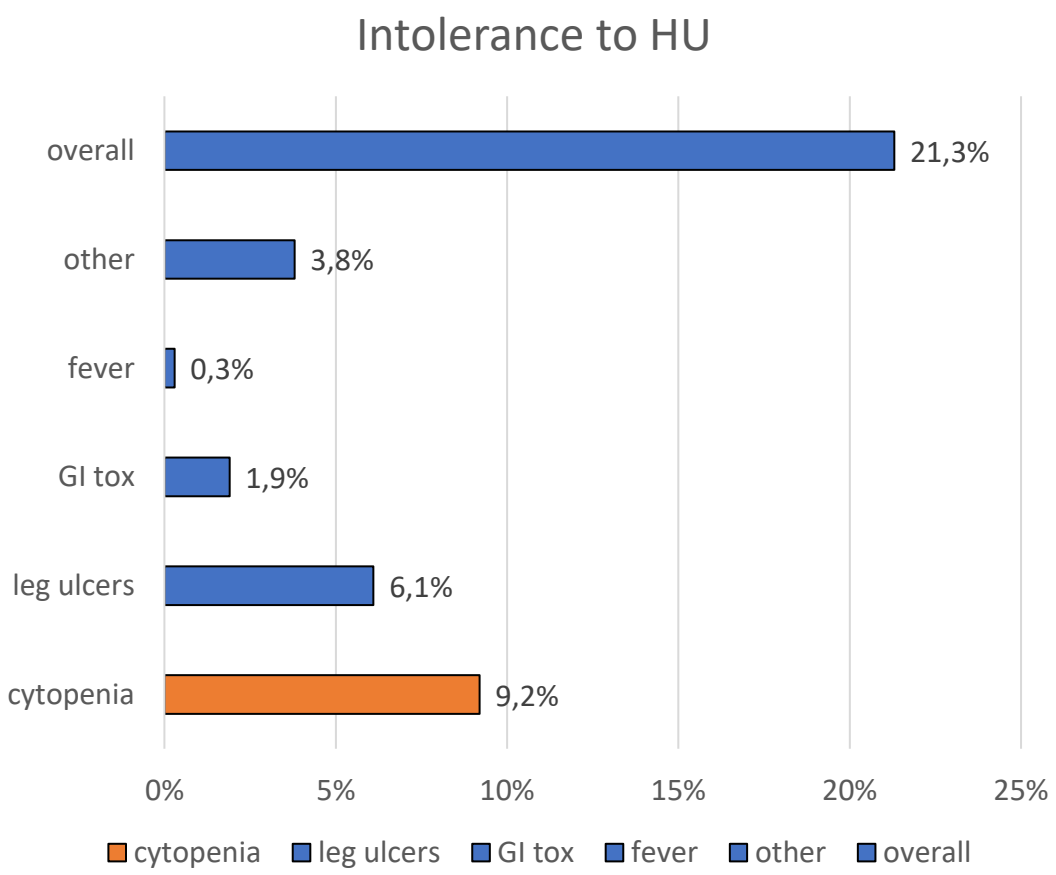
Barbuti T, Leukemia 2019, 33: 1996–2005; Polverelli N, Palandri F, Br J Haematol. 2020 Nov 21

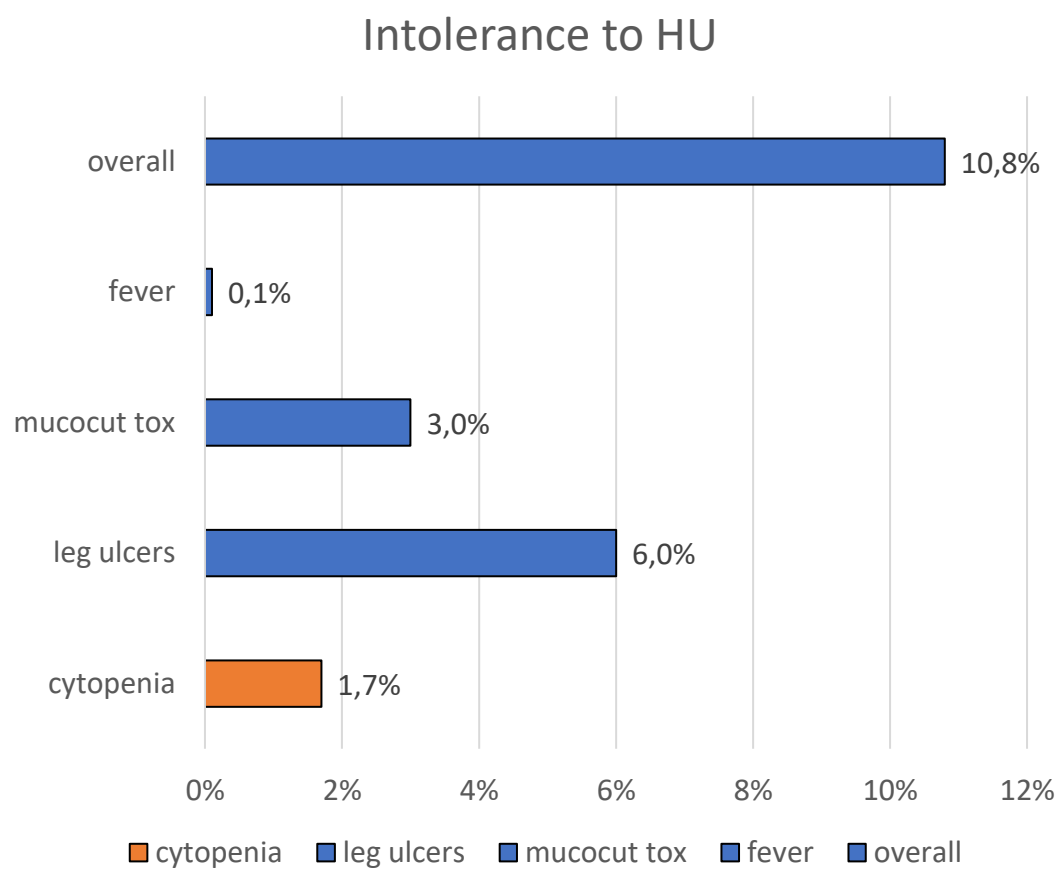
Strategies to improve HU management

PV-related symptoms must be assessed	•Assess symptoms with early and regular use of validated questionnaires •Undermanage symptoms leads to poor QoL and therapy failure
Discuss HU-related toxicities before therapy start	•Skin ulcers and oral aftosis can go unrecognized as possible side effects of HU •Early detection may avoid serious complications
Be proactive!	•Early use of antiemetics and anti-diarrotics may reduce discontinuations due to GI toxicity
Low-grade side effects may be burdensome	•Low-grade fevers, hair loss, mouth ulcers are not trivial for patients •If prolonged, they may require HU discontinuation
Hematological monitoring is necessary	•Cytopenia is a frequent HU-related Aes and correlates with worse outcome •Adequate hematological follow-up is required
Create a multidisciplinary team	•A skin doctor that is trained on HU lesions may be very helpful •Skin evaluation should be performed once a year
Do not abandon your patient!	•Regular and frequent clinical visits may detect early toxicities
HU discontinuation should not be delayed	•In case of HU-related toxicity which is severe or mild but prolonged, do not delay therapy switch! •Failure to stop HU if dysplastic precarcinomatous lesions can favor occurrence of skin cancer
Think fast!	•In case of HU toxicity, type of 2L therapy should be decided asap

Palandri F, personal considerations

Intolerance to Hydroxyurea – cytopenia in the Spanish registry





Alvarez-Larrán. Blood. 2012;119:1363; Alvarez-Larran et al; Br J Haematol. 2016 Mar;172(5):786-9