
# POLICITEMIA VERA NEL 2023:

## qualcosa è cambiato

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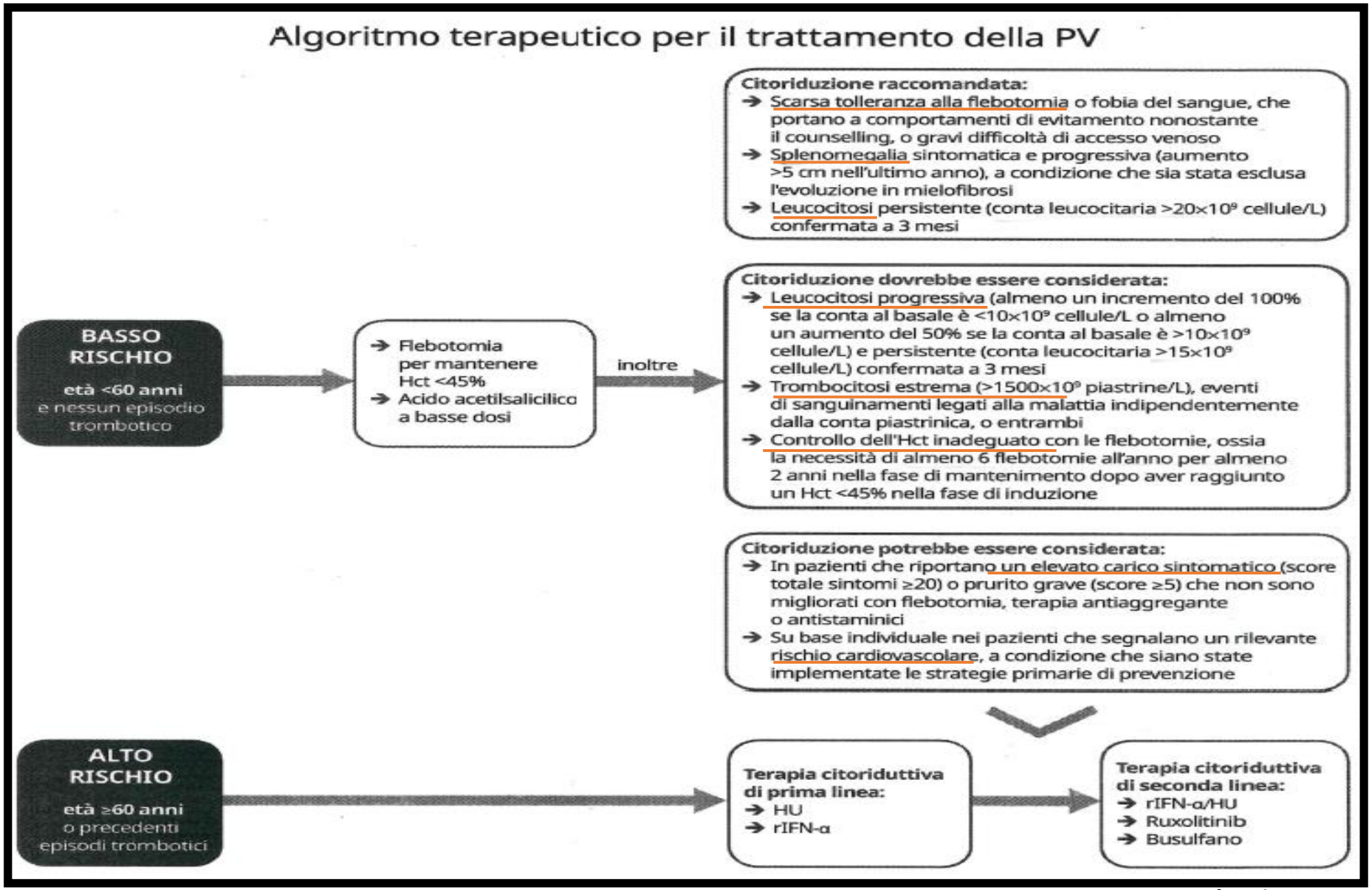
# Disclosures

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Novartis | | | | | X | X | |
| Jazz Healthcare | | | | | X | X | |
| Bristol Myers Squibb | | | | | X | | |

# Come riconoscere e gestire il problema della RESISTENZA a IDROSSIUREA

- Idrossiurea: cenni di efficacia e sicurezza
- Definizioni e raccomandazioni secondo European LeukemiaNet
- Cosa ci dice la letteratura?
- Real life

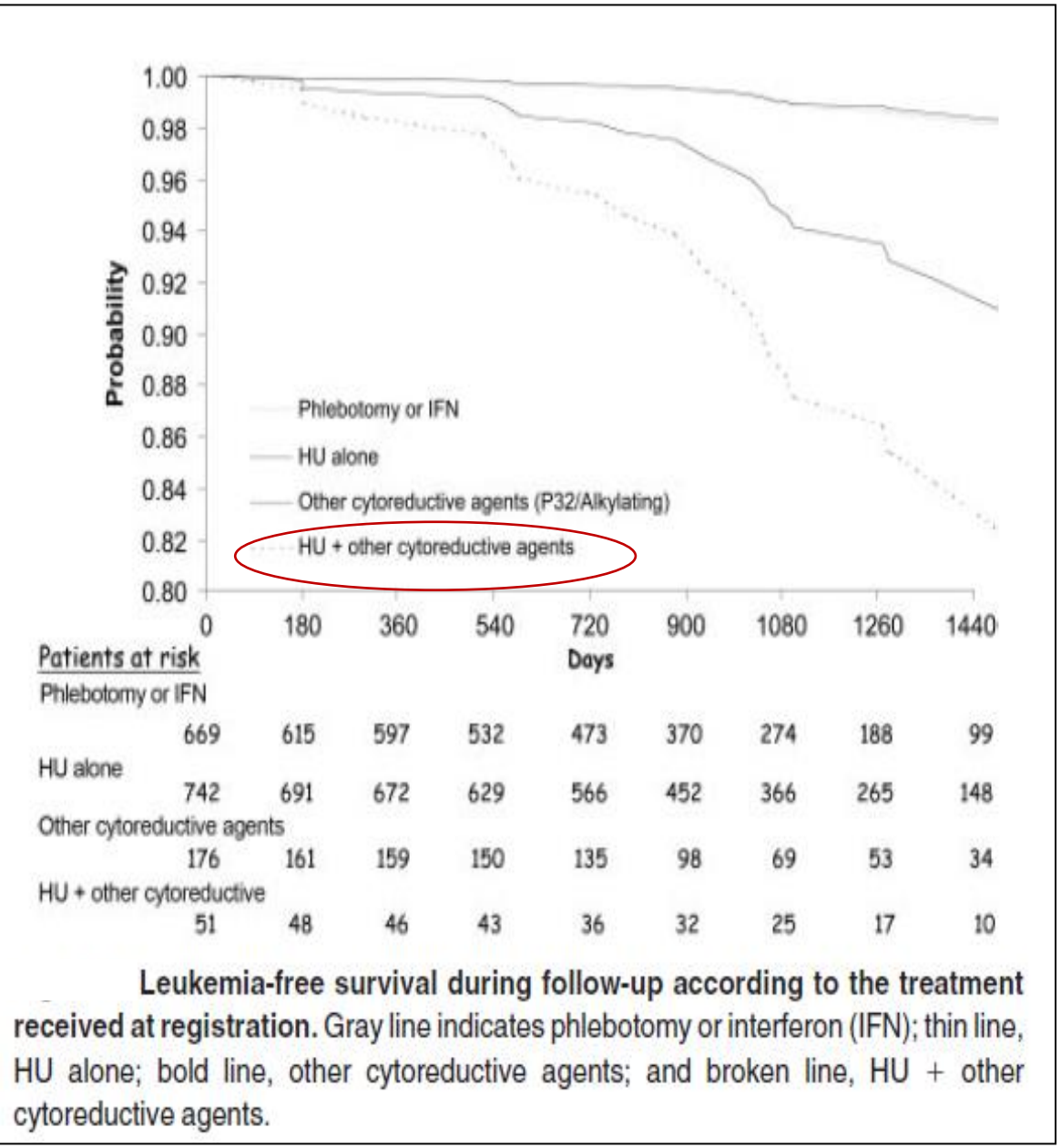



European LeukemiaNet 2021

**Number of Patients Reaching Principal Study End Points.***

| Feature | Hydroxyurea plus Aspirin (N=404) | Anagrelide plus Aspirin (N=405) | Odds Ratio (95% CI) | P Value† |
|---|---|---|---|---|
| | *no. of patients* | | | |
| **Primary end point** | | | | |
| Arterial or venous thrombosis, serious hemorrhage, or death from thrombosis or hemorrhage | 36 | 55 | 1.57 (1.04–2.37) | 0.03 |
| **Secondary end point** | | | | |
| Arterial thrombosis | 17 | 37 | 2.16 (1.27–3.69) | 0.004 |
| Myocardial infarction | 7 | 13 | 1.84 (0.76–4.41) | NS |
| Unstable angina | 2 | 4 | 1.94 (0.39–9.63) | NS |
| Stroke | 7 | 9 | 1.30 (0.49–3.47) | NS |
| Transient ischemic attack | 1 | 14 | 5.72 (2.08–15.73) | <0.001 |
| Other‡ | 2 | 0 | | NE |
| Venous thromboembolism | 14 | 3 | 0.27 (0.11–0.71) | 0.006 |
| Deep-vein thrombosis | 9 | 1 | 0.20 (0.06–0.71) | 0.009 |
| Pulmonary embolism | 5 | 2 | 0.43 (0.01–1.87) | NS |
| Hepatic-vein thrombosis | 1 | 0 | | NE |

Harrison C. N Engl J Med, 2005




**Leukemia-free survival during follow-up according to the treatment received at registration.** Gray line indicates phlebotomy or interferon (IFN); thin line, HU alone; bold line, other cytoreductive agents; and broken line, HU + other cytoreductive agents.

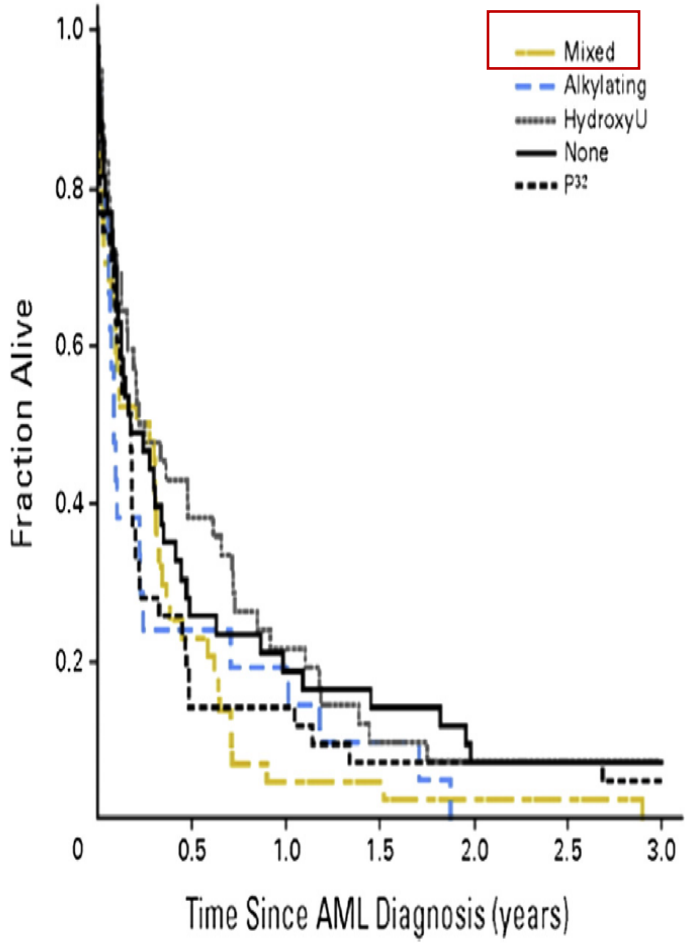
Finazzi G. Blood, 2005

Treatment groups and leukaemic transformation amongst 459 patients with polycythaemia vera.

| Treatment groups | *N* | AML incidence (%) | Age at diagnosis in years (median/range) | Disease duration in months (median/range) |
|---|---|---|---|---|
| All patients | 459 | 34 (7·4%) | 60 (11–93) | 64 (0–562) |
| No cytoreductive therapy ($n = 115$) or exposure to anagrelide or IFN only ($n = 8$) | 123 | 3 (2·4%) | 58 (11–83) | 28 (0–325) |
| Hydroxycarbamide only ($n = 123$) and/or additional exposure to anagrelide or IFN ($n = 30$) | 153 | 7 (4%) | 63 (17–93) | 67 (0–496) |
| Single agent cytotoxic drug other than hydroxycarbamide* | 129 | 15 (11·6%) | 61 (34–83) | 72 (0–562) |
| Two or more cytotoxic drugs** | 54 | 9 (16·7%) | 55 (21–90) | 161 (5–420) |

*Included radiophosphorus (P32) in 116 patients, chlorambucil in 7 patients, busulphan in 6 patients.
**Included radiophosphorus (P32) in 51 patients, hydroxycarbamide in 40 patients, chlorambucil in 13 patients, and busulphan in 10 patients.
AML, acute myeloid leukaemia; IFN, interferon.

Gangat N et al. Br J Haematol, 2007




. Acute myeloid leukemia (AML) survival in relation to previous therapy. Mixed combinations of two to three cytoreductive treatments ($n = 46$), alkylators only ($n = 21$), none ($n = 47$), hydroxyurea (HydroxyU) only ($n = 45$), and radioactive phosphorous (P32) only ($n = 47$).

- Età paziente
- Tempo dalla diagnosi
- Leucocitosi

Risk of AML/MDS transformation according to number of cytoreductive treatment types.

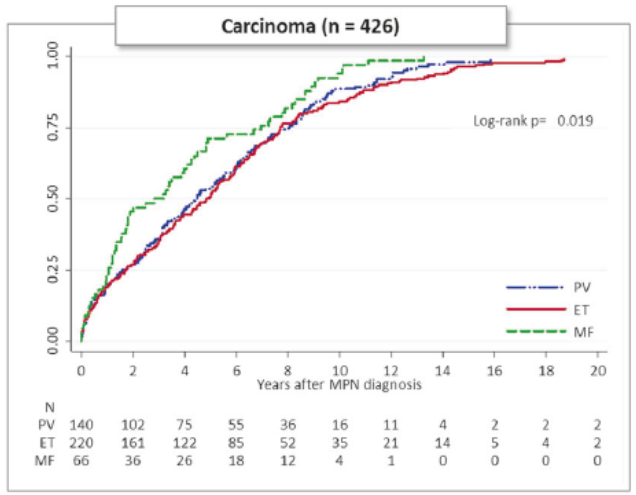
| Treatment | Odds ratio (95% confidence interval) |
|---|---|
| None | 1.0 (reference) |
| $P^{32}$ only | 1.5 (0.8–2.8) |
| Alkylating agent only | 0.9 (0.4–2.1) |
| Hydroxyurea only | 1.2 (0.6–2.4) |
| Mixed treatment (2 or 3) | 2.9 (1.4–5.9) |

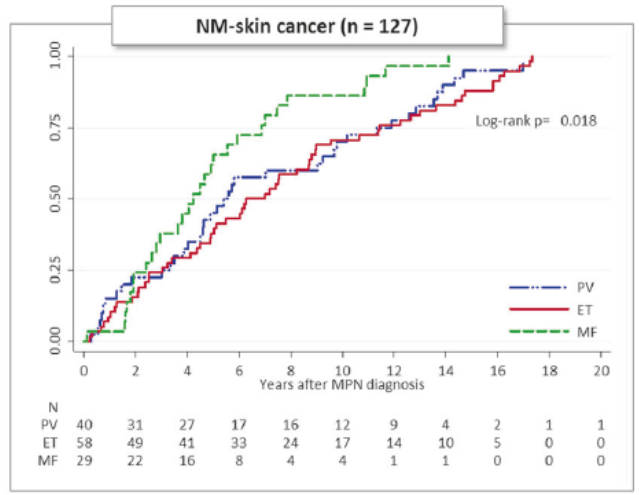
Reprinted by permission from Journal of Clinical Oncology (Bjorkholm et al., 2011)

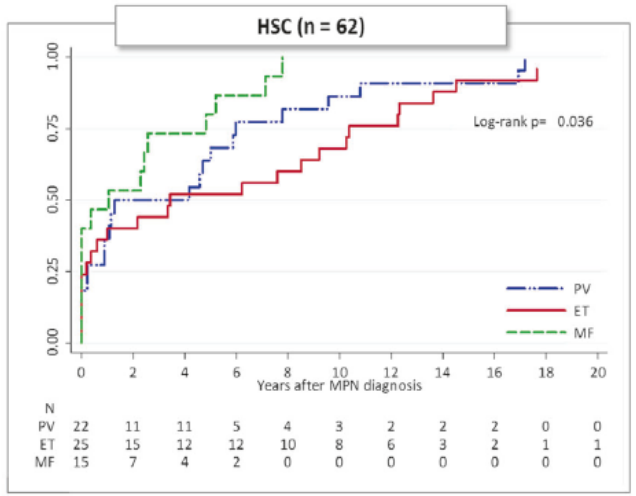
*M. Björkholm et al. / Best Practice & Research Clinical Haematology 27 (2014) 141–153*

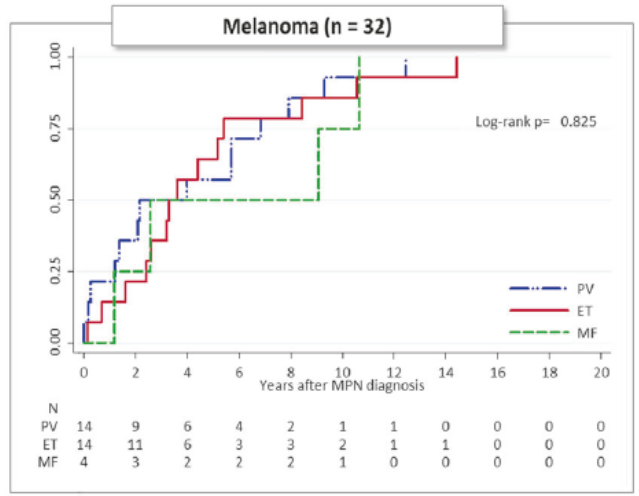
Gavini DR, Cureus 2021

| Study | Patients on HU | Patients with NMSC | Percentage of patients on HU with NMSC |
|---|---|---|---|
| Antonioli et al. 2012 | 3411 | 10 | 0.29% |
| Barbui et al. 2019 | 1316 | 127 | 9.6% |
| Kissova et al. 2014 | 66 | 9 | 13.6% |
| Verner et al. 2014 | 149 | 51 | 34.2% |




-Età paziente
-Esposizione luce UV
-Dose e durata HU

Barbui T, Leukemia 2019

European LeukaemiaNet 2013 criteria for response assessment in Polycythemia Vera.

| Complete Remission | Partial Remission |
|---|---|
| Durable[a] resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement[b] AND | Durable[a] resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement[b] AND |
| Durable[a] peripheral blood count remission, defined as hematocrit lower than 45% without phlebotomies; platelet count $\leq 400 \times 10^9$/L, WBC count $< 10 \times 10^9$/L, AND | Durable[a] peripheral blood count remission, defined as hematocrit lower than 45% without phlebotomies; platelet count $\leq 400 \times 10^9$/L, WBC count $< 10 \times 10^9$/L, AND |
| Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND | Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND |
| Bone marrow histological remission defined as the presence of age-adjusted normocellularity and disappearance of trilinear hyperplasia, and absence of > grade 1 reticulin fibrosis | Without bone marrow histological remission defined as persistence of trilinear hyperplasia |

No response: any response that does not satisfy partial remission. Progressive disease: transformation into post-PV myelofibrosis, myelodysplastic syndrome or acute leukemia. Adapted with permission from Barosi et al. [12].

[a]Lasting at least 12 weeks.

[b]Large symptom improvement (≥10-point decrease) in Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) cytokine total symptom score (TSS-C).

Barosi et al, Blood 2013

| Criteri originali ELN (ELNo) di resistenza/ intolleranza a idrossiurea (HU) | Criteri ELN modificati (ELNm) di resistenza/ intolleranza a idrossiurea (HU) |
|---|---|
| 1. Necessità di flebotomie per mantenere l'ematocrito <45% dopo 3 mesi di almeno 2 g/die di HU | 1. Necessità di flebotomie per mantenere l'ematocrito <45% dopo 3 mesi di almeno 2 g/die di HU **O** alla massima dose tollerata |
| *OPPURE* | *OPPURE* |
| 2. Mieloproliferazione non controllata, ovvero conta piastrinica >400×10$^9$/L e conta leucocitaria >10,0×10$^9$/L dopo 3 mesi di almeno 2 g/die di HU | 2. Mieloproliferazione non controllata, ovvero conta piastrinica >400×10$^9$/L e conta leucocitaria >10,0×10$^9$/L dopo 3 mesi di almeno 2 g/die di HU **o** alla massima dose tollerata |
| *OPPURE* | *OPPURE* |
| 3. Mancata riduzione della splenomegalia massiva* di oltre il 50% misurata dalla palpazione **O** mancato completo sollievo dei sintomi correlati alla splenomegalia dopo 3 mesi di almeno 2 g/die di HU | 3. Mancata riduzione della splenomegalia massiva* di oltre il 50% misurata dalla palpazione **O** mancato completo sollievo dei sintomi correlati alla splenomegalia dopo 3 mesi di almeno 2 g/die di HU **O** alla massima dose tollerata |
| *OPPURE* | *OPPURE* |
| 4. Conta assoluta dei neutrofili <1,0×10$^9$/L **O** conta piastrinica <100×10$^9$/L **O** emoglobina <10,0 g/dL alla dose più bassa di HU richiesta per ottenere una risposta clinico-ematologica completa o parziale | 4. Conta assoluta dei neutrofili <1,0×10$^9$/L **O** conta piastrinica <100×10$^9$/L **O** emoglobina <10,0 g/dL alla dose più bassa di HU richiesta per ottenere una risposta clinico-ematologica completa o parziale |
| *OPPURE* | *OPPURE* |
| 5. Presenza di ulcere alle gambe o altre tossicità non ematologiche correlate ad HU inaccettabili, come manifestazioni muco-cutanee, sintomi gastrointestinali, polmonite o febbre a qualsiasi dose di HU | 5. Presenza di ulcere alle gambe o altre tossicità non ematologiche correlate ad HU inaccettabili, come manifestazioni muco-cutanee, sintomi gastrointestinali, polmonite o febbre con qualsiasi dose di HU |

Barosi G, Br J Haematol 2010

Passamonti F, Lancet Oncol 2017

| Studio | Numero di pazienti PV | Resistenza | Intolleranza |
|---|---|---|---|
| Alvarez-Larrán A et al., Blood 2012 | 261 | 11,5% (ELNo) | 12,6% (ELNo) |
| Alvarez-Larrán A et al., Br J Haematol 2016 | 890 | 10,7% (ELNo) | 5,7% (ELNo) |
| Demuynck T et al., Ann Hematol 2019 | 106 | 4,7% (ELNo)<br>23,6% (ELNm) | 16% (ELNo)<br>16% (ELNm) |

*Studi in cui sono state valutate la resistenza e l'intolleranza ad HU secondo le linee guida ELN, originali (ELNo) o modificate (ELNm)*

| | Original ELN criteria | Modified ELN criteria |
|---|---|---|
| Total patients, *n* | 106 | 106 |
| Median length of treatment with HU, years* | 5.1 (0.1–24.8) | 5.1 (0.1–24.8) |
| Ongoing therapy, *n* (%) | 66 (62.3) | 66 (62.3) |
| Resistance/intolerance, *n* (%) | 22 (20.7) | 42 (39.6) |
| Resistance, *n* (%) | 5 (4.7) | 25 (23.6) |
| Hematocrit > 45%, *n* (%) | 0 (0.0) | 18 (16.7) |
| Leukocyte count > $10.0 \times 10^9$/L, *n* (%) | 0 (0.0) | 1 (0.9) |
| Platelet count > $400 \times 10^9$/L, *n* (%) | 0 (0.0) | 1 (0.9) |
| Palpable splenomegaly, *n* (%) | 0 (0.0) | 0 (0.0) |
| Hemoglobin < 10.0 g/dL, *n* (%) | 1 (0.9) | 1 (0.9) |
| Neutrophil count < $1.0 \times 10^9$/L, *n* (%) | 0 (0.0) | 0 (0.0) |
| Platelet count < $100 \times 10^9$/L, *n* (%) | 4 (3.8) | 4 (3.8) |
| Intolerance, *n* (%) | 17 (16.0) | 17 (16.0) |
| Leg ulcer, *n* (%) | 11 (10.4) | 11 (10.4) |
| Fever, *n* (%) | 3 (2.8) | 3 (2.8) |
| Mucocutaneous manifestations, *n* (%) | 3 (2.8) | 3 (2.8) |

*HU* hydroxyurea

*Data are median (range)

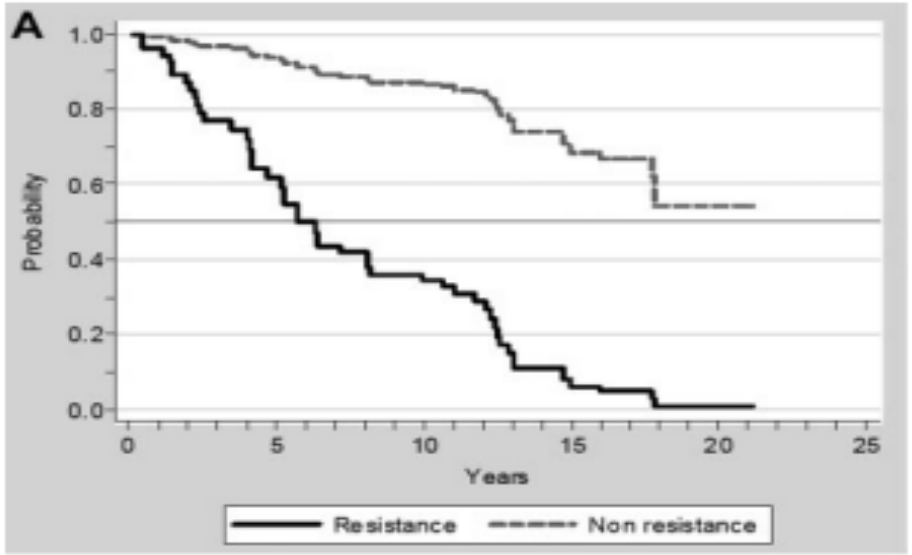
*Demuynck T, Annals of Hematology 2019*

**Multivariate analysis of initial factors predicting survival in 261 patients with PV treated with HU**

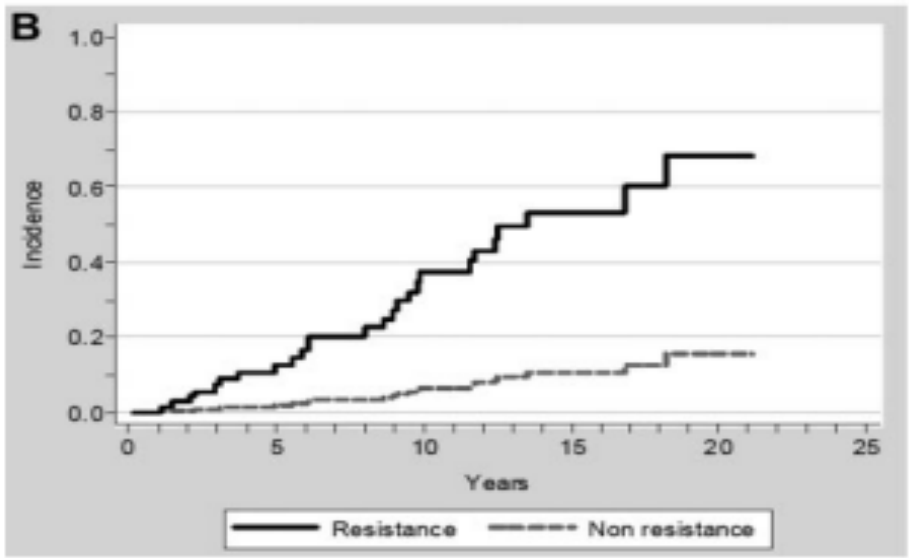
| | HR | 95% CI | P |
|---|---|---|---|
| Age > 65 y | 3.0 | 1.6-5.9 | .001 |
| Male sex | 2.3 | 1.2-4.3 | .008 |
| Cardiovascular risk factors* | 1.6 | 0.8-3.2 | .2 |
| History of thrombosis | 1.4 | 0.8-2.6 | .2 |
| **Hematologic values at diagnosis** | | | |
| Hemoglobin > 180 g/L | 0.7 | 0.4-1.3 | .2 |
| Leukocyte count > 10 × $10^9$/L | 2.9 | 1.5-5.9 | .002 |
| Platelet count > 500 × $10^9$/L | 0.9 | 0.5-1.8 | .9 |

**Effect of response in WBC count and resistance to HU on survival in 261 patients with PV**

| | HR | 95% CI | P |
|---|---|---|---|
| Age > 65 y | 4.1 | 1.9-9.0 | < .001 |
| Male sex | 2.0 | 1.1-3.6 | .03 |
| Cardiovascular risk factors* | 1.8 | 0.9-3.7 | .1 |
| **Hematologic values at diagnosis** | | | |
| Hemoglobin > 180 g/L | 0.8 | 0.4-1.6 | .6 |
| WBC > 10 × $10^9$/L | 1.6 | 0.8-3.4 | .2 |
| Platelet count > 500 × $10^9$/L | 1.0 | 0.5-1.9 | .9 |
| Thrombosis during follow-up | 1.6 | 0.8-3.2 | .1 |
| Bleeding during follow-up | 0.8 | 0.3-1.9 | .6 |
| No response in WBC† | 2.7 | 1.3-5.4 | .007 |
| Resistance to HU | 5.6 | 2.7-11.9 | < .001 |




survival



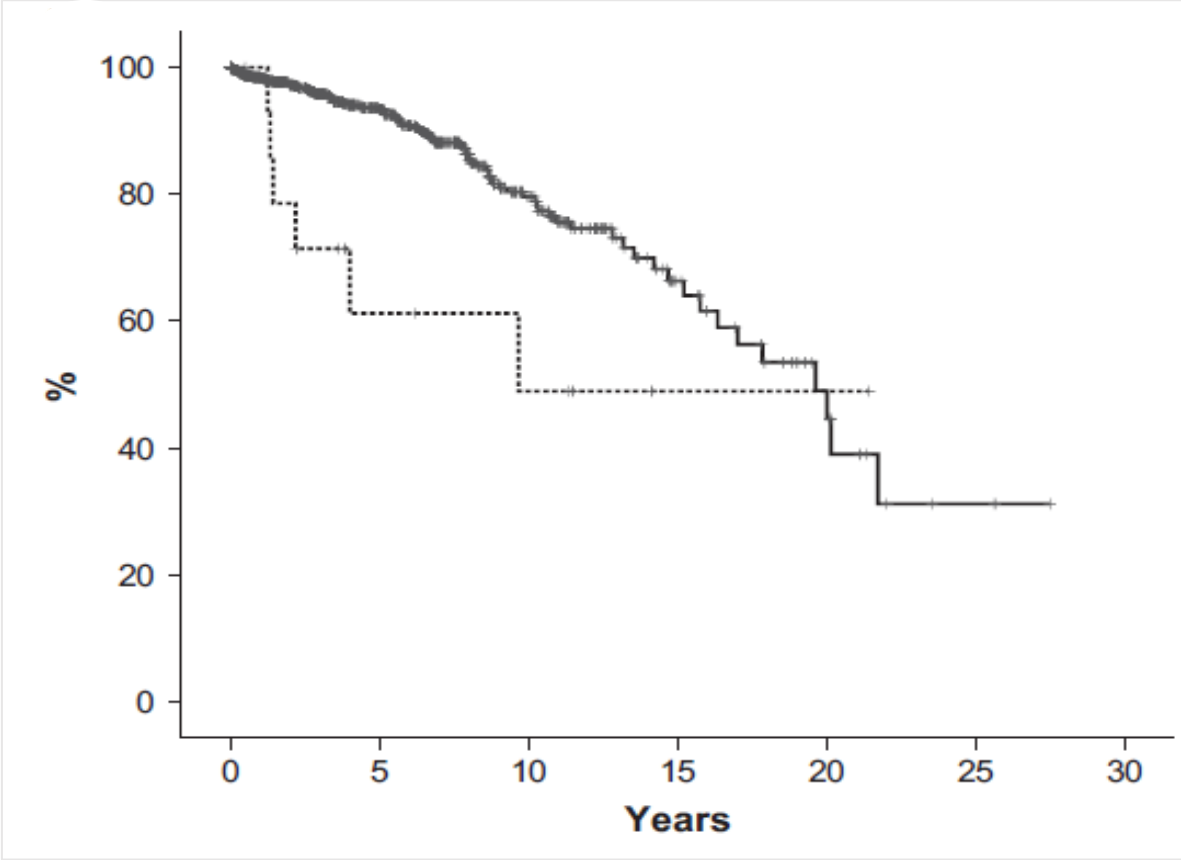

LA / MF

*Alvarez Larran, Blood 2012*

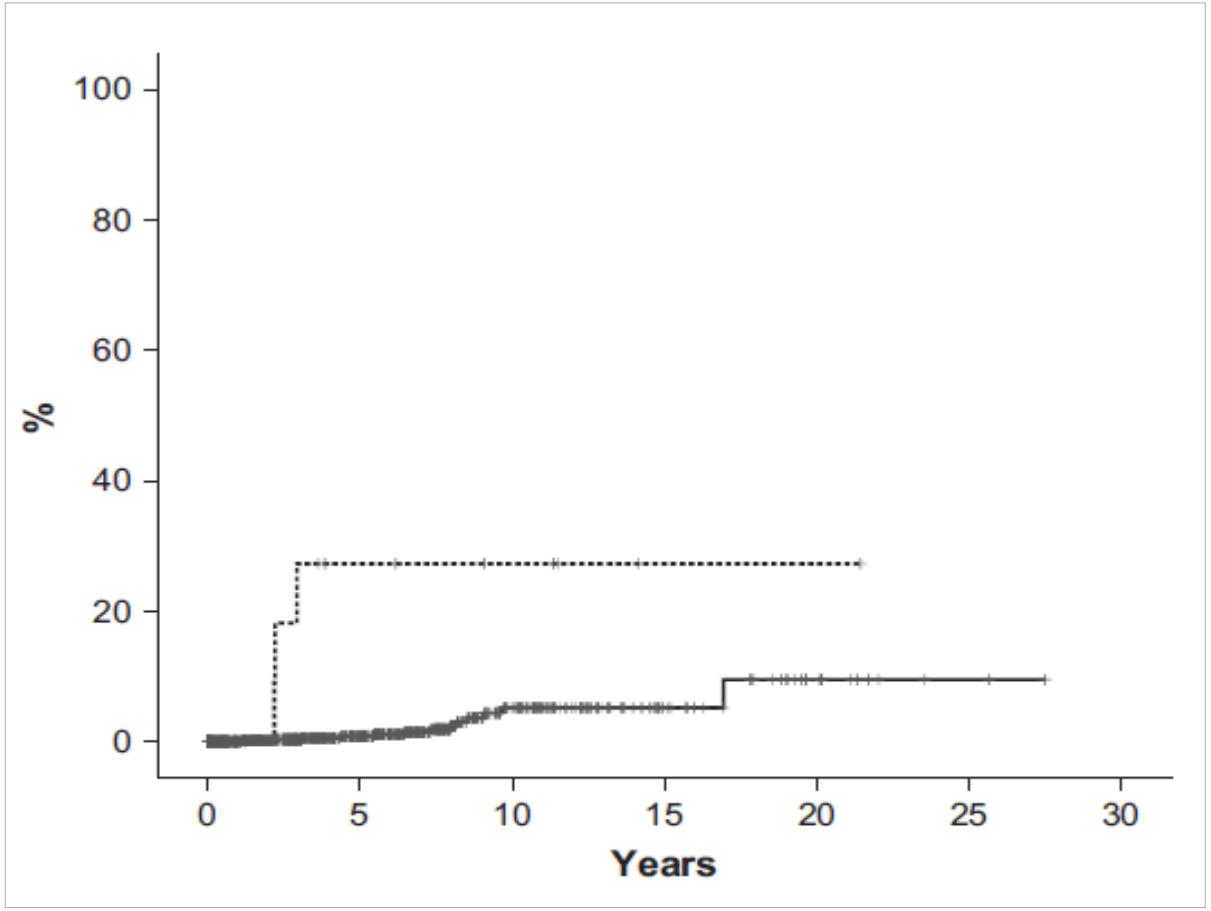
Multivariate analysis of the individual criteria of resistance/intolerance as predictors of different outcomes in 890 patients with polycythaemia vera treated with hydroxycarbamide.

| | Thrombosis | | Major Bleeding | | Myelofibrosis | | Acute leukaemia | |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Requirement for phlebotomies | 0·6 (0·1–2·7) | 0·5 | – | – | 1·2 (0·2–9·2) | 0·8 | – | – |
| Uncontrolled myeloproliferation | 2·6 (0·9–8·4) | 0·09 | – | – | 0·2 (0·02–2·2) | 0·2 | – | – |
| Progressive splenomegaly | 0·4 (0·04–3·3) | 0·4 | 2·3 (0·3–17·7) | 0·4 | 9·1 (2·3–35·9) | 0·002 | – | – |
| Cytopenia | 2·6 (0·6–10·7) | 0·2 | 1·3 (0·2–9·8) | 0·8 | 5·1 (1·9–13·7) | 0·001 | 9·5 (2·6–34·5) | 0·001 |
| Extra-haematological toxicity | 0·8 (0·3–1·8) | 0·5 | 0·7 (0·2–1·9) | 0·5 | 1·6 (0·7–3·6) | 0·2 | 0·9 (0·2–4·3) | 0·9 |

*Alvarez Larran, Br J Haematol 2016*

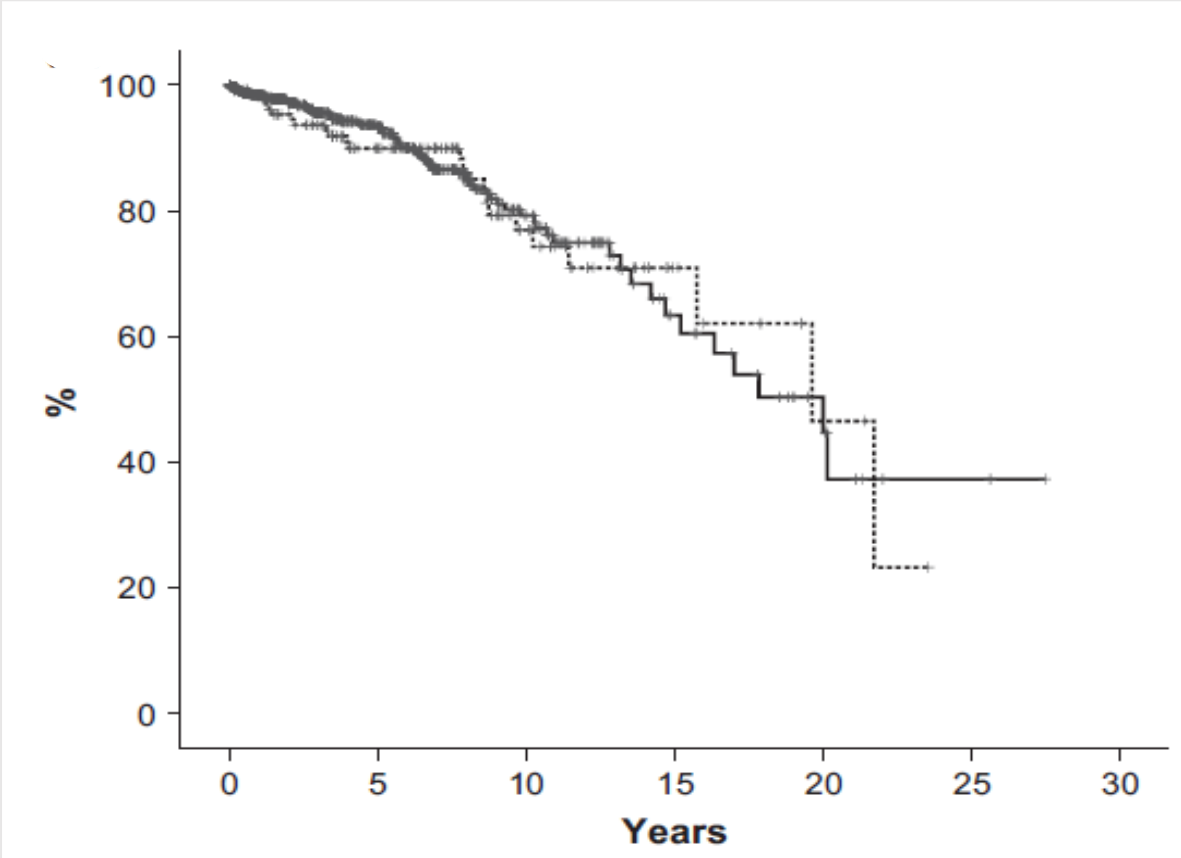



Development of cytopenia (dotted line) or not (solid line)

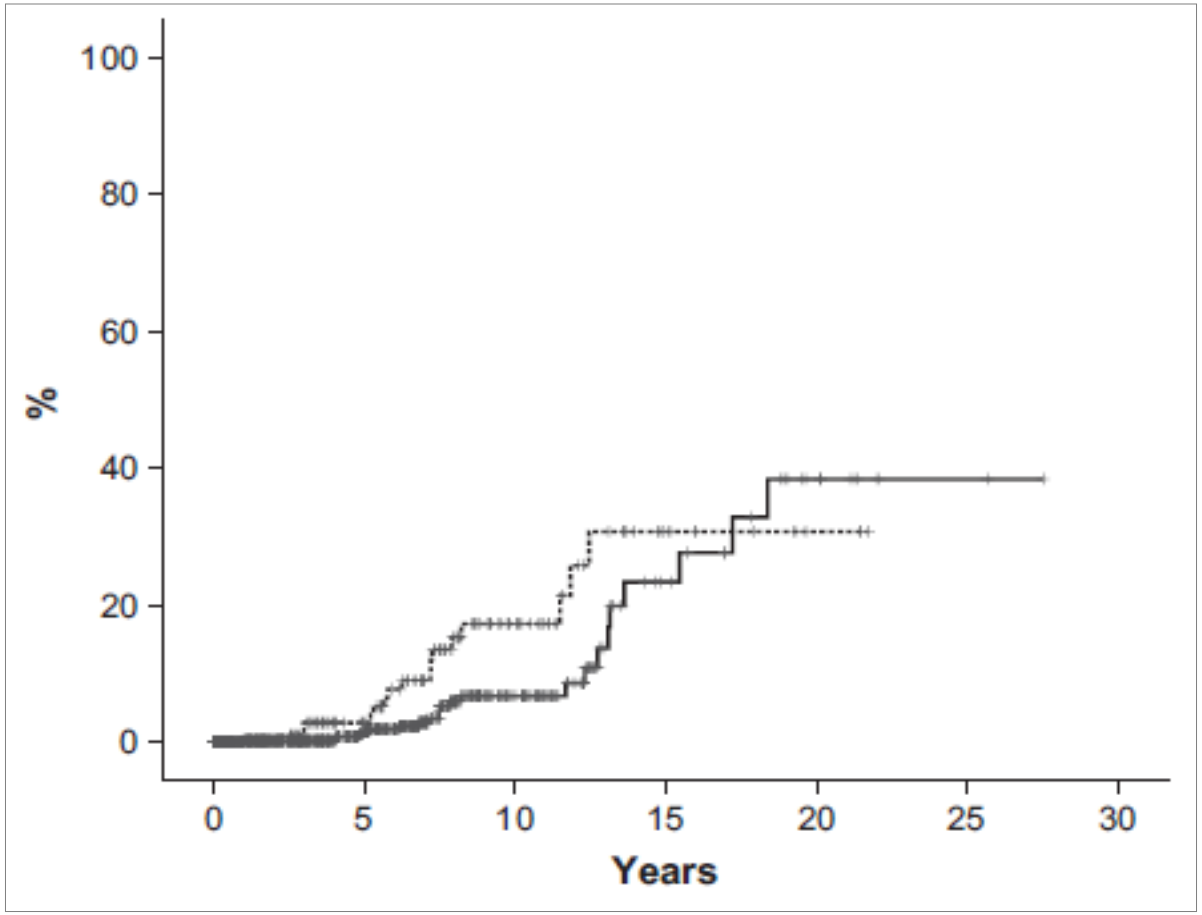



Time to AML according to the development of cytopenia (dotted line) [N<1000/mmc, Hb <10g/dl, Plt<100,000/mmc]

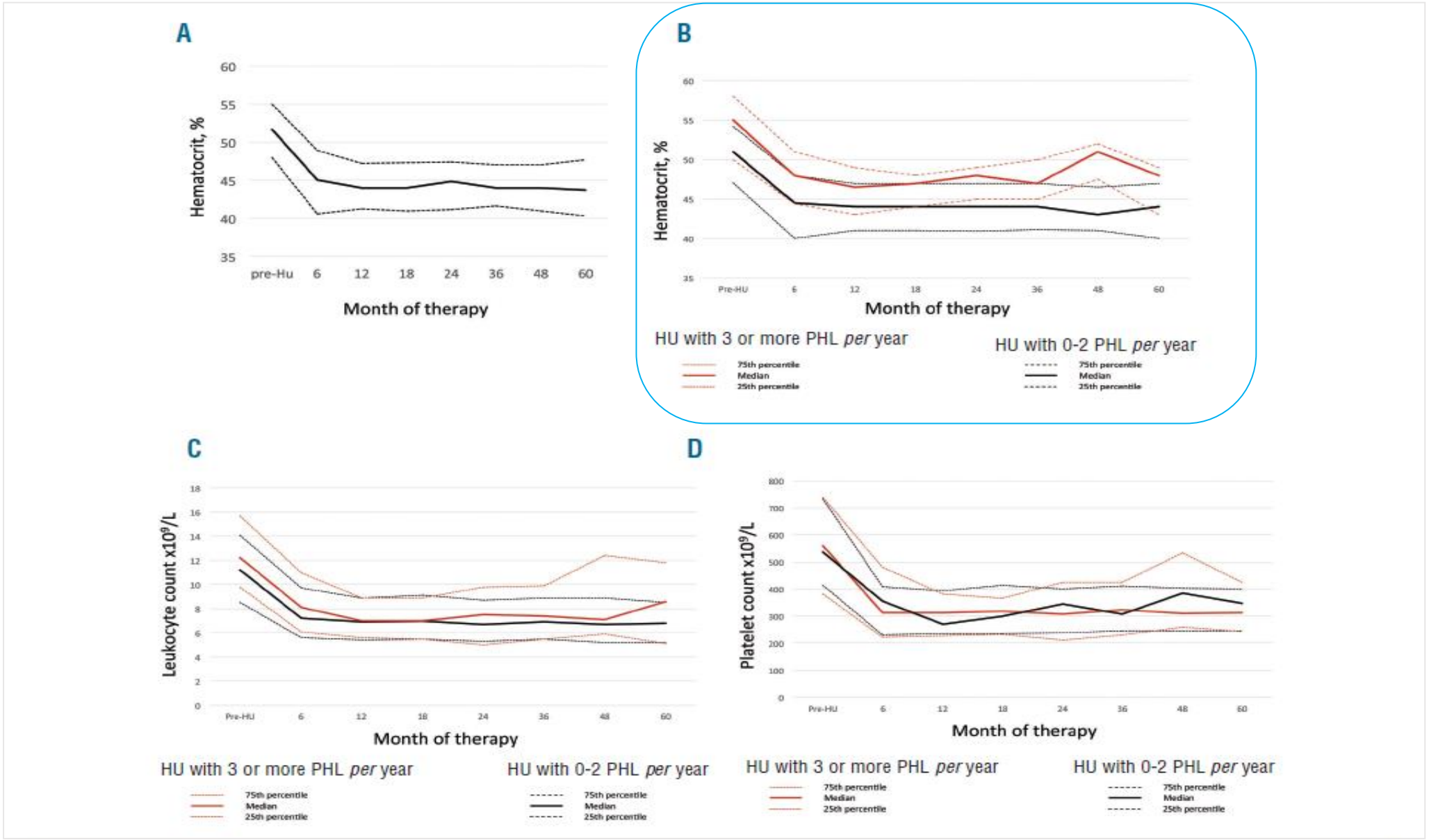
*Alvarez Larran, Br J Haematol 2016*



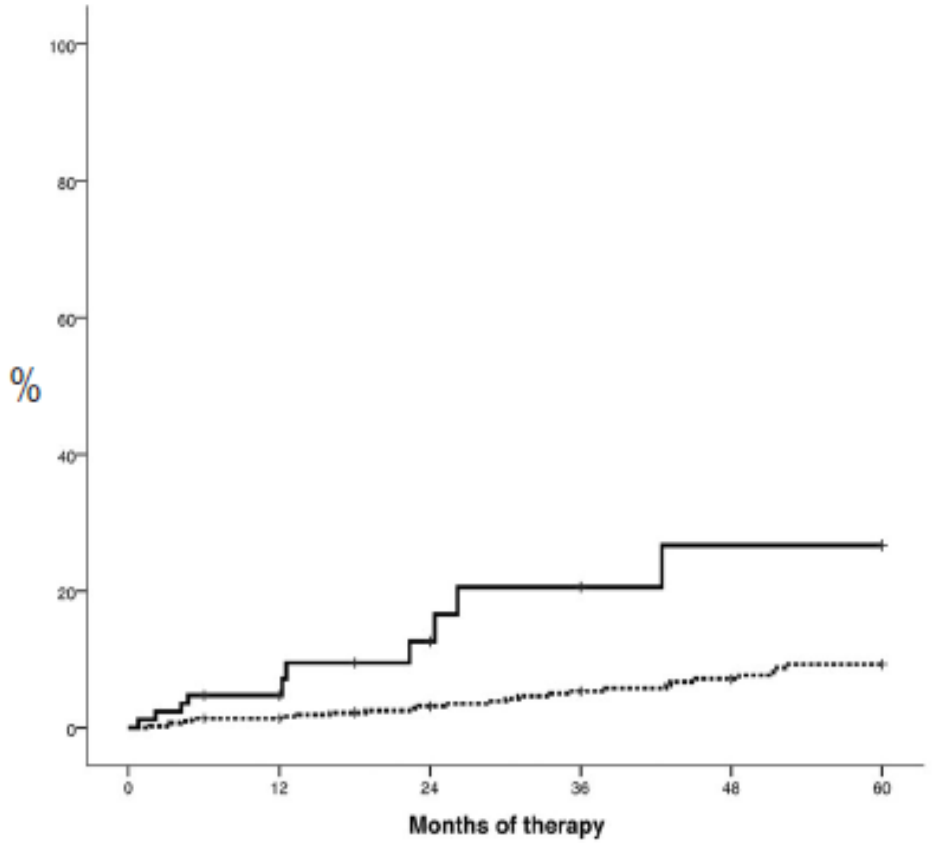

Patients included in the definition of resistance or intolerance to HU (dotted line) or no (solid line)



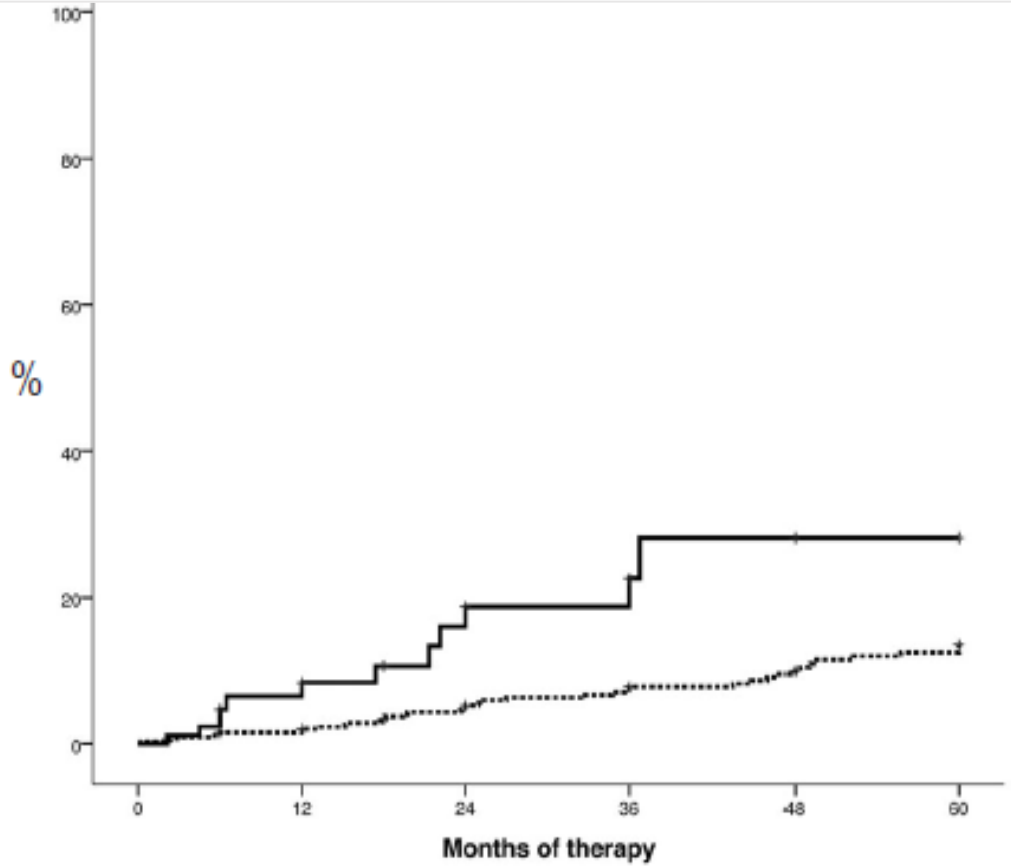

Time to myelofibrosis in patients with resistence/intolerance to HU (dotted line)




Alvarez-Larran, Haematologica | 2017



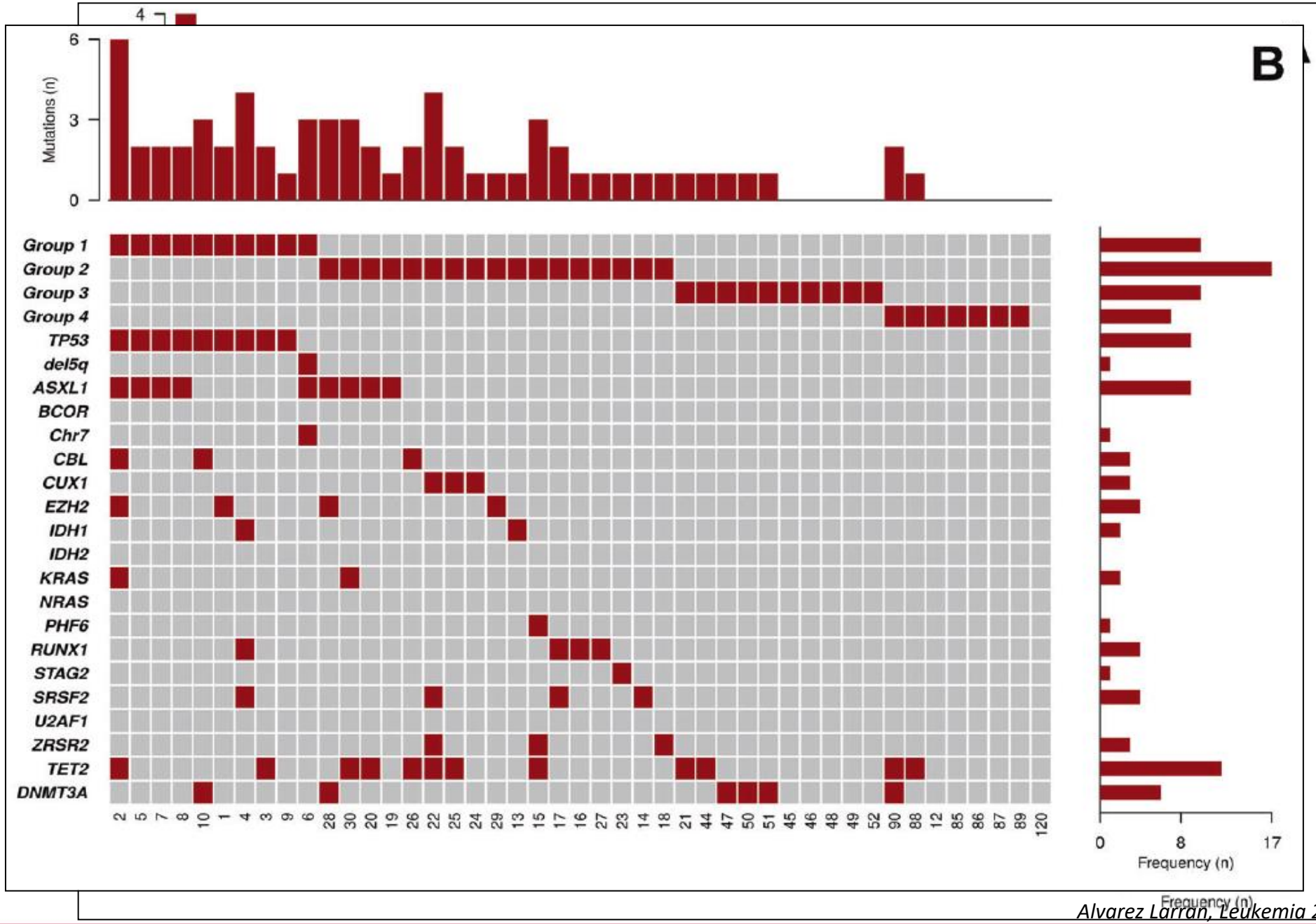

Time to thrombosis in patients with polycythemia vera treated with hydroxyurea (HU) and 3 or more phlebotomies *per* year (solid line) or with HU and 0-2 phlebotomies *per* year (dotted line). *P*<0.0001.




Time to resistance/intolerance to hydroxyurea according to European LeukemiaNet (ELN) criteria in patients with polycythemia vera treated with hydroxyurea (HU) and 3 or more phlebotomies *per* year (solid line) or with HU and 0-2 phlebotomies *per* year (dotted line). *P*=0.0001.

Alvarez-Larran, Haematologica | 2017

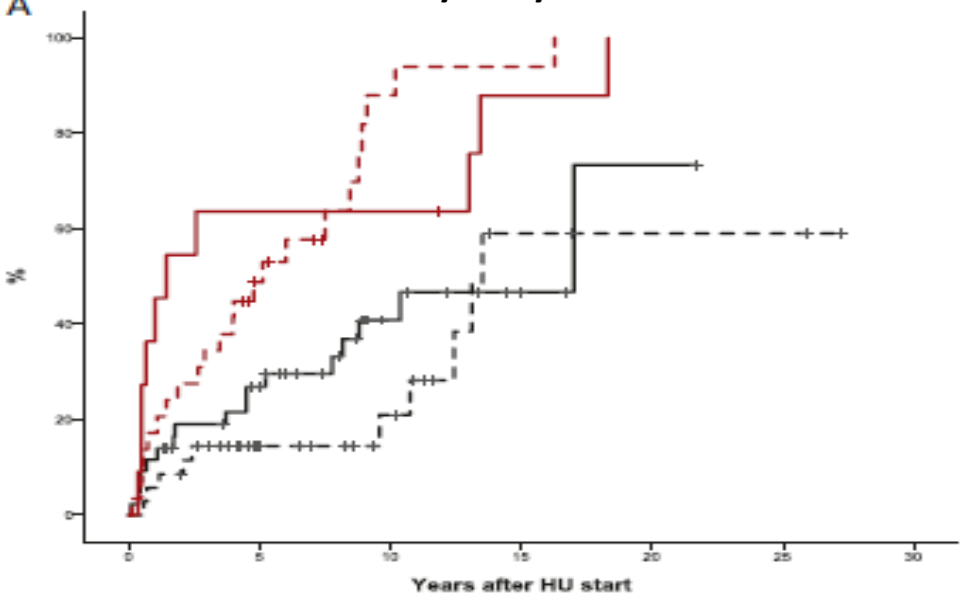
Probabilità di sviluppare R a 5 anni:
64% TP53
49% alterazioni cromatina
27% JAK2 omozigote
14% JAK2 eterozigote




*Alvarez Larran, Leukemia 2021*

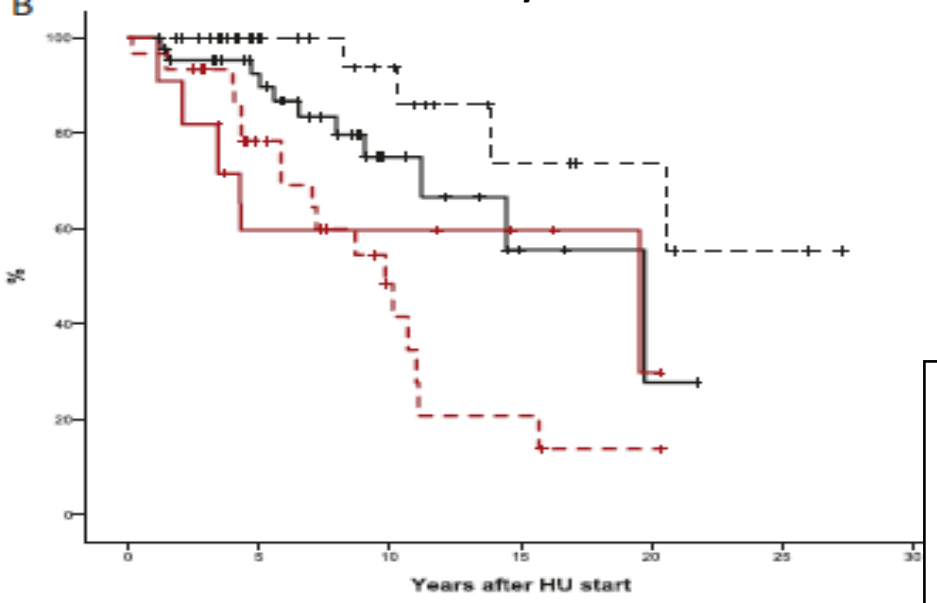
A

## Time to Hydroxyurea Resistance



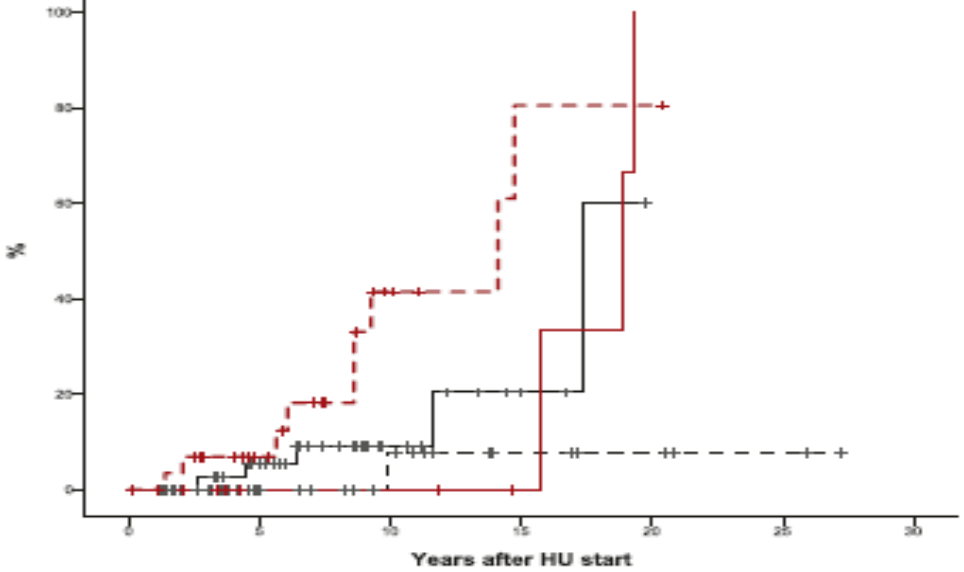

B

## Probability of survival



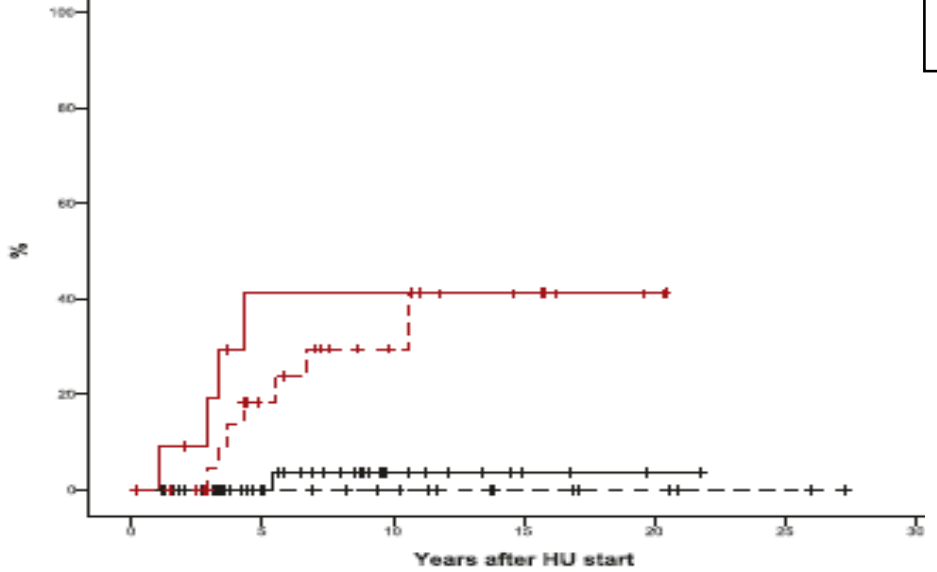

C

## Probability of Myelofibrotic transformation




D

## Probability of Progression to AML




- TP53 disruption/aneuploidy
- Spliceosome/chromatin aberration
- Homozygous JAK2 mutation
- Heterozygous JAK2 mutation

## Raccomandazioni per il passaggio a una terapia citoriduttiva di seconda linea nei pazienti in trattamento con idrossiurea (HU)

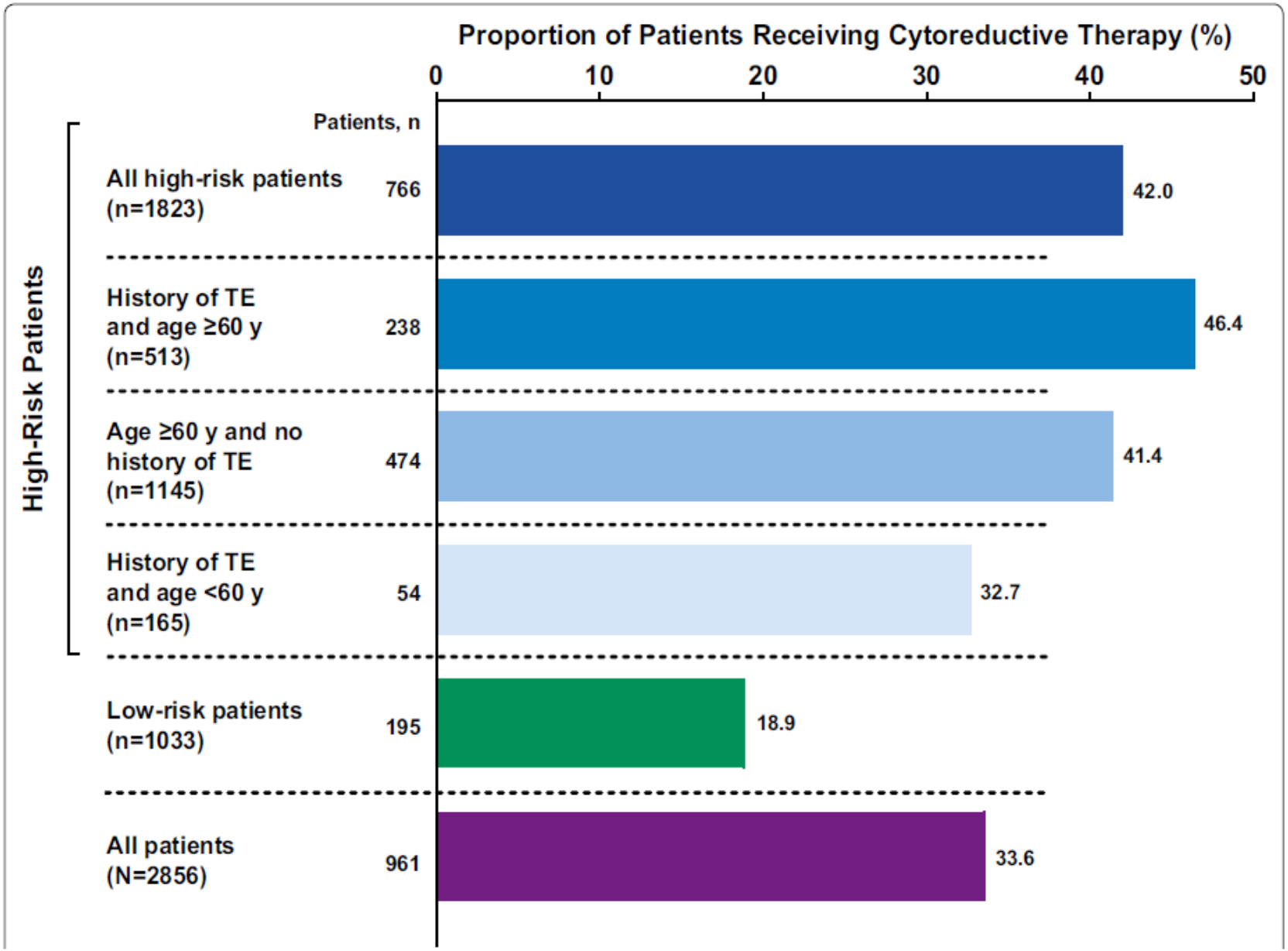
**Una nuova terapia citoriduttiva è RACCOMANDATA se si verifica almeno una delle seguenti condizioni:**

- Intolleranza ad HU per tossicità non ematologica di grado 3-4 oppure di grado 2 prolungata (ad es., manifestazioni muco-cutanee, sintomi gastrointestinali, febbre o polmonite) con qualsiasi dose
- Intolleranza ad HU a causa di tossicità ematologica (emoglobina <100 g/L, conta piastrinica $<100\times10^9$ cellule/L, o conta dei neutrofili $<1\times10^9$ cellule/L) con la dose più bassa di HU che consente di ottenere una risposta
- Comparsa di tumori cutanei non-melanoma
- Comparsa di eventi vascolari: sanguinamento clinicamente rilevante, trombosi venosa o trombosi arteriosa

**Una nuova terapia citoriduttiva DOVREBBE ESSERE CONSIDERATA in caso di risposta clinica insufficiente ad HU (≥1,5 g/die per almeno 4 mesi e senza riportare intolleranza), come definito da almeno uno dei seguenti criteri:**

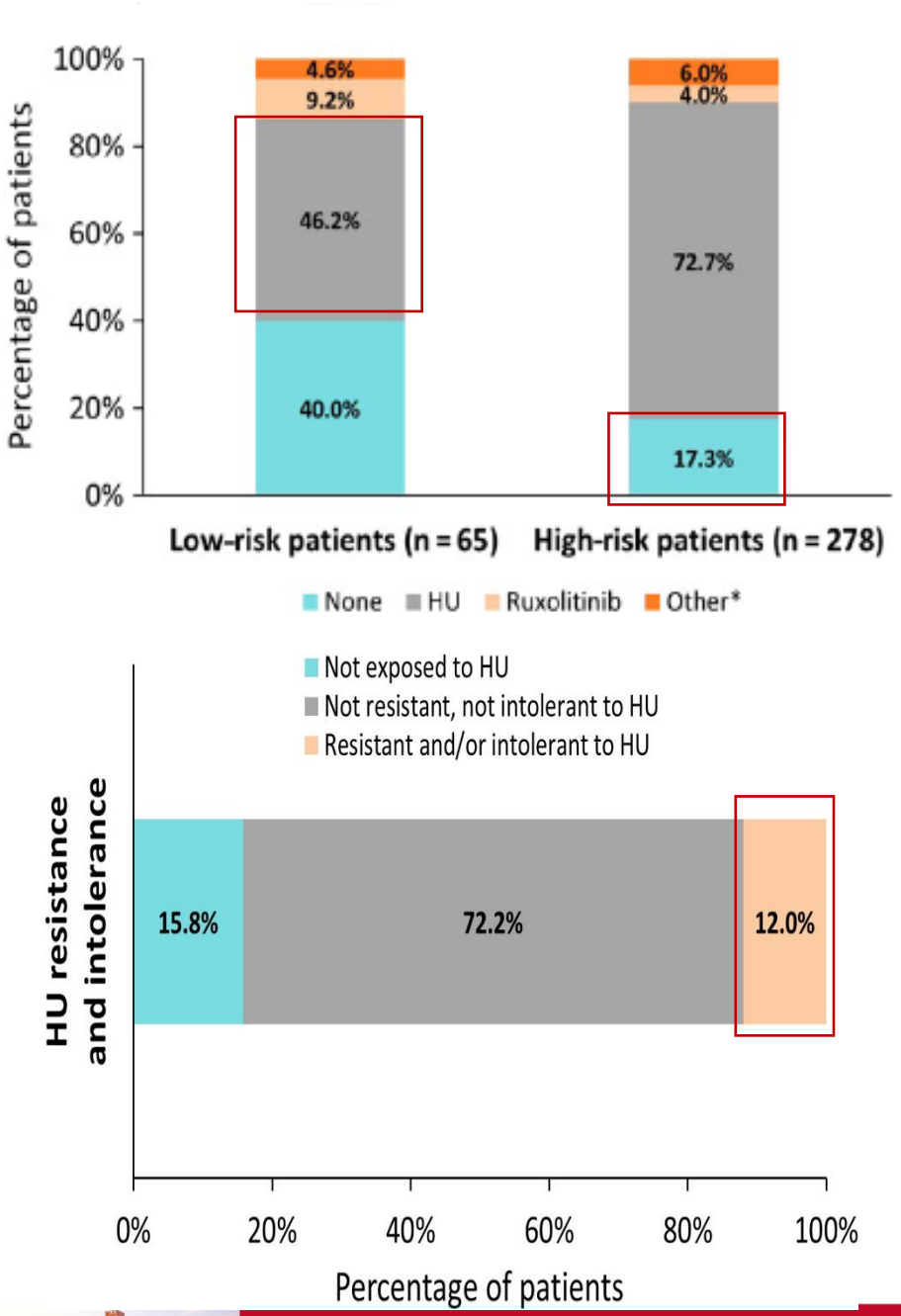
- Persistenti sintomi correlati alla malattia: score totale sintomi ≥20 o score prurito ≥10 per almeno 6 mesi
- Trombocitosi persistente: conta piastrinica $>1000\times10^9$ cellule/L, sintomi microvascolari, o entrambi, persistenti per più di 3 mesi
- Splenomegalia sintomatica o progressiva: aumento delle dimensioni della milza di oltre 5 cm dal margine costale sinistro in 1 anno
- Leucocitosi progressiva (aumento di almeno il 100% se la conta al basale è $<10\times10^9$ cellule/L o almeno del 50% se la conta al basale è $>10\times10^9$ cellule/L) e persistente ($>15\times10^9$ cellule/L confermata a 3 mesi)
- Controllo dell'ematocrito insufficiente: necessità di 6 o più flebotomie all'anno per mantenere l'ematocrito <45%

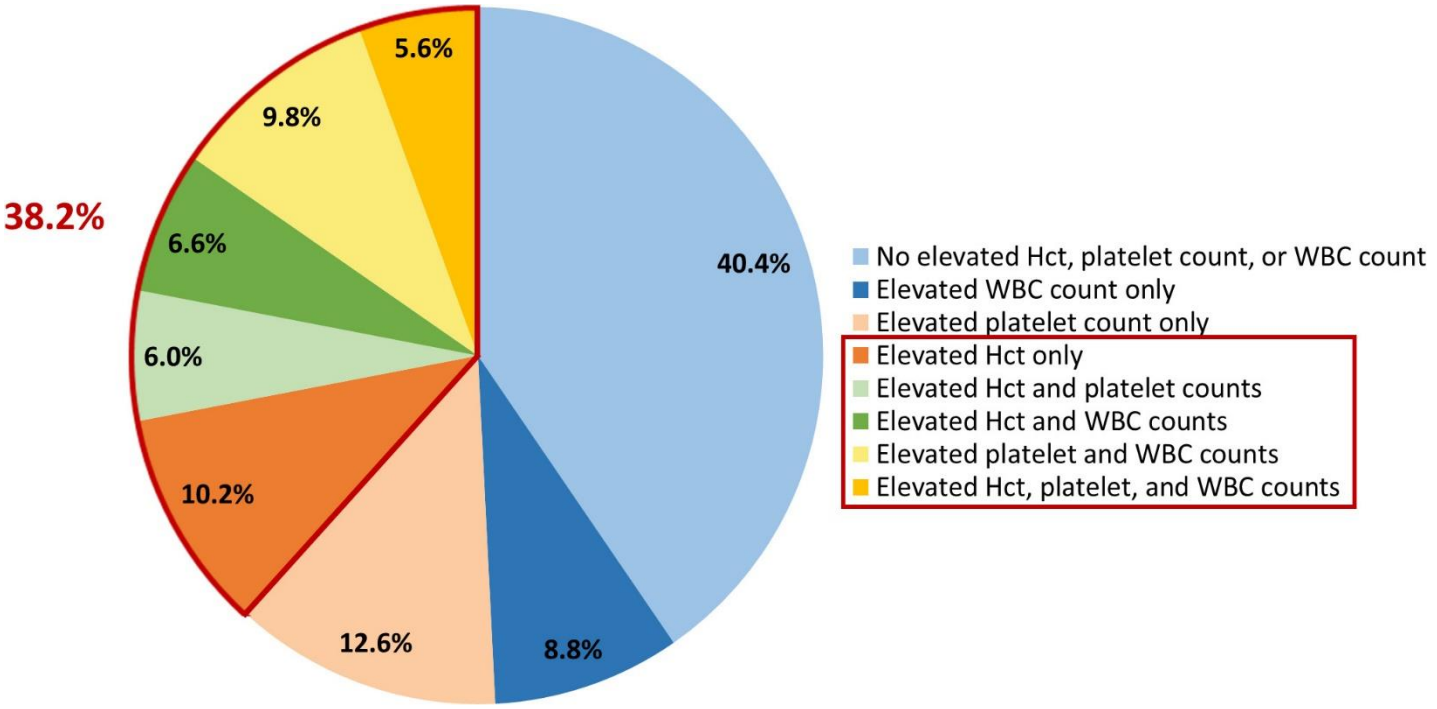
Marchetti M. Lancet Haematol, 2022




*Paranagama D, Exp Hematol Oncol 2018*

# Applicazione dei criteri ELN in real-world: survey in Belgio




Devos T. European J Haematol, 2017

# REVEAL STUDY

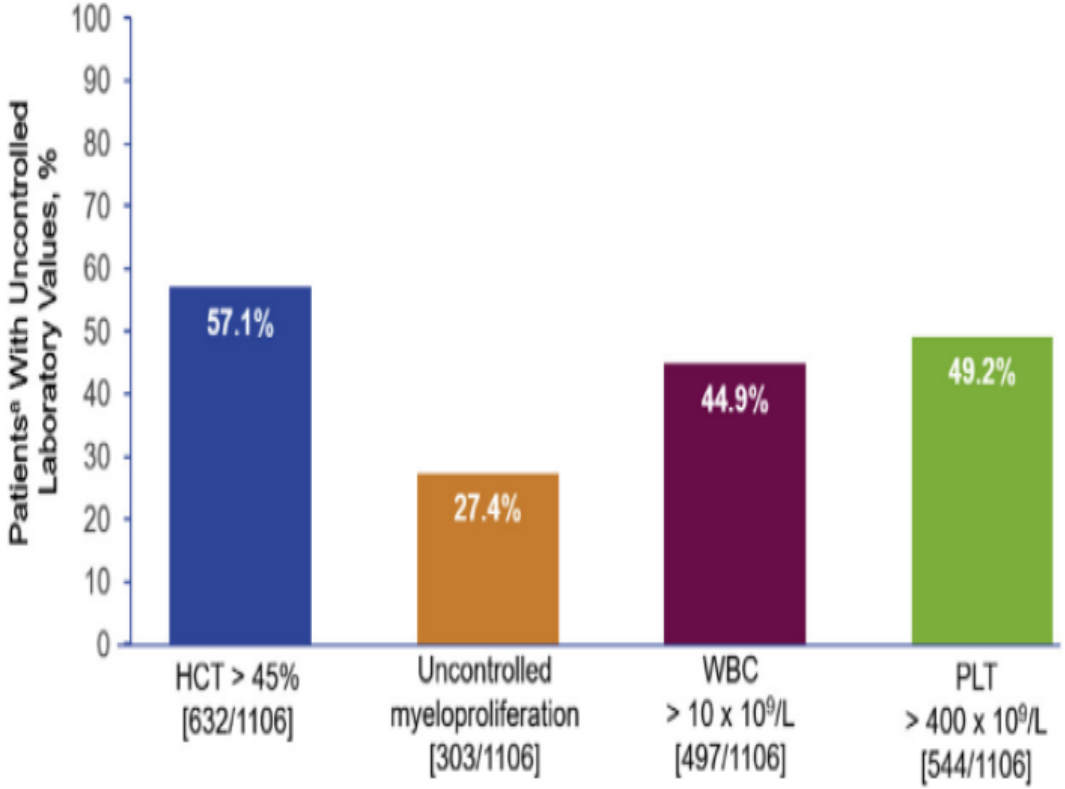
**Table 3 HU Dose Intensity and Exposure**

| | Received HU for ≥ 3 Months (n = 1381) |
|---|---|
| Median maximum daily dose (range), mg/d | 1000.0 (71.4-5571.4) |
| Maximum daily dose, mg/d, n (%) | |
| < 400 | 91 (6.6) |
| 500 | 415 (30.1) |
| 750 | 159 (11.5) |
| 1000 | 423 (30.6) |
| 1500 | 204 (14.8) |
| 2000 | 61 (4.4) |
| > 2000 | 28 (2.0) |
| Median duration of maximum daily dose, (range), mos | 19.6 (0.0-38.5) |
| Median HU exposure post-index (range), mos | 23.6 (3.1-38.5) |
| Risk category at enrollment, n (%) | |
| High | 1165 (84.4) |
| Low | 216 (15.6) |

32% variazioni dose HU
24% interruzione temporanea HU (intolleranza 37%, resistenza 35%)
19% interruzione definitiva HU (intolleranza 54%, resistenza 22%)

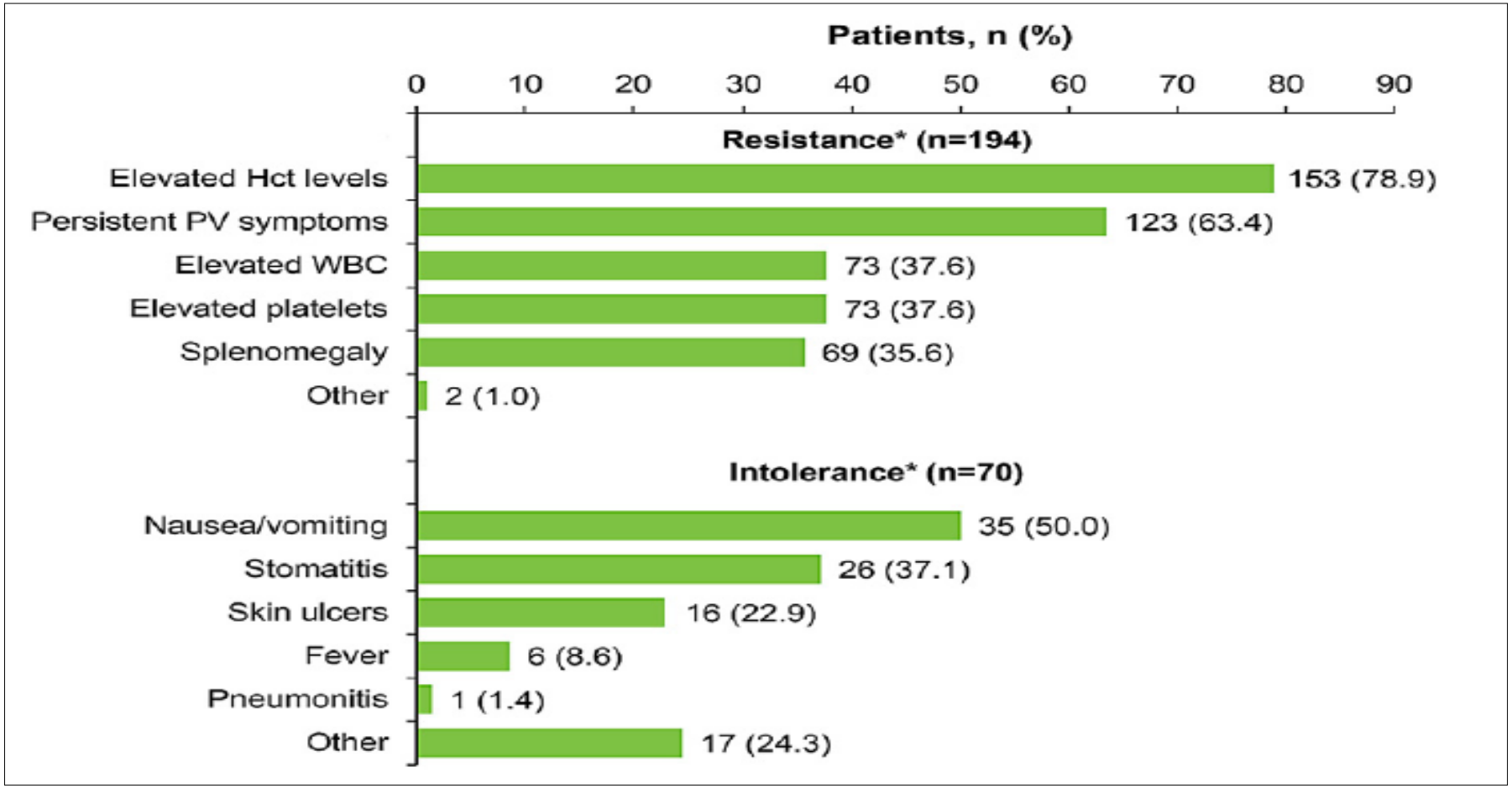
*Grunwald et al, Clinical Lymphoma, Myeloma & Leukemia 2020*

## Uncontrolled Laboratory Values in Patients With PV Who Received HU for ≥ 3 Months




*Grunwald et al, Clinical Lymphoma, Myeloma & Leukemia 2020*

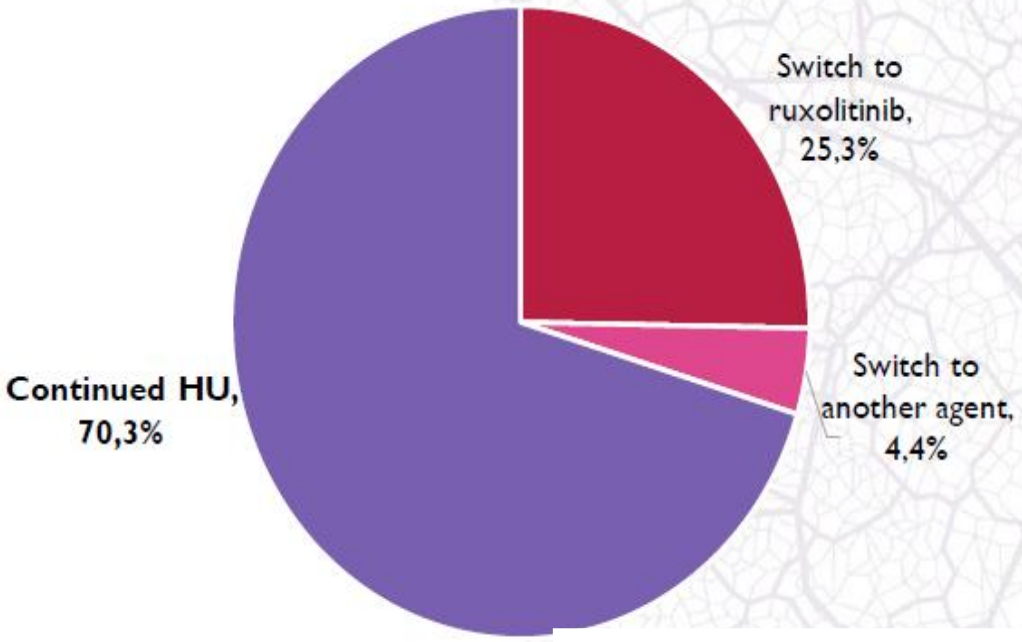
**Rationale for treatment discontinuation among patients resistant to or intolerant of hydroxyurea. * Multiple reasons for intolerance or resistance could be reported for each patient. Hct, hematocrit; PV, polycythemia vera; WBC, white blood cell.**




*Altomare, Clinical Lymphoma, Myeloma and Leukemia 2021*

# Switch a Ruxolitinib: real-world

**Treatment in patients with stable suboptimal response to HU (EU cohort study, N=411)[1]**




**Type of HU suboptimal response criteria according to treatment (EU cohort study, N=411)[1]**

| % | Continue HU/switch to another agent | Switch to ruxolitinib | P value |
|---|---|---|---|
| PHL need | 50.2 | 58.7 | 0.13 |
| Uncontrolled WBC/PLT | 53.8 | 77.7 | <0.001 |
| Spleen | 23.5 | 37.5 | 0.005 |
| Symptoms | 29.6 | 48.1 | 0.001 |

Palandri F. Blood, 2020

# CONCLUSIONI I

Come riconoscere il problema della resistenza a idrossiurea?

- Splenomegalia severa e/o sintomatica nonostante idonea dose di HU
- Prurito incoercibile con impatto significativo sulla qualità di vita, nonostante idonea dose di HU
- Piastrinosi non controllata, nonostante idonea dose di HU
- Leucocitosi progressiva, nonostante idonea dose di HU
- Mancato mantenimento dell'ematocrito target < 45% nonostante frequente salasso-terapia (> 6 trattamenti all'anno) e idonea dose di HU

# CONCLUSIONI II

## Come gestire il problema della resistenza a idrossiurea?

- Idrossiurea è il trattamento di prima linea raccomandato e ampiamento utilizzato nei pazienti con PV ad alto rischio.
- E’ efficace nel prevenire gli eventi avversi, sicuro e ben tollerato.
- Il 15-24% dei pazienti sviluppa intolleranza o resistenza (criteri definiti da ELN). La resistenza, non sempre facile da identificare, correla con un significativo incremento del rischio di progressione e di morte.
- In caso di resistenza è raccomandato il passaggio ad una seconda linea con ruxolitinib o IFN alfa a seconda delle caratteristiche individuali del paziente.

Grazie per l’attenzione