ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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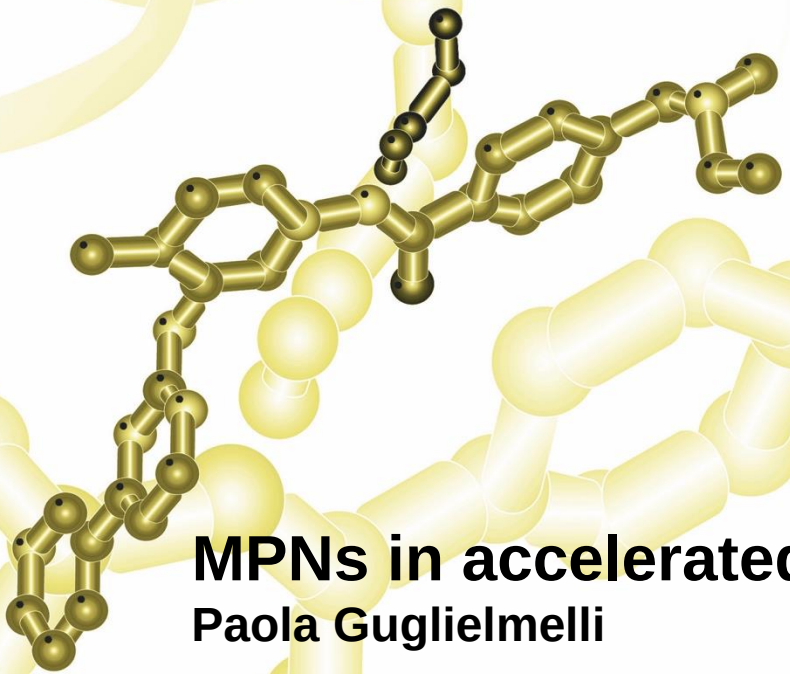

# New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
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# MPNs in accelerated/blast phase

**Paola Guglielmelli**

# Disclosures of Paola Guglielmelli

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Novartis | | | | | x | x | |
| Abbvie | | | | | x | x | |
| GSK | | | | | x | x | |
| BMS | | | | | x | x | |

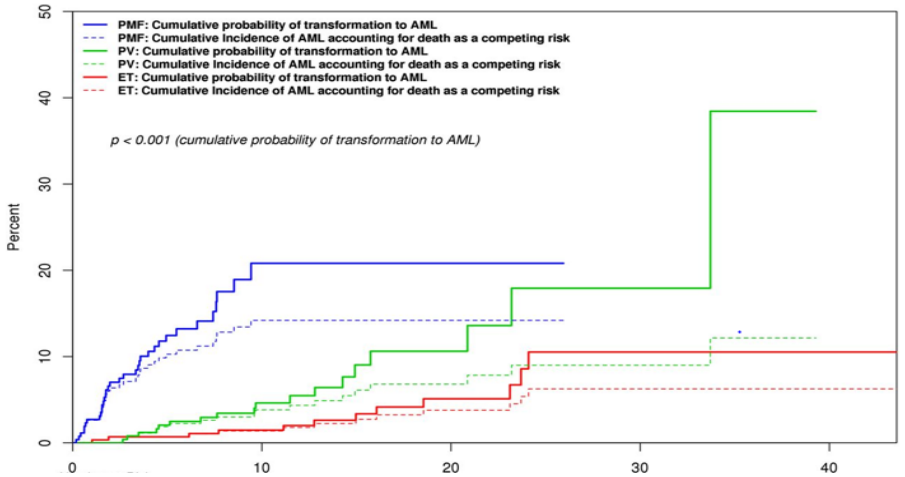
# Progression to Blast Phase in MPNs

- **Blast phase** is defined by the presence of ≥ 20% blasts in either peripheral blood or bone marrow
- **Accelerated phase** is defined by 10-19% blasts and sometimes can precede BP; should be considered separately in prognostic data

10-year risk of leukemic progression:

- PMF 10% to 20% →30 % of causes of death
- PV 2% to 4%
- ET 1%

} 6 % of causes of death

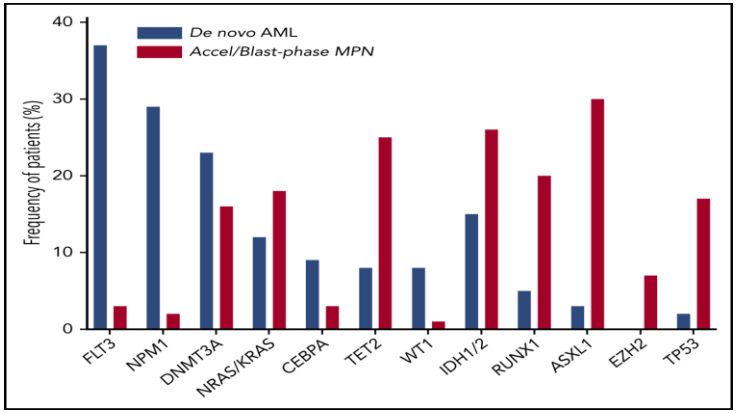


# Why post-MPNs Leukemia is Still a Challenge and an Unmet Need?

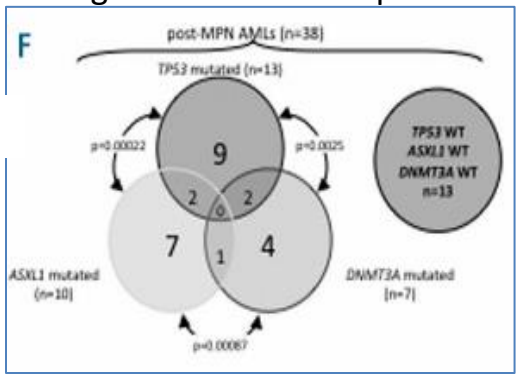
- Leukemogenic mechanisms not fully understood; data from NGS on paired (chronic and blast phase) do not display homogeneous patterns of transformation with different representation for recurrent gene mutations in published reports

# MPN Blast Phase Molecular Genetics

- ✓ Over-representation for *TP53*, *RUNX1*, *EZH2*, *ASXL1*, *IDH1/2* gene mutations




- ✓ Highly heterogeneous mutation profile at blast phase onset

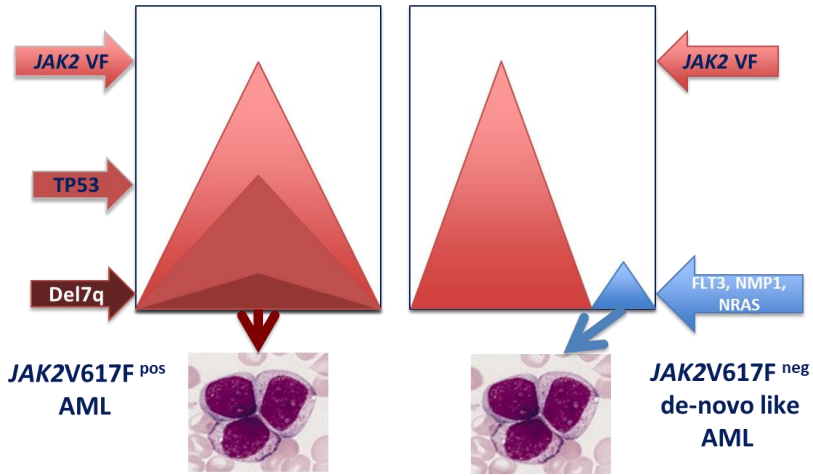



**Rare co-occurring mutations *DNMT3A - ASXL1 - TP53*** suggests different mechanisms of transformation:

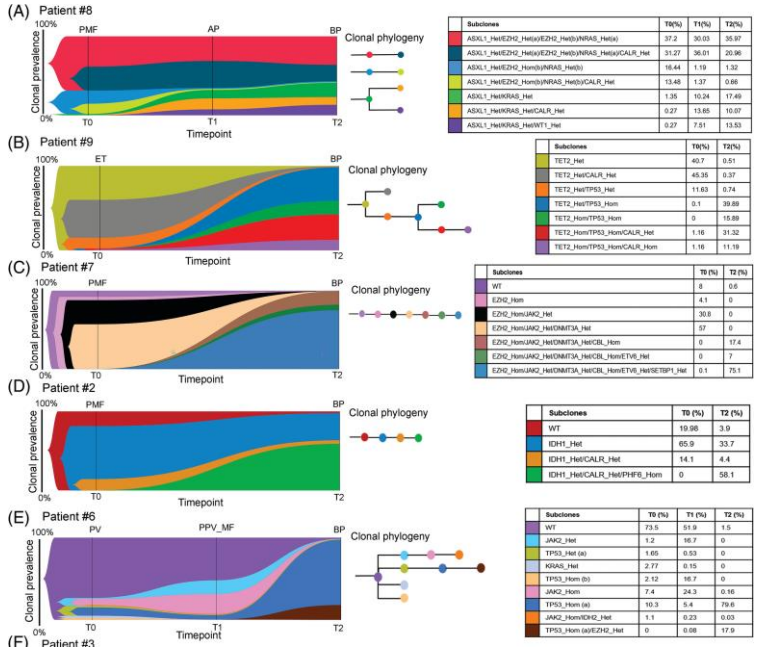
- ✓ *TP53* o *DNMT3A* especially in AML post PV/ET
- ✓ *ASXL1* in post MF

# Models of Leukemic Transformation in MPN

- ✓ 2 main mutational *patterns* at transformation:




- ✓ Heterogeneous trajectories of transformation to BP from complex patterns of oligoclonal representation at chronic phase




Vannucchi AM et al, Leukemia 2013; 27:1861-9. Tefferi A et al, Bood Adv 2016; 1:21-30; Tefferi A et al, Blood Adv 2016; 1:105-111;
Guglielmelli P et al, Blood; 2017:129:3227-3236; Klampfl T, Blood 2011; 118:167-76; ; Milosevic JD, Am J Hematol 2012 ; Milosevic and Kralovics, Int J Hematol 2013 Dunbar AJ, Rampal RK, Levine R. Blood. 2020;136(1):61. Calabresi L et al. Am J Hematol. 2023 Oct;98(10):1520-1531.

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- Conventional prognostic risk model (age, Karyotype, ELN2022) fail to predict the pts outcome and a validated predictive model for AL progression is still lacking.

# Risk Factors for Leukemia Transformation in MPNs

| Risk Factors | | |
|---|---|---|
| Clinical | • Age<br>• Anemia<br>• RBC-transfusion dependence<br>• Thrombocythopenia<br>• Thrombocythosis<br>• Cytopenic phenotype in MF | • Leukocytosis<br>• PB blasts<br>• Prior thrombosis<br>• Weight loss<br>• Cytotoxic drugs<br>• High risk catgories ( MIPSS70/plus; GIPSS) |
| Biological | • Circulating $CD34^+$ cells (≥ 300/μl)<br>• Original diagnosis (consider ET *vs* pre-fibrotic MF)<br>• *JAK2*V617F VAF | |
| Genetic | • Unfavorable Karyotype [monosomal karyotype, Chr17 abnormalities, Inv3/I(17q)]<br>• Gene mutations (Adverse mutations in PV/ET; HMR status in MF: IDH1, SRSF2, ASXL1, TP53,Ras Pathway....) | |

Barbui T, JCO 2011; Passamonti F, Haematologica 2008 ; Tefferi A, Eur J Haematol 2008; Gangat N, BJH 2007; Kiladjian JJ, Semin Thromb Hemost 2006; Finazzi G, Blood 2005;
Bjorkholm M, JCO 2011; Rago A et al.Leuk Res. 2015 Mar;39(3):314-7; Passamonti F Am J Med 2004;Barosi G, Blood 2001;Morel P, Blood 2010; Passamonti F, BJH 2010; Tefferi A, BJH 2001; Tefferi et al. Blood Adv 2016; Guglielmelli P JCO 2018; coltro G et al BCJ 2022;

# Why post-MPNs Leukemia is Still a Challenge and an Unmet Need?

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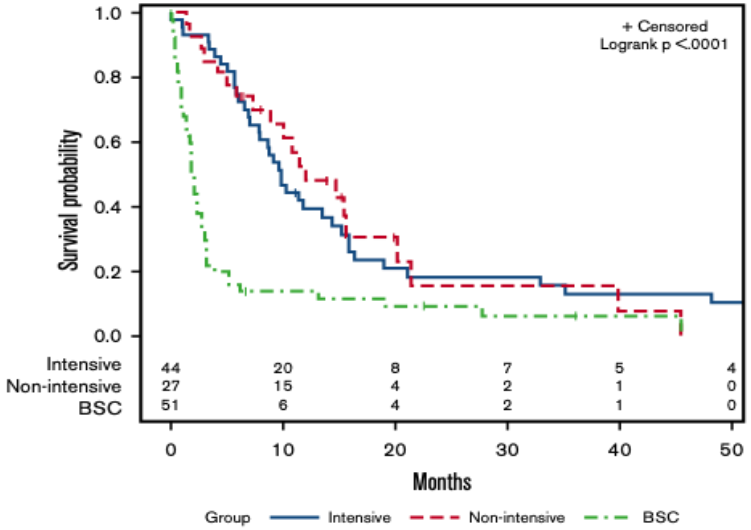
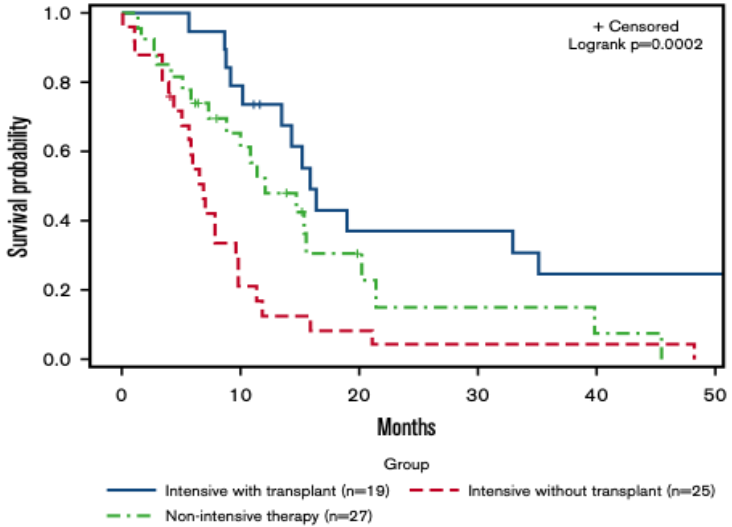
- Conventional prognostic risk model (age, Karyotype, ELN2022) fail to predict the pts outcome and a validated predictive model for AL progression is still lacking
- Median survival 3-6 months
- Often advanced age: just a minority of pts are eligible for intensive treatment.
- Available data mainly retrospective and on small groups of pts

# Post-MPN AML demonstrates limited response to conventional AML therapy




- CR status at the time of conditioning regimen starting was associated with favorable outcome
- Blast-reduction strategies in MPN-AP/BP most commonly result in reversion to chronic phase MPN with significant residual disease burden.
- Mutations in *TP53* (OR 8.2 [95% CI 2.01, 37.1], p=0.004) and RAS pathway (OR 5.1 [95%CI 1.2, 23.7], p=0.03) were associated with inferior treatment response for intensively treated patients.

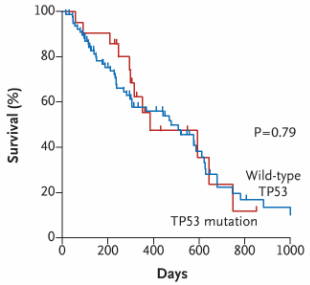
Kennedy JA et al. Blood 2013; Cahu X et al. Bone marrow transplantation 2014;49(6):756–60; McNamara CJ et al. Blood Advances 2018;2(20):2658–71; Davidson MB et al Blood Adv 2024..

# Non Intensive Treatment Approach

➢ **Hypometilating agents**

✓ Rationale for HMA in MPN-BP derived from the demonstrated efficacy in MDS and pauciblastic AML

*TP53* and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes




✓ 10-days Decitabine 20 mg/sqm

✓ Transient bone marrow blast clearance

*Welch et al, NEJM 2016; 375, 2023–36*

✓ Complete responses generally scarce (about 10%) in blast phase

| Study | Design | Subset | Treatment | Pt n | Outcomes |
|---|---|---|---|---|---|
| *Andriani et al 2015* | Retrospective | MPN-BP | AZA | 19 | OS 8 months |
| *Badar et al 2015* | Retrospective | MPN-BP | DEC | 21 | OS 7 months |
| *Thepot et al 2010* | Prospective | MPN-BP | AZA | 26 | ORR 38%; CR/CR1 12% |

Potential therapeutic option in unfit patients

*Andriani, et al. Leuk Res 2015;39(8):801–4;Badar, et al. Leuk Res 2015;39(9):950-6;Thepot, et al. Blood 2010;116(19):3735–42*

# Addition of ruxolitinib to HMA Might Improves Response Rate

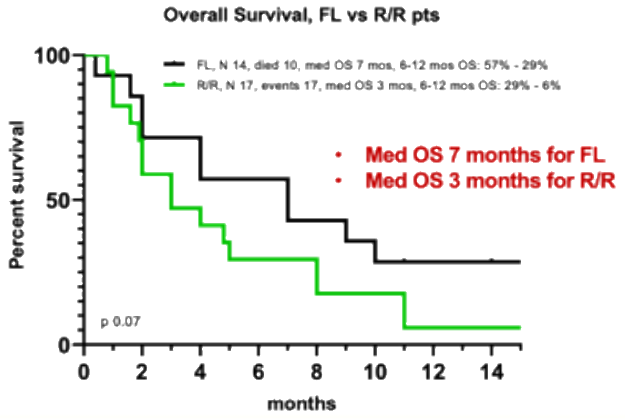
| JAK inhibitor-including regimens | Study | Therapy | Response Rate | Overall Survival |
|---|---|---|---|---|
| Drummond et al 2020[22] | Phase 1b study of 34 patients with MPN-AP (n=19) and MPN-BP (15) | Ruxolitinib + Azacitidine | MPN-AP CR/mCR rate: 26%<br>MPN-BP ALR-P rate: 27% | 1-y OS: 42% |
| Bose et al 2020[23] | Phase I/II study of 29 patients with MPN-BP | Ruxolitinib + Decitabine | ORR: 45% | mOS: 6.9 mo |
| Mascarenhas et al 2020[24] | Phase II study of 25 patients with MPN-AP/BP | Ruxolitinib + Decitabine | ORR: 44% | mOS: 9.5 mo |

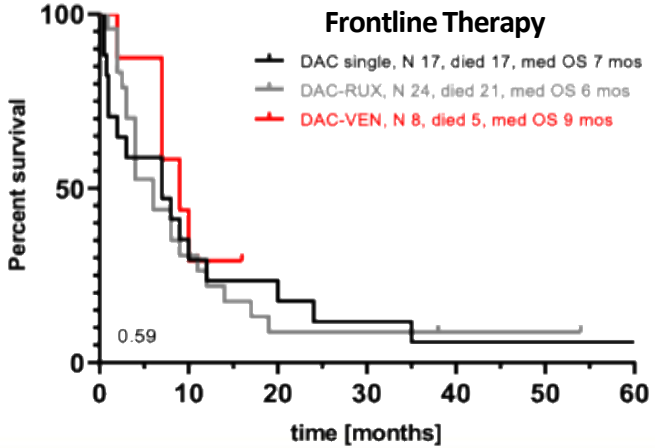
- ✓ Overall, limited single-center experiences and case reports
- ✓ Often patients evolved to BP upon ruxolitinib; feasible in combination with chemotherapy

# No Apparent Benefit on OS from Venetoclax-Based Combinations in MPN-BP

Preclinical data provide rationale for clinical study: Bcl-xL expression is high in MPN cells; Sensitivity of AML cells to Venetoclax correlates positively with BCL-2 levels; Synergistic Targeting of Bcl-xL and JAK2 in JAK2-Driven MPN cells shows high apoptotic rate.

| Venetoclax-containing regimens | Study | Therapy | Response Rate | Overall Survival |
|---|---|---|---|---|
| Tremblay et al[40] | Retrospective analysis of 9 patients with MPN-AP/BP | HMA-VEN | CR/CRi Rate: 33% | mOS: 4 mo |
| Gangat et al 2021[42] | Retrospective analysis of 32 patients with MPN-BP (frontline and R/R treatment) | HMA-VEN | CR/CRi Rate: 44% | mOS: 8 mo |
| Masarova et al 2021[41] | Retrospective analysis of 31 patients with MPN-BP (frontline and R/R treatment) | VEN-including regimens | CR/CRi Rate: 23% | mOS: 4 mo |
| King et al 2021[43] | Retrospective analysis of 27 patients with MPN-AP/BP (frontline and R/R treatment) | VEN-including regimens | ALR-C/CCR Rate: 37% | MPN-BP mOS:: 6 mo<br>MPN-AP mOS: 3.6 mo |




Adapted from Patel AA and Odenike O. Clinical Lymphoma, Myeloma and Leukemia 2023

**A Phase 2, prospective, multi-center intervention trial in patients with acute myeloid leukemia secondary to myeloproliferative neoplasms unfit for intensive chemotherapy investigating a treatment combination including decitabine and venetoclax**

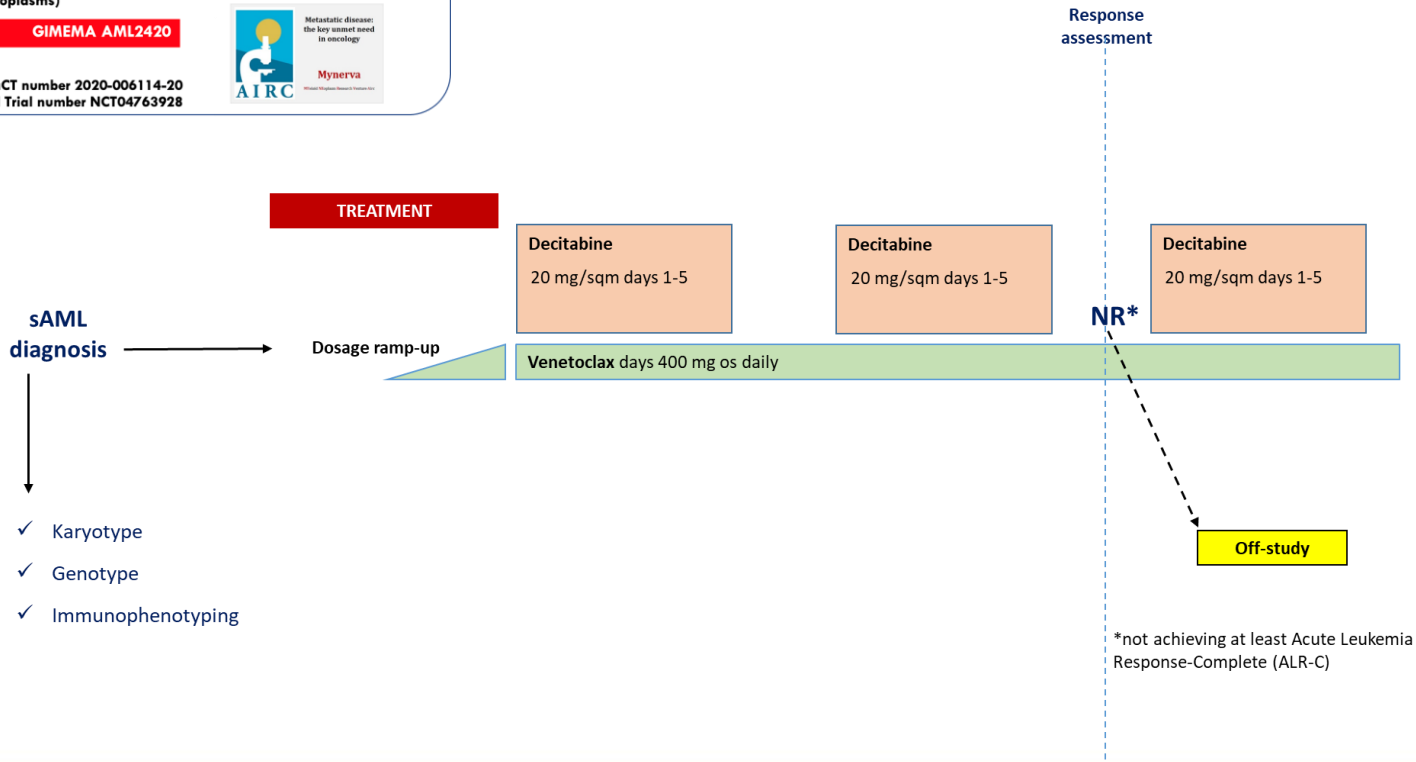
**ENABLE (vENetoclax plus decitAbine treatment in Blastic phase of myeLoproliferative nEoplasms)**

**GIMEMA AML2420**

**EudraCT number 2020-006114-20**
**Clinical Trial number NCT04763928**

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche FRANCO MANDELLI

AIRC Metastatic disease: the key unmet need in oncology Mynerva



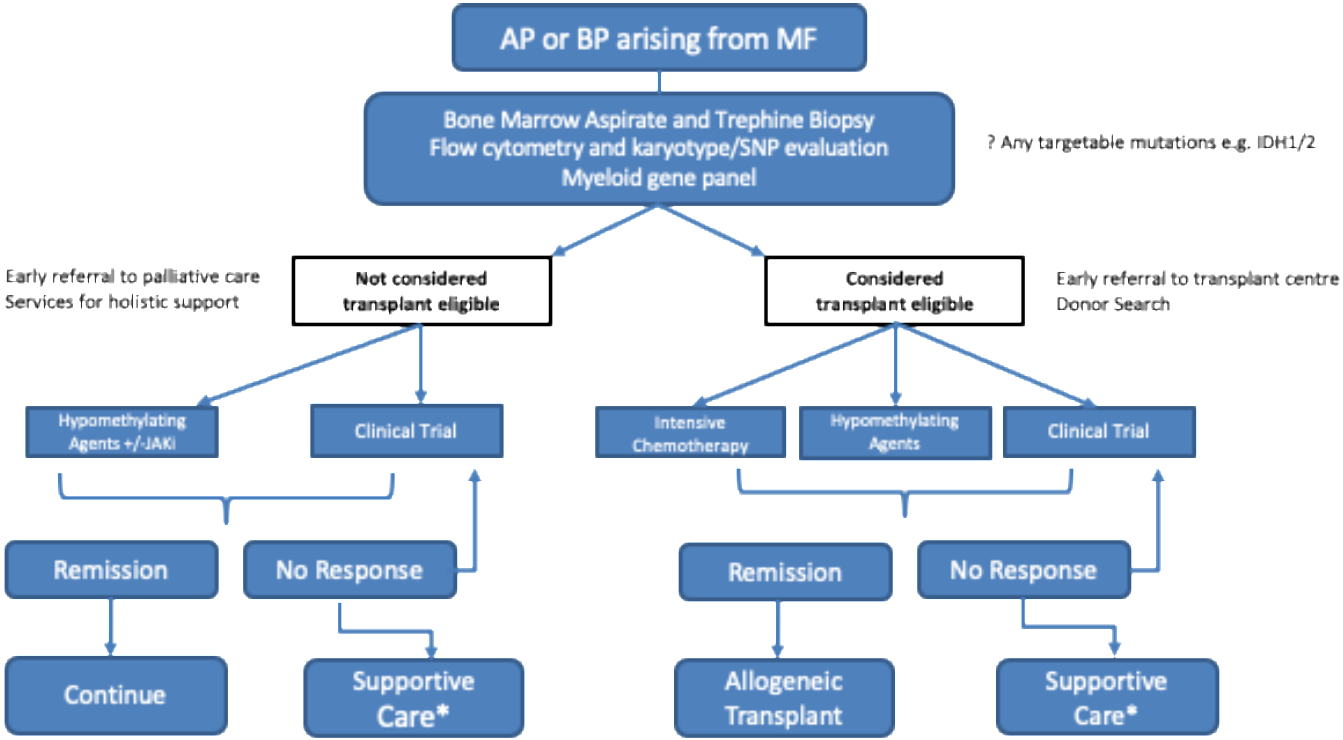
# Targeted IDH1/2 Inhibitor-based Treatments in *IDH1/2*-Mutated post-MPN AML Patients

| IDH inhibitor-including regimens | Study | Therapy | Response Rate | Overall Survival |
|---|---|---|---|---|
| Patel et al 2020[2] | Retrospective analysis of 8 patients with *IDH2*-mutated MPN-AP/BP (frontline and R/R treatment) | Enasidenib-including regimens | ORR: 37.5% | NR (median follow-up 9 mo) |
| Chifotides et al 2020[3] | Retrospective analysis of 12 patients with *IDH1* or *IDH2*-mutated MPN-BP (frontline and R/R treatment) | IDH inhibitor-including regimens | CR Rate: 25% | mOS: 10 mo |
| Bar-Natan et al, 2022[55] | Ongoing phase II study of 5 patients with *IDH2*-mutated MPN-AP/BP | Ruxolitinib + Enasidenib | CR Rate: 40% | Not reported |

## Targeted TP53-based Treatments

- MDM2i (Navtemadlin - KRT232) demonstrated clinical activity in a phase Ib dose escalation study in TP53 WT patients with MPN BP ( GI toxicity)
- Ongoing: multicenter phase Ib/II study in patients with R/R AML (including those with MPN-BP) as Navtemadlin in monotherapy and in combination with LDAC or decitabine

# Suggested Management of Accelerated or Blastic Phase Disease




* Includes transfusion support, count control with hydroxycarbamide or alternatives, symptom control and palliative care.

AP= accelerated phase; BP= blast phase; JAKi = JAK inhibitor; IDH= isocitrate dehydrogenase

Adapted from BSH-HSCT Recommendations 2023; NCCN. Myeloproliferative Neoplasms (Version 1.2021),

# CRIMM-Center Research and Innovation of Myeloproliferative Neoplasms Florence

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