VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

# La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

## Il Panorama delle Molecole Target e Differenziative nelle Leucemie Acute: Risvolti Clinici


***Jacopo Nanni***

*Dipartimento di Scienze Mediche e Chirurgiche, University of Bologna, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seragnoli"*

*jacopo.nanni5@unibo.it*


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# Disclosures of Jacopo Nanni

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Astellas Pharma | | | | | X | | |
| Daiichi-Sankyo | | | | | | | X |
| Servier | | | | | | | X |
| Pfizer | | | | | | | X |
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# AGENDA

- General **Background** on **AML therapy**
- **Background** on **AML Differentiating Agents**: Which Ones and How
- **Details** on currently adopted **AML Differentiating Agents** in **routine clinical practice**
- **Spotlight** on some exemplary **Clinical Cases**

# AGENDA

- General Background on **AML therapy**
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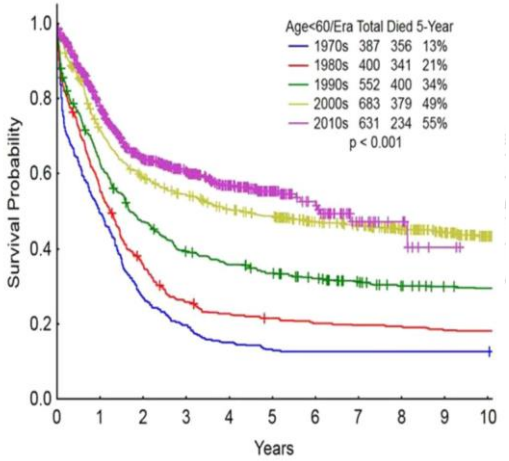
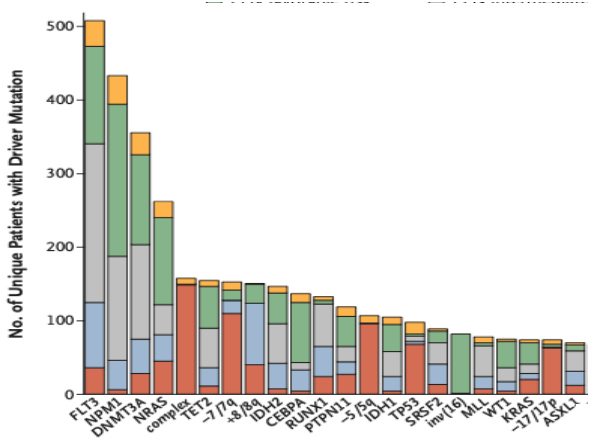
# BACKGROUND ➢ ACUTE MYELOID LEUKEMIA: State of The Art



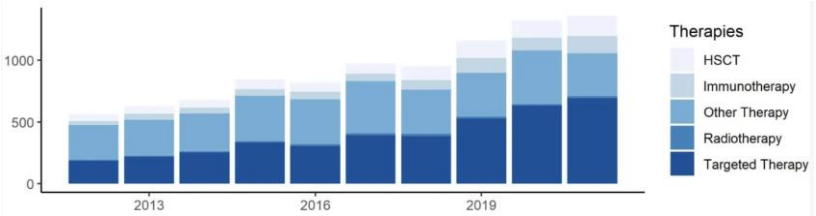

| Risk category† | Genetic abnormality |
|---|---|
| Favorable | • t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*†,‡<br>• inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*†,‡<br>• Mutated *NPM1*†,§ without *FLT3*-ITD<br>• bZIP in-frame mutated *CEBPA*‖ |
| Intermediate | • Mutated *NPM1*†,§ with *FLT3*-ITD<br>• Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions)<br>• t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*†,¶<br>• Cytogenetic and/or molecular abnormalities not classified as favorable or adverse |
| Adverse | • t(6;9)(p23.3;q34.1)/*DEK::NUP214*<br>• t(v;11q23.3)/*KMT2A*-rearranged#<br>• t(9;22)(q34.1;q11.2)/*BCR::ABL1*<br>• t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*<br>• inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*<br>• t(3q26.2;v)/*MECOM(EVI1)*-rearranged<br>• −5 or del(5q); −7; −17/abn(17p)<br>• Complex karyotype,** monosomal karyotype††<br>• Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*‡‡<br>• Mutated *TP53*ª |

❖ **AML prognosis** especially for R/R cases is still **unsatisfactory**, however significant **improvements** were registered **over decades**;

❖ **High-resolution molecular techniques** allowed the elucidation of **AML genomic background:**

✓ Better **prognostication systems** ameliorated AML therapeutic paradigm;

***Kantarjian H. et al, Blood Cancer Jorunal, 2021***

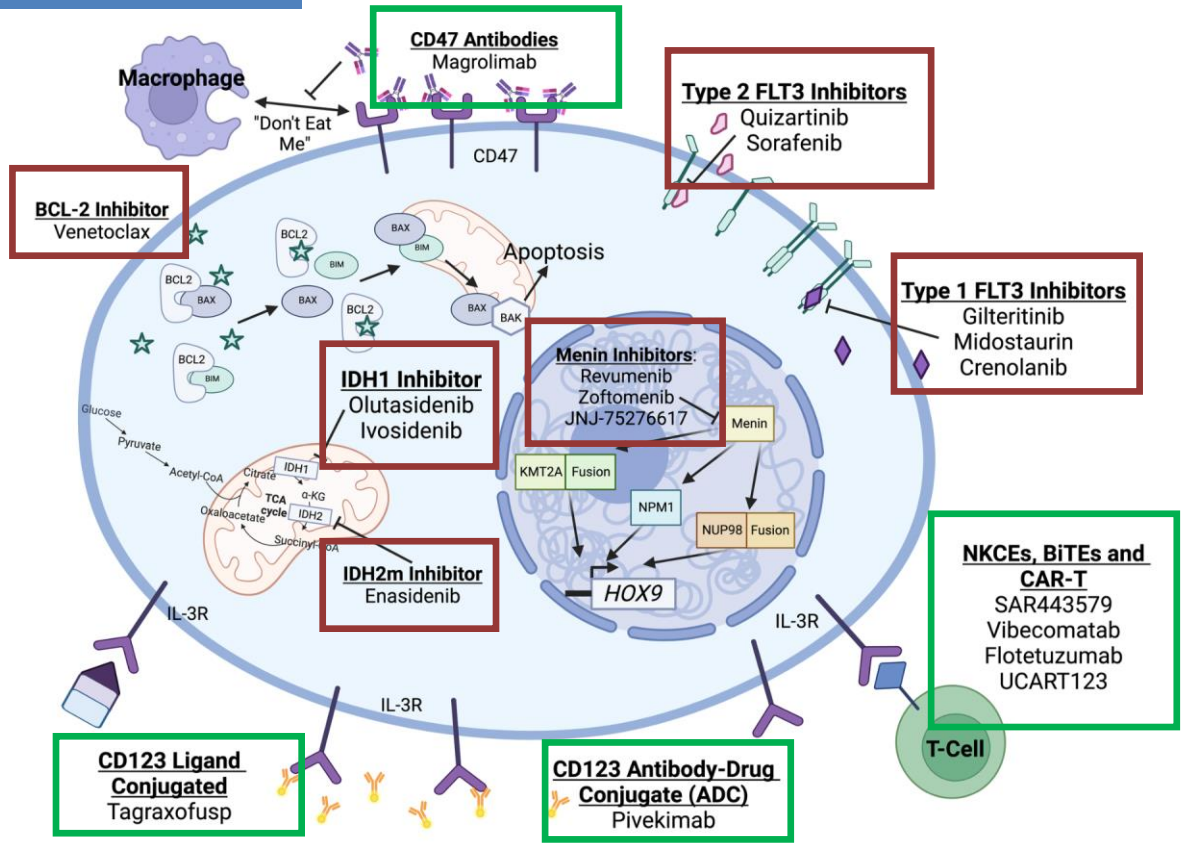



✓ **Target therapies** (FLT3 inhibitors, IDH inhibitors, Venetoclax,...) revolutioned AML treatment.

***E. Papaemmanuil et al, NEJM, 2016***

***Dohner H. et al, Blood, 2022***

# BACKGROUND ➢ ACUTE MYELOID LEUKEMIA: Target Therapies




**Different types of Targets:**

- ➢ **Intrinsic / singaling molecules;**
- ➢ **Extrinsic: immunotherapies / drug conjugates (ADCs)**

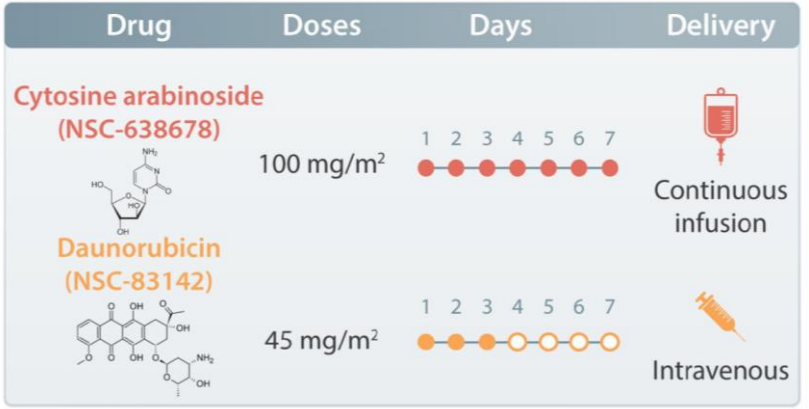
*Adapted from Wysota M. et al, Currents Hematology Reports, 2024*

# BACKGROUND ➢ AML therapy: Historical Chemotherapy Backbone

## The "7+3" Regimen

1973

- Landmark paper in 1973 reported on an astounding **CR rate of 63%** among patients with AML;
- **"7 and 3"** regimen, dramatically changed the prognosis of patients, has **remained the backbone of standard therapy for close to five decades**, and, amazingly, is still going strong.




## National Comprehensive Cancer Network Guidelines 2026 for AML > 18 yo

**Favorable-risk AML by molecular mutation profile[d] or Intermediate-risk AML per ELN (AML-A)**

**Preferred:**
- Standard 7 + 3 (daunorubicin or idarubicin)[j] (category 1)

**Other Recommended:**
- Standard 7 + 3 (daunorubicin or idarubicin)[j] + gemtuzumab ozogamicin[l,o] (CD33 positive)[m]
- FLAG-IDA[n] (category 2B; use with caution in patients >60 y)
- FLAG-IDA[n] + gemtuzumab ozogamicin[l,o] (CD33 positive)[m] (category 2B; use with caution in patients >60 y)
- CLAG-M (cladribine + cytarabine + G-CSF - mitoxantrone) (category 2B; use with caution in patients >60 y)

**AML with *FLT3* mutation**

- Standard 7 + 3 (daunorubicin or idarubicin)[j] + midostaurin[p] (*FLT3*-internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) (category 1)
- Standard 7 + 3 (daunorubicin or idarubicin)[j] + quizartinib (*FLT3*-ITD only)

**Poor-risk AML without *TP53* mutation or del(17p) abnormality**

**Preferred:**
- No regimens are considered preferred, clinical trial is recommended

**Other Recommended:**
- Standard 7 + 3 (daunorubicin or idarubicin)[j]
- CPX-351/dual-drug liposomal cytarabine and daunorubicin[r] (category 2B)
- FLAG-IDA[n] (category 2B) (use with caution in patients >60 y)
- Decitabine (days 1–5) + venetoclax[s,u]
- Azacitidine + venetoclax[s,u]
- CLAG-M (category 2B)
- CLIA + venetoclax (category 2B)
- FLAG-IDA[n] + venetoclax (category 2B; use with caution in patients >60 y)

*Yates JW et al, Cancer Chemother Rep., 1973*



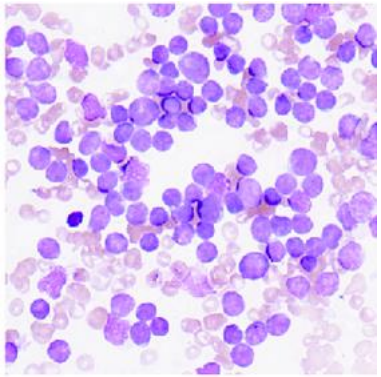
*https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf*

# BACKGROUND

## ➢ AML: Cht Mechanism of Action and Response Achievement

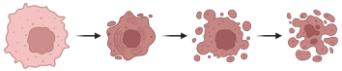
- ✓ **Cytarabine**, a pyrimidine analog, acts as an antimetabolite by stopping DNA replication, which halts S-phase replication and leads to cell death.
- ✓ **Daunorubicin** intercalates DNA and inhibits topoisomerase II, resulting in single- and double-strand DNA breaks.
- ✓ Beyond **direct genotoxic effect**, chemotherapy is effective through addional mechanims (**immunogenic cell death**).

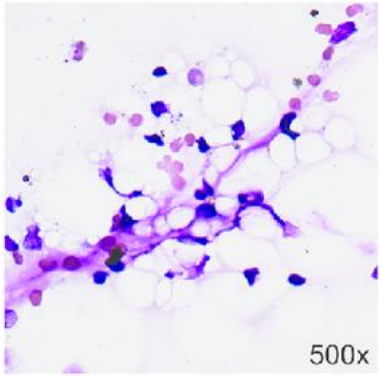
| Drug | Doses | Days | Delivery |
|---|---|---|---|
| Cytosine arabinoside (NSC-638678) | 100 mg/m² | 1 2 3 4 5 6 7 | Continuous infusion |
| Daunorubicin (NSC-83142) | 45 mg/m² | 1 2 3 4 5 6 7 | Intravenous |



Acute Myeloid Leukemia

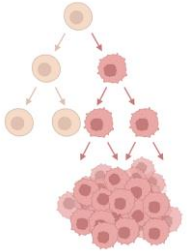
Chemotherapy - induced cell death

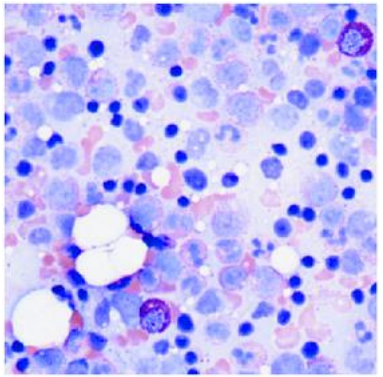





Aplastic Phase

Healthy BM Regeneration





Normal Bone Marrow

*R. Sharma et al, Pediatrics in Review, 2016*

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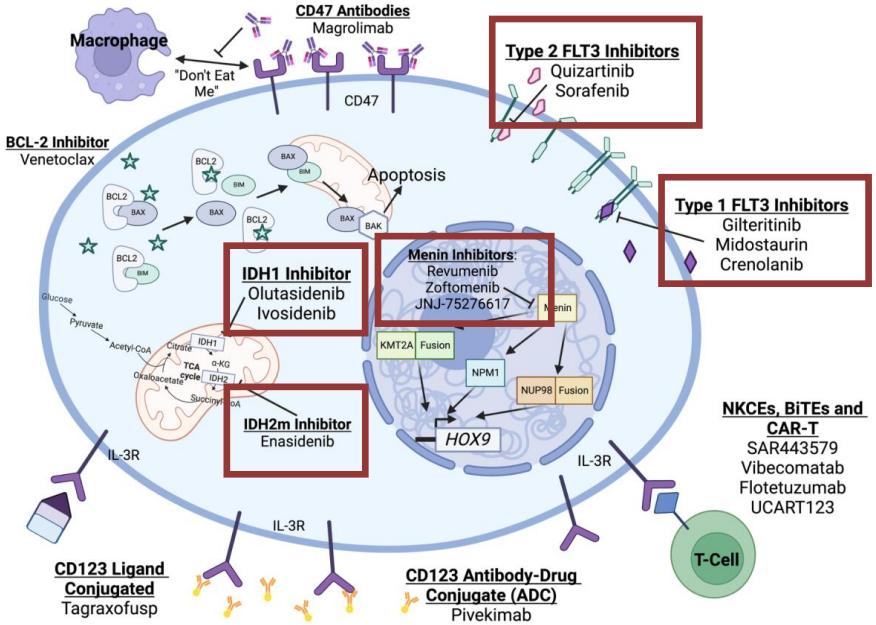
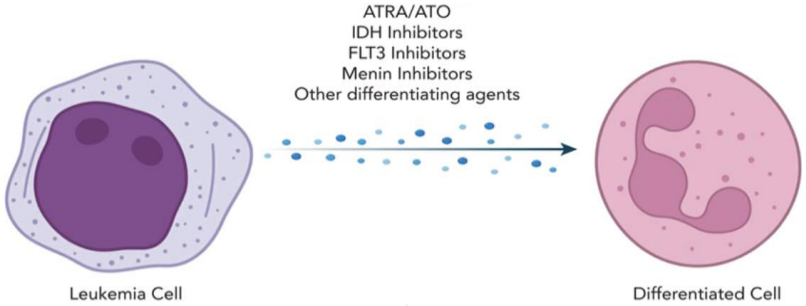
# Differentiating Agents ➢ Which Ones?

## Nover target Agents for AML




## History of FDA Drug Approval for AML


## Differentiating Agents for AML




*Adapted from Wysota M. et al, Curr. Hem. Reports, 2024*



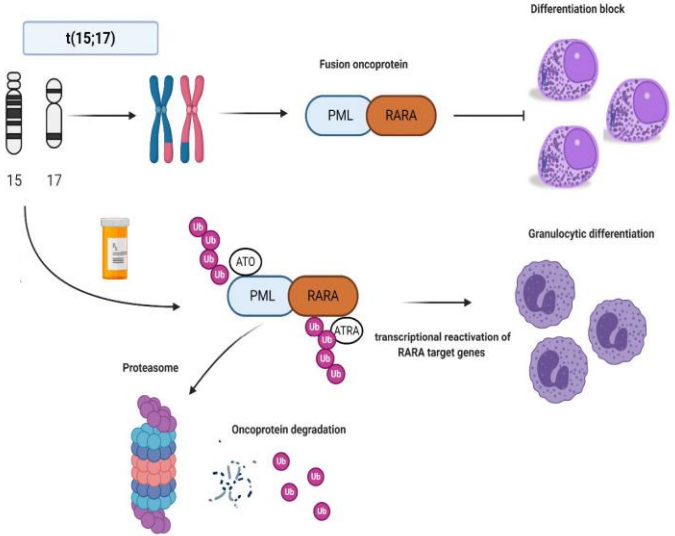
*G. Issa et al, Blood, 2025*

# Differentiating Agents

## ➢ HOW: The marvelous story of APL therapy

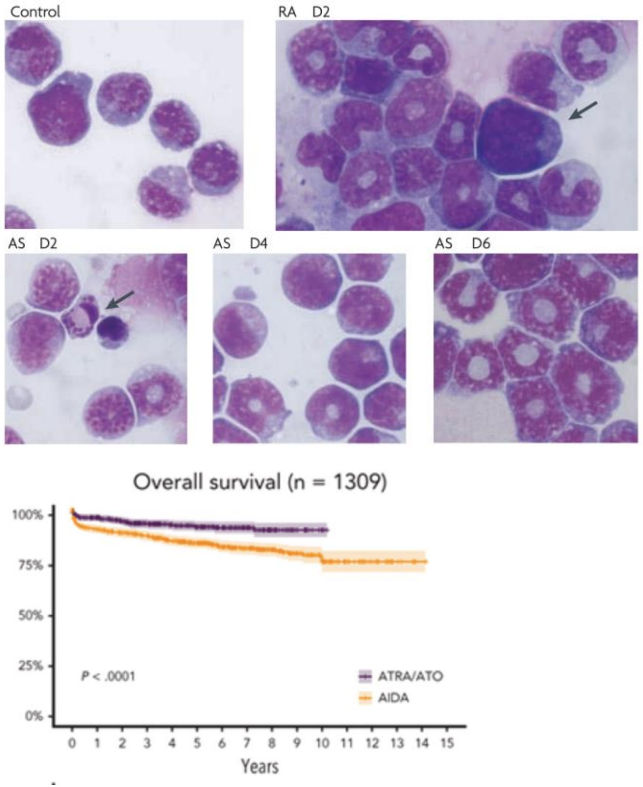
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 11, 2013 VOL. 369 NO. 2

Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia




*Adapted from Gurnari C. et al, Int. J. Mol. Sci., 2021*

*F.Lo-Coco et al, NEJM, 2013*




*M.T.Voso et al, Blood, 2025*

**Leukemic** Cells infiltration/presence

↓

**Maturation** and **proliferation** of leukemic cells (Hyperleukocytosis and inflammatory state)

↓

**Death of Mature Cells**, reduction in Residual Leukemia

↓

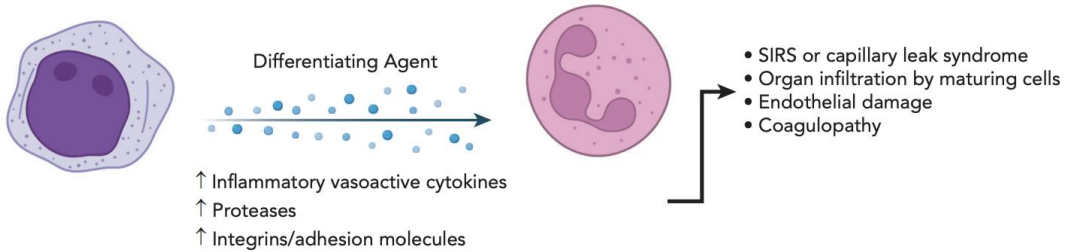
Repopulation of **Healthy BM (CR)**

*Adapted from Hugues D. et al, Nature Reviews, 2010*

# Differentiating Agents

## ➢ HOW: Different Mechanism → Different clinical consequences

- ✓ **Differentiating agents**, generally, have less **myelosuppression** and fewer standard chemotherapeutic side effects such as mucositis and alopecia.
- ✓ An increasingly recognized AE is **Differentiation Syndrome (DS):**
  - occur in the setting of neutrophil recovery, with leukocytosis, fever, hypotension, dyspnea, pleural/pericardial effusions, weight gain, peripheral edema, and AKI;
  - **Pathogenesis of DS** is thought to stem from exuberant cytokine production (IL1, IL6, IL8, CCL2,...) in differentiating/maturing leukemic cells, leading to a hyperinflammatory state analogous to SIRS, associated with vascular capillary leak, and increased organ infiltration by maturing cells
- ✓ **Diagnosis of DS may be challenging** and **differential diagnosis** is crucial.
- ✓ **Treament**: prophylactic or therapeutic steroids, hydroxyurea, additional chemotherapy (GO and cytarabine), supportive care, temporary treatment discontinuation.




Diagnosis of DS if ≥1 of the following signs or symptoms (Frankel et al[12]):

Fever

Hypotension

Dyspnea

Pulmonary infiltrates

Pleural and or pericardial effusion

Acute renal failure

Weight gain ≥ 5 Kg

Grading of DS (Montesinos et al.[10]):

- Moderate: 2 or 3 signs or symptoms
- Severe: 4 to 7 signs or symptoms

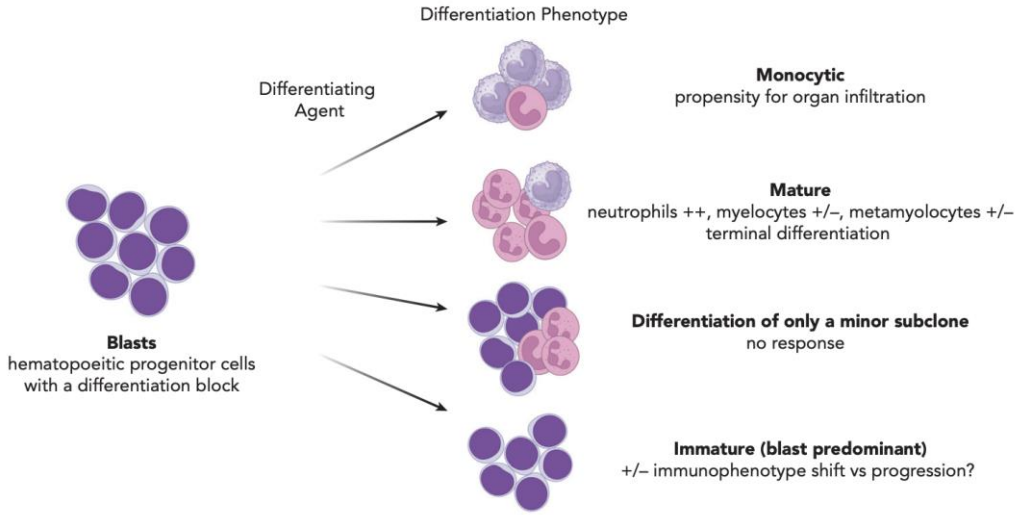
No single sign or symptom is considered sufficient for the diagnosis of DS based on this scoring system.



*G. Issa et al, Blood, 2025*

# Differentiating Agents

➢ **HOW: Difficult to predict response in the meanwhile**




**LEUKOCYTOSIS – MONOCYTOSIS – BLAST CELLS persistence**:
Signs of **Differentiation**?
Signs **predictive** of a future Response?
**Disease Progression**?

- ✓ In some DS cases associated with **IDH or MENIN inhibitors**, leukocytosis can be predominantly **monocytic**, making the distinction of **DS vs leukemia progression** even more **challenging**;
- ✓ the **development of DS** is not always associated with **clinical response;**
- ✓ **Median time to CR longer** (3-4 months): be **patient**.

- ✓ **unsuccessful terminal differentiation** process leading to a more monocytic but still **dysfunctional leukemia clone.**



*G. Issa et al, Blood, 2025*

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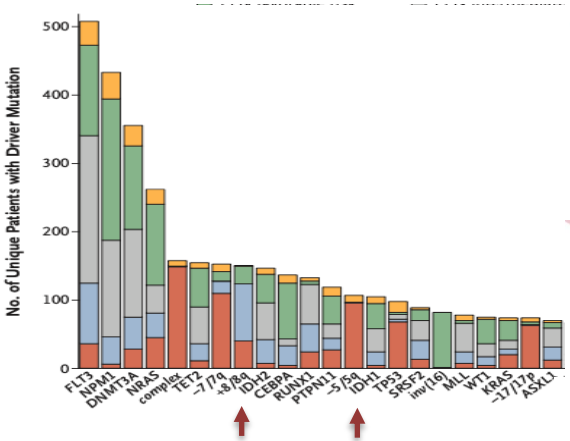
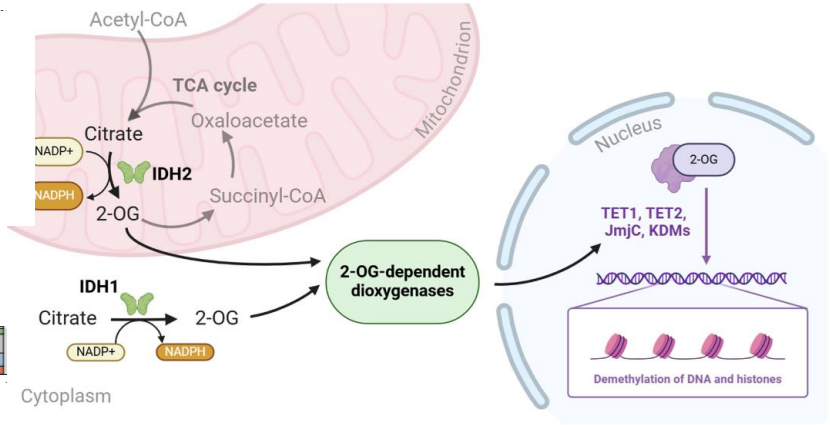
## Differentiating Agents

# ➢ IDH1/IDH2 mutations in AML and IDH1/2 inhibition

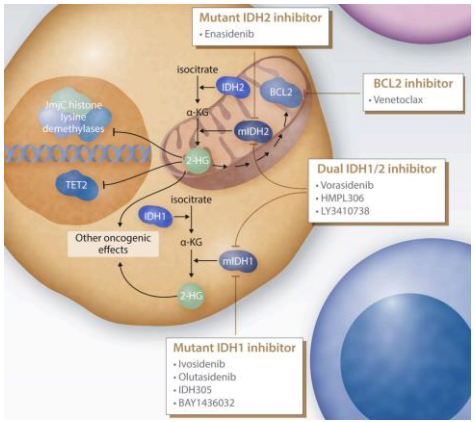
- ✓ Around the **8%** and **12%** of **AML** harbor an **IDH1 or IDH2 mutations**, respectively; **IDH** mutations also present in a minority of other **MM** such as **MDS** and **accelerated MPNs**.
- ✓ ***IDH1*** and ***IDH2*** mutations are associated with: an older age at presentation; diploid or other intermediate-risk cytogenetics (i.e. trisomy 8); and a sustained platelet count at presentation.
- ✓ The **impact of *IDH1*** and ***IDH2*** **mutations are also context dependent**, with *IDH* mutations that occur in the setting of *NPM1* mutations (without *FLT3*-ITD) appearing to confer more favorable outcomes.




*G.Issa, et al, Blood Cancer Journal, 2021*




*A. Kowalczyk, Int. Journal Molecular Sciences*




*Wouters B., Hemasphere, 2021*

# Differentiating Agents

## ➢ IDH1/2 inhibitors in clinical pratice: State of the Art

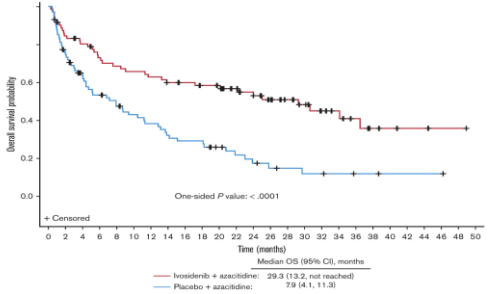
✓ **Ivosidenib (IDH1 inhibitor):**

Several FDA Approval

**Relapsed/Refractory AML (July 2018):** As monotherapy for adults with an IDH1 mutation;

**Relapsed/Refractory MDS (Oct 2023):** For adult patients with an IDH1 mutation.

**Newly Diagnosed AML (May 2022): EMA approval 2023 / AIFA approval (2024): For adult patients with de novo AML harboring R132- IDH1 mut and unfit for intensive treatment, in combination with azacitidine.**




✓ 148 patients: ivosidenib-azacitidine (n = 73) or placebo-azacitidine (n = 75):

✓ Median OS longer with ivosidenib (29.3 months) than with placebo (7.9 months; P < .0001).

✓ CR occurred in 34/72 pts (47%)

✓ Responses were associated with **cellular differentiation** and maturation, typically **without evidence of aplasia**.

✓ **DIFFERENTIATION SYNDROME incidence**:

- 14% in Ivosidenib plus Azacitidine;
- 7% in Enasidenib single-agent trial;
- 14 % in Olutasidenib single-agent trial.

✓ **Olutasidenib (IDH1 inhibitor):**

**FDA single-agent approval in 2022 to treat R/R IDH1-mut AML / never approved by EMA/AIFA**:

Phase I/II study (153 pts): CR/CRh rate was 35% (95% CI: 27–43%); 29/86 became TI (34%).

✓ **Enasidenib (IDH2 inhibitor):**

**FDA single-agent approval in 2017 to treat R/R IDH2-mut AML / never approved by EMA/AIFA**

Phase I/II study (239 pts): ORR 40.3%. Median OS among relapsed/refractory patients was 9.3 months, and for the 34 patients (19.3%) who otteined CR, OS was 19.7 months.

***De Botton S. et al, Blood Advances, 2023***

***Stein E. et al, Blood, 2017***

***Pau Montesinos et at, NEJM, 2022***

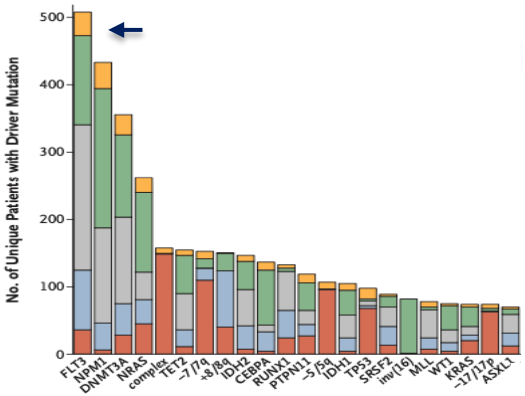
## Differentiating Agents

# ➢ FLT3 inhibitors in clinical pratice: State of the Art

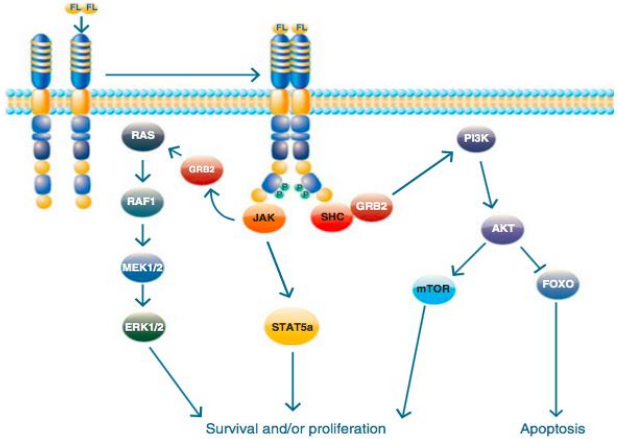
- ✓ **FLT3 gene**, located in chromosome 13 (13q12.2), encodes for a type III receptor tyrosine kinase.
- ✓ **1/3 adult de novo AML cases harbor at least a mutation in FLT3 gene**: ITD 23-25 % of AML cases and point mutations in the TKD2 about 7-10 % of AML cases.

→ **DIFFERENT FLT3 inhibitors have been developed and reached routine clinical practice in different setting**:

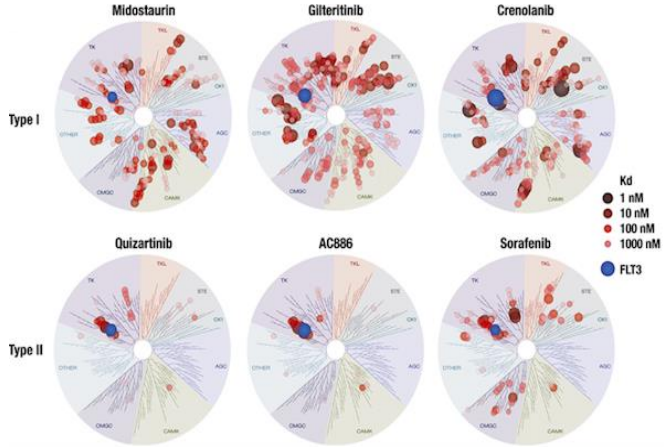
- **First line of treatment of Newly-Diagnosed Fit FLT3-mut AML patients**: «7+3» and **Midostaurin** or **Quizartinib**;
- **Single agent salvage for R/R FLT3-mut AML cases**: **Gilteritinib** (**Quizartinib** did not obtain approval);
- **After Allogeneic Stem Cell Transplantation Maintenance**: **Sorafenib** (L648) or **Gilteritinib** (not yet approved) or **Quizartinib**.




*Papaemmanuil E. et al, NEJM, 2016*




*Swords C. et al, Leukemia, 2012*




*Takeshi D. et al, Oncotarget, 2020.*

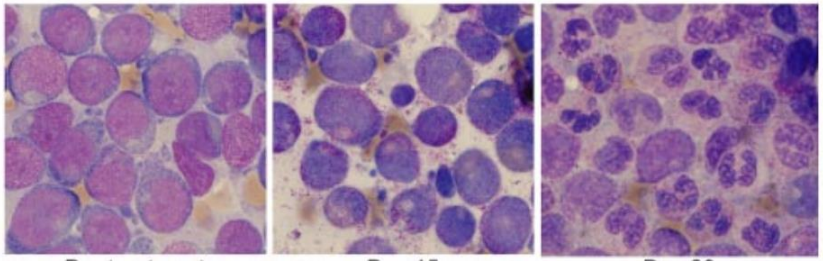
# Differentiating Agents

## ➢ Differentiation associated with FLT3-inhibition:

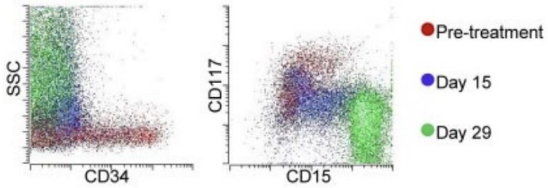
- Since **chemotherapy exerts a potent cytotoxic effect → differentiation is not seen** when **a FLT3-i is administered** in association with **chemotherapy** («7+3» and Midostaurin or Quizartinib);
- **Post-transplant maintenance** is administered with **a limited/absent residual disease →** differentiation is not documented;

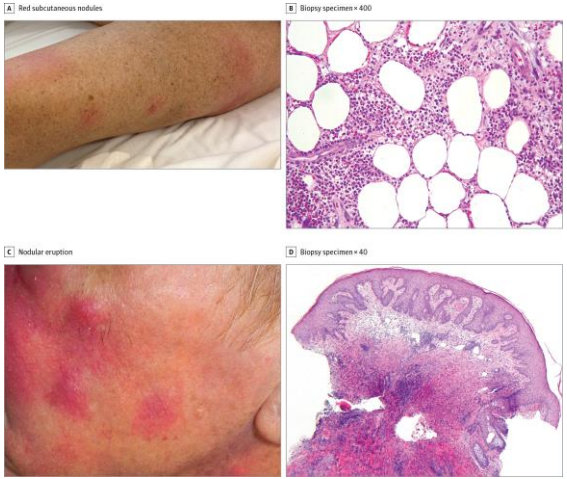
- **Single agent salvage** [**Gilteritinib monotherapy**] is the setting where we may frequently observe **signs of differentiations**.
- **Activation** of **FLT3** also suppresses myeloid differentiation by **inhibiting the function of CEBPA** via ERK1/2-mediated phosphorylation, while pharmacological inhibition of FLT3 causes granulocytic differentiation of AML cells.

- Early studies with FLT3 inhibitors demonstrated **clinical manifestation** of differentiation with evidence of **neutrophilic dermatoses**.



**Quizartinib induced terminal differentiation**




**77 patients** were treated with **FLT3 inhibitors for AML**; 3 developed confirmed neutrophilic dermatoses: here a **neutrophil-predominant lobular panniculitis** (Gilteritinib-above) and an **interstitial neutrophil-rich inflammatory infiltrate** and clusters of atypical mononuclear cells (Gilteritinib-below)

*Sexaur A. et al, Blood, 2015*

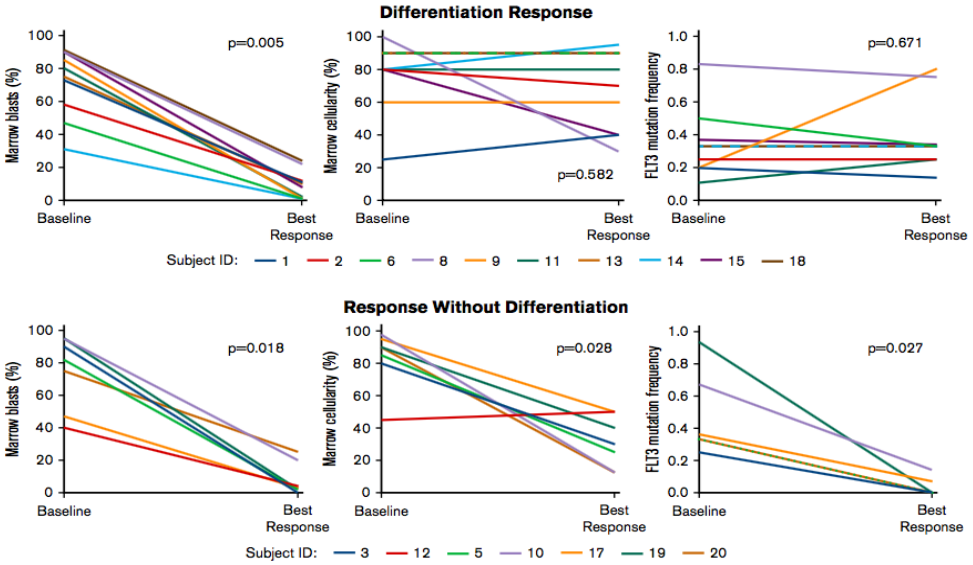
*Vadarajan N. et al, JAMA Dermatology, 2016*

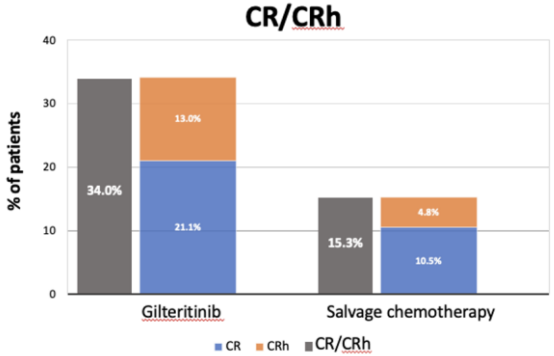
# Differentiating Agents

## ➢ FLT3-inhibition (GILTERITINIB): the role of Molecular Markers

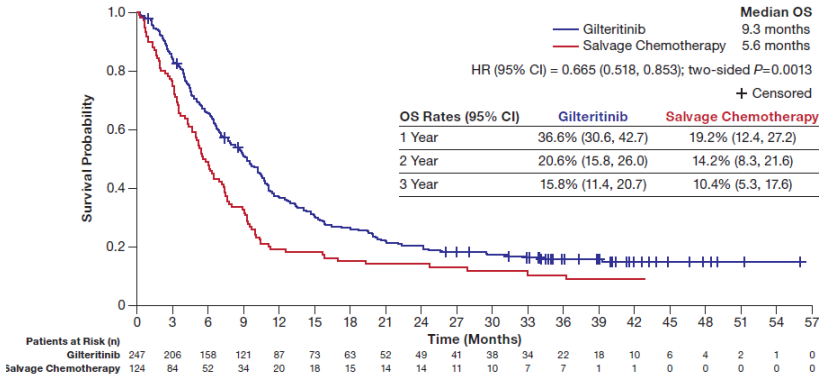
**Monitor FLT3 allelic ratio as a marker of response during FLT3 inhibitor single-agent therapy?**

**Among 17/21 (81.0%) had a ≥50% reduction in BM blasts:**
**2 distinct patterns of responses**




Perl A et al, NEJM, 2019;381:1728–1740.

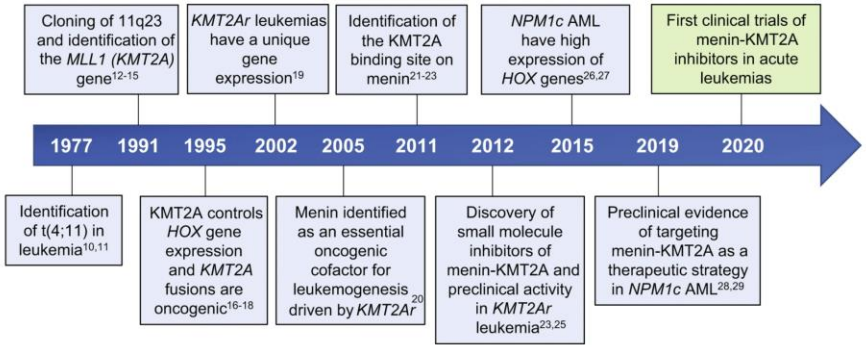


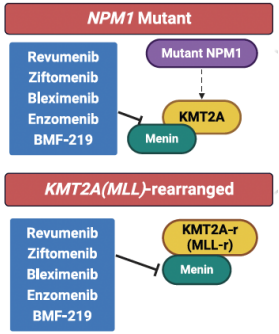

Christine M. McMahon et al., Blood Advances 2019

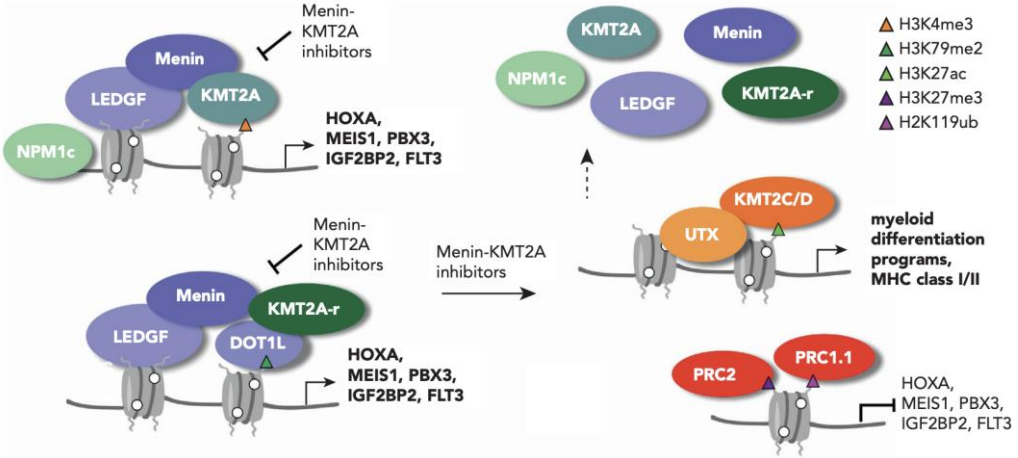


Personal data

# Differentiating Agents ➢ Menin-Inhibitors Development




✓ Relevant for **Leukemogenesis** in: **KMT2A-rearranged, NPM1-mutated**, NUP98-rearranged? CEBPA-mutated? GMP-like? other?

✓ **Drug Mechanism of action**:

- induction of **KMT2C/D-driven myeloid differentiation programs**
- loss of menin-KMT2A/KMT2A-r driven oncogenic self-renewal programs
- loss of **immune evasion via MHC class I/II upregulation**

*Issa G. et al, Leukemia, 2021* *G. Huls et al, Blood, 2025*



*Thakur R.K. et al, Cancer 2025*

# Differentiating Agents

| Agent (route) | Phase 1/ 2 expansion cohorts For relapsed/refractory disease | Phase /# pts |
|---|---|---|
| **Revumenib** (SNDX-5613) PO BID | (a) ALL or MPAL with *KMT2Ar* (b) AML with *KMT2Ar; (c) NPM1* | Phase 1 /2 (n=186) |
| **Ziftomenib** (KO-539) PO QD | (a) AML with *KMT2Ar* (b) AML with *NPM1c* | Phase 1 /2 (n=199) |
| **Bleximenib** (JNJ-75276617) PO QD | (a) AML/ALL with *KMT2Ar* (b) AML with *NPM1c* | Phase 1 (n=110) |
| **Enzomenib** (DSP-5336) PO QD | RR-AML/RR-ALL Ph2:*NPM1/KMT2Ar* | Phase 1/2 (n=70) |
| BMF-219 PO | (a) AML/ ALL (*KMT2Ar, NPM1*) (b)DLBCL; (c) MM; (d) CLL/SLL | Phase 1 (n=177) |

# ➢ Menin-Inhibitors Development

✓ **Revumenib for R/R KMT2A-R [AUGMENT-101 Phase I/II][FDA approval]**

**94 patients** : In the efficacy-evaluable patients (n = 57), the CR + CRh rate was 22.8%, ORR was 63.2 %. DS (any grade) in 26 patients (27.7%).

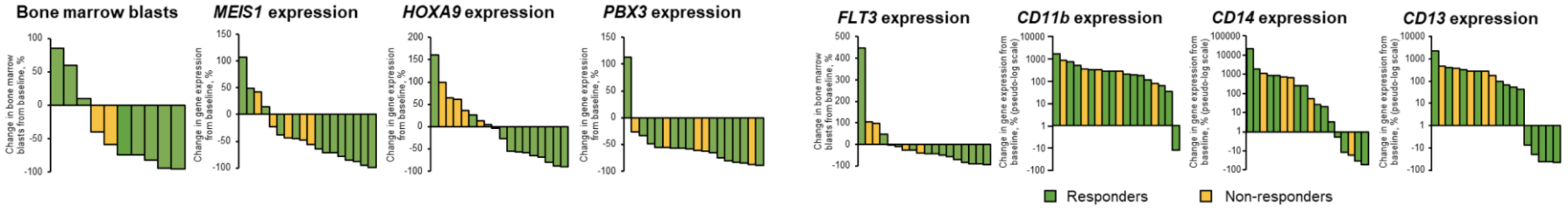
✓ **Revumenib for R/R NPM1-mut AML [AUGMENT-101 Phase II][FDA approval]**

**84 patients** received ≥1 dose of revumenib. 64 adult patients evaluable for efficacy: the CR + CRh rate was 23.4%; the ORR was 46.9%. DS (any grade) occurred in 16 patients (19.0%)

✓ **Ziftomenib for R/R NPM1-mut AML [KOMET-001 phase 1/2 trial] [FDA approval]**

83 patients: At the RP2D of 600 mg, 9/36 (25%) patients with KMT2A-R or NPM1 mutation had CR or Cri

Of 83 patients: grade 3 or worse DS (12 [15%]).DS rate and severity influenced the decision to halt enrolment of patients with *KMT2A* rearrangements.



# Differentiating Agents

## ➢ MENIN-I: Morphology – Flow – Cytogenetic/Molecular Data → Discordant results due to differentiation

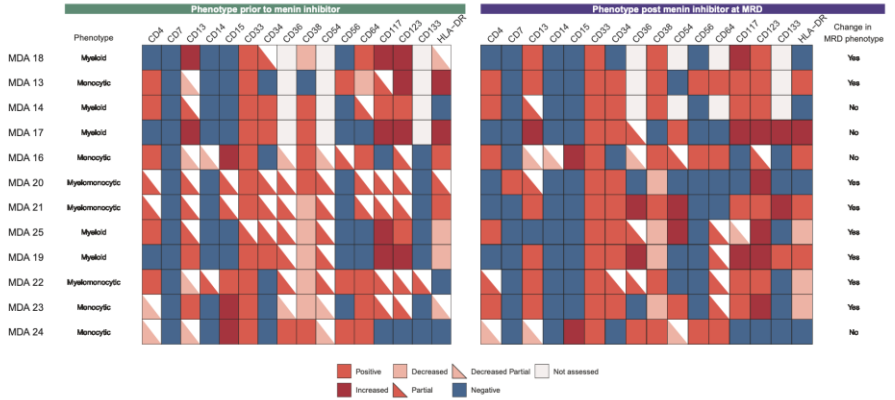
Examined the immunophenotype in sequential **BM specimens from 48 patients** with **R/R AML treated with Revumenib**:

1. a **switch in immunophenotype in 52% of cases**, from a myeloid/stem-like to a monocytic or myelomonocytic profile.

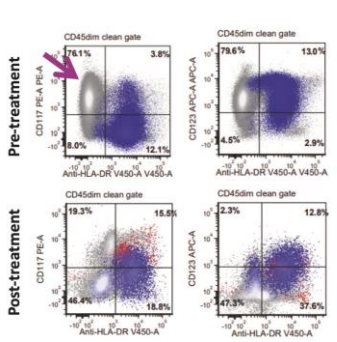
2. among 12 patients who attained a CR MRD + by FC, 8 (67%) had aberrant blasts with **an immunophenotypic shift;**

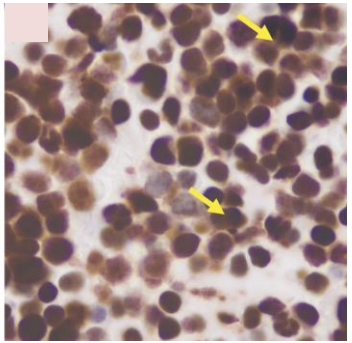
3. **14 pts experienced relapse**: in this subset, 9 (64%) of 14 showed an **immunophenotypic shift at relapse.**

4. compared the results of **FC and FISH in patients with KMT2Ar or NUP98r**: focusing on discordant results, two of 11(18%) evaluable patients with undetectable MRD by FC had detectable KMT2A rearrangements in >90% of cells, suggesting differentiation of leukemic cells.




**IHC for NPM1 mutations offers a "unique opportunity to visualize morphology and the types of cells retaining mutant NPM1, thereby providing greater clarity".**



*Longhavi S. et al, Leukemia, 2026*

# AGENDA

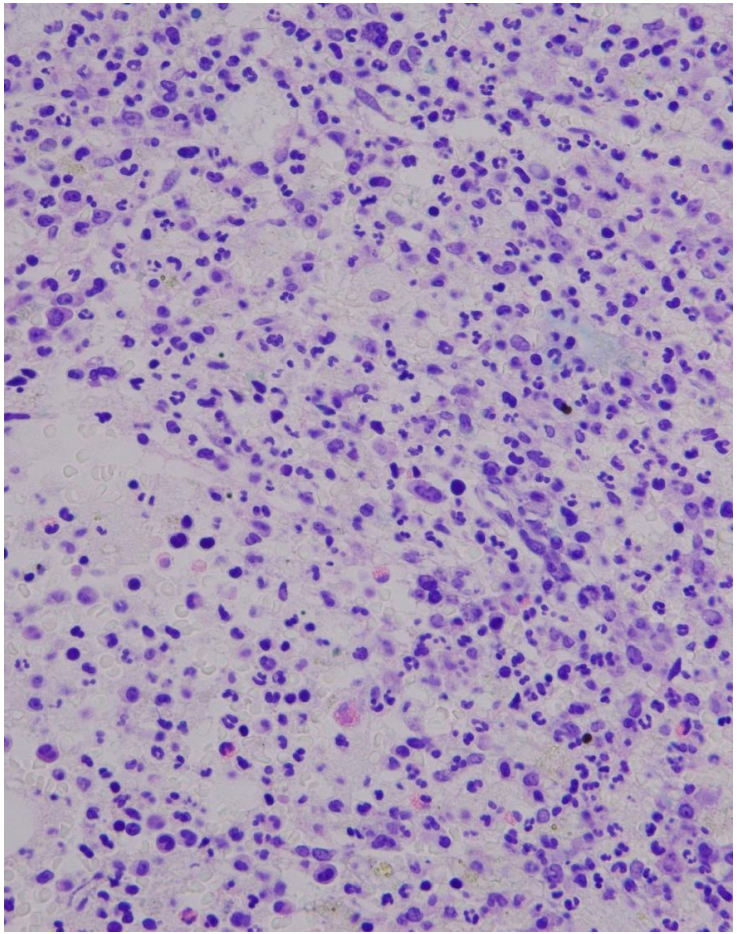
- General Background on **AML therapy**
- Background on **AML Differentiating Agents**: Which ones and How
- Details on currently adopted **AML Differentiating Agents** in **routine clinical practice**
- Spotlight on some exemplary **Clinical Cases**

**Case 1.**
**69 yo Male**
**Sep 2025: Diagnosis of AML, secondary to MPN**
**Molecular Characterization: IDH1-mut, JAK2 V617F, RUNX1, tp53, U2AF1, ASXL1**

**Oct 2025: start 1st line: IVOSIDENIB plus Azacitidine;**
**Day 15: WBC 36.000/mmc, persistence of circulating blast cells (but with myeloid precursor and dysplastic PMNs), AKI and pleural effusion → DIFFERENTIATION SYNDROME.**
**treated with HU + steroids + temporary Ivosidenib withdrawn.**

**Dec 2025: BM Biopsy (not evaluable citology) →**
**90% cellularity (hypercellular), myeloid expansion with maturation, no excess of blasts (CD34/CD117) not even myeloid precursors, reduction in erythroid compartment as well as megacaryocytes.**
**MRD IF 0.042%, IDH1 mutated.**

1. **Not easy to discriminate initial signs Differentiation with disease progression: careful evaluation/management may lead to response;**
2. **After Differentiation process may ends «successfully»: bone marrow changes consistent with response but also with a marked myeloid stimulation.**



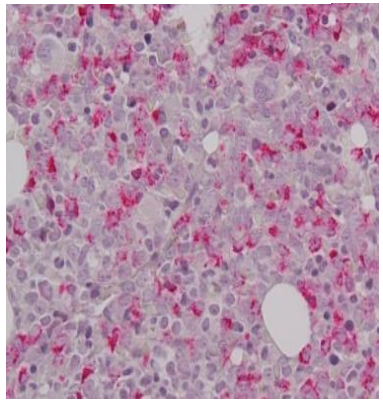
**Case 2.**
**49 yo Male**
**Dec 2023: Diagnosis of AML, NPM1-mut, FLT3-ITD/FLT3-TKD mut**
**IF at diagnosis: CD33/HLA-DR+, CD34/CD117/CD13/MPO partial and CD7+.**

**1st line of therapy: "7+3" plus Midostaurin**

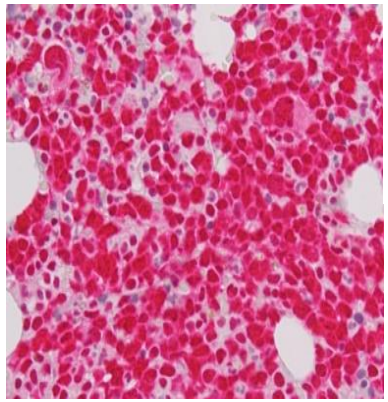
**After an initial response (MRD IF 0.037%, NPM1 1.51, no excess of blasts)**
**→ RELAPSE: CD34+ 18% (IF 42%, NPM1 96,89, FLT3-ITD positive).**

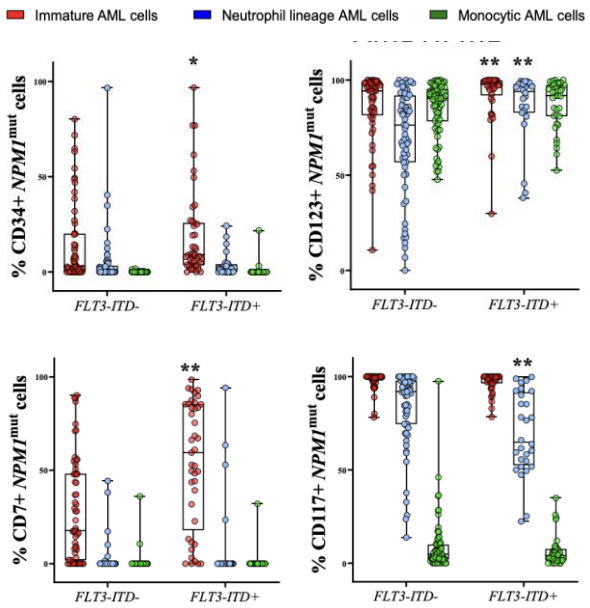
**1st Relapse**

**CD34**



**NPM1**






*Matarraz S. et al, Blood Cancer Journal, 2023*

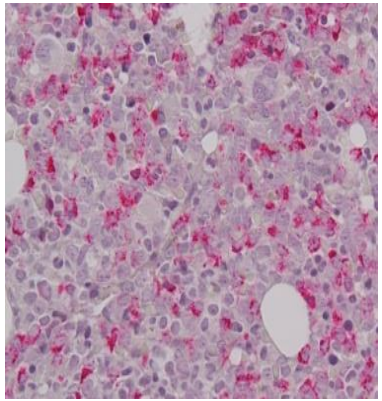
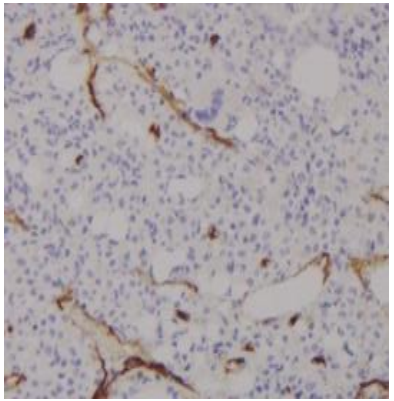
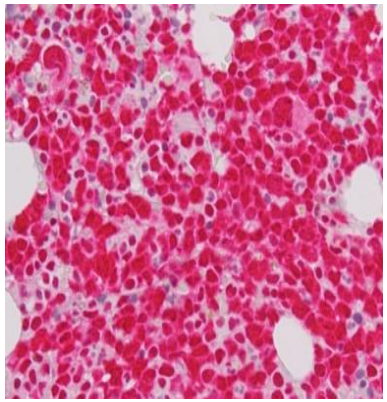
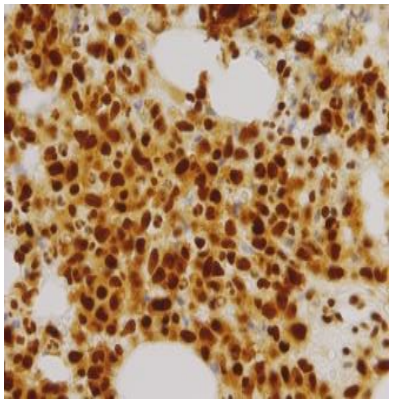
**Case 2.**
**49 yo Male**

→ RELAPSE: CD34+ 18% (IF 42%, NPM1 96,89, FLT3-ITD positive).

GILTERITINIB (FLT3-inhibitor) - Mar 2024
Lab Parameters: WBC 8.580/mmc, HB 13 g/dL, Plt 94.000/mmc

+ 3 moths Gilteritinib:
MRD IF-LAIP negative, NPM1-mut 222, FLT3-ITD mut, Cellularity 90%, low/no CD34+ cells, expansion "myelomonocytic compartment, NPM1+ IHC".
Lab Parameters: WBC 4.510/mmc, HB 8.2 g/dL, Plt 40.000/mmc

1. Difficult to analyse IF and IHC changes which may be due to differentiation therapy;
2. IHC cytoplasmic NPM1+ expression in «differentiating» cells may be a potential sign of therapeutic effectiveness
3. For CLINICAL RESPONSE ASSESSMENT: Need to integrate IF, IHC, molecular biology, citology and Peripheral Counts

| | Before-Gilteritinib | Post-Gilteritinib |
|---|---|---|
| CD34 |  |  |
| NPM1 |  |  |

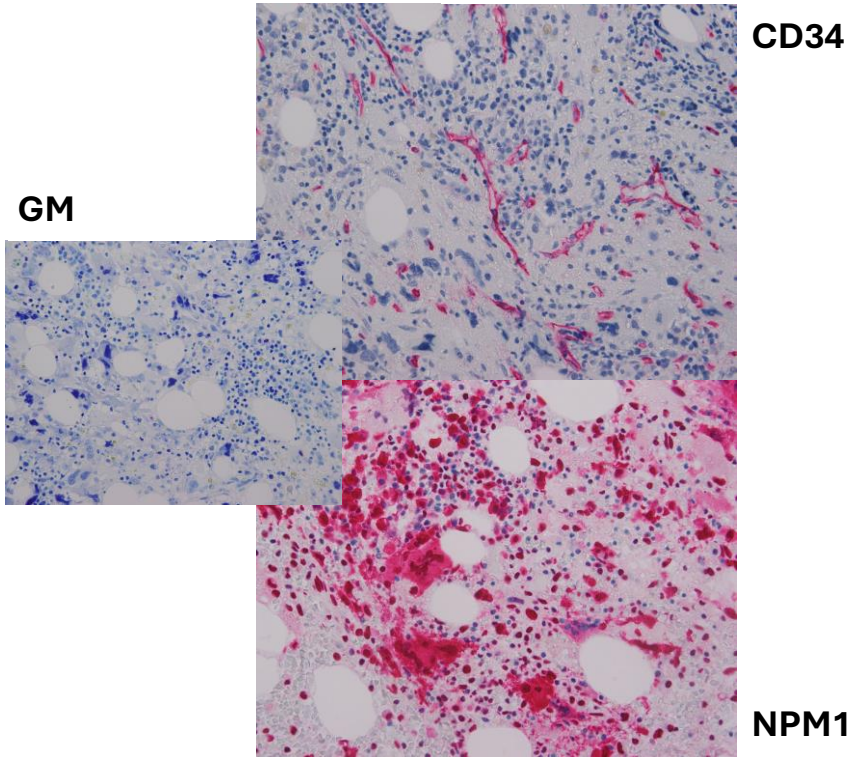
**Case 3.**
**67 yo Male**
**Sep 2020: Diagnosis of AML secondary to CMML, NPM1-mut FLT3-ITD mut low AR (0.3)**

**1st line of therapy: "7+3" plus Midostaurin**

**→ refractory: persistence of blast cells, NPM1 191, FLT3-ITD + AR 1.1**

**→ Gilteritinib SALVAGE Dec 2020.**
**Lab Parameters: WBC 1.280/mmc, HB 6.8 g/dL, Plt 17.000/mmc**

**→ +3 months Gilteritinib:**
**Cellularity 40%, Persistence of 30% + IHC cytoplasmic NPM1+ in «immature» cells (NPM1-mut 72).**
**Lab Parameters: WBC 780/mmc, HB 7 g/dL, Plt 23.000/mmc**



## CONCLUSIONS

➢ **Il Panorama delle Molecole Target e Differenziative nelle Leucemie Acute: Risvolti Clinici**

- ✓ **AML Therapeutic Armamentarium** is (fortunately) evolving, with **novel "differentiating agents"** and each one has its peculiarities in terms of **pathophysiology** and so **clinical features**.
- ✓ Physicians need to **carefully manage** and evaluate **drug safety** and **effectiveness** especially in the presence of **drug-related leukocytosis**, **cytological signs of differentiation**, newly-onset **clinical symptoms**.
- ✓ **Response assessment** is not so straightforward: need to **integrate** cytological, hystological, flow-cytometry data, cytogenetic, molecular biology and laboratory/clinical **findings**.
- ✓ Need to build a **Multidisciplinary Team** involving different figures for an optimal management of differentiating therapies

# ACKNOWLEDGEMENTS

## ➢ THANK YOU FOR YOUR ATTENTION!

***Dipartimento di Scienze Mediche e Chirurgiche, IRCCS Policlinico Sant'Orsola Malpighi, Istituto di Ematologia "Seràgnoli", Università di Bologna*** **- Prof. Pierluigi Zinzani**

ALL/AML/MDS team di ricerca clinica:
Responsabile: Dr. Antonio Curti
Cristina Papayannidis
Giovanni Martinelli
Sartor Chiara
Carlo Finelli
Stefania Paolini
Sarah Parisi
Federico Zingarelli
Caterina Azzimondi
Chiara Comparin
Raffaele Ciruolo
Giulia Masala
Benedetta Pagano

Centro di Ricerca Clinica:
Francesco Ingletto
Gaia Chinnici
Riccardo Mennuti

Lab. Biologia Molecolare:
Emanuela Ottaviani
Carolina Terragna
Simona Soverini
Silvia Armuzzi
Ilaria Vigliotta
Lorenza Bandini
Samantha Bruno
Claudia Venturi
Agnese Patuelli
Valentina Robustelli
Giulia Atzeni

Lab. Citogenetica:
Carmen Baldazzi

Lab. Microambiente Midollare:
Marilena Ciciarello
Karyna Volkava
Dorian Forte
Valentina Salvestrini
Darina Ocadlikova

Emolinfopatologia:
Responsabile: Elena Sabattini
Claudio Agostinelli
Clara Bertuzzi
Carlo Sagramoso