3rd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 21-22, 2023

Starhotels Majestic

Scientific board:
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Disclosures of Ana Alfonso Piérola

- Honoraria from lectures: Novartis, BMS, Abbvie, Jazz Pharma, Janssen
- Participation in Ad Board meetings: BMS, Syros, Jazz Pharma
- Consultant: Astellas, Jazz Pharma
- Research Founding: Astra Zeneca

New approaches for treatment of MDS

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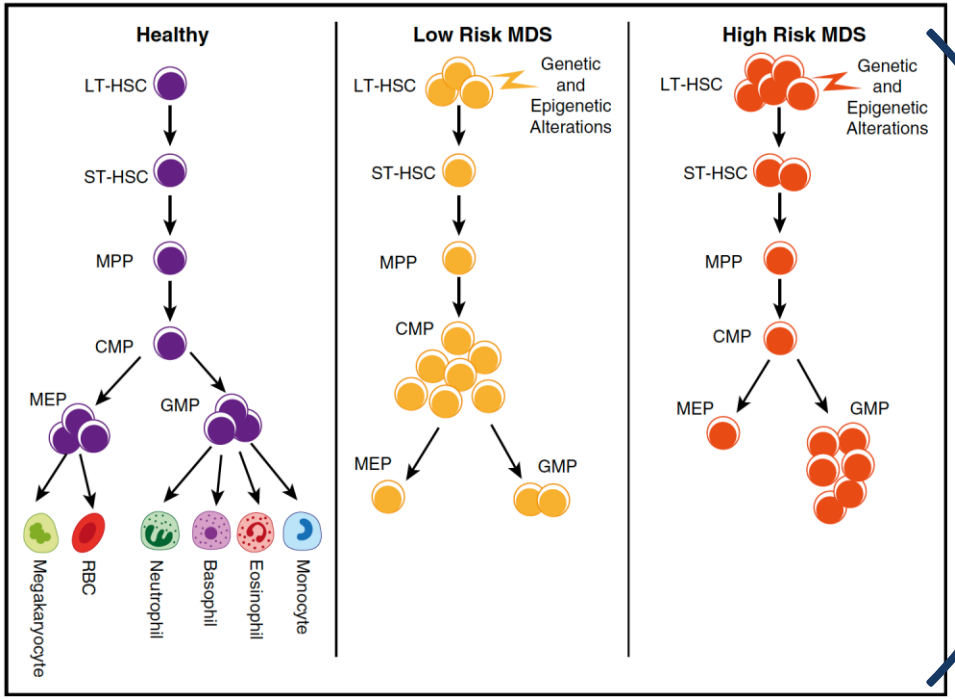
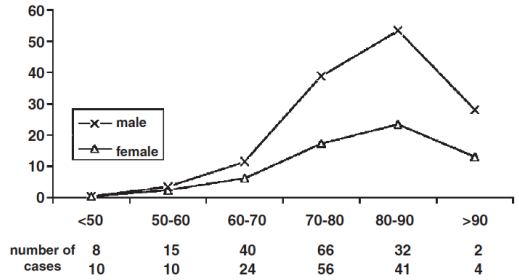
IdiSNA INSTITUTO DE INVESTIGACIÓN SANITARIA DE NAVARRA



Incidence 5.0/100,000/year

- Male/female 6.8 vs. 3.7/100,000
- Increases with age. Median age at diagnosis 70 years (80% over 60 years of age).



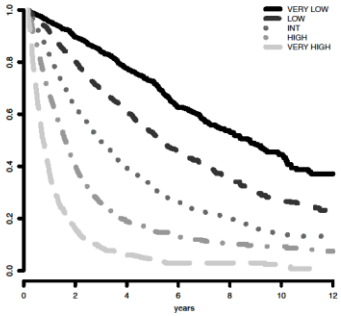
Shastri A et al. Blood. 2017 Mar 23;129(12):1586-1594. Tefferi A et al. N Engl J Med. 2009;361:1872-85.Germing U et al. Haematologica. 2004;89:905-10.

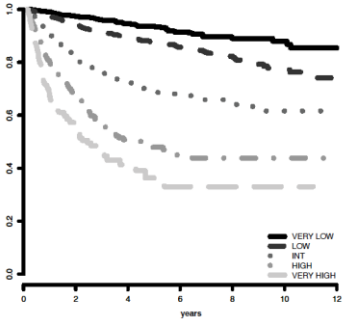
IPSS-R

	0	0.5	1	1.5	2	3	4
Karyotype*	Muy bueno		Bueno		Inter	Pobre	Muy pobre
BM blasts	0-2 %		3-4.9 %		5-10%	> 10%	
Hgb (g/dL)	≥ 10		8-9.9	< 8			
Plt (x10^9/L)	≥ 100	50-99	< 50				
ANC (x10^9/L)	≥ 0.8	< 0.8					

*** Karyotype**	
Very Good	-Y, del(11q)
Good	Normal, del(20q), isolated del(5q) or +1 additional abndormality, del(12p)
Intermediate	+8, del(7q), i(17q), +19, any other single or double independent clones
Poor	3q abnormalities, -7, -7/del(7q), complex with 3 abnormalities
Very Poor	Complex ≥ 3 abnormalities

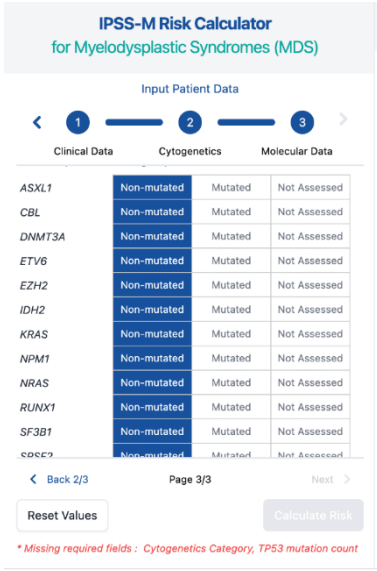
- IPSS-R groups
  - ✓ Very low: 0-1.5
  - ✓ Low: 2-3
  - ✓ Intermediate: 3.5-4.5
  - ✓ High: 5-6
  - ✓ Very high: >6

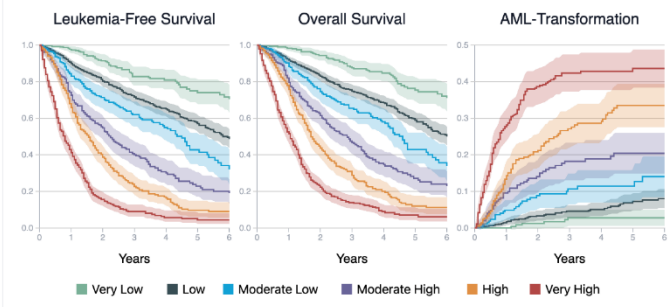




Greenberg P et al. Blood 1997; 89(6): 2079-88

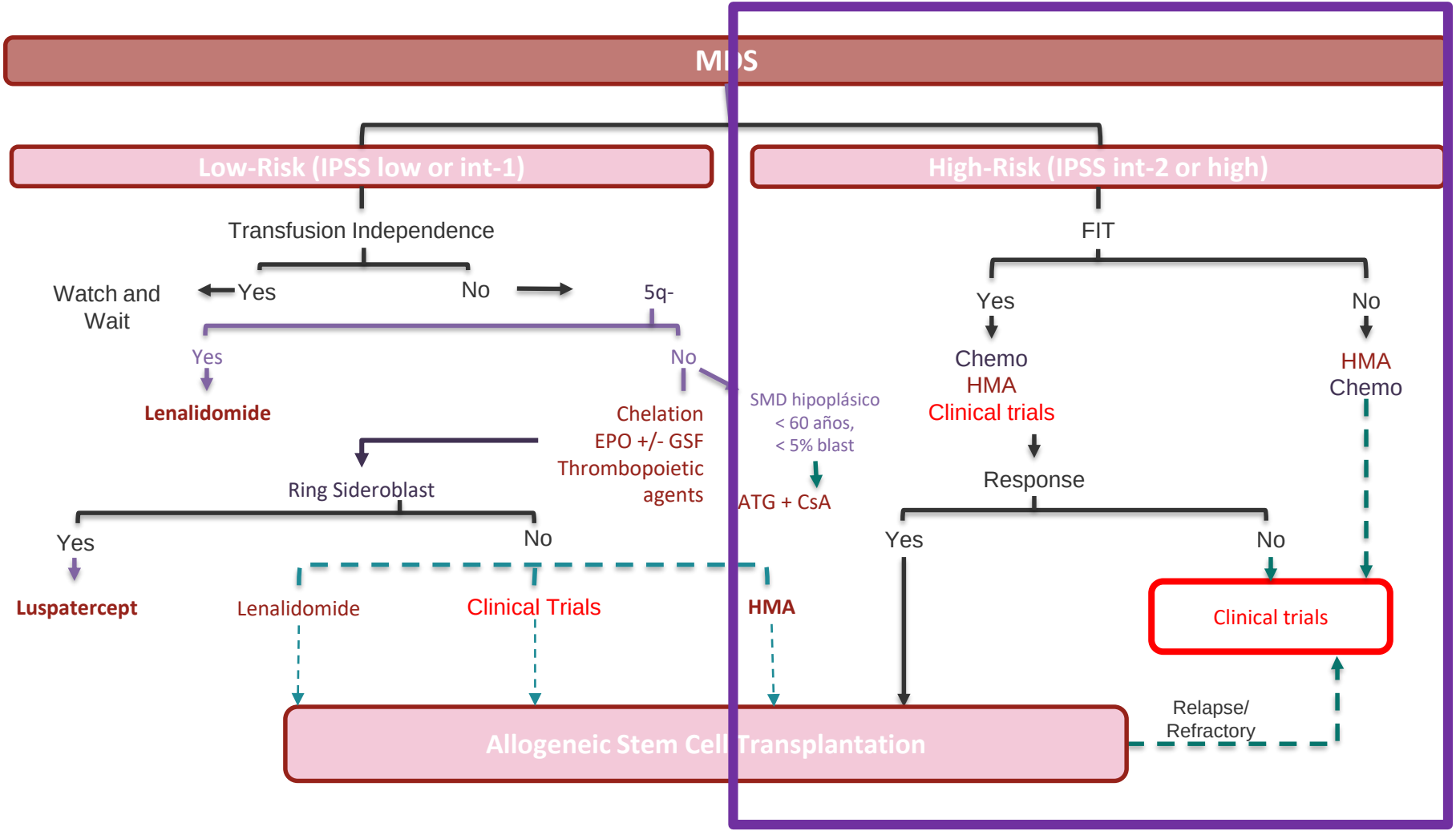
IPSS-M





Bernard et al. NEJM Evidence 2022.https://mds-risk-model.com/

MDS treatment

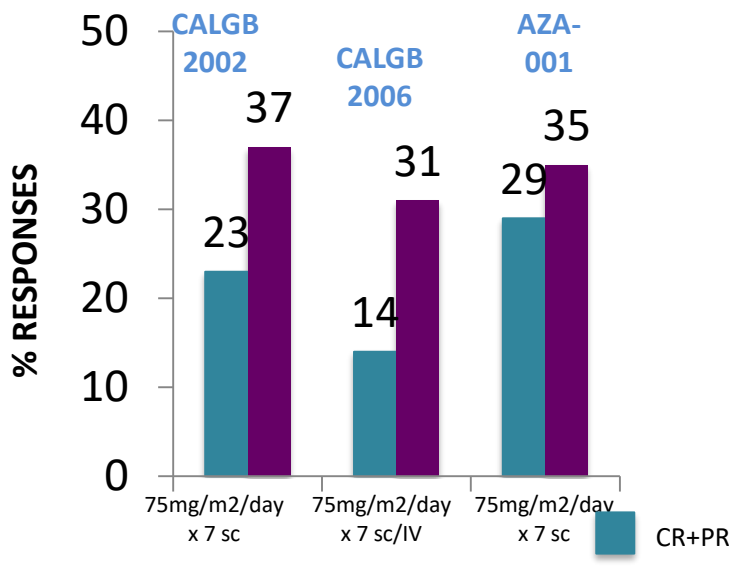


HMA-based regimens

AZA EMA approved: HR-MDS

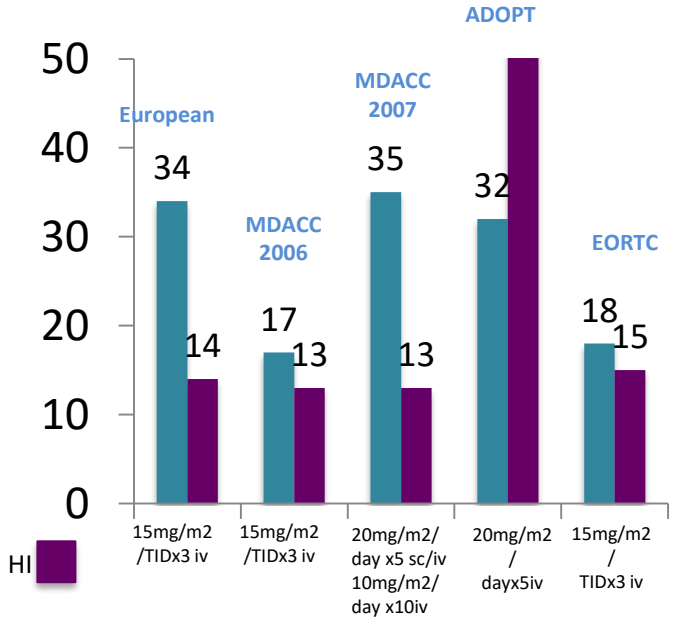
ORR

AZACITIDINE



Silverman LR. J Clin Oncol. 2002;20(10):2429-40
Silverman LR. J Clin Oncol. 2006 ;24(24):3895-903.
Fenaux P et al. Lancet Oncol. 2009 Mar;10(3):223-32

DECITABINE

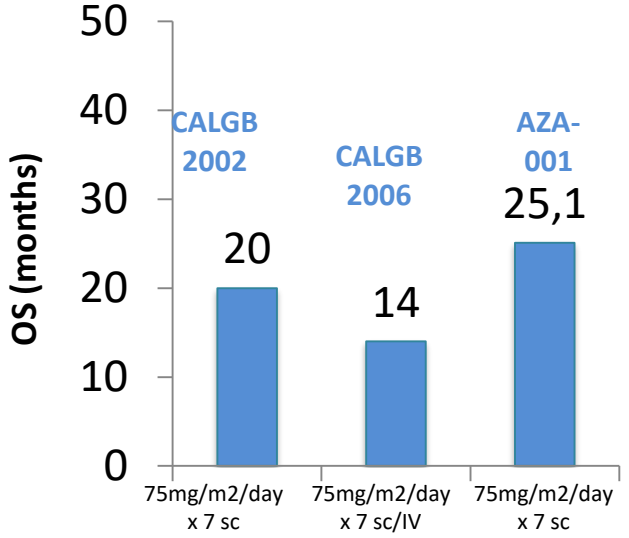


Wjiermans Ann Hematol 2005;84:9-17
Kantarjian H et al. Cancer 2006;106:1794-803
Kantarjian H et al. Blood 2007;109:52-7
Steensma DP et al. JCO 2009;24:3842-8
Lubberrt M et al. JCO. 2011;29(15):1987-96.

HMA

OS

AZACITIDINE



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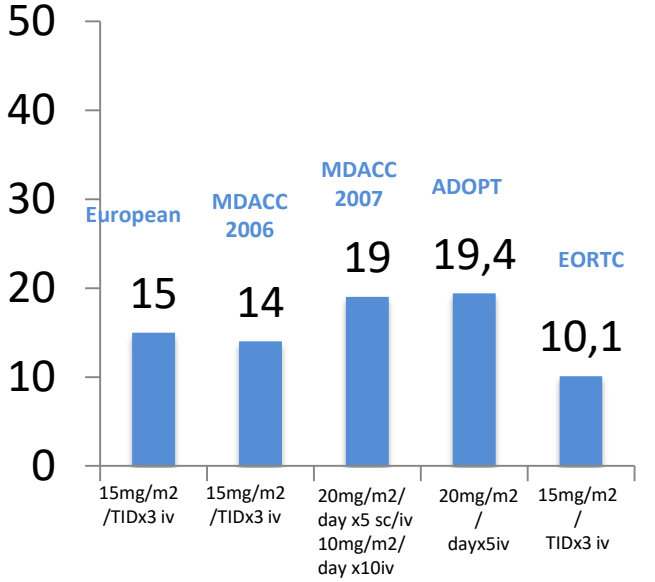

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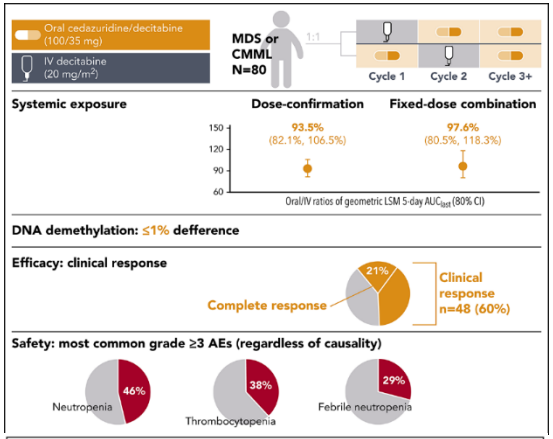
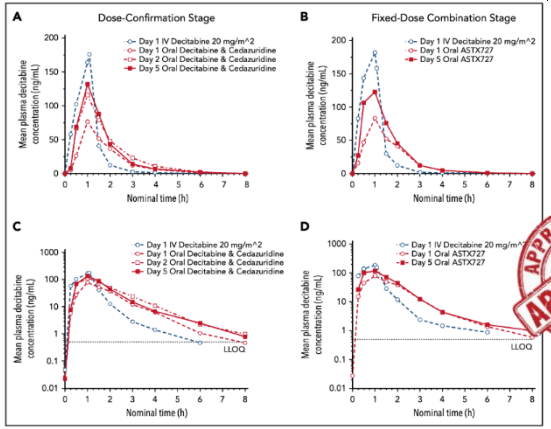
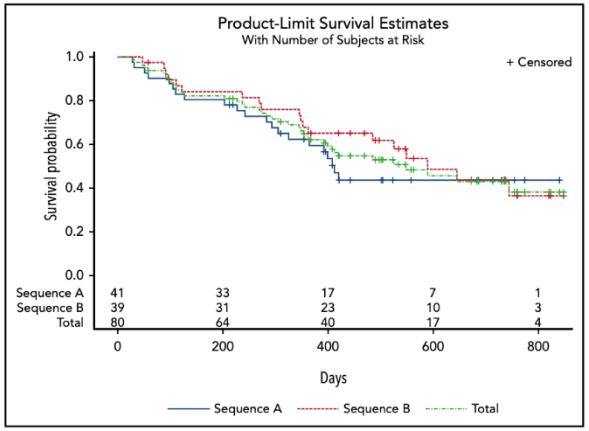
HMA

Oral cedazuridine/decitabine





Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13-32
PR	0	
mCR	18 (22)	14-33
mCR with HI	6 (7)	3-16
HI	13 (16)	9-26
HI-E	8 (10)	4-19
HI-N	2 (2)	0-9
HI-P	11 (14)	7-23
Overall response* (CR + PR + mCR + HI)	48 (60)	48-71
No response	32 (40)	29-52



- **Similar PK**
- **Similar ORR**
- **Median FUP: 24.3 months (range, 12.0-29.2 months)**
- **Median overall survival for all patients treated was 18.3 months (95% CI, 9.1-not estimable).**

FDA approved: previously untreated MDS patient with IPSS int-1, int-2 and HR

ASCERTAIN Ph III trial: pending results

HMA combos

Sabatolimab

PH. III: STIMULUS

Venetoclax

PH. III: VERONA

Tamibarotene

PH. III: SELECT-MDS

IDH inh

PH. III?

HMA combos

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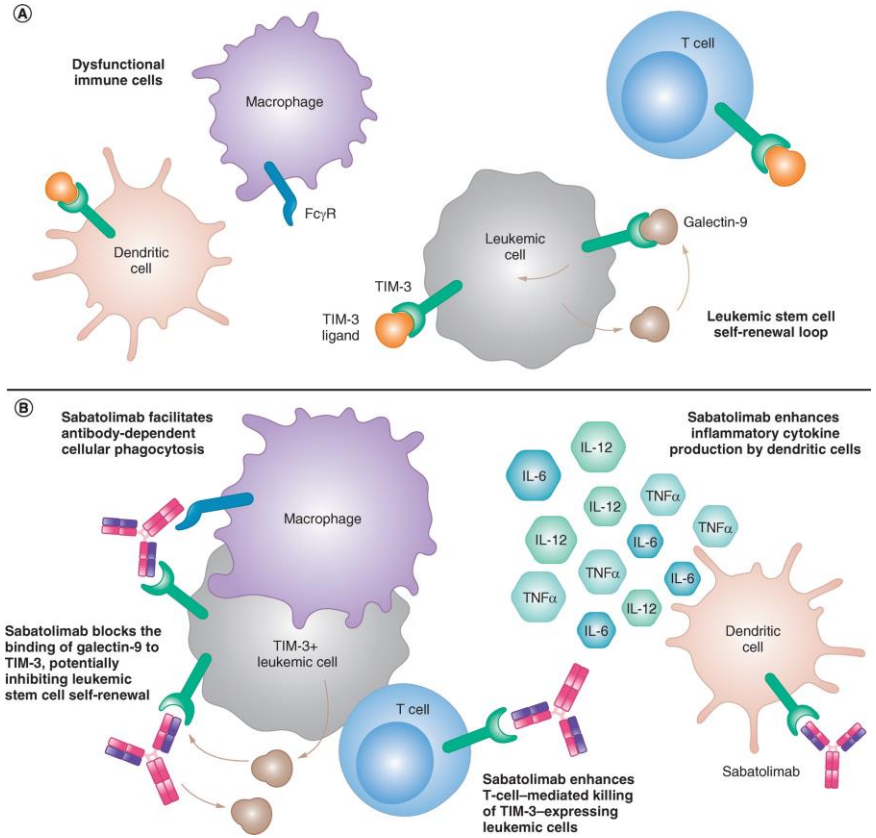
Sabatolimab



- TIM-3 plays a key role in regulating innate and adaptive immune responses[1,2]
- TIM-3 is aberrantly expressed on LSCs and blasts, but not on normal HSCs,[1-5] which makes it a promising target in treatment for MDS and AML[2,4,6]
- TIM-3/galectin-9 interaction forms an autocrine stimulatory loop, which promotes LSC self-renewal[2,7,8]

Zeidan A. Future Oncology 2023

Phase II: HMA +/- Sabatolimab in HR MDS

Patients

- Age ≥18 years
- Morphologically confirmed MDS
- IPSS-R risk: **Very high**, **high**, or **intermediate with ≥5% bone marrow blasts** at baseline
- Not suitable for intensive chemotherapy
- No planned HSCT
- ECOG PS 0-2

ClinicalTrials.gov identifier: **NCT03946670**

1:1 Randomization

Stratified by HMA[a] and IPSS-R[b]

Sabatolimab IV Q2W
(400 mg Day 8 and Day 22)
+
Decitabine IV (20 mg/m²/day, Day 1-5) **or**
Azacitidine SC or IV (75 mg/m²/day, Day 1-7 or Day 1-5+Day 8-9)

Placebo IV Q2W
(Day 8 and Day 22)
+
Decitabine IV (20 mg/m²/day, Day 1-5) **or**
Azacitidine SC or IV (75 mg/m²/day, Day 1-7 or Day 1-5+Day 8-9)

28-day cycles until disease progression

The study was unblinded following the final PFS analysis.
Follow-up will continue up to 4 years after the last patient was randomized.

Primary Endpoints:
Complete remission (CR)[c]
Progression-free survival (PFS)[d]

Secondary Endpoints:
Overall survival (OS)
Duration of CR
Response rates
Event-free survival
Leukemia-free survival
Transfusion independence
Safety
Pharmacokinetics
Immunogenicity

17 countries

47 study centers

Final PFS analysis data cutoff: March 1, 2022
Median duration of follow-up (randomization to cutoff): 24 months

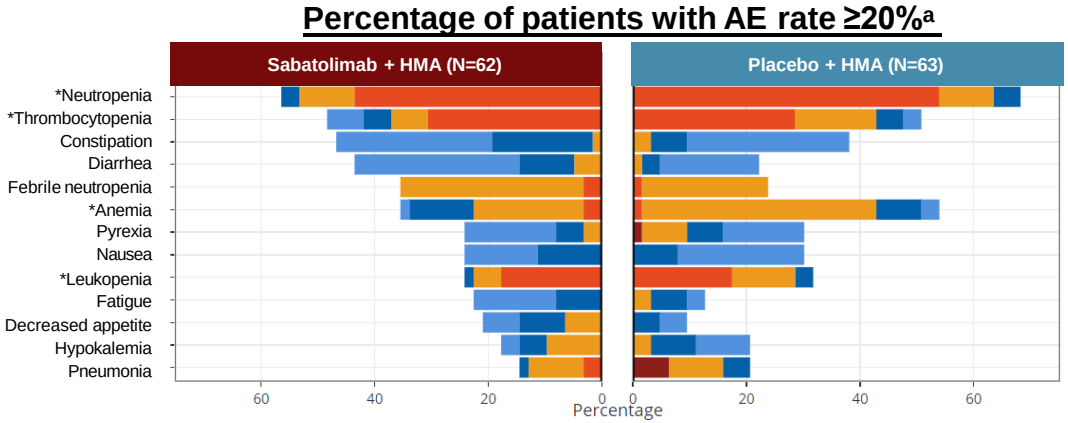
Phase II: HMA +/- Sabatolimab in HR MDS

	Sabatolimab + HMA n=65 (%)	Placebo + HMA n=62 (%)	All Patients N=127 (%)
Sabatolimab + decitabine	12.3	9.7	11.0
Sabatolimab + azacitidine	87.7	90.3	89.0
Median age (range), y	73.0 (48-86)	73.0 (32-89)	73.0 (32-89)
Male	63.1	72.6	67.7
ECOG performance status			
0	35.4	33.9	34.6
1	56.9	56.5	56.7
2	7.7	9.7	8.7
IPSS-R category			
Intermediate with ≥5% blasts	16.9	16.1	16.5
High	36.9	38.7	37.8
Very high	46.2	45.2	45.7
Cytogenetic category			
Very good/good	40.0	41.9	40.9
Intermediate	21.5	16.1	18.9
Poor/very poor	38.5	41.9	40.2
Bone marrow blast category			
<5%	10.8	9.7	10.2
5 to <10%	38.5	37.1	37.8
10 to <20%	50.8	53.2	52.0

Zeidan A. ASH 2022

Phase II: HMA +/- Sabatolimab in HR MDS

Sabatolimab + HMA is associated with a favorable safety profile in patients with higher-risk MDS



- The grade ≥3 AEs with ≥20% in either arm (sabatolimab + HMA vs placebo + HMA) were
  - Neutropenia (53.2% vs 63.5%)
  - Thrombocytopenia (37.1% vs 42.9%)
  - Febrile neutropenia (35.5% vs 23.8%)
  - Anemia (22.6% vs 42.9%)
  - Leukopenia (22.6% vs 28.6%)

  No potential immune-toxicity signal was identified in either arm (sabatolimab + HMA vs placebo + HMA)
  - imAEs all grades (9.7% vs 17.5%)
  - imAEs grade ≥3 (4.8% vs 7.9%)

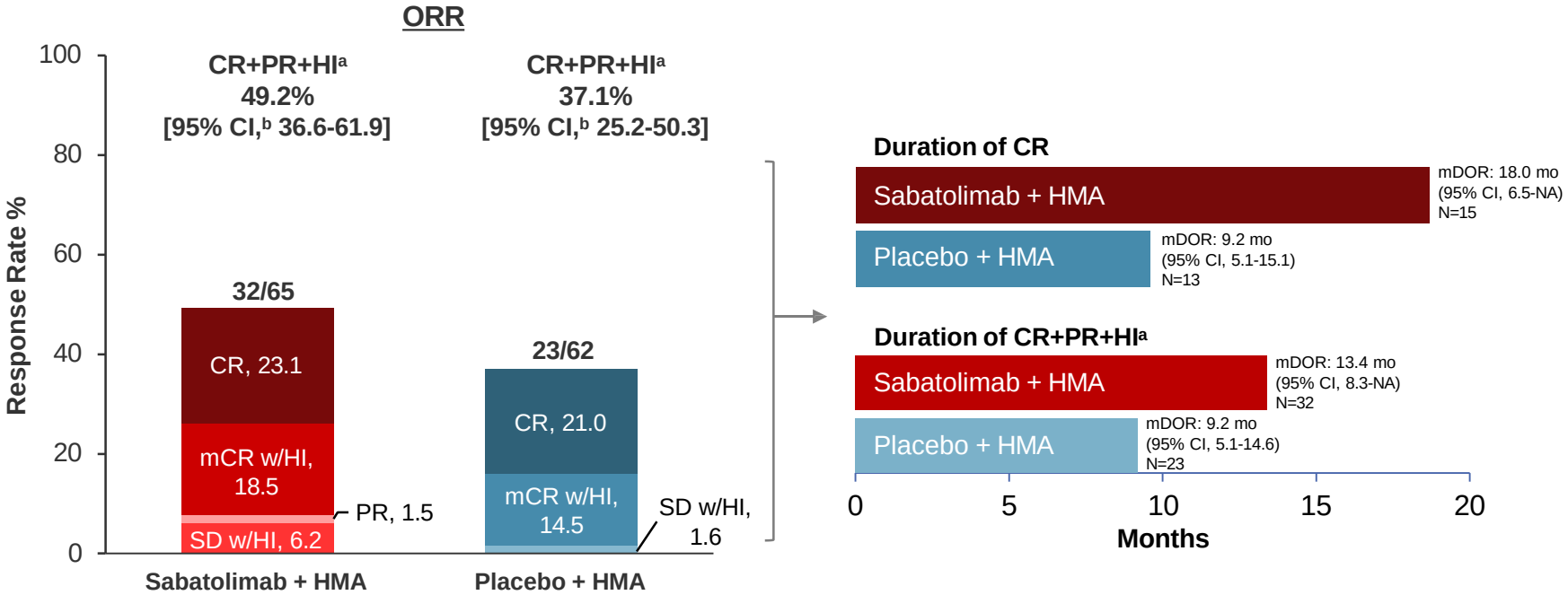
- Overall, sabatolimab + HMA was safe and well tolerated as compared to placebo + HMA
- Safety findings in this study are consistent with previous reports[1]

AE, adverse event assessed by CTCAE version 5; CTCAE, Common Terminology Criteria for Adverse Events; imAE, immune-mediated adverse event.
*Grouped preferred term.
[a]Safety analysis set, defined as patients who received ≥1 dose of any component of study treatment. Patients who were randomized but did not receive treatment (1 in each arm) were excluded. Patients who were treated with HMA only (2 in sabatolimab + HMA arm and 1 in placebo + HMA arm) were included in the placebo + HMA arm for the safety analyses.

Reference: 1. Brunner AM, et al. ASH 2021. Abstract 244. Oral presentation.

Phase II: HMA +/- Sabatolimab in HR MDS

Sabatolimab + HMA demonstrated a potential benefit in duration of response



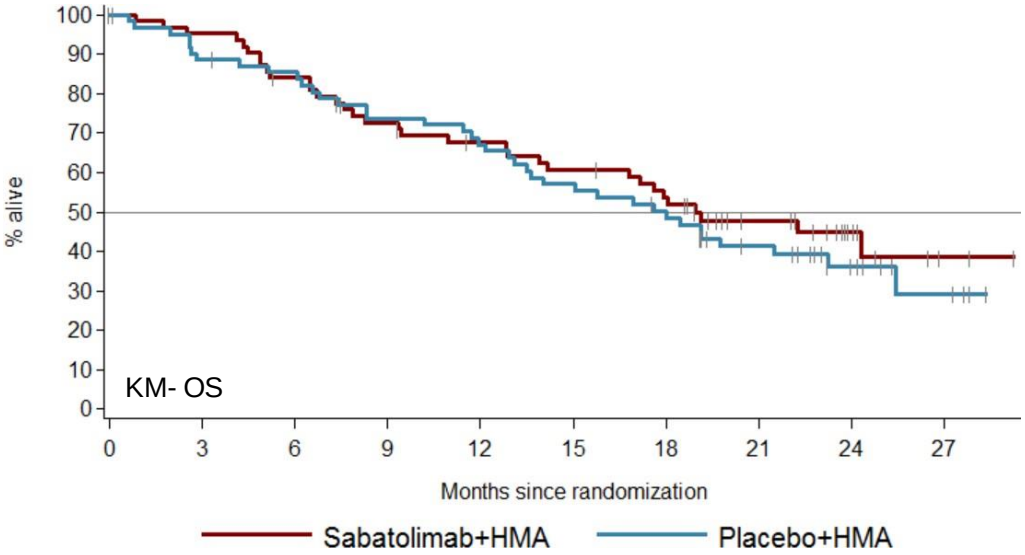
- Updated CR rate assessed at primary analysis (data cutoff March 1, 2022).

HI, hematologic improvement; HR, hazard ratio; mCR, marrow CR; mDOR, median duration of response; NA, not available; ORR, overall response rate; PR, partial remission; SD, stable disease.
[a]HI includes marrow CR with HI and SD with HI, and HI must be concurrent with best overall response. [b]The 95% CIs were computed using exact Clopper-Pearson 1934.

Zeidan A. ASH 2022

Phase II: HMA +/- Sabatolimab in HR MDS

OS and leukemia-free survival in patients receiving sabatolimab + HMA compared with placebo + HMA



	Sabatolimab + HMA n=65	Placebo + HMA n=62
OS,[a] median (95% CI) , mo	19.0 (13.9-NE)	18.0 (13.1-23.2)
Hazard ratio (95% CI)[b]	0.905 (0.565-1.450)	
LFS, median (95% CI), mo	16.8 (8.8-NE)	13.6 (9.8-19.8)
Hazard ratio (95% CI)[b]	0.951 (0.578-1.567)	

STIMULUS-MDS Ph III trial: pending results

LFS, leukemia-free survival; NE, not estimable; OS, overall survival.
[a]The median follow-up time for OS (time from the date of randomization to the date of OS event or the date of censoring for OS [i.e., the last contact date]) was 17.15 months
[b]Calculated via Cox model stratified by IPSS-R.

HMA combos

Sabatolimab

PH. III: STIMULUS

Venetoclax

PH. III: VERONA

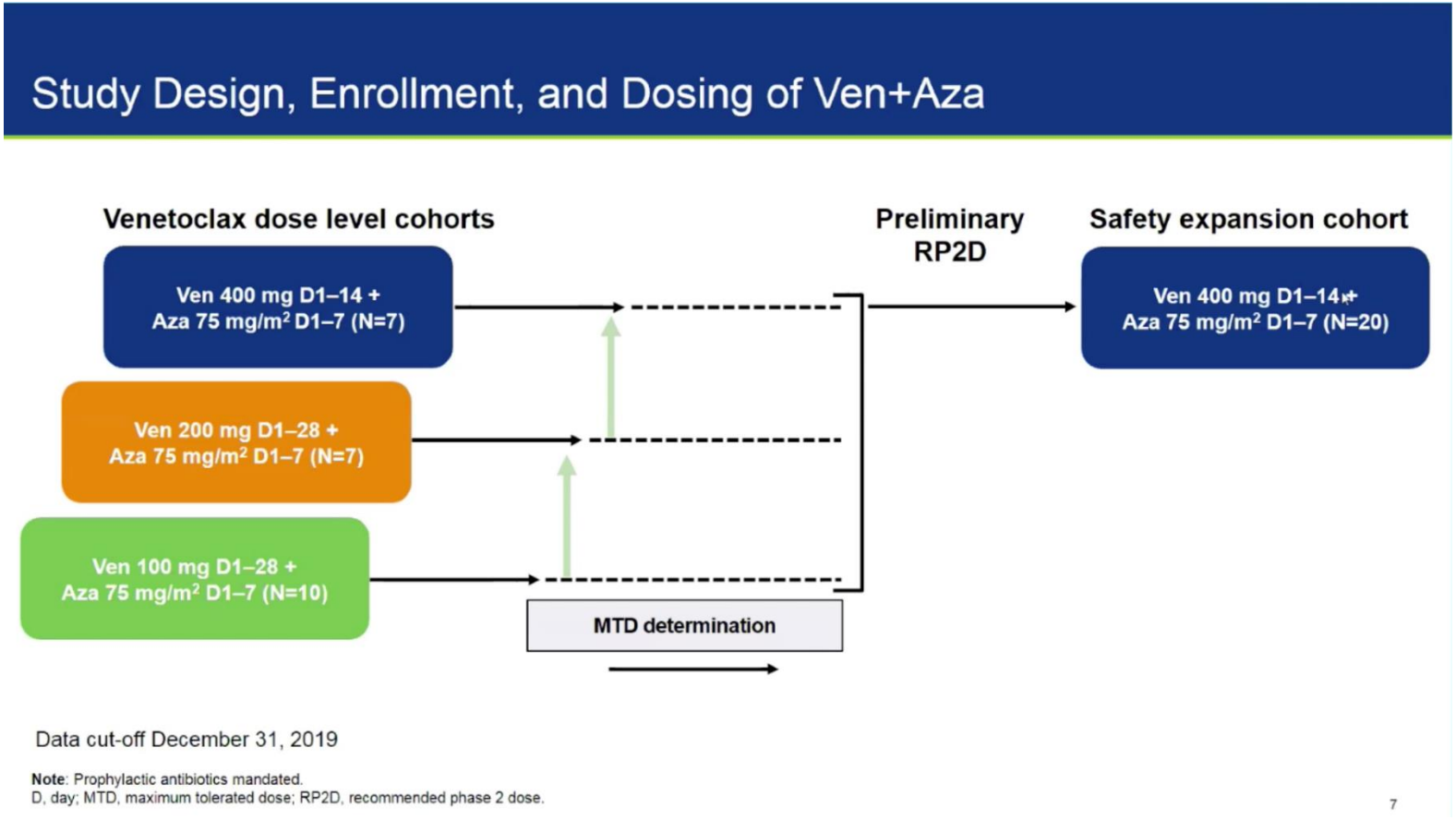
Tamibarotene

PH. III: SELECT-MDS

IDH inh

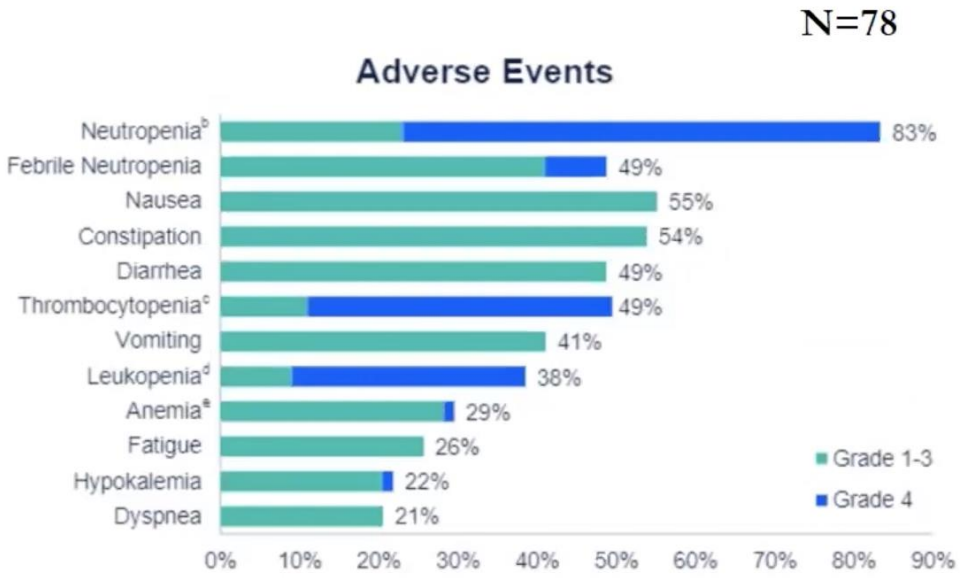
PH. III?

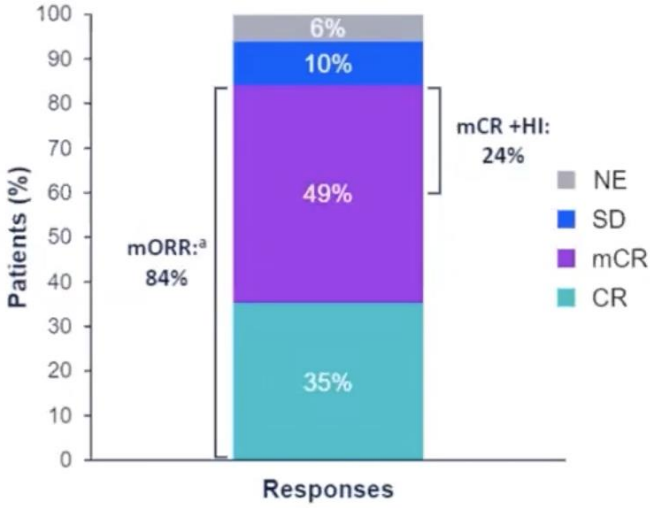
Phase Ib: HMA + VEN



Zeidan A. EHA 2020;.

Phase Ib: HMA + VEN (1st line)

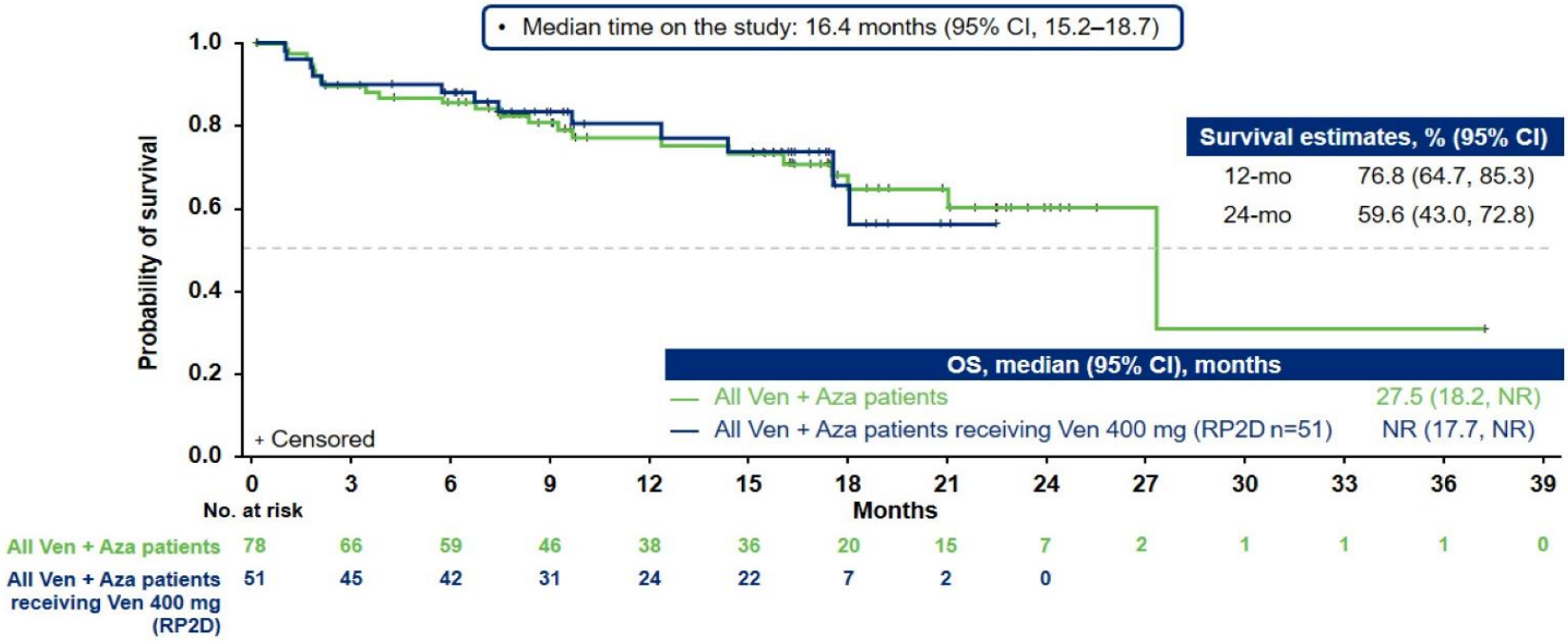




- Median time to response: 0.9 months (95% CI, 0.7–5.8)
- Median duration of response: 12.4 months (95% CI, 9.9–NR)

García . ASH 2021

Phase Ib: HMA + VEN



Aza, azacitidine; CI, confidence interval; NR, not reached; OS, overall survival; RP2D, recommended phase 2 dose; Ven, venetoclax

Data cutoff: June 30, 2020

VERONA Ph III trial: pending results

García . ASH 2021

HMA combos

Sabatolimab

PH. III: STIMULUS

Venetoclax

PH. III: VERONA

Tamibarotene

PH. III: SELECT-MDS

IDH inh

PH. III?

Ph II. HMA + Tamibarotene

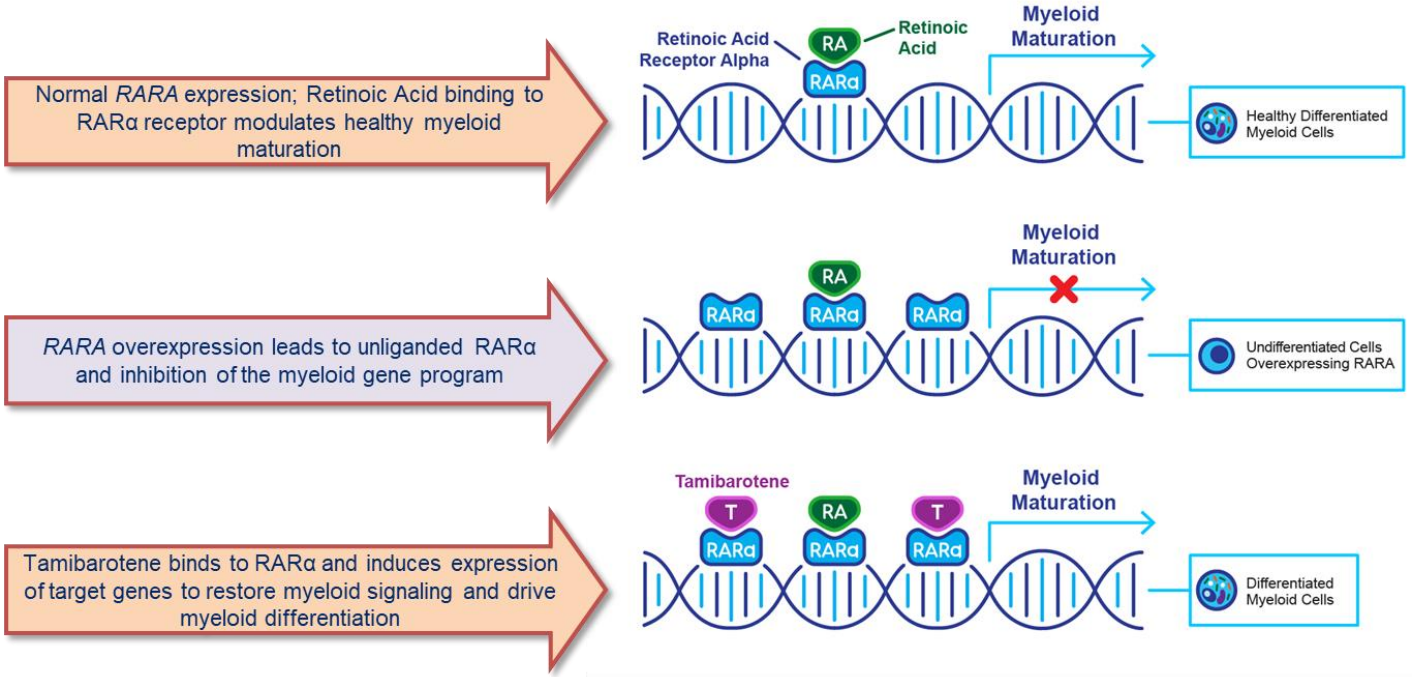
Approximately 50% of higher-risk MDS patients and ~30% of AML patients are positive for *RARA* overexpression[1]

- ***RARA* encodes retinoid acid receptor alpha (RARα)**
- **RARα** is a ligand-regulated nuclear receptor that acts as a **transcriptional switch for myeloid differentiation.** RARα also has well documented **roles in stem cell self-renewal and blast proliferation in AML[2-4]**
  - When RARα is **not bound** by ligand it shuts off transcription and acts as a **negative regulator of promyelocyte differentiation**
  - When RARα is **bound** by its ligand it **stimulates transcription and drives differentiation[2-4]**
- ***RARA* overexpression** inhibits downstream transcription of the myeloid differentiation gene program[5]
- ***RARA* overexpression** (but not *RARB* or *RARG*) induces **myeloid progenitor immortalization[5]**

1. RARA overexpression rates based on Syros data on file from Study SY-1425-201 and the SELECT-MDS-1 Study (27May2022) from over 175 patients with MDS: 2. McKeown, Cancer Discovery 2017; 3. Kastner, Oncogene 2001; 4. Geoffery, Blood 2021 5. Du, Blood 1999

Ph II. HMA + Tamibarotene

In cells that overexpress *RARA*, tamibarotene induces transcription of RARα target genes and restores m**yeloid differentiation**



McKeown, Cancer Discovery 2017

Ph II. HMA + Tamibarotene

Key entry criteria: Treatment naïve non-APL AML unfit for intensive induction chemotherapy

Screen for *RARA* overexpression via peripheral blood-based assay

51 patients enrolled in total

RARA-positive N=22

RARA-negative N=29

Regimen: Azacitidine 75 mg/m2 IV or SC D1-7 followed by tamibarotene 6 mg/m2/day PO D8-28 of a 28-day cycle

Primary objective: ORR per IWG

Other analyses:

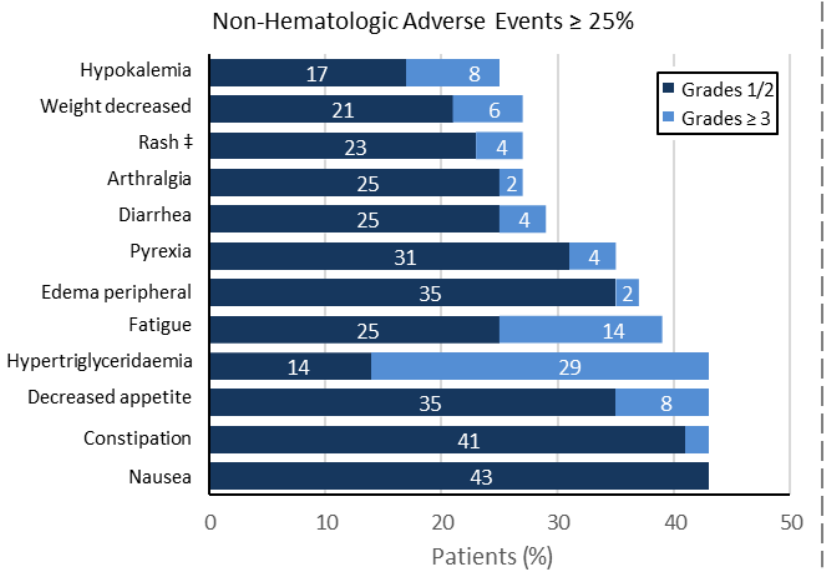
- Composite CR rate
- Time to response
- Duration of response
- Transfusion independence
- OS
- Safety and tolerability
- Exploration of molecular and cytogenetic characteristics associated with response

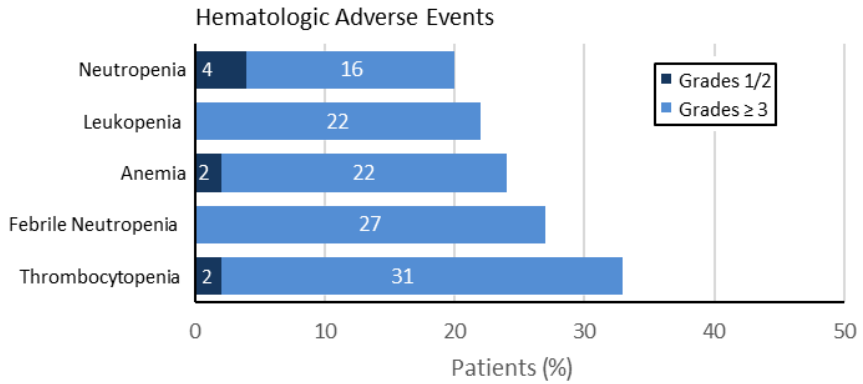
De Botton, Blood Adv 2022 (SY-1425-201 Study, NCT02807558

Ph II. HMA + Tamibarotene

Tamibarotene and azacitidine combination generally well-tolerated

- No increase in neutropenia, anemia and thrombocytopenia compared to single-agent aza[1-3]
- Majority of non-hematologic AEs are low grade and reversible





[a]Includes all enrolled ND unfit patients, N=51. ‡ Rash included preferred terms of rash maculo-papular, rash, drug eruption, nodular rash, rash erythematous, and rash pruritic. Rash maculopapular and rash were each reported in 5 (10%) of patients, with other terms reported in 1 patient each (2%).

De Botton, Blood Adv 2022 (SY-1425-201 Study, NCT02807558)

Ph II. HMA + Tamibarotene

Patients with RARA overexpression have a high complete remission rate with a rapid time to response

Best IWG response[1]	*RARA* overexpression status	
	RARA-positive n (%)	*RARA*-negative n (%)
Response Evaluable, N[a]	18	28
ORR	12 (67)	12 (43)
CR/CRi	11 (61)	9 (32)
• CR	9 (50)	7 (25)
– CRm	5 (28)	3 (11)
– CRc	3 (17)	1 (4)
– CRi	2 (11)	2 (7)
MLFS	1 (6)	1 (4)
PR	0 (0)	2 (7)

RARA overexpression status: _RARA_-positive

- High CR/CRi response rate
- Deep CR with 89% (8/9) CRm or CRc
- Rapid time of onset of initial complete response[b] with median 1.2 months
- CR rate of 67% (4/6) in response evaluable low-blast count AML patients
- Median duration of complete response[b] 10.8 months (95% CI: 2.9, 15.2)

RARA overexpression status: _RARA_-negative

- Response rates comparable to historical response rates for single agent azacitidine[2-4]
- Median time to initial complete remission[b] delayed relative to patients with *RARA* overexpression at 3.0 months

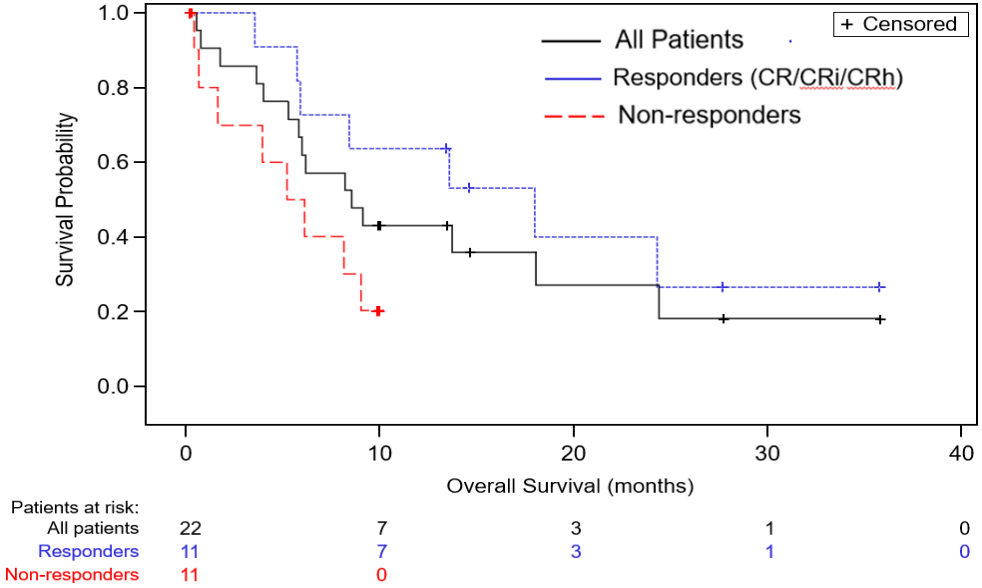
[b]Complete remission includes CR, CRi, CRh

[1] Cheson, JCO 2003; [2] Fenaux, JCO 2010; [3] Dombret, Blood 2015; [4] VIDAZA® Prescribing Information; De Botton, Blood Adv 2022 (SY-1425-201 Study, NCT02807558)

Ph II. HMA + Tamibarotene

Overall survival in patients with RARA overexpression summarized by response status

Overall survival in *RARA*-positive patients summarized by response status



Patients with *RARA* overexpression with CR/CRi/CRh (N=11)

- mOS = 18.0 months (95% CI: 5.7, NE)

Patients with *RARA* overexpression without CR/CRi (N=11)

- mOS = 5.6 months (95% CI: 0.4, 9.0)

The overall survival graph includes all *RARA*-positive patients who enrolled in the study. Responders (CR/CRi/CRh) - patients who achieved complete remission (CR), complete remission with incomplete blood count recovery (CRi) or complete remission with partial hematological recovery (CRh). Non-responders – patients who did not achieve CR/CRi or CRh.

SELECT-MDS Ph III trial: currently enrolling

The overall survival graph includes all RARA-positive patients who enrolled in the study.

Responders (CR/CRi/CRh) - patients who achieved complete remission (CR), complete remission with incomplete blood count recovery (CRi) or complete remission with partial hematological recovery (CRh).

Non-responders – patients who did not achieve CR/CRi or CRh.

De Botton, Blood Adv. 2022

HMA combos

Sabatolimab

PH. III: STIMULUS

Venetoclax

PH. III: VERONA

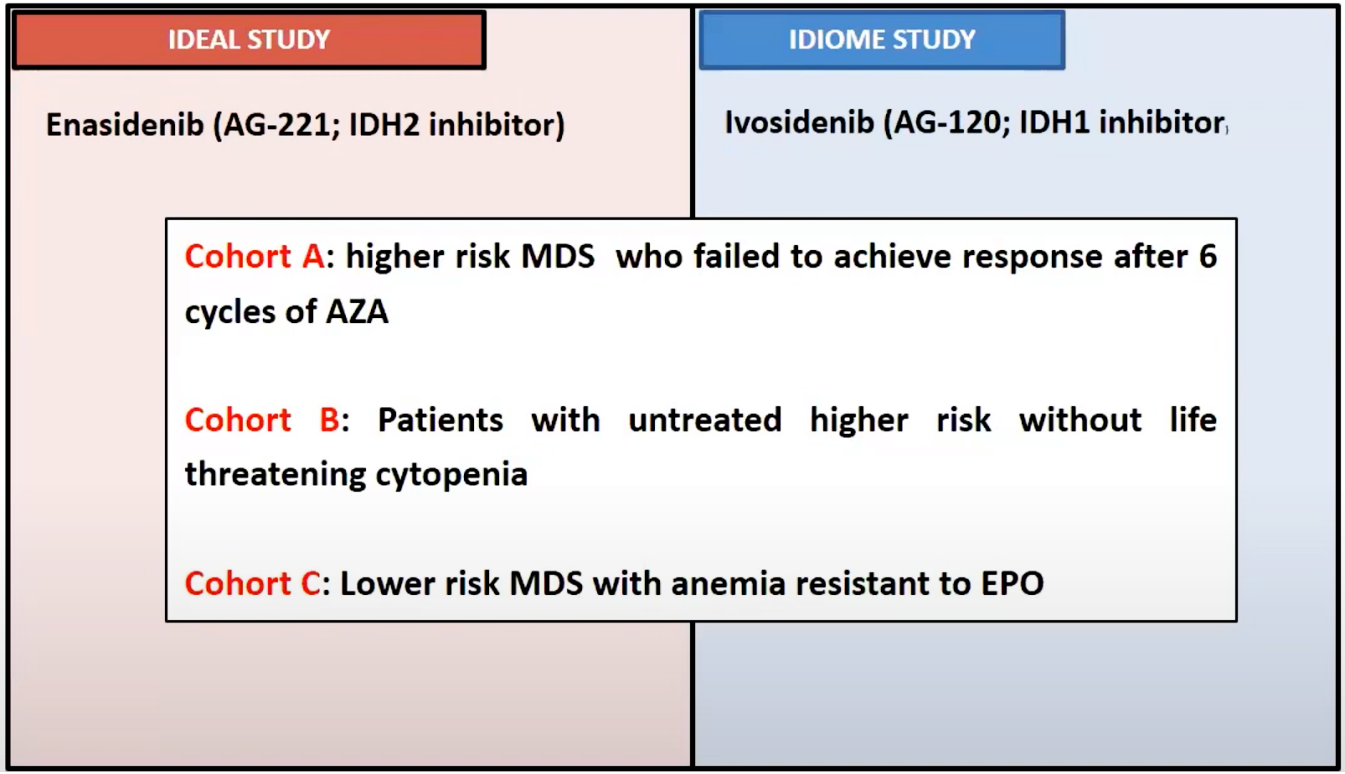
Tamibarotene

PH. III: SELECT-MDS

IDH inh

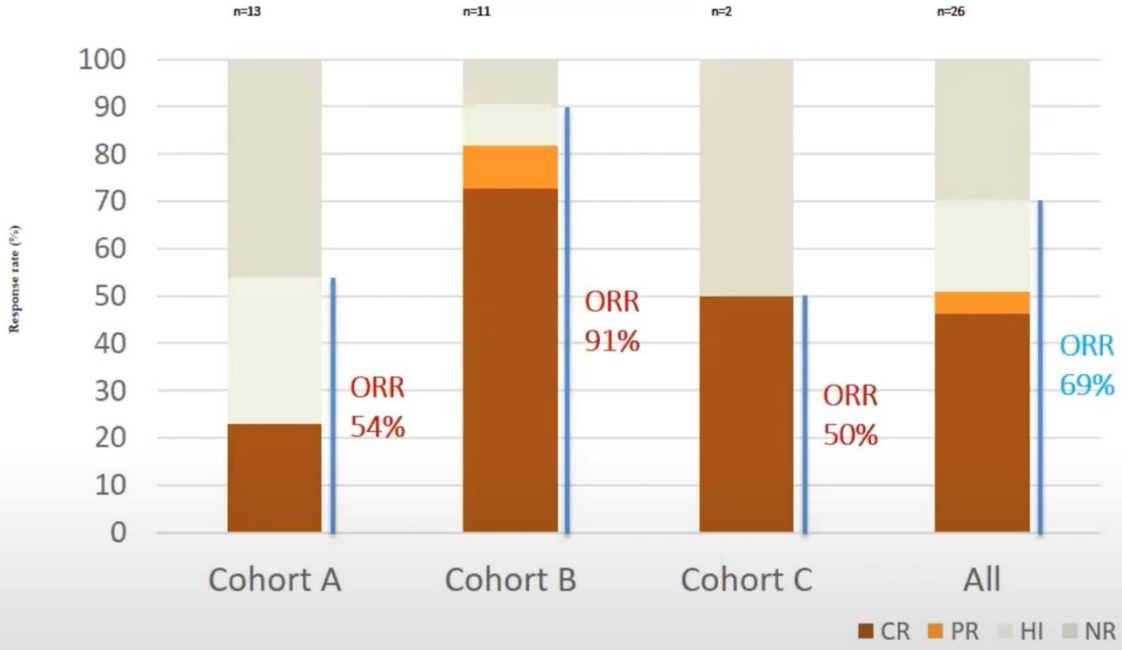
PH. III?

IDH1 & IDH2 inhibitors in MDS (L Adès, M Sébert, ASH 2021)



IDH1 & IDH2 inhibitors in MDS (L Adès, M Sébert, ASH 2021)

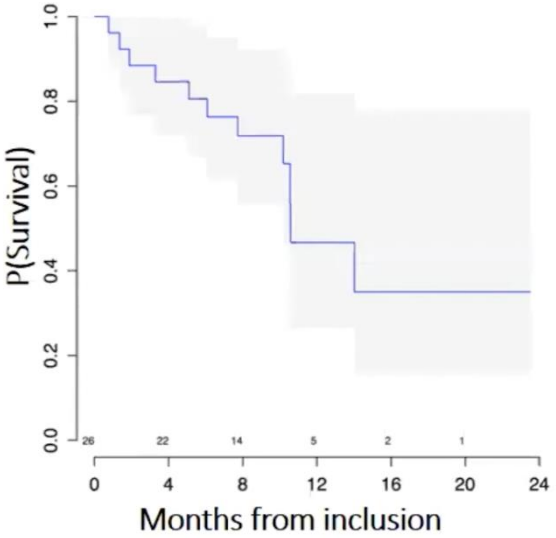
Overall response rate (Ivosidenib)

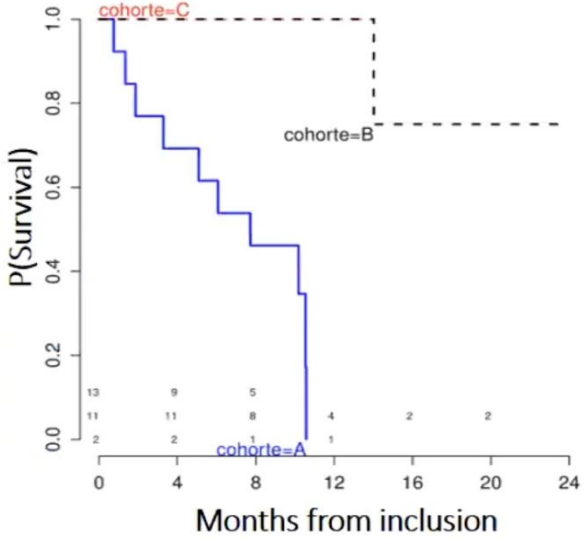


- 46% of CR (including 73% in cohort B)
- 94,4% of the responders achieved response at 3 cycles
- Only one patient received azacitidine in association with Ivo after three cycles of Ivo in cohort B, without additional response

IDH1 & IDH2 inhibitors in MDS (L Adès, M Sébert, ASH 2021)

- Median overall survival was 14 months in the whole cohort
- Median OS was
  - 7.7 months in cohort A
  - Not reached in cohort B
- 11 patients had died, 10 in cohort A, and 1 in cohort B, mostly from relapse/progression





Intensive Chemotherapy

Intensive Chemotherapy

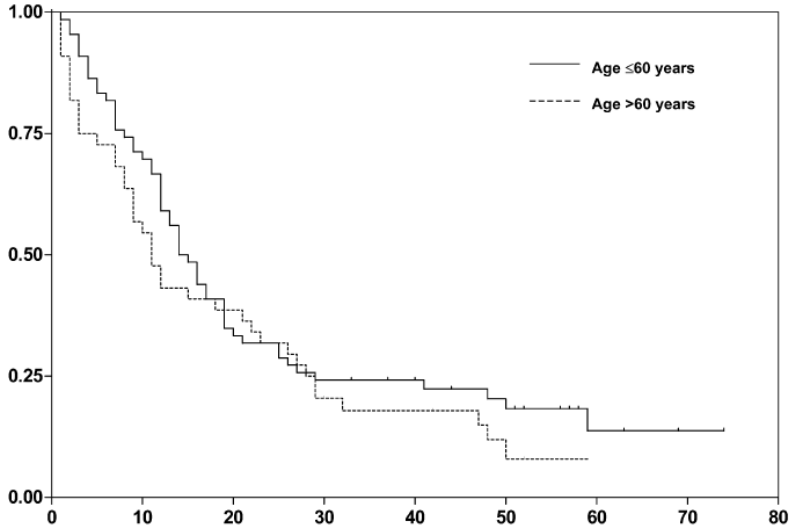
Intensive chemotherapy with idarubicin, cytarabine, etoposide, and G-CSF priming in patients with advanced myelodysplastic syndrome and high-risk acute myeloid leukemia

Table 2 Treatment results according to age groups

Age	No. of patients	CR (%)	Failure (%)	ED (%)
<30	2	2 (100)	–	–
30–39	8	6 (75)	2 (25)	–
40–49	16	11 (69)	4 (25)	1 (6)
50–59	36	23 (64)	11 (30)	2 (6)
60–69	42	24 (57)	11 (26)	7 (17)
>69	8	4 (50)	1 (12)	3 (38)
Total	112	70 (62)	29 (26)	13 (12)

Table 1 Overall treatment results

CR	70 (62%)
Failure	29 (26%)
Early death	13 (12%)
Overall survival at 5 years	
≤60 years	14%
>60 years	8%
Relapse-free survival at 5 years	
≤60 years	20%
>60 years	13%



Median OS

Hofmann WK, Ann Hematol. 2004

Intensive Chemotherapy - Vyxeos

COHORT A

First-line treatment

Inclusion Criteria

- Untreated intermediate-2 or higher risk of chronic myelodysplastic syndrome or myelomonocytic leukemia (including proliferative forms with WBC ≥13×10^9 cells per L).
- 18 to 70 years, no contraindications for intensive chemotherapy, less than 20% blasts in the marrow and ECOG of 0 to 1.

COHORT B

After HMA failure

Exclusion Criteria

- Active, uncontrolled infection, HIV, clinically active HIV-related infection or cancer, hepatitis B or C infection, allergy or hypersensitivity to any component of CPX-351, currently active secondary. malignancy (other than non-melanoma skin cancer and carcinoma in situ of the cervix).
- History of Wilson's disease or other copper-related disorder, treatment with growth factors within 30 days prior to inclusion, treatment with systemic steroids that had not been stabilized to the equivalent of 10 mg/day or less of prednisone for 4 weeks prior to initiation of study drugs, clinical.
- Evidence of CNS leukemia and pregnancy or breastfeeding for the duration of the study.

Intravenous CPX-351 (100 mg/m² cytarabine and 44 mg/m² daunorubicin) was administered on days 1, 3 and 5, with a second induction cycle administered (same daily dose on days 1 and 3) if at least a partial response was not achieved. Responding patients could receive up to four monthly consolidation cycles (same daily dose on day 1) or allogeneic hematopoietic stem cell transplantation (HSCT).

	Patients (N=31)
Age (years)	62 (56 to 66)
Gender	
Male	21 (68%)
Female	10 (32%)
At baseline	
Myelodysplastic syndrome subtype	
EB-2	26 (84%)
CMML-2	5 (16%)
Bone marrow blasts	13% (11 to 15)
Peripheral blasts	1% (0-00 to 2-25)
IPSS	
Intermediate 2	26 (84%)
High	5 (16%)
ECOG	
0	22 (71%)
1	9 (29%)
Comorbidities by patient*	2-0 (1-0 to 3-7)
Time between diagnosis and induction (days)	55 (28 to 154)
Previous treatment	
ESA	3 (10%)
Lenalidomide	1 (3%)
None	27 (87%)
Transfusion dependency in the 8 weeks before enrolment	12 (39%)
After induction treatment	
Recovery of CD13/CD16 neutrophil maturation pattern	15/19 (79%)
FCM progenitors decrease	−65·2 (−95·6 to −27·9)
nmVAF decrease†	−97·8 (−91·6 to −99·0)
VAF <2%‡	18/29 (62%)
VAF <0·1%§	8/29 (28%)

Paterlin P. Lancet Haematol. 2023 Jul;10(7):e521-e529.

Intensive Chemotherapy - Vyxeos

	Grade 1		Grade 2		Grade 3		Grade 4	
	Drug-related	Not drug-related	Drug-related	Not drug-related	Drug-related	Not drug-related	Drug-related	Not drug-related
Induction (any event)	0	0	0	0	14	40	0	4
Cardiovascular	0	0	0	0	1	2	0	2
Pulmonary	0	0	0	0	1	7	0	2
Hepatic	0	0	0	0	1	0	0	0
Gastrointestinal	0	0	0	0	1	1	0	0
Genito-urinary	0	0	0	0	1	2	0	0
Endocrine-metabolic	0	0	0	0	0	4	0	0
Neurological	0	0	0	0	0	2	0	0
Cutaneous	0	0	0	0	2	1	0	0
Other	0	0	0	0	7*	21	0	0
Consolidation (any event)	1	0	2	4	2	24	0	2
Cardiovascular	0	0	0	0	0	1	0	0
Gastrointestinal	1	0	0	4	1	1	0	0
Musculoskeletal	0	0	0	0	0	2	0	0
Cutaneous	0	0	2	0	0	0	0	0
Other	0	0	0	0	1	20	0	2

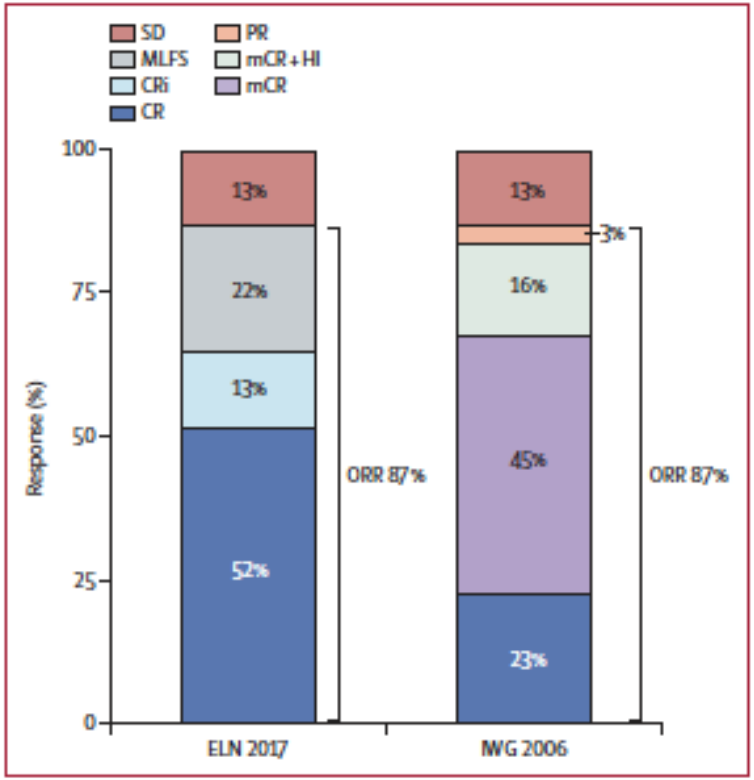
All grade 1–4 events are shown. *One case of sepsis (*Pseudomonas aeruginosa*), three of febrile aplasia, one of aplasia, one of epistaxis, and one alanine aminotransferase increase.

Table 2: Number of non-haematological adverse events according to treatment cycle and grade

- The most common grade 3-4 adverse events were **pulmonary** (eight [26%] of 31 patients) and **cardiovascular** (six [19%] of 31 patients).
- **14 serious adverse** events (mainly hospitalization for **infection** [n=5] and only one was treatment-related).
- There were **no treatment-related deaths.**

Paterlin P. Lancet Haematol. 2023 Jul;10(7):e521-e529.

Intensive Chemotherapy - Vyxeos



- Overall response rate was observed in 87% (95% CI 70-96) of 31 patients.
- 16 (52%) of 31 patients had CR, 4 (13%) had CRi, 7 (22%) had MLFS and 4 (13%) remained in stable disease.
- 30 of 31 (97%) patients included were initially considered eligible for allogeneic HSCT and **29 (94%) underwent the procedure.**

Paterlin P. Lancet Haematol. 2023 Jul;10(7):e521-e529.

Intensive Chemotherapy - Vyxeos

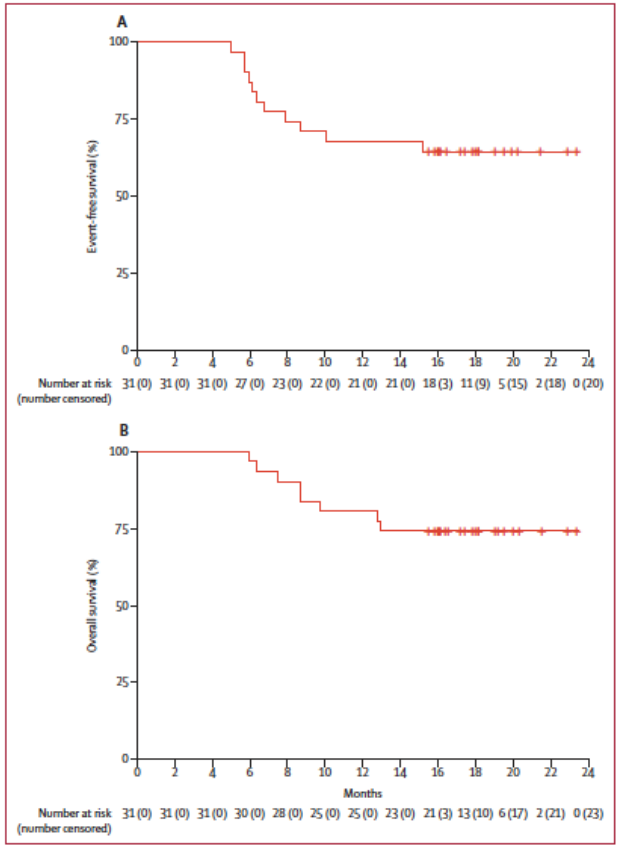


Figure 3: Survival outcomes
(A) Event-free survival and (B) overall survival.

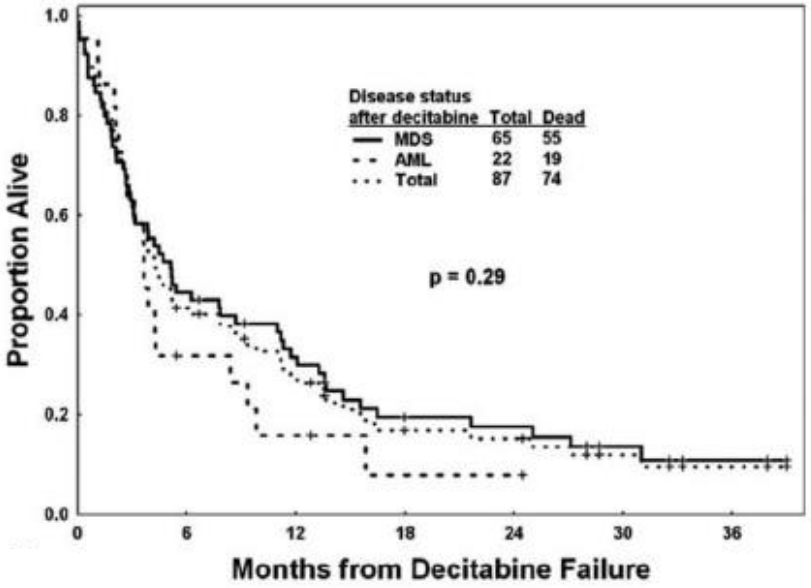
- Median follow-up was 16.1 months (IQR 8.3-18.1).
- Median EFS was not reached, with an estimated 12-month EFS of 67.7 % (95 % CI 53.1-86.4).
- Median OS was also not reached, estimated 12-month OS of 80.6 % (95 % CI 67.9-95.8).

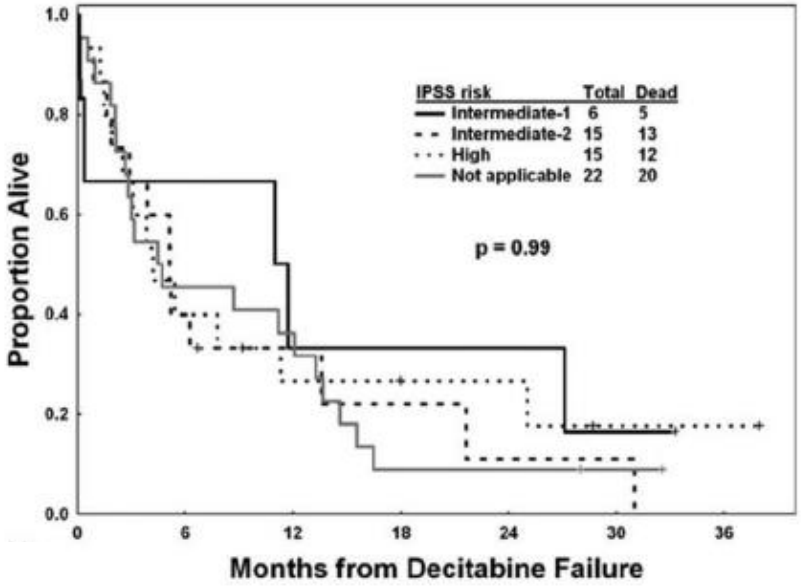
Paterlin P. Lancet Haematol. 2023 Jul;10(7):e521-e529.

HMA failure

HMA failure

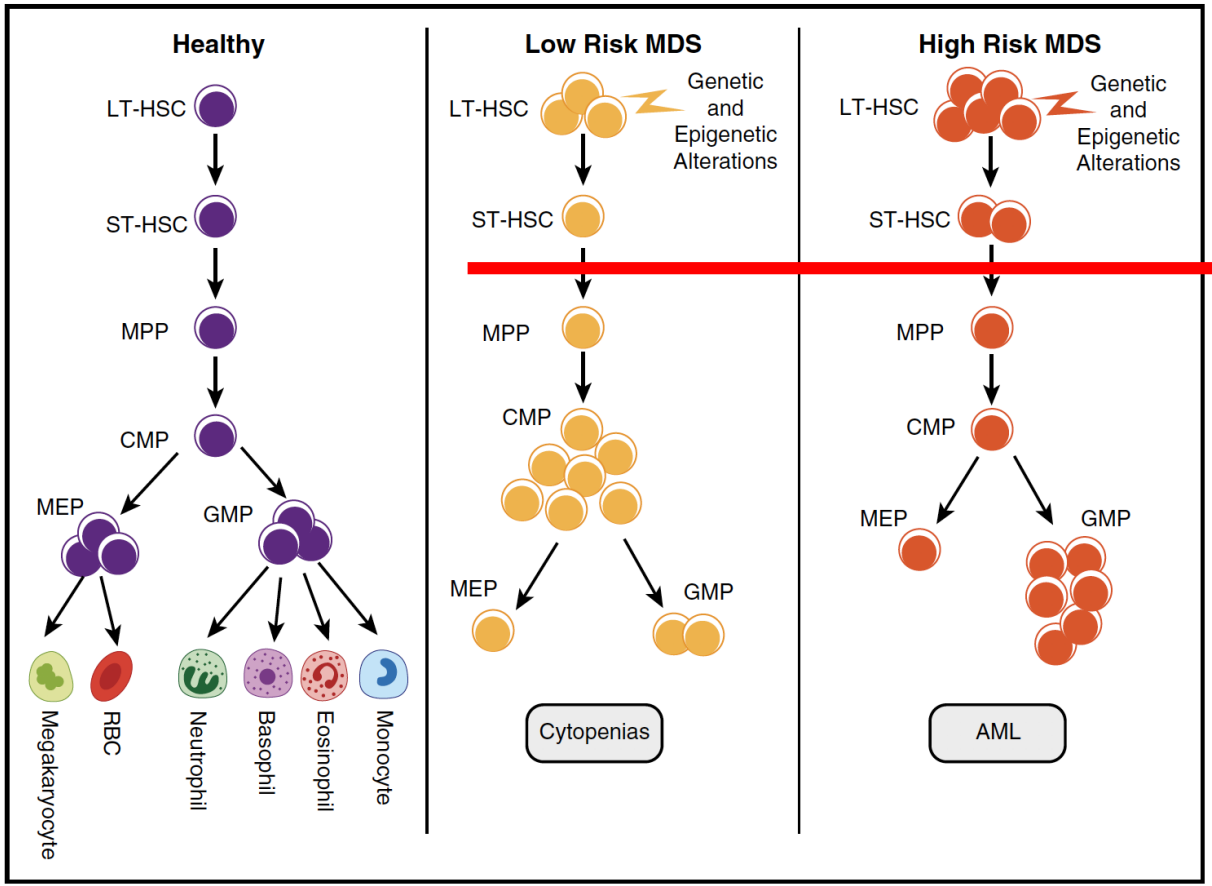
- Failure to hypomethylating agents (HMA) associated to disease progression and dismal prognosis
- Poorly understood, unpredictable, unpreventable
- Independent of genetic alterations





Jabbour, E. J. et al. Cancer 121, 876–882 (2015)

HMA failure



Allogeneic Stem- Cell Transplant

Lenalidomide

Hypomethylating Agents

Shastri A et al. Blood. 2017 Mar 23;129(12):1586-1594.

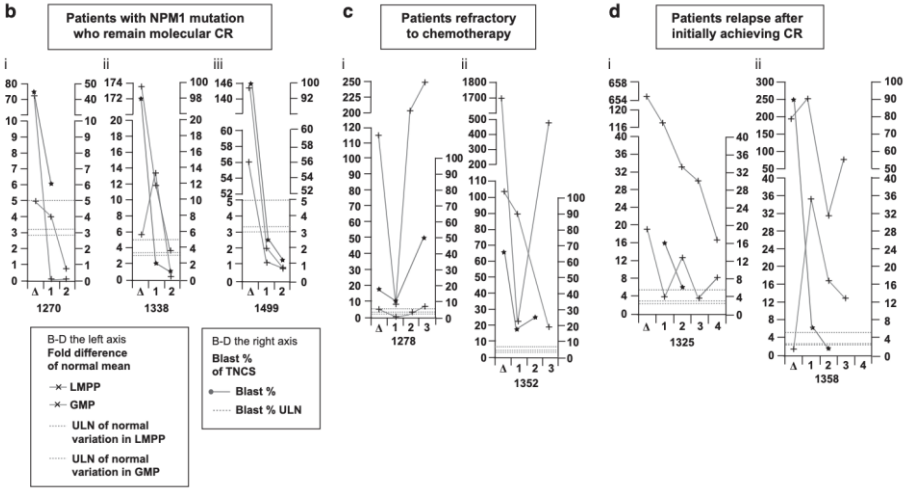
HMA failure

Role of HSPCs in disease relapse

ORIGINAL ARTICLE

Azacitidine fails to eradicate leukemic stem/progenitor cell populations in patients with acute myeloid leukemia and myelodysplasia

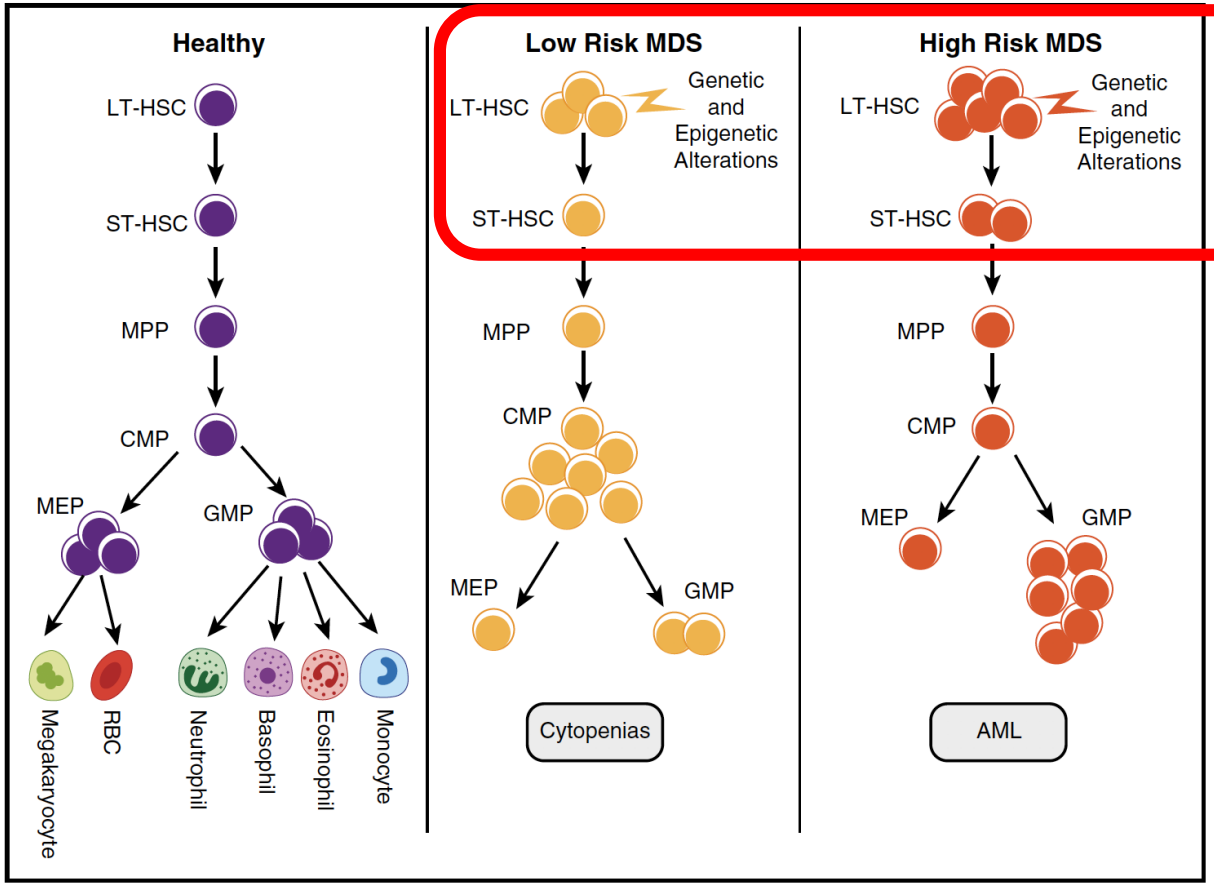
C Craddock[1,2], L Quek[3,4,14], N Goardon[3,14], S Freeman[1,5], S Siddique[1,2], M Raghavan[1,2], A Aztberger[3], A Schuh[4], D Grimwade[6,7], A Ivey[6,7], P Virgo[8], R Hills[9], T McSkeane[1,2], J Arrazi[1], S Knapper[9], C Brookes[2], B Davies[10], A Price[10], K Wall[11], M Griffiths[11], J Cavenagh[12], R Majeti[13], I Weissman[13], A Burnett[9] and P Vyas[3,4]



Persistence of leukemic stem/progenitor cells in patients treated with epigenetic therapies responsible of clinical relapse in AML/MDS patients treated with Azacitidine + Sodium Valproate

Craddock C et al. Leukemia. 2013;27(5):1028-1036.

HMA failure



- **Understand altered pathways in HSC**
- **Design treatments aimed at reversing these HSC alterations → Improve the outcomes of MDS patients**

Shastri A et al. Blood. 2017 Mar 23;129(12):1586-1594.

New approaches for treatment of MDS

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