Myelodysplastic Neoplasms and the Challenge of Therapeutic Targets: Genetics, Epigenetics, or Inflammation?

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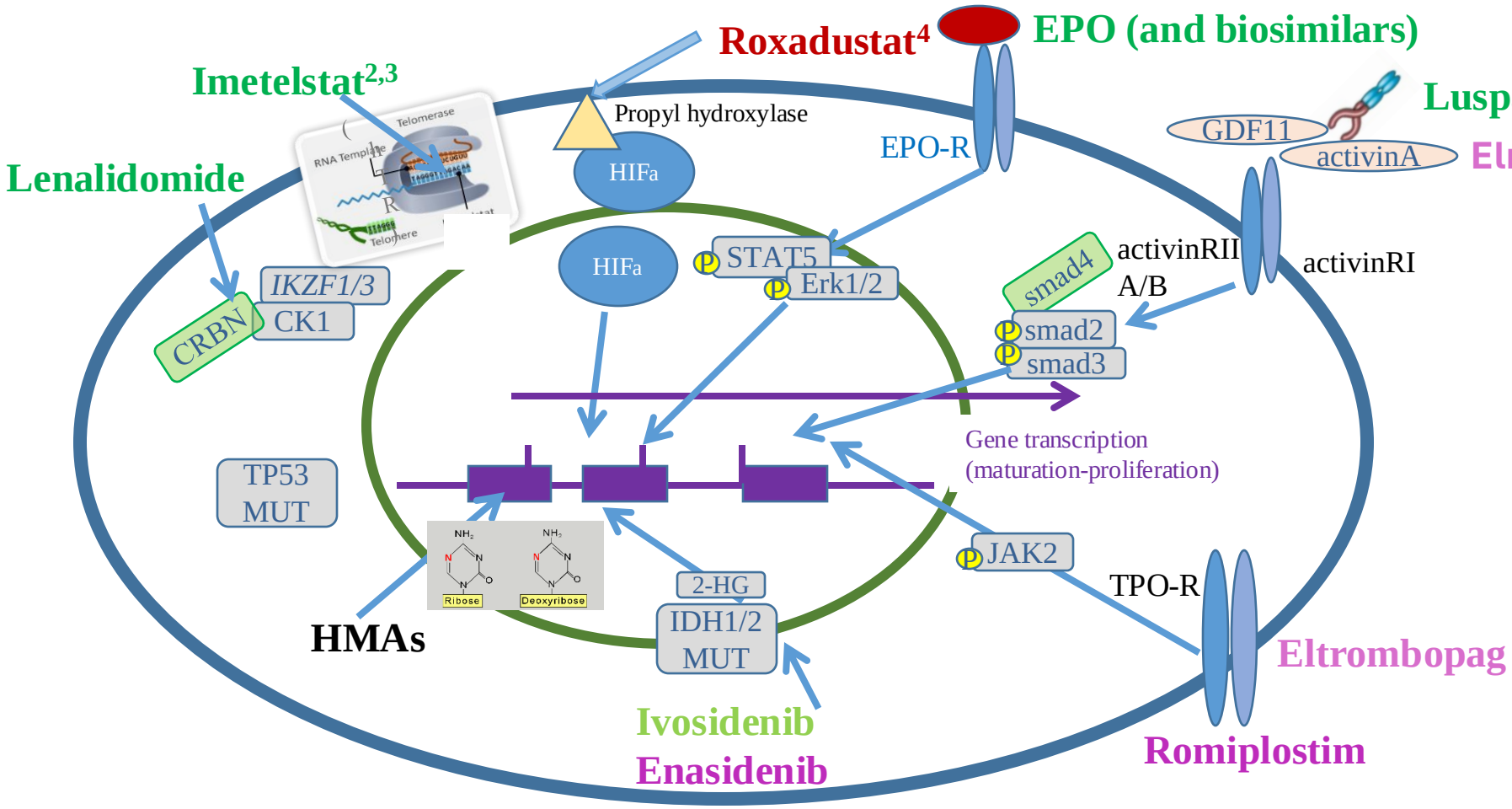
A constellation of agents with different MoA for MDS treatment:[1]

Some success and many failures and mainly only empiric approaches



Additional targets:

- **TP53 mut (APR246)[5]**
- **BCL2 (Venetoclax)[6]**
- **NEDD8NAE (Pevonedistat)[7]**
- **Tim-3 (Sabatolimab)[8]**
- **CD47 (Magrolimab)[9]**
- **Irak-4 (R289)[10]**

Approved drugs
Failed studies
Successful studies
Under investigation

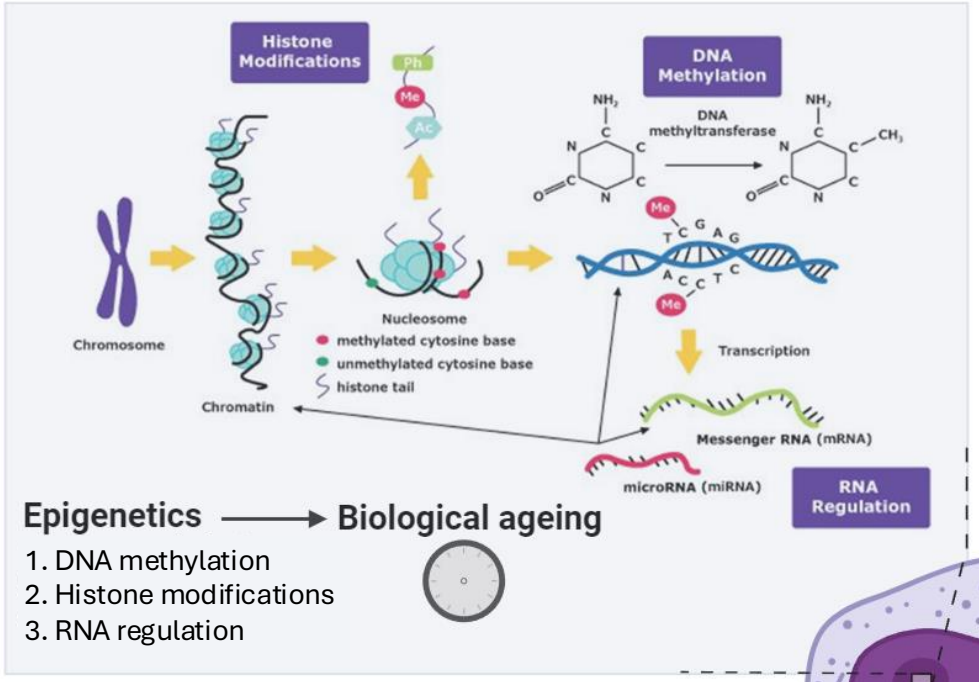
EPO: erythropoietin; EPO-R: erythropoietin receptor; HMA: hypomethylating agents; MDS: myelodysplastic syndrome; MUT: mutation; TPO-R: plasma thrombopoietin receptor.

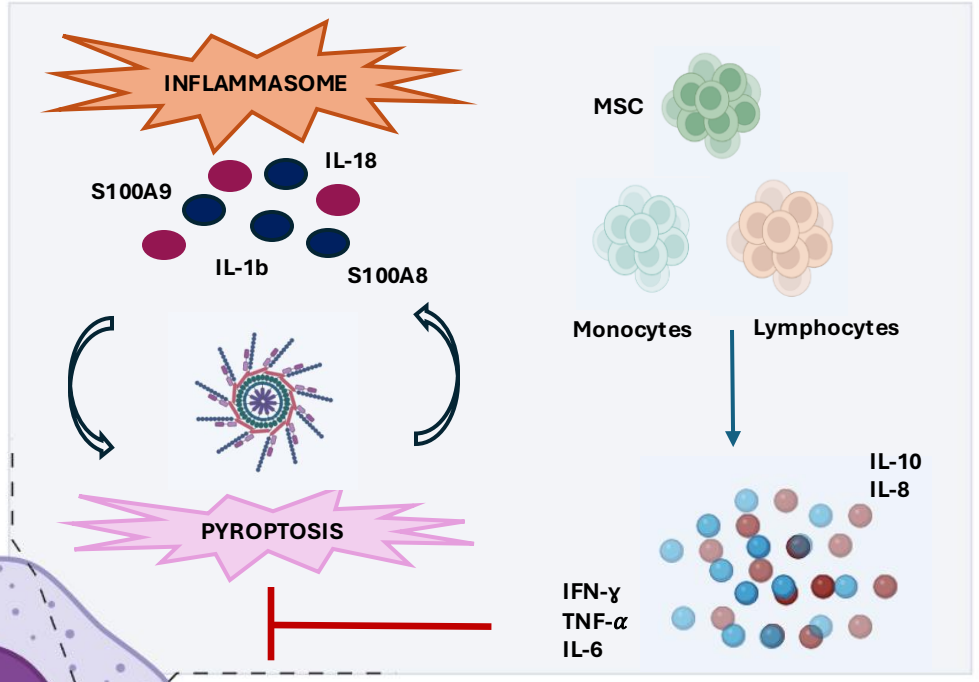
1. Santini V. *Hemato* 2022;3:153-162. 2. Santini V, et al. EHA 2024; (Abstract S184). 3. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-imetelstat-low-intermediate-1-risk-myelodysplastic-syndromes-transfusion-dependent (Accessed Jun 2024)
3. https://www.targetedonc.com/view/roxadustat-misses-efficacy-end-point-for-in-3-phase-mds-study (Accessed Jun 2024). 4. https://www.targetedonc.com/view/minimal-efficacy-observed-with-eprenetapopt-plus-azacitidine-in-tp53-mutant-mds (Accessed Jun 2024).
5. El-Cheikh J, et al. *Clin Hematol Int* 2023;5:143–154. 6. https://ascopost.com/issues/february-25-2022/no-significant-benefit-for-pevonedistat-plus-azacitidine-in-higher-risk-myelodysplastic-syndrome/ (Accessed Jun 2024). 7. Zeidan AM, et al. *Future Oncol* 2023;19:631–642.
8. https://www.gilead.com/news-and-press/press-room/press-releases/2023/7/gilead-to-discontinue-phase-3-enhance-study-of-magrolimab-plus-azacitidine-in-higher-risk-mds (Accessed Jun 2024).
9. https://clinicaltrials.gov/study/NCT05308264 (Accessed Jun 2024). 8. https://www.gilead.com/news-and-press/press-room/press-releases/2023/7/gilead-to-discontinue-phase-3-enhance-study-of-magrolimab-plus-azacitidine-in-higher-risk-mds (Accessed Jun 2024).

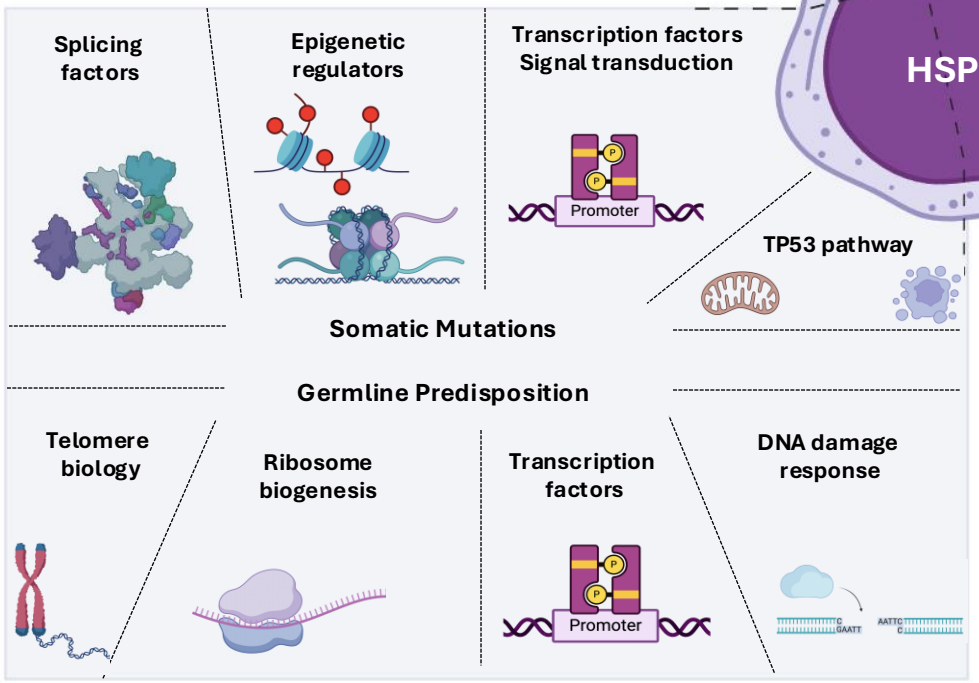
Is the multifaceted pathophysiology of MDS responsible for suboptimal therapeutic approaches ?

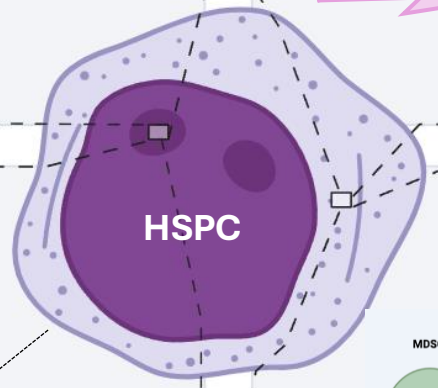
Do we have too incomplete/limited/wrong targets?

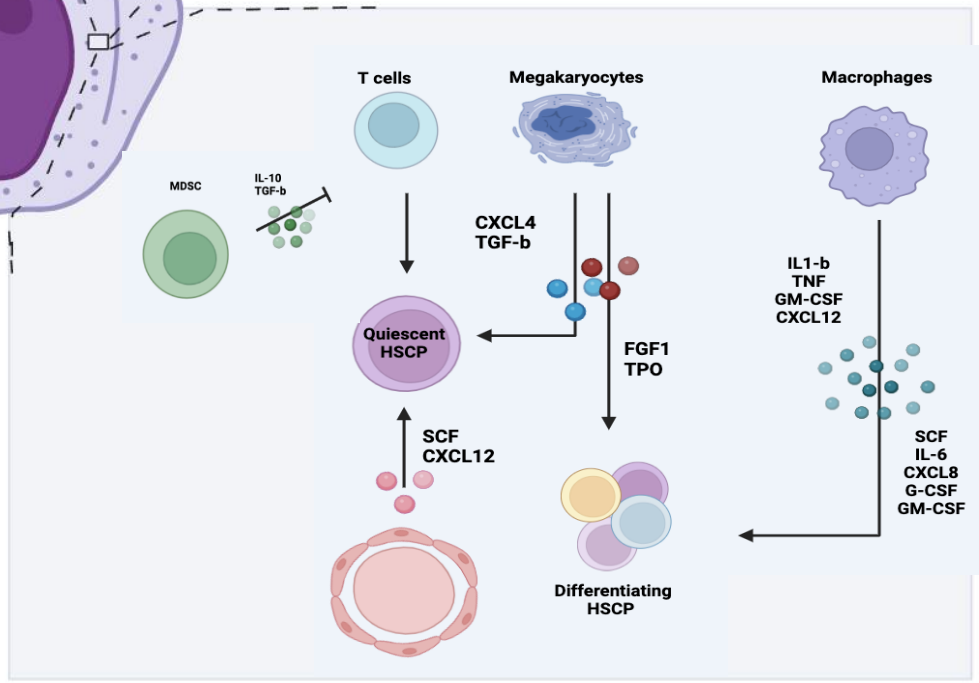
CELL INTRINSIC





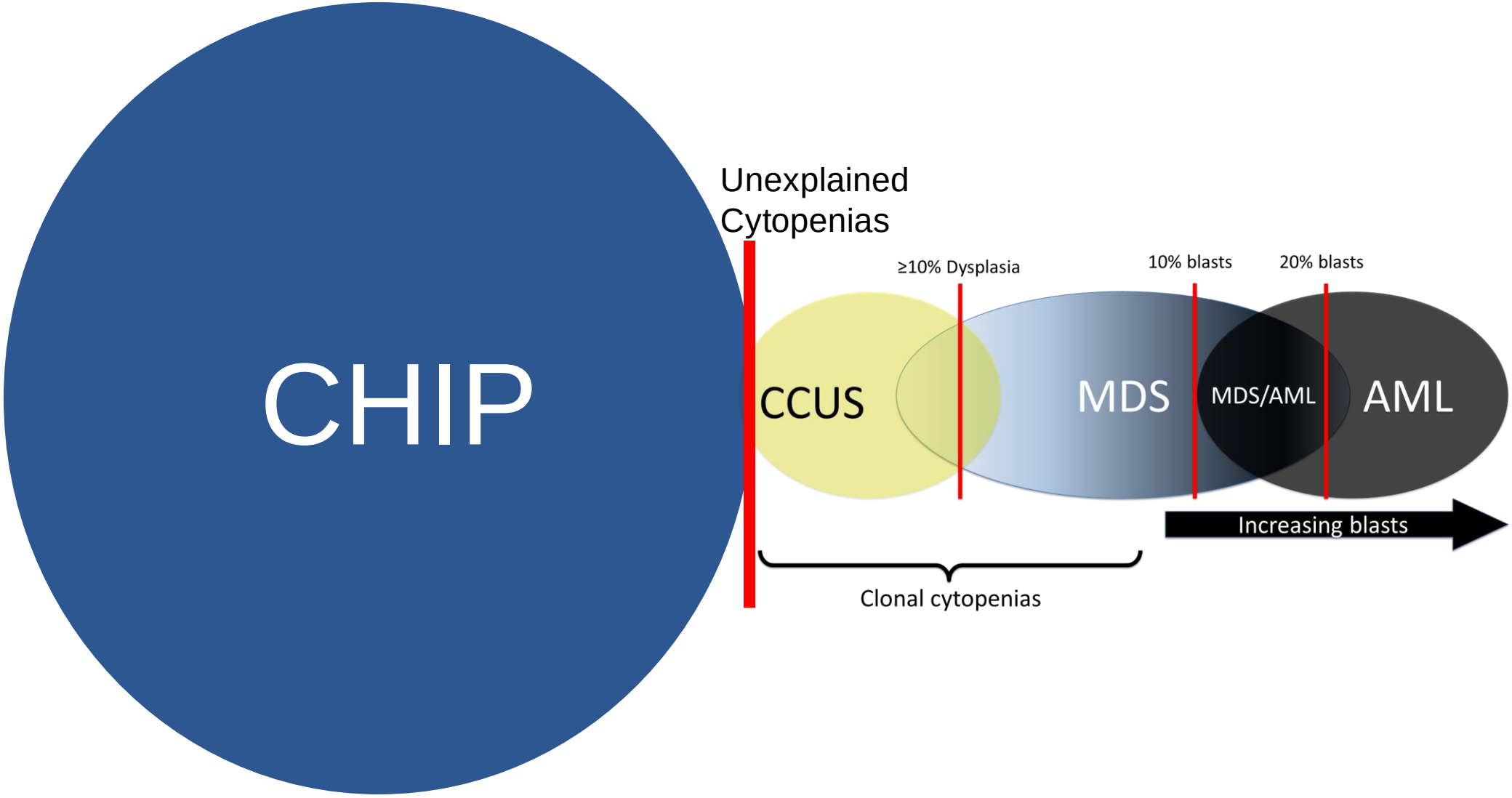






CELL EXTRINSIC

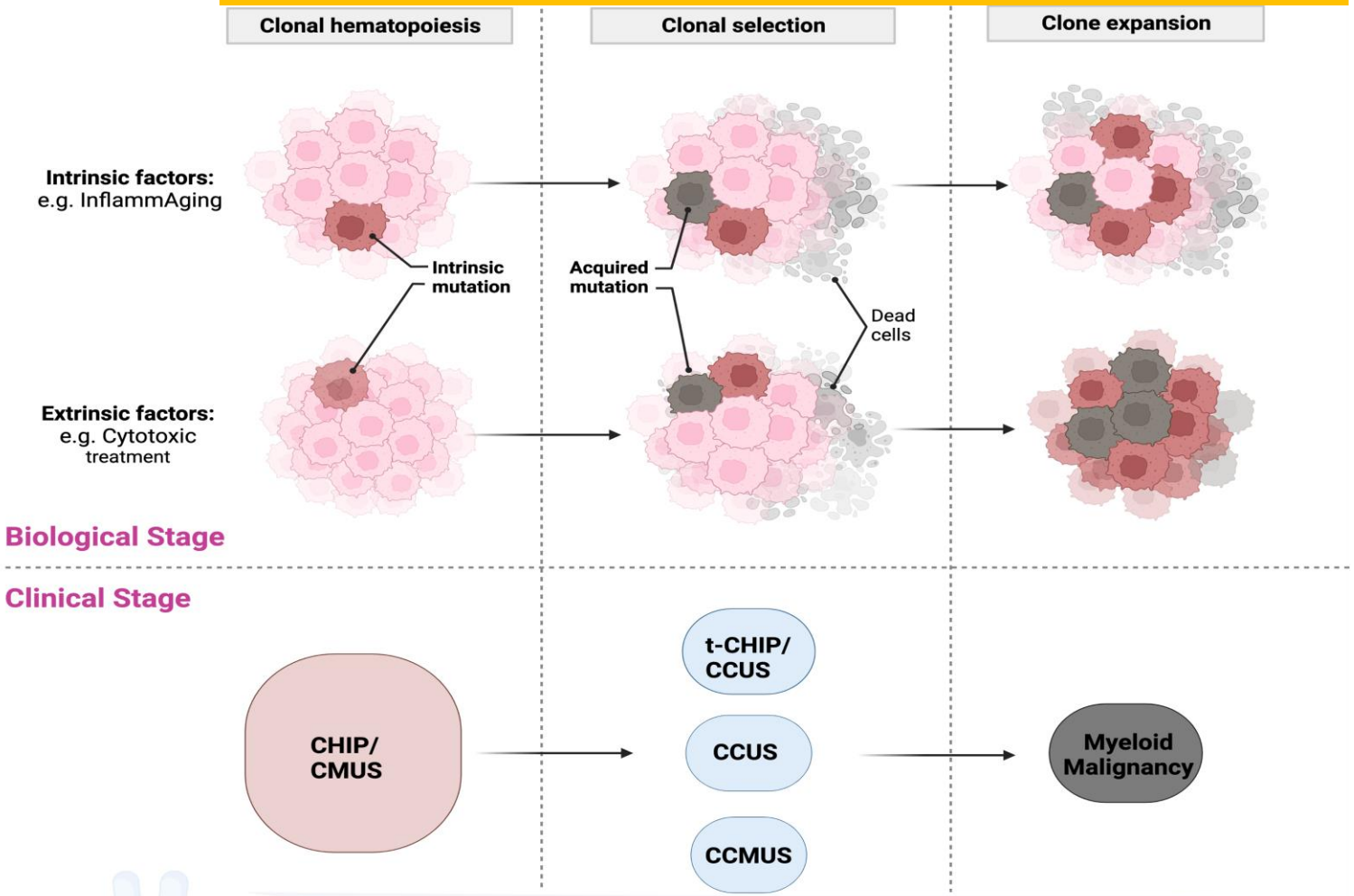
Which alterations are driving the progression from CHIP to MDS and to AML ?



Slide from Robert P Hasserjian

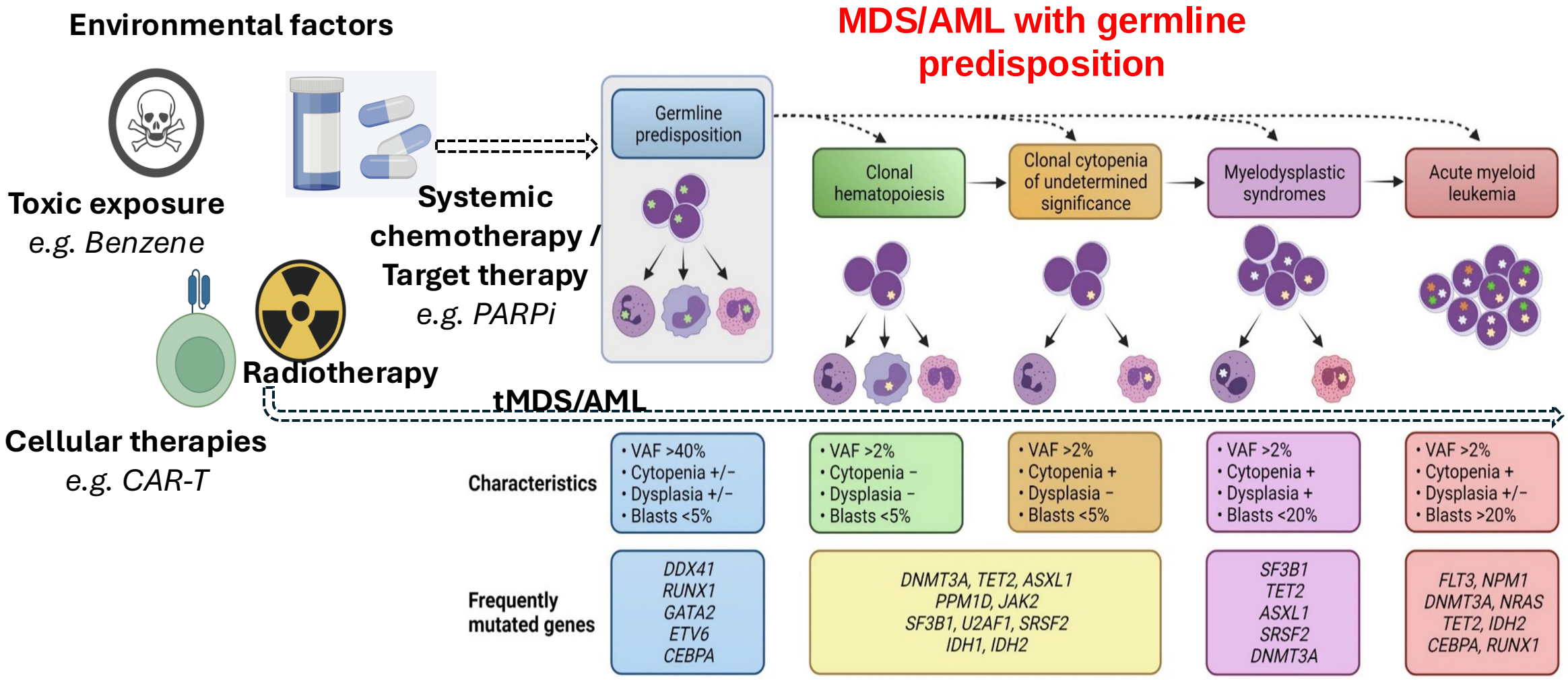
Which alterations are driving the progression from CHIP to MDS and to AML ?

Where is the therapeutical window to block progression?



Xie Z, Chen EC, Mendez L, Komrokji R, Zeidan AM, in press
Clonal Hematopoiesis to Myelodysplastic Neoplasm/Syndrome Spectrum

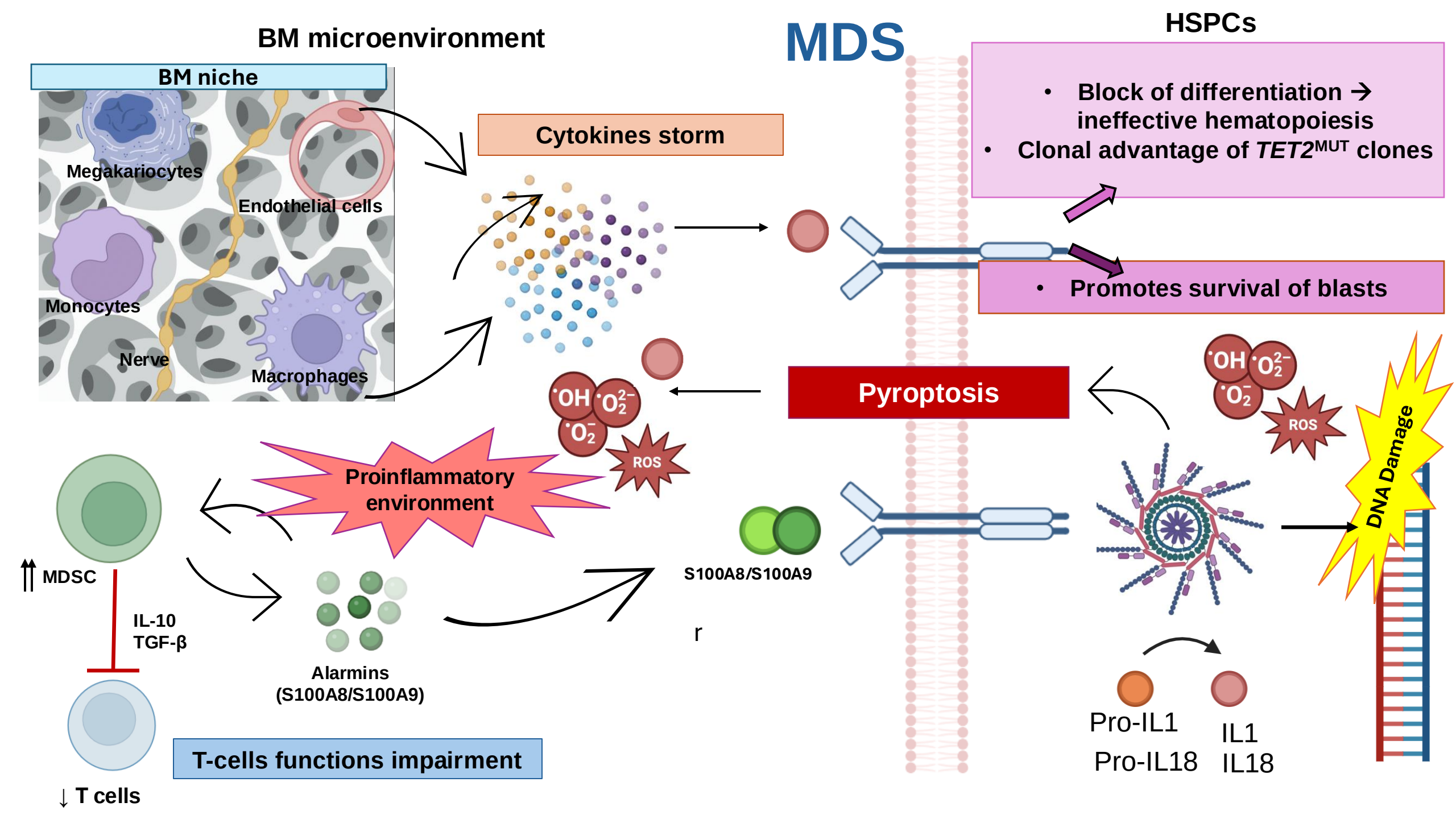
Which alterations are driving the progression from CHIP to MDS and to AML ?



We should implement biological agents for treatment of neoplasias in germline predisposition carriers

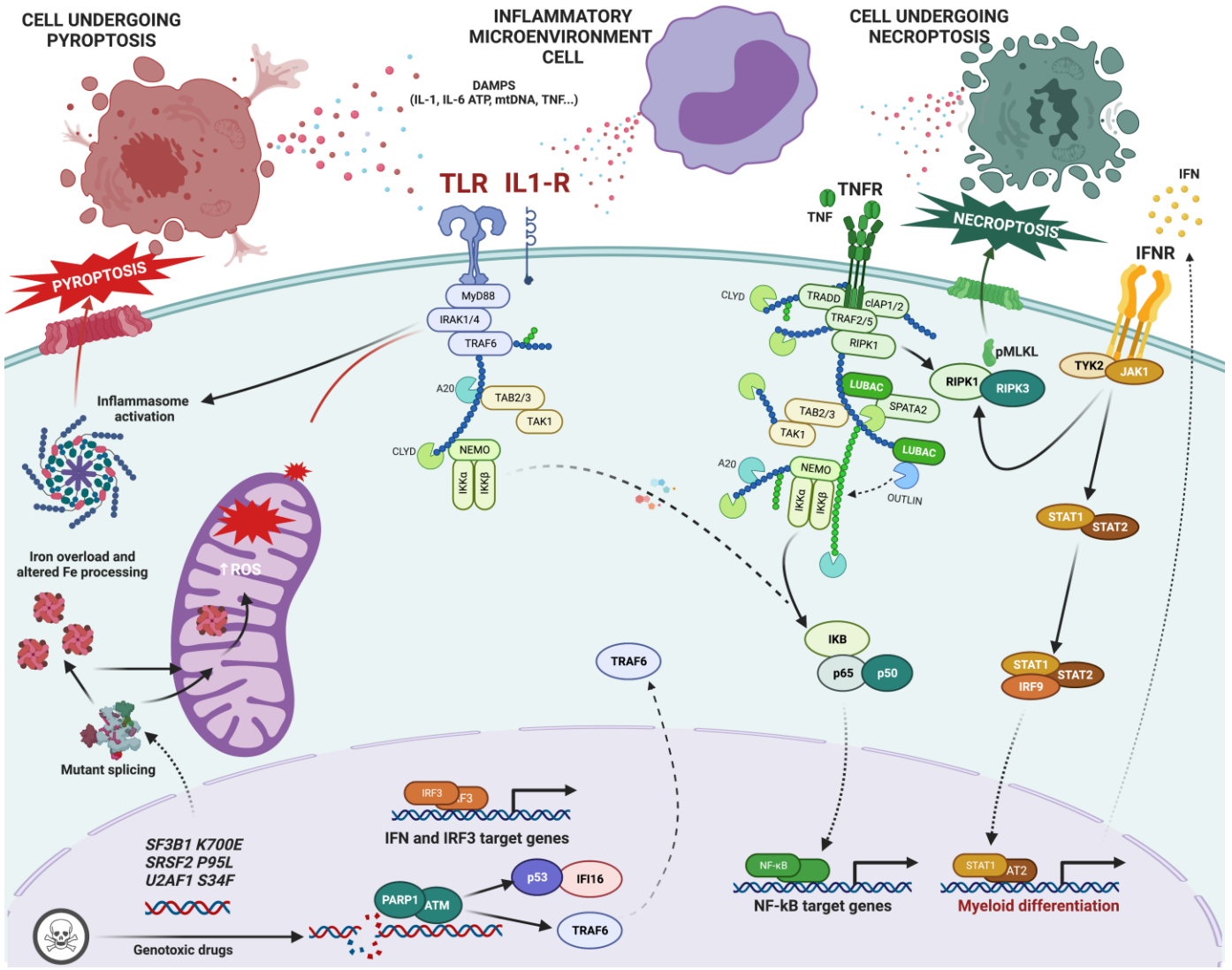
Adapted from Saygin C, Godley LA. 2021, Cancers

Is inflammation one of the triggers for progression?


BM microenvironment
MDS
HSPCs
BM niche
Megakariocytes
Endothelial cells
Monocytes
Nerve
Macrophages
Cytokines storm
• Block of differentiation → ineffective hematopoiesis
• Clonal advantage of TET2MUT clones
• Promotes survival of blasts
Pyroptosis
ROS
DNA Damage
Proinflammatory environment
MDSC
IL-10
TGF-β
Alarmins
(S100A8/S100A9)
S100A8/S100A9
Pro-IL1
Pro-IL18
IL1
IL18
T-cells functions impairment
↓ T cells

IL-1β Signaling Activates NF-κB Pathway and Amplifies Inflammation

- IL-1β binding to IL1R1 activates NF-$_K$B pathway
- NF-$_K$B pathway activation induces the production of other cytokines (e.g., TNFα) that amplify the inflammatory response from the microenvironment



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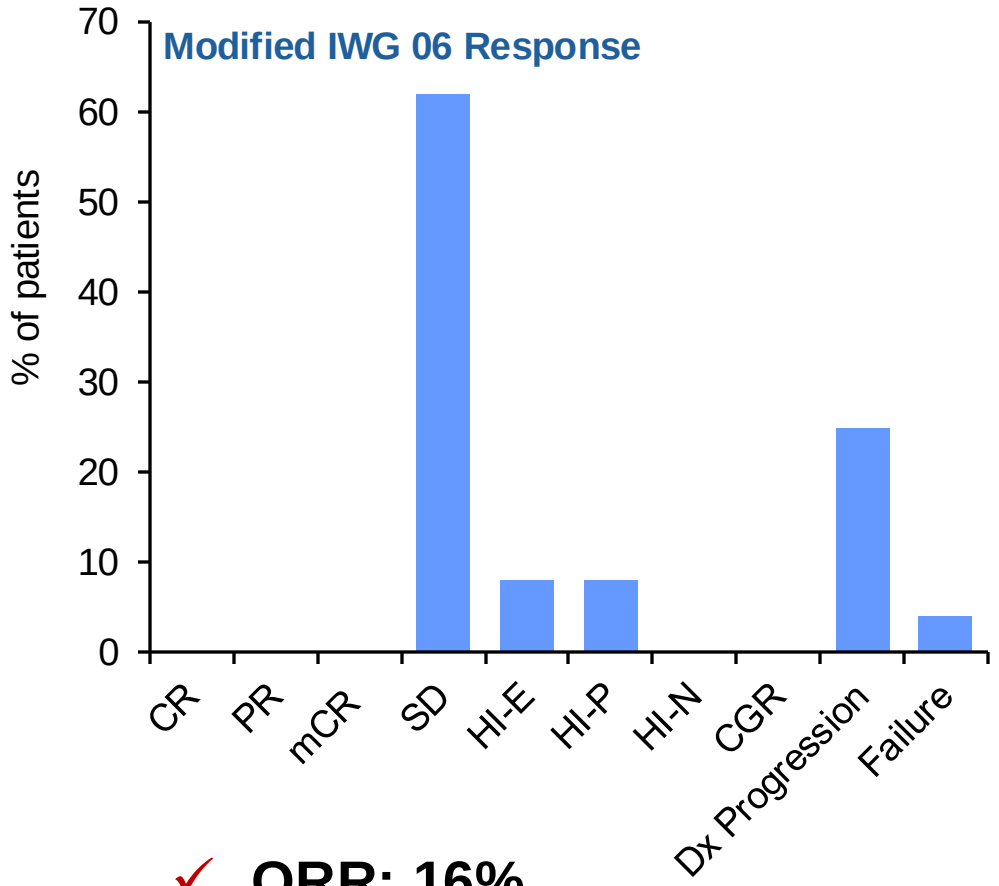
Canakinumab in Lower risk MDS

- **Primary objectives:** safety and clinical activity
- **Secondary objectives:**
  - Rate of transfusion independency
  - Duration of response
  - Progression
  - TFR, correlative studies
- **Phase I** (cohorts, n=3): 3+3 design starting 150mg SC daily q28 days and escalating to 300mg
- **Next Steps:**
  - Expansion cohort #1 (n=20): Transfusion dependent LR-MDS after at east one line of therapy. Stopping rules for toxicity.
  - Other planned: #2: TD LR-MDS no prior therapy; #3: TI LR-MDS and #4: CCUS

Eligibility Criteria

- Age ≥ 18 years old
- MDS
- Risk:
  - IPSS: low or int-1 risk
  - IPSS-R ≤ 3.5 points
- At least one prior line of therapy
- **Symptomatic anemia or transfusion dependence**
- Adequate renal and hepatic functions or performance status



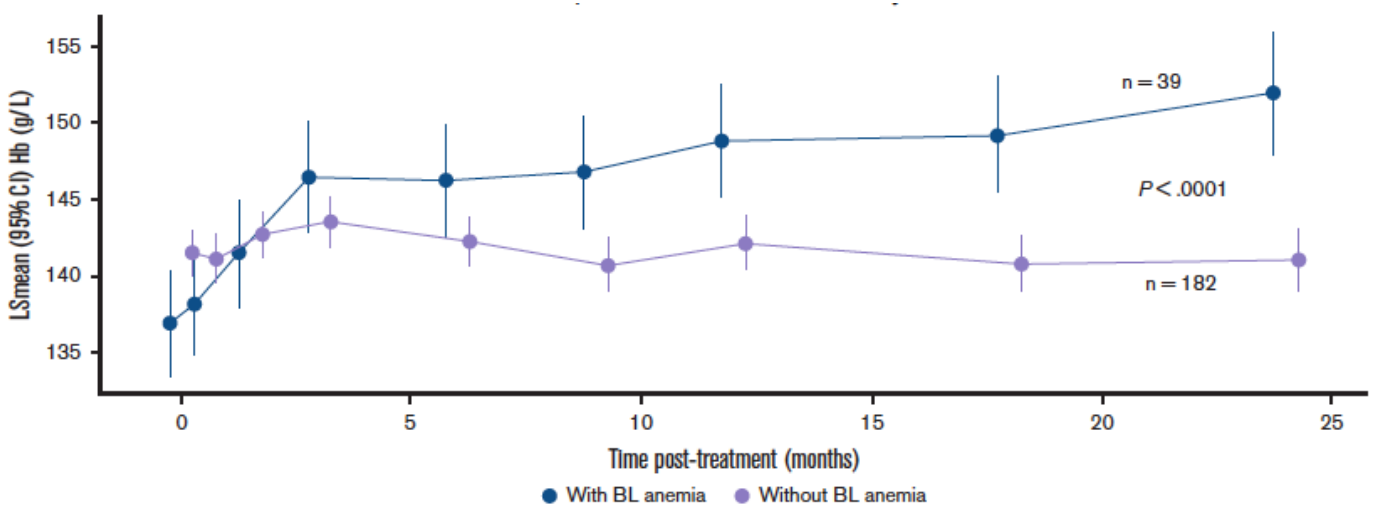
- ✓ **ORR: 16%**
- ✓ **HI-P: 2 patients**
- ✓ **TI: 2 patients**

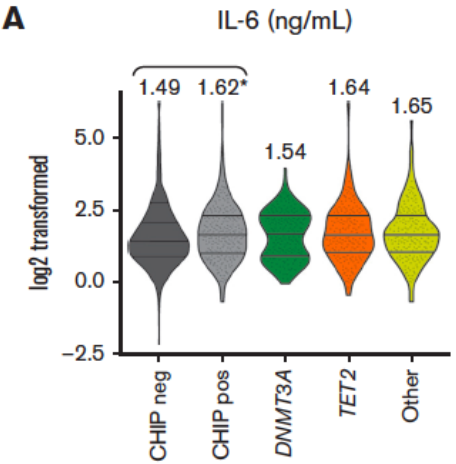
IWG, International Working Group; TFR, Treatment-free remission; LR, low risk; TD, transfusion dependence; TI, transfusion independence

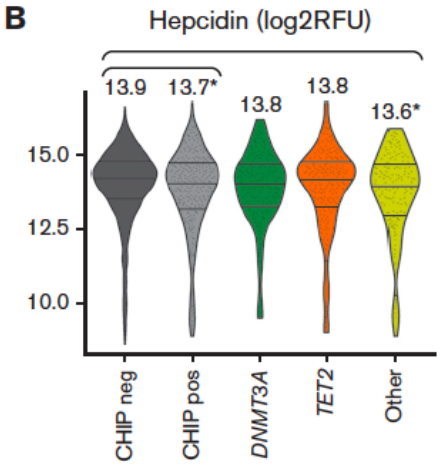
Abstract #858; *Session: 637. Myelodysplastic Syndromes — Clinical and Epidemiological I; ASH Meeting 2022*

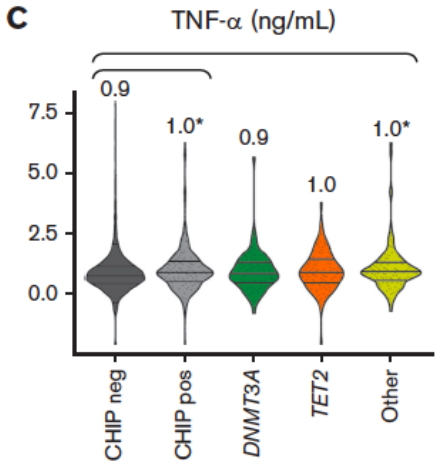
Effects of IL-1β inhibition on anemia and clonal hematopoiesis

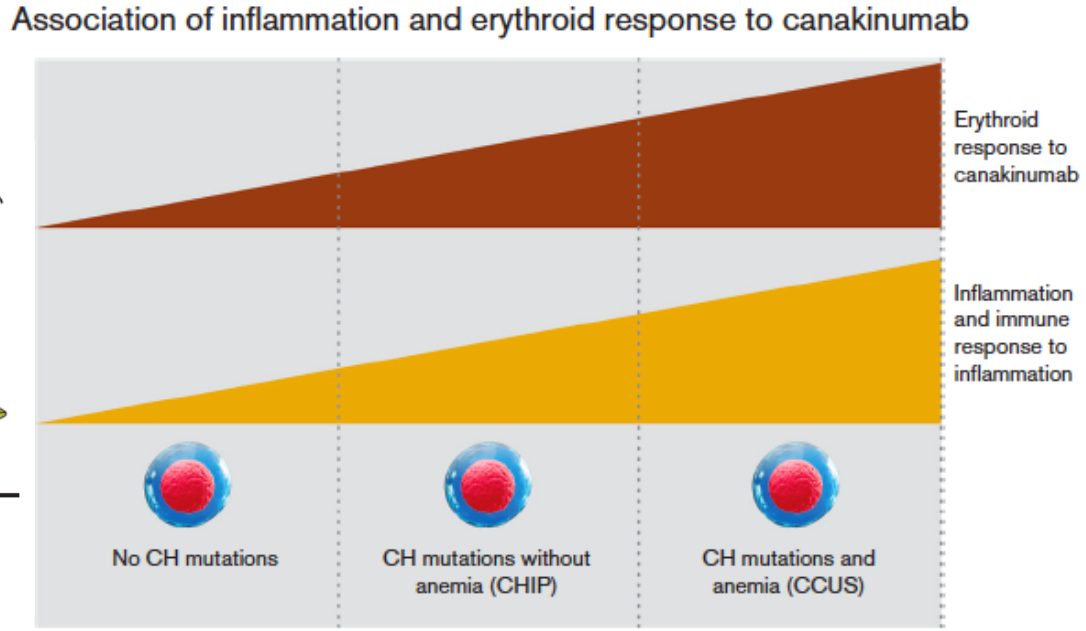
Canakinumab in CHIP and CCUS







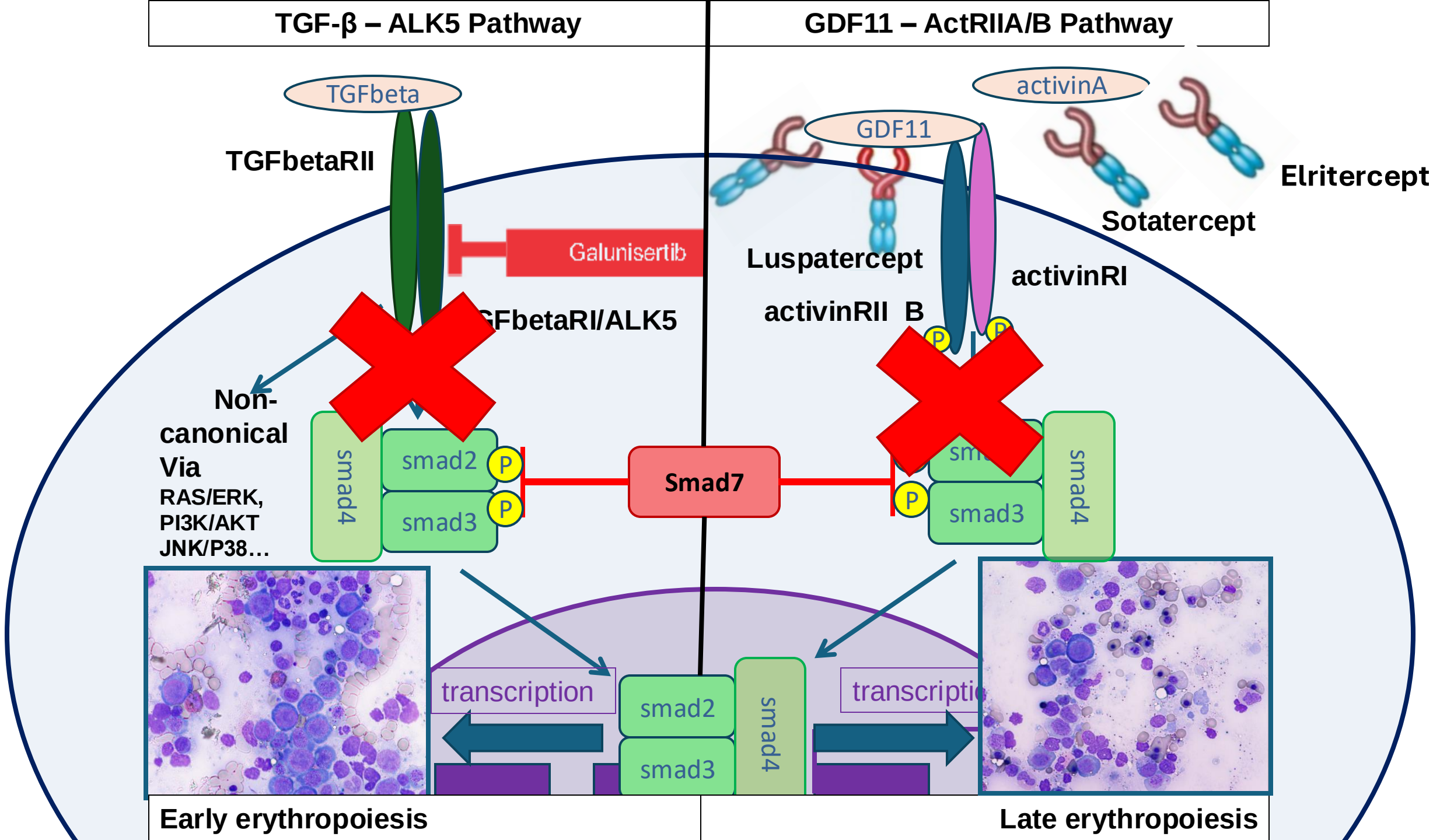




Woo J et al, Blood Adv 2023

Effective targeting of altered “multi-tasks” pathways ?

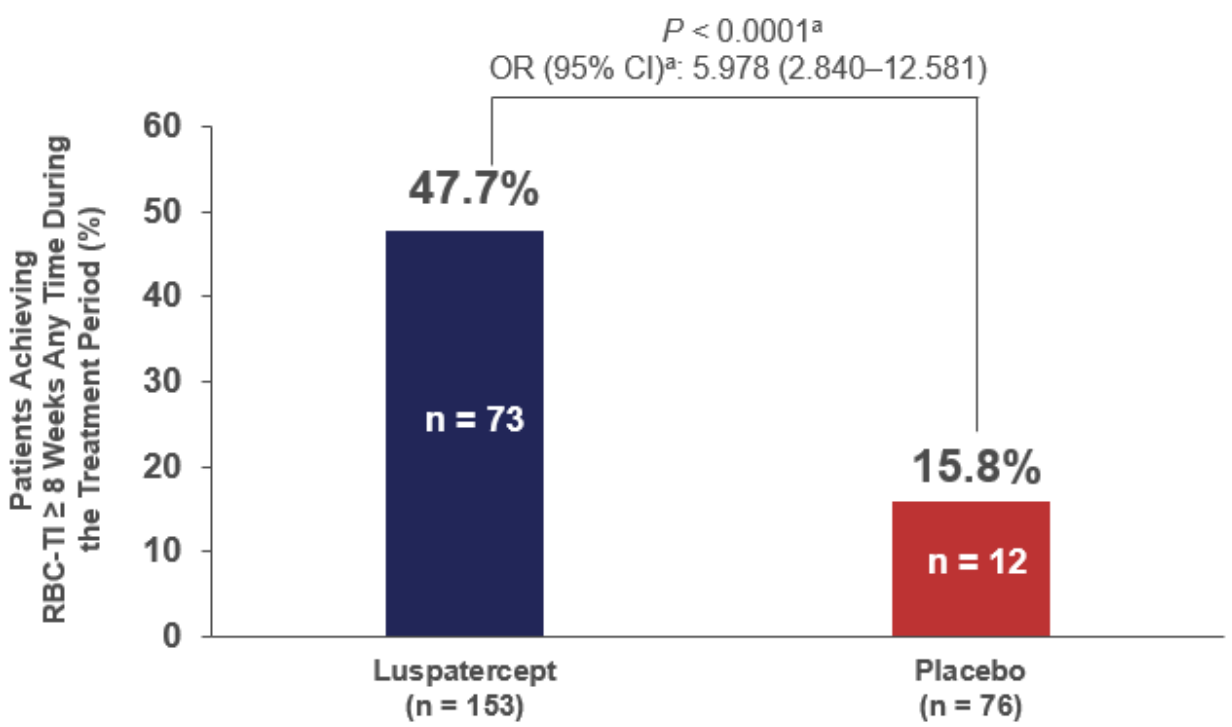
TGFbeta/Activin pathway modulates apoptosis , cell growth and differentiation, bone morphogenesis, immunosuppression……


TGF-β – ALK5 Pathway
GDF11 – ActRIIA/B Pathway
TGFbeta
TGFbetaRII
Galunisertib
GFbetaRI/ALK5
activinA
GDF11
Elritercept
Sotatercept
Luspatercept
activinRI
activinRII B
Non-
canonical
Via
RAS/ERK,
PI3K/AKT
JNK/P38…
smad4
smad2
smad3
P
Smad7
transcription
Early erythropoiesis
Late erythropoiesis

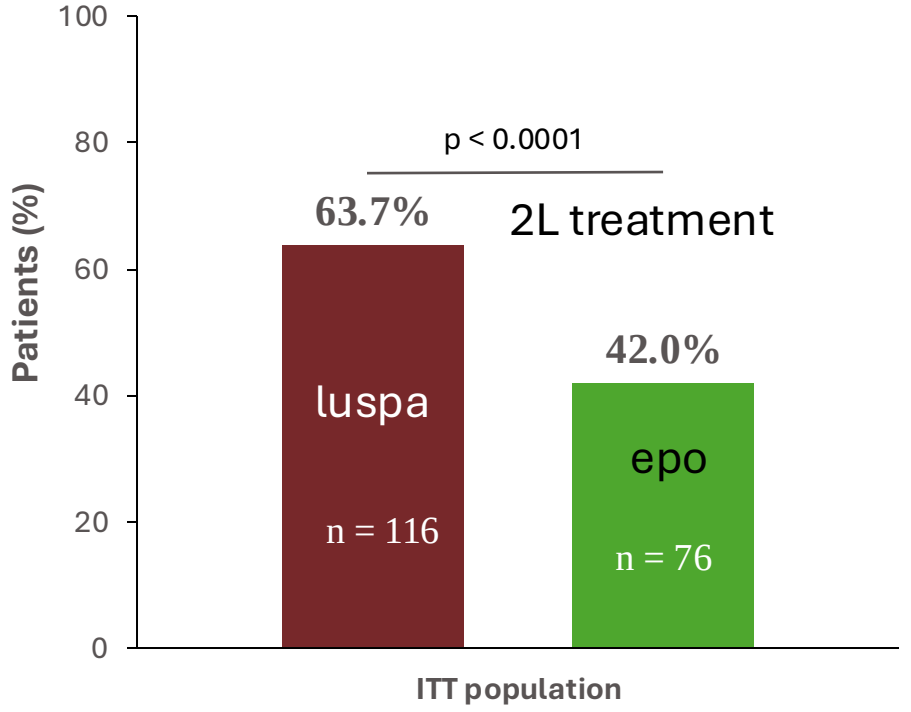
TGFbeta family pathway modulation induces transfusion independence in LR-MDS

RBC-TI response

2L treatment



1L treatment



Fenaux et al, N Engl J Med. 2020 Jan 9;382(2):140-151.

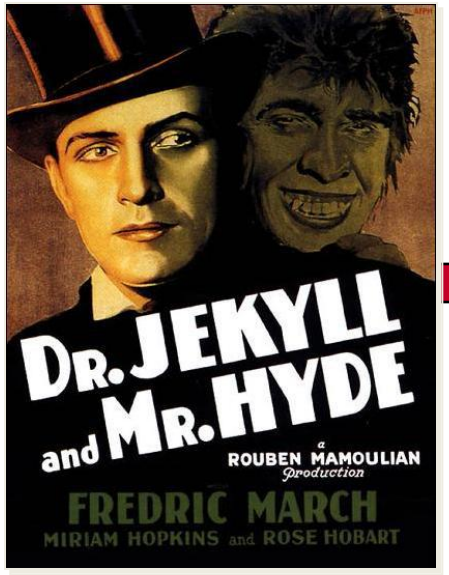
Della Porta MG , Garcia Manero G et al, Lancet Hematol 2024

Can we target efficiently the alterations in epigenetic regulation typical of MDS?

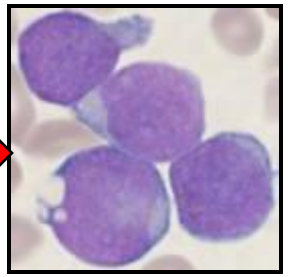
Normal maturation

Altered epigenome and dysplasia

Stem Cell



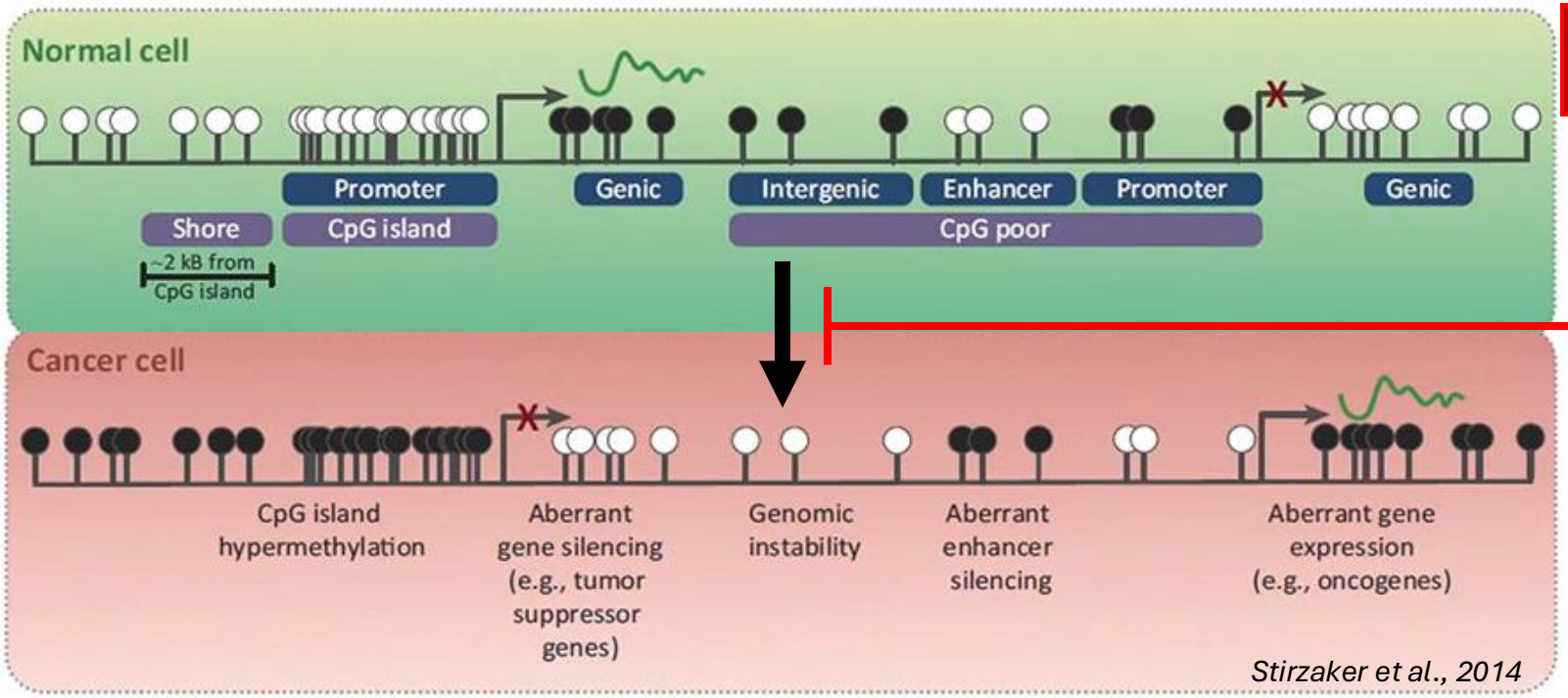
Leukemic Cell



One DNA, multiple phenotypes?

Epigenetic alterations in MDS

DNA methylation



Stirzaker et al., 2014

DNMTis
Hypomethylating agents

Azacitidine **Decitabine**

10 – 20%

80 – 90%

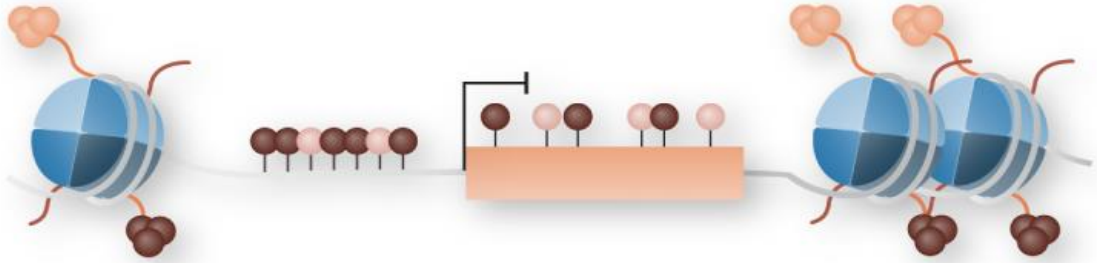
RNA

DNA

azadC

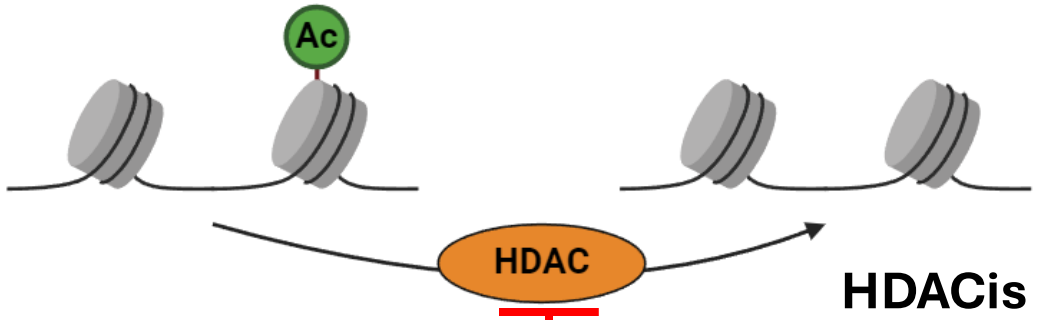
DNMT

Epigenetic dysregulation



DNA methylation	Histones
DNMT3A	MLL fusions
TET2	EZH2 (PcG)
IDH1 and IDH2	ASXL1
	HATs/HDACs
	PRMT5
	BRD4

Huang & Figueroa, 2021



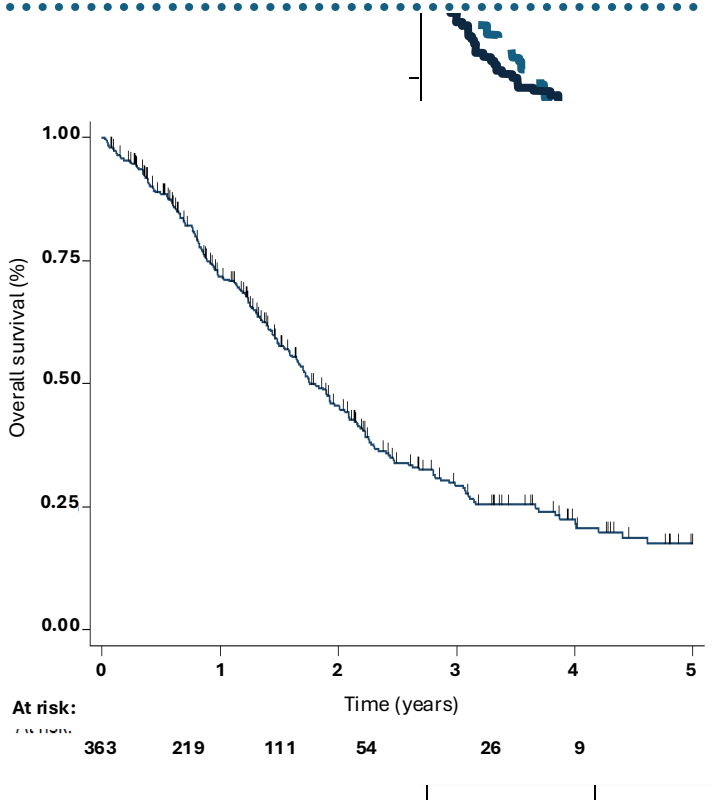
Histone modifiers

HDACis

Vorinostat
Pracinostat
Panabinostat
Entinostat

Overall Survival: Azacitidine vs CCR ITT Population

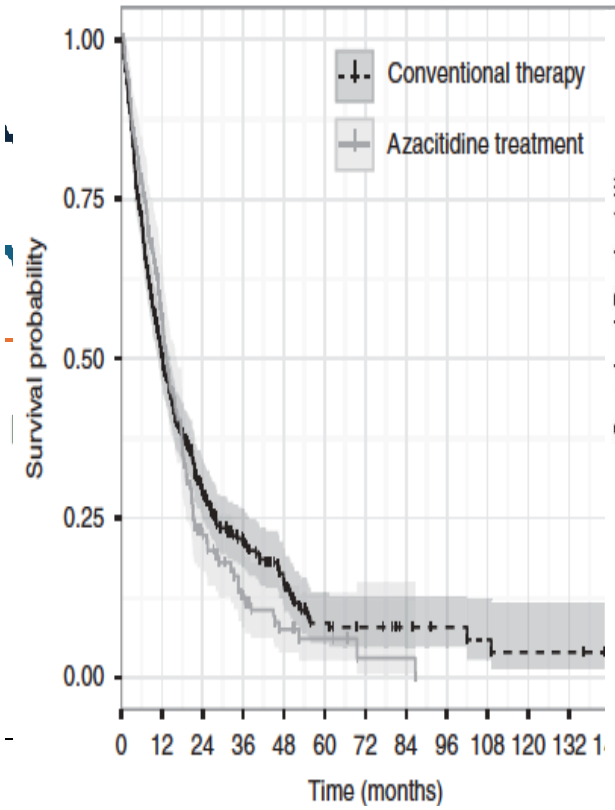
Italian FISiM registry[1]



Median AZA cycles 7

Median OS from start AZA: 16 mo

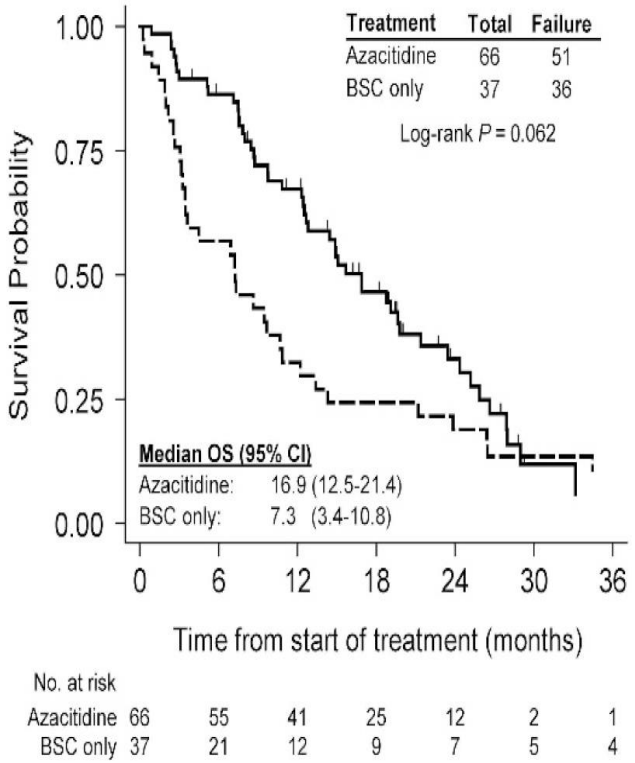
Spanish registry[2]



Time (months) from Randomization

Median OS 13.4 vs 12.2 mo

Dutch registry[3]

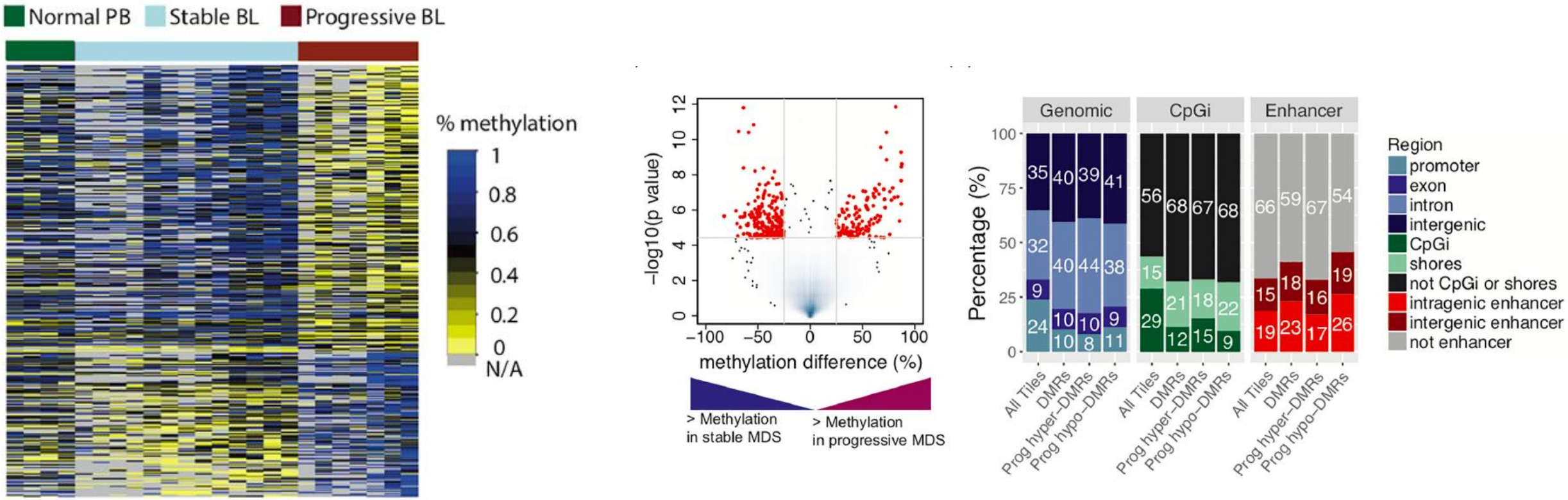


Median OS 16.9 vs 7.3 mo

Fenaux et al., 2009

DNMTis work also in patients with LR- MDS….we know it is effective….but which is MoA?

DNA methylation profiles correlate with clinical outcome in LR- MDS



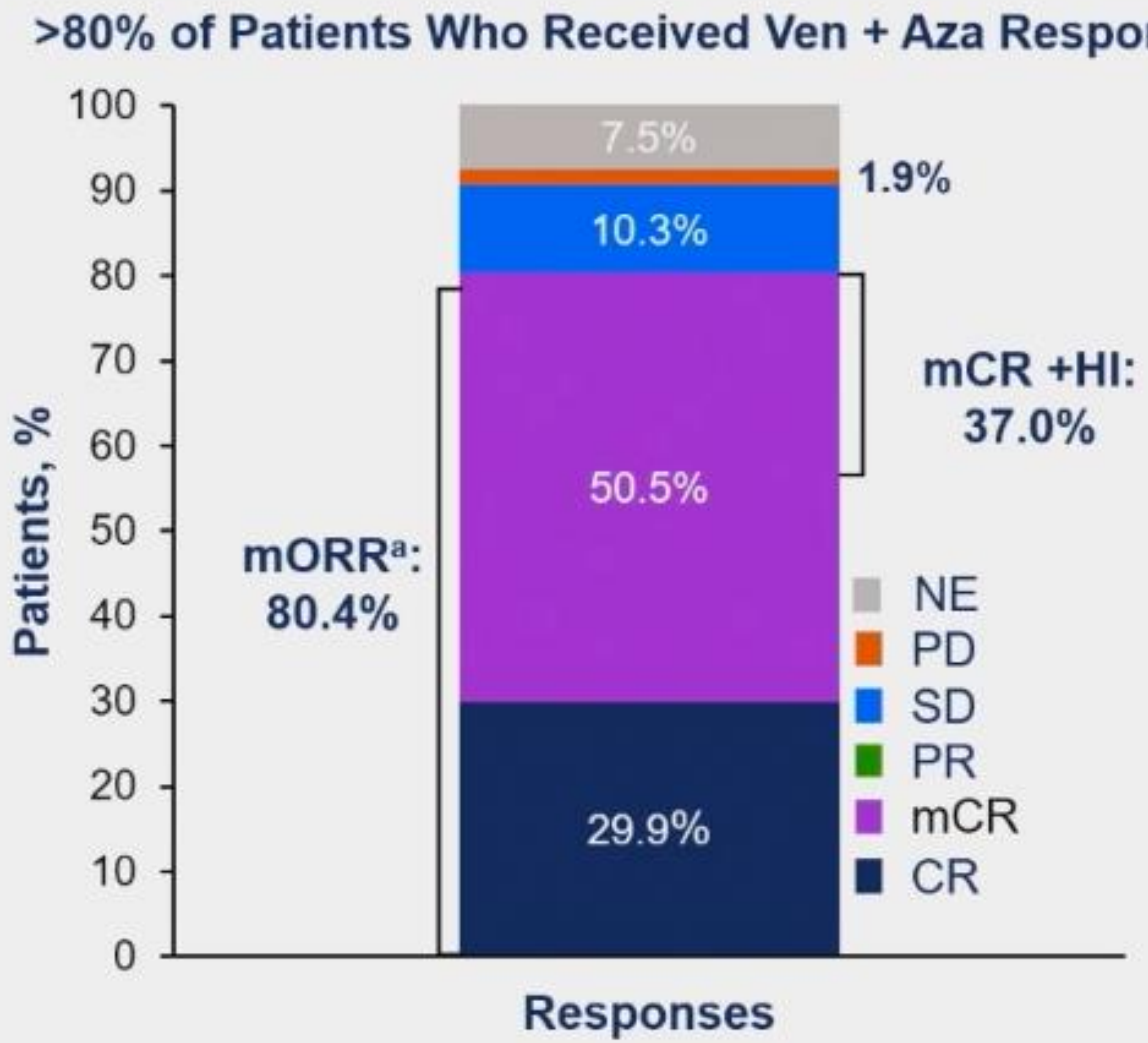
Approx 2/3 of DMRs were hypomethylated in LR MDS with progressive disease

Qin et al , Leukemia. 2019 Nov;33(11):2753-2757.

Combination Epigenetic Therapy AZA + HDACi in MDS/AML

Reference	Year	Dose (mg/m2)	Add Agent	Eval Pts N	CR (%)	ORR (%)
Gore	2006	5AC: 20-75 x5-14d	PB	29	13	38
Gore	2006	5AC: 30-50 x 10d	Entinostat	32	7.4	44
Garcia-Manero	2006	DAC: 20 x 5d	VPA	54	19	22
Blum	2007	DAC: 20 x 10d	VPA	25	16	44
Soriano	2007	5AC: 75 x 7d	VPA+ATRA	53	22	44
Silverman**	2013	5AC: 55-75 x 7d	Vorinostat	28	45	70
Garcia-M	2011	5AC: 75 x 5d	Vorinostat	30 unfit		40
Prebet **	2014	5AC: 50 x10d	MS-275 (C)	149	8	44
How**	2015	DAC: 20 x 5d	Vorinostat (S/C)	36	14	23
Issa **	2015	DAC: 20 x5d	DAC vs DAC+VPA	149	34	55
Voso**	2009	5AC 75 x 7d	Valproic acid	62	30	46

BCL2 : a possible successful target in MDS ? azacitidine + venetoclax. Waiting for OS results



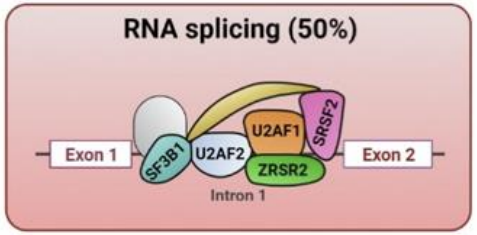
- Median number of treatment cycles with Ven 400 + Aza: 4.0 (range, 1–57)
- Median time to CR: 2.8 months (range, 1.0–16.1)
- Median duration of CR: 16.6 months (95% CI, 10.0–NR)
- MDS to AML transformation: in 13 (12.3%) patients (95% CI, 6.7–20.1)
  - Median time to AML transformation was 5.95 months (range, 0.72–29.31)

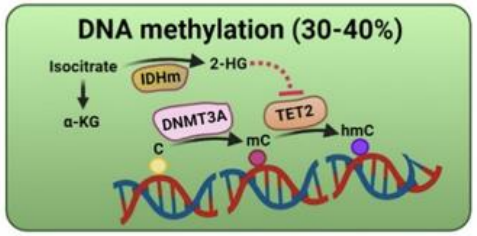
Garcia J et al, EHA 2023

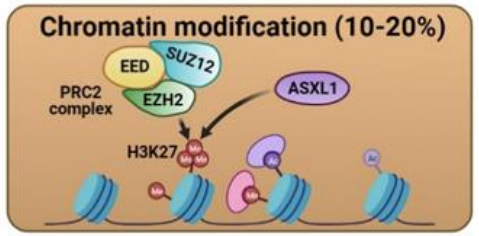
[a]mORR=CR+mCR+PR; PR, n=0; response rates based on International Working Group 2006 response criteria.
AML, acute myeloid leukemia; Aza, azacitidine; CR, complete remission; HI, hematologic improvement; mCR, marrow complete remission; MDS, myelodysplastic syndromes; mORR, modified overall response rate; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial remission; RP2D, recommended phase 2 dose; SD, stable disease; Ven, venetoclax.

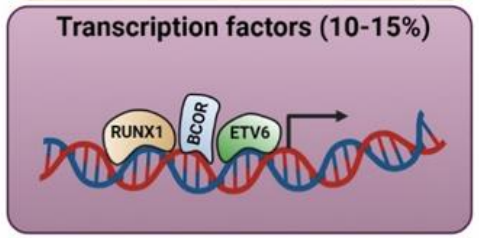
>90% of MDS pts carry genetic alterations conferring specific phenotypes

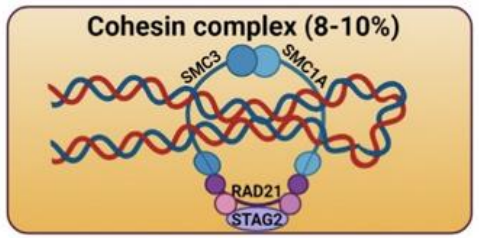
Can we obtain clinical success by targeting specific gene mutations?

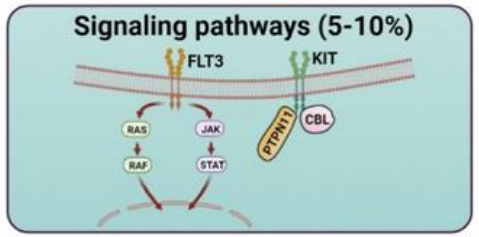


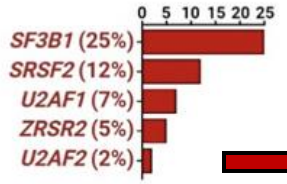




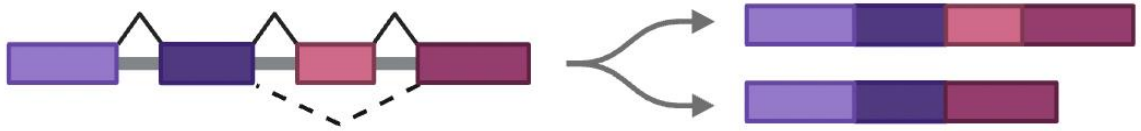


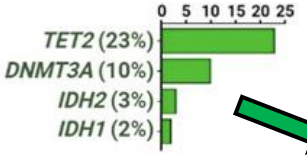




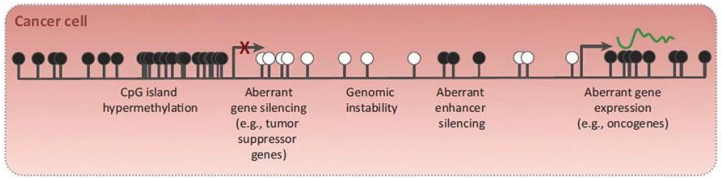


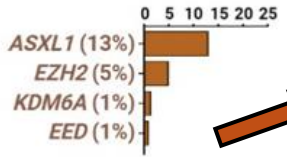
mRNA misplicing → nonsense mediated decay/protein variant



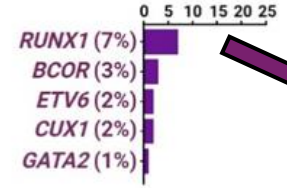


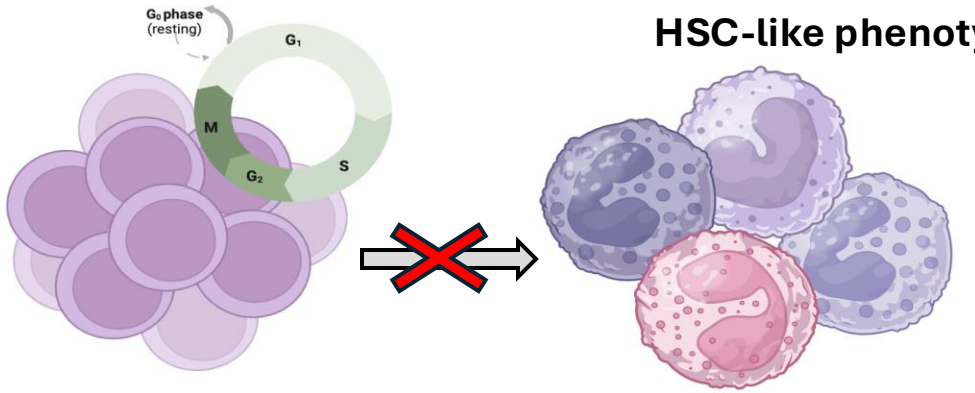
Abnormal DNA methylation

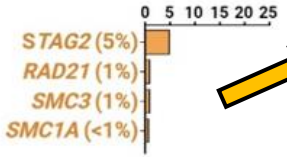




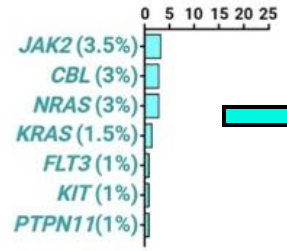
Increased survival and acquisition of HSC-like phenotype

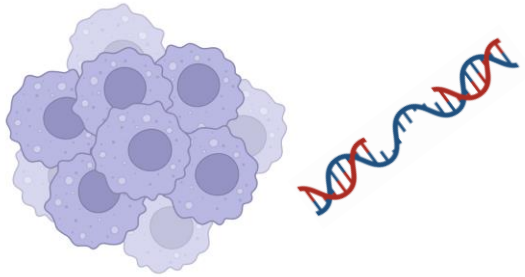






Myeloproliferation and AML evolution

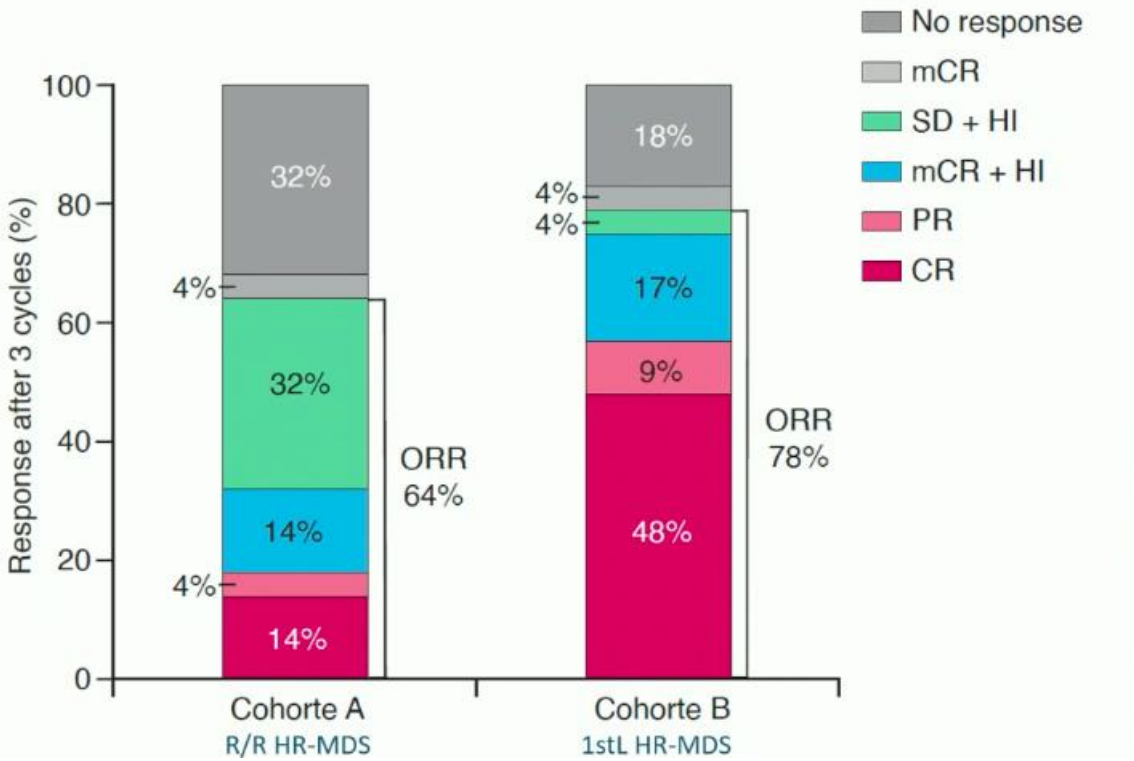




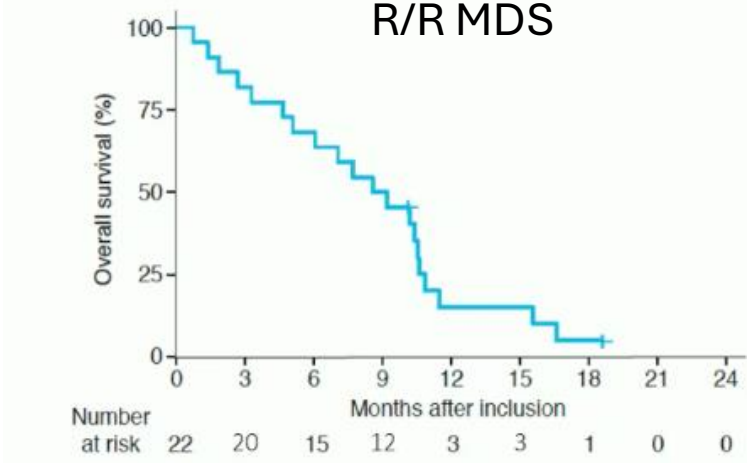
Adapted from Saygin C, Godley LA. 2021, Cancers

Ivosidenib Monotherapy in IDH1 Mutated Myelodysplastic Syndrome, Final Results of the IDIOME Trial, a GFM Study

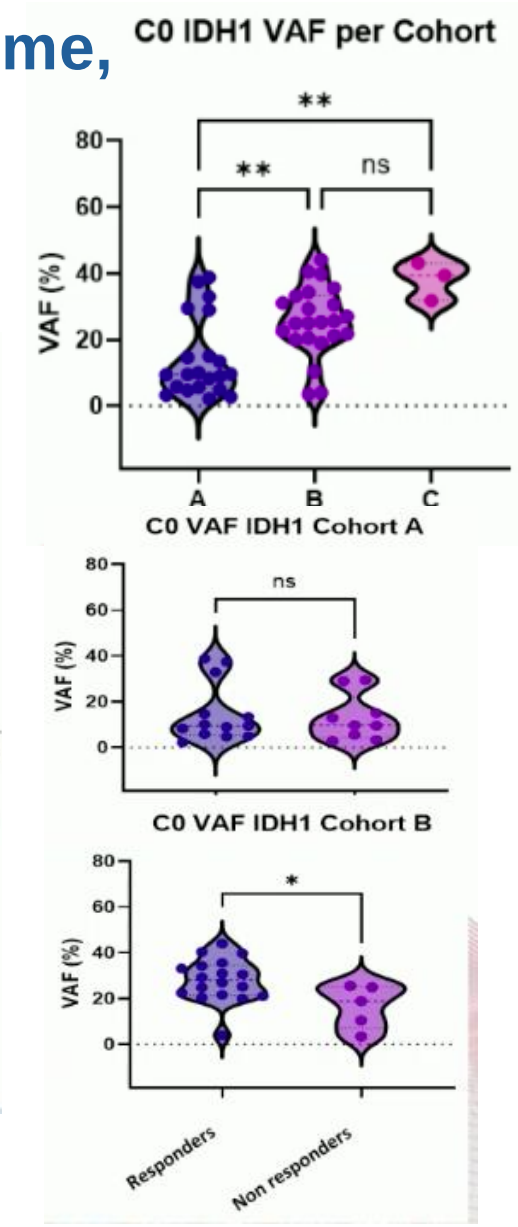
Overall response rate



Cohort A
R/R MDS



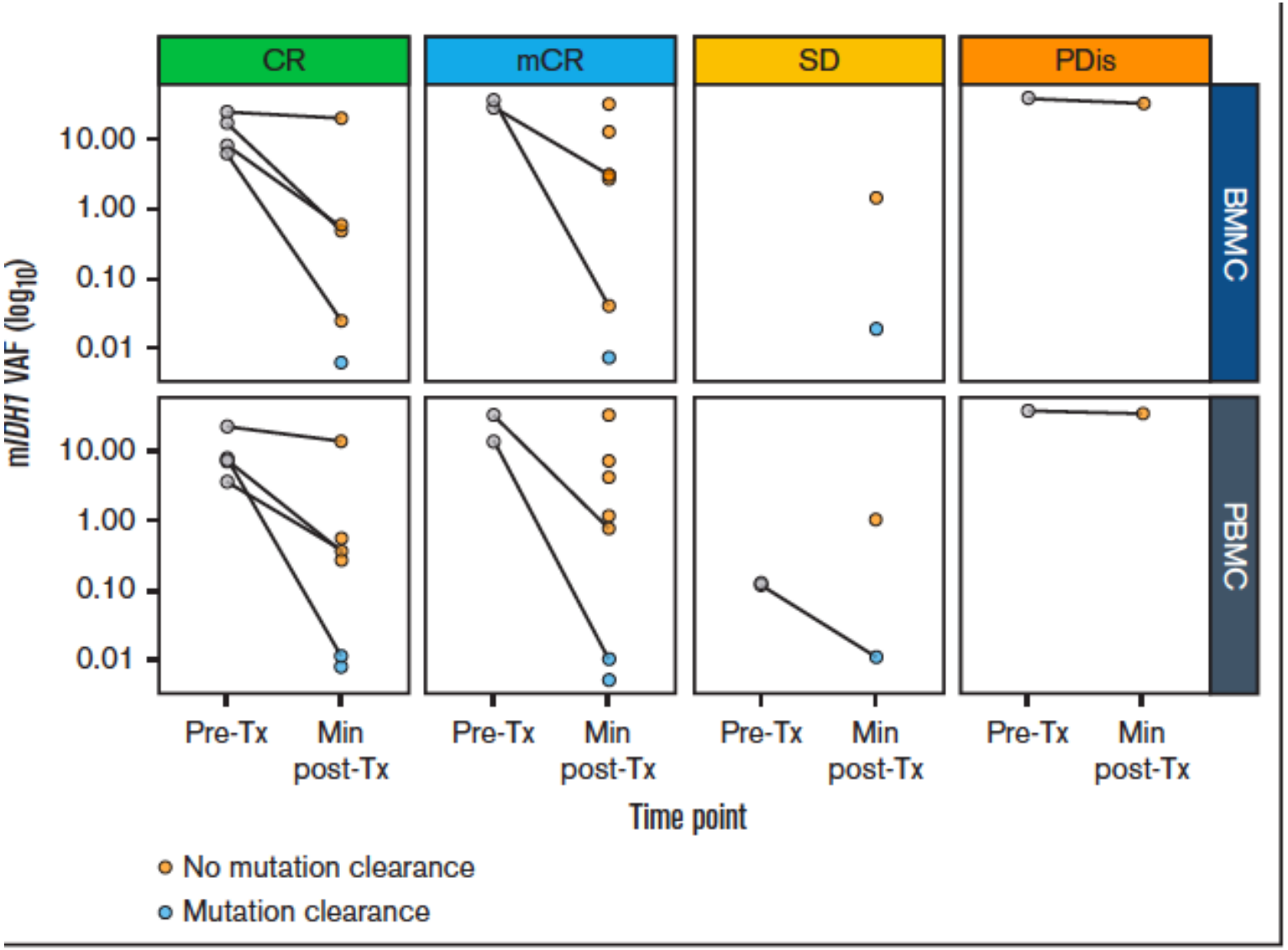
- Median OS was 8.9 months
- 12-month OS rate was 15.2% (95%CI, 5.4-42.5)
- 2 patients are still alive on therapy
- 14 progressed
- 20 died



Sebert M et al abs EHA 2024

Ivosidenib Monotherapy in IDH1 Mutated R/R MDS: clinical response and decrease of VAF

- Ivosidenib resulted in a CR rate of 38.9% and an OR rate of 83.3% in m*IDH1* R/R MDS; median duration of response was not reached.
- Median OS in this R/R MDS cohort was ~36 months; ~75% of RBC- and platelet-transfusion–dependent patients became transfusion independent.

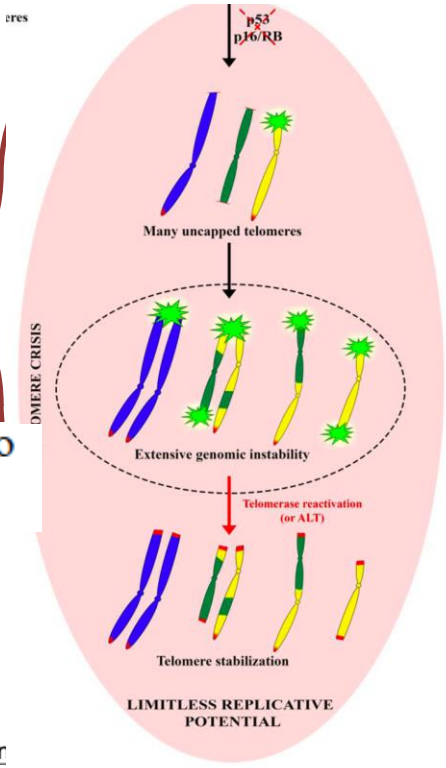


Di Nardo C et al *Blood Adv* (2024) 8 (15): 4209–4220.

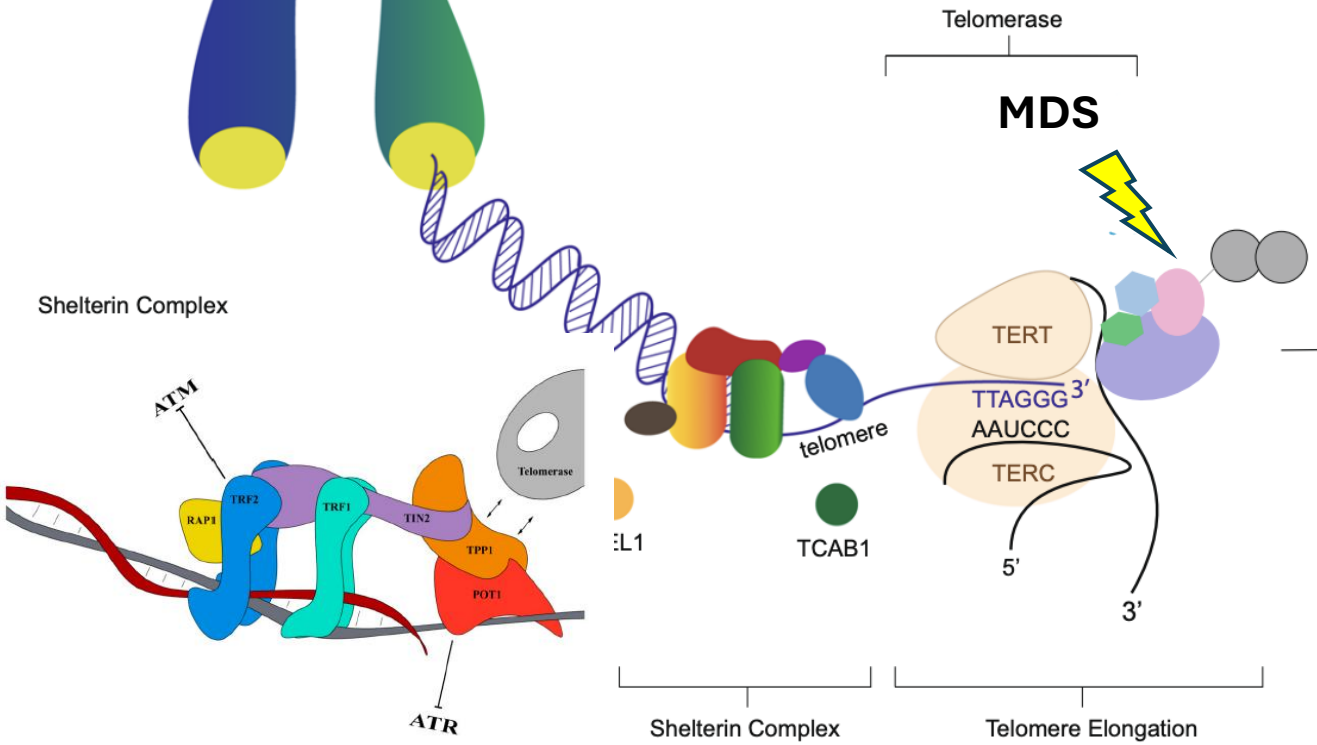
Telomere dysfunction in MDS

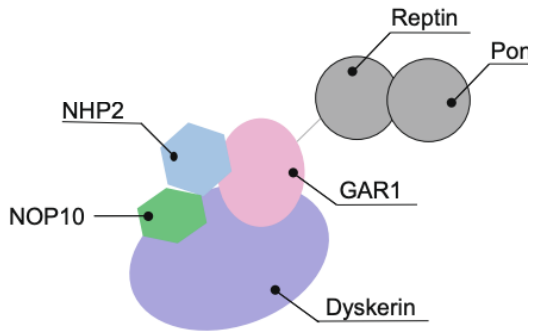
- *TERT* and *TERC* mutations in ≈ 3% of MDS, with a high rate of AML transformation
- Shorter telomere lenght in HSC in MDS mouse model and increased hTERT expression in MDS

Extremely complex modulation of HSC



mutant HSCs' residual telomerase activity could be sufficient to maintain the clonal expansion of the cells once they acquire tumorigenic potential.

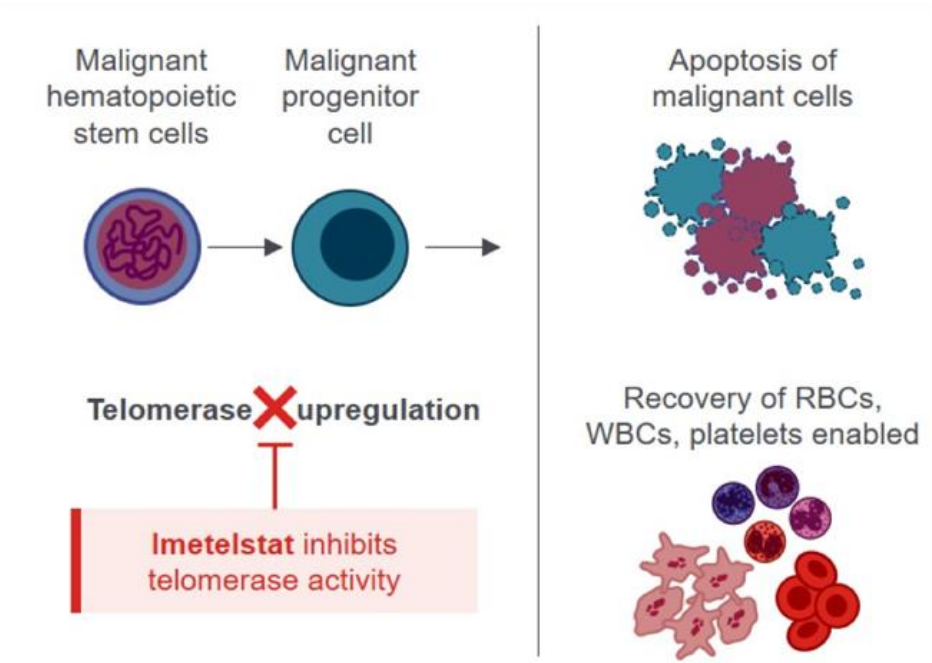




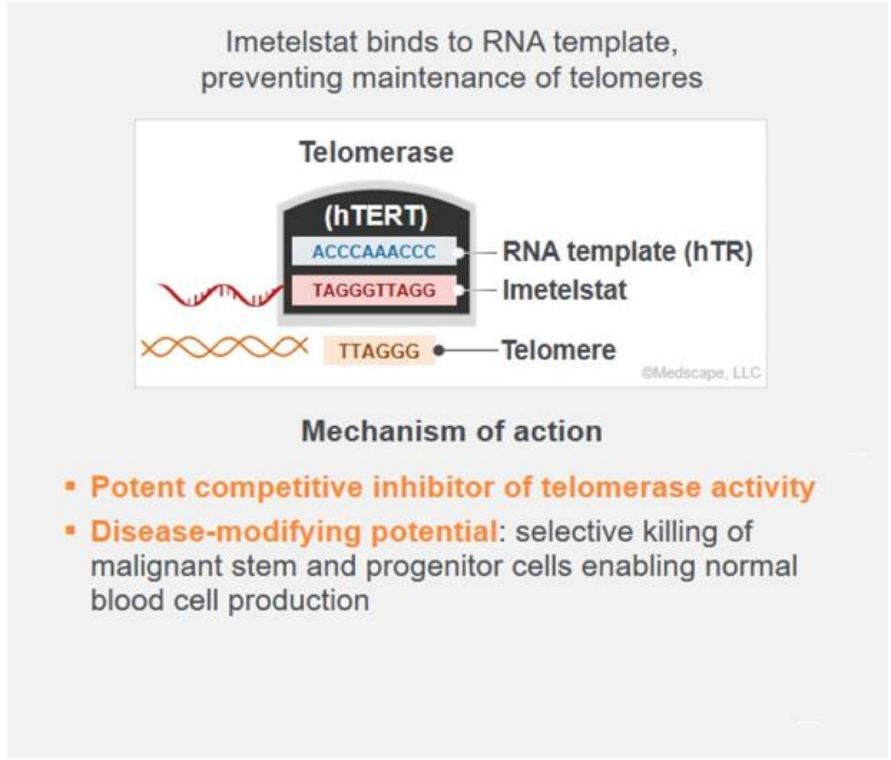
Adapted from Kam et al., NPJ Genom Med 2021

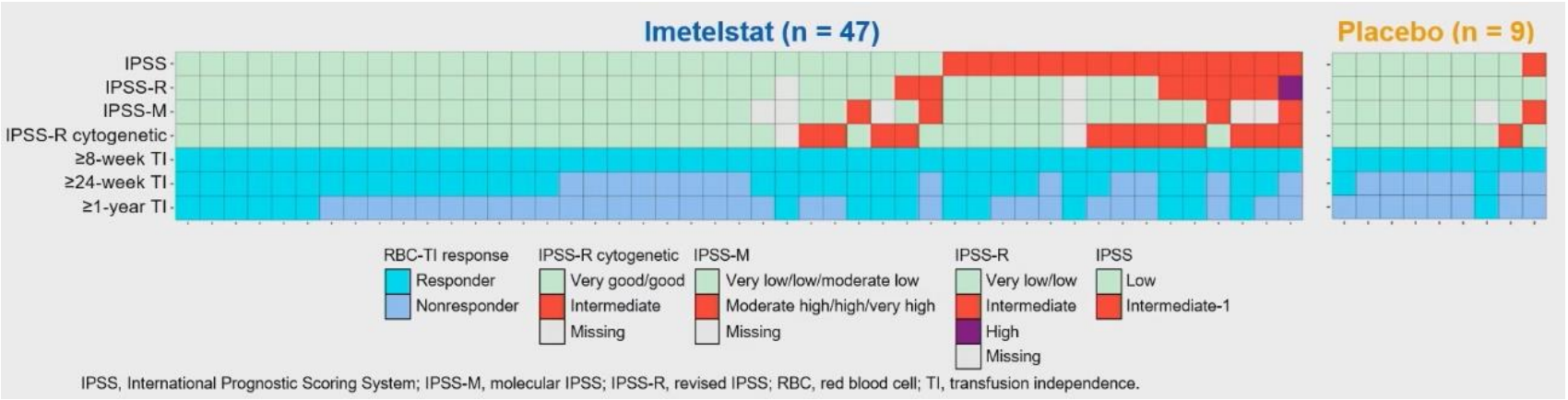
Fiorini E et al *Differentiation* 2018

Targeting the telomere ? Imetelstat as telomerase inhibitor



hTERT, human telomerase reverse transcriptase; hTR, human telomerase RNA component; WBC, white blood cell.
Mascarenhas J, et al. Future Oncol. 2022;18(22):2393-2402.

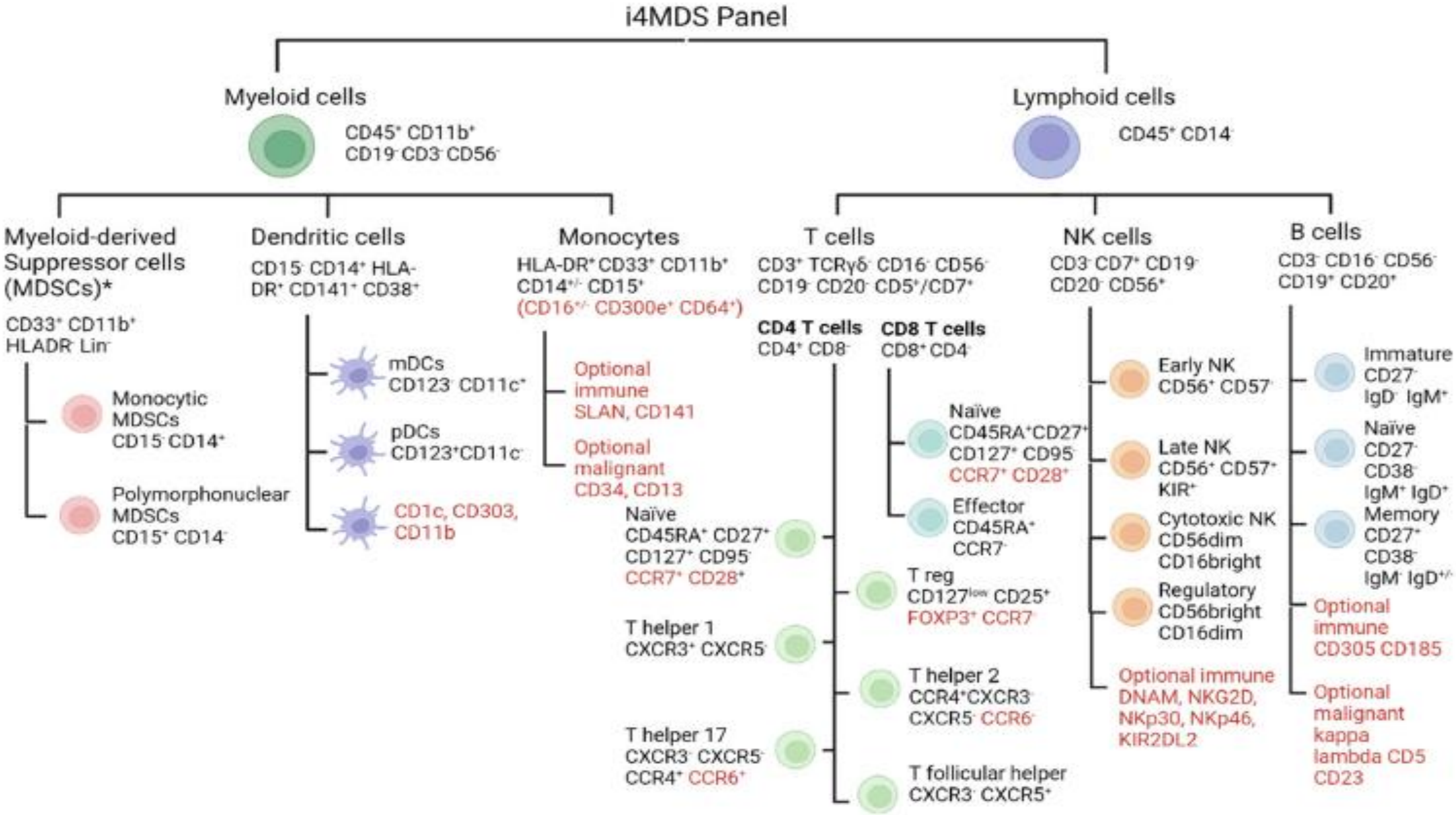




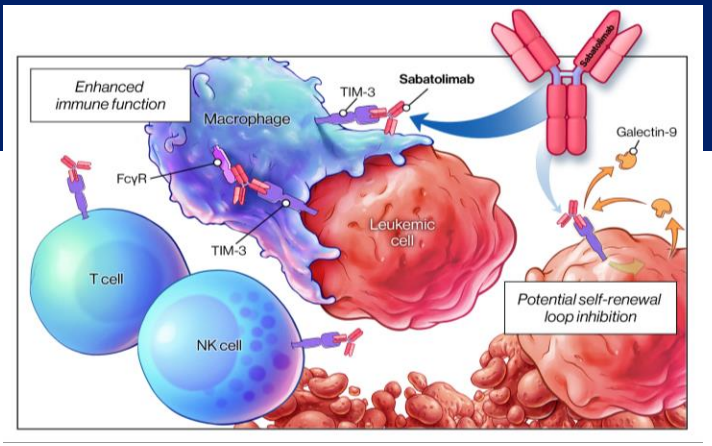
IPSS, International Prognostic Scoring System; IPSS-M, molecular IPSS; IPSS-R, revised IPSS; RBC, red blood cell; TI, transfusion independence.

Komrokji et al ASH 2023
Abstract #194

Can we obtain clinical success by targeting Immune dysregulation in MDS ?



Sabatolimab: anti-Tim3 ab in HR MDS



Randomized, double-blind, placebo-controlled, multi-centered Phase III study

530 Patients

- Aged ≥18 years with morphologically confirmed intermediate-, high- or very high-risk MDS[a], or CMML-2[b]
- Not eligible for HSCT or intensive chemotherapy

1:1 Randomization

Stratified by IPSS-R[c] and CMML

Sabatolimab IV Q4W
(800 mg on day 8 of each cycle)
+
Azacitidine SC or IV
(75 mg/m^2/day on days 1-7 or 1-5 and 8-9 of each cycle)
N=265

Placebo IV Q4W
(800 mg on day 8 of each cycle)
+
Azacitidine SC or IV
(75 mg/m^2/day on days 1-7 or 1-5 and 8-9 of each cycle)
N=265

28-day cycles until disease progression

Primary Endpoint:
Overall Survival

Key secondary endpoints:[d]
- Time to definitive deterioration of fatigue
- RBC transfusion-free intervals
- Improvement of fatigue
- Improvement of physical functioning
- Improvement of emotional functioning

Secondary endpoints included:
PFS, LFS and response rates

Target enrolment was 500 but patients who were in screening when the target was reached were randomized if they met the inclusion/exclusion criteria

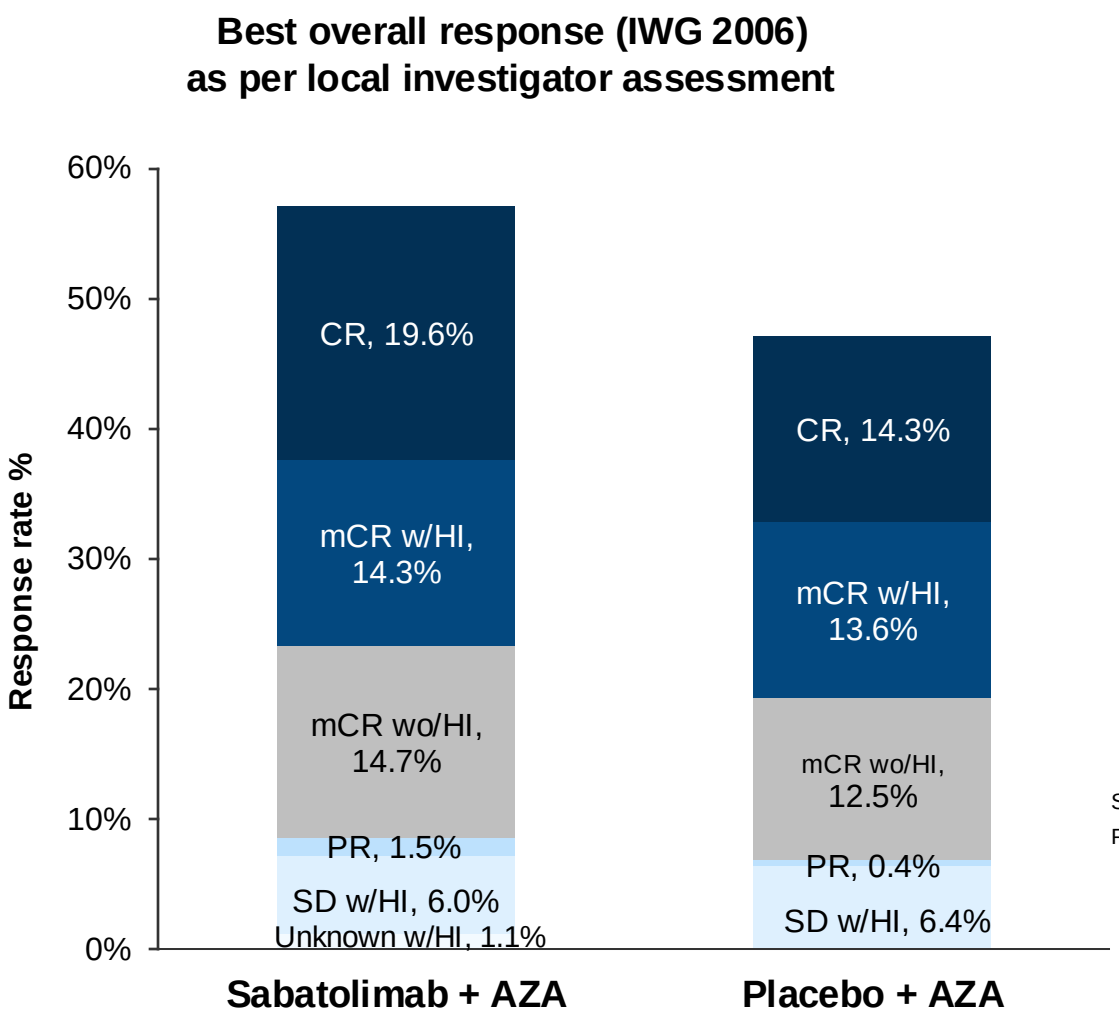
Randomization: Jun 15, 2020 - Jan 17, 2022
Primary analysis data cut-off: Sept 15, 2023
Median duration of follow-up (randomization to cut-off): 27.8 months

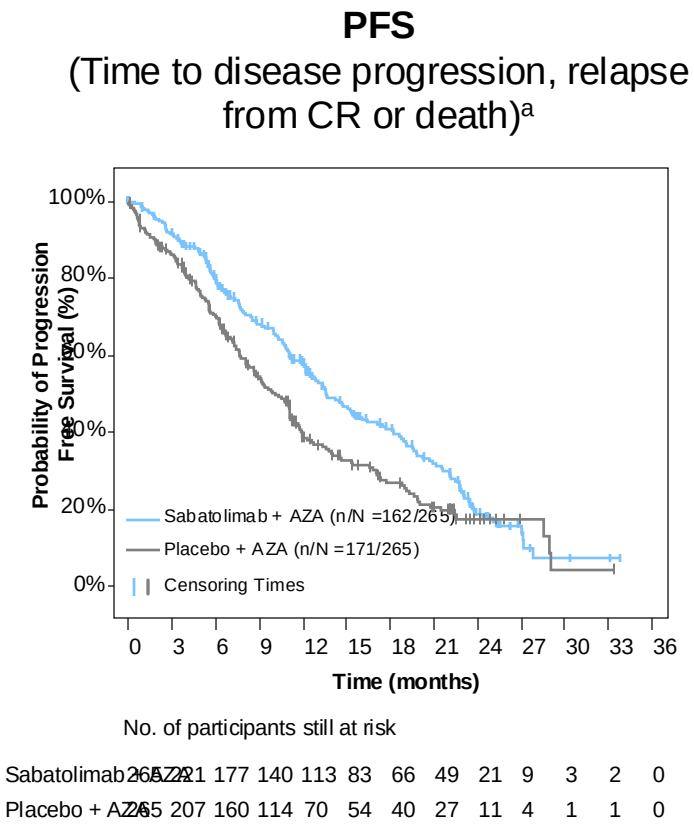
36 countries

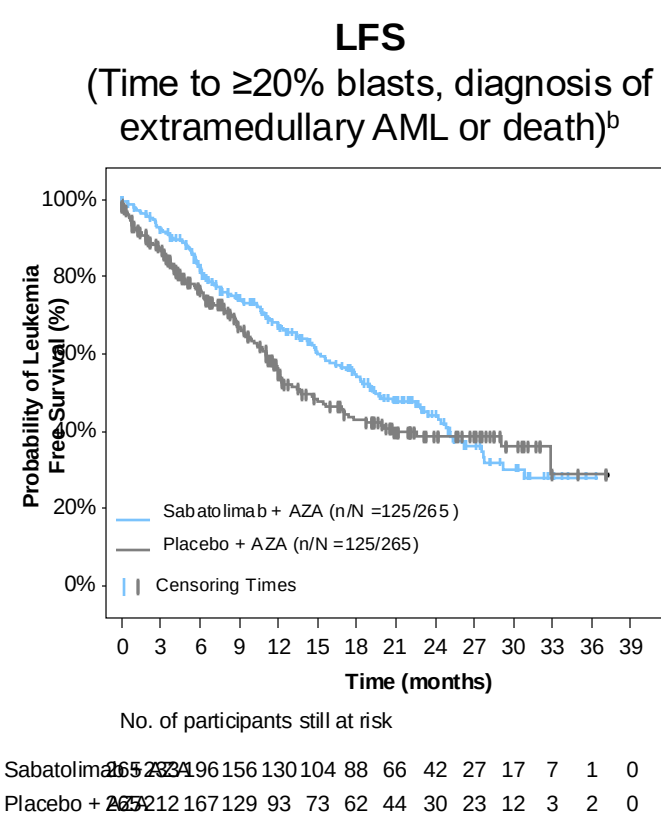
151 study centers

Oral presentation at: EHA 2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain, and online.

Best overall response







AZA, azacitidine; CI, confidence interval; CR, complete remission; (w/wo) HI, (with/without) hematological improvement; IWG, International Working Group; mCR, marrow CR; PD, progressive disease; PR, partial remission; SD, stable disease; w/wo, with/without. Full analysis set. [a]CR bone marrow assessments were performed less frequently than in the STIMULUS-MDS1 study and therefore CRs are not directly comparable; first assessment performed after 6 cycles. [b]HI must be concurrent with best overall response.

Oral presentation at: EHA 2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain, and online.

The multifaceted pathophysiology of MDS requires careful characterization of single cases and implementation of multiple targeting agents in combination or sequence

UNIVERSITÀ DEGLI STUDI FIRENZE

DIPARTIMENTO DI MEDICINA SPERIMENTALE E CLINICA

Azienda Ospedaliero Universitaria Careggi

INTERCEPT-MDS

THANKS !!!
From the MDS UNIT:

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Cristina Amato
Barbara Caciagli

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EMSCO MYELODYSPLASTIC SYNDROMES

FISiM FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

AIRC