Emerging Tx for High Risk MDS



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Bumrungrad International

Emerging Tx for High Risk MDS

What do we have, now?
What is the future hope?
Compare today and tomorrow

SUMMARY

Response Rate

Treatment	CR+mCR	Duration of response (Mo)
Azacitidine	15-20%	8-10
Venetoclax + Azacitidine	60-70%	12-14
Magrolimab (target CD47) + Azacitidine	33%	10-12
Sabatolimab (target TIM-3) + HMAs	40%	9-11

From ASH 2023, 2024

Progression to AML

Treatment	AML Transformation Rate
Azacitidine	30-40%
Venetoclax + Azacitidine	15-20%
Allo-SCT	<10%

From ASH 2023, 2024

OS : compare new std vs std treatment

Treatment	Med OS (mos)	1-yr OS	3-yr OS
Azacitidine (std)	12-14	50%	<10%
Venetoclax + Azacitidine	16-20%	65%	20%
Magrolimab (target CD47) Azacitidine	14-16%*	58%*	15%*
Allo HSCT	24-36	75%	40-50%

Magrolimab is during safety review by FDA (ASH 2023)

From ASH 2023, 2024

Safety profile

Treatment	Complication
Venetoclax + Azacitidine	Cytopenia (60%), infection (25%)
Magrolimab (target CD47) + Azacitidine	Anemia (58%), Infusion reaction (20%)
Imetelstat (telomerase inh)	Thrombocytopenia (45%), Fatigue (30%)
Allo-SCT	GVHD (40%), Infection (35%)

From ASH 2023, 2024

Conclusion : tx in HR MDS

- Venetoclax + Azacitidine -> best survival and respond rate, but more cytopenia
- Magrolimab -> good potential, but be careful about anemia
- Allo-HSCT -> only way to cure the dz in suitable patient

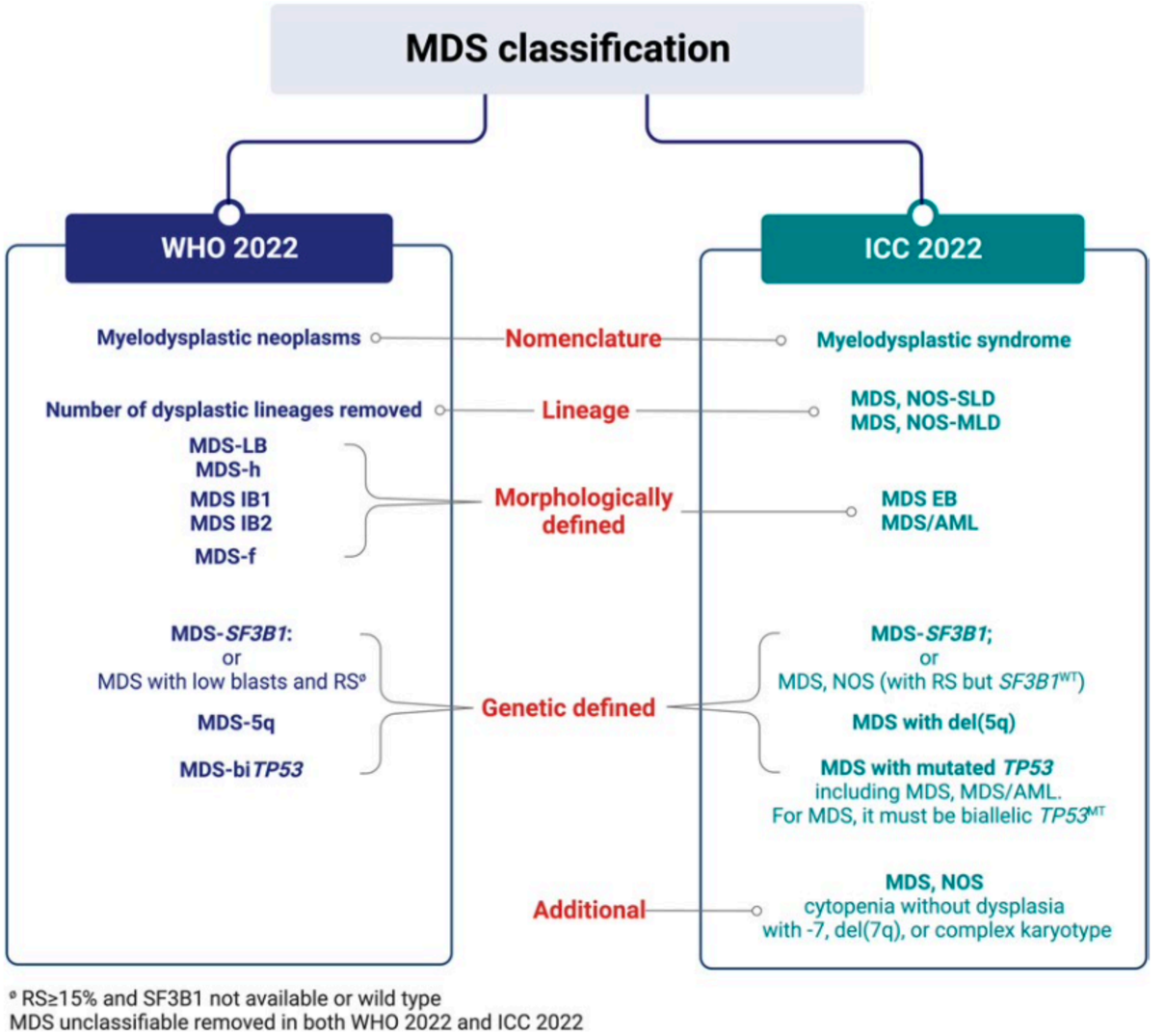


Figure 1. MDS classification comparison between WHO 2022 and ICC 2022. Bi, biallelic; f, fibrosis; h, hypocellular; IB, increased blasts; LB, low blasts; NOS-MLD, not otherwise specified with multi-lineage dysplasia; NOS-SLD, not otherwise specified with single-lineage dysplasia; NOS-MLD RS, ringed sideroblasts.

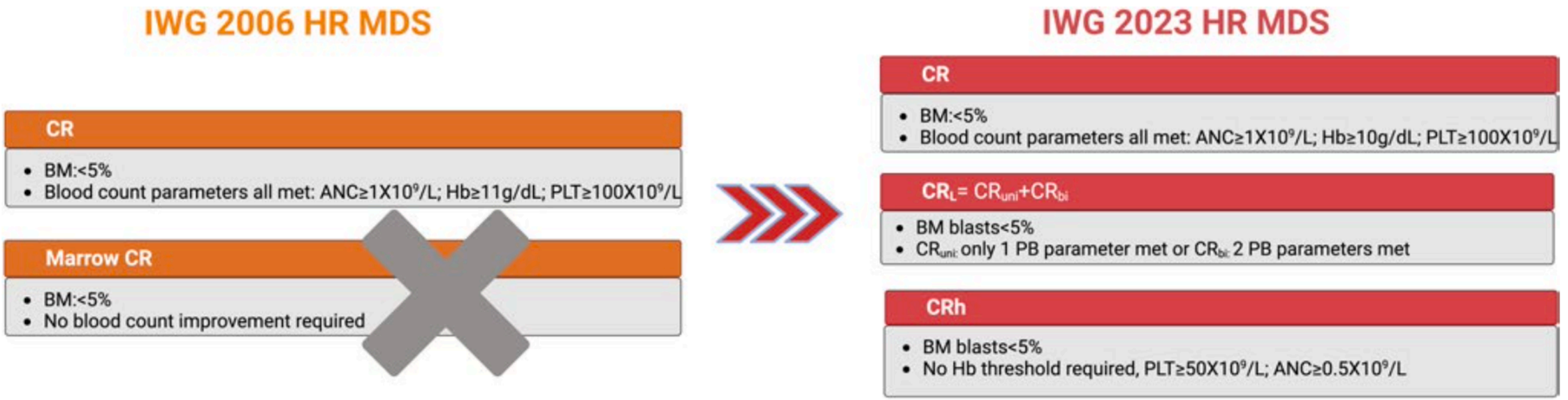


Figure 2. Comparison between IWG 2006 vs 2023 HR MDS response criteria. BM, bone marrow; CR_L, CR with limited count recovery; CRh, CR with partial hematologic recovery; CR_{bi}, CR with bilineage; CR_{uni}, CR with unilineage; Hb, hemoglobin; PB, peripheral blood; PLT, platelet.

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Historical Prognostic Scoring Systems for MDS

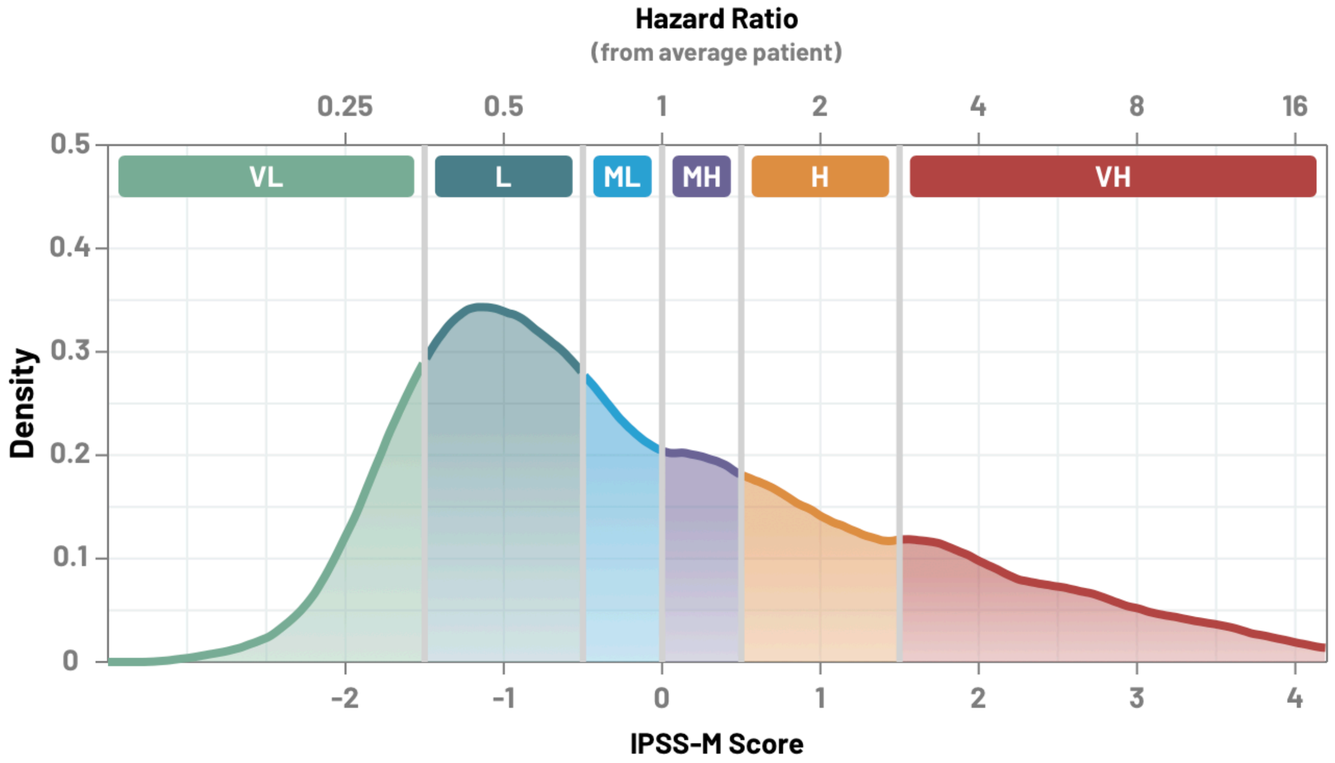
	Blasts	Cyto	HGB	Plts	ANC	Txn	Age	PS
1. IPSS (a bit out of date now)	✚	✚	✚	✚	✚		✚	
2. WPSS(time dependent)	✚	✚				✚		
3. MDS-LR (lower risk only)	✚	✚		✚		✚	✚	
4. MDAS (more variables)	✚	✚		✚	✚	✚	✚	✚
5. FPSS (higher risk + AZA)	✚	✚	✚			✚		✚
6. IPSS-R (most common)	✚	✚	✚	✚	✚		✚	✚

- None incorporated gene mutations
- Only WPSS was designed as a time-dependent model
- Prognostication for any individual is less certain
- None accounted for comorbidities
- None intended to predict benefit from any particular therapy

IPSS: Greenberg P, et al. *Blood*. 1997;89(6):2079-88.
IPSS-R: Greenberg PL, et al. *Blood*. 2012;120(12):2454-65.
WPSS: Malcovati L, et al. *J Clin Oncol*. 2007;25(23):3503-10.
MDAPP: Kantarjian H, et al. *Cancer*. 2008;113(7 Suppl):1933-52.

IPSS-M

(Molecular International Prognostic Scoring System)



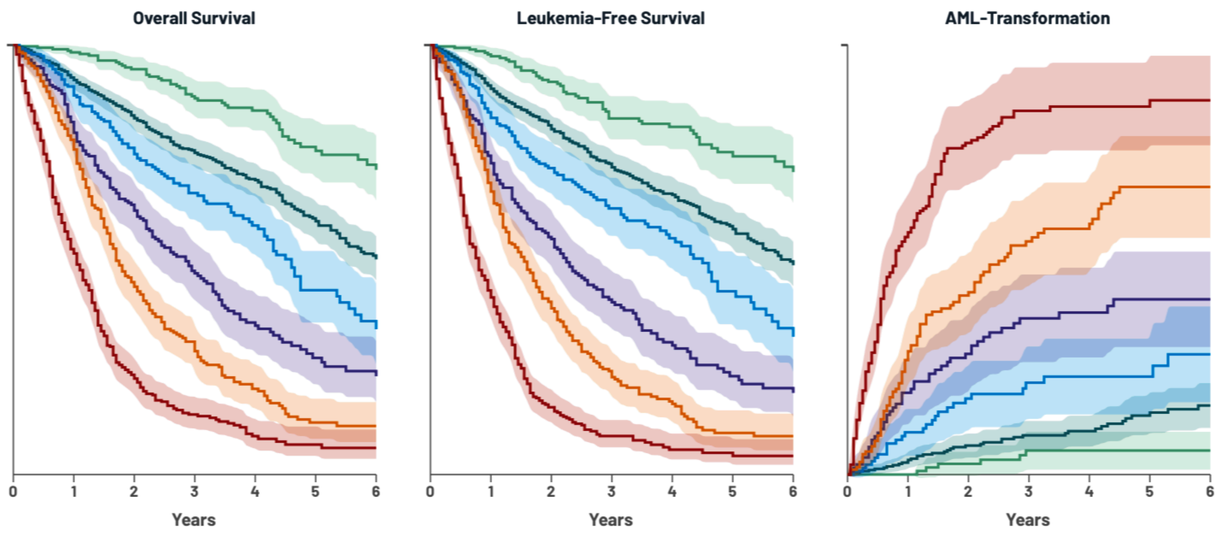
IPSS-M	Very Low	Low	Moderate Low	Moderate High	High	Very High
Patients, % (n=2,701)	14% (381)	33% (889)	11% (302)	11% (281)	14% (379)	17% (469)
Risk score	≤ -1.5	> -1.5 to -0.5	> -0.5 to 0	> 0 to 0.5	> 0.5 to 1.5	> 1.5
Hazard ratio* (95% CI)	0.51 (0.39 - 0.67)	1.0 reference	1.5 (1.2 - 1.8)	2.5 (2.1 - 3.1)	3.7 (3.1 - 4.4)	7.1 (6.0 - 8.3)
Median LFS, yrs 25-75% LFS range, yrs	9.7 5.0 - 17.4	5.9 2.6 - 12.0	4.5 1.6 - 6.9	2.3 0.91 - 4.7	1.5 0.80 - 2.8	0.76 0.33 - 1.5
Median OS, yrs 25-75% OS range, yrs	10.6 5.1 - 17.4	6.0 3.0 - 12.8	4.6 2.0 - 7.4	2.8 1.2 - 5.5	1.7 1.0 - 3.4	1.0 0.5 - 1.8
AML-t by 1 yr, % 2 yrs, % 4 yrs, %	0.0 1.2 2.8	1.7 3.4 5.1	4.9 8.8 11.4	9.5 14.0 18.9	14.3 21.2 29.2	28.2 38.6 42.8
Death w/o AML by 1 yr, % 2 yrs, % 4 yrs, %	2.2 7.0 15.9	8.5 16.2 29.5	12.0 19.8 33.6	18.0 31.1 51.1	19.3 39.8 54.2	30.6 45.6 51.3

Very Low | 14%
Low | 33%
Moderate Low | 11%
Moderate High | 11%
High | 14%
Very High | 17%

*Hazard ratio for risk of AML-t or death from the average patient.

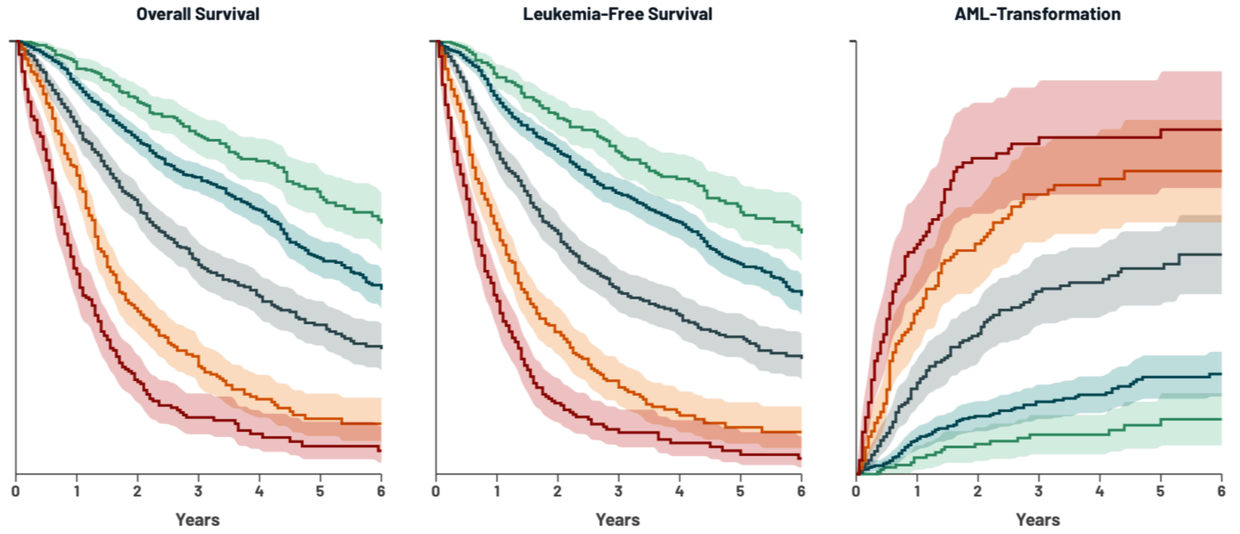
Bernard E, Tuechler H, Greenberg PL, et al, The Molecular International Prognosis Scoring System (IPSS-M) for risk stratification in myelodysplastic syndromes. New Eng J Med Evidence, 1(7). doi:10.1056/evidoa2200008. Study supported by the MDS Foundation.

Clinical Outcomes By IPSS-M

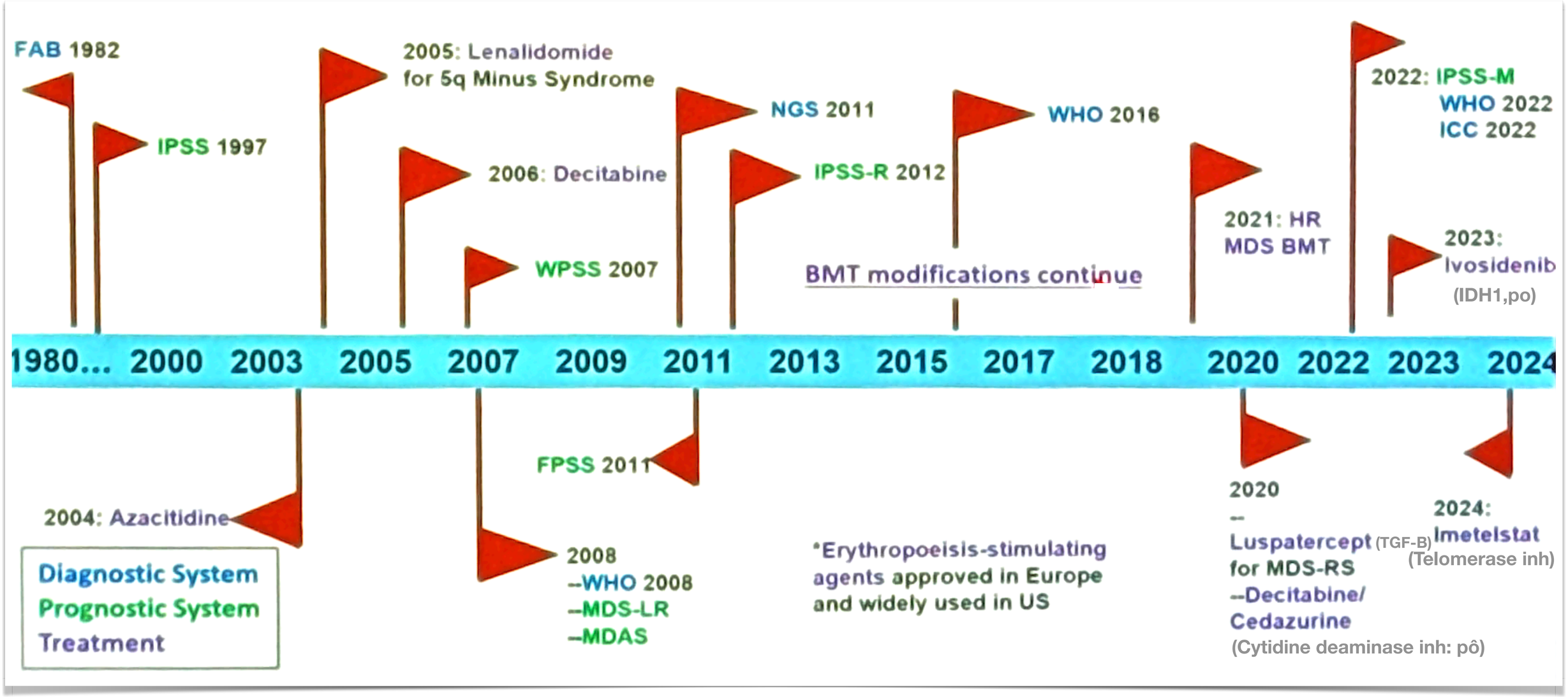


- Lower-risk MDS (VL,L and ML) median OS 6.3 yr (95% CI 5.8-7.2 yr)
- Higher-risk MDS (VH, H, and MH) median OS 1.5 yr (95% CI 1.4-1.6 yr)
- Compared with IPSS-R, IPSS-M re-stratified 46% of patients

Clinical Outcomes By IPSS-R



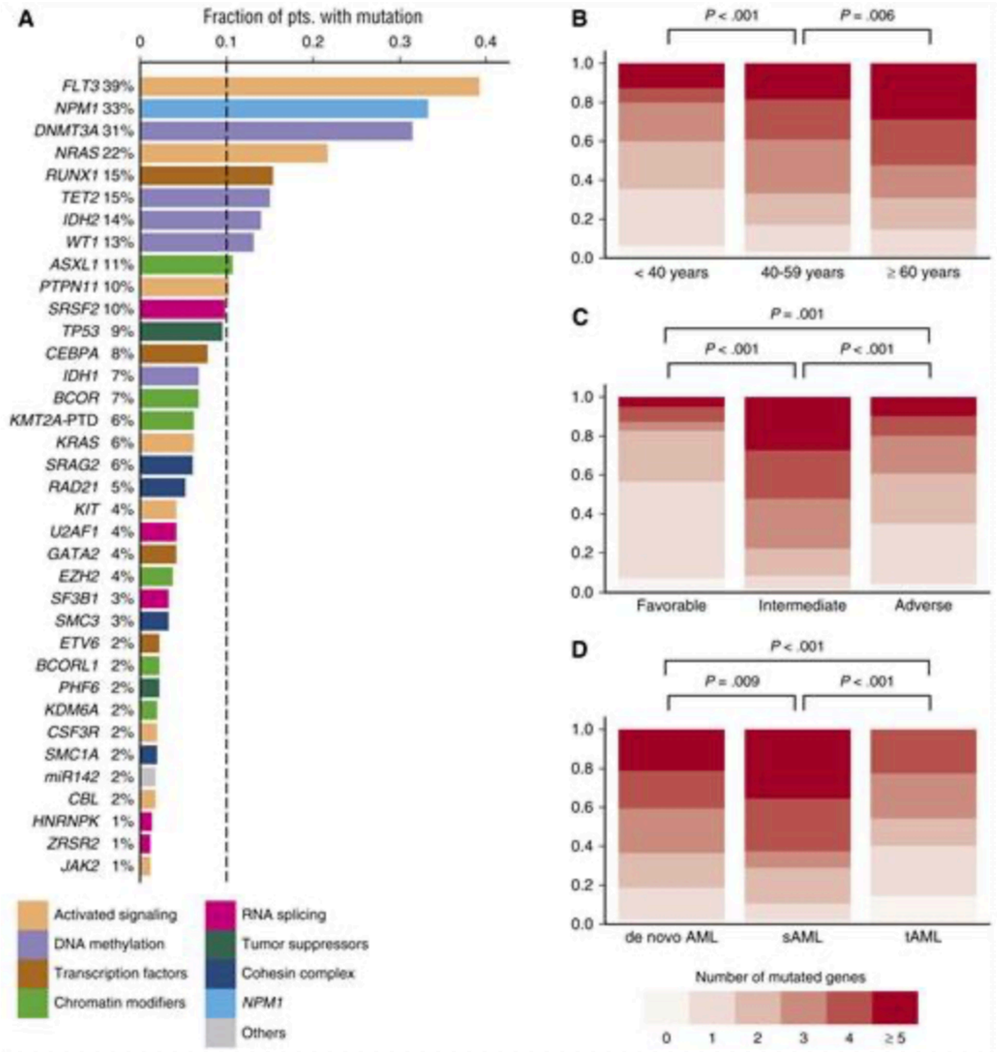
Evolution of Medical Knowledge in MDS



AML genetic abnormality

ELN 2022

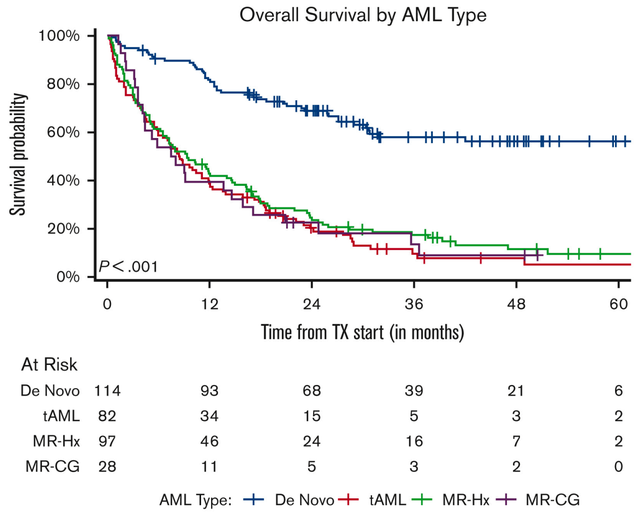
Risk category†	Genetic abnormality
Favorable	▪ t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ ▪ inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ *CBFB*::*MYH11*†,‡ ▪ Mutated *NPM1*†,§ without *FLT3*-ITD ▪ bZIP in-frame mutated *CEBPA*‖
Intermediate	▪ Mutated *NPM1*†,§ with *FLT3*-ITD ▪ Wild-type *NPM1* with *FLT3*-ITD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



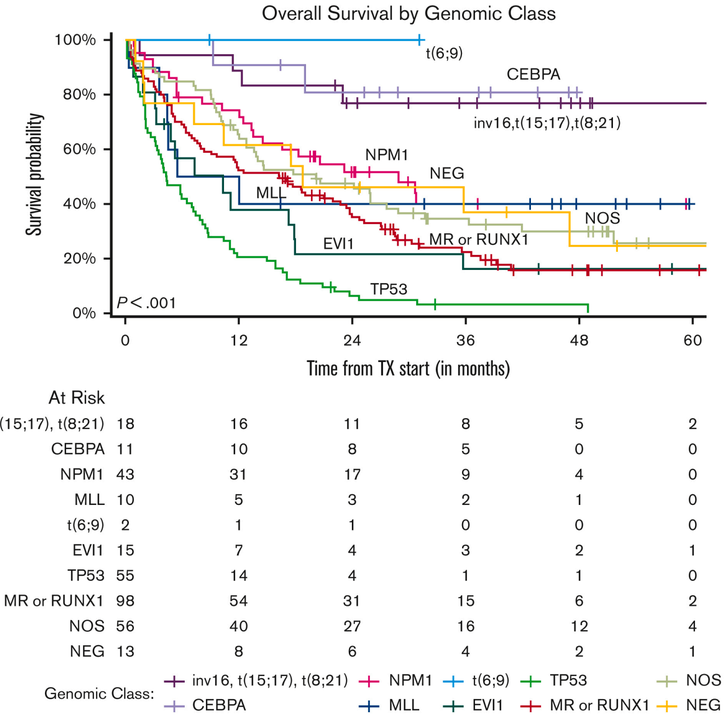
Haferlach C, et al. Blood 2016

Interaction between myelodysplasia-related gene mutations and ontogeny in acute myeloid leukemia

A



B



C

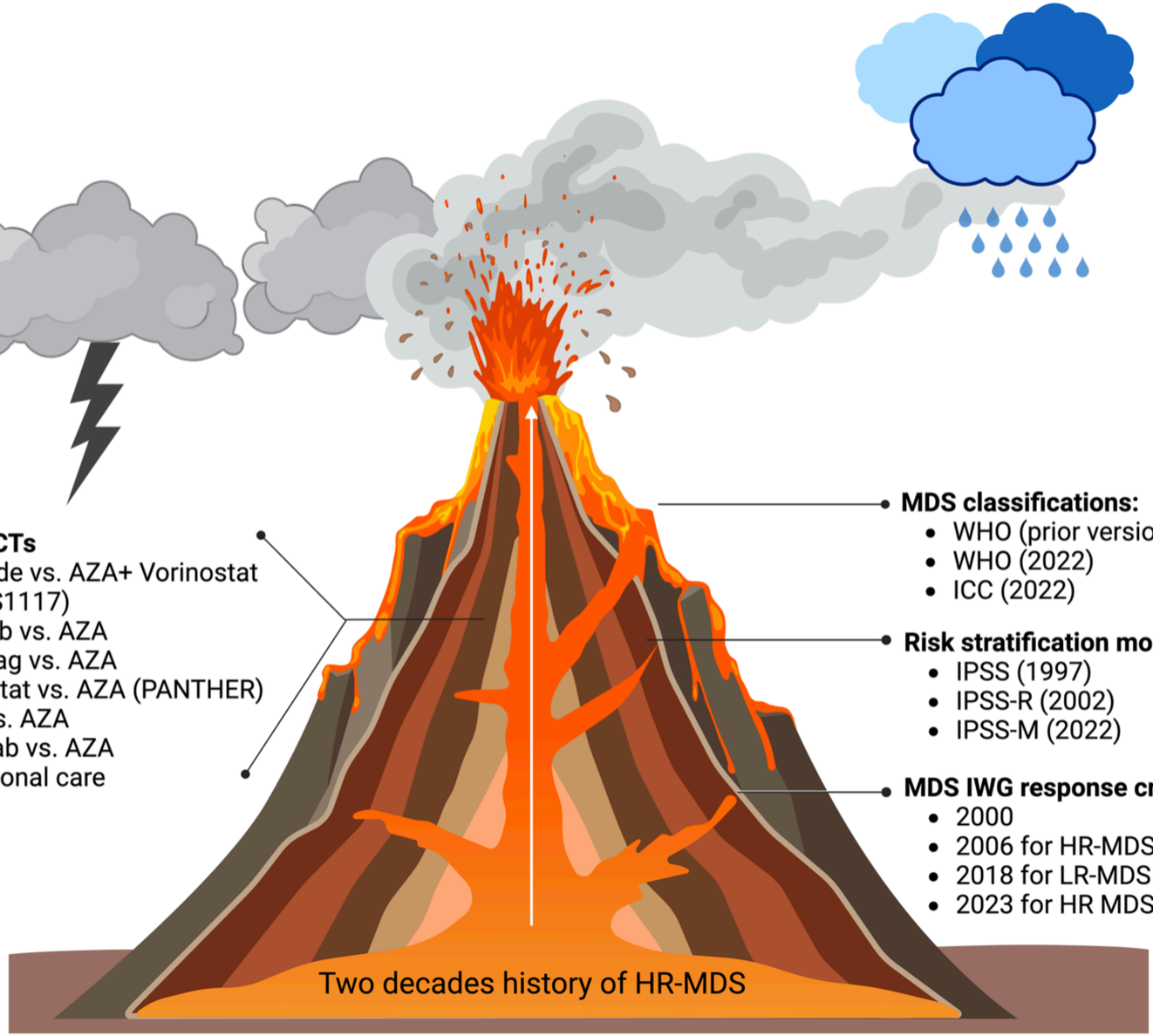
Cox PH model adjusting for age (as a cubic spline), treatment, transplant, AML type, and genomic class

Characteristic	HR[1]	95% CI[1]	*P*-value
Age[2]			**<.001**
Treatment			**<.001**
7+3	Ref.	Ref.	
Venetoclax + HMA/low DAC	0.83	0.44, 1.56	
HMA	0.87	0.55, 1.39	
Trial	1.18	0.76, 1.81	
None/Supportive Care	5.89	3.39, 10.3	
Transplant	0.60	0.40, 0.90	**.012**
AML Type			**<.001**
De Novo	Ref.	Ref.	
tAML	2.18	1.39, 3.43	
MR-Hx	2.41	1.58, 3.68	
MR-CG	2.31	1.32, 4.04	
Molecular Group			**<.001**
inv16, t(15;17), t(8;21)	Ref.	Ref.	
CEBPA	0.99	0.18, 5.57	
NPM1	4.06	1.34, 12.3	
MLL	3.51	0.94, 13.0	
t(6;9)	NE[3]	NE[3]	
EVI1	6.26	1.96, 20.0	
TP53	6.56	2.27, 19.0	
MR or RUNX1	3.91	1.35, 11.3	
NOS	3.28	1.13, 9.55	
NEG	2.93	0.85, 10.2	

[1] HR = Hazard Ratio, CI = Confidence Interval
[2] A cubic spline was used for the age covariate
[3] Not Estimable; No t(6;9) patients experienced an event

Joseph G. W. McCarter,David Nemirovsky,Christopher A. Famulare,Noushin Farnoud,Abhinita S. Mohanty,Zoe S. Stone-Molloy,Jordan Chervin,Brian J. Ball,Zachary D. Epstein-Peterson,Maria E. Arcila,Aaron J. Stonestrom,Andrew Dunbar,Sheng F. Cai,Jacob L. Glass,Mark B. Geyer,Raajit K. Rampal,Ellin Berman,Omar I. Abdel-Wahab,Eytan M. Stein,Martin S. Tallman,Ross L. Levine,Aaron D. Goldberg,Elli Papaemmanuil,Yanming Zhang,Mikhail Roshal,Andriy Derkach,Wenbin Xiao, Interaction between myelodysplasia-related gene mutations and ontogeny in acute myeloid leukemia, Blood Adv, 2023, Figure 3.

Haferlach C, et al. Blood 2016



Selected historical RCTs

- AZA+Lenalidomide vs. AZA+ Vorinostat vs. AZA (SWOG S1117)
- AZA+ Durvalumab vs. AZA
- AZA+ Eltrombopag vs. AZA
- AZA + Pevonedistat vs. AZA (PANTHER)
- AZA+ APR-246 vs. AZA
- AZA+ Sabatolimab vs. AZA
- AZA vs. Conventional care

MDS classifications:

- WHO (prior versions)
- WHO (2022)
- ICC (2022)

Risk stratification models:

- IPSS (1997)
- IPSS-R (2002)
- IPSS-M (2022)

MDS IWG response criteria:

- 2000
- 2006 for HR-MDS
- 2018 for LR-MDS
- 2023 for HR MDS

Phase 3 RCTs:

- AZA+Venetoclax
- AZA+ Sabotolimab (TIM-3)
- AZA+ Magrolimab (CD47)
- AZA+ Tamibarotene (STAT1/3)

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Table 1. Randomized trials in higher-risk MDS

Trial name	Phase	Investigational arm	Control arm*	Patient population	Eligibility	Primary endpoint	Results of primary endpoint	Secondary endpoint	Reference #
SWOG S1117	2	azacitidine + lenalidomide (10 mg/day days 1–21)	azacitidine	HR-MDS/CMML	Blasts ≥5%; IPSS ≥1.5	↑ ORR 20% (CR/PR/HI)	49% vs 38% ($P = 0.16$)	No improvement in OS	[27]
SWOG S1117	2	azacitidine + vorinostat (300 mg twice daily on days 3–9)	azacitidine	HR-MDS/CMML	Blasts ≥5%; IPSS ≥1.5	↑ ORR 20% (CR/PR/HI)	27% vs 38%; ($P = 0.16$)	11.6 versus 16.7 months (p=0.74)	[27]
E1905 Study	2	azacitidine + entinostat (4 mg/m^2/day on days 3 and 10)	azacitidine	Therapy-related MDS/AML	Any IPSS	CR, PR, or trilineage HI	17% vs 46%	OS versus 13 months	[28]
FUSION-AML-001 (MDS Cohort)	2	azacitidine + durvalumab (1500 mg IV q 4 weeks)	azacitidine	Int to very high MDS	IPSS-R int to very high	ORR (CR, mCR, HI)	61.9% vs 47.6% ($P = 0.18$)	No Increase PDL1 on BM Blasts	[29]
SUPPORT	3	azacitidine + eltrombopag (200 mg/day, up to 300 mg/day)	azacitidine	Int to HR-MDS	int-1, int-2, high IPSS	Platelet transfusion-free interval	16% vs 31% ($P = 0.001$)	ORR 20% vs 35%	[25]
NCT02610777	2	azacitidine + pevonedistat (20 mg/m^2 IV days 1,3,5)	azacitidine	HR-MDS/CMML/ oligoblastic AML	IPSS-R int to very high	OS	21.8 vs 19.0 months ($P = 0.334$)	EFS 20.2 vs 14.8 months ($p = 0.045$) for HR-MDS	[34]
NCT03745716	3	azacitidine + eprenetapopt (4.5 g IV days 1–4)	azacitidine	*TP53* mutant HR-MDS	IPSS-R int to very high	CR	34.6% vs 22.4%; $P = 0.13$	NA	NA
PANTHER	3	azacitidine + pevonedistat (20 mg/m^2 IV days 1,3,5)	azacitidine	HR-MDS/CMML/ oligoblastic AML	IPSS-R int to very high	EFS	17.7 months vs 15.7 months ($P = 0.447$)	OS 21.6 vs17.5 (0.293) in HR-MDS	[26]
STIMULUS-MDS1	2	azacitidine/decitabine + sabatolimab (400 mg day 8 and 22)	azacitidine/ decitabine	Int to very high MDS	IPSS-R int to very high	CR and PFS	PFS 11.1 vs 8.5 months ($P = 0.102$); CR 21.5% vs 17.7% ($P = 0.769$)	Lower risk and <10% blasts with improved PFS	[30]
STIMULUS-MDS2	3	azacitidine + sabatolimab (800 mg day 8)	azacitidine	Int to very high MDS/CMML-2	IPSS-R int to very high	OS			
ENHANCE	3	azacitidine + magrolimab (priming/loading over C1–2; C3+30 mg/kg days 1 and 15)	azacitidine	Int to very high MDS	IPSS-R int to very high	CR and OS			
VERONA	3	azacitidine + venetoclax (400 mg days 1–14)	azacitidine	Int to very high MDS; excludes t-MDS	IPSS-R int to very high	OS			

*Azacitidine 75 mg/m^2 in all studies with exception of E19905 study, which used 50mg/m^2×10 days).

BM, bone marrow; CMML, chronic myelomonocytic leukemia; HI, hematologic improvement; Int, intermediate; IPSS-R, revised International Prognostic Scoring System; mCR, marrow CR; PR, partial remission.

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Azacitidine, the unbeaten standard of care for HR-MDS

There has been ***only 1 positive*** randomized ***control*** trial in patients with HRMDS, which was ***azacitidine vs conventional*** care regimens. This trial showed an ***improved OS of 24.5 vs 15 months***. Unfortunately, ***real world data***, including current prospective clinical trials, ***have shown inferior outcomes***, with median ***OS*** ranging from ***14 to 19 months***. In addition, many randomized clinical trials (RCTs) comparing novel therapies vs azacitidine have failed.

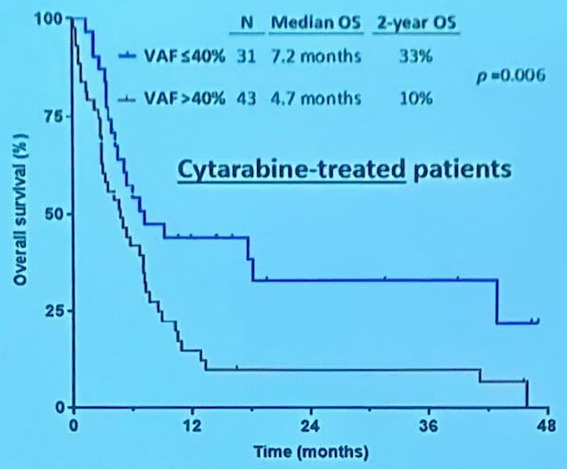
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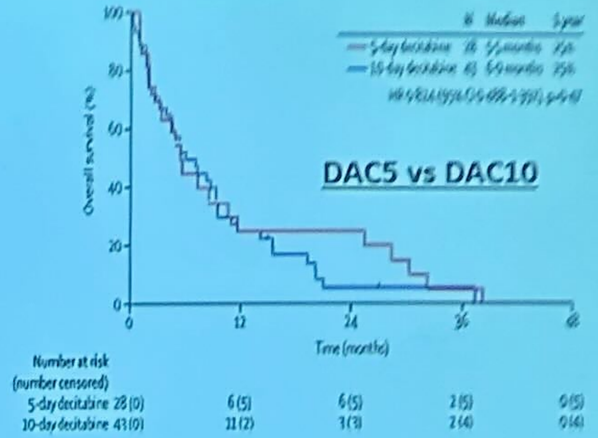
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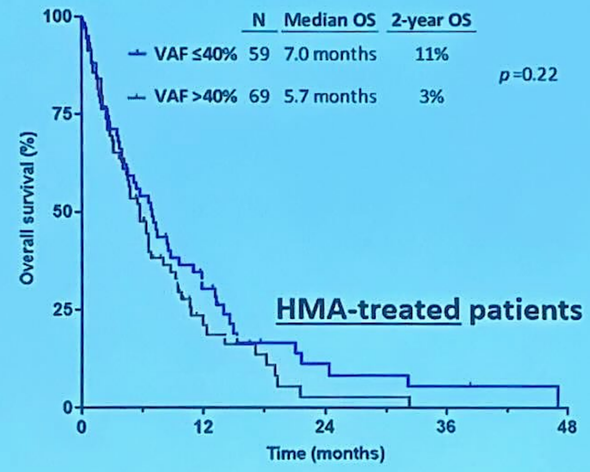
Impact of *TP53 mutations* in MDS/AML therapies

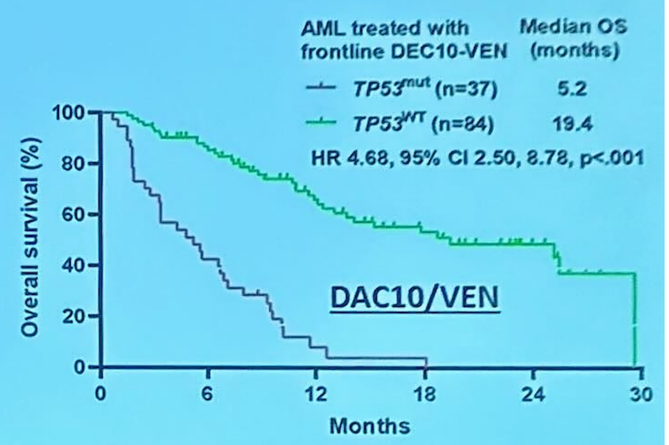
Current therapies in *TP53*m MDS/AML

- **Hypomethylating agents** (HMA) result in 15-20% CR and 40-45% ORR, similar to *TP53* wildtype patients
- Despite HMA responses, significantly inferior OS in *TP53* mutant patients (6-12 months)
- No Improvement in extended decitabine duration +/- **venetoclax** in AML
- **IC** maybe an option for patients with *TP53* subclone (40% single hit)



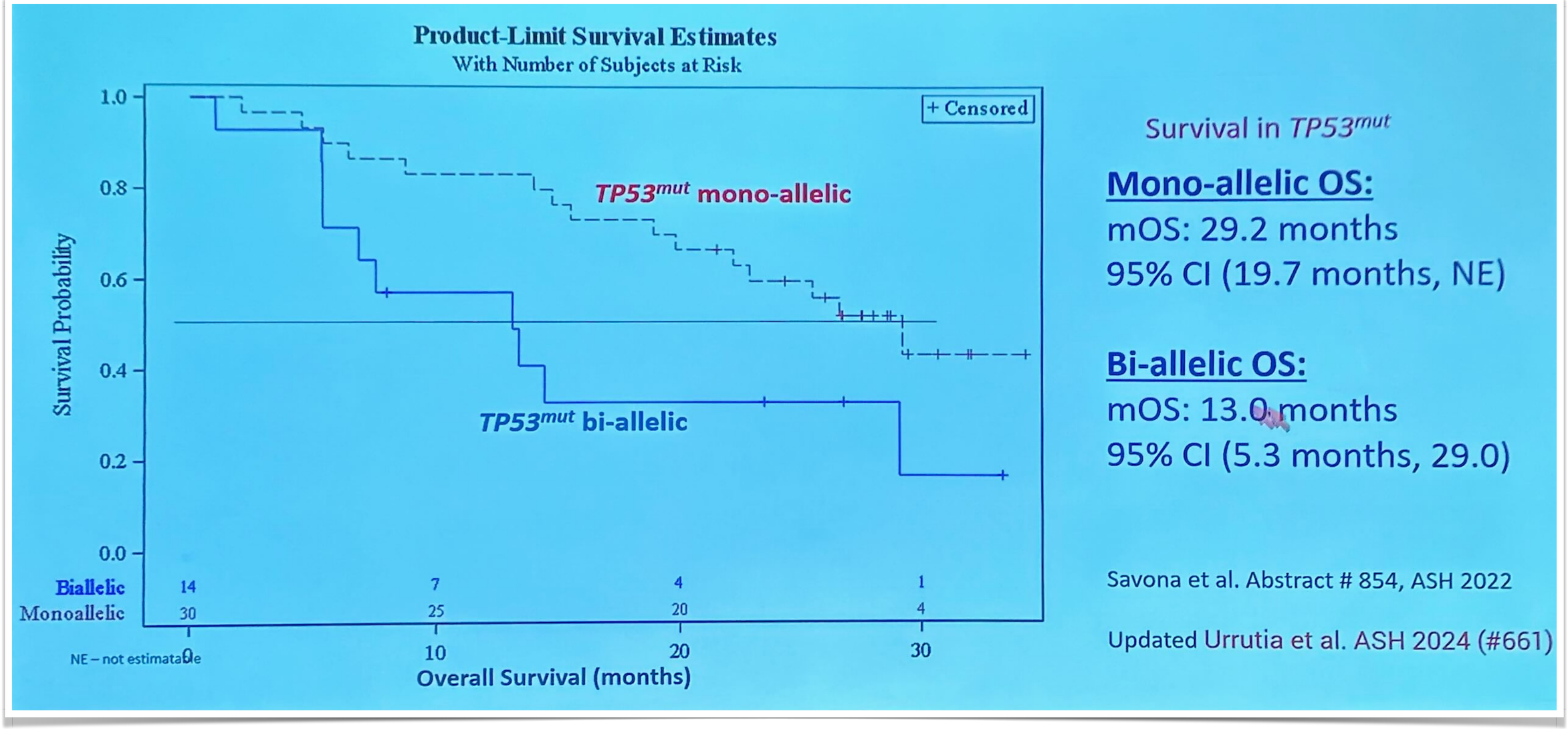






Bally C, et al. Leuk Res. 2014; Welch JS, et al. NEJM 2016; Haase D, et al. Leukemia 2019; Bejar R, et al. JCO. 2014; Lindsley R et al. NEJM 2017; Della Porta MG et al. JCO 2016; Yoshizato T, et al. Blood 2017; Sallman et al. Leukemia 2016; DiNardo C ,et al. Blood 2019; Wei A, et al. J Clin Oncol, 2019. Hunter A et al., Blood Advances 2021; **Short et al., Lancet Haematology 2019; Short N et al., Blood Adv 2020; Kim K, et al. Cancer. 2021**

Prolonged Survival in Mono-allelic TP53-Mutated ($TP53^{mut}$) MDS Subjects Treated With *Decitabine/Cedazuridine* in the ASCERTAIN Trial (ASTX727-02)



Survival in *TP53mut*

Mono-allelic OS:

mOS: 29.2 months

95% CI (19.7 months, NE)

Bi-allelic OS:

mOS: 13.0 months

95% CI (5.3 months, 29.0)

Savona et al. Abstract # 854, ASH 2022

Updated Urrutia et al. ASH 2024 (#661)

A *Weekly Low-Dose* **Regimen of** *Decitabine and Venetoclax* **In** *TP53*-**mutated** *AML/MDS* **(ongoing, NCT05184842)**

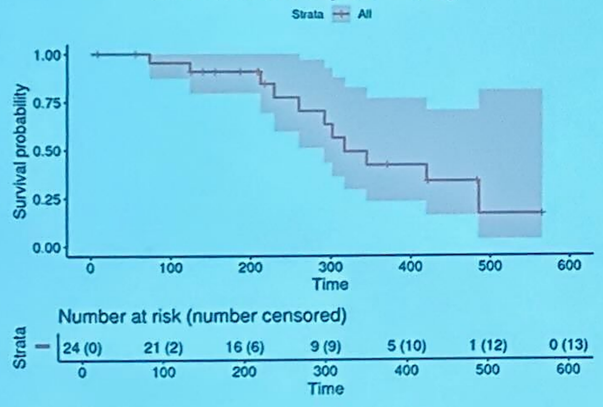
Week 1-12 (Induction phase) → Week 13 and beyond (Long-term treatment phase)

Treatment (28-day cycles):

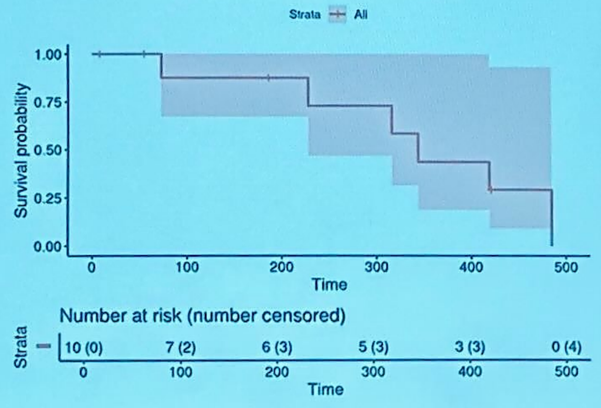
- Venetoclax 400 mg on days 1, 8, 15, 22
- Decitabine 0.2 mg/kg SQ on days 1, 8, 15, 22

Cohort	AML ITT (n = 10) n (%)	AML ITT-PP (n = 7) * n (%)	HR-MDS (n = 14) n (%)
ORR (CR + CRi) ORR (CR + mCR)	4 (40%)	4 (57%)	9 (64%)
Overall Survival	11.3 months		9.9 months

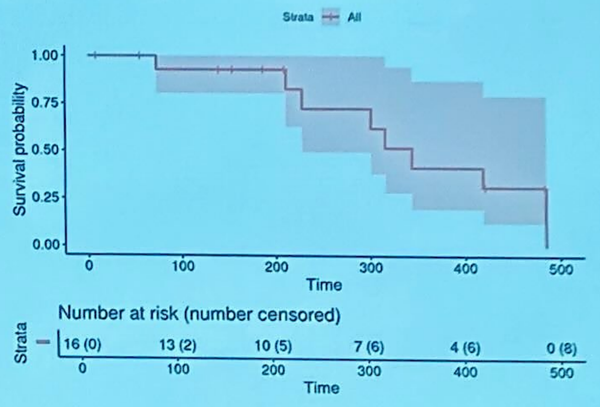
Entire Cohort (MDS + AML, n =24)
10.4 months (9.6 – NR)



AML (n=10)
11.3 months (7.5 – NR)

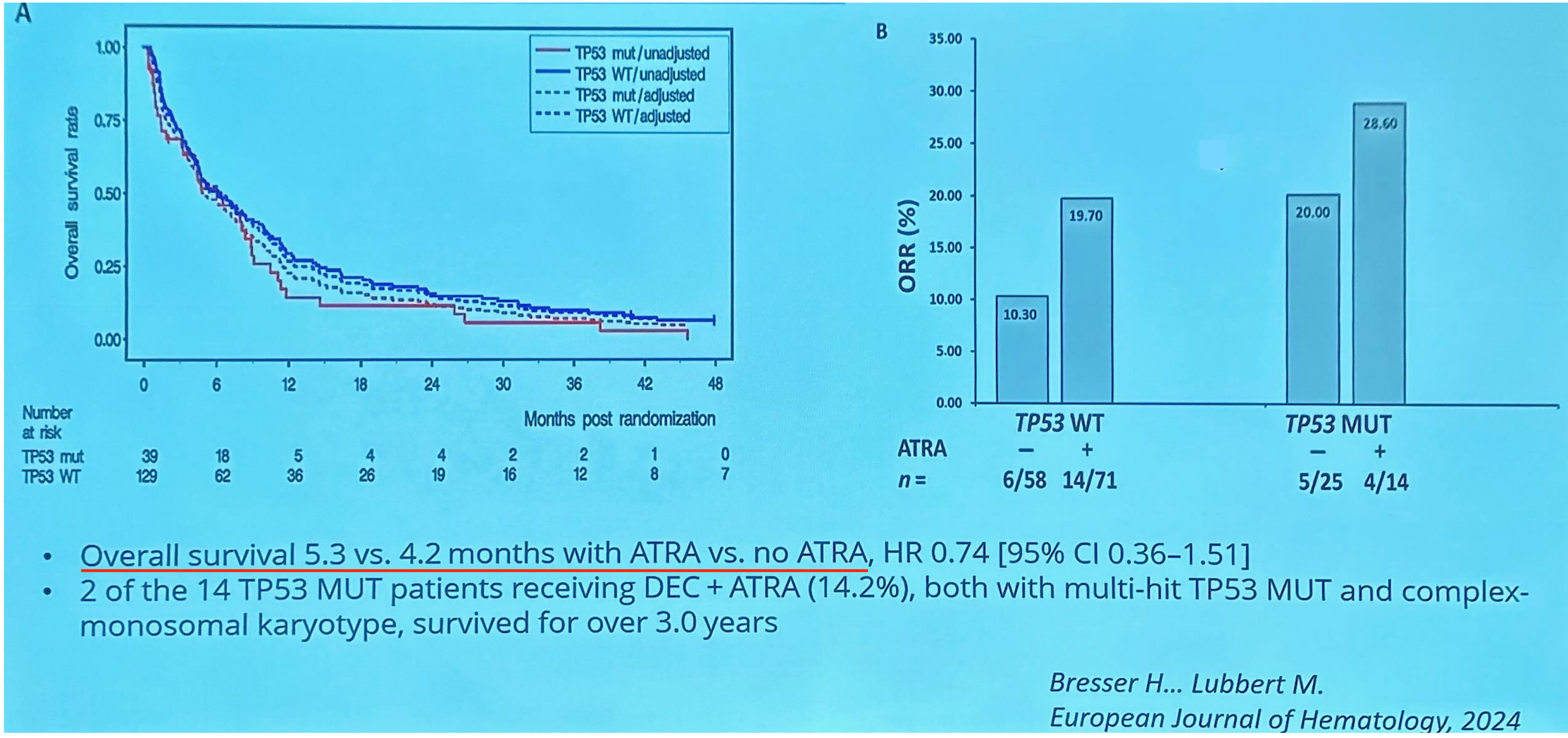


>/= 10% blasts (n=16)
11.3 months (7.5 – NR)



Goldfinger M. et al., Blood 2024 Sep 24; and unpublished

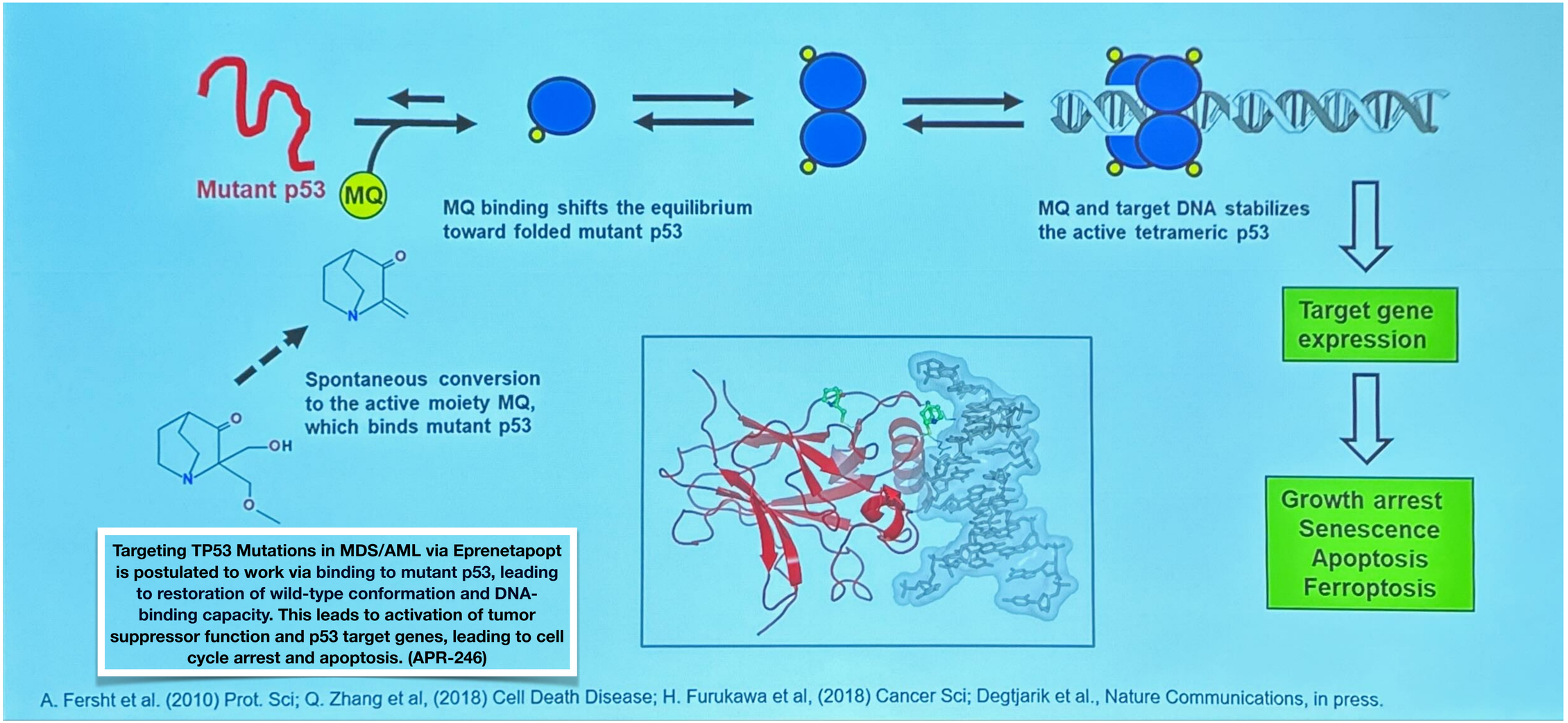
ATRA **combined** *with decitabine* **in** *TP53* **mutated Elderly AML**
DECIDER randomized trial (AMLSG 14-09)



- Overall survival 5.3 vs. 4.2 months with ATRA vs. no ATRA, HR 0.74 [95% CI 0.36–1.51]
- 2 of the 14 TP53 MUT patients receiving DEC + ATRA (14.2%), both with multi-hit TP53 MUT and complex-monosomal karyotype, survived for over 3.0 years

Bresser H... Lubbert M.
European Journal of Hematology, 2024

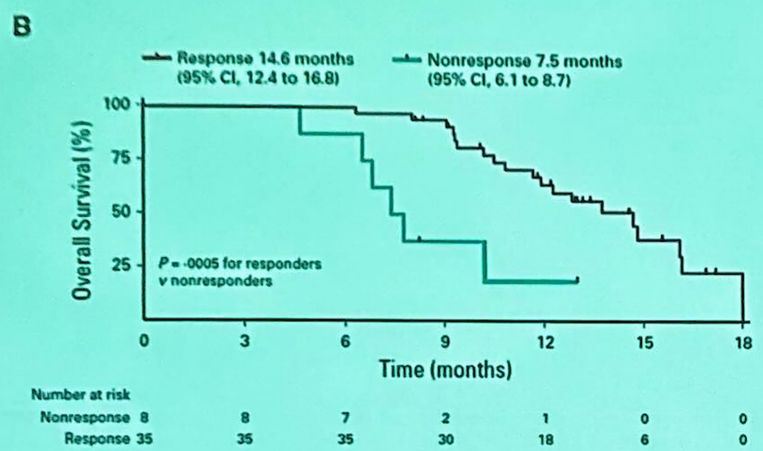
Targeting TP53 Mutations in MDS/AML via Eprenetapopt (APR-246)

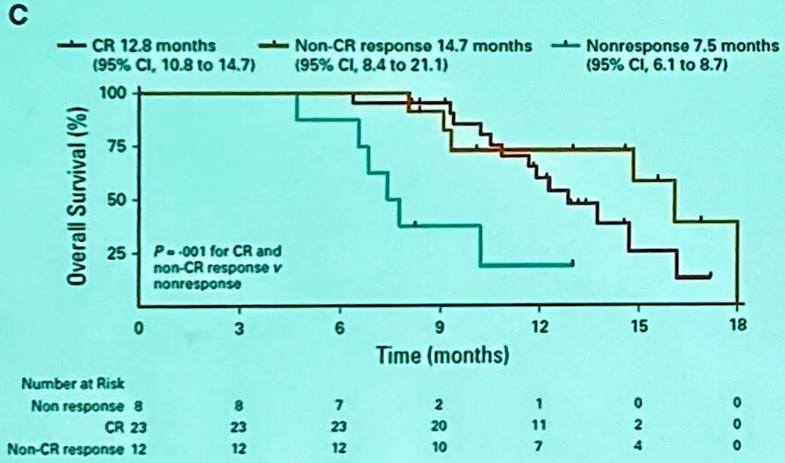


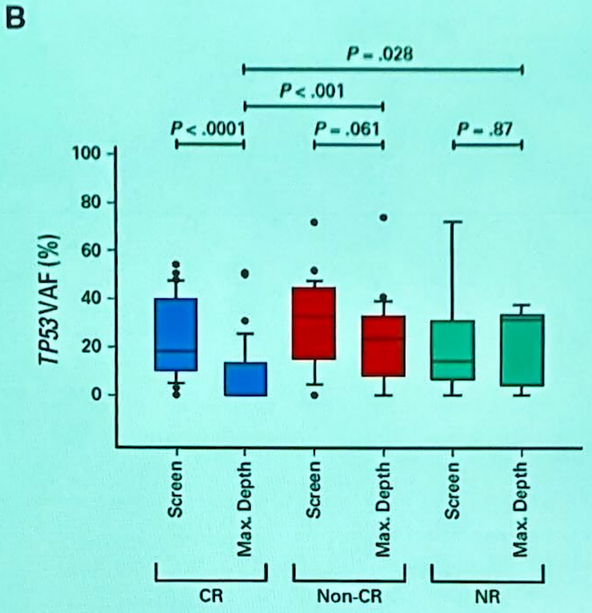
Targeting TP53 Mutations in MDS/AML via Eprenetapopt is postulated to work via binding to mutant p53, leading to restoration of wild-type conformation and DNA-binding capacity. This leads to activation of tumor suppressor function and p53 target genes, leading to cell cycle arrest and apoptosis. (APR-246)

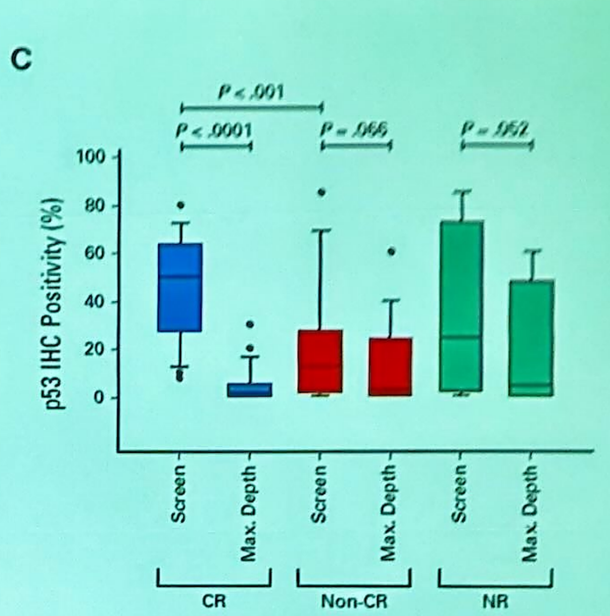
A. Fersht et al. (2010) Prot. Sci; Q. Zhang et al, (2018) Cell Death Disease; H. Furukawa et al, (2018) Cancer Sci; Degtjarik et al., Nature Communications, in press.

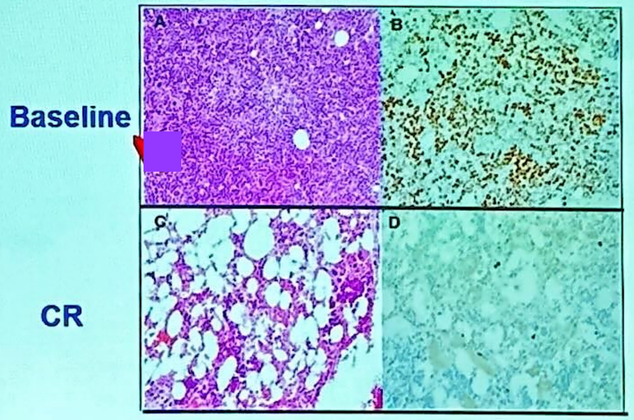
Eprenetapopt **(APR-246) and** *Azacitidine* **in** *TP53*-**Mutant** *MDS*









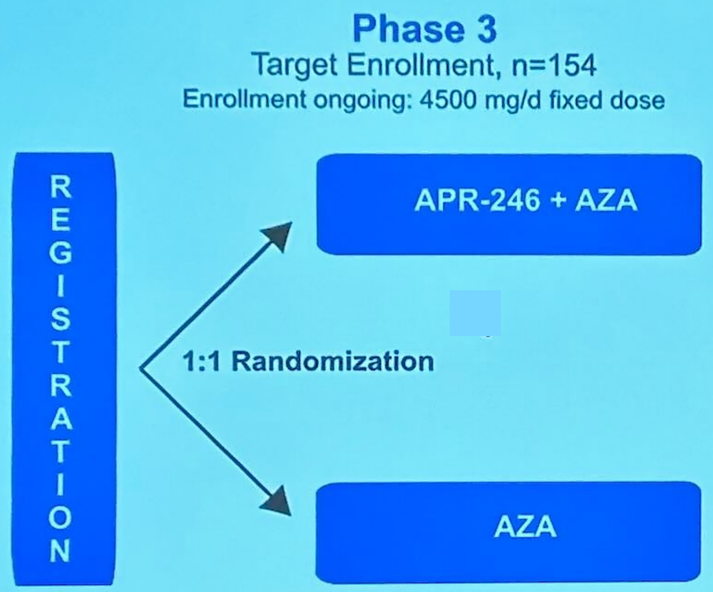


- Patients with ≥ 10% p53 IHC⁺ BM-MNCs was predictive of CR (66% vs 13%; P =0.01)

Sallman D et al., JCO 2021

Pivotal Phase 3 MDS Trial in TP53 Mutant MDS

- Randomized study of frontline azacitidine ± APR-246 in *TP53* mutant MDS



- Intermediate/High/Very High Risk *TP53* mutant MDS
- Primary endpoint: CR rate
- Secondary endpoints: ORR, DoR, PFS, LFS, OS, transplant rate

- Status

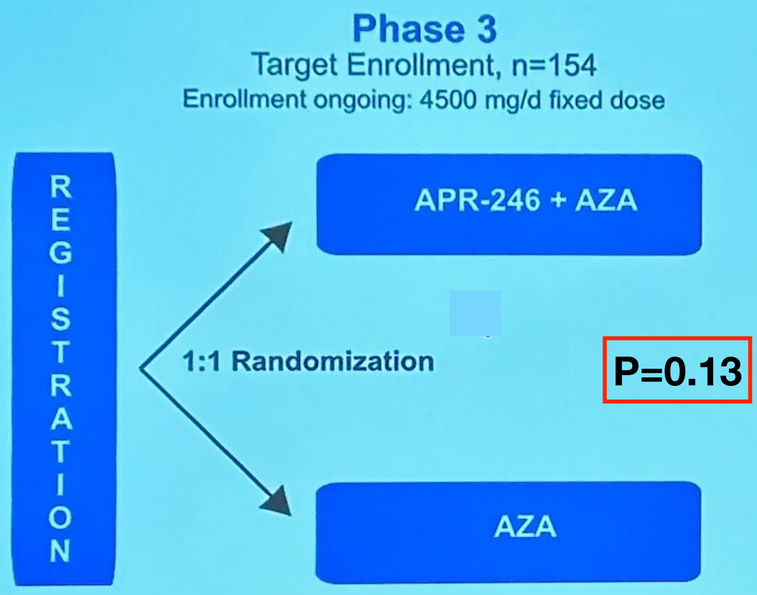
The trial failed to meet its primary endpoint of complete remission (CR) rate

- CR rate was higher in eprenetapopt with AZA arm compared to AZA alone, but did not reach statistical significance
- 33.3% (95% CI: 23.1% - 44.9%) compared to 22.4% (95% CI: 13.6% - 33.4%) in the AZA alone arm (P = 0.13).

ClinicalTrials.gov NCT03745716

Pivotal Phase 3 MDS Trial in TP53 Mutant MDS

- Randomized study of frontline azacitidine ± APR-246 in *TP53* mutant MDS



CR 33.3%

P=0.13

CR 22.4%

- Intermediate/High/Very High Risk *TP53* mutant MDS
- Primary endpoint: CR rate
- Secondary endpoints: ORR, DoR, PFS, LFS, OS, transplant rate

- Status

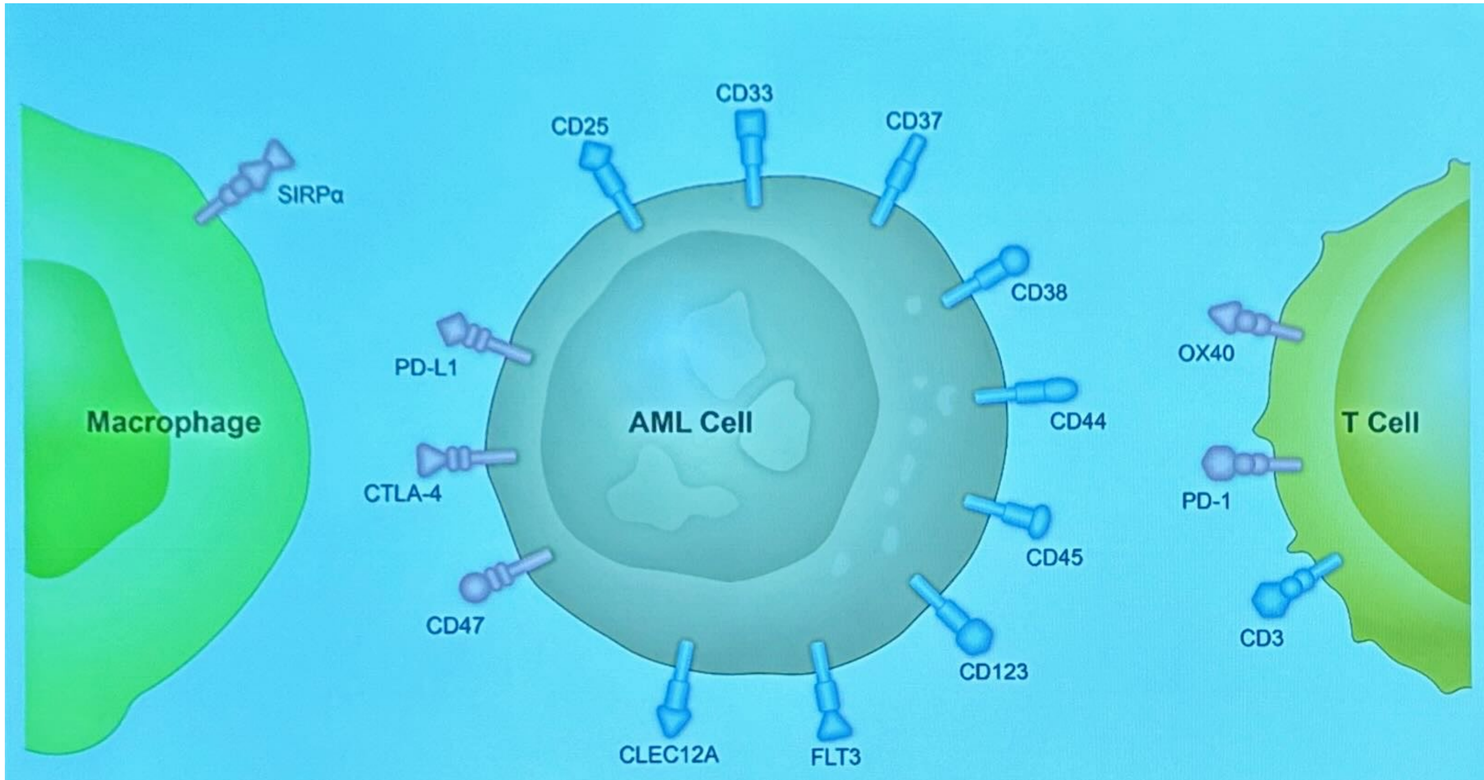
The trial failed to meet its primary endpoint of complete remission (CR) rate

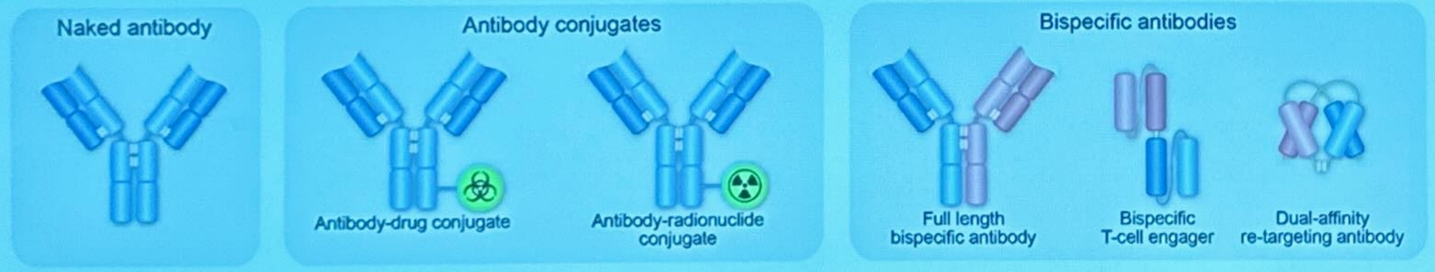
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ClinicalTrials.gov NCT03745716

New drugs and new hope

Immune Based Approaches in AML





Short N....Daver N, et al, Cancer Discovery 2020

Two major approaches:

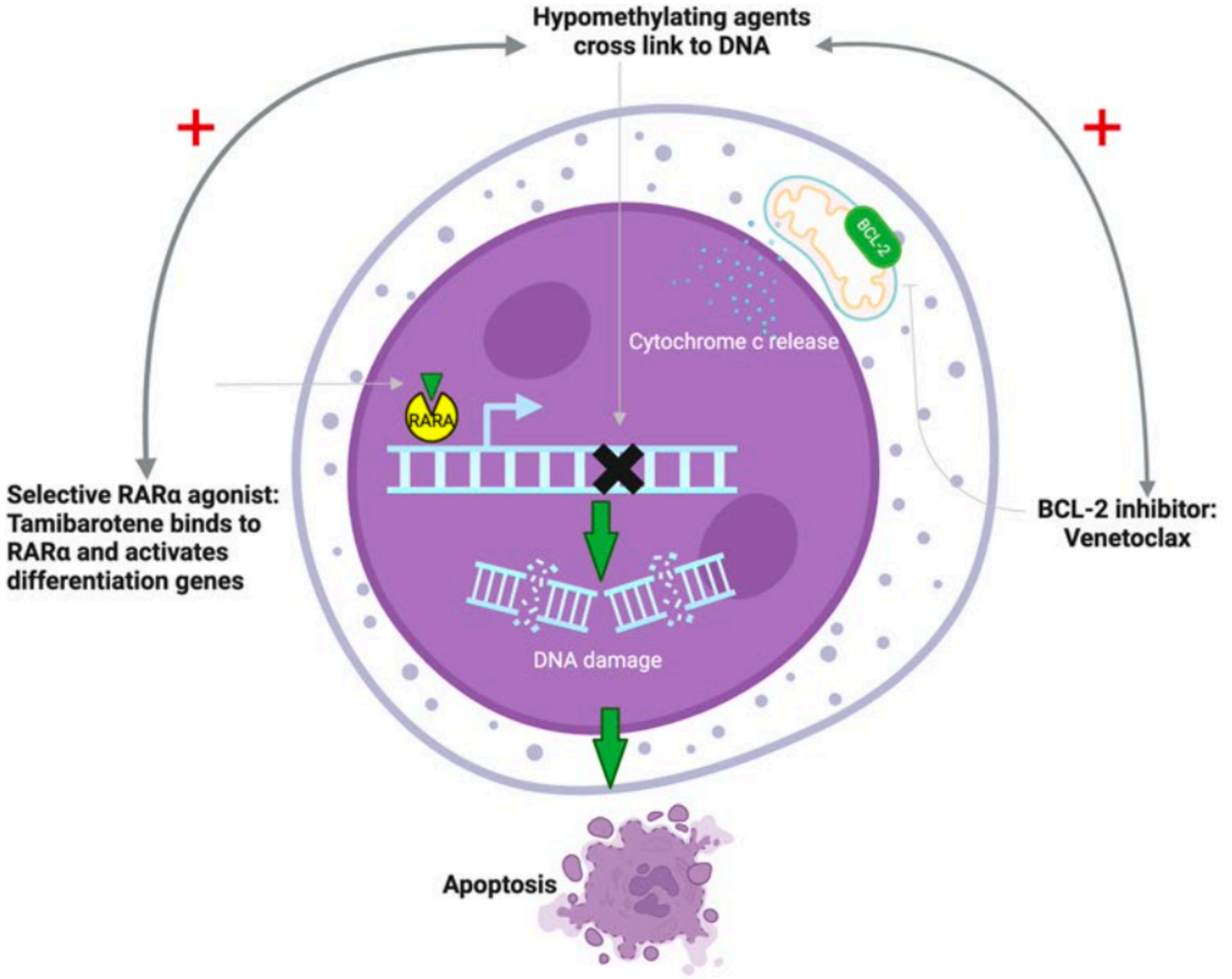
1. Antibody drug conjugates (CD33, CD123, CLL1)
2. Adaptive or Innate immune system harnessing therapies:

a. Bi-specific antibodies (CD3 x AML antigen; CD47 x CD3, others)

b. Immune checkpoint based approaches: T-cell and macrophage checkpoints

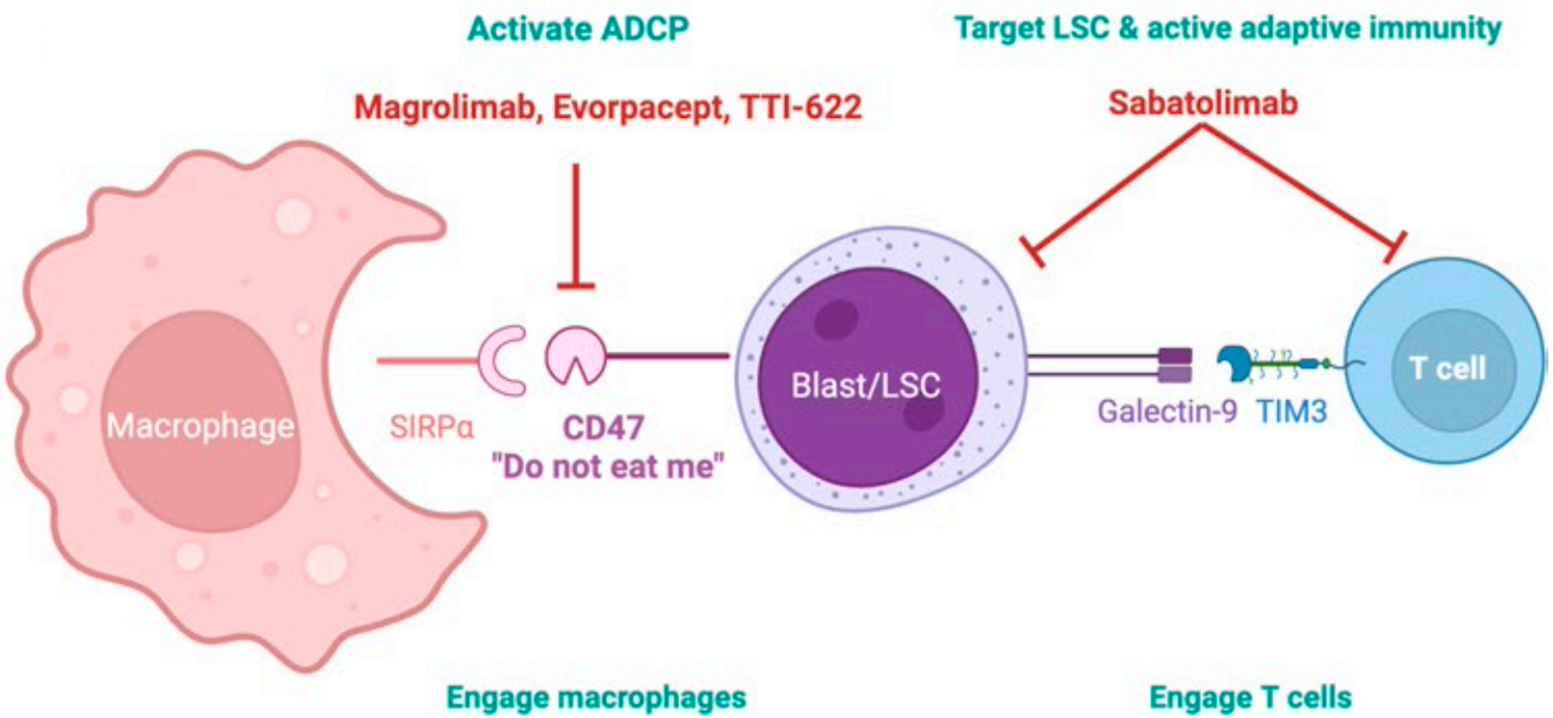
c. CART, CAR NK, High volume hn-NK cells

d. Vaccines



Novel therapy in higher-risk myelodysplastic neoplasms (HR-MDS). (A) Targeted therapy in patients with RARα overexpressing cells with tamibarotene (SY1425), a selective RARa agonist and blockade of the antiapoptotic protein BCL2 via the BH3 mimetic venetoclax; ultimately leading to apoptosis induction with the combination of hypomethylating agents.

David A. Sallman and Zhuoer Xie Malignant Hematology Department, Moffitt Cancer Center, Tampa, FL



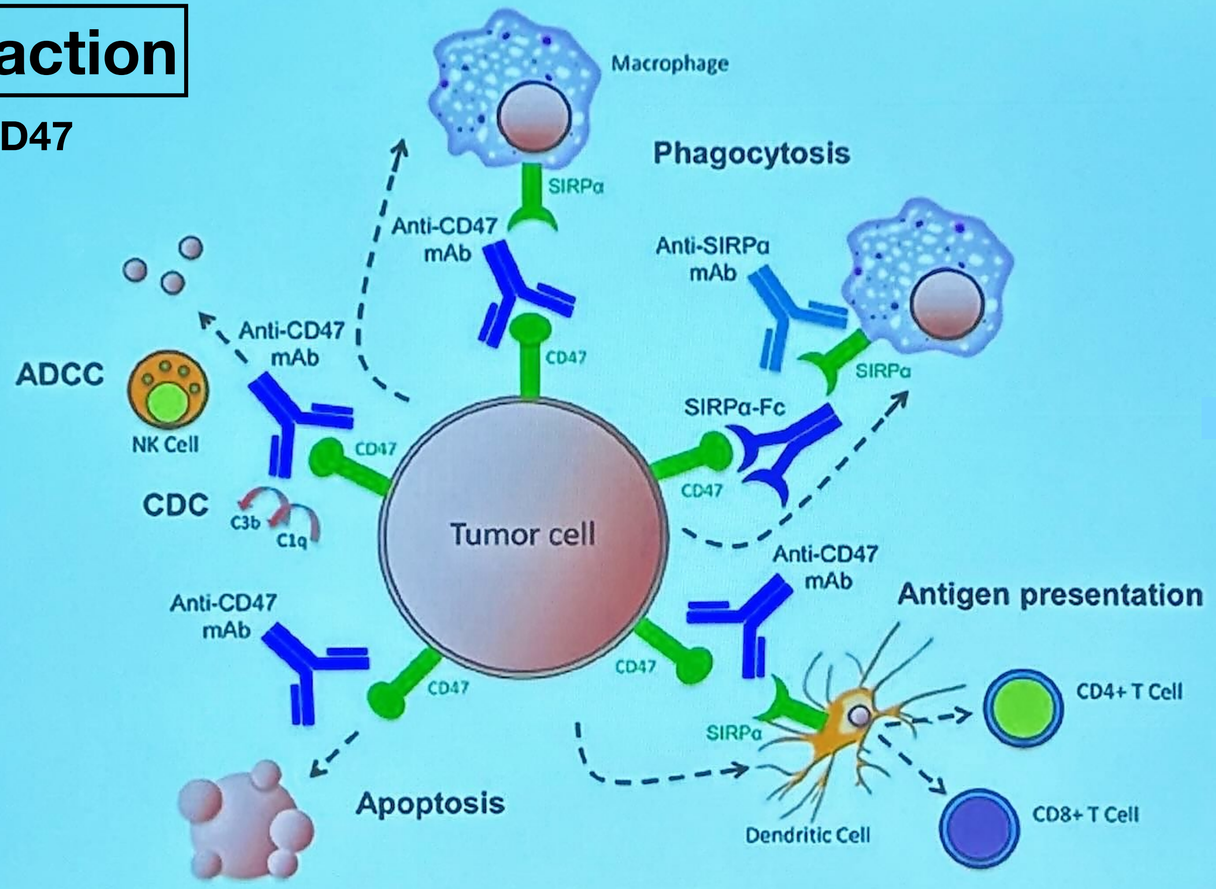
Novel therapy in higher-risk myelodysplastic neoplasms (HR-MDS).(B) Novel immune myeloid therapy targeting both the underlying leukemic stem cell (LSC)/blast as well as activating both innate and adaptive immunity. Magrolimab, and other inhibitors of the CD47/SIRPα axis, allowing for activation of antibody dependent cellular phagocytosis (ADCP) and likely subsequent adaptive immune activation via increased antigen presentation. Sabatolimab blocks the galectin9/TIM3 path way leading to direct targeting of the LSC as well as Tcell activation and potentially augmentation of ADCP.

David A. Sallman and Zhuoer Xie Malignant Hematology Department, Moffitt Cancer Center, Tampa, FL

SIRP alpha / CD47 checkpoint

Magrolimab action

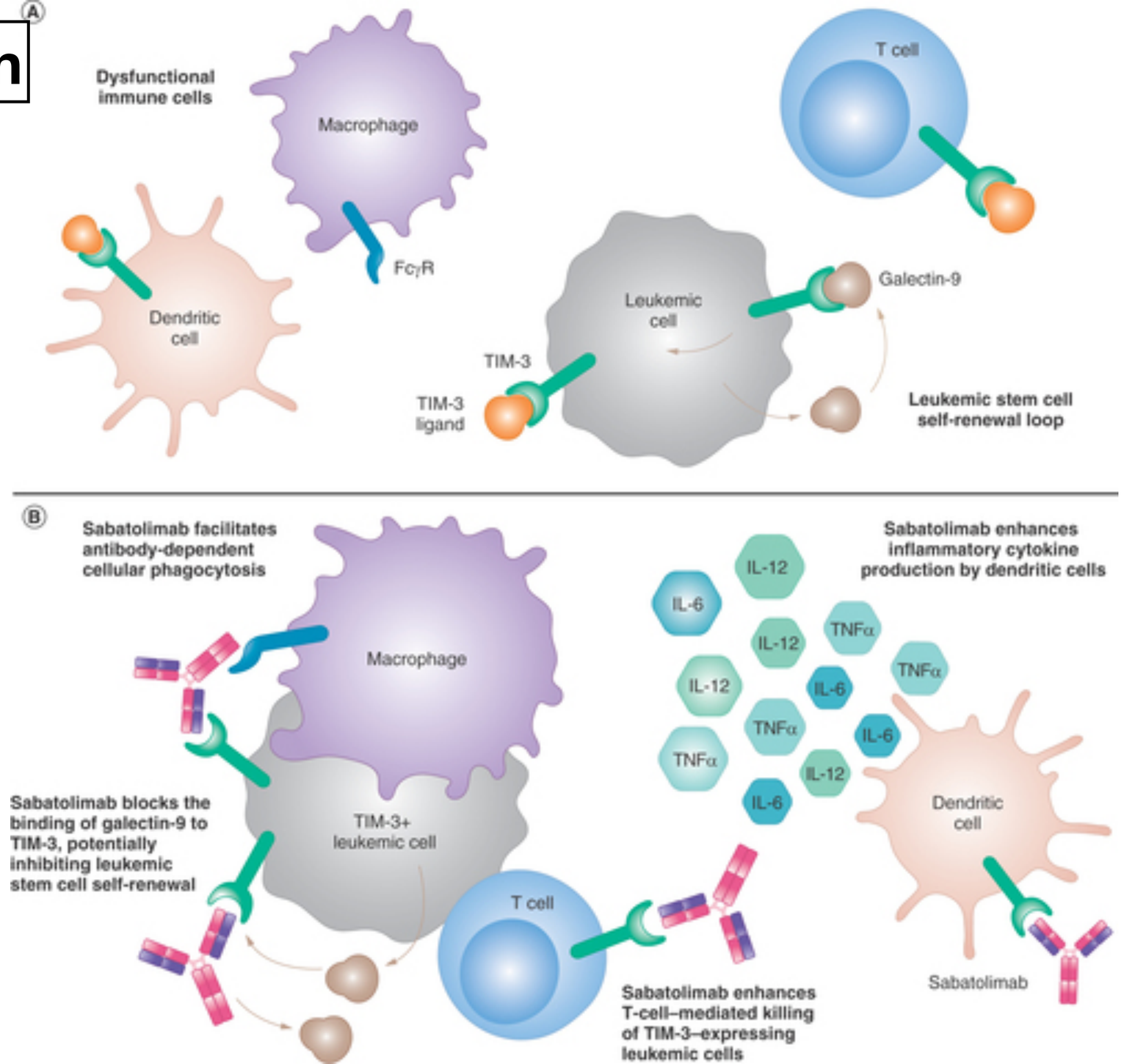
Targeting on CD47



Zhang W et al., *Frontiers in Immunology* 2020; Chao M et al., *Curr Opin Immunol* 2012

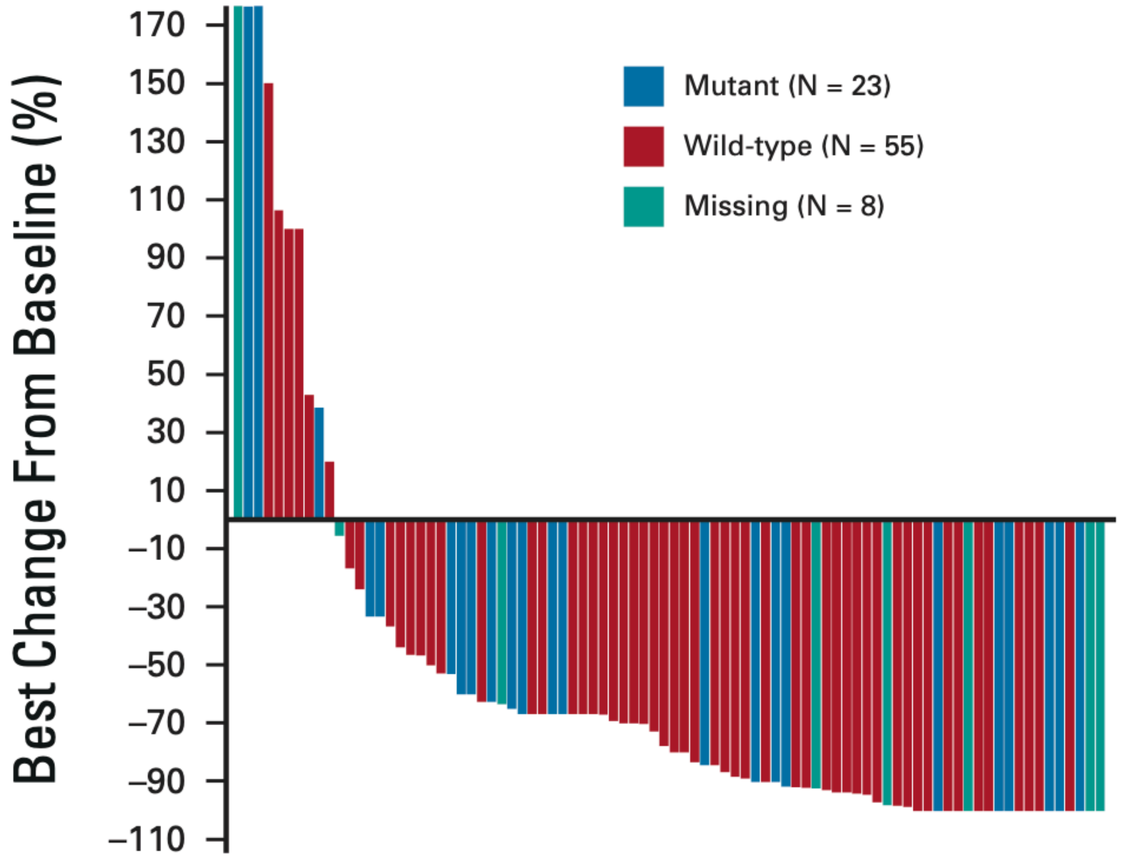
Sabatolimab : action

Targeting on TIM-3



Magrolimab + AZA overall response rates in HR-MDS

Outcome	All (N = 95)*	*TP53*-wt (N = 61)	*TP53*-mut (N = 25)
ORR, %*	74.7	78.7	68.0
CR, % (95% CI)	32.6 (23.4, 43.0)	31.1 (19.9, 44.3)	40.0 (21.1, 61.3)
DCR, median (95% CI), mo	11.1 (7.6, 13.4)	12.9 (8.0, NR)	7.6 (3.1, 13.4)
DOR, median (95% CI), mo	9.8 (8.8, 12.9)	9.8 (8.5, 18.5)	9.2 (5.0, 12.2)
CCyR, n/N† (%)	19/65 (29.2)	13/41 (31.7)	6/20 (30)



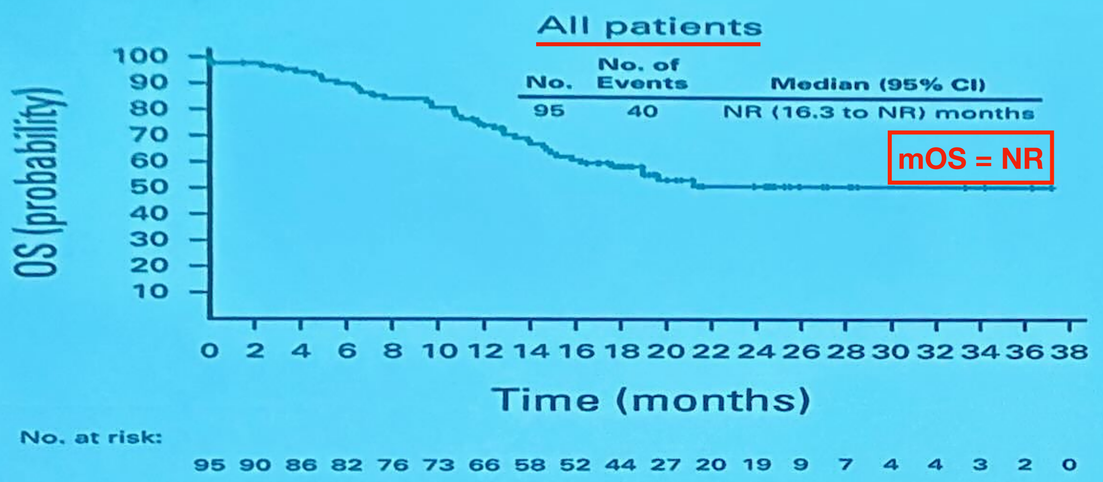
– CR rate was 32.6% and ORR was 74.6%, with response rates similar in *TP53*-mut and *TP53*-wt.

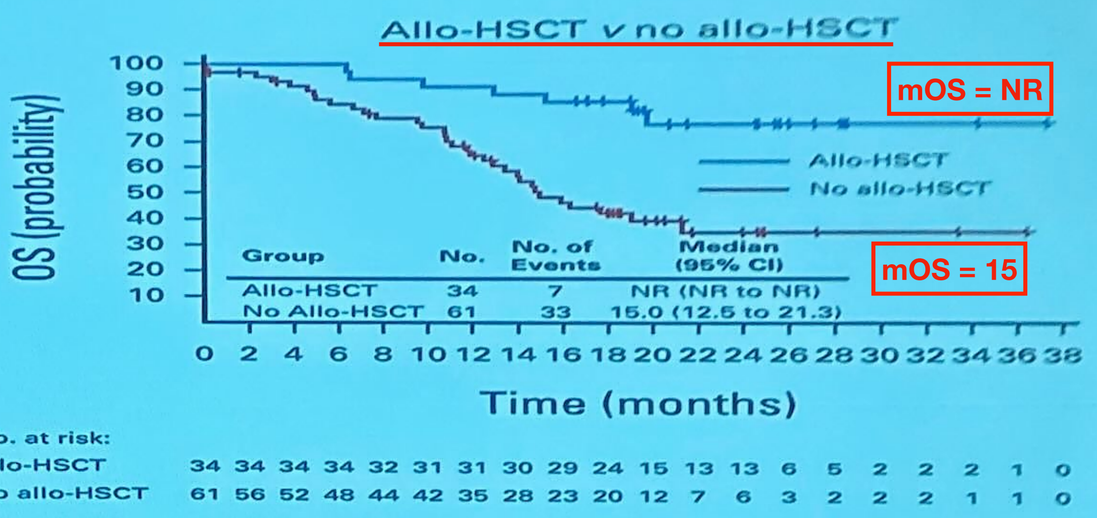
*Defined as CR + PR + marrow CR + HI without PD in all patients who received ≥ 1 magrolimab dose. †N = number with abnormal cytogenetics at baseline.
CR = complete remission; CCyR = complete cytogenetic remission; DCR = duration of CR; DOR = duration of response; mut = mutant; ORR = objective response rate; OS = overall survival; PFS = progressio

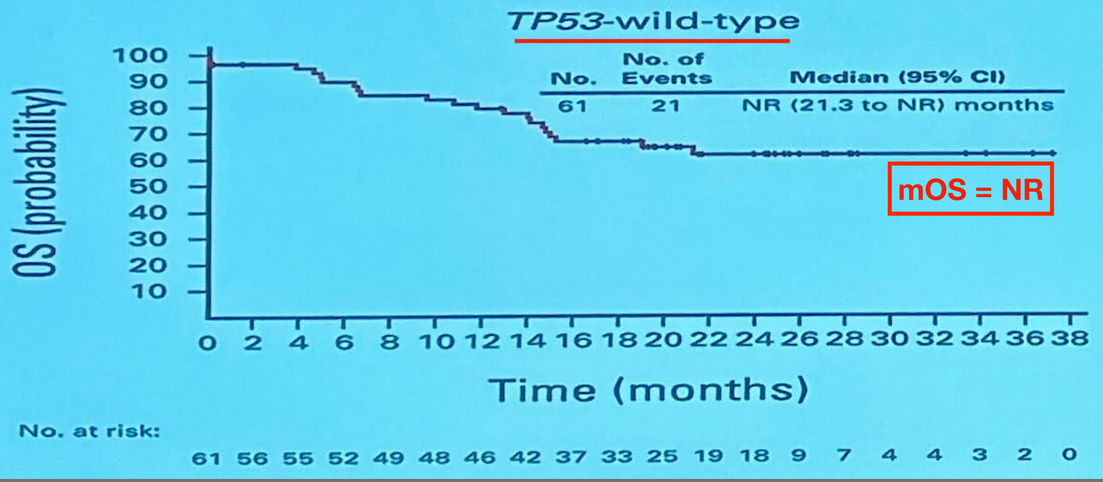
Sallman D ….. Dayer N. JCO, March 2023

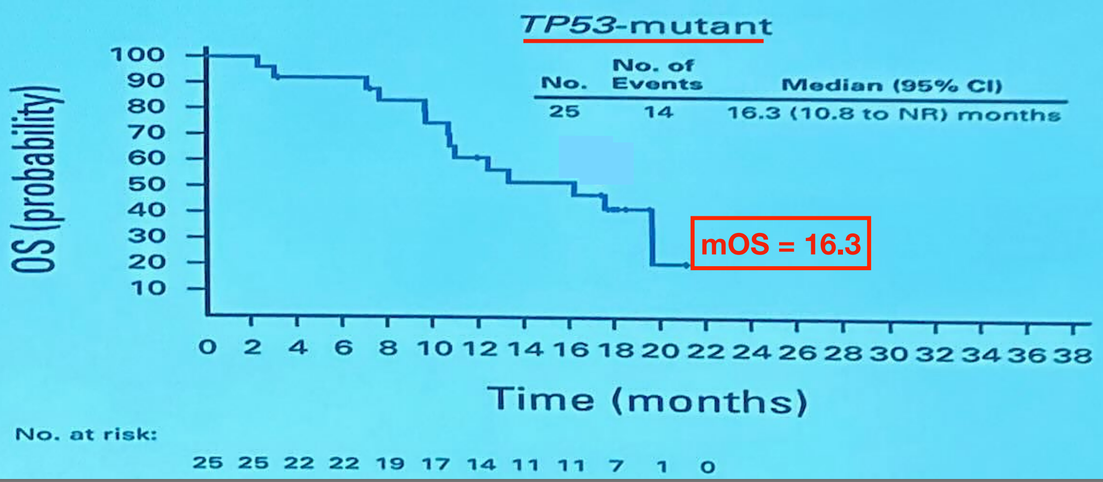
Median OS **Encouraging in Both** *TP53-Wild Type* **and Mutant HR-MDS Patients**

– With a median follow-up of 17.1 months, median OS was not reached and was 16.3 months in *TP53*-mut MDS.





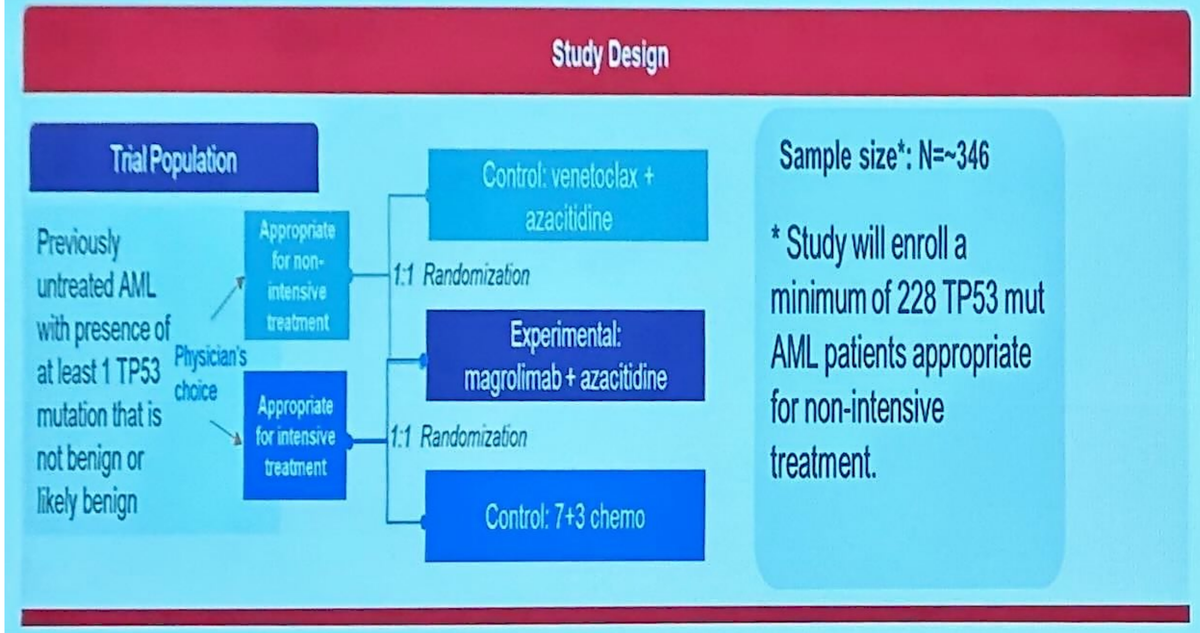




Sallman D ….. Dayer N. JCO, March 2023

Phase 3 Studies with *Magrolimab* in *Frontline* AML

Phase III AZA+Magro vs Investigator Choice in TP53 AML (ENHANCE-2) 9/2023



Stratification:

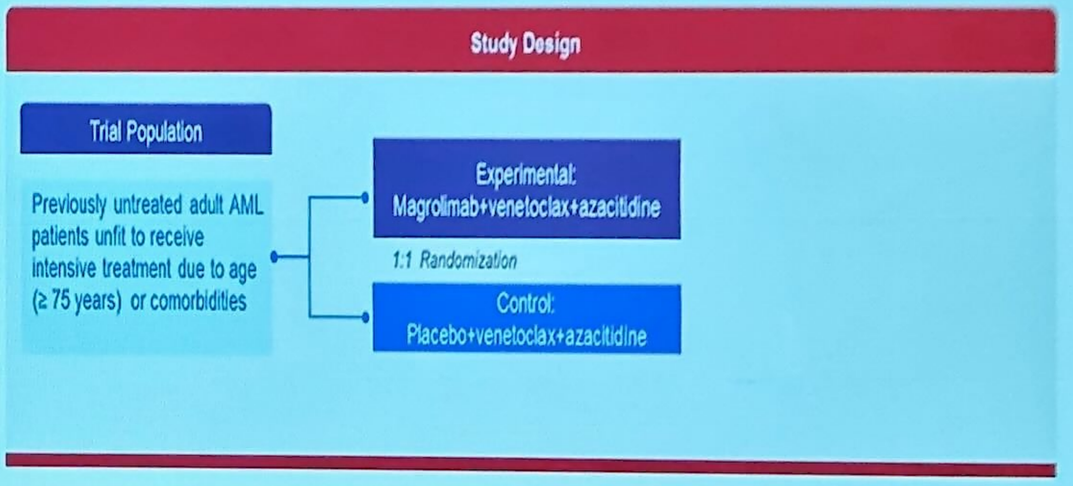
1) Appropriateness for non-intensive therapy vs. intensive therapy
2) Age <75 vs. ≥75
3) Geographic region: US vs. outside the US

Endpoints:

- **Primary endpoint:** OS in TP53 mut AML population appropriate for non-intensive treatment
- **First secondary endpoint (alpha controlled):** OS in all TP53 mut AML population
- **Other key secondary endpoints (alpha controlled):** EFS, Transfusion independence, CR/CR_{MRD-}, PRO in all TP53 mut AML population

Phase III AZA+VEN+Magro vs AZA+VEN in older/unfit AML (ENHANCE-3) 2/2024

ENHANCE-3: Phase 3 study of 1L unfit All Comer AML with magrolimab +venetoclax+ azacitidine



Endpoints:

Primary endpoint: CR, Overall survival

Secondary endpoints: 1. MRD-ve CR 2.CR+CRh, 3. Duration of CR, 4. Duration of CR+CRh 5. Transfusion independence 6. EFS 6. QOL/PRO

ENHANCE Trial Closed for Futility 7/2023; ENHANCE 2 9/2023 and ENHANCE 3 2/2024

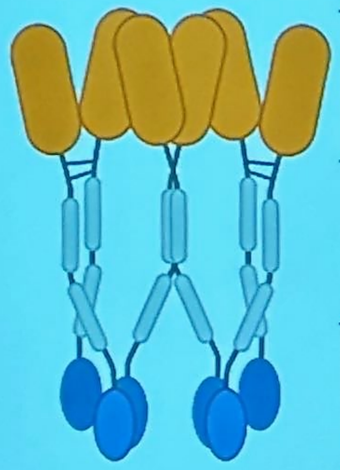
Conclusion :

Magrolimab target on CD47 + AZA
Look good esp TP53wt
Phase III still on going trial
Also in combination with AZA/Ven

Phase 1 Study of SL-172154 in MDS and TP53 Mutant AML

- SL-172154 (SIRPα-Fc-CD40L), a hexameric, bi-functional fusion protein, consists of SIRPα domains linked to CD40L domains through an inert Fc linker
- CD40 Activation can increase antigen processing and cross-presentation by antigen presenting cells (APCs) to CD8 T cells, thus bridging innate and adaptive immunity

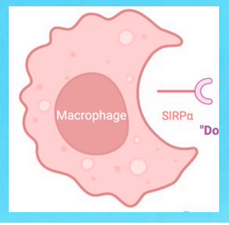
SL-172154 (SIRPα-Fc-CD40L)



Six SIRPα Binding Domains: Blocks "don't eat me" CD47 Signal

Inert IgG4 Fc

Two CD40L Trimers: Provides CD40 Stimulation to Antigen Presenting Cells



SL-172154 monotherapy

- 6 mg/kg (n=7)
- 3 mg/kg (n=8)
- 1 mg/kg (n=4)

SL-172154 + AZA

- SL-172154 6 mg/kg + AZA (n=1)
- SL-172154 3 mg/kg + AZA (n=9)
- SL-172154 1 mg/kg + AZA (n=8)

CD40 = CD134 : on B-cell, APCs
CD40L = CD154 on CD4+ T cell

Daver N et al ASH 2023, abst 4278
Zeidan et al., EHA 2024

Phase 1 Study of SL-172154 in MDS

	TP53m (n=21*)	TP53wt (n-2)	Total (n=24*)
OR (%)	14 (67%)	2	16 (67%)
95% CI	43%, 85%		45%, 84%
CR (%)	9 (43%)	1	10 (42%)
95% CI	22%, 66%		22%, 63%
mCR	3 (14%)	1	4 (17%)
mCR with HI	2 (10%)	1	3 (13%)
SD	6 (29%)	0	7 (29%)
SD with HI	2 (10%)	0	2 (8%)
PD	1 (5%)	0	1 (4%)
Not done	2 (10%)	0	2 (8%)

No repeat CBC monitoring or Hgb Threshold Prior to Treatment Needed
IRR most common TRAE (mitigated with dex pre-medication)

- Out of 10 Pts who achieved CR,
  - 9 Pts had abnormal cytogenetics at baseline; 6/9 Pts (67%) achieved cytogenetic CR
  - 8/10 Pts (80%) were negative for MRD by MFC**
  - 4/5 TP53 VAF Clearance.
- All 3 Pts who achieved mCR+HI were negative for MRD by MFC**; 2/4 TP53 VAF Clearance
- 3 Pts (13%) proceeded to allogeneic HCT after achieving CR following 4-7 cycles of study treatment
- Median baseline hemoglobin was 8.3 g/dL (range: 7.0 to 12.4)
- Median hemoglobin change from baseline was -0.7 g/dL (range: -2.0 to 1.5) at 24 hours post 1st SL-172154 infusion, median hemoglobin value returned to baseline on Day 9
- 54% patients (7/13) converted to RBC transfusion independent

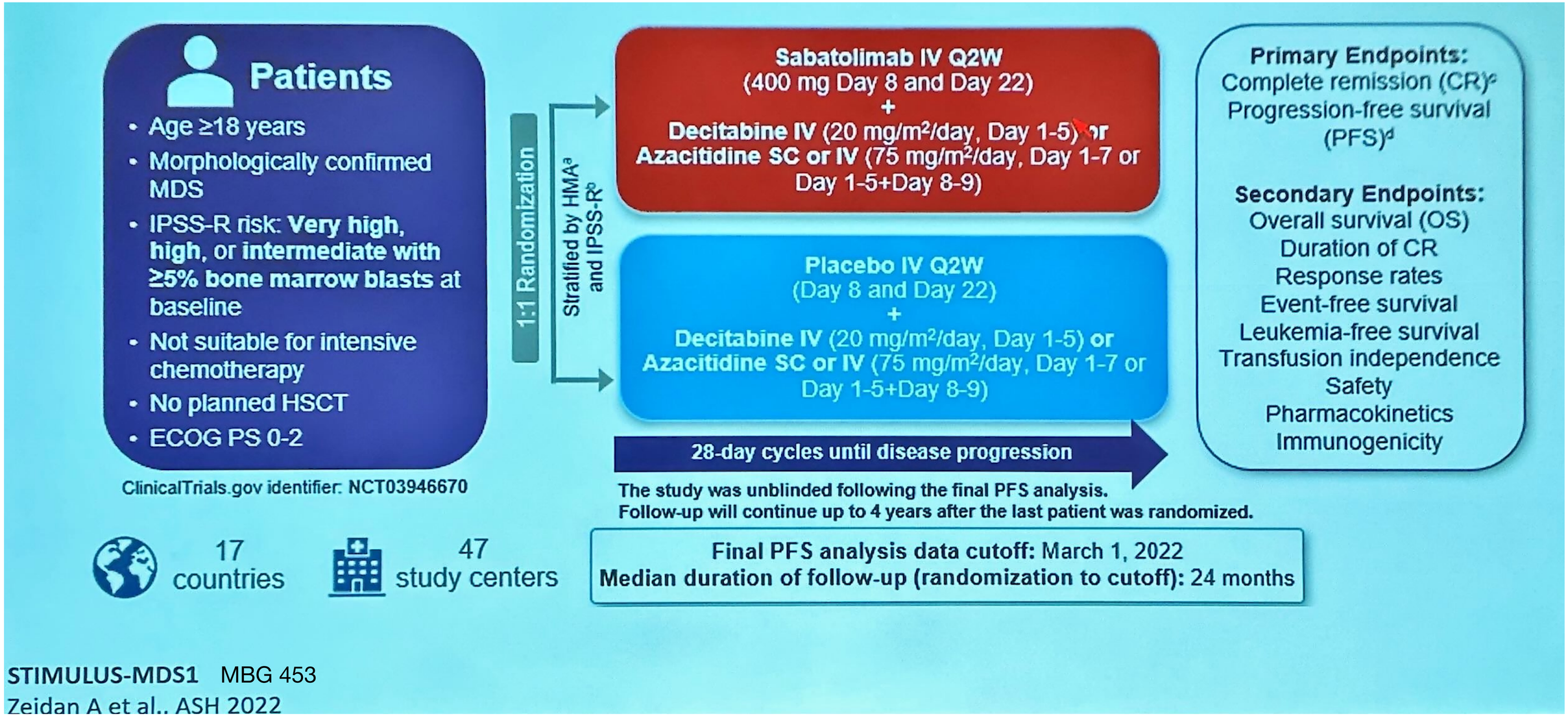
Zeidan et al., EHA 2024;
Daver N et al ASH 2023

Conclusion :

SL-172154 target on SIRPa-Fc-CD40L
Look good : but early phase

Study design : *Phase II*, randomized, double-blind placebo-controlled

Sabatolimab is a novel immuno-myeloid therapy that binds to **TIM-3** on immune cells, facilitating immune activation and phagocytosis of leukemic cells. Sabatolimab also binds to TIM-3 on leukemic cells, potentially impeding self-renewal of leukemic stem cells (LSCs).

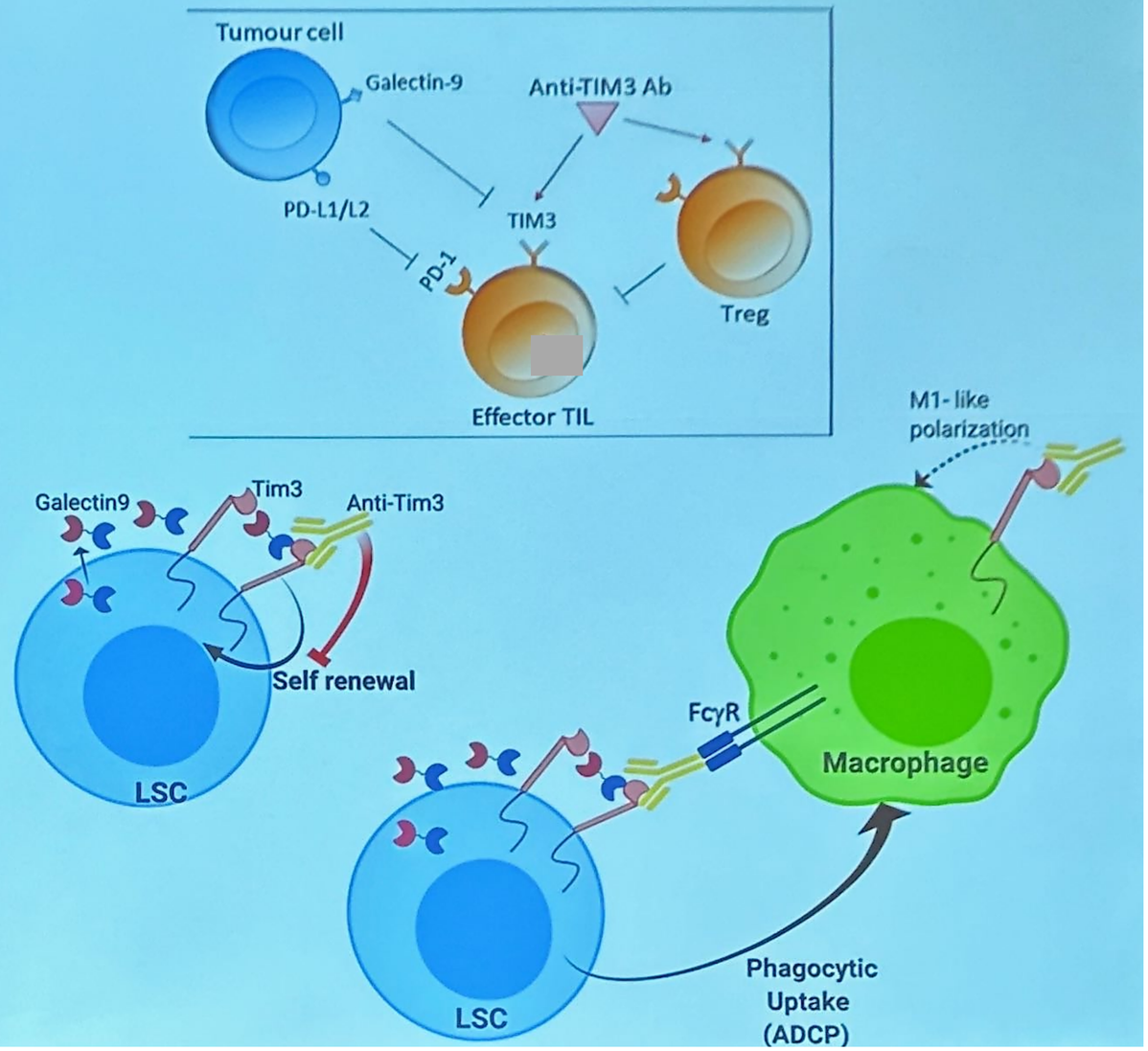


STIMULUS-MDS1 MBG 453

Zeidan A et al.. ASH 2022

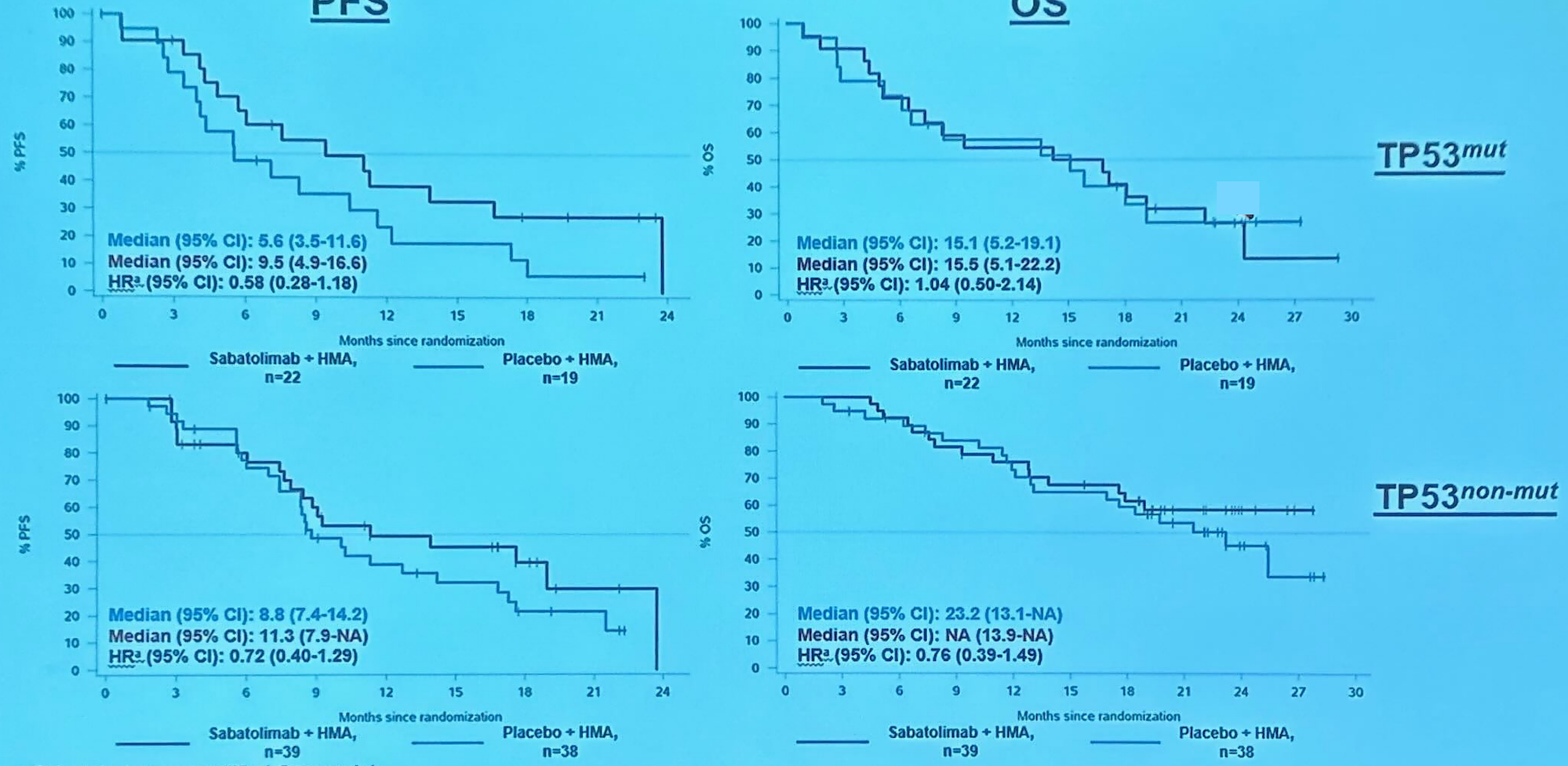
Targeting TIM3 and Sabatolimab

- TIM-3 promotes autocrine LSC self-renewal
- Blocking TIM-3 inhibits downstream signaling that promotes self-renewal
- TIM-3 ligation on T-Cells leads to apoptosis of the effector cell
- May also promote phagocytosis by myeloid cells, macrophages



Acharya N, et al. *J Immunother Cancer*. 2020;8:e000911. Kikushige et al., *Cell Stem Cell* 2015

STIMULUS MDS1: A randomized phase 2 study
Survival in TP53 mutated HR-MDS patients

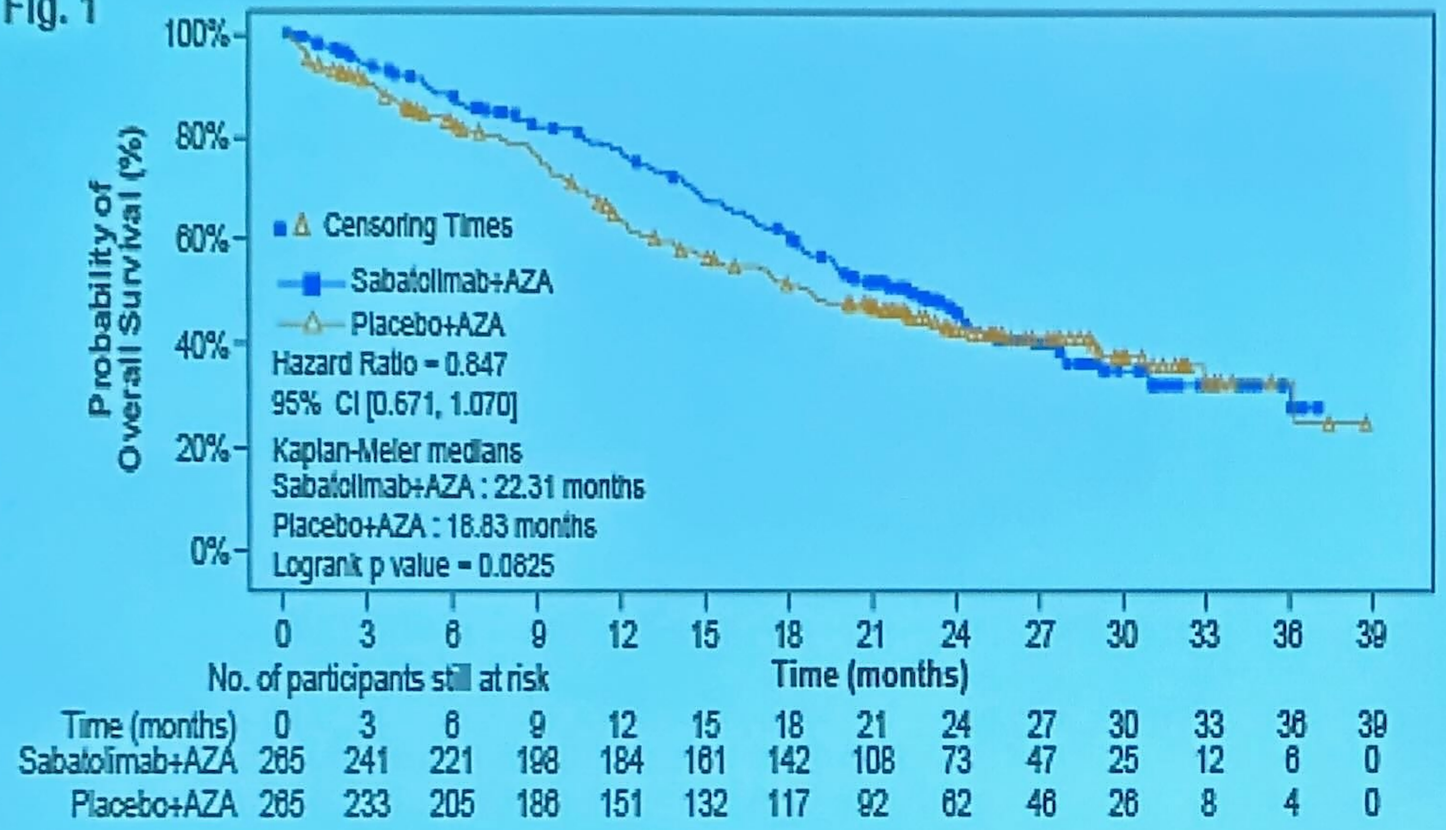


[a]Calculated via unstratified Cox model.

Zeidan A et al., ASH 2022;
Zeidan A et al., *Lancet Haematology* 2024

STUMULUS-MDS2:
A Randomized *Phase 3* trial of Sabatolimab + *AZA* vs PBO + AZA
In Patients With Higher Risk MDS

Fig. 1



No. of participants still at risk

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Sabatolimab+AZA	285	241	221	198	184	161	142	108	73	47	25	12	6	0
Placebo+AZA	285	233	205	188	151	132	117	92	62	46	26	8	4	0

In favor of Aza-Sabato arm:
Median PFS 13.6 vs 10.1 mos
(HR,0.70 [0.56–0.86])
Median LFS 19.4 vs 13.7 mos
(HR, 0.78 [0.61–1.00])
CR 19.6 vs 14.3%,

Zeidan A et al, EHA 2024

Despite a favorable trend in OS, CR rate, PFS, and LFS, the study did not meet its primary endpoint of OS

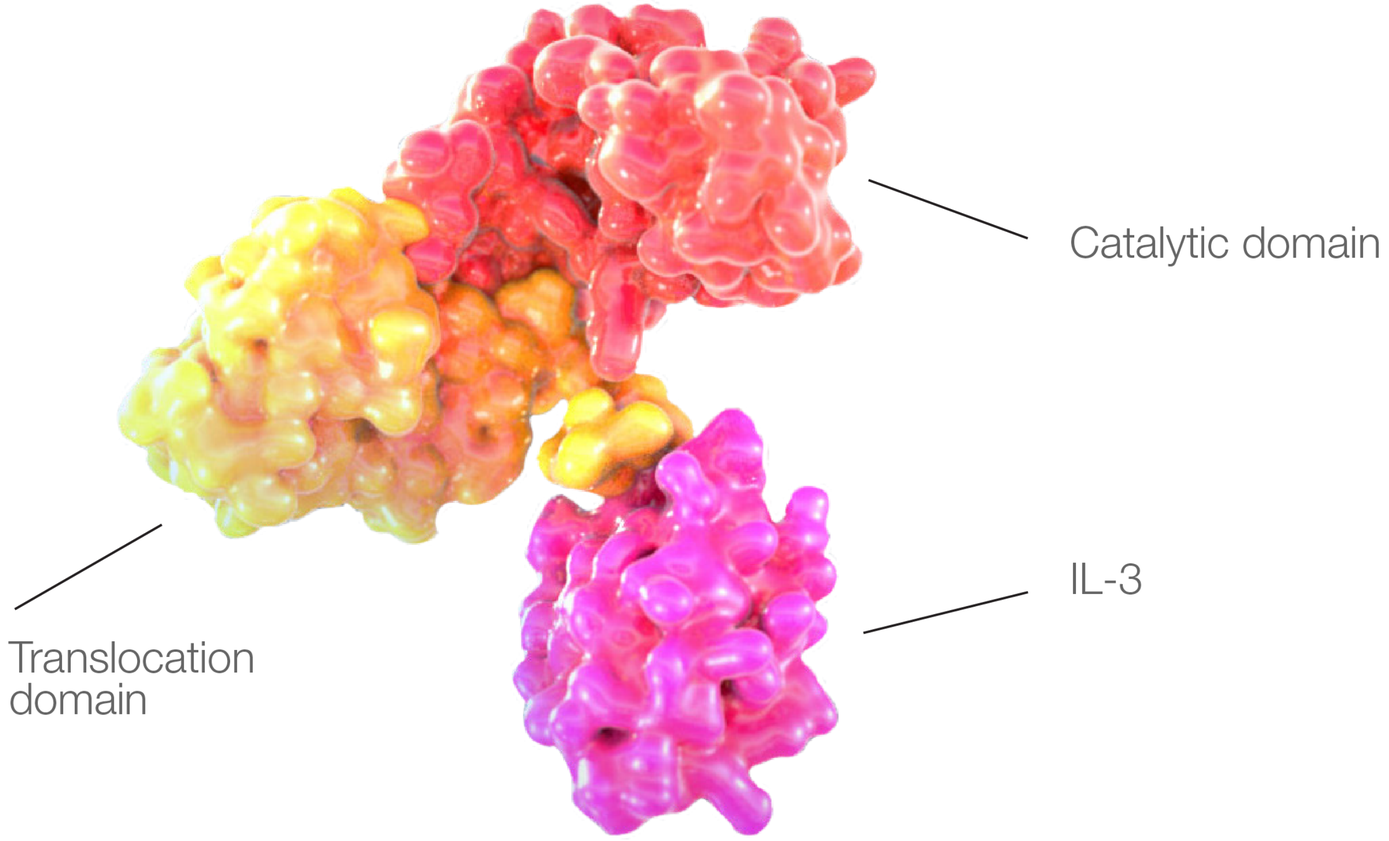
Conclusion :

Sabatolimab (target on TIM-3) + HMA look doesn’t work in HR MDS

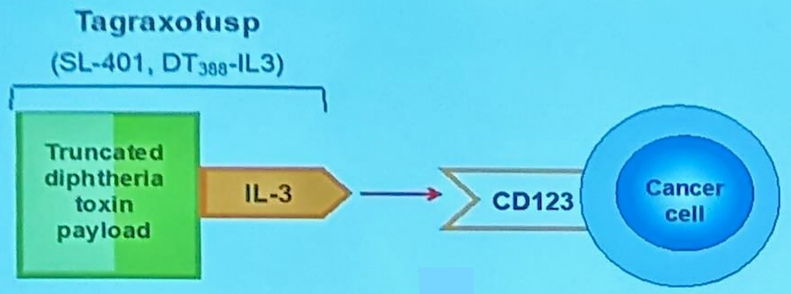
Tagraxofusp

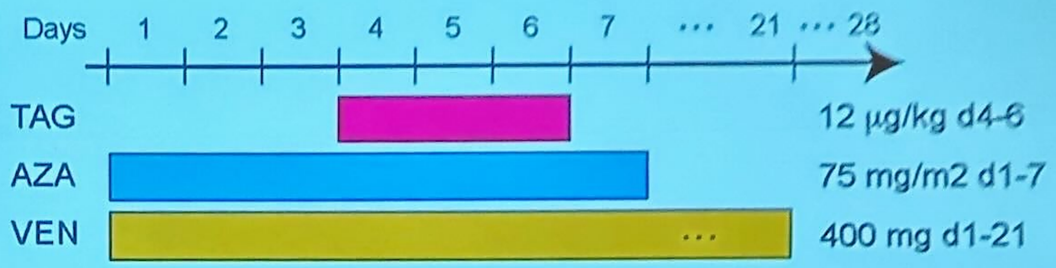
Medicine used to treat blastic plasmacytoid dendritic cell neoplasm (BPDCN)

Diphtheria toxin-IL-3 fusion protein targeting IL-3 receptor

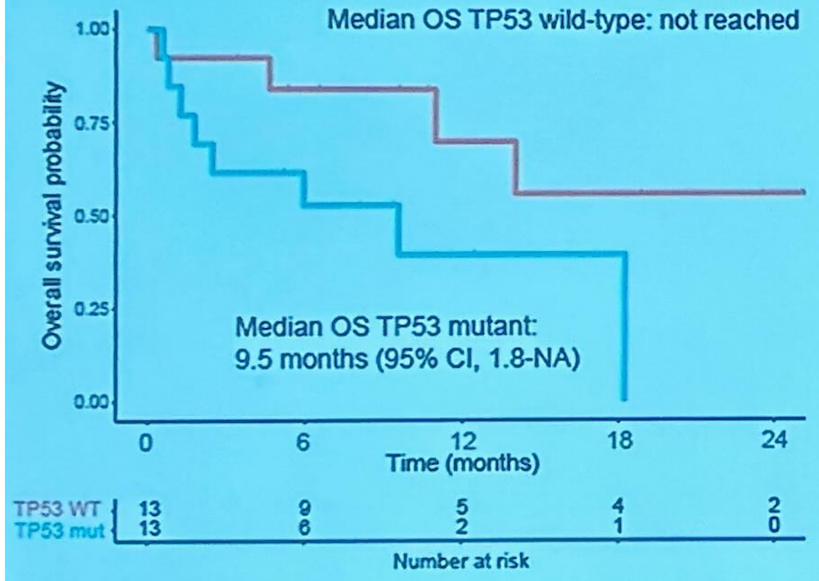


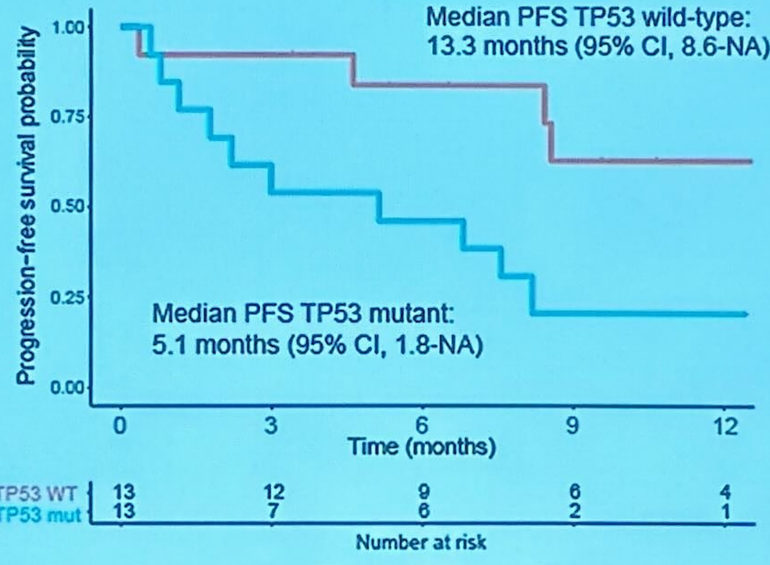
Tagraxofusp + AZA/Ven :
Phase 1b Study for CD123+ AML, MDS, BPDCN





Tagraxofusp (TAG, SL-401) is a first-in-class CD123-targeted therapy that delivers a truncated diphtheria toxin payload to CD123-expressing cells, and is approved for BPDCN





Response summary TP53m

- **54%** (n=7 of 13) achieved CR (4), CRi (2) or MLFS (1)
- 7 of 7 (**57%**) MRD (-) by FCM
- **46%** went for transplant (6 of 13)

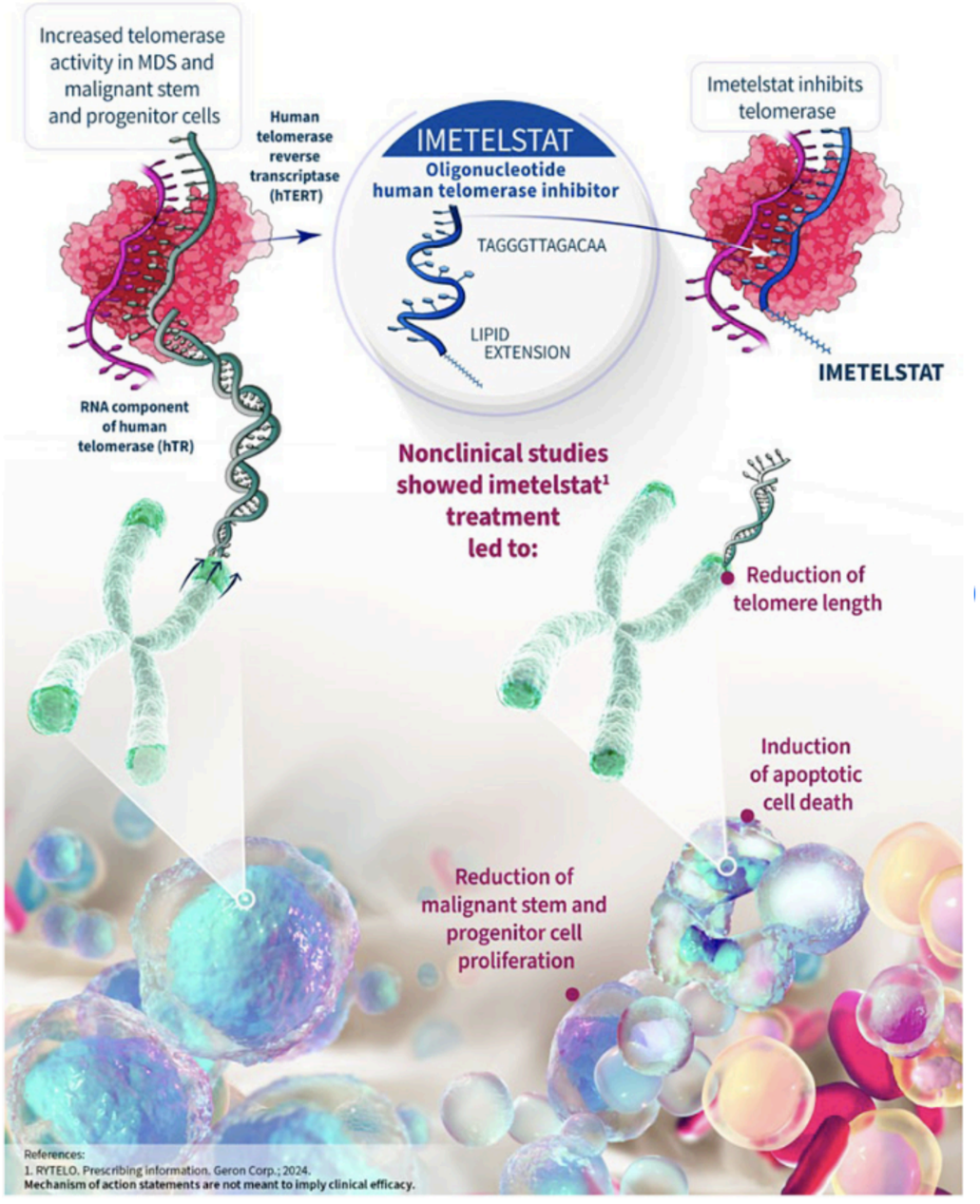
Lane A et al, Blood advances 2023

Conclusion :

Tagraxofusp (target on IL3 receptor) + HMA/Ven
Too early, but good potential

Telomerase inhibitor
Imetelstat (first-in-class)

Acts on cells with hyperactive telomerase and short telomere lengths



Imetelstat mechanism of action. MDS, myelodysplastic syndromes.

In June 2024 :

- Imetelstat -> the first telomerase inhibitor, approved by the FDA
- Indicated for transfusion-dependent lower-risk (LR) MDS who are ESA ineligible or relapsed/refractory.
- Its clinical activity in HR-MDS or AML is unknown.

blood®

MENU

637.MYELODYSPLASTIC SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 5, 2024

A Phase II Study Evaluating the Efficacy and Safety of Imetelstat in Patients with Advanced Myelodysplastic Neoplasms or AML Failing HMA-Based Therapy - Interim Analysis Results of the Impress Study

Uwe Platzbecker, Steven W Lane, Alice Garnier, Thomas Cluzeau, Odile Rauzy, Katharina S. S. Götze, Aristoteles Giagounidis, Deepak Singhal, Aicha Kopecky, Fatiha Chermat, Lionel Ades

23 patients (17 with AML and six with HR MDS)
Imetelstat, 7.5 mg/kg, every 4 weeks.
Average 2.8 doses administered
- only one pt had hematologic improvement
- seven exhibited stable disease
- eight experienced progression.
- short-term declines in leukocyte and blast counts suggested limited antiproliferative effects
- no patient had significant response after four months of tx

30 serious adverse events (SAEs) occurred in 18 patients
10 of the 30 SAEs resulted in death
5 due to disease progression
4 due to infectious complications
1 due to ileus

Conclusion :

Imetelstat (telomerase inhibitor) look doesn’t work in HR MDS

Thank You for Your Attention