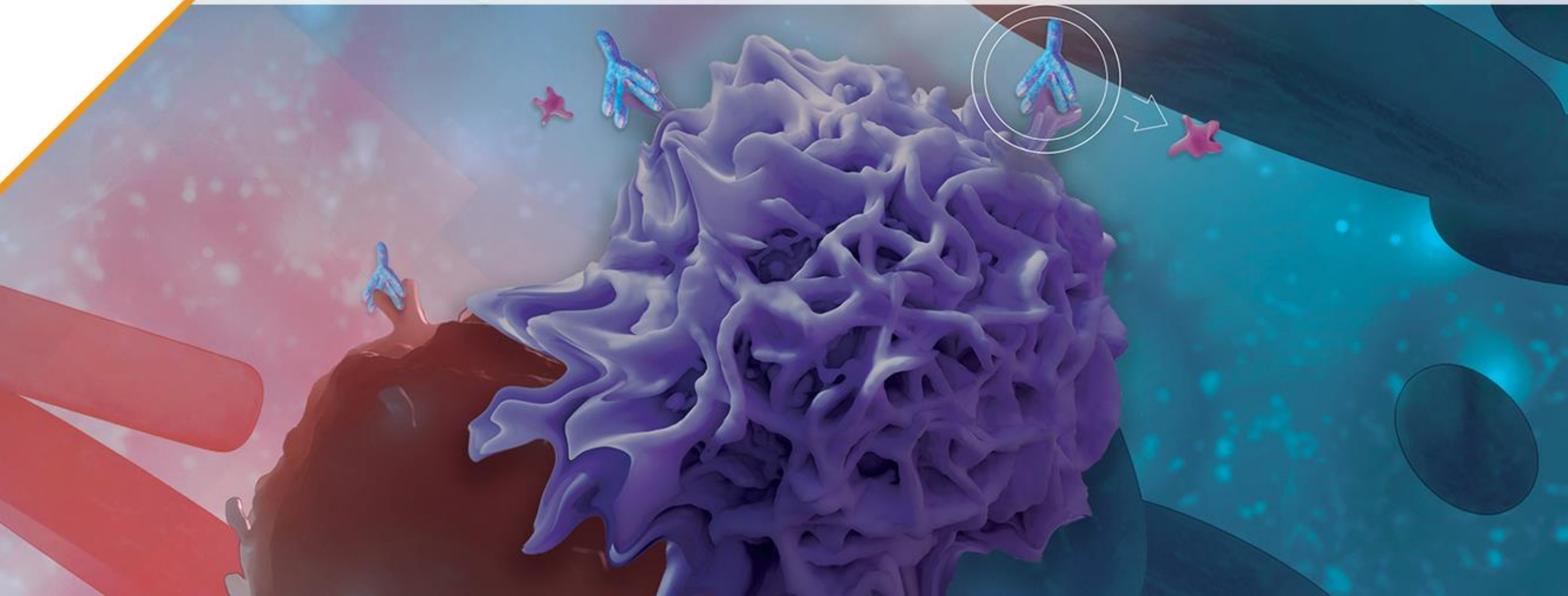
AXIS Medical Education

Harnessing the Power of the Immune System to Manage Higher-Risk MDS



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Disclosure of Conflicts of Interest

Consultant: Acceleron Pharma; Agios Pharmaceuticals, Inc; Bristol-Myers Squibb Co; Celgene Corp; Gilead; Keros Therapeutics; Novartis Pharmaceuticals Corp; Taiho Pharmaceutical Co, Ltd; and Takeda Oncology.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Utilize biomarker testing and prognostic scoring systems to define higher-risk myelodysplastic syndrome (MDS) and to guide treatment
- Discuss the evolving role of the immune system in MDS, including the various pathways involved in dysregulation such as the TIM-3 pathway
- Review efficacy results of immuno-myeloid therapy targeting TIM-3 in combination with HMAs as treatment for higher-risk MDS
- Develop management plans to address adverse events related to novel and emerging therapies for MDS

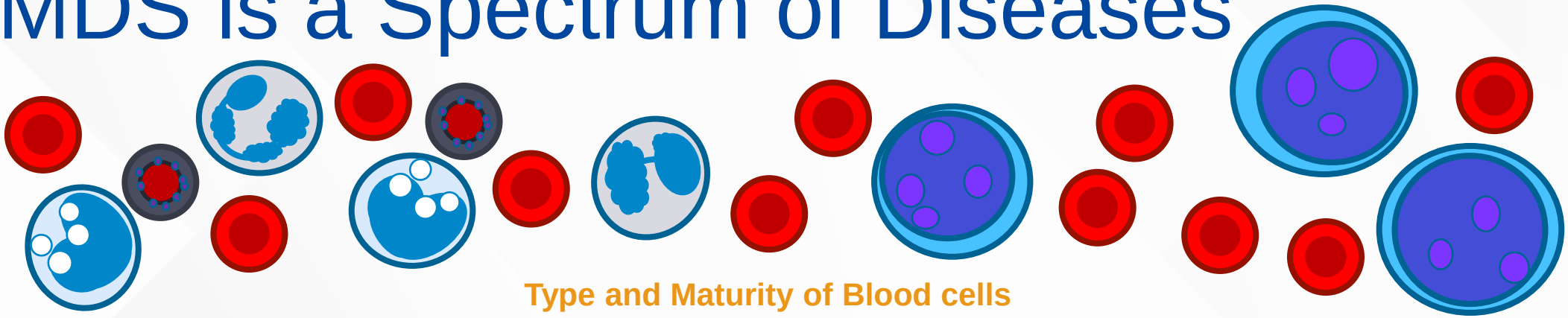
What Are ‘Higher-Risk’ Myelodysplastic Syndromes?

Patient Presentation

- The clinical features that can be used to identify and characterize high-risk MDS subtypes
- Risk stratification systems based on the modern MDS prognostic models, including IPSS and IPSS-R, along with IPSS-M
- Identifying higher-risk MDS subtypes based on blood counts, percentage of blast cells, cytogenetics, subclonal heterogeneity, hypermethylation of tumor suppressor genes, and unfavorable genetic mutations
- Burden of disease, diagnosis, and biomarker testing in higher risk MDS

IPSS-M, molecular international prognostic scoring system; IPSS-R, revised international prognostic scoring system; MDS, myelodysplastic syndrome.

MDS is a Spectrum of Diseases



Type and Maturity of Blood cells

MDS-SLD

MDS-RS

MDS-MLD

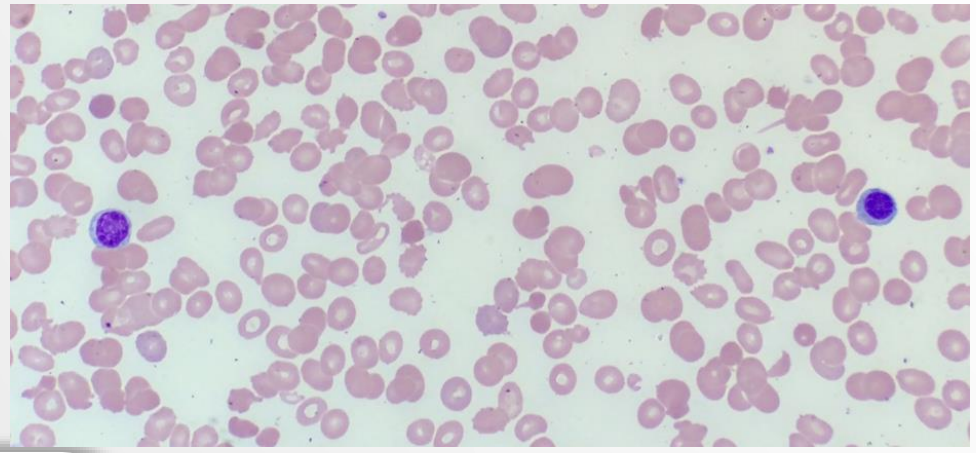
MDS-del(5q)

MDS-EB1

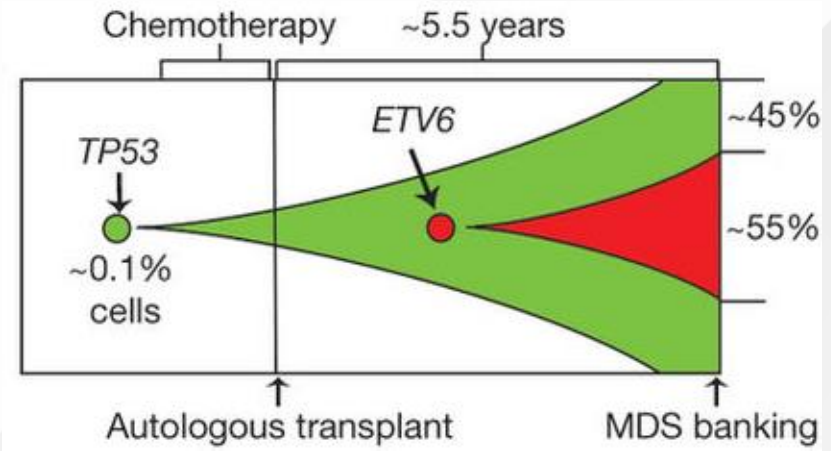
MDS-EB2

MDS-U

Variation in Blood Counts



Variation in Driver Mutations



EB, excess blasts; MDS, myelodysplastic syndrome; MLD, multilineage dysplasia; RS, ring sideroblasts; SLD, single lineage dysplasia; U, unclassifiable.

Wong et al. *Nature* 2015;518(7540):552–555.

Characterizing MDS

Newly Diagnosed MDS
Evaluate Type and Depth of Cytopenias

- CBC count and differential
- Full cytogenetic analysis
- Bone marrow core/aspirate
- Molecular diagnostics

Risk Stratification:

IPSS-R

Consideration of LR-PSS, WPSS, IPSS-M, Molecular Diagnostics

CBC, complete blood cell; IPSS-M, molecular international prognostic scoring system; IPSS-R, revised international prognostic scoring system; LR-PSS, low-risk prognostic scoring system; MDS, myelodysplastic syndrome; WPSS, WHO prognostic scoring system.

IPSS-R Calculation

Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
BM blast %	≤2	-	>2 - <5	-	5 - 10	>10	-
Hemoglobin	≥10	-	8 - <10	<8	-	-	-
Platelets	≥100	50 - <100	<50	-	-	-	-
ANC	≥0.8	<0.8	-	-	-	-	-

Cytogenetics

Very good: -Y, del(11q)

Good: normal, del(5q), del(12p), del(20q) double clone w/ del(5q)

Intermediate: del(7q), +8, +19, i(17q), other single/double clone

Poor: -7, inv(3)/t(3q)/del(3q), double clone including -7/del(7q), complex w/ 3 abnl

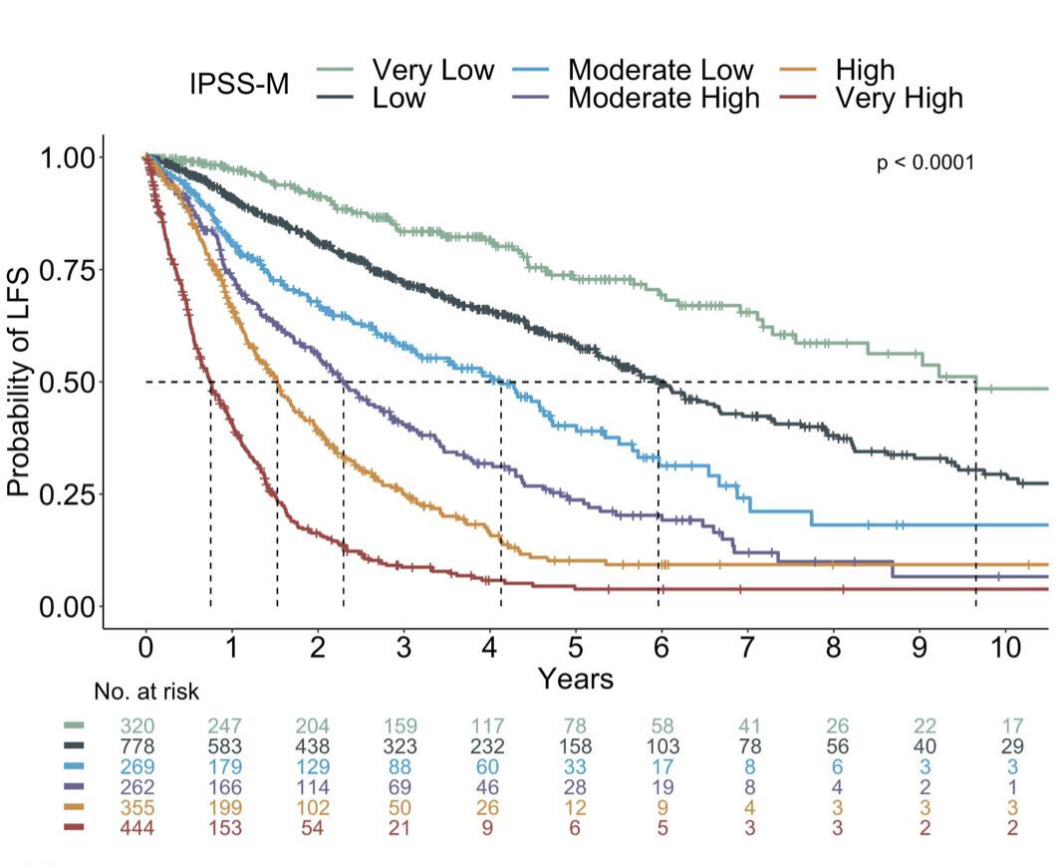
Very poor: Complex (>3 abnormalities)

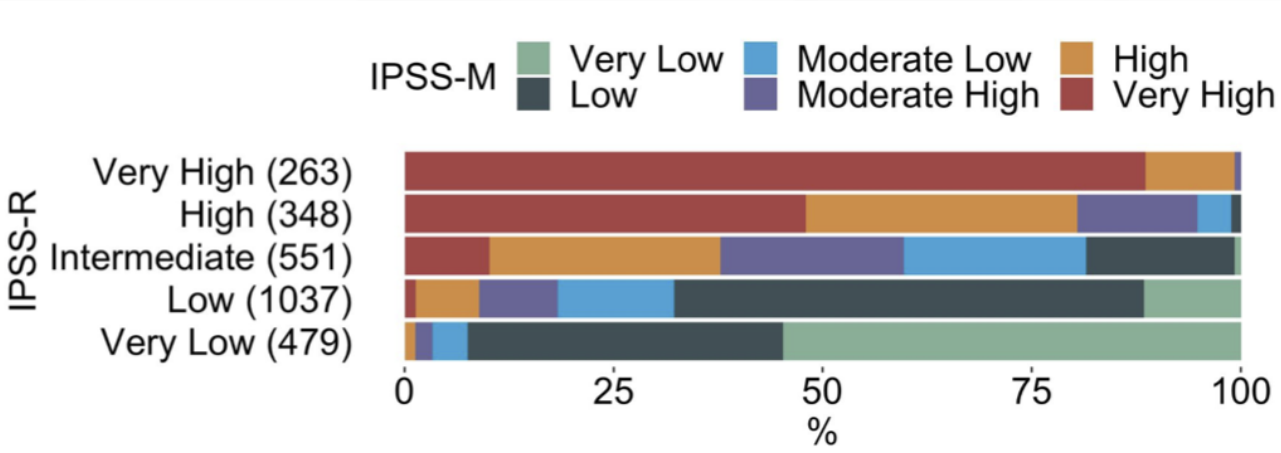
	Very Low	Low	Intermediate	High	Very High
SCORE	≤1.5	>1.5-3	>3-4.5	>4.5-6	>6
OS (years)	8.8	5.3	3.0	1.6	0.8
25% AML (years)	NR	10.8	3.2	1.4	0.73

AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; IPSS-R, revised international prognostic scoring system; NR, not reached; OS, overall survival.

Greenberg et al. *Blood* 2012;120:2454-2465.

IPSS-M





- Poor LFS, OS, and AML transformation:
  - TP53 multi-hit mutations (7%)
  - MLL PTD (2.5%)
  - FLT3 mutations (1%)
- More favorable clinical course:
  - SF3B1, depending on commutations

AML, acute myeloid leukemia; IPSS-M, molecular international prognostic scoring system; LFS, leukemia-free survival; OS, overall survival; PTD, partial tandem duplication.

Bernard et al. ASH Annual Meeting & Exposition, December 2021, Abstract 61.

MDS Treatment Is Based on Disease Risk

Risk Stratification by IPSS or IPSS-R
Blood Counts, Blasts, and Karyotype

Risk for Serious or Life-threatening Complication related to MDS:
Infection
Bleeding

Risk for Progression to Acute Myeloid Leukemia

IPSS and IPSS-R Risk do not always match the risk of the WHO disease subtype

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IPSS, international prognostic scoring system; IPSS-R, revised IPSS; MDS, myelodysplastic syndrome; WHO, World Health Organization.

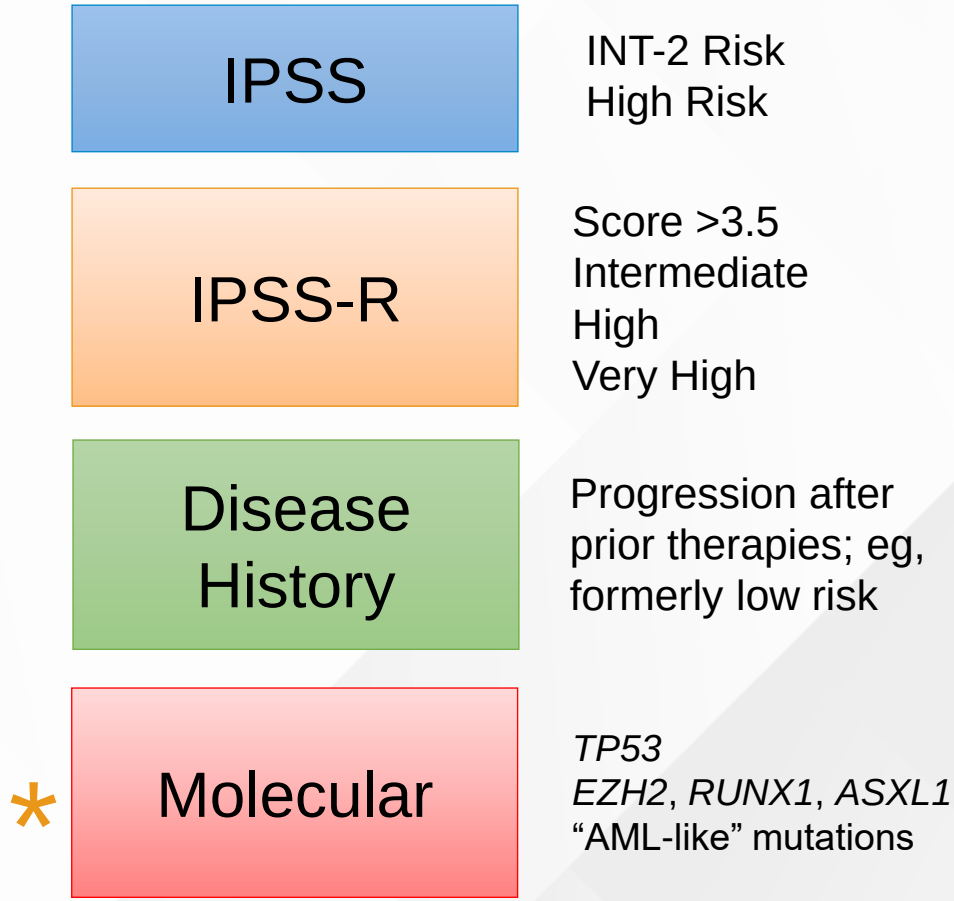
Defining Higher-Risk MDS

Goal: Identify patients whose disease, left untreated, is at high risk of:

- Death (most often from infection/bleeding/cardiac disease)

  or

- Leukemic progression within months (generally <18 months)

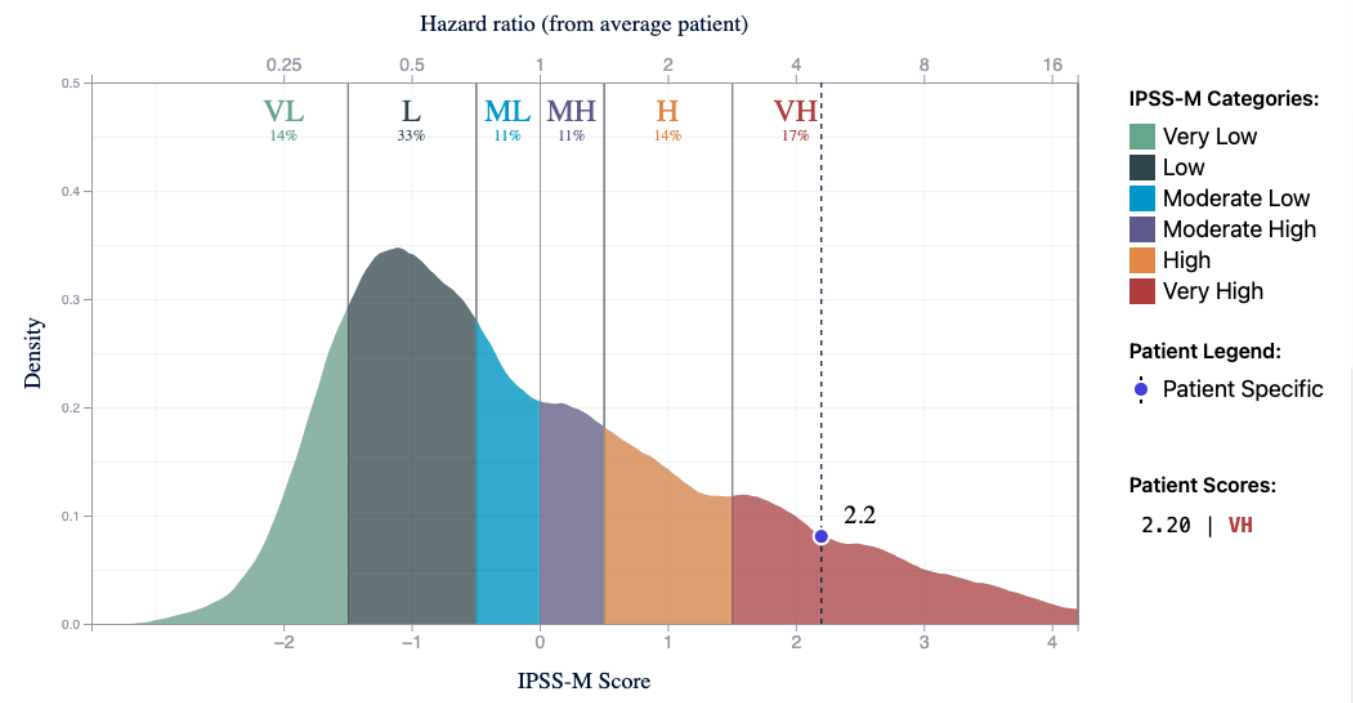


AML, acute myeloid leukemia; INT, intermediate; IPSS, international prognostic scoring system; IPSS-R, revised IPSS; MDS, myelodysplastic syndrome.

Higher-Risk MDS Case

Patient JB:

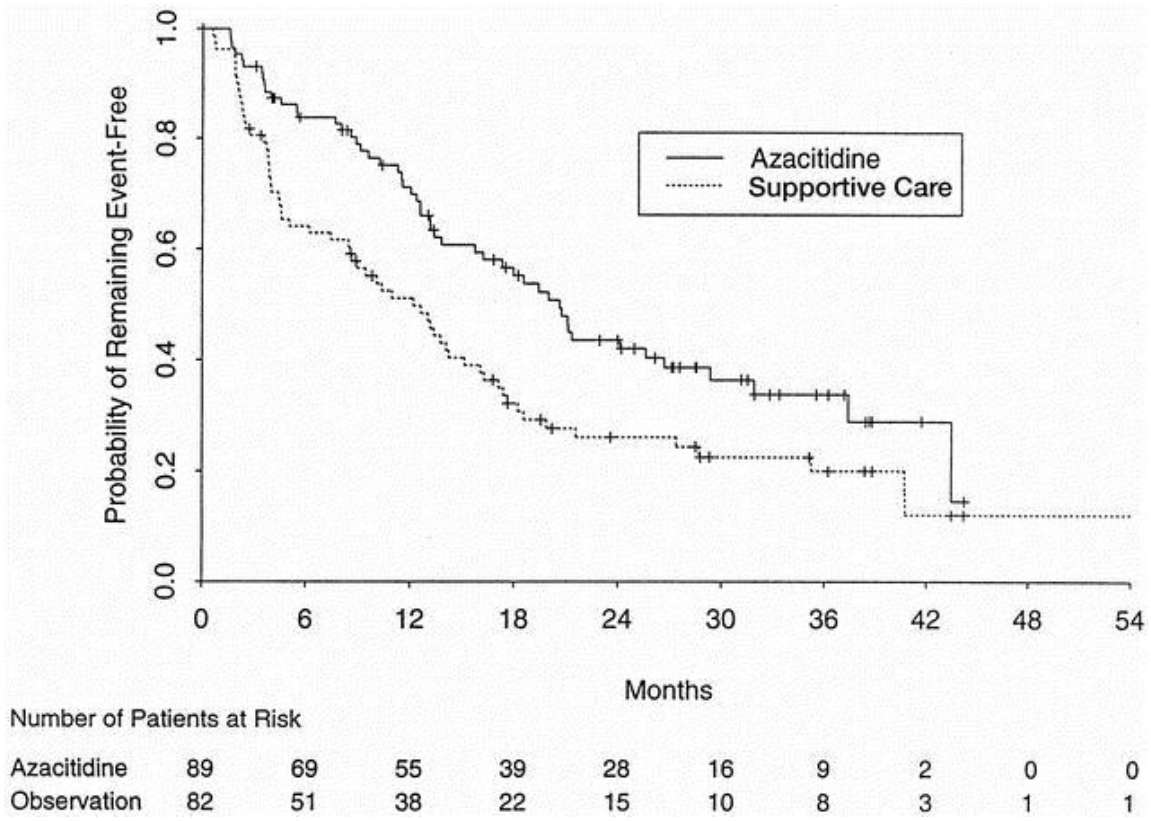
- 80-year-old woman with progressive anemia
- CBC and differential with WBC 2, ANC 0.6, Hgb 8 g/dL, platelets 45
- Bone marrow biopsy: hypercellular, 12% CD34+ blasts, no ring sideroblasts
- Cytogenetics: 46,XX,del7q
- Molecular studies: mutations in *BCOR*, *CBL*, *U2AF1*



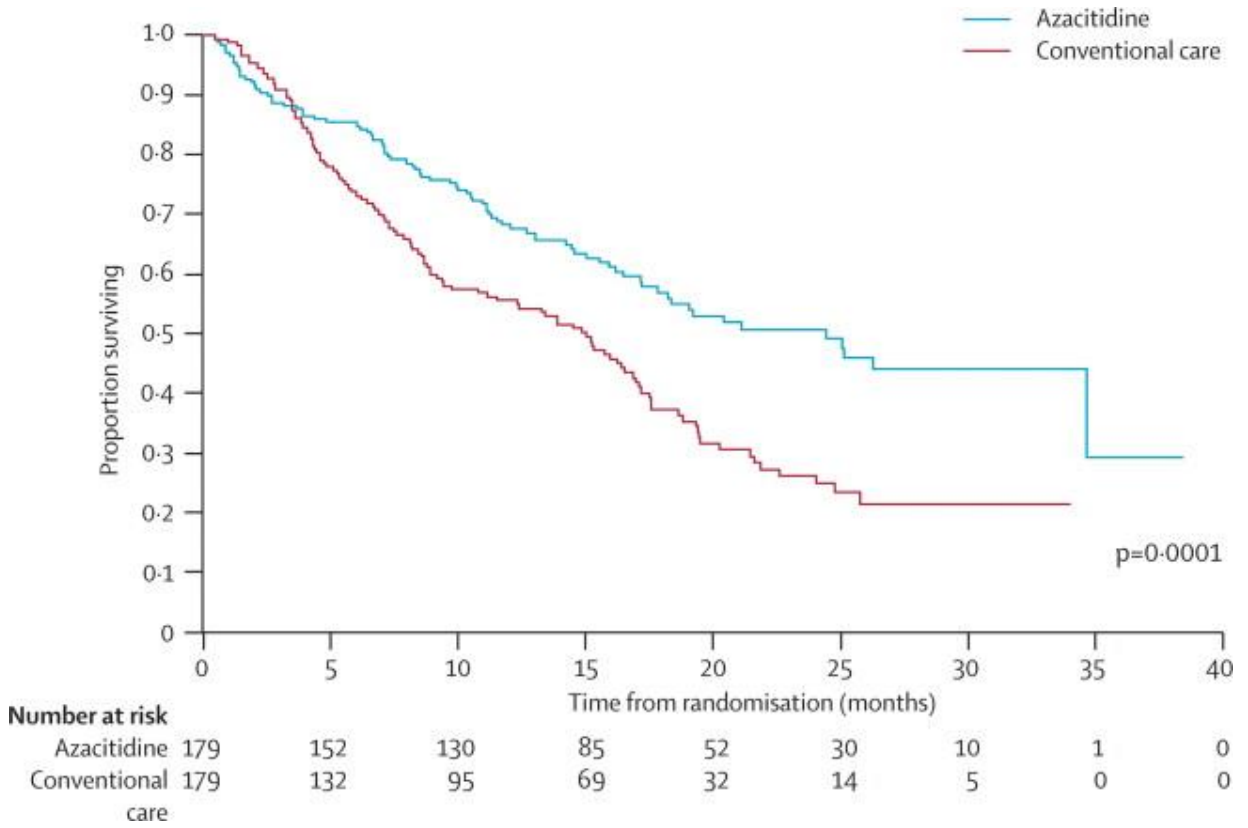
ANC, absolute neutrophil count; CBC, complete blood cell; Hgb, hemoglobin; IPSS-M, Molecular International Prognostic Scoring System; WBC, white blood cells.

Bernard et al. ASH Annual Meeting & Exposition, December 2021, Abstract 61.

Higher-Risk MDS: Hypomethylating Agents



CALGB 9221: OS 20 mo (AZA) vs. 14 mo (Conventional Care)

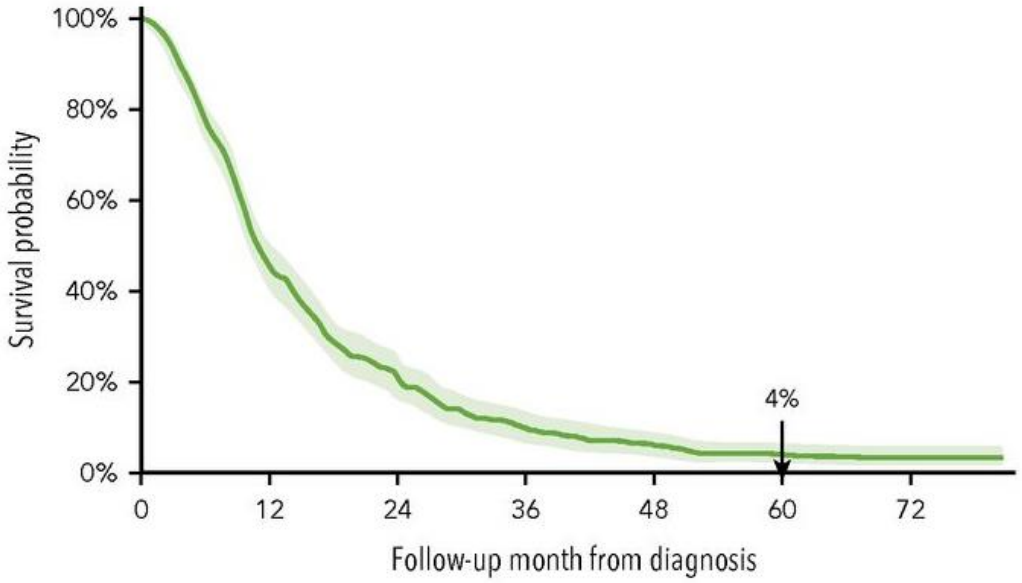


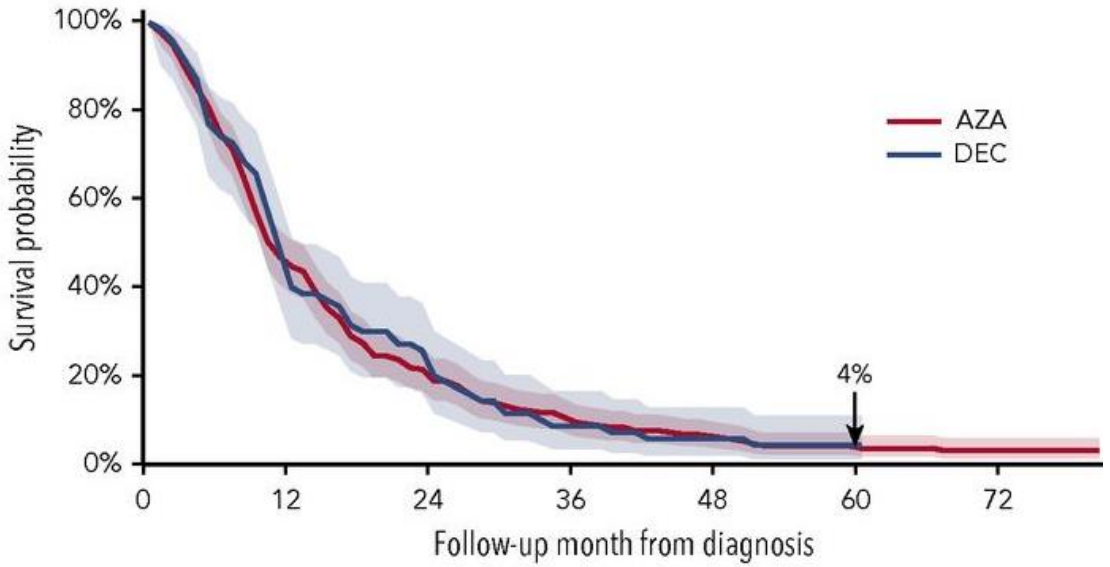
AZA001: OS 21.1 mo (AZA) vs. 15.0 mo (Conventional Care)

CALGB, Cancer and Leukemia Group B; AZA, azacytidine; OS, overall survival; mo, months.

Silverman et al. *J Clin Oncol*. 2002;20(10):2429-2440; Fenaux et al. *Lancet Oncol*. 2009;10(3):223-232.

HMAs in Myelodysplastic Syndromes



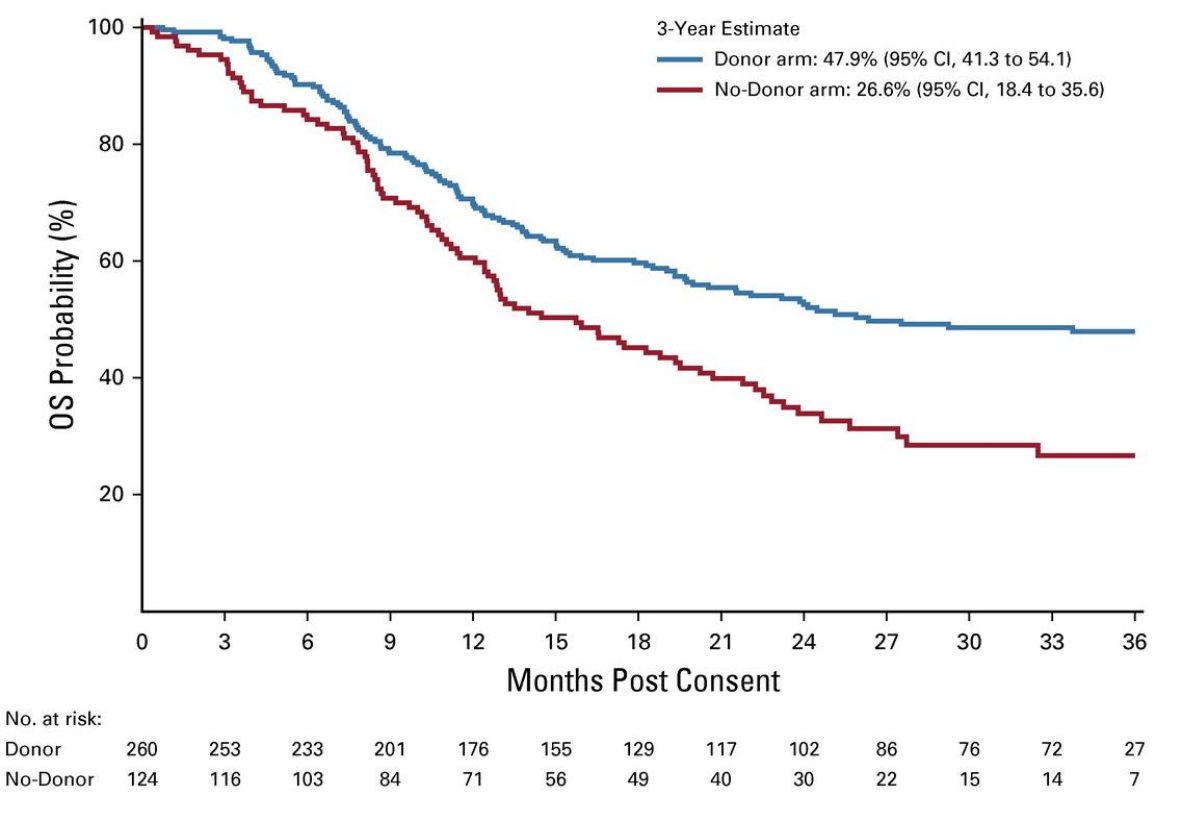


SEER-Medicare, all patients, irrespective of MDS disease risk

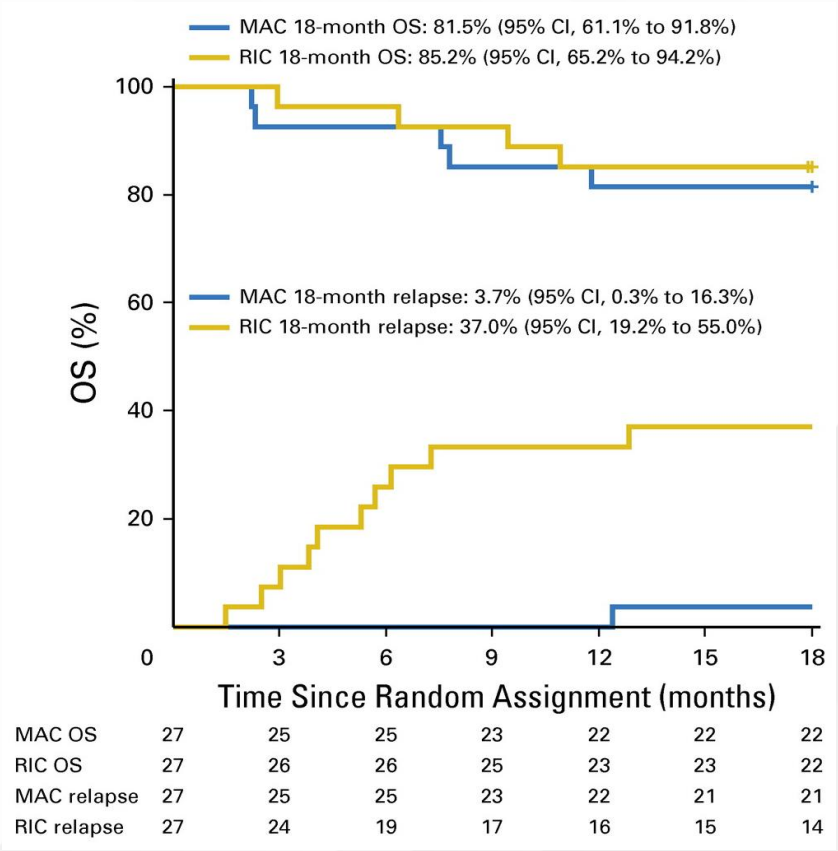
AZA, azacitidine; DEC, decitabine; HMAs, hypomethylating agents; MDS, myelodysplastic syndrome; SEER, Surveillance, Epidemiology, and End Results.

Zeidan et al. *Blood* 2018;131:818-821.

Role of Transplant



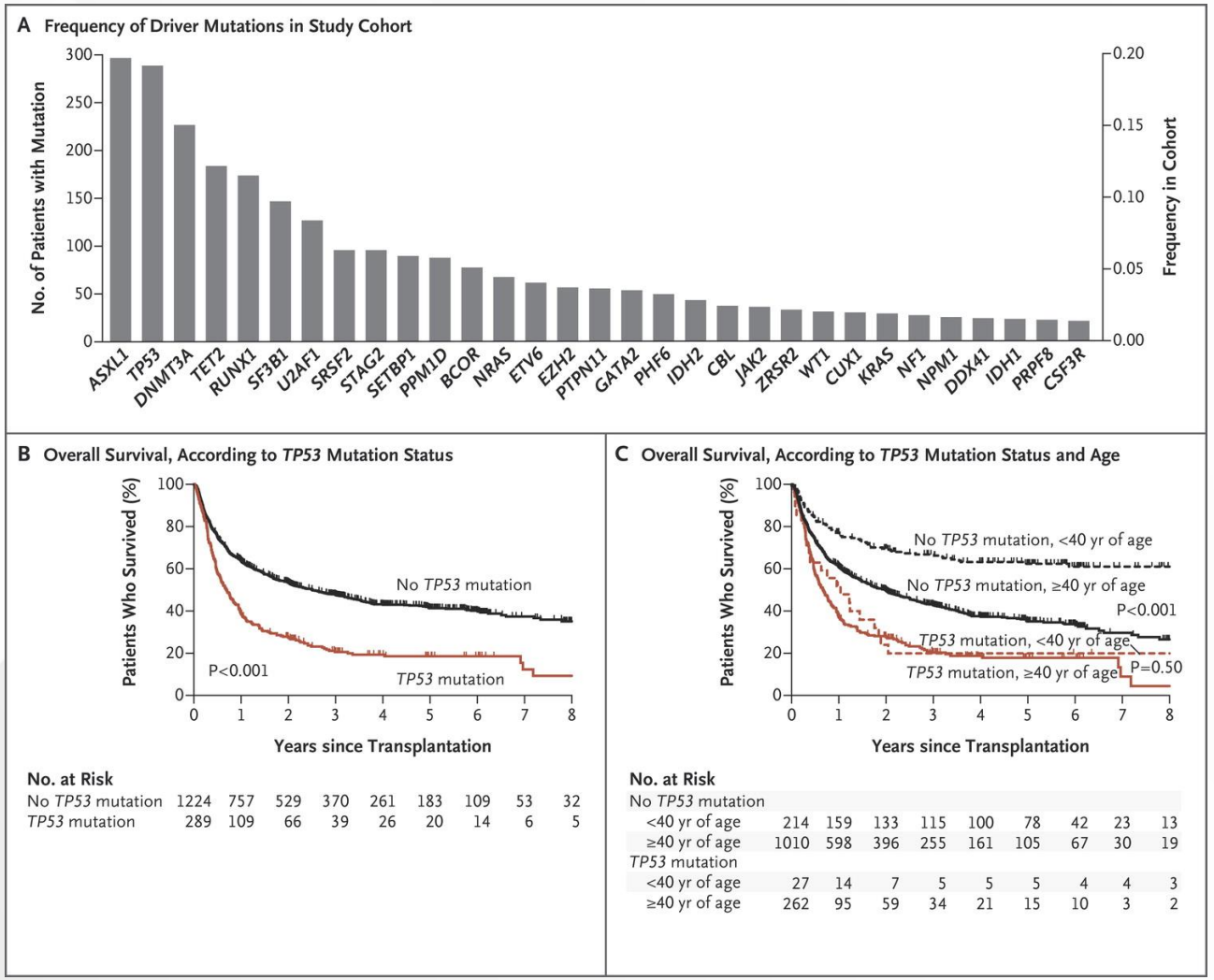
MAC vs RIC in MDS

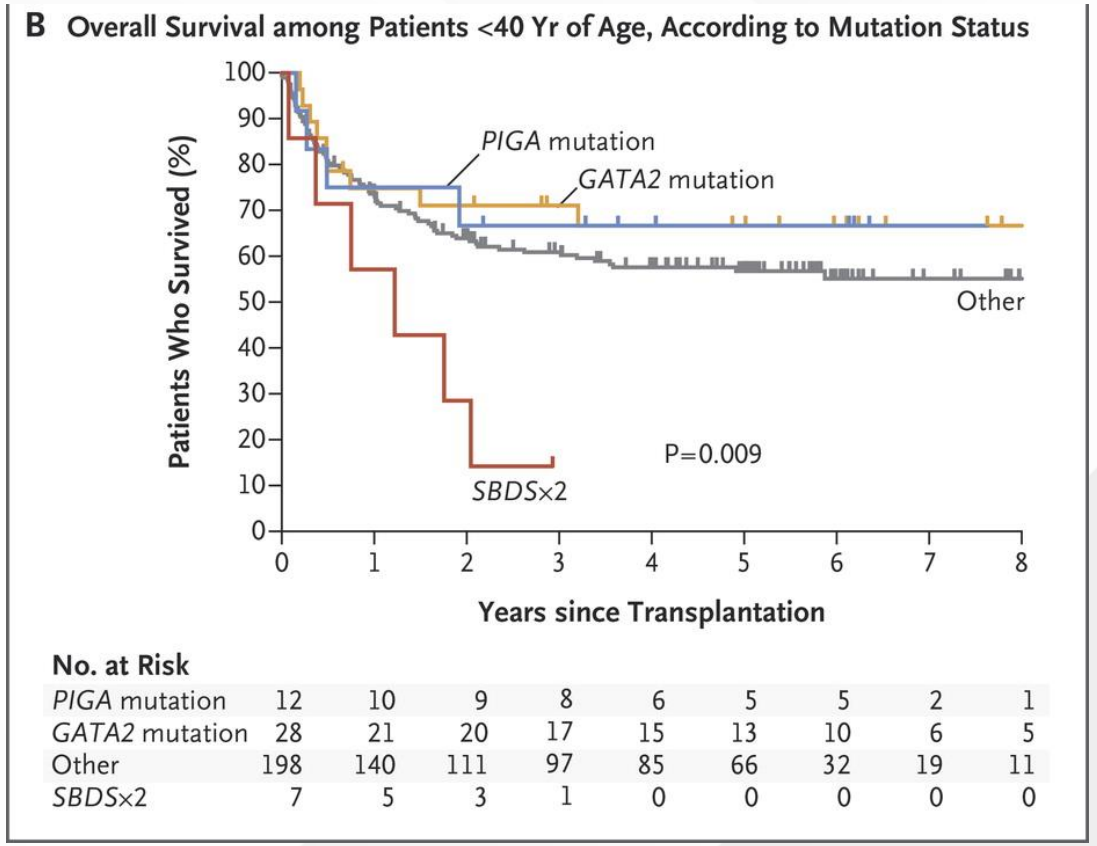


MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; RIC, reduced-intensity conditioning; OS, overall survival.

BMT CTN 1102. Nakamura et al. *J Clin Oncol*. 2021;39(3):3328-3339; Scott et al. *J Clin Oncol*. 2017;35(11):1154-1161.

Mutations and Transplant

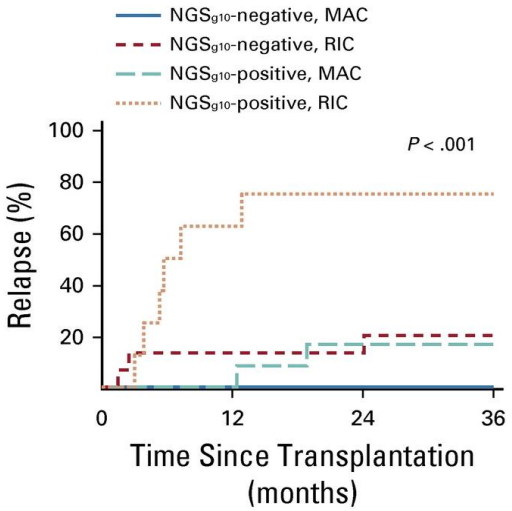


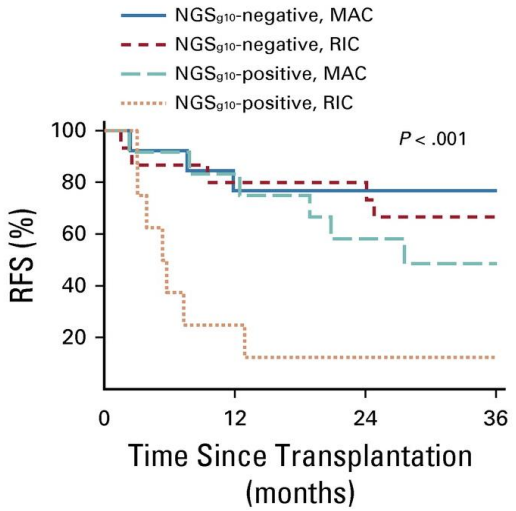


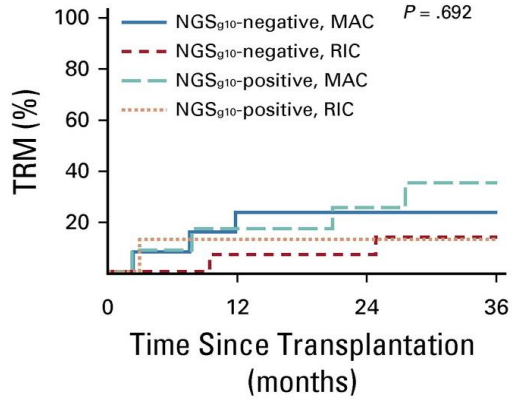
Does pre-transplant therapy/response impact post-transplant outcomes?

Lindsley et al. *N Engl J Med*. 2017;376:536-547.

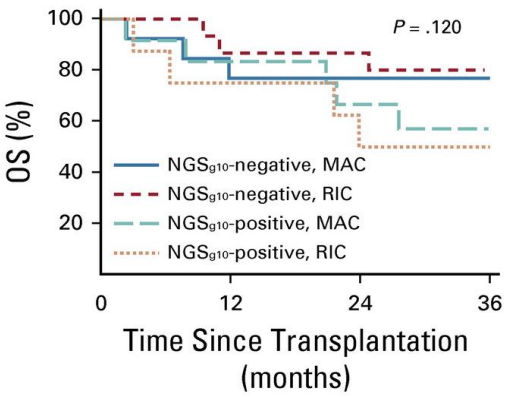
RIC vs. MAC Transplant







No. at risk					
NGS$_{g10}$-negative	MAC	13	10	10	10
	RIC	15	12	12	10
NGS$_{g10}$-positive	MAC	12	10	7	4
	RIC	8	2	1	1



No. at risk					
NGS$_{g10}$-negative	MAC	13	10	10	10
	RIC	15	13	13	12
NGS$_{g10}$-positive	MAC	12	10	8	5
	RIC	8	6	4	4

MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; OS, overall survival; TRM, transplant-related mortality; RFS, relapse-free survival; NGS, next generation sequencing.
Dillon et al. *JCO Precision Oncol.* 2021;5:265-274.

Innovative Therapeutics for High-Risk MDS

Rationale for Use and Integration Into Treatment Plans

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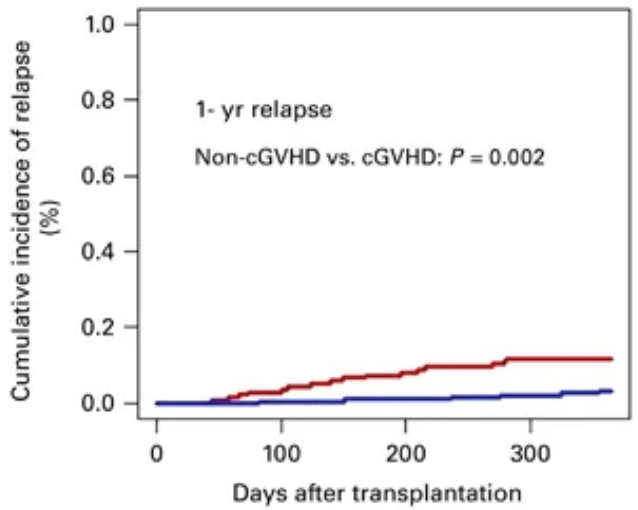
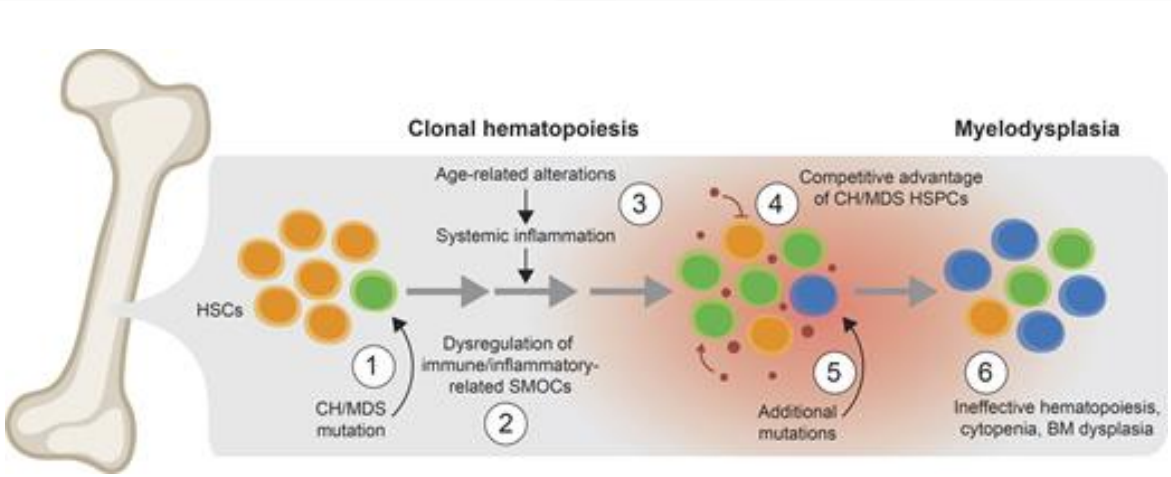
Altered Immunity in MDS

- How the altered immune system may play a therapeutic role in MDS
- How an altered immune system may impact MDS pathogenesis

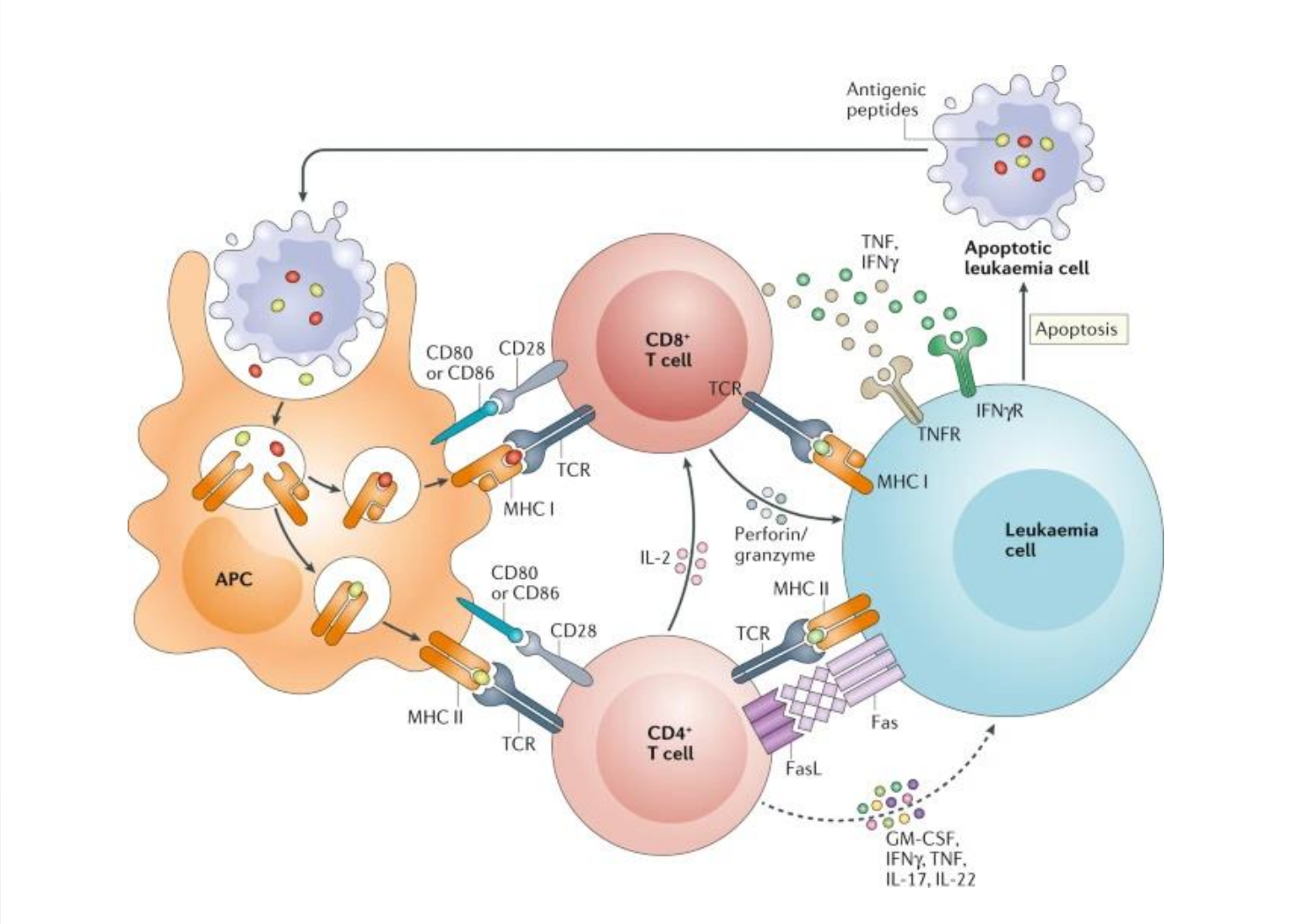




BM, bone marrow; cGVHD, chronic GVHD; GVHD, graft vs host disease; MDS, myelodysplastic syndrome; HSCs, hematopoietic stem cells; CH, clonal hematopoiesis; SMOCs, supramolecular organizing centers; HSPCs, hematopoietic stem and progenitor cells.

Mo et al. *Bone Marrow Transplant*. 2015;50:127-133; Trowbridge et al. *J Exp Med*. 2021;218:e20201544.

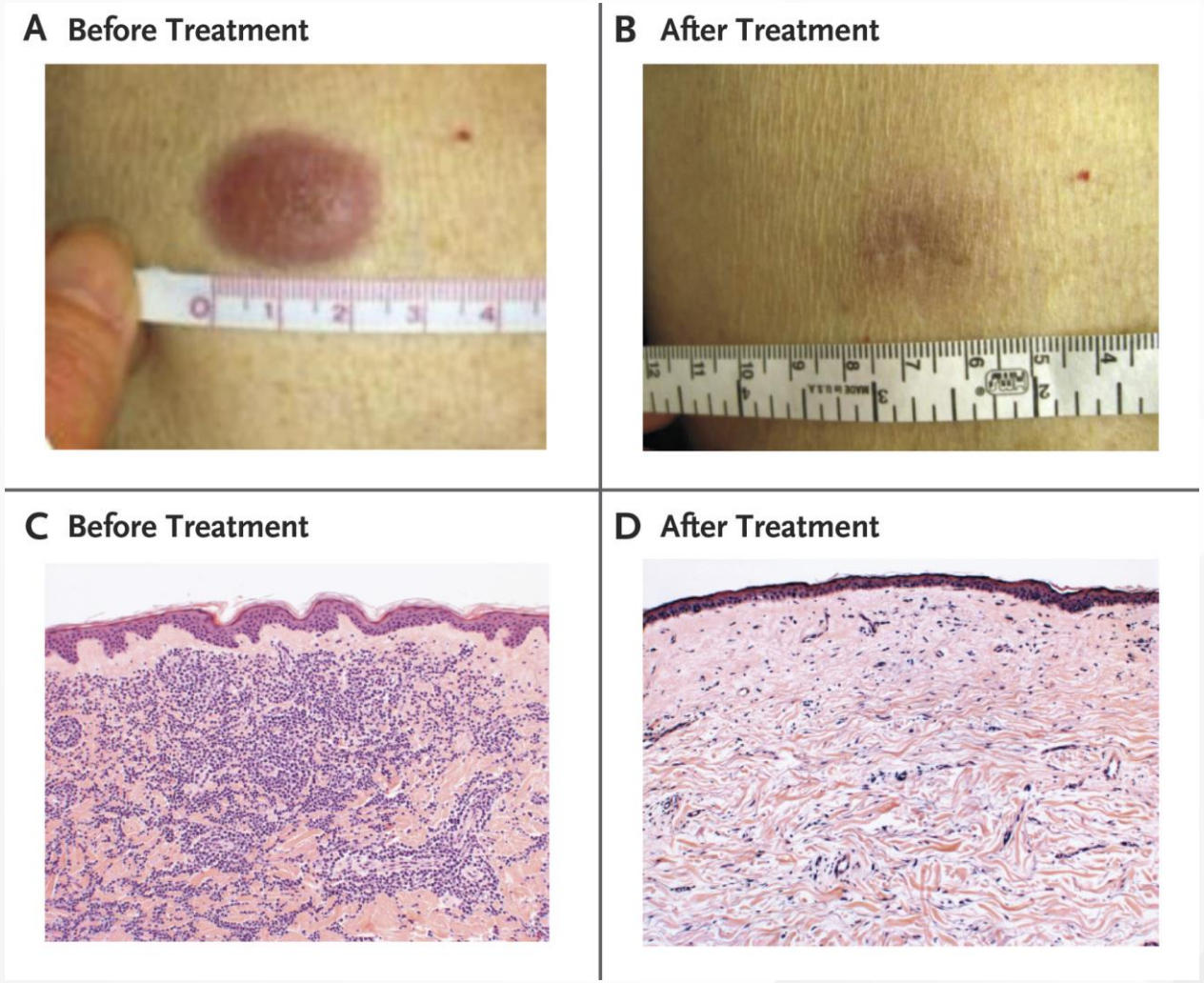
Allogeneic Transplant and MDS/AML



AML, acute myeloid leukemia; APC, antigen-presenting cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; MDS, myelodysplastic syndrome; TCR, T-cell receptor; TNF, tumor necrosis factor.

Blazar et al. *Nat Rev Clin Oncol*. 2020;17:475-492.

Immune Checkpoint Inhibition in MDS/AML



AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.
Davids et al. *N Engl J Med*. 2016;375:143-153.

Challenges with Canonical ICIs in MDS

Response	Arm A (azacitidine + durvalumab) (N = 42)		Arm B (azacitidine) (N = 42)		*P*
	No. (%)	95% CI	No. (%)	95% CI	
ORR (CR + PR + mCR + HI)	26 (61.9)	47.22-76.59	20 (47.6)	32.51-62.72	.1838
CR	3 (7.1)	0.00-14.93	4 (9.5)	0.65-18.40	
mCR	15 (35.7)	21.22-50.21	8 (19.0)	7.17-30.92	
PR	0		0		
HI only	8 (19.0)	7.17-30.92	8 (19.0)	7.17-30.92	
SD	6 (14.3)		3 (7.1)		

Median OS (11.6 months vs 16.7 months; *P* = .74)

Median PFS (8.7 months vs 8.6 months; *P* = .93)

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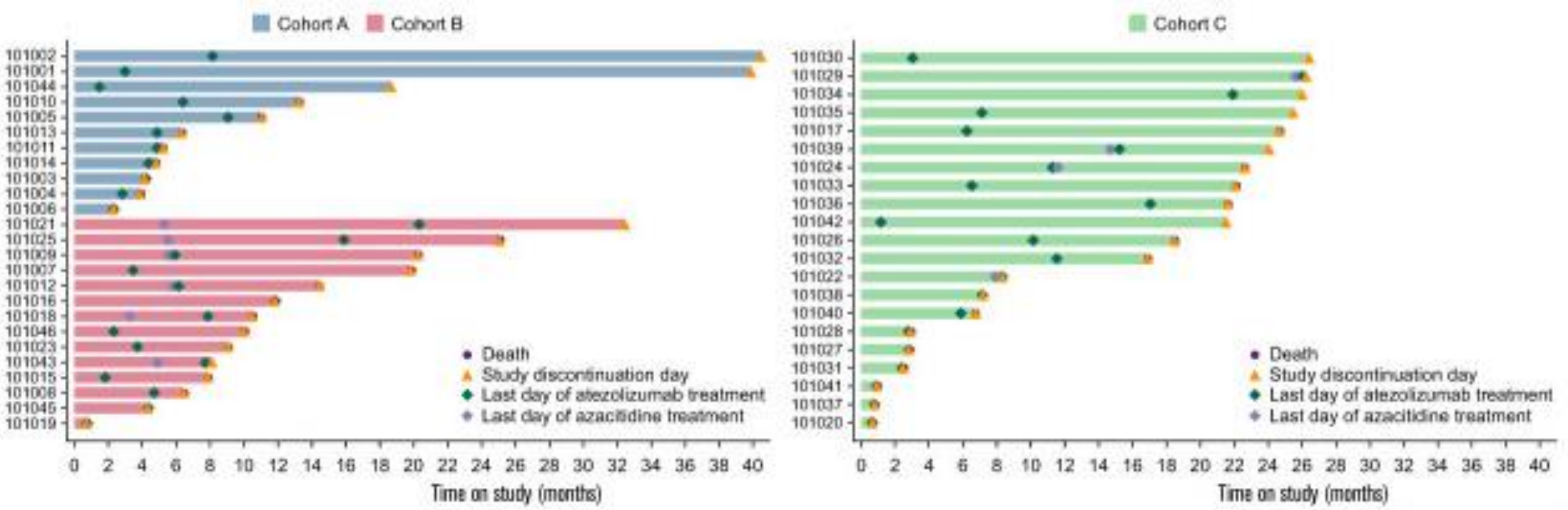
CR, complete response; HI, hematologic improvement; mCR, median CR; MDS, myelodysplastic syndrome; ICI, immune checkpoint inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

Gerds et al. *Blood Adv*. 2022;6(4):1152-1161.

Challenges with Canonical ICIs in MDS

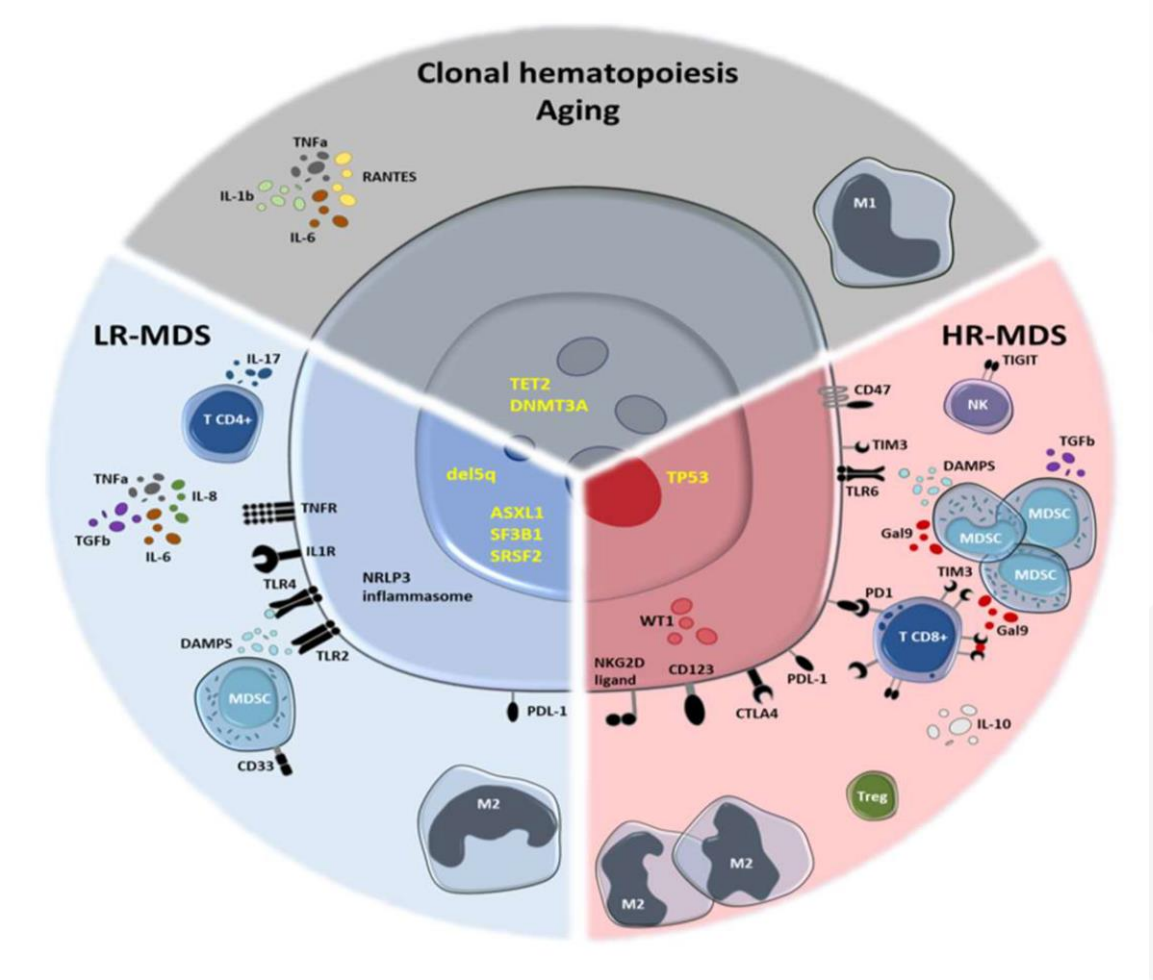
- The combination of atezolizumab plus azacitidine in HMA-naïve patients was associated with high early mortality rates, which led to early study termination
- Atezolizumab alone or in combination with azacitidine had limited clinical activity in patients with MDS previously exposed to HMAs, although this was without excessive or unexpected toxicity



Atezo, atezolizumab; AZA, azacytidine; HMA, hypomethylating agent; ICI, immune checkpoint inhibitor; IV, intravenous; MDS, myelodysplastic syndrome.

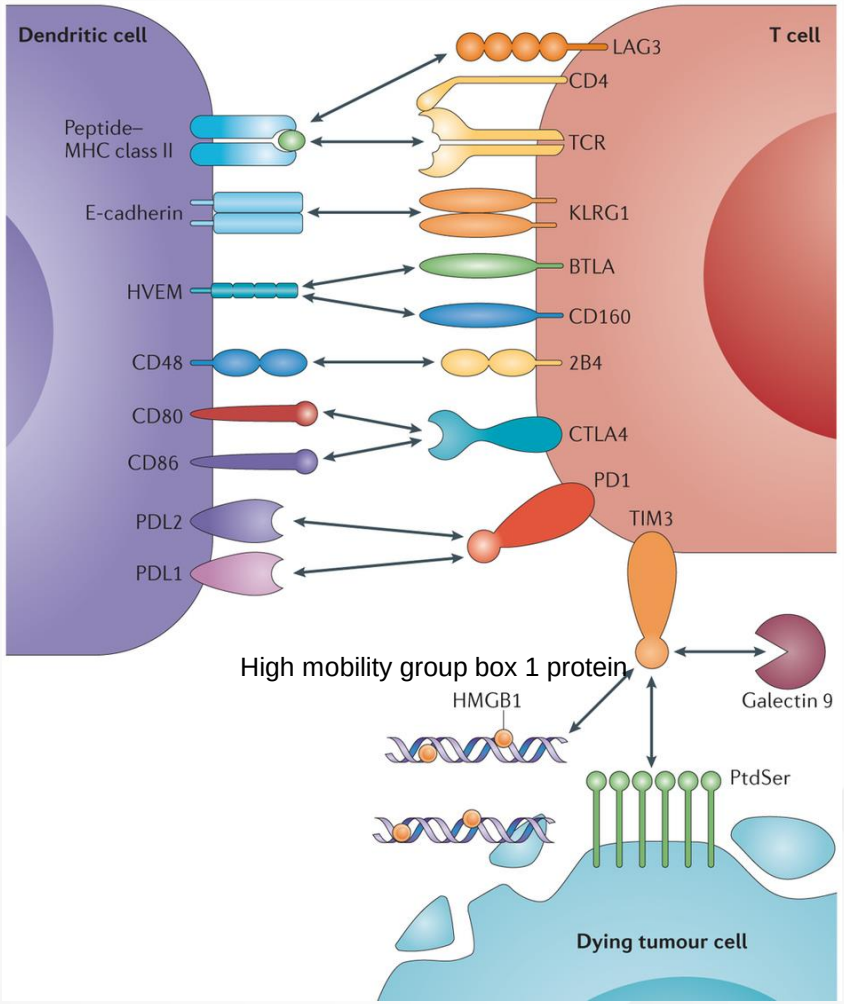
Gerds et al. *Blood Adv*. 2022;6(4):1152-1161.

Immune Key Hubs Involved in Early Stages, Low-Risk MDS, and High-Risk MDS



HR, high risk; LR, low risk; MDS, myelodysplastic syndrome; NK, natural killer; MDSC, myeloid-derived suppressor cells.
Comont et al. *Diagnostics* 2021;11(11):982.

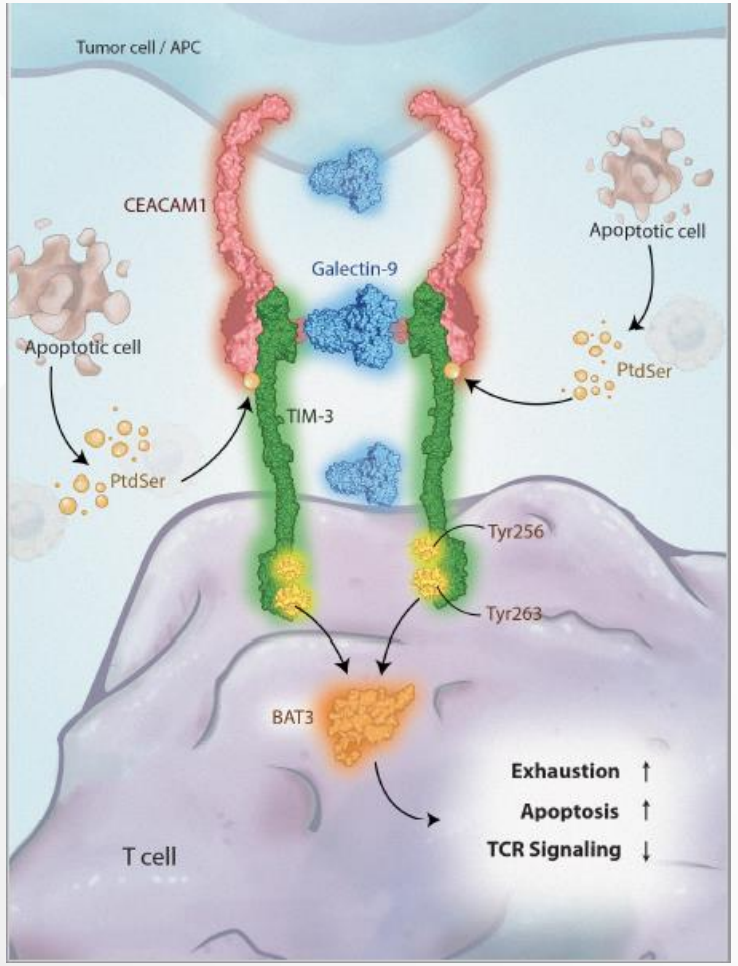
Clinical Blockade of PD-1 and LAG3: Potential Mechanisms of Action



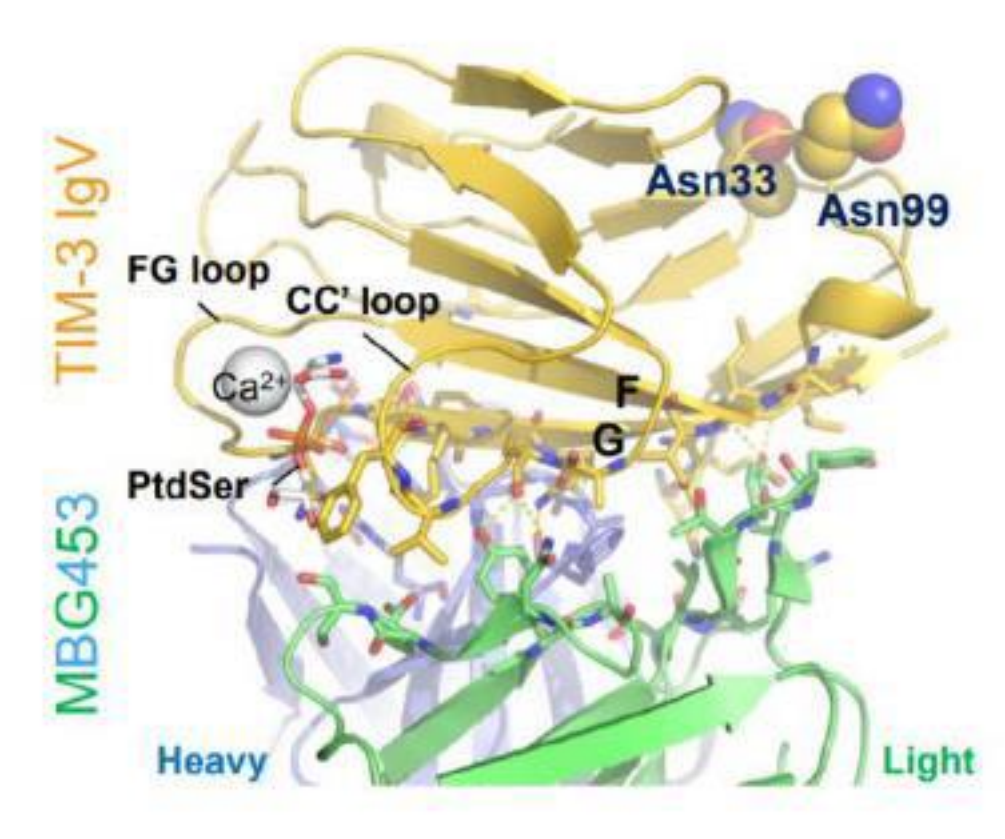
MHC, major histocompatibility; PD-1, programmed-death 1; LAG3, lymphocyte activating 3.

Nguyen and Ohashi. *Nat Rev Immunol*. 2015;15:45-56.

T-cell Immunoglobulin Domain and Mucin Domain 3



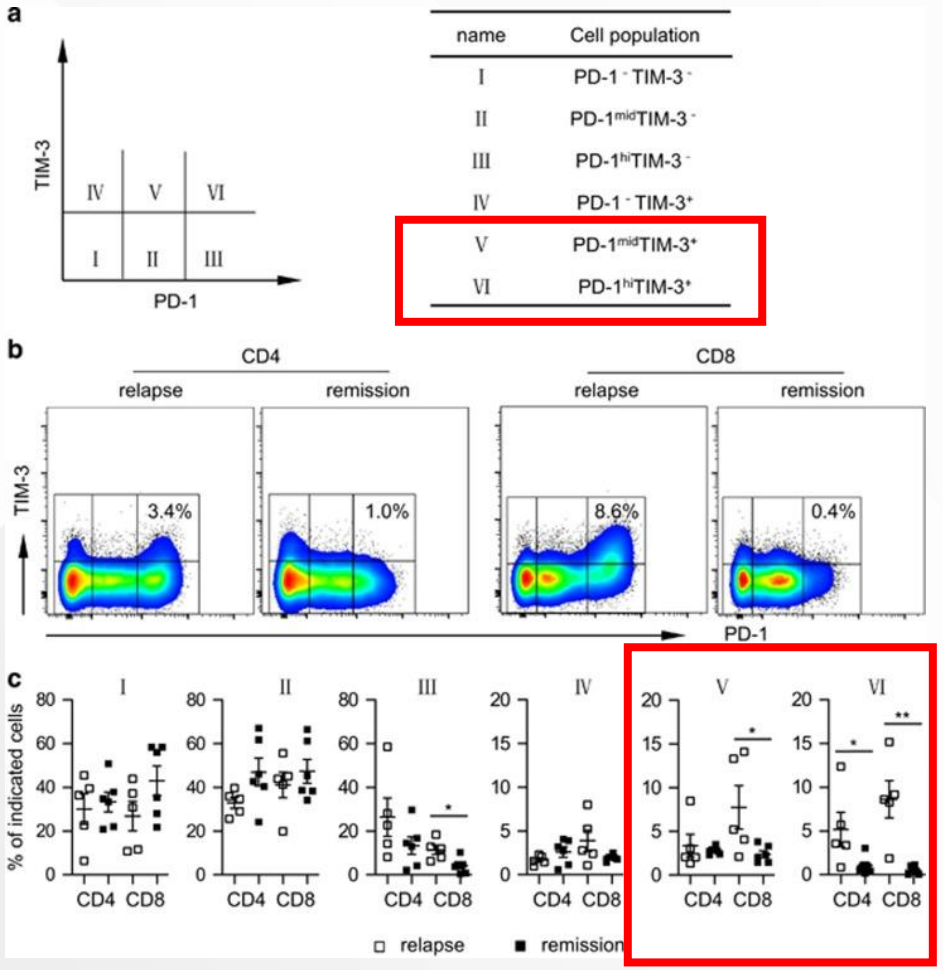
Sabatolimab (MBG453)



APC, antigen-presenting cell; TCR, T-cell receptor.

Sabatos-Peyton C. MBG453: A high affinity, ligand-blocking anti-TIM-3 monoclonal mAb. AACR 2016.

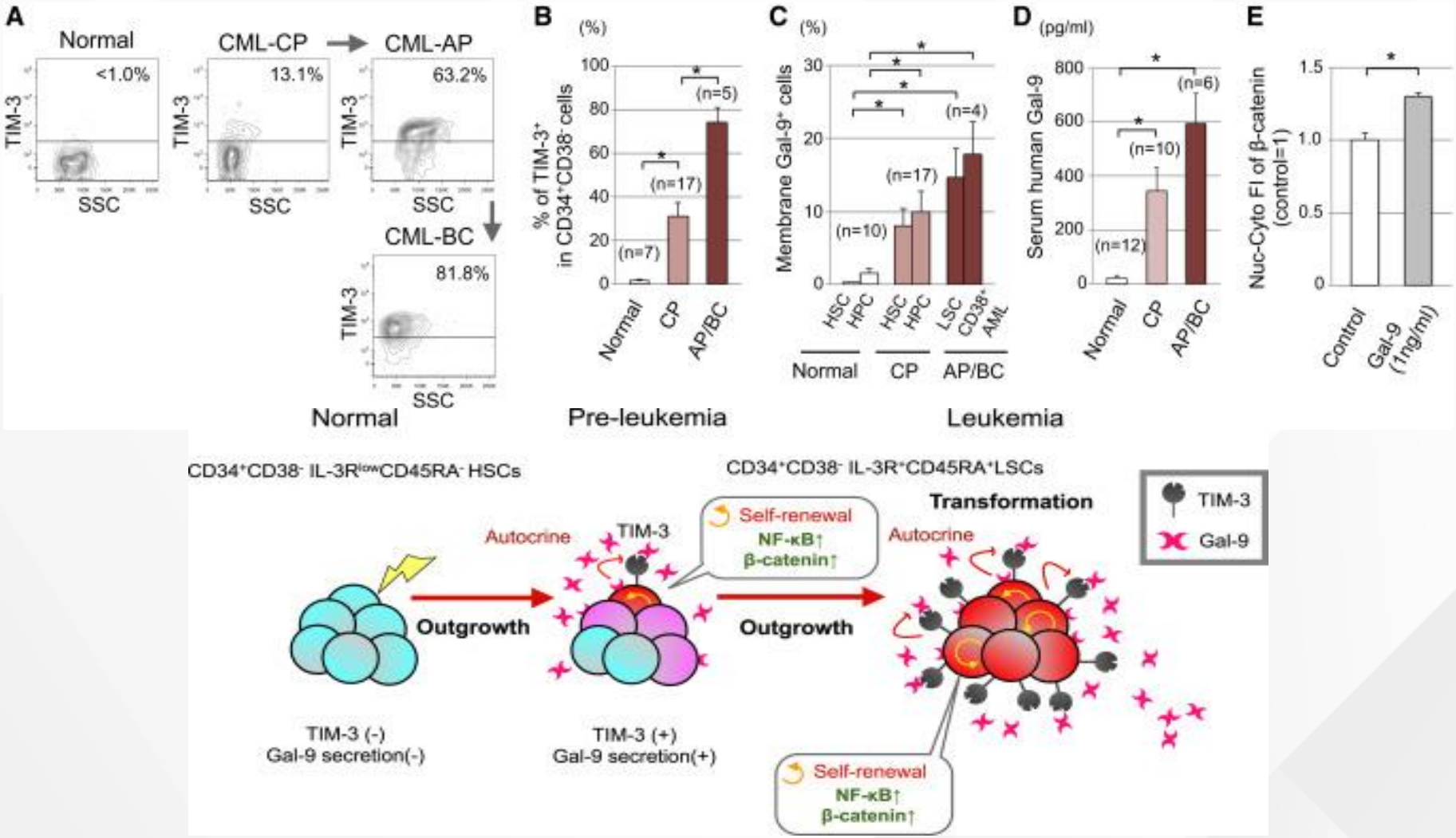
TIM3/PD-1 Expression and Post-HCT Relapse



- Increase in PD-1+/TIM3+ CD8 T-cells at relapse
- Consistent with immune evasion and TIM3 upregulation playing a potential role

HCT, hematopoietic stem cell transplantation; PD-1, programmed-death 1; TIM3, T-cell immunoglobin mucin-3.
Kong et al. *Blood Cancer J*. 2015;5(7):e330.

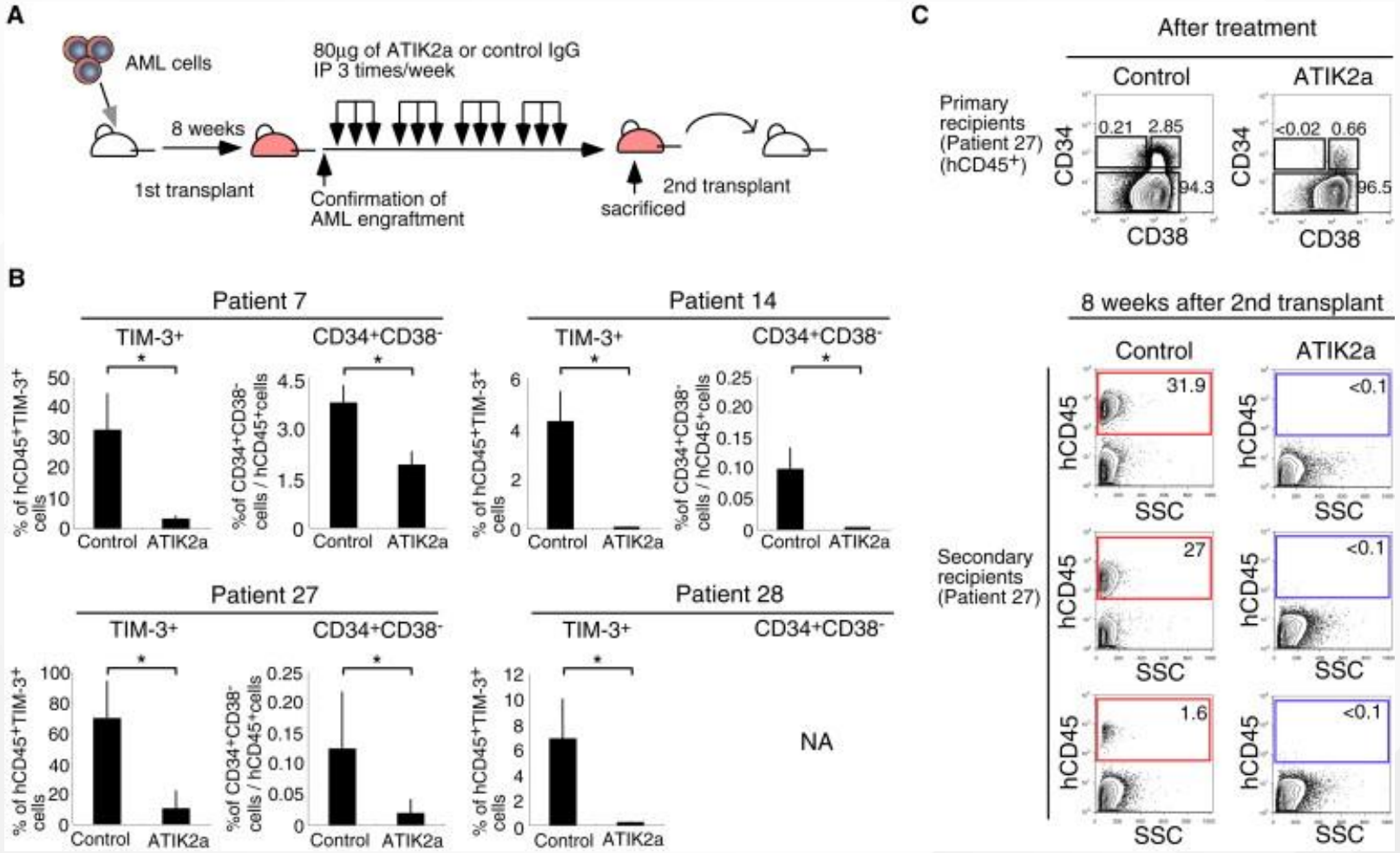
TIM3 Expression on Leukemic Progenitors



CML-CP, chronic myelogenous leukemia-chronic phase; CML- AP, chronic myelogenous leukemia-accelerated phase; CML-BC, chronic myelogenous leukemia-blast crisis; HSCs, hematopoietic stem cells; LCSs, leukemic stem cells; TIM3, T-cell immunoglobin mucin-3.

Kikushige et al. *Cell Stem Cell* 2015;17(3):341-352.

TIM3 Inhibition in AML



AML, acute myeloid leukemia; TIM3, T-cell immunoglobin mucin-3.
Kikushige et al. *Cell Stem Cell* 2010;7:708.

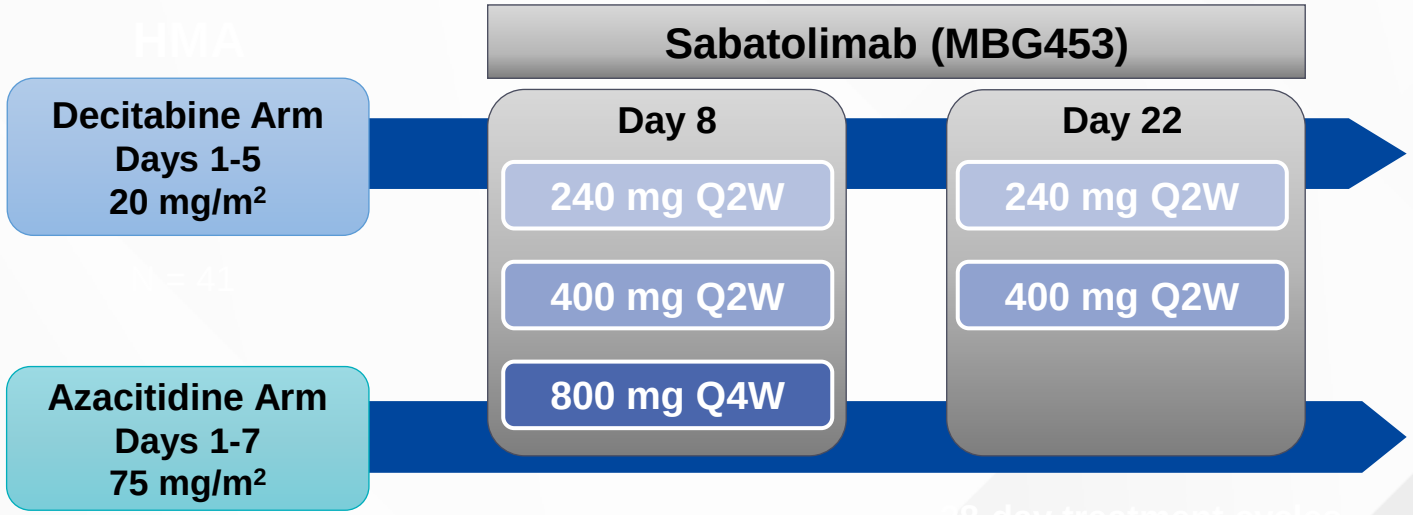
Phase 1b Study of Sabatolimab + HMA in MDS and AML

vHR/HR-MDS: IPSS-R high- or very high-risk MDS

ND-AML: Unfit, newly diagnosed AML, ineligible for standard chemotherapy

No prior HMA treatment

ClinicalTrials.gov Identifier: **NCT03066648**[a]

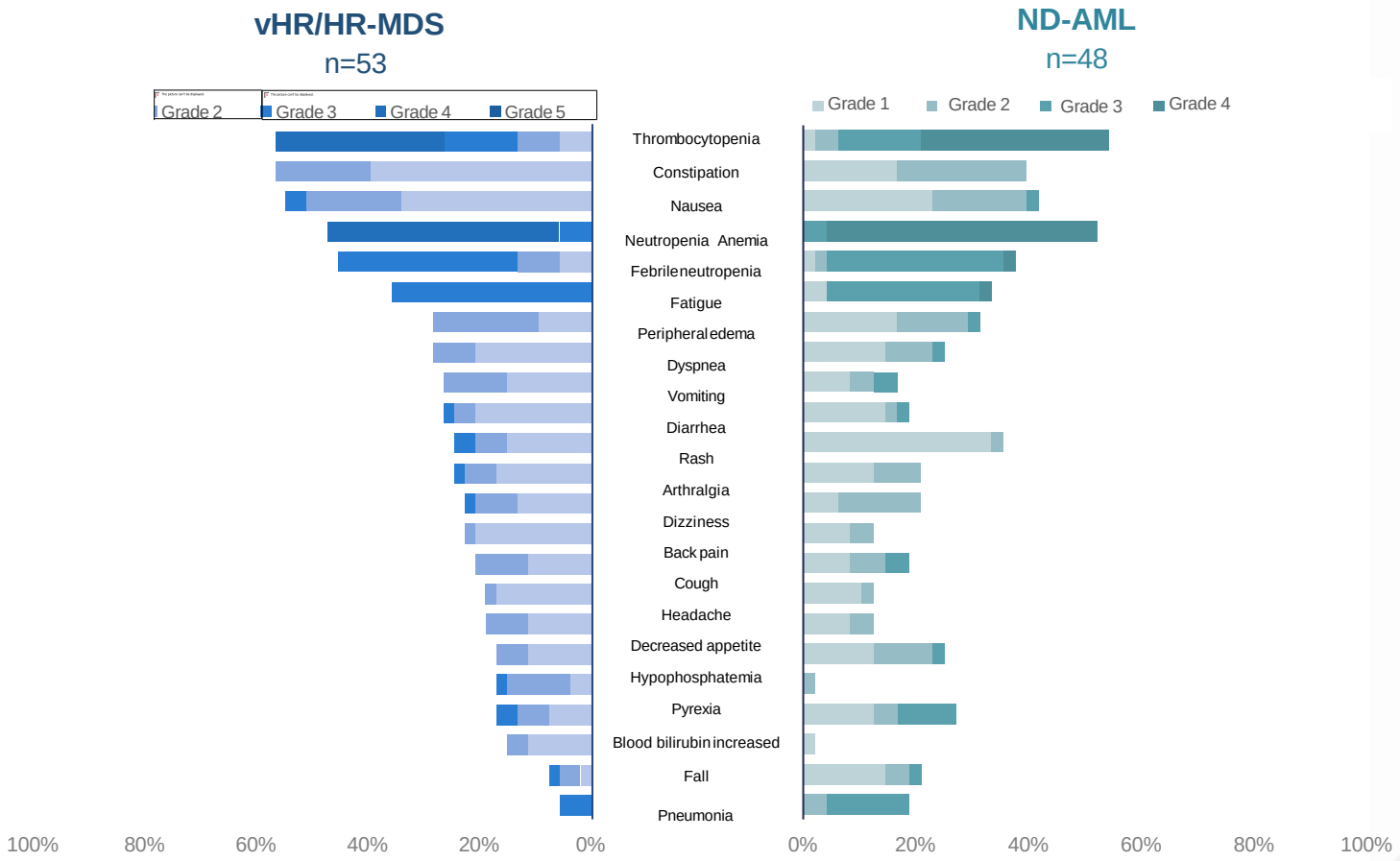


Primary Endpoints:
Maximum tolerated dose/recommended dose, safety, and tolerability
Secondary Endpoints:
Preliminary efficacy: Response rates and duration of response

AML, acute myeloid leukemia; HMA, hypomethylating agent; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; HMA, hypomethylating agent; HR, high risk; ND, newly diagnosed; vHR, very high risk.
Brunner et al. *Blood* 2021;138(suppl 1):244.

Most Commonly Occurring Adverse Events

(≥15% in either population, regardless of relationship to treatment)



vHR/HR-MDS and ND-AML AEs

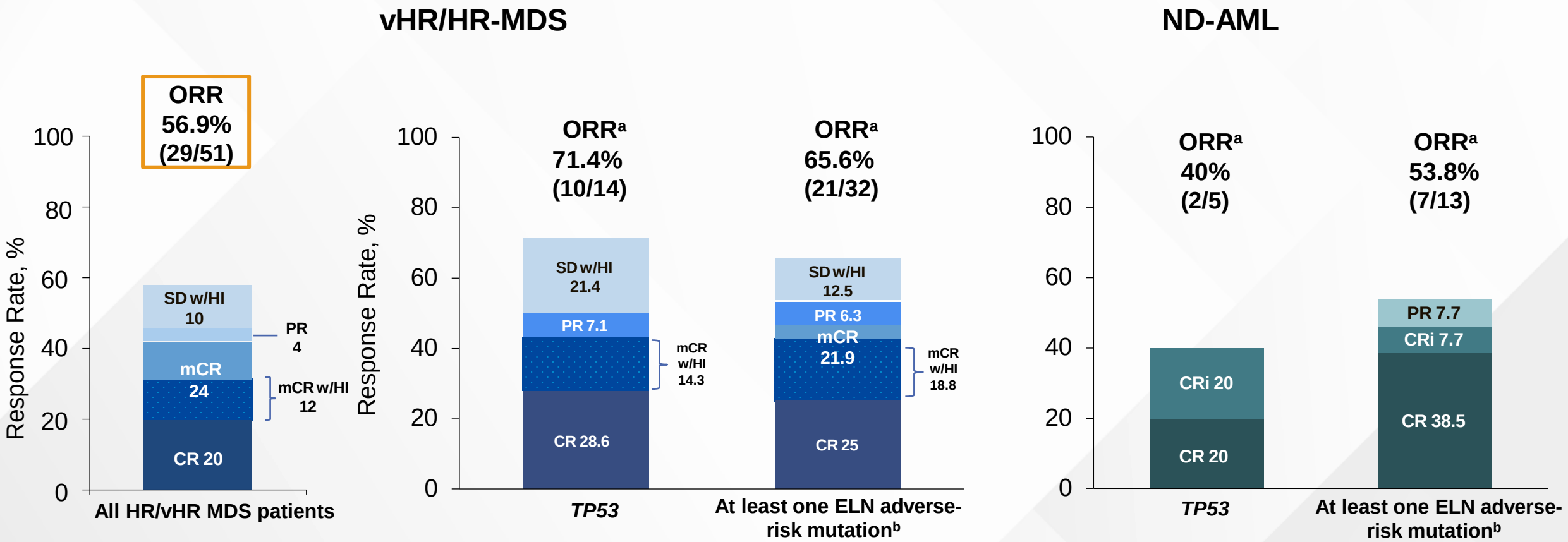
- Most common reported AEs were cytopenias, GI symptoms, fatigue
- Low rate of sabatolimab dose modification:
  - 1/101 (1%) patients had dose reduction
- 38/101 (38%) patients had dose interruption (cycle delay >7d) due to AE
  - No patient with vHR/HR-MDS and only 3 with ND-AML discontinued treatment due to an AE
- One patient with neutropenic colitis reported as suspected to be related to study treatment died of septic shock. No other treatment-related deaths were reported
- No DLTs in vHR/HR-MDS and only 1 in ND-AML

AXIS Medical Education

AEs, adverse events; ND-AML, newly diagnosed acute myeloid leukemia; DLT, dose-limiting toxicities; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; HMA, hypomethylating agent; HR, high risk; vHR, very high risk.

Brunner et al. *Blood* 2021;138(suppl 1):244.

Sabatolimab + HMA Response Rates



Medical Education

[a]Evaluable patients included patients with a valid baseline and at least 1 postbaseline bone marrow assessment or if they had disease progression or disease-related death prior to the first marrow assessment.
CR, complete response; CRi, CR with incomplete blood recovery; ELN, European LeukemiaNet; HI, hematologic improvement; HMA, hypomethylating agent; mCR, marrow complete response; ND-AML, newly diagnosed acute myeloid leukemia; ORR, overall response rate; PR, partial response; SD, stable disease; HR, high risk; vHR, very high risk. Brunner et al. *Blood* 2021;138(suppl 1):244.

Duration of Responses to Sabatolimab + HMA in MDS

17.1 mo

Median DOR
[CR / mCR / PR]
(95% CI, 6.7-NE)

54.0%

Estimated 12-mo
PFS rate
(95% CI, 33.0%-71.0%)

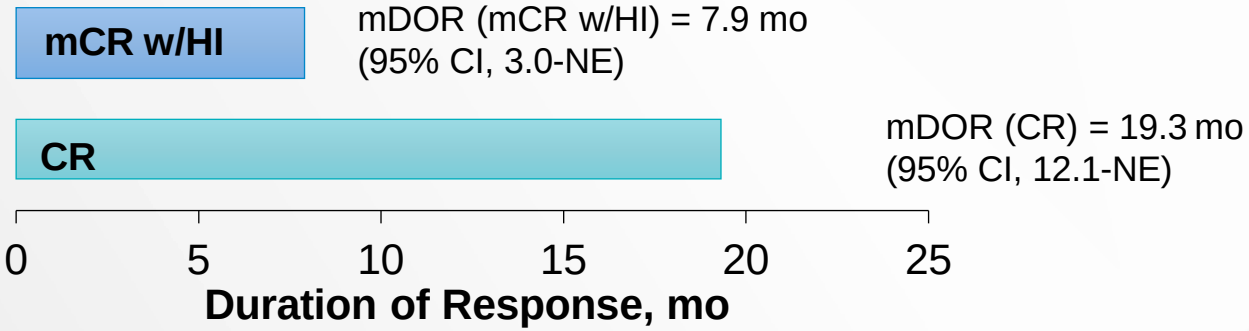
TP53

21.5 mo

95% CI, 6.7-NE
Events, 3/7[c]

Median Duration of Response by response category

mDOR for mCR and PR could not be estimated



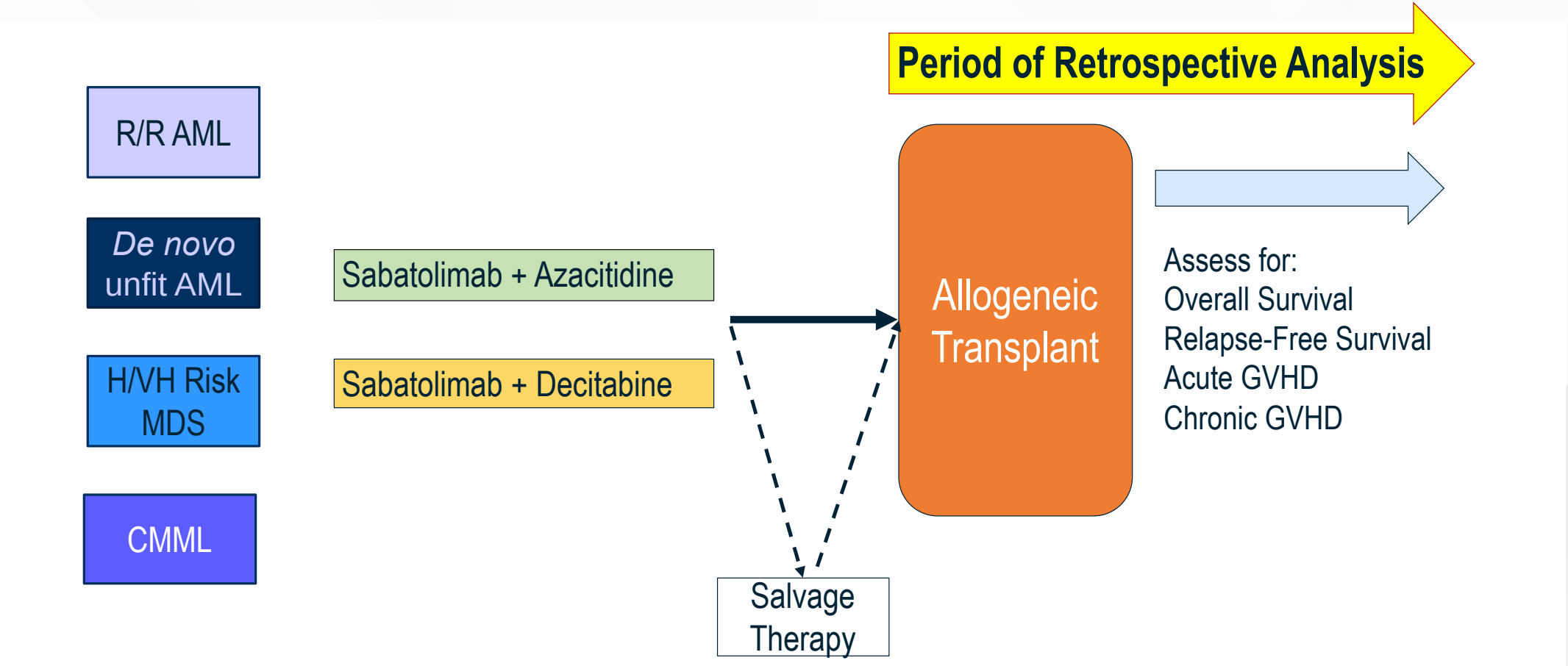
At least one ELN adverse-risk mutation[b]

16.1 mo

95% CI, 6.7-NE
Events, 7/17[c]

[a]ORR for patients with MDS was defined as CR + mCR + PR + SD with HI; ORR for patients with ND-AML was defined as CR + CRi + PR; [b]ELN adverse-risk mutations: *TP53*, *ASXL1*, and *RUNX1*; [c]DOR events (including progression/relapse and death) reported out of the number of patients with a BOR of CR, mCR, or PR (for MDS) or CR, CRi, or PR (for AML).
CR, complete response; mCR, marrow complete response; DOR, duration of response; ELN, European LeukemiaNet; HI, hematologic improvement; HMA, hypomethylating agent; mDOR, median DOR; NE, not evaluable; PFS, progression-free survival; PR, partial response. Döhner et al. *Blood* 2017;129(4):424-447; Brunner et al. *Blood* 2021;138(suppl 1):244.

Retrospective Study: Transplant After Sabatolimab Exposure



AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; GVHD, graft vs host disease; H/VH, high/very high; R/R, relapsed/refractory.

Brunner et al. *Blood* 2021;138(suppl 1):3677.

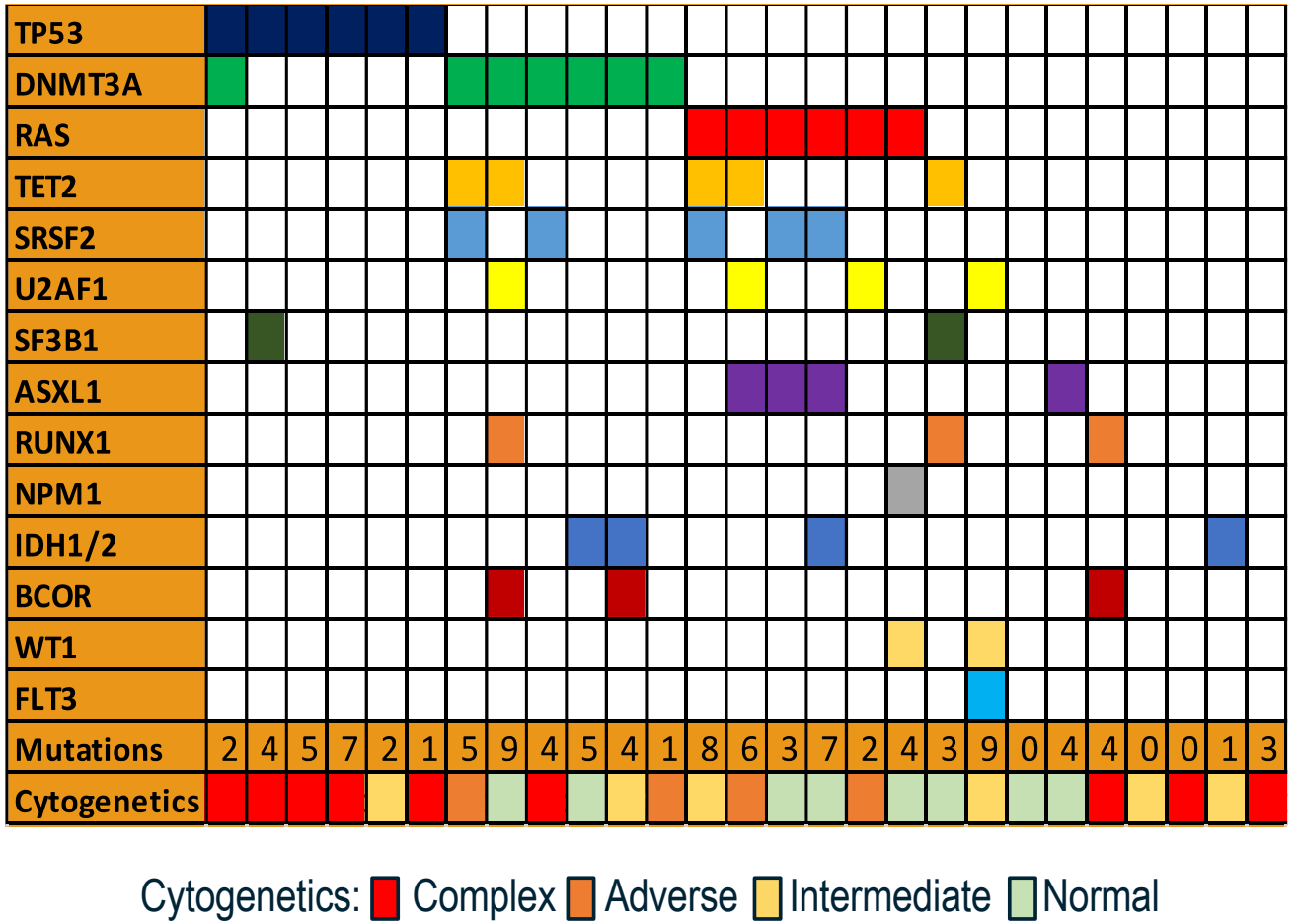
Patient Characteristics

Age (median, range)	67 (23-77)
Male Sex	18 (64%)
WHO Category	
AML	6 (21%)
MDS	19 (68%)
CMML	3 (11%)
Cytogenetic Risk	
Intermediate	14 (52%)
Normal	8 (30%)
Adverse	13 (48%)
Complex	9 (33%)
IPSS-R (median, range)	5.5 (3.5-9.0)
ELN High Risk Mutation	14 (50%)

HMA Therapy	
Azacitidine	16 (57%)
Decitabine	12 (43%)
Best Overall Response Prior to HCT	
CR	10 (36%)
mCR/CRi	9 (32%)
PR/HI	2 (8%)
NR/SD	7 (25%)
Conditioning Intensity	
MAC	4 (17%)
RIC	20 (83%)
Donor Source	
MRD	6 (21%)
MUD	18 (64%)
MMUD/Haplo	4 (14%)

N = 28. AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete response; CRi, CR with incomplete blood count recovery; ELN, European LeukemiaNet; Haplo, haploidentical; HCT, hematopoietic stem cell transplantation; HI, hematologic improvement; HMA, hypomethylating agent; IPSS-R, revised International Prognostic Scoring System; MAC, myeloablative conditioning; mCR, marrow CR; MDS, myelodysplastic syndrome; MMRD, mismatched unrelated donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; NR, no response; RIC, reduced intensity conditioning; SD, stable disease; WHO, World Health Organization. Brunner et al. *Blood* 2021;138(suppl 1):3677.

Molecular Profiling Identified Several Very High-Risk Molecular Features



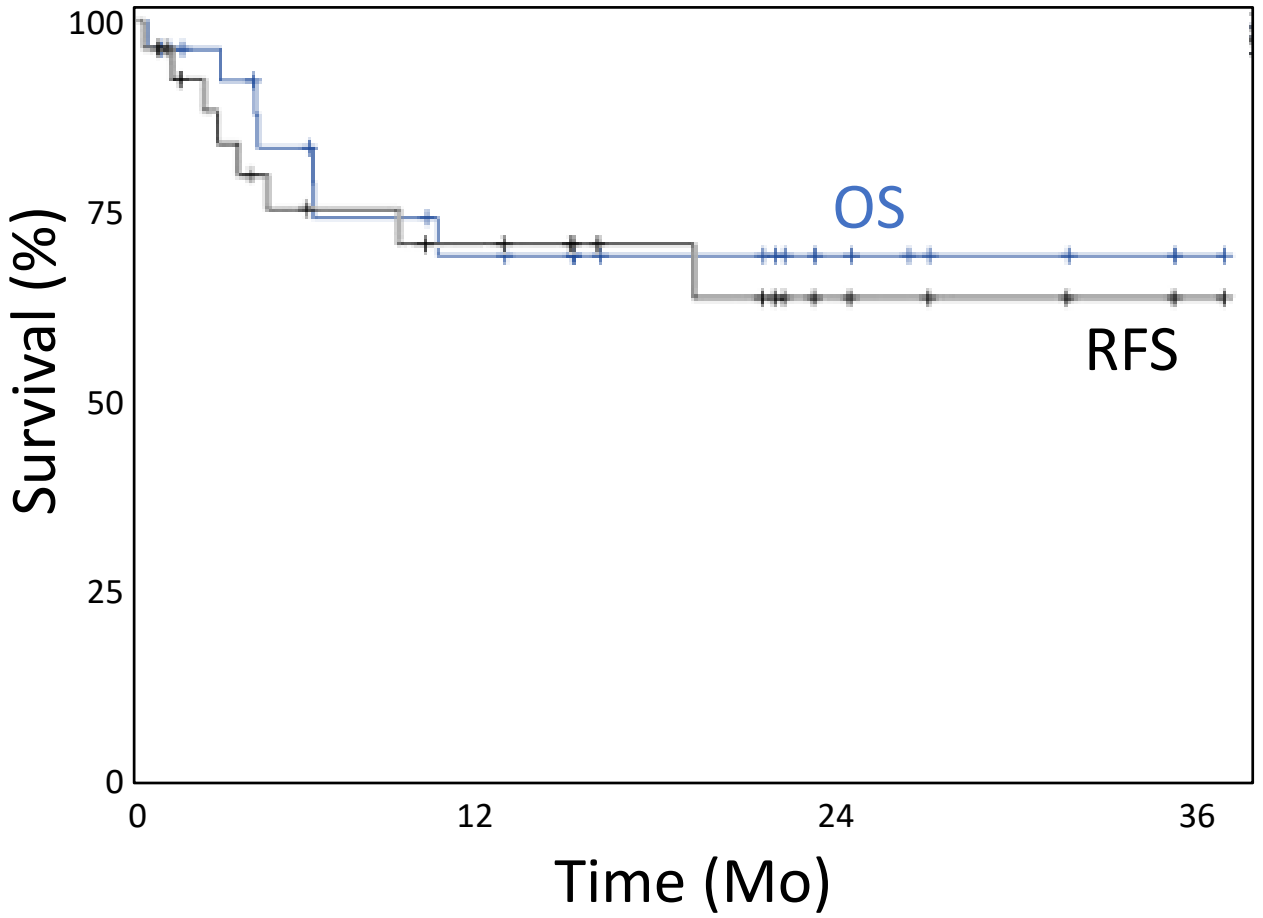
Brunner et al. *Blood* 2021;138(suppl 1):3677.

Investigator Reported GVHD Events

- Acute GVHD was seen in 16 patients; maximum grade 3-4 aGVHD occurred in 4 patients:
  - 2 patients with stage 4 GI disease, 1 with stage 3 GI disease, and 1 patient with stage 4 skin GVHD
  - One patient died on hospice after G4 aGVHD
- Chronic GVHD requiring systemic immunosuppression was seen in 8 patients, none of which have died or relapsed
- One patient also received spartalizumab (PD-1) and had grade 2 skin aGVHD and no cGVHD

aGVHD, acute graft vs host disease; cGVHD, chronic GVHD; GI gastrointestinal; PD-1, programmed-death 1.
Brunner et al. *Blood* 2021;138(suppl 1):3677.

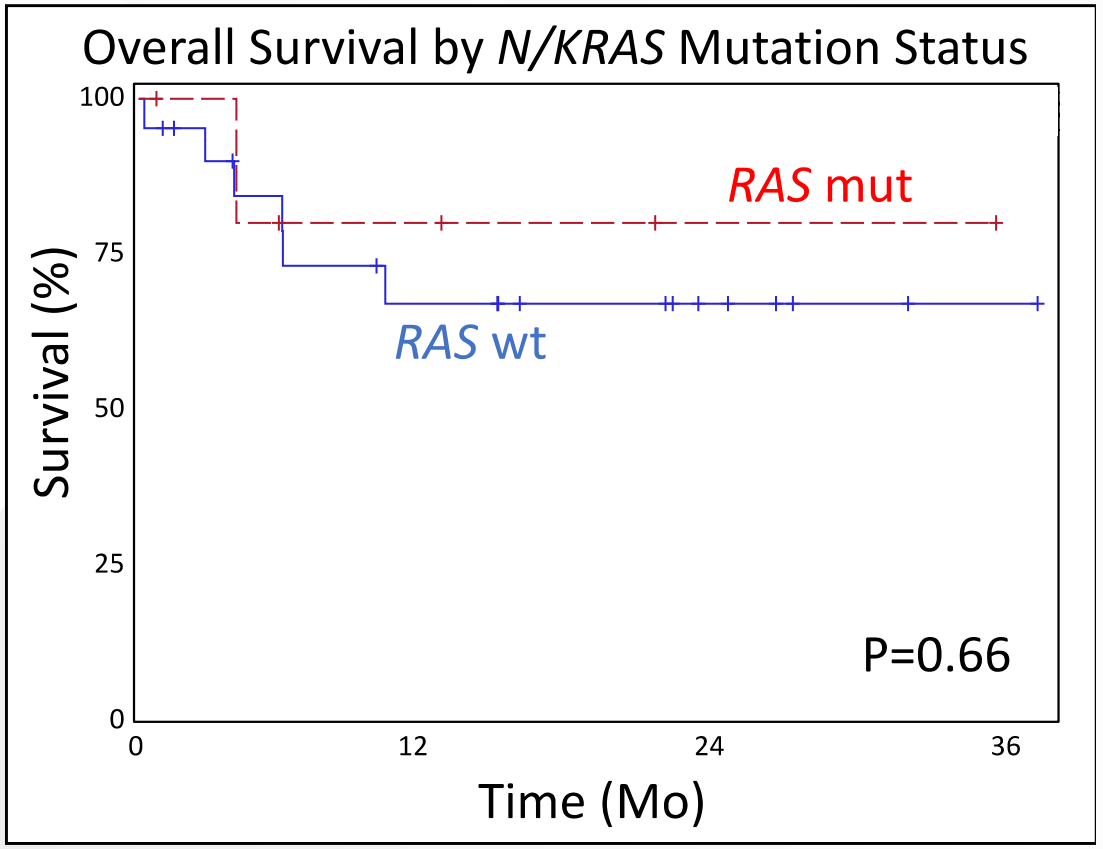
Overall and Relapse-Free Survival Post-HCT

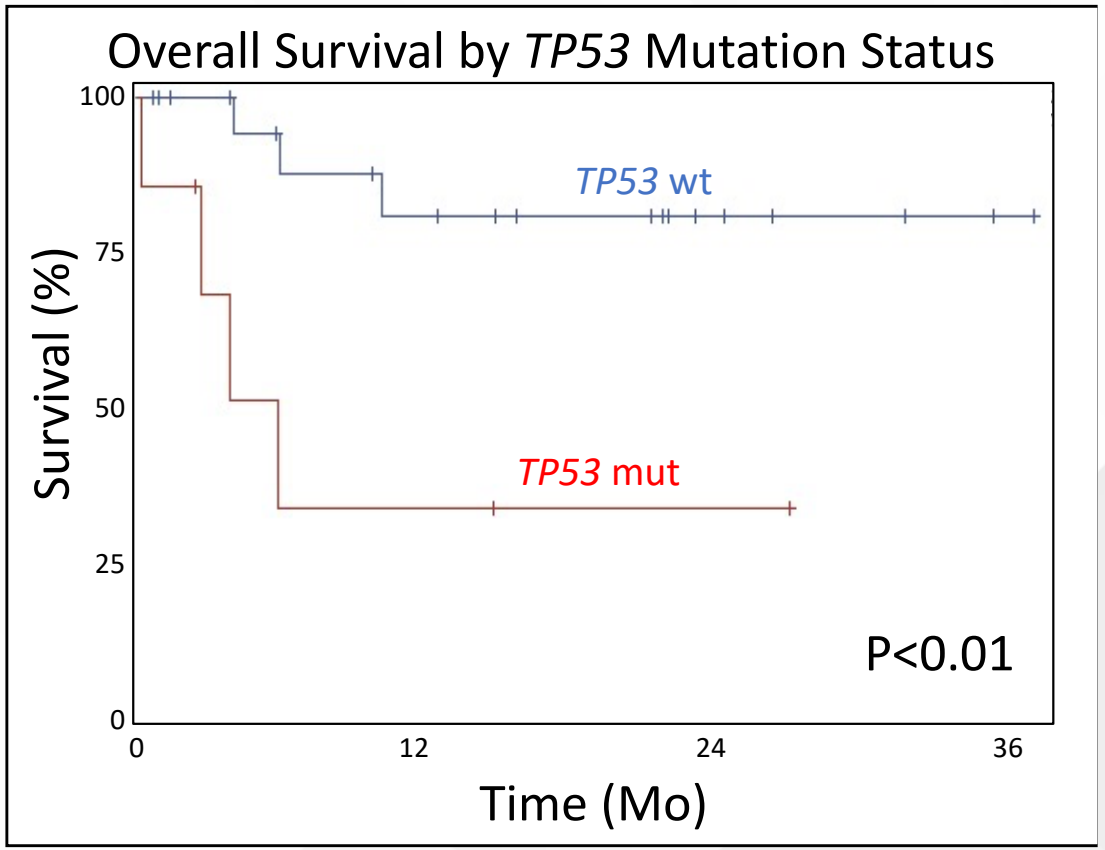


HCT, hematopoietic stem cell transplantation; OS, overall survival; RFS, relapse-free survival.

Brunner et al. *Blood* 2021;138(suppl 1):3677.

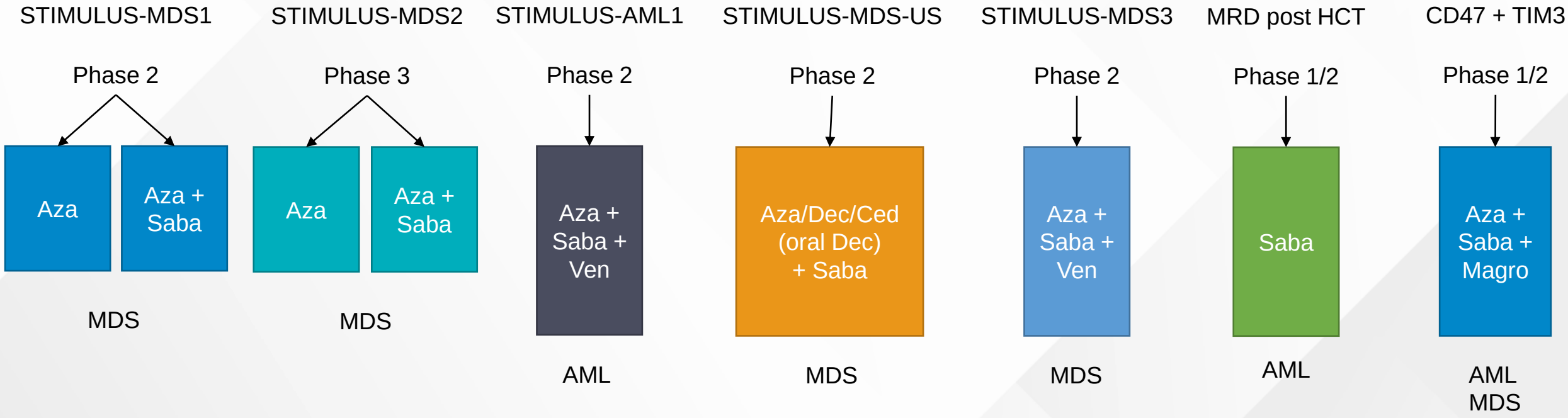
Overall Survival by Mutation Status





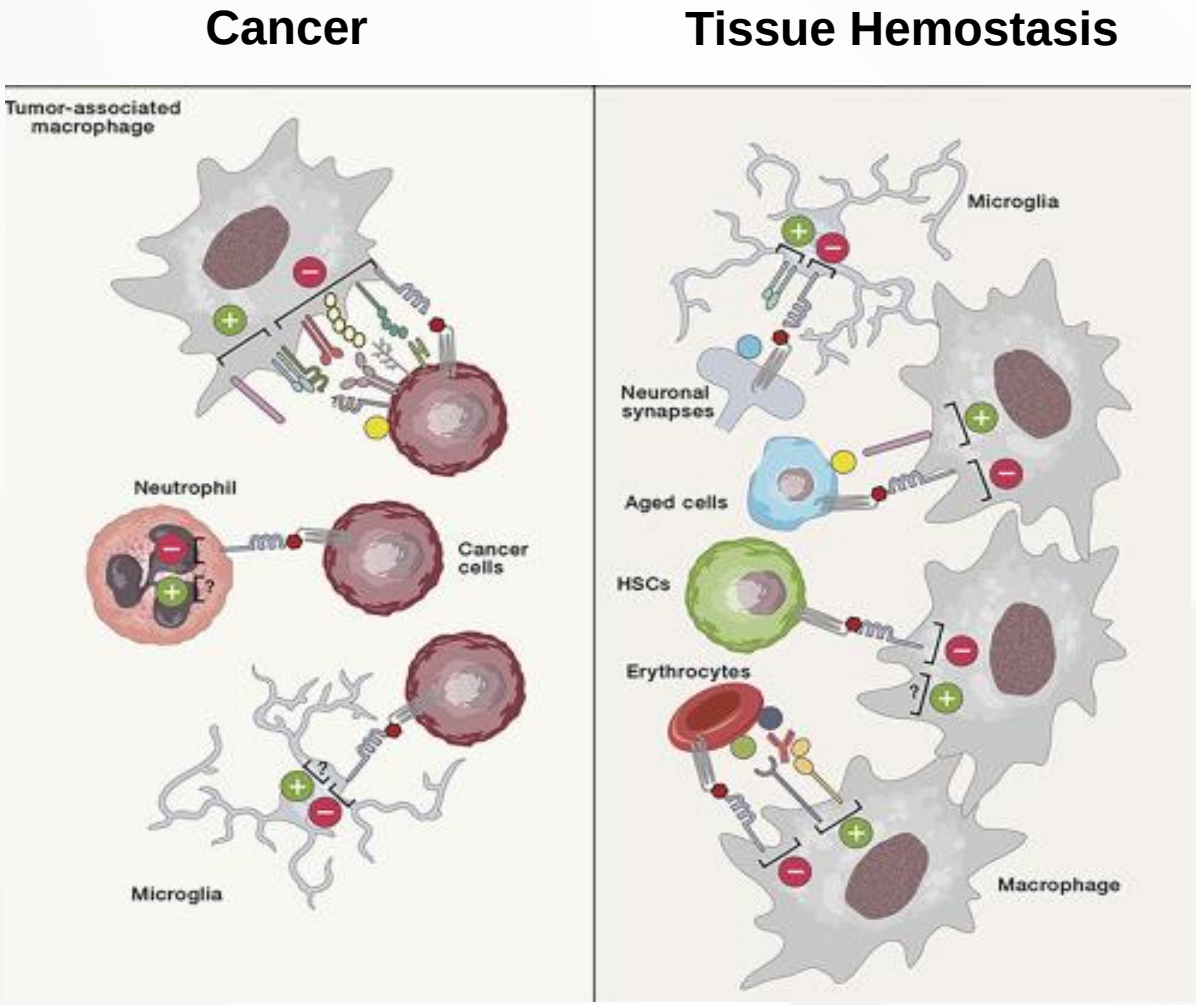
Brunner et al. *Blood* 2021;138(suppl 1):3677.

Sabatolimab in MDS and AML



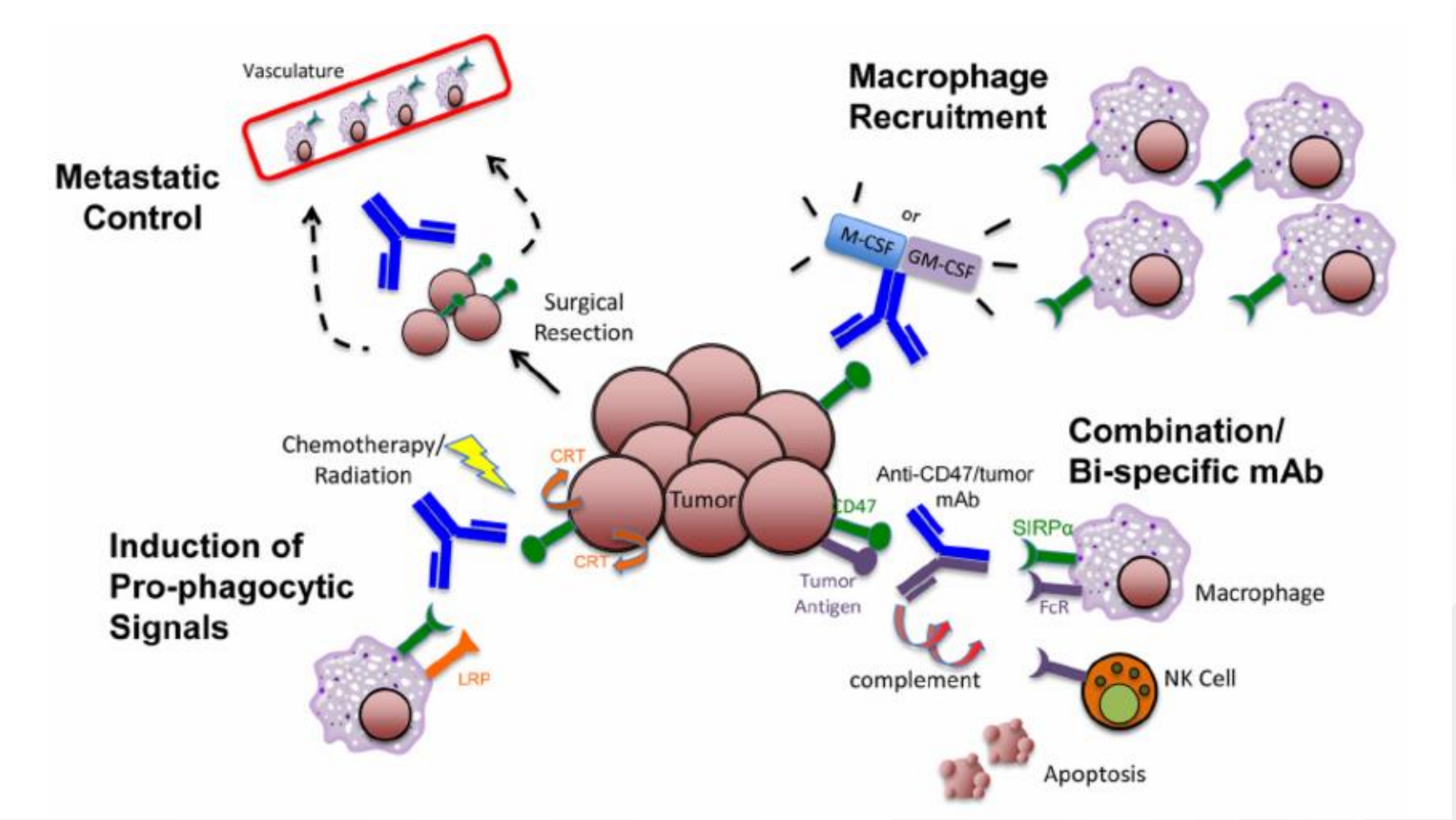
AML, acute myeloid leukemia; Aza, azacitidine; Ced, cedazuridine; Dec, decitabine; Magro, magrolimab; HCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; Saba, sabatolimab; Ven, venetoclax.

Targeting CD47 in MDS



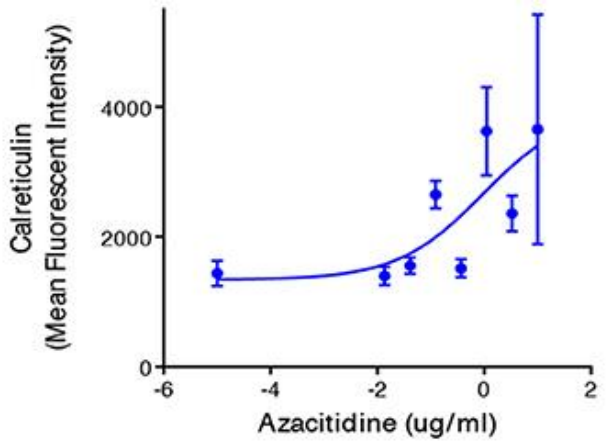
MDS, myelodysplastic syndrome; HSCs, hematopoietic stem cells.
Logtenberg et al. *Immunity* 2020;52(5):742-752.

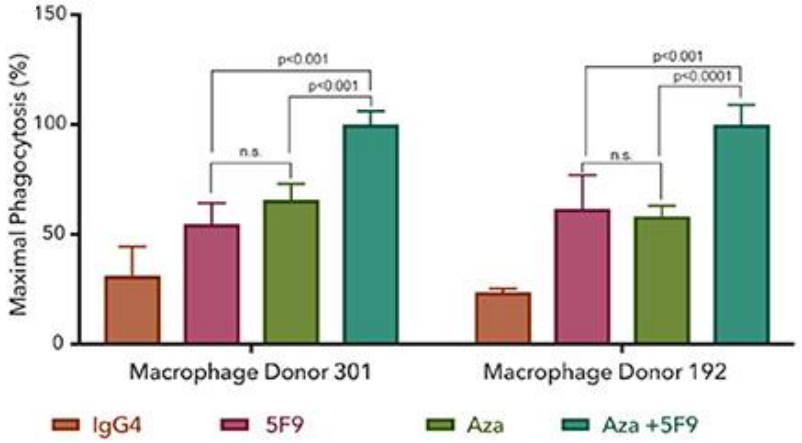
Targeting CD47 in MDS

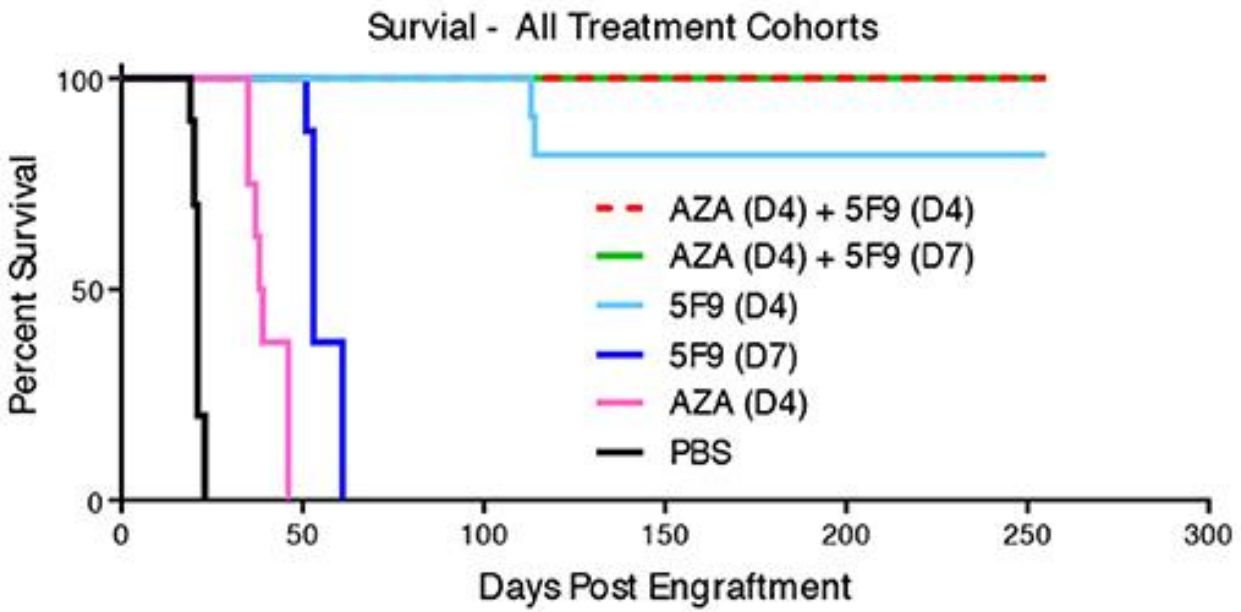


mAb, monoclonal antibody; MDS, mylelodysplastic syndrome; NK, natural killer.
Chao et al. *Curr Opin Immunol*. 2012;24(2):225-232.

CD47 and Azacitidine







AZA, azacytidine; PBS, phosphate buffered saline.
Chao et al. *Front Oncol*. 2020;9:1380.

Magrolimab and Azacitidine for HR-MDS

Eligibility Criteria

- Untreated INT/High/Very High Risk MDS
- AML ineligible for induction

Combination Safety
N=6

Magrolimab + Azacitidine
Dose ramp up 1 – 30 mg/kg Weekly

Expansion

Placebo
(3/1 schedule)

Primary endpoint
Safety and Efficacy

Secondary endpoints
PD and immunogenicity
DOR, EFS, OS

Exploratory
–CD47 occupancy
–Immune cell activity

AML, acute myeloid leukemia; DOR, duration of response; EFS, event-free survival; HR-MDS, high-risk myelodysplastic syndrome; INT, intermediate; OS, overall survival; PD, progressive disease.
Sallman et al. *Blood* 2019;134(suppl 1):569.

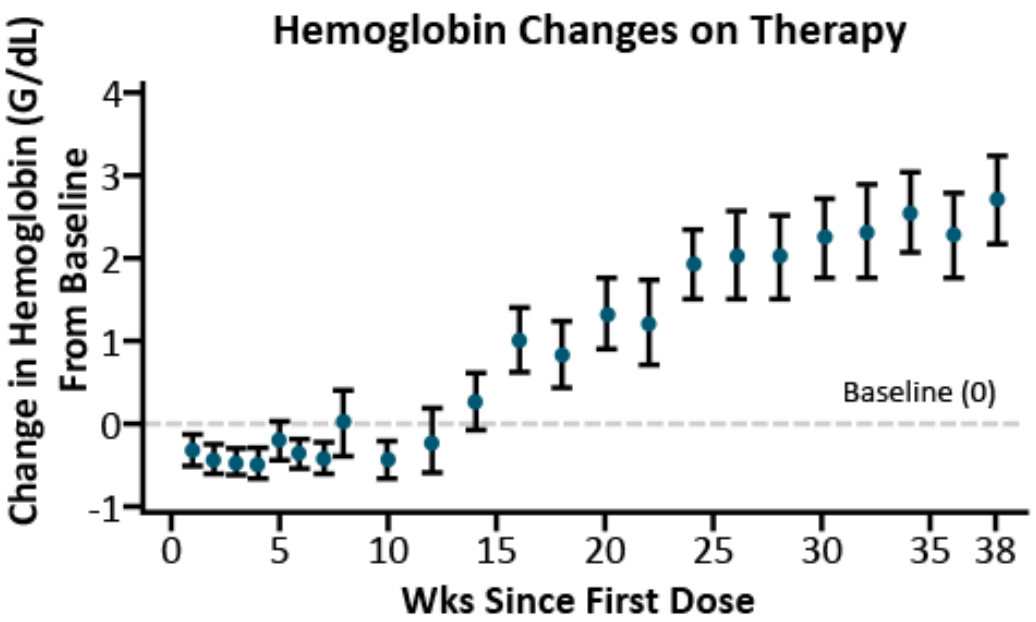
Patient Characteristics

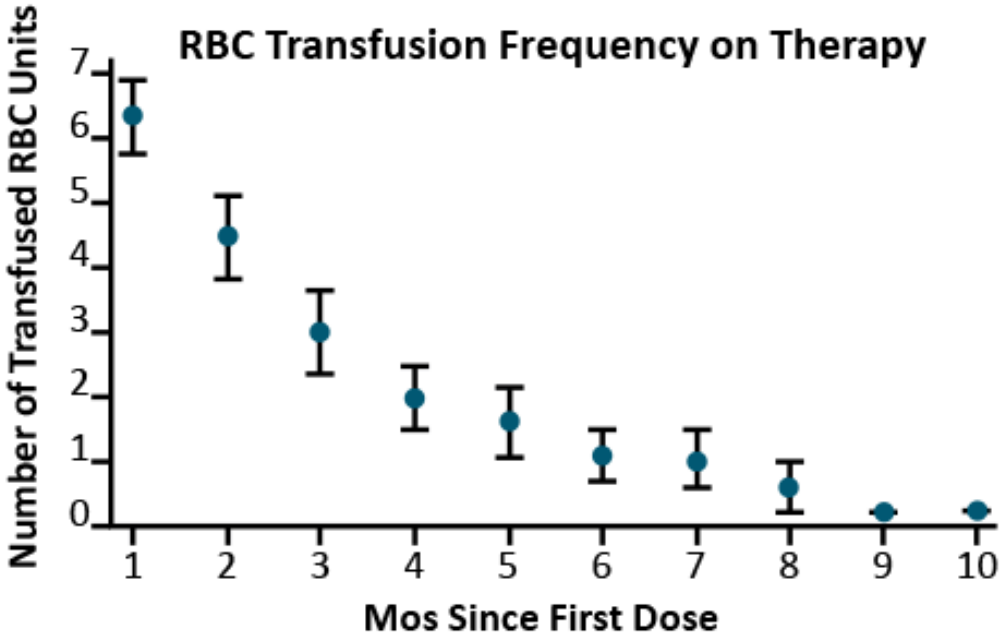
Characteristic	1L MDS 5F9+AZA (N=35)	1L AML 5F9+AZA (N=27)
Median age (range)	70 (47-80)	74 (60-89)
ECOG Performance Status: 0 **1** **2**	13 (37%) 21 (60%) 1 (3%)	9 (33%) 16 (59%) 2 (7%)
Cytogenetic Risk: Favorable **Intermediate** **Poor** **Unknown/missing**	**0** **10 (29%)** **23 (66%)** **2 (6%)**	**0** **2 (7%)** **18 (67%)** **7 (26%)**
WHO AML classification: MRC **Recurrent abnormalities** **Therapy-related** **NOS**	–	**19 (70%)** 2 (7%) 1 (4%) 5 (19%)
WHO MDS classification: **RS and single/multi-lineage dysplasia** **Multilineage dysplasia** **Excess blasts** **Unclassifiable/unknown/missing**	3 (9%) 6 (17%) 19 (54%) 7 (20%)	–
IPSS-R (MDS): Intermediate **High** **Very High** **Unknown/missing**	**11 (31%)** **18 (51%)** **5 (14%)** **1 (3%)**	–
Therapy-related MDS **Unknown/missing**	**11 (31%)** **1 (3%)**	–
Harboring a *TP53* mutation	**4 (11%)**	**11 (41%)**

AML, acute myeloid leukemia; AZA, azacitidine; ECOG PS, Eastern Cooperative Oncology Group performance status; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; MRC, myelodysplasia related changes; NOS, not otherwise specified; RS, ring sideroblasts; WHO, World Health Organization; 1L, first line; 5F9, magrolimab.

Sallman et al. *Blood* 2019;134(suppl 1):569.

Hemoglobin and Transfusions with Magrolimab and Azacitidine





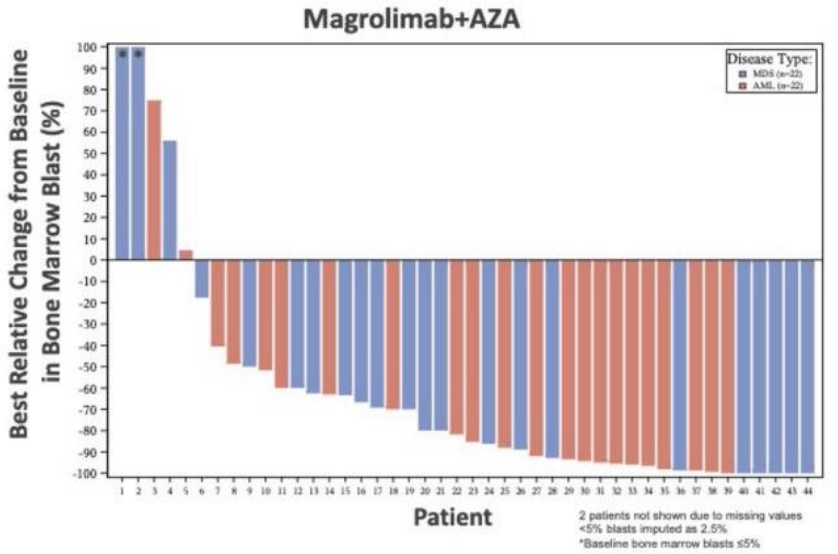
RBC, red blood cell.

Sallman et al. *Blood* 2019;134(suppl 1):569.

CD47 “Don’t Eat Me” Checkpoint

Anti-Leukemic Activity is Observed with Magrolimab + AZA in MDS and AML

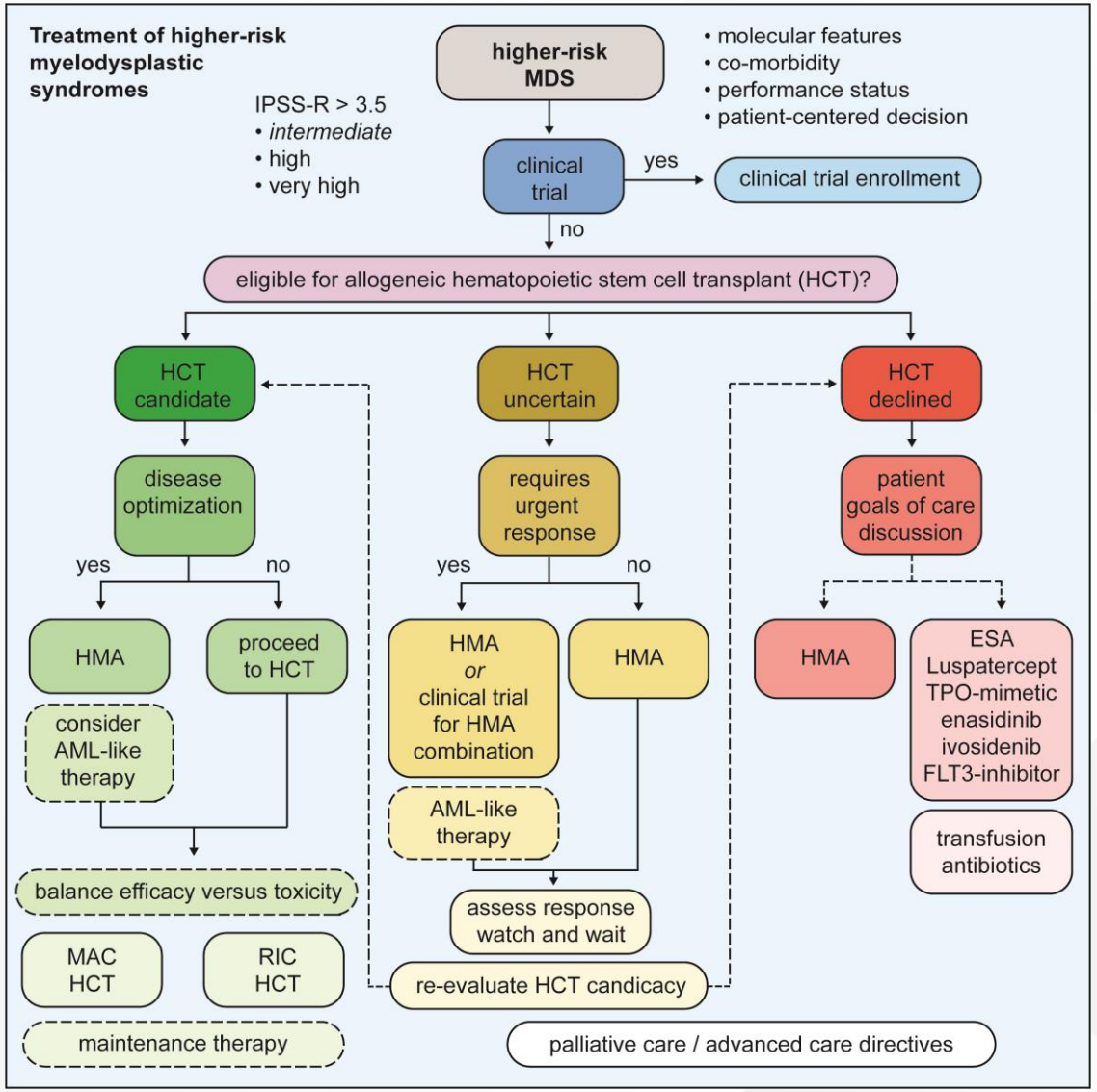
Best Overall Response	1L MDS (N = 24)	1L AML (N=22)
ORR	22 (92%)	14 (64%)
CR	12 (50%)	9 (41%)
CRi	-	3 (14%)
PR	0	1 (5%)
MLFS/marrow CR	8 (33%) 4 with marrow CR = HI	1 (5%)
Hematologic improvement (HI)	2 (8%)	-
SD	2 (8%)	7 (32%)
PD	0	1 (5%)



- Magrolimab + AZA induces a 92% ORR (50% CR) in MDS and 64% ORR (55% CR/CRi) in AML
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy

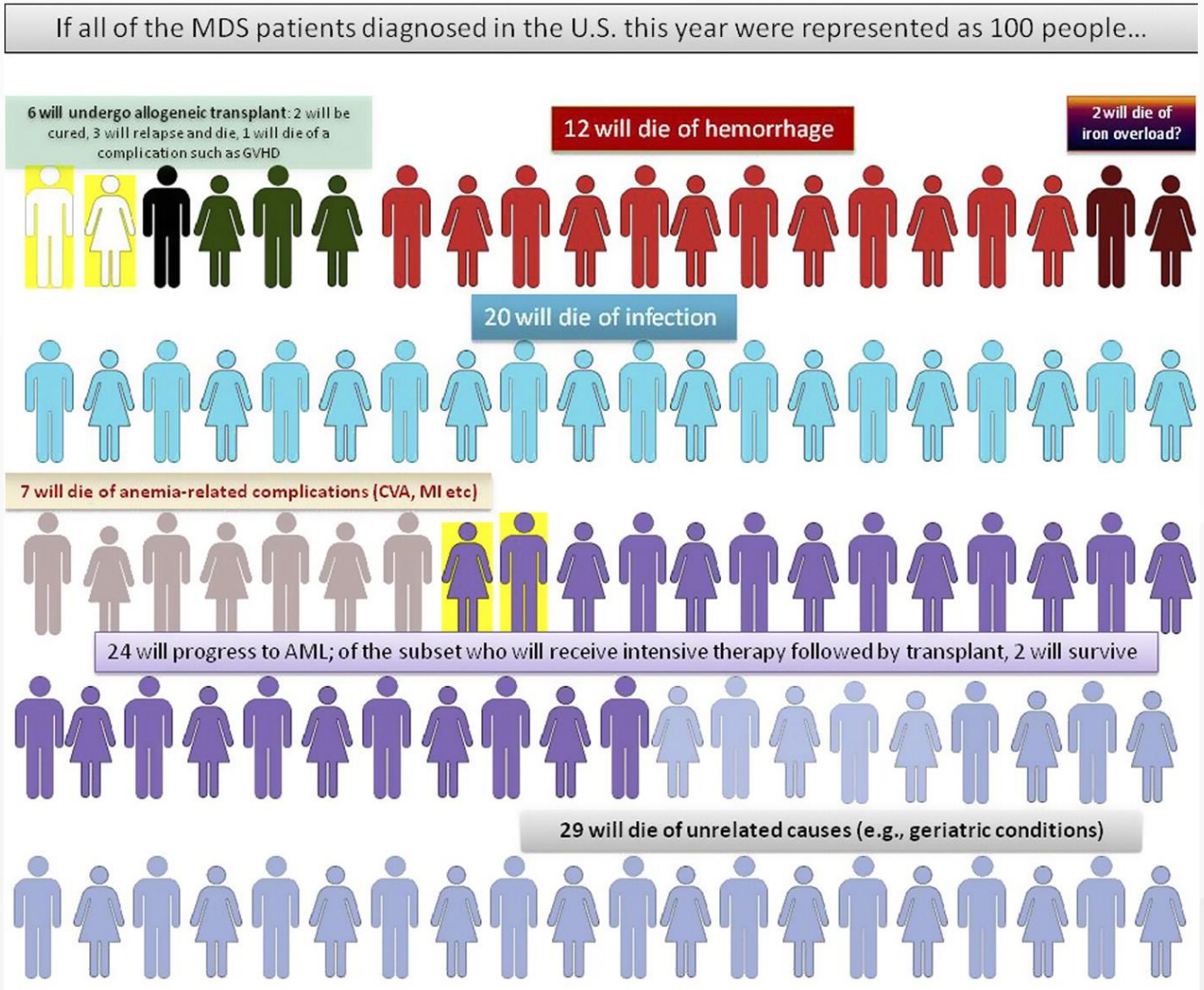
Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria; Patients with at least one post-treatment response assessment are shown, all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML (1 AE, 2 early withdrawal). *Not applicable
1L, first line; AML, acute myeloid leukemia; AZA, azacitidine; CR, complete response; CRi, CR with incomplete blood count recovery; HI, hematologic improvement; MLFS, morphologic leukemia-free state; MDS, myelodysplastic syndrome; ORR, overall response rate; PR, partial response; SD, stable disease, PD, progressive disease. Sallman et al. *Blood* 2019;134(suppl 1):569.

Treatment of Higher-Risk MDS



AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; HCT, hematopoietic stem cell transplantation; HMA, hypomethylating agent; IPSS-R, revised International Prognostic Scoring System; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; RIC, reduced intensity conditioning; TPO, thrombopoietin.
Brunner and Aubrey, in press. Courtesy of Andrew M. Brunner, MD.

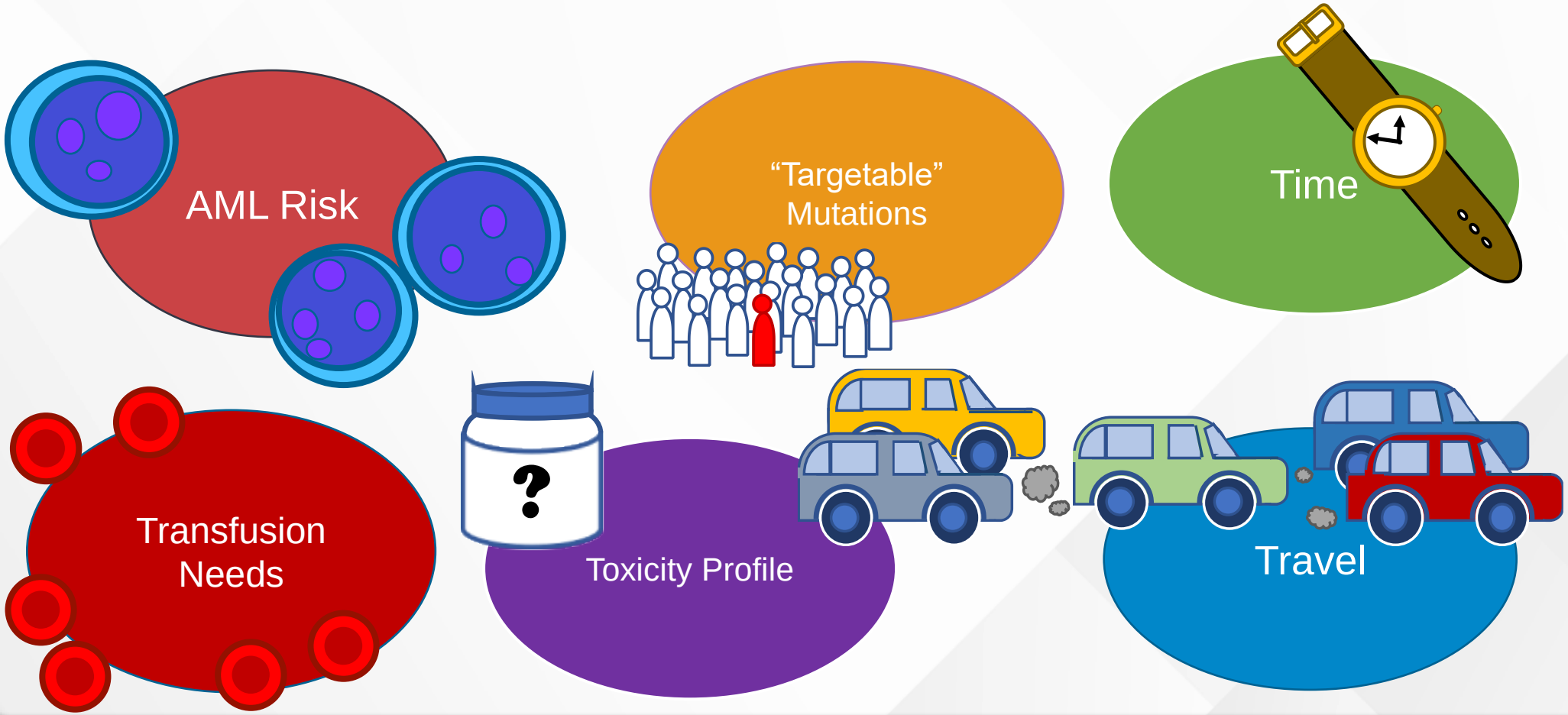
Clinical Outcomes for Patients with MDS



AML, acute myeloid leukemia; CVA, cerebrovascular accident; MDS, myelodysplastic syndrome; MI, myocardial infarction.

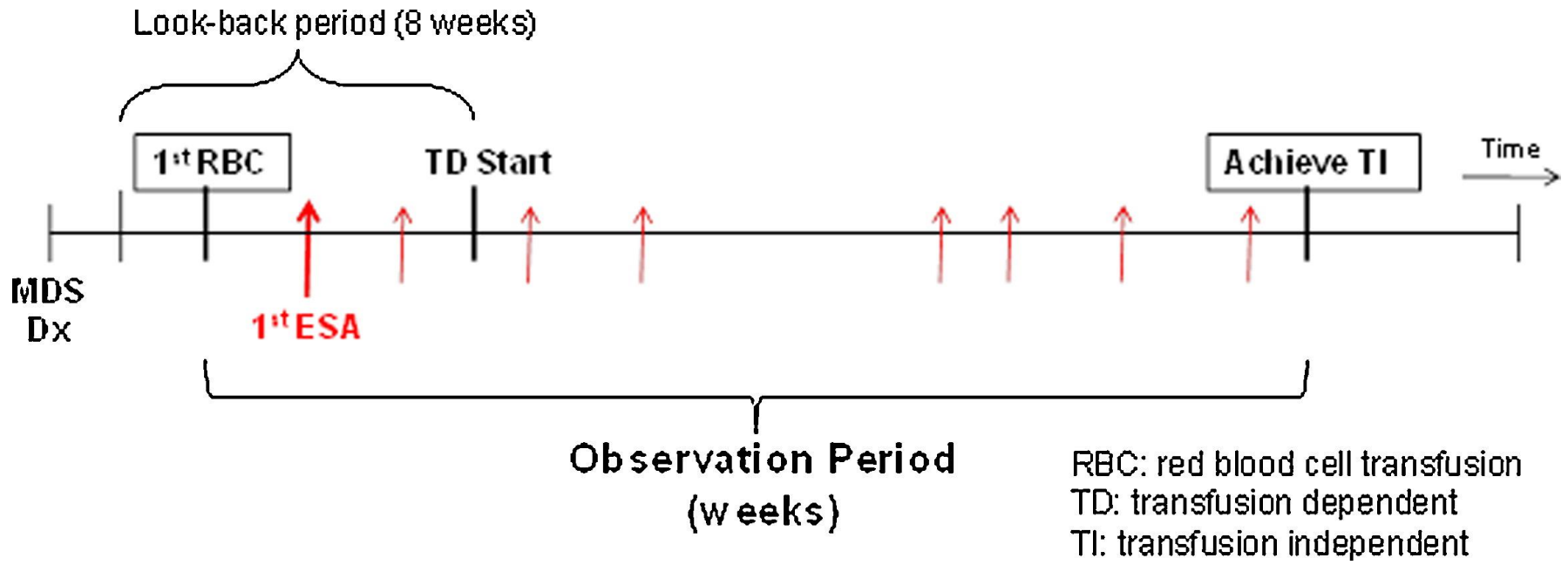
Steensma. *Leuk Lymphoma* 2016;57(1):1-8.

MDS Management: Integrating Many Factors



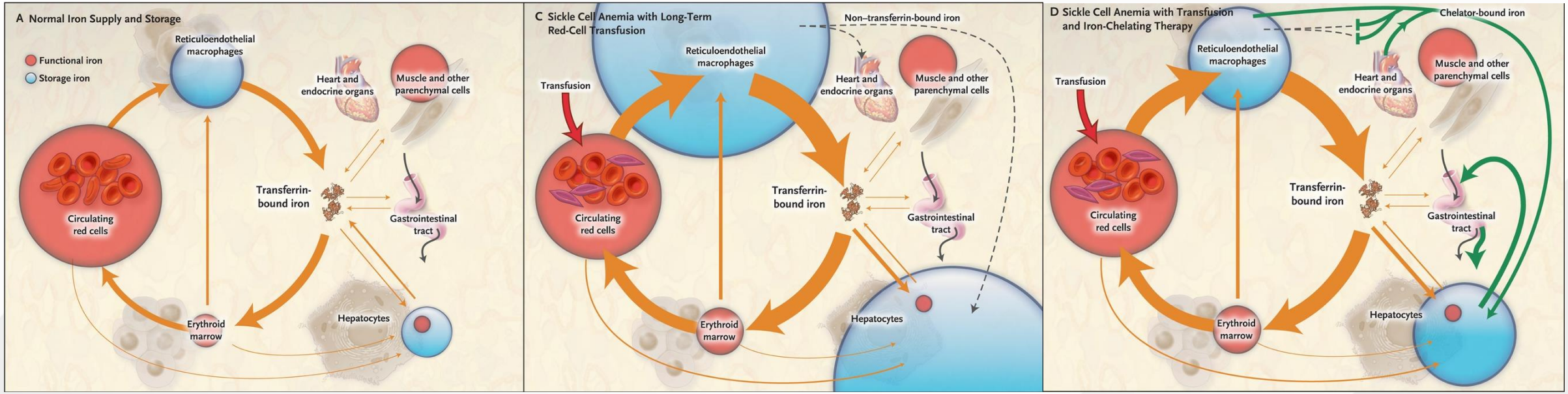
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

Transfusion Burden in MDS



Duong et al. *Leukemia Res*. 2015;39(6):586-591.

Iron Overload From Transfusions

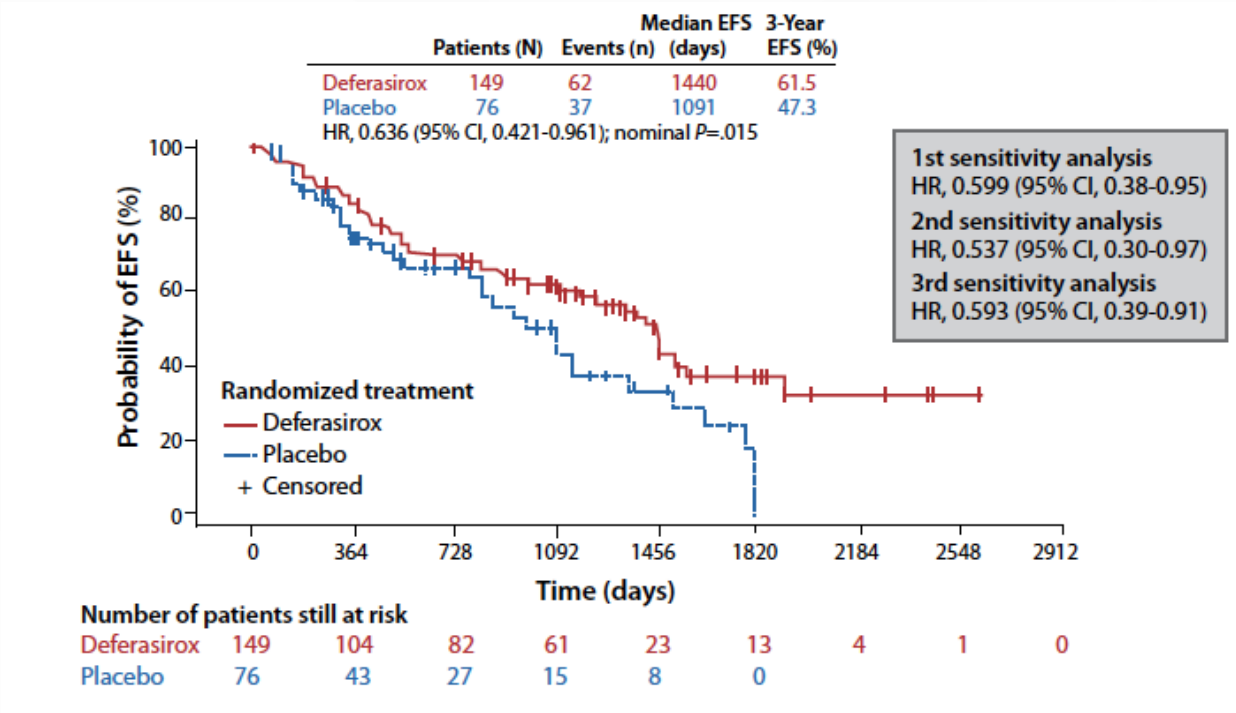


Brittenham et al. *N Engl J Med.* 2011;364:146-156.

Iron Chelation: TOLESTO

- Patients with Low/Intermediate-1 MDS randomized to deferasirox or placebo

Event	Deferasirox	Placebo
Death	32.2%	32.9%
AML	6.7%	7.9%
CHF Hospitalization	0.7%	3.9%
Liver Impairment	0.7%	1.3%
Cardiac function decline	2.3%	2.6%



AML, acute myeloid leukemia; CHF, congestive heart failure; EFS, event-free survival; MDS, myelodysplastic syndrome.
Angelucci et al. *Clin Adv Hematol Oncol*. 2019;17(2):4-6.

Key Takeaways

- The initial evaluation of MDS requires specialized histopathologic, cytogenetic, and molecular analysis
- Risk stratification is key to determining the treatment goals in MDS
- Patient treatment goals inform treatment selection
- There are numerous alterations in the immune system in MDS that are potential targets to enhance disease control and the duration of responses

MDS, myelodysplastic syndrome.

Clinical Trial Summary

Therapy	Target	Combination	Trial	Phase	Status (July 2022)
Magrolimab	CD47	+ azacitidine	ENHANCE NCT04313881	3	Recruiting
Sabatolimab	TIM3	+ HMA	STIMULUS-MDS1 NCT03946670	2	Active, not recruiting
		+ azacitidine	STIMULUS-MDS2 NCT04266301	3	Active, not recruiting
		+ azacitidine and venetoclax	STIMULUS-MDS3 NCT04812548	2	Recruiting
		+ HMA	STIMULUS-MDS-US NCT04878432	2	Recruiting
		+ siremadlin (HDM201)	NCT03940352	1b	Recruiting

HMA, hypomethylating agent; TIM3, T-cell immunoglobin mucin-3.

AXIS Medical Education

Harnessing the Power of the Immune System to Manage Higher-Risk MDS