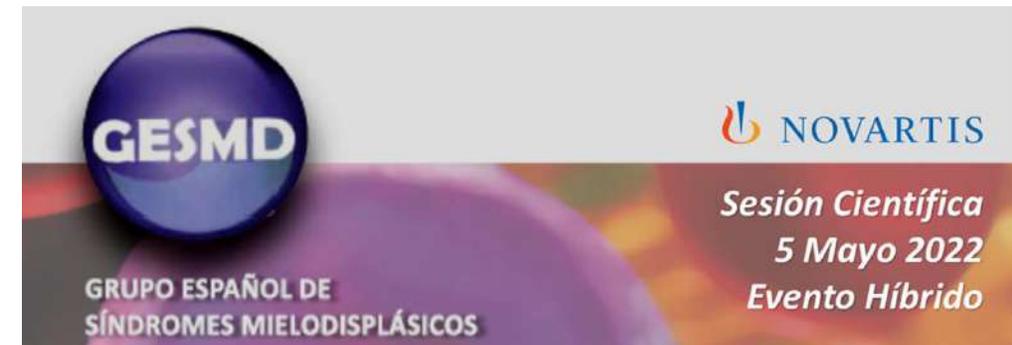


Moléculas en desarrollo y rol de la inmunoterapia en HR-MDS

Patricia Font López

**Hospital General Universitario
Gregorio Marañón**

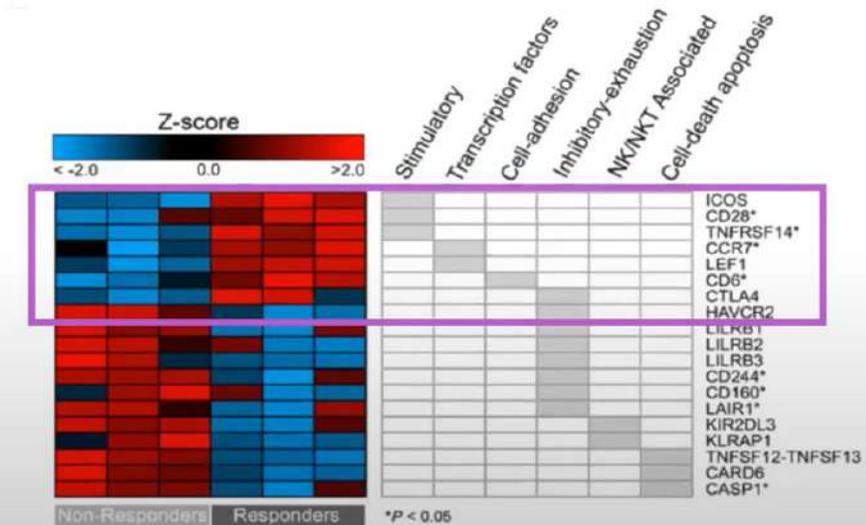
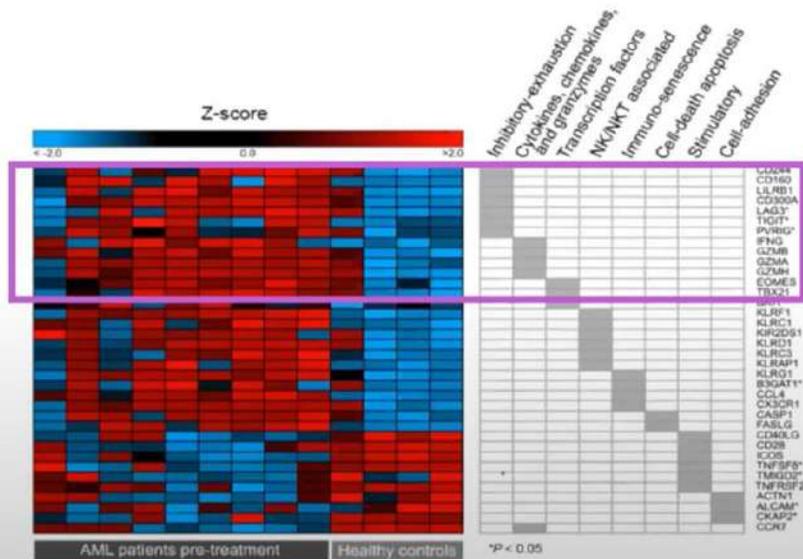


Disclosures.

- **Novartis.** Ponente en charlas patrocinadas, gastos de inscripción a congresos.
- **Abbvie.** Gastos de inscripción a congresos
- **Gilead.** Advisory Board
- **BMS** Advisory Board

Disregulación inmune en neoplasias mieloides

- Múltiples evidencias de defectos inmunes en LMA y HR-MDS: cel T exhaustas, senescencia precoz...
- Cel T efectoras disfuncionales
- Aumento Tregs
- Cel NK disfuncionales y deficientes
- Cel dendríticas tolerogénicas
- Aumento de expresión de moléculas coinhibitorias

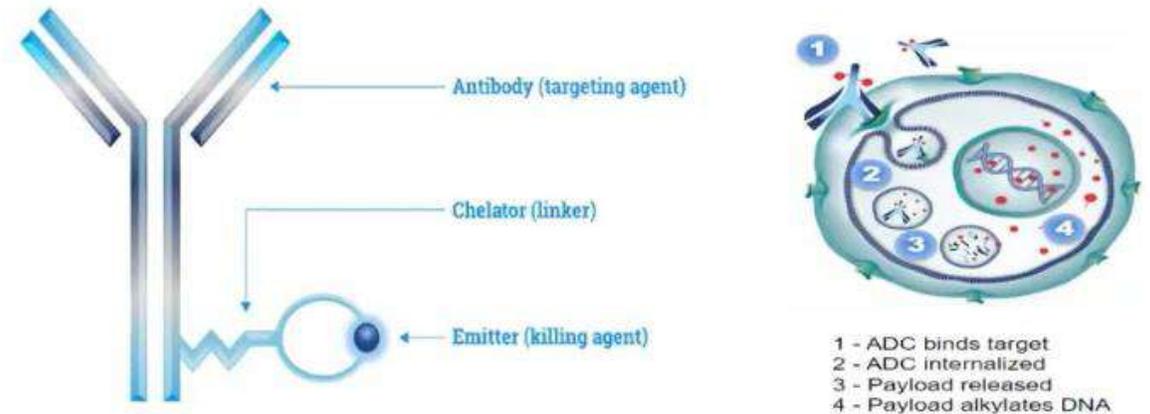


Walter RB et al, Leukemia
2015;29:2104-07
Ustun C et al. Blood
2011;118:5084-95

Inmunoterapia basada en anticuerpos

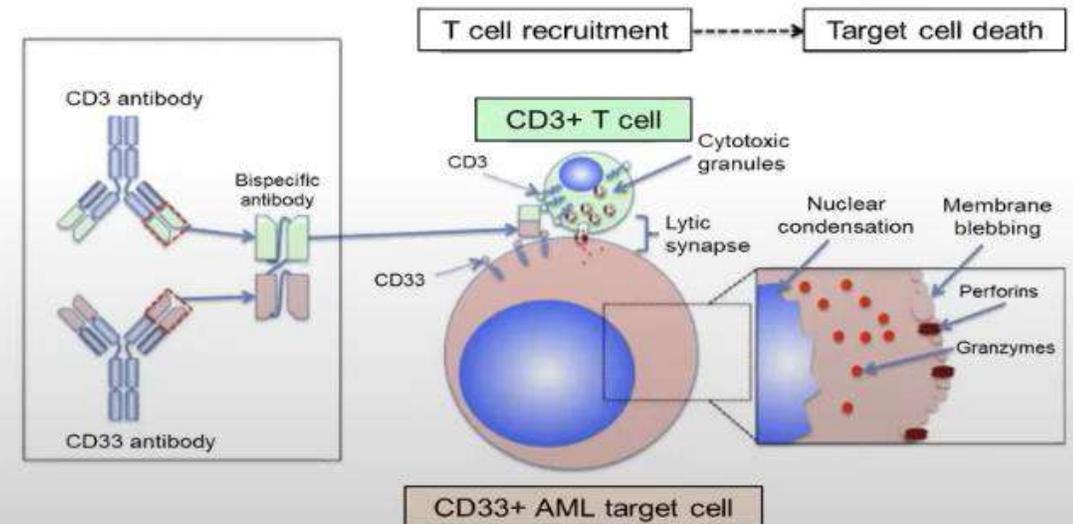
Deliver cytotoxic agents to leukemic cells

- ^{225}Ac -lintuzumab (CD33 radioimmunoconjugate)
- Iomab-B (CD45 radioimmunoconjugate)
- IMGN779 (CD33 antibody-drug conjugate)
- IMGN632 (CD123 antibody-drug conjugate)



Bring T-cells into proximity of leukemic cells

- AMG 330 (Bispecific CD3/CD33 antibody)
- Flotetuzumab (Bispecific CD3/CD123 antibodies)
- XmAb14045
- MCLA-117 (Bispecific CD3/CLL1 antibody)
- AMV564 (Bispecific CD3/CD33 T cell engager)



HMA e inmunidad

- Actividad inmunomoduladora

- Regula genes que

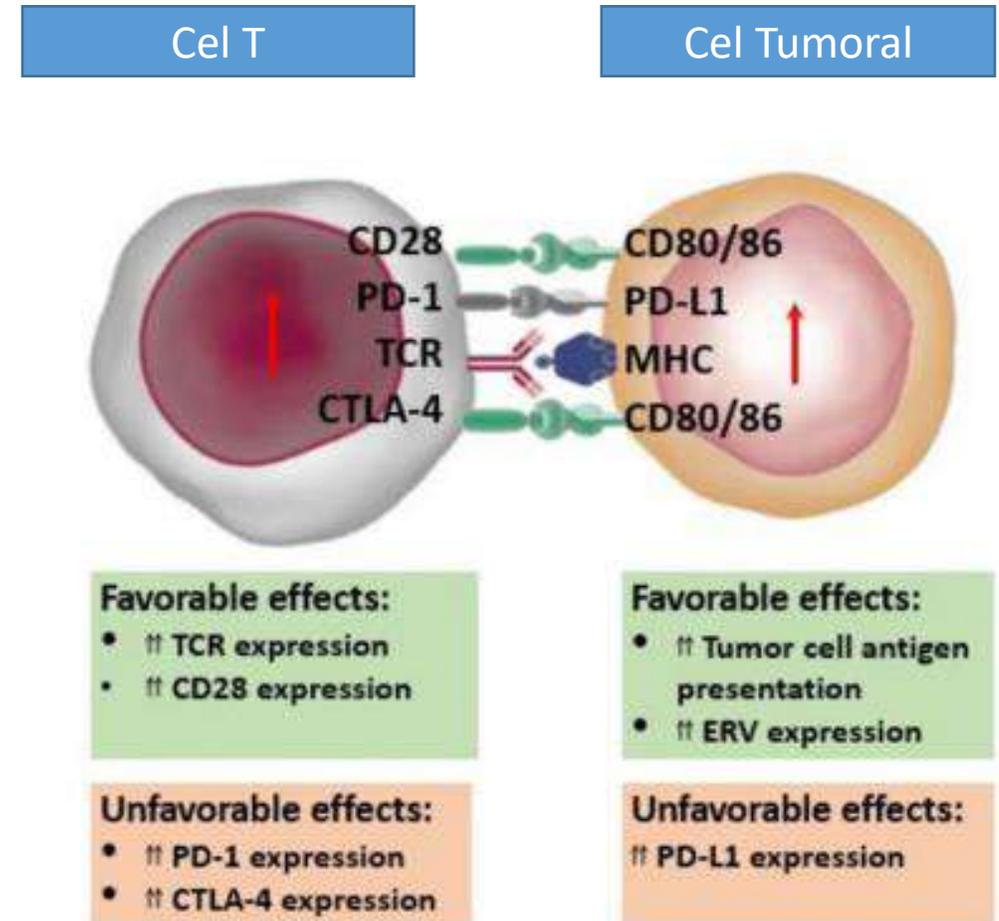


- expresión ag del tumor
- mol HLA clase I,
- ICOS (CD28, CD40)

- Demetilación

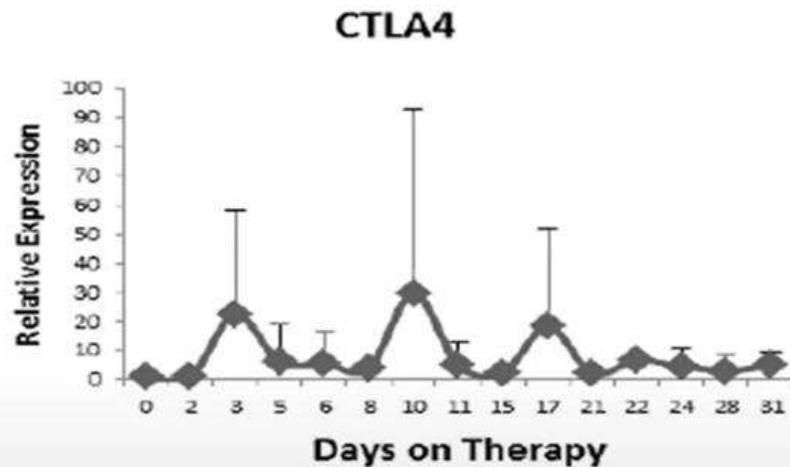


- expresión PD1, CTLA-4 en cel T: inmunidad T **exhausta**
- expresión PDL1 en el tumor



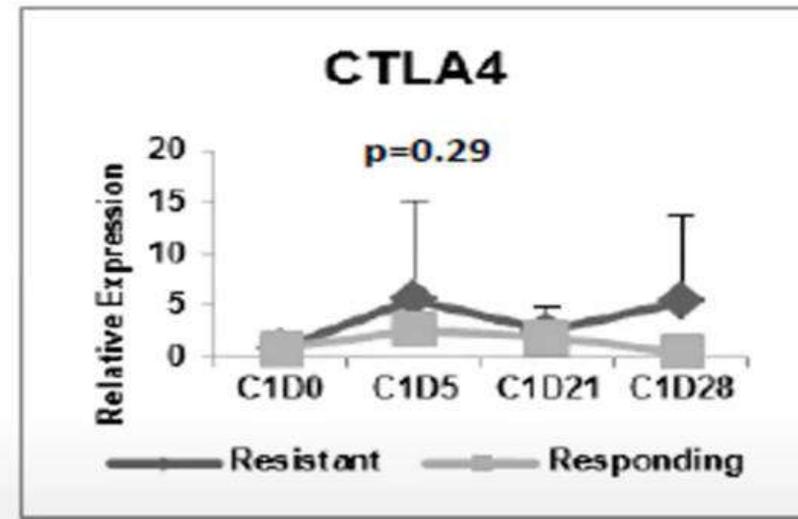
HMA e inmunidad

CTLA-4 expression increases with epigenetic therapy in MDS



Aza

Aza administered day 1 to 5

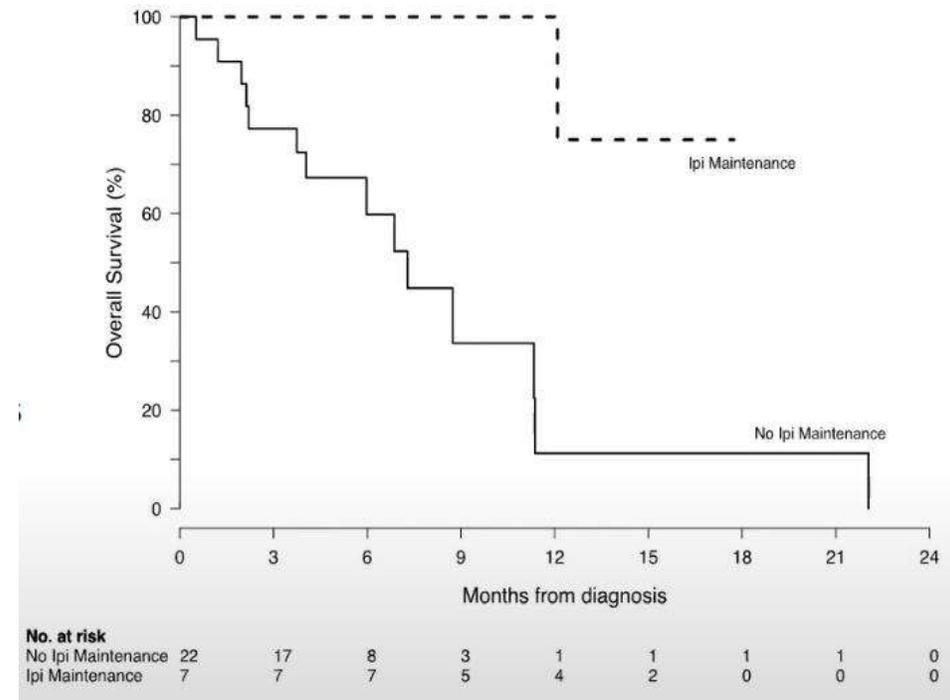


Aza + vorinostat

Resistance to Aza was associated with relatively higher increments in CTLA-4 expression

Ipilimumab: estabilización prolongada en SMD R/R

- Fase I multicéntrico
- 29 pacientes
- DL1 (3mg/Kg) y DL2(10 mg/Kg)
- DL2 tóxica (IRAEs G2-4 en 4/5 ptes)
- Fase expansión DL1 18 pacientes
- Todos los IRAEs fueron reversibles
- Mejor rpta: mCR en un caso
- Enfermedad estable más de 46 sem en 7 pacientes, 3 >1 año
- 5 llevados a HSCT
- OS 9.8 meses (294 d,95%CI 240-671+)



Nivolumab+/-Aza, Ipilimumab+/-Aza. Fase 2. Respuestas

	Frontline		HMA failure	
	Nivo + AZA N = 20	Ipi + AZA N = 21	Nivo N = 15	Ipi N = 20
ORR	14 (70)	13 (62)	0 (0)	6 (30)
CR	8 (40)	3 (14)	0 (0)	0 (0)
mCR+HI	2 (10)	0 (0)	0 (0)	1 (5)
mCR	3 (15)	7 (33)	0 (0)	3 (15)
HI	1 (5)	3 (14)	0 (0)	3 (15)
SD	0 (0)	1 (5)	0 (0)	0 (0)
NR	5 (25)	5 (24)	15 (100)	13 (65)

Overall Survival	TN		HMA Failure	
	Nivo+AZA (n=20)	Ipi+AZA (n=21)	Nivo (n=15)	Ipi (n=20)
1-y OS, %	50	68	25	45
Median OS, months	11.8	NR	8.0	8.5

Median follow-up: 20.1 months. Median number of cycles: 4 (range 1-29). Median number of cycles to response: 3 (range 1-15)

Fusion HR-MDS/Older AML 001 Study (NCT02775903)

Randomized, multicenter, open-label, phase 2 study [N=213]

Screening

MDS cohort [N=84]

Inclusion criteria:

- Age ≥ 18 y; ECOG PS 0-2
- Previously untreated primary or secondary MDS
- IPSS-R intermediate ($>10\%$ blasts or poor/very poor cytogenetics) or high or very high risk

AML cohort [N= 129]

Inclusion criteria:

- Age ≥ 65 y; ECOG PS 0-2; unfit for intensive chemotherapy
- Untreated AML per WHO classification:
 - Newly diagnosed, histologically confirmed de novo AML (BM blasts $\geq 20\%$)
 - AML secondary to prior MDS or to exposure to potentially leukemogenic therapies/agents with primary malignancy in remission for 2 y

Randomization

1:1

1:1

Treatment Phase

AZA

75 mg/m²/d SC D1-7 q4w

AZA

75 mg/m²/d-SC D1-7 q4w

Durvalumab

1500 mg IV D1 qw4

AZA

75 mg/m²/d SC D1-7 q4w

AZA

75 mg/m²/d SC D1-7 q4w

Durvalumab

1500 mg IV D1 qw4

Treatment until disease progression or toxicity

Follow-up

Safety:

- Day 28
- Day 90

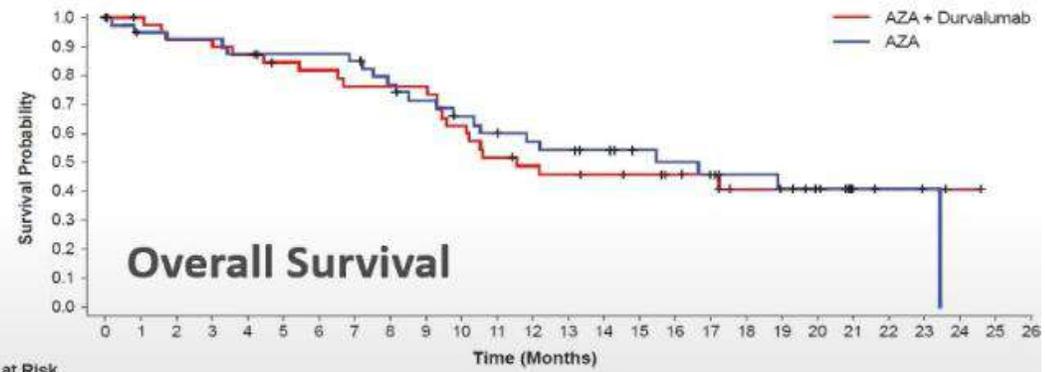
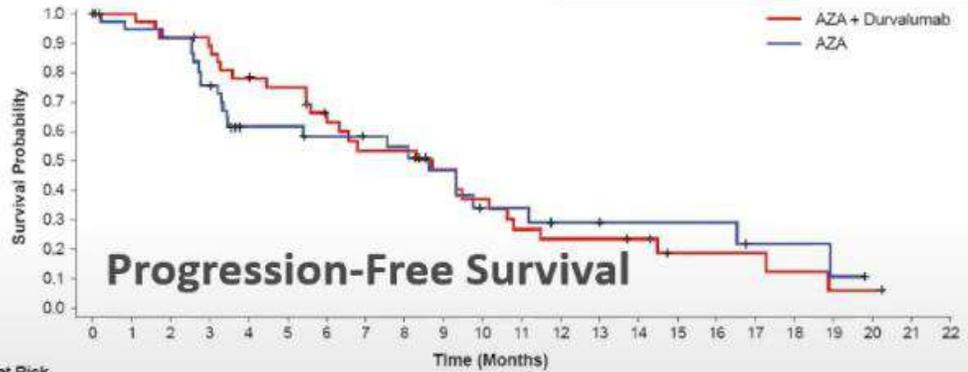
Efficacy, every 3 mo:

- Survival
- Subsequent MDS/AML treatments
- Transformation to AML (MDS only)

- Last patient randomized: MDS, October 30, 2017; AML, September 29, 2017. Data cutoff: October 31, 2018

Fusion 001 Trial: First randomized trial of Immune checkpoint blockade in MDS-azacitidine vs. azacitidine+anti-PDL1 durvalumab in frontline HR-MDS

Response, n (%) [95% CI]	AZA + Durvalumab n=42	AZA n=42
ORR (CR + PR + mCR + HI)	26 (61.9) [47.2, 76.6]	20 (47.6) [32.5, 62.7]
	P=0.1838	
CR	3 (7.1) [0.0, 14.9]	4 (9.5) [0.7, 18.4]
PR	0	0
mCR	15 (35.7) [21.2, 50.2]	8 (19.0) [7.2, 30.9]
HI only	8 (19.0) [7.2, 30.9]	8 (19.0) [7.2, 30.9]
SD, n (%)	6 (14.3)	3 (7.1)
PD, n (%)	1 (2.4)	8 (19.0)
NE/Missing,† n (%)	6 (14.3)	7 (16.7)



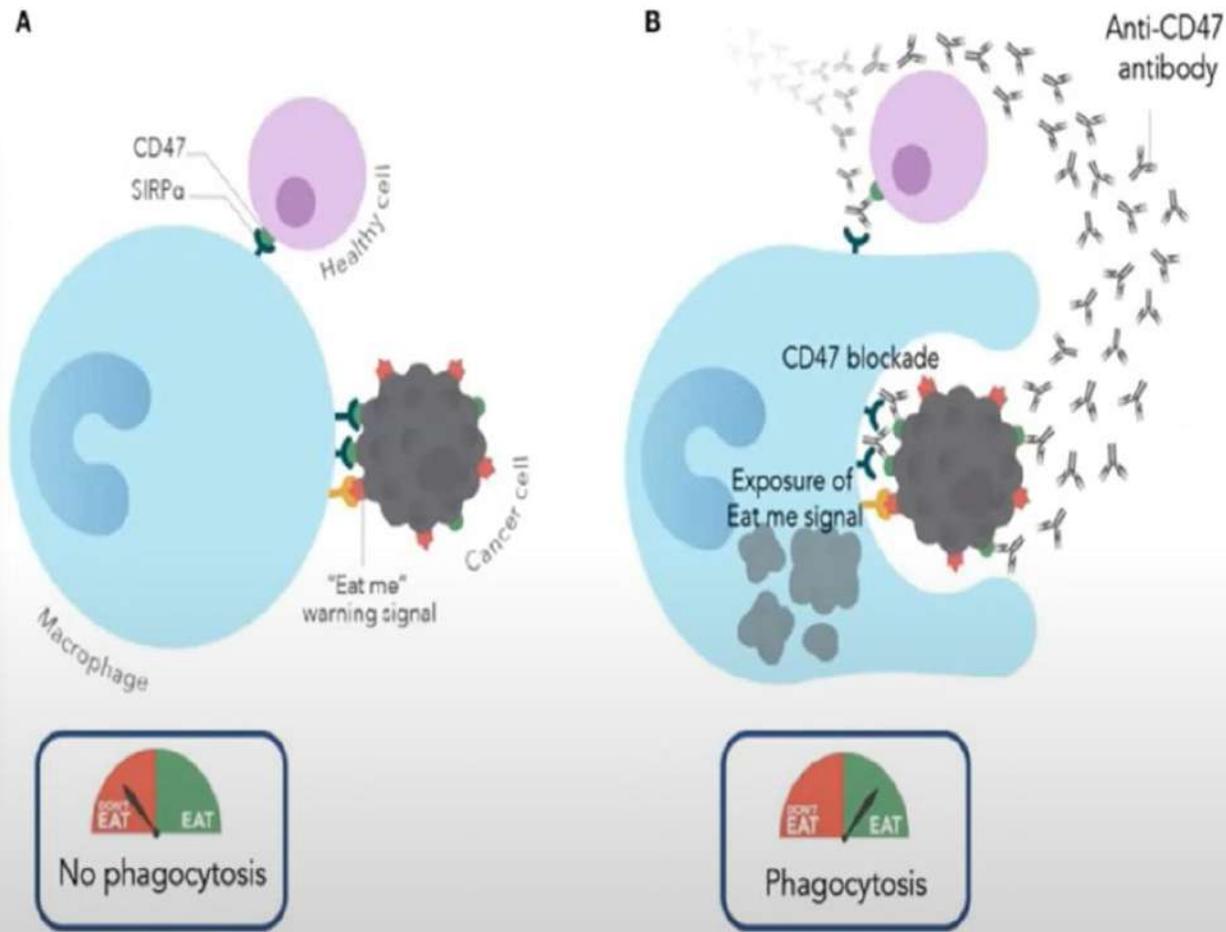
No. at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
AZA + Durvalumab	42	37	34	32	28	25	21	17	17	14	11	8	7	7	6	3	3	3	2	1	1		
AZA	42	35	34	28	19	19	17	16	15	11	7	7	5	5	4	4	4	2	2	1	1		

Treatment	Events, n (%)	Median PFS, mo (95% CI)
AZA + durvalumab (n=42)	28 (67)	8.7 (5.6–10.2)
AZA (n=42)	24 (57)	8.6 (3.4–11.2)

No. at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
AZA + Durvalumab	42	39	36	36	34	31	30	28	28	28	23	19	17	16	15	13	11	10	6	6	5	3	3	3	1		
AZA	42	38	37	37	35	34	34	33	29	26	23	21	19	18	16	13	12	11	9	7	5	2	1	1	0		

Treatment	Events, n (%)	Median OS, mo (95% CI)
AZA + durvalumab (n=42)	21 (50)	11.6 (9.5–NE)
AZA (n=42)	21 (50)	16.7 (9.8–23.5)

AntiCD47. Mecanismo de acción

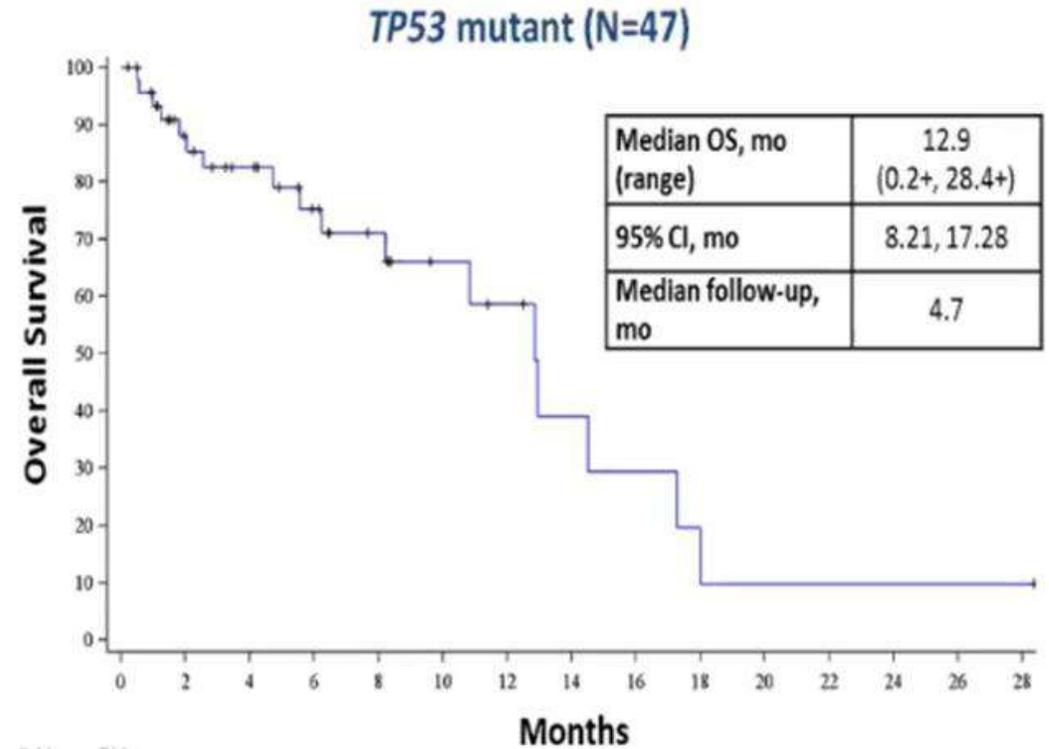


Chao MP et al. *Front Oncol.* 2019;9:1380.

Aza induce señales profagocíticas "*eat me*"
Acción sinérgica con el bloqueo CD47 de la señal "*don't eat me*", aumentando la fagocitosis

Fase1b Magrolimab + aza

Best Overall Response	All AML (N=43)	TP53-mutant AML (29)
ORR	27 (63%)	20 (69%)
CR	18 (42%)	13 (45%)
<u>CRi</u>	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)



ORR 63% y CR 42%, similar en mut TP53

Respuestas rápidas, m 1.95 meses

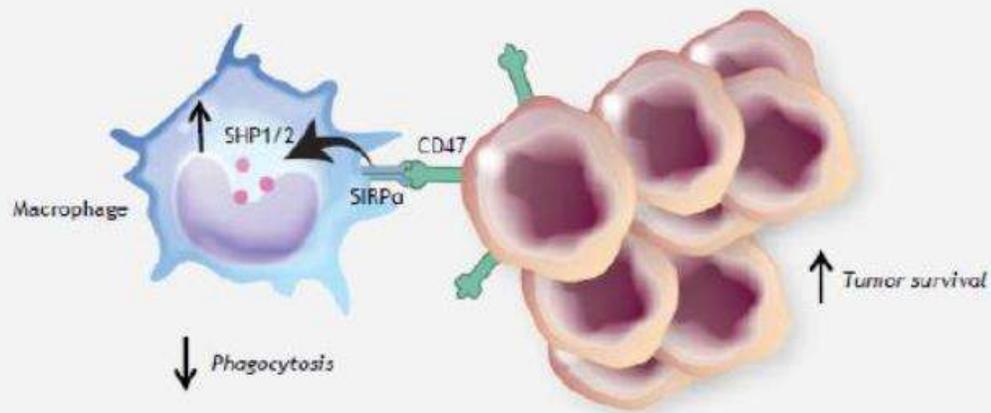
OS: mediana 19.8 meses en TP53wt y 12.9 m en TP53 mutado

Anti CD47 efectos adversos

- CD47 se expresa en cel sanas, stem cells y progenitoras normales.
- AntiCD47: agregación plaquetaria, hemólisis, hemaglutinación.
- Efectos adversos descritos con Magrolimab: anemia hemolítica y de rápida instauración, hiperbilirrubinemia, cefalea
- Anemia: toxicidad limitante de dosis
- Nuevas moléculas que bloquean SIRP α y CD47 y no producen anemia

SIRPα (CC-95251) MoA

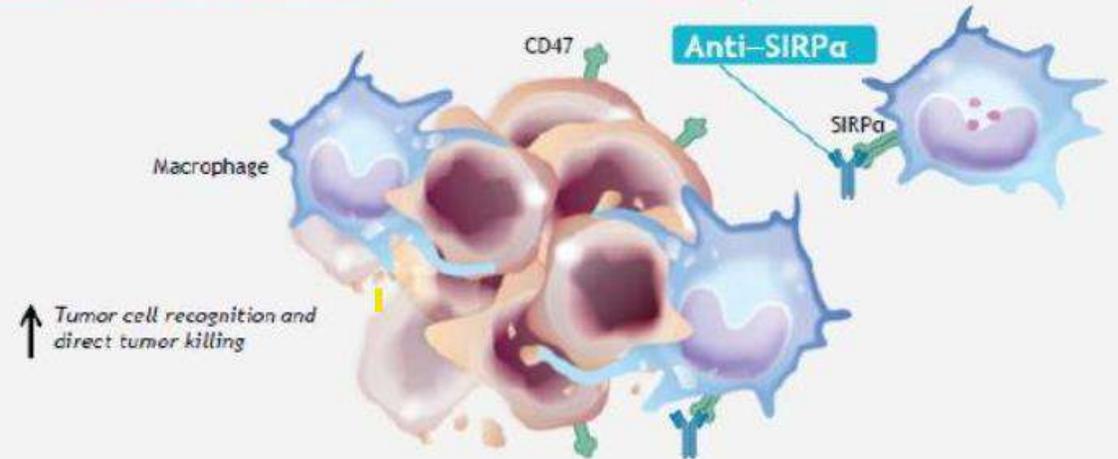
SIRPα biology



Biology¹⁻³

- SIRPα is an inhibitory receptor expressed on macrophages and dendritic cells
- CD47 is a cell-surface glycoprotein ubiquitously expressed on normal cells and overexpressed by some cancer cells
- The CD47-SIRPα axis is an early checkpoint in immune activation, regulating phagocytosis and antigen presentation to T cells
- Under physiological conditions, binding of CD47 to SIRPα initiates an inhibitory signaling pathway that helps maintain immunotolerance by nonmalignant cells
- In cancer, overexpression of CD47 on the surface of tumor cells allows tumors to escape detection,

Therapeutic intervention

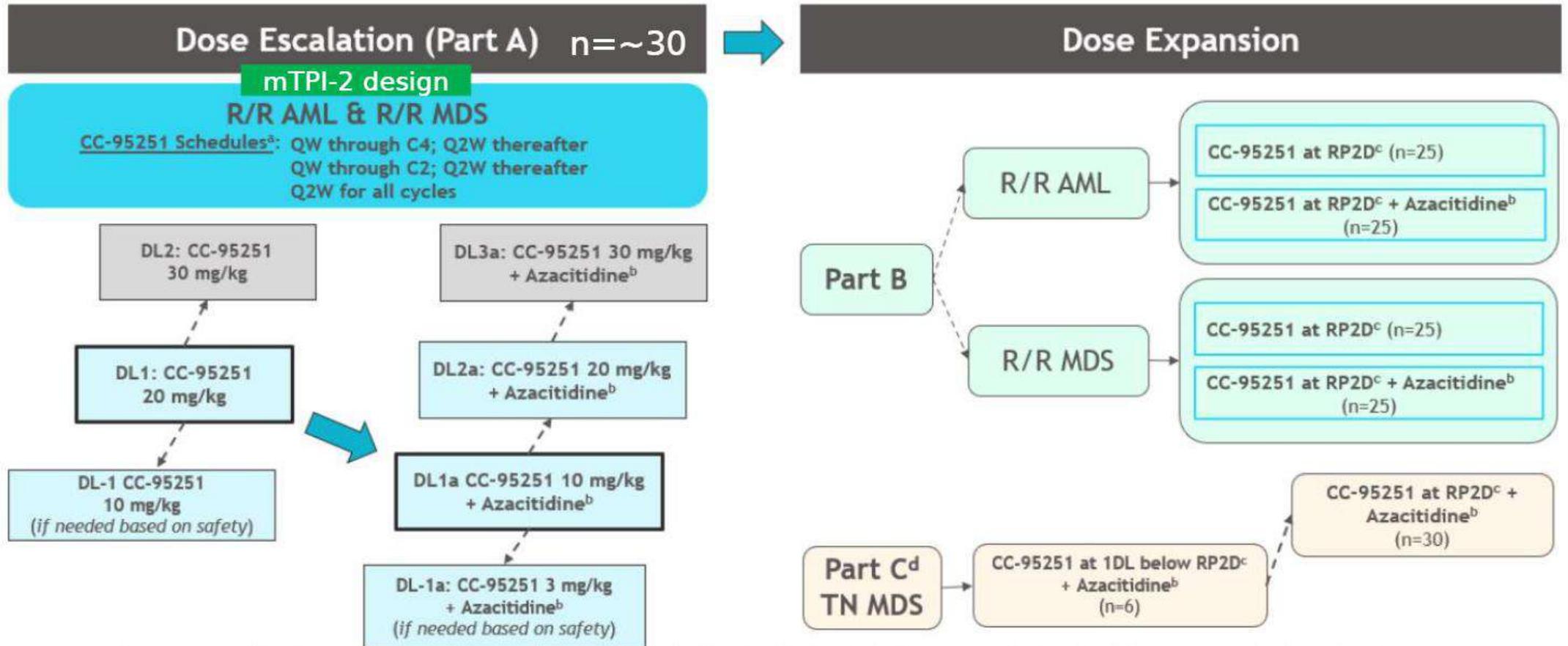


Anti-SIRPα monoclonal antibody^{4,5}

- Inhibition of the CD47-SIRPα signaling pathway is intended to improve the recognition of and enhance phagocytosis of tumor cells by macrophages
- BMS' anti-SIRPα antibody (CC-95251) alone or in combination with cetuximab or rituximab has the potential for antitumor activity

CA059-001 Fase 1

Study Design Schematic

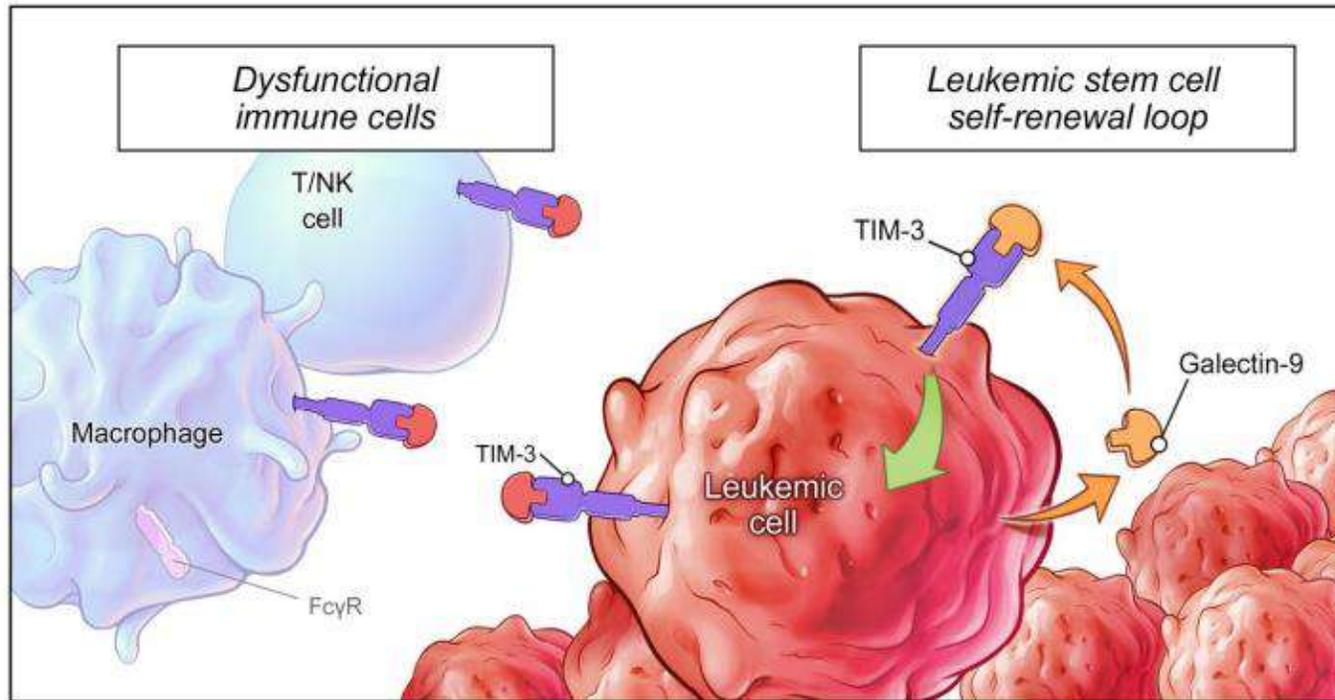


Objetivos

Seguridad y tolerabilidad de CC95251 en monoterapia y combinación

Dosis recomendada para fase 2

TIM-3 is an immuno-myeloid regulator expressed on immune and leukemic cells

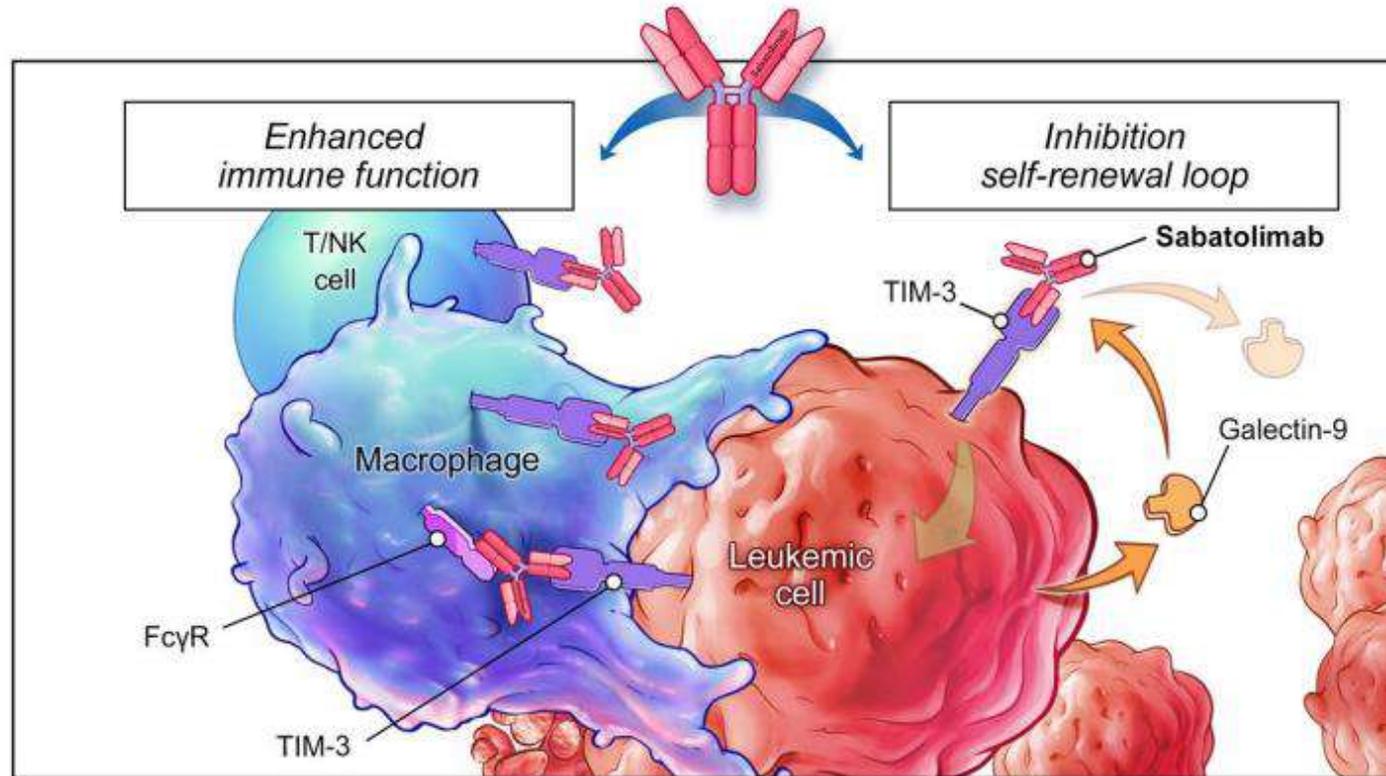


- TIM-3 plays a key role in regulating innate and adaptive immune responses^{1,2}
- TIM-3 is aberrantly expressed on LSCs and blasts, but not on normal HSCs,¹⁻⁵ which makes it a promising target in treatment for MDS and AML^{2,4,6}
- TIM-3/galectin-9 interaction forms an autocrine stimulatory loop, which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

FcγR, Fc gamma receptor; HSC, hematopoietic stem cell; LSC, leukemic stem cell; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264; 2. Das M, et al. *Immunol Rev*. 2017;276(1):97-111; 3. Kikushige Y, Miyamoto T. *Int J Hematol*. 2013;98(6):627-633; 4. Kikushige Y, et al. *Cell Stem Cell*. 2010;7(6):708-717; 5. Ngjow SF. *Cancer Res*. 2011;71(10):3540-3551; 6. Sakuishi K, et al. *Trends Immunol*. 2011;32(8):345-349; 7. Sabatos-Peyton C. AACR 2016. Oral presentation; 8. Borate U, et al. ASH 2019. Oral presentation.

Sabatolimab targets TIM-3 on immune and leukemic cells: A novel immuno-myeloid therapy



- Sabatolimab binds TIM-3 on immune cells, which enhances antileukemic immune function and phagocytic killing of LSCs and blasts¹⁻⁴
- Sabatolimab directly targets TIM-3 on LSCs, inhibiting TIM-3/galectin-9–driven self-renewal^{1,2}

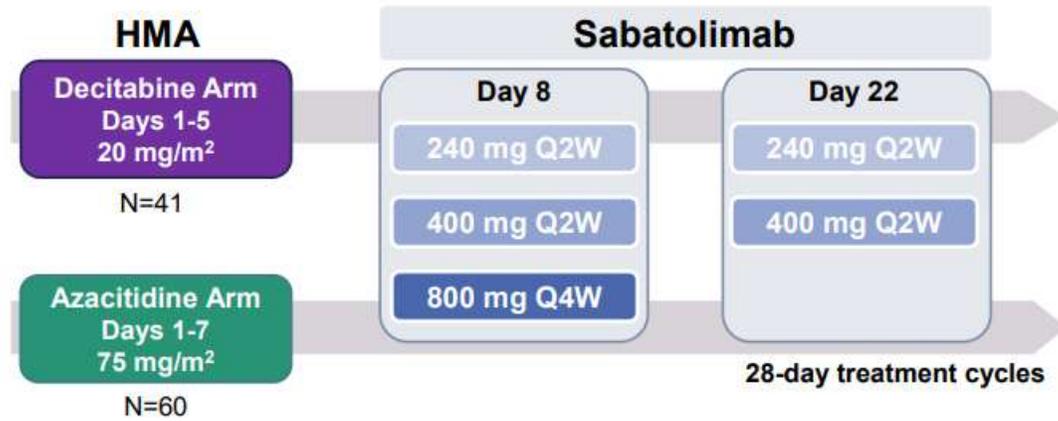
Trial design: Phase Ib study of sabatolimab + HMA in MDS and AML

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

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

Patients with prior HMA treatment excluded

ClinicalTrials.gov Identifier: **NCT03066648***



 8 countries

 11 trial centers

Primary Endpoints:
Maximum tolerated dose/recommended dose, safety, and tolerability

Secondary Endpoints:
Preliminary efficacy: Response rates and duration of response

*Multi-arm, open-label, Phase Ib dose-escalation and -expansion study of sabatolimab as a single agent or in combination with HMAs or spartalizumab. AML, acute myeloid leukemia; HMA, hypomethylating agent; HR, high-risk; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; ND, newly diagnosed; Q2W, every 2 weeks; Q4W, every 4 weeks; vHR, very high-risk.

Patient characteristics

Parameter	vHR/HR-MDS n=53	ND-AML n=48
Sabatolimab + decitabine, n	19	22
Sabatolimab + azacitidine, n	34	26
Median age (range), years	70 (23-90)	75 (59-89)
Male, n (%)	29 (54.7)	26 (54.2)
ECOG performance status, n (%)		
0	18 (34.0)	14 (29.2)
1	30 (56.6)	29 (60.4)
2	5 (9.4)	5 (10.4)
Risk Category n (%)	IPSS-R ¹	2017 ELN risk ²
	High: 32 (60.4) Very high: 21 (39.6)	Intermediate: 18 (37.5) Adverse: 30 (62.5)
Select available mutation data:	TP53 (n)	≥1 ELN adverse risk mutation (n)^a
vHR/HR-MDS (n=42 ^b)	15	33
ND-AML (n=33 ^b)	6	14

^aELN adverse risk mutations: TP53, ASXL1, and RUNX1; ^bPatients with any reported mutation
ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; IPSS-R, Revised International Prognostic Scoring System.
1. Greenberg PL, et al. *Blood*. 2012;120(12):2454-2465; 2. Döhner H, et al. *Blood*. 2017;129(4):424-447.

Patient disposition

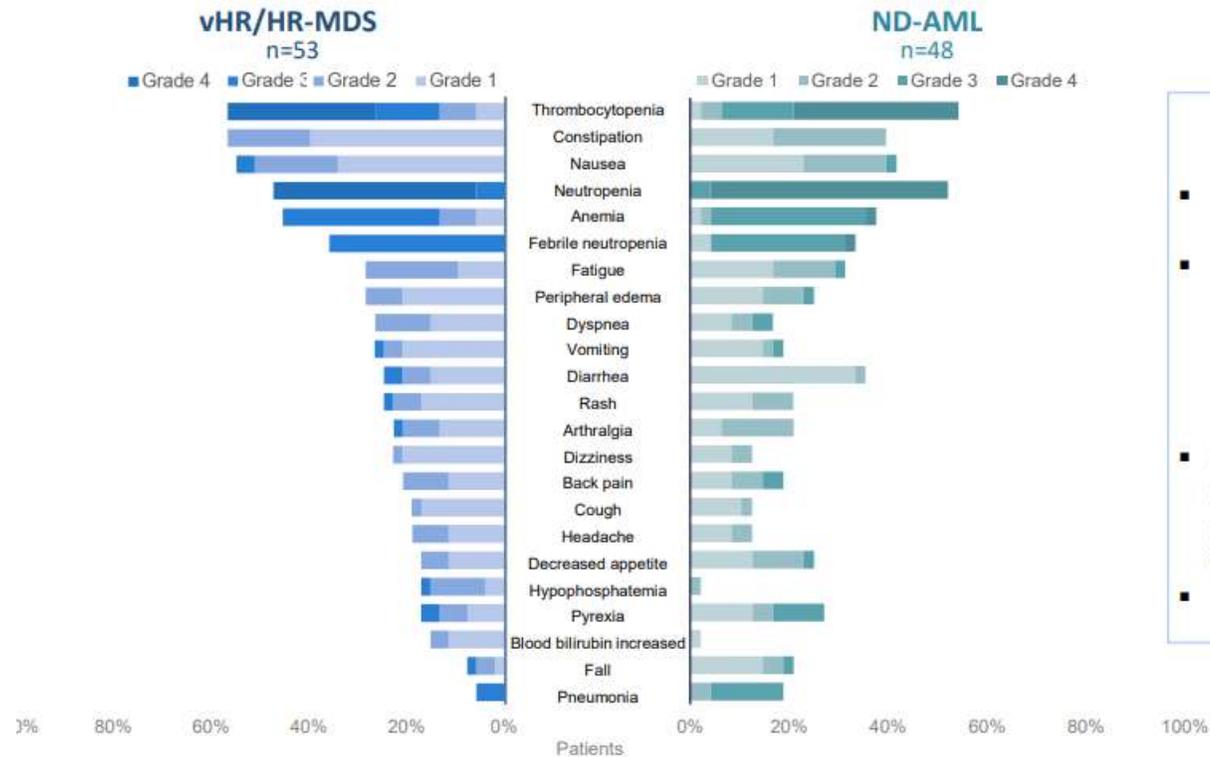
		vHR/HR-MDS n=53	ND-AML n=48
Median exposure (range), mo	Sabatolimab + decitabine ^a	8.02 (0.9-33.5)	6.8 (0.8-33.9)
	Sabatolimab + azacitidine ^b	4.45 (0.8-18.1)	5.98 (1.1-21.6)
Ongoing, ^c n (%)		9 (17)	2 (4.2)
Discontinued, n (%)		44 (83)	46 (95.8)
Reason for discontinuation			
SCT		13 (24.5)	0
Disease progression		16 (30.2)	29 (60.4)
AE: Unrelated to study treatment		0	2 (4.2)
Related to study treatment		0	1 (2.1)
Death: Unrelated to study treatment		2 (3.8)	4 (8.3)
Related to study treatment		1 ^d (1.9)	0
Patient decision		5 (9.4)	2 (4.2)
Physician decision		8 (15)	8 (16.7)
DLT		0	1 (2.1) ^e

^aEnrollment started August 2017; ^bEnrollment started February 2019; ^cAs of the cutoff date of September 6, 2021;

^d1 patient with neutropenic colitis reported as suspected to be related to study treatment died of septic shock; ^eSingle DLT was a grade 3 event of elevated ALT/hepatitis. AE, adverse event; ALT, alanine aminotransferase; DLT, dose-limiting toxicity; SCT, stem cell transplant.

Sabatolimab + HMA was safe and well tolerated in patients with vHR/HR-MDS and ND-AML

Most commonly occurring AEs (≥15% in either population, regardless of relationship to treatment)



- ### vHR/HR-MDS and ND-AML AEs
- Most common reported AEs were consistent with HMA alone
 - Low rate of sabatolimab dose modification:
 - 1/101 (1%) patients had dose reduction
 - 38/101 (38%) patients had dose interruption^a 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

^aDose interruption: Cycle delay >7 days.

Few patients had clinically significant possible imAEs with sabatolimab + HMA

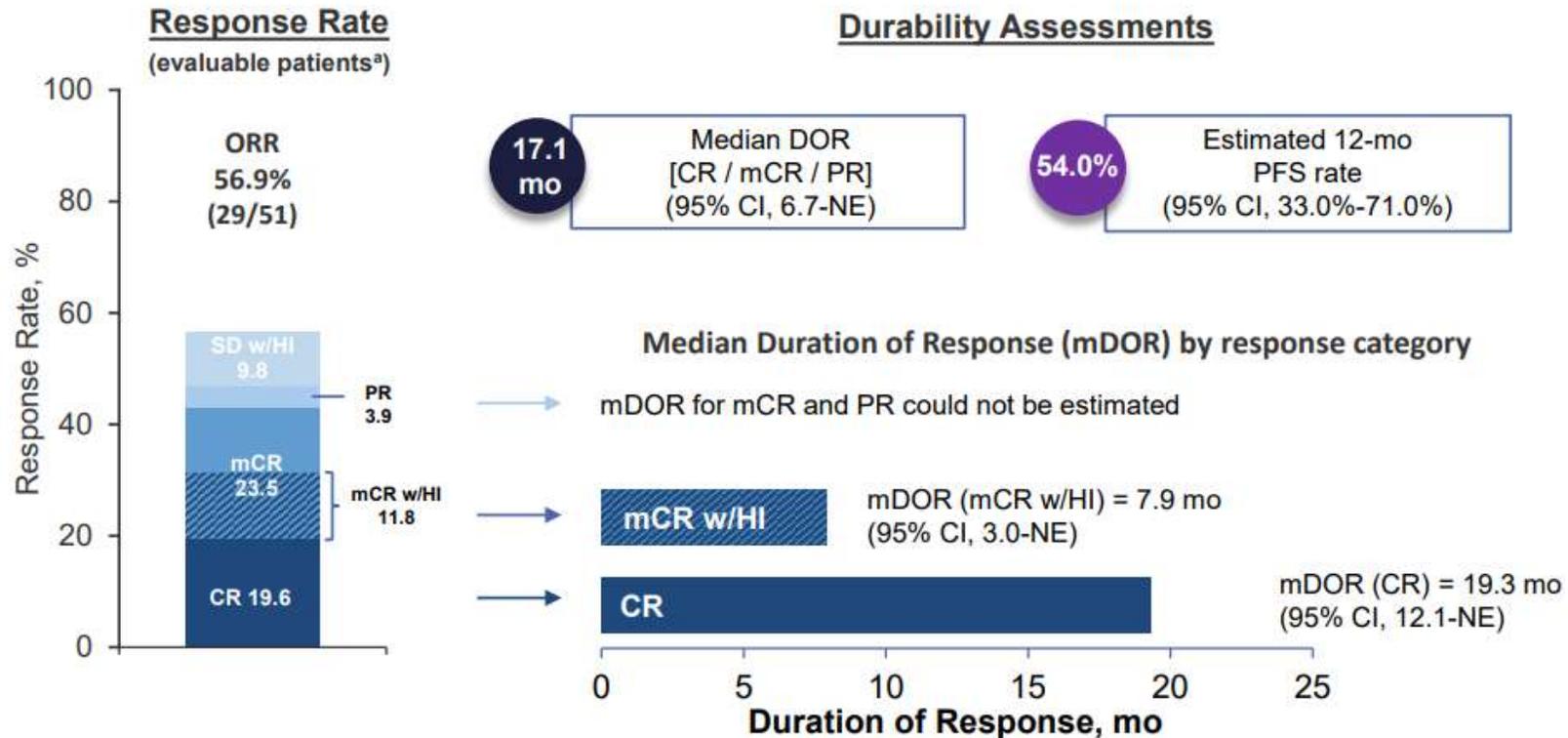
	vHR/HR-MDS n=53	ND-AML n=48	
		Gr 1/2	Gr 3
Patients with possible imAEs regardless of relationship to study treatment ^a	7 (13.2)	5 (10.4)	5 (10.4)
Peripheral neuropathy	2 (3.8)	1 (2.1)	1 (2.1)
Acute febrile neutrophilic dermatosis	1 (1.9)	0	0
Autoimmune hepatitis	1 (1.9)	0	0
Dermatitis	1 (1.9)	1 (2.1)	0
Pericarditis	1 (1.9)	0	0
Pneumonitis	1 (1.9)	0	0
Arthritis	0	3 (6.3)	0
Colitis	0	1 (2.1)	1 (2.1)
Cutaneous vasculitis	0	0	0
Encephalopathy	0	0	1 (2.1)
Hemophagocytic lymphohistiocytosis	0	0	1 (2.1)
Hepatitis	0	0	1 (2.1)
Hypothyroidism	0	0	1 (2.1)
Immune-mediated lung disease	0	0	1 (2.1)

- 7/53 (13%) patients with vHR/HR-MDS and 10/48 (21%) patients with ND-AML experienced ≥ 1 possible imAEs
- No grade ≥ 3 possible imAEs were observed in patients with vHR/HR-MDS; no grade 4/5 possible imAEs were observed in patients with AML
- No patient with vHR/HR-MDS and 1 patient with ND-AML discontinued treatment due to a possible imAE suspected to be related to sabatolimab
- No serious late-onset sabatolimab-related imAEs were identified^b
- Of the 7 patients with vHR/HR-MDS who had an imAE, all achieved remission
- Among patients with ND-AML, the frequency of possible imAEs was similar regardless of remission status

^aBased on maximum grade. Events retrieved based on pre-defined case retrieval strategy including MedDRA SMQ immune-mediated disorder terms.

^bEvents 150 days after last dose of sabatolimab

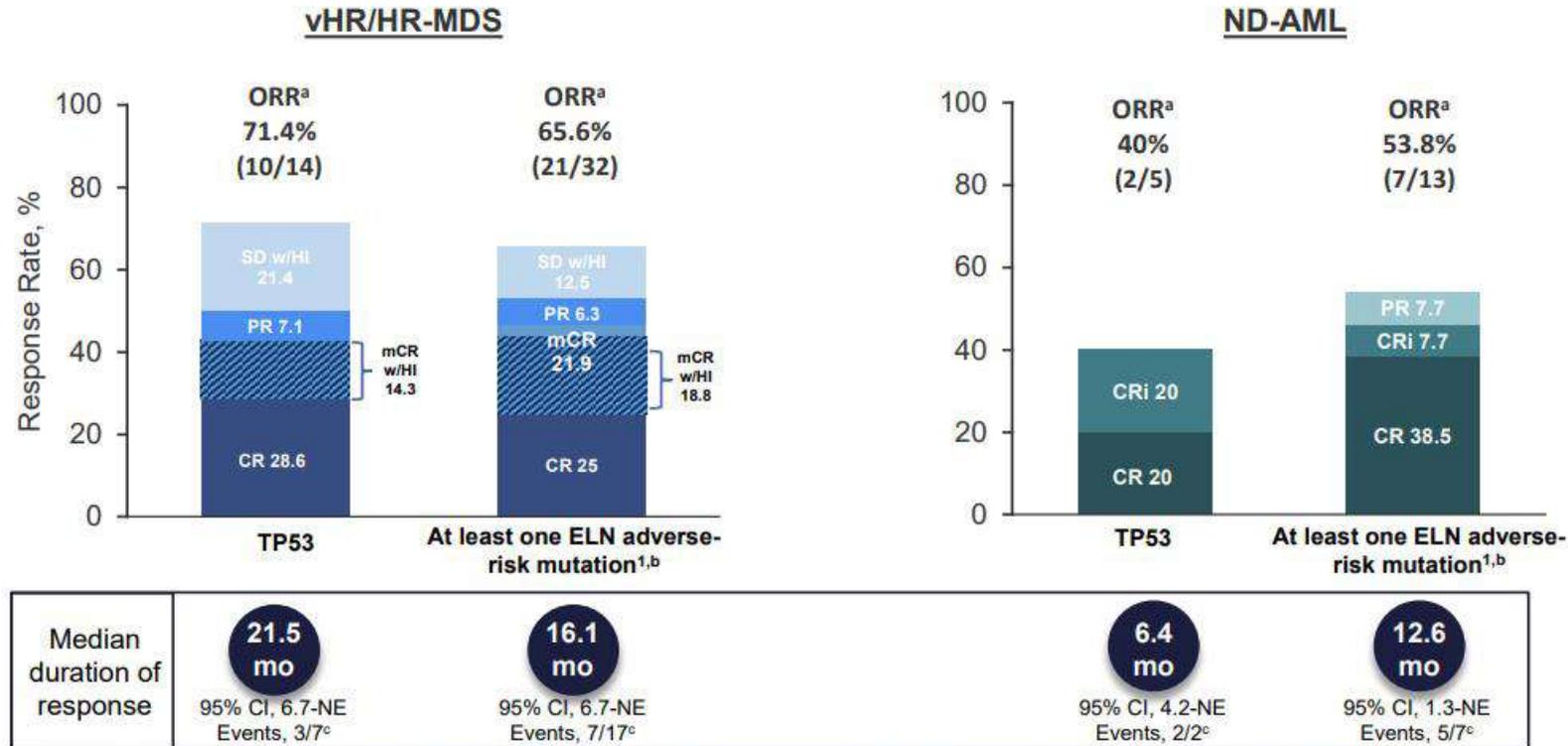
Sabatolimab + HMA demonstrates durable clinical responses in vHR/HR-MDS



^aEvaluable patients, including 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 remission; DOR, duration of response; HI, hematologic improvement; mCR, bone marrow CR; mDOR, median duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial remission; SD, stable disease.

Patients with adverse-risk disease were able to achieve durable responses



^aORR 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; ^bELN adverse-risk mutations: TP53, ASXL1, and RUNX1; ^cDOR 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). 1. Döhner H, et al. *Blood*. 2017;129(4):424-447.

The STIMULUS Program: Clinical Trials Evaluating Sabatolimab (MBG453) Combination Therapy in Patients With HR-MDS or AML

- Broad clinical trial program committed to evaluating the potential for sabatolimab to emerge as a transformative first-in-class immunotherapeutic agent for patients with myeloid malignancies
- Includes numerous trials evaluating early and long-term efficacy and safety of sabatolimab combination therapy in patients with MDS and AML

MDS

STIMULUS-MDS1

(NCT03946670)

Phase II¹

- Sabatolimab or placebo + HMA
- Very high-, high-, or intermediate- risk^a MDS^b

 Ongoing, recruitment completed

STIMULUS-MDS2

(NCT04266301)

Phase III²

- Sabatolimab or placebo + azacitidine
- Very high-, high-, or intermediate- risk MDS^b or CMML-2

Recruiting

AML

STIMULUS-AML1

(NCT04150029)

Phase II³

- Sabatolimab + venetoclax and azacitidine
- AML

Recruiting

Conclusiones.

- Nuevas moléculas dirigidas a múltiples dianas
- Inhibidores check point: resultados prometedores, todavía en fases tempranas
- Dificultad intrínseca de las neoplasias mieloides: antígenos del tumor se expresan también en células sanas y progenitoras.
- Sinergia con terapia epigenética para aumentar la inmunogenicidad del tumor
- Nuevos efectos adversos inmunomediados y derivados de la diana específica
- Estabilidad de las respuestas, mantenidas y duraderas en el tiempo