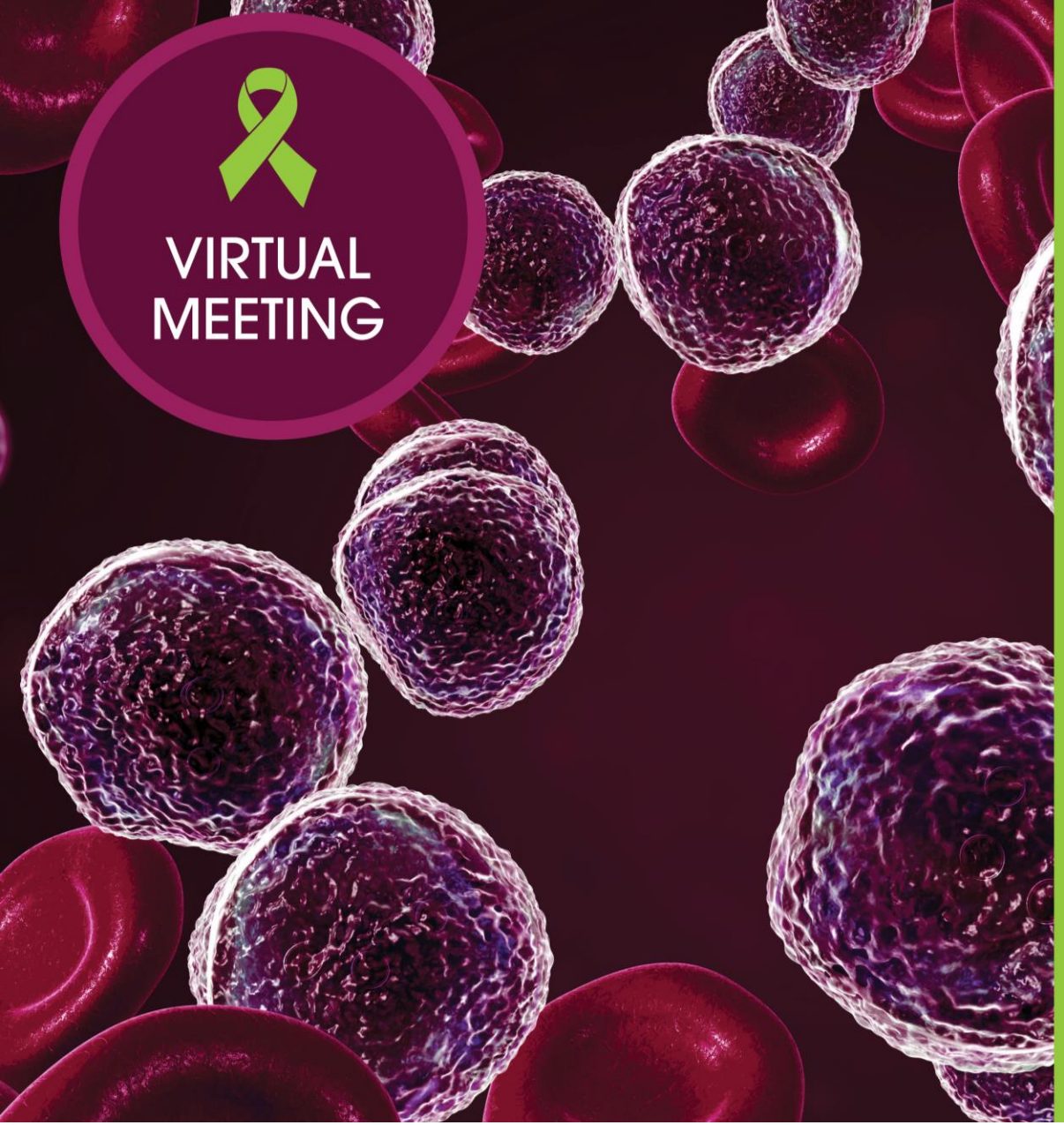
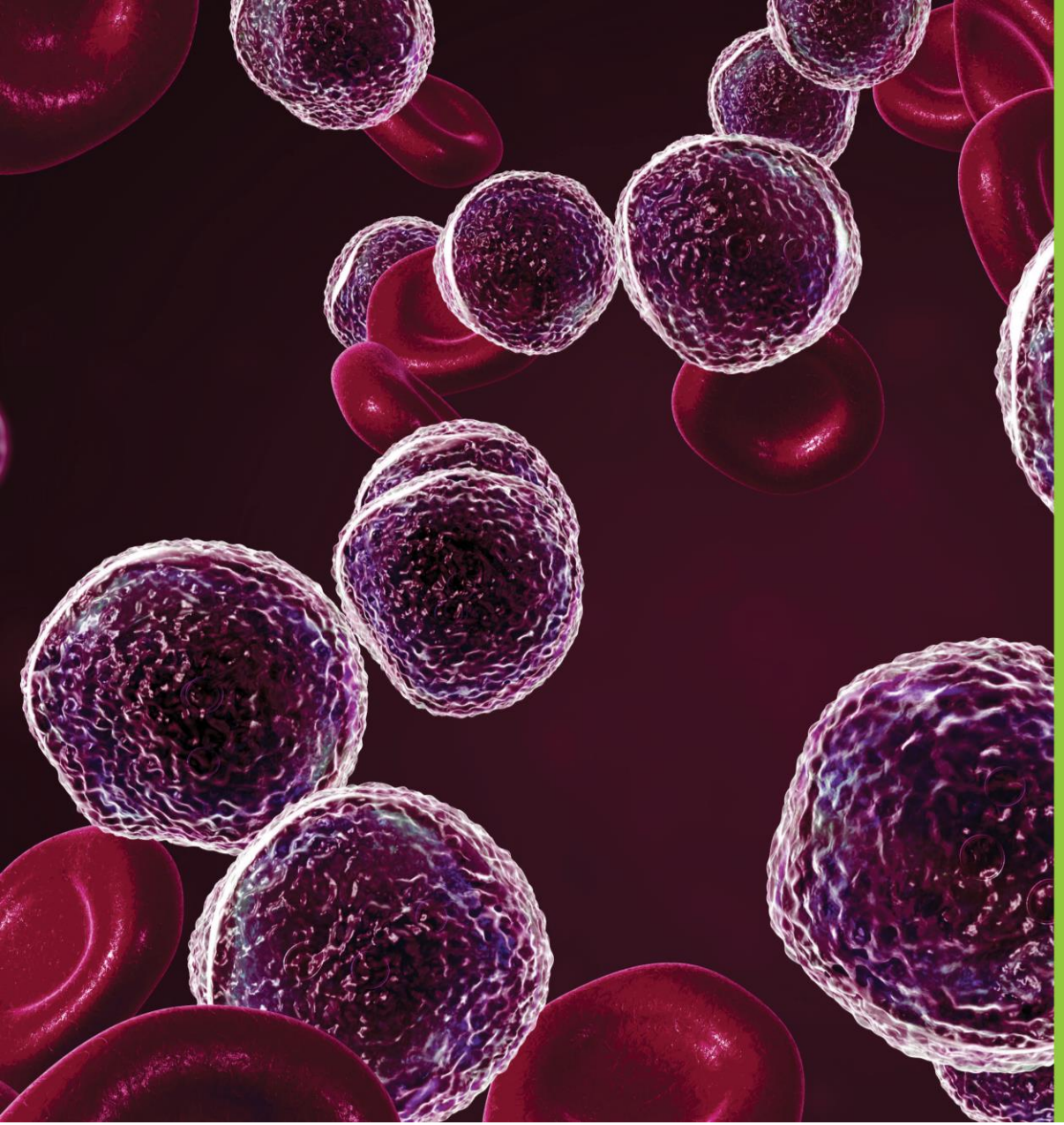


BEYOND THE CONGRESS

Key Conversations from the 2021 Hematology Annual Meeting™

FRIDAY, FEBRUARY 4, 2022

This activity is jointly provided by PIM Postgraduate Institute for Medicine and Bio Ascend™



BEYOND THE CONGRESS

Key Conversations from the 2021 Hematology Annual Meeting™

FRIDAY, FEBRUARY 4, 2022

This activity is jointly provided by PIM Postgraduate Institute for Medicine and Bio Ascend™

Emerging Themes and Concepts in the Treatment of MDS

Michael R. Savona, MD
Professor of Medicine and Cancer Biology
Vanderbilt University Medial Center, Nashville, TN, USA

Disclosures

I have the following financial relationships to disclose:

Advisory and consulting: Abbvie, Celgene, CTI, Geron, Karyopharm, Novartis, Ryvu, Taiho, Takeda, TG Therapeutics; *Research Support:* ALX Oncology, Astex, Incyte, Takeda, TG Therapeutics; *Equity:* Karyopharm, Ryvu; *Data Safety Monitoring Board:* Celgene, Sierra Oncology, TG Therapeutics; *Licensing Agreement:* Boehringer-Ingelheim

Myelodysplastic syndromes: Emerging Themes and Ideas

1. **Prognostication** via IPSS/IPSS-R includes marrow fitness, transformational features, and large structural changes in somatic DNA → critical small mutational changes are now formally part of the prognostication

2. **Metabolic changes** in MDS cells provide vulnerability for treatment

3. **Targeting Inflammation** as part of the pathophysiology of MDS

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

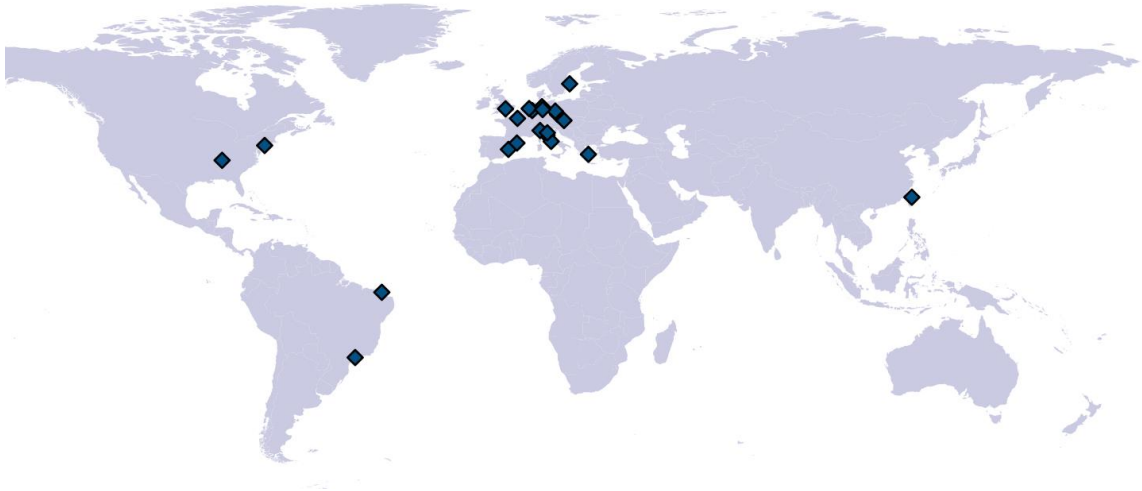
Use of NGS in Prognostication

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

International Working Group for the Prognosis of MDS (IWG-PM)

Study objective: Integrate gene mutations into the International Prognostic Scoring System (IPSS/IPSS-R)

IWG cohort (discovery)



n=2,957

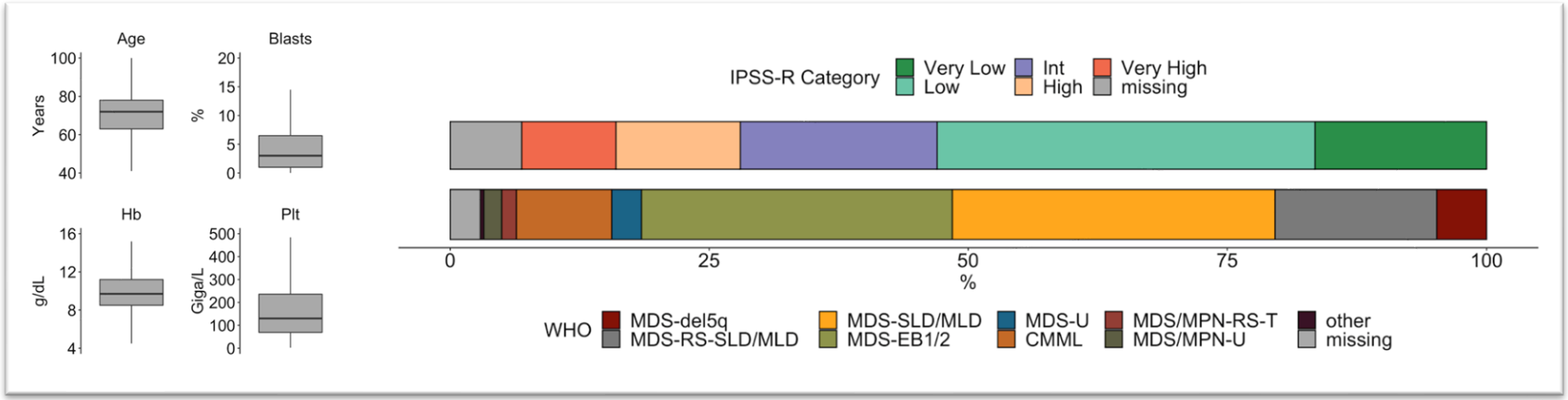
Japan cohort (validation)

n=754

Bernard et al. Blood; Abstract 61: 2021.

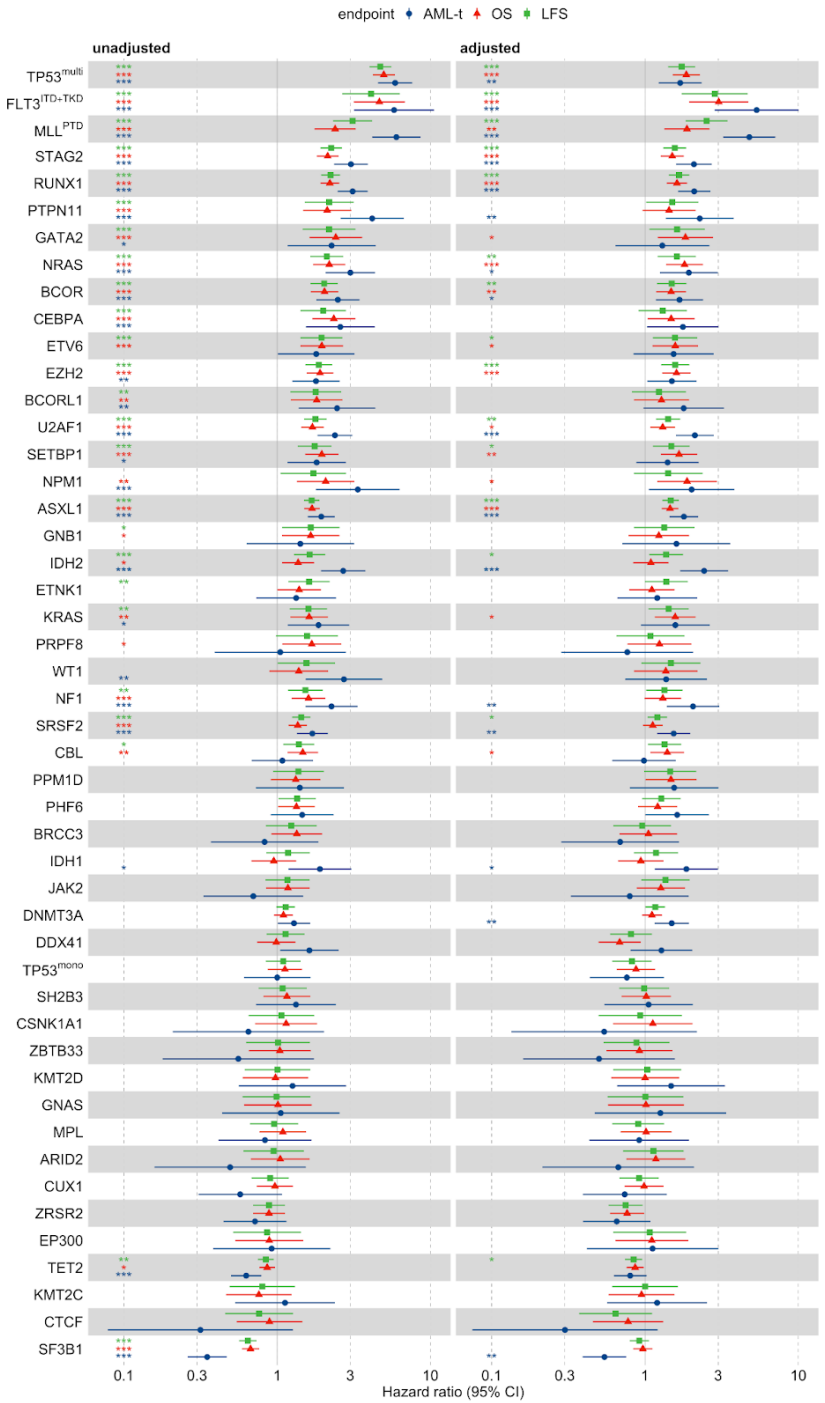
IWG-PM cohort clinical characteristics

Inclusion criteria: diagnostic samples | blast percentages < 20% | white blood cell count < $13x10^9/L$



- Median age of presentation 72 years (39-88, 95th range).
- Representative of all IPSS-R risk categories and WHO subtypes.
- 8% of patients had therapy-related MDS.
- 30% of patients treated with disease-modifying agents according to established guidelines.
- Median follow-up 3.8 years.

Bernard et al. Blood; Abstract 61: 2021.



Association between gene mutations and clinical endpoints

Leukemia free survival (LFS)

Overall survival (OS)

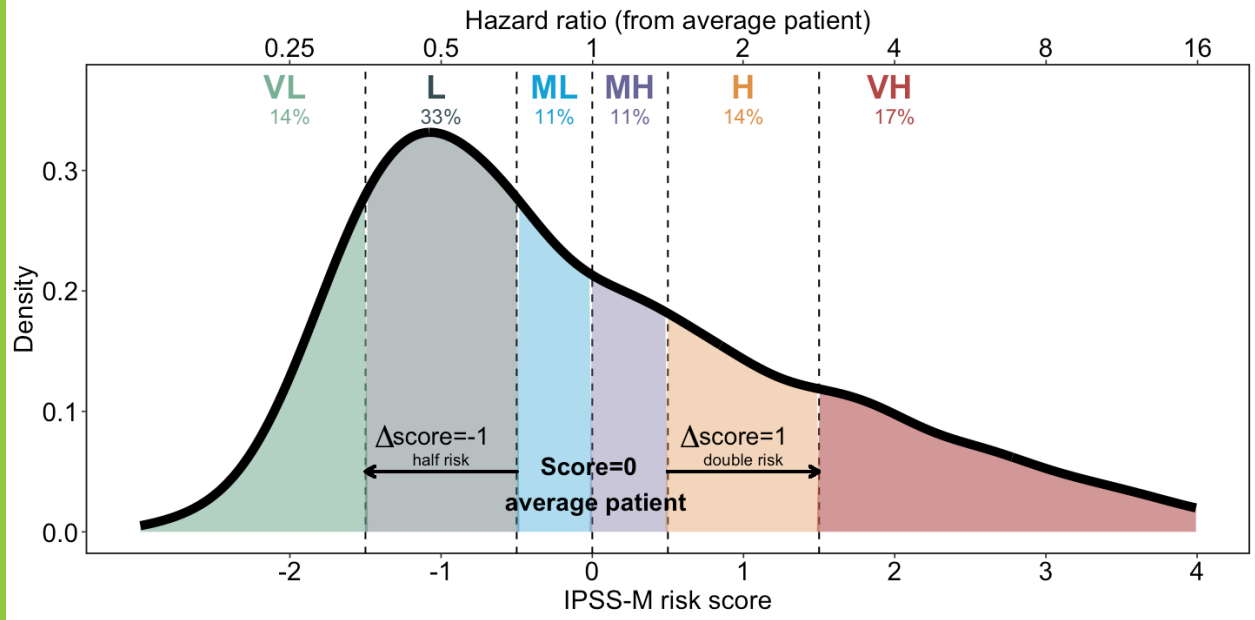
AML transformation (AML-t)

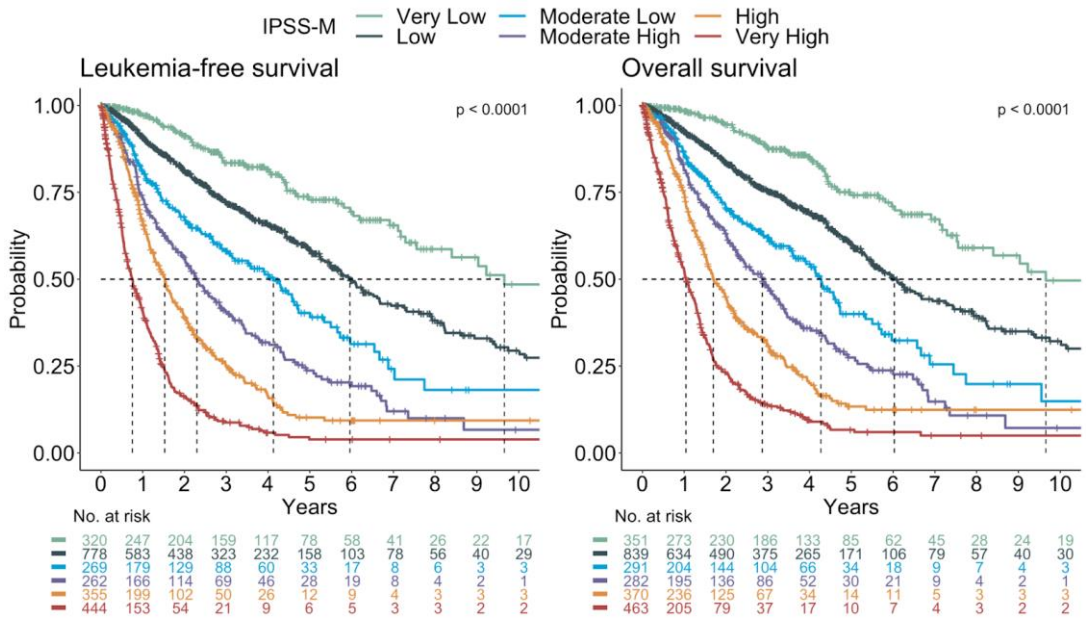
Adjusting for age, sex, MDS type (primary vs. therapy-related), and IPSS-R raw score, 14, 16 and 15 genes were significantly associated with adverse outcomes for the three endpoints, respectively.

Bernard et al. Blood; Abstract 61: 2021.

The IPSS-M risk categories

A six-category risk schema



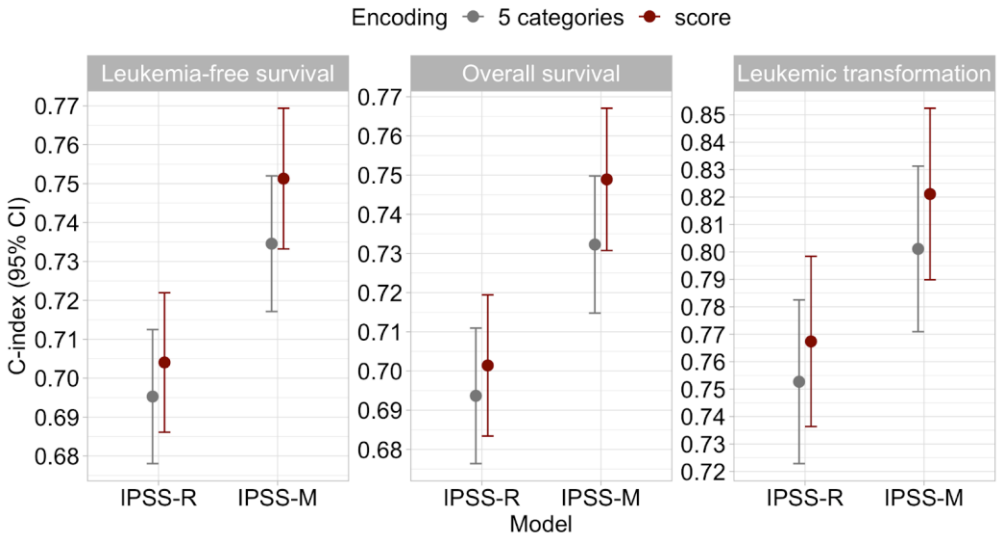


Very Low | Low | Moderate Low | Moderate High | High | Very High

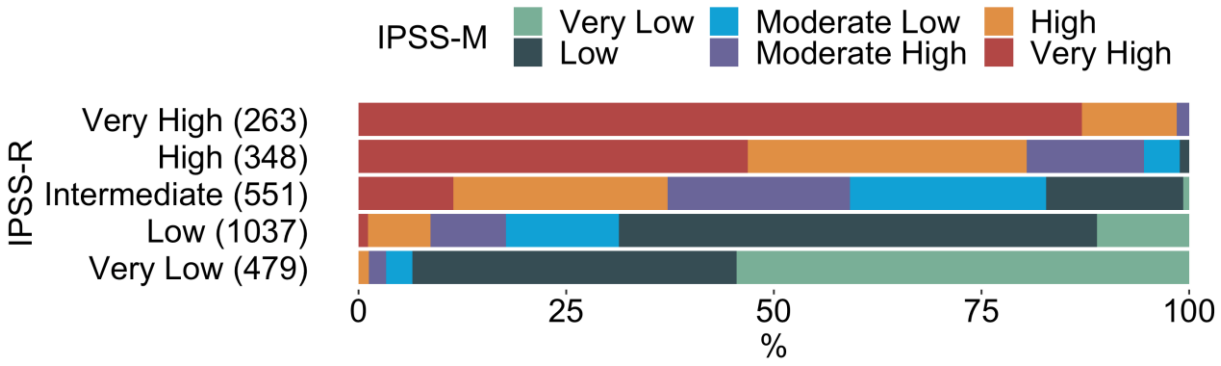
Bernard et al. Blood; Abstract 61: 2021.

From the IPSS-R to the IPSS-M

Improved prognostic discrimination



Extensive patient re-stratification



Five points increase in concordance index from IPSS-R to IPSS-M across all endpoints

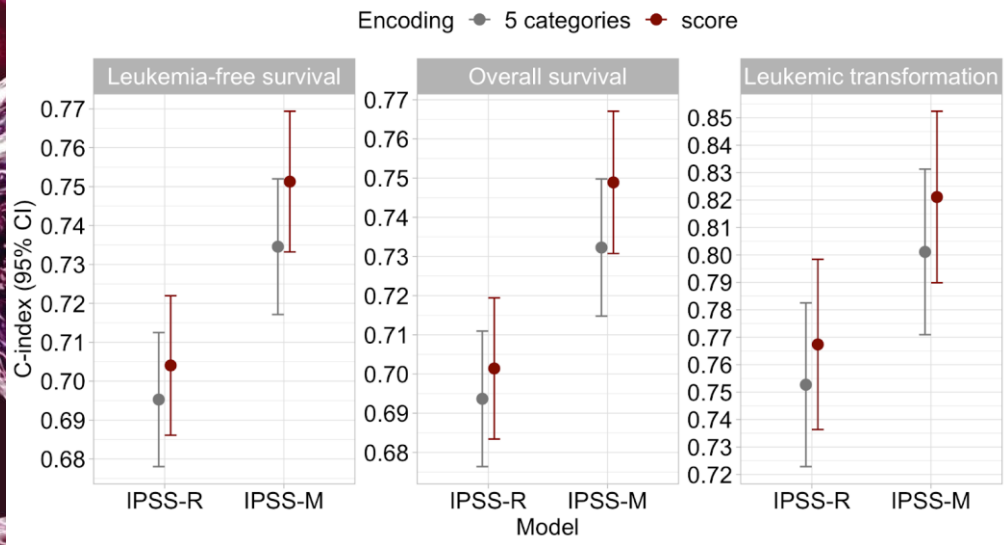
46% (n=1,223) of patients were re-stratified

7% (n=196) of patients were re-stratified by more than one strata

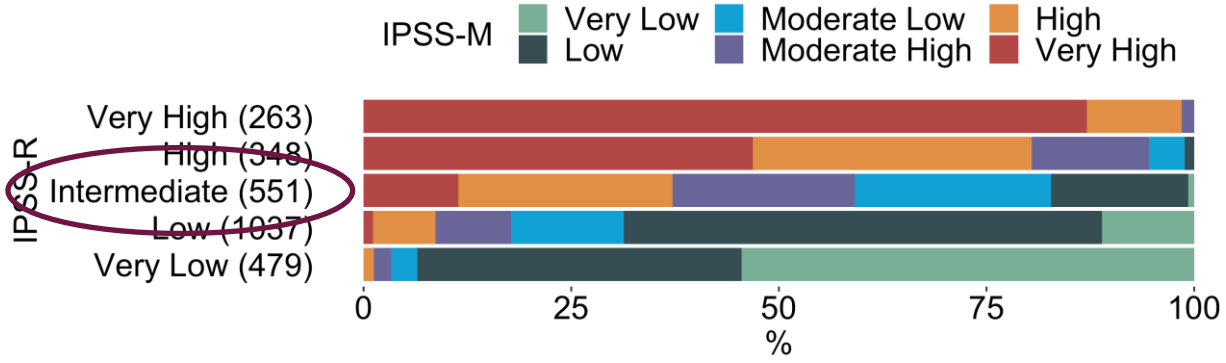
Bernard et al. Blood; Abstract 61: 2021.

From the IPSS-R to the IPSS-M

Improved prognostic discrimination



Extensive patient re-stratification



Five points increase in concordance index from IPSS-R to IPSS-M across all endpoints

46% (n=1,223) of patients were re-stratified

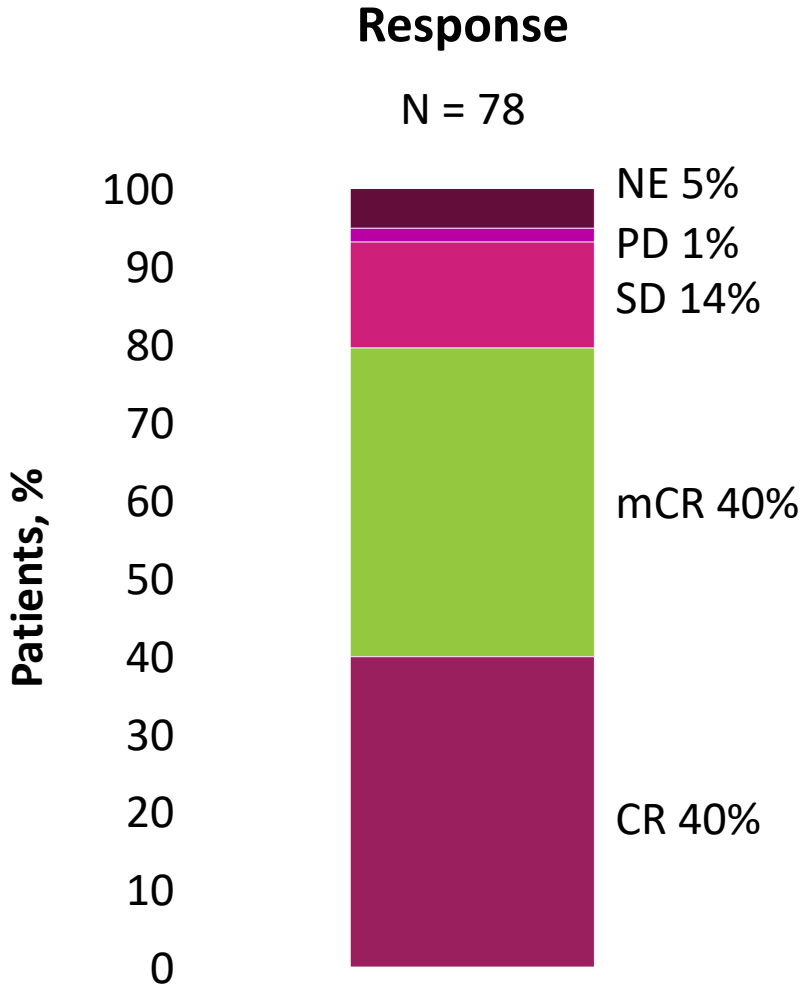
7% (n=196) of patients were re-stratified by more than one strata

Bernard et al. Blood; Abstract 61: 2021.

Metabolism and Apoptosis

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

Phase Ib Study Adding Venetoclax to Azacitidine in Higher-risk MDS Shows Safety and Efficacy

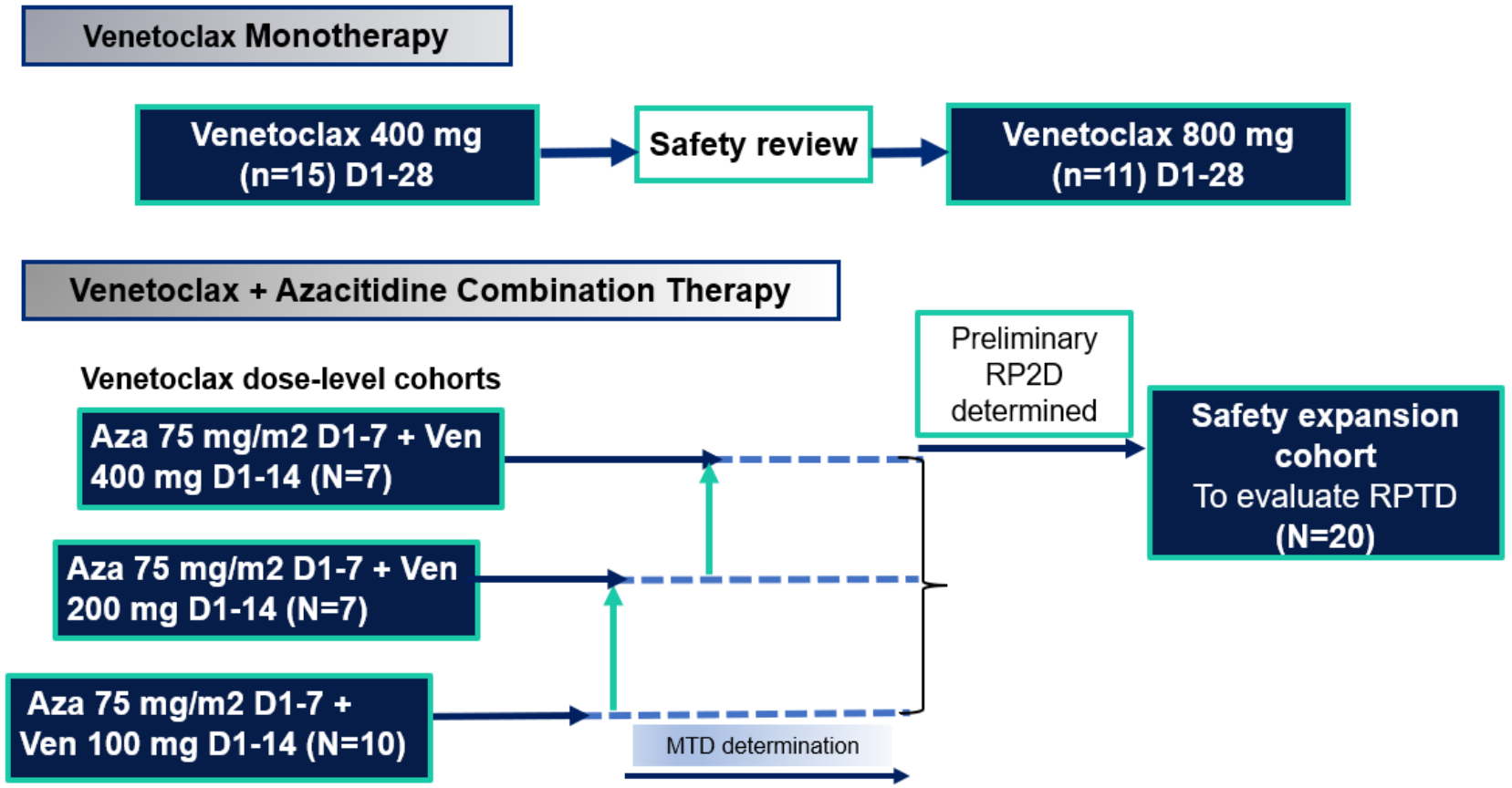


Median time to mCR, mo (range)	0.9 (0.7-4.6)
Median time to CR, mo (range)	2.6 (1.2-19.6)
Transfusion independence rate n/N (%) [95% CI]	20/43 (46.5) [31.2-62.3]
Duration of response for CR, median	13.8 (8.9-NE)

- Prior to other post-study systemic cancer therapies, 23% of the study population moved to post-study allogeneic HSCT

Wei. SOHO 2021. Poster 158.

Study of Venetoclax and Azacitidine in R/R MDS



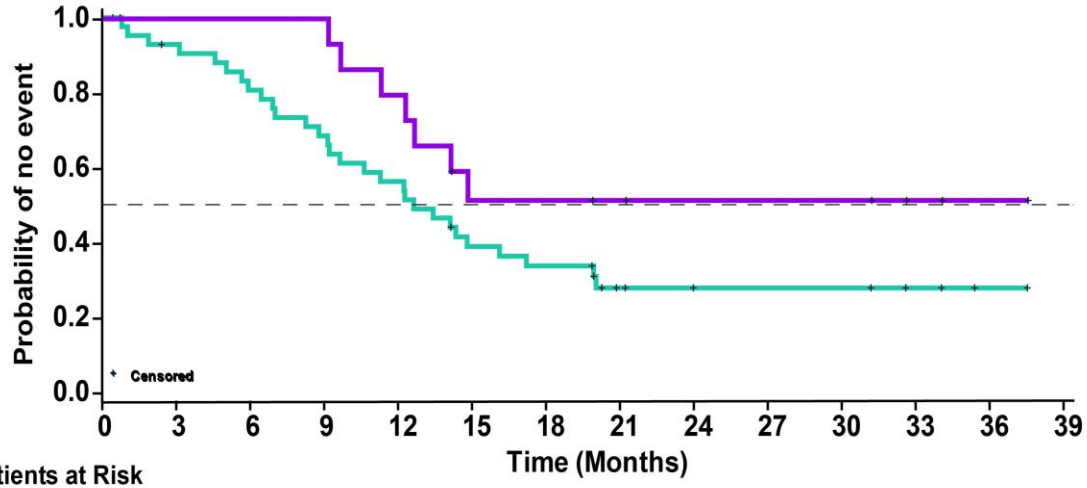
Zeidan et al. Blood; Abstract 537: 2021.

Safety of Venetoclax and Azacitidine in R/R Higher-risk MDS

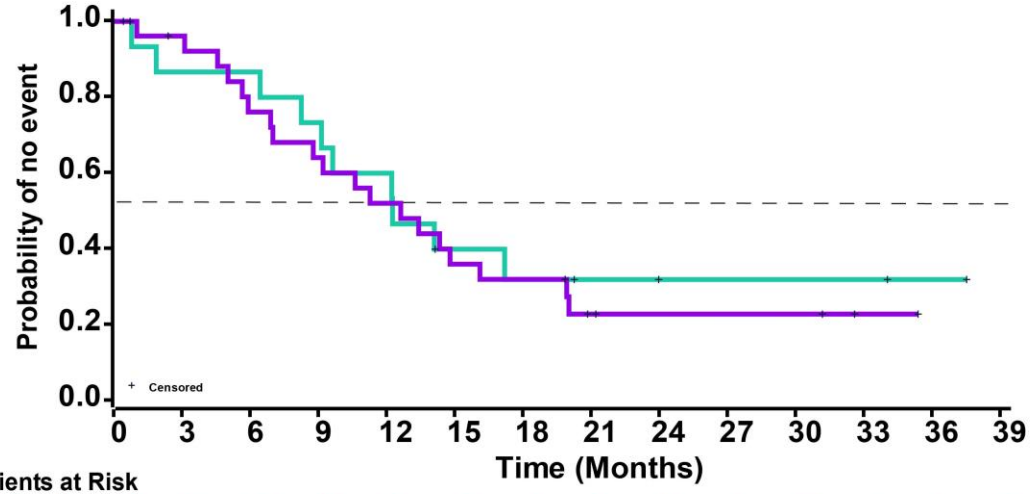
	Ven n (%)	Aza n (%)
Study drug discontinuation[a]	9 (20.5)	7 (15.9)
Dose interruption[b]	21 (47.7)	18 (40.9)
Febrile neutropenia	7 (15.9)	7 (15.9)
Neutropenia	4 (9.1)	3 (6.8)
Pneumonia	3 (6.8)	1 (10)
Pneumonia fungal	2 (4.5)	1 (10)
Oral infection	1 (2.3)	1 (10)

Zeidan et al. Blood; Abstract 537: 2021.

Survival in Ongoing Study of Venetoclax and Azacitidine in R/R Higher-risk MDS



Patients at Risk														
Ven+Aza (All patients)	44	38	33	28	23	15	13	7	5	5	5	3	1	0
Ven+Aza (mCR)	14	14	14	14	11	6	6	5	4	4	4	2	1	0



Patients at Risk														
≤6 Cycles	15	13	13	11	9	5	4	3	2	2	2	2	1	0
>6 Cycles	28	24	19	16	13	9	8	4	3	3	3	1	0	

OS	# of events	12-month, % (95% CI)	24-month % (95% CI)	Median OS, months (95% CI)
Ven+Aza (All patients)	29	56.2 (39.8 — 69.7)	27.7 (14.8 — 42.3)	12.6 (9.1 — 17.2)
Ven+Aza (mCR)	7	78.6 (47.2 — 92.5)	49.0 (21.6 — 71.7)	14.8 (11.3 — NE)

OS	# of events	12-month, % (95% CI)	24-month % (95% CI)	Median OS, months (95% CI)
≤ 6 cycles of prior HMA	10	60.0 (31.8 — 79.7)	32.0 (10.9 — 55.7)	12.3 (6.4 — NE)
> 6 cycles of prior HMA	19	52.1 (31.3 — 69.3)	22.9 (8.8 — 40.9)	12.6 (7.0 — 19.9)

Zeidan et al. Blood; Abstract 537: 2021.

Untreated High Risk MDS is Largely BCL2 Dependent

Venetoclax (μM)	0.23	2.54	5.00	3.69	5.00	1.05	0.25	3.61	1.41	0.29	5.00	5.00	3.82	0.84	0.27	0.23	5.00	0.25	1.57	0.27	0.20	0.47	0.26	0.11	0.36	0.18	0.15	0.12	0.08	0.14	5.00	1.15	5.00	0.18	0.13
S63845 (μM)	0.21	0.56	0.33	0.30	0.18	1.70	0.20	0.34	0.62	0.30	0.13	0.36	0.44	0.22	0.30	0.13	0.41	0.06	0.64	0.14	0.30	0.39	0.99	0.13	0.12	0.33	0.13	0.82	0.36	0.17	1.73	1.73	0.52	1.84	0.57
A-1155463 (μM)	5.00	5.00	5.00	4.00	1.46	1.70	3.17	1.68	0.53	5.00	5.00	5.00	5.00	0.58	2.99	5.00	5.00	5.00	5.00	5.00	5.00	X	5.00	5.00	5.00	5.00	0.03	5.00	5.00	5.00	0.12	5.00	5.00	5.00	5.00
MDS WHO 2016 Classification	MDS-RS-SLD				MDS-RS-MLD					MDS-MLD									MDS-EB1										MDS-EB2						
	MDS001	MDS002	MDS003	MDS004	MDS005	MDS006	MDS007	MDS008	MDS009	MDS010	MDS011	MDS012*	MDS013*	MDS014*	MDS015	MDS016	MDS017	MDS018	MDS019	MDS020	MDS021	MDS022	MDS023	MDS024	MDS025	MDS026	MDS027	MDS028	MDS029#	MDS030*	MDS031	MDS032*	MDS033	MDS034	MDS035

Fischer et al. BioRx. 2021.

Untreated High Risk MDS is *Largely* BCL2 Dependent

Venetoclax (μM)	0.23	2.54	5.00	3.69	5.00	1.05	0.25	3.61	1.41	0.29	5.00	5.00	3.82	0.84	0.27	0.23	5.00	0.25	1.57	0.27	0.20	0.47	0.26	0.11	0.36	0.18	0.15	0.12	0.08	0.14	5.00	1.15	5.00	0.18	0.13
S63845 (μM)	0.21	0.56	0.33	0.30	0.18	1.70	0.20	0.34	0.62	0.30	0.13	0.36	0.44	0.22	0.30	0.13	0.41	0.06	0.64	0.14	0.30	0.39	0.99	0.13	0.12	0.33	0.13	0.82	0.36	0.17	1.73	1.73	0.52	1.84	0.57
A-1155463 (μM)	5.00	5.00	5.00	4.00	1.46	1.70	3.17	1.68	0.53	5.00	5.00	5.00	5.00	0.58	2.99	5.00	5.00	5.00	5.00	5.00	5.00	X	5.00	5.00	5.00	5.00	0.03	5.00	5.00	5.00	0.12	5.00	5.00	5.00	5.00
MDS WHO 2016 Classification	MDS-RS-SLD				MDS-RS-MLD					MDS-MLD									MDS-EB1										MDS-EB2						
	MDS001	MDS002	MDS003	MDS004	MDS005	MDS006	MDS007	MDS008	MDS009	MDS010	MDS011	MDS012*	MDS013*	MDS014*	MDS015	MDS016	MDS017	MDS018	MDS019	MDS020	MDS021	MDS022	MDS023	MDS024	MDS025	MDS026	MDS027	MDS028	MDS029#	MDS030*	MDS031	MDS032*	MDS033	MDS034	MDS035

Fischer et al. BioRx. 2021.

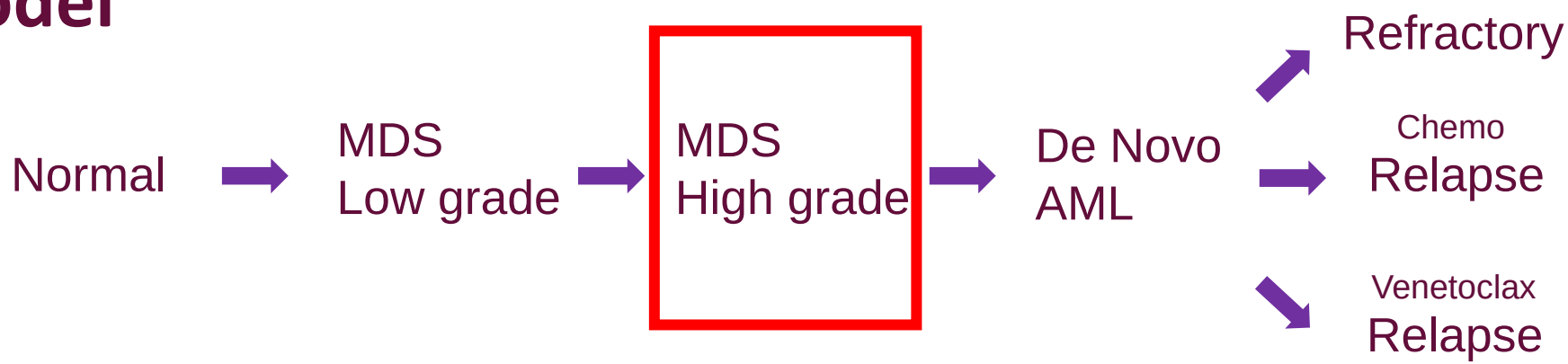
Untreated High Risk MDS is *Largely* BCL2 Dependent

Venetoclax (μM)	0.23	2.54	5.00	3.69	5.00	1.05	0.25	3.61	1.41	0.29	5.00	5.00	3.82	0.84	0.27	0.23	5.00	0.25	1.57	0.27	0.20	0.47	0.26	0.11	0.36	0.18	0.15	0.12	0.08	0.14	5.00	1.15	5.00	0.18	0.13
S63845 (μM)	0.21	0.56	0.33	0.30	0.18	1.70	0.20	0.34	0.62	0.30	0.13	0.36	0.44	0.22	0.30	0.13	0.41	0.06	0.64	0.14	0.30	0.39	0.99	0.13	0.12	0.33	0.13	0.82	0.36	0.17	1.73	1.73	0.52	1.84	0.57
A-1155463 (μM)	5.00	5.00	5.00	4.00	1.46	1.70	3.17	1.68	0.53	5.00	5.00	5.00	5.00	0.58	2.99	5.00	5.00	5.00	5.00	5.00	5.00	X	5.00	5.00	5.00	5.00	0.03	5.00	5.00	5.00	0.12	5.00	5.00	5.00	5.00
MDS WHO 2016 Classification	MDS-RS-SLD				MDS-RS-MLD					MDS-MLD									MDS-EB1										MDS-EB2						
	MDS001	MDS002	MDS003	MDS004	MDS005	MDS006	MDS007	MDS008	MDS009	MDS010	MDS011	MDS012*	MDS013*	MDS014*	MDS015	MDS016	MDS017	MDS018	MDS019	MDS020	MDS021	MDS022	MDS023	MDS024	MDS025	MDS026	MDS027	MDS028	MDS029#	MDS030*	MDS031	MDS032*	MDS033	MDS034	MDS035

...R/R High Risk MDS is *less* BCL2 Dependent

Fischer et al. BioRx. 2021.

Stem Cell Energy Metabolism During Myeloid Pathogenesis: Working Model



Metabolic fuel	Glucose	?	AA*	AA	AA or FA
Oxphos	?	?	Yes	Yes	Yes
Glycolysis	Yes	?	No*	No	No

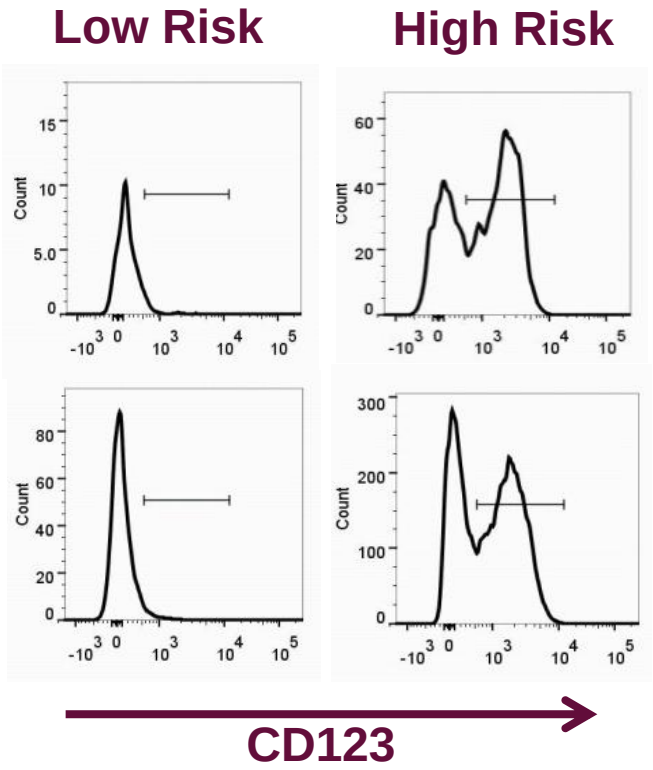
*indirect evidence only, AA = amino acids, FA = fatty acids

Lagadinou et al, *Cell Stem Cell*, 2013; Stevens et al, *Nat. Comm*, 2018,; Jones et al, *Cancer Cell*, 2018; Pollyea, Stevens, Jones et al, *Nature Medicine*, 2018; Pei et al, *Cancer Discovery*, 2020; Jones et al, *Cell Stem Cell*, 2020; Stevens et al, *Nature Cancer*, 2020

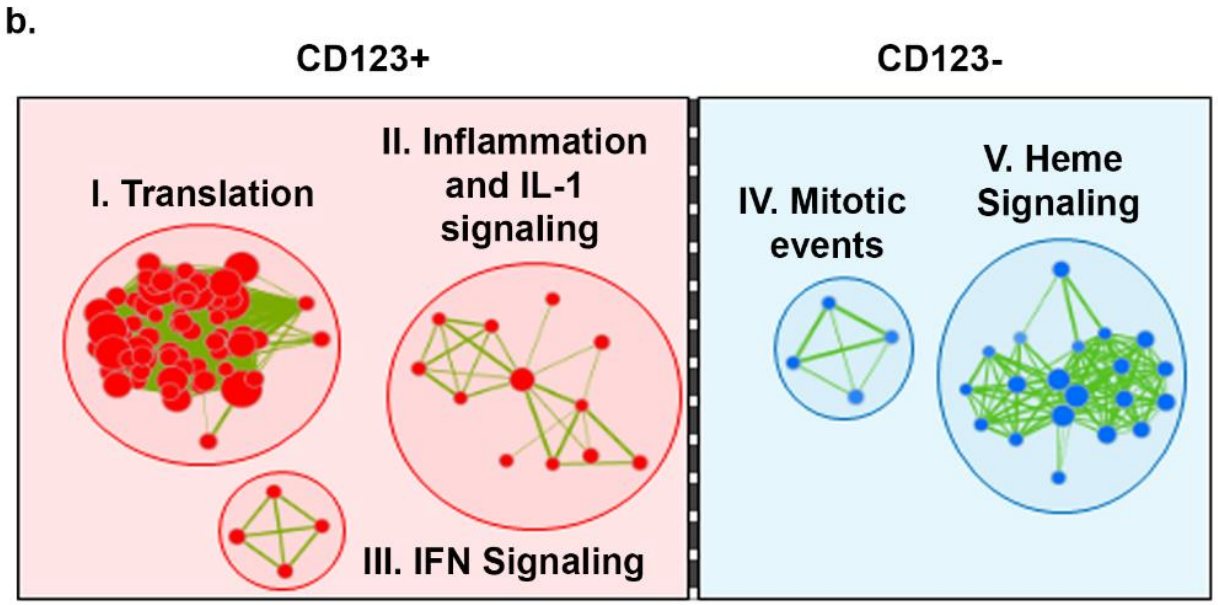
Stevens et al. Blood; Abstract 1604: 2021.

MDS stem cells can be marked by CD123

Immunophenotype



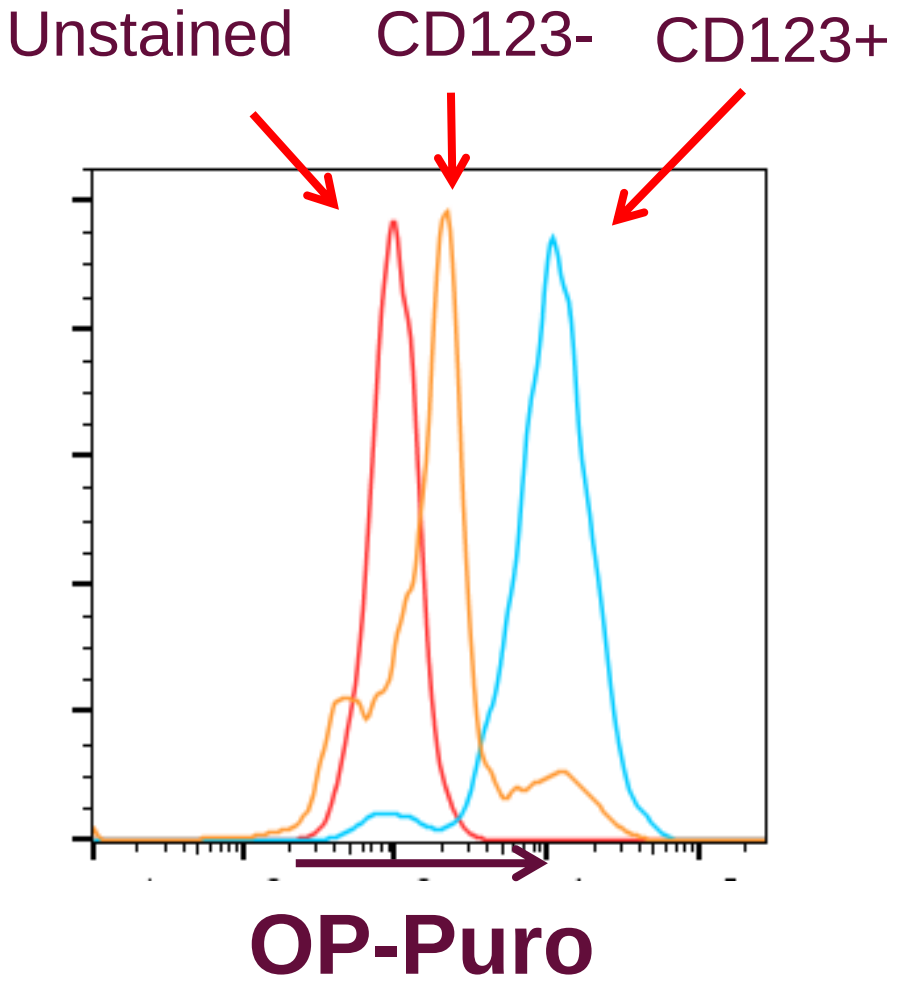
Transcriptional Differences

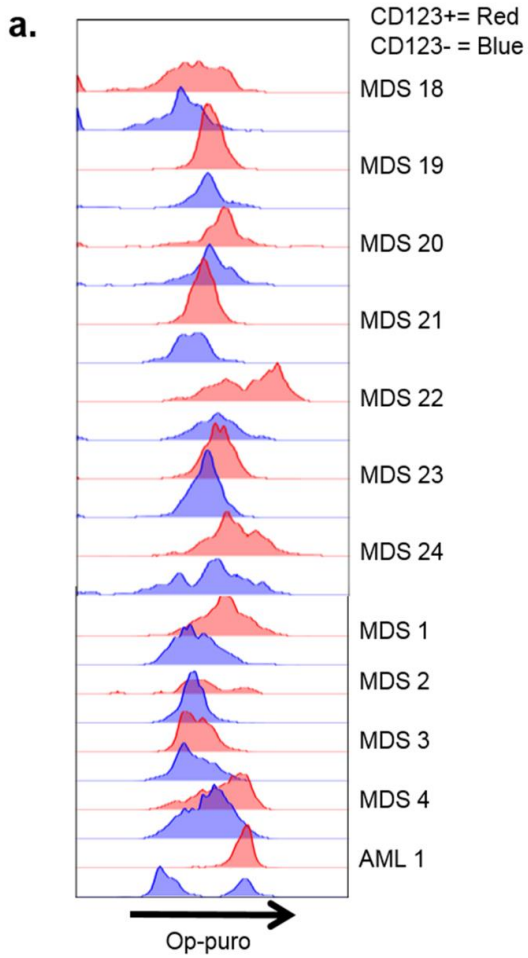


Stevens et al, 2018, Nature Communications.

Stevens et al. Blood; Abstract 1604: 2021.

MDS stem cells have increased protein translation

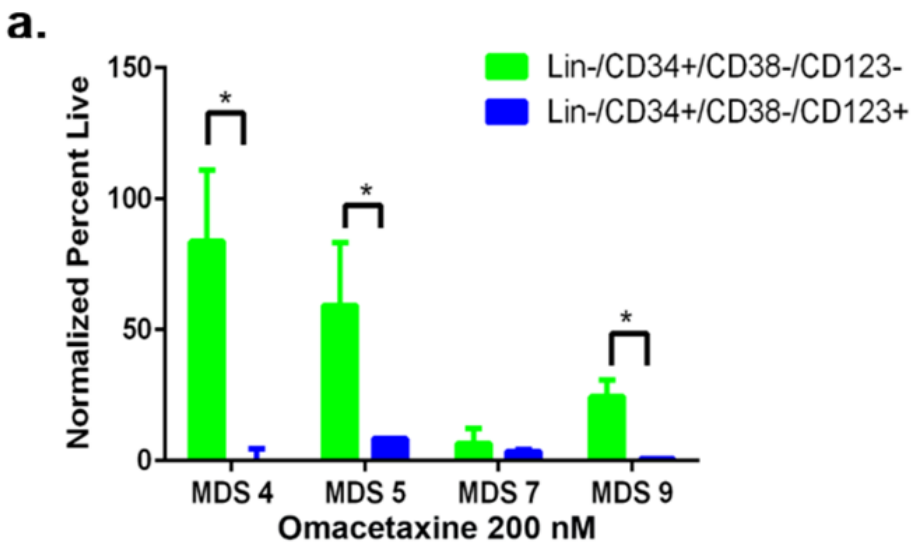


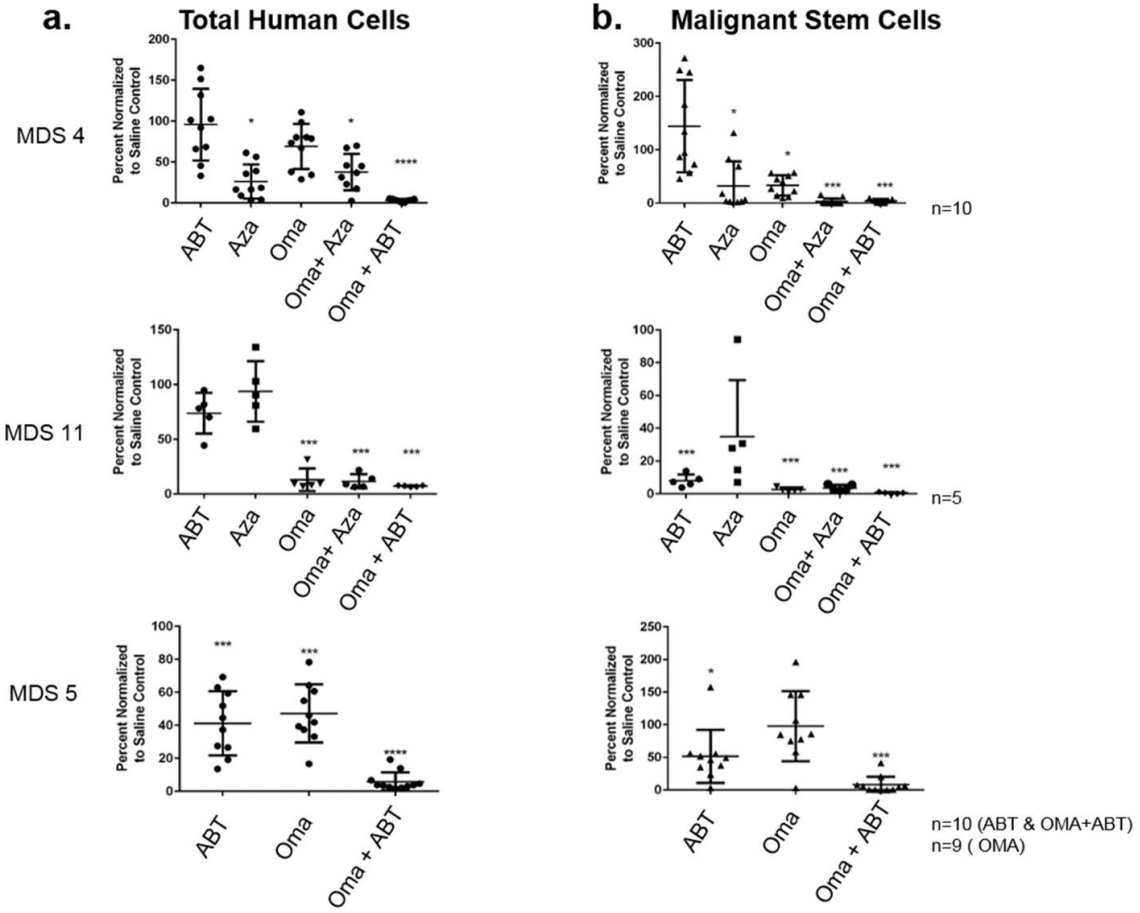


Stevens et al, 2018, Nature Communications.

Stevens et al. Blood; Abstract 1604: 2021.

MDS Stem cells can be targeted *in vitro* and *in vivo* through unique metabolic properties including translation





Stevens et al. Blood; Abstract 1604: 2021.

Stevens et al, 2018, Nature Communications.

Omacetaxine and Azacitidine in TN MDS Phase I Baseline Characteristics

Patient	Cohort	IPSS-R	Blast %	Complex/ Monosomal Karyotype	Molecular	Treatment Related
1236	1	7.5 (Very High)	12	N	STAG2, U2AF1	N
1385	1	5 (High)	7	N	RUNX1, U2AF1, BCOR, STAG2	N
1485	1	8.5 (Very High)	7	Y	None	N
1362	0	5.5 (High)	9.5	N	ASXL1, SRSF2, STAG2	N
1595	0	8 (Very High)	13	N	DNMT3A, SETBP1, SRSF2, TET2, CSF3R	N
1676	0	5.5 (High)	10	Y	RUNX1, PHF6	Y
1748	0	4 (Intermediate)	13.5	N	SF3B1	N
1843	0	7 (Very High)	11	Y	TP53	Y
1726	0	5 (High)	8	N	DDX41, JAK2, CBL	N

Stevens et al. Blood; Abstract 1604: 2021.

Omacetaxine and Azacitidine Phase I Preliminary Efficacy

Patient	Cohort	Best IWG Response	Hematologic Improvement	Number of Cycles	Bridged to Transplant	Alive
1236	1	Marrow CR	No	2	Yes	Y
1385	1	Marrow CR	• Erythroid • Platelets • Neutrophils	1	Yes	Y
1485	1	Marrow CR	• Neutrophils	1	No	N
1362	0	Marrow CR	• Erythroid • Neutrophils	3	Yes	Y
1595	0	Marrow CR	No	1	Yes	Y
1676	0	No Response	No	1	No	N
1748	0	Marrow CR	• Erythroid • Platelets • Neutrophils	3	Yes	Y
1843	0	Marrow CR	No	3	No	N
1726	0	Marrow CR	• Erythroid • Neutrophils	2	Yes	Y

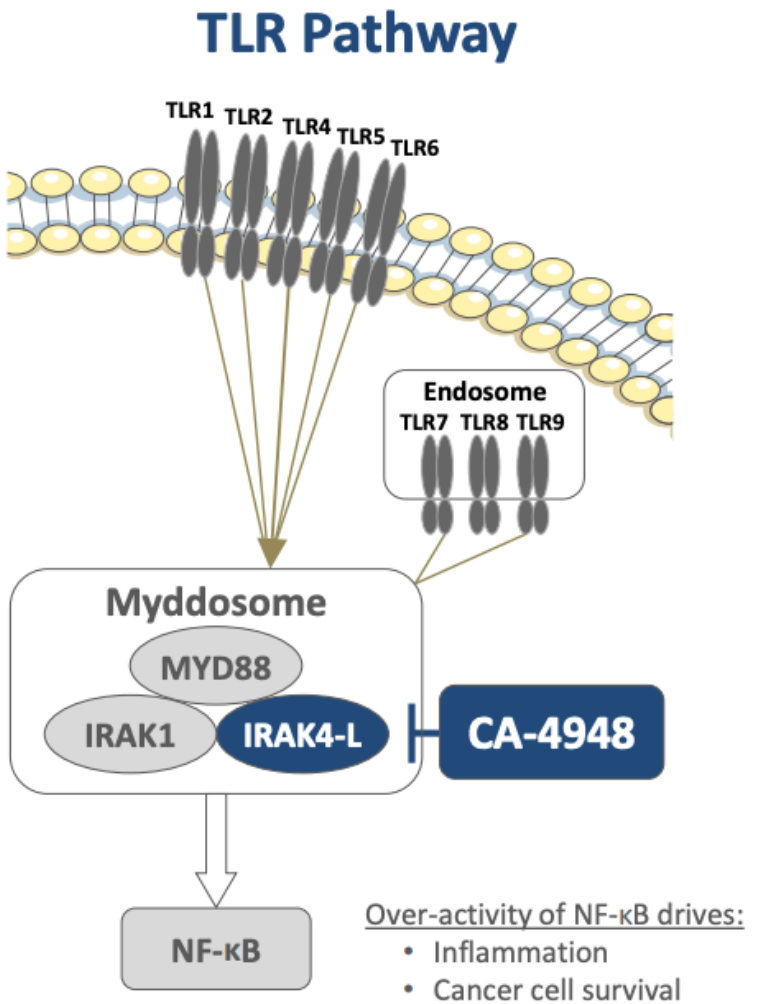
- 8 of 9 Marrow CR
- 6 of 8 Bridge to transplant
- 5 of 9 Hematologic improvement

Stevens et al. Blood; Abstract 1604: 2021.

Inflammation and the Niche

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

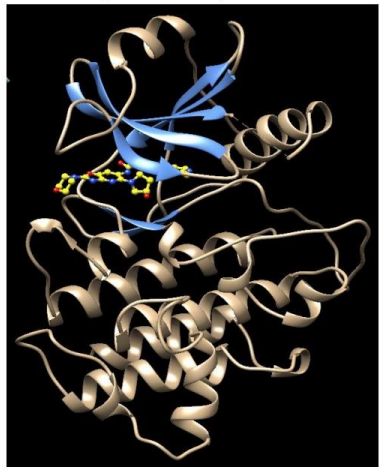
IRAK-4 Inhibition to Disrupt MDS/AML in the Niche



Over-activity of NF-κB drives:

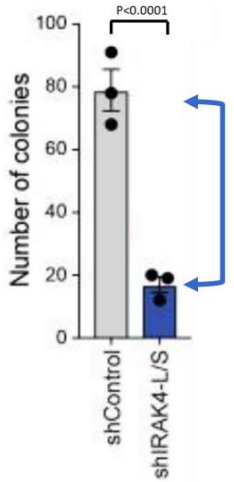
- Inflammation
- Cancer cell survival
- Malignant proliferation
- Suppression of apoptosis

IRAK4/CA-4948 Co-crystal Structure



ATP-competitive, type 1 reversible inhibitor

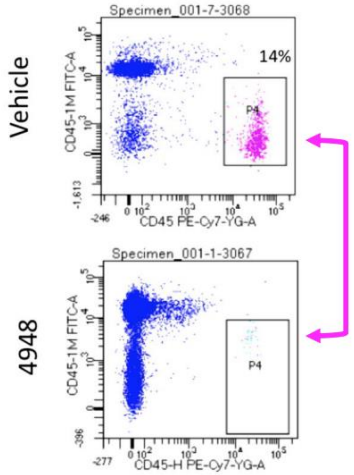
IRAK4-L is oncogenic



Blocking IRAK4-L reduces formation of leukemia colonies in preclinical studies[1]

IRAK4-L knockdown models demonstrate genetic link to oncogenic immune signaling in AML/MDS[1]

CA-4948 targets IRAK4-L



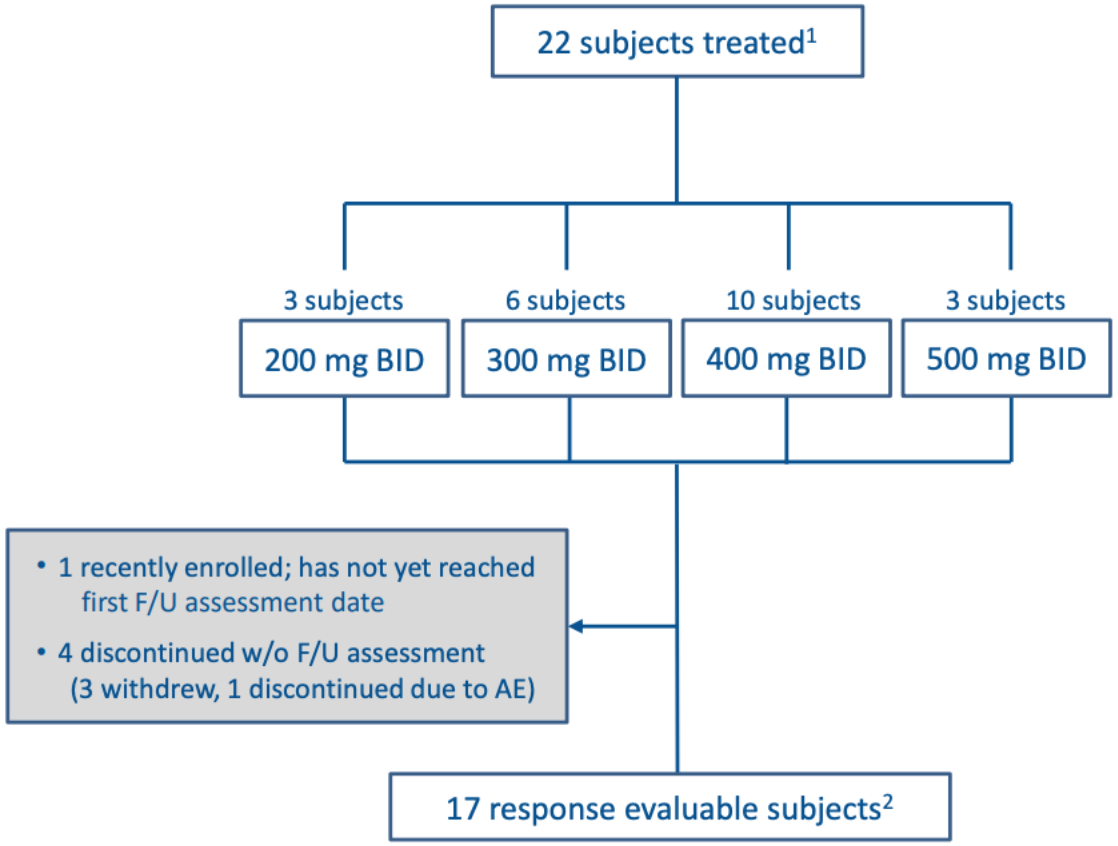
CA-4948 treatment reduces leukemic blasts in patient-derived xenografts[2]

In preclinical model, IRAK4-L inhibition with CA-4948 demonstrates anti-cancer activity consistent with knockdown models[2]

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

CA-4948

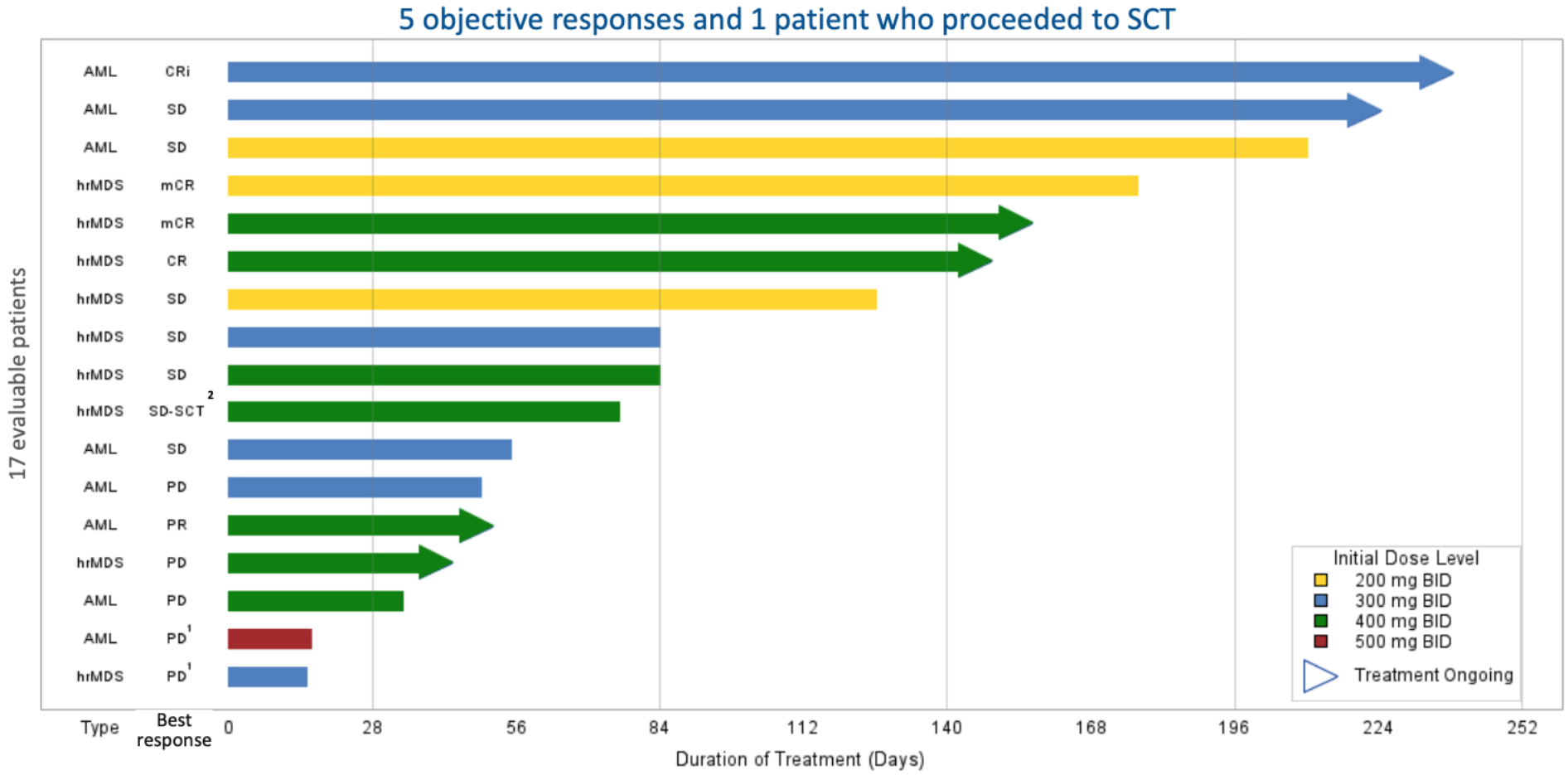
200 mg BID → 300 mg BID → 400 mg BID → 500 mg BID



Characteristics		Patients (n=22)
Female n (%) : Male n (%)		5 (23) : 17 (77)
Age (yrs): median (range)		74 (32-87)
Race, n (%)	White	18 (82)
	African American	1 (4)
	Not reported	3 (14)
ECOG: n 0/1/2		7/11/4
Diagnosis	AML, n (%)	11 (50)
	hrMDS, n (%)	11 (50)
Median platelets (10^3/mm^3) (range)		33 (7, 275)
Median ANC (10^3/mm^3) (range)		1.2 (0.1, 14.8)
Median lines of prior therapy (range)		2 (1-4)
Prior therapy, n (%)	Azacitidine	14 (64)
	Decitabine	7 (32)
	Cytarabine	3 (14)
	Venetoclax	10 (45)
Cytogenetic risk, n (%)[3]	AML (favorable/intermediate/ adverse)	1 (10) / 2 (20) / 7 (70)
	hrMDS (good/intermediate/poor/ very poor)	1 (9) / 4 (36) / 3 (27) / 3 (27)
Relavant mutations[4]	FLT3	1
	SF3B1	2
	U2AF1	2

Garcia-Manero et al. EHA. 2021.

Preliminary Efficacy of CA-4948 in MDS/AML



Best Response

hrMDS (n=9)

CR	1
mCR	2
SD	4
PD[1]	2

AML (n=8)

CRi	1
PR	1
SD	3
PD[1]	3

Garcia-Manero et al. EHA. 2021.
Garcia-Manero et al. ASH abstract

Summary of Key Advances in Myelodysplastic syndromes

1. In Prognostication → IPSS-M
2. Use of venetoclax and address venetoclax metabolic vulnerabilities
3. Therapeutic relationship between somatic changes and inflammation

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

Thank you

This activity is jointly provided by PIM Postgraduate Institute for Medicine Bio Ascend™

Thank you

Acknowledgments

The patients

The MDS community

NIH National Institutes of Health

NIH National Cancer Institute

National Heart Lung and Blood Institute

mds foundation the myelodysplastic syndromes foundation, inc.

Beverly and George Rawlings Directorship in Hematology Research

MDS/MPN International Working Group

The Biff Ruttenberg Foundation

Serodino Family Compact

Leukemia & Lymphoma Society fighting blood cancers

someday is today

EvansMDS A funding initiative of The Edward P. Evans Foundation

Lovell Family Fellowship

Postgraduate Institute for Medicine

Bio Ascend