

Anemia in MDS: Biology and Clinical Implications

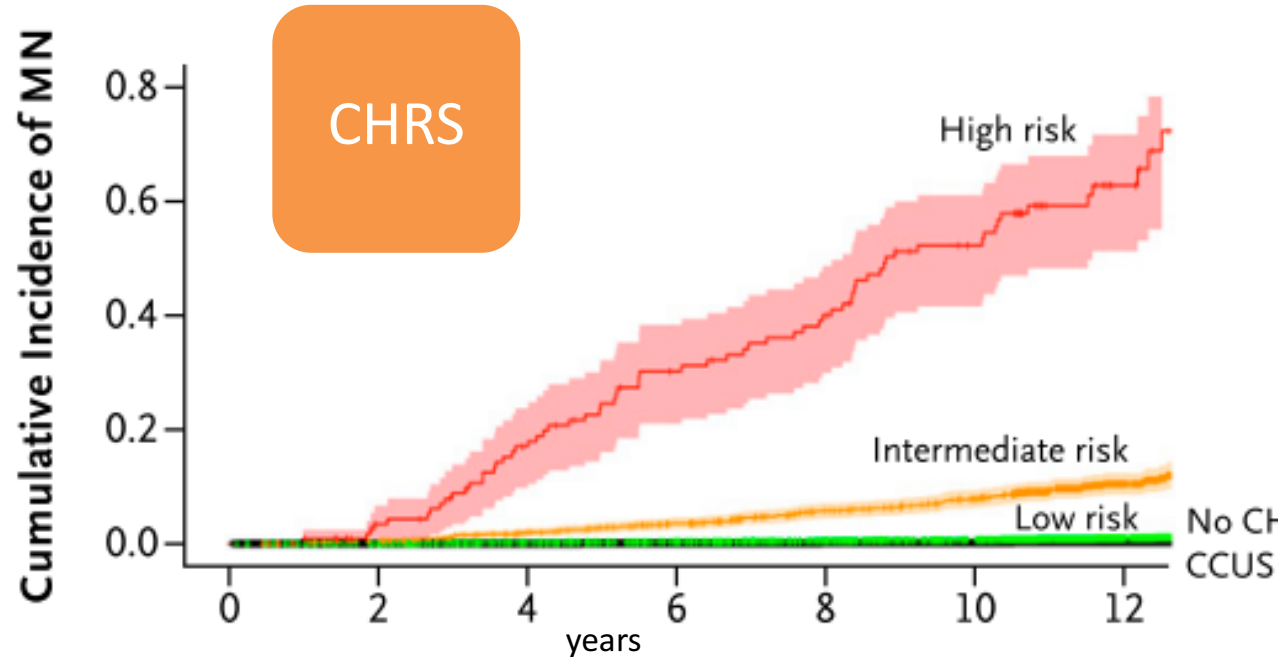
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Disclosures

I disclose the following financial relationship(s):

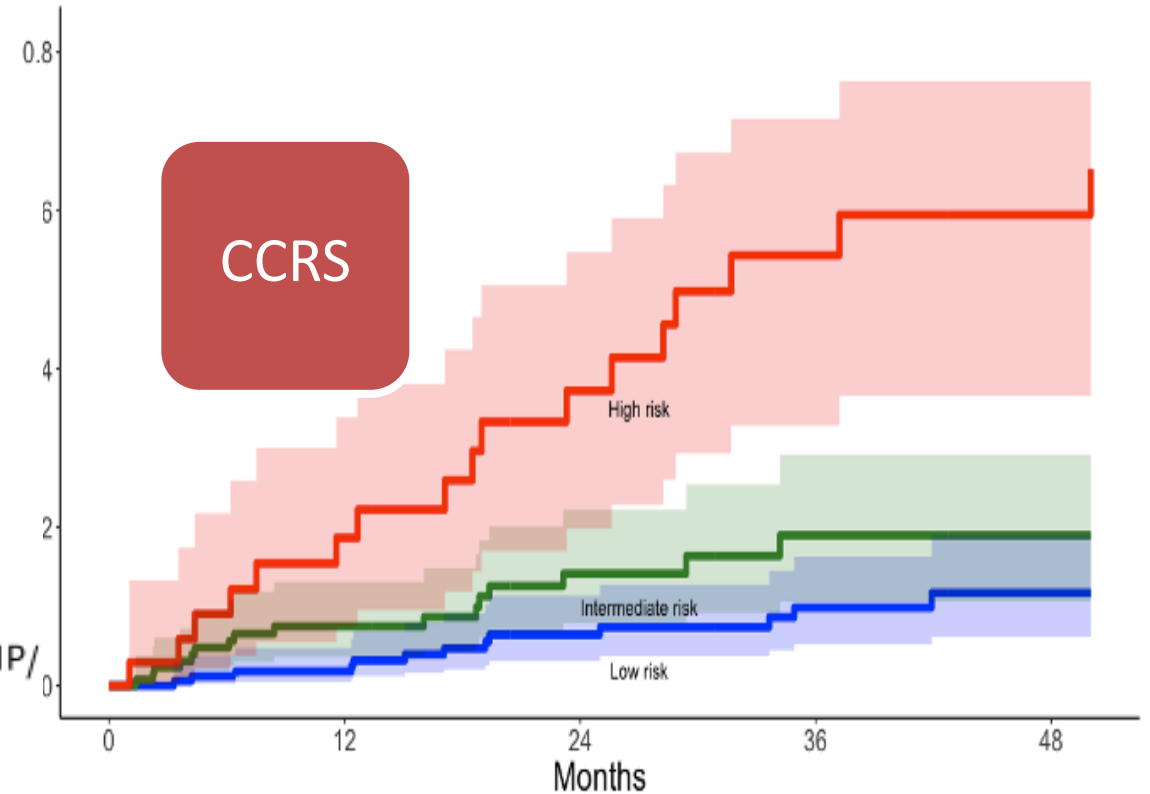
- Agios, Advisory Board or Panel,
- Servier, Advisory Board or panel
- Jazz, Grants/Research Support
- Incyte, Speaker's Bureau
- Novartis Advisory Board or Panel,
- Abbvie, Advisory Board of Panel,
- Intellia – Advisory Board or Panel
- BMS – Advisory Board or Panel
- Janssen – Steering Committee/Advisory Board
- Curis – Advisory Board or Panel
- Shattuck Labs – Advisory Board or Panel
- Aprea – Research Support
- Gilead – Advisory Board or Panel, Steering Committee
- Syros – Advisory Board or Panel
- Syndax – Consulting
- Akesobio – Consulting

CCUS Risk Stratification Tools



Clonal Hematopoiesis Risk Score

- Population based study
- Variables: age, MCV, RDW, clonality, high-risk mutations, mutation numbers, and clonal burden
- Predict risk of myeloid neoplasm, not OS

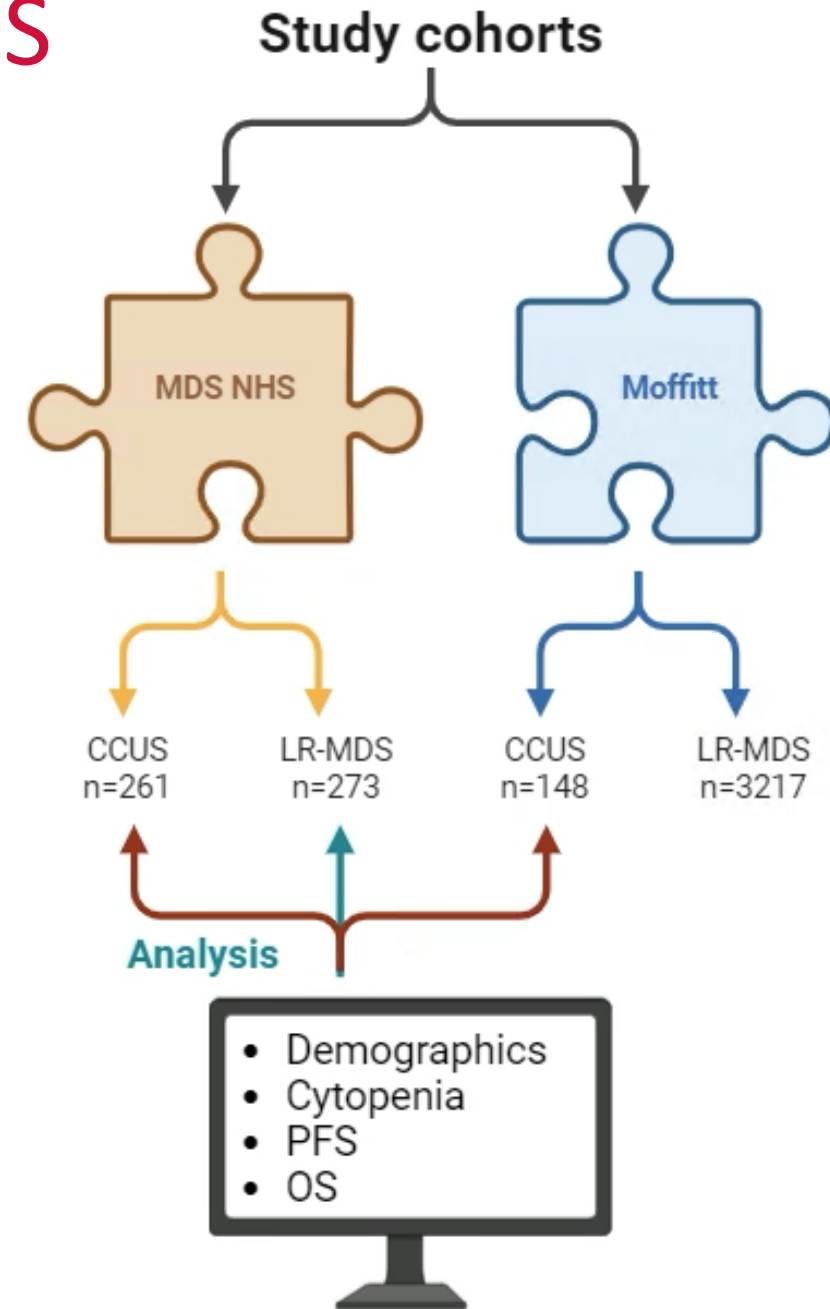


Clonal Cytopenia Risk Score

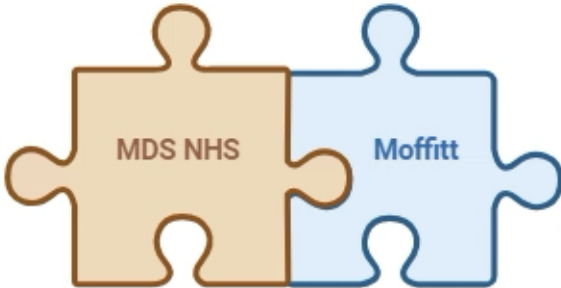
- Real world data
- Variables: splicing mutations, mutation numbers, and thrombocytopenia
- Predict risk of myeloid neoplasm, not OS

Is High Risk CCUS Different than LRMDS

1. **The primary analysis** combined patients from MDS NHS cohort and Moffitt cohort pathologically confirmed CCUS (n=409) vs. LR-MDS (n=273)
2. CCUS and LR-MDS were compared in terms of
 - **Demographics**
 - **Cytopenia**
 - **Progression-free survival (PFS):** time to disease progression or death
 - **Overall survival (OS):** time to death



Cytopenia

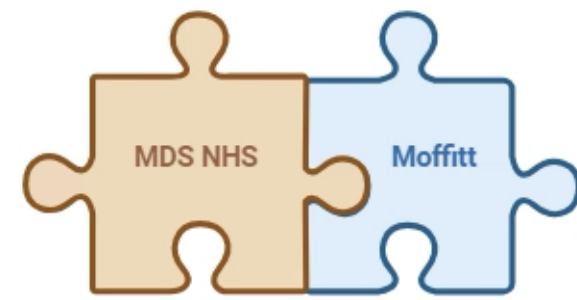


LR-MDS vs CCUS, by CHRS and CCRS risk category

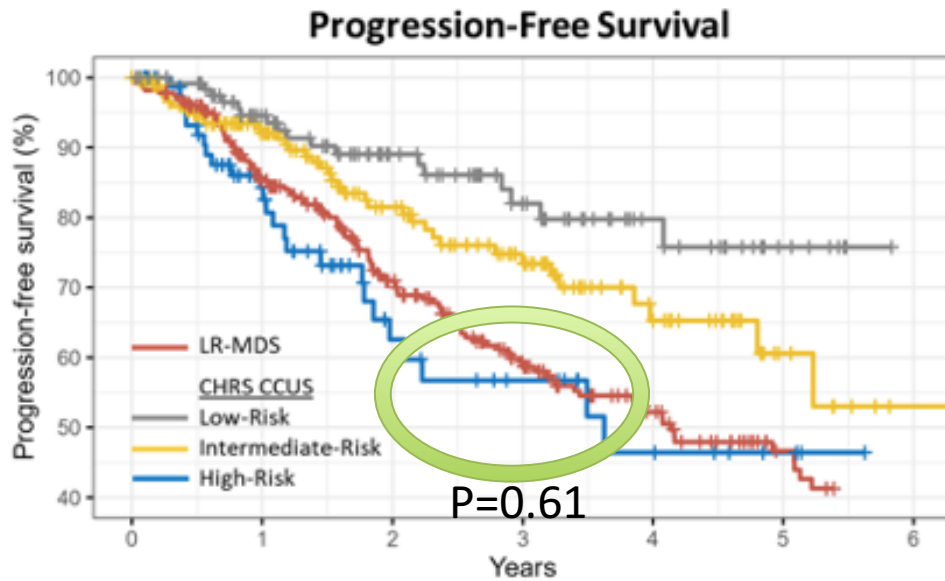
- High-Risk CCUS were more similar to LR-MDS in terms of median (IQR) hemoglobin, platelets and absolute neutrophil count (ANC)

		CCUS, CHRS Risk Category			CCUS, CCRS Risk Category		
	LR-MDS	Low	Inter-mediate	High	Low	Inter-mediate	High
Hemoglobin g/dL	10.5 (9.0-11.6)	12.3 (10.9-13.4)	11.6 (9.6-13.2)	10.4 (9.5-12.5)	11.8 (9.8-13.1)	11.5 (10.0-13.0)	11.9* (9.9-13.3)
Platelets x 10 ⁹	138 (96-232)	145 (105-207)	132 (97-184)	138 (89-203)	167 (131-231)	116 (67-159)	99* (68-154)
ANC x 10 ⁹	2.0 (1.2-3.0)	2.6 (1.8-4.1)	2.6 (1.6-3.9)	2.2 (1.4-3.8)	3.1 (1.7-4.2)	2.4 (1.7-3.8)	2.0 (1.1-3.6)

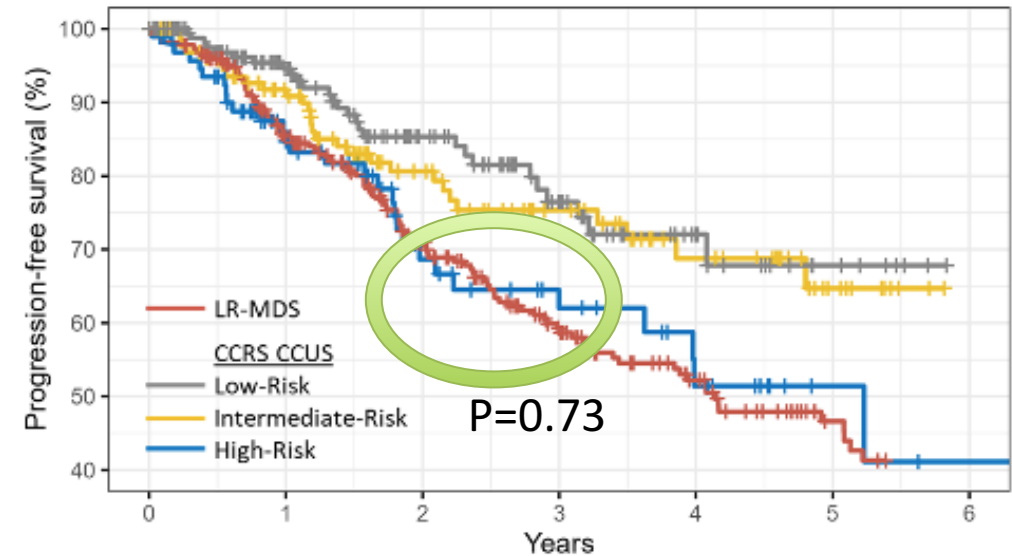
Progression free survival



- PFS: LR-MDS vs CCUS by CHRS and CCRS risk category

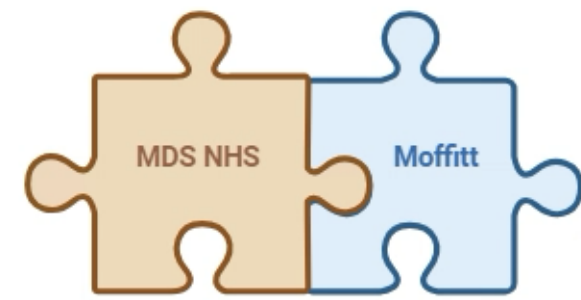


CCUS Risk Category	CHRS CCUS vs LR-MDS	
	HR	P-value
Low-Risk	0.36 (0.21-0.61)	< 0.001
Intermediate-Risk	0.62 (0.44-0.89)	0.01
High-Risk	1.12 (0.72-1.73)	0.611

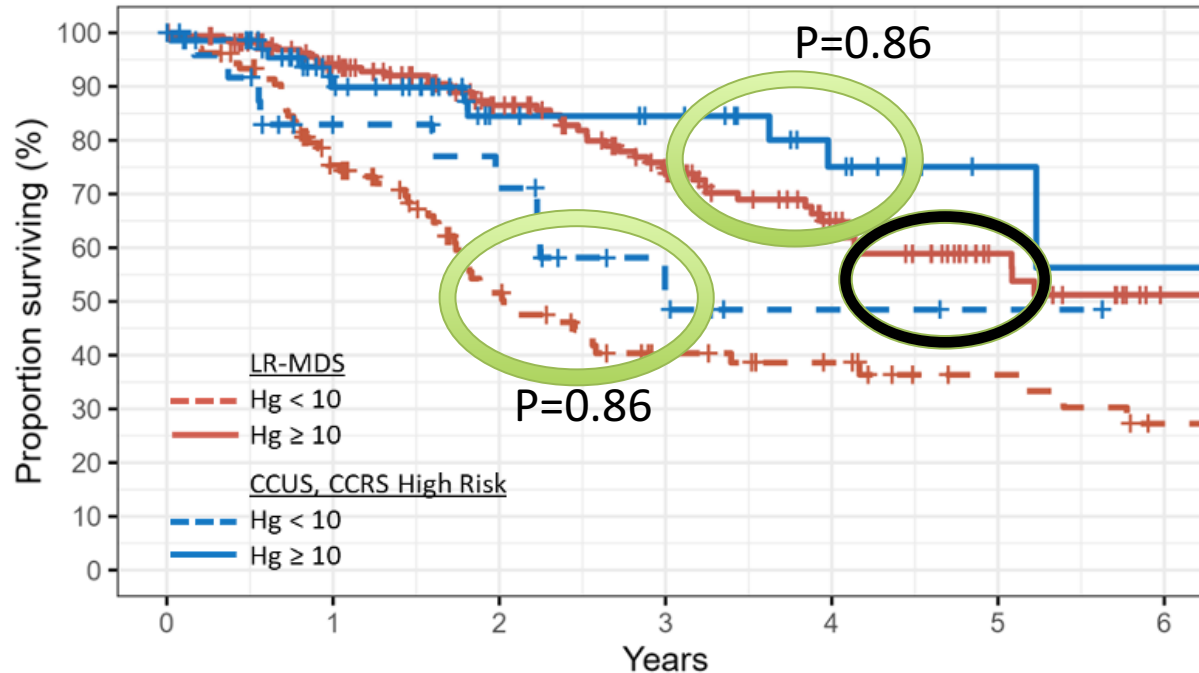


CCUS Risk Category	CCRS CCUS vs LR-MDS	
	HR	P-value
Low-Risk	0.49 (0.32-0.75)	< 0.001
Intermediate-Risk	0.58 (0.39-0.88)	0.009
High-Risk	0.93 (0.62-1.40)	0.726

Stratified OS by hemoglobin level



- Adjustment for hemoglobin further reduce the differences between LR-MDS and High-Risk CCUS



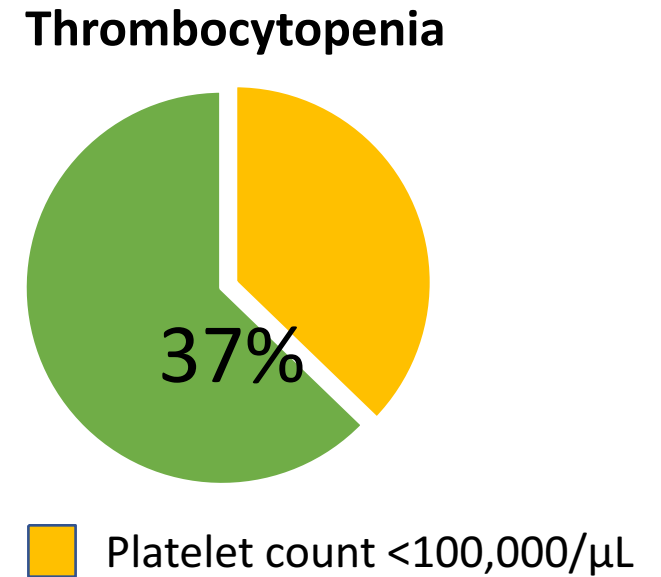
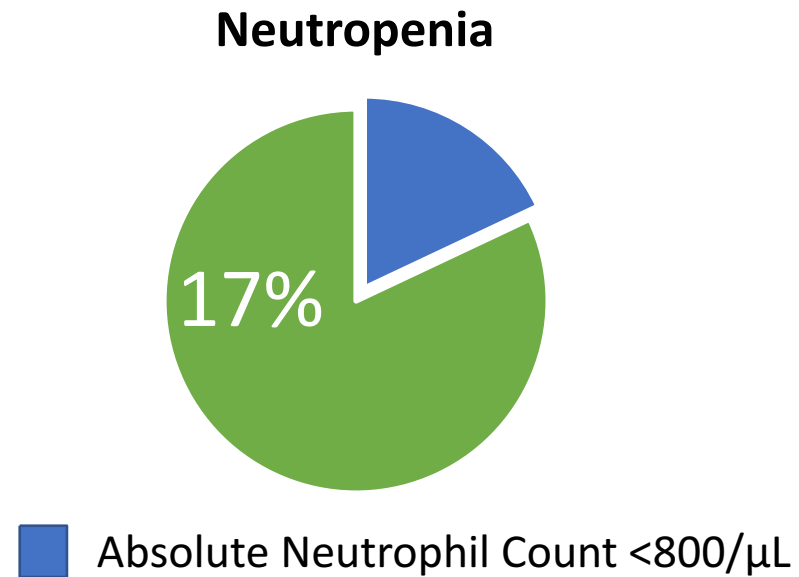
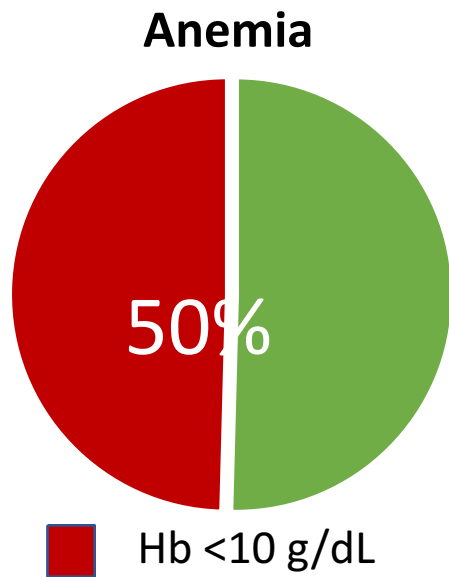
Characteristic	HR	P-value
CCUS Risk category		
Low vs LR-MDS	0.47 (0.28-0.77)	0.003
Intermediate vs LR-MDS	0.60 (0.39-0.93)	0.024
High vs LR-MDS	0.74 (0.46-1.21)	0.237

Anemia is the hallmark of MDS

- Lower-risk MDS is characterized foremost by anemia¹
- 50% of MDS patients will need RBC transfusions during the course of their disease²

Frequency of cytopenias in patients with Lower-risk MDS:^{3,4}

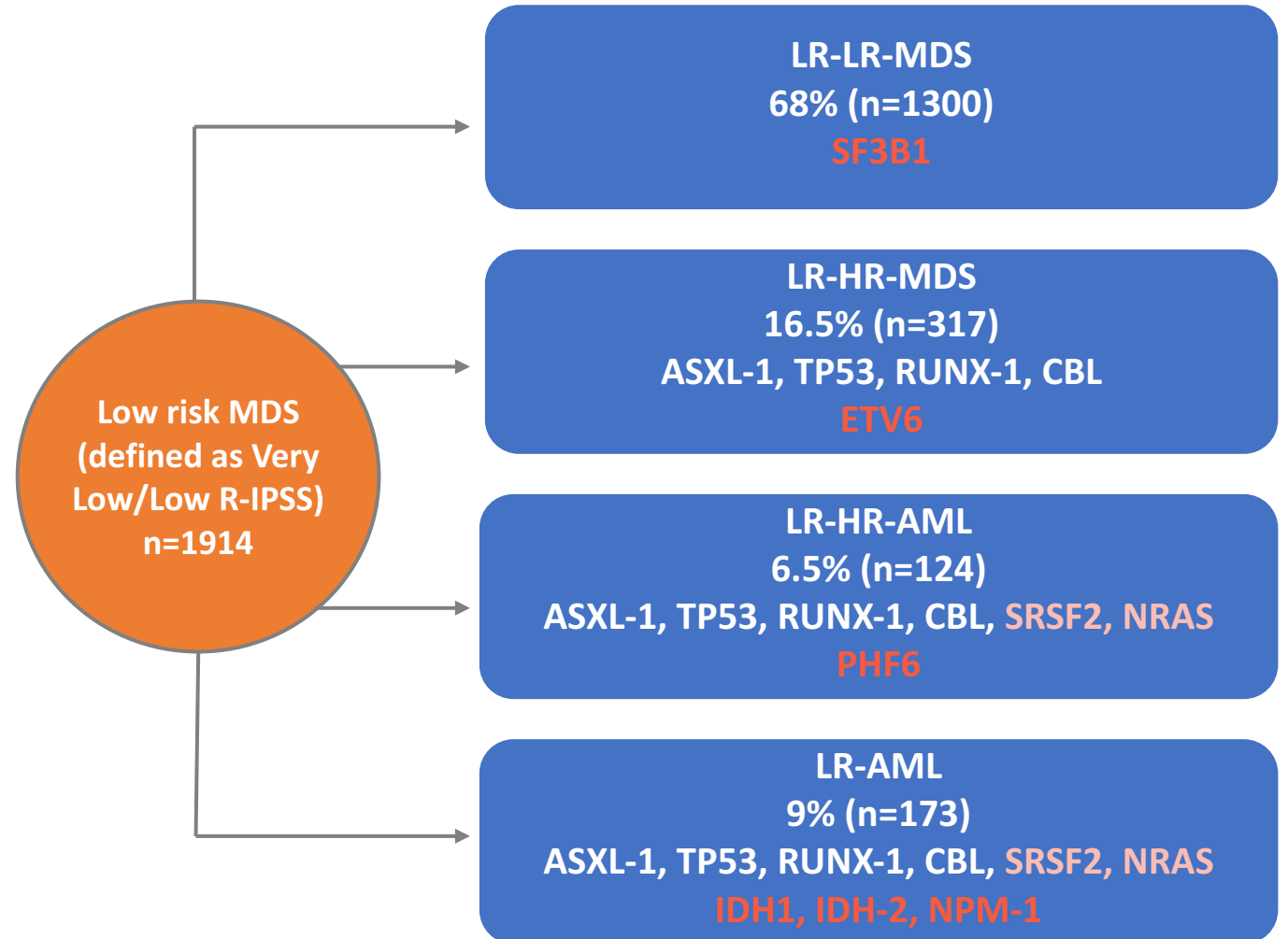
- Data from FISiM Italian registry



1. Fenaux P, et al. *Br J Haematol.* 2019;189(6):1016-1027; 2. Germing U, et al. *Hemasphere.* 2019;3(6):e314;
 3. Lanino L, et al. *Am J Hematol.* 2023; 10.1002/ajh.26960; 4. Santini V. *Hemato.* 2022;3(1):153-162

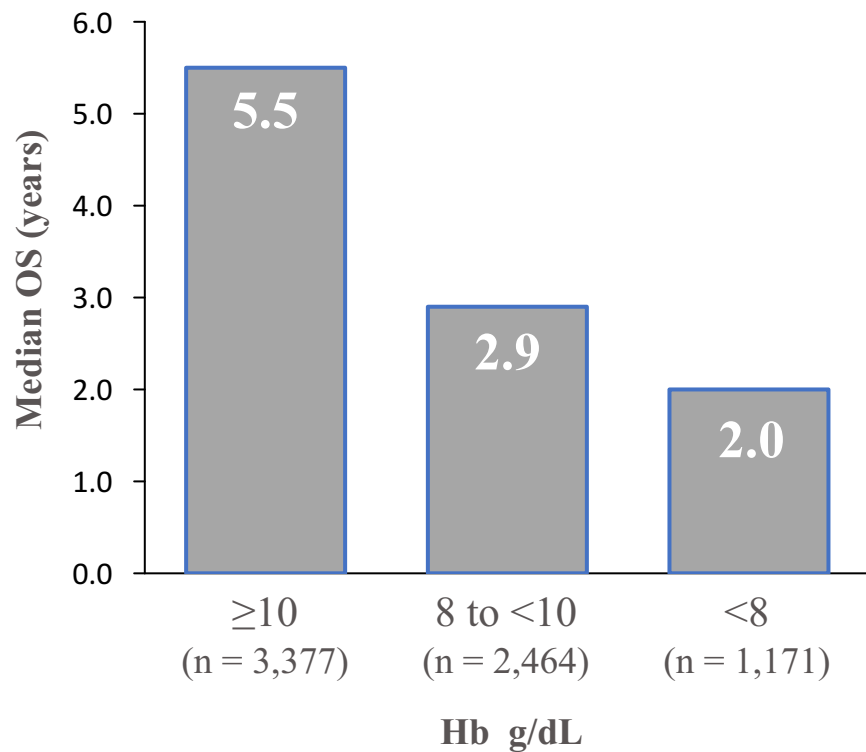
Majority of LR-MDS patients don't progress

- Single-center assessment of 1,914 patients with low-risk (LR) MDS
- Patients divided into 4 cohorts based on disease progression
 - Patients who remained low risk (LR-LR)
 - Patients who progressed from low risk to high risk (LR-HR) without AML transformation
 - Patients who progressed from low risk to high risk and then to AML transformation (LR-HR-AML)
 - Patients who progressed from low-risk MDS directly to AML (LR-AML)

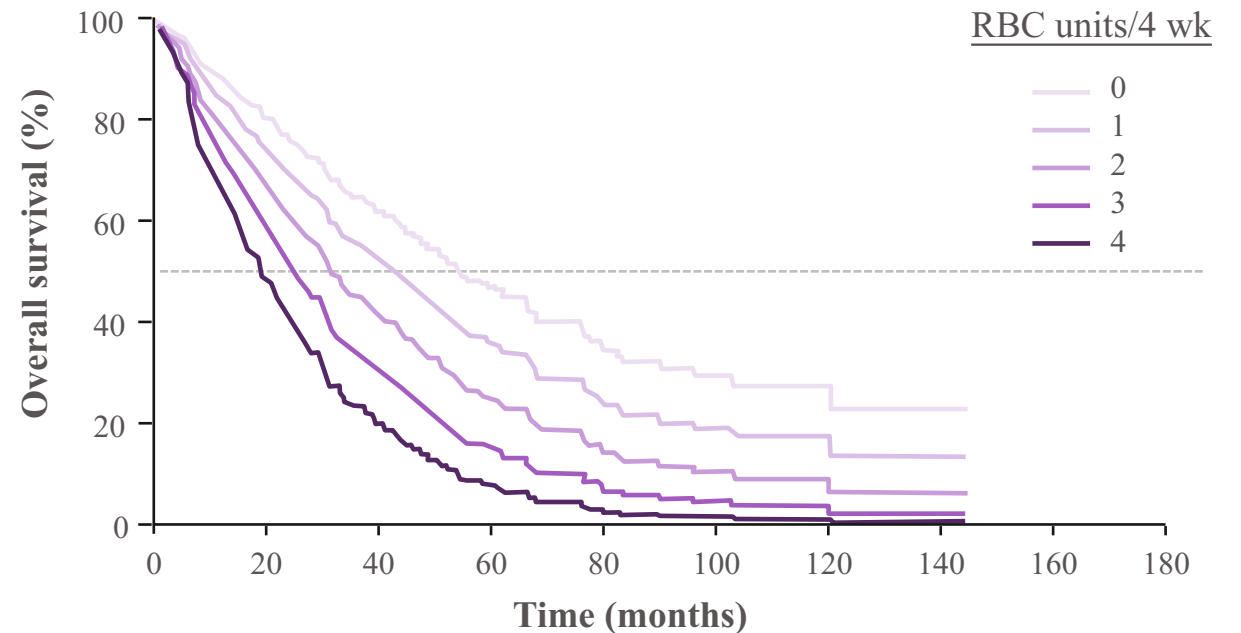


The severity of anemia in MDS, which can be identified by Hb level and/or RBCT requirement, impacts patient survival

mOS in patients with MDS by Hb level (N = 7,012)^{1,a}



OS in patients with MDS by RBCT requirement (N = 426)^{2,b}



- The effect of transfusion dependence is more noticeable in patients with low-risk MDS²

^a Combined international databases of untreated MDS. 77% of the cohort had lower-risk MDS; ^b Italian cohort between 1992-2004; risk category of patients unknown
Hb: haemoglobin; MDS: myelodysplastic syndrome; mOS: median overall survival; OS: overall survival; RBC: red blood cell; RBCT: red blood cell transfusions; wk: weeks
1. Greenberg PL, et al. *Blood*. 2012;120:2454-2465; 2. Malevati L, et al. *Haematologica*. 2006;91:1588-1590.

Anemia and Transfusion Dependency Impact QoL

Predictive factors of QoL E-scores in patients with MDS

QoL index*	Factor	Univariate analysis		Multivariate analysis†	
		Effect (95% CI)‡	p value	Effect (95% CI)‡	p value
QoL-E, Physical	Age (1 year)	-0.73 (-1.00, -0.46)	<0.0001	-0.48 (-0.74, -0.22)	0.0003
	Charlson's index (2-5 vs 0-1)§	-16.3 (-23.0, -9.5)	<0.0001	-14.2 (-20.4, -8.0)	<0.0001
	Hb (1 g/dL)¶	+2.48 (+1.50, +3.45)	<0.0001	+1.69 (+0.71, +2.67)	0.0008
	Transfusions (yes vs no)¶	-9.1 (-13.6, -4.7)	0.0002	-7.2 (-11.7, -2.6)	0.0029
	Time from baseline (1 month)	-0.22 (-0.45, +0.01)	0.061	-0.29 (-0.52, -0.06)	0.014
QoL-E, Functional	Age (1 year)	-0.34 (-0.66, -0.01)	0.042	-0.01 (-0.33, +0.30)	0.93
	Charlson's index (2-5 vs 0-1)§	-14.8 (-22.6, -7.1)	0.0002	-15.5 (-22.9, -8.1)	<0.0001
	Hb (1 g/dL)¶	+3.79 (+2.49, +5.09)	<0.0001	+2.99 (+1.61, +4.36)	<0.0001
	Transfusions (yes vs no)¶	-13.0 (-19.3, -6.6)	0.0002	-8.3 (-15.1, -1.6)	0.017
	Time from baseline (1 month)	-0.10 (-0.47, +0.27)	0.60	-0.21 (-0.59, +0.16)	0.26

An observational, non-interventional, prospective, multicenter study in which QoL was evaluated in 148 patients with newly diagnosed low- and intermediate-risk IPSS MDS

*scaled from 0 (worst possible value) to 100 (best possible value); †variables with p<0.05 are included in the basic model, for other factors the reported p-value tests the addition to this model; ‡mean difference of predicted dependent variable between levels (first - second) of binomial factors or for each 1-unit increase of quantitative factors; §at baseline; ¶ at each visit; ¶any transfusion within 3 months before the day of visit

Hematological Response to Frontline Treatment in LRMDs Is Associated with Better Overall Survival

- 603 LRMDs pts with no disease progression who received ESA, 43% were RBC-TD.

HI was observed in 42%

Response was higher among non-RBC-TD (52% vs 31%, $P < .001$).

Among responders to ESA ($n = 255$), the mOS was better among non-RBC-TD patients at baseline ($n = 175$) compared to RBC-TD pts ($n = 80$) (109 months (95% CI 98-120) compared to 85 months (95%CI 60-111), $P = .003$ respectively)

There was no difference in mOS among nonresponders ($n = 340$) whether they were RBC-TD ($n = 178$) or not ($n = 162$) (62 mo (95%CI 50-74) vs 63 mo (49-77), $P = .8$ respectively).

- 331 pts (55%) received SL therapy which included HMA 43% ($n= 142$), lenalidomide 39% ($n=130$), luspatercept 7% ($n=24$), ATG 2% ($n=8$), investigational agent 4% ($n=14$), and other 4% ($n=13$).

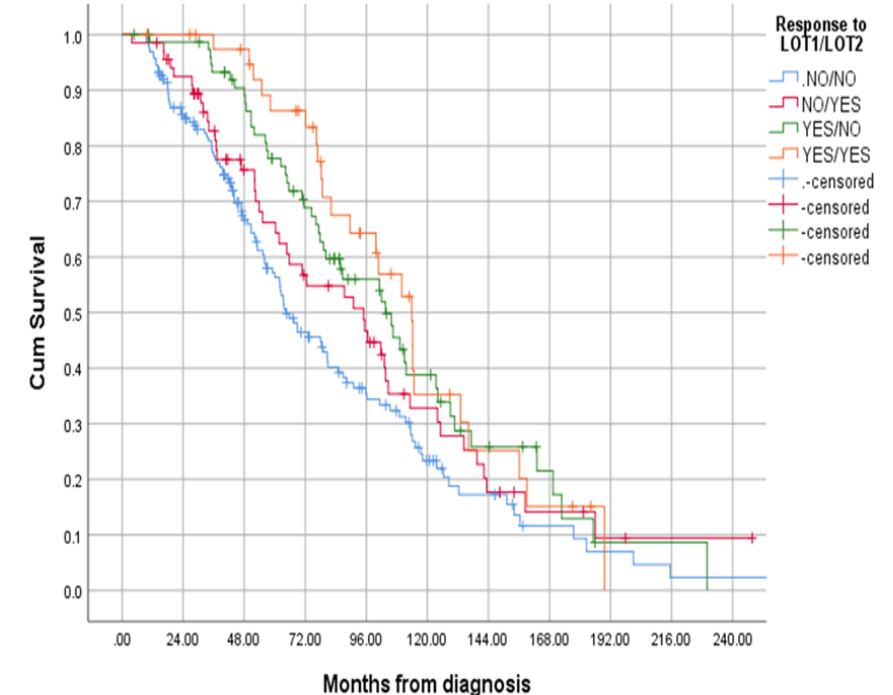
The HI rate was 27% (91/331).

170 pts (28%) received 3rd line of therapy with 7% HI

88 pts (15%) received 4th line of therapy with 3% HI

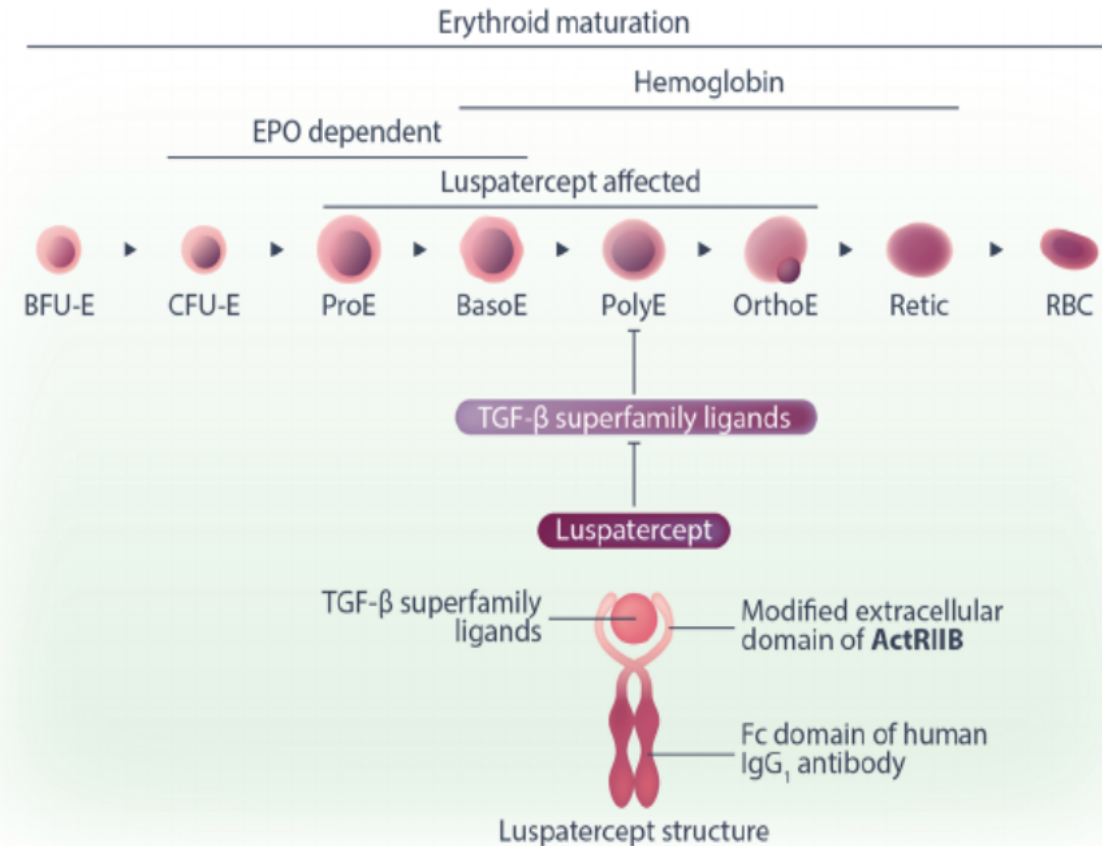
39 pts (7%) had 5th line of therapy with 2% HI.

Table-2	Baseline characteristics of the groups based on Response to FL and SL				
	NO/NO (n=163)	NO/YES (n=60)	YES/NO (n=77)	YES/YES (n=31)	P Value
Age (median)	72	73	69.6	68.2	.15
Sex (male)	111 (68%)	36 (60%)	50 (65%)	22 (71%)	.65
Race (white)	151 (93%)	58 (97%)	72 (95%)	31 (100%)	.27
SF3B1 MT	41/86	16/26	23/40	16/18	.051
IPSS-R					.03
Very low	39 (24%)	6 (10%)	19 (25%)	11 (36%)	
low	127 (76%)	54 (90%)	58 (75%)	20 (64%)	
RBC-TD	101 (62%)	38 (63%)	36 (47%)	16 (52%)	.1

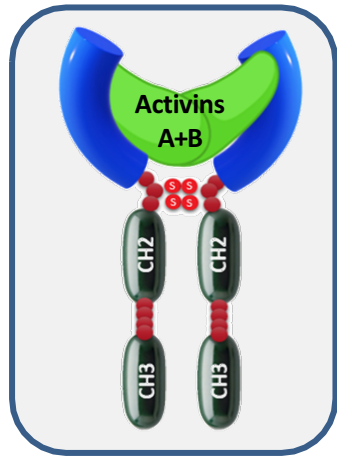


Luspatercept in MDS

- Luspatercept is a recombinant fusion protein consisting of a modified extracellular domain of the human activin receptor type IIB (ActRIIB) fused with the Fc domain of human immunoglobulin G1
- Traps with high affinity the transforming growth factor- β (TGF- β) superfamily members to inhibit ActRIIB-Smad2/3-dependent signaling.
- Activation of the Smad pathway interferes with late-stage erythroid maturation.
- By inhibiting the GDF11-mediated Smad2/3 signaling, both in steady-state and stress conditions, regardless of EPO levels (other ligands are clearly important).
- Distinct from ESAs which work on early hematopoiesis (thus supporting combination with ESA)
- It remains to be established what TGF- β ligand is the specific target of luspatercept and why patients with RS or SF3B1 mutation show higher response rates.







KER-050 (elritercept) is Designed to Target Bone Marrow Disorders of Ineffective Hematopoiesis Including MDS




KER-050 (elritercept)

- Designed to inhibit select TGF-beta ligands, including Activin A, which has been associated with ineffective hematopoiesis, disease pathogenesis and progression^{1,2}

- Preclinical data showed that **KER-050 (elritercept)** acts on early and late stages of hematopoiesis, supporting a differentiated MOA³

Domain	Effect
 Erythropoiesis	ALL stages of differentiation and maturation
 Thrombopoiesis	ALL stages of differentiation and maturation
 Bone	Increased bone formation
 Iron Metabolism	Improved iron utilization

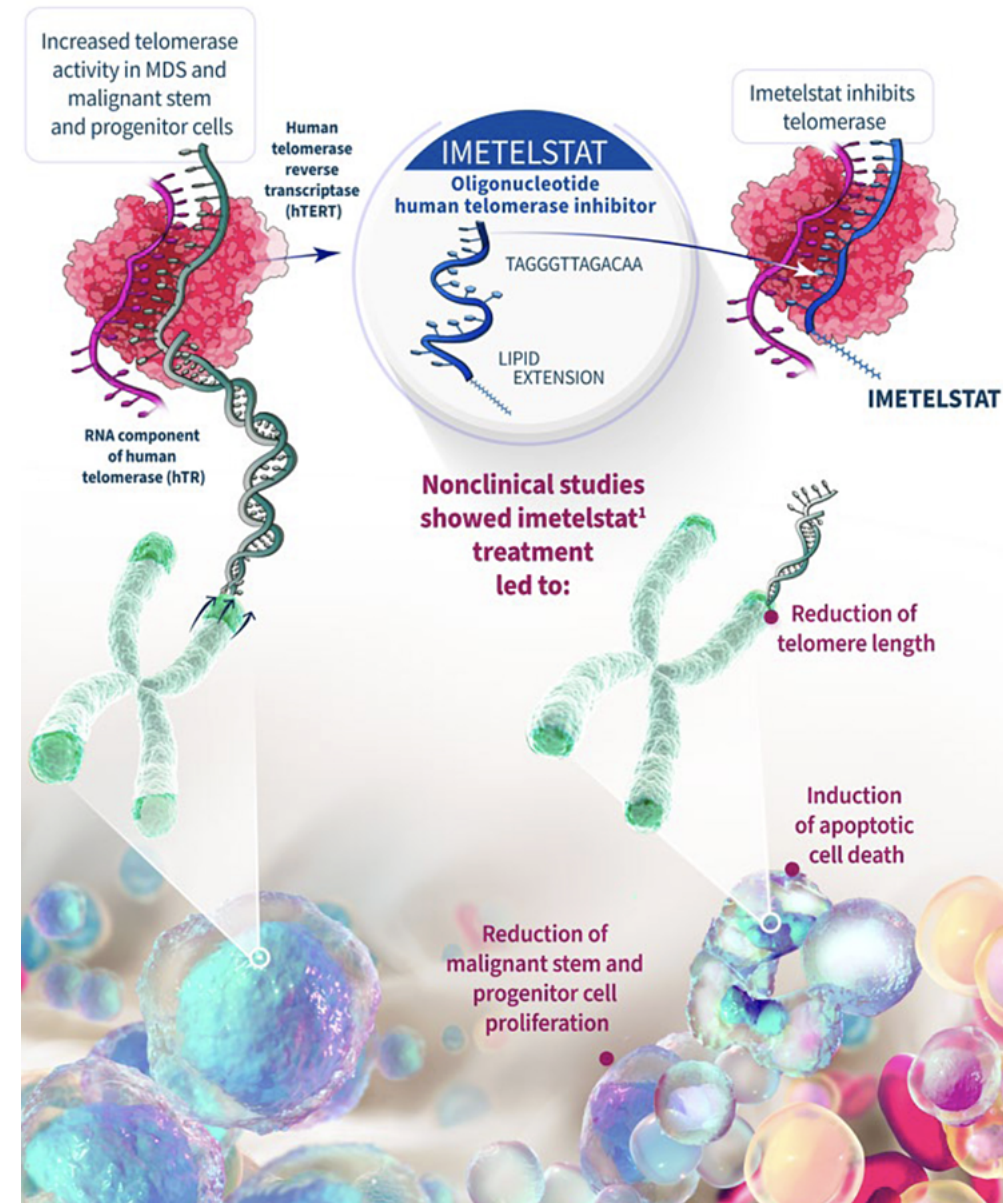
Feature 	Luspatercept (Reblozyl)	Elritercept (KER-050)
Receptor Type	Modified ActRIIB-Fc fusion protein.	Modified ActRIIA-Fc fusion protein.
Target Ligands	Primarily GDF11, GDF8, and activin B.	Activin A, activin B, GDF8, and GDF11.
Erythroid Stage	Specifically targets late-stage maturation.	Targets both early and late stages of progenitor differentiation.
Lineage Impact	Primarily erythroid (red blood cells).	Multilineage ; also increases platelets and potentially neutrophils.

P3 RENEW Study ongoing with Elritercept (similar to MEDALIST Design although RS+/-)

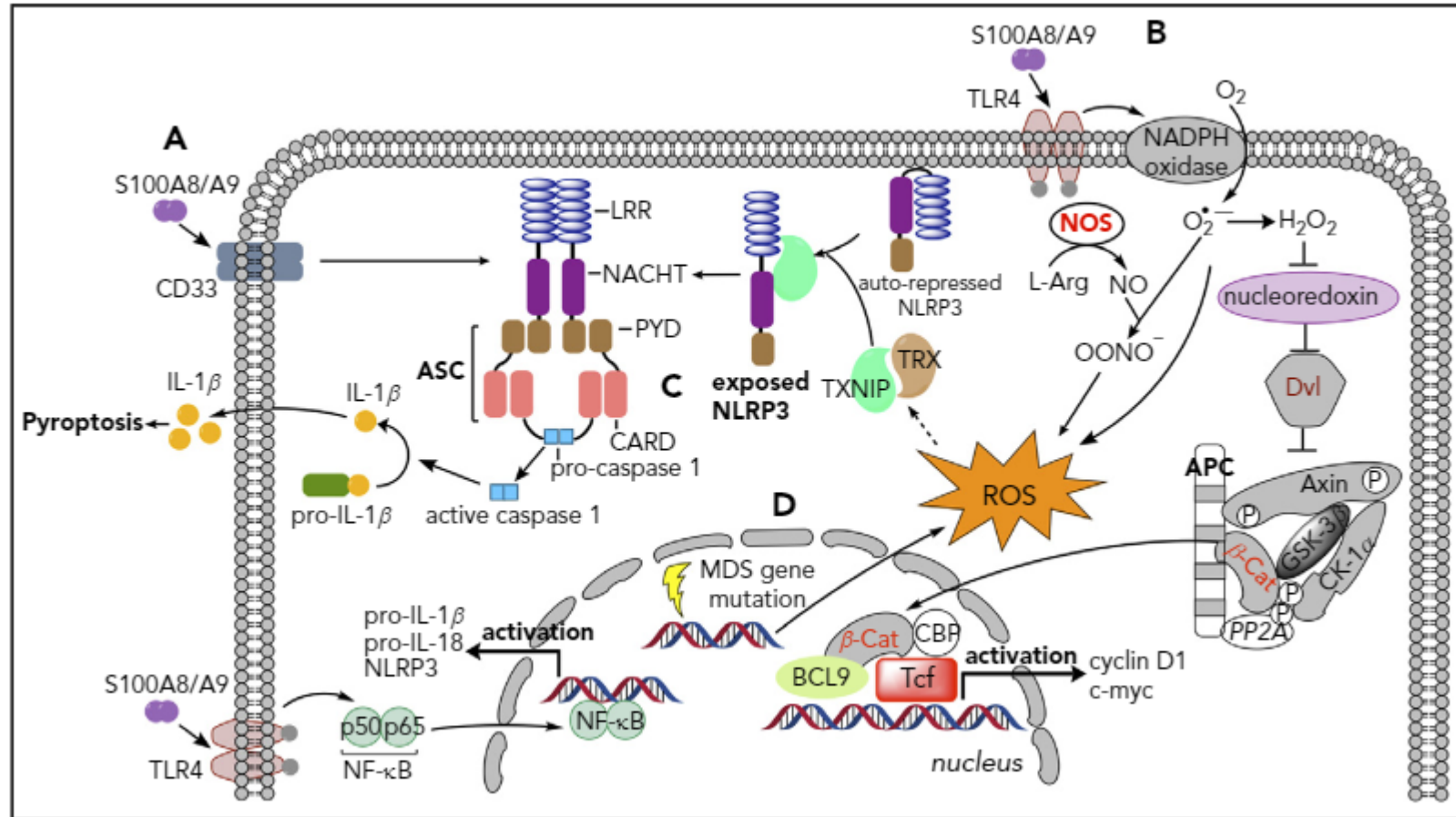
¹Verma A, et al. *J Clin Inv* 2020; ²Portale F, et al., *Haematologica*. 2019; Giagounidis A, et al. *Blood* 2024;144(Suppl. 1):1825 [abstract and poster]

Telomerase Inhibition and MDS

- Imetelstat is a first-in-class, 13-mer oligonucleotide that binds with high affinity to the template region of the RNA component of human telomerase and acts as a competitive inhibitor of human telomerase enzymatic activity.
- Imetelstat has demonstrated preferential activity against cancer cells and malignant hematopoietic stem cells/progenitor cells (HSCs/HPCs) and leukemia stem cells (LSCs) while having minimal effect on normal HSCs/HPCs.
- Unclear Biomarkers of response to date.



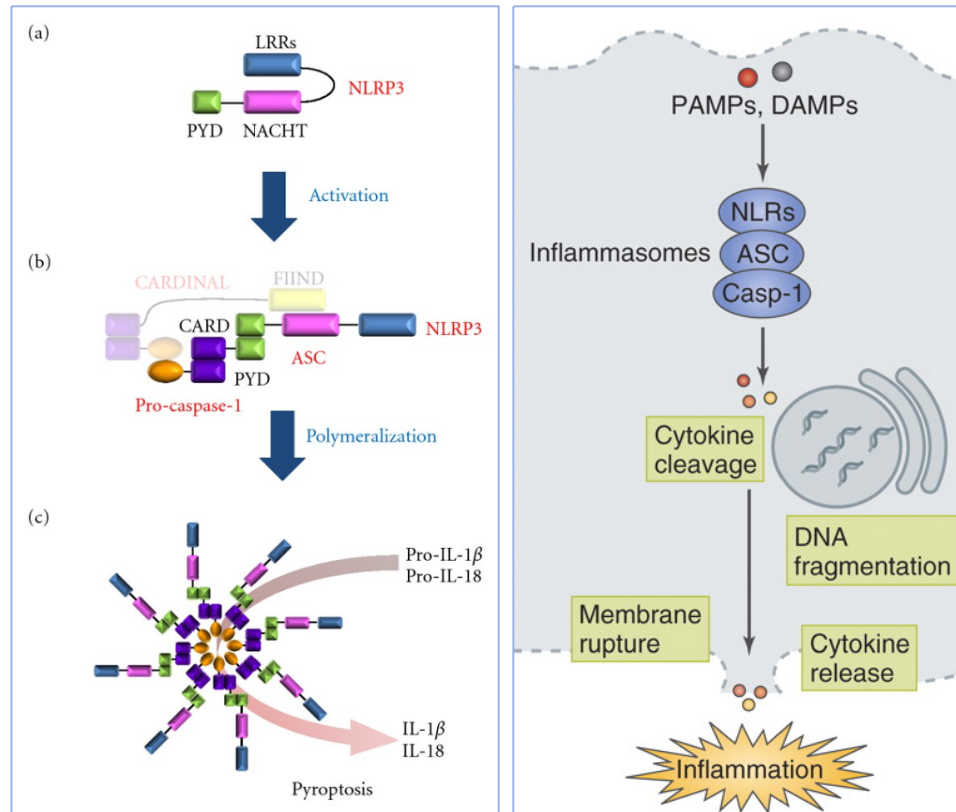
Inflammasome Pathway



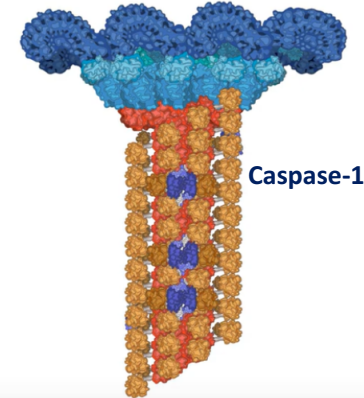
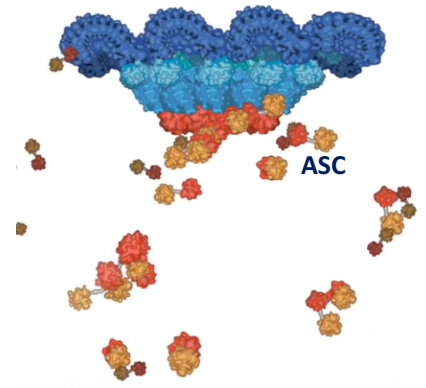
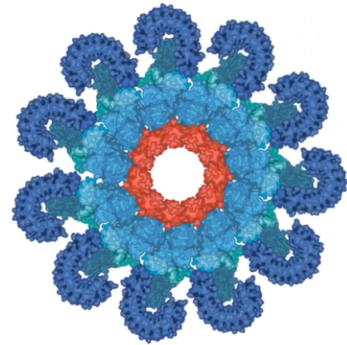
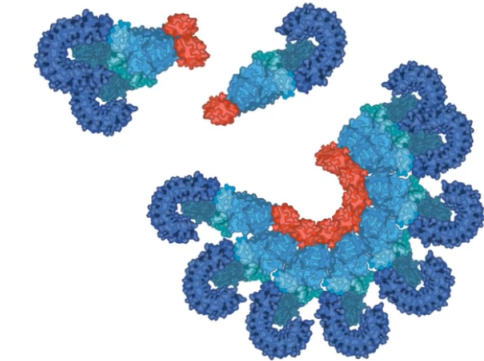
Molecular Abnormalities and Innate/Inflammatory Signaling Effects

Genetic abnormality	Gene class	Mutant gene/ Chromosome alteration	Innate immune-signaling effect*	Inflammasome-signaling effect†	Ref.
Somatic mutations	Epigenetic modifiers	<i>TET2</i>	↑ IL-6 production via ↓ HDAC2 recruitment; ↑ IL-1β	↑ Pyroptosis and β-catenin signaling	28, 30, 40
		<i>DNMT3A</i>	↑ Type 1 IFN production via ↑ HDAC9 expression		29
		<i>ASXL1</i>	↑ NADPH oxidase ROS; ↑ TLR4, TICAM2	↑ Pyroptosis and β-catenin signaling	31, 40
		<i>EZH2</i>	↑ S100A8/A9 via NF-κB derepression		25
	Spliceosomes	<i>SF3B1</i>	↑ NF-κB activation via ↓ MAP3K7	↑ Pyroptosis and β-catenin signaling	32, 40
		<i>SRSF2</i>	↑ S100A8 and S100A9, DNA-RNA hybrids; ↑ NF-κB activation via caspase 8 isoform	↑ Pyroptosis and β-catenin signaling	24, 32, 40
		<i>U2AF1</i>	↑ DNA-RNA hybrids, ATG7 alternate splicing impairing autophagy	↑ Pyroptosis and β-catenin signaling ; impaired autophagy leading to NLRP3 activation	40, 43, 44
Chromosomal abnormality	N/A	Deletion 5q	Haploinsufficiency: RPS14 ↑ S100A8/A9; miR-145/146 + TIFAB ↑ TRAF6/IRAK1	↑ Pyroptosis and β-catenin signaling	8, 11, 22

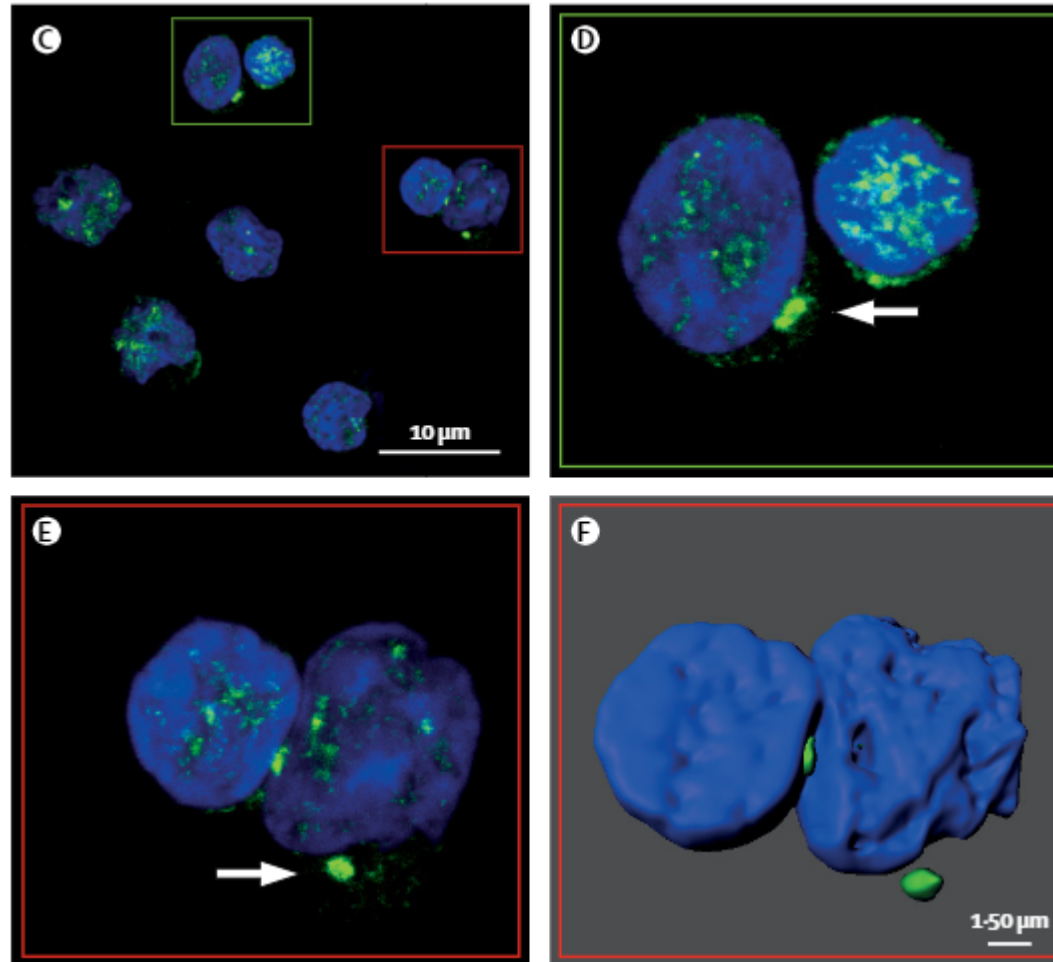
NLRP3 Inflammasome



NLRP3 Inflammasome

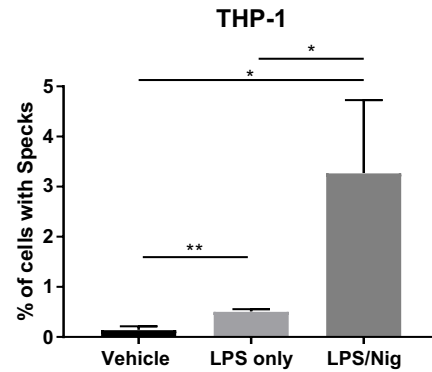


ASC Specks and MDS

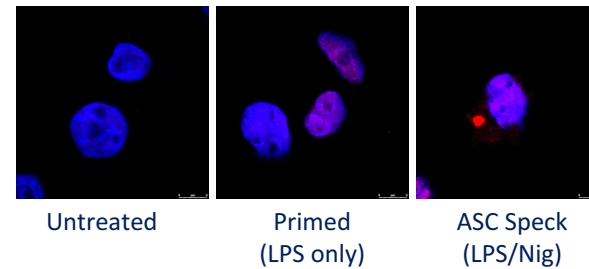
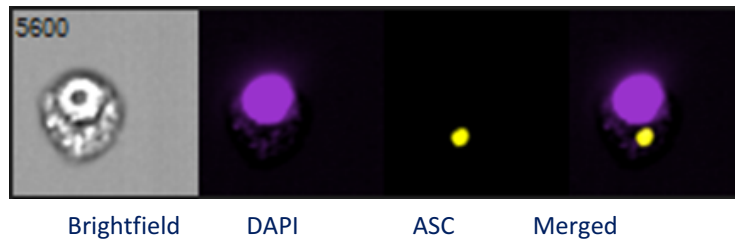
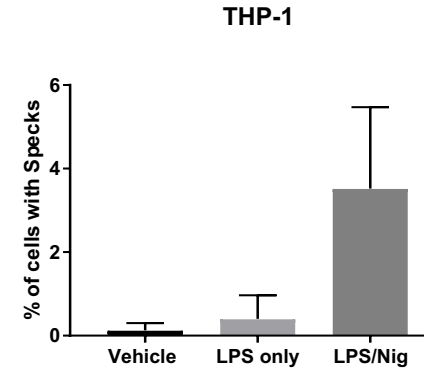


Novel Imaging Techniques for ASC Specks

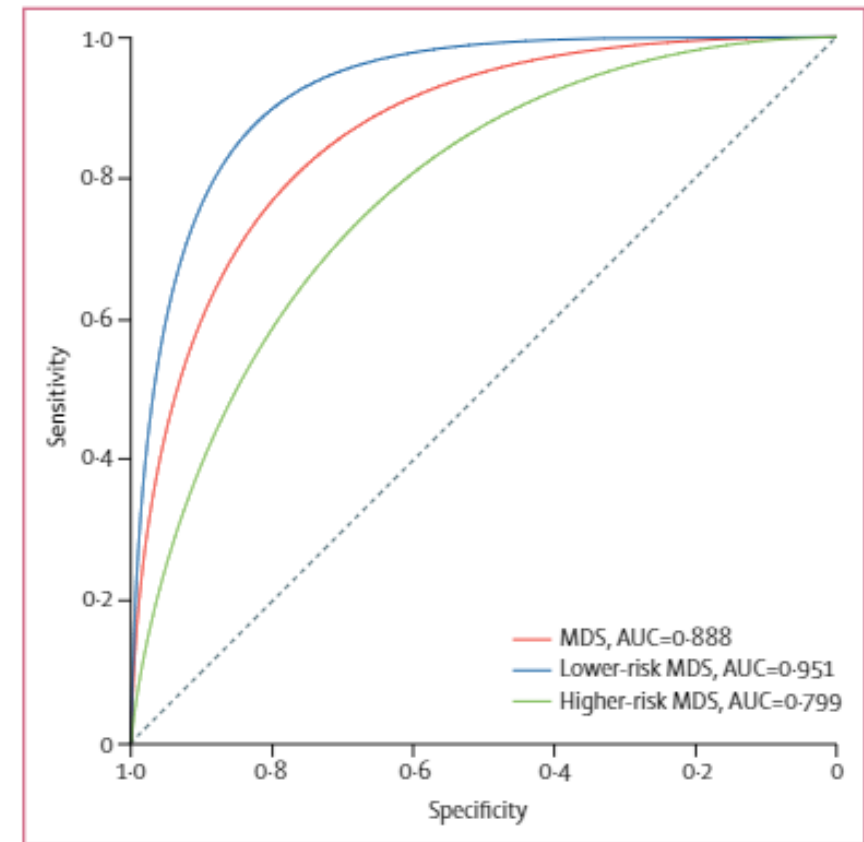
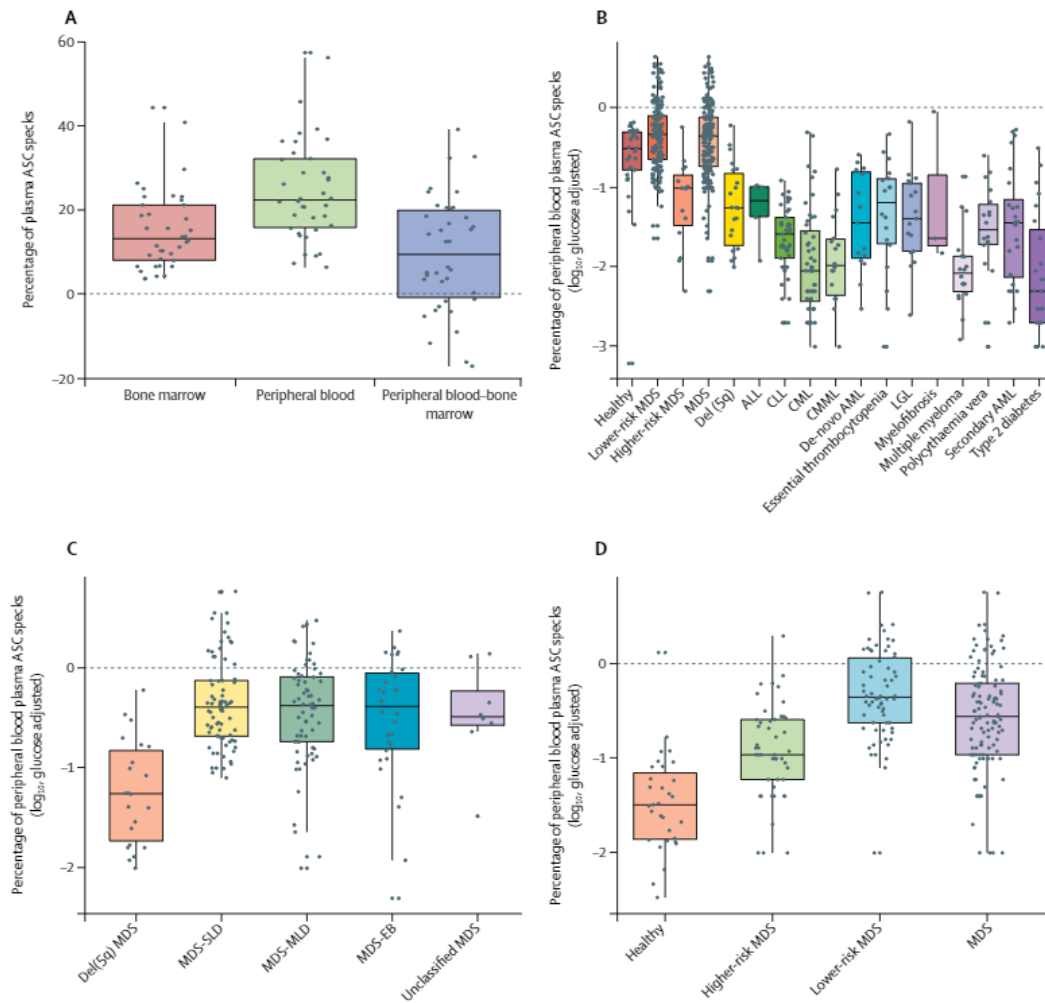
Imagestream



Microscopy

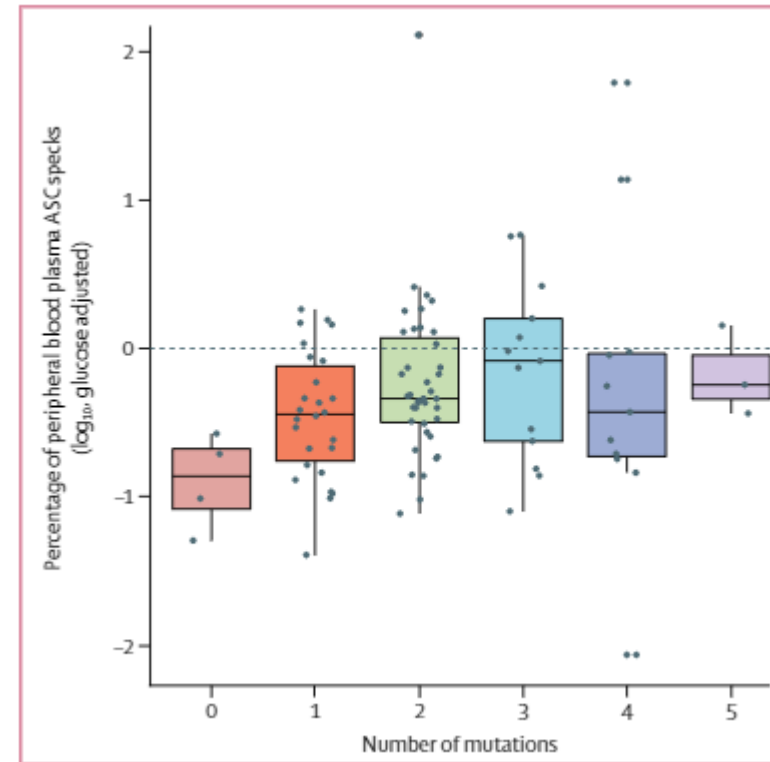


ASC Specks Highest in Peripheral Blood and LR-MDS

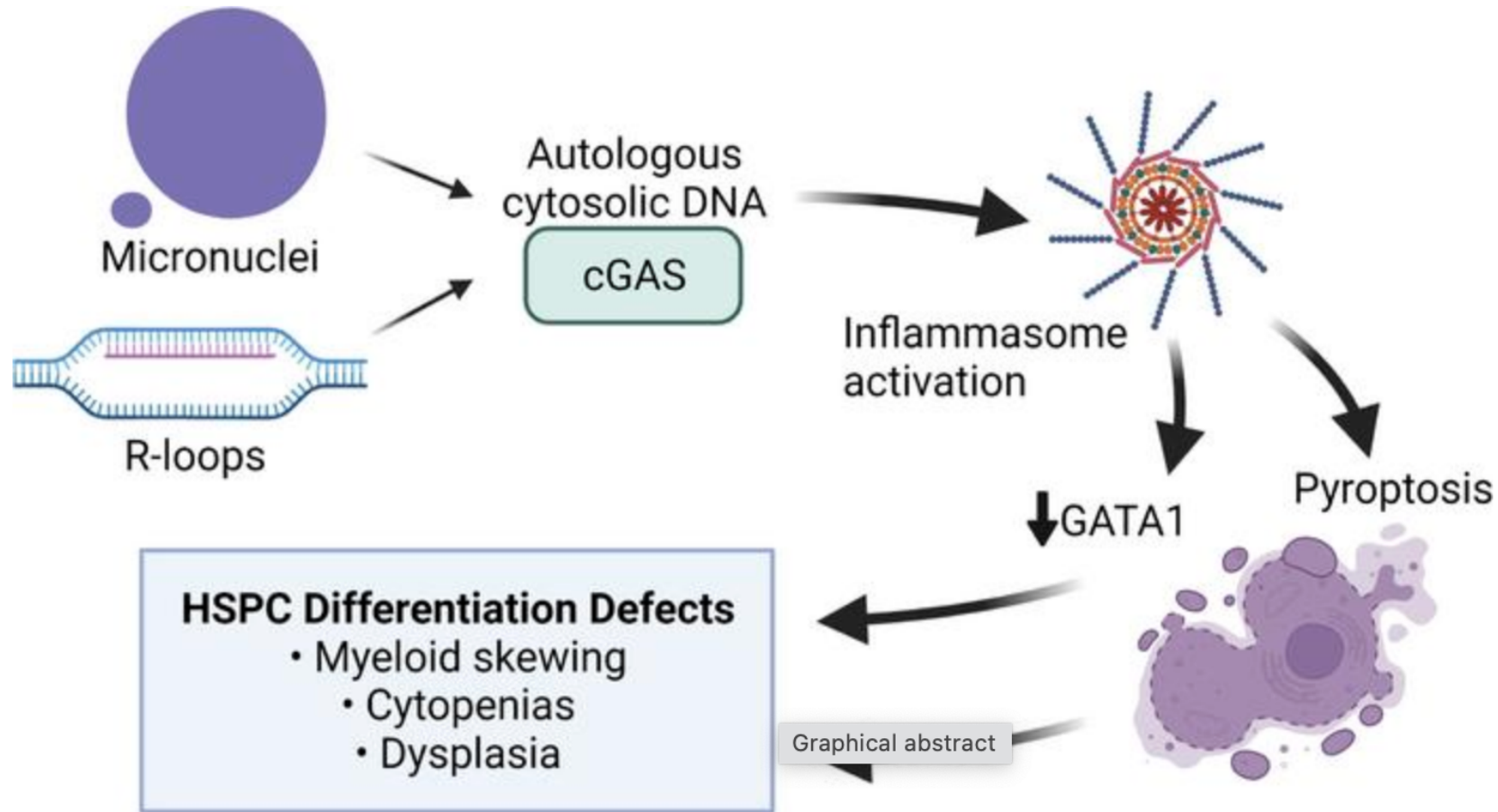


Pathogenic Correlations with ASC Specks

	n	Mean (SD)	Median (IQR)	p value
Splicing gene mutations*				
Yes	78	-0.25 (0.61)	-0.35 (-0.62 to 0.07)	0.026
No	18	-0.54 (0.44)	-0.52 (-0.80 to -0.24)	..
Methylation gene mutations†				
Yes	52	-0.20 (0.69)	-0.32 (-0.61 to 0.11)	0.039
No	44	-0.44 (0.43)	-0.42 (-0.75 to -0.13)	..
Transcriptional gene mutations‡				
Yes	37	-0.29 (0.66)	-0.34 (-0.62 to 0.08)	0.821
No	59	-0.32 (0.56)	-0.40 (-0.70 to -0.04)	..
Signalling gene mutations§				
Yes	11	-0.26 (0.66)	-0.44 (-0.79 to -0.11)	0.787
No	85	-0.31 (0.59)	-0.36 (-0.67 to 0.03)	..

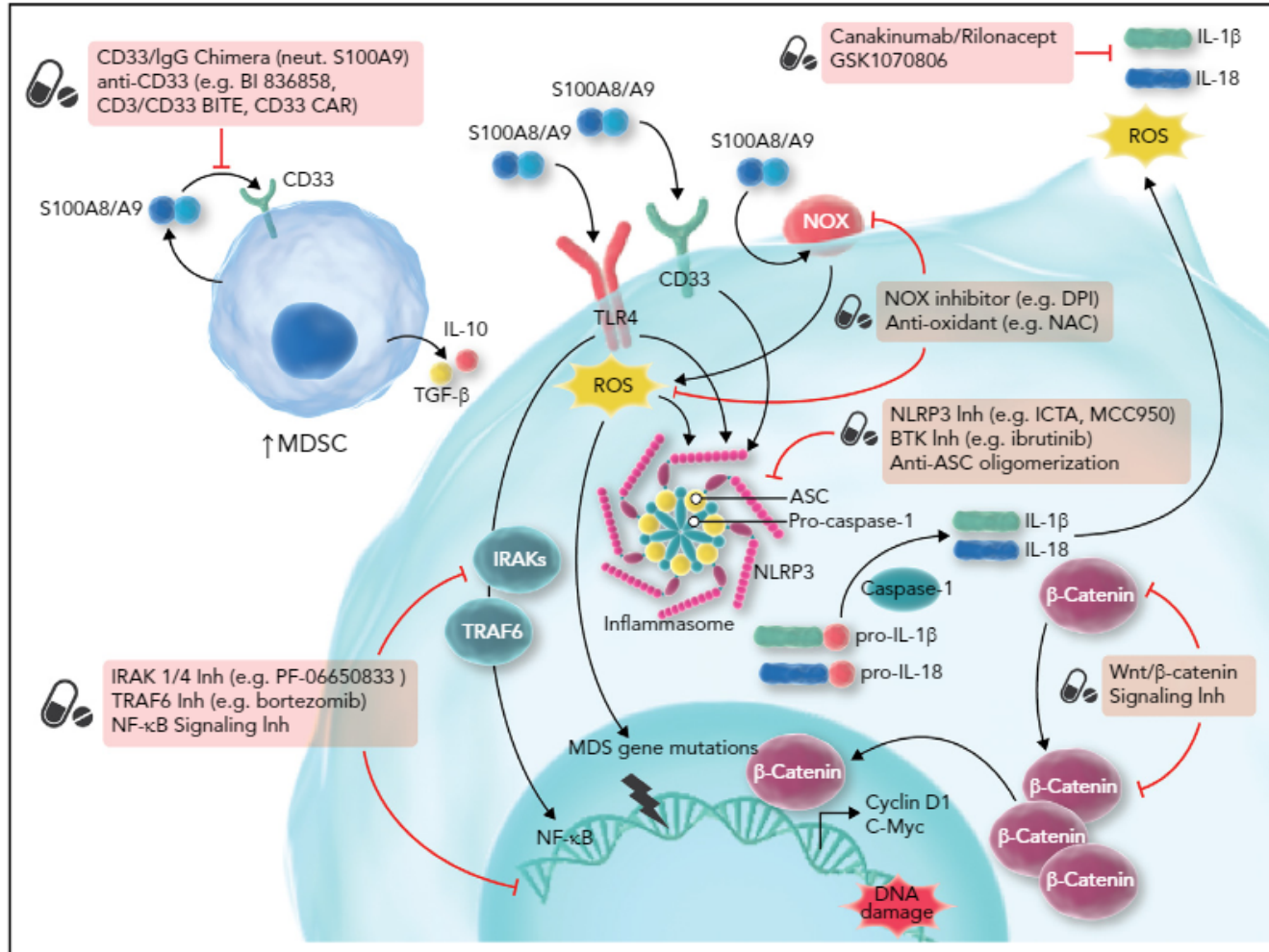


cGAS-STING



Myelodysplastic Syndrome

Inflammasome Targets Under Investigation

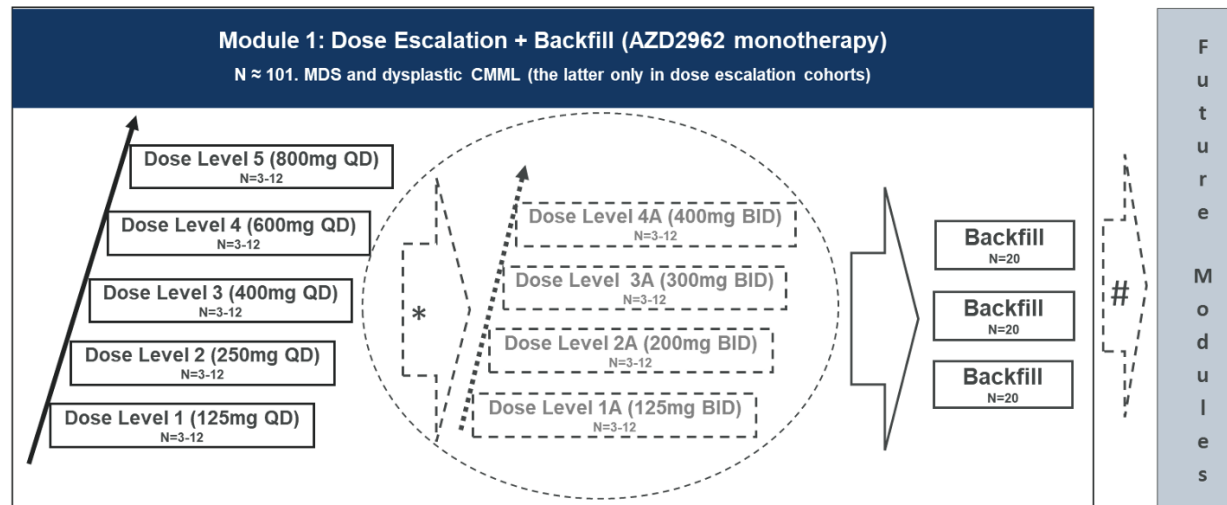


IRAK4 Inhibition: CA-4948 in MDS/AML

- IRAK4-L expression driven by Spliceosome mutations (*SF3B1/U2AF1*)
- Can Inhibit Adaptive Resistance to Chemotherapy; preclinical data for synergy with BCL-2 inhibitors
- CA-4948/emavusertib is a novel small molecule oral inhibitor of interleukin-1 receptor associated kinase 4 (also inhibits FLT3)
 - In R/R MDS, Among the 40 response evaluable patients, the ORR and CR rate were 27.5% and 2.5%; 36% in splicing mutant

Next Steps with IRAK inhibitors?

R289 IRAK 1/4 inh presented at ASH, 3/11 HTB pts had HI-E although f/u short AZD2962 FIH study will enter trials by Q3 2025 in both LR and HR MDS patients. (IRAK4 selective inhibitor; 700 fold sensitive over IRAK1; minimal activity with other targets)



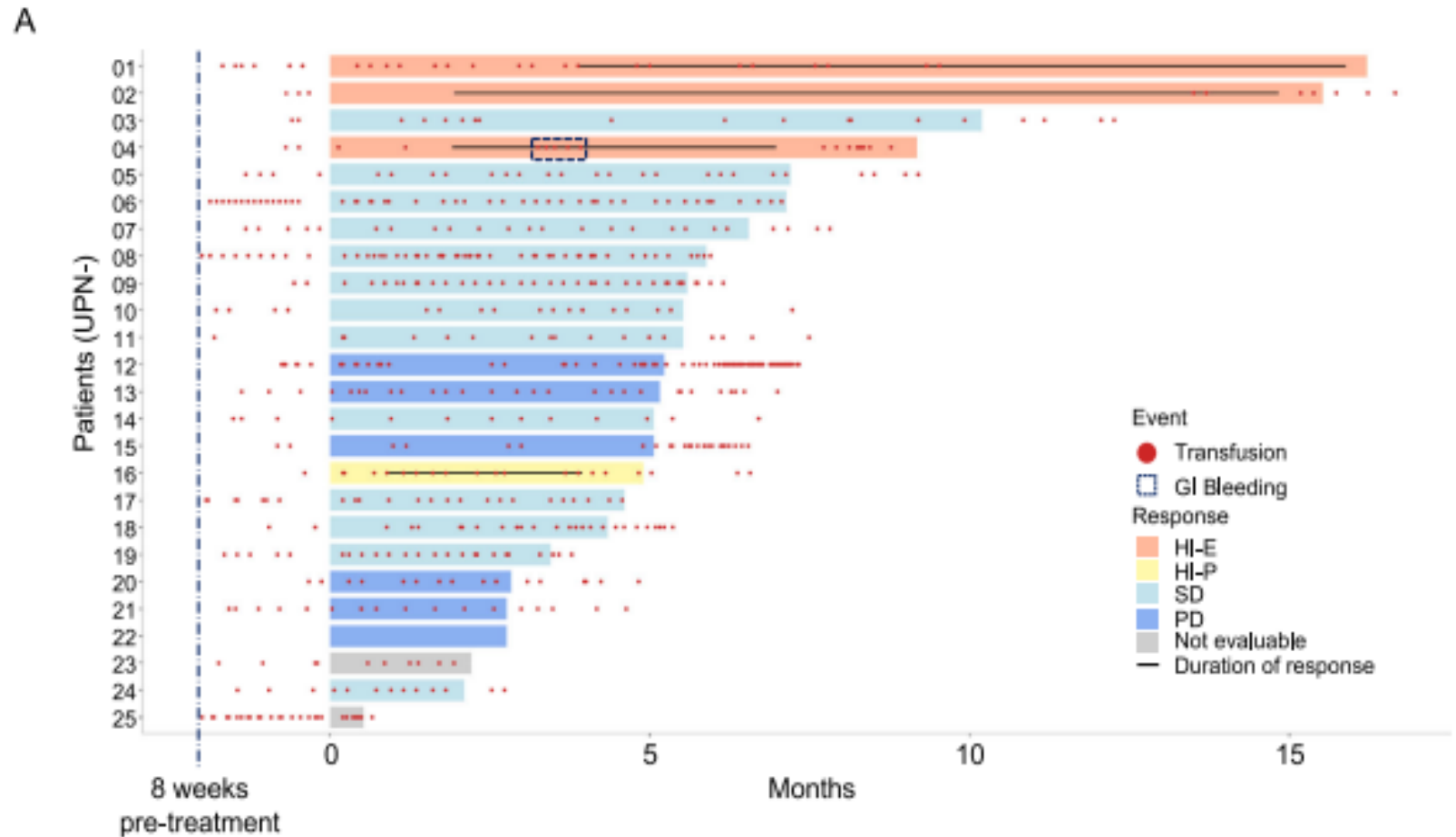
* After Dose Level 1 (125mg QD) has been cleared, SRC may recommend/mandate switching to BID cohorts at any time during dose escalation (e.g., the emerging PK profile does not support QD dosing, or toxicity associated with $f_{C_{max}}$).

Will require a protocol amendment.

Intermediate and alternative dose levels may be explored based on emerging data and decision of the SRC.

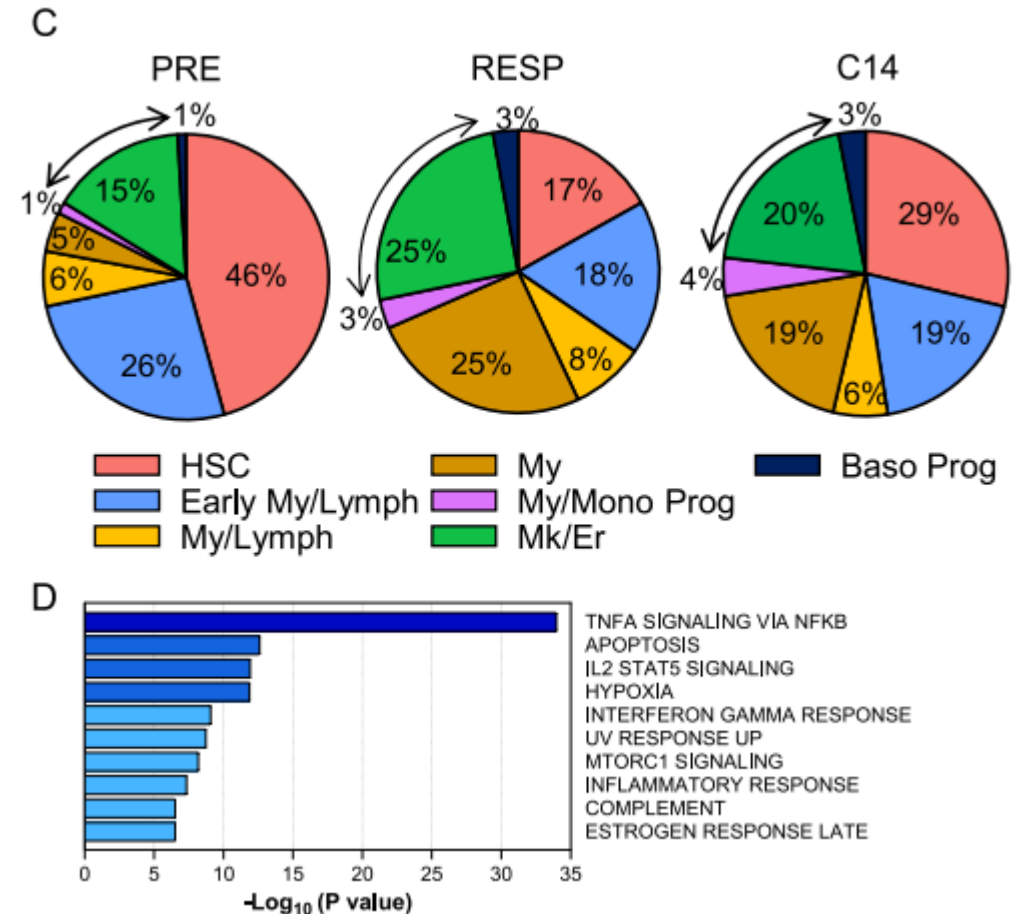
Canakinumab in LR MDS

- 17% response rate
- 3 HI-E and 1 HI-P
- 14% HI-E by 2018 IWG criteria
- All responders had LR disease by IPSS-M
- No patients with SF3B1 responded



Canakinumab in LR MDS

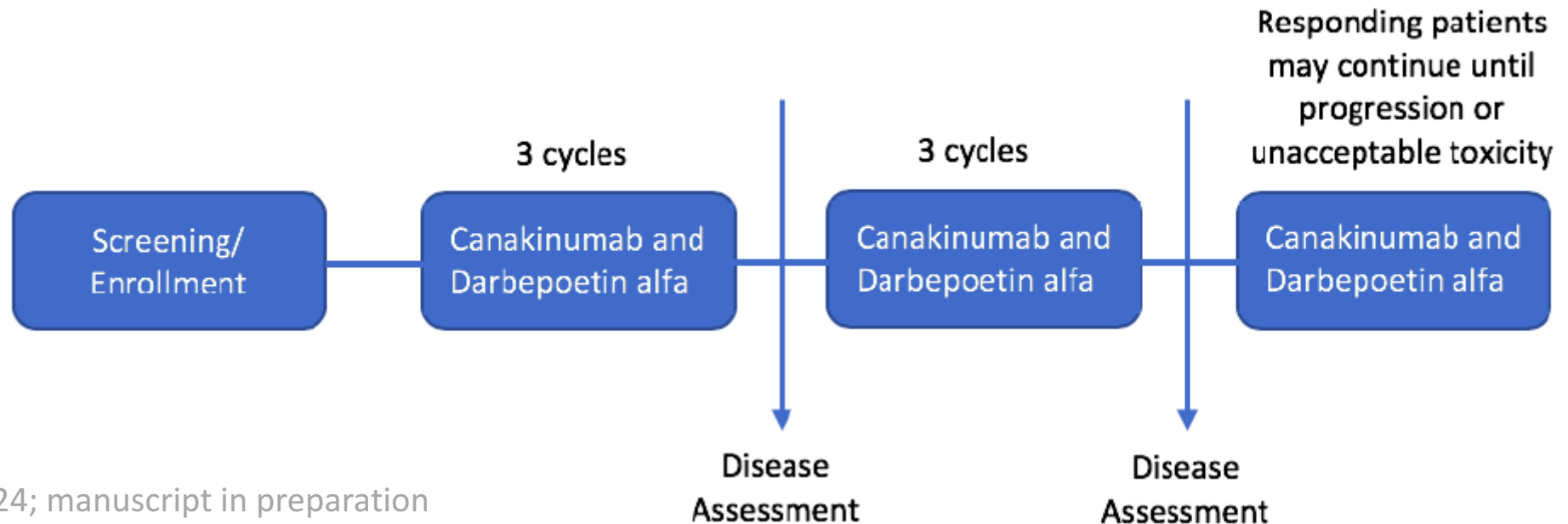
- Increased HSCs' differentiation towards the erythroid and myeloid lineage
- Genes involved in the NF- κ B signaling pathway, including IL-1 β , CXCL2, CXCL3, and MIF, were significantly downregulated in HSCs obtained at canakinumab response compared with those in HSCs obtained before treatment



Canakinumab in LR-MDS

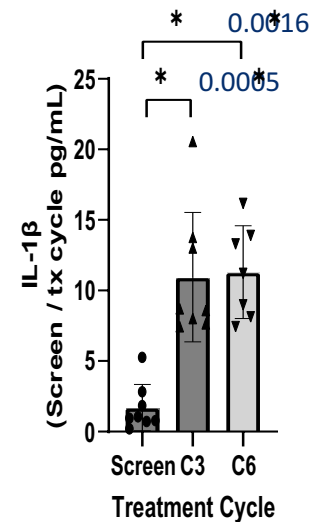
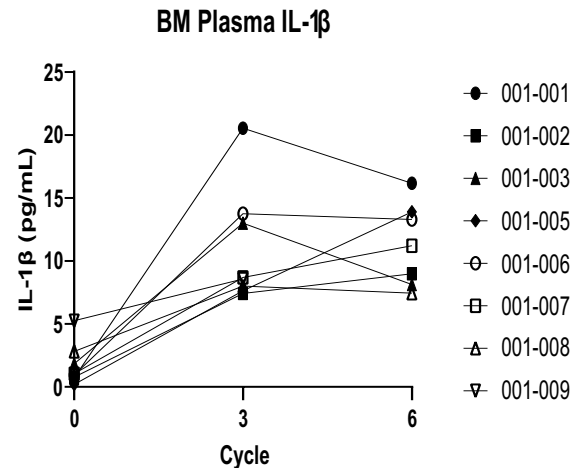
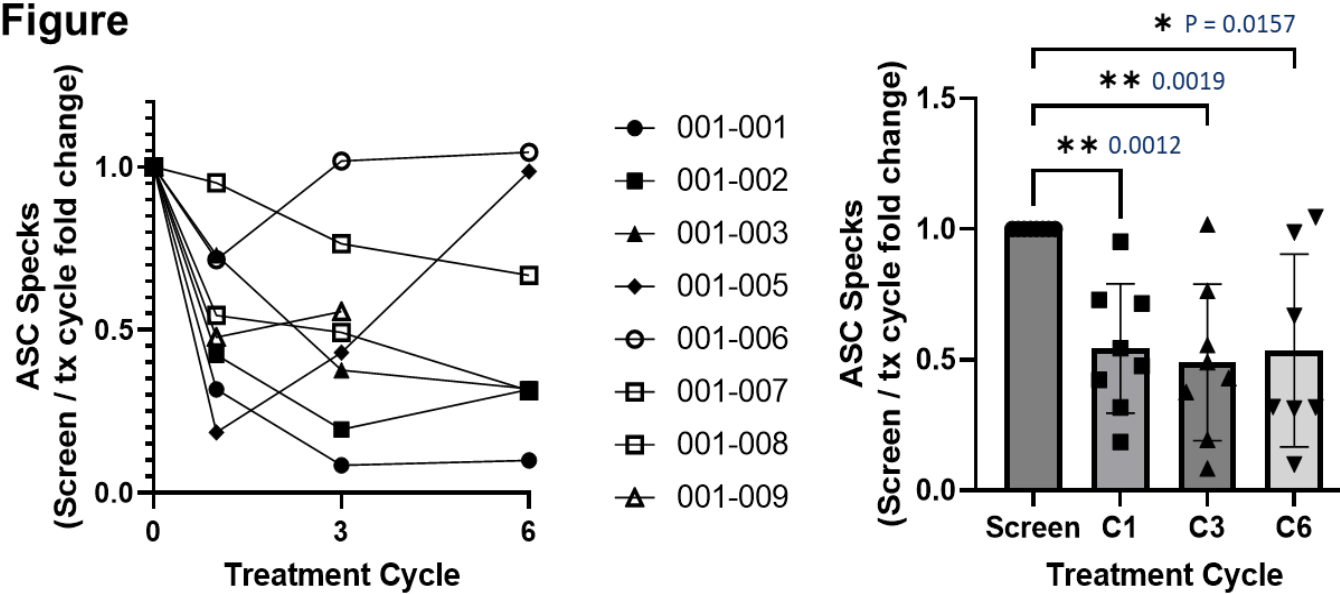
Table 1. Dose levels for phase 1b

Dose Level	Canakinumab (mg)	Darbepoetin alfa (μg)
-1	75	300
1 (Starting dose)	150	300
2	300	300



PBMC ASC SPECKS DECREASE WITH CANAKINUMAB

Figure



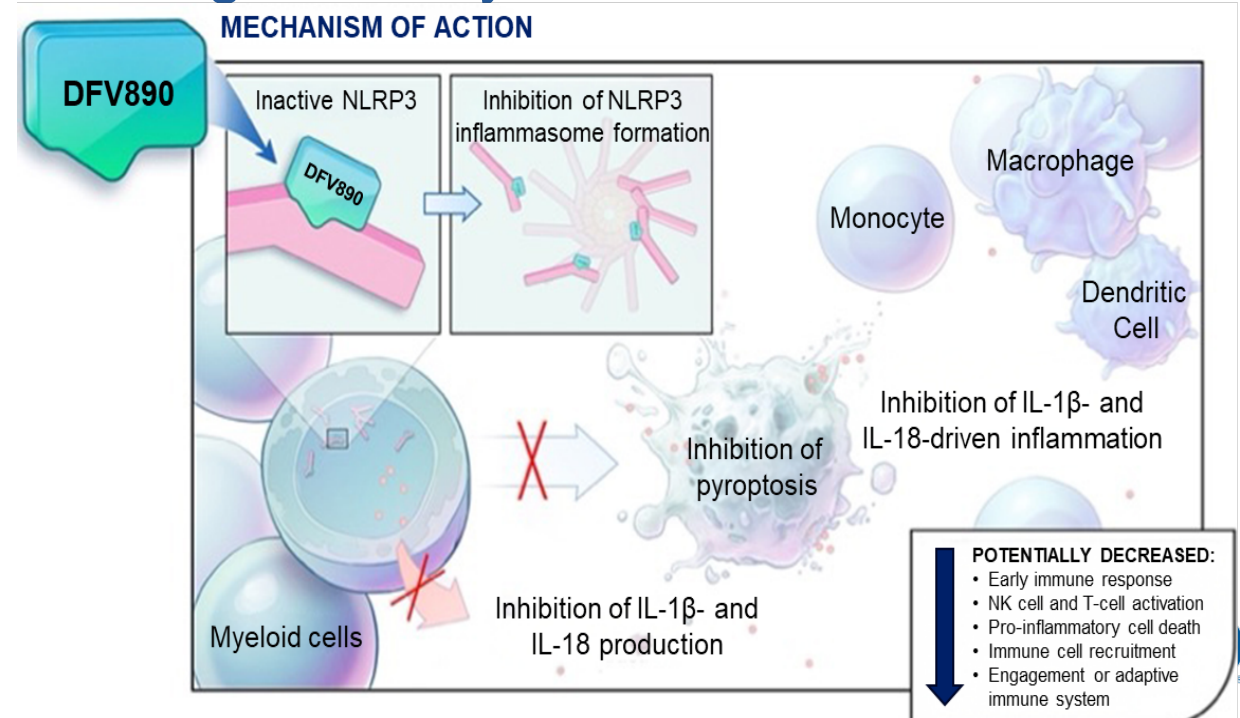
No Objective Responses

Additional IL-1B Studies

- Canakinumab is being evaluated in CCUS both in single arm study (Garcia-Manero G et al.,
- Borate U and colleagues leading a randomized P2 Trial of canakinumab for High Risk CCUS (IMPACT Study)

NLRP3 Inflammasome Inhibition

- DFV890 without significant response in LRMDs who were heavily pretreated (only inhibits inactive form of NLRP3)
- Ofirnoflast (HT-6184) is a NEK7 inhibitor of both active and inactive NLRP3
 - Of 18 pts, 72% achieved HI-E and 55% TI with median duration of TI of 29 weeks
 - 90% reduction of IL-1B and additional on-target activity with reduction of oxidized mitochondrial DNA.
 - Global P3 Study in preparation



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