MDS: New Developments

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AAMAC April 22, 2023

Disclosures

Research Support/PI	Astex, Forma Therapeutics, F. Hoffmann-La Roche, Genentech, Geron, Gilead Sciences, Janssen, Jazz, Novartis, Treadwell Therapeutics
Employee	N/A
Consultant	N/A
Stockholder	N/A
Speakers Bureau	N/A
Honoraria	AbbVie, Novartis
Advisory Board	Bristol Myers Squibb/Celgene, F. Hoffmann-La Roche, GSK, Jazz, Novartis, Pfizer, Shattuck Labs, Taiho Oncology, Takeda

Topics to be discussed:

1. Two new classifications of myelodysplastic syndromes (aka myelodysplastic neoplasms) – WHO 2022 & ICC 2022

2. New International Prognostic Scoring System – IPSS-M

3. Newer treatments in MDS & Phase 3 (later phase) studies in MDS

Next Generation Sequencing in Patients with MDS

- December 1, 2022 Ontario Health – Cancer Care Ontario (OH-CCO) approved gene testing for newly diagnosed cases of MDS, MPN and MDS/MPN

- This is important for:
  a) Diagnosis
  b) Prognosis
  c) Treatment

CCO/OH Recommended Biomarkers for NGS for Myeloid Neoplasms

ABL1	*EZH2*	*NPM1*	*STAG2*
ASXL1	*ETV6*	*NRAS*	*TET2*
BCOR	*FLT3 (ITD/TKD)*	*PHF6*	*TP53*
BCORL1	*IDH1*	*PPM1D*	*U2AF1*
BRAF	*IDH2*	*PTPN11*	*WT1*
CALR	*JAK2*	*PRPF8*	*ZRSR2*
CBL	*GATA2*	*RAD21*	*ANKRD26*
CEBPA	*KIT*	*RUNX1*	*TERC*
CUX1	*KMT2A/MLL (PTD)*	*SETBP1*	*TERT*
CSF3R	*KRAS*	*SH2B3*	
DDX41	*MPL*	*SF3B1*	
DNMT3A	*NF1*	*SRSF2*	

UHN Hematological Malignancies Panel (UHN-HMP) v3.0 (roll-out mid/end April 2023)

ABL1	*ETV6*	*KRAS*	*SF3B1*
ANKRD26	*EZH2*	*MPL*	*SH2B3*
ASXL1	*FBXW7*	*MYD88*	*SRSF2*
BCOR	*FLT3*	*NF1*	*STAG2*
BCORL1	*GATA2*	*NOTCH1*	*TERC*
BRAF	*GNAS*	*NPM1*	*TERT*
CALR	*GNB1*	*NRAS*	*TET2*
CBL	*IDH1*	*PAX5*	*TP53*
CEBPA	*IDH2*	*PHF6*	*U2AF1*
CSF3R	*IKZF1*	*PPM1D*	*UBA1*
CTNNA1	*IRF1*	*PRPF8*	*WT1*
CUX1	*JAK1*	*PTPN11*	*ZRSR2*
DDX41	*JAK2*	*RAD21*	
DNMT3A	*KIT*	*RUNX1*	
ETNK1	*KMT2A*	*SETBP1*	

New Classifications of MDS

World Health Organization (WHO) 2022

International Consensus Classification (ICC) 2022

MDS (Myelodysplastic Neoplasms) Classification

WHO 2016 (4th ed)	WHO 2022 (5th ed)	ICC 2022
MDS with single lineage dysplasia (MDS-SLD)	**MDS with defining genetic abnormalities** MDS with low blasts & isolated 5q deletion (MDS-5q) MDS with low blasts & *SF3B1* mutation (MDS-*SF3B1*)[a] MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	MDS with mutated *SF3B1*
MDS with multilineage dysplasia (MDS-MLD)		MDS with del(5q)
MDS with ring sideroblasts (MDS-RS) MDS-RS-SLD MDS-RS-MLD		MDS with mutated *TP53*
MDS with isolated del(5q)		MDS, not otherwise specified (MDS, NOS) MDS, NOS without dysplasia MDS, NOS with single lineage dysplasia MDS, NOS with multilineage dysplasia
MDS with excess blasts (MDS-EB) MDS-EB-1 MDS-EB-2	**MDS, morphologically defined** MDS with low blasts (MDS-LB) MDS, hypoplastic (MDS-h) MDS with increased blasts (MDS-IB) MDS-IB1 MDS-IB2 MDS with fibrosis (MDS-f)	MDS with excess blasts
MDS, unclassifiable (MDS-U)		MDS/AML[a] MDS/AML with mutated *TP53* MDS/AML with myelodysplasia-related gene mutations MDS/AML with myelodysplasia-related cytogenetic abnormalities MDS/AML[a], NOS

[a] 10-19% blasts

Arber et al. Blood 2016; Arber et al. Blood 2022; Khoury et al. Leukemia 2022

MDS with low blasts & *SF3B1* mutation (MDS-*SF3B1*); MDS with mutated *SF3B1*

- Diagnosis:

(a) *SF3B1* mutation with ≥5% ring sideroblasts (>80-90% cases)

(b) No *SF3B1* mutation with ≥ 15% ring sideroblasts (WHO 2022)

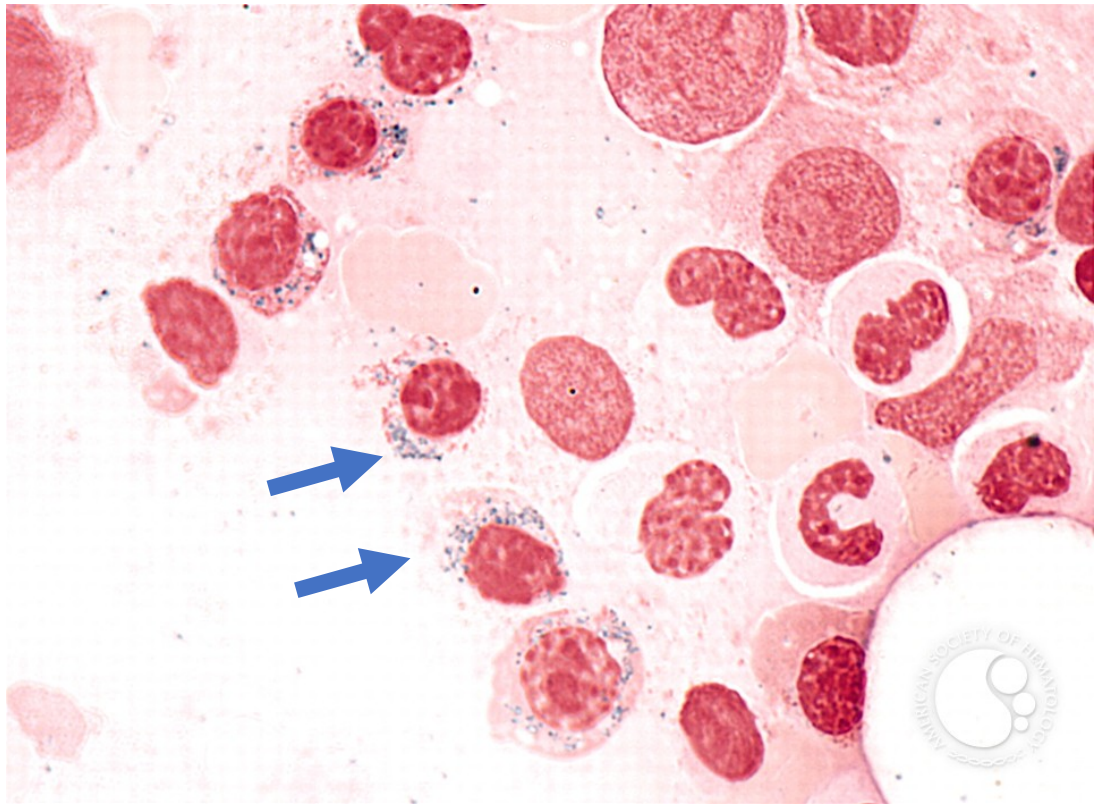
- Clinical Features:

(a) Occurs at slightly older age compared with other MDS subtypes

(b) Good prognosis with longer overall survival

- Treatment:

May respond to luspatercept (approved for IPSS-R Lower risk MDS with ≥ 15% ring sideroblasts ***or*** MDS with SF3B1 mutation with ≥5% ring sideroblasts)



Prussian blue stain is used to identify ring sideroblasts.

MDS with biallelic *TP53* inactivation (MDS-bi*TP53*); MDS with mutated *TP53*

- Diagnosis:

(a) ≥ 2 mutations in *TP53* gene

(b) Loss of chromosome 17 or deletion 17p + *TP53* mutation

- Clinical Features:

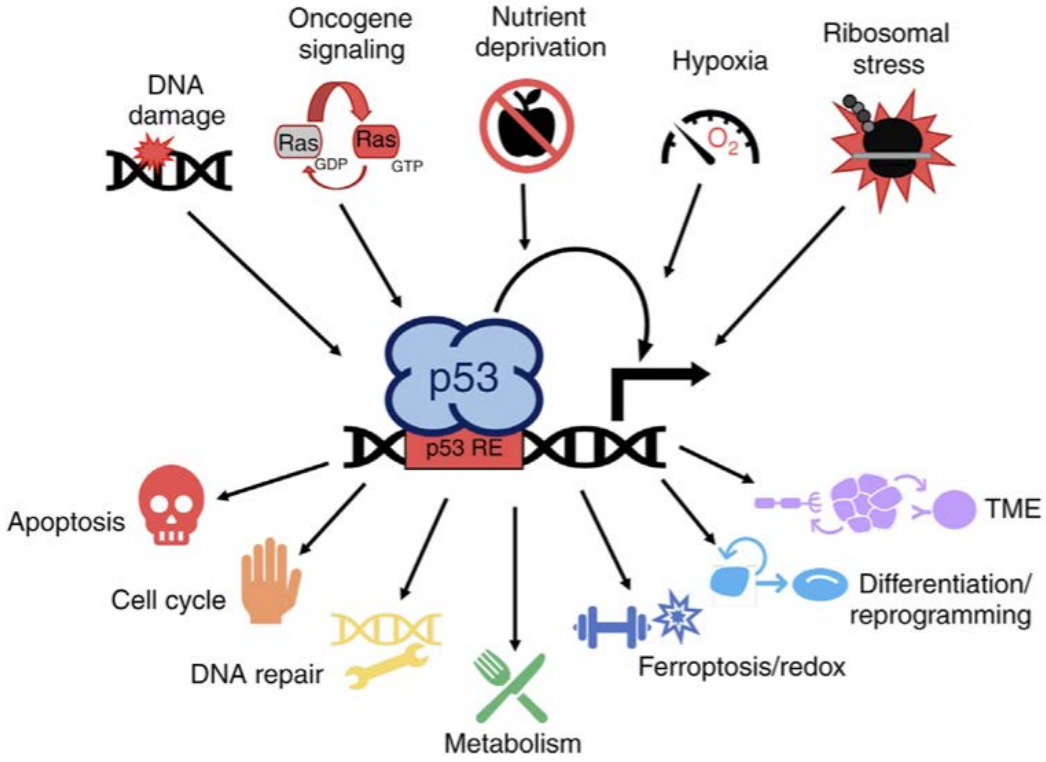
(a) Incidence: 5-10% in *de novo* MDS; 70-80% in MDS with complex karyotype; 40% in therapy-related MDS

(b) Lower overall survival

- Treatment:

(a) Difficult to treat;

(b) Under investigation CD47 antibodies (e.g. magrolimab), SIRPα, eprenetapopt (APR-246), etc



Boutelle and Attardi. Trends in Cell Biology 2021; 31:298-310; Daver et al. Cancer Discovery 2022; 12:2516-29

Prognostic Scoring System in MDS

International Prognostic Scoring System (IPSS) 1997

Revised International Prognostic Scoring System (IPSS-R) 2012

Molecular International Prognostic Scoring System (IPSS-M) 2022

Comparison of MDS Prognostic Scoring Systems

	IPSS (Greenberg 1997)	IPSS-R (Greenberg 2012)	IPSS-M (Bernard 2022)
Includes CMML	Yes (if WBC $\leq$ 12 x 10^9/L)	Yes (if WBC $\leq$ 12 x 10^9/L)	Yes[a] (if WBC < 13 x 10^9/L)
Includes secondary MDS	No	No	Yes
Includes previously treated patients	No	No	Yes
Sensitivity to degree of cytopenias	Limited	Anemia, thrombocytopenia & neutropenia	Anemia & thrombocytopenia[b]
Range of karyotypes	3 categories	5 categories	5 categories
Marrow blasts	< 30%	< 30%	< 20%
Includes gene mutations	No	No	Yes (31)
Number of prognostic variables	3	5	5[c]
Number of risk groups	4	5	6

Greenberg et al. Blood 1997; Greenberg et al. Blood 2012; Bernard et al. NEJM Evid 2022

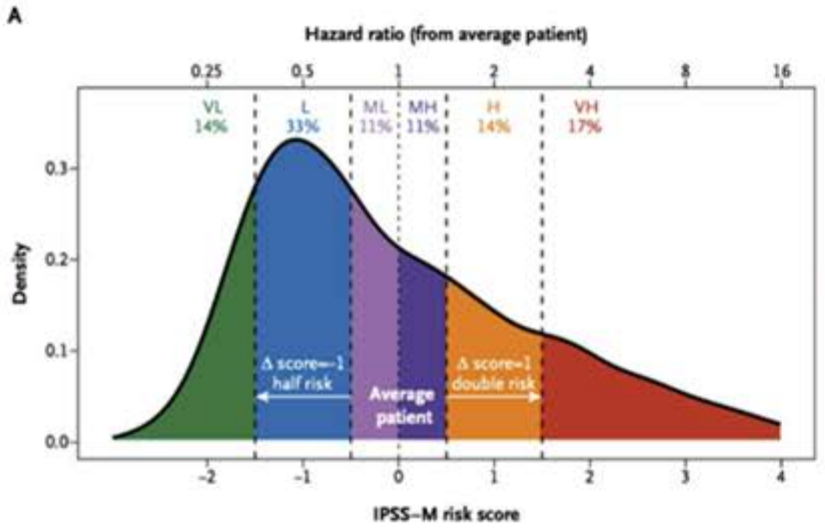
Molecular International Prognostic Scoring System (IPSS-M)

IPSS-M model

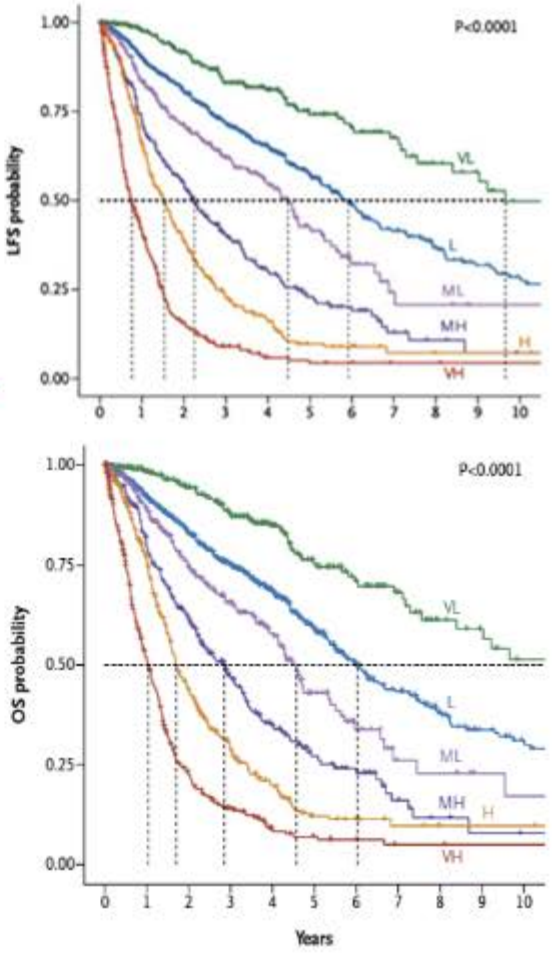
Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10⁹/l	0.998 (0.997–0.999)	−0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	−0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multihit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{HR}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1*	0.92 (0.74 1.16)	−0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231

IPSS-M risk score and strata



Risk discrimination



https://mds-risk-model.com/

Undergoing real world validation; issues with missing/incomplete data?

Bernard et al. NEJM Evid 2022

Menu

IPSS-M Risk Calculator

CLINICAL DATA

CYTOGENETICS

MOLECULAR DATA

*Number of TP53 mutations

Mutation Count	0	1	2+

*Loss of heterozygosity at TP53 locus (If known)

TP53 LOH	No	Yes	N/A

*MLL (KMT2A) and FLT3 Mutations

MLL PTD	No	Yes	Not Assessed
FLT3 ITD or TKD	No	Yes	Not Assessed

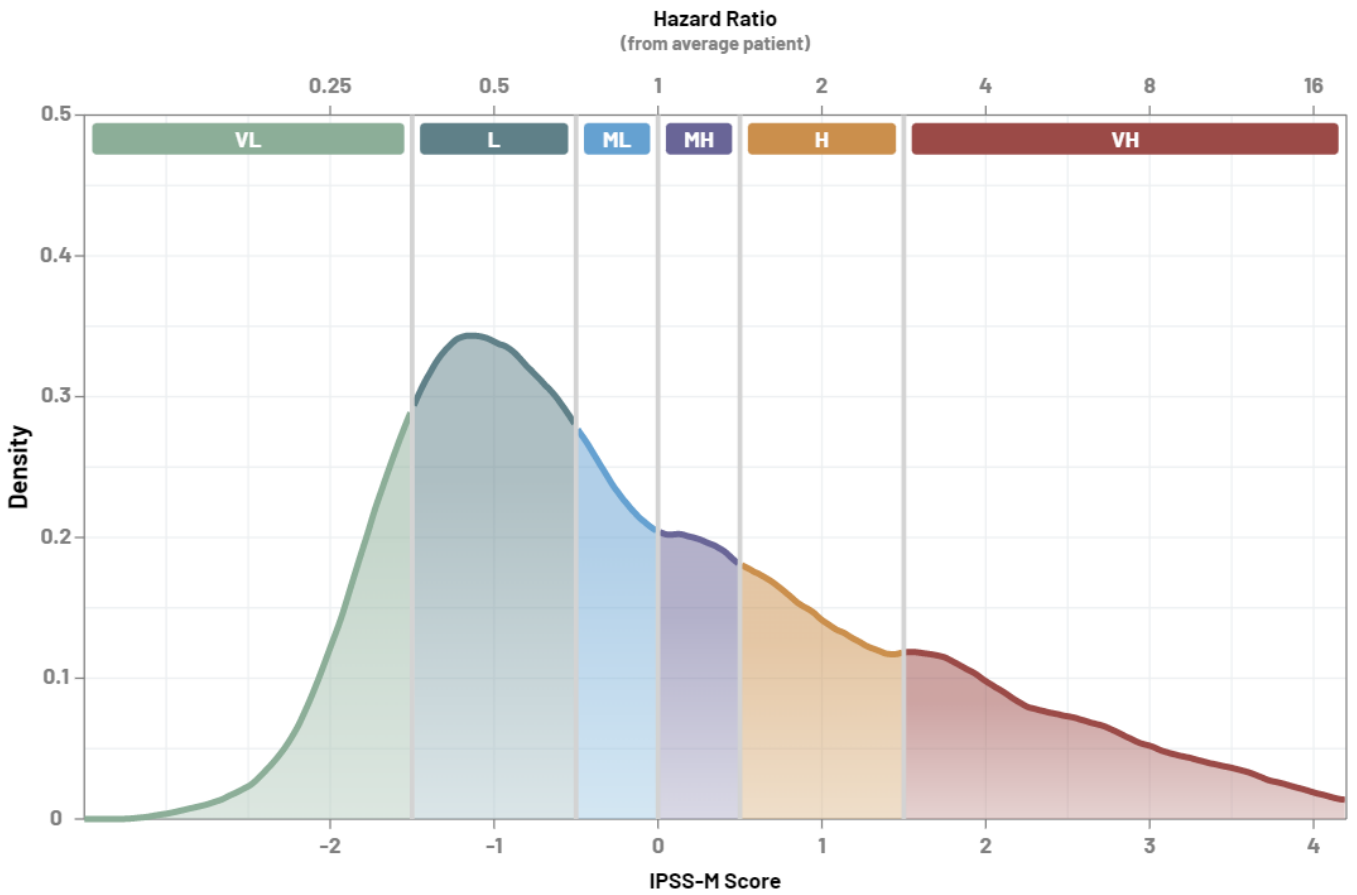
Calculate Risk

Auto update

Reset Values

Risk Stratification | Clinical Outcomes

Graph | Table



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

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

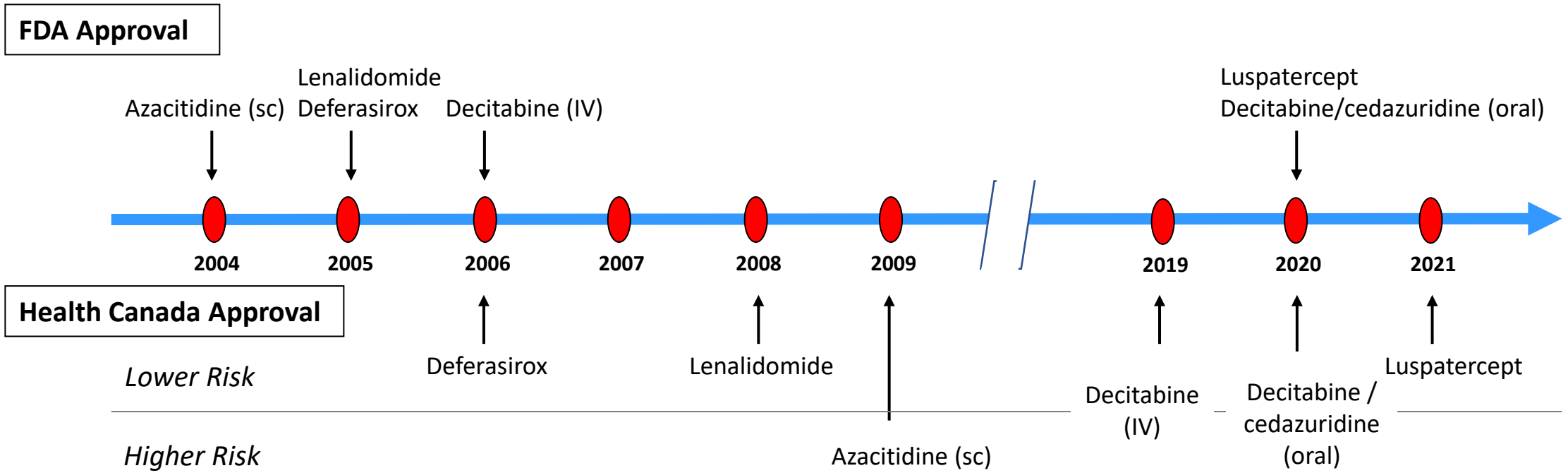
Bernard E, Tuechler H, Greenberg PL, et al, The Molecular International Prognosis Scoring System (IPSS-M) for risk stratification in myelodysplastic syndromes. New Eng J Med Evidence, 1(7). doi:10.1056/evidoa2200008.
Study supported by the MDS Foundation.

Currently Approved Treatments

Luspatercept

Decitabine/cedazuridine

MDS New Drug Approval Timelines

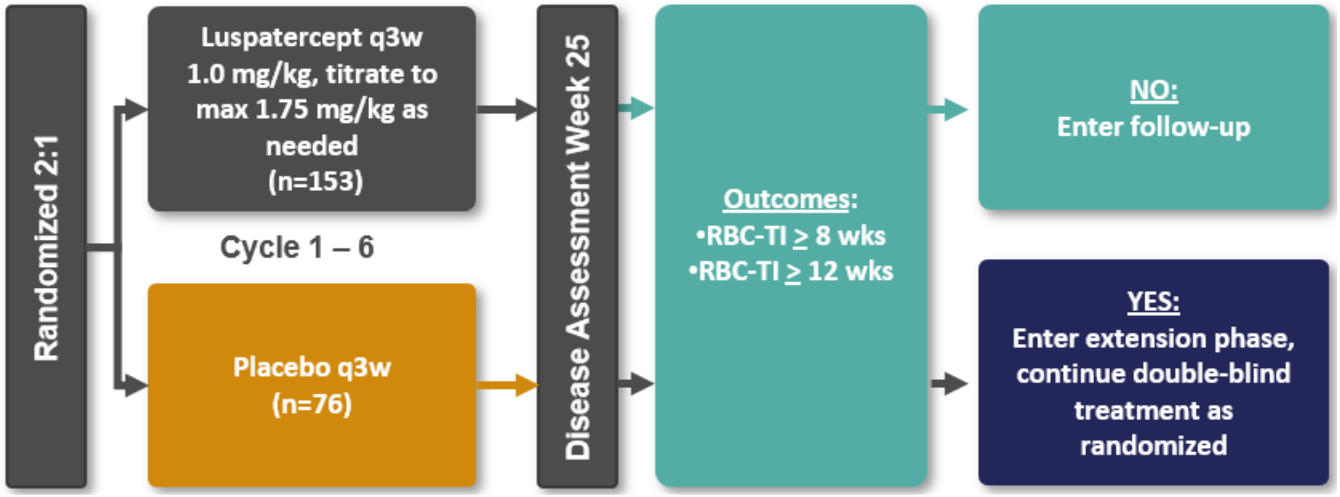


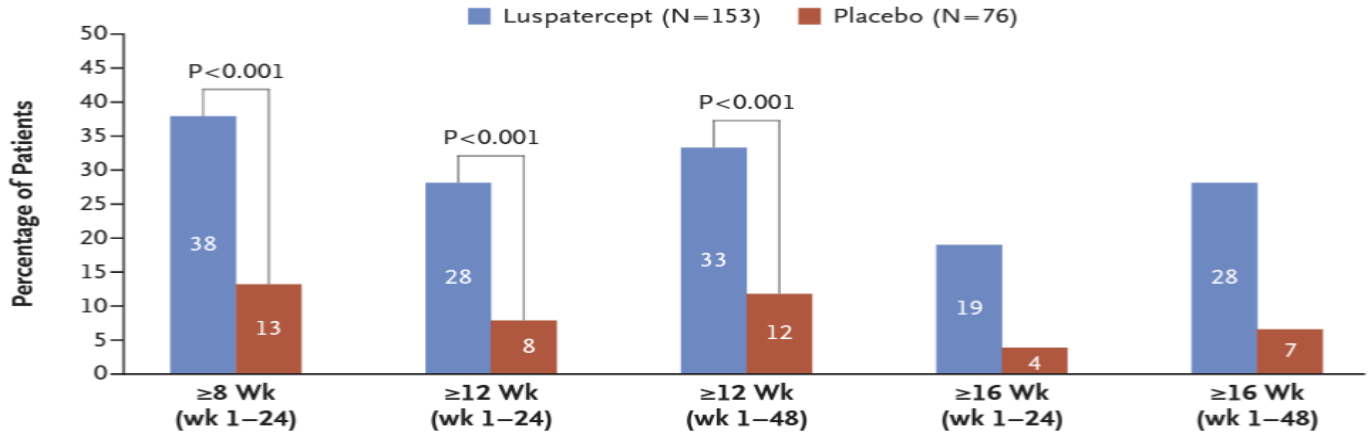
Phase 3 Trial: Luspatercept *versus* Placebo in Lower-Risk MDS (MEDALIST)

KEY INCLUSION CRITERIA

N=229

- Age ≥ 18 years
- MDS-RS (WHO): ≥ 15% RS or ≥ 5% with SF3B1 mutation
- No del(5q) MDS
- IPSS-R Very low-, Low-, or Intermediate-risk
- Prior ESA response:
  - Refractory, intolerant
  - ESA naïve: EPO > 200 U/L
- RBC transfusion dependent
- No prior treatment with disease-modifying agents (e.g. iMIDs, HMAs)





No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

	Luspatercept (n=58)	Placebo (n=10)
Median duration TI (RBC-TI ≥ 8 wks), weeks	30.6	13.6

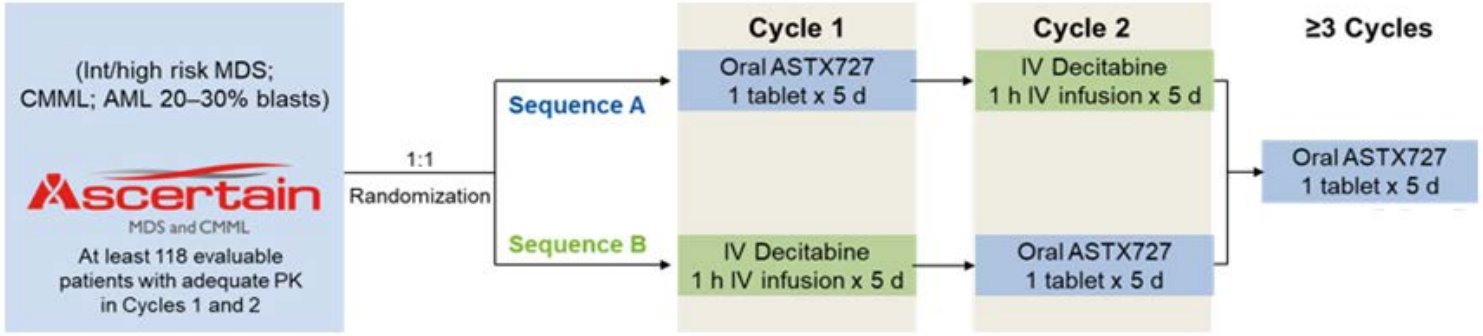
Fenaux et al. N Engl J Med 2020; 382:140-51

Phase 3 Cross-over Study of Oral Decitabine/Cedazuridine (ASTX727) *versus* IV Decitabine in MDS & CMML (ASCERTAIN)

KEY INCLUSION CRITERIA

N=133

- Age ≥ 18 years
- MDS
- IPSS Intermediate-1, Intermediate-2 or High risk
- ECOG status 0-1



PRIMARY ENDPOINT:

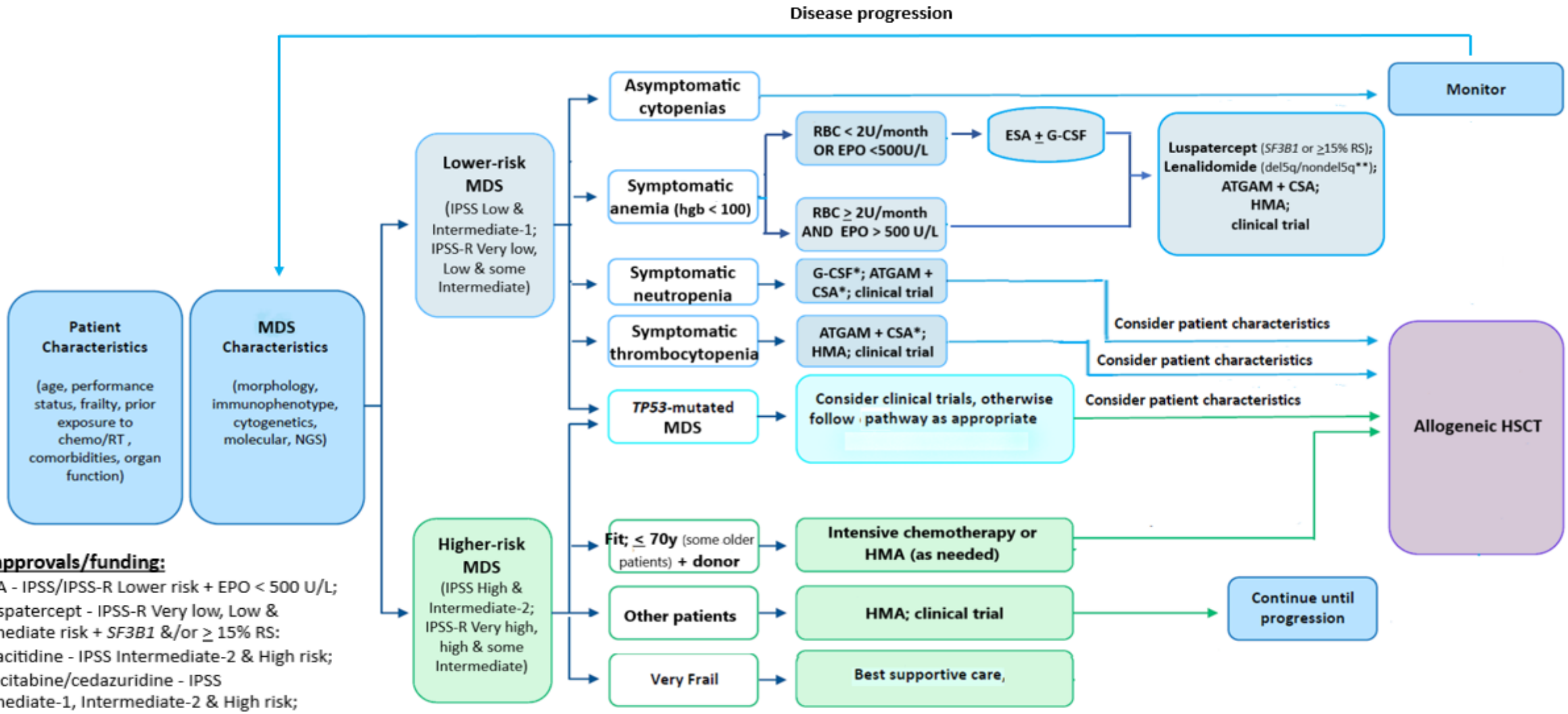
Pharmaco kinetic equivalence (AUC) between 5 days oral decitabine/cedazuridine and IV decitabine

The study met its primary endpoint of equivalence with high confidence: Oral/IV 5-day AUC 98.9% (90% CI 97.7, 105.6)

	All patients (N=133)
Complete remission (CR)	29 (22%)
Marrow CR Marrow CR + Hematologic improvement (HI)	43(32.3%) 22 (16.5%)
Hematologic Improvement (HI)	10 (7.5%)
Overall response	**82 (62%)**
Median OS , mos	**31.7** (after 32 months follow-up)

Garcia-Manero et al. Blood. 2019; 134(Supplement 1); Savona et al. International MDS Symposium 2021 (abstract P48)

MDS: Treatment Algorithm



EAP approvals/funding:

(a) ESA - IPSS/IPSS-R Lower risk + EPO < 500 U/L;
(b) Luspatercept - IPSS-R Very low, Low & Intermediate risk + *SF3B1* &/or ≥ 15% RS:
(c) Azacitidine - IPSS Intermediate-2 & High risk;
(d) Decitabine/cedazuridine - IPSS Intermediate-1, Intermediate-2 & High risk;
(e) Lenalidomide - IPSS Lower risk & del5q;
(f) Deferasirox - IPSS Lower risk + iron overload due to red cell transfusions

No medications have been approved with the IPSS-M prognostic scoring system

Adapted & modified from Fenaux et al. Ann Oncol 2020; 32:142-56

Newer Treatments Under Investigation

LOWER RISK MDS

- Phase 3 luspatercept *vs* epoietin
- Phase 3 imetelstat *vs* placebo
- Phase 3 oral azacitidine *vs* placebo

Erythropoietin: Predictor of Response & Responses

NORDIC Decision Model: EPO +/- G-CSF:

Variable	Value	Score	Value	Score
Transfusion need*	< 2 U/month	0	≥ 2 U/month	1
Serum-Epo*	< 500 U/liter	0	≥ 500 U/liter	1

* Pre-treatment evaluation
Predicted response rate: Total score 0 = 74%, 1 = 23%, 2 = 7%
Predicted value of model $P < 0.001$ [14]
Patients with score 2 do not benefit from treatment with Epo + G-CSF

Phase 3 EPO *versus* Placebo in IPSS Lower risk MDS

	EPO (n=85)	Placebo (n=45)
Response	39 (45.9%)	2 (4.4%)

Hellstrom-Lindberg et al. British J Haematol 2003; 120:1037-46; Fenaux et al. Leukemia 2018; 32:2648-48

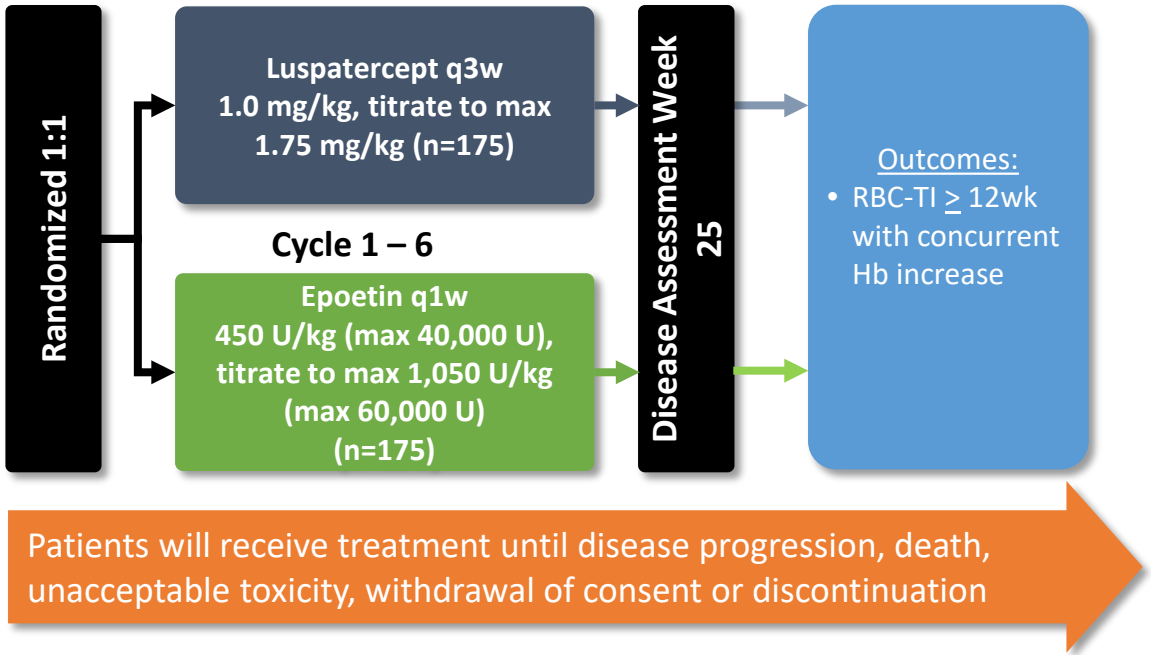
Phase 3 Luspatercept *versus* Epoetin as First-Line Treatment for RBC Transfusion-dependent IPSS-R Lower-Risk MDS (COMMANDS)

KEY INCLUSION CRITERIA

N=350

- Age ≥ 18 years
- MDS
- No del(5q) MDS
- IPSS-R Very low-, Low-, or Intermediate-risk
- <5% marrow blasts
- EPO < 500 U/L
- RBC transfusion dependent
- No prior ESA, G-CSF, disease-modifying agents (e.g. lenalidomide, HMAs)

STUDY DESIGN



Enrolment completed; results pending

Preliminary results (October 31, 2022): The trial met its primary endpoint, demonstrating a highly statistically significant and clinically meaningful improvement in red blood cell transfusion independence (RBC-TI) with concurrent hemoglobin (Hb) increase in the first-line treatment of adult patients with very low-, low- or intermediate-risk MDS who require RBC transfusions

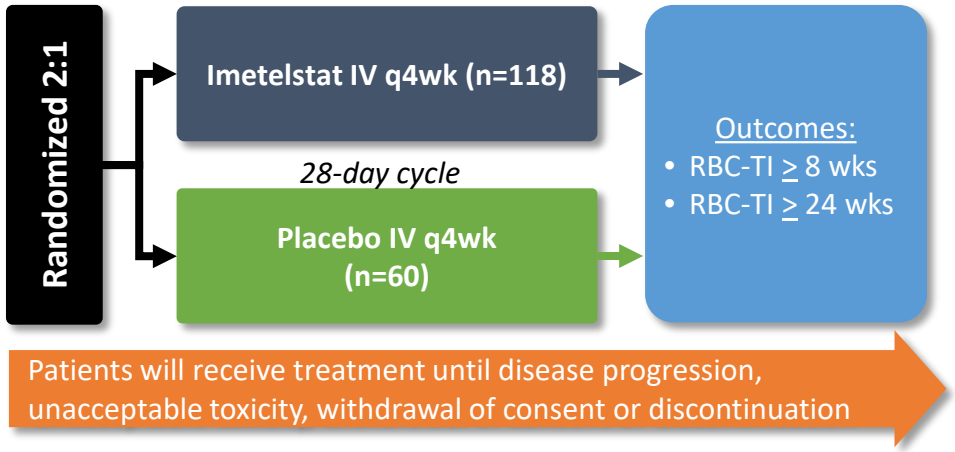
Phase 3 Imetelstat (GRN163L) *versus* Placebo in Transfusion-Dependent IPSS Lower-Risk MDS that is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA)

KEY INCLUSION CRITERIA

N=178 (Part II)

- Age ≥ 18 years
- MDS
- No del(5q) MDS
- IPSS Low or Intermediate-1 risk
- ECOG status 0-2
- Refractory to or ineligible for ESA
- No prior hypomethylating agents or lenalidomide

PART II: PHASE 3



Preliminary results January 4, 2023:

	Imetelstat (n=118)	Placebo (n=60)
8-week RBC-TI, n (%)	47 (39.8)	9 (15.0)
24-week RBC-TI, n (%)	33 (28.0)	2 (3.3)
Median TI duration (RBC-TI ≥ 8 wks), y	1 y	13 weeks
Median TI duration (RBC-TI ≥ 24 wks), y	1.5 y	-

Geron filing for FDA approval; cardiac (ventricular repolarization) substudy still enrolling patients

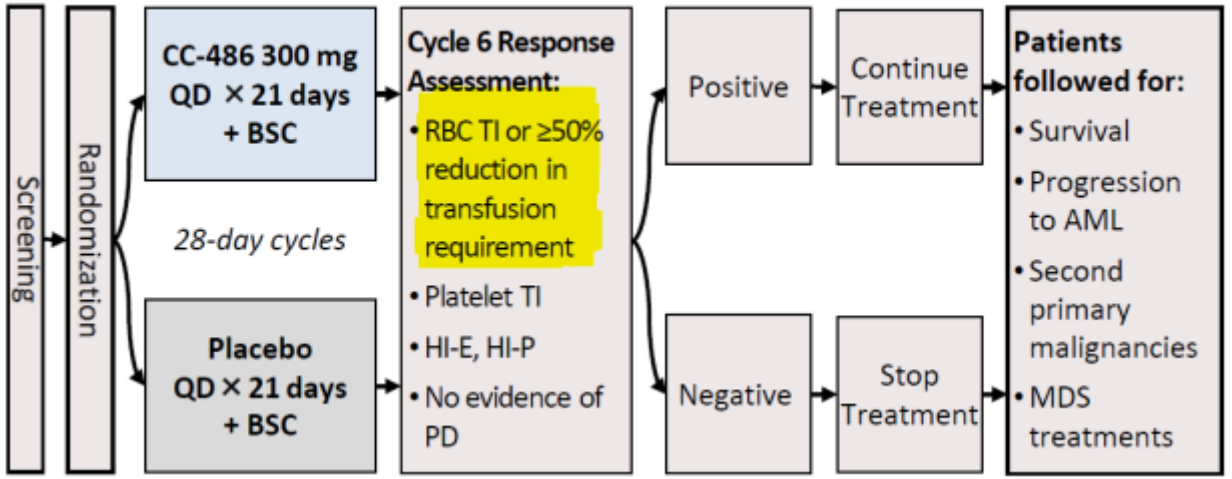
Phase 3 Trial: Oral Azacitidine *versus* Placebo for Red Blood Cell Transfusion-Dependent Lower Risk MDS (with low platelet counts)

KEY INCLUSION CRITERIA

N=215

- Age > 18 years
- IPSS Low or Intermediate-1 risk MDS
- ECOG 0-2
- RBC transfusion dependence
- Platelet count $\leq$ 75 x 10^9/L

STUDY DESIGN



Parameter	Oral azacitidine (N=107)	Placebo (N=108)
	n/N (%)	
RBC Transfusion Independence (RBC-TI)	31%	11%
Median duration RBC-TI	11.1 mos	5 mos
Hematologic improvement (HI) HI – Erythroid (HI-E) HI – Platelet (HI-P) HI – Neutrophil (HI-N)	 46/107 (43%) 26/107 (24%) 6/41 (15%)	 34/108 (31%) 7/108 (6%) 3/41 (7%)

Garcia-Manero et al. J Clin Oncol 2021; 39:1426-36

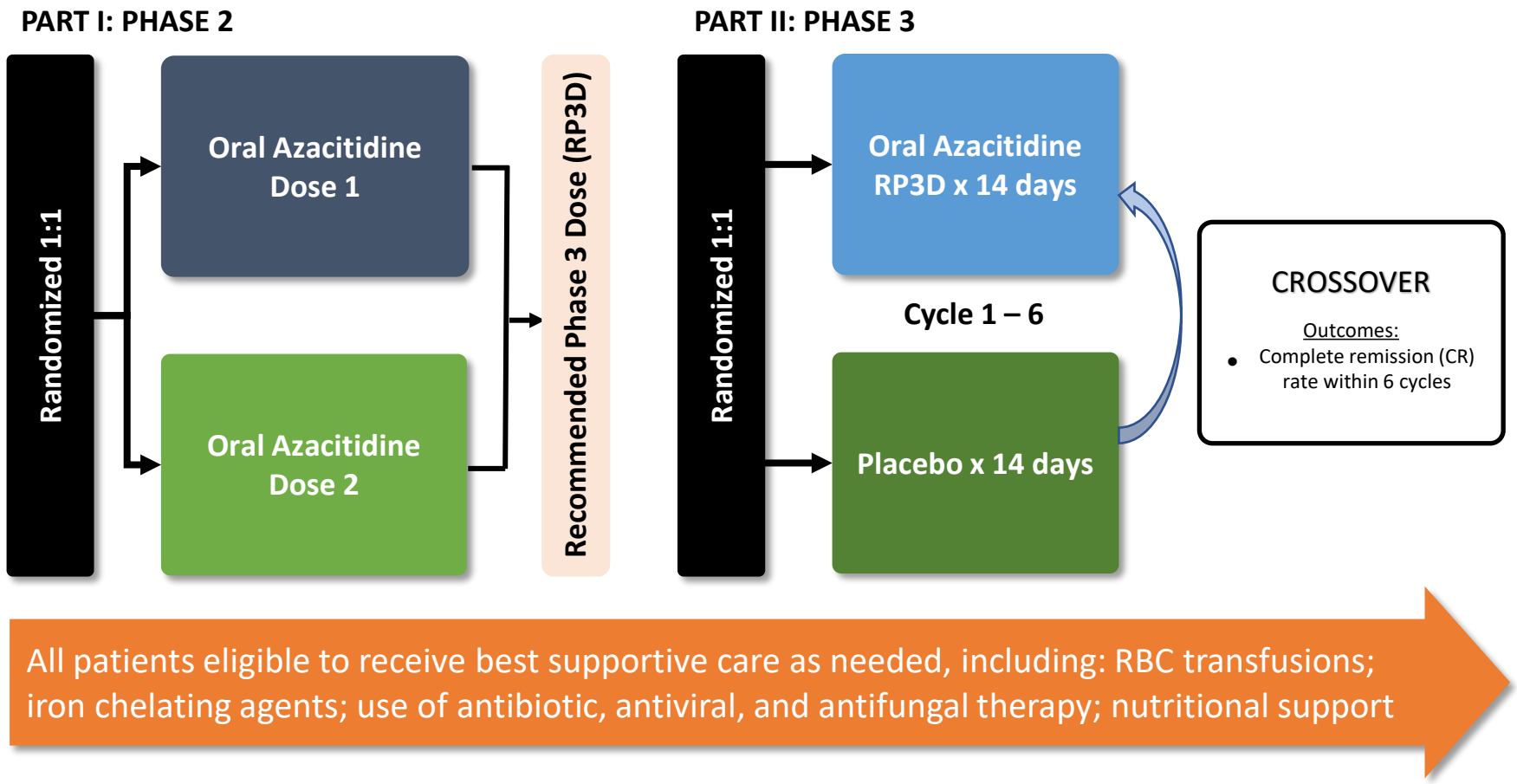
Phase 2/3 Oral Azacitidine *versus* Placebo in IPSS-R Lower-Risk MDS

KEY INCLUSION CRITERIA

N=250

- Age ≥ 18 years
- MDS (not MDS-EB2)
- IPSS-R Low- or Intermediate-risk
- ECOG status 0-2
- No prior hypomethylating agents (such as azacytidine, decitabine)

Opening for enrolment



Newer Treatments Under Investigation

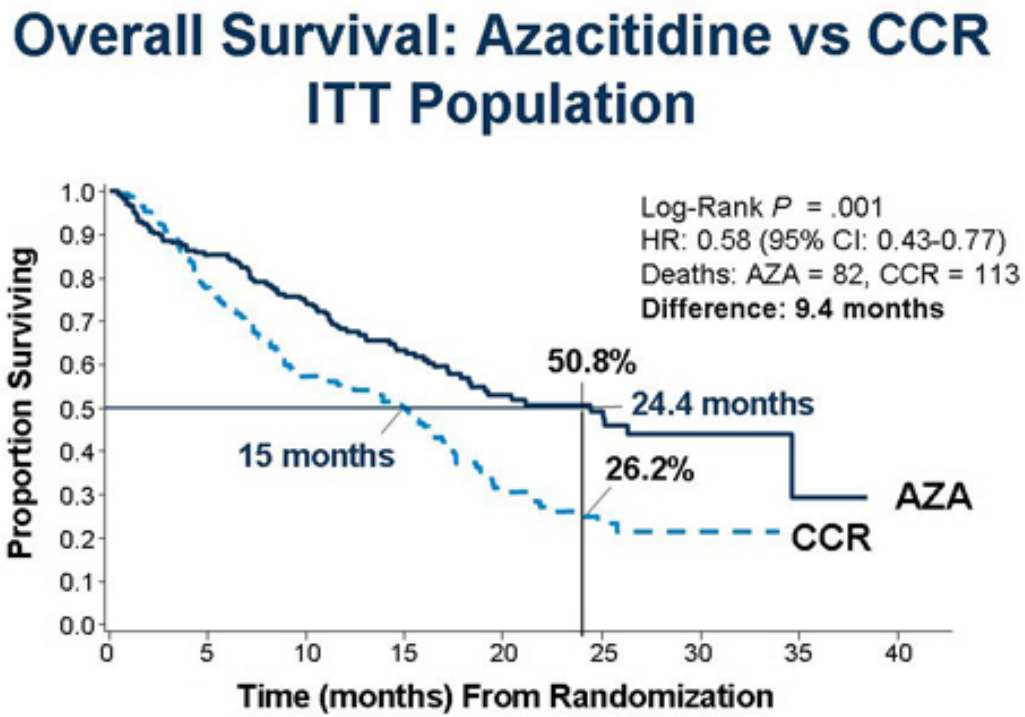
HIGHER RISK MDS

- Phase 3 magrolimab + azacitidine *vs* placebo + azacitidine
- Phase 3 venetoclax + azacitidine *vs* placebo + azacitidine

AZA-001: Phase 3 Azacitidine versus Conventional Care Regimens (Best Supportive Care, Low Dose Cytarabine and Intensive Chemotherapy) in Higher-risk MDS

	Azacitidine (n=179)	CCR (n=179)
Overall Response (CR+PR, %)	**29**	**12**
CR	17	8
PR	12	4
RBC-TI	45%	11%

Azacitidine was administered for a median of 9 cycles; 81% achieved a first response by 6 cycles & 90% achieved a first response by 9 cycles



Real World Data:

Overall survival 10-19 months with azacitidine

Fenaux et al. Lancet Oncol 2009; 10(3): 223-32

Phase 1b Trial: Magrolimab + Azacitidine in Untreated Higher Risk MDS

	Magrolimab + Azacitidine (N=95)
Age, y (range)	69 (28-91)
IPSS-R risk group, No. (%) Intermediate High Very high	 26 (27.4%) 49 (51.6%) 20 (21.1%)
Cytogenetics, No. (%) Favorable Intermediate Adverse Complex cytogenetics Unknown/missing	 12 (12.6%) 17 (17.9%) 59 (62.1%) 26 (27.45) 7 (7.4%)
Mutations at baseline, No. (%) *TP53* *IDH1/2* *FLT3* *NPM1*	 25 (26.3%) 5 (5.3%) 1 (1.1%) 1 (1.15)
Therapy-related MDS	21 (22.1%)

	Magrolimab + Azacitidine (N=95)
Complete remission (CR) CR in *TP53* mutated	31 (32.6%) 10/25 (40%)
Marrow CR	30 (31.6%)
SD with hematologic improvement (HI)	10 (10.5%)
Overall response	**71 (74.7%)**
Median duration of CR, mos (range)	11.1 (7.6-13.4)
Median time to CR, mos (range)	3.7 (1.7-7.2)
Median OS , mos Median OS in *TP53* mutated	**Not reached (16.3 mos to NR)** (after 17.1 months follow-up) 16.3 (10.8 to NR)

Sallman et al. J Clin Oncol 2023 Mar 8:JCO2201794. doi: 10.1200/JCO.22.01794. Online ahead of print

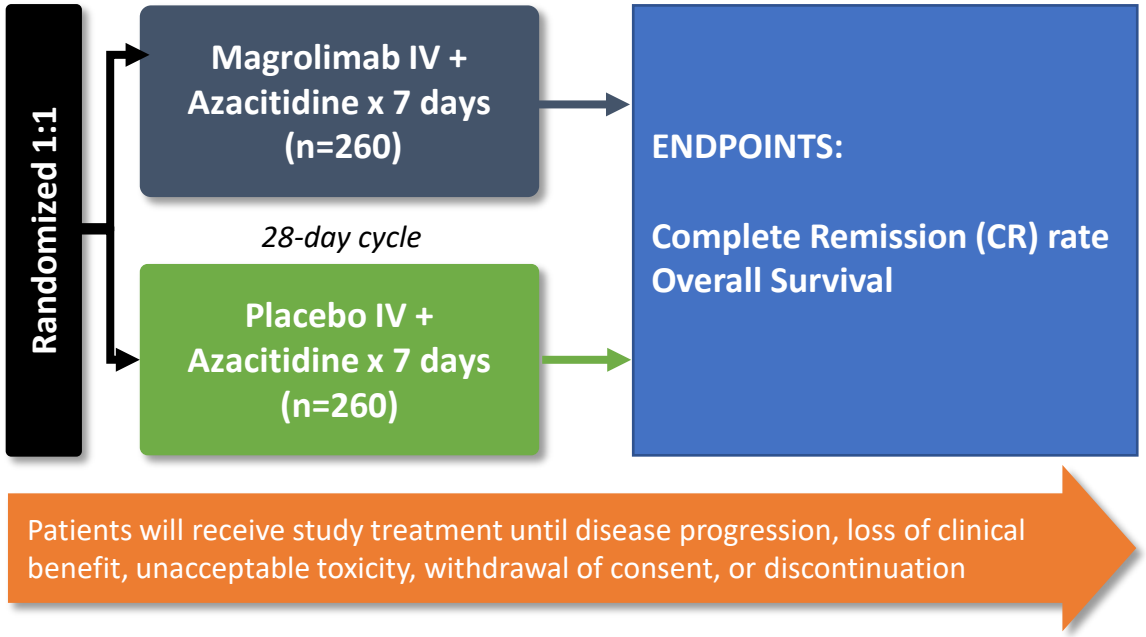
Phase 3 Magrolimab + Azacitidine *versus* Azacitidine + Placebo in Treatment-naïve Patients with Higher Risk MDS (ENHANCE)

KEY INCLUSION CRITERIA

N=520

- Age ≥ 18 years
- MDS
- IPSS-R Intermediate, High or Very high-risk
- EC0G Performance Status 0-2
- No prior treatment for IPSS-R Intermediate, High or Very high-risk MDS
- No prior therapy with CD47 or Signal-regulatory protein alpha (SIRPα)-targeting agents

STUDY DESIGN



Enrolment completed; Results pending

Phase 1b Trial: Venetoclax + Azacitidine in Untreated Higher Risk MDS

	Venetoclax + Azacitidine (N=57)
Age, y (range)	71 (36-85)
IPSS risk group, No. (%) Intermediate-2 High	57 (100%)
ECOG Performance Status 0-1 2	52 (91%) 5 (9%)

	Venetoclax + Azacitidine (N=57)
Complete remission (CR)	24 (42%)
Marrow CR Marrow CR + Hematologic improvement (HI)	20 (35%) 8 (40%)
Overall response	**44 (77%)**
Median duration of response, mos (range)	14.8 (12.9-NR)
Median OS , mos	**Not reached (16.2 mos to NR)** (after 13 months follow-up)

Garcia et al. Blood 2020; 136(Supplement 1): 55-57

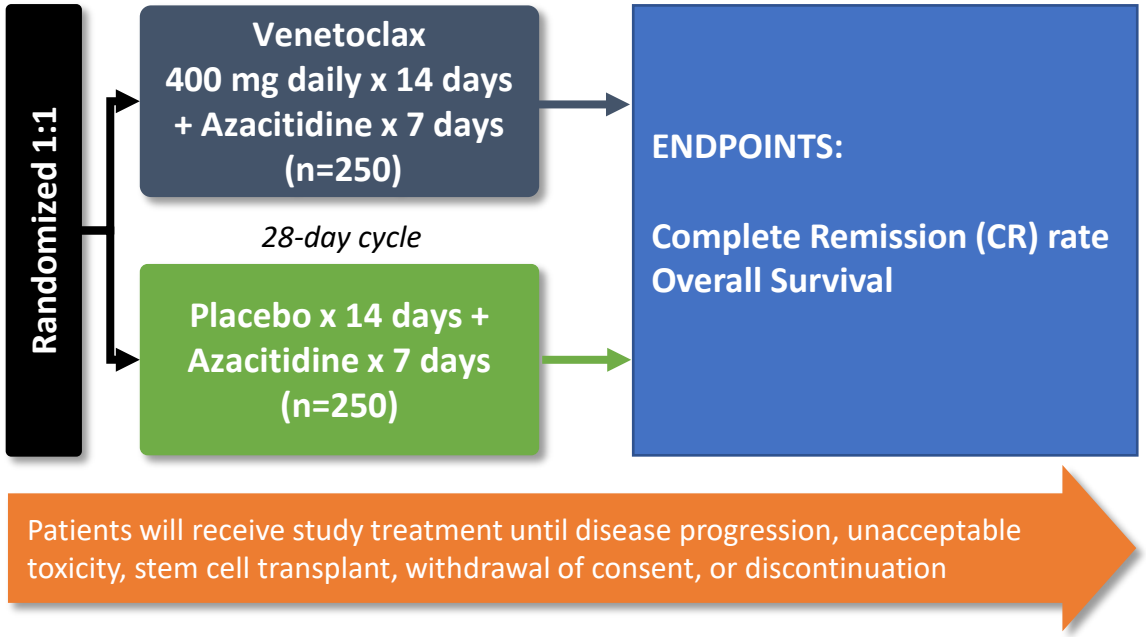
Phase 3 Venetoclax + Azacitidine versus Placebo + Azacitidine in Treatment-naïve Patients with Higher Risk MDS (VERONA)

KEY INCLUSION CRITERIA

N=500

- Age ≥ 18 years
- *De novo* MDS
- IPSS-R Intermediate, High or Very high-risk
- ECOG Performance Status 0-2
- No prior treatment with hypomethylating agents, venetoclax, disease modifying agents (Lenalidomide, ATGAM, CSA), chemotherapy or allogeneic stem cell transplant
- Not therapy-related MDS

STUDY DESIGN



Enrolment completed; Results pending

Conclusions

- New World Health Organization (WHO) 2022 and International Consensus Classification (ICC) 2022 for MDS
- New Molecular International Prognostic Scoring System (IPSS-M)
- Health Canada approval + Ontario Health funding:
  - Lusptercept – IPSS-R Very low, Low or Intermediate risk + *SF3B1* mutation &/or ≥ 15% ring sideroblasts
  - Decitabine/cedazuridine – IPSS Intermediate-1, Intermediate-2 and High risk
- Phase 3 studies:
  - Lower risk: Luspatercept frontline (positive study), Imetelstat relapsed/refractory ESA (positive study) & oral Azacitidine (under study)
  - Higher risk (awaiting results): Magrolimab + azacitidine & Venetoclax + azacitidine

Thank you!