1:30–2:15 PM

MDS

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THE 2nd ANNUAL HemOnc Pulse LIVE | AUSTIN 2025

MDS: Updates and Next Questions

Presenter

Uma Borate, MD, MSc

The Ohio State University

Updates and Next Questions in MDS

- Uma M Borate MD, MS
- Associate Professor,
- Division of Hematology
- Acute Leukemia Clinical Section head
- Acute Leukemia Clinical Research Disease Group Leader
- The James Cancer Hospital
- OSU-CCC, Columbus,OH

Agenda

Low risk MDS

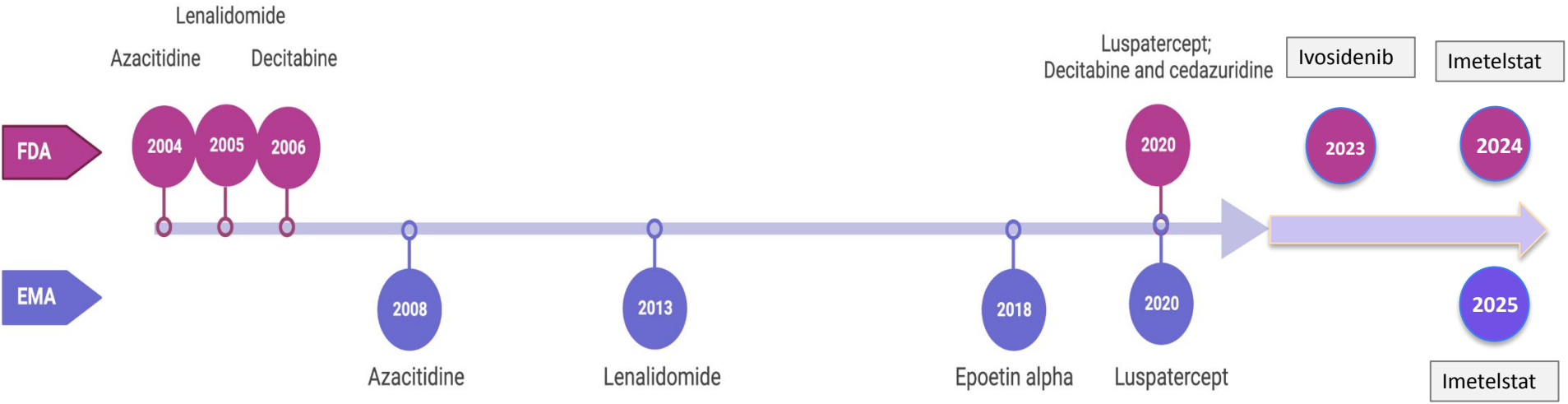
- Advances in low risk MDS

High risk MDS

- Advances in high risk MDS

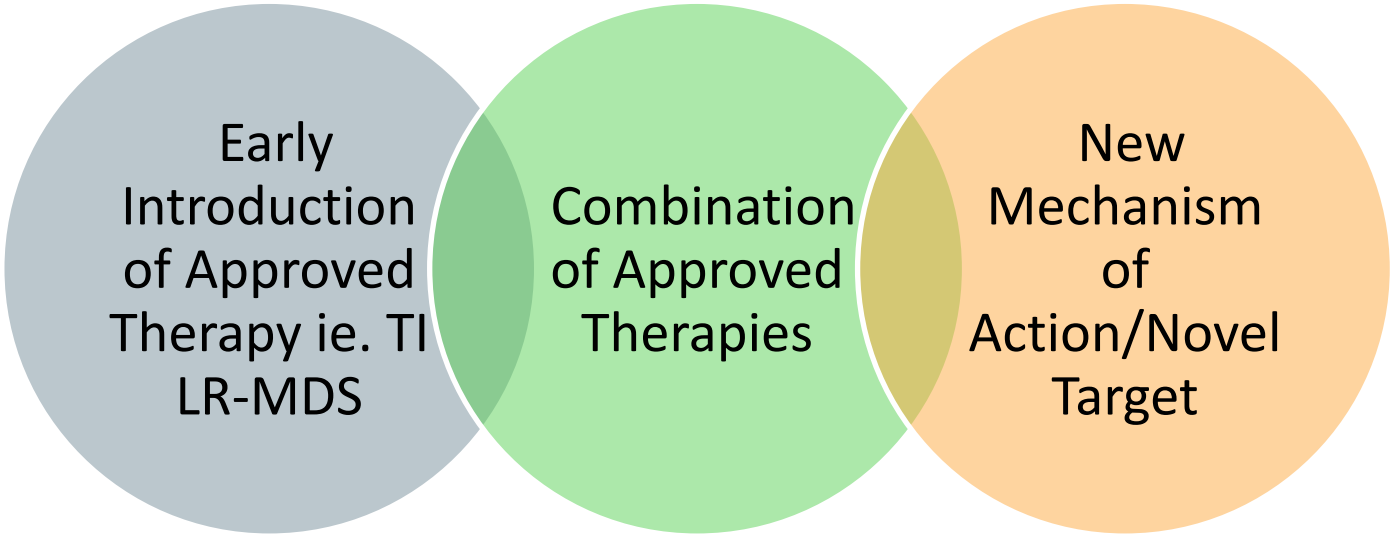
Next questions in MDS

U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) drug approvals for Myelodysplastic syndromes



Madanat Y, Xie Z, Zeidan A.. Expert Rev of Hematol. 2023

Main Themes



Slide courtsey of Dr. Yazan Madanat

LEN in TI LR-MDS

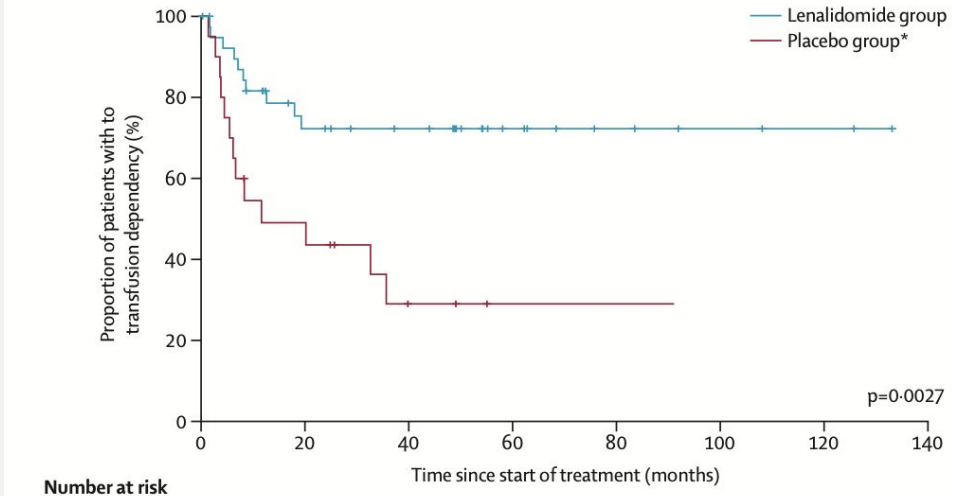
SintraRev Trial – Phase III Trial (**NCT01243476)**

- 22 sites in Europe,Between Feb, 2010 & Feb 2018
- N=61 (LEN=40; placebo=21).
- LEN 5 mg for 2 years for TI LR-Del(5q) Pts
- Primary endpoint: median time to TD

Results:

- Not reached (LEN) vs 11·6 months (PL) (p=0·0027).
- Cytopenias + skin rash – most common AE's.
- Complete cytogenetic response (28 [70%] of 40)
- Among baseline TP53-mutated cases, two (40%) of five patients achieved an erythroid response versus 20 (83%) of 24 patients with TP53 wild-type.
- SF3B1 co-mutated patients had shorter DOR

Limitations:
Did not assess QOL
Did not monitor for secondary malignancies

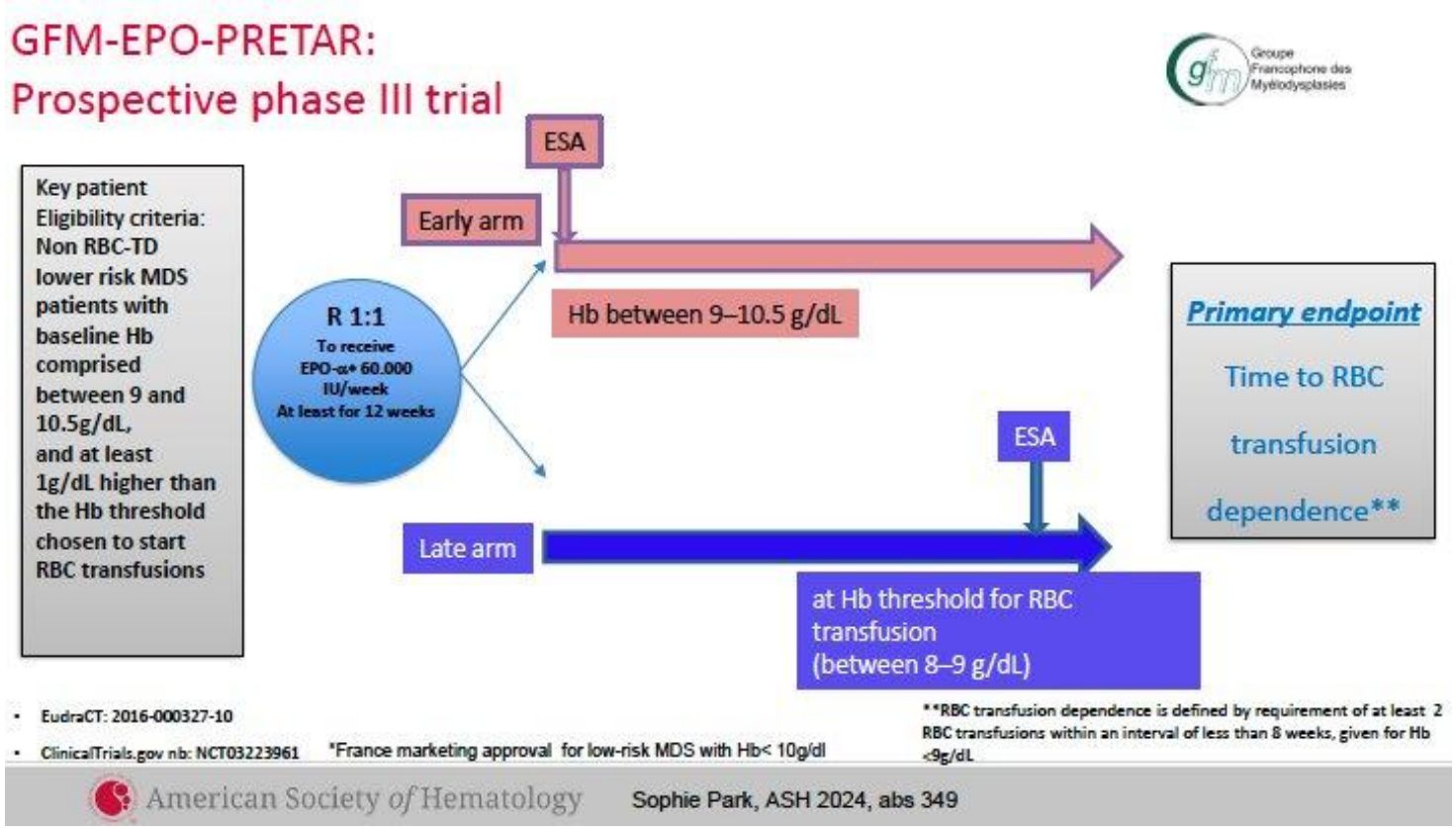


Number at risk (number censored)								
Lenalidomide group	40 (7)	23 (11)	19 (21)	9 (25)	5 (27)	3 (28)	2 (30)	0 (0)
Placebo group	20 (1)	9 (4)	3 (6)	1 (6)	1 (7)	0 (0)	0 (0)	0 (0)

Díez-Campelo et al. Lancet Haematol. 2024

Slide courtsey of Dr. Yazan Madanat

EPO-PRETAR



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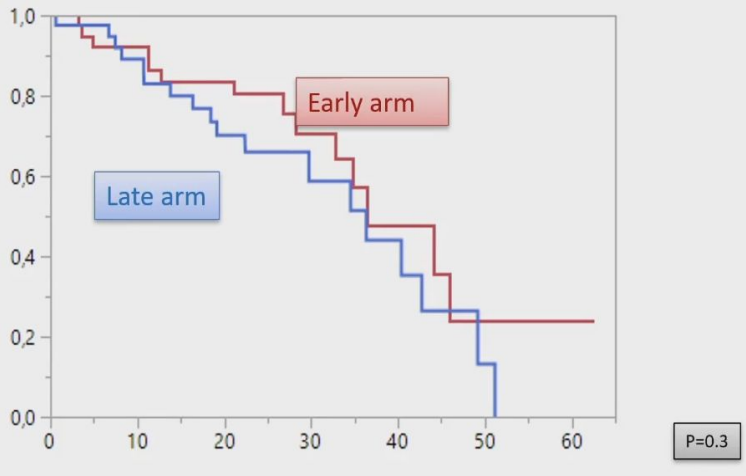
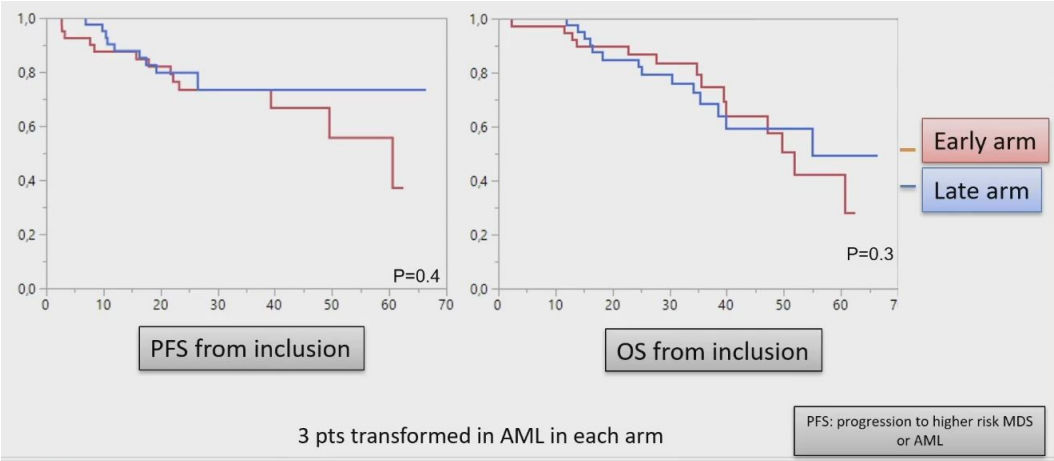
No difference in time to RBC-TD

Median time to RBC-TD of 36 months

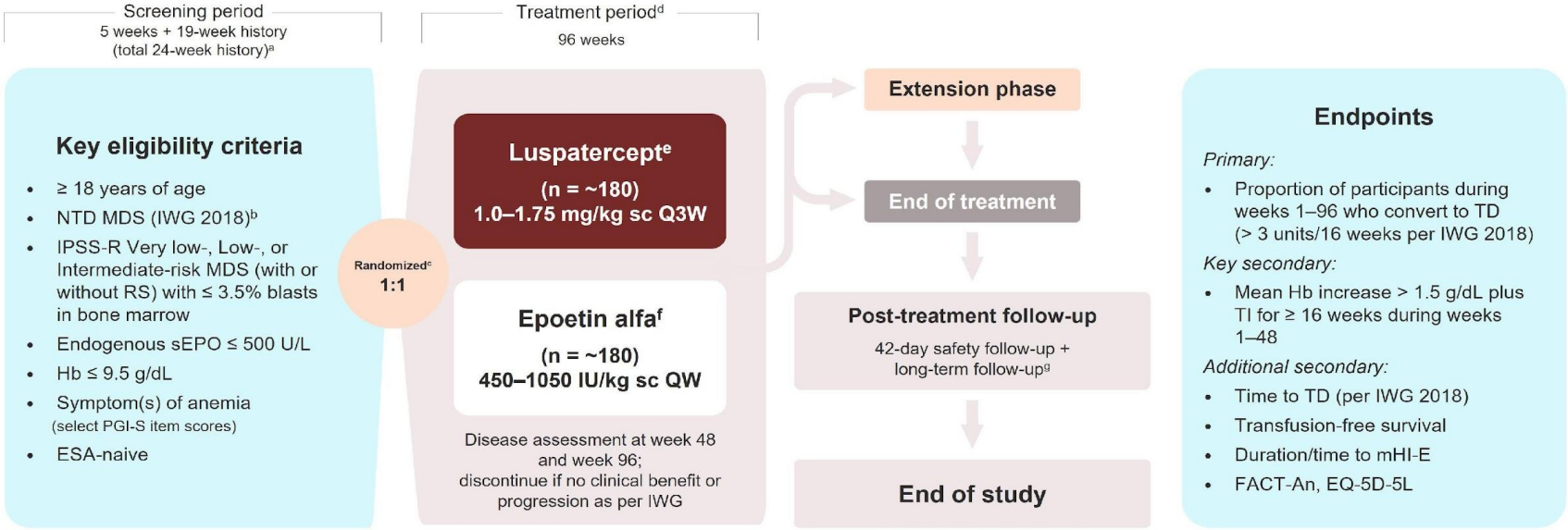


No significant difference in PFS and OS



Slide courtsey of Dr. Yazan Madanat

Figure. The ELEMENT-MDS study design



[a]RBC transfusion history must be available for ≥ 24 weeks; [b]Zero (0) RBC units over 16 weeks prior to randomization; 1–2 RBC units within the 16 weeks prior to enrollment are allowed provided transfusion was administered for an acute event/illness (ie, surgical procedure, bleeding, infection) or presence of comorbidity, and not for the treatment of low Hb (with or without symptoms) alone; [c]Stratified by baseline (1) sEPO level: 0-200 vs 200-500; (2) RS status (50% cap for RS negative); (3) IPSS-R Very low-, Low- vs Intermediate-risk; [d]Crossover between the treatment arms is not permitted during the study treatment period; [e]Starting dose 1.0 mg/kg, dose escalation up to 1.75 mg/kg to maintain Hb between 10–11.5 g/dL; [f]Starting dose = 450 IU/kg, dose escalation up to 1050 IU/kg (max 80,000 IU) to maintain Hb between 10–11.5 g/dL; [g]≥ 5 years post 1st dose of IP or 3 years from last dose (whichever occurs later) for AML progression, MDS treatment, OS. Abbreviations: AML, acute myeloid leukemia; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FACT-An, Functional Assessment of Cancer Therapy-Anemia; Hb, hemoglobin; IP, investigational product; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; MDS, myelodysplastic syndromes; mHI-E, modified hematologic improvement–erythroid response; NTD, non-transfusion-dependent; OS, overall survival; PGI-S, Patient Global Impression of Severity; QW, every week; Q3W, every 3 weeks; RBC, red blood cell; RS, ring sideroblasts; sc, subcutaneous; sEPO, serum erythropoietin; TD, transfusion dependent; TI, transfusion independent.

Theme 1 Conclusions: Treatment in TI LR-MDS

LEN

- YES: *Symptomatic patients without TP53 or SF3B1 mutated patients
- Use low dose, limit to 2 years

ESA

- No
- EPO-Pretar Trial

Luspa

- Await ELEMENT Trial Results
- Key – PRO Info

Slide courtesy of Dr. Yazan Madanat

L2 Study (Len-Luspa – Sekeres, ASH 2024)

Baseline Patient Characteristics (N=12)	Median, N or %
Age (Range)	69 (49-84)
IPSS-R: Low Int	8 (67%) 4 (33%)
Prior Tx: ESAs HMAs	6 (50%) 4 (33%)
NGS: SF3B1 DNMT3A, TET2, ASXL1, CALR, U2AF1, NRAS, IDH2, JAK2	3 (25%) 1 (8%) each
WHO: MDS-RS MDS-MLD	3 (25%) 4 (33%)
CBC (Range): HgB ANC PLT	8.3 g/dl (8.2-9.5) 1.28/L (.49-3.19) 247/L (97-510)
pRBC txf need/16w	4 (2-15)

Responses (N=10)	Median, N or %
Hematologic Improvement	5 (50%)
HI-erythroid RBC TI HI-platelet	4 (40%) 3 (30%) 1 (10%)
Prior Tx: ESAs HMAs	6 (50%) 4 (33%)
NGS among HI Pts: (N) SF3B1 TET2, U2AF1, IDH2, JAK2 No mutations	 1 1 1 2

Slide Courtesy: Mikkael Sekeres

Activity of luspatercept and ESAs combination for treatment of anemia in lower-risk myelodysplastic syndromes

Sample size 36 patinets

Overall response (n = 28)	**36 (10)**
Hgb increase >1.5 g/dL in NTD or Hgb increase >1.5 g/dL with RBC-TI in RBC-TD	18 (5/28)
RBC-TI without Hgb 1.5 g/dL increase	14 (4/28)
>50% reduction in RBC-TB	4 (1/28)
Response in NTD (n = 3)	
Hgb increase >1.5 g/dL	33 (1/3)
Response in LTB (n = 13)	**38 (5/13)**
Hgb increase >1.5 g/dL and RBC-TI	15 (2/13)
RBC-TI without Hgb 1.5 g/dL increase	23 (3/13)
>50% reduction in RBC-TB	0
Response in HTB (n = 12)	**33 (4/12)**
Hgb increase >1.5 g/dL and RBC-TI	17 (2/12)
RBC-TI without Hgb 1.5 g/dL increase	8 (1/12)
>50% reduction in RBC-TB	8 (1/12)

Predictors of response included

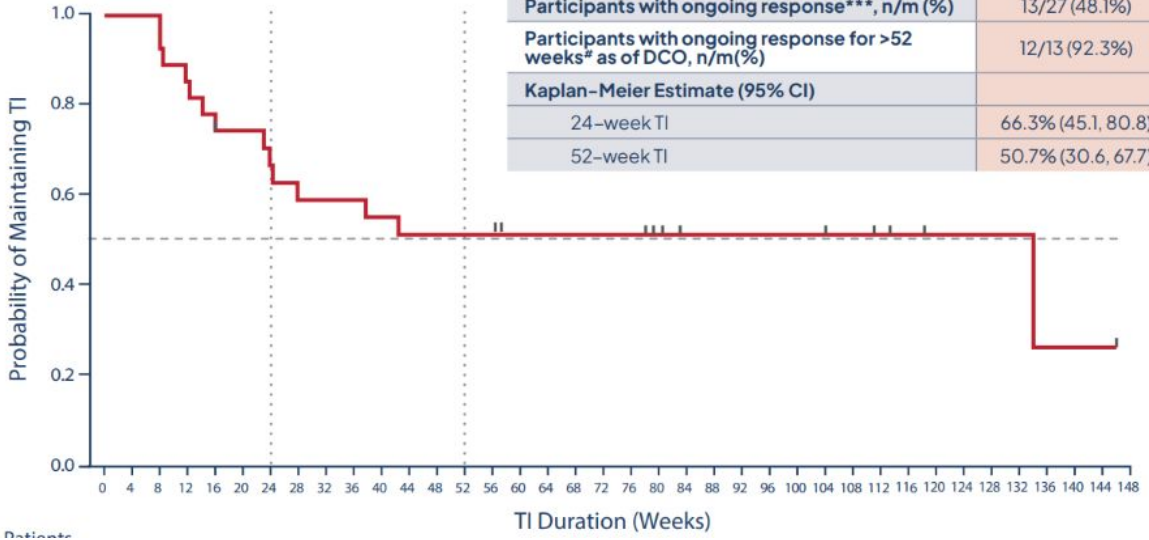
- previous response to luspatercept monotherapy,
- endogenous serum EPO levels
- SF3B1 mutation,
- lower RBC TB and
- being HMA/Len treatment naive

Elritercept (KER-050)

Durable TI Responses Observed With Elritercept Treatment

Longest TI Interval in $mITT_{24}$ Participants
Who Achieved TI ≥ 8 Weeks from Baseline Through Week 24*

Duration of Transfusion Independence (TI)	
Median** (95% CI), weeks	134.1 (23.0, NE)
Participants with ongoing response***, n/m (%)	13/27 (48.1%)
Participants with ongoing response for >52 weeks# as of DCO, n/m(%)	12/13 (92.3%)
Kaplan–Meier Estimate (95% CI)	
24-week TI	66.3% (45.1, 80.8)
52-week TI	50.7% (30.6, 67.7)

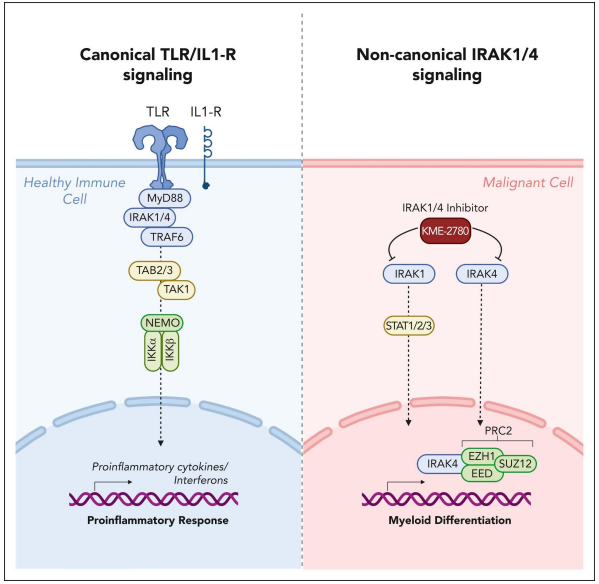


Slide courtsey of Dr. Yazan Madanat

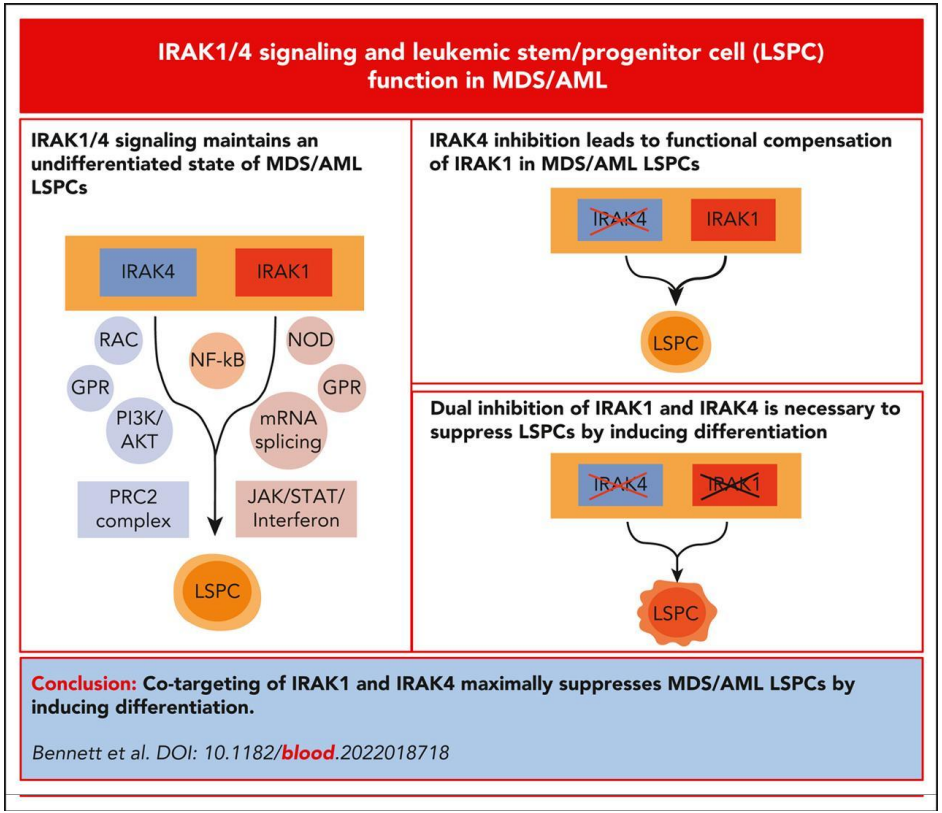
Giagounidis et all. ASH 2024

Targeting Inflammatory pathway in MDS

- MDS and AML exhibit extensive dysregulation of immune and inflammatory pathways and have many genetic alterations affecting Toll-like receptor (TLR) and interleukin 1 receptor (IL-1R) pathways.
- These pathways converge at IRAK1/4, essential components of the innate immune response



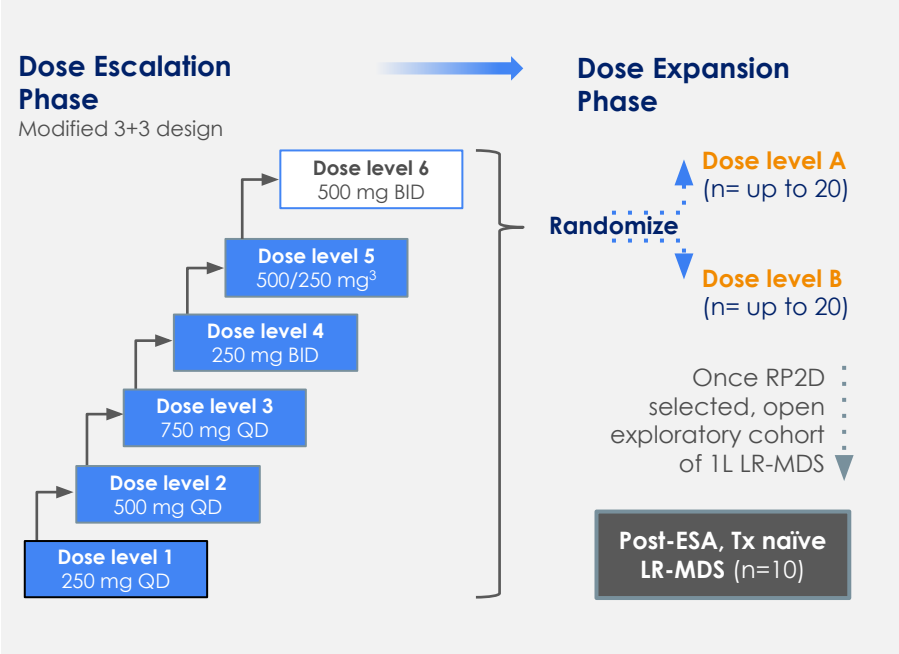
Bennett al. 2023



Slide courtesy of Dr. Yazan Madanat

Phase 1b Study in Relapsed/Refractory Lower-Risk MDS

Open-label, multicenter study to evaluate the safety, tolerability, PK and preliminary activity of R289 in patients with LR-MDS (NCT05308264)



Slide courtesy of Dr. Yazan Madanat

Key Eligibility Criteria:

- R/R LR-MDS or inadequate response to prior therapies. Del(5q): R/R to lenalidomide
- Symptomatic anemia (Hb ≤9.0 g/dL) or TD (≥2u RBCs/16wks)

Assessments:

- Hematologic responses [TI and HI-E] per IWG 2018 criteria and other responses per IWG 2006 criteria, from 8 weeks

Primary Endpoints:

- Incidence of adverse events and dose-limiting toxicities

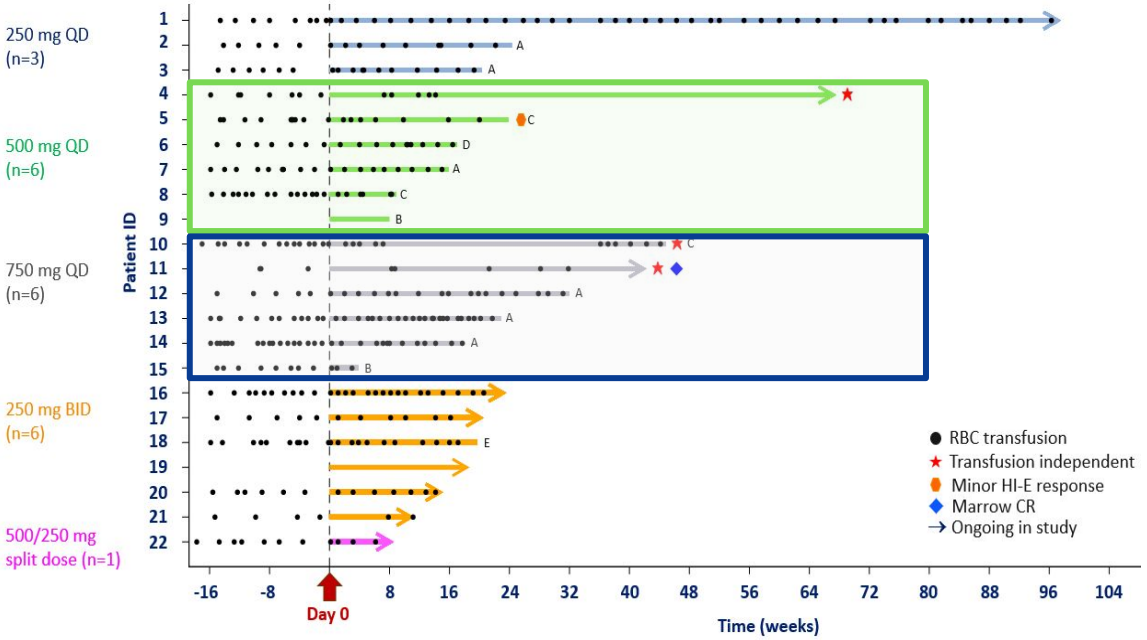
Secondary Endpoints:

- Transfusion independencePatient-reported outcomes (FACIT-Fatigue scale)
  , hematologic improvement, response rates
  - PK / PD
-

Efficacy: Hematologic Responses

- 18 patients were evaluable for efficacy
- 3 patients achieved RBC-TI ≥8 wks:
  1 at 500 mg QD and 2 at 750 mg QD
- 2 patients achieved RBC-TI ≥ 24 wks
- Median duration of RBC-TI: 29 wks (range 12.7-51.9 wks)
- 1 HTB patient at 500 mg QD had a minor HI-E response (64% reduction in RBCs compared to BL)
- At doses ≥500 mg QD, R835 plasma concentrations reached or exceeded those correlating with 50% or 90% LPS-induced cytokine inhibition previously observed in HVs
- At 500 & 750 mg QD doses, RBC-TI/HI-E responses occurred in 4/10 (40%) of evaluable TD patients

RBC Transfusion Frequency by Dose Level



Garcia-Manero G et al. Blood 2024; 144 (Supplement 1): 4595

Reasons for discontinuation - A: no clinical benefit (6); B: adverse event [2 - Pt 9: hyperuricemia (not related); Pt 15: G3 AST/G4 ALT increase (related)]; C: Investigator decision (3); D: progressive disease (1); E: patient withdrew consent (1)

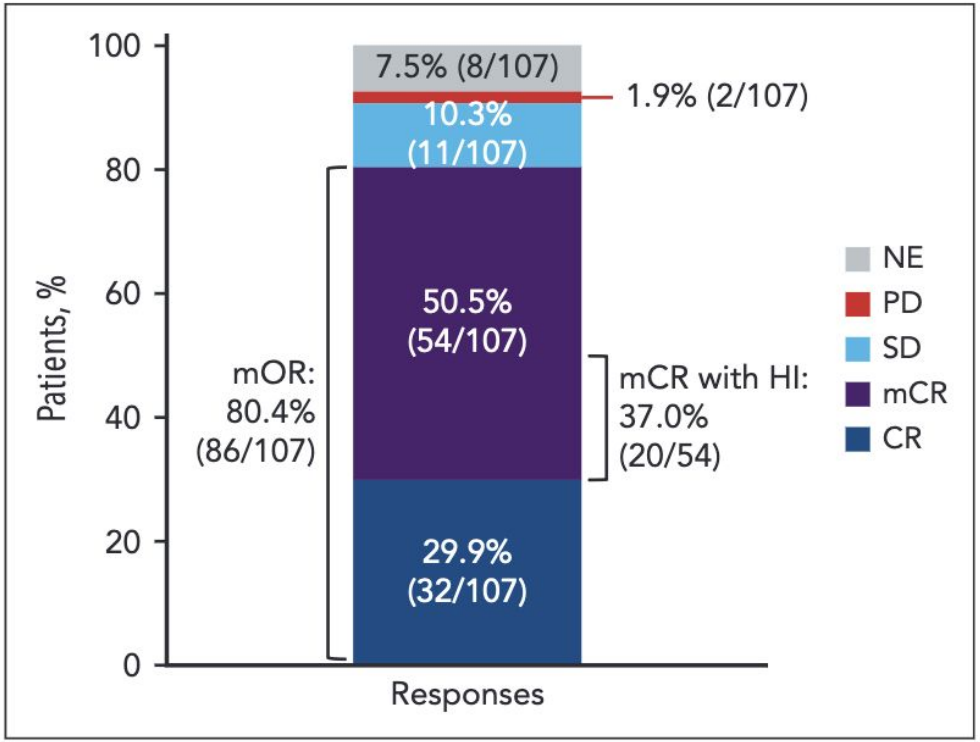
Agenda

High risk MDS

- Advances in high risk MDS

Next questions in MDS

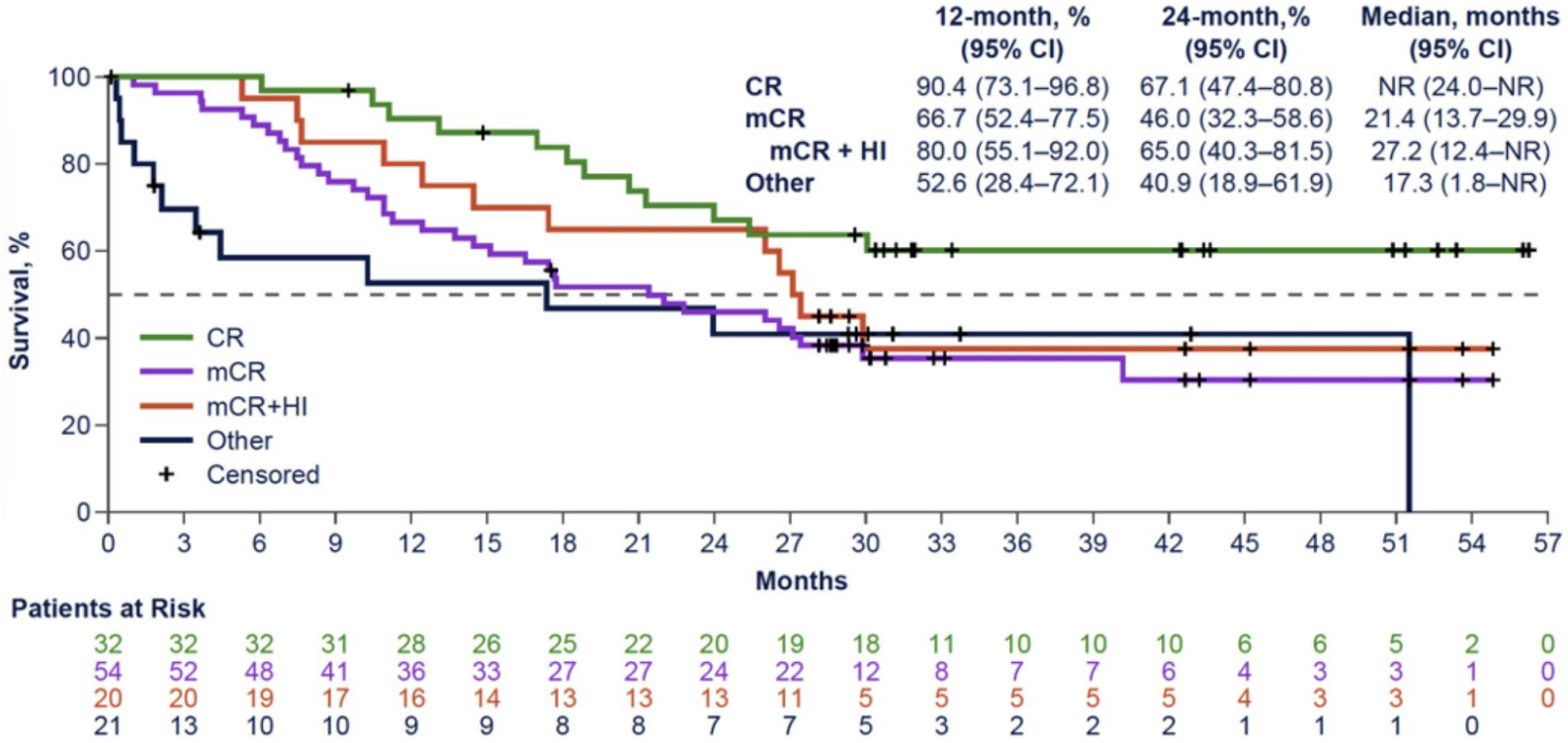
Combination azacitidine and venetoclax in HR-MDS is active and durable: final results of a multi-site phase 1b study



- Protocol-defined objective response: 80.4%
- IWG 2023 not yet applied
- Clinically meaningful response per IWG 2023: at least 49% (CR 29.9% + HI 18.7%)

Garcia JS et al., *Blood* (2025) 145 (11): 1126–1135.

Combination azacitidine and venetoclax in HR-MDS has encouraging survival

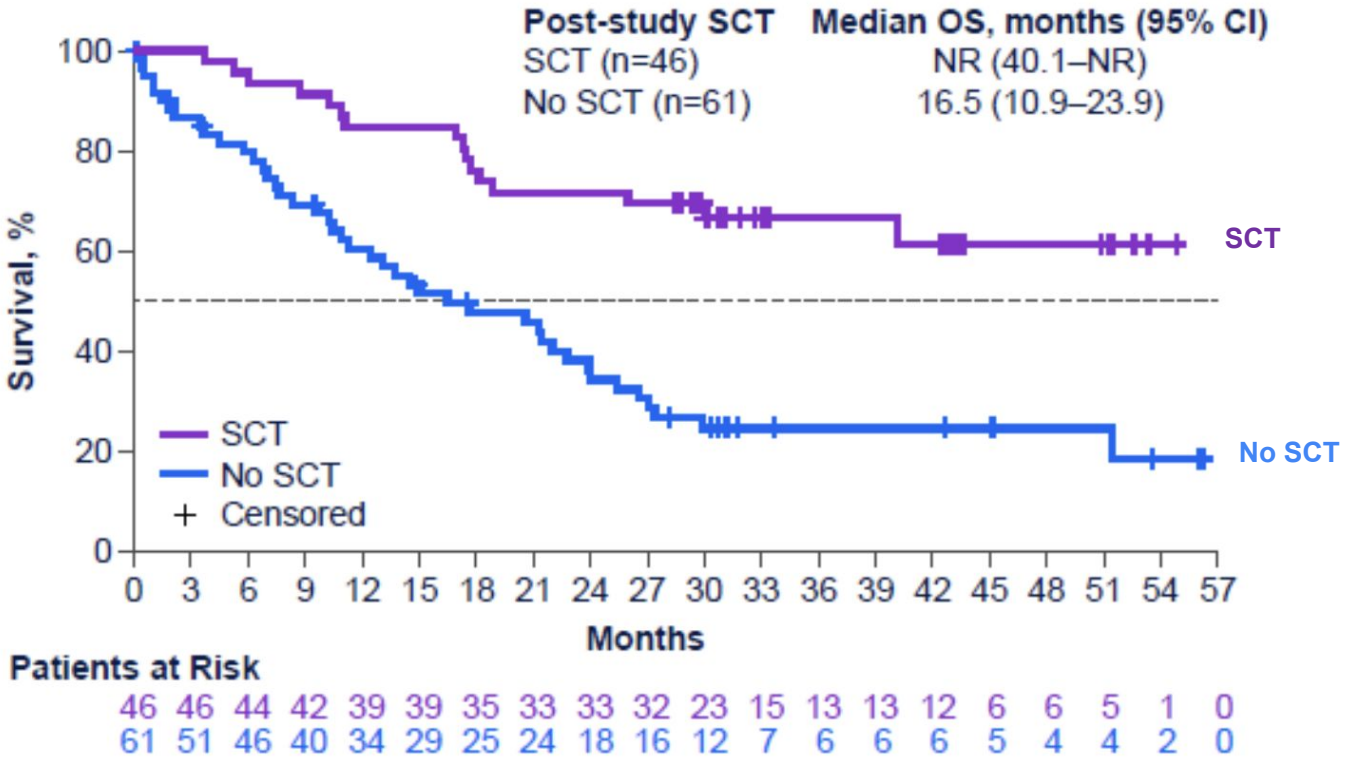


Median follow-up was 31.9 months (range, 0.1-56.2 months)

Garcia JS et al., *Blood* (2025) 145 (11): 1126–1135.

Waiting for VERONA

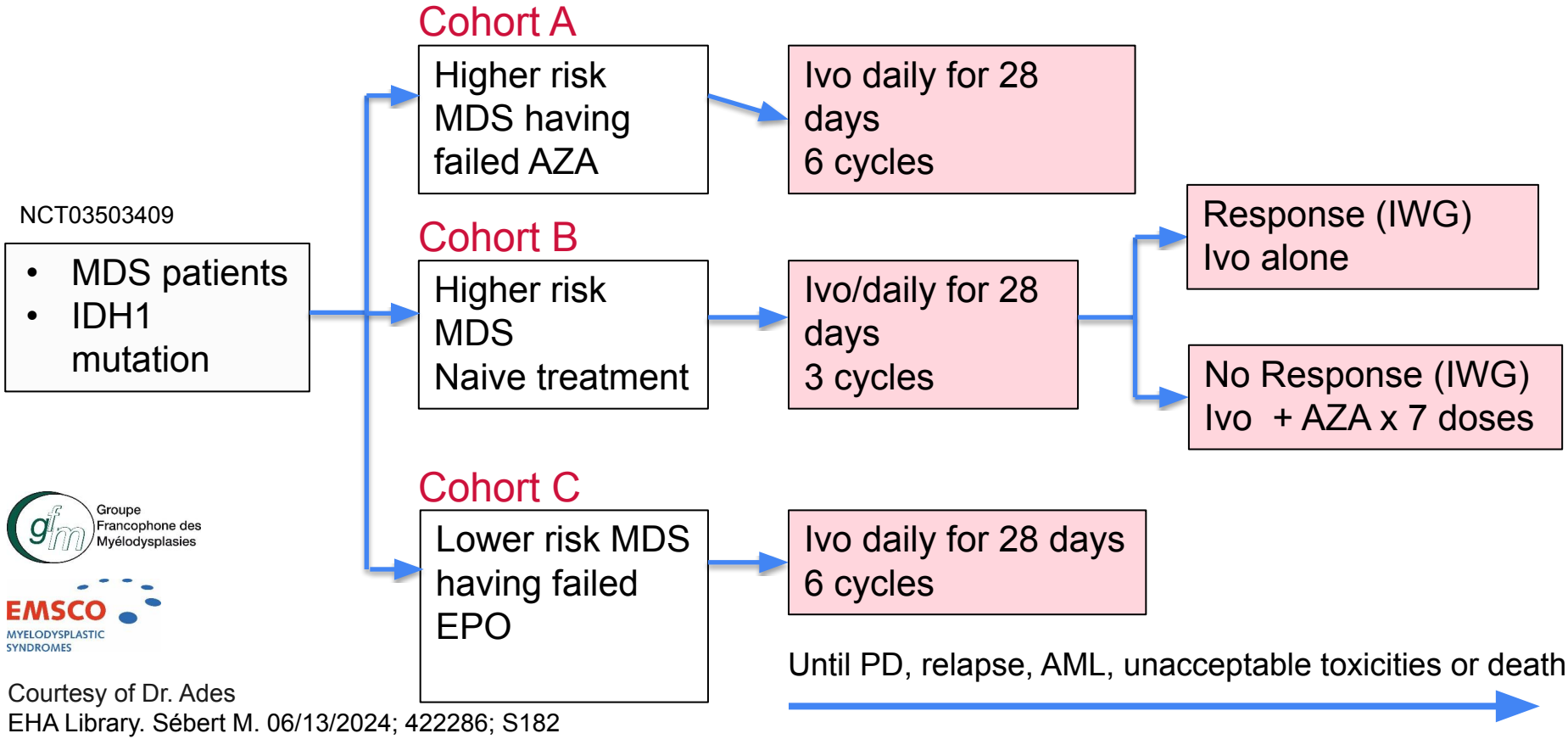
Aza/ven (14d) as a bridge to transplant results in impressive overall survival



Garcia JS et al., *Blood* (2025) 145 (11): 1126–1135.

IDH mutated MDS

Ivosidenib in IDH1mut MDS (IDIOME): a phase 2 GFM/EMSCO study

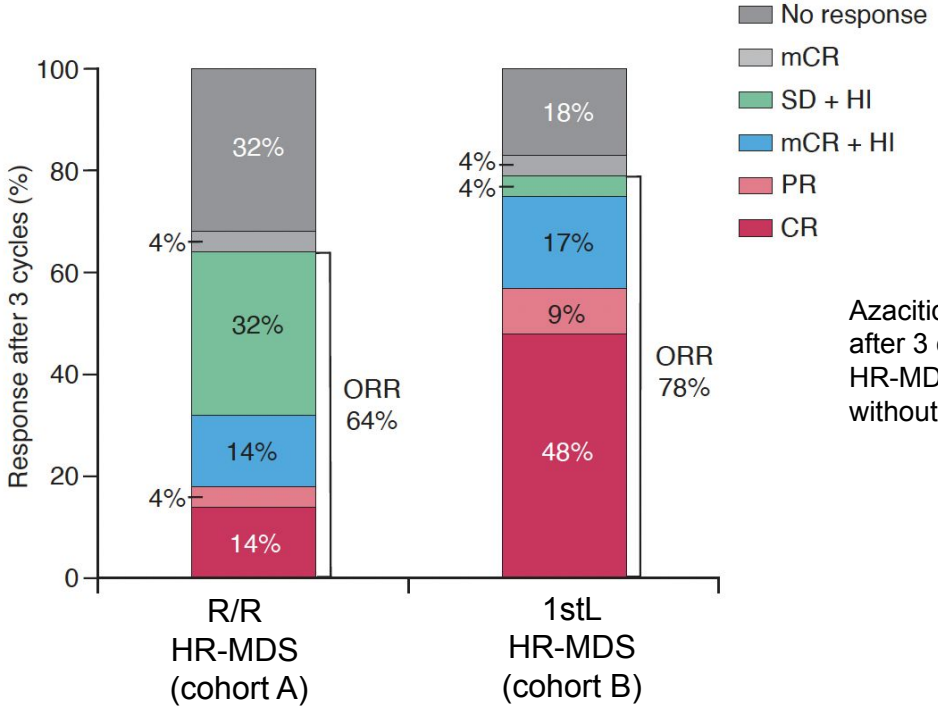


Groupe Francophone des Myélodysplasies

EMSCO MYELODYSPLASTIC SYNDROMES

Courtesy of Dr. Ades
EHA Library. Sébert M. 06/13/2024; 422286; S182

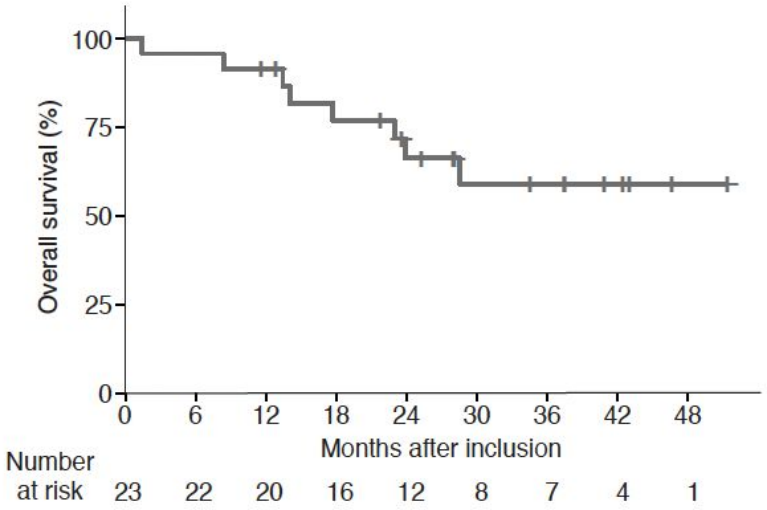
IDIOME study: overall response rate (Cohorts A and B)



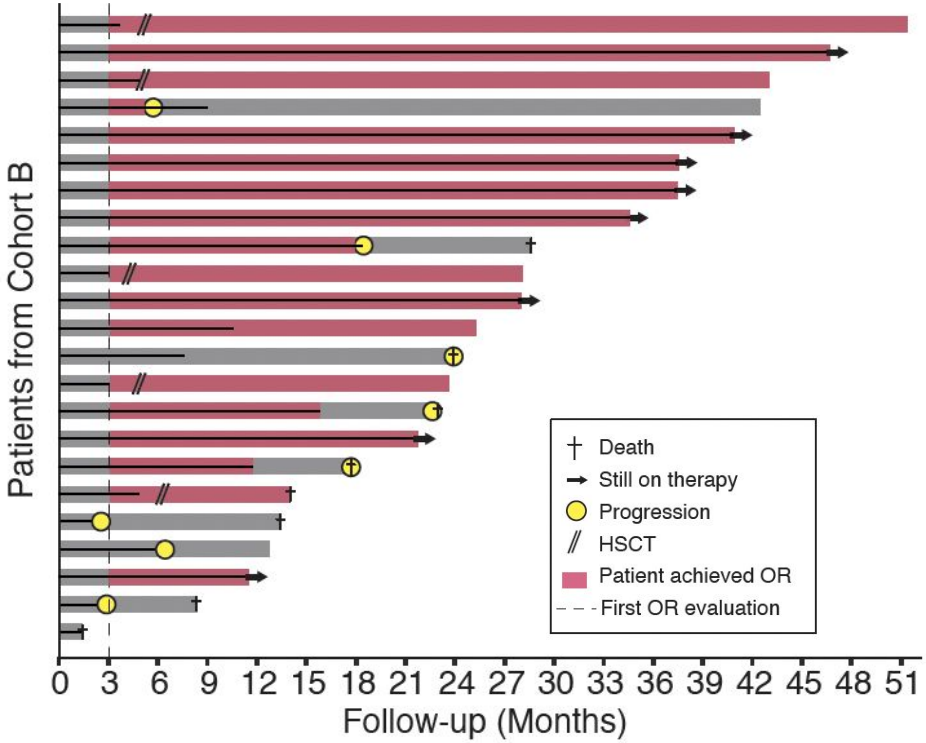
Azacitidine was added to Ivosidenib after 3 cycles in 3 patients (1stL HR-MDS),
without additional response

Courtesy of Dr. Ades
EHA Library. Sébert M. 06/13/2024; 422286; S182

IDIOME study: Duration of responses and survival (Cohort B, 1st line HR-MDS)

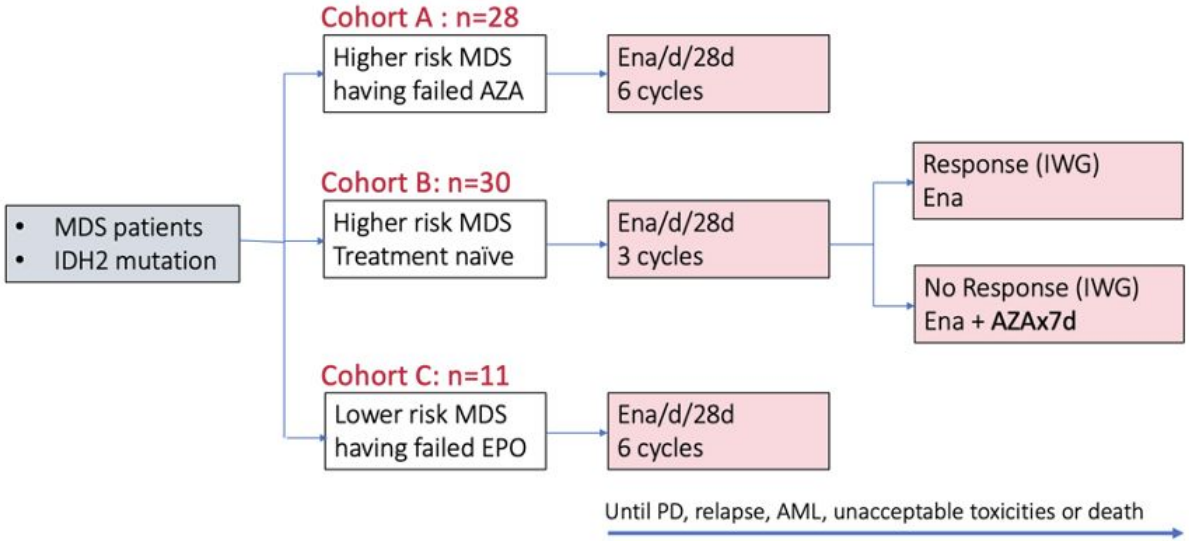


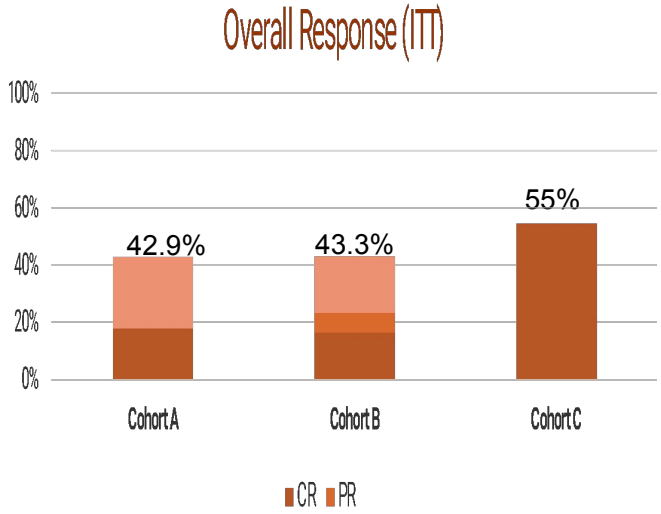
- Median FU: 25.2 months
- Median OS and DOR were not reached
- 12-month OS rate was 91.3% (95%CI, 80.5-100)
- 5 patients (22%) bridged to transplant
- 8 patients progressed
- 8 patients still on therapy



Courtesy of Dr. Ades
EHA Library. Sébert M. 06/13/2024; 422286; S182

Enasidenib in IDH2mut MDS (IDEAL): a phase 2 GFM/EMSCO study





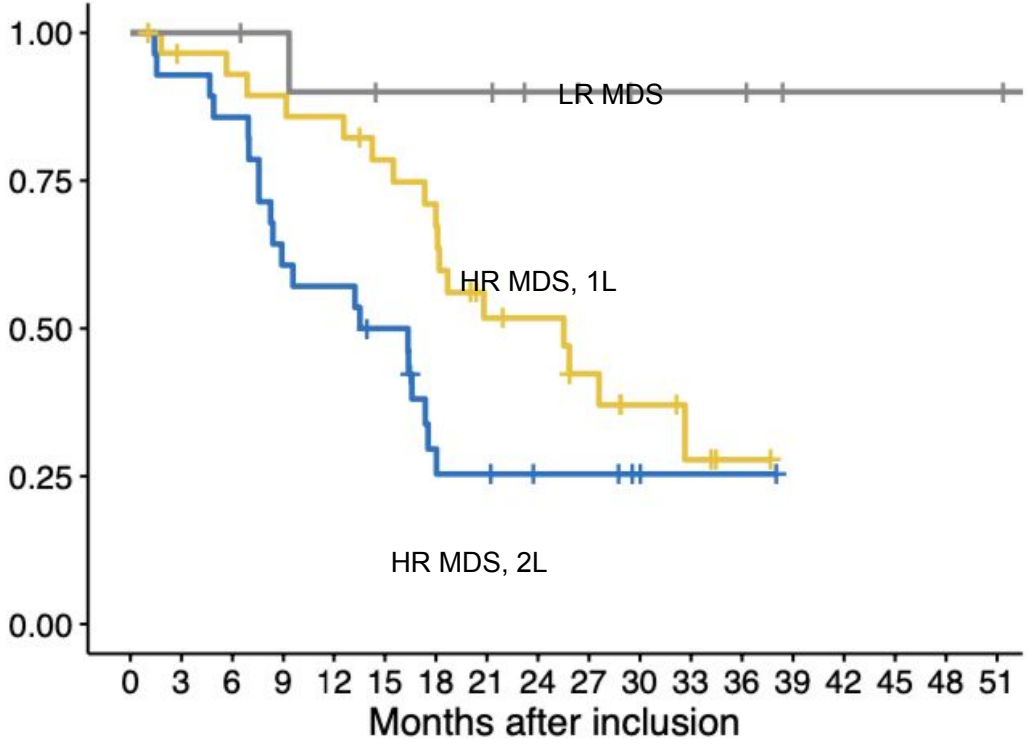
- **Population:** N=69 patients; Median age 76 years; 36% female; IPSS-R high/very high (65%); VAF 36.6%
- **Safety**: Differentiation syndrome 5/58 (8.6%)

Courtesy of Dr. Ades

Sebert M et al., Blood (2024) 144 (Supplement 1): 1839.

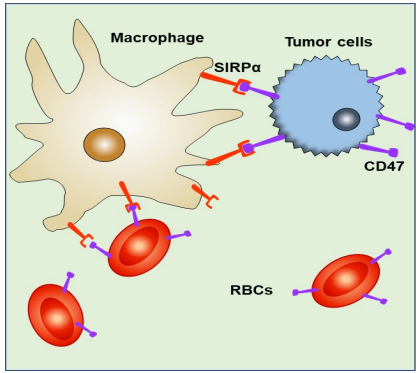
IDEAL Study: Enasidenib in IDH2mut MDS has encouraging survival

- Cohort A –14.9 months
- Cohort B –25.5 months
- Cohort C – NR

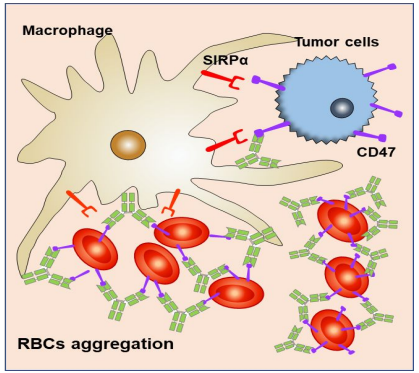


Courtesy of Dr. Ades
Sebert M et al., Blood (2024) 144 (Supplement 1)

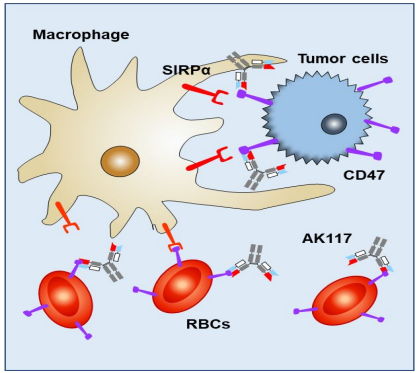
MOA and Safety Aspects of Anti-CD47 Antibody



- CD47 is highly expressed by various types of tumors and often associated with poor prognosis
- CD47 is also ubiquitously expressed by non-malignant cells of the hematopoietic system, including normal red blood cells



- Anti-CD47 antibodies enhance the phagocytosis of tumor cells by macrophages.
- **The first generation of anti-CD47 antibody** causes aggregation of red blood cells and show **severe on-target side effects such as anemia**



- **AK117** was designed to achieve a differentiated profile from first generation CD47 antibody such as magrolimab
- AK117 showed **no hemagglutination** and minimal anemia in patients in clinical trials
- **-does not need priming doses**

MOA: Mechanism of Action

Study Status

Study Design: A randomized, placebo-controlled, global phase 2 study of AK117/placebo in combination with azacitidine in patients with newly diagnosed HR-MDS

Newly diagnosed HR-MDS
- •ECOG: 0-2
- •IPSS-R: ≥3.5

Randomization:
- 1:1:1

Stratification factor:
- IPSS-R: ≤ 4.5 vs ＞4.5-6 vs ＞6

Arm A:
AK117 30mg/kg Q2W + azacitidine 75 mg/m^2
N=30

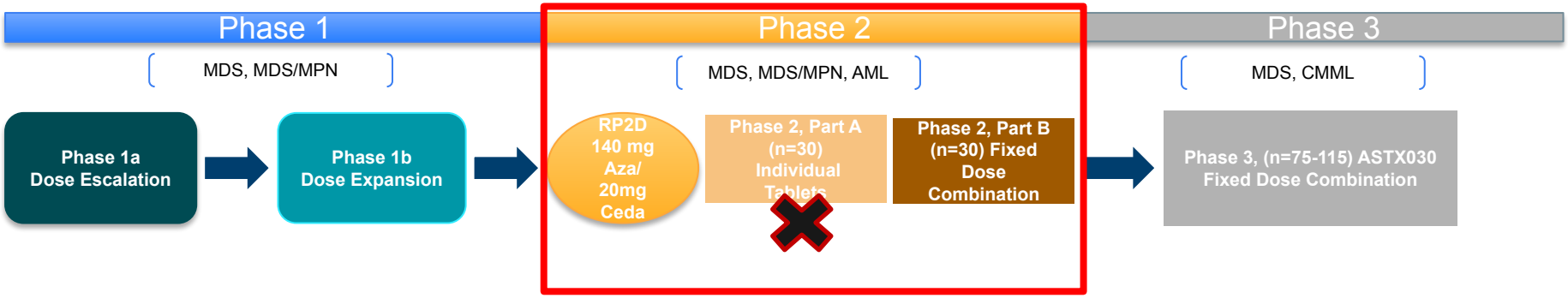
Arm B:
AK117 20mg/kg Q2W + azacitidine 75 mg/m^2
N=30

Arm C:
Placebo Q2W + azacitidine 75 mg/m^2
N=30

Overall Study Progress:

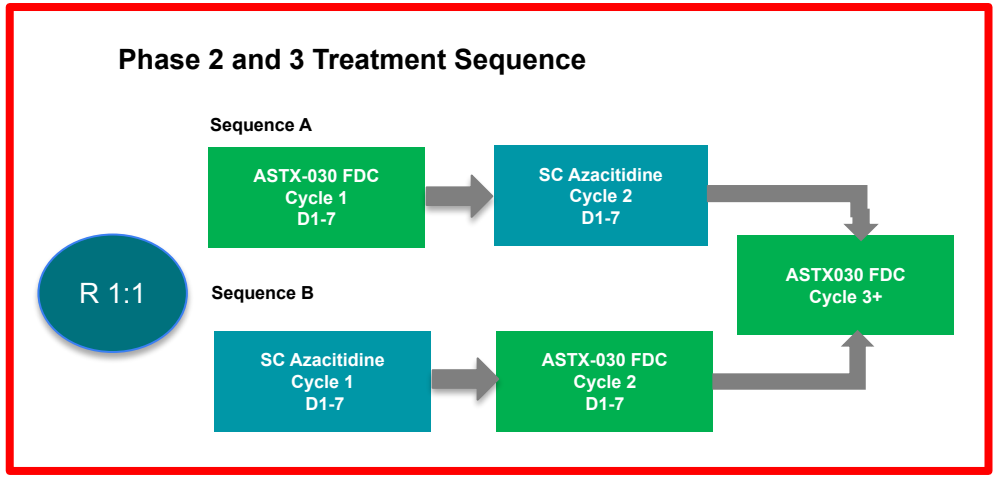
- **Completed enrollment of 45 patients in China**
- **Completed Enrollment of 45 Subjects in US**

ASTX030-01: Study Design Phase 1-3, Monotherapy



ASTX030-01 Study Design:
A Multi-phase, Dose-Escalation followed by an Open-label, Randomized, Crossover Study of Oral ASTX030 (Cedazuridine and Azacitidine Given in Combination) Versus Subcutaneous Azacitidine in Subjects with MDS, MDS/MPN including CMML, or AML

Primary Endpoint:
Total cycle area under the curve $(AUC)_{0\text{-}24}$ exposures. Ratio of azacitidine total cycle $AUC_{0\text{-}24}$ exposures after oral ASTX030 over SC azacitidine



ASTX030-01: Results

PK data for the DR azacitidine formulation

Cohort	Azacitidine dose, mg	Cedazuridine dose, mg	Bioavailability, F	Oral/SC AUC, %
3 (n=7)	60	100	3.77	129
4 (n=6)	60	60	2.44	86
5 (n=7)	60	40	1.78	58
6 (n=6)	100	20	~1.0	73[a]
7 and 104 (n=14)	136	20	~1.0	100 and 91[b]
103 (n=14)	144	20	~1.0	111

[a]Body-weight adjusted ratio for representative population range.
[b]Excluded one patient with an atypical (low and incomplete) SC profile.

- The DR azacitidine formulation allowed for an optimized interaction with cedazuridine, with ~100% azacitidine bioavailability with cedazuridine 20 mg
- Two dose combinations were evaluated in the phase 1b (dose expansion) cohorts: 136/20 and 144/20 mg azacitidine/cedazuridine

140/20 mg azacitidine/cedazuridine was selected as the RP2D

AUC, area under the concentration-time curve; DR, delayed-release capsule; PK, pharmacokinetic; RP2D, recommended phase 2 dose; SC, subcutaneous.

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ASTX030-01 Phase 2: Results

- Phase-2 PK results **confirm the 140/20mg AZA+CED dose** combination
- BSA-based dosing is needed to assure all patients achieve on average SC-AZA-like AUC exposures regardless of body size

Phase 2 PK Population	N	GMR (90% CI)	Intra-CV
Total Population	29	0.913 (0.78 - 1.07)	39%
Intermediate BSA 1.55 to 2.15 m^2	15	0.980 (0.85 - 1.13)	24%
High BSA $\geq$2.15 m^2	12	0.700 (0.55 - 0.89)	37%
Low BSA $\leq$ 1.55 m^2	2	N/A due to small n	

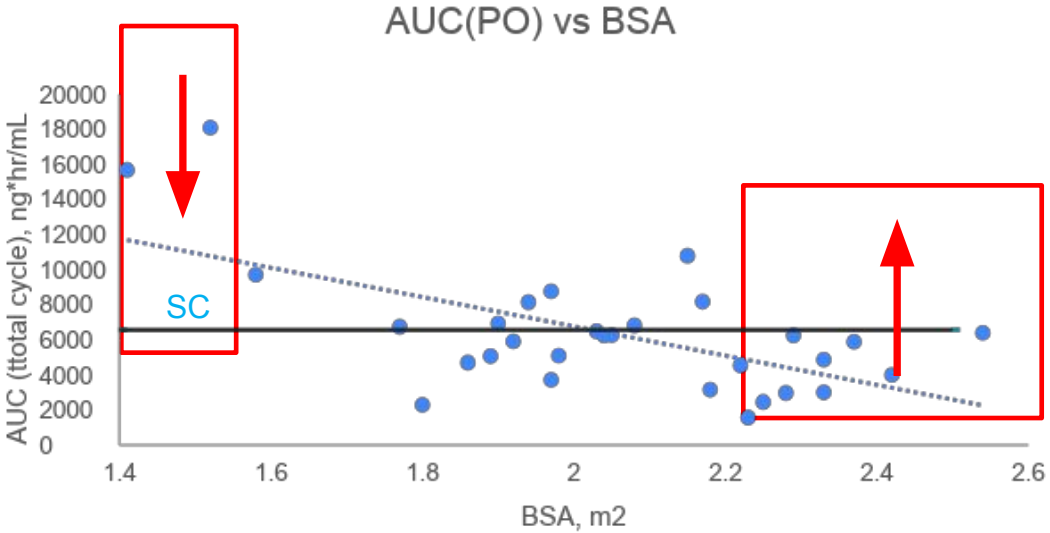
- BSA-based dosing will reduce both intra-and inter-subject variability and will assure point estimate for GMR closer to 1.0 with 90% CI within 0.80-1.25 in Phase-3

Recommendation for Dosing by BSA

105mg AZA / 20mg CED
(BSA ≤ 1.55 m^2)

140mg AZA / 20mg CED
(BSA 1.55-2.15 m^2)

175mg AZA / 20mg CED
(BSA ≥ 2.15 m^2)

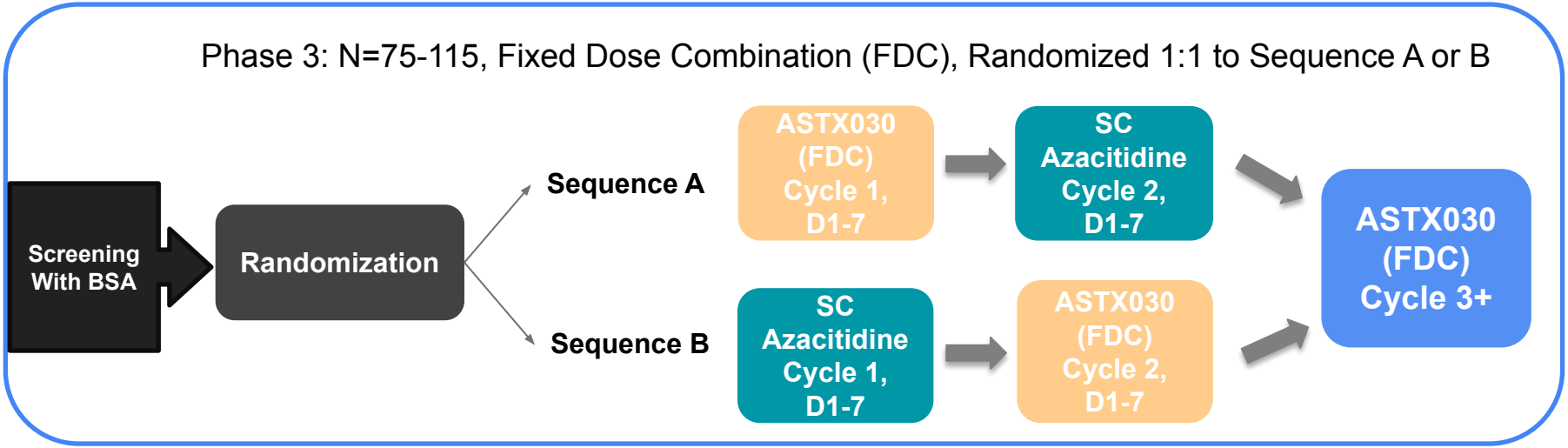


- BSA-based dosing will reduce variability and dampen the body-size effect on AUC exposures

Intra-patient **CV = 39%** (Phase 2); expected lower if dosed by BSA

Intra-patient CV for ASTX727 was **~32%**

ASTX030-01 Study Design and Objectives: Phase 3 Monotherapy



Phase 3	
Primary Objectives	**Endpoint**
Establish azacitidine AUC equivalence (90% CI 0.8, 1.25) between the final selected dose of ASTX030 from Phase 2 using FDC and SC azacitidine at 75 mg/m^2/day	Ratio of azacitidine total cycle $AUC_{0\text{-}24}$ exposures after oral ASTX030 over SC azacitidine at 75 mg/m^2/day

Summary of HR-MDS and future directions

- Lets just have one new therapy approved ……..
- Awaiting VERONA
- Phase 3 study in IDH1 mutated MDS just launched
- Oral azacitidine being evaluated in HR-MDS
- We need ‘smarter’ trials and better drugs in HR-MDS

PANEL DISCUSSION

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THANK YOU