

What is to come in low and high risk MDS?

Rami komrokji, MD

Professor of Oncologic Sciences

Vice Chair, Department of Malignant Hematology

H Lee Moffitt Cancer Center

Tampa, Florida

Goal of therapy in LR-MDS is Restoring hematopoiesis namely erythropoiesis in majority of patients

- Majority of LR-MDS pts do not progress to HR-MDS/AML (70%).
- Anemia and RBC-TD are the hallmark of the disease which are associated with worse outcomes.
- RBC-TI is associated with better overall survival.
- We should think of LR-MDS as several group of diseases not one entity as the biology of the disease is different as well as the mechanism of anemia.

Treatment of LR-MDS

Targeting the clone

- **Eradication of the MDS clone restoring normal hematopoiesis ?**
 - Lenalidomide in del5q
 - Telomerase inhibitors?
 - IDH- inhibitors
 - Spliceosome inhibitors
 - Immune based approach: Antibody, ADC, bispecific AB, CART
- **Differentiating the MDS clone to adequate hematopoiesis?**
 - ESA
 - Luspatercept
 - HMA
 - KER-05

Targeting inflammation

- Canakinumab
- NLRP
- IRAK

Targeting R/R *IDH1/IDH2*^{mut} MDS with ivosidenib/enasidenib

IDIOME: phase 2 study of Ivo in 3 cohorts (N=26)¹

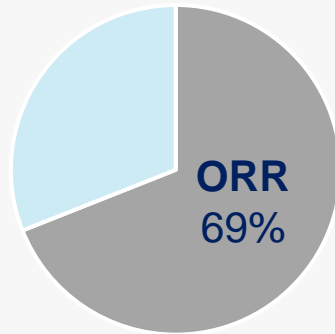
- **A:** HR-MDS, failed AZA (n=13)
- **B:** Untreated HR-MDS (n=11)
- **C:** LR-MDS, failed EPO (n=2)

Median follow-up: 9.1 months

Median DoR: 7.4 months

Median OS: 14 months

Differentiation syndrome, n=4,
febrile neutropenia, n=1



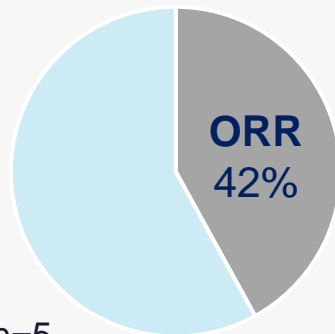
IDEAL: phase 2 study of Ena in 3 cohorts (N=26)²

- **A:** HR-MDS, failed AZA (n=11)
- **B:** Untreated HR-MDS (n=9)
- **C:** LR-MDS, failed ESA (n=6)

Median follow-up: 8.6 months

Median OS: 17.3 months

Differentiation syndrome, n=3;
nausea/diarrhea, n=4; thrombocytopenia, n=5



Ivosidenib in R/R *IDH1/IDH2*^{mut} MDS³

Updated results of a phase 1 dose-escalation study (500 mg QD)

| Efficacy outcomes | N=16 | Safety outcomes | N=16 |
|--------------------------------|------|-----------------------|------|
| ORR | 81% | Grade ≥3 AEs | 69% |
| CR | 44% | Grade ≥3 TRAEs | 13% |
| mCR | 31% | SAEs | 44% |
| PR | 6% | | |
| HI | 69% | | |
| 12-month duration CR+PR | 60% | | |

50% RR in LR-MDS after ESA failure

1. Sebert M, *et al.* ASH 2021. Abstract 62 (oral presentation);
2. Ades L, *et al.* ASH 2021. Abstract 63 (oral presentation)
3. Sallman DA, *et al.* ASCO 2022. Abstract 7053 (Poster 284)

IDH Mutations are Enriched in Myelodysplastic Syndrome Patients with Severe Neutropenia: A Potential Targeted Therapy

Percent of Different Mutations in Severe Neutropenia (SN) vs. Non-severe Neutropenia (NSN)

R-IPSS: SN vs. NSN

LR 3% vs. 4%
HR 3% vs. 5%

LR 3% vs. 7%
HR 4% vs. 5%

LR 8% vs. 28%, ***
HR 4% vs. 5%

LR 6% vs. 2%, **
HR 5% vs. 3%

LR 8% vs. 3%, **
HR 9% vs. 4%, **

LR 15% vs. 12%
HR 8% vs. 10%

LR 11% vs. 10%
HR 12% vs. 11%

LR 14% vs. 6%, ***
HR 13% vs. 6%, ***

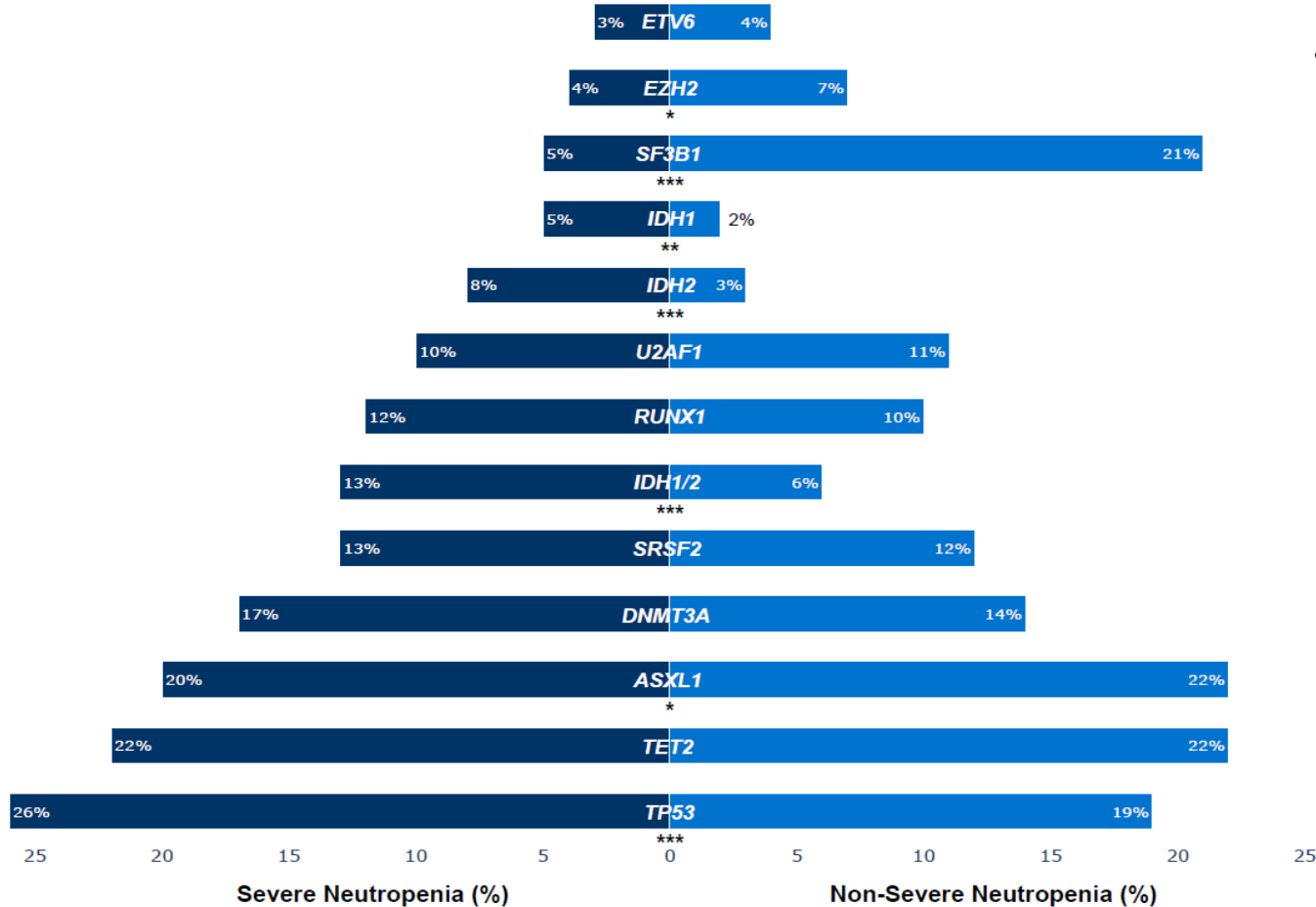
LR 17% vs. 13%
HR 11% vs. 10%

LR 15% vs. 13%
HR 18% vs. 17%

LR 25% vs. 23%
HR 18% vs. 19%

LR 29% vs. 26%
HR 19% vs. 12%

LR 4% vs. 8%
HR 36% vs. 42%



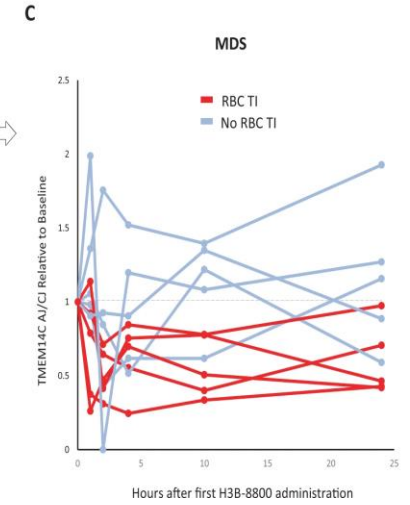
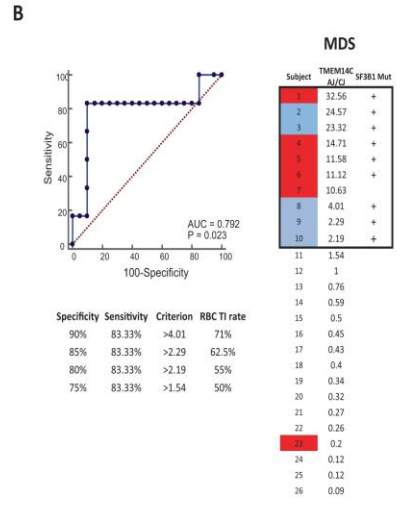
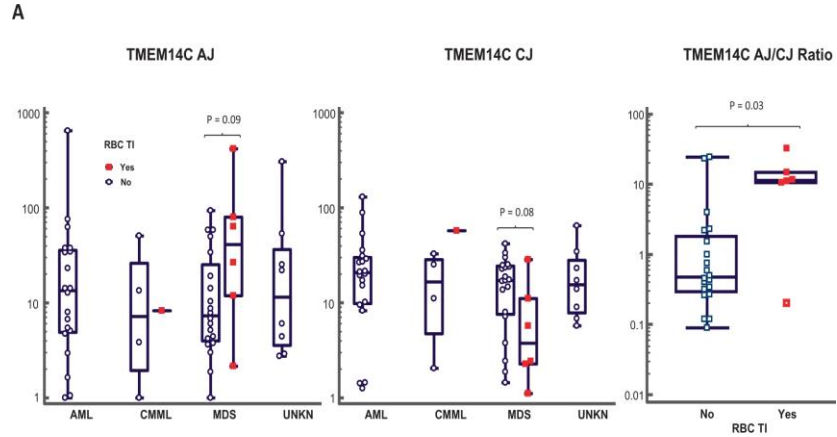
- Two symptomatic *IDH1* SN lower risk MDS pts have been treated with ivosidenib.
 - The first pt had *IDH1* R123 C (variant allele frequency [VAF] 44%) and *SRSF2* P95R (VAF 43%). Hemoglobin improved from 9.4 g/dL to 14 g/dL, platelets were normal at baseline. The pt has been in remission for 31 months.
 - The second pt had *DNMT3A* and *IDH1* R132 C mutations at baseline (VAF at 7% for both). Platelets improved from $111 \times 10^9/L$ to $180 \times 10^9/L$. Hgb also improved from 11.8 g/dL to 14.1 g/dL. The pt has been in durable remission for 11 months now.
 - Both pts achieved a complete hematologic response within 2 weeks of initiation of therapy (ANC 0.3 to 2.8 and ANC 0.21 to 2.4), which has been durable, with therapy ongoing.

Spliceosome inhibitors in MDS

Phase I First-in-Human Dose Escalation Study of the oral SF3B1 Modulator H3B-8800 in Myeloid Neoplasms

| Disease Type | IPSS | Age, Gender | Starting Dose (mg) | Number of RBC TI Periods | Longest RBC TI Period (days) | Time to First RBC TI (days) |
|--------------|--------|-------------|--------------------|--------------------------|------------------------------|-----------------------------|
| MDS | Higher | 78,M | 7 | 1 | 107 | 104 |
| MDS/MPN† | Lower | 85,M | 2 | 1 | 56 | 111 |
| MDS | Lower | 68,M | 2 ** | 5 | 85 | 88 |
| MDS | Higher | 68,F | 2 | 1 | 121 | 126 |
| MDS | Lower | 80,M | 3.5 | 2 | 98 | 101 |
| MDS* | Lower | 69,M | 5 | 1 | 87 | 398 |
| CMML | Lower | 78,F | 7 | 1 | 66 | 4 |
| MDS | Lower | 72,F | 7 | 6 | 91 | 129 |
| MDS | Lower | 84,M | 7 | 4 | 98 | 73 |

Pre-treatment *TMEM14C* AJ/CJ ratio may predict the RBC TI of MDS subjects on H3B-8800 treatment.

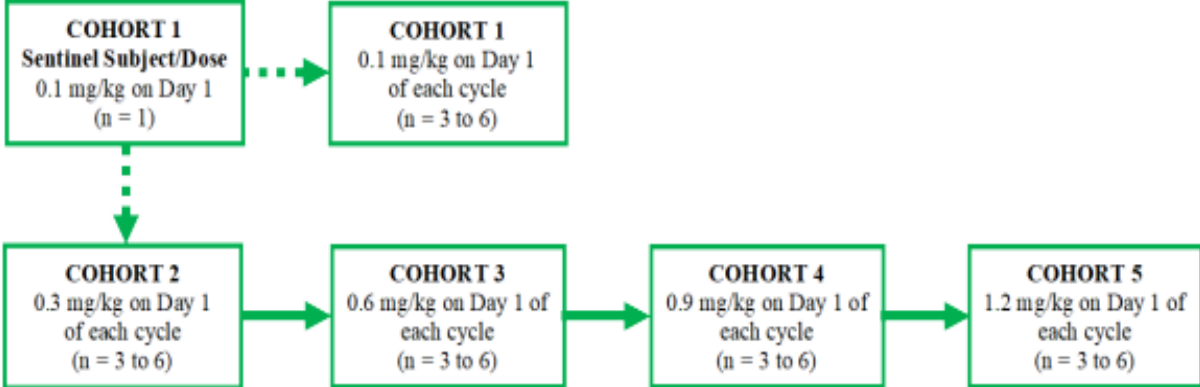


- 9 of 62 patients (15%) who were transfusion dependent at study entry according to IWG criteria
- Of the seven MDS patients with *TMEM14C* AJ/CJ > 4.01, five experienced RBC TI with H3B-8800 (71%).
- SF3B1 mutations were detected in all but one of them.
- Downregulation of the *TMEM14C* AJ/CJ ratio with H3B-8800 dosing was also observed in the patients who experienced RBC TI

A PHASE 1 OPEN-LABEL, DOSE-ESCALATION, SAFETY, AND TOLERABILITY STUDY OF JSP191 (Briquilimab) AS A SECOND-LINE THERAPY IN SUBJECTS WITH LR-MDS

Study Schema:

Dose Escalation Cohorts



Treatment Cycles

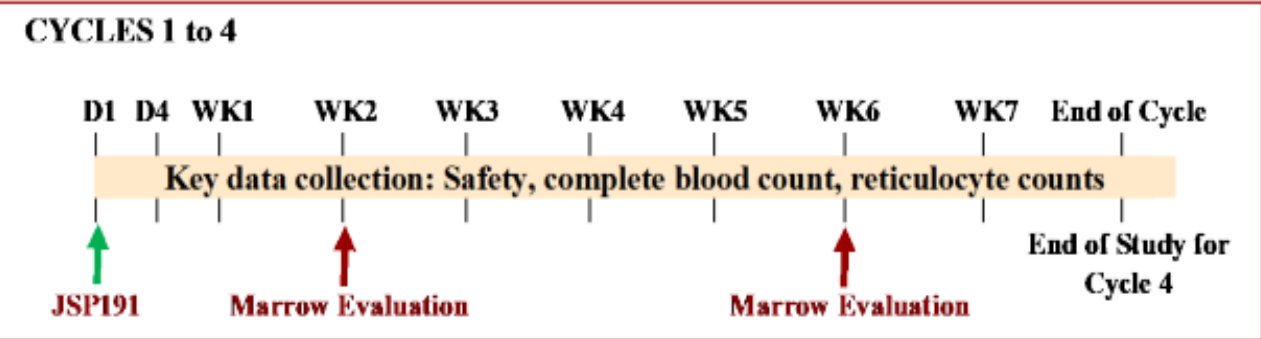
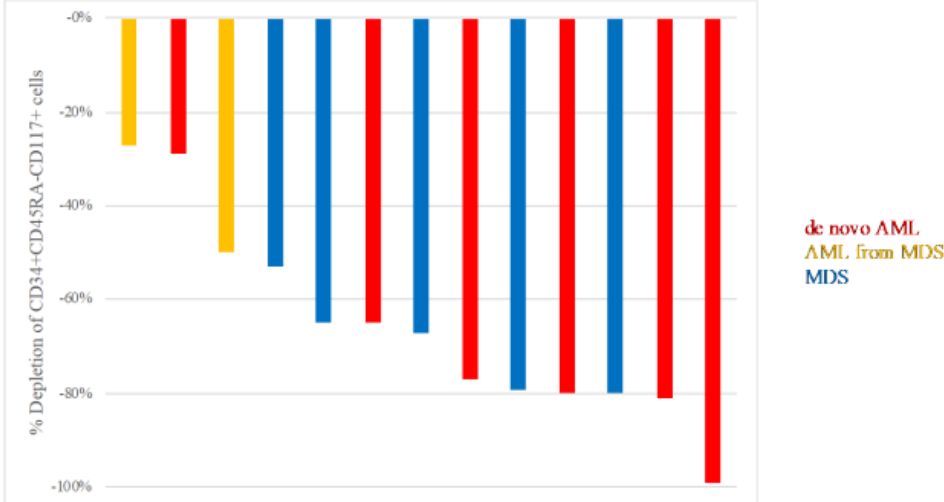
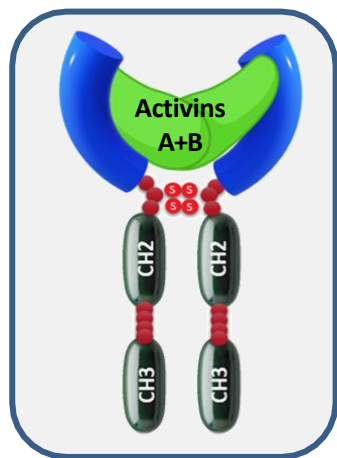


Figure 2: Depletion of HSPCs in MDS and AML Subjects with JSP191 Monotherapy



The waterfall plot depicts depletion of HSPCs between 5 to 7 days after JSP191 administration, compared to screening, in individual subjects. CD34+CD45RA-CD117+ HSPCs include immunophenotypic HSC, MPP, and CMP, as well as LSC and pre-leukemic stem cells.





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
- KER-050 has the potential to:
 - Treat a broad range of patients with lower-risk (LR) MDS
 - Provide clinical benefit beyond improving hematopoiesis (Chee, et al. ASH 2023 Poster #1089)

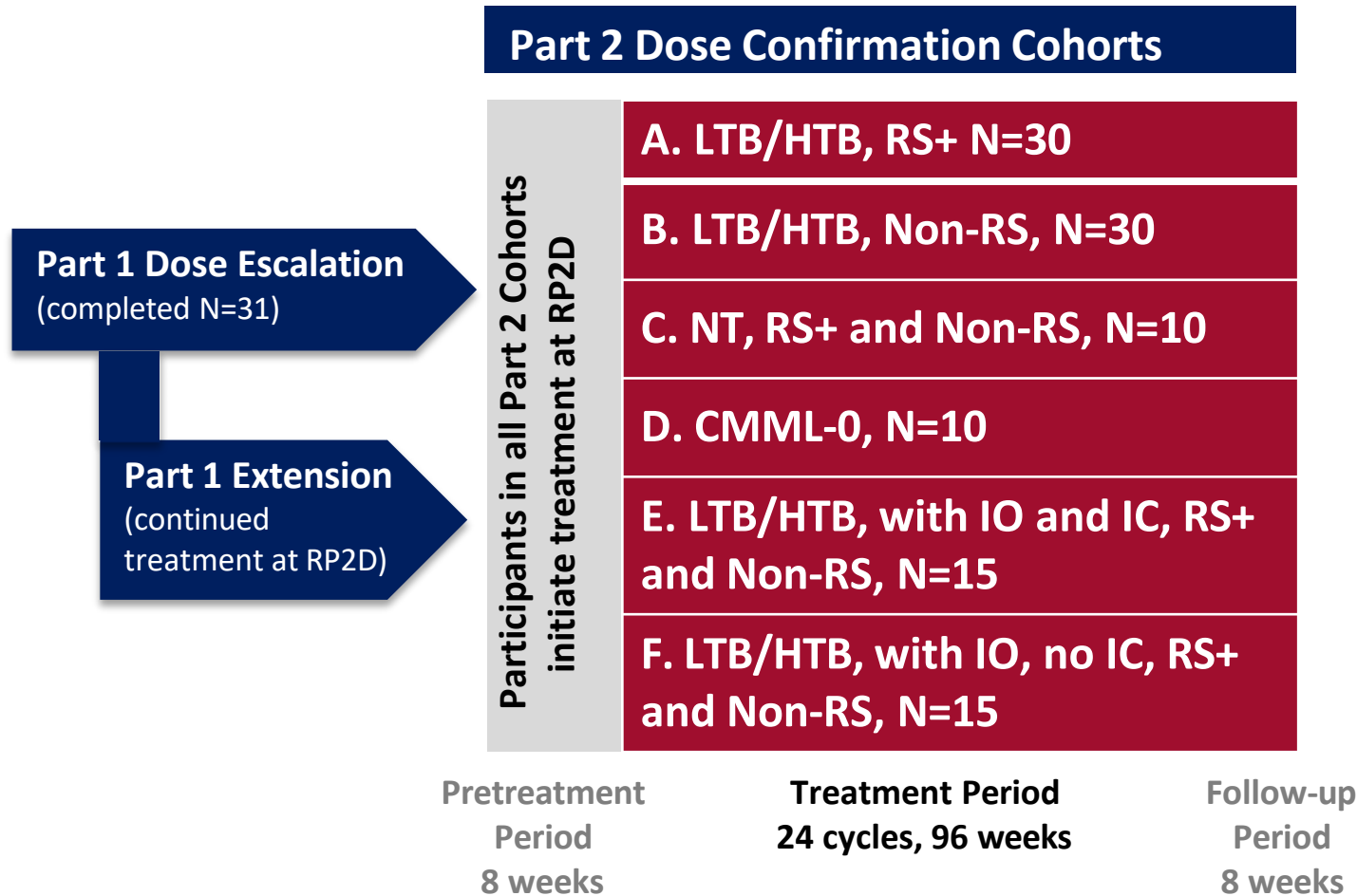
| | Domain | Effect |
|--|-----------------|--|
|  | Erythropoiesis | ALL stages of differentiation and maturation |
|  | Thrombopoiesis | ALL stages of differentiation and maturation |
|  | Bone | Increased bone formation |
|  | Iron Metabolism | Improved iron utilization |

Preliminary results from an ongoing open-label Phase 2 trial evaluating KER-050 (elritercept) in participants with LR-MDS Presented ASH 2023 Diez-Campelo et al



Study Design, KER050-MD-201 (NCT04419649)

Ongoing global, 2-part, open-label Phase 2 trial evaluating KER-050 (elritercept) in participants with LR-MDS



Key Eligibility Criteria

- MDS per 2016 WHO criteria, RS+ or non-RS, very-low, low, or intermediate risk disease (LR-MDS) by IPSS-R with anemia (NT, LTB, HTB)
 - CMML in Cohort D

Primary Objective

- Safety and tolerability

Secondary Endpoints include

- Modified 2006 IWG Hematological Improvement-Erythroid (HI-E)
- Transfusion Independence (TI) ≥ 8 weeks

Status as of Data Cutoff Date

- Part 1 Extension ongoing
- RP2D: 3.75 mg/kg with titration to 5 mg/kg Q4W
- Part 2 Dose Confirmation ongoing and enrolling

Data presented as of a data cutoff date of 01-September-2023



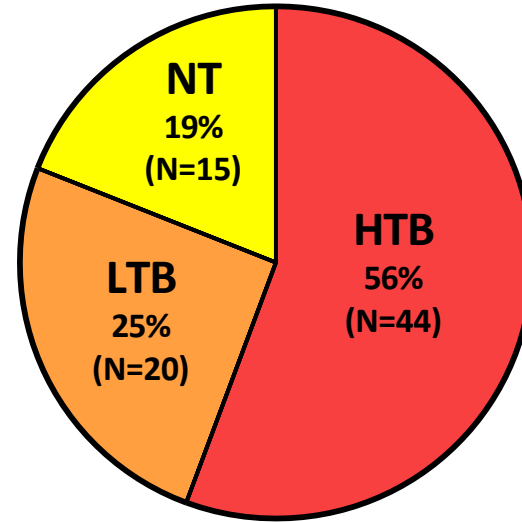
Study Enrolled Hard-to-Treat Patients With High Disease Burden

Majority had high transfusion burden or multi-lineage dysplasia at baseline

| Baseline Characteristic | RP2D (N=79) |
|--|------------------|
| Median age, years (range) | 75 (53, 89) |
| Sex, male, n (%) | 50 (63.3) |
| Hemoglobin, g/dL, median (range) | 8.37 (3.7, 10.5) |
| RS+, n (%) | 57 (72.2) |
| Non-RS, n (%) | 22 (27.8) |
| Prior ESA, n (%) | 21 (26.6) |
| Median baseline EPO level, U/L (range)* | 127.8 (1, 4000) |
| Thrombocytopenia, n (%) (platelets < 150 x 10 ⁹ /L) | 20 (25) |

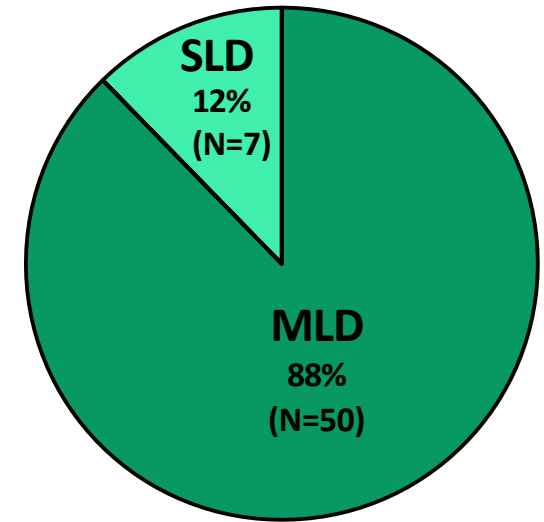
*9 RP2D participants had missing baseline EPO

Baseline Transfusion Burden



- 44 (56%) had high transfusion burden (HTB, ≥ 4 RBC units/8 weeks)
- 25 (32%) heavily transfused (≥ 6 RBC units/8 weeks)

Baseline Dysplasia Category**



- 50 (88%) had multi-lineage dysplasia (MLD)

**Excludes 22 RP2D participants with unknown dysplasia category

Data presented as of a data cutoff date of 01-September-2023



Hematologic Responses Observed in a Broad Array of Participants

| Responders/N (%) | mITT ₂₄ ^a | |
|---|---------------------------------|---------------------|
| | All (N=60) | HTB (N=33) |
| Overall Response^{a,b} | 30/60 (50) | 15/33 (45.5) |
| Modified IWG 2006 HI-E^c | 28/60 (47) | 15/33 (45.5) |
| RS+ | 23/40 (58) | 12/23 (52.2) |
| non-RS | 5/20 (25) | 3/10 (30) |
| TI ≥8 weeks^d | 18/46 (39.1) | 11/33 (33.3) |
| RS+ | 15/32 (46.9) | 8/23 (34.8) |
| non-RS | 3/14 (21.4) | 3/10 (30) |

^a Includes data for weeks 0-24 in mITT₂₄ participants.

^b Defined as achieving modified IWG 2006 HI-E and/or TI.

^c Modified HI-E = mean increase in hemoglobin ≥1.5 g/dL (NT+LTB) or reduction in transfusion of ≥4 RBC units (HTB) over 8 weeks on treatment compared to 8-week pre-treatment period.

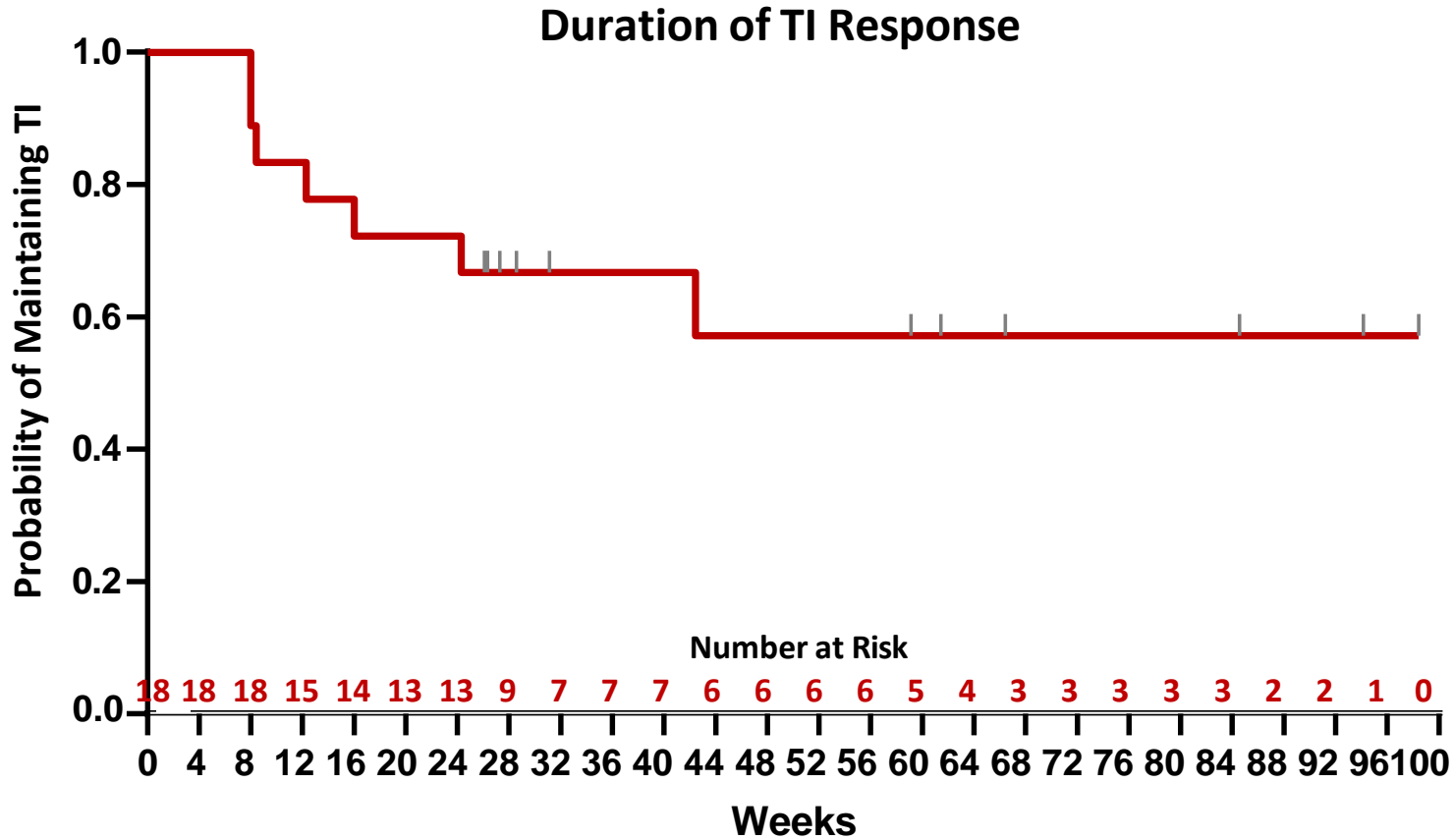
^d TI-evaluable participants received at least 2 RBC units in the 8-week pre-treatment period.

Data presented as of a data cutoff date of 01-September-2023

HI-E and TI response rates in mITT₂₄ participants with HTB were similar to those observed in the overall mITT₂₄ population, supporting the potential for KER-050 (elritercept) to treat a broad array of patients with MDS including those with greater bone marrow dysfunction



Durable TI Responses Observed with KER-050 (elriterccept) Treatment



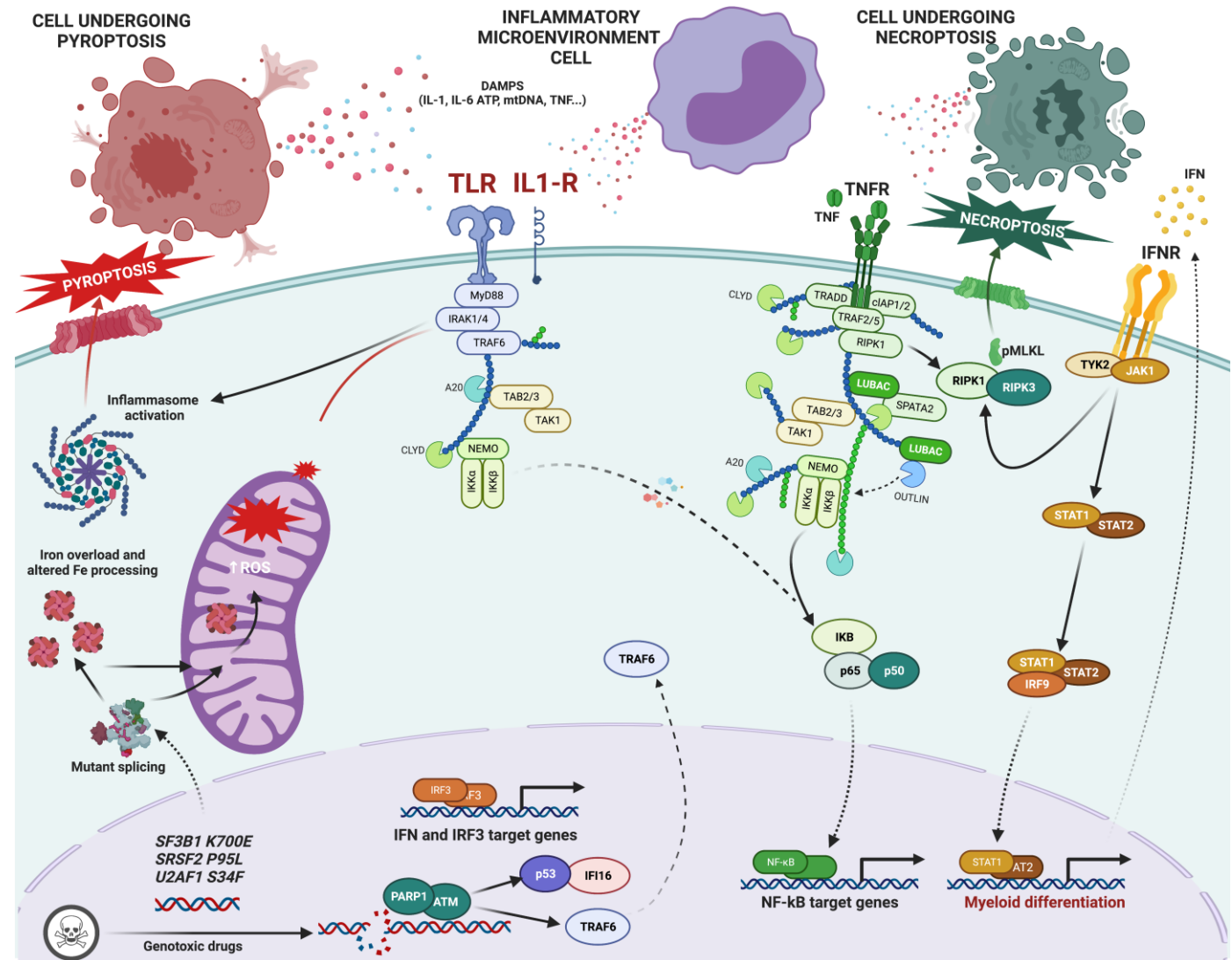
Longest TI interval through KER-050 treatment for mITT₂₄ participants who achieved TI ≥8 weeks during weeks 0-24; Participants with ongoing response censored at time of data cutoff (denoted by vertical lines);

Data presented as of a data cutoff date of 01-September-2023

- 18 participants in the mITT₂₄ population had TI ≥ 8 weeks
 - 11/18 (61.1%) had HTB
 - 13/18 (72%) had TI ≥ 24 weeks
- 11/18 (61.1%) had ongoing TI at time of data cut-off
 - Median baseline transfusion burden: 4 RBC units/8 weeks (range 2 to 11)
 - 6/11 (54.5%) had ongoing TI for > 52 weeks including participants who had received up to 11 RBC units/8 weeks at baseline
- **Median duration of response not reached (range: 8 to 98 weeks)**

IL-1 β Signaling Activates NF- κ B Pathway and Amplifies Inflammation

- IL-1 β binding to IL1R1 activates NF- κ B pathway
- NF- κ B pathway activation induces the production of other cytokines (e.g., TNF α) that amplify the inflammatory response from the microenvironment



Canakinumab in Lower risk MDS: Objectives and Design

- **Primary objectives:** safety and clinical activity by IWG-06*
- **Secondary objectives:**
 - Rate of transfusion independency
 - Duration of response
 - Progression
 - TFR, correlative studies
- **Phase I** (cohorts, n=3): 3+3 design starting 150mg SC daily q28 days and escalating to 300mg
- **Next Steps:**
 - Expansion cohort #1 (n=20): Transfusion dependent LR-MDS after at east one line of therapy. Stopping rules for toxicity.
 - Other planned: #2: TD LR-MDS no prior therapy; #3: TI LR-MDS and #4: CCUS

Eligibility Criteria

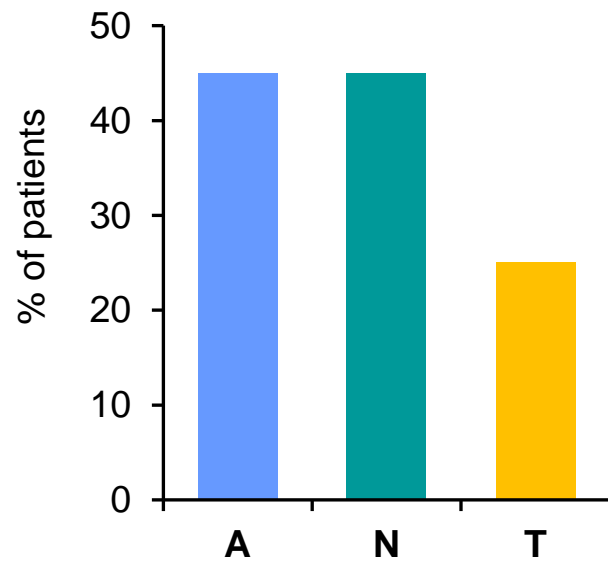
- Age \geq 18 years old
- MDS
- Risk:
 - IPSS: low or int-1 risk
 - IPSS-R \leq 3.5 points
- At least one prior line of therapy
- Symptomatic anemia or transfusion dependence
- Adequate renal and hepatic functions or performance status

IWG, International Working Group; TFR, Treatment-free remission; LR, low risk; TD, transfusion dependence; TI, transfusion independence

Patients' Characteristics: Toxicity and Responses

Treatment Related Toxicity

- Grade 1 related toxicity n=1
(soft tissue necrosis at the site of injection)
- Grade 3 or 4 toxicity in $\geq 20\%$ of patients

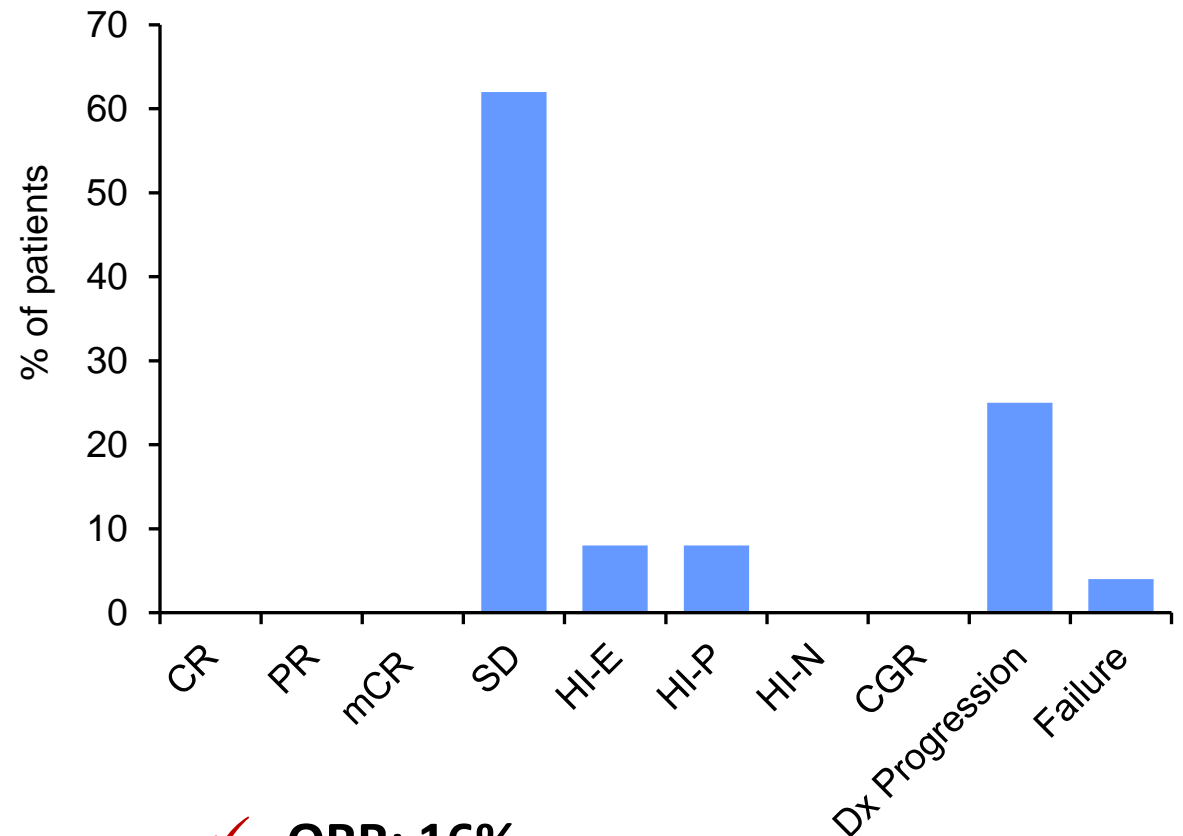


A, Anemia (n=11)

N, Neutropenia (n=11)

T, Thrombocytopenia (n=6)

Modified IWG 06 Response



✓ **ORR: 16%**

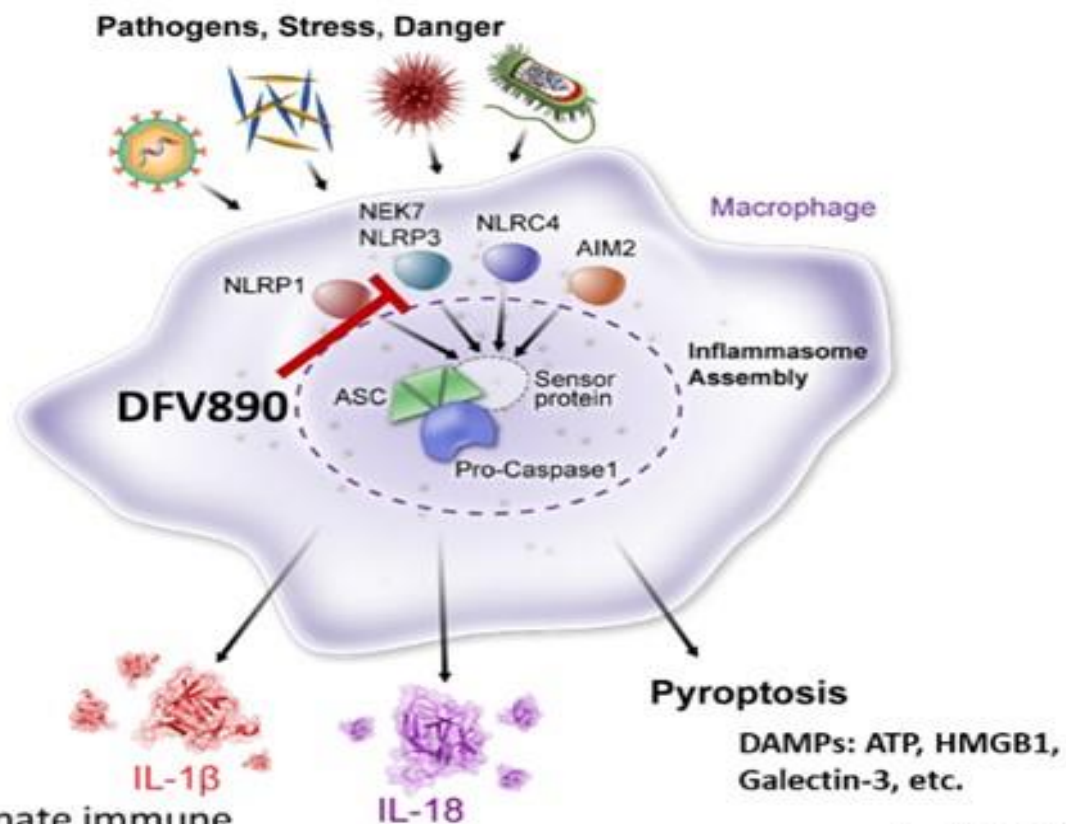
✓ **HI-P: 2 patients**

✓ **TI: 2 patients**

Characteristics of Patients with TI and Progression

| | Age | Sex | Hgb | Plt | ANC | Baseline % BM Blast | CG | N mutations | IPSS | IPSS-R | IPSS-M | N previous therapies | Total Cycles | Baseline Transfusion burden | Time to response | Progression % Blast |
|-------------|-----|-----|------|-----|------|---------------------|----------|------------------------|------|--------|--------|----------------------|--------------|-----------------------------|------------------|---------------------|
| TI | 72 | F | 8 | 34 | 2.3 | 2 | 5q-/20q- | 1 (<i>TET2</i>) | 0.5 | 3 | ML | 2 | 13+ | 6 | Cycle 10 | - |
| | 73 | M | 8.8 | 164 | 1.82 | 2 | Diploid | 1 (<i>DNMT3A</i>) | 0 | 2 | L | 1 | 16 | 2 | Cycle 1 | - |
| Progression | 80 | M | 8 | 20 | 1 | 2.5 | 13q- | 4 | 0.5 | 3.5 | MH | 2 | 3 | 2 | - | 6 |
| | 73 | F | 10.3 | 137 | 1.61 | 3 | Diploid | 4 | 0 | 2 | L | 3 | 3 | 2 | - | 8 |
| | 77 | M | 7 | 268 | 2.1 | 2 | i(14q) | 3 | 0.5 | 3.5 | ML | 1 | 5 | 3 | - | 9 |
| | 72 | F | 6.5 | 27 | 2.15 | 4 | +8 | 5 | 1 | 5.5 | VH | 1 | 5 | 6 | - | 7 |
| | 75 | M | 9.1 | 162 | 0.98 | 3 | Diploid | 3 | 0.5 | 3 | MH | 1 | 5 | 2 | - | 37 |
| | 80 | M | 9.2 | 115 | 1.56 | 6 | Diploid | 8 | 1 | 4 | H | 3 | 3 | 0 | - | 15 |

NLRP3 and inflammasome

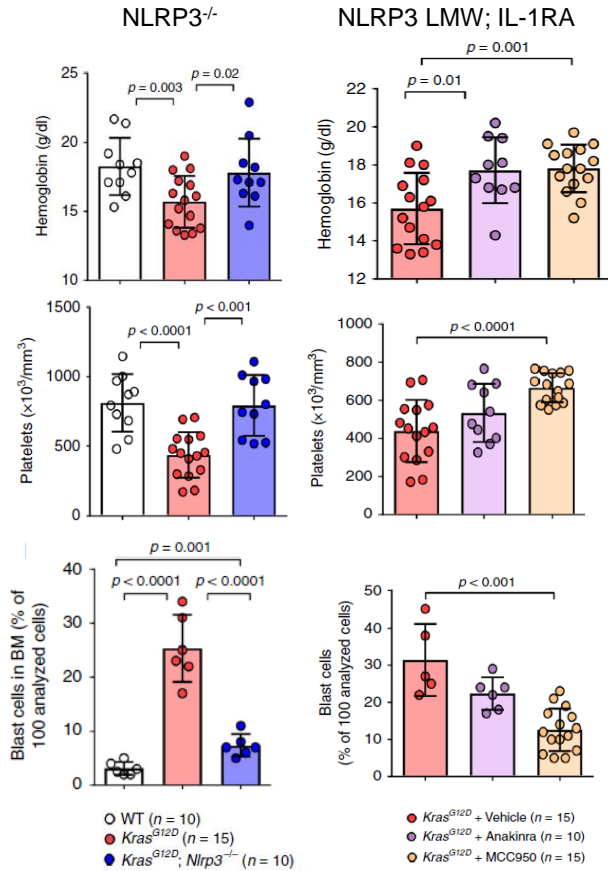


DFV890 prevents NLRP3-mediated IL-1 β and IL-18 secretion, and pyroptotic cell death caused by sterile inflammatory danger signals

- Early innate immune response
- Fever
- Acute tissue injury
- Tissue remodeling
- NK, T-cell activation
- Engagement with adaptive immune system
- Pro-inflammatory cell death

Linkage between inflammasome activation, oncogenic drivers and erythropoiesis/anemia

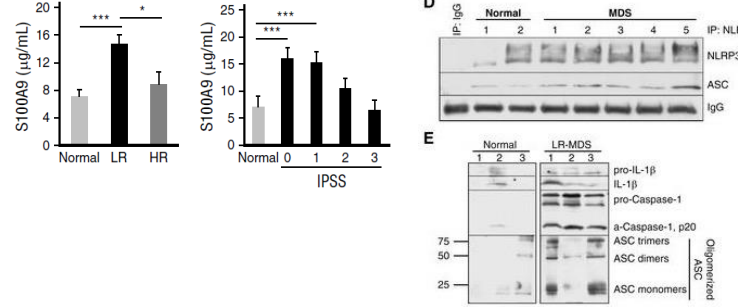
NLRP3 inhibition can normalize cytopenia and myeloproliferation in *Kras*^{G12D} mouse CMML models



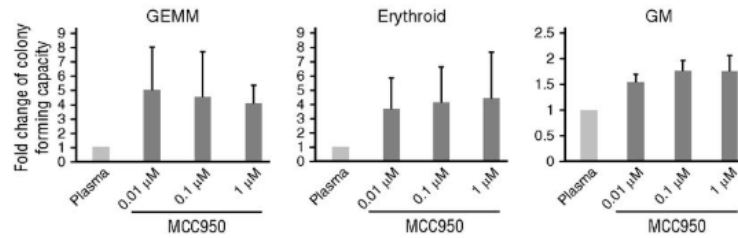
Nature Communications, 2020

NLRP3 inflammasome pathway is activated and regulates effective hematopoiesis in MDS patients

LR/HR MDS patients exhibit increased levels of the DAMP S100A9 and NLRP3 pathway activation

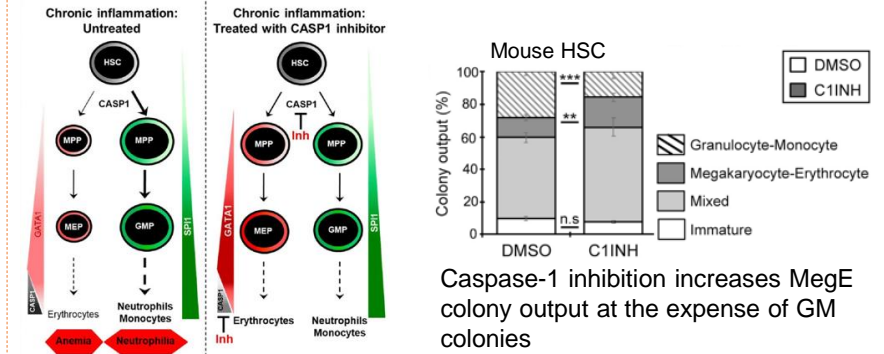


Pharmacological inhibition of NLRP3 modulates erythropoiesis and hematopoiesis

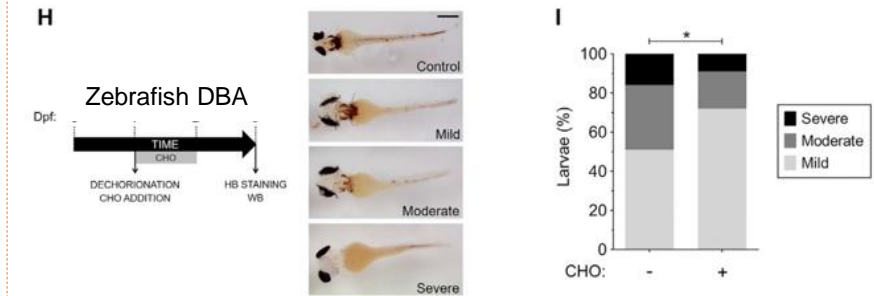


Blood, 2016

Inflammasome pathway inhibition enhances erythropoiesis under inflammatory conditions



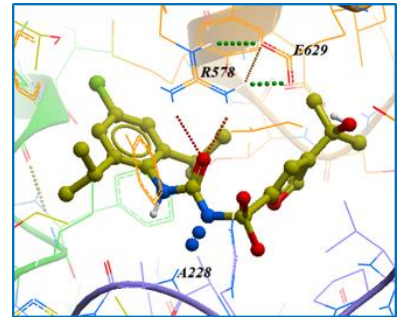
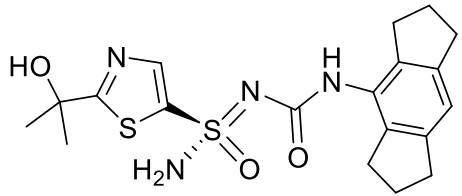
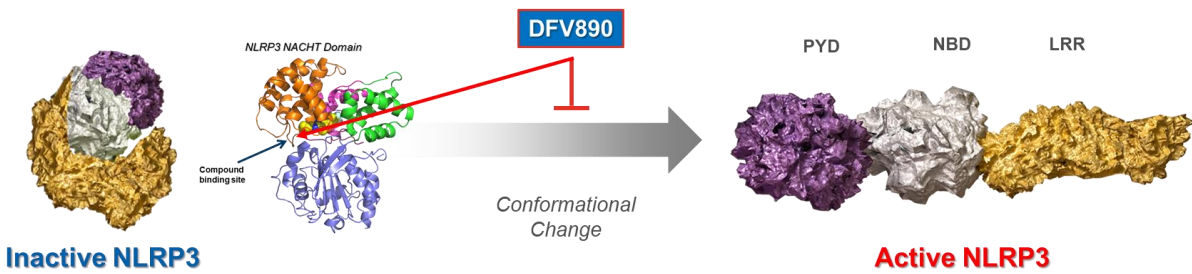
Inflammasome pathway inhibition rescues zebrafish models of neutrophilic inflammation and anemia



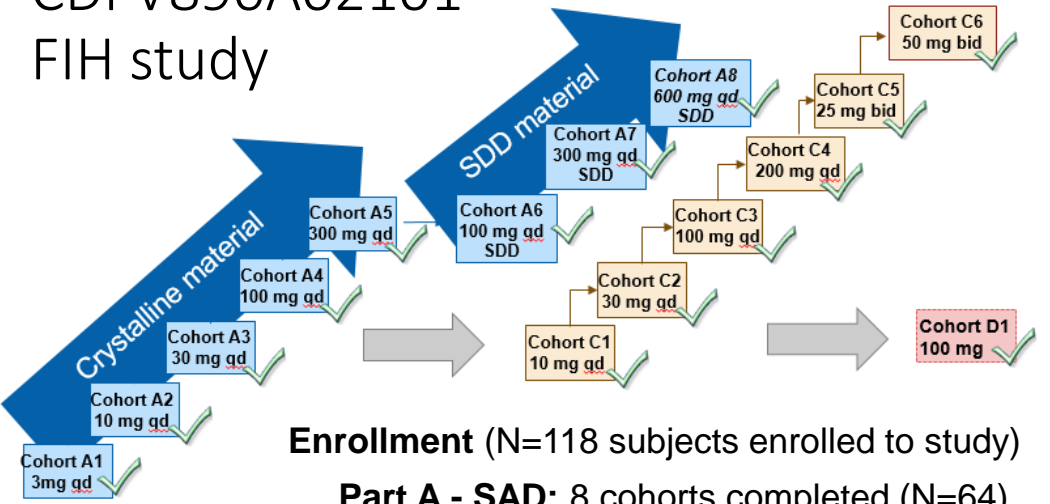
Tyrkalska et al., Immunity 2019

DFV890 is a potent, first in class LMW molecule blocking activation of NLRP3

DFV890 MoA



CDFV890A02101 FIH study



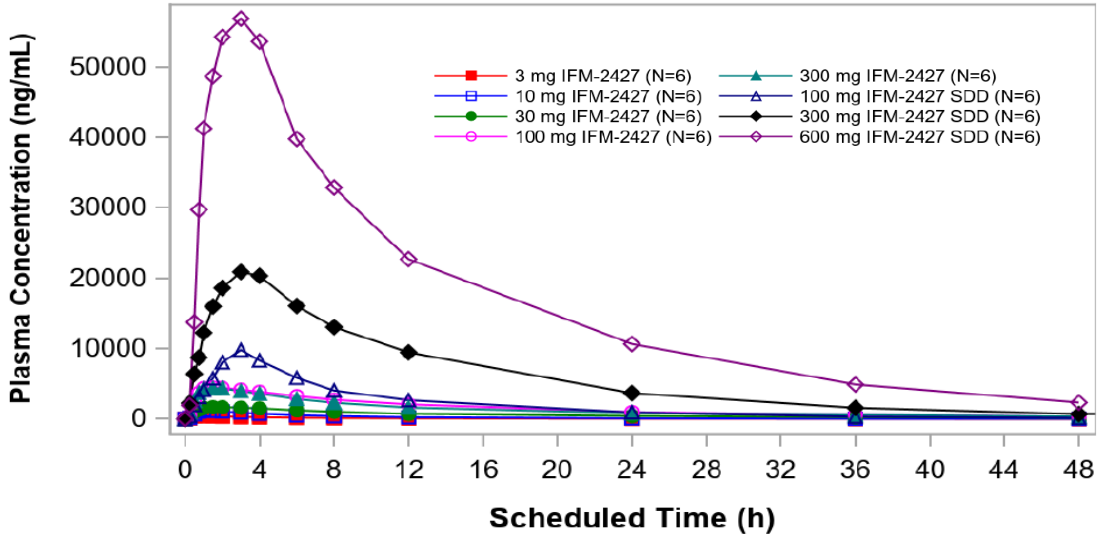
Enrollment (N=118 subjects enrolled to study)

Part A - SAD: 8 cohorts completed (N=64)

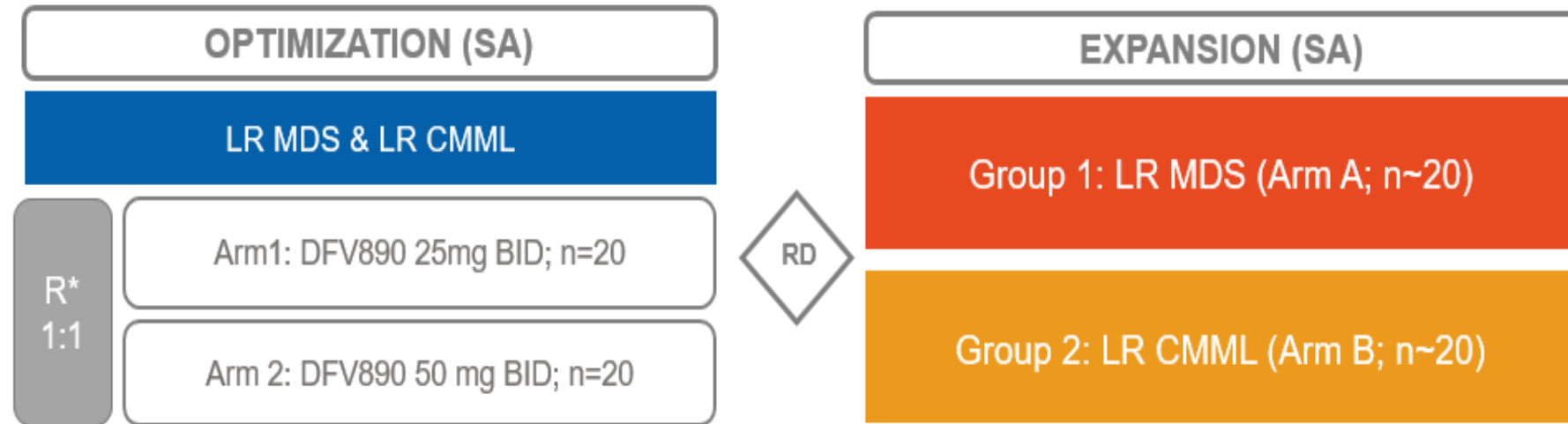
Part D - Food effect: 1 cohort completed (N=6)

Part C - MAD (2w): 6 cohorts completed (N=48)

Part A (SAD) IFM-2427



A phase 1b, open label, multi-center, dose optimization and dose expansion study to assess the safety and efficacy of DFV890 in adult patients with myeloid diseases



*Randomization 1:1, stratified by indication.

Phase 1b Clinical Study of IRAK 1/4 Inhibition for Lower-Risk Myelodysplastic Syndromes Refractory/Resistant to Prior Therapies: A Trial in Progress

Guillermo Garcia-Manero¹; Lucy Yan²; and Wolfgang Dummer²

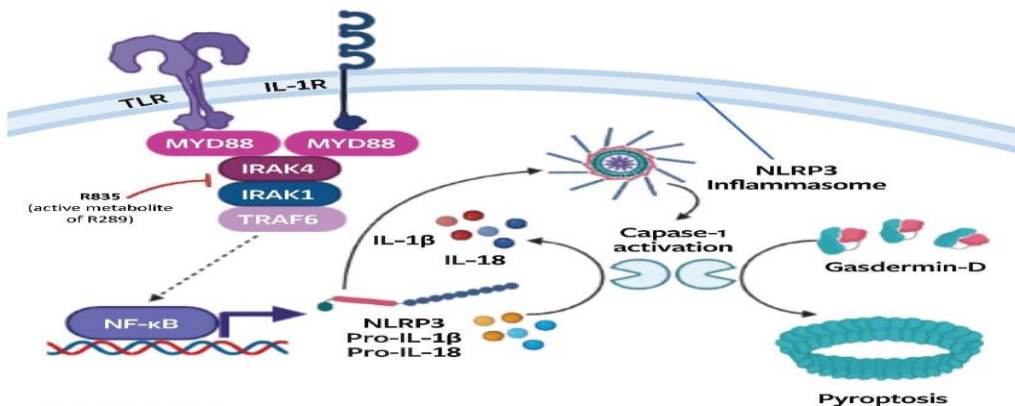
¹The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX;

²Rigel Pharmaceuticals, Inc. South San Francisco, CA

Background

- Chronic stimulation of both interleukin-1 receptor (IL-1R) and toll-like receptors (TLRs) in myeloid progenitors is thought to cause a bone marrow proinflammatory environment responsible for persistent cytopenia in patients with low-risk myelodysplastic syndrome (LR-MDS)¹
 - Interleukin receptor-associated kinases (IRAK) 1 and 4 are serine/threonine kinases critical in downstream signaling of IL-1R and most TLRs, which drives production of proinflammatory cytokines and NOD-like receptor protein 3 (NLRP3) inflammasome-driven pyroptosis, leading to bone marrow inflammation and cell death² (Figure 1)
 - IRAK1/4 inhibition shows potential for treatment of LR-MDS by decreasing inflammation and cell death in bone marrow, allowing the restoration of hematopoiesis
- R289 is a prodrug that is converted to the active drug R835 in the gastrointestinal (GI) tract
 - R835 is a potent and selective inhibitor of IRAK1/4 and inhibits TLR and IL-1R-dependent proinflammatory cytokine production in multiple cell types
 - In vivo, R835 blocks TLR4 and IL-1R-dependent systemic cytokine release in mice
- The safety and pharmacokinetic properties of R289/R835 were evaluated in a phase 1 healthy volunteer study (Study C-906289-001)
 - R289 was well tolerated with no serious or severe adverse events (AEs) reported. Most AEs were mild and transient; the most common AEs (mild/moderate) were headache and GI disturbance
 - Overall, the trial supported the advancement of R289 into further studies
- An open-label phase 1b study to determine the tolerability and preliminary efficacy of R289 for patients with LR-MDS refractory to prior therapies is currently enrolling patients

Figure 1. Low-Risk Myelodysplastic Syndromes and IRAK1/4 Inhibition



Created with BioRender.com

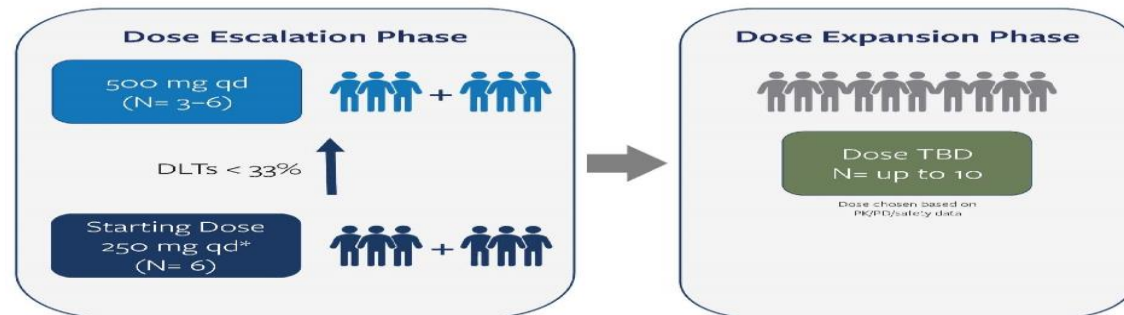


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Methods

- The current study (NCT05308264) includes a dose escalation phase (up to 12 patients) and a dose expansion phase (up to 10 patients) (Figure 2)
- Inclusion criteria for both phases include patients ≥ 18 years with a definitive diagnosis of LR-MDS
- Exclusion criteria include prior treatment for MDS concluding < 4 weeks prior to study treatment

Figure 2. R289, an IRAK1/4 Inhibitor, in Patients With Lower-Risk Myelodysplastic Syndromes: A Phase 1B, Open-Label Study



Dose Escalation Phase

- Dose escalation will utilize a 3+3 design to determine the maximum tolerated dose (MTD)
- R289 tablets can be taken orally with or without food
- Dose limiting toxicity (DLT) will be assessed at each dose level, with a 28-day evaluation period
- After completion of the DLT evaluation period, patients not experiencing DLTs may remain on treatment at their respective dose levels if they continue to demonstrate clinical benefit without toxicity

Dose Expansion Phase

- Up to 10 additional patients with LR-MDS will be enrolled
- R289 will be administered to all patients at a dose not to exceed the MTD determined in the dose escalation phase
- The primary endpoint of the study will be safety and tolerability of R289
- Secondary endpoints will include
 - Assessment of preliminary efficacy
 - Characterization of the pharmacokinetics of R289

The trial is currently recruiting at 9 US sites

References

1. Sallman DA, et al. *Front Oncol.* 2016;6:151. 2. Flannery S, Bowie AG. *Biochem Pharmacol.* 2010;80(12):1981-91.

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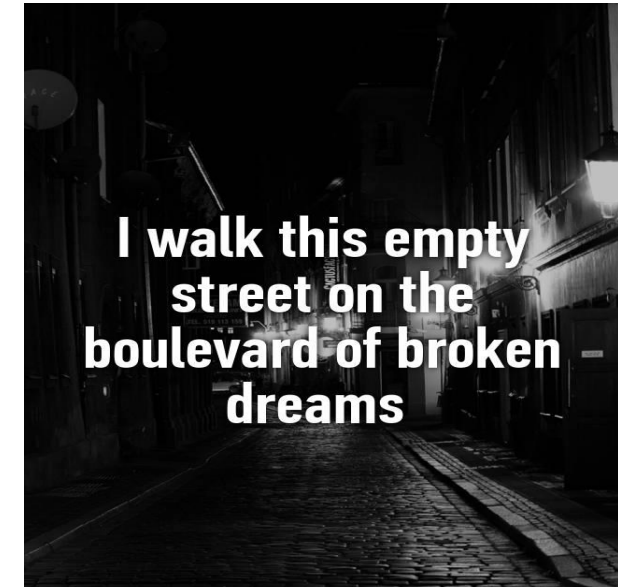
Contact for questions: Lucy Yan, MD, PhD; lyan@rigel.com

Goal of therapy in HR-MDS is achieving remission and improving overall survival

- Majority of HR-MDS have median OS < 2-3 years.
- 5-year OS in HR-MDS without allo-SCT < 10%.
- Phase III Clinical trials adding to back bone of HMA failed to demonstrate OS benefit.
- Treatment after HMA failure is unmet need.
- Short of allogeneic SCT immune therapy in HR-MDS has not been successful partly because of the immune deregulation and T cell exhaustion.

Lessons Learned from Phase III clinical trials in HR-MDS

| Drug | Patient characteristics | Intervention | Study outcomes |
|---------------------------|--|--|--|
| Venetoclax | Newly-diagnosed HR-MDS Estimated enrollment: 500 | Venetoclax + AZA vs. placebo + AZA | Primary Outcome: - Complete Remission (CR) based on IWG 2006 MDS criteria (Up to 36 Months) - Overall survival (OS) (Up to 5 years) |
| MBG453 (Sabatolimab) | Newly-diagnosed HR-MDS or CMML-2 Estimated enrollment: 500 | MBG453+ AZA vs. placebo + AZA | Primary Outcome: - Overall Survival (Up to 5 years after last patient randomized) |
| Pevonedistat | Newly-diagnosed HR-MDS, CMML, or Low-Blast AML Estimated enrollment: 502 | Pevonedistat + AZA vs. AZA alone Open-label | Primary Outcome: - Event-Free Survival (From randomization until transformation to AML, or death due to any cause; up to 6 years) |
| Magrolimab | Newly-diagnosed HR-MDS Estimated enrollment: 520 | Magrolimab + AZA vs. AZA + placebo | Primary Outcomes: - Complete Remission (CR) based on IWG 2006 MDS criteria (Up to 24 Months) - Overall survival (OS) (Up to 5 years) |
| APR-246 | Newly-diagnosed TP53-mutated HR-MDS Estimated enrollment: 154 | APR-246 + AZA Vs. AZA alone Open-label | Primary Outcome: - Complete response rate (CR) with APR 246 + azacitidine vs. azacitidine only |
| SY-1425 (Tamibarotene) | Newly-diagnosed RARA-positive HR-MDS Estimated enrollment: 190 | SY-1425 + AZA Vs. placebo + AZA | Primary outcome: - Complete response rate (CR) with SY-1425 + azacitidine vs. azacitidine only |

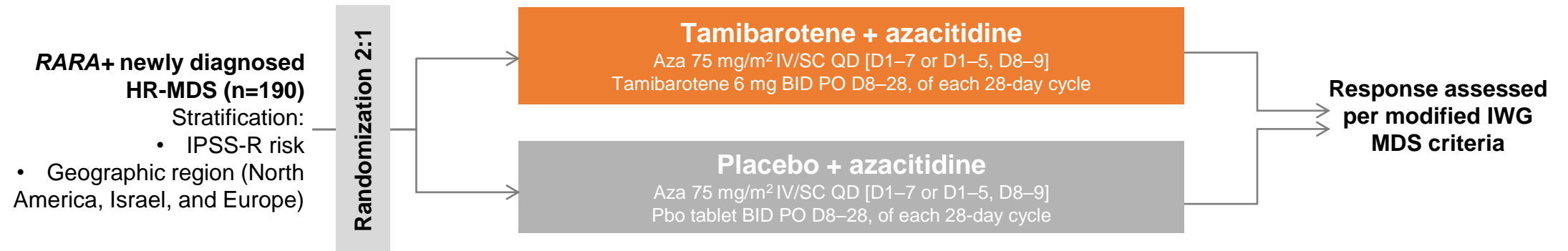


I walk this empty
street on the
boulevard of broken
dreams

- Bi-allelic *TP53* MDS specific clinical trials.
- Survival= CR rate x duration
- Studies are under-powered to detect small improvements

Tamibarotene + Aza vs Pbo+Aza

Phase 3, double-blind, randomized trial in patients with *RARA+* newly diagnosed HR-MDS



Key inclusion criteria

- Adults ≥18 years old
- *RARA+* based on the investigational biomarker test
- Newly diagnosed with HR-MDS by 2016 WHO classification and classified by IPSS-R as very high, high, or intermediate risk
- Blast count >5% at study entry

Key exclusion criteria

- Patients suitable for transplant at the time of screening

Primary endpoint

- Proportion of participants with CR [Timeframe: up to 5 years]

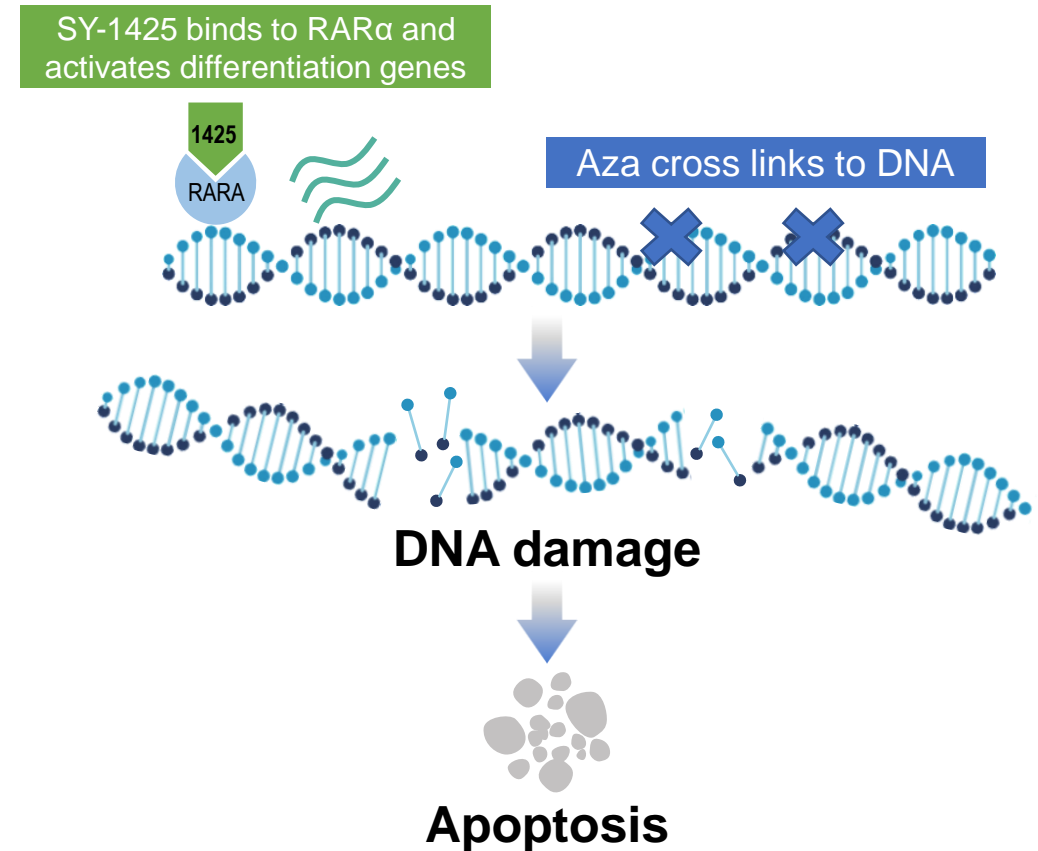
Key secondary endpoints

- ORR
- EFS, OS
- Transfusion independence

SY-1425, an Oral, Selective RAR α Agonist for RARA-positive AML

- Subset of non-APL AML patients characterized by overexpression of the *RARA* gene
 - Novel blood-based biomarker test identifies patients for treatment with SY-1425, with typical 2 to 3-day turnaround time^{1,2}
 - Approximately 30% of AML patients are RARA-positive
- Preclinical synergy of SY-1425 with azacitidine (Aza) supported development of the combination in RARA-positive myeloid malignancies³

| Best IWG Response ¹ | RARA-positive n (%) | RARA-negative n (%) |
|------------------------------------|------------------------|------------------------|
| Response Evaluable, N ^a | 18 | 28 |
| ORR | 12 (67) | 12 (43) |
| CR/CRi | 11 (61) | 9 (32) |
| CR | 9 (50) | 7 (25) |
| CRm | 4 (22) | 3 (11) |
| CRc | 4 (22) | 3 (11) |
| CRi | 2 (11) | 2 (7) |
| MLFS | 1 (6) | 1 (4) |
| PR | 0 (0) | 2 (7) |



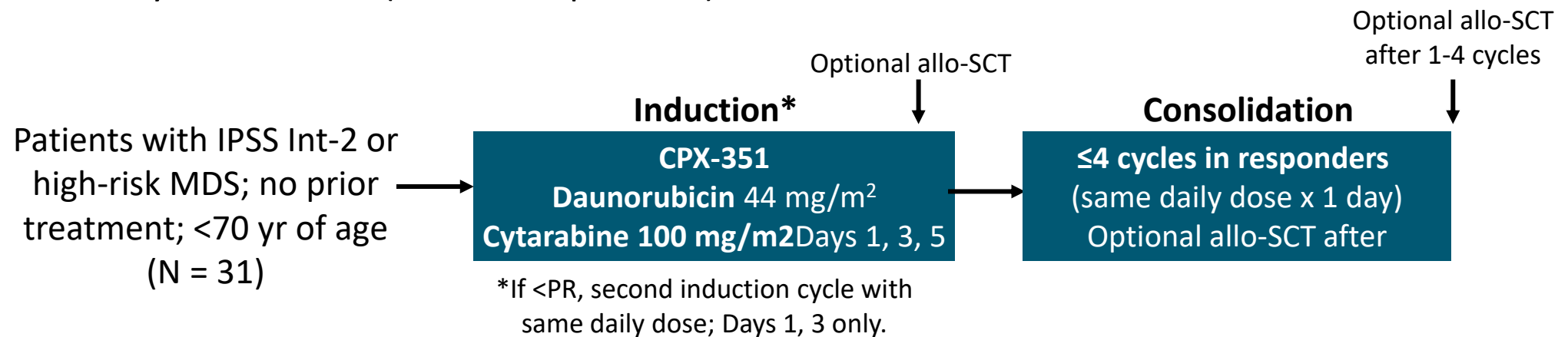
¹McKeown, Cancer Discovery 2017; ²Vigil, ESH 2017; ³McKeown, Haematologica 2018

Treatment Options in MDS After HMA Failure

- Add additional agent to HMA
- Intensive chemotherapy
- Mini-CLA ± venetoclax: normal karyotype
- *IDH2* (5-10%): enasidenib
- *IDH1* (5%): ivosidenib
- *FLT3* (15%): multiple *FLT3* agents
- *NPM1* (1%): ara-C based, ? Menin inhibitors
- MLL rearrangement: ?Menin inhibitors

CPX-351 as First-line Treatment in Higher-Risk MDS: Study Design

- Prospective study involving 12 GFM centers
- Current analysis: cohort A (untreated patients)



- **Primary endpoint:** response to induction (CR, CRi, or PR)
 - Evaluated Days 28-42; delays due to prolonged cytopenias
 - Responses evaluated using ELN 2017 criteria for AML and IWG 2006 criteria for MDS
- **Secondary endpoints:** ORR (CR/CRi/PR/Hi) to induction, EFS, DoR, OS, safety, MRD

CPX-351 as First-line Treatment in Higher-Risk MDS: Efficacy (Primary Endpoint)

| Response | IWG 2006 Criteria (N = 31) | ELN 2017 Criteria (N = 31) |
|------------------------------------|----------------------------|----------------------------|
| ORR, % | 87 | 87 |
| ▪ CR | 23 | 52 |
| ▪ mCR | 45 | - |
| ▪ mCR+H | 16 | - |
| ▪ PR | 3 | - |
| ▪ CRi | - | 13 |
| ▪ MLFS | - | 22 |
| SD, % | 13 | 13 |
| CMML-2 (n = 5) | 2 MLFS + 3 CR | 4 mCR + 1 CR |
| Poor + very poor karyotype (n = 4) | 1 CR, 1 CRi, 1 MLFS, 1 SD | 2 mCR, 1 mCR + HI, 1 SD |

Ivosidenib Demonstrated Rapid and Durable Complete Responses

Primary endpoint: CR+PR¹

All observed responses were CRs with no PRs

| | TIBSOVO (500 mg Daily) (N=18) |
|--------------------|-------------------------------------|
| CR, % ^a | 38.9 |
| 95% CI | 17.3-64.3 |

Secondary endpoint: DOCR+PR¹

All observed responses were CRs with no PRs

| | TIBSOVO (500 mg Daily) (N=18) |
|---|-------------------------------------|
| Median DOCR, ^b months (range) | NE (1.9, 80.8+) |

- The **median time to CR** was **1.9 months** (range, 1.0-5.6)¹

- CR was defined by 2006 International Working Group Response Criteria for MDS, which requires responses lasting at least 4 weeks. Response criteria include²:
 - ≤5% bone marrow myeloblasts with normal maturation of all cell lines (persistent dysplasia will be noted)
 - Hgb ≥11 g/dL
 - Platelets ≥100 × 10⁹/L
 - Neutrophils ≥1.0 × 10⁹/L^c
 - 0% peripheral blasts
- One (6%) of the 18 patients went on to stem cell transplantation following TIBSOVO treatment¹

NE, not evaluable.

^a43% of CR responders had baseline bone marrow blasts <5%.

^bDate of first documented CR (lasted at least 4 weeks) to date of first documented confirmed relapse or death, whichever is earlier.

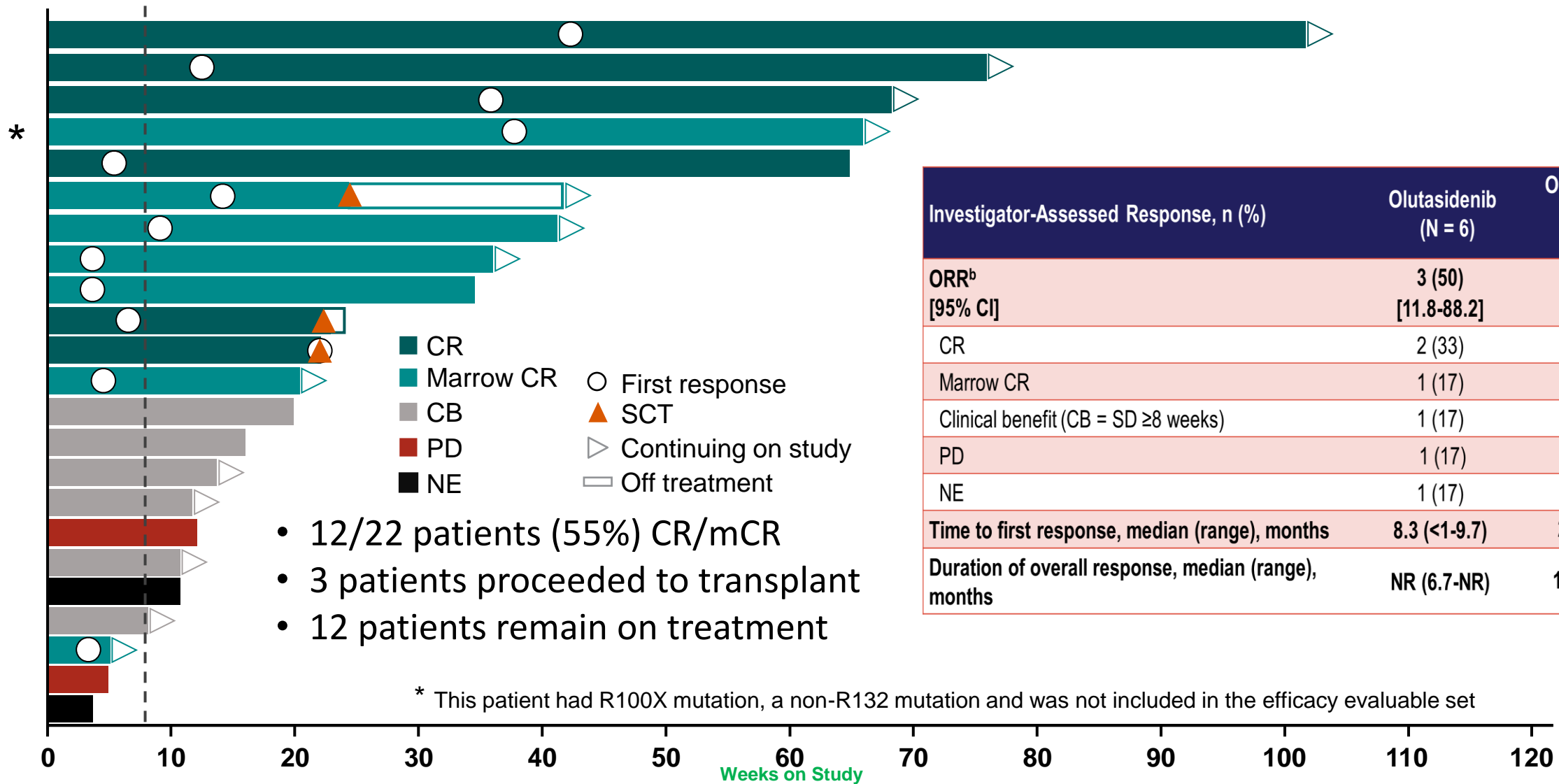
^cNeutrophil recovery was observed in all patients with CR. Among the 7 non-CR/PR responders eligible for neutrophil improvement, 4 subjects (57.1%) achieved neutrophil recovery.²

1. Tivoso. Package insert. Servier Pharmaceuticals LLC; 2023. 2. Data on file. Servier Pharmaceuticals LLC.

Please see Important Safety Information on slides 53-56 and Full Prescribing Information, including BOXED WARNING for AML and MDS patients, provided at this presentation.



Efficacy of FT-2102 (Olutasidenib) in IDH1-mutated MDS

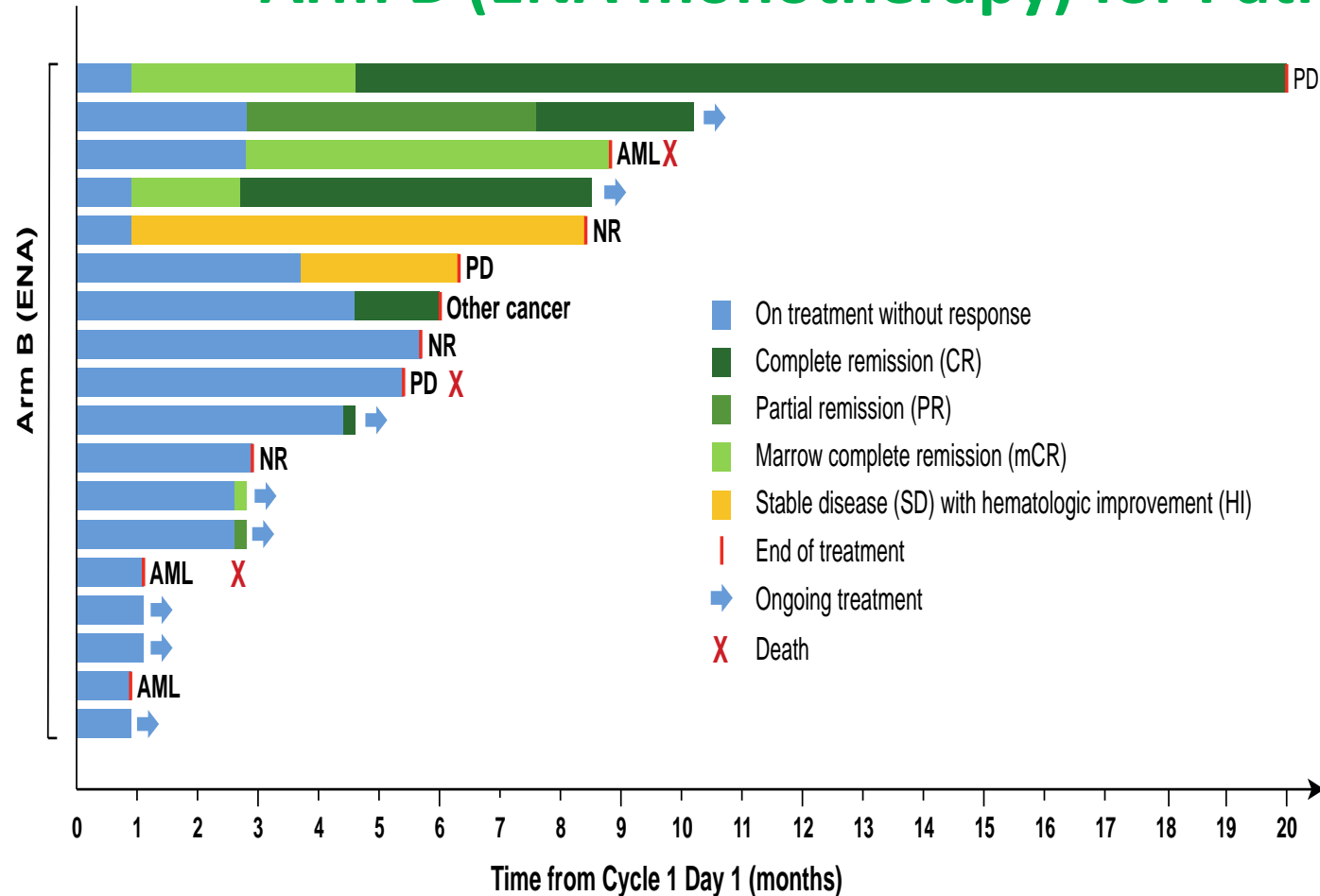


- 12/22 patients (55%) CR/mCR
- 3 patients proceeded to transplant
- 12 patients remain on treatment

| Investigator-Assessed Response, n (%) | Olutasidenib (N = 6) | Olutasidenib + AZA (N = 16) ^a |
|--|----------------------|--|
| ORR^b | 3 (50) | 9 (56) |
| [95% CI] | [11.8-88.2] | [29.9-80.2] |
| CR | 2 (33) | 4 (25) |
| Marrow CR | 1 (17) | 5 (31) |
| Clinical benefit (CB = SD ≥8 weeks) | 1 (17) | 5 (31) |
| PD | 1 (17) | 1 (6) |
| NE | 1 (17) | 1 (6) |
| Time to first response, median (range), months | 8.3 (<1-9.7) | 2.8 (<1-5.1) |
| Duration of overall response, median (range), months | NR (6.7-NR) | 12.9 (<1-NR) |

Phase II Study of Enasidenib in Patients With *IDH2*-Mutated HR-MDS

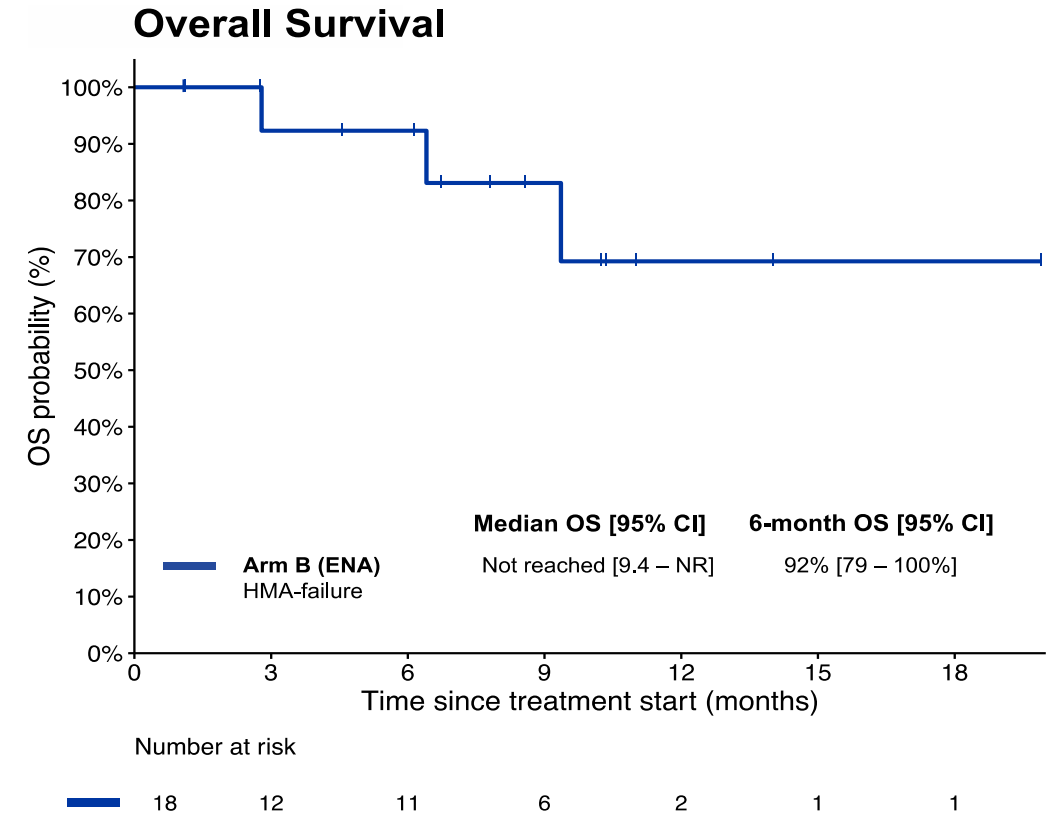
Arm B (ENA monotherapy) for Patients with HMA-failure



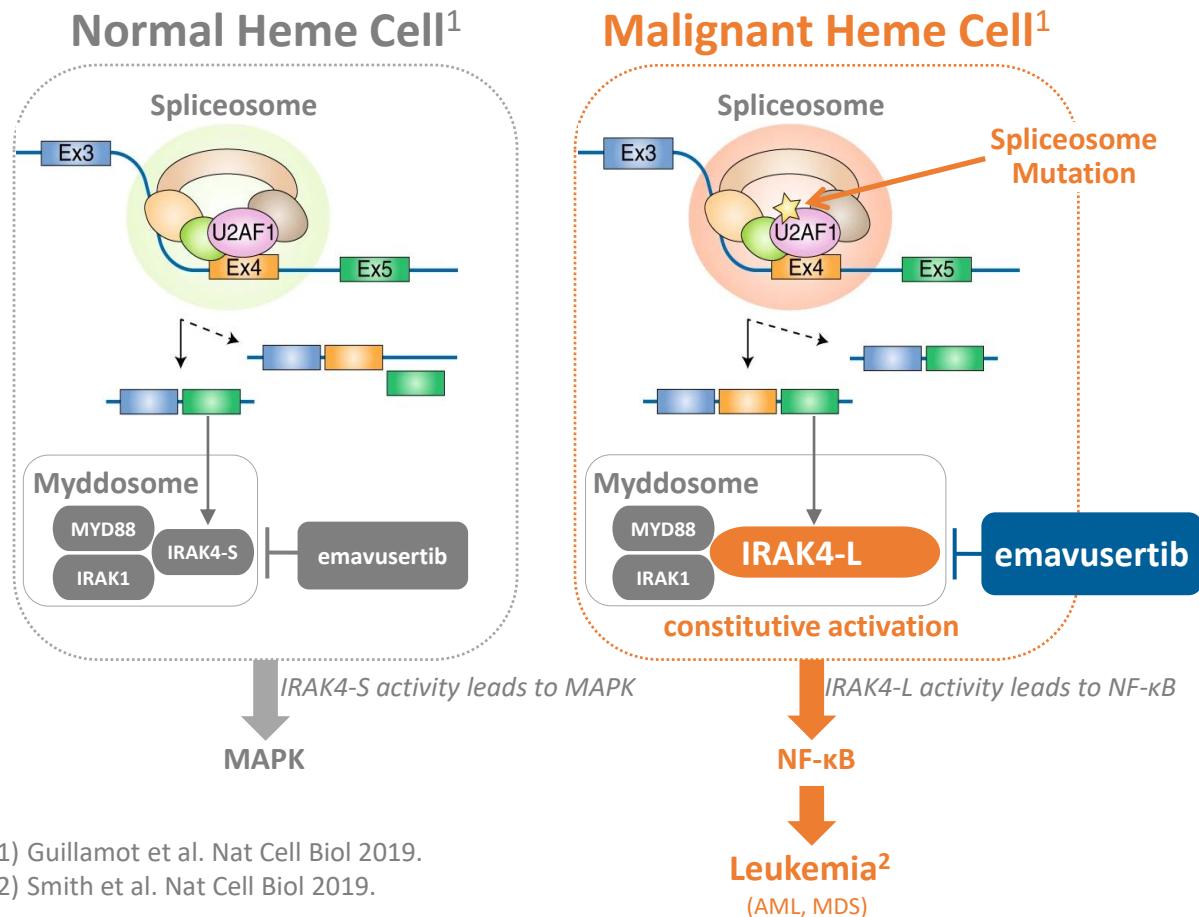
Median Follow-Up: 6.6 months [range, 1.1 – 19.9 months]

Median time to **INITIAL** response: **2.8 months** [range, 0.9 — 4.6 months]

Median time to **BEST** response: **4.6 months** [range, 2.7 — 7.6 months]



Emavusertib: Introduction



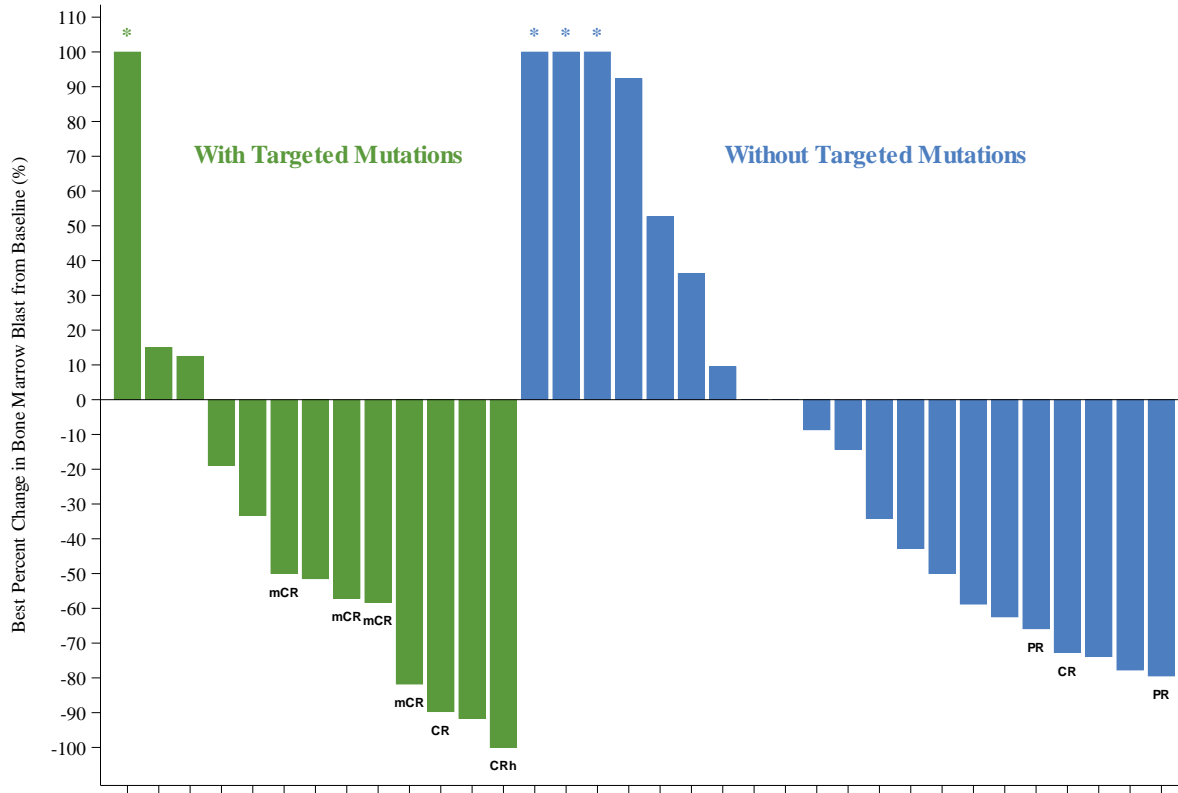
1) Guillamot et al. Nat Cell Biol 2019.

2) Smith et al. Nat Cell Biol 2019.

- Emavusertib (CA-4948), a novel oral IRAK4 inhibitor has potential antileukemia activity
- Specific genetic mutations (*SF3B1*, *U2AF1*) in the spliceosome drive overexpression of IRAK4 long isoform (IRAK4-L)
- IRAK4-L then causes constitutive activation of the myddosome, leading to overactivity of NF-κB
- Therefore, this drug can target patients with splicing mutations
- Emavusertib also targets FLT3 and has shown potential synergetic activity with other drugs

Targeting IRAK4: Emavusertib Exhibits: Single-Agent Activity in AML and HR-MDS

All Patients



Only evaluable patients with baseline and post-treatment bone marrow blast counts are included in the waterfall plot; among the patients w/o targeted mutations (*SF3B1* / *U2AF1* / *FLT3* mutation), 1 reached CR and 2 PR

* Indicates the best percentage change from baseline >100%

Subset of Patients With Targeted Mutations (*SF3B1* / *U2AF1* / *FLT3* Mutation)

| Best Response | Efficacy |
|---|------------------|
| Population #1: AML Spliceosome Patients^{1, 2} | |
| CR/CRh Rate | 2/5 (40%) |
| CR | 1/5 (20%) |
| CRh | 1/5 (20%) |
| Population #2: MDS Spliceosome Patients | |
| Objective Response Rate (ORR) | 4/7 (57%) |
| CR | 0/7 (0%) |
| mCR | 4/7 (57%) |
| Population #3: AML <i>FLT3</i> Patients¹ | |
| CR/CRh Rate | 1/3 (33%) |
| CR | 1/3 (33%) |
| CRh | 0/3 (0%) |

- Two AML patients have both a spliceosome and *FLT3* mutation and are included in both populations (there are 13 total evaluable patients with spliceosome or *FLT3* mutation)
- One patient was not response evaluable because of discontinuation due to patient decision

Phase 1 Results of the First-in-Class CXCR1/2 Inhibitor SX-682 in Patients with Hypomethylating Agent Failure Myelodysplastic Syndromes

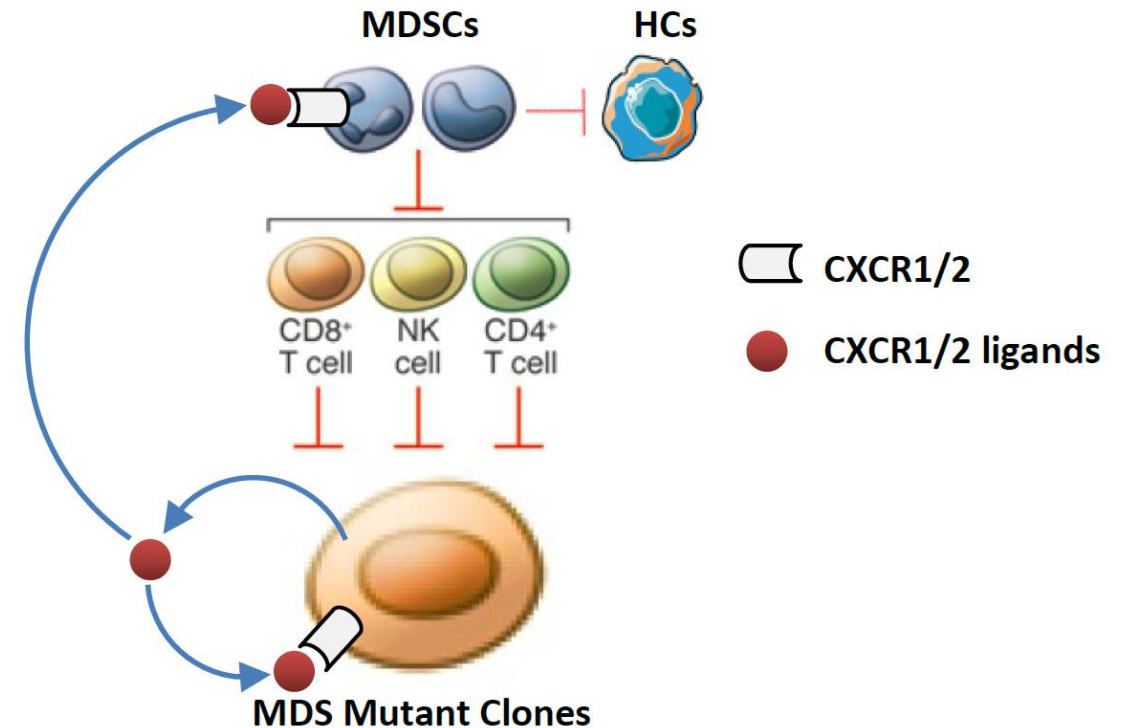
Oral abstract 855 of the *2022 ASH Annual Meeting, December 10-13, 2022; New Orleans, Louisiana**

*Session 637. Myelodysplastic Syndromes – Clinical and Epidemiological I. Monday, December 12, 2022, 3:15 pm.

David A. Sallman, MD, Amy E. DeZern, MD, Arlene A. Gayle, MD, Stuart J. Kahn, MD, Eric Padron, MD, Jeffrey E. Lancet, MD, Andrew Kuykendall, MD, Kendra Sweet, MD, Onyee Chan, MD, Dean Y. Maeda, PhD, Aaron D. Schuler, PhD, John A. Zebala, MD, PhD and Rami S. Komrokji

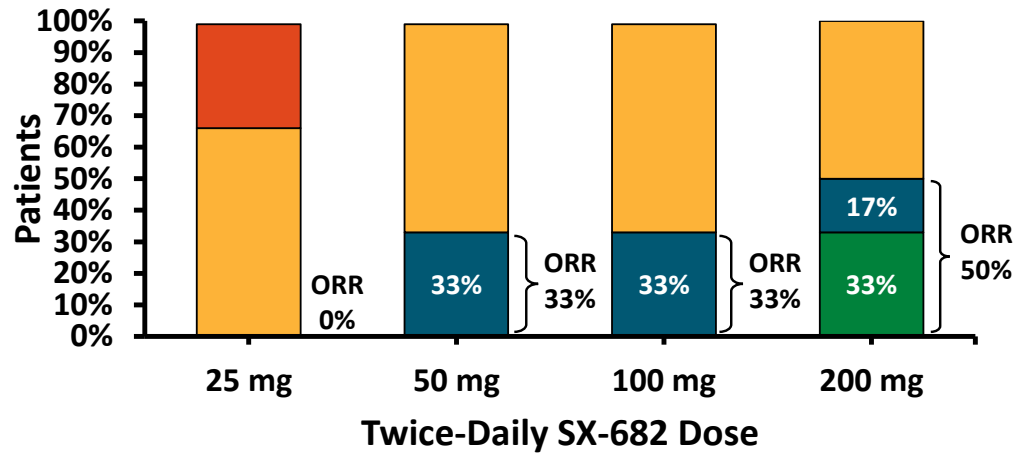
First-in-Class SX-682 in HMA Failure MDS: Background

- Prognosis remains poor for patients with MDS who fail HMA therapy
 - After azacitidine failure, median OS is 5.6 mos and estimated 24-mo OS rate is 15%^[1]
 - After decitabine failure, median OS is 4.3 mos and estimated 12-mo OS rate is 28%^[2]
- CXCR1/2 receptors drive mutant clone growth and recruit MDSCs that suppress anti-clone marrow immunity and kill hematopoietic cells (HCs)^[3,4]



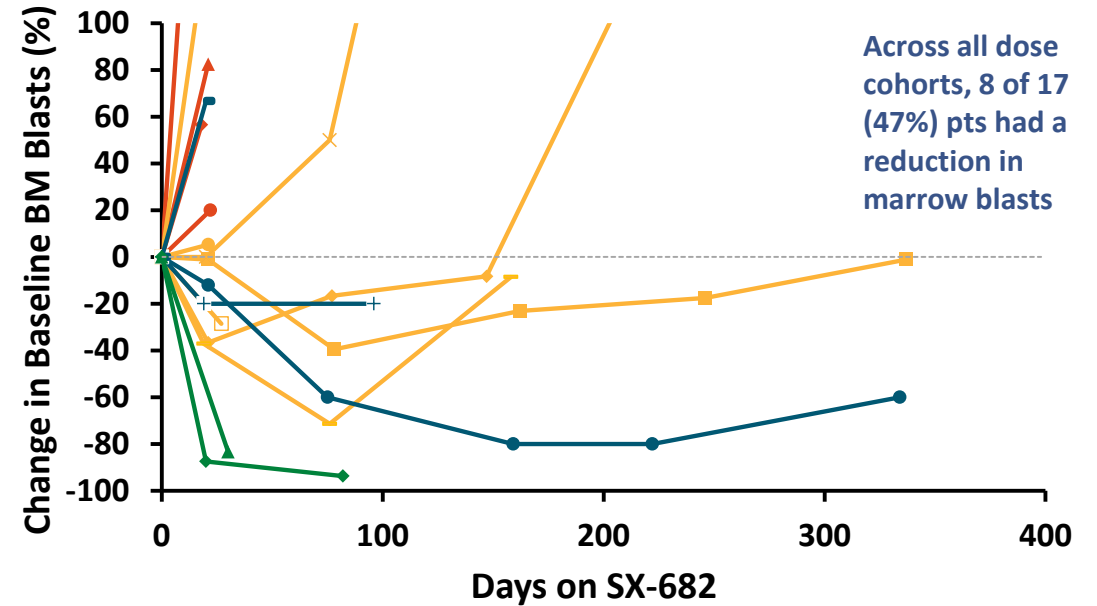
First-in-Class SX-682 in HMA Failure MDS: Response

Best Overall Response



- Progressive Disease (PD)
- Stable Disease (SD)
- SD + Hematologic Improvement (HI)
- Marrow Complete Remission (mCR)

BM Blast Reductions



- 25 mg, PD
- ▲ 50 mg, PD
- 200 mg, withdrew
- 400 mg, PD
- 25 mg, SD
- ▲ 25 mg, SD
- × 50 mg, SD (platelet units/100 days 18→3)
- 100 mg, SD
- ▲ 100 mg, SD
- ▲ 200 mg, SD
- 200 mg, SD → on treatment
- 50 mg, SD + HI-E/P + TI x 4 mos
- ▲ 100 mg, SD + HI-P/N
- 200 mg, HI-P, SD → on treatment
- 200 mg, mCR
- ▲ 200 mg, mCR/SD

Summary

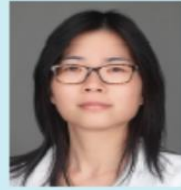
- Novel therapies in LR-MDS targets MDS clone or its differentiation and inflammatory bone marrow milieu.
- HMA remains standard of care in higher risk MDS, a combination therapy with higher CR rates is needed to provide OS advantage.
- After HMA failure in HR-MDS treatment and clinical trials should be tailored based on molecular profile.

Thank You
Rami.Komrokji@moffitt.org

MEET THE TEAM



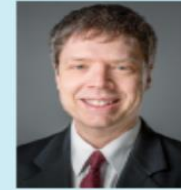
Dr. Rami Komrokji



Dr. Onyee Chan



Dr. Andrew Kuykendall



Dr. Jeffrey Lancet



Dr. Eric Padron



Dr. David Sallman



Dr. Kendra Sweet



Dr. Sara Tinsley

Moffitt MDS team: Only perfect counts !!!

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