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New Therapeutic Options in the Myelodysplastic Syndromes

Brian A. Jonas, MD, PhD, FACP

Associate Professor of Medicine

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Disclosures

- Consulting/Advising:
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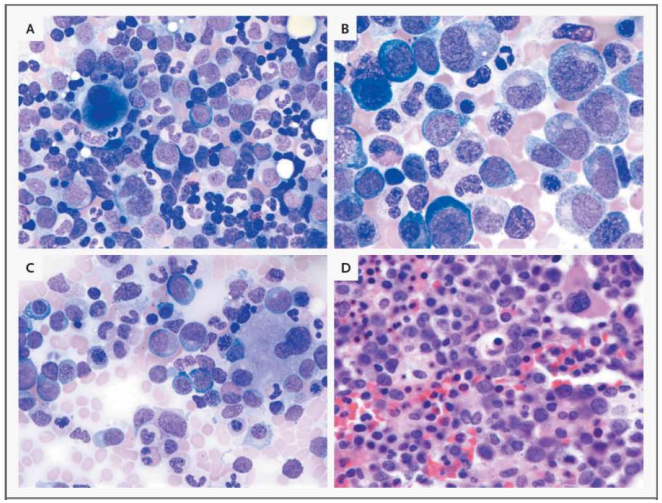
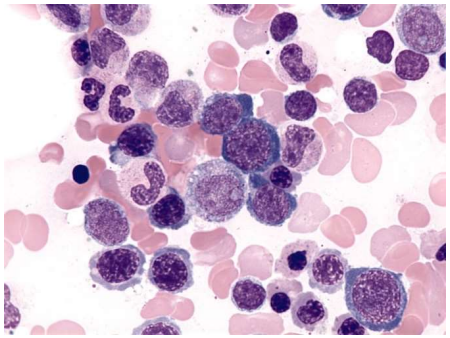
The Myelodysplastic Syndromes (MDS)

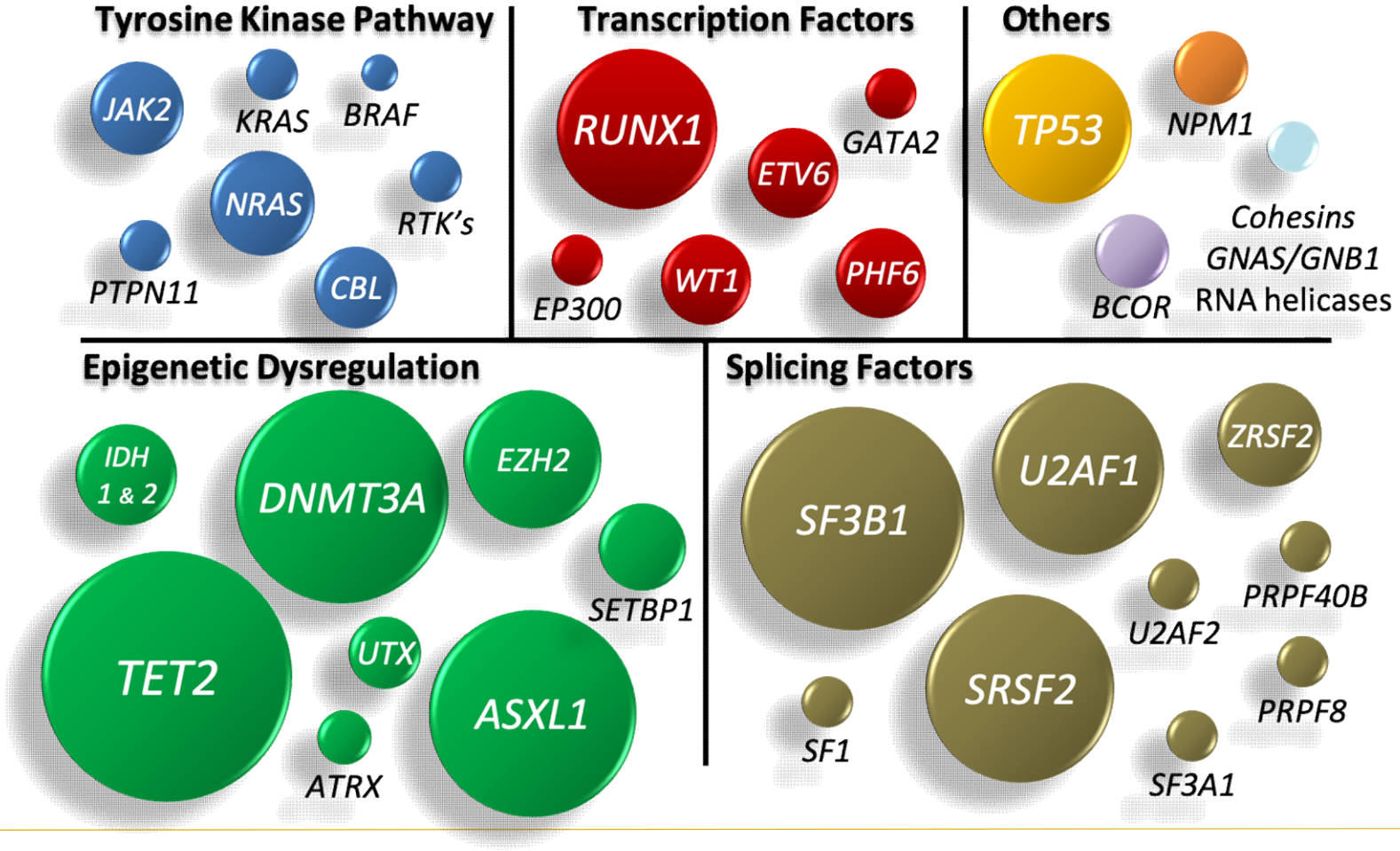
- Heterogeneous group of clonal bone marrow failure syndromes
- 10-30,000 cases per year in US
- Median age 76, > in males
- Ineffective hematopoiesis
  - Bleeding, infections, anemia
- Transformation to AML
- Variable clinical course
  - Need for accurate prognostication



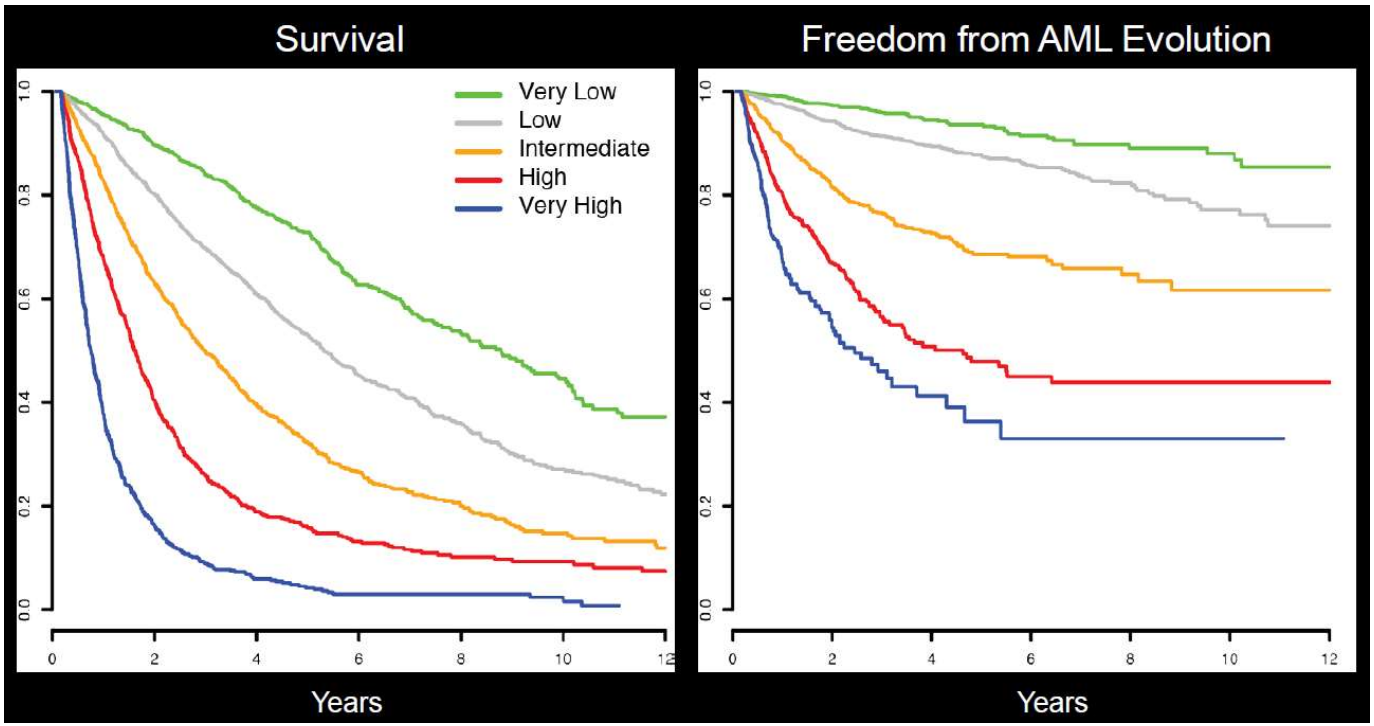


List et al. NEJM 2005.
Ma et al. Cancer 2007.

Recurrent Mutations in MDS



IPSS-R: Risk Stratification and Prognosis



BM blasts, cytogenetics and CBC values

Very low risk ≤1.5 points; Low risk >1.5-3 points; Intermediate risk >3-4.5 points; High risk >4.5-6 points; Very High risk >6 points

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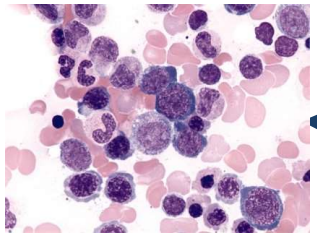
Greenberg et al, Blood 2012.
Schanz et al, JCO 2012.

Current Treatment Approach and Options in MDS

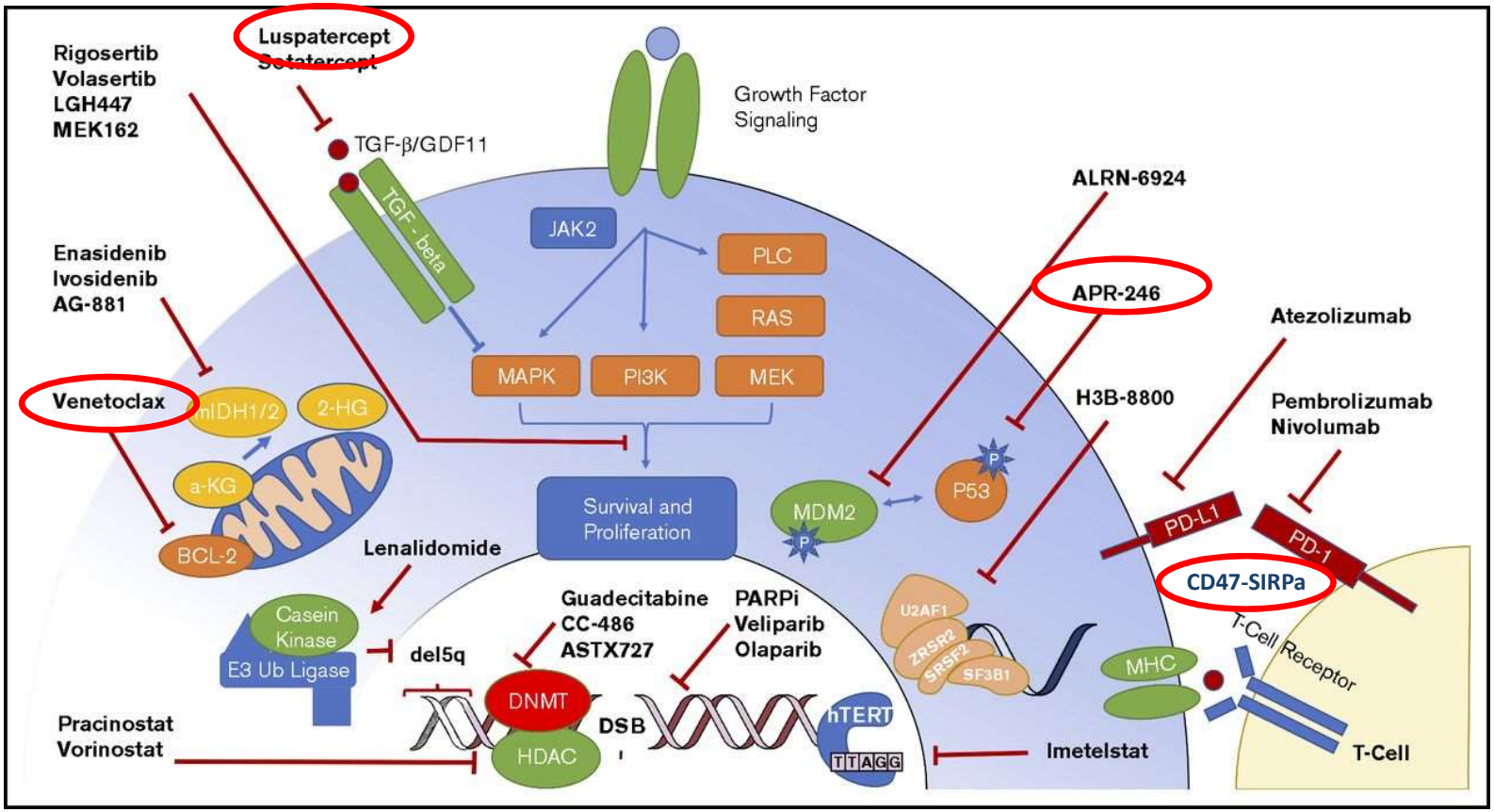


Diagnosis of MDS

	Treatment Goal	Treatment Options
Higher Risk: IPSS-R Int*, HR, VHR	Alter disease natural history	• Hypomethylating agents (HMA) • High-intensity chemotherapy (IC) • Allogeneic HCT • Clinical Trial
Lower Risk: IPSS-R VLR, LR, Int*	Hematologic improvement	• Growth factors • Lenalidomide • Immune suppressive therapy (IST) • HMA • Watch and Wait • Clinical Trial

* Differentiating features: age, performance status, ferritin, LDH

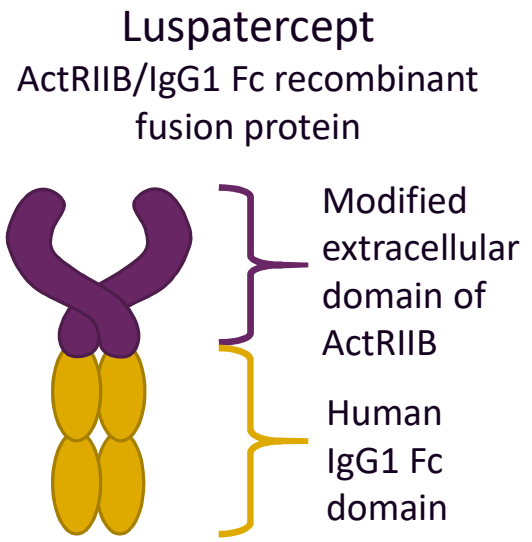
Emerging Molecular Targets and Therapeutics in MDS



Alex Aleshin and Peter L. Greenberg, Blood Adv 2018;2:2787-2797

Luspatercept

- Investigational first-in-class erythroid-maturation agent
- Neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase II study in lower-risk non-del(5q) MDS, luspatercept yielded a high frequency of transfusion reduction or RBC-TI in patients with ring sideroblasts vs other subtypes[2]

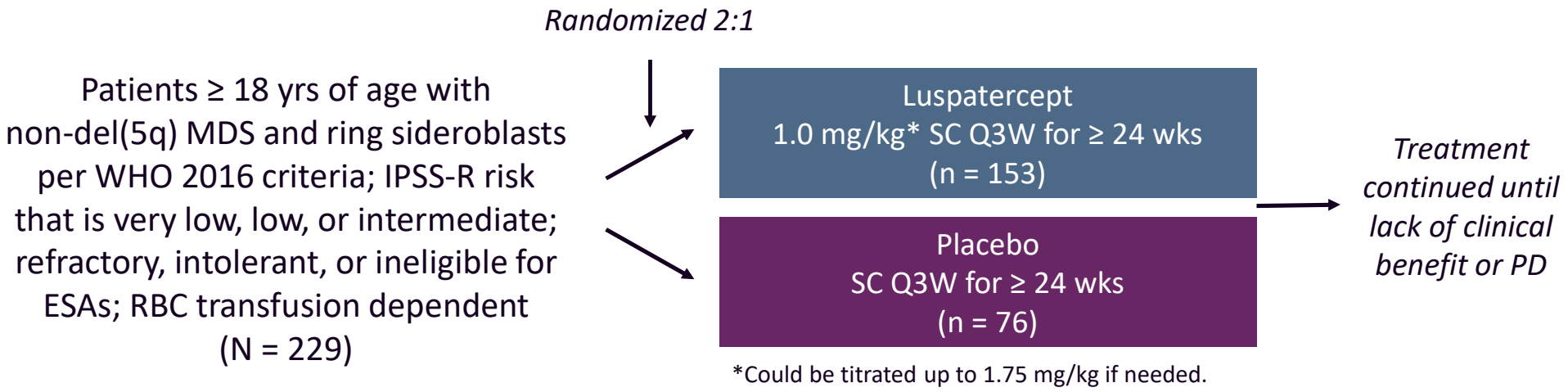


1. Suragani. Nat Med. 2014;20:408. 2. Platzbecker. Lancet Oncol. 2017;18:1338.

Slide credit: clinicaloptions.com

Phase III MEDALIST Trial of Luspatercept vs Placebo in Lower-Risk Non-del(5q) MDS-RS

- International, randomized, double-blind, placebo-controlled phase III trial



Primary endpoint: RBC TI for ≥ 8 wks between Wk 1 and Wk 24

Secondary endpoints: RBC TI for ≥ 12 wks between Wk 1 and Wk 24, modified hematologic improvement–erythroid response per IWG 2006 criteria, DoR, Hb change from baseline

Medalist: Patient Characteristics

Characteristic	Luspatercept (n = 153)	Placebo (n = 76)
Median age, yrs (range)	71 (40-95)	72 (26-91)
Male, n (%)	94 (61.4)	50 (65.8)
Median time from diagnosis, mos (range)	44.0 (3-421)	36.1 (4-193)
Median RBC burden, units (range)*	**5 (1-15)**	**5 (2-20)**
▪ ≥ 6 units/8 wks, n (%)	66 (43.1)	33 (43.4)
▪ < 6 units/8 wks, n (%)	87 (56.9)	43 (56.6)
Median pre-transfusion Hb, g/dL (range)	7.6 (6-10)	7.6 (5-9)
Baseline serum erythropoietin, n (%)		
▪ < 200 IU/L	88 (57.5)†	50 (65.8)
▪ ≥ 200 IU/L	64 (41.8)†	26 (34.2)
IPSS-R risk category in 16 wks prior to randomization, n (%)‡		
▪ Very low, Low	127 (83.0)	63 (82.9)
▪ Intermediate	25 (16.3)	13 (17.1)
SF3B1 mutation, n (%)	141 (92.2)	65 (85.5)†

*In the 16 weeks prior to randomization. †Data were missing for 1 patient. ‡1 (0.7%) patient in the luspatercept arm was classified as IPSS-R high risk.

Fenaux. ASH 2018. Abstr 1.

Medalist: Efficacy

Outcome, %	Luspatercept (n = 153)	Placebo (n = 76)	*P* Value
RBC TI ≥ 8 wks in Wks 1-24	37.9	13.2	< .0001
RBC TI ≥ 12 wks in Wks 1-24	28.1	7.9	.0002
RBC TI ≥ 12 wks in Wks 1-48	33.3	11.8	.0003
mHI-E* ≥ 8 wks in Wks 1-24	**52.9**	**11.8**	**< .0001**
▪ Reduction of ≥ 4 RBC units/8 wks	48.6	14.3	
▪ Hb increase of ≥ 1.5 g/dL	63.0	5.0	
mHI-E* ≥ 8 wks in Wks 1-48	**58.8**	**17.1**	**< .0001**
▪ Reduction of ≥ 4 RBC units/8 wks	54.2	21.4	
▪ Hb increase of ≥ 1.5 g/dL	69.6	5.0	

*Defined as transfusion reduction of ≥ 4 units/8 wks or mean hemoglobin increase ≥ 1.5 g/dL/8 wks in absence of transfusions

- Among primary endpoint responders, the median duration of RBC TI response was 30.6 wks in the luspatercept arm vs 13.6 wks in the placebo arm

Fenaux. ASH 2018. Abstr 1.

Medalist: Safety

TEAE of Any Grade, %	Luspatercept (n = 153)	Placebo (n = 76)
Fatigue	26.8	13.2
Diarrhea	22.2	9.2
Asthenia	20.3	11.8
Nausea	20.3	7.9
Dizziness	19.6	5.3
Back pain	19.0	6.6
Cough	17.6	13.2
Peripheral edema	16.3	17.1
Headache	15.7	6.6
Dyspnea	15.0	6.6
Bronchitis	11.1	1.3
Constipation	11.1	9.2
UTI	11.1	5.3
Fall	9.8	11.8

TEAE, %	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥ 1 TEAE	98.0	92.1
▪ ≥ 1 serious TEAE	31.4	30.3
▪ ≥ 1 grade 3/4 TEAE	42.5	44.7
▪ TEAEs leading to death	3.3	5.3
▪ ≥ TEAE causing discontinuation	8.5	7.9

- 4 patients progressed to acute myeloid leukemia: 3 in luspatercept arm, 1 in placebo arm
- The most common grade 3/4 TEAEs in luspatercept arm were anemia (6.5%), fatigue (4.6%), and fall (4.6%)

Fenaux. ASH 2018. Abstr 1.

Medalist: Conclusions

- Luspatercept significantly reduced RBC transfusion burden compared with placebo in transfusion-dependent patients with very low- to intermediate-risk MDS with RS
  - Met primary endpoint of improving proportion of patients achieving RBC transfusion independence for ≥ 8 wks in Wks 1-24
  - Significantly more patients achieved RBC transfusion independence for ≥ 12 wks in Wks 1-24 and in Wks 1-48
  - Significantly more patients achieved increase in Hb of ≥ 1.5 g/dL
- Treatment generally well tolerated
- Luspatercept may offer a new treatment option for transfusion-dependent anemia in lower-risk RS-positive MDS patients – approval decision by 4/2020

Fenaux. ASH 2018. Abstr 1.

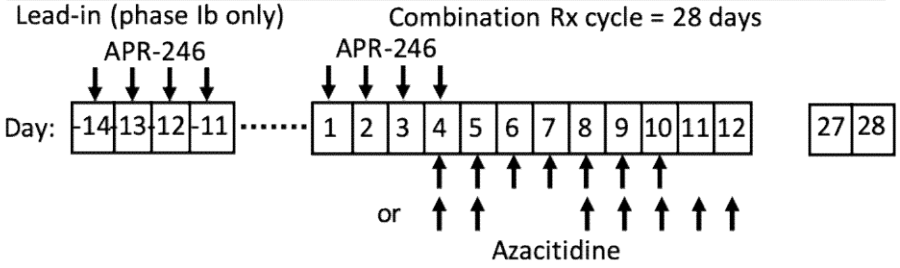
APR-246

- TP53 mutations confer a poor prognosis in patients with MDS
- APR-246 restores the wild-type conformation of mutant p53
- Phase Ib/II trial of APR-246 and Azacitidine in HMA-naïve TP53-mutated MDS and AML (≤ 30% blasts)

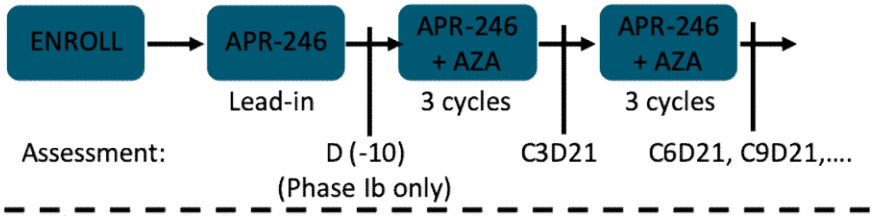
Dosing

Drug	Dose	Admin.	Duration
APR-246	PhIb: 50/75/100 mg/kg LBM PhII: 4500 mg fixed dose	IV	6 hrs
Azacitidine	75 mg/m^2	SC (or IV)	

Dosing Schedule



Assessment Schedule



Endpoints

	Phase Ib	Phase II
Primary:	Safety	CR rate
Secondary:	ORR, PFS, OS, *TP53* VAF	ORR, PFS, OS, *TP53* VAF

Sallman. ASH 2018. Abstr 3091.

APR-246 plus Azacitidine: Safety

Most common TEAEs with any relation to APR-246 or AZA, n (%)

	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5
Nausea	9 (42)	3 (14)	0	0	0
Peripheral neuropathy	8 (38)	0	0	0	0
Vomiting	6 (29)	2 (10)	0	0	0
Dizziness	4 (19)	2 (10)	0	0	0
Thrombo-cytopenia	0	1 (5)	0	0	0
Neutropenia	0	0	0	0	0
Pruritus	4 (19)	1 (5)	0	0	0
Tremor	4 (19)	0	0	0	0
Constipation	3 (14)	1 (5)	0	0	0
Headache	4 (19)	0	0	0	0
Leukopenia	0	0	1 (5)	3 (14)	0

TEAEs in > 1 patient with any relation to APR-246 only, n (%)

	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5
Nausea	3 (14)	0	0	0	0
Peripheral neuropathy	6 (29)	0	0	0	0
Dizziness	2 (10)	1 (5)	0	0	0
Tremor	3 (14)	0	0	0	0
Edema	1 (5)	1 (5)	0	0	0

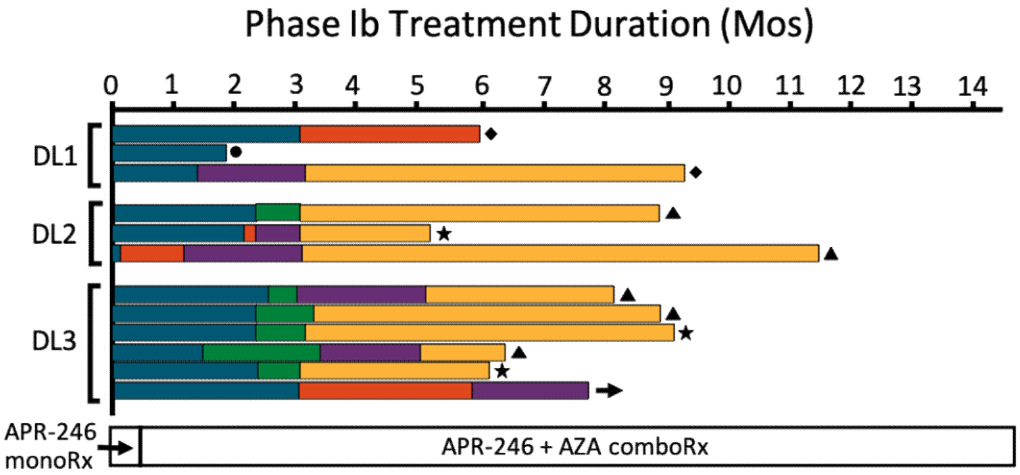
G3/4 hematologic TEAEs by APR-246 dose level, n (%)

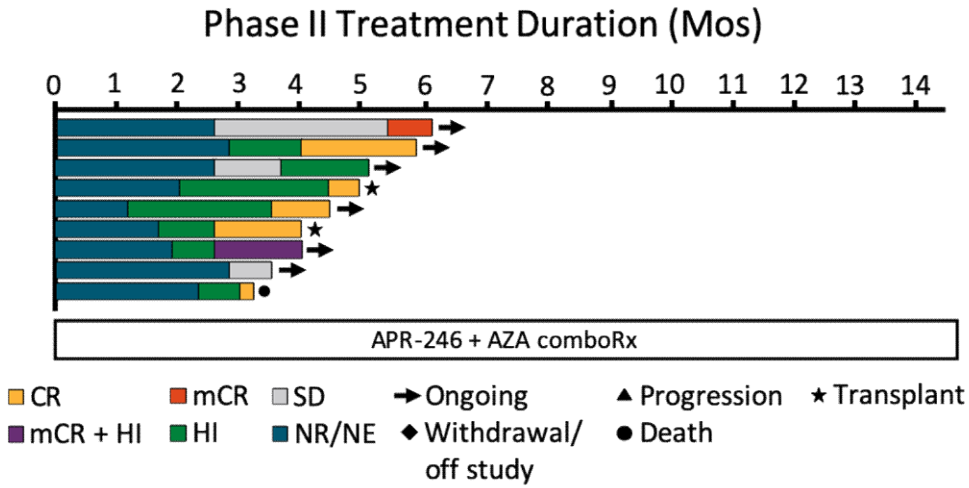
	Phase Ib DL1	Phase Ib DL2	Phase Ib DL3	Phase II
Febrile neutropenia	1 (33)	0	3 (50)	2 (10)
Neutropenia	2 (66)	3 (100)	1 (17)	2 (10)
Thrombocytopenia	1 (33)	2 (66)	2 (33)	1 (5)
Leukopenia	2 (66)	1 (33)	1 (33)	1 (5)
Anemia	1 (33)	0	2 (33)	0

- No DLTs experienced to date
- No correlation of TEAE frequency, severity with increasing APR-246 dose
- No increase in grade 3/4 hematologic TEAEs above that expected for AZA

Sallman. ASH 2018. Abstr 3091.

APR-246 plus Azacitidine: Efficacy





Best Response at Cutoff

	Phase Ib	Phase II	MDS	AML	Total	AZA Historical
Evaluable patients, n	11	9	15	5	20	
ORR, %	100	89	93	100	95	30-50
CR, %	82	56	67	80	70	20-30

Sallman. ASH 2018. Abstr 3091.

APR-246 plus Azacitidine: Conclusions

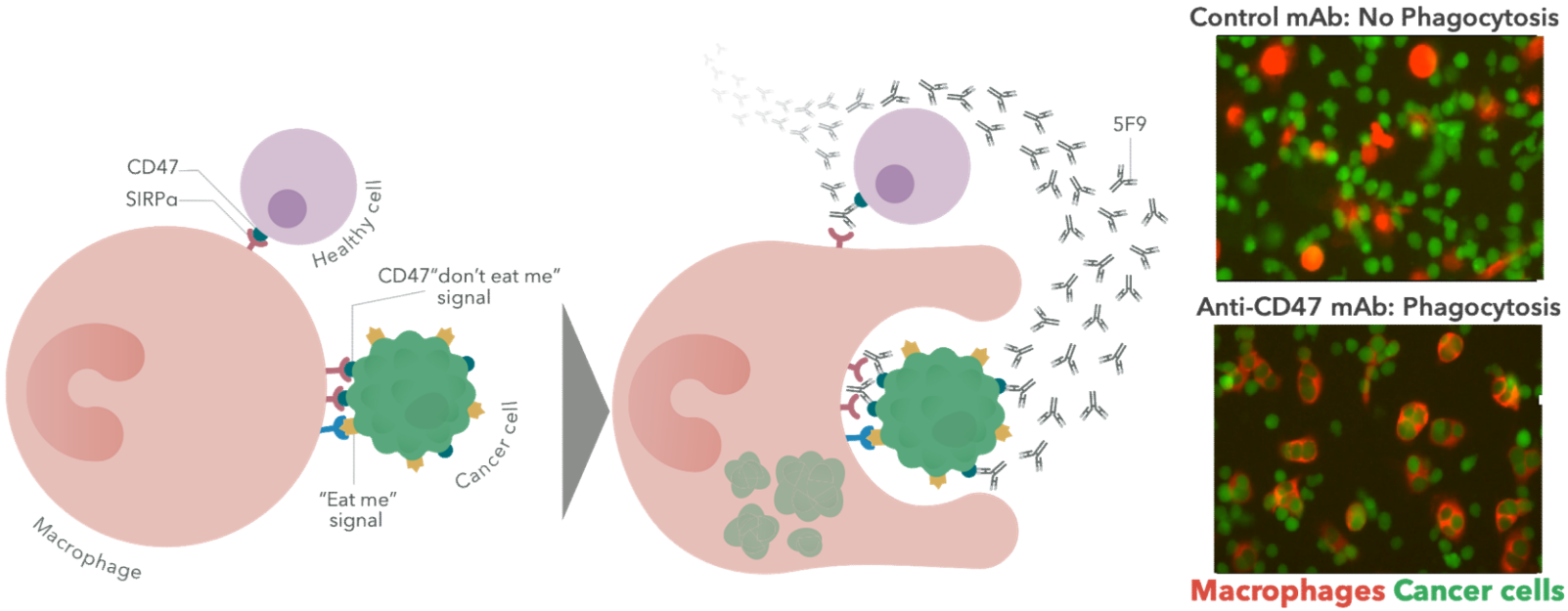
- The combination of APR-246 and Azacitidine is well tolerated in patients with mTP53 MDS and AML
- Responses have been achieved in 95% of patients overall including 70% with CR
- Median OS and PFS not reached
- Normalization of p53 positivity by IHC and TP53 mutations by NGS along with MRD responses by ddPCR were seen
- Transcriptional activation of p53 targets, including pathways involved in cell cycle arrest, apoptosis, DNA repair and regulation of TP53 activity, were observe
- The phase II portion of the trial is ongoing

The First-in-Class Anti-CD47 Antibody Hu5F9-G4 is Well Tolerated and Active Alone or with Azacitidine in AML and MDS Patients: Initial Phase 1b Results

David A Sallman[1], William Donnellan[2], Adam Asch[3], Daniel Lee[4], Monzr Al Malki[5], Guido Marcucci[5], Daniel Pollyea[6], Suman Kambhampati[7], Rami Komrokji[1], Joanna Van Elk[8], Ming Lin[8], James Y Chen[8], Jens-Peter Volkmer[8], Chris Takimoto[8], Mark Chao[8], Paresh Vyas[9]

[1]Moffitt Cancer Center, Tampa, FL; [2]Sarah Cannon Research Institute, Nashville, TN; [3]University of Oklahoma, Oklahoma City, OK, City of Hope, Duarte, CA; [4]Columbia University, New York, NY; [5]City of Hope, Duarte, CA; [6]University of Colorado, Denver, CO; [7]Healthcare Midwest, Kansas City, MO; [8]Forty Seven, Inc., Menlo Park, CA; [9]University of Oxford, Oxford, UK

5F9 is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47



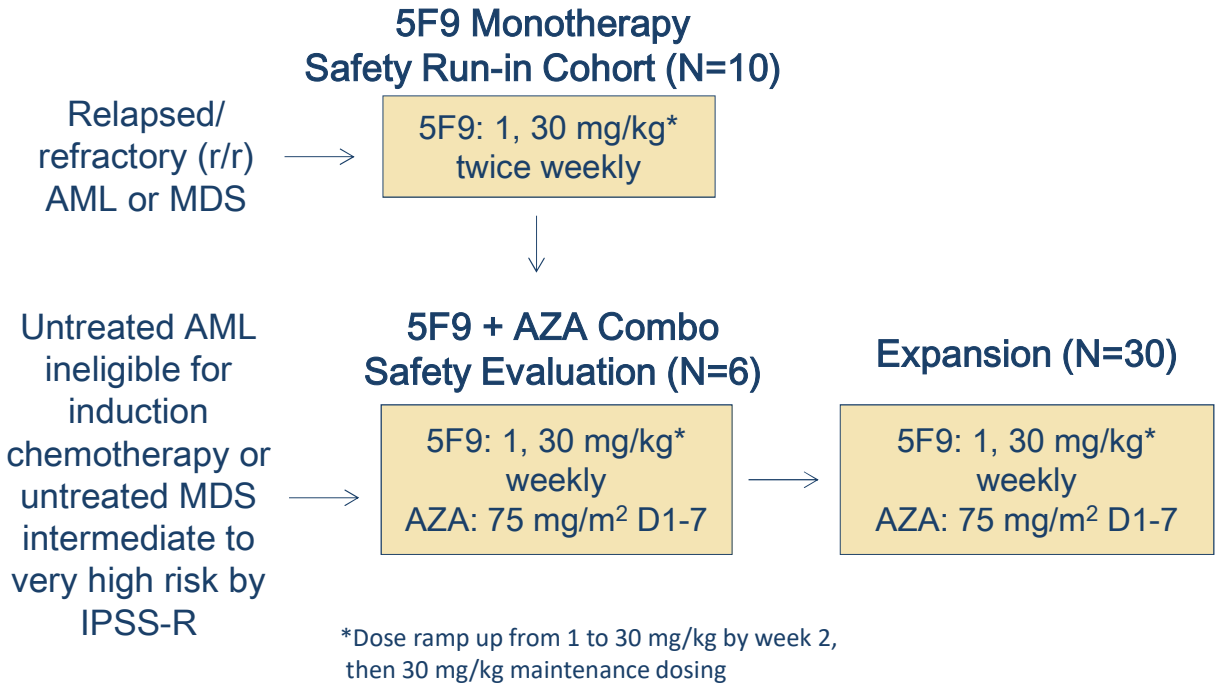
- 5F9 was well tolerated in a UK Phase 1 trial in r/r AML with no MTD reached (Vyas et al., EHA abs 2018)

- Aza induces "eat me" signals on cancer cells and synergizes with 5F9 in AML xenograft models

Sallman et al. Hemasphere. 3:394. June 2019; Feng et al., ASH Abs 2018.

Slide credit: FortySeven

5F9005 Study: Design



Primary objectives

1) Safety of 5F9 alone or with AZA
2) Efficacy of 5F9 in r/r AML/MDS and 5F9+AZA in untreated AML/MDS

Secondary objectives

1) PK, PD and immunogenicity of 5F9
2) Additional measures of efficacy (DOR, PFS, OS)

Exploratory objectives

1) To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

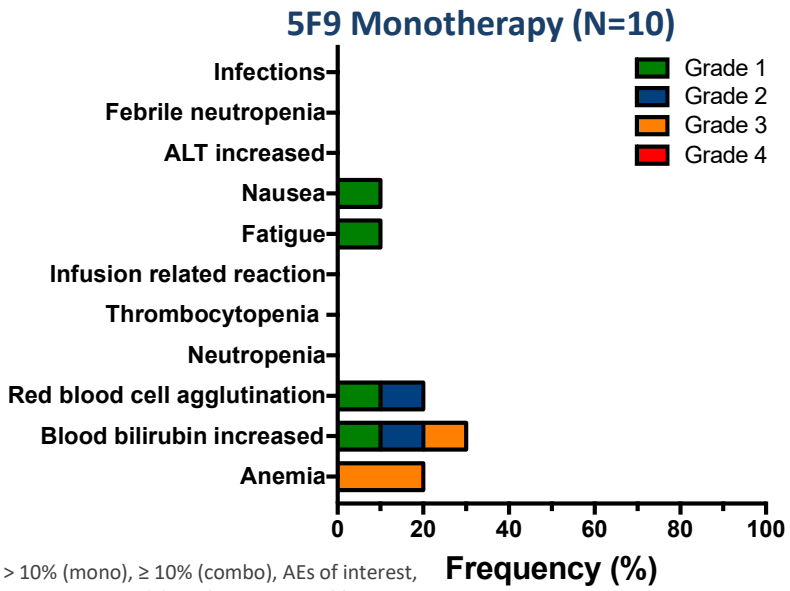
- A 5F9 priming dose (1 mg/kg) and dose ramp up was utilized to mitigate on target anemia
- 5F9 monotherapy safety was confirmed in r/r AML/MDS patients prior to 5F9+AZA combination

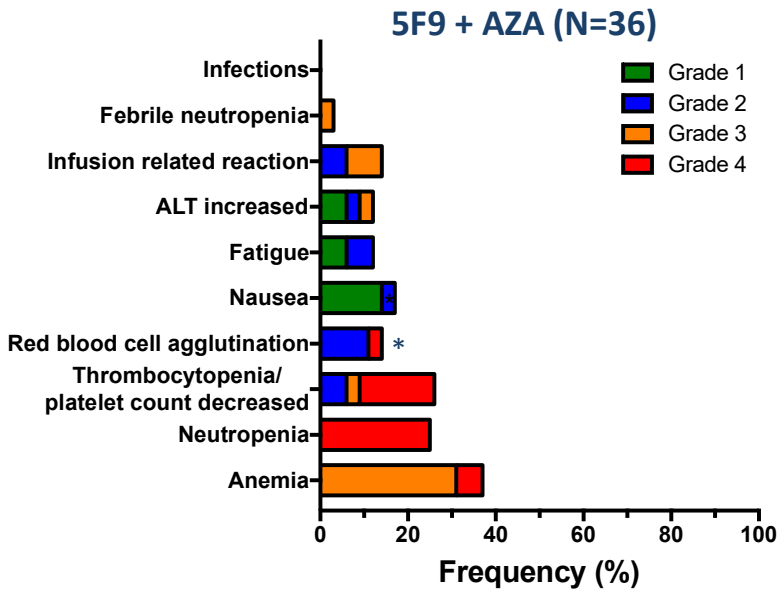
Sallman. Hemasphere. 3:394. June 2019.

Slide credit: FortySeven

5F9005 Study: Safety

Treatment-related AEs to 5F9 and/or AZA





TRAEs > 10% (mono), ≥ 10% (combo), AEs of interest, dose limiting toxicities* (DLTs) regardless of frequency are shown
All patients dosed with 5F9 are shown

- No MTD reached with 5F9 alone or in combo; 5F9+AZA profile consistent with AZA monotherapy
- 1 DLT observed with 5F9+AZA: G4 hemagglutination: patient with IRR symptoms/extremity tremulousness on first dose, with peripheral smear agglutination, resolved after 24 hours, neurologic work-up was negative
- No significant cytopenias, infections, or autoimmune AEs occurred (most patients cytopenic at baseline)
- No study deaths observed within the first 60 days of treatment on 5F9+AZA
- Treatment discontinuation due to AE occurred in only 1 of 46 (2%) in all patients treated with 5F9

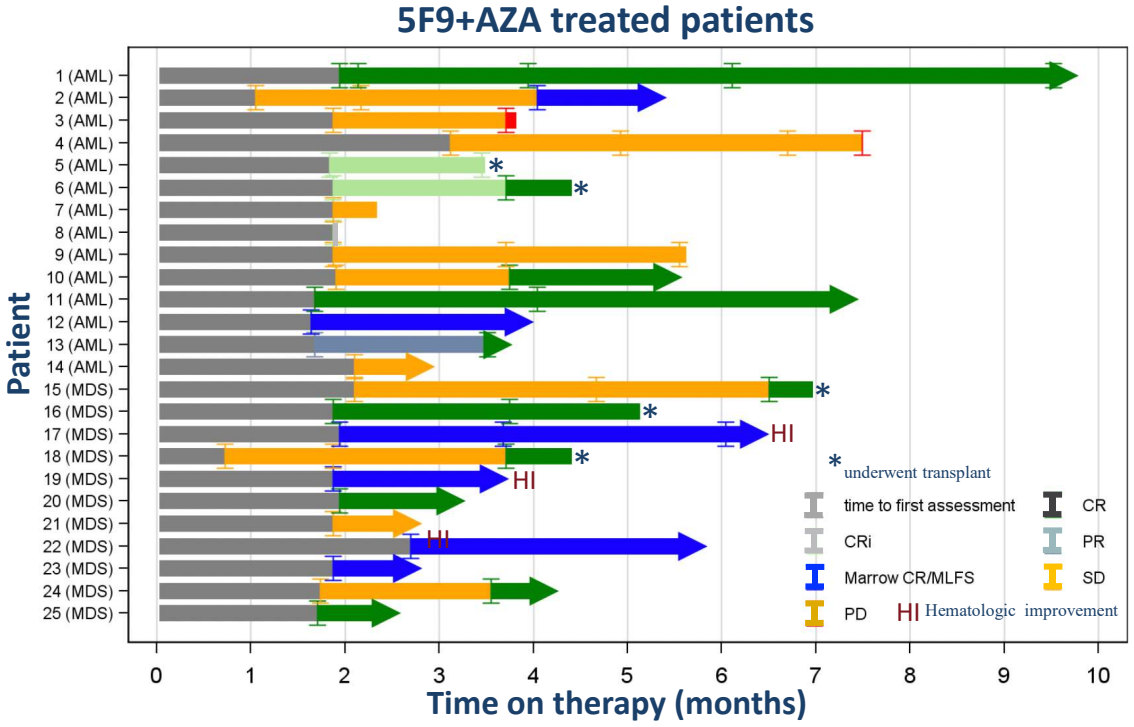
Sallman. Hemasphere. 3:394. June 2019.

Slide credit: FortySeven

5F9005 Study: Efficacy

Best Overall Response	R/R AML/MDS 5F9 mono N=10	1L AML 5F9+AZA N=14	1L MDS 5F9+AZA N=11
ORR	1 (10%)	9 (64%)	11 (100%)
CR	0	5 (36%)	6 (55%)
CRi	0	2 (14%)	-
PR	0	0	0
MLFS/ marrow CR	1 (10%)	2 (14%)	4 (36%) 2 with marrow CR+HI
Hematologic improvement (HI)	-	-	1 (9%)
SD	7 (70%)	5 (36%)	0
PD	2 (20%)	0	0

Response assessments per 2017 AML ELN criteria and 2006 IWG MDS criteria; Patients with at least one post-treatment response assessment are shown
"-" not applicable



- Median time to response is more rapid (1.9 months) than AZA alone

Sallman. Hemasphere. 3:394. June 2019.

Slide credit: FortySeven

5F9005 Study: Conclusions

- 5F9 is a first-in-class antibody targeting the macrophage checkpoint CD47 and is a promising novel immunotherapy in AML and MDS
- 5F9 is well tolerated alone or in combination with AZA with no MTD achieved
- On target anemia is transient and mitigated by priming/maintenance dosing with hemoglobin improving on therapy
- Encouraging efficacy is observed with 5F9+AZA (ORR 100% in MDS, 64% in AML)
- No responding patient has progressed on therapy, with a median follow up of 3.8 months
- 5F9 + AZA eliminates putative LSCs in responding patients
- Expansion cohorts have been initiated in AML and MDS (NCT03248479)

Sallman. Hemasphere. 3:394. June 2019.

Slide credit: Forty Seven

Venetoclax in MDS

- Preclinical data suggest activity of venetoclax in higher risk MDS
- No significant clinical evidence for safety and efficacy to date
- Two ongoing trials, results of which are eagerly anticipated (? ASH 2019)
  - NCT02966782 – Phase 1b study of venetoclax alone or in combination with azacitidine for higher risk *de novo* MDS with excess blasts with prior HMA failure
  - NCT02942290 – Phase 1b study of venetoclax plus azacitidine for untreated higher risk *de novo* MDS with excess blasts not candidates for intensive chemotherapy or allo-HCT

Fong et al, ASCO 2019 Abstract #TPS7082.

Summary and Conclusions

- MDS is heterogeneous group of BM failure syndromes
- Variable clinical presentation and course
- Choice of therapy is primarily based on prognostic scoring systems, symptoms, age and comorbidities
- Understanding of pathogenesis, prognostication and treatment is evolving
- Novel molecularly targeted therapies are being evaluated
- Luspatercept may receive FDA approval in 2020 for LR MDS with RS