“Myelodysplastic Syndromes and Promising New Drugs in Genome Era”

Carlos E. Vigil-Gonzales, MD FACP
Clinical Assistant Professor
University of Iowa Hospitals and Clinics

OBJECTIVES

To learn about MDS and mechanism of disease .

To understand available treatment options in clinic.

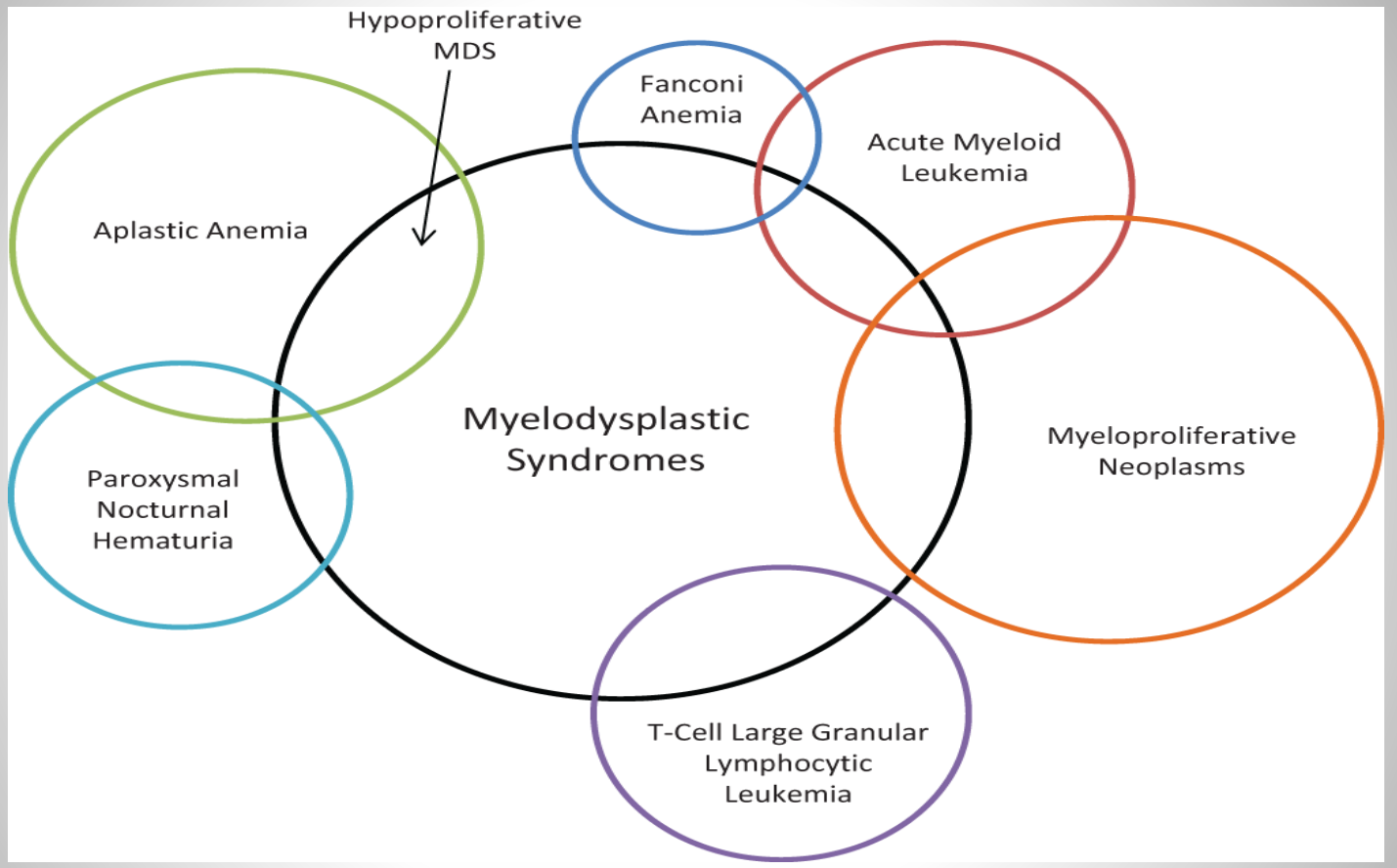
To discuss new clinical trial and research opportunities.

DISCLOSURES

Relevant Financial Relationship(s)
Tolero- Research
Bergenbio – Research
Syros- Research
Aprea-Research

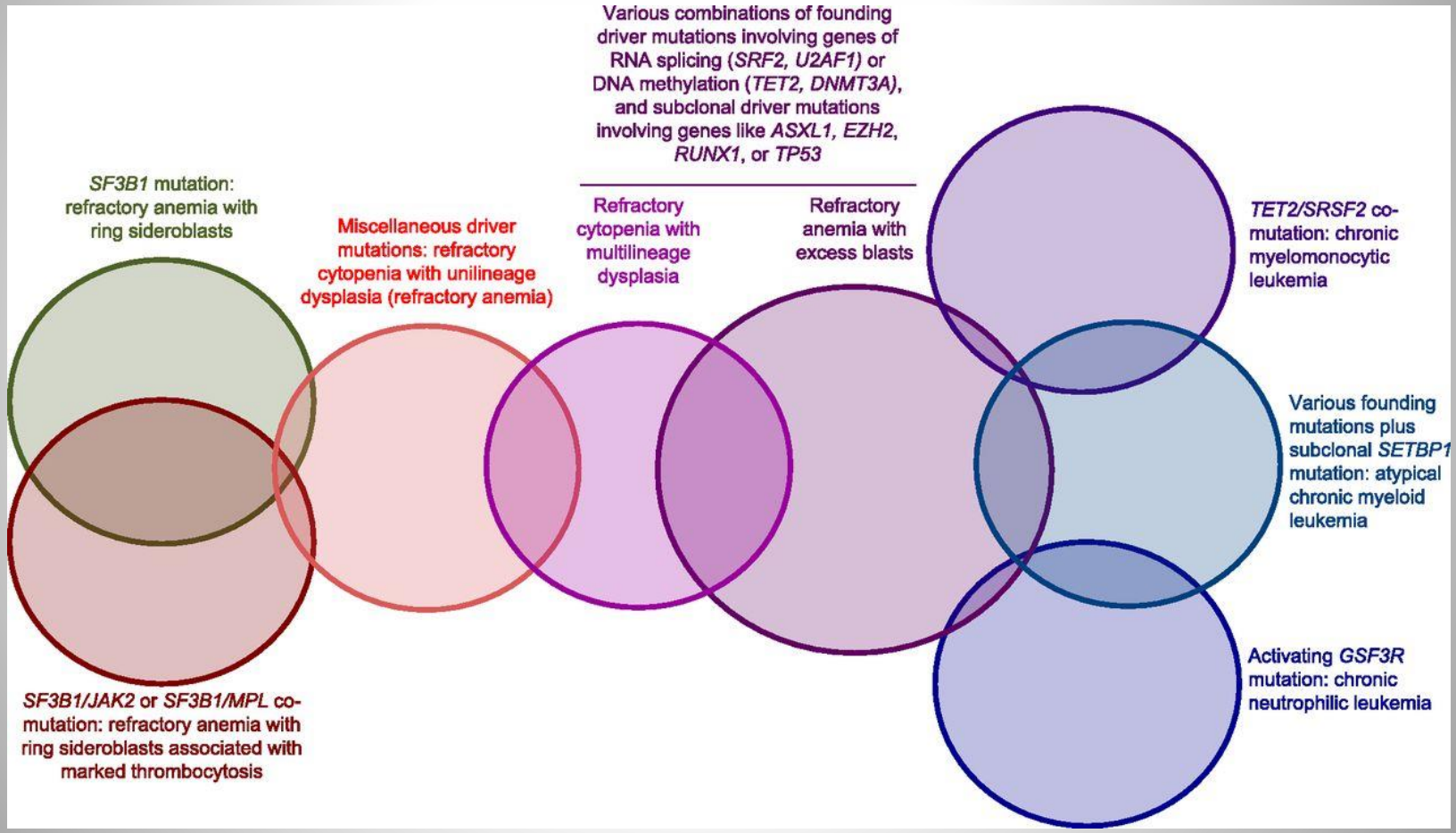
Off Label Usage
Venetoclax

MDS



Wong-Sefidan, I., & Bejar, R. Myelodysplasia, Cambridge (Ed) 2017.

MDS



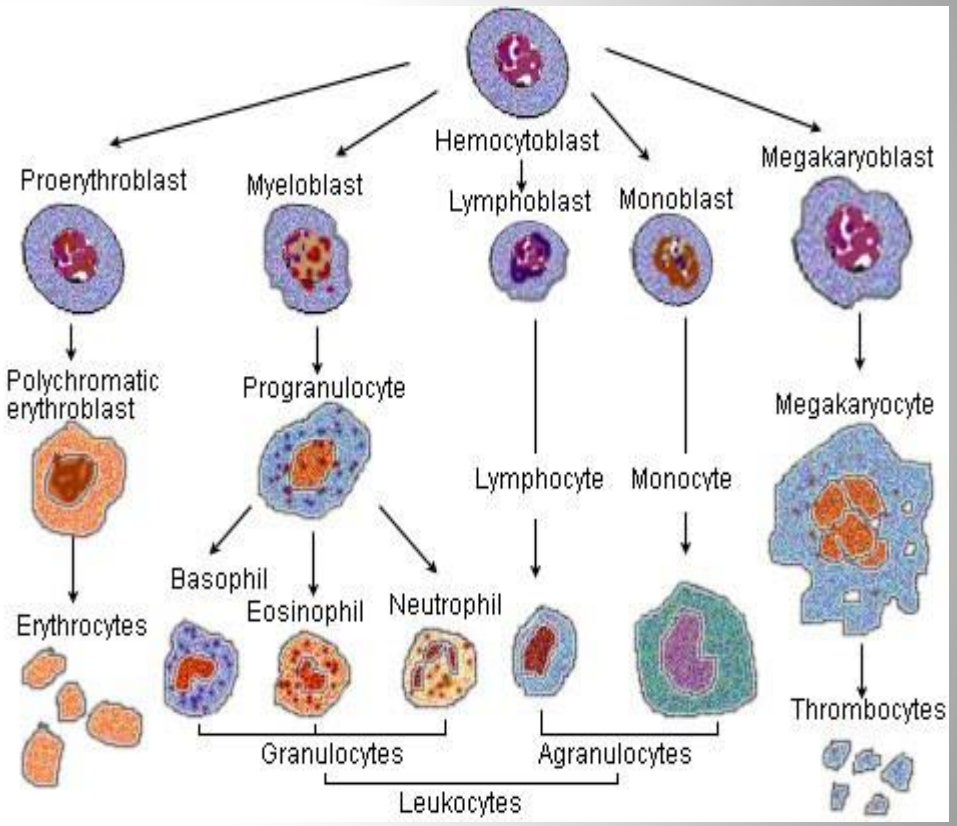
Cazzola, et al . Blood 2013.

MDS- Introduction

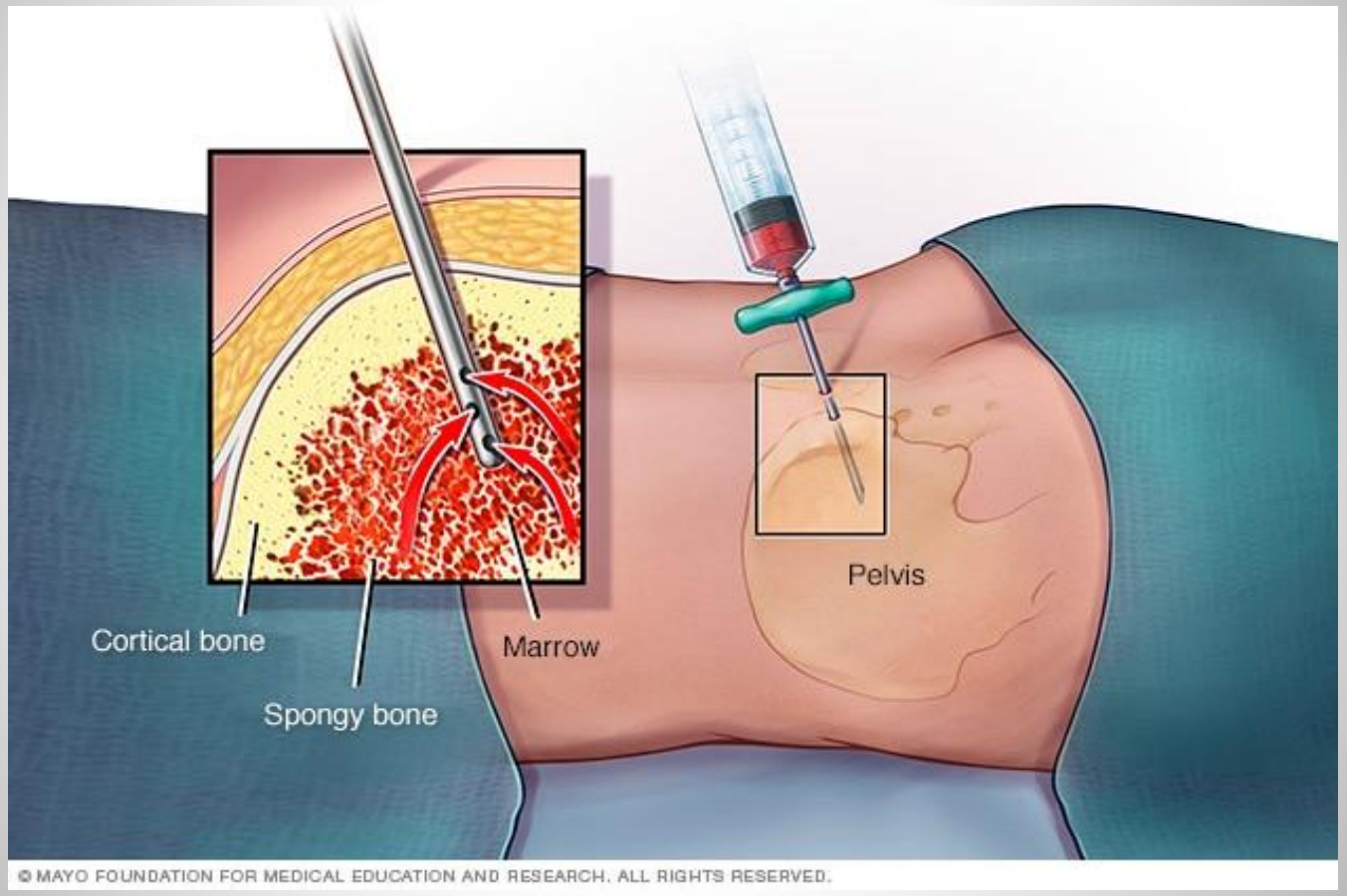
- Heterogeneous process
- Characterized by dysplasia of cellular agents, an ineffective hematopoiesis.
- considered by SEER as a CANCER
- Treatment approaches had changed a bit from the last years.
- Newer applications are reviewed.

MDS

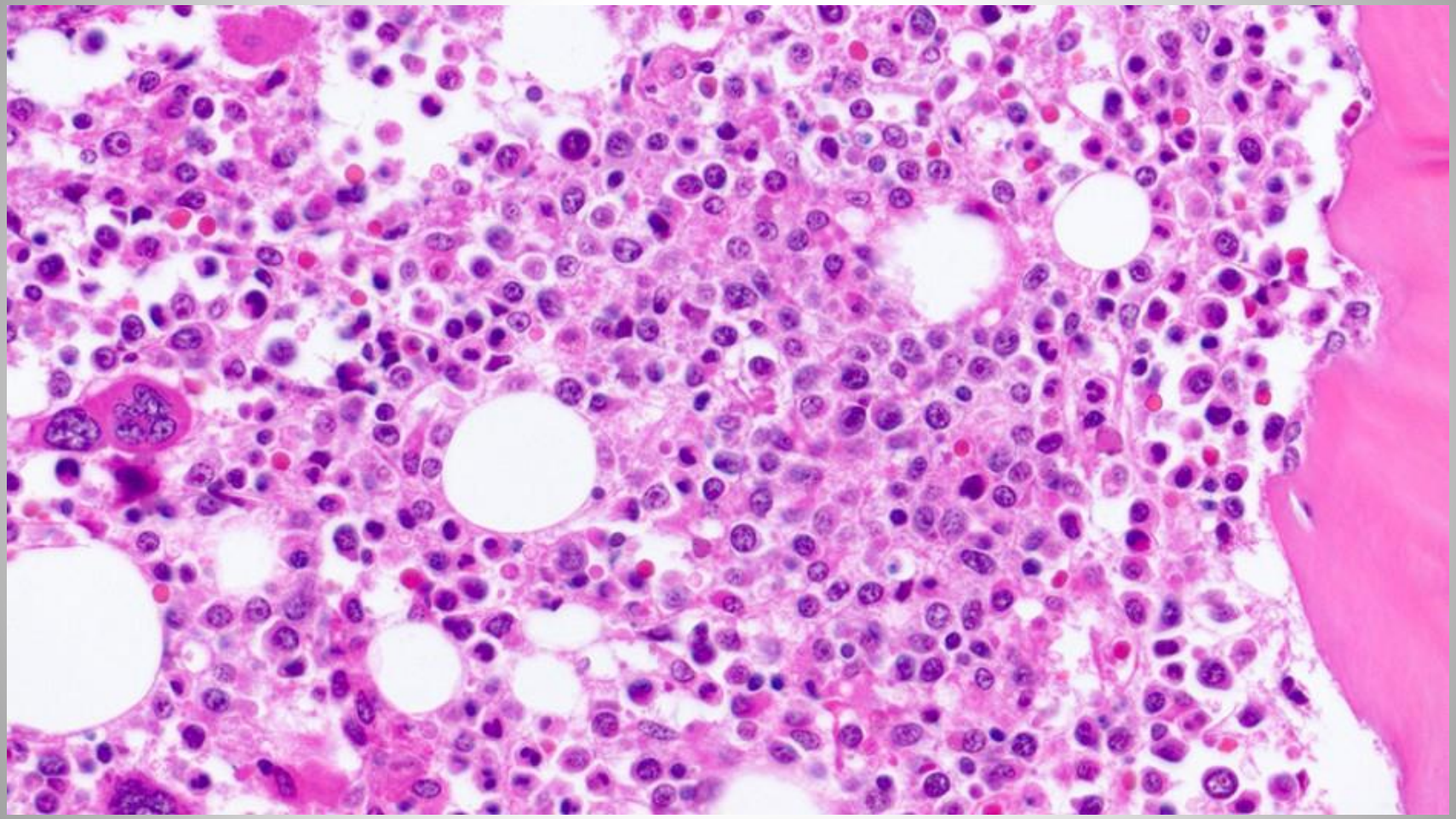
- Neutropenia
- Anemia
- Thrombocytopenia
- Dysplasia



MDS



MDS



Prognosis

- Cytopenias
- BM blasts
- Cytogenetics
- Molecular Markers

IPSS

Risk Cat	Score	Med sv (yr)	25% aml
Low	0	5.7	9.4
Int-1	0.5-1	3.5	3.3
Int-2	1.5-2	1.1	1.1
High	≥2.5	0.4	0.2

sub	N pts	Died %	D Leuk
Low	235	48	19
Int-1	295	61	30
Int-2	171	86	33
High	58	88	45
Total	759	65	30

Greenberg P et al. Blood 1997;89:2079-2088

IPSS-R

Parameter	Categories and Associated Scores (Scores in italics)				
Cytogenetic risk group[a]	Very good	Good	Intermediate	Poor	Very Poor
	0	*1*	*2*	*3*	*4*
Marrow blast proportion	≤2.0%	>2.0–<5.0%	5.0–<10.0%	≥10.0%	
	0	*1*	*2*	*3*	
Hemoglobin	≥10 g/dL	8–<10 g/dL	<8 g/dL		
	0	*1*	*1.5*		
Absolute neutrophil count	≥0.8 × 10^9/L	<0.8 × 10^9/L			
	0	*0.5*			
Platelet count	≥100 × 10^9/L	50–100 × 10^9/L	<50 × 10^9/L		
	0	*0.5*	*1*		

Risk group	Total score[b]	Proportion of patients in category (%)	Median survival (survival data based on $n = 7012$) (years)	Time until AML progression (AML data available based on $n = 6485$) (years)
Very low	0–1.0	19	8.8	Not reached
Low	1.5–3.0	38	5.3	10.8
Intermediate	3.5–4.5	20	3.0	3.2
High	5.0–6.0	13	1.5	1.4
Very high	>6.0	10	0.8	0.7

[a] Cytogenetic risk group, very good: -Y, del(11q); good: normal; del(5q) ± 1 other abnormality del(20q), or del(12p); intermediate: + 8, i(17q), del(7q), + 19, any other abnormality not listed including the preceding with 1 other abnormality; poor: −7 ± del(7q), inv(3)/t(3q)/del(3q), any 3 separate abnormalities; very poor: more than 3 abnormalities, especially if 17p is deleted or rearranged
[b] Sum scores on a 0–10 point scale
Source: adapted from Greenberg P et al, *Blood* 120(12):2454–65

Table

Revised IPSS (IPSS-R)

Updated cytogenetic classification for use in IPSS-R

Risk group	Included karyotypes	Median survival, years	25% of patients to AML, years	Proportion of patients in this group
Very good	del(11q), -Y	5.4	N/R	4%
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	4.8	9.4	72%
Intermediate	+8, del(7q), i(17q), +19, any other single or double abnormality not listed	2.7	2.5	13%
Poor	Abnormal 3q, -7, double abnormality include -7/del(7q), complex with 3 abnormalities	1.5	1.7	4%
Very poor	Complex with >3 abnormalities	0.7	0.7	7%

IPSS-R

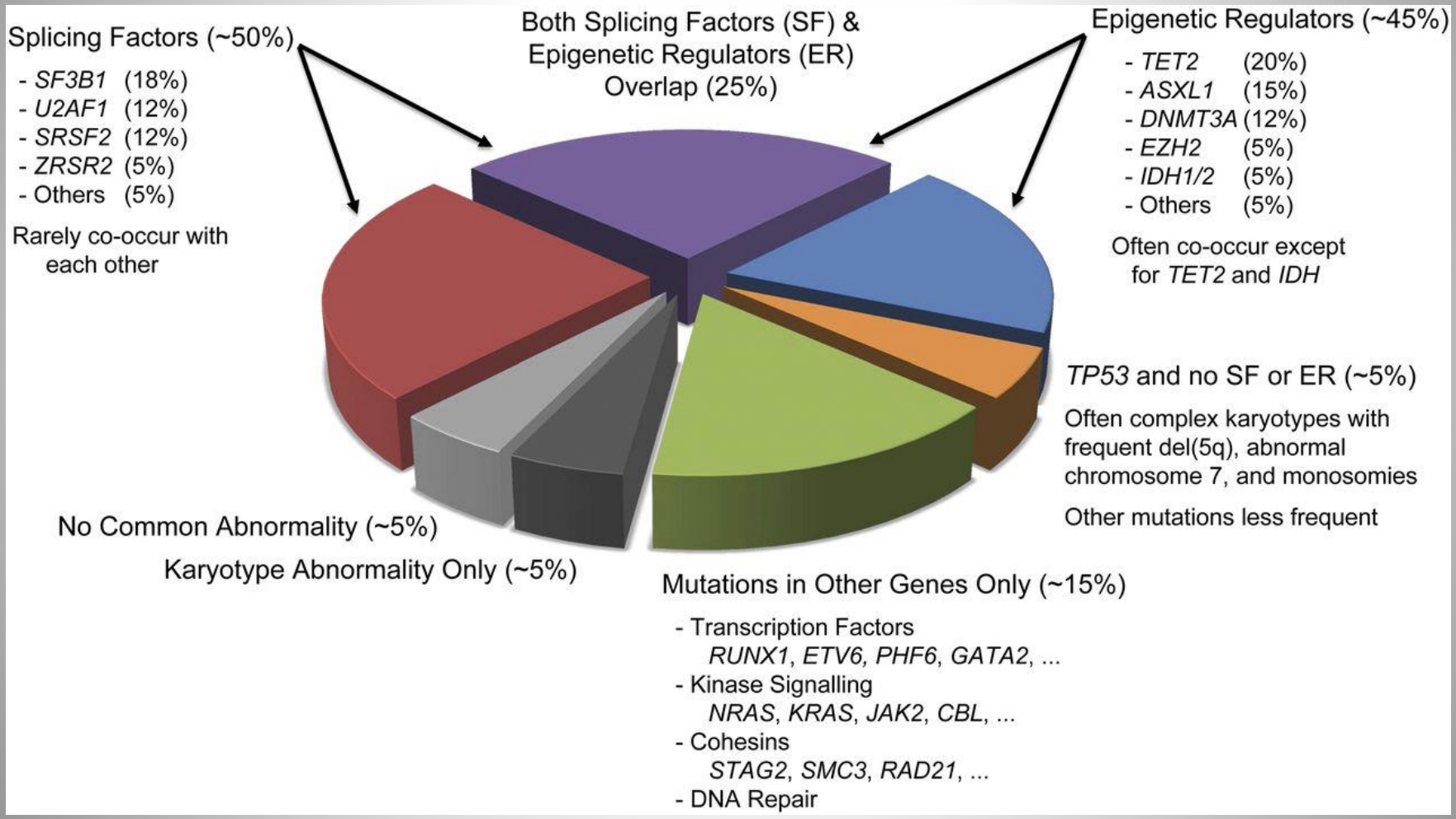
Parameter	Categories and associated scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow blast proportion	≤2%	>2 - <5%	5 - 10%	>10%	
	0	1	2	3	
Hemoglobin	≥10 g/dL	8 - <10 g/dL	<8 g/dL		
	0	1	1.5		
Absolute neutrophil count	≥0.8 x 10^9/L	<0.8 x 10^9/L			
	0	0.5			
Platelet count	≥100 x 10^9/L	50 - 100 x 10^9/L	<50 x 10^9/L		
	0	0.5	1		

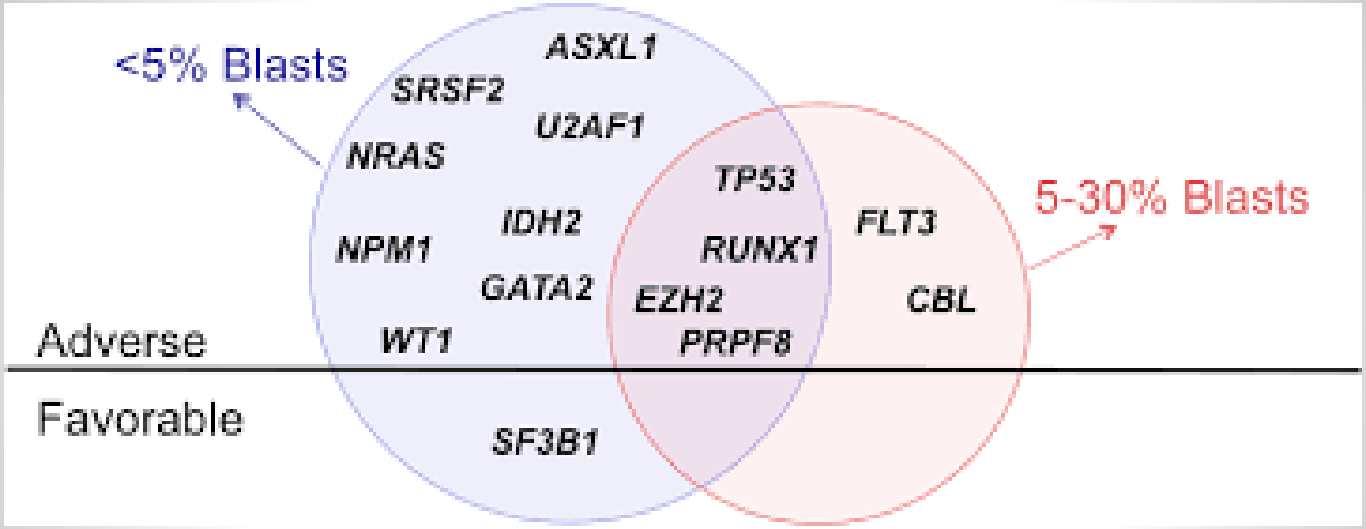
Possible range of summed scores: 0-10

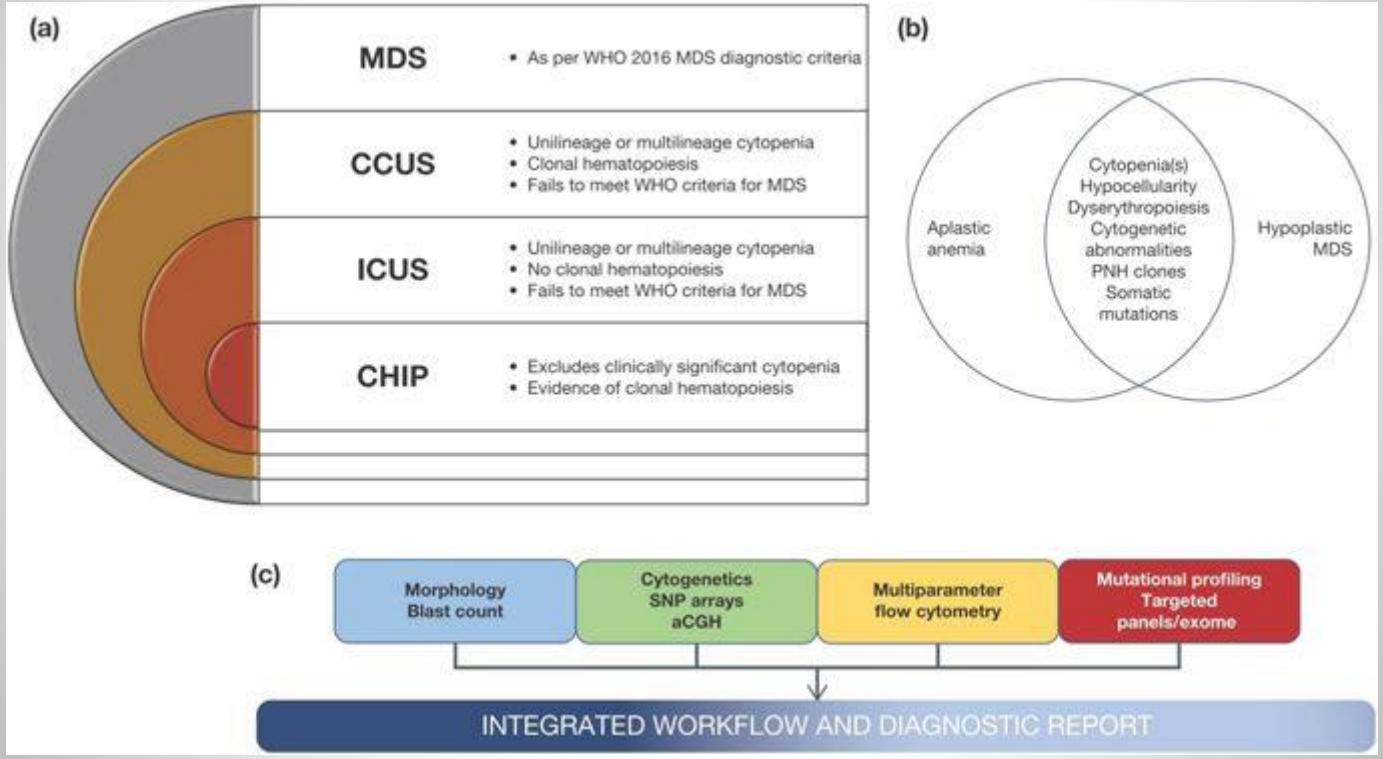
IPSS-R

Risk group	Points	% patients (n=7,012; AML data on 6,485)	Median survival, years	Median survival for pts under 60 years	Time until 25% of patients develop AML, years
Very low	0-1.5	19%	8.8	Not reached	Not reached
Low	2.0-3.0	38%	5.3	8.8	10.8
Intermediate	3.5-4.5	20%	3.0	5.2	3.2
High	5.0-6.0	13%	1.5	2.1	1.4
Very high	>6.0	10%	0.8	0.9	0.7

Molecular markers




<5% Blasts
ASXL1
SRSF2
U2AF1
NRAS
TP53
IDH2
FLT3
5-30% Blasts
NPM1
RUNX1
GATA2
EZH2
CBL
Adverse
WT1
PRPF8
Favorable
SF3B1


(a)
MDS
• As per WHO 2016 MDS diagnostic criteria
CCUS
• Unilineage or multilineage cytopenia
• Clonal hematopoiesis
• Fails to meet WHO criteria for MDS
ICUS
• Unilineage or multilineage cytopenia
• No clonal hematopoiesis
• Fails to meet WHO criteria for MDS
CHIP
• Excludes clinically significant cytopenia
• Evidence of clonal hematopoiesis
(b)
Aplastic anemia
Cytopenia(s)
Hypocellularity
Dyserythropoiesis
Cytogenetic abnormalities
PNH clones
Somatic mutations
Hypoplastic MDS
(c)
Morphology
Blast count
Cytogenetics
SNP arrays
aCGH
Multiparameter flow cytometry
Mutational profiling
Targeted panels/exome
INTEGRATED WORKFLOW AND DIAGNOSTIC REPORT

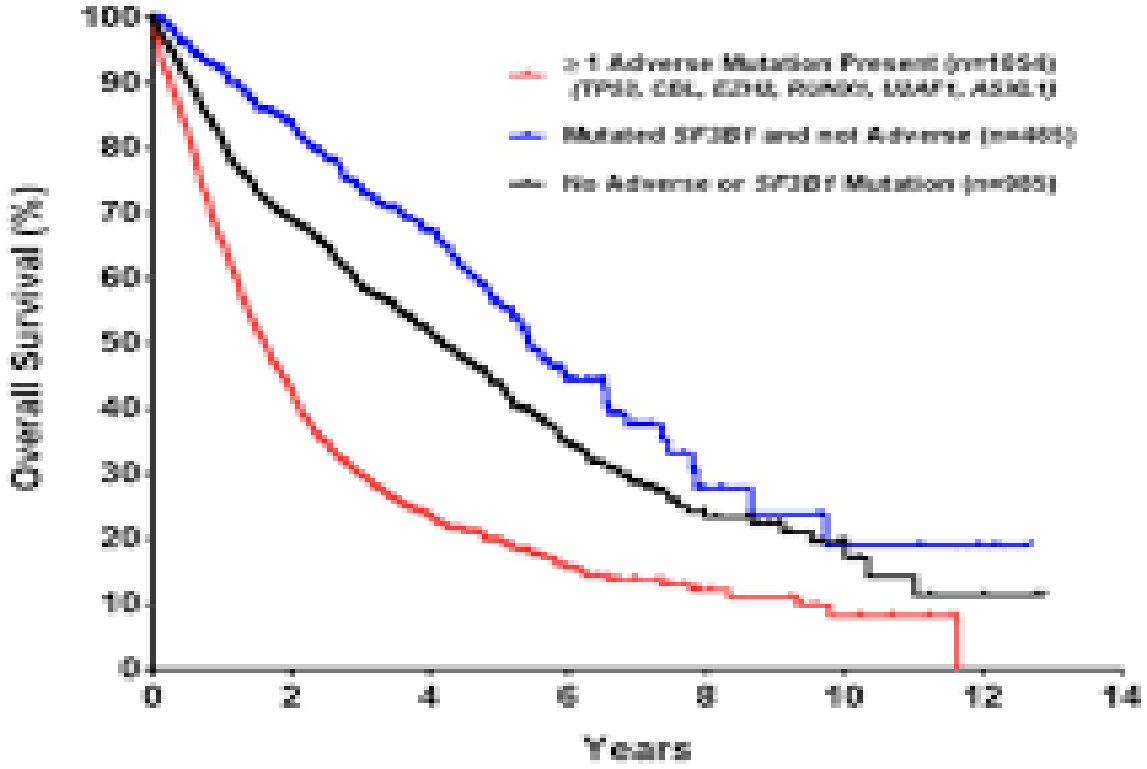
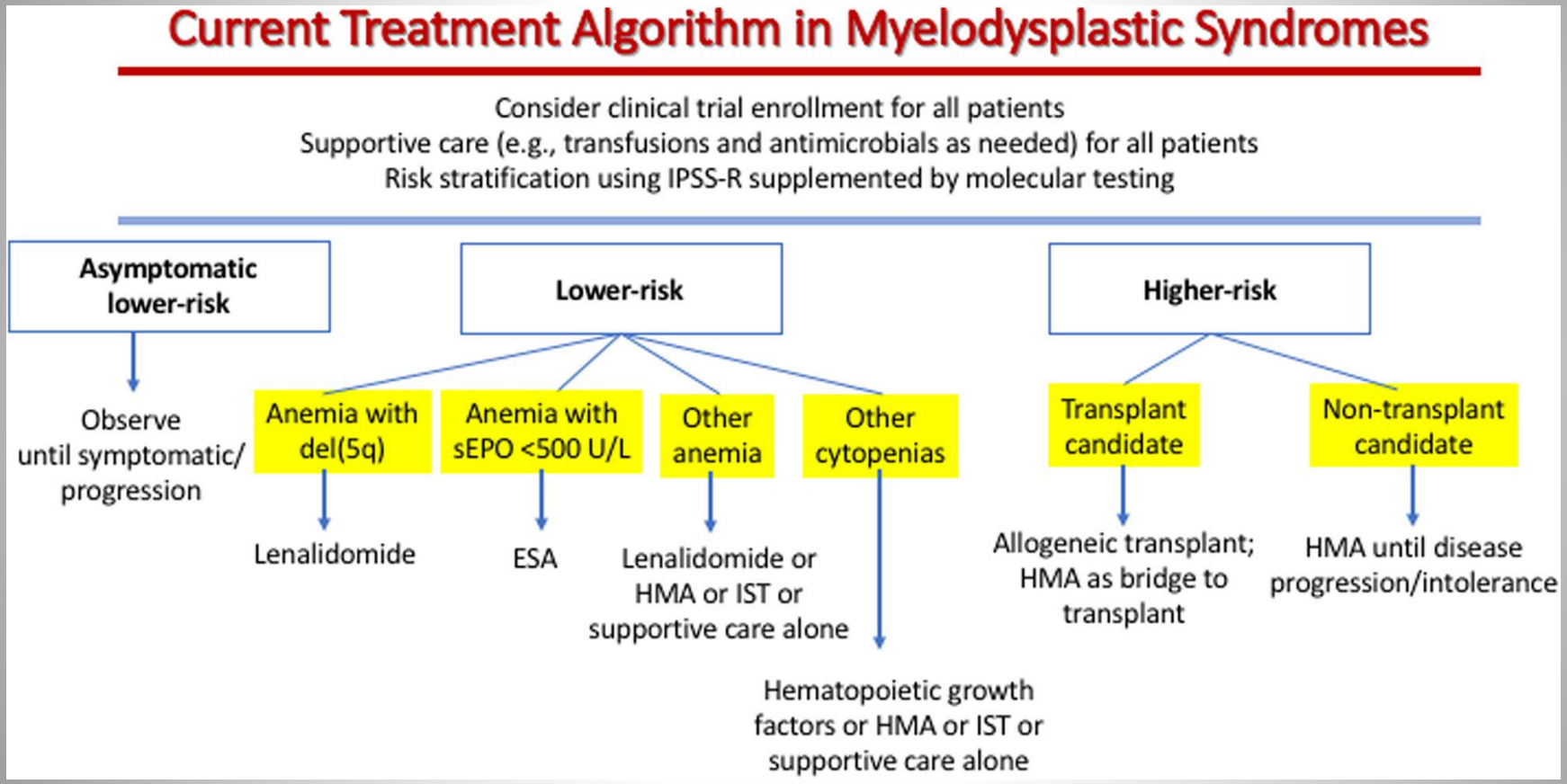


Figure 2: Kaplan-Meier curve of overall survival in years for the 2504 patients with sequence results for *SF3B1* and all six adverse genes (*TP53*, *CBL*, *EZH2*, *RUNX1*, *U2AF1*, and *ASXL1*).

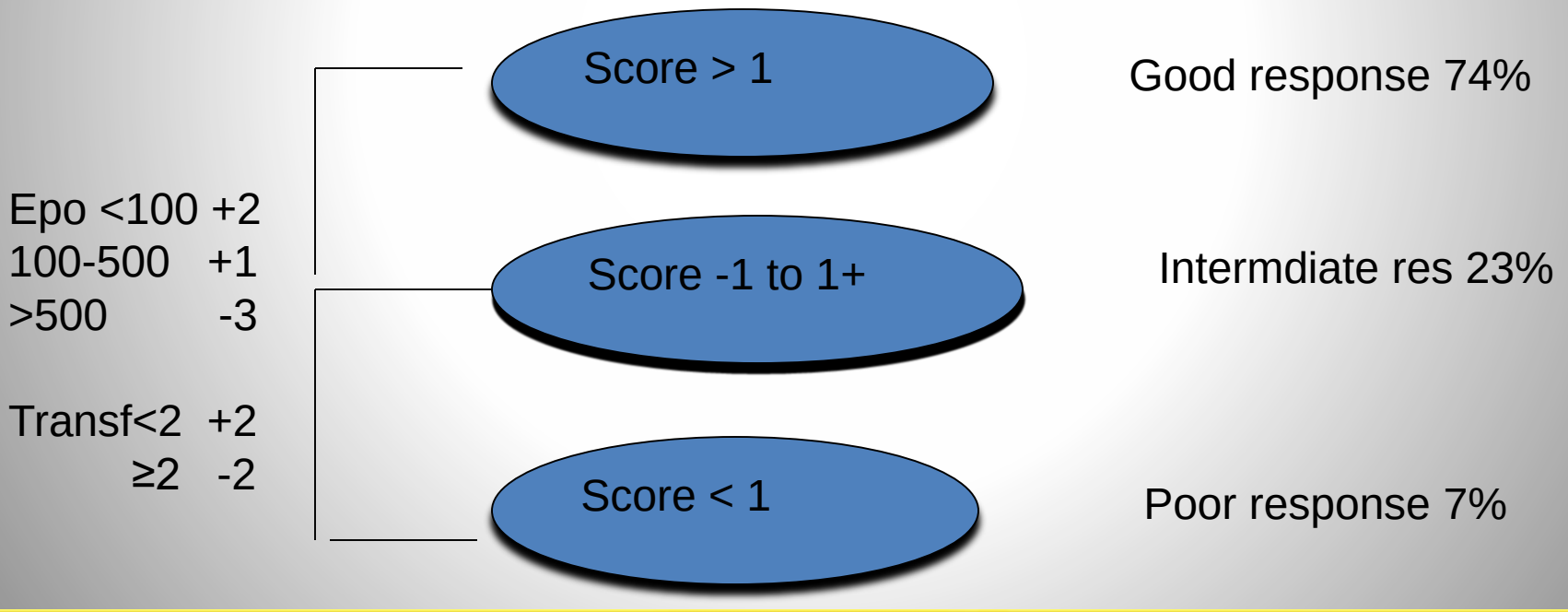
MDS Treatment 2019



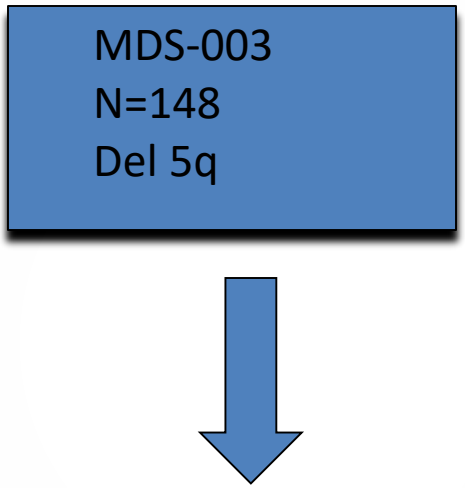
Steenesma, Blood Cancer Journal ,2018.

Lower Risk Therapy

- Lower risk cat→ growth factors/lenalidomide



Revlimid Low risk/int-1



1- LEN 10 mg po once a day
2- LEN 10 mg po 3 wk on/1 wk off

RBC TI in 2/3 patients and median duration of 2.2 y

LIST , AF. N Engl J Med 2006; 355:1456-1465

-

Risk of DVT, even in monotherapy for MDS

MDS-004
N=138
Del 5q

SAE
Mainly
Hematol.

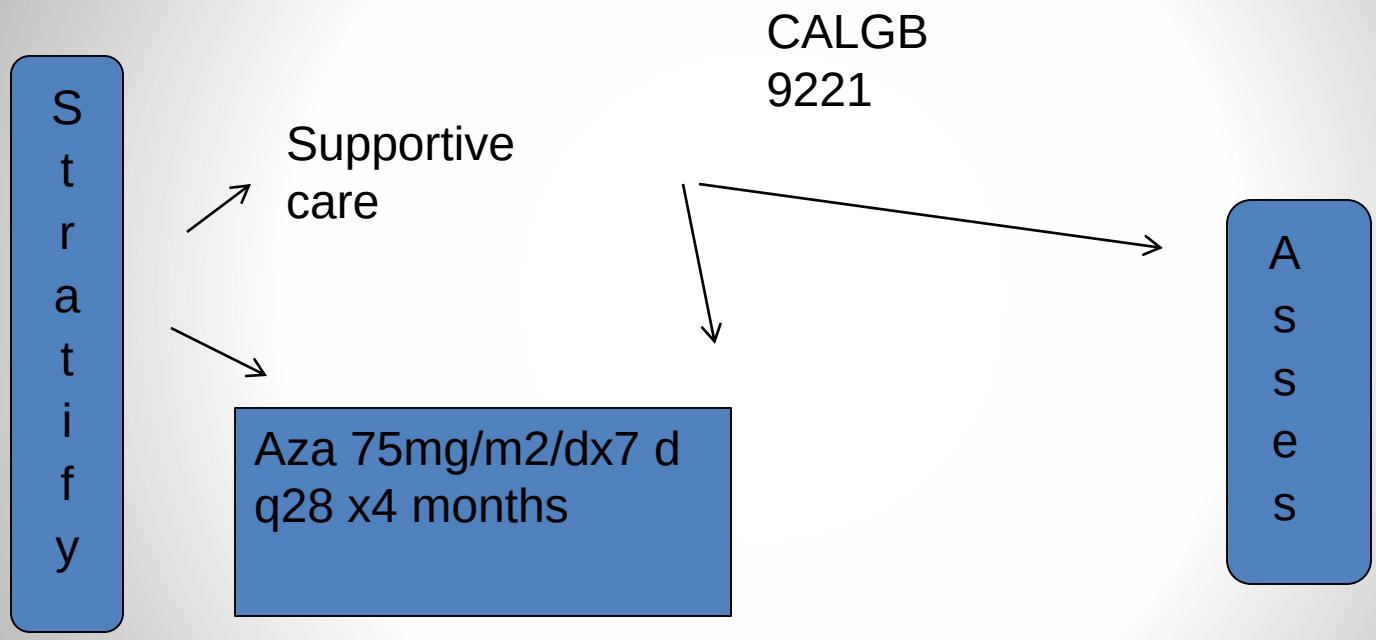
1-LEN 10mg po a 21d
2-LEN 5mg po a 28 d
3- Placebo

↓

However MDS-003/004 LEN 10 mg higher RBC-TI,more CyR andmore prolonged Responses than 5 mg po qd.

Feanux P. J Clin Oncol 28:15s, 2010 (suppl; abstr 6598)

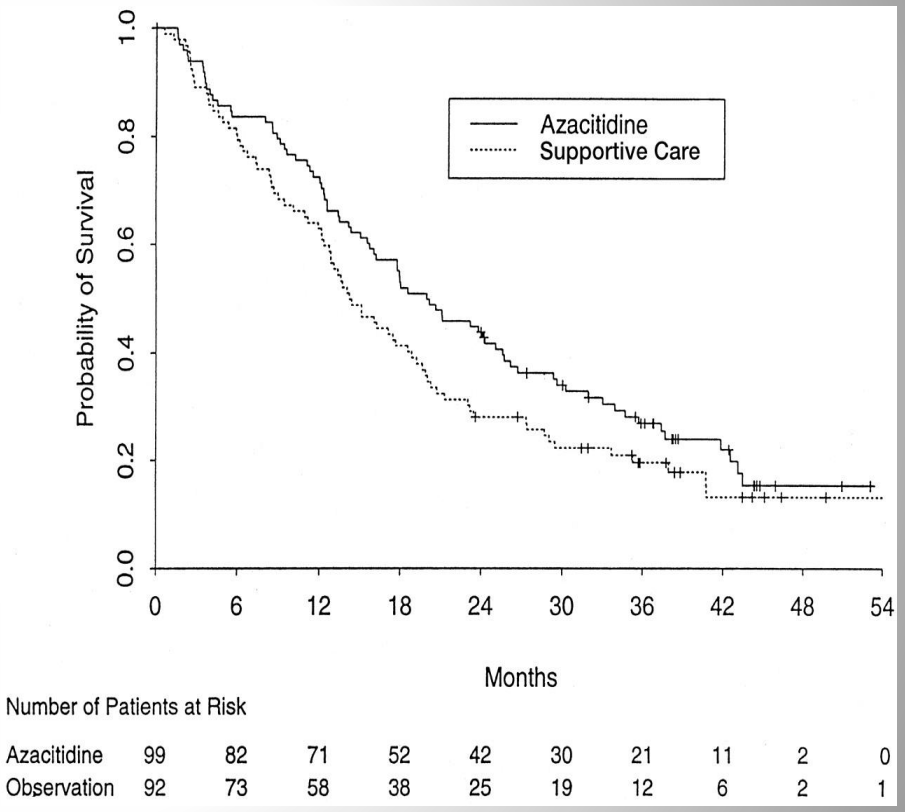
High Risk



Silverman et al. JCO.2002;20:2429-2440

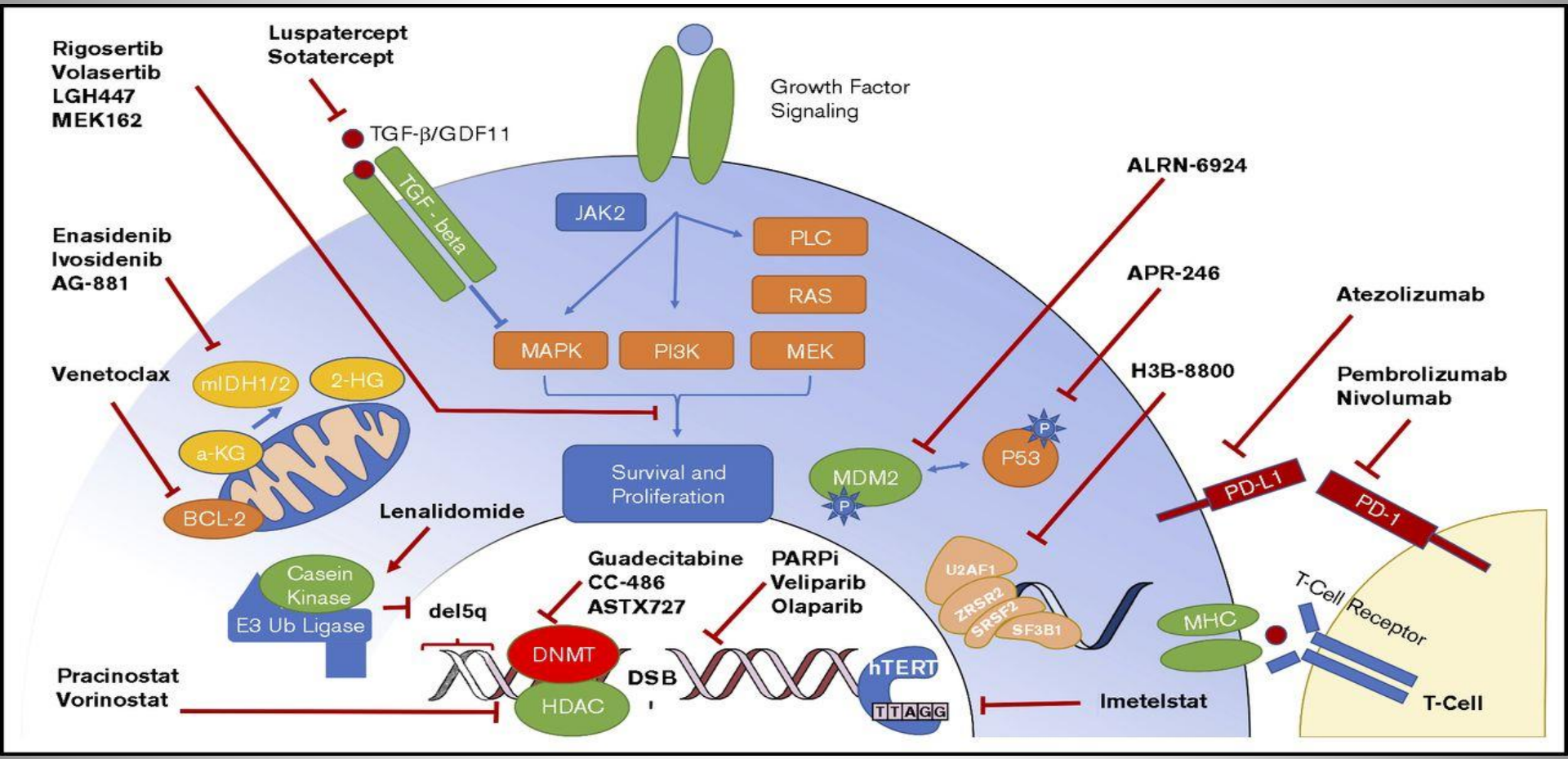
AZA 001

	AZA	SC	Cross over
N pt	99 pt	92	49
CR	7%	0%	10%
PR	16%	0%	4%
Improv	37%	5%	33%
Total	60%	5%	47%



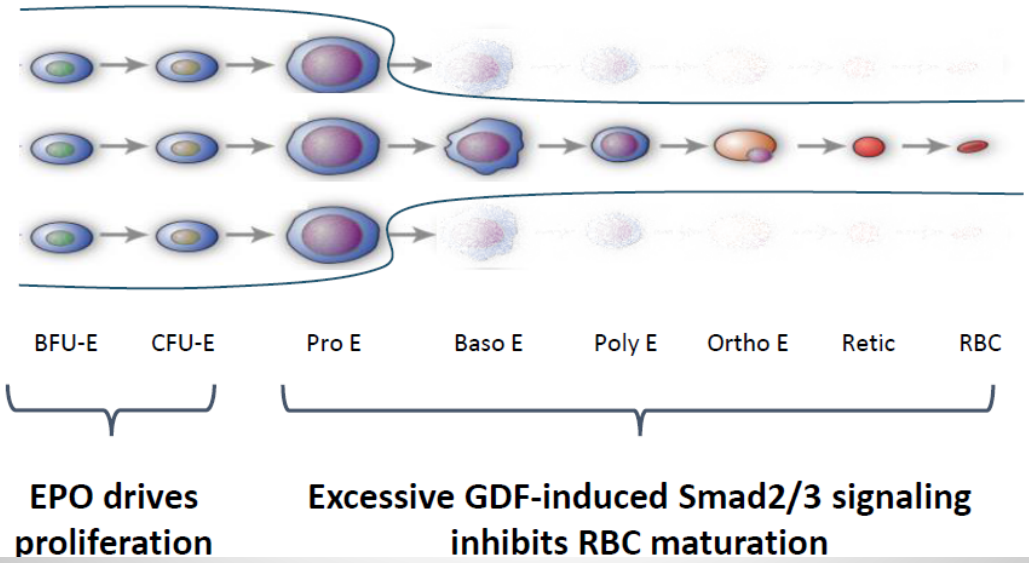
Silverman et al. JCO.2002;20:2429-2440

Novel approaches



Novel approaches

- Anemia, a hallmark of MDS, is a significant clinical challenge to treat, particularly after failure of ESAs[1]
- Defects in maturation of erythroid precursors (ineffective erythropoiesis) lead to erythroid hyperplasia and anemia
- Ineffective erythropoiesis is driven by excessive Smad2/3 signaling[2]



1. Fenaux P, et al. Blood. 2013;121:4280
2. Zhou L, et al. Blood 2008;112:3434

Luspatercept

- Luspatercept, a modified activin receptor type IIB (ActRIIB) fusion protein, acts as a ligand trap for GDF11 and other TGF-β family ligands to suppress Smad2/3 signaling; increased hemoglobin in healthy volunteers[1]
- In a murine model of MDS, murine analog RAP-536 corrected ineffective erythropoiesis, reduced erythroid hyperplasia and increased hemoglobin[2]

Luspatercept

Modified Extracellular Domain of ActRIIB receptor

Fc domain of human IgG_1 antibody

GDF: growth and differentiating factor
TGF: transforming growth factor

1. *Attie, K et al. Am J Hematol 2014;89:766*
2. *Suragani R et al., Nat Med 2014;20:408*

Medalist trial

- Phase III placebo control study
- N =229 patients. Randomization 2:1
- Very low, low and intermediate risk IPSS-R MDS with RS.
- Refractory, intolerant or ineligible for ESAs.
- 1 mg/kg or 1.75mg/kg SQ q3wks or placebo.
- SF3B1 in 90% of the cases.

Medalist trial

MEDALIST Trial

Demographics and Baseline Disease Characteristics

Characteristic	Luspatercept (n = 153)	Placebo (n = 76)
Age, median (range), years	**71 (40–95)**	**72 (26–91)**
Male, n (%)	**94 (61.4)**	**50 (65.8)**
Time since original MDS diagnosis, median (range), months	**44.0 (3–421)**	**36.1 (4–193)**
WHO classification		
RCMD-RS, n (%)	**145 (94.8)**	**74 (97.4)**
RBC transfusion burden, median (range), units/8 weeks[a]	5 (1–15)	5 (2–20)
≥ 6 units/8 weeks, n (%)	**66 (43.1)**	**33 (43.4)**
< 6 units/8 weeks, n (%)	87 (56.9)	43 (56.6)
Pre-transfusion Hb, median (range), g/dL	**7.6 (6–10)**	**7.6 (5–9)**
IPSS-R risk category[b]		
Very Low, Low, n (%)	127 (83.0)	63 (82.9)
Intermediate, n (%)	25 (16.3)	13 (17.1)
***SF3B1* mutation, n (%)**	**141 (92.2)**	**65 (85.5)[c]**
Serum EPO		
< 200 U/L, n (%)	88 (57.5)[c]	50 (65.8)
≥ 200 U/L, n (%)	64 (41.8)[c]	26 (34.2)

[a] In the 16 weeks prior to randomization. [b] 1 (0.7%) patient in the luspatercept arm was classified as IPSS-R High-risk. [c] Data were missing for 1 patient.
RCMD-RS, refractory cytopenia with multilineage dysplasia with RS.

MEDALIST Trial
Treatment Exposure

Parameter	Luspatercept (n = 153)	Placebo (n = 76)
Treatment duration, median (range), weeks	**49 (6–114)**	**24 (7–89)**
Completed ≥ 24 weeks of treatment (primary phase), n (%)	128 (83.7)	68 (89.5)
Completed ≥ 48 weeks of treatment, n (%)	78 (51.0)	12 (15.8)
Number of doses received, median (range)	16 (2–37)	8 (3–30)
Maximum dose escalation, n (%)[a]		
1.0 mg/kg	35 (22.9)	5 (6.6)
1.33 mg/kg	28 (18.3)	8 (10.5)
1.75 mg/kg	90 (58.8)	63 (82.9)
Patients remaining on treatment, n (%)	**70 (45.8)**	**6 (7.9)**
Patients discontinued from treatment, n (%)	**83 (54.2)**	**70 (92.1)**
Lack of benefit	51 (33.3)	50 (65.8)
Patient withdrawal	14 (9.2)	10 (13.2)
AE	10 (6.5)	4 (5.3)
Disease progression	3 (2.0)	2 (2.6)
Other	5 (3.3)	4 (5.3)

[a] Dose may be titrated up to a maximum of 1.75 mg/kg.
AE, adverse event.

Medalist trial

RBC-TI ≥ 8 weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**58 (37.9)**	**10 (13.2)**
95% CI	30.2–46.1	6.5–22.9
P value[a]	< 0.0001	

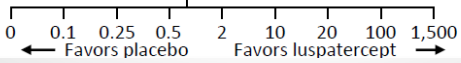
[a] Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).
CI, confidence interval.

Medalist trial

MEDALIST Trial

Primary Endpoint: Subgroup Analysis

	Luspatercept, n (%)	Placebo, n (%)	OR (95% CI)	*P* Value
Overall	58/153 (37.9)	10/76 (13.2)	5.06 (2.28–11.3)	< 0.0001
Average baseline RBC transfusion requirement				
≥ 6 units/8 weeks	6/66 (9.1)	1/33 (3.0)	3.20 (0.37–27.7)	0.2699
< 6 units/8 weeks	52/87 (59.8)	9/43 (20.9)	5.61 (2.40–13.1)	< 0.0001
4 to < 6 units/8 weeks	15/41 (36.6)	1/23 (4.3)	12.7 (1.55–104)	0.0046
< 4 units/8 weeks	37/46 (80.4)	8/20 (40.0)	6.17 (1.95–19.5)	0.0013
Baseline serum EPO (U/L)				
< 100	23/51 (45.1)	7/31 (22.6)	2.82 (1.03–7.71)	0.0413
100 to < 200	14/37 (37.8)	2/19 (10.5)	5.17 (1.04–25.9)	0.0338
200–500	17/43 (39.5)	1/15 (6.7)	9.15 (1.10–76.2)	0.0188
Age group				
≤ 64 years	17/29 (58.6)	3/16 (18.8)	6.14 (1.43–26.3)	0.0108
65–74 years	23/72 (31.9)	4/29 (13.8)	2.93 (0.91–9.41)	0.0635
≥ 75 years	18/52 (34.6)	3/31 (9.7)	4.94 (1.32–18.5)	0.0120
Gender				
Male	32/94 (34.0)	4/50 (8.0)	5.94 (1.96–18.0)	0.0006
Female	26/59 (44.1)	6/26 (23.1)	2.63 (0.92–7.48)	0.0673
Time since initial diagnosis at baseline				
≤ 2 years	14/40 (35.0)	3/19 (15.8)	2.87 (0.71–11.6)	0.1312
> 2–5 years	30/62 (48.4)	4/34 (11.8)	7.03 (2.21–22.3)	0.0004
> 5 years	14/51 (27.5)	3/23 (13.0)	2.52 (0.65–9.83)	0.1756
Baseline IPSS-R risk				
Very Low or Low	48/127 (37.8)	9/63 (14.3)	3.65 (1.65–8.05)	0.0009
Intermediate	10/25 (40.0)	1/13 (7.7)	8.00 (0.89–71.6)	0.0398
Baseline platelet count				
< 100 × 10^9/L	2/8 (25.0)	1/6 (16.7)	1.67 (0.11–24.3)	0.7171
100–400 × 10^9/L	42/128 (32.8)	8/61 (13.1)	3.24 (1.41–7.42)	0.0042
> 400 × 10^9/L	14/17 (82.4)	1/9 (11.1)	37.3 (3.31–422)	0.0006



OR, odds ratio.

Medalist trial

RBC-TI ≥ 12 Weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**43 (28.1)**	**6 (7.9)**
95% CI	21.14–35.93	2.95–16.40
P value[a]	0.0002	
Weeks 1–48, n (%)	**51 (33.3)**	**9 (11.8)**
95% CI	25.93–41.40	5.56–21.29
P value[a]	0.0003	

[a] Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).

Medalist trial

MEDALIST Trial

TEAEs ≥ 10% Incidence in Either Arm

n (%)	Luspatercept (n = 153)	Placebo (n = 76)
Fatigue	41 (26.8)	10 (13.2)
Diarrhea	34 (22.2)	7 (9.2)
Asthenia	31 (20.3)	9 (11.8)
Nausea	31 (20.3)	6 (7.9)
Dizziness	30 (19.6)	4 (5.3)
Back pain	29 (19.0)	5 (6.6)
Cough	27 (17.6)	10 (13.2)
Edema peripheral	25 (16.3)	13 (17.1)
Headache	24 (15.7)	5 (6.6)
Dyspnea	23 (15.0)	5 (6.6)
Bronchitis	17 (11.1)	1 (1.3)
Constipation	17 (11.1)	7 (9.2)
Urinary tract infection	17 (11.1)	4 (5.3)
Fall	15 (9.8)	9 (11.8)

TEAEs ≥ 10% incidence in either arm by preferred term

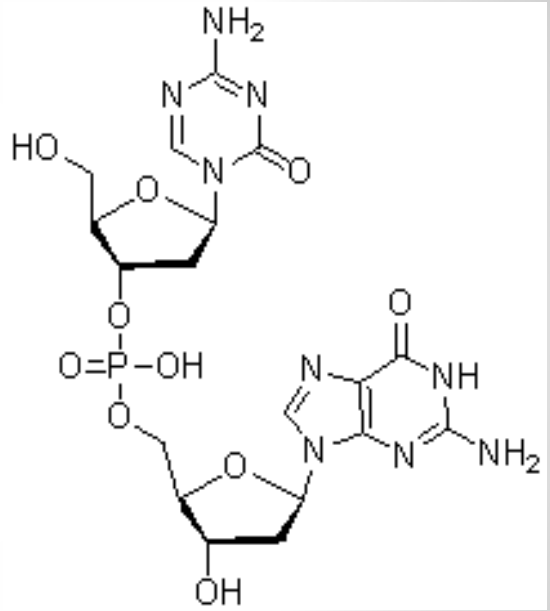
Medalist trial

Conclusions

- 37.9% RBC-TI for ≥ 8 weeks and (28.1%) achieved the key secondary endpoint of RBC-TI for ≥ 12 weeks (weeks 1–24) compared to placebo.
- Well tolerated.
- Arising as new potential drug in LR MDS.

Guadecitabine

- Next generation HMA designed to be resistant to degradation by cytidine deaminase.
- 60mg/m2 d 1-5 vs 90 mg/m2 day 1-5.
- N=102 Phase II of MDS and CMML. (Abst 231)
- Treatment naïve MDS=49.
- R/r MDS N=53.

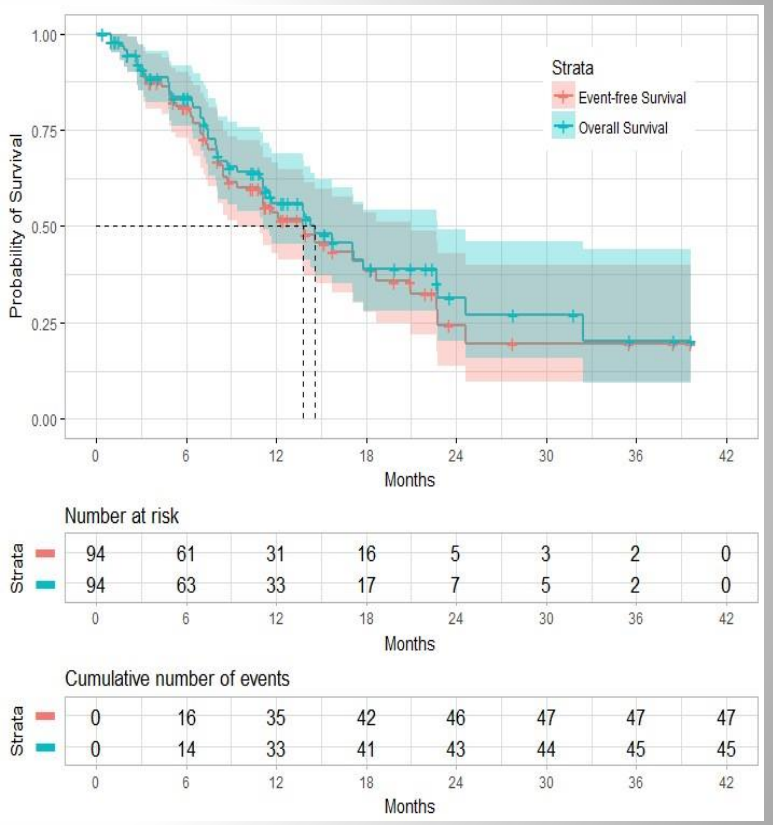


Guadecitabine

- Median fu 3.2 y.
- Median of 5 cycles.
- MDS TN CR 22% ORR 37% OS 23.4 months.
- R/r MDS, CR 4%, ORR 32%, with a median duration of response of 7.9 months, and median OS of 11.7 months.
- No major differences in OS based on DNMT3A or TET2 mutation status while patients with TP53 mutations had worse median OS 7.4 mo compared to those without TP53 22 mo.
- Astral -3 is currently ongoing in r/r MDS vs doctor's choice.

Guadecitabine

- (Abstract 232) Previously untreated MDS.
- N=94 pts with higher risk MDS.
- CR 22%, ORR 61%
- Median OS 15 mo.
- Seems better than first generation but randomization studies needed.



Rigosertib

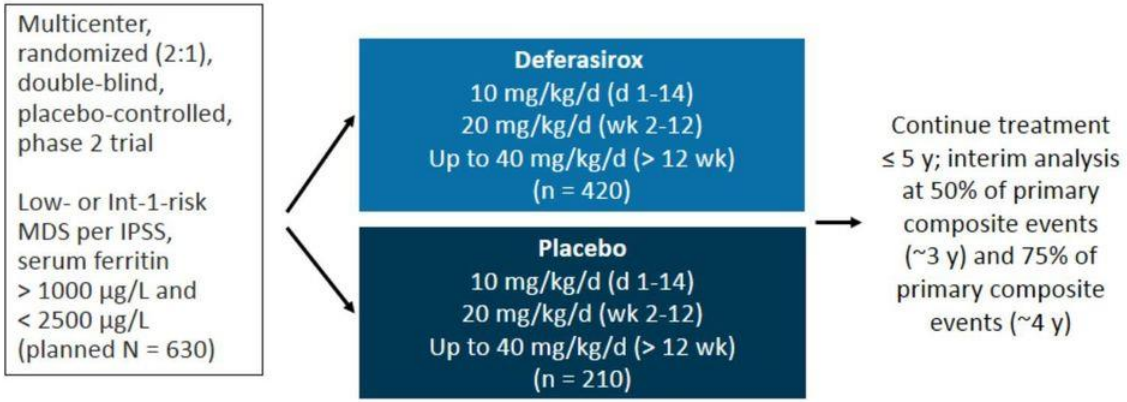
- First in class small molecule Ras mimetic.
- Responses were seen as single drug around 59% ORR.
- A phase II, of 45 patients HR MDS and non proliferative AML.

Table 2: ORR by Patient Cohort			
Dose	Response All patients (%)	HMA naïve (%)	HMA Rel/Ref (%)
560/280 (n=26)	20 (77)	14/16 (88)	6/10 (60)
1120 (n = 31)	21 (68)	11/14 (79)	10/17 (59)
560 BID (n=13)	8 (62)	3/5 (60)	5/8 (63)
840/280 (n=18)	13 (72)	8/9 (89)	5/9 (56)

Table 3: Hematuria Comparison Various Rigosertib Combination Doses	
Patients on Rigosertib 560mg/280mg + Azacitidine	42
Patients with hematuria	20 (48%)
Patients with grade 1 or 2 hematuria	17 (40%)
Patients with grade ≥3 hematuria	5 (12%)
Patients on (Rigosertib (1120mg) + Azacitidine with risk mitigation strategy	43
Patients with hematuria	16 (37%)
Patients with grade 1 or 2 hematuria	16 (37%)
Patients with grade ≥3 hematuria	2 (5%)

* AEs were graded per National Cancer Institute's Common Toxicity Criteria version 4.0

TELESTO
Deferasirox in LR/Int-1 MDS With Transfusional Iron Overload



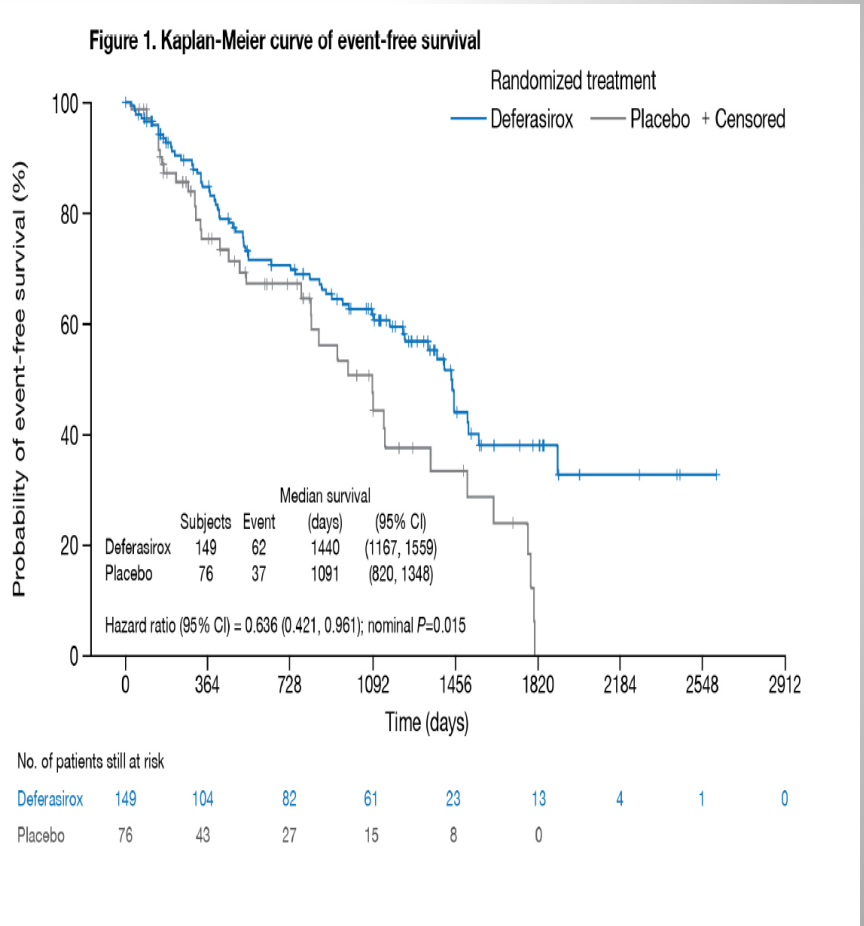
- Primary endpoint: EFS (includes death and nonfatal cardiac and liver function events)
- Secondary endpoints: hematologic improvement, OS, disease progression, endocrine and metabolic function, safety, serum ferritin > 2 × BL

ClinicalTrials.gov. NCT00940602.

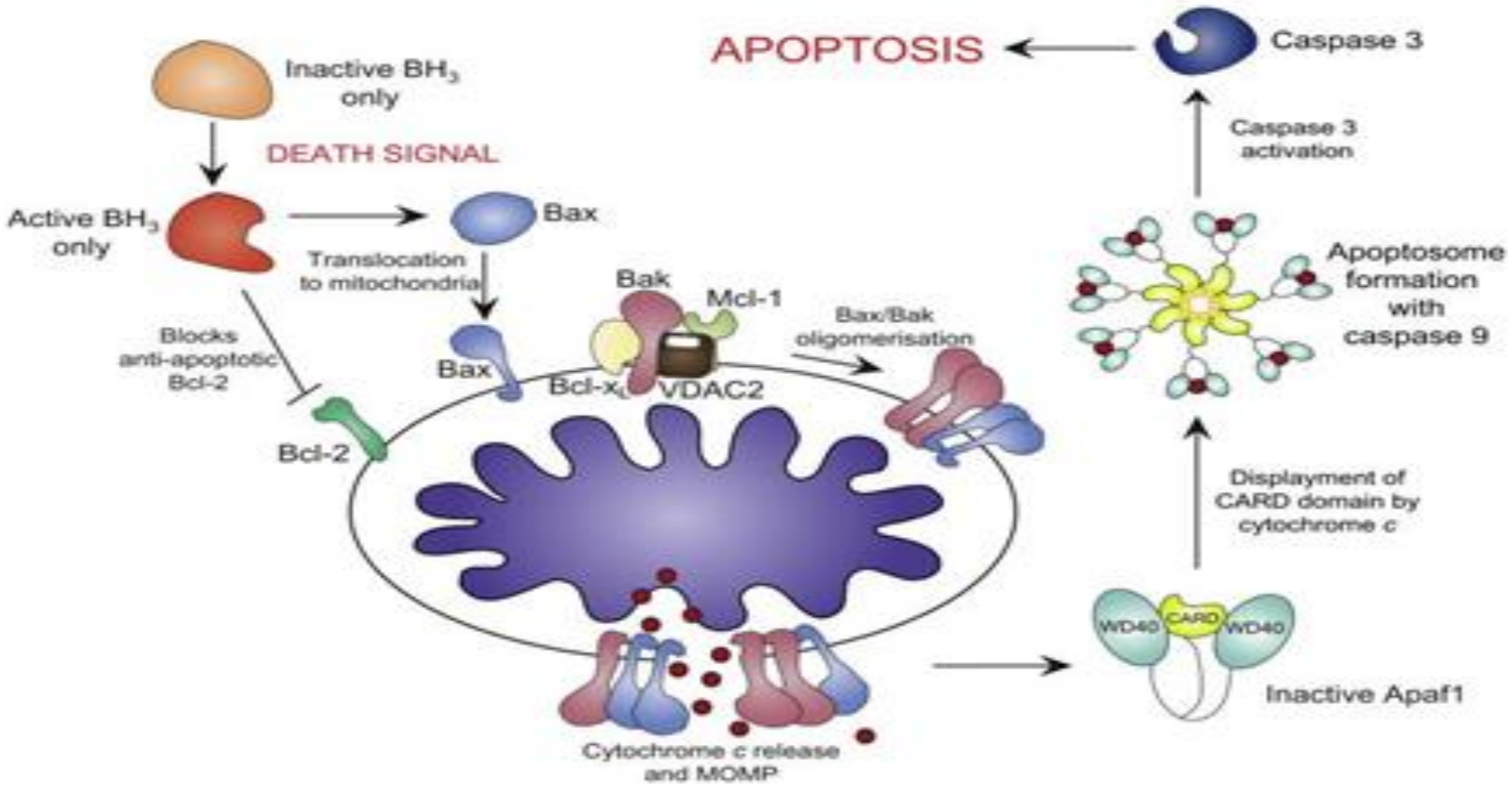
Telesto study

N=225 pts
Rand 2:1 DFX vs PBO
149 vs 76 pts.
72.4% Int-1 risk
Median EFS prolonged DFX
Median OS 1907 days with DFX and 1509 days with PBO; HR 0.832 (95%CI 0.54–1.28, P=0.200).
AE: pirexia, diarrhea,URI.

Conclusions: improve EFS (cardiac, liver and AML transform).



Apoptosis



Adapted from Letai et al, 2018

Venetoclax

Monotherapy

- Phase II N=32

R/r AML

- Ramp-up dose

20mg/50/100/400/800

- ORR 19%
- CR +CRi 15%
- Short lived responses 2.5months

- Toxicities G3/4 febrile neutropenia.
- IDH1/2 33% responses
- FLT3 ITD +IDH→ no responses

Konopleva et al Cancer Discov. 6(10);1-12

Characteristic	*N* = 32
Median age (range), years	71 (19–84)
Sex, *n* (%)	
Female	16 (50)
Male	16 (50)
Diagnosis, *n* (%)	
Relapsed/refractory	30 (94)
Newly diagnosed	2 (6)
Ethnicity, *n* (%)	
White	25 (78)
Black	4 (13)
Asian	3 (9)
ECOG performance score, *n* (%)[a]	
0	3 (9)
1	14 (44)
2	14 (44)
Missing	1 (3)
Any prior therapy, *n* (%)	30 (94)
Prior regimens ≥3	13 (41)
Prior standard induction (3+7) therapy	17 (53)
Prior hypomethylating agents	24 (75)
Prior allogeneic stem cell transplant	4 (13)
Treatment naïve	2 (6)
Prior myeloid disorder, *n* (%)	
Prior myelodysplastic syndrome[b]	11 (35)
Prior myeloproliferative neoplasm	2 (6)
Molecular markers[c], *n* (%)	
IDH mutations[d]	12 (38)
FLT3-ITD[e]	4 (13)
BCR–ABL	1 (3)
JAK2	1 (3)
KRAS	1 (3)
MLL	1 (3)
NPM1	4 (13)
CEBPα	2 (6)
Cytogenetics, *n* (%)	
del(7q)	10 (31)
Complex	10 (31)
None	2 (6)

Combinations
Low dose Ara-C

ASCO Phase 1b/2 LDAC 20mg/m2 QD 1-10

Treatment naïve AML ≥ 65

N=18 RP2D 600mg

AE: febrile neutropenia (33%)

ORR: 44% (CR=4,CRi=4).

Lin et al. JCO 2016 Abstract 7007.

ASH 2016 Update N=20

5- day ramp-up schedule to 600mg.

14/20 (70%) CR+Cri

16/19 (84%) blast<5% in BM

12-month estimated OS 86.7%

Wei et al. Blood 2016;128:102

ASH 2017 Update

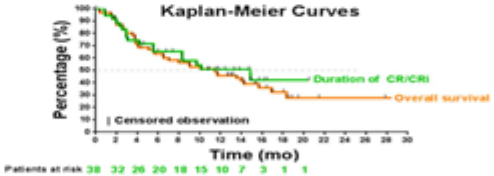
N=71

38 (62%) CR/CRi

Median duration 14.9 months

Median OS 11.4 months

Wei et al . Blood.2017;130:890



VEN 600 mg Patients	n	CR/CRi (%)	Median (months) Duration of CR/CRi	Median (months) OS
Cytogenetic risk				
Intermediate	37	76	NR	15.7
Poor	19	47	3.1	5.7
Biomarker				
NPM1	7	100	NR	NR
DNMT3A	11	82	NR	NR
FLT3-ITD	9	78	7.4	14.0
TP53	9	44	3.0	6.6
IDH1/2	10	70	NR	9.3
SRSF2	16	75	NR	9.0
RUNX1	9	56	9.0	3.8

NR, not yet reached.

Combinations HMA

Phase 1b ≥ 65 yo
Treatment naïve
Decitabine 20mg/m2 day 1-5
Or Azacitidine 75mg/m2 day 1-7
For 4 courses
ORR 75%(9/12) for decitabine and 70%(7/10) for azacitidine.

DiNardo et al Blood 2015;126:327.

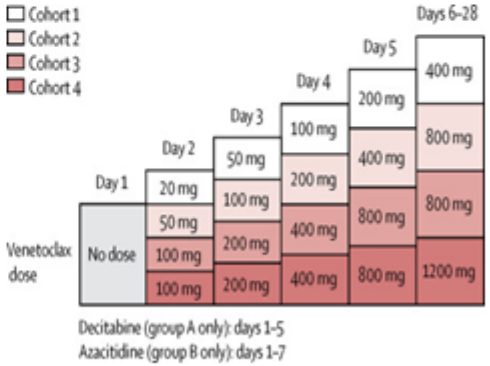
N=57

23 group A and 22 B and 12 C

AE thrombocytopenia (47%), febrile neutropenia (42%) and neutropenia (40%).

Responses 61% CR

400 mg optimal dose.



DiNardo. Lancet Oncol 2018;19216-28

Combinations HMA

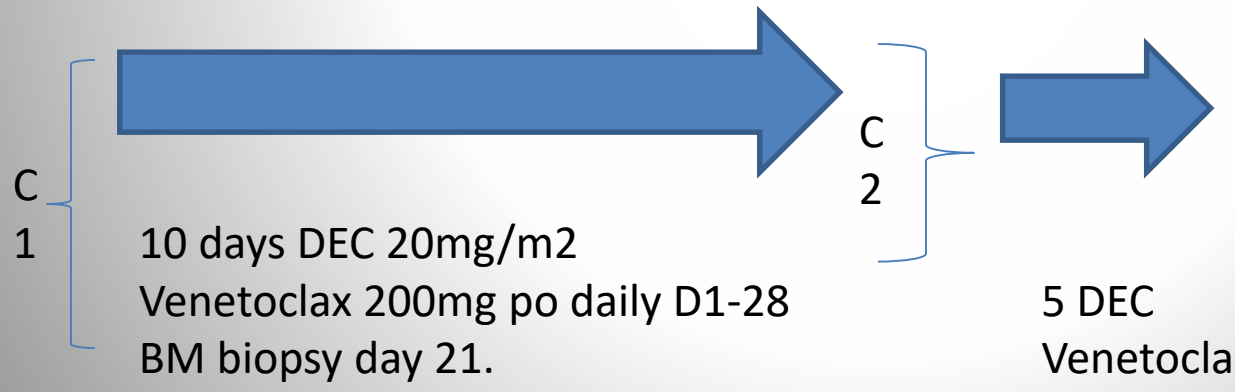
Patient subgroup	n	CR/CRi n (%)	Duration of CR/CRi median months	OS
All VEN doses	145	97 (67)	11.3	17.5
Intermediate cytogenetic risk	74	55 (74)	12.9	NR
Poor cytogenetic risk	71	42 (59)	6.7	9.6
Secondary AML	36	24 (67)	NR	NR
Age ≥75 years	62	40 (65)	9.2	11.0
VEN 400 mg				
+ AZA	29	22 (76)	NR	NR
+ DEC	31	22 (71)	12.5	15.2
VEN 800 mg				
+ AZA	37	21 (57)	11.7	14.2
+ DEC	37	27 (73)	9.2	17.5

OS, overall survival; NR, not yet reached (if applicable)

DiNardo et al .J Clin Oncol 36, 2018 (suppl; abstr 7010)

Dec+ venetoclax

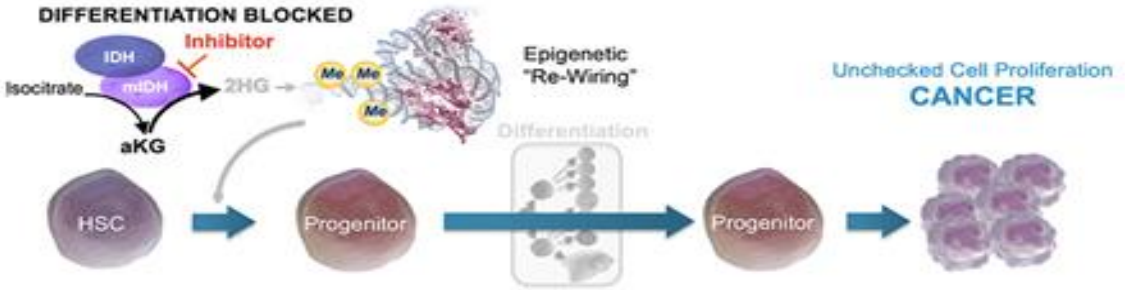
- Decitabine 10 day (AML and high risk MDS)
- N= 48, 50% ND AML, 16% R/R AML.
- CR/CRi 92% ND, 71% sAML, 44% r/r AML.



Maiti et al . Abstract 286.

IDH mutation

- Prevalence-15% IDH2,8% IDH1
- Enasidenib - (IDH2 inh) AG221-C-001: ORR 41% 18% CR, minimal GI toxicity.
- Ivosidenib –(IDH1 inh) AG120 CR 16%



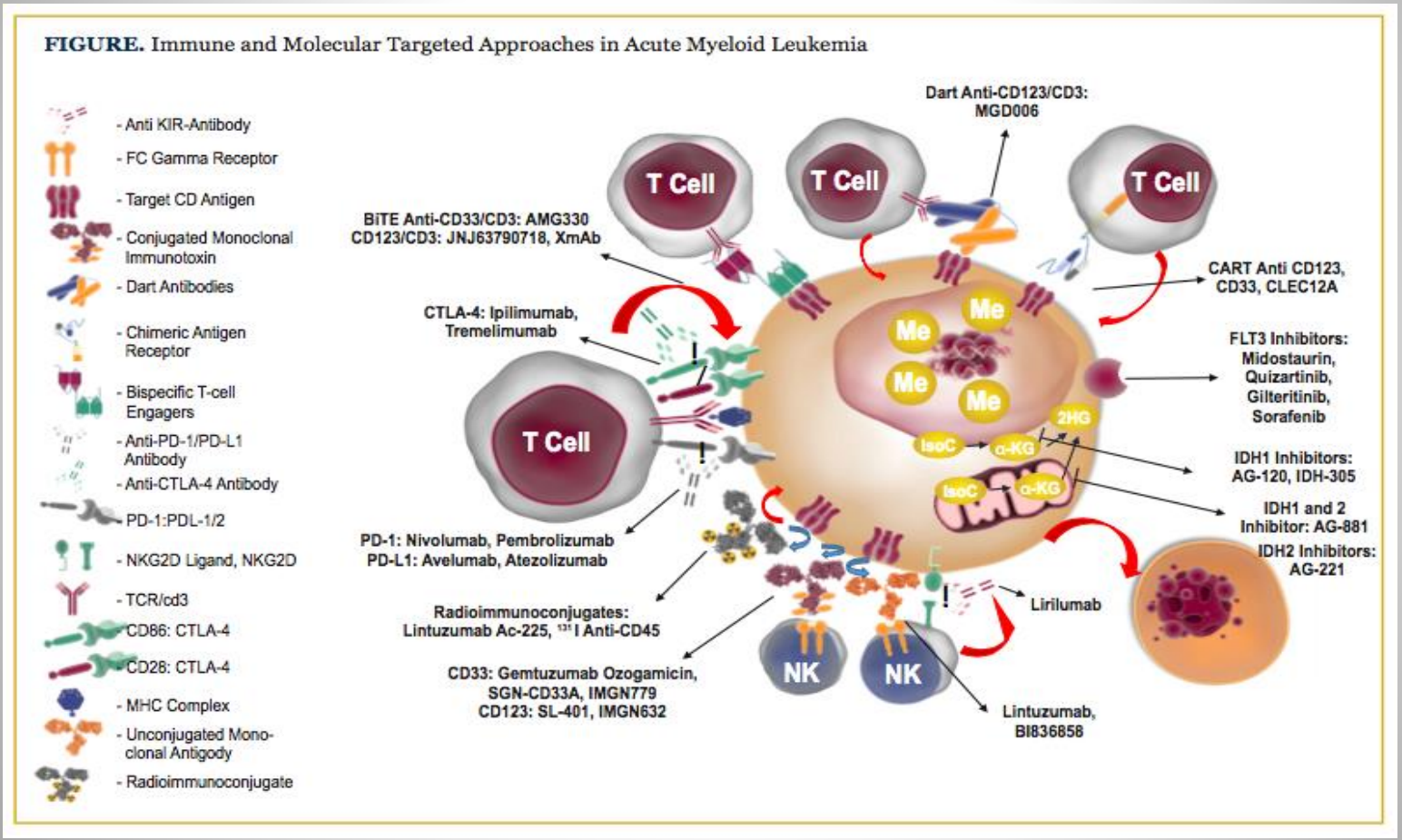
IDH1/2

- Among the 41 ivosidenib-treated patients evaluable for efficacy, a response of CR, CRi or CRp was achieved in 26/28 (93%) patients with de novo AML and 6/13 (46%) patients with sAML. Twenty-one patients received ≥1 cycle of consolidation therapy and 11 patients received maintenance after consolidation. Seventeen patients proceeded to HSCT.

- Among the 77 enasidenib-treated patients evaluable for efficacy, a response of CR, CRi, or CRp was achieved in 33/45 (73%) patients with de novo AML and in 20/32 (63%) patients with sAML . Thirty-seven patients received ≥1 cycle of consolidation therapy, 6 patients received maintenance directly after induction and 11 patients received maintenance after consolidation. Thirty-three patients proceeded to HSCT

Stein, E. et al. Abstract 560

Immunotherapy



Boddu P, et al AJHO. 2017;13(4):4-15

In the pipeline

- Syros 1425 + AZA (on going)
- Syros 1425 + Daratumumab (completed)
- APR 246 + AZA – tp53 mutated.
- Zella 202 alvocidib

Transplant

	Transp inmed	In 2 y	progression
Low	6.51	6.86	7.21
Int-1	4.61	4.74	5.16
Int 2	4.93	3.21	2.84
High	3.20	2.75	2.75

Cullen et al .

Conclusions

- We are beginning to learn how to combine targeted agents that are now approved and available with either hypomethylating agents or other treatment strategies.
- The area of immune-based therapy for MDS is beginning to further advance particularly with the introduction of various bispecific antibodies; there may be a role for these immune-based strategies in the future.