ASH Updates

MDS

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Outline

- MDS – genetics and changes to risk assessment
- ARCH, CHIP, CCUS – do we care? Do we treat?
- Low risk MDS – new drugs and management
- High risk MDS – starting to look more like AML
- Immunotherapy in MDS – seems like it should work?

IPSS-R: Cytogenetics, blasts, CBC predict risk

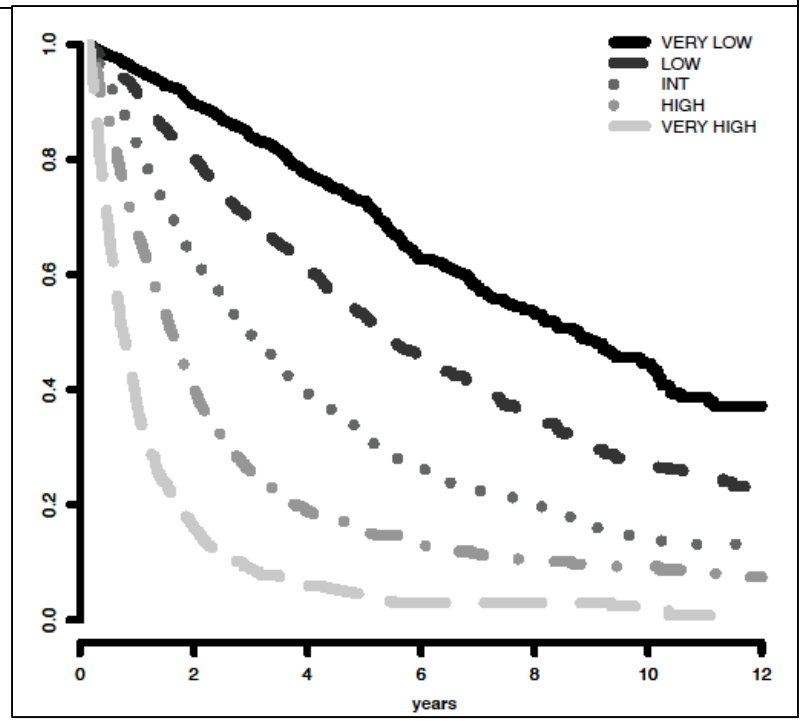
Table 3. IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

— indicates not applicable.

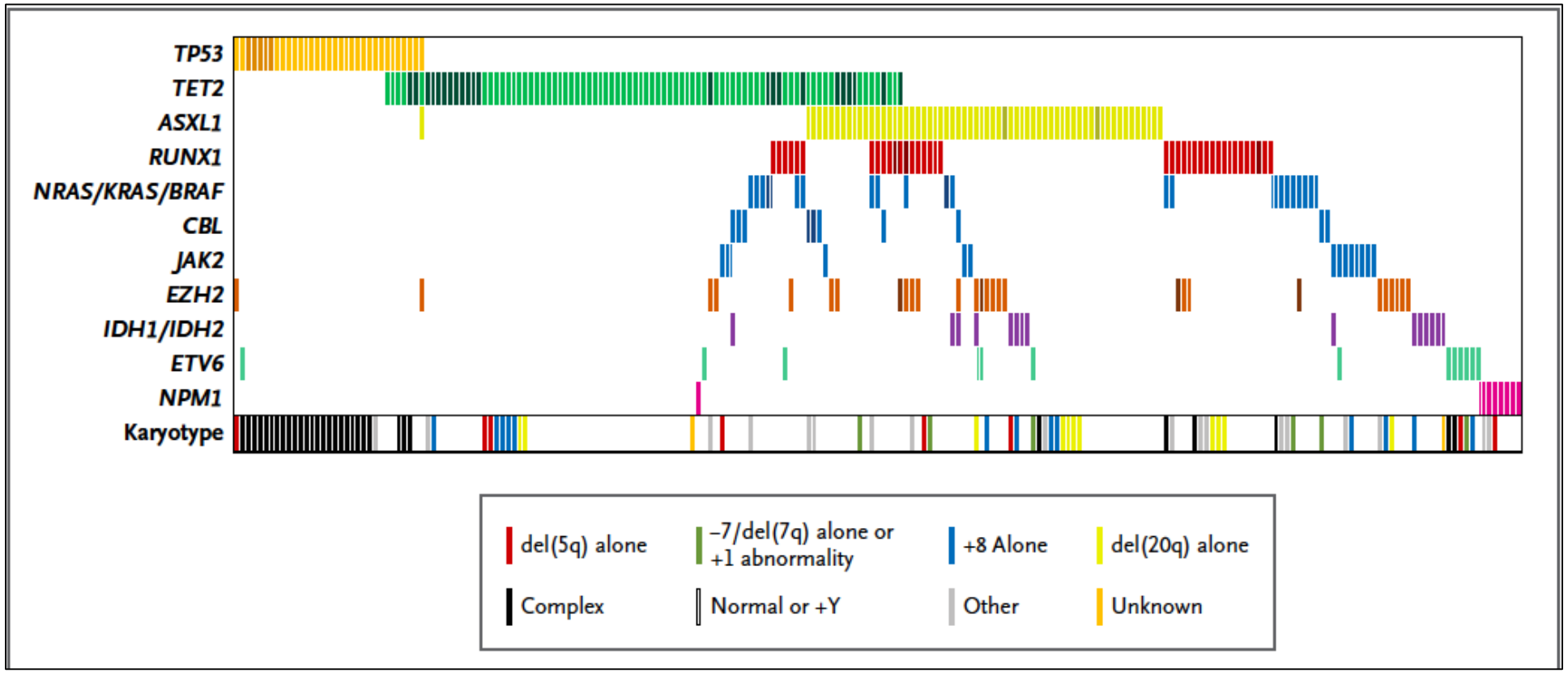
Table 4. IPSS-R prognostic risk categories/scores

Risk category	Risk score
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6



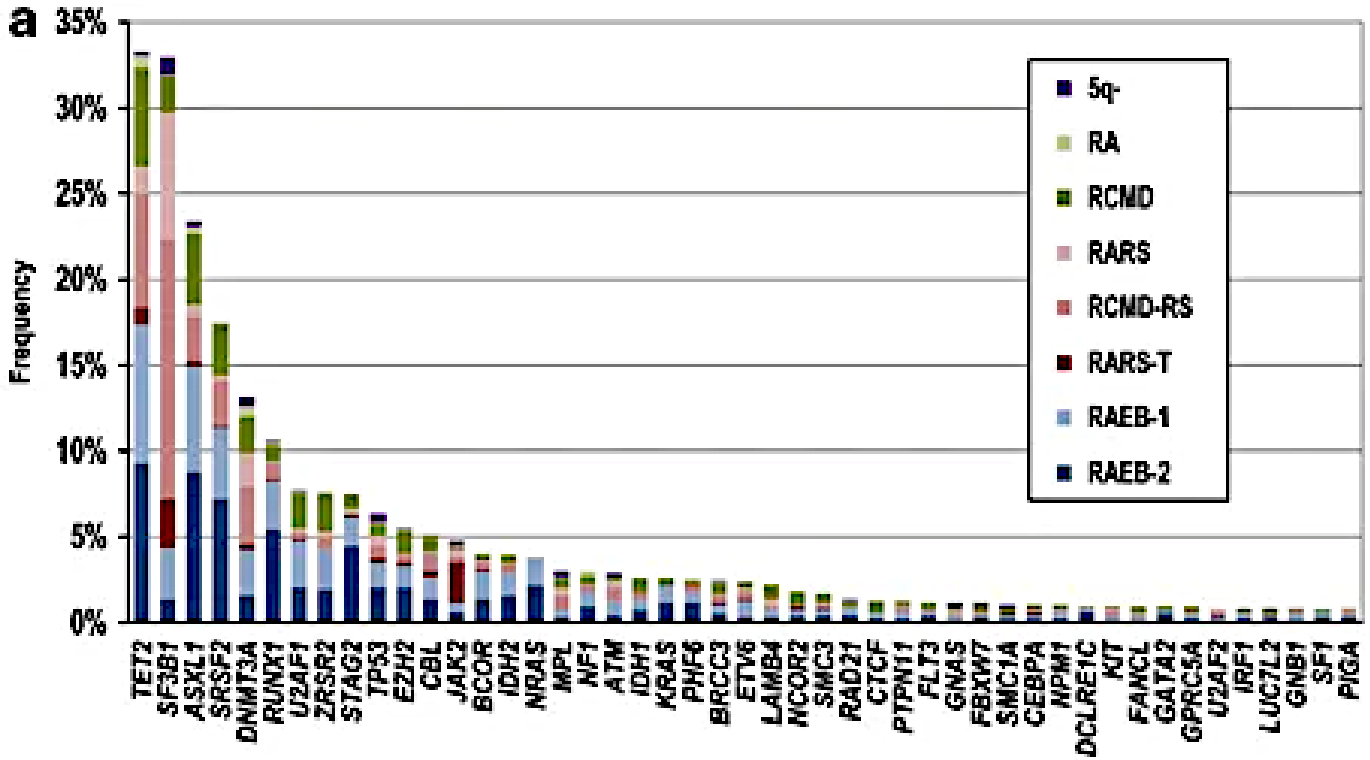
Blood. 2012;120(12):2454

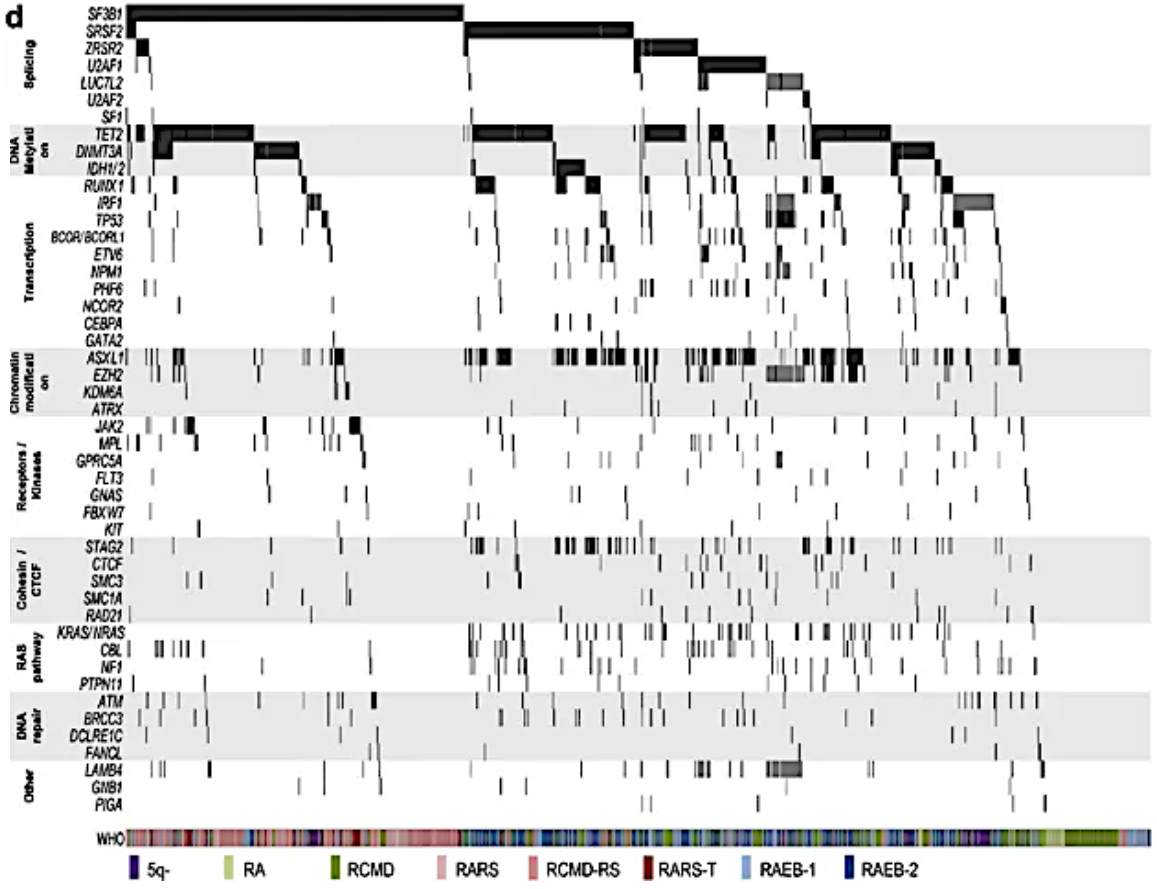
MDS point mutations



N Engl J Med. 2011 364(26):2496-506

More MDS mutations

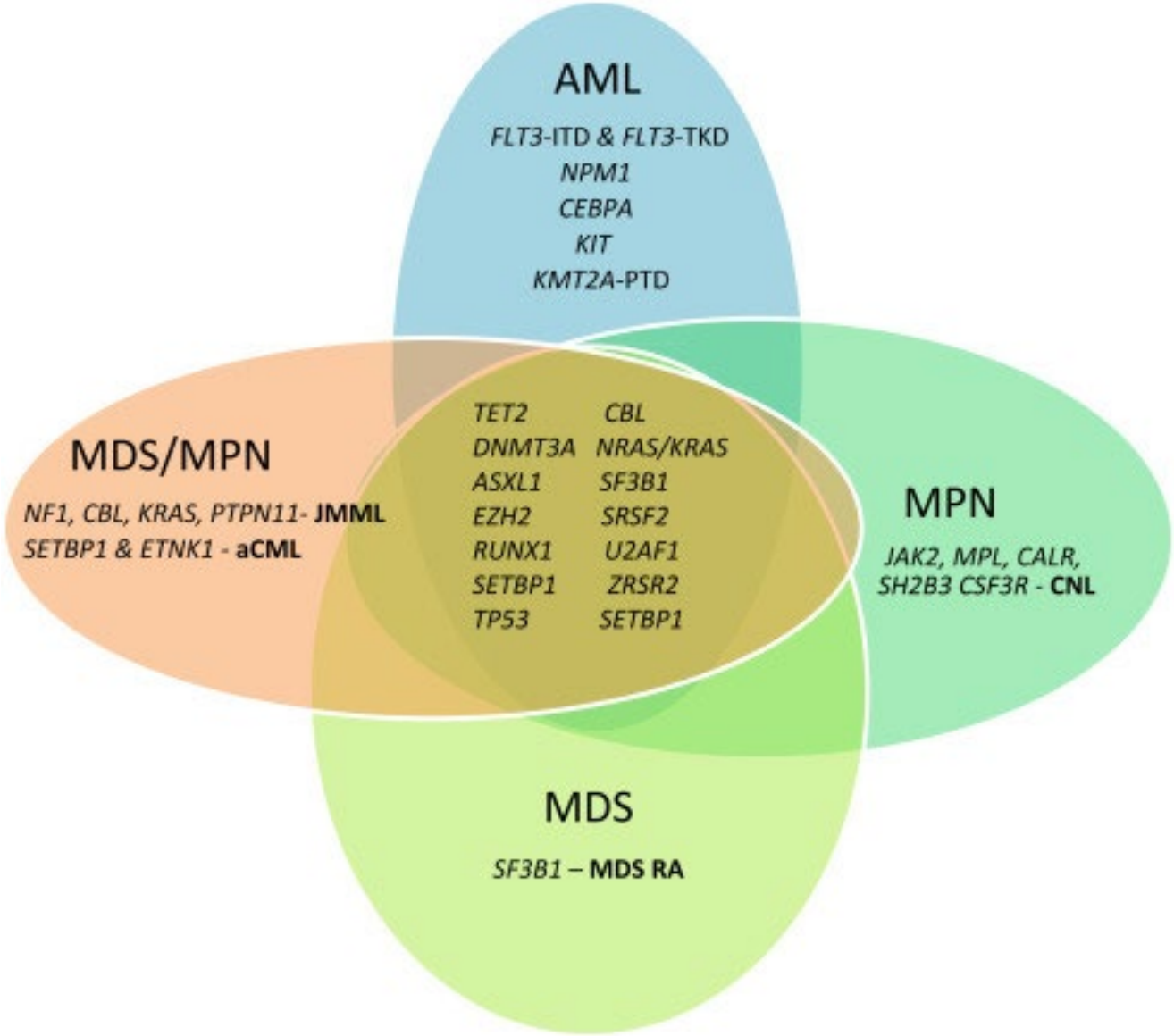




Haferlach T et al. Leukemia 2014

Spliceosome, epigenetic, transcription, chromatin mutations very common

Myeloid neoplasms – genetic overlap



Patel et al. Clin Lymph Myeloma and Leuk. July 2017, Pages S62-S74

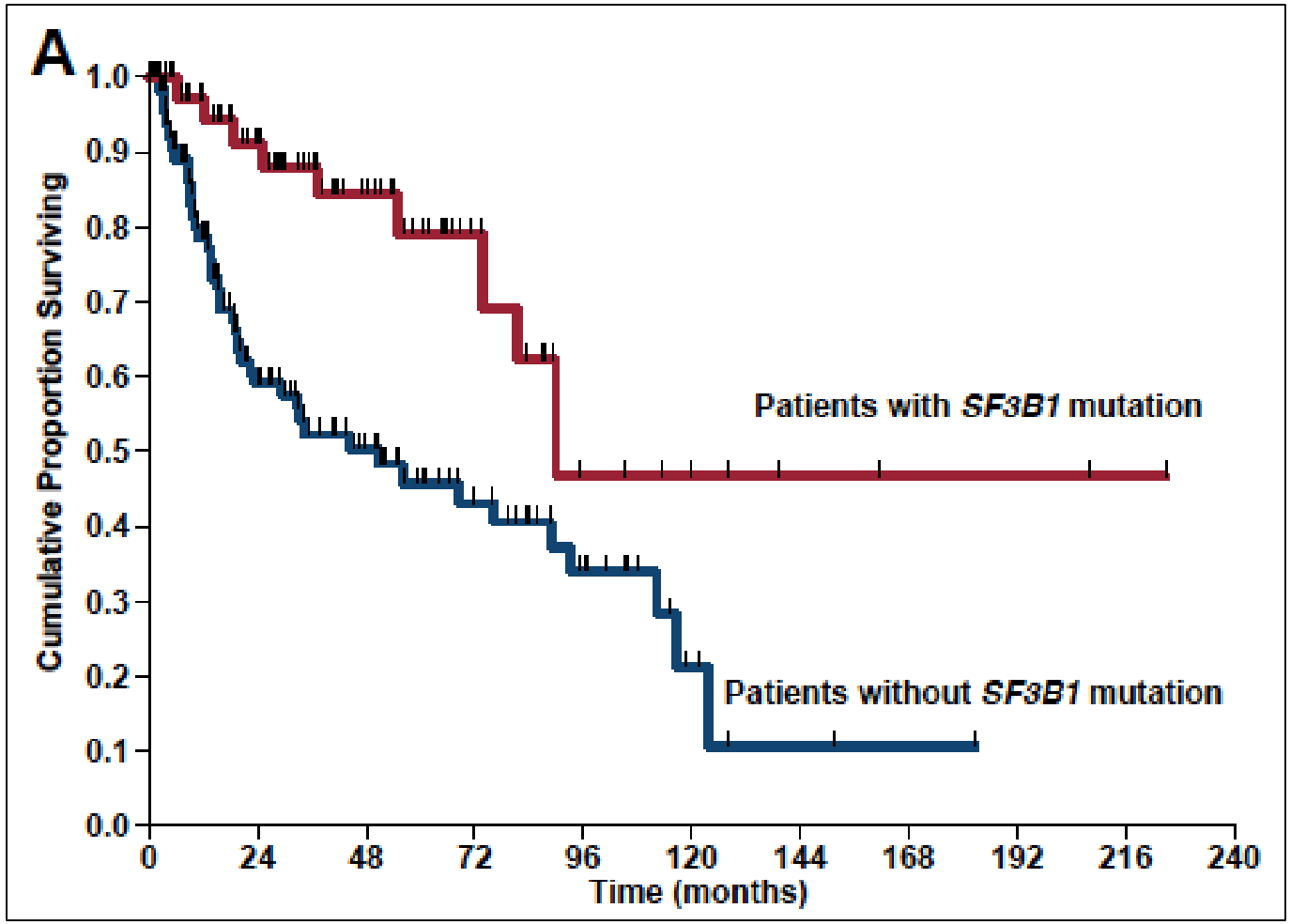
Mutations also affect risk

Table 2. Hazard Ratios for Death in a Multivariable Model.*

Risk Factor	Hazard Ratio (95% CI)	P Value
Age ≥55 yr vs. <55 yr	1.81 (1.20–2.73)	0.004
IPSS risk group		
Intermediate-1 vs. low	2.29 (1.69–3.11)	<0.001
Intermediate-2 vs. low	3.45 (2.42–4.91)	<0.001
High vs. low	5.85 (3.63–9.40)	<0.001
Mutational status		
TP53 mutation present vs. absent	2.48 (1.60–3.84)	<0.001
EZH2 mutation present vs. absent	2.13 (1.36–3.33)	<0.001
ETV6 mutation present vs. absent	2.04 (1.08–3.86)	0.03
RUNX1 mutation present vs. absent	1.47 (1.01–2.15)	0.047
ASXL1 mutation present vs. absent	1.38 (1.00–1.89)	0.049

N Engl J Med. 2011 364(26):2496-506

SF3B1 mutations – improved OS!



Blood 2011 118(24):6239-46

* Not independent of morphology

Development of IPSS-M: Background and Method

- Current risk stratification guidelines, including IPSS/IPSS-R, do not account for mutations that are now recognized to affect prognosis in MDS[1,2]
- Current report details efforts by the IWG-PM to integrate key mutations into the IPSS/IPSS-R, yielding the IPSS-M
  - Developed in an IWG discovery cohort (n = 2957) and validated in a Japanese cohort (n = 754)

1. Greenberg. Blood. 1997;89:2079. 2. Greenberg. Blood. 2012;120:2454. 3. Bernard. ASH 2021. Abstr 61.

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Development of IPSS-M: Patient Characteristics and Molecular Characterization in Discovery Cohort

- Inclusion criteria: diagnostic samples; blasts <20%, WBC <13 x 10^9/L

Characteristic	All Patients (N = 2957)
Median age, yr (95th range)	72 (39-88)
Therapy-related MDS, %	8
Treated with disease-modifying agents according to guidelines, %	30
Median follow-up, yr	3.8
≥1 oncogenic lesion, %*	94
Median number oncogenic lesions per patient, n (range)	4 (0-20)

*48 genes mutated in >1% of patients.

- Molecular characterization: conventional cytogenetics; assessed oncogenic mutations from 152 genes (VAF >2%)
  - Findings: 48 genes mutated in ≥1% of patients; ≥1 oncogenic mutation in 94% of patients

Bernard. ASH 2021. Abstr 61.

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Slide credit: clinicaloptions.com

Development of IPSS-M: Association Between Gene Mutations and Clinical Endpoints in Discovery Cohort

- After adjusting for age, sex, MDS type (primary vs therapy related), and IPSS-R raw score, multiple genes were associated with adverse outcomes including LFS (14 genes), OS (16 genes), and AML transformation (15 genes)[1]
- Strongest associations found with:
  - *TP53* multi-hit (multiple mutations, mutation with deletion or copy-neutral LoH)[2] (7% of patients)
  - *MLL* partial tandem duplication (2.5% of patients)
  - *FLT3* mutations (1.1% of patients)

1. Bernard. ASH 2021. Abstr 61. 2. Bernard. Nat Med. 2020. 26:1549.

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Slide credit: clinicaloptions.com

Development of IPSS-M: Association Between Gene Mutations and Clinical Endpoints in Discovery Cohort

- *SF3B1* mutations were associated with favorable outcomes, modulated by pattern of comutations
  - *SF3B1*^{5q}: concomitant isolated del(5q) (7%)
  - *SF3B1*$^{\beta}$: co-occurrence of mutations in *BCOR, BCORL1, RUNX1, NRAS, STAG2, SRSF2* (15%)
  - *SF3B1*$^{\alpha}$: any other *SF3B1* mutations

1. Bernard. ASH 2021. Abstr 61.

Slide credit: clinicaloptions.com

Development of IPSS-M: Model Development Steps 1 and 2

Step	Development
Encoding for clinical and molecular variables	▪ Continuous encoding of clinical variables; linear function for BM blasts, Hg ▪ Platelet values capped at 250 x 10^9/L; ANC not included ▪ Maintained 5 IPSS-R cytogenetic categories ▪ Gene mutations incorporated as binary variables aside from *TP53* allelic state and *SF3B1* subsets accounting for comutations
Determination of independent IPSS-M prognostic variables	▪ Model fit with a Cox multivariable regression adjusted for confounder variables (age, sex, primary vs therapy-related MDS) ▪ Continuous clinical parameters ▪ IPSS-R cytogenetic categories ▪ 17 genetic variables from 16 main effect genes ▪ 1 genetic variable from 15 residual genes (*BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2, WT1*)

1. Bernard. ASH 2021. Abstr 61.

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Slide credit: clinicaloptions.com

Development of IPSS-M: Model Development Steps 3 and 4

Step	Development
Construction of IPSS-M risk score as a continuous patient-specific score	▪ Interpretable risk scoring system ▪ Prominent 0 value established for a hypothetical average patient ▪ 1 unit increase/decrease in risk score = double/half risk
Definition of IPSS-M risk categories for discrete risk grouping	▪ 6 risk groups established – Very low: 14% – Low: 33% – Moderate low: 11% – Moderate high: 11% – High: 14% – Very high: 17%

- IPSS-M demonstrated improved prognostic discrimination vs IPSS-R with 5-point increase in concordance index across all endpoints
- **46% of patients restratified from IPSS-R to IPSS-M, with 7% restratified by >1 strata**

1. Bernard. ASH 2021. Abstr 61.

Slide credit: clinicaloptions.com

Development of IPSS-M: Clinical Applicability

- IPSS-M web calculator returns individualized risk score and category
- Strategy for missing variables: IPSS-M calculated for best, average, and worst scenarios

Bernard. ASH 2021. Abstr 61.

Slide credit: clinicaloptions.com

Development of IPSS-M: Conclusions

- IPSS-M combines conventional parameters with mutations in 31 key genes to improve MDS risk stratification
- Risk score is personalized as a continuous score, reproducible, and interpretable, as 1-unit increase in score doubles risk
- 6-category risk schema developed
- Includes a strategy to handle missing data and a web calculator

Bernard. ASH 2021. Abstr 61.

Slide credit: clinicaloptions.com

Summary

- IPSS-R is still useful, and frequently used in clinical trials
- However, mutation analysis can improve risk stratification and “highly recommended” in NCCN guidelines
- With development of targeted therapies, can be opportunities for clinical trials
  - IDH1 inhibitor in AML for R/R MDS at OHSU
- **Next-gen panel should be done routinely on all new MDS pts**

What’s new

CCUS and low risk MDS

MDS treatment – 2019 summary

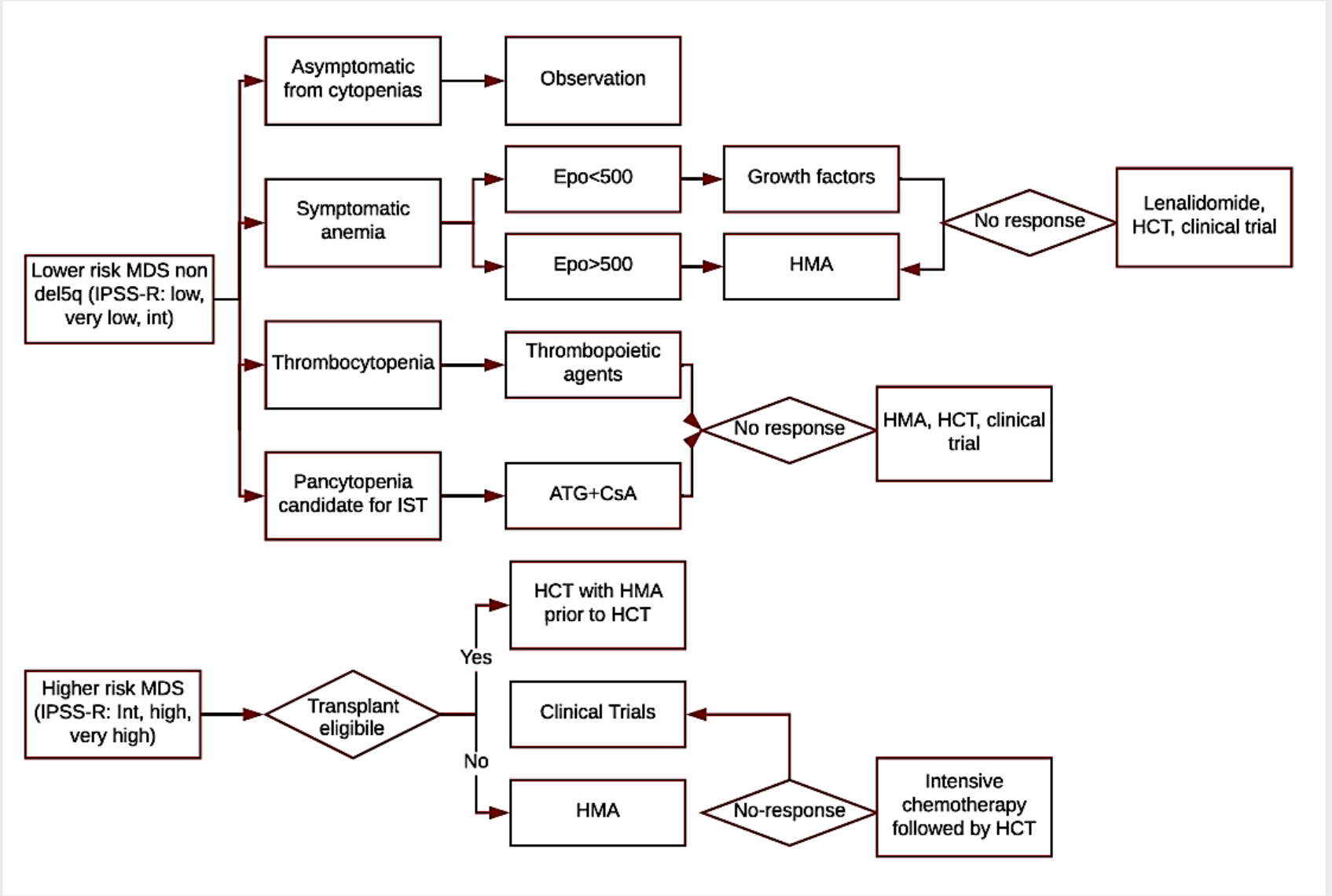
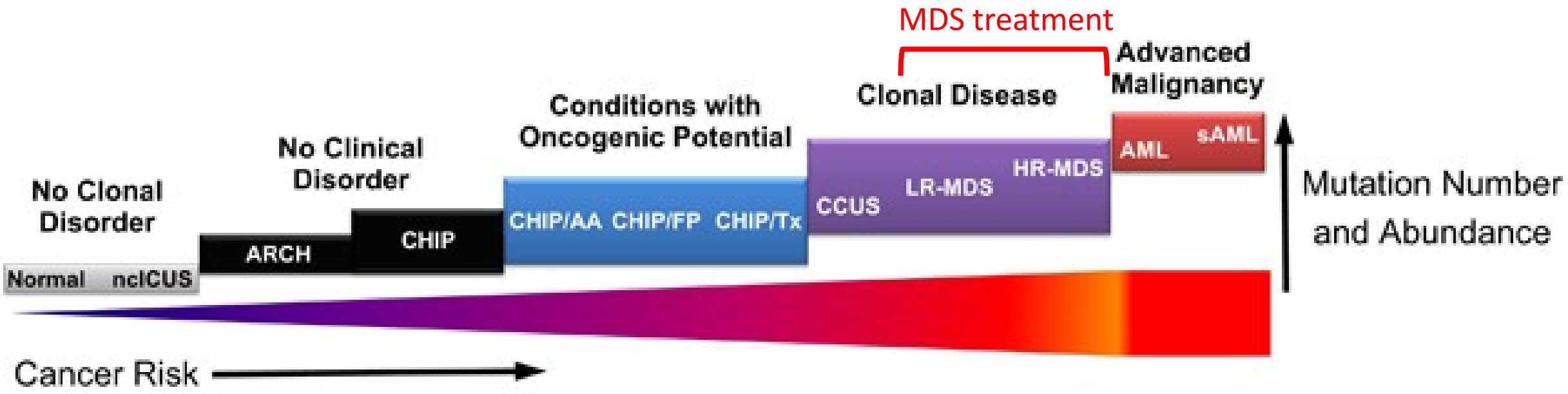


Figure 1. Clinical pathway for patients without del(5q) type MDS disease management

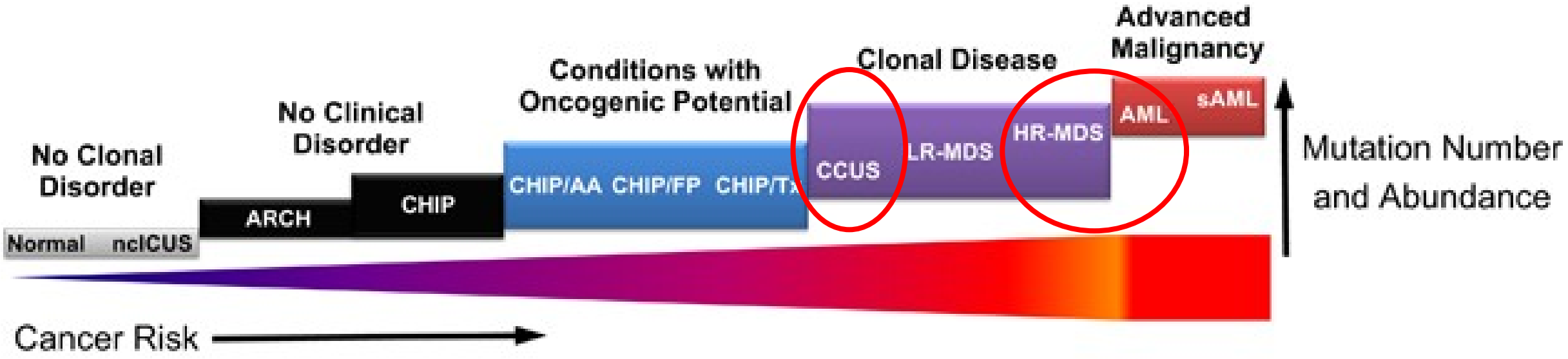
Faber MG et al.
J Clin Pathways. 2019

Increasing spectrum of myeloid malignancies - and terminology!



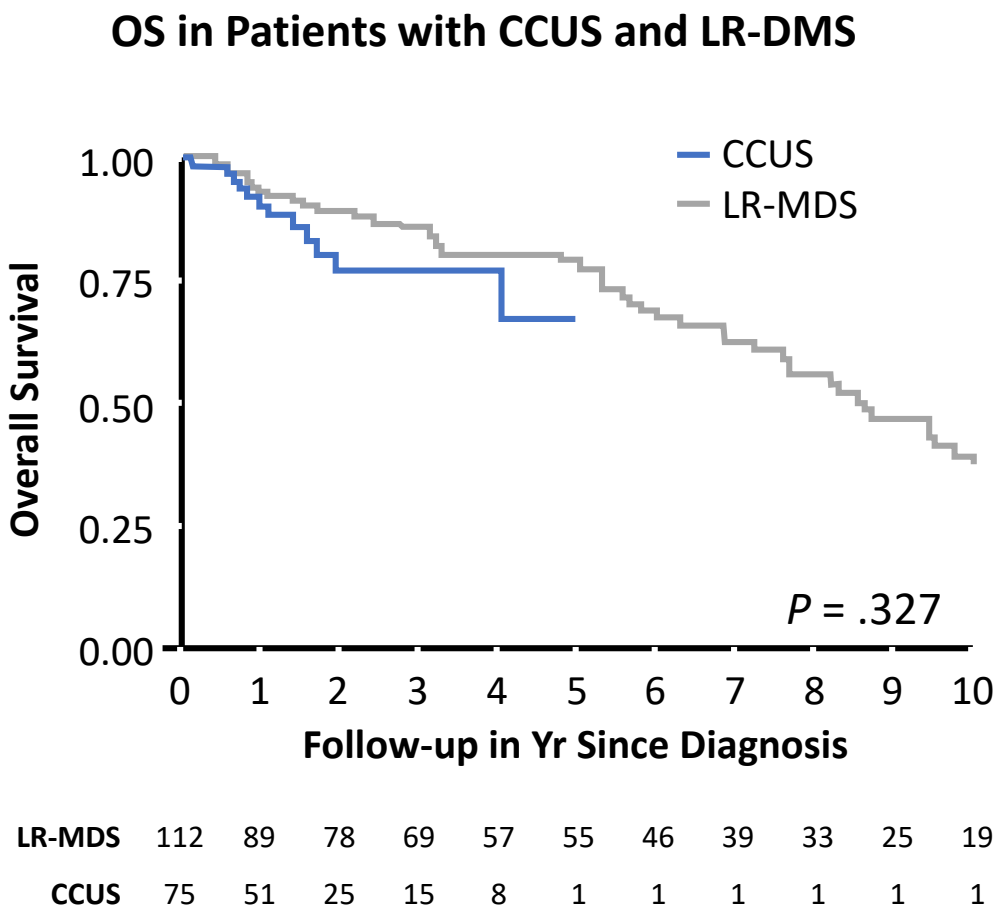
Bejar, R. CHIP, ICUS, CCUS and other four-letter words. *Leukemia* **31,** 1869–1871 (2017)

Changes happening at ends of spectrum



Bejar, R. CHIP, ICUS, CCUS and other four-letter words. *Leukemia* **31,** 1869–1871 (2017)

CCUS is Evolving to an *Interventional* State



- NCT05030441: ivosidenib for patients with CCUS and mutations in IDH1
  - US multi-institutional study
  - Ivosidenib: IDH1 inhibitor, 500 mg daily for up to 18 mo
- NCT04741945: repurposing metformin as a leukemia-preventive drug in CCUS and LR-MDS
  - Denmark multi-institutional study
  - 2000 mg/daily for 12 mo with a slow up-titration 2 wk before to full dose
- NCT03418038: IV ascorbic acid in *TET2*-mutated CCUS
- Canakinumab in CCUS
  - Multi-institutional study
  - Canakinumab: a human monoclonal antibody targeting IL-1β

Li. Blood Advances. 2021;5:2272. NCT05030441. NCT04741945. NCT03418038.

Slide credit: clinicaloptions.com

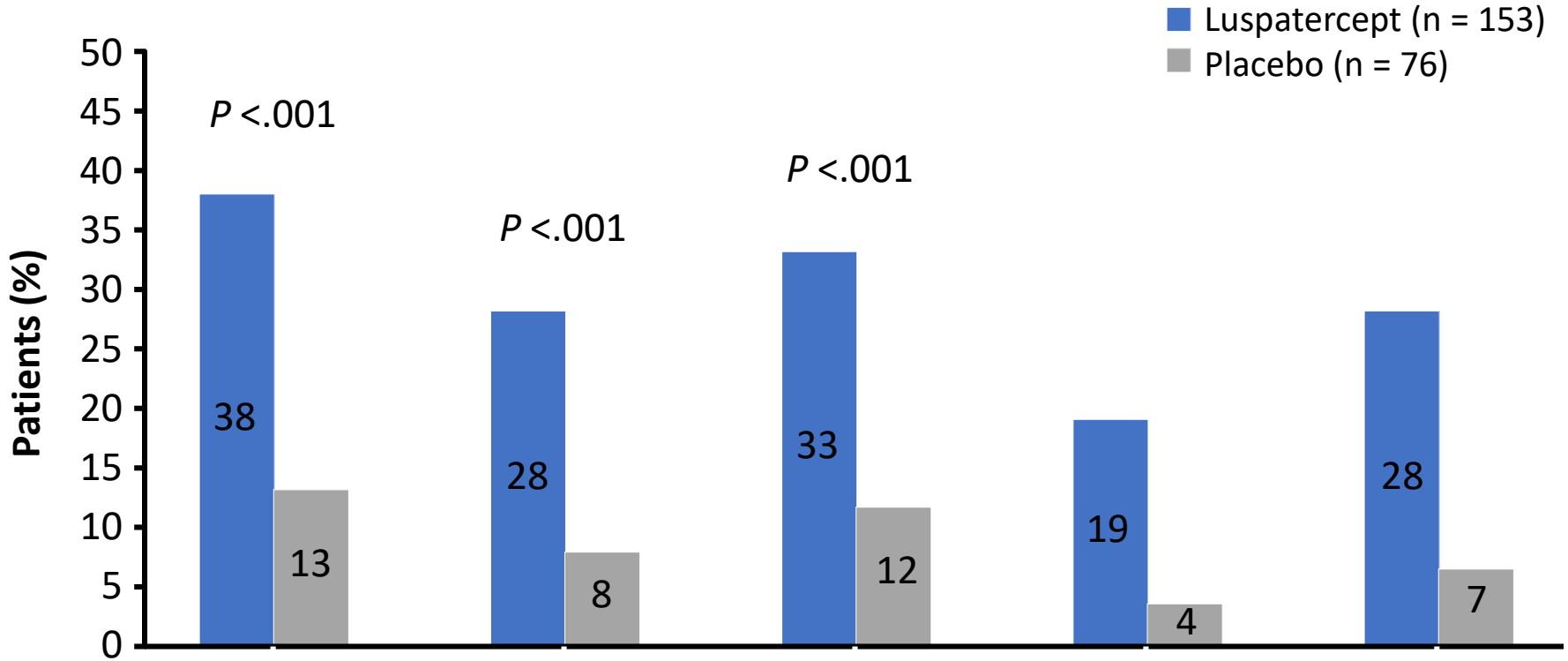
Early Erythropoiesis Stimulation in Low-Risk MDS Remains Standard of Care

- Recombinant erythropoietin can lead to long-term responses in LR-MDS
  - With MDS with isolated anemia
  - EPO levels <500 U/L, usually <200 U/L
  - Considerable variation in dose and schedule
- Low thromboembolic risk if given with lower Hgb
- Sequencing of ESAs with other therapy for LR-MDS: unclear

NCCN. Clinical practice guidelines in oncology: myelodysplastic syndromed. v2.2022. nccn.org.

Slide credit: clinicaloptions.com

Luspatercept vs Placebo in MDS (MEDALIST): Red Blood Cell Transfusion Independence

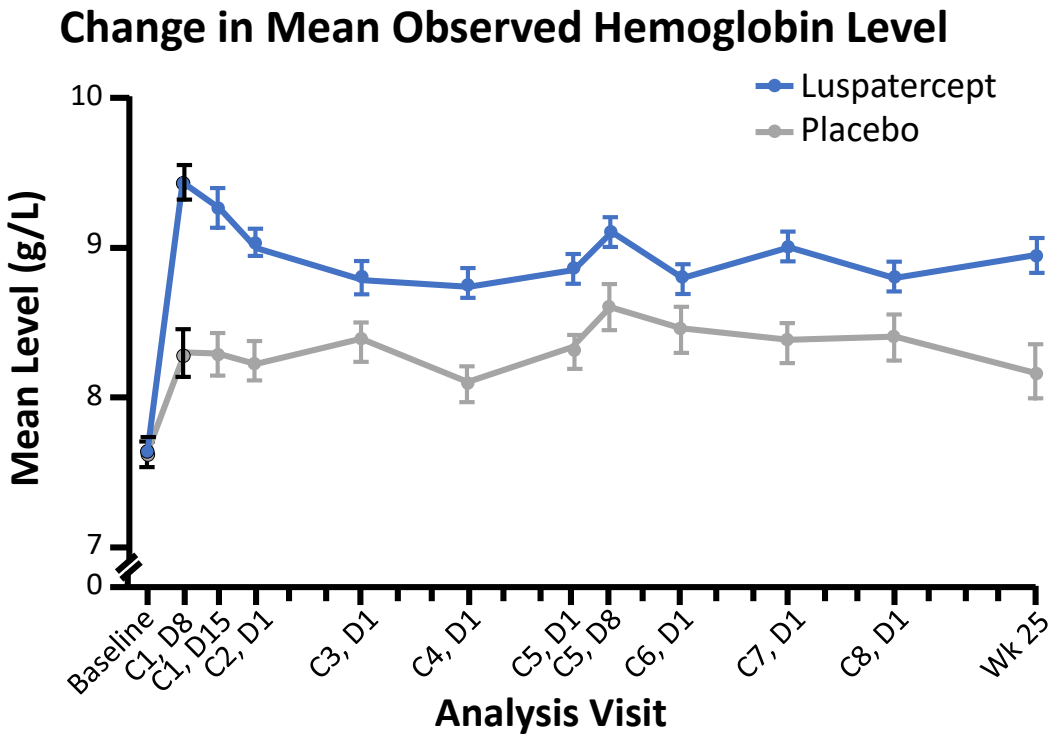


Patients With Response, n (%) (95% CI)	≥8 Wk (Wk 1-24)	≥12 Wk (Wk 1-24)	≥12 Wk (Wk 1-48)	≥16 Wk (Wk 1-24)	≥16 Wk (Wk 1-48)
Luspatercept	58 (38) (30-46)	43 (28) (21-36)	51 (33) (26-41)	29 (19) (13-26)	43 (28) (21-36)
Placebo	10 (13) (6-23)	6 (13) (3-16)	6 (12) (6-21)	3 (4) (1-11)	5 (7) (2-15)

Fenaux. NEJM. 2020;382:140.

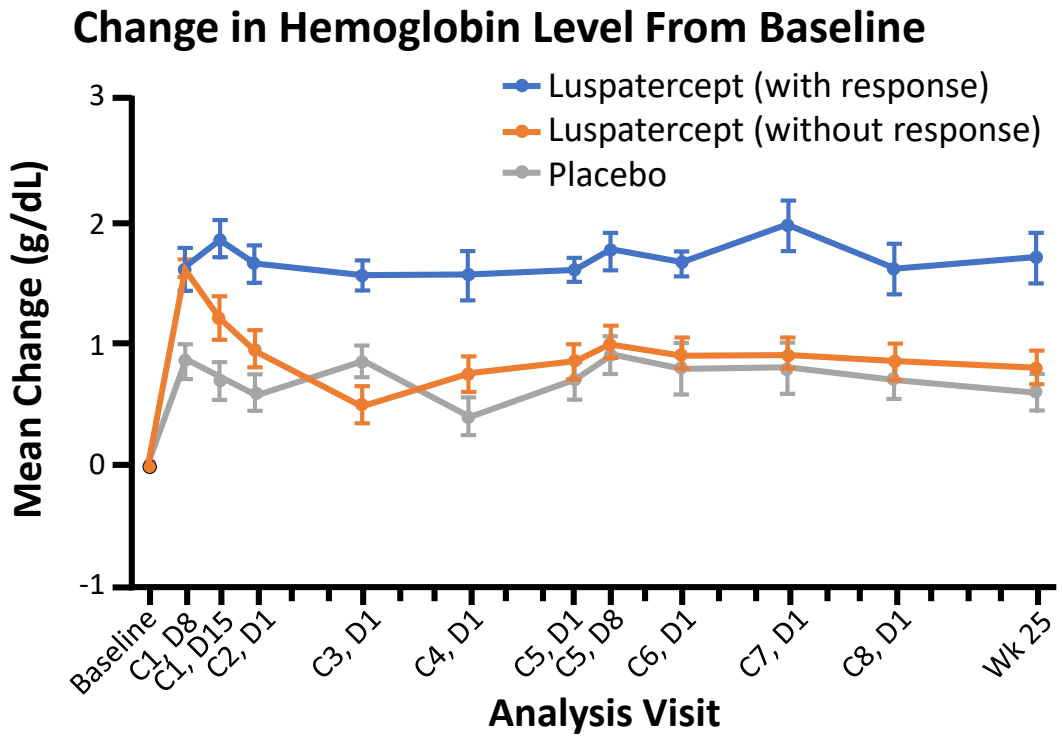
Slide credit: clinicaloptions.com

MEDALIST: Change in Hemoglobin Levels



Patients at Risk, n

Luspatercept	153	57	87	116	105	112	103	76	92	106	90	80
Placebo	76	32	36	41	47	44	52	29	44	47	44	32



Patients at Risk n

Luspatercept (with response)	–	24	36	55	53	52	50	42	47	50	42	45
Luspatercept (without response)	–	33	51	61	52	60	53	34	45	56	48	35
Placebo	–	32	36	41	47	44	52	29	44	47	44	32

Fenaux. NEJM. 2020;382:140.

Slide credit: clinicaloptions.com

MEDALIST: Adverse Events

AE in ≥10% of patients*	Luspatercept (n = 153)		Placebo (n = 76)	
	Any Grade	Grade 3	Any Grade	Grade 3
General or administration-site condition				
▪ Fatigue	41 (27)	7 (5)	10 (13)	2 (3)
▪ Asthenia	31 (20)	4 (3)	9 (12)	0
▪ Peripheral edema	25 (16)	0	13 (17)	1 (1)
Gastrointestinal disorder				
▪ Diarrhea	34 (22)	0	7 (9)	0
▪ Nausea†	31 (20)	1 (1)	6 (8)	0
▪ Constipation	17 (11)	0	7 (9)	0
Nervous system disorder				
▪ Dizziness	30 (20)	0	4 (5)	0
▪ Headache	24 (16)	1 (1)	5 (7)	0
Musculoskeletal/connective tissue disorder	29 (19)	3 (2)	5 (7)	0
▪ Back pain†	8 (5)	1 (1)	9 (12)	2 (3)
▪ Arthralgia				

AE in ≥10% of patients*	Luspatercept (n = 153)		Placebo (n = 76)	
	Any Grade	Grade 3	Any Grade	Grade 3
Respiratory, thoracic, or mediastinal disorder				
▪ Dyspnea	23 (15)	1 (1)	5 (7)	0
▪ Cough	27 (18)	0	10 (13)	0
Infection or infestation				
▪ Bronchitis†	17 (11)	1 (1)	1 (1)	0
▪ UTI†	17 (11)	2 (1)	4 (5)	3 (4)
Injury, poisoning or fall	15 (10)	7 (5)	9 (12)	2 (3)

Fenaux. NEJM. 2020;382:140.

Slide credit: clinicaloptions.com

Lenalidomide and Eltrombopag for Low-Risk/ Intermediate-Risk MDS: Study Design

Multicenter, open-label phase II trial

Patients ≥18 yr with low-risk/intermediate-1–risk MDS per IPSS (or non-proliferative CMML); symptomatic anemia untransfused with Hb ≤10 g/dL or with RBC transfusion dependence, or PLTs <50,000 with Hb >10 g/dL; no prior exposure to LEN (for >2 mo) or ELT (N = 52)

Arm A: PLTs ≥50,000
LEN 10 mg PO QD
on Days 1-21
(n = 28)

If PLTs <50,000

LEN d/c and ELT
100-300 mg PO QD given until PLTs ≥50,000 for 2 wk; patients then resumed LEN

If PLTs <50,000

LEN d/c and ELT
100-300 mg PO QD given until PLTs ≥50,000 for 2 wk; patients then resumed LEN + ELT in combination

Arm B: PLTs <50,000
ELT 100-300 mg PO QD on Days 1-28 until PLTs ≥50,000 for 2 wk, then followed treatment scheme in Arm A
(n = 24)

Patients were allowed to stay on ELT alone if they reached HI-E and HI-PLT on ELT

Primary endpoints: HI (per 2006 IWG criteria), safety and tolerability

Secondary endpoints: HI duration, time to HI, clinically significant bleeding events, BM response (CR + PR), cytogenetic response

Gonzalez-Lugo. ASH 2021. Abstr 65.

Slide credit: clinicaloptions.com

Lenalidomide and Eltrombopag for Low-Risk/ Intermediate-Risk MDS: Baseline Characteristics

Characteristic	ELT (n = 21)	LEN (n = 16)	ELT + LEN (n = 15)	Total (N = 52)
Mean age, yr (range)	68 (34-93)	74 (59-86)	73 (56-85)	71 (34-93)
Male, n (%)	17 (81)	9 (56)	11 (73)	36 (71)
Mean Hb, g/dL (range)	8.6 (6.1-11.7)	8.2 (6.2-9.5)	8.14 (6.4-10.8)	8.35 (6.1-11.7)
Mean PLT count, cells/mm^3 (range)	21.8 (1-97)	256.7 (88-457)	133.5 (16-280)	126.3 (1-457)
Treatment naïve, n (%)	NR	NR	NR	21 (40)
IPSS risk, n (%)				
▪ Very low	0	1	0	1 (2)
▪ Low	6	8	10	24 (46)
▪ Intermediate	15	7	5	27 (52)
MDS WHO category, n (%)				
▪ MDS-SLD	0	5	0	5 (10)
▪ MDS-MLD	18	3	6	27 (52)
▪ MDS-RS-SLD	0	6	3	9 (17)
▪ MDS-RS-MLD	0	0	3	3 (6)
▪ MDS-EB-1	1	1	1	3 (6)
▪ MDS del(5q)	0	1	1	2 (4)
▪ CMML	2	0	1	3 (6)

Gonzalez-Lugo. ASH 2021. Abstr 65.

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Lenalidomide and Eltrombopag for Low-Risk/ Intermediate-Risk MDS: Safety

	ELT		LEN	
AEs, n (%)	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Anemia	0	0	3 (6)	0
Neutropenia	0	0	3 (6)	6 (12)
Febrile neutropenia	0	0	0	1 (2)
Thrombocytopenia	0	0	6 (12)	3 (6)
Bilirubin rise	1 (2)	0	2 (4)	0
ALT/AST elevation	1 (2)	0	0	0
Diarrhea	0	0	1 (2)	0
Rash	0	0	2 (4)	0
Arthralgia	0	0	1 (2)	0
Bleeding	2 (4)	0	0	0

- 3 deaths occurred
  - 1 each due to pneumonia, sepsis, and gallbladder cancer
- 2 patients had major bleeding events
- 1 patient on ELT had reversible increase in peripheral blasts during an episode of acute cholecystitis
- 1 patient developed BM fibrosis after 6 yr on ELT
- 5 patients discontinued treatment due to AEs

Gonzalez-Lugo. ASH 2021. Abstr 65.

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Lenalidomide and Eltrombopag for Low-Risk/ Intermediate-Risk MDS: Efficacy

Efficacy Outcome	ELT (n = 21)	LEN (n = 16)	ELT + LEN (n = 15)	Total (N = 52)
ORR (ITT), %	33	38	33	35
Evaluable responses, %				
▪ RBC-TI	24	46	21	30
▪ HI-PLT	35	0	21	20
▪ Bilineage response	29	0	14	16
▪ CR	6	0	14	7
Median TTR, wk (range)	9.4 (6-12.4)	10.9 (2.4-16)	9.9 (2-20)	10.05
Median DoR, wk (range)	102 (8-295)	63 (25-141)	66 (8.3-107)	77.08

- At the time of data cutoff (Sept 22, 2021), 2 patients on ELT, 1 patient on LEN, and 2 patients on ELT + LEN are still on trial with ongoing responses

Gonzalez-Lugo. ASH 2021. Abstr 65.

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Lenalidomide and Eltrombopag for Low-Risk/ Intermediate-Risk MDS: Investigators' Conclusions

- Treatment with ELT and LEN showed good efficacy and safety in patients with low-risk/intermediate-risk MDS
  - ORR of 35% in ITT population
  - Median DoR: 1.5 yr
  - Acceptable safety profile
- ELT monotherapy yielded responses with a sizeable proportion of bilineage responses
- 1 patient developed BM fibrosis and only 1 patient had transient increase in blasts, allaying these preexisting safety concerns

Gonzalez-Lugo. ASH 2021. Abstr 65.

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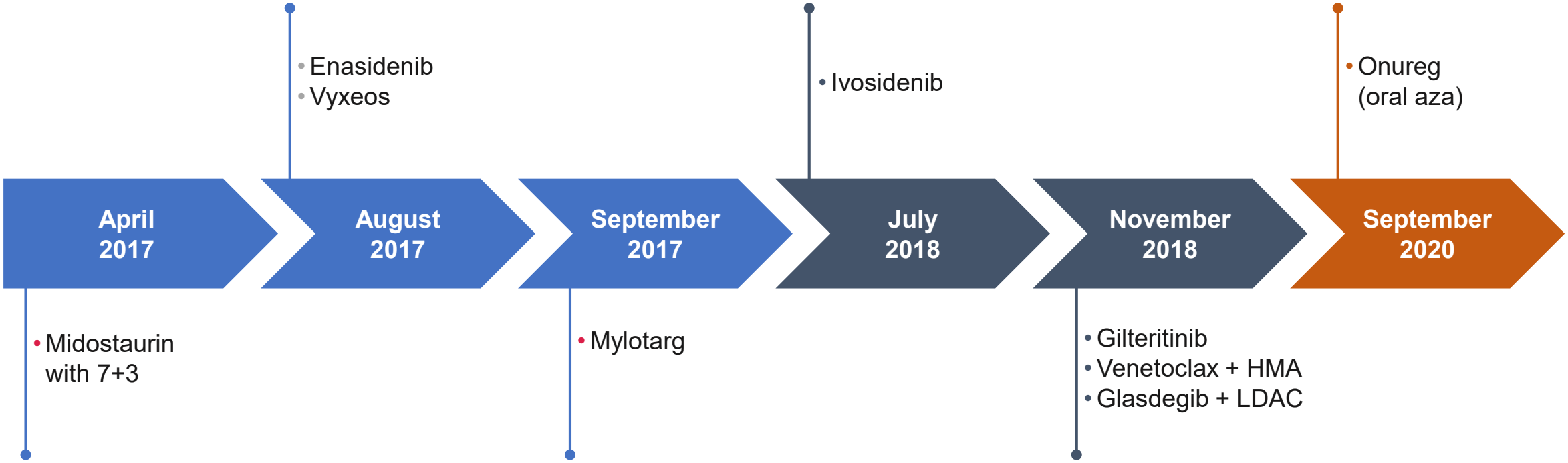
What's new

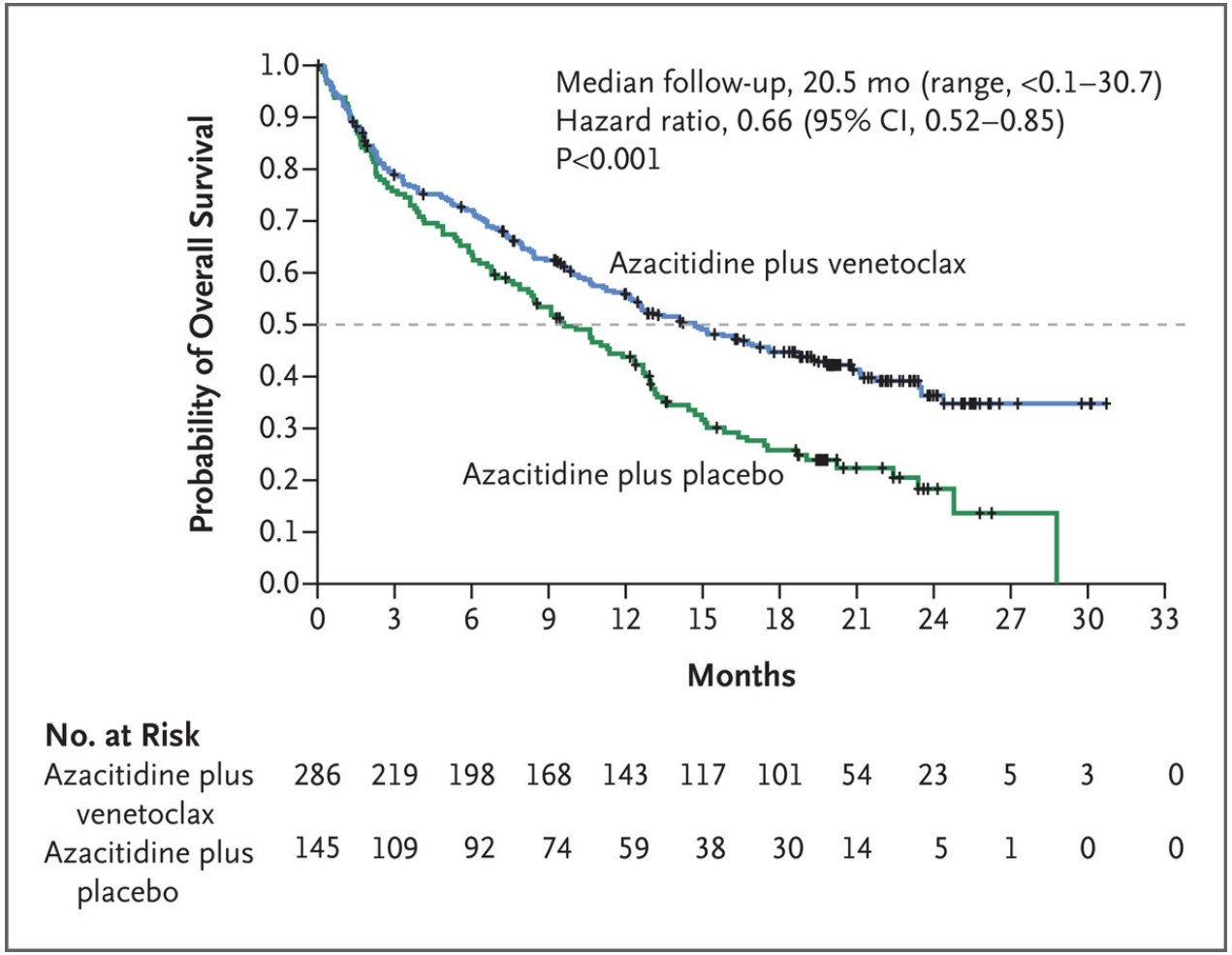
High risk MDS – starting to look more like AML!

And even being incorporated into AML trials

9 drugs approved in AML since 2017!



Aza + ven: VIALE-A trial results
One combo to treat all AML?



CD DiNardo et al. N Engl J Med 2020;383:617-629.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Azacitidine–Venetoclax Group (N=286)	Azacitidine–Placebo Group (N=145)
Age		
Median (range) — yr	76 (49–91)	76 (60–90)
≥75 yr — no. (%)	174 (61)	87 (60)
Male sex — no. (%)	172 (60)	87 (60)
AML type — no (%)		
De novo	214 (75)	110 (76)
Secondary	72 (25)	35 (24)
Secondary AML — no./total no. (%)		
History of myelodysplastic syndrome or CMML	46/72 (64)	26/35 (74)
Therapy-related AML	26/72 (36)	9/35 (26)
ECOG performance-status score — no. (%)†		
0–1	157 (55)	81 (56)
2–3	129 (45)	64 (44)
Bone marrow blast count — no. (%)		
<30%‡	85 (30)	41 (28)
≥30 to <50%	61 (21)	33 (23)
≥50%	140 (49)	71 (49)
AML with myelodysplasia-related changes — no. (%)	92 (32)	49 (34)
Cytogenetic risk category — no. (%)§		
Intermediate	182 (64)	89 (61)
Normal karyotype — no.	128	62
Trisomy 8; +8 alone — no.	13	10
Poor	104 (36)	56 (39)
7 or 7q deletion — no.	20	11
5 or 5q deletion — no.	46	22
Complex, ≥3 clonal abnormalities — no.	75	36
Somatic mutations — no./total no. (%)		
IDH1 or *IDH2*	61/245 (25)	28/127 (22)
FLT3 ITD or TKD	29/206 (14)	22/108 (20)
NPM1	27/163 (17)	17/86 (20)
TP53	38/163 (23)	14/86 (16)
Baseline cytopenia grade ≥3¶		
Anemia — no. (%)	88 (31)	52 (36)
Neutropenia — no./total no. (%)	206/286 (72)	90/144 (62)
Thrombocytopenia — no. (%)	145 (51)	73(50)
Baseline transfusion dependence — no. (%)‖		
Red cells	144 (50)	76 (52)
Platelets	68 (24)	32 (22)
≥2 Reasons for ineligibility to receive intensive therapy — no. (%)	141 (49)	65 (45)

* AML denotes acute myeloid leukemia, CMML chronic myelomonocytic leukemia, ITD internal tandem duplications, and TKD tyrosine kinase domain.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.
‡ These bone marrow blast counts were between 20 and 29%.
§ Only cytogenetic risks of interest are shown.
¶ Cytopenia was graded according to the Common Terminology Criteria for Adverse Events.
‖ Baseline transfusion dependence was transfusion within 8 weeks before the first dose of azacitidine–venetoclax or azacitidine–placebo or randomization.

Venetoclax and HMA in Higher-Risk MDS: Background

- HMAs remain standard of care for patients with higher-risk MDS
  - HMA treatment associated with <20% CR rate and median OS of 12-18 mo[1]
- Early suggestions of higher response rate with the addition of venetoclax to HMAs in higher-risk MDS[2,3]
- The current retrospective analysis compared clinical outcomes in patients with higher-risk MDS treated with first-line HMA, first-line HMA + venetoclax, or HMA with venetoclax given after HMA failure[4]

1. Zeidan. Br J Haematol. 2016;175:829. 2. Garcia. ASH 2020. Abstr 656.
3. Zeidan. ASH 2020. Abstr 3109. 4. Komrokji. ASH 2021. Abstr 536.

Slide credit: clinicaloptions.com

Venetoclax and HMA in Higher-Risk MDS: Study Design

- Retrospective analysis of clinical outcomes in patients with MDS who were classified as intermediate or higher risk by R-IPSS and received first-line treatment with HMA at Moffitt Cancer Center (N = 1193)
  - Single-agent HMA: n = 1158 (azacitidine n = 1027; decitabine n = 131)
  - **First-line HMA + venetoclax*: n = 35 (azacitidine n = 26; decitabine n = 9)**
  - Of patients who received single-agent HMA, n = 31 subsequently received HMA + venetoclax for R/R MDS without transformation to AML
- Response rate and median OS assessed (OS from diagnosis)
  - Median follow-up from diagnosis: 96 mo for first-line single-agent HMA, 15 mo for first-line HMA + venetoclax, 36 mo for HMA + venetoclax in R/R MDS

Komrokji. ASH 2021. Abstr 536.

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Venetoclax and HMA in Higher-Risk MDS: Baseline Characteristics by First-line Therapy

Characteristic	HMA Alone (n = 1127)	HMA + Ven (n = 35)	*P* Value
Mean age, yr	68.4	67.8	.76
Male, %	66	71	.5
White, %	90	97	.66
t-MDS, %	24	23	.86
WHO 2016 classification, %			.04
▪ MDS-SLD/MLD	18	4	
▪ MDS-RS	6	4	
▪ MDS-EB1	33	9	
▪ MDS-EB2	39	78	
R-IPSS, %			.22
▪ Intermediate	31	17	
▪ High	31	37	
▪ Very high	38	46	

Characteristic	HMA Alone (n = 1127)	HMA + Ven (n = 35)	*P* Value
Mean myeloblasts, %	8	13	<.005
Mean Hb, g/dL	9	9	1.0
Mean WBC x 10^9/L	4	10.6	<.005
Mean ANC x 10^9/L	1.8	4.1	<.005
Platelets x 10^9/L	96	100	.80
Somatic mutations, %*			
▪ *SF3B1*	5	0	.3
▪ *TET-2*	16	23	.3
▪ *IDH-1*	3	3	.7
▪ *IDH-2*	5	14	.056
▪ *ASXL-1*	21	46	.002
▪ *TP53*	27	34	.6
▪ *NRAS*	4	11	.07

Komrokji. ASH 2021. Abstr 536.

Slide credit: clinicaloptions.com

Venetoclax and HMA in Higher-Risk MDS: Efficacy of First-line Therapy

Best Response, %	HMA + Ven (n = 35)	HMA Alone (n = 1127)	*P* Value
ORR	77	40	<.005
▪ CR	34	13	
▪ mCR	37 (62 + HI)	11	
▪ PR	3	1	
▪ HI	3	15	
***ASXL-1* mut**	**(n = 16)**	**(n = 106)**	
ORR	87	32	<.005
▪ CR	44	8	
***TP53* mut**	**(n = 12)**	**(n = 137)**	
ORR	75	44	.038
▪ CR	25	17	.47

Outcome	HMA + Ven (n = 35)	HMA Alone (n = 1127)	*P* Value
Median OS, mo			
▪ From diagnosis (95% CI)	21 (11-32)	20 (19-22)	.86
▪ From start of treatment*	19.4	17.2	.88
AML transformation, %	23	37	.08
AHSCT cohort†	**(n = 13)**	**(n = 256)**	
Median OS, mo (95% CI)	NR	38 (27-50)	.20
2-yr OS, %	91	51	

*Median time from diagnosis to treatment was 1 mo in both arms.
†Patients who went on to AHCST.

Komrokji. ASH 2021. Abstr 536.

Slide credit: clinicaloptions.com

Venetoclax and HMA in Higher-Risk MDS: Conclusions

- In this retrospective analysis, treatment with first-line HMA + venetoclax was associated with significantly higher CR rates vs HMA alone in patients with higher-risk MDS, including those with *ASXL-1*–mutant MDS
  - Investigators suggested promising clinical activity of first-line HMA + venetoclax in patients who proceed to AHSCT
  - Caveats: small population, short follow-up of combination therapy group
  - No adverse event or dose adjustment data available
- Adding venetoclax to HMA after relapse may prolong OS
- Prospective, randomized trial needed to confirm findings

Komrokji. ASH 2021. Abstr 536.

CCO
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Venetoclax/Azacitidine in Treatment-Naive HR-MDS: Background

- The BCL-2 inhibitor venetoclax has shown synergy with hypomethylating agents such as azacitidine in preclinical studies and in clinical trials in patients with myeloid malignancies[1-4]
  - Mechanism of action: Azacitidine targets BCL-X_L and MCL-1, and venetoclax targets BCL-2; all 3 targets are expressed on HR-MDS blast cells
- Current study undertaken to evaluate combination of venetoclax and azacitidine in patients with treatment-naive HR-MDS[5]

1. Jin. Clin Cancer Res. 2020;26:3371. 2. Jilg. Exp Hematol Oncol. 2019;8:9.
3. DiNardo. Am J Hematol. 2018;93:4014. 4. DiNardo. NEJM. 2020;383:617. 5. Garcia. ASH 2021. Abstr 241.

CCO
Slide credit: clinicaloptions.com

Venetoclax/Azacitidine in Treatment-Naive HR-MDS (Phase Ib): Study Design

- Ongoing phase Ib clinical trial in higher-risk MDS, including assessment of molecular determinants of response

Patients with treatment-naive MDS with IPSS ≥1.5 (amended to include IPSS-revised int, high, very high, and planning to undergo ASCT); BM blasts <20%; ECOG PS 0-2
(n = 78)

Randomization Phase (28 Days Venetoclax)

- Azacitidine* + Venetoclax 400 mg D1-28 (n = 5)
- Azacitidine* + Venetoclax 800 mg D1-28 (n = 5)
- Azacitidine* (n = 2)

- No DLTs in cycle 1
- 2 deaths in cycle 2
- Protocol amended to assess 14-d venetoclax

Dose-Escalation Phase (14 Days Venetoclax)

- Azacitidine* + Venetoclax 100 mg D1-14 (n = 8)
- Azacitidine* + Venetoclax 200 mg D1-14 (n = 59)
- Azacitidine* + Venetoclax 400 mg D1-14 (n = 8)

Cohort 3: Safety Expansion After Preliminary Safety and Efficacy Analysis

Safety Expansion 1 (14 Days Venetoclax)
Azacitidine* + Venetoclax 400 mg D1-14 (n = 22)

Safety Expansion 2 (14 Days Venetoclax)
Azacitidine* + Venetoclax 400 mg D1-14 (n = 21)

Primary endpoints
- Safety, establish RP2D

Secondary endpoints
- ORR, OS

Garcia. ASH 2021. Abstr 241.

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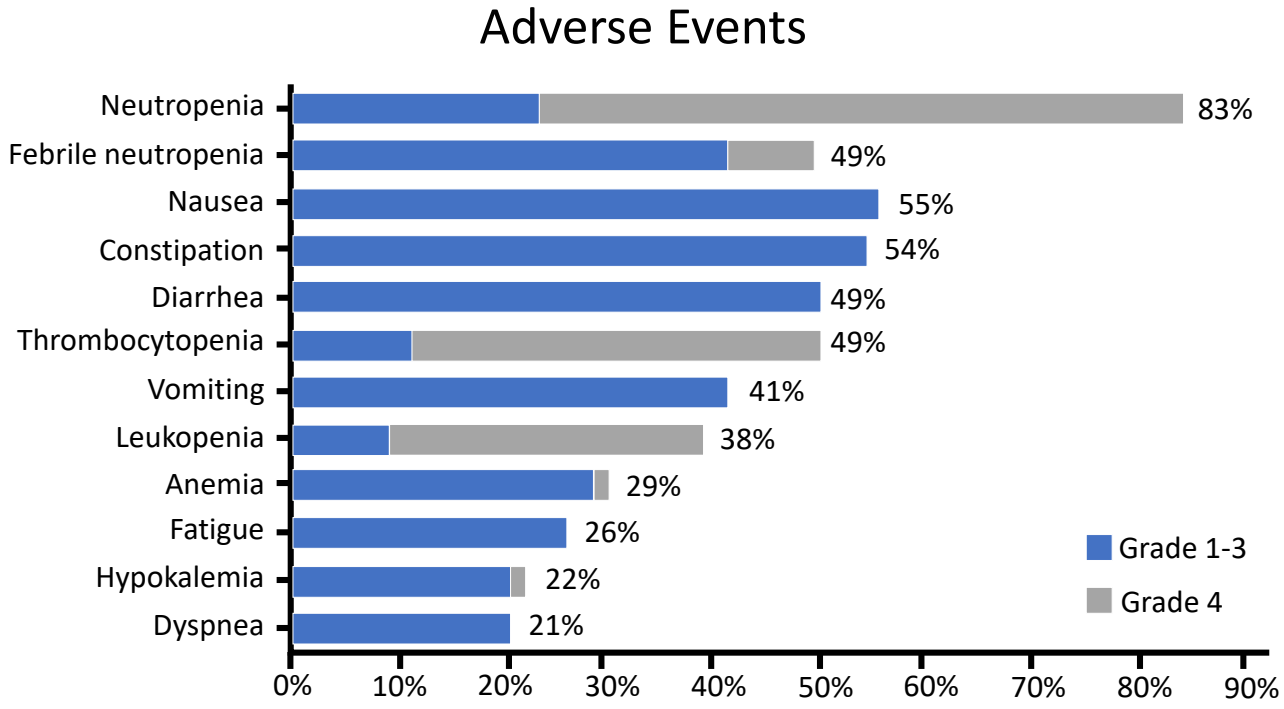
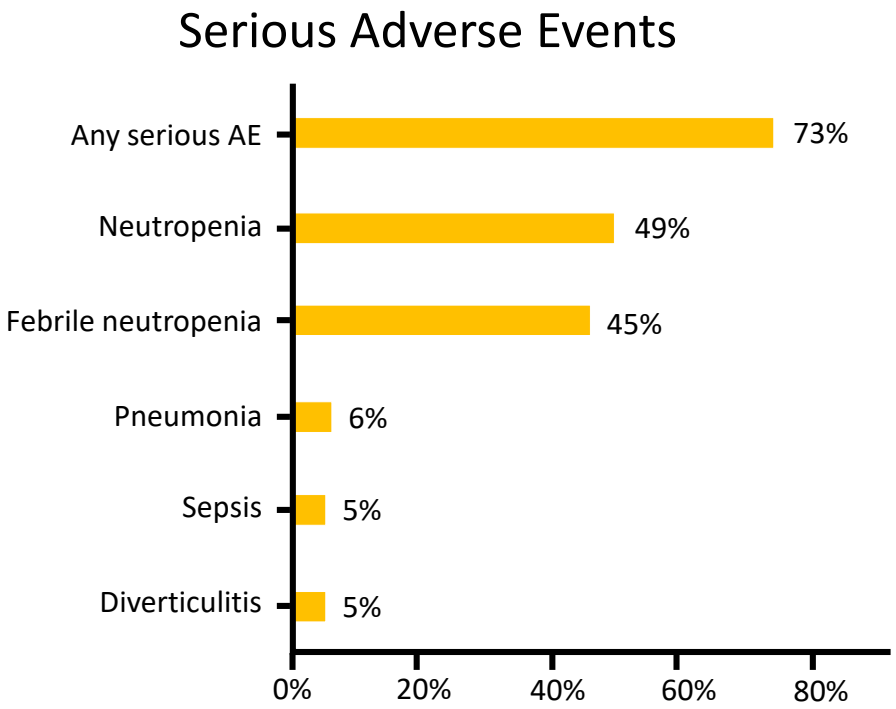
Venetoclax/Azacitidine in Treatment-Naive HR-MDS (Phase Ib): Safety

- Median cycles received: azacitidine, 4 (range: 1-27); venetoclax, 4 (range: 1-27)
- 30-day mortality after first dose: 1%; AEs leading to death: n = 7 (9%)

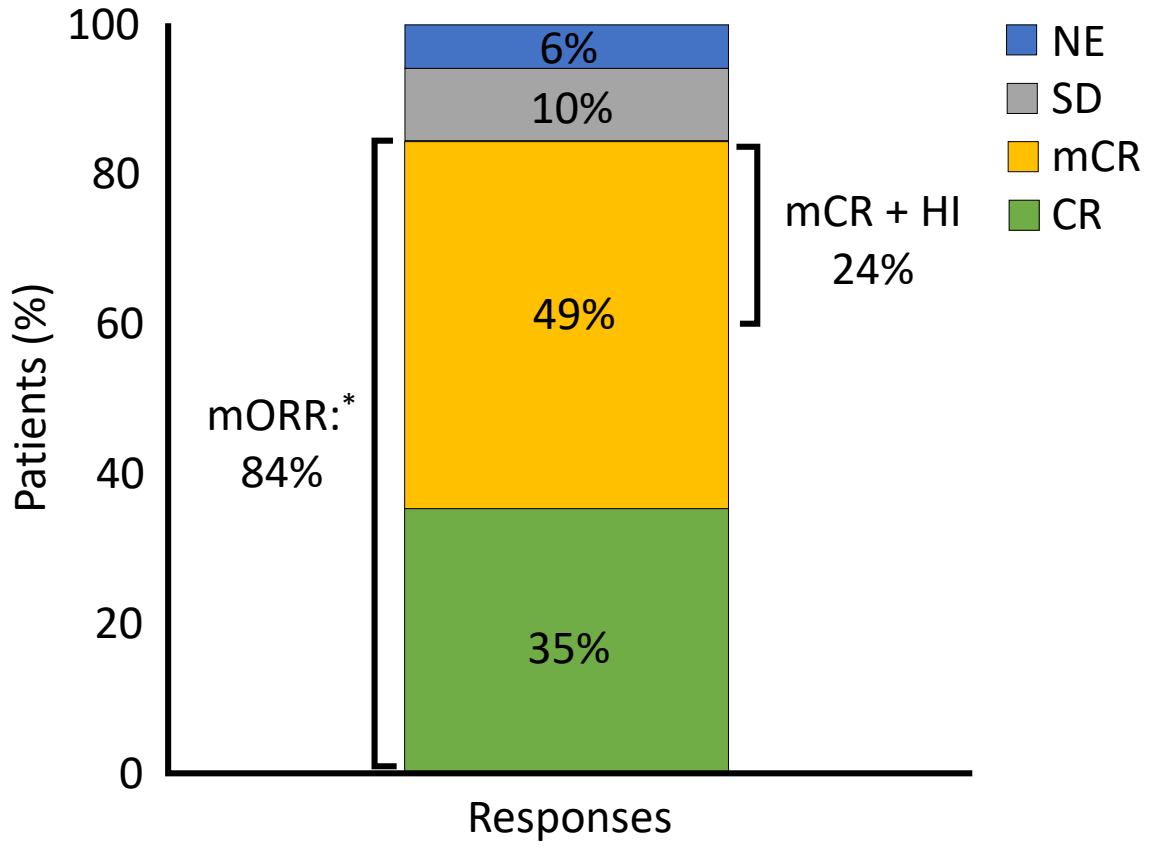




Garcia. ASH 2021. Abstr 241. Reproduced with permission.

Slide credit: clinicaloptions.com

Venetoclax/Azacitidine in Treatment-Naive HR-MDS (Phase Ib): Responses



- Median time to response: 0.9 mo (95% CI: 0.7-5.8)
- Median duration of response: 12.4 mo (95% CI: 9.9-NR)

*mORR: CR + mCR + PR.

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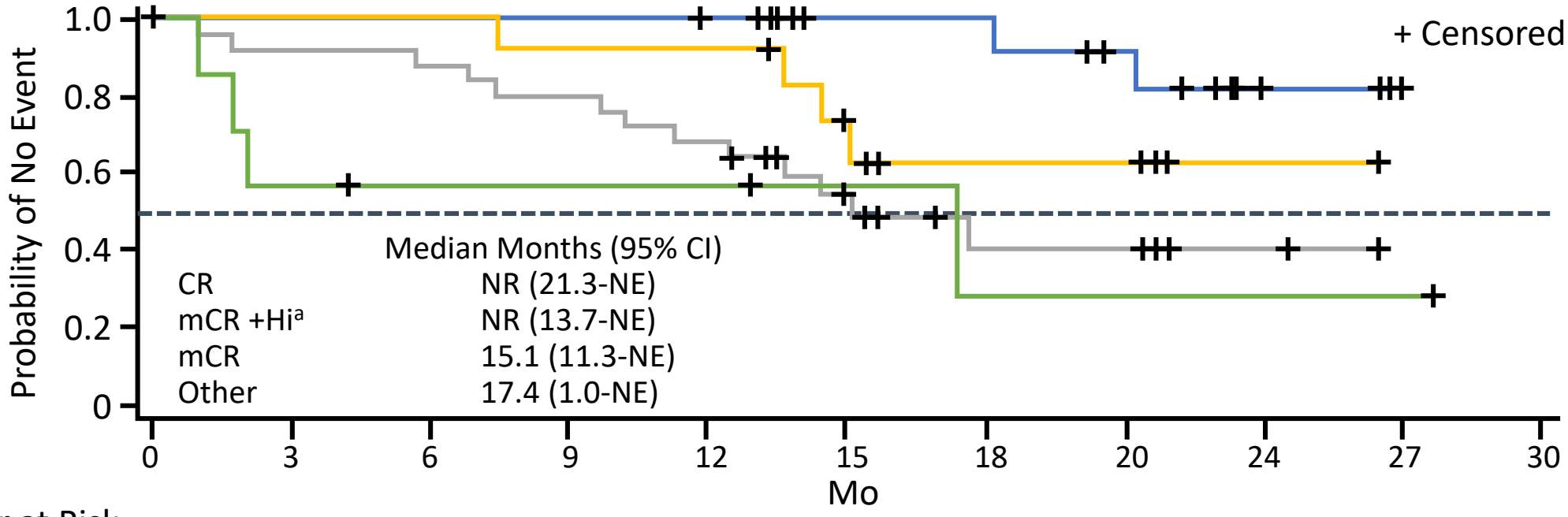
Slide credit: clinicaloptions.com

Venetoclax/Azacitidine in Treatment-Naive HR-MDS (Phase Ib): Overall Survival by Best Response at RP2D



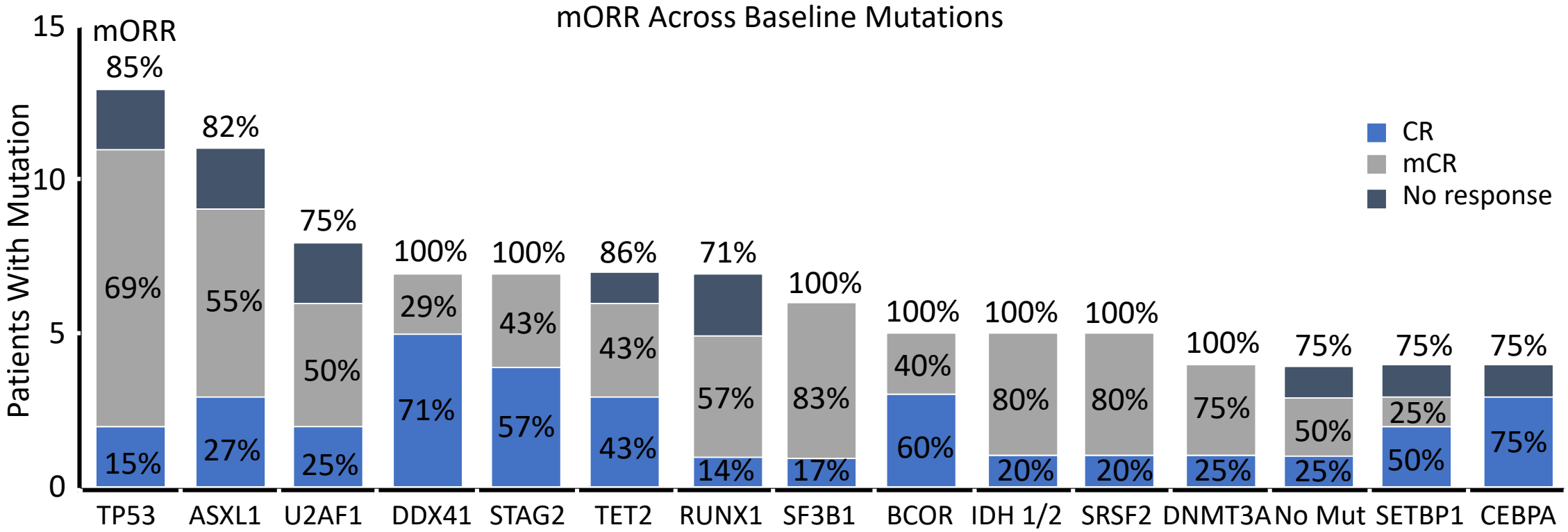
Number at Risk

CR	18	18	18	18	17	12	12	9	3	1	0
mCR +Hia	12	12	12	11	11	8	4	4	1	0	
mCR	25	23	22	20	17	11	5	5	2	0	
Other	8	4	3	3	3	2	1	1	1	1	0

Garcia. ASH 2021. Abstr 241.

Slide credit: clinicaloptions.com

Venetoclax/Azacitidine in Treatment-Naive HR-MDS (Phase Ib): mORR Across Baseline Mutations



Responses in patients with multi-hit/biallelic *TP53* mutations similar to those in patients with any *TP53* mutations

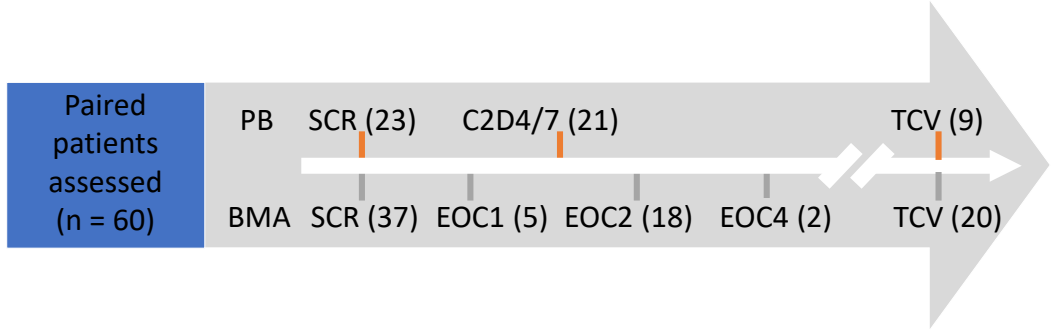
CR: 28.6%; mORR: 71.4%

Garcia. ASH 2021. Abstr 241. Reproduced with permission.

Slide credit: clinicaloptions.com

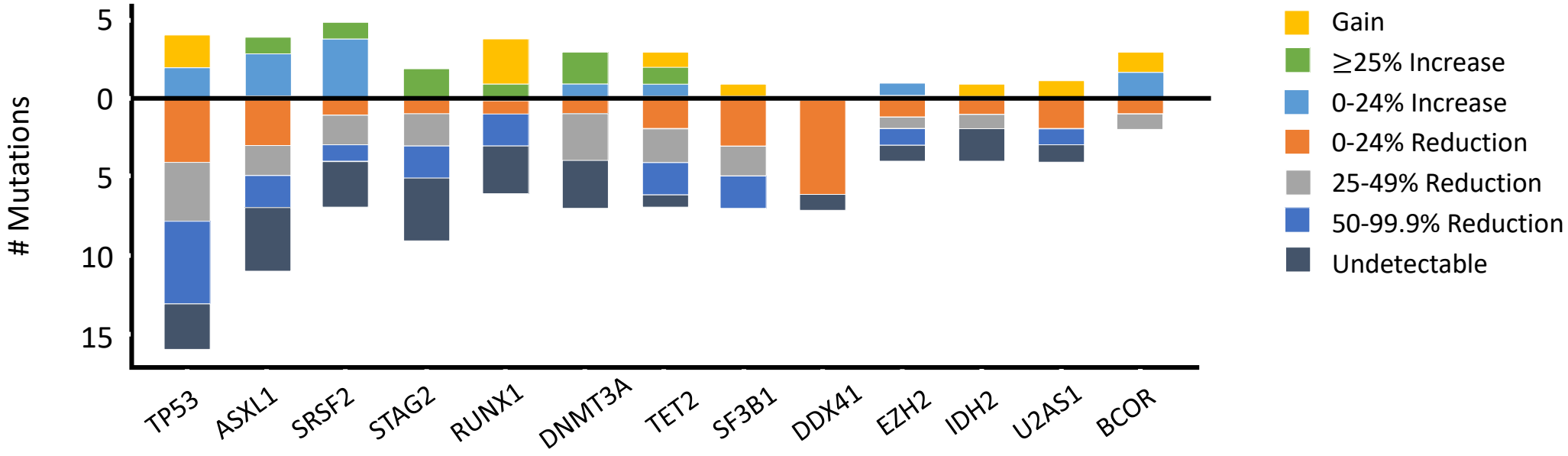
Venetoclax/Azacitidine in Treatment-Naive HR-MDS (Phase Ib): VAF Changes

Timing of Molecular Response Assessment



Differences in VAF for individual genes compared for similar specimen types: PB pre- vs PB post-therapy initiation or BMA pre- vs BMA post-therapy initiation

VAF Changes in Patients With ≥1 On-Treatment/TCV Sequenced Sample



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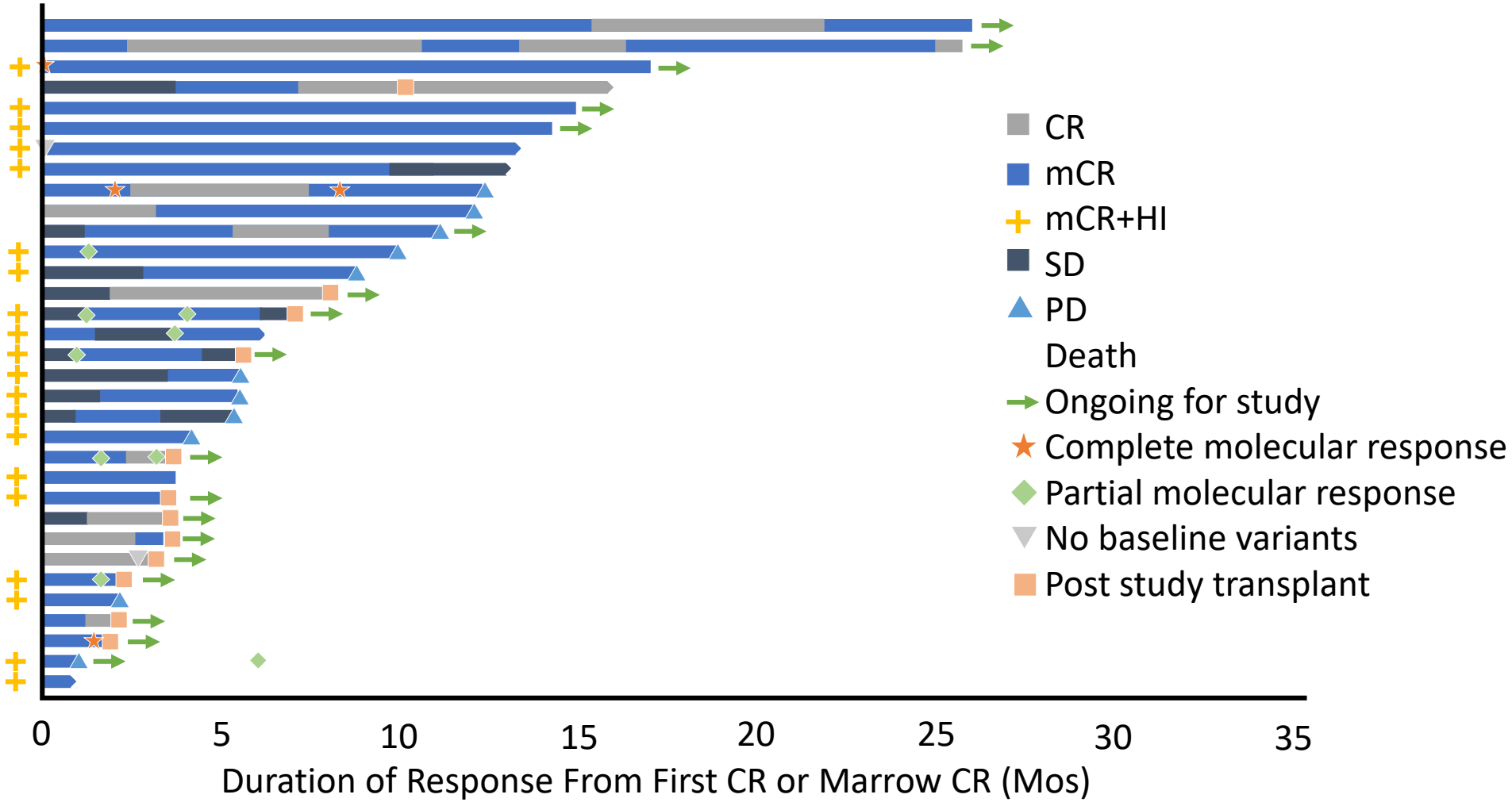
Slide credit: clinicaloptions.com

Venetoclax/Azacitidine in Treatment-Naive HR-MDS (Phase Ib): Molecular Responses



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Venetoclax/Azacitidine in Treatment-Naive HR-MDS (Phase Ib): Investigator Conclusions

- In this phase Ib trial, venetoclax/azacitidine had an acceptable safety profile in patients with treatment-naive higher-risk MDS
- RP2D venetoclax 400 mg on D1-14 + azacitidine 75 mg/m^2 induced rapid, durable responses and a high remission rate
- Clinical and molecular responses were observed across mutational profiles, including in patients with poor prognostic mutations

Garcia. ASH 2021. Abstr 241.

Slide credit: clinicaloptions.com

VERONA: Venetoclax + Azacitidine in Treatment-Naive Patients With Higher-Risk MDS

- Randomized phase III trial

Patients with newly diagnosed MDS, IPSS-R >3 (intermediate, higher, very high risk); HSCT eligible; no previous HMA or venetoclax therapy; ECOG PS ≤2 (planned N = 500)

Stratified by IPSS-R, HSCT eligible vs ineligible, geography

Venetoclax 400 mg QD (Days 1-14) +
+ Azacitidine 75 mg/m^2
(7 days within 9 calendar days/28-day cycle)

Placebo + Azacitidine 75 mg/m^2
(7 days within 9 calendar days/28-day cycle)

Until relapse, disease progression, unacceptable toxicity, or HSCT

- Primary endpoints: CR, OS
- Secondary endpoints: transfusion independence, ORR, modified ORR, QoL, PRO

Zeidan. ASCO 2021. Abstr TPS7054. NCT04401748.

Slide credit: clinicaloptions.com

Aza + ven in MDS summary

- Good activity and higher response rates
  - Similar to AML
- Toxicity and neutropenia still an issue
  - Similar to AML
- Not very durable responses… Wait for phase III results
- Good for high risk and transition to transplant (getting into CR)

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

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

Patients with IPSS Int-2 or high-risk MDS; no prior treatment; <70 yr of age (N = 31)

Optional allo-SCT

Induction*

CPX-351
Daunorubicin 44 mg/m^2
Cytarabine Days 1, 3, 5

*If <PR, second induction cycle with same daily dose; Days 1, 3 only.

Optional allo-SCT after 1-4 cycles

Consolidation

≤4 cycles in responders (same daily dose x 1 day)
Optional allo-SCT after

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

Peterlin. ASH 2021. Abstr 243. NCT04273802.

Slide credit: clinicaloptions.com

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

Hematologic Recovery, Days (Range)	Patients (n = 31)
Median days to platelets >20 x 10^9 g/L	16 (0-55)
Median days to platelets >50 x 10^9 g/L	28 (8-51)
Median days to ANC >1 x 10^9 g/L	26 (2-60)

AEs during induction

- 1 grade 3 mucositis
- 4 grade 1-2 alopecia

No deaths or ICU management required during induction

Peterlin. ASH 2021. Abstr 243.

Slide credit: clinicaloptions.com

CPX-351 as First-line Treatment in Higher-Risk MDS: Investigators' Conclusions

CPX-351 is an effective first-line treatment for patients with higher-risk MDS/CMML, particularly to achieve blast clearance, and as a **bridge to allogeneic SCT**

Safety

- Myelosuppression not longer than classical 7 + 3 intensive chemotherapy
- Mucous toxicity lower than 7 + 3, similar to that observed in AML

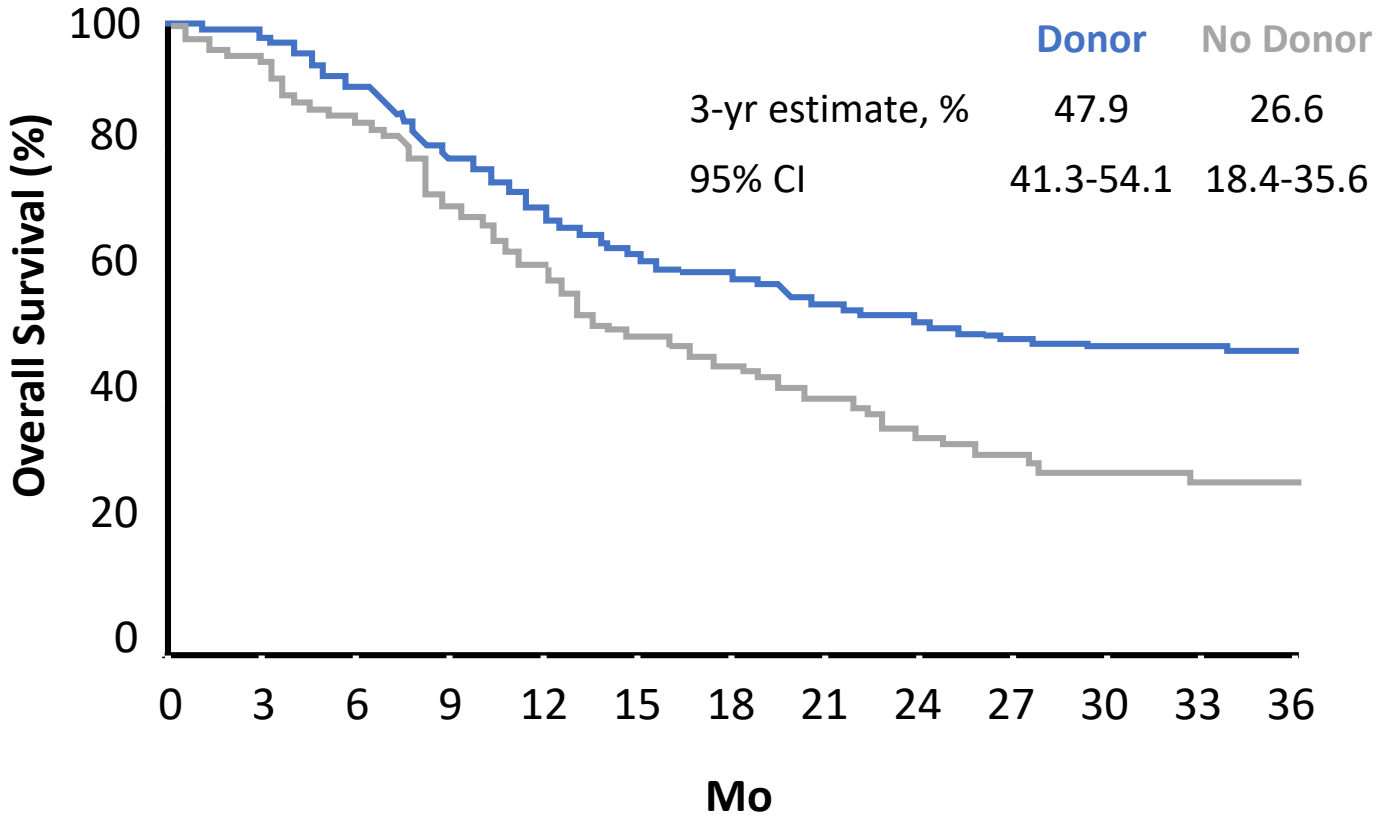
Normal karyotype was observed in most patients

Peterlin. ASH 2021. Abstr 243.

Slide credit: clinicaloptions.com

RIC + Allogeneic HSCT Improves Survival in Higher-Risk MDS With Matched Donor

- BMT CTN 1102 study: N = 384 patients aged 50-75 yr with intermediate-2 or high-risk MDS



Patients at Risk, n

Donor	260	253	233	201	176	155	129	117	102	86	76	72	27
No donor	124	116	103	84	71	56	49	40	30	22	15	14	7

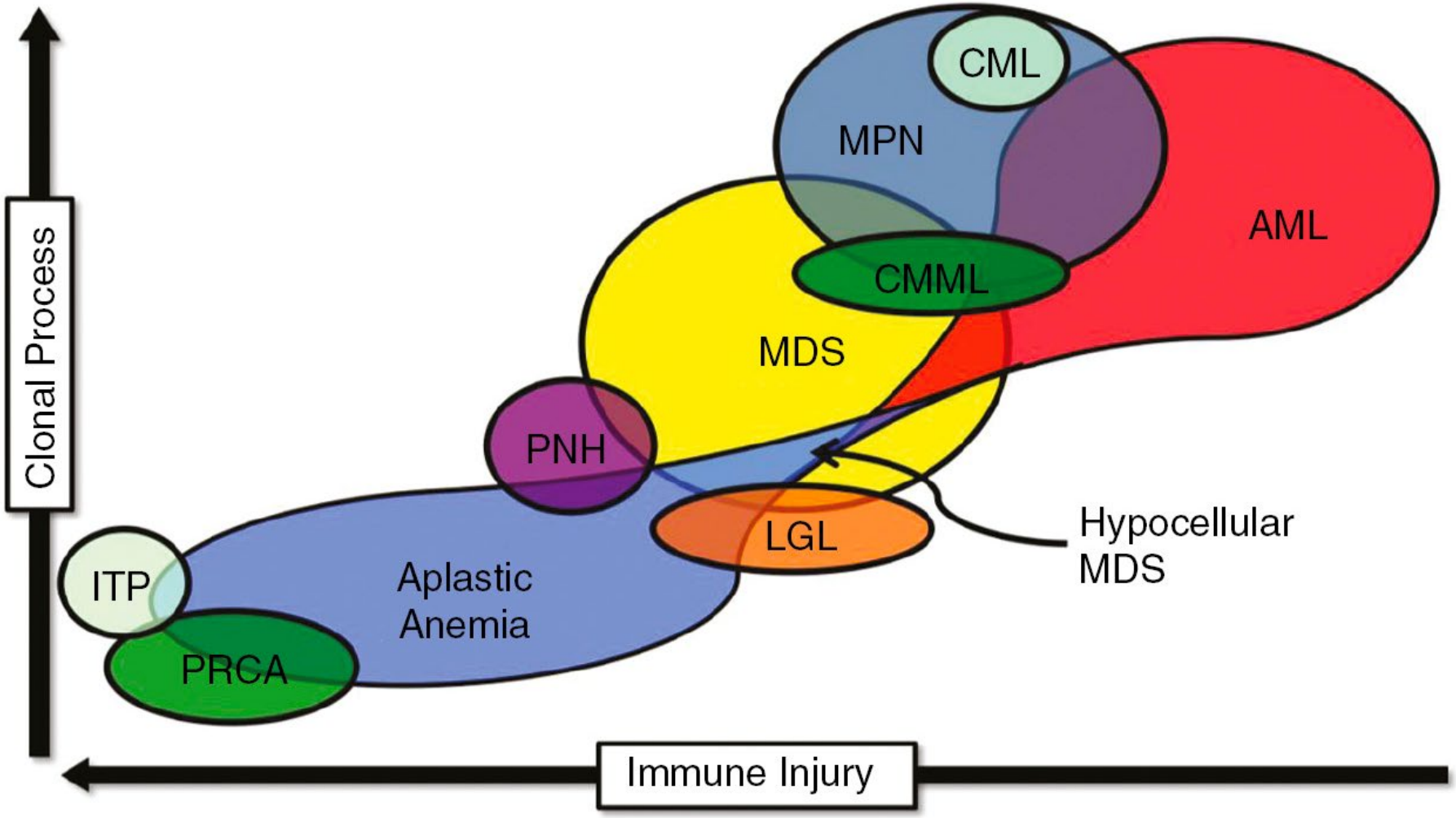
Nakamura. JCO. 2021;39:3328.

Slide credit: clinicaloptions.com

What’s new

Immunotherapies… are we there yet?

Myeloid neoplasms – genetic + immune overlap



Gerds, A., Tiu, R., & Sekeres, M. (2016). Myelodysplastic/myeloproliferative neoplasm overlap syndromes. In R. Mesa & C. Harrison (Eds.), *Managing Myeloproliferative Neoplasms: A Case-Based Approach* (pp. 120-128). Cambridge: Cambridge University Press. doi:10.1017/CBO9781316017852.015

Targets

- PD1/PDL1
- CD47
- TIM3

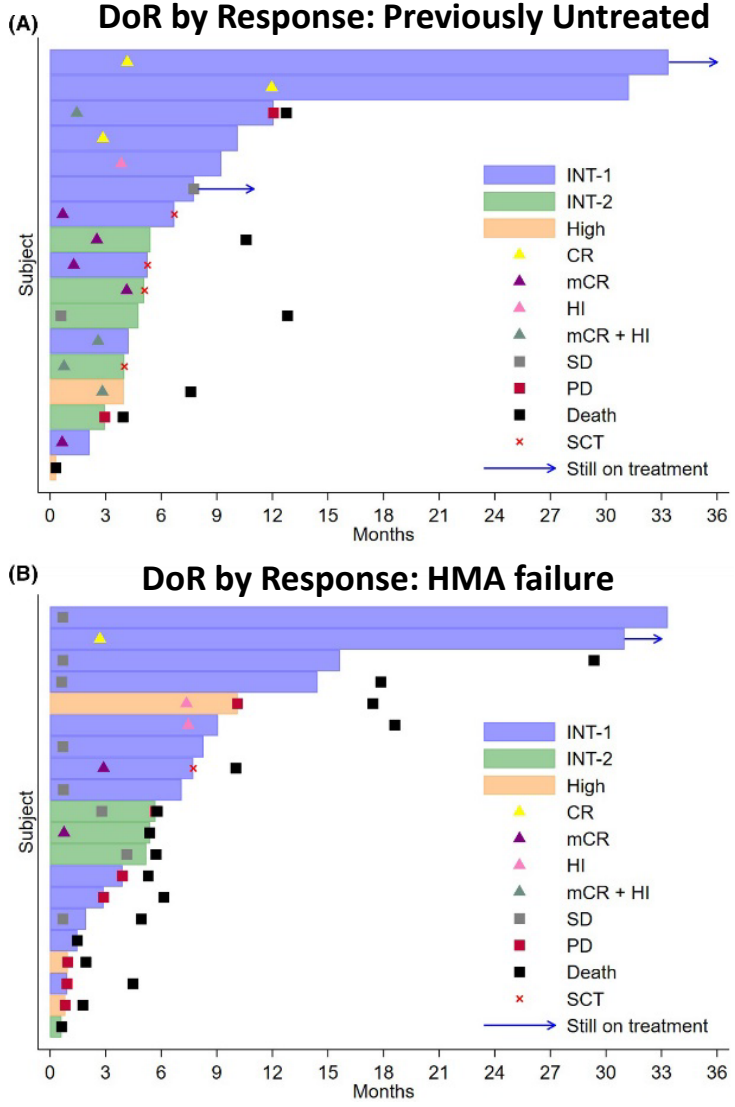
Phase II Trial: Azacitidine + Pembrolizumab in HR-MDS

- N = 37 patients with intermediate-1 or higher-risk MDS

Result	Previously Untreated (n = 17)	HMA Failure (n = 20)
ORR, %	76	25
CR, %	18	5
Median OS, mo	Not reached	5.8
Median follow-up, mo	12.8	5.8

Most common toxicities: pneumonia (32%), arthralgias (24%), and constipation (24%)

Immune-related AEs requiring corticosteroids: 43%



Chien. Br J Haematol. 2021;195:378.

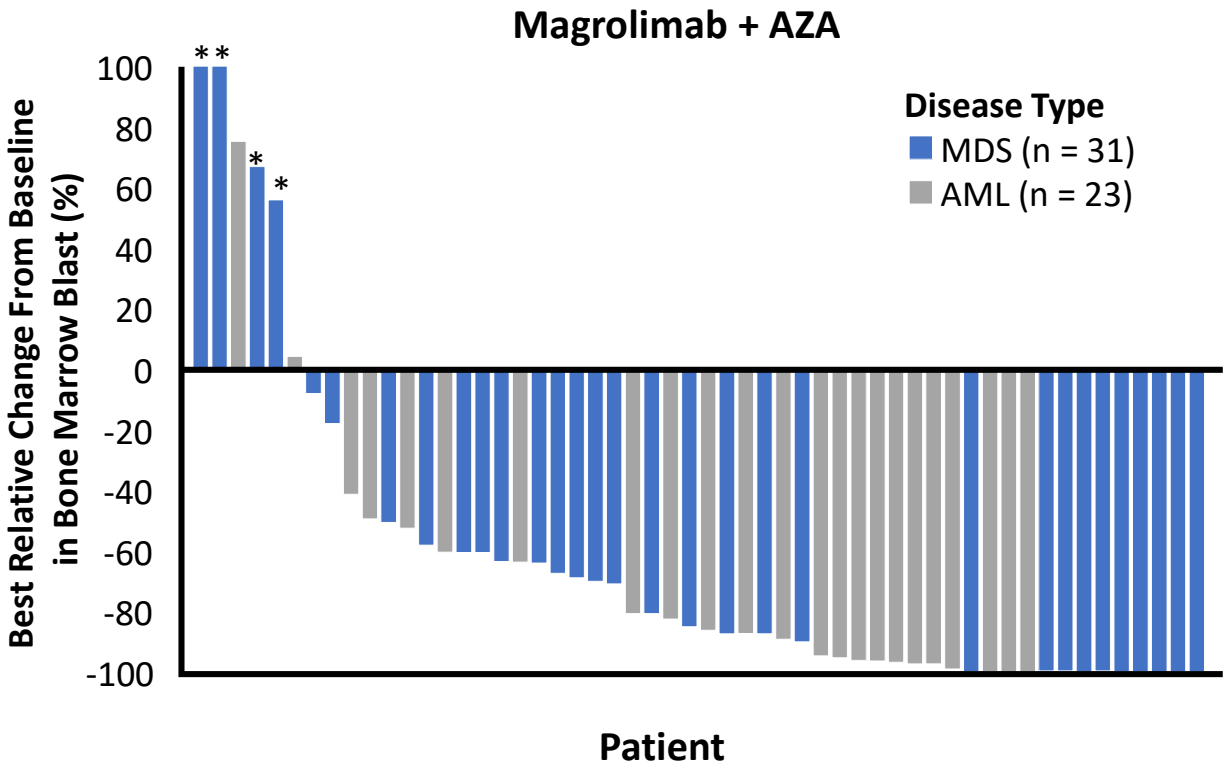
Slide credit: clinicaloptions.com

Anti-Leukemic Activity is Observed with Magrolimab + AZA in MDS and AML

Best Overall Response*	1L MDS N = 33	1L AML N = 25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	-	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	-
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

*Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with ≥1 post-treatment response assessment are shown. Patients not evaluable: 2 MDS patients (withdrawal of consent) and 3 AML (1 AE, 2 early withdrawal).

- Magrolimab + AZA ORR
  - MDS: 91% ORR (50% CR)
  - AML: 64% ORR (56% CR/CRi)
- Median time to response: 1.9 mo, more rapid than AZA alone
- Magrolimab + AZA response higher than AZA monotherapy



4 patients not shown due to missing values.
<5% blasts imputed as 2.5%.
*Baseline bone marrow blasts ≤5%.

Sallman. ASCO 2020. Abstr 7507.

Slide credit: clinicaloptions.com

ENHANCE: Magrolimab + Azacitidine vs Placebo + Azacitidine in Treatment Naive Higher-risk MDS

- Randomized, double-blind, phase III trial

Patients with untreated intermediate to very high risk MDS by IPSS-R, adequate PS
(Planned N = 520)

Magrolimab* +
+ Azacitidine 75 mg/m^2 days 1-7

Placebo +
Azacitidine 75 mg/m^2 days 1-7

Until disease progression, loss of benefit, unacceptable toxicity, or 5 yr

*Cycle 1: 1mg/kg priming dose on D1, D4; 15 mg/kg on D8; 30 mg/kg on D11, 15, 22.
Cycle 2: 30 mg/kg once weekly (D1, 8, 15, 22). Cycle ≥3: 30 mg/kg Q2W on D1, D15.

- Primary endpoints: CR, OS
- Secondary endpoints: Duration of CR, ORR, DoR, RBC TI, PFS, EFS, MRD negative RR, time to transformation to AML, safety, PK

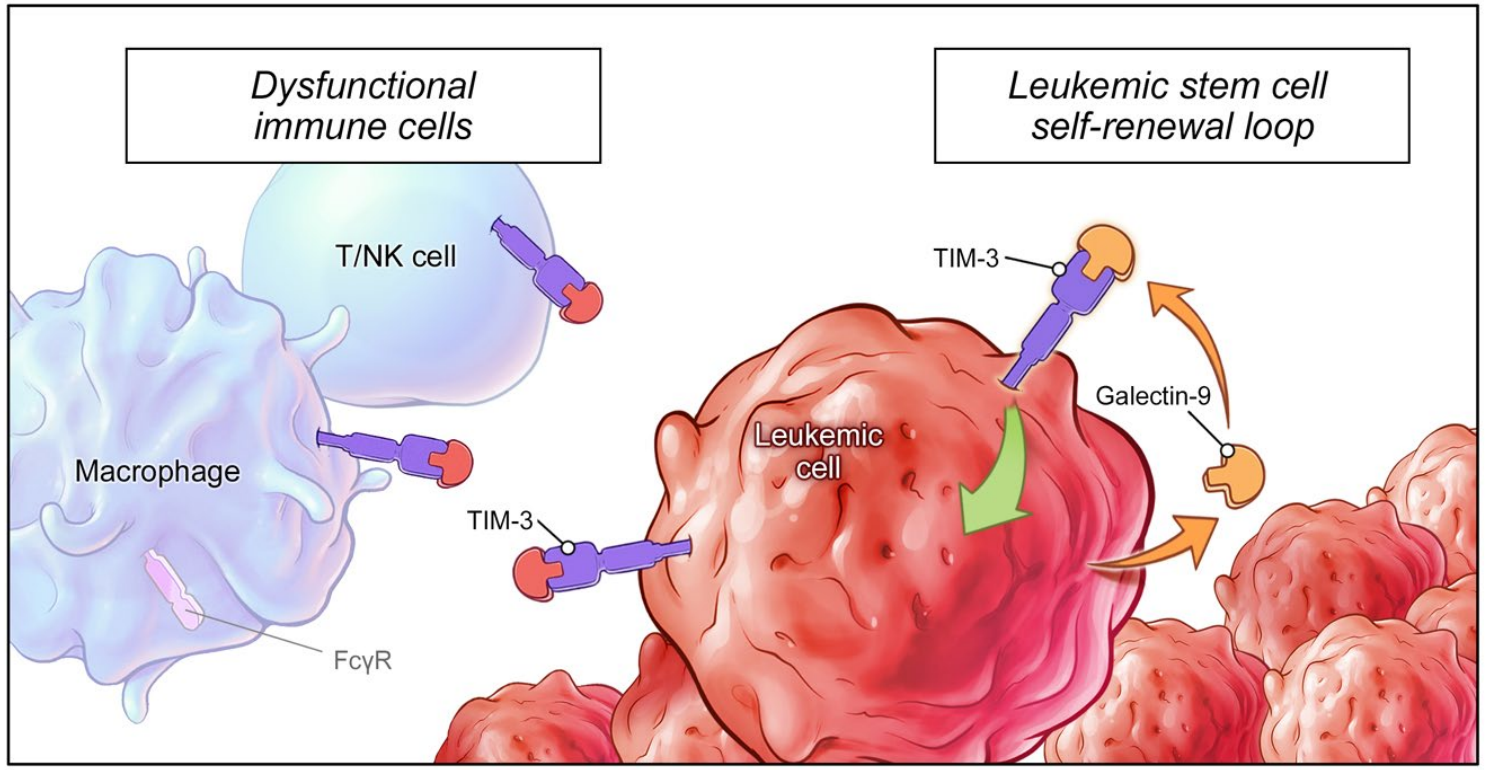
Open at OHSU but currently on hold – anticipate we will open again soon!!

Other Agents Targeting CD47 in Development

Agent	Type of Agent	Patient Population	Phase	Trial Identifier
Lemzoparlimab (TJC4)	Anti-CD47 monoclonal Ab	Newly diagnosed patients not candidates for induction therapy (+ Aza)	II	NCT04202003
Evorpacept (ALX148)	Fusion protein, CD47/SIRPα	Newly diagnosed patients not candidates for induction therapy (+ Aza/Ven)	I/II	NCT04755244 (ASPEN-05)
TTI-622	Fusion protein, SIRPα-IgG4 Fc	Cohort: Older patients with newly diagnosed *TP53* wild-type AML (+ Aza/Ven) Cohort: Newly diagnosed *TP53* mutant AML (+ Aza)	I	NCT03530683
TTI-621	Fusion protein, SIRPα-IgG1 Fc	R/R hematologic malignancies	I	NCT02663518
DSP107	Bifunctional protein, CD47x41BB	R/R AML ≤2 prior therapies	I	NCT04937166

Slide credit: clinicaloptions.com

TIM-3 is an immuno-myeloid regulator expressed on immune and leukemic cells

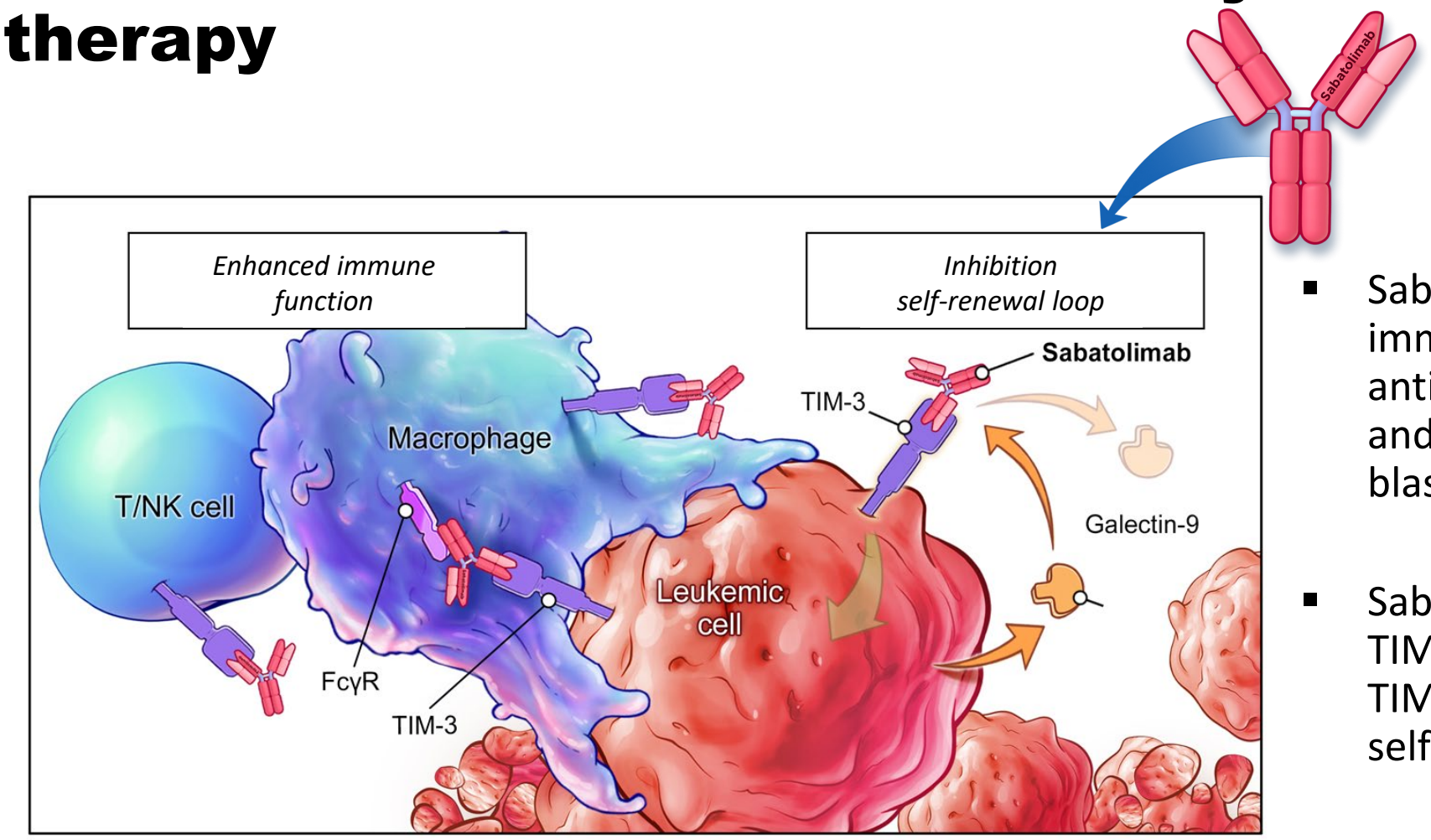


- TIM-3 plays a key role in regulating innate and adaptive immune responses[1,2]
- TIM-3 is aberrantly expressed on LSCs and blasts, but not on normal HSCs,[1-5] which makes it a promising target in treatment for MDS and AML[2,4,6]
- TIM-3/galectin-9 interaction forms an autocrine stimulatory loop, which promotes LSC self-renewal[2,7,8]

FcγR, Fc gamma receptor; HSC, hematopoietic stem cell; LSC, leukemic stem cell; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.

1. Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252-264; 2. Das M, et al. *Immunol Rev.* 2017;276(1):97-111; 3. Kikushige Y, Miyamoto T. *Int J Hematol.* 2013;98(6):627-633; 4. Kikushige Y, et al. *Cell Stem Cell.* 2010;7(6):708-717; 5. Ngiow SF. *Cancer Res.* 2011;71(10):3540-3551; 6. Sakuishi K, et al. *Trends Immunol.* 2011;32(8):345-349; 7. Sabatos-Peyton C. AACR 2016. Oral presentation; 8. Borate U, et al. ASH 2019. Oral presentation.

Sabatolimab targets TIM-3 on immune and leukemic cells: A novel immuno-myeloid therapy



- Sabatolimab binds TIM-3 on immune cells, which enhances antileukemic immune function and phagocytic killing of LSCs and blasts[1-4]
- Sabatolimab directly targets TIM-3 on LSCs, inhibiting TIM-3/galectin-9–driven self-renewal[1,2]

1. Acharya N, et al. *J Immunother Cancer*. 2020;8(1):e000911; 2. Sabatos-Peyton C, et al. SITC 2020. Abstract 439; 3. Borate U, et al. *HemaSphere*. 2020;4(suppl 1):Abstract S185; 4. Borate U, et al. EHA 2020. Oral presentation.

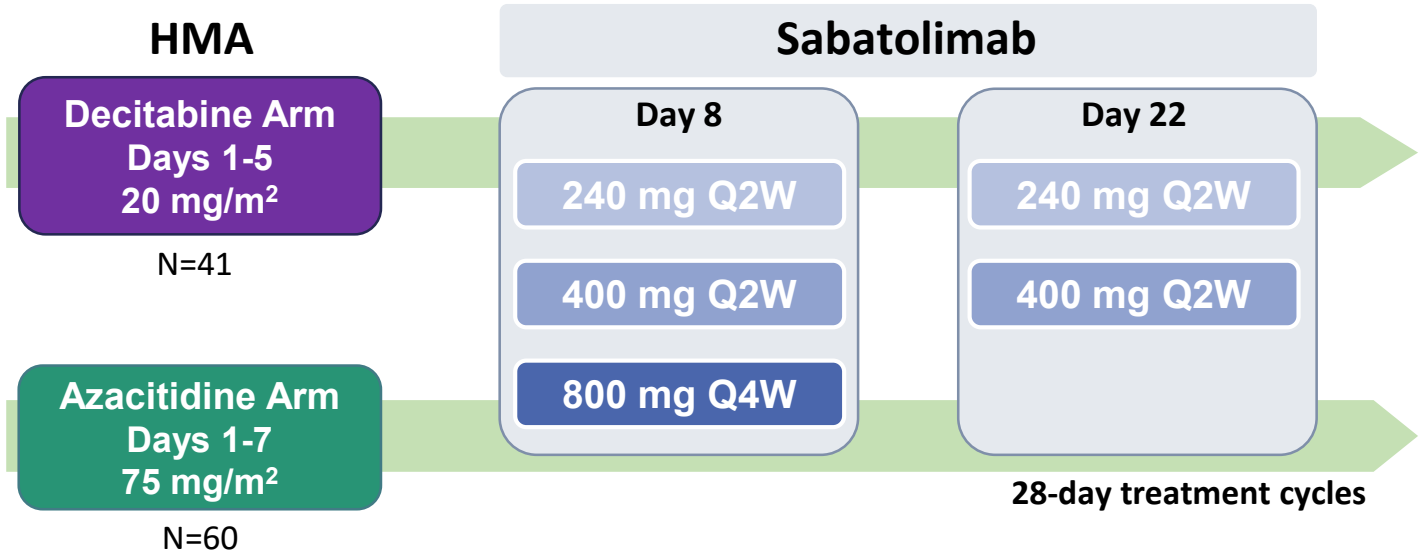
Trial design: Phase Ib study of sabatolimab + HMA in MDS and AML

vHR/HR-MDS: IPSS-R high- or very high-risk MDS

ND-AML: Unfit, newly diagnosed AML, ineligible for standard chemotherapy

Patients with prior HMA treatment excluded

ClinicalTrials.gov Identifier: **NCT03066648**[a]



8 countries

11 trial centers

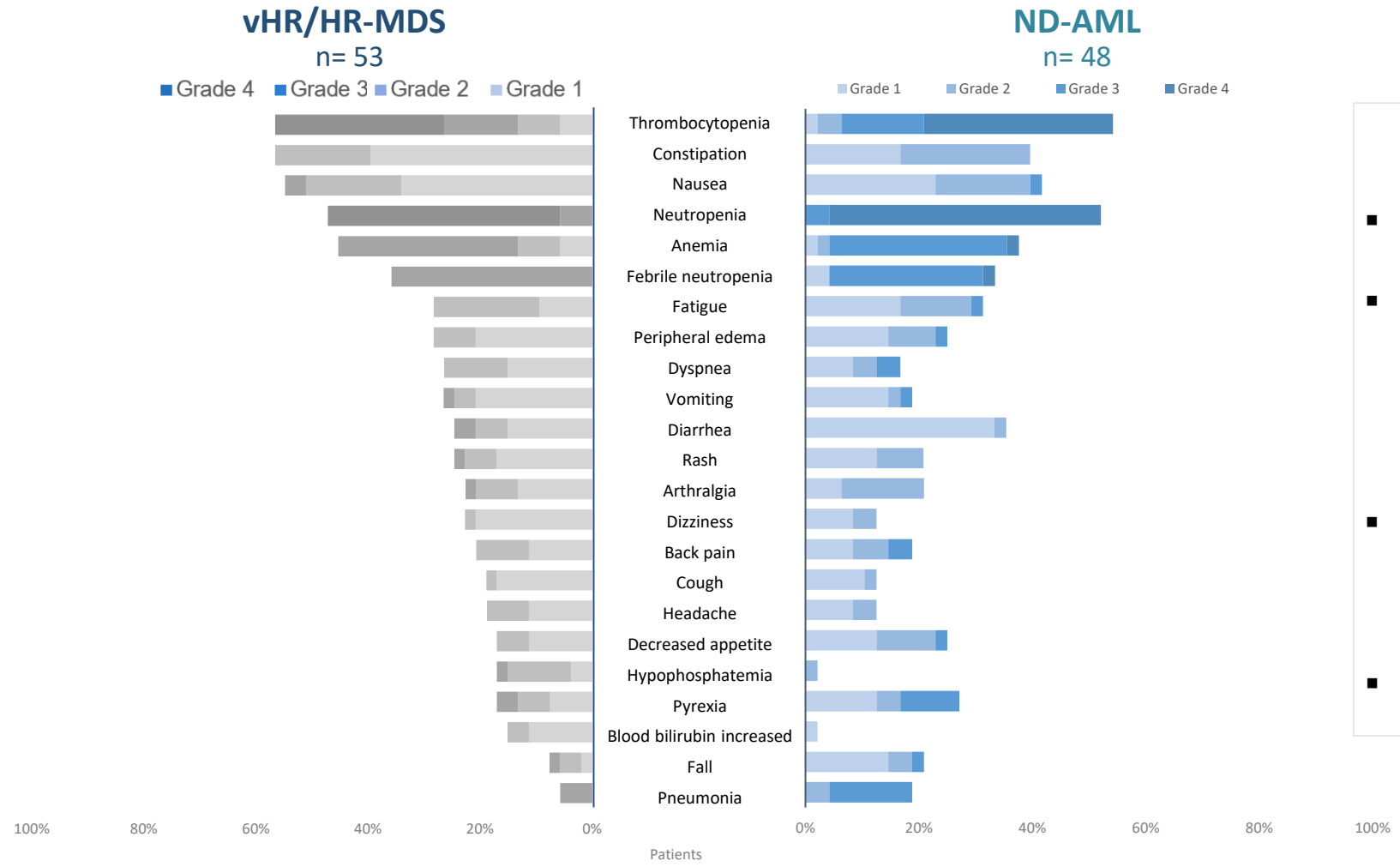
Primary Endpoints:
Maximum tolerated dose/recommended dose, safety, and tolerability

Secondary Endpoints:
Preliminary efficacy: Response rates and duration of response

[a]Multi-arm, open-label, Phase Ib dose-escalation and -expansion study of sabatolimab as a single agent or in combination with HMAs or spartalizumab.
AML, acute myeloid leukemia; HMA, hypomethylating agent; HR, high-risk; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; ND, newly diagnosed; Q2W, every 2 weeks; Q4W, every 4 weeks; vHR, very high-risk.

Sabatolimab + HMA was safe and well tolerated in patients with vHR/HR-MDS and ND-AML

Most commonly occurring AEs (≥15% in either population, regardless of relationship to treatment)



vHR/HR-MDS and ND-AML AEs

- Most common reported AEs were consistent with HMA alone
- Low rate of sabatolimab dose modification:
  - 1/101 (1%) patients had dose reduction
  - 38/101 (38%) patients had dose interruption[a] due to AE
  - No patient with vHR/HR-MDS and only 3 with ND-AML discontinued treatment due to an AE
- One patient with neutropenic colitis reported as suspected to be related to study treatment died of septic shock. No other treatment-related deaths were reported
- No DLTs in vHR/HR-MDS and only 1 in ND-AML

[a]Dose interruption: Cycle delay >7 days.

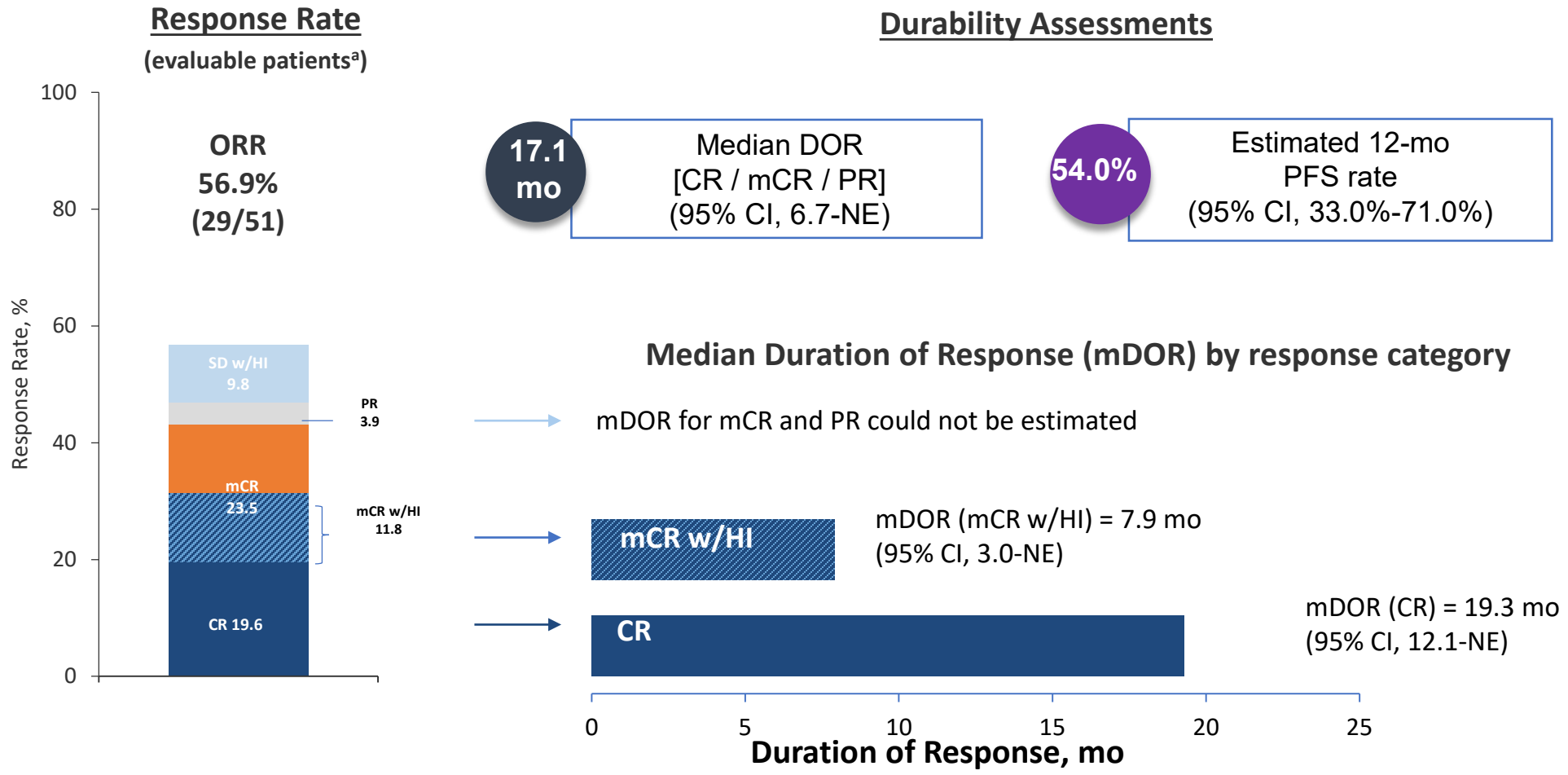
Few patients had clinically significant possible imAEs with sabatolimab + HMA

	vHR/HR-MDS n=53	ND-AML n=48	
	Gr 1/2	Gr 1/2	Gr 3
Patients with possible imAEs regardless of relationship to study treatment[a]	7 (13.2)	5 (10.4)	5 (10.4)
Peripheral neuropathy	2 (3.8)	1 (2.1)	1 (2.1)
Acute febrile neutrophilic dermatosis	1 (1.9)	0	0
Autoimmune hepatitis	1 (1.9)	0	0
Dermatitis	1 (1.9)	1 (2.1)	0
Pericarditis	1 (1.9)	0	0
Pneumonitis	1 (1.9)	0	0
Arthritis	0	3 (6.3)	0
Colitis	0	1 (2.1)	1 (2.1)
Cutaneous vasculitis	0	0	0
Encephalopathy	0	0	1 (2.1)
Hemophagocytic lymphohistiocytosis	0	0	1 (2.1)
Hepatitis	0	0	1 (2.1)
Hypothyroidism	0	0	1 (2.1)
Immune-mediated lung disease	0	0	1 (2.1)

- 7/53 (13%) patients with vHR/HR-MDS and 10/48 (21%) patients with ND-AML experienced ≥1 possible imAEs
- No grade ≥3 possible imAEs were observed in patients with vHR/HR-MDS; no grade 4/5 possible imAEs were observed in patients with AML
- No patient with vHR/HR-MDS and 1 patient with ND-AML discontinued treatment due to a possible imAE suspected to be related to sabatolimab
- No serious late-onset sabatolimab-related imAEs were identified[b]
- Of the 7 patients with vHR/HR-MDS who had an imAE, all achieved remission
- Among patients with ND-AML, the frequency of possible imAEs was similar regardless of remission status

[a]Based on maximum grade. Events retrieved based on pre-defined case retrieval strategy including MedDRA SMQ immune-mediated disorder terms.
[b]Events 150 days after last dose of sabatolimab

Sabatolimab + HMA demonstrates durable clinical responses in vHR/HR-MDS



[a]Evaluable patients, including patients with a valid baseline and at least 1 postbaseline bone marrow assessment or if they had disease progression or disease-related death prior to the first marrow assessment.

CR, complete remission; DOR, duration of response; HI, hematologic improvement; mCR, bone marrow CR; mDOR, median duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial remission; SD, stable disease.

Conclusions

- Sabatolimab + HMA is well tolerated in MDS/AML
  - The most commonly observed AEs similar to HMA alone
  - Very few patients had clinically significant treatment-related possible imAEs
- Sabatolimab + HMA demonstrated durable clinical benefits in patients with vHR/HR-MDS and ND-AML
  - vHR/HR-MDS, ORR: 56.9%; Median DOR: 17.1 months (95% CI, 6.7-NE)
  - ND-AML, ORR: 42.5%; Median DOR: 12.6 months (95% CI, 5.2-18.0)
- Durable responses seen in patients with mutations conferring adverse risk
- The STIMULUS clinical trial program is evaluating sabatolimab-based combination therapy in multiple Phase II and III studies in MDS and AML

Oral HMAs

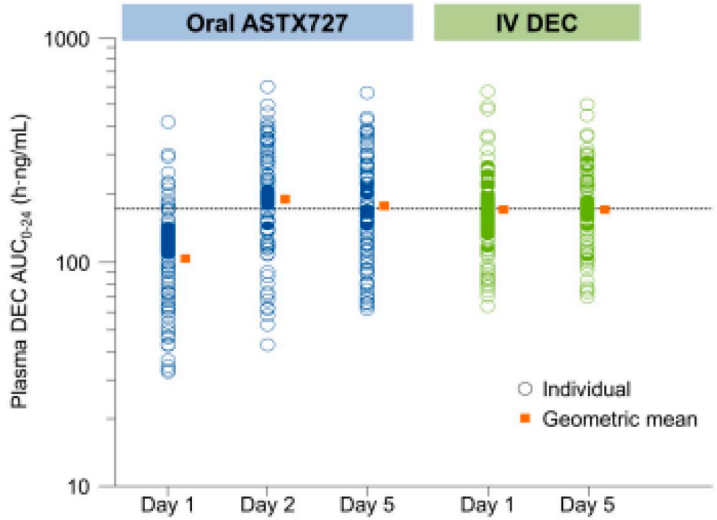
- Onureg approved for maintenance in AML
- Oral decitabine-cedurazedine approved for MDS
- Oral azacitidine-cedurazedine in clinical trials now

More tools for combinations, all oral regimens?

ASCERTAIN Primary Endpoint: 5-Day Decitabine AUC Equivalence

		IV DEC (n = 123)	Oral ASTX727 (n = 123)	Ratio of Geo LSM Oral/IV, % (90% CI)	Intrasubject (% CV)
Decitabine 5-day AUC0-24 (h ng/mL)		**Geo LSM**	**Geo LSM**		
Primary analysis	Paired*	864.9	855.7	98.9 (92.7, 105.6)	31.7

*Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.



- Primary endpoint met: oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93% to 106%
- All PK AUC analyses (sensitivity and secondary) confirmed findings from primary analysis

Garcia-Manero. ASH 2019. Abstr 846. Savona. ASH 2020. Abstr 1230. Savona. MDS 2021. Abstr P48.

Slide credit: clinicaloptions.com

ASCERTAIN: Response in MDS/CMML (IRC)

Response Measure, n (%)	Treated Patients (N = 133)	95% CI
CR	29 (22)	15-29.8
PR	0	
Marrow CR	43 (32.3)	24.5-41.0
▪ Marrow CR with hematologic improvement	22 (16.5)	10.7-24.0
Hematologic improvement	10 (7.5)	3.7-13.4
▪ HI: erythroid	2 (1.5)	0.2-5.3
▪ HI: neutrophils	1 (0.8)	0.0-4.1
▪ HI: platelet	7 (5.3)	2.1-10.5
Overall response (CR + PR + marrow CR + HI)	82 (61.7)	52.8-69.9
• PD	6 (4.5)	1.7-9.6
• No response	28 (21.1)	14.5-29.0
• NE	17 (12.8)	7.6-19.7

*Patients becoming transfusion independent (n)/patients transfusion dependent at baseline.

- Median duration of CR was 14.0 mo, and median duration of best response was 12.7 mo
- 26% of patients proceeded to hematopoietic cell transplantation

Garcia-Manero. ASH 2019. Abstr 846. Savona. ASH 2020. Abstr 1230. Savona. MDS 2021. Abstr P48.

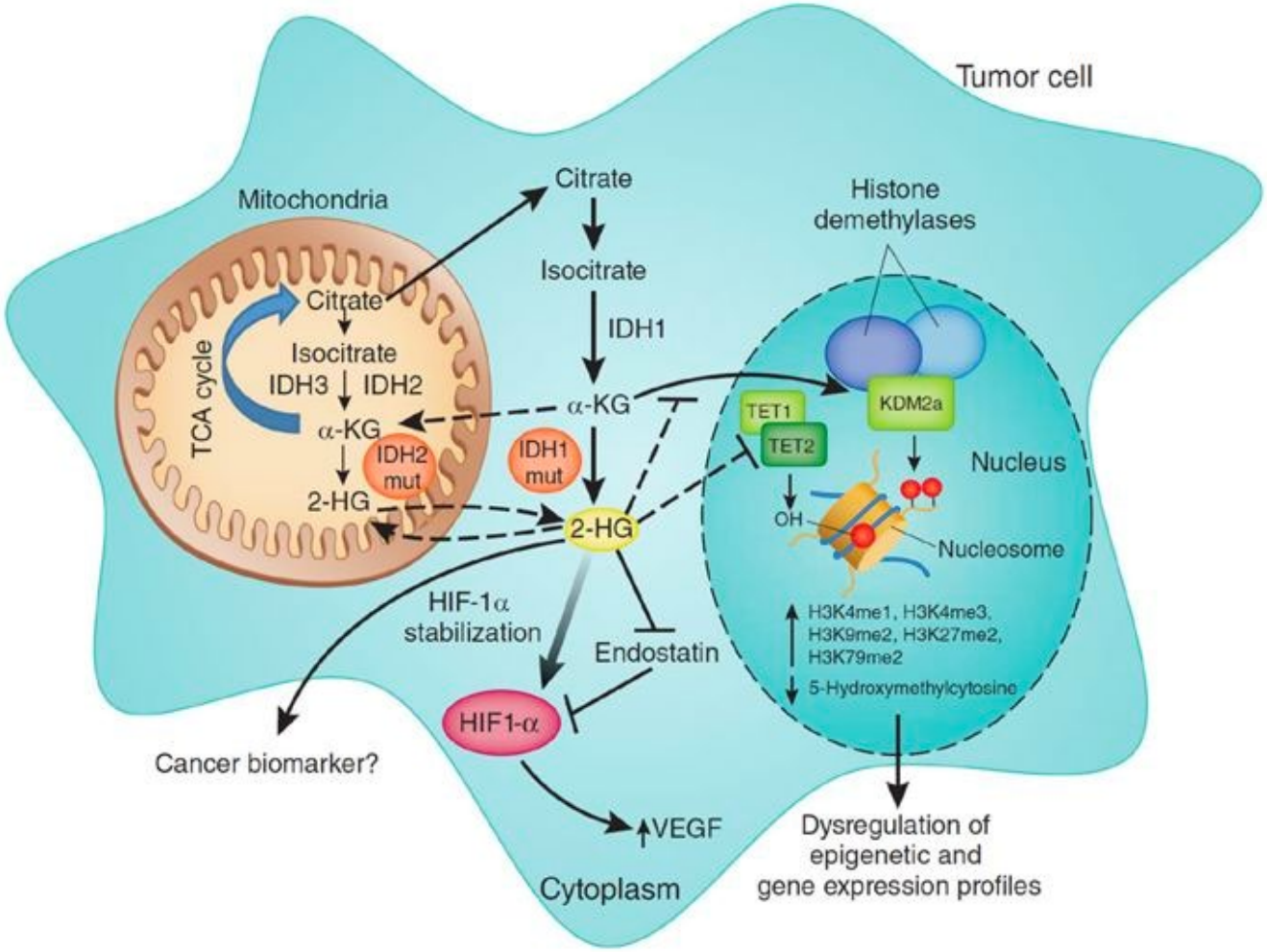
Slide credit: clinicaloptions.com

What’s new

Targeted therapies

IDH1/2 inhibitors in myeloid malignancies

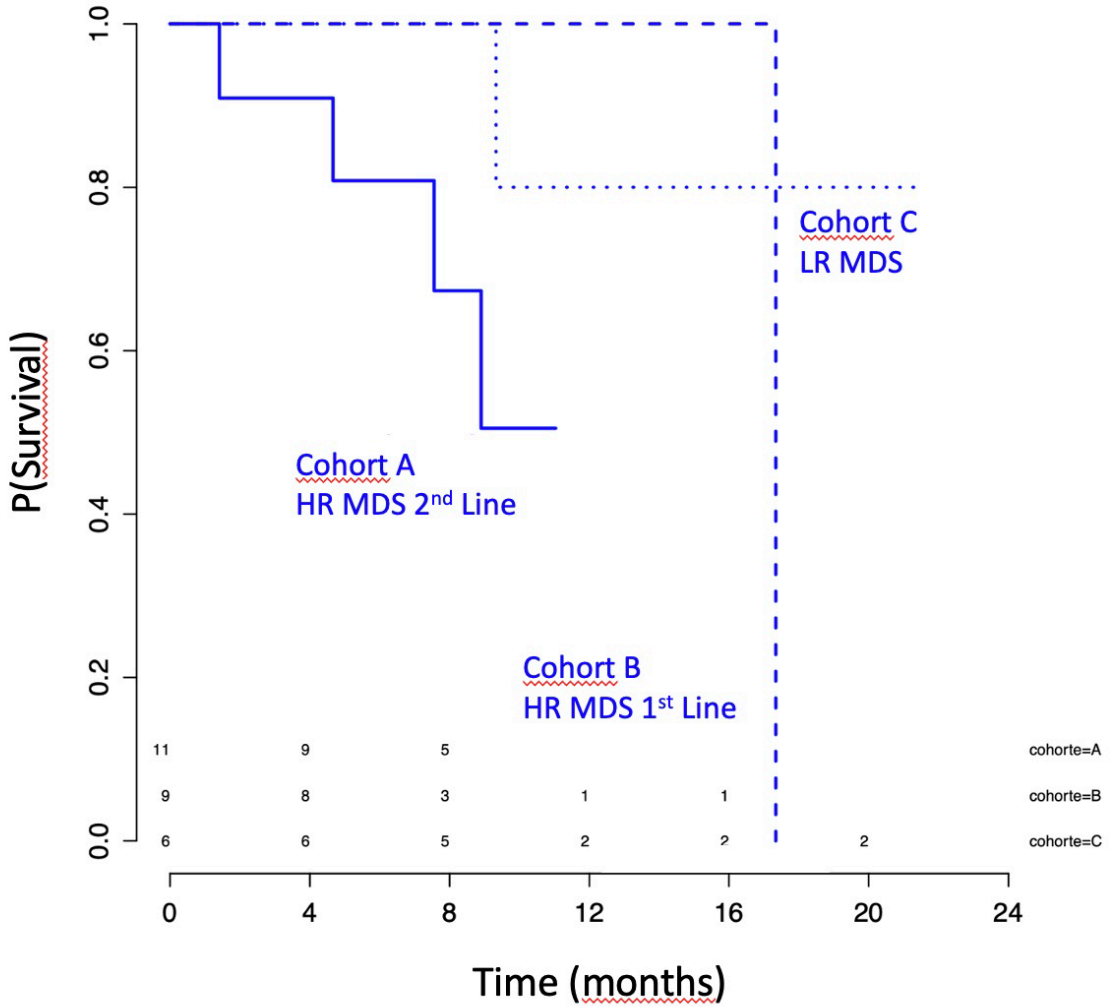
- IDH mutations cause production of 2-HG instead of α-KG
- 2-HG inhibits TET2 and methylation of DNA
- This blocks normal maturation of white blood cells
- Drugs developed to block the mutated IDH1 or IDH2 proteins



Prensner JR and Chinnaiyan AM
Nature Medicine 2011

Promising data with IDH inhibitors in MDS

- Enasidenib for IDH2m in MDS
  - 3 cohorts
    - A – failed HMA
    - B – High Risk MDS 1st line therapy
    - C – Low risk
  - Tolerable safety profile
  - N=26 patients
  - ORR (42 %) 11 patients
    - 6 CR (55%), 2 PR (18%), 2 mCR with HI (18%)
  - Encouraging results
  - Study ongoing



Promising data with IDH inhibitors in MDS

- Ivosidenib for IDH1m in MDS
  - 3 cohorts
    - A – failed HMA
    - B – High Risk MDS 1st line therapy
    - C – Low risk
  - Tolerable safety profile
  - N=32 patients
  - ORR 69% (18 patients)
    - CR (46%) 12 patients, 1 PR and 5 HI
  - Encouraging results
  - Study ongoing

Trials for MDS at OHSU

Low risk

- ASTEX-03 – oral decitabine for low risk AML

Immunotherapy

- Aza + magrolimab phase III (hope to re-open soon)
- anti-TIM3 antibody sabatolimab – opening soon

Targeted agents

- IDH1 inhibitor for R/R MDS

Thank you!

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