Can we do better than HMA in HR-MDS?

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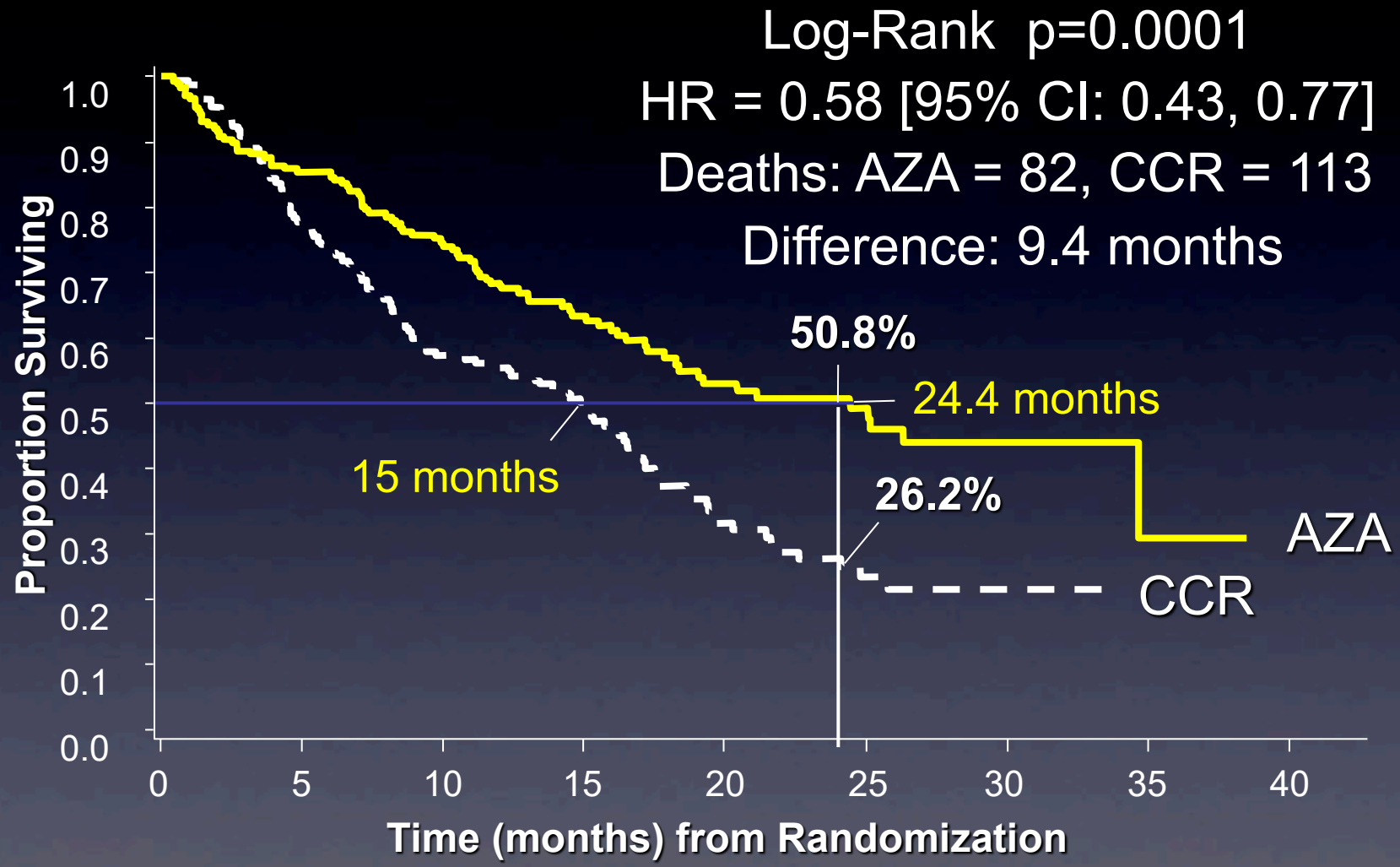
ASH 2023

Agenda

- The standard to beat: single agent azacitidine
- Definition of HR-MDS
- Oral HMAs: decitabine/cedazuridine
- Update on combinations
- Targeted approaches
- AML-like therapy
- Role of SCT and the concept of total therapy
- Conclusions

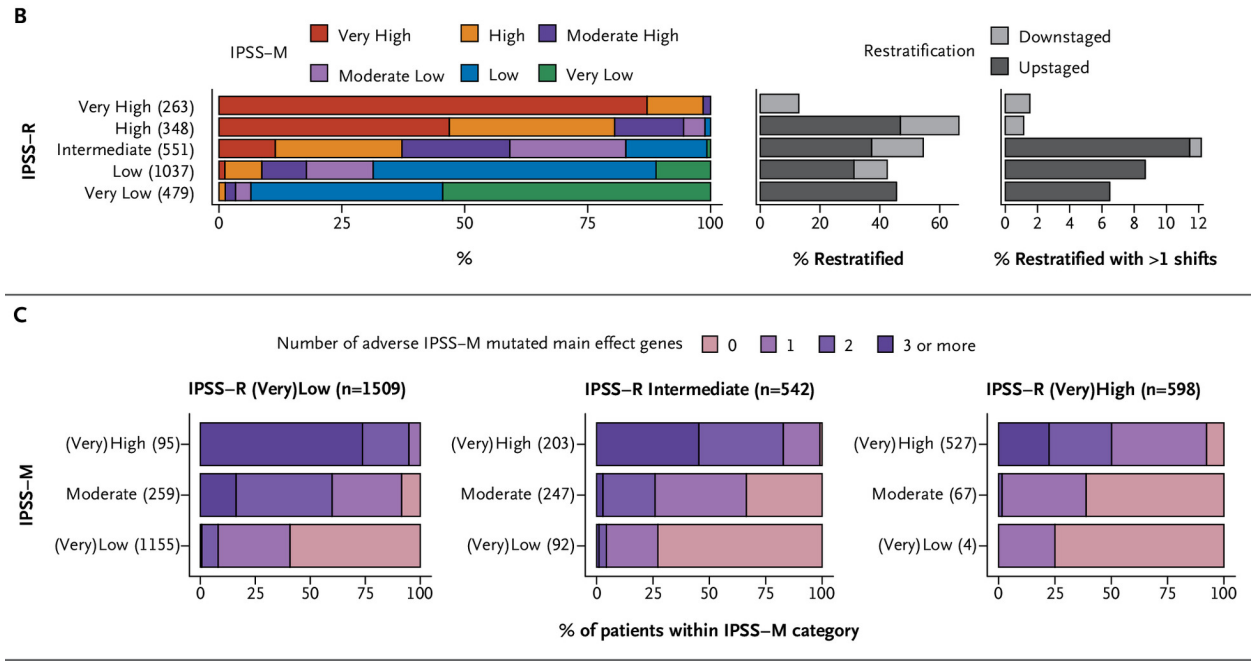
Azacitidine in HR-MDS



Fenaux et al. *Lancet Oncology* 2010

Definition of HR-MDS

- **IPSS: int-2 and high-risk disease**
- **IPSS-R: intermediate, high and very high risk**
- **IPSS-M: moderate high, high and very high risk**



Greenberg *Blood* 1997; Greenberg *Blood* 2012, Benton *AJH* 2018, Bernard *Nature Med* 2020, Montalban-Bravo *Oncotarget* 2018, Bernard *NEJM Evid* 2022

Oral HMAs in MDS

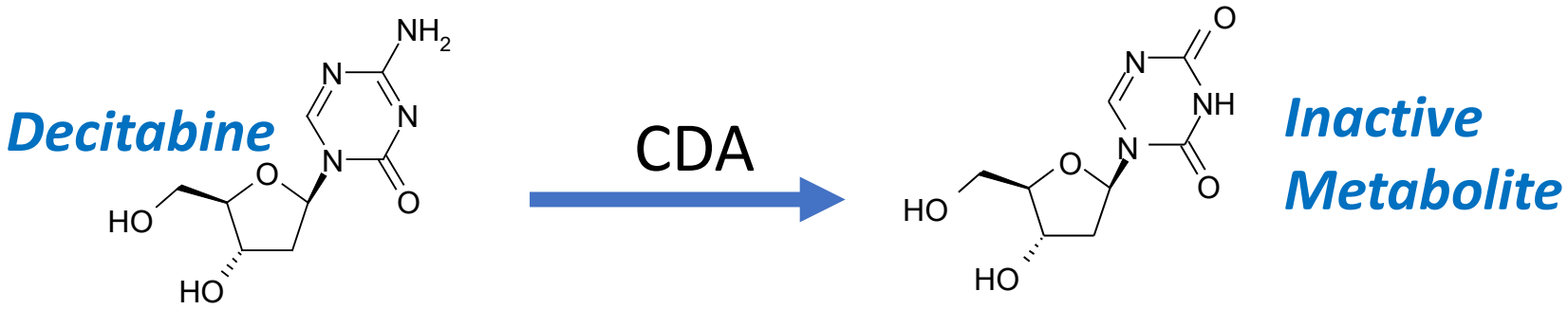
Two approaches to oral HMA development

- **Combined with cytidine deaminase inhibitor**
  - **Cedazuridine (ASTX727, ASTX030)**
  - **Tetrahydrouridine**
- **Single agent uncombined (CC-486)**
- **Significant differences in PK profile**

Garcia-Manero *Blood* 2020; Molokie *Plos Med* 2017; Garcia-Manero *JCO* 2011; Garcia-Manero *Lancet Hematology* in press

Oral decitabine/cedazuridine

- Intravenous (IV) Decitabine(DAC) is an approved therapy for MDS
- Oral bioavailability of DAC is low due to degradation in the gut by cytidine deaminase (CDA)



- MDS treatment requires continued treatment for long periods.
- An oral decitabine would provide significant benefit
- Development of a potent safe CDA inhibitor should enable decitabine oral bioavailability

Garcia-Manero ASH 2016; Savona *Lancet Hematology*, 2019

ASCERTAIN Primary Endpoint (5-day Decitabine AUC Equivalence)

Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
		N	Geo. LSM	N	Geo. LSM		
Primary Analysis	**Paired[1]**	**123**	**864.9**	**123**	**855.7**	**98.9 (92.7, 105.6)**	**31.7**

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

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All Sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Garcia-Manero ASH 2019 and *Lancet Hematology* in press

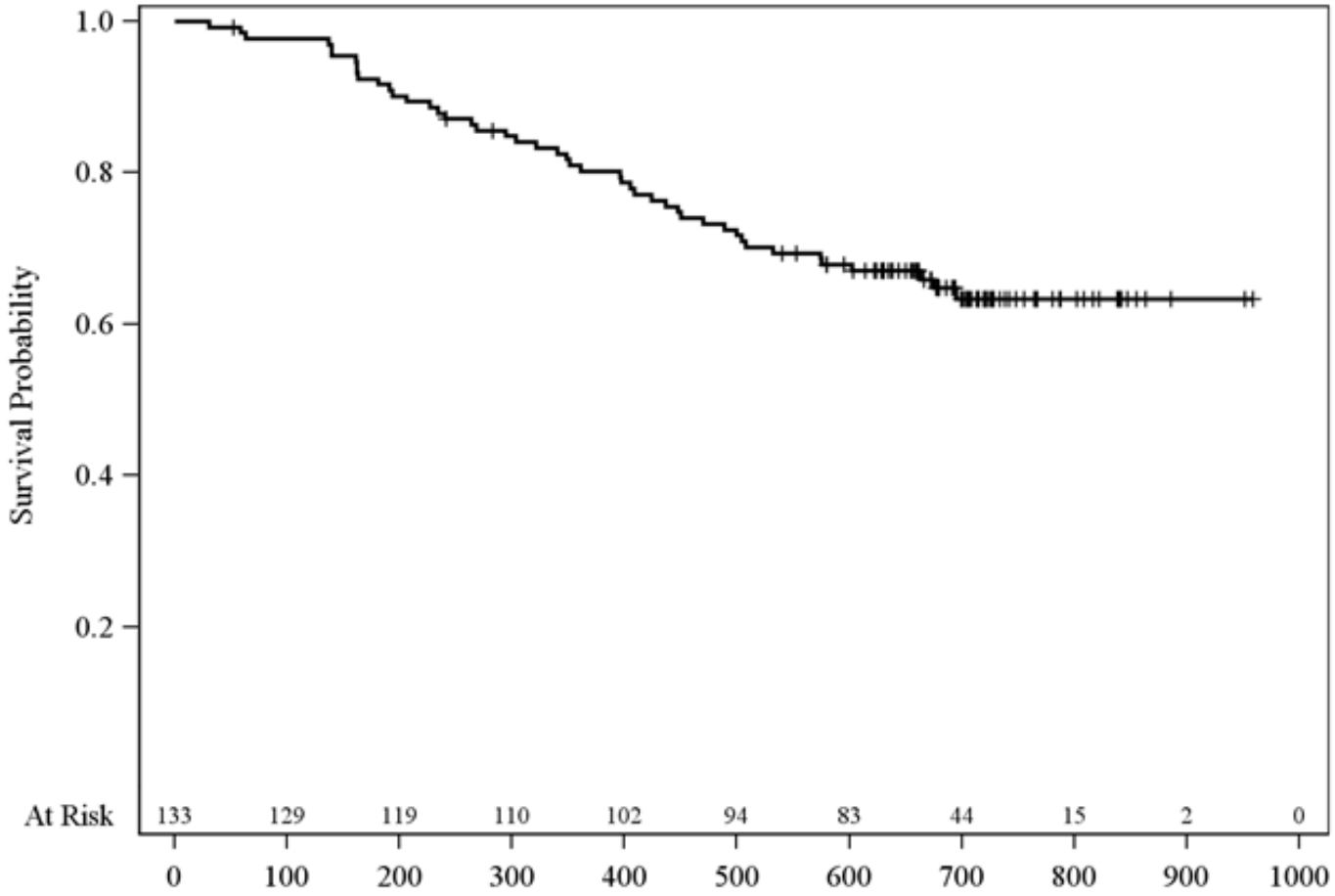
Oral decitabine/cedazuridine Efficacy Response

Response category	Treated Patients (N=133), n (%)	95% CI
Complete response (CR)	29 (22)	(15.1,29.8)
Partial response (PR)	0	
Marrow CR (mCR)	43 (32.3%)	(24.5,41.0)
mCR with hematologic improvement	22 (16.5%)	(10.7,24.0)
Hematologic improvement (HI)	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 + mCR + HI)	82 (61.7)	(52.8,69.9)
Progressive Disease	6 (4.5%)	(1.7,9.6)
No Response	28 (21.1%)	(14.5, 29.0)
Non-evaluable	17 (12.8%)	(7.6, 19.7)

- Median CR duration was 14.0 months
- Median duration of best response was 12.7 months
- 34 (26%) of subjects proceeded to HCT

Garcia-Manero *Lancet Hematology* in press

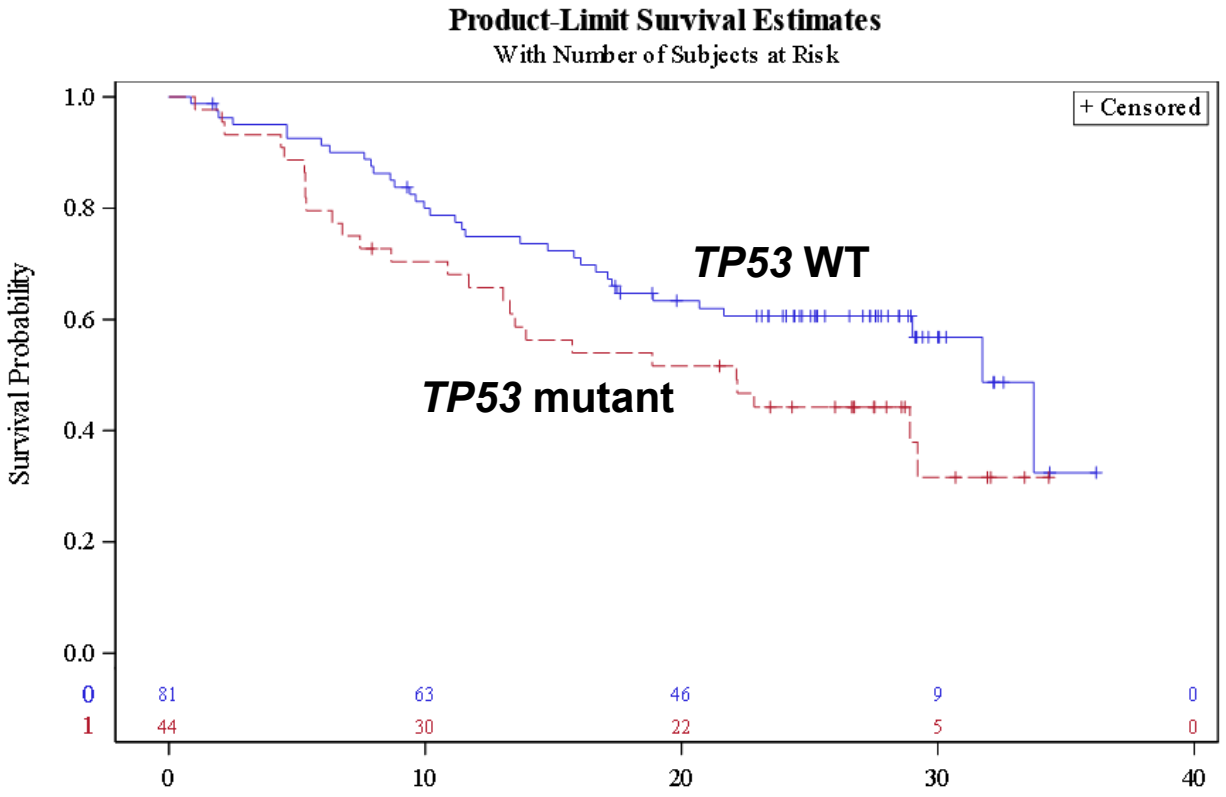
Oral decitabine/cedazuridine: OS



Savona ASH 2021, Garcia-Manero *Lancet Hematology* in press

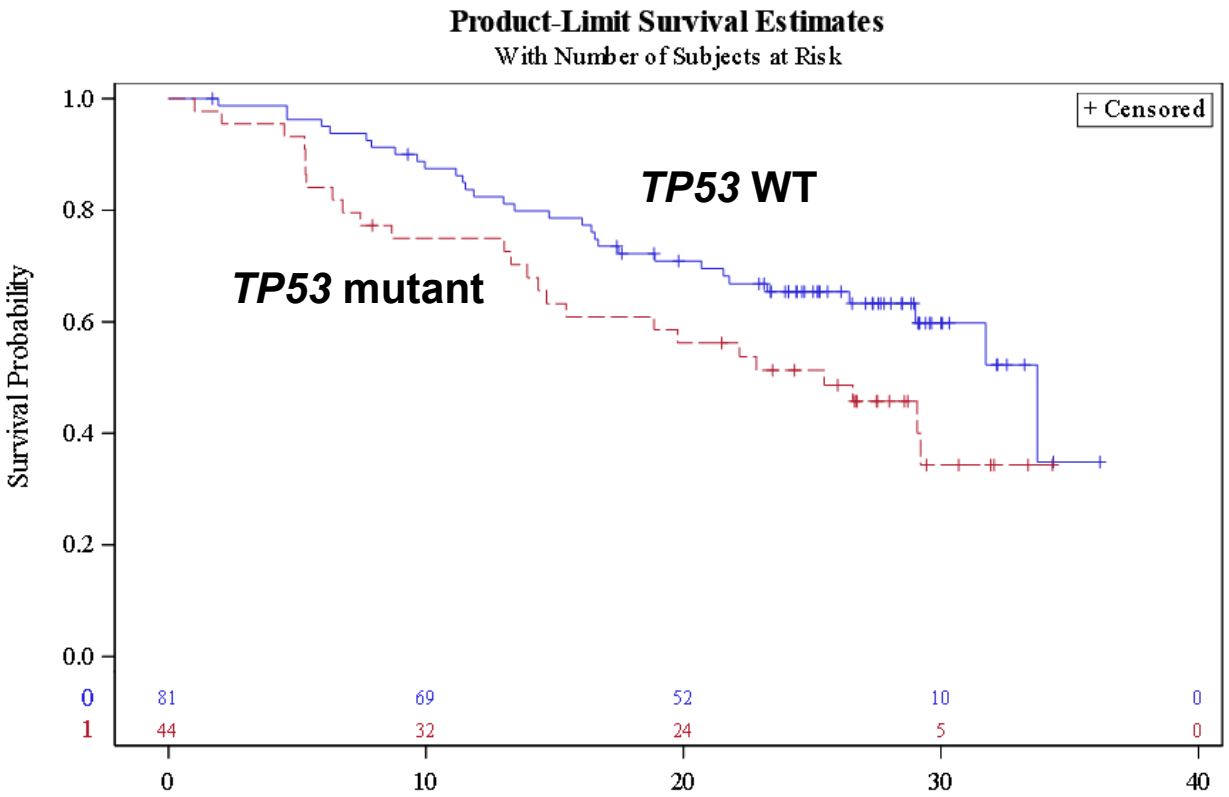
Oral decitabine OS and LFS in *TP53*^{mut} MDS

Leukemia-Free Survival



LFS: WT 31.7 months (21.7, NE)
Mut 22.1 months (11.7, 29.2)

Overall Survival



OS: WT 33.7 months (29.0, NE)
Mut 25.5 months (14.4, NE)

NE – not estimatable

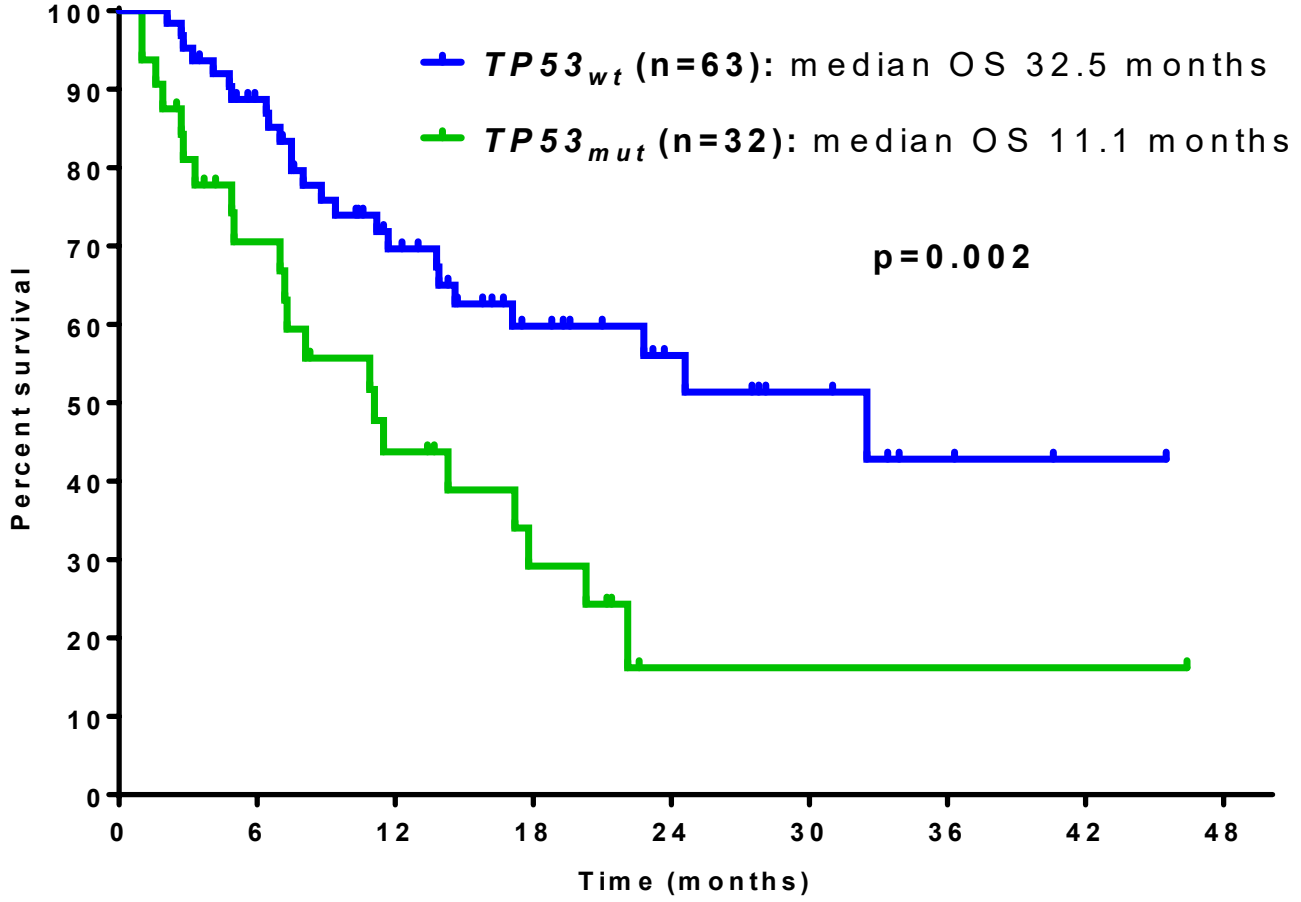
Savona ASH 2022

Recent Doublets in Higher Risk MDS

- Panther: azacitidine +/- pevonedistat
- Azacitidine +/- APR-246 for $p53^{mut}$ MDS
- HMA+/- anti CD47
- HMA +/- sabatolimab
- HMA+/- venetoclax
- HMA +/- RAR

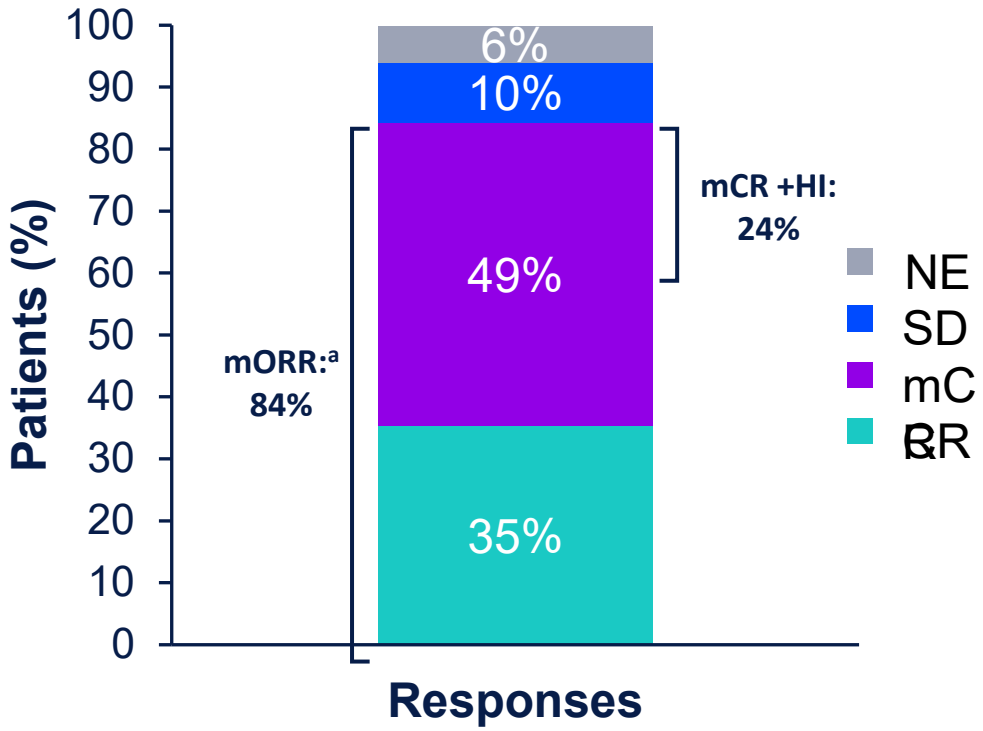
Garcia-Manero *Lancet Hematology* 2022, Ades *Blood Adv* 2022, Sallman *JCO* 2021; Sallman *JCO* 2023, Zeidan *ASH* 2022, Garcia ASH 2023, Bazinet *Lancet Hematology* 2022, Bataller *Lancet Hematology* in press

Guadecitabine: Survival by *TP53* Mutation



Garcia-Manero ASH 2018 and Urrutia ASH 2023

Phase 1 study of Azacytidine + Venetoclax: Response

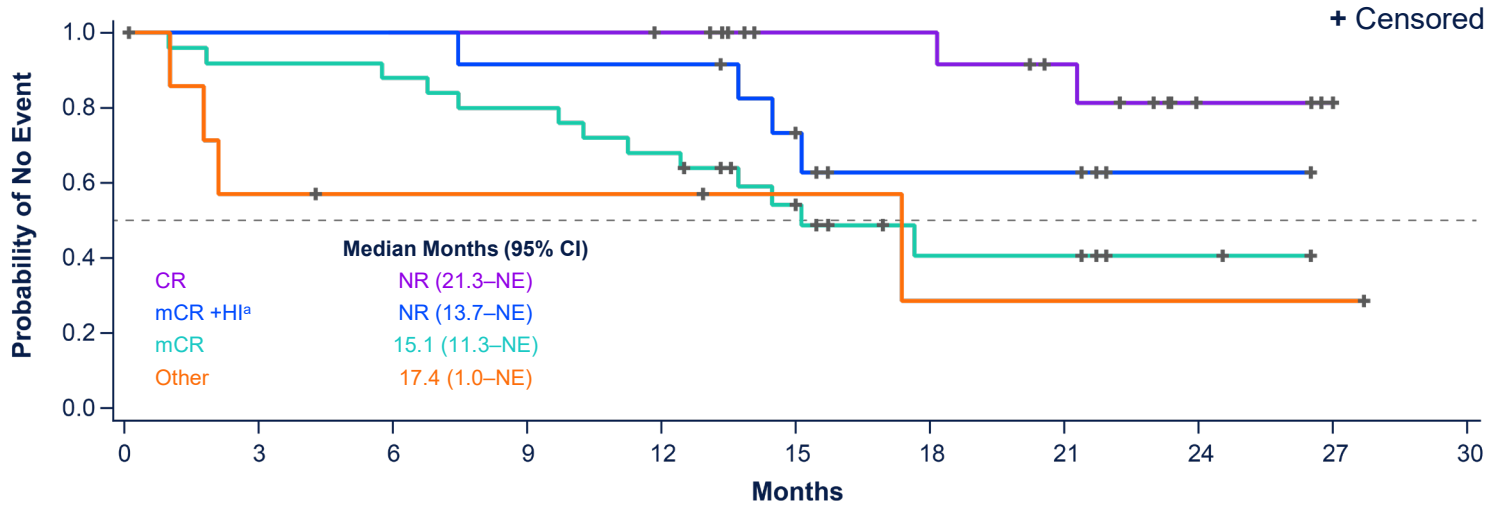


- Median time to response:
  0.9 months (95% CI, 0.7–5.8)
- Median duration of response:
  12.4 months (95% CI, 9.9–NR)

Data cutoff: Dec 15, 2020

Garcia et al ASH 2021

Phase 1 study of Azacytidine + Venetoclax: Survival



Number at Risk

CR	18	18	18	18	17	12	12	9	3	1	0
mCR +HI[a]	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

Data cutoff: Dec 15, 2020

Garcia et al ASH 2021

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A phase 1 study of azacitidine combined with venetoclax for myelodysplastic syndrome and chronic myelomonocytic leukemia

Alexandre Bazinet, MD, MSc, FRCPC

Updated EHA 22 P757
Lancet Hematology 2022

Department of Leukemia

University of Texas MD Anderson Cancer Center

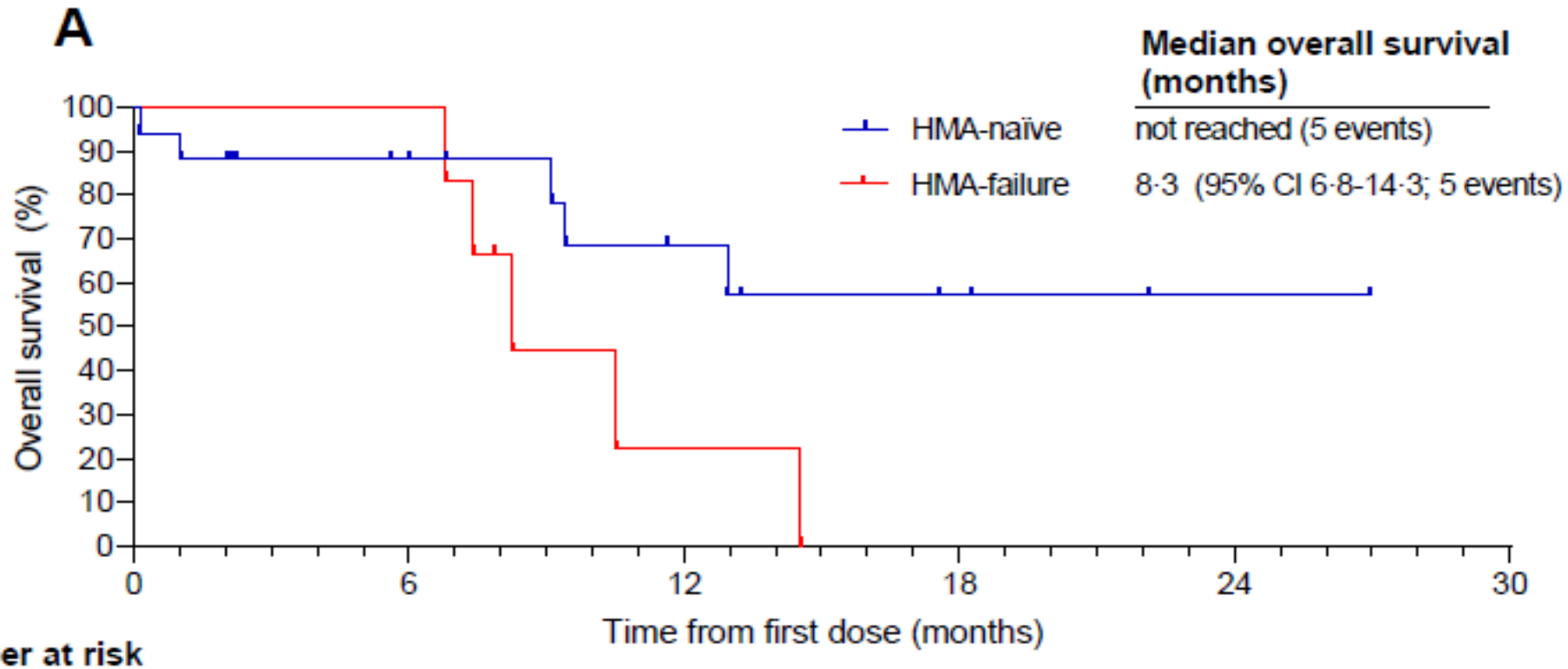
Responses (N = 23 ITT analysis)

Response (Modified IWG)	All (n = 23) n (%) or median [range]	HMA-naïve (n = 17) n (%) or median [range]	HMA-failure (n = 6) n (%) or median [range]
ORR	20 (87)	14 (82)	6 (100)
CR	3 (13)	3 (18)	0 (0)
mCR	17 (74)	11 (65)	6 (100)
mCR + HI	5 (22)	5 (29)	0 (0)
mCR alone	12 (52)	6 (35)	6 (100)
Median DOR (months)		12.2	5.4
Median cycles given	3 [1 – 11]	3 [1 – 11]	5 [2 – 8]
Median cycles to response	1 [1 – 2]	1 [1 – 2]	1 [1 – 2]

Cytogenetic response rate in patients with baseline abnormality: 17% (2/12)

Overall survival (N = 23)

Median follow-up: 13.2 months



Number at risk (number censored)

HMA-naïve	17 (0)	13 (3)	11 (5)	10 (6)	7 (7)	5 (8)	4 (9)	3 (10)	2 (11)	0 (12)	0 (12)
HMA-failure	6 (0)	6 (0)	6 (0)	3 (1)	2 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)

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Phase 1/2 study of oral decitabine/cedazuridine in combination with venetoclax in treatment-naïve higher-risk myelodysplastic syndromes or chronic myelomonocytic leukemia

Alex Bataller, Guillermo Montalban-Bravo, Alexandre Bazinet, Yesid Alvarado, Kelly Chien, Sangeetha Venugopal, Jo Ishizawa, Danielle Hammond, Mahesh Swaminathan, Koji Sasaki, Ghayas C. Issa, Nicholas J. Short, Lucia Masarova, Naval G. Daver, Tapan M. Kadia, Simona Colla, Wei Qiao, Xuelin Huang, Rashmi Kanagal-Shamanna, Stephany Hendrickson, Farhad Ravandi, Elias Jabbour, Hagop Kantarjian, Guillermo Garcia-Manero

Leukemia Department, The University of Texas MD Anderson Cancer Center, Houston (TX, USA)

June 10th 2023
s424 Clinical updates in MDS

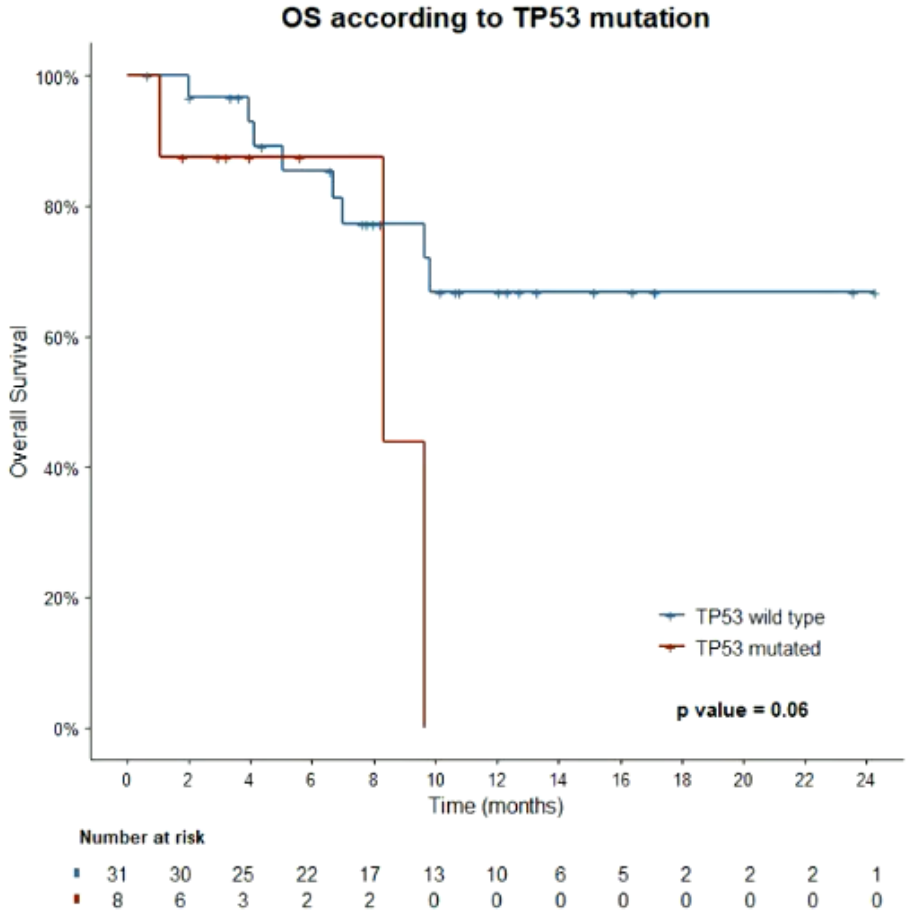
In press, Lancet Hematology

	Full cohort (n=39)	Phase 1 cohort (n=9)	Phase 2 cohort (n=30)
Age, years, median (range)	71 (27-94)	72 (53-84)	71 (27-94)
Sex, male, n (%)	28 (71.8)	8 (88.9)	20 (66.7)
Bone marrow blasts, median (range) [%]	12 (6-18)	14 (7-15)	12 (6-18)
WHO 2016 diagnosis, n (%) MDS CMML Atypical CML	 32 (82.1) 6 (15.4) 1 (2.6)	 5 (55.6) 3 (33.3) 1 (11.1)	 22 (90) 3 (10) 0 (0)
Cytogenetic category (IPSS), n (%) Good Intermediate Poor	 11 (28.2) 13 (33.3) 15 (38.5)	 4 (44.4) 4 (44.4) 1 (11.1)	 7 (23.3) 9 (30) 14 (46.7)
Complex cytogenetics, n (%)	9 (23.1)	1 (11.1)	8 (26.7)
Therapy-related neoplasm, n (%)	10 (25.6)	1 (11.1)	9 (30)
IPSS-R, n (%) Intermediate High Very high	 3 (9.4) 11 (34.4) 18 (56.2)	 0 (0) 3 (60) 2 (40)	 3 (11.1) 8 (29.6) 16 (59.3)
IPSS-M, n (%) Moderate high High Very high	 3 (9.4) 7 (21.9) 22 (68.7)	 1 (20) 1 (20) 3 (60)	 2 (7.4) 6 (22.2) 19 (70.4)

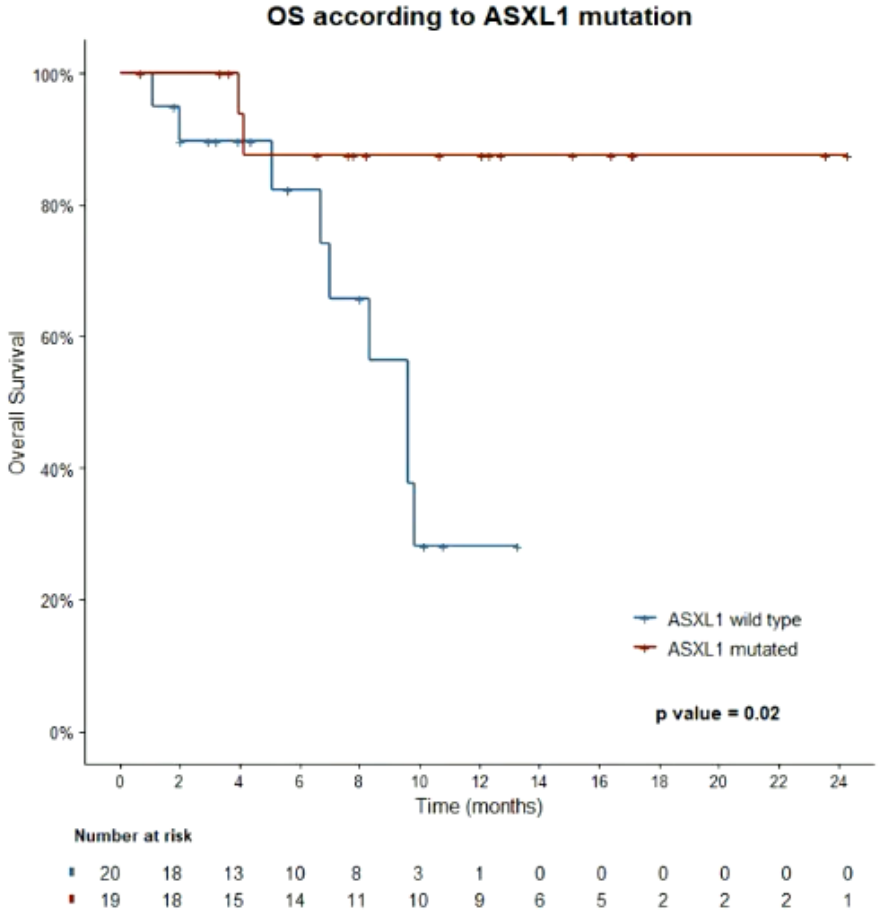
Efficacy

	Full cohort (n=39)	Phase 1 (n=9)	Phase 2 (n=30)
ORR, n (%) CR mCR mCR mCR + HI	37 (94.9) 14 (35.9) 23 (59) 11 (28.2) 12 (30.8)	9 (100) 6 (66.7) 3 (33.3) 2 (22.2) 1 (11.1)	28 (93.3) 8 (26.7) 20 (66.7) 9 (30) 11 (36.7)
Cytogenetic response, n (%)	14/26 (53.8)	4/5 (80)	10/21 (47.6)
Cycles to first response, n (range)	1 (1-2)	1 (1-1)	1 (1-2)
Cycles to best response, n (range)	1 (1-6)	1 (1-6)	1 (1-4)
Cycles received, n (range)	2 (1-13)	6 (2-13)	2 (1-8)
HSCT, n (%)	19 (48.7)	5 (55.6)	14 (46.7)

Survival

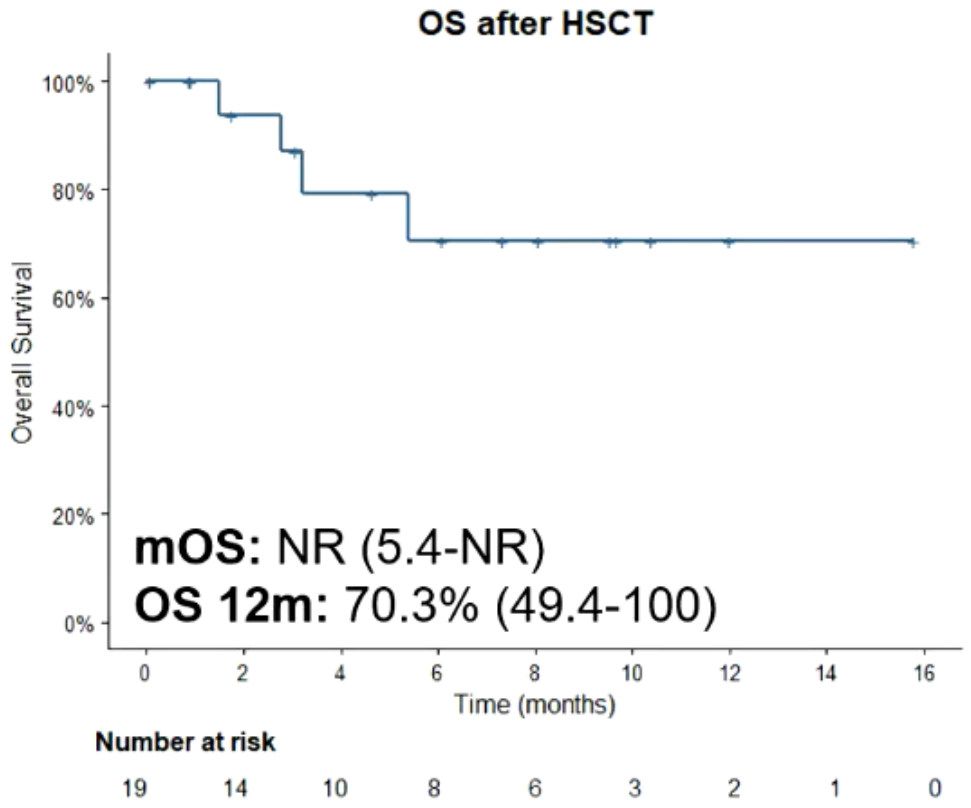


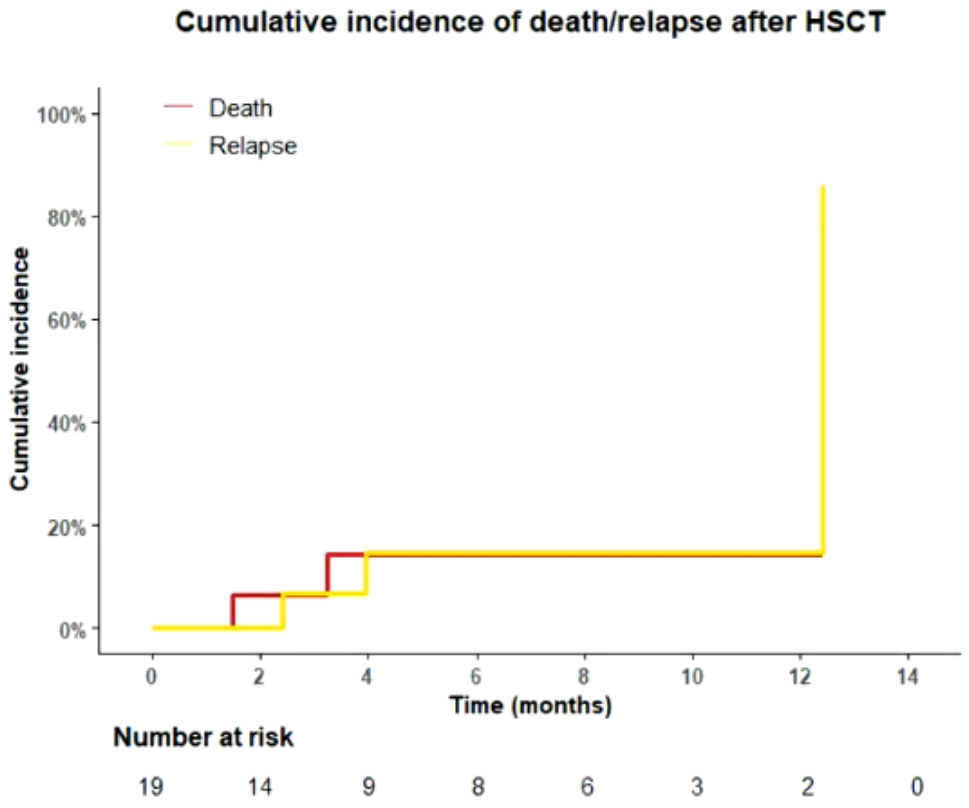
mOS: NR vs 8.3m (8.3-NR)



mOS: NR vs 9.6m (7-NR)

Survival after HSCT

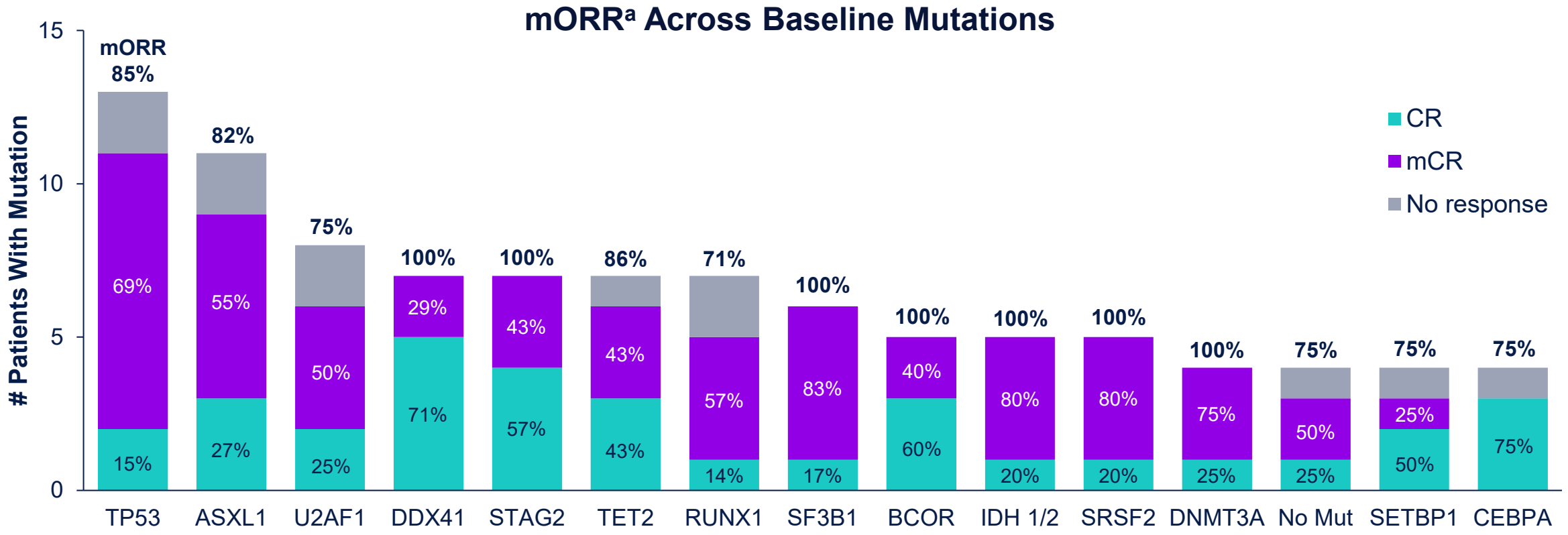




- Median n of cycles: 2 (2-11)
- Median time to HSCT: 3.7m (2.3-15)

- 4 patients died (2 TRM, 2 disease progression)
- 3 patients relapsed after HSCT

Aza+ven: Clinical responses observed in patients with HR-MDS across the mutational spectrum



Garcia et al ASH 2021

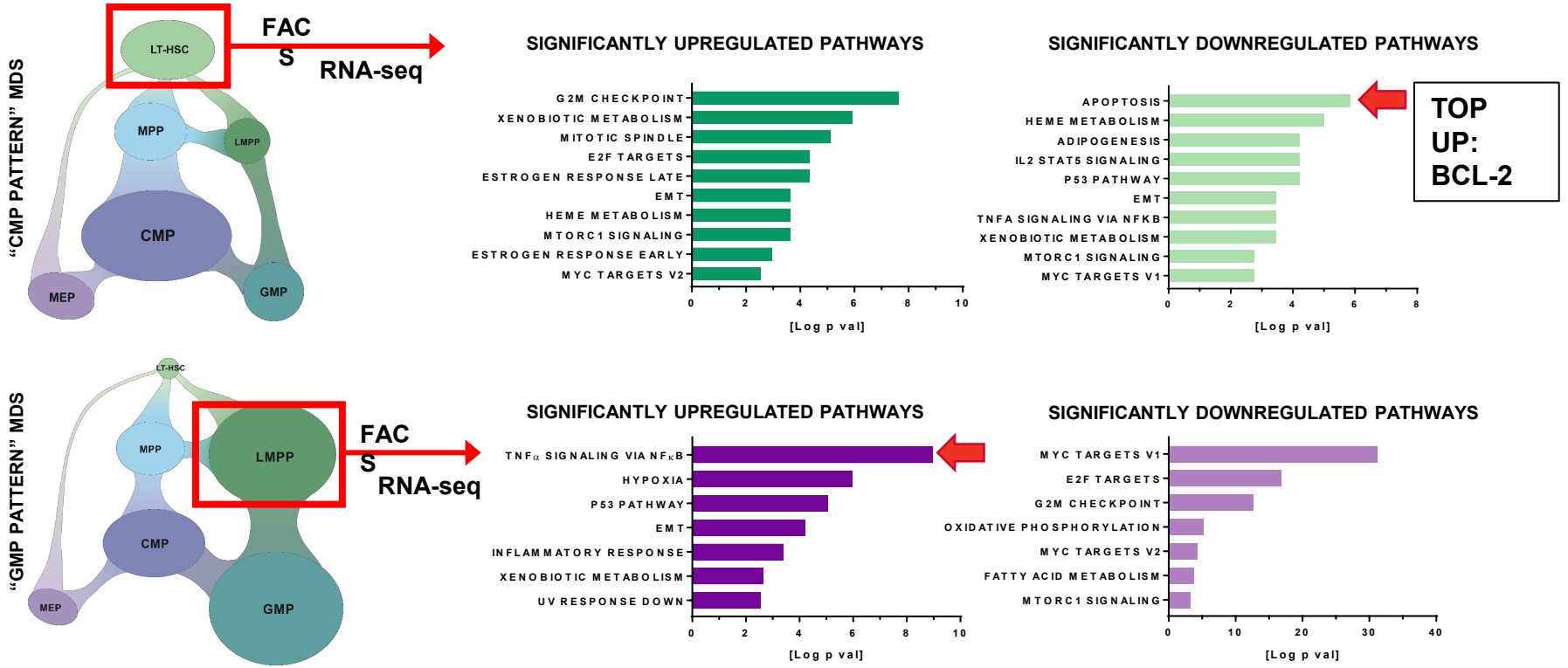
- 7 of 13 patients with *TP53* mutations had multi-hit/bi-allelic *TP53* mutations
- Responses of those with multi-hit/bi-allelic *TP53* were similar to responses in patients with any *TP53* mutation:
  - CR: 28.6% (2/7); mORR: 71.4% (5/7)

Data cutoff: Dec 15, 2020

[a]mORR=CR+mCR+PR; Baseline mutational profiling was available for 49/51 patients who received the RP2D of Ven + Aza. Mutations assessed from BMA at screening using Archer® VariantPlex® Myeloid, or peripheral blood at screening using Illumina TruSight® Myeloid Panel. Response rates based on IWG 2006 response criteria. Analysis of patients receiving RP2D.

Aza, azacitidine; BMA, bone marrow aspirate; CR, complete remission; HR-MDS, higher-risk myelodysplastic syndrome; mCR, marrow complete remission, mORR, modified overall response rate; RP2D, recommended phase 2 dose; Ven, venetoclax.

Distinct Oncogenic Pathways Underpin HSC Expansion During Blast Progression

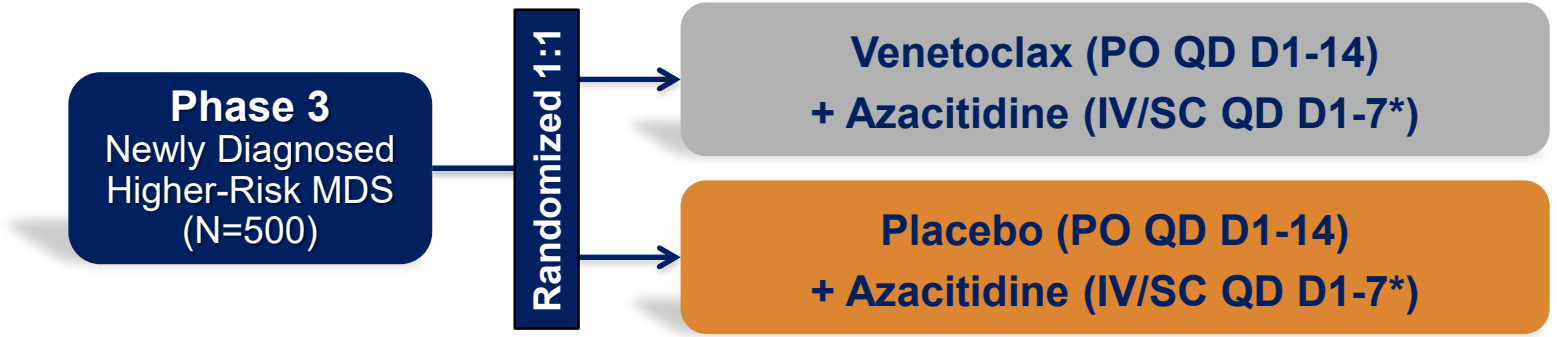


Ganan-Gomez and Colla *Nature Med* 2022

Phase 3 VERONA (NCT04401748)

Study Design and Endpoint

VERONA Study Design



*7 days within the first 9 calendar days/28 day cycle

Select Inclusion Criteria

+ ≥18 years old with newly diagnosed MDS according to 2016 WHO classification
+ <20% BM blasts
+ ECOG PS 0-2
+ IPSS-R score of >3 (Intermediate, High, Very High)
+ No planned HSCT at the time of C1D1

Select Exclusion Criteria

– Prior therapy for MDS with HMA, chemotherapy, or allo-HSCT
– Prior diagnosis of therapy-related MDS, MDS evolved from MPN, MDS/MPN including CMML, aCML, JMML, and unclassifiable MDS/MPN

End Points

Primary: *CR, OS*

Secondary: *mOR, TI, ORR, fatigue score, physical functioning score, time to deterioration in physical functioning*

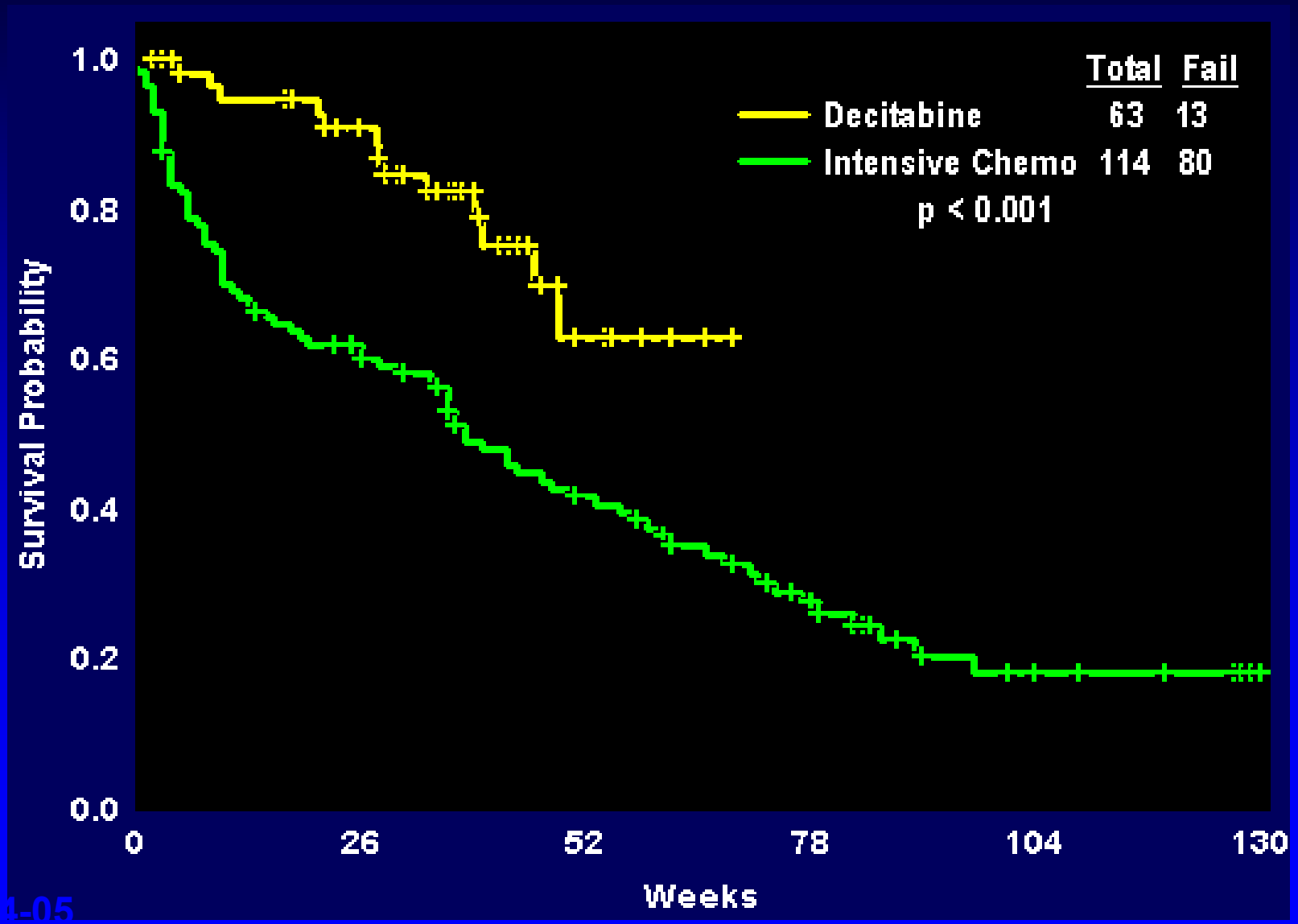
aCML=Atypical Chronic Myeloid Leukemia. allo-HSCT=Allogeneic Hematopoietic Stem Cell Transplant. AML=Acute Myeloid Leukemia. BM=Bone Marrow. C=Cycle. CMML=Chronic Myelomonocytic Leukemia. CR=Complete Remission. D=Day. ECOG PS=Eastern Cooperative Oncology Group Performance Status. HMA=Hypomethylating Agent. HSCT=Hematopoietic Stem Cell Transplantation. IPSS-R=Revised International Prognostic Scoring System. IV=Intravenous. JMML=Juvenile Myelomonocytic Leukemia. MDS=Myelodysplastic Syndrome. mOR=Modified Overall Response. MPN=Myeloproliferative Neoplasm. ORR=Overall Response Rate. OS=Overall Survival. PO=Oral. QD=Daily. SC=Subcutaneous. TI=Transfusion Independence. WHO=World Health Organization. 1. ClinicalTrials.gov. NCT04401748. https://clinicaltrials.gov/ct2/show/NCT04401748. Accessed July 2021

Targeted options in HR-MDS

- **IDH-2 (5-10%): enasidenib, venetoclax**
- **IDH-1 (5%): ivosidenib, venetoclax**
- **Flt-3 (15%): multiple agents**
- **NPM1 (1%): ara-C based + SCT**
- **TP53 (10%): HMAs, oral decitabine/cedazuridine, clinical trial, SCT**
- **ASXL1 ?**

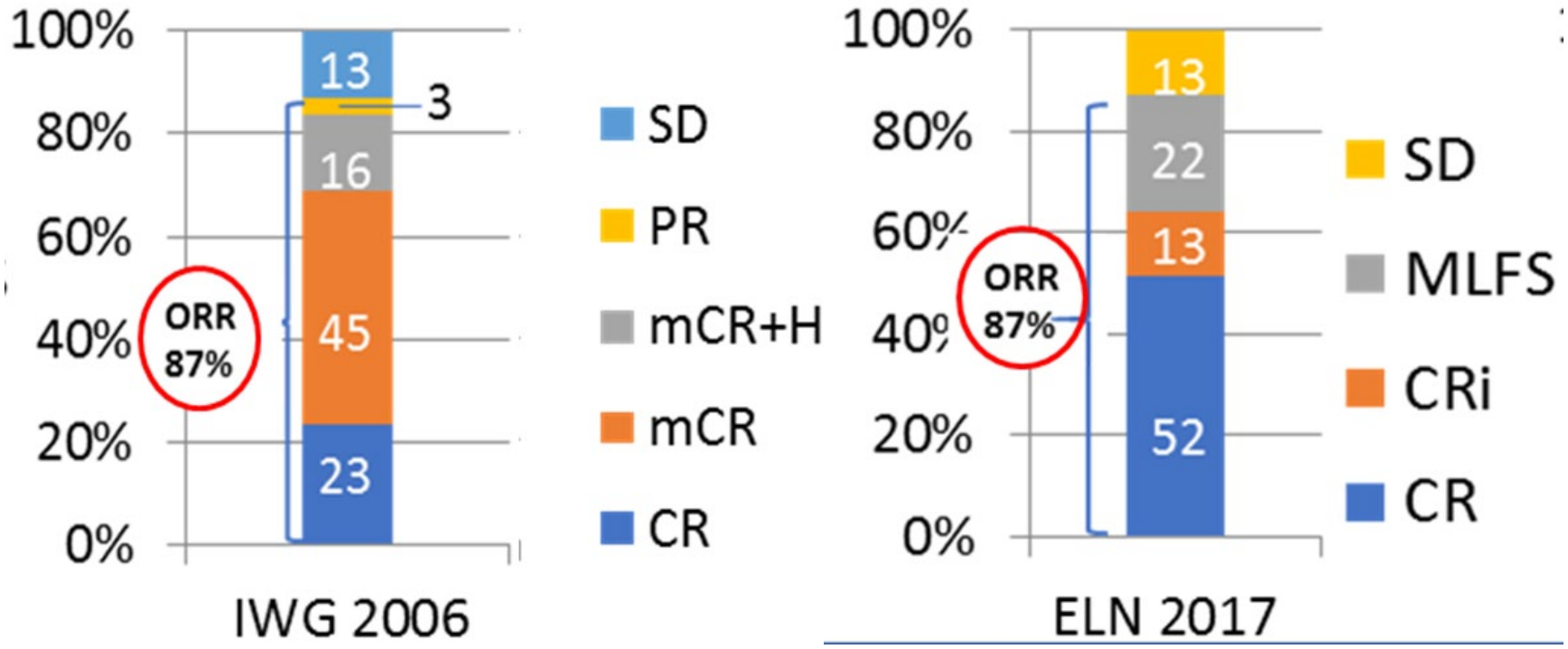
DiNardo Blood Adv 2023, Ravandi *Blood* 2013, Montalban-Bravo *Blood Adv* 2019, Gener-Rico ASH 2023

Decitabine vs. Intensive Chemotherapy—Survival



Courtesy Dr. Hagop Kantarjian

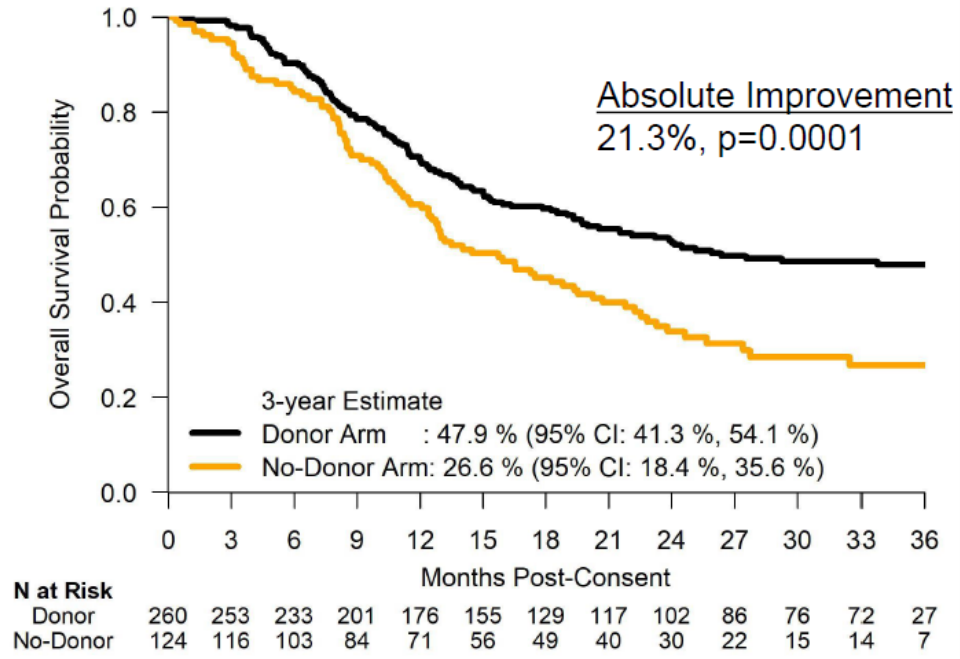
CPX-351 in HR-MDS

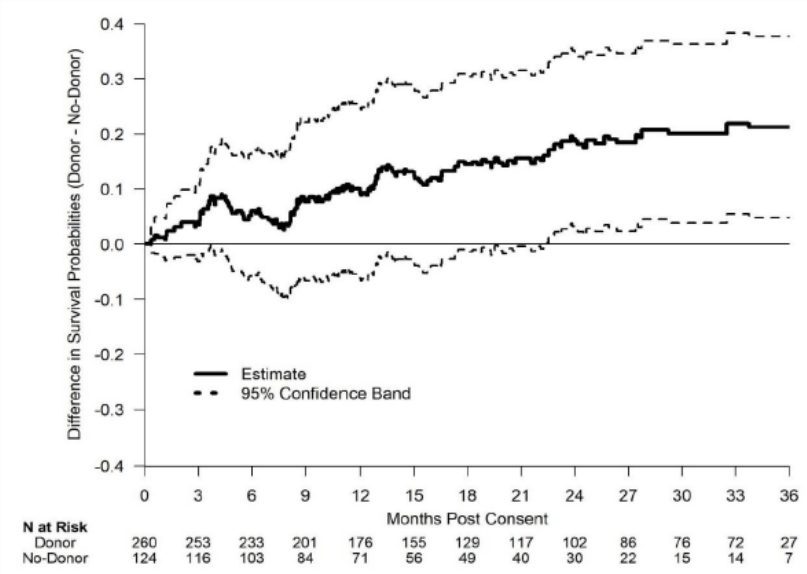


Peterlin *Lancet Hematology* 2023

SCT in MDS

Primary Endpoint: 3 Year Overall Survival



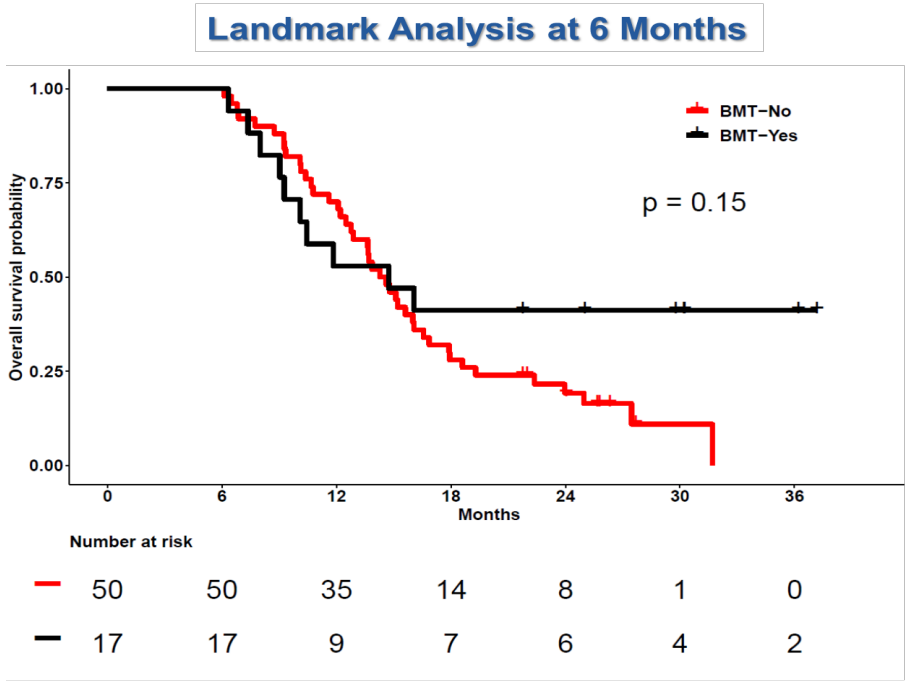


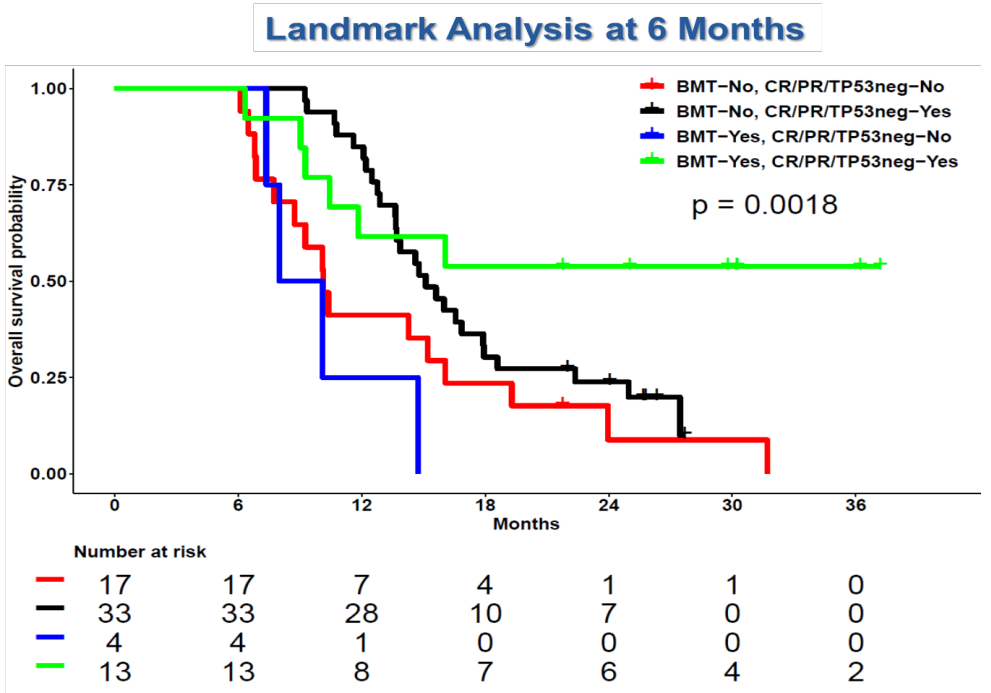
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Sensitivity Analysis: Adjusted OS: 48.0% vs. 28.1%, p=0.0004

Nakamura *JCO* 2021

APR-246 + AZA: Outcomes with Allogeneic Stem Cell Transplantation





TP53 mutation pts who achieved CR/PR/NGS negativity and were bridged to allo-HSCT had a median OS that was not reached (95% CI 10.4-NR) vs 9.1 months (95% CI 7.4-NR) in allo-HSCT pts who did not achieve this response (P=0.02)

Sallman ASH 2021

MDACC Approach Front Line HR MDS

Age	Risk	Treatment	SCT
Younger	Standard	HMA/AML-like Clinical trial	YES
Younger	Favorable (ie NPM1)	HMA/AML-like Clinical trial	YES
Younger	Adverse (ie p53)	HMA/clinical trial	individualize
Older	Standard	HMA/clinical trial	individualize
Older	Favorable (ie NPM1)	HMA/AML-like Clinical trial	individualize
Older	Adverse (ie p53)	HMA/clinical trial	individualize
Targetable lesion *(IDH1, IDH2, Flt-3, ASXL1)*		HMA/target/ Ven/trial	individualize

Conclusions

- Up to December 2023: single agent HMA still SOC in HR-MDS
- Verona trial may change this statement
- New classifications and molecular data help understand different subsets of patients
- Stem cell transplantation taking a more prominent role in MDS

Major needs in HR MDS

- New doublets
- P53 mutated directed therapy
- HMA failure
- More targeted approaches: IDH2, IDH1, other ??
- Redefine role of “chemo” in MDS
- Integration with SCT
- Should we abandon HMAs if Verona negative?

Thank you

Guillermo Garcia-Manero

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