Quali opzioni dopo il fallimento con HMA e

prima del trapianto?

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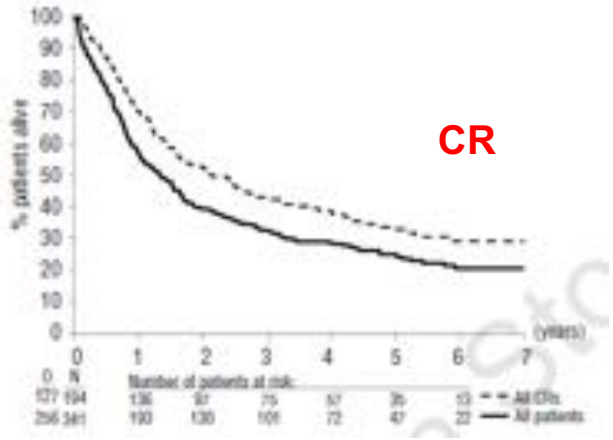
Bridge al trapianto

Role of intensive CHT before HSCT (1-2 ICE, 1 HDARAC/Ida)

❖ 341 patients (113 MDS, 131 RAEB-T, 20 CMML, 77sAML), median age: 51 years (range, 16-67 years).

❖ CR achieved in 173 patients after 1 course and in 194 (57%) after 1-2 courses. **HSCT** was administered to 56 pts (**16%**).

❖ Median survival was 1.3 years (95% CI, 1.0 - 1.7 years) and the 4-year OS was 28% (SE=2.5%)

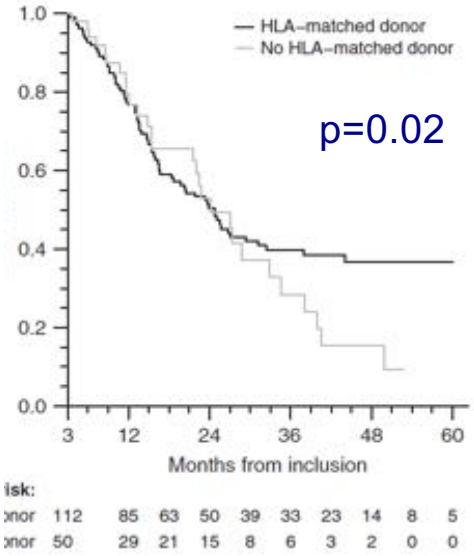


De Witte et al, Haematologica 2010

Biologic Randomization, Donor vs No Donor

- ❖ Prospective observational study, on 162 MDS, mostly Int-2/high risk
- ❖ 4/2007 to 1/2013, median age 60 yrs (range 50-70)
- ❖ 89% of patients received a treatment as bridge to HSCT, including IC (28%), HMT (76%) or both (17%).
- ❖ No differences in CR rates

Outcome	No donor n=50	HLA matched donor n=112	P
Treatment after inclusion			
Intensive chemotherapy, n (%)	12 (24)	33 (29)	0.57
Demethylating agents, n (%)	44 (88)	79 (71)	0.017
Any, n (%)	46 (92)	98 (88)	0.59
Probability of achieving < 10% blasts at 6 months (95% CI)	68% (53–79)	57% (47–66)	0.27[a]
Probability of remission at 6 months (95% CI)	22% (10–33)	21% (14–28)	0.78[a]
Probability of AML at 6 months (95% CI)	4% (0–9)	8% (4–14)	0.28[a]
Probability of death with disease at 6 months (95% CI)	0% (0–6)	4% (1–8)	0.048[a]
Overall survival at 48 months (95% CI)	15% (6–39)	37% (28–48)	0.020[b]
Probability of AML at 48 months (95% CI)	30% (12–45)	24% (16–33)	0.84[b]
Probability of death with the disease at 48 months (95% CI)	73% (47–87)	37% (27–46)	0.001[b]



❖**The early transplant-related mortality and the delay in HSCT explain the absence of significant difference between the 2 groups in the first two years**

Robin et al, Leukemia 2015

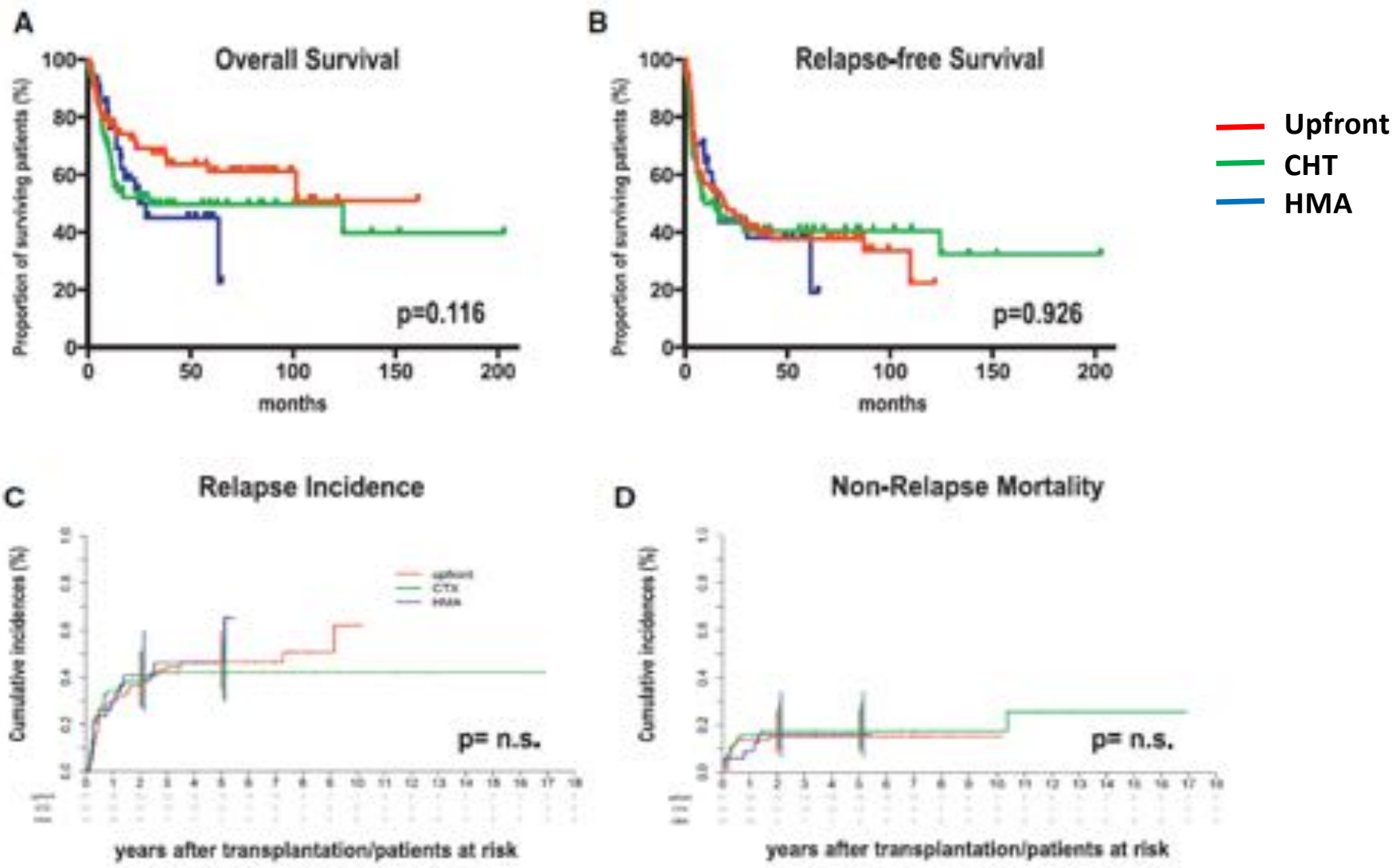
Upfront HSCT vs CHT vs HMT

Retrospective study, 1999-2016
MDS-EB (n=126, 76%), sAML (n=39, 24%)

		Upfront (n=67, 41%)	CHT (n=64, 39%)	HMT (n=34, 20.5%)	p
Age		52 (21-68)	57 (26-72)	62 (42-72)	*0.0451 ** < 0.0001 ***0.0073
WHO 2008	RAEB-II RAEB-II CMML I+II MDS/MPN AML-MRC	28 (42%) 19 (28%) **13 (19%)** 2 (3%) 5 (8%)	8 (12%) 20 (31%) 5 (8%) 1 (2%) **30 (47%)**	7 (21%) 21 (61%) 1 (3%) 1 (3%) 4 (12%)	signif
Therapy-related	yes no	**22 (33%)** 45 (67%)	**6 (9%)** 58 (91%)	7 (21%) 27 (79%)	signif
CR			59%	18%	<0.0001

Schroeder et al, Biol Blood BM Transplant, 2019

After HSCT



Schroeder et al, Biol Blood BM Transplant, 2019

Multivariable analysis

OS & RFS

	OS			RFS		
Variable	HR	95% CI	p value	HR	95% CI	p value
Poor risk cytogenetics yes vs. no	2.63	1.45 to 3.85	0.001	2.18	1.43 to 3.30	<0.0001
Age >Median	0.75	0.41 to 1.37	0.340	–		
Conditioning standard-dose vs. reduced-intensity	0.42	0.23 to 0.75	0.002	0.50	0.32 to 0.80	0.004
Donor related vs. unrelated	–			0.49	0.29 to 0.82	0.006
Type of therapy upfront vs. cytoreduction	1.45	0.76 to 2.77	0.259	1.48	0.83 to 2.65	0.186

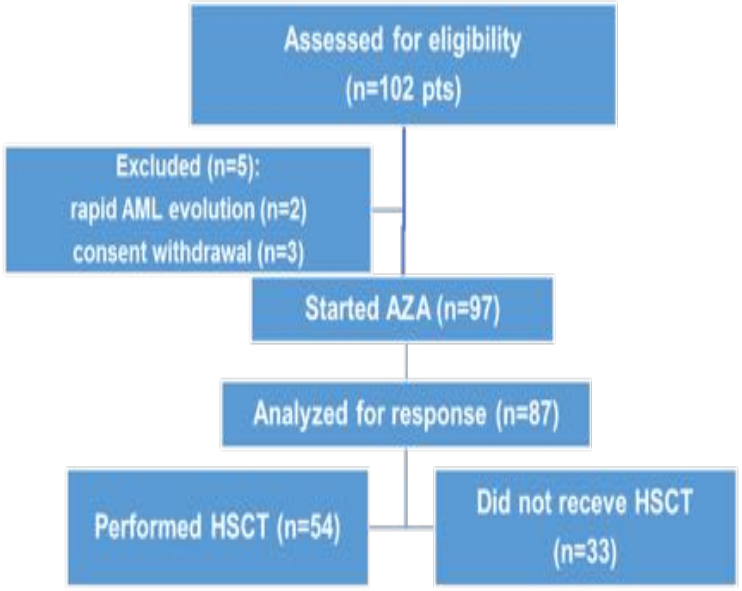
CIR & NRM

	CIR			NRM		
Variable	HR	95% CI	p value	HR	95% CI	p value
Cytogenetics abnormal vs. normal	1.789	1.06 to 3.03	0.030	–		
Donor related vs. unrelated	0.330	0.16 to 0.64	0.002	–		
Conditioning standard-dose vs. reduced-intensity	0.450	0.25 to 0.80	0.006	–		
Therapy-related yes vs. no	0.546	0.26 to 1.12	0.098	–		
Type of therapy upfront vs. cytoreduction	1.197	0.72 to 1.98	0.486	0.767	0.32 to 1.83	0.551
Age >Median	–			–		

Schroeder et al, Biol Blood BM Transplant, 2019

Feasibility of allogeneic stem-cell transplantation after azacitidine bridge in higher-risk myelodysplastic syndromes and low blast count acute myeloid leukemia: results of the BMT-AZA prospective study

M. T. Voso, G. Leone, A. Piciocchi, L. Fianchi, S. Santarone, A. Candoni, M. Criscuolo, A. Marcucci, E. Cerqui, A. Molteni, C. Finelli, M. Parma, A. Poloni, A. M. Caella, F. Spina, A. Consiglio, F. Salvi, E. P. Alessandrino, A. Ramondi & S. Sica

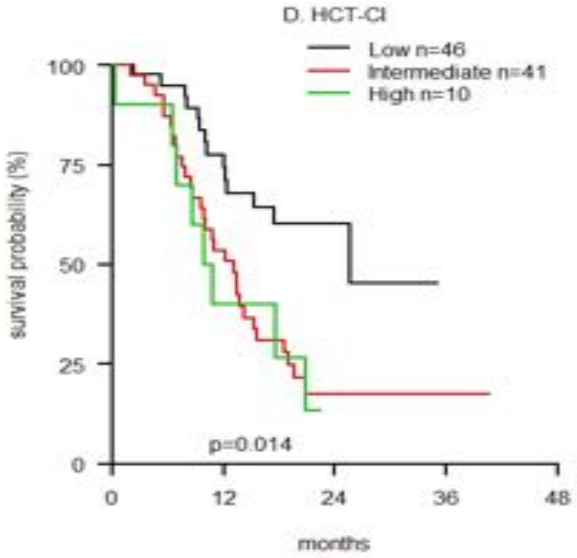


74% of pts with a donor

HR-MDS: 70
AML: 19
CMML: 8

CR: 22%
PR: 12%
HI: 9%
SD: 29%
PD: 20%

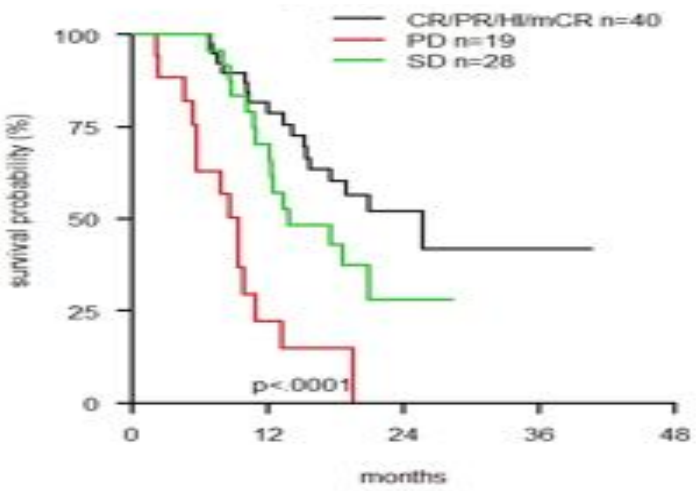
Overall survival



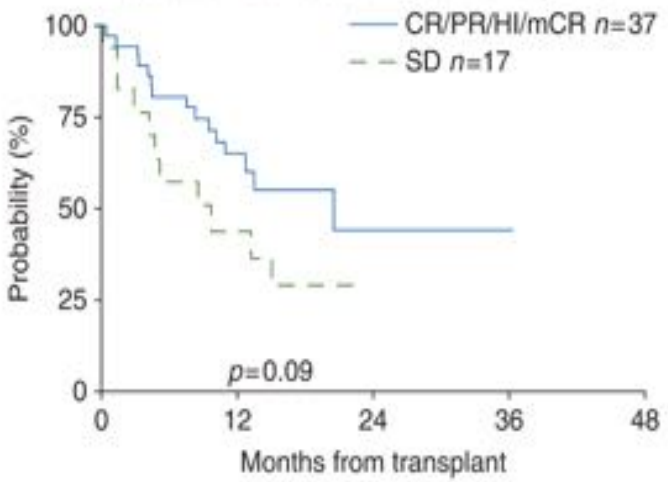
Ann Oncol 2017

Survival according to AZA response

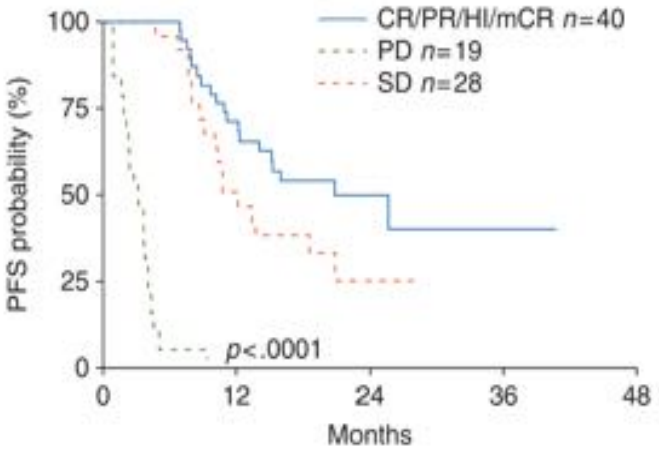
OS ITT



OS after HSCT



PFS ITT

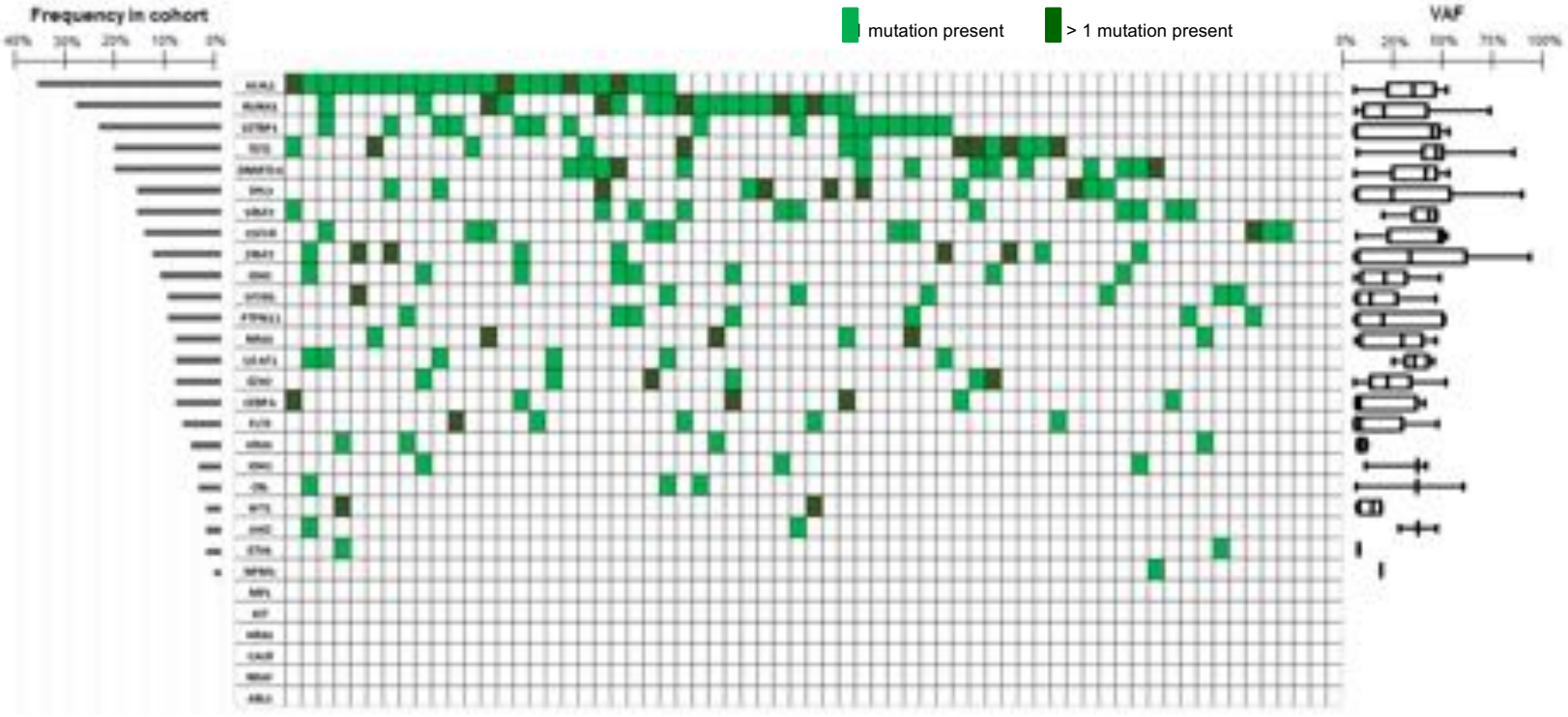


Multivariate analysis including HSCT as time-dependent covariate: confirmed AZA response as independent prognostic factor for survival

Voso et al, Ann Oncol 2017

Mutations identified before AZA treatment start

n=65 pts with available samples before and after AZA



VAF≥1.1%

- 95.4% of patients had at least 1 mutation
- 50% of patients had >1 mutation in the same gene
- The median number of mutated genes wass 3 per patient (range, 0-6)

Falconi G et al., Leukemia 2019

Prognostic role of mutations

OS

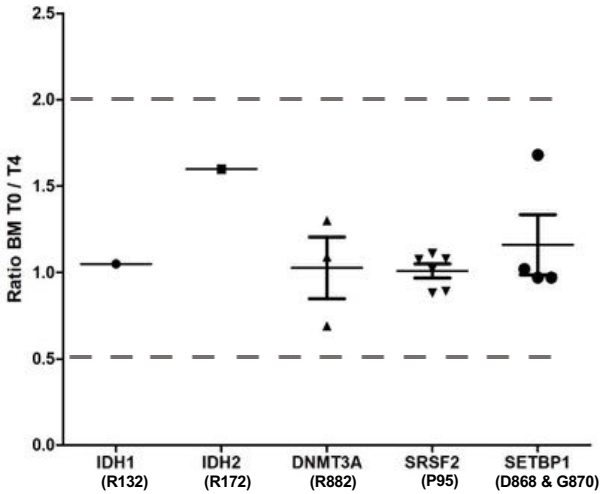
	OS: UNIVARIATE ANALYSIS		OS: MULTIVARIATE ANALYSIS	
PARAMETER	HR (95%CI)	p-value	HR (95%CI)	p-value
FEMALE VS MALE	0.784 (0.36-1.708)	0.541		
R-IPSS	1.728 (1.011-2.955)	0.0455		
AGE	1.013 (0.973-1.054)	0.5431		
WBC	1.024 (0.987-1.064)	0.2069		
KAR GOOD VS POOR	0.588 (0.266-1.301)	0.1901		
KAR INTERMEDIATE VS POOR	0.831 (0.276-2.499)	0.7415		
CR/PR/HI VS SD/PD	0.373 (0.175-0.796)	0.0108	0.344 (0.159-0.745)	0.0068
ASXL1 WT VS MUT	0.715 (0.348-1.472)	0.3628		
CEBPA WT VS MUT	4.155 (0.565-30.546)	0.1618		
CSF3R WT VS MUT	1.051 (0.367-3.01)	0.9256		
DNMT3A WT VS MUT	0.774 (0.334-1.798)	0.5519		
ETV6 WT VS MUT	0.636 (0.191-2.11)	0.4591		
EZH2 WT VS MUT	2.615 (0.356-19.223)	0.3448		
FLT3 WT VS MUT	1.116 (0.338-3.681)	0.8568		
IDH2 WT VS MUT	0.433 (0.151-1.247)	0.1209		
KRAS WT VS MUT	0.625 (0.189-2.067)	0.4411		
NRAS WT VS MUT	4.155 (0.563-30.638)	0.1624		
PTPN11 WT VS MUT	0.647 (0.225-1.859)	0.4185		
RUNX1 WT VS MUT	0.783 (0.358-1.709)	0.5388		
SETBP1 WT VS MUT	0.424 (0.201-0.893)	0.0239	0.420 (0.197-0.893)	0.0241
SF3B1 WT VS MUT	2.156 (0.514-9.036)	0.2934		
SRSF2 WT VS MUT	0.701 (0.287-1.712)	0.4352		
TET2 WT VS MUT	2.861 (1-8.188)	0.05	3.573 (1.185-10.773)	0.0237
TP53 WT VS MUT	0.38 (0.173-0.833)	0.0157	0.225 (0.094-0.537)	0.0008
U2AF1 WT VS MUT	0.392 (0.15-1.026)	0.0563		
ZRSF2 WT VS MUT	0.351 (0.138-0.893)	0.0279		

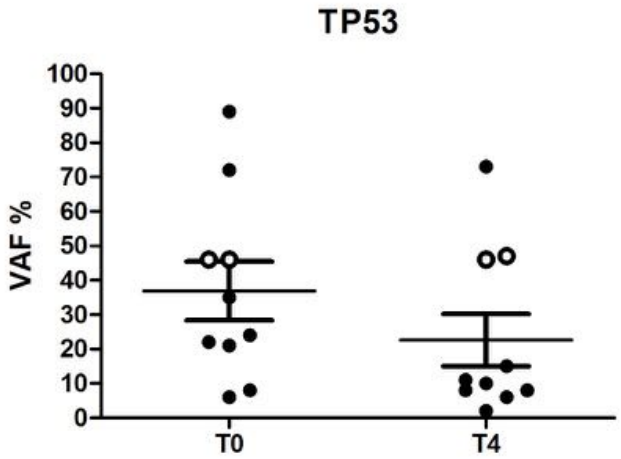
PFS

	PFS: UNIVARIATE ANALYSIS		PFS: MULTIVARIATE ANALYSIS	
PARAMETER	HR (95%CI)	p-value	HR (95%CI)	p-value
FEMALE VS MALE	1.131 (0.578-2.213)	0.7189		
R-IPSS	1.51 (0.935-2.44)	0.0921		
AGE	1.02 (0.983-1.058)	0.3003		
WBC	1.027 (1.001-1.053)	0.0397	1.042 (1.012-1.073)	0.0062
KAR GOOD VS POOR	0.603 (0.289-1.258)	0.1778		
KAR INTERMEDIATE VS POOR	0.815 (0.323-2.057)	0.6644		
CR/PR/HI VS SD/PD	0.315 (0.158-0.628)	0.001	0.264 (0.129-0.541)	0.0003
ASXL1 WT VS MUT	0.89 (0.465-1.704)	0.7254		
CEBPA WT VS MUT	2.194 (0.527-9.133)	0.2802		
CSF3R WT VS MUT	0.838 (0.35-2.009)	0.692		
DNMT3A WT VS MUT	0.53 (0.257-1.092)	0.085		
ETV6 WT VS MUT	0.704 (0.249-1.993)	0.5084		
EZH2 WT VS MUT	0.923 (0.283-3.01)	0.8943		
FLT3 WT VS MUT	1.222 (0.375-3.979)	0.7398		
IDH2 WT VS MUT	0.496 (0.206-1.195)	0.1179		
KRAS WT VS MUT	0.862 (0.264-2.812)	0.8059		
NRAS WT VS MUT	1.577 (0.482-5.154)	0.4511		
PTPN11 WT VS MUT	0.682 (0.265-1.756)	0.4279		
RUNX1 WT VS MUT	0.919 (0.454-1.862)	0.8148		
SETBP1 WT VS MUT	0.526 (0.268-1.031)	0.0612		
SF3B1 WT VS MUT	1.781 (0.547-5.797)	0.3377		
SRSF2 WT VS MUT	0.514 (0.235-1.122)	0.0948		
TET2 WT VS MUT	1.793 (0.749-4.293)	0.19		
TP53 WT VS MUT	0.463 (0.217-0.988)	0.0463	0.255 (0.111-0.585)	0.0013
U2AF1 WT VS MUT	0.628 (0.245-1.614)	0.3342		
ZRSF2 WT VS MUT	0.426 (0.191-0.949)	0.0369		

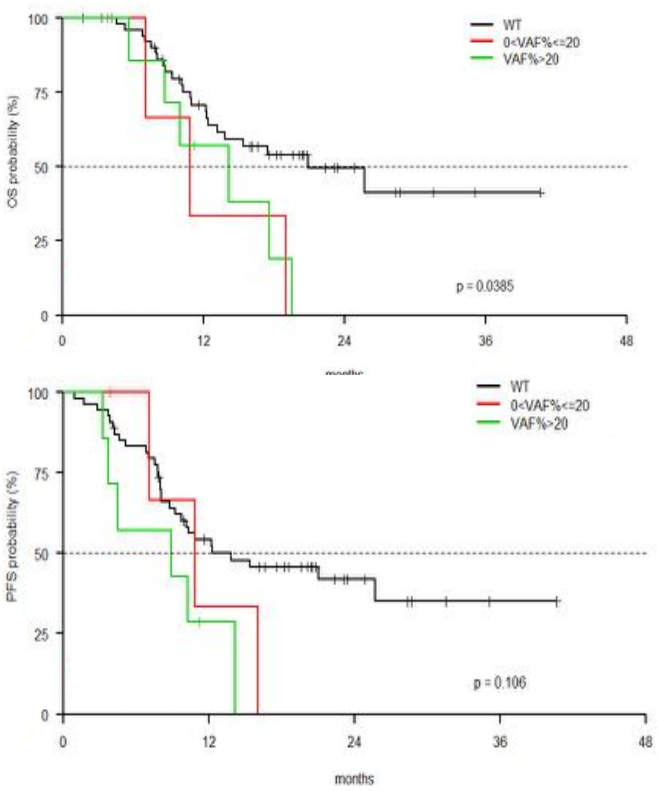
Falconi G et al., Leukemia 2019

Role of mutation burden





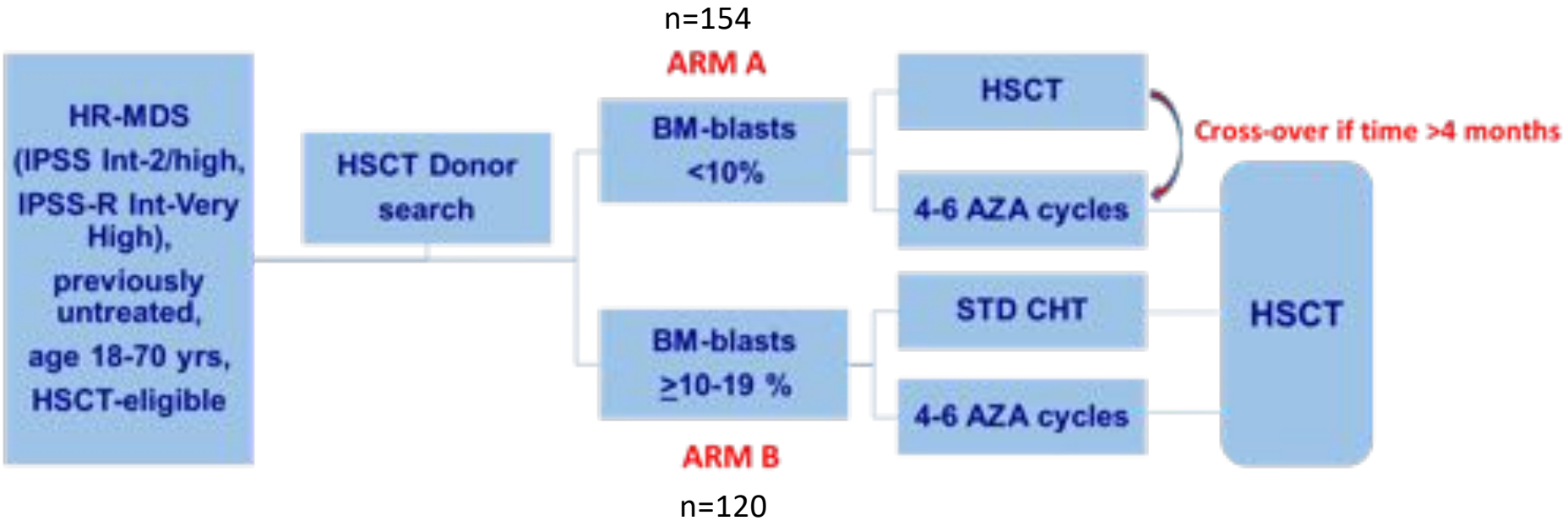
TP53 (n=11 pts)



- The allelic frequency of most mutations did not change upon Azacitidine treatment.
- Conversely, Aza treatment induced a statistically significant decrease in TP53 mutational burden.

Falconi G et al., Leukemia 2019

Protocollo ACROBAT



- AZACITIDINE 75mg/mq/day subcutaneously for 7 days every 28 days

- STANDARD CHEMOTHERAPY
1. cycle (induction): i.v. 3+7 (Citarabine 200 mg/m^2 iv ci 7 d, Daunorubicine 60 mg/mq iv 3d
2. Cycle **optional** 3+7 (Citarabine 200 mg/m^2 iv ci 7 d, Daunorubicine 45 mg/mq iv day 3 d

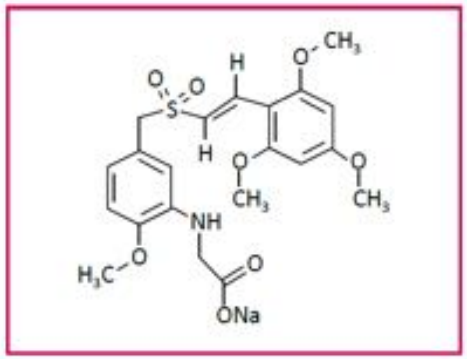
Fallimento della terapia ipometilante

Rigosertib

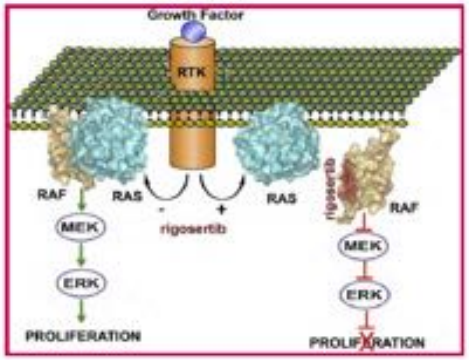
RIGOSERTIB MECHANISM OF ACTION

- Inhibits cellular signaling as a Ras mimetic by targeting the Ras-binding domain (RBD)[a]
- Novel MOA blocks multiple cancer targets and downstream pathways PI3K/AKT and Raf/PLK
- Can ameliorate multiple dysregulated signaling transduction pathways in higher-risk MDS[b]

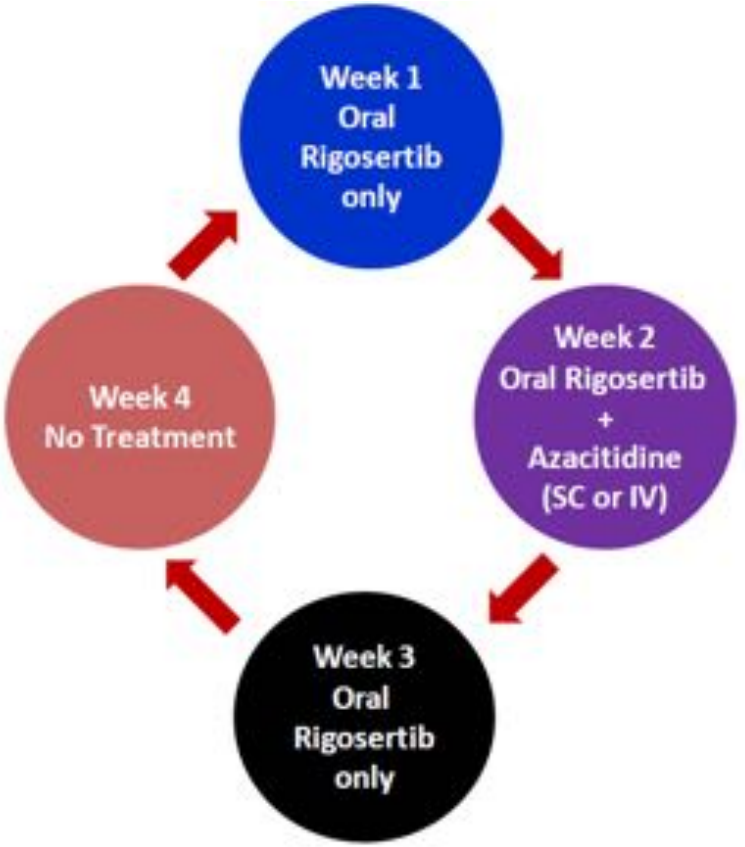
Rigosertib



RAS targeted novel mode of action



[a]Olivkar, S.K.,et al. (2016). "A Small Molecule RAS-Mimetic Disrupts Association with Effector Proteins to Block Signaling." Cell 165, 643-655
[b]Feng Xu, Qi He, Xiao Li, Chun-Kang Chang, et al: SCIENTIFIC REPORTS; 4 : 7310; DOI: 10.1038/srep07310



Navada et al, ASH 2018

HR-MDS: > 840 mg/day / HMA naive and HMA failure

Number of patients treated		74
Age	Median	69
	Range	42-90
Sex	Male	44 (59%)
	Female	30 (41%)
IPSS classification	Intermediate-1	24 (32%)
	Intermediate-2	26 (35%)
	High	21 (28%)
	Unknown	3 (4%)
IPSS-R classification	Low	3 (4%)
	Intermediate	14 (19%)
	High	23 (31%)
	Very high	33 (45%)
	Unknown	1 (1%)
Prior HMA therapy	Azacitidine	26 (35%)
	Decitabine	6 (8%)
	Both	3 (4%)

Navada et al, ASH 2018

HMA naive (≥ 840 mg/d)

Evaluable for response	29*
Overall response per IWG 2006	26 (90%)
CR+PR	10 (34%)
Complete remission (CR)	10 (34%)
Partial remission (PR)	0
Marrow CR + Hematologic Improvement	5 (17%)
Hematologic Improvement alone	3 (10%)
Marrow CR alone	8 (28%)
Stable disease	3 (10%)
Progression	0
Median duration of response (months)	12.2 (range, 0.1-24.2+)
Median duration of treatment (months)	7.8 (range, 0.7-25.1+)
Median time to initial/best response (cycles)	1/4

** Includes 2 patients treated with non-HMA, chemotherapy*

HMA failure (≥ 840 mg/d)

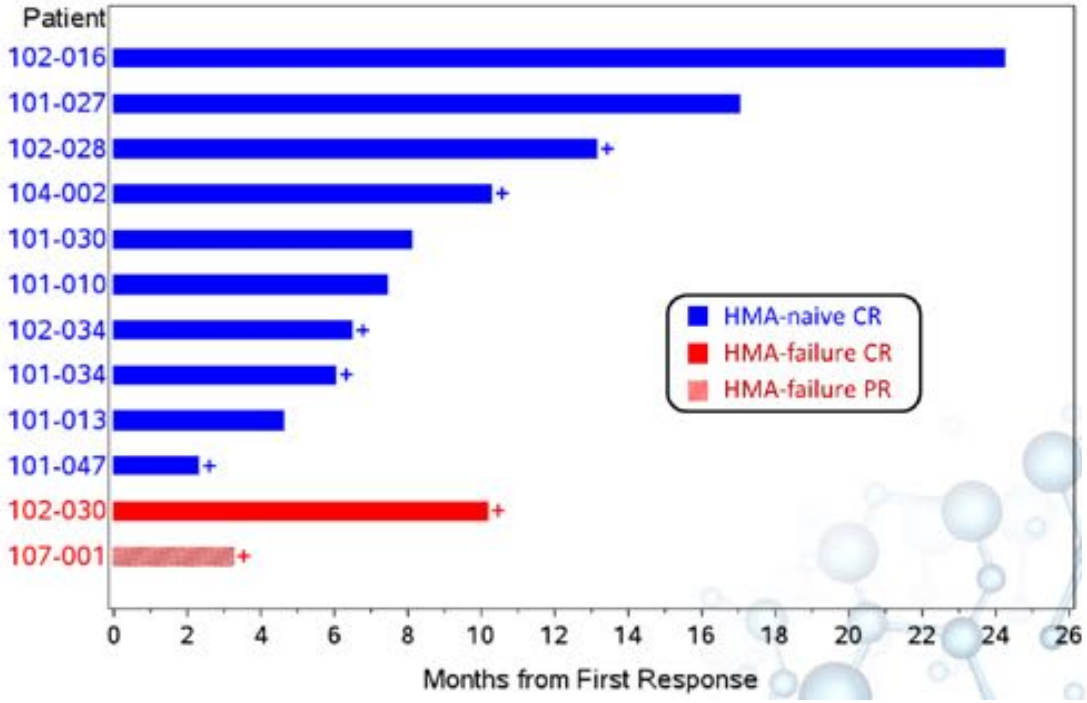
Evaluable for response	26*
Overall response per IWG 2006	14 (54%)
CR+PR	2 (8%)
Complete remission (CR)	1 (4%)
Partial remission (PR)	1 (4%)
Marrow CR + Hematologic Improvement	5 (19%)
Hematologic Improvement alone	2 (8%)
Marrow CR alone	5 (19%)
Stable disease	7 (27%)
Progression	5 (19%)
Median duration of response (months)	10.8 (range, 0.1-11.8+)
Median duration of treatment (months)	4.9 (range, 1.1-20.9+)
Median time to initial/best response (cycles)	2/5

** Includes 9 patients treated with non-HMA, chemotherapy in addition to HMA*

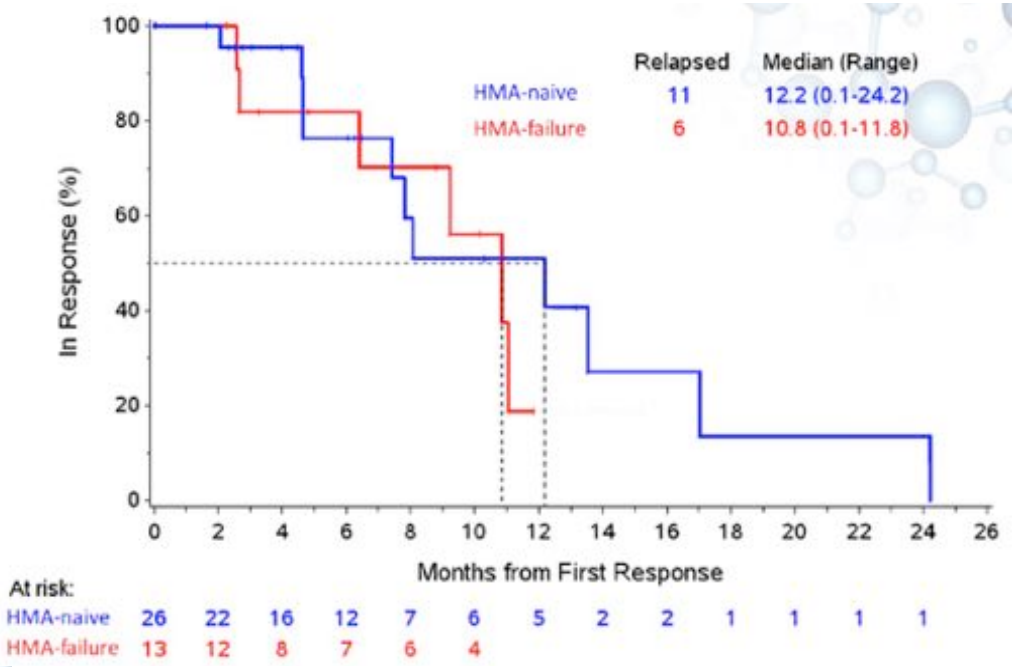
Similar results for doses > 1120 mg/day

Navada et al, ASH 2018

Duration of CR and PR



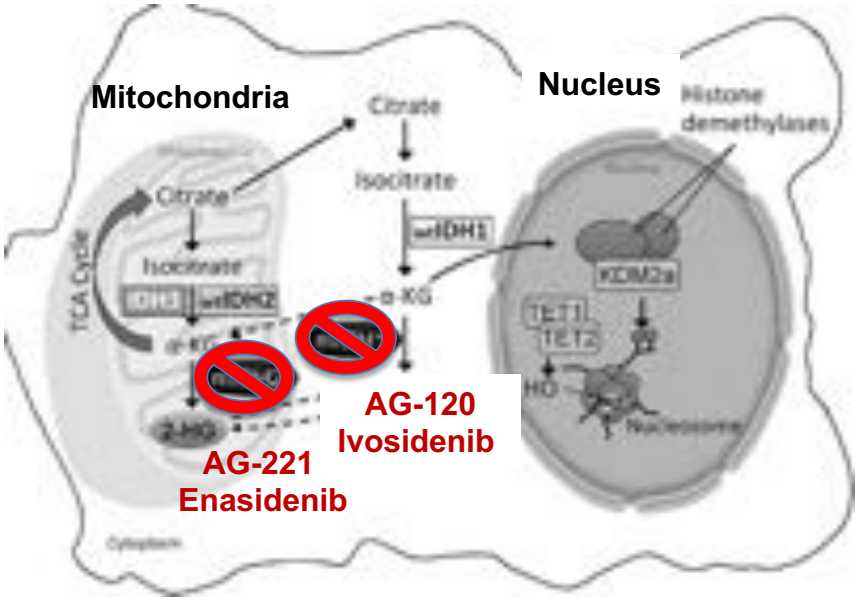
Duration of OR



Navada et al, ASH 2018

IDH mutations in AML/MDS

Mutated gene	AML	MDS
IDH1	7-14%	3%
IDH2	8–19%	~5%



- IDH enzymes catalyze citrate to α-ketoglutarate (α-KG)
- α-KG catalyzes histone demethylases and TET hydroxylation of 5-methylcytosine
- **Mutant IDH1/ IDH2** result in an increase of the oncometabolite, 2-hydroxyglutamate (2-HG)
- 2-HG induces a block of cell differentiation by inhibiting the chromatin-modifying enzymes, DNA and histone demethylases, which results in hypermethylated DNA, blocking cell differentiation

Medeiros et al, Leukemia 2016

Enasidenib: results in MDS

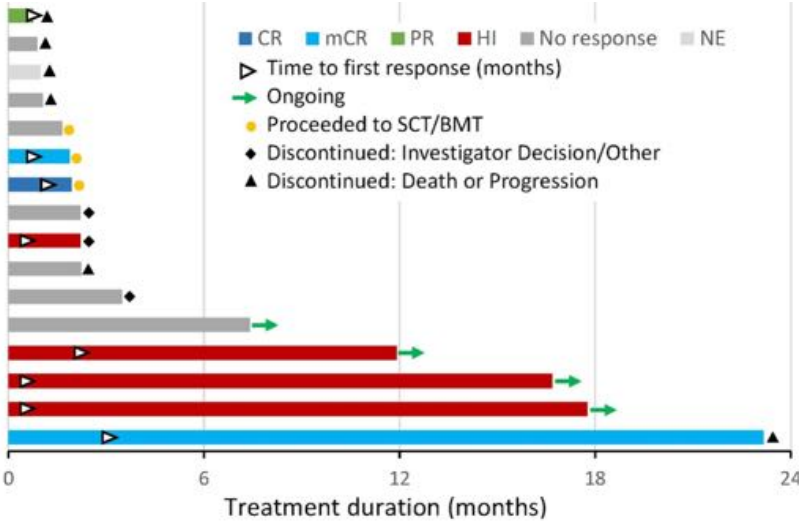
- Daily oral enasidenib 100 mg QD in 28-day cycles in16 MDS patients

Table 1. Baseline characteristics of MDS patients treated with enasidenib

Characteristic	MDS Patients N=16
Age (years), median (range)	67 (45, 78)
Gender, % male / % female	73 / 27
***IDH2* mutation**, % R140, % R172	88 / 12
ECOG performance status, n (%)	
0-1	12 (75)
2	4 (25)
Number of prior anti-cancer regimens, n (%)	
0	4 (25)
1	6 (38)
≥2	6 (38)
Type of prior MDS treatment, n (%)	
Hypomethylating agents	11 (69)
Lenalidomide	2 (13)
Others*	5 (31)
Untreated	4 (25)
Time since diagnosis (months), mean [SD]	15.7 [10.4]
IPSS risk status, n (%)	
Low / Intermediate-1	5 (31)
Intermediate-2 / High	8 (50)
Missing	3 (19)
IPSS-R risk status, n (%)	
Very Low / Low	3 (19)
Intermediate	2 (13)
High / Very High	8 (50)
Missing	3 (19)
ANC (10^9/L), median (min, max)	0.7 (0.2, 32.1)
Platelets (10^9/L), median (min, max)	64 (19, 246)
WBC (10^9/L), median (min, max)	2.0 (0.5, 44.4)
Hemoglobin (g/dL), median (min, max)	8.8 (7.3, 12.2)

*Vosaroxin, pracinostat, cytarabine and clofarabine, ruxolitinib, and sorafenib (n=1 pt each)
ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; ANC, absolute neutrophil count; WBC, white blood cells

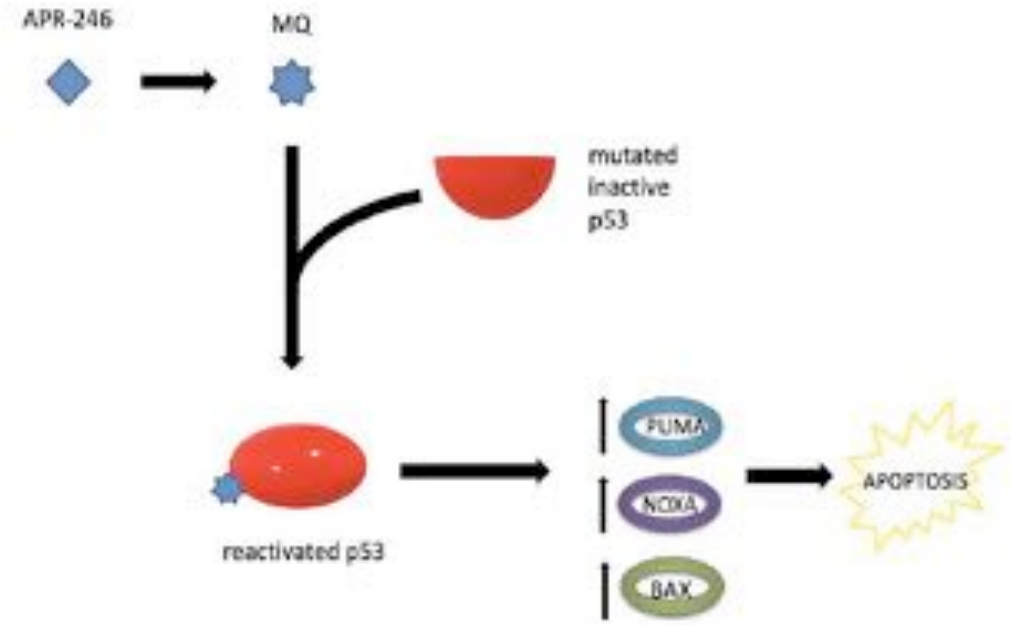
	MDS Patients (N=16) n (%)
Overall response rate (CR + PR + mCR + HI)	**8/15 (53)**
Best response	
Complete Remission*	1/9 (11)
Partial Remission*	1/9 (11)
Marrow CR*	2/9 (22)
Hematologic Improvement	4/15 (27)
Not Evaluable†	1 (6)



Stein EM, et al ASH 2016

Anti-TP53 drugs: APR-246

APR-246 is a prodrug that is converted to methylene quinuclidinone (MQ) and binds covalently to the mutant p53 core domain, restoring the upregulation of apoptotic transcriptional programs

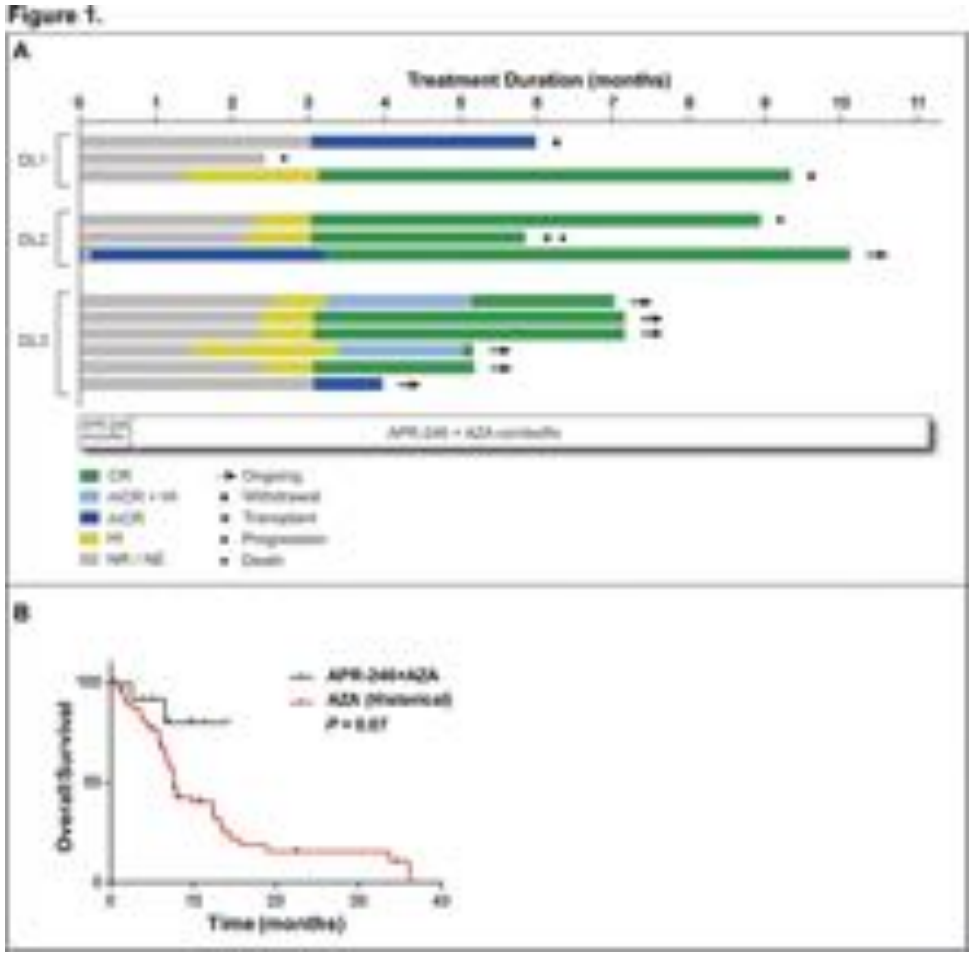


- APR-246 esc-doses IV daily over 4 days in a lead-in phase (days -14 to -10) followed by the same dose of APR-246 (days 1-4) + AZA 75 mg/m^2 SC/IV over 7 days (days 4-10 or 4-5 and 8-12) in 28 day cycles.
- 9 MDS, 3 AML

Sallman et al, ASH 2018

APR-246

- 11 of 12 pts were response evaluable with 1 pt discontinuing tx prior to 1st disease assessment.
- ORR by IWG was 100% (11/11) with 9 CR (82%) and 2 mCR (18%).
- Median time to first response was 70 days (4-91) and 1 CR patient achieved mCR and partial cytogenetic response after APR-246 lead-in
- All CR pts had high p53 positivity by IHC at baseline (25-80%) which normalized on serial assessment with the 2mCR pts having <5% p53+ at baseline.
- Serial NGS with a variant allele frequency (VAF) cutoff of 5% was negative in 73% of patients (8/11).



Sallman et al, ASH 2018

Acknowledgements

fondazione GIMEMA
FRANCO MANDELLI

AIRC

Metastatic disease: the key unmet need in oncology

Mynerva

Laboratorio di diagnostica avanzata oncoematologica
«Francesco Lo-Coco»

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