Icahn School of Medicine at Mount Sinai

Advances in the Treatment of The Myelodysplastic Syndrome - 2019

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The Myelodysplastic Syndrome

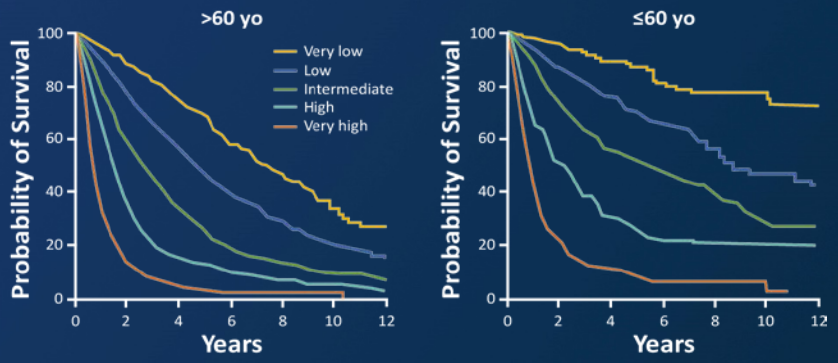
- Clonal Hematopoietic Stem Cell Disorder
- Median age 65-75 years
- Dominant clinical feature is bone marrow failure
- Majority of patients succumb to bleeding and infection
- Transformation to AML in 35-40% of Patients
- Smoldering leukemia death from bone marrow failure
- Treatment options limited include: HMA, iMIDS, ESAs and cytokines and stem cell transplant (15% of patients)

IPSS-R: Survival Outcomes

Estimated Overall Survival and Risk Category					
Score	**Risk Category**	**% of 7012 Patients**	**Median survival, years (95% CI)[a]**	**% of 6485 Patients**	**Median time to 25% AML evolution, years (95% CI)[b]**
≤1.5	**Very Low**	19	8.8 (7.8-9.9)	19	NR (14.5-NR)
>1.5-3	**Low**	38	5.3 (5.1-5.7)	37	10.8 (9.2-NR)
>3-4.5	**Intermediate**	20	3 (2.7-3.3)	20	3.2 (2.8-4.4)
>4.5-6	**High**	13	1.6 (1.5-1.7)	13	1.4 (1.1-1.7)
>6	**Very High**	10	0.8 (0.7-0.8)	11	0.73 (0.7-0.9)

[a]*P*<0.001; [b]*P*<0.001.
CI, confidence interval; NR, not reached.

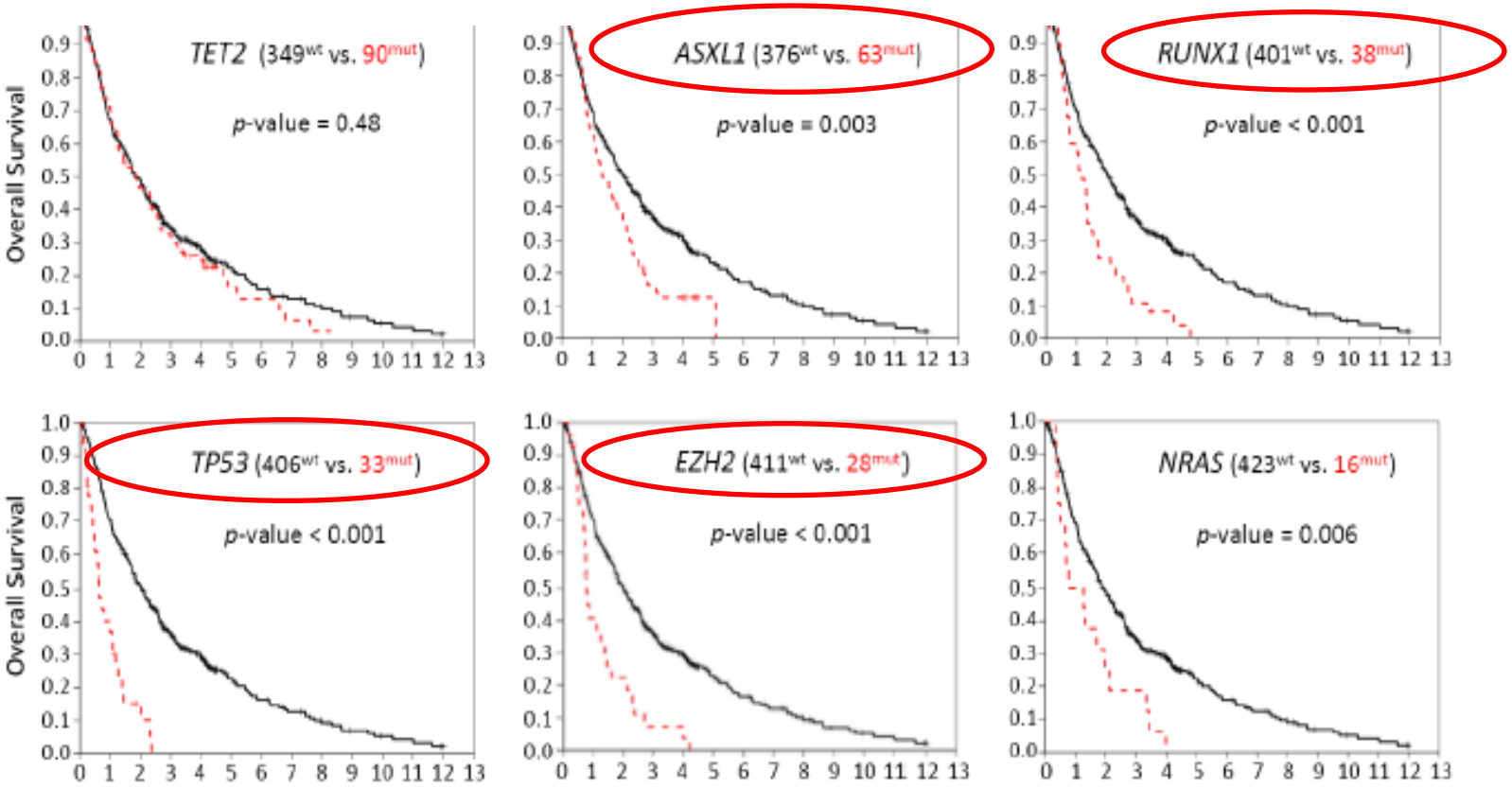
Survival Based on Patient Ages



The IPSS-R score can be extrapolated to generate an age-adjusted score (IPSS-RA) and demonstrates that patient age has an impact on survival

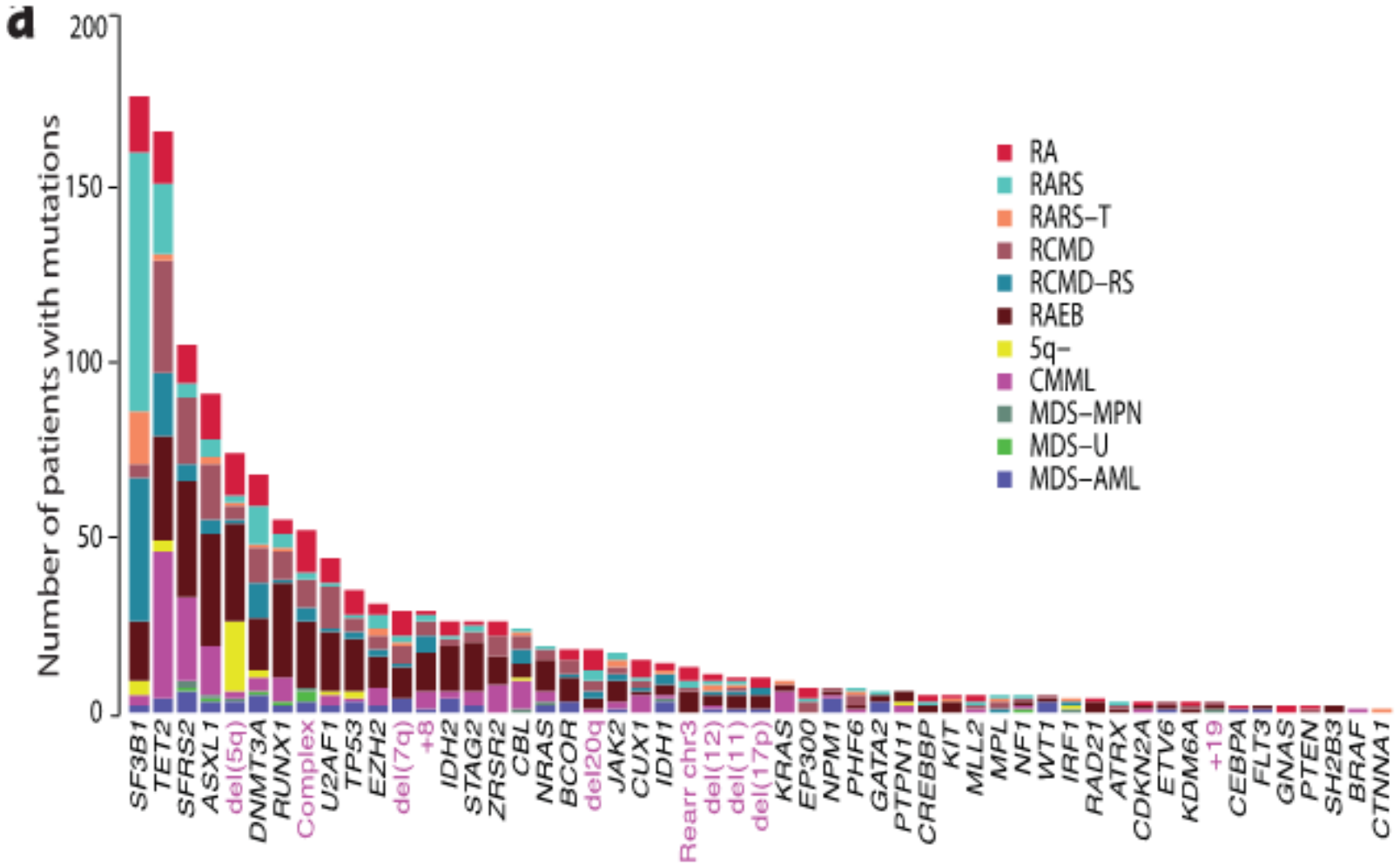
Greenberg PL et al. Blood. 2012;120(12):2454-65.

Mutations and Survival



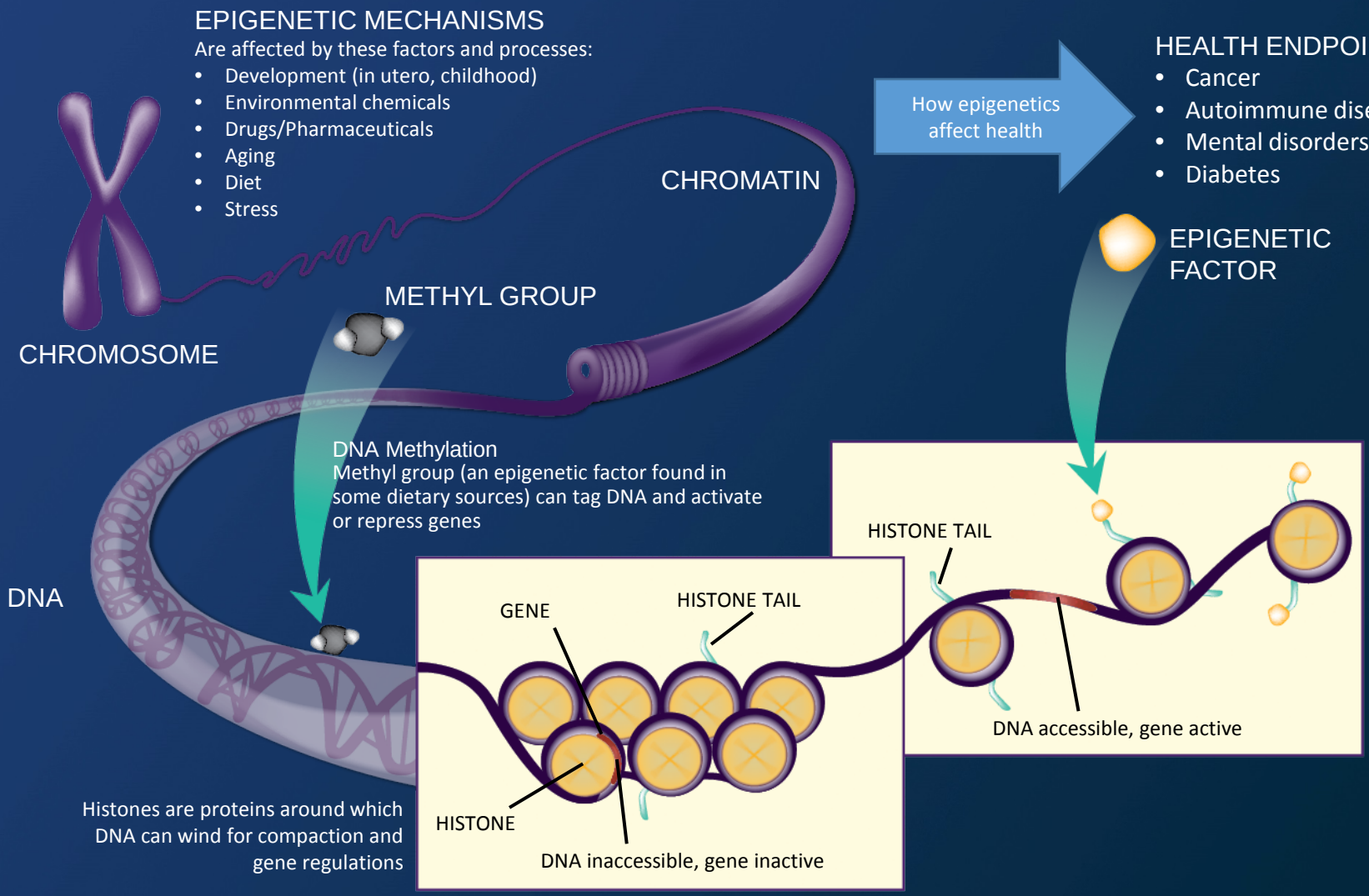
Bejar, et al. *N Engl J Med*. 2011.

Genomics of MDS



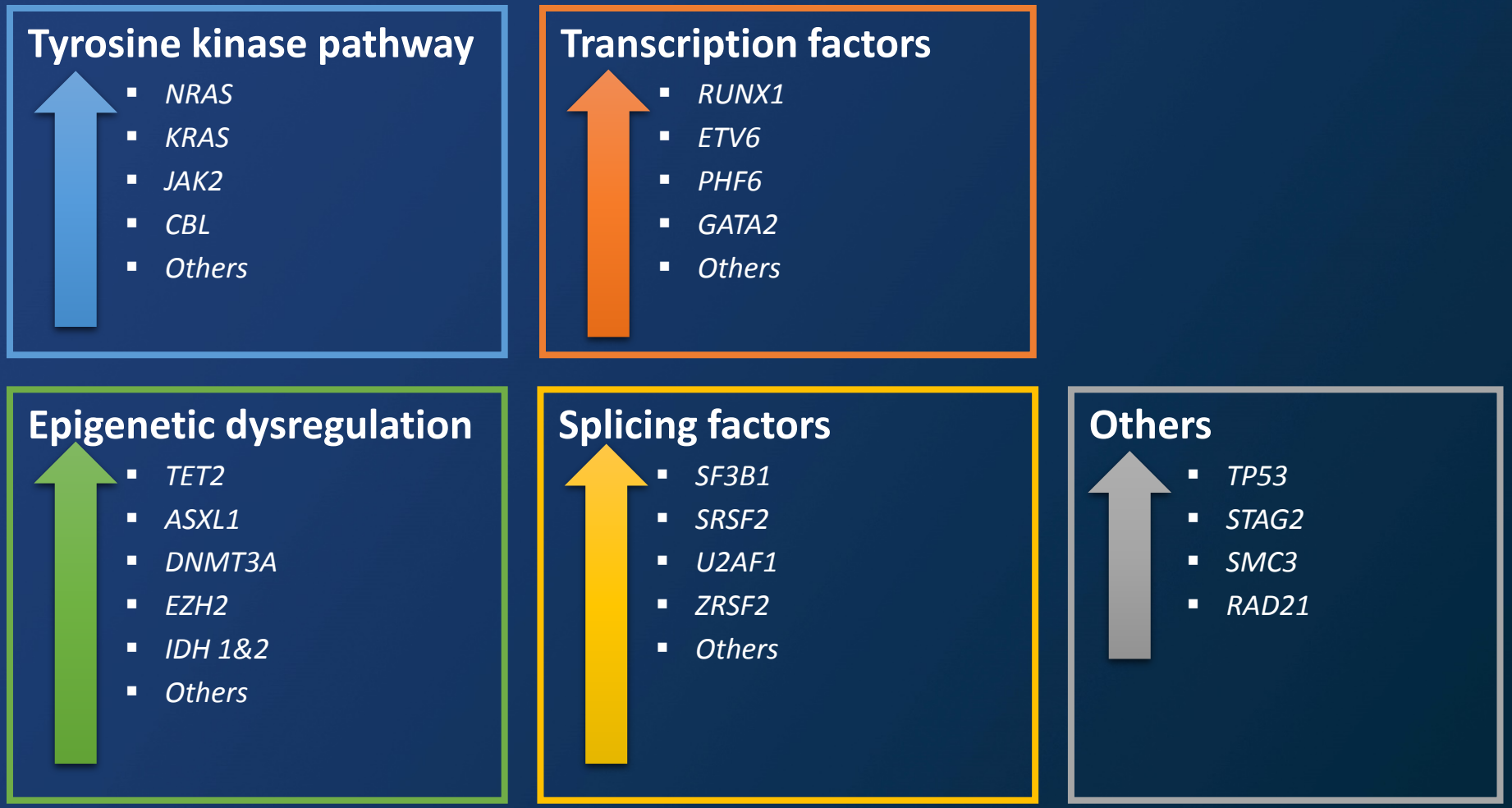
Papaemmanuil et al Blood 2013;122:3616-27

Epigenetic Changes Contribute to MDS



NIH. A Scientific Illustration of How Epigenetic Mechanisms Can Affect Health. https://commonfund.nih.gov/epigenomics/figure. Accessed May 8, 2016.

Somatic Mutations are Clustered in Specific Pathways Involved in MDS Pathogenesis

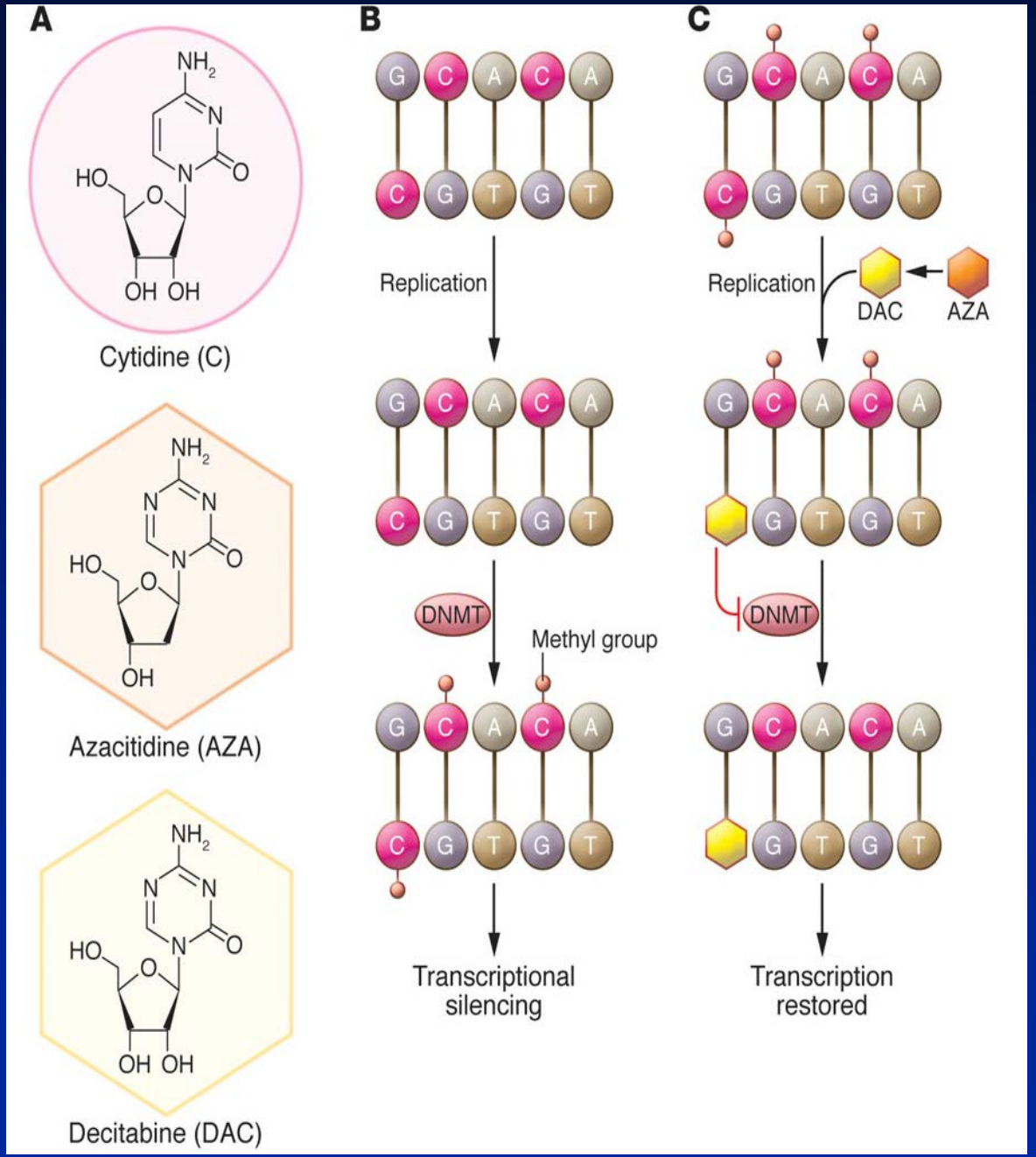


Bejar R, Steensma DP. Blood. 2014;124(18):2793-803.

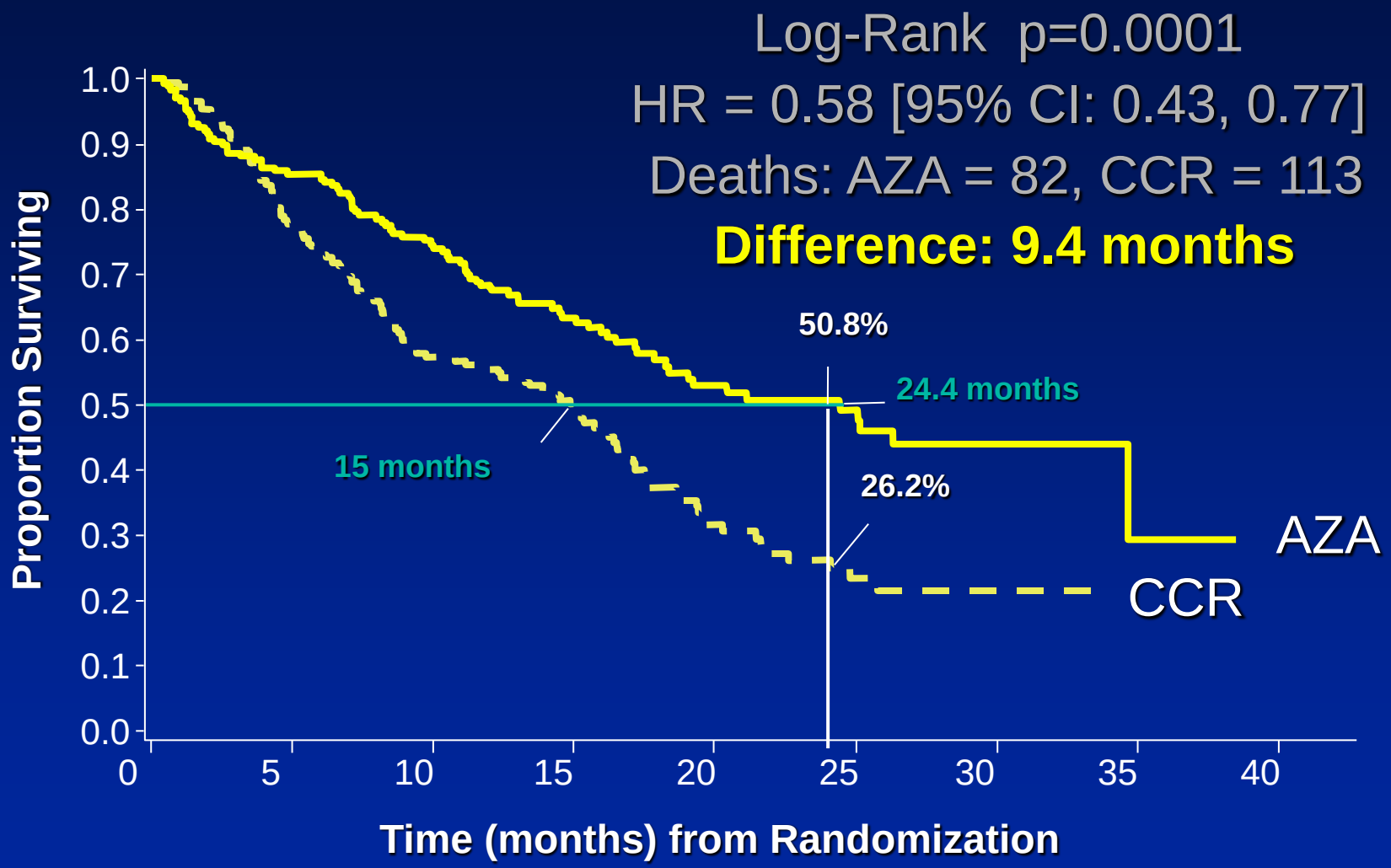
Goals of Care

- Higher Risk Disease
- IPSS-R – Very High, High
  - Blast %, Cytogenetics, blood counts, gene mutations
  - Goals –
    - Survival
    - Symptom relief
    - Reduce/eliminate risk of leukemic transformation
    - QOL
    - Eliminate transfusions

Methyltransferase Inhibitor Induced DNA Hypomethylation and Gene Activation



Overall Survival: Azacitidine vs CCR
ITT Population

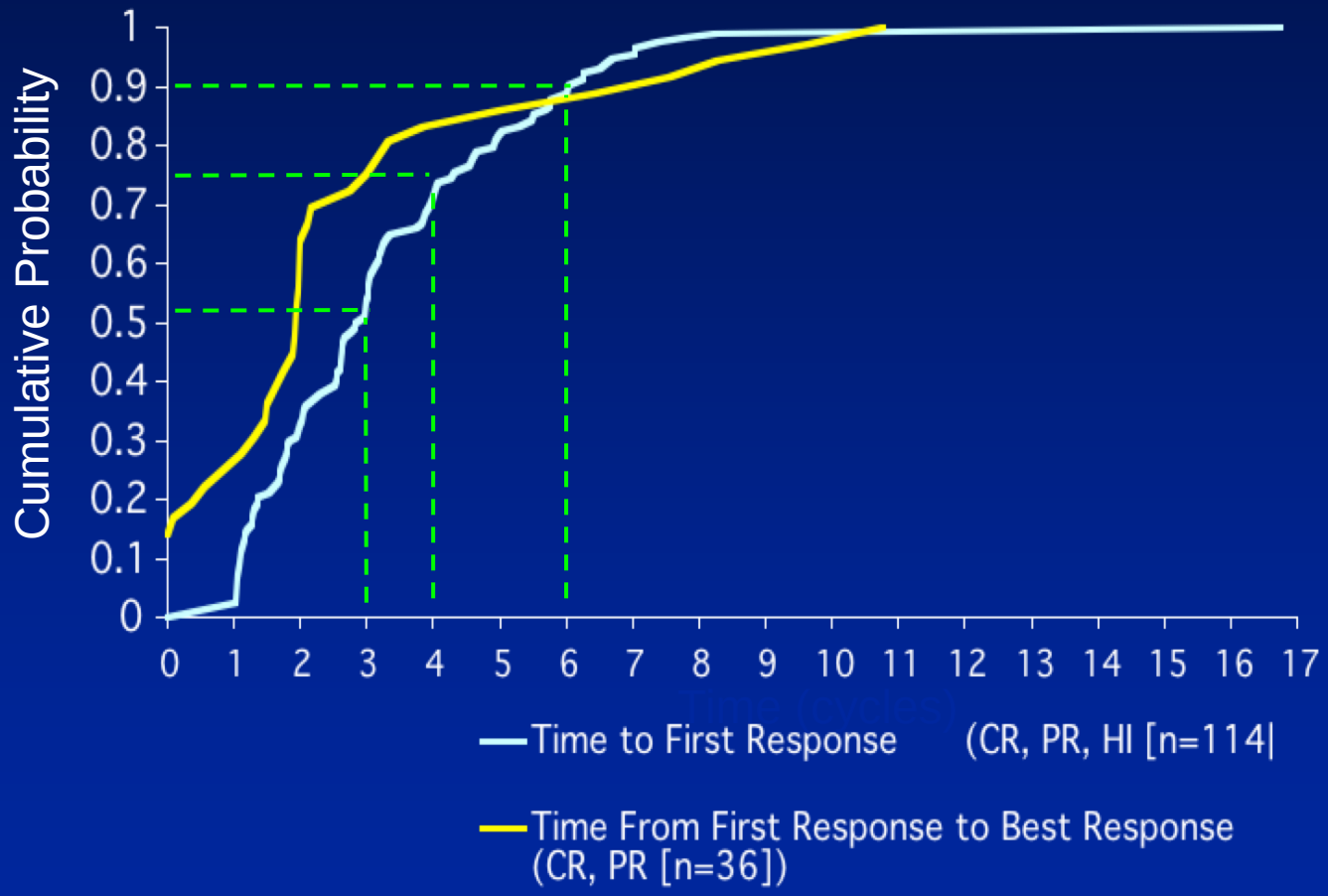


Fenaux et al Lancet Oncology 2009

Summary of Phase III Clinical Trials Using HMA agents In MDS

Trial	Drug	# of pts	Dose/ duration	Route	ORR CR/PR /HI%	Time to AML or Death	OS	P value
CALGB 9221 Silverman JCO 2002	AZA	99	75 mg/m2/d x7	SC	60% 7/16/37	21	20	P=0.1 P=0.03
	BSC	92			5%	12	14	
AZA-001 Fenaux Lancet Oncology 2009	AZA	179	75 mg/m2/d x7	SC	51% 17/12/22	17.8	24.5	P=0.0001
	CCR	179			29%	11.5	15	
D-0007 Kantarjian JCO 2005	DEC	89	Q8h x3 d	IV	30% (9/8/13)	12.1	14	P=0.636
	BSC	81			7% (0/0/7)	7.8	14.9	
EORTC 06011	DAC	119	Q8h x3 d	IV	34% (13/6/15)	8.8	10.1	P=0.38
Lubbert JCO 2010	BSC	114			2%	6.1	8.5	

Times to First Response and From First Response to Best Response Using IWG MDS Response Criteria



Silverman et. al. JCO 24;3895, 2006

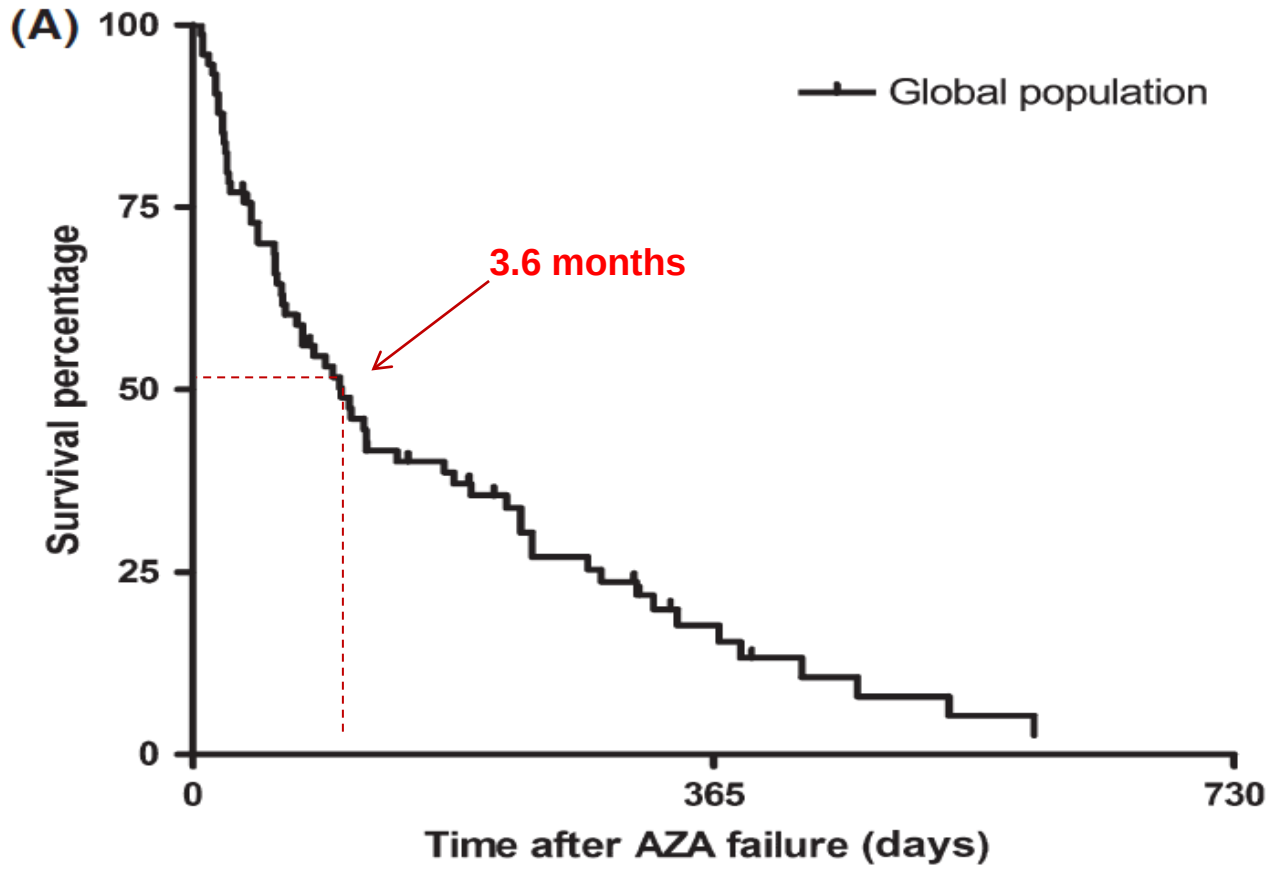
Key Points - Azacitidine

- Responses occur in 45 to 50% of patients
- Treatment is associated with improved Quality of Life and reduction of symptoms over what transfusions can achieve
- There is a 2.3 fold reduction in the risk of transformation to AML
- Treatment is associated with a significant increase in survival compared to control
- Continued treatment with maintenance azacitidine is associated with ongoing benefit and improved quality of response
- 4-6 Cycles of treatment to assess response

What are the major needs in MDS?
(problems that limit significant cure rate)

- **Identification of poor prognosis "lower risk" patients with higher risk behavior**
- **Development of new therapies for patients with higher risk MDS**
- **Understanding mechanisms of resistance to epigenetic modulators in MDS (critical)**
- **How to effectively combine agents and control toxicity**
- **Understanding mechanisms of transformation to AML**
- **Incorporation of alloSCT in MDS**
- **Minimizing risk of GVHD and relapse post alloSCT in MDS**

Outcome after azacitidine failure: patients with secondary AML – survival

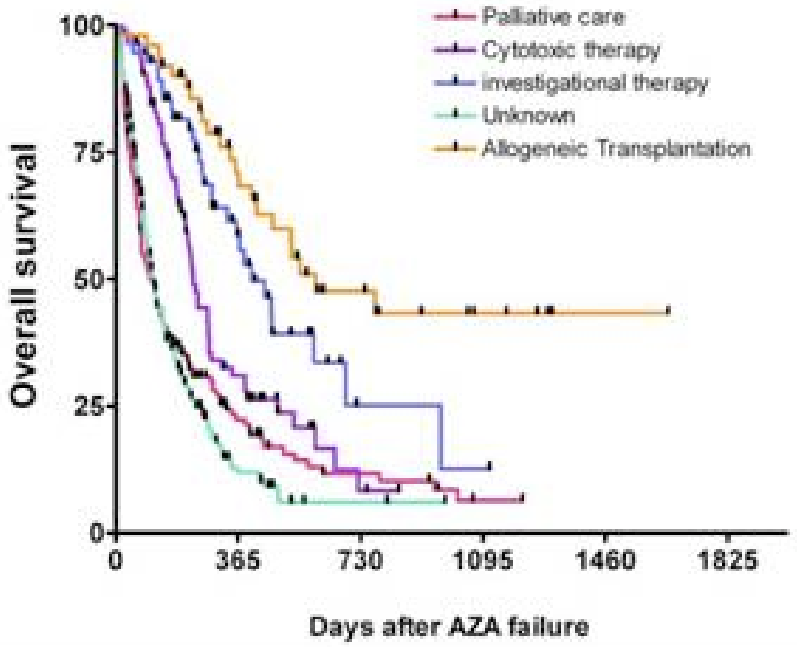


Prébet T, et al. Br J Haematol 2012;157:762–74

Outcome of Patients Treated for Myelodysplastic Syndromes and Secondary Acute Myeloid Leukemia After Azacitidine Failure

At a median follow-up of 15 months after azacitidine failure, the median OS of patients with MDS or secondary AML (sAML) was 6 months.

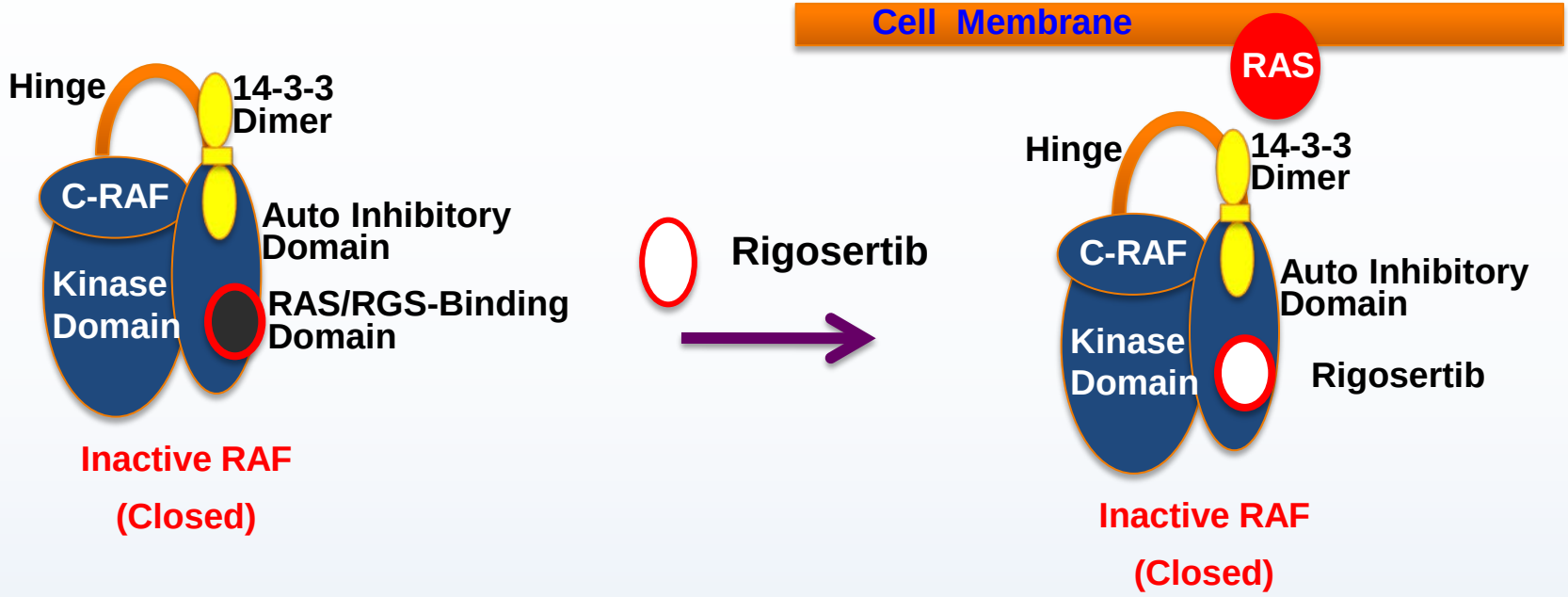
Figure 1

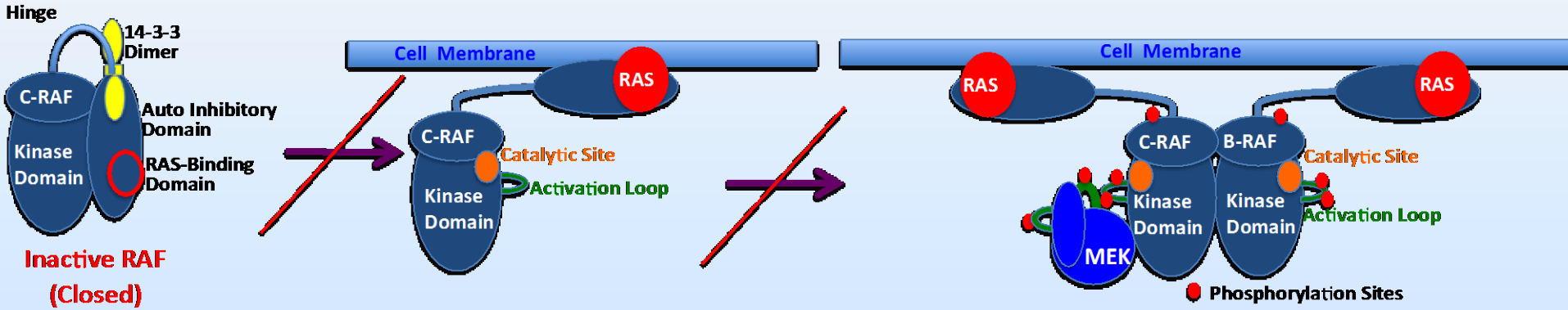


Type of salvage	N=	Response rate*	Median OS
Unknown (UNK)	215	NA	3.6 months
Palliative care (PC)	160	NA	3.3 months
Cytotoxic therapy (CT)	84	1/25 and 5/33**	7.6 months
Investigational therapy (IT)	56	4/39	13.2 months
Allogeneic Transplantation (ASCT)	50	17/25	18.3 months

Prébet T, et al. Br J Haematol 2012;157:762–74

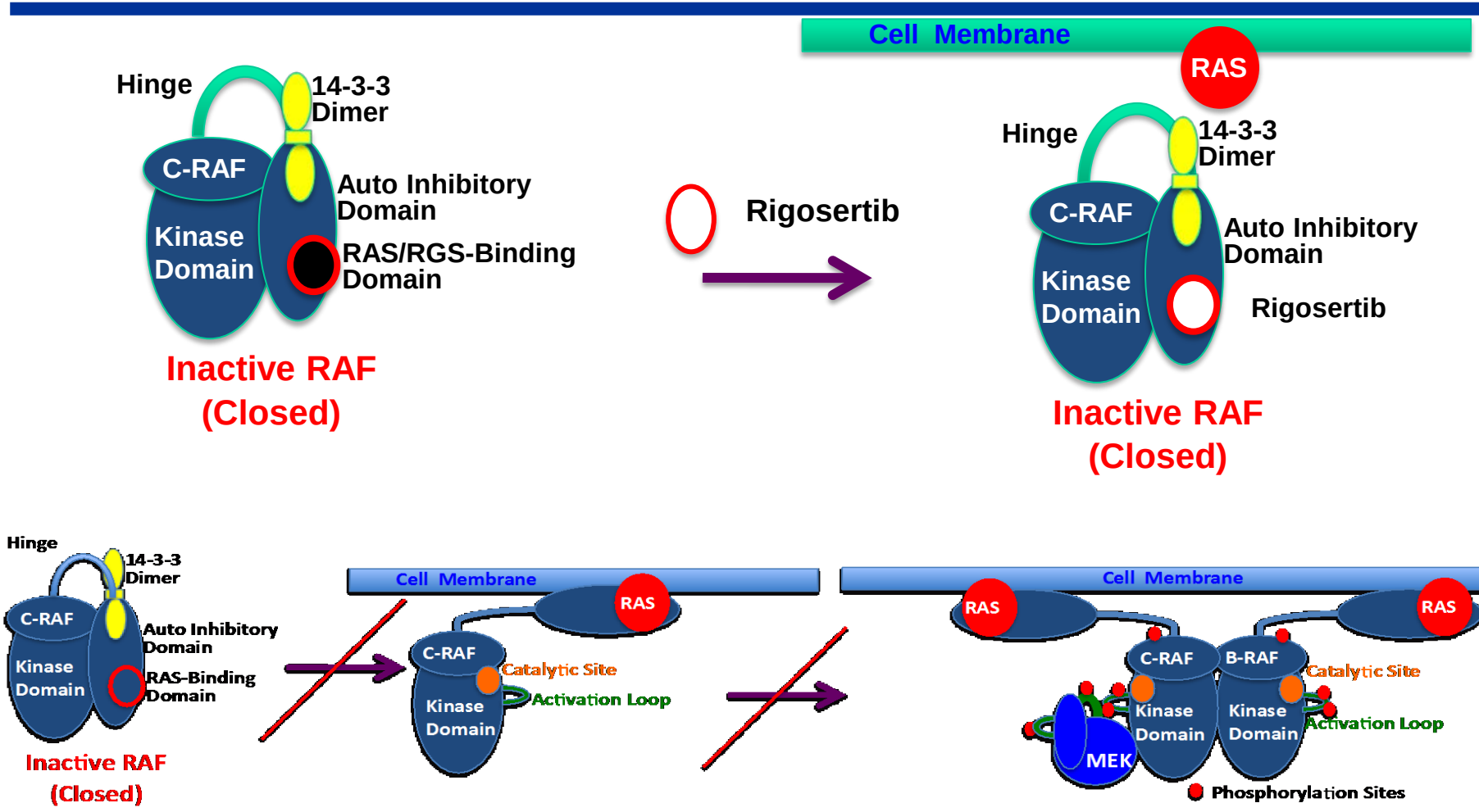
Binding of Rigosertib to RAF Disrupts RAS-RAF Interaction





Athuluri-Divakar et al., 2016, Cell 165, 643–655

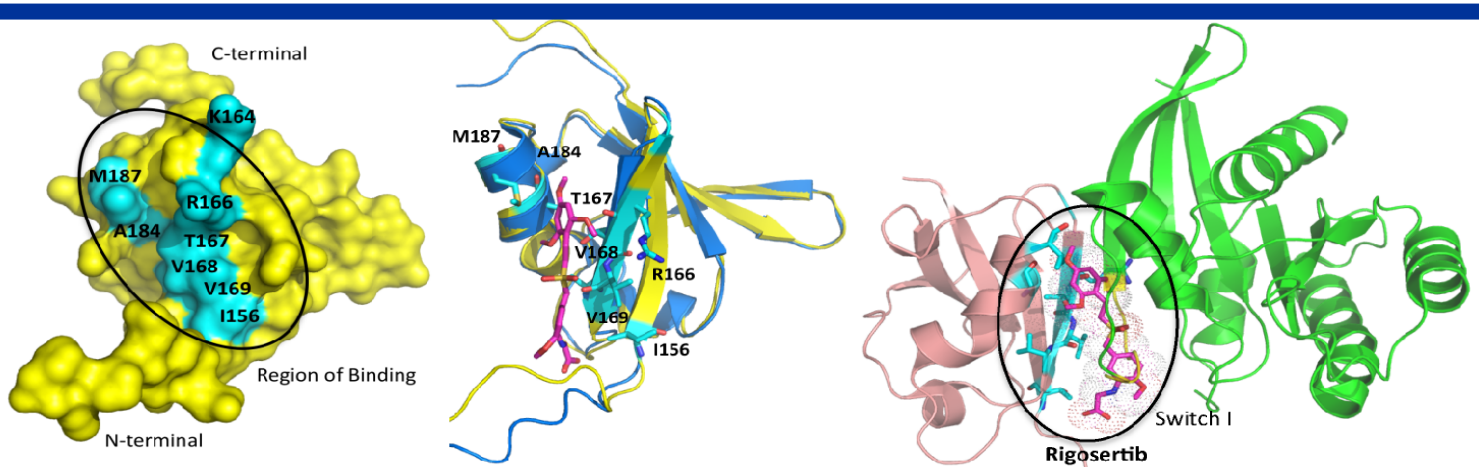
Binding of Rigosertib to RAF Disrupts RAS-RAF Interaction



Athuluri-DivakarCell *165*, 643–655, April 21, 2016

P Reddy

Mutations in the RBD domain that abolish binding of Rigosertib also abolish Binding of RAS



D

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BRBD  155 PIVRVFLPNKQRTVVEARCGVTVRDSLKKALMMRGLIPECCAVYRIQ 201
CRBD   56 NTIRVFLPNKQRTVVNVRNGMSLHDCLMKALKVRGLQPECCAVFRLL 102
ARBD   19 GTVKVYLPNKQRTVVTVRDGMSVYDSLDKALKVRGLNQDCCVVYRLI  65
          :::*:*********  .* *::: *.* *** :***   :**.*:*:
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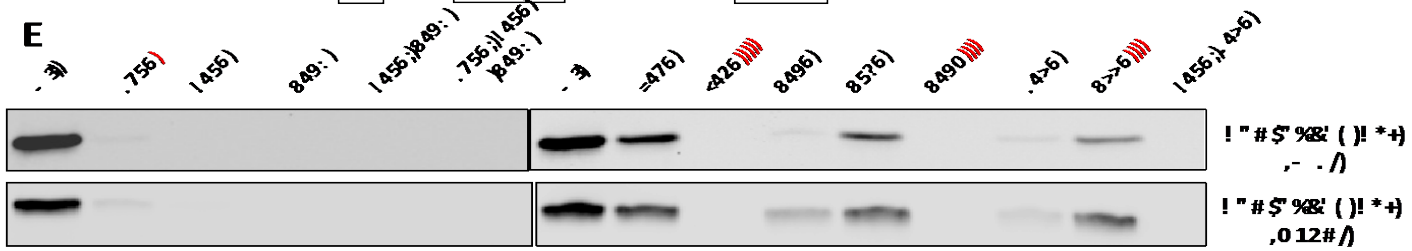

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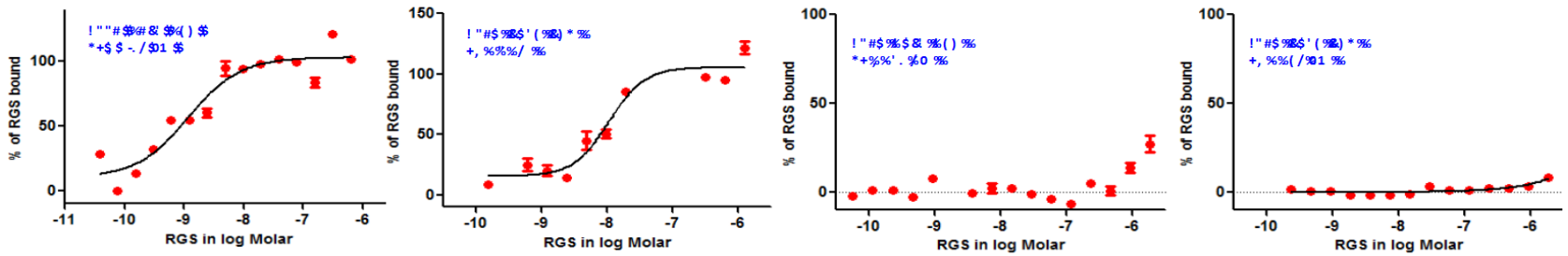
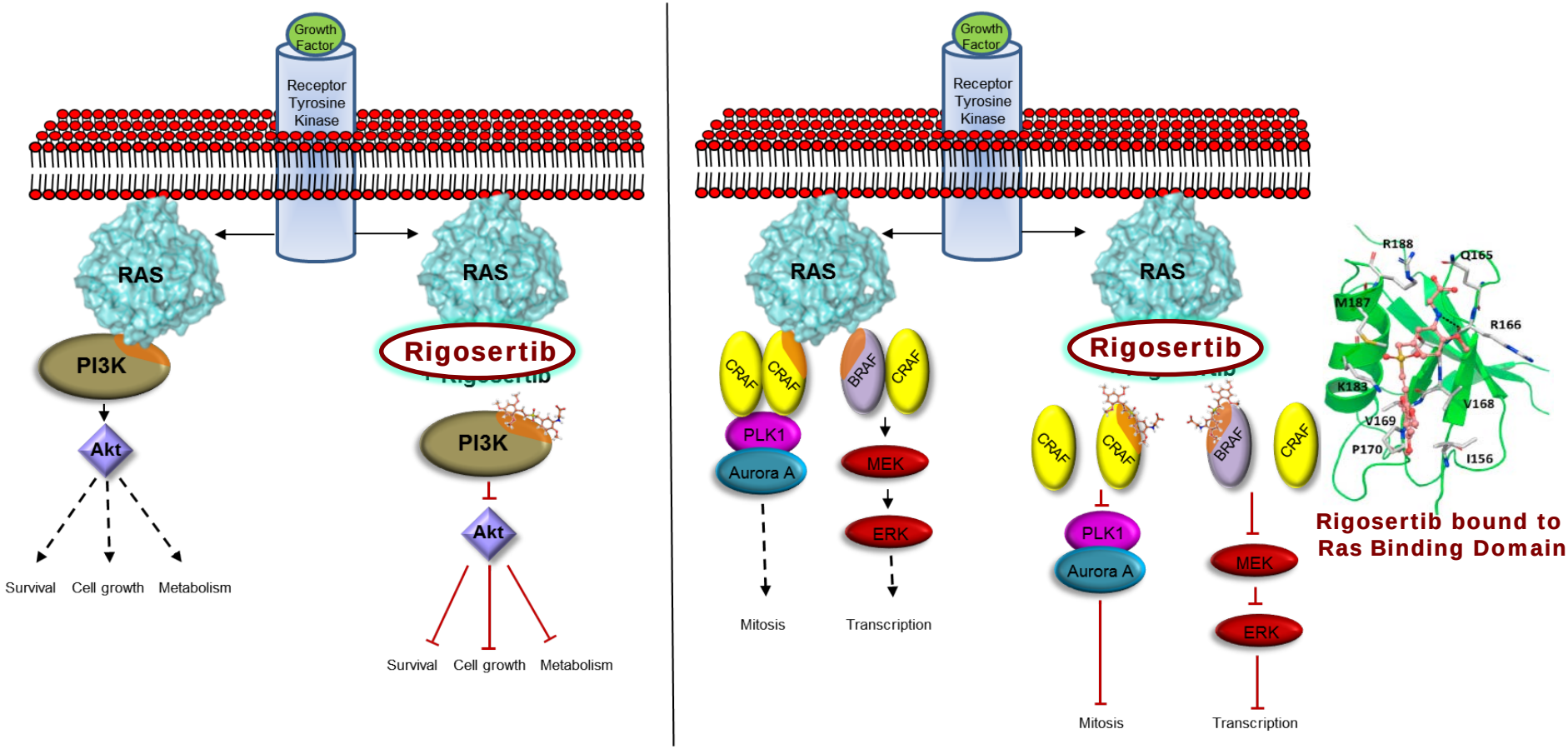


P Reddy

Athuluri-DivakarCell *165*, 643–655, April 21, 2016

Novel Mechanism of Action Presents Opportunities for Rasopathies

Rigosertib blocks downstream signaling by RAS effectors including PI3K and RAF by binding to Ras Binding Domain (RBD) found in many effector proteins



Athuluri-DivakarCell *165*, 643–655, April 21, 2016

SCIENTIFIC REPORTS | 4 : 7310 | DOI: 10.1038/srep07310

2014

Rigosertib as a selective anti-tumor agent can ameliorate multiple dysregulated signaling transduction pathways in high-grade myelodysplastic syndrome

Feng Xu, Qi He, Xiao Li, Chun-Kang Chang, Ling-Yun Wu, Zheng Zhang, Li Liu, Wen-Hui Shi, Yang Zhu, You-Shan Zhao, Shu-Cheng Gu, Cheng-Ming Fei, Juan Guo, Dong Wu & Liyu Zhou

Department of Hematology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital.

Rigosertib has demonstrated therapeutic activity for patients with high-risk myelodysplastic syndrome (MDS) in clinical trials. However, the role of rigosertib in MDS has not been thoroughly characterized. In this study, we found out that rigosertib induced apoptosis, blocked the cell cycle at the G2/M phase and subsequently inhibited the proliferation of CD34+ cells from MDS, while it minimally affected the normal CD34+ cells. Further studies showed that rigosertib acted via the activation of the P53 signaling pathway. Bioinformatics analysis based on gene expression profile and flow cytometry analysis revealed the abnormal activation of the Akt-PI3K, Jak-STAT and Wnt pathways in high-grade MDS, while the p38 MAPK, SAPK/JNK and P53 pathways were abnormally activated in low-grade MDS. Rigosertib could markedly inhibit the activation of the Akt-PI3K and Wnt pathways, whereas it activated the SAPK/JNK and P53 pathways in high-grade MDS. A receptor tyrosine kinase phosphorylation array demonstrated that rigosertib could increase the activation of RET and PDGFR-β while reducing the activation of Tie2 and VEGFR2 in MDS cells. Taken together, these data indicate that rigosertib is a selective and promising anti-tumor agent that could ameliorate multiple dysregulated signaling transduction pathways in high-grade MDS.

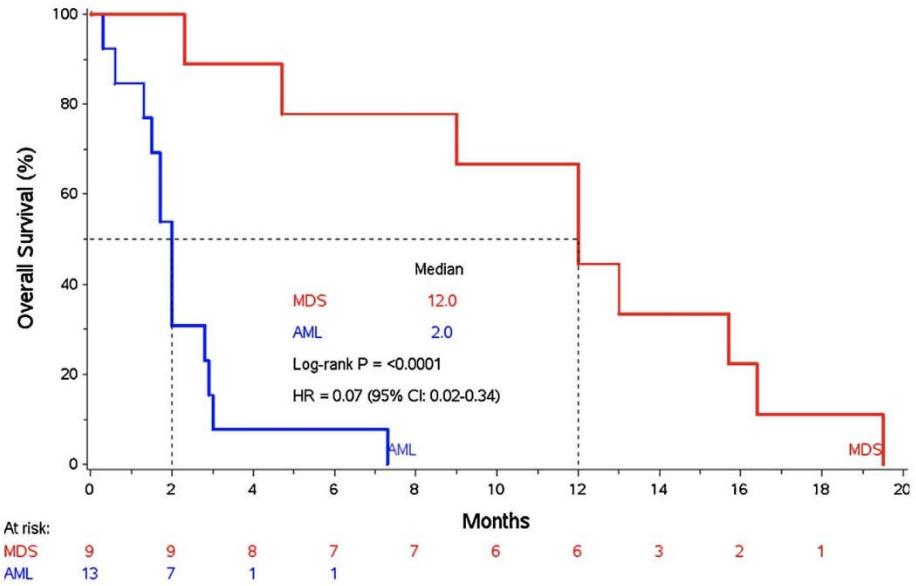
Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

A phase 1/2 study of rigosertib in patients with myelodysplastic syndromes (MDS) and MDS progressed to acute myeloid leukemia



Navada et al Leuk Res 64:10-16, 2018

Single-agent IV Rigosertib for HR-MDS Failing HMA

Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial

*Guillermo Garcia-Manero, Pierre Fenaux, Aref Al-Kali, Maria R Baer, Mikkael A Sekeres, Gail J Roboz, Gianluca Gaidano, Bart L Scott, Peter Greenberg, Uwe Platzbecker, David P Steensma, Suman Kambhampati, Karl-Anton Kreuzer, Lucy A Godley, Ehab Atallah, Robert Collins Jr, Hagop Kantarjian, Elias Jabbour, Francois E Wilhelm, Nozar Azarnia, Lewis R Silverman, for the ONTIME study investigators**

Summary

Background Hypomethylating drugs are the standard treatment for patients with high-risk myelodysplastic syndromes. Survival is poor after failure of these drugs; there is no approved second-line therapy. We compared the overall survival of patients receiving rigosertib and best supportive care with that of patients receiving best supportive care only in patients with myelodysplastic syndromes with excess blasts after failure of azacitidine or decitabine treatment.

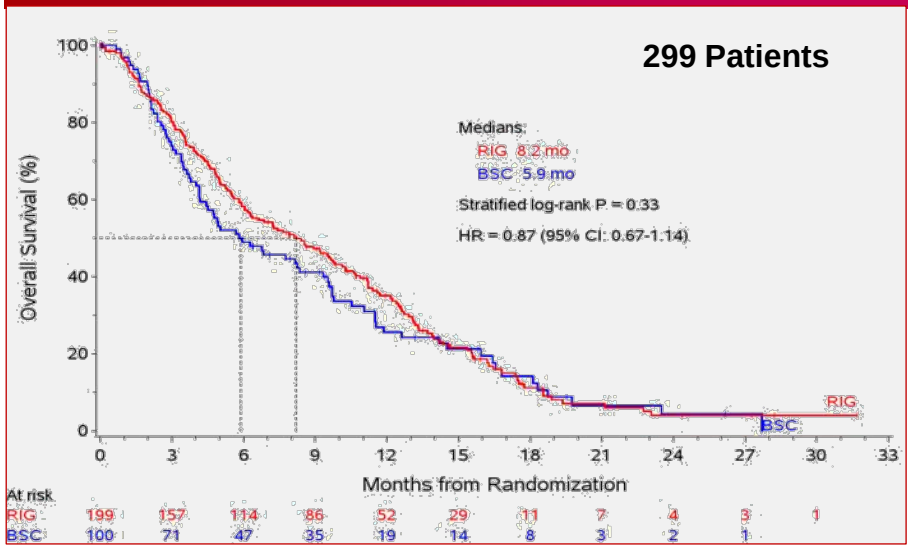
Lancet Oncol 2016

Published Online
March 8, 2016
http://dx.doi.org/10.1016/S1470-2045(16)00009-7

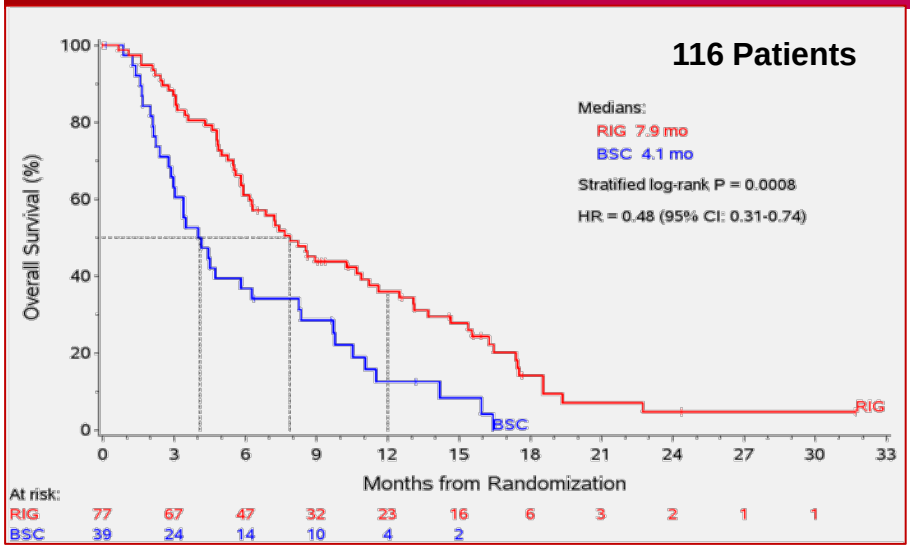
Garcia-Manero et al. Lancet Oncology 2016

Patient Population for Phase 3 INSPIRE Trial from Rigosertib ONTIME Trial

ITT for ONTIME Trial



Subpopulation for INSPIRE Trial (ONTIME subset)



- ITT OS analysis of ONTIME – HR= 0.87; NS survival benefit
- ITT OS of proposed INSPIRE population – HR = 0.48; P = 0.0008

*Guillermo Garcia-Manero, Pierre Fenaux, Aref Al-Kali, Maria R Baer, Mikkael A Sekeres, Gail J Roboz, et al. Rigosertib versus best supportive care for patients with higher-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial; *The Lancet Oncology* 2016 (17): 496–508

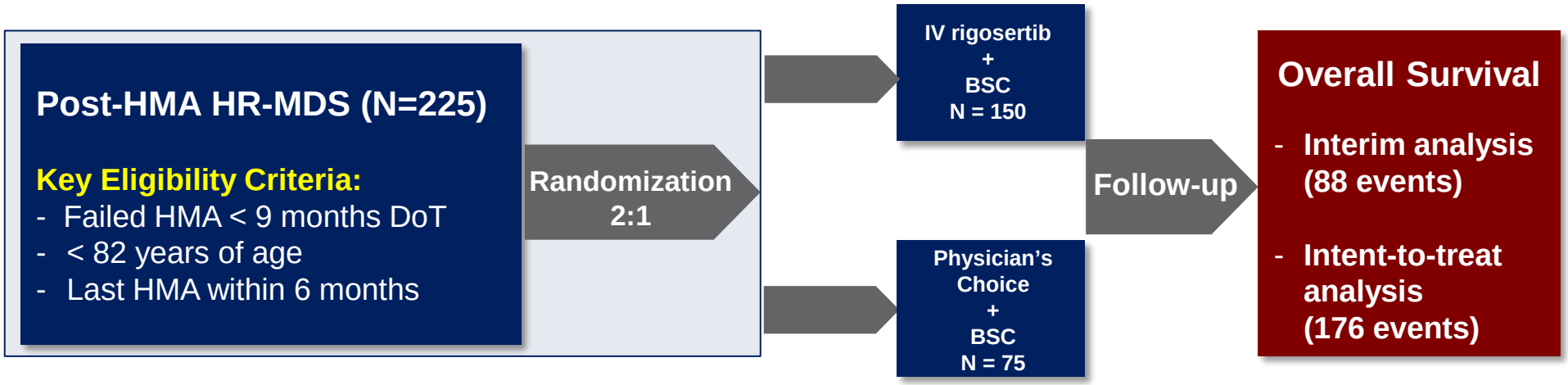
Garcia-Manero et al. Lancet Oncology 2016

ONTIME Trial: ITT Subgroups Correlated with Better Survival Benefit

Subgroup	Rigosertib		BSC		HR (95% CI)	p-value
	N	Median (mos)	N	Median (mos)		
Monosomy 7	16	5.6	13	2.8	0.24 (0.09-0.66)	0.003
Trisomy 8	22	9.5	8	4.5	0.34 (0.12-0.95)	0.035
Very high risk per IPSS-R	93	7.6	41	3.2	0.56 (0.37-0.84)	0.005

Garcia-Manero et al. Lancet Oncology 2016

INSPIRE:
Rigosertib Phase 3 Trial



- Statistical analysis: two analysis planned

  1. Power 0.80; Target HR < 0.625; (reduce mortality by > 37.5%)
  2. α for ITT = 0.04; α for IPSS-R VHR = 0.01
  3. Trial can succeed in two ways: ITT population or IPSS-R Very High Risk

- Genomic sequencing of patient samples

Commentary on new trial in recent publication: Emilio P Alessandrino, Matteo G Della Porta. Novel trial designs for high-risk myelodysplastic syndromes;*The Lancet Oncology* 2016 (17): 410–412

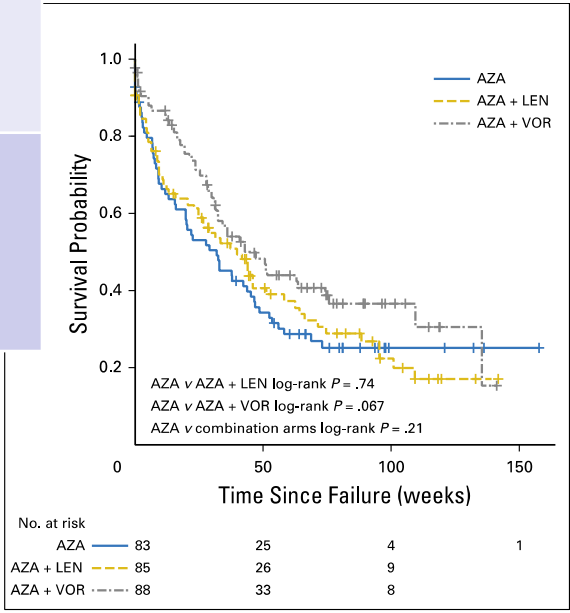
Experience with Hypomethylating Agents in Combination in MDS/AML

	Disease	No	Dose (mg/m2) Schedule	CR	ORR
Gore	MDS/AML	36	azacitidine/phenylbutyrate	14%	38%
Prebert/Gore	MDS/AML	136	azacitidine/entinostat	12%	44%
			azacitidine	7%	43%
Soriano	MDS/AML	53	azaC/VPA/ATRA	22%	42%
Garcia-Manero	MDS/AML	37	azacitidine/MGCD0103	11%	52%
Silverman	MDS/AML	23	azacitidine/vorinostat	48%	87%
				61%CRi	
Garcia-Manero	AML/MDS	54	decitabine/VPA	19%	22%
	AML	10		40%	50%
Kirschbaum	MDS/AML	60	decitabine/Vorinostat	22%	45%
Blum	AML	25	decitabine/VPA	16%	44%
Issa	MDS/AML	31	decitabine/vorinostat	3%	17%
Yee	MDS/AML	27	decitabine/vorinostat	4%	16%

Navada, Steinmann, Lubbert, Silverman JCI 2014

Randomized Phase II Study of Azacitidine alone or in Combination with Lenalidomide or Vorinostat in Higher-Risk MDS or CMMoL: SWOG 1117

	AZA 92	AZA+LEN 93	AZA+VOR 92	TOTAL
ORR	35 (38)	46 (49)	25 (27)	106 (38)
CR/PR/HI %	24/0/14	24/1/25	17/1/9	22/1/16
Med ORR dur months	10	14	15	14

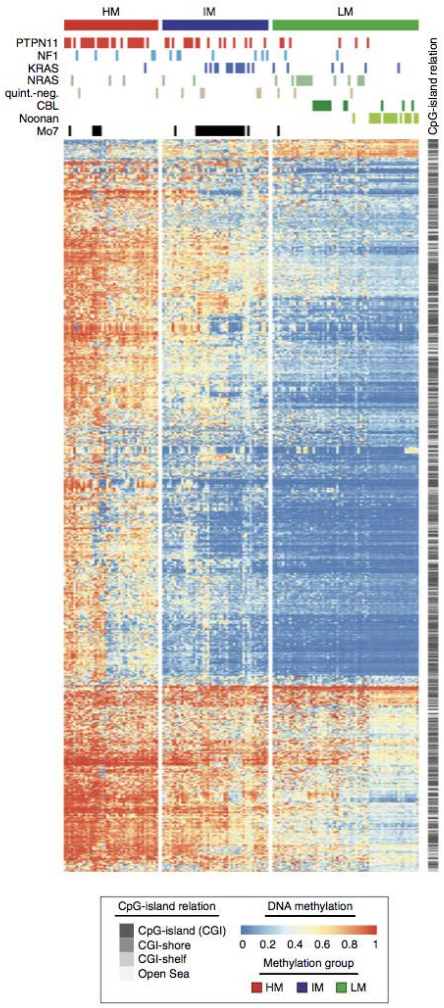


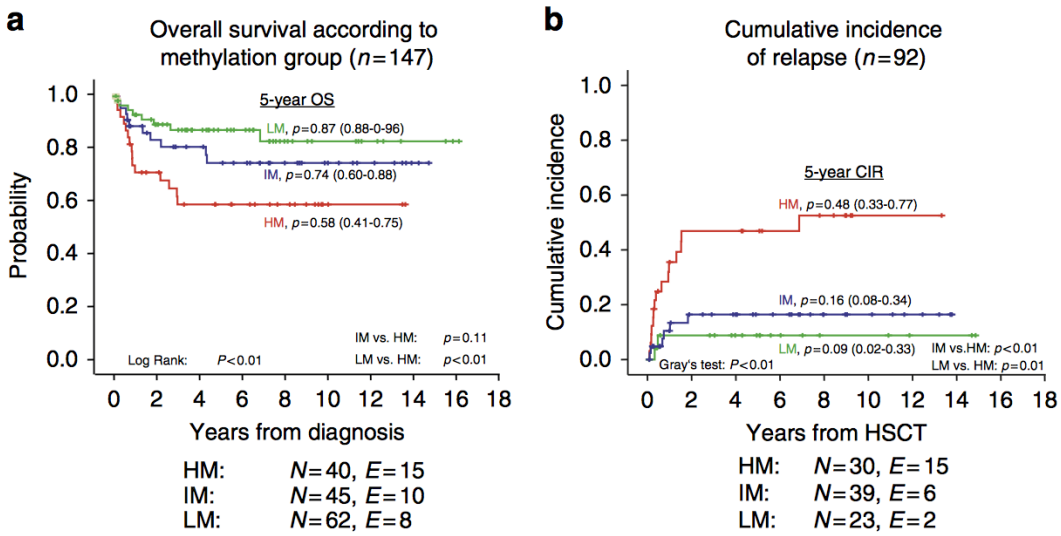
Sekeres et al JCO 35:2745-2753, 2017

JMML: A Well Studied Rasopathy involving Blood Cells

- Unique disorder of infancy caused by proliferation of monocytes/granulocytes; infiltrates the spleen/liver, intestines and lungs
- 2% of pediatric hematologic malignancies (in the US about 50 new cases per year)
- Median survival <1 year
- Fatal; allogeneic stem cell transplant only curative approach
- 5 year survival 50%
- KRAS, NRAS, PTPN11 mutations in 50%
- Recently new mutations identified result in activation of Ras Jak/Stat pathway

RAS-pathway mutation patterns define epigenetic subclasses in juvenile myelomonocytic leukemia





HM (hypermethylation) group associated with PTPN11 mutations and poor outcome
LM (low methylation group) group associated with patients with Noonans, NRAS and low-risk features
IM (intermediate methylation) associated with monosomy 7 and KRAS mutations

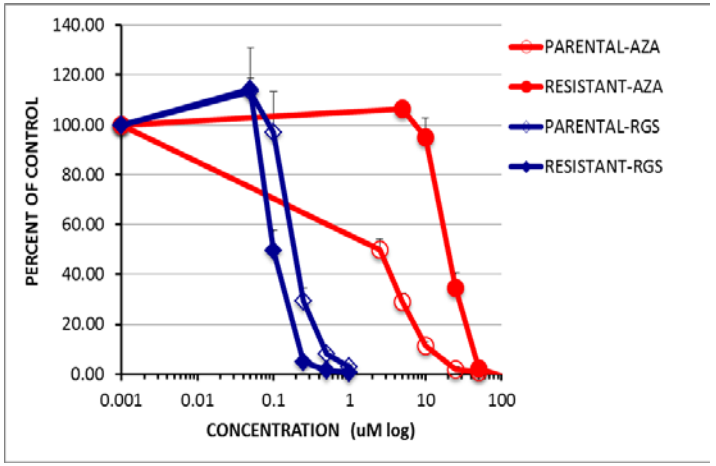
Ras Signaling mediates DNA hypermethylation and transcriptional silencing
RAS-RAF-MEK-ERK mediates epigenetic remodeling possibly through DNMT1 and DNMT3a

Lipka et al Nature Comm 2017 |DOI: 10.1038/s41467-017-02177

Rigosertib is Synergistic with Azacitidine in Preclinical Studies

- Rigosertib and Azacitidine in combination have synergistic activity
- Sequential exposure achieved maximum synergy
- Rigosertib is active in azacitidine resistant cells

Combination Drug	CI	Ratio	Description
Rigosertib* (125nM) + 5AzaC (2uM)	0.44	1:62.5	Synergism
Rigosertib (125nM) + 5AzaC (4uM)	**0.30**	**1:31.25**	**Strong synergism**
Rigosertib (250nM) + 5AzaC (2uM)	0.68	1:125	Synergism
Rigosertib (250nM) + 5AzaC (4uM)	0.57	1:62.5	Synergism
Rigosertib (500nM) + 5 AzaC (2uM)	0.63	1:250	Synergism
Rigosertib (500 nM) + 5AzaC (4uM)	0.75	1:125	Moderate synergism

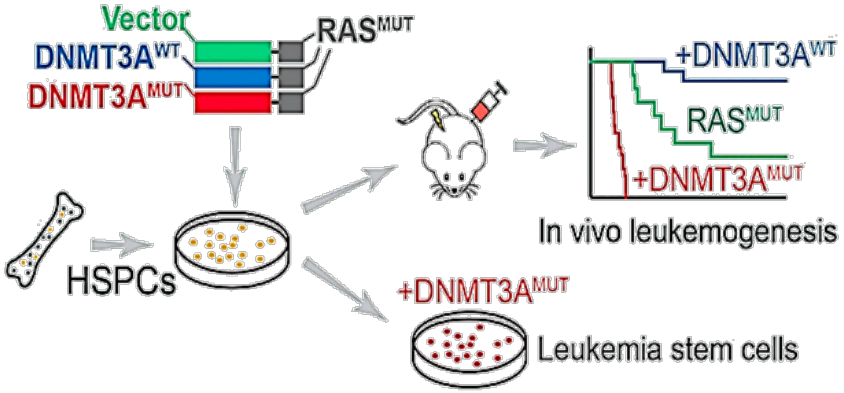


Combination Studies conducted by Dr. Silverman (MSSM);
Resistant cells developed in Japan; studies conducted at Mount Sinai Hospital

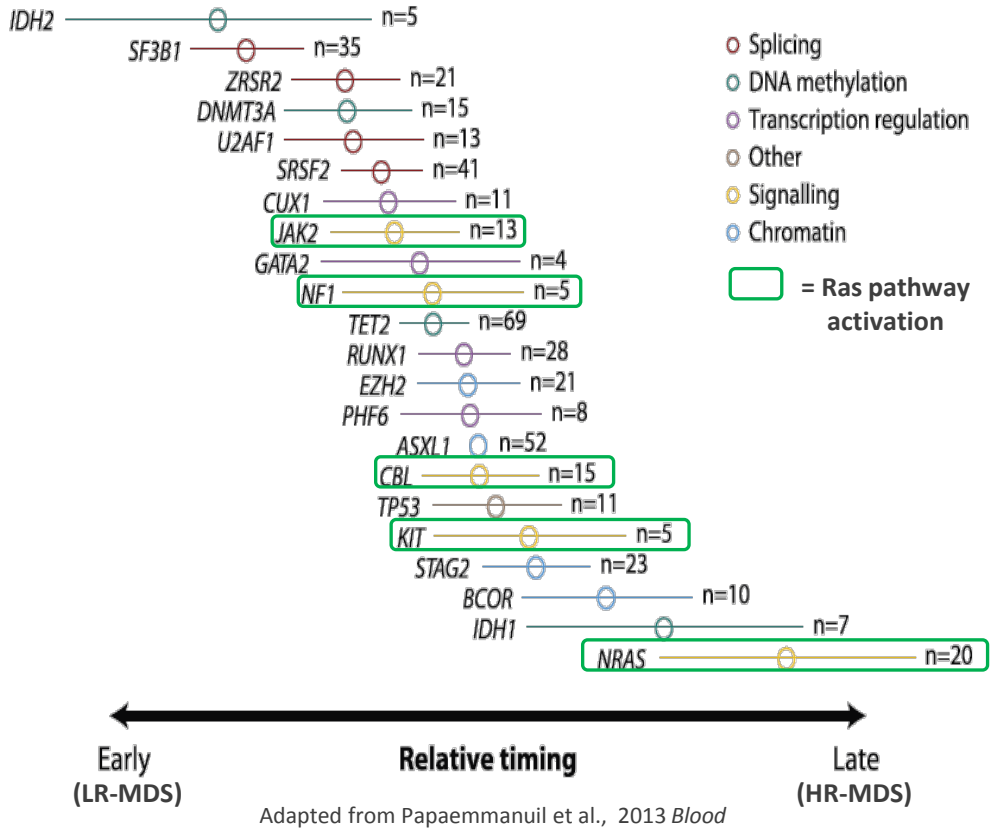
Skiddan et al

Epigenetic and Growth Factor Pathway Mutations Synergize Inducing Leukemic Transformation

AML Animal Model



Temporal Order of Gene Mutations in 107 MDS Patients



Adapted from Papaemmanuil et al., 2013 *Blood*

Preclinical/clinical evidence suggest combination of epigenetic therapy plus growth factor signaling inhibitor could be effective in curbing MDS pathogenesis

Lu et al., 2016 *Cancer Cell*

Treatment of Higher-risk MDS

- Azacitidine is standard of care for HR-MDS patients
- Clinical responses in MDS 38-50%[a]
  - CR rate 7-24%
  - Recent studies failed to demonstrate improved clinical benefit with combination therapies compared to single agent AZA
    - (Ades L, et al., #467, ASH 2018)
    - (Sekeres M, et al., JCO 2017)
- All patients ultimately relapse or fail to respond; these patients have a poor prognosis, with a median overall survival (OS) of only 4-6 months[b]
- Novel, better tolerated combination strategies for patients with MDS are required to improve the clinical outcome

a Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006;24(24): 3895-3903.
b Prebet T, Gore SD, Estemi B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol 2011;29(24):3322-7.

Combination dose administration

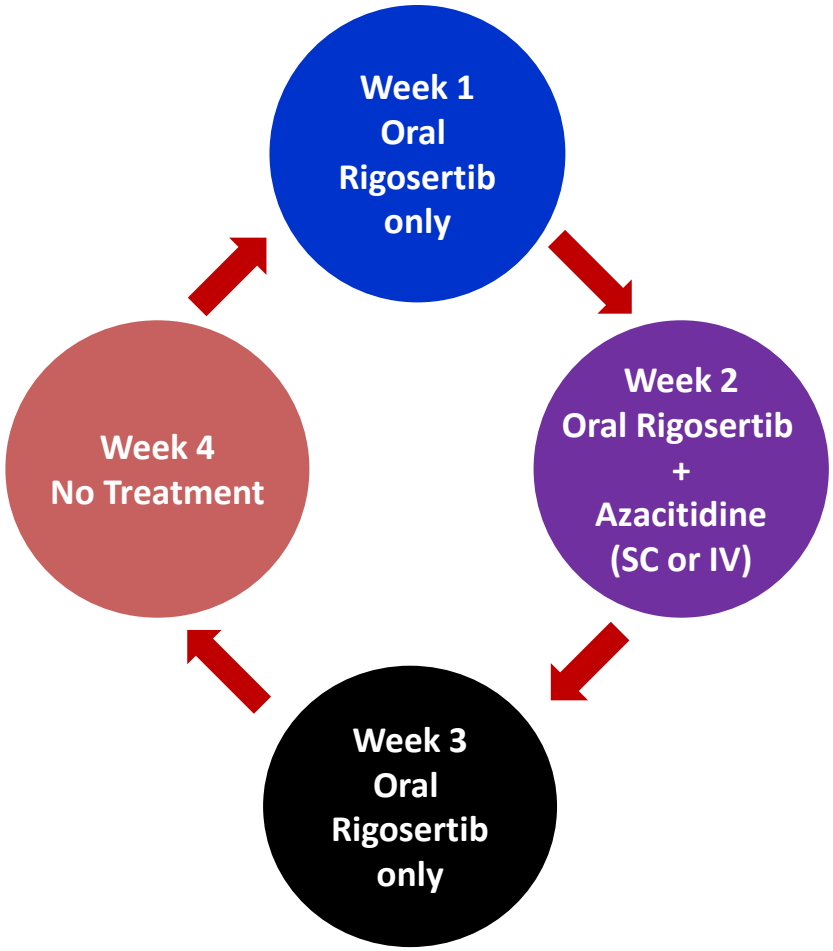
oral rigosertib 840 mg or 1120 mg in divided doses

Week 1: Oral rigosertib twice daily*

Week 2: Oral rigosertib twice daily* + azacitidine (75 mg/m^2/day SC or IV)

Week 3: Oral rigosertib twice daily*

Week 4: No treatment



*early AM/mid-afternoon PM

Navada S, EHA 2017 Abstract #S488

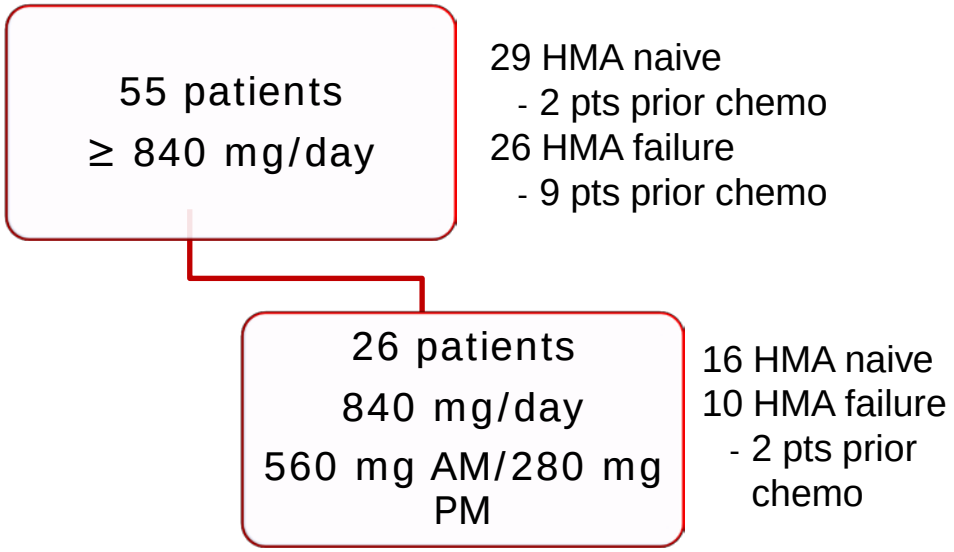
Patient Characteristics – HR-MDS ≥ 840 mg/Day

HMA Naïve & 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%)

Patients with HR-MDS Evaluable for response PER Rigosertib treatment group

HMA Naïve & HMA Failure

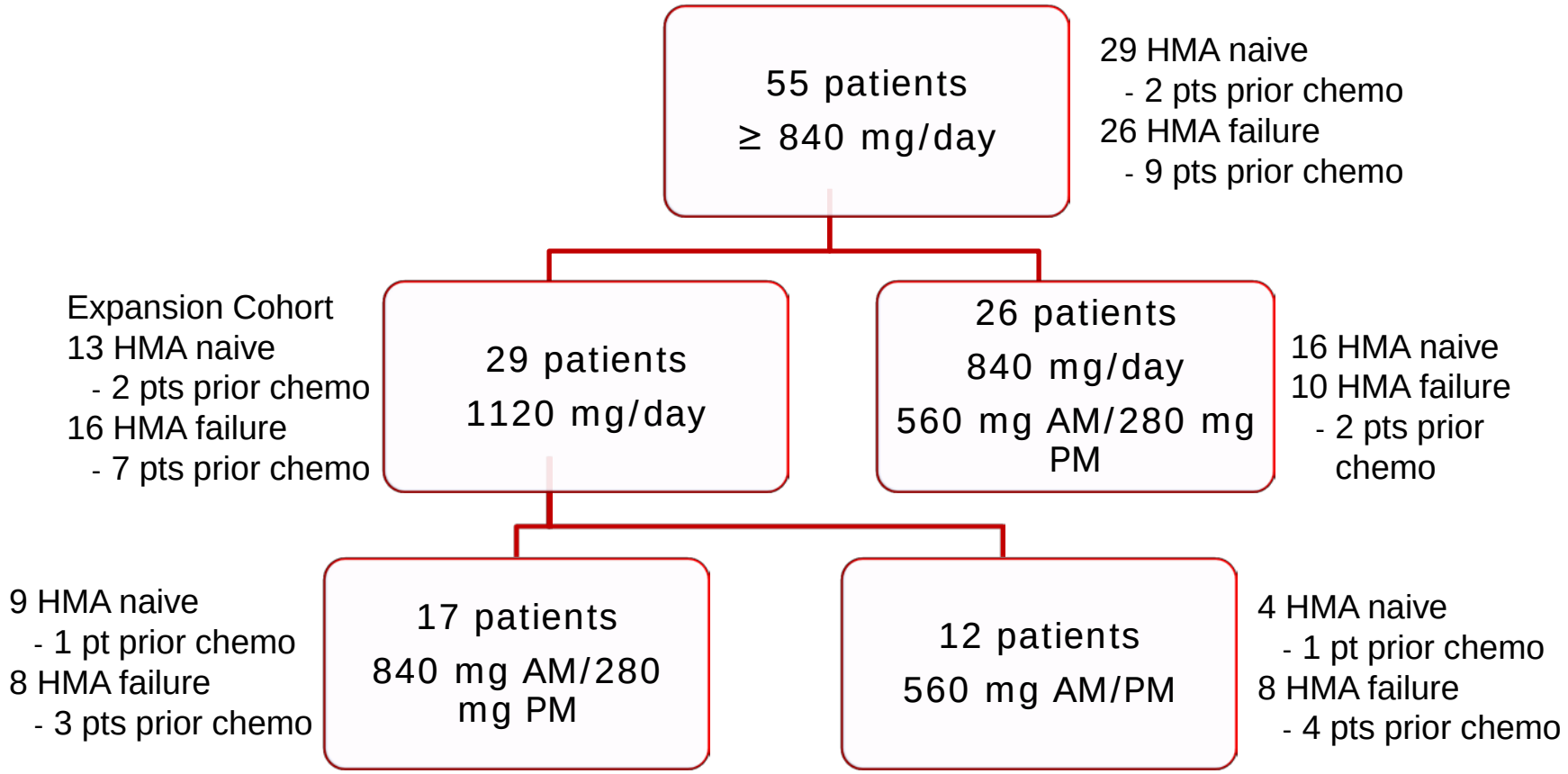


Rationale for Expansion Cohort at a dose of 1120mg/day:

- Rigosertib as a single agent administered orally at dose of 1120 mg/day yielded the highest response rate of transfusion independence (44%) in lower risk MDS (Raza A, et al., #1689 ASH 2017)
- Pursue Safety Optimization Strategies in additional patients at a higher daily dose

Patients with HR-MDS Evaluable for response PER Rigosertib treatment group

HMA Naïve & HMA Failure



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HMA Naïve or Failure 1120mg/day

EFFICACY

	HMA Naive	HMA Failure
Evaluable for response	13*	16**
Overall response per IWG 2006	12 (92%)	8 (50%)
CR+PR	4 (31%)	2 (12%)
Complete remission (CR)	4 (31%)	1 (6%)
Partial remission (PR)	0	1 (6%)
Marrow CR + Hematologic Improvement	2 (15%)	3 (19%)
Hematologic Improvement alone	2 (15%)	2 (12%)
Marrow CR alone	4 (31%)	1 (6%)
Stable disease	1 (8%)	3 (19%)
Progression	0	5 (31%)
Median duration of response (months)	13.5 (range, 1.6-13.5+)	9.2 (range, 0.1-10.2+)
Median duration of treatment (months)	6.7 (range, 3.0-17.1+)	3.6 (range, 1.1-13.7+)
Median time to initial/best response (cycles)	1/4	3/3

2 patients received prior chemotherapy **7 patients received prior chemotherapy

HMA Naïve ≥ 840mg/day

EFFICACY

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

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

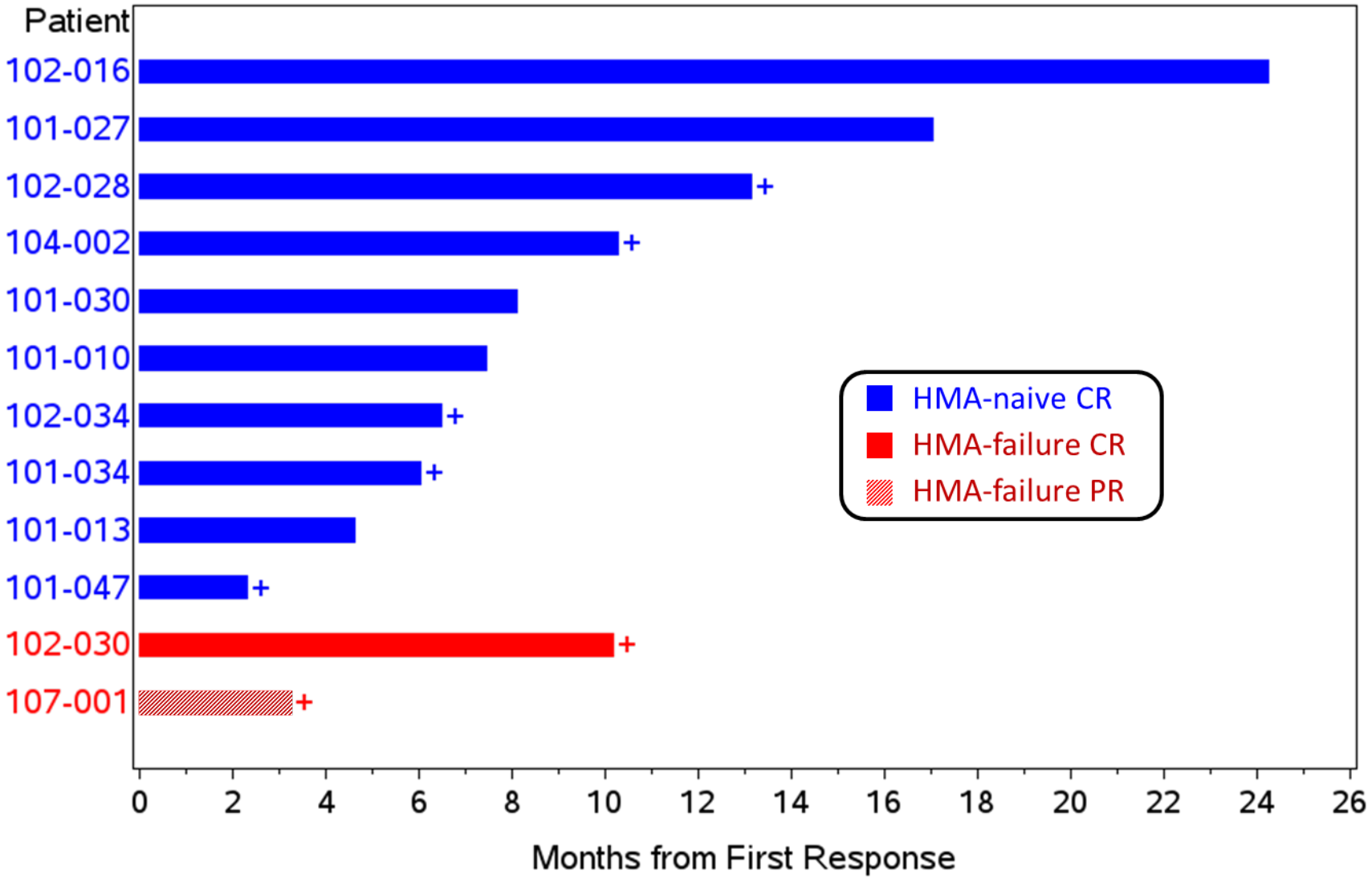
HMA Failure ≥ 840mg/day

EFFICACY

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

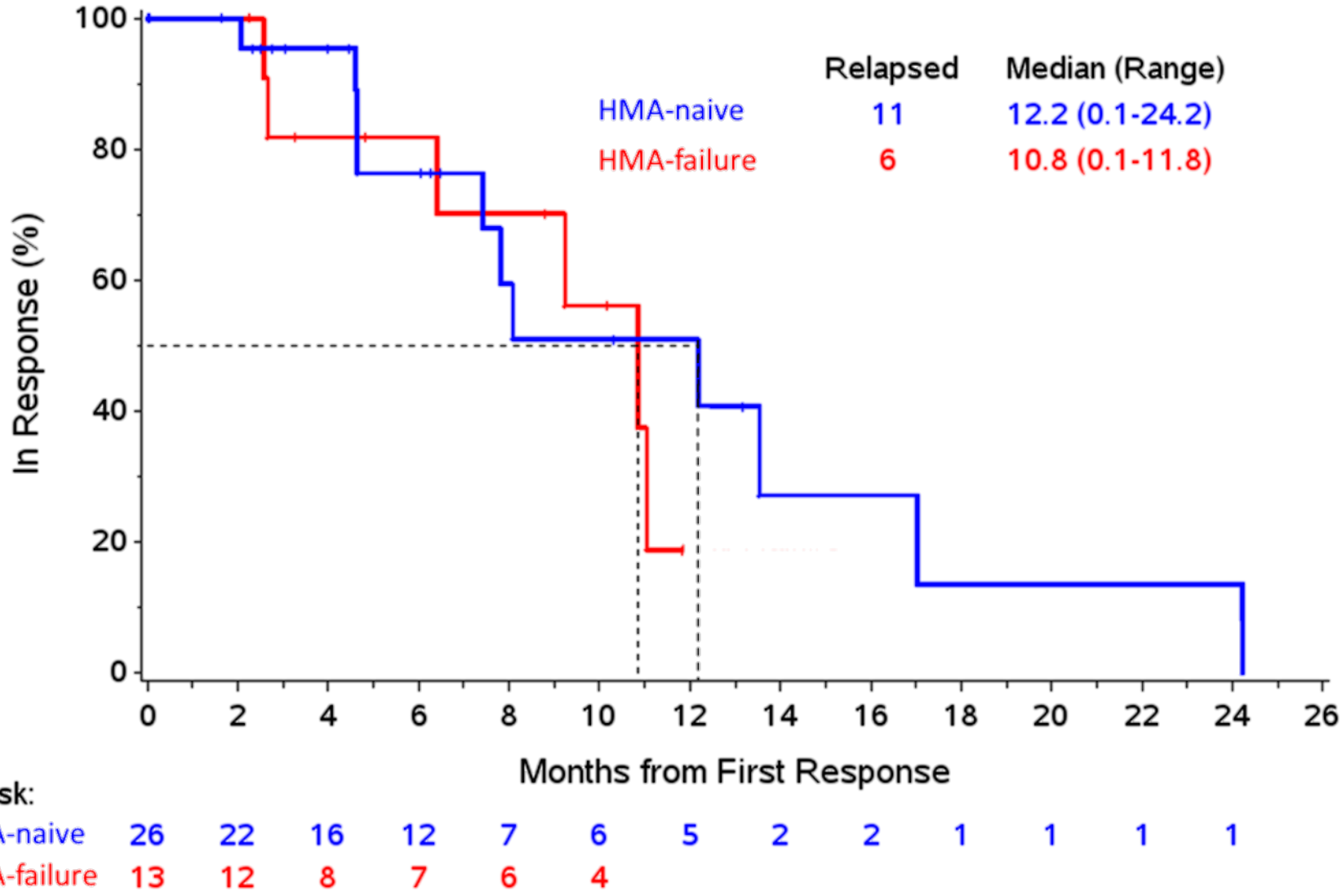
**** Includes 9 patients treated with non-HMA chemotherapy in addition to HMA***

Duration of Complete and Partial REMISSION

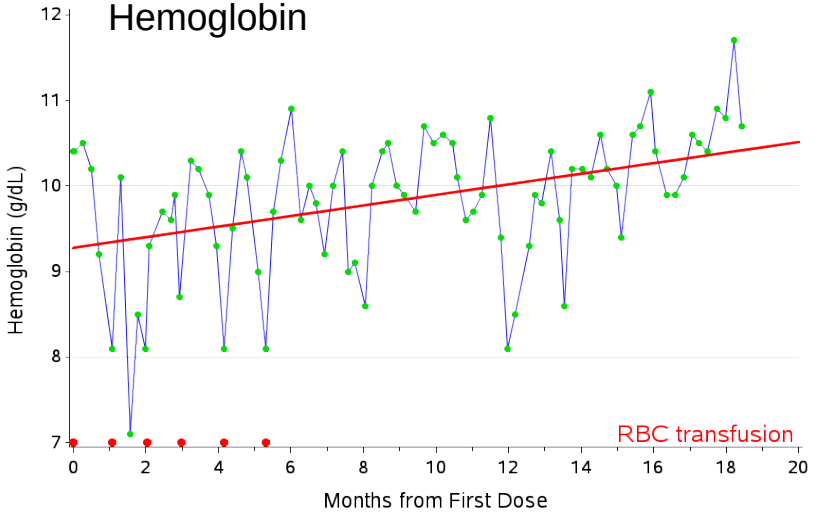


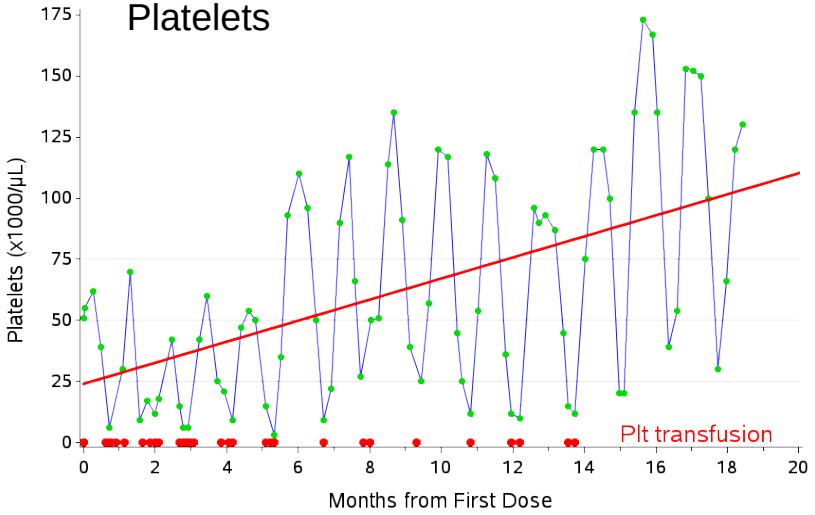
(+) continuing in response or in response at time of censoring

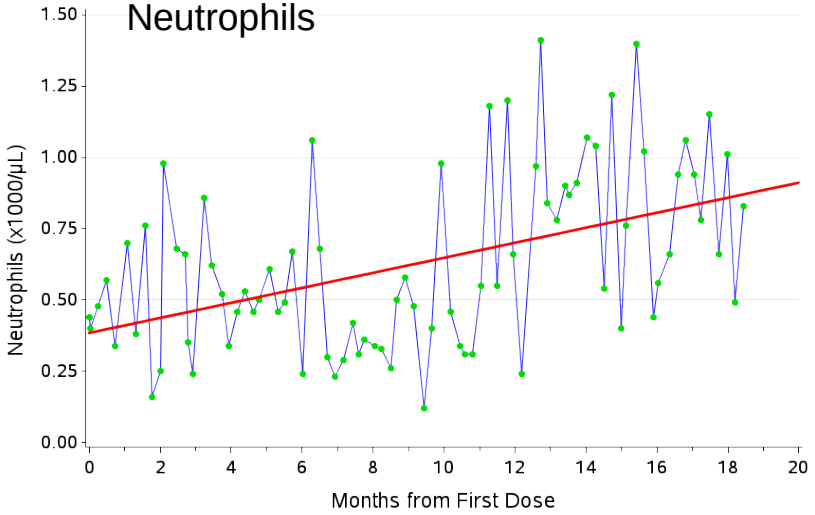
Duration of the Overall Response



Hematopoietic Response to Rigosertib Combination after HMA Failure







- 12 cycles of AZA – stable disease
- RBC and platelet transfusion
- Baseline blasts 7%
- Monosomy 7
- Runx-1
- AZA + RIG for 20+ months
- RBC & platelet transfusion independent
- Blasts < 5% - CR achieved following addition of Rigosertib

43

Adverse Events

Treatment Emergent Adverse Events (≥30%) in MDS Patients (N = 74)

	Number (%) of Patients			
MedDRA Preferred Term	All grades	Grade 1	Grade 2	Grade ≥3
Any Event	74 (100)	74 (100)	70 (95)	65 (88)
Hematuria	33 (45)	12 (16)	14 (19)	7 (9)
Constipation	32 (43)	19 (26)	13 (18)	-
Diarrhea	31 (42)	22 (30)	5 (7)	4 (5)
Fatigue	31 (42)	6 (8)	22 (30)	3 (4)
Dysuria	28 (38)	15 (20)	6 (8)	7 (9)
Pyrexia	27 (36)	22 (30)	4 (5)	1 (1)
Nausea	26 (35)	21 (28)	5 (7)	-
Neutropenia	23 (31)	2 (3)	1 (1)	20 (27)
Thrombocytopenia	22 (30)	-	3 (4)	19 (26)

SafetyOptimization Strategies

Comparison of Rigosertib Dosing Groups

Safety Optimization Strategies			
2nd RIGO dose must be administered at 3 PM (±1 hour) at least 2 hours after lunch to avoid a nocturnal bladder dwell time	Oral hydration of at least two liters of fluid per day is encouraged	Mandatory bladder emptying prior to bedtime	Urine pH approximately 2 hrs after AM dose. Sodium bicarbonate suggested administration of 650 TID if pH tests < 7.5

	Rigosertib 840mg	Safety Optimization Strategies Applied Rigosertib 1120mg
	42	43
Patients with hematuria	19 (45%)	17 (40%)
Patients with grade 1 or 2 hematuria only	14 (33%)	15 (35%)
Patients with grade 3 hematuria	5 (12%)	2 (5%)
Patients with dysuria	18 (43%)	13 (30%)
Patients with grade 1 or 2 dysuria only	13 (31%)	10 (23%)
Patients with grade 3 dysuria	5 (12%)	3 (7%)

No GR 4 reported

Safety of Single-agent IV Rigosertib in MDS

Treatment-related Adverse Events Reported in ≥5% of Patients with MDS Treated with IV Rigosertib as Monotherapy (N=355)

MedDRA Preferred Term	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any treatment-related AE	238 (67)	55 (15)	70 (20)	71 (20)	37 (10)	5 (1)
Nausea	64 (18)	51 (14)	10 (3)	3 (1)	0	0
Fatigue	63 (18)	18 (5)	38 (11)	6 (2)	1 (<1)	0
Diarrhoea	51 (14)	37 (10)	10 (3)	4 (1)	0	0
Constipation	40 (11)	32 (9)	7 (2)	1 (<1)	0	0
Anaemia	25 (7)	1 (<1)	4 (1)	18 (5)	1 (<1)	1 (<1)
Vomiting	24 (7)	17 (5)	5 (1)	2 (1)	0	0
Dysuria	20 (6)	14 (4)	3 (1)	3 (1)	0	0
Abdominal pain	19 (5)	14 (4)	4 (1)	1 (<1)	0	0

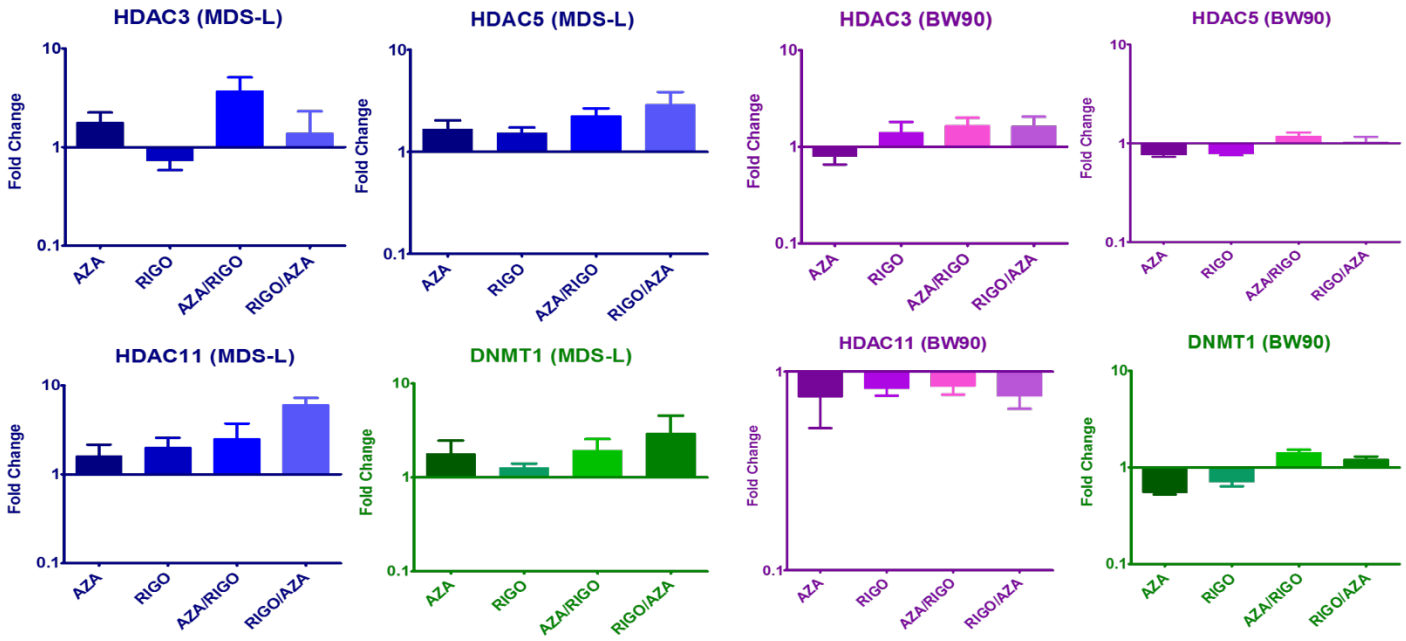
Navada et al EHA 2017

Reasons for discontinuation

Reason for discontinuation	N=68 *	
	HMA Naive	HMA Failure
Progressive Disease	7	12
Toxicity / Adverse Event	8	5
Investigator Decision	5	4
Patient Request	7	2
Bone Marrow Transplant	5	3
No hematological response	3	3
Death	0	2
Disease relapse	1	1

***6 patients still on treatment**

RIGO modulates HDACs (class I, II and IV) and DNMT1 differentially in cell specific manner

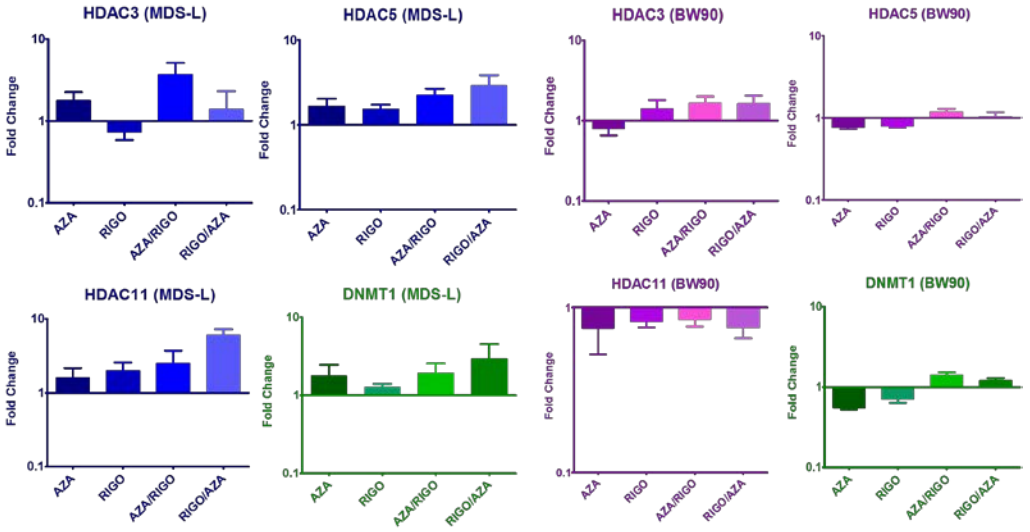


- Global Chromatin Post Translational Modification
- Epigenetic Reprogramming of Pluripotency Genes
- Epigenetic Effects lead to HSPC reprogramming
- May lead to reversal of clinical HMA resistance and improvement of hematopoietic function

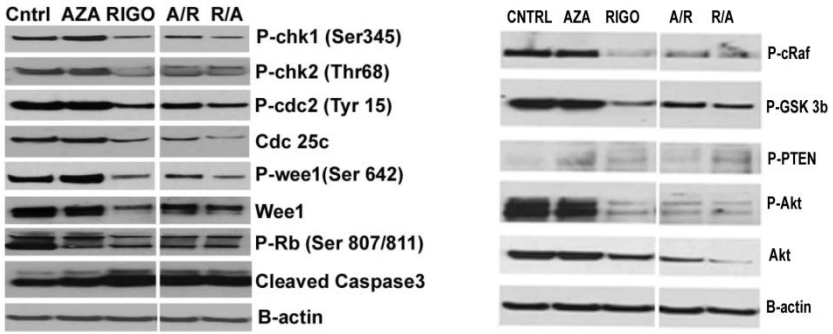
Silverman, Melana, Navada et al. ASH abstract 4235, Blood 2017

Rigosertib alone and in combination with azacitidine has Epigenetic effects in vitro and in vivo

- Rigosertib modulates HDACs (class I, II and IV) and DNMT1 in MDS and AML cells in vitro
- Rigosertib alone or in combination with AZA leads to different levels of histone methylation and acetylation altering activator/repressor marks
- Rigosertib alone or in combination with Azacitidine down regulated the AKT pathway and reduced cell cycle check point protein levels; an increase in apoptosis was demonstrated only with the combination.
- Similar effects on chromatin were seen in preliminary data from patients before and after the first cycle of treatment



Effects of rigosertib on HDACs (class I, II and IV) and DNMT1



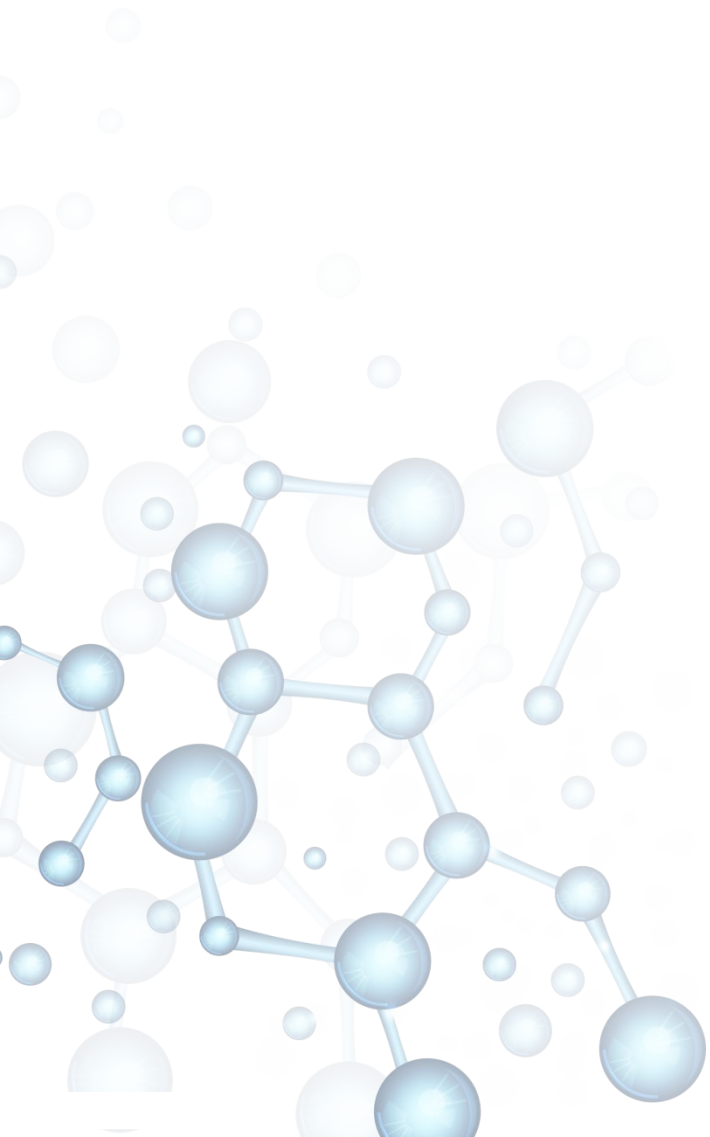
Effect of RIGO alone or in combination with AZA on cell cycle check proteins, apoptosis and AKT cell signaling pathway

Chaurasia et al EHA, 2017

Conclusions

- Oral rigosertib in combination with AZA demonstrated efficacy in both HMA-naïve and HMA-refractory MDS patients
- In HMA-naïve MDS patients oral rigosertib at doses ≥ 840 mg/day administered with AZA is associated with an ORR of 90% and a CR rate of 34%
- Oral rigosertib in combination with AZA was well tolerated and administered in repetitive cycles for more than two years
- Safety optimization strategies mitigated urinary AEs in the expansion cohort
- Based on the safety and efficacy profile of the combination in MDS, a pivotal Phase III trial is planned in an HMA naïve population

Questions?



Thanks to our patients and their families, investigators, Nurses and research staff

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Phase 2 Expansion Study of Oral Rigosertib Combined with Azacitidine (AZA) in Patients with Higher-Risk (HR) Myelodysplastic Syndromes: Efficacy and Safety Results in HMA Treatment Naïve & Relapsed/Refractory Patients

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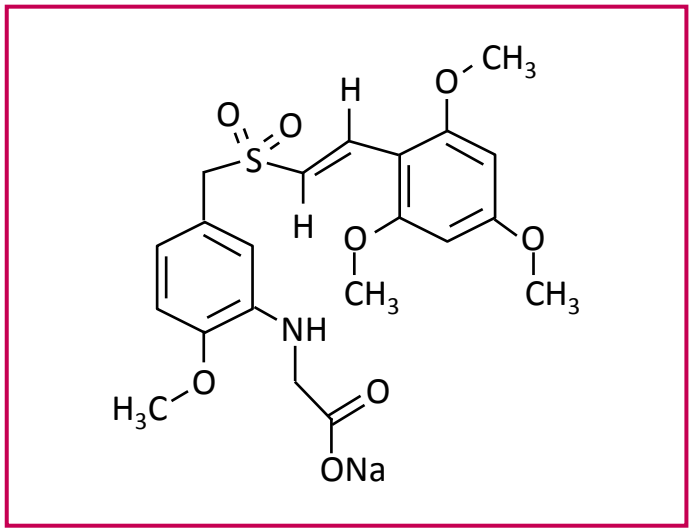
Guillermo Garcia-Manero, MD, Ehab L. Atallah, MD, M. Nabeel Rajeh, MD, Jamile M. Shammo, MD, Elizabeth A. Griffiths, MD, Samer K. Khaled, MD, Shaker R. Dakhil, MD, David E. Young, MD, Rosalie Odchimar-Reissig, RN, Yesid Alvarado Valero, MD, Maro N. Ohanian, DO, Naveen Pemmaraju, MD, Rosmy B. John, MSN, Patrick S. Zbyszewski, MBA, Manoj Maniar, PhD, Michael E. Petrone, MD, Steven M. Fruchtman, MD, Lewis R. Silverman, MD.

60th ASH Annual Meeting & Exposition 2018: San Diego, CA, USA

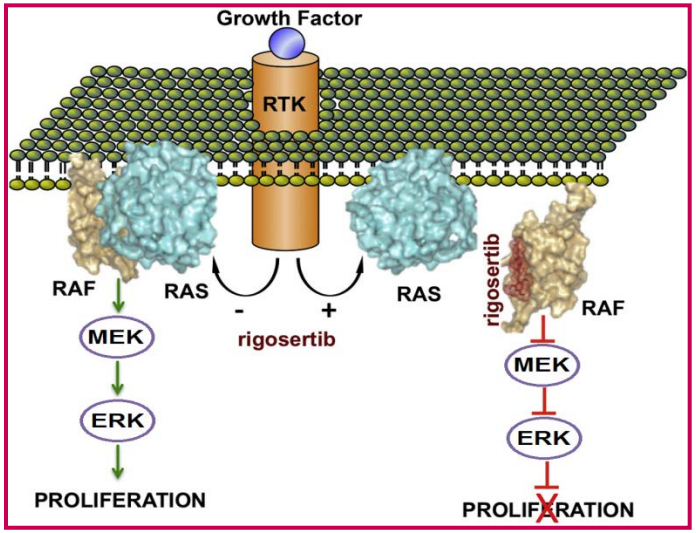
RIGOSERTIB MECHANISM OF ACTION

- 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, MEK/ERK and Raf/PLK
- Can ameliorate multiple dysregulated signaling transduction pathways in higher-risk MDS[b]

Rigosertib



RAS targeted novel mode of action



[a]*Divikar, 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*