ONCONOVA THERAPEUTICS

TARGETING CANCER, PROTECTING HEALTHY CELLS

Rigosertib

Strategies to Rasopathies and JMML

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DESCRIPTION OF RIGOSERTIB AS A RAS MIMETIC

Article

Cell

A Small Molecule RAS-Mimetic Disrupts RAS Association with Effector Proteins to Block Signaling

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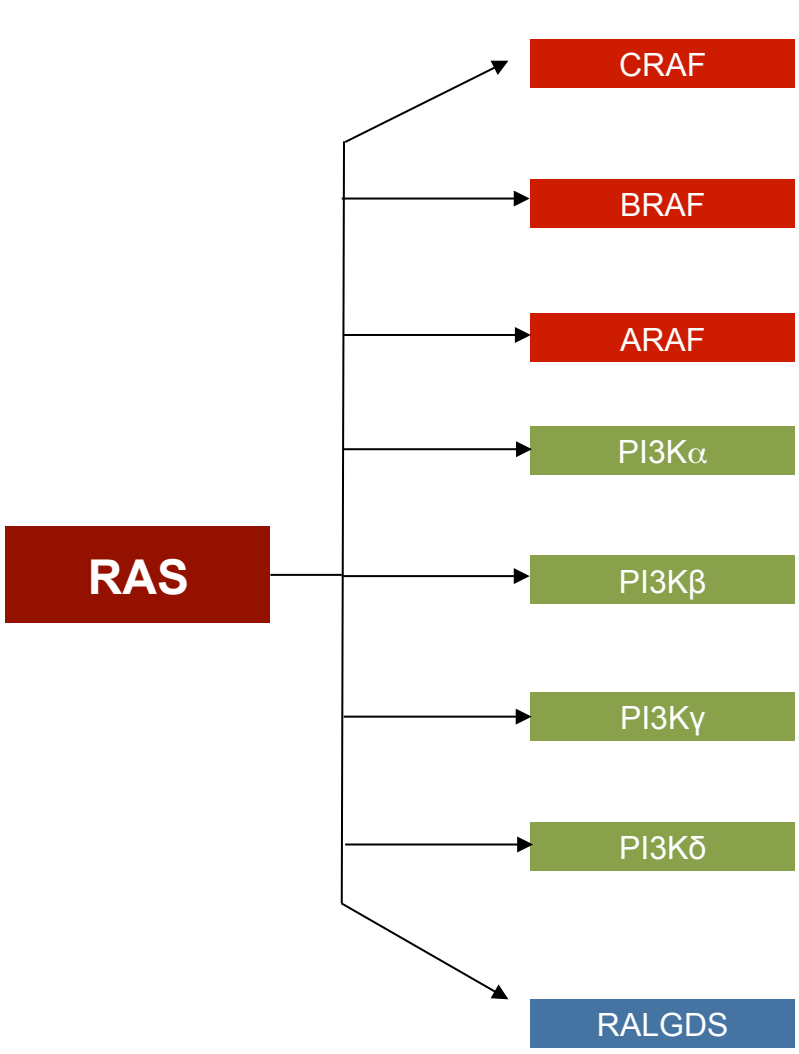
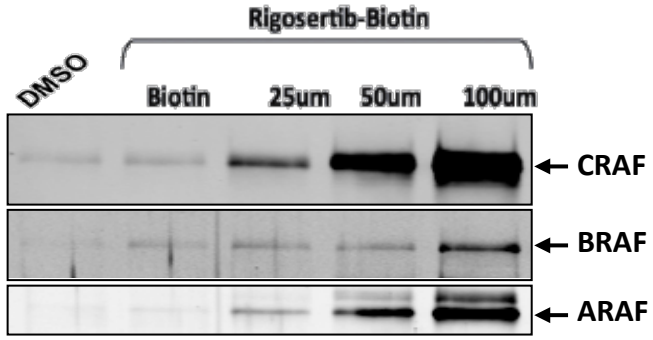
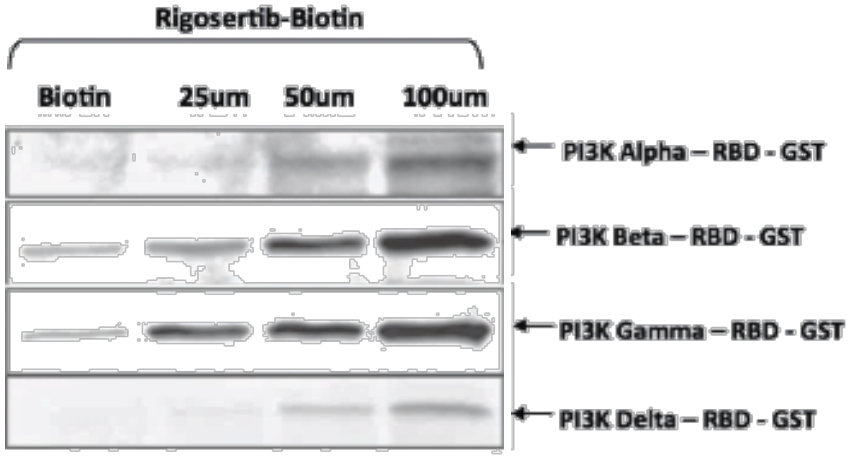
PRIOR KNOWLEDGE REGARDING RIGOSERTIB MECHANISM

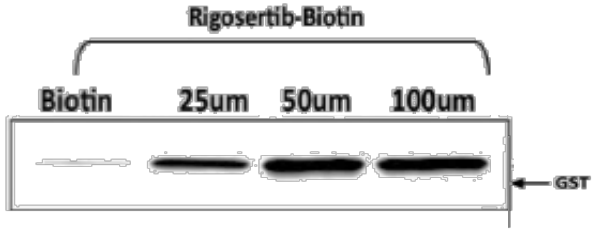
- Broad anti-cancer activity in vitro (cell lines) and in vivo (tumor xenografts); no resistance mechanism identified
- Induction of apoptosis through inhibition of intracellular PI3K signaling
- Prominent phenotype of G2/M arrest
- Precise molecular MOA connecting observations remained elusive

RIGOSERTIB BINDS TO MULTIPLE RAS EFFECTOR RBDS



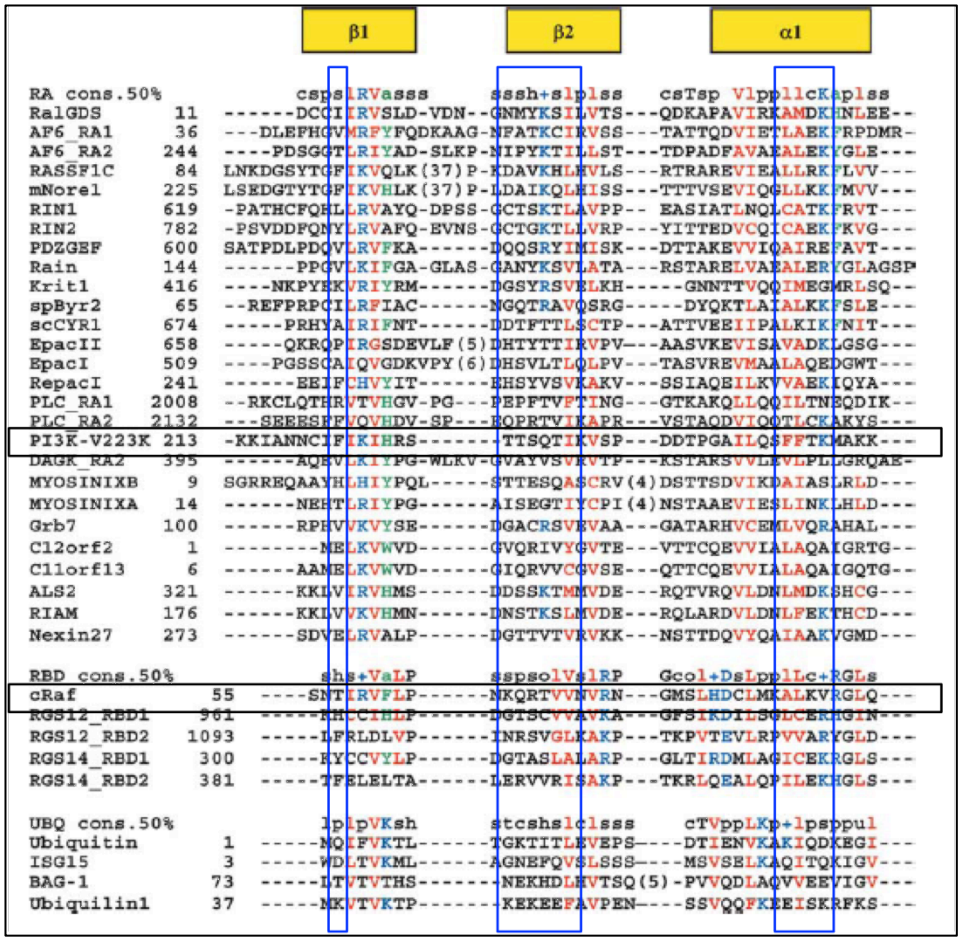






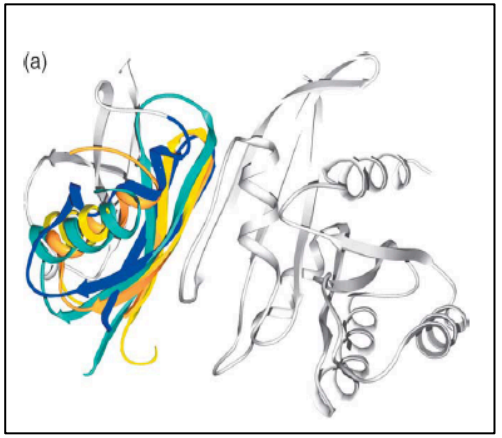
SECONDARY/TERTIARY STRUCTURAL SIMILARITY OF RBDS DESPITE LACK OF EXTENSIVE SEQUENCE HOMOLOGY

Sequence Alignment of RA and RB Domains

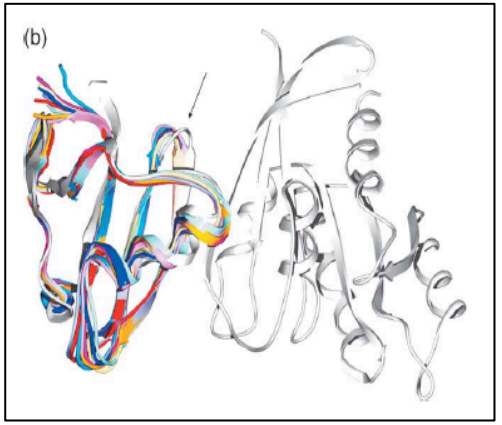


Yellow: Hydrophobic Core; Cyan: Conserved Charged Amino Acids
Red: Conserved Hydrophobic AA; Green: Conserved Aromatic AA

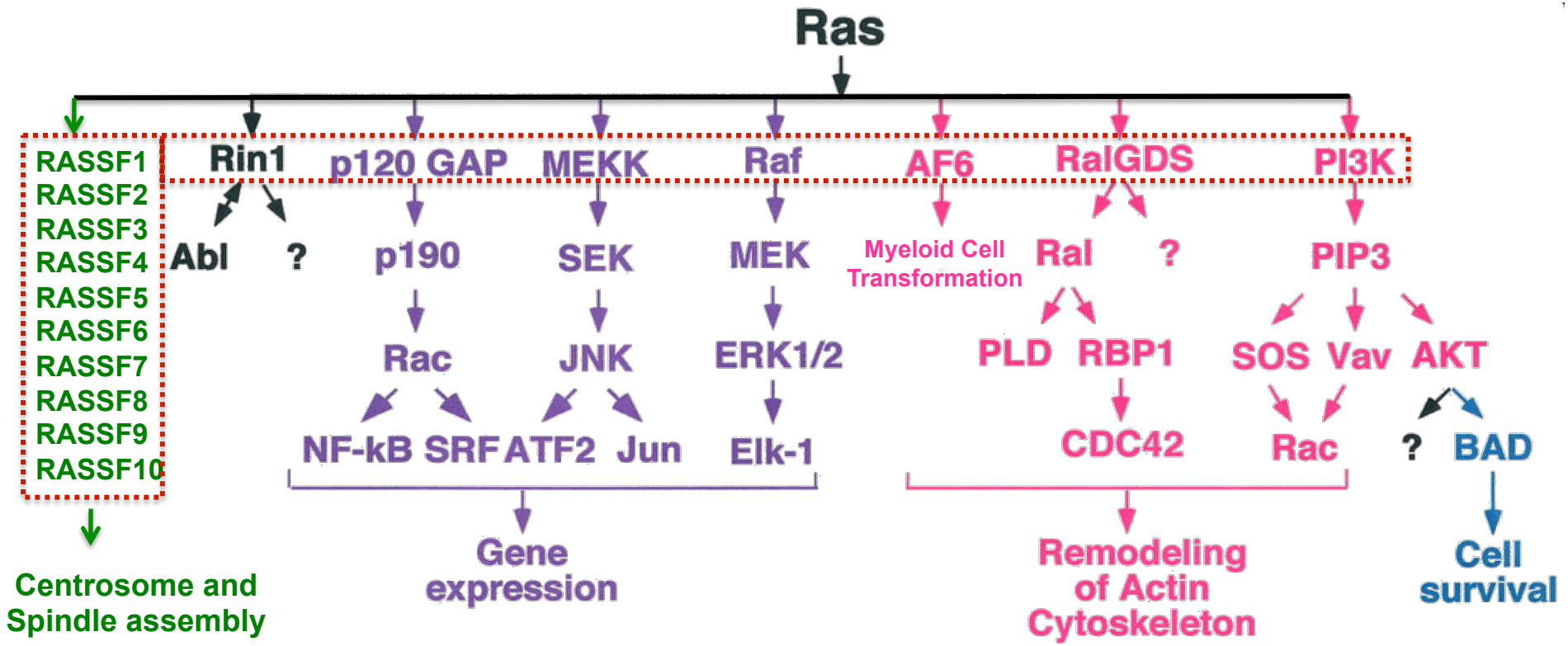
RAF/Ral-GDS/PI3K Crystal Structures Superimposed



NMR Structures of 10 RBDs Superimposed



RAS SIGNALS VIA MULTIPLE EFFECTORS



Effector proteins contain common RAS-binding domain (RBD)

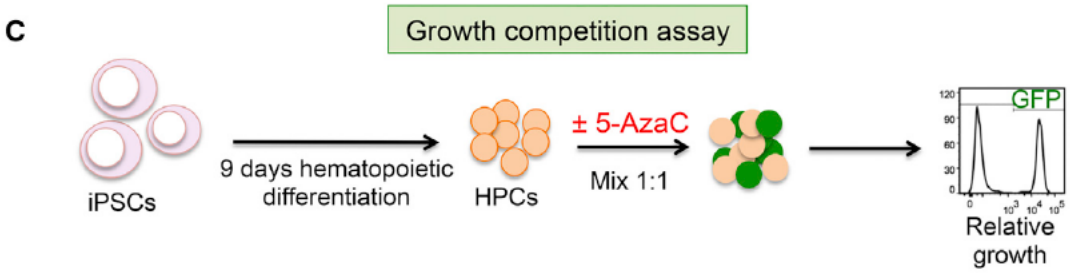
NOVEL MECHANISM OF ACTION OF RIGOSERTIB

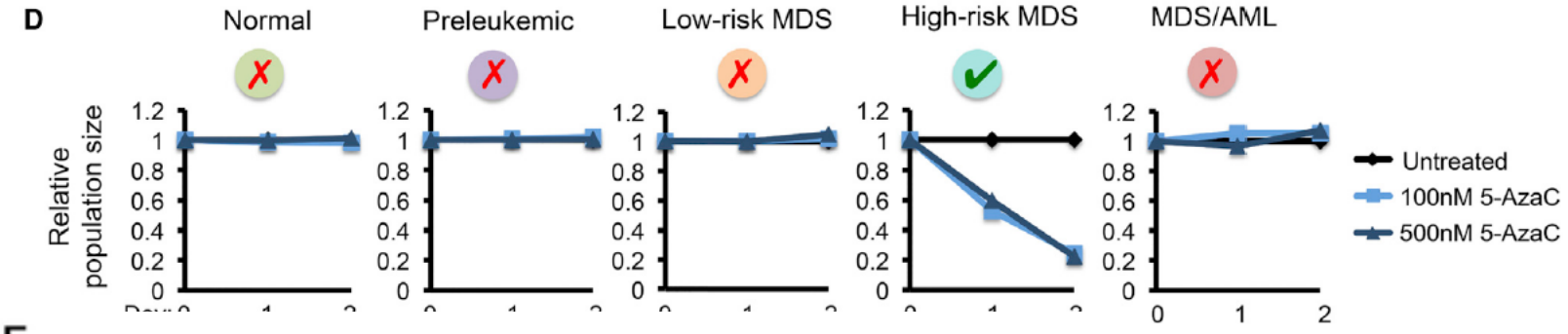
- Rigosertib is a first-in-class molecule that targets the multiple signaling pathways driven by RAS.
- **Rigosertib achieves this by binding to the RBD of Ras effector proteins including PI3K and Raf, thereby leading to their inactivation.**
- This novel mechanism helps to explain the pleiotropic effects of rigosertib, such as inhibition of the PI3K and PLK pathways.

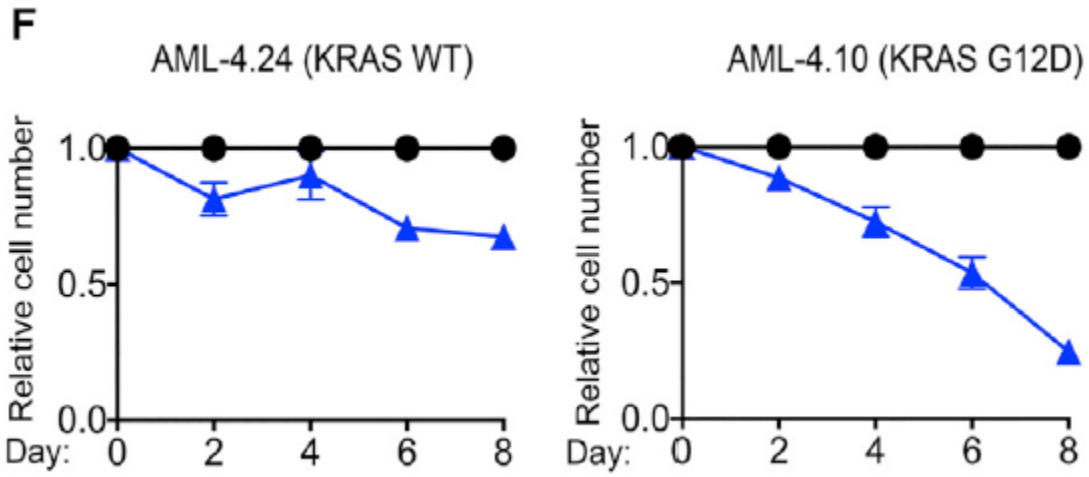
Future directions:

- Exploit the new knowledge to determine the extent of Ras effector proteins targeted by rigosertib and their role in additional tumor types.
- Further characterize the potential for rigosertib in Ras-driven tumors:
  - Tumors with activation of Ras pathways
  - Tumors that are resistant to targeted agents due to Ras activating mutations

GROWTH COMPETITION ASSAY WITH AZA & RIGOSERTIB ON IPSC IN MDS / AML







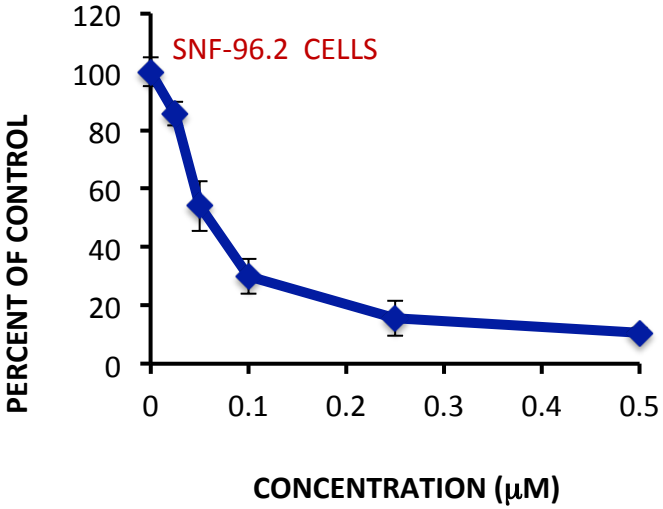
Cell Stem Cell
Article

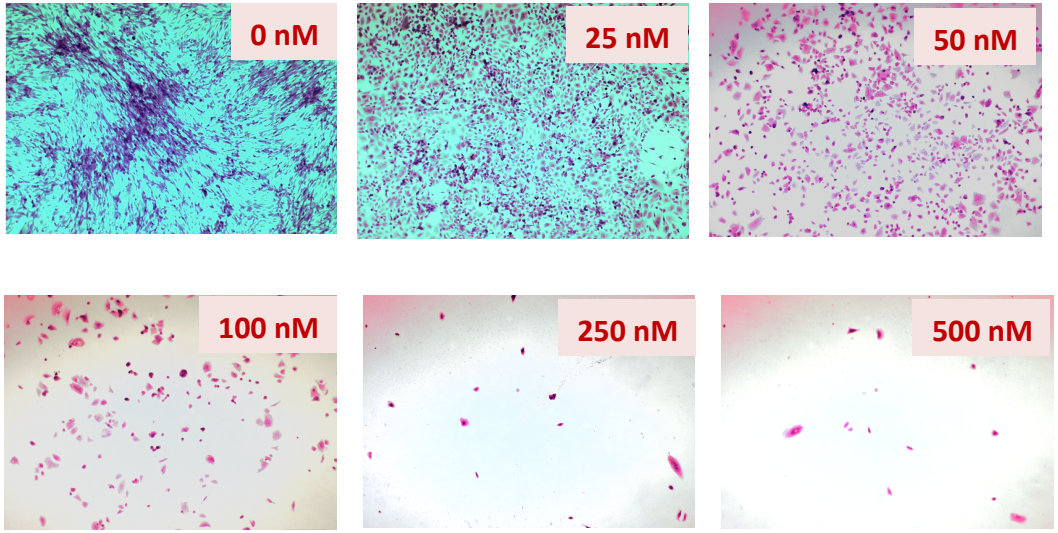
Stage-Specific Human Induced Pluripotent Stem Cells Map the Progression of Myeloid Transformation to Transplantable Leukemia

Andriana G. Kotini,[1,2,3,4] Chan-Jung Chang,[1,2,3,4] Arthur Chow,[5,6,7,8] Han Yuan,[9] Tzu-Chieh Ho,[5,6,7,8] Tiansu Wang,[1,2,3,4] Shailee Vora,[1,2,3,4] Alexander Solovyov,[1,2,4,10] Chrystel Husser,[1,2,3,4] Malgorzata Olszewska,[1,2,3,4] Julie Teruya-Feldstein,[10] Deepak Perumal,[1,2,4] Virginia M. Klimek,[11] Alexandros Spyridonidis,[12] Raajit K. Rampal,[11] Lewis Silverman,[2,4] E. Premkumar Reddy,[2,4] Elli Papaemmanuil,[13] Samir Parekh,[1,2,4] Benjamin D. Greenbaum,[1,2,4,10] Christina S. Leslie,[9] Michael G. Kharas,[5,6,7,8,*] and Eirini P. Papapetrou[1,2,3,4,14,*]

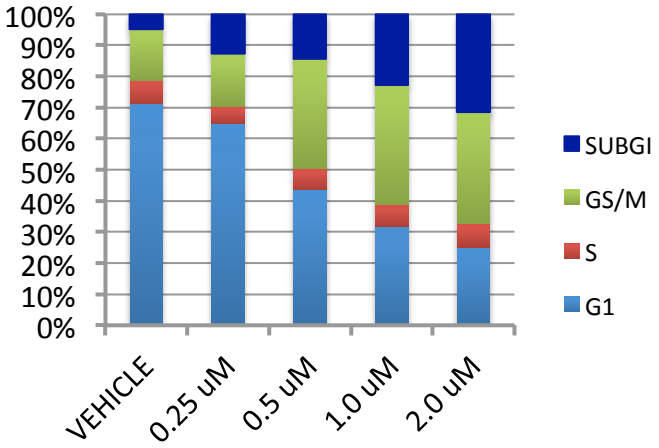
GROWTH INHIBITION AND INDUCTION OF APOPTOSIS WITH RIGOSERTIB IN NF1 CELLS

Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

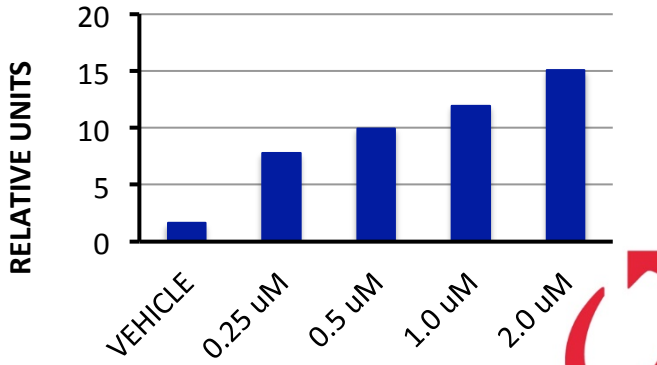




FACS Analysis of SNF 96.2 Cells Treated With Rigosertib



PARP Cleavage Assay



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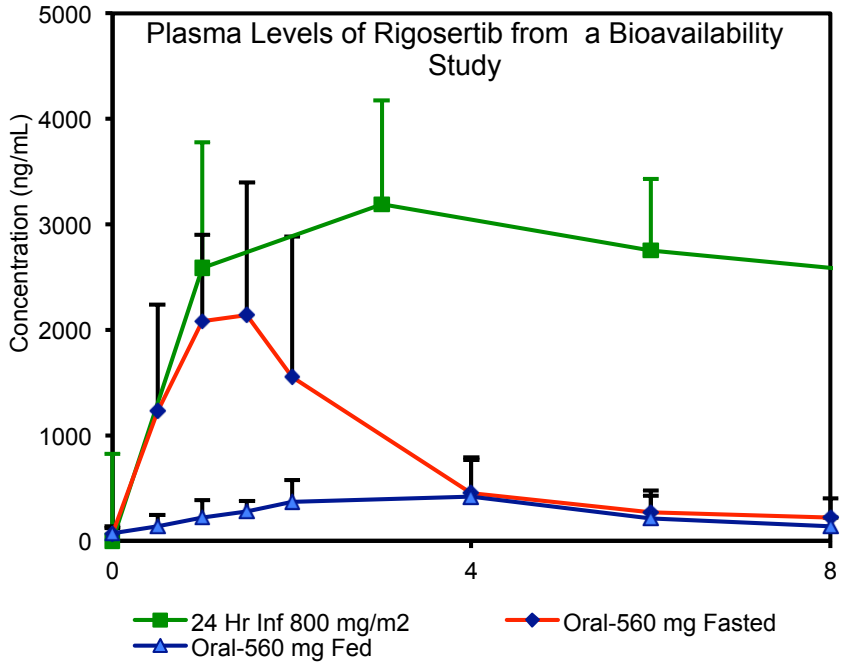
Clinical Trials in MDS

TWO RIGOSERTIB FORMULATIONS

- IV (Phase 3 INSPIRE ongoing)
  - Continuous infusion using a portable pump
  - >500 patients treated in trials
  - Lead indication 2nd-line HR-MDS
- Oral (Phase 2 enrolled)
  - Bioavailability ~35%
  - >200 patients treated
  - Combination with azacitidine for HR-MDS and AML



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.

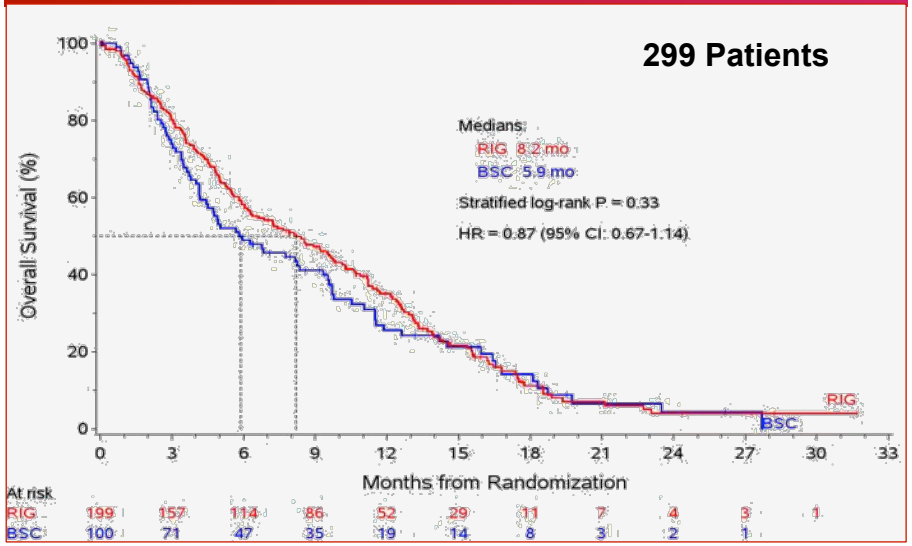
Lancet Oncol 2016

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

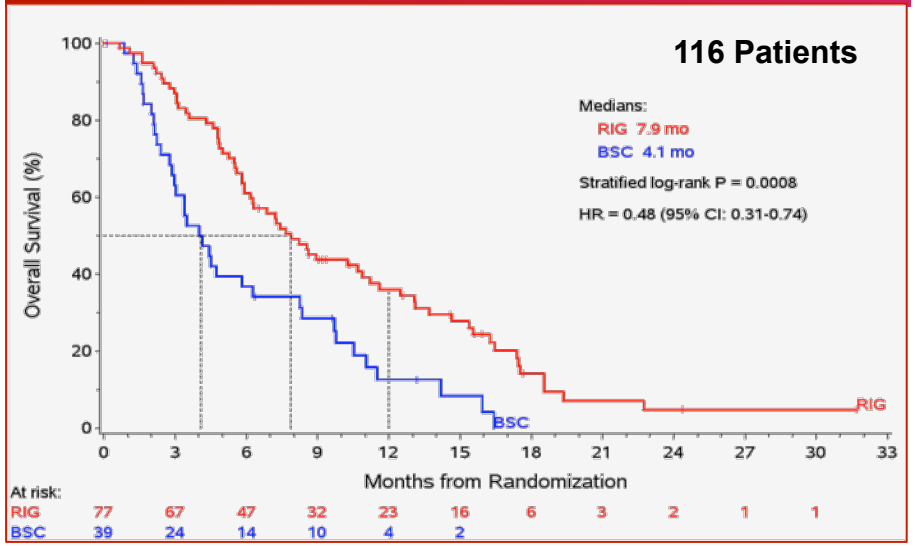
PATIENT POPULATION FOR PHASE 3 INSPIRE TRIAL

Data from ONTIME Paper* Recently Published in *Lancet Oncology*

ITT for ONTIME Trial



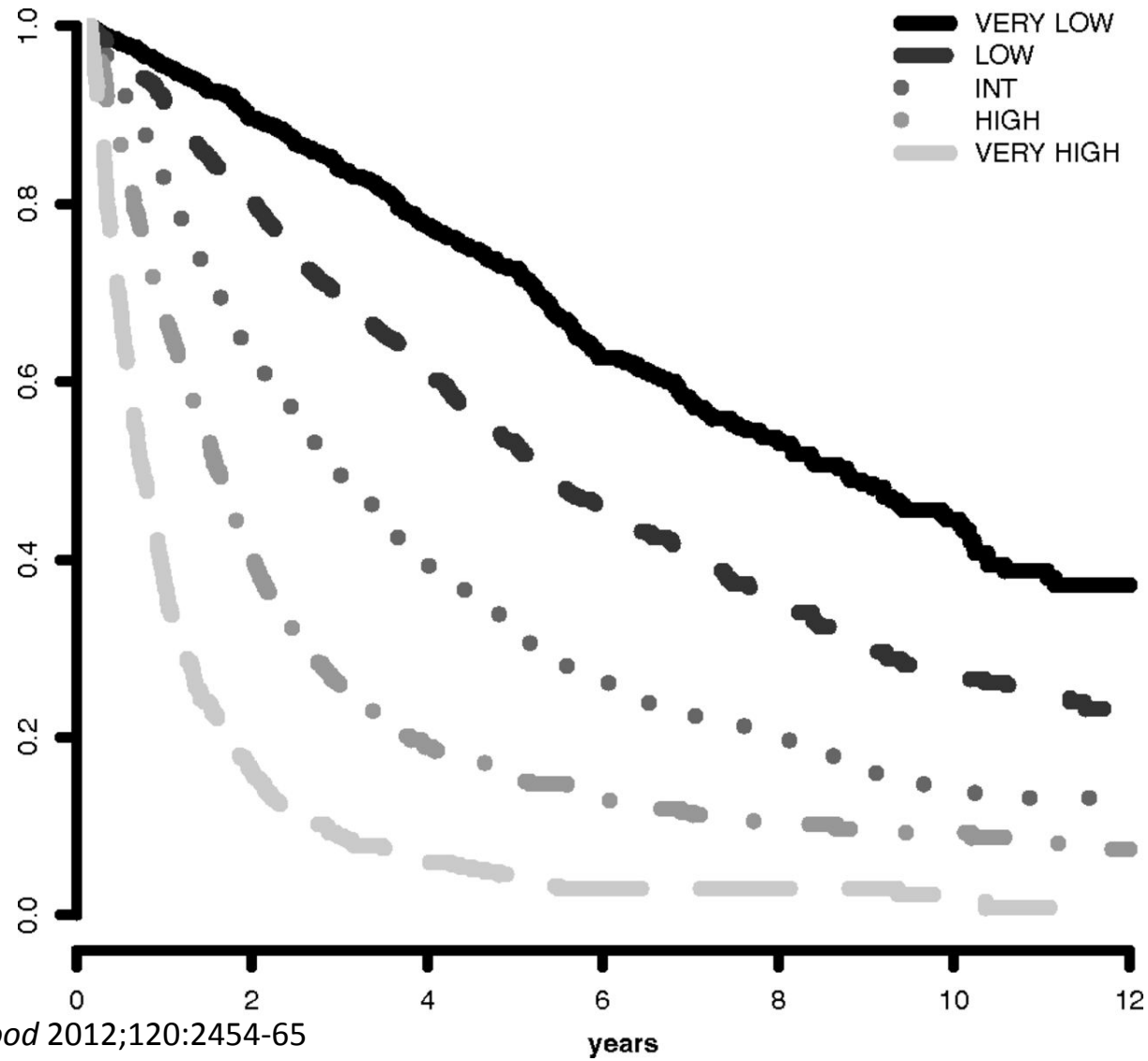
Subpopulation for INSPIRE Trial (ONTIME subset)



- 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

REVISED IPSS-R IN RELATION TO SURVIVAL



Greenberg et al. *Blood* 2012;120:2454-65

ONTIME TRIAL: ITT SUBGROUPS CORRELATED WITH BETTER SURVIVAL BENEFIT

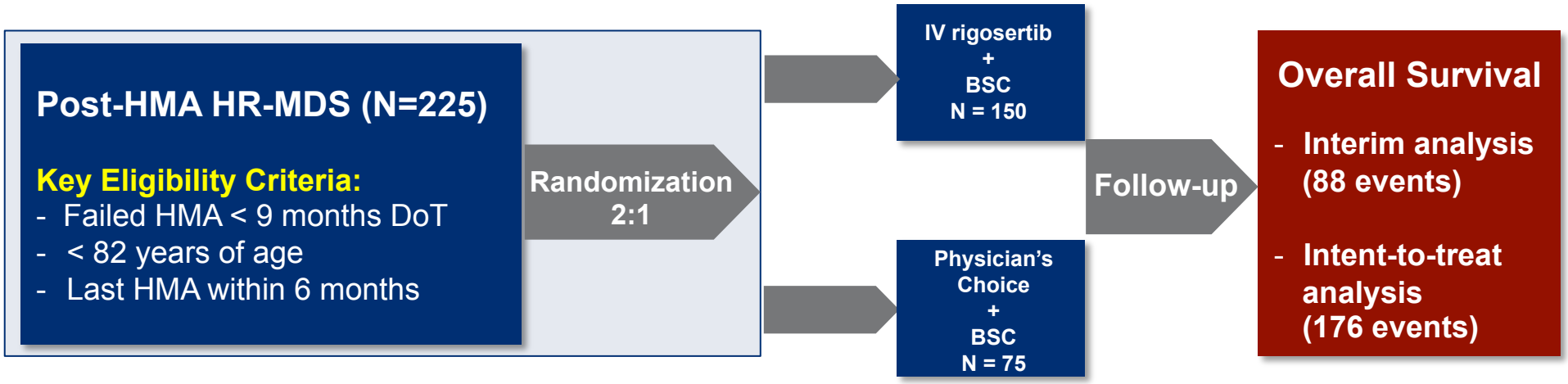
Subgroup	Rigosertib		BSC		HR (95% CI)	p-value
	N	Median (mos)	N	Median (mos)		
Monosomy 7	16	5.6	13	2.8	0.24 (0.09-0.66)	0.003
Trisomy 8	22	9.5	8	4.5	0.34 (0.12-0.95)	0.035
Very high risk per IPSS-R	93	7.6	41	3.2	0.56 (0.37-0.84)	0.005

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

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

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Oral Rigosertib + Azacitidine for HR-MDS

RIGOSERTIB + AZACITIDINE

- Despite activity in MDS, single-agent DNMT inhibitors are limited by low CR and PR rates (7-20%) with median duration of 15 months
- Combinations should not add burdensome toxicities
- DNMT inhibition may be complemented by combination with novel mechanisms to improve response rates and duration

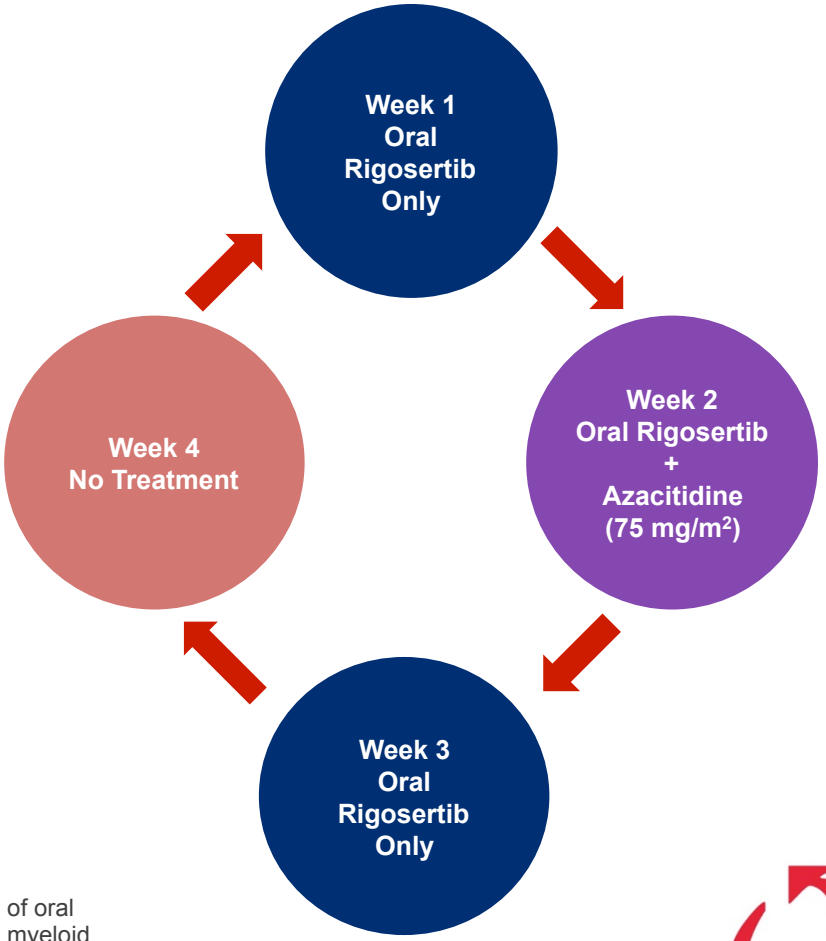
PRE-CLINICAL BACKGROUND

- Combination of rigosertib with AZA produced an increase of 1.7- to 2.9-fold in cytotoxicity ($p<0.05$) in HL-60 cells*
- Interaction resulted in a synergistic effect with combination indexes between 0.3 and 0.75
- Sequence of administration influenced degree of cytotoxicity; rigosertib priming offered optimal results
- These pre-clinical results provided rationale for combining agents in a Phase 1/2 study in MDS and AML patients with optimal sequence

*Skidan I, Zinzar S, Holland J, Silverman. Toxicology of a novel small molecule ON01910Na on human bone marrow and leukemic cells in vitro. *AACR Meeting Abstracts*, Apr 2006:309

RIGOSERTIB + AZACITIDINE COMBINATION

- Phase 1 combination was well tolerated with evidence of efficacy in patients with MDS*
- Azacitidine given one week per month (full dose and administrative scheme per label)
- Rigosertib given 3 of 4 weeks (at recommended Phase 2 dosing of 560/280 mg BID)
- Adverse event profile of combination similar to single-agent azacitidine (per label)



*Navada S, Garcia-Manero G, Wilhelm F, et al. A phase I/II study of the combination of oral rigosertib and azacitidine in patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). *ASH* 2014; Abstract 3252.

RIGOSERTIB + AZACITIDINE

*UPDATED PHASE 2 DATA ASH 2016**

- ORR of 85% in 20 HMA naïve patients
- ORR of 62% in 13 patients who progressed/failed prior HMA
- Median DoR for CR is 8.0 months; median time to best response is 3.3 cycles

Response Assessment per 2006 IWG Criteria

Patient Characteristics	Eval (n=33)	HMA Naïve (n=20)	HMA Failure** (n=13)
Complete Remission (CR %)	8 (24%)	7 (35%)	1 (8%)
Overall Response Rate (ORR %)	25 (76%)	17 (85%)	8 (62)

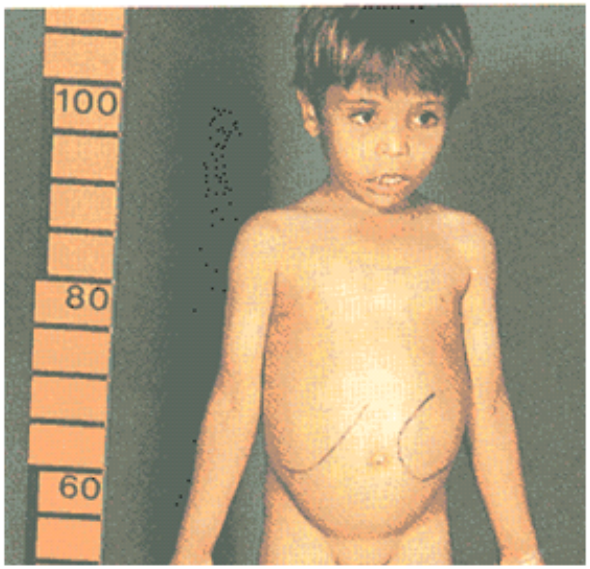
* Data shown as of data cut off Oct 1, 2016; response based on IWG 2006 criteria

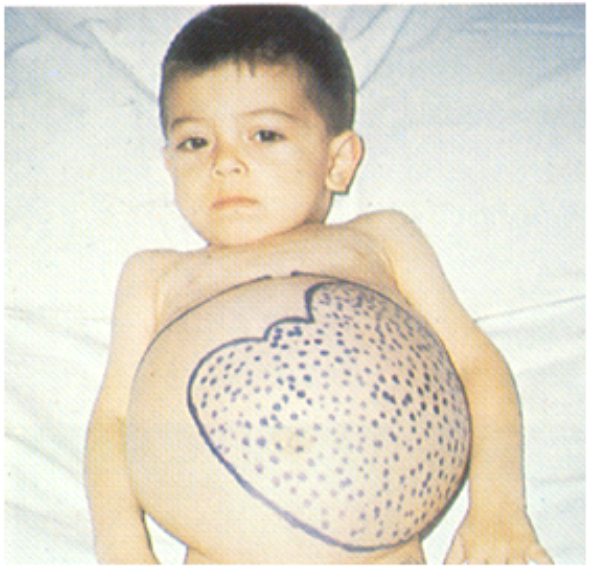
**10 patients received previous therapy with azacitidine, 2 with decitabine and 1 with both HMAs; prior HMA cycles ranged from 4-20

Navada S, et al. A phase 2 study of the combination of oral rigosertib and azacitidine in patients with myelodysplastic syndrome (MDS). *ASH* 2016

Rasopathies and JMML

JUVENILE MYELOMONOCYTIC LEUKEMIA OVERVIEW





- Hematopoietic disorder of infancy caused by excessive proliferation of monocytic and granulocytic cells; which infiltrate the spleen/liver, intestines and lungs
- Rare- 2% of pediatric hematologic malignancies (in the US about 50 new cases per year); 1.2 cases per million annually, median age is 2 years
- Present with fever, thrombocytopenia, failure to thrive, and splenomegaly.
- Frequently fatal, allogeneic stem cell transplant only curative approach; which carries an event-free survival (EFS) at 5 years of only 52% due to relapsed disease or transformation to AML
- Historically, myeloid progenitor hypersensitivity to granulocyte macrophage colony-stimulating factor (GM-CSF) is a key diagnostic feature of JMML

OVERVIEW (2)

- About 90% of JMML patients have some sort of genetic abnormality in their leukemia cells.
- This includes:
  - 15-20% of patients with neurofibromatosis 1 (NF1)
  - 25% of patients with mutations in one of the RAS family of oncogenes
  - Another 35% of patients with a mutation in PTPN11

RAS AND GENOMICS

- Major progress in understanding the pathogenesis of JMML has been achieved by deciphering the genetic lesions that initiate the disease, the majority of which encode proteins that signal in the RAS/MAPK pathway
- With the complete genomic landscape of JMML nearly defined, molecular testing has taken a fundamental role in establishing the diagnosis.
- JMML is fundamentally a disease of hyperactive Ras signaling, with somatic mutations (superimposed on germ-line lesions in some instances) in the NF1, NRAS, KRAS, PTPN11, and CBL genes found in more than 90% of cases
- Somatic point mutations in NRAS and KRAS genes occur in about 25% of JMML cases, with the most common amino acid substitutions occurring at codons 12, 13, and 61

CLINICAL DEVELOPMENT PATHWAY
(REQUIRES CLINICAL EXPERT DISCUSSION)

- JMML
  - Intravenous rigosertib
  - Oral rigosertib in combination with azacitidine
    - De novo
    - Azacitidine failures
- After MEK Failure (underway at COG)
- Post transplant recurrence

OTHER Considerations?

- Langerhans cell histiocytosis (LCH)
- driver somatic mutations in BRAF in up to 55% of patients
- activation of the RAS-RAF-MEK-ERK pathway in nearly 100% of patients with LCH.

QUESTIONS ??

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THANK YOU