Rasopathy Education Day

Precision Medicine in

Juvenile Myelomonocytic Leukemia

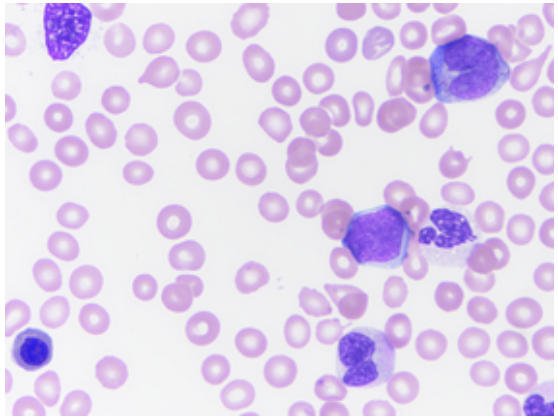
UCSF Benioff Children's Hospital
San Francisco

Elliot Stieglitz, MD

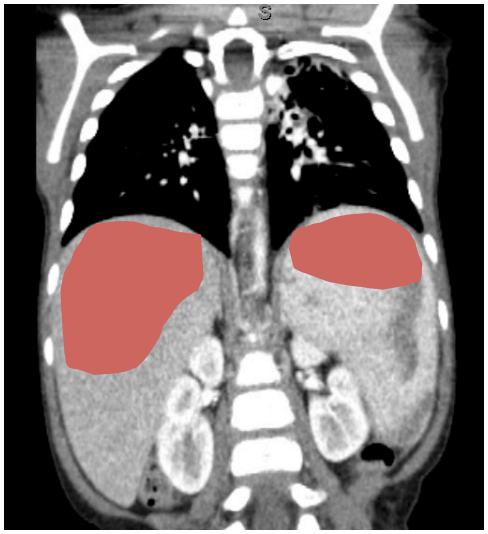
10/11/17

Juvenile Myelomonocytic Leukemia (JMML)

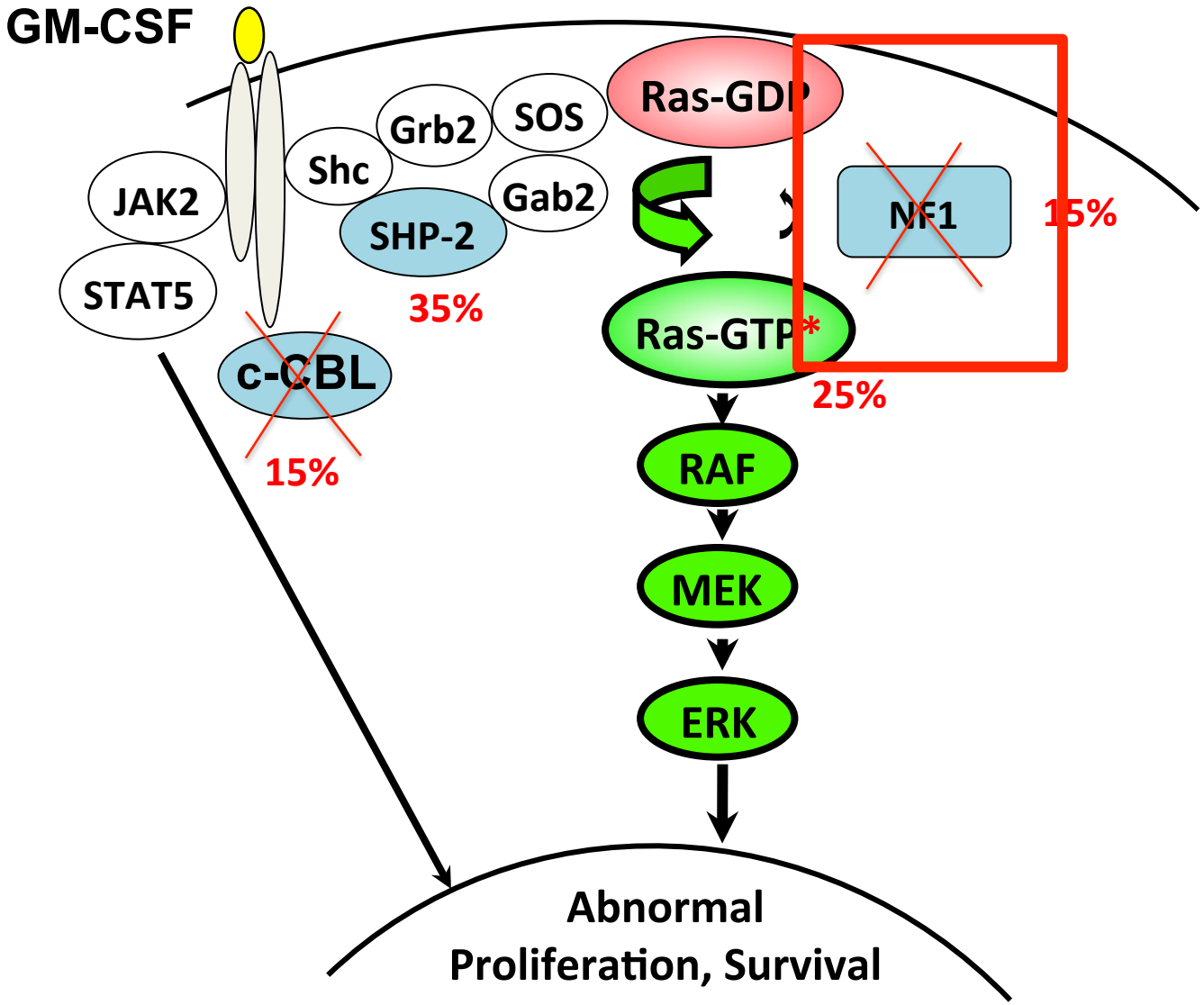
Overlapping myelodysplastic / myeloproliferative disorder



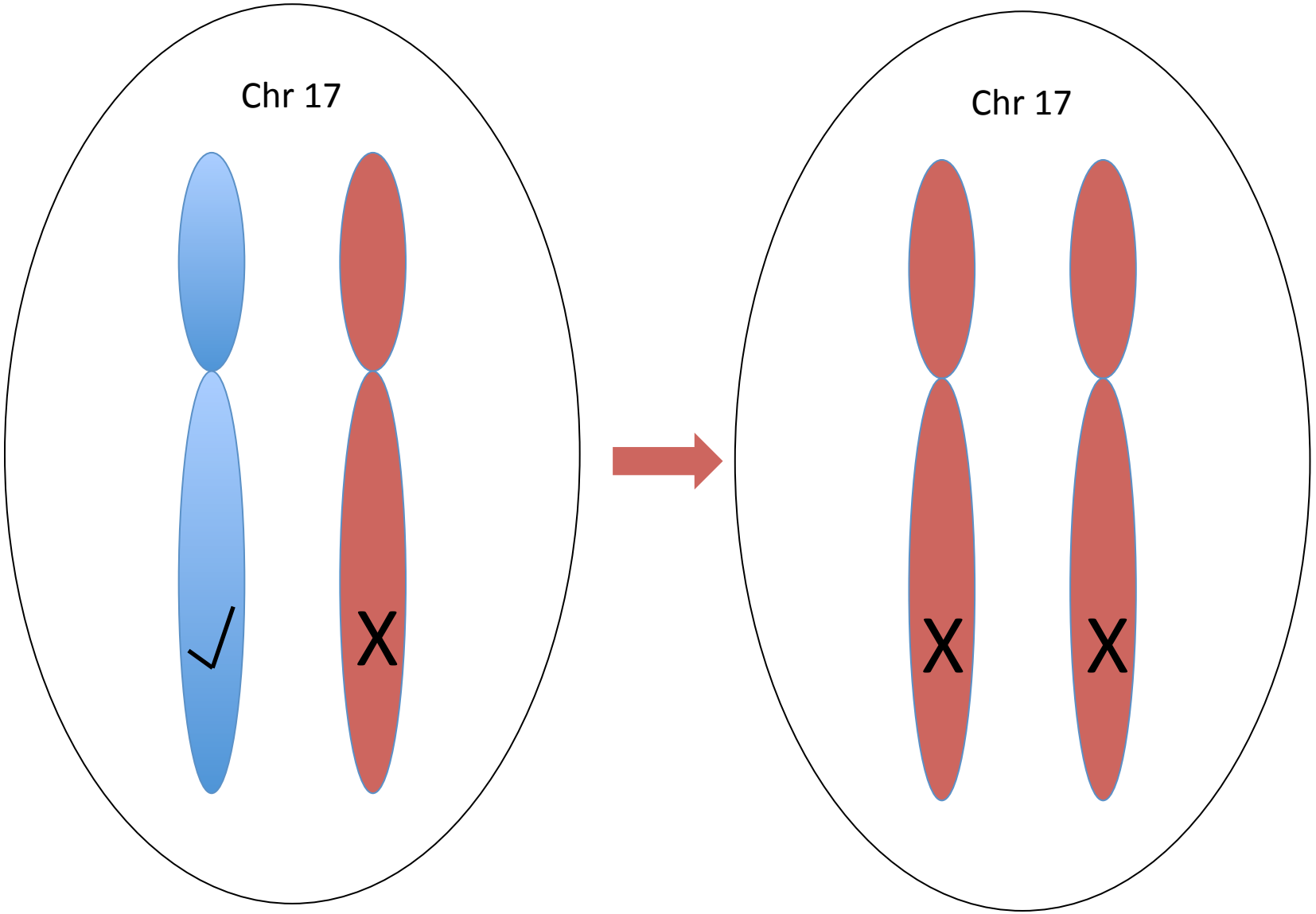
K. White, UCSF Dept. of Hematopathology



JMML is Initiated by Hyperactive Ras



Genetics of Neurofibromatosis Type I

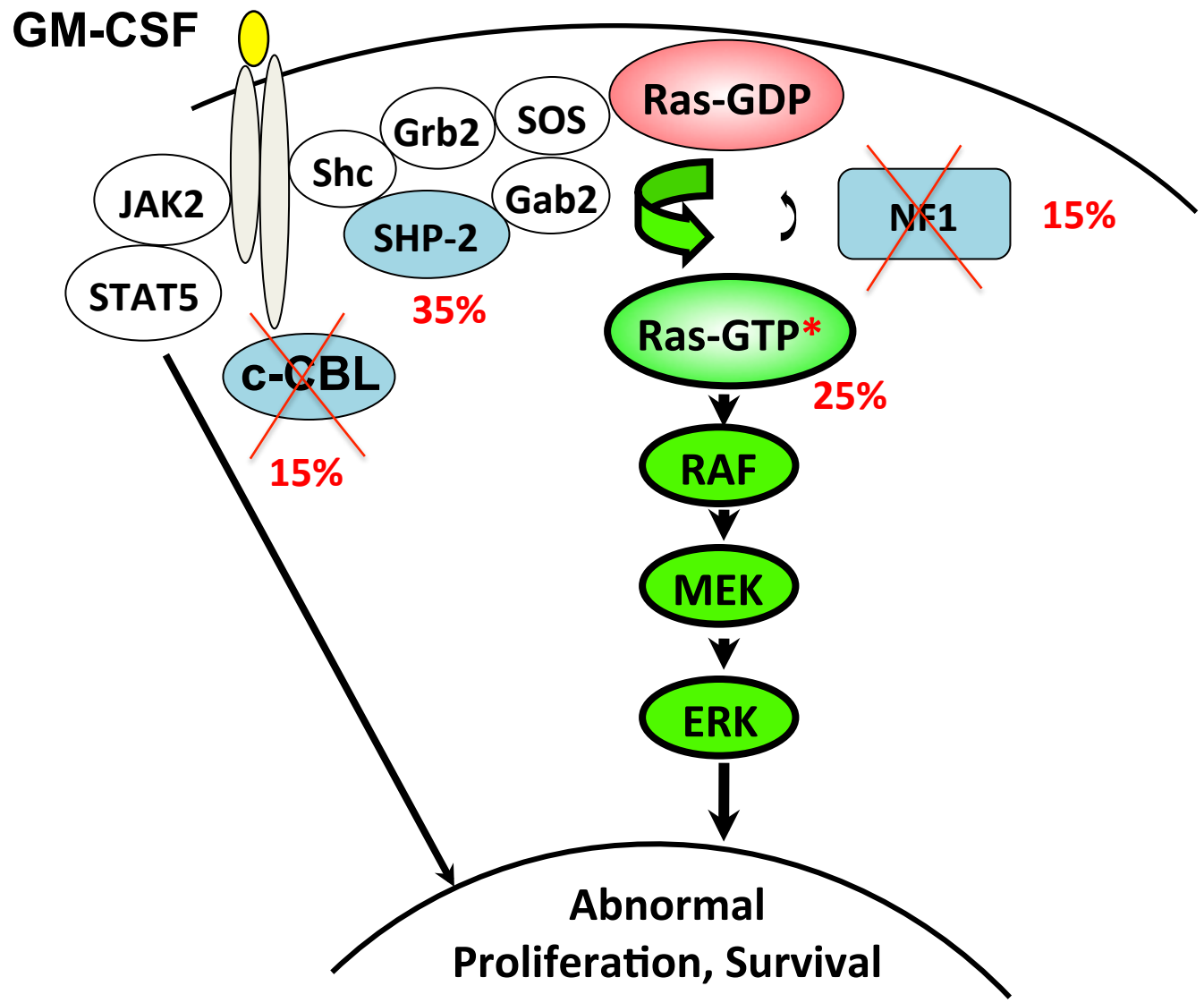


Neurofibromatosis Type 1 Related Cancers

1) Germline condition with one NF1 mutation in every cell

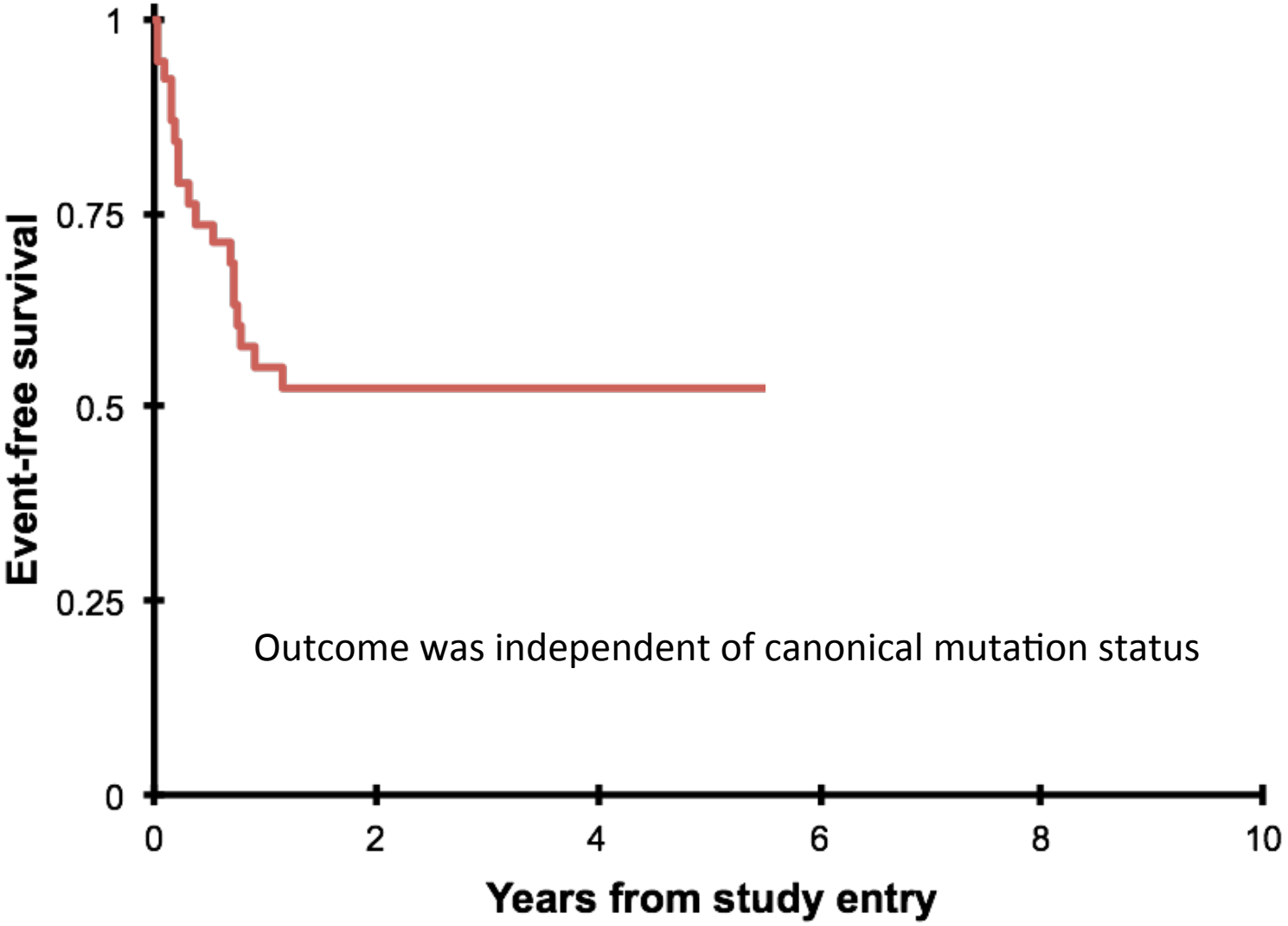
2) Patients develop cancer when the 2nd copy is lost
    1) Optic glioma
    2) Glioblastoma
    3) Leukemia
    4) Neuroblastoma
    5) MPNST
    6) GIST…

JMML is Initiated by Hyperactive Ras



NF1
KRAS
NRAS
CBL
PTPN11

Event Free Survival on AAML0122



Outcome was independent of canonical mutation status

Stieglitz et. al. *Pediatric Blood & Cancer*. (2015)

Can We Predict Which Child Will Survive?

PTPN11

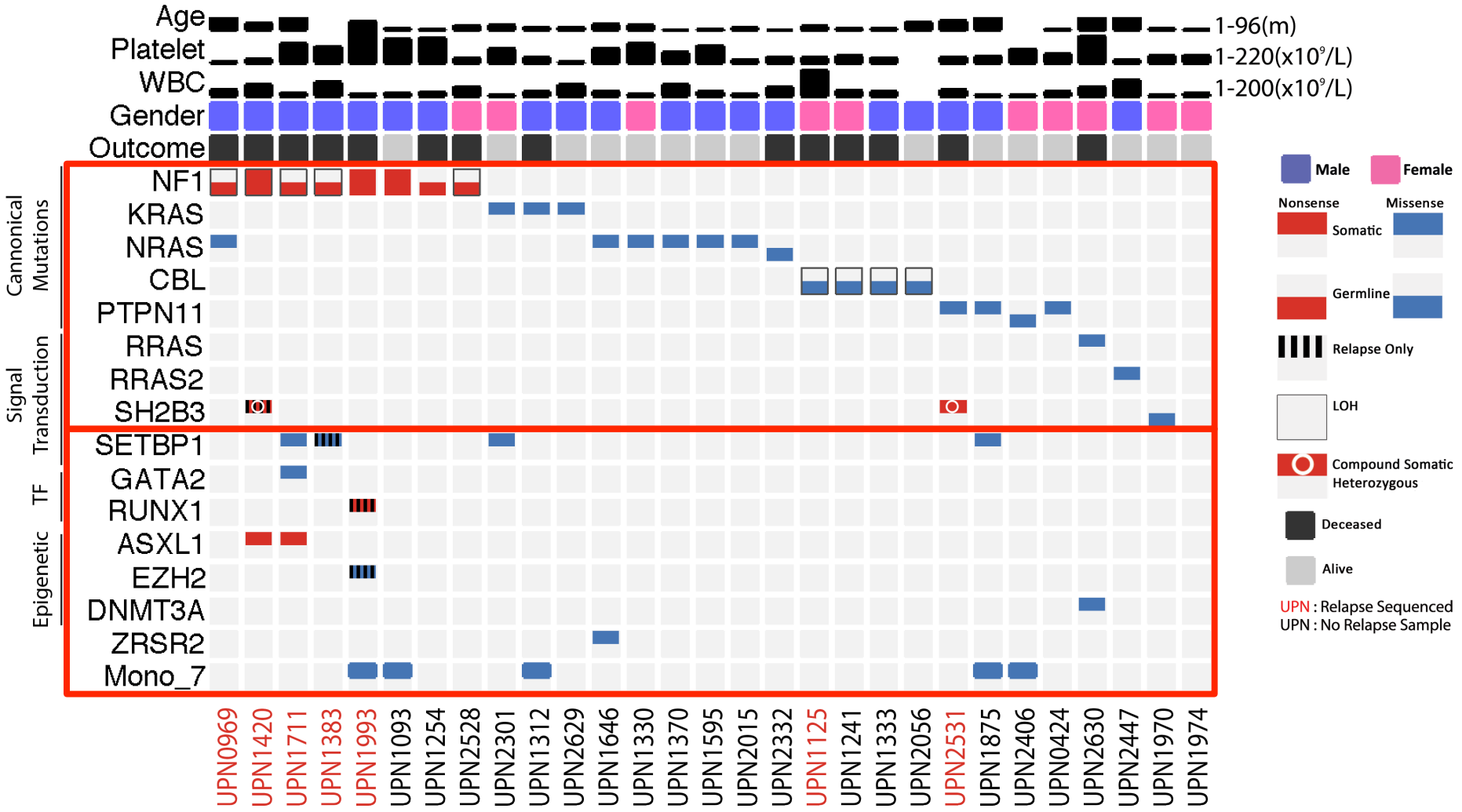
PTPN11

Hypotheses

1) *Underlying genetics and epigenetics influence outcome*

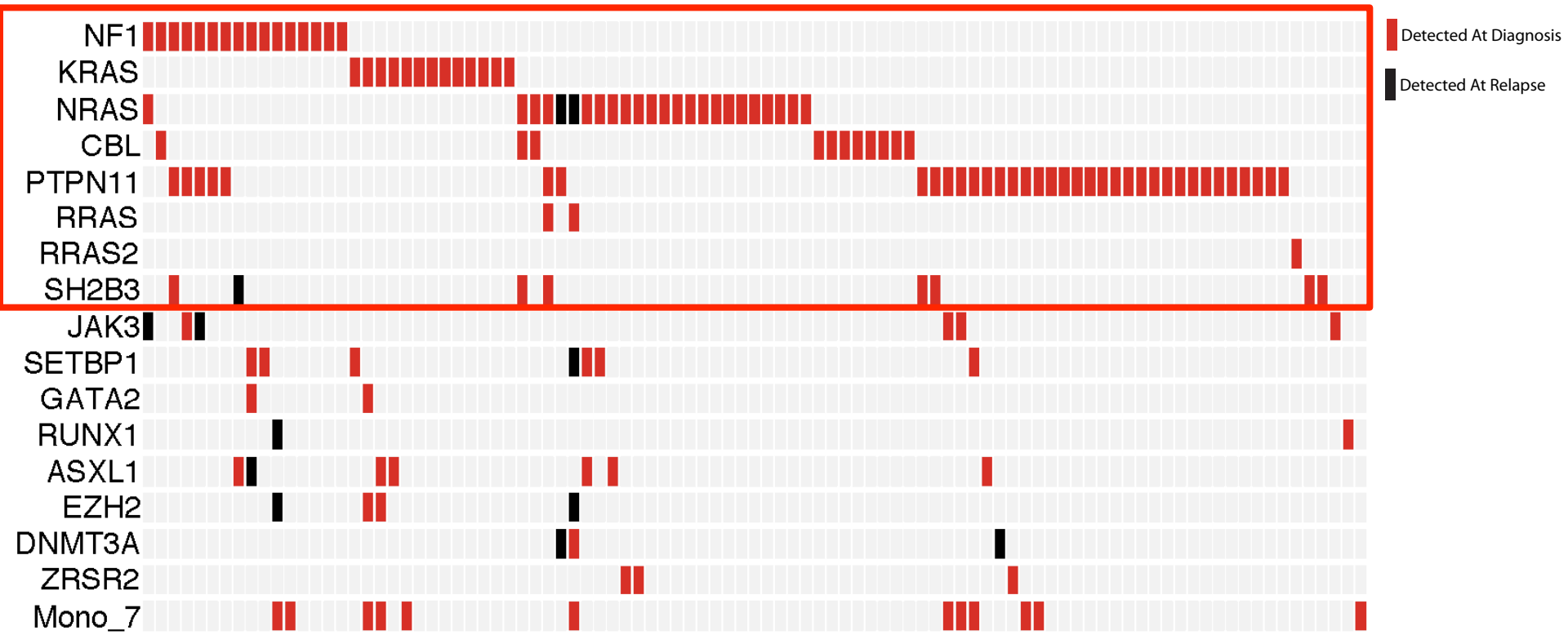
2) *Focusing on relapsed disease will yield new therapeutic opportunities*

Exome Sequencing Landscape

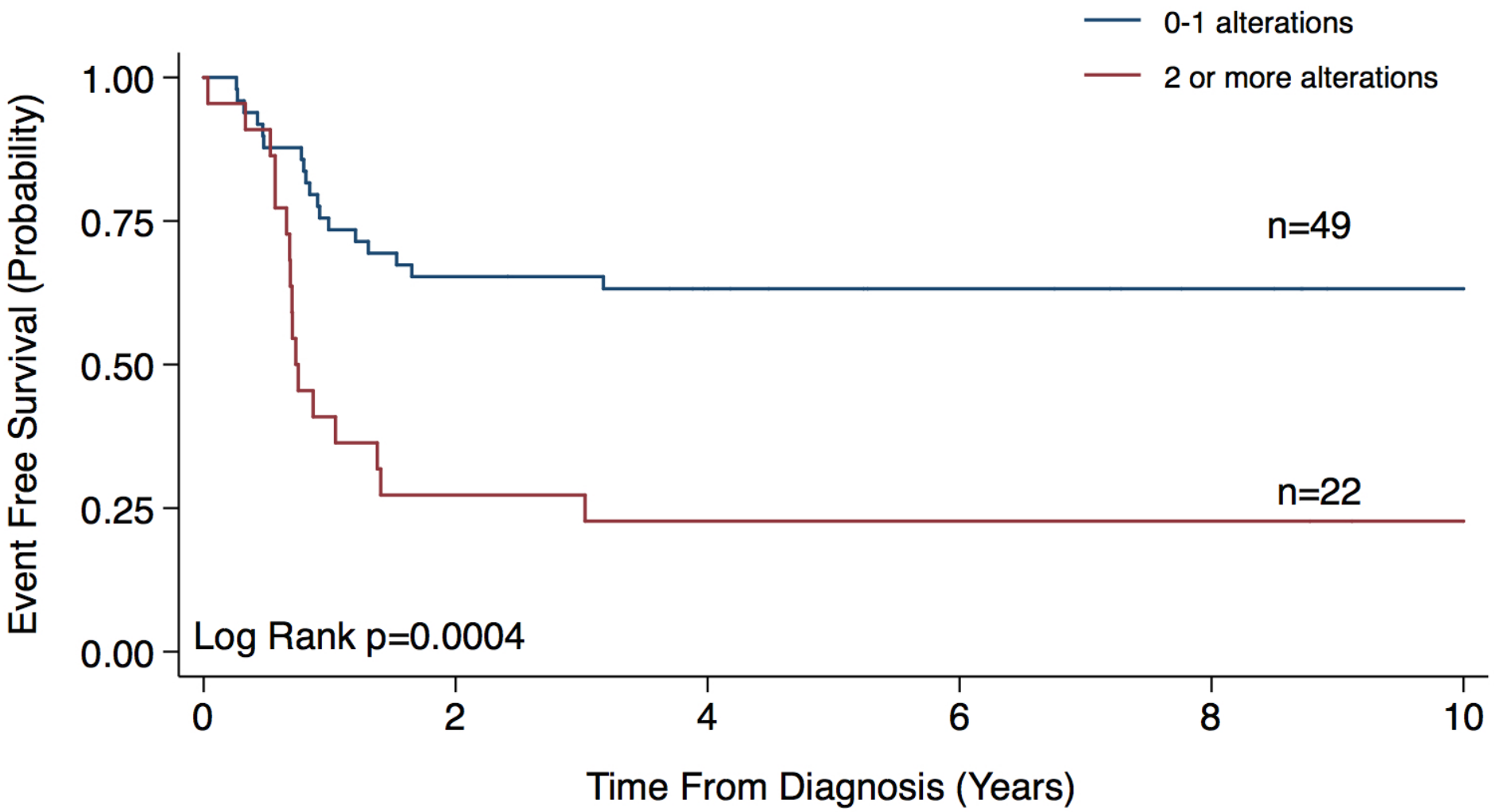


Stieglitz E & Taylor-Weiner A, et. al., *Nature Genetics*. (2015)

Mutations Identified in 100 Paitients



Validation Cohort

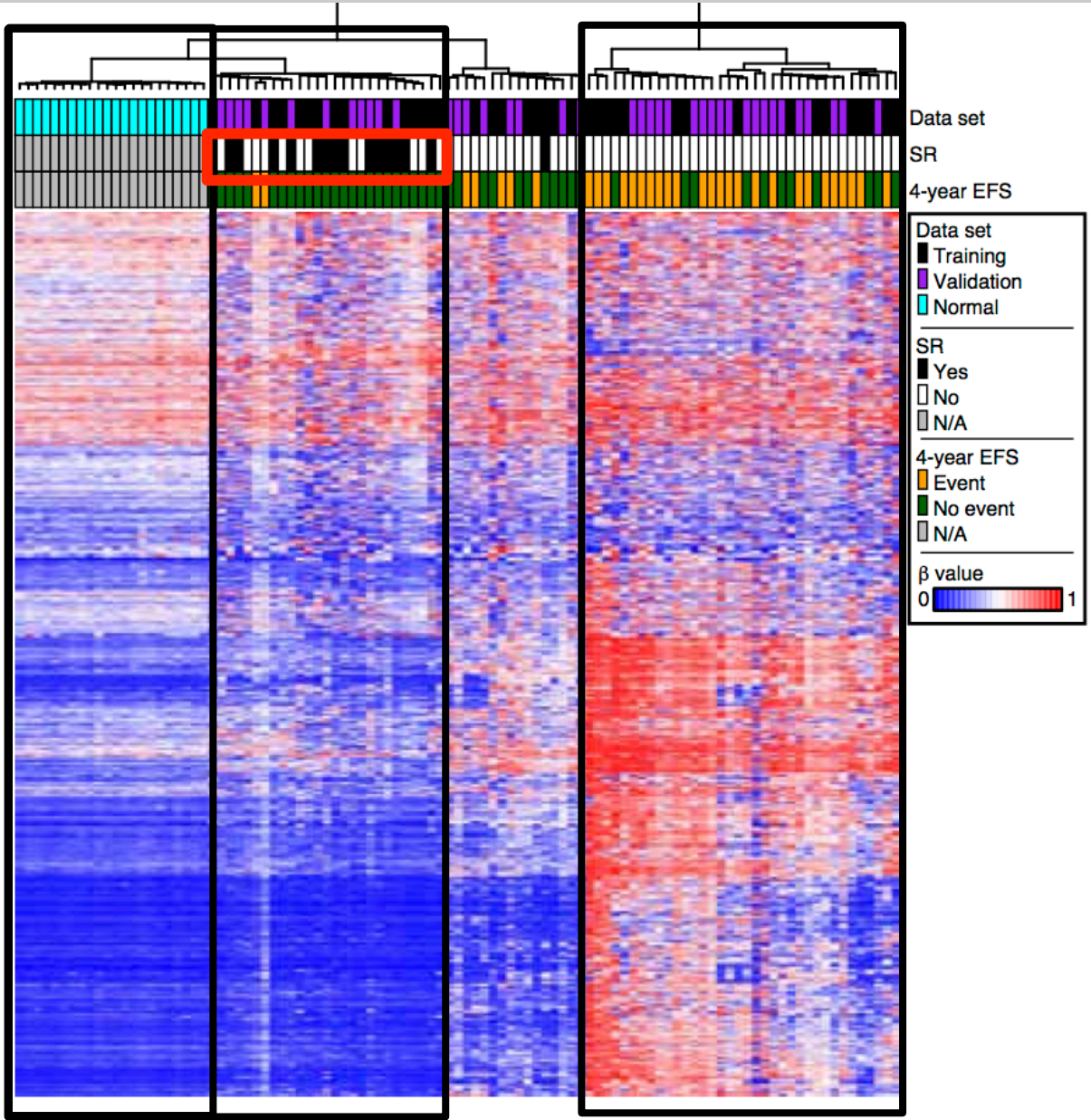


Can We Predict Which Child Will Survive?

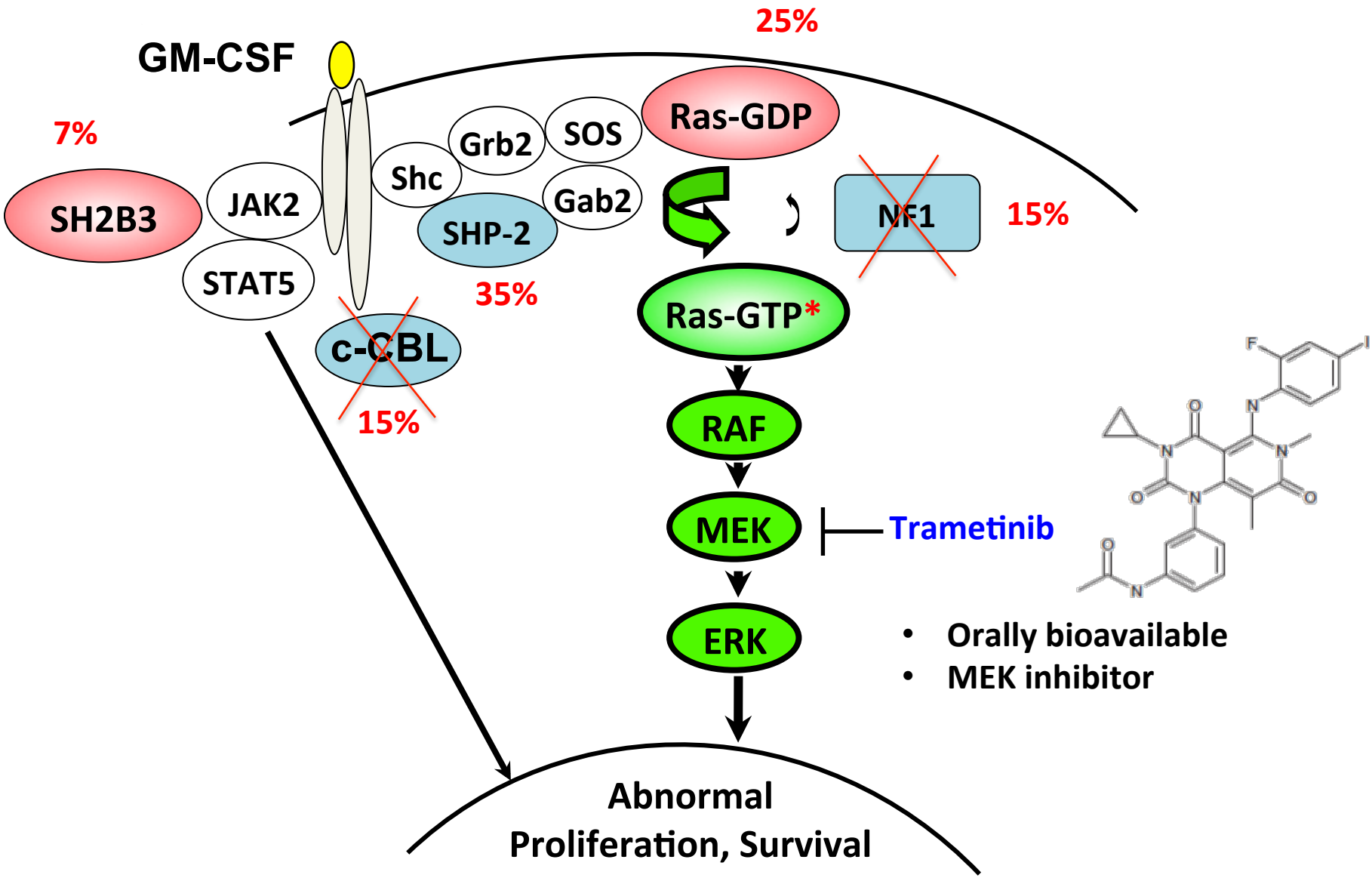
PTPN11

PTPN11 + SH2B3

Altered DNA Methylation



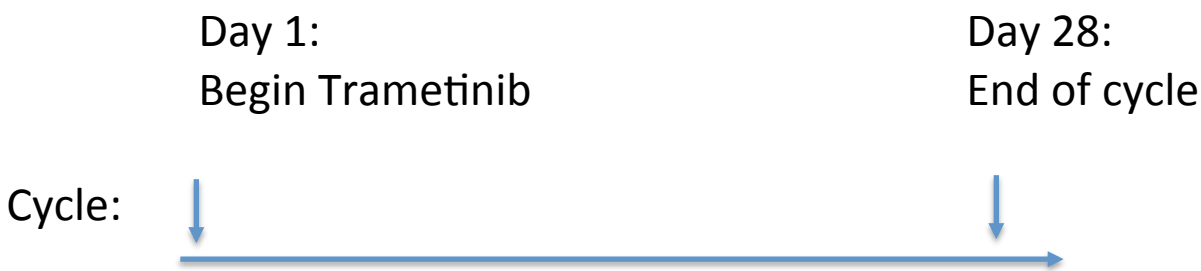
JMML is Initiated by Hyperactive Ras



ADVL1521

Phase II Study of Trametinib in children with relapsed or refractory JMML

*First trial in relapsed JMML in the United States



*Trametinib is administered orally.

ADVL1521

NIH U.S. National Library of Medicine

ClinicalTrials.gov

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Home > Study Record Detail

Save this study | Saved Studies (0)

Trametinib in Treating Patients With Relapsed or Refractory Juvenile Myelomonocytic Leukemia

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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Memo

To: Principal Investigators and Clinical Research Associates

From: Catalina Martinez, Protocol Coordinator

Re: Study Activation

Study: **ADVL1521**, *A Phase 2 study of the MEK inhibitor Trametinib (IND#119346, NSC#763093) in Children with Relapsed or Refractory Juvenile Myelomonocyti Leukemia*

Date: October 6, 2017

Concept for an International Clinical Trial

Study Entry
Genotyping and Methylation analysis
HLA typing

Ras pathway alteration
Low Methylation

↓

MEK inhibitor monotherapy x 2-3 cycles

Ras pathway alteration
Intermediate or High Methylation

↓

MEK inhibitor + Azacitidine x 2-3 cycles

↓

Stem cell transplant

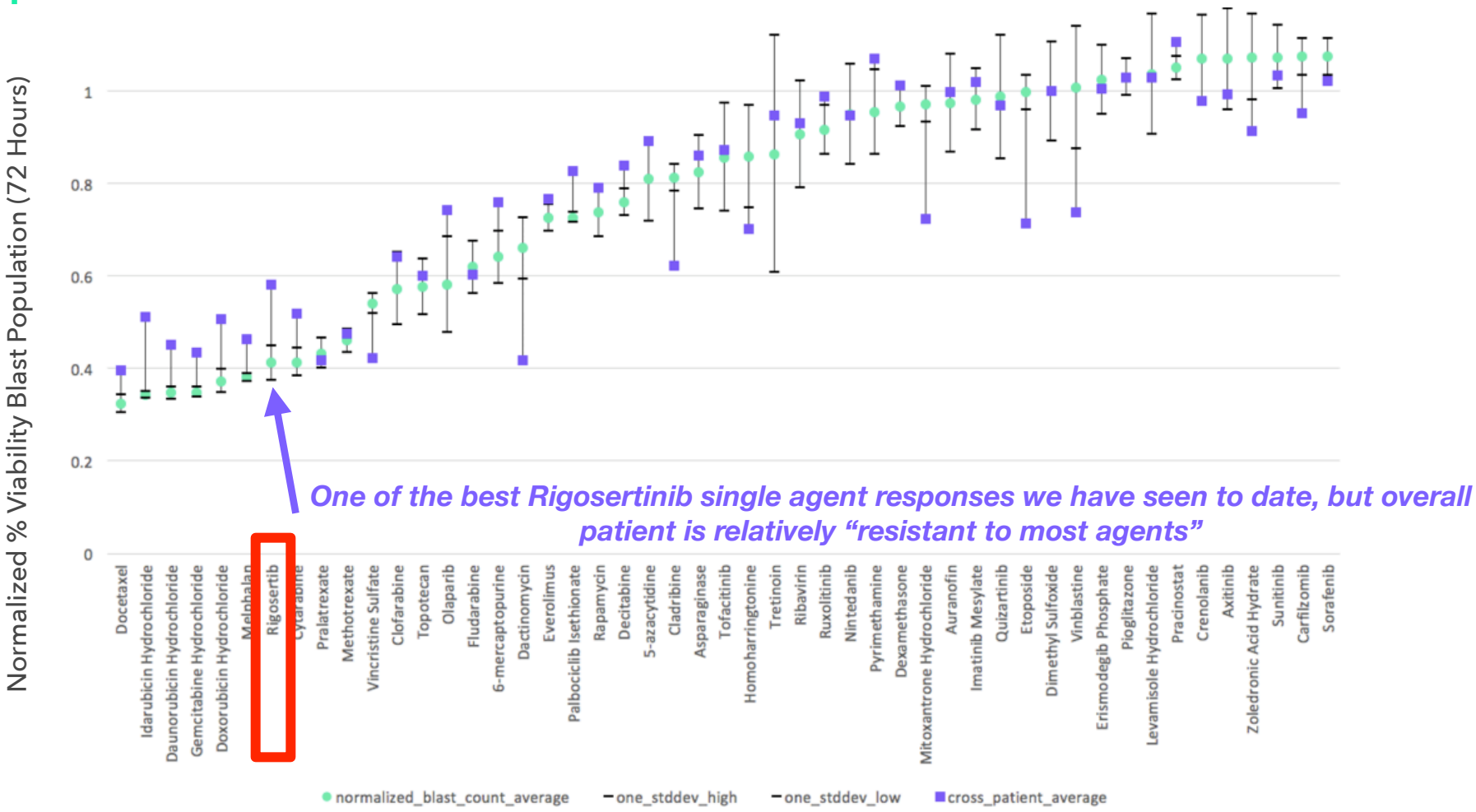
CHILDREN'S ONCOLOGY GROUP

If disease progression, roll into relapsed clinical trials…

Rigosertib in JMML?

HM5071 Overall Single Agent Results

Comparison with cross screen drug sensitivity averages (all patients)



NOONAN SYNDROME AND RELATED DISORDERS: Opportunities for Therapy

Bruce D. Gelb, M.D.
Mindich Child Health and Development Institute
Departments of Pediatrics &
Genetics and Genomic Sciences
Icahn School of Medicine at Mount Sinai

October 2017

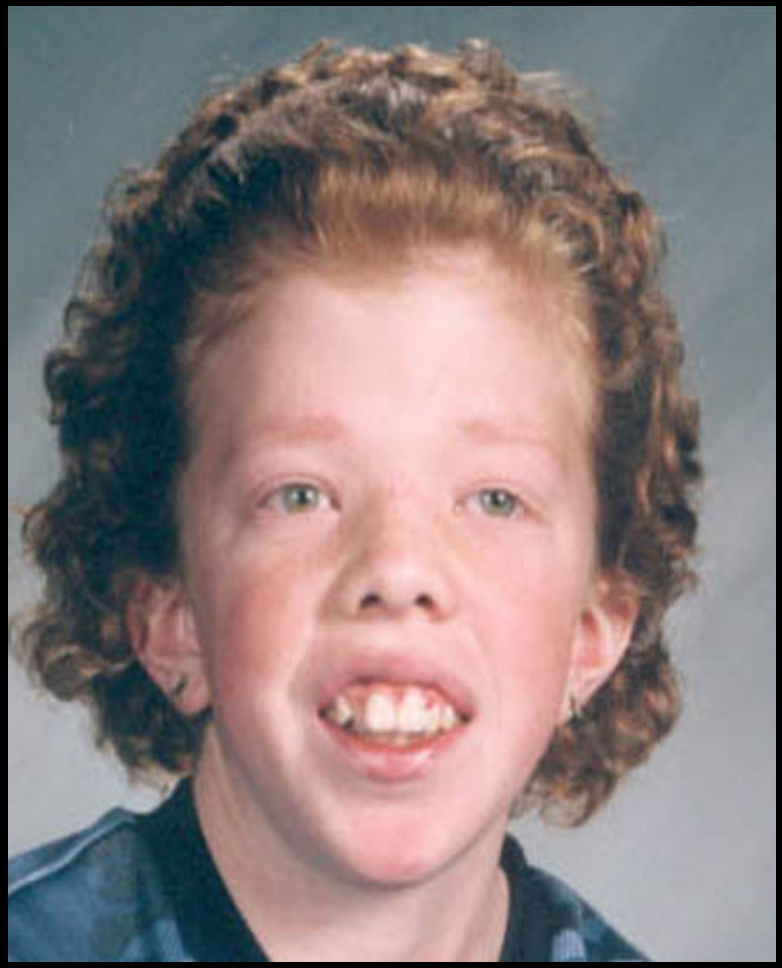
"Of particular interest was the recognition of a previously unreported syndrome in 9 patients with valvular pulmonary stenosis. These children were characterized by small stature, hypertelorism, mild mental retardation, and in some instances by ptosis, undescended testes, and skeletal malformations."

Jacqueline A. Noonan
Midwest Society for Pediatric Research
1962

Published: Am J Dis Child, 1968

Noonan Syndrome
PHENOTYPE

- Major Features
  - Short Stature
  - Facial Dysmorphism
  - Cardiovascular Disease
    - Pulmonic Valve Narrowing
    - Hypertrophic Cardiomyopathy
    - Holes in the heart
    - Aortic Narrowing



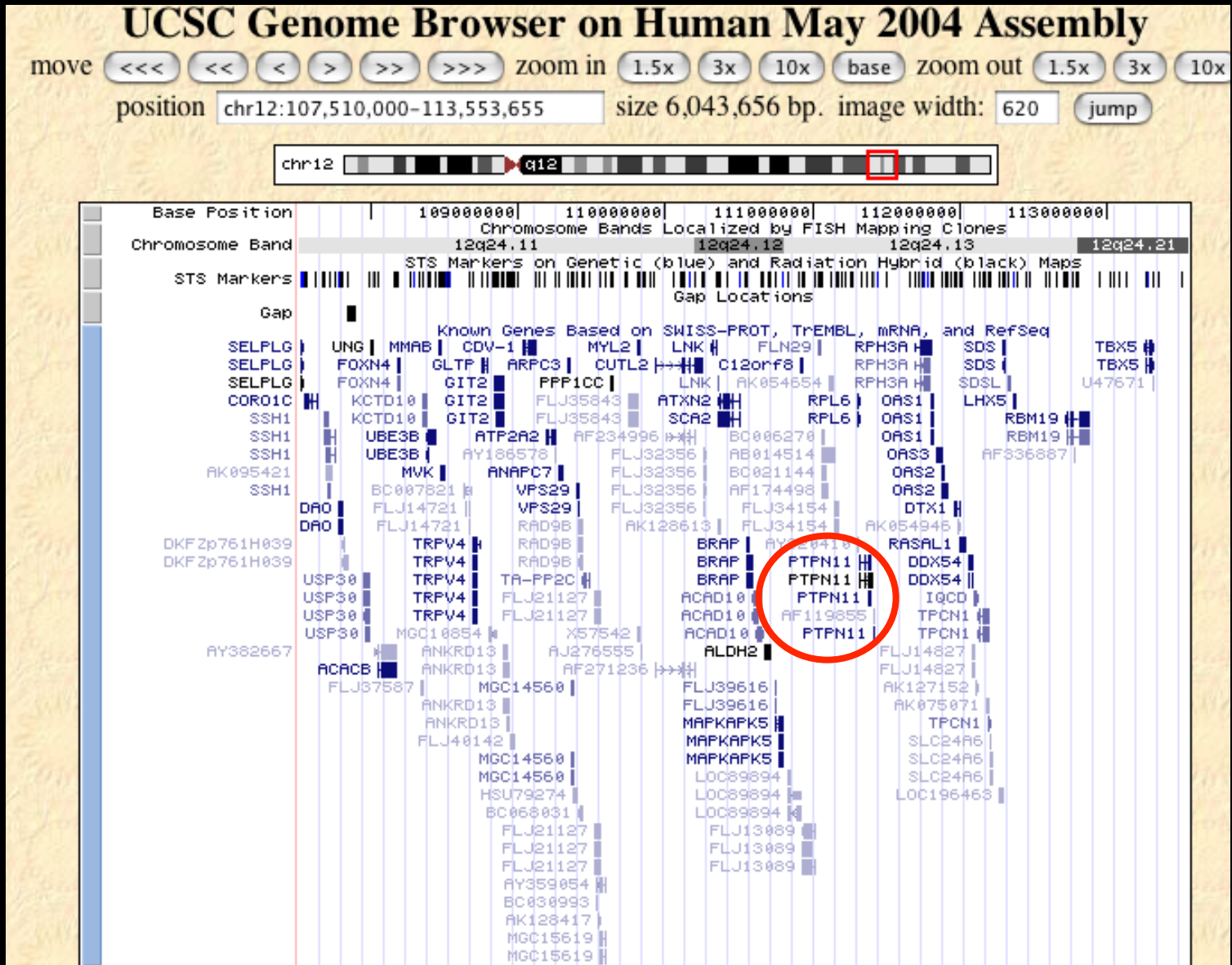
Noonan Syndrome
PHENOTYPE

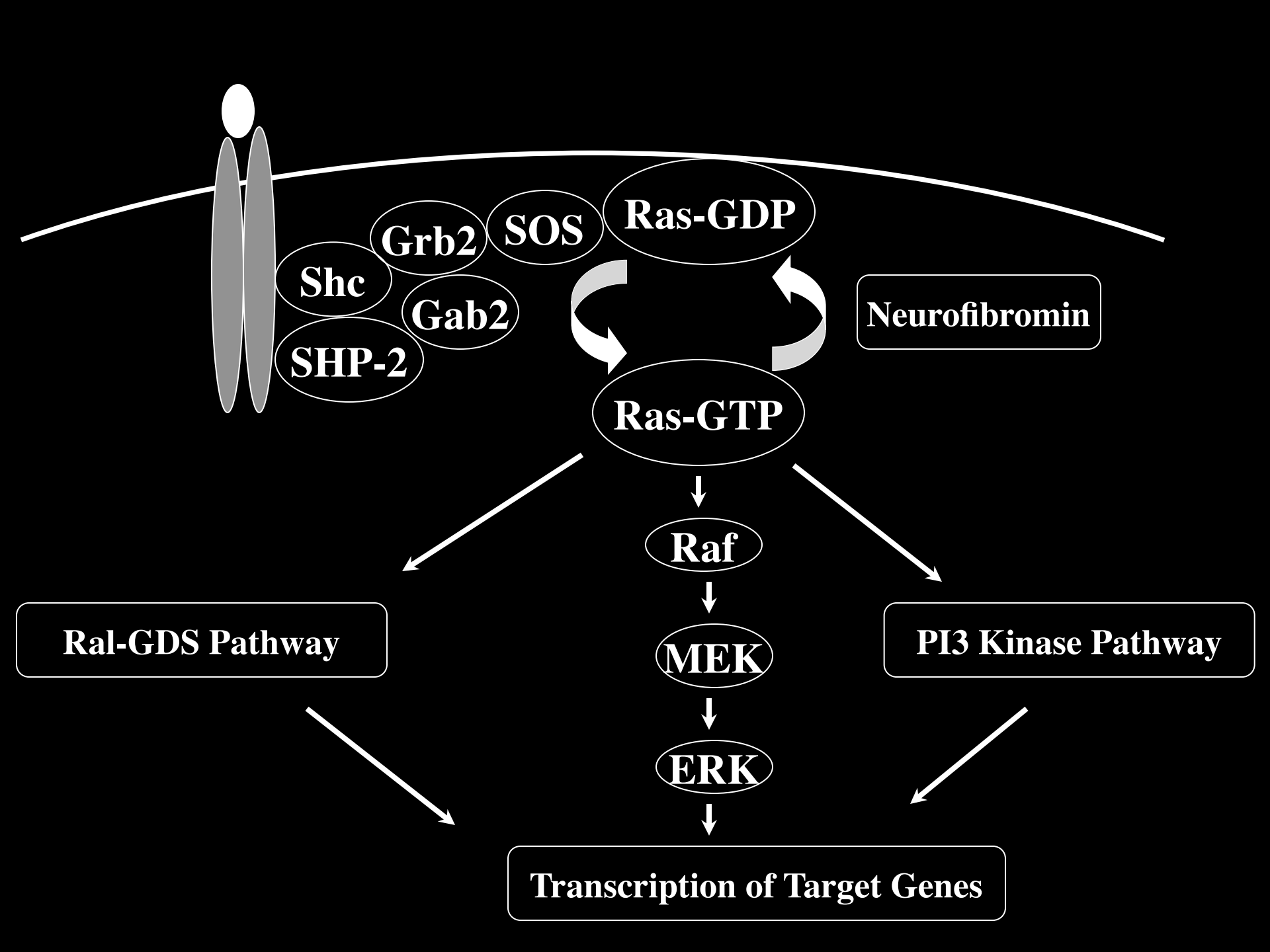
- Skeletal
  - Abnormal breastbone
  - Vertebral
  - Abnormal elbows
- Webbed/Short Neck
- Undescended testes
- Bleeding Tendency
- Intellectual and Developmental Delays (IDD)

Noonan Syndrome
EPIDEMIOLOGY & GENETICS

- Prevalence: 1 in 1,000 - 2,500 Live Births
- Autosomal Dominant
  - High Percentage of Sporadic Cases
- Genetically Heterogeneous

NS Gene Identification
POSITIONAL CANDIDACY

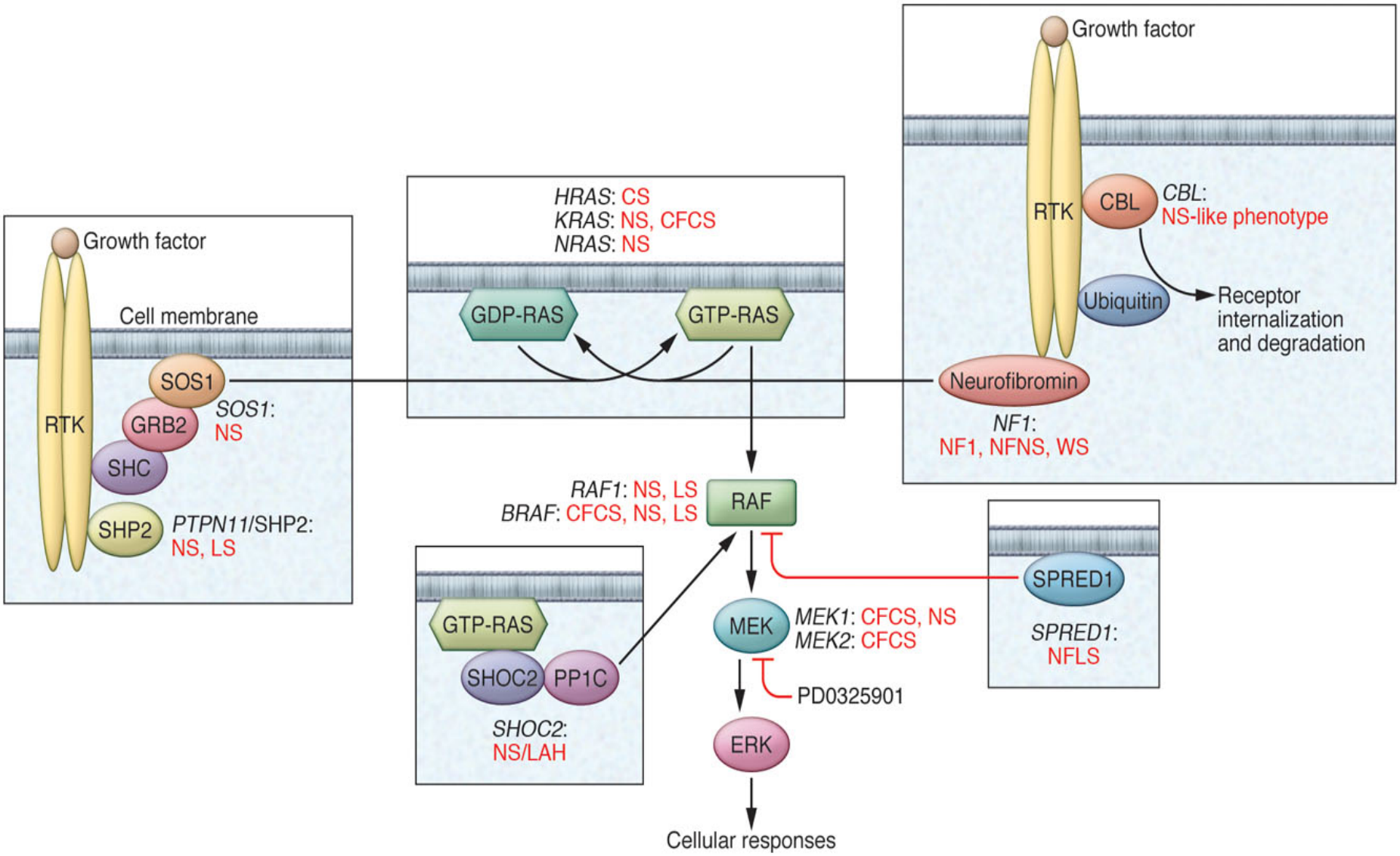



Grb2
SOS
Ras-GDP
Shc
Gab2
SHP-2
Neurofibromin
Ras-GTP
Raf
Ral-GDS Pathway
MEK
PI3 Kinase Pathway
ERK
Transcription of Target Genes

Noonan Syndrome
RELATED PHENOTYPES

- Noonan Syndrome with Multiple Lentigines (formerly LEOPARD Syndrome)
- Noonan-Like with Loose Anagen Hair
- Cardiofaciocutaneous Syndrome
- Costello Syndrome

RAS PATHWAY DISORDERS



Gelb and Tartaglia, *J Clin Invest* 2011

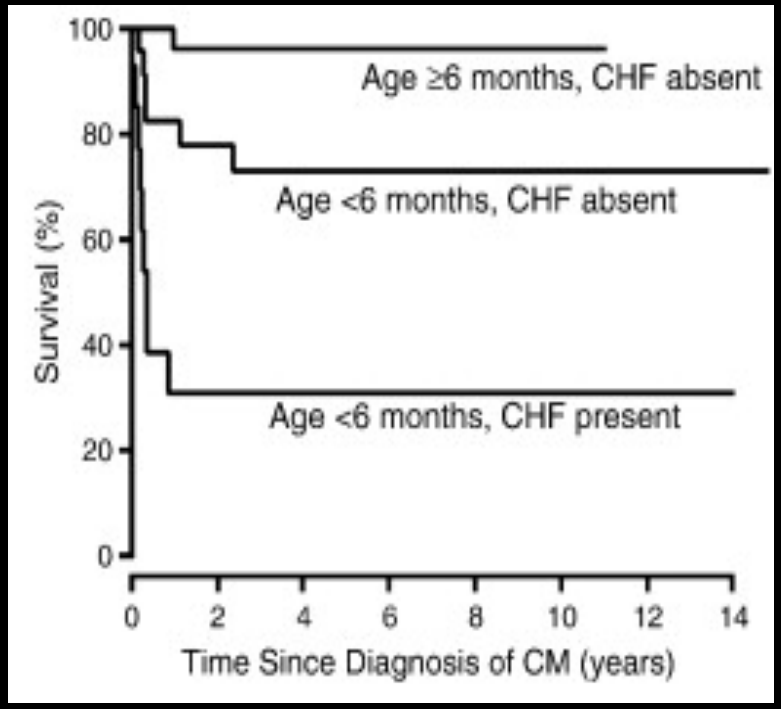
Noonan Syndrome
GENOTYPE-PHENOTYPE

- *PTPN11*
  - Increased Pulmonic Valve Narrowing and Atrial Holes
  - JMML (Leukemia)
- *KRAS*
  - Severe with Skin Involvement and IDD
- *SOS1*
  - Normal Stature and Development
  - Skin Involvement
- *RAF1*
  - Hypertrophic Cardiomyopathy
- *SHOC2*
  - Abnormal Hair

RASopathy Drug Therapy POSSIBILITIES

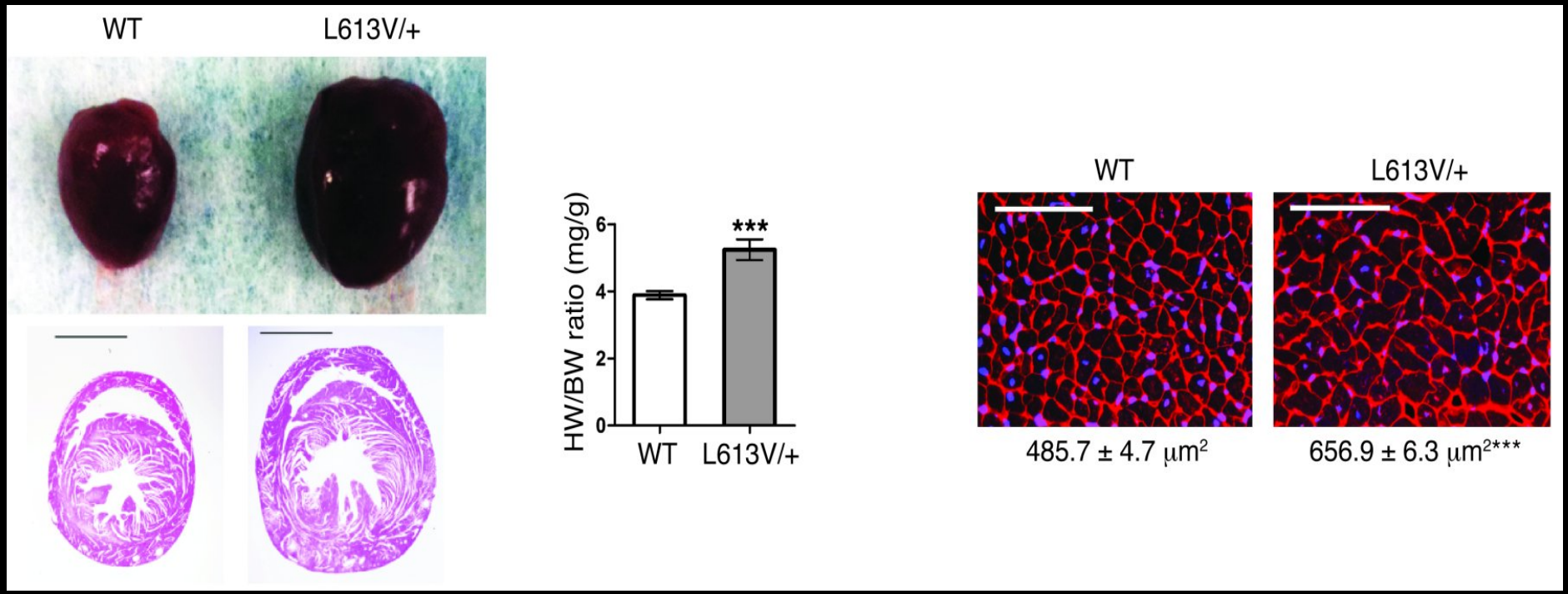
- Hypertrophic Cardiomyopathy
- Developmental Delay
- Postnatal Valve Narrowing
- Short Stature
- Craniofacial Abnormalities

NS Hypertrophic Cardiomyopathy
SURVIVAL



Wilkinson *et al*., *Am Heart J* 2012

Raf1 L613V Mutant MOUSE KNOCK IN

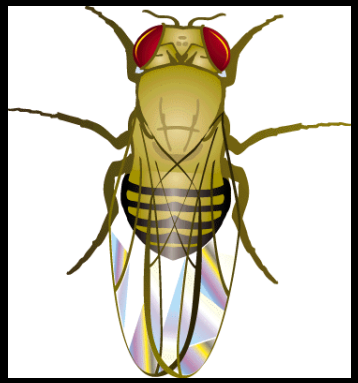


Wu *et al*., *J Clin Invest* 2011

Raf1 L613V Knock-In Mouse Study SUMMARY

- Mapk Signaling
  - Increased Erk Activation
  - No Change in p38 or JNK
- Mek Inhibitor (PD0325901)
  - 6-Week Treatment from 4 Weeks of Age
  - Rescued Hypertrophic Cardiomyopathy

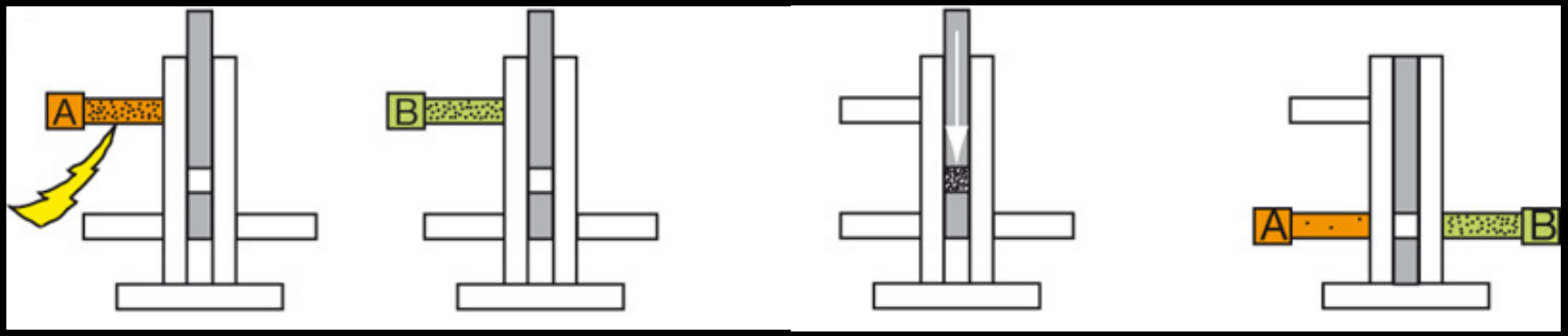
NOONAN SYNDROME AND NSML



- Generated Transgenic NS and NSML Flies
- NS Flies
  - Gain-of-Function Ectopic Wing Veins
- NSML Flies
  - Gain-of-Function Wing Veins & R7 Photoreceptors

Drosophila Learning & Memory

OLFACTORY CONDITIONING



Training Test

Vosshall, *Nature* 2007

Drosophila Memory Deficit

SUMMARY

- Specific Long-Term Memory Deficit
- Due to Increased MAPK Activation
- Not Developmental
  - Can Be Induced in Adulthood
- Treatable
  - SHP-2 Inhibitor
  - Altered Training Paradigms

- Does This Apply to Patients with Noonan Syndrome?

LEANING ON CANCER

- Human Cancers
  - 30-40% RAS Pathway Mutations
    - Acquired, Not Inherited
  - Gain in Pathway Signaling
    - Blocking Pathway → Cancer Cell Death
- Drug Companies
  - Developing RAS/MAPK Inhibitors

CAUTIONARY NOTES

- MEK Inhibitor Side Effects
  - Serious Skin Rashes
  - Diarrhea
  - Severe Leukopenia
- Time Course
  - Cancer: Relatively Short
  - RASopathy: ?????

POTENTIAL FOR RIGOSERTIB

- Side Effect Profile
  - Data from MDS Encouraging
  - No Data for Children
    - Could be from JMML Studies?
- Target
  - Severe Hypertrophic Cardiomyopathy
    - Need Pre-Clinical Data
      - Mouse Models Available

Acknowledgments

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Susumu Hirabayashi

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Maria Kontaridis
Amy Roberts

Duke
Matthew Wolf

ONCONOVA THERAPEUTICS

Rigosertib

Strategies to the Rasopathies

Steven Fruchtman, M.D.
Chief Medical Officer & Senior Vice President
Research & Development

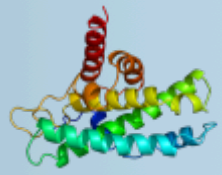
Rasopathy Conference NYC

Oct 11 2017

GENETIC BASIS OF CANCER ACQUIRED MUTATIONS

Boveri proposes existence of tumor suppressor genes and oncogenes

Knudson proposes "2-hit" hypothesis to explain genetic basis of inherited and sporadic retinoblastomas



The first human tumor suppressor gene (*RB1*) is cloned

1st human tumor exomes are sequenced (breast and colon)

COSMIC
Catalogue of somatic mutations in cancer
v78

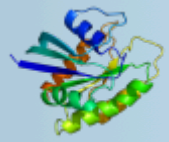
602 genes are listed in the Cancer Gene Census

1914 1960 1971 1976 1982 1987 2003 2006 2008 2016

1st human chromosome abnormality (Ph) identified

Viral *src* oncogene is derived from normal gene

The first mutated genes (*RAS*) identified in human cancer*



The Human Genome Project is completed

1st human tumor genome is sequenced

The three RAS genes (HRAS, KRAS and NRAS) comprise the most frequently mutated gene family in cancer (~25%)

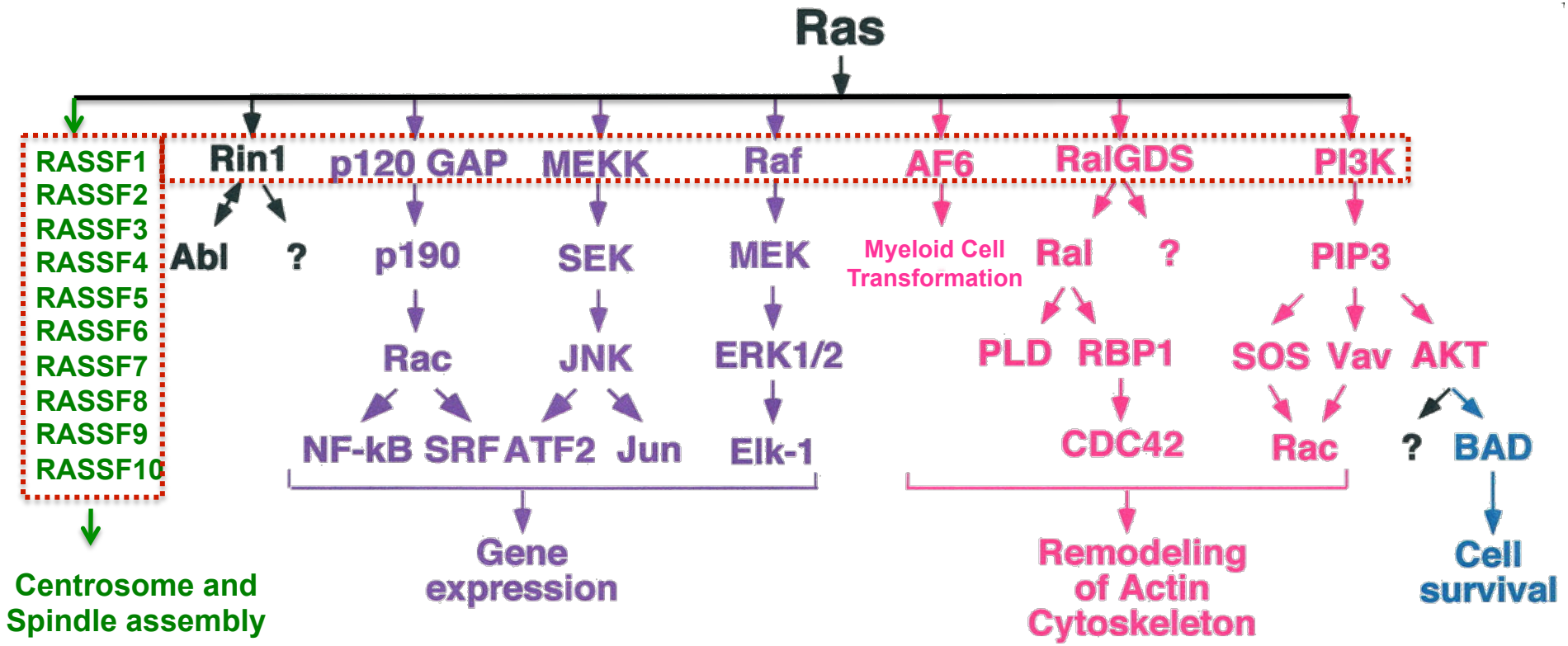
RASOPATHIES:

RARE PEDIATRIC DISEASES LINKED BY A COMMON MECHANISM

- A group of genetic syndromes caused by germline and/or somatic mutations in genes that encode components or regulators of the Ras/mitogen-activated protein kinase (MAPK) pathway.

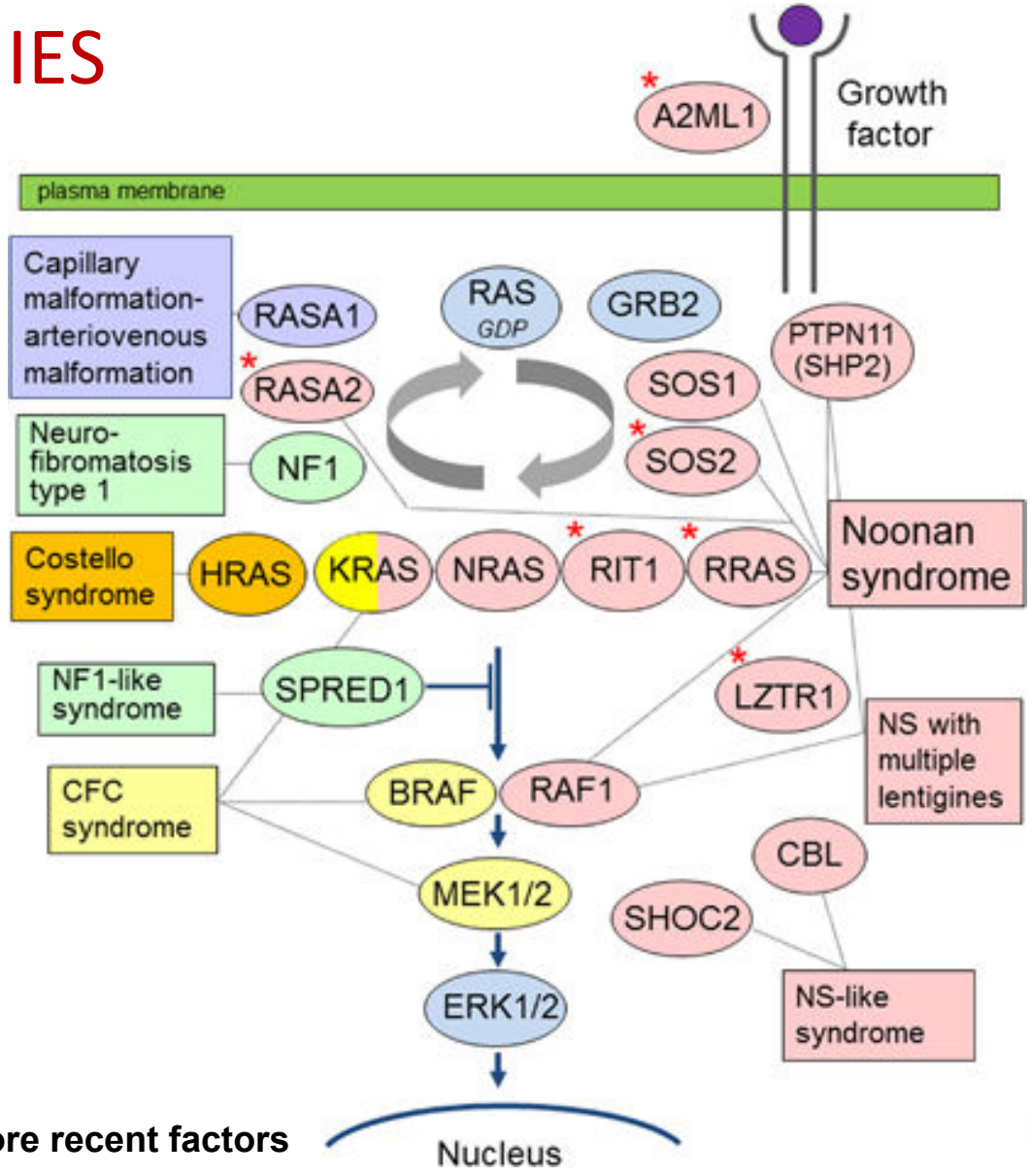
- Typically involve tumors of the bone marrow (JMML- referred to as a Pediatric MDS or MPN)) or the nervous system/soft tissue fascia and may be associated with other end organ abnormalities (cardiac, cranio-facial).

RAS SIGNALS VIA MULTIPLE EFFECTORS



Effector proteins contain common RAS-binding domain (RBD)

RAS/MAPK/ERK PATHWAY AND RASOPATHIES



*More recent factors

DESCRIPTION OF RIGOSERTIB AS A RAS MIMETIC

Article

Cell

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

Sai Krishna Athuluri-Divakar,[1,2] Rodrigo Vasquez-Del Carpio,[1,2] Kaushik Dutta,[3] Stacey J. Baker,[1,2] Stephen C. Cosenza,[1,2] Indranil Basu,[5] Yogesh K. Gupta,[1,2] M.V. Ramana Reddy,[1,2] Lynn Ueno,[4] Jonathan R. Hart,[4] Peter K. Vogt,[4] David Mulholland,[1,2] Chandan Guha,[5] Aneel K. Aggarwal,[1,2] and E. Premkumar Reddy[1,2,*]

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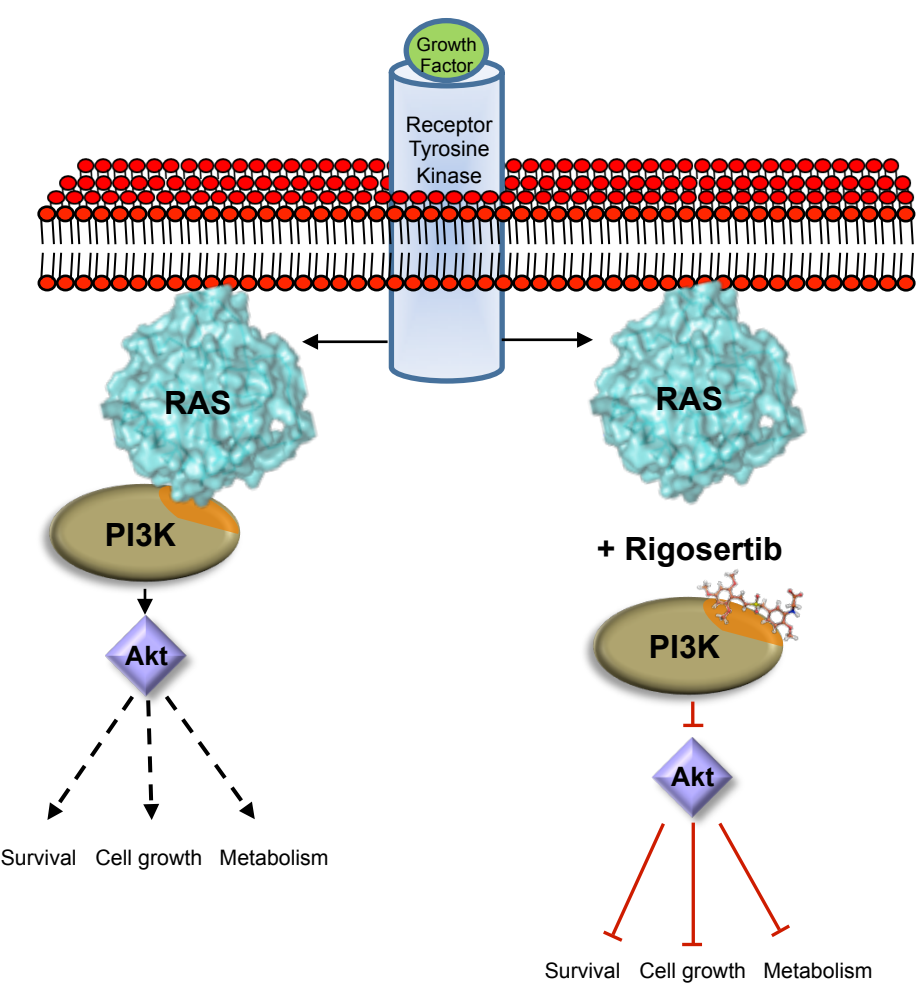
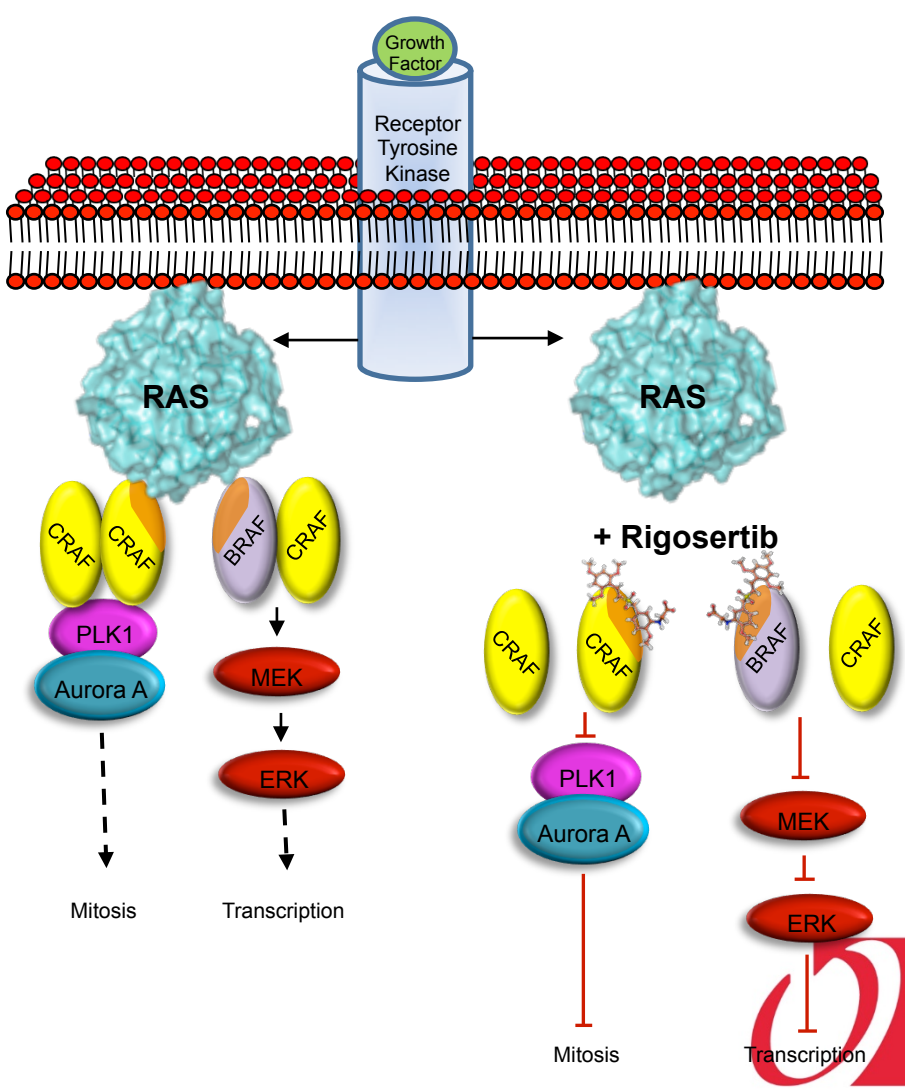
*Correspondence: ep.reddy@mssm.edu

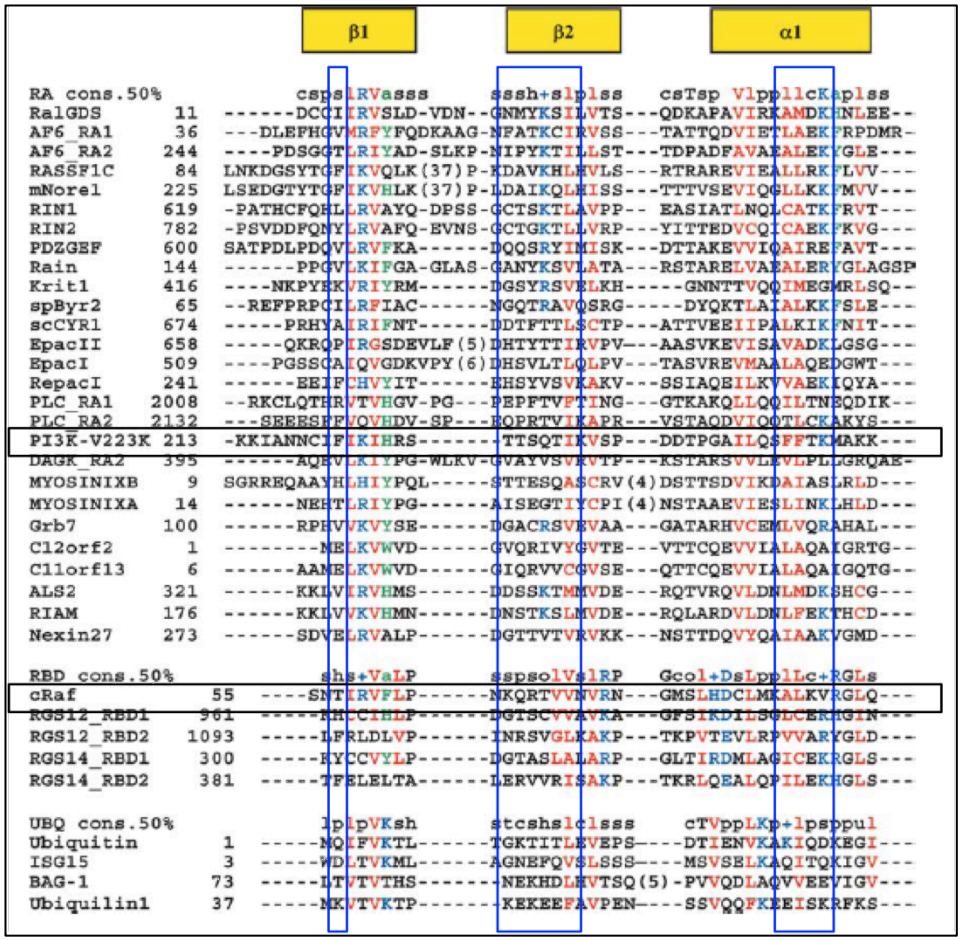
RIGOSERTIB MECHANISM OF ACTION





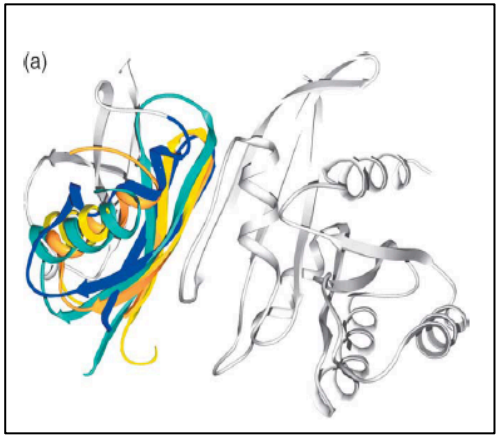
SECONDARY/TERTIARY STRUCTURAL SIMILARITY OF RBDS DESPITE LACK OF EXTENSIVE SEQUENCE HOMOLOGY

Sequence Alignment of RA and RB Domains

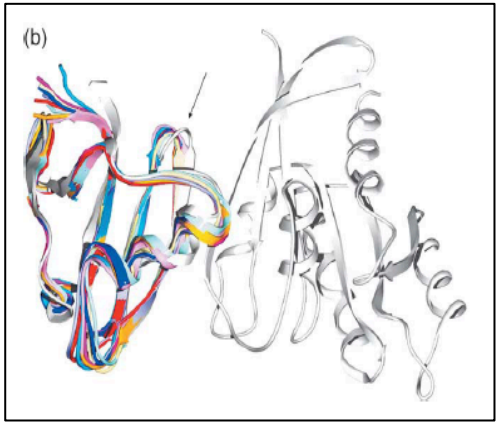


Yellow: Hydrophobic Core; Cyan: Conserved Charged Amino Acids
Red: Conserved Hydrophobic AA; Green: Conserved Aromatic AA

RAF/Ral-GDS/PI3K Crystal Structures Superimposed



NMR Structures of 10 RBDs Superimposed



NOVEL MECHANISM OF ACTION OF RIGOSERTIB

History:

- 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.**

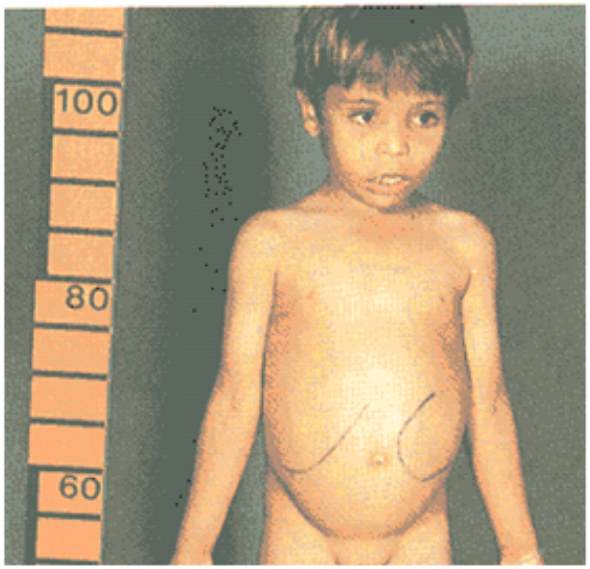
- This novel mechanism helps to explain the pleiotropic effects of rigosertib, such as inhibition of the PI3K and PLK pathways.

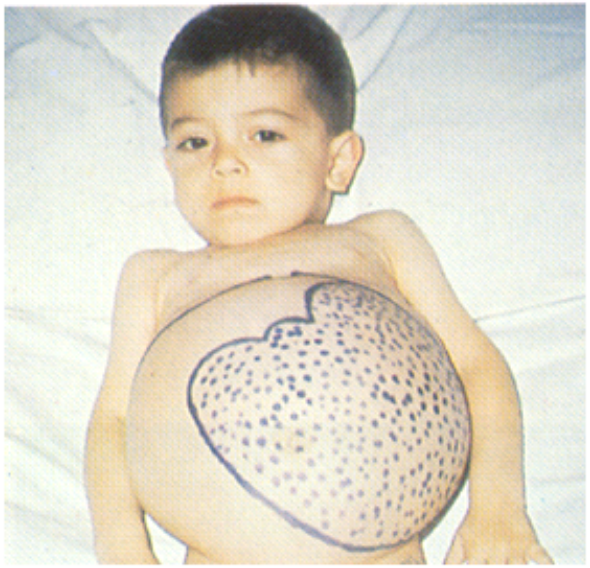
Future directions:

- 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 due to Ras activating mutations**

JUVENILE MYELOMONOCYTIC LEUKEMIA OVERVIEW

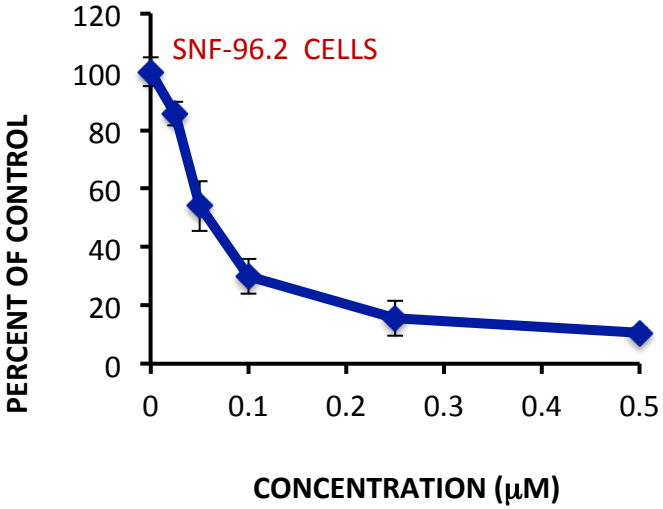


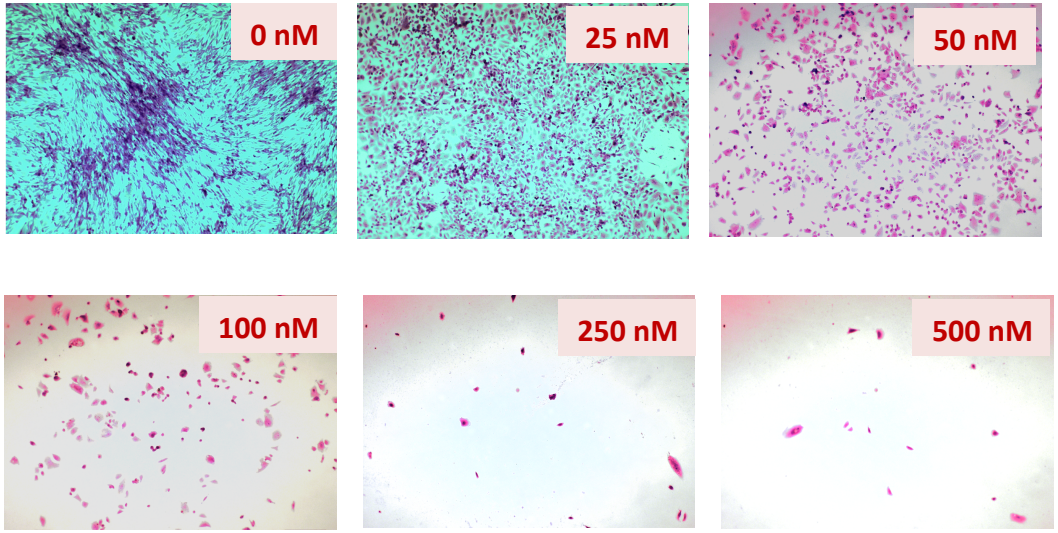


- Hematopoietic disorder of infancy caused by excessive proliferation of monocytic and granulocytic cells; which infiltrate the spleen/liver, intestines and lungs
- Rare- 2% of pediatric hematologic malignancies (in the US about 50 new cases per year); 1.2 cases per million annually, median age is 2 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

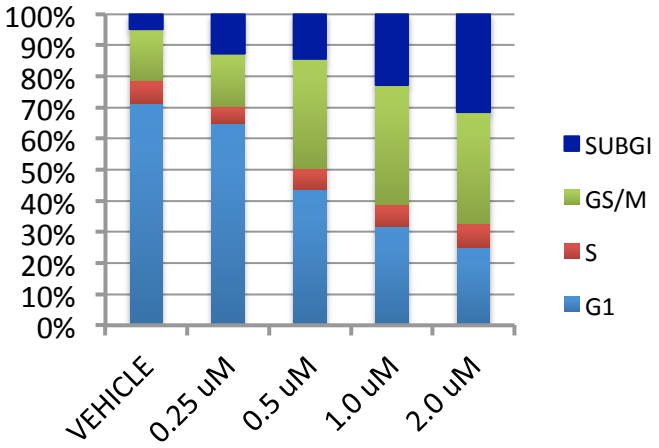
GROWTH INHIBITION AND INDUCTION OF APOPTOSIS WITH RIGOSERTIB IN NF1 CELLS

Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

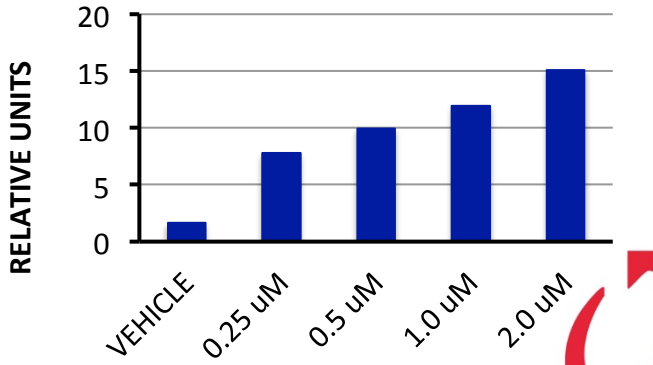




FACS Analysis of SNF 96.2 Cells Treated With Rigosertib



PARP Cleavage Assay



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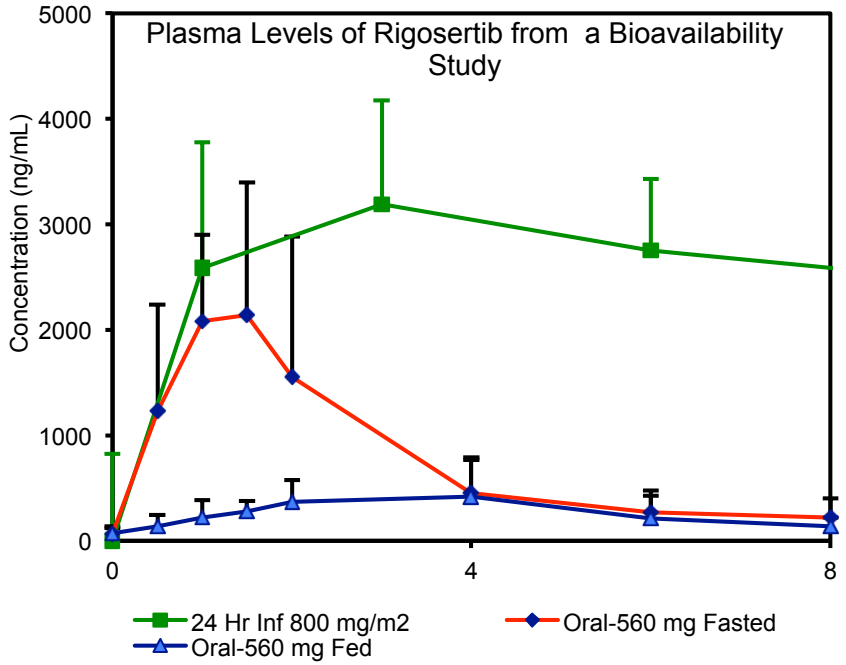
Clinical Trials in MDS

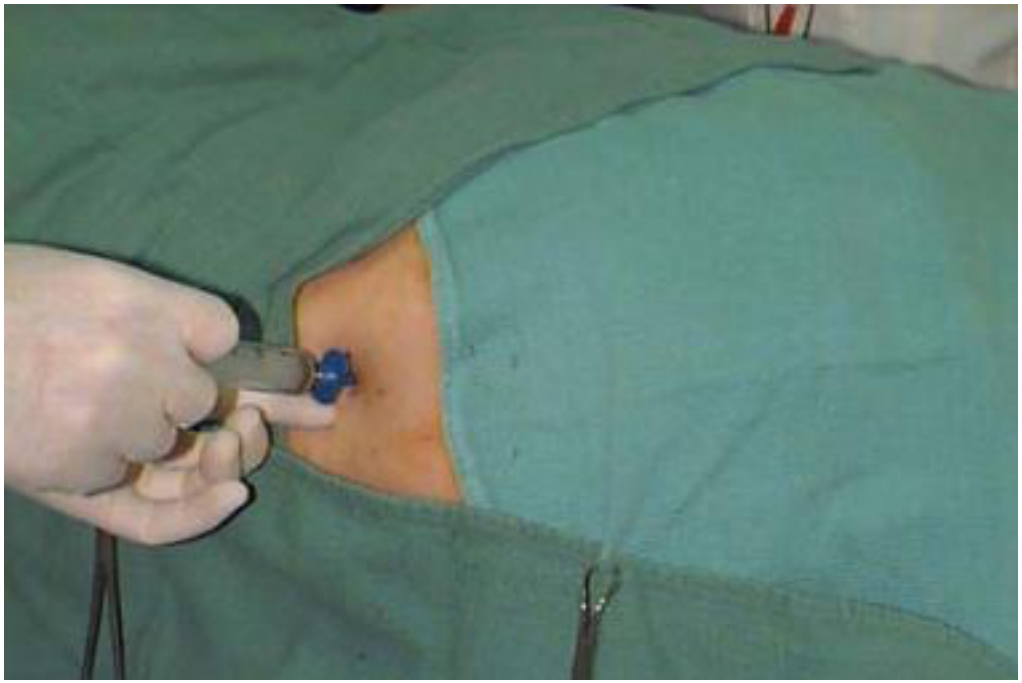
TWO RIGOSERTIB FORMULATIONS

- 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

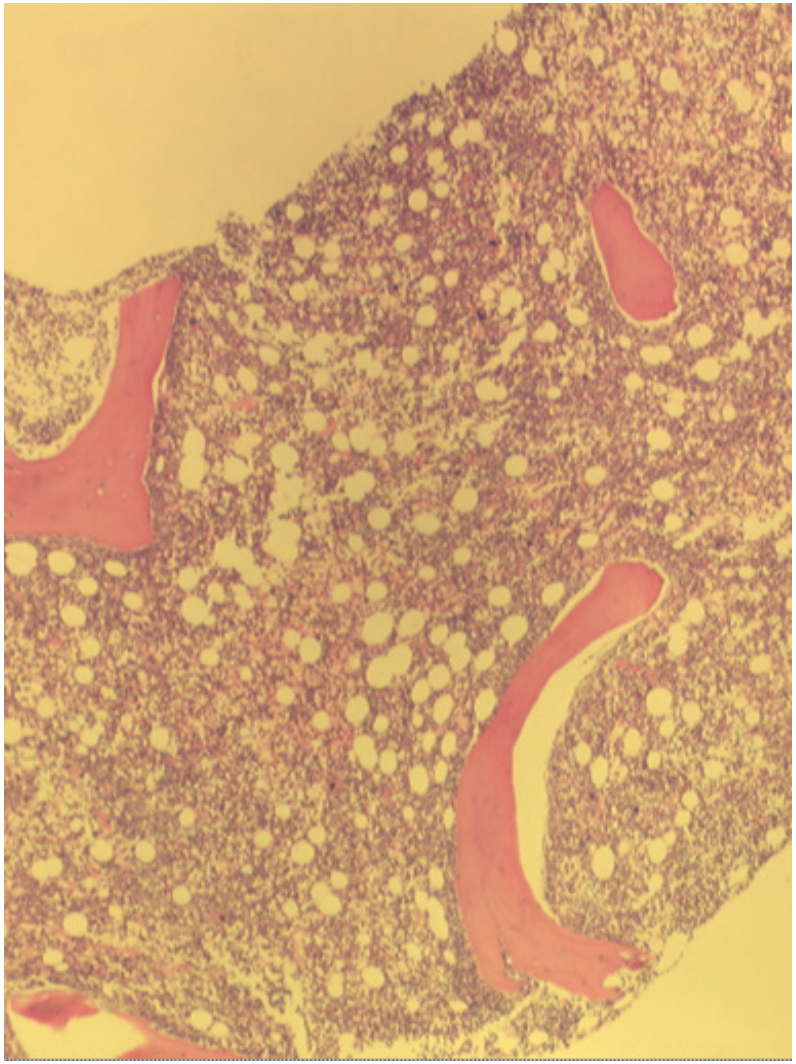


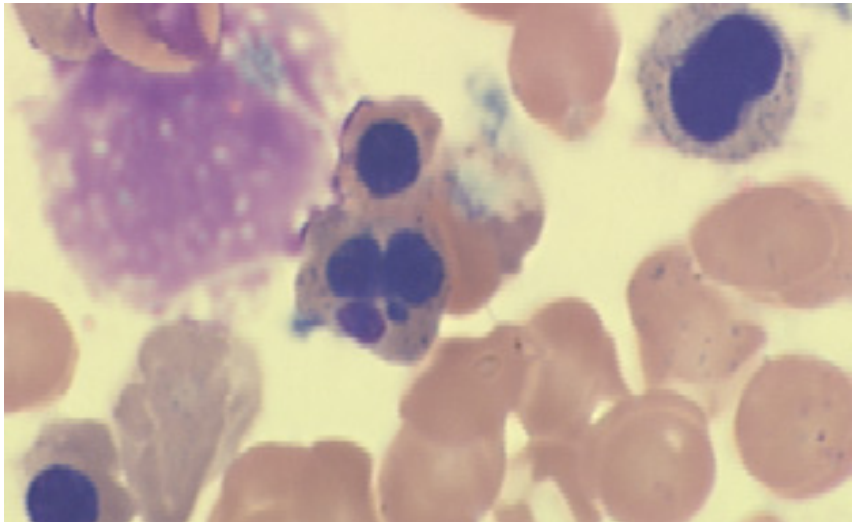
BONE MARROW ASPIRATE

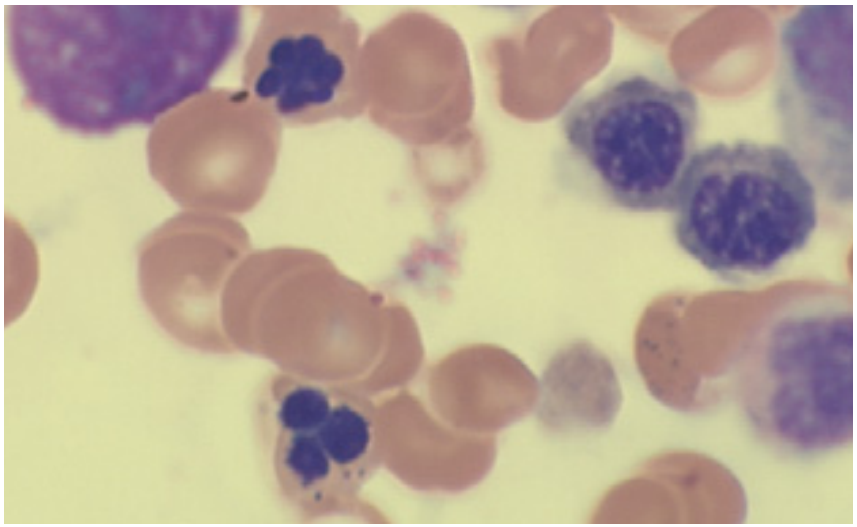
BEST FOR CELLULAR MORPHOLOGY



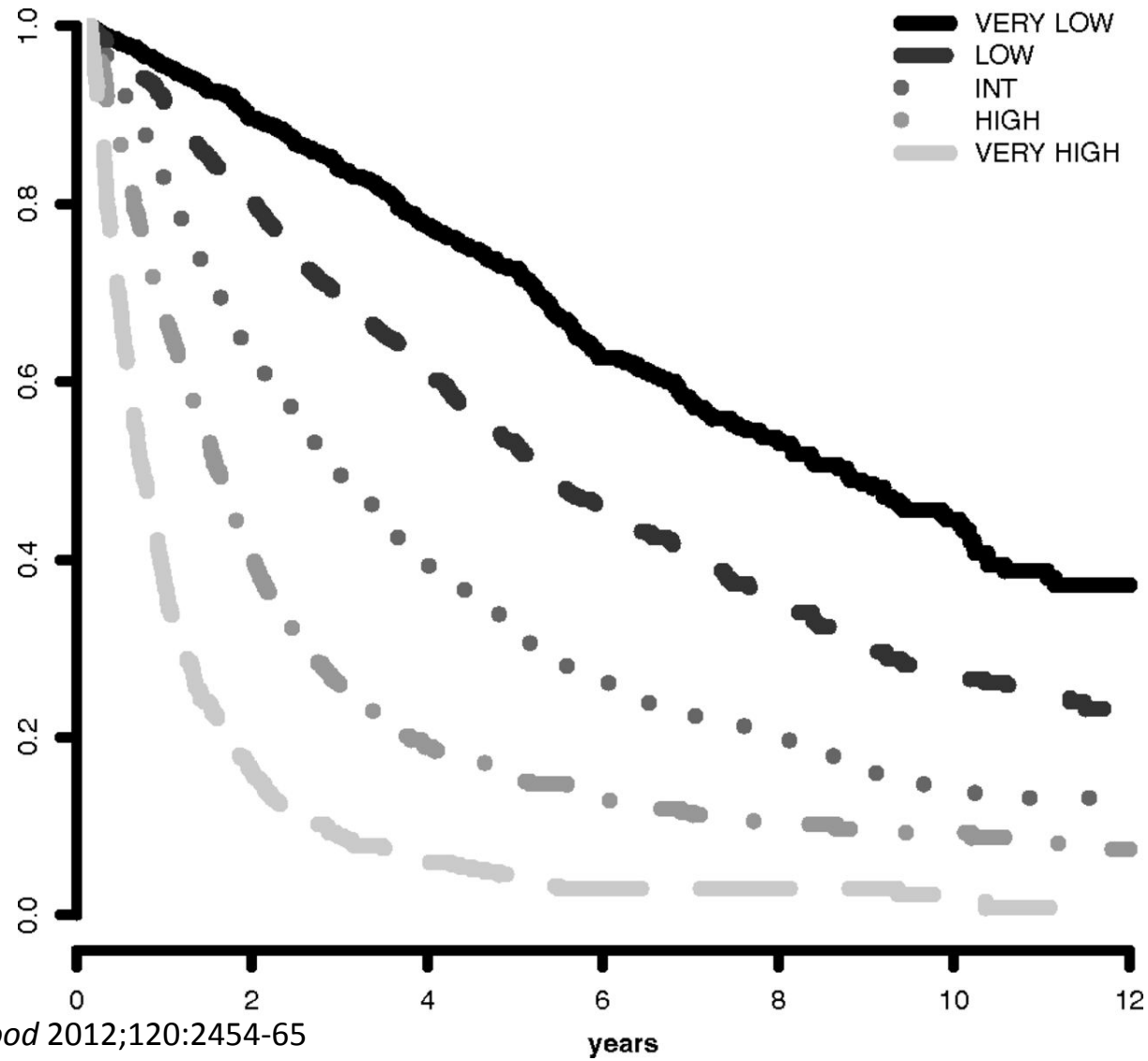
DIAGNOSIS OF MDS IS BASED ON MORPHOLOGY





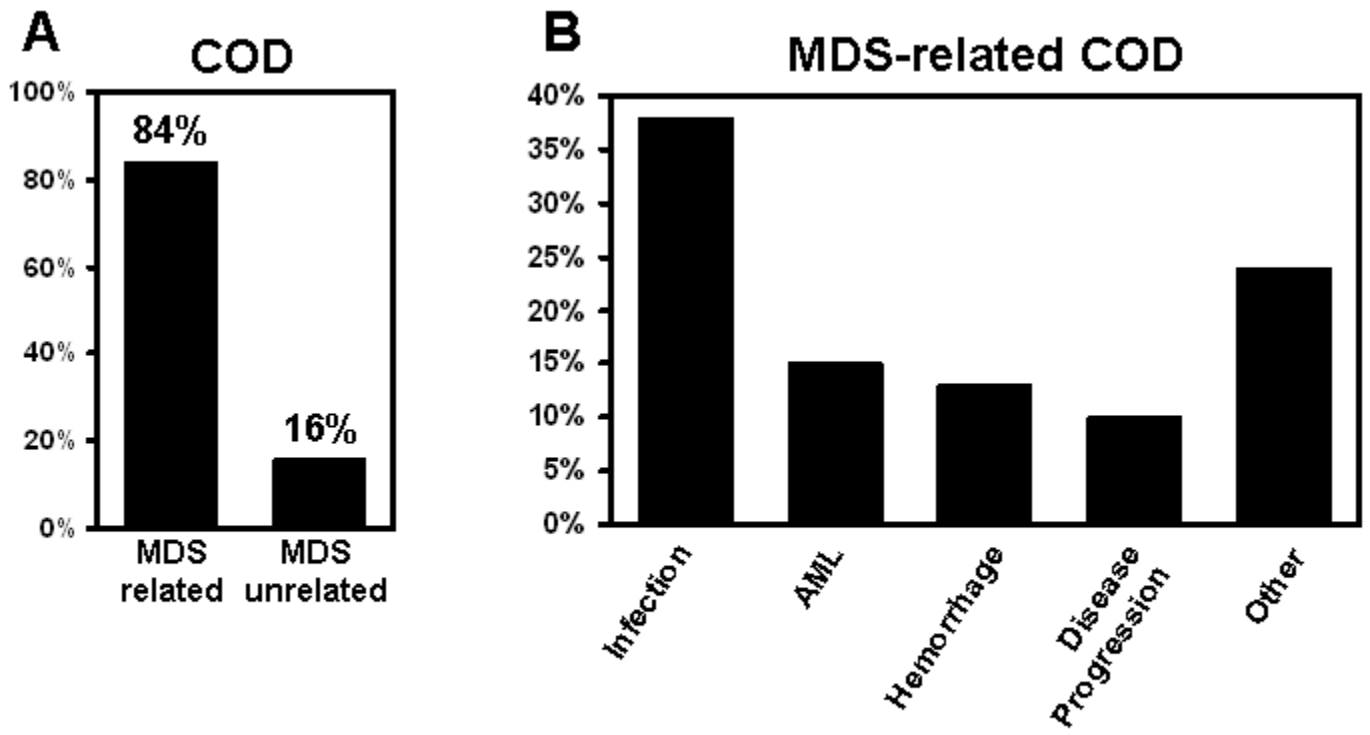


REVISED IPSS-R IN RELATION TO SURVIVAL



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

CAUSE OF DEATH IN MDS



Dayyani et al. Cause of death in lower risk MDS. Cancer 2010;116:2174-9

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.

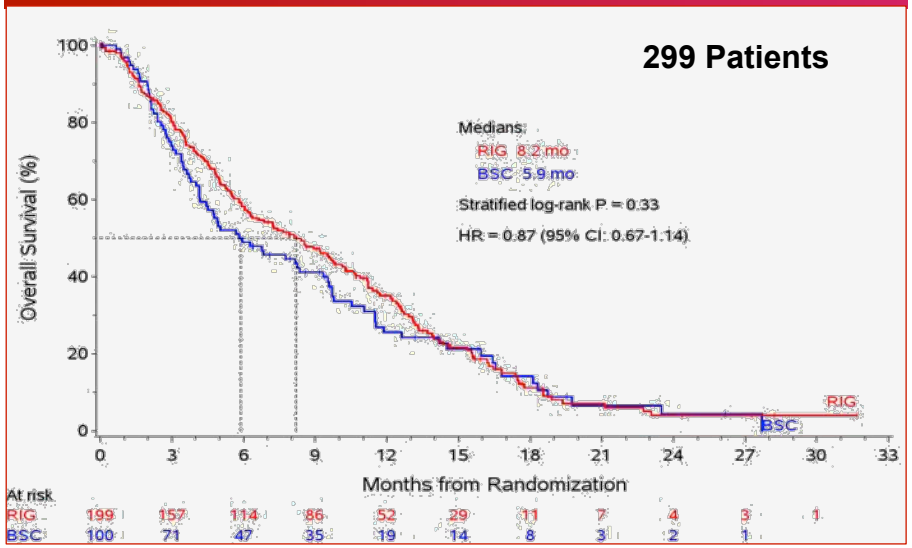
Lancet Oncol 2016

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

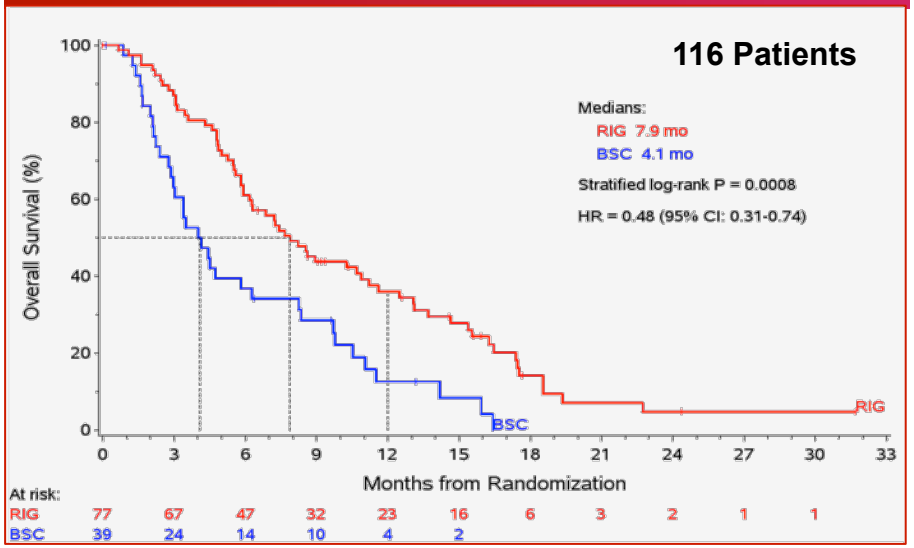
PATIENT POPULATION FOR PHASE 3 INSPIRE TRIAL

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

ONTIME TRIAL: ITT SUBGROUPS CORRELATED WITH BETTER SURVIVAL BENEFIT

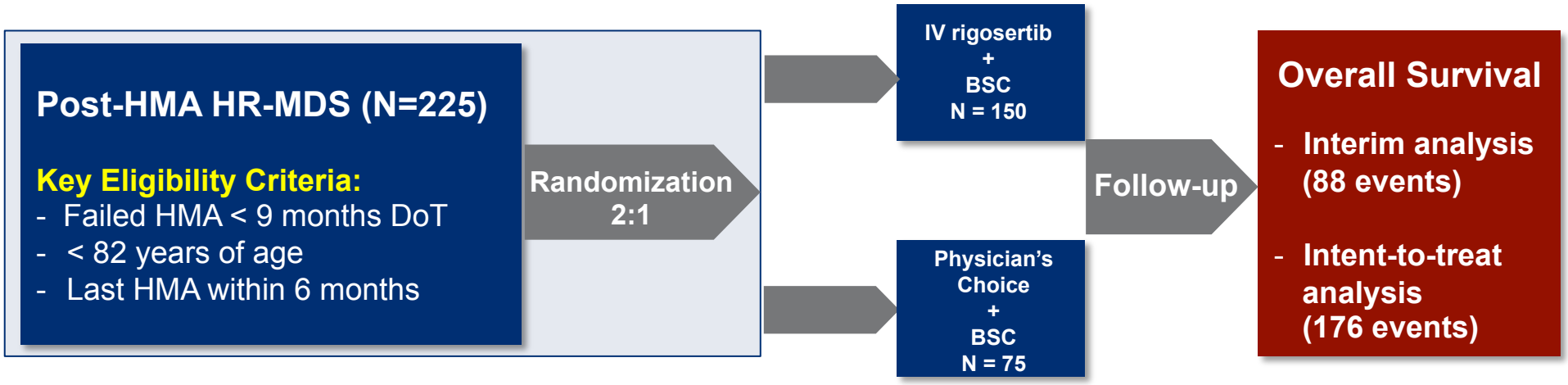
Subgroup	Rigosertib		BSC		HR (95% CI)	p-value
	N	Median (mos)	N	Median (mos)		
Monosomy 7	16	5.6	13	2.8	0.24 (0.09-0.66)	0.003
Trisomy 8	22	9.5	8	4.5	0.34 (0.12-0.95)	0.035
Very high risk per IPSS-R	93	7.6	41	3.2	0.56 (0.37-0.84)	0.005

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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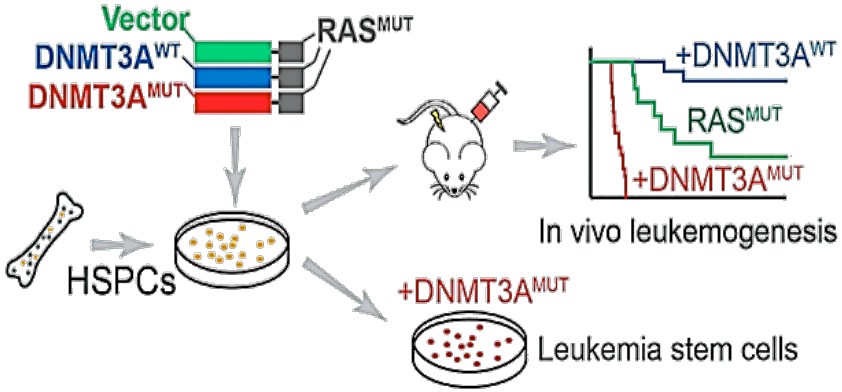
Oral Rigosertib + Azacitidine for HR-MDS

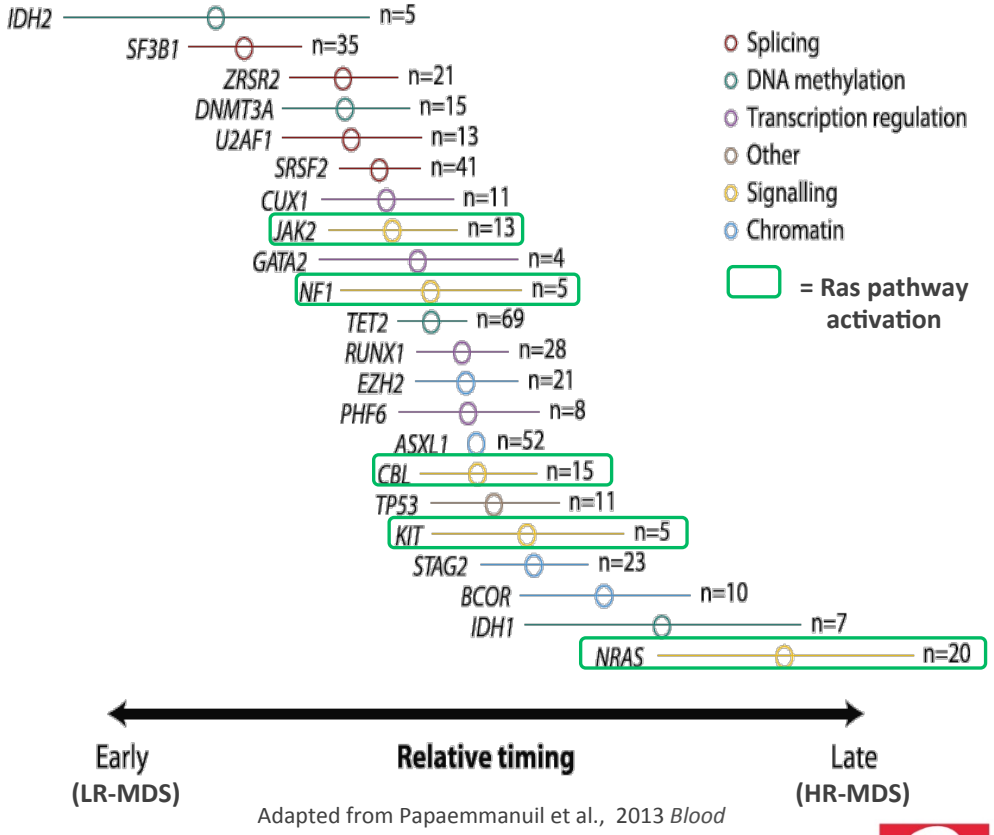
EPIGENETIC AND GROWTH FACTOR PATHWAY MUTATIONS SYNERGIZE INDUCING LEUKEMIC TRANSFORMATION

AML Animal Model



Lu et al., 2016 *Cancer Cell*

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

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

*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

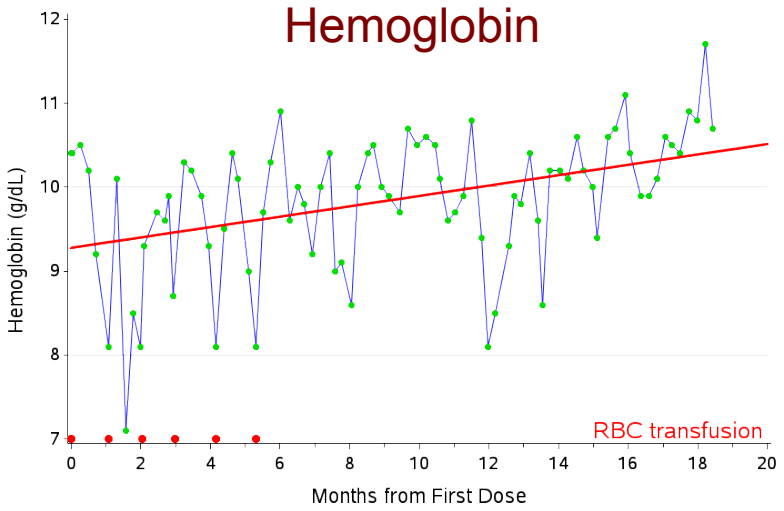
Patient Characteristics	Eval (n=33)	HMA Naïve (n=20)	HMA Failure** (n=13)
Complete Remission (CR %)	8 (24%)	7 (35%)	1 (8%)
Overall Response Rate (ORR %)	25 (76%)	17 (85%)	8 (62)

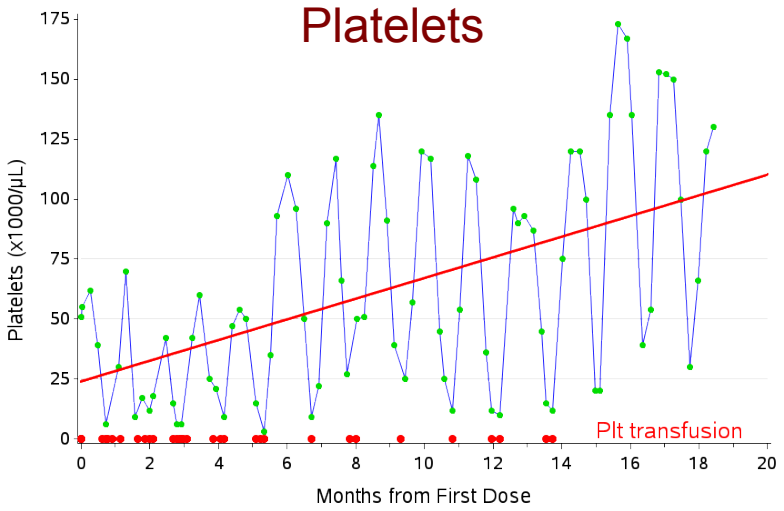
* Data shown as of data cut off Oct 1, 2016; response based on IWG 2006 criteria

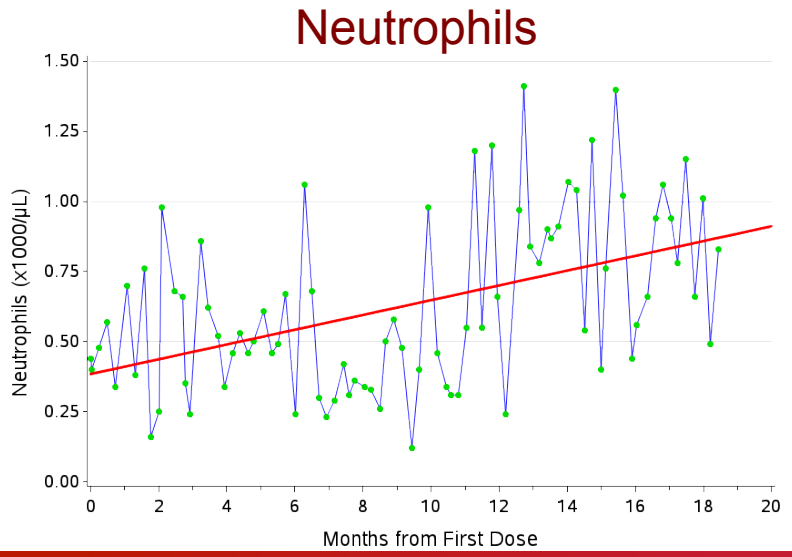
**10 patients received previous therapy with azacitidine, 2 with decitabine and 1 with both HMAs; prior HMA cycles ranged from 4-20

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

CBC TRENDS FOR PATIENT ON RIGO + AZA







- 12 cycles of AZA – stable disease
- RBC and platelet transfusions
- Blasts 7%
- Monosomy 7
- Runx-1
- AZA + RIG in 09-08 for 20+ months
- Complete remission
- RBC transfusion independent
- <5% blasts
- PB CR criteria

Rigosertib in Rasopathies - Status

Target	Collaboration	Goal	Status
Non-clinical studies	Dr. E. P. Reddy Mount Sinai School of Medicine, New York Dr. Elliot Stieglitz UCSF, San Francisco	Proof of concept	• NF1 studies conducted • Models of JMML & rigosertib testing
Clinical trials	National Institutes of Health	Pediatric tumor rasophathies	CRADA and protocol being developed
	Academic collaborator, USA (UCSF)	Explore JMML	Protocol discussions
	Academic collaborator, EU (Dr Charlotte Niemeyer, Freiburg, Germany)	Explore JMML	Early discussions
Advocacy	Leukemia & Lymphoma Society RasopathyNet Foundation	Collaboration and support for studies	Discussion

THANK YOU

- **Please hold questions for a panel following all 3 presentations.**