ONCONOVA THERAPEUTICS

Rigosertib

Ras Targeted Drug Discovery

Vienna, Austria

February 27, 2020

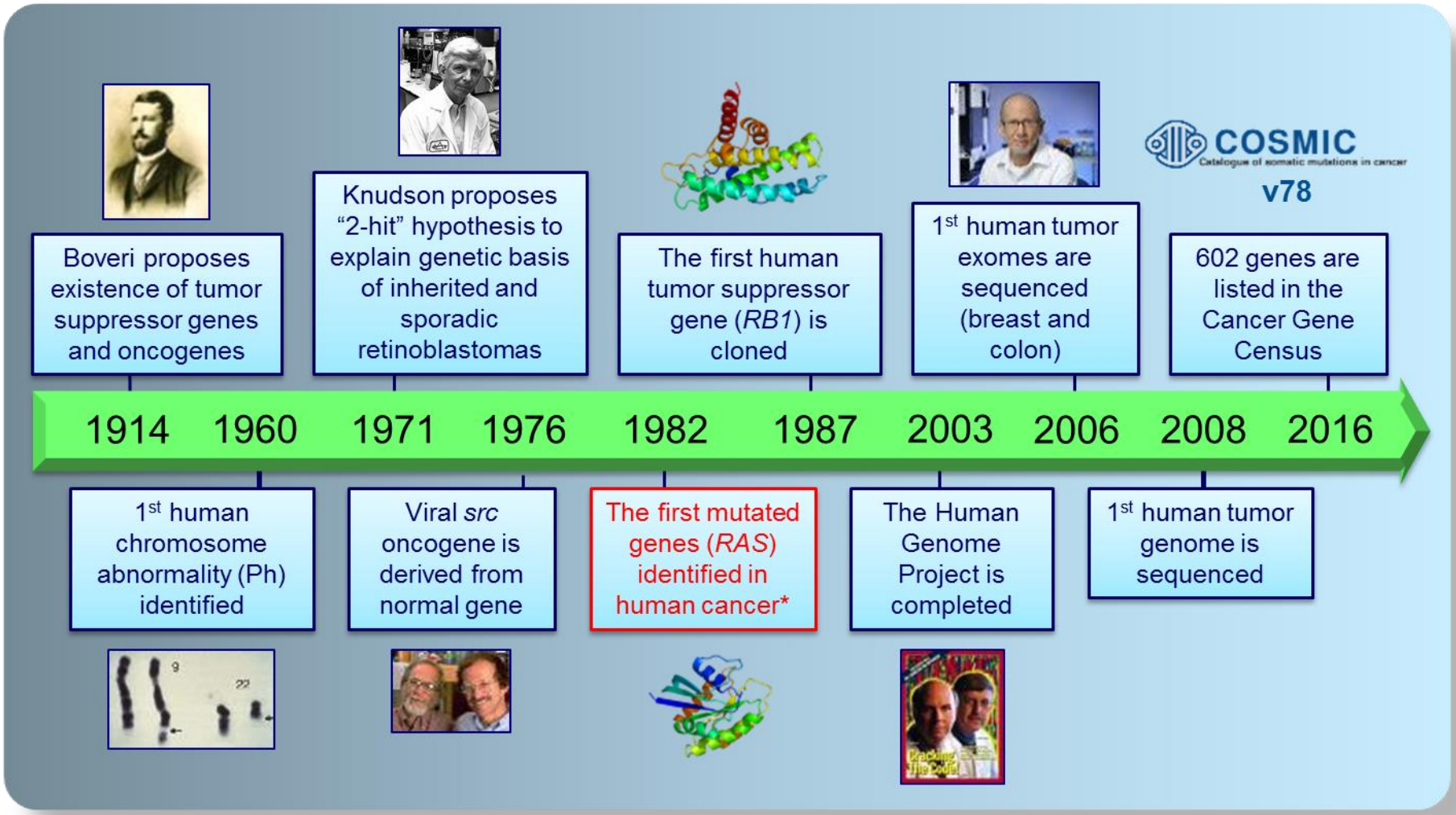
Steven M. Fruchtman, M.D.

President and CEO

Onconova Therapeutics, Inc.

GENETIC BASIS OF CANCER

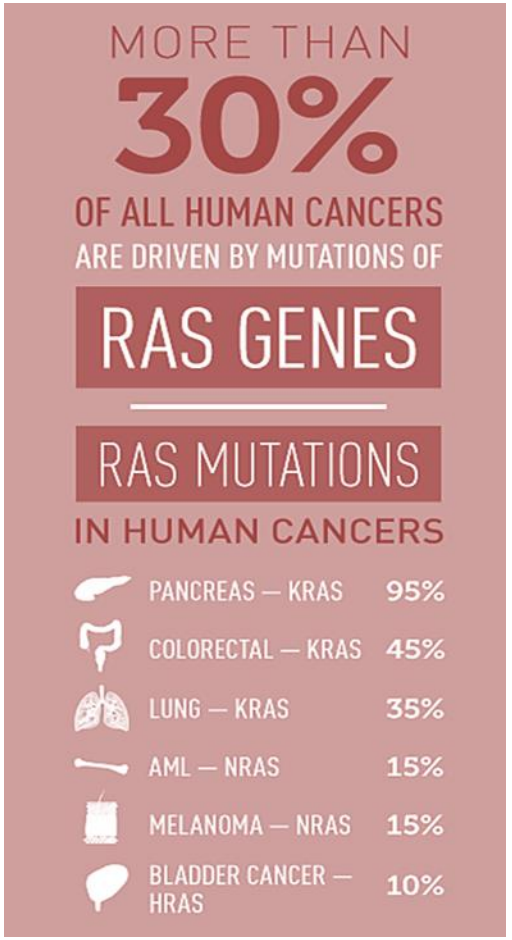
ACQUIRED MUTATIONS



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

RAS IN ONCOLOGY

- Three RAS genes (KRAS, NRAS, HRAS)
- Cancer-associated RAS genes characterized by single base missense mutations
- Wild type RAS, through aberrant signaling pathways, may play a key role in neoplastic transformation and proliferation
- Mutations of RAS and signaling pathways that activate wild type RAS are present in myelodysplastic syndromes (MDS) and other tumors



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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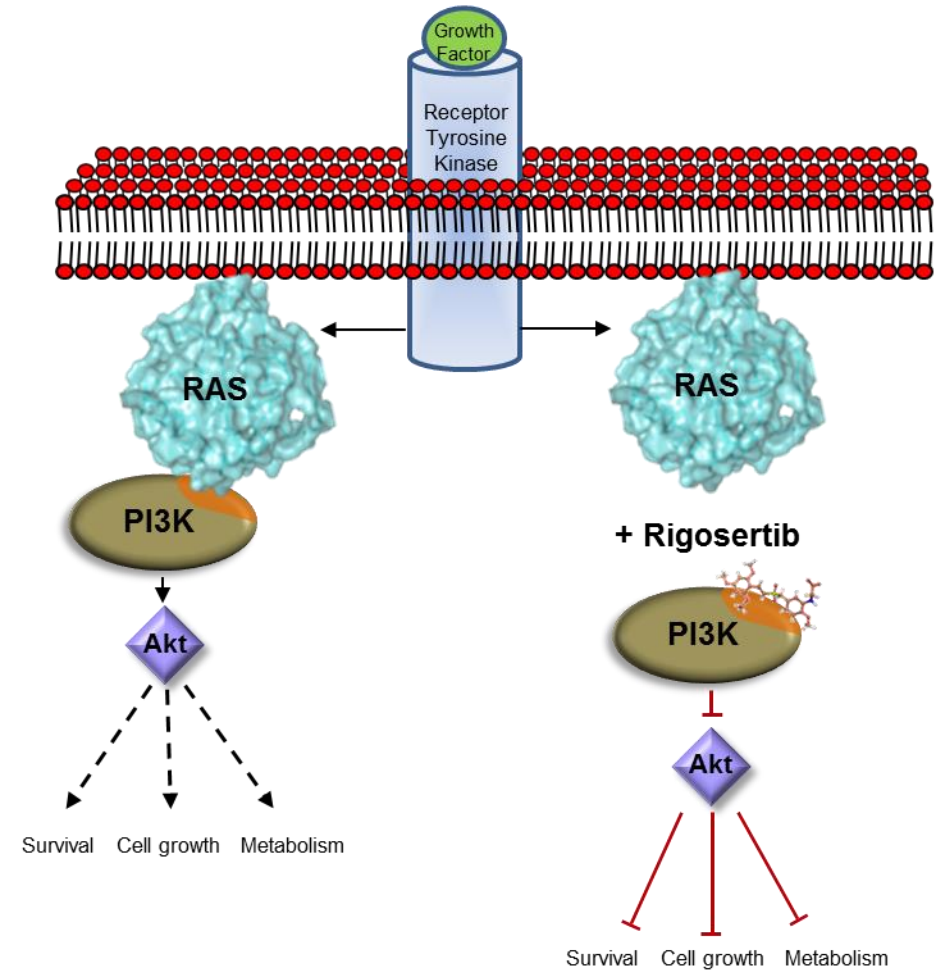
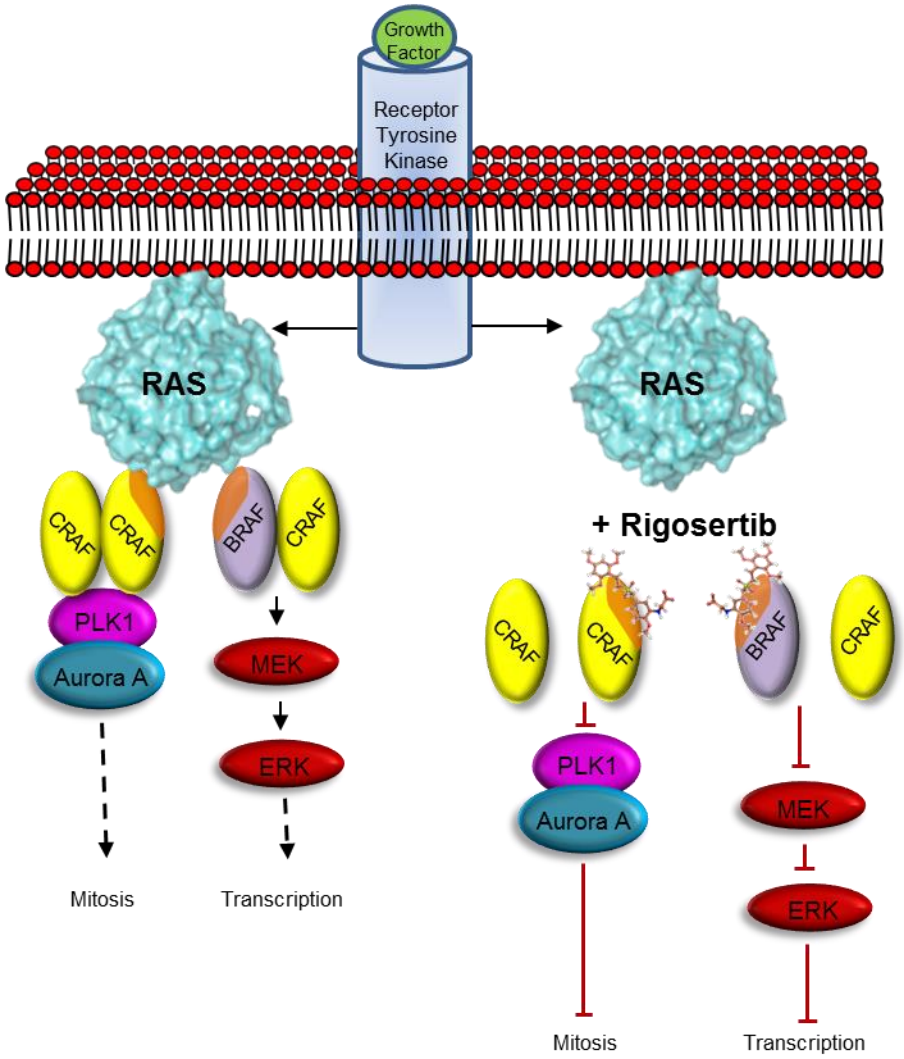
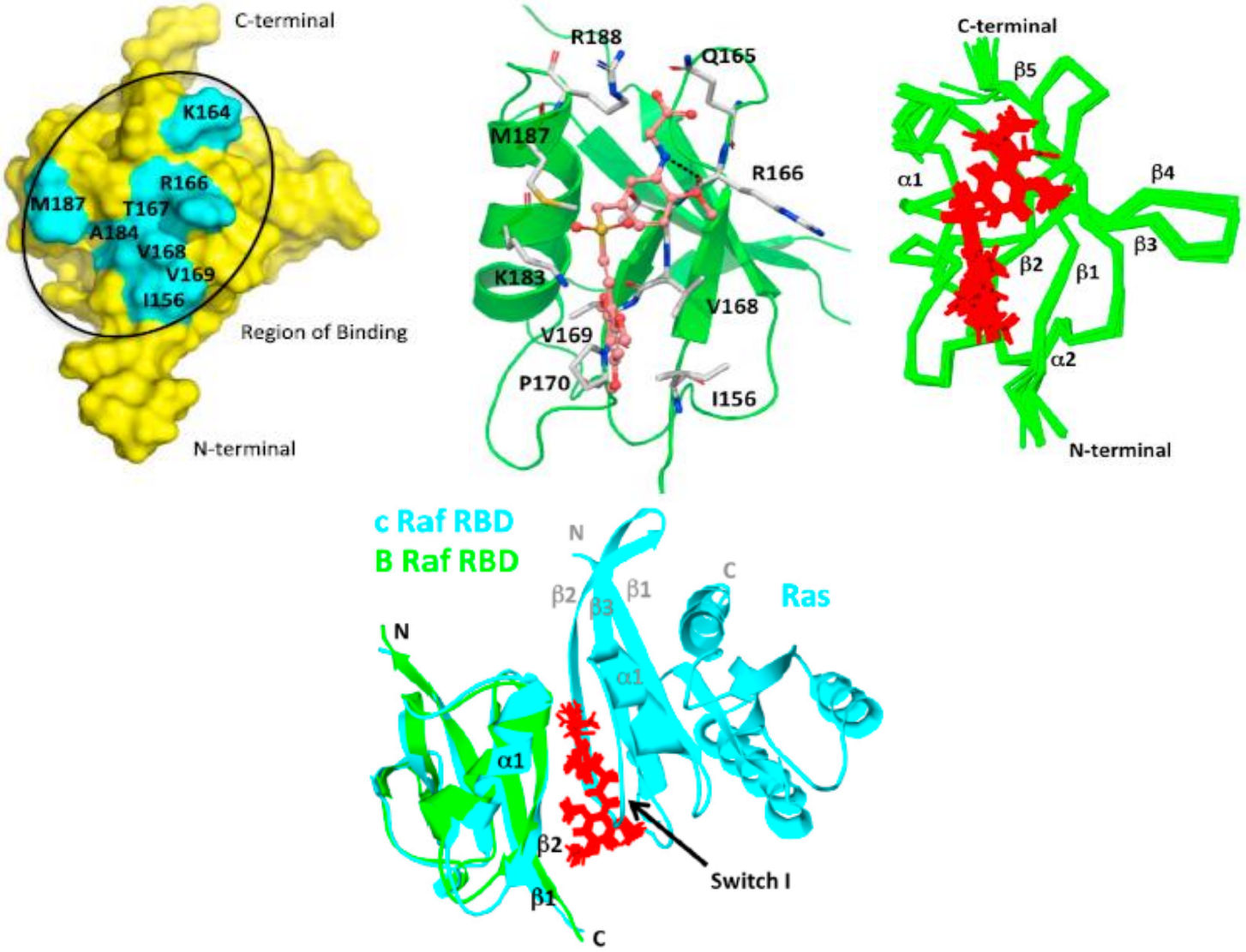
RIGOSERTIB MECHANISM OF ACTION

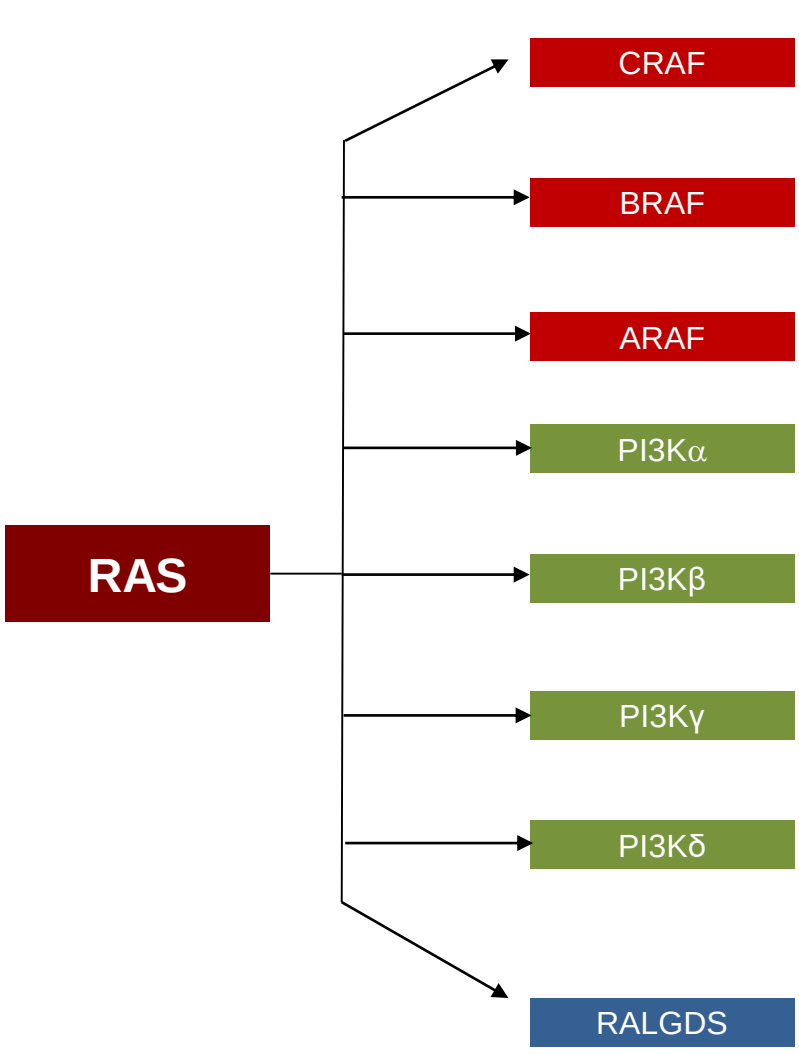


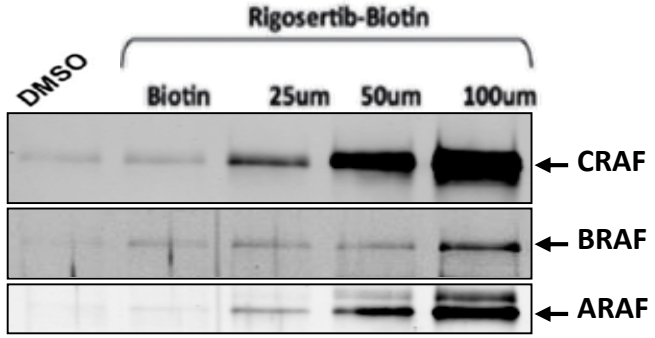


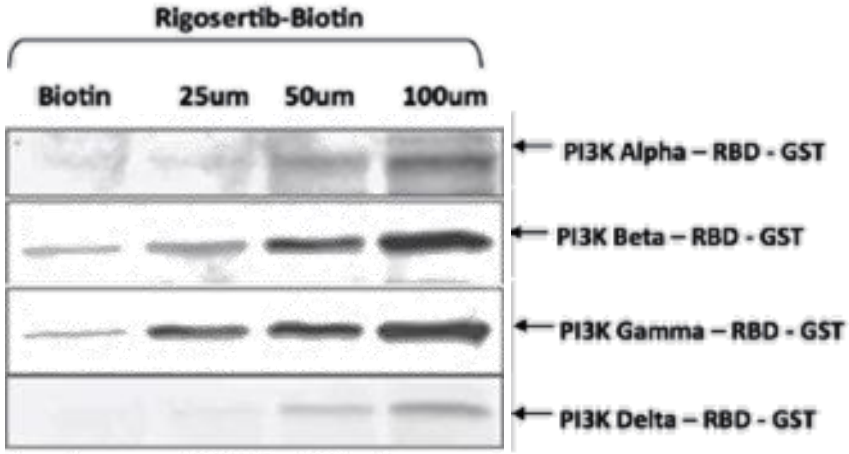
NMR MODELS OF RIGOSERTIB/RBD BINDING

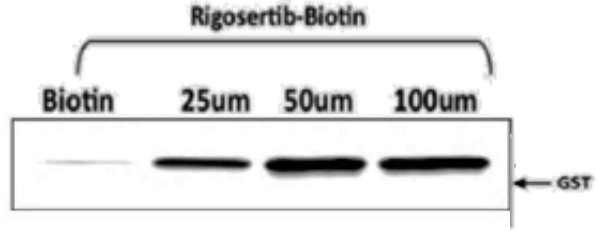


RIGOSERTIB BINDS TO MULTIPLE RAS EFFECTOR RBDS



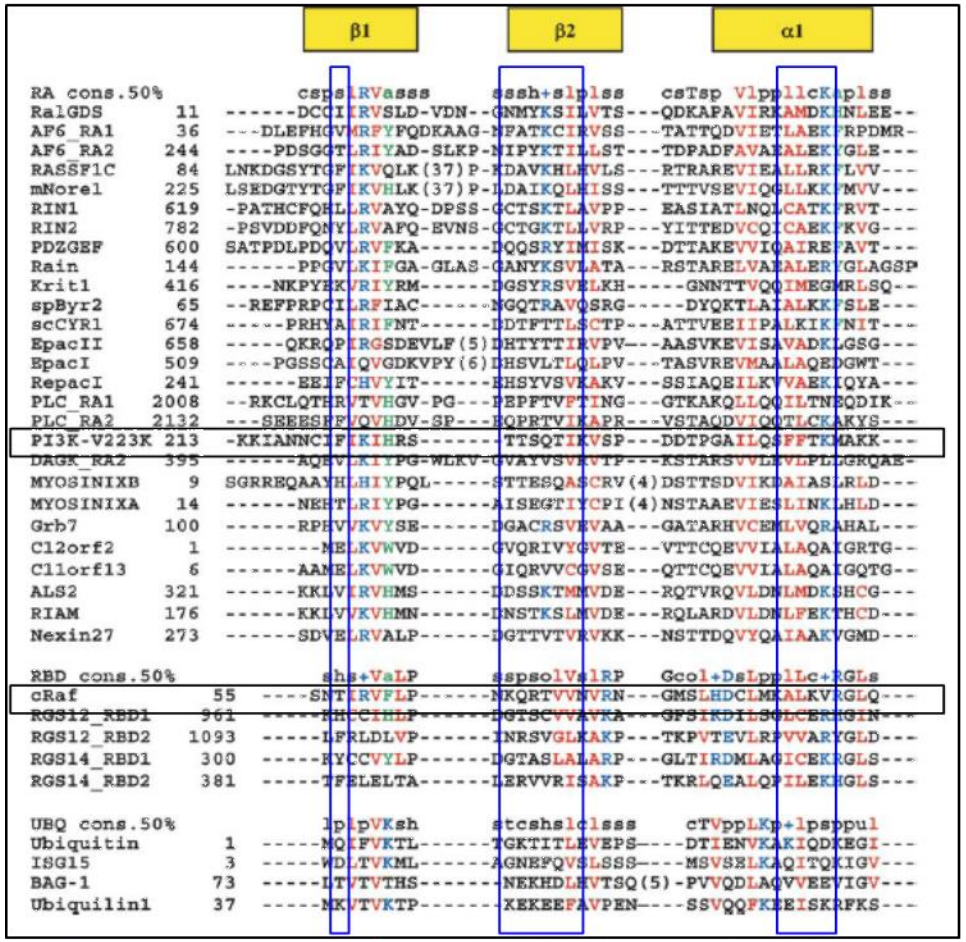






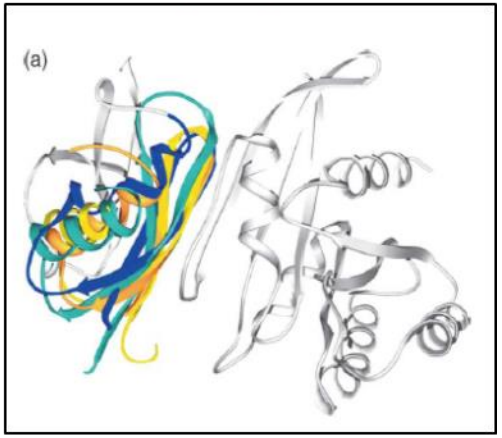
SECONDARY/TERTIARY STRUCTURAL SIMILARITY OF RBDS DESPITE LACK OF EXTENSIVE SEQUENCE HOMOLOGY

Sequence Alignment of RA and RB Domains

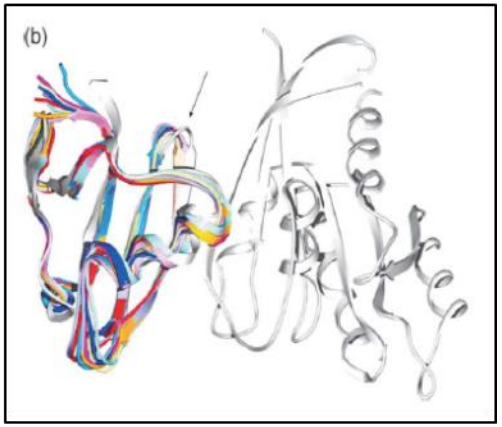


Yellow: Hydrophobic Core; Cyan: Conserved Charged Amino Acids
Red: Conserved Hydrophobic AA; Green: Conserved Aromatic AA

RAF/Ral-GDS/PI3K Crystal Structures Superimposed



NMR Structures of 10 RBDs Superimposed



ONCONOVA THERAPEUTICS

CLINICAL TRIALS

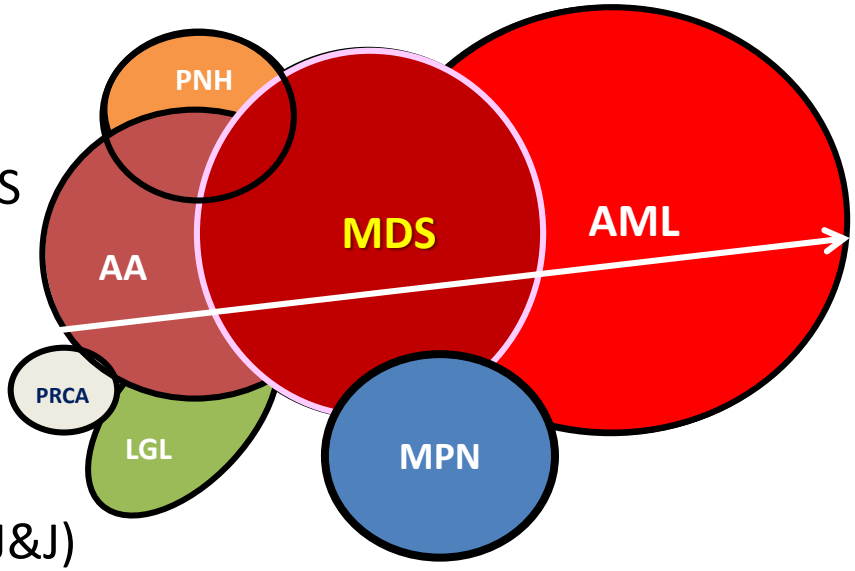
A humbling statement !!

RAS oncogenes were discovered in human tumors 37 years ago

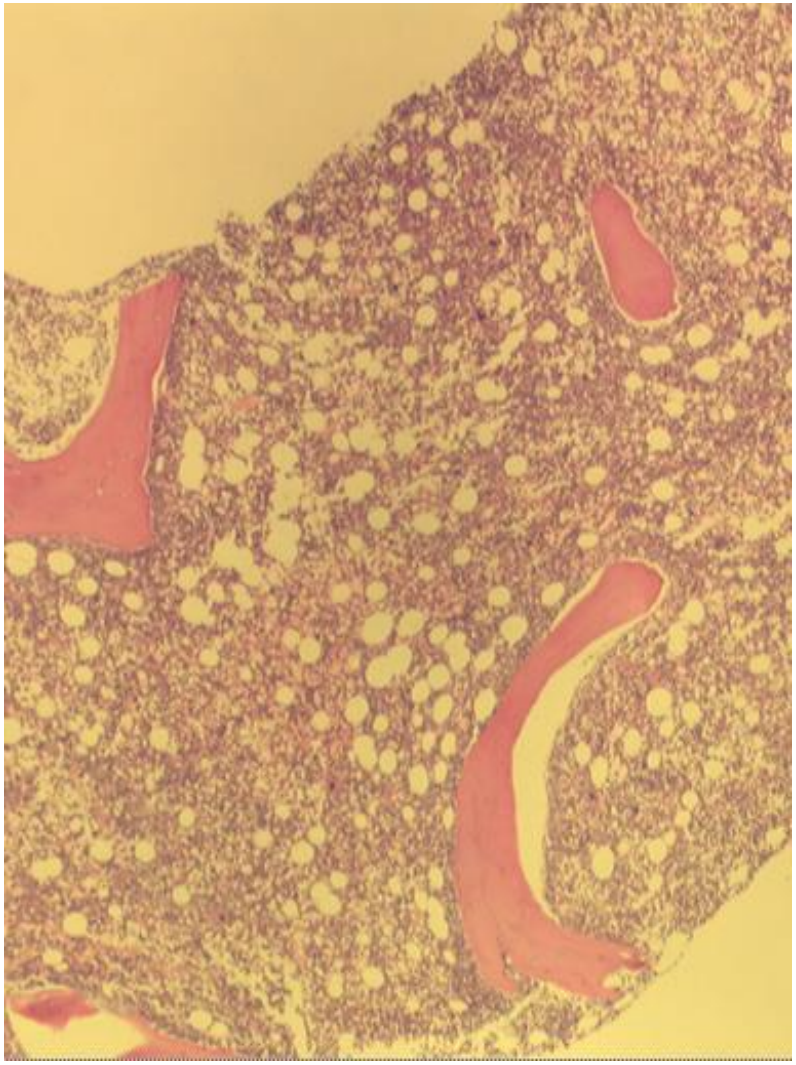
Yet, thirty-five thousand publications later [see Pubmed: RAS and CANCER] and countless unpublished efforts in industry, no selective inhibitor against RAS mutant tumors has been approved by the FDA.

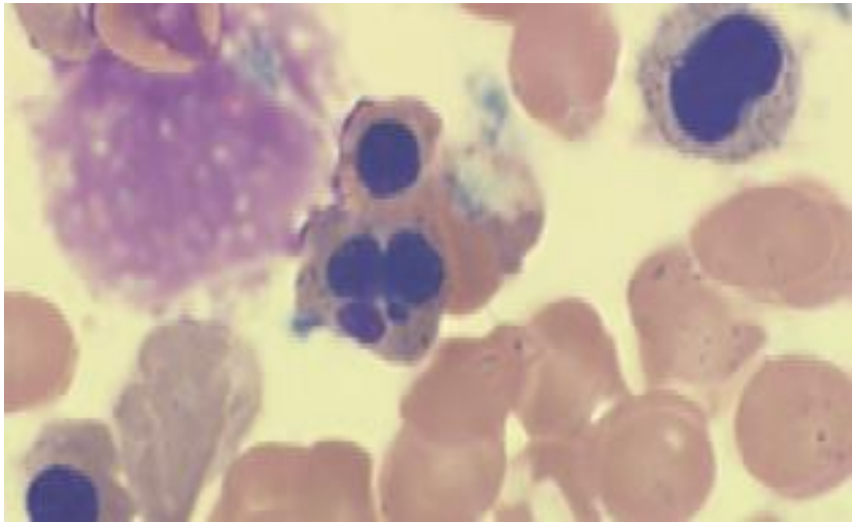
MDS IS RELATED TO OTHER BONE MARROW DISEASES

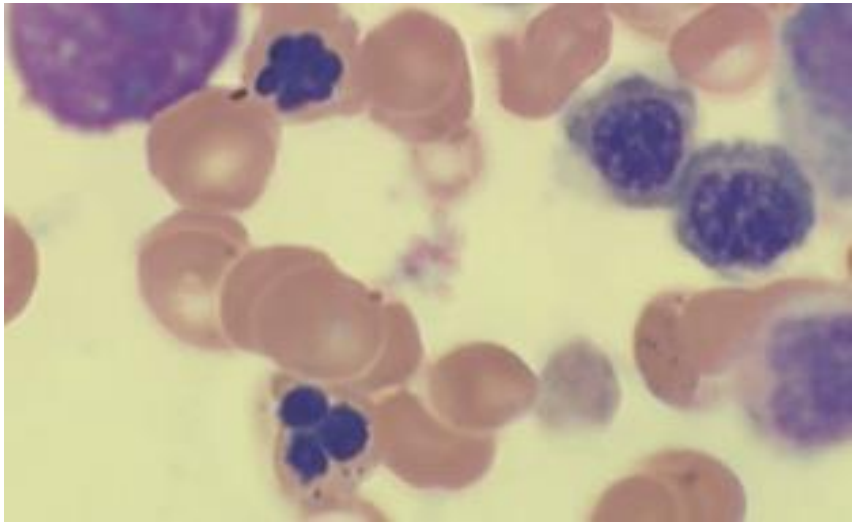
- MDS: malignant bone marrow disorder characterized by:
  - Acquired cytogenetic and genomic abnormalities, but typically only in the marrow
- US prevalence is 59,000
  - ~13,000 have higher risk (HR) MDS
  - ~10,000 second-line patients
- Available Treatments limited to hypomethylating agents
  - Vidaza (Celgene); Dacogen (Eisai/J&J)
  - Approved >decade ago; now off-patent
  - No approved therapy following HMA failure
  - New therapy could have $billions opportunity



DIAGNOSIS OF MDS IS BASED ON MORPHOLOGY







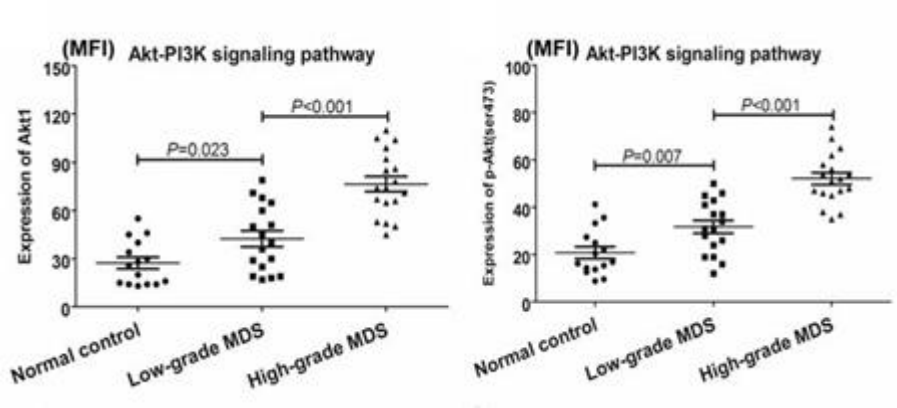
RIGOSERTIB ACTIVITY IN MDS

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

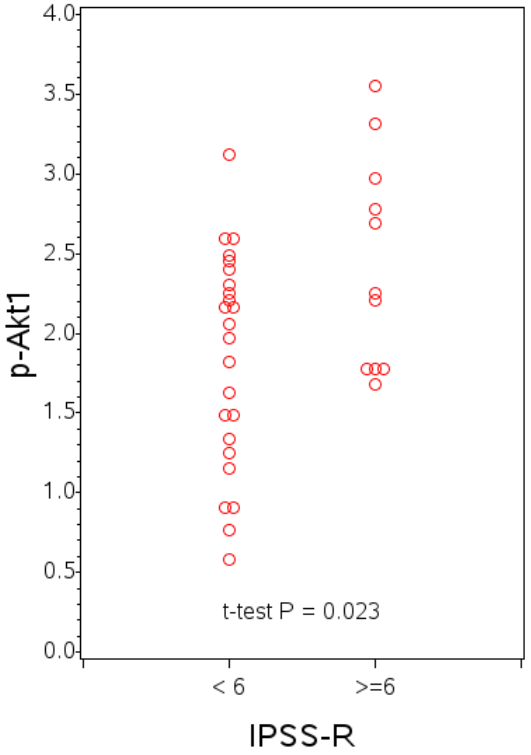
Department of Hematology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital.

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.



Multiple signal transduction abnormalities in MDS

- PI-3K pathway and Akt signaling are targets
- Higher-risk MDS has more Akt activation
- IPSS-R Very High Risk has more activation

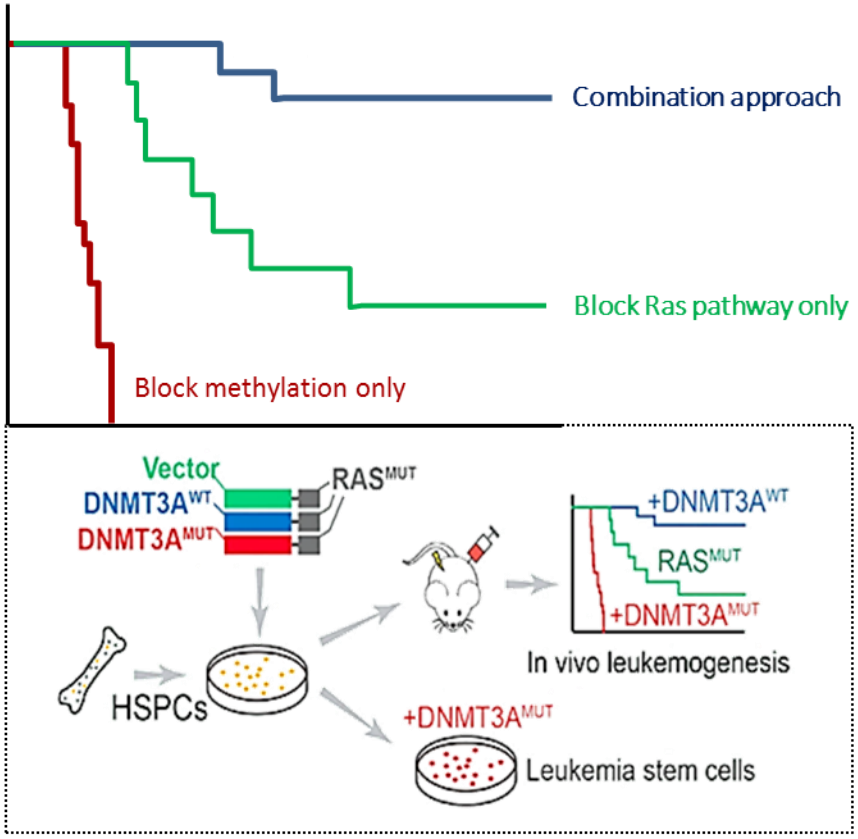


COMBINATION THERAPY WITH RIGOSERTIB + AZACITIDINE

Preclinical evidence supports synergism of rigosertib + azacitidine combination

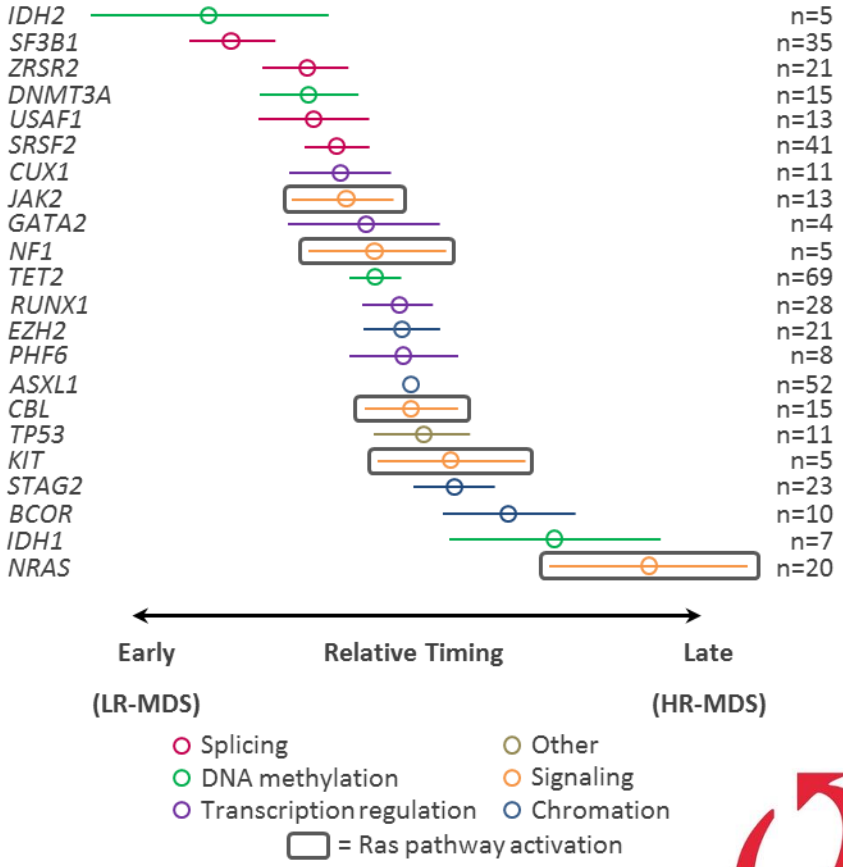
AML Mouse Model

Validation of combination approach



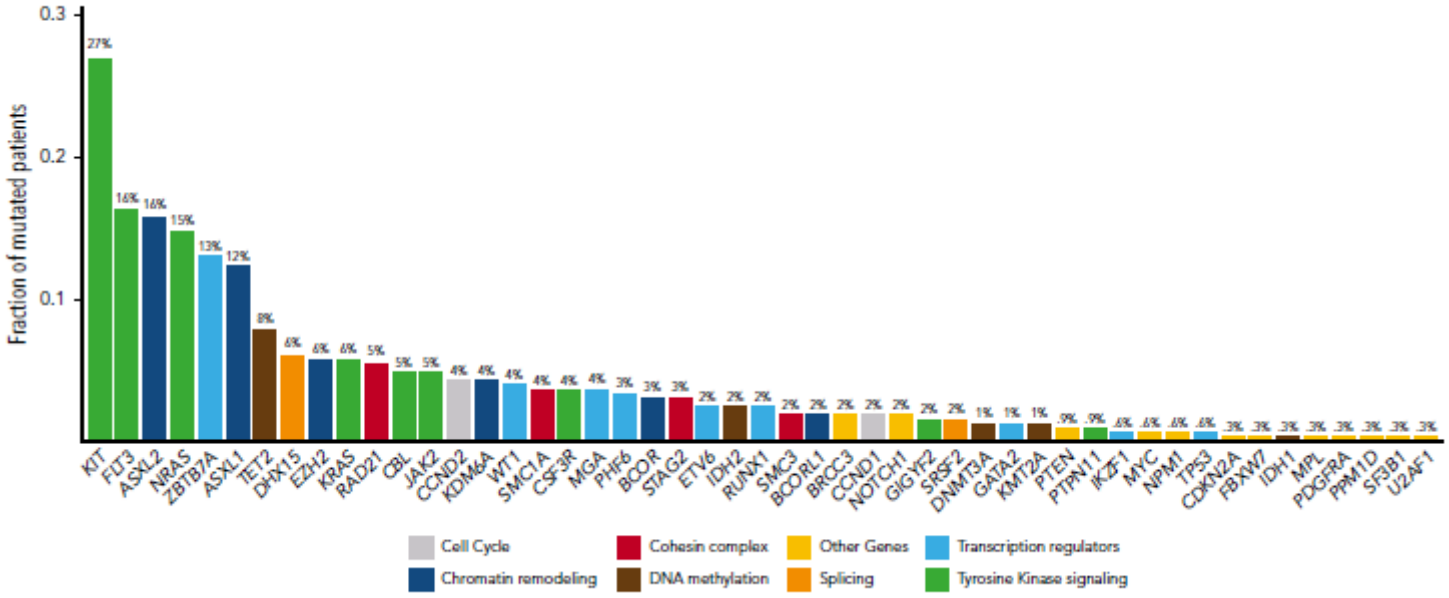
Lu et al., 2016 *Cancer Cell*

Temporal Order of Gene Mutations in 107 MDS Patients



Adapted from Papaemmanuil et al., 2013 *Blood*

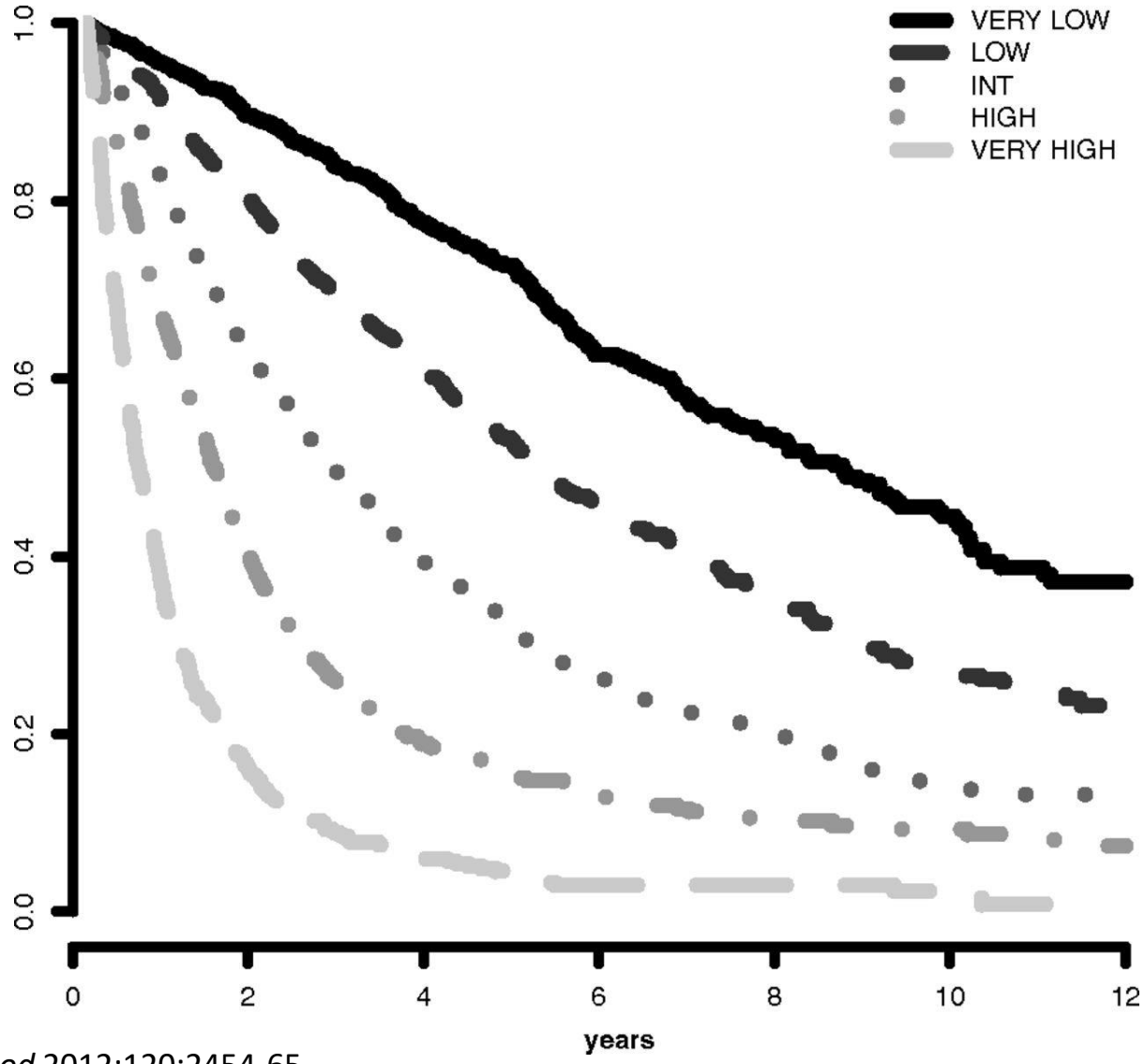
FREQUENCY OF MUTATED GENE PER PATIENTS FOR ALL GENES WITH DETECTED VARIANTS (AML)



Bars are colored according to the functional category of the gene (supplemental Table 16). Mutation frequencies are shown above the bars (%). FLT3 variants include FLT3-ITD and FLT3-TKD.

Christen, F., et. al. (2019). Genomic landscape and clonal evolution of acute myeloid leukemia with t(8;21): an international study on 331 patients. Blood, (), blood-2018-05-852822. Accessed June 20, 2019. https://doi.org/10.1182/blood-2018-05-852822.

REVISED IPSS-R IN RELATION TO SURVIVAL



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

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

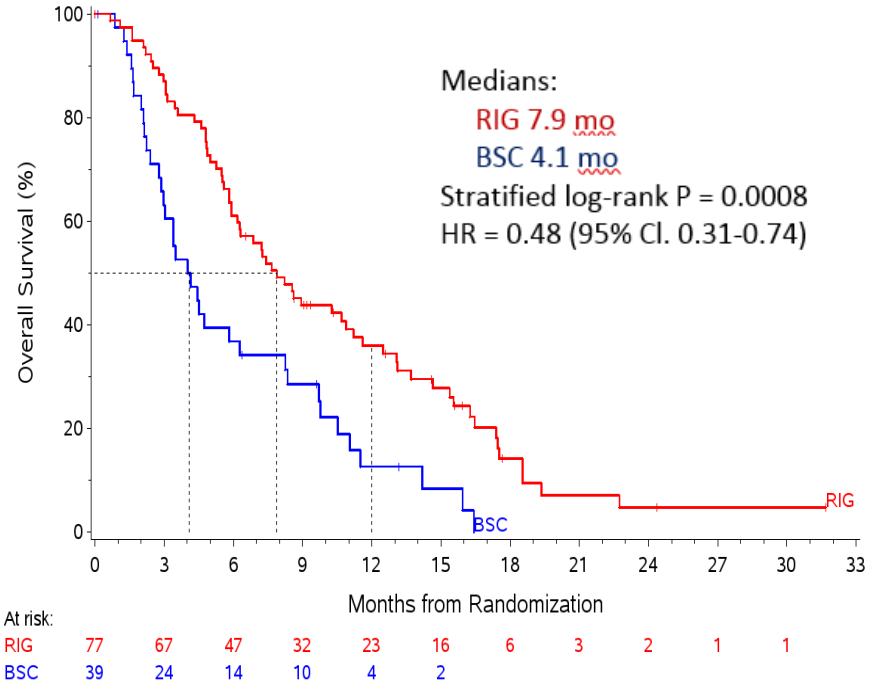
Background Hypomethylating drugs are the standard treatment for patients with high-risk myelodysplastic syndromes. Survival is poor after failure of these drugs; there is no approved second-line therapy. We compared the overall survival of patients receiving rigosertib and best supportive care with that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

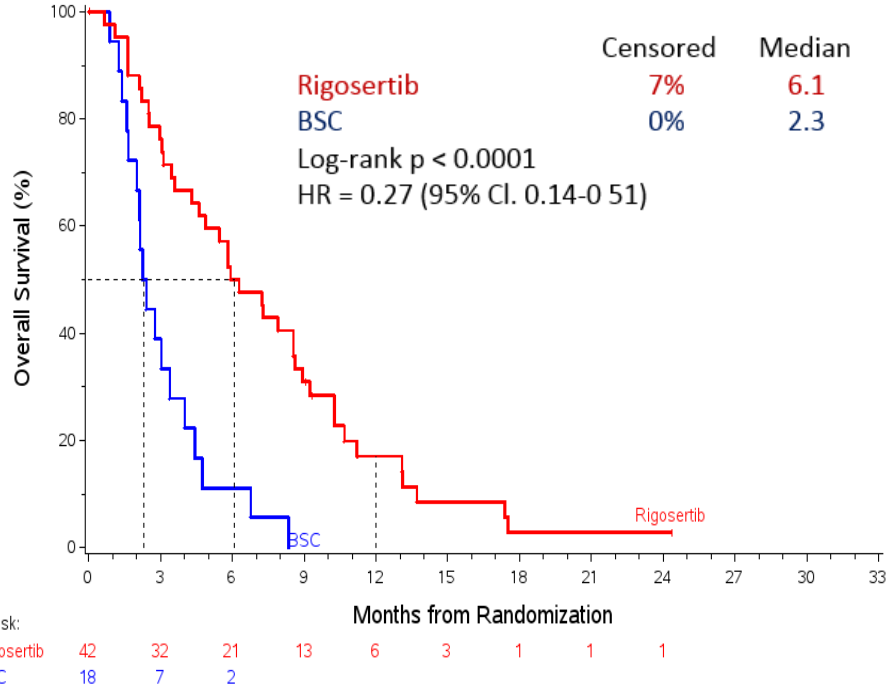
Published Online
March 8, 2016
http://dx.doi.org/10.1016/S1470-2045(16)00009-7

STUDY 04-21 : PROPOSED PATIENT POPULATION FOR INSPIRE

Entire ITT population

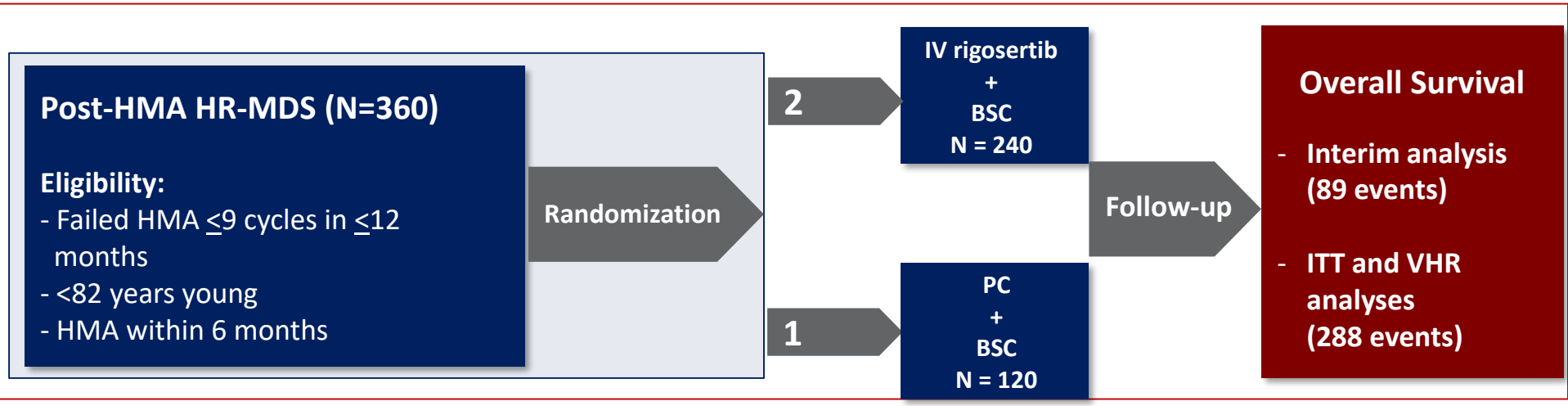


Very High Risk (VHR) population



- Age < 82 years
- Duration of prior HMA ≤ 9 cycles of prior HMA in ≤ 12 months
- Time from last dose of prior HMA to random assignment ≤ 6 months.

INSPIRE STUDY DESIGN AND STATISTICAL OBJECTIVES



Innovative features of INSPIRE study design

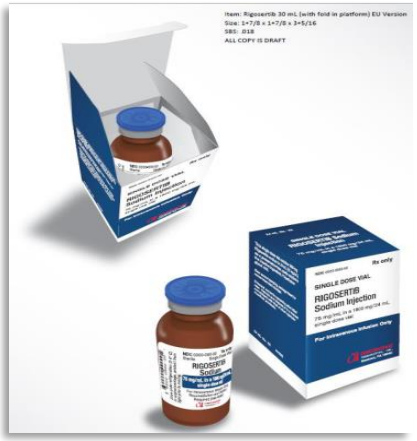
- **Interim Analysis (January 2018) showed promising survival signal for rigosertib arm**
- **Genomic profiling at study entry and at key time points**
- **Over 90% of required 360 patients randomized as of November 2019**

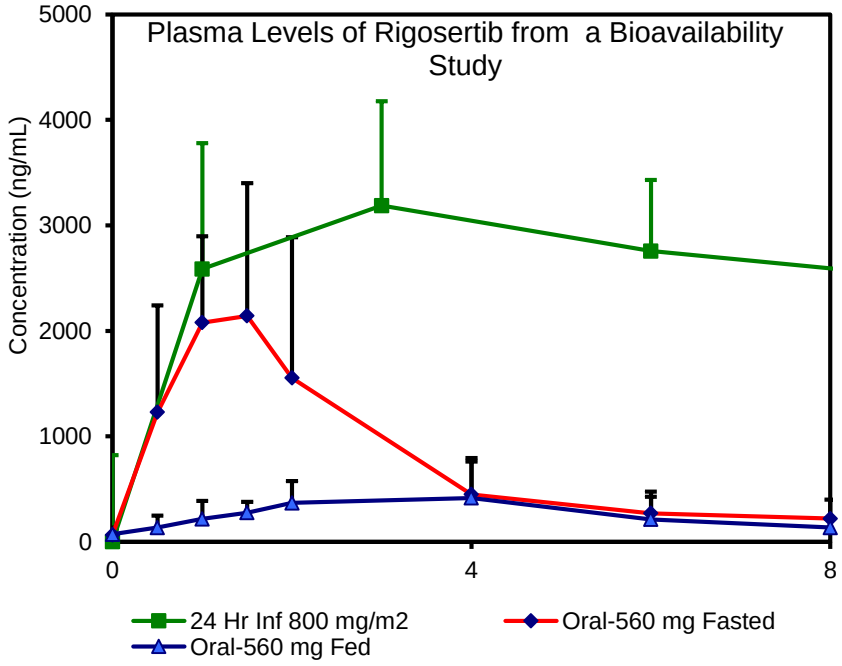
- **Stratification at randomization**
  - **VHR vs. non-VHR**
  - **U.S. vs. EUROPE vs. Asia**
- **Post Interim Analysis**
  - **ITT population**
    - **$\alpha = 0.04$**
    - **Power = 0.80**
    - **Target HR ≤ 0.72**
    - **Reduce mortality by ≥ 28%**
  - **VHR subgroup**
    - **$\alpha = 0.01$**
    - **Power = 0.80**
    - **Target HR ≤ 0.55**
    - **Reduce mortality by ≥ 45%**

ORAL RIGOSERTIB DEVELOPMENT PROGRAM

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





RIGOSERTIB IS SYNERGISTIC WITH AZACITIDINE IN PRECLINICAL STUDIES

- Sequential exposure with rigosertib followed by azacitidine achieved maximum synergy at concentrations achievable in the clinical setting

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

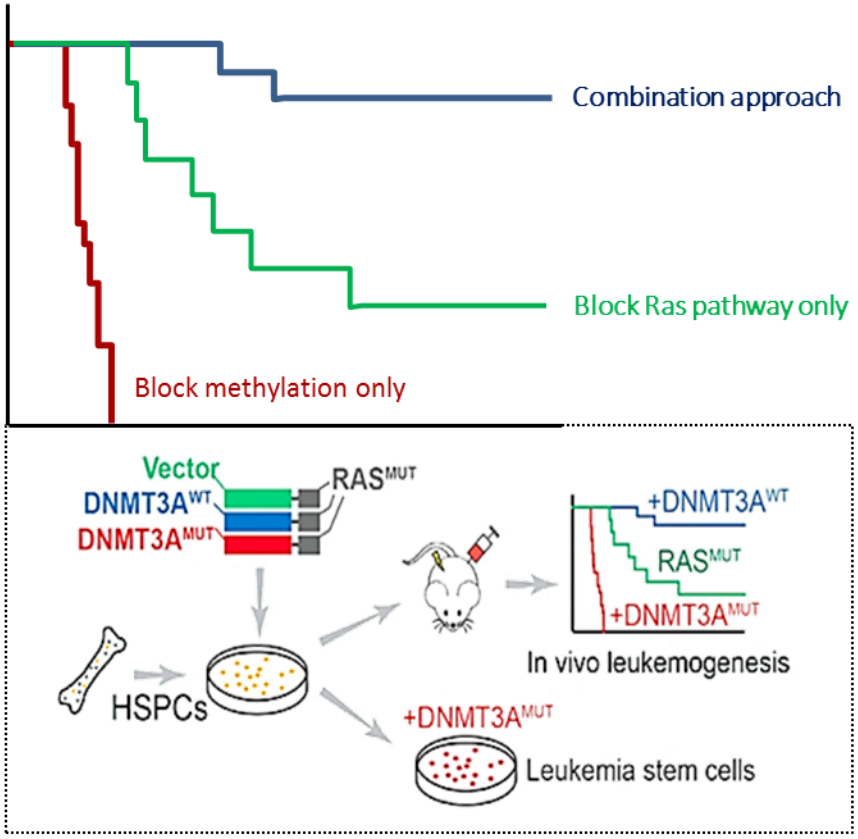
Skiddan I et al. AACR Abstract 1310, April 2006; 47:309.

COMBINATION THERAPY WITH RIGOSERTIB + AZACITIDINE

Preclinical evidence supports synergism of rigosertib + azacitidine combination

AML Mouse Model

Validation of combination approach



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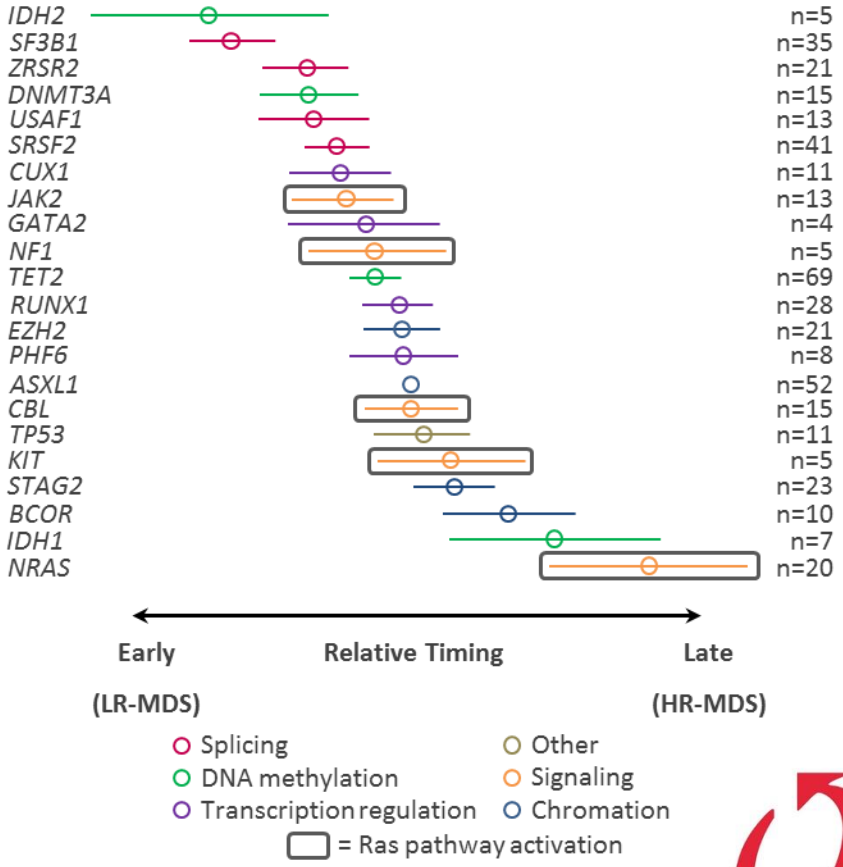


Adapted from Papaemmanuil et al., 2013 *Blood*

HMA NAIVE ≥ 840MG/DAY

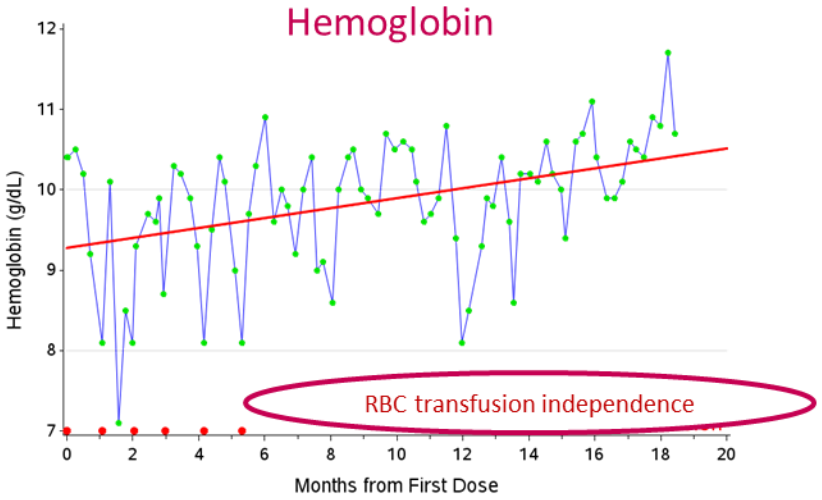
EFFICACY

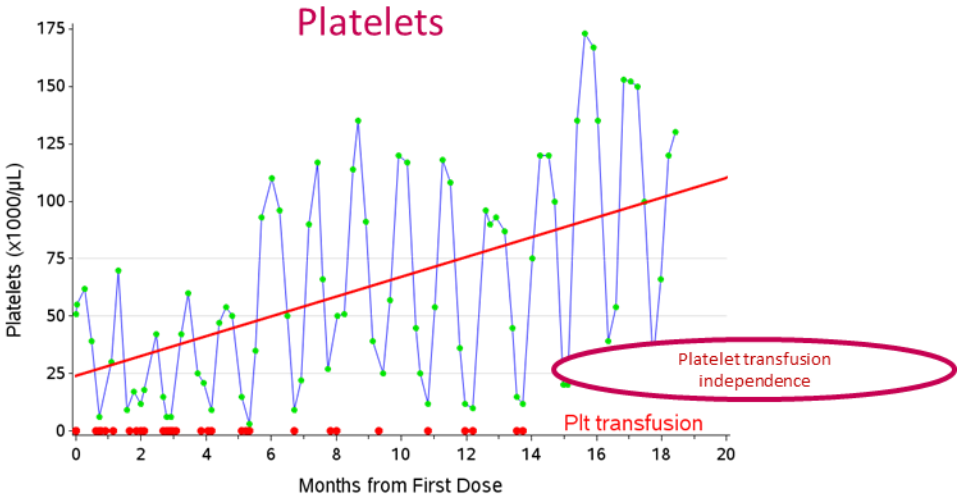
Evaluable for response	29*
Overall response per IWG 2006	26 (90%)
CR+PR	10 (34%)
Complete remission (CR) Partial remission (PR) Marrow CR + Hematologic Improvement Hematologic Improvement alone Marrow CR alone Stable disease Progression	10 (34%) 0 5 (17%) 3 (10%) 8 (28%) 3 (10%) 0
Median duration of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

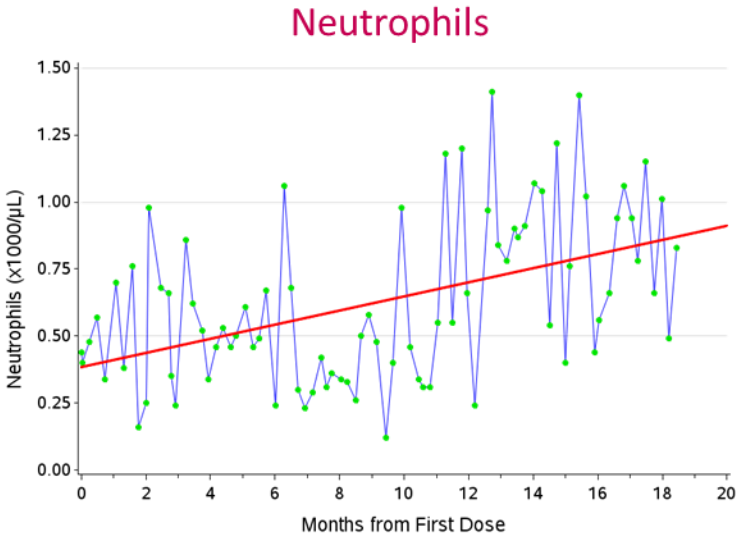
**** Includes 2 patients treated with non-HMA, prior chemotherapy***

COMBINATION THERAPY MAY LEAD TO TRANSFUSION INDEPENDENCE

Single patient case data:*





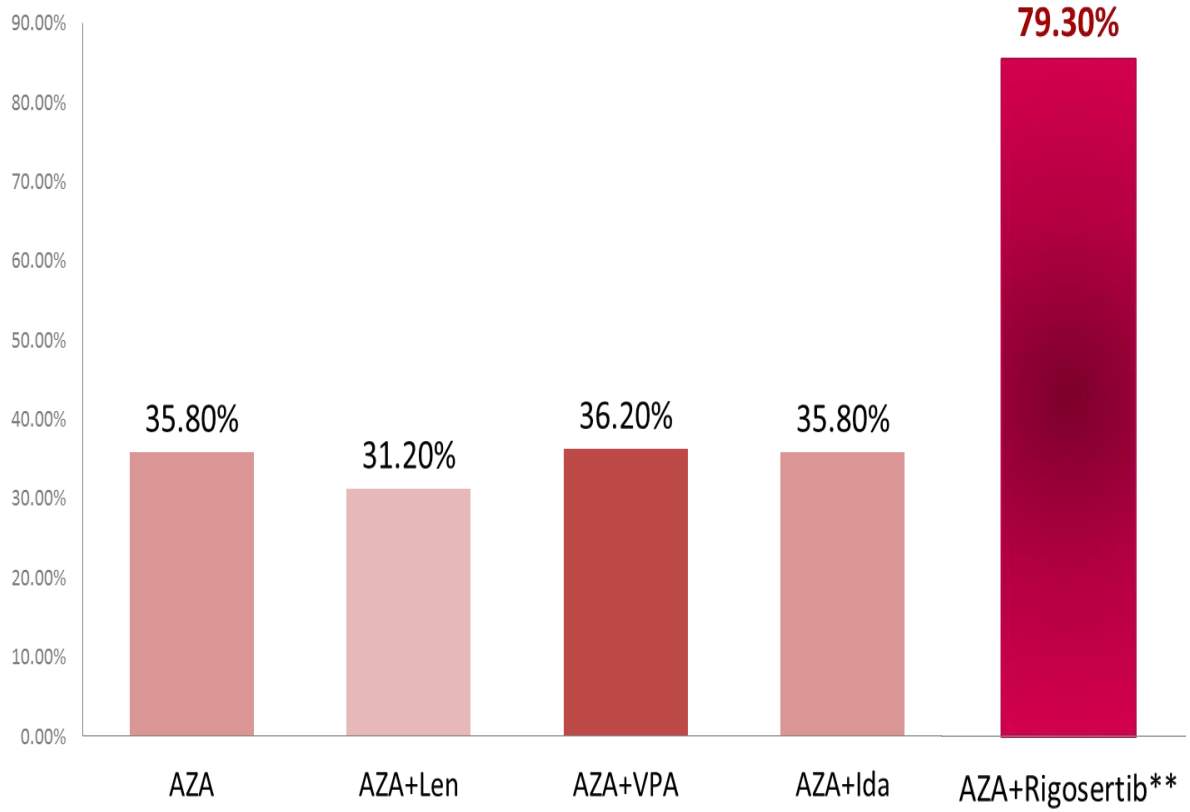


- 12 cycles of AZA – stable disease
- RBC and platelet transfusions
- Blasts 7%
- Monosomy 7
- Runx-1
- AZA + RIG in 09-08 for 20+ months
- Complete remission
  - RBC transfusion independence
  - <5% blasts
  - PB CR criteria

** Individual patient response data may vary*

COMBINATION OF ORAL RIGOSERTIB AND STANDARD DOSE AZACITIDINE: VARIOUS DOUBLET RESPONSE RATES (CR/PR/MCR*)

PATIENTS RECEIVED A MEDIAN OF 7 CYCLES



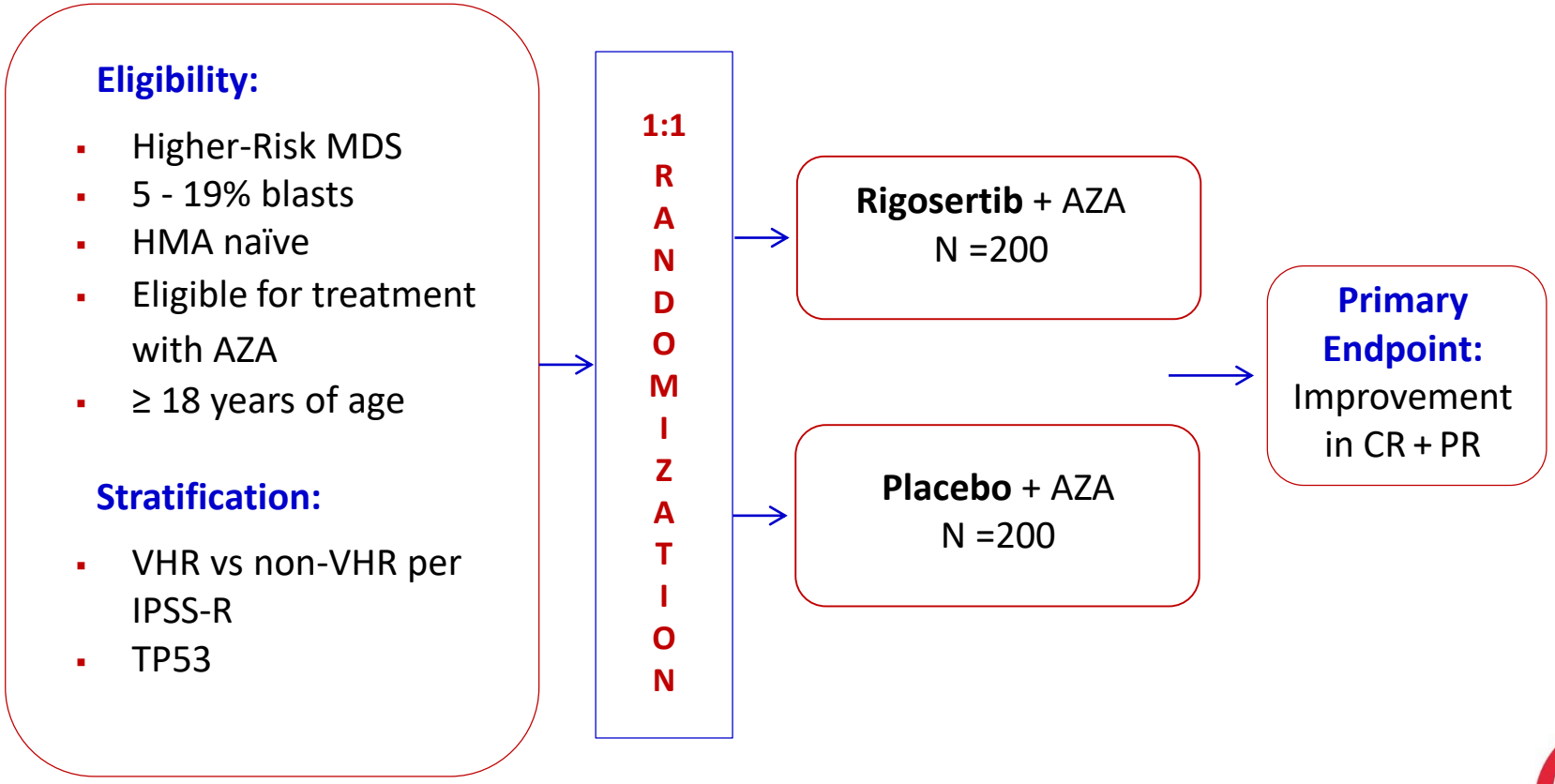
Note: these are not head-to-head studies from which inferences or comparisons can be drawn, but rather serve as part of the basis for company's further investigation

*Lionel Adès et al: ASH; 2018

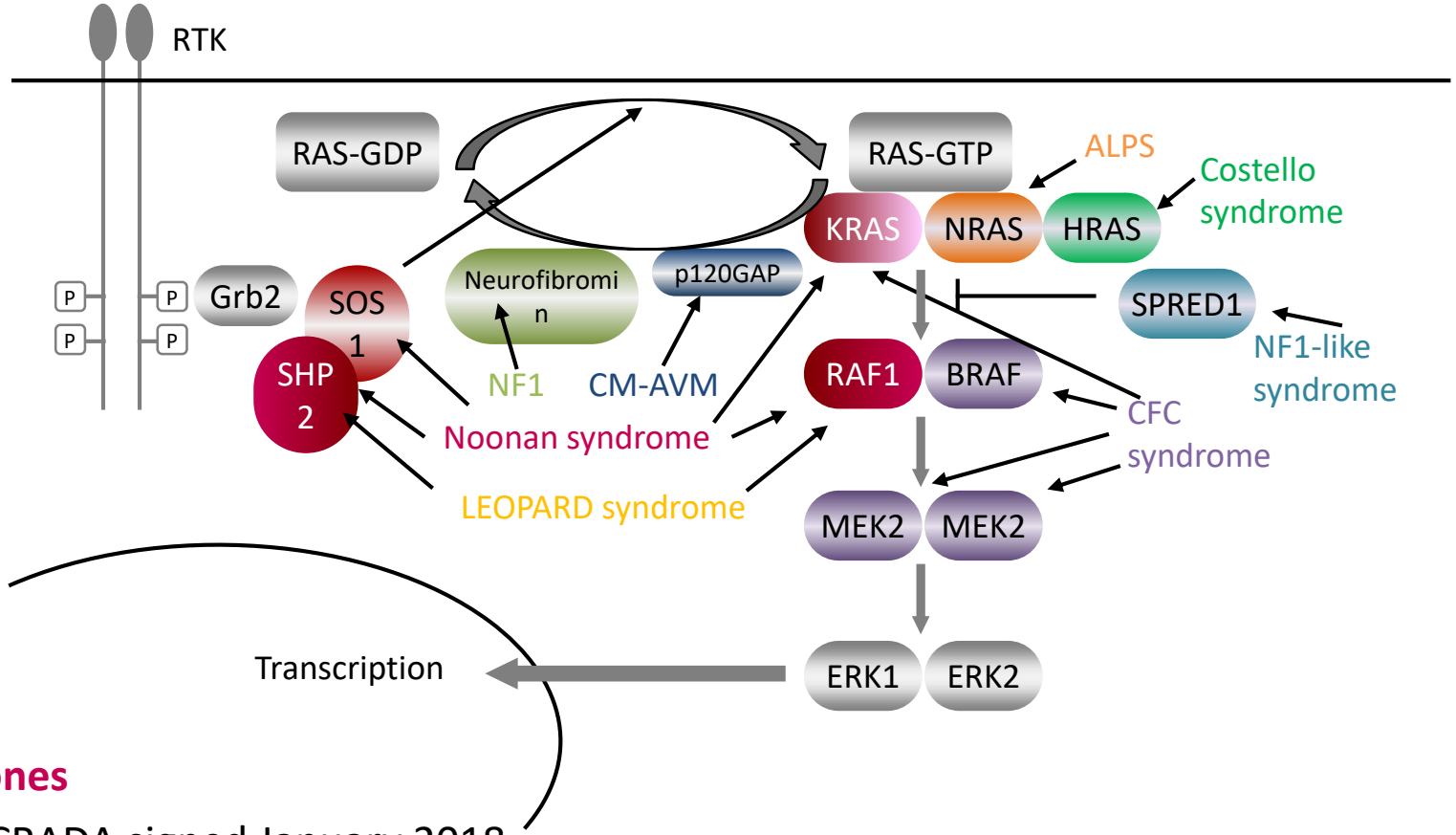
**Navada et al: ASH; 2018 Median Duration of Treatment is 7.8 months (0.7-25.1)

PHASE 2/3 PROPOSED DESIGN FOR TREATMENT NAIVE HR MDS
(TO BE REVIEWED WITH FDA)

Phase 3, multi-center, international, randomized, double-blind, placebo- controlled study of oral rigosertib + injectable azacitidine (AZA) versus injectable AZA plus oral placebo in patients who are hypomethylating agent treatment-naïve with higher-risk myelodysplastic syndrome (MDS)



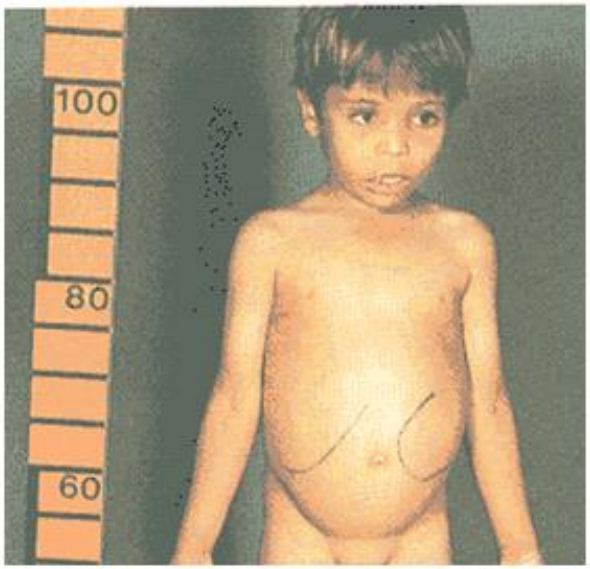
RASOPATHIES: RIGOSERTIB FOR RARE PEDIATRIC DISEASES

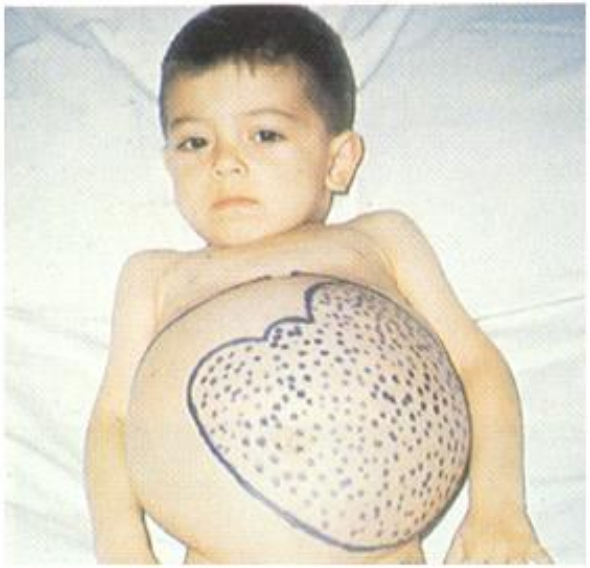


Milestones

- NCI CRADA signed January 2018
- Potential for first patient in 2019-1H2020
- UCSF non-clinical program initiated
  - Funded by LLS

JUVENILE MYELOMONOCYTIC LEUKEMIA OVERVIEW

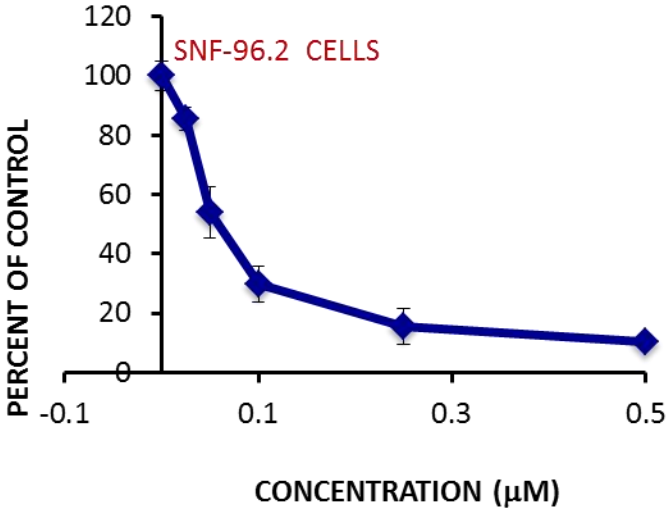


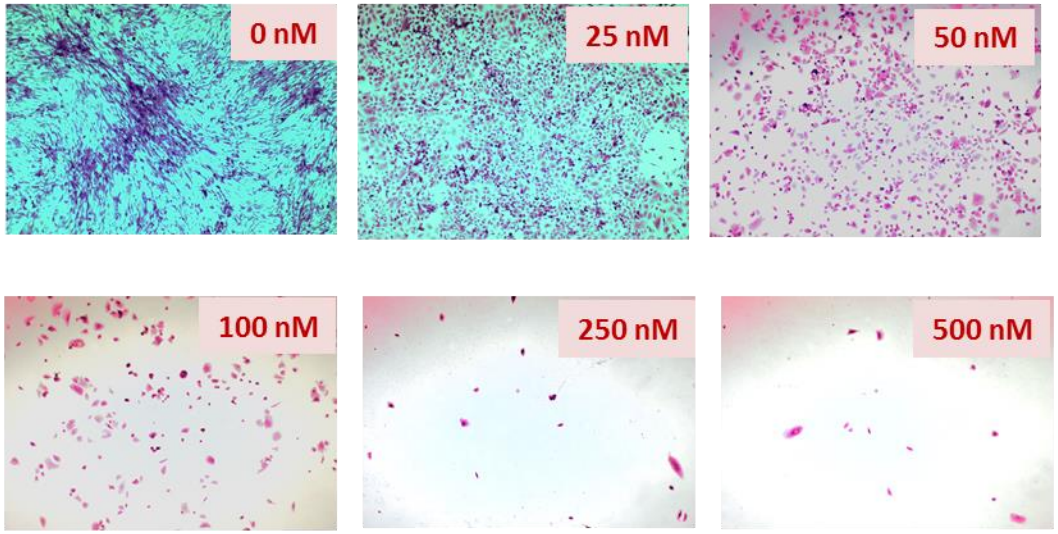


- Hematopoietic disorder of infancy caused by excessive proliferation of monocytic and granulocytic cells; which infiltrate the spleen/liver, intestines and lungs
- Rare- 2% of pediatric hematologic malignancies (in the US about 50 new cases per year); 1.2 cases per million annually, median age is 2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

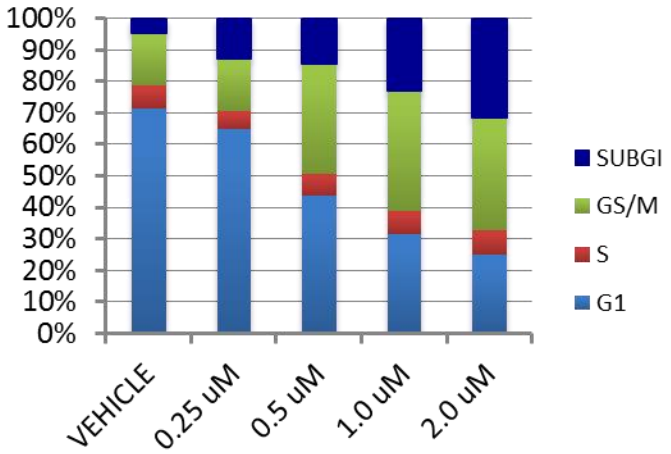
GROWTH INHIBITION AND INDUCTION OF APOPTOSIS WITH RIGOSERTIB IN NF1 CELLS

Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

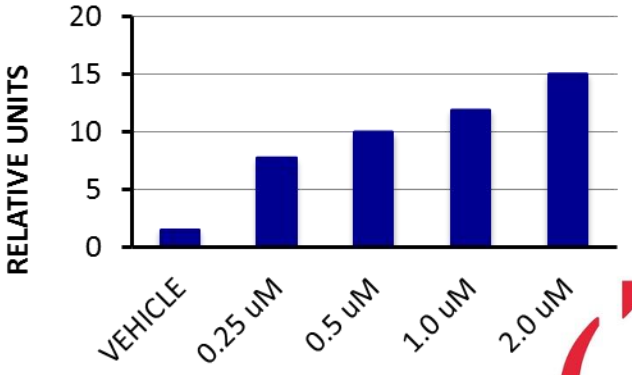




FACS Analysis of SNF 96.2 Cells Treated With Rigosertib



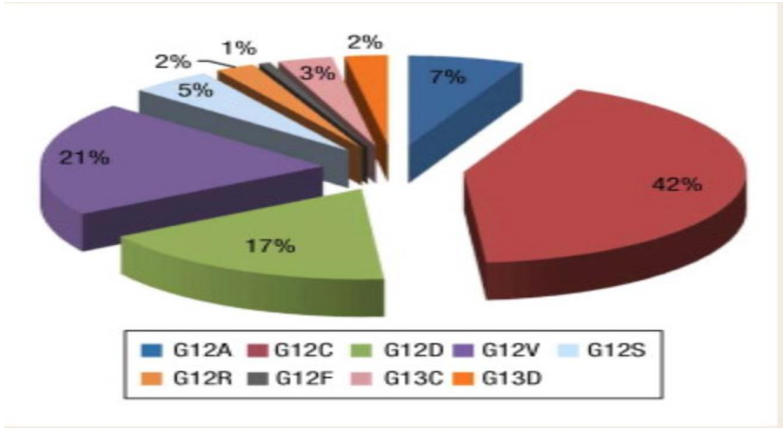
PARP Cleavage Assay

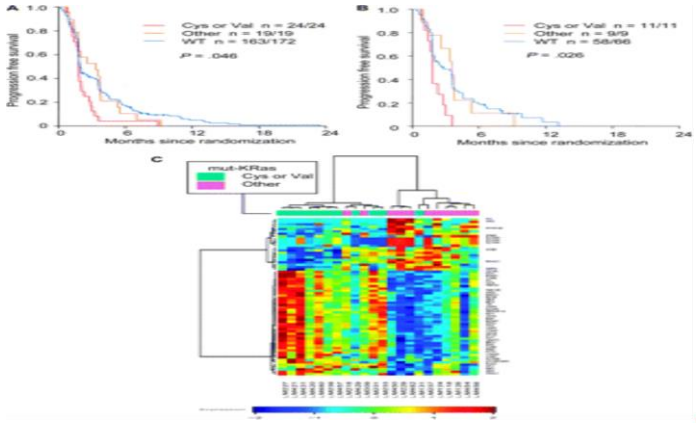


NSCLC & CRC

GENOMIC VARIABILITY OF KRAS MUTATIONS

- Not all KRAS mutations the same
  - Different mutations
  - Different phenotypes (Epithelial vs. Mesenchymal)
  - Overlap with other genetic alterations (i.e., TP53, STK11, CDKN2A/B)





Neil Vasan et al. Clin Cancer Res 2014
Karachaliu N et al., Clin Lung Cancer 2013

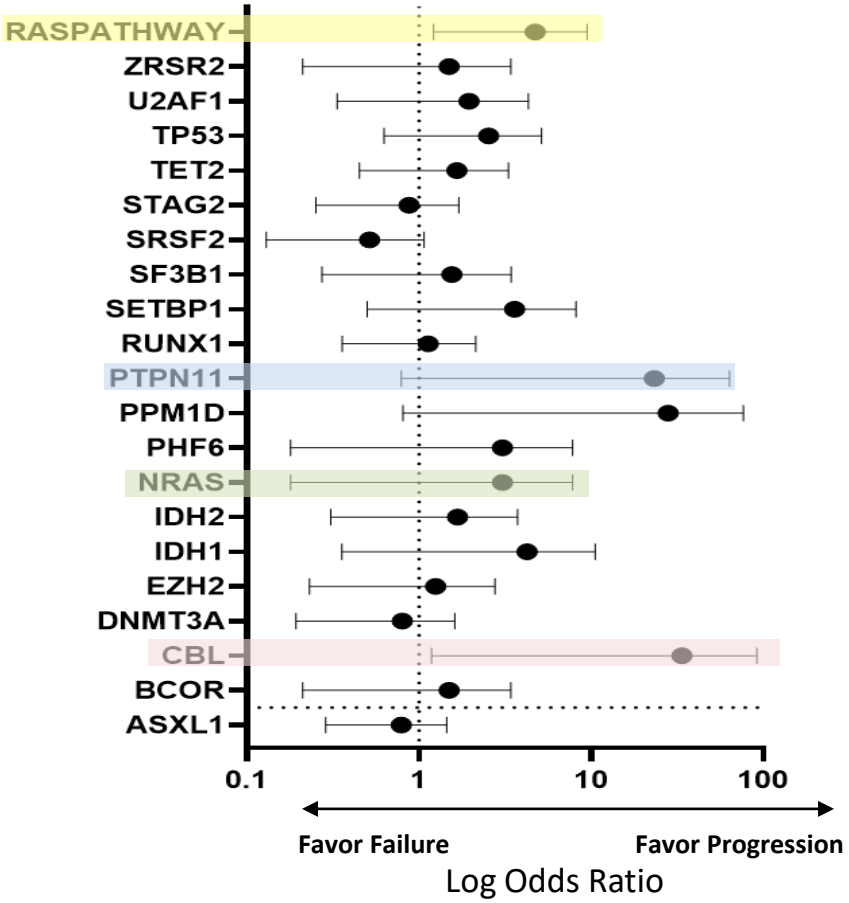
ONCONOVA THERAPEUTICS

Genomic Profiling in Patients with Higher Risk Myelodysplastic Syndrome (HR MDS) Following HMA Failure: Baseline Results from the Inspire Study (04-30)

Guillermo Garcia-Manero, MD[1], Anna Jonasova, MD, PhD[2], Selina M. Luger, MD, FRCPC[3], Aref Al-Kali, MD[4], David Valcárcel, MD[5], Erica D. Warlick, MD[6], Wieslaw W. Jedrzejczak, MD, PhD[7], María Díez-Campelo, MD, PhD[8], Patrick S. Zbyszewski, MBA[9], Christopher Cavanaugh[9], Richard C. Woodman, MD[9], Steven M. Fruchtman, MD[9] & Koichi Takahashi, MD[10]

[1]University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX; [2]1st Medical Department - Hematology, General Hospital, Prague, Czech Republic; [3]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [4]Division of Hematology, Mayo Clinic, Rochester, MN; [5]Planta Baixa, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [6]Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN; [7]MTZ Clinical Research, Medical University of Warsaw, Warsaw, Poland; [8]Hematology Department, Institute of Biomedical Research of Salamanca, University Hospital of Salamanca, Salamanca, Spain; [9]Onconova Therapeutics, Inc., Newtown, PA; [10]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

MUTATIONAL RESULTS ACCORDING TO DISEASE PROGRESSION OR HMA FAILURE AT TIME OF STUDY ENTRY



*RAS PATHWAY includes NRAS, KRAS, CBL, PTPN11, and NF1

Mutations identified in ≥ 4 patients are listed individually

N=159

- ***136 enrolled***
- ***23 screen failures***

THANKS TO HANSON WADE
FOR ORGANIZING THIS GREAT
MEETING ON RAS