



ONCONOVA
THERAPEUTICS

Rigosertib Overview

Ras-Targeted Drug Discovery Summit

Boston, MA

September 2019

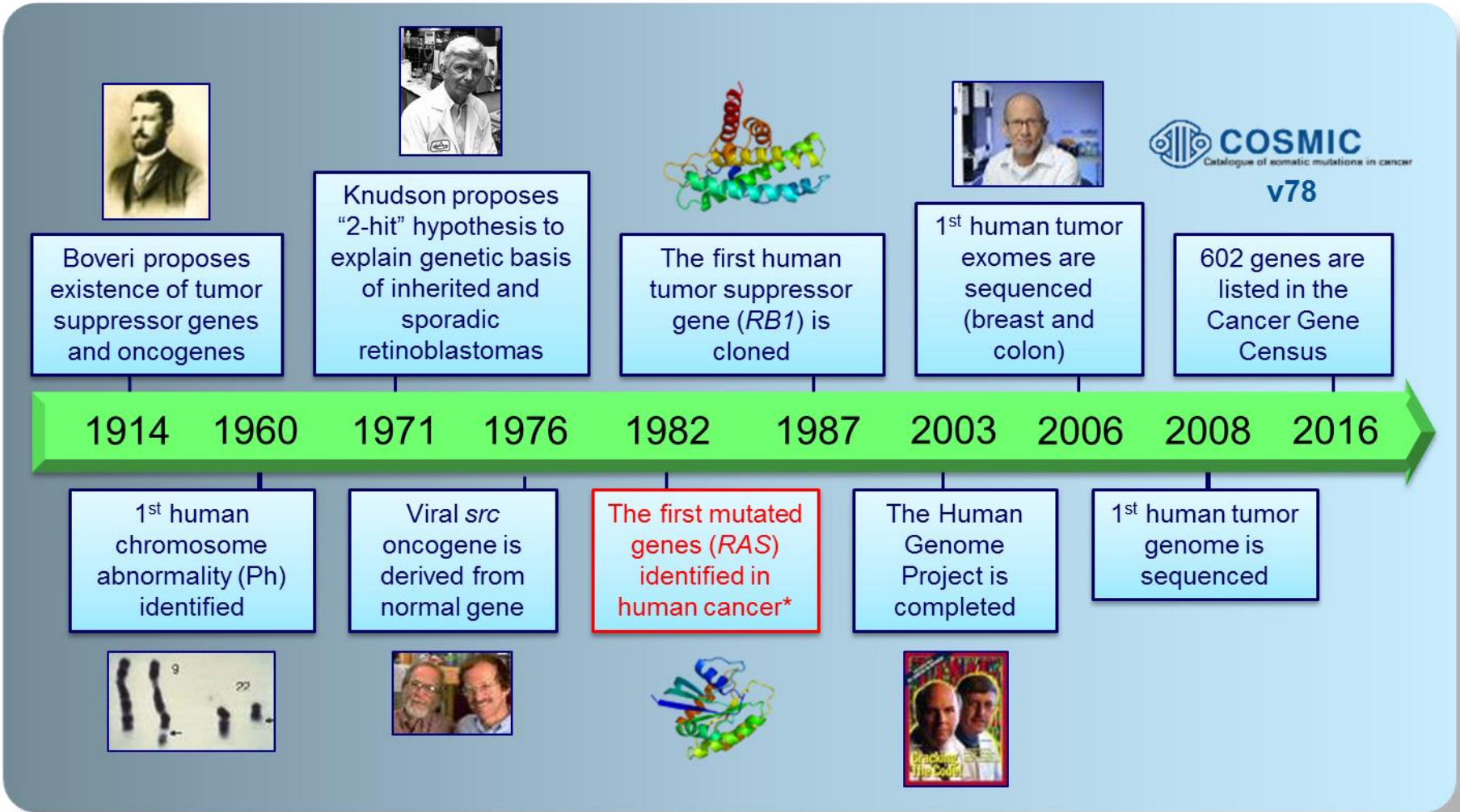
Steven M. Fruchtman, M.D.

President and CEO

Onconova Therapeutics, Inc.

GENETIC BASIS OF CANCER

ACQUIRED MUTATIONS

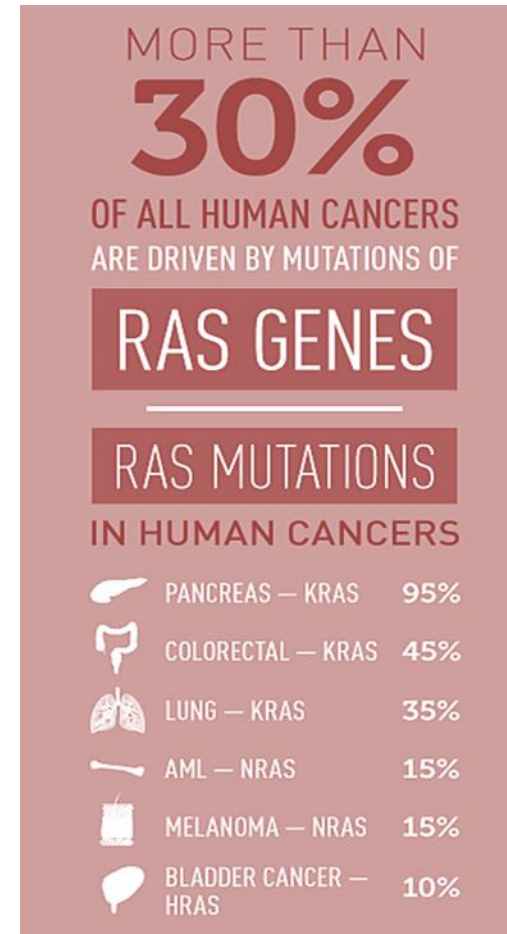


The three RAS genes (HRAS, KRAS and NRAS) comprise the most frequently mutated gene family in cancer (~25%)



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, plays key role in neoplastic transformation and proliferation
- Mutations of RAS and signaling pathways that activate wild type RAS present in myelodysplastic syndromes (MDS)



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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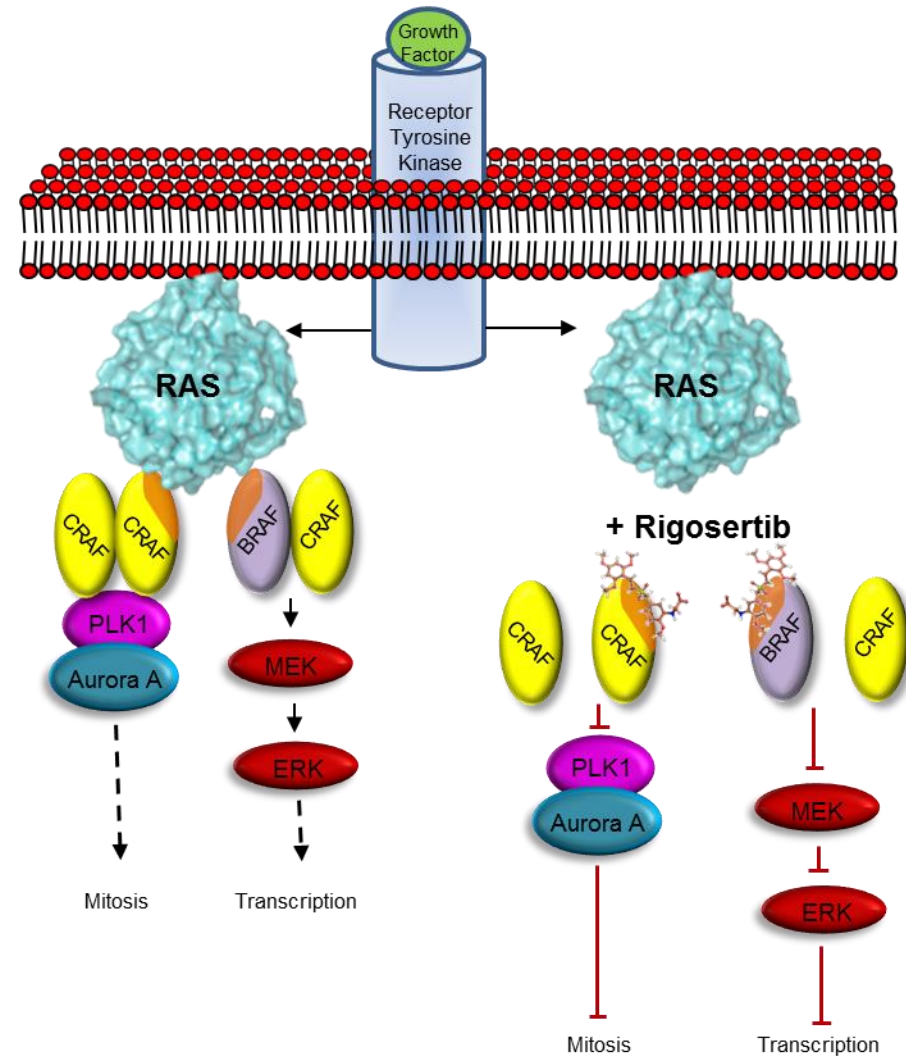
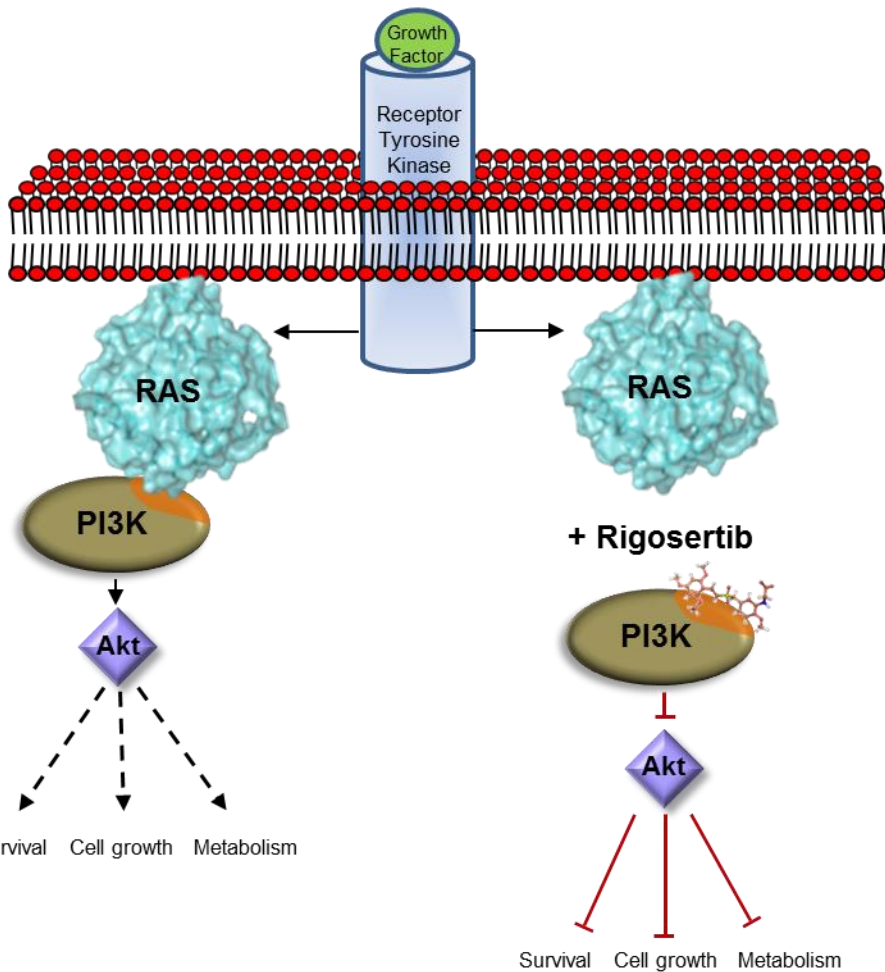
⁵Department of Radiation Oncology, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Avenue, Bronx, NY 10461, USA

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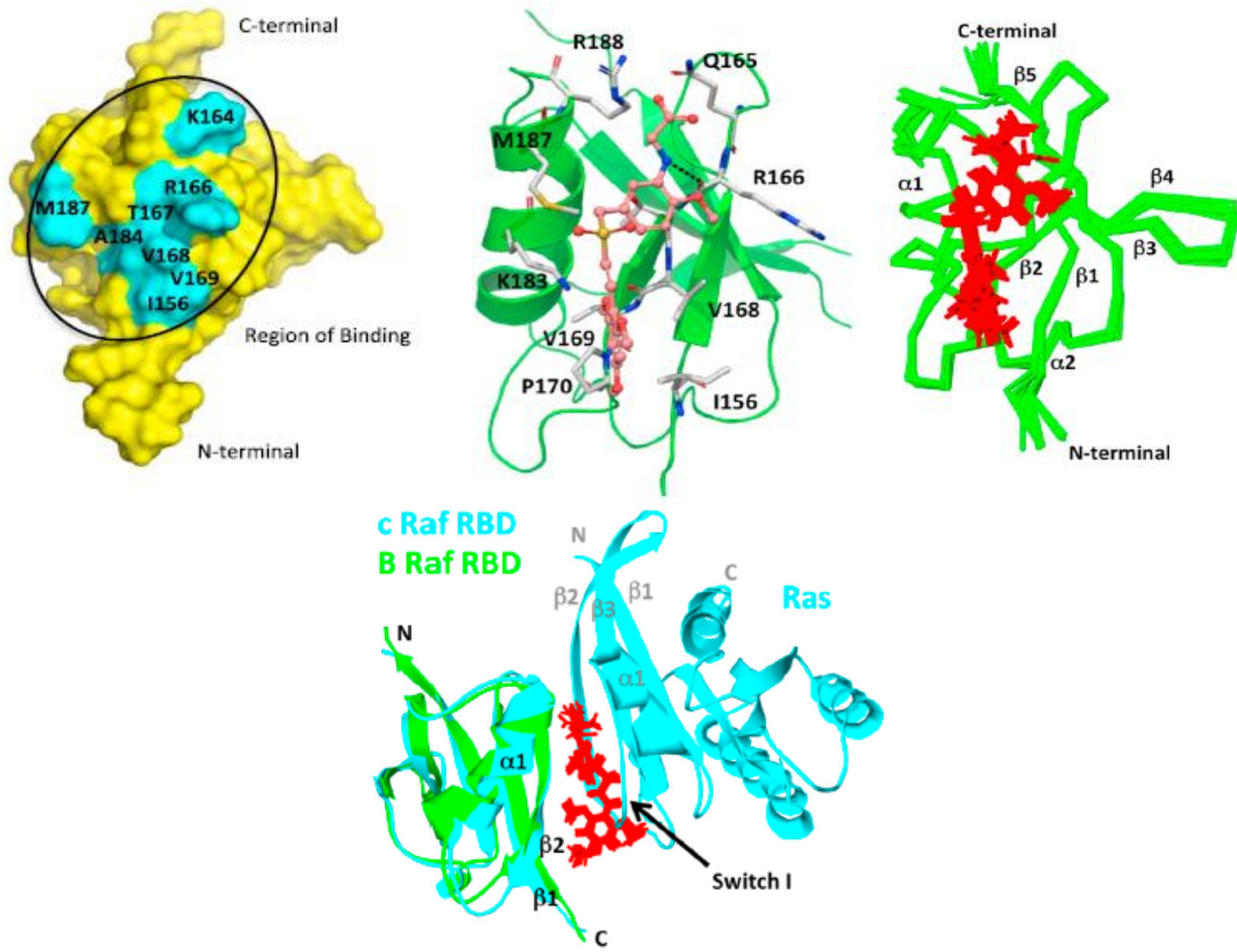




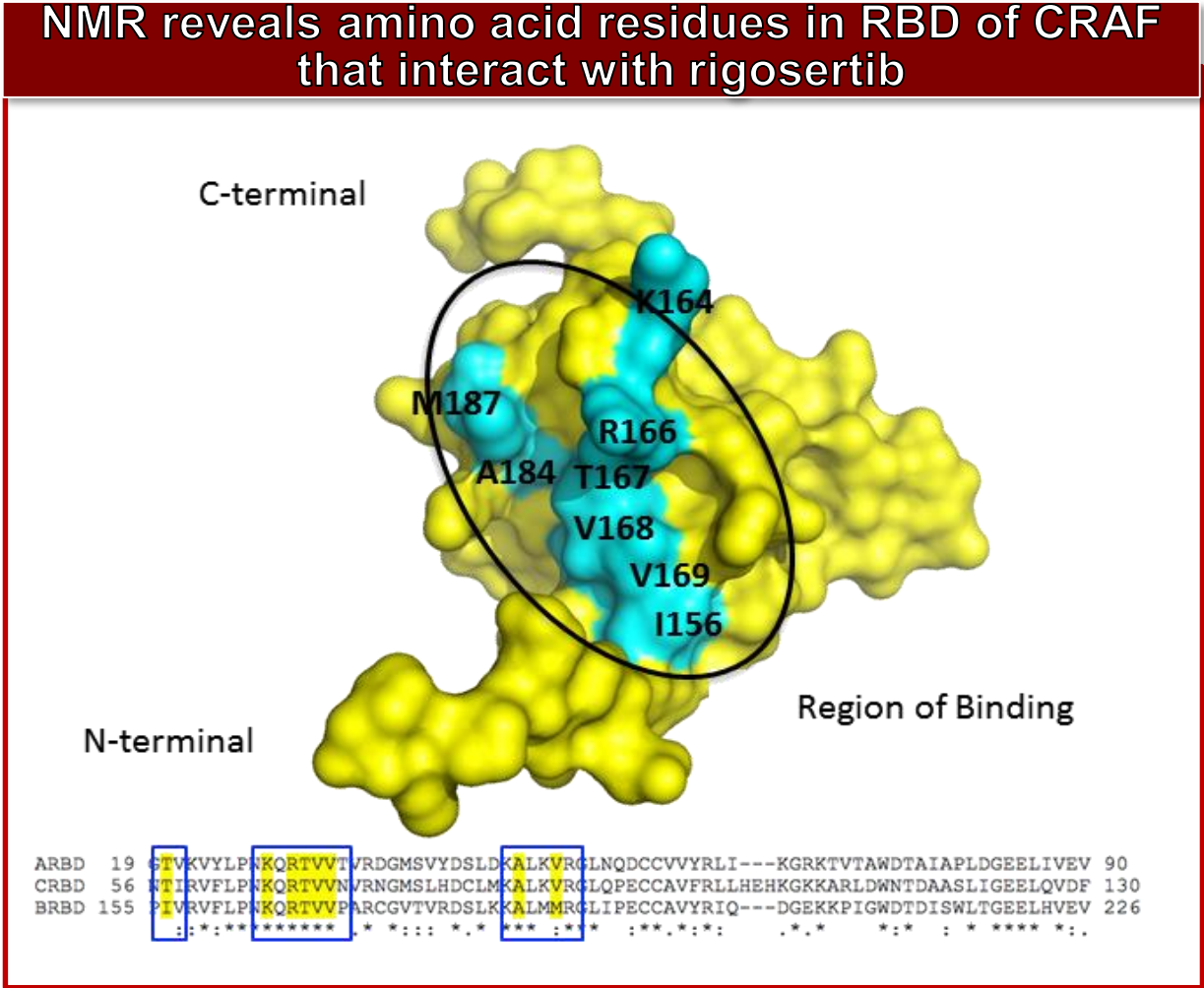
RIGOSERTIB MECHANISM OF ACTION



NMR MODELS OF RIGOSERTIB/RBD BINDING



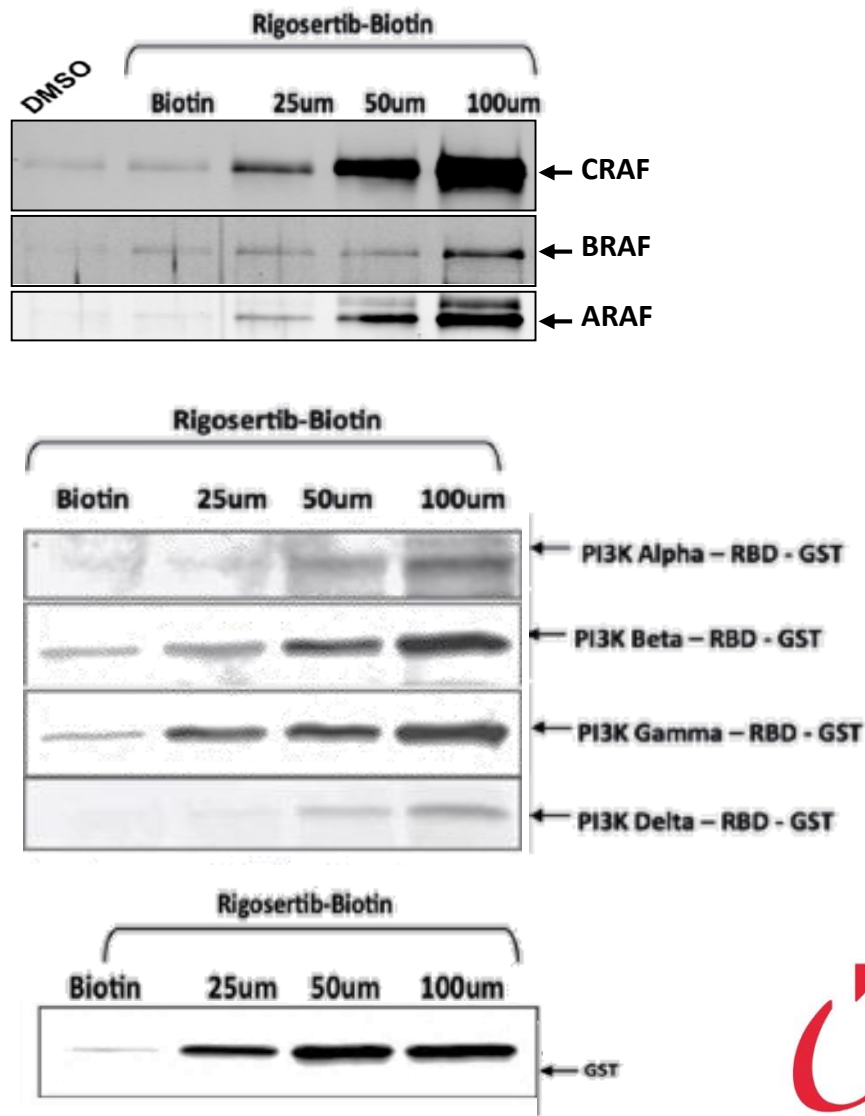
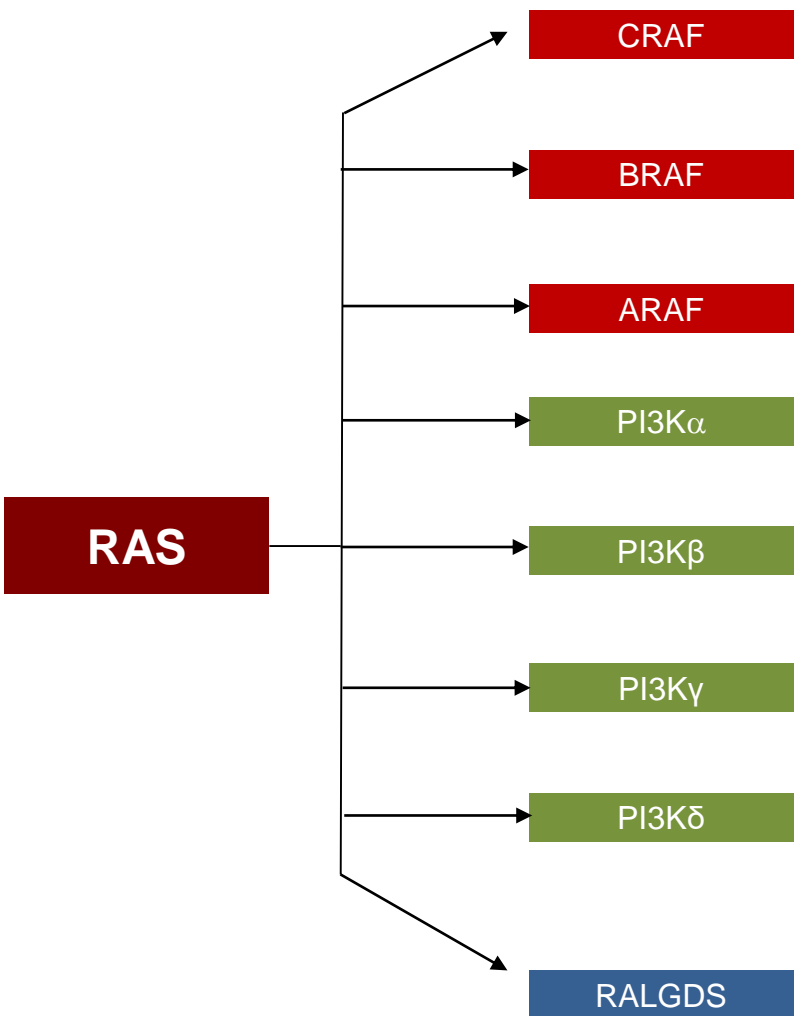
NMR BINDING OF RIGOSERTIB TO RAS



Cyan area represents region of interaction



RIGOSERTIB BINDS TO MULTIPLE RAS EFFECTOR RBDS



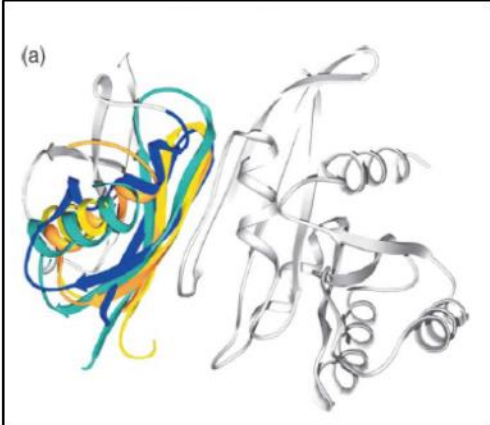
SECONDARY/TERTIARY STRUCTURAL SIMILARITY OF RBDS DESPITE LACK OF EXTENSIVE SEQUENCE HOMOLOGY

Sequence Alignment of RA and RB Domains

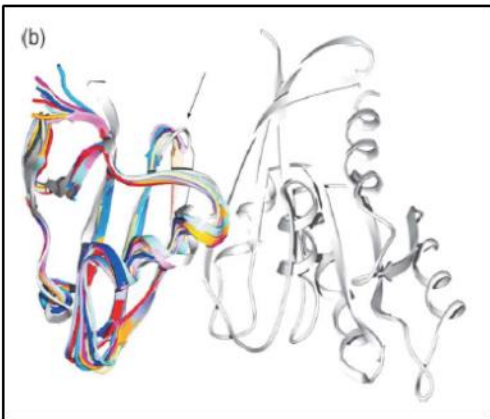
		β1	β2	α1
RA cons.50%		cspsLRVasss	sssh+slpss	csTsp VlppllcKaplss
RaIGDS	11	-----DCCIRVSLD-VDN--	GNMYKSIILVTS---	QDKAPAVIRKAMDKENLEE--
AF6 RA1	36	---DLEPHGVRFYFQDKAAG-NPATKCI	RVSS---	TATTQDVIETLAEEKFRPDMR-
AF6 RA2	244	---PDSGGTLRIYAD-SLKP-NIPYK	TILVST---	TDPADFVAVALAEKVGLE---
RASSF1C	84	LNKDGSGYTGF	IKVQLK (37) P-KDAVKHLVLS---	RTAREVIEALLRKFLVV---
mNorel	225	LSRDGTYTGF	IKVHLK (37) P-LDAIKQLHSS---	TTTVEVIEQGLLKKFMVV---
RIN1	619	-PATHCFQRL	LRVAYQ-DPSS-GCTSKTLAVPP-	EASIALTNQLCATKFRVT---
RIN2	782	-PSVDDFQNY	LRVAFQ-EVNS-GCTGKTLVLRP-	YITTEDVCOICAEKPKVG---
PDZGEF	600	SATPDLDDQV	LRVFKA-----	DQGSRYINISK---DTTAKEVVIAIREFAVT---
Rain	144	-----PPCVLKIFGA-GLAS-	CANYKSVLATA---	RSTARELVALLERYGLAGSP
Krit1	416	---NKPYEKVRIYRM-----	DGSYRSVLEKH---	GNNTTVQIMEGMRLSQ---
spByr2	65	--REFPPRCILRFIAC-----	NGQTRAVOSRG---	DVQKTLAIALKKFVLE---
scCYR1	674	---PRHYAIRIFNT-----	DDTFTLLSCTP---	ATTVEEIIIPALKIKFNIT---
EpacII	658	---QKRQPIRGSEDEVLF (5)	DHTYTTIRVPV---	AASVKEVISAIVADKLGSG---
EpacI	509	---PGSSCAIQVGDKVPY (6)	DHSVLTLQLPV---	TASVREVMALLAQEDGWT---
RepacI	241	---EELFCHVYIT-----	EHSYSVVKAKY---	SSIAQEIIKVVAEKIQYA---
PLC RA1	2008	---RKCLQTHRTVHGV-PG---	PEPFTVFTING---	GTKAKQLLQOILTNQDIK---
PLC RA2	2132	---SEESSEFQVHDV-SP---	EQPTVLIKAPR---	VSTAQDVIOOTLCKAKYS---
PI3K-V223K	213	-KKIANNCIFKIIRS-----	TTSQTIKVSF---	DDTPGAILQFFTKMAKK---
DAGK_RA2	395	---RQEVKTIYPG-WLKV-	GVAVSVVRVP---	KSTARSVVLVPLDGGRAE---
MYOSINIXB	9	SGRRQQAAYHLHIYPQL---	STTESQASCRV (4)	DSTTSDEVKDAIASRLD---
MYOSINIXA	14	---NEETLRIYPG-----	AISEGTIYCPI (4)	NSTAAEVIESLINKLHLD---
Grb7	100	---RPFVVKVYSE-----	DGACRSVVVAA---	GATARHVCEMLVQRAHAL---
Cl2orf2	1	---NELKVWVD-----	GVQRIVYGVTE---	VTTCCQEVVIALAQAIQRTG---
Cl1orf13	6	---AAMELVWVD-----	GIQRVVCVSE---	QTTCCQEVVIALAQAIQGTG---
ALS2	321	---KKLVKVHMS-----	DDSSKTMVDE---	RQTVRQVLDNLMDSKSHCG---
RIAM	176	---KKLVKVHNM-----	DNSTKSLMVE---	RQLARDVLDNLFKETHCD---
Nexin27	273	---SDVELRVALP-----	DGTTTVTVRVKK---	NSTTDQVYQIAIAKVGMGMD---
RBD cons.50%		shs+VaLP	sspsolVslRP	Gcol+DsLppllc+RGLs
cRaf	55	---SNTIRVFLP-----	NKQRTVVVVRN---	GMSLHDCIMKALKVRGLQ---
RGS12_RBD1	961	---LHCILHL-----	DTISCVVAVKA---	GFSIKDILSLCERKGIN---
RGS12_RBD2	1093	---LPRLDLVP-----	INRSVGLKAKP---	TKPVTVELRPFVVARYGLD---
RGS14_RBD1	300	---KYCCVYLP-----	DGTASLALARP---	GLTIRDMLAGICEKRGLS---
RGS14_RBD2	381	---TFELELTA-----	LERVVRISAKP---	TKRLQALQPILEKKGLS---
UBQ cons.50%		lpipVKsh	etcshslclss	ctVppLkp+lpappul
Ubiquitin	1	---NQKFVKTL-----	TGKTITLLEVPS---	DTIENVKAKIQDKEGI---
ISG15	3	---VDTVKML-----	AGNEFQVSLSSS---	MSVSELKAQITQKIGV---
BAG-1	73	---LTVVTHS-----	NEKHDLVTSQ (5)	PVVQDLAQGVVEEVIGV---
Ubiquilin1	37	---MKVTVKTP-----	KEKEEFVAPEN---	SSVQQFKLEISKRFKS---

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

RAF/RaI-GDS/PI3K
Crystal Structures
Superimposed



NMR Structures of 10 RBDS
Superimposed



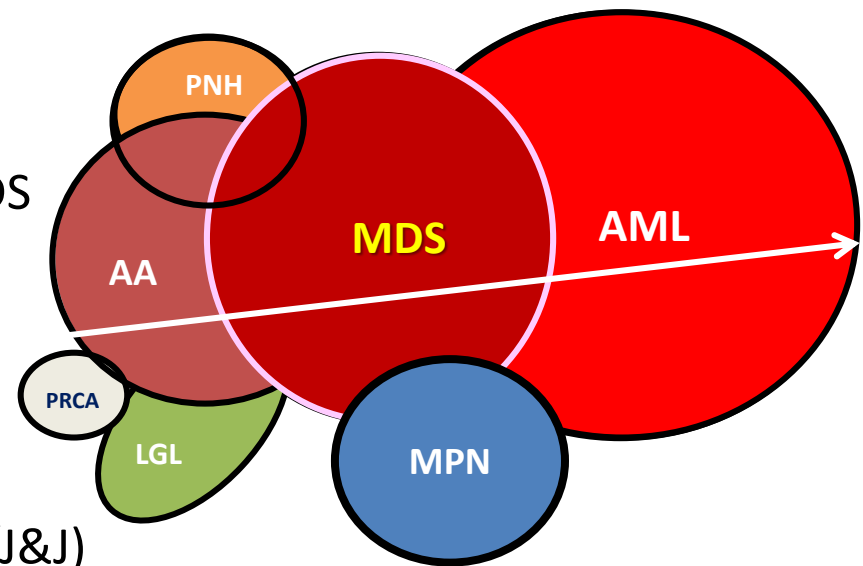


ONCONOVA
THERAPEUTICS
TARGETING CANCER, PROTECTING HEALTHY CELLS

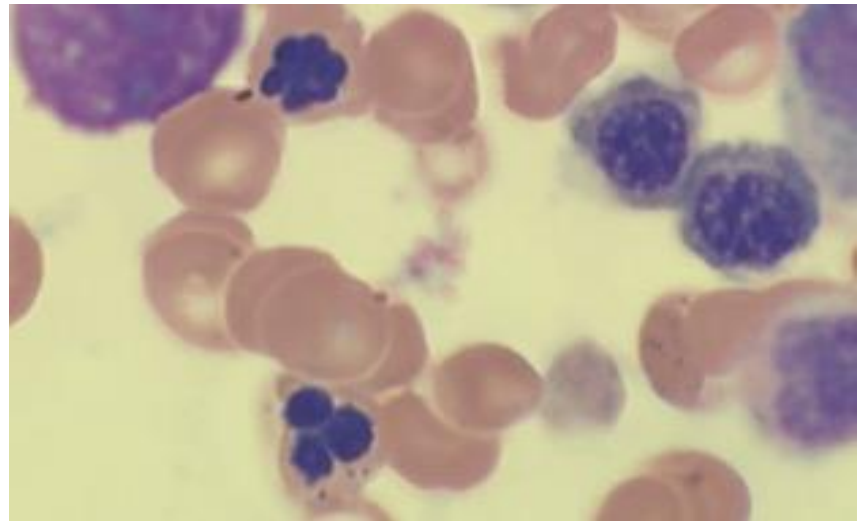
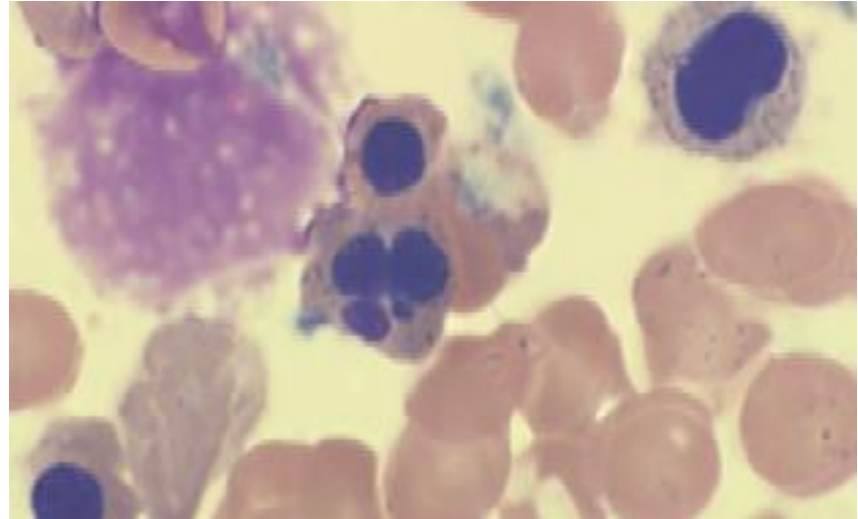
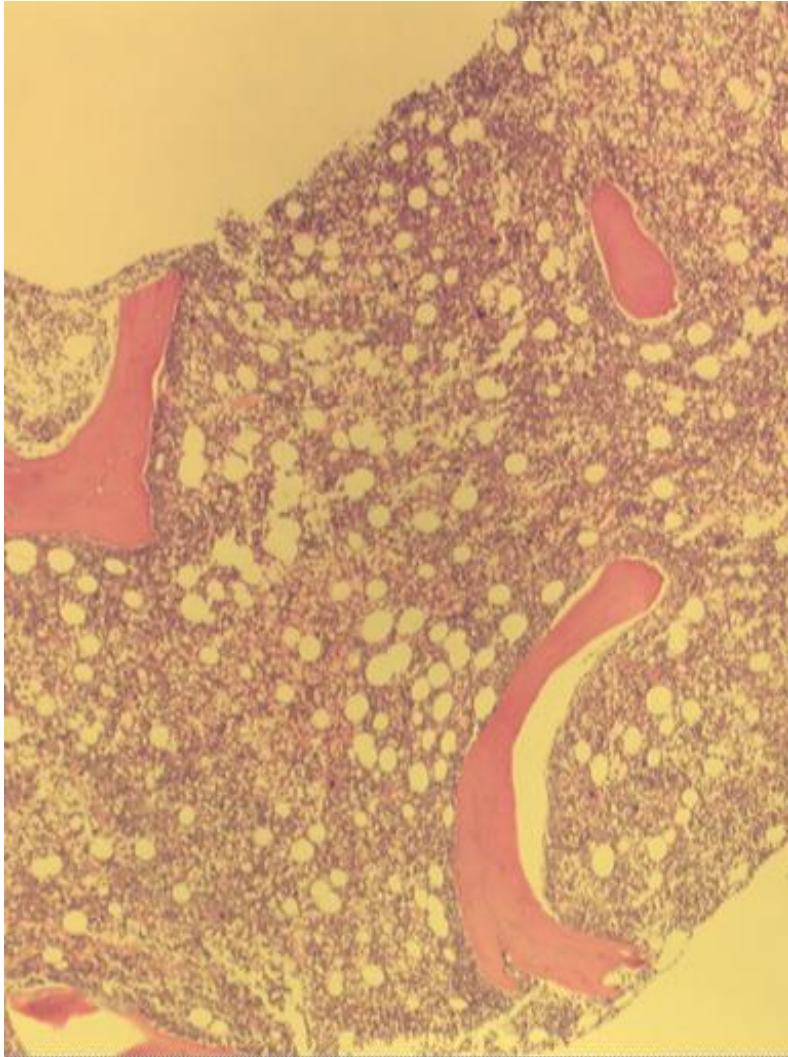
Clinical Trials

MDS IS RELATED TO OTHER BONE MARROW DISEASES

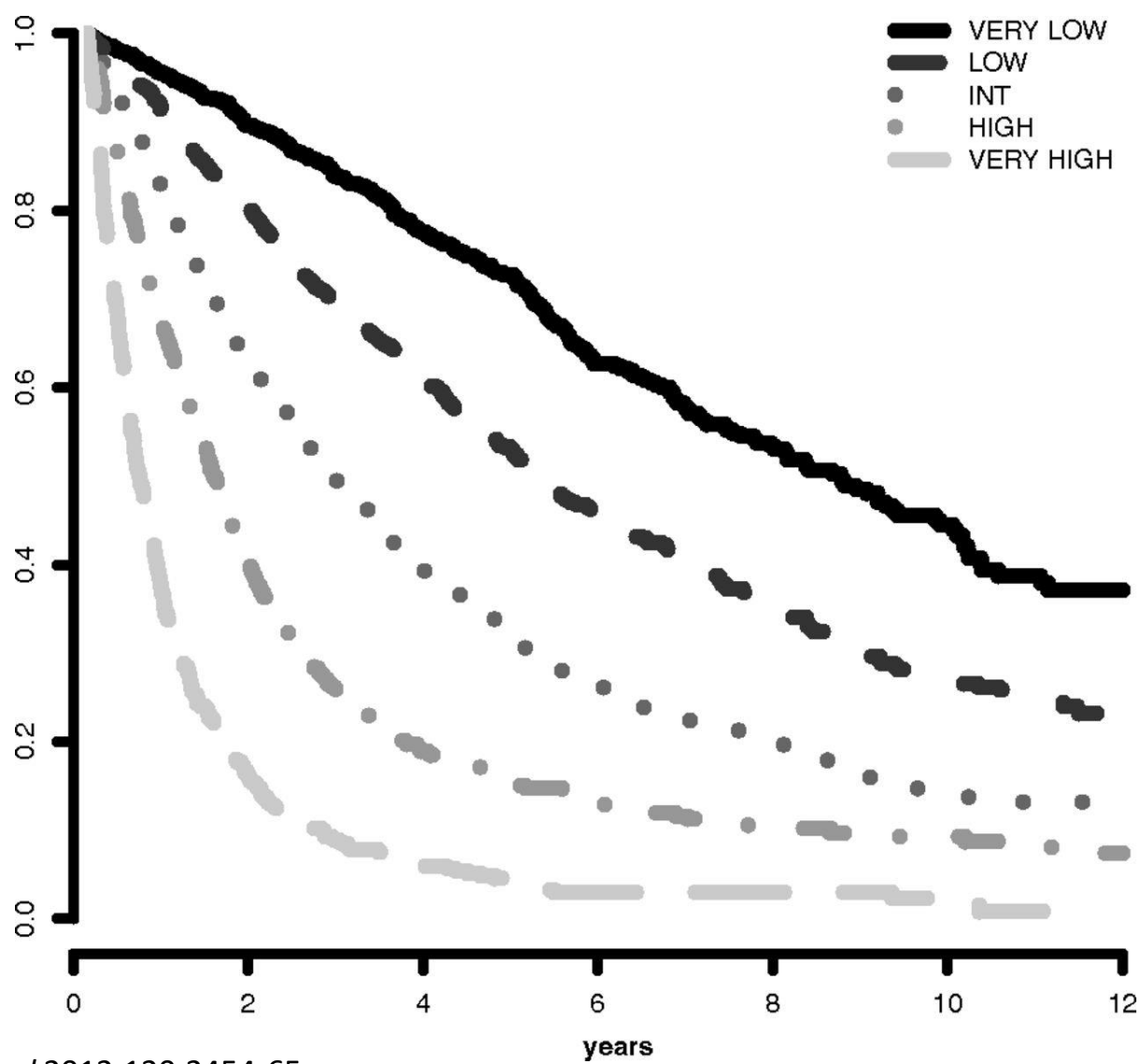
- MDS: malignant bone marrow disorder characterized by:
 - Acquired cytogenetic and genomic abnormalities, but typically only in the marrow
- US prevalence is 59,000
 - ~13,000 have higher risk (HR) MDS
 - ~10,000 second-line patients
- Available Treatments limited to hypomethylating agents
 - Vidaza (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



REVISED IPSS-R IN RELATION TO SURVIVAL



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



RIGOSERTIB ACTIVITY IN MDS

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

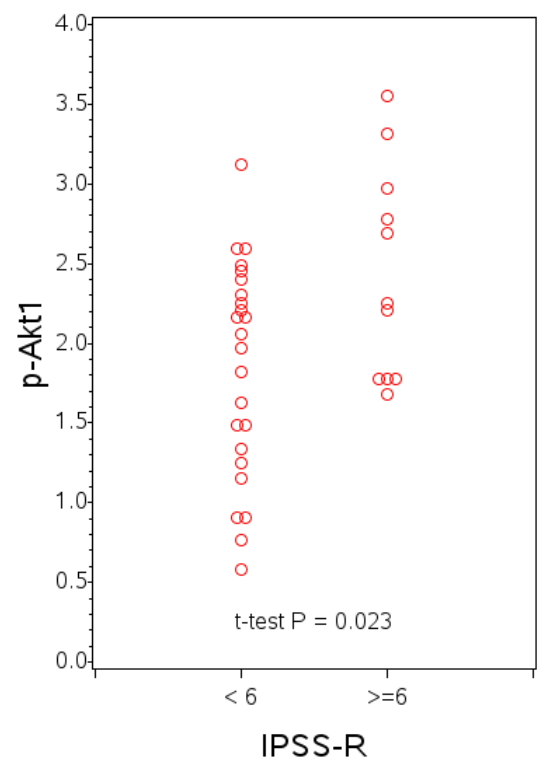
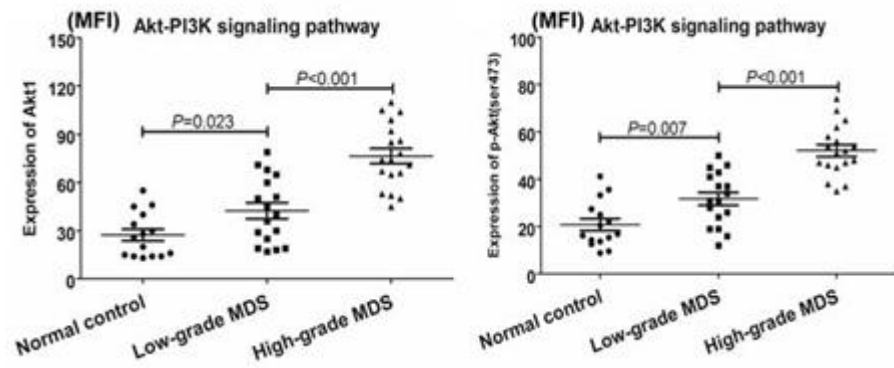
Feng Xu, Qi He, Xiao Li, Chun-Kang Chang, Ling-Yun Wu, Zheng Zhang, Li Liu, Wen-Hui Shi, Yang Zhu, You-Shan Zhao, Shu-Cheng Gu, Cheng-Ming Fei, Juan Guo, Dong Wu & Liyu Zhou

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

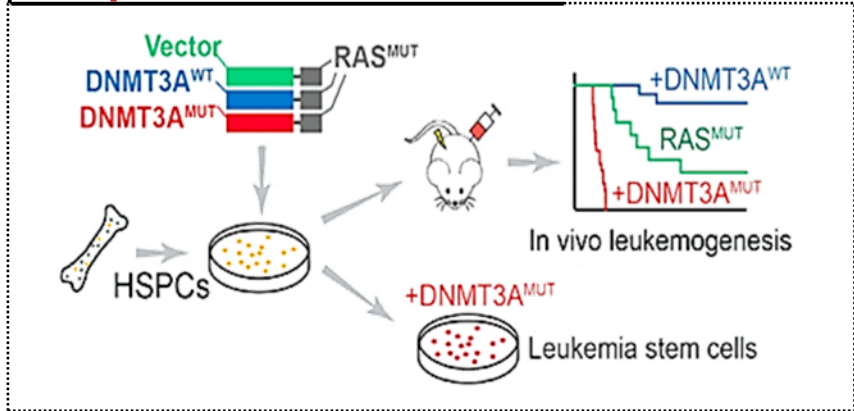
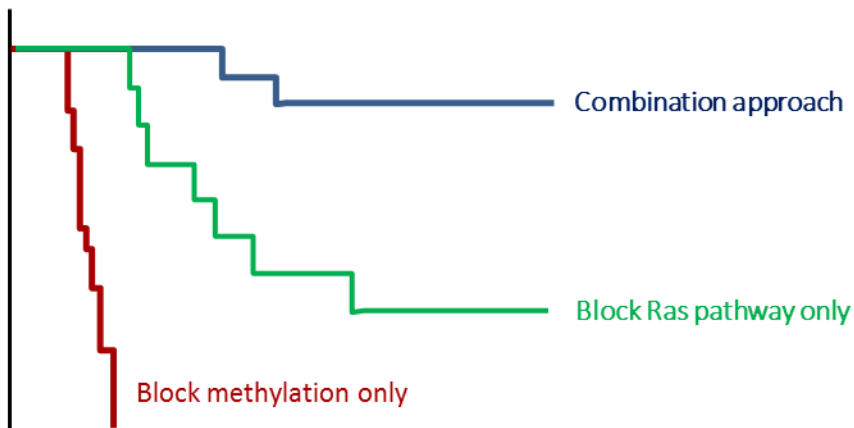


COMBINATION THERAPY WITH RIGOSERTIB + AZACITIDINE

Preclinical evidence supports synergism of rigosertib + azacitidine combination

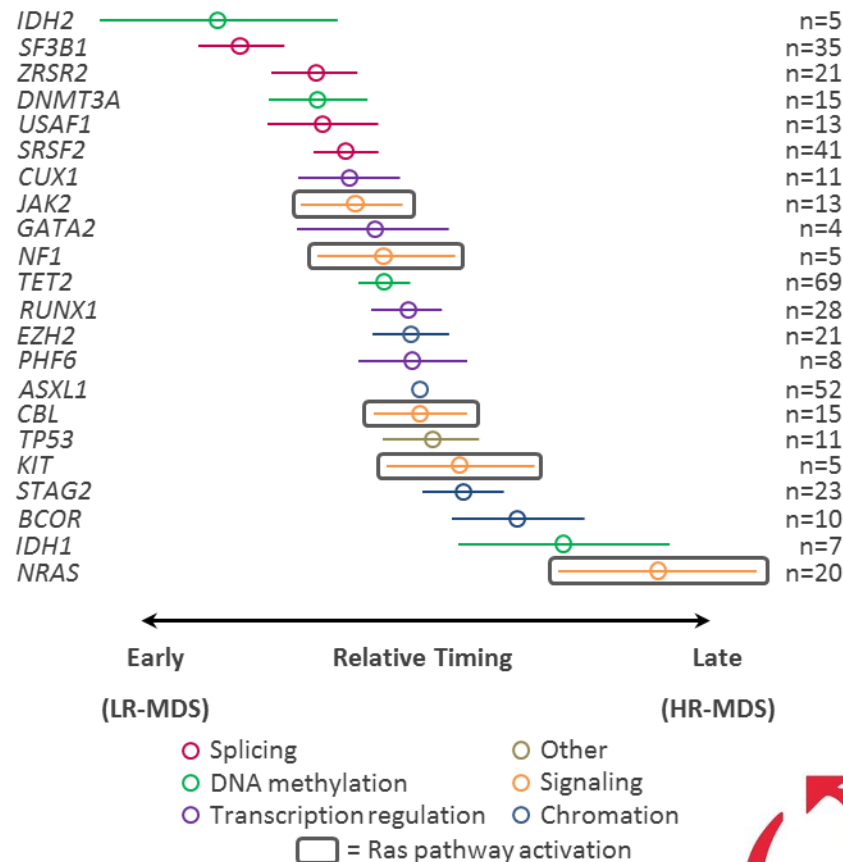
AML Mouse Model

Validation of combination approach



Lu et al., 2016 *Cancer Cell*

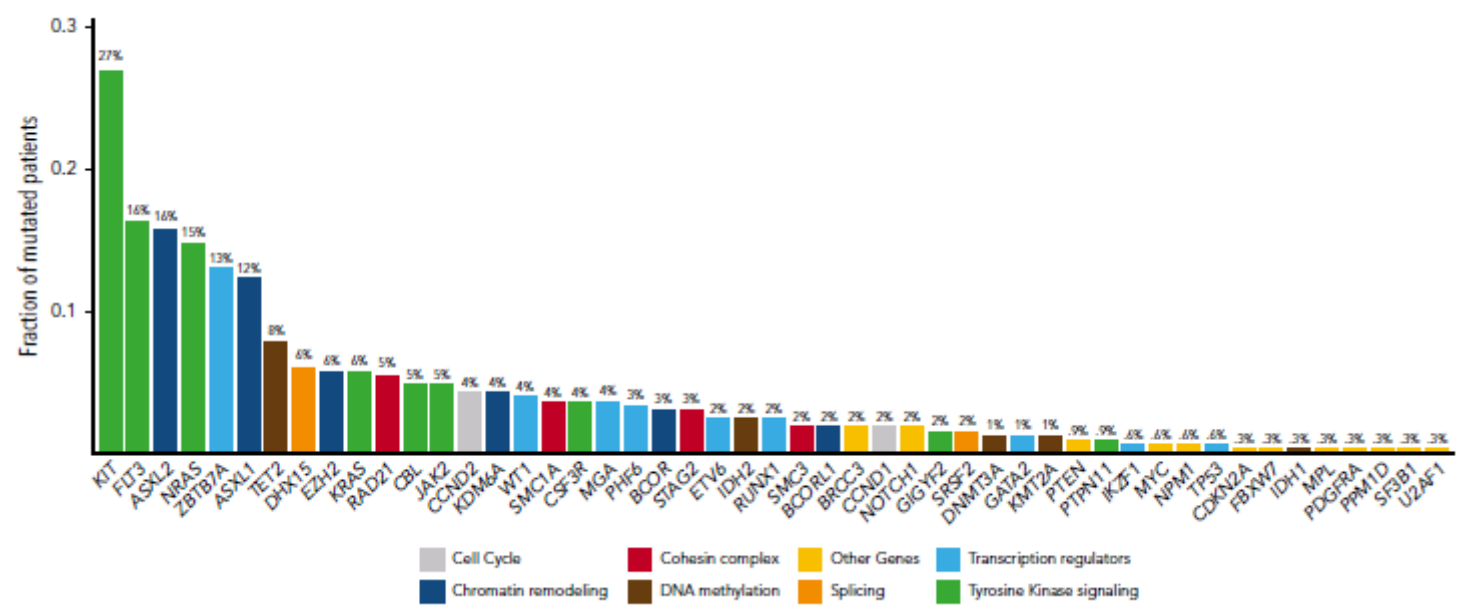
Temporal Order of Gene Mutations in 107 MDS Patients



Adapted from Papaemmanuil et al., 2013 *Blood*



FREQUENCY OF MUTATED PATIENTS PER GENE 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>.



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

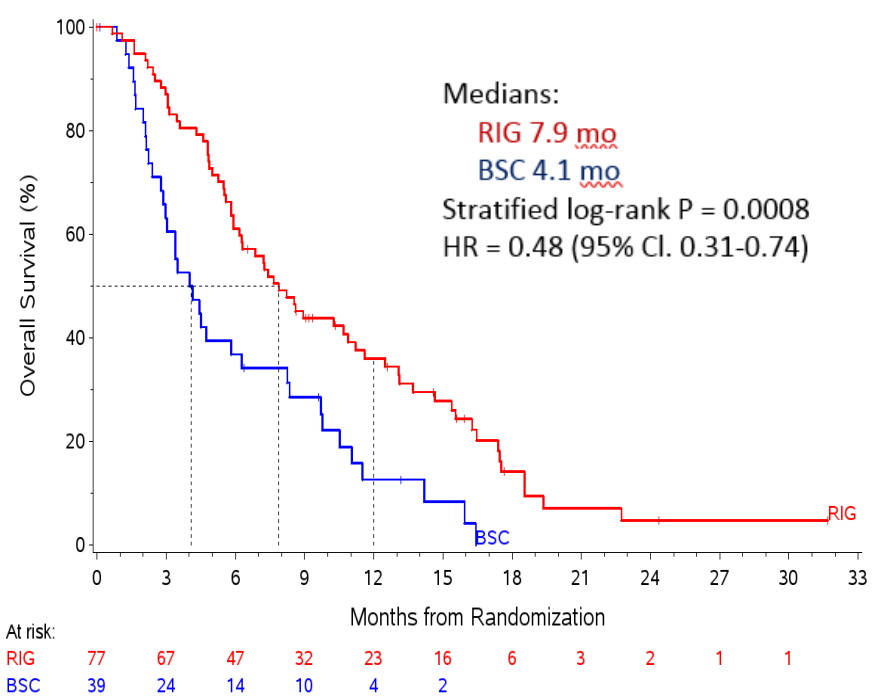
[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S1470-2045(16)00009-7)

[S1470-2045\(16\)00009-7](http://dx.doi.org/10.1016/S1470-2045(16)00009-7)

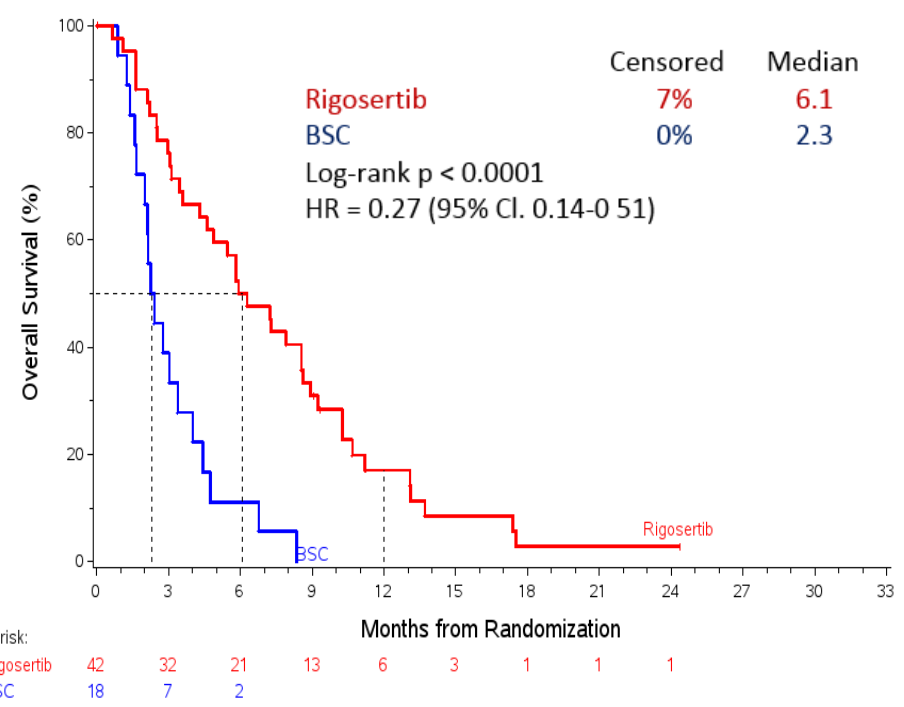


STUDY 04-21 : PROPOSED PATIENT POPULATION FOR INSPIRE

Entire ITT population



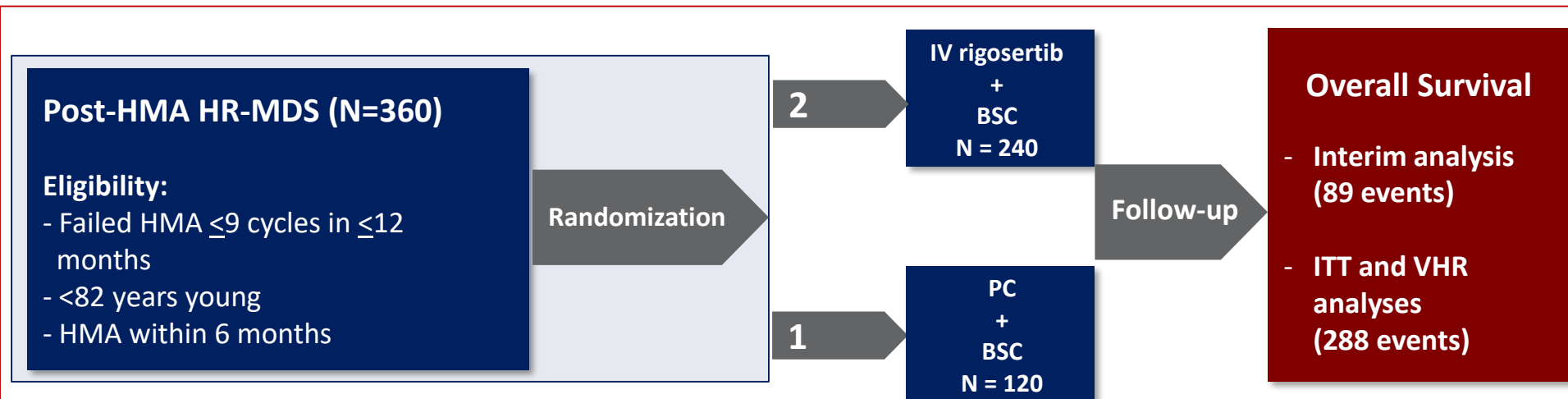
Very High Risk (VHR) population



- 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**

- **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 $\geq 28\%$
 - **VHR subgroup**
 - $\alpha = 0.01$
 - Power = 0.80
 - Target HR ≤ 0.55
 - Reduce mortality by $\geq 45\%$

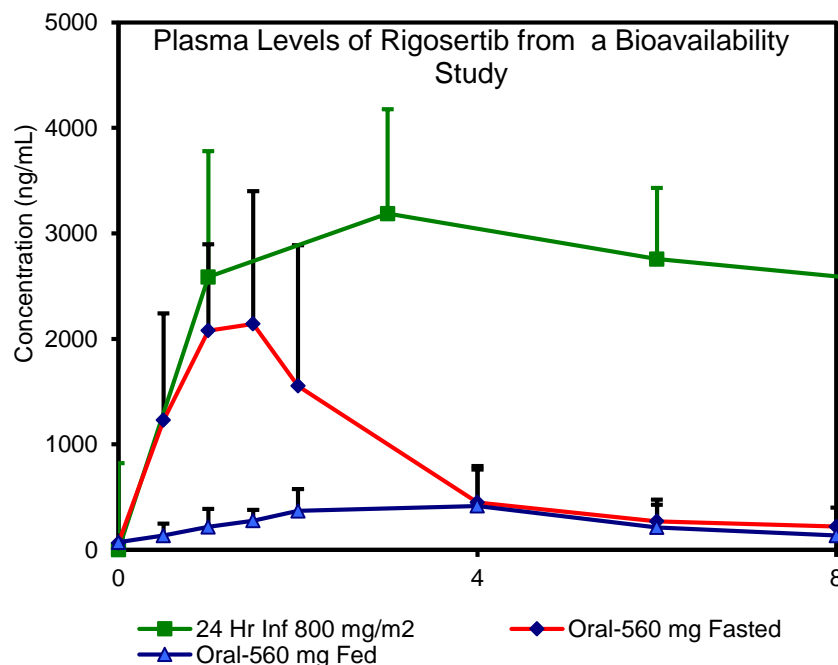


ORAL RIGOSERTIB DEVELOPMENT PROGRAM



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.

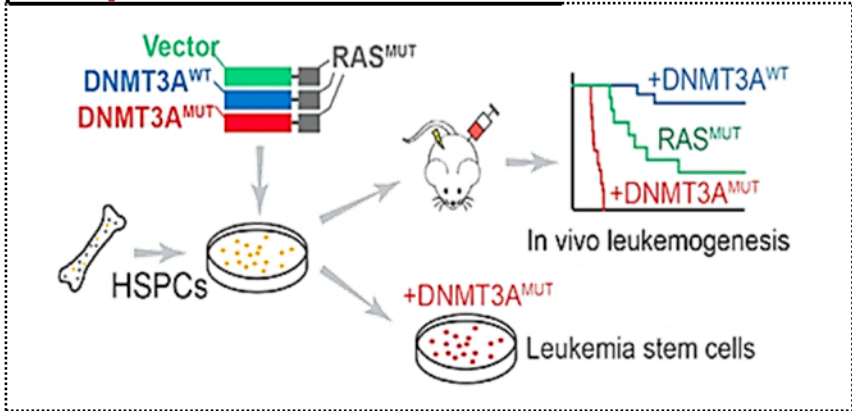
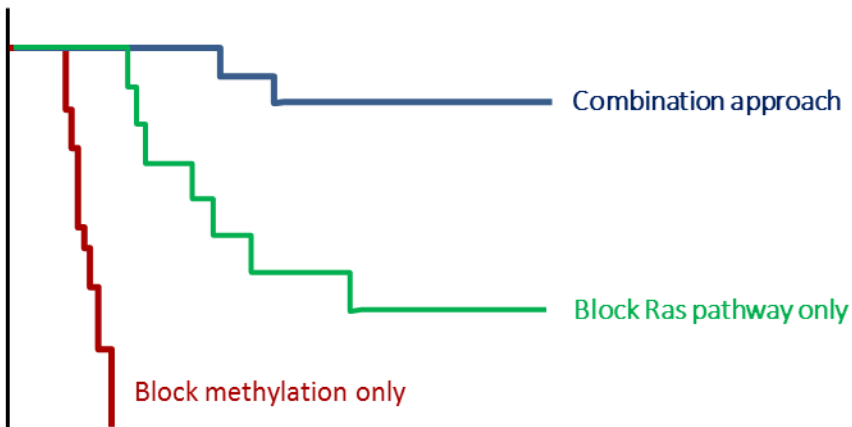


COMBINATION THERAPY WITH RIGOSERTIB + AZACITIDINE

Preclinical evidence supports synergism of rigosertib + azacitidine combination

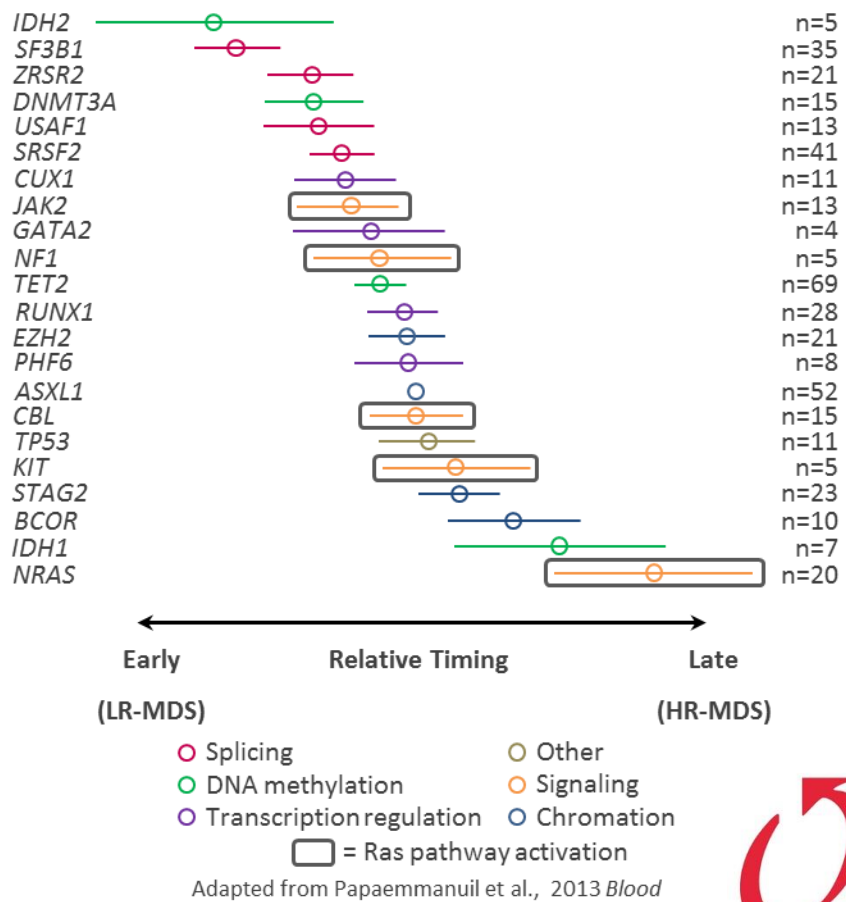
AML Mouse Model

Validation of combination approach



Lu et al., 2016 *Cancer Cell*

Temporal Order of Gene Mutations in 107 MDS Patients



HMA NAIVE ≥ 840MG/DAY

EFFICACY

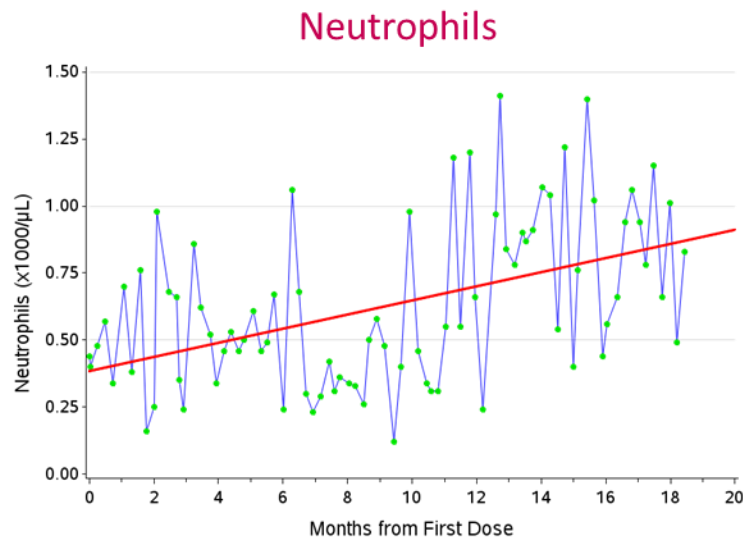
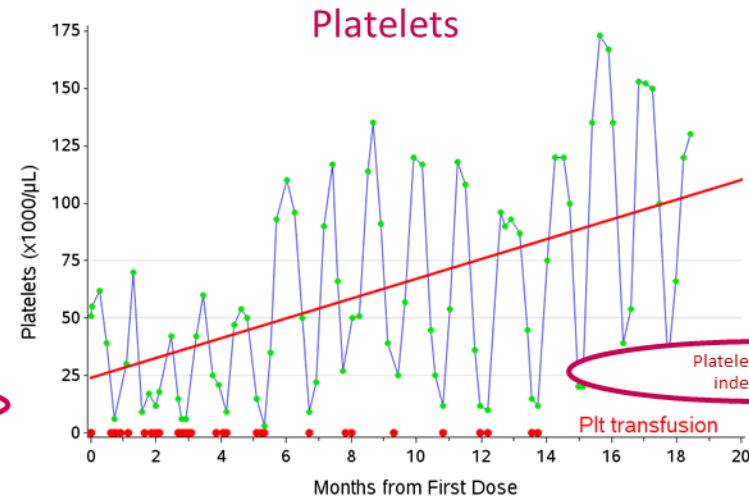
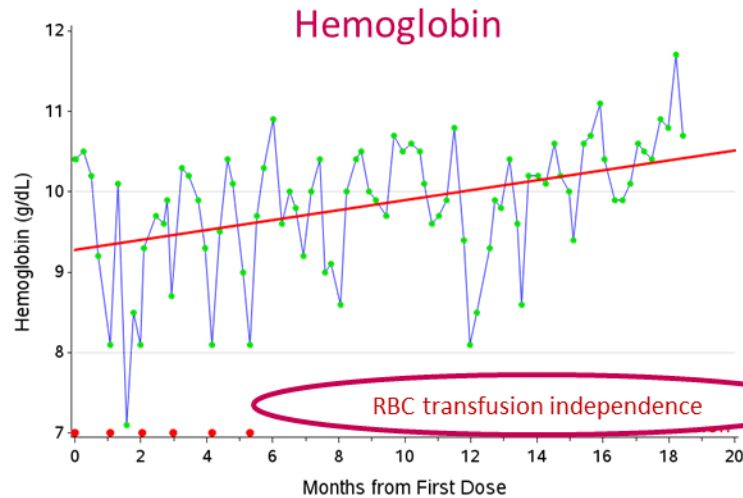
Evaluable for response	29*
Overall response per IWG 2006	26 (90%)
CR+PR	10 (34%)
Complete remission (CR)	10 (34%)
Partial remission (PR)	0
Marrow CR + Hematologic Improvement	5 (17%)
Hematologic Improvement alone	3 (10%)
Marrow CR alone	8 (28%)
Stable disease	3 (10%)
Progression	0
Median duration of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

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



COMBINATION THERAPY MAY LEAD TO TRANSFUSION INDEPENDENCE

Single patient case data*:



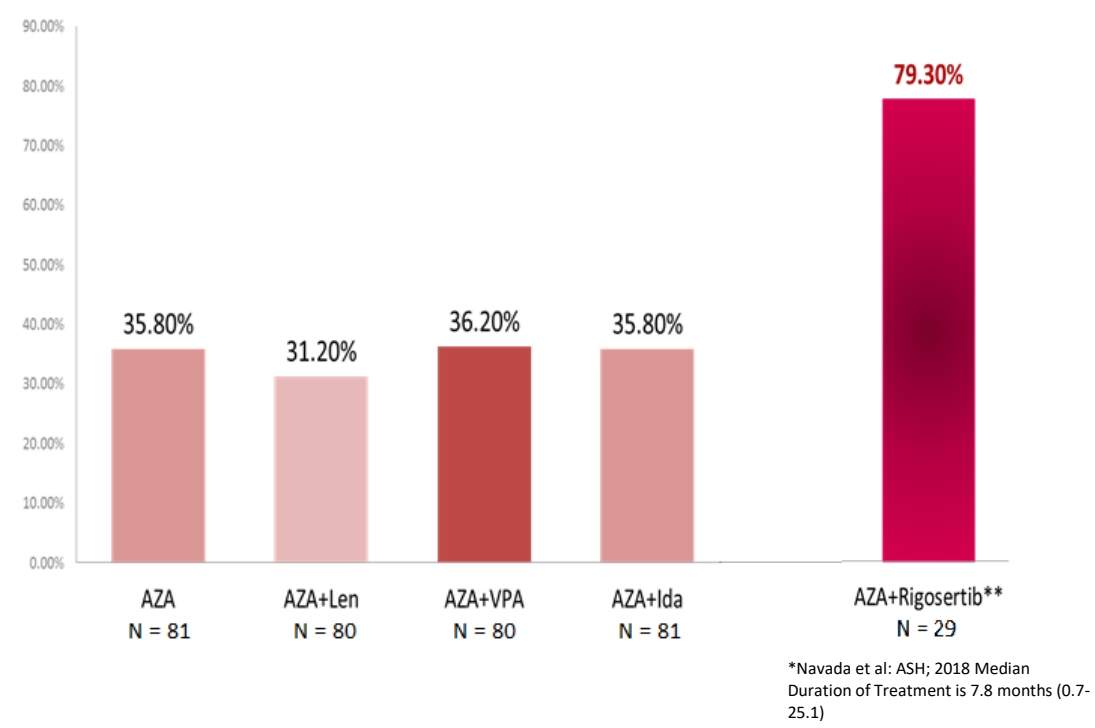
- 12 cycles of AZA – stable disease
- RBC and platelet transfusions
- Blasts 7%
- Monosomy 7
- Runx-1
- AZA + RIG in 09-08 for 20+ months
- **Complete remission**
 - RBC transfusion independence
 - <5% blasts
 - PB CR criteria

* 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



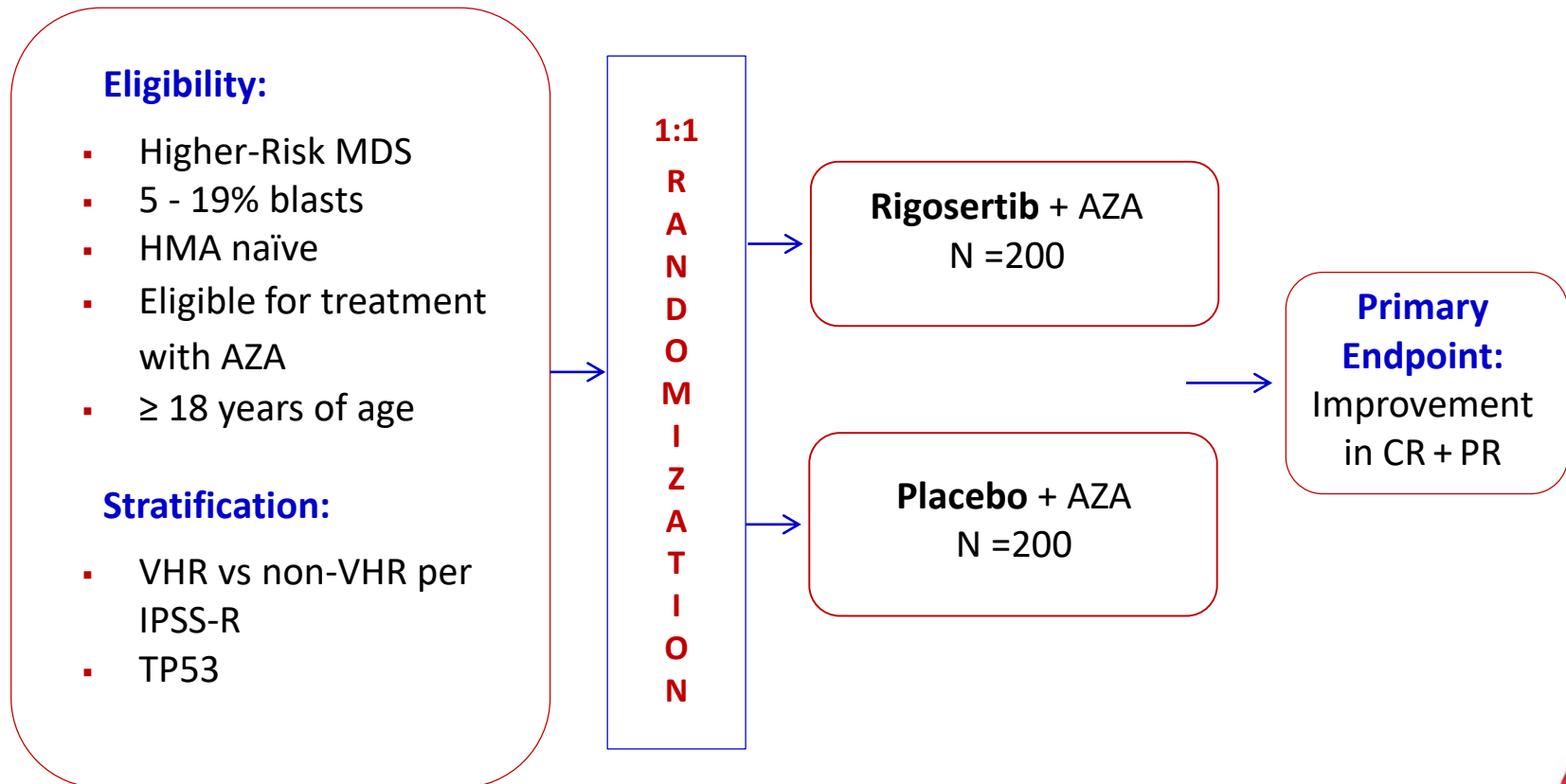
Note: these are not head-to-head studies from which inferences or comparisons can be drawn, but rather serve as part of the basis for company's further investigation

Lionel Adès et al: ASH; 2018

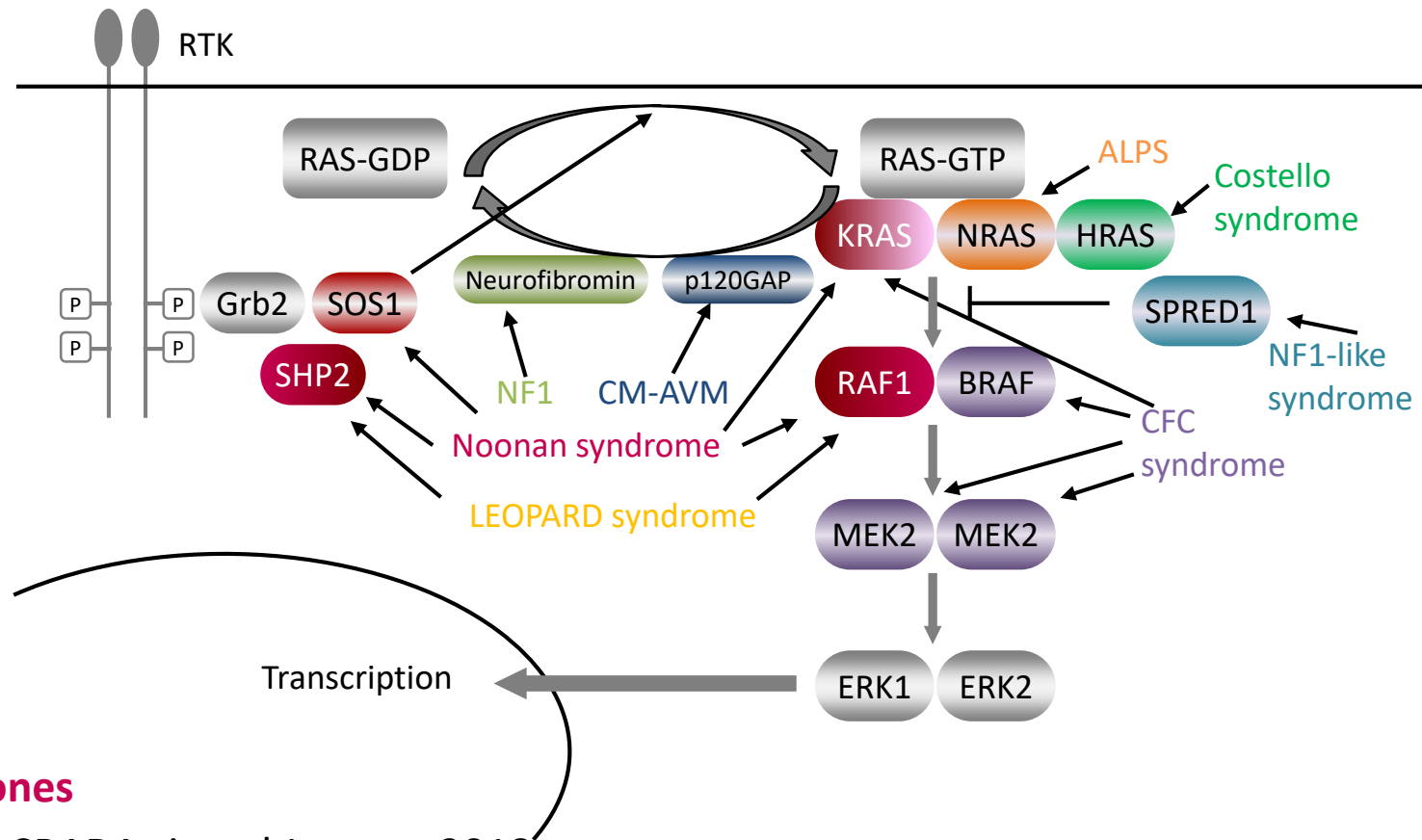


PHASE 3 PROPOSED DESIGN FOR TREATMENT NAÏVE HR MDS

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

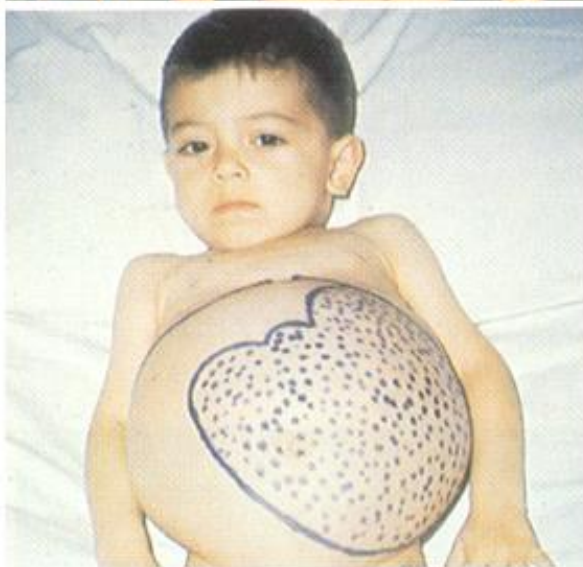
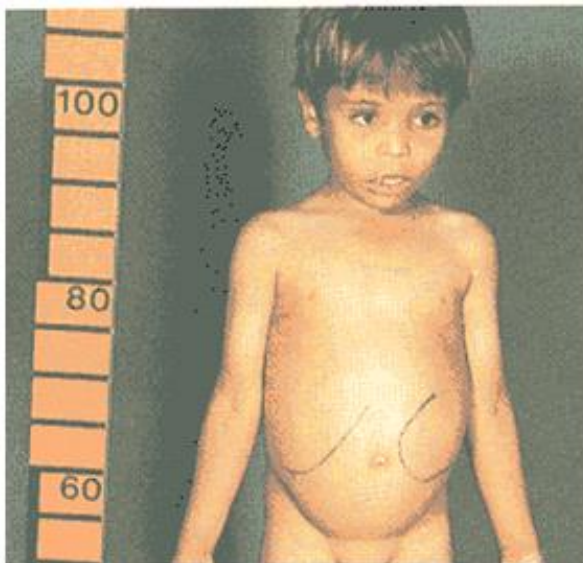


Milestones

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



JUVENILE MYELOMONOCYTIC LEUKEMIA OVERVIEW

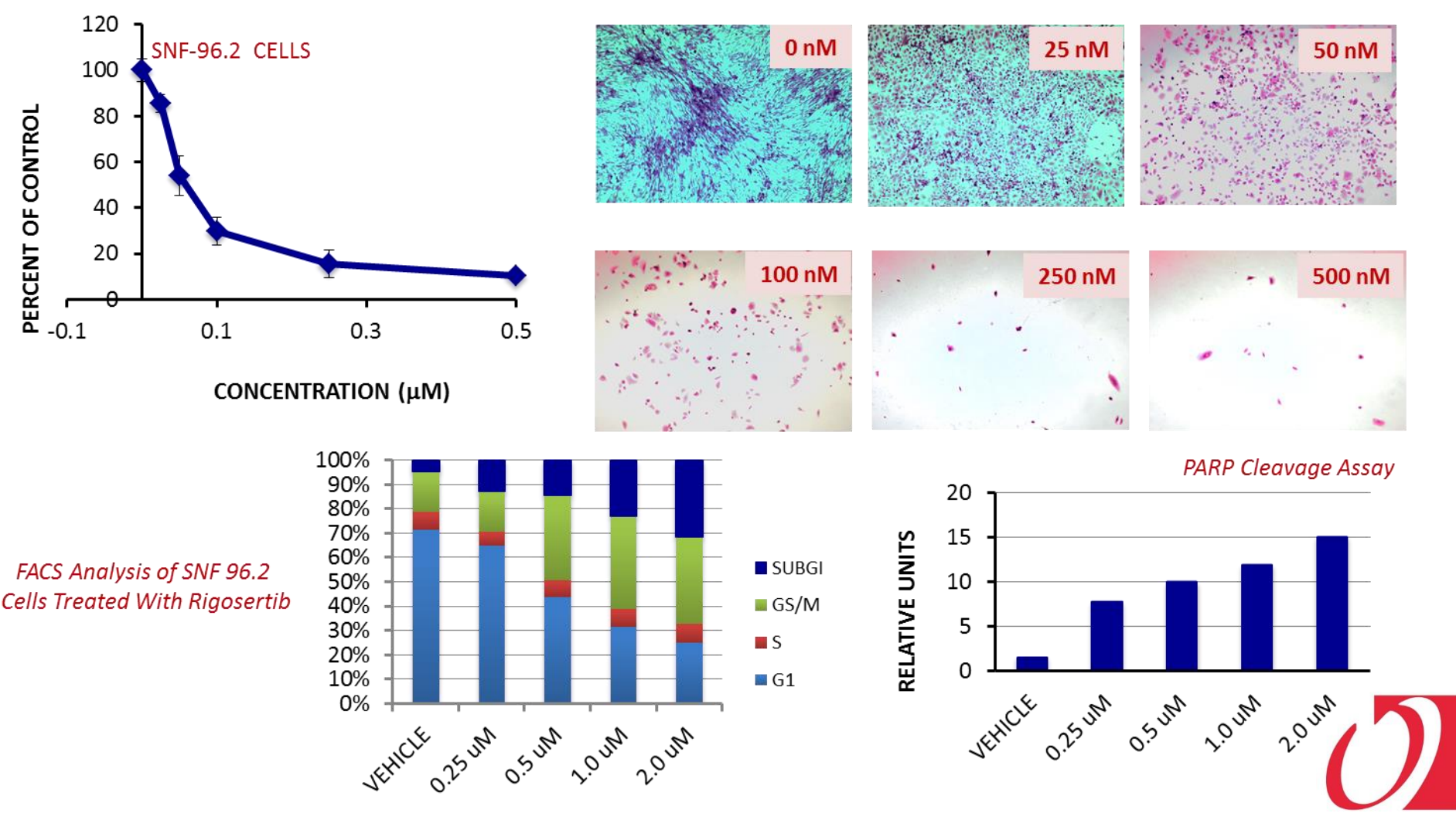


- Hematopoietic disorder of infancy caused by excessive proliferation of monocytic and granulocytic cells; which infiltrate the spleen/liver, intestines and lungs
- Rare- 2% of pediatric hematologic malignancies (in the US about 50 new cases per year); 1.2 cases per million annually, median age is 2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

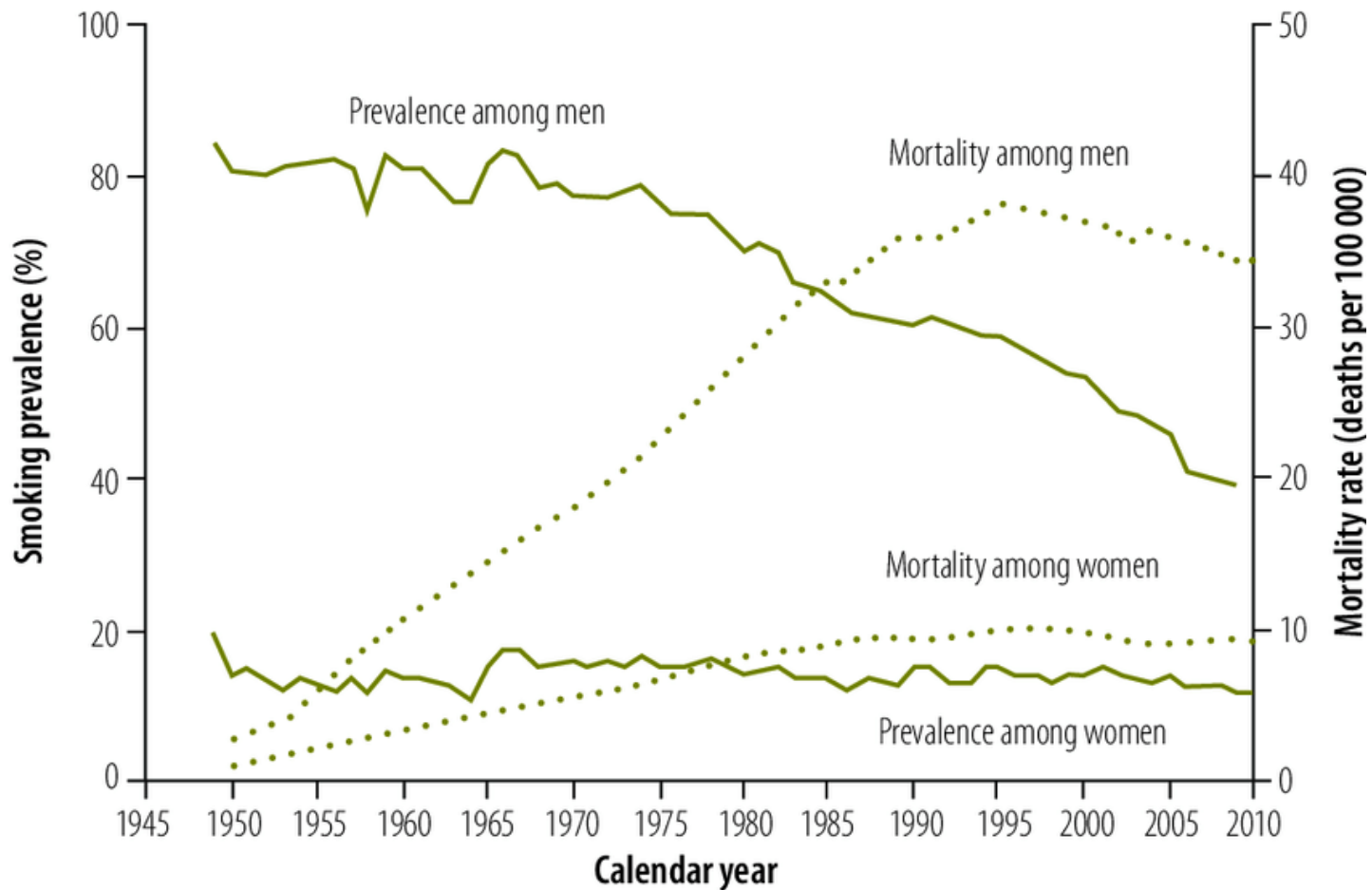


NSCLC & CRC



AGE-STANDARDIZED LUNG CANCER MORTALITY & SMOKING PREVALENCE

JAPAN, 1950–2010

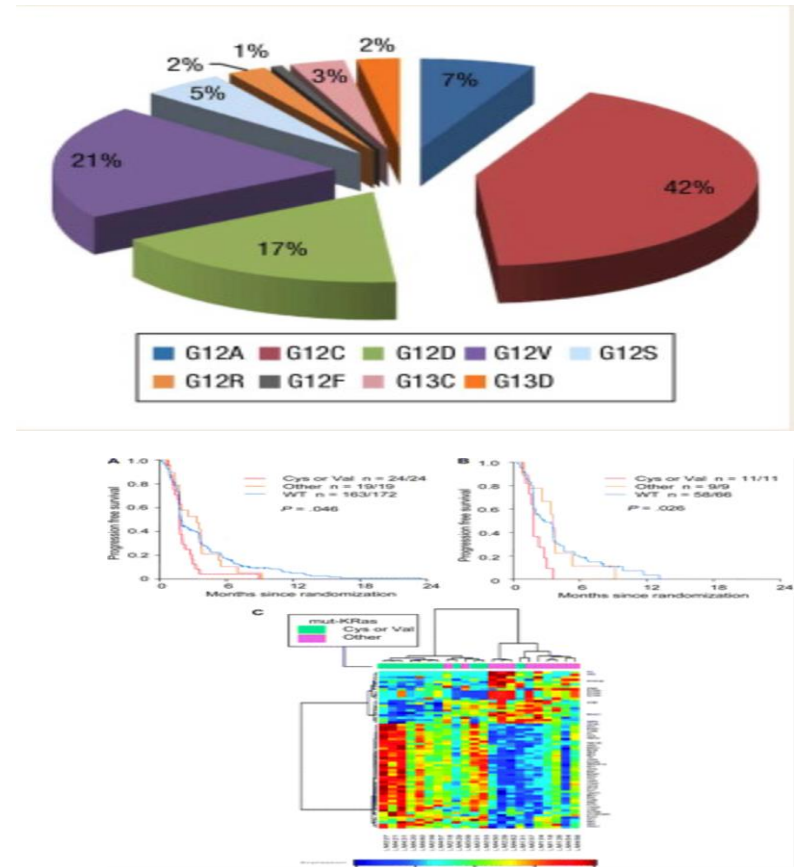


Funatogawa, Ikuko & Funatogawa, Takashi & Yano, Eiji. (2013). Trends in smoking and lung cancer mortality in Japan, by birth cohort, 1949–2010. *Bulletin of the World Health Organization*. 91. 332–40. 10.2471/BLT.12.108092.



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



EFFECT OF RIGOSERTIB ON PATIENT-DERIVED XENOGRAFTS NSCLC

Metastatic lung adenocarcinoma

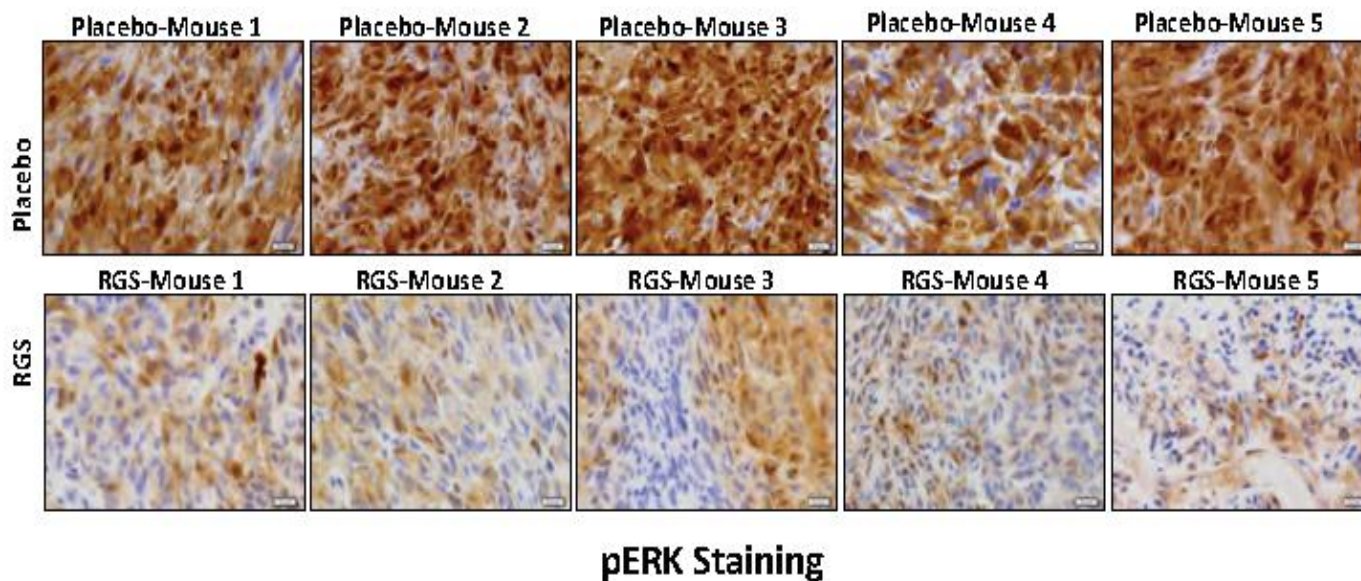
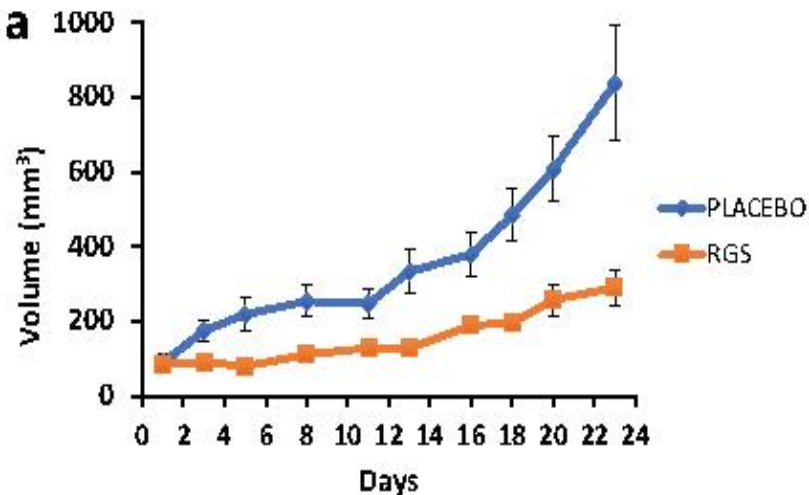
AJCC IV

53 y/o female

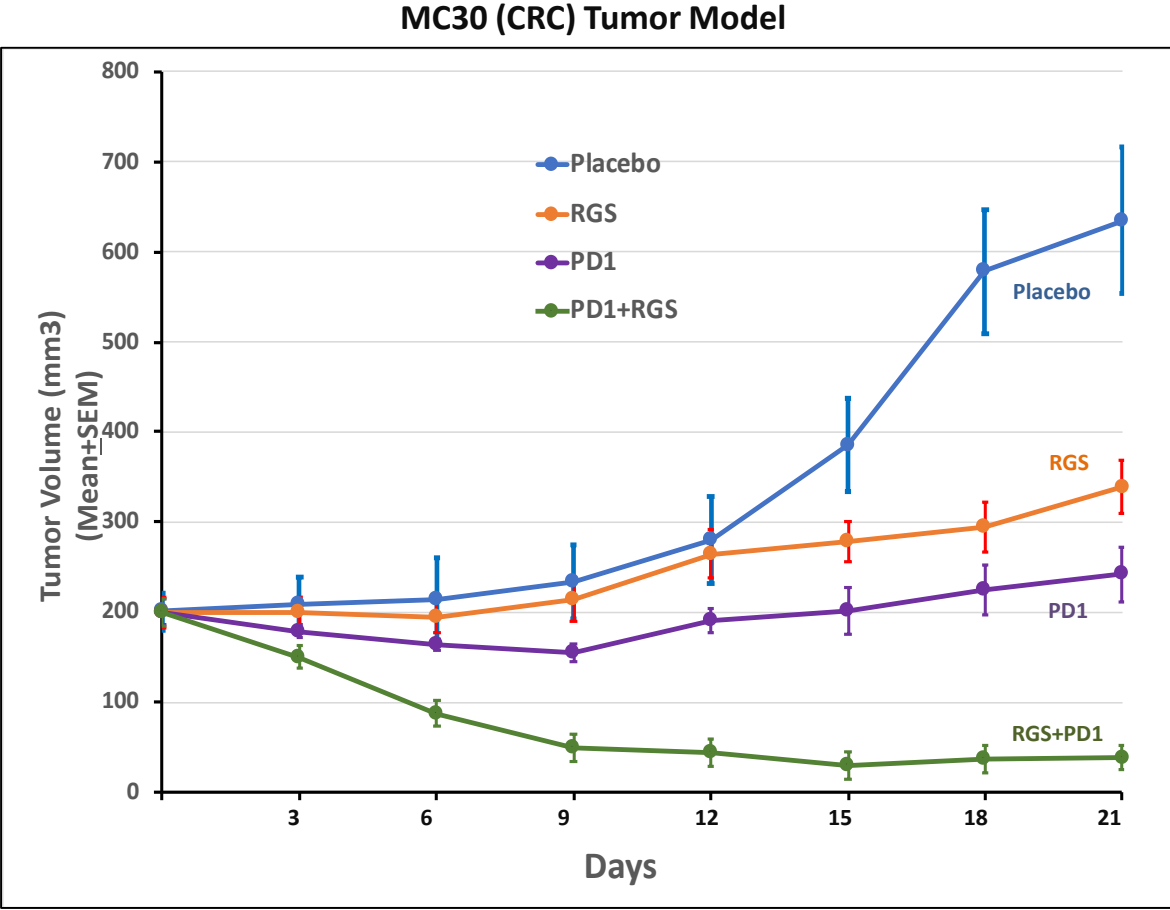
KRAS^{G12D}

ALK+

89.1% PD-L1+ (surface)



RIGOSERTIB AND HX-008 (PD-1) ACT SYNERGISTICALLY



DATA BY HANX BIOPHARMACEUTICALS



Phase 1 Study: Rigosertib and PD-1 in Advanced Kras+ NSCLC

PI: Raj Veluswamy, MSSM

Rigosertib plus Nivolumab in Stage IV Lung Adenocarcinoma Patients with KRAS Mutation who Progressed on First-Line Treatment

Patient Selection

Main Inclusion Criteria

1. Metastatic lung adenocarcinoma with KRAS mutation
2. Progressed on standard 1st line treatment
3. ≥18 years old with ECOG PS 0-2

Main Exclusion Criteria

1. ECOG PS 3 or 4
2. EGFR mutation or ALK translocation
3. Active autoimmune disease or on systemic steroids > 10mg
4. Untreated CNS metastases

Translational Research/Correlatives

1. Genomic studies
2. Immunophenotyping
3. Radiomics

Dosage and Administration: 28 day cycles

Rigosertib – oral; days 1-21
Dose 1 (D1): 140mg twice daily
Dose 2 (D2): 280mg twice daily
Dose 3 (D3): 560mg twice daily
Nivolumab – intravenous; days 1 and 14
240 mg every 2 weeks

Pre-Treatment with Rigosertib + Nivolumab

1. Core needle biopsy of target lesion
2. Peripheral blood sample
3. CT Imaging

Dose Escalation Phase (8-18 patients)

Accelerated Titration Design (ATD):
Single patient cohorts until:
• D3 tolerated → expand to 6 patient cohort to establish MTD
• Grade 2 toxicity → ATD ends; 3+3 Design starts using DLT
Primary Objective: MTD/RPTD (≤1 out of 6 patients experiences DLT)

After 3 Cycles with Rigosertib + Nivolumab

1. Core needle biopsy of same target lesion
2. Peripheral blood
3. CT Imaging

Expansion Phase

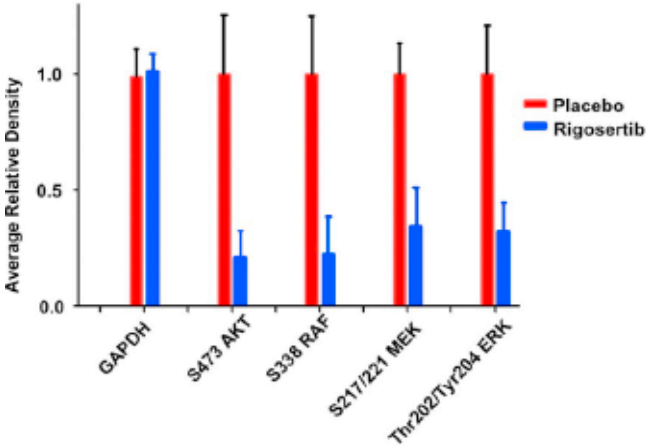
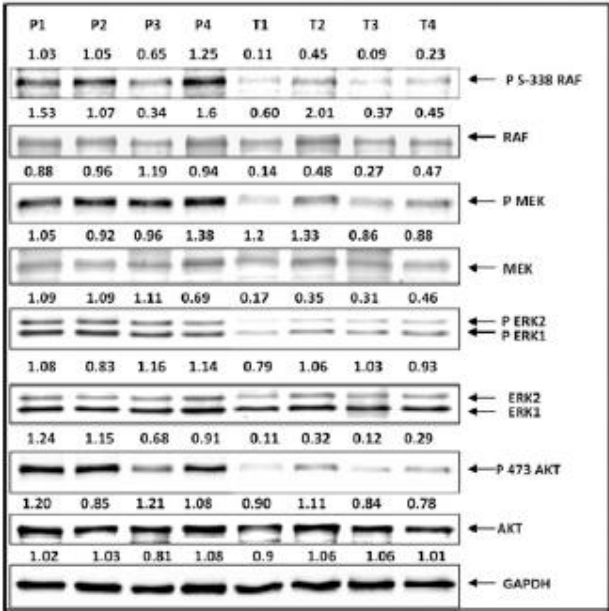
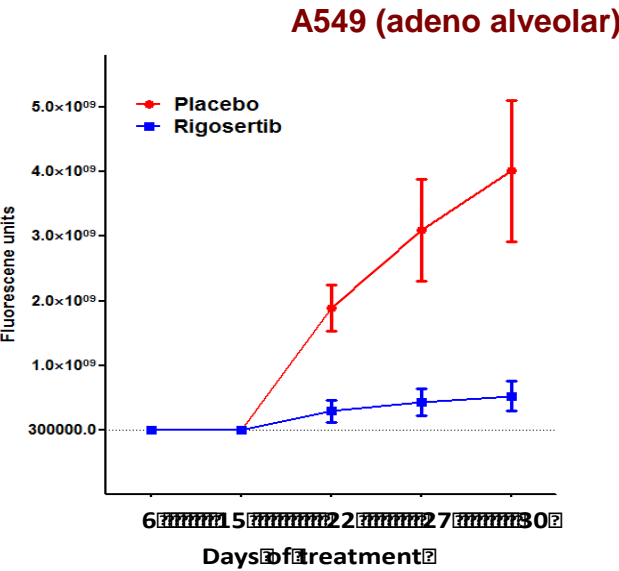
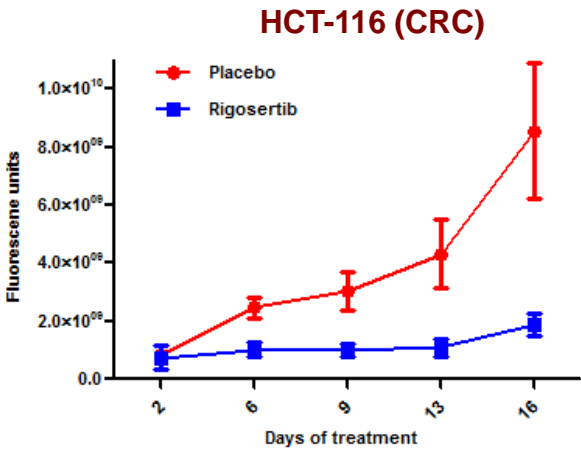
12 patients at MTD of Rigosertib with Nivolumab x 6 cycles
Secondary objectives:
• Confirm safety and tolerability of MTD
• Evaluate efficacy through ORR
• Assess PFS and OS

After 6 Cycles with Rigosertib + Nivolumab

1. Peripheral blood for follow up labs
2. CT Imaging

PS: Performance status; CNS: EGFR: Epidermal Growth Factor Receptor; ALK: Anaplastic Lymphoma Kinase; IV: Central Nervous System; MTD = maximally tolerated dose; RPTD: Recommended Phase Two Dose; DLT = dose limiting toxicity; ORR = overall response rate, PFR = progression free survival, OS = overall survival

RIGOSERTIB INHIBITS TUMOR GROWTH AND SIGNALING IN XENOGRAFTS OF HUMAN CANCER



Tumor growth inhibition is associated with reduced RAF and AKT signaling

THANKS TO HANSON WADE
FOR ORGANIZING THIS GREAT
MEETING ON RAS

