



**ONCONOVA**  
THERAPEUTICS

## Corporate Update

November 2017 | Nasdaq: ONTX

# FORWARD LOOKING STATEMENTS

This presentation contains forward-looking statements about Onconova Therapeutics, Inc. based on management's current expectations which are subject to known and unknown uncertainties and risks. Onconova has attempted to identify forward-looking statements by terminology including "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "should," "approximately" or other words that convey uncertainty of future events or outcomes. Our actual results could differ materially from those discussed due to a number of factors, including, but not limited to, our ability to raise additional financing on favorable terms, the success of our clinical trials and our ability to obtain regulatory approvals and other risk factors outlined in our annual and quarterly reports filed with the Securities and Exchange Commission. We are providing this information as of the date of this presentation and do not undertake any obligation to update any forward-looking statements, whether written or oral, that may be made from time to time, as a result of new information, future events or otherwise except as required by law.



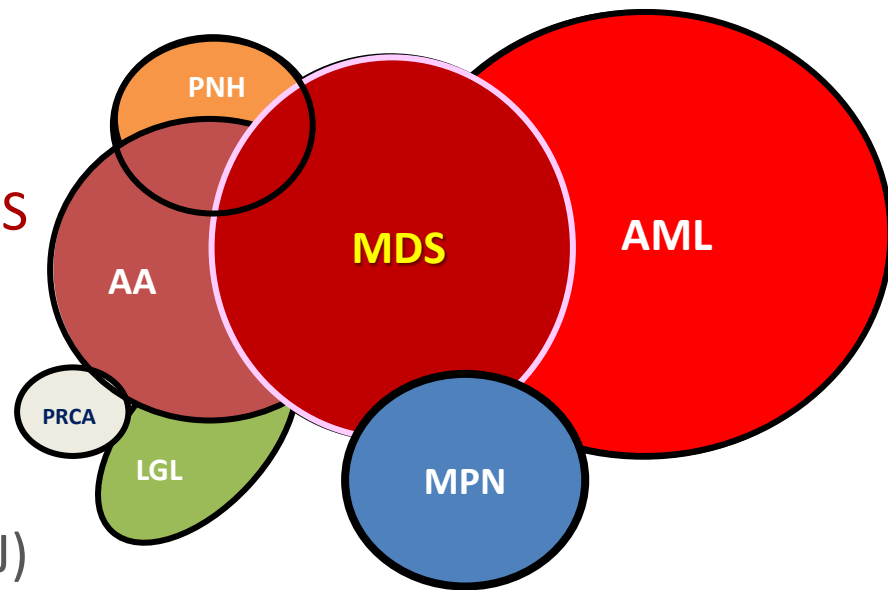
# ONCONOVA AT A GLANCE

- Founded in 1998; IPO in 2013 (Nasdaq: ONTX)
- Phase 3 stage clinical candidate: rigosertib
  - Targets RAS effector pathways (Cell, 2016)
  - Two formulations (IV & Oral)
  - Focused on Myelodysplastic Syndromes (MDS)
- Broad pipeline with earlier stage drug candidates
- Rigosertib partnered with SymBio in Japan/Korea
  - Additional partnerships sought



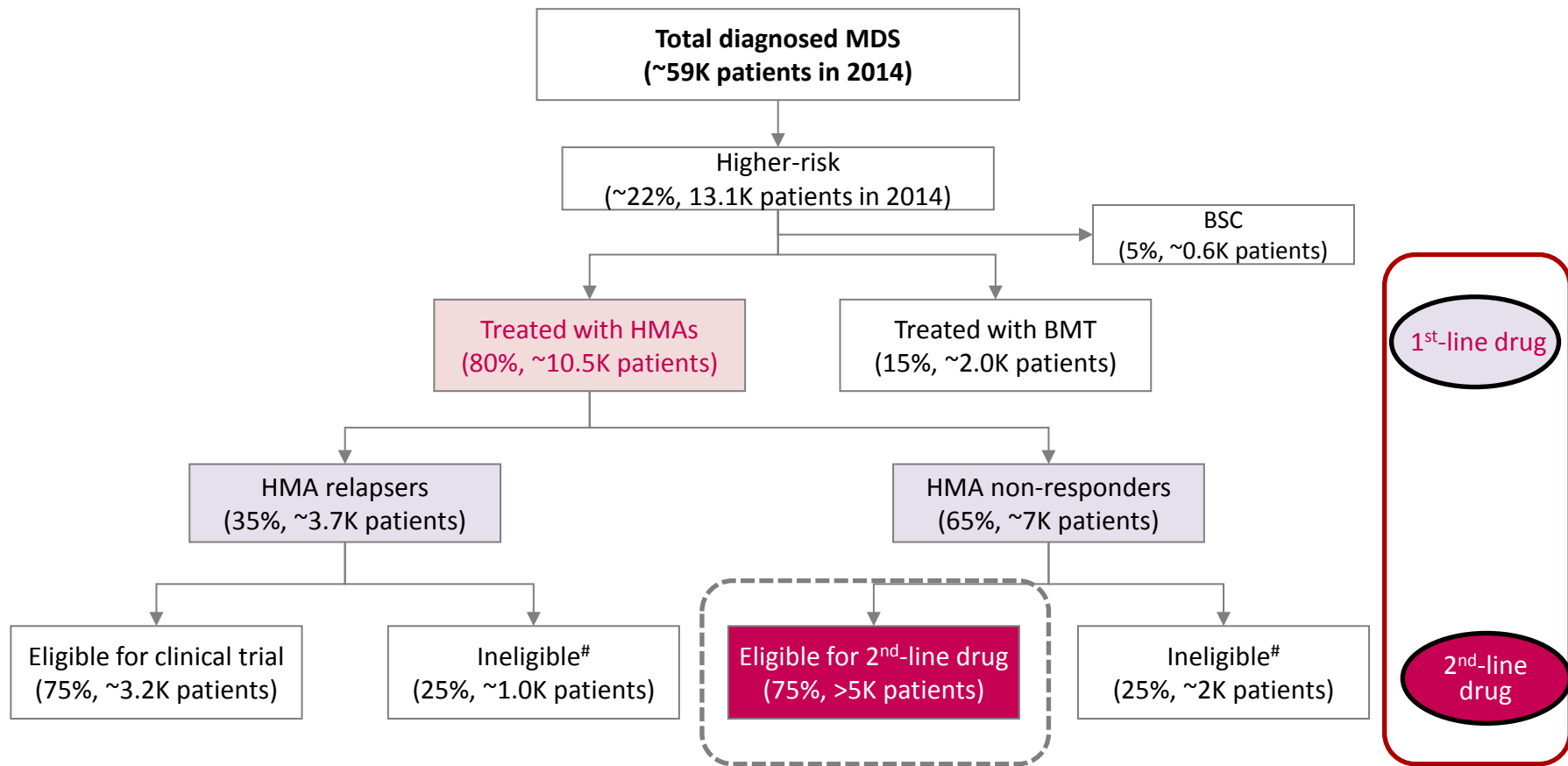
# MDS OVERLAPS WITH OTHER DISEASES

- MDS, a malignant hematopoietic disorder characterized by:<sup>[1]</sup>
  - Bone marrow failure
  - Cytopenias
  - 30% of patients progress to AML
- US prevalence estimate is 59,000
  - 18,000 patients have higher risk MDS
  - ~10,000 have 2<sup>nd</sup> line HR-MDS
- Treatment options limited to hypomethylating agents (HMAs)
  - Vidaza (Celgene); Dacogen (Eisai/J&J)
  - Both approved a decade ago



<sup>1</sup>Young NS. Ann Intern Med. 2002;136:534-546.

# RIGOSERTIB IN HIGHER-RISK MDS



- Rigosertib for 2<sup>nd</sup>-line patients (INSPIRE Phase 3 trial)
- For 1<sup>st</sup>-line patients, in combination with Azacitidine, the current standard of care



# RIGOSERTIB HIGHLIGHTS

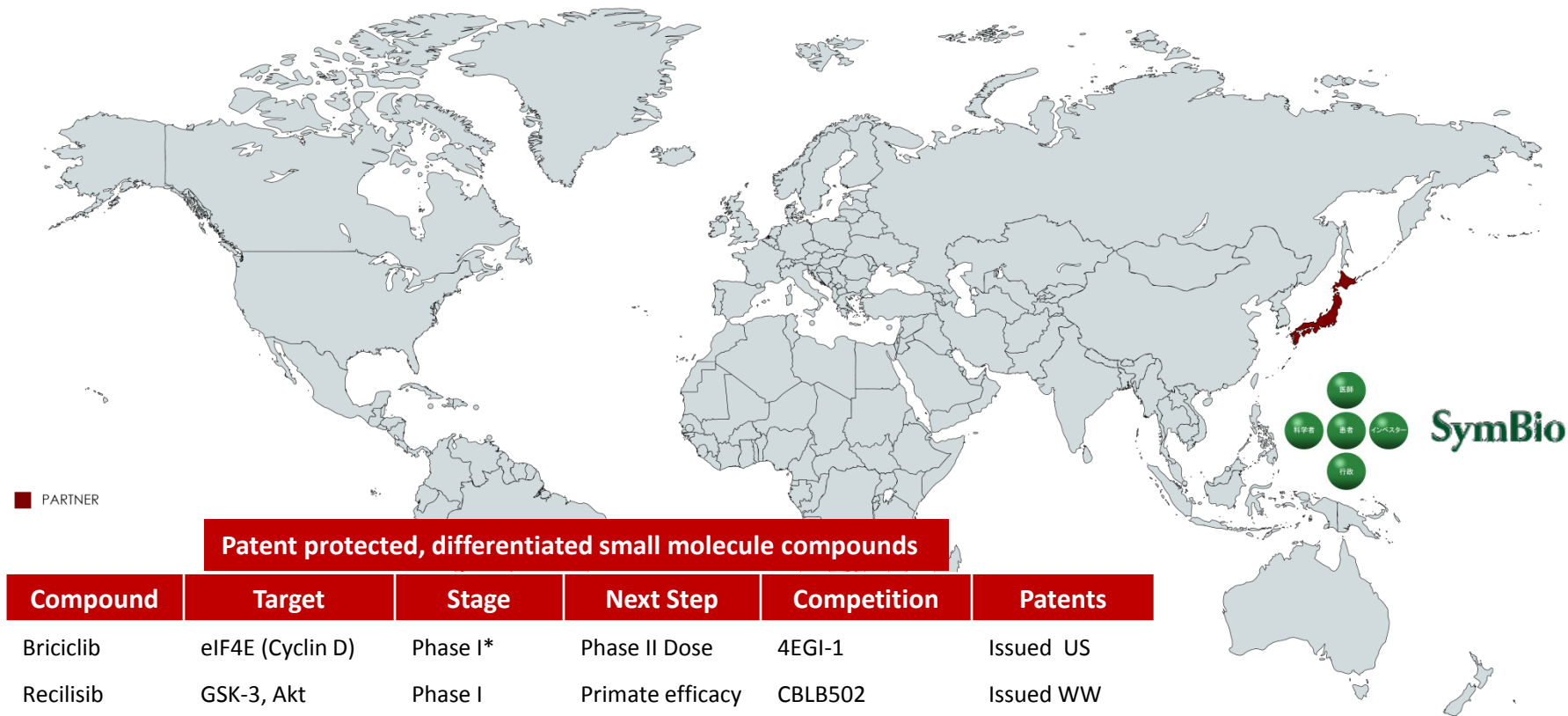
- Rigosertib in Phase 3 “INSPIRE” trial for 2<sup>nd</sup> line HR MDS
- Patents & Orphan Designation in the US, Europe and Japan
- Designing Phase 3 trial for 1<sup>st</sup> line HR MDS
  - Oral rigosertib + azacitidine combination
  - End of Phase 2 meeting discussions with FDA and EMA
- Key upcoming milestones
  - INSPIRE (IV) Phase 3 interim analysis expected in **Q4-2017**
  - Full trial enrollment and Top-line Phase 3 data in **2018**



# BUSINESS DEVELOPMENT OPPORTUNITIES:

RIGOSERTIB IS PARTNERED IN JAPAN/KOREA SINCE 2011

*Partnerships for pipeline products sought in other territories*



\*On hold, pending new drug product

\*\*New data presented at 2017 AACR conference



# MULTIPLE CDKS & CELL CYCLE INHIBITORS\*

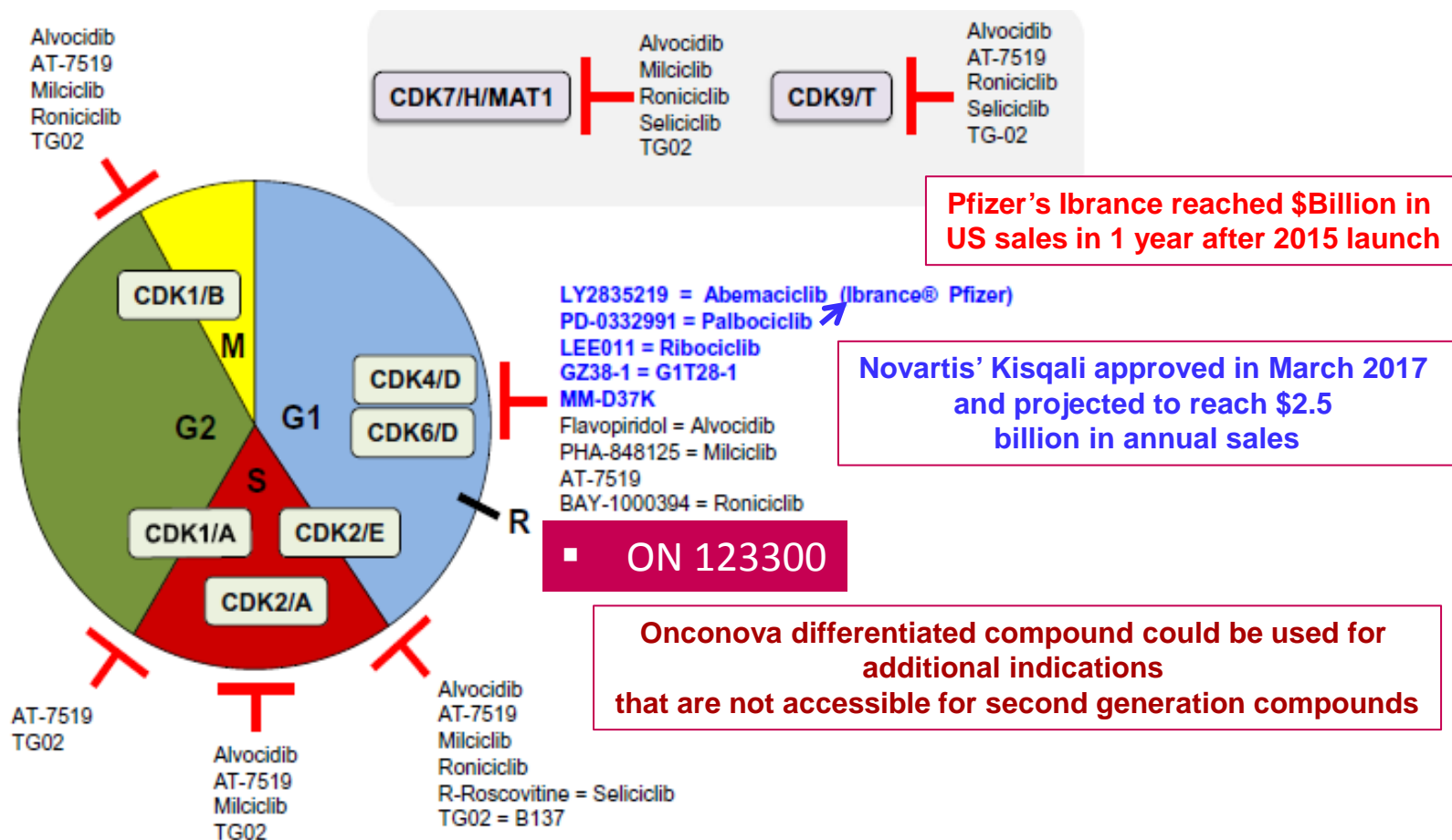
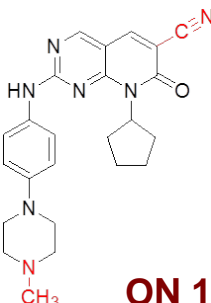
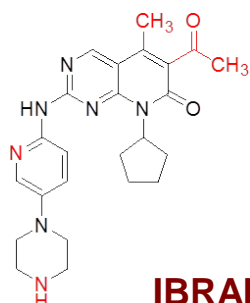


Figure 5. Cell cycle and transcription regulation CDK inhibitors under clinical evaluation. Specific CDK4 and CDK6 inhibitors are indicated in blue.





# DIFFERENTIATED KINASE INHIBITION: TARGETING OF ARK5

Comparison of Two Compounds in Reaction Biology Kinase Assays		
	 <b>ON 123300</b>	 <b>IBRANCE®</b>
Kinase	Comparative IC <sub>50</sub> profile (nM)	
	ON 123300	IBRANCE®
ARK5	4.95	>5000
CDK4/D1	3.87	5.36
CDK6/D1	9.82	3.76

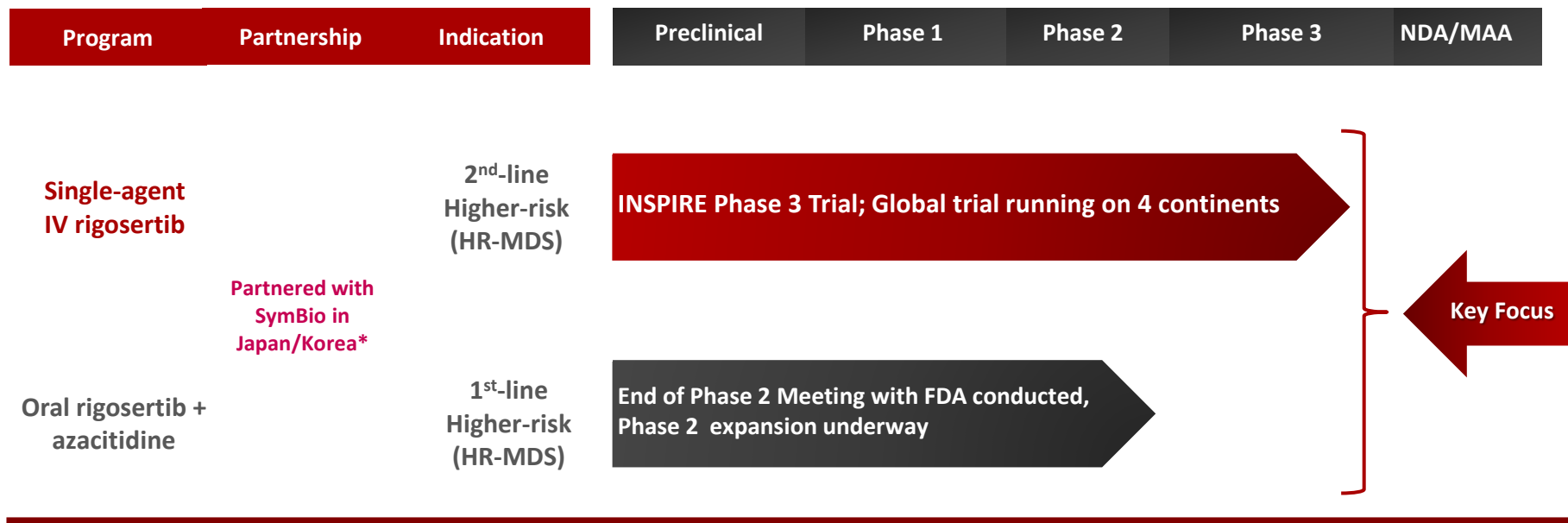
Reddy MVR et al., Journal of Medicinal Chemistry 2014 57 (3), 578-599



# LEAD INDICATIONS FOR RIGOSERTIB IN MDS



# ONCONOVA MDS PIPELINE



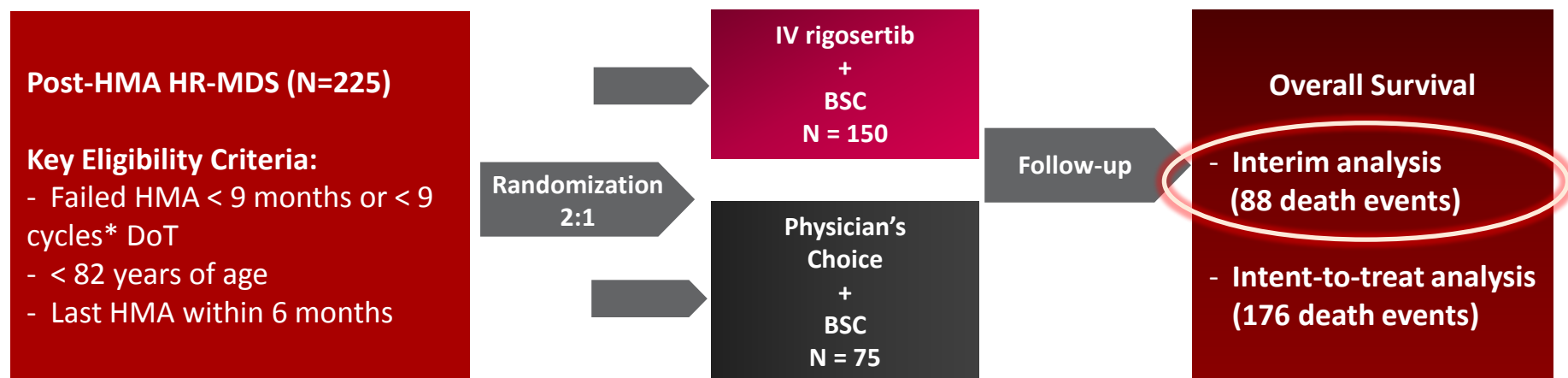
IV product for infusion



Oral soft gel capsules



# INSPIRE STUDY DESIGN FOR GLOBAL PHASE 3 TRIAL



\*9 cycles within 12 months of starting treatment

- Survival endpoint with two successive analyses planned
  - ITT population enriched for higher-risk MDS
  - Second analysis of IPSS-Very High Risk (VHR) predefined group
    - Second cut allows for another chance to succeed in this subpopulation

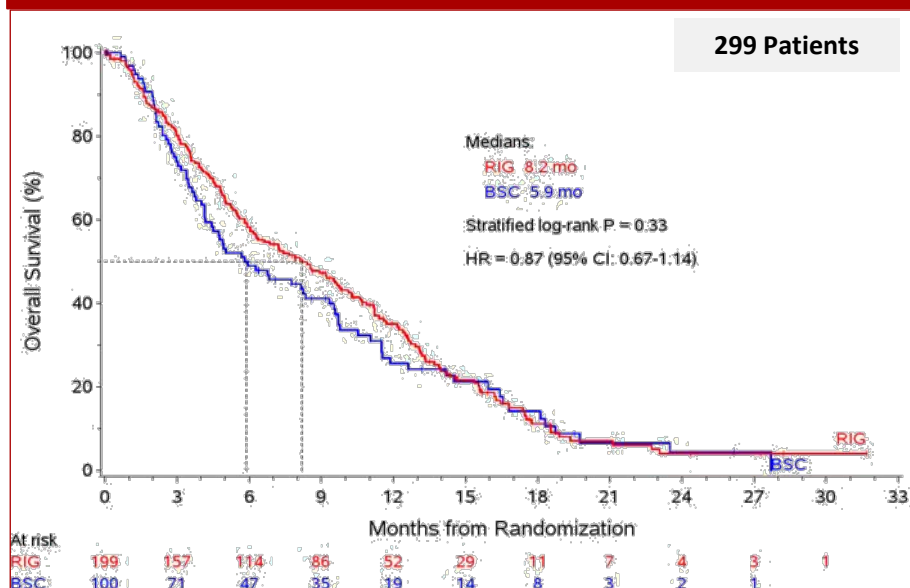
*Commentary on new trial in recent publication: Emilio P Alessandrino, Matteo G Della Porta. Novel trial designs for high-risk myelodysplastic syndromes; The Lancet Oncology 2016 (17): 410–412*



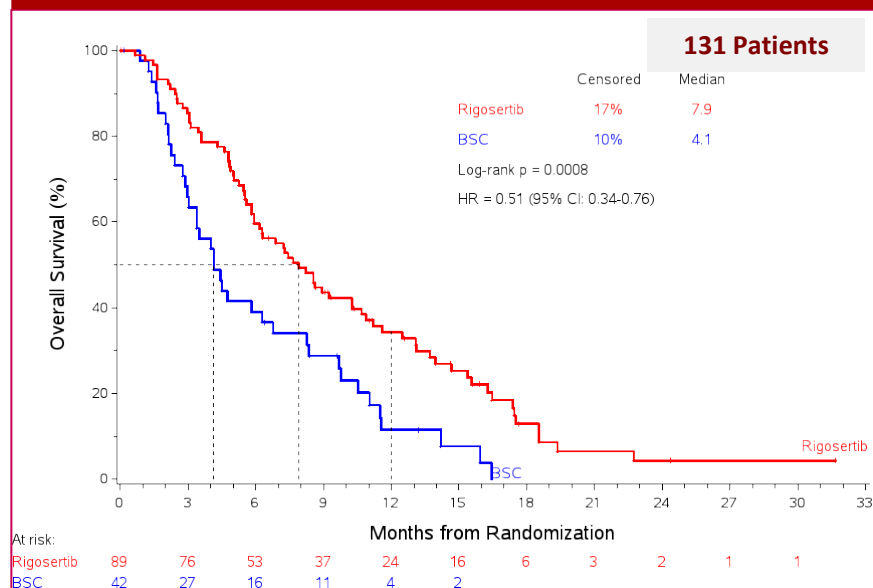
# SELECTING PATIENT POPULATION FOR PHASE 3 INSPIRE TRIAL

Data from ONTIME paper\* 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 = 0.51; P = 0.0008

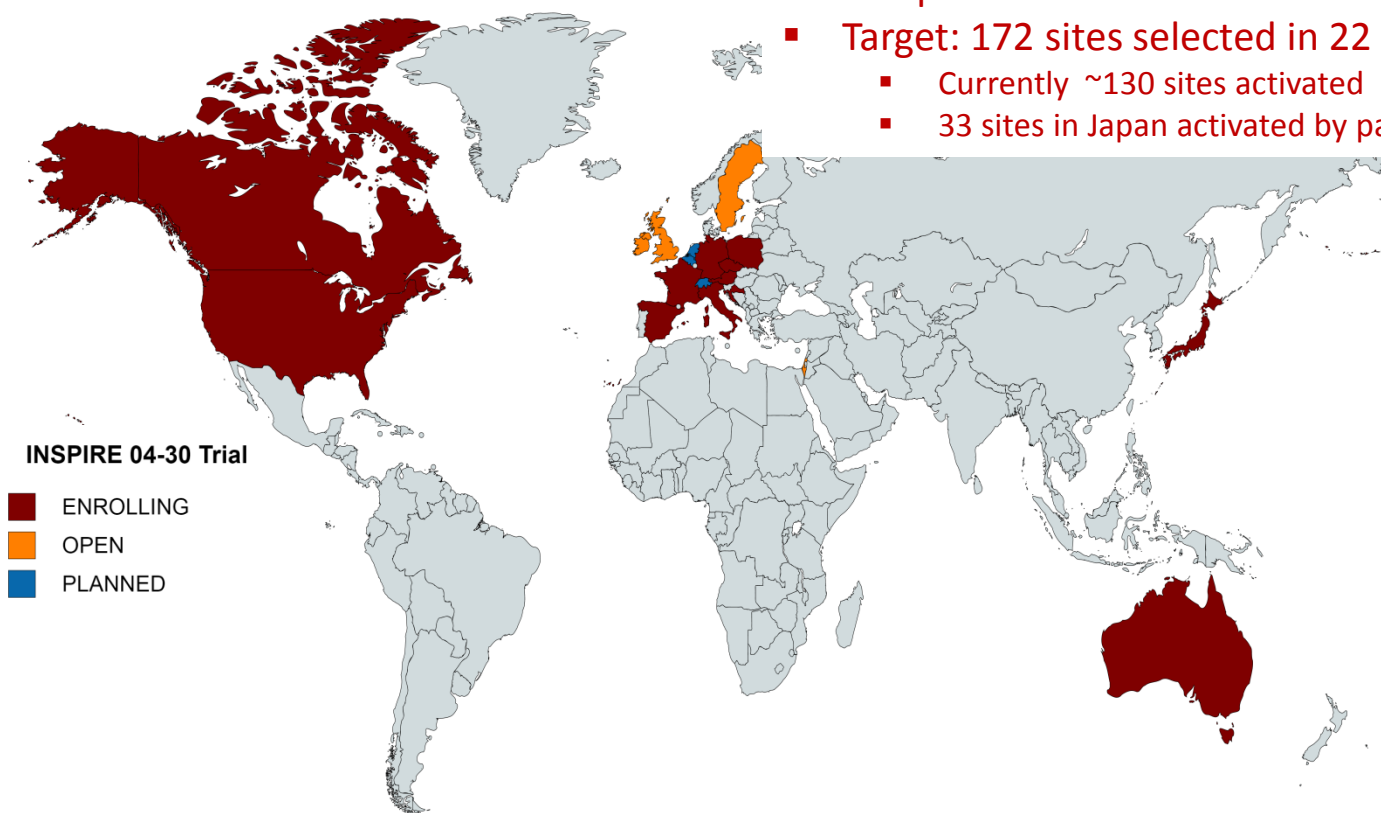
\*Guillermo Garcia-Manero, Pierre Fenaux, Aref Al-Kali, Maria R Baer, Mikkael A Sekeres, Gail J Roboz, et al. Rigosertib versus best supportive care for patients with higher-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, Phase 3 trial; *The Lancet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



# GLOBAL INSPIRE TRIAL PROGRESS

The **I**nternational **S**tudy of **P**hase III **I**V **R**igos**E**rtib, or **INSPIRE**, designed following feedback from the U.S. Food and Drug Administration and European Medicines Agency and derives from findings of the ONTIME Phase 3 trial. Our partner SymBio is enrolling in Japan after discussions with the PMDA.

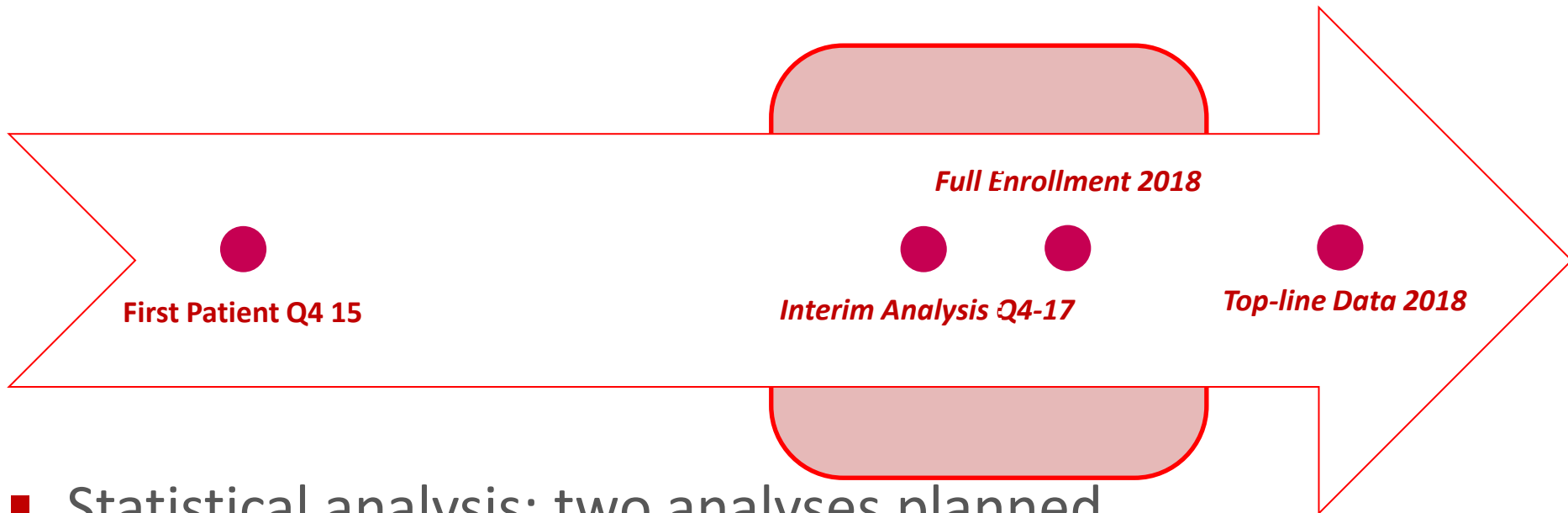
- 225 patients to be enrolled
- Target: 172 sites selected in 22 countries on 4 continents
  - Currently ~130 sites activated by Onconova
  - 33 sites in Japan activated by partner SymBio



Created with mapchart.net ©



# TIMELINES FOR DATA ANALYSIS FOR INSPIRE TRIAL



- Statistical analysis: two analyses planned
  - Power 0.80; Target HR < 0.625; (reduce mortality by > 37.5%)
  - $\alpha$  for ITT = 0.04;  $\alpha$  for IPSS-R VHR = 0.01
    - Dual primary endpoints: Overall survival in ITT population or IPSS-R Very High Risk
- Exploratory genomic sequencing of patient samples



# OVERVIEW OF SAFETY IN TRIAL PATIENTS

- Over 1,180 patients treated with rigosertib in 27 Phase 1-3 trials evaluated
  - MDS/other hematologic malignancies (N = 672)
  - advanced cancer/solid tumors (N = 508) were treated in 27 Phase 1-3 clinical trials
- No treatment emergent myelosuppression, cardiotoxicity, or neurotoxicity
  - Minimal myelosuppression by rigosertib might represent a distinct advantage given the compromised bone marrow function of patients with MDS
- Generally, no need for premedication during the studies
- Potential safety signals are being monitored on an ongoing basis
- Current Investigator Brochure and Development Safety Update Report
  - July 2017



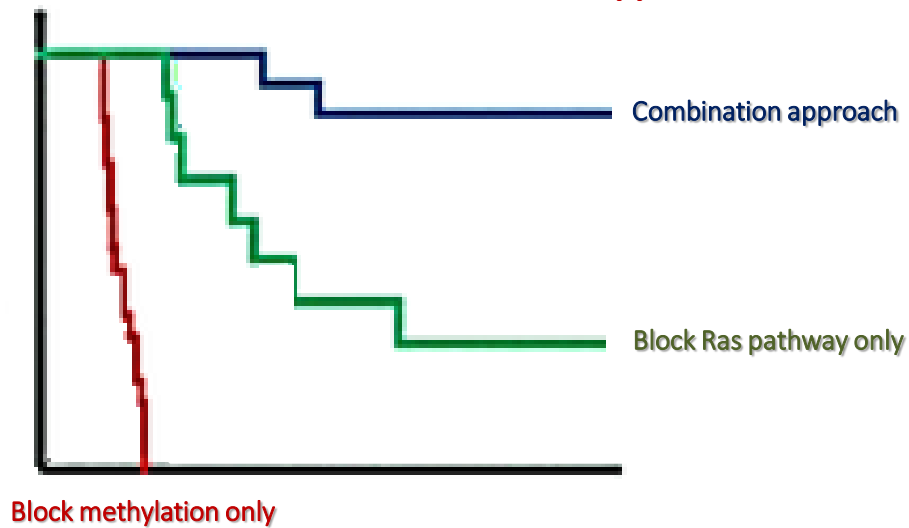


# MECHANISTIC RATIONALE FOR COMBINATION THERAPY WITH RIGOSERTIB + AZACITIDINE

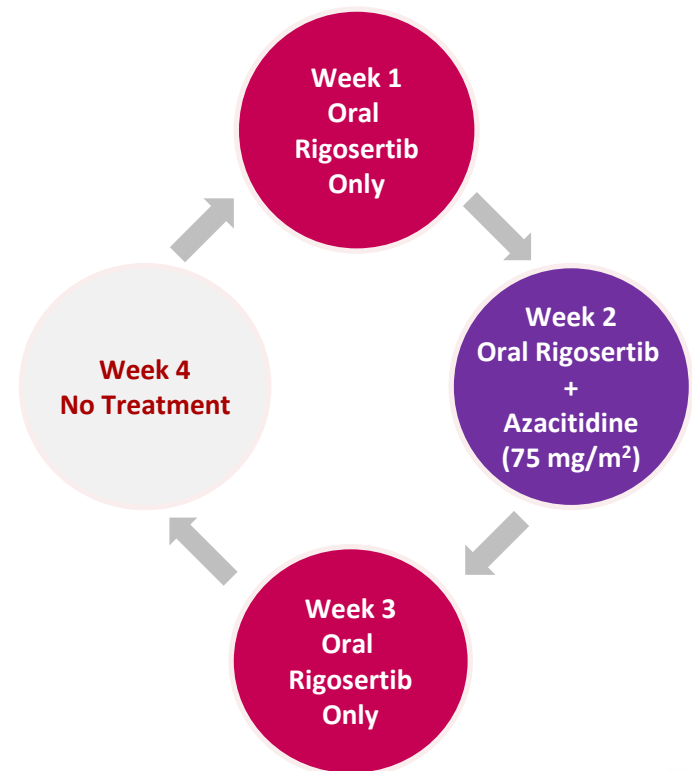
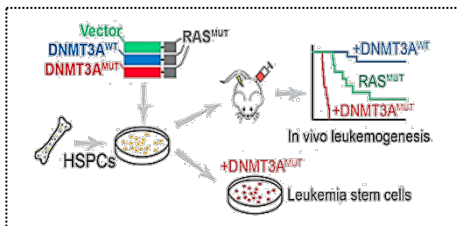
Preclinical evidence supports synergism of rigosertib + azacitidine combination

## AML Animal Model

Validation of combination approach



Lu et al., 2016 *Cancer Cell*



More than 60 patients enrolled



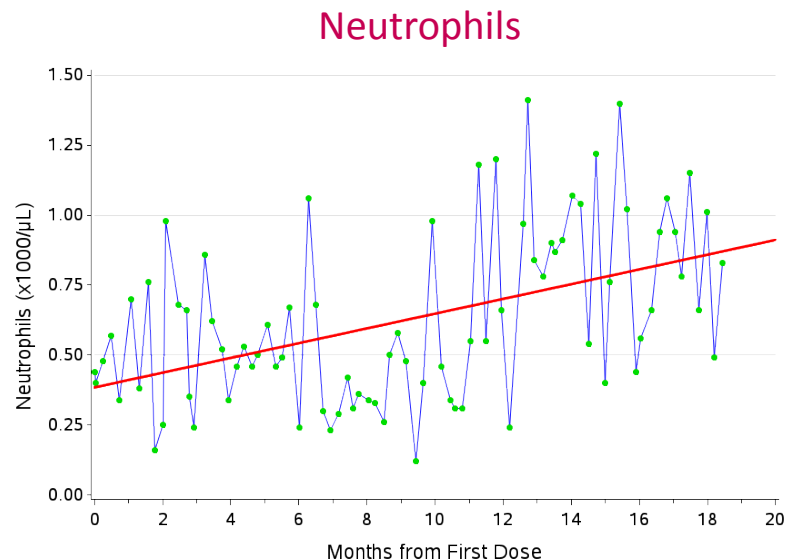
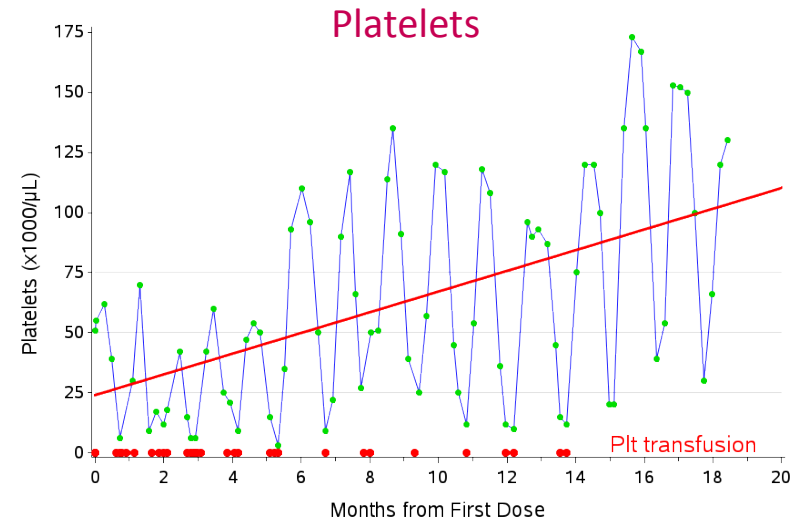
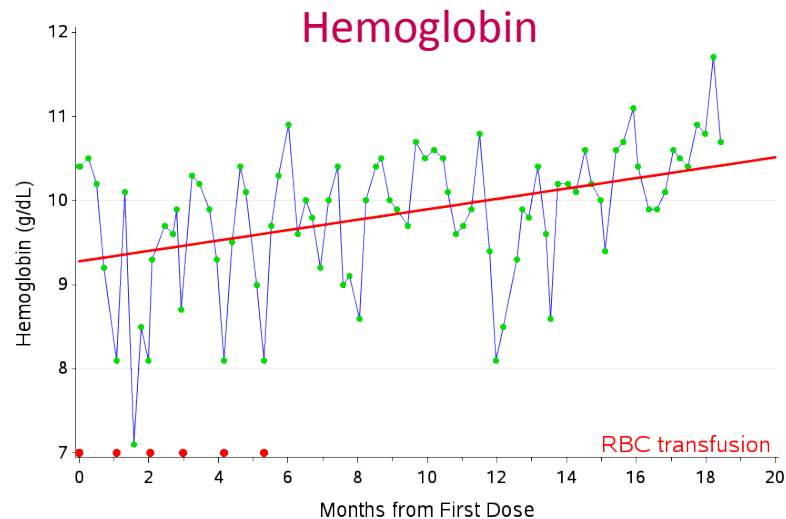
# EFFICACY RESULTS FOR COMBINATION TRIAL

Response Criteria	Response per IWG 2006		
	Overall evaluable (N=33)	No prior HMA (N=20)	HMA resistant (N=13)
<b>Complete Remission*</b>	<b>8 (24%)</b>	<b>7 (35%)</b>	<b>1 (8%)</b>
Marrow CR + Hematologic Improvement (HI)	10 (30%)	6 (30%)	4 (31%)
Marrow CR alone	6 (18%)	3 (15%)	3 (23%)
Hematologic Improvement alone	1 (3%)	1 (5%)	0
Stable Disease	8 (24%)	3 (15%)	5 (38%)
<b>Overall IWG Response</b>	<b>25 (76%)</b>	<b>17 (85%)</b>	<b>8 (62%)</b>
Clinical Benefit Response	19 (58%)	14 (70%)	5 (38%)

\*All responders had CR and no PR was noted in this study



# HEMATOLOGY TRENDS FOR PATIENT 101-006



- 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



# KEY SAFETY DATA FROM RIGOSERTIB COMBINATION TRIAL (STUDY 09-08)

Azacitidine Package Insert<sup>1</sup>

Adverse Event	Grade ≥3
Haematuria	2.3%
Anemia	13.7%
Neutropenia	61.1%
Thrombocytopenia	58.3%

Oral Rigosertib + Aza

Adverse Event	Grade ≥3
Haematuria	7.0%
Anemia	0
Neutropenia	19.0%
Thrombocytopenia	27.0%

- Rigosertib + azacitidine generally well tolerated
  - 4/37 MDS patients withdrew due to AE
  - 2/37 MDS patients had dose reduction
- Safety profile of combination did not differ from reported toxicities of azacitidine alone

<sup>1</sup><http://www.vidaza.com/pi.pdf>



# NEXT STEPS FOR RIGOSERTIB + AZACITIDINE DEVELOPMENT

## Key Parameters and Milestones for Oral Rigosertib + Azacitidine Phase 3 Program

Phase 3 Design	Randomized Controlled	1:1 randomization between Aza + placebo and Aza + oral rigosertib
Patient Population	First-line MDS	Higher risk patients indicated for azacitidine (Vidaza)
Primary Endpoint	Composite Response	Complete and Partial Remission per IWG 2006 criteria for MDS
Regulatory Path	To be explored	Special Protocol Assessment (SPA), Fast-track etc.
Protocol Details	2017/18	After regulatory discussions are completed

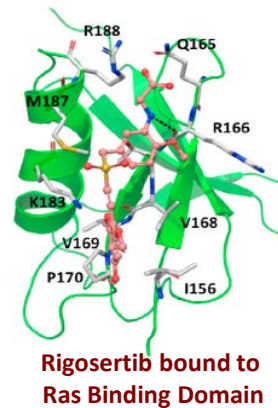
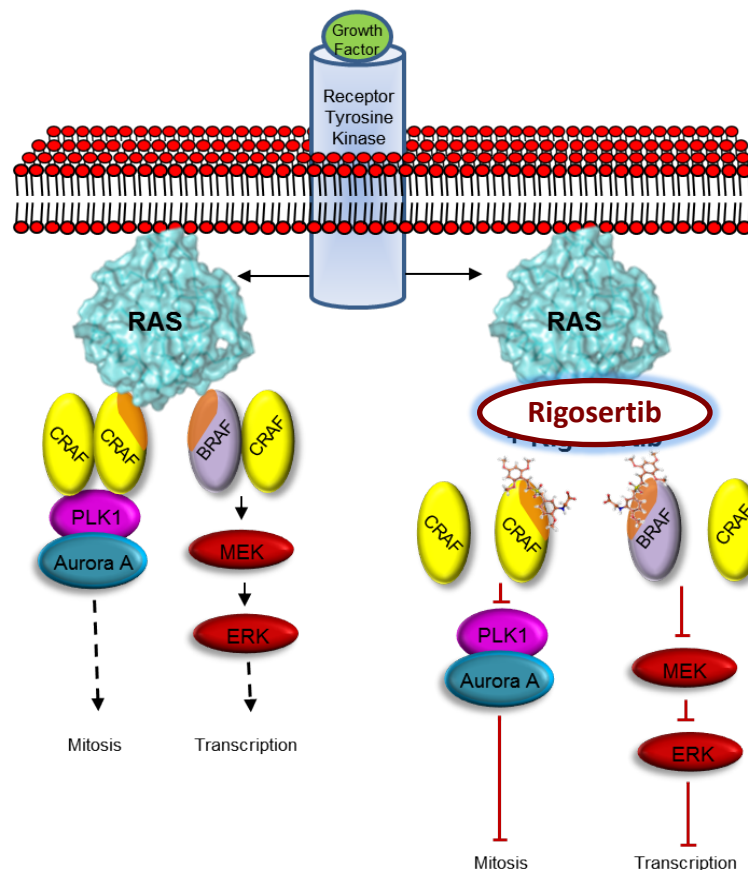
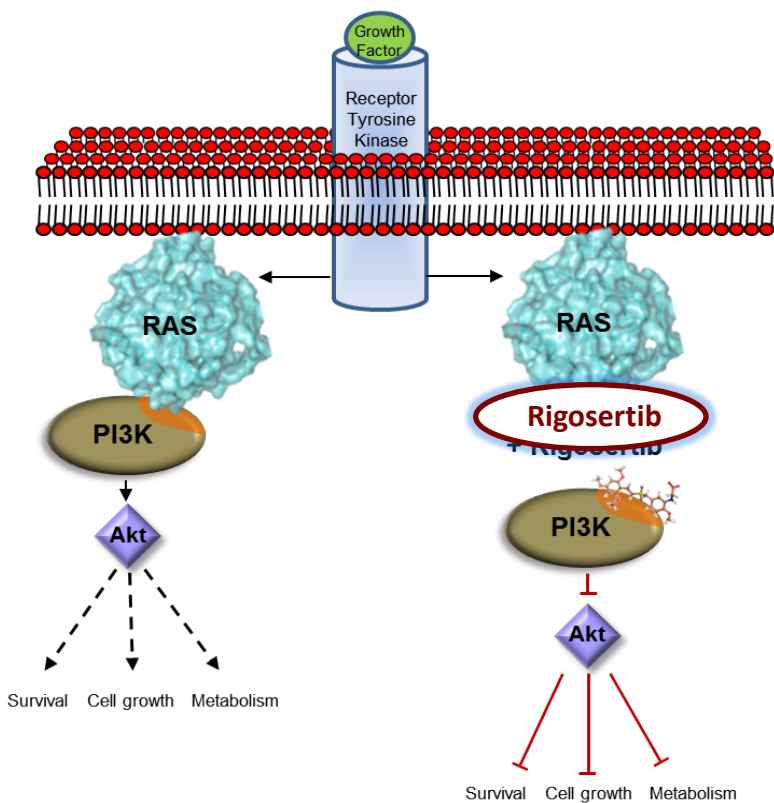
### Current activities:

- **Phase 2 trial expanded**
  - Up to 40 more patients; more than 10 sites
  - Dose and schedule optimization
  - Gain additional efficacy data
  - **Enrollment proceeding briskly**
- Phase 3 protocol synopsis created
- Scientific advice obtained from EMA
- FDA Special Protocol Assessment process to start after completing expansion



# NOVEL MECHANISM OF ACTION

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



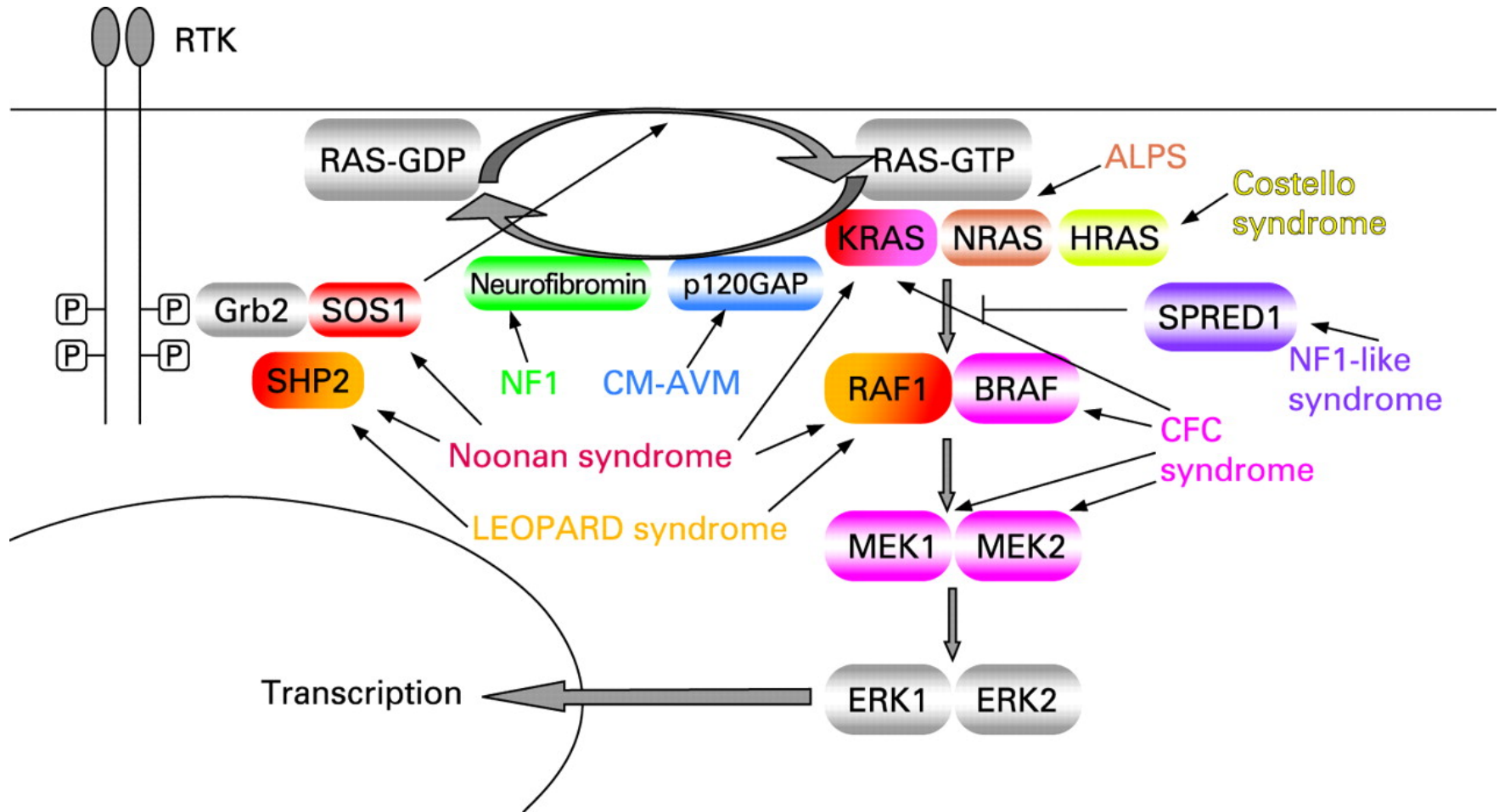
Rigosertib bound to Ras Binding Domain

Published in Cell, 2016

November 2017



# RASOPATHIES: CAUSATIVE MUTATIONS NOT LIMITED TO RAS IN RARE PEDIATRIC DISEASES



Key Opinion Leader meeting held on October 11<sup>th</sup>, in New York City;  
webcast at [www.onconova.com](http://www.onconova.com)



# FINANCIAL DETAILS & SUMMARY

**Onconova founded in 1998; public since 2013**

<b>Ticker</b>	Nasdaq ONTX	<b>Debt</b>	\$0
<b>Stock Information</b>	<ul style="list-style-type: none"> <li>9.9 million shares</li> <li>Public float &gt;84%</li> <li>52-week range: \$1.51 - \$3.50</li> <li>52-week average daily volume: 117,000</li> <li>Oct-2017 average daily volume: 348,000</li> </ul>	<b>Liquidity</b>	<ul style="list-style-type: none"> <li>Cash and cash equivalents of \$15 million as of 6-30-2017</li> <li>Funded to deliver key milestones in 2017</li> </ul>
<b>Ownership</b>	Tyndall, Tavistock, Sabby, Shire; insiders including management	<b>Burn-rate</b>	Average \$5.6 million per quarter over the last 5 quarters
<b>Analyst Coverage</b>	H.C. Wainwright, Laidlaw, Maxim, LifeSci Capital, Van Leeuwenhoeck Research (VLR), SeeThru Equity, Dawson James	<b>Partnerships</b>	Rigosertib is partnered with SymBio Pharmaceuticals in Japan/Korea; Onconova retains rights to the rest of the world

- Advanced clinical trials
  - Phase 3 underway (IV rigosertib)
- Funded to deliver key 2017 milestones
  - IV Phase 3 interim analysis Q4-2017; top-line data 2018
- Underserved and growing market in MDS
  - >10,000 patients diagnosed annually
  - No new approved therapies in over a decade
- Rigosertib + pipeline present business development opportunities
- Seasoned management team and board of directors





# MANAGEMENT TEAM



**Ramesh Kumar, Ph.D.**  
*President & CEO*  
*Co-founder*

- Bristol-Myers Squibb
- DNX
- Baxter
- Kimeragen
- Princeton University



**Steven M. Fruchtman, M.D.**  
*Chief Medical Officer*

- Novartis
- Janssen
- Syndax
- Allos Therapeutics
- Spectrum Pharmaceuticals
- Mount Sinai



**Mark Guerin**  
*Chief Financial Officer*

- Barrier Therapeutics
- Cardiokine
- PriceWaterhouseCooper

**Manoj Maniar, Ph.D.**

Senior VP,  
Product Development

Alcon, SRI

**Wolfgang Meyer, Ph.D.**

Sr. VP Regulatory Affairs  
GM, Onconova GmBh

Amgen, Micromet, GPC, Fujisawa

**Michael Petrone, M.D.**

VP Clin. Dev. Medical Affairs and  
Pharmacovigilance

GSK, Roberts, GPC





**ONCONOVA**  
THERAPEUTICS

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# BACK-UP SLIDES



# BOARD OF DIRECTORS

Michael B. Hoffman Chairman	Partner, Riverstone Holdings LLC
Henry S. Bienen Ph.D.	Served as the 15th President of Northwestern University
Jerome E. Groopman M.D.	Chief of Experimental Medicine at the Beth Israel Deaconess Medical Center, Harvard
Ramesh Kumar Ph.D.	President and CEO, Onconova Therapeutics Inc., co-founder
Viren Mehta Pharm.D.	Managing Member of Mehta Partners
E. Premkumar Reddy Ph.D. Co-founder, Lead Scientific Advisor	Professor in the Department of Oncological Sciences & Department of Structural & Chemical Biology at the Mount Sinai School of Medicine
James J. Marino, Esq.	Former partner at Dechert LLP
Jack Stover	CEO, Interpace Diagnostics; former partner PwC



# ADVISORY BOARD

Ross C. Donehower, M.D.	Johns Hopkins Sidney Kimmel Comprehensive Cancer Center
James F. Holland, M.D.	Mount Sinai School of Medicine
Stephen Nimer, M.D.	Sylvester Cancer Center at the University of Miami Hospitals and Clinics
David R. Parkinson, M.D.	Venture Partner at NEA
Alan R. Williamson, Ph.D. Chairman	Retired Merck and Glaxo pharmaceutical executive; former Abingworth
Anna Marie Skalka, Ph.D.	Fox Chase Cancer Center
George F. VandeWoude, Ph.D.	Van Andel Research Institute
Peter K. Vogt, Ph.D.	The Scripps Institute



# KEY PARAMETERS OF INSPIRE TRIAL

- A 2:1 random assignment ratio; 225 patients total
- Type 1 error  $\alpha = 0.04$  using a 2-sided log-rank test
  - Primary endpoint of overall survival in the intention-to-treat population
  - Exponential distribution of survival on treatment groups with constant death rate
- Type 2 error  $\beta = 0.20$  (80% power)
- Expected mOS of 4.5 (control) and 7.2 months (rigosertib) groups
  - Target hazard ratio of 0.625
- An interim look for futility after the observation of 50% of deaths on both arms
- A uniform accrual period of 24 months
  - An additional follow-up period of 6 months after the last patient is randomized



# REVISED IPSS: PROGNOSTIC SCORE VALUES AND RISK CATEGORIES/SCORES

Prognostic Variable	Prognostic Score Value						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics	Very good	--	Good	--	Intermediate	Poor	Very poor
BM blast, %	$\leq 2$	--	$> 2$ to $< 5$	--	5-10	$> 10$	--
Hemoglobin, g/dL	$\geq 10$	--	8 to $< 10$	$< 8$	--	--	--
Platelets, $\times 10^9/L$	$\geq 100$	50 to $< 100$	$< 50$	--	--	--	--
ANC, $\times 10^9/L$	$\geq 0.8$	$< 0.8$	--	--	--	--	--

Risk	Score
Very low	$\leq 1.5$
Low	$> 1.5$ to 3.0
Intermediate	$> 3.0$ to 4.5
High	$> 4.5$ to 6.0
Very high	$> 6$

Greenberg PL, et al. Blood. 2012;120:2454-2465.

Slide credit:  [clinicaloptions.com](http://clinicaloptions.com)



# INSPIRE: KEY OPINION LEADERS PARTICIPATING IN THE PHASE 3 TRIAL

*ONTIME participants in red (highest accruing sites in bold)*

*Sites in Japan not included in this list*

## Sites in USA

- **Maria R. Baer, MD - University of Maryland Greenebaum Cancer Center, Baltimore**
- Robert H. Collins, Jr., MD, FACP - University of Texas Southwestern Medical Center, Dallas
- **Guillermo Garcia-Manero, MD - University of Texas MD Anderson Cancer Center, Houston\***
- **Lucy Godley, MD, PhD - University of Chicago Comprehensive Cancer Center, Chicago**
- **Aref Al-Kali, MD – Mayo Clinic Rochester, Minnesota**
- **Gail J. Roboz, MD - Weill Medical College of Cornell University New York Presbyterian Hospital, New York**
- **Bart Scott, MD – Fred Hutch Cancer Center, Seattle, Washington**
- Jamile Shammo, MD - Rush University Medical Center, Chicago
- **Lewis R. Silverman, MD - Icahn School of Medicine at Mount Sinai, New York\*\***
- Selina Luger, MD - University of Pennsylvania Cancer Center, Philadelphia
- Rafael Bejar, MD, PhD - Moores Cancer Center at the University of California, San Diego
- Christopher R. Cogle, MD - University of Florida Shands Hospital, Gainesville
- Azra Raza, MD - Columbia University Medical Center, New York

## Sites in Europe, Israel and Australia

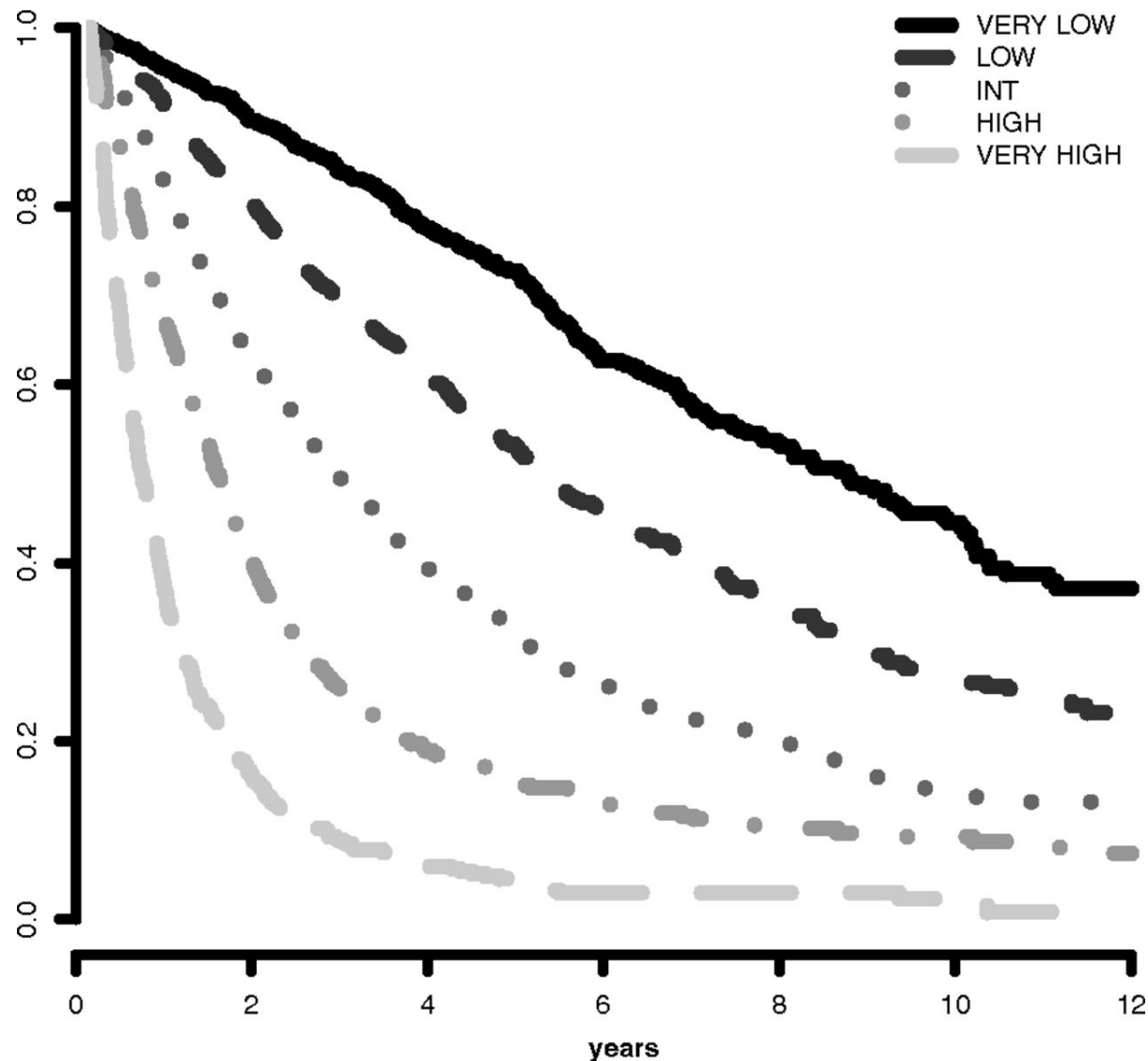
- **Pierre Fenaux, MD, PhD - Hôpital St Louis/ Université Paris, France**
- Norbert Vey, MD - Institut Paoli- Calmettes, Marseille, France
- Aristotle Giagounidis, MD, PhD - St. Johannes Hospital Heinrich-Heine Universität, Duisburg, Germany
- Detlef Haase, MD, PhD - Georg-August- Universität Göttingen, Göttingen, Germany
- **Uwe Platzbecker, MD - Universitätsklinikum Carl Gustav Carus, Dresden, Germany**
- Valeria Santini, MD - University of Florence Azienda OSP Careggi, Florence, Italy
- María Díez-Campelo, MD, PhD - Hospital Universitario de Salamanca, Salamanca, Spain
- Guillermo F. Sanz, MD - Hospital Universitario La Fe, Valencia, Spain
- Jaroslav Cermák, MD, PhD - Institute of Hematology and Blood Transfusion, Prague, Czech Republic
- Eva Hellstrom-Lindberg, MD, PhD - Karolinska Institutet, Karolinska, Sweden
- Ghulam J. Mufti, DM, FRCP, FRCPath - King's College London & King's College Hospital, London, UK
- Moshe Mittelman, MD - Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel
- Michael Pfeilstöcker, MD - Hanusch Hospital Medical Univ of Vienna, Vienna, Austria
- Jake Shortt, MD – Monash Health, Monash Medical Centre, Melbourne, Victoria, Australia
- Arjan A. van de Loosdrecht, MD, PhD - Vrije Universiteit Medical Center, Amsterdam, The Netherlands

**First\* & senior\*\* author in Lancet Oncology, 2016 paper on ONTIME results**





# REVISED IPSS-R IN RELATION TO SURVIVAL



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



# IPSS-R RISK AND CLINICAL OUTCOME FOR FRONT-LINE PATIENTS

7012 patients, at diagnosis, on Best Supportive Care

Parameter	Very Low	Low	Intermediate	High	Very High
IPSS-R score	<=1.5	>1.5-3	>3-4.5	>4.5-6	>6
Patients^ (%)	19	38	20	13	10
Survival, years***	8.8	5.3	3.0	1.6	0.8
Median months to 25% of patients in AML	NR	10.8	3.2	1.4	0.7
ONTIME Study (%) 15% were "unknown"	0	0	9	31	45

***Median survival of VHR patients on BSC arm in the ONTIME study was 3.2 months***

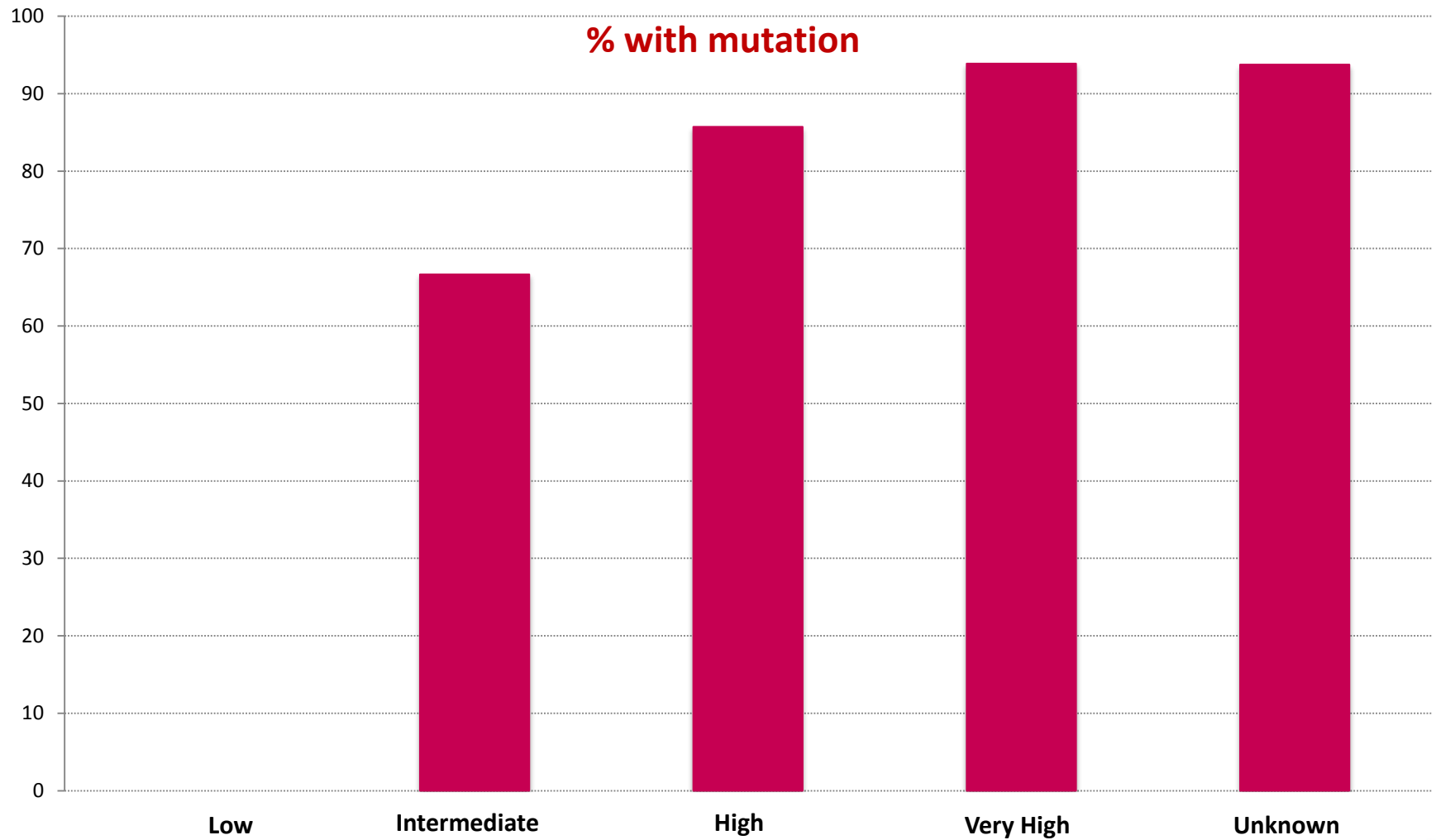
\*\*\*Medians, years ^Median time to 25% AML evolution

\*Greenberg, Tuechler, Schanz et al, Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndrome, Blood 120: 2454, 2012.

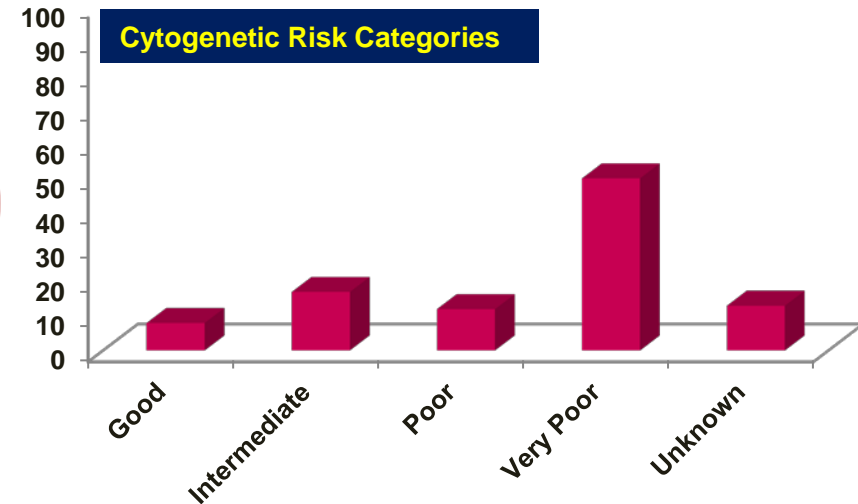
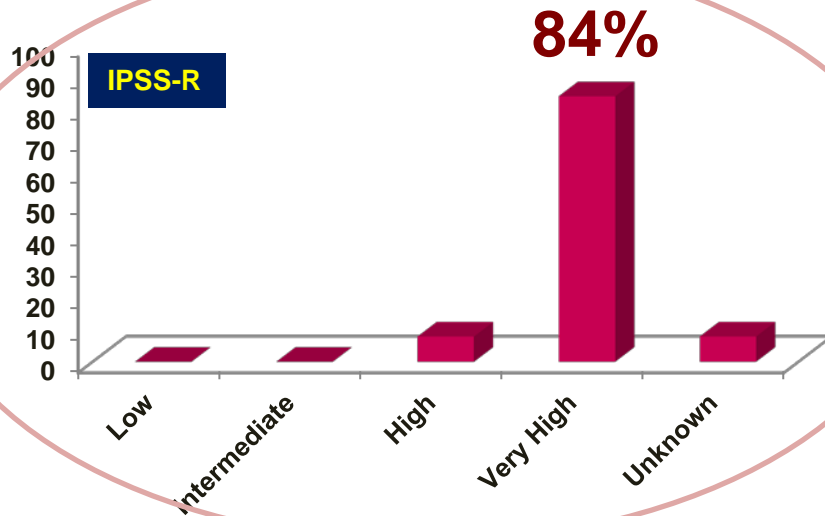
\*\*Schanz J et al, J Clin Oncology 2012; 30:820



# ONTIME TRIAL: MUTATION FREQUENCY IN IPSS-R CLASSES



# DISTRIBUTION (%) OF TP53 MUTATIONS BY PROGNOSTIC RISK CLASSIFICATION



- 100% of Monosomy 7 and Trisomy 8 patients tested carried one or more myeloid mutations
- Older patients (>80 years) had fewer TP53 mutations
- Complex karyotype patients had more mutations

