UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 8-K

CURRENT REPORT

PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of Report (Date of earliest event reported): **December 19, 2013**

Onconova Therapeutics, Inc.
(Exact name of Registrant as specified in its charter)

Delaware	**001-36020**	**22-3627252**
(State or Other Jurisdiction of Incorporation or Organization)	(Commission File Number)	(I.R.S. Employer Identification No.)

375 Pheasant Run
Newtown, PA 18940
(267) 759-3680
(Address, Including Zip Code, and Telephone Number, Including Area Code, of Registrant's Principal Executive Offices)

Not Applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 8.01 Other Events

On December 19, 2013, Onconova Therapeutics, Inc. (the "Company") conducted an analyst and investor event focusing on the treatment landscape of myelodysplastic syndromes ("MDS") and the development of the Company's most advanced product candidate, rigosertib, as a treatment for MDS and other cancers. The slides presented at the event, together with a slide setting forth certain cautionary language intended to qualify the forward-looking statements included in the presentation, are furnished as Exhibit 99.1 to this Current Report on Form 8-K and are incorporated herein by reference. The slides are also available in the "Investors and Media—Events & Presentations" section of the Company's website, located at www.onconova.com. Materials on the Company's website are not part of or incorporated by reference into this Current Report Form 8-K.

Item 9.01. Financial Statements and Exhibits

(d) Exhibits.

99.1 Analyst and Investor Event Slides, dated December 19, 2013.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Dated: December 24, 2013

Onconova Therapeutics, Inc.

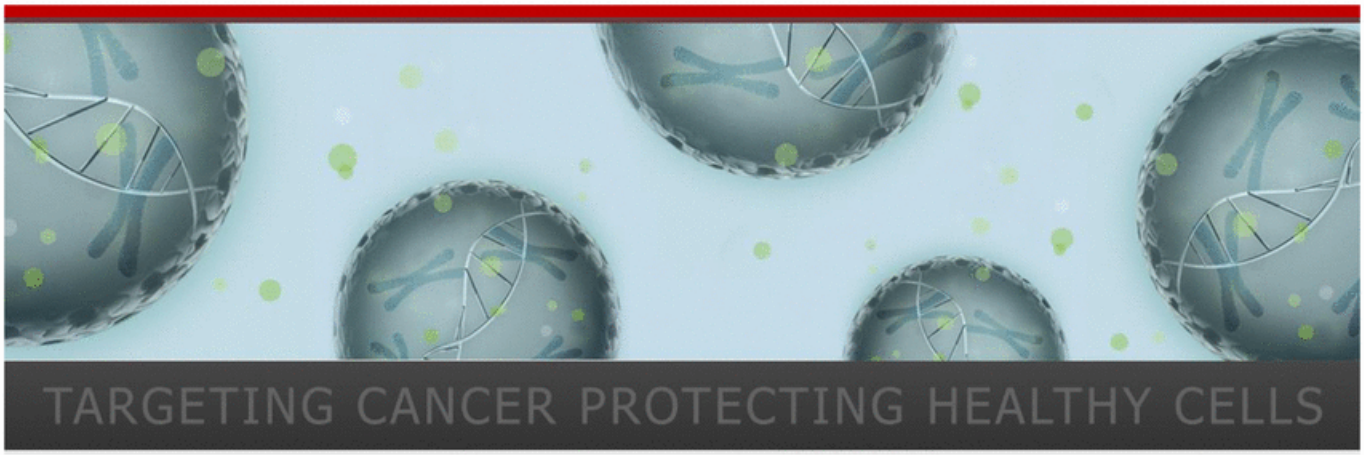
By: /s/ Ajay Bansal

Name: Ajay Bansal
Title: Chief Financial Officer

EXHIBIT INDEX

Exhibit No.	Description
99.1	Analyst and Investor Event Slides, dated December 19, 2013.

ONCONOVA THERAPEUTICS



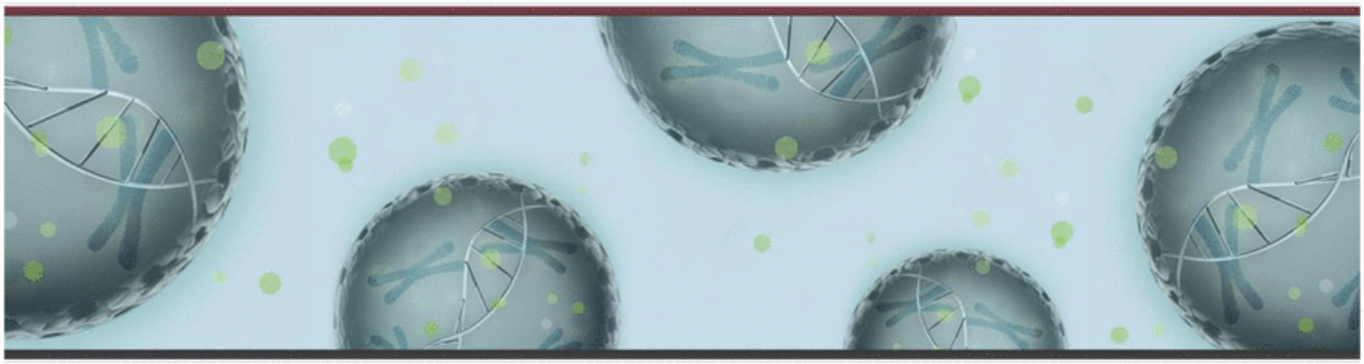
Analyst Day

December 19, 2013

Safe Harbor Summary

ONCONOVA THERAPEUTICS

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. 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 equity and debt financing on favorable terms, the success of our Phase 2 and Phase 3 trials of rigosertib, our ability to obtain regulatory approval of rigosertib and other risk factors included in our preliminary prospectus. We are providing this information as of the date of this presentation and do not undertake any obligation to update any forward-looking statements contained in this presentation as a result of new information, future events or otherwise.



Welcome
Alan Williamson, Ph.D.

Agenda

Session 1:
- An Overview of Rigosertib Clinical Trials
- An Overview of Rigosertib Safety & Tolerability
- Rigosertib Preclinical Studies and the Potential for Combination Therapy

Session 2:
- Mechanism of Action of Rigosertib
- Lower Risk MDS and Rigosertib Phase I and 2 trials with Oral Rigosertib

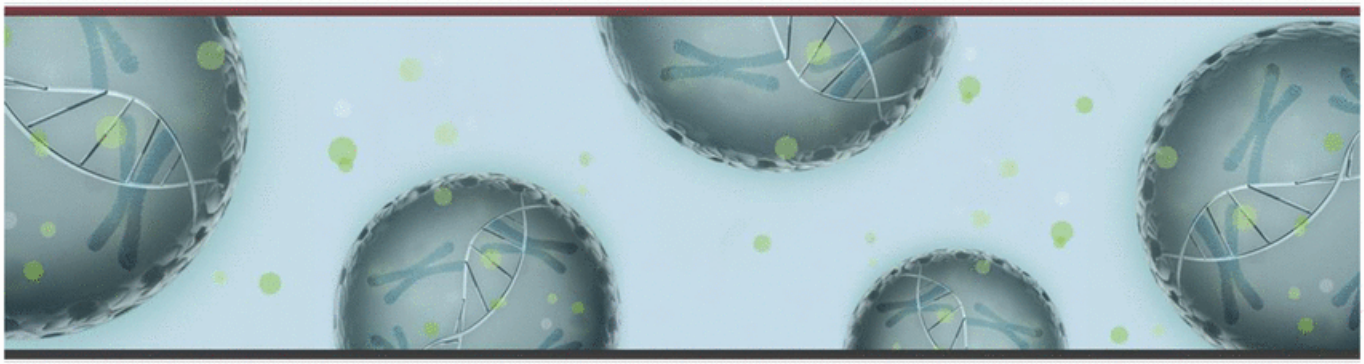
Session 3:
- Higher Risk MDS and Rigosertib Development in Post-Hypomethylating Agent MDS Patients
- Quality of Life Assessment and Impact on Clinical Trials

Today's Speakers

- Jerome Groopman, M.D.
  - The Dina and Raphael Recanati Chair of Medicine at Harvard Medical School and Chief of Experimental Medicine at Beth Israel Deaconess Medical Center
- Francois Wilhelm, M.D., Ph.D.
  - Chief Medical Officer and Senior Vice President, Onconova Therapeutics
- Michael Petrone, M.D.
  - Vice President Clinical Development, Medical Affairs & Pharmacovigilance, Onconova Therapeutics
- James F. Holland, M.D.
  - Distinguished Professor of Neoplastic Diseases at the Icahn School of Medicine at Mount Sinai; Lasker Award winner for contributions to the cure of childhood leukemias

Today's Speakers

- E. Premkumar Reddy, Ph.D.
  - Professor of Oncological Sciences and Structural and Chemical Biology at the Icahn School of Medicine at Mount Sinai; Scientific Founder of Onconova
- Azra Raza, M.D.
  - Director of the MDS Center at Columbia University
- Lewis R. Silverman, M.D.
  - Associate Professor Medicine, Hematology and Medical Oncology and Assistant Professor Oncological Sciences at the Icahn School of Medicine at Mount Sinai
- Jimmie C. Holland, M.D.
  - Wayne E. Chapman Chair in Psychiatric Oncology at Memorial Sloan-Kettering Cancer Center; pioneer in assessing quality of life measures in clinical trials



Overview of Rigosertib Clinical Trials

Francois Wilhelm, M.D., Ph.D.

Patients Enrolled in Rigosertib Trials

Indication	Phase	Line/Modality	Oral/IV	Patients Enrolled*	
MDS/AML	1/2	1st/2nd-line; Single agent	CIV 48-148h	86	86
AML	1	2nd/3rd-line; Single agent	CIV 72-120h	30	89
CLL and others	1	2nd line; Single agent	CIV 48h	16	
MDS	1	2nd-line; Single agent	Oral BID	43	
MDS Lower-risk	2	1st-line; single agent	Oral BID	77	77
MDS; HMA fail; higher risk	3/3B	2nd-line; Single agent	CIV 72h	306	306
Solid tumors	1/2	Single agent or combi	IV	200	331
Solid Tumors	1, 2	Single agent	Oral BID	131	
Ovarian	2	Single agent	IV	18	
Pancreatic	3	With Gemcitabine	IV	160	
Compassionate protocols				3	
Total patients in all rigosertib trials					1,070

- *Count as of November 26, 2013; does not include patients enrolled by SymBio in Japan*
- *If ongoing trials are completed as planned, another 400+ patients will be added in 2014*
- *CIV: Continous IV infusion of varying duration; IV: 2,4 or 8 hour infusion; Oral BID: twice a day dosing with oral capsules*
- *Boxed trials are approval track studies*
- *251 patients treated with oral rigosertib; 819 in IV studies*
- *All except one study conducted at the NIH were Company sponsored trials*

Key Rigosertib Trials and Milestones

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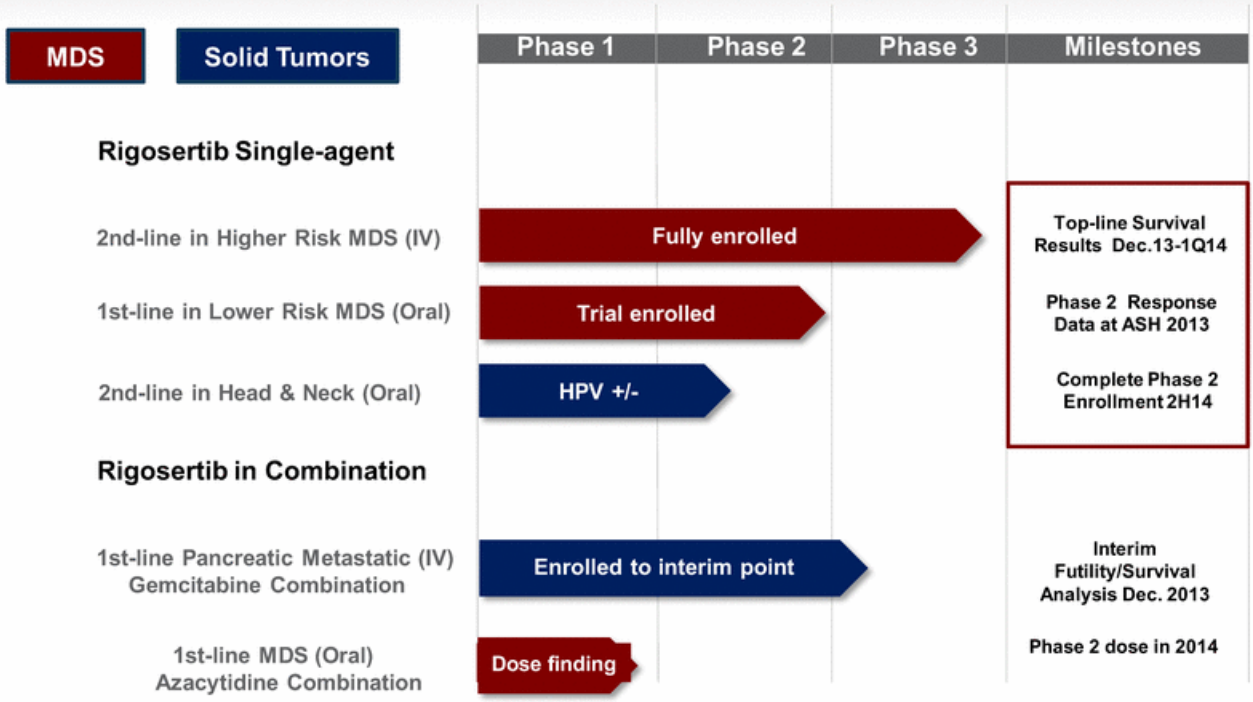

Advanced Rigosertib Trials in Myelodysplastic Syndromes

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Approval track Studies

Indication	Phase	Line/Modality	Oral/IV	Remarks
MDS; HMA failed; higher risk	3/SPA	2nd-line; Single agent	CIV 72hr	~300 Pts; Randomized; ~90 sites USA, EU
MDS; as above	3B	2nd-line; Single agent	CIV 72hr	90 Pts; 1 arm; Multiple sites USA, EU
MDS; lower risk	2	1st-line; Single agent	Oral BID	60 Pts; 4 USA sites; accrual in Q4-13
MDS; lower risk EPO refractory	2	1st-line; Single agent	Oral BID	MDACC and other sites in USA, EU

Supporting Studies

Indication	Phase	Line/Modality	Oral/IV	Remarks
RAEB MDS; Pediatric	1/2	Single agent	CIV 72hr	2 to 46 Pts; ~10 sites USA, EU
Lower risk MDS; PK/PD	1/2	Single agent, 1 arm	Oral	18 Pts; 1 USA site (Columbia)

Trial Coding
Completed
In process
In planning
With oral drug

Mass-balance studies are also in planning for IV and Oral rigosertib

Design of US/Europe Pivotal Phase 3 MDS Trial Under SPA

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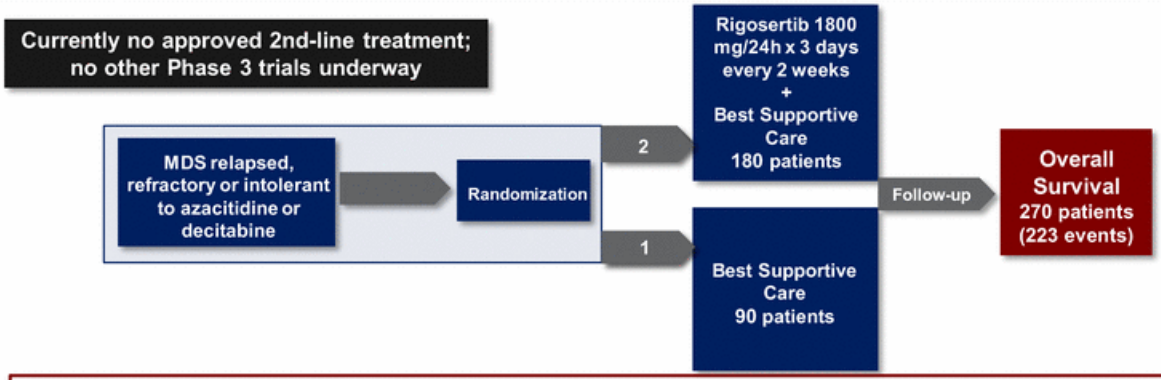
- Rigosertib IV as a single agent in patients with MDS after failed prior azacitidine or decitabine therapy
- Continuous infusion using a portable pump; 1800 mg daily dose



Assumptions and Power Calculations

- The key assumptions used to calculate the required size of the trial were based on hypothesized median survival differences **of 10 or 13 weeks between the two treatment arms.**
- A sample size of 270 (180 patients in the rigosertib group and 90 patients in BSC group), after 223 events (deaths) yields **>90% statistical power to detect a significant difference in overall survival** between the two groups.
- The trial is also well powered for other clinically relevant benefits of rigosertib over BSC.

New Protocol 04-24 for HR-MDS

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- **Key Objectives for new Phase 3B study:**
  - **Provide continued access to rigosertib for the unmet medical need**
  - **Collect additional data on activity and tolerability**

Protocol	04-21 (ONTIME)	04-24
Randomization	Yes (to BSC)	No (single-arm trial)
Total Patients	270+	90
Primary endpoint	Overall survival	Bone marrow response and OS relationship
Centers (US/EU)	88 sites	Top enrolling 04-21 sites and a few new sites

Phase 1/2 Front-line Combination Study in MDS

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- **09-08 study**
  - a 40 patient study testing the combination of **oral rigosertib** and azacitidine
- **Phase I ascending dose 3/6 cohorts:**
  - 140, 280 and 560 mg BID 3/4 weeks oral rigosertib combined to Vidaza labeled dose
- **Phase II: Minimax Simon stage II design:**
  - 15, followed by 13 patients
- **Objectives:**
  - Determine safety, PK, efficacy (IWG 2006 criteria)
  - Dose selection for next stage
- **Sites:**
  - Two open in US
  - One pending in EU

Proof of Concept in HNSCC Patients

Oral Rigosertib

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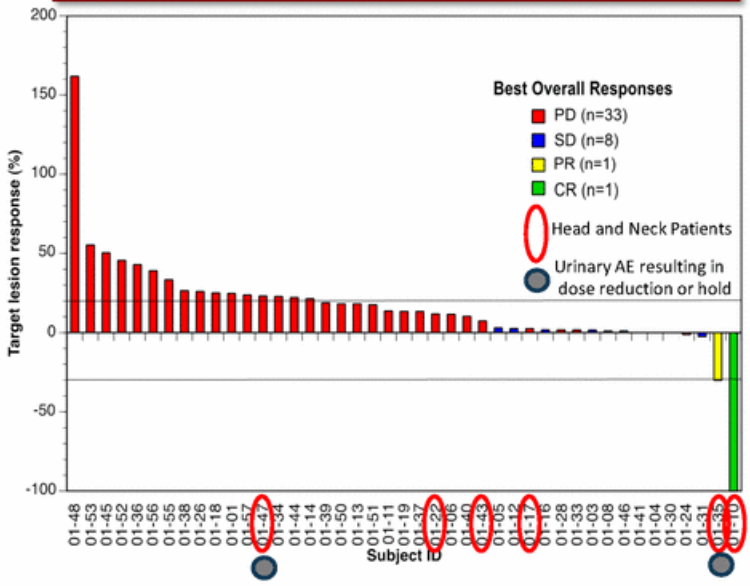
- Single agent rigosertib in Phase 1 population of all comers including 6 HNSCC patients who had failed previous therapies

Best Overall Response in Phase 1 Patients

Dose	Site	Best response	Duration of Response/SD
70	Ovarian carcinoma	SD	36 weeks
70	Ovarian carcinoma	SD	12
140	Pancreatic neuroendocrine	SD	24
280	Carcinoid tumor	SD	20
280	HNSCC	CR	96+
560	Adenoid cystic carcinoma	SD	22
560	Craniopharyngioma	SD	12
560	HNSCC	PR	40
560	Hepatocellular carcinoma	SD	15
700	Renal cell carcinoma	SD	23

Two of Six Treated HNSCC Patients had an Objective Response



www.onconova.com

Interaction between Rigosertib and Azacitidine
US Patents: 8106033B2; 20100305059

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In vitro studies conducted by Dr. Lewis Silverman et. al., Mount Sinai Medical School

Combination Drug	CI	Ratio	Description
ON1910.Na* (125nM) + 5AzaC (2uM)	0.44	1:62.5	Synergism
ON1910.Na (125nM) + 5AzaC (4uM)	**0.30**	**1:31.25**	**Strong synergism**
ON1910.Na (250nM) +5AzaC (2uM)	0.68	1:125	Synergism
ON1910.Na (250nM) + 5AzaC (4uM)	0.57	1:62.5	Synergism
ON1910.Na (500nM) + 5 AzaC (2uM)	0.63	1:250	Synergism
ON1910.Na (500 nM) + 5AzaC (4uM)	0.75	1:125	Moderate synergism

ON 01910.Na is rigosertib

Exploratory Rigosertib Trials in Hematology/Oncology

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Indication	Phase	Line/Modality	Oral/IV	Remarks
MDS/AML	1/2	1st/2nd-line; Single agent	CIV 48-148hr	76 Pts; 4 sites; active in 1st/2nd-line MDS
AML	1	2nd/3rd-line; Single agent	CIV 72-120hr	30 Pts; MDACC; stable blasts in 7 Pts
CLL	1	2nd-line; Single agent	CIV 48hr	Stable disease in 5/10 Pts
MDS	1	2nd-line; Single agent	Oral BID	37 Pts; 2 sites; active in high and low risk
MDS Higher-risk	1/2	1st-line; + SC or IV Vidaza	Oral BID	2 USA sites/1 EU site
Myelofibrosis	1	1st/2nd-line; with Oral Jakafi	Oral BID	Mayo Clinic
AML	1/2	2nd-line; Combination	Oral BID	Elderly Pts with Ara-C; younger with 7+3
CLL	1/2	2nd-line; Combination	Oral BID	Bendamustine and/or ibrutinib
MDS Lower-risk	1/2	1st/2nd-line; Combination	Oral BID	Combination with Revlimid
MDS	2	2nd-line; Single agent	Oral BID	Hypomethylating failures
MDS	2	1st-line; Single agent	Oral BID	Trisomy 8, RCMD; Cyclin D+?
MDS/CMML(K-ras)	2	2nd-line; Single agent	Oral BID	Targeted exploratory

Trial Coding
Completed
In process
In planning
Combination
Oral rigosertib
BID: Twice daily

Earlier Stage Rigosertib IV Trials in Solid Tumors

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Trial	Location	Phase and Objective	ClinTrial No.	IV/Oral	Mono/Combo	Status, Patients (Pts)
04-01	USA	Phase 1 study with 2-hr IV infusion in advanced solid tumors	None	IV	Monotherapy	Completed, 20 Pts treated
04-02	USA	Phase 1 study with 3-day continuous infusion in advanced cancer	NCT01538537	IV	Monotherapy	Completed, 28 Pts treated
04-03	USA	Phase 1 study with 24-hr infusion per week in advanced cancer	NCT01538563	IV	Monotherapy	Completed, 40 Pts treated
04-04	India	Phase 1 study with 2, 4, or 8-hr infusion twice/week in advanced cancer	None	IV	Monotherapy	Completed, 25 Pts treated
04-06	USA	Phase 1 study in combination with irinotecan, oxaliplatin or FOLFOX in patients with advanced solid tumors	NCT00861328	IV	Combination with IRI or OXA	Completed, 18 Pts treated
04-08	USA	Phase 1 study in combination with irinotecan, OXA or FOLFOX in patients with hepatoma and other solid tumors	NCT00861783	IV	Combination with IRI or OXA	Completed, 16 Pts treated
04-09	USA	Phase 1 study in combination with gemcitabine in advanced or metastatic solid tumors	NCT01125891	IV	Combination (2hr infusion of rigosertib)	Closed, 40 Pts treated
04-10	USA	Phase 1 dose-escalation study in combination with gemcitabine in advanced or metastatic solid tumors	NCT01165905	IV	Combination (24hr infusion of rigosertib)	Completed, 10 Pts treated

Trial Coding
Phase 1 monotherapy
Phase 1 combination

Later Rigosertib Trials in Solid Tumors

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Trial	Location	Phase and Objective	ClinTrial No.	IV/Oral	Mono/Combo	Status, Patients (Pts)
04-12	USA	Phase 2 single-arm study by 2-hour infusion in recurring platinum-resistant ovarian cancer	NCT00856791	IV	Monotherapy	Completed, 1 Pt treated
04-12A	India	Phase 2 single-arm study by 4-hour infusion in patients with recurring platinum-resistant ovarian cancer	CTRI/2010/091/001281	IV	Monotherapy	Closed, 17 Pts treated
04-22	USA, India, Eastern EU	Phase 3 study to compare the efficacy and safety of gemcitabine alone vs. combination with gemcitabine in previously untreated metastatic pancreatic cancer	NCT01360853 ONTRAC	IV	Combination with GEM	Ongoing, 160 Pts treated
09-03	India	Phase 1 study to assess the tolerability, pharmacokinetics and clinical activity of rigosertib capsules administered orally in patients with advanced cancer	None	Oral	Monotherapy	Closed, 6 Pts treated
09-04	USA	Phase 1 study to assess the tolerability, pharmacokinetics and clinical activity of rigosertib administered orally in patients with advanced cancer	NCT01168011	Oral	Monotherapy	Ongoing, 61 Pts treated
09-09	USA	Phase 2 study in patients with relapsed or metastatic, platinum-resistant, HPV positive or negative squamous cell carcinoma (SCC)	NCT01807546	Oral	Monotherapy	Ongoing, 25/60 Pts treated
09-12	USA	Phase 1 study of Platinum-based chemoradiotherapy with oral rigosertib in patients with intermediate or high-risk head & neck SCC	NCT01928537	Oral	Combination with cisplatin and RT	Ongoing, Up to 24 Pts

Trial Coding
Phase I monotherapy
Phase 1 combination
Phase 2 or Phase 3
With oral rigosertib

Key Ongoing Trials

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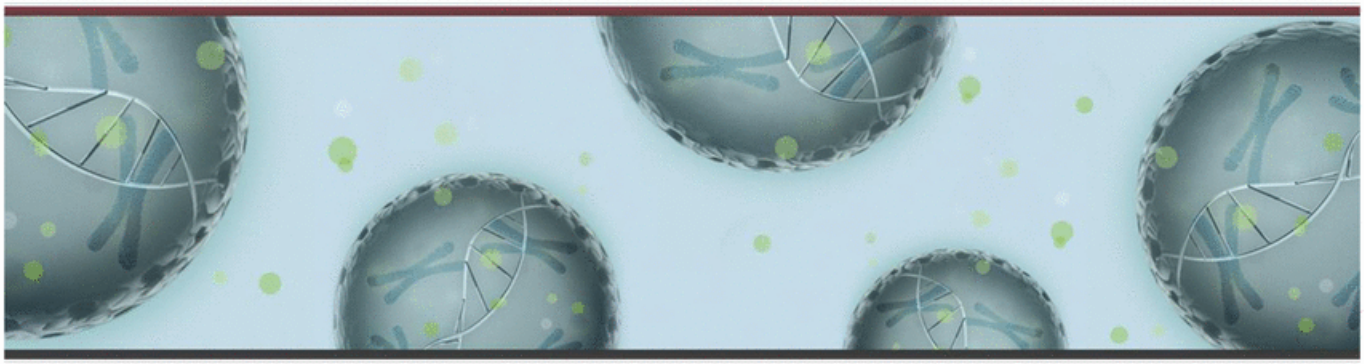


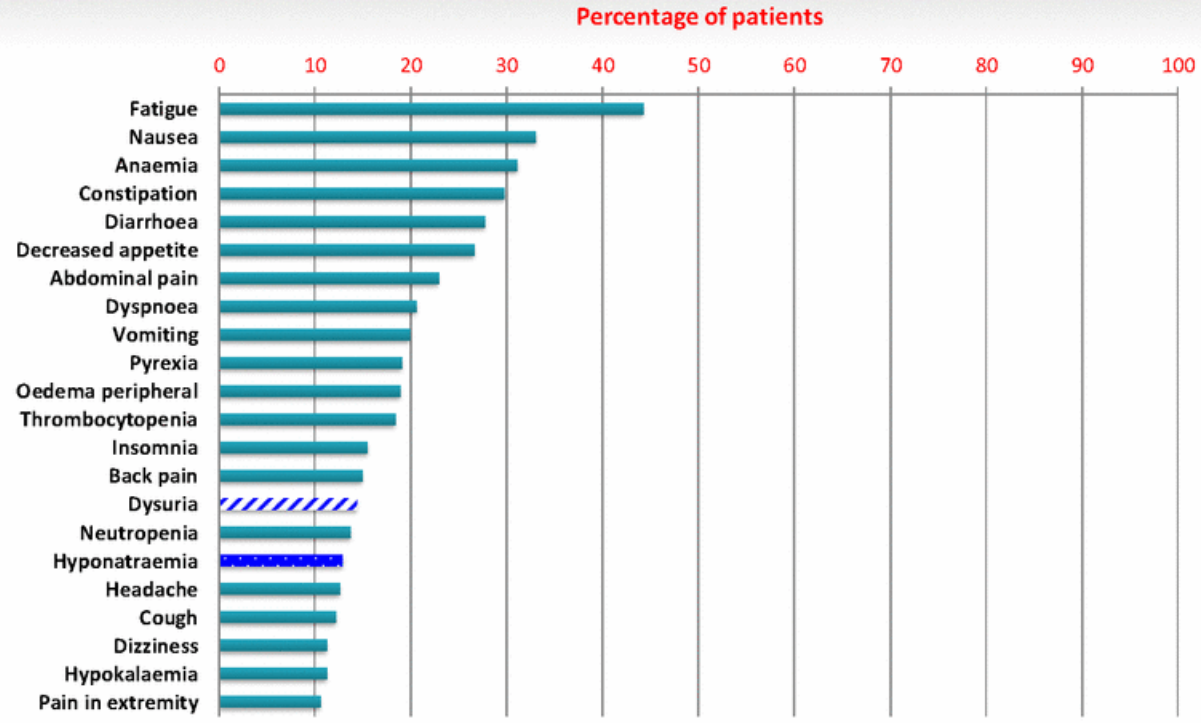
Rigosertib Safety Profile
Michael Petrone, M.D.

Overview of safety findings

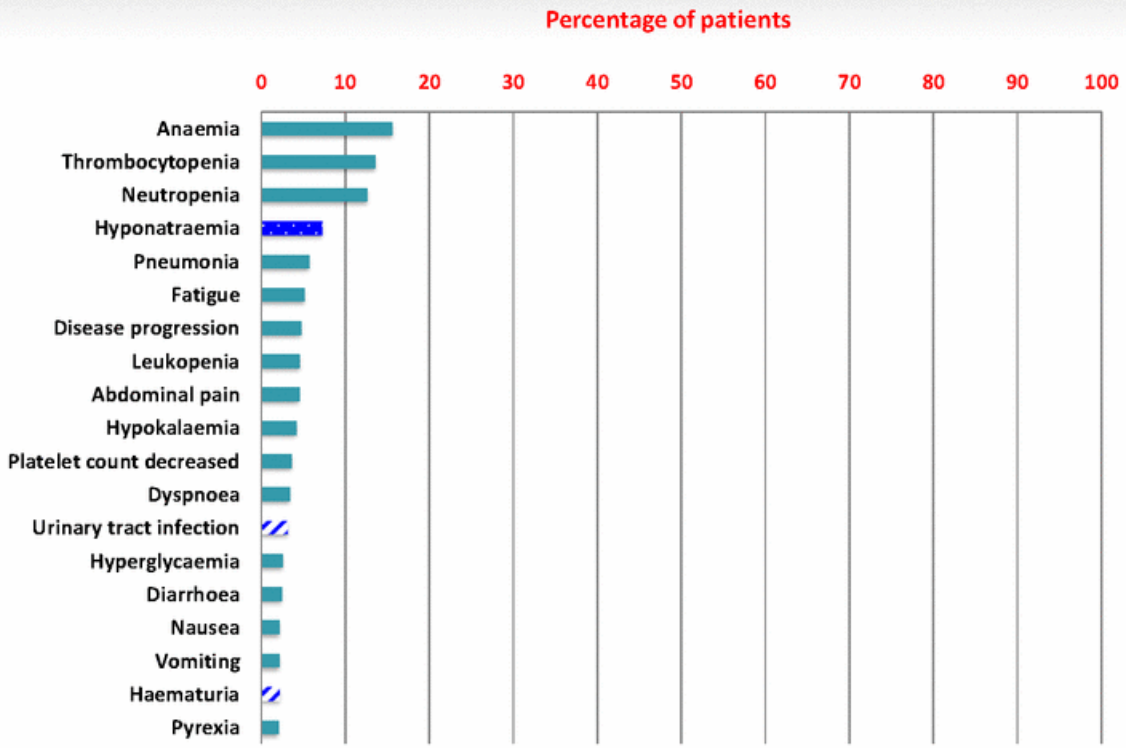
- Over 1000 patients with hematological malignancies and solid tumors have been enrolled in Phase I - III clinical trials.
- Favorable risk-benefit profile overall to date
- Lack of significant myelosuppression, cardiotoxicity, or neurotoxicity
- Generally, no need for premedication during the studies
- Potential safety signals are being monitored on an ongoing basis.
- Risk-benefit analysis by DSMC set up for pivotal study at consecutive 4 meetings have recommended further continuation of studies without modifications.

Adverse events in ≥ 10% of patients receiving IV or oral rigosertib, irrespective of causality - All grades

Cut-off: 5-Sep-2013 (N = 730)



≥ Grade 3 adverse events in ≥ 2% of patients receiving IV or oral rigosertib, irrespective of causality Cut-off: 5-Sep-2013 (N = 730)



Drug-related AEs in ≥ 5% of patients in combined formulations: All grades and ≥ Grade 3+ (Cut-off: 5 Sep 2013; N = 730)

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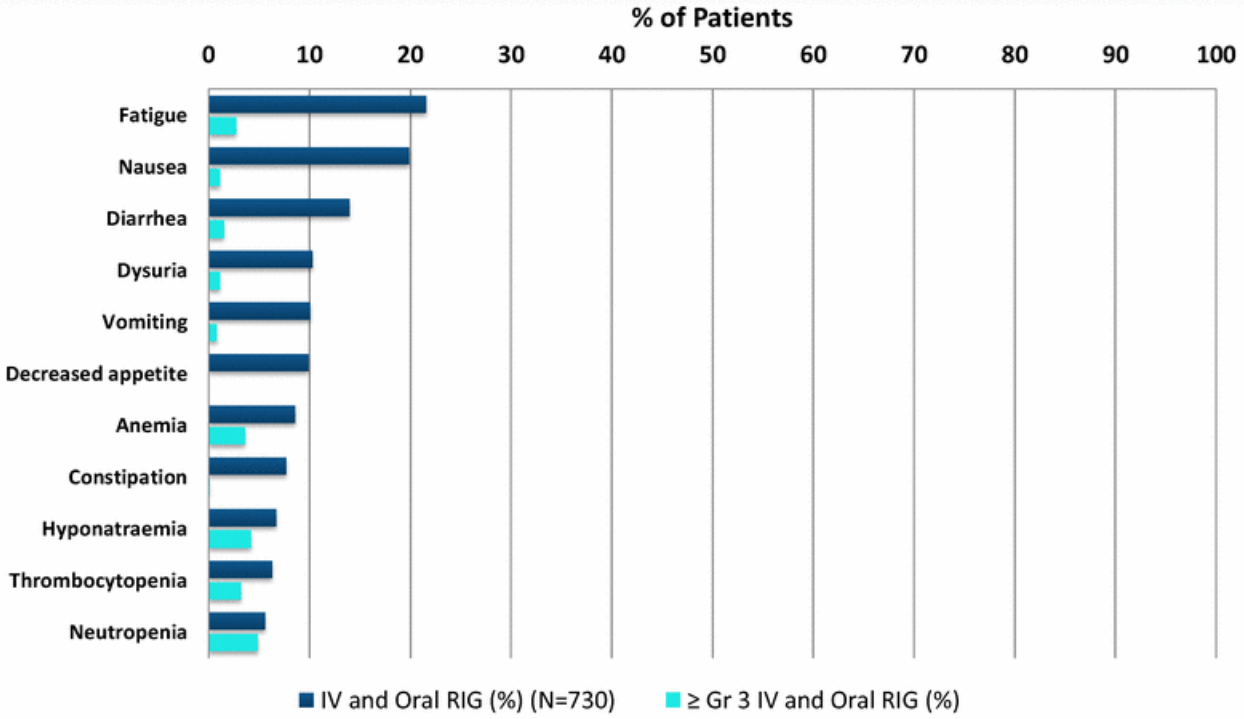

Most frequent (≥ 5% of patients) drug-related AEs by formulation - All grades (Cut-off: 5 Sep 2013, N = 730)

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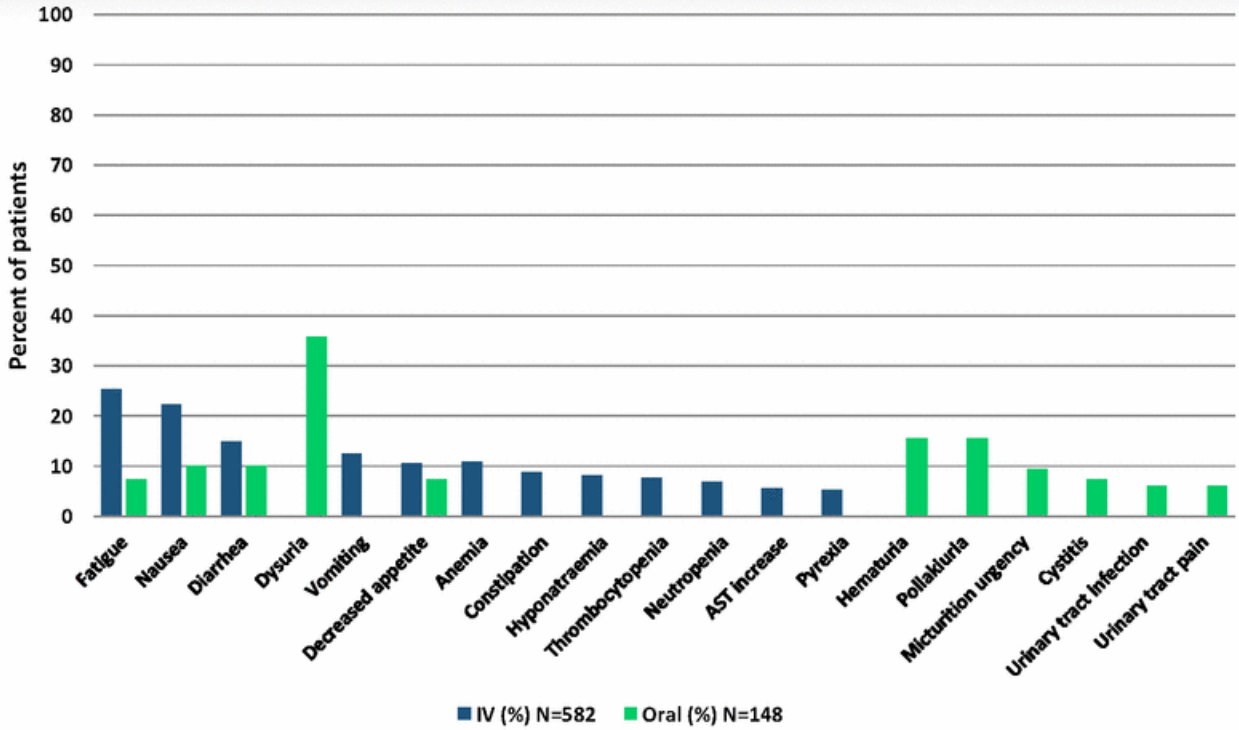
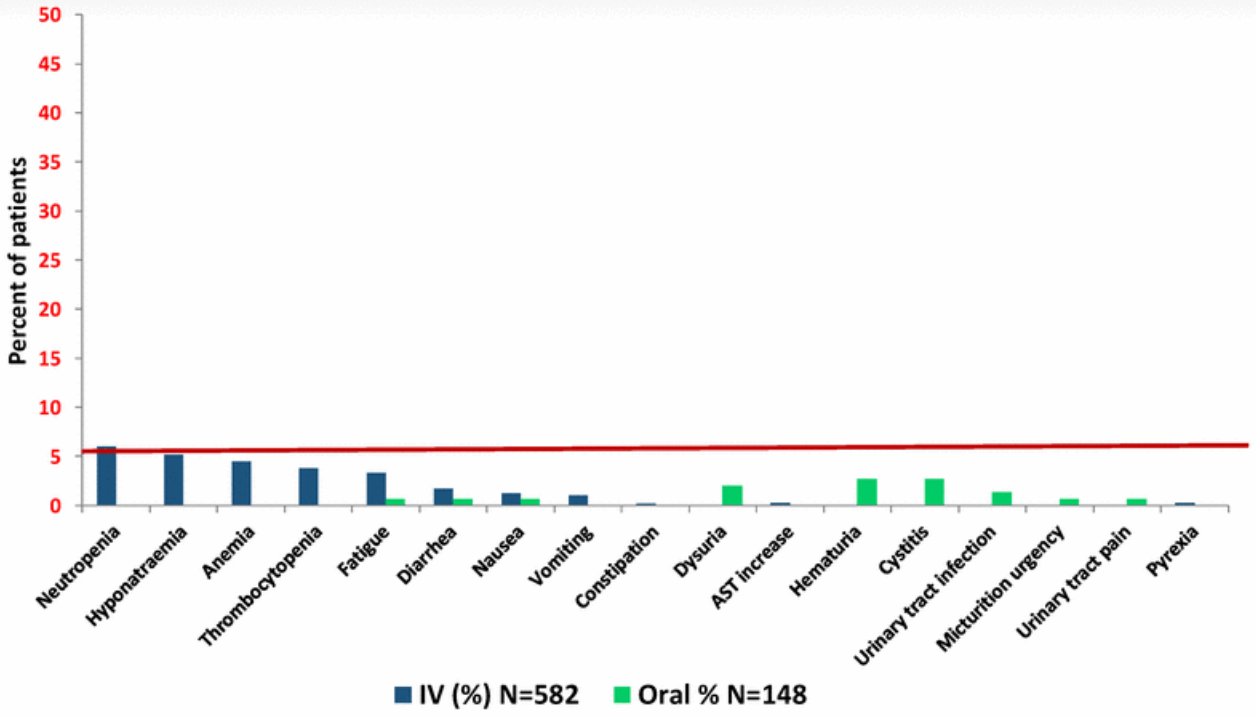


Most frequent Grade 3+ drug-related AEs by formulation (Cut-off: 5 Sep 2013, N = 730)



Management of urinary toxicity in patients treated with rigosertib

- Urinary toxicity with IV rigosertib:
  - ✓ If ≥ Grade 2, stop infusion until restoration to Grade 1 or baseline
  - ✓ Reintroduce first at full dose
  - ✓ If reoccurs, 25% dose reduction (2 dose reductions are allowed)
  - ✓ If symptoms persist, stop rigosertib
- Urinary toxicity with oral rigosertib:
  - ✓ Oral dosing was switched to intermittent dosing (2 weeks of 3-week cycles), from initial continuous dosing
  - ✓ Initial 560 mg BID regimen switched to 560 mg in the morning/280 mg in the afternoon, with greatly improved urinary tolerability to date
  - ✓ Step-by-step dose reduction in case of ≥ Grade 2 urinary events
  - ✓ Dysuria questionnaire administered to all patients throughout the study
- For both formulations, prevention strategy recommending good hydration (~2L/day) and bicarbonate tablets PRN. No premedication needed.

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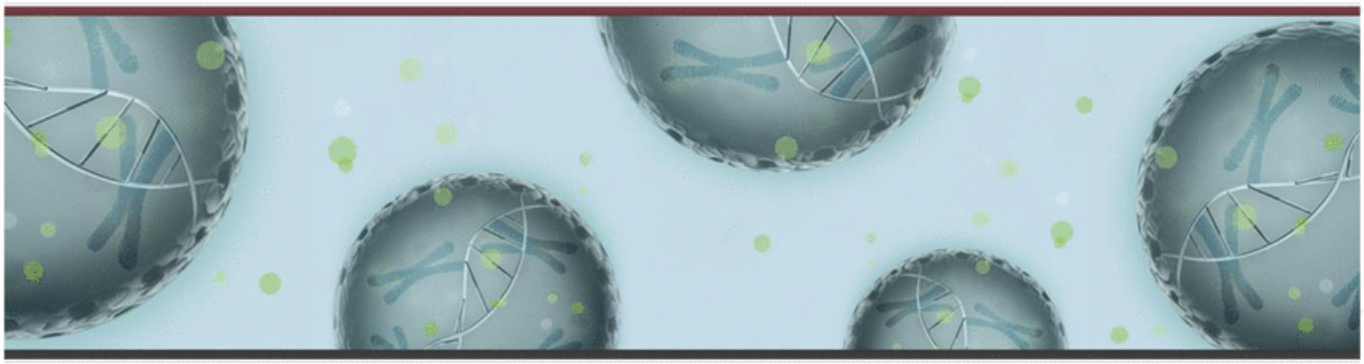
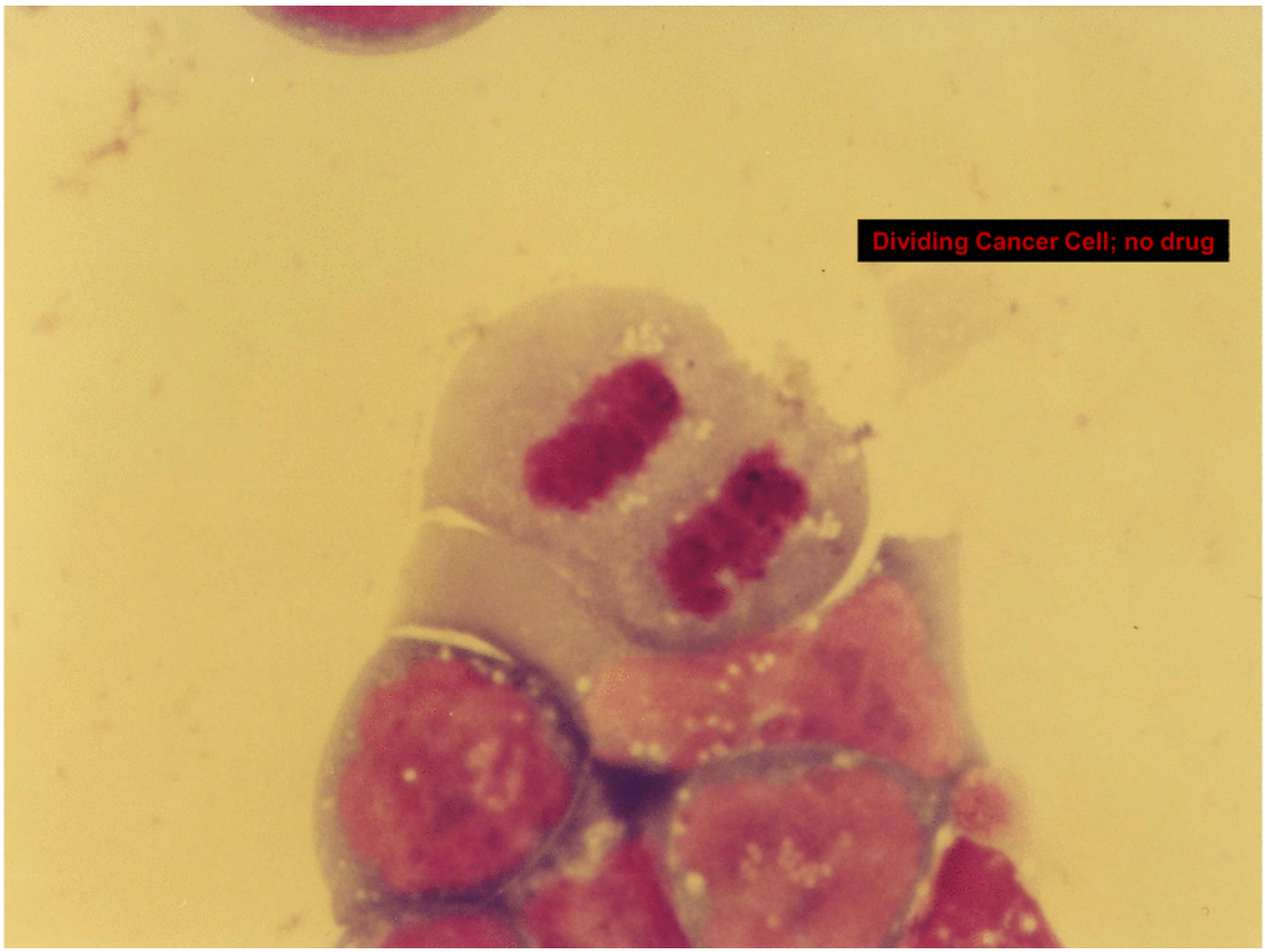


Rigosertib Preclinical Studies and the Potential for Combination Therapy

James F. Holland, M.D.



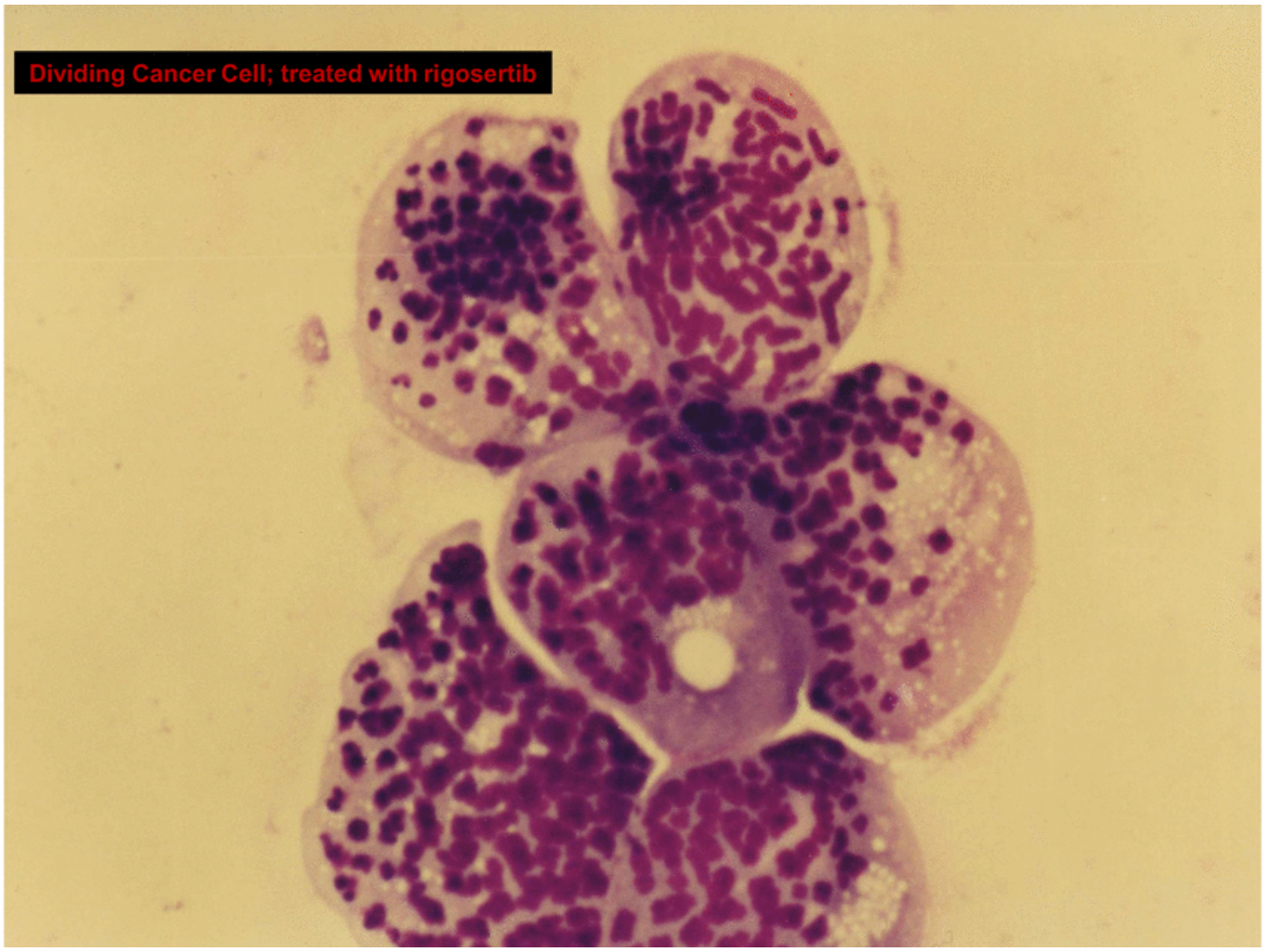
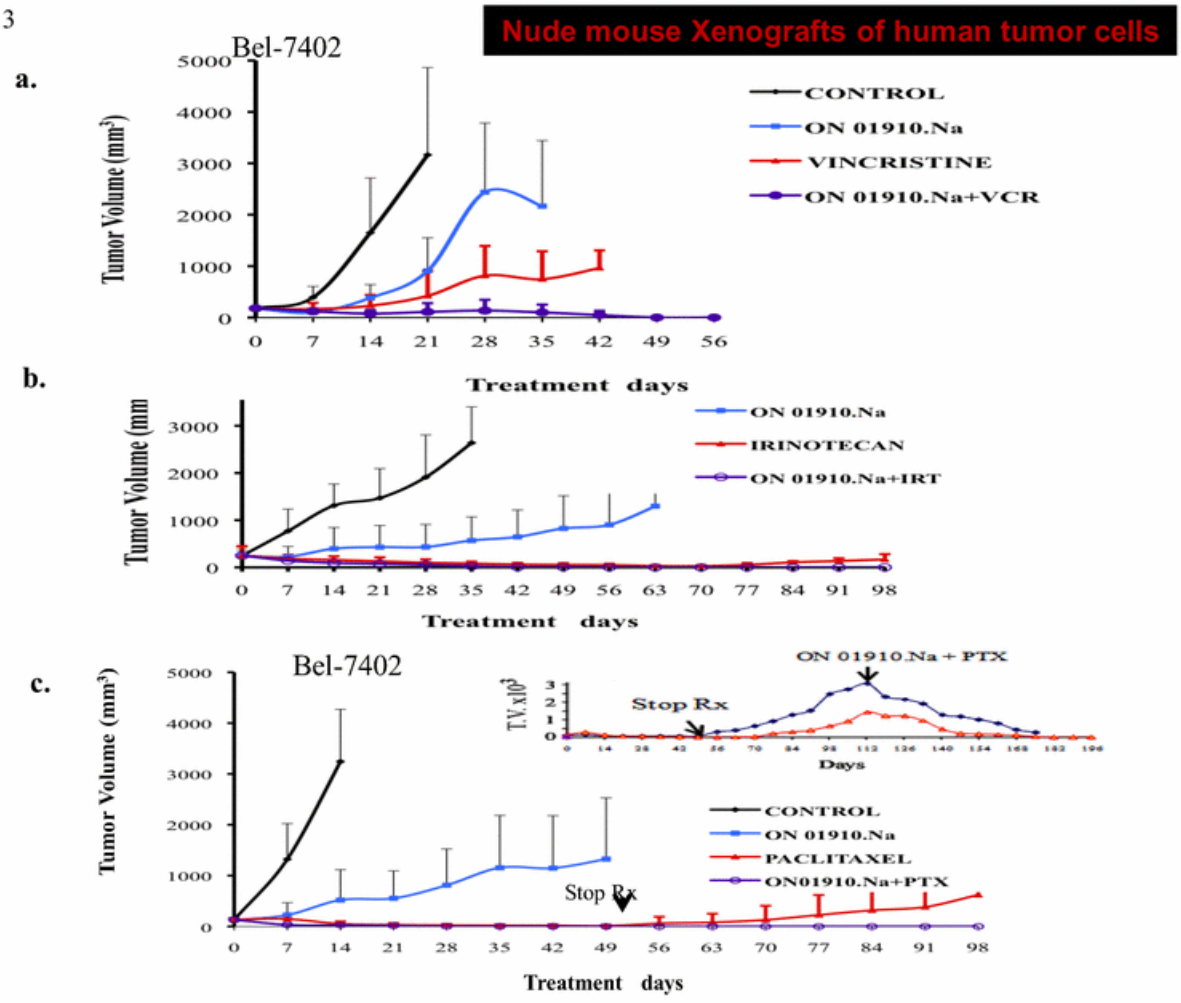
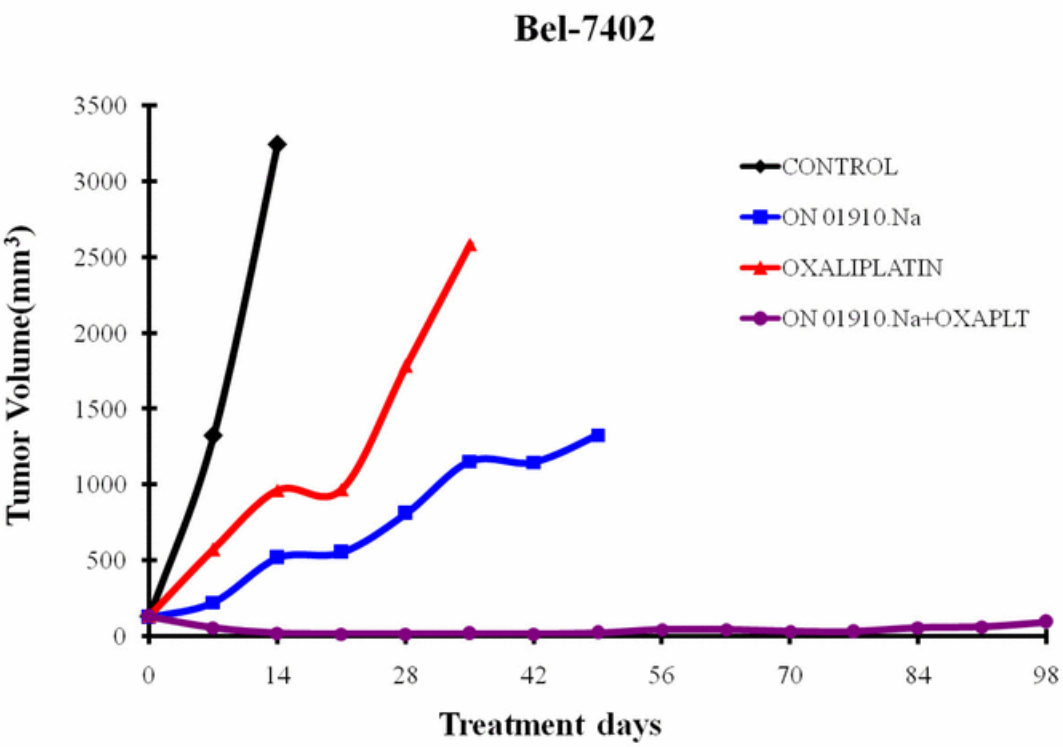

Dividing Cancer Cell; treated with rigosertib

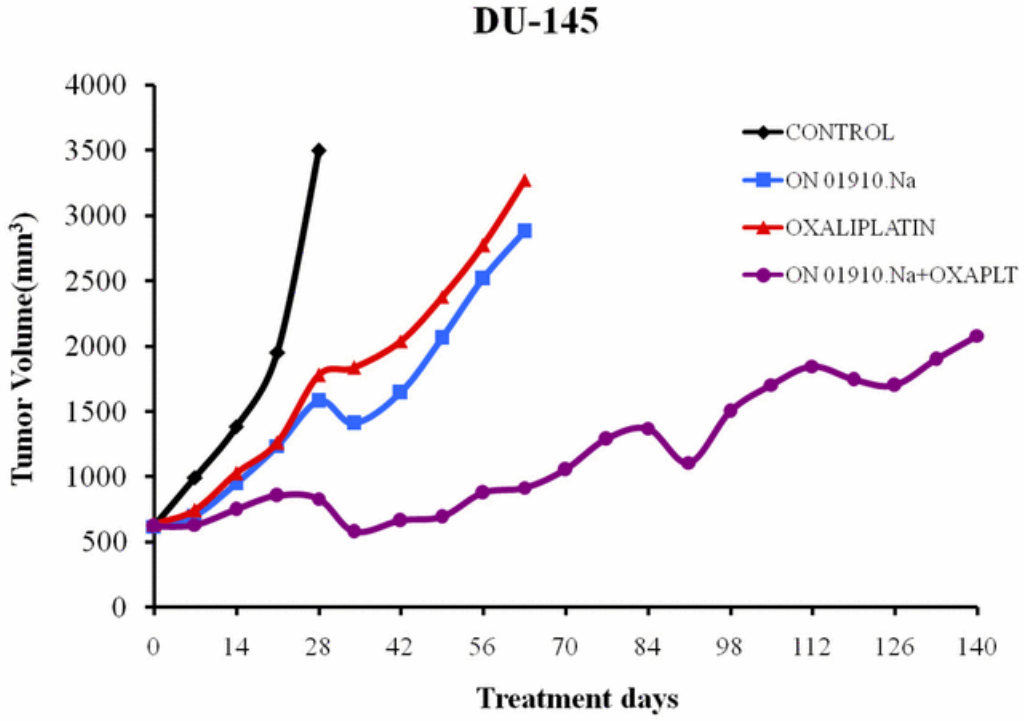
Fig. 3


Nude mouse Xenografts of human tumor cells
a.
Bel-7402
Tumor Volume (mm³)
5000
4000
3000
2000
1000
0
0 7 14 21 28 35 42 49 56
Treatment days
CONTROL
ON 01910.Na
VINCRISTINE
ON 01910.Na+VCR
b.
Tumor Volume (mm
3000
2000
1000
0
0 7 14 21 28 35 42 49 56 63 70 77 84 91 98
Treatment days
ON 01910.Na
IRINOTECAN
ON 01910.Na+IRT
c.
Bel-7402
Tumor Volume (mm³)
5000
4000
3000
2000
1000
0
0 7 14 21 28 35 42 49 56 63 70 77 84 91 98
Treatment days
Stop Rx
ON 01910.Na + PTX
T.V.x10³
Stop Rx
Days
CONTROL
ON 01910.Na
PACLITAXEL
ON01910.Na+PTX

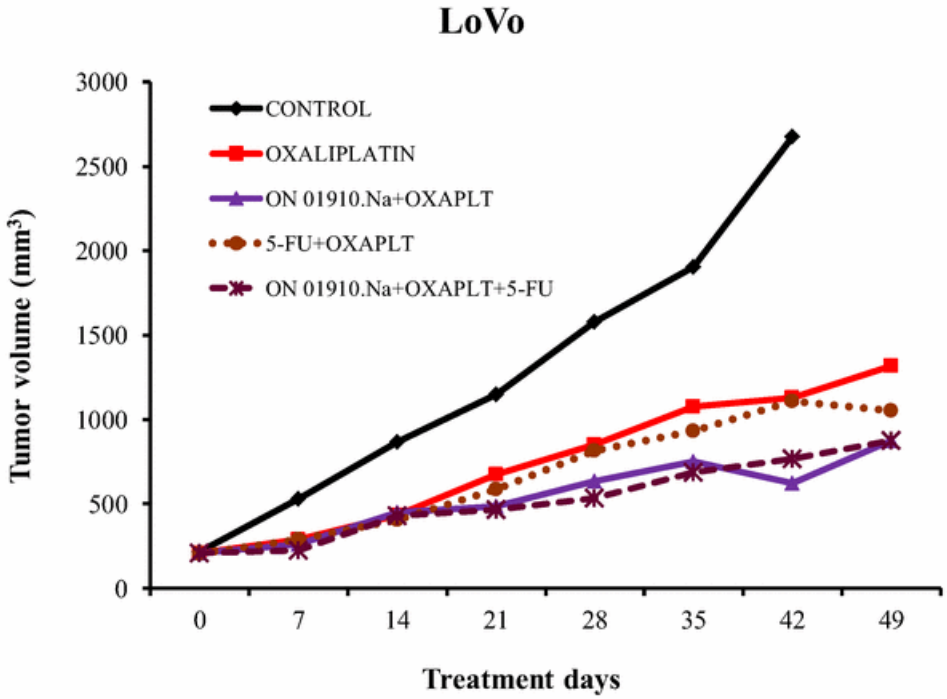
Liver cancer model

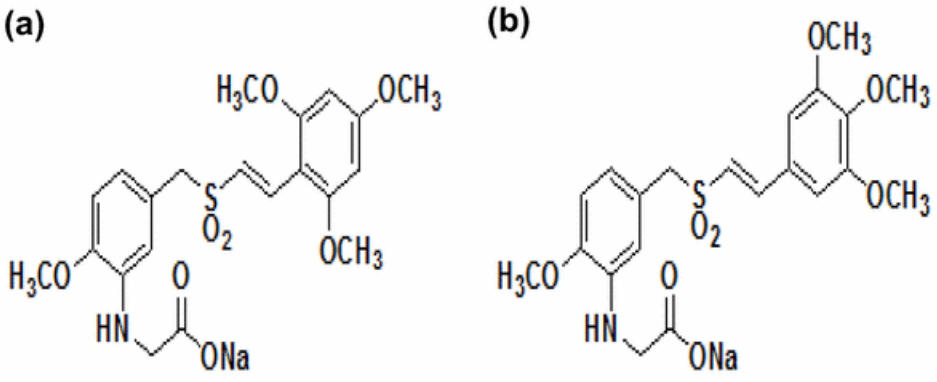


Prostate cancer model



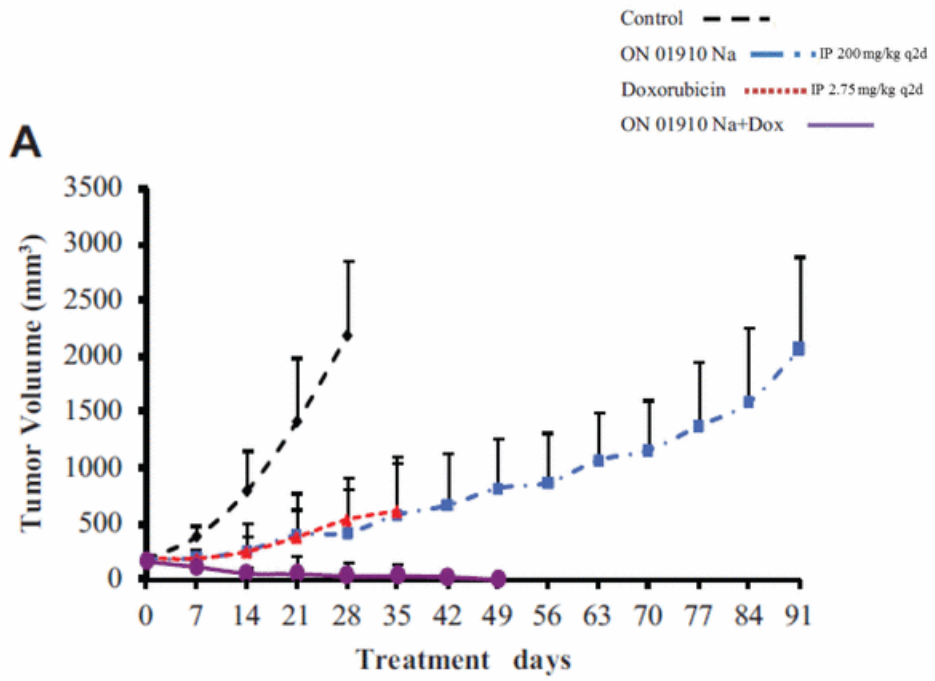
Colon cancer model





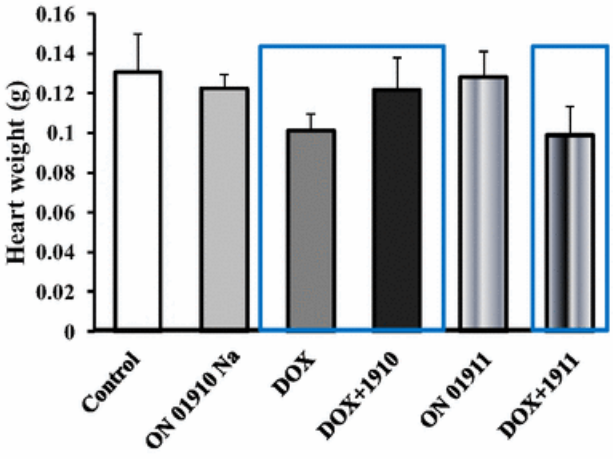
Rigosertib, ON 01910.Na, left; ON 01911.Na, negative control in studies

Rigosertib is Synergistic with Doxorubicin for Breast Cancer



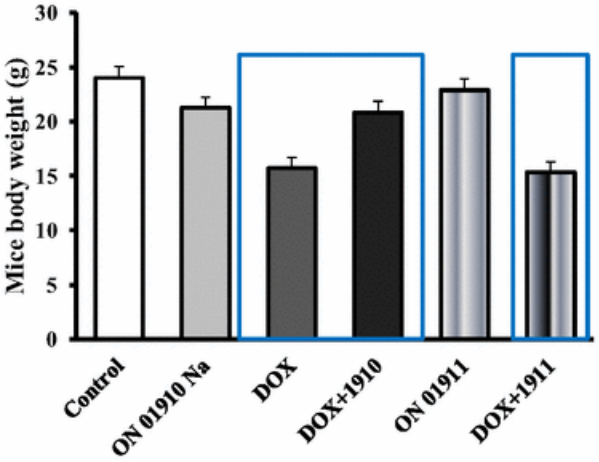
Rigosertib Prevents Cardiotoxicity Caused by Doxorubicin

Rigosertib prevented reduction in cardiac muscle



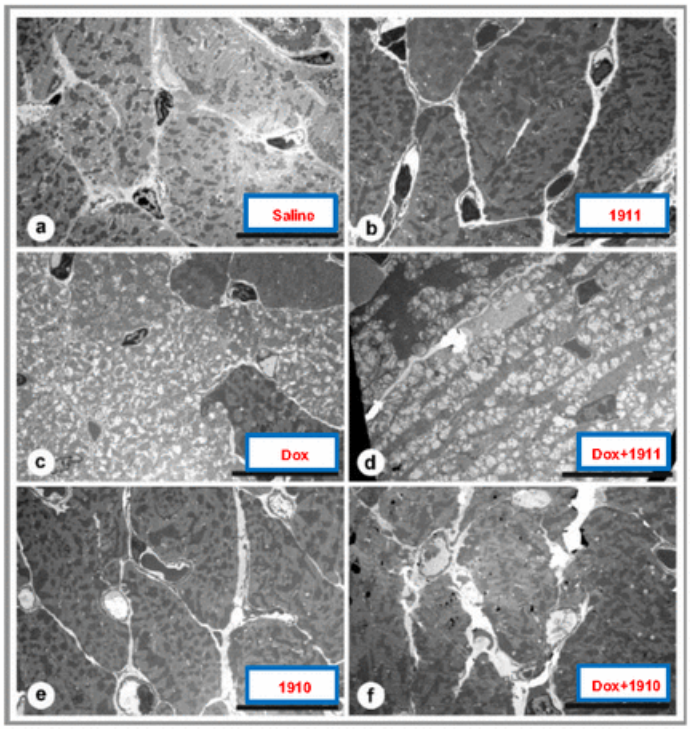
- Rigosertib prevented cardiac atrophy caused by doxorubicin
- Inactive version of rigosertib (1911) **did not** have same effect

Rigosertib prevented reduction in body weight



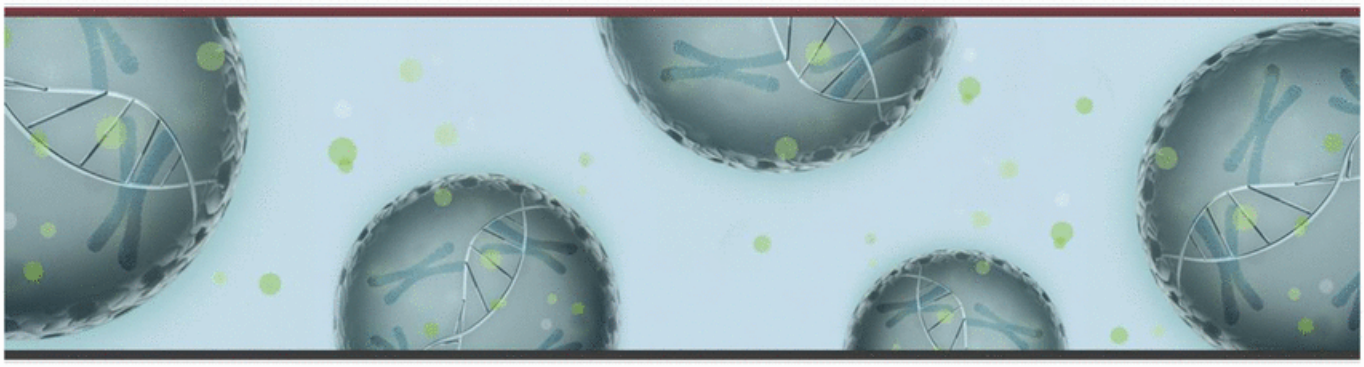
- Rigosertib prevented reduction in gross body weight caused by doxorubicin
- Inactive version of rigosertib (1911) **did not** have same effect

Rigosertib Prevents Cardiotoxicity Caused by Doxorubicin



- Cardiac tissue from treated mice shows doxorubicin effects on morphology:
  - Fenestration of mitochondria
  - Fragmentation of myofibrils
- Rigosertib + Doxorubicin-treated hearts are indistinguishable from controls
- Inactive version of rigosertib (1911) **did not** achieve same effect

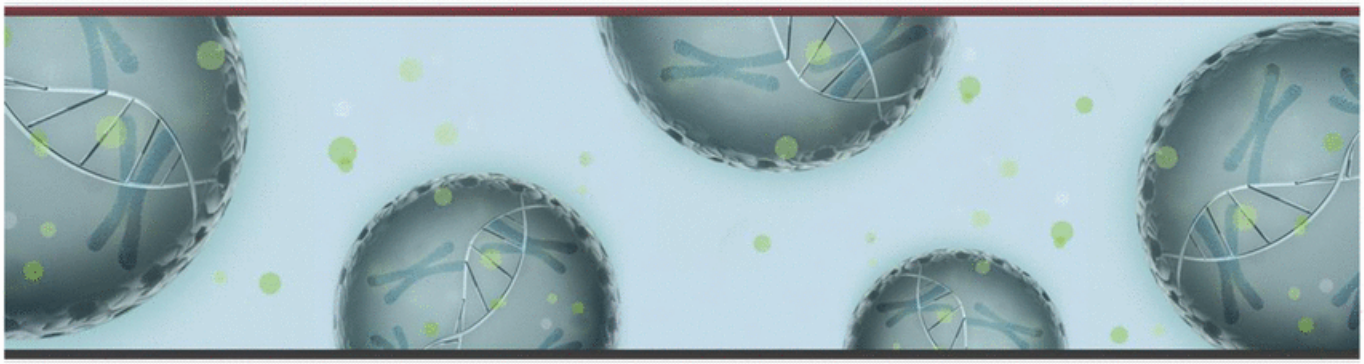
ONCONOVA THERAPEUTICS



Question & Answer Session

-Break-

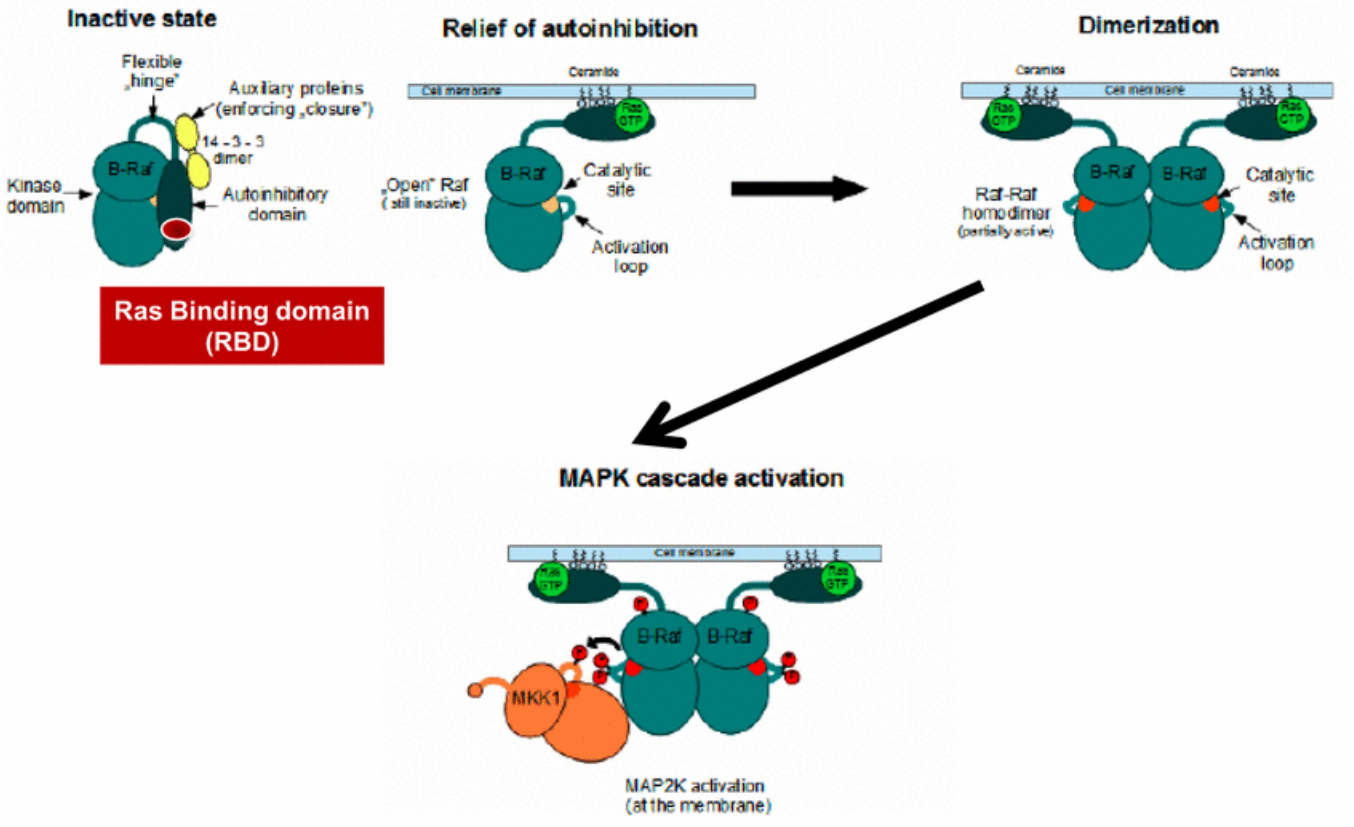
ONCONOVA THERAPEUTICS



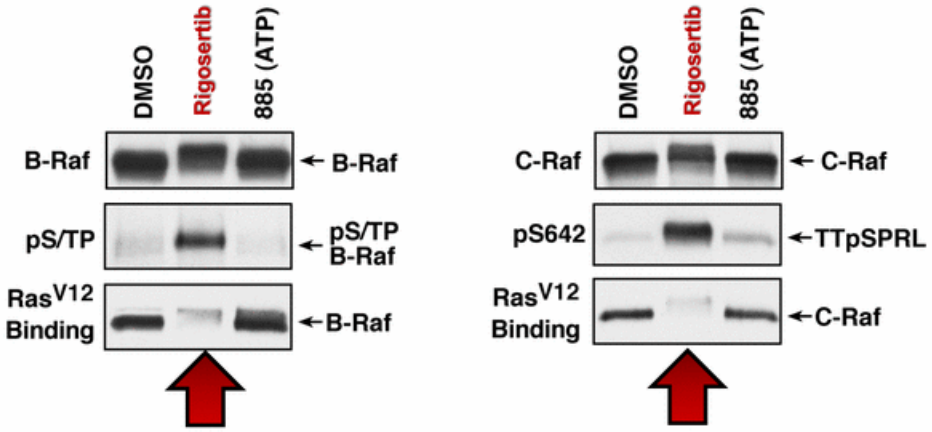
New Insight Into Rigosertib MOA
Connecting Pathways

Premkumar Reddy, Ph.D.

Background: Ras and Raf Function Requires Dimerization



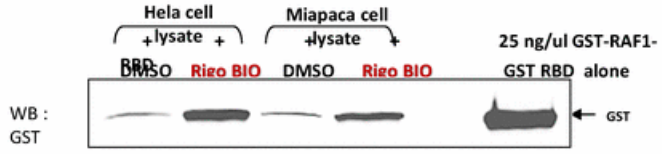
Ras Binding to Raf is Disrupted by Rigosertib



Both B-Raf and C-Raf are hyperphosphorylated on pS/TP sites in ON01910-treated cells. This hyperphosphorylation disrupts the ability of the Rafs to bind actvated Ras.

Rigosertib Binds to a Specific Domain: RAS Binding Domain (RBD)

RAF1-RBD peptide domain- Pull down assay

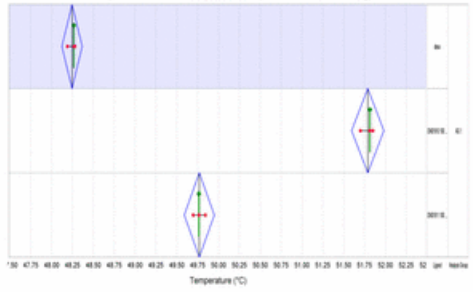


Hela or Miapaca-2 cell lysates were prepared in pull down assay buffer. 25 ng/ul of GST-RBD-RAF1 was added to these cell lysate . DMSO or 1910-BIOTIN was added to the cell lysates and Pull down assay was done using Neutra avidin biotin beads. The beads were washed thrice and boiled in 1x SDS buffer and proteins analyzed by western blot for the presence of GST-RBD protein.

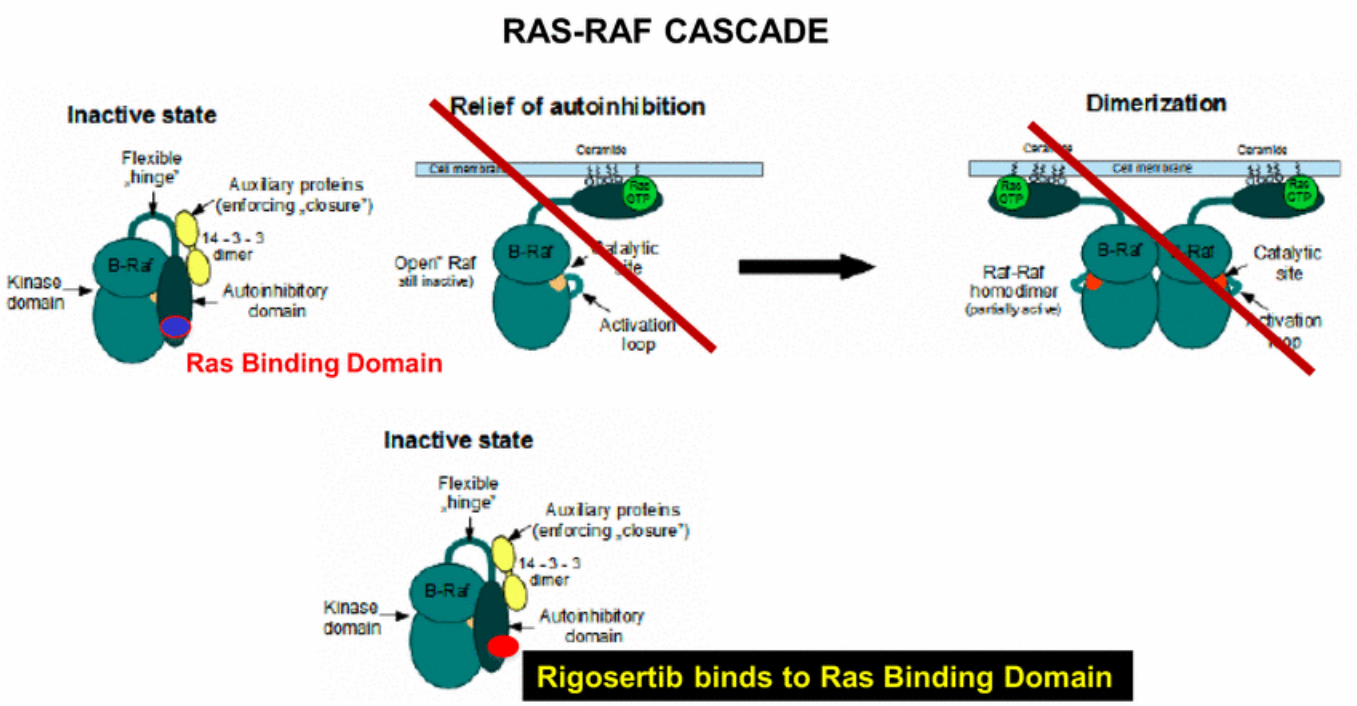
Rigosertib Binding to RBD Analyzed by Thermal Shift Assay

Binding to Ras Binding Domain (RBD)

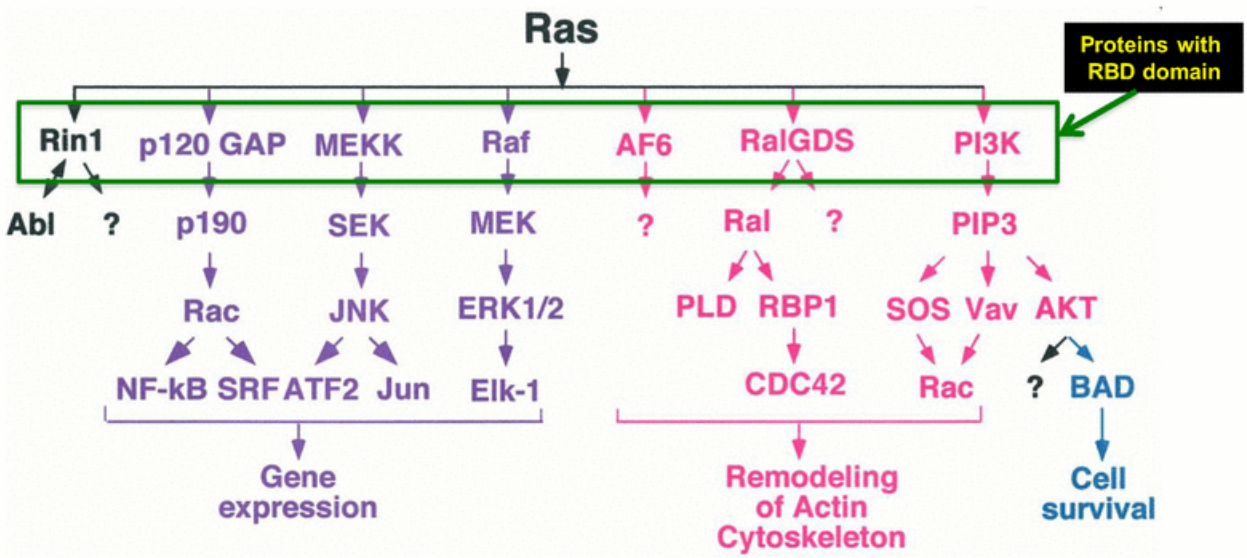
Binding to RBD of c-Raf



Rigosertib Disrupts the Signaling Cascade



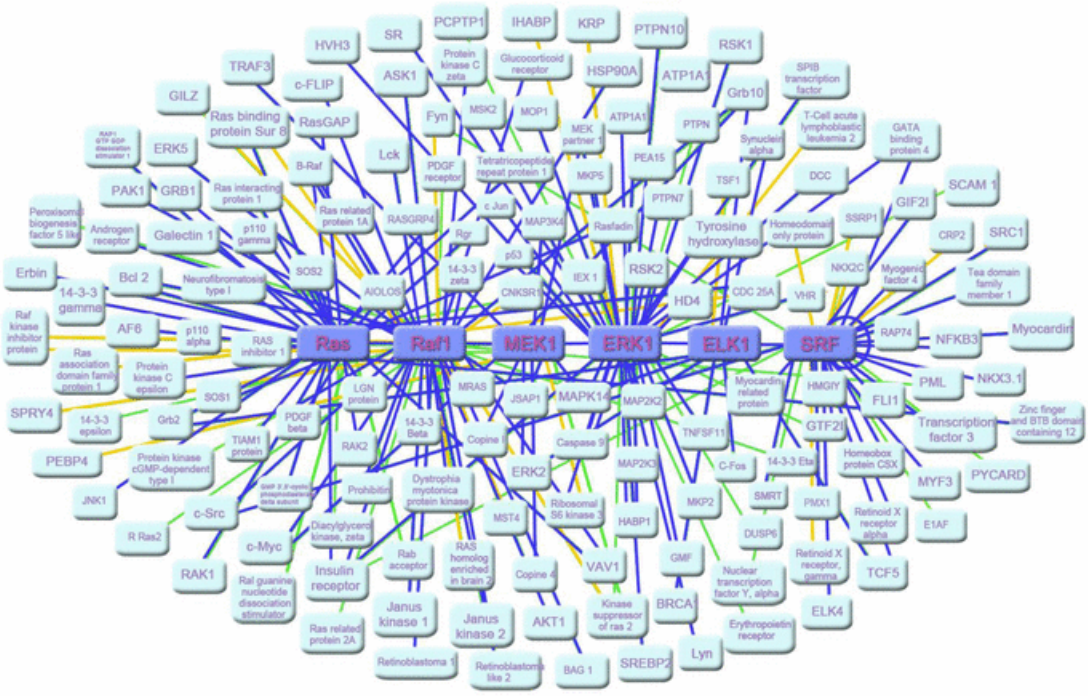
Multiple Critical Pathways Employ the Ras Binding Domain (RBD)



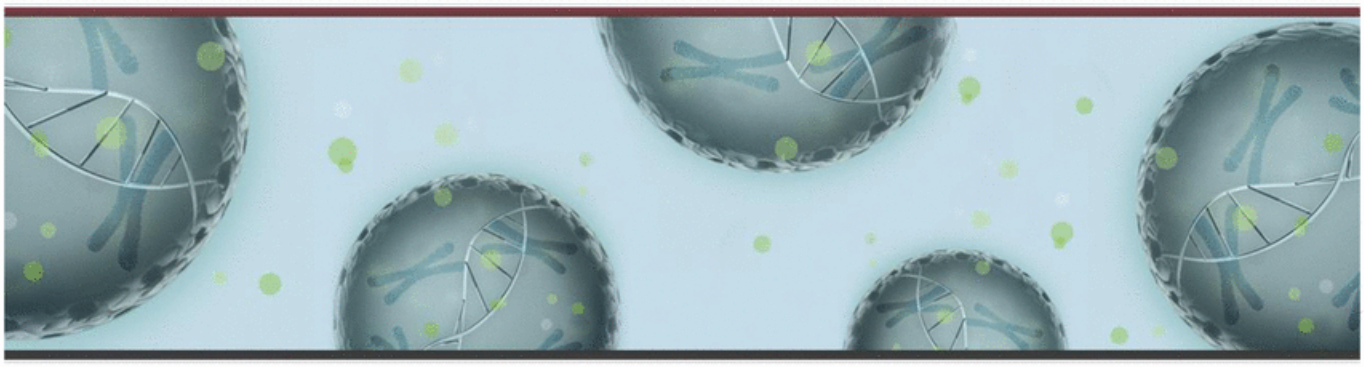
Vojtek A B , and Der C J J. Biol. Chem. 1998;273:19925-19928

jbc

The Ras/Raf Pathway is Central to Signal Transduction



ONCONOVA THERAPEUTICS

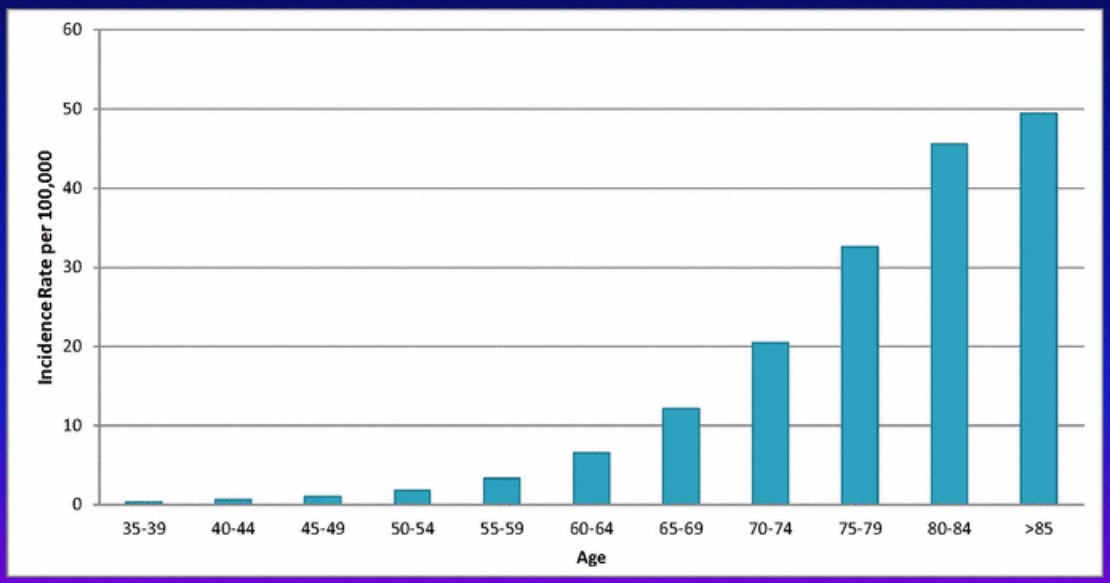


Lower Risk MDS: What's new in 2013?

Azra Raza, M.D.

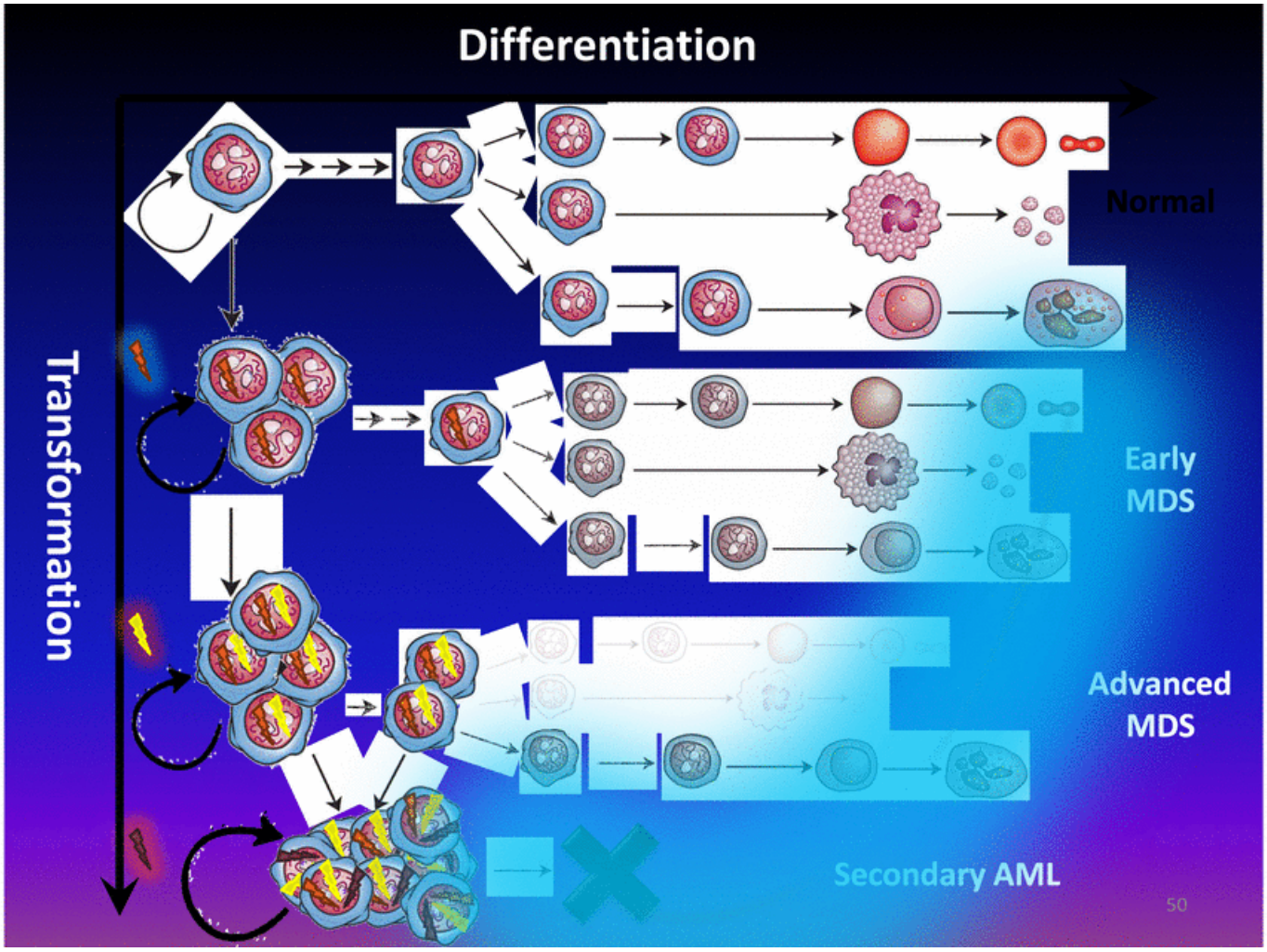
- Epidemiology
- Clonality
- Classification
- Biology
- Treatment

Age-Specific SEER Incidence Rates for Myelodysplastic Syndromes, 2000-2008



Goldberg SL, et al. *J Clin Oncol*. 2010;28(17):2847-2852.

- Epidemiology
- Clonality
- Classification
- Biology
- Treatment



- Epidemiology
- Clonality
- Classification
- Biology
- Treatment

Milestones in Disease Characterization and Treatment

Development	Description	Year(s)
FAB	Morphologic classification	1982
IPSS	Prognostic stratification	1997
WHO	Morphologic classification	2000
IWG	Response criteria	2000
FDA approvals	AZA, DAC, LEN	2004–2005
IWG revised	Response criteria	2006
WPSS	Prognostic stratification	2007
WHO revised	Morphologic classification	2008

FAB = French-American-British; IPSS = International Prognostic Scoring System; WHO = World Health Organization; IWG = International Working Group; WPSS = WHO-based PSS; AZA = azacitidine; DAC = decitabine; LEN = lenalidomide.
Aul et al, 2007; Gatterman, 2008; Cheson et al, 2006; Ghoshal et al, 2007; Hazarka et al, 2008; Alessandrino et al, 2008; Weinberg et al, 2008.

IPSS for Risk Stratification

	Score Value				
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone marrow blasts	< 5%	5% to 10%	--	11% to 20%	21% to 30%
Karyotype*	Good	Intermediate	Poor	--	--
Cytopenias†	0/1	2/3	--	--	--

Greenberg P et al. Blood. 1997;89:2079-2088.

IPSS

Accurately predicts prognosis in ~40% patients at best

Revised IPSS -- 2012

Table 3. IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

— indicates not applicable.

SURVIVAL BY R-IPSS

	No. of patients	Very low	Low	Intermediate	High	Very high
Patients, %	7012	19	38	20	13	10
Survival, all*		8.8	5.3	3.0	1.6	0.8

Greenberg P L et al. Blood 2012;120:2454-2465

MDS Heterogeneity

Further refinement will only emerge when biologic information is added to the classification

Summary of Incidence and Classification

- Heterogeneous group of bone marrow stem cell diseases
- 10-15,000 new cases/year in the US
- Can be essentially divided into lower (low and Int-1) and higher (Int-2 and high) risk MDS
- Approximately 75% are lower risk at diagnosis

- Epidemiology
- Clonality
- Classification
- Biology
- Treatment

APOPTOSIS

- The paradox of cellular BM with peripheral cytopenias explained on the basis of premature apoptosis
- All lineages prone to apoptosis
- Mediated via pro-inflammatory cytokines like TNFa, TGFb, IL1b

Raza A et al. 1995 Blood 86; 268-79

Point Mutations in MDS Are Associated With Clinical Features and Are Independent Predictors of Overall Survival

Rafael Bejar, Kristen Stevenson, Omar Abdel-Wahab, Katherine Lin, Randall McAuley, Marie McConkey, Kevin Cheung, Naomi Galili, Guillermo Garcia-Manero, Hagop Kantarjian, Azra Raza, Ross Levine, Donna Neuberg, Benjamin Ebert

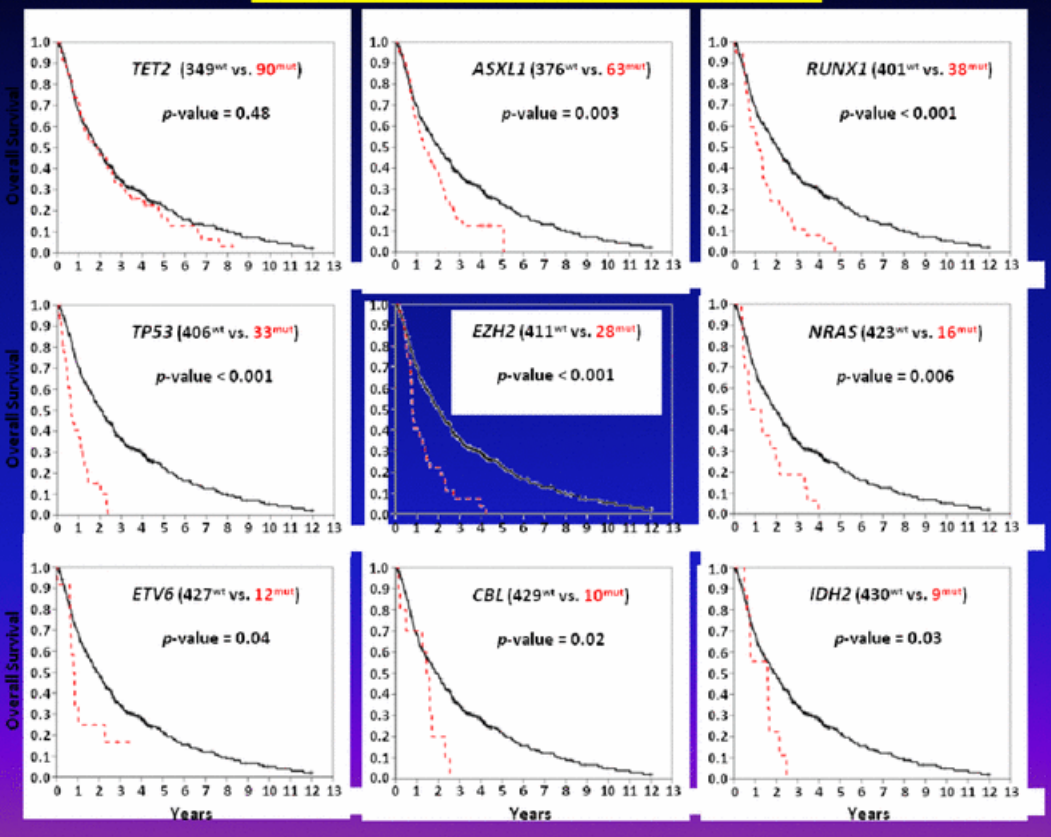
N Engl J Med 364:2496-2506, June 2011

OncoMap

- 438 MDS patients (with 200 matched controls) examined for mutations in cancers genes
- 1233 known oncogenic mutations in over 130 cancer-related genes using a high-throughput, mass spectroscopic genotyping platform

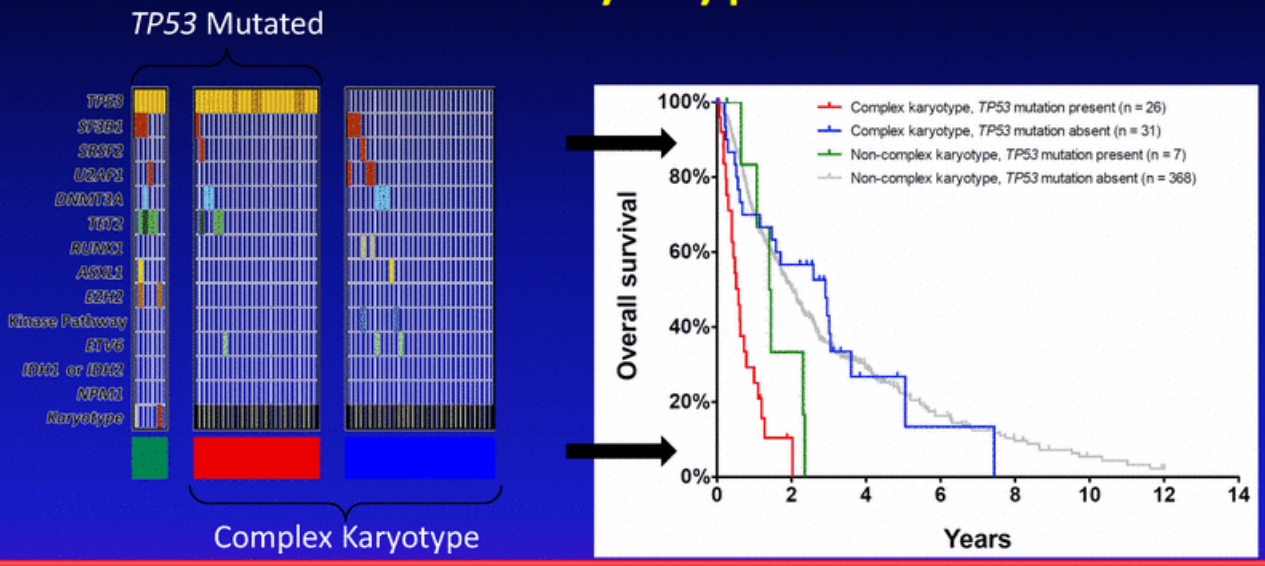
ASH 2010

Survival Curves II



Kristen Stevenson & Donna Neuberg

TP53 Mutations and Complex Karyotypes



The adverse prognostic impact of the complex karyotype is entirely driven by its frequent association with mutations of *TP53*

Bejar R, et al. *N Engl J Med.* 2011;364(26):2496-2506; Bejar R, et al. *N Engl J Med.* 2011;364(26, supp 1):2496-2506;

Conclusions

- Point mutations are common in MDS
  52% of those with normal cytogenetics
- Mutations of 5 genes, present in over 30% of samples are independent predictors of overall survival:

  TP53 *EZH2* *ETV6* *RUNX1* *ASXL1*
- The adverse prognostic impact of the complex karyotype is entirely driven by p53 mutations

Abnormalities in the RNA Splicing Machinery associated with dysplasia

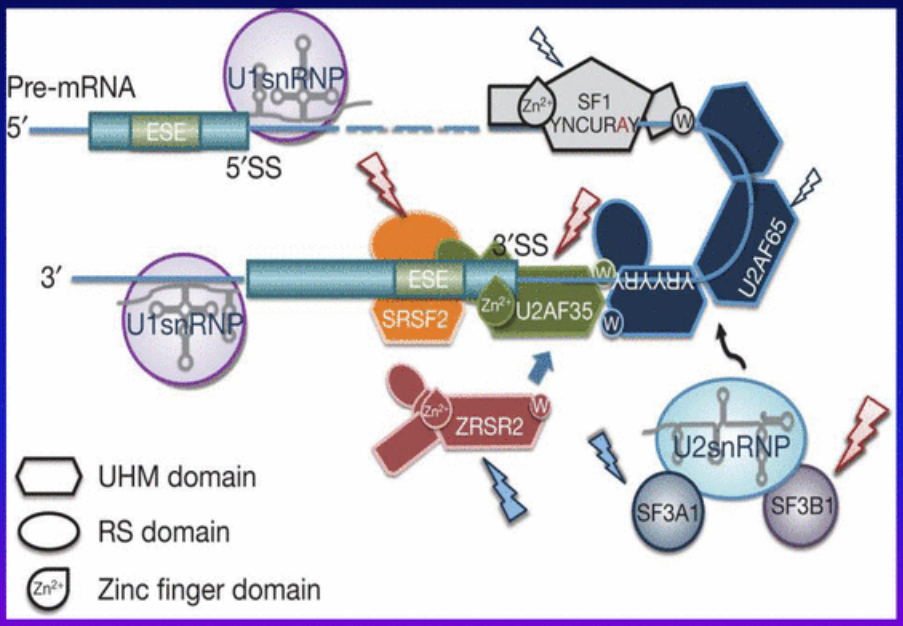
Three new studies by 2 groups used whole exome sequencing of paired tumor and control DNA to further identify the genetic changes that may be causative events in the evolution of MDS

I. Frequent pathway mutations of splicing machinery in myelodysplasia
Kenichi Yoshida, Masashi Sanada, Yuichi Shiraishi, et.al.
Nature 478, 64-69 doi:10.1038/nature10496 2011 Sept 11

II. Somatic SF3B1 Mutation in Myelodysplasia with Ring Sideroblasts
E. Papaemmanuil, M. Cazzola, J. Boultwood, et.al
N Engl J Med 2011; 365:1384-1395 October 13, 2011

III. Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms
Malcovati L, Papaemmanuil E, Bowen DT, et. al.
Blood. 2011 Oct 12. [Epub ahead of print]

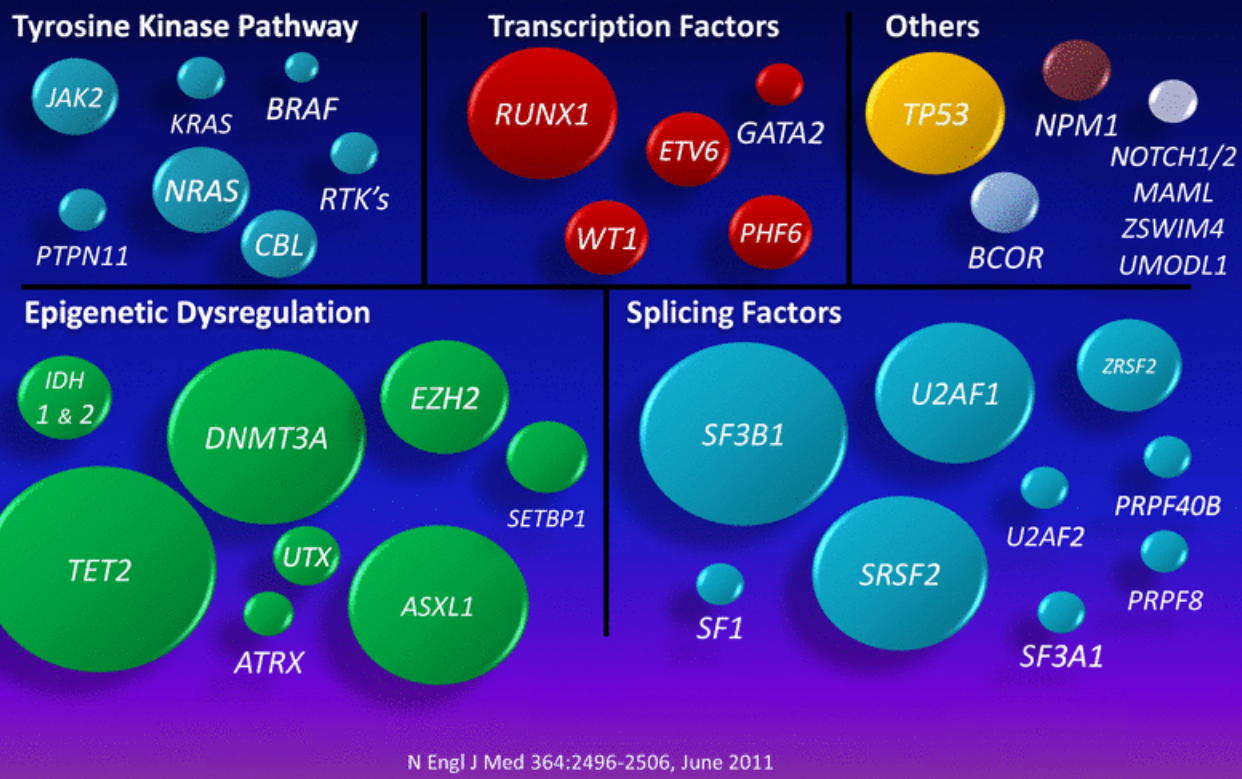
Mutually exclusive mutations of the splicing machinery genes found in various myeloid malignancies



Nature 478, 64-69 doi:10.1038/nature10496 2011

Epigenetics

Genes and Pathways affected in MDS



N Engl J Med 364:2496-2506, June 2011

- Epidemiology
- Clonality
- Classification
- Biology
- Treatment

- Curative
  - Stem cell transplant
- Palliative
  - Erythroid stimulating agents
  - Lenalidomide
  - Hypomethylating agents
  - Experimental therapies

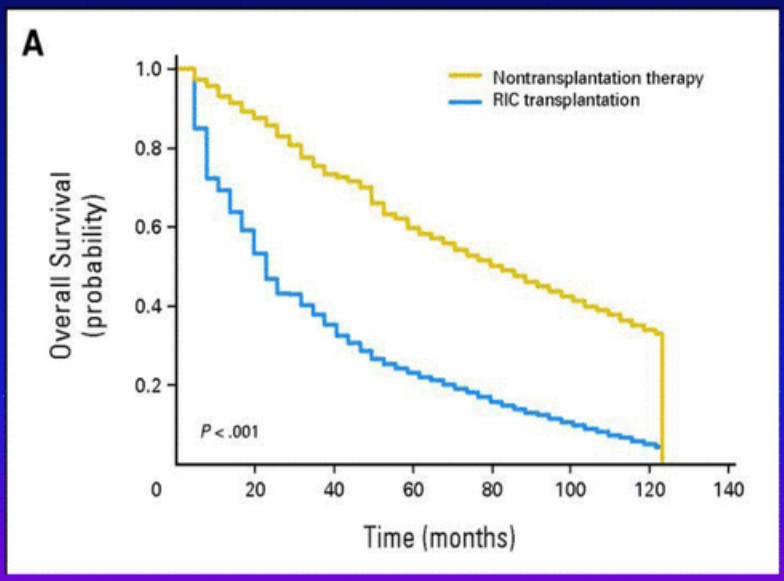
Bone Marrow Transplantation is the only potentially curative option

Approximation of Life Expectancy for Alternative Transplant Strategies (Years)

	Transplant at Diagnosis	Transplant in 2 Years	Transplant at Progression
Low	**6.51**	**6.86**	**7.21**
Int-1	**4.61**	**4.74**	**5.16**
Int-2	**4.93**	**3.21**	**2.84**
High	**3.20**	**2.75**	**2.75**

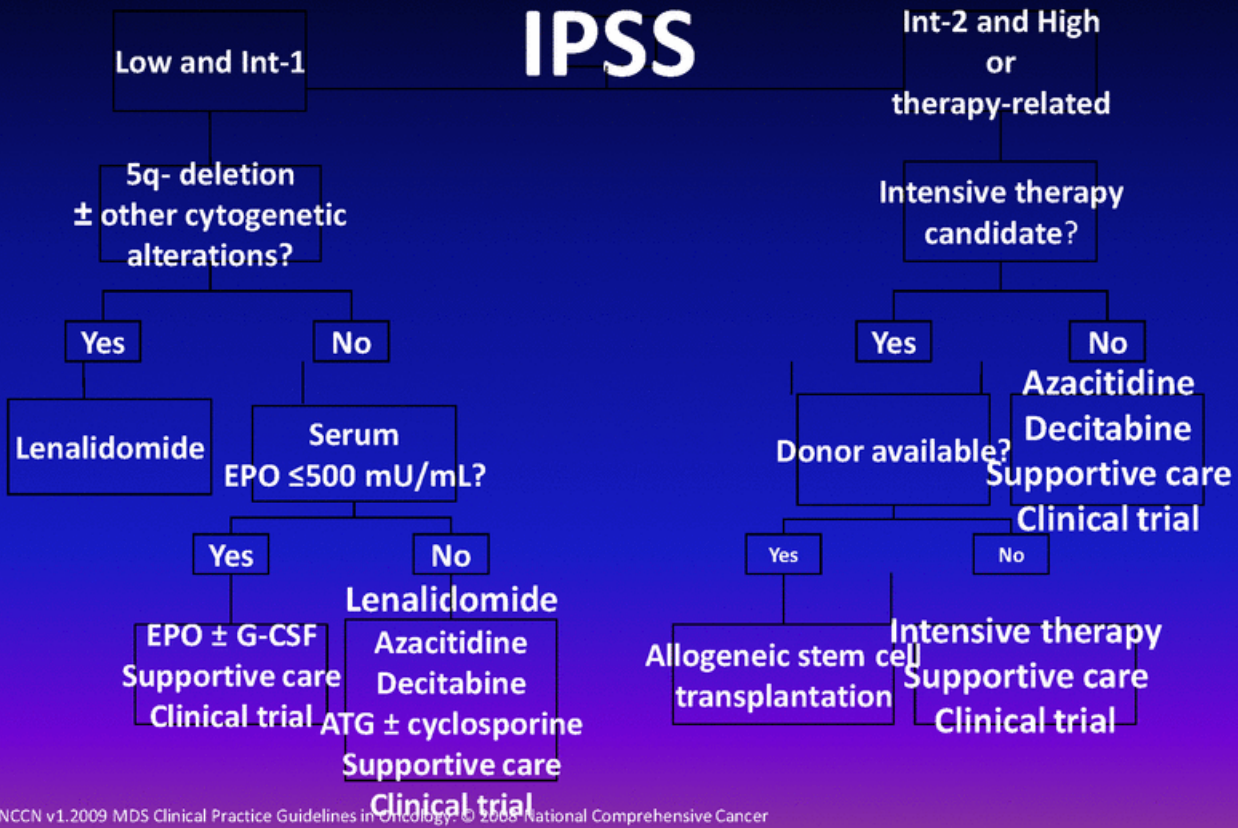
Cutler C, et al. *Blood* July 2004; 104:2

Reduced Intensity Conditioning SCT for Low/Int-1 Risk MDS between 60-70 years



Koreth J et al. JCO 2013;31:2662-2670

NCCN Practice Guidelines for MDS



NCCN v1.2009 MDS Clinical Practice Guidelines in Oncology. © 2008 National Comprehensive Cancer Network, Inc. http://www.nccn.org/professionals/physician_gls/PDF/mds.pdf

Anemia

- At diagnosis, ~87% of patients have anemia (WHO criteria Hb<12 g/dl)
- ~30% are transfusion-dependent
- Anemia and transfusions more in higher (65%) than in lower-risk MDS (37%)

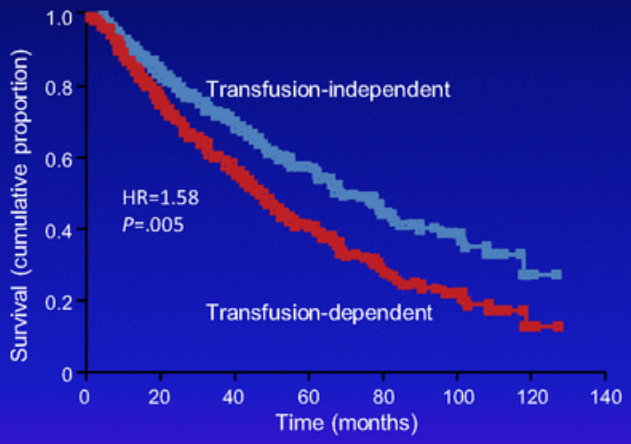
Best Practice & Res Clin Haemato (2013) 1–10

Prognostic Significance of Anemia

- Impairs daily physical, emotional, cognitive and social functioning
- Degree of anemia has an impact both on overall and leukemia-free survival
- Transfusion therapy might improve anemia related symptoms but require frequent visits to the hospital with impact on social and emotional functioning

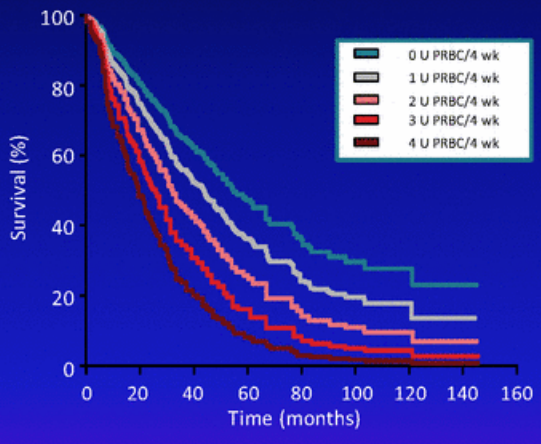
Severity of Transfusion Requirement May Correlate With Worse Overall Survival

Cumulative Probability of Survival By Transfusion Dependency[1]



- Cumulative probability of survival among 374 patients diagnosed with MDS between 1992 and 2002

Correlation Between Degree of Transfusion Dependency and Survival[2]



- Survival based on transfusion requirement in 426 patients diagnosed with MDS between 1992 and 2004

HR, hazard ratio; U PRBC/4 wk, units of packed RBCs required every 4 weeks.

1. Cazzola M, Malcovati L. *N Engl J Med*. 2005;352(6):536-538. 2. Malcovati L, Della Porta MG, Cazzola M. *Haematologica*. 2006;91(12):1588-1590.

Recombinant Erythropoietin

- Two recombinant human erythropoietins are available in the US: Erythropoietin and Darbepoetin
- Patients with lower-risk MDS without ring sideroblasts had a higher probability of response
- Responses in RARS no different than placebo

Erythropoietin in combination with other growth factors

- A Nordic phase II study showed that the addition of G-CSF could induce erythroid responses in patients resistant to Epo, especially those with RARS
- A US phase II study showed that patients responding to the combination could lose their response when G-CSF was withdrawn, and regain it when G-CSF was reintroduced

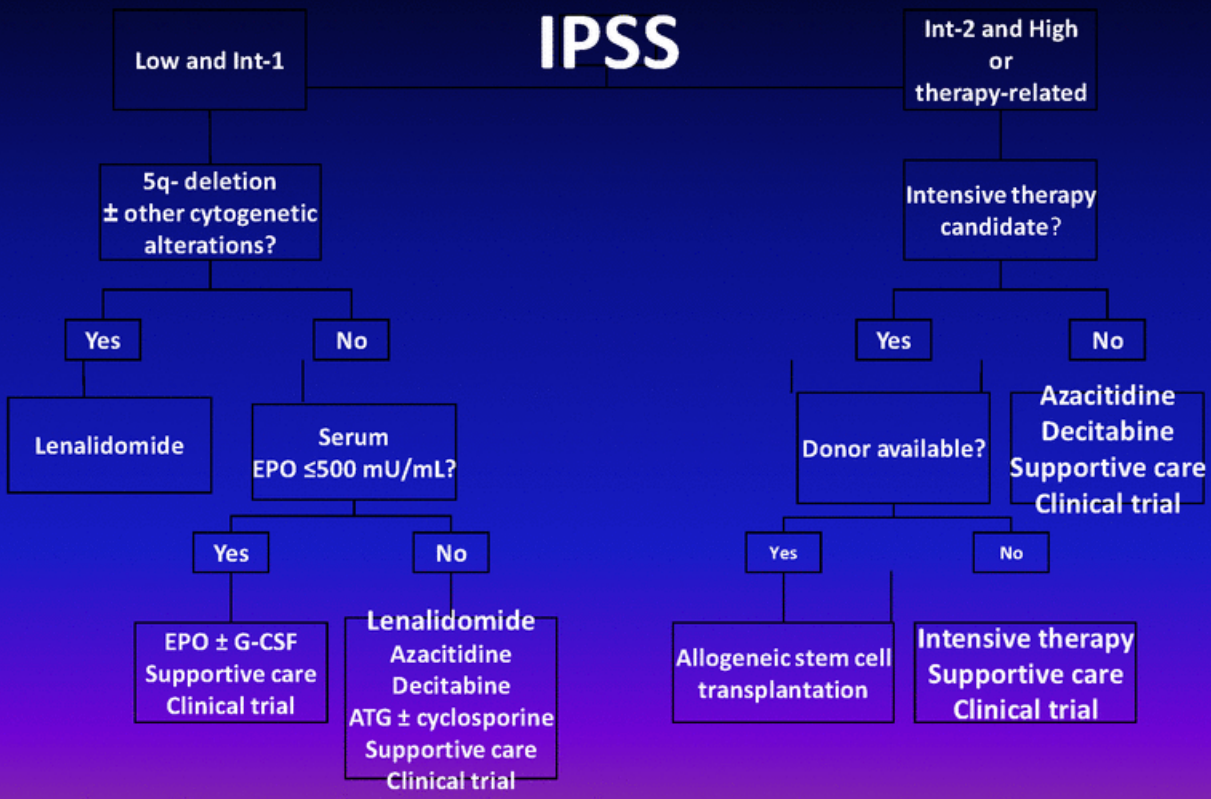
Best Practice & Res Clin Haemato (2013) 1

Erythropoietin in MDS

- Mean response rate: 16% to 20%
- Predictors for good response were serum EPO level
  < 500 U/L and lack of previous need for transfusion
- Most responses to ESA occur within 8 weeks of treatment, some patients respond after 12 weeks

Ludwig H. Semin Oncol. 2002;29(3 suppl 8):45-54. Hellström-Lindberg E. Br J Haematol. 1995;89:67-71.
Casadevall N, et al. Blood. 2004;104:321-327.

NCCN Practice Guidelines for MDS



Lenalidomide

- Thalidomide analogue; has immunomodulatory, antiangiogenic, and antineoplastic properties
- Approved for use in
  - Transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with del(5q) with or without additional abnormalities

RESPONSE TO Lenalidomide Transfusion Independence

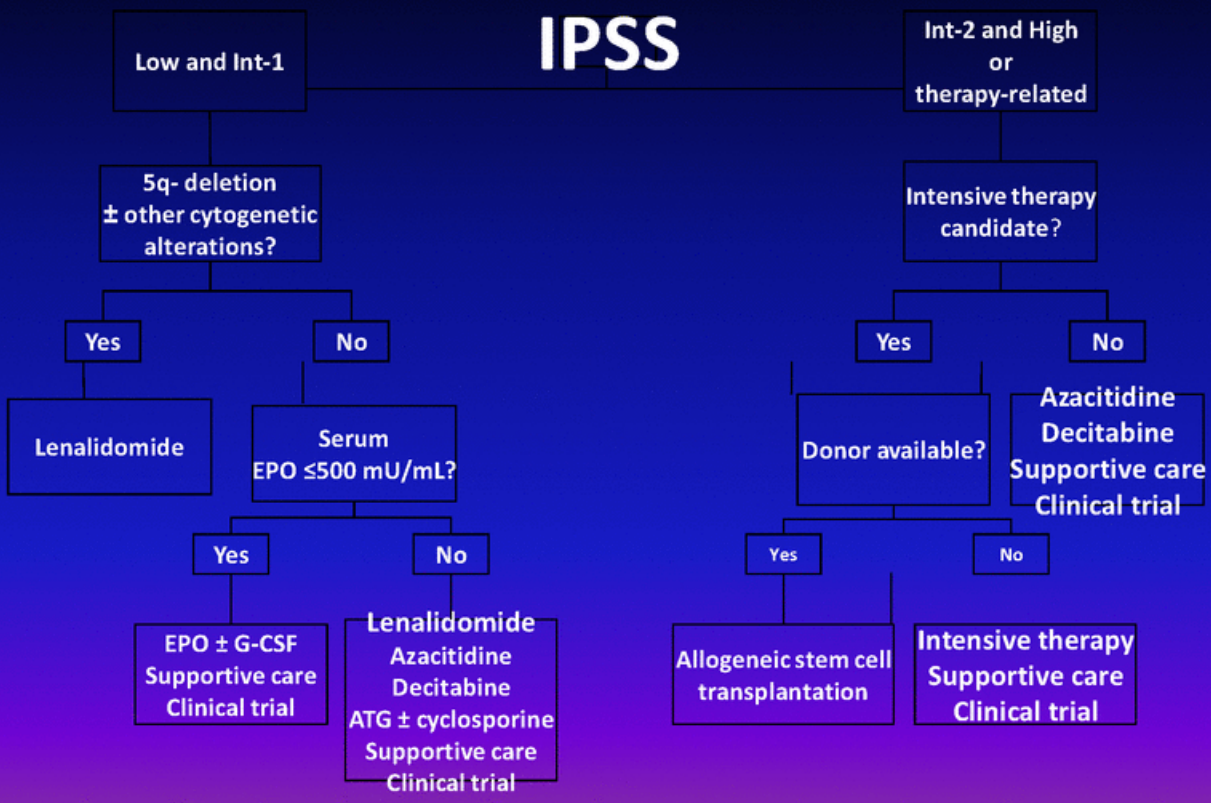
- 67% patients with del(5q)

(List et al NEJM, 2007)

- 26% patients without del(5q)

(Raza et al, Blood, Jan 2008)

NCCN Practice Guidelines for MDS



NCCN v1.2009 MDS Clinical Practice Guidelines in Oncology. © 2008 National Comprehensive Cancer Network, Inc. http://www.nccn.org/professionals/physician_gls/PDF/mds.pdf

FDA approved Hypomethylating Agents

- Azacitidine
- Decitabine

Azacitidine induces responses and prolongs overall survival compared to conventional care regimens in higher-risk MDS

However, limited data are available in patients who have lower risk MDS

HMA in Lower Risk MDS

- In a phase II trial randomizing AZA and AZA + EPO in transfusion dependent lower-risk MDS resistant to ESA ~17% RBC-TI suggesting lower efficacy in patients who are clearly ESA resistant

Fenaux et al Blood 2013 May 23;121(21):4280

Summary of Treatment Options for Lower Risk MDS (non-del5q)

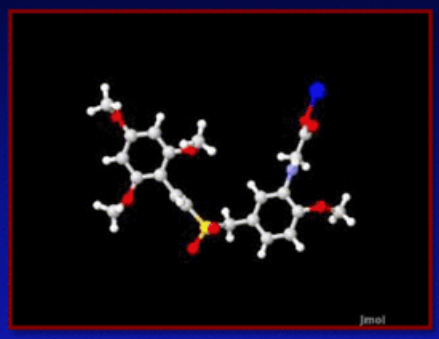
- ESA (~20% response)
- Lenalidomide (~10% patients)
- Hypomethylating agents (~17% patients)

Experimental Trials

- Rigosertib (Multi-kinase inhibitor)
- Telintra (Glutathione S1 Transferase inhibitor)
- Arry-614 (p38-Tie2 inhibitor)
- ACE-011 (TGFb inhibitor)

Rigosertib is a dual pathway inhibitor

- Targets PI3K survival + PLK mitotic pathways
- Small molecule, first in class of unsaturated sulfones
- 2 formulations: IV and oral
- Active as single agent or in combination
- Selective to cancer cells, sparing normal cells
  - ✓ Validated in the clinic
  - ✓ More than 850 patients treated
- Activity demonstrated in MDS and solid tumors



70 mg Softgel

280 mg Softgel

Oral Rigosertib

- Prior Phase I Study of Oral Formulation in 37 MDS patients (R Komrokji et al, BJH 2013 in press):
- Absolute bioavailability of oral Rigosertib = 35%
- In High-risk patients
  - 2 BM CR in RAEB-1 pts previously treated with Azacitidine
  - 1 Platelet and 1 ANC responses
- In Low-Int-1 transfusion dependent patients
  - 4 cases of transfusion independence and
  - 1 erythroid response
- Toxicity noted ay 560mg RPTD: urinary frequency, dysuria, hematuria

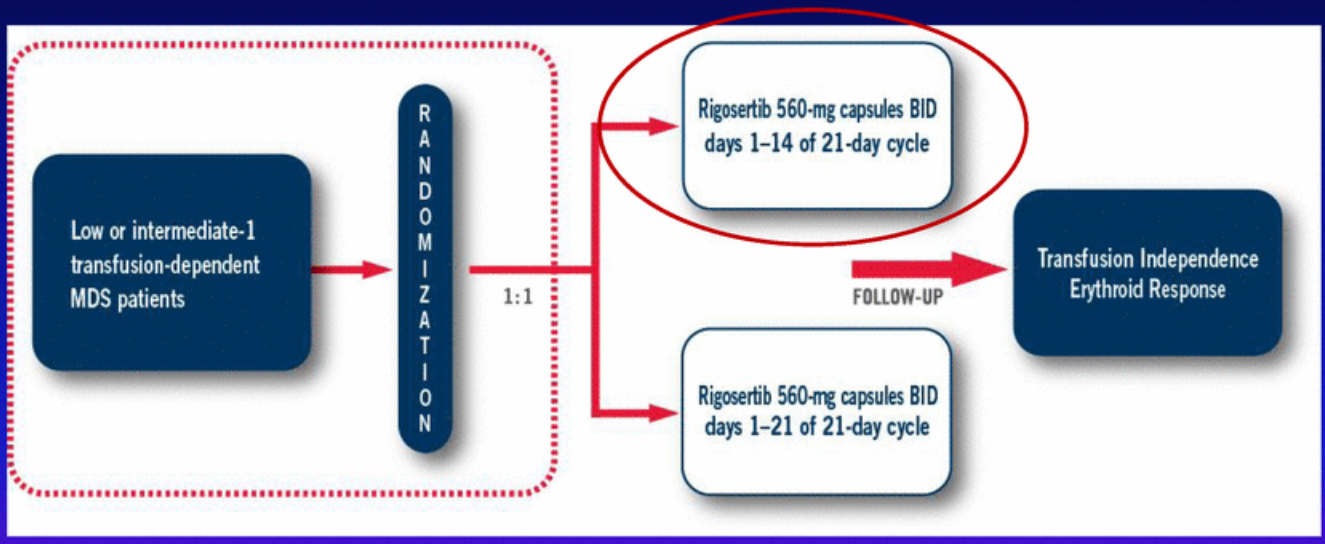
Oral Rigosertib: Phase II

Disclosures

- **Raza, Mukherjee, Eisenberger, Tycko, Al-Kali, Tibes, Spitzer: Onconova Research Funding.**
- **Wilhelm: Onconova: Employment, Equity Ownership.**
- **Lee, Gallili, Ali, Mears: No relevant conflicts of interest to disclose**

Study Design of Oral Rigosertib in Lower Risk Transfusion Dependent MDS Patients

60 patients enrolled as of 11/5/2013

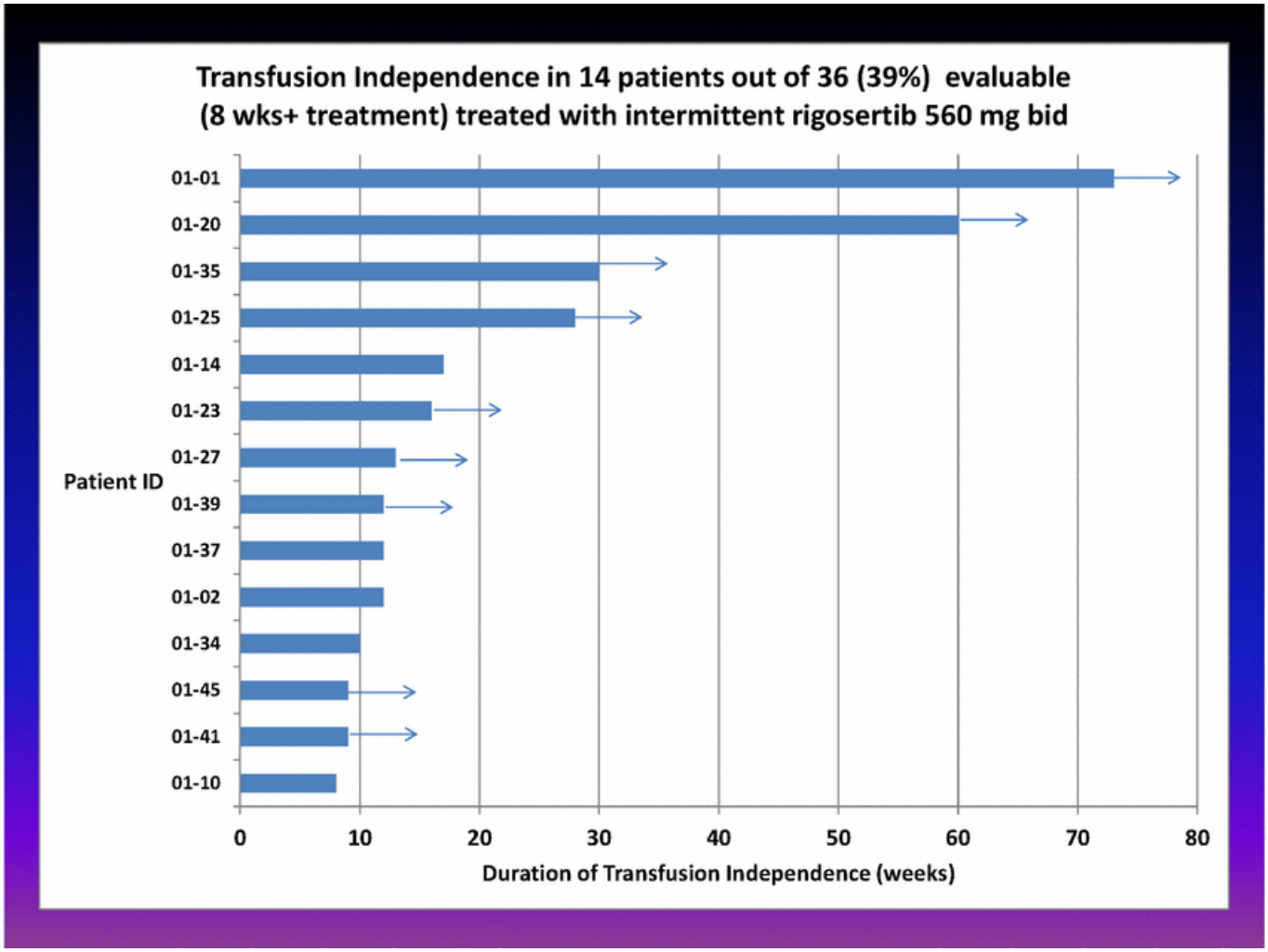


Only 9 patients randomized to continuous dosing
Protocol amended to enroll further patients on intermittent dosing (N=51)

Characteristic	N=60
Median Age, years (range)	74 (54-86)
Male/Female	41/19
Median years from MDS diagnosis (range)	2 (0-12)
Median number prior MDS therapies (range)	2 (0-6)
Prior treatment with HM agents	28
Prior treatment with Lenalidomide	20
Prior treatment with ESAs or EPO>500 mU/mL	46
Median pre-study EPO (mU/mL) (range)	128 (14-11199)
Median# (range) RBC transfusions in 8 weeks prior study	4 (4-11)
# patients with thrombocytopenia grade 3+	16
# patients with neutropenia grade 3+	15
# patients with anemia grade 3+	14
IPSS risk at screen (Low/Int-1)	12/46/2
ECOG PS (0/1/2)	41/11/6
FAB/WHO Classification	
Refractory Anemia	19
Refractory Cytopenia with Multiple Dysplasia	33
RAEB-1	7
RAEB-2	1
Cytogenetics (Normal/Tri8/del5q/Other)	29/7/3/21

Demographics

FAB/WHO Classification	
Refractory Anemia	19
Refractory Cytopenia with Multiple Dysplasia	33
RAEB-1	7
RAEB-2	1
Cytogenetics (Normal/Tri8/del5q/Other)	29/7/3/21



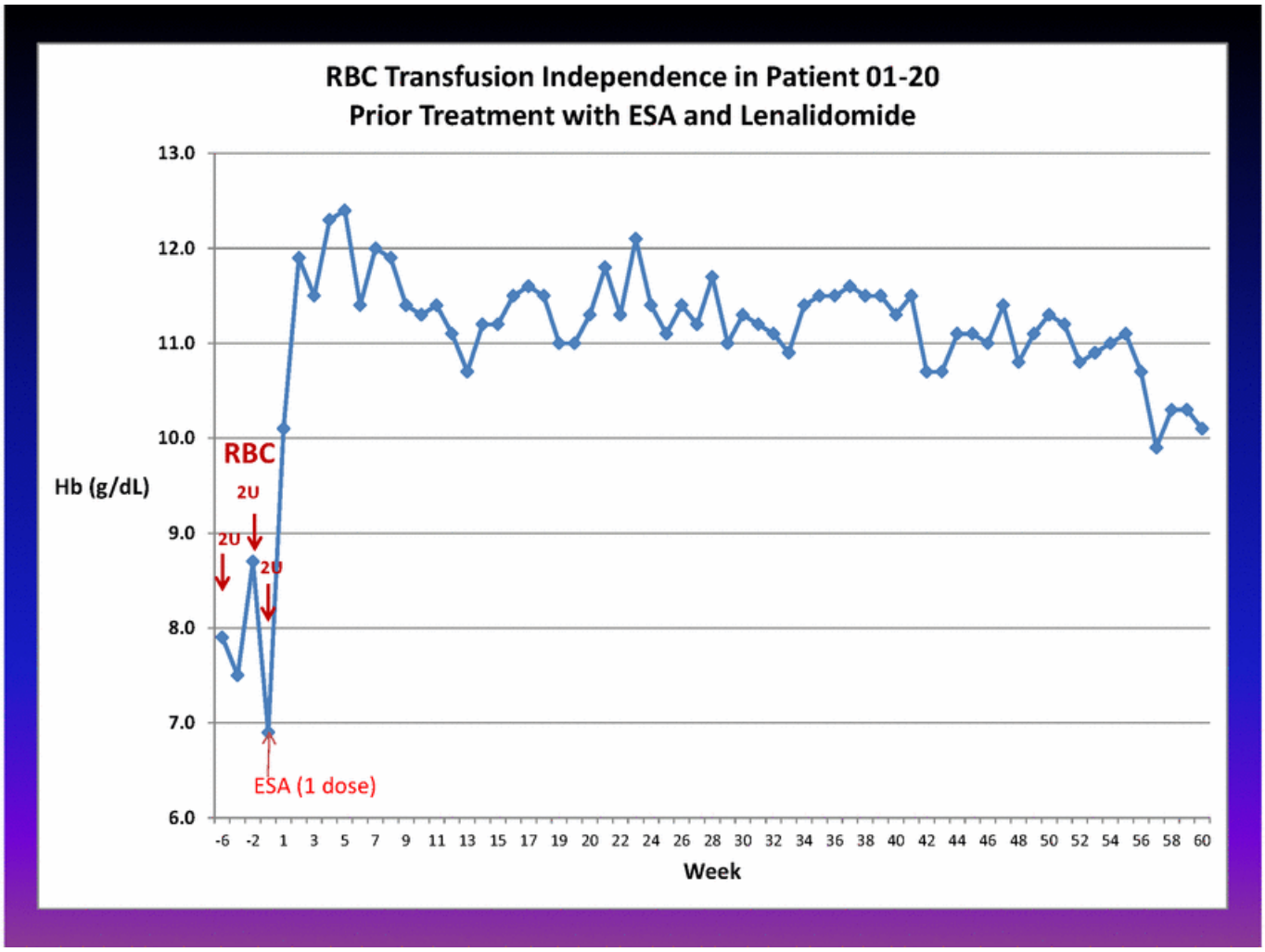
Rigosertib Induces Transfusion Response Alone or Combined with ESA

Concomitant ESA		None	1 dose	2 to ≤ 12 wks	≥ 12 wks	Total
No Prior ESA	N pts	2	0	2	1	5
	TI	0	0	0	0	0 (0%)
Prior ESA	N pts	4	4	12	12	32
	TI	2	2	6	4	14 (44%)
Total	N pts	6	4	14	13	37
	TI	**2 (33%)**	**2 (50%)**	**6 (43%)**	**4 (31%)**	**14 (38%)**

TI=at least 8 weeks transfusion independence;
ESA=erythrocyte stimulating agent; wks=weeks

Serum Epo in 5 patients with no prior ESA

Study #	Epo
3	41
11	125
15	829
25	15
28	31
40	105



Incidence of Urinary Toxicity (gr=grade)

Dosing	Total N	gr1	gr2	gr3	Incidence gr 2+	Overall incidence
Continuous 560mg bid	9	0	4	2	67%	67%
Intermittent 560mg bid	35	6	15	4	54%	71%
Intermittent 560mg/280mg	13	2	1	0	8%	23%

Incidence of Urinary Toxicity in Intermittent Dosing Group

- **Nineteen of the 35 patients (43%) developed Gr2+ urinary toxicity and 4/35 (11%) developed grade 3 urinary toxicity**
    - **Fifteen patients (43%) developed Gr2+ urinary urgency (14 Gr2/1 Gr3). Seven patients (20%) developed Gr2+ dysuria (6 Gr2/ 1 Gr3); 6 patients (17%) developed Gr2+ hematuria (3 Gr2/3 Gr3); 2 patients (6%) developed Gr3 cystitis.**
- **New intermittent 560 mg am/280 mg afternoon dosing selected to minimize nocturnal symptoms of urinary urgency.**
    - **Thirteen patients have received this new dosing regimen for a median duration of 6 weeks (range: 1-12 weeks). Only one patient so far developed grade 2 urinary toxicity (urinary tract infection).**

Other Toxicities

Few other grade 3+ drug related adverse events:

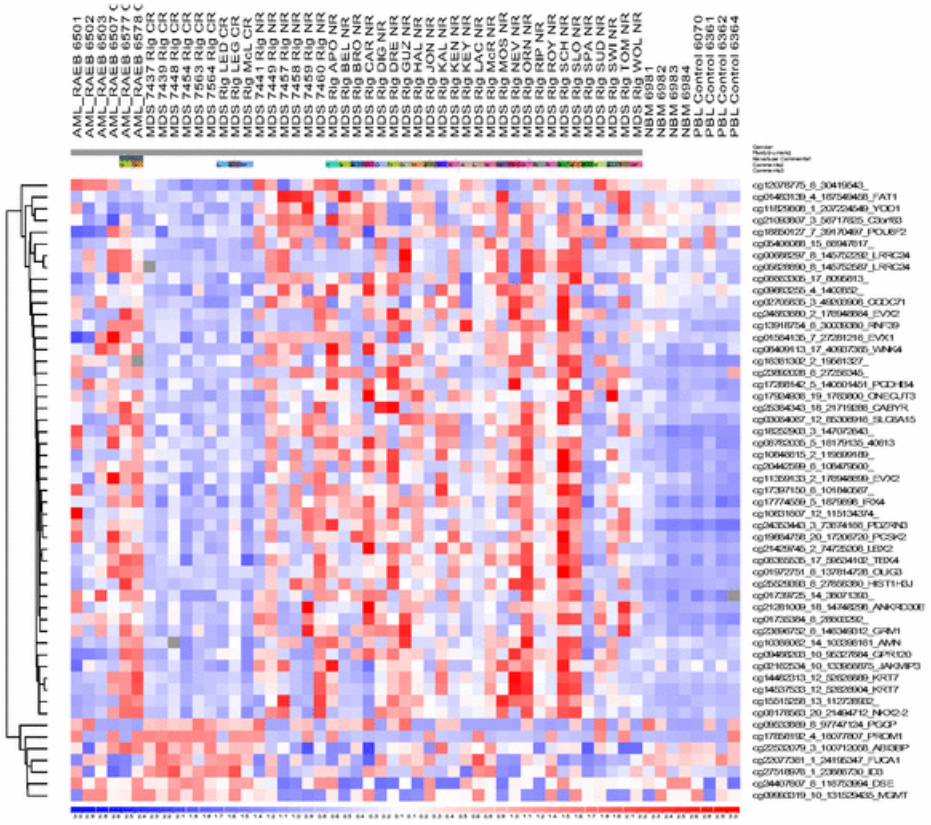
- **3 neutropenia, 1 leucopenia**
- **1 hyponatremia**
- **1 transitional cell carcinoma of the bladder**

Genomics - Methods

- Methylation profile of pretherapy BM using a discrete panel of DNA methylation biological markers comprising fifty differentially methylated genes
- Illumina 450K arrays as main method followed by validations of selected loci using bisulfite sequencing
- Analysis of DNA methylation profile of multiple CpG dinucleotide sequences
- Test samples classified into two distinct types (responders or non responders), whereas patients displaying one type of gene methylation profile, or “DNA methylation signature,” are more likely to be responsive to rigosertib treatment.

Panel of DNA methylation biological markers associated with differentially methylated genes

RERE, CASZ1, KIAA1026, ID3, ADCY10, RNASEL, PGBD5, AKT3, SLC8A1, PLEKHH2, SGPP2, GNAT1, ALDH1L1, AGTR1, MSX1, KCNIP4, G3BP2, FLJ44606, PCDHA1, PCDHGA4, ARSI, CPEB4, SCAND3, BAT2, HLA-DRB1, MOCS1, SPACA1, LOC389458, EVX1, WNT16, SNAI2, HEY1, CRTAC1, HCCA2, C11orf58, AHNAK, ASAM, GALNT6, GALNT9, FLT1, DZIP1, ALOX12P2, CCDC144B, TANC2, ONECUT3, MRI1, FOSB, CDH22, CLDN14 and *SEC14L4*



Genomic Results

- Functional annotation of hypo and hypermethylated genes which best distinguished CRs from NRs showed that the genes most affected by methylation were related to regulation of transcription followed by genes involved in cell-cell adhesion, inflammatory response, apoptosis and proliferation
- Ongoing work to select small gene panel of best markers to predict response

Conclusions

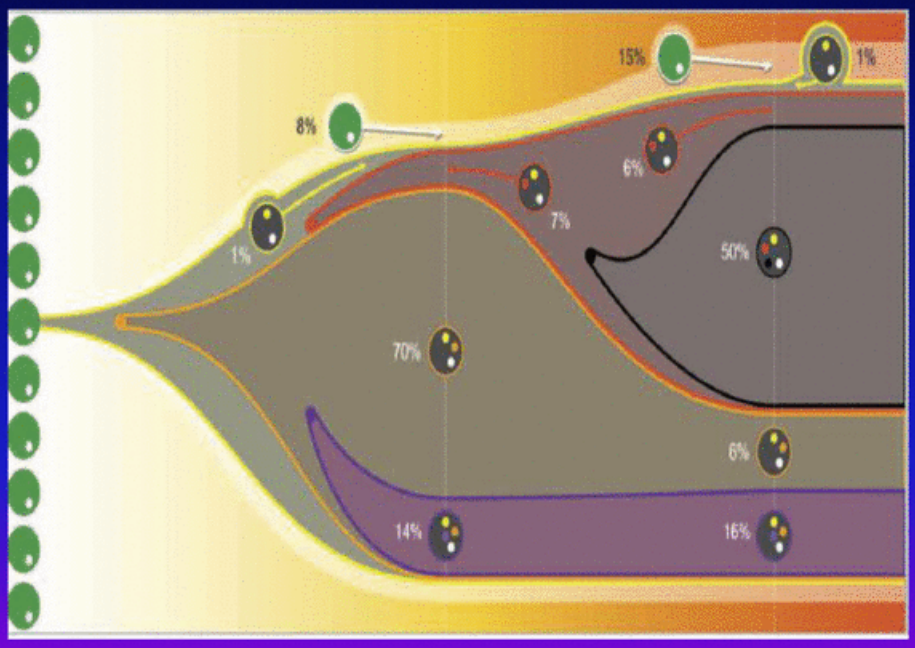
- Rigosertib active in inducing transfusion responses, HI-N and bone marrow response in ESA refractory transfusion dependent lower risk MDS patients
  - Combined response rate (TI, HI and BMCR) = 53% in 36 patients (50%) treated for at least 8 consecutive weeks with rigosertib intermittent dosing
- Urinary tolerability improved with new intermittent 560/280 mg rigosertib dosing regimen
- Identification of an epigenetic signature able to predict transfusion response

Future challenges?

Response Duration

Those patients who achieve transfusion independence may revert back to transfusion dependence over time

Clonal Evolution



Walter MJ, et al. *N Engl J Med*. 2012;366(12):1090-1098.

Sequential Use of Effective Therapies

- Erythroid Stimulating Agents
- Lenalidomide
- Hypomethylating Agents
- Experimental Trials

If I had all the money in the world, what would be my dream research project for MDS?

- Art is I but science is We
- Use the latest technology to study individual patients and use targeted therapy
- Study the same patient longitudinally and identify expansion of the next clone

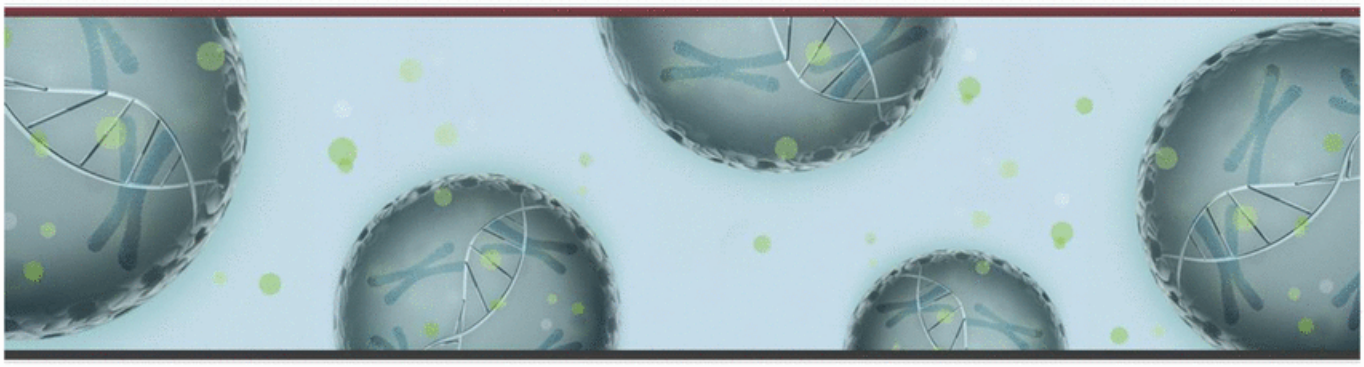
Future Directions

- Serial monogamy…individualize therapy serially
- MDS can be converted into a disease that patients can live with and not die from

COLUMBIA UNIVERSITY MEDICAL CENTER, NEW YORK

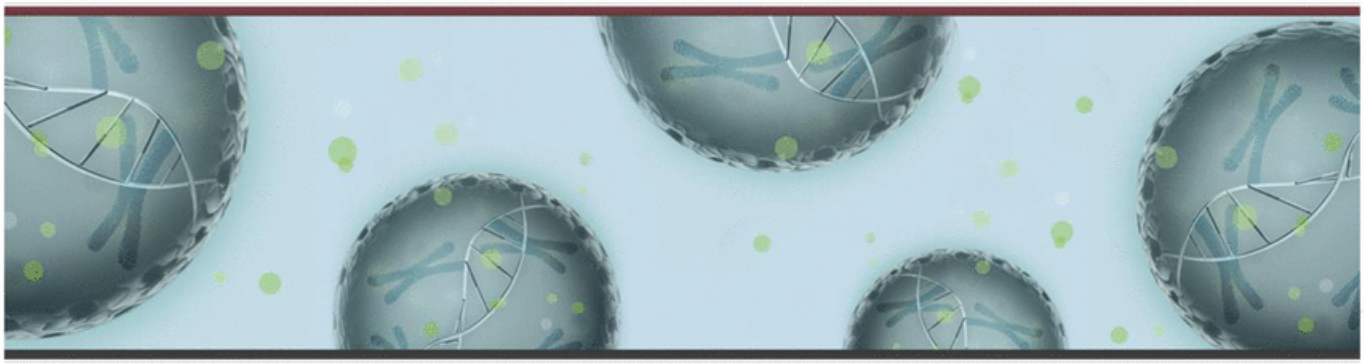
THE END
THE END
THE END
THE END

ONCONOVA THERAPEUTICS



Question & Answer Session

-Break-



Combination Therapy for High Risk MDS

Lewis R. Silverman, M.D.

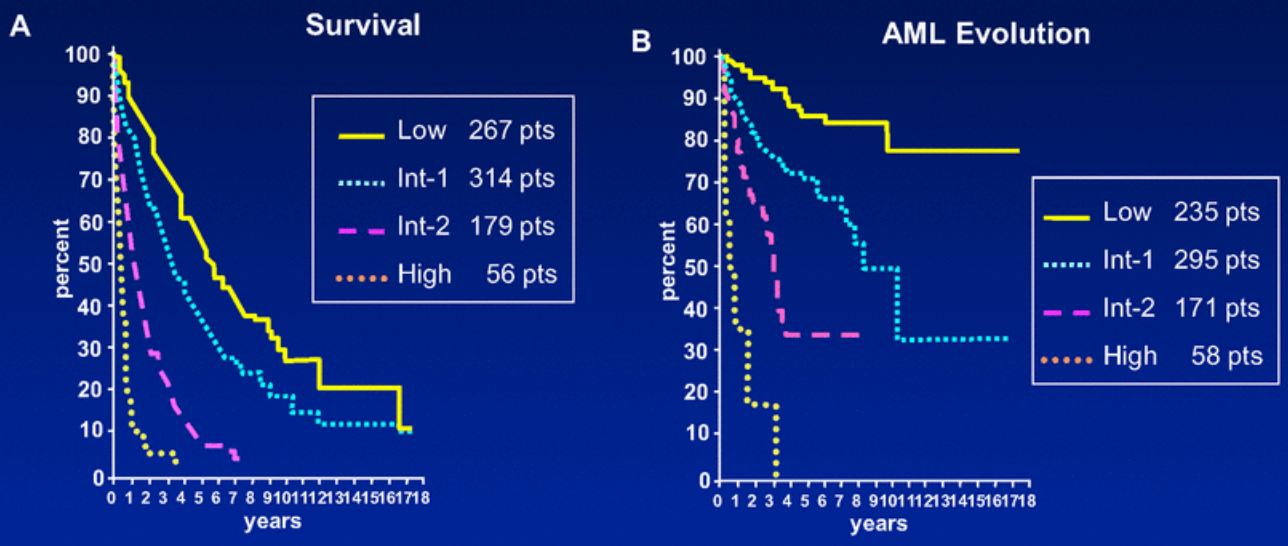
Higher Risk Myelodysplastic Syndrome

- Disease of older patients, median age > 60
- Clonal disorder - multilineage hematopoietic progenitor
- Dominant feature: Ineffective hematopoiesis with peripheral blood cytopenias
- Bone Marrow Failure
  - Majority succumb from infection or bleeding
  - Transformation to acute leukemia in 35 to 40%
- High Mortality Rate

Approach to Patients with Lower and Higher Risk Myelodysplastic Syndrome

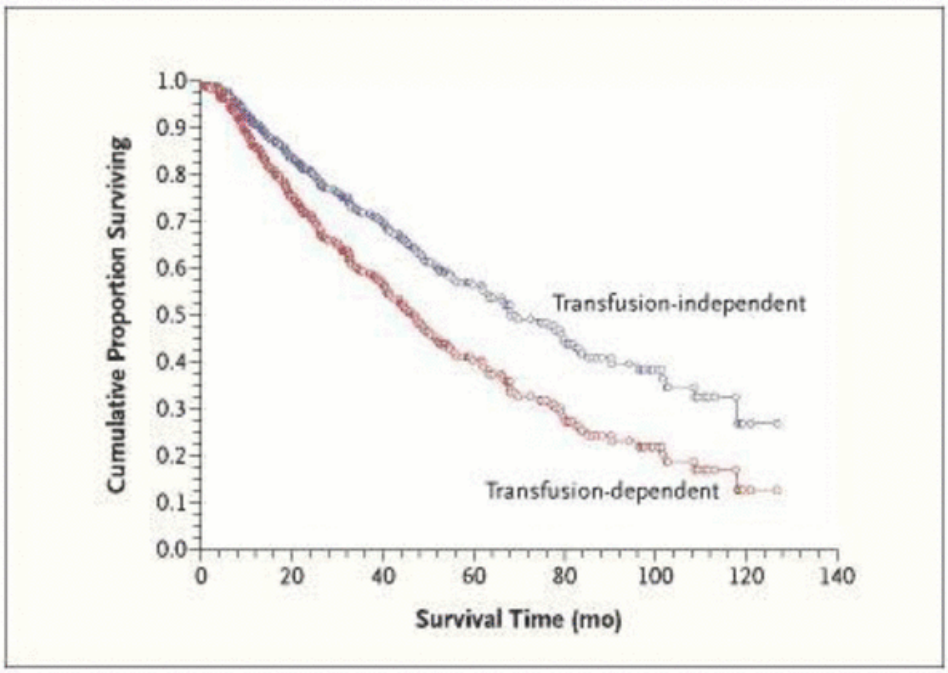
- **Who should be treated?**
  - Lower vs Higher
- **When should treatment be initiated?**
  - Early vs Late
- **Is there an age considered too old for therapy?**
  - Co-Morbidities
- **How long should a patient be treated? Response Target?**
  - Finite vs Open ended (progression or relapse)
- **Can extended therapy be delivered?**
- **Targeted Populations?**

Survival and AML Progression IPSS MDS Risk Classification:



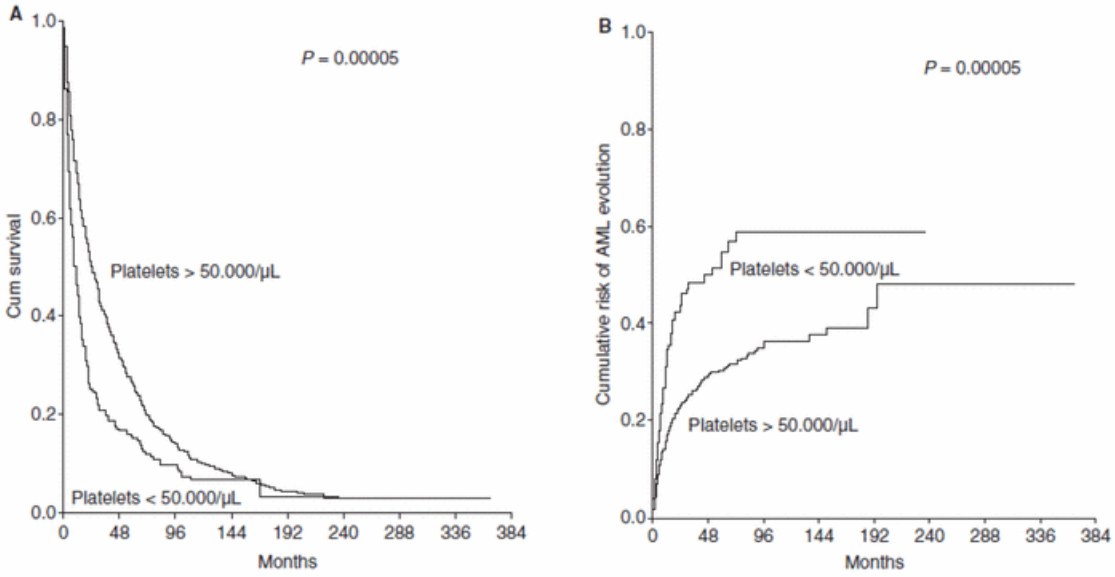
Greenberg P, et al. *Blood* 1997:89:2079-88.

Impact of RBC Transfusion Dependence on Survival of MDS Patients



Cazzola M, Malcovati L. *N Engl J Med.* 2005;352:536

Survival and AML Evolution



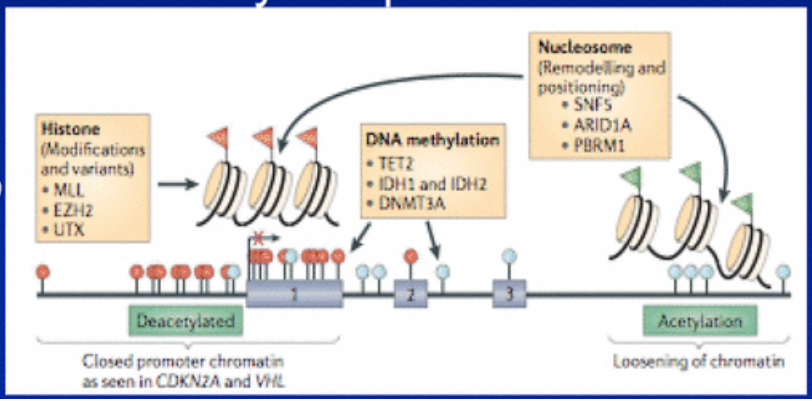
Neukirchen, et al. *Eur J Haematol.* 2009.

Azacitidine and Vorinostat in MDS – NYCC 6898

Azacitidine

- Hypomethylating agent reverses epigenetic silencing
- Clinical responses in MDS 45-50%
- CR rate 7-17%
- Trilineage response rate of 24%
- Median survival ranges from 14 - 24 months
- All patients either ultimately relapse or fail to respond

Silverman et al JCO 2002
Fenaux et al Lancet Oncology 2009
Baylin and Jones Nature Rev 2011



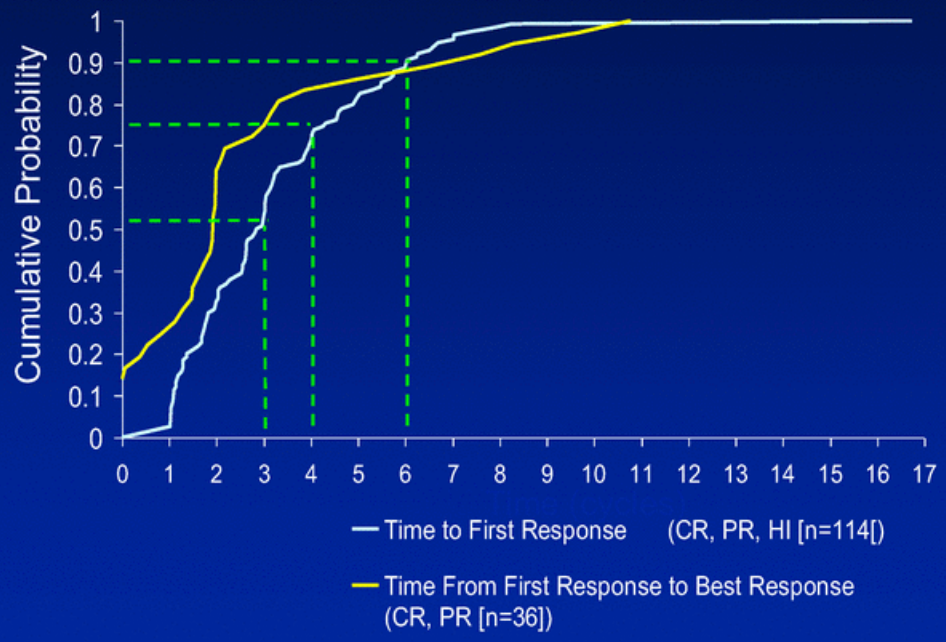
5-Aza vs Supportive Care in MDS
CALGB 9221

Care	Azacitidine	Supportive
No. pts	99	92
Overall Response	60%	5%
p<0.001		
Complete	7%	0
Partial	15%	0
Improved	37%	5%
p<0.001		
Crossover	0	47%
Mos to AML/death	21	12
p=0.007		

No, number
Mos, months
Med., median

Silverman. J Clin Oncol 18: 2414. 2002

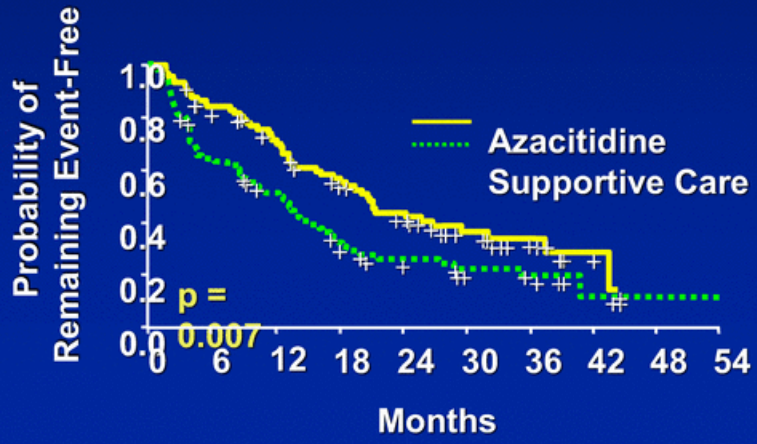
Times to 1st Response & From 1st Response to Best Response Using IWG MDS Response Criteria



Silverman et. al. JCO 24;3895, 2006

MDS : Time to AML Transformation or Death

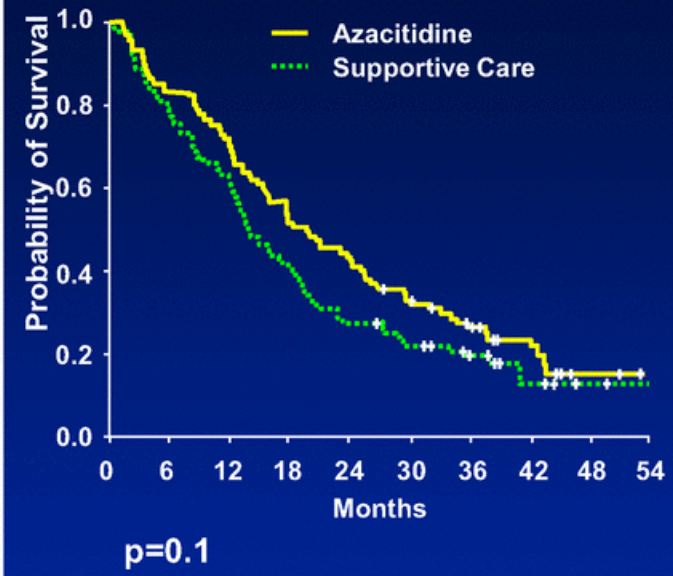
		Aza-C SC	
Med to Event	21	12	p=0.007
AML 1st Event	15%	38%	p=0.001
AML 1st Six mo. p<0.0001		3%	24%



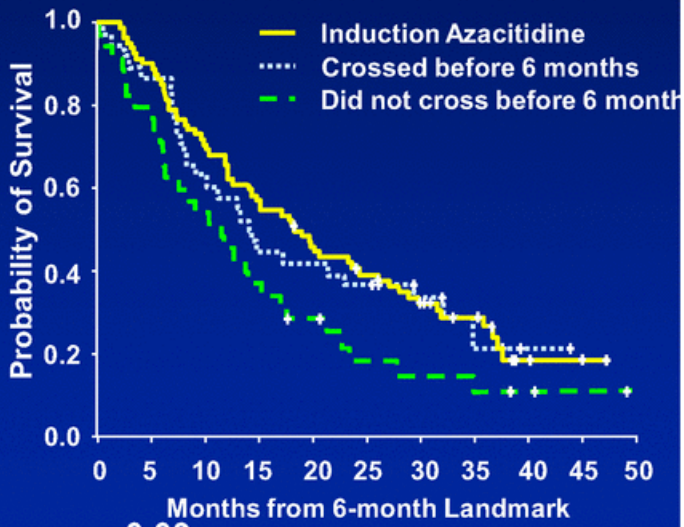
SC, supportive care
Med, Median

Silverman et al J Clin Oncol 18: 2414.

Survival: Landmark Analysis



p=0.1



p=0.03

Silverman L, et al. *J Clin Oncol* 2002. 18:2414-26.

AZA 001 - Azacitidine Survival Study

Screening/Central Pathology Review

Investigator CCR Tx Selection

Randomization

AZA 75 mg/m²/d x 7 d q28 d

CCR

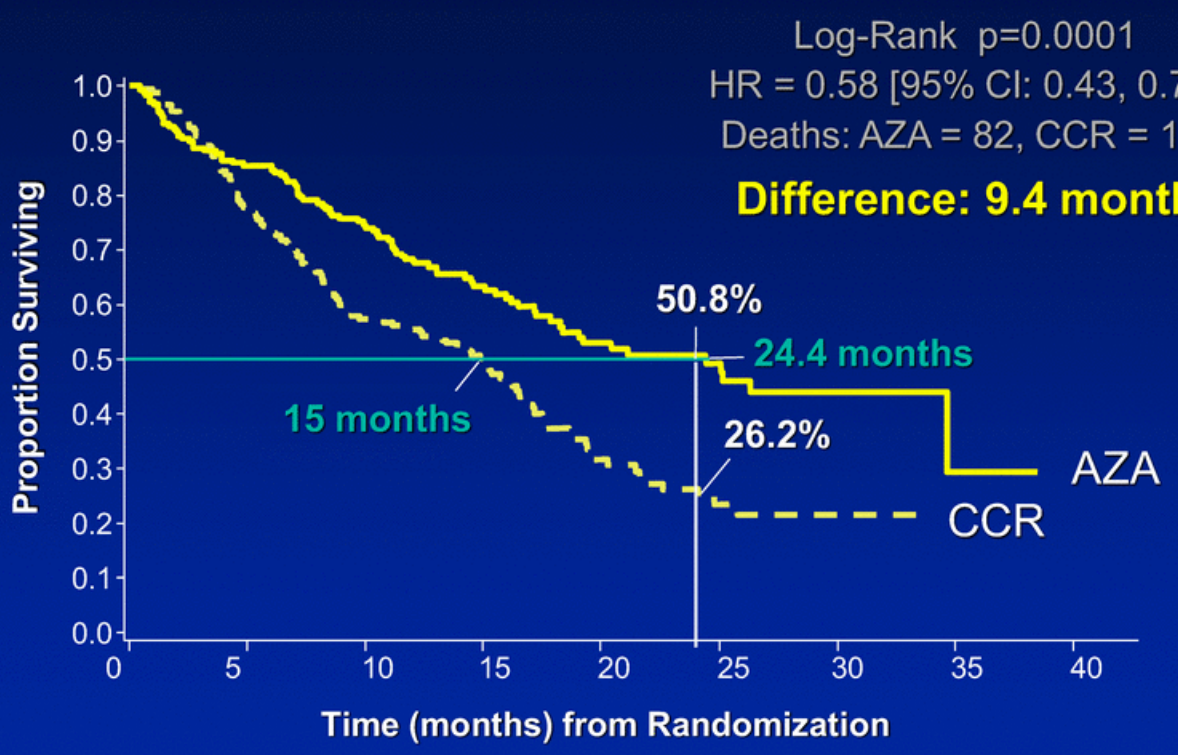
- Best Supportive Care (BSC) only
- Low Dose Ara-C (LDAC, 20 mg/m²/d x 14 d q28-42 d)
- Std Chemo (7 + 3)

CCR, conventional care regimen
BSC, best supportive care

BSC was included with each arm
Tx continued until unacceptable toxicity or AML transformation or disease progression

Fenaux et al, Lancet Oncology 2009

Overall Survival: Azacitidine vs CCR
ITT Population



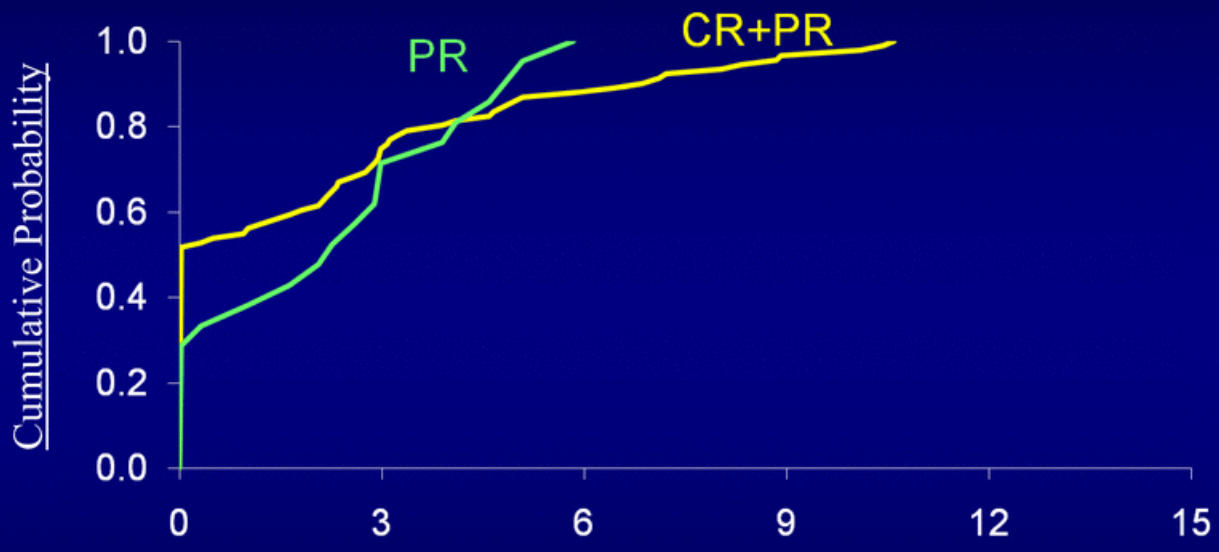
Fenaux et al, Lancet Oncology 2009

Secondary Endpoints

- Time to AML or death
  - 13 mos with AZA vs 7.6 mos with CCR, p=0.003
- Time to AML
  - 26.1 mos with AZA vs 12.4 with CCR, p=0.004
- RBC Transfusion Independence
  - 45% with AZA vs 11% with CCR, p<0.0001
- Infections Requiring IV Antimicrobials
  - Reduced by 33% with AZA vs CCR

Fenaux et al Lancet Oncology 2009

Time to Best Response After a First Response

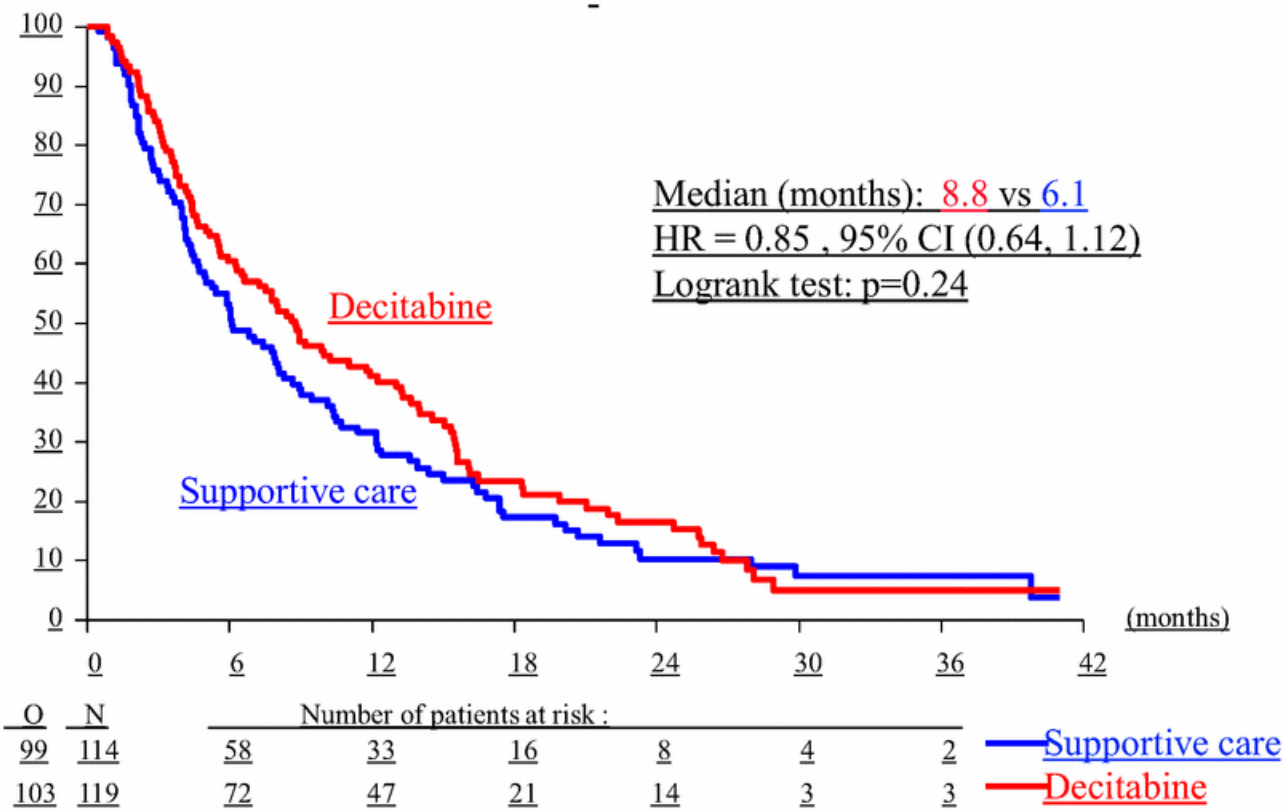


Number of Subjects					
CPH	91	29	12	6	0
PR	21	9	1	0	0

Silverman et al. Cancer Epub 2011

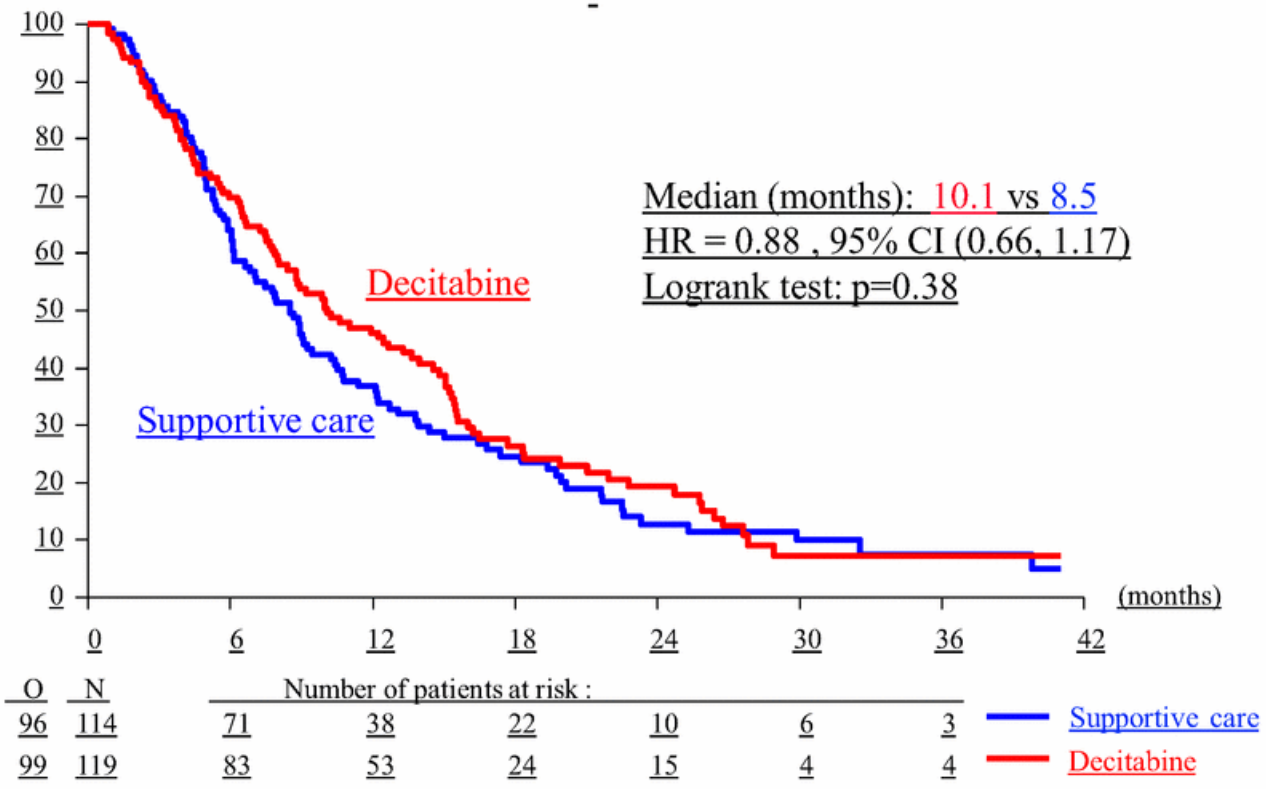
EORTC European Organization for Research and Treatment of Cancer

Time to AML or death



ıbbert JCO 29:1987, 2011

Overall survival



ıbbert JCO 29:1987, 2011

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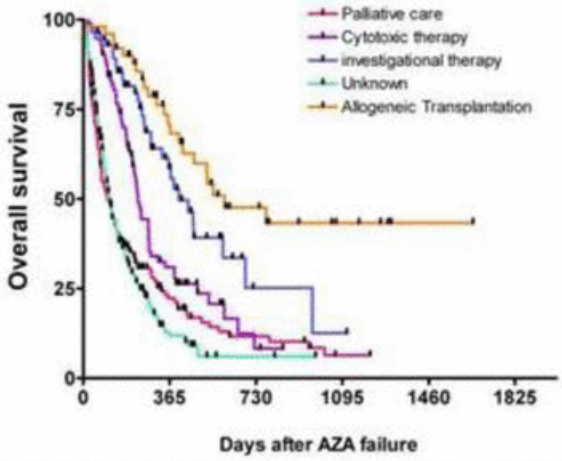
Nucleoside analogs in the clinic: Azacitidine vs Decitabine (II)

Study	Time to first response	Time to response	Endpoint
CALGB	3 cycles	90% of responses by cycle 6	RR + QoL Time to AML or Death
AZA-001	2 cycles	90% of responses by cycle 6	Overall survival (SS benefit)
D-007	2 cycles	NA	RR + QoL
ADOPT	2 cycles	80% of responses by cycle 2	RR + QoL
EORTC 06011	3-4 mo.s	3-4 mo.s	Overall survival (no benefit)

Outcome of Patients Treated for Myelodysplastic Syndromes and Secondary AML After Azacitidine Failure

At a median follow-up of 15 months after azacitidine failure, the median OS of patients with MDS or secondary AML (sAML) was 6 months.

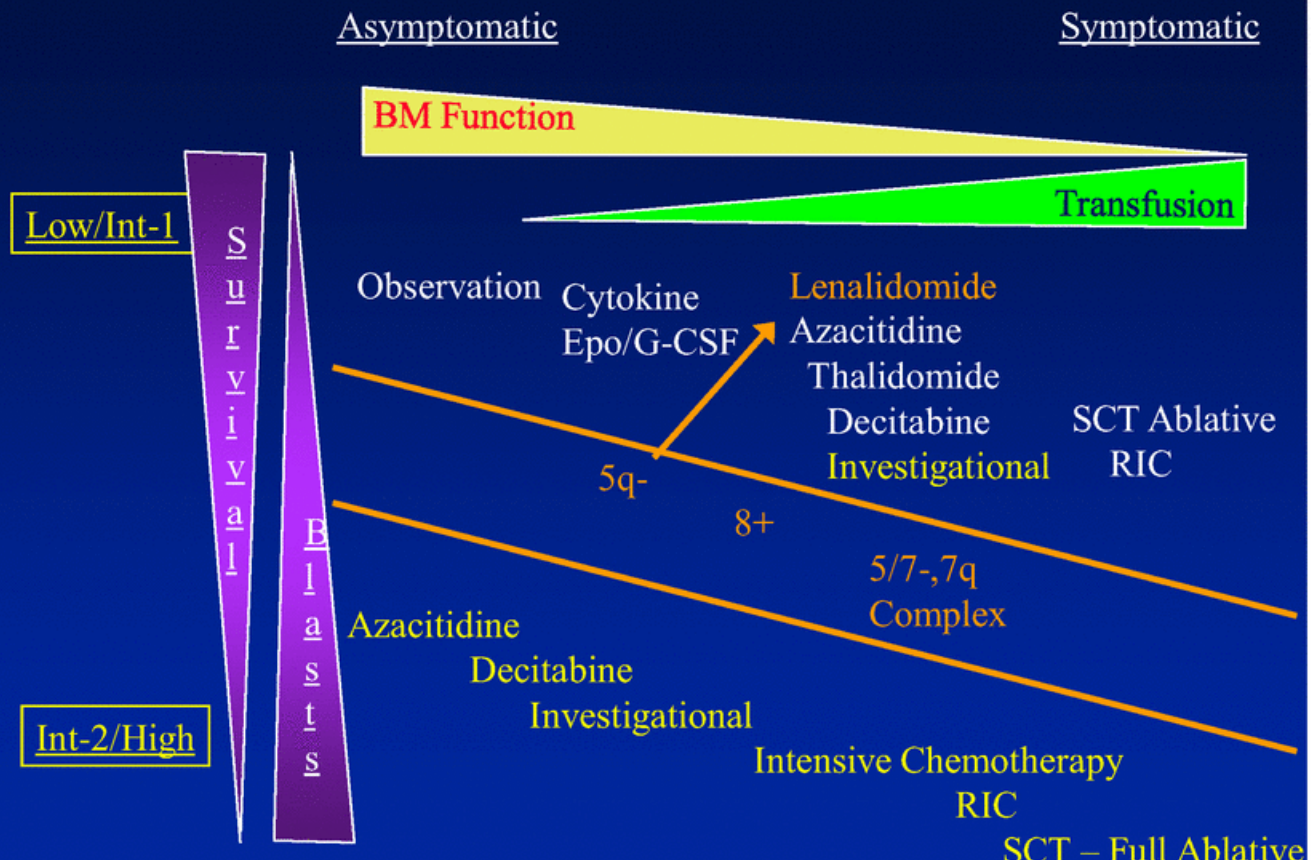
Figure 1



Type of salvage	N=	Response rate*	Median OS
Unknown (UNK)	215	NA	3.6 months
Palliative care (PC)	160	NA	3.3 months
Cytotoxic therapy (CT)	84	1/25 and 5/33**	7.6 months
Investigational therapy (IT)	56	4/39	13.2 months
Allogeneic Transplantation (ASCT)	50	17/25	18.3 months

Prebet et al. Blood 2012.

Treatment Algorithm for Patients with the Myelodysplastic Syndrome



Silverman in Cancer Medicine 8th ed. 2009

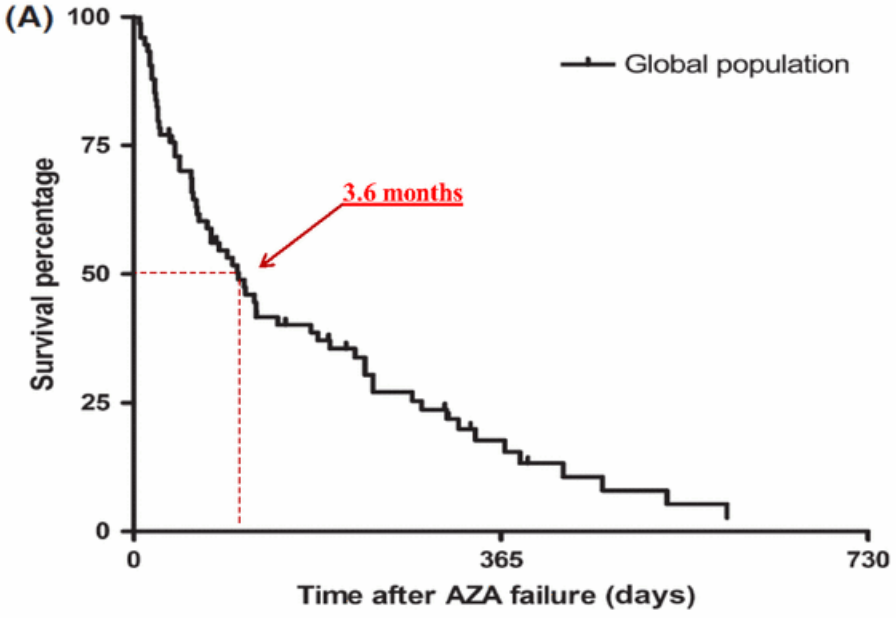
Outcome after azacitidine failure: patients with secondary AML

Characteristics of patients following AZA failure	n=74
Median age, years,	70
Treatment-related AML, %	6
BM blasts before azacitidine, median (range), %	48 (30–74)
Cytogenetics risk (IPSS), % (intermediate/high)	64/36
First-line azacitidine, %	49
Cycles of azacitidine, % (≤6/7–12/>12)	73/18/9
No. cycles of azacitidine, median	4

Reasons for AZA discontinuation	Patients (%)
Primary failure with SD	42
Primary failure without SD	28
Secondary failure	28
Intolerance	2

Prébet T, et al. Br J Haematol 2012;157:762–74

Outcome after azacitidine failure: patients with secondary AML – survival



Prébet T, et al. Br J Haematol 2012;157:762–74

Survival of Patients after Failing Hypomethylating Agents

	Population	treatment	Phase	N	ORR	OS
Borthakur Leuk lymph 2009	MDS and AML	Decitabine	Retro	14	28	6 months
Prebet JCO 2011	High risk MDS	BSC	Retro	160	NA	3.3 months
		chemotherapy	Retro	84	1/25 and 5/33[2]	7.6 months
		Investigational agents	retro	56	4/39	13.2 months
		Allogeneic transplantation	retro	50	17/25	18.3 months
Greenberg ASH 2010	High risk MDS	rigosertib	retro	39	23%	9 months
Prebet Leuk Res 2013	High risk MDS	Vorinostat and cytarabine	1	40	17%	7 months
Braun ASH 2011	High risk MDS	Clofarabine	1	27	28%	unk
Prebet Leuk lymph 2012	MDS and AML	lenalidomide	retro	10	40%	19 months
Thepot ASH 2011	High risk MDS	Erlotinib	1	29	13%	7 months
Jaglai ASH 2011	sAML	CLAG-M (cladribine, Ara-C mitoxantrone G CSF)	Retro	25	56%	6.7 months
Paubelle PloSOne 2013	sAML/ AML-MRC	Deferasirox/ vit. D	Retro	17	0	10 months

Rigosertib Design Rationale

- In vitro Leukemic cells more sensitive to effects than normal hematopoietic progenitors
  - Trial in MDS and AML
- Longer exposures achieve increased cell kill
  - 72 h > 48 h > 24h
    - Prolonged infusions 72 h to 144 h
- Repetitive exposures more effective
  - Cycles every 2 weeks for 4 to 8 cycles then q month

Rigosertib in Patients with MDS or AML Relapsed or Refractory to a Hypomethylating Agent A Phase I/II Study Mount Sinai 04-05

- Twenty-two pts with MDS or AML who had failed treatment with hypomethylating agents were treated with rigosertib
- Study cohort comprised patients with a diagnosis of
  - Intermediate-2 MDS (2 pts)
  - High-risk MDS (6 pts)
  - Chronic myelomonocytic leukemia (1 pt)
  - AML (13 pts)

Navada et al ASH abstr527 Blood 122:21 2013

Rigosertib in Patients with MDS or AML Relapsed or Refractory to a Hypomethylating Agent A Phase I/II Study Mount Sinai 04-05

- Responses according to IWG 2006 criteria observed in the BM and peripheral blood:
  - Marrow Complete Response (4)
    - Survival of these pts was 12, 15.7, 16.4, and 19.5 months
  - Hematologic improvement (HI) (2); erythroid (1) platelet (1)
  - An additional 2 pts had a >50% BM blast decrease from baseline but not to < 5%
- 10/19 evaluable pts (53%) demonstrated a bone marrow/peripheral blood response (6) or stable disease (4)

Navada et al ASH abstr527 Blood 122:21 2013

Rigosertib in Patients with MDS or AML Relapsed or Refractory to a Hypomethylating Agent A Phase I/II Study Mount Sinai 04-05

- Early bone marrow response at 4-8 weeks correlates with improvement in overall survival
- Patients who did have a marrow complete or partial response responded early with a median time to response of 2-4 cycles
- Less than 20% blasts at study entry was a positive predictor of response ($p=0.047$). All 8 MDS pts in the study had <20%.
- Patients with proliferative disease with rapidly rising or high white blood cell counts did not respond
- Age, cytogenetic profile, prior response to hypomethylating agents were not predictors of response

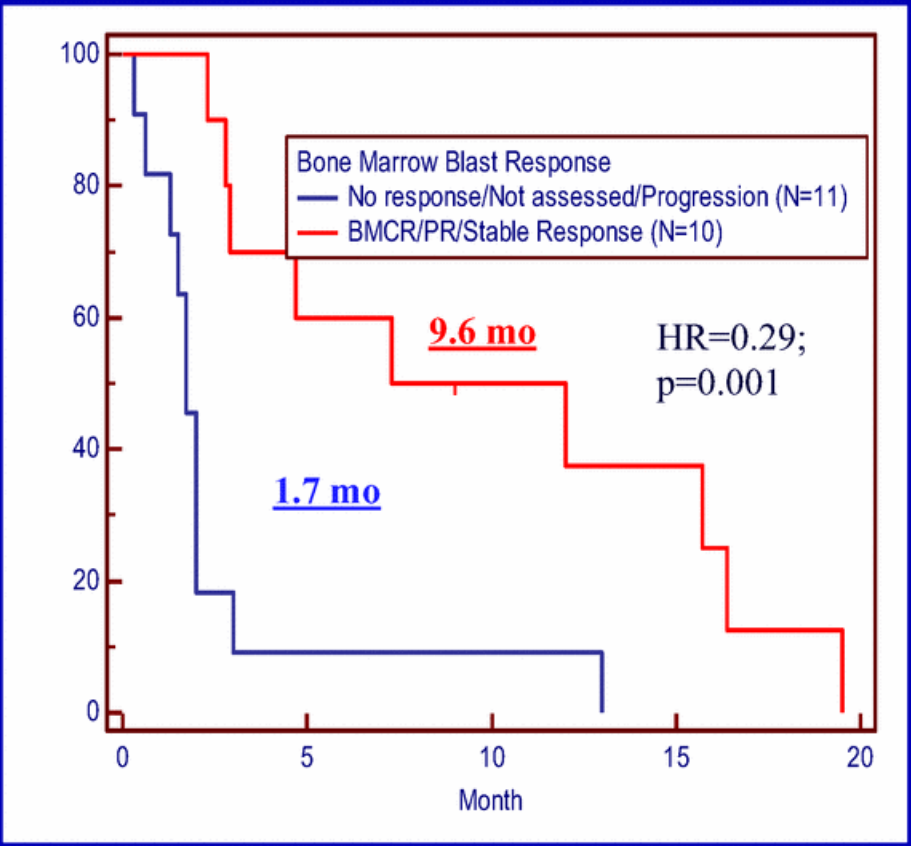
Navada et al ASH abstr527 Blood 122:21 2013

Rigosertib in Patients with MDS or AML Relapsed or Refractory to a Hypomethylating Agent A Phase I/II Study Mount Sinai 04-05

- Rigosertib has biologic activity with reduction in BM blasts associated with increased survival and improvement in peripheral blood counts in a subset of patients with MDS and AML who failed prior treatment with hypomethylating agents
- Patients with <20% blasts at study entry have a greater likelihood of response to rigosertib
- Early bone marrow response at 4-8 weeks in patients treated with rigosertib correlates with improvement in overall survival
- Combination studies with other agents, such as azacitidine, are ongoing

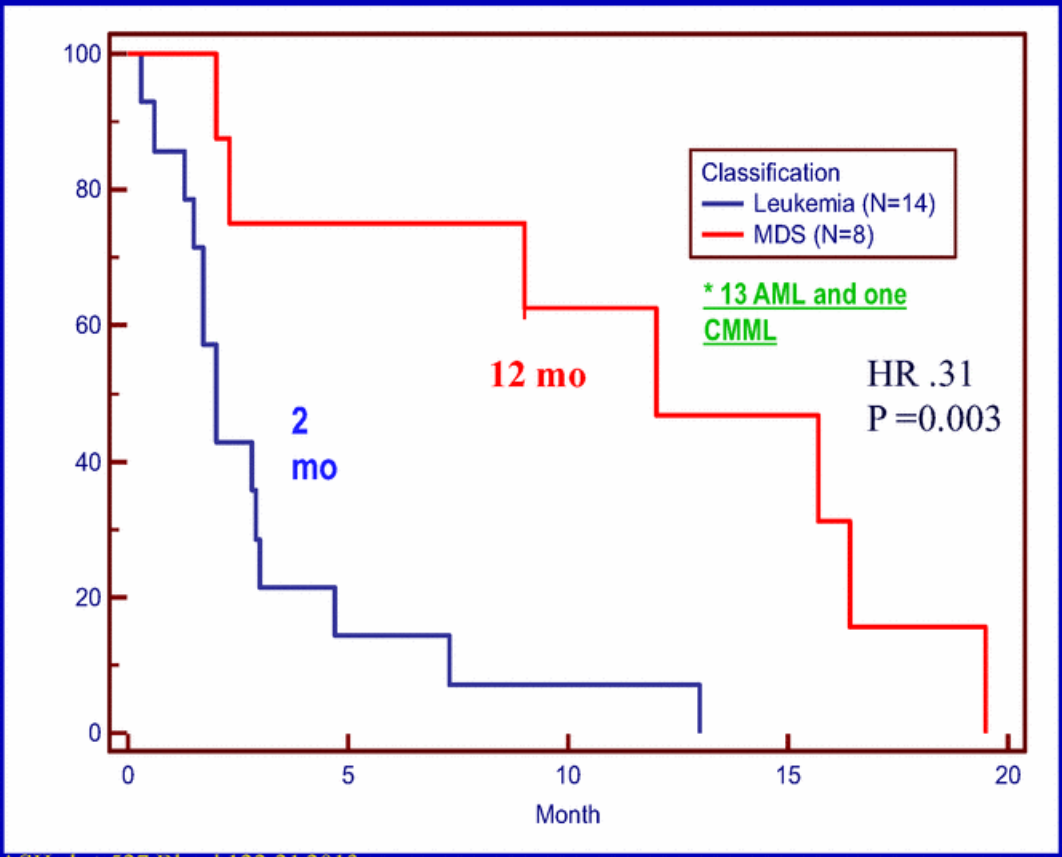
Navada et al ASH abstr527 Blood 122:21 2013

Relation Between Bone Marrow Early Response at 4-8 Weeks and Overall Survival

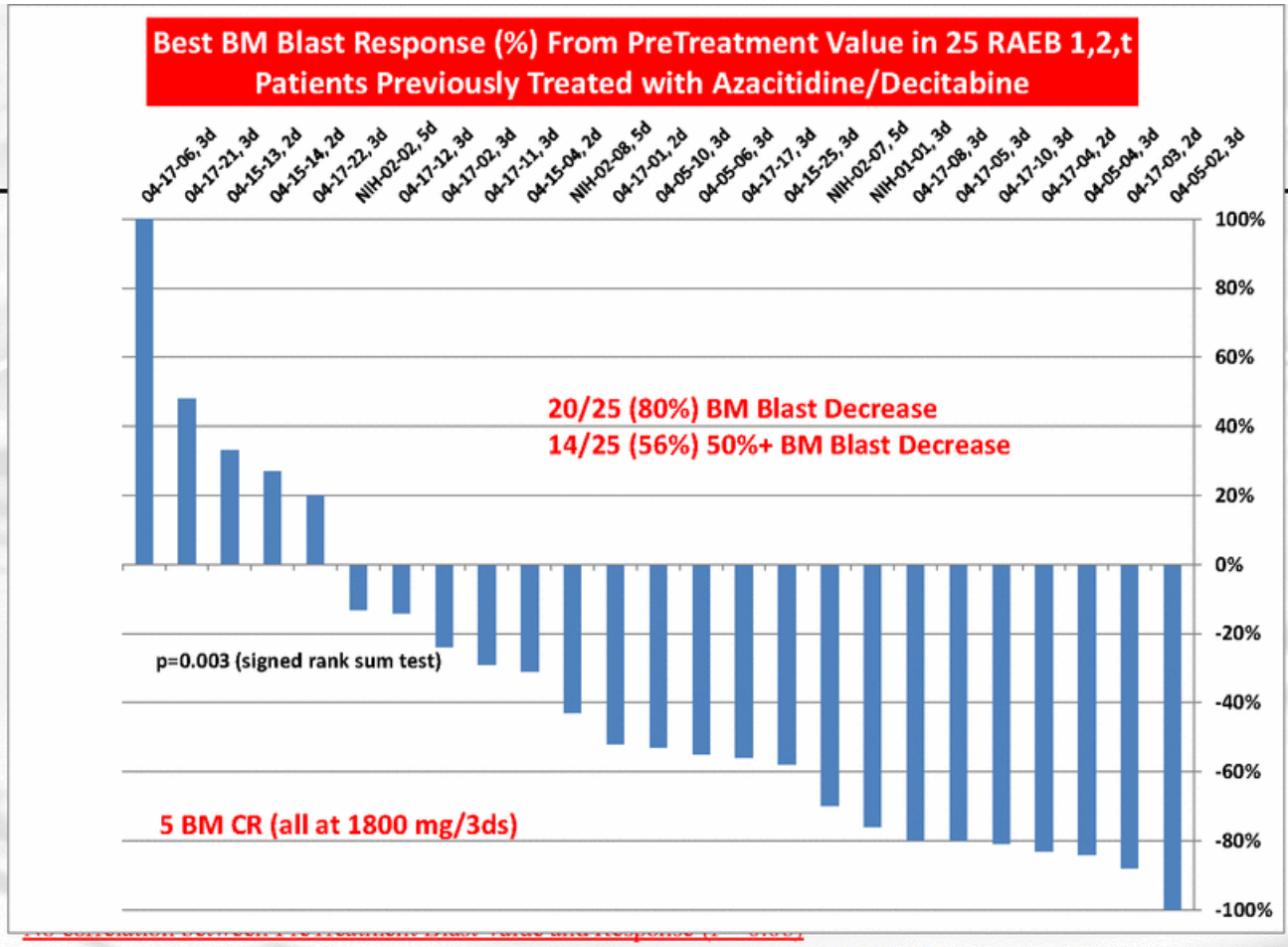


Navada et al ASH abstr527 Blood 122:21 2013

Overall Survival in Patients with MDS vs AML



Navada et al ASH abstr527 Blood 122:21 2013



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Lenalidomide + Azacitidine: Dosing Table

Dose Level	Azacitidine Schedule	Lenalidomide Schedule
1	75 mg/m² SC days 1-5	5 mg PO days 1-14
2	75 mg/m² SC days 1-5	5 mg PO days 1-21
3	75 mg/m² SC days 1-5	10 mg PO days 1-21
4	50 mg/m² SC days 1-5, 8-12	5 mg PO days 1-14
5	50 mg/m² SC days 1-5, 8-12	5 mg PO days 1-21
6	50 mg/m² SC days 1-5, 8-12	10 mg PO days 1-21

Sekeres et al. Blood epub 2012

Lenalidomide + Azacitidine Phase I/II Toxicities and Response

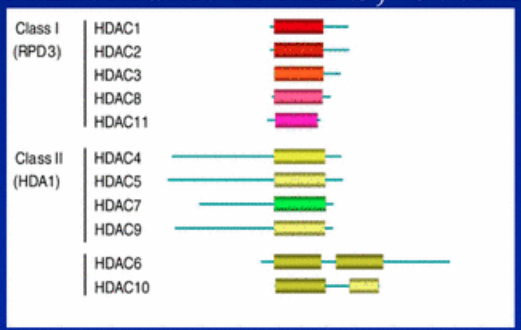
Grade 3 or 4 non-hematologic	Response
cardiac (2)	ORR = 26/36 (72%)
monocular blindness (1)	16 CR (44%)
basal cell skin carcinoma (1)	10 HI (28%)
CNS hemorrhage (2)	Med Survival 13.6
febrile neutropenia (5)	Med Dur CR Resp 17+
shortness of breath (1)	Med Time to Resp 3.7 mo
perforated appendix (1)	
renal failure (1)	

Sekeres Blood Epub Aug 2012

Azacitidine and Vorinostat in MDS – NYCC 6898

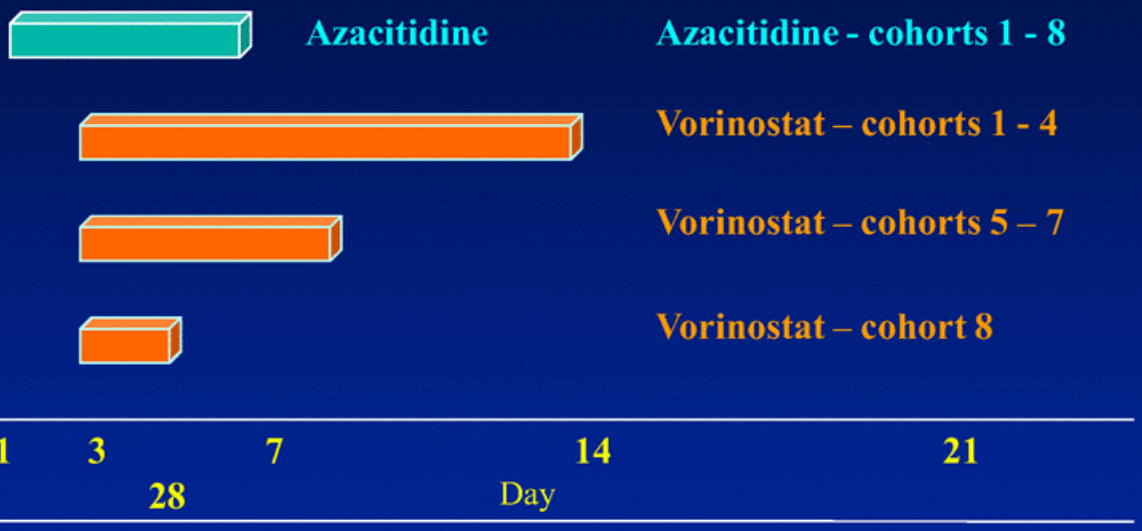
Vorinostat

- Chromatin modifier inhibitor of histone deacetylase
- Multi-enzyme inhibitor
- In vitro synergy with azacitidine in reversing epigenetic silencing
- Effect is sequence dependent, hypomethylator followed by the HDAC in vitro models
- Vorinostat monotherapy less active than azacitidine in MDS, overall response rate 20% (Garcia-Manero Blood 2006)



Silverman ASH 2013 Abstract #386

Azacitidine and Vorinostat in MDS / AML – NYCC 6898



This represents 1 cycle. Cycle will be repeated every 28 days for a minimum of 4 cycles.

Schedule overlap

Silverman et al. ASH 2008

Azacitidine and Vorinostat in MDS / AML – NYCC 6898

Cohort	Azacitidine Dose mg/m2 Subcutaneous (SC) bolus	Vorinostat Dose Mg PO	Dose Frequency	Day	Total Dose Azacitidine (mg/m2/cycle) Vorinostat (mg/cycle)
1	55	200	QD BID	1 – 7 3-16	385 5600
2	55	200	QD TID	1 – 7 3-16	385 8400
3	75	200	QD TID	1 – 7 3-16	525 8400
4	75	200	QD BID	1 – 7 3-16	525 5600
5	75	300	QD BID	1 – 7 3-9	525 4200
6	55	300	QD BID	1 – 7 3-9	385 4200
7	55	200	QD BID	1 – 7 3-9	385 2800
8	55	300	QD BID	1 – 7 3-5	385 1800

Silverman et al. ASH 2008

Azacitidine and Vorinostat in MDS / AML – NYCC 6898

Response Phase I

Enrolled	28	
Evaluable for response	23	
Overall Response*	20	(87%)+
CR	11	(48%)
CRi	3	(13%)
CR+CRi	14	(61%)
PR	0	(0%)
HI	6	(26%)
Stable	2	(09%)
NR	1	(4.3%)
Too Early	1	
IE for response	3	
Withdrew prior to Rx/Ineligible	1	
Transfusion Independence (n = 14)	11	(79%)

*IWG 2000 MDS
IWG 2006 MDS
IWG AML

+Response Confirmed by NCI Audit

Silverman et al. ASH 2008

US Leukemia Intergroup Trial E1905: Azacitidine With or Without Entinostat

- **136 evaluable patients (88 MDS, 43 AML, 5 CMML) were randomized to 1 of 2 treatment arms:**
  - Azacitidine 50 mg/m²/day × 10 × 6 cycles (arm A)
  - Azacitidine × 10 plus entinostat on days 3 and 10 × 6 cycles (arm B)
- **Responders received 24 cycles or treatment until progression.**

	Arm A	Arm B	*P* Value
	Azacitidine	Azacitidine/ Entinostat	
Complete Response	12%	7%	NS
Partial Response	9%	7%	NS
Trilineage Response[a]	31%	24%	NR
Trilineage response in AML	19%	27%	NR
Median Overall Survival	18 months	13 months	.15

[a] CR + PR + trilineage hematologic improvement

Entinostat did not improve the response to azacitidine, but the rate of hematologic normalization in both groups was significantly higher than that seen in the CALGB 9221 trial (15%).

Prebet et al. ASH 2010; abstract 601.

Experience with Hypomethylating Agents in Combination in MDS/AML

	Disease	No	Dose (mg/m2) Schedule	CR	ORR
Gore	MDS/AML	36	azacitidine/phenylbutyrate	14%	38%
Prebert/Gore	MDS/AML	136	azacitidine/entiostat	12%	44%
			azacitidine	7%	43%
Soriano	MDS/AML	53	azaC/VPA/ATRA	22%	42%
Garcia-Manero	MDS/AML	37	azacitidine/MGCD0103	11%	52%
Silverman	MDS/AML	23	azacitidine/vorinostat	48%	87%
				61%CRi	
Garcia-Manero	AML/MDS	54	decitabine/VPA	19%	22%
	AML	10		40%	50%
Kirschbaum	MDS/AML	60	decitabine/Vorinostat	22%	45%
Blum	AML	25	decitabine/VPA	16%	44%
Issa	MDS/AML	31	decitabine/vorinostat	3%	17%
Yee	MDS/AML	27	decitabine/vorinostat	4%	16%

COMBINATION STUDIES MDS AND AML

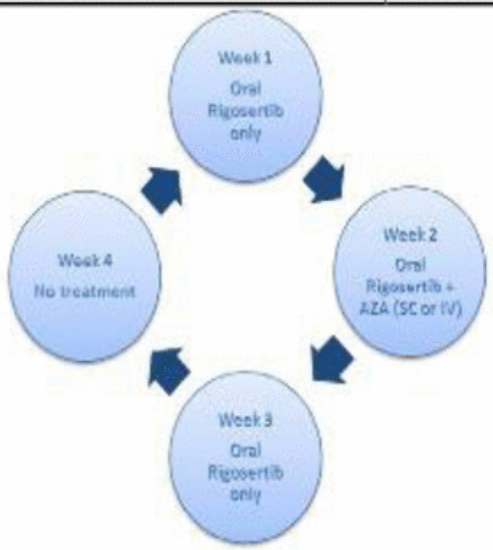
SWOG – S1117 MDS higher risk Azacitidine Azacitidine + Lenalidomide Azaicitidine + Vorinostat	Phase II Ongoing
AML – low proliferative Azacitidine Lenalidomide Azacitidine + Lenalidomide	Phase II Ongoing
MDS and AML Azacitidine + Rigosertib	Phase I/II Ongoing

In Vitro Interaction between Rigosertib and Azacitidine

Combination Drug	CI	Ratio	Description
ON1910.Na (125nM) + 5AzaC (2uM)	0.44	1:62.5	Synergism
ON1910.Na (125nM) + 5AzaC (4uM)	0.30	1:31.25	Strong synergism
ON1910.Na (250nM) +5AzaC (2uM)	0.68	1:125	Synergism
ON1910.Na (250nM) + 5AzaC (4uM)	0.57	1:62.5	Synergism
ON1910.Na (500nM) + 5 AzaC (2uM)	0.63	1:250	Synergism
ON1910.Na (500 nM) + 5AzaC (4uM)	0.75	1:125	Moderate synergism

Phase I/II Study of the Azacitidine and Rigosertib in MDS and AML

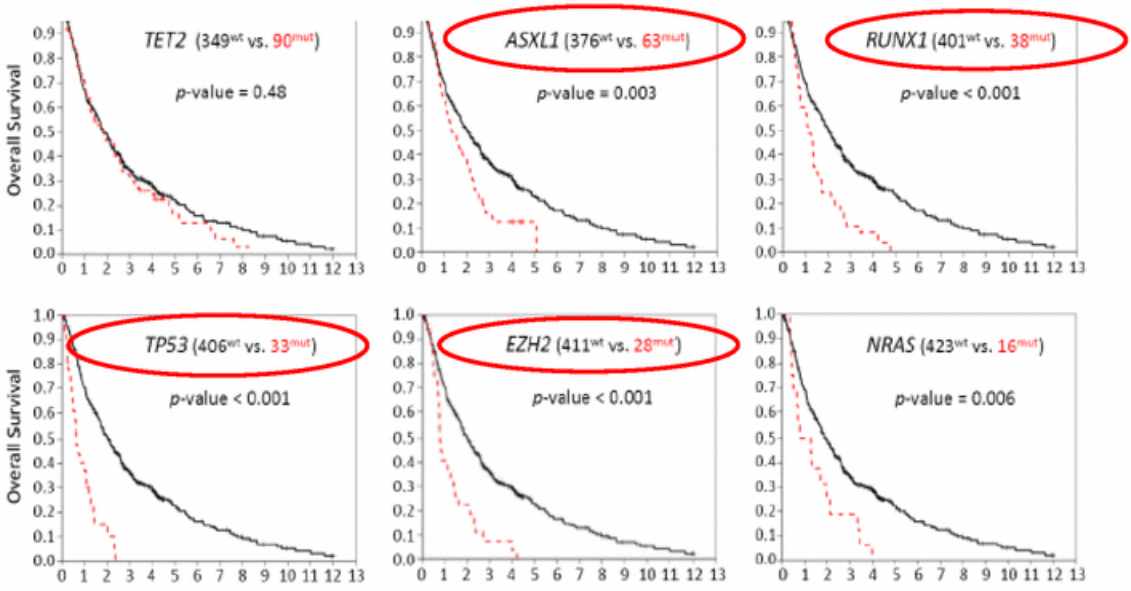
Cohort	No of Patients	Oral Rigosertib BID (Weeks 1, 2, and 3 of a 4-week cycle) (mg)	AZA SC or IV Daily for 7 days Week 2 of a 4-week cycle (mg/m^2)
1	3-6	140 (two 70 mg capsules) BID	75
2	3-6	280 (one 280 mg capsule) BID	75
3	3-6	560 (two 280 mg capsules) BID	75



Mechanisms of Action of Therapies Under Investigation

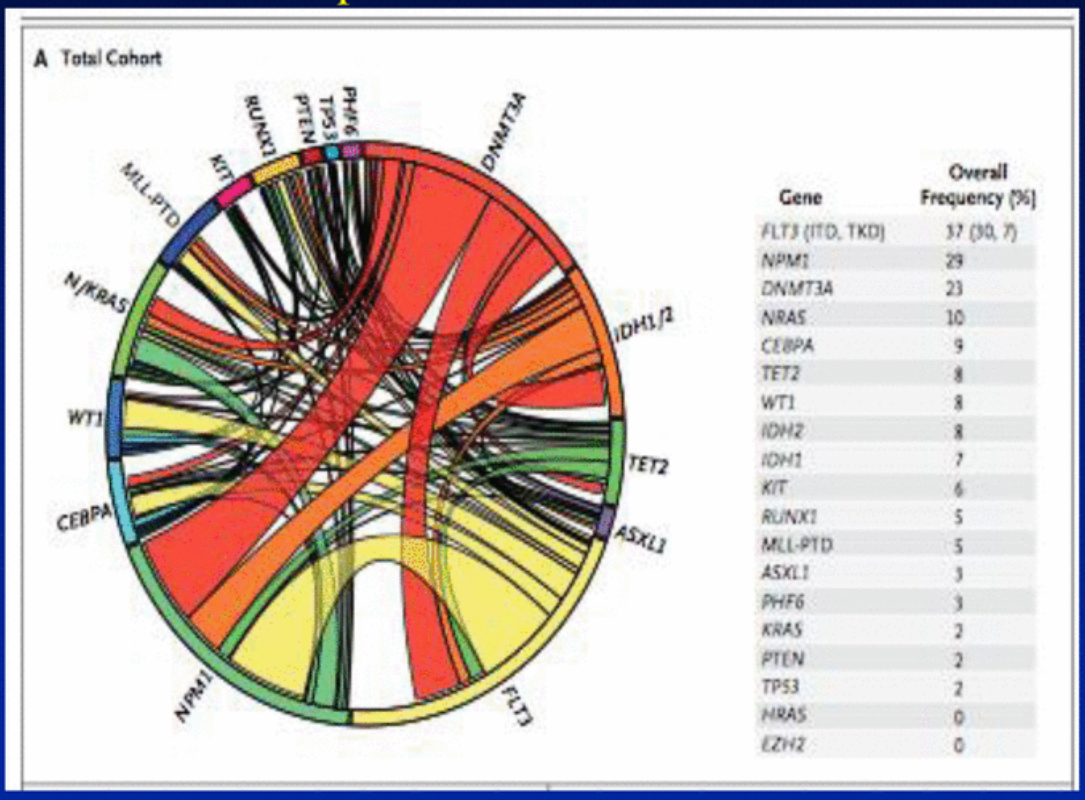
AGENT	TARGET	MOA	TRIAL/POPULATION	RESPONSE	GRADE 3/4 AES
ARRY-614[a]	P38/Tie-2	Antineoplastic, anti-inflammatory, and antiangiogenic activity	Phase I/low or Int-1 risk (N = 100)	–	–
Entinostat (SNDX-275/MS-275)[b]	Histone DAC	Class 1 HDAC1 and HDAC3 inhibitor	Combination with azacitidine; phase III/high risk (N = 150)[c]	HR and CyR did not differ between AZA/Pbo versus AZA/entinostat	• Thrombo: 63% • Fatigue 23%
Erlotinib[d]	EGFR signaling leads to DNA synthesis and proliferation	Tyrosine kinase inhibitor that blocks EGFR signaling	Phase II/Int-2 and high risk (N = 24)[e]	ORR: 17%	• Diarrhea: 21% • Thrombo: 17% • Rash: 17%
Everolimus (RAD-001)[f]	mTOR	Inhibitor of mTOR that induces G_1 arrest	Phase II/low and Int-1 risk (not yet recruiting)[g]	–	–
Ezatiostat[h]	GST P1-1	Stimulates proliferation of myeloid precursors	Phase I/Int-2 (N = 45)	HI: 38%	• Neutropenia: 7%
ON-0110.Na[i]	Polo-1 kinase, PI3K, AKT	Inhibits mitotic progression and induces apoptosis	Phase II/Int-1, Int-2, high risk (N = 10)[j]	ORR: 50%	• GI: 10% • Dysuria: 10% • Fatigue: 10% • Epistaxis: 10% • No heme toxicities
Panobinostat (LBH589)[k]	Histone DAC	Pan DAC inhibitor, inhibits differentiation and induces apoptosis	Phase II/relapsed or refractory MDS (N = 10)[l]	70% had stable disease	• Thrombo: 80% • Neutropenia: 70% • Leukopenia: 60% • Anemia: 50% • Febrile neutropenia: 20%

Mutations and Survival



Bejar, et al. *N Engl J Med*. 2011.

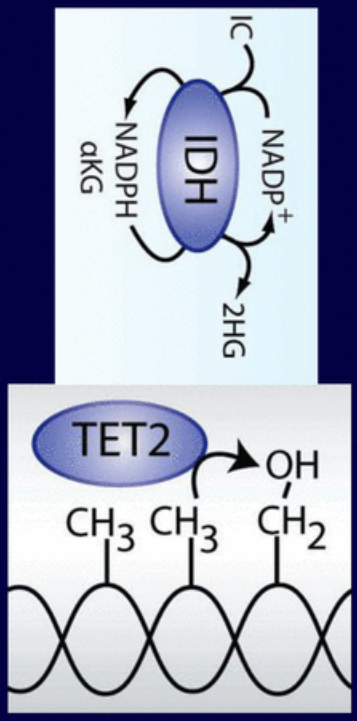
Mutational Complexity of Acute Myeloid Leukemia
Relationship of co-occurrence of mutations



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Patel et al NEJM 166: 1079, 2012

Role of IDH1/IDH2 and TET2 Mutations in MDS/MPN and AML



Mutations may result in changes in methylation marks and alterations in gene expression

Ko M et al Nature 2010; Bejar et al JCO 2011

Presence of *TET2* Mutation Predicts a Higher Response Rate to Azacitidine in Myelodysplastic Syndromes and Acute Myeloid Leukemia Post-MDS

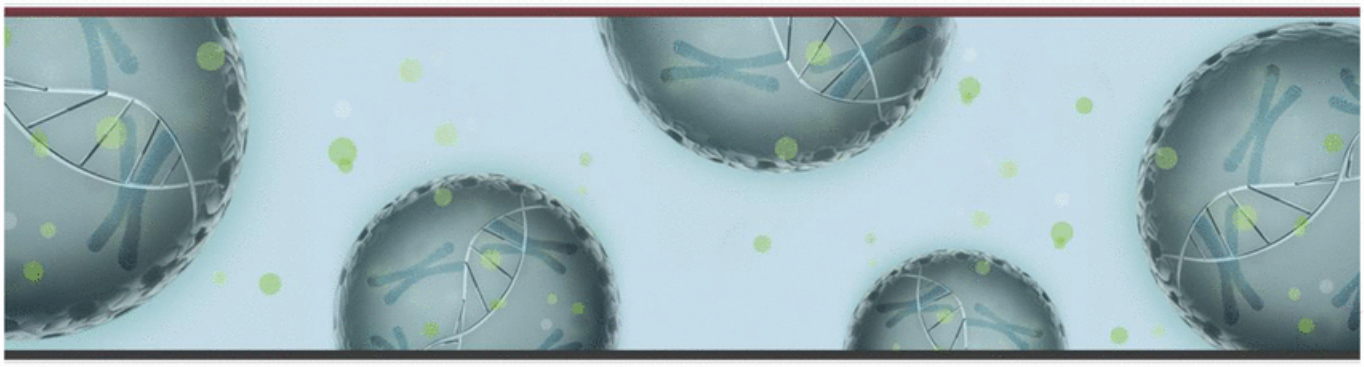
	Overall (n = 103)	Mutant *TET2* (n = 17)	Wild-Type *TET2* (n = 86)	*P* Value
Complete Response	23%	41%	20%	.07
Overall Response Rate				
CR, PR, marrow CR/incomplete CR	36%	65%	30%	.01
Including hematologic improvement	52%	82%	45%	.007

***TET2* mutation:**

- **Was associated with a higher rate of response to azacitidine, independent of conventional cytogenetics and duration of exposure**
- **Had no influence on survival 15.3 vs. 16.2 (p=0.4)**

Itzykson et al. ASH 2010; abstract 439.

ONCONOVA THERAPEUTICS



QUALITY OF LIFE MEASUREMENT

Jimmie Holland, M.D.

Jimmie Holland, M.D.
Wayne E Chapman Chair in Psychiatric Oncology
Memorial Sloan-Kettering Cancer Center
New York, New York

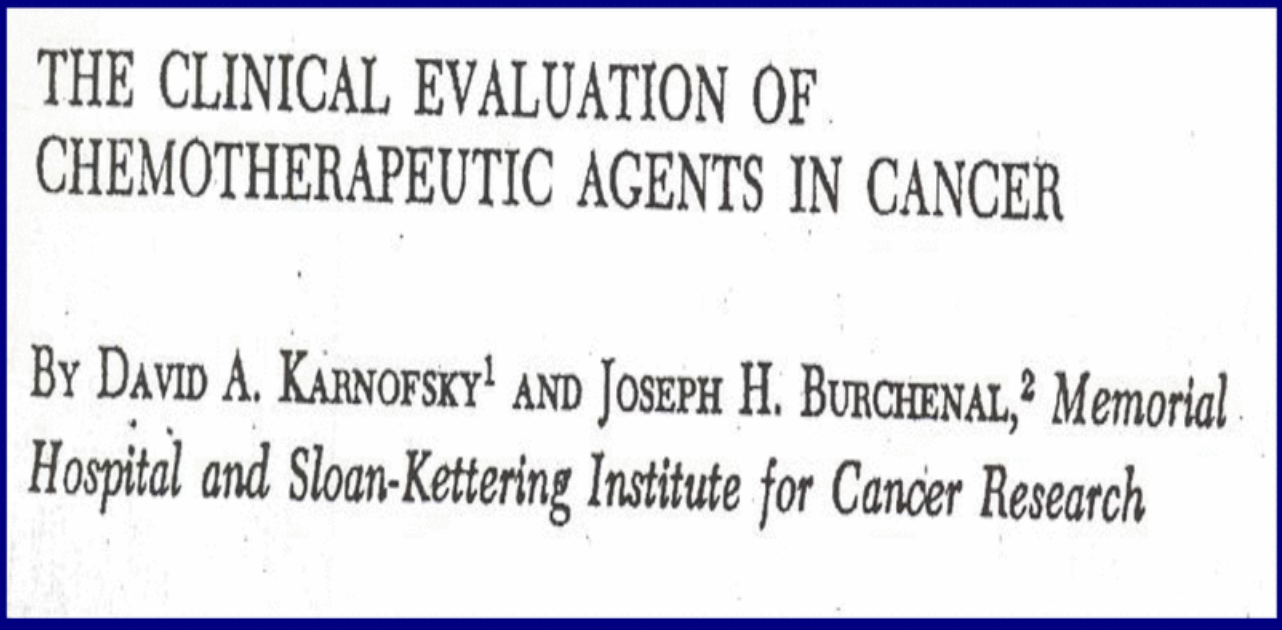
HISTORICAL BARRIERS – 1

Double Stigma

- Patients not told their diagnosis and psychological responses could not be explored
- Mental disorders/illness long feared and stigmatized

HISTORICAL BARRIERS – 2

- Belief that subjective phenomena (pain, feelings) could not be quantitatively measured
- Patient's self-report was considered unreliable (only observer ratings reliable)
- Social science methods were not understood by basic scientists



THE CLINICAL EVALUATION OF CHEMOTHERAPEUTIC AGENTS IN CANCER

By David A. Karnofsky[1] and Joseph H. Burchenal,[2] *Memorial Hospital and Sloan-Kettering Institute for Cancer Research*

***New York Acad. Med.* 2:191-205, 1948**

Karnofsky and Burchenal, 1948

Evaluation of chemotherapeutic agents

- SUBJECTIVE improvement
- OBJECTIVE improvement
- PERFORMANCE status
  0 – 100% normal activity
- LENGTH OF REMISSION and prolongation of life

Evaluation of Objective Improvement

- Regression of tumor size
- Improvement of altered lab values
- Reaching specific clinical outcome measures

Evaluation of Performance Status

Karnofsky Performance Scale

100% Normal activity

70% Unable to do active work

40% Disabled, requires care and assistance

10 – 0% Moribund, Dead

Karnofsky and Burchenal, 1948

Evaluation of Subjective Improvement

"Subjective improvement is measured in terms of improvement of his MOOD and attitude, his general feelings of WELL-BEING, his ACTIVITY, APPETITE, and ALLEVIATION of distressing symptoms such as pain, weakness, and dyspnea."

Karnofsky and Burchenal, 1948

1977 Clinical Trials Groups

- EORTC, Amsterdam began Quality of Life Committee – Aronson, QOL outcomes of trials (EORTC-QOL)
- CALGB, added Psychiatry Committee and we conducted the first clinical trials which measured "subjective improvement" as an outcome variable
- Cella, developed FACT (Functional Assessment for Cancer Therapy) scales for US trials

Psycho-Oncology in First Cancer Center Since 1977

- Major research effort: to develop quantitative measurement of subjective symptoms with scales that were validated and reliable
- 2000 – evidence-based psychotropic and psycho through interventions

1980s – 90s

- Greater concern for ethics of
  - Clinical trials
  - Quality of consent to be informed
  - Presented in patient non-terms
- Patient-centered “Humanistic” medicine

Health-related Quality of life (HRQOL)

- Assessment is more appropriately called Functional Assessment in all areas of living
  - Physical
  - Social
  - Sexual
  - Psychological
  - work
- Cella, US and Aronson, EORTC

Health Related Quality of Life (HRQOL)

"Extent to which one's usual or expected physical, emotional, and social well being are affected by a medical condition or its treatment"

Cella, 1994

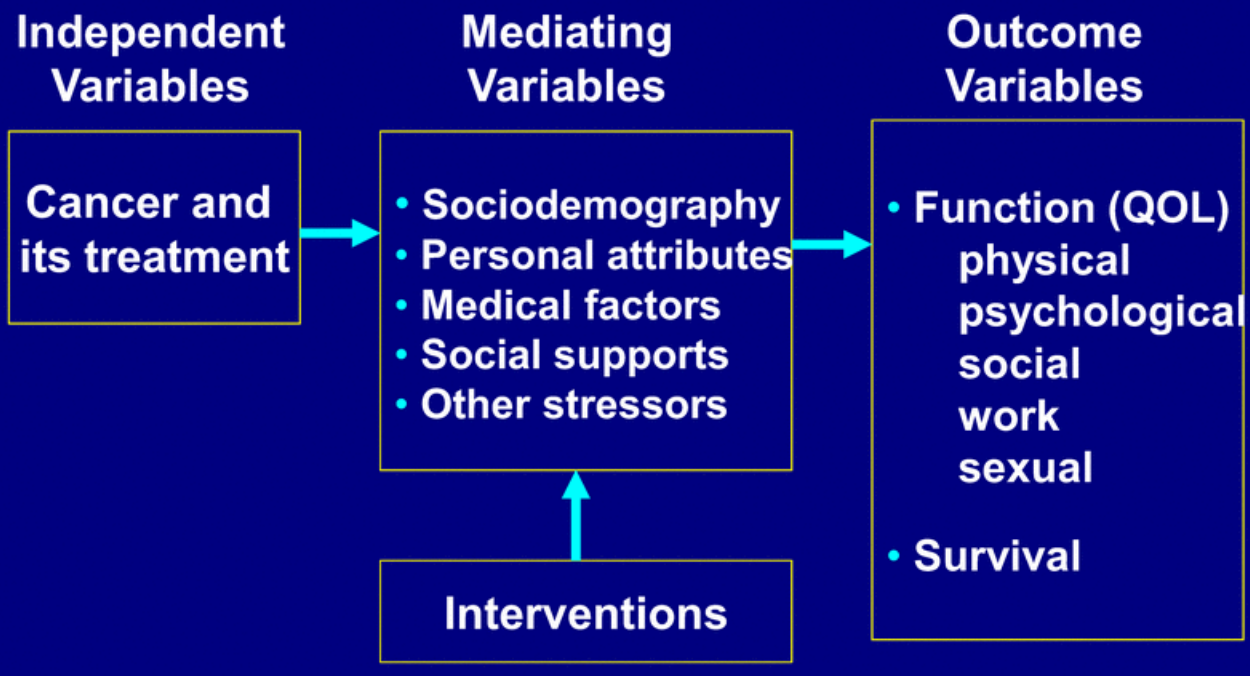
EORTC and FACT Scales

- Have a core of questions common to function
- A module is added to assess function related to a particular organ / site (eg. prostate, breast)

Basic to Psycho-Oncology Research

- Developed validated quantitative measures of subjective dimensions
  - QOL (Cella)
    Core and disease specific modules
  - Pain
  - Fatigue
  - Distress
  - Anxiety
  - Depression
  - Delirium

RESEARCH MODEL FOR PSYCHOSOCIAL & QUALITY OF LIFE RESEARCH IN ONCOLOGY



Recent Changes in Cooperative Trials

- Increasing use of directly using patients own symptom and side effects report, called Patient Report Outcomes (PROs)
- Patients participate in development of trials (Basch, CALGB/Alliance)

To Develop a specific QOL Assessment

- Literature search to identify primary toxicities expected
- Qualitative interviews with expert clinicians, patients receiving the treatment; traumatic content; analysis of common side-effects
- Collect poll of candidate items-related for importance reduce to most endorsed
- Pilot with patients for clarity, feed back, translatiblity and reading

CALGB 9221

A Randomized Phase III Controlled Trial of Subcutaneous Azacitidine in the Myelodysplastic Syndrome

RA
RARS
RAEB
RAEB-t
CMML

Stratify

Randomize

1) Supportive Care*

2) Aza C 75mg/m^2/d x 7 days q28 x 4

Exit Criteria

No → Continue until Endpoint+

Yes → Aza C (dose as per arm #2)

ASSESS

Response
- continue Rx

No Response
- Off Study

QOL M — QOL M — QOL M

0 — 29 — 57 — 113

Day

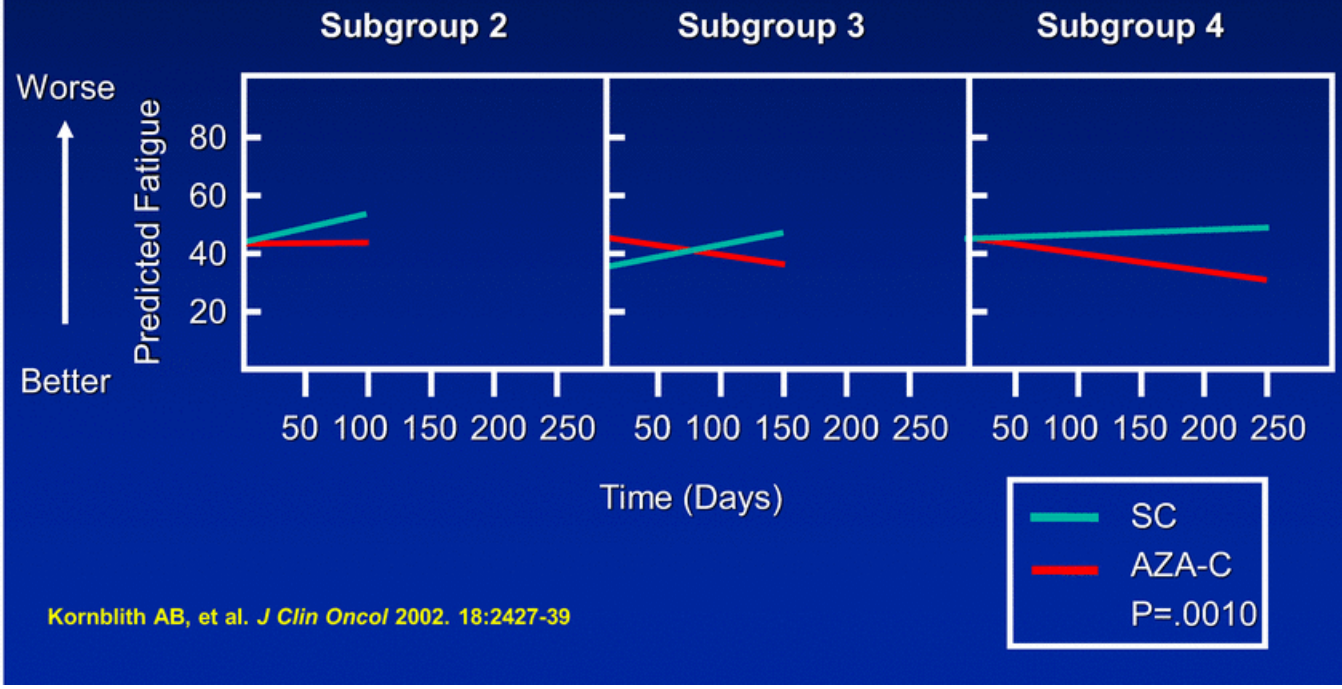
* Minimum duration on supportive care = 4 months unless transform to AML; death or plts ≤ 20 x 10^9/L at week 8 or later

QOL - Quality of Life Assessment
M = Bone Marrow Aza C- Azacitidine S.C.

Silverman L. *The Oncologist* 2001. 6 (S5): 8-14.
Silverman L, et al. *J Clin Oncol* 2002. 18:2414-26.
Kornblith AB, et al. *J Clin Oncol* 2002. 18:2427-39

CALGB 9221: Azacitidine vs. Supportive Care

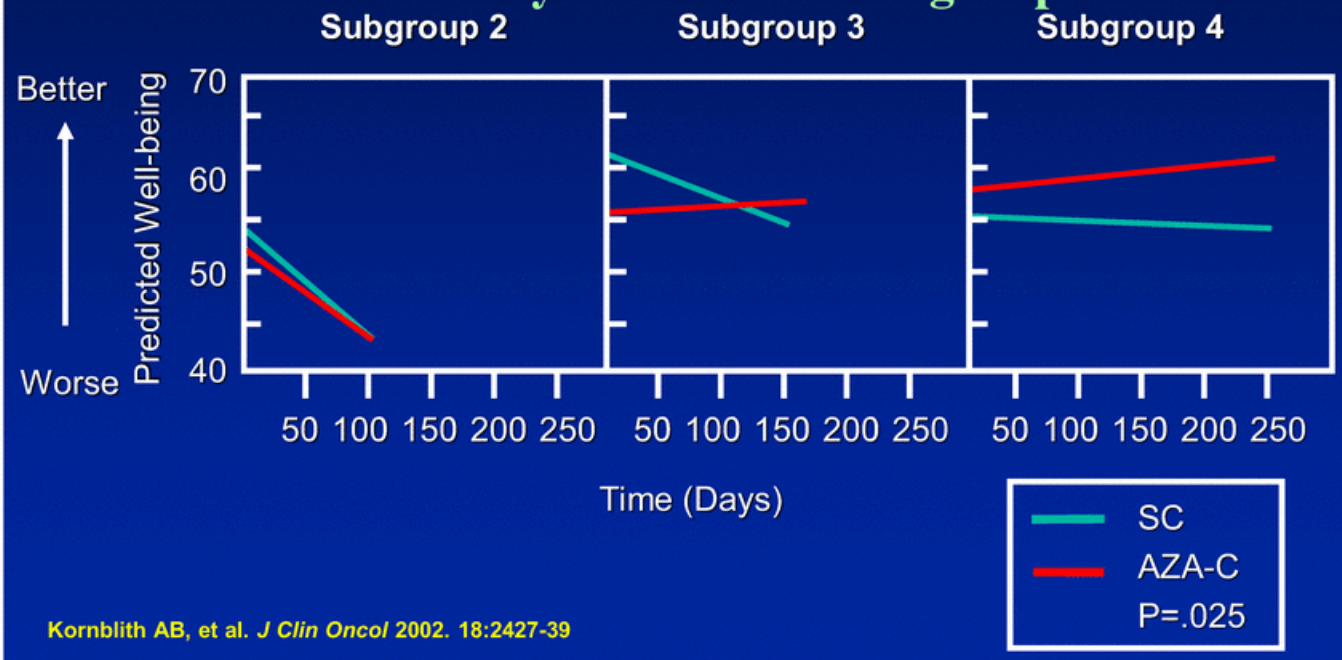
EORTC Fatigue Subscale by Assessment Subgroup



Kornblith AB, et al. *J Clin Oncol* 2002. 18:2427-39

CALGB 9221: Azacitidine vs. Supportive Care

MHI Psychological Well-Being Subscale by Assessment Subgroup



Kornblith AB, et al. *J Clin Oncol* 2002. 18:2427-39

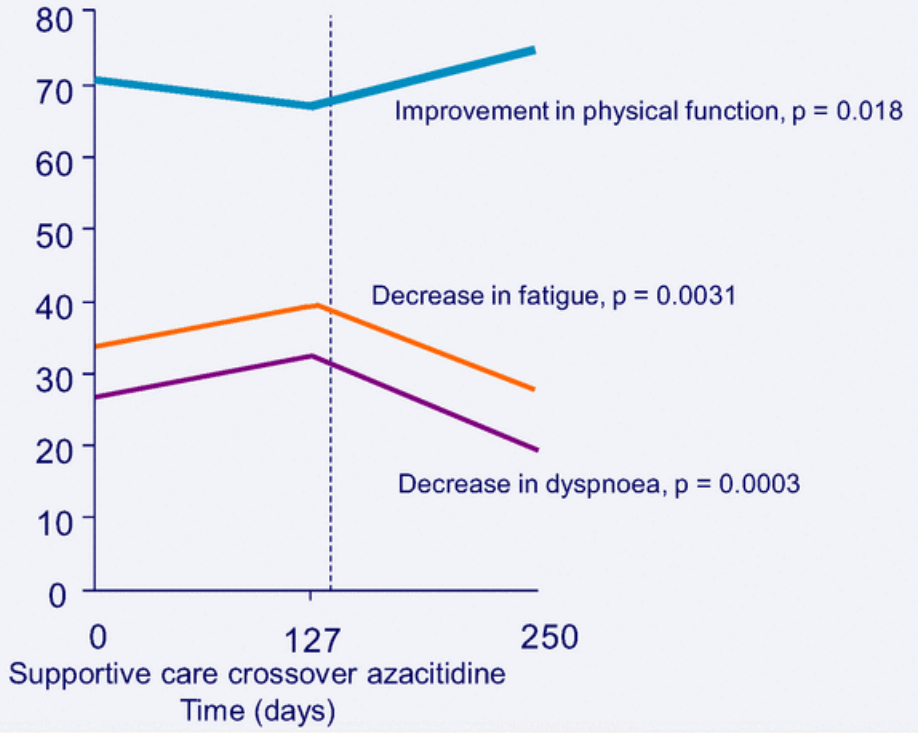
CALBG 9221: azacitidine vs supportive care – summary of quality of life findings

EORTC QoL Scale	Azacitidine vs supportive care (n = 191), p value	Crossover subset (n = 38), p value
Physical functioning	0.002	0.0040
Fatigue	0.010	0.0001
Dyspnoea	0.0014	0.0002
Insomnia	0.35	0.25
Social functioning	0.41	0.156
Overall QoL	< 0.0001	< 0.0001

EORTC = European Organisation for Research and Treatment of Cancer; QoL = quality of life.

Kornblith AB, et al. J Clin Oncol. 2002;20:2441-52.

Significant improvements in physical functioning, fatigue, and dyspnoea after crossover to azacitidine



Kornblith AB, et al. J Clin Oncol. 2002;20:2441-52.

Azacitidine vs. Supportive Care: Summary of Quality of Life Findings

QoL	QoL Scale	Aza-C vs. Supportive Care [n=191] [p]	Crossover Subset [n=38] [p]
	EORTC		
•	Physical Functioning	.0002	.0040
•	Fatigue	.0010	.0001
•	Dyspnea	.0014	.0002
•	Insomnia	.035	.025
•	Social Functioning	.041	.156
•	Overall QoL	<.0001	<.0001

Kornblith AB, et al. *J Clin Oncol* 2002. 18:2427-39

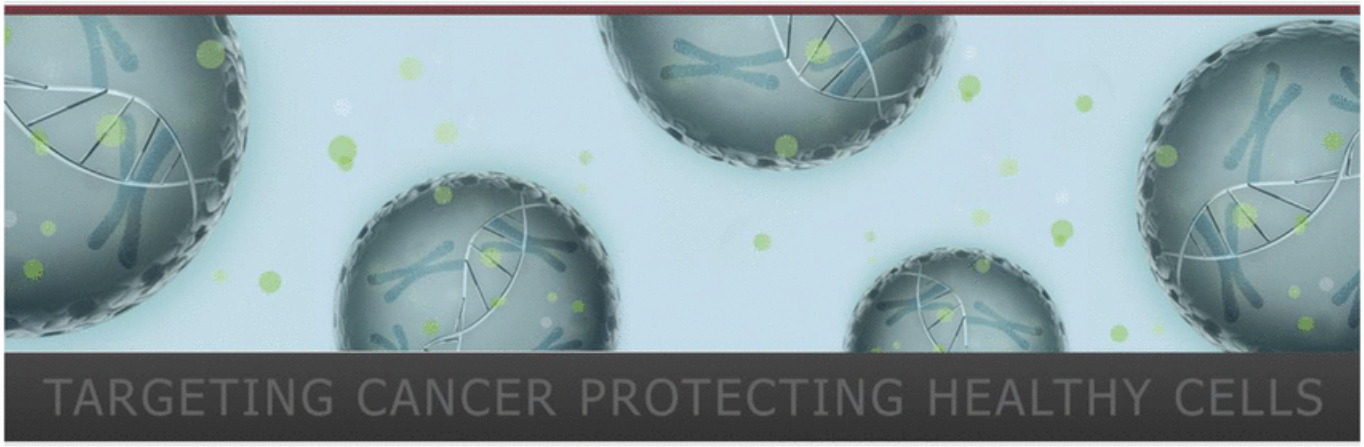
QOL Measurement

- Important in Research
- Important in Clinical Care

"Psycho-Oncology is the only subspecialty in cancer that is involved in the clinical care of every patient at every visit, irrespective of disease or treatment – "The Human Side of Cancer Care"

James F. Holland, MD
Oncologist and Supportive

ONCONOVA THERAPEUTICS



Thank You!