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): **November 6, 2014**

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 7.01. Regulation FD Disclosure.

On November 6, 2014, Onconova Therapeutics, Inc. (the "Company") issued a press release announcing that ten abstracts related to the Company's products, clinical trials and research were accepted for presentation at the 56th American Society of Hematology (ASH) Annual Meeting in San Francisco, California, to be held on December 6-9, 2014. All ten presentations are listed in the press release, which is attached hereto as Exhibit 99.1 and incorporated herein by reference.

On November 6, 2014, in connection with such presentations, ASH released such abstracts to the public by posting them on its website. The full text of each of the ten abstracts are attached to this Current Report on Form 8-K as Exhibits 99.2 through 99.11 and are incorporated herein by reference.

The information in Item 7.01 of this Form 8-K, and the related exhibits, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Press release issued by the Company dated November 6, 2014.
99.2	*Overall Survival and Subgroup Analysis from a Randomized Phase III Study of Intravenous Rigosertib Versus Best Supportive Care (BSC) in Patients (pts) with Higher-risk Myelodysplastic Syndrome (HR-MDS) After Failure of Hypomethylating Agents (HMAs)*
99.3	*Relationship of Bone Marrow Blast (BMBL) Response to Overall Survival (OS) in Patients with Higher-risk Myelodysplastic Syndrome (HR-MDS) Treated with Rigosertib After Failure of Hypomethylating Agents (HMAs)*
99.4	*Mutational Profile and Karyotypic Abnormalities of a Cohort of Clinical Trial Patients with Higher-risk Myelodysplastic Syndromes (MDS) Following Failure of Hypomethylating Agents (HMAs): Impact on Response to Rigosertib Therapy*
99.5	*A Phase I/II Study of the Combination of Oral Rigosertib and Azacitidine in Patients with Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML)*
99.6	*An in Vitro Platform to Dissect Drug Responsiveness in Refractory Anemia with Ringed Sideroblasts (RARS)*
99.7	*Incidence and Treatment of Myelodysplastic Syndrome in the US: Treatment Approaches, Optimization of Care and the Need for Additional Therapeutic Agents*
99.8	*Cost Effectiveness of Treatments after Failure of a First-Line Hypomethylating Agent in Myelodysplastic Syndromes (MDS)*
99.9	*Treatment Patterns Among Patients with Myelodysplastic Syndromes: Observations of 1st-Line Therapy, Discontinuation and the Need of Additional Therapies*
99.10	*Healthcare Resource Utilization and Costs Among Patients with Myelodysplastic Syndrome Who Failed 1st-Line Therapy*
99.11	*Weighted Gene Co-Expression Network Analysis (WGCNA) Identifies Highly Proliferative Myeloma Subgroup Responsive to CDK4/ARK5 Inhibition*

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: November 6, 2014

Onconova Therapeutics, Inc.

By: /s/ AJAY BANSAL
Name: Ajay Bansal
Title: Chief Financial Officer

EXHIBIT INDEX

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99.10 *Healthcare Resource Utilization and Costs Among Patients with Myelodysplastic Syndrome Who Failed 1st-Line Therapy*

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ONCONOVA
TARGETING CANCER | PROTECTING HEALTHY CELLS

Onconova Announces Ten Presentations at the 2014 ASH Annual Meeting

—Phase 3 ONTIME Trial Data Selected for Oral Presentation—

—Data from Phase 1/2 Trial of Oral Rigosertib and Azacitidine Combination Highlighted—

NEWTOWN, PA, November 6, 2014 — Onconova Therapeutics, Inc. (NASDAQ: ONTX), a clinical-stage biopharmaceutical company focused on discovering and developing novel products to treat cancer, today announced that ten abstracts were selected for presentation at the 56th American Society of Hematology (ASH) Annual Meeting in San Francisco, California, December 6-9, 2014. The key presentations include, the first detailed description of Phase 3 results from the ONTIME study of IV rigosertib in higher risk MDS, safety and efficacy data from the Phase 1 combination trial of oral rigosertib and azacitidine in MDS and AML, as well as studies with oral rigosertib in lower risk MDS.

Phase 3 ONTIME Trial Presentations:

Abstract #163
Overall Survival and Subgroup Analysis from a Randomized Phase III Study of Intravenous Rigosertib Versus Best Supportive Care (BSC) in Patients (pts) with Higher-risk Myelodysplastic Syndrome (HR-MDS) After Failure of Hypomethylating Agents (HMAs)

Date: Sunday, December 7, 2014
Presentation Time: 4:30 PM
Session: 637. Myelodysplastic Syndromes — Clinical Studies: Clinical Studies and Disease Characterization
Location: San Francisco Marriott Marquis, Yerba Buena Ballroom Salon 7
Presenter: Guillermo Garcia-Manero, MD, MD Anderson Cancer Center, Houston, TX

Abstract #3258
Mutational Profile and Karyotypic Abnormalities of a Cohort of Clinical Trial Patients with Higher-risk Myelodysplastic Syndromes (MDS) Following Failure of Hypomethylating Agents (HMAs): Impact on Response to Rigosertib Therapy

Date: Sunday, December 7, 2014
Time: 6:00 PM - 8:00 PM
Session: 637. Myelodysplastic Syndromes — Clinical Studies: Poster II
Location: Moscone Center, West Building, Level 1
Presenter: Ghulam J. Mufti, MD, Department of Haematological Medicine, King’s College London, London, United Kingdom

Abstract #3259
Relationship of Bone Marrow Blast (BMBL) Response to Overall Survival (OS) in Patients with Higher-risk Myelodysplastic Syndrome (HR-MDS) Treated with Rigosertib After Failure of Hypomethylating Agents (HMAs)

Date: Sunday, December 7, 2014
Time: 6:00 PM - 8:00 PM
Session: 637. Myelodysplastic Syndromes — Clinical Studies: Poster II
Location: Moscone Center, West Building, Level 1
Presenter: Lewis R. Silverman, MD, Division of Hematology/Oncology, Icahn School of Medicine at Mount Sinai, New York, NY

Oral Rigosertib/Azacitidine Combination Trial Presentation:

Abstract #3252
A Phase I/II Study of the Combination of Oral Rigosertib and Azacitidine in Patients with Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML)

Date: Sunday, December 7, 2014
Time: 6:00 PM - 8:00 PM
Session: 637. Myelodysplastic Syndromes — Clinical Studies: Poster II
Location: Moscone Center, West Building, Level 1
Presenter: Shyamala C. Navada, MD, Division of Hematology/Oncology, Icahn School of Medicine at Mount Sinai, New York, NY

Lower Risk MDS with Rigosertib Presentation:

Abstract #3243
An *in Vitro* Platform to Dissect Drug Responsiveness in Refractory Anemia with Ringed Sideroblasts (RARS)

Date: Sunday, December 7, 2014
Time: 6:00 PM - 8:00 PM
Session: 636. Myelodysplastic Syndromes — Basic and Translational Studies: Poster II
Location: Moscone Center, West Building, Level 1
Presenter: Siddhartha Mukherjee, MD, PhD, Department of Medicine, Division of Oncology, Columbia University Medical Center, New York, NY

MDS Epidemiology and Health Economics Presentations:

Abstract #1287
Incidence and Treatment of Myelodysplastic Syndrome in the US: Treatment Approaches, Optimization of Care and the Need for Additional Therapeutic Agents

Date: Saturday, December 6, 2014
Time: 5:30 PM - 7:30 PM
Session: 902. Health Services and Outcomes Research — Malignant Diseases: Poster I
Location: Moscone Center, North Building, Hall E
Presenter: Erin P. Demakos, RN, Division of Hematology/Oncology, Icahn School of Medicine at Mount Sinai, New York, NY

Abstract #1928
Cost Effectiveness of Treatments after Failure of a First-Line Hypomethylating Agent in Myelodysplastic Syndromes (MDS)

Date: Saturday, December 6, 2014
Time: 5:30 PM - 7:30 PM
Session: 637. Myelodysplastic Syndromes — Clinical Studies: Poster I
Location: Moscone Center, West Building, Level 1
Presenter: Christopher R. Cogle, MD, University of Florida, Gainesville, FL

Abstract #2598
Treatment Patterns Among Patients with Myelodysplastic Syndromes: Observations of 1st-Line Therapy, Discontinuation and the Need of Additional Therapies

Date: Sunday, December 7, 2014
Time: 6:00 PM - 8:00 PM
Session: 902. Health Services and Outcomes Research — Malignant Diseases: Poster II
Location: Moscone Center, North Building, Hall E
Presenter: Sudipto Mukherjee, MD, MPH, Cleveland Clinic Foundation, Cleveland, OH

Abstract #2627
Healthcare Resource Utilization and Costs Among Patients with Myelodysplastic Syndrome Who Failed 1st-Line Therapy

Date: Sunday, December 7, 2014
Time: 6:00 PM - 8:00 PM
Session: 902. Health Services and Outcomes Research — Malignant Diseases: Poster II
Location: Moscone Center, North Building, Hall E
Presenter: Christopher R. Cogle, MD, University of Florida, Gainesville, FL

Nonclinical Stage Onconova Pipeline Compound Presentation:

Abstract #3445
Weighted Gene Co-Expression Network Analysis (WGCNA) Identifies Highly Proliferative Myeloma Subgroup Responsive to *CDK4/ARK5* Inhibition

Date: Sunday, December 7, 2014
Time: 6:00 PM - 8:00 PM
Session: 652. Myeloma: Pathophysiology and Pre-Clinical Studies, Excluding Therapy: Poster II
Location: Moscone Center, West Building, Level 1
Presenter: Deepak Perumal, PhD, Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY

About Onconova Therapeutics, Inc.

Onconova Therapeutics is a clinical-stage biopharmaceutical company focused on discovering and developing novel products to treat cancer. Onconova's clinical and pre-clinical stage drug development candidates are derived from its extensive chemical library and are designed to work against specific

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cellular pathways that are important in cancer cells, while causing minimal damage to normal cells. In addition to rigosertib, the Company's most advanced product candidate, two other candidates are clinical stage, and several candidates are in pre-clinical stages. For more information, please visit http://www.onconova.com.

About Rigosertib

Rigosertib is a small molecule that inhibits cellular signaling by acting as a Ras mimetic. This is believed to be mediated by direct binding of rigosertib to the Ras-binding domain (RBD) found in many Ras effector proteins, including the Raf kinases and PI3K. The initial therapeutic focus for rigosertib is myelodysplastic syndromes (MDS), a group of bone marrow disorders characterized by ineffective hematopoiesis that often develop into acute myeloid leukemia (AML). Clinical trials with intravenous (IV) and oral formulations of rigosertib are being conducted at leading institutions in the U.S. and abroad. To date, more than 500 MDS patients have been enrolled in clinical trials with rigosertib. Rigosertib is covered under composition of matter patents issued worldwide. Orphan designation has been granted for rigosertib in MDS in the U.S., Europe and Japan.

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Abstract 163

Overall Survival and Subgroup Analysis from a Randomized Phase III Study of Intravenous Rigosertib Versus Best Supportive Care (BSC) in Patients (pts) with Higher-risk Myelodysplastic Syndrome (HR-MDS) After Failure of Hypomethylating Agents (HMAs)

Guillermo Garcia-Manero, MD(1), Pierre Fenaux, MD(2), Aref Al-Kali, MD(3), Maria R. Baer, MD(4), Mikkael Sekeres, MD(5), Gail Roboz, MD(6), Gianluca Gaidano, MD(7), Bart Scott, MD(8), Peter Greenberg, MD(9), Uwe Platzbecker, MD(10), David P. Steensma, MD(11), Suman Kambhampati, MD(12), Karl-Anton Kreuzer, MD(13), Lucy Godley, MD(14), Robert Collins, Jr, MD(15), Ehab Atallah, MD(16), Francois Wilhelm, MD, PhD(17), Isabelle Darnis-Wilhelm, MD(17), Nozar Azarnia, PhD(17), Manoj Maniar, PhD(17), Lewis R. Silverman, MD(18)

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(9) Stanford Medical School, Stanford, CA
(10) Universitätsklinikum Dresden, Dresden, Germany
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(13) Universitätsklinikum Köln, Köln, Germany
(14) University of Chicago Medical Center, Chicago, IL
(15) Univ of Texas, Southwestern Medical Center at Dallas, Dallas, TX
(16) Froedtert Hospital and Medical College of Wisconsin, Milwaukee, WI
(17) Onconova Therapeutics, Inc., Newtown, PA
(18) Division of Hematology/Oncology, Icahn School of Medicine at Mount Sinai, New York, NY

Background: No approved treatment options are available to HR-MDS pts after HMA therapy. Study 04-21 (“ONTIME” trial) was a Phase III, randomized, controlled study of the efficacy and safety of rigosertib, a novel small molecule inhibitor of PI3-kinase and PLK pathways, in a heterogeneous population of MDS pts who had relapsed after, failed to respond to, or progressed during administration of HMAs. The study was conducted at 87 sites in the United States and 5 European countries.

Methods: From Dec 2010 to Aug 2013**,** 299 HR-MDS pts [<30% bone marrow blasts (BMBL)] who had progressed on (37% of total enrollment), failed to respond to (25%), or relapsed after (38%) HMA treatment were stratified on BMBL count and randomized 2:1 to receive rigosertib (199 pts) or BSC (100 pts). Rigosertib was administered at 1800 mg/24 hr for 72-hr as a continuous intravenous (CIV) ambulatory infusion, every 2 weeks for the first 16 weeks, and

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then every 4 weeks. The primary endpoint was overall survival (OS), analyzed on an intention- to-treat (ITT) basis using the Kaplan-Meier method stratified on BMBL (5% to 19% vs. 20% to 30%). The trial had a 95% power to detect a 13-wk increase in median OS from 17 wks on BSC, with a 2-sided alpha = 0.05. The following results are based on 242 deaths: 161 in the rigosertib arm and 81 in the BSC arm.

*Results***:** Overall, the 2 arms were balanced in terms of baseline characteristics, with the majority of pts being male (66%), and White (82%). Age ranged from 50-90 yrs in the rigosertib arm and 55-86 years in the BSC arm (median, 74 yrs). The majority of pts (85%) had an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1. The median duration of the last HMA therapy was 8.8 months (mo) in the rigosertib arm and 10.3 mo in the BSC arm; 127 (64%) of rigosertib pts and 57% of BSC pts were classified as “primary HMA failure” (ie, they failed to respond to or progressed during HMA therapy, as defined by Prebet et al, J Clin Oncol, 2011).

A 2.3-mo improvement in median OS was found in the overall (ITT) population (8.2 mo rigosertib vs. 5.9 mo BSC) (Figure 1). The ITT survival for rigosertib was similar to that noted in Phase I/II studies (35 weeks). The stratified log-rank p-value was 0.33. The stratified hazard ratio was 0.87, which was quite different from the ratio of medians (5.9/8.2 = 0.72), due to the fact that the 2 survival curves converged at 15 mo.

Notably, among the 184 patients with primary HMA failure, the median OS was 8.6 mo in the rigosertib arm (N = 127) vs. 5.3 mo in the BSC arm (N = 57), HR= 0.69, p= 0.040 (Figure 2).

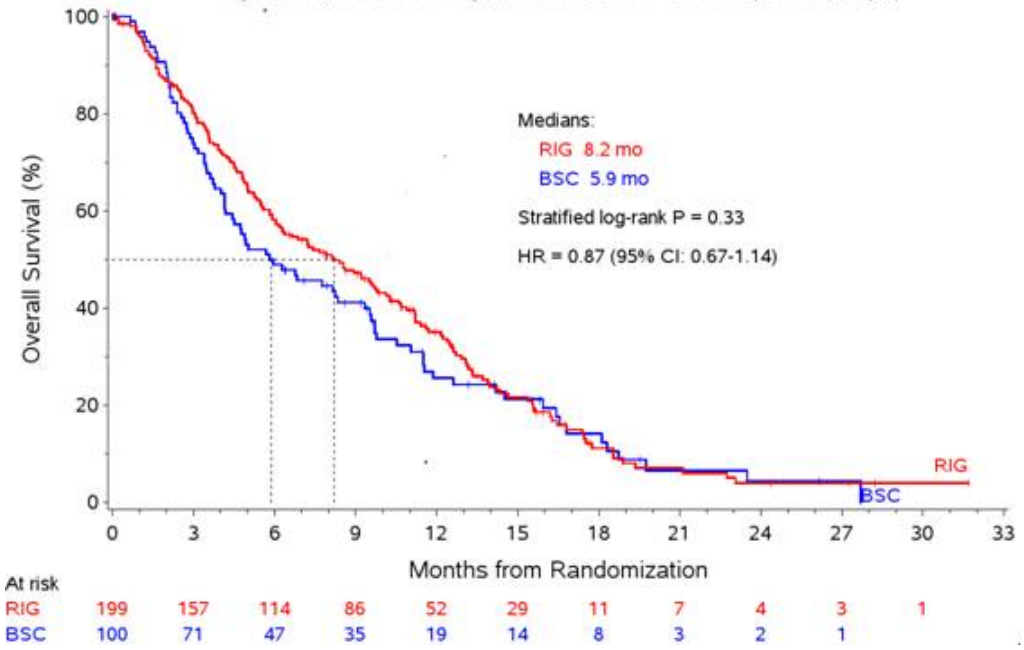
Multivariate Cox regression, adjusting for pretreatment prognostic factors, showed little change in the treatment effect. The following subgroups were correlated with better OS: pts with failure of/progression on HMA treatment, pts with duration of HMA treatment $\leq$ 9 mo, pts < 75 years of age, and pts with very high risk per IPSS-R (Figure 3).

Rigosertib was well tolerated, with a median dose intensity of 92%. There were no significant compliance or operations issues related to ambulatory continuous infusion. Protocol-defined dose reductions were reported in 5% of pts, with 24% experiencing dose delays of >7 days, mostly due to unrelated adverse events (AEs). No obvious differences between rigosertib and BSC were found in the incidence of AEs (rigosertib, 99%; BSC, 85%) or of $\geq$ Grade 3 AEs (rigosertib, 79%; BSC, 68%). In the rigosertib arm, AEs reported by $\geq$ 20% of pts, irrespective of severity or causality, were nausea (35%), diarrhea (33%), constipation (31%), fatigue (30%), fever (27%), anemia (22%), and peripheral edema (21%). Rigosertib had low myelotoxicity, consistent with previous clinical experience.

Conclusions: Although the primary endpoint in this Phase III study of rigosertib vs BSC in pts with HR-MDS did not reach statistical significance in the ITT population, encouraging rigosertib treatment-related improvement in OS was noted in several subgroups of MDS pts, including those with “primary HMA

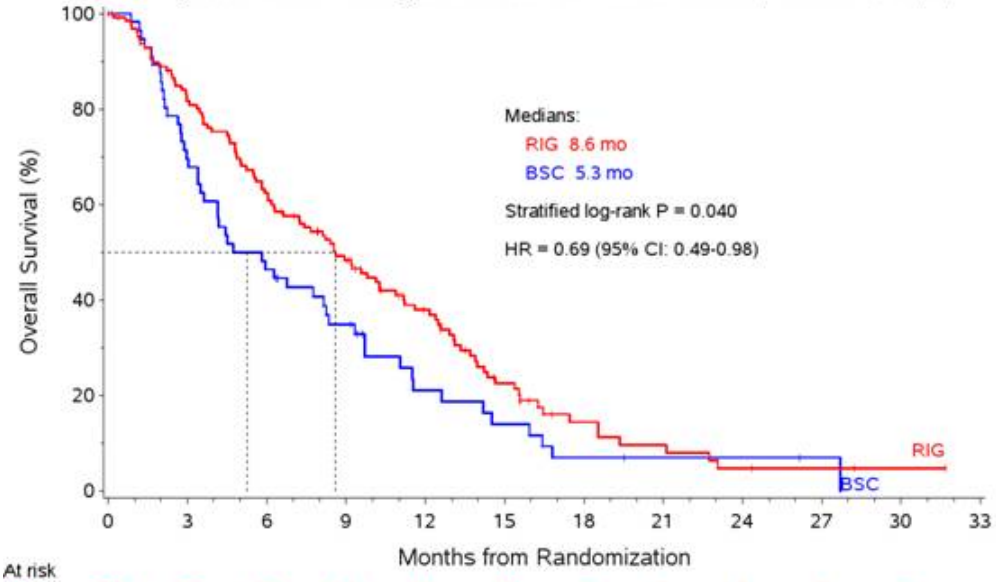
failure and in patients in the IPSS-R Very High Risk category. CIV therapy with rigosertib had a favorable safety profile in this orphan population of elderly pts with MDS.

Figure 1: Overall Survival in Rigosertib and BSC Arms - Overall Population (299 pts)



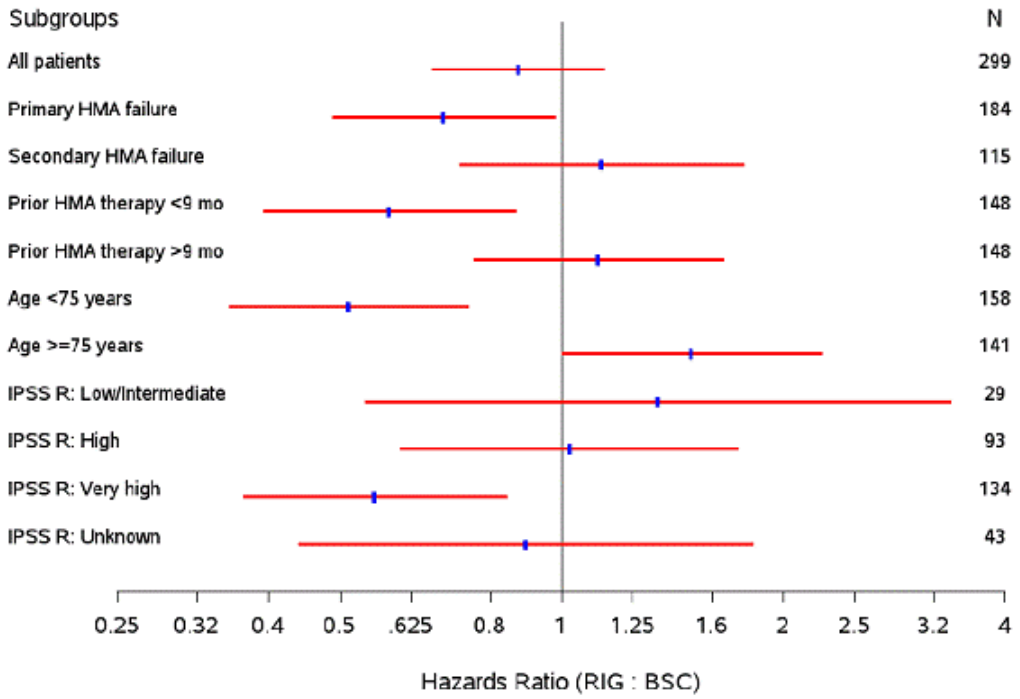
At risk											
RIG	199	157	114	86	52	29	11	7	4	3	1
BSC	100	71	47	35	19	14	8	3	2	1	

Figure 2: Overall Survival in Rigosertib and BSC Arms - Patients with Primary HMA Failure (184 pts)



At risk											
RIG	127	102	78	56	37	19	9	6	3	2	1
BSC	57	39	26	18	9	6	3	2	2	1	

Figure 3: Overall Survival in Selected Subgroups



Primary HMA failure = pts who failed to respond to or progressed during HMA therapy; Secondary HMA failure = pts who relapsed after HMA therapy; IPSS-R = International Prognostic Scoring System - Revised

Abstract 3259

Relationship of Bone Marrow Blast (BMBL) Response to Overall Survival (OS) in Patients with Higher-risk Myelodysplastic Syndrome (HR-MDS) Treated with Rigosertib After Failure of Hypomethylating Agents (HMAs)

Lewis R. Silverman, MD(1), Pierre Fenaux, MD(2), Aref Al-Kali, MD(3), Maria R. Baer, MD(4), Mikkael Sekeres, MD(5), Gail Roboz, MD(6), Gianluca Gaidano, MD(7), Bart Scott, MD(8), Peter Greenberg, MD(9), Uwe Platzbecker, MD(10), David P. Steensma, MD(11), Suman Kambhampati, MD(12), Karl-Anton Kreuzer, MD(13), Lucy Godley, MD(14), Robert Collins, Jr, MD(15), Ehab Atallah, MD(16), Shyamala C Navada, MD(1), Francois Wilhelm, MD, PhD(17), Nozar Azarnia, PhD(17), Guillermo Garcia-Manero, MD(18)

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Background: Patients (pts) with HR-MDS have a median OS of 4 to 6 months (mo) after HMA failure (Prebet et al, J Clin Oncol 2011) and no approved salvage therapy. Development of new therapeutics for this population will benefit from the availability of surrogate endpoints and markers that can predict survival. Gore et al established response to azacitidine (Vidaza®) in first-line therapy for HR-MDS as a reasonable surrogate to predict survival (Gore et al, Haematologica 2013). Rigosertib, a novel dual PI3K/PLK pathway inhibitor, has been shown to reduce bone marrow blasts (BMBL) in these pts (Seetharam et al, Leuk Res 2012). Silverman et al described complete or partial bone marrow (BM) response, or stabilization after 4-8 weeks (wks) of treatment with rigosertib as a potential surrogate for predicting survival in pts with HR-MDS after failure of primary HMA therapy (Silverman et al, Hematol Oncol 2014). We tested this hypothesis in the context of a randomized Phase III trial.

Methods: Pts with HR-MDS were randomly assigned 2:1 to rigosertib or best supportive care (BSC) after progressing on, failing to respond to, or relapsing after HMA treatment. BM aspirates were assessed pretreatment, at 4 weeks and at 8-week intervals thereafter. Central slide review was undertaken in a representative population of samples. The BMBL response at each

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time point was assessed using the following definitions: bone marrow complete response (mCR) = BMBL $\leq$ 5% and decrease of $\geq$ 50% from baseline; bone marrow partial response (mPR) = BMBL decrease from baseline of $\geq$ 50%, but BMBL still > 5%; stable disease (SD) = BMBL decrease or increase from baseline of < 50%; progressive disease (PD) = BMBL increase from baseline of $\geq$ 50% by an absolute minimum of 5%; Not evaluable (NE).

Results: Bone marrow assessment was carried out in 156 patients (pts) on the rigosertib arm and 24 pts on the BSC arm at 4 wks after enrollment, and in 86 and 20 pts, respectively, at 12 wks. The invasive BM procedure was optional on the BSC arm, which accounts for the low number of assessments in this group. BM responses at the 2 time points are presented in Table 1.

Since no difference in overall survival was noted between pts who had objective BM response and those who did not progress (ie, stable disease), a landmark analysis was conducted that separated pts who were alive at the 4-wk landmark time into two 4-wk response categories: BM response + SD vs. PD. Results of this analysis in rigosertib-treated patients were statistically significant at p = 0.011, with a hazard ratio (HR) of 0.62 and a median OS (from 4 wks onward) of 9.8 months in the mCR + mPR + SD group vs. 4.6 months in the PD group (Figure 1).

Another landmark analysis was conducted at 12-wks. Results of this analysis were also significant (p < 0.001) in rigosertib-treated patients, with an HR of 0.39 and a median OS (from 12 wks onward) of 10.4 months in the mCR + mPR + SD group vs.7.5 months in the PD group (Figure 2).

A time-dependent Cox regression of OS by 4-wk BMBL response reinforced the validity of the 4-wk and 12-wk BM assessments as surrogate biomarkers for survival (Table 2).

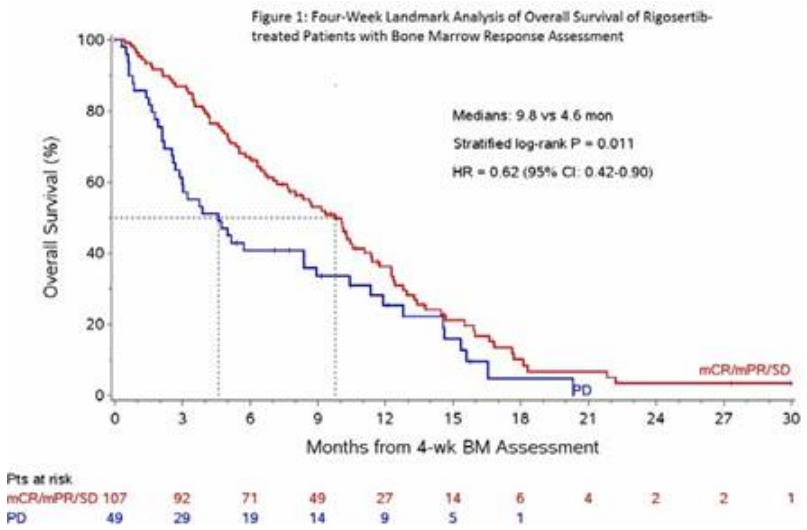
Conclusions: These data suggest that BMBL response at 4 or 12 weeks was correlated with OS in this population of pts with HR-MDS treated with rigosertib after HMA failure and are consistent with previous observations in Phase II studies.

Table 1
4- and 12-week Bone Marrow Blast Response (Intention-to-Treat Population)

	Number (%) of Patients

	4-wk BMBL Response		12-wk BMBL Response	
	Rigosertib N = 199	BSC N = 100	Rigosertib N = 199	BSC N = 100
Pts with BMBL assessment	156 (78)	24 (24)*	86 (43)	20 (20)*
BM complete response (mCR)	22	4	11	5
BM partial response (mPR)	8	2	9	2
Stable disease (SD)	77	9	32	8
Progressive disease (PD)	49	9	34	5

* Bone marrow assessment was not required on the BSC arm.



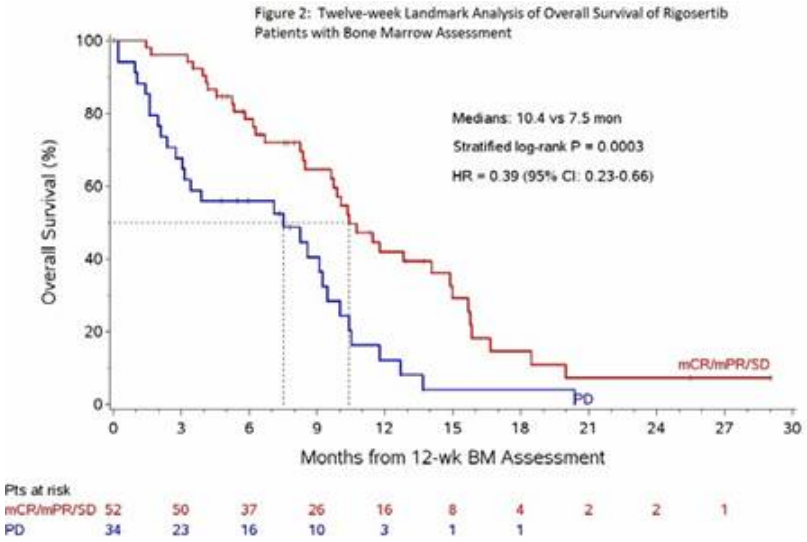


Table 2
Time-dependent Cox Regression of Overall Survival by Bone Marrow Blast Response

	Rigosertib		BSC	
Analysis	Wald P-value	Hazard Ratio (95% Confidence Interval)	Wald P-value	Hazard Ratio (95% Confidence Interval)
By 4-wk BMBL response	0.051	0.72 (0.51 - 1.00)	0.56	0.83 (0.45 - 1.54)
By 12-wk BMBL response	0.0005	0.55 (0.39 - 0.77)	0.16	0.68 (0.39 - 1.17)

*Stratified by pretreatment BMBL: 5%-19% vs. 20%-30%

Abstract 3258

Mutational Profile and Karyotypic Abnormalities of a Cohort of Clinical Trial Patients with Higher-risk Myelodysplastic Syndromes (MDS) Following Failure of Hypomethylating Agents (HMAs): Impact on Response to Rigosertib Therapy

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Background: The last decade has seen impressive advances in identifying the genetic landscape and clinical heterogeneity of MDS. Diverse cytogenetic abnormalities and specific aberrations in RNA splicing, cell-signaling, transcription regulation and tumor suppressor genes are increasingly being applied for the prognostic stratification of these pts at diagnosis. Despite these advances, treatment options are limited to HMA therapy and lenalidomide; the survival advantage of these agents is established, but most pts eventually relapse. Furthermore, the prognosis for pts in whom HMA therapy has failed is grim, with a median OS of 4.3 to 5.6 months (Jabbour et al, Cancer, 2010; Prébet et al, J Clin Oncol, 2011). The clonal architecture and evolution of molecular changes has been chronicled in newly diagnosed MDS pts but the assessment of these abnormalities in pts who have failed or relapsed after HMAs is limited. Here we document for the first time the very high incidence of these molecular changes in higher-risk MDS patients after failure of HMAs and assess the relationship between the genetic and cytogenetic abnormalities and response to a novel agent, rigosertib. We correlate the results of cytogenetic abnormalities in HMA failures with response to rigosertib in the context of a clinical trial that compared this treatment with best supportive care.

Methods: Genomic DNA was isolated from single microscopic slides from 153 pts from Study 04-21 and subjected to sequence analysis of a "myeloid panel" comprising of 24 selected loci known to be frequently mutated in MDS and AML. Standardized cytogenetic investigations were performed using G banding and centrally reviewed. Whenever possible, 25 metaphases were analysed. Description of chromosome aberrations and clone definition followed the International System for Cytogenetic Nomenclature. FISH for deletion 5q was included. Depending on the aberrations detected during karyotyping, further probes were applied. A complex karyotype was defined as $\geq$3 independent aberrations within 1 clone.

Results: Adequate DNA samples were obtained from 92 (60%) of 153 patients. All but 8 of the 92 samples carried at least 1 mutation (91%), with 16 of the 24 myeloid mutations detected. The most frequently mutated loci were TP53 (23%, mutations were detected at multiple coding regions of the protein), SRSF2 (17%), U2AF1 (16%). SF3B1 (13%), ASXL1 (13%) and TET2 (10%). Mutations were found in RUNX1 (5 samples); 4 samples each carried a mutation in

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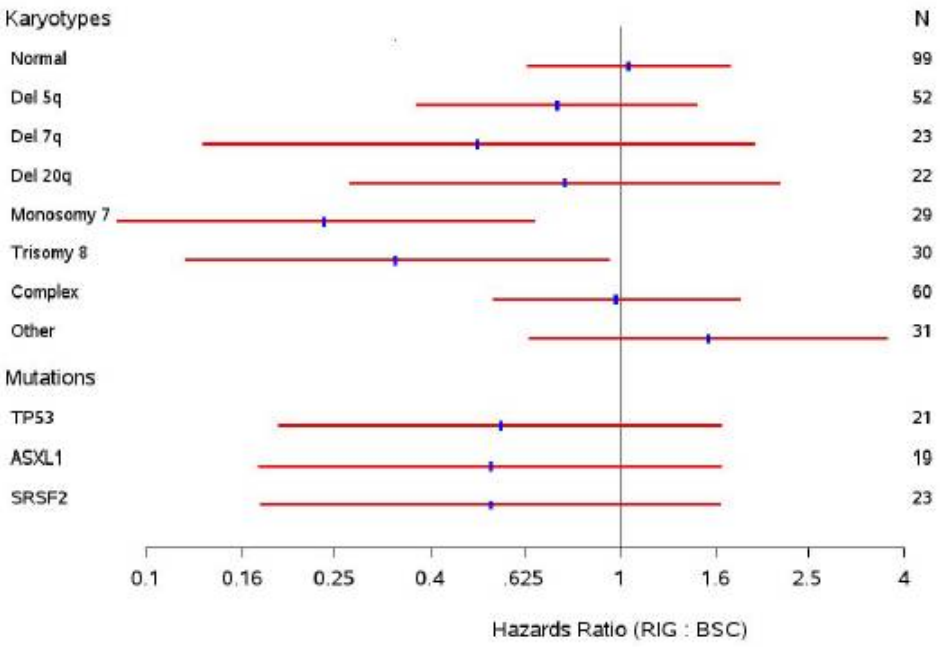
ETV6 (4), EZH2 and N- and K-ras. All but 1 of the mutations were represented at >10% of the alleles, with a range of 9.2-94%. Sixty-two percent of mutations detected in rigosertib patients who did not respond to initial HMA therapy ("primary" HMA failure, 61% of the study population) carried single or multiple mutations. The effect of single and multiple mutations on OS is summarized in Figure 1. Patients carrying mutations in TP53, ASXL1, and SRSF2 showed a trend toward increased survival benefit of rigosertib therapy. It is noteworthy that pts with monosomy 7 and trisomy 8 mutations demonstrated a survival benefit with rigosertib therapy compared to BSC (monosomy 7: HR = 0.24, p = 0.0033; trisomy 8: HR = 0.34, p = 0.035). The significance of individual and combined mutations, in the context of "founder" and "subclonal" lesions is being evaluated further.

Conclusions: We have investigated the role of karyotype and point mutations in MDS patients after failure of HMA therapy and evaluated these changes to response in a clinical trial. Certain karyotypes were linked to enhanced survival benefit of rigosertib. The majority of second-line MDS patients carry mutations including those associated with poor prognosis. These results have important implications on designing therapeutic approaches and trials for MDS pts after failure of HMAs.

Figure 1
Overall Survival by Karyotype/Mutations


Karyotypes
N
Normal
99
Del 5q
52
Del 7q
23
Del 20q
22
Monosomy 7
29
Trisomy 8
30
Complex
60
Other
31
Mutations
TP53
21
ASXL1
19
SRSF2
23
0.1
0.16
0.25
0.4
.625
1
1.6
2.5
4
Hazards Ratio (RIG : BSC)

Abstract 3252

A Phase I/II Study of the Combination of Oral Rigosertib and Azacitidine in Patients with Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML)

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Background: Rigosertib is a small molecule anti-cancer agent targeting PI3/polo-like kinase pathways that promotes G2/M arrest and has effects on the B-Raf and Ras pathways. It is currently being tested as a single agent with the intravenous (IV) formulation in patients (pts) who have relapsed or are refractory to hypomethylating agents (HMAs) as well as with the oral formulation in lower-risk, red-cell transfusion-dependent MDS patients. Azacitidine (AZA) is first-line therapy for pts with higher-risk MDS. In vitro, the combination of rigosertib with AZA acts synergistically to inhibit growth and induce apoptosis of leukemic cells (Skidan et al 2006). This effect appears to be sequence dependent, requiring exposure to rigosertib first, followed by AZA. These nonclinical results provided the rationale to combine the 2 agents in a phase I/II study in pts with MDS and AML.

Methods: Pts with MDS and non-proliferative AML, who were previously untreated or had failed or progressed on an HMA were included in the phase I component of the study. Oral rigosertib was administered twice daily from day 1 through day 21 of a 28-d cycle. AZA 75 mg/m^2/d was administered for 7 days starting on day 8 of the 28-d cycle. Pts were entered in 3 escalating-dose cohorts of rigosertib in a classic 3+3 design: [1] 140 mg twice daily; [2] 280 mg twice daily; [3] 560 mg qAM and 280 mg qPM. A CBC was performed weekly and a bone marrow (BM) aspirate and/or biopsy was performed at baseline and every 4-8 weeks afterwards.

Results: Eighteen pts have been treated with the combination of oral rigosertib and AZA. Pts had diagnoses of intermediate-1 MDS (3), intermediate-2 MDS (6), high-risk MDS (2), CMML (1), and AML (6); median age was 70.5 years; 61% of pts were male. Pts have received 1-10+ cycles of treatment with the total number of cycles administered thus far being 58. Cytogenetic profiles by IPSS were good (8 pts), poor (8 pts), and intermediate (2 pts). 11 of 18 patients were transfusion dependent at baseline [RBC (11), platelet (6)]. One patient became RBC transfusion independent after 3 cycles of treatment. 5 additional patients have had a reduction in their RBC and platelet transfusion requirements. 56% of patients received prior treatment with HMAs:

AZA (6 pts), decitabine (4 pts). The most frequent adverse events (AEs) in Cycle 1 included constipation, diarrhea, nausea, fatigue, hypotension, and pneumonia. The AEs did not differ significantly among the 3 cohorts. Elevation in creatinine in 1 pt in cohort 1 was a possibly related grade 3 dose-limiting toxicity that required subsequent expansion of the cohort. Drug- related dysuria/cystitis was not reported in this pt population**.** Responses according to IWG 2006 criteria were observed in the BM and peripheral blood: Complete Response (CR) (1 pt), Cr_i (CR with incomplete blood count recovery) (4 pts), stable disease (2), hematologic improvement- erythroid (1)**.** Six pts received fewer than 4 cycles of treatment and are too early to evaluate. Six pts came off study for the following reasons: progression of disease (1), pt request (1), death from pneumonia (2), received stem cell transplant (1), persistent fungal pneumonia (1). Two evaluable pts have responded to the combination after progression or failure on HMA alone.

Conclusions: The combination of oral rigosertib at 560/280 mg BID (recommended phase II dose) and standard-dose AZA can be safely administered and appears to be well tolerated in repetitive cycles in pts with MDS and non-proliferative AML. The AE profile does not differ significantly from that of AZA alone. Data from the Phase I component of this study suggest activity in patients with MDS after HMA failure. Additional data are required to evaluate this observation. The Phase II segment of this study is underway to further assess the response of the combination.

Patient ID	Diagnosis	Prior HMA	% Blasts in BM at Baseline	% Blasts in BM after Treatment	IWG Response
1	MDS	No	2	1	CRi
2	AML	No	40	0	CRi
3	AML	No	22	N/A	NE
4	MDS	Azacitidine	0	0	NE
5	AML	No	59	N/A	NE
6	MDS	No	21	<5	CRi
7	MDS	No	2	1	CR
8	MDS	No	2.5	2	SD
9	AML	Decitabine	25	N/A	NE
10	MDS	Decitabine	12	3	CRi
11	CMML	Azacitidine	2	3	SD
12	MDS	Azacitidine	4	1	HI-E
13	AML	Azacitidine	47	40	TE
14	AML	Decitabine	7	7	TE
15	MDS	No	9	5	TE
16	AML	No	25	6	TE
17	AML	No	15	19	TE
18	AML	Azacitidine	64	45	TE

IWG = International Working Group

CR = Complete Response
CRi = Complete Response with incomplete blood count recovery
NE = Not Evaluable
SD = Stable Disease
HI-E = Hematologic Improvement - Erythroid
TE = Too Early

Abstract 3243

An *in Vitro* Platform to Dissect Drug Responsiveness in Refractory Anemia with Ringed Sideroblasts (RARS)

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Background: Despite intensive investigation, the pathophysiology of low-risk myelodysplastic syndrome (LR-MDS) remains unknown and therapeutic options are limited. In a phase-II trial, treatment with oral rigosertib, a small molecule inhibitor of PI3K and PLK pathways, was shown to have a 39% response rate (i.e., transfusion independence), in patients with LR-MDS. Notably, rigosertib caused an increase in hemoglobin, a decrease in transfusion requirements, and, in some patients who were previously refractory, “re-sensitization” to erythropoietin (EPO) therapy. However, thus far, the mechanism of this responsiveness remains unknown. Whole exome sequencing revealed a broad spectrum of mutations in these patients, including mutations in *SF3B1*, *SRSF2* and *TET2*. However, there was no correlation between mutational spectrum and responsiveness.

Methods: Here, we have devised an in vitro platform to predict responsiveness, and dissect the rigosertib mechanism of action. This study is approved by the Institutional Review Board of Columbia University and informed consent was obtained from all the individuals participated in the study. CD34+ cells were isolated from bone marrow (BM) mono nuclear cells derived from BM aspirates. Bone marrow stromal cells (BMSC) were isolated from bone biopsies of patients with MDS. Normal CD34+ cells and BMSC were obtained from commercial sources. CD34+ cells were co-cultured with stromal cells plated a day before and stimulated with various concentration of EPO and rigosertib. Differentiation was assessed by staining cells with various markers of erythroid differentiation including GPA, band 3, Integrin alpha 4 antibodies conjugated with fluorophores and analyzed by FACS. We show that co-culture of CD34+ stem cells from the bone marrow of patients with their own BMSC recapitulates key features of the MDS phenotype and rigosertib responsiveness.

Results: Normal (non-MDS) CD34+ cells co-cultured with normal BMSC showed striking responsiveness to EPO stimulation, as evidenced by the increased production of CD45- low/GPA+/ band 3+/Integrin-Alpha4+ erythroid cells (2.47 fold increase compared to no EPO). In contrast, RARS CD34+ cells co-cultured with MDS stromal cells showed no erythroid differentiation with EPO stimulation (1.09 fold change compared to EPO). Notably, LR-MDS co-cultures showed increased erythroid differentiation with the addition of 20 nm and 100 nm rigosertib in the presence of EPO (1.28 and 1.4 fold increase, respectively, compared to EPO alone). Moreover, co-cultures obtained from 3/3 patients that showed responsiveness in vivo were responsive to combined EPO/rigosertib stimulation in vitro, while 2/2 non-responsive patients were not responsive in vitro.

Conclusions: We have created an in vitro platform to dissect the mechanism of rigosertib responsiveness in RARS patients. This platform is a novel co-culture-based system that recapitulates key features of the RARS phenotype. In the absence of reliable animal models for this disease, this platform may offer a viable method to characterize drug responsiveness, dissect mechanisms, and offer patient-specific drug responsiveness information, since individual CD34+ cells are co-cultured with a patient’s own BMSC. In future, we wish to use this in vitro co- culture test to prospectively predict responsiveness to experimental drugs in patients, thereby focusing the drug on only selected patients.

Abstract 1287

Incidence and Treatment of Myelodysplastic Syndrome in the US: Treatment Approaches, Optimization of Care and the Need for Additional Therapeutic Agents

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*Background***:** The incidence of myelodysplastic syndromes (MDS) - a heterogeneous group of malignant myeloid stem cell disorders - increases with age and commonly affects older people. The prevalence of MDS in the US has been constantly rising as a result of increasing longevity of the overall population. Analyses of healthcare claims data using associated medical claims information (ICD-9-CM diagnosis codes) are a common way to estimate the number patients (pts) receiving care in specific disease states. We examined the total of unique US claims for MDS submitted over a 3-year period and also analyzed the claims according to type of treatment.

*Methods***:** We conducted a retrospective cohort study of patients (pts) with an MDS-associated medical claim (ICD-9-CM diagnosis code 238.7x) in the observation (OB) period (calendar years 2009-2011). In each year of the OB period, pts were classified according to type of treatment: watch and wait (ie, receiving no drug therapy) or interventional treatment [ie, supportive care treatment with erythropoietin stimulating agents (ESA) or growth factors (GF) and active drug treatment (ie, the hypomethylating agents (HMA) azacitidine (AZA) and decitabine (DEC) and the immunomodulating agent lenalidomide (REV)]. A subgroup of newly diagnosed MDS pts was also identified in Years 2 and 3, but this group was not included in Year 1 of the OB period (calendar year 2009); this group of new-to-treatment patients had a claim for MDS in Years 2 and 3 of the OB period. MDS incidence rates were then determined within Years 2 and 3 of the OB period for this group. The total number of physicians treating pts coded for MDS was also collected.

*Results***:** We identified more than 100,000 unique pts with an MDS-associated claim in each of the 3 years of the OB period. Our calculated incidence of newly treated MDS pts (34,000) in Years 2 and 3 is consistent with recently reported estimates (Cogle et al, Blood 2011; Goldberg et al, J Clin Oncol 2010) but higher than the SEER database. Over the 3-year OB period, the number of diagnosed and treated MDS pts grew year on year and grew at a slower rate than that of the US population. Watch-and-wait is the mainstay treatment for 47% of MDS pts. We found that 6000 pts per month are treated with an HMA by 2100 physicians, or 2.8 pts per physician and 14,000 pts receive therapy for MDS comprised of ESA, GF, AZA, DEC or REV per year. AZA and DEC were the predominant HMA treatments prescribed for higher-risk MDS. Approximately 30% of HMA-treated reached the target number of 6 cycles. HMA therapies were used in 13.1% of pts. A larger percentage of the AZA- and DEC-treated pts (69.1%) stopped therapy before reaching the target number of doses, with approximately 32% of pts who initiated therapy dropping out after the first cycle.

*Conclusions***:** The total number of pts coded for MDS-associated ICD-9 billing in the US each year is substantial. The estimated incidence of 34,000 patients per year with MDS in the US in 2010 and 2011 is similar to results found in other epidemiological databases. The majority of pts are not treated with the optimal number of cycles with an HMA. The average physician treats only a limited number of pts with MDS, which may influence treatment decisions. These data suggest a need for further educational efforts to optimize care with additional insight into past population-based estimates of diagnosis and treatment (Cogle et al, Blood 2011; Goldberg et al, J Clin Oncol 2010). The data showing early discontinuation or failure of HMA therapy accentuates the poor prognosis of patients post-HMA, who have a predicted median survival of 4-6 months (Prebet et al, J Clin Oncol 2011). These data may serve to better inform the medical community of the unmet need of pts who are not successfully treated with first-line MDS therapies, underscoring the need for optimization of care and the need for additional agents beyond those currently available.

HMA Cycle and Administration Metrics per Line of Therapy

		Moving Annual Total		
Treatment	**Metric**	**2010**	**2011**	**2012**
Dacogen	Median number of cycles	3.00	4.00	3.00
	4-day admin schedule	14.7%	11.4%	12.6%
	5-day admin schedule	64.0%	67.6%	66.2%
Vidaza	Median number of cycles	4.00	4.00	4.00
	5-day admin schedule	47%	49%	46%
	7+ day admin schedule	20%	20%	20%

Abstract 1928

Cost Effectiveness of Treatments after Failure of a First-Line Hypomethylating Agent in Myelodysplastic Syndromes (MDS)

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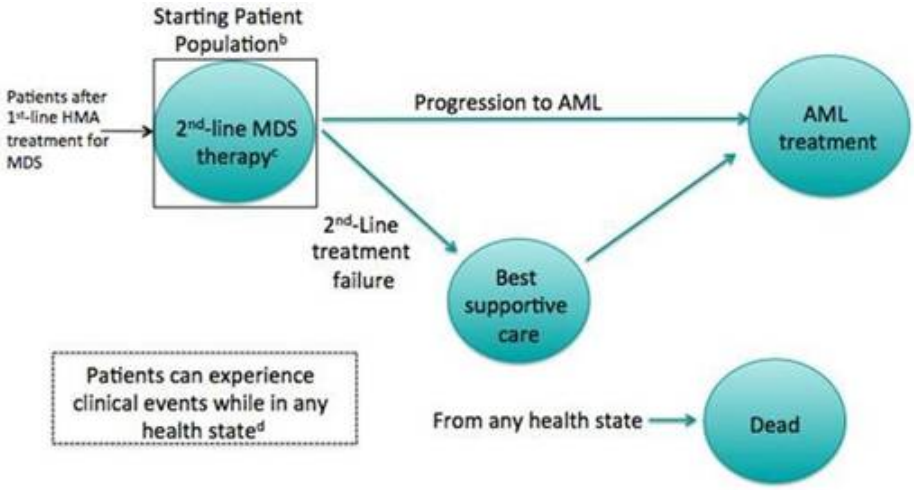
Background: The choice of optimal salvage therapy in patients with MDS is challenging due to a current lack of therapeutic options and a lack of data in regard to the risks and benefits of existing disease management. We undertook this study with the aim of evaluating the clinical outcomes, economic impact, and cost effectiveness of currently available treatment options for MDS patients who failed first-line hypomethylating agent (HMA) therapy.

Methods: We developed a Markov model to compare five second-line MDS treatment options: low- and high-intensity chemotherapy; switching HMA treatment; hematopoietic stem cell transplant (HSCT); and best supportive care (BSC). Hypothetical cohorts of patients who had failed a first-line HMA were simulated, and initiated each of these strategies. During each four-week cycle, patients could progress to acute myeloid leukemia (AML), experience a treatment- or disease-related adverse event (thrombocytopenia, anemia and neutropenia), discontinue treatment, or die (Figure 1). Costs were considered from the payer perspective and included those related to drug acquisition and administration, adverse event treatment, hospitalization, and supportive care. Inputs were based on published literature and expert opinion. Results were reported as lifetime costs (2013 USD), life expectancy in life years (LY), and incremental cost-effectiveness ratios (ICERs).



AML, acute myeloid leukemia; HMA, hypomethylating agent; MDS, myelodysplastic syndrome.
(a) Green circles represent model health states.
(b) MDS patients who have failed initial HMA therapy.
(c) Second-line treatments considered for model strategies/comparators are: best supportive care (BSC), HMA, low or high intensity chemotherapy, or hematopoietic stem cell transplant.
(d) Adverse events: thrombocytopenia, anemia, and neutropenia.

Results: The model predicted that treating patients who had failed a first-line HMA with BSC was the least expensive option ($55,343 per person) but provided the shortest survival: 0.48 years. Switching patients to a second HMA increased costs to $84,625 and could extend survival modestly. Patients treated with low- and high-intensity chemotherapy had lifetime costs of $89,877 and $146,519 and life expectancy of 0.88 and 1.08 years, respectively. HSCT patients had the highest lifetime costs ($492,359) and survival (2.26 years). Compared with BSC, the ICER for low intensity chemotherapy was $87,343/LY gained, while high intensity chemo and transplant had ICERs of $284,303 and $291,375/LY, respectively. The strategy of switching patients to a second HMA was removed during the calculation of ICERs due to extended dominance, i.e., there was another strategy, namely low intensity chemotherapy, that provided greater clinical benefit and had a more attractive ICER.

Conclusions: For MDS patients who had relapsed after, failed to respond, or progressed during administration of a first-line HMA, subsequent alternative active treatments provide some clinical benefit. However, such therapies substantially increase costs and a relatively small population of patients may be eligible due to functional status or matching donors. Although our results suggest that high intensity chemotherapy and transplant provide the greatest clinical benefits, they may cause substantial treatment-related morbidity. The increases in cost of care could thus be interpreted as an inefficient use of resources according to current societal standards, especially as the availability of these therapies is restricted to a limited number of patients. These findings suggest that there is an unmet need among MDS patients failing first-line HMA therapy; more research and treatment options would benefit clinical decision-making, patient outcomes, and healthcare resource allocation.

Abstract 2598

Treatment Patterns Among Patients with Myelodysplastic Syndromes: Observations of 1st-Line Therapy, Discontinuation and the Need of Additional Therapies

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Background: The myelodysplastic syndromes (MDS) include a group of hematopoietic malignancies that typically affect older individuals. Healthcare claims data have not been previously used to describe treatment patterns of MDS patients who progressed while on, failed to respond to, or became intolerant to hypomethylating agents (HMA; azacitidine [AZA] and decitabine [DEC]) and were eligible for 2nd-line therapy.

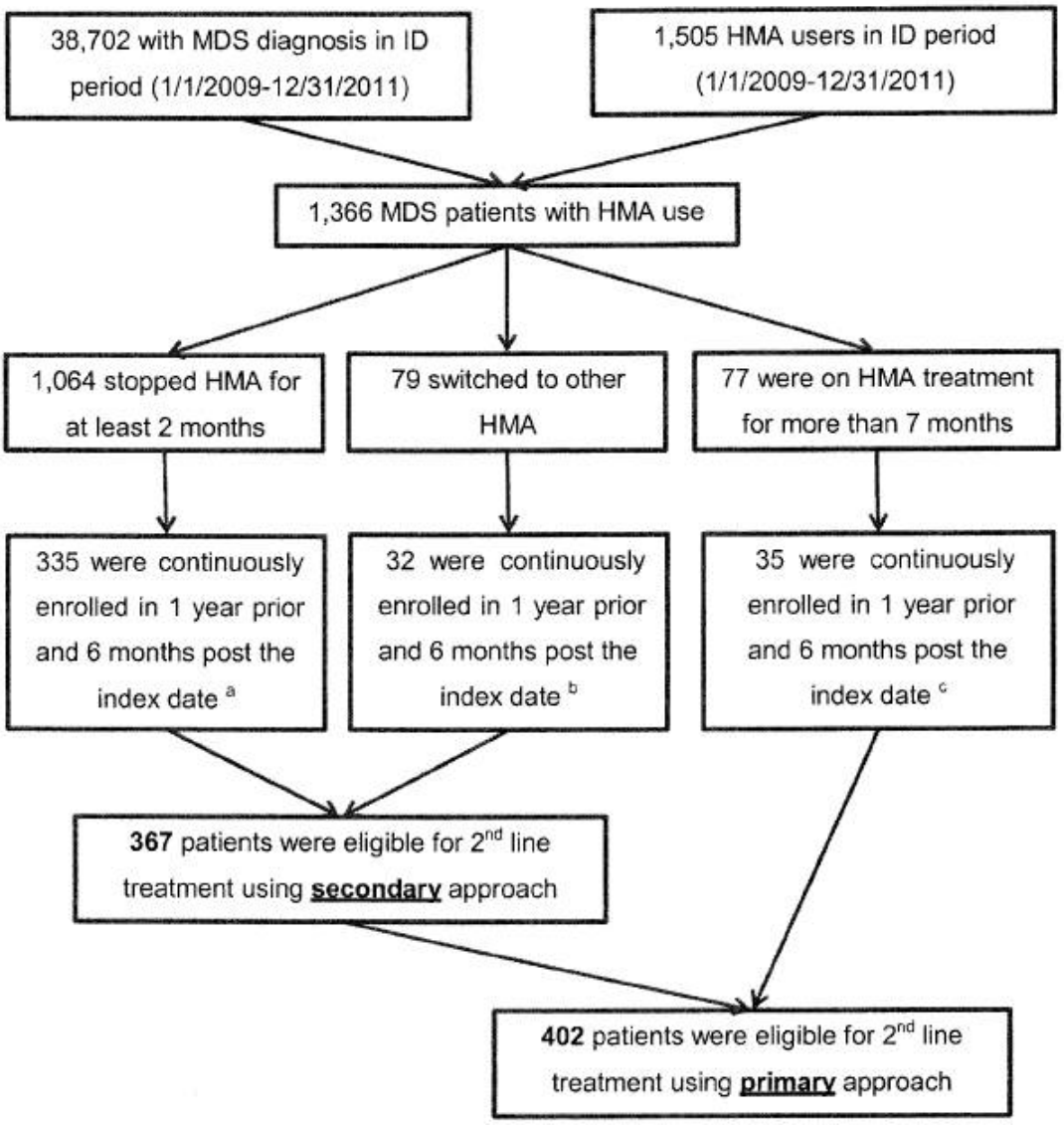
Methods: We conducted a retrospective cohort study using a US commercial health insurance claims database. The database contained adjudicated pharmacy and medical claims on 13 million annual lives submitted by providers, healthcare facilities, and pharmacies and included data on physician visits, medical procedures, hospitalizations, dispensed drugs, and performed tests. We identified patients with MDS (ICD-9-CM diagnosis code 238.7x) who were using an HMA in the identification (ID) period (1/1/2009—12/31/2011). The index date was the date on which the patient had used the same HMA for > 7 months, discontinued HMA treatment for ≥ 2 months, or switched to another HMA. Patients were defined as eligible for 2nd-line therapy after reaching the index date and were followed for ≥6 months after they became candidates for 2nd-line treatment until the end of enrollment or study end (12/31/2012).

We examined treatment use patterns from 1/1/2008 to the index date. MDS-specific chemotherapy included AZA, DEC, and lenalidomide (LEN). We defined AZA or DEC cycles as continuous treatment periods without a gap of >7 days, and the gap between observed cycles could not be ≥ 60 days. Hematologic supportive care agents included erythropoiesis-stimulating agents (ESA), growth factors (ie, granulocyte and granulocyte-macrophage colony- stimulating factors), and blood transfusions.

Results: Of 38,702 patients diagnosed with MDS in the ID period, we identified 1,366 who used an HMA. Three hundred eighty-six (96.0%) patients had a cytopenia potentially associated with HMA use, including anemia (92.8%), neutropenia (53.0%), and thrombocytopenia (52.7%). Of this group, 402 patients were eligible for 2nd-line MDS therapy: 283 (70.4%) had used AZA, 123 (30.6%) DEC, and 16 (4.0%) LEN. Patients averaged 6.1 HMA treatment cycles (6.4 for AZA,

5.4 for DEC) prior to being considered potential candidates for 2nd-line therapy. One hundred ninety-three (48.0%) patients had “early” discontinuation, defined as <5 treatment cycles before stopping or switching among HMAs. The proportions of patients who discontinued either AZA or DEC early were similar (47.1% vs. 50.0%). Among all 402 patients eligible for 2nd-line therapy, 320 (79.6%) received at least 1 hematologic supportive care agent: 208 (51.7%) received transfusions, 206 (51.2%) ESA, and 170 (42.3%) growth factors. Furthermore, among those eligible for 2nd-line therapy, 367 specifically switched to another HMA or did not have HMA treatment for 2 months. In this group, the rate of early discontinuation was 52.6%.

Conclusions: About half of patients completed < 5 HMA treatment cycles before discontinuation. AZA was used more often than DEC as 1st-line MDS therapy. These data suggest that a significant number of patients treated with AZA and DEC discontinue and become candidates for 2nd-line MDS therapy. The clinical reasons for early HMA discontinuation warrant further investigation; effective 2nd-line therapies for these patients are needed.



[a] 2 months after the last HMA treatment
[b] The date of new HMA treatment
[c] The first date in ID period for which the duration of HMA is more than 7 months

Abstract 2627

Healthcare Resource Utilization and Costs Among Patients with Myelodysplastic Syndrome Who Failed 1st-Line Therapy

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Background: The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic malignancies that primarily affect older adults. Although first-line therapies are available for treating MDS, the majority of patients will not achieve clinical improvements and nearly all MDS patients suffer from refractory disease. The health resource burden of MDS patients who fail first-line therapies is unknown, but estimated to exceed $24,000 (Craig et al, Leuk Res 2011).

Methods: To more accurately estimate burden, we examined healthcare resource utilization (HRU) and costs in MDS patients before and after failure of 1st line therapy with hypomethylating agents (HMAs) azacitidine and decitabine. We conducted a retrospective cohort study of US commercial health insurance claims data to describe, among patients considered to have failed initial HMA treatment, the economic burden and health resource utilization associated with MDS. We identified patients with an MDS-associated medical claim (ICD-9-CM diagnosis codes 238.7x) using an HMA in the identification (ID) period (1/1/2009—12/31/2011).

The index date was the date on which patients were defined as eligible for 2nd-line therapy (ie, initiated HMA treatment but then stopped treatment for $\geq$ 2 months, switched to another HMA, or > 7 months of using the same HMA). Patients were followed for $\geq$ 6 months after they became candidates for 2nd-line treatment. Outcomes of interest included MDS-specific and overall HRU and costs. HRU included physician office visits, emergency department (ED) visits, hospitalizations, and hospital length of stay. MDS-related events were defined as claims with a primary diagnosis of MDS, acute myeloid leukemia, anemia, neutropenia, thrombocytopenia, or pancytopenia. We examined outcomes during the 1 year before and 6 months immediately after the index date.

Results: We identified 402 MDS patients who failed 1st-line therapy. Mean age was 72.9 years; 39.8% were female. Mean Charlson comorbidity index was 3.6, and patients had a mean of 6.8 chronic conditions. Three hundred eighty- six (96.0%) patients had a cytopenia (e.g., anemia, neutropenia, etc.).

During the 1 year prior to 1st-line treatment failure, the 402 patients in the cohort had a mean 42.7 MDS-specific office visits. Patients with $\geq$ 1 MDS-specific ED visit comprised 7.7% of the cohort; 3.0% had an ED visit due to hemorrhage, and 4.2% due to infection. Patients with $\geq$ 1 MDS-specific hospitalization comprised 29.6% of the cohort; 3.0% were hospitalized due to hemorrhage, and 8.7% due to infection. Mean length of stay for MDS-specific hospitalizations was 8.7 days. Mean MDS-specific healthcare costs totaled $80,673, or 63.4% of total costs. MDS- specific treatment accounted for 60.2% of MDS-specific costs, including those for chemotherapy and hematologic supportive care agents such as erythropoietin-stimulating agents, growth factors, and blood transfusions.

During the initial 6 months after 1st-line treatment failure, the 402 patients in the cohort had a mean 18.9 MDS-specific office visits. Patients with $\geq$ 1 MDS-specific ED visit comprised 6.7% of the cohort; 1.0% had an ED visit due to hemorrhage, and 2.5% due to infection. Patients with $\geq$ 1 MDS-specific hospitalization comprised 16.9% of the cohort; 1.0% was hospitalized due to hemorrhage, and 6.0% due to infection. Mean length of stay for MDS-specific hospitalizations was 12.9 days. Mean 6-month MDS-specific healthcare costs totaled $45,564, or 59.2% of total costs. MDS-specific treatment accounted for 46.3% of MDS-specific costs.

Conclusions: The healthcare and economic burden of illness of MDS patients is substantial after 1st-line HMA treatment failure. The costs of care of commercially insured MDS patients in this study were approximately 3 times higher than previously published costs in Medicare patients.

Abstract 3445

Weighted Gene Co-Expression Network Analysis (WGCNA) Identifies Highly Proliferative Myeloma Subgroup Responsive to *CDK4/ARK5* Inhibition

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Multiple myeloma (MM) is an incurable plasma cell malignancy accounting for more than 10,000 deaths in the US each year. Hence the pursuit for novel therapeutic agents remains critically important. Myeloma pathogenesis is associated in part with aberrant cell cycle progression. Inhibition of cyclin dependent kinases *CDK4/6* results in cell cycle arrest and sensitization to Bortezomib and other active agents in MM (Huang, *Blood 2012*). Here, we show that *ARK5*, a novel member of the human *AMPK* family, is overexpressed in 70% of MM and helps promote proliferation and cell cycle progression via G1/S phase activation in an mTOR dependent manner.

We examined the role of *ARK5* using loss of function studies by *ARK5* siRNA transfection in MM1.S, NCI-H929 cells as well as treatment with ON 123300, a dual *CDK4*/*ARK5* kinase inhibitor. *ARK5* siRNA knockdown decreased MM cell viability and cell proliferation via G1/S arrest compared to control siRNA. *ARK5* siRNA treatment significantly (~70%) induced apoptosis in MM cells as detected by Annexin V/PI staining. We observed that phosphorylation of Rb, a critical cell cycle protein was significantly reduced in *ARK5* depleted cells. Moreover, mTOR pathway inhibition was confirmed by reduction of pS6K in *ARK5*depleted cells as compared to control siRNA treated cells.

ON 123300 decreased viability in MM cell lines and patient cells but was not lethal to normal PBMCs. A single treatment of 50 nM drug stratified MM cell lines into 2 groups, 5 resistant (MM.1R, KMS11, U266, RPMI-8226 and ARP1) and 4 sensitive cell lines (>80% cell kill- MM.1S, EJM, JJN3, NCI-H929). ARK5 protein expression by western blot analysis was much higher in sensitive cell lines. ON 123300 triggered G0/G1 cell cycle arrest and induced apoptosis similar to the effect of *ARK5* siRNA (80% vs 70%). ON 123300 treatment also reduced phosphorylation of pRb and pS6K downstream of mTOR pathway. These results confirm that cell inhibitory effects of ON 123300 in MM are mediated in a large part via inhibition of ARK5.

Co-culture experiments with BMSCs showed that ON 123300 not only targets MM cells but also overcomes the cytoprotective effects of the MM-host BM microenvironment. 4/5 *ARK5* positive primary samples with adverse cytogenetics including 1q amplification and CyclinD1 translocation were sensitive to ON 123300 (>80% cytotoxicity) at 50nM. Further, IP injection of ON 123300 (100mg/kg) in tumor xenograft models (MM1.S, NCI-H929) showed that ON 123300 is well tolerated and significantly inhibits tumor growth *in vivo* ($p<0.001$).

To study the mechanism of action for ON 123300, we performed geneset enrichment analysis (GSEA) on drug induced gene expression signature of RNA-Seq data from pre-post treated cell lines. We interrogated a wide array of geneset libraries, including MSigDB (Subramanian, *PNAS 2005*), drug induced transcriptional modules (Iskar, *Mol Sys Bio. 2013*) and disease signatures (Sirota, *Sci Transl Med 2011*). GSEA showed significant representation of genes that are enriched in normal plasma cells and rapamycin sensitive geneset.

Next, we developed a weighted co-expression network (WGCNA, Langfelder *BMC Bioinformatics 2008*) based classifier using 304 MM samples from MMRC collection and RNA- Seq from 28 MM patients from Mt. Sinai Hospital. WGCNA defines a network that continuously links all genes and then clusters the most highly co-expressed genes in defined modules. These network modules were associated with clinical traits and UAMS GEP classification (Zhan, *Blood 2006*) of each sample. There was significant overlap between highly proliferative “PR” and “Cyclin D1/2” patient subsets based on classification and sensitivity to *CDK4/ARK5* inhibition. Our classifier accurately discriminated 4 sensitive primary samples from one resistant sample, all tested *in vitro*. All sensitive samples were either Cyclin D1/2 or PR as per UAMS classification.

Our preclinical studies provide the basis for clinical evaluation of *CDK4/ARK5* inhibitor ON 123300 due to its selective cytotoxicity on MM cells *in vitro* and *in vivo*. Using WGCNA we establish a systematic framework by constructing for the first time, MM-associated gene co- expression networks contributing to tumorigenesis and progression. Thus, WGCNA modeling is a novel approach for identification of MM patient subgroups that have a higher likelihood of response in clinical trials with *CDK4/ARK5* inhibitors.