Overall Survival and Subgroup Analysis from a Randomized Phase III Study of Intravenous Rigosertib vs Best Supportive Care in Patients with Higher-risk Myelodysplastic Syndrome After Failure of Hypomethylating Agents (ONTIME Trial of ON 01910)

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Background

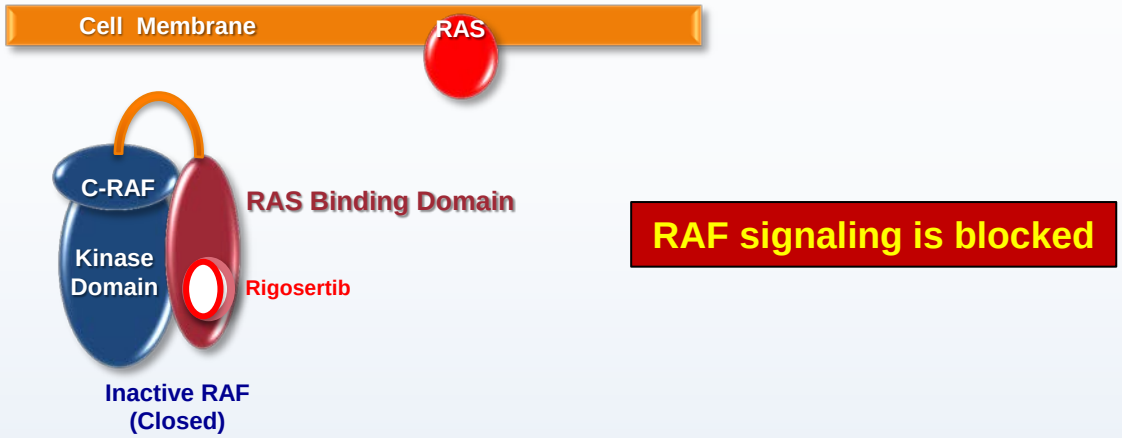
- **Prognosis of pts with HR MDS HMA failure is very poor**
- **Median survival is < 6 months***
- **Etiology of HMA failure is unknown at this time**
- **Currently, no effective therapies after HMA failure**

**Jabbour et al, Cancer 2010;116:3830-4; Prebet et al, J Clin Oncol 2011;29:3322-7*

Rigosertib (ON 01910.Na)

- **Novel small molecule targets RAS Binding Domain (RBD) of signaling proteins**

Rigosertib blocks RAS/RAF interaction



- **Novel MoA: targets pathways including PI-3 Kinase and Polo-Like Kinase**
- **Initial studies indicate clinical activity in pts with MDS and AML**
- **Both oral and IV rigosertib available – ONTIME trial used the IV formulation**

Divakar et al, AACR Annual Meeting 2014; abst LB-108; Olnes et al, Leuk Res 2012;36:964-5; Chapman et al, Clin Cancer Res 2012;18:1979-91.

ONTIME Trial: Study Design

- **Phase III, randomized, controlled, safety & efficacy study comparing rigosertib + BSC* vs BSC* alone (2:1)**
  - **Adult pts who had relapsed after, failed to respond to, or progressed during HMA therapy**
  - **299 pts enrolled at 87 sites in US and Europe**
  - **Rigosertib administered as 1800 mg/24 hr for 72 hrs as a continuous IV ambulatory infusion**
- **Pts stratified by bone marrow blast count (5-19% vs 20-30%)**
  - **Additional information on the relationship between OS and BMBL is available in Poster #3259**
- **Primary endpoint = overall survival**
- **Analysis based on 242 events (deaths; ≥ 80% maturity)**
- **Median follow-up of >18 months**

*BSC=Best supportive care: RBC & platelets; growth factors; hydroxyurea to manage blastic crises when pts transition to leukemia; pts on the BSC arm also allowed low-dose cytarabine, as medically justified.

ONTIME Trial: Patient Characteristics

	Percentage of Patients		
	Rigosertib N = 199	BSC N = 100	p-value
Age (yr)			0.63
Median	74	74	
Range	50 - 90	55 - 86	
Bone marrow blasts			0.98
5-19%	75	76	
20-30%	25	24	
IPSS-R cytogenetics class			0.74
Very good	1	6	
Good	42	36	
Intermediate	19	13	
Poor	15	11	
Very poor	13	17	
Unknown	12	17	
Revised IPSS score			0.37
Low	1	0	
Intermediate	7	14	
High	34	26	
Very High	47	41	
Unknown	12	19	

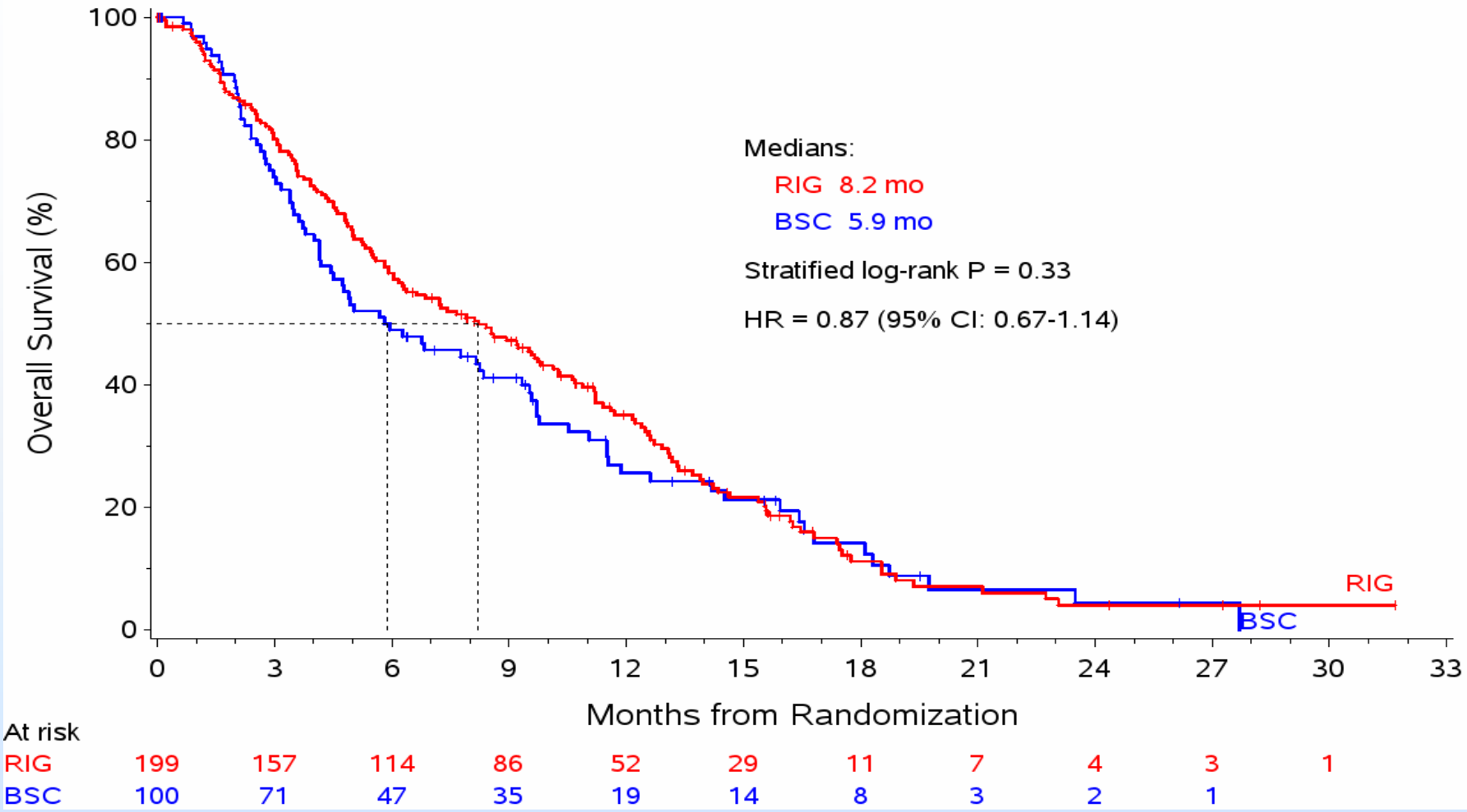
	Percentage of Patients		
	Rigosertib N = 199	BSC N = 100	p-value
Performance Status			0.66
ECOG 0	29	28	
ECOG 1	58	54	
ECOG 2	13	16	
Hemoglobin (g/dL)			0.24
Median	8.8	9.0	
< 9 g/dL	54	48	
≥ 9 g/dL	46	50	
Platelet count ($\times 10^9$/L)			0.52
Median	37	35	
< 40 $\times 10^9$/L	52	50	
≥ 40 $\times 10^9$/L	47	48	
Neutrophil count ($\times 10^9$/L)			0.21
Median	0.6	0.7	
< 0.8 $\times 10^9$/L	56	50	
≥ 0.8 $\times 10^9$/L	43	48	

ONTIME Trial: Primary Efficacy Results - ITT

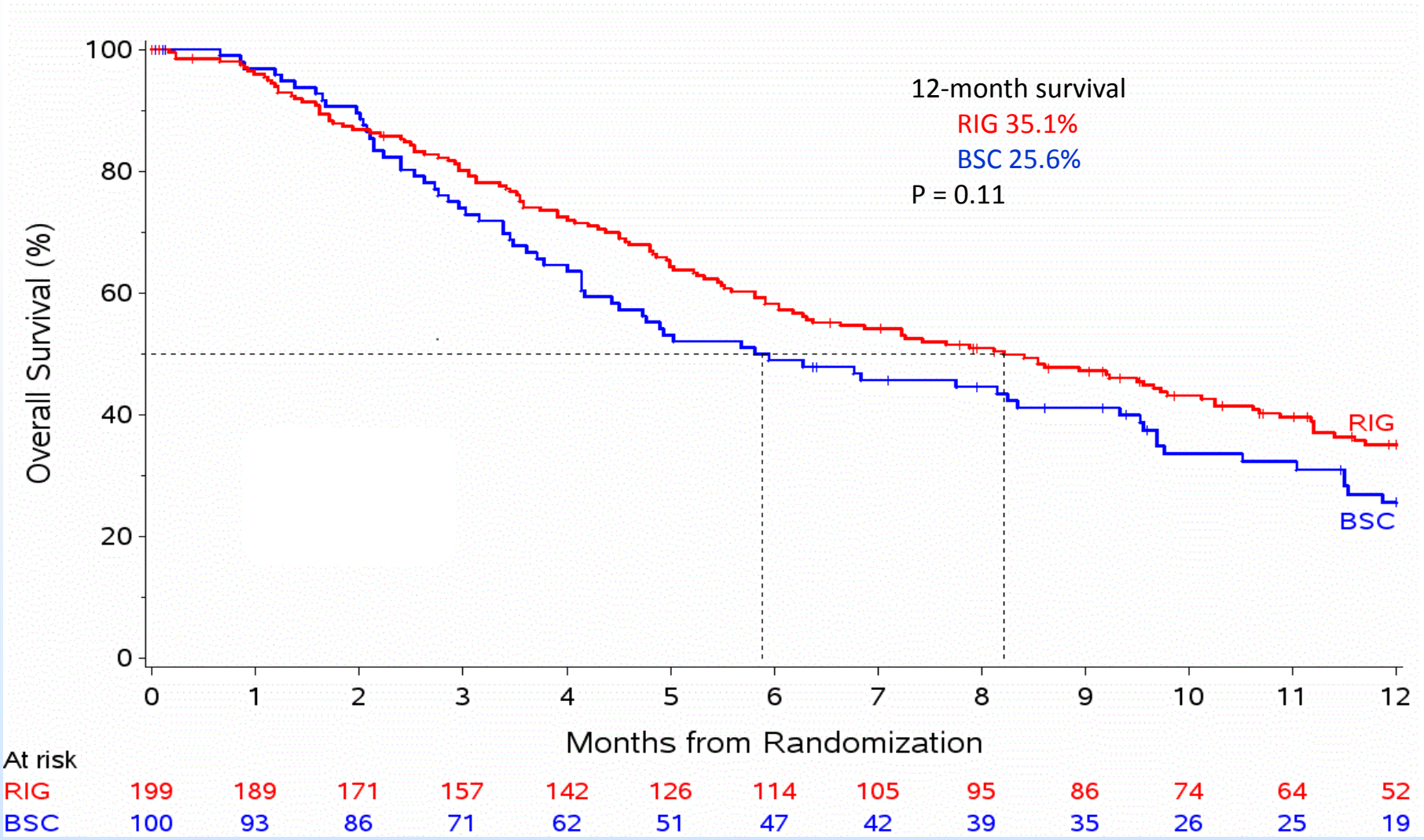
	Rigosertib N = 199	BSC N = 100
Number (%) of deaths	161 (81%)	81 (81%)
Median follow-up (months)	17.6	19.5
Median survival (months)	8.2	5.9
95% CI	6.0 - 10.1	4.1 - 9.3
Stratified HR (rigosertib/BSC)	0.87	
95% CI	0.67 - 1.14	
Stratified log-rank p-value*	0.33	

* Stratification factor: bone marrow blast at randomization (5-19% versus 20-30%)

ONTIME Trial: Primary Efficacy Results – ITT



ONTIME Trial: 12-month Analysis of Overall Survival

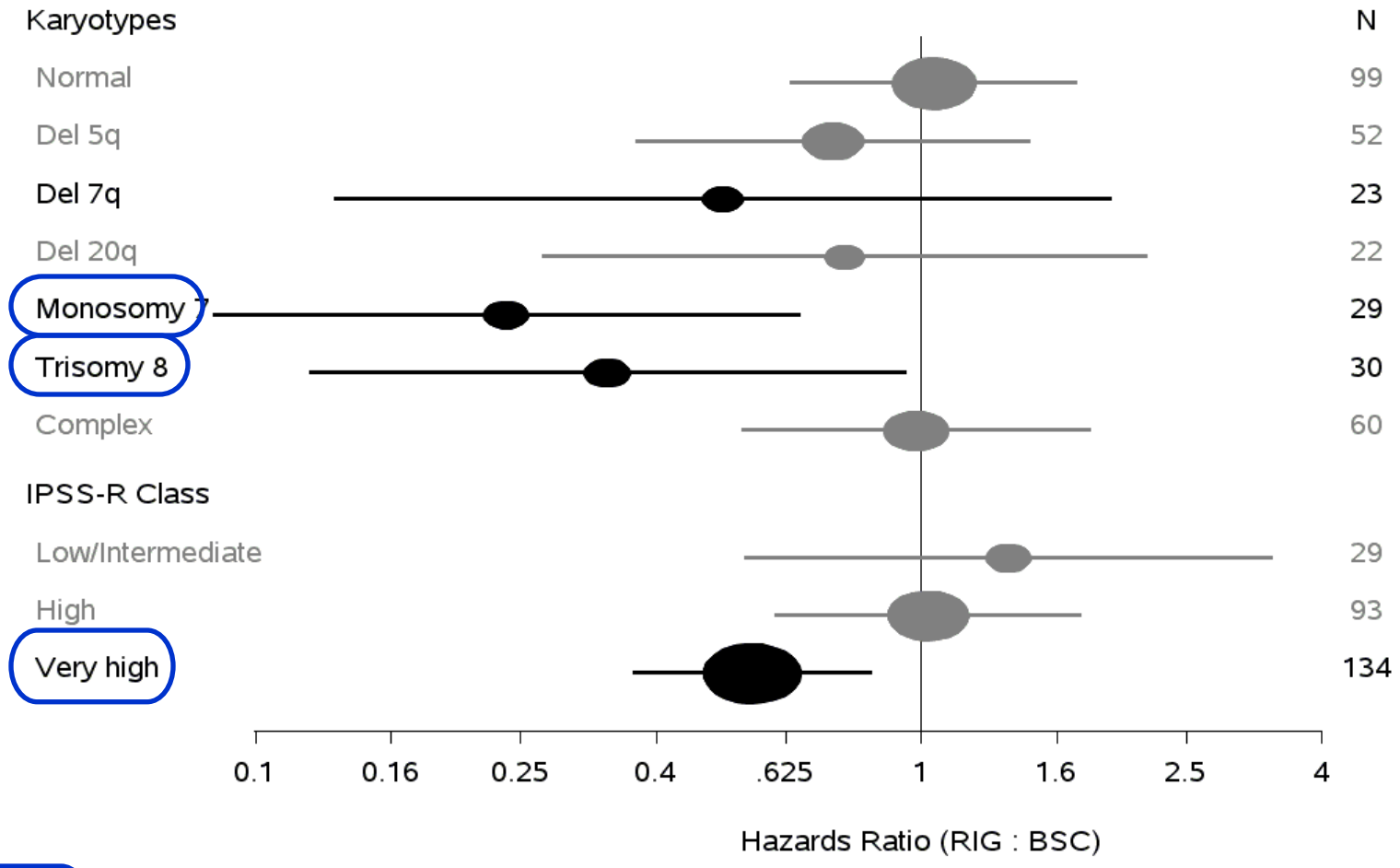


ONTIME Trial: Secondary Response Endpoints

	Percentage of Patients	
	Rigosertib N = 199	**BSC N = 100**
Response per IWG 2006 criteria*		
Marrow complete response	9	5
Stable disease	22	10
Failure	12	7
Progressive disease	42	27
Not evaluable	16	51
Best bone marrow blast response		
Marrow complete response	7	6
Unconfirmed marrow complete response	12	8
Marrow partial response	7	3
Stable disease	35	15
Progressive disease	24	16
Not evaluable	15	52
Erythroid response	2	3
Platelet response	3	5
Neutrophil response	5	6
Transition to AML	41	25
Transfusion independence (TI)		
Transfusion dependence at entry	54	57
TI for any 4 weeks in 26 weeks	19	19
TI for any 6 weeks in 26 weeks	8	8
TI for any 8 weeks in 26 weeks	6	3

**Cheson et al. Blood 2006;108(2):419-25.*

ONTIME Trial: Subgroups Correlated with Longer Median OS - ITT



$p < 0.05$

Additional information on the relationship between rigosertib and karyotype mutations is available in Poster #3258

ONTIME Trial: ITT Subgroups Correlated with Better Survival Benefit - ITT

Subgroup	Rigosertib		BSC		HR (95% CI)	p-value
	N	Median (mos)	N	Median (mos)		
Monosomy 7	16	5.6	13	2.8	0.24 (0.09-0.66)	0.003
Trisomy 8	22	9.5	8	4.5	0.34 (0.12-0.95)	0.035
Del 7q	17	5.0	3	2.7	0.38 (0.10-1.48)	0.14
Very high risk per IPSS-R	93	7.6	41	3.2	0.56 (0.37-0.84)	0.005

ONTIME Trial: Primary vs Secondary HMA Failure

- **"Primary HMA failure" was defined as no response to or progression during HMA therapy (median OS = 4.6 months)**
  - **55% of population in Prebet paper**
  - **64% of population in ONTIME**
- **"Secondary HMA failure" was defined as relapse after HMA therapy (median OS = 7.4 months)**
  - **36% of population in Prebet paper**
  - **36% in ONTIME**
- **An independent, centralized, blinded, retrospective evaluation of response provided similar results as the investigator assessments**

Prebet et al, J Clin Oncol 2011;29:3322-7; Jabbour et al, Cancer 2010;116:3830-4

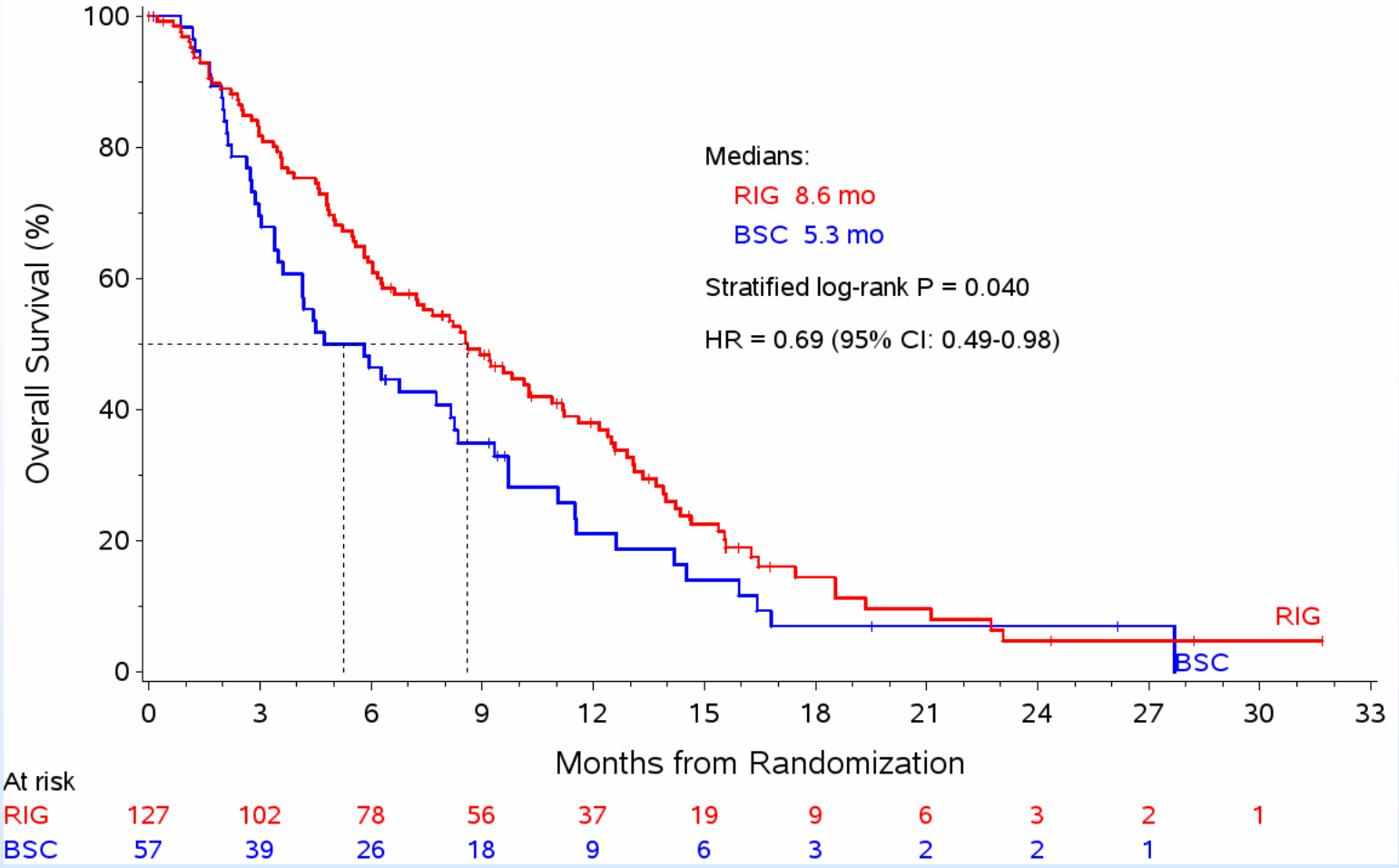
ONTIME Trial: Patient Characteristics Primary and Secondary HMA Failure

	Percentage of Patients					
	Primary HMA Failure			Secondary HMA Failure		
	Rigosertib N = 127	BSC N = 57	p-value	Rigosertib N = 72	BSC N = 43	p-value
Age (yr)			0.77			0.51
Median	73	74		75	75	
Range	50 - 86	55 - 86		62 - 90	57 - 86	
Bone marrow blasts			0.12			0.06
5-19%	80	70		67	84	
20-30%	20	30		33	16	
IPSS-R cytogenetics class			0.49			0.71
Very good	1	7		0	5	
Good	40	39		44	33	
Intermediate	20	11		17	16	
Poor	18	11		8	12	
Very poor	12	18		15	16	
Unknown	9	16		15	19	
Revised IPSS score			0.35			0.78
Low	1	0		0	0	
Intermediate	6	12		8	16	
High	35	30		32	21	
Very High	48	39		44	44	
Unknown	10	19		15	19	

ONTIME Trial: Patient Characteristics Primary and Secondary HMA Failure

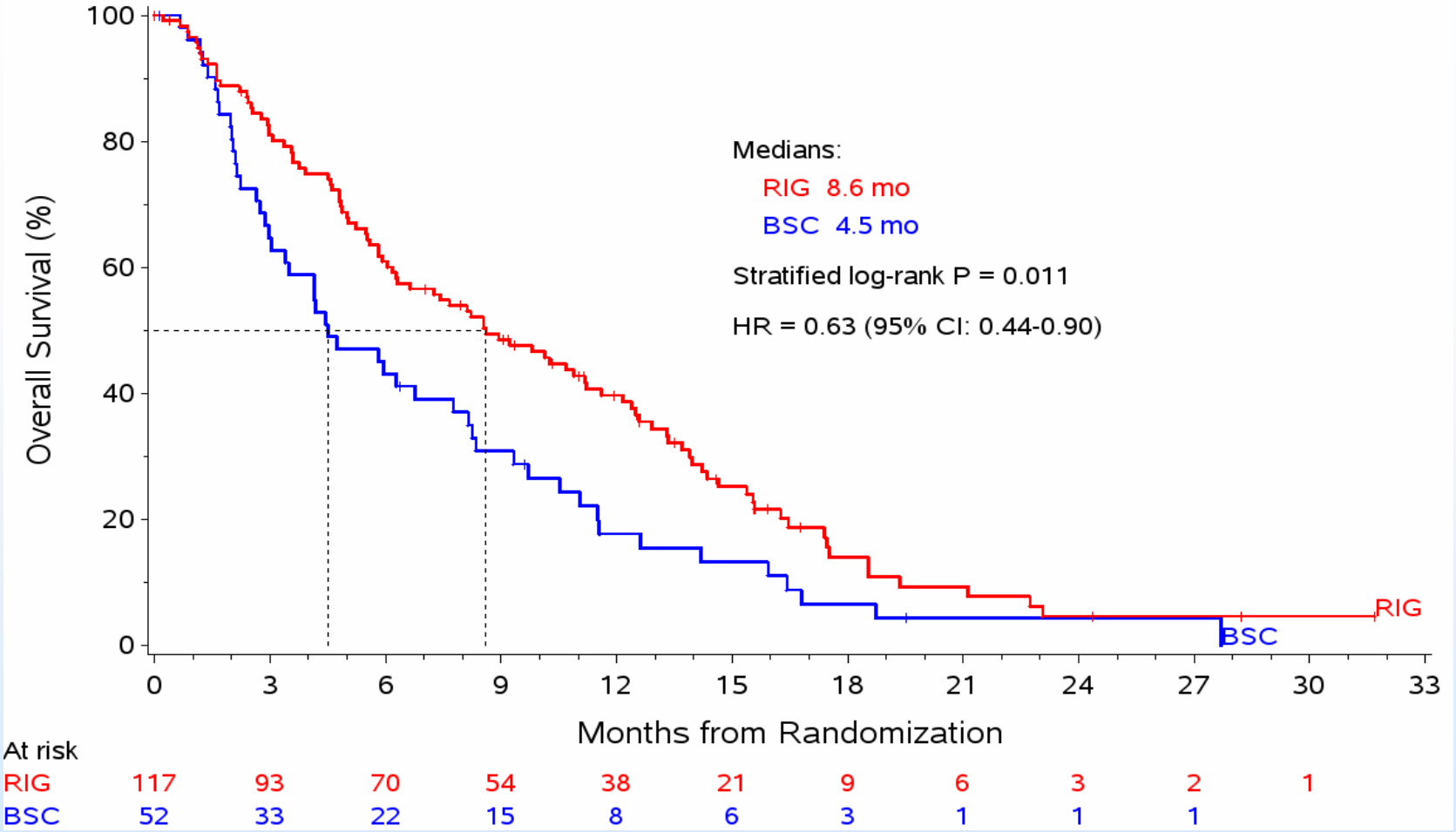
	Percentage of Patients					
	Primary HMA Failure			Secondary HMA Failure		
	Rigosertib N = 127	BSC N = 57	p-value	Rigosertib N = 72	BSC N = 43	p-value
Performance Status			0.55			0.16
ECOG 0	22	26		42	30	
ECOG 1	65	60		46	47	
ECOG 2	13	12		13	21	
Hemoglobin (g/dL)			0.52			0.29
Median	8.8	8.9		8.9	9.4	
< 9 g/dL	54	51		53	44	
≥ 9 g/dL	45	47		47	53	
Platelet count ($\times 10^9$/L)			0.18			0.54
Median	39	30.5		35.5	45.5	
< 40 $\times 10^9$/L	50	53		56	47	
≥ 40 $\times 10^9$/L	49	46		44	51	
Neutrophil count ($\times 10^9$/L)			0.31			0.30
Median	0.7	0.9		0.4	0.7	
< 0.8 $\times 10^9$/L	51	46		65	56	
≥ 0.8 $\times 10^9$/L	48	53		35	42	

ONTIME Trial: Median Overall Survival for Pts with Primary HMA Failure – Investigator Assessment



Per Prebet 2011, "Primary HMA Failure" was defined as either no response to or progression during HMA therapy

ONTIME Trial: Median Overall Survival for Pts with Primary HMA Failure - Blinded, Centralized Assessment



Per Prebet 2011, "Primary HMA Failure" was defined as either no response to or progression during HMA therapy

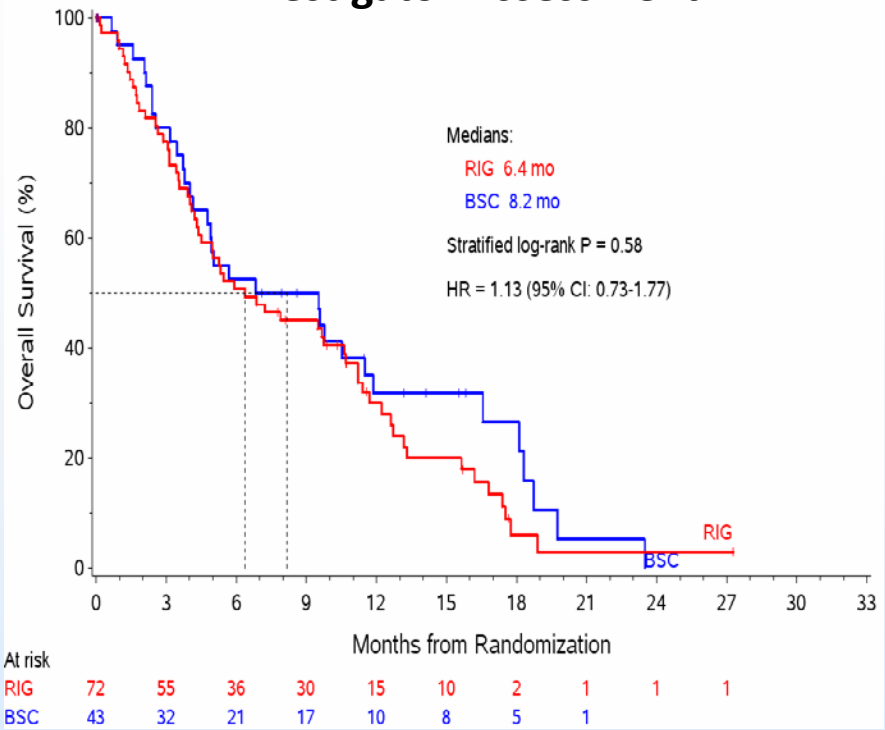
ONTIME Trial: Patients with Primary and Secondary HMA Failure – Investigator Assessment and Blinded Centralized Assessment vs Historical Reference

	Investigator Assessment N = 199	Blinded, Centralized Assessment N = 172	Prebet 2011 N = 458
Primary HMA Failure	**64%**	**68%**	**55%**
Progression	61%	62%	60%
Non-response	39%	38%	40%
Secondary HMA Failure	**36%**	**32%**	**36%**
AZA Intolerance	**0**	**0**	**9%**

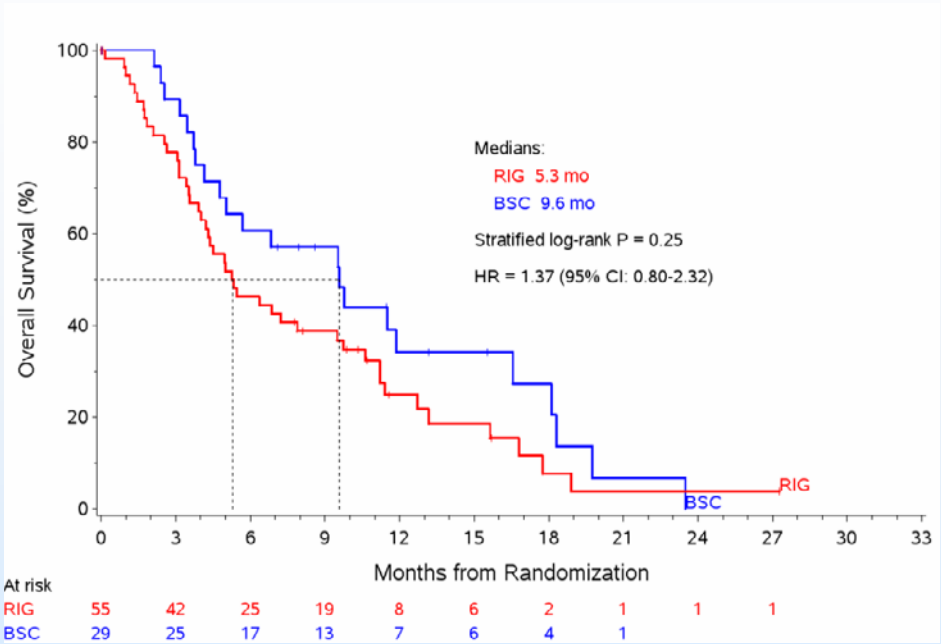
Prebet et al, J Clin Oncol 2011; 29:3322-7

ONTIME Trial: Median Overall Survival for Pts with Secondary HMA Failure

Investigator Assessment



Blinded, Centralized Assessment



Per Prebet 2011, "Secondary HMA Failure" was defined as relapse after HMA therapy

ONTIME Study: Safety and Tolerability

- **Median dose intensity = 92%**
  - **Dose reductions in 5% of pts**
- **No significant compliance or operational issues related to ambulatory continuous infusion**
- **AEs ≥ Grade 3: 79% rigosertib, 68% BSC**
- **Low incidence of myelotoxicity (anemia 23%, thrombocytopenia 21%, leukopenia 7%)**
  - **No cardiac signal**

ONTIME Trial: Most Common Treatment-emergent AEs (≥20%) and ≥ Grade 3 TEAEs

	Percentage of Patients			
	Rigosertib N = 184		BSC N = 91	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Patients with any TEAE	99%	79%	85%	68%
Nausea	35	2	18	-
Diarrhea	33	2	20	-
Constipation	31	1	11	1
Fatigue	30	4	18	1
Pyrexia	27	1	21	-
Anemia	23	18	9	8
Edema peripheral	21	1	16	-
Thrombocytopenia	21	19	8	7

ONTIME Trial: Conclusions

- **Primary endpoint of OS did not reach statistical significance in the ITT population**
  - **2.3-month improvement in median OS in the ITT population**
- **Rigosertib treatment-related improvement in OS was noted in the following well-balanced subgroups:**
  - **Primary HMA failure (64% of pts: HR = 0.69; p = 0.04)**
  - **IPSS-R Very High Risk (45% of pts: HR = 0.56; p = 0.005)**
  - **Cytogenetic criteria also important prognostic factors**
    - **Monosomy 7 (HR = 0.24; p = 0.003)**
    - **Trisomy 8 (HR = 0.34; p = 0.035)**
- **Continuous IV infusion with rigosertib had a favorable safety profile in this population of elderly pts with HR MDS**

ONTIME Trial: Conclusions

- **Pts with HMA failure represent a significant unmet medical need and have a poor prognosis with few treatment options**
- **Future research with rigosertib should include pts with primary HMA failure and pts in the IPPS-R Very High Risk category**
- **Additional study of IV rigosertib in pts with high-risk MDS post-HMA is planned**

ONTIME Trial: Acknowledgements

Guillermo Garcia-Manero, Anderson Cancer Center, Houston, TX
Pierre Fenaux, MD, Hospital St Louis, Paris, France
Aref Al-Kali, MD, Mayo Clinic, Rochester, MN
Maria R. Baer, MD, University of Maryland, Baltimore, MD
Mikkael Sekeres, MD, Cleveland Clinic, Cleveland, OH
Gail Roboz, MD, Weill Cornell Medical College, New York, NY
Gianluca Gaidano, MD, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy
Bart Scott, MD, Fred Hutchinson Cancer Research Center, Seattle, WA
Peter Greenberg, MD, Stanford Medical School, Stanford, CA
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David P. Steensma, MD, Dana-Farber Cancer Institute, Boston, MA
Suman Kambhampati, MD, University of Kansas Medical Center, Westwood, KS
Karl-Anton Kreuzer, MD, Universitätsklinikum Köln, Köln, Germany
Lucy Godley, MD, University of Chicago Medical Center, Chicago, IL
Robert Collins, Jr, MD, Univ of Texas, Southwestern Medical Center at Dallas, Dallas, TX
Ehab Atallah, MD, Froedtert Hospital and Medical College of Wisconsin, Milwaukee, WI
Francois Wilhelm, MD, PhD, Isabelle Darnis-Wilhelm, MD, Nozar Azarnia, PhD, Manoj Maniar, PhD, Onconova Therapeutics, Inc., Newtown, PA
Lewis R. Silverman, MD, Division of Hematology/Oncology, Icahn School of Medicine at Mount Sinai, New York, NY
For the ONTIME investigators