Long Term Survival Results and Prognostic Factors Results of Higher Risk MDS and CMML treated with guadecitabine

On Behalf of the guadecitabine Investigative Team

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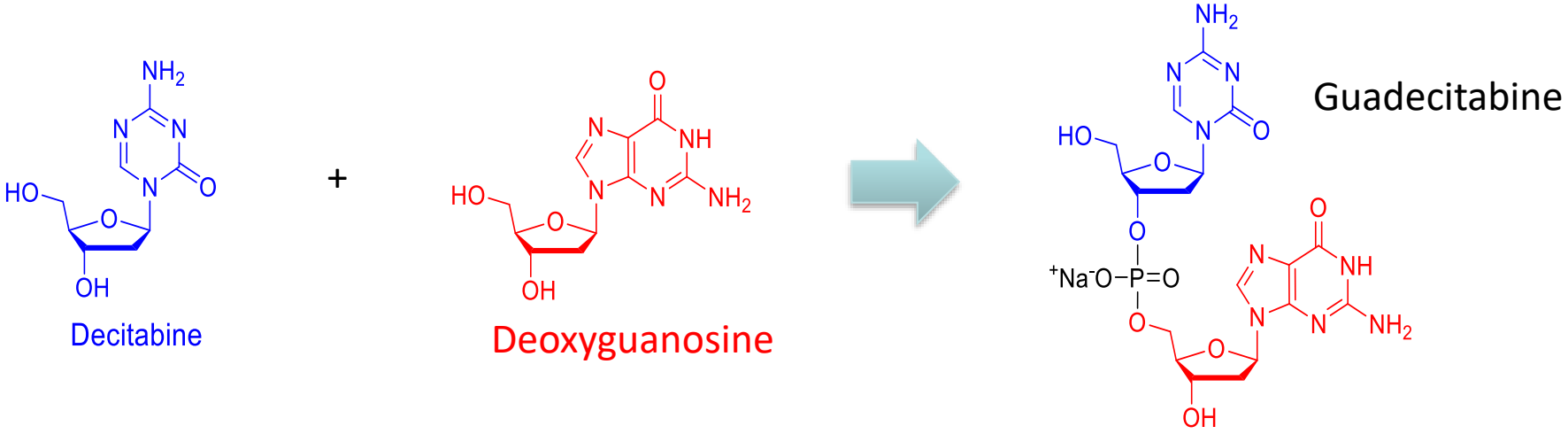
Faculty Disclosure

- Dr. Guillermo Garcia-Manero has received research support from Astex Pharmaceuticals, Inc.; advisory board for Otsuka Pharmaceutical
- Dr. Casey O'Connell has received research support from Astex Pharmaceuticals, Inc.; advisory board for Otsuka Pharmaceutical
- Dr. Jean-Pierre Issa has received research support from Astex Pharmaceuticals, Inc.; consulted for Astex and Teva;
- Dr. Michael Savona has received research support from Astex Pharmaceuticals, Inc., Boehringer Ingelheim, Incyte, Millennium, Sunesis, and TG Therapeutics; consulted for Astex, Celgene, Gilead, Incyte, Karyopharm, Merck, Millennium, Sunesis, and TG Therapeutics; and has equity in Karyopharm.
- Harold Keer and Mohammad Azab are full time employees of Astex Pharmaceuticals, Inc.

Guadecitabine (SGI-110) Background
A Next Generation HMA

- **Decitabine is rapidly eliminated by Cytidine Deaminase (CDA), limiting drug exposure time to cancer cells *in vivo***
- **Guadecitabine is a dinucleotide of Decitabine and Deoxyguanosine resistant to deamination by CDA**
- **Following SC administration, active metabolite decitabine is gradually released resulting in longer exposure time *in vivo***



Guadecitabine Phase 2 Study Design
Higher Risk MDS/CMML

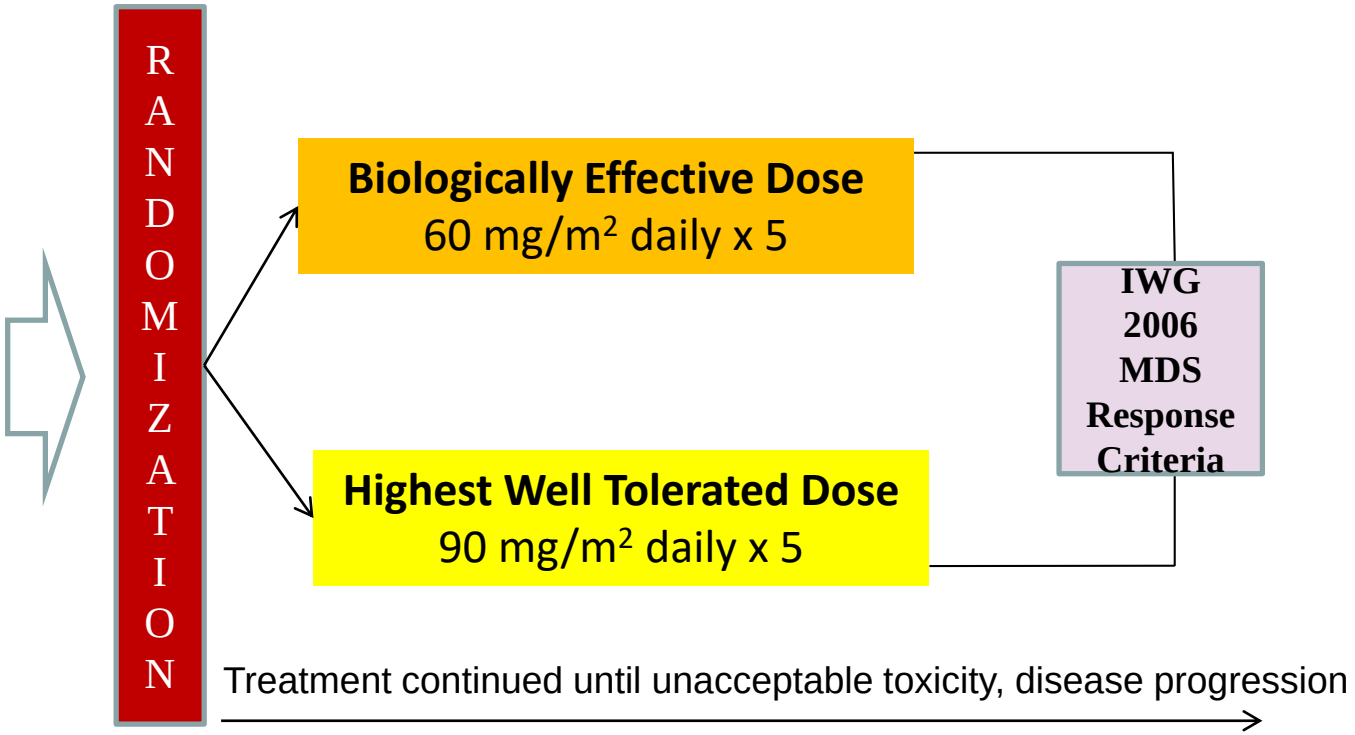
Major Eligibility

Previously Treated MDS/CMML with 1st generation HMA

or

HMA Treatment Naïve MDS/CMML

- IPSS Int-1,2 and HR or CMML
- ECOG PS 0-2
- Adequate hepato-renal function



- **Primary Endpoint: Overall Response Rate (CR, PR, mCR, HI)**
- **Secondary Endpoints: Transfusion independence, LINE-1 demethylation, time to AML, overall survival**

Patients Characteristics by Dose Cohort

Patient Characteristics	60 mg/m^2 (n=53)	90 mg/m^2 (n=49)
Median Age, (range)	71.7 (18-86)	72.5 (52-89)
Gender, M n (%) F n (%)	37 (70) 16 (30)	30 (61) 19 (39)
ECOG PS n (%): 0-1 2	45 (85) 8 (15)	43 (88) 6 (12)
Disease Category (IPSS) n (%) Intermediate High Risk CMML	 23 (43) 15 (28) 15 (28)	 22 (44) 19 (39) 7 (14)
BM Blast >5% n (%)	20 (38)	33 (67)
Median Neutrophils (10^9/L)	1.19	1.16
Median Platelets (10^9/L)	42.5	45.0
Median Hb (g/dL)	9.25	9.30
RBCs Transfusion Dependence n (%)	31 (58)	27 (55)

Patients Characteristics by Prior Treatment

Patient Characteristics	HMA Prev. Treated (n=53)	HMA Tx Naïve (n=49)
Median Age, (range)	72.5 (52-89)	71.7 (18-85)
Gender, M n (%) F n (%)	32 (60) 21 (40)	35 (71) 14 (29)
ECOG PS n (%): 0-1 2	42 (79) 11 (21)	46 (94) 3 (6)
Disease Category (IPSS) n (%) Intermediate High Risk CMML	 17 (33) 25 (47) 10 (19)	 28 (57) 9 (18) 12 (24)
BM Blast >5% n (%)	34 (64)	19 (39)
Median Neutrophils (10^9/L)	0.81	1.64
Median Platelets (10^9/L)	37.0	62.5
Median Hb (g/dL)	9.30	9.10
RBCs Transfusion Dependence n (%)	34 (64)	24 (49)

Extent of Treatment in Previously HMA Treated MDS/CMML

Prior Treatment	Prev Treated MDS/CMML N = 53
Prior azacitidine n (%)	41 (77)
Prior decitabine n (%)	17 (32)
Duration of prior HMA: ≥ 6 months < 6 months	41 (80) 10 (20)
Time since last HMA: < 3 months ≥ 3 months	 30 (59) 21 (41)

Long Term Follow Up and Treatment Duration

Treatment	Prev Treated MDS	Tx naive MDS
Median # cycles (range)	5 (1-37)	5 (1-49)
Treatment Duration: ≥ 6 cycles	21 (40)	23 (47)
% of delayed Cycles	47%	35%
% of Dose-reduced cycles	34%	37%

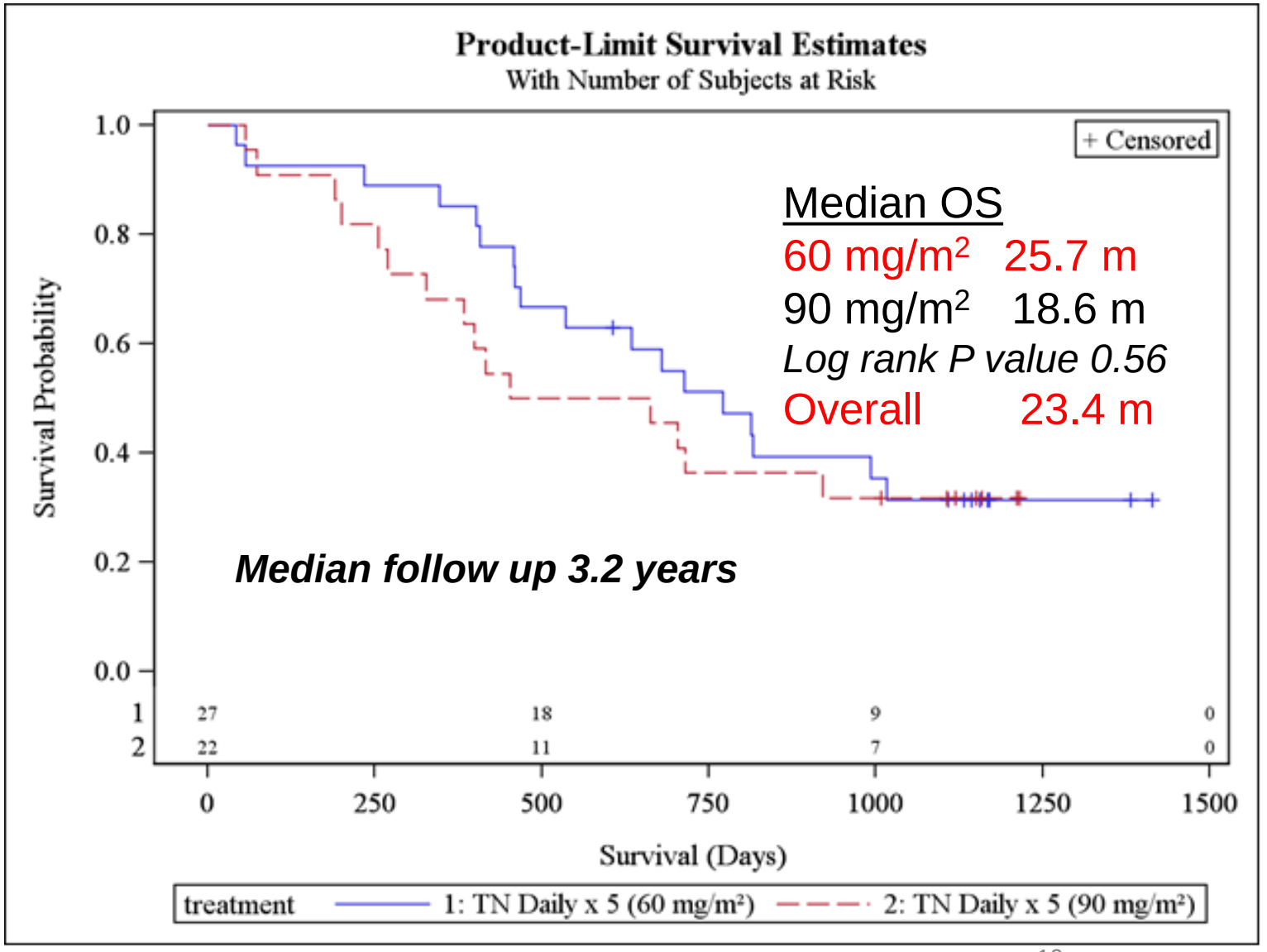
- **Median Follow Up 3.2 Years (IQR 2.8-3.5 y)**
- **Over half the patients did not get 6 cycles**

Best Response[1] Prior Treatment Status

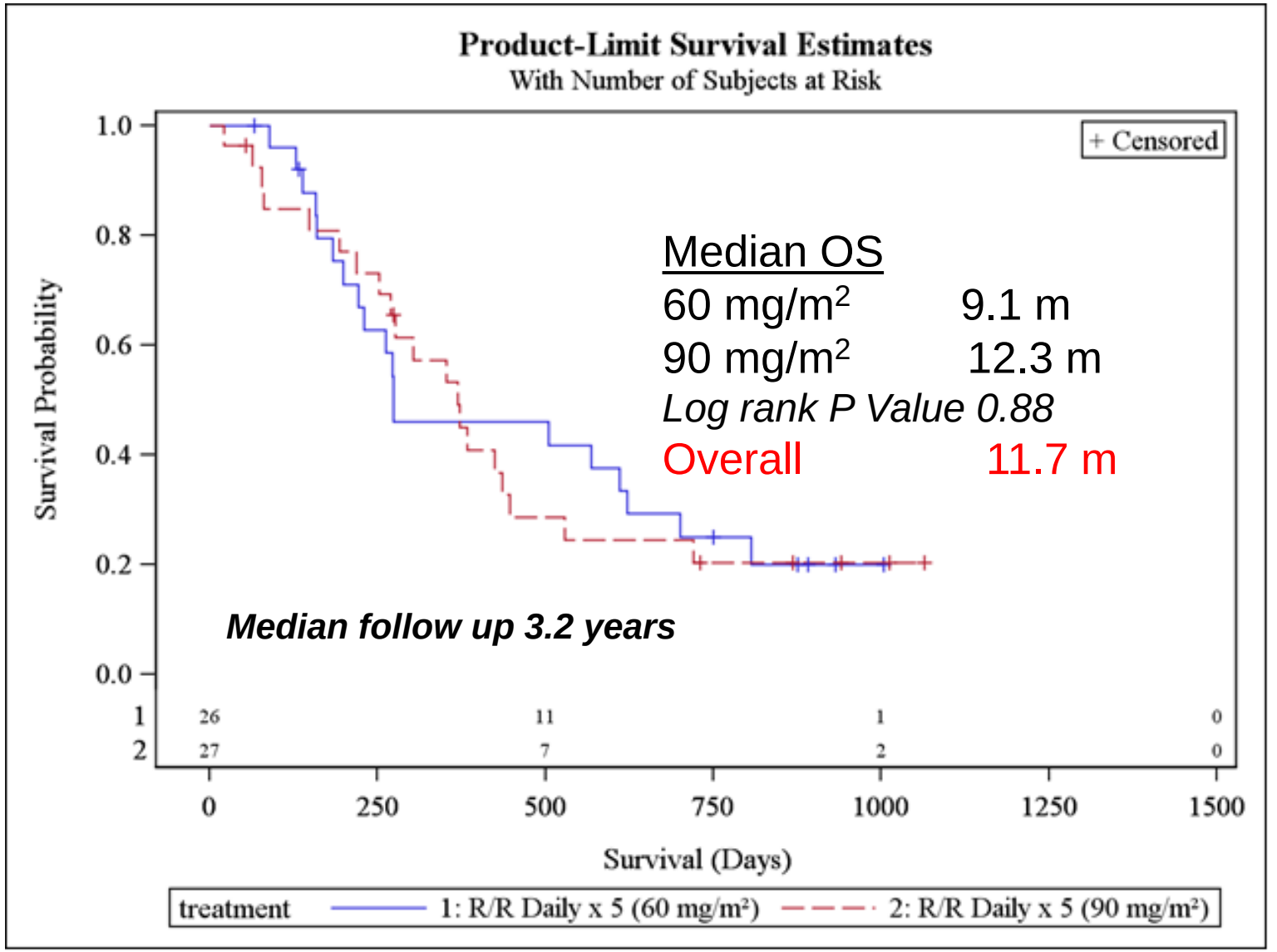
Response Category[1]	Prev Treated [2] (n=53)	HMA Tx Naïve [2] (n=49)
	Response rate n (%)	**Response rate n (%)**
CR	2 (4)	11 (22)
mCR	15 (28)	7 (14)
CR+mCR	17 (32%)	18 (36)
HI	15 (28)	21 (43)
Overall Response Rate	23 (43)	25 (51)
RBCs Transfusion Independence	5/34 (15%)	10/24 (42%)

[1] International Working Group 2006 MDS Response Criteria
[2] No significant difference in response between dose groups

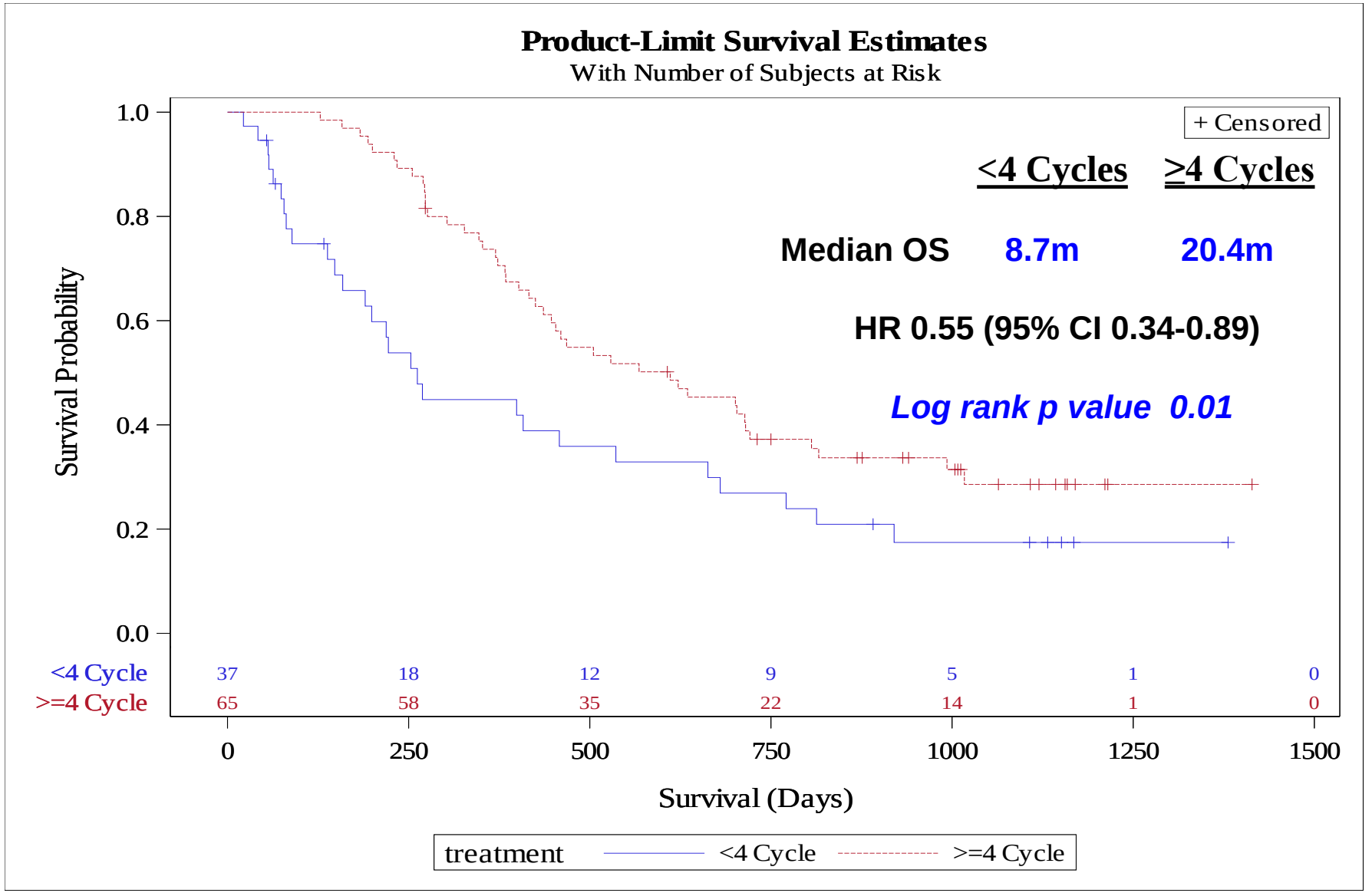
Overall Survival in HMA Tx Naïve MDS/CMML



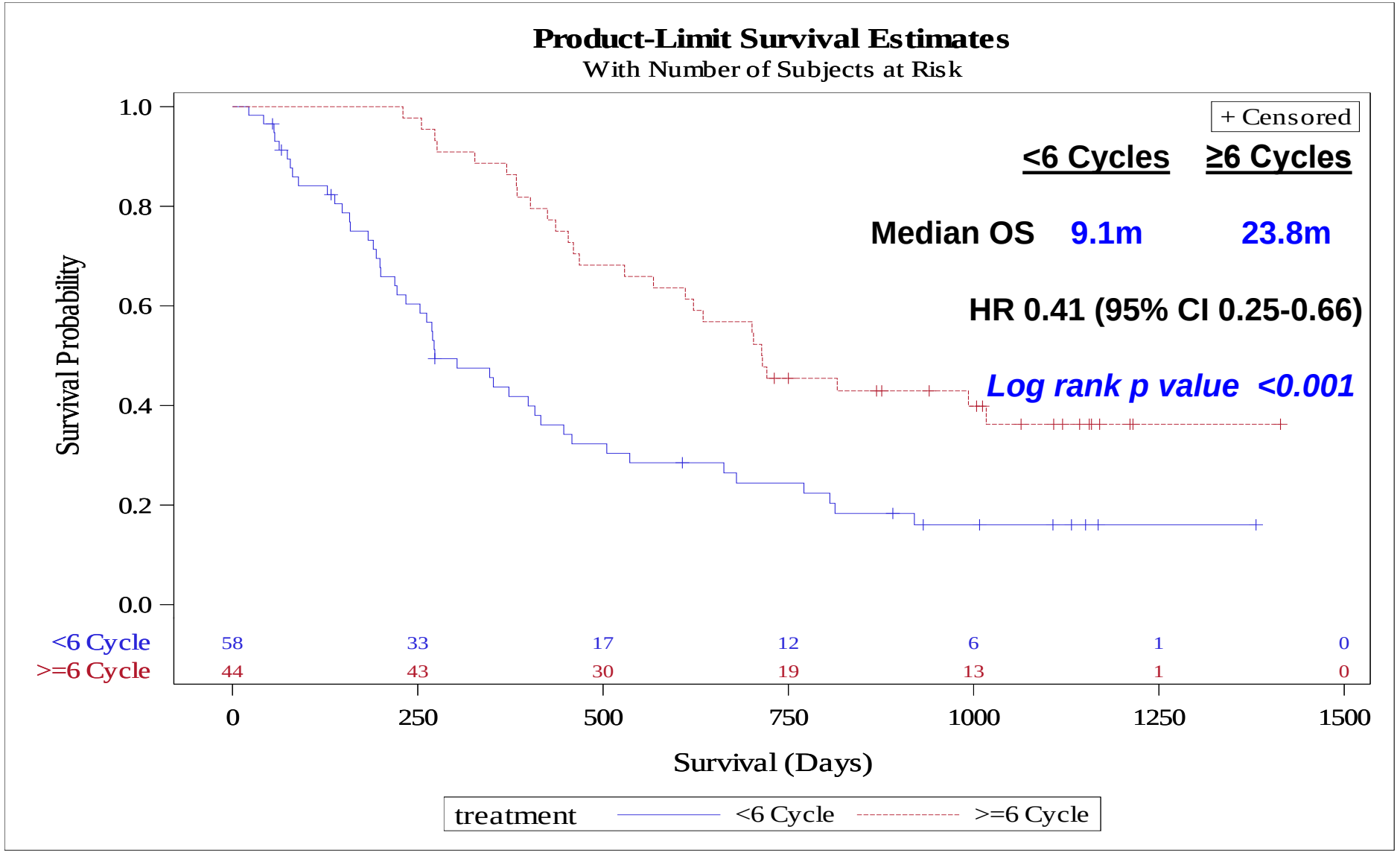
Overall Survival in HMA Prev Treated MDS/CMML



Survival Analysis by number of cycles (minimum 4 cycles)
All 102 Patients (TN and Previously Treated)



Survival Analysis By Number of Cycles (minimum 6 cycles)
All 102 Patients (TN and Previously Treated)



Clinical Prognostic Factors for Overall Survival in MDS/CMML Patients Treated with Guadecitabine

	Median OS (months)	*P value**
Baseline BM Blasts		0.005
>5%	12.3	
≤ 5%	22.7	
Baseline RBCs Transfusion Dependence		0.006
Transfusion Dependent	11.7	
Transfusion Independent	20.4	
Baseline ECOG PS		0.161
0-1	15.6	
2	8.7	

**P value* is based on log-rank test of the overall survival curves

Common Genetic Mutations Prognostic Factors in MDS/CMML Patients Treated with Guadecitabine

	Median OS (months)	*P value**
DNMT3a		0.983
Mutation (n=17)	17.8	
No mutation (n=76)	16.8	
TET-2		0.240
Mutation (n=20)	22.6	
No Mutation (n=73)	14.9	
TP53		<0.001
Mutation (n=16)	7.4	
No Mutation (n=77)	22.7	

**P value* is based on log-rank test of the overall survival curves

Safety: Related AEs Grade ≥ 3 in ≥ 10% of Patients

Adverse Event	60 mg/m^2 (n=53) N (%)	90 mg/m^2 (n=49) N (%)	*P value**
Any Grade ≥ 3 AE	32 (60)	43 (88)	0.003
Neutropenia	20 (38)	21 (43)	0.687
Thrombocytopenia	16 (30)	25 (51)	0.043
Anemia	19 (36)	19 (39)	0.837
Leukopenia	6 (11)	6 (12)	1.000
Febrile Neutropenia	6 (11)	5 (10)	1.000

* *P value* is based on Fisher's exact test

Guadecitabine Long Term Results in higher risk MDS/CMML Conclusions

- Guadecitabine is a next generation HMA that may offer benefits and/or overcome pharmacological resistance to 1st generation HMAs
- No major significant difference between 60 and 90 mg/m^2
- Tx Naïve patients long term results compare well with 1st generation HMAs:
  - **CR 22%**
  - **Median OS 23.4 months (~26 months for 60 mg/m^2 dose group)**
- Previously Treated patients results are promising:
  - **CR+mCR 32%**
  - **Median OS of 11.7 months**
- Patients who received 4-6 cycles had significantly longer survival than those who did not
- Phase 3 trial is actively recruiting relapsed/refractory MDS/CMML to guadecitabine 60mg/m^2 vs Treatment Choice (LDAC, BSC, IC): *ASTRAL-3 study (NCT02907359)*

Guadecitabine Phase 2 in MDS and CMML

Articles

Guadecitabine (SGI-110) in patients with intermediate or high-risk myelodysplastic syndromes: phase 2 results from a multicentre, open-label, randomised, phase 1/2 trial

Guillermo Garcia-Manero, Gail Roboz, Katherine Walsh, Hagop Kantarjian, Ellen Ritchie, Patricia Kropf, Casey O'Connell, Raoul Tibes, Scott Lunin, Todd Rosenblat, Karen Yee, Wendy Stock, Elizabeth Griffiths, Joseph Mace, Nikolai Podoltsev, Jesus Berdeja, Elias Jabbour, Jean-Pierre J Issa, Yong Hao, Harold N Keer, Mohammad Azab, Michael R Savona

Summary

Background Guadecitabine is a next-generation hypomethylating agent whose active metabolite decitabine has a longer in-vivo exposure time than intravenous decitabine. More effective hypomethylating agents are needed for the treatment of myelodysplastic syndromes. In the present study, we aimed to compare the activity and safety of two doses of guadecitabine in hypomethylating agent treatment-naive or relapsed or refractory patients with intermediate-risk or high-risk myelodysplastic syndromes.

Methods This phase 2 part of the phase 1/2, randomised, open-label study enrolled patients aged 18 years or older from 14 North American medical centres with International Prognostic Scoring System intermediate-1-risk, intermediate-2-risk, or high-risk myelodysplastic syndromes, or chronic myelomonocytic leukaemia. They were either hypomethylating agent treatment-naive or had relapsed or refractory disease after previous hypomethylating agent treatment as determined by the investigators' judgment. Eligible patients had Eastern Cooperative Oncology

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