Long Term Results of a Randomized phase 2 Dose-Response Study of Guadecitabine, a Novel Subcutaneous (SC) Hypomethylating Agent (HMA), in 102 Patients with Intermediate or High Risk MDS or CMML

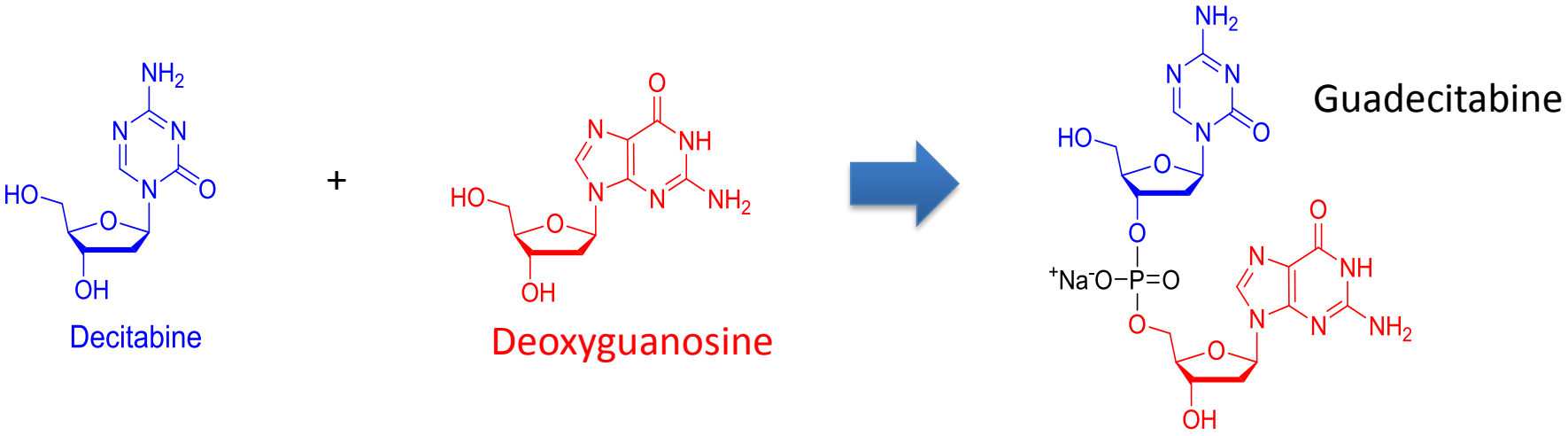
On Behalf of the SGI-110 Investigative Team

Guillermo Garcia Manero[1], Ellen Ritchie[2], Katherine Walsh[3] ,Michael Savona[4] , Hagop Kantarjian[1] , Casey O'Connell[5] , Raoul Tibes[6] , Naval Daver[1] , Elias Jabbour[1], Scott Lunin[7], Todd Rosenblat[8] , Karen Yee[9], Wendy Stock[10], Elizabeth Griffiths[11], Joseph Mace[12], Nikola Podoltsev[13], Jesus Berdeja[14] , Jean-Pierre Issa[15], Sue Naim[16], Yong Hao[16], Mohammad Azab[16],Gail Roboz[2]

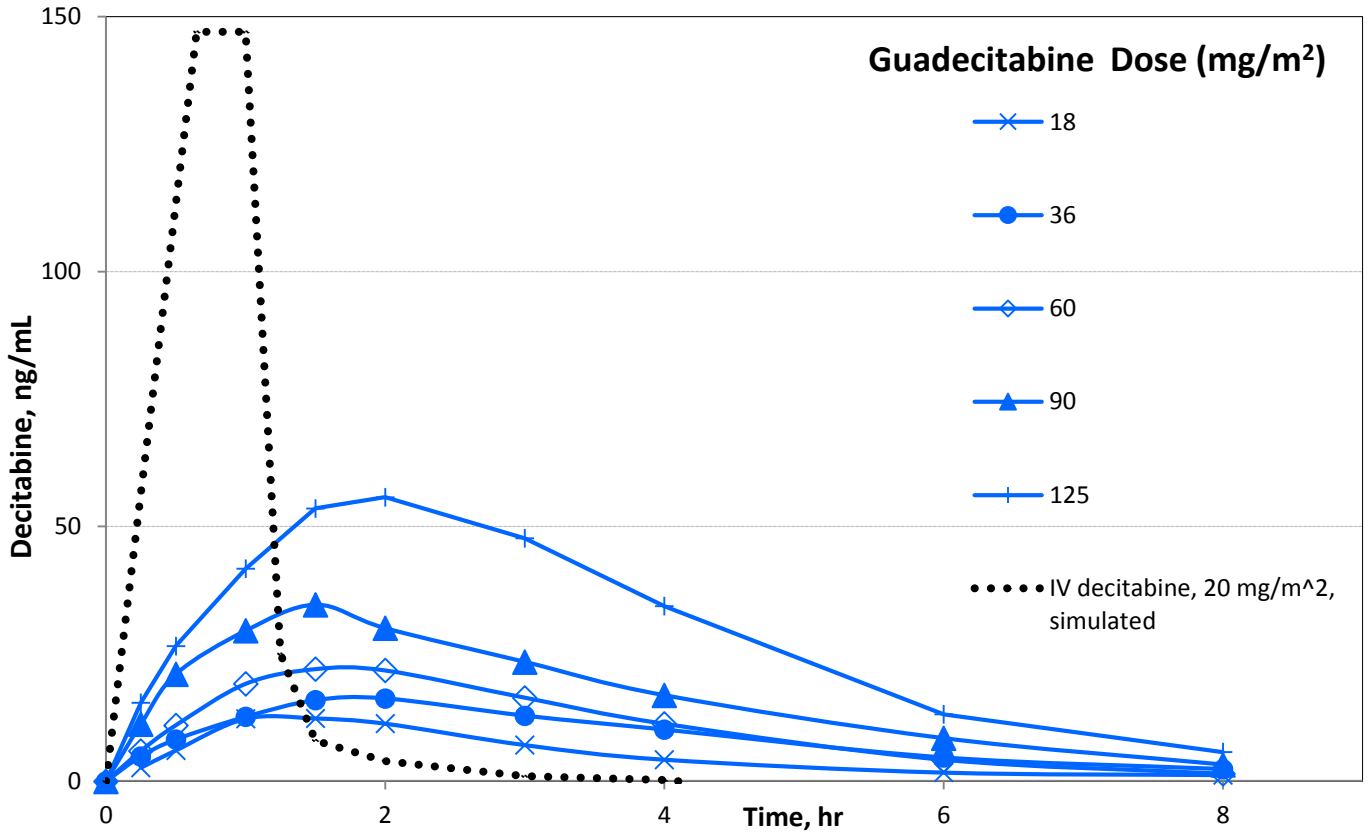
[1] MD Anderson Cancer Center, Houston, TX, [2]Weill Cornell Medical College, New York, NY , [3]The Ohio State University, Columbus, OH , [4]Vanderbilt University Medical Center, Nashville, TN,, [5]USC Keck School of Medicine, University of Southern California, Los Angeles, CA, [6] NYU School of Medicine, [7] Florida Cancer Specialist, Englewood , FL , [8]New York Presbyterian/Columbia University Medical Center, New York, NY , [9] Princess Margaret Cancer Center, Toronto, Canada, [10]University of Chicago Medical Center, Chicago, IL , [11]Roswell Park Cancer Institute, Buffalo, NY, [12]Florida Cancer Specialists, St Petersburg, FL, [13]Yale University School of Medicine, New Haven, CT, [14]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN [15]Fels Institute, Temple University, Philadelphia, PA,[16]Astex Pharmaceuticals Inc., Pleasanton, CA.

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 differentiated Clinical Pharmacology



- **Prolonged release of decitabine from SC guadecitabine at escalating doses provides *8+ hrs.* of decitabine exposure duration**
- **This doubles decitabine exposure expected from IV decitabine (*4 hrs.*, simulated)**
- **This may confer different pharmacology profile for guadecitabine**

Guadecitabine Dose-response Randomized Phase 2 Study in Higher Risk MDS/CMML – Study Design

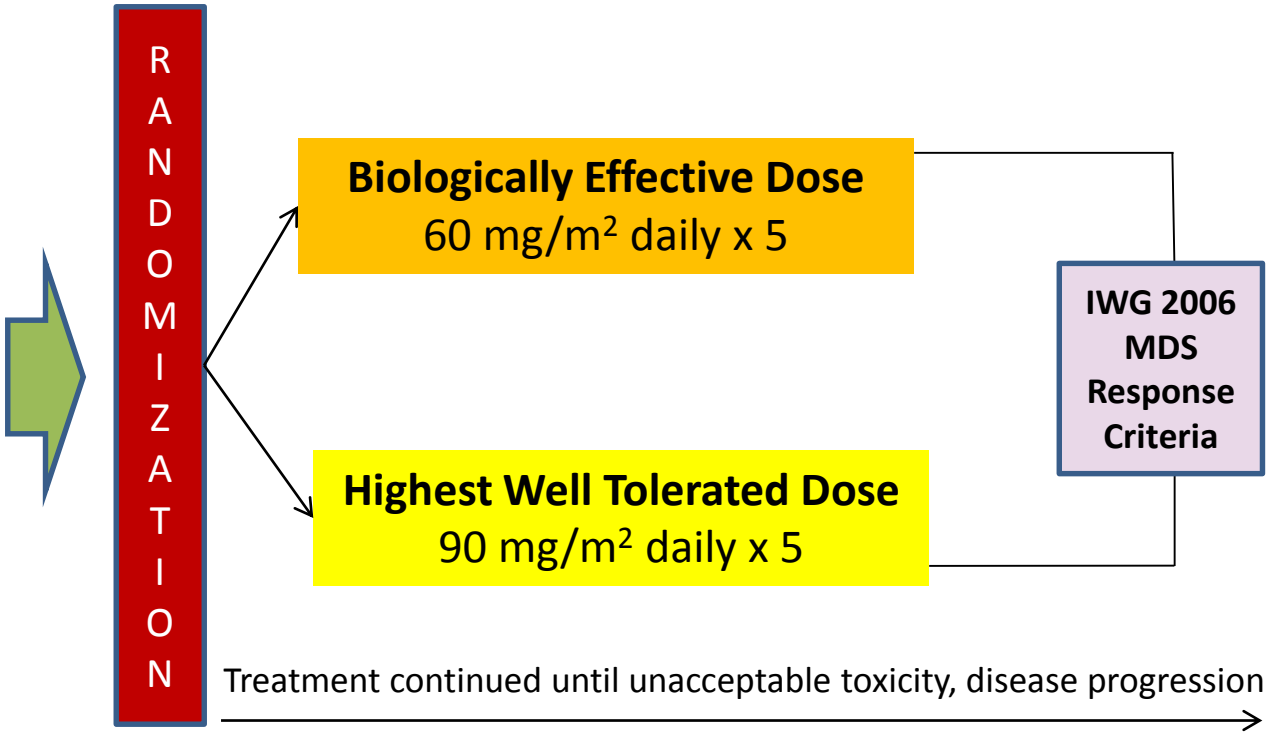
Major Eligibility

Previously Treated MDS/CMML with 1st generation HMA

or

Treatment Naïve MDS/CMML

- IPSS Int-1,2 and HR
- 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	Prev. Treated (n=53)	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 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)

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)**

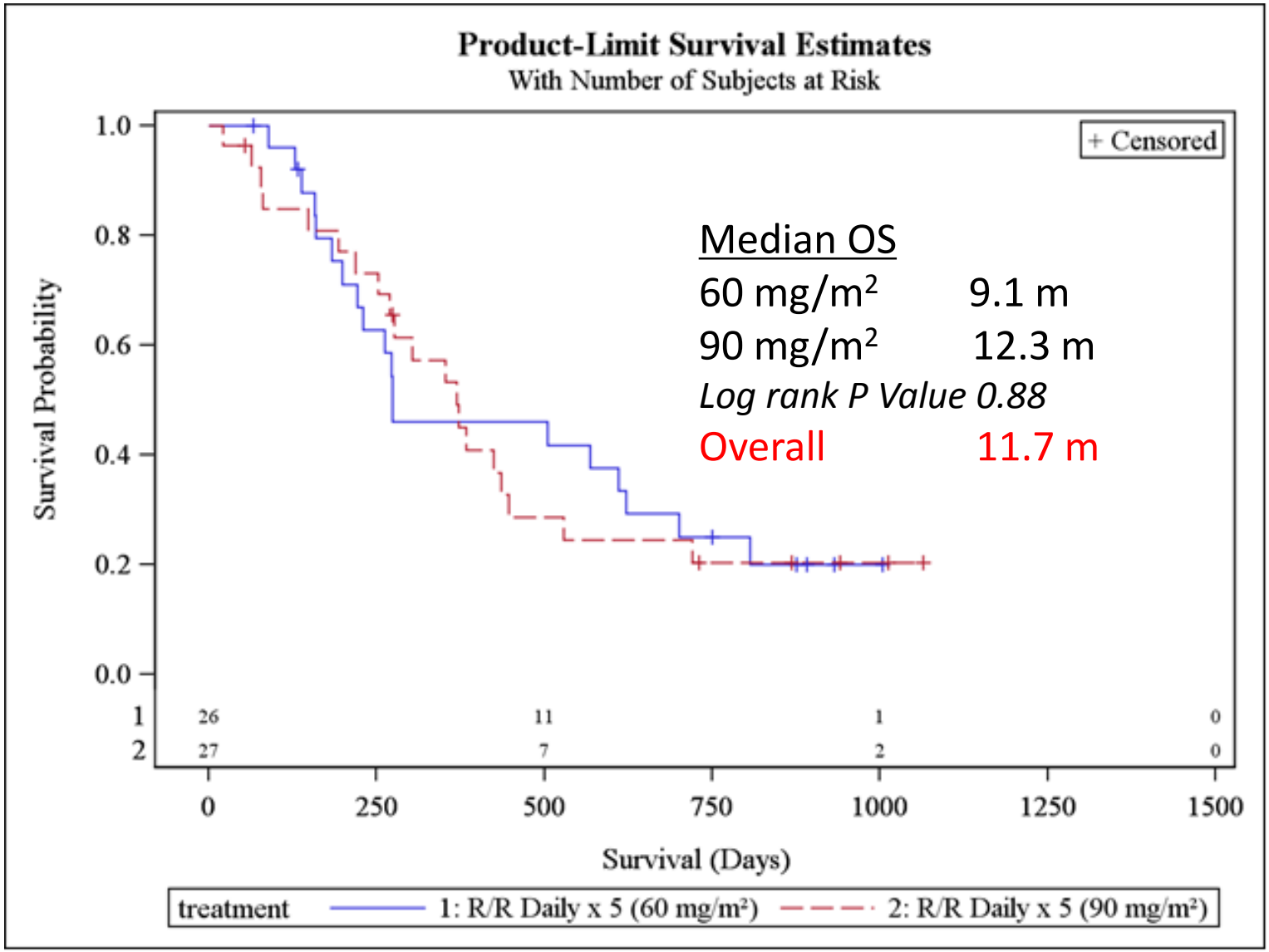
Best Response[1] By MDS/CMML Status

Response Category[1]	Prev Treated [2] (n=53)	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 Prev Treated MDS/CMML



Median OS

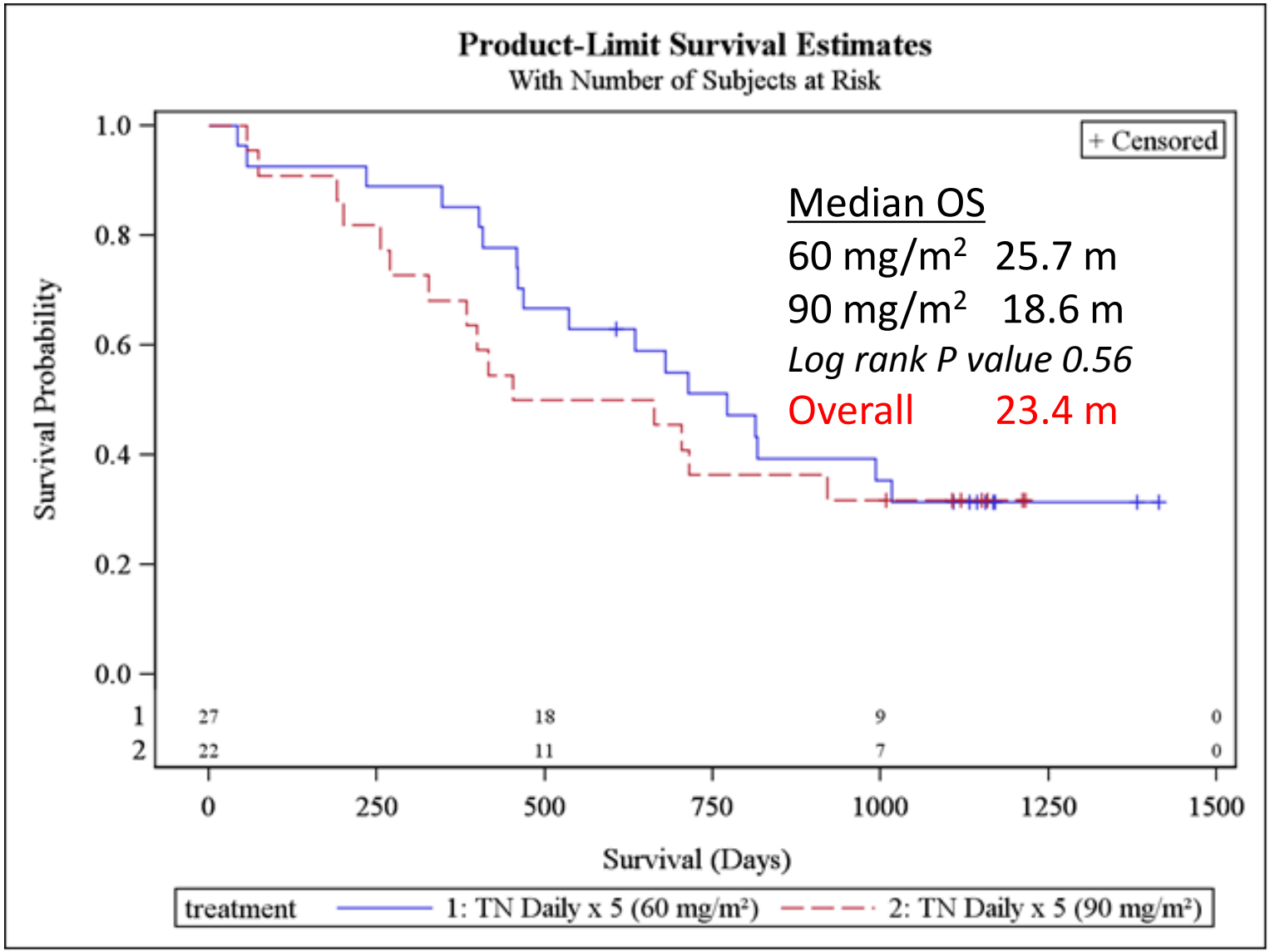
60 mg/m^2 9.1 m

90 mg/m^2 12.3 m

Log rank P Value 0.88

Overall 11.7 m

Overall Survival in Tx Naïve MDS/CMML



Prognostic Clinical Characteristics for OS

	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	

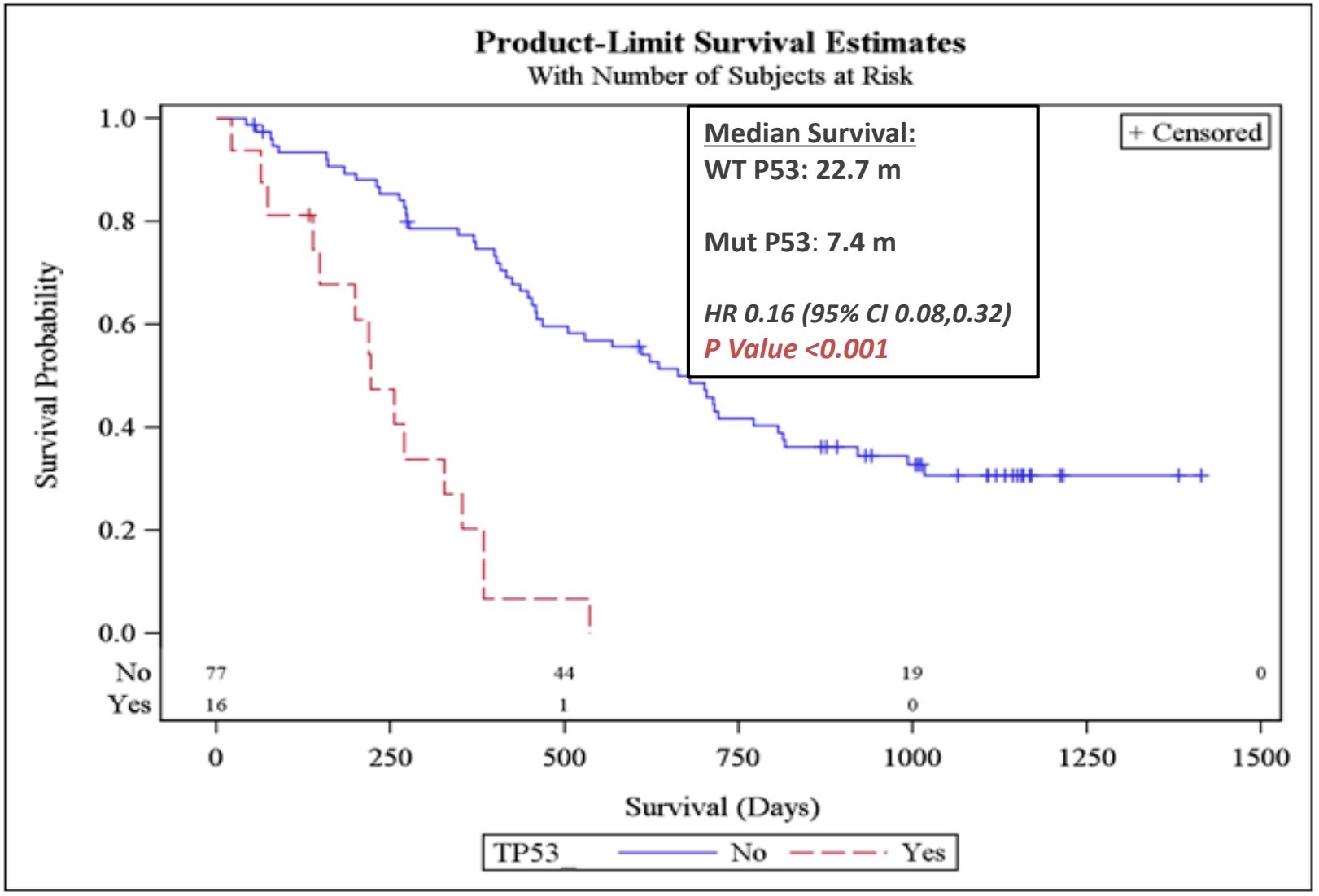
*P value is based on log-rank test of the overall survival curves

Overall Survival by Common Genetic Mutations

	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

Overall Survival by TP53 Status



Guadecitabine – American Society of Hematology 2018

Related AEs Grade ≥ 3 in ≥ 10% of Patients

Adverse Event	60 mg/m² (n=53) N (%)	90 mg/m² (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

All Cause Early Mortality	60 mg/m² (n=53) N (%)	90 mg/m² (n=49) N (%)
60-day mortality	2 (3.7)	2 (4.0)
90-day mortality	3 (5.7)	6 (12.2)

Guadecitabine Long Term Results in higher risk MDS/CMML Conclusions

- Guadecitabine is a next generation HMA with a differentiated pharmacology profile that may overcome pharmacological resistance to 1st generation HMAs
- No significant difference between 60 and 90 mg/m^2 doses except for higher incidence of Grade ≥3 related AEs with 90 mg/m^2
- Tx Naïve patients results compare well with 1st generation HMAs:
  - CR 22%
  - Median OS 23.4 months
- Previously Treated patients results are promising:
  - CR+mCR 32%
  - Median OS of 11.7 months
- Phase 3 trial is actively recruiting relapsed/refractory MDS/CMML to guadecitabine 60m/m^2 vs Treatment Choice (LDAC, BSC, IC): ASTRAL-3 study (NCT02907359)

Acknowledgments

- All Participating Patients
- All guadecitabine Study Investigators and All Site Staff and Care Givers