Results of ASTRAL-1, a Phase 3 Randomized Trial of Guadecitabine vs Treatment Choice (TC) in Treatment-Naïve Acute Myeloid Leukemia Not Eligible for Intensive Chemotherapy

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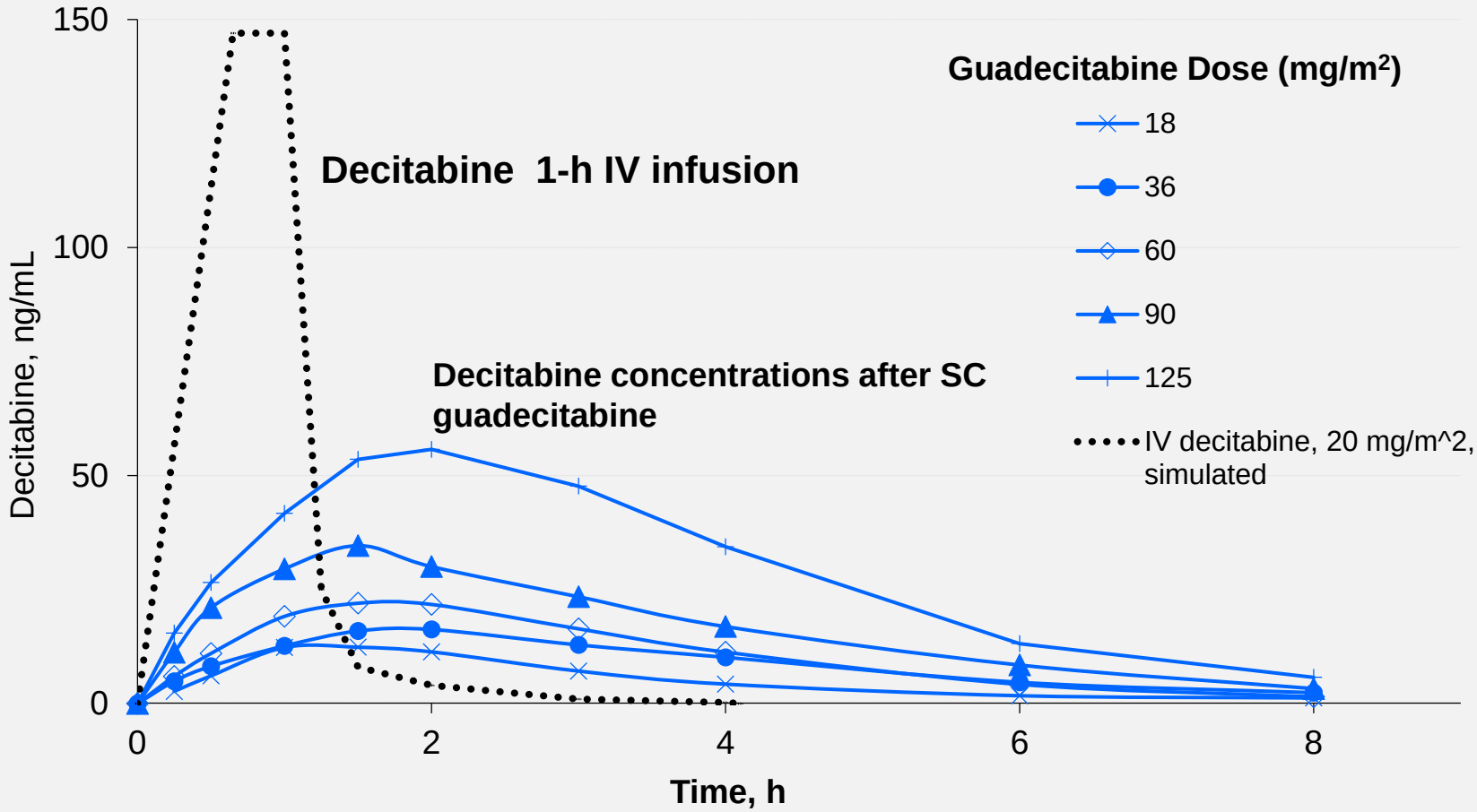
Guadecitabine (SGI-110): A Next Generation Hypomethylating Agent

- Guadecitabine is a dinucleotide of decitabine and deoxyguanosine resistant to deamination by cytidine deaminase, prolonging *in vivo* exposure to active metabolite decitabine (8-12 h decitabine exposure vs 3-4 h for decitabine IV)

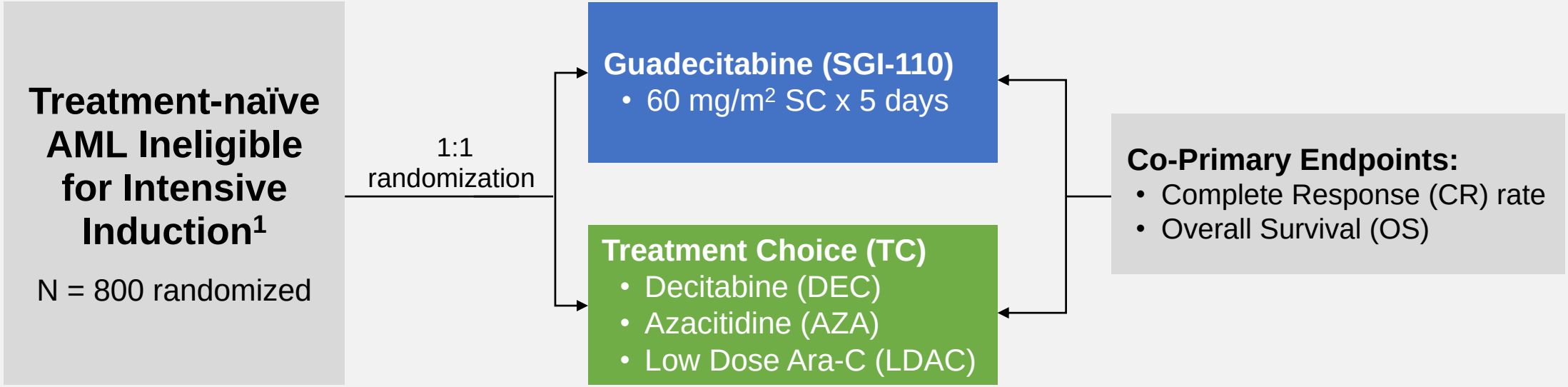


Clinical Response* in Guadecitabine Phase 2 for TN AML Not Candidates for Intensive Chemotherapy (n=103)[1]

Response*	5-day 60 mg/m^2 n=24	5-day 90 mg/m^2 n=27	10-day 60 mg/m^2 n=52	TOTAL N=103
CR	9 (38%)	11 (41%)	17 (33%)	37 (36%)
CRi	4 (17%)	3 (11%)	4 (8%)	11 (10%)
CRp	0	2 (7%)	5 (10%)	7 (7%)
CRc	13 (54%)	16 (59%)	26 (50%)	55 (53%)

CR, complete response; CRc, composite complete response; CRi, CR with incomplete neutrophil recovery regardless of platelets; CRp, CR with incomplete platelet recovery; TN AML, treatment-naive acute myeloid leukemia.
*Based on 2003 IWG response criteria (Cheson BD, et al. *J Clin Oncol*. 2003;21:4642-9).
[1]Kantarjian HM, et al. *Lancet Oncol*. 2017;18:1317-26.

ASTRAL-1: Phase 3 Study Design

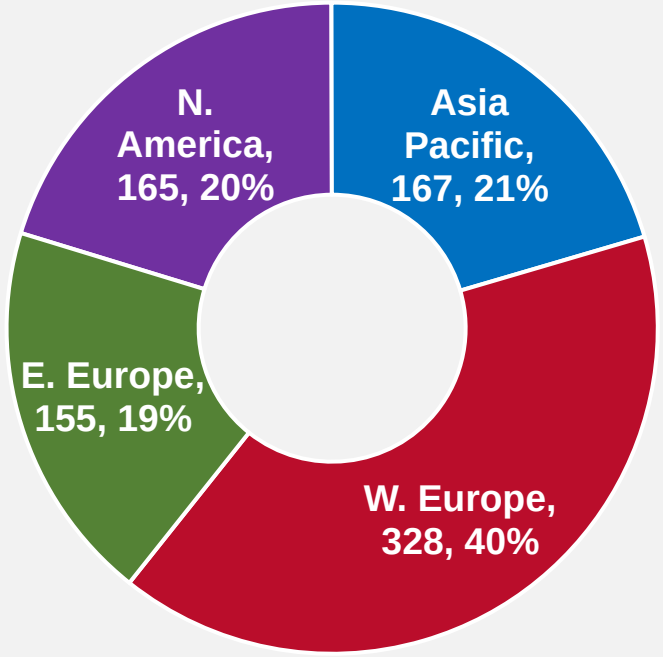


ASTRAL-1
Astex Study in Patients with TReatment Naïve AML

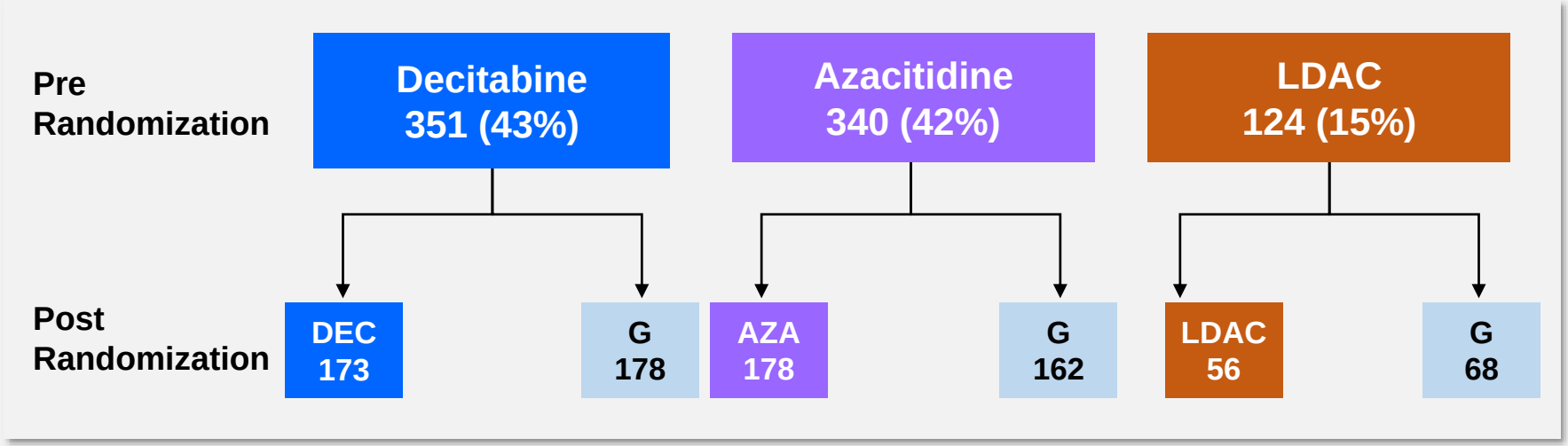
[1]Age 75 years or older; or major organ comorbidities, and poor Eastern Cooperative Oncology Group (ECOG) Performance Status 2-3.

Largest Randomized Global Study in TN AML Not Eligible For IC: 815 Patients

Enrollment by Region, %



Countries	Total Enrolling Sites	Total Patients Randomized	Total Patients Treated
24	144	815	793



IC, intensive chemotherapy.

ASTRAL-1: Baseline Clinical Characteristics

		Guadecitabine n=408	Treatment Choice n=407
Age (Y): Median (min, max)		76 (56, 93)	76 (59,94)
	<75 years	155 (38.0%)	153 (37.6%)
	≥75 years	253 (62.0%)	254 (62.4%)
Sex, n (%)	Male	231 (56.6%)	242 (59.5%)
	Female	177 (43.4%)	165 (40.5%)
ECOG PS	0-1	202 (49.5%)	202 (49.7%)
	2	162 (39.7%)	169 (41.5%)
	3	44 (10.8%)	36 (8.8%)
Secondary AML, n (%)		148 (36.3%)	150 (36.9%)
Poor-risk Cytogenetics		140 (34.3%)	141 (34.6%)
Bone Marrow Blasts	≤30%	116 (28.4%)	130 (31.9%)
	>30%	291 (71.3%)	277 (68.1%)
WBCs	<20,000/μL	346 (84.8%)	349 (85.7%)
	≥20,000/μL	62 (15.2%)	58 (14.3%)

ASTRAL-1: Common Gene Mutations at Baseline

Gene Mutations	Guadecitabine n=408	Treatment Choice n=407
Flt-3 ITD[1]	29 (7.1%)	32 (7.8%)
NPM1[2]	66 (16.2%)	59 (14.5%)
CEBPA (Biallelic)[1]	4 (1%)	13 (3.2%)
TP53[2]	51 (12.5%)	43 (10.5%)

[1]As assessed by PCR followed by capillary electrophoresis.
[2]As assessed by PCR followed by sequencing (TP53: exons 4-8).

ASTRAL-1: Treatment Exposure

	Guadecitabine n=401	Treatment Choice n=392
Median no. of treatment cycles received (min, max)	5.0 (1, 38)	5.0 (1, 34)
Patients with < 4 cycles	42.4%	40.8%
Patients with < 6 cycles	54.2%	53.8%

- ~41% and 54% of patients did not receive 4 and 6 cycles, respectively, necessary to achieve maximum benefit from hypomethylating agent (HMA) treatment
- Proportions were similar in both arms

ASTRAL-1: Co-primary Efficacy Endpoints (ITT analysis)

Complete Response (CR)

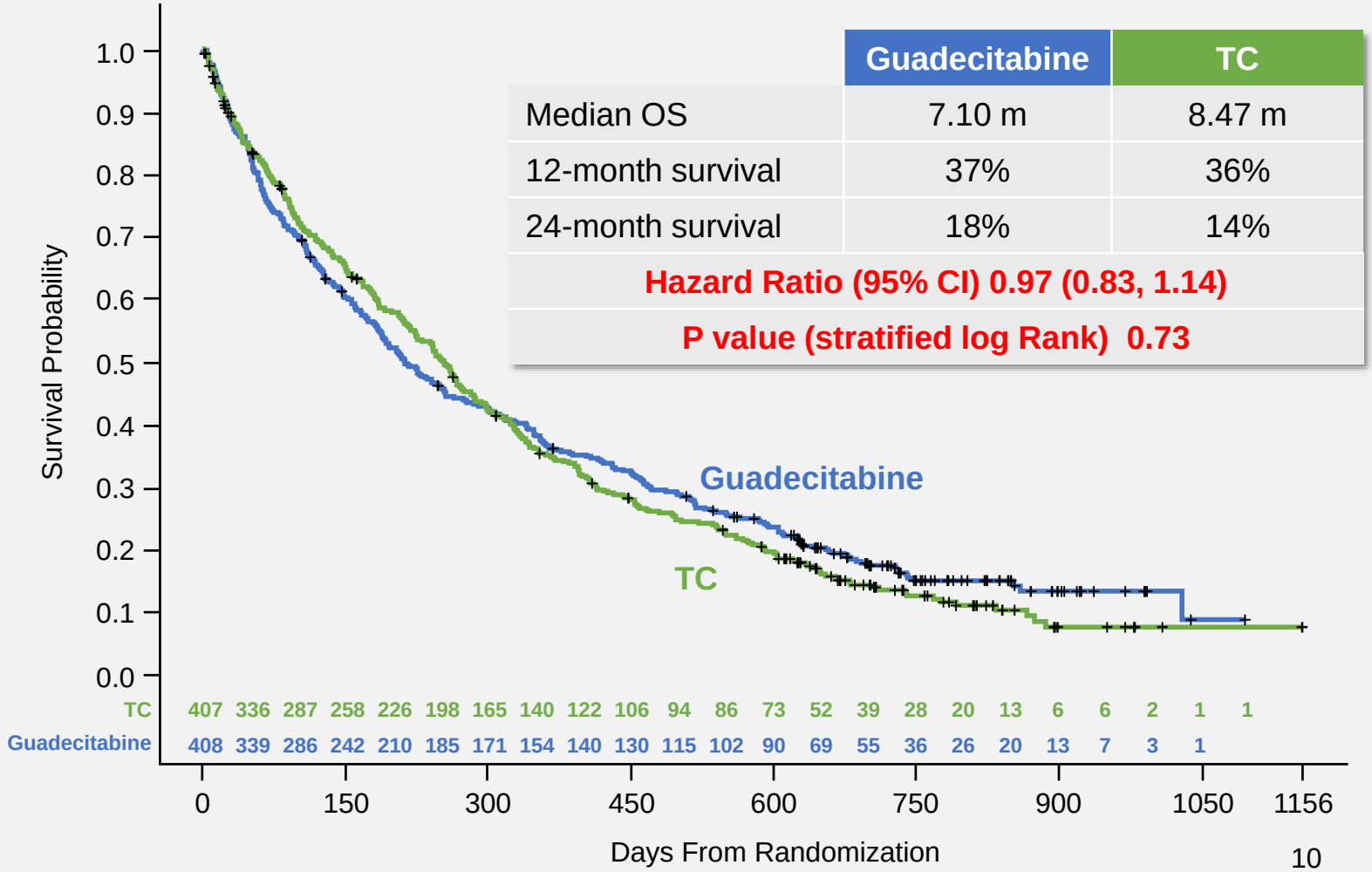
Guadecitabine	TC
79 (19.4%)	71 (17.4%)
Stratified p value	0.48

Median Time to CR (min, max): months

Guadecitabine	TC
4.5 (1.9, 19.1)	4.4 (1.9, 15.1)

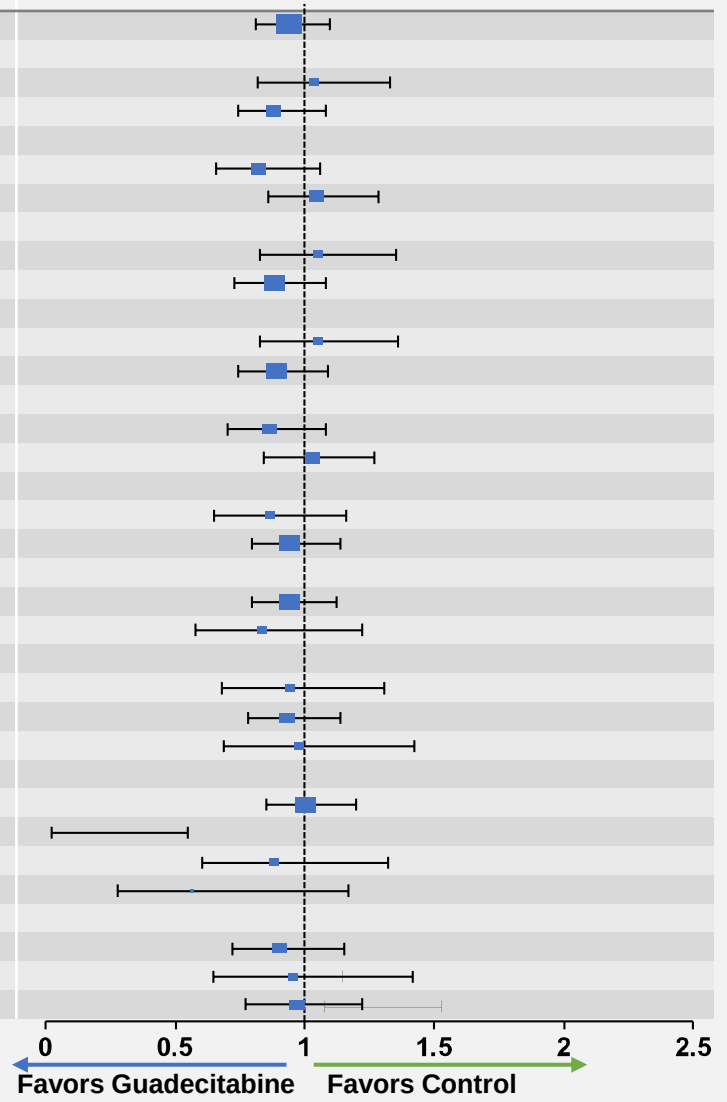
Overall Survival

	Guadecitabine	TC
Median OS	7.10 m	8.47 m
12-month survival	37%	36%
24-month survival	18%	14%
Hazard Ratio (95% CI) 0.97 (0.83, 1.14)		
P value (stratified log Rank) 0.73		



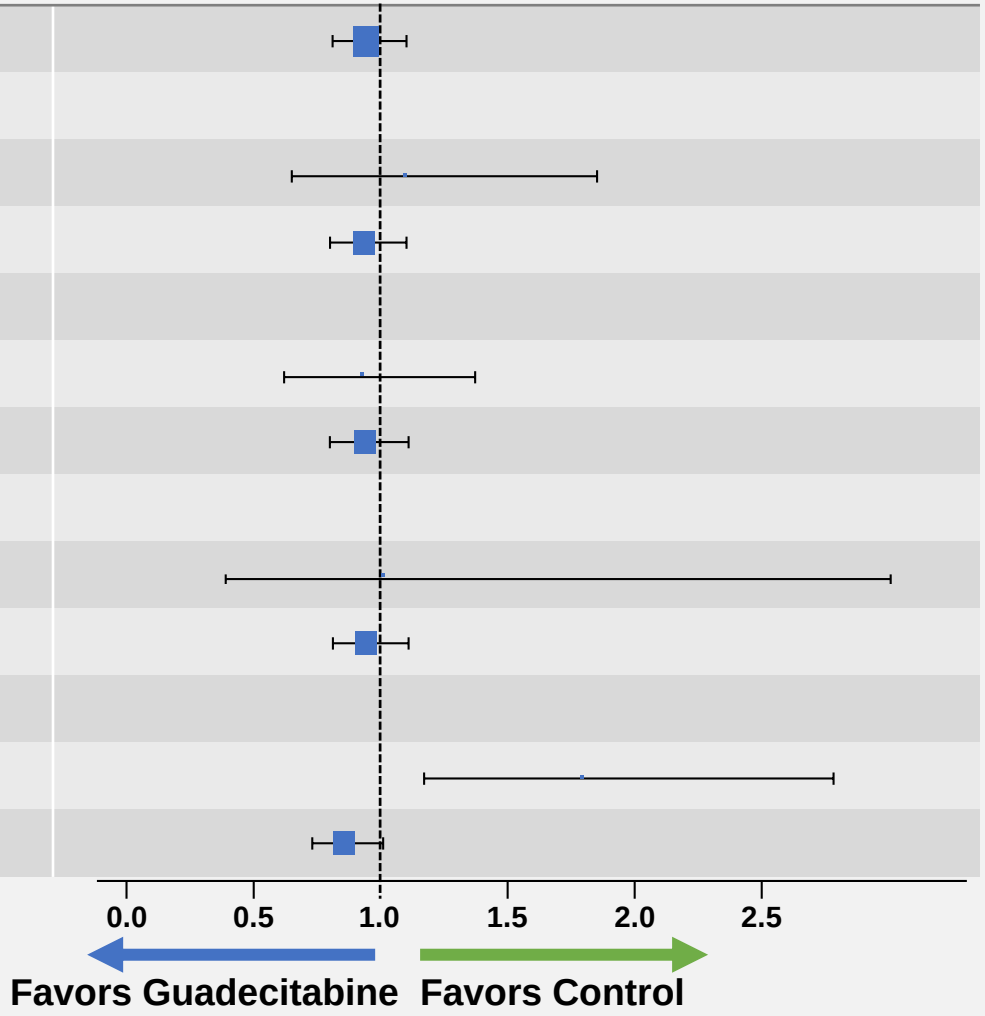
ASTRAL-1: Overall Survival in Prospective Subgroups (demographic and clinical variables)

Subgroup	N (%)	HR	LCL	UCL
All Subjects	**815 (100)**	**0.95**	**0.81**	**1.1**
Age Group				
< 75 years	308 (38)	1.04	0.82	1.33
≥ 75 years	507 (62)	0.89	0.74	1.08
Sex				
Female	342 (42)	0.83	0.66	1.06
Male	473 (58)	1.05	0.86	1.28
Secondary AML				
Yes	298 (37)	1.06	0.83	1.35
No	517 (63)	0.89	0.73	1.08
Baseline Cytogenetic Risk				
Poor-risk	281 (34)	1.06	0.83	1.36
Others (a)	534 (66)	0.9	0.74	1.09
Baseline ECOG				
0-1	404 (50)	0.87	0.70	1.08
2-3	411 (50)	1.03	0.84	1.27
Baseline bone marrow blasts (b)				
≤ 30%	246 (30)	0.87	0.65	1.16
> 30%	568 (70)	0.95	0.80	1.14
Baseline WBC				
< 20,000/μL	695 (85)	0.95	0.80	1.12
≥ 20,000/μL	120 (15)	0.84	0.58	1.22
Region				
North America	164 (20)	0.95	0.68	1.31
Europe	483 (59)	0.94	0.78	1.14
ROW	167 (20)	0.99	0.69	1.42
Race				
White	602 (74)	1.01	0.85	1.20
Black or African American	14 (2)	0.10	0.02	0.55
Asian	145 (18)	0.89	0.60	1.32
Other	54 (7)	0.58	0.28	1.17
Pre-selected				
Azacitidine	340 (42)	0.91	0.72	1.15
Cytarabine	124 (15)	0.96	0.65	1.142
Decitabine	351 (43)	0.98	0.78	1.23



ASTRAL-1: Overall Survival in Prospective Subgroups (molecular genetics variables)

Subgroup	N (%)	HR	LCL	UCL	Hazard Ratio and 95% CI
All Subjects	**815 (100)**	**0.95**	**0.81**	**1.1**	
FLT3-ITD					
Yes	61 (7)	1.1	0.65	1.85	
No	735 (90)	0.94	0.8	1.1	
NPM1					
Yes	125 (15)	0.93	0.62	1.37	
No	677 (83)	0.94	0.8	1.11	
CEBPA					
Biallelic	17 (2)	1.01	0.31	3.26	
Wild type/monoallelic	785 (96)	0.95	0.81	1.11	
TP53					
Yes	94 (12)	1.8	1.17	2.78	
No	696 (85)	0.86	0.73	1.01	



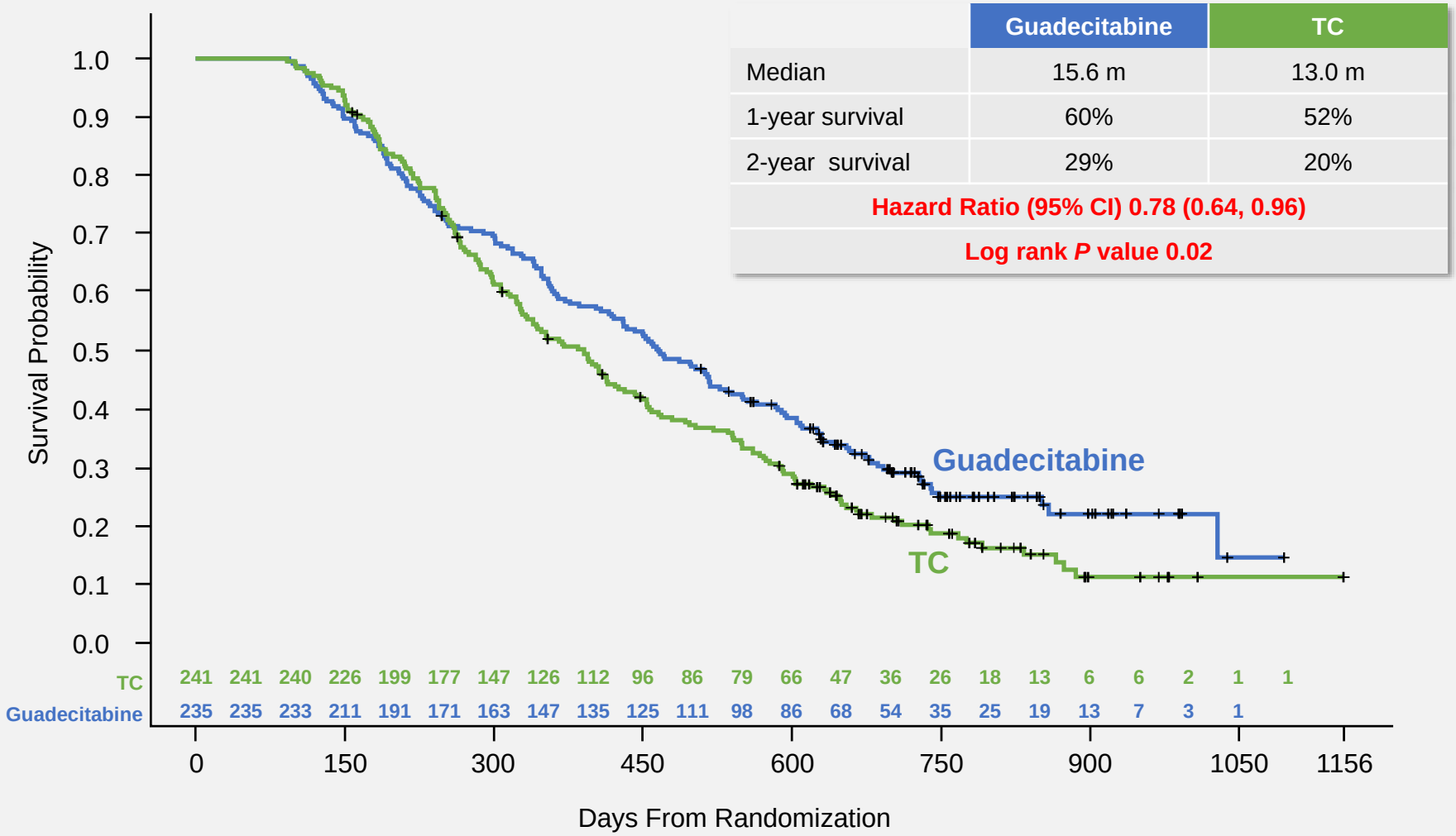
Primary Reasons for Treatment Discontinuation in Patients Who Received <4 Cycles

	Guadecitabine n=408	Treatment Choice n=407
Randomized but not treated	1.7%	3.7%
Adverse event	6.4%	5.2%
Death	17.6%	15.7%
Progressive disease	7.6%	7.6%
Alternative anti-leukemia therapy	0.7%	0.5%
Patient decision to permanently stop treatment	5.7%	5.4%
Lost to follow-up	0.2%	0
Other	2.5%	2.7%
Total % of Patients with < 4 Cycles	**42.4%**	**40.8%**

Primary Reasons for Treatment Discontinuation in Patients Who Received <6 Cycles

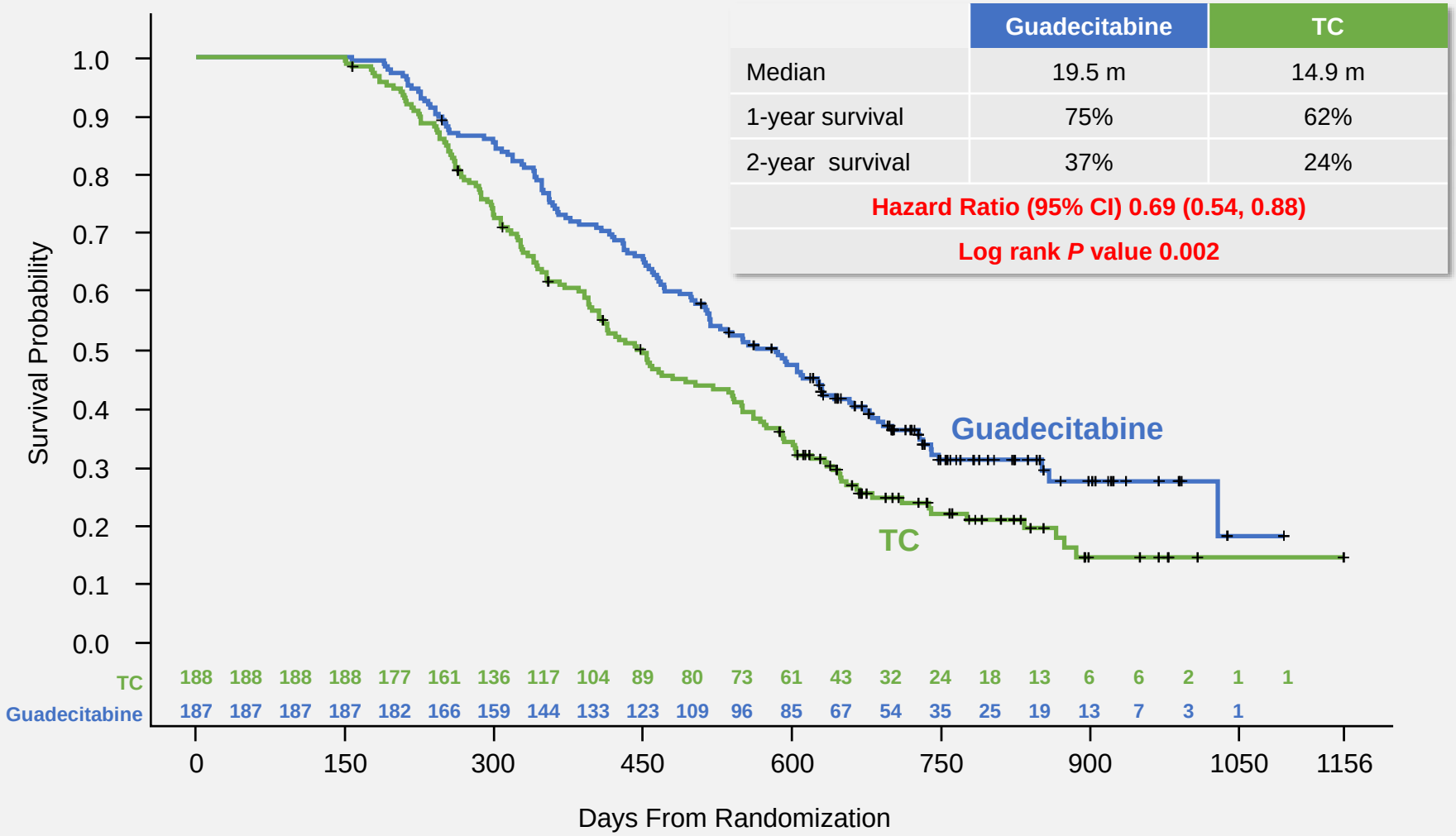
	Guadecitabine n=408	Treatment Choice n=407
Randomized but not treated	1.7%	3.7%
Adverse event	7.4%	6.4%
Death	22.5%	18.9%
Progressive disease	10.8%	12.0%
Alternative anti-leukemia therapy	0.7%	1.2%
Patient decision to permanently stop treatment	6.6%	7.6%
Lost to follow-up	0.5%	0
Other	3.9%	3.9%
Total % of Patients with < 6 Cycles	**54.2%**	**53.8%**

ASTRAL-1: Survival Analysis in Patients Treated for Minimum of 4 Cycles (n=476)



	Guadecitabine	TC
Median	15.6 m	13.0 m
1-year survival	60%	52%
2-year survival	29%	20%
Hazard Ratio (95% CI) 0.78 (0.64, 0.96)		
Log rank *P* value 0.02		

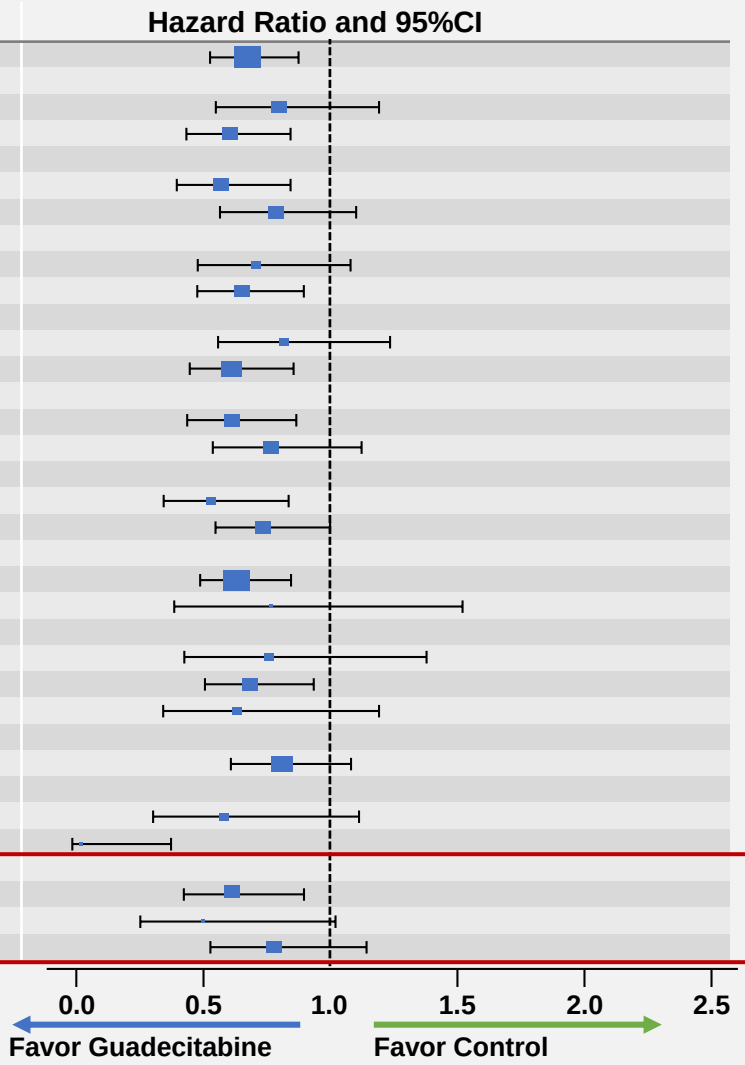
ASTRAL-1: Survival Analysis in Patients Treated for Minimum of 6 Cycles (n=375)



	Guadecitabine	TC
Median	19.5 m	14.9 m
1-year survival	75%	62%
2-year survival	37%	24%
Hazard Ratio (95% CI) 0.69 (0.54, 0.88)		
Log rank *P* value 0.002		

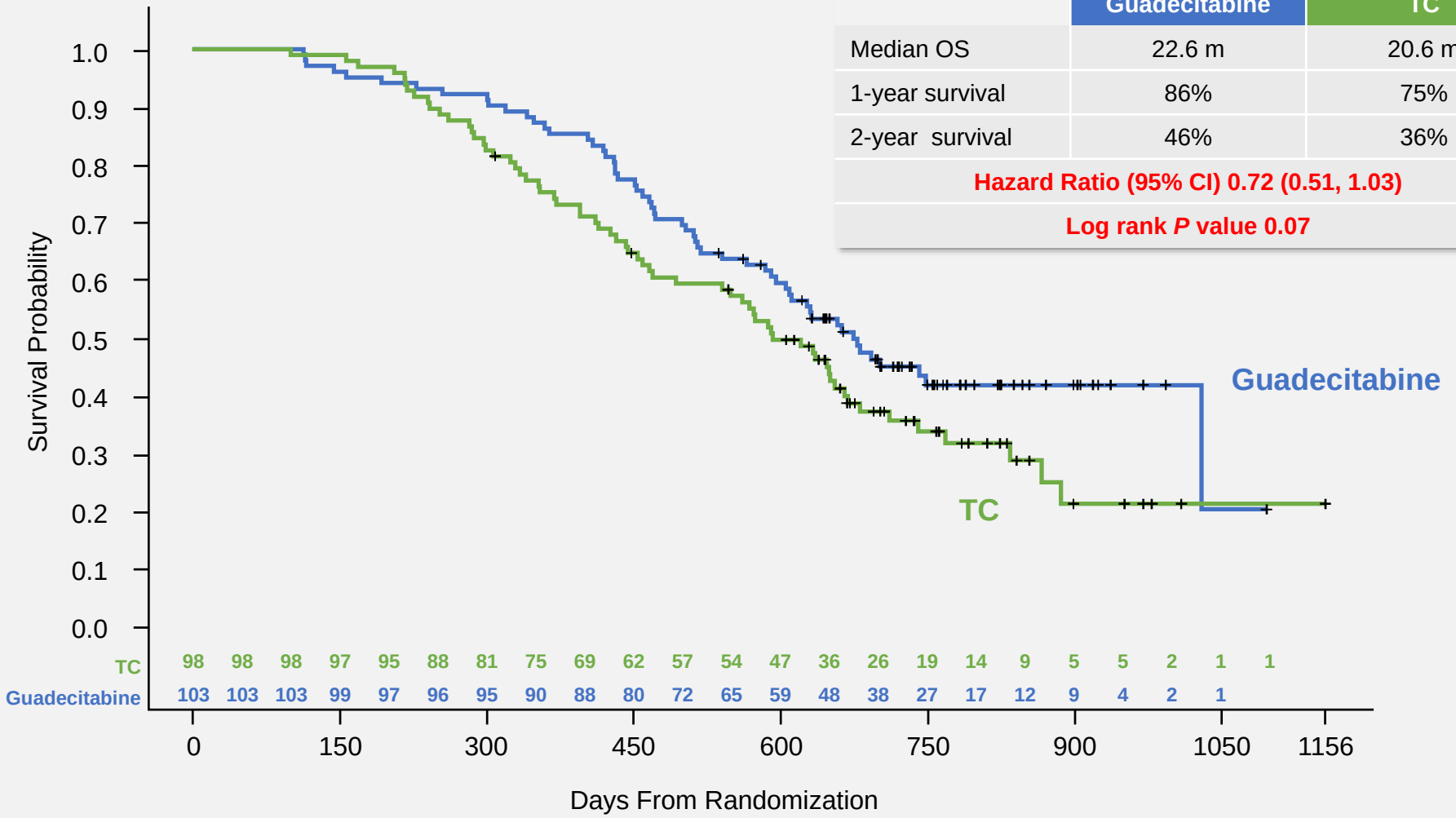
ASTRAL-1: Survival Subgroups in Patients Treated for Minimum of 6 Cycles

Subgroup	N (%)	HR	LCL	UCL
All Subjects	375 (100)	0.69	0.54	0.88
Age Group				
< 75 years	148 (39)	0.81	0.56	1.19
≥ 75 years	227 (61)	0.62	0.45	0.85
Sex				
Female	168 (45)	0.59	0.41	0.85
Male	207 (55)	0.8	0.58	1.1
Secondary AML				
Yes	132 (35)	0.72	0.49	1.08
No	243 (65)	0.67	0.49	0.9
Baseline Cytogenetic Risk				
Poor-risk	123 (33)	0.83	0.57	1.23
Others (a)	252 (67)	0.63	0.46	0.86
Baseline ECOG				
0-1	211 (56)	0.63	0.45	0.87
2-3	164 (44)	0.78	0.55	1.12
Baseline bone marrow blasts (b)				
≤ 30%	139 (37)	0.55	0.36	0.84
> 30%	236 (63)	0.75	0.56	1
Baseline WBC				
< 20,000/μL	336 (90)	0.65	0.5	0.85
≥ 20,000/μL	39 (10)	0.78	0.4	1.51
Region				
North America	65 (17)	0.77	0.44	1.37
Europe	233 (62)	0.7	0.52	0.94
ROW	77 (21)	0.65	0.36	1.19
Race				
White	269 (72)	0.82	0.62	1.08
Black or African American	6 (2)			
Asian	71 (19)	0.6	0.32	1.11
Other	29 (8)	0.05	0.01	0.39
Pre-selected				
Azacitidine	167 (45)	0.63	0.44	0.9
Cytarabine	52 (14)	0.52	0.27	1.02
Decitabine	156 (42)	0.79	0.54	1.14



ASTRAL-1: Overall Survival in Responding Patients (CR, CRp, CRi, or PR): N= 201 patients

	Guadecitabine	TC
Median OS	22.6 m	20.6 m
1-year survival	86%	75%
2-year survival	46%	36%
Hazard Ratio (95% CI) 0.72 (0.51, 1.03)		
Log rank *P* value 0.07		



ASTRAL-1: Safety Results (regardless of causality)

Patients, n (%)	Guadecitabine n=401	TC n=392
Any AE	393 (98.0%)	387 (98.7%)
AE leading to discontinuation of study treatment	41 (10.2%)	26 (6.6%)
Any SAE	325 (81.0%)	296 (75.5%)
Death (due to an AE)	115 (28.7%)	117 (29.8%)
Any Grade ≥3 AE	367 (91.5%)	343 (87.5%)
Grade ≥3 AEs in >5% of subjects (either group)		
Febrile neutropenia	136 (33.9%)	104 (26.5%)*
Pneumonia	118 (29.4%)	77 (19.6%)*
Thrombocytopenia	114 (28.4%)	92 (23.5%)
Neutropenia	110 (27.4%)	81 (20.7%)*
Anemia	81 (20.2%)	70 (17.9%)
Sepsis	61 (15.2%)	47 (12.0%)
Hypokalemia	33 (8.2%)	35 (8.9%)
Leukopenia	32 (8.0%)	28 (7.1%)

*Febrile neutropenia, pneumonia, and neutropenia $p<0.05$

Summary and Conclusions (1)

- ASTRAL-1 was the largest global, randomized study investigating efficacy and safety of low intensity therapy (mainly HMAs) in TN AML not eligible for Intensive Chemotherapy

- Primary ITT analysis on all randomized patients did not show statistically significant differences between guadecitabine and TC in the primary efficacy endpoints of CR and Overall Survival
  - Results were consistent against each of the 3 TCs with Survival HR <1 for guadecitabine arm

- A relatively large and equal proportion of patients (41–54%) did not receive the minimum 4 to 6 cycles necessary for maximum HMA benefit in the 2 treatment arms

Summary and Conclusions (2)

- Patients who received adequate treatment (≥ 4 – 6 cycles) achieved clinically significant survival benefit on guadecitabine compared to control arm:
  - Survival benefit on guadecitabine was consistent against each of the 3 TCs (azacitidine, decitabine, LDAC)
  - The study highlights the importance of adequate HMA treatment duration (at least 4 to 6 cycles) to achieve maximum benefit
- Patients who responded seemed to have a better survival benefit on guadecitabine compared to TC
- Safety profile of guadecitabine was generally similar to TC but with a higher incidence of Grade ≥3 febrile neutropenia, and pneumonia which should be carefully managed to avoid early treatment discontinuation
- Overall serious AEs and deaths due to AEs were similar between the 2 arms

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