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GUADECITABINE (SGI-110) VS. TREATMENT CHOICE (TC) IN RELAPSED/REFRACTORY(R/R) MYELODYSPLASTIC SYNDROME (MDS), RESULTS OF A GLOBAL, RANDOMIZED, PHASE 3 STUDY

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BACKGROUND

- **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 hours for decitabine IV).**
- **As a next-generation hypomethylating agent (HMA), guadecitabine is administered as a small-volume subcutaneous injection, designed with the potential to overcome pharmacokinetic resistance to first-generation HMAs (decitabine and azacitidine).**
- **Preliminary guadecitabine phase 2 data in r/r MDS showed an overall survival of almost 12 months leading to the ASTRAL-3 study (Garcia-Manero, G, et al; Lancet Haematol http://dx.doi.org/10.1016/S2352-3026(19)30029-8)**
- **Aims:**
  - Compare overall survival of guadecitabine to that of Treatment Choice (either low-dose Ara-C [LDAC], intensive chemotherapy [IC], or best supportive care [BSC]) in adults with MDS or CMML previously treated with a HMA (azacitidine, decitabine, or both)
  - Compare multiple other standard assessments of safety and efficacy in this population (transfusion independence [TI], marrow complete response [mCR] with TI, survival at 1 year, leukemia-free survival, disease response based on IWG 2006 criteria, quality of life [QOL], and safety)

METHODS

- **Multicenter, randomized open-label, parallel-group study of guadecitabine vs. TC.**
- **Approximately 408 subjects were to be randomly assigned to either guadecitabine or TC in a 2:1 ratio.**
  - Randomization was stratified by disease category (MDS vs CMML), bone marrow blasts (>10% vs ≤ 10%), TC option, and study center region (North America vs. rest of world).
  - Before randomization, the investigator was to assign each subject to one of the following TC options:
    - LDAC
    - IC of an anthracycline-containing "7+3" regimen.
    - BSC
  - BSC was provided to all subjects consistent with institutional practice.
  - Subjects randomized to TC were not allowed to cross over to guadecitabine.
  - Data was reviewed by an independent data monitoring committee (DMC) at regular intervals.
- **Primary endpoint:**
  - Overall survival (OS): the study was designed with ~90% power to detect a hazard ratio of 0.68 (approximately 2.8 month difference in median survival).

Figure 1: ASTRAL-3 Schema and End Points

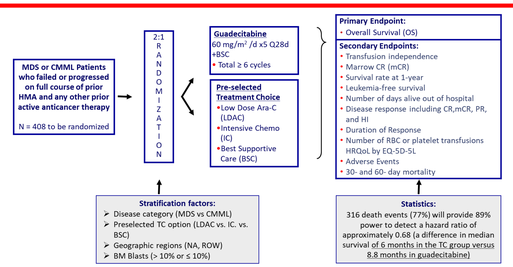

Table 1: Demographics

	Guadecitabine (N = 277)	Treatment Choice (N = 140)	All Subjects (N = 417)
Age (Years)			
n	277	140	417
Median (mean, SD)	74.0 (73.5, 7.0)	74.0 (73.7, 6.1)	74.0 (73.6, 6.7)
Min, Max	44, 91	57, 88	44, 91
Age Category (Years), n (%)			
18 - 64 years	23 (8.3)	11 (7.9)	34 (8.2)
65 - 84 years	245 (88.4)	125 (89.3)	370 (88.7)
≥85 years	9 (3.2)	4 (2.9)	13 (3.1)
Sex, n (%)			
Male	194 (70.0)	96 (68.6)	290 (69.5)
Female	83 (30.0)	44 (31.4)	127 (30.5)
Region, n (%)			
North America	99 (35.7)	51 (36.4)	150 (36.0)
Rest of world	178 (64.3)	89 (63.6)	267 (64.0)
BSA (m^2)			
Median	1.81	1.82	1.81
Min, Max	1.1, 2.6	1.2, 2.5	1.1, 2.6

BSA=body surface area; SD=standard deviation

RESULTS

Table 2: Patient Population (Disease and Performance Status)

	Guadecitabine (N = 277)	Treatment Choice (N = 140)	All Subjects (N = 417)
Preselected TC option, n (%)			
LDAC	164 (59.2)	82 (58.6)	246 (59.0)
Standard IC	11 (4.0)	4 (2.9)	15 (3.6)
BSC Only	102 (36.8)	54 (38.6)	156 (37.4)
ECOG performance status [a] n (%)			
0	86 (31.0)	41 (29.3)	127 (30.5)
1	156 (56.3)	78 (55.7)	234 (56.1)
2	33 (11.9)	19 (13.6)	52 (12.5)
3	1 (0.4)	2 (1.4)	3 (0.7)
4	1 (0.4)	0	1 (0.2)
Cytogenetic Risk Levels, n (%)			
Better-risk	94 (33.9)	54 (38.6)	148 (35.5)
Intermediate-risk	76 (27.4)	38 (27.1)	114 (27.3)
Poor-risk	90 (32.5)	39 (27.9)	129 (30.9)
Not evaluable	15 (5.4)	9 (6.4)	24 (5.8)
Missing	2 (0.7)	0	2 (0.5)
RBC or platelet transfusion dependence [b] n (%)			
Yes	235 (84.8)	111 (79.3)	346 (83.0)
No	42 (15.2)	29 (20.7)	71 (17.0)
RBC transfusion dependence [c] n (%)			
Yes	220 (79.4)	100 (71.4)	320 (76.7)
No	57 (20.6)	40 (28.6)	97 (23.3)
Platelet transfusion dependence [c] n (%)			
Yes	114 (41.2)	51 (36.4)	165 (39.6)
No	163 (58.8)	89 (63.6)	252 (60.4)

[a] Based on Cycle 1 Day 1 values. Screening value was used if Cycle 1 Day 1 value was missing. Levels were within acceptable limits for all subjects at time of screening.
[b] RBC transfusion dependence at baseline or platelet transfusion dependence at baseline.
[c] Transfusion dependent = 2 units or more of transfusion within 56 days of the first dose of study treatment.
BSC=best supportive care; ECOG=Eastern Cooperative Oncology Group; IC=intensive chemotherapy; LDAC= low dose cytarabine; SD=standard deviation; TC=treatment choice

Table 3: Patient Population (Hematology Parameters)

	Guadecitabine (N = 277)	Treatment Choice (N = 140)	All Subjects (N = 417)
Peripheral Blood Blasts, (%)			
n	170	89	259
Mean	3.36	4.37	3.70
SD	6.01	8.16	6.83
Median	1.00	1.72	1.00
Min, Max [a]	0.0, 55.6	0.0, 51.7	0.0, 55.6
Bone Marrow Blasts (%)			
Median	8.00	7.10	8.00
Min, Max	0.0, 19.5	0.0, 19.4	0.0, 19.5
Bone Marrow Blasts, n (%)			
≤10%	174 (62.8)	91 (65.0)	265 (63.5)
>10%	103 (37.2)	49 (35.0)	152 (36.5)
Hemoglobin (g/L)			
Median	86.50	86.50	86.50
Min, Max	56.0, 154.5	51.0, 149.0	51.0, 154.5
Neutrophils (10^9/L)			
Median	0.76	1.06	0.85
Min, Max	0.0, 66.7	0.0, 34.5	0.0, 66.7
Total WBC counts (10^9/L)			
Median	2.12	2.76	2.21
Min, Max	0.3, 122.3	0.7, 94.5	0.3, 122.3
Platelet counts (10^9/L)			
Median	36.00	40.00	37.50
Min, Max	1.5, 824.0	3.5, 538.0	1.5, 824.0

[a] Based on Cycle 1 Day 1 values. Screening value was used if Cycle 1 Day 1 value was missing. Levels were within acceptable limits for all subjects at time of screening.
BSC=best supportive care; ECOG=Eastern Cooperative Oncology Group; IC=intensive chemotherapy; LDAC= low dose cytarabine; SD=standard deviation; TC=treatment choice

Figure 2: Primary Efficacy Endpoint of Overall Survival

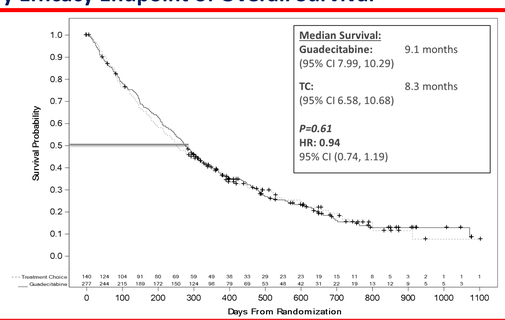

Table 3: Response

	Guadecitabine (N = 277)	Treatment Choice (N = 140)
Secondary Endpoints		
Transfusion independence (8 weeks), n (%)	44 (15.9)	22 (15.7)
Platelet transfusion independence, n (%)	89 (32.1)	53 (37.9)
RBC transfusion independence, n (%)	62 (22.4)	28 (20.0)
mCR		
mCR with transfusion independence, n (%)	16 (5.8)	4 (2.9)
12-month Survival		
Survival Rate (95% CI)	0.39 (0.34, 0.45)	0.39 (0.30, 0.47)
24-month Survival		
Survival Rate (95% CI)	0.16 (0.11, 0.21)	0.17 (0.10, 0.25)
Leukemia-free Survival		
Events	230 (83.0)	114 (81.4)
K-M Estimate, (Days (95% CI))		
Median	173.0 (135.0, 206.0)	181.0 (125.0, 213.0)
NDAOH in First 6 Months (Days)		
LS Mean	130.6	134.6
Disease Response		
Complete response, % (95% CI)	1.4 (0.0, 2.8)	0.7 (0.0, 2.1)
Partial response, % (95% CI)	0	0
mCR, % (95% CI)	17.3 (12.9, 21.8)	8.6 (3.9, 13.2)
HI, % (95% CI)	3.2 (1.2, 5.3)	5.7 (1.9, 9.6)
HI-E, % (95% CI)	1.1 (0.0, 2.2)	2.1 (0.0, 4.5)
HI-P, % (95% CI)	1.8 (0.2, 3.3)	2.1 (0.0, 4.5)
HI-N, % (95% CI)	0.7 (0.0, 1.7)	2.1 (0.0, 4.5)

Number of subjects in the analysis set. n=Number of subjects with observed data.
[a] Survival time was censored on the last date the subject is known alive with no event of death.
[b] Primary analysis based on the log-rank test, stratified by the factors used at randomization.
Note: Response based on IWG 2006 criteria (Cheson et al 2006). CI=confidence interval; HI=hematological improvement; HI-E=HI with erythroid; HI-N=HI with neutrophil; HI-P=HI with platelet; K-M=Kaplan-Meier; LS=Least Squares; mCR=marrow complete response; NDAOH=number of days alive and out of hospital; RBC=red blood cells; WBC=white blood cell

Table 4: Safety: Grade ≥3 Adverse Events in ≥5% of Subjects in Either Treatment Group

System Organ Class Preferred Term	Guadecitabine (N = 270) n (%)	Treatment Choice (N = 122) n (%)	All Subjects (N = 392) n (%)
Subjects Experiencing Any Event	249 (92.2)	86 (70.5)	335 (85.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	192 (71.1)	57 (46.7)	249 (63.5)
Febrile Neutropenia	104 (38.5)	23 (18.9)	127 (32.4)
Neutropenia	89 (33.0)	18 (14.8)	107 (27.3)
Thrombocytopenia	81 (30.0)	23 (18.9)	104 (26.5)
Anaemia	58 (21.5)	20 (16.4)	78 (19.9)
Leukopenia	32 (11.9)	12 (9.8)	44 (11.2)
INFECTIONS AND INFESTATIONS	155 (57.4)	37 (30.3)	192 (49.0)
Pneumonia	80 (29.6)	20 (16.4)	100 (25.5)
Sepsis	28 (10.4)	4 (3.3)	32 (8.2)
Cellulitis	18 (6.7)	2 (1.6)	20 (5.1)
Septic Shock	16 (5.9)	2 (1.6)	18 (4.6)

- Investigator text for AEs encoded using MedDRA version 21.0. CTCAE version 4.03 is used. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
- For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
- Table includes treatment emergent AEs which are those with onset date on or after the date of the first dose of study drug on C1D1 until 30 days after the last dose of study treatment, or the start of an alternative anticancer treatment, whichever occurs first. Events that occurred after 30 days beyond the last dose of study treatment or the start of an alternative anti-leukemia treatment will also be considered treatment emergent if the events are both serious and related to the study treatment.

SUMMARY

- **This was a large, global, randomized phase 3 study in MDS subjects who were refractory or relapsed after full course of prior HMA treatment.**
- **There was no statistically significant difference between guadecitabine and TC (LDAC, IC, or BSC) for the primary endpoint of OS.**
  - Median OS for guadecitabine was 9.11 months compared with 8.28 months for TC.
  - All-cause mortality was marginally higher for guadecitabine than TC.
- **There were no clinically meaningful differences between guadecitabine and TC for the secondary endpoints of 8-week transfusion independence, 12-month survival, leukemia free survival, NDAOH, or duration of response in subjects with CR.**
  - Due to the pre-specified hierarchical testing plan, secondary endpoints were not evaluated for statistical significance.
- **The safety profile of guadecitabine and TC were generally similar, however:**
  - AEs were generally more common in the guadecitabine group with the most common AEs (≥30% overall; febrile neutropenia, pneumonia, neutropenia, and thrombocytopenia) occurring more frequently in subjects treated with guadecitabine than TC.
- **Treatment for MDS patients who are never or no longer responsive to HMAs remains a major challenge and unmet need.**

Poster presented at: EHA Annual Meeting, Vienna, Austria June 9 – 12, 2022

Poster can be downloaded from www.astx.com 22US-ASTX_PB(104)