Abstract # 2591

Results from a Global Randomized Phase 3 Study of Guadecitabine (G) vs Treatment Choice (TC) in 815 Patients with Treatment Naïve (TN) AML Unfit for Intensive Chemotherapy (IC) ASTRAL-1 Study: Analysis By Number of Cycles

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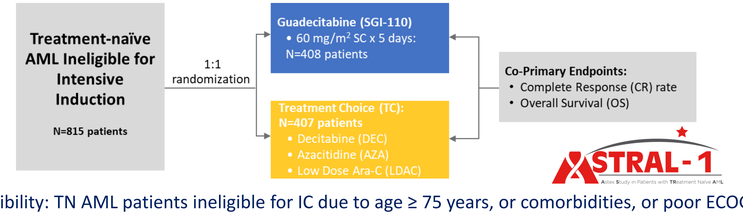
BACKGROUND

- Guadecitabine (G) is a next generation small volume Subcutaneous (SC) hypomethylating agent (HMA) resistant to degradation by cytidine deaminase resulting in prolonged in vivo exposure to its active metabolite decitabine
- ASTRAL-1 is a large global randomized Phase 3 study of G vs preselected Treatment Choice (TC) of azacitidine (AZA), decitabine (DEC), or low dose Ara-C (LDAC) in 815 TN AML patients
- Primary ITT results of ASTRAL-1 were previously presented (Fenaux et al, 2019)
- International guidelines recommend a minimum of 4 cycles of HMAs for maximum benefit (Dohner et al, 2017)
- Here we present Patients Characteristics and Overall Survival results based on patient subgroups who received at least 4 or 6 cycles

METHODS

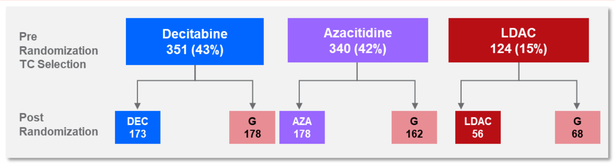
Figure 1. ASTRAL-1: Phase 3 Study Design



- Eligibility: TN AML patients ineligible for IC due to age ≥ 75 years, or comorbidities, or poor ECOG PS 2 or 3
- Patients randomized 1:1 to G: 60 mg/m2 SC dailyx5 or preselected TC (AZA, DEC, or LDAC) using their approved dose and regimen. Cycles repeated Q 28 days. Treatment to be continued till progression or unacceptable toxicity
- Complete Response (CR) was assessed by an independent central pathologist blinded to randomization assignment
- CR and Overall survival (OS) were co-primary endpoints
- Results are presented for the subgroups of patients wo received at least 4 or 6 cycles: patient characteristics; CR; and OS.
- Reasons for treatment discontinuation before 4 or 6 cycles are also presented

RESULTS

Figure 2. TC Randomization Assignment



- Primary ITT analyses of co-primary endpoints CR rate, and OS showed no statistically significant differences between G and TC. Results were also similar between G and each of the TC choices (AZA, DEC, and LDAC) (Fenaux et al, 2019)

Table 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 discontinued treatment before 4 and 6 cycles, respectively
- Proportions were similar in both arms

RESULTS

Table 2. Primary Reasons for Treatment Discontinuation Before 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%**

Table 3. Primary Reasons for Treatment Discontinuation Before 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%**

- Number of patients and primary reasons for treatment discontinuation before 4 or 6 cycles well balanced between Guadecitabine and TC

Table 4. Key Baseline Patient Characteristics: Patients Who Received ≥4 Cycles

	Guadecitabine n=235	Treatment Choice n=241
Median Age (range) years	76 (57-93)	76 (59-89)
Age ≥ 75 years	63%	59%
ECOG Poor PS 2-3	43%	47%
Secondary AML	35%	40%
Poor Risk Cytogenetics	32%	34%
Bone Marrow Blasts > 30%	67%	61%
Total WBCs ≥ 20,000/µL	12%	9%

Table 5. Key Baseline Characteristics: Patients Who Received ≥6 Cycles

	Guadecitabine n=187	Treatment Choice n=188
Median Age (range) years	76 (60-93)	76 (59-89)
Age ≥ 75 years	63%	59%
ECOG Poor PS 2-3	41%	47%
Secondary AML	34%	37%
Poor Risk Cytogenetics	31%	35%
Bone Marrow Blasts > 30%	66%	60%
Total WBCs ≥ 20,000/µL	12%	9%

- Key baseline patient characteristics well balanced between Guadecitabine and TC patients who received at least 4 or 6 cycles

Figure 3. Survival Analysis in Patients Treated for Minimum of 4 Cycles (n=476)

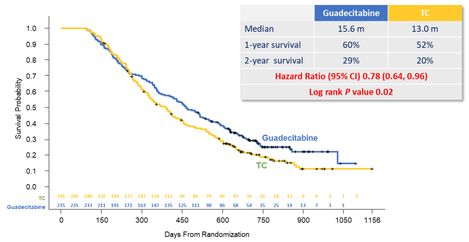
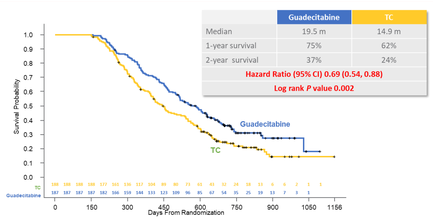


Figure 4. Survival Analysis in Patients Treated for Minimum of 6 Cycles (n=375)



In patients who received at least 4 or 6 cycles:

- OS favored Guadecitabine in all subgroups and against each of the TC choices (AZA, DEC, and LDAC)
- OS benefit with guadecitabine was observed in both responders and non-responders

Table 6. CR and OS in Patient Who Received ≥ 4 or ≥ 6 cycles

	Patients with ≥ 4 Cycles		Patients with ≥ 6 Cycles	
	Guadecitabine N= 235	TC N= 241	Guadecitabine N=187	TC N= 188
CR rate	33.6%	28.6%	40.1%	36.2%
Median OS months	15.6	13.0	19.5 m	15.0 m
OS HR (95% CI) , log rank p value	0.78 (0.64, 0.96), p 0.02		0.69 (0.54, 0.88), p 0.002	

SUMMARY/CONCLUSIONS

- ASTRAL-1 was the largest randomized study conducted in TN AML unfit for IC
- Primary ITT analyses showed no significant differences between G and TC in the co-primary endpoints of CR rate or OS
- ~ 41 to 54% of patients did not receive the minimum of 4 to 6 cycles recommended to achieve maximum benefit with HMAs. Number and characteristics of patients of those who received at least 4 or 6 cycles were well balanced between G and TC
- OS for Guadecitabine was superior to TC in the subgroups of patients who were able to receive at least 4 or 6 cycles
- The OS benefit from guadecitabine in these subgroups was independent of baseline characteristics, and of the TC (AZA, DEC, or LDAC); and was observed for both responders and non-responders (data on file)

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2. Dohner H, Estey E, Grimwade D, et al. Blood; 2017; 129: 424-447

Conflict-of-interest statement: **Roboz**: Consultancy: Pfizer, Roche/Genentech, Sandoz, Takeda, Trovagene, Celgene, Bayer, Orsenix, Astellas, Astex, AbbVie, Actinium, Amphivena, Agios, MEI Pharma, Novartis, Jazz, Janssen, Daiichi Sankyo, Celltrion, Eisai; BOD/advisory committee: Otsuka, Pfizer, Roche/Genentech, Sandoz, Takeda, Trovagene, Celgene, Bayer, Orsenix, Astellas, Astex, AbbVie, Actinium, Amphivena, Agios, MEI Pharma, Novartis, Jazz, Janssen, Daiichi Sankyo, Celltrion, Eisai; **Dohner**: Consultancy: Abbvie, Agios, Amgen, Astellas, Astex, Celator, Janssen, Jazz, Seattle Genetics; Research funding: AROG, BMS, Pfizer; Celgene, Novartis, Sunesis; Honoraria: Abbvie, Agios, Amgen, Astellas, Astex, Celator, Janssen, Jazz, Seattle Genetics; **Mayer**: Research funding: AOP Orphan; **Robak**: Consultancy: Takeda, Janssen, Amgen, Roche, Abbvie, Gilead, BeiGene; Research funding: Takeda, LICB, Roche, Abbvie, Gilead, BeiGene; Honoraria: LICB, Janssen; Travel grant: Janssen, Amgen, Roche, Abbvie; **Kantarjian**: Research funding: Daiichi-Sankyo, Jazz Pharma, Cyclacel, Pfizer, Ariad, AbbVie, Agios, Novartis, Immunogen, Astex, BMS, Amgen; Honoraria: Pfizer, Actinium, AbbVie, Agios, Amgen; BOD/advisory committee: Actinium, Takeda; **Jedrzejczak**: Consultancy: Amgen, Takeda: Research Funding: Novartis; Travel support: Amgen, Celgene, Roche; **Thomas**: Honoraria: Pfizer, Daiichi, Incyte, Abbvie; **Miyazaki**: Research funding: Chugai; Honoraria: Otsuka, Novartis, Nippon-Shinyaku, Dainippon-Sumitomo, Kyowa-Kirin; **Brandwein**: Brandwein: Consultancy: Novartis, Celgene, Pfizer, Jazz; Research funding: Celgene, Pfizer, Roche; Honoraria: Novartis, Celgene, Pfizer, Otsuka, Jazz; **Demeter**: Advisory committee: Novartis, BMS, Amicus, Angelini, Pfizer, Amgen, Roche; Griffiths: Consultancy: Celgene, Inc., Appelis, Abbvie, Genentech, New Link Genetics, Astex, Otsuka Pharmaceuticals, Novartis Inc., ; Boston Scientific, Persimmune, Partner Therapeutics; Research funding: Celgene, Inc , Appelis, Genentech, New Link Genetics, Astex, Otsuka, Novartis, Partner; PI on clinical trial: Appelis, Onconova, Abbvie; **Yee**: Research funding: Astex, Hoffman La Roche, Celgene, Novartis, MedImmune, Merck, Millennium; Honoraria: Celgene, Novartis, Pfizer; BOD/advisory committee: Celgene, Novartis, Takeda, Pfizer, Astellas; **Hao**: Astex employment; **Azab**: Astex employment; Fenaux: Research funding: Celgene, Astex, Jazz, Aprea; Honoraria: Celgene, Astex, Jazz, Aprea; Honoraria: Celgene, Astex, Jazz, Aprea.
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