Abstract # 2344

Results From a Global Randomized Phase 3 Study of Guadecitabine (G) Vs Treatment Choice (TC) in 302 Patients With Relapsed or Refractory (r/r) Acute Myeloid Leukemia After Intensive Chemotherapy (ASTRAL-2 Study)

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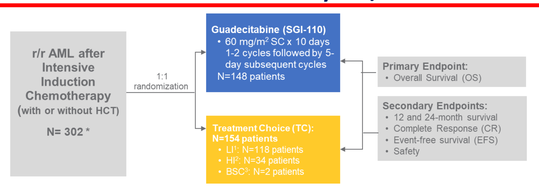
BACKGROUND

- 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-2 is a global randomized Phase 3 study of guadecitabine vs preselected Treatment Choice (TC) of Low Intensity (LI) azacitidine (AZA), decitabine (DEC), or low dose Ara-C (LDAC), High Intensity (HI) high dose Ara-C (HiDAC), MEC, FLAG± Ida combination chemotherapy, or Best Supportive Care (BSC).

METHODS

- Eligibility: Adult AML patients who were refractory to or relapsed after intensive anthracycline-based induction chemotherapy with or without prior hematopoietic cell transplant (HCT); ECOG PS 0-2; and adequate hepatic and renal function. Patients in first relapse after a response duration >12 months, and those who received prior HMAs were excluded.
- Patients randomized 1:1 to guadecitabine: 60 mg/m^2 SC dailyx10 for 1-2 cycles followed by 60 mg/m^2 SC dailyx5 for subsequent cycles; or preselected TC (LI, HI, or BSC) using their approved dose and regimen. Cycles repeated Q 28 days. LI treatment to be continued until progression or unacceptable toxicity.
- Primary endpoint: Overall Survival (OS).
- Secondary endpoints include: 12 and 24-month survival rates; complete response (CR), event-free survival (EFS), and safety.
- P-values for are nominal as there was no adjustment for interim analysis and multiple comparisons.

Figure 1. ASTRAL-2 Guadecitabine Phase 3 Study in r/r AML



LI: Low Intensity, azacitidine; decitabine; or LDAC; HI: Hi Intensity Chemotherapy: high dose Ara-C; MEC: or FLAG± Ida; BSC: Best Supportive Care

* Initial sample size was 404 patients. Independent Data and Safety Monitoring Board (DSMB) recommended to stop randomization as study was unlikely to show significantly superior OS. By that time 302 patients were randomized and followed up for final analyses.

RESULTS

Figure 2. ASTRAL-2 Results: TC Randomization Assignment

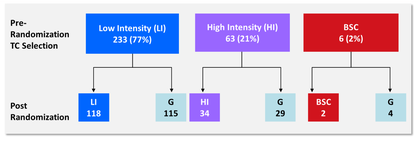


Table 1. Patient Characteristics

	Guadecitabine (N = 148)	Treatment Choice (N = 154)
Median Age (min, max) years	65 (19,84)	63 (18,84)
Sex (M/F)	58% / 42%	51% / 94%
ECOG PS 0-1	84.5%	79%
2	15.5%	21%
Cytogenetic Risk Good or Intermediate	54%	58%
Poor Risk	45%	42%
Peripheral blood blasts ≤ 30%	59%	59%
> 30%	24%	23%
Refractory AML	45%	33%
Relapsed AML	55%	67%
Prior HCT	18%	26%
Number of prior anti-leukemia therapies, (%)		
1	45.3%	43.5%
2	29.1%	29.9%
≥ 3	25.7%	26.6%

- Patient characteristics were generally well balanced between the 2 treatment arms.

RESULTS

Table 2. Treatment Exposure

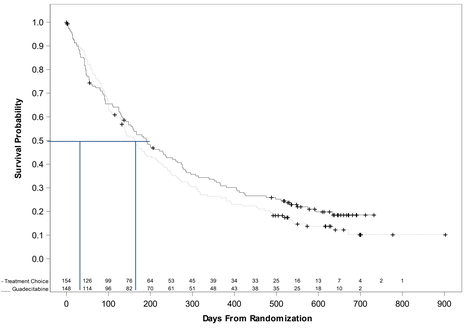
	Guadecitabine (N Treated =145)	Treatment Choice (N Treated =147)
Number of cycles per subject		
Median number of cycles	3.0	2.0
Min, Max	1, 24	1, 17

- Median number of cycles is lower than the recommended number of cycles for adequate HMA treatment.
- Median follow-up: 21.6 months.

Table 3. Reasons for Treatment Discontinuation

	Guadecitabine (N = 148)	Treatment Choice (N = 154)
Received Study Treatment	145	147
Treatment Discontinuation (Primary Reason)	%	%
Progressive Disease	35.2%	38.1%
Death	15.2%	18.4%
Alternative Anti-Leukemia Therapy	16.6%	23.1%
Adverse Event	14.5%	8.2%
Patient Decision to Permanently Stop Treatment	10.3%	6.1%
Other	8.3%	6.1%

Figure 3. Primary Endpoint: Overall Survival. Secondary Endpoints: 12 and 24-month Survival Rates



Guadecitabine:
mOS: 6.4 months
12-month survival: 32%
24-month survival: 19%

Treatment Choice:
mOS: 5.4 months
12-month survival: 26%
24-month survival: 10%

HR: 0.88 (95% CI 0.67,1.14)

Primary Analysis: Logrank *p = 0.3*

Figure 5. Survival Prospective Subgroups: Multiple Subgroups Show Significant Benefit for Guadecitabine (OS 95% CI Hazard Ratios Upper Limit ≤1)

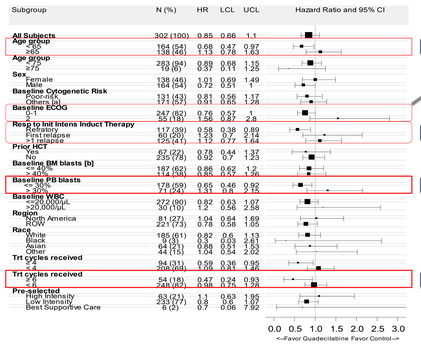


Table 4. Secondary Endpoints: Complete Response (CR); CR+CRh; Overall CR Rates all Favor Guadecitabine

	Guadecitabine (N = 148)	Treatment Choice (N = 154)	P-Value
	%	%	
Best Response			
CR	12.8%	7.1%	0.051
CR + CRh	16.9%	7.8% (p 0.007)	0.007
Overall Composite CR (CR + Cri)	27%	14.3% (p 0.003)	0.003

P-values: Cochran Mantel-Haenszel Test

CR: Complete Response, CRh: Complete Response with partial hematologic recovery, CRi: Complete Response with incomplete hematologic recovery

Safety

Table 5. Safety Summary Independent of Relationship to Study Treatment

	Guadecitabine (N = 145)	Treatment Choice (N = 147)
Subjects with any AE	96.6%	97.3%
Subjects with any AE Grade ≥3	89%	84.4%
Most Common Grade ≥3 AEs		
Febrile Neutropenia	38.6%	38.1%
Neutropenia	32.4%	17%*
Thrombocytopenia	28.3%	29.9%
Anemia	21.4%	24.5%
Pneumonia	18.6%	20.4%
Sepsis	11.7%	10.9%

*All differences are non-significant except neutropenia P-value 0.003

CONCLUSIONS

- Global Phase 3 study in relapsed/refractory AML comparing guadecitabine to preselected Treatment Choice. Low Intensity treatment with other HMAs and LDAC was the dominant preselected TC in 77% of patients.
- Primary OS analysis not significant (log rank P-value 0.3).
- Multiple prospective subgroups showed nominal significant survival benefit for guadecitabine arm (Age <65 years; PS 0-1; lower PB blasts burden ≤30%, refractory AML).
- Patients receiving adequate number of cycles (≥ 4 and 6 cycles) regardless of treatment assignment did significantly better on guadecitabine (similar to ASTRAL-1 study results[1] in treatment naïve AML not eligible for intensive chemotherapy).
- Secondary efficacy endpoints favored guadecitabine (EFS; CR+CRh; overall composite CR).
- Safety profile consistent with the expected safety profile of treatment in the study population with no clinically significant differences between treatment arms.

REFERENCES

1. Fenaux, et al. (2019). S879. HemaSphere. 3. 394-395. 10.1097/01.HS9.0000561796.30124.a4.

Conflict-of-interest statement:
Roboz has research funding from Janssen; consultancy and/or honoraria with AbbVie, Actinium, Agios, Amgen, Astex Pharmaceuticals, Inc., Astellas, AstraZeneca, bayer, Blueprint Medicines, BMS, Celgene, Daiichi Sankyo, Glaxo SmithKline, Helsinn, Janssen, Jasper Therapeutics, Jazz, MEI Pharma, Mesoblast, Novartis, Otsuka, Pfizer, & Roche/Genentech; **Sanz** research funding from Celgene-BMS, Hoffman-La Roche, Janssen-Cilag & Novartis; consultancy/ad board: AbbVie, Amgen, Astellas, Böehringer-Ingelheim, Celgene/BMS, Helsinn Healthcare, Hoffmann – La Roche, Janssen – Cilag, Novartis, Onconova, and Takeda; speaker bureau from Celgene/BMS, Hoffmann - La Roche, Novartis, and Takeda ; **Griffiths** has research funding from Astex Pharmaceuticals, Inc., Genentech, Celgene/BMS, Apellis, & Alexion; consultancy and/or honoraria from Astex Pharmaceuticals, Inc., Taiho Oncology, Celgene/BMS, Novartis, Alexion, Takeda Oncology, Abbvie, & Boston Biomedical; **Yee** has research funding from Astex Pharmaceuticals, Inc., F. Hoffmann La Roche, Genentech, Geron, Janssen, Jazz, Medimmune, Novartis, Onconova, & Tolero; consultancy and/or honoraria from Novartis & AbbVie; membership on a BOD or advisory committee from Astex Pharmaceuticals, Inc., F. Hoffmann La Roche, Novartis, BMS, Otsuka, Paladin, Pfizer, Shattuck Labs, Taiho, & Takeda; **Kantarjian** has research funding from Abbvie, Amgen, Ascentage, BMS, Daiichi-Sankyo, Immunogen, Jazz, Novartis, & Pfizer; honoraria with AbbVie, Amgen, Novartis, Pfizer, Aptitude Health, Astellas, AstraZeneca, Ipsen, KAHR medical, NOVA Research, Precision Biosciences, Taiho Pharmaceutical Canada; **Recher** has research funding from Jazz, MaatPharma, Astellas, BMS/Celgene, Daiichi Sankyo, Novartis, Amgen, Agios, AbbVie; consultancy and/or honoraria with Incyte, Janssen, Jazz, Pfizer, Macrogenics, Astellas, BMS/Celgene, Daiichi Sankyo, Novartis, Takeda, Amgen, Agios, AbbVie; **Byrne** has research funding from Karyopharm; **Patkowska** has honoraria or consultancy with Astellas Pharma, Inc, KCR US, Inc., Angelini Pharma, Novartis, Servier, Amgen; Other: travel, accommodations & expenses with Astellas Pharma, Inc, Bristol-Myers Squibb, Jazz Pharmaceuticals, Angelini Pharma, Novartis, Servier, Pfizer; **Kim** has research funding from BI, & H; honoraria and/or consultancy with AbbVie, AIMS Bioscience, Amgen, AML-Hub, Astellas, BMS & Celgene, Boryung Pharm Co, Daiichi Sankyo, Janssen, Handok, LG Chem, Novartis, Pfizer, Pintherapeutics, Sanofi Genzyme, Si VaxiGen, VigenCell; membership on entity's BOD or advisory committee from AbbVie, AML-Hub, Astellas, BMS & Celgene, Daiichi Sankyo, Janssen, Novartis, Pintherapeutics; speakers bureau with Sanofi Genzyme; **Stock** research funding from Pfizer; honoraria and/or consultancy with Pfizer, Amgen, Agios, Jazz, Kura, Kite, Morphosys, Servier, Syndax, Pluristem; **Illes** has research funding from Takeda & Seattle Genetics; honoraria and/or consultancy with Janssen, Celgene, Novartis, Pfizer, Takeda, Roche; other: travel, accommodations & expenses with Novartis, Janssen, Pfizer, Roche; **Fenaux** has research funding from Abbvie, Takeda, Janssen, Jazz, Celgene/BMS, Novartis; honoraria and/or consultancy with Abbvie, Takeda, Janssen, Jazz, Celgene/BMS, Novartis, Taiyo Pharmaceuticals; **Miyazaki** has research funding from Sumitomo-Dainippon; honoraria or consultancy with Novartis, Nippon-Shinyaku, Pfizer, Bristol-Myers Squibb, Janssen, Daiichi-Sankyo, AbbVie, Takeda, Kyowa-Kirin, Chugai, Astellas, Eisai, Sumitomo-Dainippon, Sanofi; **Yamauchi** has research funding from Daiichi Sankyo, Astellas, AbbVie, Pfizer, Otsuka, Solasia Pharma; honoraria or consultancy with Chugai, Pfizer, Ono-Pharmaceutical; **Hao & Keer** are current employees of Astex Pharmaceuticals, Inc.; **Azab** has membership on BOD or advisory committee with Astex Pharmaceuticals, Inc.; **Dohner** has research funding from Celgene, Bristol-Myers Squibb, AbbVie, Agios, Amgen, Astellas, Jazz, Novartis, Pfizer; honoraria or consultancy with Celgene, Bristol Myers Squibb, Berlin-Chemie, AbbVie, AstraZeneca, Agios, Astex Pharmaceuticals, Inc., Amgen, Astellas, GEMoaB, Gilead, Helsinn, Janssen, Jazz, Novartis, Oxford Biomedica, Roche; **Thomas, Moors, & O'Connell** have no conflicts to disclose.

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Poster presented at: ASH Annual Meeting, Atlanta, GA Dec. 11 – 13, 2021

Poster can be downloaded from www.astx.com 21US-ASTX_PB(139)