Abstract # 4235

Progression free survival (PFS) and Event Free Survival (EFS) 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

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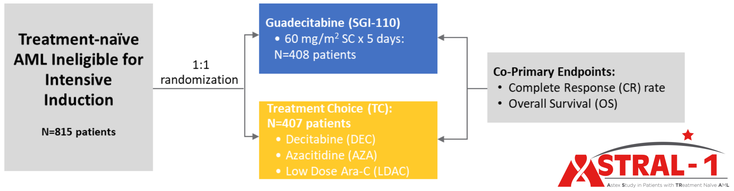
BACKGROUND

- 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)
- AML disease progression criteria are not defined in the IWG 2003 (Cheson et al, 2003). ELN 2017 disease progression criteria (Dohner et al, 2017) are complex and may be difficult to implement in practice to assess PFS
- There is no consensus on the definition of events to be used for EFS
- Treatment with HMAs may continue to provide survival benefit with stable disease or in the absence of objective response (Silverman et al, 2011)
- Here we present results of PFS and EFS analyses using simple criteria from ASTRAL-1 and how they compare with the ITT OS analysis

METHODS

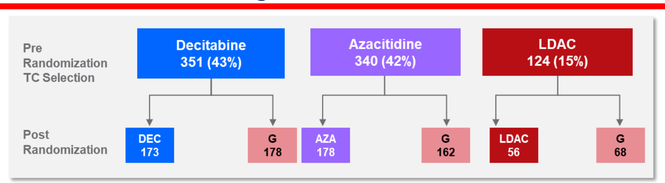
Figure 1. ASTRAL-1: Phase 3 Study Design



- 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/m^2 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. PFS was a secondary endpoint
- PFS: defined as from date of randomization to disease progression or death defined as the earliest occurrence of relapse in a responding patient; clinically significant increase in blasts % that necessitate alternative therapy; investigator determined progression, or death.
- EFS: defined as from date of randomization to the earliest occurrence of treatment discontinuation, start of alternative therapy, or death. This simple definition avoids assigning a progression date, and is inclusive of patients who may continue treatment due to clinical benefit in the absence of response or overt clinical progression that necessitate alternative therapy

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)

RESULTS

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
- No imbalance in early treatment discontinuation between the 2 arms

Table 2. Table 2: OS; PFS; EFS results for ITT; and subgroups receiving at least 4 or 6 cycles

	ITT Population N= 815		Patients who had ≥ 4 cycles N= 476		Patients who had ≥6 cycles N= 375	
Overall Survival (OS)	**G**	**TC**	**G**	**TC**	**G**	**TC**
Median (months)	7.1	8.5	15.6	13.0	19.5	15
HR (95% CI), p value	0.97 (0.83-1.14), ***p 0.73***		0.78 (0.64-0.96), ***p 0.02***		0.69 (0.54-0.88), ***p 0.002***	
Progression Free Survival (PFS)						
Median (months)	5.3	5.5	10.3	8.7	11.9	10.5
HR (95% CI), p value	0.99 (0.86-1.15), ***p 0.93***		0.88 (0.73-1.06), ***p 0.17***		0.86 (0. 70-1.07), ***p 0.17***	
Event Free Survival (EFS)						
Median (months)	5.1	5.3	12.1	8.9	14.9	11.1
HR (95% CI), p value	0.85 (0.74-0.98), ***p 0.02***		0.74 (0.61-0.9), ***p 0.002***		0.69 (0.56-0.86), ***p 0.001***	

- Number of patients balanced in each comparison: ITT (G, 408 patients; TC 407 patients); Subgroup with ≥ 4 cycles (G, 235 patients, TC 241 patients); Subgroup with ≥ 6 cycles (G, 187 patients, TC 188 patients)
- OS: no difference between G and TC for the ITT analysis. G better than TC in the subgroups receiving ≥ 4 and ≥ 6 cycle
- PFS: No significant difference between G and TC in the ITT population, or the subgroups
- EFS: G was superior to TC in the ITT population; and the subgroups receiving ≥ 4 and ≥ 6 cycles

Figure 3. EFS in the Primary ITT Population (N=815)

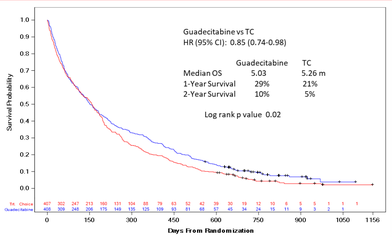
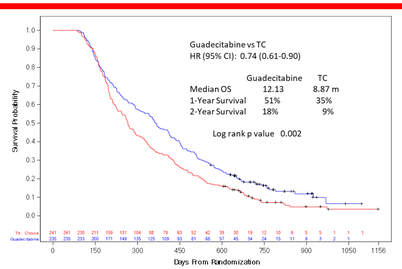


Figure 4. EFS in subgroup who received at least 4 cycles (N=476)



RESULTS

Figure 5. EFS in subgroup who received at last 6 cycles (N=375)

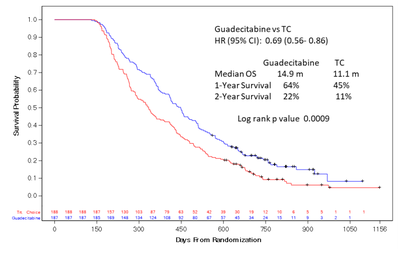
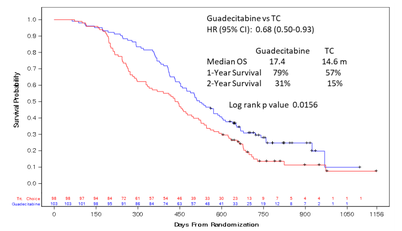


Figure 6. EFS in responders (CRc or PR): N= 201 patients



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 (balanced between the 2 arms) did not receive the minimum of 4 to 6 cycles recommended to achieve maximum benefit with HMAs. G was superior to TC in OS in subgroups who received at least 4 or 6 cycles
- EFS defined as from date of randomization to the earliest of treatment discontinuation, start of alternative therapy, or death is simple and provide a more definite event date (cessation of HMA treatment or start of alternative therapy) as opposed to defining a progression date
- Using EFS as defined, G treatment was associated with superior OS benefit over TC in the ITT population, as well as in the subgroups of patients who received at least 4 or 6 cycles, and the subgroup of patients who responded to treatment
- The data suggest that continuation of HMA treatment with guadecitabine is associated with survival benefit

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