Abstract # 3846

Landmark Response and Survival Analyses from 206 AML Patients Treated with Guadecitabine in a Phase 2 Study Demonstrate the Importance of Adequate Treatment Duration to Maximize Response and Survival Benefit. Survival Benefit Not Restricted to Patients with Objective Response

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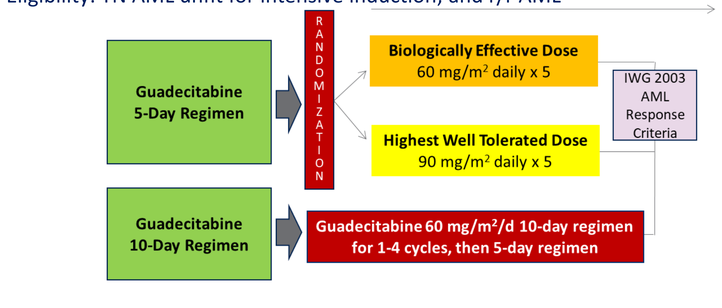
BACKGROUND

- 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
- In a Phase 2 Study of in AML both Treatment Naïve (TN), and relapsed/refractory (r/r), we treated 206 patients with guadecitabine using different doses and schedules
- Primary results in TN AML and r/r AML were previously published (Kantarjian et al, 2017; and Roboz et al, 2018)
- International guidelines recommend treatment with HMAs for at least 4 or 6 cycles to gain maximal response, however some suggest that if patients do not respond after 3 cycles, they are unlikely to respond.
- HMAs have shown the potential of improved survival with continued treatment of patients with stable disease even in the absence of objective response (Silverman et al, 2011)
- Here we present the landmark survival analyses in patients who were still alive at 3 and 5 months from start of treatment respectively (the scheduled start time of Cycle 4 and 6) to see the survival effect of continued vs discontinued treatment
- To see if the survival effect of continued treatment is only driven by responders, we repeated the landmark survival analyses in patients with no response (no CR, CRp, or CRi)

METHODS

Figure 1. Study Design in AML



- Primary Endpoint: Overall CR rate (CR + CRp + CRi)
- Secondary Endpoints: Safety, response duration, overall survival

RESULTS

Table 1. Data Set for Landmark Analyses and Treatment Exposure of Guadecitabine Phase 2

Data Set For Landmark Analyses	TN AML : N= 103	r/r AML: N=103	Total AML: N = 206
Alive at 3 Months[1]	76 (74%)	85 (83%)	161 (78%)
Discontinued (< 4 cycles)[3]	17 (22%)	47 (55%)	64 (40%)
Continued (≥ 4 cycles)[3]	59 (78%)	38 (45%)	97 (60%)
Alive at 5 Months[2]	66 (64%)	67 (65%)	133 (65%)
Discontinued (< 6 cycles)[4]	26 (39%)	56 (84%)	82 (62%)
Continued (≥ 6 cycles)[4]	40 (61%)	11 (16%)	51 (38%)

[1] Data Set for Landmark analysis at 4 Cycles
[2] Data Set for Landmark analysis at 6 cycles
[3] % calculated from the dataset alive at 3 Months
[4] % calculated for dataset alive at 5 Months

- From 206 AML patients treated with guadecitabine, 78% and 65% were alive at 3 and 5 months respectively
- Of those alive at 3 and 5 months, 40% and 62% received < 4 and < 6 cycles respectively

RESULTS

Table 2. Baseline Characteristics of Patients in Landmark Analyses

	Alive at 3 Months (N=161)		Alive at 5 Months (N=133)	
	< 4 Cycles (N=64)	≥ 4 Cycles (N=97)	< 6 Cycles (N=82)	≥ 6 Cycles (N=51)
Age Median (range) y	67 (22-92)	76 (33-85)	67 (22-85)	77 (49-85)
Sex M/F %	59%/41%	55%/45%	56%/44%	53%/47%
ECOG PS 0-1/2-3 %	80%/20%	77%/23%	83%/17%	75%/25%
BM Blasts % Median (range)	38% (4-94)	39% (7-95)	33% (4-95)	40% (9-90)
WBCs ≥ 20,000/µL	9%	8%	4%	14%
Poor risk cytogenetics	38%	36%	33%	37%
Secondary AML	25%	30%	24%	31%

In Patients Alive at 3 and 5 Months there were no major difference in baseline characteristics between those who discontinued treatment (< 4 cycles) and those who continued treatment (≥ 4 cycles) other than patients who continued treatment tended to be older (median age 76-77y) compared with those who discontinued treatment (median age 67 y)

Table 3. Primary Reasons for Treatment Discontinuation in Landmark Analysis Data Set

	Alive at 3 Months N=161	Alive at 5 Months N=133
Treatment Discontinuation	< 4 cycles N=64	< 6 cycle N=82
Primary Reasons for Treatment Discontinuation[1]		
Progressive Disease	48%	48%
Patient or Investigator Decision	16%	16%
Death	3%	6%
Adverse Events	5%	2%
Other	27%	28%

[1] % calculated for those who had discontinued treatment but alive at 3 and 5 Months respectively
About half discontinued treatment due to disease progression but a large number also discontinued due to patients or investigator decision or other reasons

Table 4. Response (CR, CRp, or CRi) in the Landmark Analysis Data Set

	Alive at 3 Months N=161		Alive at 5 Months N=133	
	< 4 cycles N= 64	≥ 4 cycles N= 97	< 6 cycles N= 82	≥ 6 cycles N= 51
CRc (CR, CRp, CRi) N (%)	16 (25%)	60 (62%)	29 (35%)	42 (82%)
P Value	***<0.0001***		***< 0.0001***	

In the Landmark Analysis Data Set, continued guadecitabine treatment for at least 4 or 6 cycles was associated with a highly significant Response Rate compared to those who discontinued treatment before 4 or 6 cycles *(p <0.0001)*

Figure 2. OS in Patients by Number of Cycles in Patients Alive at 3 Months (N=161 patients)

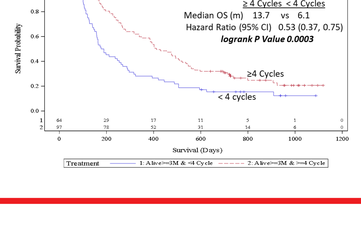


Figure 3. OS by Number of Cycles in Patients alive at 5 months (N=133)

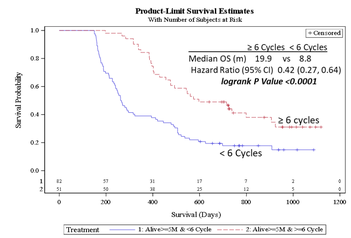


Figure 4. OS in Patients by Number of Cycles in Patients Alive at 3 Months with No Response (no CR, CRp, or CRi) N= 85

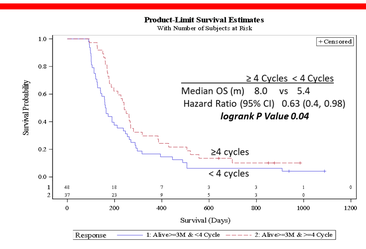
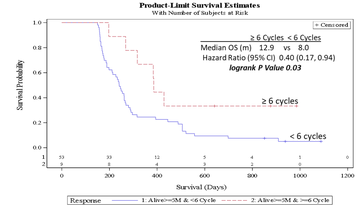


Figure 5. OS by Number of Cycles in Patients alive at 5 months with No Response (No CR, CRp, or CRi) N=62



SUMMARY/CONCLUSIONS

- In a Prospective Series of 206 AML patients treated with guadecitabine in Phase 2, 78% and 65% were alive at the landmark timepoint of 3 and 5 months from start of treatment respectively (scheduled start of 4 and 6 cycles)
- In the landmark analyses at 3 and 5 months those who continued treatment for at least 4 or 6 cycles had a highly significant higher Response rate (p<0.0001); and highly significant survival benefit (p<0.001) compared to those who discontinued treatment before 4 or 6 cycles
- Survival benefit in those who received at least 4 or 6 cycles was also seen in patients who did not have an objective response (no CR, CRp, or CRi)
- Patients treated with HMA guadecitabine and alive at 3 or 5 months should continue treatment for at least 4 to 6 cycles respectively regardless of whether or not they are in CR, CRp, or CRi as long as patient continues to benefit

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Conflict-of-interest statement: Yee: Research funding: Astex, Hoffman La Roche, Celgene, Novartis, MedImmune, Merck, Millennium; Honoraria: Celgene, Novartis, Pfizer; BOD/advisory committee: Celgene, Novartis, Takeda, Pfizer, Astellas; **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; **O'Connell**: Research Funding: Astex, Genentech; BOD/Advisory committee: BMS, Shionogi, Astex, Pfizer; **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, Abbvi; **Stock**: Honoraria: Research to Practice, UpToDate; BOD/advisory committee: Astellas, Daiichi, Pfizer, Kite, Agios; **Garcia-Manero**: Research funding: Astex; **Savona**: Savona: Consultancy: Karyopharm; Research funding: Incyte, TG Therapeutics, Sunesis; BOD/advisory committee: Abbvie, Celgene, Incyte, Karyopharm, Selvita, Takeda, TG Therapeutics; Patents & Royalties: Boehringer Ingelheim; Equity ownership: Karyopharm; **Ravandi**-Ravandi: Consultancy: Macrogenix, Xencor; Research funding: Macrogenix, Astellas, Abbvie, Amgen, Xencor, Menarini Ricerche, Selvita; Honoraria: Astellas, Abbvie, Amgen; BOD/advisory committee: Macrogenix, Astellas, Abbvie, Amgen; **Daver**: Consultancy, Research funding & honoraria: Genentech, Abbvie, Astellas, Daiichi-Sankyo, BMS, Pfizer, Servier, Immunogen; **Jabbour**: Consultancy: Takeda, BMS, Adaptive, Amgen, AbbVie, Pfizer; Research Funding: Takeda, BMS, Adaptive, Amgen, AbbVie, Pfizer, Cyclacel; **Su**: Employment: Astex; **Azab**: Employment: Astex; **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
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