Abstract # 2957

Landmark Response and Survival Analyses from 102 MDS and CMML Patients Treated with Guadecitabine in a Phase 2 Study Showing that Maximum Response and Survival is Best Achieved with Adequate Treatment Duration

Michael R. Savona[1], Hagop M. Kantarjian[2], Gail J. Roboz[3], Casey L. O'Connell[4], Katherine J. Walsh[5], Raoul Tibes[6], Karen W.L. Yee[7], Wendy Stock[8], Elizabeth A. Griffiths[9], Elias Jabbour[2], Scott D. Lunin[10], Todd L. Rosenblat[11], Nikolai A. Podoltsev[12], Jean-Pierre Issa[13], Xiang Yao Su[14], Mohammad Azab[14], Guillermo Garcia-Manero[2]

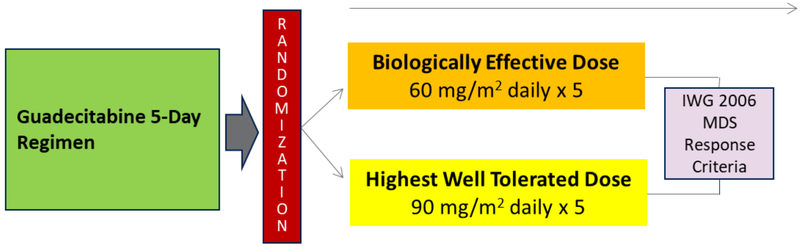
[1]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Weill Cornell/NY Presbyterian Medical Center, New York, NY; [4]USC Keck School of Medicine, University of Southern California, Los Angeles, CA; [5]The Ohio State University, Columbus, OH; [6]Mayo Clinic Arizona, Scottsdale, AZ; [7]Princess Margaret Cancer Centre, Toronto, ON, CAN; [8]University of Chicago Medical Center, Chicago, IL; [9]Roswell Park Cancer Institute, Buffalo, NY; [10]Sarah Cannon Research Institute, Florida Cancer Specialists, Venice, FL; [11]Columbia University Irving Medical Center, New York, NY, [12]Yale School of Medicine, New Haven, CT; [13]Fels Institute, Temple University, Philadelphia, PA; [14]Astex Pharmaceuticals, Inc., Pleasanton, CA

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, 102 MDS/CMML patients both Treatment Naïve (TN), and relapsed/refractory after prior HMA (r/r), were treated 102 with guadecitabine. The primary results were previously published (Garcia-Manero et al, 2019)
- International guidelines recommend treatment with HMAs for at least 4 or 6 cycles to gain maximal response, but no studies compared the effect on response rate and survival using landmark methodology
- Here we present the landmark response and 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 before 4 or 6 cycles

METHODS

Figure 1. Study Design in MDS/CMML



- Primary Endpoint: Objective Response (OR) rate (CR+PR+mCR+HI)
- Secondary Endpoints: Safety, response duration, overall survival (OS)

RESULTS

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

Data Set For Landmark Analyses	Total MDS/CMML (N = 102)
Alive at 3 Months[1]	91 (89%)
Discontinued (< 4 cycles)[3]	26 (29%)
Continued (≥ 4 cycles)[3]	65 (71%)
Alive at 5 Months[2]	87 (85%)
Discontinued (< 6 cycles)[4]	43 (49%)
Continued (≥ 6 cycles)[4]	44 (51%)

[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 from dataset alive at 5 Months

- Of 102 MDS/CMML patients treated with guadecitabine, 89% and 85% were alive at 3 and 5 months respectively
- Of those alive at 3 and 5 months, 29% and 49% received < 4 and < 6 cycles respectively

RESULTS

Table 2. Baseline Characteristics of Patients in Landmark Analyses

	Alive at 3 Months (N=91)		Alive at 5 Months (N=87)	
	< 4 Cycles (N=26)	≥ 4 Cycles (N=65)	< 6 Cycles (N=43)	≥ 6 Cycles (N=44)
Age Median (range) y	74 (18-85)	71 (52-86)	67 (18-83)	72 (52-82)
Sex M/F %	58%/42%	71%/29%	58%/42%	75%/25%
ECOG PS 0-1/2-3 %	73%/27%	91%/9%	88%/12%	89%/11%
BM Blasts > 5%	50%	49%	51%	43%
RBCs Transfusion Dependence	62%	51%	56%	48%
MDS IPSS Int 2/ High Risk %	46%	49%	49%	45%
CMML	23%	23%	23%	23%

There were no major differences in baseline disease characteristics between patients who received < 4 or 6 cycles and those who received ≥ 4 or ≥ 6 cycles except that the latter tended to have more males

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

	Alive at 3 Months N=91	Alive at 5 Months N=87
Treatment Discontinuation	< 4 cycles N=26	< 6 cycle N=43
Primary Reasons for Treatment Discontinuation N (%)[1]		
Patient or Investigator Decision	13 (50%)	17 (39%)
Progressive Disease	4 (15%)	11 (26%)
Adverse Events	1 (4%)	2 (5%)
Death	0	0
Other	8 (31%)	13 (30%)

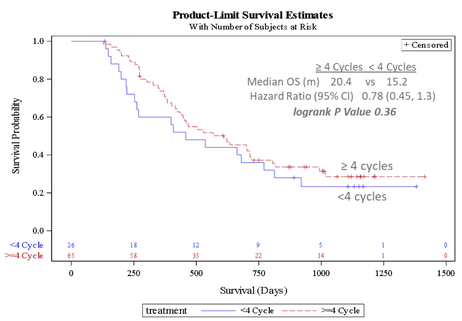
[1] % calculated for those who had discontinued treatment but alive at 3 and 5 Months respectively
About half of patients alive at 3 months discontinued treatment before 4 cycles because of patient or investigator decision which was the primary cause of discontinuation in patients alive at 3 and 5 months

Table 4. Objective Response (OR): CR+PR+mCR+HI in the Landmark Analysis Data Set

	Alive at 3 Months N=91		Alive at 5 Months N=87	
	< 4 cycles N= 26	≥ 4 cycles N= 65	< 6 cycles N= 43	≥ 6 cycles N=44
OR (CR+PR+mCR+HI) N (%)	4 (15%)	44 (68%)	11 (26%)	36 (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 Objective 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=91 patients)



RESULTS

Figure 3. OS by Number of Cycles in Patients alive at 5 months (N=87)

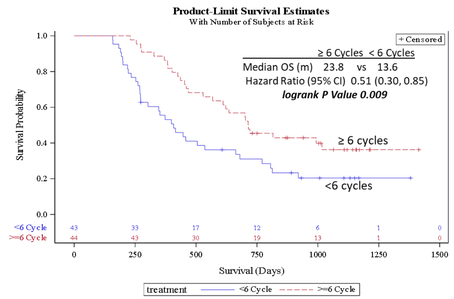
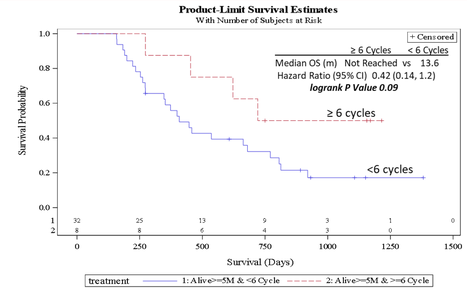


Figure 4. OS by Number of Cycles in Patients alive at 5 months with No Objective Response (N=40)



SUMMARY/CONCLUSIONS

- In a Prospective Series of 102 MDS/CMML patients treated with guadecitabine in Phase 2, 89% and 85% were alive at the landmark timepoint of 3 and 5 months 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)
- In the landmark analysis at 5 months, patients who continued treatment for at least 6 cycles gained a highly significant survival benefit compared to those who discontinued treatment before 6 cycles (p 0.009)
- Survival benefit in those who received at least 6 cycles was also seen in patients who did not have an objective response (p 0.09)
- 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 have an objective response as long as patient continues to benefit

REFERENCES

1. Garcia-Manero G, Roboz G, Walsh K, et al. Lancet Hematology 2019, 6 (6): PE317-E327

Conflict-of-interest statement:
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; **Kantarjian:** 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; **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; **Yee:** Research funding: Astex, Hoffman La Roche, Celgene, Novartis, MedImmune, Merck, Millennium; Honoraria: Celgene, Novartis, Pfizer; BOD/advisory committee: Celgene, Novartis, Takeda, Pfizer, Astellas; **Stock:** Honoraria: Research to Practice, UpToDate; BOD/advisory committee: Astellas, Daiichi, Pfizer, Kite, Agios; **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; **Jabbour:** Consultancy: Takeda, BMS, Adaptive, Amgen, AbbVie, Pfizer; Research Funding: Takeda, BMS, Adaptive, Amgen, AbbVie, Pfizer, Cyclacel; **Podolstev:** Consultancy: Alexion, Pfizer, Agios, Blueprint Medicines, Incyte, Novartis; Research funding: Kartos, Boehringer Ingelheim, Astellas, Daiichi Sankyo, Sunesis, Jazz, Pfizer, Astex, CTI Biopharma, Celgene, Genetech, Al Therapeutics, Samus, Arog; Honoraria: Alexion, Pfizer, Agios, Blueprint Medicines, Incyte, Novartis; BOD/advisory committee: Alexion, Pfizer, Agios, Blueprint Medicines, Incyte, Novartis; Grant funding: Celgene; **Su:** Employment: Astex; **Azab:** Employment: Astex; **Garcia-Manero:** Research funding: Astex.
There are no relationships to disclose for: **Walsh, Tibes, Lunin, Rosenblat,** and **Issa**

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