Blood 2021

Abstract # 182

Clinical Efficacy and Safety of Oral Decitabine/Cedazuridine in 133 Patients with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML)

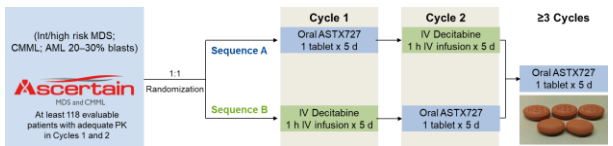
Michael R. Savona[1], James K. McCloskey[2], Elizabeth A. Griffiths[3], Karen W.L. Yee[4], Aref Al-Kali[5], Amer M. Zeidan[6], H. Joachim Deeg[7], Prapti A. Patel[8], Mitchell Sabloff[9], Mary-Margaret Keating[10], Kim-Hien Dao[11, 26], Nancy Zhu[12], Nashat Gabrail[13], Salman Fazal[14], Joseph Maly[15], Olatoyosi Odenike[16], Hagop M. Kantarjian[17], Amy E. DeZern[18], Casey L. O'Connell[19], Gail J. Roboz[20], Lambert Busque[21], Richard A. Wells[22], Harshad Amin[23], Jasleen K. Randhawa[24], Brian Leber[25], Yong Hao[26], Harold N. Keer[26], Mohammad Azab[26] and Guillermo Garcia-Manero[17]

[1]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN; [2]John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ; [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [4]Princess Margaret Cancer Centre, Toronto, Canada; [5]Mayo Clinic, Rochester, MN; [6]Yale University and Yale Cancer Center, New Haven, CT; [7]Fred Hutchinson Cancer Research Center, Seattle, WA; [8]University of Texas Southwestern Medical Center, Dallas, TX; [9]Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada; [10]Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; [11]Oregon Health & Science University, Portland, OR; [12]University of Alberta, Edmonton, AB, Canada; [13]Gabrail Cancer Center Research, Canton, OH; [14]West Penn Hospital, Allegheny Health Network, Pittsburgh, PA; [15]Norton Cancer Institute, Louisville, KY; [16]University of Chicago, Chicago, IL; [17]The University of Texas MD Anderson Cancer Center, Houston, TX; [18]Johns Hopkins University Hospital, Baltimore, MD; [19]USC Keck School of Medicine, University of Southern California, Los Angeles, CA; [20]Division of Hematology and Oncology, Weill Cornell Medicine and The New York-Presbyterian Hospital, New York, NY; [21]Research Center, Maisonneuve-Rosemont Hospital, Montreal, QC, Canada; [22]Sunnybrook Health Sciences Centre, Toronto, Canada; [23]Boca Raton Clinical Research, Boca Raton, FL; [24]Houston Methodist Cancer Center, Houston; [25]McMaster University, Hamilton, ON, Canada; [26]Astex Pharmaceuticals, Inc., Pleasanton, CA

INTRODUCTION

- Cedazuridine is a novel, potent, and safe inhibitor of cytidine deaminase
- When given in combination with decitabine, cedazuridine enables efficient oral availability

BACKGROUND/STUDY DESIGN[1]



Major entry criteria
- Candidates for IV decitabine
- ECOG PS 0 – 1
- Life expectancy of ≥3 months
- Adequate organ function
- One prior cycle of HMA is allowed

Primary endpoint
- Total 5-day decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

Secondary endpoints
- Efficacy: Response rate; transfusion independence; duration of response; Leukemia-free and overall survival
- Safety of ASTX727
- Maximum LINE-1 demethylation

RESULTS

Patient Characteristics/Demographics

Characteristics		Total Treated N=133
Median age, years (range)		71 (44–88)
Sex	Male	87 (65%)
	Female	46 (35%)
Median weight, kg (range)		83 (45 -158)
Median BSA, m^2 (range)		1.98 (1.4 - 2.9)
CMML		16 (12%)
MDS, IPSS classification	High risk	21 (16%)
	Int-1 and 2	90 (68%)
	Low risk	6 (5%)
Transfusion dependent	RBCs	53 (40%)
	Platelets	12 (9%)
ECOG PS	0	55 (41%)
	1	78 (59%)

Primary Endpoint: (5-day Decitabine AUC Equivalence) [1]

Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC N	IV DEC Geo. LSM	Oral ASTX727 N	Oral ASTX727 Geo. LSM	Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
Primary Analysis	Paired[1]	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7

[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

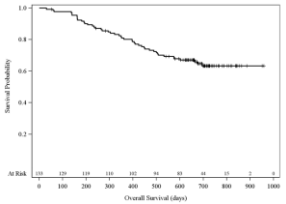
Results: Efficacy Response

Response category	Treated Patients (N=133), n (%)	95% CI
Complete response (CR)	29 (22%)	(15.1,29.8)
Partial response (PR)	0	
Marrow CR (mCR)	43 (32.3%)	
mCR with hematologic improvement	22 (16.5%)	
Hematologic improvement (HI)	10 (7.5%)	
HI-erythroid	2 (1.5%)	
HI-neutrophils	1 (0.8%)	
HI-platelet	7 (5.3%)	
RBC Transfusion Independence*	27/53 (51%)	
Platelet Transfusion Independence*	6/12 (50%)	
Overall response (CR + PR + mCR + HI)	82 (61.7)	(52.8,69.9)

*represents number becoming transfusion independent/number transfusion dependent at baseline

- Median CR duration was 14.0 months
- Median duration of best response was 12.7 months
- 34 (26%) of subjects proceeded to HCT

Results: Overall Survival



- Median follow up is 24.7 months
- mOS has not yet been reached
- Patients will continue to be followed

Safety Results: Treatment-Emergent Adverse Events in >10% of Patients*

Preferred Term	Phase 3 Total (N=133, n[%])	Phase 3 Total Grade 3 or higher
Neutropenia	69 (52%)	66 (50%)
Thrombocytopenia	71 (53%)	62 (47%)
Anaemia	54 (41%)	47 (35%)
Leukopenia	33 (25%)	29 (22%)
Febrile Neutropenia	18 (14%)	18 (14%)
Fatigue	33 (25%)	3 (2%)
Diarrhea	22 (17%)	2 (2%)
Nausea	33 (25%)	0 (0%)
Decreased Appetite	19 (14%)	0 (0%)
Constipation	18 (14%)	0 (0%)

*Events attributed to oral decitabine/cedazuridine

- Safety profile consistent with that of decitabine
- Most grade 3 or higher events related to myelosuppression

CONCLUSIONS

- Oral Decitabine/cedazuridine demonstrates:
  - PK AUC equivalence to IV decitabine
  - Similar pharmacodynamic activity
- With over 24 months median follow up, new results show:
  - Median Overall Survival has not been reached
  - CR rate is 22% and ORR is 62%
  - 26% of subjects have been able to proceed to HCT
  - No new noteworthy safety signals have emerged
- Oral decitabine and cedazuridine (35 mg/100 mg tablets) is the only HMA with equivalent exposure to its injectable form

Reference: 1. Garcia-Manero, et al, [ASH Abstract 846] Blood. 2019;134 (suppl 1).

This research was originally published in *Blood*. Savona, etal. *Blood (2020) 136 (Supplement 1): 37–38.*.

Poster presented at: Blood Australia Virtual Annual Meeting, Sept. 20 – 23, 2021

Available for download at www.astx.com

21US-ASTX_PB(126)