Abstract MDS-634

Efficacy and Safety of Oral Decitabine/Cedazuridine (ASTX727) in the CMML Subpopulation from Phase 2 and ASCERTAIN Phase 3 Studies

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

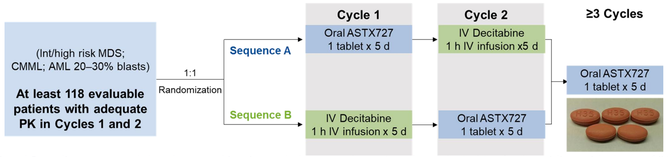
[1]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN; [2]John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ; [3]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [4]Princess Margaret Cancer Centre, Toronto, Canada; [5]Yale University and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

INTRODUCTION

- Chronic myelomonocytic leukemia (CMML) is a hematologic malignancy characterized by persistent monocytosis, and dysplastic and/or proliferative features, as well as the risk of transformation to acute myeloid leukemia (AML; ~15% over 3–5 years).[1,2]
- The only potential cure is allogeneic hematopoietic stem-cell transplantation (HSCT), for which many patients are not eligible due to age (median 73 years at diagnosis), comorbidities, or the absence of a match.[3]
- The DNA methyltransferase inhibitors (DNMTis) parenteral azacitidine, parenteral decitabine, and oral decitabine/cedazuridine are the only agents approved by the U.S. Food & Drug Administration (FDA) for the treatment of CMML, and azacitidine is approved for advanced CMML in Europe.
- ASTX727, an orally available fixed dose (FDC) combination of 35 mg decitabine (DEC) and 100 mg cedazuridine (CED), a cytidine deaminase inhibitor, produces comparable pharmacokinetic (PK) AUC exposure to intravenous (IV) decitabine.[3]
- Here, we present outcome data from subjects with CMML enrolled in the Phase 2 and 3 studies that led to the approval of oral decitabine/cedazuridine. The present analysis reports the combined clinical experience for the subset of patients with CMML in the prospective, randomized, phase 2 and 3 trials of oral decitabine/cedazuridine

STUDY DESIGN

Figure 1. Study Design



- The phase 2 and 3 studies compared the pharmacokinetics and pharmacodynamics of oral decitabine/cedazuridine with those of IV decitabine. In both studies, eligible patients were adults (aged ≥18 years) who were candidates to receive IV decitabine (i.e., all French-American-British subtypes of previously treated or untreated myelodysplastic syndromes (MDS), or CMML that scored intermediate-1 or -2, or high-risk on the International Prognostic Scoring System (IPSS), with ECOG performance status 0 or 1 (0-2 for phase 2). Only 1 prior treatment cycle with decitabine or azacitidine was permitted.
- Patients in both studies were randomized 1:1 to one of 2 sequences for the first two 28-day treatment cycles: either oral decitabine/cedazuridine daily for 5 days in cycle 1, followed by IV decitabine daily for 5 days in cycle 2 (sequence A), or the reverse order (sequence B). All patients received oral decitabine/cedazuridine from cycle 3 forward. Treatment continued until disease progression, unacceptable toxicity, study withdrawal, or other reasons. Treatment could be delayed or dose reduced if necessary for hematologic or non-hematologic recovery, as standard with parenteral DNMTi.

Table 1. Baseline Characteristics

Baseline Characteristics	MD-CMML N=25	MP-CMML N=8	Total N=33
Age			
Mean (SD)	70.6 (9.57)	73.4 (8.02)	71.2 (9.18)
Median (Range)	72.0 (44, 82)	69.5 (66, 86)	71.0 (44, 86)
Male Sex, n (%)	18 (72)	8 (100)	26 (78.8)
Race, n (%)			
White	21 (84)	8 (100)	29 (88)
Black	2 (8)	0	2 (6)
Asian	1 (4)	0	1 (3)
Not Reported	1 (4)	0	1 (3)
Median Weight, kg (range)	87.0 (62.3, 123.7)	88.5 (73.1, 100.2)	87 (62.3, 123.7)
Mean BSA, m² (SD)	2.04 (0.20)	2.11 (0.12)	2.05 (0.19)
ECOG Performance Status			
0	9 (36)	4 (50)	13 (39)
1	16 (64)	2 (25)	18 (55)
2	0	2 (25)	2 (6)
Cytogenetic Risk Classification, n (%)			
Poor	2 (8.0)	1 (13)	3 (9)
Intermediate	4 (16.0)	3 (38)	7 (21)
Better	17 (68)	2 (25)	19 (58)
Missing	2 (8)	2 (25)	4 (12)
Prior Anticancer Therapy, n (%)			
Yes	4 (16)	1 (13)	5 (15)
No	21 (84)	7 (88)	28 (85)
Prior DNMTi, n (%)			
Azacitidine	1 (4)	0	1 (3)
Decitabine	0	0	0
RBC Transfusion Dependent, n (%)	8 (32)	3 (38)	11 (33)
Platelet Transfusion Dependent, n (%)	1 (4)	1 (13)	2 (6)

Baseline Characteristics	MD-CMML N=25	MP-CMML N=8	Total N=33
BM blasts (%), n[a]	25	7	32
Median (range)	7 (2, 19)	5 (1, 10)	7 (1, 19)
>5% BM blasts	14 (56)	3 (43)	17 (53)
Baseline PB blasts (%), n[a]	23	8	31
Median (range)	0 (0, 6)	1 (0, 8)	1 (0, 8)
CMML classification			
CMML-1	17 (68)	6 (75)	23 (70)
CMML-2	8 (32)	2 (25)	10 (30)
Median hemoglobin, g/L (range)	6.3 (4.6, 9.3)	6.0 (4.2, 8.6)	6.2 (4.2, 9.3)
<80, n (%)	2 (8)	3 (38)	5 (15)
80-<100, n (%)	10 (40)	1 (13)	11 (33)
100-<110, n (%)	6 (24)	2 (25)	8 (24)
≥110, n (%)	7 (28)	2 (25)	9 (27)
Median neutrophils, 10^9/L (range)	1.42 (0.16, 8.71)	12.09 (4.95, 43.81)	2.49 (0.16, 43.81)
<0.5, n (%)	5 (20)	0	5 (15)
0.5-<1, n (%)	4 (16)	0	4 (12)
1 -1.5, n (%)	4 (16)	0	4 (12)
>1.5, n (%)	12 (48)	8 (100)	20 (61)
Median platelets, 10^9/L (range)	66 (18, 523)	41 (16, 156)	66 (16, 523)
<25, n (%)	3 (12)	2 (25)	5 (15)
25-<50, n (%)	4 (16)	3 (38)	7 (21)
50-<75, n (%)	6 (24)	2 (25)	8 (24)
75-<100, n (%)	1 (4)	0	1 (3)
≥100, n (%)	11 (44)	1 (13)	12 (36

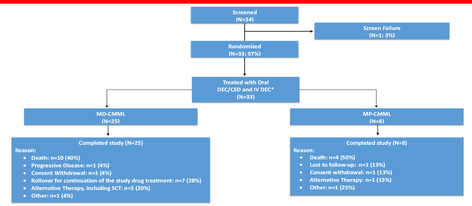
[a]Patients for whom data were available.

BM – bone marrow; BSA – body surface area; MD – myelodysplastic; MP – myeloproliferative; PB – peripheral blood; RBC – red blood cell.

Dysplastic type (MD-CMML) defined by WBC < 13x109/L; proliferative type (MP-CMML) defined by WBC ≥ 13x109/L

STUDY DESIGN cont.

Figure 2. Patient Randomization and Disposition

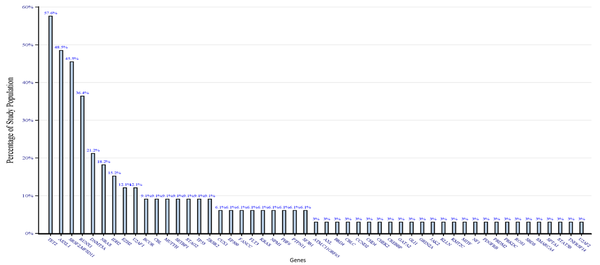


RESULTS

- Overall response rate was 76% (CR + PR + marrow CR + HI; Table 2), with 21% of patients attaining CR.
- Median times to first response (12 patients, all with MD-CMML, for whom data were available) and best response (20 patients with MD-CMML and 5 with MP-CMML) for the full cohort were 1.8 months (range 0–4) and 2.3 months (range 1–7), respectively.
- Almost two-thirds of patients (64%) who were RBC-transfusion dependent at baseline, including all of those with MP-CMML, attained transfusion independence for ≥8 weeks. Nearly half of patients (46%) who were RBC-transfusion dependent at baseline, including all of those with MP-CMML, attained transfusion independence for ≥8 and ≥12 weeks.
- Two patients (6%) were platelet-transfusion dependent at baseline; 1 attained transfusion independence for ≥8 and ≥12 weeks. Three patients (9%) underwent HSCT, all of whom had MD-CMML.
- Median overall and Transformation-Free survival were 35.7 and 28.3 months, respectively (figure 5 & 6)
- All patients had ≥1 treatment-emergent adverse event. Most patients (94% [n=31]) had ≥1 adverse event of grade ≥3 higher severity (Table 3). The most common adverse events (overall and grade ≥3) were related to myelosuppression (neutropenia, thrombocytopenia, and anemia).

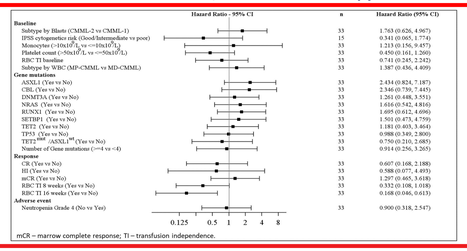
CR – complete response; HI – hematologic improvement; HSCT - hematopoietic stem-cell transplantation; PR – partial response.

Figure 3. Mutational landscape



Frequency of detected gene mutations in subjects (VAF >2%). CMML-1, for cases with 2 to 4 percent blasts in the blood and/or 5 to 9 percent blasts in the bone marrow CMML-2, for cases with 5 to 19 percent blasts in the blood and 10 to 19 percent blasts in the bone marrow

Figure 4. Effect on Overall Survival After Oral Decitabine/Cedazuridine Therapy



mCR – marrow complete response; TI – transfusion independence.

RESULTS

Table 2. Analysis of Best Response

Response Category N (% [95%CI])	MD-CMML (N=25)	MP-CMML (N=8)	Total (N=33)
Complete response (CR)	5 (20 [6.8, 40.7])	2 (25 [3.2, 65.1])	7 (21 [9.0, 38.9])
Partial response (PR)	0	0	0
Marrow CR (mCR)	12 (48 [27.8, 68.7])	2 (25 [3.2, 65.1])	14 (42 [25.5, 60.8])
mCR with hematologic improvement	4 (16 [4.5, 36.1])	1 (13 [0.3, 52.7])	5 (15 [5.1, 31.9])
Hematologic improvement (HI)	3 (12 [2.5, 31.2])	1 (13 [0.3, 52.7])	4 (12 [3.4, 28.2])
HI-erythroid	1 (4 [0.1, 20.4])	1 (13 [0.3, 52.7])	2 (6 [0.7, 20.2])
HI-neutrophil	1 (4 [0.1, 20.4])	0	1 (3 [0.1, 15.8])
HI-platelet	1 (4 [0.1, 20.4])	1 (13 [0.3, 52.7])	2 (6 [0.7, 20.2])
Total responders[a] (CR + PR + mCR + HI)	20 (80 [59.3, 93.2])	5 (63 [24.5, 91.5])	25 (76 [57.7, 88.9])
Progressive disease	3 (12 [2.5, 31.2])	0	3 (9 [1.9, 24.3])
No response[b]	1 (4 [0.1, 20.4])	3 (37 [8., 75.5])	4 (12 [3.4, 28.2])
Not evaluable	1 (4 [0.1, 20.4])	0	1 (3[0.1, 15.8])

[a]Total of all response categories; [b]includes stable disease.

Subjects are counted only once by their best response, according to the following hierarchy: CR, PR, mCR, HI, stable disease, progressive disease, and non-evaluable. Within HI, subjects may be counted in more than one lineage, according to the HI observed. The category 'mCR with HI' is a subset of subjects with mCR who also achieved HI.

Figure 5. Transformation-Free Survival for the CMML Subpopulation

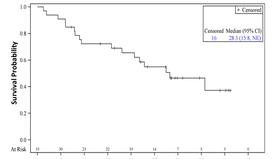


Figure 6. Overall Survival for the CMML Subpopulation

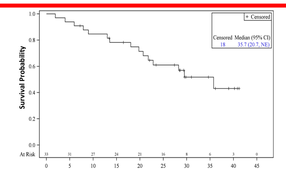


Table 3. Most Common Treatment-Emergent Adverse Events (TEAE)[a]

Preferred Term	MD-CMML (N=25), n (%)	MP-CMML (N=8), N (%)	Total (N=33), n (%)
≥1 TEAE Regardless of Relation to Treatment[b]	25 (100)	8 (100)	33 (100)
Neutropenia	17 (68)	5 (63)	22 (67)
Thrombocytopenia	17 (68)	5 (63)	22 (67)
Anemia	14 (56)	1 (13)	15 (46)
Constipation	11 (44)	3 (38)	14 (42)
Fatigue	10 (40)	3 (38)	13 (39)
Leukopenia	8 (32)	2 (25)	10 (30)
Arthralgia	9 (36)	0	9 (27)
Cough	7 (28)	2 (25)	9 (27)
Decreased appetite	8 (32)	1 (13)	9 (27)
Diarrhea	8 (32)	1 (12)	9 (27)
Febrile Neutropenia	8 (32)	1 (13)	9 (27)
Nausea	7 (28)	2 (25)	9 (27)
Dyspnea	7 (28)	1 (13)	8 (24)
Contusion	0	7 (21)	
Headache	7 (28)	0	7 (21)

Preferred Term	MD-CMML (N=25), N (%)	MP-CMML (N=8), N (%)	Total (N=33), N (%)
≥1 Grade ≥3 TEAE Regardless of Relation to Treatment[c]	23 (92)	8 (100)	31 (94)
Neutropenia	15 (60)	5 (63)	20 (61)
Thrombocytopenia	13 (52)	5 (63)	18 (55)
Anemia	11 (44)	1 (13)	12 (36)
Febrile Neutropenia	8 (32)	1 (13)	9 (27)
Leukopenia	6 (24)	2 (25)	8 (24)
Cellulitis	2 (8)	0	2 (6)
Dyspnea	2 (8)	0	2 (6)
Fatigue	2 (8)	0	2 (6)
Pneumonia	1 (4)	1 (13)	2 (6)
Sepsis	1 (4)	1 (13)	2 (6)

[a]Treatment-emergent adverse events (TEAEs) were coded using Medical Dictionary for Regulatory Activities Version 22.0 and are listed in descending order of incidence in the treated population.
[b]≥20% of treated population.
[c]≥5% of treated population.

CONCLUSIONS

The safety profile of oral decitabine/cedazuridine in the present analysis was consistent with other studies of IV decitabine.[4,5,6] Anemia, neutropenia, and thrombocytopenia occurred in 36%, 61%, and 55% of patients, respectively.

The overall response rate (76%) and median overall survival (35.7 months) reported in the present study come from prospective data and compare favorably with findings from earlier series.

A strength of this analysis is that data were derived from two prospective, randomized trials, including a phase 3 study.

Study limitations include the small number of patients, response assessment by the 2006 International Working Group in MDS, and pooling of data from two independent prospective trials, albeit with similar design and entry criteria.

The survival impact of oral decitabine/cedazuridine treatment in subjects with the 8 mutations recommended by NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) (e.g. ASXL1 and CBL)[7] appeared to be less favorable, but the difference was not markedly pronounced, and the number of cases insufficient to meet statistical significance.

This analysis supports the labeled indication of oral decitabine/cedazuridine in CMML patients based on the subset of patients with CMML in the phase 2 and 3 registration trials. Oral decitabine/cedazuridine appears to be an effective and well-tolerated treatment for patients with CMML.

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CONTACT INFORMATION

For more information on this study email: clinicaltrials@astx.com

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