Abstract # 3682

Efficacy of Oral Decitabine/Cedazuridine (ASTX727) in the CMML Subpopulation From ASCERTAIN Phase 3 Study

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INTRODUCTION

Chronic myelomonocytic leukemia (CMML)[1]:

- Is a clonal hematopoietic stem cell disorder characterized by presence of persistent monocytosis together with dysplastic and myeloproliferative changes in the bone marrow
- Hematopoietic Stem Cell Transplantation (HCT) is potentially the only curative option for patients with CMML, but most patients are not eligible
- Hypomethylating agents (HMAs) were approved for CMML under the umbrella of MDS trials, however CMML patients typically represent about 10% of these studies
- Treatment with parenteral HMAs over 5-7 days monthly has been SOC

BACKGROUND

- Oral Decitabine and Cedazuridine (ASTX727)
  - Orally available fixed-dose (FDC) combination of 35 mg decitabine and the cytidine deaminase (CDA) inhibitor cedazuridine (100 mg) that produces equivalent PK AUC exposure compared to IV decitabine[2]

  - The Phase 2 study of oral decitabine/cedazuridine included 17 subjects with CMML and produced an overall response rate (ORR) [CR + PR + mCR + HI] of 76.5%, including 29.4% complete responses

STUDY DESIGN

Figure 2. Study Design

- ASCERTAIN, a phase 3 study leading to the approval of oral decitabine/cedazuridine, enrolled subjects who were candidates for parenteral decitabine, which included 16 subjects with CMML

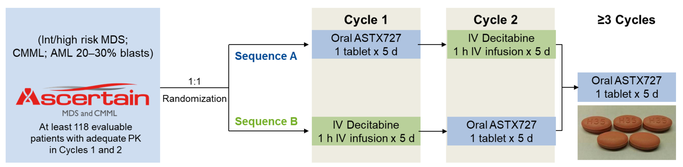


Table 1. Patient Characteristics & Demographics

Characteristics		Total Treated N=16
Median age, years (range)		72 (44–82)
Sex: Male/Female		11 (69%)/5 (31%)
Median weight, kg (range)/Median BSA, m^2 (range)		87 (65-124)/2.0 (1.7 - 2.4)
CMML-0/ CMML-1/CMML-2		5 (31%)/7 (44%)/4 (25%)
ECOG 0/1		4 (25%)/12 (75%)
Prior anticancer therapy		4 (25%)
Prior azacitidine/decitabine		1 (6.3%)/0 (0%)
Transfusion Dependent (RBC/platelets)		6 (38%)/0 (0%)
Baseline Hematology parameters:		Median (range)
Hemoglobin	g/L	89.5 (73.5-111.5)
Neutrophils	10^9/L	1.27 (0.31-7.47)
Platelets	10^9/L	84 (25-344)
Bone Marrow Blasts	%	5 (2-18)

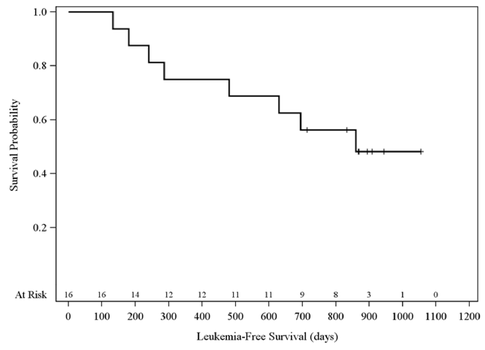
RESULTS

Table 2. Efficacy Response

- 50% of those transfusion dependent at baseline became transfusion independent
- Median duration of CR and mCR were 6.8 months and 21 months, respectively
- Median duration of best response was 13.1 months
- 3 (19%) of subjects proceeded to HCT ranging from 159-362 days on study

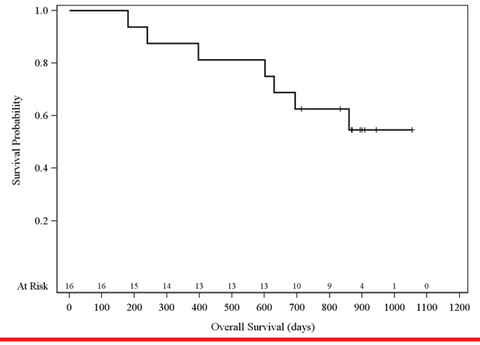
Response category	Treated Patients (N=16), n (%)	95% CI
Complete response (CR)	2 (13%)	(1.6,38.3)
Partial response (PR)	0	
Marrow CR (mCR)	8 (50%)	(24.7, 75.3)
mCR with hematologic improvement	3 (18.8%)	(4.0, 45.6)
Hematologic improvement (HI)	2 (12.5%)	(1.6, 38.3)
HI-erythroid	1 (1.5%)	(0.2, 30.2)
HI-neutrophils	1 (1.5%)	(0.2, 30.2)
HI-platelet	0	0
Overall response (CR + PR + mCR + HI)	12 (75%)	(47.6, 92.7)
Time to first response: months (range)	1.9 months (7-126 days)	
Time to Best Response: months (Range)	2.6 months (28-168 days)	

Figure 3. Leukemia-Free Survival for the CMML Subpopulation



Median follow up is 31.7 months and Leukemia-Free survival is estimated at 28.9 months (95% CI: 9.5 months, not estimable)

Figure 4. Overall Survival for the CMMML Subpopulation



Median follow up is 31.7 months and mOS has not yet been reached

SAFETY RESULTS

Table 3. Grade ≥ 3 Treatment-Emergent Adverse Events in >10% of Patients

- Safety profile consistent with that of decitabine
- Most grade 3 or higher events related to myelosuppression
- Febrile neutropenia and pneumonia increased with duration of treatment often reflecting progressive disease

Preferred Term	Total in Cycles 1- 2 (N=16)	Total for Treatment Duration (N=16)
Neutropenia	4 (25%)	11 (68.8%)
Thrombocytopenia	4 (25%)	10 (62.5%)
Anaemia	5 (31.3%))	9 (56.3%)
Febrile Neutropenia	2 (12.5%)	5 (31.3%)
Leukopenia	2 (12.5%)	3 (18.8%)
Fatigue	1 (6.3%)	2 (12.5%)

- There were no deaths in the first 60 or 90 days in patients receiving ASTX727

CONCLUSIONS

- A subset of the MDS subjects enrolled in the ASCERTAIN study of oral decitabine and cedazuridine with CMML demonstrates:
  - Tolerability consistent to expected with HMA:
    - No early deaths
    - Safety profile similar to decitabine
  - Clinical activity similar to that seen in Phase 2:
    - Overall response rate of 75%
    - First and best responses seen within 3 months of treatment
    - Leukemia-free survival estimated at 28.9 months and with almost 32 months follow up median overall survival has not been reached
- Oral decitabine and cedazuridine (35 mg/100 mg tablets) is the only HMA with equivalent exposure to its injectable form

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REFERENCES

1. Alfonso A, et al Am.J.Hematol. 2017 Jul;92(7): 599-606
2. Garcia-Manero, et al, [ASH Abstract 846] Blood. 2019;134 (suppl 1)

Conflict-of-interest statement:
Savona has research funding from ALX Oncology Astex, Incyte, Takeda, & TG Therapeutics; consultancy with Abbvie, Astex, CTI, Geron, Karyopharm, Novartis, Ryvu, Sierra Oncology, Taiho, TG Therapeutics, & Takeda; current equity holder in publicly-traded company Karyopharm; **McCloskey** has speakers bureau from Amgen, BMS, Incyte, Jazz, & Takeda; honoraria & consulting from BMS, Jazz, Novartis, Pfizer & Takeda; equity ownership with COTA; **Griffiths** has research funding from Astex, Genentech, Celgene/BMS, Apellis, & Alexion; honoraria & consultancy from Astex, Taiho Oncology, Celgene/BMS, Novartis, Alexion, Takeda Oncology, Abbvie, & Boston Biomedical; **Yee** has research funding from Astex, F. Hoffmann La Roche, Genentech, Geron, Janssen, Jazz, Medimmune, Novartis, Onconova, & Tolero; honoraria from Novartis & AbbVie; membership on a BOD or advisory committee from Astex, F. Hoffmann La Roche, Novartis, BMS, Otsuka, Paladin, Pfizer, Shattuck Labs, Taiho, & Takeda; **Zeidan** has research funding from AbbVie, Acceleron, ADC Therapeutics, Amgen, Aprea, Astex, Boehringer Ingelheim, Cardiff Oncology, BMS, Incyte, Pfizer; consultancy from AbbVie, Acceleron, Agios, Amgen, Aprea, Astellas, Beyond Spring, Boehringer Ingelheim, Cardiff Oncology, BMS, Daiichi Sankyo, Epizyme, Genentech, Gilead, Incyte, Kura, Ionis, Loxo Oncology, Novartis, Janssen, AstraZeneca, Jasper, & Jazz; clinical trial committee for AbbVie, BioCryst, BMS, Geron, Gilead, Kura, Loxo Oncology, & Novartis; travel support from Cardiff Oncology, Novartis, & Pfizer; **Al-Kali** has research funding from Novartis & Astex; **Patel** has honoraria from PVI; membership on BOD or advisory committee with Celgene/BMS & Agios; **Sabloff** has membership on BOD or advisory committee with Celgene, Jaxx, Pfizer, Novartis, Astellas, BMS, Taiho, Takeda, Roche, & AbbVie; **Zhu** has membership on an advisory committee with Advisory committee for Bristol-Myers Squibb Canada, Takeda; **Fazal** has consultancy, honoraria & speakers bureau with Agios, Amgen, BMS, Gilead Sciences, Glaxo Smith Kline, Incyte, Janssen Oncology, Jazz, Karyopharm, Novartis, Sanofi-Genzyme, Stemline Therapeutics, Taiho, & Takeda; **Odenike** has research funding from Celgene, Incyte, AstraZeneca, Astex, NS Pharma, AbbVie, Gilead, Janssen, Oncotherapy, Agios, CTI/Baxalta, & Aprea; consultancy with AbbVie, Celgene, Impact Biomedicines, Novartis, Taiho, & Takeda; **Kantarjian** has research funding with Abbvie, Amgen, Ascentage, BMS, Daiichi-Sankyo, Immunogen, Jazz, Novartis, & Pfizer; honoraria with AbbVie, Amgen, Novartis, Pfizer, Aptitude Health, Astellas, AstraZeneca, Ipsen, KAHR medical, NOVA Research, Precision Biosciences, Taiho Pharmaceutical Canada; **DeZern** has consultancy and membership on a BOD or advisory committee with BMS, Novartis, Taiho & Takeda; **Roboz** has research funding with Janssen; consultancy with AbbVie, Actinium, Agios, Amgen, Astex, Astellas, AstraZeneca, bayer, Blueprint Medicines, BMS, Celgene, Daiichi Sankyo, Glaxo Smithkline, Helsinn, Janssen, Jasper Therapeutics, Jazz, MEI Pharma, MecoBast, Novartis, Otsuka, Pfizer, & Roche/Genentech; **Busque** has consultancy with Novartis; **Leber** has membership on BOD or advisory committee with Novartis, Pfizer, BMS, AbbVie, Amgen, Taiho, Celgene, Otsuka, Astellas, & Jazz; **Dao, Hao & Keer** are current employees of Astex Pharmaceuticals, Inc. ; **Azab** has membership on BOD or advisory committee with Astex; **Garcia-Manero** has research funding from Amphivena, Merck, H3 Biomedicine, Astex, Onconova, BMS , AbbVie, Novartis & Helsinn; Consultancy from Astex, Helsinn, & BMS; **Deeg, Keating, Gabrail, Maly, O'Connell, Wells, Amin, & Randhawa** have no conflicts to disclose.

Off-label disclosure:
This presentation contains information about the investigational use of decitabine + cedazuridine (ASTX727) in combination with venetoclax. Safety and efficacy have not been determined by any regulatory agency in this combination. Decitabine + cedazuridine is a prescription medicine approved in the United States and Canada to treat adults with myelodysplastic syndromes and chronic myelomonocytic leukemia. Venetoclax is a prescription medicine approved in the United States for multiple indications, including adults with newly diagnosed acute myeloid leukemia 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy in combination with azacitidine, decitabine, or low-dose cytarabine.

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