
EUROPEAN
HEMATOLOGY
ASSOCIATION
EHA25
VIRTUAL
25th Congress of the European Hematology Association
VIRTUAL EDITION

EUROPEAN HEMATOLOGY ASSOCIATION

EHA25 VIRTUAL

Comparative Results of Azacitidine (AZA) and Decitabine (DEC) from a Large Prospective Phase 3 Study in Treatment Naive (TN) AML Not Eligible for Intensive Chemotherapy

Amer M. Zeidan[*1], Pierre Fenaux[2], Marco Gobbi[3], Jiří Mayer[4], Gail J. Roboz[5], Jürgen Krauter[6], Tadeusz Robak[7], Hagop M. Kantarjian[8], Jan Novák[9], W.W. Jedrzejczak[10], Xavier Thomas[11], Mario Ojeda-Uribe[12], Yasushi Miyazaki[13], Yoo Hong Min[14], Su-Peng Yeh[15], Joseph Brandwein[16], Liana Gercheva[17], Judit Demeter[18], Elizabeth A. Griffiths[19], Karen W.L. Yee[20], Jean-Pierre Issa[21], Yong Hao[22], Mohammad Azab[22], Hartmut Döhner[23]

[1]Yale University and Yale Cancer Center, New Haven, United States, [2]Hôpital Saint Louis, Paris, France, [3]Ospedale Policlinico San Martino, Genova, Italy, [4]Fakultní Nemocnice, Brno, Czech Republic, [5]Weill Cornell Medical College, New York, United States, [6]Städtisches Klinikum Braunschweig, Braunschweig, Germany, [7]Wojewódzkie Wielospecjalistyczne Centrum Onkologii i Traumatologii im. M. Kopernika w Lodzi, Łódź, Poland, [8]The University of Texas MD Anderson Cancer Center, Houston, United States, [9]Fakultní Nemocnice Královské Vinohrady, Praha, Czech Republic, [10]Samodzielny Publiczny Centralny Szpital Kliniczny, Warsaw, Poland, [11]Centre Hospitalier Lyon Sud, Pierre Bénite, [12]GHR Mulhouse Sud-Alsace, Mulhouse, France, [13]Nagasaki University Hospital, Nagasaki, Japan, [14]Severance Hospital, Yonsei University Health System, Seoul, Korea, Republic Of, [15]China Medical University Hospital, Taichung, Taiwan, Republic of China, [16]University of Alberta Hospital, Edmonton, Canada, [17]Multiprofile Hospital for Active Treatment Sveta Marina EAD, Varna, Bulgaria, [18]Semmelweis Egyetem, Budapest, Hungary, [19]Roswell Park Cancer Institute, Buffalo, United States, [20]Princess Margaret Hospital, Toronto, Canada, [21]Fels Institute, Temple University, Philadelphia, [22]Astex Pharmaceuticals, Inc., Pleasanton, United States, [23]Universität Ulm, Ulm, Germany

Abstract # S142 Friday June 12, 2020 AML Therapy

Disclosures

Amer M. Zeidan, MBBS, MHS

Associate Professor of Medicine
Department of Internal Medicine
Section of Hematology
Yale University School of Medicine
Yale Cancer Center

Amer.Zeidan@yale.edu
Dr_AmerZeidan

AMZ Disclosures

Received research funding (institutional) from Trovagene, Celgene, AbbVie, Astex, Pfizer, Medimmune/AstraZeneca, Boehringer-Ingelheim, Incyte, Takeda, Novartis, Aprea, and ADC Therapeutics

Consultancy with and received honoraria from Trovagene, AbbVie, Otsuka, Pfizer, Celgene, Jazz, Incyte, Agios, Boehringer-Ingelheim, Novartis, Acceleron, Astellas, Daiichi Sankyo, Cardinal Health, Taiho, Seattle Genetics, BeyondSpring, Takeda, Ionis, Janssen, Amgen, and Epizyme

Received travel support for meetings from Pfizer, Novartis, and Trovagene

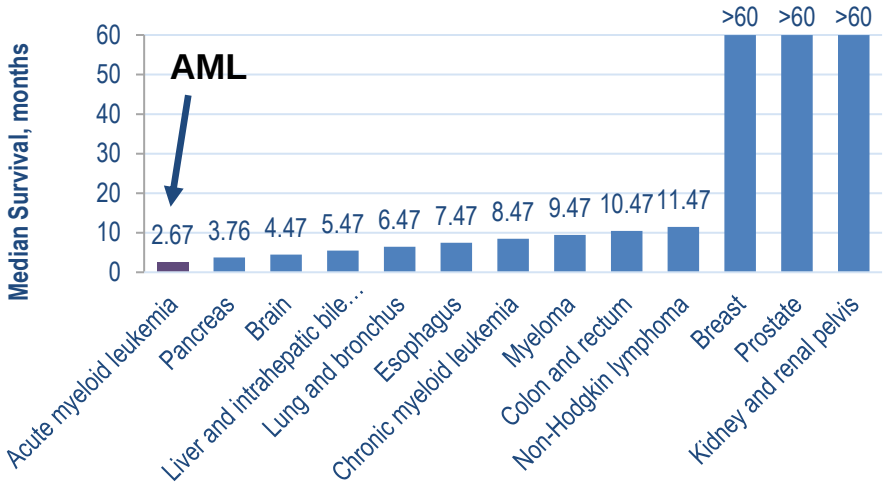
Serves on Clinical trial Steering committees for Novartis

Serves on Clinical trial Independent Review Committee for Janssen

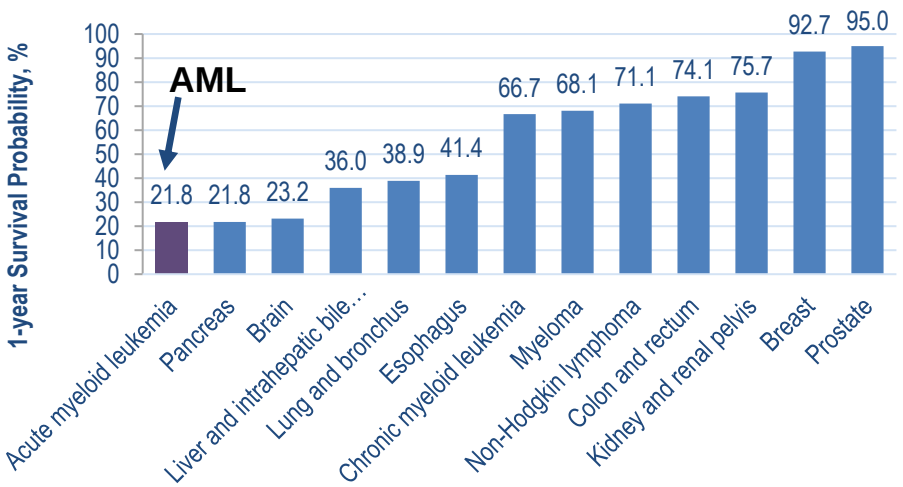
Friday June 12, 2020
AML Therapy

Older AML patients have very poor outcomes

Median survival (months) by cancer type (≥ 65 years of age)[1]



One-year survival % by cancer type (≥ 65 years of age)[1]

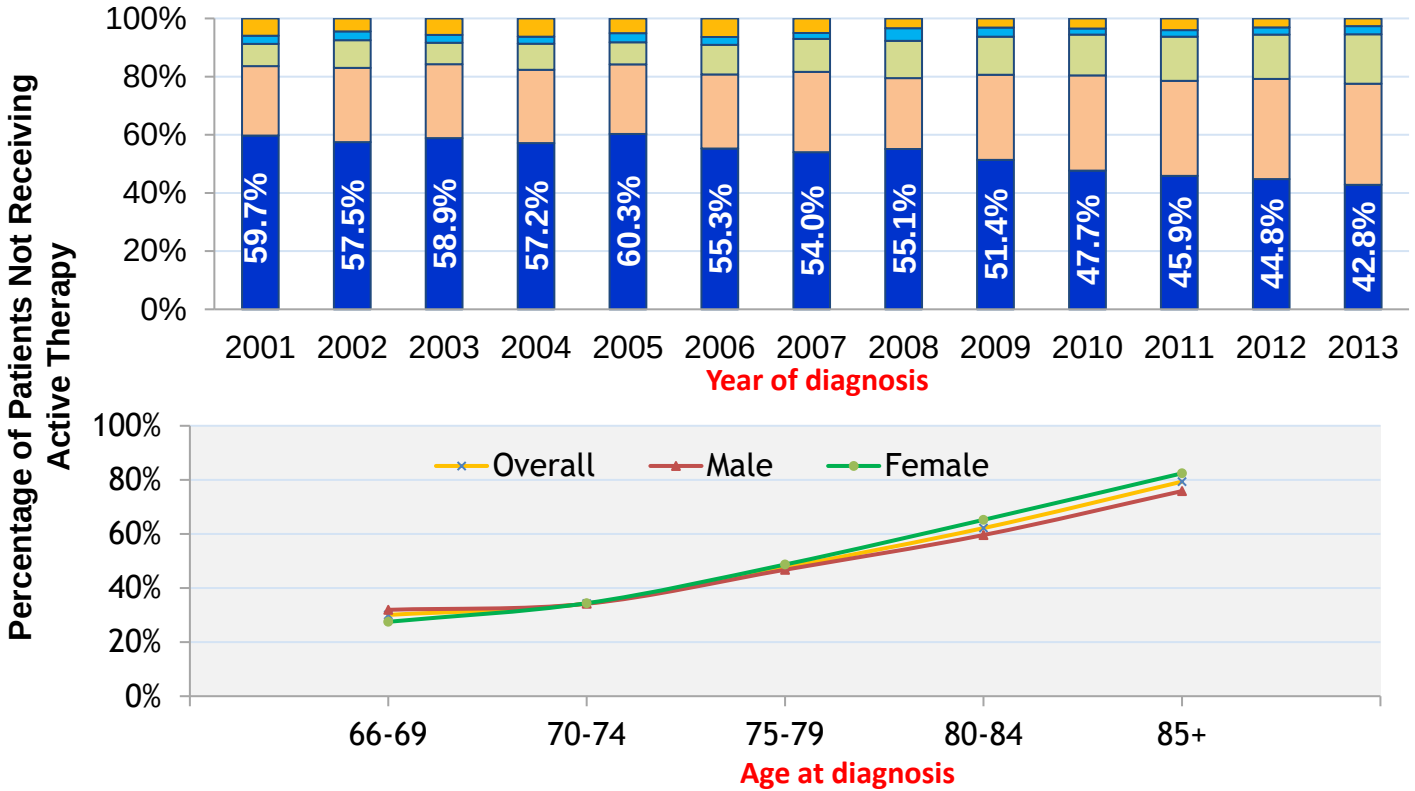


- Survival among older AML patients in USA has not substantially improved over last 4 decades
  Median OS (diagnosed 1975-1979): 2 months
  Median OS (diagnosed 2015-2016): 4 months

2000-2016 (SEER)

Shallis RM, et al. *Blood Rev*. 2020;40:100639. Epub 2019 Nov 8; Zeidan A et al. ASH 2019; Abstract 646.
1. Figures reproduced from SEER Acute Myeloid Leukemia Cancer Stat Facts. https://seer.cancer.gov/statfacts/html/amyl.html.

Many older patients with AML in the United States do not even receive active therapy

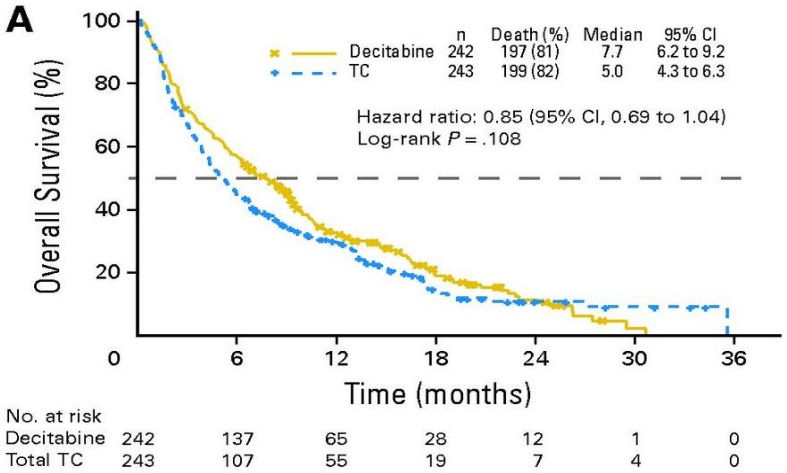


SEER-Medicare: 52% of older AML patients in USA diagnosed 2001-2013 did not receive active therapy

Zeidan A, et al. *Cancer*. 2019;125:4241-4251; Wang R, et al. *J Clin Oncol*. 2017;35:3417-3424.

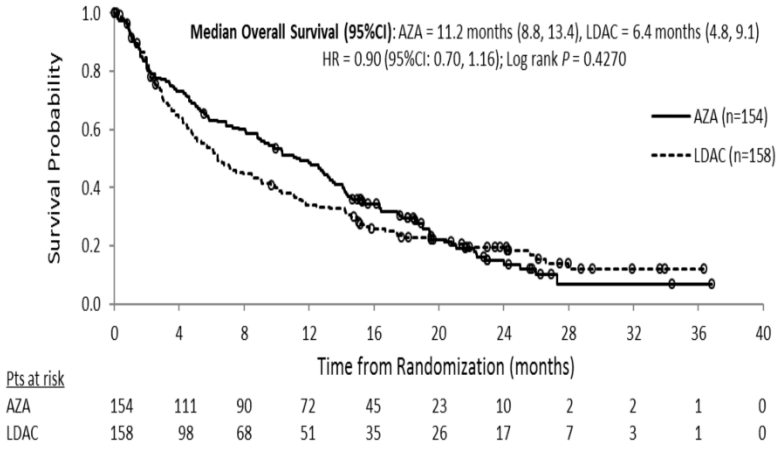
How Do HMAs Perform in First-Line Therapy of Older Unfit AML Patients?

AML-DACO-016[1]



Decitabine
CR+CRi, 28%
CR, 16%

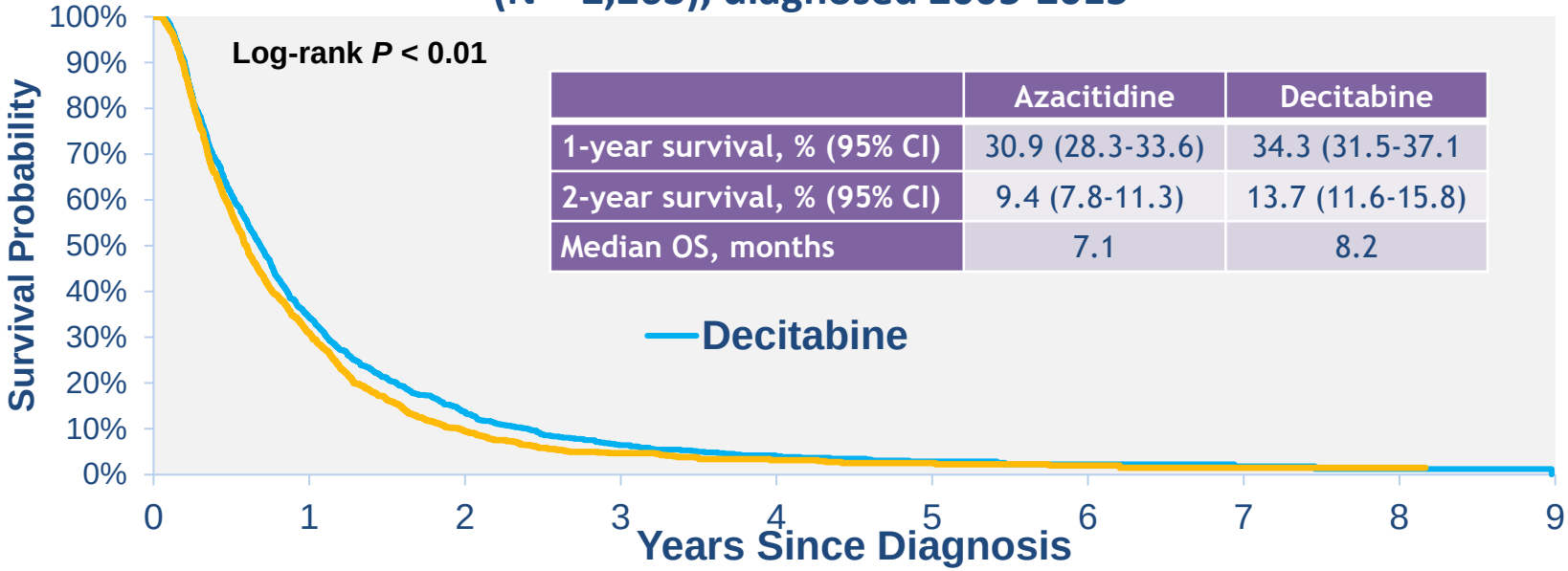
AML-AZA-001[2]



Azacitidine
CR+CRi, 28%
CR, 20%

1: Kantarjian H, et al. J Clin Oncol. 2012;30:2670-2677. 2: Dombret H, et al. Blood. 2015;126:291-299.

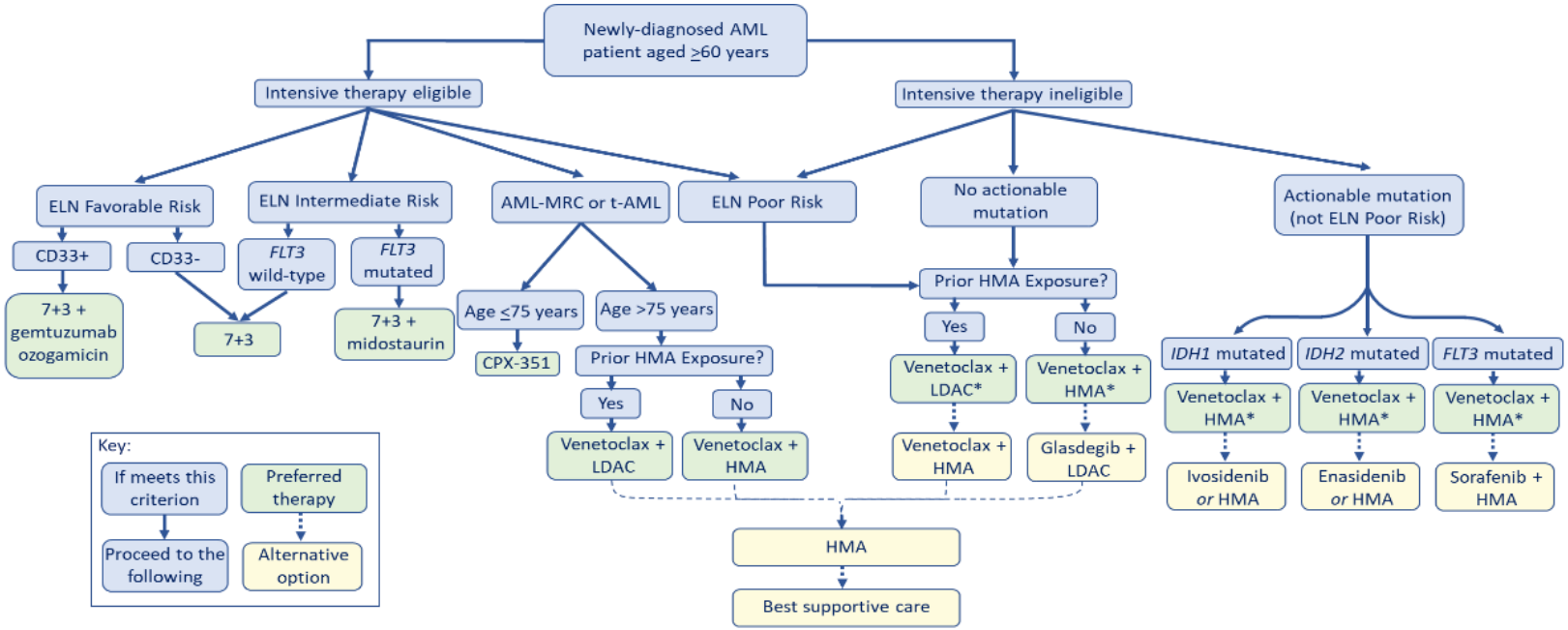
Real-life HMA performance in older AML patients in USA SEER-Medicare (N = 2,263), diagnosed 2005-2015



- With additional analyses evaluating the impact of receiving HMA on a standard dosing schedule, the difference between decitabine vs azacitidine (HR 1.14; 95% CI, 0.98-1.39; *P* = 0.08) did not reach statistical significance

Figure reproduced from Zeidan A, et al. *Blood*. 2019;134: Abstract 646 [oral presentation]. Blood Advances, in press

Treatment of patients with AML is getting more complicated: Which HMA backbone to use?



Proposed optimal approach to the treatment of the newly diagnosed acute myeloid leukemia patient aged ≥60 years 7+3, induction with anthracycline on days 1 to 3 plus cytarabine days 1 to 7.
AML-MRC, AML with myelodysplasia-related changes; LDAC, low-dose cytarabine.
*Based on a single-arm, phase 1b dose-escalation and expansion study

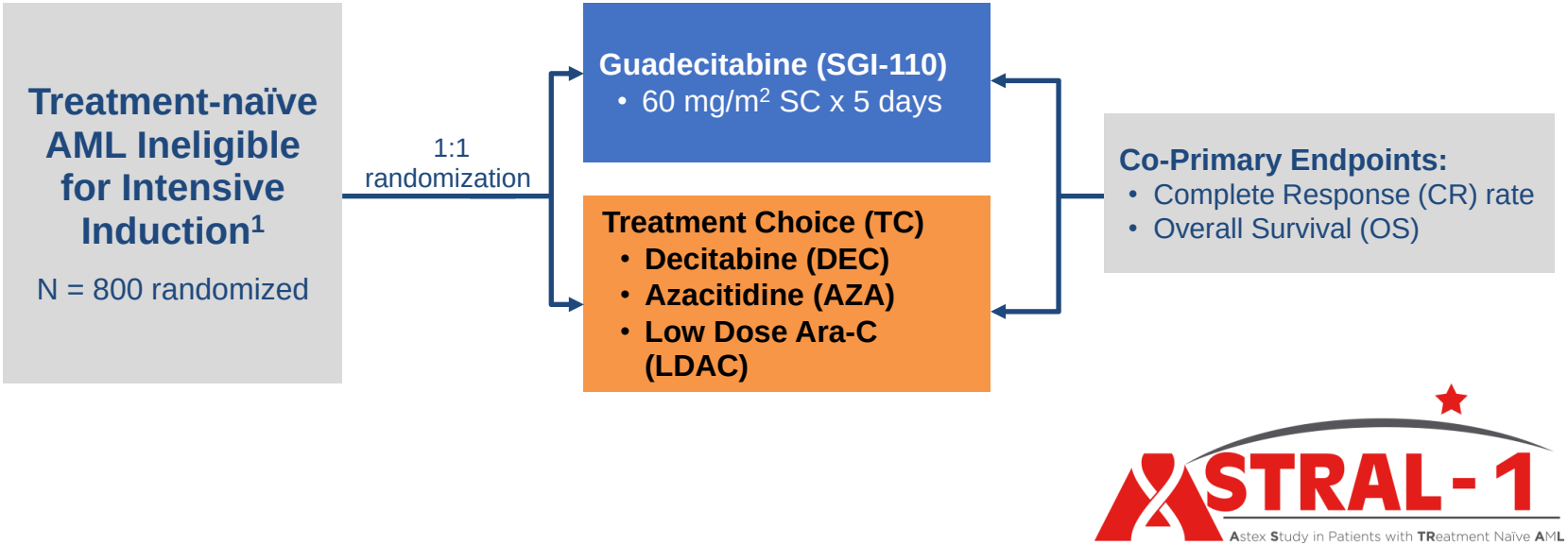
Figure reproduced from Shallis RM, et al. *Blood Rev*. 2020;40:100639. Zeidan A, et al. *Blood*. 2019;134: Abstract 646 [oral presentation].

Objectives

- Compare complete response rate, and overall survival, and safety in treatment naive (TN) older unfit patients with AML who received AZA or DEC
- We took advantage of ASTRAL-1 trial to compare outcomes of patients who were treated with AZA or DEC within the same prospective randomized trial
- ASTRAL-1 is the largest Phase 3 randomized trial in TN AML ineligible for IC (815 patients)[1] . The study compared Guadecitabine to a preselected Treatment Choice of AZA, DEC, or LDAC
- Of those, 388 patients received AZA or DEC as the Treatment Choice in the control arm.

[1] *Fenaux et al, EHA 24, Amsterdam, June 2019*

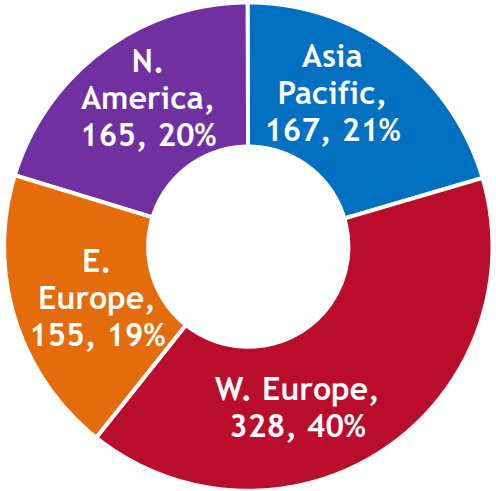
ASTRAL-1: Phase 3 Study Design



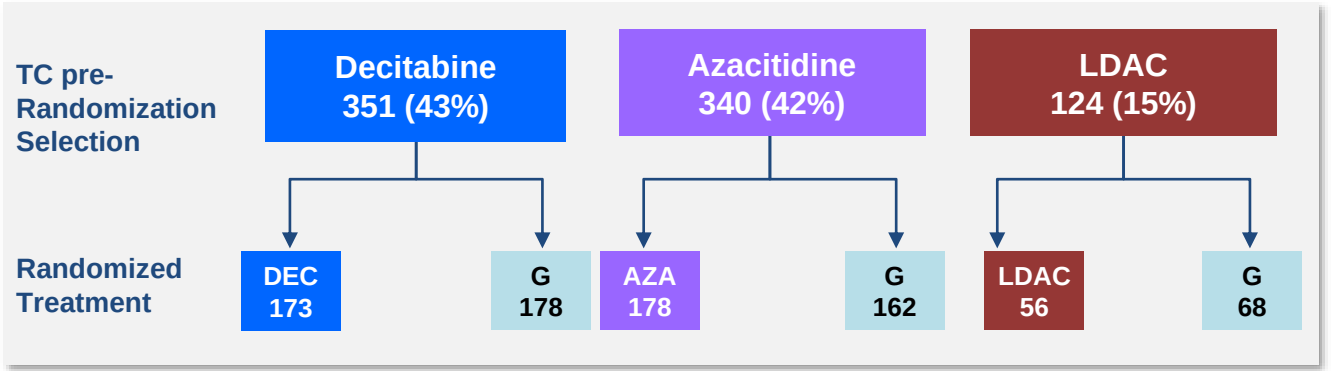
[1]Age 75 years or older; or major organ comorbidities, and poor Eastern Cooperative Oncology Group (ECOG) PS 2-3.

ASTRAL-1 Treatment Assignments - Patient Disposition

Enrollment by Region, %



Countries	Total Enrolling Sites	Total Patients Randomized	Total Patients Treated
24	144	815	793



Treated DEC 167 + AZA 171 = N = 388

G: Guadecitabine; AZA: azacitidine; DEC: decitabine; LDAC: Low Dose Ara-C

Results: Baseline Characteristics

Characteristics	Azacitidine (N=171)	Decitabine (N=167)
Median Age (range)	76 (59,94)	76 (60, 87)
% Male/Female	61% / 39%	56% / 44%
PS ECOG 0-1	53%	46%
ECOG 2-3	47%	54%
Secondary AML	38%	37%
Poor Risk Cytogenetics	38%	34%
Total WBCs ≥20,000/µL	15%	13%
BM Blasts >30%	64%	71%
TP53 mutation %	11.7%	11.4%

Baseline Characteristics well balanced between azacitidine and decitabine treated patients

Efficacy Results: Treatment Exposure - Response Rate[1]

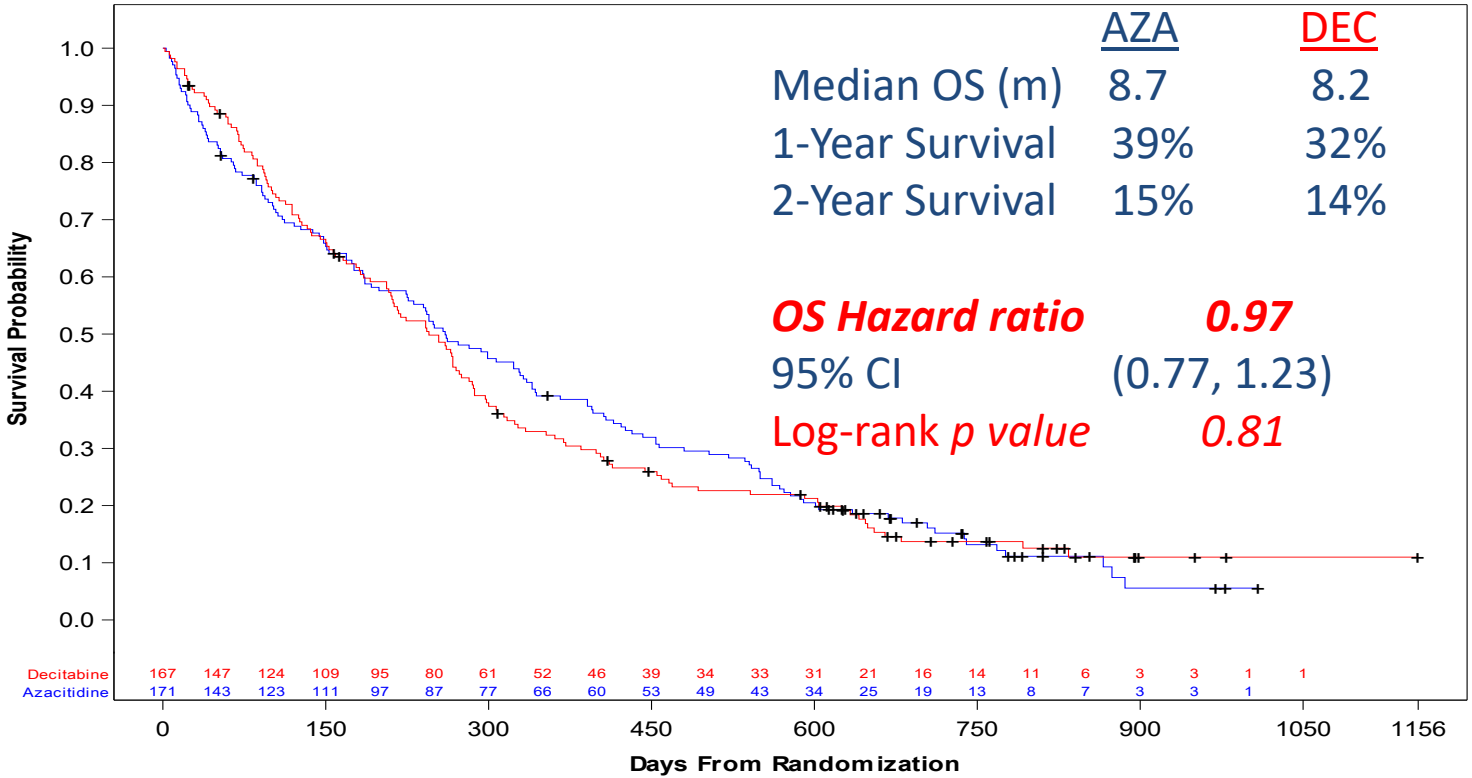
	Azacitidine (N=171)	Decitabine (N=167)	*P Value*[2]
Median #cycles (range)	6 (1, 31)	5 (1, 34)	
Complete Response (CR)	30 (17.5%)	32 (19.2%)	*0.78*
CRp	2 (1.2%)	2 (1.2%)	
CRi	6 (3.5%)	8 (4.8%)	
CRc (CR+CRp+CRi)	38 (22.2%)	42 (25.1%)	

[1] Response was assessed by central pathologist blinded to treatment assignment

[2] Co-Primary Endpoint. Fisher's Exact Test

No difference in clinical response between azacitidine and decitabine

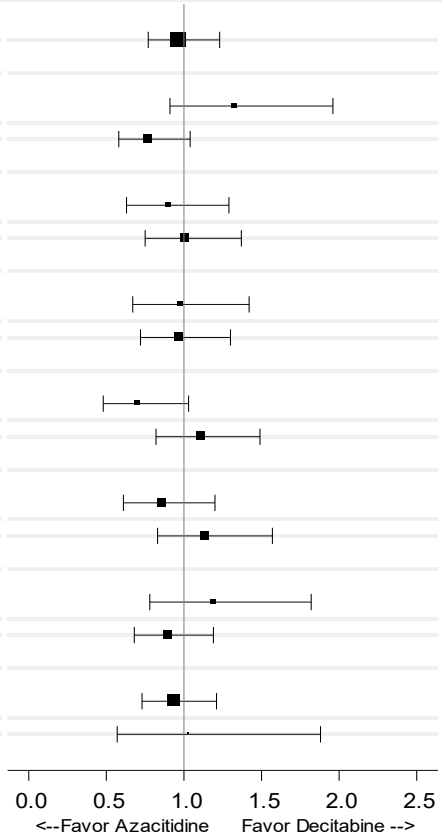
Efficacy – Overall Survival



Overall Survival Clinical Subgroups

- Survival Hazard Ratio 95% CI include one in all subgroups
- No difference between AZA and DEC in any subgroup

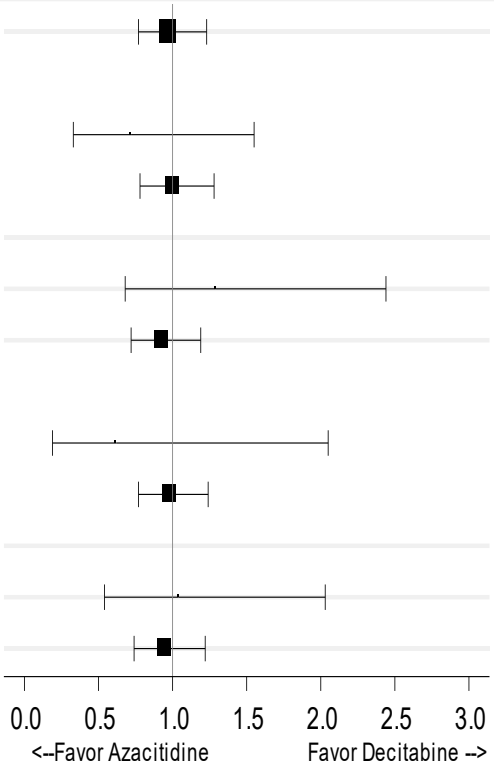
Subgroup	N (%)	HR	LCL	UCL
All Subjects (Aza + Dec)	338 (100)	0.97	0.77	1.23
Age group				
<75 years	128 (38)	1.33	0.91	1.96
≥75 years	210 (62)	0.77	0.58	1.04
Sex				
Female	139 (41)	0.9	0.63	1.29
Male	199 (59)	1.01	0.75	1.37
Secondary AML				
Yes	126 (37)	0.98	0.67	1.42
No	212 (63)	0.97	0.72	1.3
Baseline Cytogenetic Risk				
Poor-risk	121 (36)	0.7	0.48	1.03
Others [a]	217 (64)	1.11	0.82	1.49
Baseline ECOG				
0-1	167 (49)	0.86	0.61	1.2
2-3	171 (51)	1.14	0.83	1.57
Baseline BM blasts [b]				
≤ 30%	110 (33)	1.19	0.78	1.82
> 30%	228 (67)	0.9	0.68	1.19
Baseline WBC				
<20,000/µL	292 (86)	0.94	0.73	1.21
≥20,000/µL	46 (14)	1.03	0.57	1.88



Overall Survival
Major Genetic Subgroups

- Survival Hazard ratio similar in all subgroups
- No difference between AZA and DEC in any subgroup

Subgroup	N (%)	HR	LCL	UCL
All Subjects (Aza + Dec)	338 (100)	0.97	0.77	1.23
FLT3-ITD				
Yes	28 (8)	0.72	0.33	1.55
No	302 (89)	1	0.78	1.28
NPM1				
Yes	49 (14)	1.29	0.68	2.44
No	283 (84)	0.93	0.72	1.19
CEBPA				
Yes	18 (5)	0.62	0.19	2.05
No	314 (93)	0.98	0.77	1.24
TP53				
Yes	39 (12)	1.04	0.54	2.03
No	291 (86)	0.95	0.74	1.22



Results: Safety

	Azacitidine (N=171)	Decitabine (N=167)
Grade ≥3 AEs with ≥ 10% Incidence		
Febrile Neutropenia	29%	26%
Pneumonia	23%	19%
Thrombocytopenia	18%	23%
Neutropenia[1]	16%	25%
Anemia	16%	19%
Sepsis	14%	12%
Serious AE leading to death[2]	38%	26%
All-Cause 30-Day Mortality	12%	8%
All-Cause 60-Day Mortality[3]	21%	13%

Fisher's Exact Test of differences: [1] Neutropenia difference *p value 0.06*

[2] *Fatal Serious AE difference p value 0.02 ;* [3] *60-Day mortality difference p value 0.08*

Conclusions

- This is the largest comparative dataset of AZA vs. DEC treated in the same Phase 3 Trial in TN AML ineligible for IC
- Poor patient population with baseline ECOG PS 2-3 ~50% (47% in AZA and 54% in DEC patients). Baseline characteristics well balanced between the 2 HMAs.
- No difference in CR, composite CR, or Survival in the overall group and all major clinical and genetic subgroups
- No major safety differences although fatal SAEs and early 60-day mortality trended higher on AZA

Acknowledgments

All Investigators and Patients in the ASTRAL-1 study

Questions

Amer.Zeidan@yale.edu
Dr_AmerZeidan