Recent Advances in Acute Leukemia

Brian A. Jonas, MD, PhD, FACP
Associate Professor
University of California, Davis
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Learning Objectives

- Using a case-based approach:
  - Review recently approved oral hypomethylating options for MDS and AML
  - Discuss the role of MRD and transplant for older patients with AML on low intensity therapy
  - Learn about upfront treatment options for younger patients with ALL

Case 1

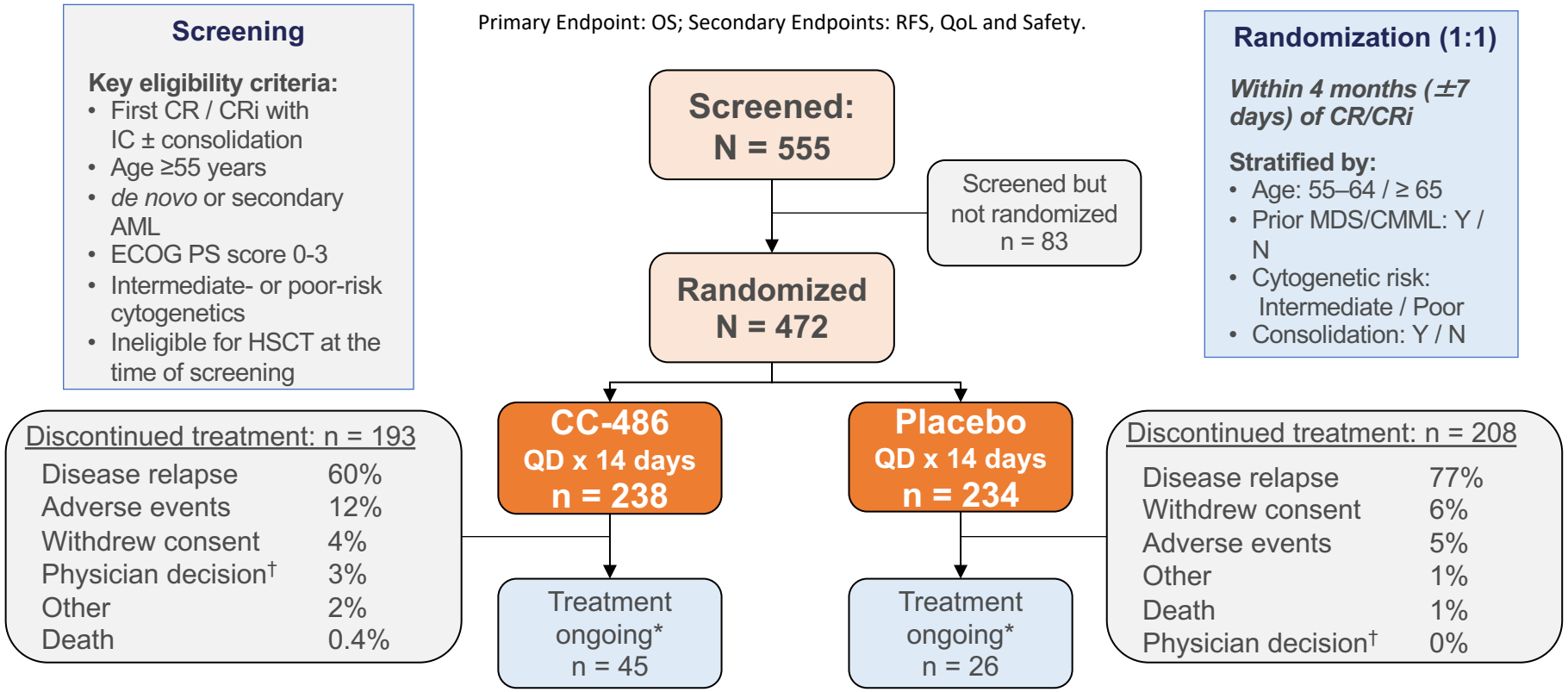
A 68-year-old man was diagnosed with AML after presenting with fatigue and SOB. BMBx showed 70% CD33 negative myeloblasts and trisomy 8 and BCOR mutation. He is medically fit for induction and transplant.

He is induced with 7+3 and achieves an MRD negative CR. He has one cycle of intermediate dose cytarabine for consolidation but tolerates it poorly and it is determined not to pursue additional chemotherapy. He is now unfit for transplant and he currently has no identified donor. He has an end of treatment BMBx that confirms MRD negative CR.

What is the next step: Surveillance or maintenance?

QUAZAR AML-001 Maintenance Trial
CC-486 (Oral Azacitidine)

Patient DISPOSITION / SCHEMA



*Still receiving study drug at data cutoff (July 15, 2019).
†Became eligible for hematopoietic stem cell transplant during treatment. Requirement of ANC >/= 500 and and Plt >/= 20 at the time of screening

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

QUAZAR Trial – Patient Characteristics

Table 1. Baseline Demographic and Disease Characteristics.*

Characteristic	CC-486 (N = 238)	Placebo (N = 234)	Total (N = 472)
Response after induction therapy — no. (%)			
Complete remission	187 (79)	197 (84)	384 (81)
Complete remission with incomplete blood count recovery	51 (21)	37 (16)	88 (19)
Receipt of consolidation therapy — no. (%)			
Yes	186 (78)	192 (82)	378 (80)
No	52 (22)	42 (18)	94 (20)
Median time from induction therapy to randomization (range) — mo	4.0 (1.4–8.8)	4.0 (1.3–15.1)	4.0 (1.3–15.1)
Median time from complete remission to randomization (range) — days‡	84.5 (7–154)	86.0 (7–263)	85.0 (7–263)
Median bone marrow blasts (range) — %§	2.0 (0.0–5.0)	2.0 (0.0–6.5)	2.0 (0.0–6.5)
Positive for measurable residual disease — no. (%)¶	103 (43)	116 (50)	219 (46)
Median platelet count (range) — $\times 10^{-9}$/liter§	154 (22–801)	179 (16–636)	165 (16–801)
Median absolute neutrophil count (range) — $\times 10^{-9}$/liter§	3.0 (0.3–15.9)	2.8 (0.5–9.6)	2.9 (0.3–15.9)

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

QUAZAR Trial – Safety

- Median treatment durations:
  - CC-486: 12 cycles (range 1–80)
  - Placebo: 6 cycles (range 1–73)
- CC-486 safety profile was generally consistent with that of injectable AZA[1]
- Gastrointestinal adverse events (AEs) in the CC-486 arm were most common during the first 2 treatment cycles
- Serious AEs were reported for 34% and 25% of patients in the CC-486 and placebo arms, respectively
- No treatment-related deaths

	CC-486 n = 236		Placebo n = 233	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Preferred term	n (%)			
Patients with ≥1 AE	**231 (98)**	**169 (72)**	**225 (97)**	**147 (63)**
Gastrointestinal				
Nausea	153 (65)	6 (3)	55 (24)	1 (0.4)
Vomiting	141 (60)	7 (3)	23 (10)	0
Diarrhea	119 (50)	12 (5)	50 (22)	3 (1)
Constipation	91 (39)	3 (1)	56 (24)	0
Hematologic				
Neutropenia	105 (45)	97 (41)	61 (26)	55 (24)
Thrombocytopenia	79 (34)	53 (23)	63 (27)	50 (22)
Anemia	48 (20)	33 (14)	42 (18)	30 (13)
Other				
Fatigue	70 (30)	7 (3)	45 (19)	2 (1)
Asthenia	44 (19)	2 (1)	13 (6)	1 (0.4)
Pyrexia	36 (15)	4 (2)	44 (19)	1 (0.4)
Cough	29 (12)	0	39 (17)	0

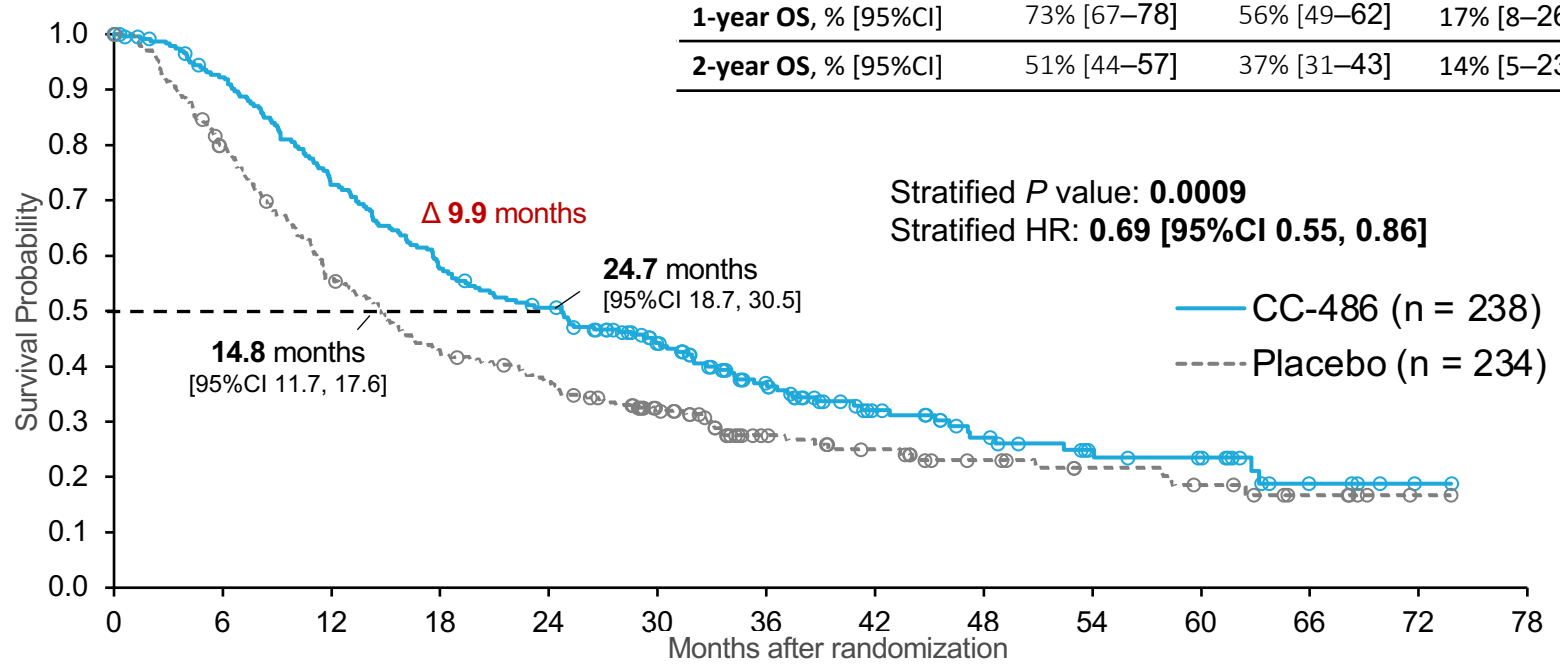
1. Dombret et al. *Blood.* 2015;126(3):291-9.
AE, adverse event; AZA, azacitidine; GI, gastrointestinal.

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

QUAZAR Trial – Primary Endpoint OS

- Median follow-up: 41.2 months

	CC-486	Placebo	Difference
1-year OS, % [95%CI]	73% [67–78]	56% [49–62]	17% [8–26]
2-year OS, % [95%CI]	51% [44–57]	37% [31–43]	14% [5–23]



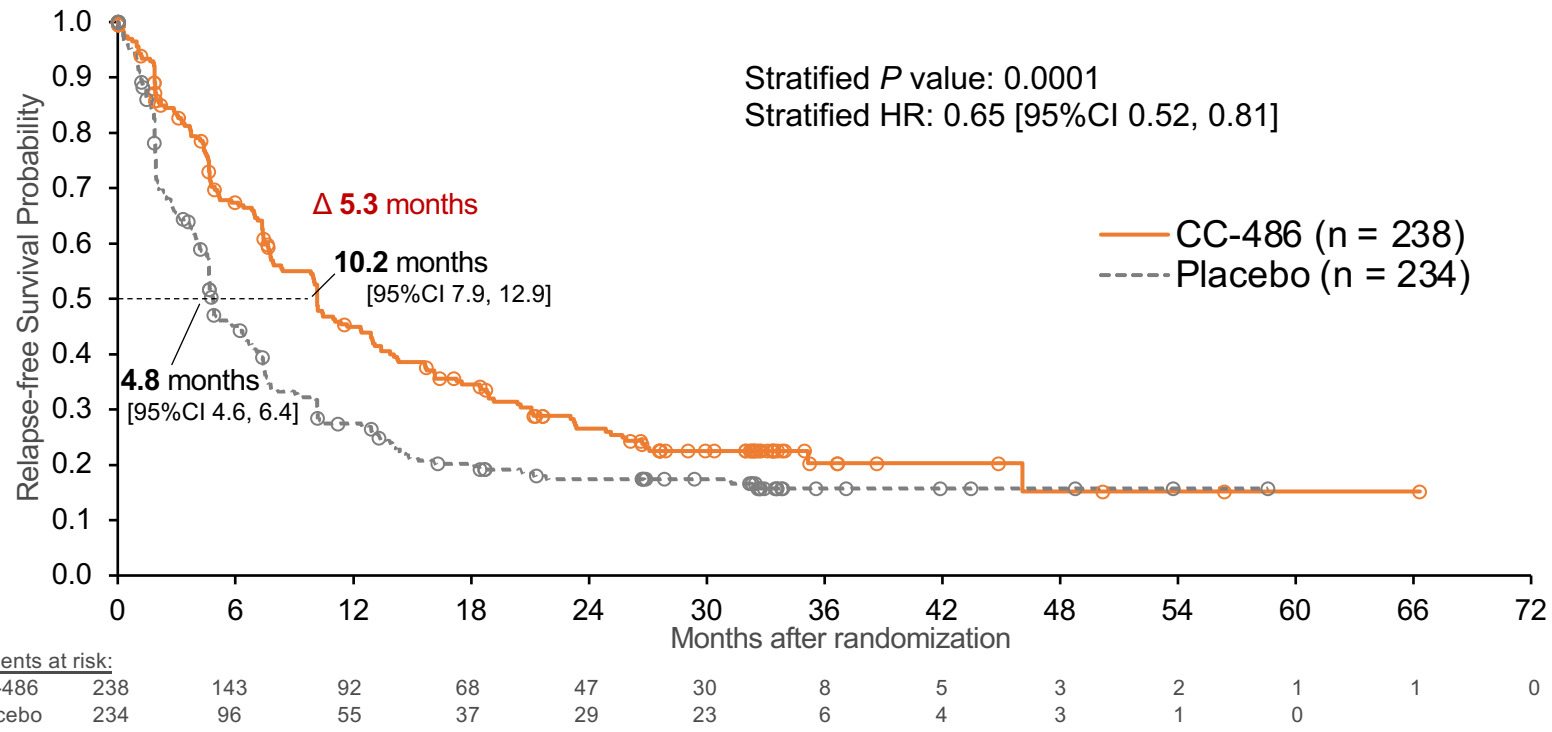
Patients at risk:

CC-486	238	213	169	133	115	87	59	37	26	18	15	5	1	0
Placebo	234	183	128	96	82	58	34	27	19	15	11	6	1	0

Data cutoff: July 15, 2019
OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for CC-486 vs. placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

QUAZAR Trial – Secondary Endpoint RFS



- 1-year relapse rate was 53% in the CC-486 arm [95%CI 46, 59] and was 71% in the placebo arm [65, 77]

Data cutoff: July 15, 2019
RFS was defined as the time from randomization to relapse or death by any cause, whichever occurred first. Kaplan-Meier estimated RFS was compared for CC-486 vs. placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.

Wei et al, ASH 2019. Abstr LBA 3.
Wei et al, NEJM 2020.

Case 2

A 75-year-old medically fit woman was diagnosed with AML after being found to have anemia on routine CBC. BMBx showed 40% blasts, normal cytogenetics and mutations in DNMT3A, ASXL1 and SRSF2.

She is treated with venetoclax and decitabine and achieves a MRD positive CR after cycle 1. She continues on treatment and her end of cycle 4 bone marrow biopsy shows an MRD negative CR.

She asks about the impact of her MRD status as well as if there is a role for transplant in her care.

2021 ASCO ANNUAL MEETING

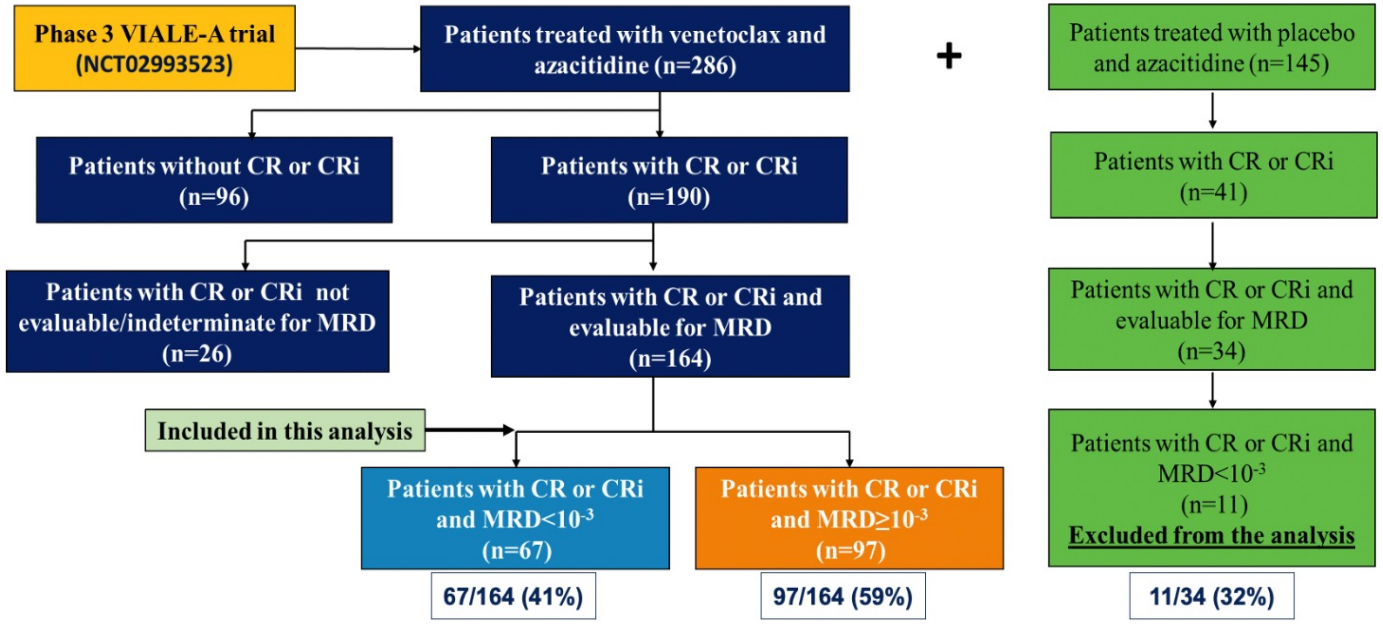
MEASURABLE RESIDUAL DISEASE RESPONSE AND PROGNOSIS IN ACUTE MYELOID LEUKEMIA WITH VENETOCLAX AND AZACITIDINE

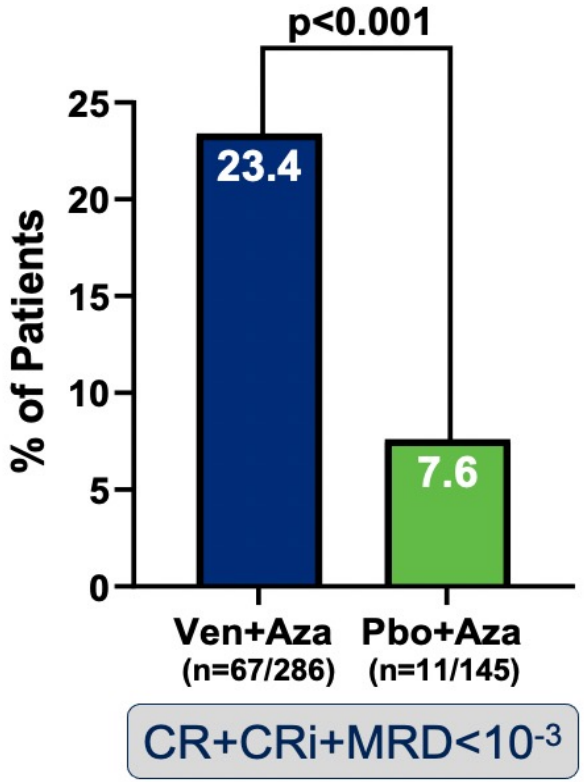
Keith W. Pratz[1], Brian A. Jonas[2], Vinod Pullarkat[3], Christian Recher[4], Andre C. Schuh[5], Michael J. Thirman[6], Jacqueline S. Garcia[7], Courtney DiNardo[8], Vladimir Vorobyev[9], Nicola Fracchiolla[10], Su-Peng Yeh[11], Jun Ho Jang[12], Muhit Ozcan[13], Kazuhito Yamamoto[14], Arpad Illes[15], Ying Zhou[16], Monique Dail[17], Brenda Chyla[16], Jalaja Potluri[16], Hartmut Döhner[18]

[1]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA, [2]Department of Internal Medicine, Division of Hematology and Oncology, University of California Davis School of Medicine, Sacramento, CA, USA, [3]Department of Hematology and Hematopoietic Cell Transplantation and Gehr Family Center for Leukemia Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA [4]Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [5]Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada, [6]Section of Hematology/Oncology, Department of Medicine, The University of Chicago Medicine, Chicago, IL, USA, [7]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [8]Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [9]Department of Hematology, S. P. Botkin City Clinical Hospital, Moscow, Russia, [10]UOC Ematologia, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy, [11]Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan [12]Department of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, [13]Department of Hematology, Ankara University School of Medicine, Ankara, Turkey, [14]Department of Hematology and Cell Therapy, Aichi Cancer Center Hospital, Nagoya, Japan, [15]University of Debrecen, Faculty of Medicine, Department of Hematology, Debrecen, Hungary, [16]AbbVie Inc., North Chicago, IL, USA, [17]Genentech Inc., South San Francisco, CA, USA, [18]Department of Internal Medicine III, University Hospital, Ulm, Germany

Pratz et al, ASCO 2021, Abstract 7018.
Pratz et al, EHA 2021, Abstract S137.

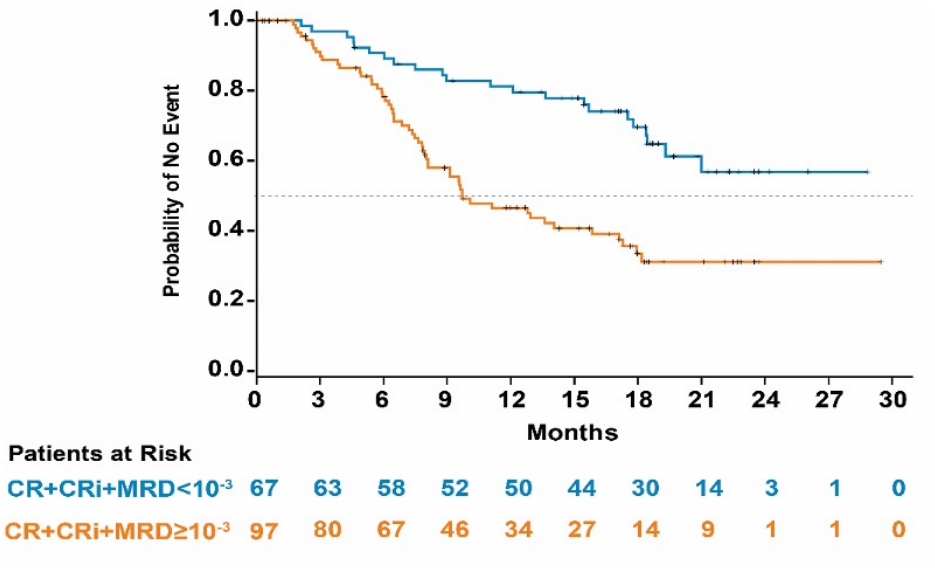
VIALE-A Trial: Measurable Residual Disease and Outcomes

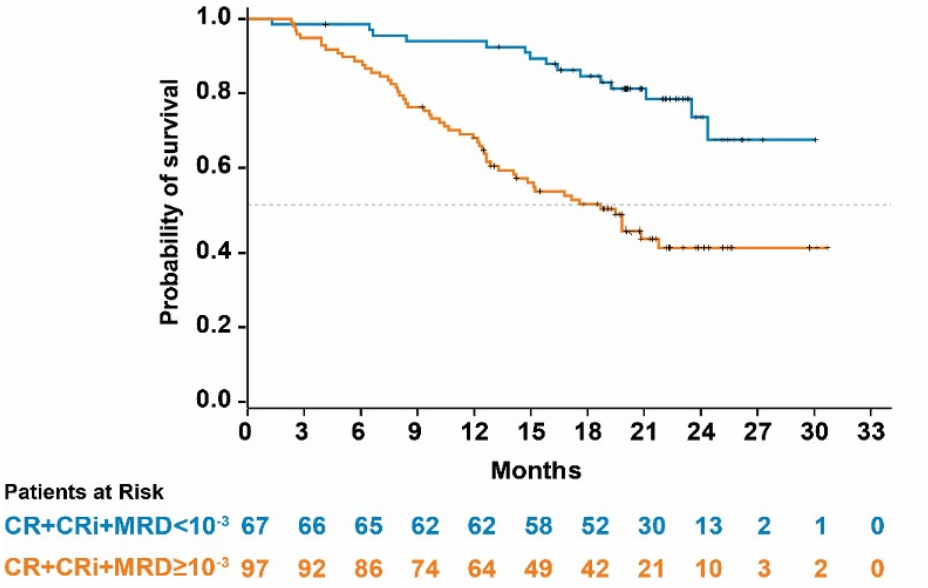




Pratz et al, ASCO 2021, Abstract 7018.
Pratz et al, EHA 2021, Abstract S137.

VIALE-A Trial: MRD Response, DoR and OS





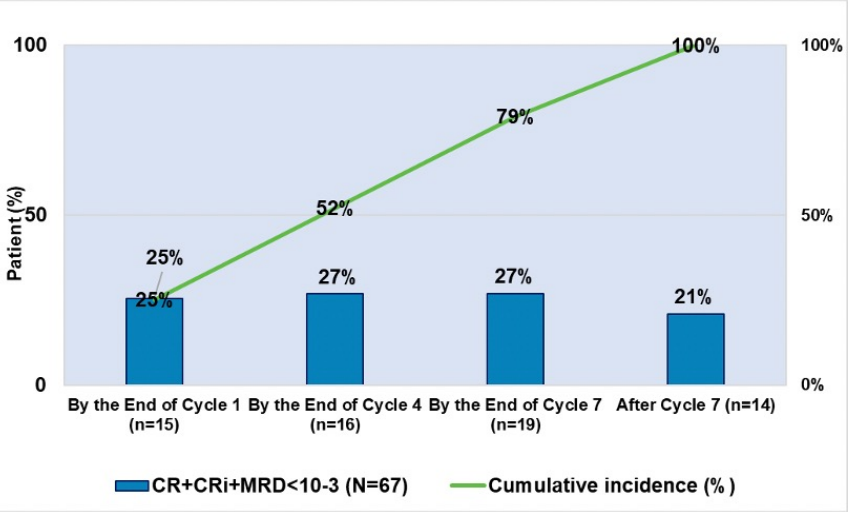
Duration of remission	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median DoR, months (95% CI)
CR+CRi+MRD<10^{-3}	22	81.2 (69.3, 88.9)	69.6 (55.9, 79.8)	NR (19.3 – NR)
CR+CRi+MRD≥10^{-3}	54	46.6 (35.6, 56.8)	33.5 (22.9, 44.5)	9.7 (8.0 – 15.8)

Overall survival	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median OS, months (95% CI)
CR+CRi+MRD<10^{-3}	15	94.0 (84.7, 97.7)	84.6 (73.3, 91.4)	NR (24.4 – NR)
CR+CRi+MRD≥10^{-3}	52	67.9 (57.6, 76.2)	50.1 (39.6, 59.8)	18.7 (12.9 – NR)

Pratz et al, ASCO 2021, Abstract 7018.
Pratz et al, EHA 2021, Abstract S137.

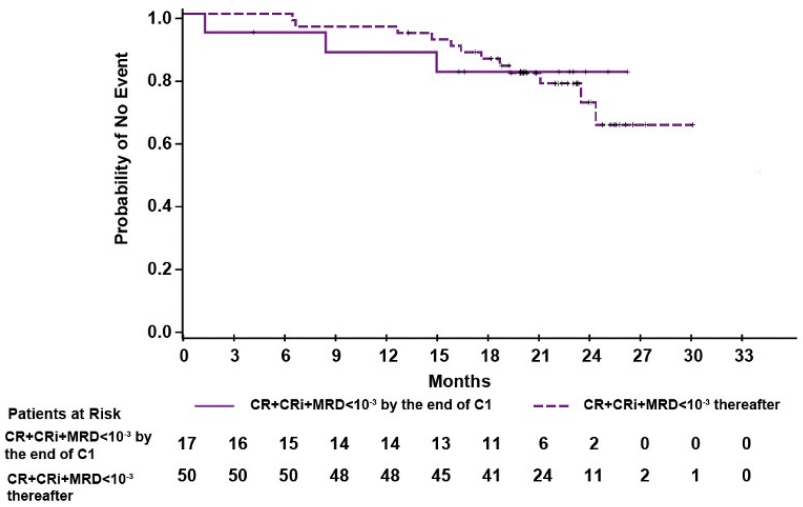
VIALE-A Trial: Timing of MRD Response and OS

MRD by treatment cycles



Note: End of cycle (C) 1: MRD<10^{-3} from C1 Day (D) 1 to end day of C1+7 days
End of C4: MRD<10^{-3} from end day of C1+8D to min (End day of C4, last dose +7 days)
End of C7: MRD<10-3 from end day of C4+1D to min (end day of C7, last dose +7 days
After C 7: End day of C7+1D and onward up to cutoff date: Jan 04, 2020.

OS by treatment cycles



Patients at Risk												
CR+CRi+MRD<10^{-3} by the end of C1	17	16	15	14	14	13	11	6	2	0	0	0
CR+CRi+MRD<10^{-3} thereafter	50	50	50	48	48	45	41	24	11	2	1	0

Overall survival	# of events	12-month, % (95% CI)	18-month % (95% CI)	Median OS, months (95% CI)
CR+CRi+MRD<10^{-3} by end of cycle 1	3	87.8 (59.5, 96.8)	81.6 (53.0, 93.7)	NR (NR – NR)
CR+CRi+MRD<10^{-3} thereafter	12	96.0 (84.9, 99.0)	85.8 (72.5, 93.0)	NR (24.4 – NR)

NR: Not reached; OS: Overall survival

Pratz et al, ASCO 2021, Abstract 7018.
Pratz et al, EHA 2021, Abstract S137.

Outcomes after stem cell transplant in older patients with acute myeloid leukemia treated with venetoclax-based therapies

Keith Pratz[1], Courtney D. DiNardo[2], Martha Arellano[3], Anthony Letai[4], Michael Thirman[5], Vinod Pullarkat[6], Gail J. Roboz[7], Pamela S. Becker[8], Wan-Jen Hong[9], Qi Jiang[10], John Hayslip[10], Jalaja Potluri[10], Daniel A. Pollyea[11]

[1]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Department of Hematology and Oncology, Emory University School of Medicine, Atlanta, GA, USA; [4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [5]University of Chicago Medical Center, Chicago, IL, USA; [6]Department of Hematology and Hematopoietic Cell Transplantation and Gehr Family Center for Leukemia Research, City of Hope National Medical Center, Duarte, CA, USA; [7]Weill Medical College of Cornell University and New York-Presbyterian Hospital, New York, NY, USA; [8]Clinical Research Division, Fred Hutchinson Cancer Research Center and Division of Hematology, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA; [9]Genentech, Inc., South San Francisco, CA, USA; [10]AbbVie Inc., North Chicago, IL, USA; [11]University of Colorado School of Medicine, Aurora, CO, USA

American Society of Hematology (ASH) – 61st Annual Meeting
Orlando, FL, USA ● December 7, 2019

HCT is Feasible in Patients After Ven-Based Regimens

- **10%** 31 of 304 patients received Allo-HCT
  - Phase 1 trials of Ven-HMA and Ven-LDAC
- Median time on study drug for patients that had HCT 3.7mo (range 0.9-20).
- **68%** (21/31) of patients remained alive at 12 months post-allo-HCT
- **55%** (17/31) of all patients that had allo-HCT had posttransplant remission of ≥12 months
  - **71%** (12/17) of those patients remained in remission for ≥2 years

Best response prior to SCT, n (%)	SCT Patients n = 31
CR/CRi	**26 (84)**
CR	16 (52)
CRi	10 (32)
CRh	6 (19)
MLFS	2 (6)
RD	3 (10)

Pratz et al, ASH 2019, Abstract 264.

#78

Allogeneic Transplant Improves AML Outcomes Compared to Maintenance Venetoclax and Azacitidine Following Response to Initial Venetoclax and Azacitidine Therapy

Daniel A. Pollyea, Amanda Winters, Craig T. Jordan, Clayton Smith, and Jonathan A. Gutman

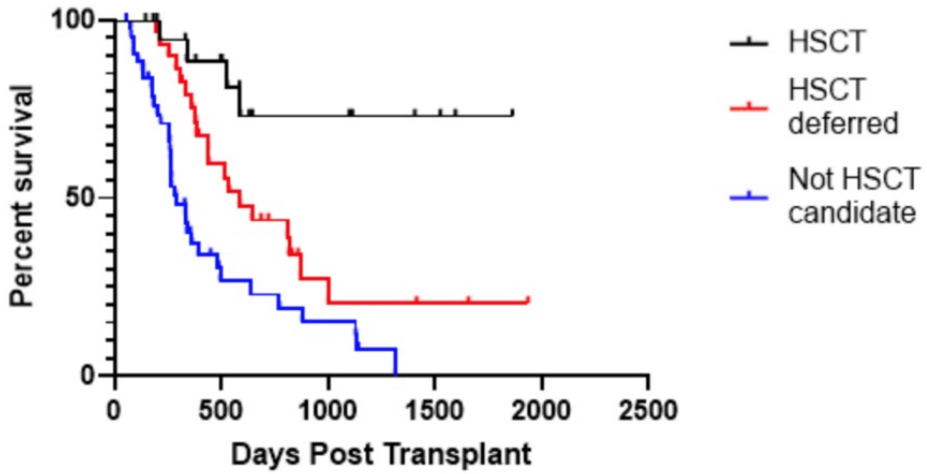
American Society of Hematology, December 2020

Outcomes of AML Patients Treated with Aza/Ven Are Improved After HSCT Compared to Maintenance Aza/Ven

Table 1: Disease status characteristics

ELN risk	SCT patients	SCT deferred patients
High	15	16
Intermediate	3	4
Favorable	3	10
Disease status at SCT consult		
CR/CRi without MRD	2	11
CR/CRi with MRD	11	11
MLFS/Aplasia/persistent disease	6	6
Disease status at time of SCT		
CR/CRi without MRD	7	
CR/CRi with MRD	10	
MLFS/Aplasia	4	
Best response in non-SCT patients		
CR/CRi without MRD		21
CR/CRi with MRD		8
MLFS/Aplasia		1

Figure 1: Overall survival



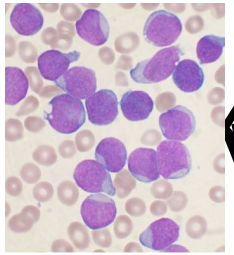
Pollyea et al, ASH 2020, Abstract 78.

Case 3

A 35-year-old woman is diagnosed with B-cell ALL after presenting with fatigue and bruising. She has no other medical history. CBC shows WBC 40, Hgb 6, Plt 30, and 85% circulating B-lymphoblasts. BMBx shows 90% B-lymphoblasts expressing CD19 and CD22 but negative for CD20. Cytogenetics, FISH and molecular studies are pending.

Which treatment regimen do we recommend to this patient?

Current Upfront Treatment Approach for ALL



Diagnosis of ALL

Risk Stratification	Induction	Post-Remission	Maintenance
Ph+ AYA (15-39)	Chemo + TKI	✓MRD → Chemo + TKI (MRD-) or Blina +/- TKI (MRD+) or Allo-HCT (MRD+ or high risk)	Maintenance plus TKI OR Post-HCT TKI
Ph+ Adult (40+)	Chemo + TKI Blina + TKI Steroids + TKI	✓MRD → Allo-HCT (MRD+ or high risk)	
Ph- AYA (15-39)	Pediatric inspired protocol	✓MRD → Chemo (MRD-) or Blina (MRD+) or Allo-HCT (MRD+ or high risk)	Maintenance
Ph- Adult (40+)	Chemo	✓MRD → Chemo (MRD-) or Blina (MRD+) or Allo-HCT (MRD+ or high risk)	

All ALL patients get CNS prophylaxis

NCCN Guidelines, ALL, v2.2021.

Principles of Pediatric-Inspired Protocols

- **Mostly based on Berlin Frankfurt Munster (BFM) backbone**
- **Multiple cycles of non-cross resistant agents**
- **Early and frequent CNS prophylaxis**
- **Repeated doses of L-asparaginase**
- **Prolonged maintenance**
- **Less myelosuppression**
- **Higher cumulative doses of active agents**

Stock et al. Blood 2019.

CALGB 10403 Regimen

Remission Induction (Course I)
- **Allopurinol** –300 mg/day (unless allergic), to continue until peripheral blasts and extramedullary disease are reduced
- **IT-Ara-C** – Ara-C 70 mg IT on D 1.
- **Pred** –60 mg/m^2/day PO or IV in two divided doses on 01-28
- **VCR** –1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 8, 15, and 22
- **DNR** –25 mg/m^2 IV on D 1, 8, 15, and 22
- **PEG** –2500 IU/m^2 IM or IV D 4
- **IT-MTX** - 15 mg IT on D 8 & D 29 (also administered on D 15 and 22 for CNS3 patient)

Extended Remission Induction (if required)(Course IA)
- **Pred** –60 mg/m^2/day PO or IV (methylprednisolone) in two divided doses on D 1-14
- **DNR** –25 mg/m^2 IV on D 1
- **VCR** – Vincristine 1.5 mg/m2 (maximum 2 mg) IV on D 1 and 8
- **PEG** –2500 IU/m^2 IM or IV D 4

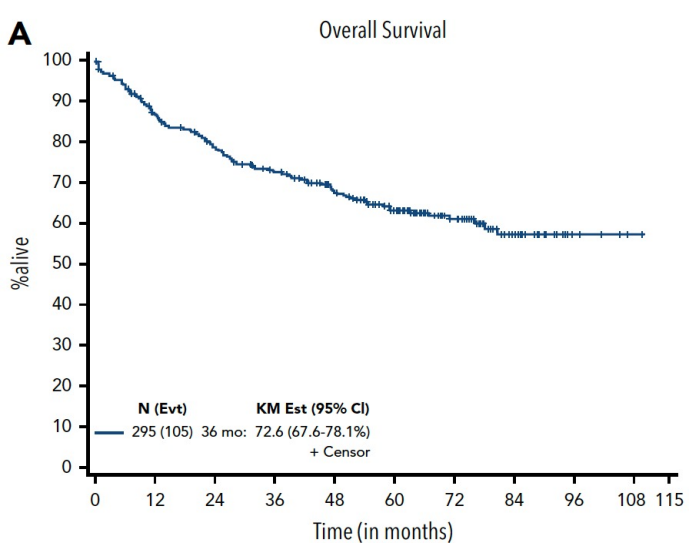
Remission Consolidation (Course II)
- **CTX** –1000 mg/m^2 IV on D 1 & 29
- **Ara-C** –75 mg/m^2 IV or SC on D 1-4, 8-11, 29-32, and 36-39
- **6-MP** –60 mg/m^2 PO on D 1-14 and 29-42
- **VCR** –1.5 mg/m^2 (maximum 2 mg) IV on D 15, 22, 43 and 50
- **PEG** –2500 IU/m^2 IM or IV on D 15 and 43
- **IT-MTX** -- 15 mg IT on D 1, 8, 15 and 22 (omit doses on D 15 & 22 for CNS3 patients)

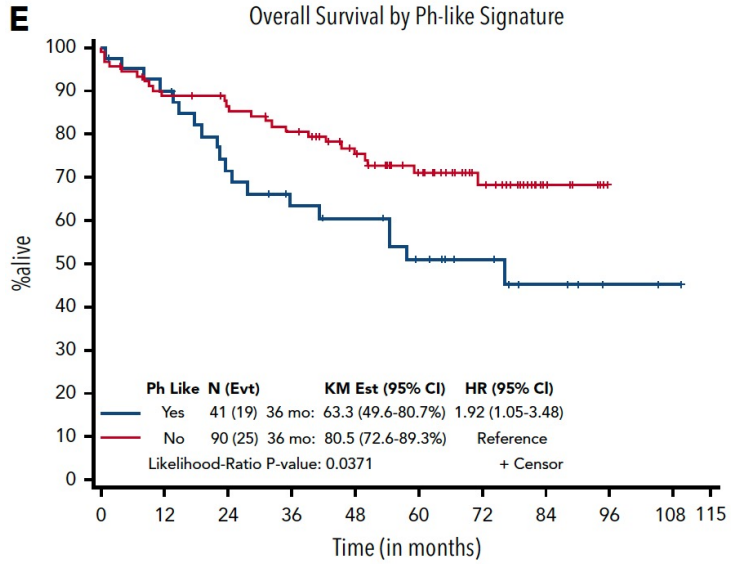
Interim Maintenance (Course III)
- **IV-MTX** –starting dose 100 mg/m^2 IV (escalate by 50 mg/m^2 /dose on D 1, 11, 21, 31 and 41
- **PEG** –2500 IU/m^2 IM or IV on D 2 and 22
- **IT-MTX** - 15 mg IT on D 1 and 31

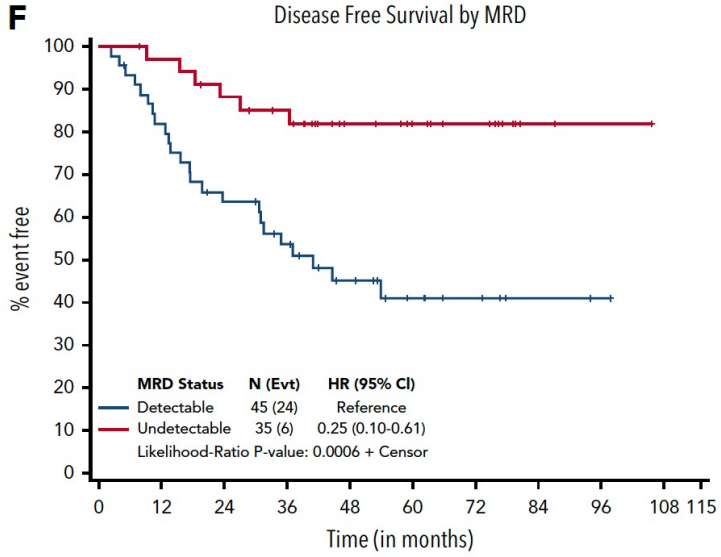
Delayed Intensification (Course IV)
- **VCR** – 1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 8, 43, and 50
- **DEX** – 10 mg/m^2 PO (or IV) divided BID on D 1-7 and 15-21
- **PEG** – 2500 IU/m^2 IM or IV D 4 (OR D 5 OR D 6) and D 43
- **CTX** – 1000 mg/m^2 IV on D 29
- **Ara-C** – 75 mg/m^2 IV or SC on D 29-32 and 36-39
- **6-TG** – 60 mg/m^2/day PO on D 29-42
- **IT-MTX** --15 mg IT on D 1, 29, & 36

Maintenance (Course V)*
- **VCR**–1.5 mg/m^2 (maximum dose 2 mg) IV on D 1, 29, and 57
- **DEX**– 6 mg/m^2/day PO (or IV) in 2 divided doses every 4 weeks on D 1-5, 29-33, and 57-61
- **6-MP**– 75mg/m^2/day PO on D 1-84
- **IT-MTX** -- 15 mg IT on D 1 (also is given on D 29 of the first 4 courses of maintenance)
  PO-MTX – 20 mg/m^2 PO weekly on D 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 (held on D 29 of the first 4 courses of maintenance when IT-MTX is given)

Pediatric-Inspired CALGB 10403 Regimen Outcomes



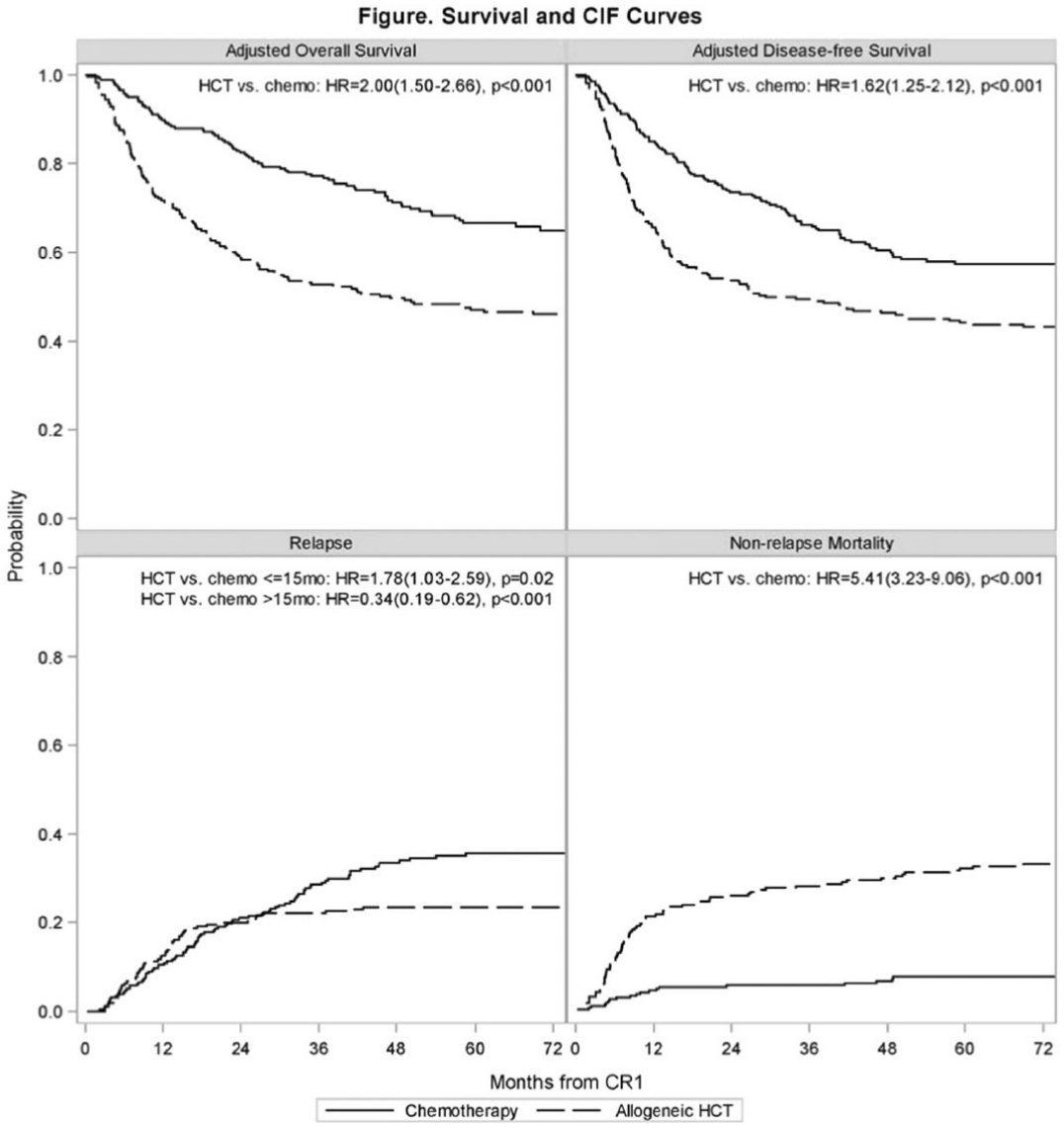




Age 18-40 (n=296)
Similar results for B- and T-cell disease (EFS, DFS, OS)
3% induction death rate
Obese pts did less well
Main toxicities were thrombosis and hyperbilirubinemia
Historically, Hyper-CVAD leads to ~40% 5yr OS
ASH 2020 update – dose reductions allow use in up to age 60

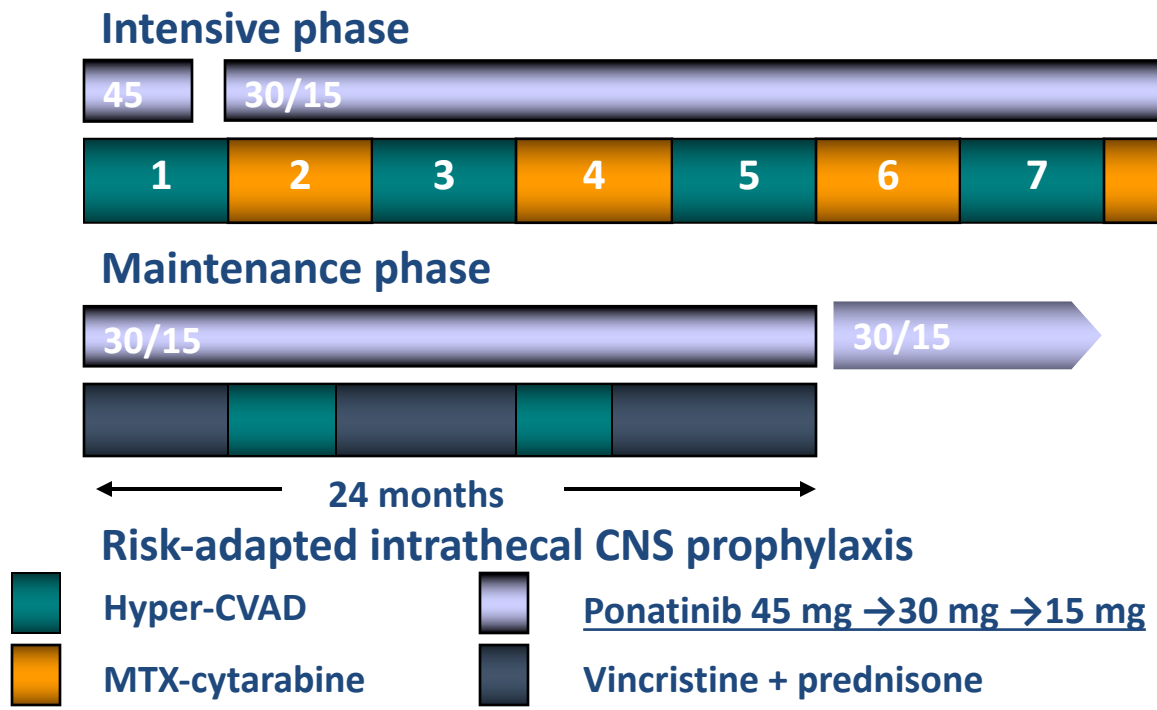
Stock et al. ASH 2014 Abstract# 796.
Stock et al. Blood 2019.
Patel et al. ASH 2020 Abstract# 2796.
Kantarjian et al. Cancer 2004.

Post-Remission Therapy with CALGB 10403 vs Allo-HCT



Wieduwilt et al. Leukemia. 2021

(R)-Hyper-CVAD plus Ponatinib Regimen for Ph+ ALL



After the emergence of vascular toxicity, protocol was amended:
Beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

Current Hyper-CVAD+TKI regimens are using 12 doses of IT chemo (d2 and d7 cycles 1-6) for all patients and 8 doses of R (cycles 1-4) for CD20+ in 20% of blasts

ASH 2016 Abstract #757.
Rausch et al, Cancer 2020.

Outcomes of (R)-Hyper-CVAD plus Ponatinib for Ph+ ALL

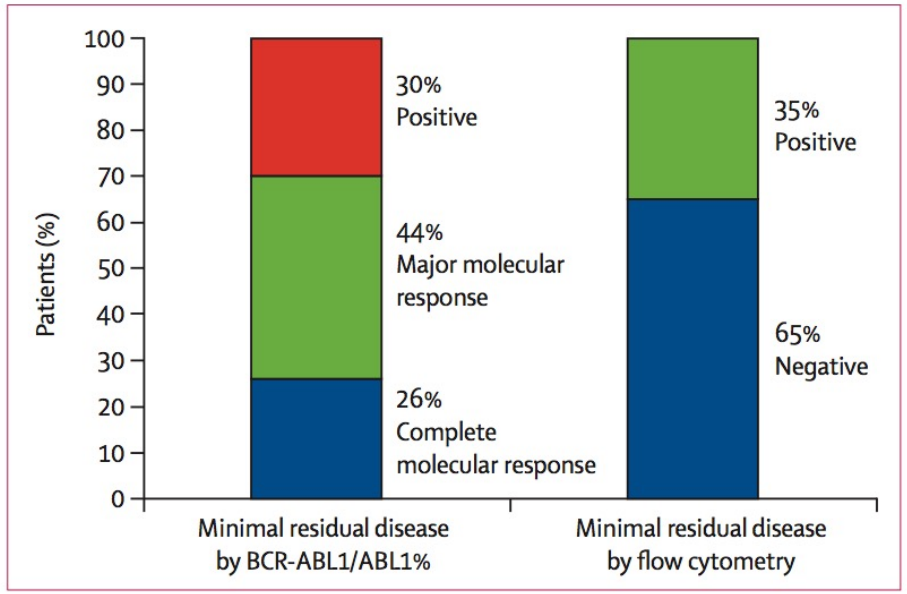


Figure 1: **Levels of residual disease after one cycle of protocol therapy in complete response**
Minimal residual disease after one cycle at complete remission by BCR-ABL1/ABL1 percentage and flow cytometry.

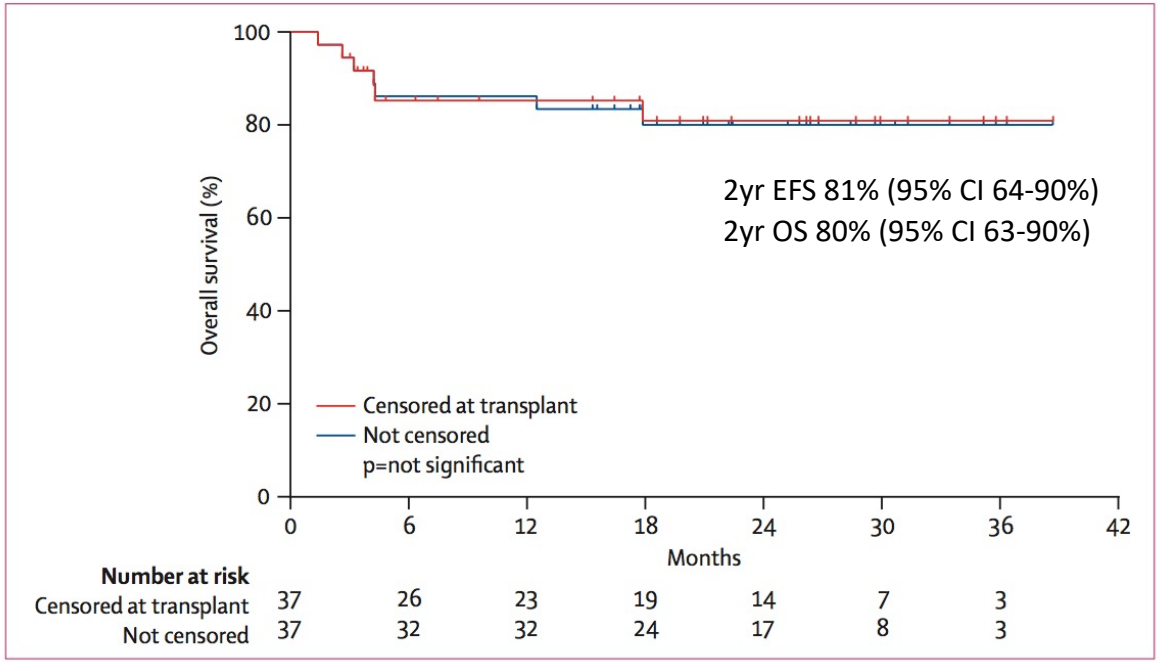


Figure 4: **Overall survival with and without censoring for allogeneic stem-cell transplantation**

Toxicities:
6 died in CR, 3 from MI
Infections, LFTs, Rash, pancreatitis

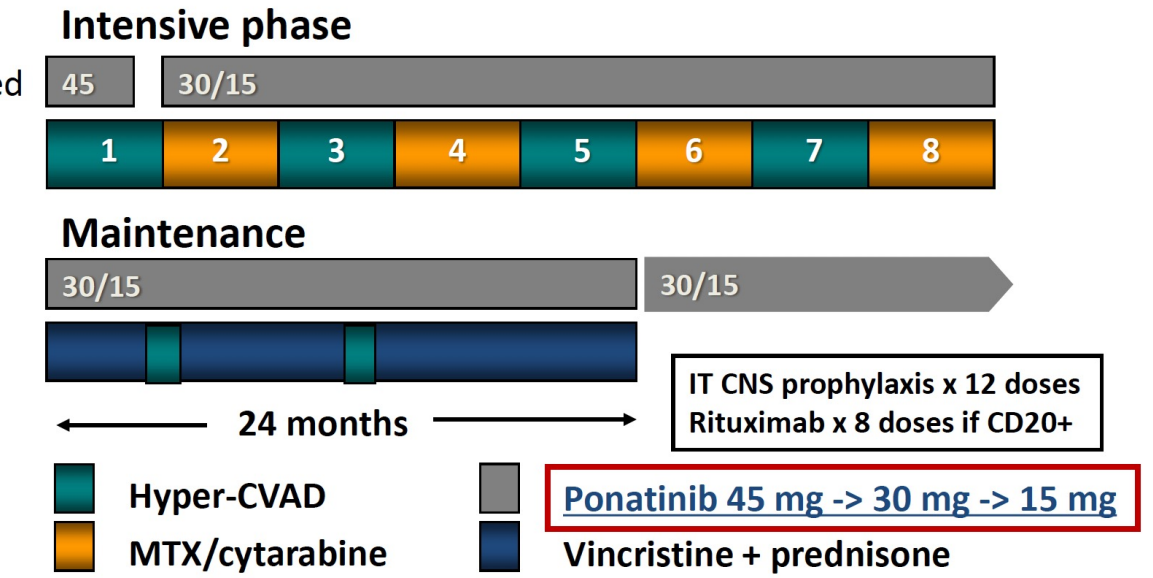
Jabbour et al Lancet Oncology 2015.

Updated Results of (R)-Hyper-CVAD plus Ponatinib for Ph+ ALL

Characteristic	Category	N (%) / median [range]
Age (years)		46 (21-80)
	≥60	20 (23)
Performance status	0-1	78 (91)
	2	8 (9)
WBC (x10^9/L)		13.6 [0.9-629.4]
CNS involvement		5 (6)
CD20 positivity		30 (35)
BCR-ABL transcript	p190	63 (73)
	p210	21 (24)
	Unknown	2 (2)
Karyotype	Ph+	58 (67)
	Diploid/IM (FISH/PCR+)	28 (33)
CNS disease at diagnosis		6 (7)
≥ 1 baseline CV risk factor		56 (65)

N=86

Modified study design



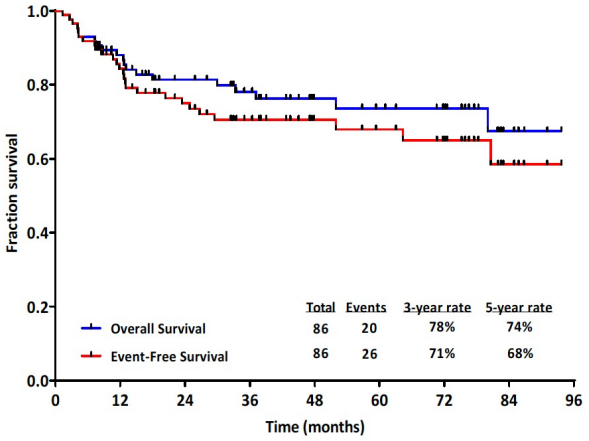
Short et al. ASH 2019 Abstract #283.

Updated Results of (R)-Hyper-CVAD plus Ponatinib for Ph+ ALL

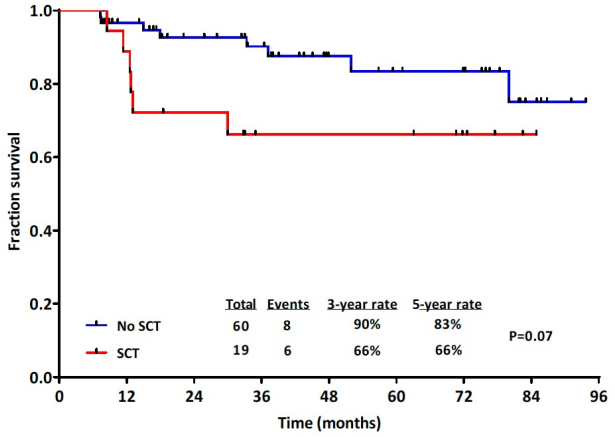
Response	n/N (%)
CR*	68/68 (100)
CCyR^	58/58 (100)
MMR#	80/85 (94)
CMR#	73/85 (86)
Flow negativity#	83/85 (95)
Early death	0

74% CMR at 3 months

EFS and OS



Impact of alloHCT: 6 month landmark



19 (22%) underwent Allo-HCT in CR1

3 relapses on ponatinib and no CNS relapses (12 IT ppx)

Toxicities– VTE (13%), Arterial CV events (7%), pancreatitis (15%), hyperbilirubinemia (15%), AST/ALT elevation (29%)

73% of VTE events at 45mg Pon; 67% of arterial CV events at 30-45mg Pon

No treatment related deaths after amendment of Pon dosing (2 prior)

Short et al. ASH 2019 Abstract #283.

Ponatinib plus Blinatumomab for Ph+ ALL

- Single arm P2 study at MDACC
- Newly diagnosed or relapsed/refractory Ph+ ALL
  - 28 treated (19 first line), median age 59 (25-83)
- Treatment:
  - Blinatumomab up to 5 cycles
  - Ponatinib 30mg daily during C1 then 15mg daily after CMR and for 5 years after blina completed
  - 12 doses of IT chemo ppx
- Outcomes:
  - 95% ORR (100% in ND cohort and 88% in R/R cohort)
  - Median time to CMR 1mo (1-13mo)
  - 1yr OS 94% and EFS 81% (1yr 100% OS and EFS in ND and 88% OS and 55% EFS in R/R)
  - No ND underwent allo-HCT; 4 (44%) of R/R pts underwent allo-HCT
- Safety: well-tolerated, no pts dc'd ponatinib due to toxicity, no early deaths in first 4 weeks
- Potentially effective, chemotherapy-free regimen

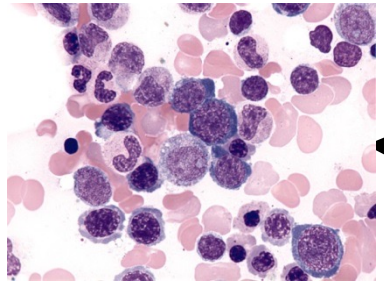
Short et al. ASCO 2021 Abstract #7001.

Case 4

A 78-year-old man was diagnosed with MDS after presenting with fatigue and macrocytic anemia. He is relatively healthy overall. CBC showed WBC 2, Hgb 7, Plt 75, and ANC 700. BMBx showed 8% blasts, del(5q) and a mutation in DNMT3A. His IPSS-R score is 5.5pts or high risk. He is interested in treatment of his MDS and his hematologist recommends standard azacitidine 75mg/m2 SQ for 7 days every 28 days.

He is interested in seeing if there is an oral option to treat his high risk MDS since he lives relatively far from the nearest infusion center.

Treatment Approaches in MDS



Diagnosis of MDS

Higher Risk:
IPSS-R Int*, HR, VHR

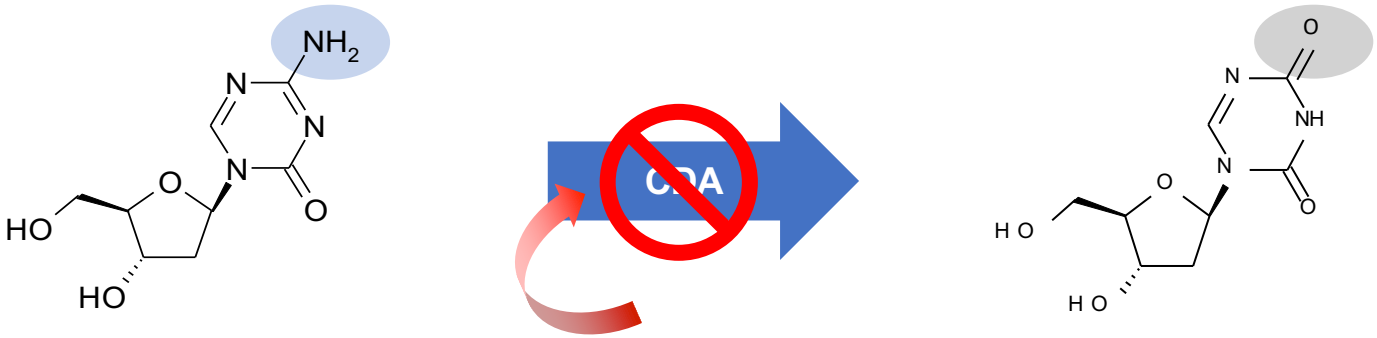
Lower Risk:
IPSS-R VLR, LR, Int*

Treatment Goal	**Treatment Options**
Alter disease natural history	• Hypomethylating agents (HMA) -/+ Ven • High-intensity chemotherapy (IC) • Allogeneic HCT • Clinical Trial
Hematologic improvement	• Growth factors • Luspatercept • Lenalidomide • Immune suppressive therapy (IST) • HMA • Watch and Wait • Clinical Trial

* Differentiating features: age, performance status, ferritin, LDH

Oral Decitabine + Cedazuridine (DEC-C)

- Current HMA treatment poses significant patient burden due to 5–7 days per month of parenteral administration in a clinic setting
- Oral bioavailability of HMAs decitabine and azacitidine is limited due to rapid degradation by CDA in the gut and liver



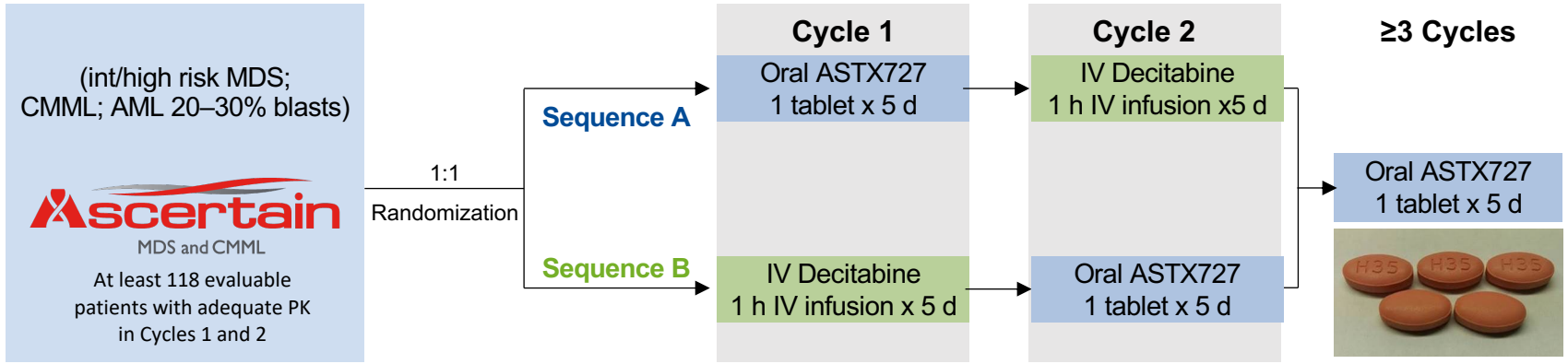
Decitabine **CDA inhibitor** **Inactive metabolite**

- Cedazuridine is a novel, potent, and safe CDA inhibitor
  - Large safety margin, with no adverse events at up to 200 mg/kg in monkeys (~2400 mg/m^2 human equivalent)

CDA, cytidine deaminase.

Savona et al. Lancet Hematogy 2019.

ASTX727-02 trial of DEC-C in MDS/CMML: Randomized Cross-Over Trial



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-d 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
- Max LINE-1 demethylation

Garcia-Manero et al. Abstract 846 ASH 2019

ASTX727-02 Primary Endpoint: 5-day Decitabine AUC Equivalence

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

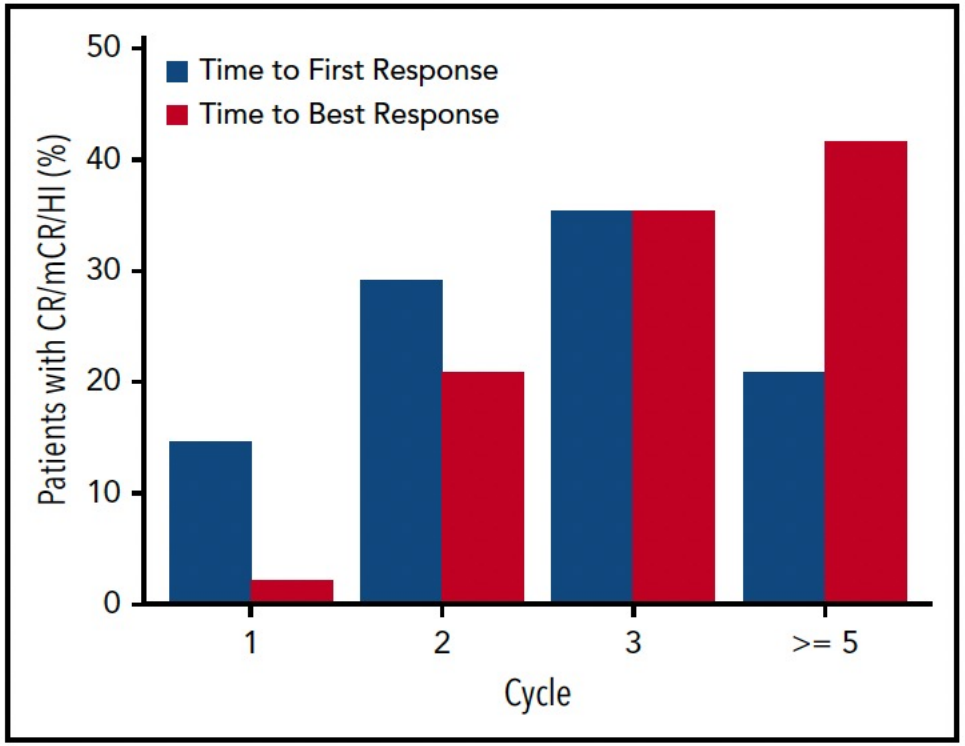
[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- 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

Garcia-Manero et al. Abstract 846 ASH 2019

ASTX727-01-B: DEC-C Responses in MDS/CMML

Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13-32
PR	0	
mCR	18 (22)	14-33
mCR with HI	6 (7)	3-16
HI	13 (16)	9-26
HI-E	8 (10)	4-19
HI-N	2 (2)	0-9
HI-P	11 (14)	7-23
Overall response* (CR + PR + mCR + HI)	48 (60)	48-71
No response	32 (40)	29-52



- Comparable safety was seen between IV decitabine and PO DEC-C

Garcia-Manero et al. Blood 2020.

Summary and Future Directions

- Exciting time for new treatments for MDS, AML and ALL
- Standards of care for MDS, AML and ALL are rapidly evolving
- Clinical trials continue to advance new treatments
- My email: bajonas@ucdavis.edu