Year In Review:
Acute Myeloid Leukemia

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Outline: AML

- VENETOCLAX+ AZACITIDINE: NEW STANDARD
- VENETOCLAX+ Other CHEMO
- HYPOMETHYLATING AGENTS as MAINTENANCE
- USE OF the FLT3 inhibitor GILTERITINIB
- IDH INHIBITORS IN COMBINATION

Courtesy of Richard M Stone, MD

Azacitidine ± Venetoclax (VIALE-A) Study Design

(NCT02993523)

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤65% or FEV_1 ≤65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment

Randomization 2:1
N = 433[#]

Venetoclax + Azacitidine
(n = 286)
Venetoclax 400 mg PO, daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine
(n = 145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

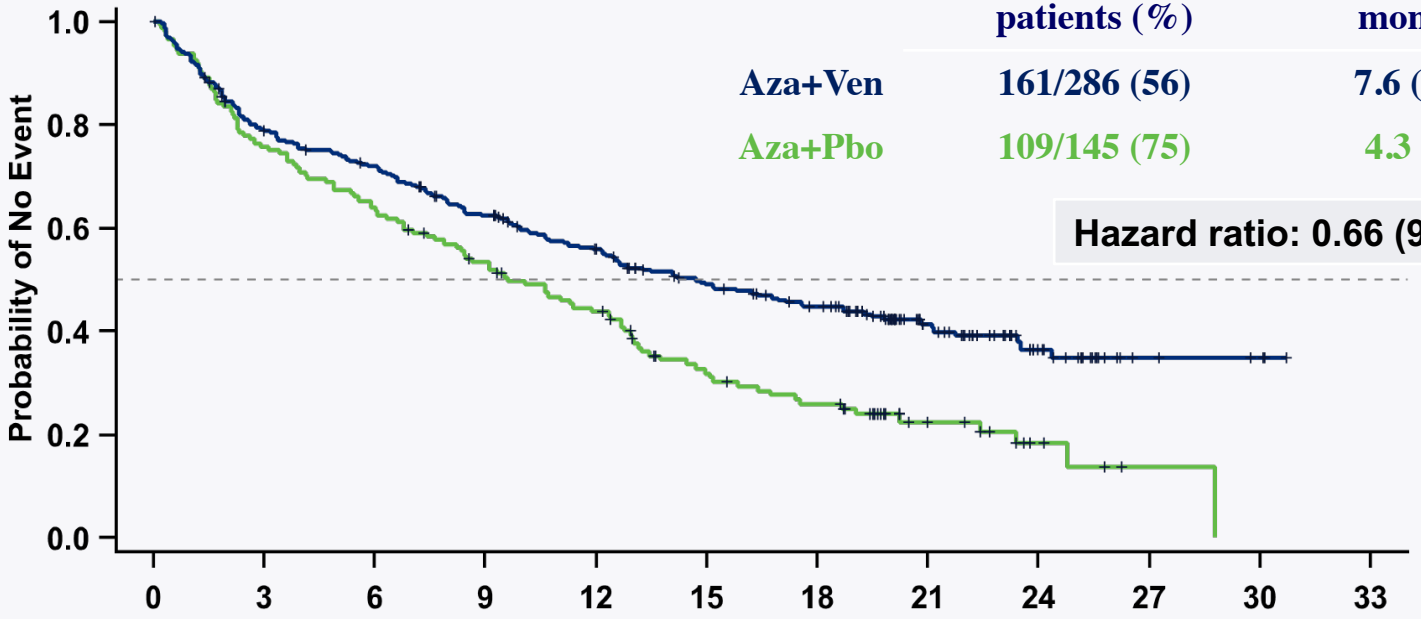
Randomization Stratification Factors	Age (<75 vs. ≥75 years); Cytogenetic risk (intermediate, poor); region
Venetoclax dosing ramp-up	**Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg **Cycle 2** Day 1-28: 400 mg

DiNardo CD et al. EHA 2020. Abstract LB2601; DiNardo CD et al. NEJM 2020

Courtesy of Richard M Stone, MD

VIALE-A: AZA ± VEN in AML — Overall Survival

	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)



Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), *P* <.001

Patients at Risk

Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

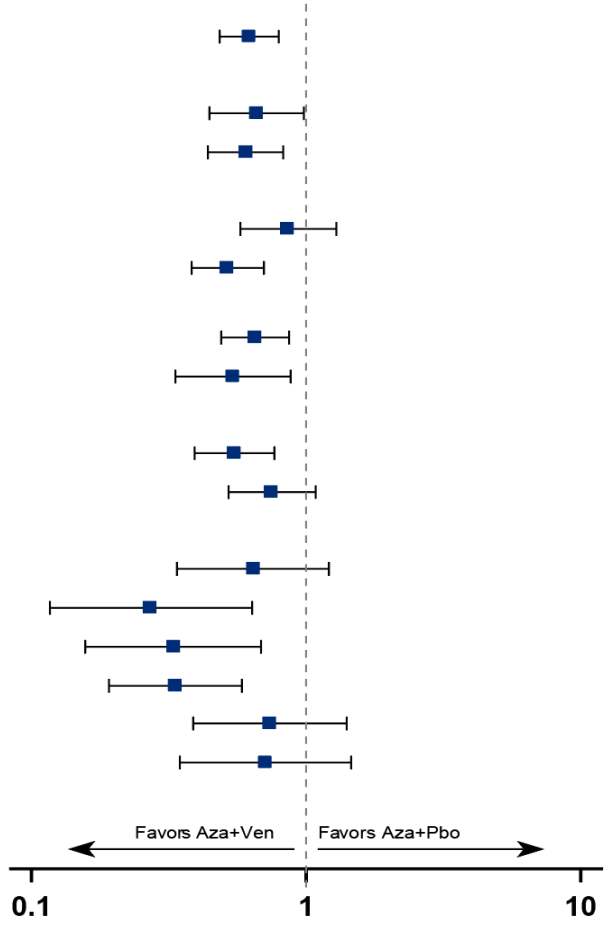
Median follow-up time: 20.5 months (range: <0.1 – 30.7)

DiNardo CD et al. NEJM 2020

Courtesy of Richard M Stone, MD

VIALE-A: AZA ± VEN in AML — Survival by Subgroups

	Aza+Ven n/N(%)	Aza+Pbo n/N(%)	HR [95% CI] Aza+Ven vs. Aza+Pbo
All Subjects	161/286 (56.3)	109/145 (75.2)	0.64 (0.50, 0.82)
Gender			
Female	61/114 (53.5)	41/ 58 (70.7)	0.68 (0.46, 1.02)
Male	100/172 (58.1)	68/ 87 (78.2)	0.62 (0.46, 0.85)
Age (Years)			
< 75	66/112 (58.9)	36/ 58 (62.1)	0.89 (0.59, 1.33)
≥ 75	95/174 (54.6)	73/ 87 (83.9)	0.54 (0.39, 0.73)
Type of AML			
De Novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51, 0.90)
Secondary	41/ 72 (56.9)	29/ 35 (82.9)	0.56 (0.35, 0.91)
Cytogenetic Risk			
Intermediate	84/182 (46.2)	62/ 89 (69.7)	0.57 (0.41, 0.79)
Poor	77/104 (74.0)	47/ 56 (83.9)	0.78 (0.54, 1.12)
Molecular Marker			
FLT3	19/ 29 (65.5)	19/ 22 (86.4)	0.66 (0.35, 1.26)
IDH1	15/ 23 (65.2)	11/ 11 (100.0)	0.28 (0.12, 0.65)
IDH2	15/ 40 (37.5)	14/ 18 (77.8)	0.34 (0.16, 0.71)
IDH1/2	29/ 61 (47.5)	24/ 28 (85.7)	0.34 (0.20, 0.60)
TP53	34/ 38 (89.5)	13/ 14 (92.9)	0.76 (0.40, 1.45)
NPM1	16/ 27 (59.3)	14/ 17 (82.4)	0.73 (0.36, 1.51)

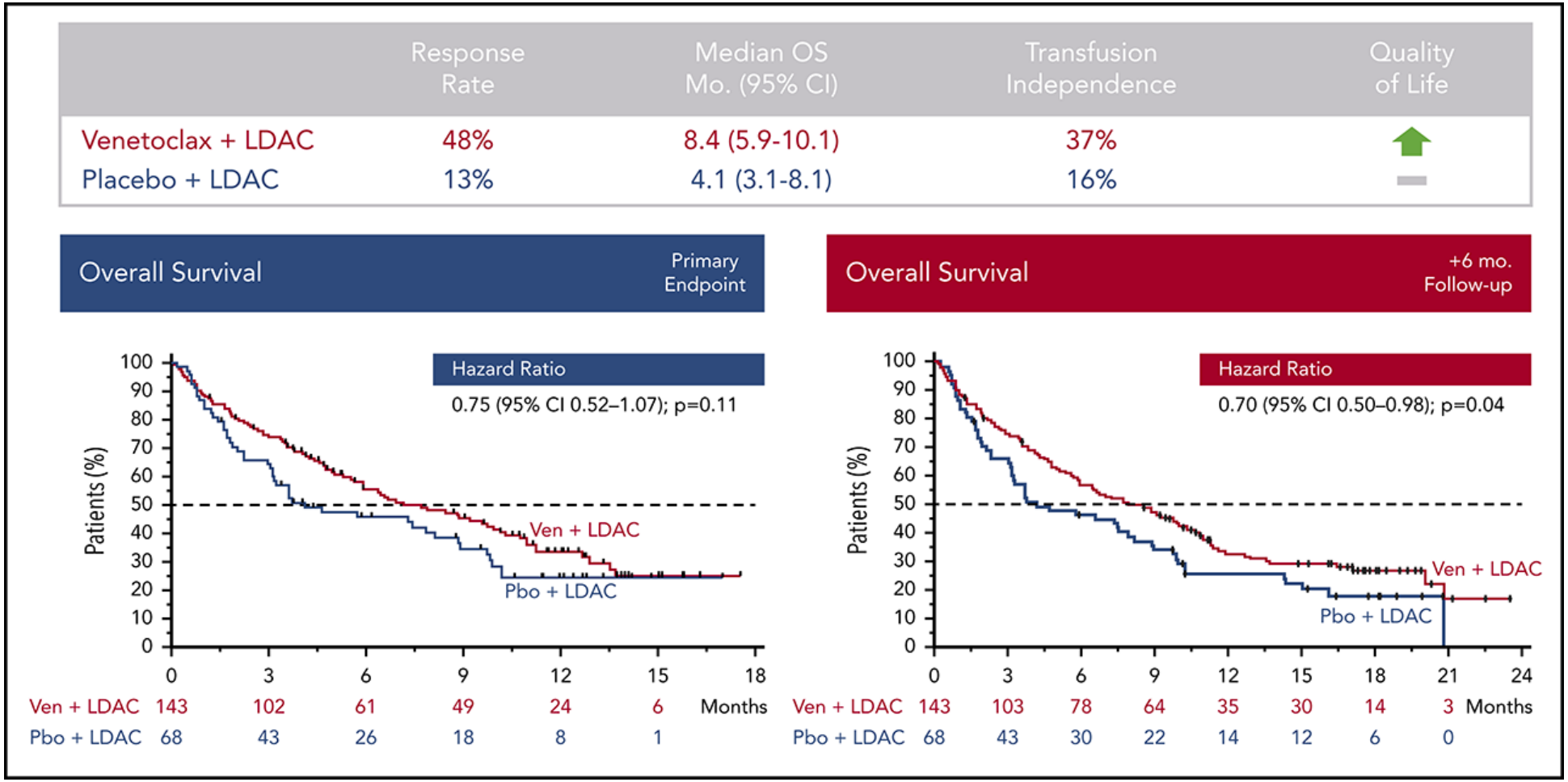


DiNardo CD et al. NEJM 2020; DiNardo CD et al. EHA 2020. Abstract LB2601.

Courtesy of Richard M Stone, MD

VIALE-C: Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy — a phase 3 randomized placebo-controlled trial

	Response Rate	Median OS Mo. (95% CI)	Transfusion Independence	Quality of Life
Venetoclax + LDAC	48%	8.4 (5.9-10.1)	37%	↑
Placebo + LDAC	13%	4.1 (3.1-8.1)	16%	—



Andrew H. Wei, Blood, 2020.

Courtesy of Richard M Stone, MD

VIALE-C trial (Wei et al, EHA, 2020)

Median f/u 17.5 mo* (OS and EFS difference statistically significant)
Note: prior HMA allowed

	Ven (600 mg/d)+ cytarabine 20 mg/^{2}/d d1-10	Cytarabine 20 mg/m^2/d d1-10
n	143	60
CR/CRh	48%	15%
Overall survival (months)	8.4	4.1
Event-free survival (months)	4.9	2.1

*w 6 add'n f/u months, OS diff became significant

Courtesy of Richard M Stone, MD

VIALE-A: DiNardo CD et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020 Aug 13;383(7):617-629.
VIALE-C: Wei AH et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: A Phase III randomized placebo-controlled trial. Blood 2020;135(24):2137-45.

- **Impact on Patient Care and Treatment Algorithm**
  - Azacitidine/venetoclax is the new standard of care for pts >75 years old with untreated AML
    - Decitabine/venetoclax or low dose cytarabine/venetoclax are acceptable alternatives, the latter relevant in countries without access to HMA
  - Responses occurred in all genetic subgroups
    - Particularly effective in IDH mutant AML
  - Toxicity manageable, though myelosuppression requires frequent dose modifications
- **Implications for Future Research**
  - Use in other patient populations (e.g , younger, MDS)
  - Combine ven/HMA in ‘triplets’ with target agents (e.g., FLT3i, IDHi, APR-246, magrolimab, pevonedistat)

Courtesy of Richard M Stone, MD

Venetoclax + Cladribine/LDAC alternating with 5-AZA

Consolidation: Alternating 2 cycles of A and B

Cladribine 5 mg/m^2 on D1-5
AraC 20 mg SQ BID on D1-10
Venetoclax on D1-21

Induction (Cycle 1)

A
Cladribine 5 mg/m^2 on D1-3
AraC 20 mg SQ BID on D1-10
Venetoclax on D1-14*

Consolidation (Cycle 2)

B
5-AZA 75 mg/m^2 on D1-7
Venetoclax on D1-14*

Consolidation (Cycle 3-4)

Venetoclax Dosing (PO Daily)			
Dose Level	Patients on strong CYP3A inhibitor	Patients on moderate CYP3A inhibitor	Patients not on CYP3A inhibitor
-1	50 mg	100 mg	200 mg
1	100 mg	200 mg	400 mg

Patients with MRD Negative remission received only 7 days of venetoclax

Kadia, abs #25, ASH 2020

Courtesy of Richard M Stone, MD

Cladribine/LDAC + Venetoclax in Older AML

Responses

Response / Outcome	N	%	MRD(-)
Evaluable for Response	54	98	
CR	42	78	39 (93)
CRi	8	15	3 (38)
CR + CRi (CRc)	50	93	42 (84)
No Response	4	7	
Died ≤ 4 weeks	1	2	
Died ≤ 8 weeks	2	4	
Median # of cycles given (Range)	2 (1 – 14)		
Median # of cycles to response (Range)	1 (1 – 3)		

Kadia, abs #25, ASH 2020

Courtesy of Richard M Stone, MD

Cladribine/LDAC + Venetoclax in Older AML

Responses by Selected Subgroup

Subgroup	N	CR/CRi (%)
Diploid Karyotype	31	28 (90)
Adverse Karyotype	6	6 (100)
Intermediate Karyotype	15	13 (87)
NPM1 Mutated	17	16 (94)
RAS Mutated	13	12 (92)
IDH2 Mutated	11	11 (100)
IDH1 Mutated	5	5 (100)
TP53 Mutated	4	4 (100)
FLT3 D835	5	4 (80)
FLT3-ITD	3	2 (67)

Kadia, abs #25, ASH 2020

Courtesy of Richard M Stone, MD

Cladribine/LDAC + Venetoclax in Older AML

Survival by Selected Subgroup

Subgroup	Median OS (m)	6-month OS	12-month OS	P-value
Diploid karyotype	NR	90%	80%	
Adverse karyotype	7.8	83%	33%	
Intermediate karyotype	NR	71%	63%	
MRD Negative	NR	92%	83%	**0.003**
MRD Positive	11.8	82%	48%	
Secondary AML	NR	83%	63%	**0.642**
de novo AML	NR	85%	74%	
SCT in CR1	NR	100%	91%	**0.059**
No SCT in CR1	NR	86%	69%	

Kadia, abs #25, ASH 2020

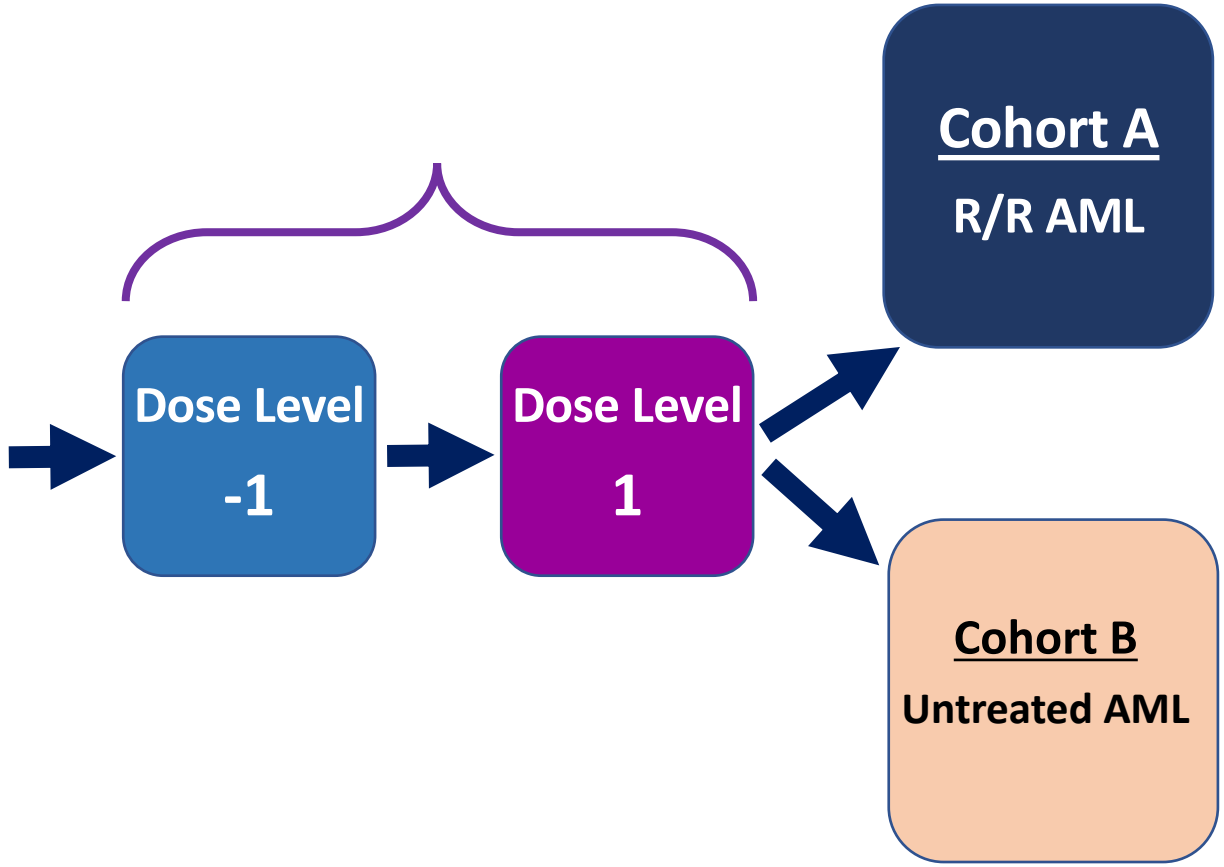
Courtesy of Richard M Stone, MD

CPX351 + Venetoclax in AML (Kadia Abst #28, ASH 2020)

Study Design

Patient Selection

- **Lead in phase:** Patients ≥ 18 years of age with relapsed and/or refractory AML will be eligible.
- **Cohort A (R/R AML):** Patients ≥ 18 years of age with R/R AML .
- **Cohort B (de novo AML):** Patients ≥ **18 to 65** years of age Patients in this cohort must have received no prior therapy for AML.
- Adequate organ function :
  - Bilirubin ≤ 2mg/dL, AST / ALT ≤3 x ULN or ≤5 x ULN if related to leukemic involvement)
  - creatinine ≤ 1.5 x ULN
  - known cardiac ejection fraction of ≥45% within the past 3 months
- ECOG performance status of ≤ 2.
- Prior Venetoclax allowed in R/R cohorts



Courtesy of Richard M Stone, MD

CPX-351 + Venetoclax in AML

Treatment Plan

- **Induction**
  - **CPX-351** IV daily on D1, 3, 5
  - **Venetoclax** PO daily on D2-21
- **Consolidation** (Up to 4 consolidation cycles):
  - **CPX-351** IV daily on D1,3
  - **Venetoclax** PO daily on D2-21

Dose-Escalation Table (Planned 28 day cycle)				
	CPX-351 [mg/m^2]	Venetoclax Dosing (PO on D 2 – 21)		
Dose Level	All Patients	Patients on strong CYP3A inhibitor	Patients on moderate CYP3A inhibitor	Patients not on moderate or strong CYP3A inhibitor
-1	44 [dauno] / 100 [araC] (induction); 29 [dauno] / 65 [araC] (consolidation)	50 mg	150 mg	300 mg
1	44 [dauno] / 100 [araC] (induction); 29 [dauno] / 65 [araC] (consolidation)	100 mg	200 mg	400 mg

Day 2	Day 3	Up	Day 4	Target Dose
100mg	200 mg		400 mg	400 mg

Kadia Abst #28, ASH 2020

Courtesy of Richard M Stone, MD

CPX-351 + Venetoclax in AML (shortened ven schedule)

Treatment Plan

- **Induction**
  - **CPX-351** IV daily on D1, 3, 5
  - **Venetoclax** PO daily on D2-21
- **Consolidation** (Up to 4 consolidation cycles):
  - **CPX-351** IV daily on D1,3
  - **Venetoclax** PO daily on D2-21

Dose-Escalation Table (Planned 28 day cycle)

	CPX-351 [mg/m²]	Venetoclax Dosing (PO)		
Dose Level	**All Patients**	**Patients on strong CYP3A inhibitor**	**Patients on moderate CYP3A inhibitor**	**Patients not on moderate or strong CYP3A inhibitor**
-2	**44** (induction); **22** (consolidation)	50 mg **on D 2 – 8**	150 mg **on D 2 – 8**	300 mg **on D 2 – 8**
-1	**44** (induction); **29** (consolidation)	**50 mg on D 2 – 21**	**150 mg on D 2 – 21**	**300 mg D 2 – 21**
1	**44** (induction); **29** (consolidation)	**100 mg on D 2 – 21**	**200 mg on D 2 – 21**	**400 mg on D 2 – 21**

Day 2	Day 3	Day 4	Target Dose
100mg	200 mg	300 mg	300 mg

Kadia Abst #28, ASH 2020

Courtesy of Richard M Stone, MD

CPX-351 + Venetoclax in AML

Responses

Response / Outcome	N	%
Evaluable for Response	18	90
CR	1	6
CRi	6	33
MLFS	1	6
ORR	8	44
Died ≤ 4 weeks	2	10
Died ≤ 8 weeks	4	20
Median # of cycles given [Range]	1 [1 – 2]	
Median # of cycles to response	1 [1 – 2]	
No. of Responding Pts Receiving SCT	7	88
Median time to count recover (days)	41 [23 – 60]	

Kadia Abst #28, ASH 2020

Courtesy of Richard M Stone, MD

CPX-351 + Venetoclax in AML

Serious Adverse Events

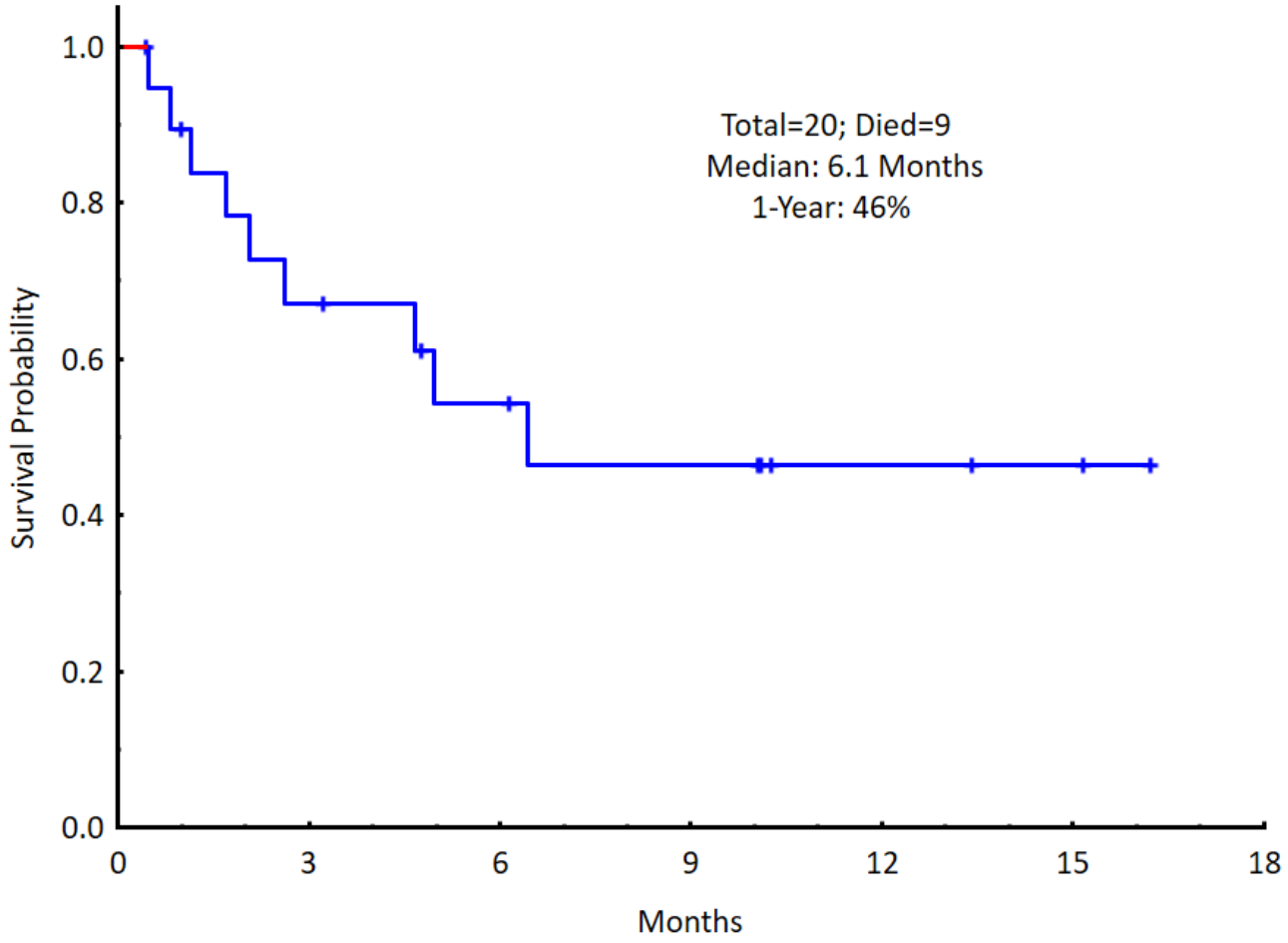
ADVERSE EVENT	TOTAL SAEs	GRADE 3 / 4	GRADE 5
INFECTIONS, NOT OTHERWISE SPECIFIED	7	7	
NAUSEA	4	4	
PNEUMONIA	4	3	1
PROLONGED THROMBOCYTOPENIA	3	3	
PROLONGED NEUTROPENIA	3	3	
VOMITING	2	2	
RASH	2	2	
BONE PAIN	1	1	
HYPOTENSION	1	1	
THRUSH	1	1	
STROKE	1	1	
RESPIRATORY FAILURE	1		1
CHOLECYSTITIS	1	1	
ELECTROLYTE ABNORMALITY	1	1	
SEPSIS	1		1
DIVERTICULITIS	1	1	

Kadia Abst #28, ASH 2020

Courtesy of Richard M Stone, MD

CPX-351 + Venetoclax in AML

Overall Survival

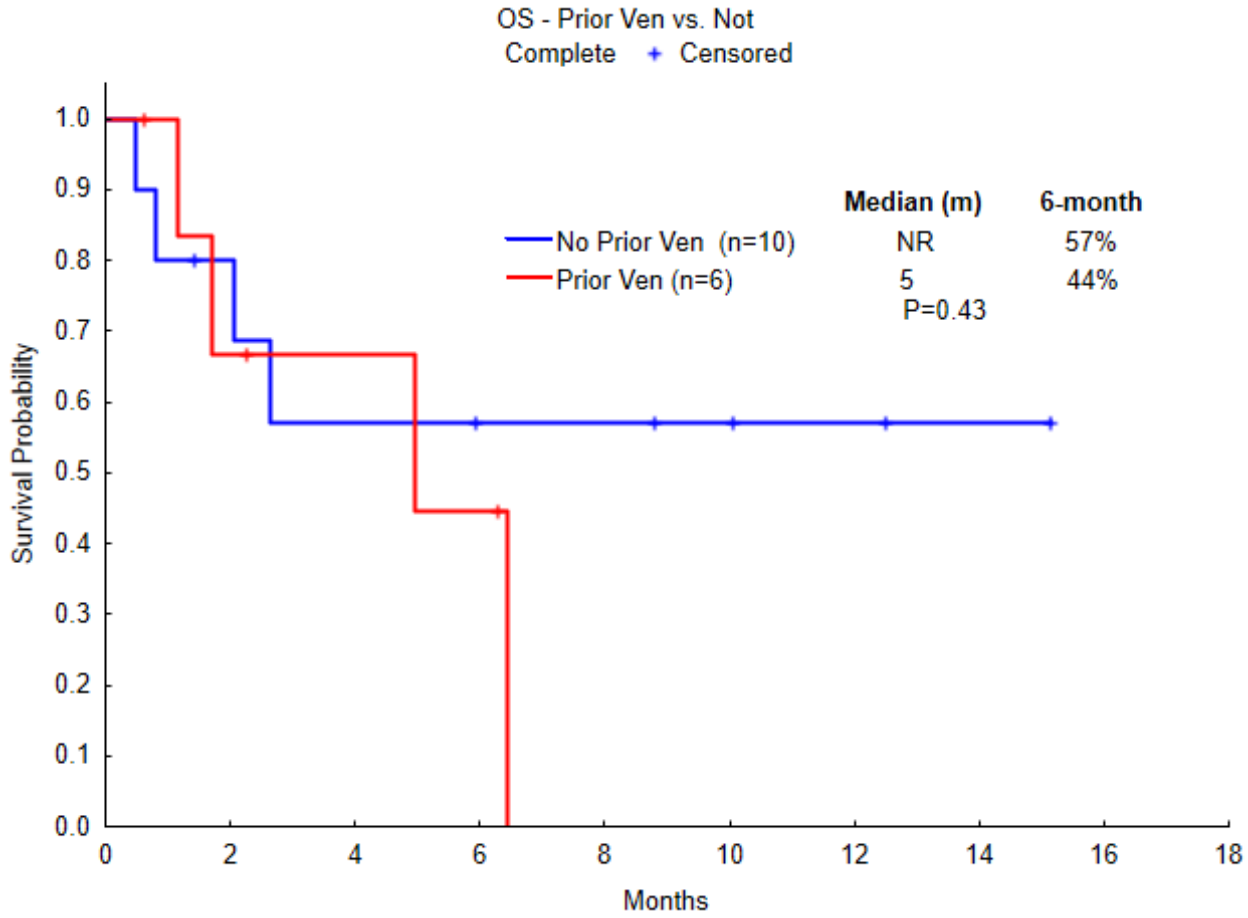


Kadia Abst #28, ASH 2020

Courtesy of Richard M Stone, MD

CPX-351 + Venetoclax in AML

OS by Prior Venetoclax



Kadia Abst #28, ASH 2020

Courtesy of Richard M Stone, MD

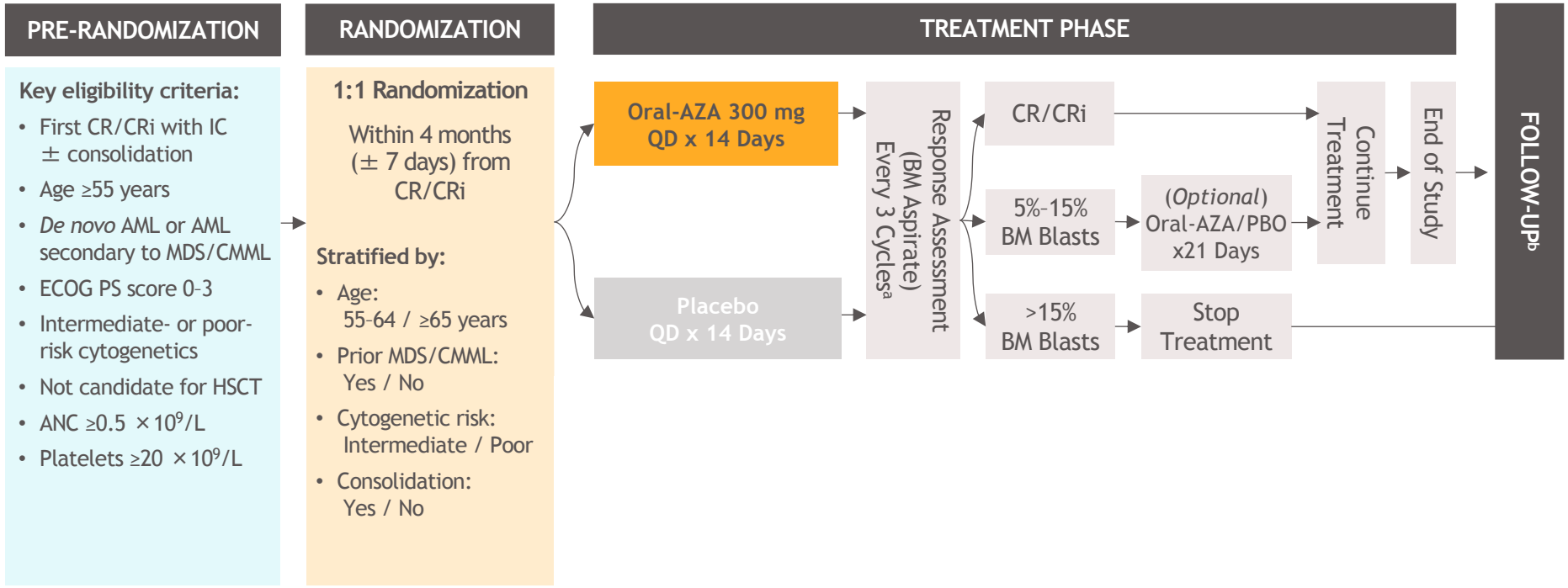
-Kadia TM et al. Phase II Study of Venetoclax Added to Cladribine + Low Dose AraC (LDAC) Alternating with 5-Azacitidine Demonstrates High Rates of Minimal Residual Disease (MRD) Negative Complete Remissions (CR) and Excellent Tolerability in Older Patients with Newly Diagnosed Acute Myeloid Leukemia (AML). ASH 2020; Abstract 25.
-Kadia TM et al. Phase II Study of CPX-351 Plus Venetoclax in Patients with Acute Myeloid Leukemia (AML). ASH 2020; Abstract 28.

- **Impact on Patient Care and Treatment Algorithm**
  - Can safely add venetoclax to low or higher dose chemo
    - See also FLAG-ida/ven (MDA abst #332) and 3+7 (DFCI, abstract 1038)
  - Venetoclax duration with more intensive chemo needs to be shortened
  - Is cladribine/cytarabine a better low dose chemo than HMA alone? It is more toxic
  - Would not use these regimens outside clinical trial
- **Implications for Future Research**
  - Randomized trials of ven/HMA v ven/alternative non-intensive chemo (e.g cladribine/cytarabine) required
  - Response rate with FLAG-IDA/VEN, 3+7/VEN, and CPX/VEN are high but clearly toxic. Randomized trials needed

Courtesy of Richard M Stone, MD

QUAZAR AML-001: Study design and eligibility criteria

International, multicenter, placebo (PBO)-controlled, double-blind, randomized, phase III study of Oral-AZA as maintenance Tx in pts with AML in first remission post-IC



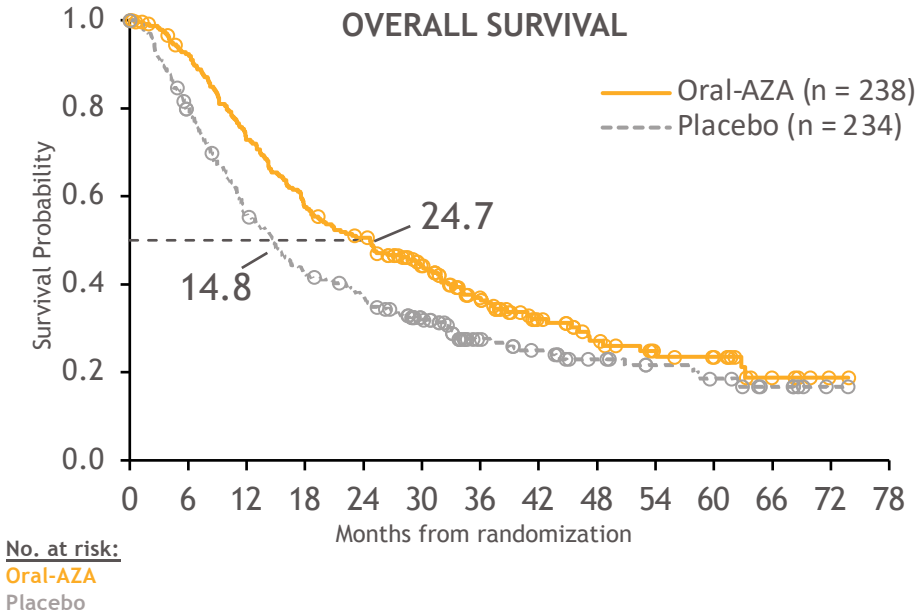
Courtesy of Richard M Stone, MD

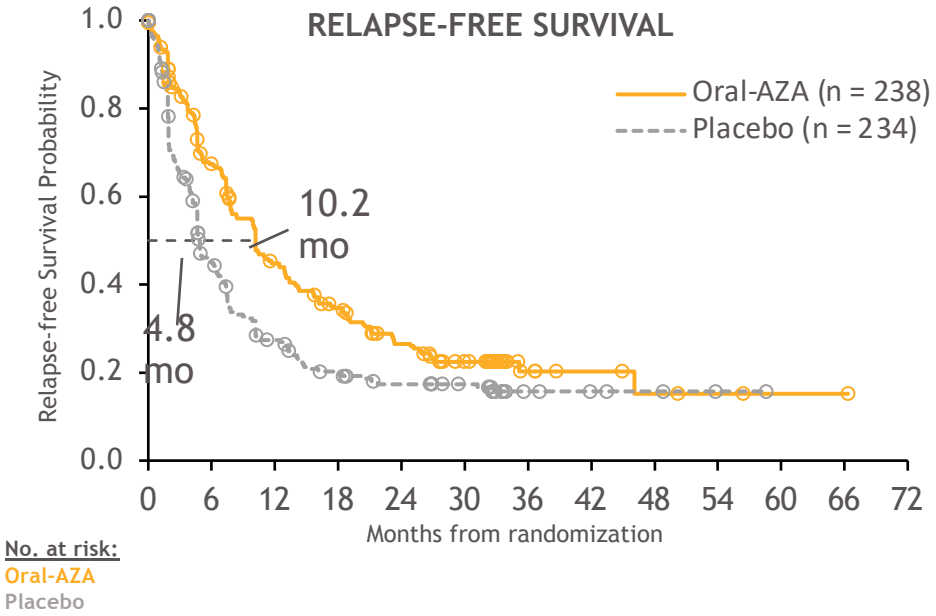
[a]BM aspirates were collected every 3 cycles through cycle 24, at cycle 30 and cycle 36, and as clinically indicated thereafter. BM assessments were also performed as clinically indicated. [b]Patients were followed until death, withdrawal of consent, study termination, or loss to follow-up.

AML, acute myeloid leukemia; ANC, absolute neutrophil count; AZA, azacitidine; BM, bone marrow; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; IC, induction chemotherapy; IWG, International Working Group; MDS, myelodysplastic syndromes; PBO, placebo.

QUAZAR AML-001: Overall and relapse-free survival

- Oral-AZA 300 mg QD was associated with significantly improved overall survival (OS) (*P* = 0.0009) and relapse-free survival (RFS) (*P* = 0.0001) vs. PBO[1]





1. Wei et al. *Blood* 2019;134(Supplement_2):LBA-3.

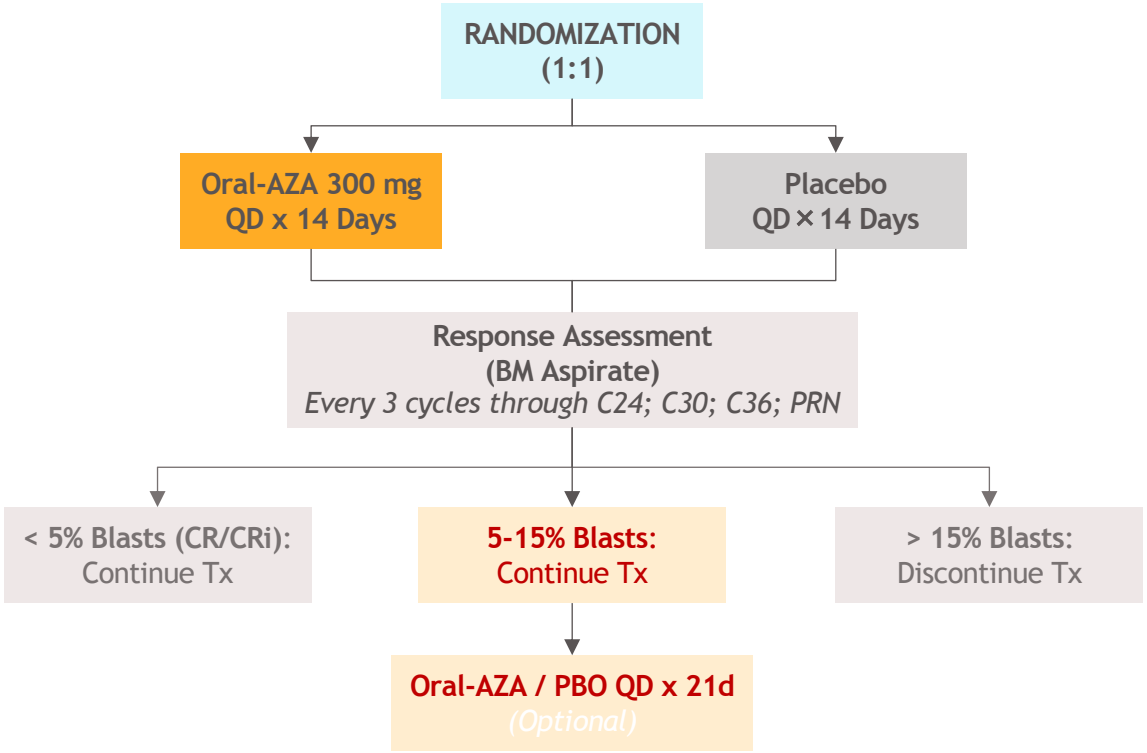
OS was defined as the time from randomization to death by any cause. Kaplan-Meier estimated OS was compared for Oral-AZA *vs.* placebo by stratified log-rank test. HRs and 95%CIs were generated using a stratified Cox proportional hazards model.

AZA, azacitidine; mo, months; No., number; OS, overall survival; PBO, placebo; RFS, relapse-free survival.

Courtesy of Richard M Stone, MD

QUAZAR AML-001: Escalated dosing (Dohner H et al, Abs #111, ASH 2020)

- BM aspirates and PB smears were reviewed centrally to assess CR/CRi status (IWG 2003 criteria[1])
  - Unscheduled BM assessments allowed for pts who exhibited signs of relapse at routine clinic visits (every 2 weeks)
- Pts who had 5–15% blasts in BM or blood could receive study drug for **21 days per cycle** at the investigator's discretion

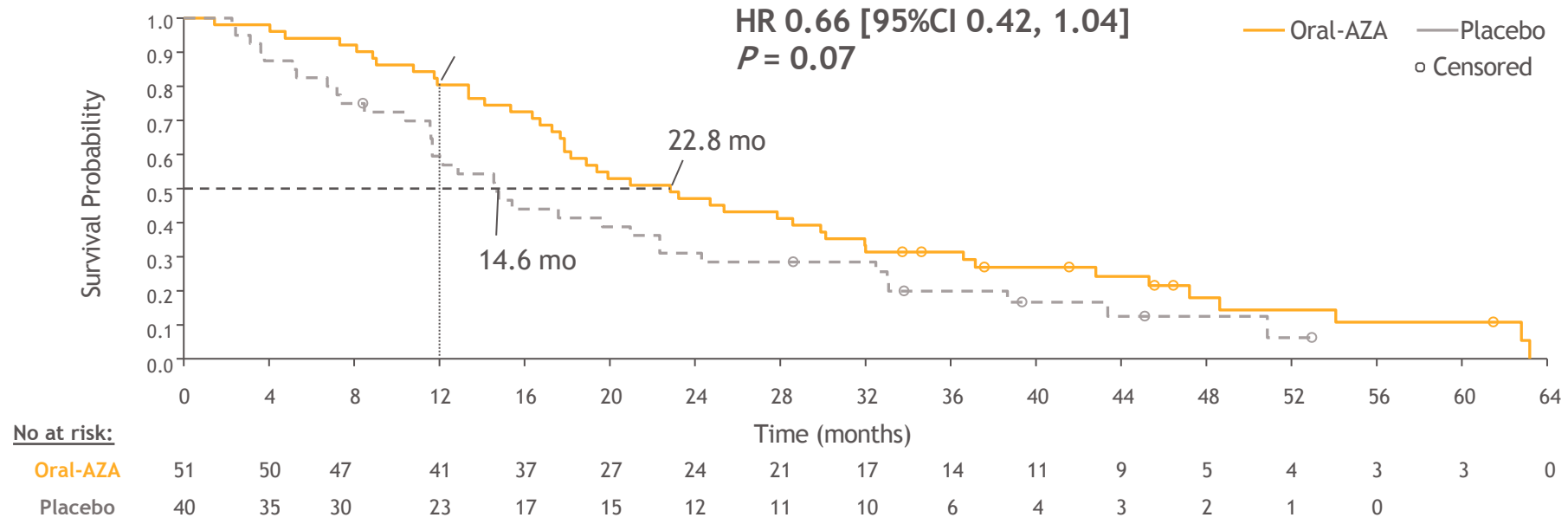


Courtesy of Richard M Stone, MD

1. Cheson et al. *J Clin Oncol*. 2003;21(24):4642-9.

AML, acute myeloid leukemia; AZA, azacitidine; BM, bone marrow; CR, complete remission; CRi, CR with incomplete blood count recovery; IWG, International Working Group; PB, peripheral blood; pts, patients; Tx, treatment.

QUAZAR AML-001: Escalated dosing cohort — Overall survival



Overall survival estimated using Kaplan-Meier methods. The hazard ratio (HR) and 95% confidence intervals comparing Oral-AZA vs. placebo are from a Cox proportional hazards model, and the *P* value is from an unstratified log-rank test.

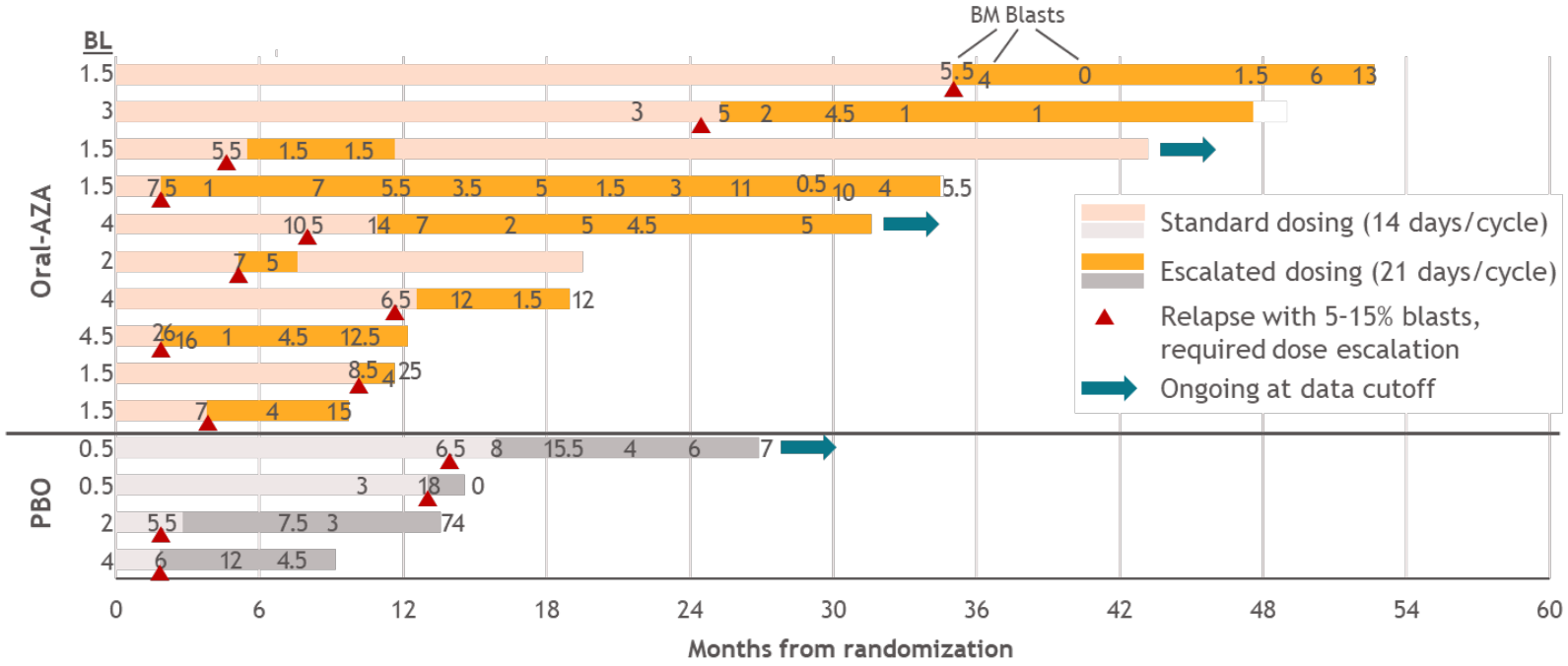
95%CI, 95% confidence interval; AZA, azacitidine; HR, hazard ratio; mo, months; OS, overall survival; No., number.

Dohner H et al, Abs #111, ASH 2020

Courtesy of Richard M Stone, MD

QUAZAR AML-001: Second CR/CRi

- 10/43 (23%) Oral-AZA pts and 4/35 (11%) PBO pts regained CR/CRi (CR2) during dose-escalation[a]
- 6 pts in the Oral-AZA arm became MRD-negative at CR2 (0 in the PBO arm)



[a]Among 78 pts with a centrally confirmed marrow with ≥5% blasts on or before the first day of 21-day dosing.
BM blast percentages are reported at baseline, at the visit nearest to the start of dose-escalation, and while receiving escalated dosing. Data cutoff: 15 July 2019.
AZA, azacitidine; BL, baseline BM, bone marrow; CR, complete remission; CR2, second CR/CRi; CRi, CR with incomplete blood count recovery; MRD, measurable residual disease; PBO, placebo; pts, patients.

Dohner H et al, Abs #111, ASH 2020

Courtesy of Richard M Stone, MD

QUAZAR AML-001: Adverse events with first onset during escalated dosing

Adverse events (all grades) reported during escalated dosing with first onset in ≥10% of patients in either Tx arm

Preferred term	Oral-AZA n = 51	Placebo n = 40
	n (%)	
Febrile neutropenia	12 (24)	1 (3)
Thrombocytopenia	11 (22)	9 (23)
Anemia	11 (22)	8 (20)
Neutropenia	10 (20)	4 (10)
Fatigue	7 (14)	1 (3)
Pyrexia	7 (14)	8 (20)
Diarrhea	6 (12)	3 (8)
Asthenia	6 (12)	0
Hypokalemia	2 (4)	5 (13)

Grade 3-4 adverse events reported during escalated dosing with first onset in ≥5% of patients in either Tx arm

Preferred term	Oral-AZA n = 51	Placebo n = 40
	n (%)	
≥1 grade 3-4 AE	**16 (31)**	**14 (35)**
Febrile neutropenia	12 (24)	1 (3)
Neutropenia	11 (22)	5 (13)
Thrombocytopenia	9 (18)	12 (30)
Anemia	8 (16)	7 (18)
Fatigue	3 (6)	0
Constipation	3 (6)	0
Pneumonia	2 (4)	2 (5)
Sepsis	1 (2)	2 (5)

Adverse events coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 and graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. A patient is counted only once for multiple events within a preferred term/system organ class.

AE, adverse event; AZA, azacitidine; Tx, treatment.

Dohner H et al, Abs #111, ASH 2020

Courtesy of Richard M Stone, MD

– Wei AH et al. The QUAZAR AML-001 Maintenance Trial: Results of a Phase III International, Randomized, Double-Blind, Placebo-Controlled Study of CC-486 (Oral Formulation of Azacitidine) in Patients with Acute Myeloid Leukemia (AML) in First Remission. Proc ASH 2019; Abstract LBA-3.
– Dohner H et al. Escalated Dosing Schedules of CC-486 Are Effective and Well Tolerated for Patients Experiencing First Acute Myeloid Leukemia (AML) Relapse: Results from the Phase III QUAZAR AML-001 Maintenance Trial. ASH 2020; Abstract 111.

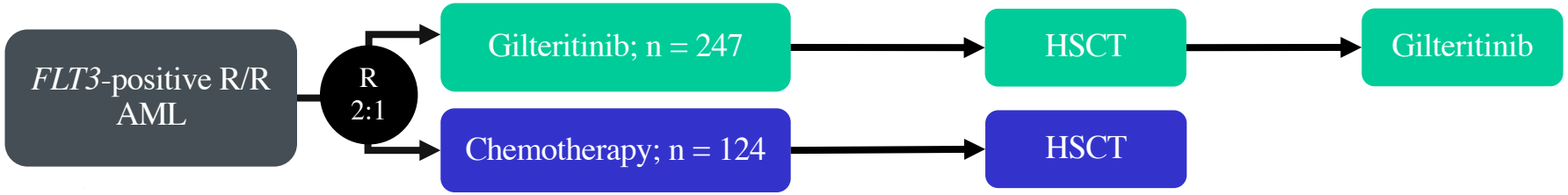
Impact on Patient Care and Treatment Algorithm

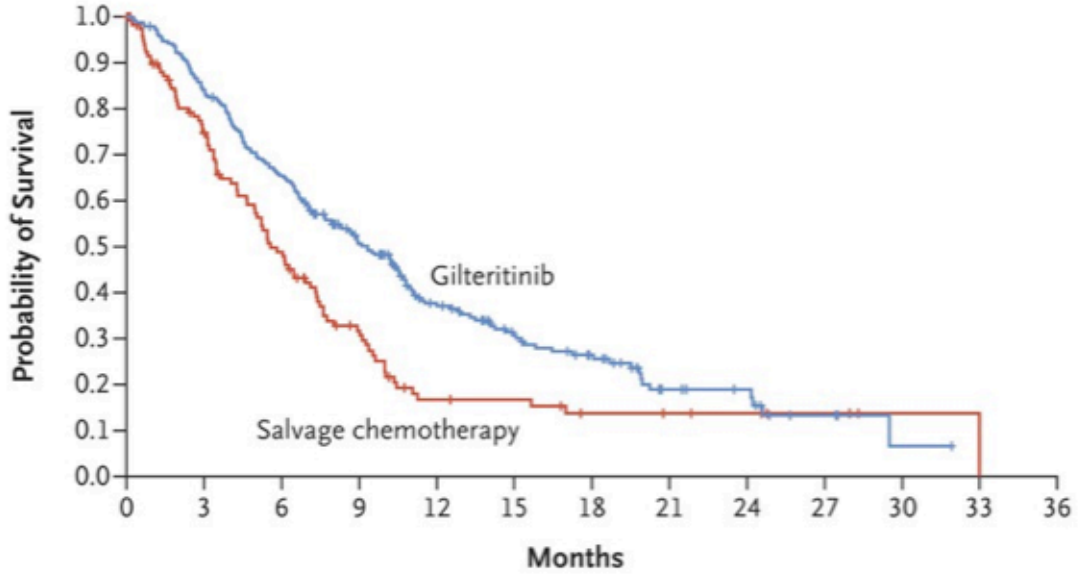
- CC-486 (oral azacitidine) new option for maintenance rx in AML
  In pts >55 yo who ach CR with stnd chemo and rec'd 0-2 consol cycles
- This is not the same as IV or sc azacitidine and should not yet be used in MDS or with ven as primary therapy in older unfit adults
- Toxicity manageable, though myelosuppression requires dose mods
- Activity in early relapse

- **Implications for Future Research**
  - Can oral aza replace consolidation chemo in older AML?
  - Need to define broader use of oral aza in other settings (? Combine with ven?, early relapse, MDS)

Courtesy of Richard M Stone, MD

Gilteritinib: Phase 3 ADMIRAL Trial





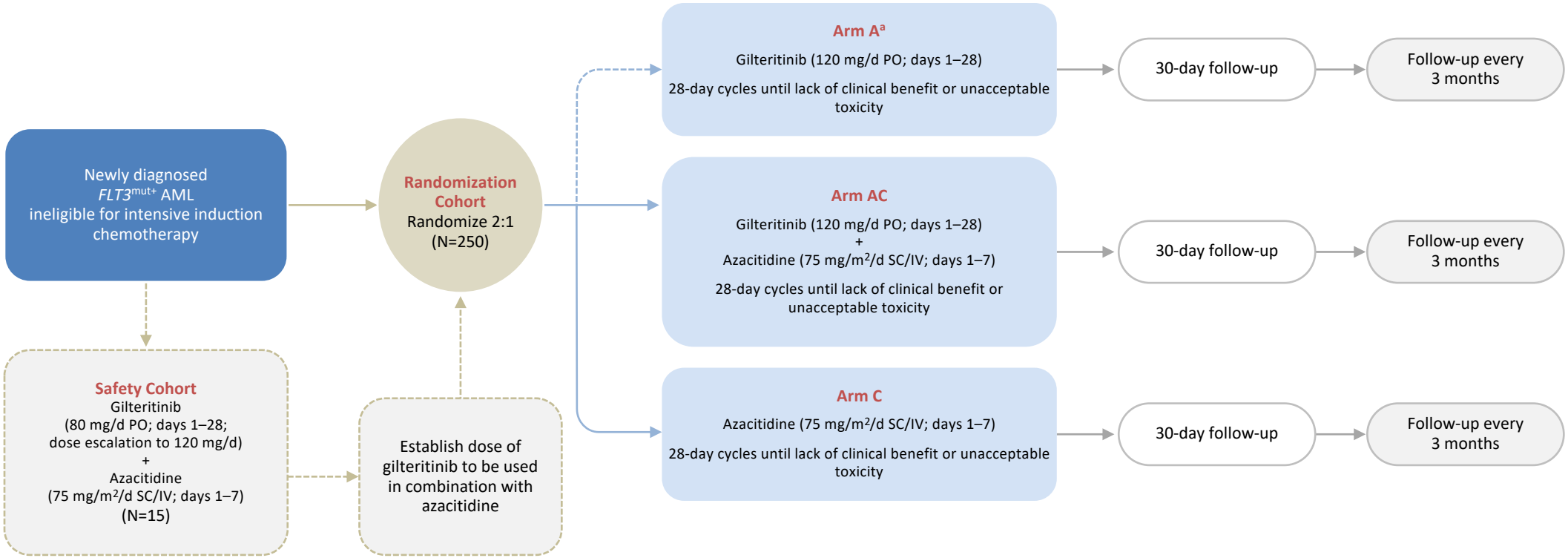
	Median Overall Survival (95% CI)
	mo
Gilteritinib	9.3 (7.7–10.7)
Salvage Chemotherapy	5.6 (4.7–7.3)

Hazard ratio for death, 0.64 (95% CI, 0.49–0.83)
P<0.001

Perl, A et al , NEJM, 2019

Courtesy of Richard M Stone, MD

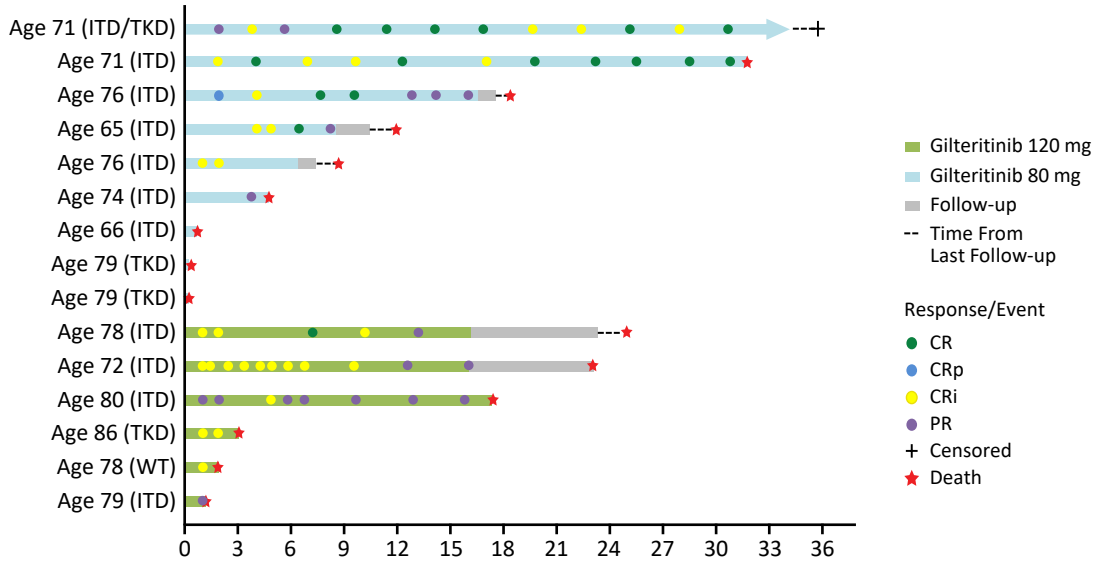
LACEWING Study Design (Wang E, et al, ASH #27, 2020)



[a]Protocol versions 6.0 and earlier included a 1:1:1 randomization ratio to receive Arm A (gilteritinib monotherapy), AC (gilteritinib + azacitidine), or C (azacitidine monotherapy). Randomization to Arm A was removed in protocol version 7.0. Patients previously randomized to Arm A should continue following treatment and assessments as outlined in the protocol.
AML, acute myeloid leukemia; *FLT3*$^{mut+}$, FMS-like tyrosine kinase 3 mutation-positive; IV, intravenously; PO, orally; SC, subcutaneously.

Courtesy of Richard M Stone, MD

Type and Duration of Response of Gilteritinib in Combination With AZA and End of Treatment Reasons *Safety Cohort (N=15)*



- CR and CRc were achieved by 33% (n=5/15) and 67% (n=10/15) of patients in the Safety Cohort, respectively.
- Among the 10 patients with CRc, the median (95% CI) duration of remission was 10.4 (0.95–NR) months, with 5 patients being censored

AZA, azacitidine; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; ITD, internal tandem duplication; NR, not reached; PR, partial remission; TKD, tyrosine kinase domain; WT, wild type.

Wang E, et al, ASH #27, 2020

Summary of Treatment-Emergent Adverse Events and Deaths
Safety Cohort (N=15)

Incidence of TEAEs, n (%)	Safety Cohort (N=15)
Any TEAE	15 (100)
Serious TEAE	14 (93.3)
Grade ≥3 TEAE	15 (100)
TEAE leading to treatment withdrawal	6 (40.0)
Drug-related TEAEs	12 (80.0)
Serious TEAE	7 (46.7)
Leading to treatment withdrawal	0 (0)
Leading to death	0 (0)
Any Death	14 (93.3)
TEAE leading to death	9 (60.0)
Occurred >30 days after last dose of study drug	5 (33.3)

TEAE, treatment-emergent adverse event.

40% of patients experienced a TEAE that led to treatment withdrawal; however, none of these were judged to be drug-related

Wang E, et al, ASH #27, 2020

Courtesy of Richard M Stone, MD

– Perl AE et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. N Engl J Med. 2019 Oct 31;381(18):1728-1740.

– Wang ES et al. Phase 3, Multicenter, Open-Label Study of Gilteritinib, Gilteritinib Plus Azacitidine, or Azacitidine Alone in Newly Diagnosed FLT3 Mutated (FLT3mut+) Acute Myeloid Leukemia (AML) Patients Ineligible for Intensive Induction Chemotherapy. ASH 2020; Abstract 27.

- **Impact on Patient Care and Treatment Algorithm**
  - Gilteritinib is a reasonable option for R/R FLT3 mut AML (better than chemo)
  - But Gilteritinib alone does not lead to a high rate of good outcomes in R/R AML.
  - In upfront unfit FLT3 mutant AML: gilt +aza is safe to combine but no results yet for aza v aza/gilt (gilt alone dropped)
- **Implications for Future Research**
  - Need to develop gilteritinb plus other drugs in R/R FLT mut AML
    - Understand mechanism of relapse
  - Major question in the field; How to treat chemo unfit newly diagnosed mut FLT3 AML: gilteritinib+aza or gilt+ven (Daver, #333) vs new SOC: aza/ven
  - Major interest in the ‘triplet’: gilt/aza/ven

Courtesy of Richard M Stone, MD

Summary of studies involving IDH inhib c/w aza/ven in IDH mut ds

- **Isocitrate dehydrogenase 1/2 (*IDH1/2*) mutations** are found in 15-20% of patients with newly diagnosed (ND) acute myeloid leukemia (AML)[1,2]
- Additional detail regarding the depth and duration of response with the various active single and combination therapies for *IDH1/2*-mutated (IDH1/2^{mut}) AML are desired

Published response rates in treatment-naive *IDH1/2*-mutated (IDH1/2^{mut}) AML in patients *ineligible for intensive chemotherapy*:[3-8]

Azacitidine	Venetoclax	Enasidenib	Ivosidenib	CR+CRi
✓				10.7%
		✓		21.0%
			✓	48.5%
✓	✓			78.5%
✓		✓		53.0%
✓			✓	69.6%
✓	✓		✓	75.0%

1. Patel JP, et al. *N Engl J Med*. 2012;366(12):1079-1089. 2. Wang J, et al. *Blood.* 2016;128(22):5058-5058. 3. Pollyea DA, et al. *Blood* 2020; 136 (suppl 1; abstr 461): 5–7. 4. Roboz GJ, et al. *Blood*. 2020;135(7):463-471. 5. DiNardo CD, et al. J *Clin Oncol.* 2020:JCO2001632. **6. Lachowiez CA, et al. *J Clin Oncol* 2020 (suppl; abstr 7500)*.** 7. Pollyea DA, et al. *Leukemia.* 2019;33(11):2575-2584. 8. DiNardo CD, et al. *J Clin Oncol*. 2020 (suppl; abstr 7501)

*Describes ivo/ven and ivo/ven aza combos

Courtesy of Richard M Stone, MD

AG-221-AML-005: RESPONSE

- ORR and CR rate were both significantly higher with ENA + AZA *vs.* AZA Only

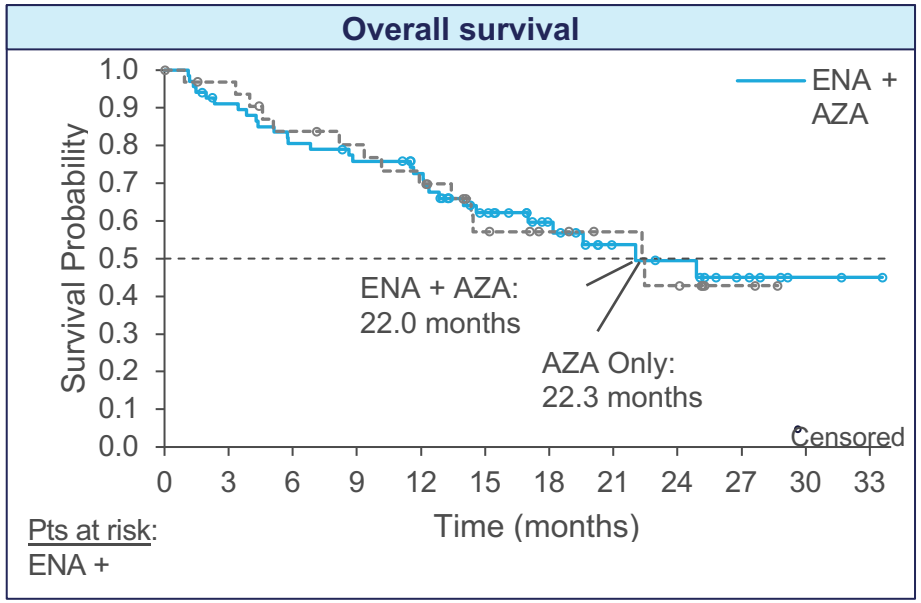
	ENA + AZA (n=68)		AZA Only (n=33)
Overall response (CR, CRi/CRp, PR, MLFS), n (%)	**48 (71)**		**14 (42)**
[ORR 95%CI]	[58, 81]		[26, 61]
***P* value**		**0.0064**	
CR, n (%)	**36 (53)**		**4 (12)**
[CR rate 95%CI]	[41, 65]		[3, 28]
***P* value**		**0.0001**	
CRi/CRp, n (%)	7 (10)		4 (12)
PR, n (%)	3 (4)		4 (12)
MLFS, n (%)	2 (3)		2 (6)
Stable disease, n (%)	13 (19)		13 (39)
Disease progression, n (%)	2 (3)		1 (3)
Not evaluable / Missing, n (%)	5 (7)		5 (15)
Time to first response, months, median (range)	1.9 (0.7–9.0)		2.0 (0.8–5.8)
Time to CR, months, median (range)	5.5 (0.7–19.5)		3.7 (3.0–4.1)
Duration of response, months, median [95%CI]	24.1 [11.1, NR]		12.1 [2.8, 14.6]

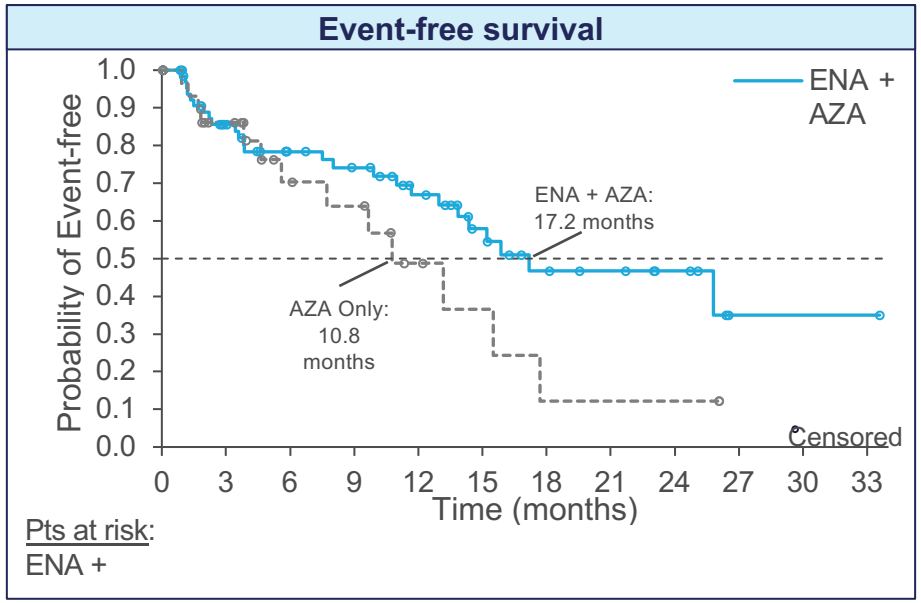
Data cutoff: August 19, 2019.
95%CI, 95% confidence interval; AZA, azacitidine; CR, complete remission; CRi/CRp, CR with incomplete hematologic or platelet recovery; ENA, enasidenib; MLFS, morphologic leukemia-free state; NR, not reached; ORR, overall response rate; PR, partial remission.

Courtesy of Richard M Stone, MD

AG-221-AML-005: SURVIVAL

- Median follow-up was 14 months in both treatment arms
- Median OS in the ENA + AZA group was 22.0 months, and in the AZA Only group was 22.3 months (HR 0.99 [95%CI 0.52, 1.87], *P*=0.9686)
  - Among pts in the ENA + AZA arm who achieved CR, median OS was not reached and estimated 1-year survival was over 90%
- Median EFS was 17.2 months in the ENA + AZA group, vs. 10.8 months in the AZA Only group (HR 0.59 [95%CI 0.30, 1.17], *P*=0.1278)
- In the AZA Only arm, 7 patients (21%) received subsequent treatment with enasidenib monotherapy





Data cutoff: August 19, 2019
EFS: time from randomization to AML relapse, disease progression (IWG AML 2003 criteria), or death from any cause, whichever occurred first.

Courtesy of Richard M Stone, MD

TABLE 3. Hematologic Response, Time to Response, and Response Duration (N = 23)

Response Category	Response
CR + CRh,[a] No. (%) [95% CI]	16 (69.6) [47.1 to 86.8]
Median time to CR/CRh, months (range)	2.8 (0.8-11.5)
Median duration of CR/CRh, months [95% CI]	NE [12.2 to NE]
CR, No. (%) [95% CI]	14 (60.9) [38.5 to 80.3]
Median time to CR, months (range)	3.7 (0.8-15.7)
Median duration of CR, months [95% CI]	NE [9.3 to NE]
CRh,[a] No. (%)	2 (8.7)
ORR,[b] No. (%) [95% CI]	18 (78.3) [56.3 to 92.5]
Median time to response, months (range)	1.8 (0.7-3.8)
Median duration of response, months [95% CI]	NE [10.3 to NE]
Best response,[c] No. (%)	
CR	14 (60.9)
CRi/CRp	2 (8.7)
MLFS	2 (8.7)
SD	4 (17.4)
NA	1 (4.3)

Abbreviations: CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; NA, not assessed; NE, not estimable; PR, partial response; ORR, objective response rate.

[a]CRh derived by sponsor.

[b]ORR comprises CR + CRi + CRp + PR + MLFS.

[c]Modified International Working Group criteria.

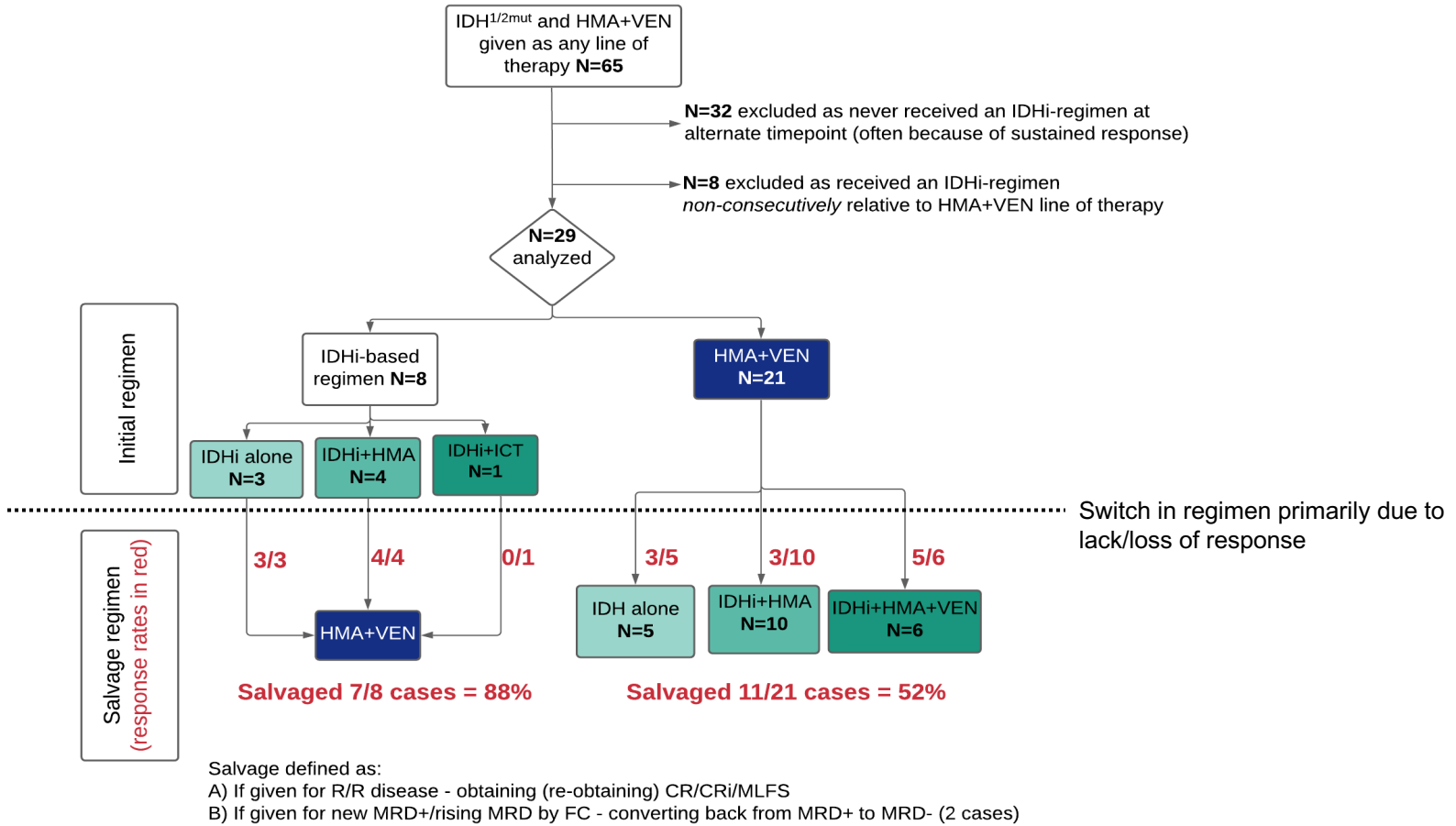
Aza/ivo combo in mutant IDH1 AML

TABLE 3. Hematologic Response, Time to Response, and Response Duration (N = 23)

Published in: Courtney D. DiNardo; Anthony S. Stein; Eytan M. Stein; Amir T. Fathi; Olga Frankfurt; Andre C. Schuh; Hartmut Döhner; Giovanni Martinelli; Prapti A. Patel; Emmanuel Raffoux; Peter Tan; Amer M. Zeidan; Stéphane de Botton; Hagop M. Kantarjian; Richard M. Stone; Mark G. Frattini; Frederik Lersch; Jing Gong; Diego A. Gianolio; Vickie Zhang; Aleksandra Franovic; Bin Fan; Meredith Goldwasser; Scott Daigle; Sung Choe; Bin Wu; Thomas Winkler; Paresh Vyas; *Journal of Clinical Oncology* Ahead of Print
DOI: 10.1200/JCO.20.01632

Courtesy of Richard M Stone, MD

Within-patient salvage rates when switching between HMA+VEN IDHi-based regimens



Hammond, D et al ASH abst 590, 2020

Courtesy of Richard M Stone, MD

3+7 + IDH inhib (Stein et al, Blood, 2020)

Phase I trial: No safety signal

	Chemo+ ivosidenib (500 mg/d for mut IDH1)	Chemo + enasidenib (100 mg/d for mutant IDH2)
n	60	91
CR/CRh	55%	47%
IDH mut clearance in responders	39%	23%
Flow MRD neg in responders	80%	67%

Courtesy of Richard M Stone, MD

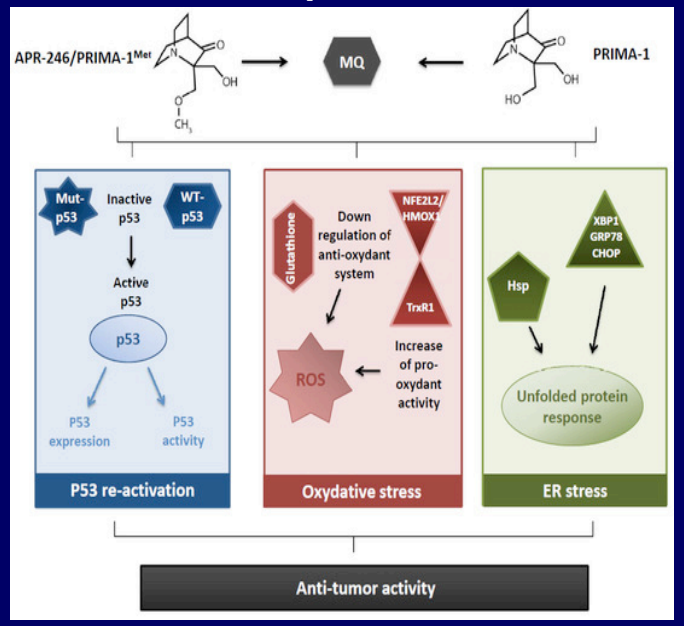
— 4.1 – Stein EM et al. Ivosidenib or enasidenib combined with intensive chemotherapy in patients with newly diagnosed AML: a phase 1 study. Blood. 2020 Sep 5: Epub ahead of print.
4.2 – DiNardo CD et al. Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination With Azacitidine for Newly Diagnosed Acute Myeloid Leukemia. J Clin Oncol. 2020 Oct 29: Epub ahead of print.
4.3 – Lachoweiz CA et al. Phase Ib/II study of the IDH1-mutant inhibitor ivosidenib with the Bcl-2 inhibitor venetoclax ± azacitidine in IDH1-mutated hematologic malignancies. ASCO 2020;Abstract 7500.
DiNardo C et al. EHA 2020; Abstract S143. Oral
4.4 – DiNardo CD et al. Effect of enasidenib plus azacitidine on complete remission and overall response versus azacitidine monotherapy in mutant-IDH2 newly diagnosed AML. ASCO 2020;Abstract 7501.

- **Impact on Patient Care and Treatment Algorithm**
  - **IDH inhibitor combinations are being intensively studied**
  - **In fit adults ivo or ena can be combined with chemo**
  - **Ivo+ aza safe and has activity: are there pts for whom it is 'easier' yet reasonably effective in pts who are not good candidate for aza/ven**
    - **Ivo or ena +aza > response rate than ivo or ena alone: superiority re survival unclear**
- **Implications for Future Research**
  - **3+7+/- IDH inhibitor trial ongoing (HOVON and others) but requires large net since only 20% of AML pts will have IDH 1 or IDH2 mutations**
  - **Major question: Is there a role for IDH inhibitors alone in newly diagnosed unfit pts given robust activity of aza/ven in that subset**
    - **Development of ivo/ven doublet and 'triplet': aza/ven/ivo or ena of major interest**
    - **?Give aza/ven first, save ivo for relapse**

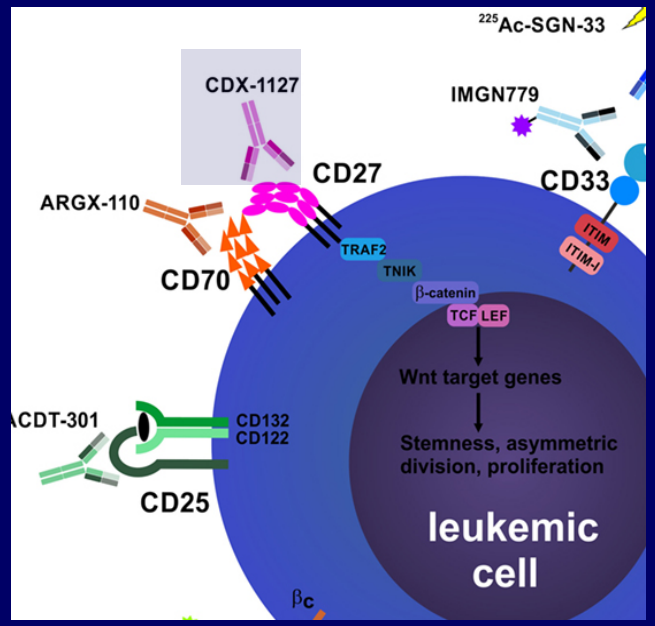
Courtesy of Richard M Stone, MD

AML: Novel Promising Strategies

APR-246 for p53 mutant AML

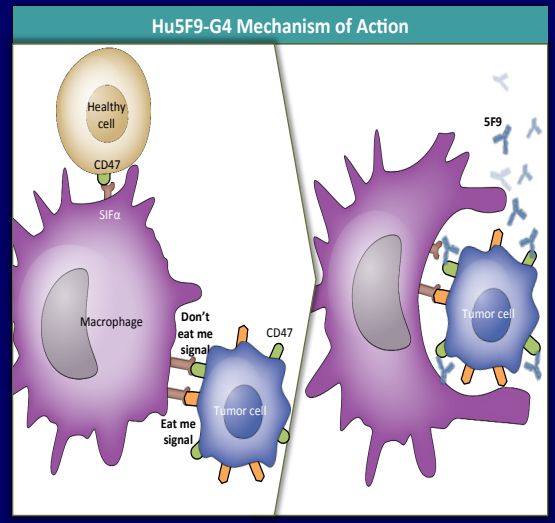


Anti-CD70 Ab



Anti-CD47 antibody (5F9)

macrophage phagocytosis



Schurch CM. *Front Oncol*. 2018;8:152.

Courtesy of Richard M Stone, MD

Acute Myeloid Leukemia: Conclusions

- Mutations/Cytogenetics/Host factors
- Still don't know how to use MRD
- Recent Approvals
  - Midostaurin (+ chemo in *FLT3* mutant upfront)
  - Gilteritinib (single agent R/R *FLT3* mutant)
  - Enasidenib/(ivosidenib) (R/R *IDH2 (1)* mutant)
    - Ivo recently approved for upfront use
  - Gemtuzumab (+chemo in CD33+ upfront)
  - CPX-351 (upfront secondary)
  - Venetoclax +low dose chemo (upfront, unfit)
  - Glasdegib + low dose cytarabine (upfront, unfit)
  - Oral aza (maint, older)
- Lots of new combos on the way, esp: aza/ven+/- targeted rx and ven+intensive chemo

Courtesy of Richard M Stone, MD

Acknowledgements

– Slide senders
  - Courtney DiNardo, MD
  - Tapan Kadia, MD
  - Eunice Wang, MD
  - Hartmut Dohner , MD

Courtesy of Richard M Stone, MD

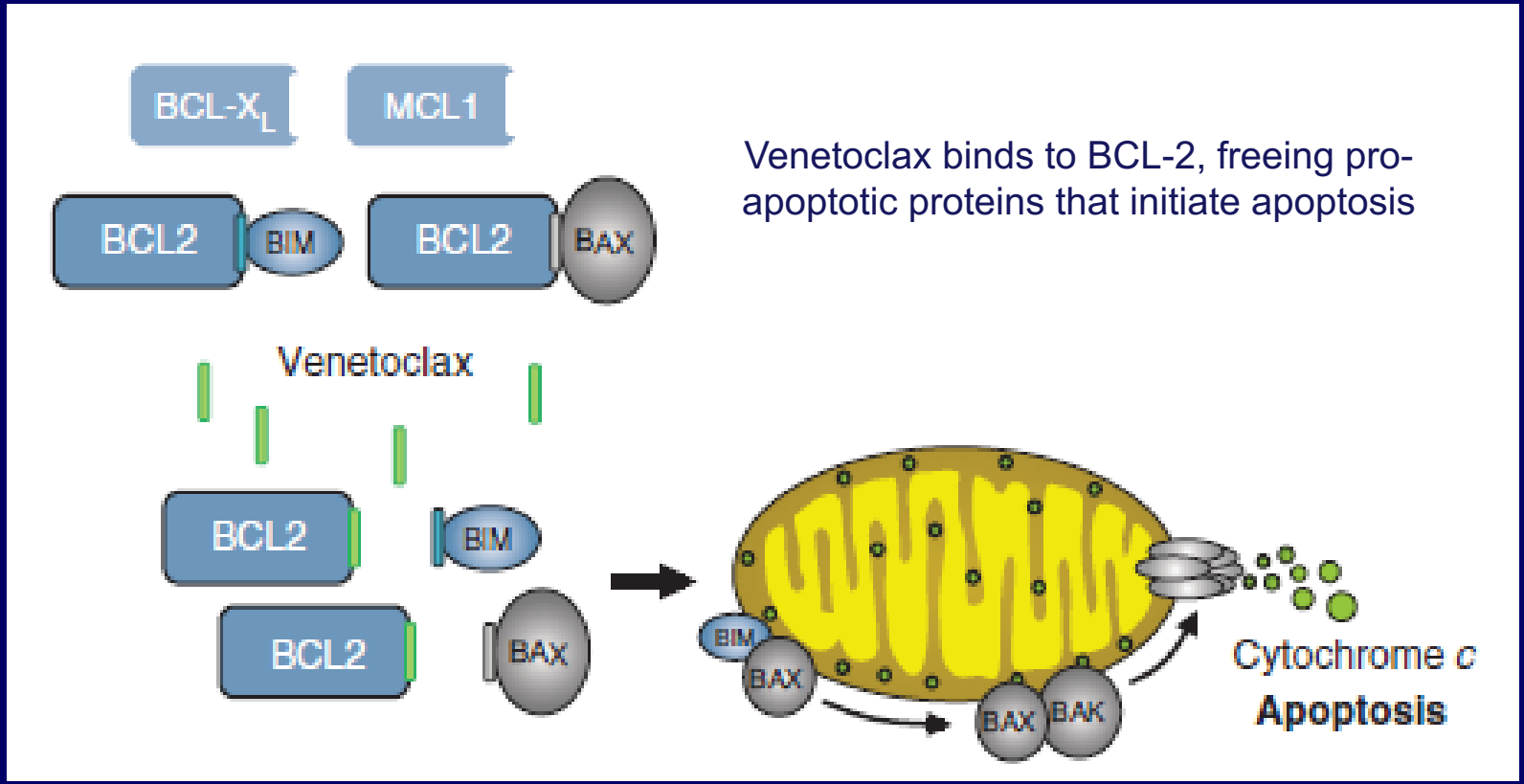
Appendix

Back-up Slides for Live Webinar

Courtesy of Richard M Stone, MD

Venetoclax: BCL-2 Selective Inhibitor

BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins

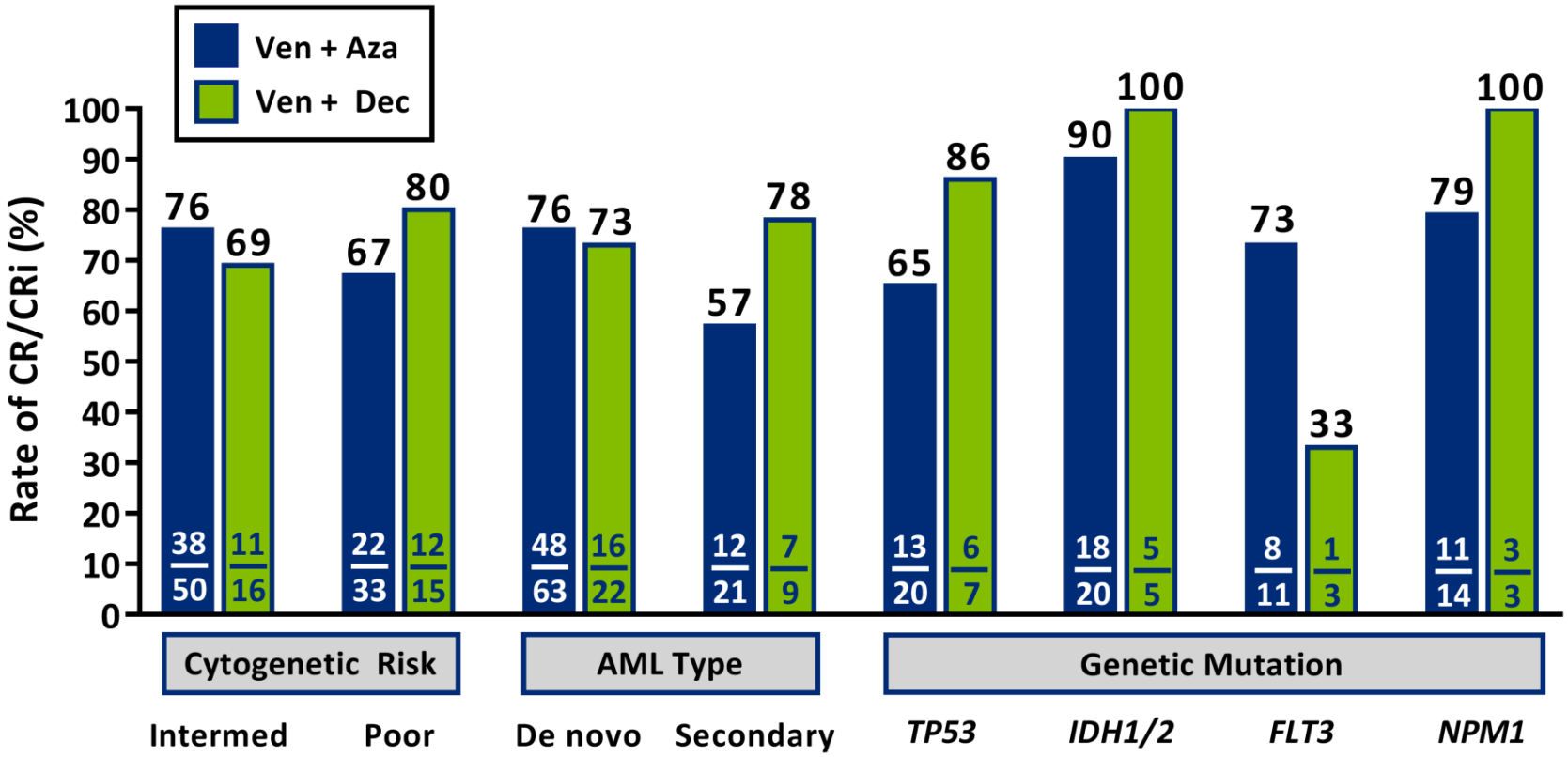


Venetoclax binds to BCL-2, freeing pro-apoptotic proteins that initiate apoptosis

Courtesy of Richard M Stone, MD

Konopleva M, et al. *Cancer Discov*. 2016. Epub ahead of print. Lin T, et al. ASCO 2016. Abstract 7007.

Response Rates of CR/CRi by Patient Subgroups



Venetoclax with HMAs induces rapid, deep, and durable responses in older patients with AML | ASH 2018

Pollyea D, et al, ASH 2018; Dinardo C, Blood, 2019

Courtesy of Richard M Stone, MD

Venetoclax Dose Adjustments

Antifungal	Package Insert Recommendation (Ven mg/D)	MDACC Dose Adjustment (Ven mg/D)
Posaconazole	70	50
Voriconazole	100	100
Isavuconazole, fluconazole	200	200
Caspofungin, echinocandins	400	400

Courtesy of Richard M Stone, MD

Cladribine/LDAC + Venetoclax in Older AML (Kadia, abs 25, ASH 2020)

Inclusion Criteria

- **Untreated AML**
  - Age **≥ 60 yrs**
  - Age < 60 if unsuitable for standard induction
  - Isolated dose of AraC / ATRA / hydrea allowed
- **Adequate organ function**
  - Bili < 2; Creat < 1.5x ULN
- **ECOG ≤ 2**
- **Negative pregnancy test**

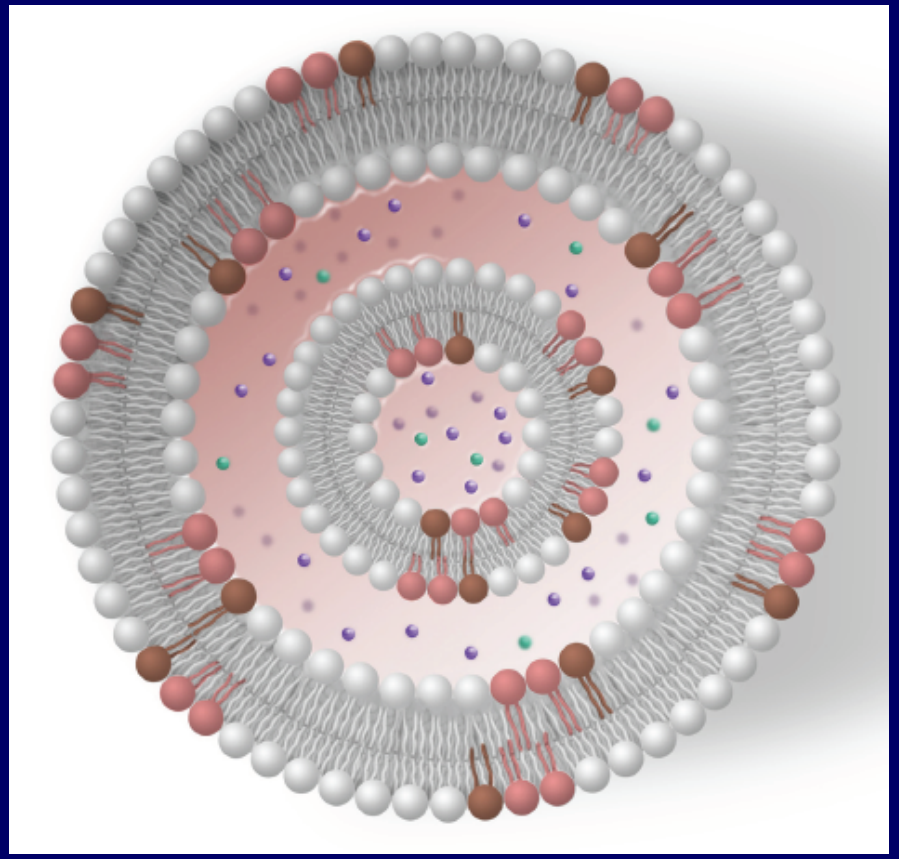
Exclusion Criteria

- **Uncontrolled intercurrent illness**
- **Hypersensitivity to component drugs**
- **Pts of childbearing age who do not practice contraception for the duration of the study**

Courtesy of Richard M Stone, MD

CPX-351

- CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin designed to achieve synergistic antileukemia activity
  - 5:1 molar ratio of cytarabine:daunorubicin provides synergistic leukemia cell killing *in vitro*[1]
  - In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days[2]
  - Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]

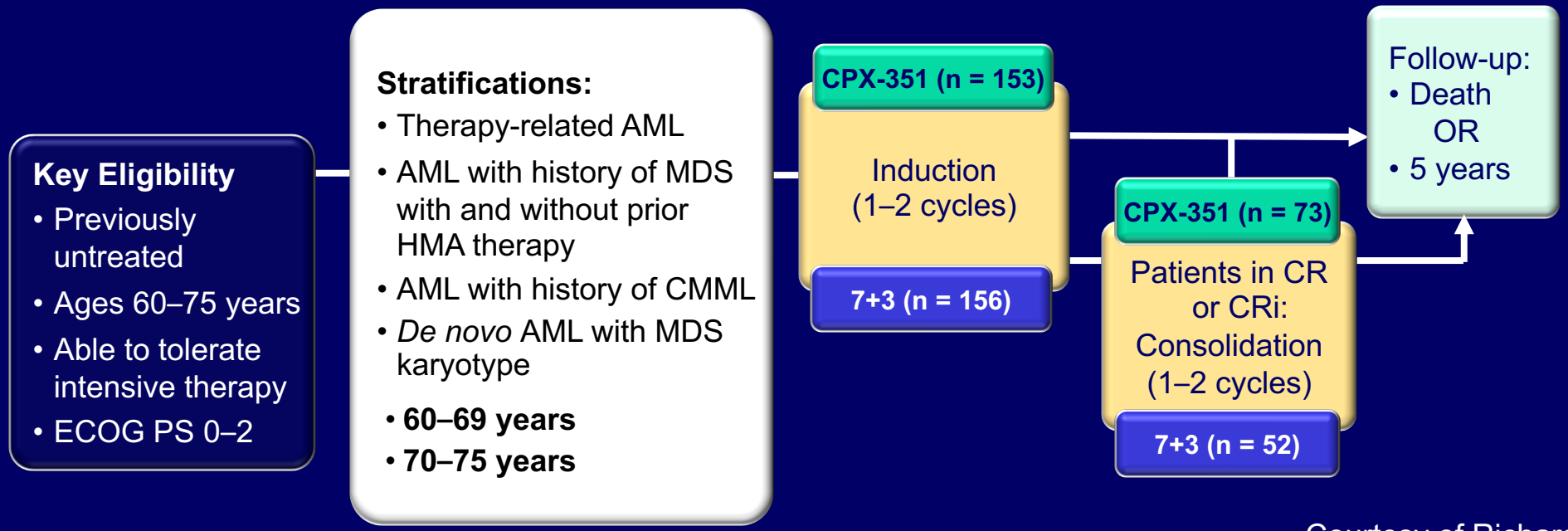


1. Tardi P et al. *Leuk Res.* 2009;33(1):129–139.
2. Feldman EJ et al. *J Clin Oncol.* 2011;29(8):979–985;
3. Lim WS et al. *Leuk Res.* 2010;34(9):1245–1223.

Courtesy of Richard M Stone, MD

CPX-351 Phase III Study Design

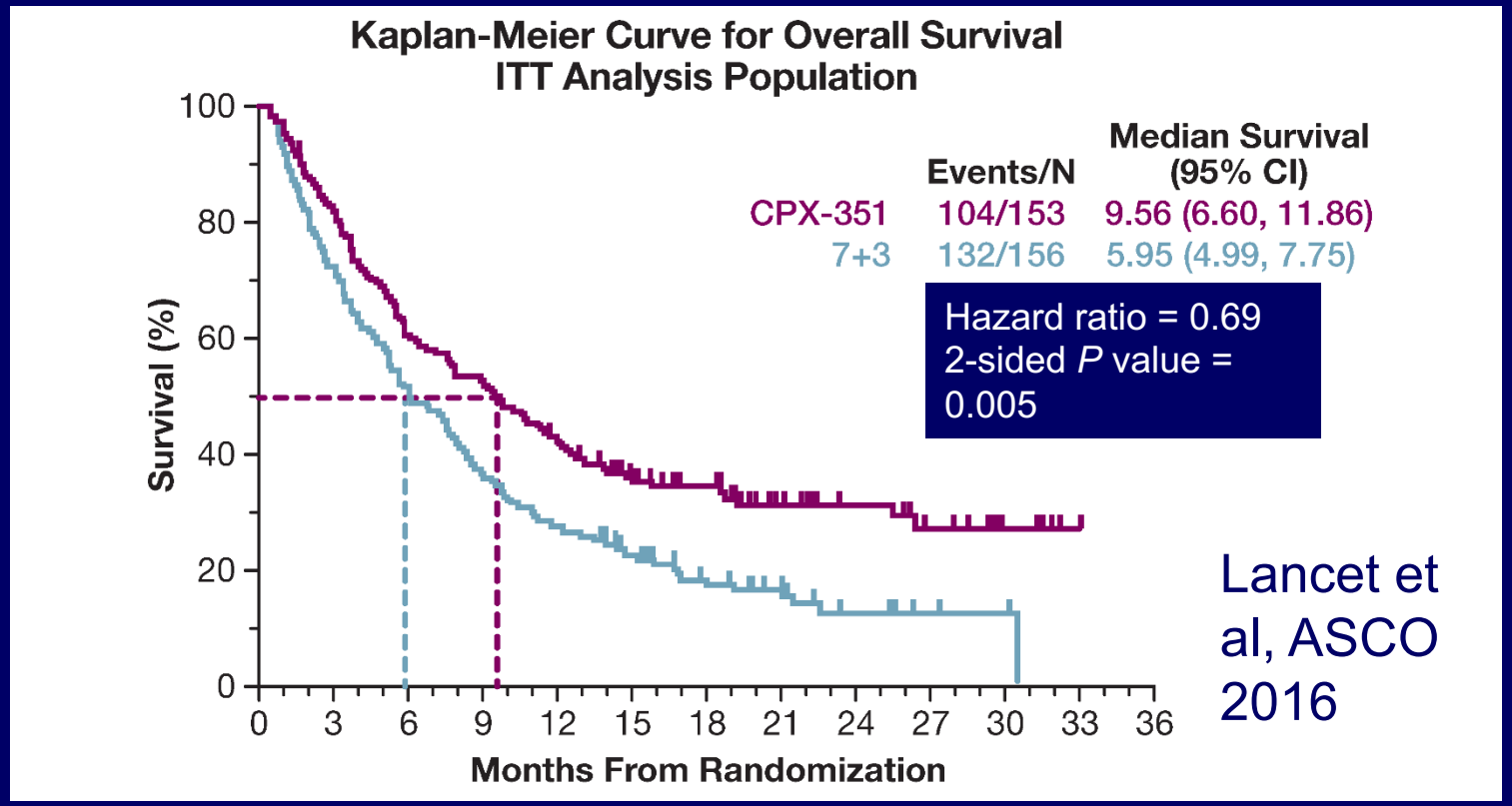
- Randomized, open-label, parallel-arm, standard therapy–controlled
  - 1:1 randomization, enrolled from December 2012 to November 2014
  - Patients with CR or CRi could be considered for allogeneic HCT, based on institutional criteria



Courtesy of Richard M Stone, MD

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete response; CRi, CR with incomplete platelet or neutrophil recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HMA, hypomethylating agents; MDS, myelodysplastic syndrome.

1. World Health Organization. *WHO Classification of Tumours of Haematopoitic and Lymphoid Tissues*. Swerdlow S et al (ed). Lyon, IRAC Press, 2008.



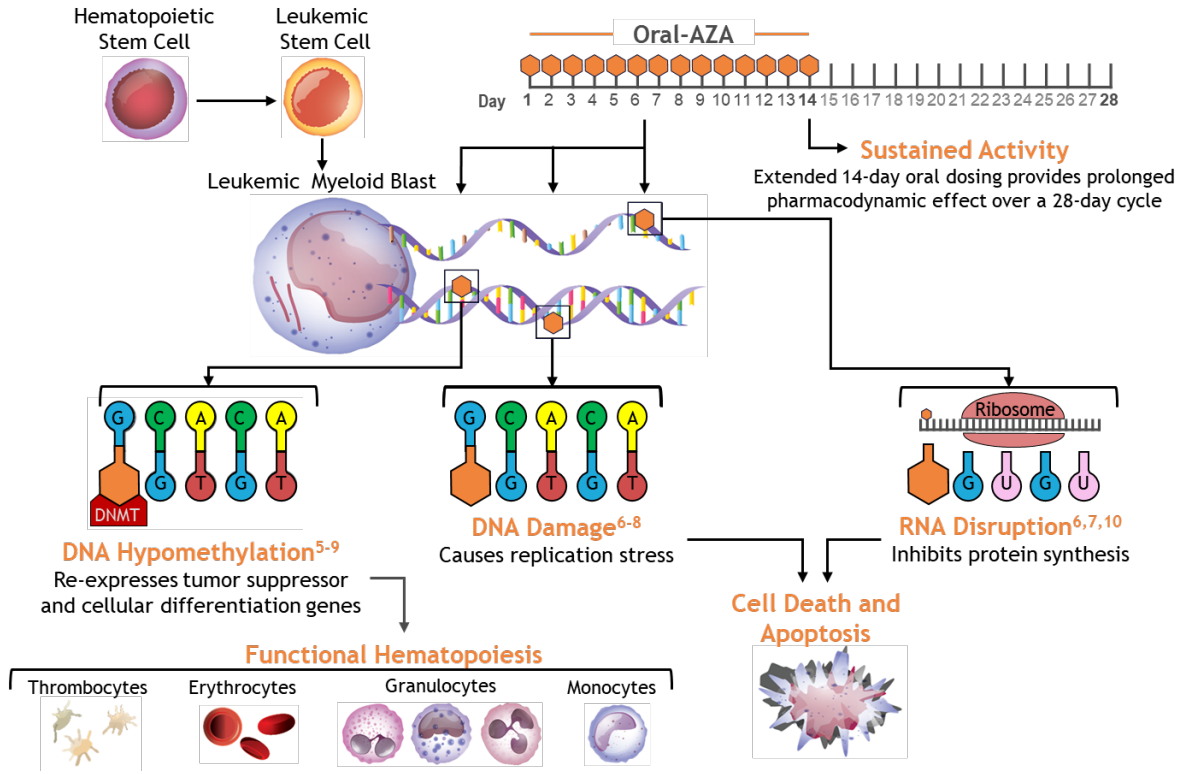
	CPX-351 (n = 153)	7+3 (n = 156)	Odds ratio	*P* value
CR+CRi	47.7%	33.3%	1.77 (1.11, 2.81)	0.016
HSCT rate	34.0%	25.0%	1.54 (0.92, 2.56)	0.098
Deaths ≤30 days*	5.9%	10.3%		
Deaths ≤60 days*	13.7%	21.2%		

*Based on Kaplan-Meier estimate for the intent-to-treat population.
Median follow-up in patients who were alive: CPX-351 (n = 49): 589 days (range: 44-1007); 7+3 (n = 24): 601 days (range: 417-917).
CI, confidence interval; CR, complete response; CRi, CR with incomplete platelet or neutrophil recovery; HSCT, hematopoietic stem cell transplant.

Courtesy of Richard M Stone, MD

QUAZAR AML-001: Oral azacitidine

- Oral azacitidine (Oral-AZA [CC-486]):
  - Oral HMA with a distinct PK/PD profile from injectable AZA; the two are not bioequivalent[1,2]
  - Approved in the United States for continued Tx of adult pts with AML in first CR/CRi post-IC and not able to complete intensive curative therapy (eg, HSCT)[3]
- Oral dosing allows for extended drug exposure during each Tx cycle to prolong AZA activity[1,2]



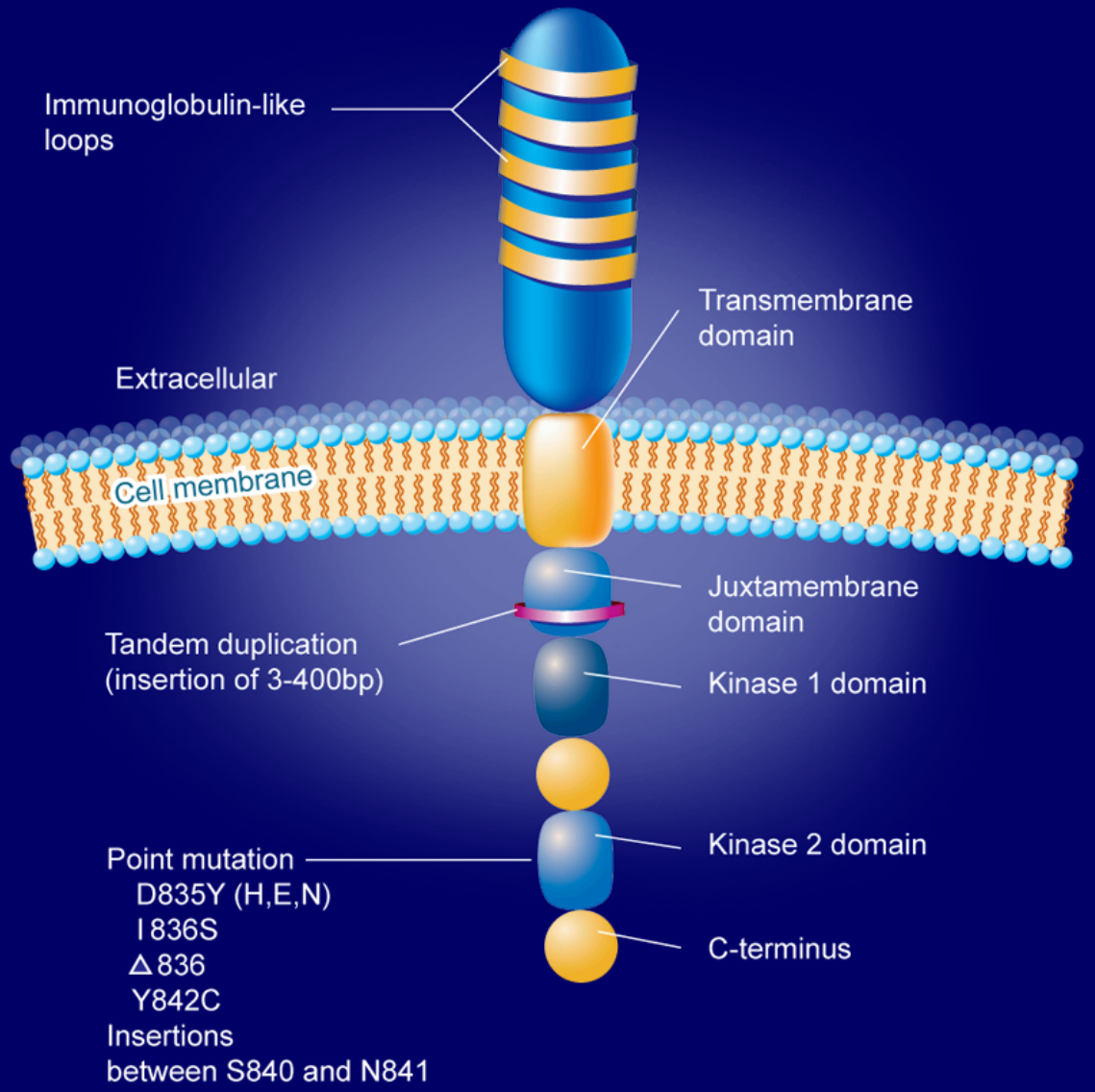
1. Garcia-Manero et al. *J Clin Oncol*. 2011;29(18):2521–7. 2. Laille et al. *PLoS One*. 2015;10(8):e0135520. 3. ONUREG® (azacitidine) tablets [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Rev. 9/2020. 4. Savona et al. *Am J Hematol*. 2018;93(10):1199–206. 5. Stresemann et al. *Mol Cancer Ther*. 2008;7:2998–3005. 6. Hollenbach et al. *PLoS One*. 2010;5(2):e9001. 7. Scott LJ. *Drugs*. 2016;76(8):889–900. 8. Stresemann C, Lyko F. *Int J Cancer*. 2008;123(1):8–13. 9. Aimiuwu et al. *Blood*. 2012;119(22):5229–38.

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; Tx, treatment.

Courtesy of Richard M Stone, MD

FLT3 Structure and Activating Mutations

Over-expression is common



25-30%

5-10%

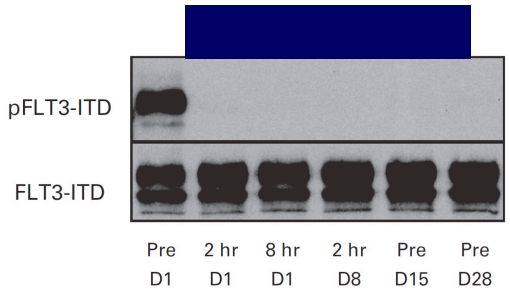
Both mutations cause spont dimerization,

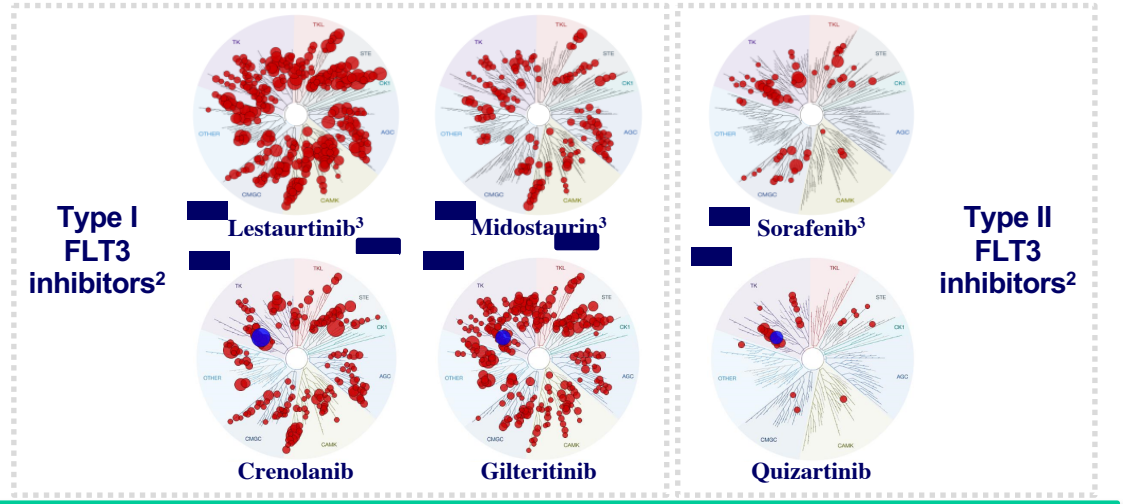
ligand independent growth, and MPD in murine model

Litzow MR. *Blood*. 2005;106:3331-3332.

Courtesy of Richard M Stone, MD

Quizartinib and Gilteritinib: Second Generation FLT3 Inhibitors



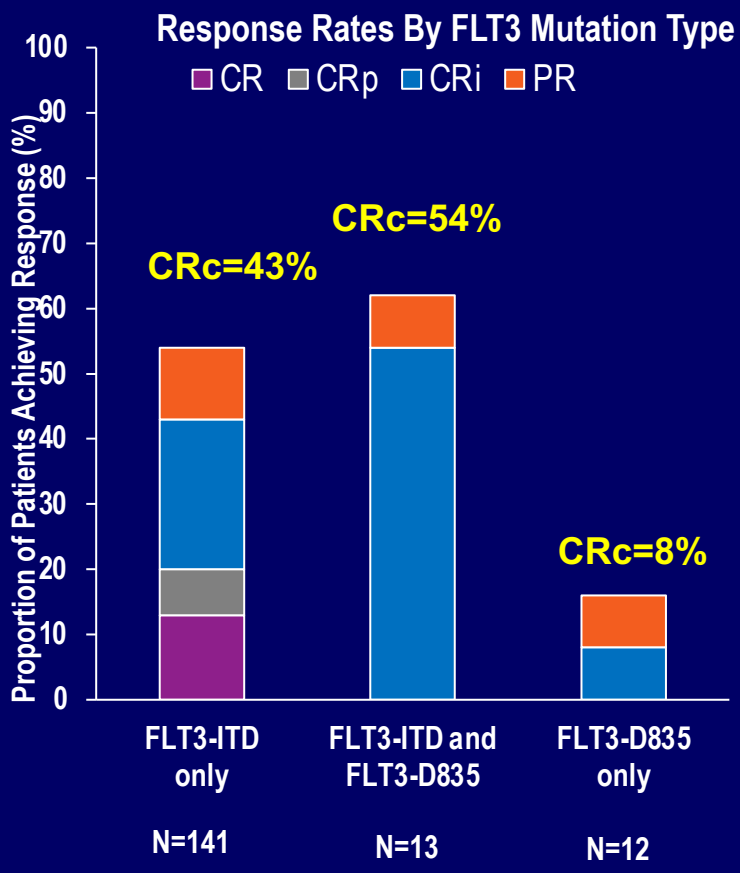


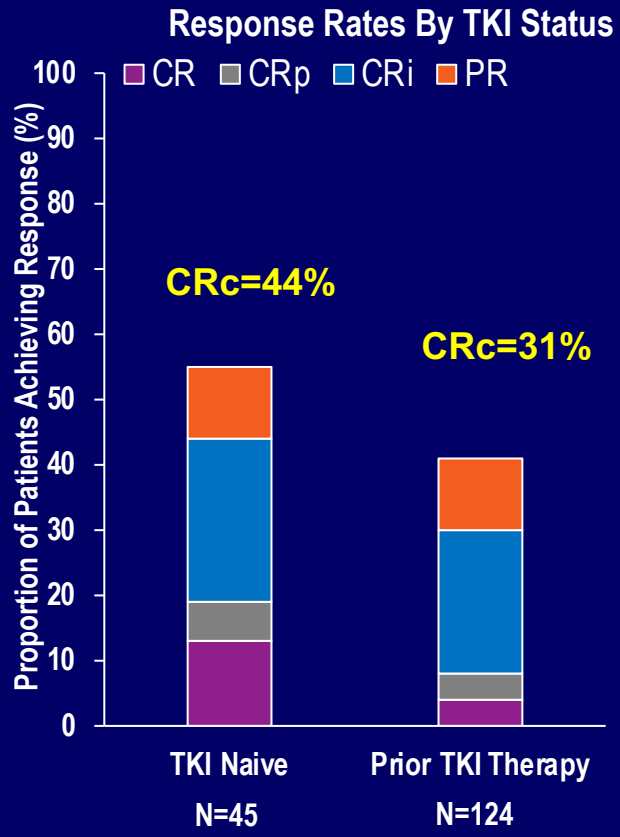
- Quizartinib is potent in vivo than any other FLT3 inhibitor to date[4,5]
- But selection of resistance with FLT3-TKD mutations
- Possible QT prolongation at higher doses

- Gilteritinib 'hits' both ITD and TKD subtypes
- Well tolerated

Courtesy of Richard M Stone, MD

Antileukemic Response to ≥80 mg/day Gilteritinib in FLT3^{mut+} Patients by Mutation Type and TKI Status





Perl et al, Lancet Oncology , 2017

Courtesy of Richard M Stone, MD

Patient Characteristics
Safety Cohort (N=15)

Characteristic	Safety Cohort (N=15)
Age, y	
Median (range)	75 (65–86)
≥75, n (%)	9 (60)
Female, n (%)	8 (53)
Race, n (%)	
Asian	2 (13)
White	11 (73)
***FLT3* mutation status, n (%)**	
ITD alone	10 (67)
TKD alone	3 (20)
ITD/TKD	1 (7)
Wild type	1 (7)
ECOG PS ≤1 at screening, n (%)	6 (40)

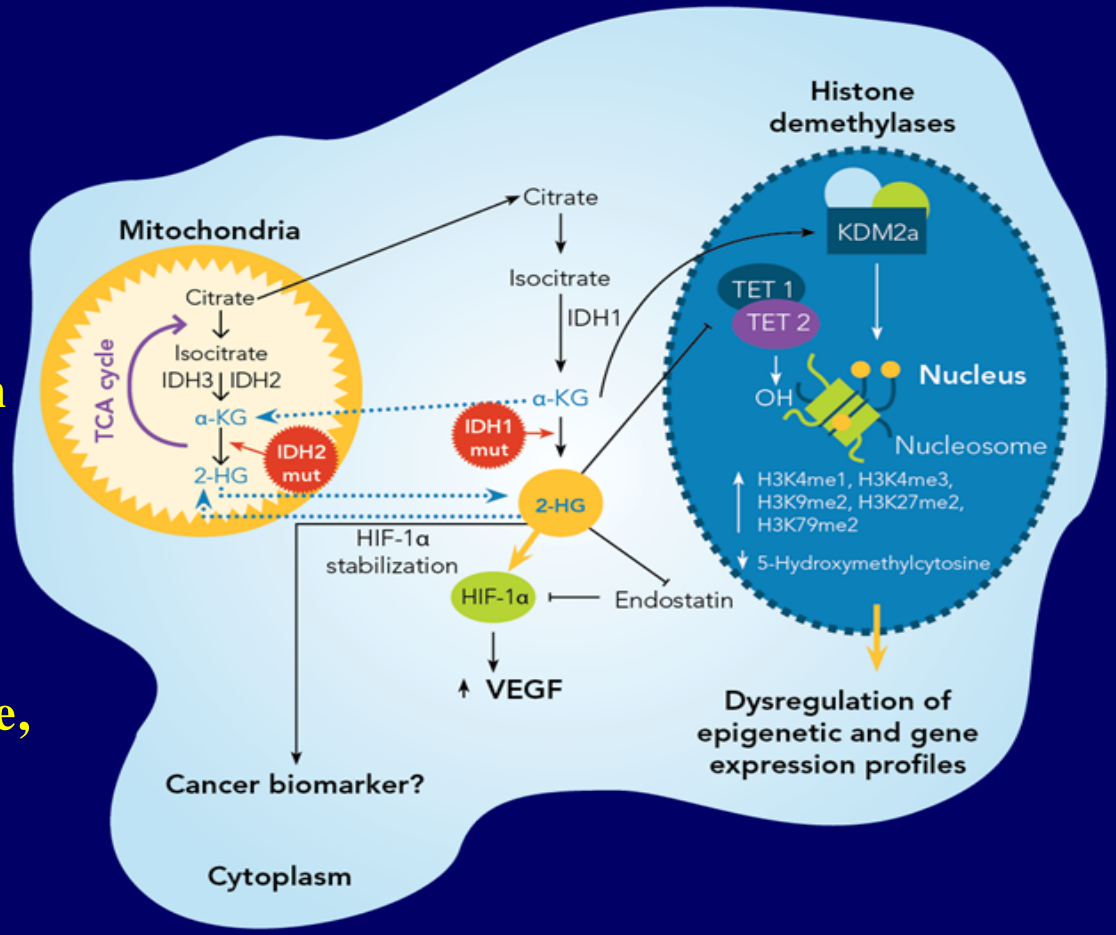
- As of 29 June 2020:
  - 15 patients were enrolled
  - 14 patients died since enrollment on 10 July 2017
  - 1 patient continues treatment for over 3 years
- Median (range) treatment duration was 6 (<1–34) cycles
- >12 cycles of treatment were received by 40% (n=6/15) of patients

ECOG PS, Eastern Cooperative Oncology Group performance status; *FLT3*, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; TKD, tyrosine kinase domain.

Wang E, et al, ASH #27, 2020

Isocitrate Dehydrogenase (IDH) Mutations as a Target in AML

- **IDH is an enzyme of the citric acid cycle**
- **Mutant *IDH2* produces 2-hydroxyglutarate (2-HG), which alters DNA methylation and leads to a block in cellular differentiation**
- **AG-221 (CC-90007) is a selective, oral, potent inhibitor of the mutant *IDH2* (m*IDH2*) enzyme**



Courtesy of Richard M Stone, MD

IDH single agent Inhibitor Data in R/R mut IDH AML

AG120=ivosidenib

- Most common AEs: diarrhea, fatigue, and pyrexia
- **Overall response rate of 35%** and a complete remission rate of 15%
- **In all response evaluable patients, an estimated 55% had treatment duration of at least 33%**
- **Differentiation syndrome**

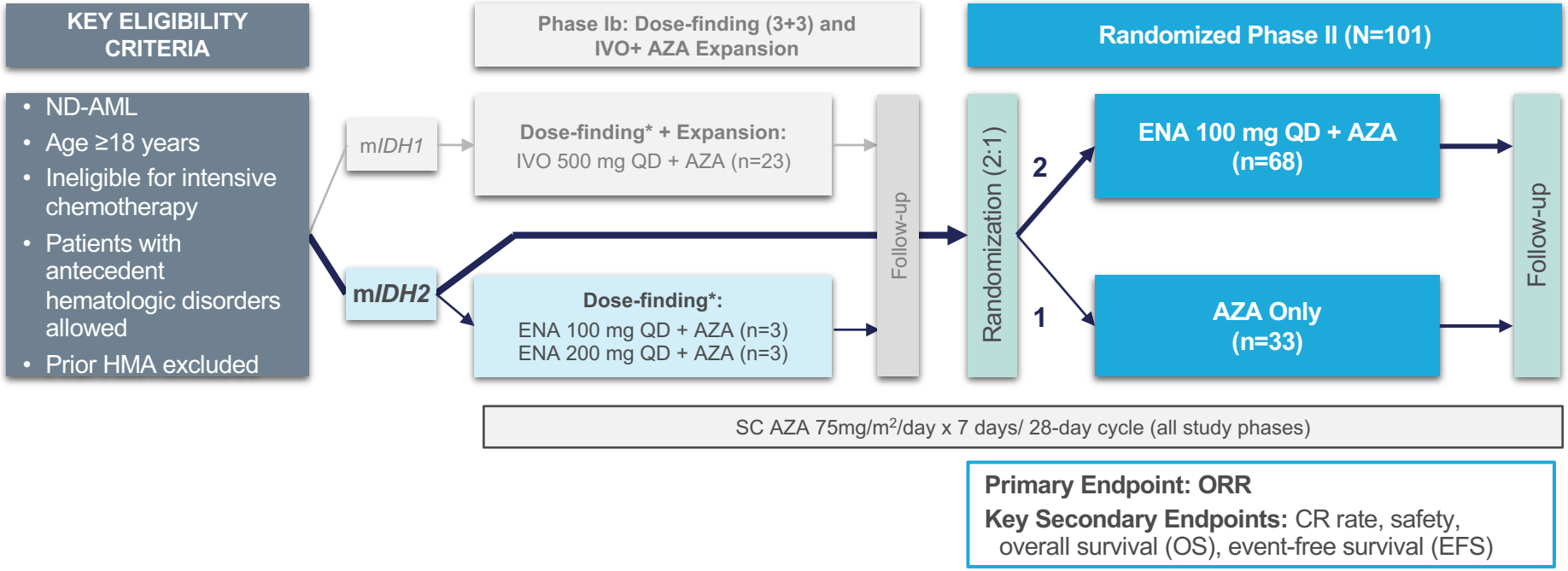
AG221=enasidenib

- Most common AEs: nausea, fatigue, increase in bilirubin, diarrhea
- ORR 37% in 159 adults w R/R AML
  - CR 18%
  - Median duration of response of 6.9 months
- Differentiation syndrome

DiNardo C, et al. NEJM 2018. Stein E, et al. Blood 2019

Courtesy of Richard M Stone, MD

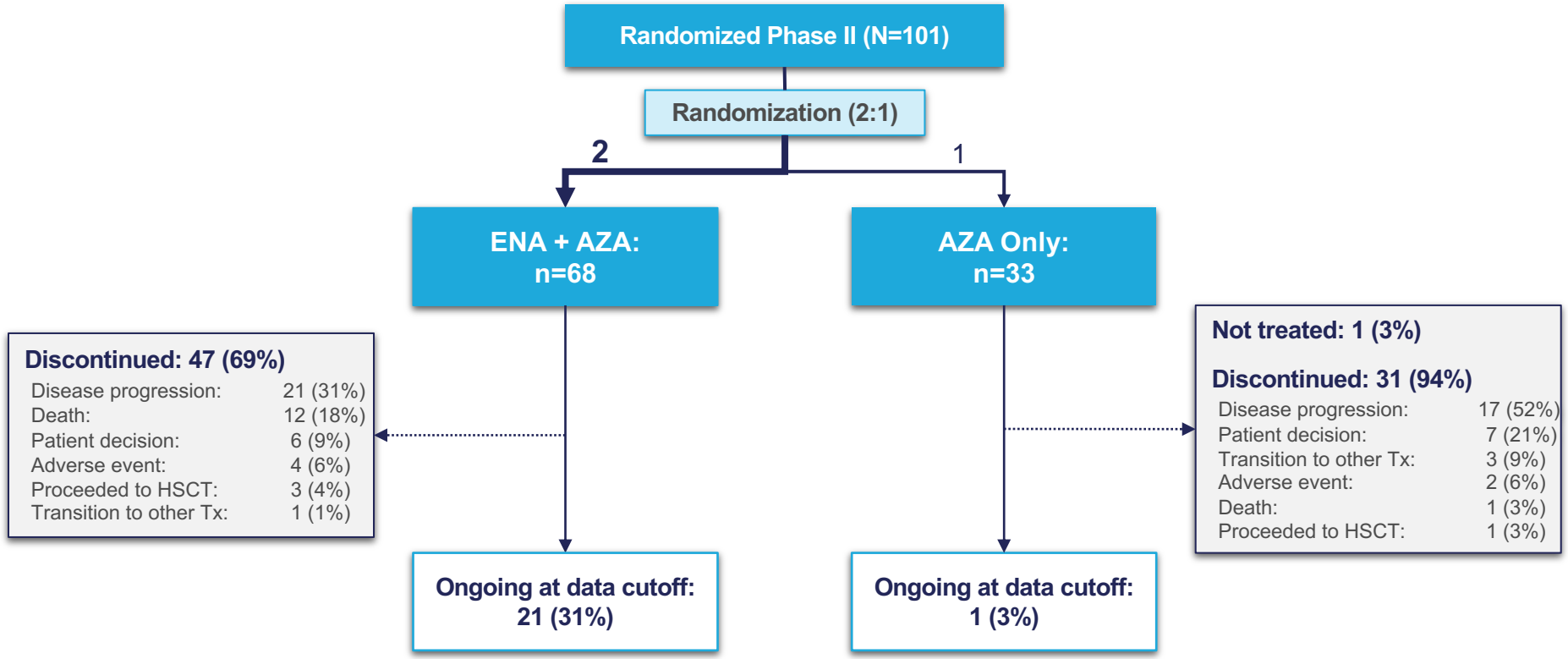
AG-221-AML-005: STUDY DESIGN (DINARDO, ASH 2019)



*Dose finding for ENA or IVO; AZA dose remained constant.
AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; EFS, event-free survival; ENA, enasidenib; HMA, hypomethylating agent; IVO, ivosidenib; m*IDH1*/m*IDH2*, mutant-*IDH1*/mutant-*IDH2*; ND, newly diagnosed; ORR, overall response rate; OS, overall survival; SC, subcutaneous.

Courtesy of Richard M Stone, MD

AG-221-AML-005: DISPOSITION



Data cutoff: August 19, 2019

AML, acute myeloid leukemia; AZA, azacitidine; ENA, enasidenib; HSCT, hematopoietic stem cell transplant; Tx, treatment.

Courtesy of Richard M Stone, MD