WHAT'S NEW IN UPFRONT TREATMENT IN AML

UPDATES FROM ASH 2021

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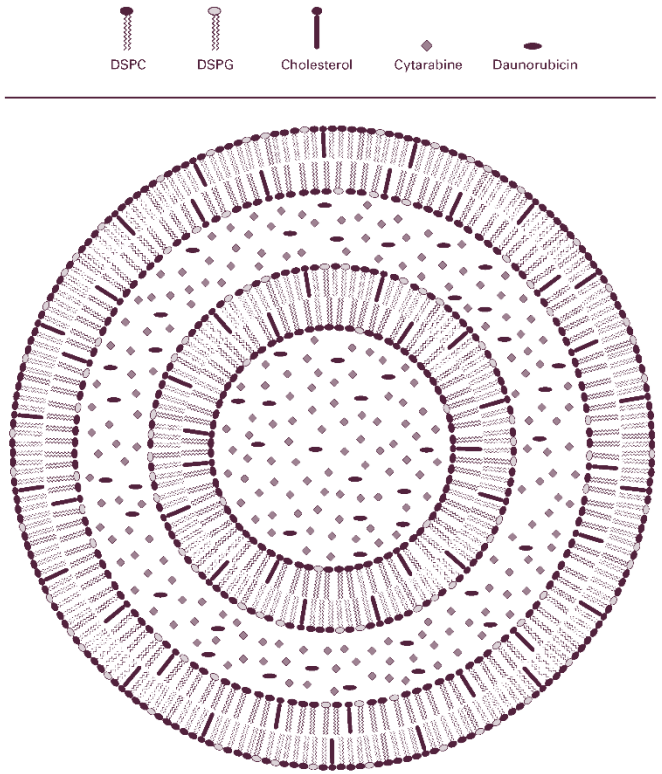
PATIENT 1

- 61 year old woman with history of myeloma, achieved a remission and underwent Mel auto transplant followed by lenalidomide maintenance
- Presented with pancytopenia, marrow with AML with complex monosomal karyotype, ASXL1 mutated
- Normal organ function

CPX-351

- CPX-351 is a liposomal formulation of cytarab encapsulated at a 5:1 molar ratio
  - Fixed molar ratio maintained in human plasma for at least 24 hours after final dose[1]
  - Drug exposure maintained for 7 days[1]
  - Selective uptake by leukemic vs normal cells in bone marrow of leukemia-bearing mice[2]



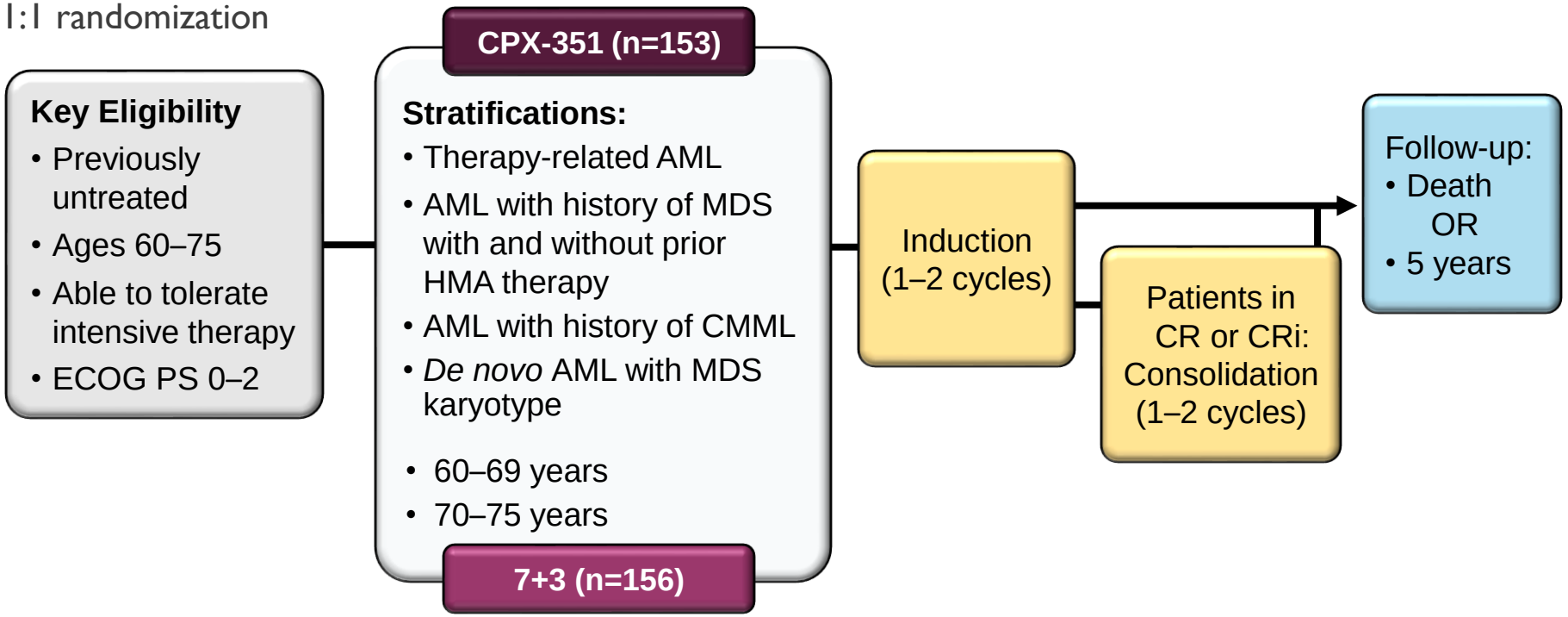
1. Feldman EJ et al. *J Clin Oncol.* 2011;29(8):979–985; 2. Lim WS et al. *Leuk Res.* 2010;34(9):1245–1223

PHASE 2 DATA IN UNTREATED AML

	Overall (n=126)		Secondary (n=52)	
	CPX-351 (n=84)	7 + 3 (n=41)	CPX-351 (n=33)	7 + 3 (n=19)
MLFS Rate	84.5%	66.7%	81.8%	64.7%
CR Rate	48.8%	48.8%	36.4%	31.6%
CRi Rate	17.9%	2.4%	21.2%	0%
Response Rate	66.7%	51.2%	57.5%	31.6%
60-Day Mortality	4.7%	14.6%	6.1%	31.6%
EFS (median)	6.5 months	2.0 months	4.5 months	1.3 months
OS (median)	14.7 months	12.9 months	12.1 months	6.1 months

CPX-351 PHASE III STUDY DESIGN

- Randomized, open-label, parallel-arm, standard therapy–controlled
  - 1:1 randomization



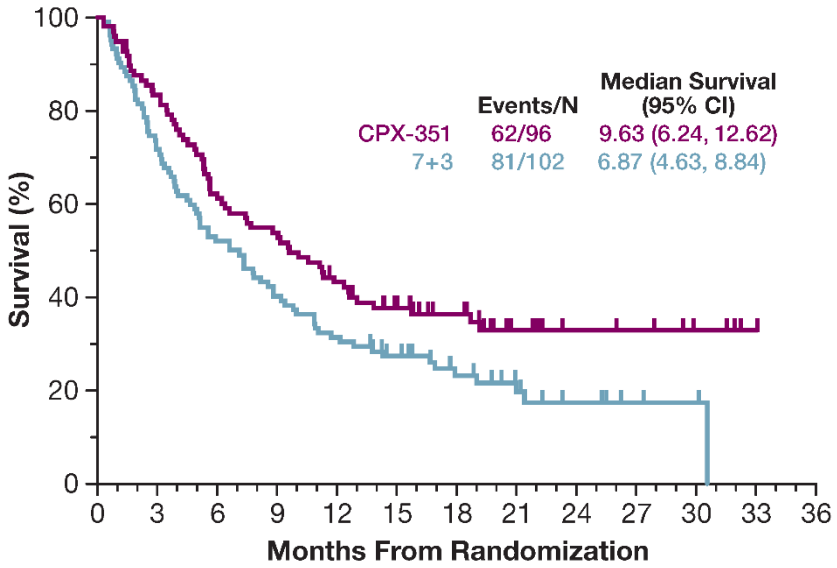
AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete response; CRi, CR with incomplete platelet/neutrophil recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HMA, hypomethylating agents; MDS, myelodysplastic syndrome.

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

EXPLORATORY ANALYSIS BY AGE: OVERALL SURVIVAL

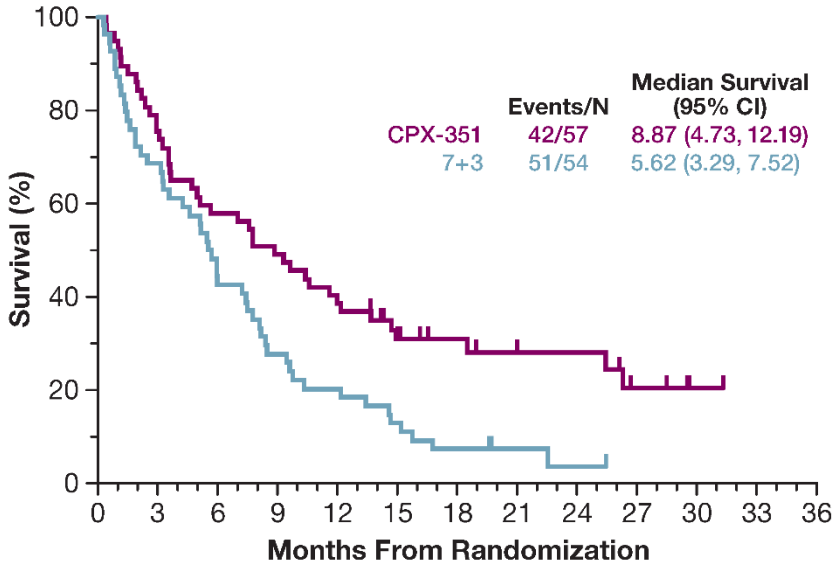
- Age 60–69 years, hazard ratio of 0.68 (95% CI: 0.49, 0.95)
- Age 70–75 years, hazard ratio of 0.55 (95% CI: 0.36, 0.84)

Age 60–69



CPX-351	96	79	59	51	40	31	23	13	8	7	4	1
7+3	102	73	53	41	32	24	16	10	6	3	2	0

Age 70–75



CPX-351	57	43	33	28	22	15	11	8	8	4	1	0
7+3	54	37	24	15	11	7	4	2	1	0	0	0

VENETOCLAX/DECITABINE IN YOUNG ADULTS WITH ADVERSE-RISK AML: CYCLE 1 RESPONSES

Response, n (%)	All Patients Venetoclax/Decitabine (N = 25)	Historical Controls Cytarabine/Idarubicin (N = 60)	*P* Value
Composite CR	19 (76)	23 (38.3)	.002
▪ CR	13 (52)	16 (27)	
▪ CRh	5 (20)	6 (10)	
▪ CRp	1 (4)	0 (0)	
▪ MLFS	0 (0)	1 (2)	
Partial remission	6 (24)	17 (28)	
Induction failure	0 (0)	17 (28)	

Chen. ASH 2021. Abstr 35.

VENETOCLAX/DECITABINE IN YOUNG ADULTS WITH ADVERSE-RISK AML: COMPOSITE CR IN CYCLE 1 BY SUBGROUP

Response, %	All Patients Venetoclax/Decitabine (N = 25)	Historical Controls Cytarabine/Idarubicin (N = 60)
Composite CR	76	38
ASXL1	80	55
TP53	67	25
RUNX1	71	45
FLT3-ITD AR ≥0.5	80	27
Complex karyotype	83	25
11q23 rearrangement	80	40

Chen. ASH 2021. Abstr 35.

VENETOCLAX/DECITABINE IN YOUNG ADULTS WITH ADVERSE-RISK AML: OTHER OUTCOMES

Response, %	All Patients Venetoclax/Decitabine (N = 25)	Historical Controls Cytarabine/Idarubicin (N = 60)	*P* Value
Composite CR at cycle 2	95.7	73.6	.044
MRD negative CR at cycle 2	73.9	43.4	.023

After median follow-up of 4.3 mo, median PFS and median OS not reached with venetoclax/decitabine

30-day and 60-day mortality: 0%

Chen. ASH 2021. Abstr 35.

VENETOCLAX/DECITABINE IN YOUNG ADULTS WITH ADVERSE-RISK AML: SAFETY

Parameter	All Patients Venetoclax/Decitabine (N = 25)	Historical Controls Cytarabine/Idarubicin (N = 60)	*P* Value
Any grade ≥4 AE, %	96	100	
▪ Neutropenia	93	97	
▪ Anemia	72	93	.049
▪ Thrombocytopenia	71	100	.004
Mean duration of grade ≥4 AE, days (range)			
▪ Neutropenia	18.1 (2-35)	16.5 (0-32)	.517
▪ Thrombocytopenia	9.5 (0-37)	15.4 (6-38)	.037
Mean number transfusions, units (range)			
▪ Platelets	2.4 (0-12.5)	5.8 (0.5-17)	.003
▪ RBCs	4.6 (0-12.5)	7.7 (0-17.5)	.012
▪ Infection, %	48.0	66.7	.01
▪ Febrile neutropenia	20.0	15.0	
▪ Pneumonia	8.0	26.7	
▪ Sepsis	0.0	15.0	
▪ Intestinal infection	0.0	5.0	
▪ Other infection	20.0	5.0	

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VENETOCLAX/DECITABINE IN YOUNG ADULTS WITH ADVERSE-RISK AML: CONCLUSIONS

In young adult patients with ELN adverse-risk AML, venetoclax/decitabine associated with 76% composite CR rate vs 38% for historical controls

- MRD negativity rate after cycle 1: 64%

Compared with historical controls, venetoclax/decitabine had:

- Lower rates of infections (48% vs 67%)
- Reduced RBC and platelet transfusions

Median PFS and OS not reached for patients receiving venetoclax/decitabine

- 30-day and 60-day mortality rate: 0%

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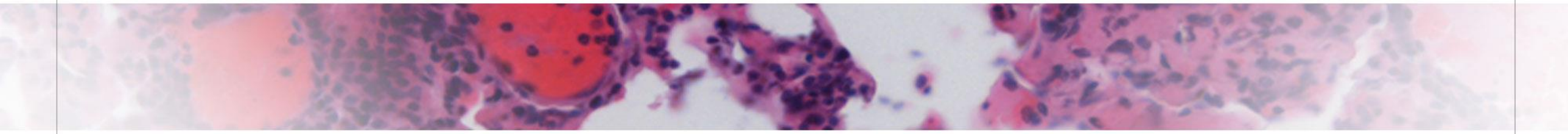

COMPARING OUTCOMES BETWEEN LIPOSOMAL DAUNORUBICIN/CYTARABINE (CPX-351) AND HYPOMETHYLATING AGENT+VENETOCLAX (HMA+V) AS FRONTLINE THERAPY IN ACUTE MYELOID LEUKEMIA

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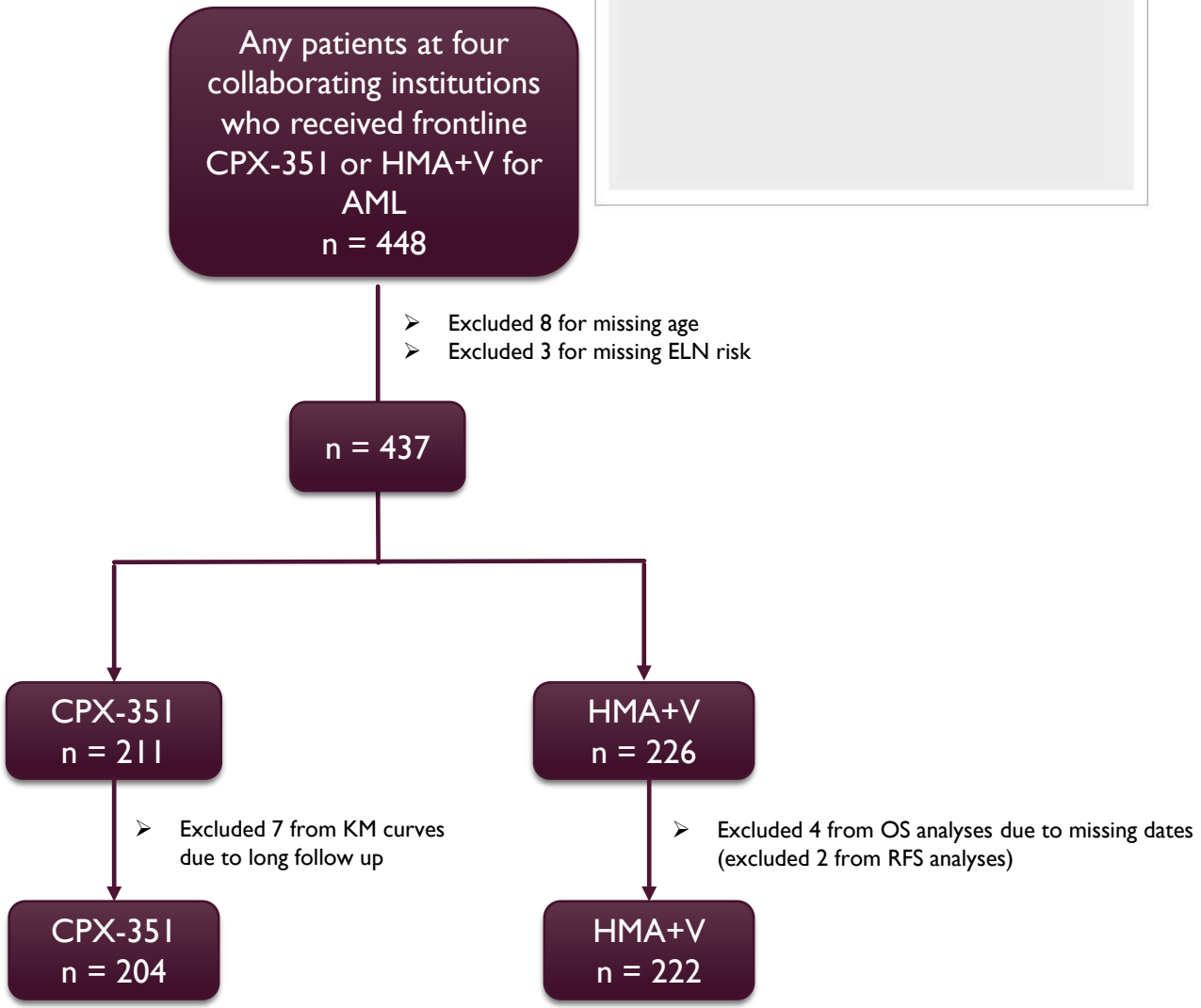
REAL-WORLD, MULTICENTER RETROSPECTIVE CHART REVIEW

- Four large academic centers: MSKCC, Northwestern, Moffitt, Cornell
- A real-world analysis of patient characteristics and outcomes in older AML patients receiving either CPX-351 or HMA+V as frontline therapy
- Primary outcomes: response rate (CR+CRi), relapse free survival (RFS), and overall survival (OS)
- Analyses were conducted for overall population (ages 34-93 yrs) and ages 60-75 yrs
- 60-75 yrs was the age group where most overlap was seen between the two treatment groups
- Subgroup analyses: TP53, Adverse ELN Risk, Prior myeloid malignancy, prior HMA therapy



BASELINE CHARACTERISTICS: OVERALL POPULATION

	CPX-351 Frontline	HMA+V Frontline	p-value
n	211	226	
Demographics			
Age, Median (IQR)	66.8 (60.8, 71.6)	75.2 (69.7, 78.8)	$p < 0.001$
Male, N (%)	121 (57.4%)	138 (61.1%)	$p = 0.430$
AML ELN Risk, N (%)			$p = 0.020$
Favorable/Intermediate	82 (38.9)	64 (28.3)	
Adverse	129 (61.1)	162 (71.7)	
Mutations			
TP53 (n=411), N (%)	37 (19.1)	58 (26.7)	$p = 0.066$
FLT3 (n=413), N (%)	12 (6.10)	19 (8.87)	$p = 0.311$
NPM1 (n=412), N (%)	13 (6.63)	23 (10.7)	$p = 0.150$
RUNX1 (n=411), N (%)	44 (22.7)	54 (24.9)	$p = 0.601$
ASXL1 (n=412), N (%)	32 (16.5)	59 (27.1)	$p = 0.010$
IDH1/IDH2 (n=411), N (%)	38 (19.7)	40 (18.4)	$p = 0.729$
Antecedent Hematologic Malignancy			
Prior myeloid disorder, N (%)	114 (54.0)	92 (40.7)	$p = 0.005$
Prior HMA therapy			$p = 0.001$
Yes, N (%)	43 (20.4)	22 (9.73)	
No, N (%)	136 (64.5)	180 (79.7)	
Other, N (%)	32 (15.2)	24 (10.6)	

- Median age was higher in HMA+V (75.2 years vs. 66.8 years)
- Adverse ELN Risk was higher in HMA+V (71.7% vs 61.1%)
- Prior myeloid malignancy was more common in CPX-351 (54% vs 40.7%)
- Prior HMA therapy was more common in CPX-351 (20.4% vs. 9.7%)
- No significant differences in mutations other than ASXL1, which was higher in HMA+V (27.1% vs 16.5%)

BASELINE CHARACTERISTICS: 60-75YO

	CPX-351 Frontline	HMA+V Frontline	p-value
n	152	100	
Demographics			
Age, Median (IQR)	68.5 (64.4, 71.7)	70.3 (67.5, 73.0)	$p = 0.002$
Male, N (%)	87 (57.2)	59 (59.0)	$p = 0.782$
AML ELN Risk, N (%)			$p = 0.001$
Favorable/Intermediate	67 (44.1)	23 (23.0)	
Adverse	85 (55.9)	77 (77.0)	
Mutations			
TP53 (n=252), N (%)	22 (14.5)	25 (25.0)	$p = 0.036$
FLT3 (n=235), N (%)	10 (7.19)	9 (9.38)	$p = 0.547$
NPM1 (n=235), N (%)	10 (7.19)	7 (7.29)	$p = 0.977$
RUNX1 (n=234), N (%)	27 (19.7)	32 (33.0)	$p = 0.021$
ASXL1 (n=233), N (%)	24 (17.5)	30 (31.3)	$p = 0.015$
IDH1/IDH2 (n=233), N (%)	32 (23.4)	18 (18.8)	$p = 0.399$
Antecedent Hematologic Malignancy			
Prior myeloid disorder, N (%)	80 (52.6)	41 (41.0)	$p = 0.071$
Prior HMA therapy			$p = 0.127$
Yes, N (%)	32 (21.1)	12 (12.0)	
No, N (%)	97 (63.8)	75 (75.0)	
Other, N (%)	23 (15.1)	13 (13.0)	

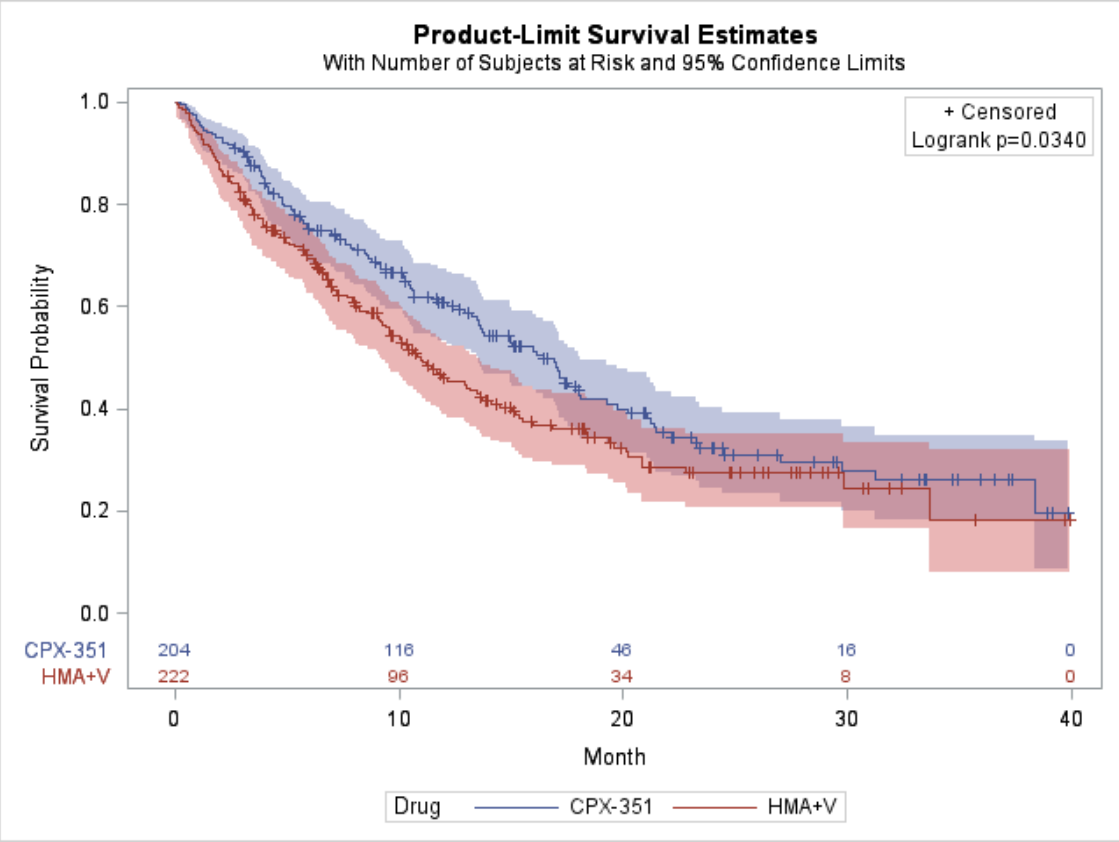
- Higher median age in HMA+V, 70.3 vs 68.5 yrs
- Higher rate of adverse ELN risk in HMA+V, 77% vs 56%
- Higher frequency of TP53, RUNX1, and ASXL1 in HMA+V
- No significant differences in frequency of prior myeloid disorder or prior HMA therapy

OVERALL POPULATION: CR/CRI RATES BETWEEN CPX-351 VS. HMA+V

	CPX-351 Frontline	HMA+V Frontline	p-value
n	211	226	
Overall population (n = 437)			
CR/CRi, N (%)	122 (57.8)	128 (56.6)	$p = 0.803$
CR, N (%)	98 (46.4)	62 (27.4)	$p < 0.001$
CRi, N (%)	24 (11.4)	66 (29.2)	$p < 0.001$
TP53 Positive (n = 95)			
CR/CRi, N (%)	11 (29.7)	28 (48.3)	$p = 0.073$
CR, N (%)	9 (24.3)	16 (27.6)	$p = 0.725$
CRi, N (%)	2 (5.4)	12 (20.7)	$p = 0.072$
Prior Myeloid Malignancy (n = 206)			
CR/CRi, N (%)	57 (50.0)	38 (41.3)	$p = 0.213$
CR, N (%)	49 (43.0)	16 (17.4)	$p < 0.001$
CRi, N (%)	8 (7.0)	22 (23.9)	$p = 0.001$
Prior HMA Therapy (n = 65)			
CR/CRi, N (%)	18 (41.9)	9 (40.9)	$p = 0.941$
CR, N (%)	16 (37.2)	2 (9.1)	$p = 0.020$
CRi, N (%)	2 (4.7)	7 (31.8)	$p = 0.005$
ELN – Adverse (n = 291)			
CR/CRi, N (%)	65 (50.4)	85 (52.5)	$p = 0.724$
CR, N (%)	49 (38.0)	40 (24.7)	$p = 0.015$
CRi, N (%)	16 (12.4)	45 (27.8)	$p = 0.001$

- No differences in combined CR/CRi rates between the two groups overall or in subgroup analyses
- Generally higher rates of CRi in HMA+V compared to CPX-351 in several subgroups consistent with clinical experience
- No differences in combined CR/CRi rates between the two groups among all mutation subgroups (TP53, FLT3, NPM1, RUNX1, ASXL1, IDH1/IDH2)

OVERALL POPULATION: MEDIAN OS IS HIGHER IN CPX-351 TREATED GROUP



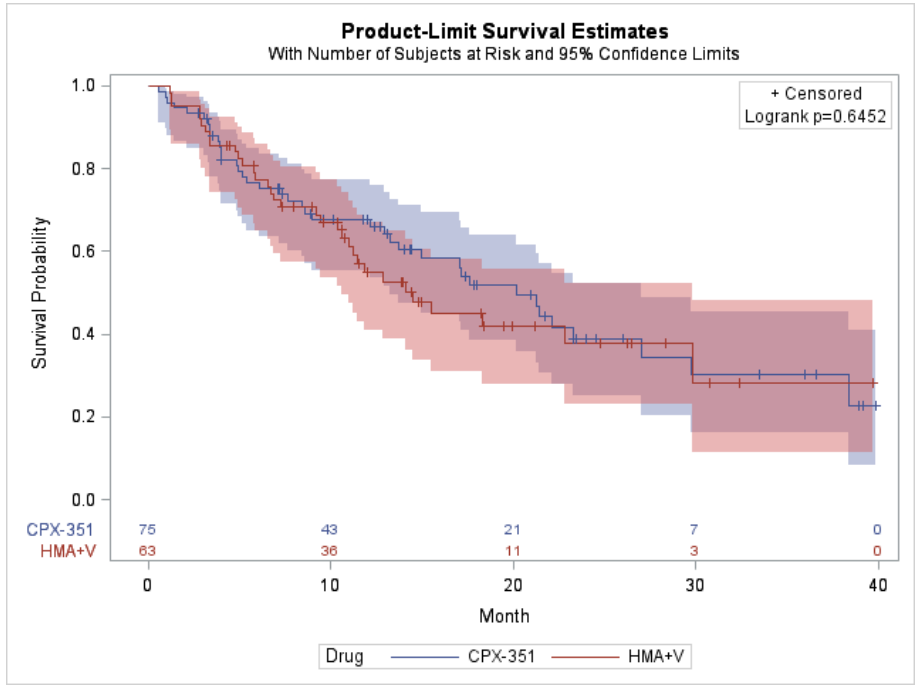
	CPX-351 Frontline	HMA+V Frontline	p-value
n	211	226	
Outcomes			
CR/CRi, N (%)	122 (57.8)	128 (56.6)	$p = 0.803$
Median survival time, months			
RFS (95% CI)	33.7 (27.4 – NA)	15.8 (11.8 – NA)	$p = 0.132$
OS (95% CI)	17.3 (13.8 – 20.5)	11.1 (9.3 – 13.6)	$p = 0.007$

- There are no significant differences in response rate (CR+CRi) or median RFS between the two cohorts
- Median overall survival was higher in the CPX-351 treatment group (17.3mo vs 11.1mo)

- Kaplan Meier curve for OS in overall cohort (excluded 7 patients from CPX-351 group due to long follow up >40mo; excluded 4 from HMA+V group due to missing dates)

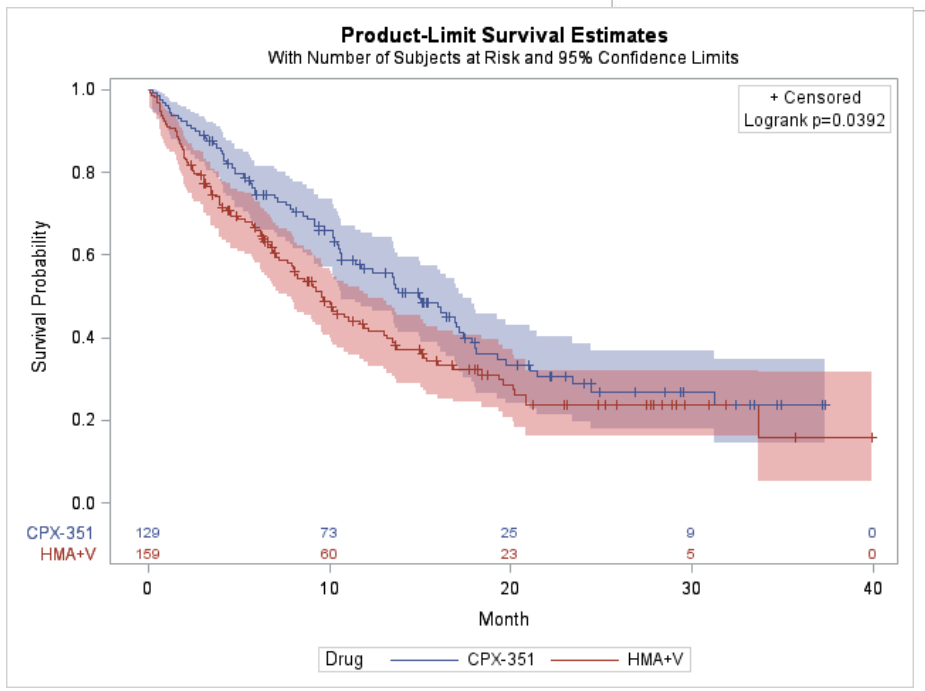
OVERALL POPULATION: OS ACCORDING TO ELN RISK

ELN favorable/intermediate



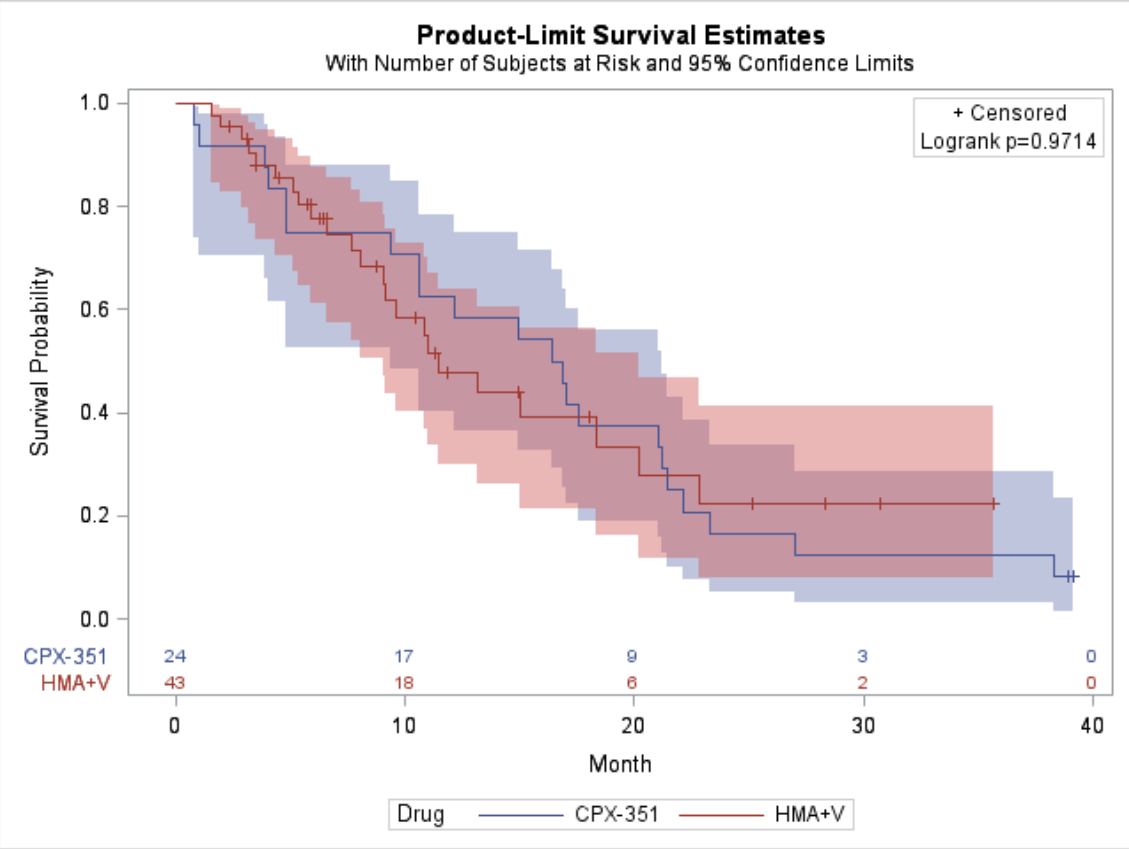
- Excluded 7 patients from CPX-351 group due to long follow up >40mo; excluded 1 from HMA+V group due to missing dates)
- No significant difference in OS

ELN adverse



- Excluded 3 from HMA+V group due to missing dates)
- **Higher OS in CPX-351 cohort**
- Maybe related to higher rates of transplant in the younger CPX351 group

60-75 YO: COMORBIDITY ANALYSES, PARTIAL DATA



Kaplan Meier curve for OS in patients with Ferrara comorbidity score 0 only (n = 68; excluded 5 patients from CPX-351 group due to long follow up >40mo; excluded 1 from HMA+V group due to missing data)

CPX-351: n = 31; HMA+V: n = 58

- **Higher rates of nonzero Ferrara score** in HMA+V cohort (24.1% vs. 6.45%, p = 0.045)
- No significant difference in total HCTCI score between patients who underwent HSCT and those who did not
- There is no difference in OS between the two cohorts in patients with pre-induction Ferrara comorbidity score 0

CONCLUSIONS FROM REAL WORLD ANALYSES OF CPX-351 AND HMA+V AS FRONTLINE AML THERAPY

- In the overall population, no significant difference in response rate (CR+CRi) between the 2 groups
- In patients aged 60-75 yrs, there was no significant difference in response rate (CR+CRi) between the 2 groups
- In overall population, CPX-351 treated patients had longer OS compared to HMA+V
- Among 60-75 yrs population, there was no significant difference in OS between the groups despite more than double the rate of HSCT in CPX-351 group
- Subgroup analyses in 60-75yo showed higher overall survival w/ CPX-351 for TP53 positive patients
- Among patients 60-75 yrs of age, there was no difference in survival after achieving CR between the two treatment groups
- There was no difference in post transplant survival between the two treatment groups
- Limitations: retrospective chart review, lack of MRD data; post-transplant analyses limited by small sample size
- Further investigation of preinduction fitness scores (Ferrara) and post-induction fitness scores (HCTCI) are pending

Penn Medicine

American Society of Hematology 2021

Real World Survival Outcomes of CPX-351 Versus Venetoclax and Azacitidine for Initial Therapy in Adult Acute Myeloid Leukemia

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December 13, 2021

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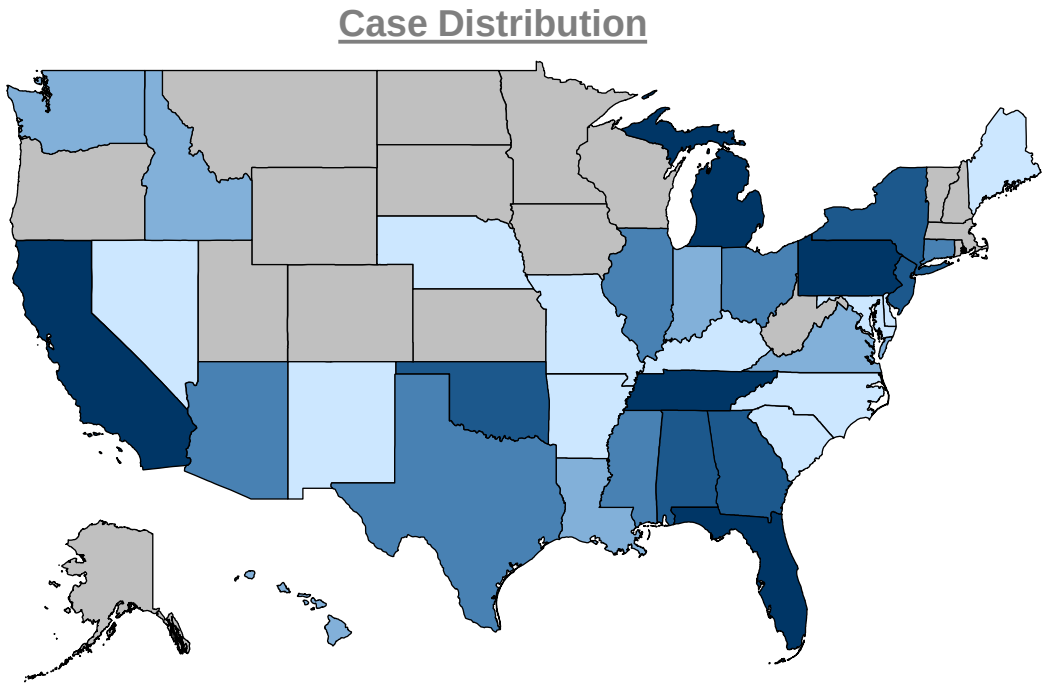
Utilized Two Data Sources: UPHS EHR and Flatiron Database

- UPHS (HUP) EHR: five hospitals system spanning inpatient and outpatient settings
- Flatiron Health database: a nationwide compilation of de-identified EHR-derived clinical, biomarker, treatment and mortality data for 2.2 million real-world oncology patients at 800 different sites of care
  - Longitudinal data spanning inpatient, outpatient visits with both structured and unstructured data sources



Patient Characteristics Show Some Imbalance at Baseline

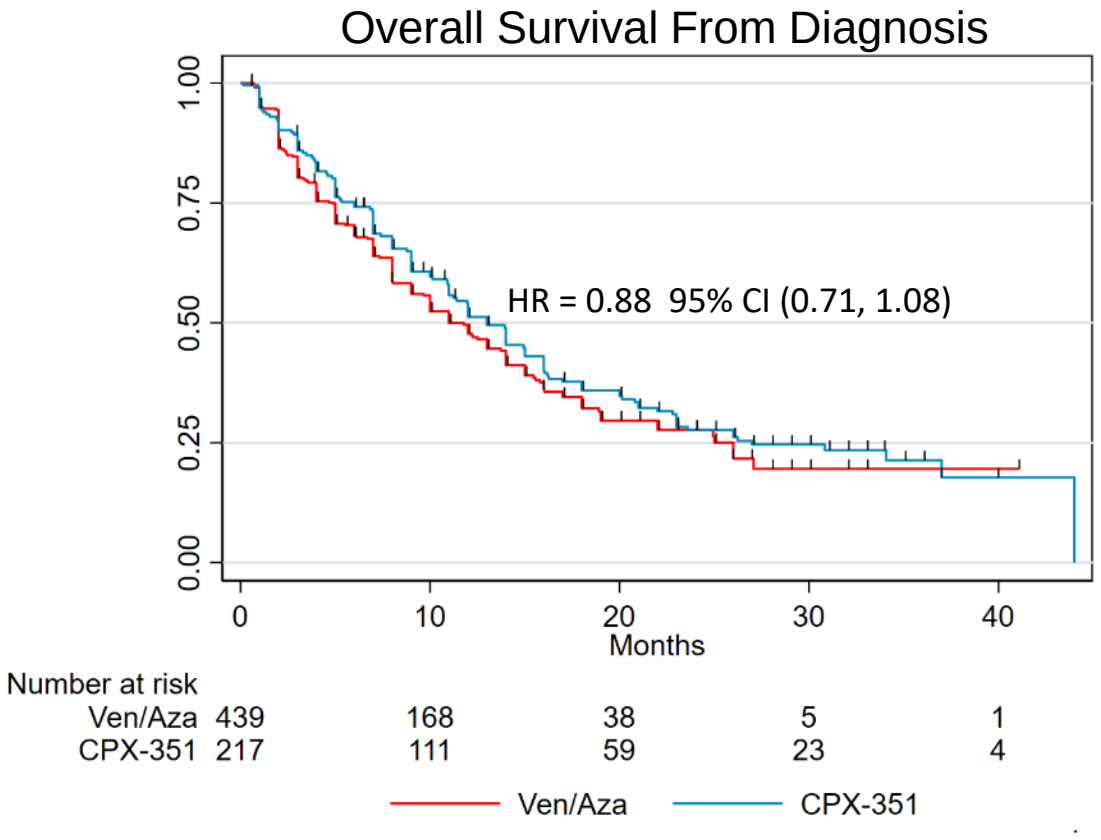
	Ven/Aza N=439	CPX-351 N=217	p-value
Age	**75 (36-88)**	**67 (21-82)**	**<0.001**
Gender			0.056
Female	191 (44%)	112 (52%)	
Male	248 (56%)	105 (48%)	
Practice Type			**<0.001**
Academic	149 (34%)	103 (47%)	
Community	290 (66%)	114 (53%)	
Type			**<0.001**
De Novo	226 (51%)	63 (29%)	
History of MDS/MPN	150 (34%)	104 (48%)	
Therapy-Related	63 (14%)	50 (23%)	
ELN Risk Group			0.84
Favorable	34 (8%)	15 (7%)	
Intermediate	117 (27%)	64 (29%)	
Adverse	172 (39%)	92 (42%)	

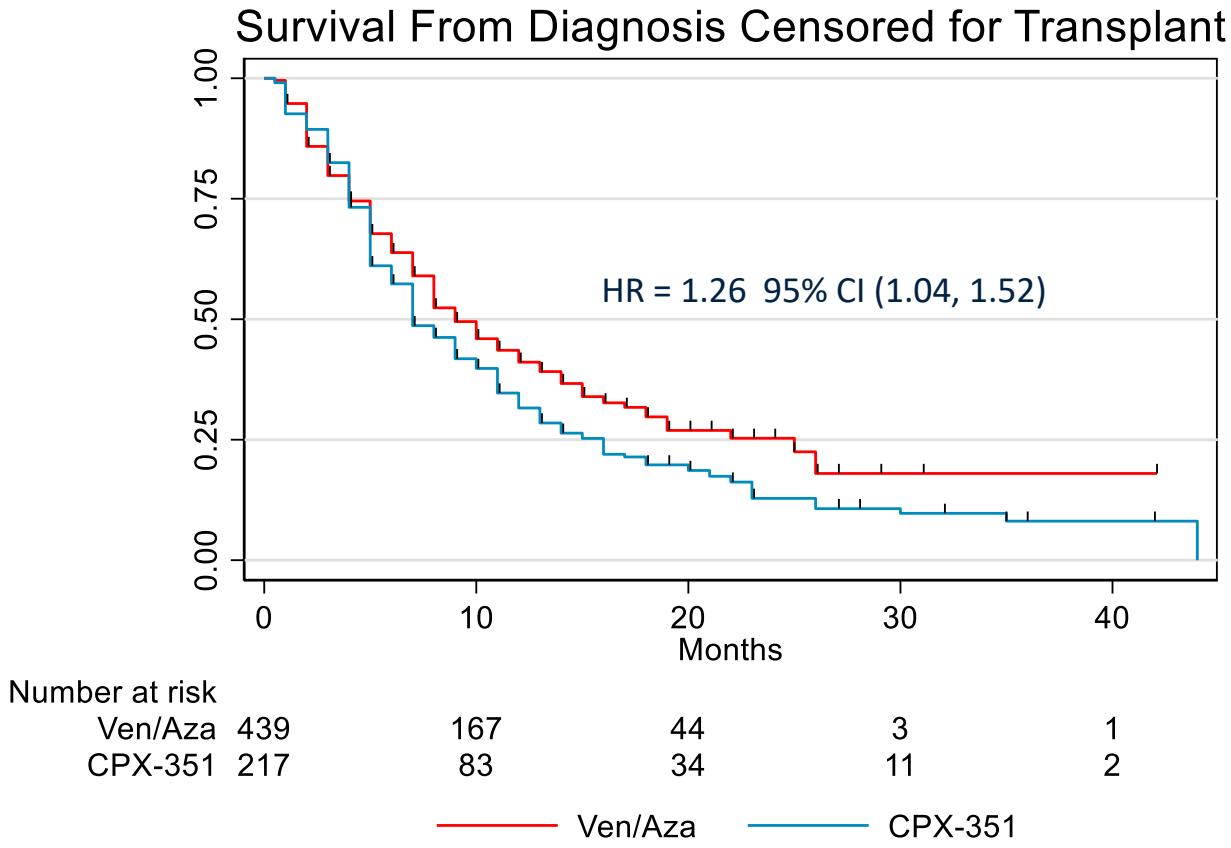
	Ven/Aza N=439	CPX-351 N=217	p-value
HCT-Comorbidity Index			0.28
0	116 (26%)	69 (32%)	
1-2	156 (36%)	69 (32%)	
>=3	82 (19%)	35 (16%)	
Missing	85 (19%)	44 (20%)	
ECOG Performance Status			0.23
0-1	62 (14%)	31 (14%)	
2-4	196 (45%)	72 (33%)	
Missing	181 (41%)	114 (53%)	
High Risk Mutations			0.17
Negative	201 (46%)	90 (41%)	
RUNX1	29 (7%)	22 (10%)	
ASXL1	42 (10%)	14 (6%)	
TP53	57 (13%)	33 (15%)	
Missing	116 (26%)	46 (21%)	

- No significant difference in risk groups, comorbidities, performance status or mutational status
- Expected differences in age, practice type and de novo vs secondary or therapy-related AML

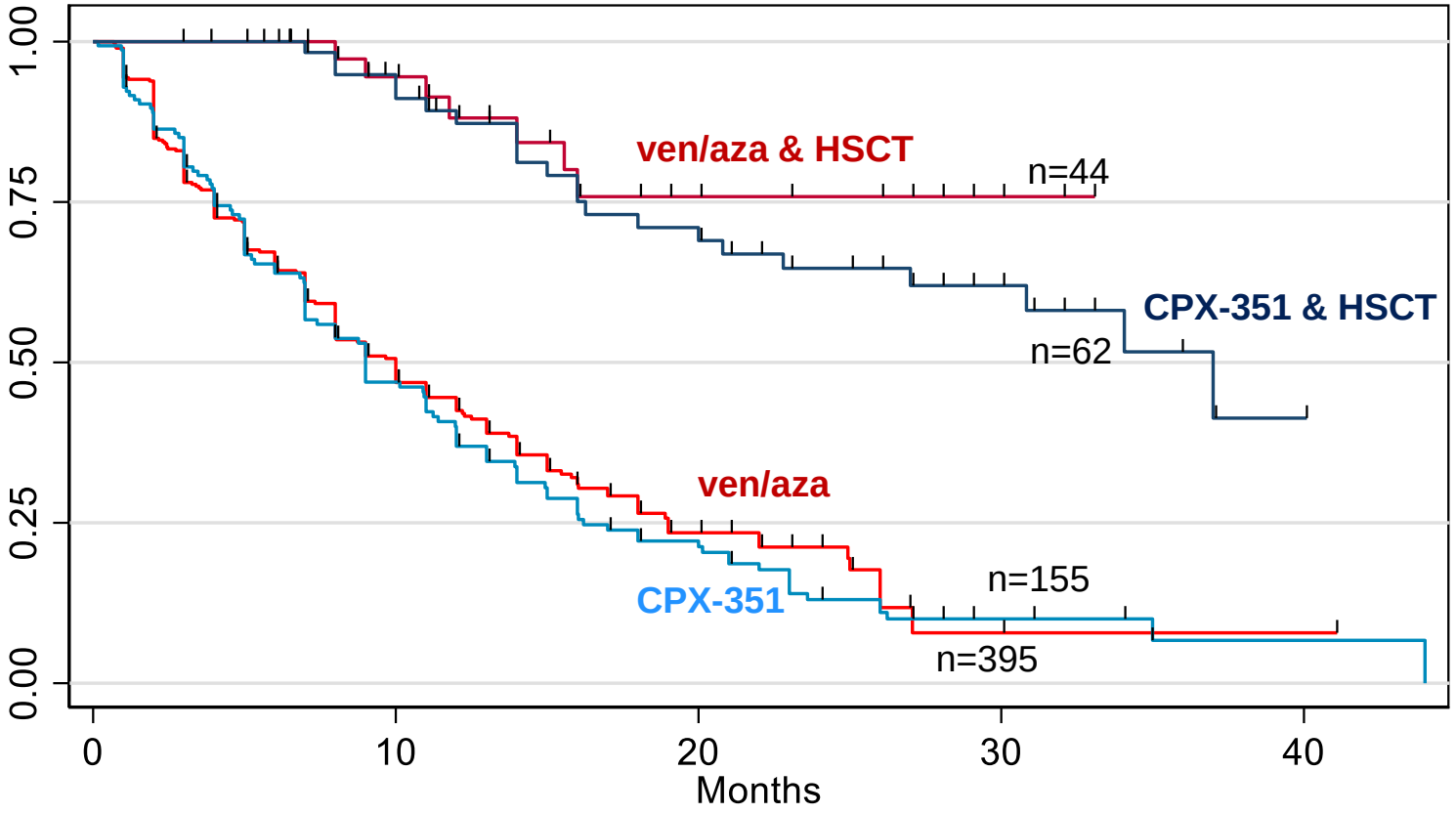
Data are presented as median (range) for continuous measures, and n (%) for categorical measures.

Ven/Aza and CPX-351 Showed Similar Overall Survival



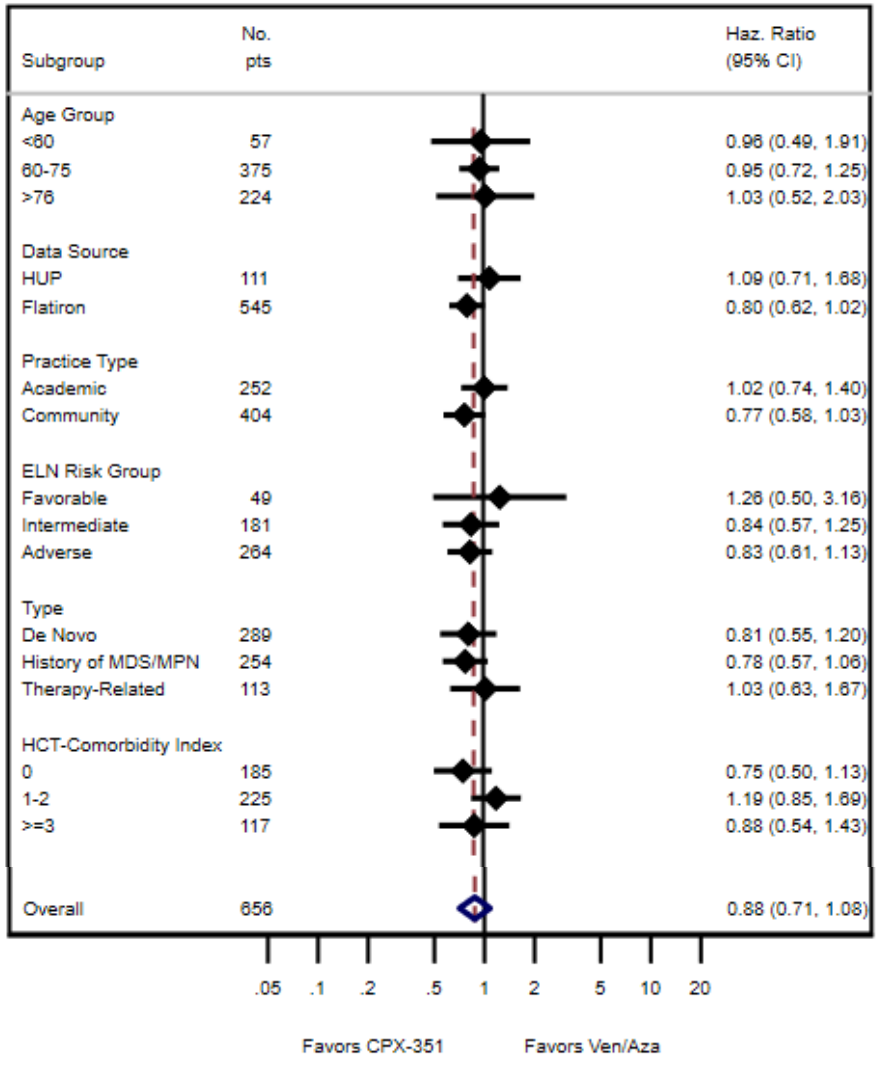


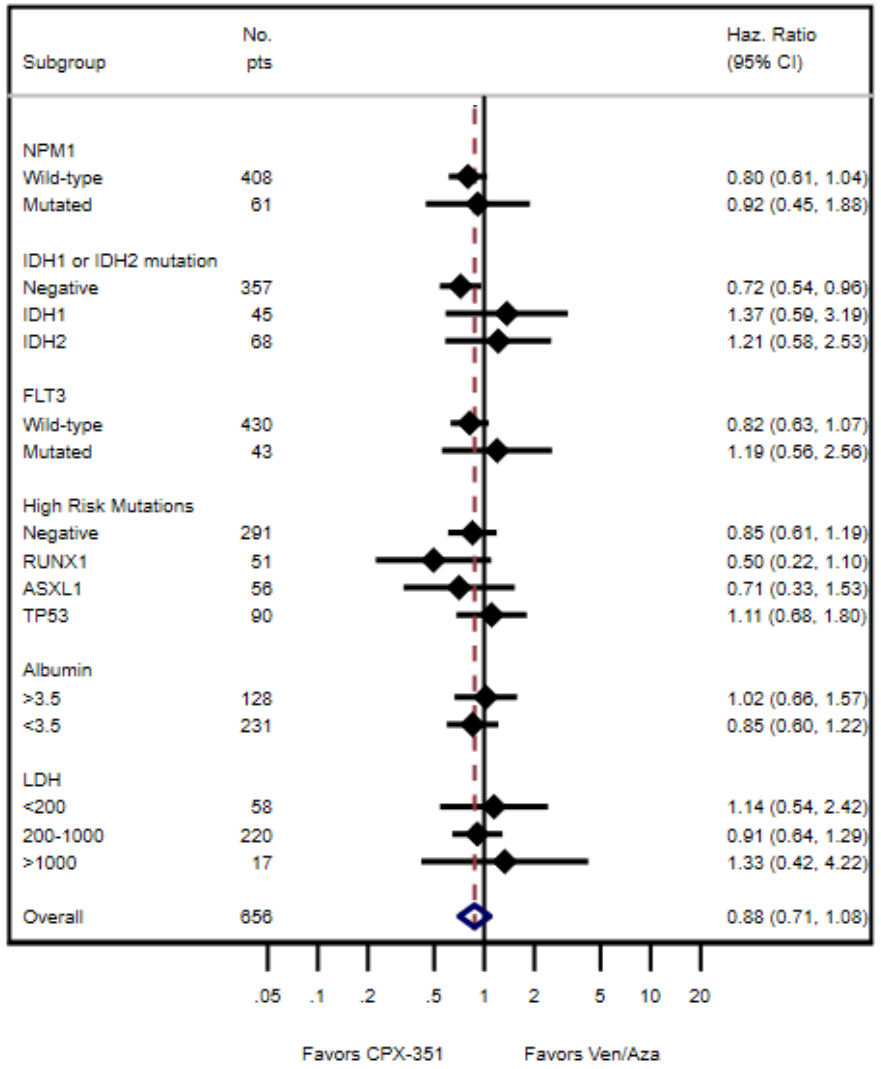
Transplant is Critical for Survival Regardless of Initial Treatment



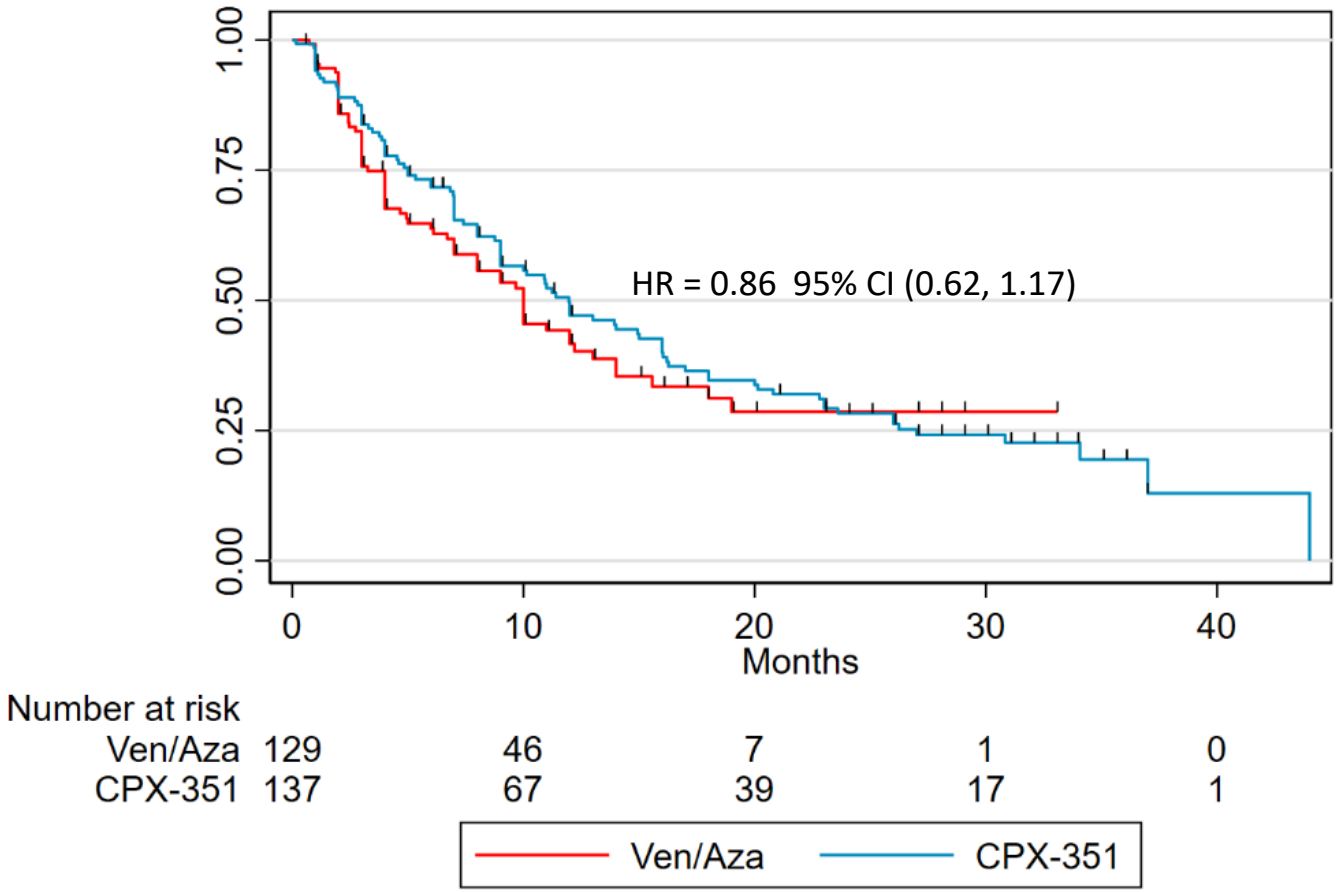
	Venetoclax / Azacitidine	CPX-351
Number (%)	44 (10%)	61 (28%)
Median Time to Transplant (range)	186 days (87 - 578)	171 days (34 - 903)
Median OS w/ HSCT	NR	37 mos
Median OS w/o HSCT	10 mos	9 mos

Key Sub-Groups Did Not Favor Ven/Aza or CPX-351





Restricting to CPX-351 Pivotal Trial Inclusion Criteria Also Showed No Significant Difference in Overall Survival



Population restricted to age 60-75 years-old with a history of a therapy-related myeloid neoplasm, myelodysplasia related cytogenetics or history of MDS/MPN (n=267). Overall survival from diagnosis to death or end of study period.

Early Mortality Similar but Febrile Neutropenia, Infections and Average Inpatient Length of Stay was Higher for CPX-351

Flatiron & UPHS	CPX-351 n = 217	Venetoclax & Azacitidine n = 439	p-value
Median Cycles (range)	2 (1-5)	4 (1-28)	n/a
30 Day Mortality % (95% CI)	5% (2%-8%	5% (3%-7%)	0.51
60 Day Mortality % (95% CI)	10% (6%-14%	13% (10%-16%)	0.10
Diagnosis of Infection[1] % (95% CI)	51% (42%-61%)	20% (15%-25%)	<0.00005

UPHS Only	CPX-351 n = 52	Venetoclax & Azacitidine n = 59	p-value
Febrile Neutropenia % (95% CI)	90% (82%-98%)	54% (42%-67%)	<0.00005
Culture Positive Infection % (95% CI)	67% (55%-80%)	36% (23-48%)	0.0004
Mean Days of Inpatient Stays[2] (95% CI)	41 (37-45)	15 (10-20)	<0.00005

1. Classified as having infection with documented ICD diagnosis code or intravenous antibiotic administration in Flatiron dataset. Culture results were available in University of Pennsylvania (HUP) cohort. 2 Includes readmission before second cycle of therapy. P-values by Fisher's exact test

Conclusions

- Overall survival similar for ven/aza and CPX-351
- CPX-351 and ven/aza had similar OS in all sub-groups and across sensitivity analyses
- Ven/aza and CPX-351 had similar early mortality
  - Ven/aza had lower rates of febrile neutropenia and documented infections
  - Ven/aza had shorter hospital length of stay
- Given similar efficacy, further work should confirm these findings and explore additional endpoints:
  - Prospective Trials (e.g., NCT04801797)
  - Additional Retrospective Replication[1,2,3,4]

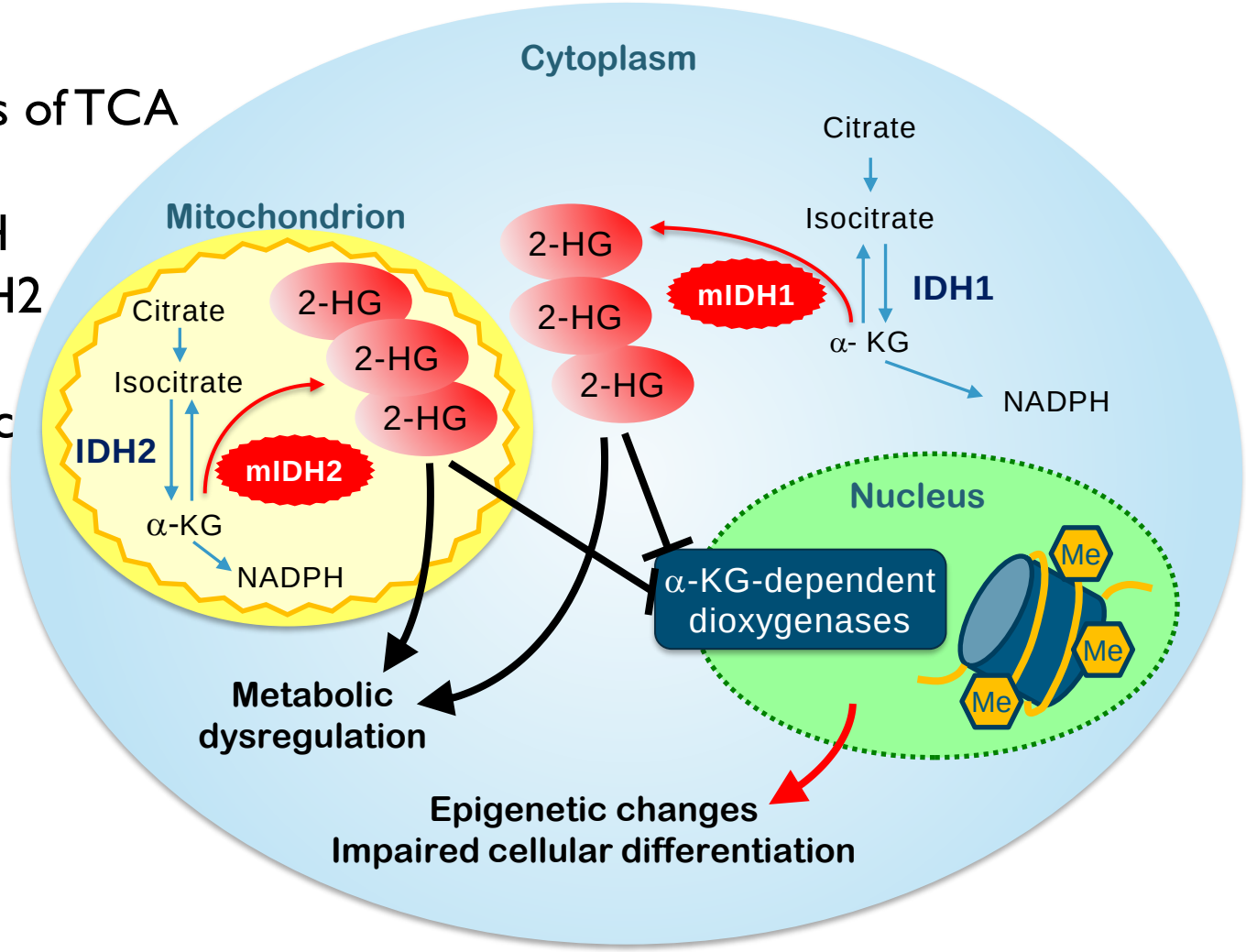
1. *Salhotra et al ASH 2020 Abstract 991* 2. *Salhotra et al AJH 2021* 3. *Cherry et al Blood Advances 2021* 4. *Grenet et al ASH 2021 Abstract 32*

CASE 2

- 77 year old male
- History of mild anemia for 2 years
- Now with pancytopenia with wbc 11.3
- Marrow with 37% blasts, normal karyotype, IDH2 mutated, NPM1 WT, FLT3 WT

IDH1 and IDH2 mutations in AML

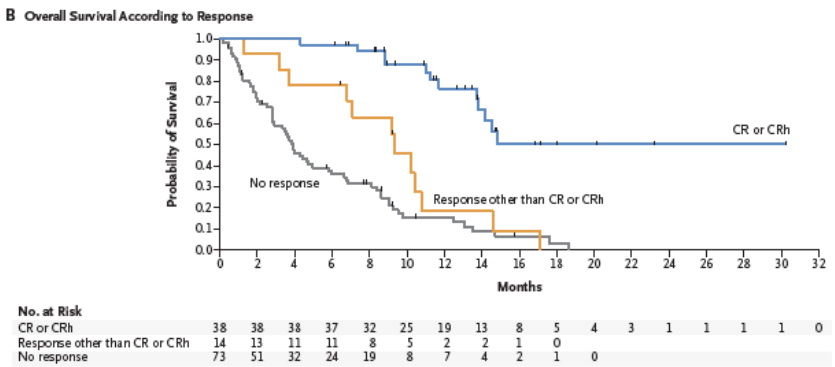
- Isocitrate Dehydrogenase 1 & 2 are members of TCA cycle
- Oncometabolite 2-HG in leukemias with IDH mutations(IDH1: *Mardis et al, NEJM 2009*, IDH2 *et al Cancer Cell 2010*)
- IDH mutations are found in ~16-20 % of AML c
  - IDH1 mutations in ~7.5%
  - IDH2 mutations in ~8-10%
- IDH mutations associated with
  - High platelets
  - Normal Karyotype
  - NPM1 mutations
  - Low WBC
  - Older age in IDH2 only



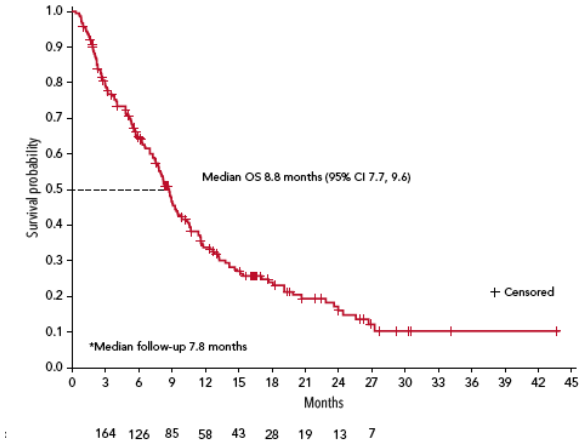
Stein et al, ASH abstract 2018

PHASE I/II IDH INHIBITOR STUDIES

- Ivosidenib (IDH1 R132 mutation only)
  - 125 pts **relapsed or refractory** AML
  - Composite Response Rate (CR or CRh) 30.4% (38/125)
  - Median time to response = 2.7 mo.
  - Median duration of response = 8.2 mo.
  - Differentiation syndrome 3.9%, Leukocytosis 1.7%



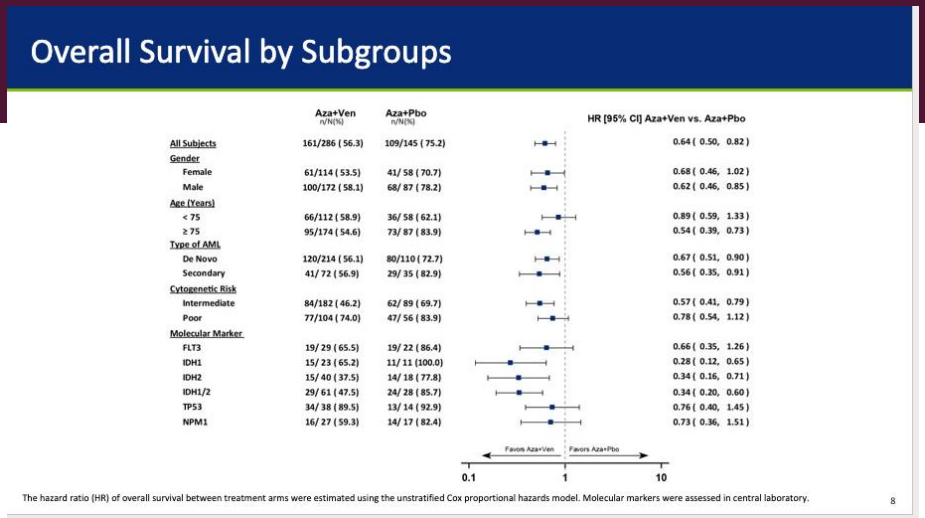
- Enasidenib (IDH2 R140 & R174 mutations only)
  - 214 pts **relapsed or refractory** AML
  - Composite Response Rate (CR or CRp) 29% (62/214)
  - Median time to best response = 3.7 mo.
  - Median duration of response = 5.6 mo.



Stein et al, Blood 2019

AZA VEN IN IDH MUTANT PATIENTS

- Data on HMA/VEN in patients with IDH mutations very encouraging



Mutation	#	CR/CRi %(N)	Duration of response	Overall Survival (mo)
FLT3	18	72 (13)	11(6.5,NR)	NR(8-NR)
IDH ½	35	71(25)	NR(6.8,NR)	24.4 (12.3-NR)
NPM1	23	91(21)	NR(6.8, NR)	NR (11-NR)
TP53	36	47(17)	5.6(1.2,9.4)	7.2(3.7-NR)

Pollyea et al, ASH 2018

Adapted from DiNardo et al, Blood 2018

FRONTLINE IDH1 OR IDH2 MUTANT AML

	Enasidenib (N=39)	Ivosidenib (N=34)	Venetoclax + Hypomethylator (N=25)
CR/CRi	21%	48% (CR30% CRi CRp 18%)	90% (N=20) 400mg & Azacitidine 100% (N=5) 400 mg & Decitabine *71%(N=35) all doses ven
Time to Best Response	3.7 months	2.8 months	1.3 (aza)*
DOR	Not reached	Not reported	Not Reached(6.8, NR)
Median EFS	5.7 months (2.8, 16.0)	Not reported	*Not reached(NR)
Median OS	11.3 months (5.7, 15.1)	12.6 mo	*24.4 m (12.3-NR) includes all dose levels
Grade 3/4 neutropenia	21%	Not reported	36%
Citation	Pollyea et al, Leukemia 2019	Roboz et al, ASH 2018, and Agios personal communication	*DiNardo et al Blood 2019, Pollyea et al, ASH 2018

AGILE: STUDY DESIGN

- Multicenter, double-blind, randomized phase III trial

Patients with untreated AML (WHO criteria); centrally confirmed *IDH1* mutation status; ineligible for IC; ECOG PS 0-2 (planned N = 200)

Ivosidenib 500 mg PO QD + Azacitidine 75 mg/m^2 SC or IV (n = 72)*

Placebo PO QD + Azacitidine 75 mg/m^2 SC or IV (n = 74)*

- Enrollment halted based on efficacy as of May 12, 2021 (N = 148)
- **Primary endpoint:** EFS with ~173 events (52 mo)
- **Secondary endpoints:** CRR, OS, CR + CRh rate, ORR

Montesinos. ASH 2021. Abstr 697.

AGILE: BASELINE CHARACTERISTICS

Characteristic	IVO + AZA (n = 72)	PBO + AZA (n = 74)
Median age, yr (range)	76.0 (58-84)	75.5 (45-94)
Sex, n (%)		
▪ Male	42 (58.3)	38 (51.4)
▪ Female	30 (41.7)	36 (48.6)
ECOG PS, n (%)		
▪ 0	14 (19.4)	10 (13.5)
▪ 1	32 (44.4)	40 (54.1)
▪ 2	26 (36.1)	24 (32.4)
Disease history, n (%)		
De novo AML	54 (75.0)	53 (71.6)
Secondary AML	18 (25.0)	21 (28.4)

Characteristic	IVO + AZA (n = 72)	PBO + AZA (n = 74)
Median m*IDH1* VAF in BMA, % (range)	36.7 (3.1-50.5)	35.5 (3.0-48.6)
Cytogenetic risk, n (%)		
Favorable	3 (4.2)	7 (9.5)
Intermediate	48 (66.7)	44 (59.5)
Poor	16 (22.2)	20 (27.0)
Median bone marrow blasts, % (range)	54.0 (20-95)	48.0 (17-100)

Montesinos. ASH 2021. Abstr 697.

AGILE: EFS AND OTHER EFFICACY OUTCOMES

Survival Outcome	IVO + AZA	PBO + AZA	HR (95% CI)	*P* Value
Median EFS in ITT population	NR	NR	0.33 (0.16-0.69)	.0011
Median EFS in patients achieving CR by Wk 24, mo (95% CI)	NE (14.8-NE)	17.8 (9.3-NE)	NR	NR
Median OS, mo	24.0	7.9	0.44 (0.27-0.73)	.0005

- EFS benefit associated with IVO consistent across subgroups: de novo status, region, age, ECOG PS at BL, sex, race, BL cytogenetic risk, WHO AML classification, WBC at BL, percentage of BM blasts at BL
- OS benefit associated with IVO consistent against same subgroups
- Change in markers of health-related QoL favored IVO + AZA over PBO + AZA

Montesinos. ASH 2021. Abstr 697.

Slide credit: clinicaloptions.com

AGILE: RESPONSE

Response	IVO + AZA (n = 72)		PBO + AZA (n = 74)
CR rate, n (%) [95% CI]	34 (47.2) [35.3-59.3]		11 (14.9) [7.7-25.0]
▪ OR (95% CI); *P* value		4.8 (2.2-10.5); <.0001	
▪ Median duration of CR, mo (95% CI)	NE (13.0-NE)		11.2 (3.2-NE)
▪ Median time to CR, mo (range)	4.3 (1.7-9.2)	5.0 (2.3-10.8); <.0001	3.8 (1.9-8.5)
CR + CRh, n (%) [95% CI]	38 (52.8) [40.7-64.7]		13 (7.6) [9.7-28.2]
▪ OR (95% CI); *P* value			
▪ Median duration of CR + CRh, mo (95% CI)	NE (13.0-NE)		9.2 (5.8-NE)
▪ Median time to CR + CRh, mo (range)	4.0 (1.7-8.6)	7.2 (3.3-15.4); <.0001	3.9 (1.9-7.2)
ORR, n (%) [95% CI]	45 (62.5) [50.3-73.6]		14 (18.9) [10.7-29.7]
▪ OR (95% CI); *P* value			
▪ Median duration of response, mo (95% CI)	22.1 (13.0-NE)		9.2 (6.6-14.1)
▪ Median time to response, mo (range)	2.1 (1.7-7.5)		3.7 (1.9-9.4)
m*IDH1* Clearance in BMMCs by Response, n/N (%)	**IVO + AZA (n = 43)**		**PBO + AZA (n = 34)**
CR + CRh	17/33 (51.5)		3/11 (27.3)
▪ CR	14/29 (48.3)		2/10 (20)
▪ CRh	3/4 (75)		1/1 (100)
Non-CR + CRh responders	2/4 (50)		0/2 (0)
Nonresponders	1/6 (16.7)		0/21 (0)

Slide credit: clinicaloptions.com

AGILE: TEAEs

TEAEs, n (%)	IVO + AZA (n = 71)		PBO + AZA (n = 73)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	70 (98.6)	66 (93.0)	73 (100)	69 (94.5)
Any hematologic TEAE	55 (77.5)	50 (70.4)	48 (65.8)	47 (64.4)
Most common hematologic TEAEs*				
▪ Anemia	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
▪ Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
▪ Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
▪ Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)
Most common TEAEs*				
▪ Nausea	30 (42.3)	2 (3.8)	28 (38.4)	3 (4.1)
▪ Vomiting	29 (40.8)	0	19 (36.0)	1 (1.4)
▪ Diarrhea	25 (35.2)	1 (1.4)	26 (35.6)	5 (6.8)
▪ Pyrexia	24 (33.8)	1 (1.4)	29 (39.7)	2 (2.7)
▪ Constipation	19 (26.8)	0	38 (52.1)	1 (1.4)
▪ Pneumonia	17 (23.9)	16 (22.5)	23 (31.5)	21 (28.8)
Bleeding	29 (40.8)	4 (5.6)	21 (28.8)	5 (6.8)
Infections	20 (28.2)	15 (21.1)	36 (49.3)	22 (30.1)

- AEs of special interest (IVO + AZA vs PBO + AZA):
  - Grade ≥2 differentiation syndrome: 14.1% vs 8.2%
  - Grade ≥3 QT prolongation: 9.9% vs 4.1%
- Fewer infections with IVO + AZA vs PBO + AZA (28.2% vs 49.3%)
- No treatment-related deaths

Slide credit: clinicaloptions.com

AGILE: INVESTIGATORS' CONCLUSIONS

- In patients with newly diagnosed *IDH1*-mutated AML ineligible for intensive CT, ivosidenib + azacitidine significantly extended EFS vs placebo + azacitidine
  - HR: 0.33 (95% CI: 0.16-0.69; *P* = .0011)
  - OS and clinical response also were significantly improved
- Overall frequency of TEAEs similar between arms
  - Fewer infections with ivosidenib + azacitidine treatment arm
- Change in markers of health-related QoL favored ivosidenib + azacitidine over placebo + azacitidine
- Investigators concluded study findings demonstrated that ivosidenib + azacitidine provides clinical benefit in this patient population

Montesinos. ASH 2021. Abstr 697.

CASE 3

- 72 year old , history of CAD, EF 40%
- Presents with wbc 77000 and 80% blasts,
- FLT3 ITD mutated

A Triplet Combination of Azacitidine, Venetoclax and Gilteritinib for Patients with FLT3-mutated AML: Results from a Phase I/II Study

NJ Short, CD Dinardo, N Daver, D Nguyen, M Yilmaz, T Kadia, G Garcia-Manero, GC Issa, X Huang, W Qiao, K Sasaki, G Montalban-Bravo, K Chien, G Borthakur, R Delumpa, A Milton, S Pierce, E Jabbour, M Konopleva, H Kantarjian, F Ravandi

Department of Leukemia

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Aza+Ven+Gilteritnib in FLT3-mutated AML: Background

- FLT3 mutations detectable in ~1/3 of newly diagnosed AML
  - Prognostic impact: ITD mutations → inferior survival (frontline and R/R)[1-2]
  - Therapeutic impact: indication for HSCT in first remission, targetable with FLT3 inhibitors (both ITD and TKD mutations)
- Gilteritinib: potent FLT3 inhibitor shown to improve response rates and OS in R/R *FLT3*-mutated AML[3]
  - Preclinical and clinical evidence for synergy of gilteritinib and venetoclax[4-5]
- Azacitidine plus venetoclax: standard of care in older, unfit pts
  - Outcomes are suboptimal, especially for *FLT3*-ITD-mutated AML[6]

[1]Frohling S et al. *Blood* 2002;100:4372-80
[2]Ravandi F et al. *Leuk Res* 2010;34(6):752-6
[3]Perl AE et al. *N Engl J* Med 2019;381(18):728-40
[4]Mali RS et al. *Haematologica* 2021;106(4):1034-46
[5]Daver N et al. ASH 2020 (abstract #333)
[6]Konopleva NY et al. ASH 2020 (abstract #1904)

Aza+Ven+Gilteritinib in FLT3-mutated AML: Regimen

- Relapsed/refractory *FLT3*-mutated* AML or high-risk MDS or CMML

or

- Newly diagnosed *FLT3*-mutated* AML unfit for intensive chemotherapy

Induction

Azacitidine
75 mg/m² IV/SC on D1-7

Venetoclax#
D1-28 (bone marrow on D14)%

Gilteritinib
80-120 mg on D1-28

Consolidation (up to 24 cycles)

Azacitidine
75 mg/m² IV/SC on D1-5

Venetoclax
400mg on D1-7

Gilteritinib
80-120 mg on D1-28

* FLT3-ITD or FLT3 D835 mutations allowed

Venetoclax ramp-up during cycle 1: 100mg on D1, 200mg on D2, 400mg on D3+

% If <5% blasts or insufficient on C1D14, venetoclax held (both cohorts) and gilteritinib held (frontline only)

- Primary endpoints: MTD of gilteritinib in combination (phase I), CR/CRi rate (phase II)
- Secondary endpoints: CR rate, MRD negativity rate, duration of response, OS, safety

Aza+Ven+Gilteritinib in FLT3-mutated AML: Patients

		Frontline (N=14)	Relapsed/Refractory (N=16)
Characteristic	Category	N (%) / median [range]	N (%) / median [range]
Age (years)		71 [61-82]	68 [19-90]
	≥60 years	14 (100)	12 (75)
	≥75 years	4 (29)	3 (19)
Diagnosis	AML	14 (100)	15 (94)
	MDS/CMML	0	1 (6)
Cytogenetics	Diploid	7 (50)	6 (37)
	Adverse-risk	3 (21)	6 (37)
	Others	4 (29)	4 (26)
FLT3 mutation type	ITD	11 (79)	7 (44)
	TKD	3 (21)	6 (37)
	ITD+TKD	0	3 (19)
FLT3 allelic ratio	ITD	0.29 [0.04-3.35]	0.61 [0.03-15.7]
	TKD	0.85 [0.03-1.11]	0.59 [0.01-1.35]
Number of prior therapies		---	2 [1-5]
Prior FLT3 inhibitor		---	5 (31)
Prior HMA + venetoclax		---	7 (44)
Prior HSCT		---	5 (31)

Aza+Ven+Gilteritinib in FLT3-mutated AML: Patients

	Frontline (N=14)	Relapsed/Refractory (N=16)
Mutations (detected in ≥2 pts)	N (%) / median [range]	N (%) / median [range]
DNMT3A	9 (73)	9 (56)
NPM1	6 (43)	7 (44)
RUNX1	3 (21)	5 (31)
TET2	5 (36)	3 (19)
WT1	1 (7)	6 (37)
BCOR	4 (29)	0
KRAS/NRAS	2 (14)	2 (13)
GATA2	1 (7)	2 (13)
TP53	1 (7)	2 (13)
ASXL1	0	2 (13)
ASXL2	0	2 (13)
BCORL1	2 (14)	0
CBL	0	2 (13)
SMC3	0	2 (13)
STAG2	0	2 (13)

Aza+Ven+Gilteritinib in FLT3-mutated AML: Phase I Safety

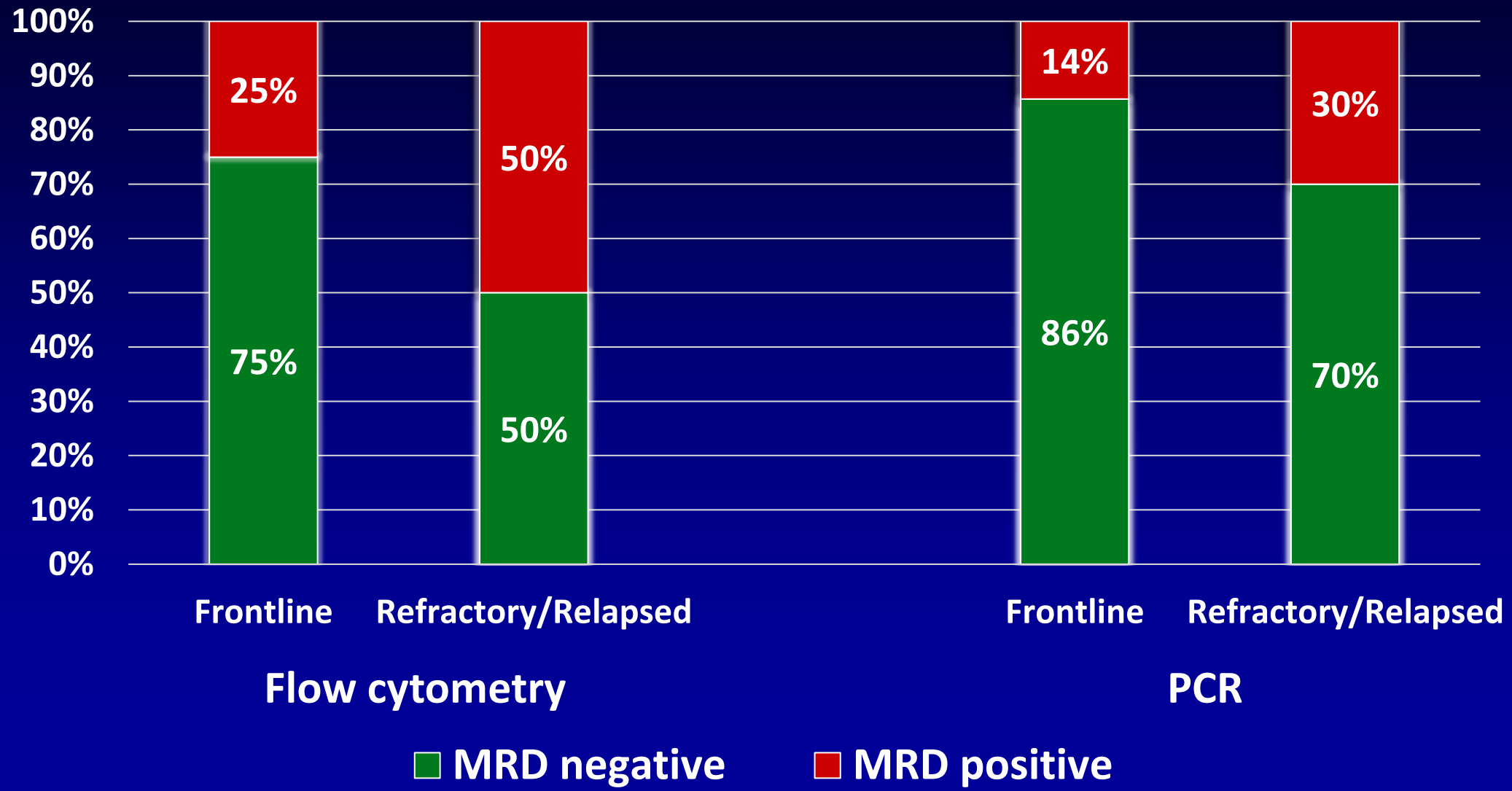
- 10 pts treated in Phase I cohort
  - Gilteritinib 80mg daily in 6 pts
  - Gilteritinib 120mg daily in 4 pts (1 pt not evaluable for DLT)
- No non-hematologic DLTs observed
- Myelosuppression appeared greater with gilteritinib 120mg dosing
  - 1/3 DLT at 120mg (grade 4 myelosuppression); 0/6 DLTs at 80mg
  - Among 3/4 responding pts at 120mg dose, MLFS was best response
  - 3/6 pts (50%) at 80mg dose responded → 1 CR and 2 CRi
  - Gilteritinib 80mg chosen as phase II expansion dose

Aza+Ven+Gilteritinib in FLT3-mutated AML: Responses

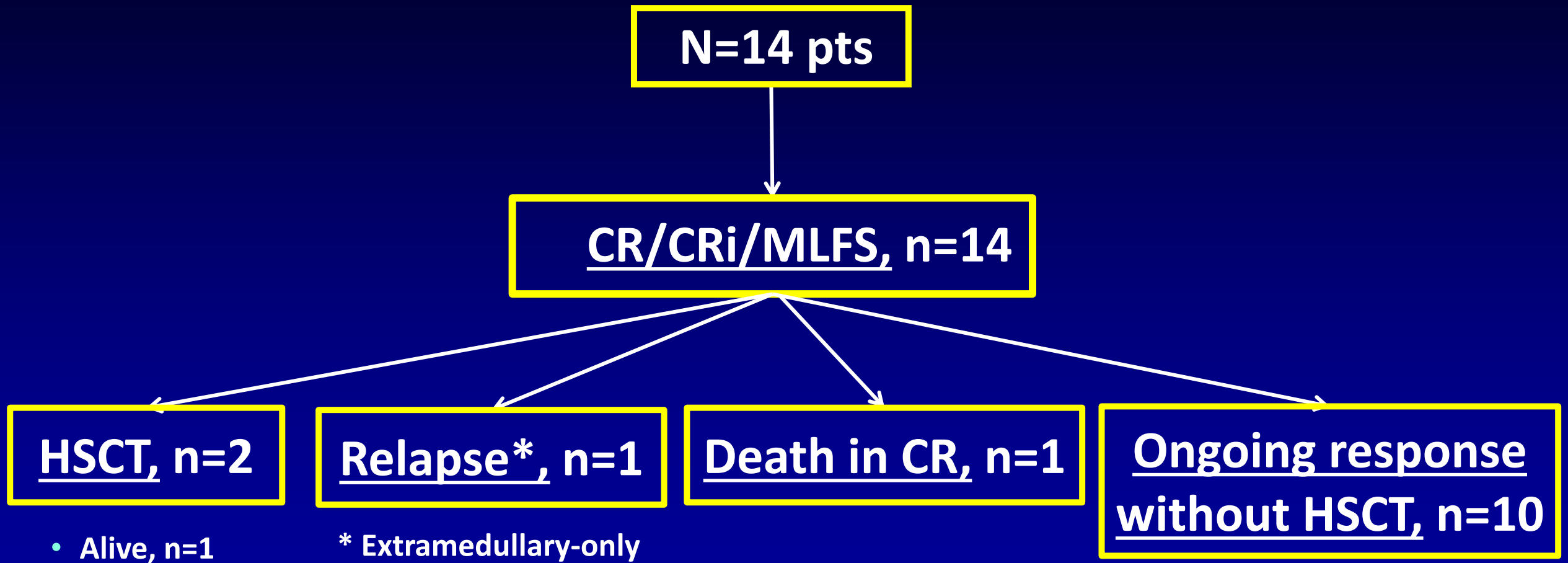
Response, n/N (%)	Frontline N = 14	R/R N = 16
mCRc (CR/CRi/MLFS)	14 (100)	11 (69)
CR	13 (93)	3 (19)
CRi	0	2 (13)
MLFS	1 (7)	6 (37)
PR**	0	1 (6)
No response	0	4 (25)
Early death	0	0

** PR in 1 patient with extramedullary-only disease (assessed by PET scan)

Aza+Ven+Gilteritinib in FLT3-mutated AML: Best MRD Response



Aza+Ven+Gilteritinib in FLT3-mutated AML: Disposition - Frontline AML

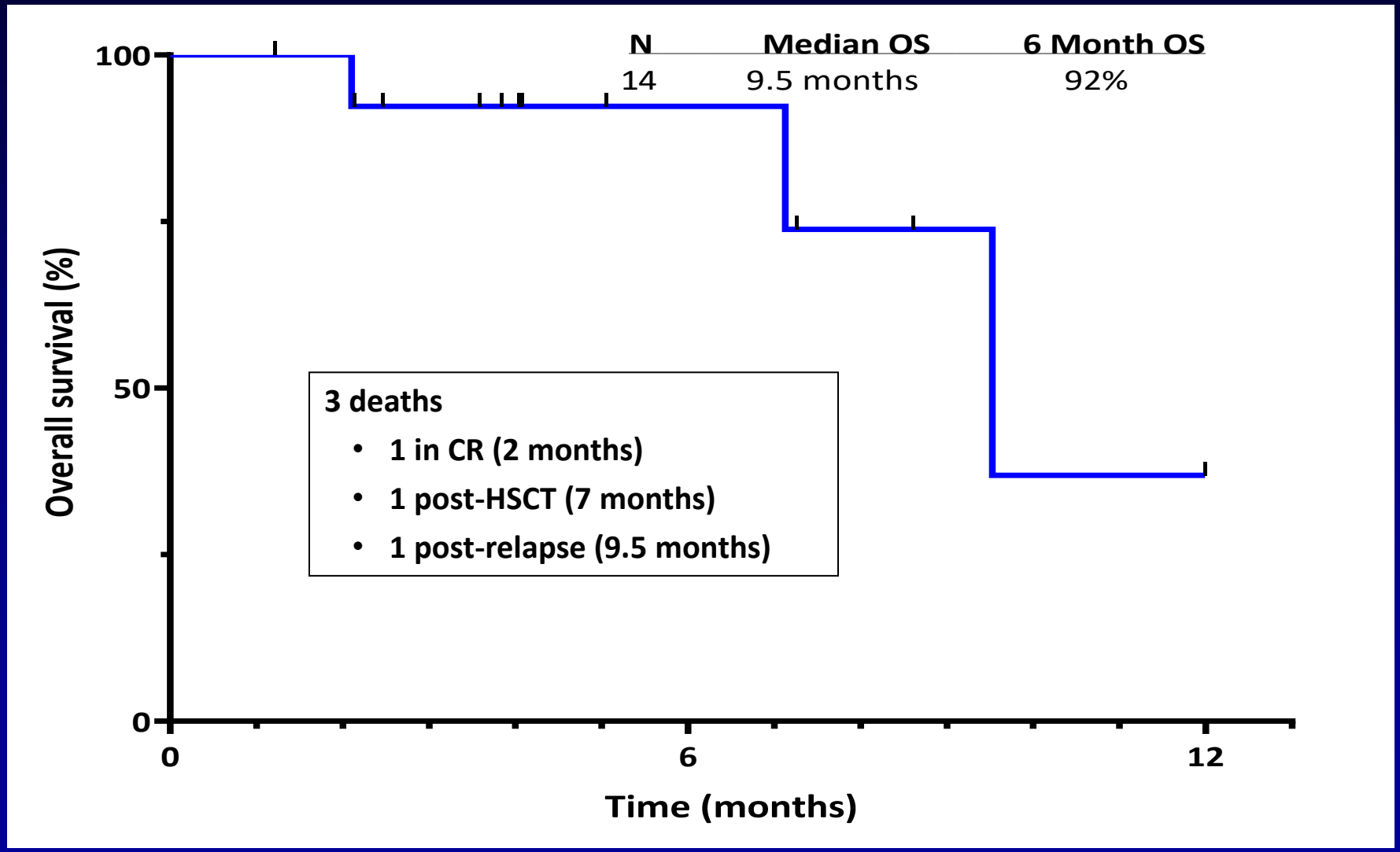


- Alive, n=1
- Died, n=1

* Extramedullary-only relapse after 7-month CR

Aza+Ven+Gilteritinib in FLT3-mutated AML: OS in Frontline Cohort

Median follow-up: 4.1 months (range, 1.2-12.0+ months)



Aza+Ven+Gilteritnib in FLT3-mutated AML: Grade ≥3 Non-Hematologic Adverse Events

	Frontline (N=14)			Refractory/Relapsed (N=16)		
Adverse events	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Acute kidney injury	0	0	0	1 (6)	0	0
Atrial fibrillation	0	0	0	1 (6)	0	0
DIC	0	0	0	0	0	1 (6)
Epistaxis	0	0	0	1 (6)	0	0
Febrile neutropenia	0	0	0	5 (31)	0	0
GI bleeding	0	0	0	0	1 (6)	0
Hyponatremia	0	0	0	1 (6)	0	0
Hypotension	0	0	0	2 (12)	1 (6)	0
Infection	4 (29)	0	1 (7)	9 (56)	0	2 (12)
Intracranial hemorrhage	0	0	0	0	0	1 (6)
Nausea/vomiting	1 (7)	0	0	0	0	0
QT prolongation	1 (7)	0	0	0	0	0
Sepsis	0	0	0	3 (19)	1 (6)	0
Tumor lysis syndrome	0	0	0	1 (6)	0	0

Aza+Ven+Gilteritnib in FLT3-mutated AML: Hematologic Recovery in Cycle 1

Hematologic parameter	Frontline cohort		R/R cohort	
	Evaluable pts	Median [range]	Evaluable pts	Median [range]
ANC >500	n=14	38 [28-117 days]	n=6	46 [35-63 days]
ANC >1000	n=13	40 [32-53 days]	n=5	53 [46-77 days]
Platelets >50K	n=14	20 [16-84 days]	n=5	26 [13-77 days]
Platelets >100K	n=13	28 [18-43 days]	n=3	21 [17-82 days]

Aza+Ven+Gilteritinib in FLT3-mutated AML: Conclusions

- Azacitidine + venetoclax + gilteritinib results in high rates of mCRc in newly diagnosed (100%) and R/R (69%) *FLT3*-mutated AML
  - CR rate 93% and FLT3 PCR negativity rate 86% in newly diagnosed pts
- Durability of responses encouraging in newly diagnosed pts
  - Only 1 relapse to date; 6-month OS rate: 92%
- Myelosuppression common but manageable with mitigation strategies
  - Use of gilteritinib 80mg
  - Day 14 bone marrow to determine course of venetoclax/gilteritinib
  - Attenuation of azacitidine/venetoclax in consolidation

CONCLUSION

2017 Approvals

April 28	August 1	August 3	September 1
Midostaurin new dx FLT3-mut AML	**Enasidenib** rel/ref IDH2-mut AML	**CPX-351** new dx therapy-related AML or AML with MRC	**Gemtuzumab ozogamicin** new dx CD33+ AML in adults and rel/ref CD33+ AML in adults and children

2018 Approvals

August 8	November	November	November	December
Ivosedinib Rel/ref IDH1m AML	**Venetoclax** new dx AML Age 75+/unfit	**Glasdegib** new dx AML Age 75+/unfit	**Gilteritinib** rel/ref FLT3-mut AML	**Tagraxofusp** BPDCN

And in 2020 Oral Azacitidine

Many new drugs for AML
Approved or shown to be of benefit in particular subsets and/or populations
Now exploring new indications , broader subgroups and combinations
Randomized trials needed to better define how to use these agents