ACC MED

ACCADEMIA NAZIONALE DI MEDICINA

Leucemia mieloide acuta
Novità da ASH 2021

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Agenda

- Venetoclax-based treatment
- Intensive induction therapy
- Combinazioni terapeutiche per AML FLT3 mutate

Agenda

- **Venetoclax-based treatment**
- Intensive induction therapy
- Combinazioni terapeutiche per AML FLT3 mutate

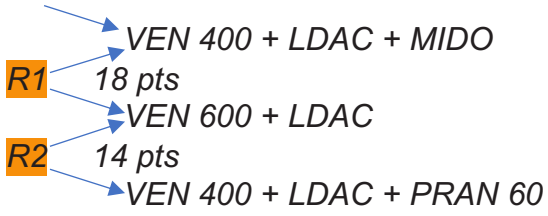
An Australasian Leukemia Lymphoma Group (ALLG) Phase 2 Study to Investigate Novel Triplets to Extend Remission with Venetoclax in Elderly (INTERVENE) Acute Myeloid Leukemia

Patients with treatment naïve AML (excluding APL), aged ≥60 y, unfit for intensive chemotherapy
Prior hypomethylating agents for antecedent MN were per mitted with a 14-day washout.
Stratification by Cytogenetic risk (Medical Research Council 2010 criteria)

Safety run in Phase (different dosages) → *Randomization Phase*

Treatment: VEN D1-28 (with dose ramp-up in cycle 1)
LDAC (20mg/m^2 SC D1-10)
MIDO (from D10 for 14 days) in non adverse risk
or PRACINOSTAT (from D10, 3/w for 9 doses) in adverse risk

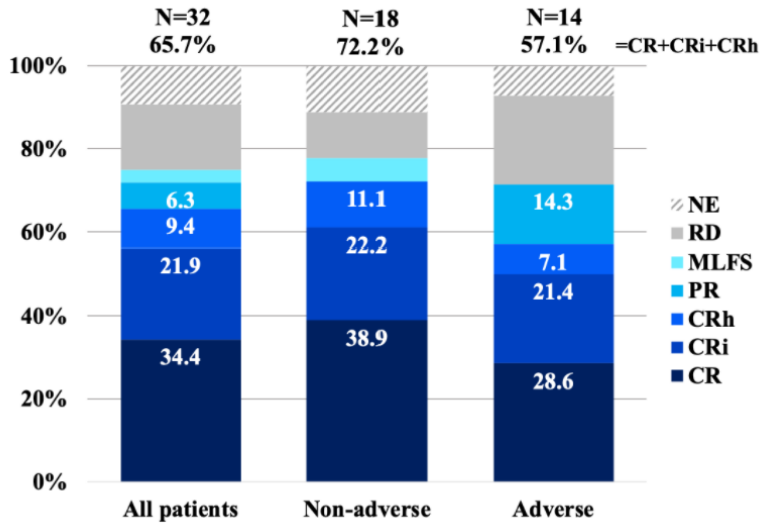
In the NON-ADV stratum (VEN-LDAC-MIDO)
L1: VEN 400mg + LDAC + MIDO 50mg
L2: VEN 600mg + LDAC + MIDO 50mg.
In the ADV stratum (VEN-LDAC-PRAN)
L1: VEN 400mg + LDAC + PRAN 45mg
L2: VEN 600mg + LDAC + PRAN 60mg
L3: VEN 600mg + LDAC + PRAN 60mg.
Azole antifungals were prohibited in cycle 1 but allowed from cycle 2 with VEN dose modification.



VEN 400 + LDAC + MIDO
18 pts
VEN 600 + LDAC
14 pts
VEN 400 + LDAC + PRAN 60

R1: 2 pts FLT3mut
R2: 6 pts TP53mut

Figure 1B. Preliminary response rates (Safety run-in phase)



Conclusion

- The addition of MIDO or PRAN to VEN-LDAC was tolerable in older/unfit patients with treatment naïve AML.
- Preliminary efficacy with this risk-stratified approach compared favorably to prior studies with VEN-LDAC alone
- The randomized phase 2 part of this tandem triplet strategy with the goal of preventing adaptive resistance is underway.

Paper Number: 368; Chong Chua, The Alfred Hospital & Monash University, Australia

Safety and Efficacy of Cusatuzumab in Combination with Venetoclax and Azacitidine (CVA) in Patients with Previously Untreated AML Not Eligible for Intensive Chemotherapy; An Open-Label, Multicenter, Phase 1b Study

Table 1. Overall best response in subjects with AML treated with CVA.

	Intention-to-treat, N (%)*	Response evaluable, N (%)*
Number of subjects	44	42
Best response		
Complete remission (CR)	20 (45.5)	20 (47.6)
CR with partial hematologic recovery (CRh)†	10 (22.7)	10 (23.8)
CR with incomplete hematologic recovery (CRi)	14 (31.8)	14 (33.3)
CR + CRh† + CRi	34 (77.3)	34 (81.0)
Morphologic leukemia-free state (MLFS)	5 (11.4)	5 (11.9)
Partial remission (PR)	0	0
Stable disease (SD)‡	3 (6.8)	3 (7.1)
Progressive disease (PD)	0	0
Not evaluable (NE)*	2 (4.5)	0

*Two subjects who did not have post-baseline disease evaluation due to death were included in the intention-to-treat analysis set but were excluded from the response evaluable analysis set.
†CRh was programmatically determined by the study sponsor. All patients who achieved CRh also met the criteria for CRi.
‡All 3 subjects had a stable disease duration of <90 days.
AML, acute myeloid leukemia; CVA, cusatuzumab, venetoclax, azacitidine.

CD70: a TNFreceptor ligand. With its receptor CD27 is expressed on LSCs and AML blasts, but not on hematopoietic stem cells. CUSATUZUMAB: a high-affinity humanized monoclonal anti-CD70 antibody, kills CD70-expressing cells by Fc domain-mediated effector functions and is a potent inhibitor of CD70-CD27 signaling.

Background:
- CULMINATE trial (Cusa + Aza)
- Sinergia con VEN in vitro

44 pts with untreated AML (*de novo* or secondary) ineligible for IC due to age ≥75 years or medical comorbidities.

Paper Number: 369; Gail Roboz, Weil Cornell Medicine, New York Presbiterian Hospital

Safety and Efficacy of Cusatuzumab in Combination with Venetoclax and Azacitidine (CVA) in Patients with Previously Untreated AML Not Eligible for Intensive Chemotherapy; An Open-Label, Multicenter, Phase 1b Study

Results

MRD neg (flow) in 47% of responders (CR, CRi or CRh)
Median time to first response: 4.2 weeks.
Median time to best response: 6.4 weeks
97.1% of responders experienced at least one cycle delay in administration of CVA post response
Mortality rate at 30 days: 4.5%
Median follow-up: 29.1 weeks

Toxicity

- Grade 3 or above TEAEs: 97.7% of patients;
- the most common AE were neutropenia (68.2%), thrombocytopenia (65.9%), febrile neutropenia (36.4%), anemia (34.1%), leukopenia (29.5%), sepsis (27.3%), and lymphopenia (15.9%).
- SAEs: 75% of patients;
- the most common SAEs were febrile neutropenia (27.3%), sepsis (22.7%), COVID-19 (6.8%), and thrombocytopenia (6.8%).
- Infusion-related reactions (IRRs): 11.4% of patients with 2.3% at grade ≥3.

CONCLUSIONS

Response rates support an additive effect of cusatuzumab to the standard of care with potential for improved clinical outcomes and the toxicity profile was favorable.
However, further clinical trials are needed for validation of these initial results.

Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed Older/Unfit or High-Risk AML and Relapsed/Refractory (R/R) AML

Background:

Outcomes in R/R AML are poor with median overall survival (mOS) 5-7 mon

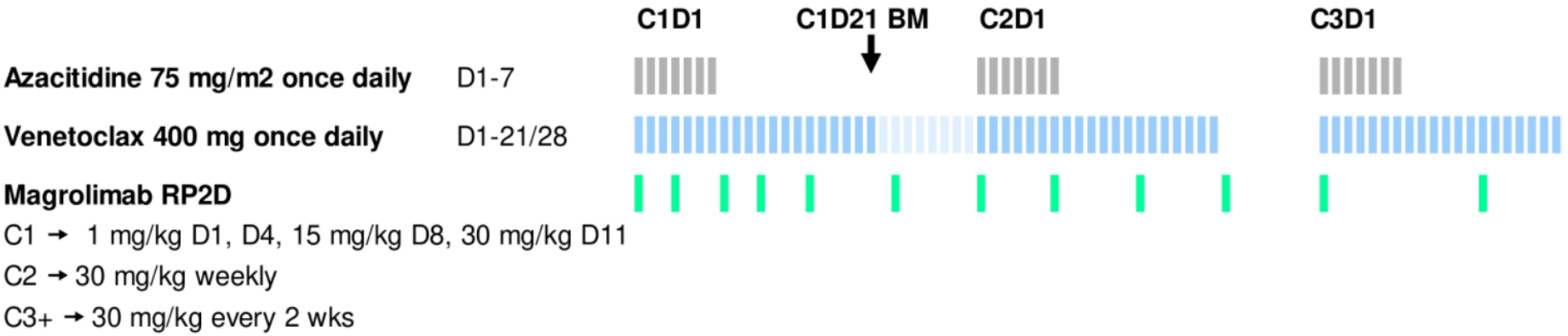
Magrolimab, an anti-CD47 antibody that blocks the “don’t eat me signal” on macrophages

Magro with AZA-VEN increased phagocytosis in AML cell lines *in vitro* regardless of $TP53^{mut}$ status, and prolonged survival *in vivo*.

Pts ≥18 years with ECOG PS ≤2 and WBC <15x10^9/L.

Phase Ib: R/R AML to establish the best dose

Phase II enrolled pts in 3 arms (frontline, VEN-naïve R/R AML, and VEN-exposed R/R AML)



Paper Number: 371; Naval Daver, MD Anderson Cancer Center

Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed Older/Unfit or High-Risk AML and Relapsed/Refractory (R/R) AML

Outcomes	Frontline AML (N=16)[1]	Relapsed / Refractory AML	
		Venetoclax-naïve (N=8)	Venetoclax failure (N=11)[2]
ORR	16 (100)	6 (75)	3 (27)
CR/CRi	15 (94)	5 (63)	3 (27)
CR	13 (81)	3 (38)	0 (0)
CRi	2 (13)	2 (25)	3 (27)
MLFS	1 (6)	1 (13)	0 (0)
No response	0 (0)	2 (25)	8 (62)
Time to first response	0.7 [0.6-1.5]	0.7 [0.6-4.1]	2.2 [1.8-2.6]
Time to best response (months)	1.1 [0.7-2.9]	1.5 [1.0-4.1]	2.3 [1.3-3.9]
Median time to ANC >0.5	28 [20 – 41]	-	-
Median time to platelet >50	24 [18 – 41]	-	-
4-week mortality	0 (0)	0 (0)	0 (0)
8-week mortality	0 (0)	1 (13)	3 (27)

All percentages are based on total number of patients in each cohort (N), unless specified. Results are reported as n (%) or median [range]. ORR = overall response rate = CR+CRi+MLFS, MLFS = morphologic leukemia-free state, 1. 1 pt from table 1 was too early to assess, 2. 2 pts from table 1 were too early to assess

ORR in TP53mut: 100% (CR: 64%)

Toxicity

Mortality at 4 wk and 8 wk: 0 and 9.7% (n=4): these 4 deaths occurred in R/R pts.
All grades AEs included hypokalemia (58%), hypophosphatemia (55%), hyperbilirubinemia (53%), hyponatremia (53%) and sinus tachycardia (47%) Grade 3/4 AEs included pneumonia (32%), febrile neutropenia (32%), hyperbilirubinemia (11%), elevated ALT (11), and skin infection (11%). Close monitoring anemia after first dose of Magro

Safety and Efficacy from a Phase 1b/2 Study of IMGN632 in Combination with Azacitidine and Venetoclax for Patients with CD123-Positive Acute Myeloid Leukemia

Background

- Overexpression of CD123, the alpha subunit of the IL-3 receptor, is seen in AML blasts.

IMGN632 is a CD123-targeting antibody-drug conjugate (ADC) comprised of a high-affinity anti-CD123 antibody coupled to a DNA-alkylating payload of the novel IGN (indolinobenzodiazepine pseudodimer) class.

- Preclinical data have demonstrated synergy between IMGN632 and AZA and/or VEN

Phase Ib study dose escalation comprising 5 cohorts.
Preliminary safety data on 35 R/R AML pts

Response

ORR: 55% - CCR: 31% (1 CR, 4 CRh, 2 CRp, 2 CRi).
in higher intensity cohorts (IMGN632 dose 45 mcg/kg or 14-21 days of VEN) on the Day 7 schedule (n=20):

ORR: 75%, CCR 40%
ORR/CCR 100%/60%, respectively in VEN naïve subset (n=10)
ORR/CCR rates of 100%/71% in FLT3 mutant subset (n=7)

Toxicity

- All grades AEs were febrile neutropenia (26%), hypophosphatemia (26%), dyspnea (26%), pneumonia (20%), and fatigue (20%).
- Cytopenias and infections were consistent with those observed with the AZA+VEN regimen in this R/R population.
- No TLS, VOD, capillary leak or cytokine release were observed. 30-day mortality was 0%.
- Infusion-related reactions (IRR, 37% [3%]),

Agenda

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- Combinazioni terapeutiche per AML FLT3 mutate

Replacing the Anthracycline By Gemtuzumab Ozogamicin in Older Patients with De Novo Standard-Risk AML Treated Intensively – Results of the Randomized ALFA1401-Mylofrance 4 Study

Aim

To investigate whether the replacement of the anthracycline by GO in combination with cytarabine might improve event-free survival in older patients with *de novo* AML of favorable- and intermediate-risk.

- Phase II (Jan 2016-March 2019) 225 de novo fav-int AML pts 60-80 y
- Randomization 2:1
- CHT-GO: 143 pts - standard CHT: 71 pts

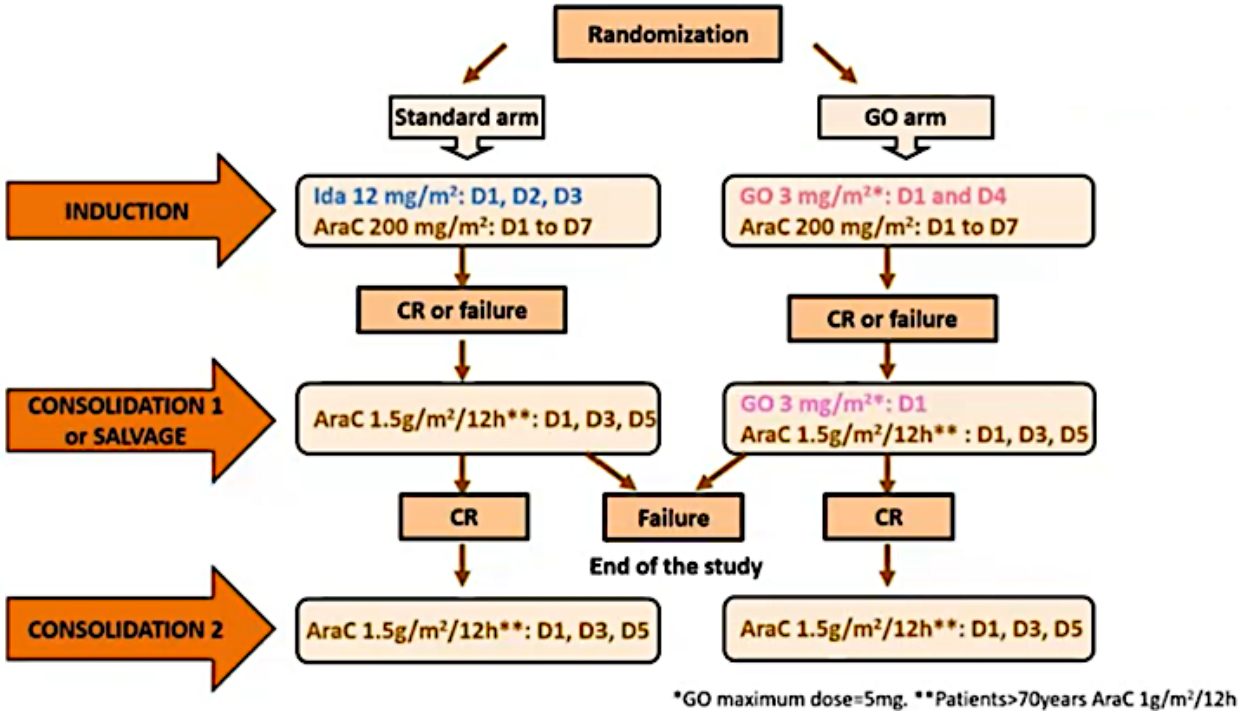
Primary End point
EFS

Secondary End points
Responses, OS, CIR, safety

Paper Number:31, Juliette Lambert, Versaille Hospital

Replacing the Anthracycline By Gemtuzumab Ozogamicin in Older Patients with De Novo Standard-Risk AML Treated Intensively – Results of the Randomized ALFA1401-Mylofrance 4 Study

Treatment scheme



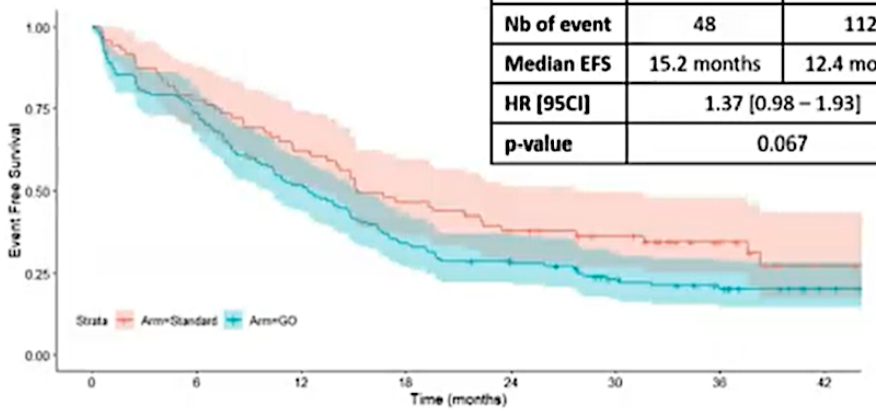
*GO maximum dose=5mg. **Patients>70years AraC 1g/m²/12h

N=214*	Standard arm (N=71)	GO arm (N=143)
Male (%)	37 (48)	89 (62)
Age, median [IQR]	69 [62-79]	70.5 [61-80]
WBC, 10^9/L, median [IQR]	5.8 [0.4-275.4]	3.8 [0.5-241.5]
ECOG 0-1 (%)	65 (92)	114 (80)
Cytogenetics (%)		
Favorable-risk	4 (6)	10 (7)
Intermediate-risk	67 (94)	133 (93)
NPM1 mutation (%)	23 (35)	36 (26)
FLT3-ITD mutation (%)	11 (17)	21 (15)
CEPBA bi-allelic mutation (%)	1 (1)	2 (1)

Replacing the Anthracycline By Gemtuzumab Ozogamicin in Older Patients with De Novo Standard-Risk AML Treated Intensively – Results of the Randomized ALFA1401-Mylofrance 4 Study

Primary endpoint: event-free survival

	Standard	GO
Nb of event	48	112
Median EFS	15.2 months	12.4 months
HR [95CI]	1.37 [0.98 – 1.93]	
p-value	0.067	

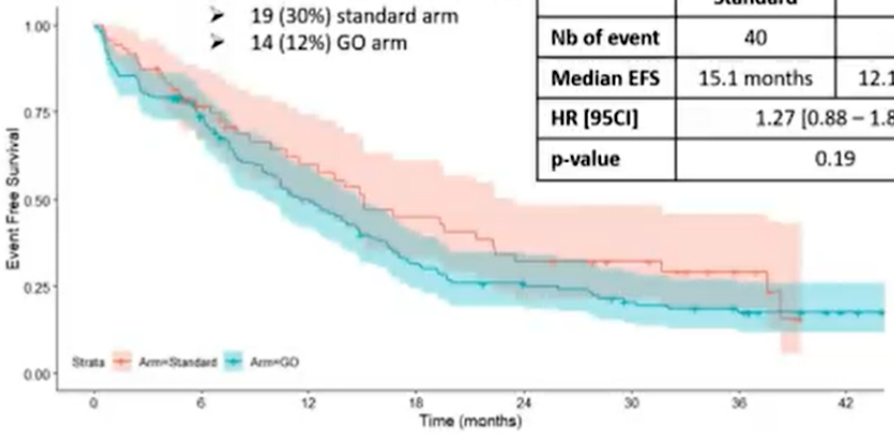


	Standard arm N=71	GO arm N=143	p-value
Early death < day 60 (%)	3 (4)	15 (10)	0.13
Nb of patients with ≥1 grade 3 to 5 AE (%)	54 (78)	112 (77)	0.73
Infection	21 (30)	31 (21)	
Cardiac disorder	10 (15)	31 (21)	
Hemorrhages	5 (7)	42 (29)	
Persistent thrombocytopenia	0	7 (5)	
Veno-occlusive disease	0	2 (1)	
Nb of patients with ≥1 SAE (%)	24 (35)	70 (48)	0.041

EFS censoring patients at allo-HSCT time

33 transplanted patients in 1st CR
- 19 (30%) standard arm
- 14 (12%) GO arm

	Standard	GO
Nb of event	40	106
Median EFS	15.1 months	12.1 months
HR [95CI]	1.27 [0.88 – 1.83]	
p-value	0.19	



Conclusions

At the dose schedule tested, front line use of GO instead of Idarubicin does not benefit older pts with de novo standard-risk AML .

The known toxicity profile of GO and the greater number of SAEs have limited allo-HSCT indications in patients receiving GO

Paper Number:31, Juliette Lambert, Versaille Hospital

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

Screening: 800 pts (CPX-351: 217 pts , HMA-VEN: 439 pts)

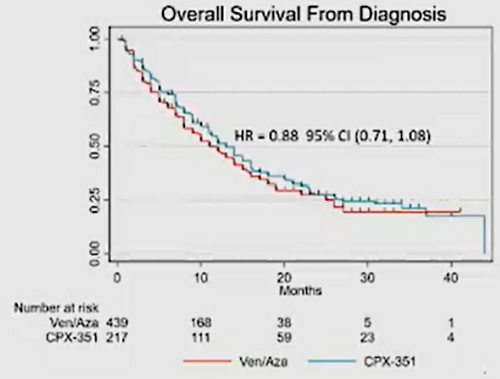
Patient Characteristics Show Some Imbalance at Baseline

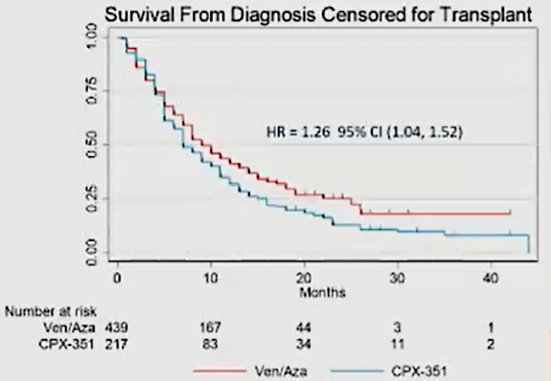
	Ven/Aza N=439	CPX-351 N=217	p-value
Age	75 (36-88)	67 (21-82)	<0.001
Gender			0.056
Female	191 (44%)	112 (52%)	
Male	248 (56%)	105 (48%)	
Practice Type			<0.001
Academic	149 (34%)	103 (47%)	
Community	290 (66%)	114 (53%)	
Type			<0.001
De Novo	226 (51%)	63 (29%)	
History of MDS/MPN	150 (34%)	104 (48%)	
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%)	
Favorable	34 (8%)	15 (7%)	

	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%)	

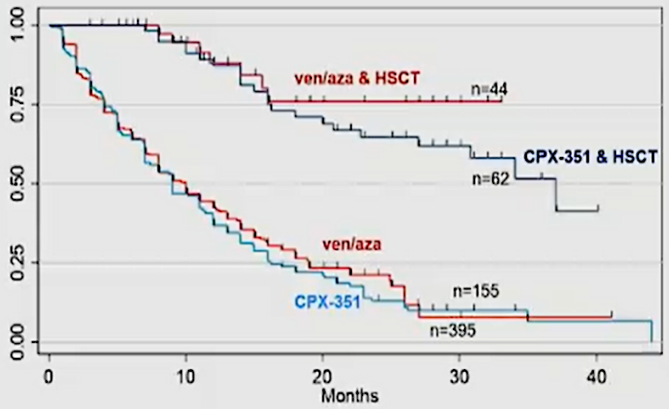
- No significant difference in risk groups, comorbidities, performance status or mutational status
- Expected differences in age, practice type and de novo vs secondary or therapy-related AML

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

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

Paper Number: 795, Andrew Matthews, Abramson Cancer Center University of Pennsylvania

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

- 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]

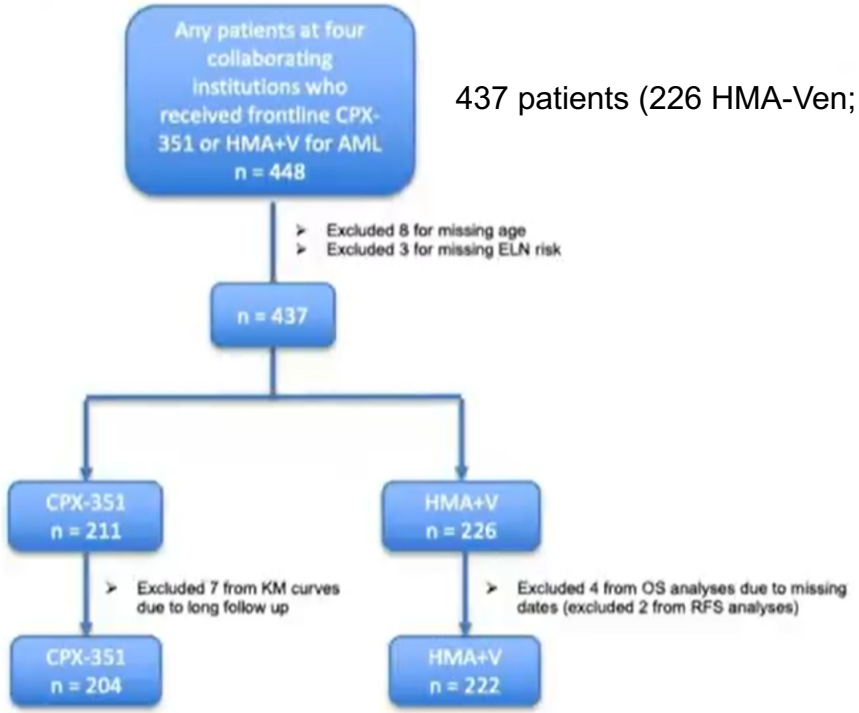
Paper Number: 795, Andrew Matthews, Abramson Cancer Center University of Pennsylvania

Comparing Outcomes between Liposomal Daunorubicin/Cytarabine (CPX-351) and HMA+Venetoclax As Frontline Therapy in Acute Myeloid Leukemia

Retrospective, real world analysis of patient characteristics and outcome in older AML patients from 4 large academic centers, receiving either CPX-351 or HMA-Venetoclax.

Primary endpoints: OR, OS, RFS

Subgroups analysis: patients 60-70 years, TP53mut, adverse ELN risk, prior myeloid malignancies, prior HMA therapy



437 patients (226 HMA-Ven; 211 CPX-351)

Baseline characteristics of pts 60-75 y

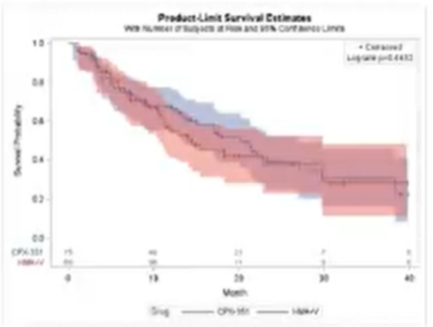
	CPX-351 Frontline	HMA+V Frontline	p-value
n	152	100	
Demographics			
Age, Median (IQR)	68.5 (64.4, 71.7)	70.3 (67.5, 73.0)	$p = 0.002$
Male, N (%)	87 (57.2)	59 (59.0)	$p = 0.782$
AML ELN Risk, N (%)			$p = 0.001$
Favorable/Intermediate	67 (44.1)	23 (23.0)	
Adverse	85 (55.9)	77 (77.0)	
Mutations			
TP53 (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)	

Comparing Outcomes between Liposomal Daunorubicin/Cytarabine (CPX-351) and HMA+Venetoclax As Frontline Therapy in Acute Myeloid Leukemia

	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)	$p = 0.001$

Multivariable analysis showed higher OS in CPX group, in all genetic and molecular subgroups

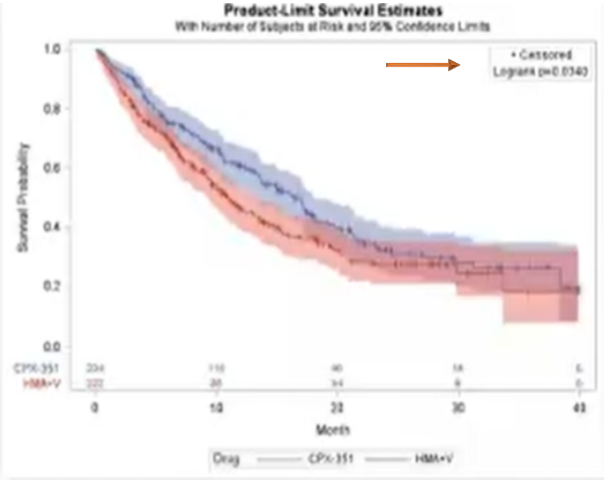
ELN favorable/intermediate



- 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



- 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)

	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)

Paper Number: 32, Justin Grenet, New York Presbyterian/Weill-Cornell Medical Center

Comparing Outcomes between Liposomal Daunorubicin/Cytarabine (CPX-351) and HMA+Venetoclax As Frontline Therapy in Acute Myeloid Leukemia

Results in 60-75 pts

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

CR+CRi, 60-75yo
CPX-351: 59.2%
HMA+V: 54.0%
$p = 0.41$

Total "n" and HSCT rates, 60-75yo
CPX-351: n = 152 (47.7% underwent HSCT)
HMA+V: n = 100 (19% underwent HSCT)
p <0.001

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

Paper Number: 32, Justin Grenet, New York Presbyterian/Weill-Cornell Medical Center

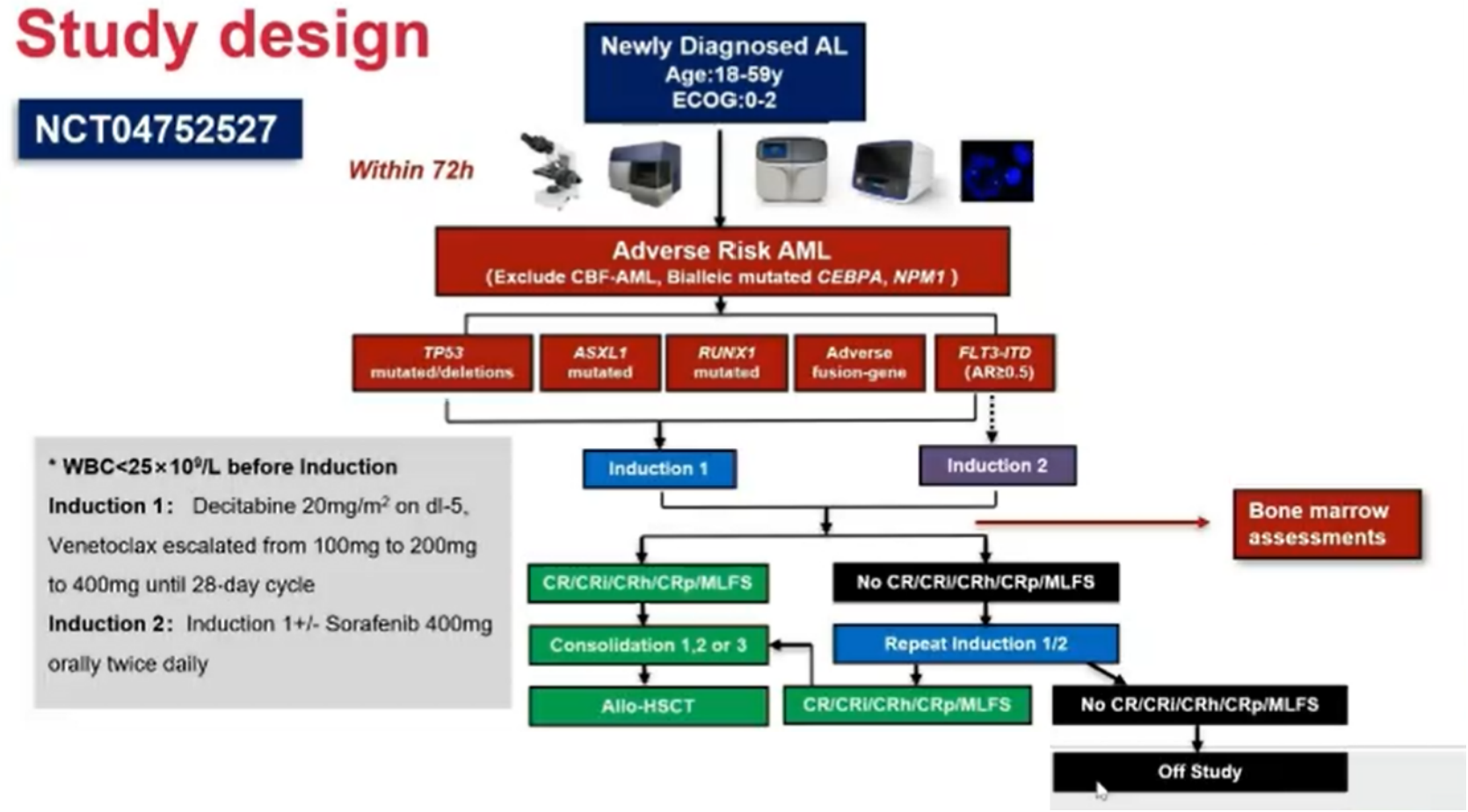
Venetoclax Plus Decitabine for Young Adults with Newly Diagnosed ELN Adverse-Risk AML: Interim Analysis of a Prospective, Multicenter, Single-Arm, Phase 2 Trial

Beat AML Master Trial

Endpoint:
Venetoclax combined with Decitabine is superior to historical controls with cytarabine and idarubicin in young adults newly diagnosed adverse risk AML ?

27 pts (Deci-Ven), 60 pts (Standard therapy)
Median age: 40 / 38 y

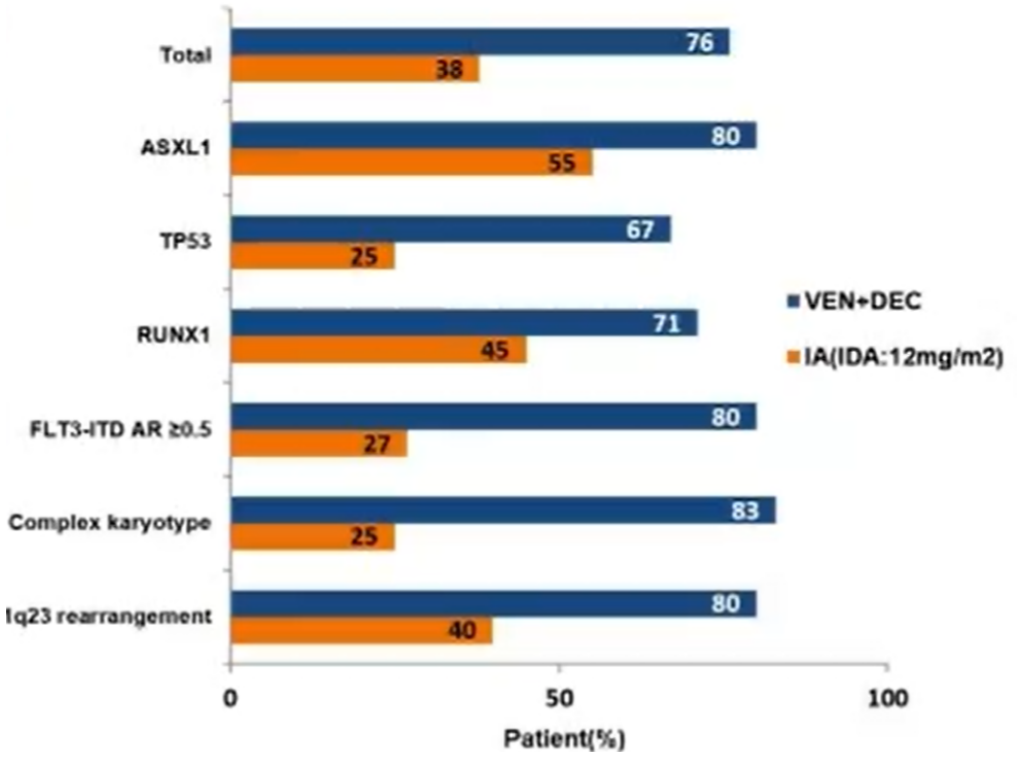
Primary Objective: CCR

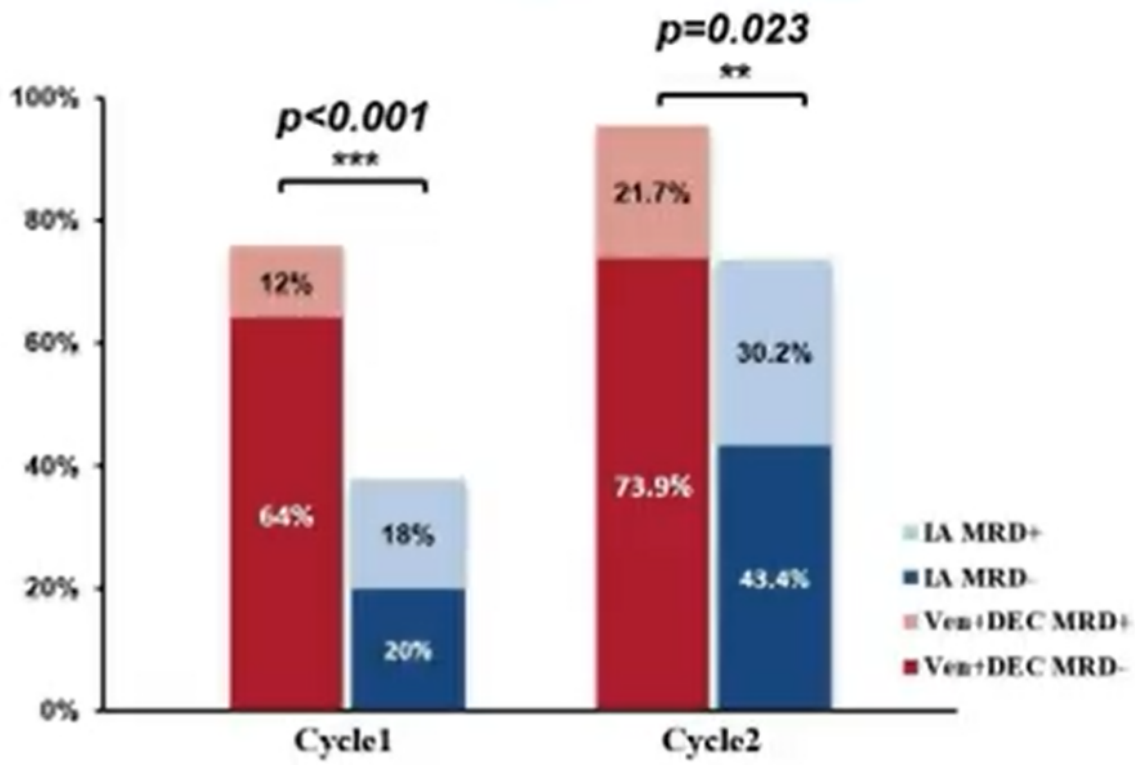


Paper Number: 35, Suning Chen, Jiangsu Institute of Hematology, China

Venetoclax Plus Decitabine for Young Adults with Newly Diagnosed ELN Adverse-Risk AML: Interim Analysis of a Prospective, Multicenter, Single-Arm, Phase 2 Trial

Responses





Venetoclax Plus Decitabine for Young Adults with Newly Diagnosed ELN Adverse-Risk AML: Interim Analysis of a Prospective, Multicenter, Single-Arm, Phase 2 Trial

Toxicity

	Clinical Trial VEN+DEC	Historical Controls IA (IDA:12mg/m^2)	P value
Duration of Neutropenia ≥ Grade 4,days			0.517
Mean(range)	18.1(2-35)	16.5(0-32)	
Duration of Thrombocytopenia ≥ Grade 4,days			0.037
Mean(range)	9.5(0-37)	15.4(6-38)	
Platelet transfusion, n(unit)			0.003
Mean(range)	2.4(0-12.5)	5.8(0.5-17)	
Red-cell transfusion, n(unit)			0.012
Mean(range)	4.6(0.12.5)	7.7(0-17.5)	

Conclusions

- Ven+ Dec achieved high rates of composite complete remission (76%) in patients with ELN-adverse-risk AML.
  - 64% achieved an MRD response after cycle-1
- The combination of Venetoclax plus Decitabine leads to low rates of infections(48%) and reduced red-cell and platelet transfusion compared with HC.
- The median remission duration and overall survival (OS) have not been reached.
  - 30-day and 60-day mortality rate was 0%

Paper Number: 35, Suning Chen, Jiangsu Institute of Hematology, China

Outcome of Therapy-Related Myeloid Neoplasms with Venetoclax-Based Therapy

Retrospective review of all WHO-defined t-MN who received Venetoclax compared with who did not

Endpoints: CR, PFS, OS, predictor factors
- A high proportion in Ven arm had complex karyotype, monosomal karyotype, abn chr17, t-AML,
- One third of pts in Ven arm had previously received HMA

Response

- Overall, 43.3% patients achieved CR as the best response
- Ultimately 78.3% patients had progressive disease at last follow up (Table 2)
- The likelihood of achieving CR was lower for—
  - Chr. 7 abnormality, $X^2 = 3$, $P<0.001$
  - Prior HMA use, $X^2 = 6.3$, $P<0.001$
  - Progressive disease, $X^2 = 2.7$, $P=0.001$
  - the use of chemotherapy backbone other than HMA
- The likelihood of achieving CR was not different based on the % blasts at VEN initiation

Median PFS: 4.9 months
Median OS: 7.6 months
Median OS and PFS did not differ whan stratified by blast % at diagnosis or at Venetoclax initiation.

Predictors of survival:
- if used early
- if used in combination with HMA
- achieving MRD
- abn chr7 (independent factor for poor survival)

Paper Number: 36, Mithun Shah, Mayo Clinic

Venetoclax Combined with FLAG-IDA Induction and Consolidation in Newly Diagnosed Acute Myeloid Leukemia

Background

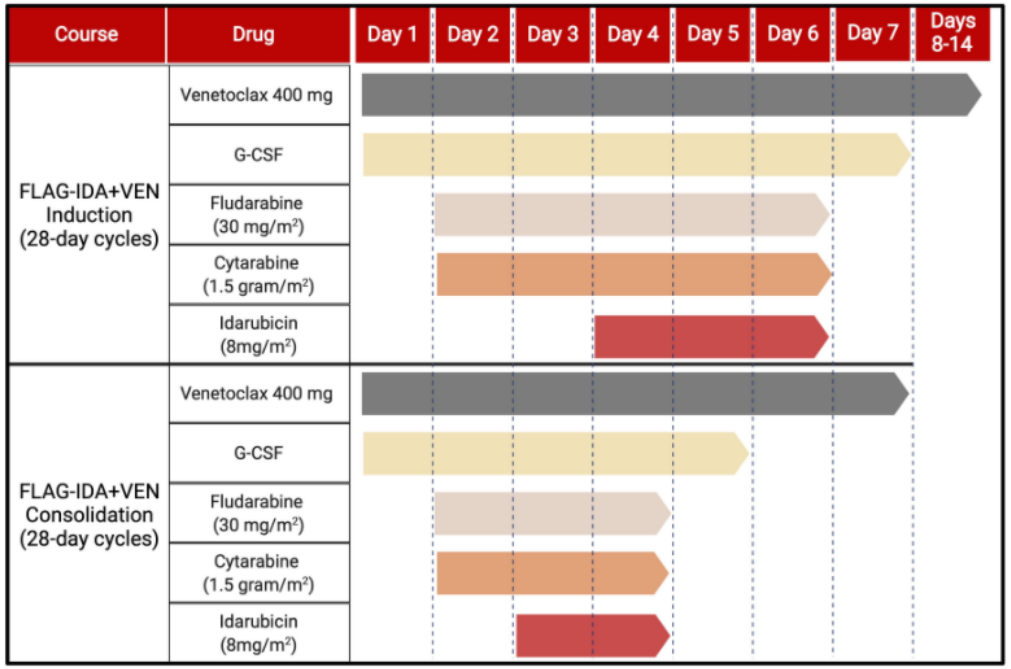
A phase 1b/2 study evaluating FLAG-IDA+VEN has previously described (Di Nardo JCO 2021)
The Phase 2 (P2) portion enrolled patients into two cohorts: ND and R/R-AML.
In this presentation are reported results on newly diagnosed AML pts.

The cohort comprised patients with de novo AML (n=29), secondary AML (n=7), and treatment-related AML (n=5).
Median age of the overall cohort was 44 years (range = 20-65).
ELN risk: favorable in 20%, intermediate in 37%, adverse in 44%.
Mutations: *NRAS* (29%), *IDH2* (17%), *RUNX1* (15%), NPM1 (15%), *TP53* (10%), *KMT2A* rearrangements (12%).

Results

ORR 98%, CRc (CR+CRh+CRi) 88%, MRD neg 92% of CRc pts
CR: n=30 [73%],
CRh: n=5 [12%],
CRi: n=1 [2%],
MLFS: n=4 [10%])

Median time to best response: 29 days (range 22-94).
27 pts (66%) proceed to Transplant



G-CSF: 5 mcg/kg the day prior to and days of IV chemotherapy followed by 1 dose of pegfilgrastim or biosimilar the day following chemotherapy each 28 D cycle

Consolidation: Idarubicin permitted on days 3 and 4 in 2 post-remission cycles (ie. C2 or C3 and C5 or C6) at physician discretion

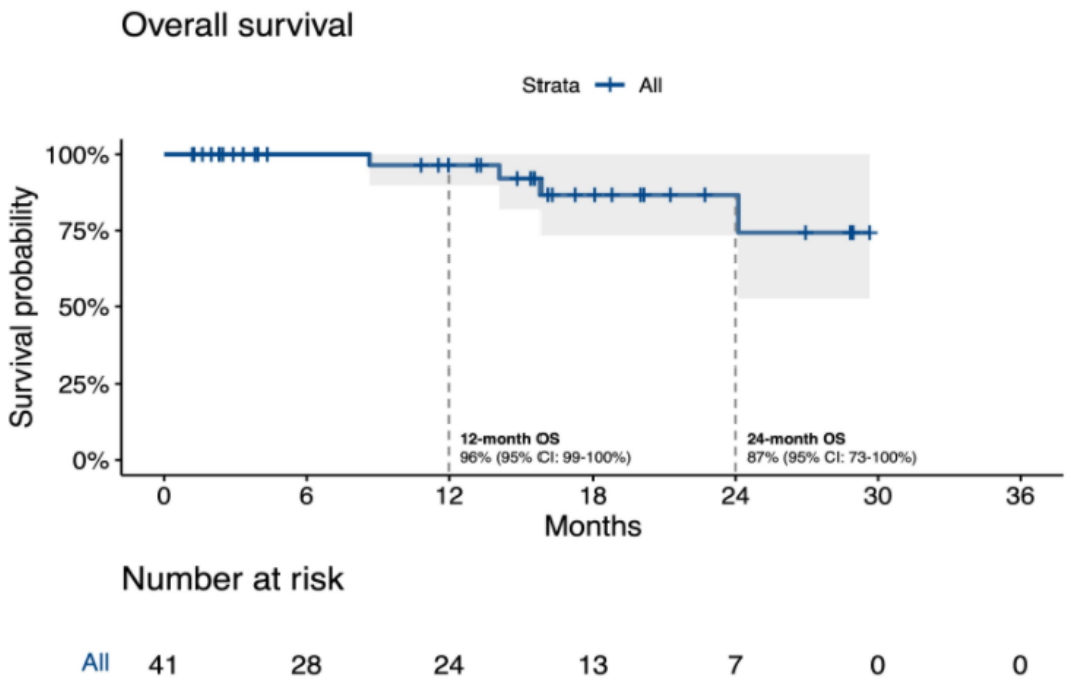
Paper Number: 701, Curtis Lachowiez, The University of Texas M.D. Anderson Cancer Center

Venetoclax Combined with FLAG-IDA Induction and Consolidation in Newly Diagnosed Acute Myeloid Leukemia

Common adverse events

febrile neutropenia (39%)
pneumonia (24%)
bacteremia (19%).
30 or 60-day mortality: 0.

Relapse: 9 patients (ELN intermediate: N=3, adverse: N=6) including 100% of patients with *TP53* mutations (N= 4)



median follow up: 16 months
median OS and EFS: both NR
1-year OS and EFS rates of 96% and 77%

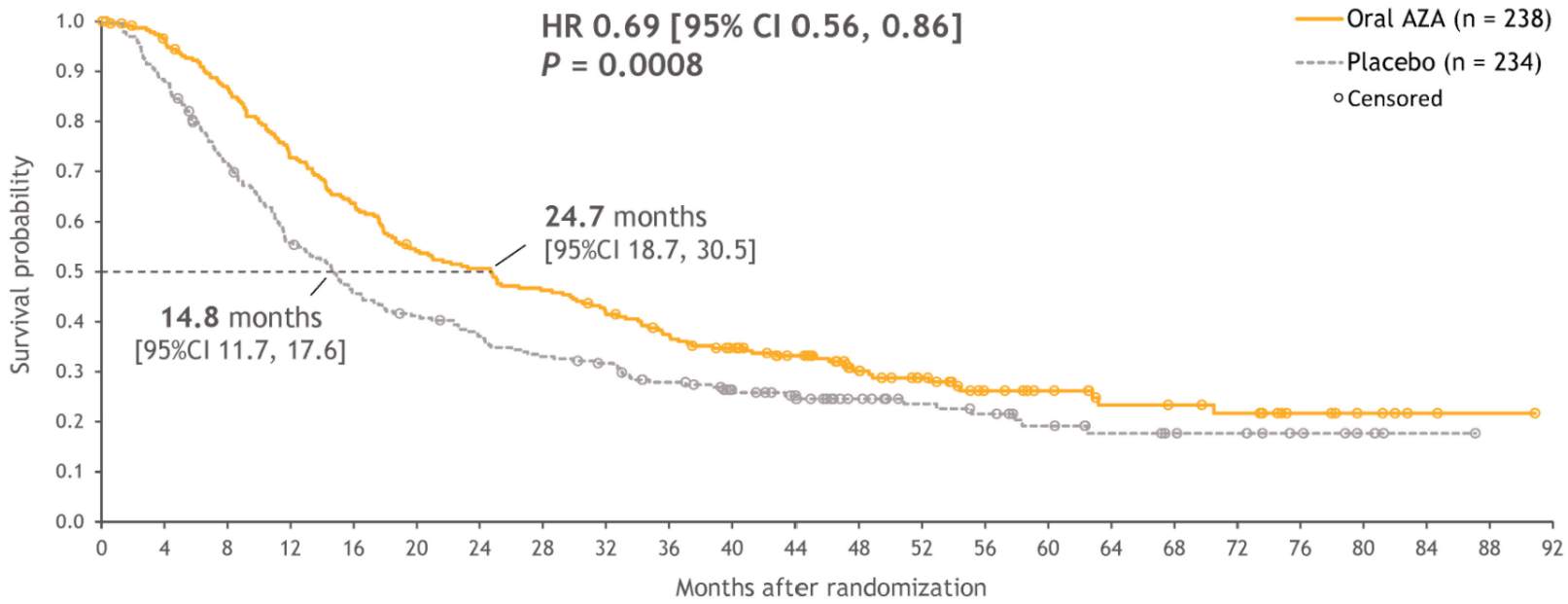
Patients with *KMT2A* rearrangements, *NPM1, IDH1*, and/or *IDH2* mutated show an 18-month survival rate of 100%.

OS in T*P53* : 24 months (vs. NR in TP53wt, p: 0.03)
EFS in TP53: 8 months (vs. NR in TP53wt, p <0.001)

Paper Number: 701, Curtis Lachowiez, The University of Texas M.D. Anderson Cancer Center

Long-Term Overall Survival (OS) with Oral Azacitidine (Oral-AZA) in Patients with AML in First Remission after Intensive Chemotherapy (IC): Updated Results from the Phase 3 QUAZAR AML-001 Trial

Eligible pts were aged ≥55 years with newly diagnosed AML, intermediate- or poor-risk cytogenetics at AML diagnosis (Dx), and ECOG PS ≤3, and had achieved first CR or CRi after IC (induction ± consolidation) before screening.
472 pts were randomized to Oral-AZA (n = 238) or PBO (n = 234).
Within 4 mo after CR/CRi, pts were **randomized 1:1 to Oral-AZA 300 mg or PBO QD for 14 days/28-day cycle**
Median age: 68 years (range 55–86), 91% of pts had *de novo* AML, and 86% had intermediate-risk cytogenetics



Intermediate-risk cytogenetics and *NPM1* mutations at AML Dx, and absence of detectable MRD post-IC, were associated with long-term survival in QUAZAR AML-001

Paper Number: 871, A. Wei, The Alfred Hospital, Melbourne, Australia

OMNIVERSE: A Phase 1b Study of Oral Azacitidine Plus Venetoclax in Patients with Relapsed/Refractory (R/R) or Newly Diagnosed (ND) Acute Myeloid Leukemia (AML)

Multicenter, open-label, 2-part phase 1b trial
Objectives: to evaluate safety and establish the maximum tolerated dose (MTD) of Oral-AZA + VEN in pts with R/R AML ineligible to receive further IC, and subsequently in pts with ND AML ≥ 75 y, or unfit to IC, ECOG performance status of 0–2

Starting dose of **Oral-AZA** is 300 mg QD × 14d/28d cycle, which can be de-escalated to 200 mg × 14d/28d cycle depending on dose-limiting toxicities.

Oral VEN is taken QD continuously (or 21d/cycle for dose level –2).

Agenda

- Venetoclax-based treatment
- Intensive induction therapy
- **Combinazioni terapeutiche per AML FLT3 mutate**

Venetoclax in Combination with Gilteritinib Demonstrates Molecular Clearance of FLT3 mutation in Relapsed/Refractory FLT3-Mutated Acute Myeloid Leukemia

Background:

- long-term survival is limited by the development of drug resistance mutations in persistent *FLT3*$^{+}$ clones
- *FLT3* TKIs + Ven have demonstrated synthetic lethality in preclinical models

Baseline characteristics[1]	Patients receiving Ven + Gilt at RP2D N=54
Median age, years (range)	64 (21 – 85)
Cytogenetic Risk, n (%)	
Favorable	2 (3.8)
Intermediate	28 (53.8)
Poor	18 (34.6)
No mitoses	4 (7.7)
Missing	2
Prior Therapy, n (%)	
≥ 1 TKI	32 (59.2)
Gilteritinib	0
Venetoclax	10 (18.5)
Median lines of prior therapy (range)	2 (1 – 5)
Prior HSCT, n (%)	17 (31.5)
Mutations Detected, n (%)	**Biomarker evaluable patients receiving Ven + Gilt at RP2D N=31**
NPM1	13 (41.9)
DNMT3A	17 (54.8)
NPM1 + DNMT3A	9 (29.0)
WT1	9 (29.0)

[1]Percentages are calculated on non-missing values

Dose escalation phase: RP2D: VEN 400/Gilte 120 mg
Expansion cohort: 54 pts (età med: 64 y)

Primary endpoint: mCRc (CR, CRp, Cri, MLFS)
mCR: 74%
79% (FLT3ITD)
78% (FLT3mut with prior TKI exposure)
molCR: 60%
OS FLT3ITD: 10 months
OS (pts receiving HSCT): not reached
OS (pts not receiving HSCT): 5 months
OS pts exposed/not exposed to TKI: 9.6/10.5 months (comparable)
DOR pts exposed/not exposed to TKI: 6.2/6.9 months (comparable)

No comutation associated with prognosis

A Triplet Combination of Azacitidine, Venetoclax and Gilteritinib for Patients with FLT3-Mutated Acute Myeloid Leukemia: Results from a Phase I/II Study

Phase I/II study, pts with either **R/R *FLT3*-mutated AML** or pts with **ND *FLT3*-mutated AML** or **high-risk MDS/CMML** who were unsuitable for intensive chemotherapy were eligible.

Characteristic, n (%) / median [range]	**Frontline (N=11)**	**Relapsed/Refractory (N=15)**
Age (years)	71 [61-79]	68 [19-90]
≥75 years	3 (27)	3 (20)
Diagnosis		
AML	11 (100)	14 (93)
MDS/CMML	0	1 (7)
Number of prior therapies	---	2 [1-5]
Prior FLT3 inhibitor	---	5 (33)
Prior HSCT	---	5 (33)
Type of FLT3 mutation		
ITD only	9 (82)	7 (47)
TKD only	2 (18)	5 (33)
ITD + TKD	0	3 (20)
FLT3 allelic ratio		
ITD	0.21 [0.04-3.35]	0.37 [0.03-15.7]
TKD	0.44 [0.03-0.85]	0.38 [0.01-1.35]
Cytogenetics		
Adverse risk (-5, -7, complex, inv(3))	3 (27)	6 (40)
Diploid	4 (36)	5 (33)
Others	4 (36)	4 (27)
Mutations detected in ≥2 of pts		
ASXL1	0	2 (13)
ASXL2	0	2 (13)
BCOR	3 (27)	0
BCORL1	2 (18)	0
CBL	0	2 (13)
DNMT3A	8 (73)	8 (53)
GATA2	0	2 (13)
KRAS/NRAS	2 (18)	2 (13)
NPM1	4 (36)	6 (40)
PTPN11	2 (18)	0
RUNX1	2 (18)	5 (33)
SMC3	0	2 (13)
STAG2	0	2 (13)
TET2	5 (45)	3 (20)
TP53	0	2 (13)
WT1	0	6 (40)

Phase I: MTD Gilte (10 pts): recommended dose: 80 mg
Phase II: CR/Cri assessment

Cycle 1
Aza 75 mg/m^2 SC/IV on days 1-7
VEN on days 1-28
Gilte dose ranged from 80mg to 120mg daily days 1-28
Bone marrow on day 14: if blasts <5% or aplastic marrow, both venetoclax and gilteritinib were held (ND cohort) or only venetoclax was held (R/R cohort).

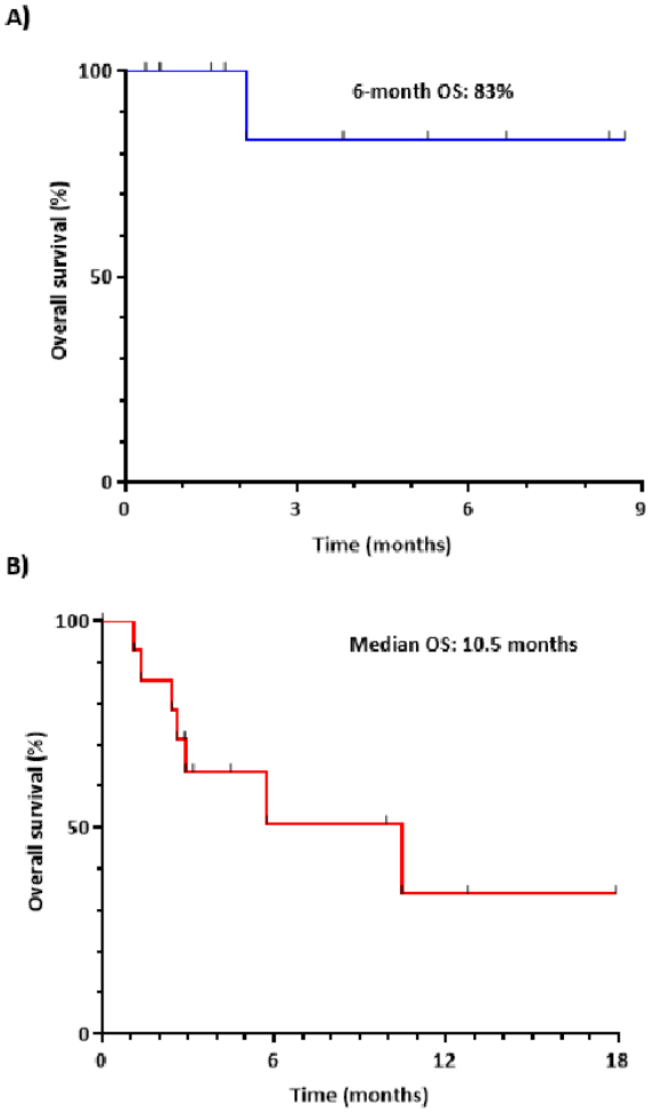
Cycle 2 and beyond
AZA 75 mg/m^2 SC/IV for 5-7 days
VEN 400 mg 7-14 days
GILTE 80/120 mg continuously

RP2D: Gilte 80 mg

Paper Number: 696; Nicholas Short, MD Anderson Cancer Center

A Triplet Combination of Azacitidine, Venetoclax and Gilteritinib for Patients with FLT3-Mutated Acute Myeloid Leukemia: Results from a Phase I/II Study

Figure 1 – Overall survival for the (A) newly diagnosed and (B) relapsed/refractory cohorts



	Frontline	**R/R**
mCR	100% (CR 93%)	69% (CR 19%)
MRD flow	75%	50%
MRD PCR	86%	70%
Follow up	3.8 mo	9.9 mo

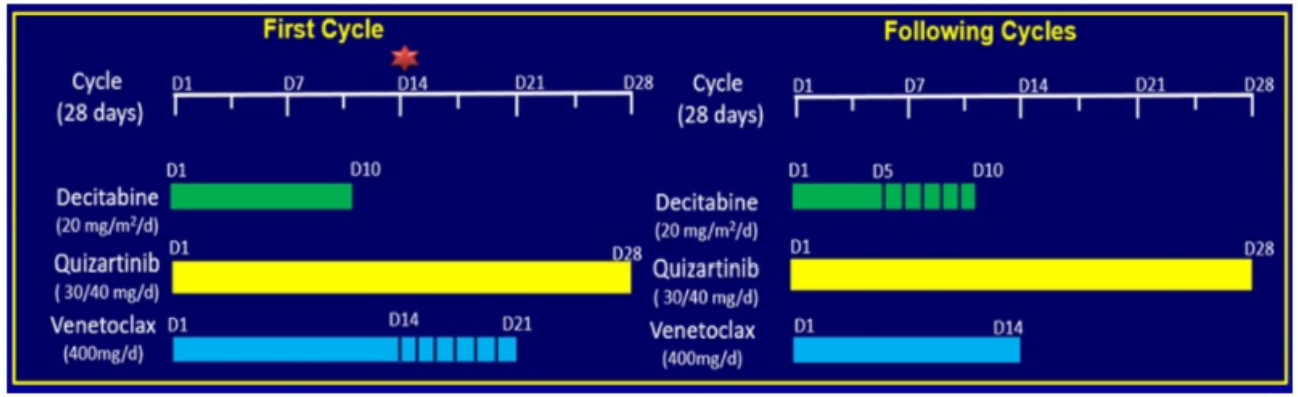
Paper Number: 696; Nicholas Short, MD Anderson Cancer Center

Quizartinib (Quiz) with Decitabine (DAC) and Venetoclax (VEN) Is Highly Active in Patients with FLT3-ITD AML – RAS/MAPK Mutations Continue to Drive Primary and Secondary Resistance

Background

IInd generation FLT3 inhibitor
Efficacy data on ORR, OS in R/R AML FLT3mut
Preclinical data of synergy with VEN

31 pts (6 De Novo, 25 R/R pts)
Prior Gilteritinib: 72%
Prior VEN: 52%
Prior ≥2 FLT3 inhibitors: 80%
Median FUP 16 months
Quiz 30 mg/day dose was declared RP2D



All patients underwent Day14 bone marrow, and venetoclax was put on hold in patients with bone marrow blasts ≤ 5% (or marrow aplasia) on Day14. Those with Day14 bone marrow blast >5% continued venetoclax for 21 days during cycle 1. All patients induced with 10 days of decitabine. In subsequent cycles, decitabine administered for 5 days. Venetoclax may be shortened to 14 days or lower in Cycle 2 onwards depending on cycle 1 count recovery timelines. Quizartinib was administered daily continuously from Cycle 2 Day 1 onwards.

Results

CCR: 78% (100% in frontline)
BM blasts<5% at day 14: 52%
Pts to Tx: 34% (8 pts), 60% (frontline)
OS at 1 y: 31%
OS med: 7,6 months, 14,5 mo in frontline
Median number of cycles to response: 1 [range 1-2] 30- and 60-day mortality rate: 4% and 16%
Safety:
Grade ≥3 non-hematologic toxicities: neutropenic fever (30%), pneumonia (42%), sepsis (9%), ipoK 67%, IpoP 58%, IpoCa 52%other infections (7%).

Paper Number: 370, Musa Yilmaz, The University of Texas M.D. Anderson Cancer Center