Denver ASH Review

2025 Highlights on AML and Allogeneic Transplantation

Mathew Angelos, MD, PhD
Assistant Professor, Division of Hematology
University of Colorado School of Medicine
Blood Disorders and Cellular Therapies Center

1

Disclosures

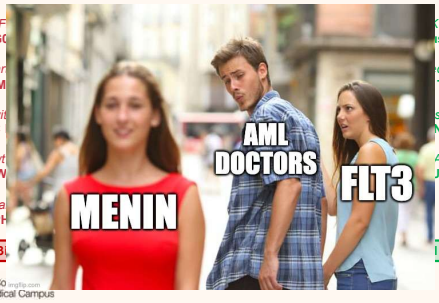
None

2

Key updates in AML and transplant in 2025

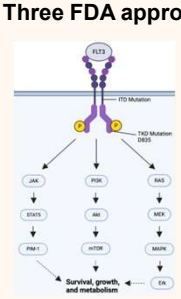
1. *Which F*
(**PrECOG**
2. *Quizar*
(**QuANTUM**
3. *Triplets wit*
(**MDACC**
4. *FLT3wt*
(**QUIW**
5. *Post-allo ma*
(**MORPH**

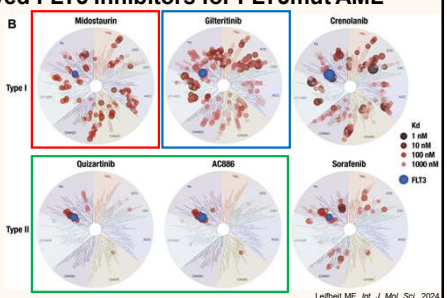
engagers
satuzumab)
dited alloHSCT
Trem-Cel)
st-allo TCR
N, ALLOHA)
AR T cells
J, CD64)
and IOs



3

Three FDA approved FLT3 inhibitors for FLT3mut AML

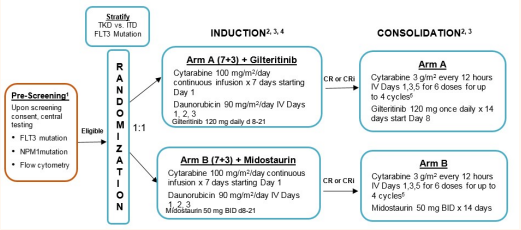




Leilheit ME, *Int. J. Mol. Sci.*, 2024
Aikawa T, *Oncotarget*, 2020

4

PrECOG0905 is the first randomized study to compare FLT3 inhibitors in ND FLT3mut AML



1° objective: Improve FLT3mut- CRc of patients with FLT3mut AML who receive induction chemotherapy + gilteritinib vs. midostaurin

Luger S, *ASH* 2024

5

Gilteritinib increased the CRc rate as compared to midostaurin

- 177 eligible and treated
- Arm A (Gilteritinib) 90, Arm B (Midostaurin) 87
  - 5 (5.6%) vs 6 (6.9%) received 2 cycles induction
- **CRc (Gilteritinib) 85.6% vs 72.4% (Midostaurin), p=0.042**

	Arm A (Gilteritinib) N=90	Arm B (Midostaurin) N=87	Overall (N=177)
CR	68 (75.6%)	57 (65.5%)	125 (70.6%)
CRi	9 (10%)	6 (6.9%)	15 (8.5%)
CRc	**77 (85.6%)**	**63 (72.4%)**	**137 (79.3%)**
No Response	13 (14.4%)	24 (27.6%)	37 (20.9%)

Luger S, *ASH* 2024

6

The rate of FLT3mut MRD negativity was no different between gilteritinib and midostaurin

MRD regardless of remission status	Arm A (Gilteritinib) N=90	Arm B (Midostaurin) N=87	Overall N=177
MRD negative	36 (40.0%)	46 (52.9%)	82 (46.3%)
MRD positive	39 (43.3%)	28 (32.3%)	67 (37.9%)
Dropped Out/Unknown	15 (16.7%)	13 (14.9%)	28 (15.8%)

***FLT3*m negative CRc post-induction**

40% Gilteritinib (A) vs 47.1% Midostaurin (B), p=0.366

University of Colorado Anschutz Medical Campus

Luger S, *ASH* 2024

Denver ASH Review

7

More patients on the gilteritinib arm proceeded to transplant in CR1 and converted to FLT3mut MRD negativity

	Gilteritinib (Arm A) N=90	Midostaurin (Arm B) N=87	Overall N=177
Received 1 cycle Induction	90 (100%)	87 (100%)	177 (100%)
Received 2 cycles Induction	5 (5.6%)	6 (6.9%)	11 (6.2%)
Received >=1 Cycle Consolidation	67 (74%)	53 (61%)	120 (68%)
CR1 Transplant without consolidation	12 (13.3%)	13 (14.9%)	25 (12.4%)
CR1 Transplant	**54 (60%)**	**40 (45.9%)**	**94 (53.1%)**

FLT3mut analysis in 27 patients who achieved CRc and were FLT3mut+ at end of induction and had MRD data available at end of consolidation cycle 1

	Gilteritinib (Arm A) N=18	Midostaurin (Arm B) N=9	Overall N=27
FLT3m Status			
Negative	**15 (83.3%)**	**4 (44.4%)**	**19 (70.4%)**
Positive	3 (16.7%)	5 (55.6%)	8 (29.6%)

University of Colorado Anschutz Medical Campus

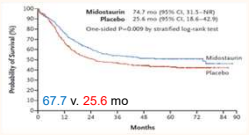
Luger S, *ASH* 2024

Denver ASH Review

8

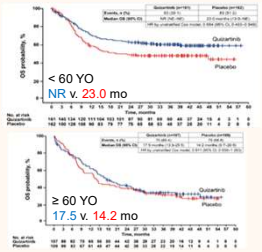
Younger patients benefit more from quizartinib

RATIFY



Arm	Event/Total	Median, Mo* (95% CI)	KM Estimate (95% CI)
Midostaurin	195/360	67.7 (33.0-111.7)	43.6 (38.7-49.3)
Placebo	199/357	25.6 (18.7-50.5)	38.6 (33.6-44.3)

QuANTUM-First



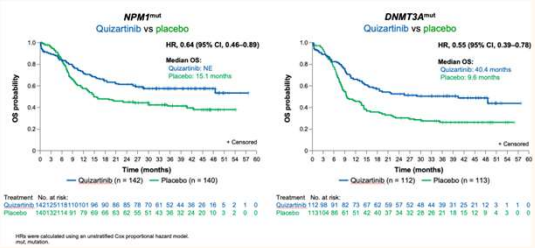
Stone R, *ASH* 2024; Erba H, *Lancet*, 2023

University of Colorado Anschutz Medical Campus

Denver ASH Review

9

Substantial OS benefits were observed with quizartinib for patients with *NPM1* or *DNMT3A* mutations



University of Colorado Anschutz Medical Campus

Erba H, *ASH*, 2024

Denver ASH Review

10

QUIWI: Quizartinib has AML-modifying activity in newly diagnosed FLT3-ITD WT AML

- Ph2. N=237 patients. Median age: 57 YO
- Randomized (2:1): 7+3+Quiz (n=180) vs. 7+3 alone (n=93)

Parameter	QUIZ	No QUIZ	HR/p value
Median EFS (mos)	18.8	9.9	0.73/.053
Median OS (mos)	NR	29.3	0.62/.009
% 3-yr OS	61	46	-
% CR-CRi	77	76	-
% allo SCT	40	32	-

FLT3 Like (N=80)
HR: 0.34; p=0.002

Non-FLT3 Like (N=81)
HR: 1.35; p=0.43

FLT3 Like (N=248)
HR: 0.27; p<0.001

Quizartinib benefit with allo HSCT (HR: 0.59; p=0.16) AND without allo HSCT (HR: 0.64; p=0.03)

University of Colorado Anschutz Medical Campus

Montesinos P, *ASH*, 2024; Orgueira A, *ASH*, 2024

Denver ASH Review

11

What about upfront FLT3i with lower intensity regimens?

Induction
Azacitidine
75 mg/m² IV/SC on D1-7

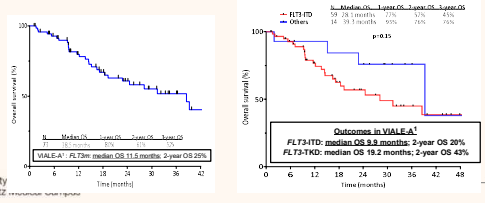
Venetoclax R/U to goal 400mg D1-14
Gilteritinib 80 mg on D1-14
(→if blasts <5% on D14, hold both GV
→if blasts >5% on D14 continue GV and repeat BM in 1 week)

Consolidation (up to 24 cycles)
Azacitidine 75 mg/m² IV/SC on D1-5

Venetoclax 400mg on D1-7

Gilteritinib 80 mg on D1-28

Med F/U: 26 months (range: 1.1-55.5 months): Med OS reached = 38.5m



University Anschutz

Short N, *ASH* 2024

Denver ASH Review

12

What about upfront FLT3i with lower intensity regimens?

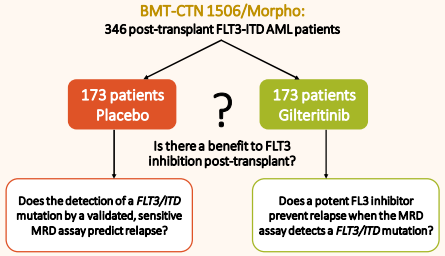
Regimen	N	CR/CRi	Survival	Reference
LDAC	9	44% (ITD/TKD)	9.8 mo (ITD/TKD)	Wei et al, *Blood* 2020 (VIALE-C subset)
LDAC + VEN	20	45% (ITD/TKD)	5.9 mo (ITD/TKD)	
AZA	13	46%	8.5 mo	Konopleva et al, *Clin Can Res*, 2022 (VIALE-A subset)
AZA + VEN	**30**	**63%**	**9.9 mo**	
AZA	42	25%	4.3-13.4 mo	Wang et al, *Blood* 2022 (Lacewing)
AZA + Gilteritinib	60	64%	10.7-11.5 mo	
AZA + VEN + Gilteritinib	**73**	**93% (ITD/TKD)**	**(38.5 months) (ITD/TKD)**	Short et al, ASH 2024
LDAC + VEN (14d) + Quizartinib 60	30	40% (MUT+WT)	11.6 mo	Burgeus et al, EHA 2023 (VEN-A-QUI)
AZA + VEN (28d) + Quizartinib 60	**31**	**45% (MUT+WT)**	**Not reached**	
LDAC + VEN	**7**	**57%**	**9.1 mo**	Chua et al, ASH 2024
LDAC + VEN + Midostaurin (FLT3-ITD)	**22**	**82%**	**16.6 mo**	

University of Colorado Anschutz Medical Campus

Denver ASH Review

13

BMT-CTN 1506/MORPHO: Efficacy of gilteritinib in post-transplant AML



University of Colorado Anschutz Medical Campus

Levis M, JCO, 2024

Denver ASH Review

14

BMT-CTN 1506/MORPHO: Safety and tolerability

Safety Parameter	Gilteritinib (N = 178)*	Placebo (N = 177)
Treatment emergent acute GVHD[1] grade II-IV	33 (18.5%)	36 (20.3%)
Treatment emergent chronic GVHD	93 (52.2%)	75 (42.4%)
Treatment emergent infection grade 3 or greater	58 (32.6%)	38 (21.5%)
TEAE[2] leading to withdrawal of treatment	35 (19.7%)	19 (10.7%)
Drug-related TEAE leading to withdrawal of treatment	27 (15.2%)	14 (7.9%)
Drug-related TEAE leading to drug interruption	32 (18.0)%	12 (6.8%)
Drug-related grade 3 or higher TEAE	109 (61.2%)	45 (25.4%)

1. GVHD = Graft versus host disease
2. TEAE = treatment emergent adverse event

* One patient randomized to gilteritinib not dosed and one patient randomized to placebo dosed with gilteritinib

University of Colorado Anschutz Medical Campus

Levis M, JCO, 2024

Denver ASH Review

15

BMT-CTN 1506/MORPHO: Drug-related G3 or higher treatment emergent adverse events

Grade 3 or higher Adverse Event, n(%)	Gilteritinib (N=178)	Placebo (N=177)
Neutrophil count decreased	44 (24.7%)	14 (7.9%)
Platelet count decreased*	27 (15.2%)	10 (5.6%)
Anemia	11 (6.2%)	3 (1.7%)
Alanine aminotransferase (ALT) increased	6 (3.4%)	4 (2.2%)
Creatine phosphokinase increased	12 (6.7%)	0 (0%)

* Includes unique cases of platelet count decrease and thrombocytopenia

University of Colorado Anschutz Medical Campus

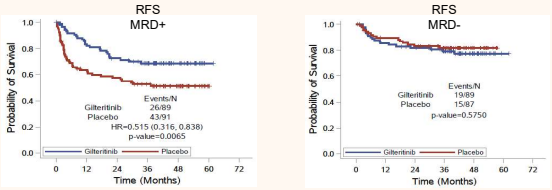
Levis M, JCO, 2024

Denver ASH Review

16

BMT-CTN 1506/MORPHO: Effect of detectable peri-transplant FLT3mut MRD6 (PCR-NGS) on RFS

51% had peri-transplant MRD6 detectable



Post-transplant gilteritinib should NOT be offered if FLT3mut MRD6 NEGATIVE pre-transplant

University of Colorado Anschutz Medical Campus

Levis M, JCO, 2024

Denver ASH Review

17

Key updates in AML and transplant in 2025

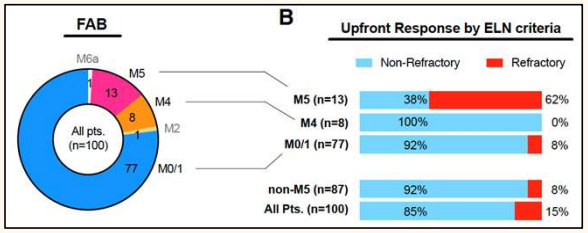
1. *Which FLT3i?* (**PrECOG0905**)	1. *Young Aza/Ven* (**CU**)	1. *Revumenib* (**AUGMENT-101**)	1. *NK engagers* (**CU, cusatuzumab**)
2. *Quizartinib* (**QuANTUM-First**)	2. *Cladribine* (**MDACC Ph2**)	2. *Ziftomenib* (**KOMET-007**)	2. *Gene-edited alloHSCT* (**Vor, Trem-Cel**)
3. *FLT3wt AML* (**QUIWI**)		3. *Bleximenib* (**JNJ-75276617**)	3. *Post-allo TCR* (**TSCAN, ALLOHA**)
4. *Triplets with FLT3i* (**MDACC Ph2**)		4. *Enzomenib* (**DSP-5336**)	4. *CAR T cells* (**CU, CD64**)
5. *Post-allo maintenance* (**MORPHO**)			
FLT3i	**New uses for Aza/Ven**	**Menin Inhibitors**	**Cell and IOs**

University of Colorado Anschutz Medical Campus

Denver ASH Review

18

Risk factors for poor efficacy outcomes from venetoclax-based therapies are emerging

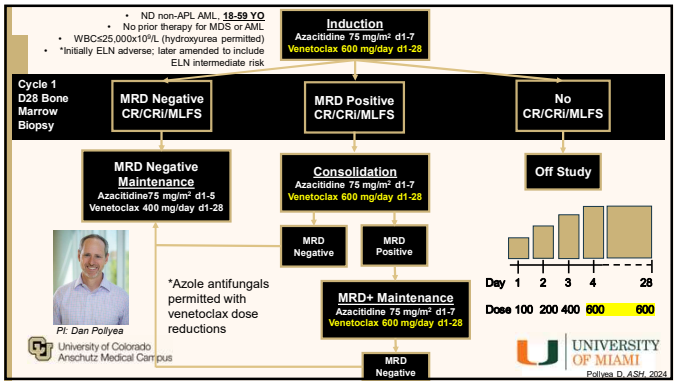


University of Colorado Anschutz Medical Campus

Pei S, *Cancer Discovery*, 2020

Denver ASH Review

19



20

Baseline Patient Characteristics (N=36)

Variable	Value
Median Age	49 years (22-59)
Male	16/36 (44%)
Baseline Blast % (median)	50%
Monocytic	8/36 (22%)
KMT2A Rearranged	6/36 (17%)
Myelodysplasia-Related (per WHO 2022)	21/36 (58%)
ELN 2017	
Intermediate	7/36 (19%)
Adverse	29/36 (81%)
Molecular Prognostic Risk Signature	
Higher Benefit *(WT for N/KRAS, FLT3 ITD and TP53)*	23/36 (64%)
Intermediate Benefit *(N/KRAS and/or FLT3 ITD; WT for TP53)*	9/36 (25%)
Lower Benefit *(TP53)*	4/36 (11%)

University of Colorado Anschutz Medical Campus

UNIVERSITY OF MIAMI

21

Responses (N=36)

Variable	Value
Overall Response Rate	25/36 (69%)
CR	18
CRi	2
MLFS	5
MRD Negative Responses	16/25 (64%)
Proceeded to transplant due to study*	16/36 (44%)

*Multiple additional subjects are pending transplant

Subset	ORR
Monocytic	4/8 (50%)*
Non Monocytic	20/28 (71%)
Myelodysplasia Related	16/21 (76%)
KMT2A Rearranged	3/6 (50%)
mPRS	
Higher Benefit	18/23 (78%)
Intermediate Benefit	5/9 (56%)
Lower Benefit	2/4 (50%)

University of Colorado Anschutz Medical Campus

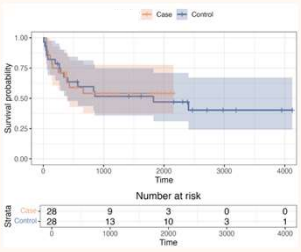
Median follow up time = 3.3 years

UNIVERSITY OF MIAMI

22

Study Subjects vs Matched Controls: Outcomes

Variable	Study Subjects (N=28)	Matched Controls (N=28)	P-Value
Overall response rate	**17 (61%)**	**14 (50%)**	**0.442**
CR	14 (50%)	8 (29%)	0.099
CRi	0	4 (14.3%)	0.594
MLFS	3 (11%)	2 (7.1%)	
Proceeded to transplant	13 (46%)	9 (32%)	0.258
60-day mortality	1 (4%)	5 (18%)	0.142
Median overall survival	Not Reached	5 years	0.819

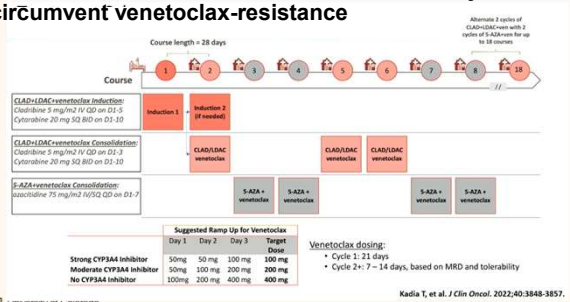


University of Colorado Anschutz Medical Campus

UNIVERSITY OF MIAMI

23

Cladribine-based treatment combinations may circumvent venetoclax-resistance



Kadia T, et al. *J Clin Oncol*. 2022;40:3848-3857.

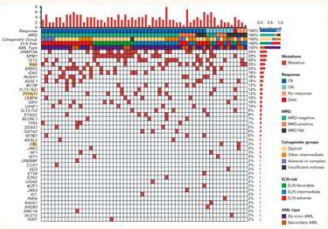
University of Colorado Anschutz Medical Campus

Denver ASH Review

24

Cladribine/LDAC/Ven alternating with HMA/Ven had high rates of CR+CR$_i$ in an older adult population

Characteristic	N = 60; No. (%)
CRc rate (CR plus CRi)	56/60 (93)
Best response	
CR	48/60 (80)
CRi	8/60 (13)
NR	3/60 (5.0)
Died	1/60 (1.7)
Patients requiring reinduction cycle	4/57 (7)
MRD at response assessment (by flow)	
Negative	43/51 (84)
Positive	8/51 (16)
Total No. of course given, median (IQR)	3.0 (2.0-5.0)
Responders who received alloSCT	19/56 (34)
Mortality rate at 4 weeks	1/60 (1.7)
Mortality rate at 8 weeks	4/60 (6.7)



Kadia T, JCO, 2022

University of Colorado Anschutz Medical Campus

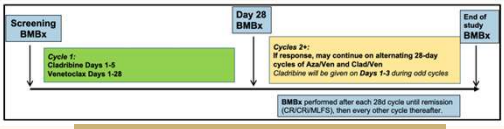
Denver ASH Review

25

Cladribine-based treatment combinations may circumvent venetoclax-resistance

PI: Christine McMahon
NCT06232655

Cladribine + Venetoclax (Clad/Ven) following failure of HMA/Ven



1. >18 YO
2. R/R AML after HMA/Ven
3. Monocytic or monoblastic immunophenotype OR
4. *Ras* pathway mutation (*K/NRAS, CBL, PTPN11, etc.*)

University of Colorado Anschutz Medical Campus

Denver ASH Review

26

Key updates in AML and transplant in 2025

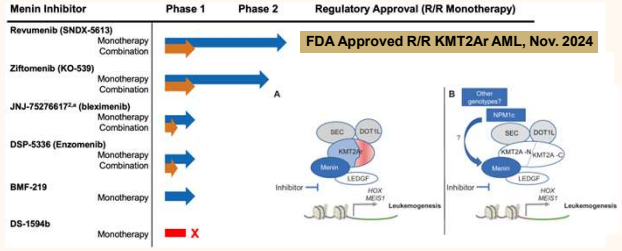
FLT3i	New uses for Aza/Ven	Menin Inhibitors	Cell and IOs
1. *Which FLT3i?* (**PrECOG0905**)	1. *Young Aza/Ven* (**CU**)	1. *Revumenib* (**AUGMENT-101**)	1. *NK engagers* (**CU, cusatuzumab**)
2. *Quizartinib* (**QuANTUM-First**)	2. *Cladribine* (**MDACC Ph2**)	2. *Ziftomenib* (**KOMET-007**)	2. *Gene-edited alloHSCT* (**Vor, Trem-Cel**)
3. *FLT3wt AML* (**QUIWI**)		3. *Bleximenib* (**JNJ-75276617**)	3. *Post-allo TCR* (**TSCAN, ALLOHA**)
4. *Triplets with FLT3i* (**MDACC Ph2**)		4. *Enzomenib* (**DSP-5336**)	4. *CAR T cells* (**CU, CD64**)
5. *Post-allo maintenance* (**MORPHO**)			

University of Colorado Anschutz Medical Campus

Denver ASH Review

27

Menin inhibitors: Current stages of clinical development



University of Colorado Anschutz Medical Campus

Issa G, *Leukemia*, 2021

Denver ASH Review

28

AUGMENT-101: Ph2 Revumenib single agent in R/R KMT2Ar AML

- 116 pt Rx; 97 evaluable. Median age 35.5 yrs (0.6-75)
- Revumenib 163 mg BID
- **CR + CR_H: 22 (23%); median DOR 6.4 mo**
- CRc 42%; ORR 64%
- 21/36 (58%) MRD-evaluable CRc with MRD-
- 21/62 ORR had HSCT allogeneic stem cell transplant
- Side effects: differentiation syndrome 15% (n=1 G4); QTC ↑ 13% (all G3)

University of Colorado Anschutz Medical Campus

Aldoss I, *ASH*, 2024

Denver ASH Review

29

Ph1 study of bleximenib single agent in KMT2Ar and *NPM1*mut AML

- 121 pts (108 AML, 6 ALL, 7 AL). Median age 61 yrs (18-85)
- *KMT2A* 73(60%); *NPM1* 48(40%)
- Bleximenib 45mg BID (n=15), 90-100mg BID (n=27), 150mg BID (n=28)
- Differentiation Syndrome: 13%, 2 fatal; QTc ↑ in 1 pt

% Response	45 mg	90-100 mg	150 mg
ORR	39	50	50
Composite CR	23	40	40
CR + CR_h	23	35	30

- **CRc at 90-100 mg BID: 44% in *KMT2A*, 33% in *NPM1***
- **Median DOR 6.4 mo**
- **Responses similar in *KMT2A* and *NPM1***

University of Colorado Anschutz Medical Campus

Searle E, *ASH*, 2024

Denver ASH Review

30

Ph1/2 study of enzomenib in KMT2Ar and *NPM1*mut AML

Arm	Dose Level	Patients	DLT
A *No azoles N=31*	40 mg BID	2	0
	80 mg BID	4	0
	100 mg BID	2	0
	120 mg BID	6	0
	140 mg BID	4	0
	200 mg BID	7	0
	300 mg BID	6	0
B *With azoles N=53*	40 mg BID	4	0
	60 mg BID	6	0
	100 mg BID	4	0
	140 mg BID	2	0
	200 mg BID	17	0
	300 mg BID	20	0

- **No DLT's seen at any dose level**
  - No treatment-related deaths
  - No discontinuations due to drug-related AEs
- Treatment-related adverse events in ≥ 10%
  - Nausea: Any grade 16.7%, G3 1.1%
  - Vomiting: Any grade 15.5%, G3 1.1%
  - Improved w/change from 20 -> 100 mg tablets
- Dose modifications due to treatment-related AE
  - Temporary interruptions in 16.7% (14/84)
  - Dose reductions in 2.4% (2/84)
- **QTc prolongation rarely seen: G3: 1.0% (1/84)**
- **Differentiation syndrome (DS): 10.7% (9/84)**
  - No mortality or permanent discontinuations of enzomenib due to DS
  - No DS prophylaxis or ramp-up used with enzomenib

University of Colorado Anschutz Medical Campus

Zeidner J, *ASH*, 2024

Denver ASH Review

31

Ph1/2 study of enzomenib in KMT2Ar and *NPM1*mut AML

Clinical responses by ELN 2017	*KMT2Ar*			*NPM1m*		
	200 mg BID n = 8	300 mg BID n = 15	Total n = 23	200 mg BID n = 10	300 mg BID n = 7	Total n = 17
Objective Response Rate (CR + CRh + CRi + MLFS)	50% (4/8)	73.3% (11/15)	65.2% (15/23)	60% (6/10)	57.1% (4/7)	58.8% (10/17)
Composite CR (CR + CRh + CRi)	37.5% (3/8)	53.3% (8/15)	47.8% (11/23)	50% (5/10)	42.9% (3/7)	47.1% (8/17)
CR + CRh	12.5% (1/8)	40.0% (6/15)	30.4% (7/23)	50% (5/10)	42.9% (3/7)	47.1% (8/17)

(patients meeting CRh and CRi were counted as CRh)

- Activity similar with and without azoles
  - Arm A (10 pts total): ORR 70% (7/10) CR+CRh 40% (4/10)
  - Arm B (30 pts total): ORR 60% (18/30) CR+CRh 36.7% (11/30)
- Among patients with primary refractory disease (n=7)
  - ORR 86% (6/7) CR+CRh 57% (4/7)

University of Colorado Anschutz Medical Campus

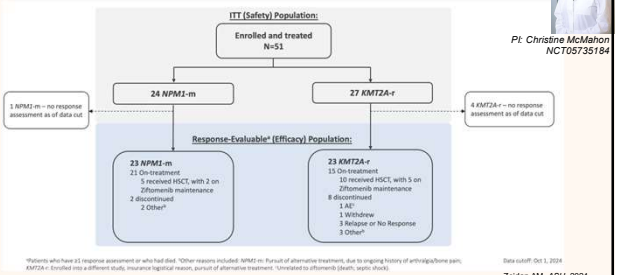
Zeidner J, *ASH*, 2024

Denver ASH Review

32

KOMET-007: Ph1 study of ziftomenib combined with 7+3 in ND KMT2Ar and *NPM1*mut AML

PI: Christine McMahon
NCT05735184



University of Colorado Anschutz Medical Campus

Zeidan AM, *ASH*, 2024

Denver ASH Review

33

Safety and tolerability of ziftomenib in combination with 7+3 in 1L AML (n=51)

Grade ≥3 TEAEs in ≥10% of All Patients

TEAEs, n (%)	All Patients (N=51)	NPM1-m 200 mg (n=8)	NPM1-m 400 mg (n=7)	NPM1-m 600 mg (n=9)	NPM1-m Total (n=24)	KMT2A-r 200 mg (n=10)	KMT2A-r 400 mg (n=9)	KMT2A-r 600 mg (n=8)	KMT2A-r Total (n=27)
Grade ≥3	**46 (90)**	8 (100)	6 (86)	8 (89)	**22 (92)**	10 (100)	8 (89)	6 (75)	**24 (89)**
Febrile neutropenia	**30 (59)**	5 (63)	4 (57)	8 (89)	**17 (71)**	7 (70)	3 (33)	3 (38)	**13 (48)**
Platelet count decreased	**21 (41)**	7 (88)	4 (57)	3 (33)	**14 (58)**	3 (30)	2 (22)	2 (25)	**7 (26)**
Anemia	**18 (35)**	4 (50)	2 (29)	3 (33)	**9 (38)**	4 (40)	3 (33)	2 (25)	**9 (33)**
Neutrophil count decreased	**18 (35)**	6 (75)	3 (43)	3 (33)	**12 (50)**	3 (30)	2 (22)	1 (13)	**6 (22)**
White blood cell count decreased	**13 (26)**	3 (38)	2 (29)	2 (22)	**7 (29)**	2 (20)	3 (33)	1 (13)	**6 (22)**
Sepsis	**7 (14)**	2 (25)	0	2 (22)	**4 (17)**	1 (10)	1 (11)	1 (13)	**3 (11)**
Pneumonia	**6 (12)**	1 (13)	2 (29)	0	**3 (13)**	2 (20)	0	1 (13)	**3 (11)**

Ziftomenib in Combination with 7+3-related Adverse Events of Interest

- One case of Gr3 differentiation syndrome (*NPM1*-m 600 mg); successfully managed and patient remained on treatment
- No ziftomenib-associated QTc prolongation
- No dose-limiting toxicities (DLTs) at any dose level

Data cutoff: Oct 1, 2024. TEAE, treatment-emergent adverse event.

University of Colorado Anschutz Medical Campus

Denver ASH Review

34

Clinical activity in all response-evaluable 1L patients (n=46)

- Historically, only 33% of 7+3 treated newly diagnosed Adverse-Risk AML patients achieve CRc, with a median overall survival of ~6 months[1-2]

Response, n (%)	All Patients (N=46)	NPM1-m 200 mg (n=8)	NPM1-m 400 mg (n=7)	NPM1-m 600 mg (n=8)	NPM1-m Total (n=23)	KMT2A-r 200 mg (n=10)	KMT2A-r 400 mg (n=9)	KMT2A-r 600 mg (n=4)	KMT2A-r Total (n=23)
CRc	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
ORR	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
CR	**42 (91)**	8 (100)	7 (100)	8 (100)	**23 (100)**	9 (90)	6 (67)	4 (100)	**19 (83)**
CRh	**0**	0	0	0	**0**	0	0	0	**0**
CRi	**0**	0	0	0	**0**	0	0	0	**0**
MLFS	**0**	0	0	0	**0**	0	0	0	**0**
PR	**0**	0	0	0	**0**	0	0	0	**0**
NR	**3 (7)**	0	0	0	**0**	0	3 (33)	0	**3 (13)**
NE	**1 (2)**	0	0	0	**0**	1 (10)	0	0	**1 (4)**
MRD negativity, n/N[a]	**28/37 (76)**	8/8 (100)	4/6 (67)	4/7 (50)	**16/21 (76)**	5/8 (63)	5/6 (83)	2/2 (100)	**12/16 (75)**

[a]Patients who have ≥1 response assessment or who had died
[b]Among CRc responders tested for MRD per local assay (NGS, RT-qPCR, FISH, flow cytometry)

1. Lin et al. *Blood Adv* 2021 Mar 23;5(6):1719-1728. 2. Lancet et al. *Blood* 2014 May 22;123(21):3239-46.
Data cutoff: Oct 1, 2024. Per ELN 2022: CR, complete remission; CRi, composite complete remission; CRh, complete remission with partial hematological recovery; CN, complete remission with incomplete hematological recovery; FISH, fluorescence in situ hybridization; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, not evaluable; NGS, next-generation sequencing; NR, no response; PR, partial remission; RT-qPCR, quantitative reverse transcription polymerase chain reaction.

University of Colorado Anschutz Medical Campus

Denver ASH Review

35

Key updates in AML and transplant in 2025

FLT3i	New uses for Aza/Ven	Menin Inhibitors	Cell and IOs
1. *Which FLT3i?* (**PrECOG0905**)	1. *Young Aza/Ven* (**CU**)	1. *Revumenib* (**AUGMENT-101**)	1. *NK engagers* (**CU, cusatuzumab**)
2. *Quizartinib* (**QuANTUM-First**)	2. *Cladribine* (**MDACC Ph2**)	2. *Ziftomenib* (**KOMET-007**)	2. *Gene-edited alloHSCT* (**Vor, Trem-Cel**)
3. *FLT3wt AML* (**QUIWI**)		3. *Bleximenib* (**JNJ-75276617**)	3. *Post-allo TCR* (**TSCAN, ALLOHA**)
4. *Triplets with FLT3i* (**MDACC Ph2**)		4. *Enzomenib* (**DSP-5336**)	4. *CAR T cells* (**CU, CD64**)
5. *Post-allo maintenance* (**MORPHO**)			

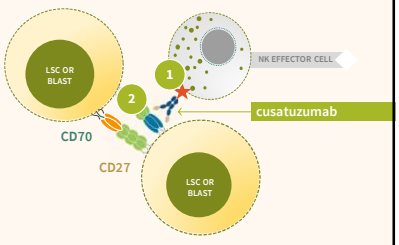
University of Colorado Anschutz Medical Campus

Denver ASH Review

36

Cusatuzumab is a first in class CD70 antibody

- Monoclonal antibody with high affinity to human CD70
- Blocks CD70/CD27 signaling, leading to inhibition of leukemia stem cell proliferation and reduction in leukemic blast cells
- Exerts direct Fc-mediated, effector functions such as enhanced antibody dependent cellular cytotoxicity
- Studied in > 300 patients



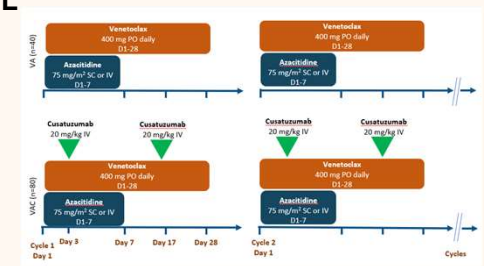
University of Colorado Anschutz Medical Campus

Denver ASH Review

37

HMA/Ven vs. HMA/Ven + Cusa in ND AML

PI: Dan Pollyea
NCT06384261

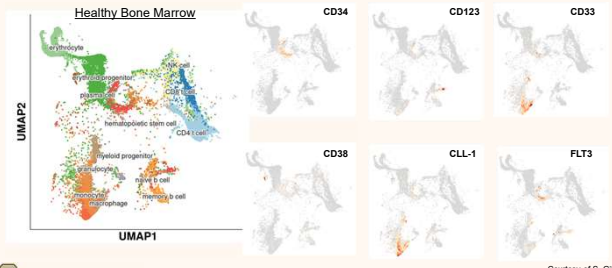


University of Colorado Anschutz Medical Campus

Denver ASH Review

38

Gene editing strategies may bypass obstacles to treat myeloid neoplasms with cell and immunotherapies



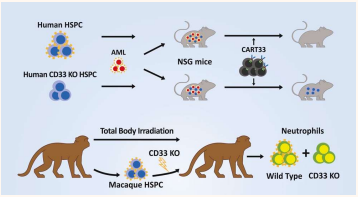
Courtesy of S. Gill

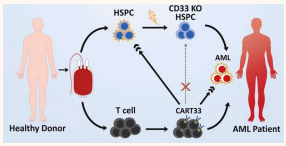
University of Colorado Anschutz Medical Campus

Denver ASH Review

39

Leukemia-specific antigens can be engineered by gene editing hematopoietic stem cells





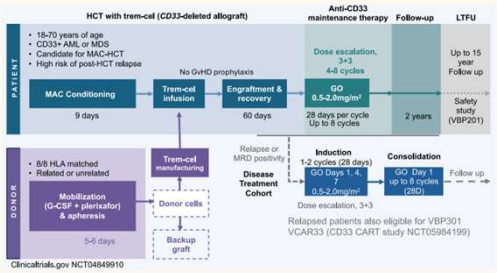
University of Colorado Anschutz Medical Campus

Courtesy of S. Gill

Denver ASH Review

40

VBP101 Ph1/2 study of Tremtelectogene empogeditemcel (Trem-cel) as allograft followed by GO maintenance for MDS/AML



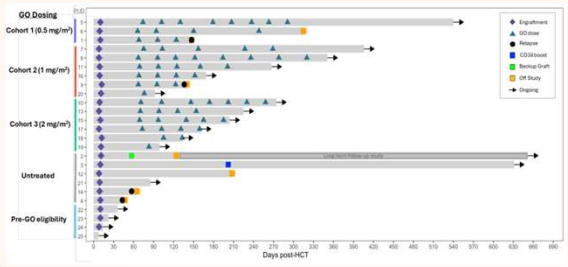
University of Colorado Anschutz Medical Campus

DiPersio J, *ASH 2024*

Denver ASH Review

41

Trem-cel allograft affords protection from deep and prolonged cytopenias following GO maintenance



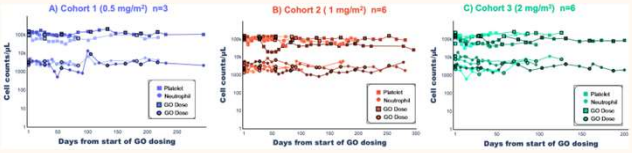
University of Colorado Anschutz Medical Campus

DiPersio J, *ASH 2024*

Denver ASH Review

42

Trem-cel provides hematologic protection and enrichment of CD33-negative myeloid cells upon GO dosing

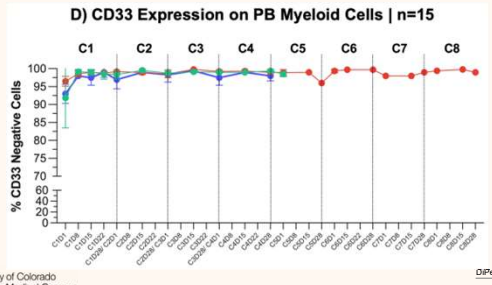


University of Colorado Anschutz Medical Campus

DiPersio J, *ASH 2024*
Denver ASH Review

43

Trem-cel provides hematologic protection and enrichment of CD33-negative myeloid cells upon GO dosing



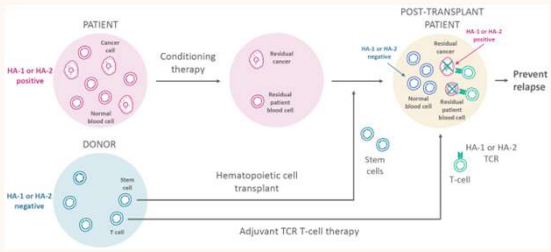
University of Colorado Anschutz Medical Campus

DiPersio J, *ASH 2024*
Denver ASH Review

44

TSC-100/TSC-101: Post-transplant allogeneic TCR T cells specific to recipient HLA to minimize relapse

PI: Mat Angelos
NCT05473910

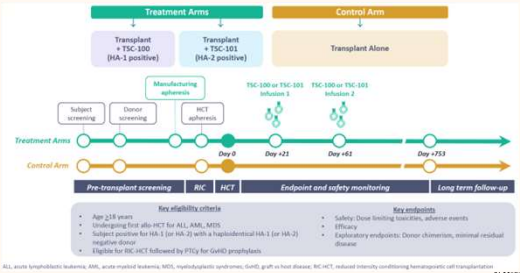


University of Colorado Anschutz Medical Campus

Al Malki M, *ASH 2024*
Denver ASH Review

45

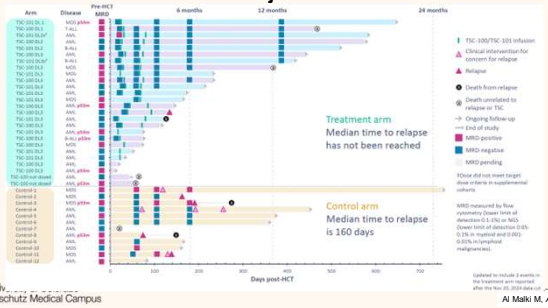
ALLOHA: Multi-arm Ph1 trial of TSC-100 and TSC-101 in RIC allogeneic stem cell transplant recipients for AML, ALL, and MDS



Al Malki M, *ASH 2024*

46

ALLOHA: MRD negativity and complete donor chimerism was achieved in all treatment-arm subjects



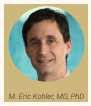
Al Malki M, *ASH 2024*

47

CD64 CAR-T Product

Novel IEC

Technology



M. Eric Kohler, MD, PhD

M. Eric Kohler, M.D., Ph.D.
Assistant Professor
Pediatrics-Heme/Onc and Bone Marrow Transplantation
University of Colorado School of Medicine
Children's Hospital of Colorado

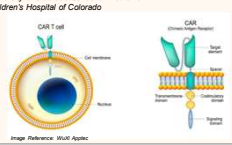


Image Reference: WuXi AppTec

Mathew Angelos, M.D., Ph.D.
Assistant Professor, Hematology
University of Colorado School of Medicine
University of Colorado Hospital

Sanam Shahid, M.D.
Assistant Professor
Pediatric Hematology
Children's Hospital of Colorado

Product Details	
Scientific Investigator	M. Eric Kohler
Principal Investigators	M. Angelos *(adult)* S. Shahid *(pediatric)*
Tech. Platform	CAR-T
Antigen Target	CD64
Indication	Acute Myeloid Leukemia (AML)

Why CD64?
CD64, also known as the Fc-gamma Receptor 1, is highly expressed on monocytic AML blasts and mono-LSCs.

AML patients presenting with a monocytic phenotype (initially or at relapse) are at high risk of treatment failure and/or relapse after the preferred treatment regimen, Ven/Aza.

Establishment of a therapy that can target CD64-expressing AML blasts/mono-LSCs has the potential to eliminate Ven/Aza resistant populations that give rise to current treatment failures.

48

Closing thoughts…

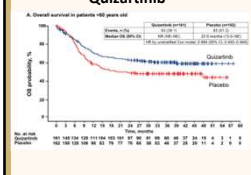
- Lower-intensity venetoclax-based regimens are appropriate in younger patients (in the right molecular contexts), but there is still a (shrinking) role for high-intensity induction.
- Venetoclax-resistance can be predicted and efforts should be made to enroll patients on clinical trials.
- More menin inhibitors are going to be approved and we will now have the (exhausting) task of deciding which one is “best” over the next 5 years.
- Immuno- and cellular therapies are not dead in myeloid neoplasms.

49

50

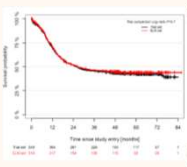
Quizartinib vs Mido vs GILT 7&3 in FLT3 ITD under age 60

Quizartinib



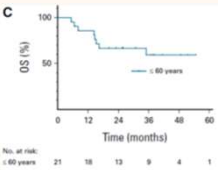
Erba et al Lancet 2023

Midostaurin



Dohner et al Blood 2020

Gilteritinib



Pratz et al JCO 2023

51