MANAGEMENT OF RELAPSED ACUTE MYELOID LEUKEMIA

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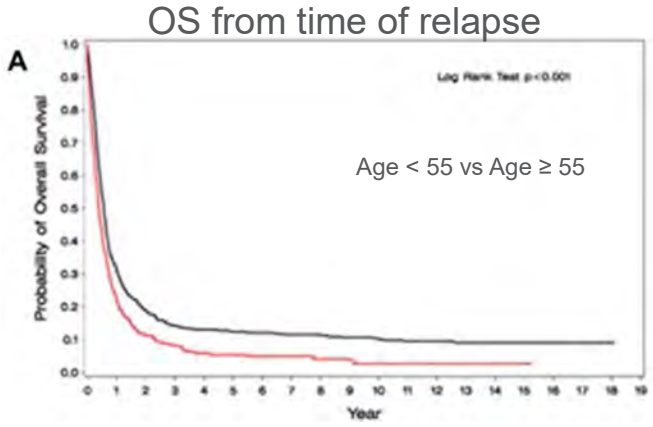
1

OVERVIEW

- Biology of relapsed / refractory AML
  - What you see at diagnosis is not necessarily what you see at relapse
  - Mechanism of relapse / resistance is influenced by the treatment
- Approved therapies for relapsed AML
  - Role of alloHCT
  - Cytotoxic chemo
  - Targeted agents: FLT3, IDH1/IDH2 inhibitors
- Novel targeted agents: menin inhibitors and immunotherapy

2

OUTCOME OF PATIENTS WITH AML TREATED ON ECOG PROTOCOLS 1984-2008 (N=3012)

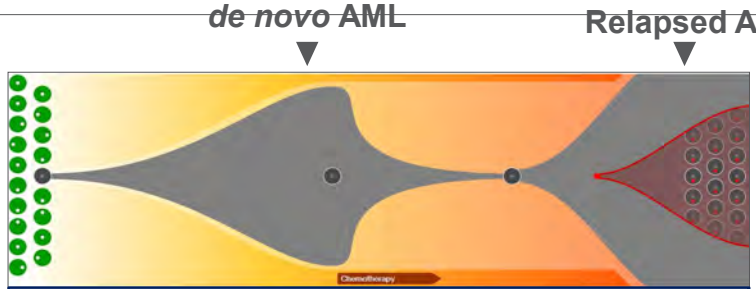


59.1% achieved CR1
58.9% relapsed

5-year OS: 10 (±1)%

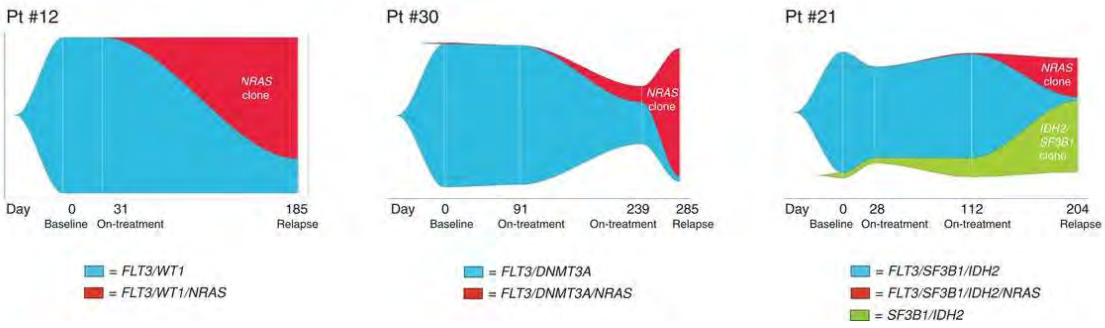
Ganzel et al., Am J Hem 2018

CLONAL DYNAMICS OF AML



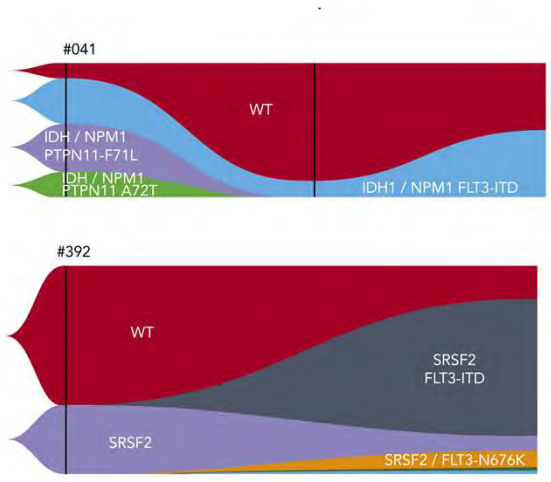
Ding *et al*, Nature 2012

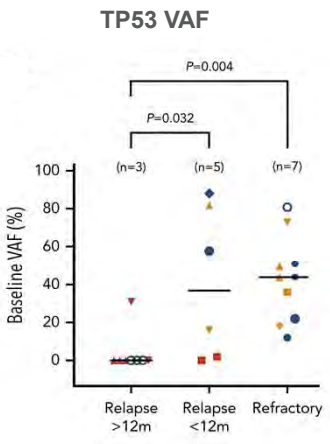
SELECTION OF RAS-MUTANT CLONAL POPULATIONS DURING TREATMENT OF GILTERITINIB



McMahon et al., Cancer Discovery 2019

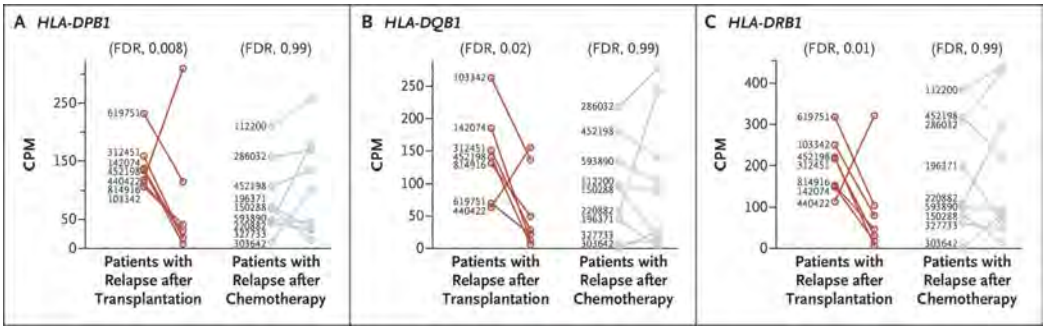
ADAPTIVE RESISTANCE TO VENETOCLAX THERAPY





DiNardo et al., Blood 2020

IMMUNE ESCAPE POST ALLOHCT

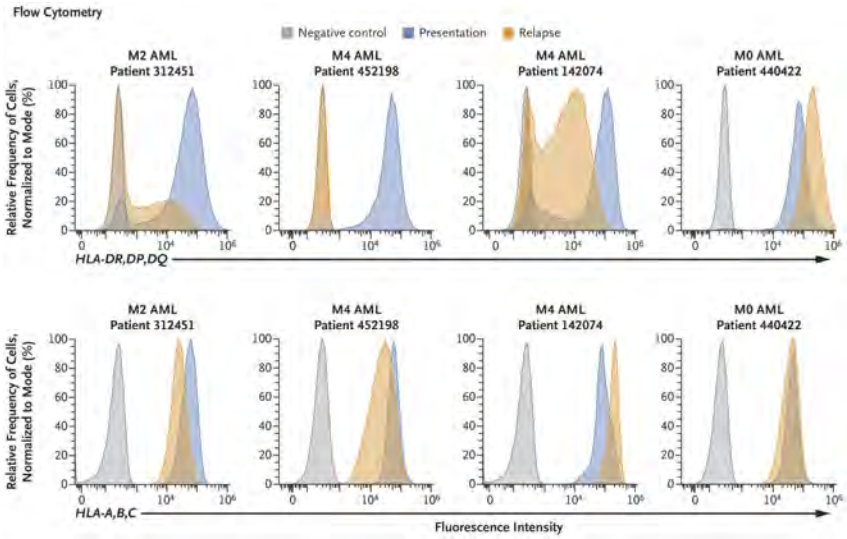


Downregulation of MHC Class II genes contributes to immune escape post alloHCT

Christopher *et al*. NEJM 2018

7

IMMUNE ESCAPE POST ALLO HCT

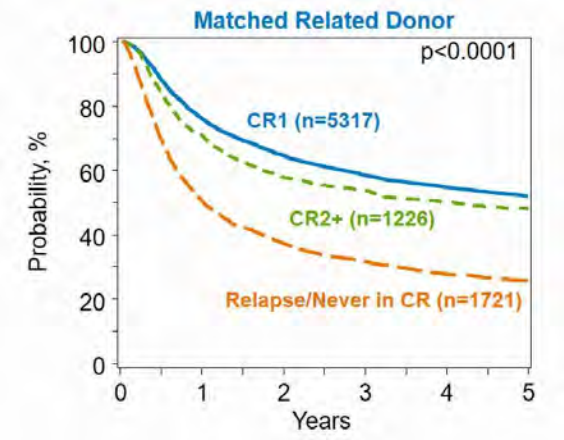


8

HOW DO I APPROACH A PATIENT WITH REL/REF AML?

1. Is the patient a candidate for alloHCT?
2. How likely is the AML to respond to cytotoxic chemotherapy?
3. Is a targetable mutation present? ie. FLT3, IDH1, IDH2

SURVIVAL AFTER ALLOHCT FOR ADULTS WITH AML



1. AlloHCT should be the goal for eligible patients
2. AlloHCT is best performed when patients are in remission

What is the best way of getting patients back into CR?

CIBMTR Summary Slides 2021

HOW LIKELY IS THE AML TO RESPOND TO CYTOTOXIC CHEMOTHERAPY?

General factors

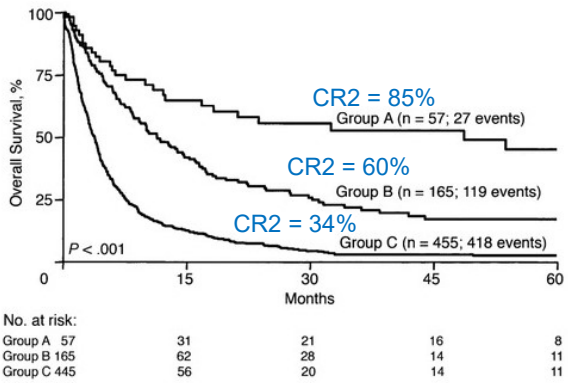
- Age
- Cytogenetics / molecular features

Relapse specific factors

- Number of prior relapses
- Prior unsuccessful salvage attempts
- Duration of CR

EUROPEAN PROGNOSTIC INDEX FOR AML IN 1ST RELAPSE

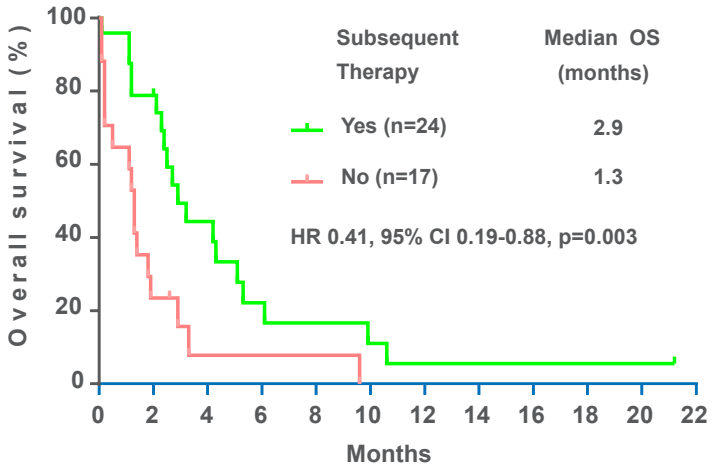
Prognostic Factor	Coefficient	Points
RFI, relapse-free interval from CR1, months		
> 18	0	0
7-18	0.69	3
≤ 6	1.28	5
CYT, cytogenetics at diagnosis		
t(16;16) or inv(16)*	0	0
t(8;21)*	0.68	3
Other†	1.19	5
AGE, age at first relapse, years		
≤ 35	0	0
36-45	0.21	1
> 45	0.47	2
SCT, stem-cell transplantation before first relapse		
No SCT	0	0
Previous SCT	0.49	2



Favorable risk group A contains patients with scores of 1 to 6 points, intermediate group B: 7 to 9 points, poor group C: 10 to 14 points.

Breems et al., JCO 2005

OUTCOMES OF R/R AML AFTER FRONTLINE VEN+HMA



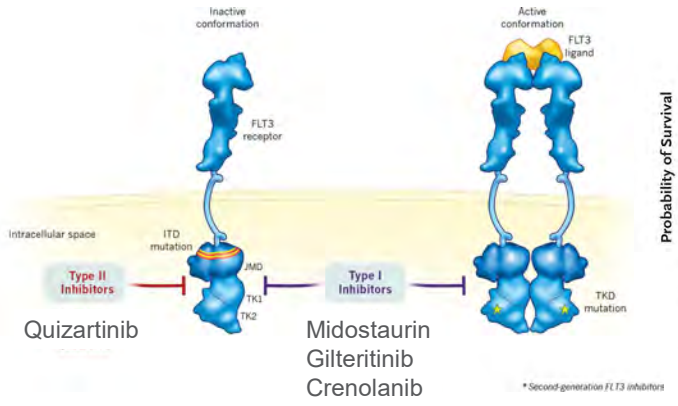
Mutational subgroups (n)	Received salvage therapy	TKI used in salvage regimen	CR/CR MLFS
FLT3-ITD (5)	4	3	2/4
IDH1/2 (6)	4	3	0/4
TP53 (6)	5	–	1/5
N/KRAS (11)	10	–	3/10

TKI = tyrosine kinase inhibitor

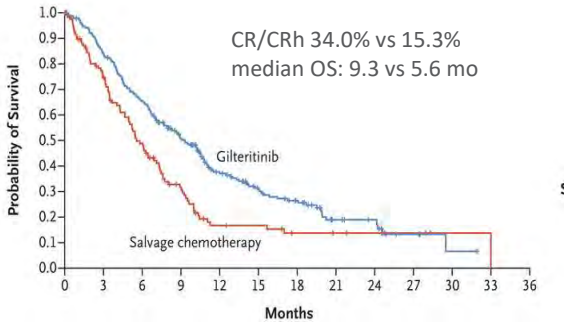
Maiti et al., Haematologica 2021

13

FLT3 INHIBITORS FOR AML



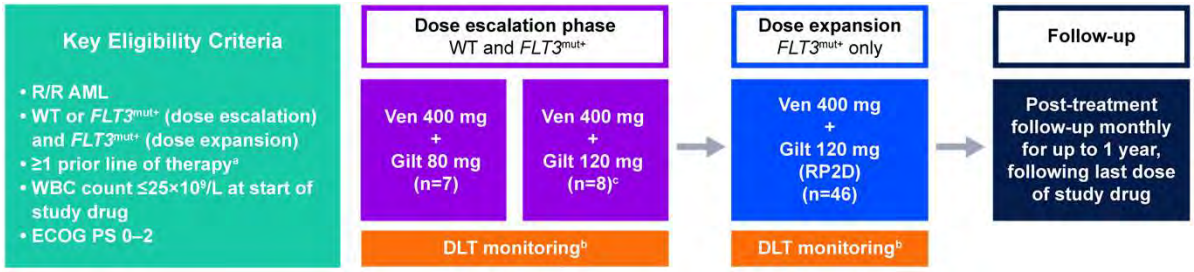
Daver et al., Leukemia 2019



Perl et al., NEJM 2019

14

PHASE 1B STUDY OF VEN + GILT IN R/R FLT3-MUT AML

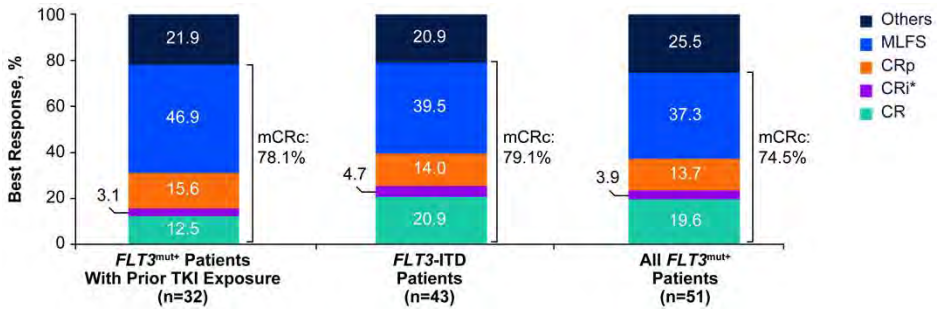


	Patients receiving Ven + Gilt at RP2D (N=54)
Prior therapy, n (%)	
≥1 prior FLT3 TKI	32 (59)
Prior Gilt	0
Prior Ven	10 (19)
Prior allo-transplant, n (%)	17 (31)

Daver et al. JCO 2022

15

SUMMARY OF BEST RESPONSES

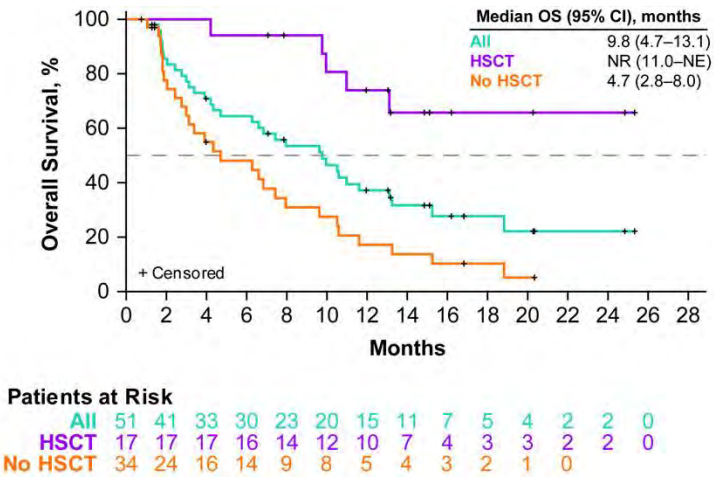


	*FLT3*mut+ Patients With Prior TKI Exposure (n=32)	*FLT3*-ITD Patients (n=43)	All *FLT3*mut+ Patients (n=51)
mCRc[a], n (%)	25 (78.1)	34 (79.1)	38 (74.5)
CR+CRp+CRi[b]*	10 (31.3)	17 (39.5)	19 (37.3)
MLFS	15 (46.9)	17 (39.5)	19 (37.3)

The mCRc rate in this study was **74.5**%. The CRc rate in the ADMIRAL Phase 3 study for single agent Gilt was 54.3% (using the same response parameters).[1]

16

OS BY TRANSPLANT STATUS



- Median duration of follow-up was 15.1 months (range, 0.8–25.3)
- Median OS for FLT3-ITD patients was 10.0 months (95% CI, 6.6–13.2)

AZA+VEN+GILTERITINIB IN FLT3-MUTATED AML

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)

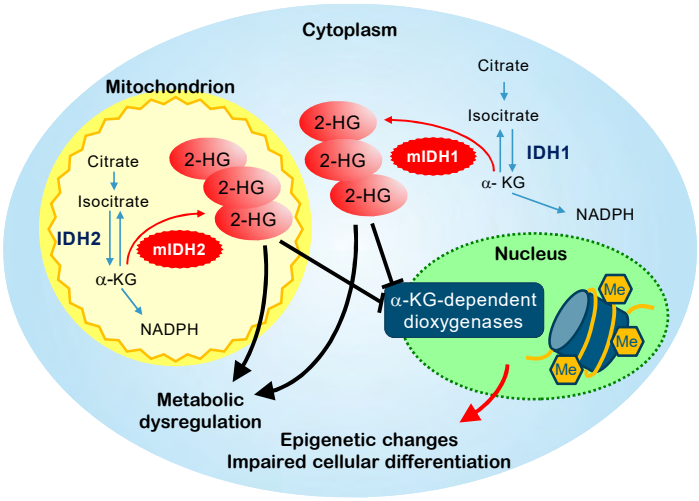
Short et al., ASH 2021

ISOCITRATE DEHYDROGENASE (IDH) MUTATIONS IN AML

- Somatic IDH1 and IDH2 mutations result in accumulation of oncometabolite 2-HG
  - epigenetic changes, impaired cellular differentiation
- mIDH identified in multiple solid and hematologic tumors

	mIDH1	mIDH2
% of AML patients	~6–10%	~9–13%

- Enasidenib (AG-221): mIDH2
- Ivosidenib (AG-120): mIDH1



19

IDH INHIBITORS FOR REL/REF AML

	Enasidenib (AG-221)[1]	Ivosidenib (AG-120)[2]
Target	IDH2	IDH1
Dosing	100 mg daily	500 mg daily
N in primary efficacy population	109	125
Response Rate % (95% CI)		
CR	20.2% (13.1-28.9)	21.6% (14.7-29.8)
CR+CRi/CRh	26.6%	30.4% (22.5-39.3)
Median duration of CR (95% CI)	8.8 months (5.3-NR)	9.3 months (5.6-18.3)
Time to CR (range)	3.7 months (0.7-11.2)	2.8 months (0.9-8.3)
IDH Differentiation syndrome	9.6%	10.6%

[1]Stein *et al.*, Blood 2017
[2]DiNardo *et al.*, NEJM 2018

20

HOW I TREAT RELAPSED OR REFRACTORY AML

Primary refractory: immediate alloHCT
FLT3m AML: Gilteritinib - > alloHCT

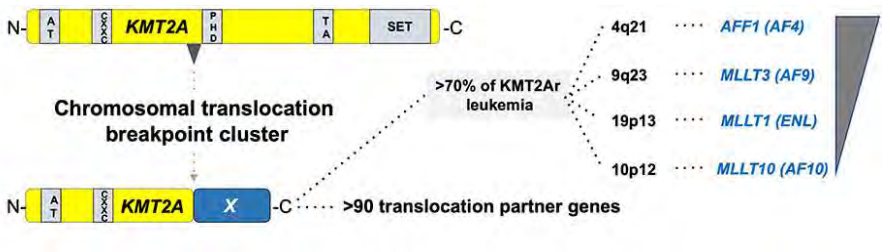
Chemotherapy "sensitive" & FLT3 WT: ONE course of cytotoxic chemo -> alloHCT

- Unlikely to benefit by giving multiple rounds of cytotoxic chemo
- No specific salvage regimen demonstrated to be superior to another

Chemotherapy "resistant" & mIDH1 or mDH2: IDH inh -> alloHCT

All others: strongly consider novel therapies including P1 clinical trials.

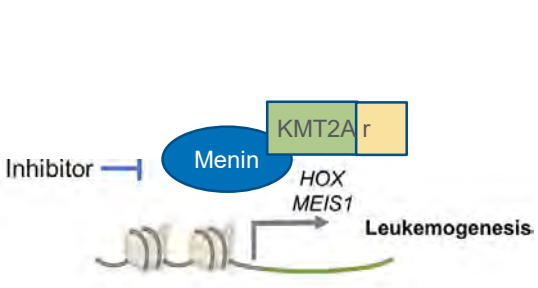
MENIN INHIBITORS FOR KMT2AR / MNPM1 ACUTE LEUKEM

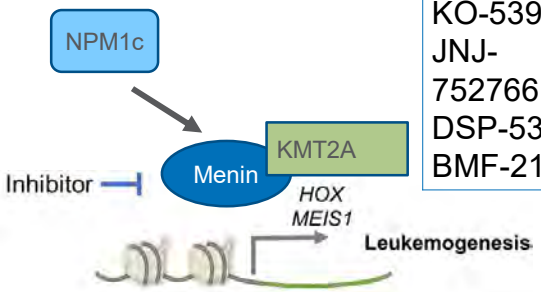


- KMT2Ar represent ~10% of acute leukemias
  - 70-80% of infantile leukemias
  - t-AML following exposure to topoisomerase II inhibitors

Mercher et al, Frontiers in Pediatrics 2019

MENIN INHIBITORS FOR KMT2Ar / mNPM1





Menin Inhibitors
SNDX-5613
KO-539
JNJ-75276617
DSP-5336
BMF-219

23

AUGMENT-101

SNDX-5613 IN REL/REF KMT2A AND mNPM1 LEUKEMIAS

	Best Response	Efficacy Population n = 51 (%)
Response	**Overall Response Rate[1]**	**28/51 (55%)**
	CR	8 (16%)
	CRh	4 (8%)
	CRp	7 (14%)
	MLFS	9 (18%)
MRD^{neg}	**CRc MRD^{neg} Rate[2]**	**16/51 (31%)**
	within CR/CRh MRD^{neg}	11/12 (92%)
	within CR/CRh/CRp MRD^{neg}	16/19 (84%)
MLLr	**Overall Response Rate[1]**	**23/38 (61%)**
	CR/CRh	9/38 (24%)
mNPM1	**Overall Response Rate[1]**	**5/13 (38%)**
	CR/CRh	3/13 (23%)

[1]Overall Response Rate = CR + CRh + CRp + MLFS; [2]CR + CRh + CRp ; MRD status assessed locally by PCR or MCF

- Morphologic evidence of differentiation
- CR/CRh of 24%
- TTR 2 months
- 6/12 patients have DOR > 6 months

Stein et al., ASH 2021

24

IMMUNOTHERAPY FOR REL/REF AML

- alloHCT most potent anti-leukemic therapy
- AML lacks ideal tumor associated antigen for targeting
  - Commonly shared on normal hematopoietic stem / progenitors
  - Prolonged neutropenia not as well tolerated as B-cell aplasia

IMMUNOTHERAPY FOR REL/REF AML

- Attempts at adapting approaches from B-cell malignancies have had modest success

Immunotherapy approach
Checkpoint inhibitors
Vaccines
Antibodies
Antibody drug conjugates
Bispecific antibodies
CART cells

Antigens	Examples	
CD33	Gemtuzumab Valdastuximab	ADC ADC
CD123	IMGN632 Flotetuzumab Vibecotamab	ADC Bispecific Ab Bispecific Ab
CLEC12A (CLL1)	KITE-222	CART
CD117	MGTA-117	ADC
WT-1	Galinpepimut-S	Peptide vaccine

OVERCOMING LACK OF IDEAL TUMOR ANTIGEN IN AML

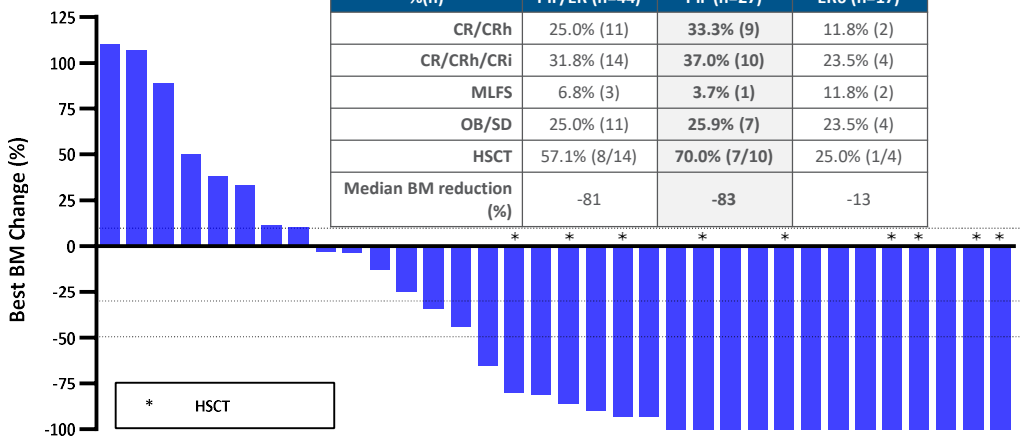
- Lack of ideal tumor antigen
  - Modest response rates
  - On target toxicity

- Innovative approaches to immunotherapy
  - MGTA-117: Targeting CD117 as conditioning prior to alloHCT
  - VOR33: CD33 CRISPR gene-edited HSC product followed by GO
  - RG6007: HLA-A2 TCR-mimetic bispecific to target intracellular WT-1

27

FLOTETUZUMAB IN PRIMARY INDUCTION FAILURE & EARLY RELAPSE AML

%(n)	PIF/ER (n=44)	PIF (n=27)	ER6 (n=17)
CR/CRh	25.0% (11)	**33.3% (9)**	11.8% (2)
CR/CRh/CRi	31.8% (14)	**37.0% (10)**	23.5% (4)
MLFS	6.8% (3)	**3.7% (1)**	11.8% (2)
OB/SD	25.0% (11)	**25.9% (7)**	23.5% (4)
HSCT	57.1% (8/14)	**70.0% (7/10)**	25.0% (1/4)
Median BM reduction (%)	-81	**-83**	-13



Uy et al, Blood 2021

28

CONCLUSIONS

- Clonal heterogeneity is AML is shaped by therapy and guides resistance and relapse
- Understanding these processes through serial and single cell analyses have the potential to inform future therapies