ManagingAML

Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

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Faculty Disclosures

- **Dr. Naval Daver** has received honoraria related to formal advisory activities and as a consultant from AbbVie Inc., Agios, Astellas Pharma US, Inc., Bristol-Myers Squibb Company, Celgene Corporation – A Bristol-Myers Squibb Company, Daiichi Sankyo, Inc., ImmunoGen, Inc., Incyte Corporation, Jazz Pharmaceuticals plc, Karyopharm Therapeutics, Novartis AG, Otsuka Pharmaceutical Co., Ltd., Pfizer Inc., and Sunesis. He has received grant support related to research activities from AbbVie, Bristol-Myers Squibb, Daiichi Sankyo, Genentech, Inc., GlycoMimetics, Inc., ImmunoGen, Incyte, Karyopharm, Nohla Therapeutics, Novartis, Pfizer, SERVIER, and Sunesis.
- **Dr. Courtney DiNardo** has received honoraria as a consultant from AbbVie Inc., Agios, Celgene Corporation – A Bristol-Myers Squibb Company, Daiichi Sankyo, Inc., Immune-Onc Therapeutics, Inc., Novartis AG, and Takeda Oncology. She has received grant support related to research activities from AbbVie, Agios, Celgene Corporation – A Bristol-Myers Squibb Company, Calithera BioSciences, Inc., Daiichi Sankyo, and Immune-Onc. She has also disclosed a financial relationship with Notable.
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Planning Committee Disclosures

- The individuals listed below from MediCom Worldwide, Inc. reported the following for this activity: Joan Meyer, RN, MHA, Executive Director, Isabelle Vacher, Vice President of Educational Strategy, Wilma Guerra, Program Director, and Andrea Mathis, Project Manager, have no relevant financial relationships.

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Learning Objectives

- Summarize best practice strategies in molecular and mutational analysis in AML which assist in developing a patient-centered treatment approach
- Improve knowledge of new and emerging evidence in maintenance therapy as a new standard of care in AML
- Outline guidelines and clinical trial evidence to identify appropriate treatment approaches for patients with AML
- Describe strategies for identifying and managing treatment including dosing, and management of toxicities associated with novel and emerging therapies in AML

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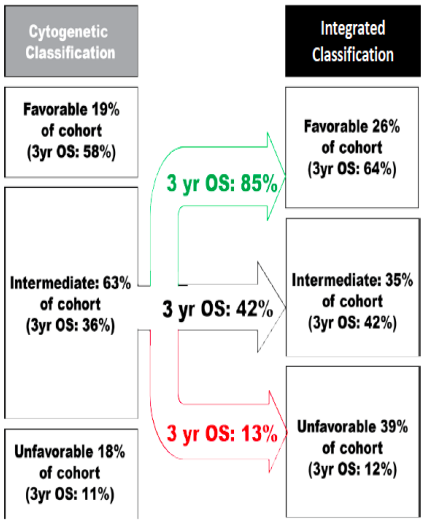
AML Genomic Profiling: *FLT3* Mutations Are Common

How Does Mutational Profiling in AML Impact Clinical Practice?

Gene	Overall Frequency, %
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPα	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

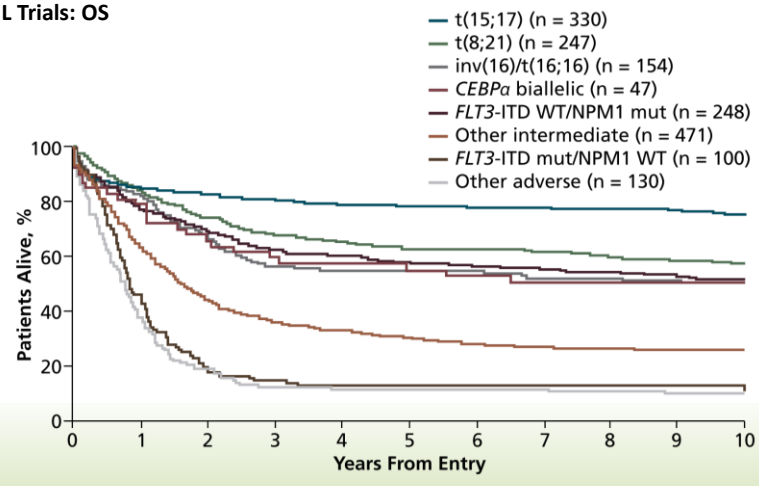


Patel JP, et al. *N Engl J Med*. 2012;366:1079-1089.

5

Cytogenetic and Molecular Abnormalities: Survival

MRC/NCRI AML Trials: OS



Smith ML, et al. *Blood Rev.* 2011;25:39-51.

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Major Targets of Past and Future Therapeutic Development

AML with *FLT3* internal tandem duplication	• Impact on both therapy and prognosis • Many *FLT3* kinase inhibitors explored in recent years…now several next-generation agents in development
***KIT* mutations in CBF AML**	• *KIT* mutations found in 30%-35% of CBF AML cases, but rare in other AML subgroups • In CBF AML, mutations cluster mainly in exons 8 and 17
IDH mutations in AML	• *IDH1/2* mutations confer a gain-of-function, including increased histone and DNA methylation and impaired cellular differentiation
***Bcl*-2 as a therapeutic target in AML**	• *Bcl*-2 binds and sequesters pro-apoptotic molecules; inhibition of *Bcl*-2 primes cancer cells for death
Epigenetic targets (EZH2, LSD1, BRD, PRMT5, others)	• Novel agents on the horizon that target specific epigenetic pathways • These are in early clinical trial development
TP53, C-CBL, MLL-Menin	• Phase 1 clinical trials

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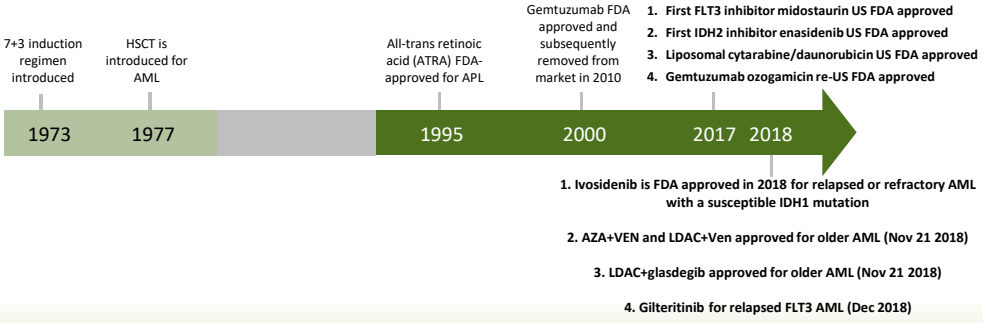
Treatment of AML (Accelerated Progress 2017-2020): History

Since its introduction in the early 1970s, 7+3 therapy (cytarabine for 7 days + anthracycline for 3 days) has been the standard of care for AML

US FDA approvals



Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

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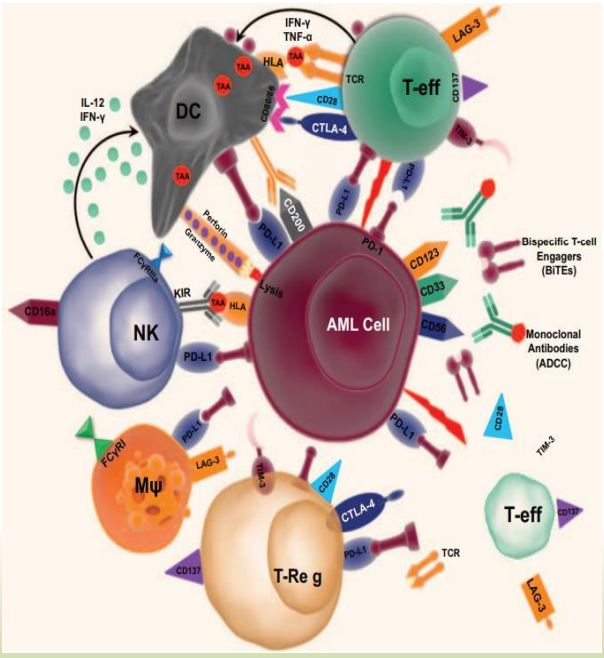

Major Approaches to Immune Therapies in AML

Two major approaches:

1. Antibody drug conjugates
2. T-cell based therapies
   a. Bi-specific antibodies (CD3 x AML antigen)
   b. Immune checkpoint-based approaches
   c. CAR T (CAR NK)

Assi R, et al. *Curr Opin Hematol*. 2018;25:136-145.

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Progress and Challenges in Frontline Treatment

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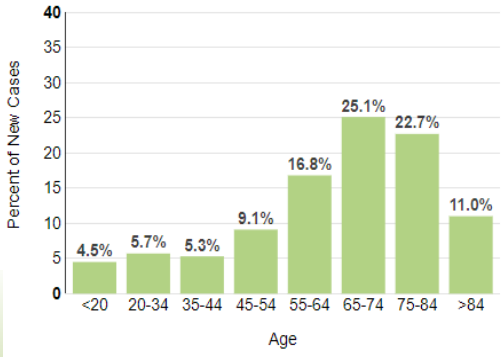
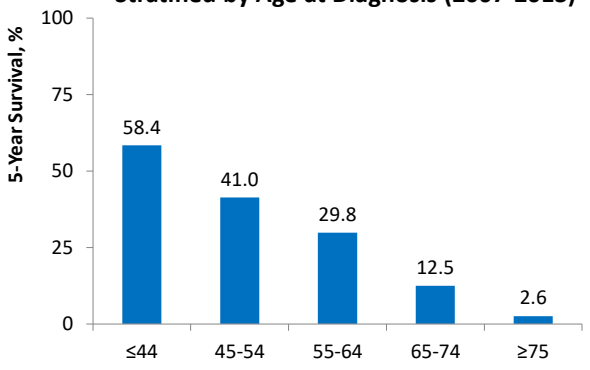
Managing AML: Staying on Track in a Rapidly Changing Treatment Landscape

Median age at diagnosis:
68 years
5-year survival is 28.3%

Incidence of AML by Age Group



5-Year Survival of Newly Diagnosed AML Stratified by Age at Diagnosis (2007-2013)



SEER 2018 data: https://seer.cancer.gov/statfacts/html

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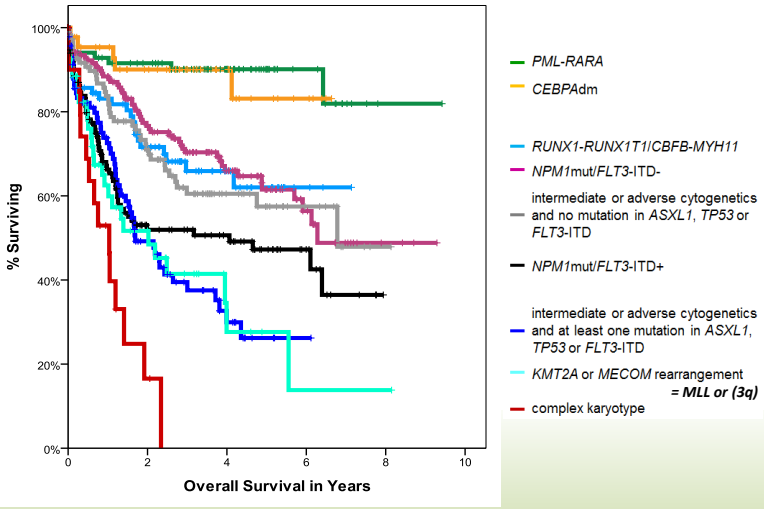
Using Genomic Classification to Improve AML Prognostication

APL:
PML-RARA = t(15;17)

Core-binding factor (CBF) leukemias:
RUNX1-RUNX1T1 = t(8;21)

CBFB-MYH11 = inv(16) or t(16;16)



Haferlach C, et al. *Blood.* 2016;128(22):286.

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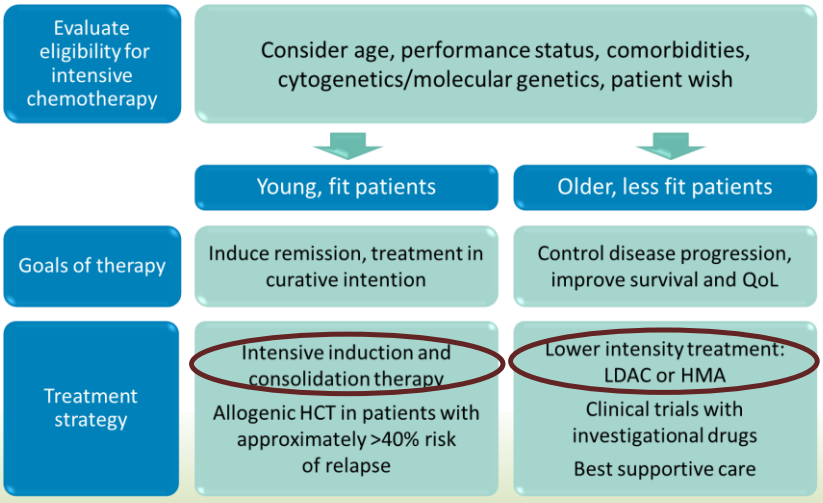
Algorithm of AML Therapy (Circa 2017)



Döhner H, et al. *Blood.* 2017;129(4):424-447.

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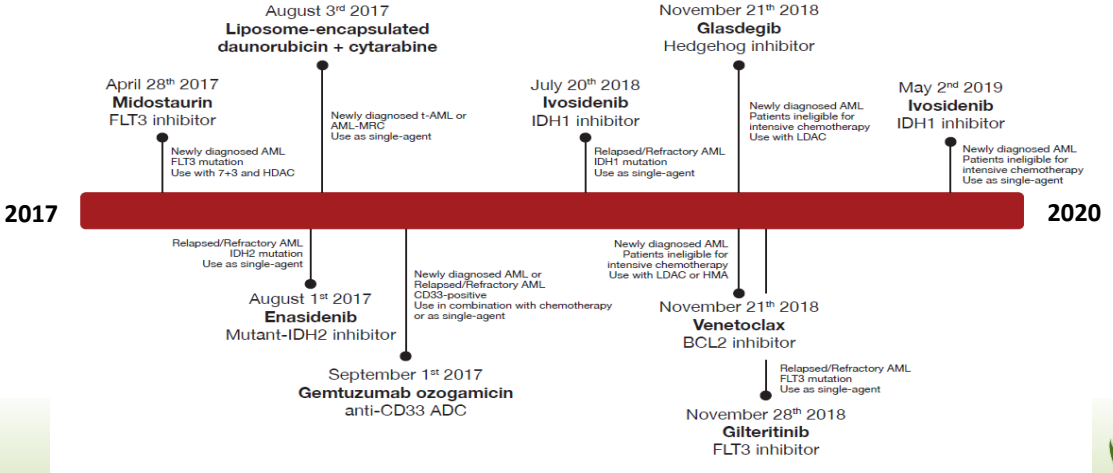
The Rapidly Evolving Treatment Landscape of AML



Richard-Carpentier G, DiNardo CD. *Hematology Am Soc Educ Program*. 2019(1):548-556.

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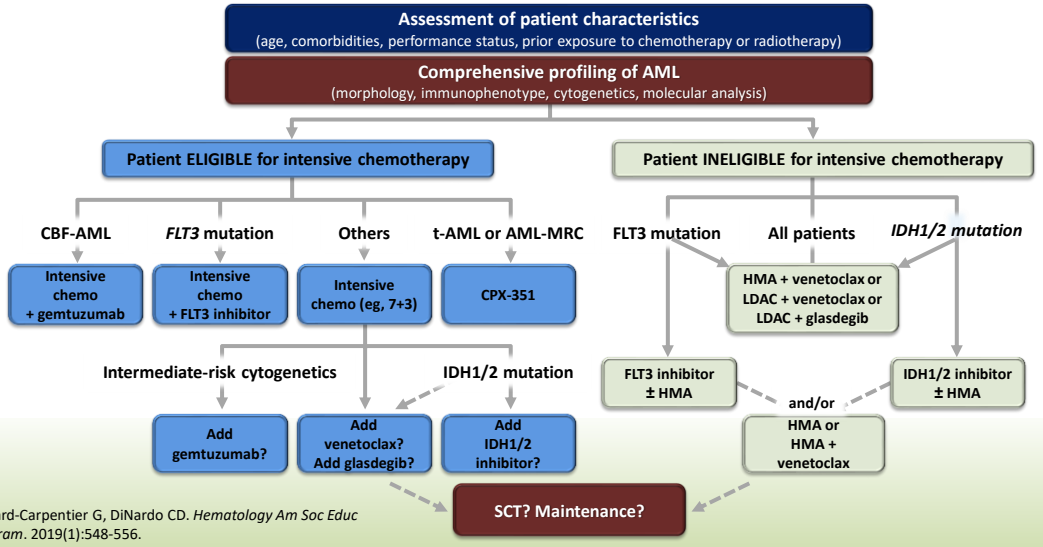
Evolving Diagnostic and Treatment Paradigm for Newly Diagnosed AML



Richard-Carpentier G, DiNardo CD. *Hematology Am Soc Educ Program*. 2019(1):548-556.

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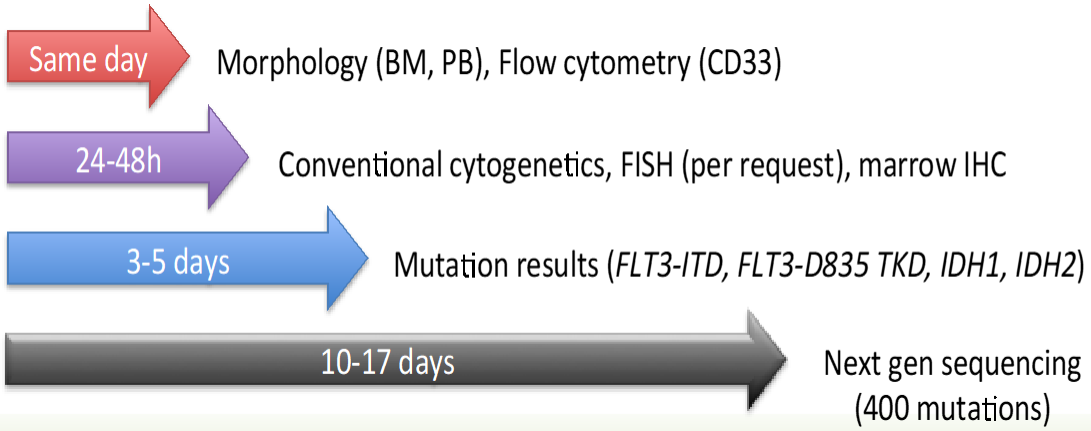
Diagnostic Workup for AML in 2020



How long can/should we wait for treatment initiation?

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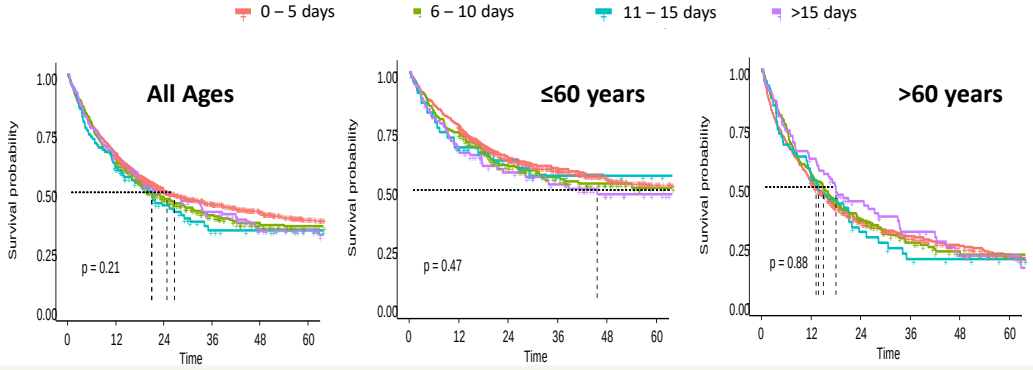
Is it Safe to Wait for Genomic Information Prior to Starting Treatment?

Over 2200 patients receiving 7+3 based therapy through German SAL Registry



Time from diagnosis to treatment did NOT affect outcome in intensively treated patients with newly diagnosed AML (CR, early mortality, or OS)

Röllig C, et al. *Blood.* 2019;134(supplement_1):Abstract 13.

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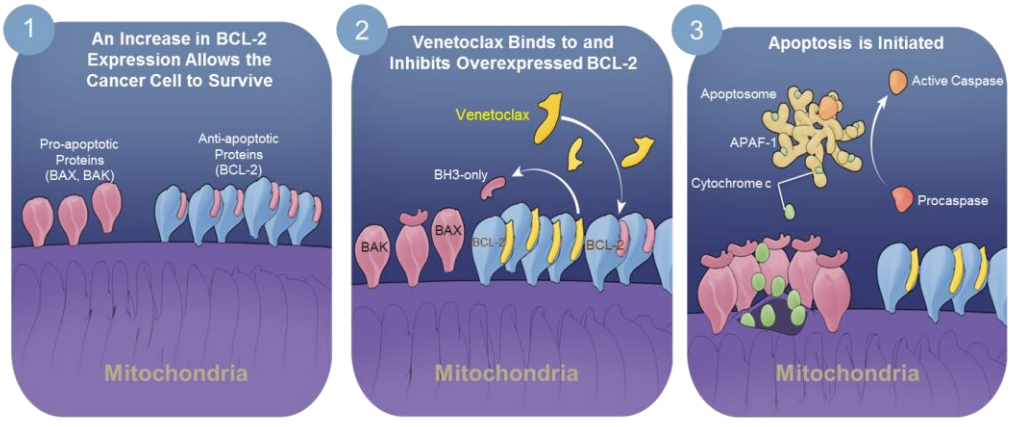
BCL2 Inhibitor Venetoclax in AML



- Cancer cells increase the expression of anti-apoptotic proteins to offset the increase in pro-apoptotic proteins, tipping the balance towards cell survival
- The large number of pro-apoptotic proteins bound and sequestered by BCL2 make cancer cells "primed" for death

Pan R, et al. *Cancer Discov.* 2014;4(3):362-372.; Leverson JD, et al. *Sci Transl Med.* 2015;7(279):279ra40.; Souers AJ, et al. *Nat Med.* 2013;19(2):202-208.; Certo M, et al. *Cancer Cell.* 2006;9(5):351-356.

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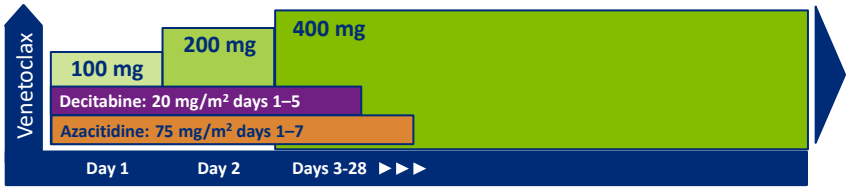
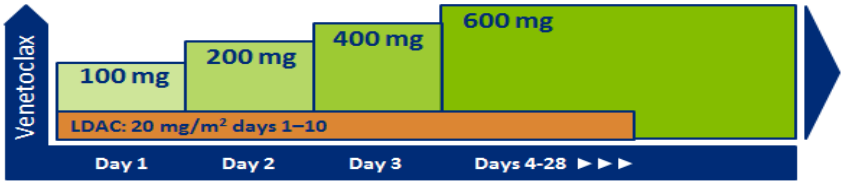
Lower-Intensity Venetoclax Combinations for Newly Diagnosed "Unfit" AML

HMA + Venetoclax



LDAC + Venetoclax



Criteria:
- Newly diagnosed
- Age ≥75 years
  OR
- ECOG 2-3
- Cardiac, lung, liver or renal disease

DiNardo CD, et al. *Lancet Oncol.* 2018;19(2):216-228.; Wei AH, et al. *J Clin Oncol.* 2019;37(15):1277-1284.

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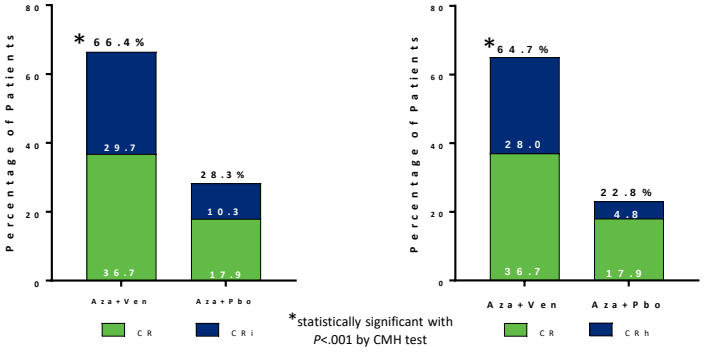
Results of VIALE-A

- CR defined as absolute neutrophil count >10^3/µL, platelets >10^5/µL, red cell transfusion independence (TI), and bone marrow with <5% blasts
- CRi defined as all criteria for CR, except for neutropenia ≤10^3/µL *or* thrombocytopenia ≤10^5/µL
- CRh defined as all criteria for CR, except for neutropenia >0.5 x 10^3/µL, *and* platelets >0.5 x 10^5/µL



	Median Time to CR/CRi, Months (range)	*CR+CRi by Initiation of Cycle 2, n (%)	Median Time to CR/CRh Months (range)	*CR+CRh by Initiation of Cycle-2, n (%)	Median Duration of CR/CRi, Months (95% CI)	Median Duration of CR, Months (95% CI)
Aza+Ven (n=286)	1.3 (0.6-9.9)	124 (43.4)	1.0 (0.6-14.3)	114 (39.9)	17.5 (13.6-NE)	17.5 (15.3-NE)
Aza+Pbo (n=145)	2.8 (0.8-13.2)	11 (7.6)	2.6 (0.8-13.2)	8 (5.5)	13.4 (5.8-15.5)	13.3 (8.5-17.6)

DiNardo CD, et al. EHA 2020. Abstract LBA 2601.

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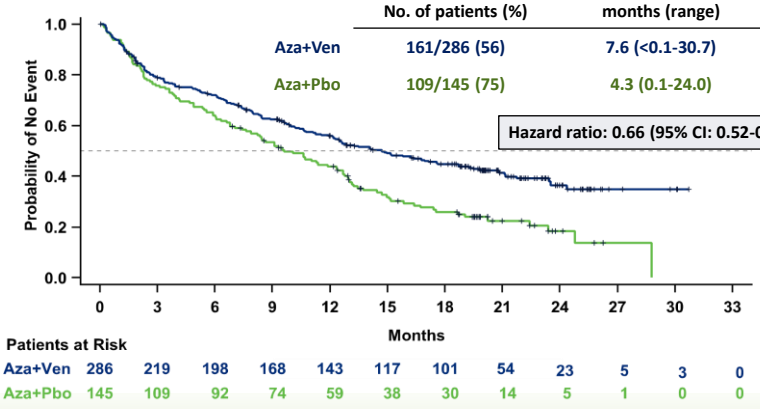
Results of VIALE-A: Overall Survival

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



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

Distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk).
The hazard ratio between treatment arms were estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test.
DiNardo CD, et al. EHA 2020. Abstract LBA 2601.

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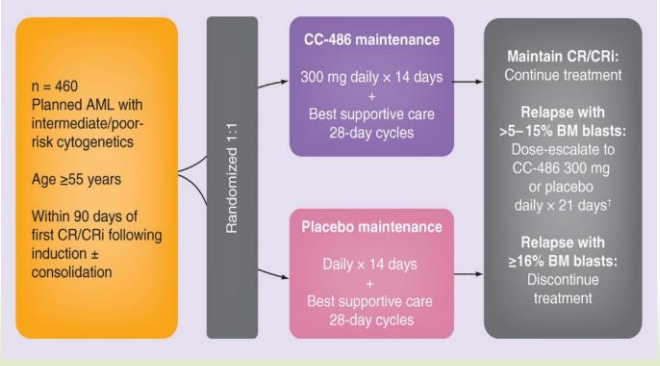
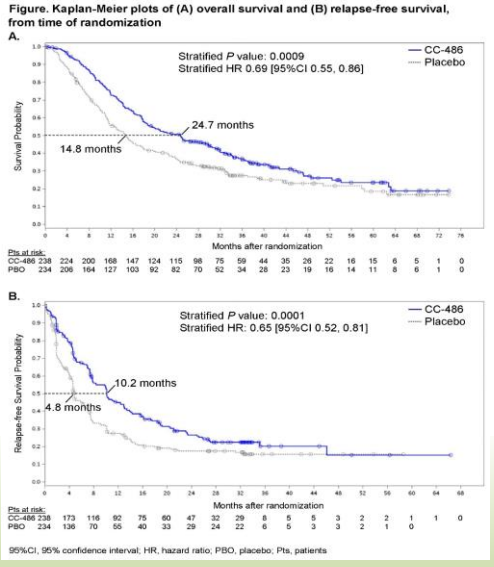
CC-486 "Oral Azacitidine" Maintenance

QUAZAR AML-001: Randomized Placebo-Controlled Phase III Study of CC-486 (oral AZA):

Clinically meaningful improvement in both OS and RFS in older patients with AML in remission following intensive chemotherapy





Roboz GJ, et al. *Future Oncol.* 2016;12(3):293-302.;
Wei AH, et al. *Blood.* 2019;134(Supplement_2):Abstract LBA-3.

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ManagingAML

Molecular and Immunotherapies:
Moving the Bar in Relapsed/Refractory AML

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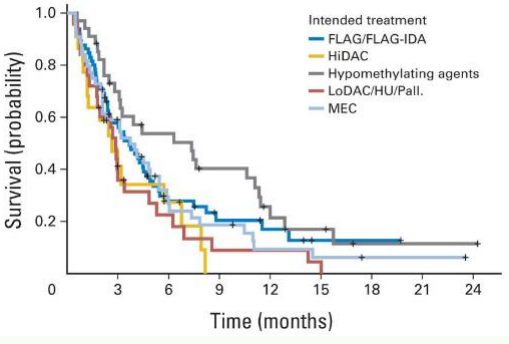
Emerging Treatment Options: Relapsed/Refractory AML

Chemotherapy[1]



Targeted Therapies

Drug Name	AML Subset	ORR	Median OS
Enasidenib[2]	*IDH2* mutant	40.3%	9.3 mos
Ivosidenib[3]	*IDH1* mutant	41.6%	8.8 mos
GO[4]	CD33+ AML	26%	11.6 mos
Gilteritinib[5]	*FLT3* mutant	34%	9.3 mos

1. Roboz GJ, et al *J Clin Oncol*. 2014;32(18)1919-1926. 2. Stein EM, et al. *Blood*. 2017;130(6):722-731. 3. DiNardo CD. *N Engl J Med*. 2019;379(12):1186.
4. Taskin A-L, et al. *Leukemia*. 2007;21(1):66-71. 5. Perl AE, et al. *N Engl J Med*. 2019;381(18):1728-1740.

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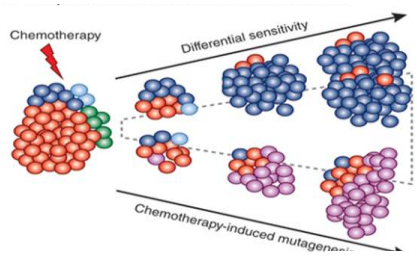
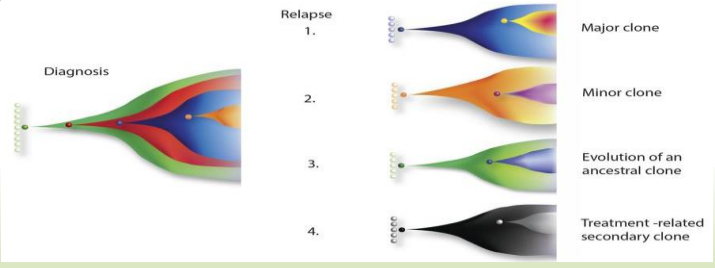
Clonal Evolution and Therapy Resistance at Relapse



Leukemia is not a static condition!

Repeat genomic analysis at relapse is necessary



Kleppe M, Levine RL. *Nat Med.* 2014;20(4):342-344.; Grimwade D, et al. *Blood.* 2016;127(1):29-41.

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Challenge of Choosing the Right Treatment Paradigm

Targeted therapy

- *FLT3 mut*
  - Gilteritinib (*FLT3-ITD* or *TKD*)
  - Sorafenib + HMA (*FLT3-ITD* only)
- *IDH mut*
  - Ivosidenib (*IDH1*)
  - Enasidenib (*IDH2*)
- CD33+
  - Gemtuzumab ozogamicin

Chemotherapy

- Less aggressive
  - Low dose AraC
  - HMA (aza, dec)
  - Venetoclax + LDAC or HMA
- Aggressive
  - CLAG + Ida/Mito
  - HIDAC + Ida/Daun/Mito
  - FLAG + Ida
  - Etop/AraC/Mito
  - Clof+AraC+Ida

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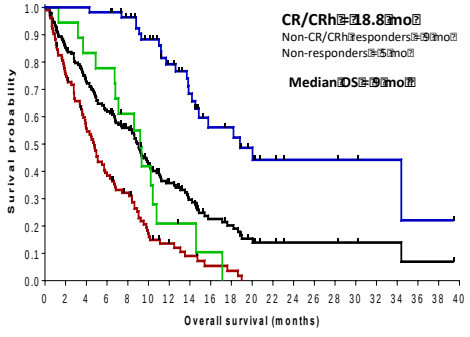
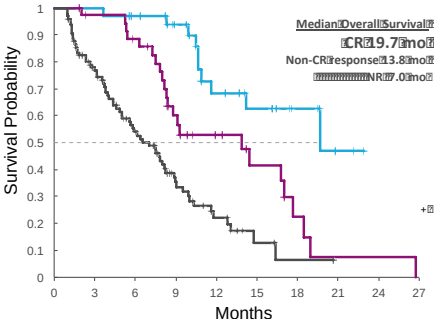
IDH1/2 Inhibitors for IDH1/2-mutant RR-AML

Ivosidenib (IDH1): RR-AML



Enasidenib (IDH2): RR-AML



Mechanisms of resistance: Mutant isoform switch (m*IDH1* <-> m*IDH2*), *IDH2* mutations (trans or cis), presence or development of co-mutations (ie, *RAS, FLT3*)

DiNardo CD, et al. *N Engl J Med.* 2018;378(25):2386.; Stein EM, et al. *Blood*. 2017;130(6):722-731.

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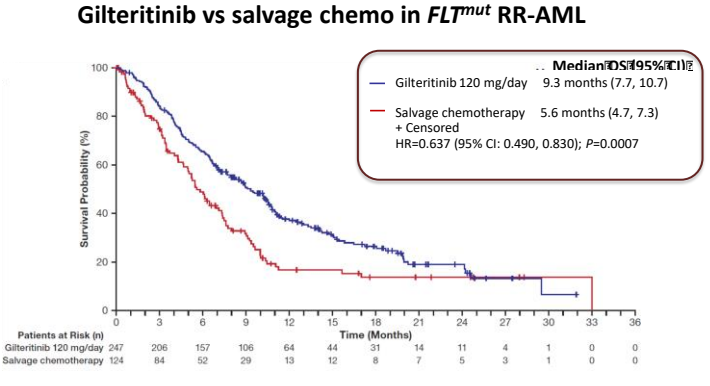
FLT3 Inhibitors for FLT3-mutant RR-AML

	Other Kinases	IC_{50} (Plasma)
Lestaurtinib	JAK2, TrkA	700 nM
Midostaurin	cKIT, PKC, PDGFR, VEGFR	1000 nM
Sorafenib	cKIT, PDGFR, RAF, VEGFR	265 nM
Quizartinib	cKIT, PDGFR, RET	18 nM
Crenolanib	PDGFR	48 nM
Gilteritinib	AXL	43 nM

Gilteritinib vs salvage chemo in *FLT^{mut}* RR-AML



Pratz KW, et al. *Blood.* 2010;115(7):1425-1432.; Zarrinkar PP, et al. *Blood.* 2009;114(14):2984-2992.; Galanis A, et al. *Blood.* 2014;123(1):94-100.; Levis MJ, et al. *J Clin Oncol.* 2015;33(15_suppl):Abstract 7003.; Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

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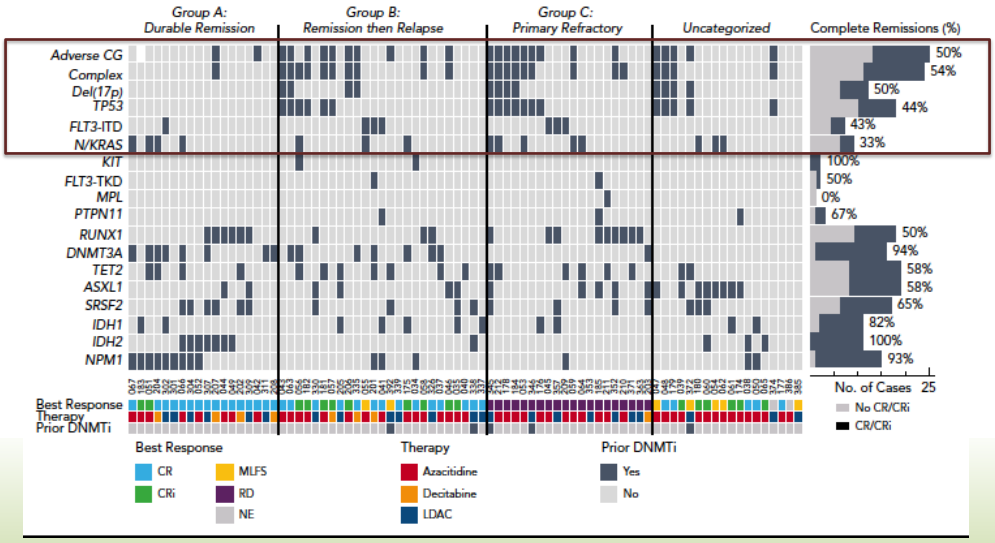
Characteristics of AML Failing Venetoclax-based Therapy



DiNardo CD, et al. *Blood*. 2020;135(11):791-803.

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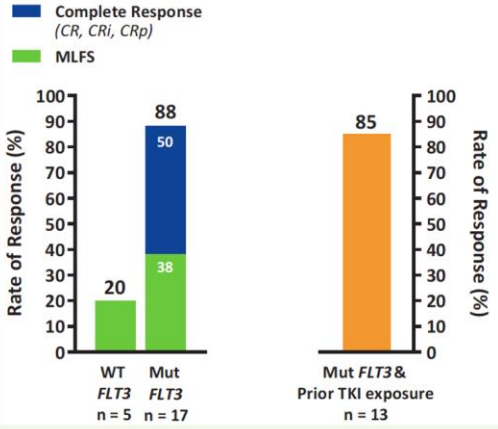
Gilteritinib and Venetoclax: Clinical Data

Characteristic	Wild-type *FLT3* n = 5	Mutant *FLT3-ITD*[a] n = 16	Mutant *FLT3-TKD* n = 2
Age, median (range) years	63 (48–81)	54 (23–73)	61 (52–70)
Female, n (%)	1 (20)	12 (75)	2 (100)
Cytogenetic risk, n (%)			
Intermediate	2 (40)	11 (69)	2 (100)
Poor	3 (60)	5 (31)	0
AML type, n (%)			
De novo	2 (40)	13 (81)	2 (100)
Secondary	3 (60)	3 (19)	0
ECOG performance status, n (%)			
0	1 (20)	2 (12)	1 (50)
1	4 (80)	11 (69)	1 (50)
2	0	3 (19)	0
No. of prior lines of therapy, median (range)	2 (2–4)	2 (1–5)	3 (3–3)
Prior *FLT3* TKI exposure, n (%)			
Any	0	12 (75)[†]	1 (50)
Midostaurin	0	7 (44)	1 (50)
Sorafenib	0	6 (38)	1 (50)
Both	0	2 (13)	1 (50)
Prior stem cell transplant, n (%)	1 (20)	6 (38)	2 (100)

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.
[a]One patient had both ITD and TKD *FLT3* mutations, they were counted in the ITD group.
[†]One patient was included for analysis of safety but did not have available disease assessment; this patient was excluded from efficacy calculations (denominator).



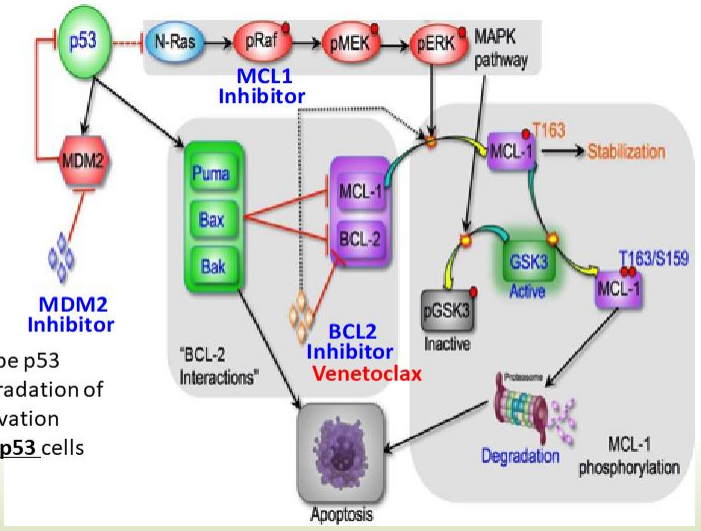
Perl A, et al. *Blood*. 2019;134(Supplement_1):Abstract 3910.

30

Novel Inhibitors of the Apoptosis Pathway

APR-246
Small molecule activator of **mutant p53**

Idasanutlin
Reactivates wildtype p53 and promotes degradation of MCL-1 via p53 activation
Active in **wildtype p53** cells



AMG167/AMG197
Inhibitor of MCL-1

Alvocidib
Inhibitor of CDK9 leading to MCL-1 inhibition

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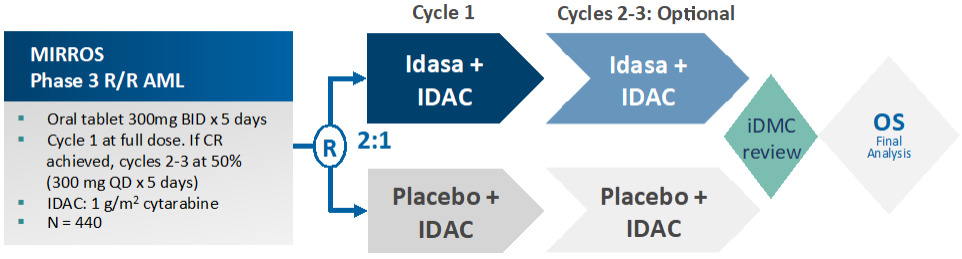
MIRROS: Phase 3 Trial of Idasa + IDAC in RR-AML



Study-specific key inclusion criteria

- Documented/confirmed 1st/2nd refractory/relapsed AML using WHO classification, except APL (AML patients with CR1 duration of >1 year AND age <60 years are excluded)
- No more than two prior induction regimens (excl. prior HSCT) and one must have included cytarabine with an anthracycline (or anthracenedione)
- ECOG performance status of 0 to 1 and patient should be a potential candidate for allogeneic HSCT

Montesinos P, et al. *Future Oncol.* 2020;16(13):807-815.; ClinicalTrials.gov Website. NCT02545283.

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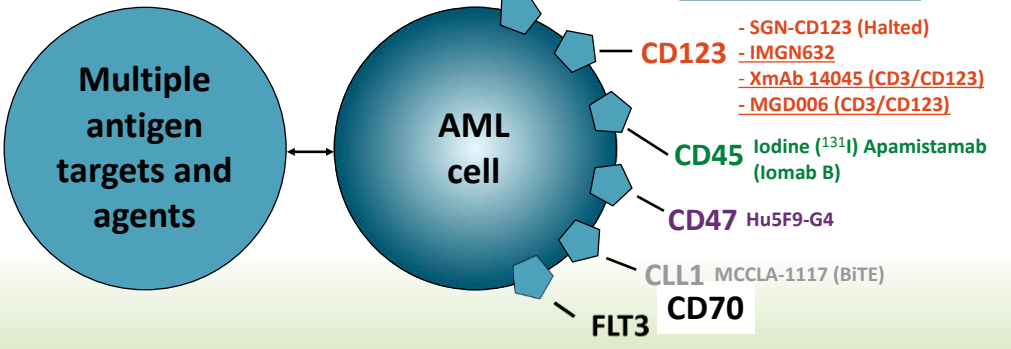
Immunotherapeutic Targets for AML Therapy

Targeting surface antigen expression



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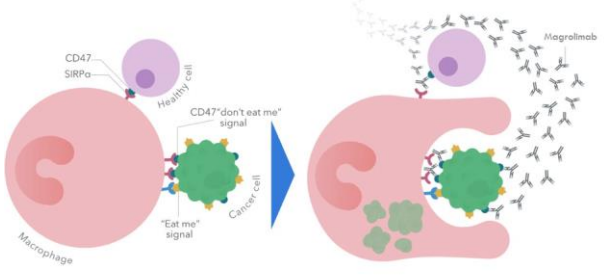
Magrolimab (anti-CD47 Ab): Macrophages "Don't Eat Me"

CD47 = macrophage immune checkpoint



Best Overall Response	1L MDS N=33	1L AML N=25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	NA	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	NA
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).

Magrolimab is a humanized IgG4 anti-CD47 monoclonal antibody

- Induces macrophage phagocytosis
- Azacitidine induces CD47 expression on AML blasts
- High response rates in p53 mutant AML

Sallman D, et al. *J Clin Oncol.* 2020;38(suppl):Abstract 7507.

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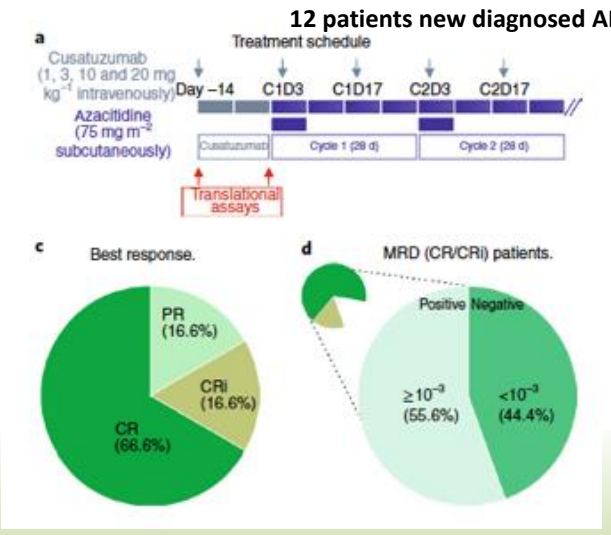
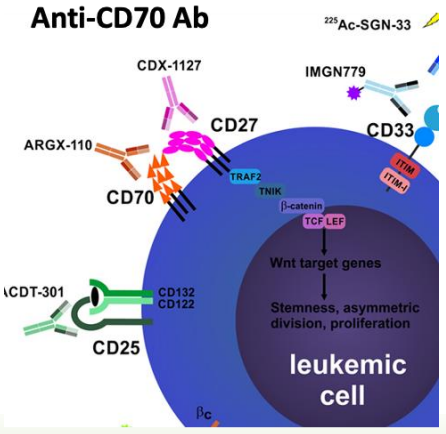
Cusatuzumab (anti-CD70 Ab) Eliminates AML Stem Cells



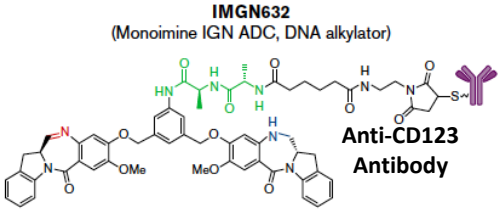


Riether C, et al. *Nat Med.* 2020 Jun 29. {Epub ahead of print].; Schurch CM. *Front Oncol.* 2018;8:152.

35

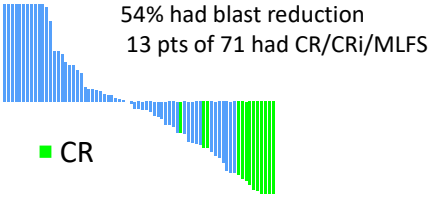
IMGN632: Anti-CD123 ADC for CD123+ Malignancies

A

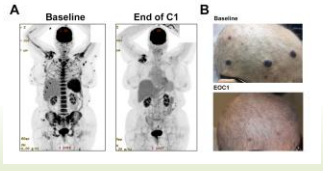


- Anti-hCD123 Ab (IL-3Rα)
- Protease cleavable linker
- Indolino-benzodiazepine
- DNA alkylating agent

AML Efficacy: BM evaluable patients (n=71)



2/3 BPDCN patients had CR/CRi



Kovtun Y, et al. *Blood Adv.* 2018;2(8):848-858.; Daver N, et al. *Blood.* 2019;134(Supplement_1):Abstract 830.

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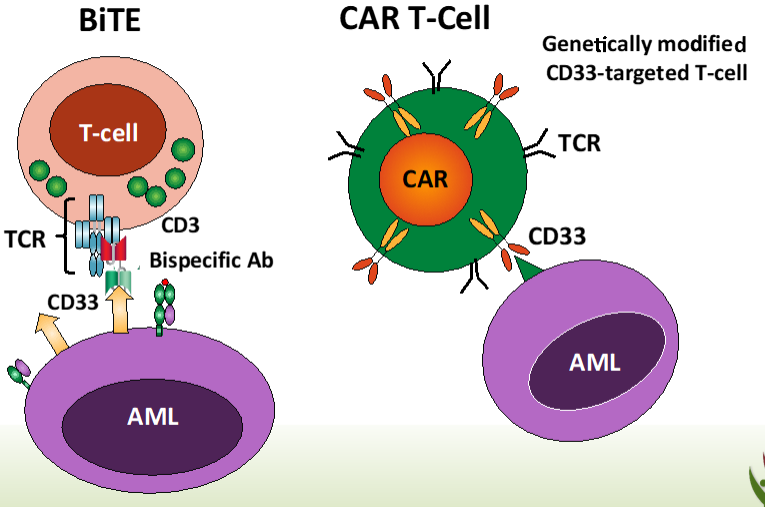
T-cell Directed Therapy for AML

AML cell antigens
- **CD33**
- **CD123**
- **NKG2D**
- Folate Rc β
- CLL1
- FLT3
- B7H6
- Lewis Y



Maino E, et al. *Expert Rev Hematol.* 2016;9(6):563-577.

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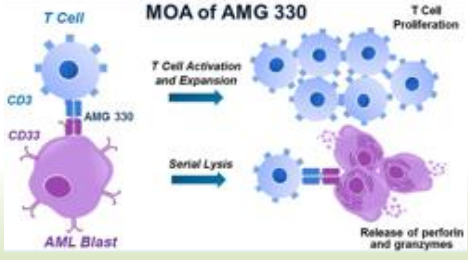
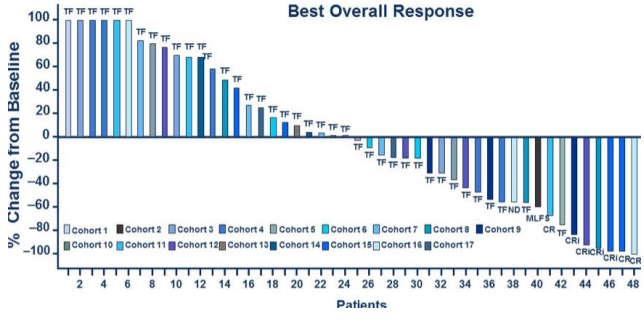
AMG 330: CD33/CD3 Bispecific Antibody





- Seven patients achieved CR/CRi at min 120mcg/day
- 21% response rate in cohorts 15-17
- Cytokine release= 40 (67%), ≥Gr 3 9 (15%)
- Lower disease burden associated with response

Ravandi F, et al. *J Clin Oncol.* 2020;14(suppl):Abstract 7508.

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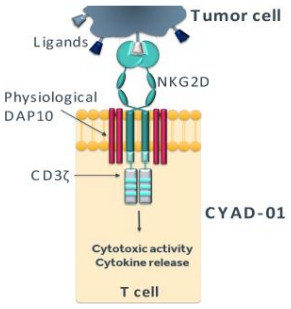
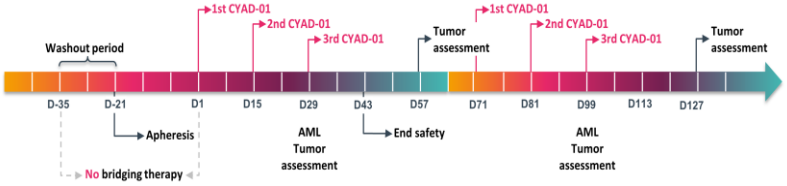
Phase 1 Trial of NKG2D-Based CAR T Cell Therapy





NKG2D = activating Rc on NK cells and expressed on AML cells

CYAD-01: Full-length NKG2D + CD3ζ chain CART construct

8 r/r AML pts evaluable per protocol (at least one CYAD-01 cycle)

- **1 CR with partial hematologic recovery (CR_h)** in DL-1
  - Pt was bridged to allo-HSCT on day +97. CR_{MRD-} for > 14 months+
- **2 CRs with incomplete blood count recovery (CR_i)** (1 in DL-1 and 1 pt in DL-3)
- **2 Stable Diseases with relevant BM blast decrease** (DL-2)
  - 1 **SD - 3 months** with BM blasts decrease from 24% to 10% and hematologic improvement
  - 1 **SD - 6 months** with BM blasts decrease from 9.8% to 5.5%
- **1 Stable Disease (2m+)** with no BM blast decrease (DL-3)
- **2 PDs** (>20% baseline peripheral blasts)

Sallman DA, et al. *Blood.* 2018;132(Supplement 1):Abstract 902.

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The Art and Science of Treatment Selection

The AML Case Study Gallery: 3 Case Presentations

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Case Presentation #1

- Matt is a 55-year-old man diagnosed with FLT3-ITD mutant AML (allelic ratio 0.45, normal karyotype)
- He completes induction with 7+3 plus midostaurin followed by HIDAC plus midostaurin consolidation and 12 months of midostaurin maintenance. After much discussion he decides he does not want an ASCT due to the risk of GVHD and QOL
- Unfortunately six months later, he is found to have new onset pancytopenia. The bone marrow shows relapsed AML (15% myeloblasts) by marrow morphology
- His performance status is 1. He is asymptomatic. His brother is a full HLA match
- What is your next course of action?

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Case Presentation #2

- 62-year-old male
- CC: Overall weakness, fatigue, dyspnea on exertion
- Timeline of events prior to presentation
  - Presented to PCP with the above symptoms for routine checkup. CBC showed significant cytopenias – WBC: 15.7 Hgb: 9.5 Platelets: 35
  - Underwent bone marrow biopsy at local hospital. Diagnosed with AML with MDS-related changes. No prior history. Local doctor planned 7+3 treatment
- Arrived to MDACC 1 day later, to ER with the following vitals/labs:
  - BP: 135/85, HR: 110, RR: 19, Temp: 98.9
  - WBC: 52.1K, Hgb: 9.1, PLT: 27K, Blasts: 35%, Neutrophils: 3%, Lymphocytes: 28%, no coagulopathy
- Admitted; started on hydroxyurea 3 g QD PO, IV fluid 50 mL/hr, allopurinol and monitor TLS labs
  - PICC line placed
  - CXR done, ECHO ordered
- Bone marrow biopsy was performed: cytogenetics, FISH for 15;17, 8;21, inv16, and molecular testing were rushed

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Case Presentation

- Past medical history
  - Aortic aneurysm
  - CAD: 1 sent 3 years ago
  - HTN
- Past surgical history
  - Appendectomy
  - Diverticulectomy
  - Back surgery
- Social history
  - Anesthesiologist
  - Married with 2 children
  - Denies tobacco or illicit substance use
  - Occasional ETOH
- Family history
  - No history of leukemia or lymphoma

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Bone Marrow Differential at Time of Diagnosis

- BM method: SMEAR
- Adequacy: Adequate quality
- Site: Right posterior iliac crest

Blasts	**71% H (0-5)**
Progranulocytes	0% L (2-8)
Myelocytes	0% L (5-20)
Metamyelocytes	0% L (13-32)
Granulocytes	2% L (7-30)
Eosinophils	0% (0-4)
Lymphocytes	11% L (3-17)
Plasma cells	1% (0-2)
Monocytes	1% (0-5)
Reticulum cells	0% (0-2)
Pronormoblasts	0% L (1-8)
Normoblasts	14% H (7-32)
M:E ratio	0.0 L (3-4)

- Granulocytes:
  - Decreased in number
- Erythrocytes:
  - Increased dyspoietic forms
- Megakaryocytes:
  - Present, hypolobulated
- Lymphocytes:
  - Unremarkable
- Blasts:
  - Mostly blasts

- Bone marrow diagnosis
  - ACUTE MYELOID LEUKEMIA WITH MINIMAL DIFFERENTIATION (M1)
  - Normocellular bone marrow (40%–50%)

Karyotype: XY

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Molecular Mutational Panel

Molecular Diagnostics						
ABL1	EGFR	GATA2	IKZF2	MDM2	NOTCH1	RUNX1
ASXL1	EZH2	HRAS	JAK2	MLL	NPM1	TET2
BRAF	FLT3	IDH1	KIT	MPL	NRAS	TP53
DNMT3A	GATA1	IDH2	KRAS	MYD88	PTPN11	WT1

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Treatment

- Enrolled on frontline protocol CLIA (cladribine, idarubicin, cytarabine)
  - Cladribine 5 mg/m^2 IV × 5 days on days 1–5
  - Idarubicin 10 mg/m^2 × 3 days on days 1–3
  - Cytarabine 2 g/m^2 × 5 days on days 1–5
- Inclusion criteria met at study entrance
  - Frontline AML treatment; fit for intensive induction, plan for ASCT once in remission
- Patient placed in protected environment room for age >50 with newly diagnosed AML receiving cytotoxic chemotherapy, close monitoring of TLS labs initial 48–72 hours
- Did well for first 9 days of therapy. On day 10 developed neutropenic fever, pneumonia, with rapid progression to sepsis
- Respiratory insufficiency, hypotension; moved to ICU. Cultures grew gram-negative rods
- Eventually confirmed to be pseudomonas

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Cycle 1 Interval History

- In ICU, placed on vasopressors, broad-spectrum antibiotics, PICC removed
- Worsening pneumonia and respiratory failure → intubated on vent
- Bronchoscopy showed necrotizing pneumonia: growing pseudomonas
- Treated aggressively with IV antibiotics, ICU, and ID teams; slow improvement after long ICU stay of about 3 weeks. Moved to floor
- C1D21: Bone marrow aspiration = 17% blasts
- C1D28: Bone marrow aspiration = 4% blasts, MRD by FCM 0.8% (IDH1, DNMT3A persisted in bone marrow)

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Cycle 2-4

- Achieved CR with full recovery of counts by day 36
- Continued on protocol with consolidations × 4
- Was counseled and recommended to go for ASCT, but after extensive discussions with leukemia and SCT teams, patient and his spouse decided they did not want to do SCT
- Was consented and enrolled on maintenance trial of CC-486 for patients 50–70 years of age who are not SCT candidates or who refuse SCT
- Completed 24 months maintenance on CC-486, bone marrow at the end of maintenance showed maintained remission
- Continue surveillance with clinic visit Q6 months

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Case Presentation #3

- **74-year-old M presenting with recurrent bronchitis**
  - Former smoker, osteoarthritis, controlled type 2 diabetes and HTN, PS 2
  - WBC 2.7K, Hgb 7.3 g/dL, Plts 39K. No circulating blasts
  - ECOG
  - Interested in leukemia directed therapies
- **Diagnosis:**
  - BM with 45% CD33+ blasts with MDS-related changes
  - Karyotype with del(5q) and del(7q)
  - RUNX1 and SRSF2 mutations

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