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New and Emerging Treatments in Acute Myeloid Leukemia

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Disclosures

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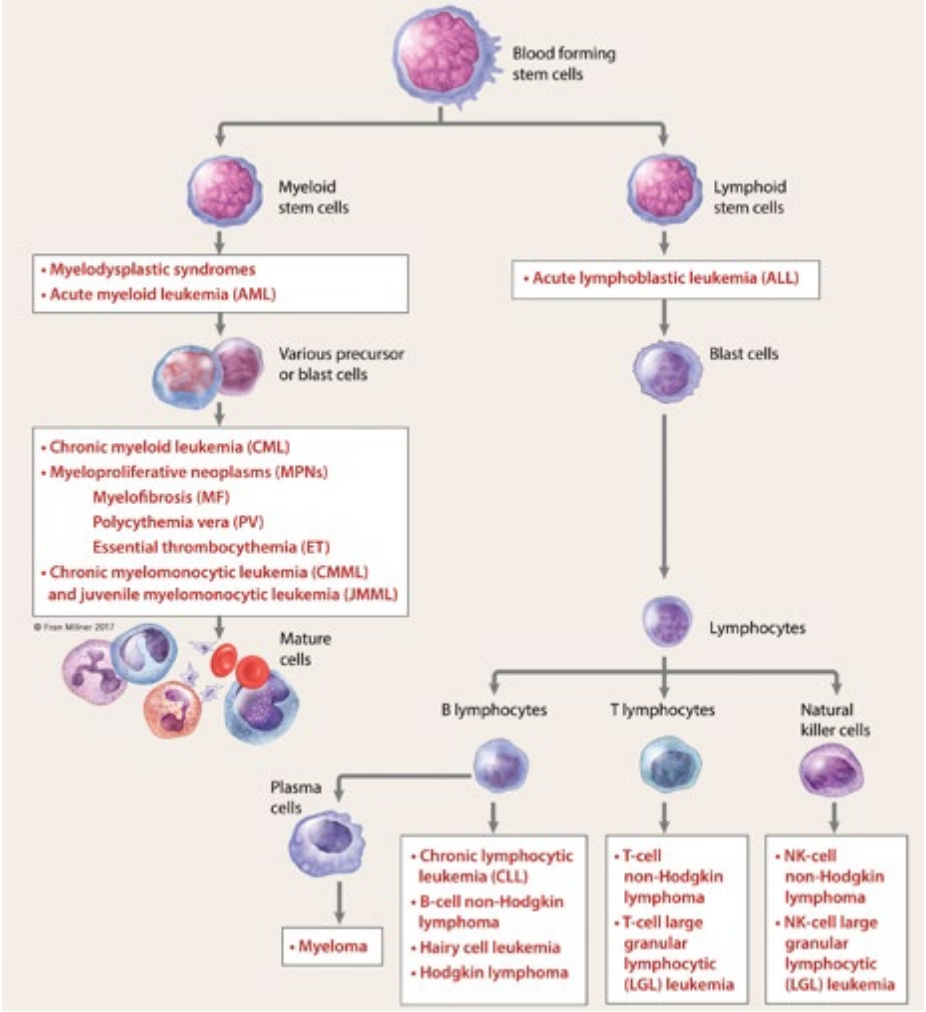
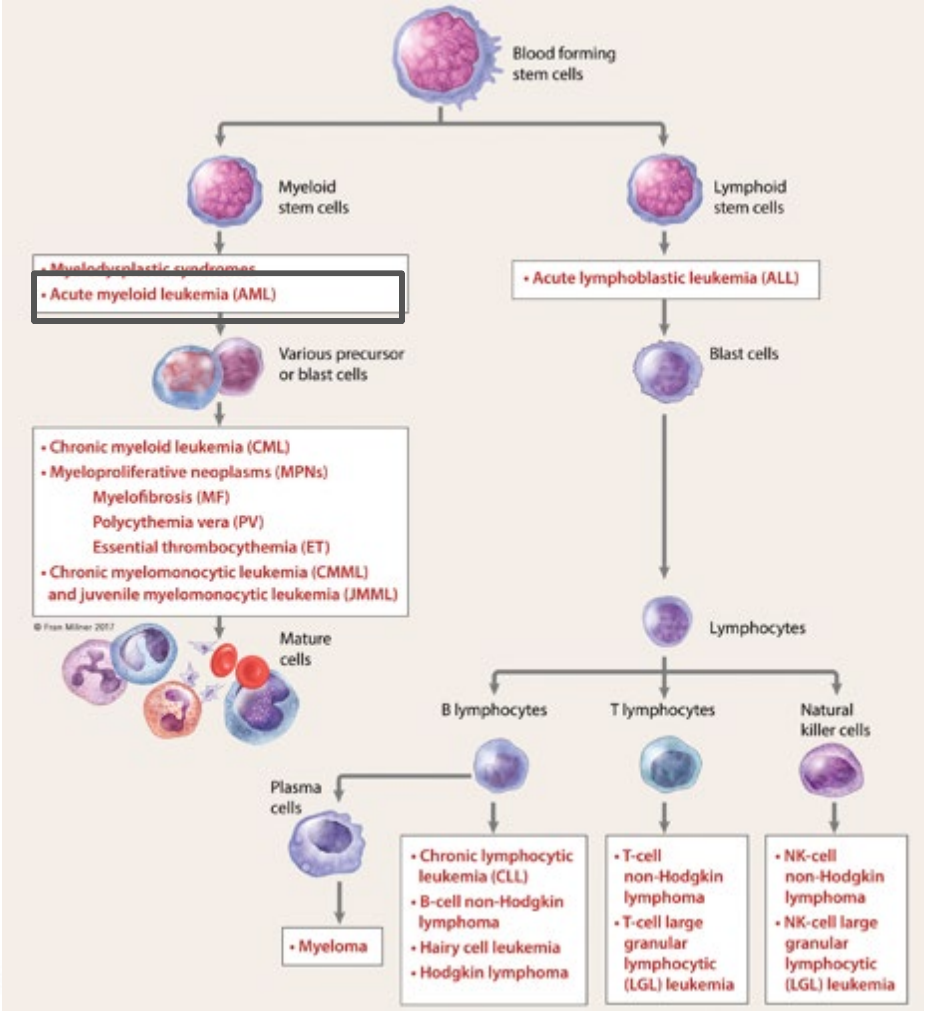
I will designate FDA-approved drugs for disease conditions and drugs that are under clinical investigation

Objectives

- Provide a general overview of acute myeloid leukemia (AML)
- Review current diagnostic workup and treatment approaches in AML
- Discuss new management strategies that are being investigated in AML





Acute Myeloid Leukemia (AML)

- Most common form of acute leukemia in adults
- ~20,000 new diagnoses and ~10,000 deaths on a yearly basis
- Median age of diagnosis: 65 years old

Siegel et al. CA Cancer J Clin 2017

AML Diagnosis and Characterization

- **Demonstration of 20% or more myeloid blasts on peripheral blood smear OR bone marrow biopsy**
  - Common additional testing includes cytogenetics (analysis of chromosomes), mutational testing, and consideration for testing of hereditary cancer syndromes

- ***De novo* AML:** AML diagnosed without a previous diagnosis of hematologic disorder or prior exposure to cytotoxic drugs and/or radiation therapy

- **Secondary AML (sAML):** AML diagnosed in a patient with a pre-existing hematologic disorder such as myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN)

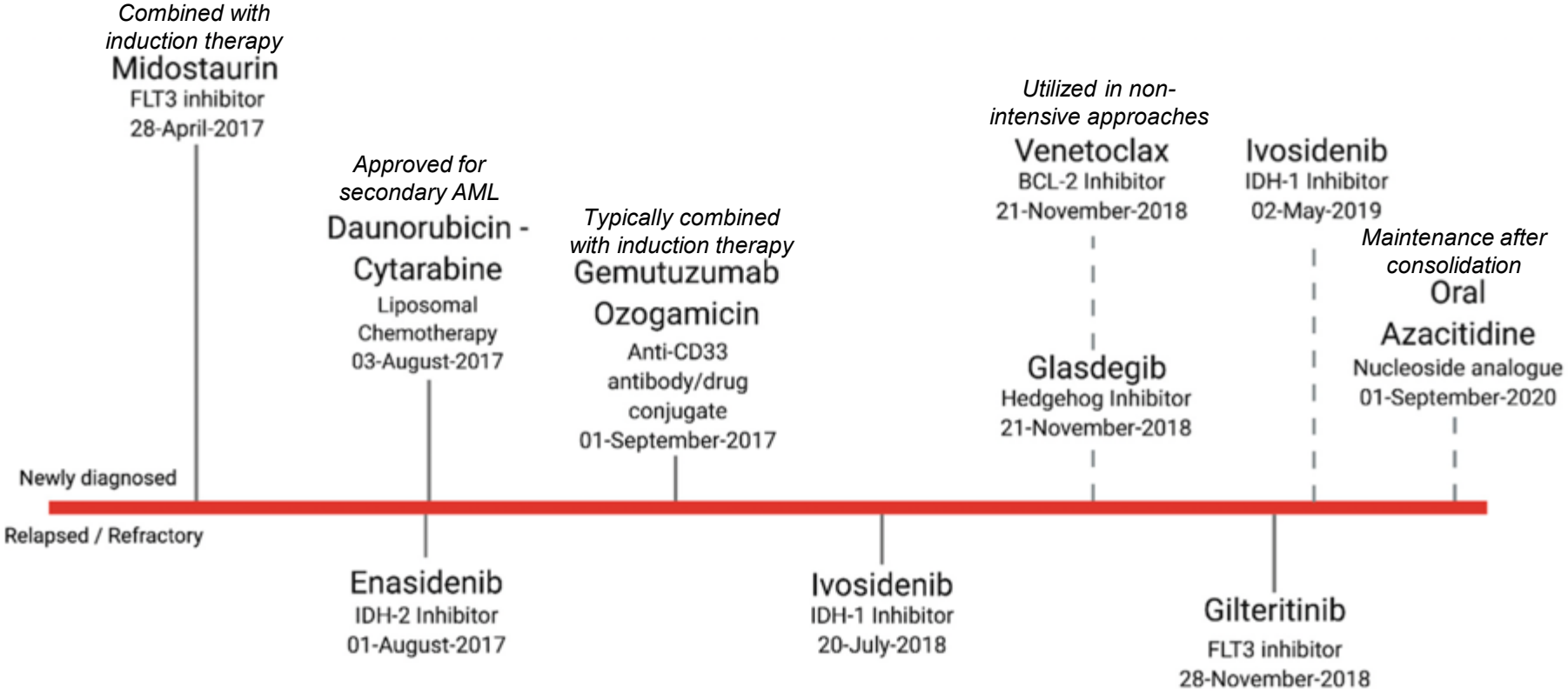
- **Therapy-related AML (t-AML):** AML diagnosed in a patient previously treated with cytotoxic therapy or radiation therapy

WHO 2016 Criteria; Soulier, Blood 2020

Standard Treatment Options pre-2017

- Intensive Induction Chemotherapy
  - Examples: Cytarabine + anthracycline (“7+3”), FLAG + Idarubidin
- Non-intensive treatment approaches
  - Examples: Azacitidine, Decitabine, Low-dose cytarabine
- Supportive care

FDA-approved Treatment Options in the Current Era



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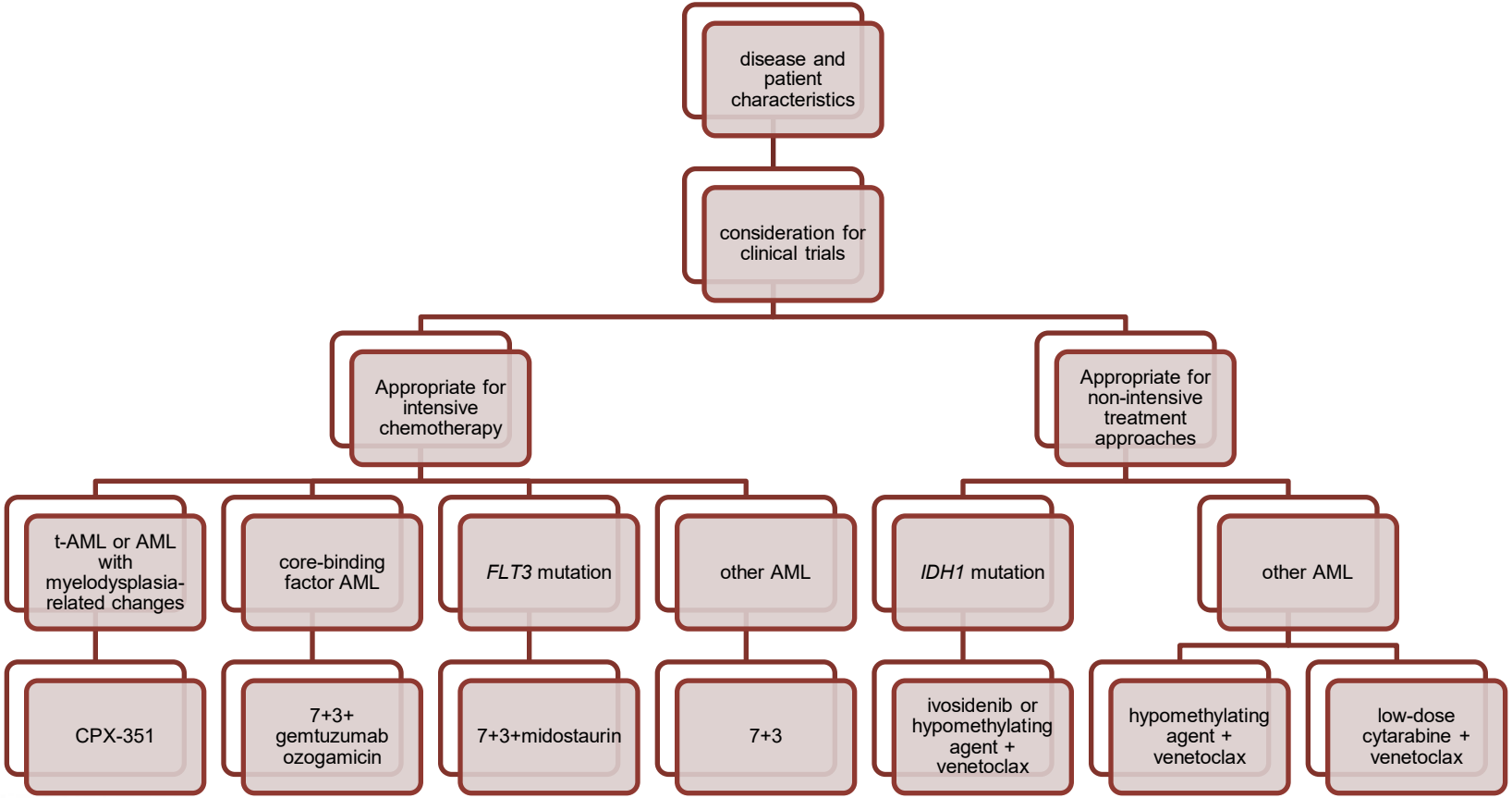
Ahmadmehrabi et al, Cancers 2021

What Factors Determine Initial AML Treatment?

- Cytogenetic and Molecular Characteristics of disease
- Other medical conditions a patient may have
- Patient input/preferences!

Treatment Approach in Newly-Diagnosed AML



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Cahill et al, Advances in Oncology 2021

Treatment Approaches in Complete Remission

- **CR after intensive induction**
  - Consolidation therapy
  - Considerations for transplant if intermediate/high-risk disease
  - Consideration for CC-486 (oral azacitidine) after consolidation if intermediate/high-risk disease but not proceeding with transplant

- **CR after non-intensive approach**
  - Continue cycles of therapy indefinitely, dose adjustments may be considered

Emerging Treatment Strategies

- **Intensive induction combination therapies**
  - Venetoclax
  - Ivosidenib
  - Enasidenib
  - Gilteritinib

- **Non-intensive combination therapies**
  - HMA + Ven + FLT3 inhibitors
  - HMA + Ven + IDH Inhibitors

- **Oral regimens in AML**

- **Therapies in *TP53*-mutated AML**

*under clinical investigation but not yet FDA-approved!

FLAG-Ida + Venetoclax in New AML and R/R AML

Outcome	All (N = 68)
ORR, No. (% [CI])	56 (82 [71 to 91])
CRc (CR + CRi + CRh), No. (% [95% CI])	52 (76 [65 to 86])
CR, No. (%)	37 (53)
CRh, No. (%)	10 (15)
CRi, No. (%)	5 (7)
MRD^- CR (flow cytometry), No. (% [95% CI])	43 (83 [70 to 92])
MLFS	4
No response	12
DOR (median, months)	NR
EFS	
Median, months (95% CI)	18 (10.1 to NE)
6-month, % (95% CI)	70 (59 to 81)
12-month, % (95% CI)	56 (44 to 71)
OS	
Median, months (95% CI)	NR
6-month, % (95% CI)	81 (71 to 91)
12-month, % (95% CI)	70 (58 to 83)

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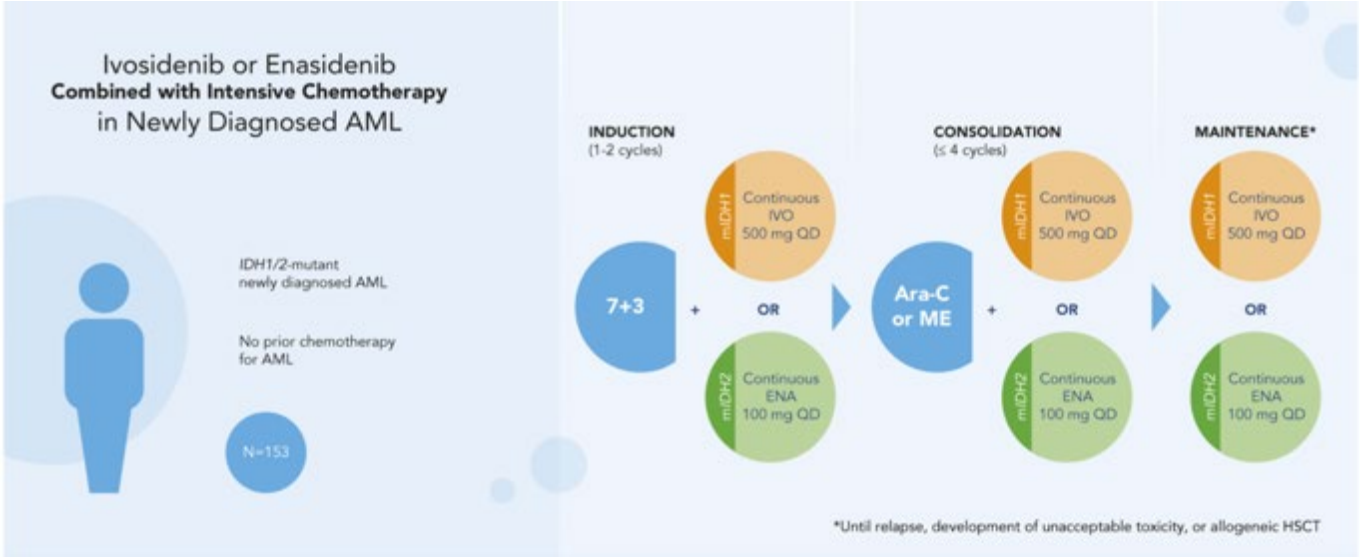
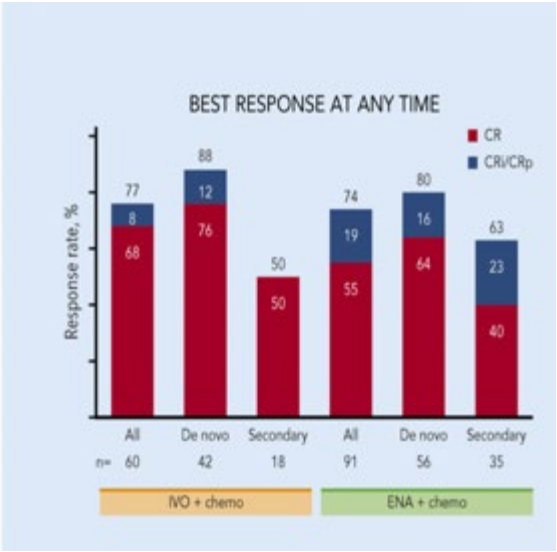
Dinardo et al, JCO 2021

IDH Inhibition + Intensive Induction Chemotherapy in Newly-Diagnosed *IDH*-mutated AML





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Stein et al, Blood 2021

Gilteritinib + Intensive Induction Chemotherapy in Newly-diagnosed *FLT3*-mutated AML

Table 2. Clinical Response to Gilteritinib in Combination with 7+3 Induction and Consolidation Chemotherapy at the End-of-Induction Time Point in *FLT3*$^{mut+}$ Patients with Newly Diagnosed AML Who Received Gilteritinib 120 mg/d

Response Parameter,[a] n (%)	*FLT3*$^{mut+}$ Patients who Received 120 mg/d (N=38)[b]
CR	15 (39.5)
CRp	1 (2.6)
CRi	15 (39.5)
CRc	31 (81.6)

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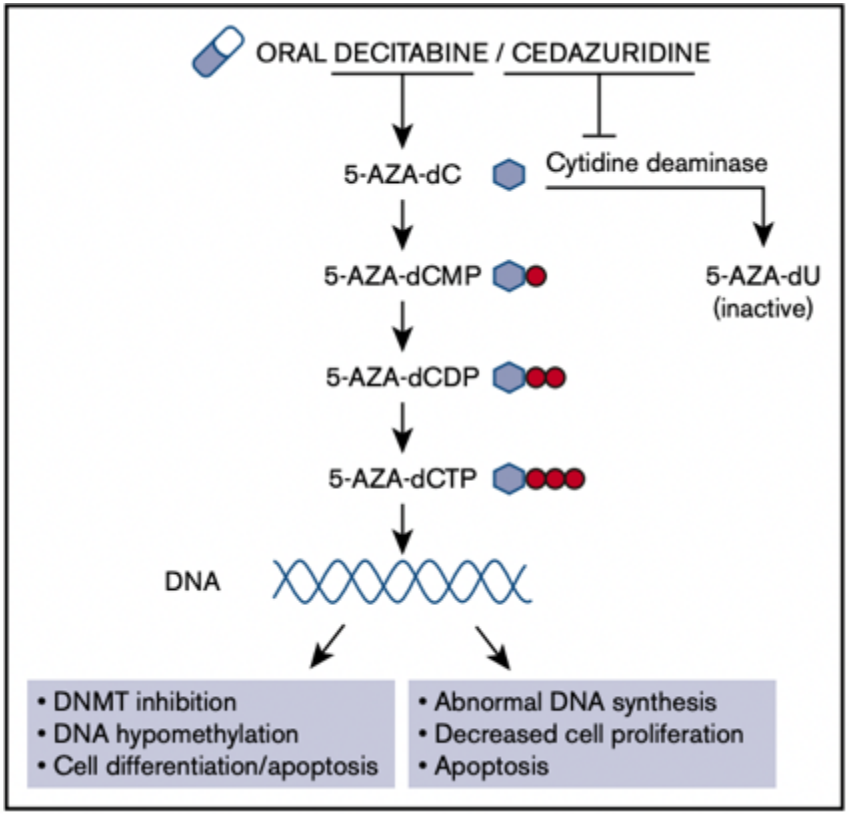
Pratz et al, Blood 2020

Select HMA+ Venetoclax Triplet Therapies in Trials

Drug Added	Target
Gilteritinib	FLT3
Quizartinib	FLT3
Ivosidenib	IDH1
Enasidenib	IDH2

Decitabine-Cedazuridine and Oral Combinations



Investigational agent(s)	Patient population	Trial number
ASTX030	MDS, CMML, AML	NCT04256317
ASTX030	MDS	NCT04608110
ASTX727	Lower-risk MDS	NCT03502668, NCT03906695
ASTX727	MDS with detectable MRD after allo-HCT	NCT04742634
ASTX727 + itacitinib, INCB053914, or INCB059872	MDS/MPN overlap syndromes	NCT04061421
ASTX727 + venetoclax	MDS, CMML	NCT04655755
ASTX727 + venetoclax	AML	NCT04657081, NCT04746235
ASTX727 + venetoclax + ivosidenib or enasidenib	*IDH1* or *IDH2*-mutated AML	NCT04774393
ASTX727 + ASTX660	AML	NCT04155580

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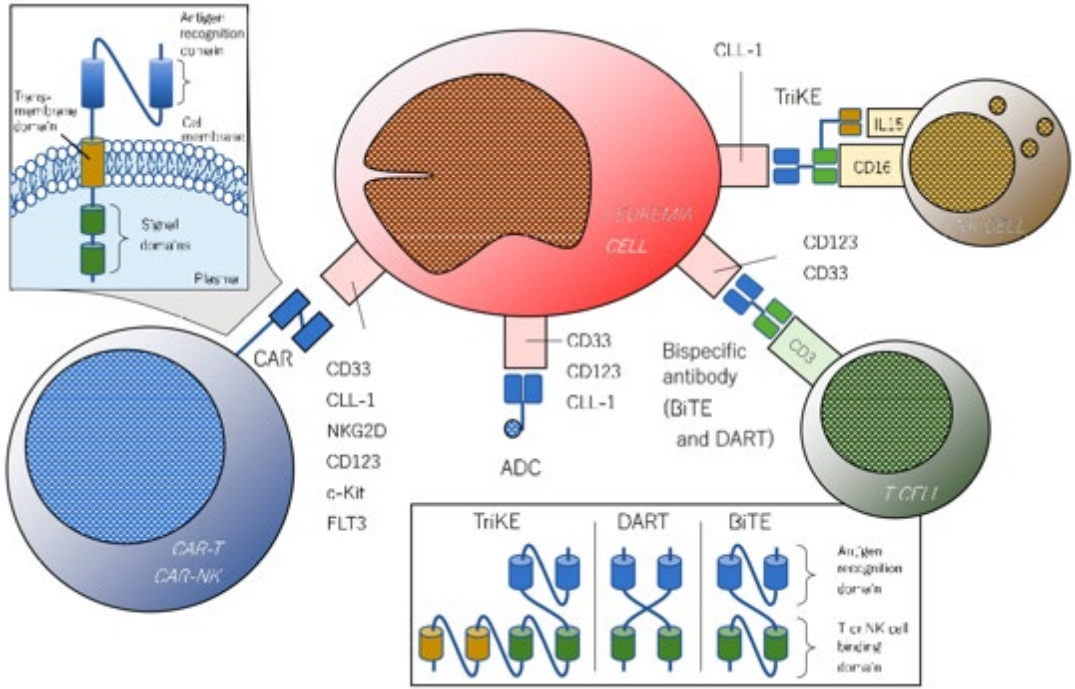
Patel et al, Blood Advances 2021

Immunotherapy in AML



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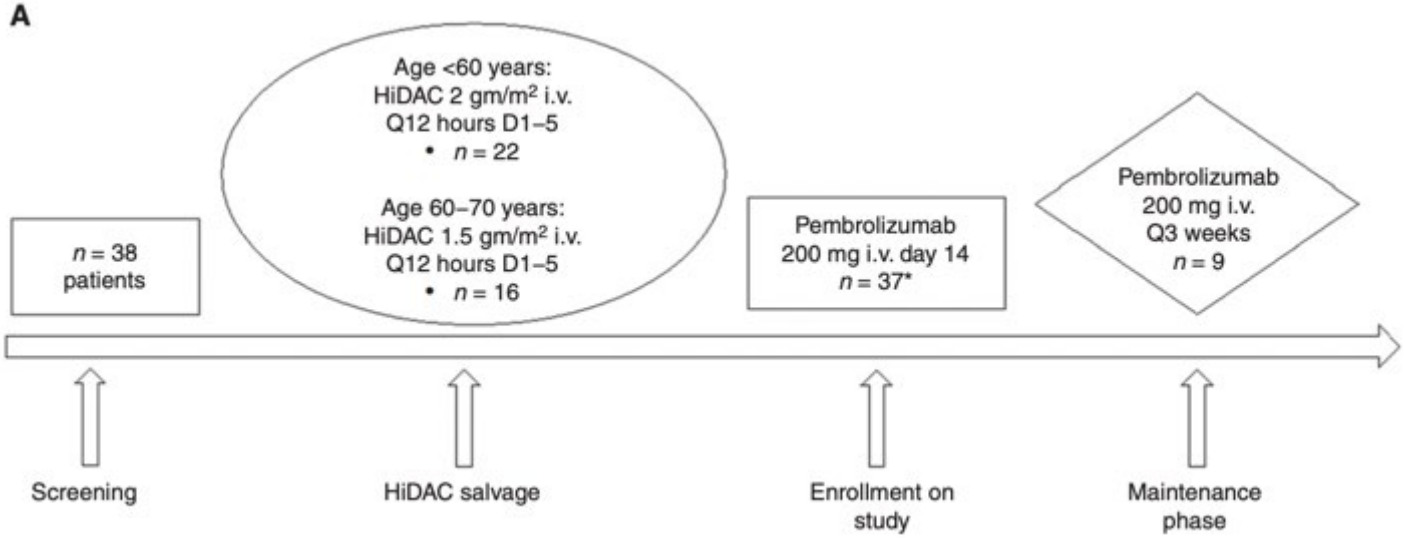
Tabata et al, International Journal of Molecular Sciences 2021

Pembrolizumab in R/R AML



38% CR Rate

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Zeidner et al, Blood Cancer Discovery 2021

Novel Therapies in *TP53*-mutated AML

Table 1. Clinical trials in *TP53* myeloid malignancies.

Treatments (NCI Number)	Phase	Number of Patients	Overall Response Rate
AZA + VEN NCT04401748	3	431 AML patients total	
		286 (AZA + VEN) (23% *TP53* mutated)	55%
		145 (AZA + Placebo) (16% *TP53* mutated)	0%
AZA + Eprenetapopt NCT03072040	1b/2	55 *TP53* mutated MDS/AML patients	71%
AZA + Eprenetapopt NCT03588078	2	52 *TP53* mutated MDS/AML patients	62%
AZA + MAGRO NCT03248479	1b	29 *TP53* mutated AML patients	59%

Table 2. Clinical trials ongoing in *TP53* myeloid malignancies.

Treatments (NCI Number)	Phase	Number of Patients	Primary Endpoint
ENHANCE-2 AZA + MAGRO vs. AZA + VEN NCT04778397	3	346 *TP53* mutated AML patients to be randomized	OS
AZA + Placebo vs. AZA + Eprenetapopt NCT03745716	3	154 *TP53* mutated MDS patients included	CR
AZA + VEN + Eprenetapopt NCT04214860	1	51 *TP53* mutated AML patients	Safety
DAC + Cytarabine + ATO NCT03381781	2	100 *TP53* mutated AML patients	RFS
AZA + Eprenetapopt following HSCT NCT03931291	2	33 *TP53* MDS/MAL patients included	RFS

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Cluzeau et al, International Journal of Molecular Sciences 2021

Summary

- **Since 2017 there have been a number of newly-approved therapies for AML**

- **Current treatment considerations should factor in disease characteristics and patient characteristics**

- **Novel treatment strategies include:**
  - Combination approaches of FDA-approved drugs
  - All oral regimens
  - Immunotherapy
  - Approaches specific to TP53-mutated AML

Thank you!