Updates in Acute Myeloid Leukemia

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Disclosures

I have nothing to disclose. I *will not* be discussing off-label indications. I will be discussing ongoing clinical trials and investigational therapies.

Objectives

1. Describe the follow-up and long-term outcomes data for previously approved acute myeloid leukemia (AML) therapies

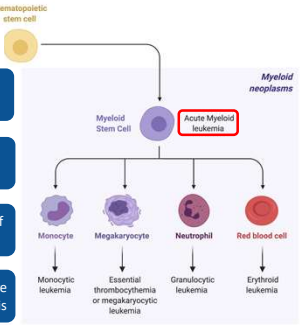
2. Evaluate new and updated FDA approvals in AML

3. Compare therapeutic strategies for the treatment of older adults with newly diagnosed AML

4. Recognize novel therapy combinations and ongoing clinical trials in AML

Background on AML

- ~1/3 of all adult leukemias
- Median age of diagnosis: 68
- Associated with 5-yr survival of nearly 30%
- Presents as bone marrow failure or consequences of leukocytosis



NCI SEER Program. Cancer Stat Facts: Leukemia – Acute Myeloid Leukemia. Available at https://seer.cancer.gov/statfacts/html/leuks.html

Background on AML

- Treatment:
  - Patient Factors: age, comorbidities, functional status, 'fitness' for intensive chemotherapy, social support, donor availability, patient's treatment goals
  - Disease Factors: cytogenetic and molecular prognostication by the 2017 ELN Risk Stratification System

Previous Treatment Algorithm (c. NCCN AML v 3.2017):

Medically fit for intensive chemotherapy → Anthracycline with cytarabine (7 + 3 regimen) → Consolidative high-dose cytarabine and/or AlloHCT

Unfit for intensive chemotherapy → Clinical Trial Hypomethylating agent Low-dose Cytarabine Palliative Care

Dohner H, et al. Blood. 2017;129:424-447.
NCCN. Acute Myeloid Leukemia. V3.2017. Available at https://jnccn.org/view/journals/jnccn/15/7/article-p926.xml#d521876e2162

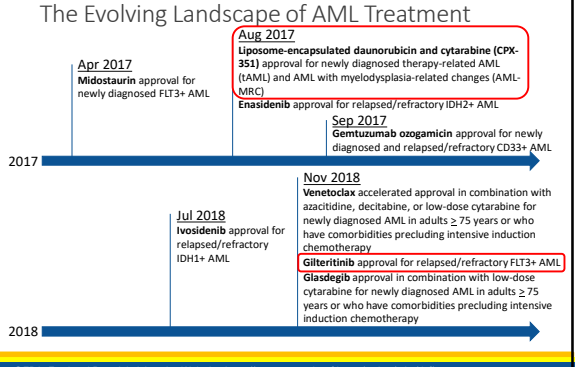
Background on AML

Common Mutations in AML*

Functional Class	Examples
Signaling and Kinase Pathway	FLT3, KRAS, NRAS, KIT, PTPN11, and NF1
Epigenetic Modifiers	DNMT3A, IDH1, IDH2, TET2, ASXL1, EZH2, and MLL/KMT2A
Nucleophosmin	NPM1
Transcription Factors	CEBPA, RUNX1, and GATA2
Tumor Suppressors	TP53
Spliceosome Complex	SRSF2, U2AF1, SF3B1, and ZRSR2
Cohesion Complex	RAD21, STAG1, STAG2, SMC1A, and SMC3

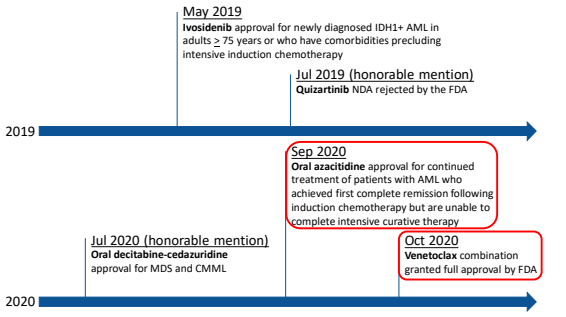
*Adapted from: Dinardo CD, Cortes J. Hematology Am Soc Hematol Educ Program. 2016;2016(1): 348–355

The Evolving Landscape of AML Treatment



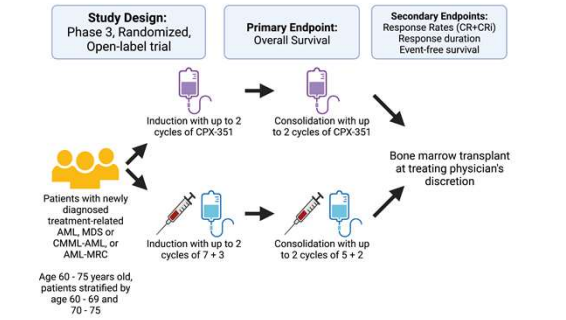
Drugs@FDA. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 28, 2021.

The Evolving Landscape of AML Treatment



Drugs@FDA. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 28, 2021.

5-Year Outcomes Data with CPX-351



Lancet et al. J Clin Oncol. 2018;36(26):2684-2692.
Lancet et al. Lancet Haematol. 2021;8:e481-91.

Results

		CPX-351 (n=153)	7 + 3 (n=156)
Baseline Demographics No. (%)	Median Age ECOG 0 ECOG 1 ECOG 2	68 (range 64-71) 37 (24) 101 (66) 15 (10)	68 (range 64-71) 45 (29) 89 (57) 22 (14)
AML Characteristics No. (%)	tAML MDS-AML -Prev HMA -No prev HMA CMML-AML AML w/ MDS karyotype Previous HMA FLT3	30 (20) 50 (33) 21 (14) 11 (7) 41 (27) 62 (41) 22 (16)	33 (21) 55 (35) 19 (12) 12 (8) 37 (24) 70 (45) 21 (15)

Lancet et al. J Clin Oncol. 2018;36(26):2684-2692.
Lancet et al. Lancet Haematol. 2021;8:e481-91.

5-Year Outcomes Data with CPX-351

Median overall survival findings maintained:

- CPX-351 9.33 months vs 7 + 3 5.95 months (HR 0.70, CI 0.55 – 0.91)

Overall survival at 5 years:

- CPX-351 18% vs 7 + 3 8%

Overall survival in HSCT patients:

- CPX-351 not reached vs 7 + 3 10.25 months

Subgroup Analysis:

- All subgroups maintained overall survival benefit of CPX-351, with the exception of ECOG 2, CMML-AML, previous HMA, and de novo AML with MDS karyotype

Lancet et al. J Clin Oncol. 2018;36(26):2684-2692.
Lancet et al. Lancet Haematol. 2021;8:e481-91.

Limitations

- Patients received 2 cycles of consolidation rather than 3 – 4 cycles
- Patients in the 7 + 3 arm received 5 + 2 consolidation rather than HIDAC
  - It is unclear if continuing CPX-351 vs HIDAC for consolidation offers benefit
- FDA approval for all ages despite population in the study (60 – 75 yo)
- Sponsored by manufacturer

Lancet et al. J Clin Oncol. 2018;36(26):2684-2692.
Lancet et al. Lancet Haematol. 2021;8:e481-91.

Phase III ADMIRAL Trial - Gilteritinib

Approval in November 2018 based on the interim analysis of the Admiral Trial.

With median follow-up of 4.6 months:
- CR + CRh rate was 21% (95% CI, 15%–29%)
- Median duration of CR + CRh was 4.6 months (range, 0.1–15.8+)
- Conversion from transfusion dependence to transfusion independence was 31%

Full analysis published October 2019.

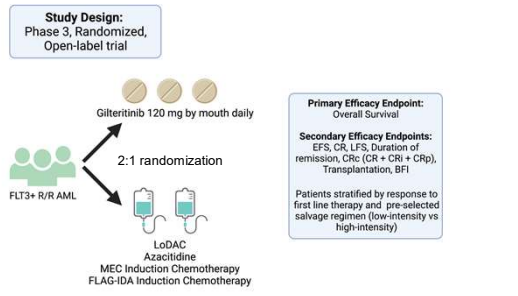
Perl et al. N Engl J Med. 2019;381:1728-1740

Phase III ADMIRAL Trial - Gilteritinib

Inclusion Criteria	Exclusion Criteria
Patients ≥ 18 years old with relapsed/refractory FLT3+ AML **after only ONE line of previous therapy**	Acute promyelocytic leukemia BCR-ABL1+ leukemia/CML blast crisis Therapy-related AML CNS leukemia

Perl et al. N Engl J Med. 2019;381:1728-1740

Phase III ADMIRAL Trial - Gilteritinib



*Patients who did not achieve CR/CRi with cycle 1 were eligible to increase to gilteritinib 200 mg daily.

Perl et al. N Engl J Med. 2019;381:1728-1740

Results

		Gilteritinib (n=247)	Salvage Chemo (n=124)
Baseline Demographics No. (%)	Median Age	62 (range 20 - 84)	61.5 (range 19 – 85)
	Pre-selected chemo		
	High-intensity	149 (60.3)	76 (61.3)
	Low-intensity	98 (39.7)	48 (38.7)
	FLT3 mut		
	ITD	215 (87)	113 (91.1)
	TKD	21 (8.5)	10 (8.1)
AML Characteristics No. (%)	Karyotype		
	Intermediate	182 (73.7)	89 (71.8)
	Adverse	26 (10.5)	11 (8.9)
	Prev FLT3i	32 (13)	14 (11.3)
	Prev HSCT	48 (19.4)	26 (21.0)

Perl et al. N Engl J Med. 2019;381:1728-1740

Results

	Gilteritinib (n=247)	Salvage Chemo (n=124)	HR (95% CI); P-value
Primary Endpoint			
Overall Survival	9.3 months	5.6 months	0.64 (0.49 to 0.83); P<0.001
Secondary Endpoints			
CR/CRi (%)	84 (34.0)	19 (15.3)	18.6 (9.8 to 27.4)
Event-free survival	2.8 months	0.7 months	0.79 (0.58 to 1.09)
Median duration of remission	11.0 months	Not evaluable	Not evaluable
Transplant	25.5%	15.3%	Not reported
Transplant-censored OS	8.3 months	5.3 months	0.58 (0.43 to 0.76)

Perl et al. N Engl J Med. 2019;381:1728-1740

Results – Overall Survival Subgroup Analysis

	Gilteritinib (n=247)	Salvage Chemo (n=124)	HR (95% CI); P-value
Previous FLT3			
Yes	**26/32**	**11/14**	0.70 (0.35 – 1.44)
No	145/215	79/110	**0.62 (0.47 – 0.82)**
Response to first therapy			
Relapse ≤ 6mo AlloHCT	24/31	16/17	**0.38 (0.20 – 0.75)**
Relapse > 6mo AlloHCT	10/17	4/8	0.86 (0.26 – 2.80)
Primary Refractory	70/89	28/48	0.99 (0.63 – 1.55)
Relapse ≤ 6mo CR no BMT	47/67	28/34	**0.49 (0.30 – 0.80)**
Relapse > 6mo CR no BMT	20/34	14/17	**0.49 (0.25 – 0.98)**
Pre-selected Chemo			
High intensity	96/149	52/75	**0.66 (0.47 – 0.93)**
Low intensity	75/98	38/49	**0.56 (0.38 – 0.84)**

Perl et al. N Engl J Med. 2019;381:1728-1740

Adverse Events

Common Adverse Events (>20%):

- Vomiting (21.5%)
- Constipation (30.9%)
- Diarrhea (32.9%)
- Hypokalemia (28.9%)
- Peripheral edema (24%)
- Pyrexia (42.7%)
- Fatigue (28.5%)
- Headache (26%)

Grade ≥ 3 Adverse Events:

- Thrombocytopenia: 22.8%
- Anemia: 40.7%
- Febrile Neutropenia: 45.9%
- AST elevation: 14.6%
- ALT elevation: 13.8%

***Post-Marketing:** Posterior reversible encephalopathy syndrome, differentiation syndrome

Perl et al. N Engl J Med. 2019;381:1728-1740

Remaining Questions and Limitations

- Only 46 patients received previous FLT3 inhibitors; standard-of-care commonly includes front-line midostaurin
  - The subgroup analysis showed no difference in overall survival outcomes in this subset of patients
- Unclear benefit in patients with ≥ 2 previous lines of therapy
  - How should therapy for patients with relapsed disease be sequenced?
- Few patients with FLT-TKD mutation only (31)
- Study sponsored by manufacturer

Perl et al. N Engl J Med. 2019;381:1728-1740

Learning Assessment #1

The ADMIRAL trial compared gilteritinib to other salvage chemotherapy options in FLT3-mutant relapsed/refractory AML and found:

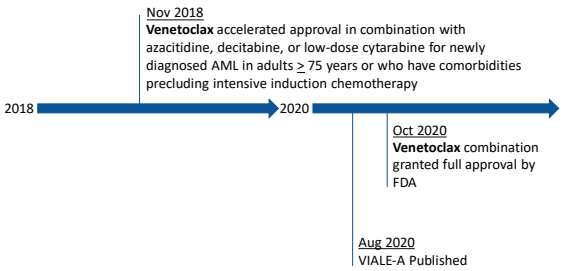
A. There was no difference in overall survival between gilteritinib and salvage chemotherapy

B. Patients with FLT3-TKD mutations benefited more from gilteritinib than patients with FLT3-ITD mutations

C. Gilteritinib was well-tolerated, with common side effects of myelosuppression, GI upset, and transaminitis

D. Patients who received previous FLT3 inhibitors and gilteritinib had a worse overall survival than patients receiving salvage chemotherapy

Updated FDA Approval - Venetoclax



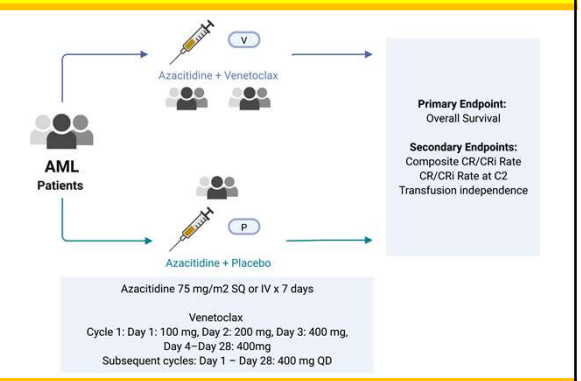
Drugs@FDA. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 28, 2021.

Phase III VIALE-A Trial

Inclusion Criteria	Exclusion Criteria

Patients ≥ 18 years old with newly diagnosed AML
 	
"Ineligible" for intensive chemotherapy
▪ Age ≥ 75 years old (ECOG < 3)
▪ Age ≥ 18 years old with at least one of the following:
  ▪ ECOG 2-3
  ▪ CHF, EF < 50%, or chronic angina
  ▪ DLCO ≤ 65% or FEV1 ≤ 65%
  ▪ CrCl ≥ 30 to < 45 ml/min
  ▪ Tbili 1.5 – 3.0 x ULN
  ▪ Any other comorbidity the physician judged incompatible with intensive chemo (independently reviewed)
	Previous treatment with hypomethylating agent or other chemotherapy for MDS
	
	History of MPN
	
	Favorable risk AML (CBF, APL)

Dinardo et al. N Engl J Med. 2020;383:617-629.



Dinardo et al. N Engl J Med. 2020;383:617-629.
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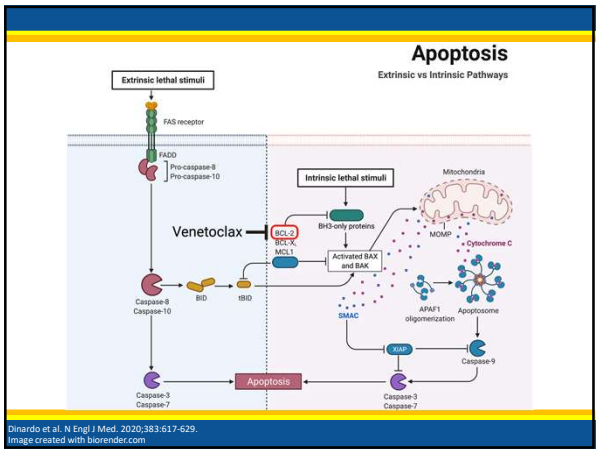


Dinardo et al. N Engl J Med. 2020;383:617-629.
Image created with biorender.com

Results

		Aza + Ven (n=286)	Aza + Placebo (n=145)
Baseline Demographics No. (%)	Median Age ECOG 0-1 ECOG 2-3	76 (range 49-91) 157 (55) 129 (45)	76 (range 60-90) 81 (56) 64 (44)
AML Characteristics No. (%)	De novo AML sAML Prior MDS/CMML tAML AML-MRC Intermediate risk Adverse risk IDH1 or IDH2 FLT3 ITD or TKD NPM1 TP53	214 (75) 72 (25) 46 (16) 26 (9) 92 (32) 182 (64) 104 (36) 61 (25) 29 (14) 27 (17) 38 (23)	110 (76) 35 (24) 26 (18) 9 (6) 49 (34) 89 (61) 56 (39) 28 (22) 22 (20) 17 (20) 14 (16)

Dinardo et al. N Engl J Med. 2020;383:617-629.

Results

	Aza + Ven (n=286)	Aza + Placebo (n=145)	Hazard Ratio (95% CI); P-value
Primary Endpoint			
Overall Survival	14.7 mo	9.6 mo	0.66 (0.52 – 0.85); P<0.001
Secondary Endpoints			
CR/CRi	66.4%	28.3%	P<0.001
CR	36.7%	17.9%	P<0.001
CR/CRi by C2	43.4%	7.6%	P<0.001
Time to response	1.3 mo (0.6 – 9.9)	2.8 (0.8 to 13.2)	P<0.001
Duration of CR	17.5 mo	13.4 mo	NR
Postbaseline transfusion independence	RBC 59.8% PLT 68.5%	RBC 35.2% PLT 49.7%	P<0.001 P<0.001

Dinardo et al. N Engl J Med. 2020;383:617-629.

Overall Survival Subgroup Analysis

Subgroup	Hazard Ratio (95% CI)
Age	
▪ < 75 yo	0.89 (0.59 – 1.33)
▪ ≥ 75 yo	**0.54 (0.39 – 0.73)**
Baseline ECOG	
▪ 0 - 1	**0.61 (0.44 – 0.84)**
▪ ≥ 2	0.70 (0.48 – 1.03)
Type of AML	
▪ De novo	**0.67 (0.51 – 0.90)**
▪ Secondary	**0.56 (0.35 – 0.91)**
Cytogenetic Risk	
▪ Intermediate	**0.57 (0.41 – 0.79)**
▪ Adverse	0.78 (0.54 – 1.12)
Molecular Subgroup	
▪ FLT3	0.66 (0.35 – 1.26)
▪ IDH1	**0.28 (0.12 – 0.65)**
▪ IDH2	**0.34 (0.16 – 0.71)**
▪ TP53	0.76 (0.40 – 1.45)
▪ NPM1	0.73 (0.36 – 1.51)

Dinardo et al. N Engl J Med. 2020;383:617-629.

VIALE-A vs Phase IB Study M14-358

Study	N	CR + CRi, N (%)	Median duration of CR + CRi, months	Median OS, months (95% CI)
M14-358: VEN 400 mg + Aza	84	59 (70)	21.2	16.9 (10.2 – NR)
VIALE-A: VEN 400 mg + Aza	286	190 (66.4)	17.5	14.7 (11.9 – 18.7)

Pollyea et al. Blood. 2018;132:285.
Dinardo et al. N Engl J Med. 2020;383:617-629.

Adverse Events

Common Adverse Events:

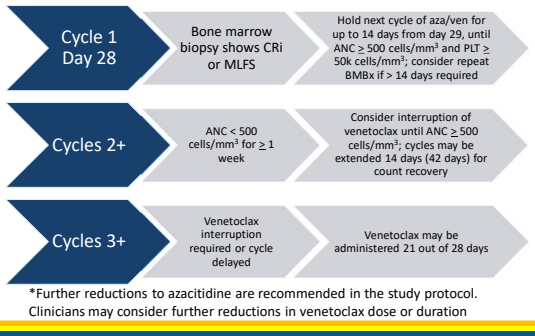
- Myelosuppression (83%)
- Nausea (44%)
- Constipation (43%)
- Diarrhea (41%)
- Peripheral edema (24%)
- Pyrexia (23%)
- Fatigue (21%)
- Decreased appetite (25%)

Grade ≥ 3 Adverse Events:

- Thrombocytopenia: 45%
- Neutropenia: 42%
- Anemia: 28%
- Febrile Neutropenia: 42%
- Pneumonia: 16%
- Sepsis: 6%

Dinardo et al. N Engl J Med. 2020;383:617-629.

Venetoclax Cytopenias



*Further reductions to azacitidine are recommended in the study protocol. Clinicians may consider further reductions in venetoclax dose or duration

Dinardo et al. N Engl J Med. 2020;383:617-629.

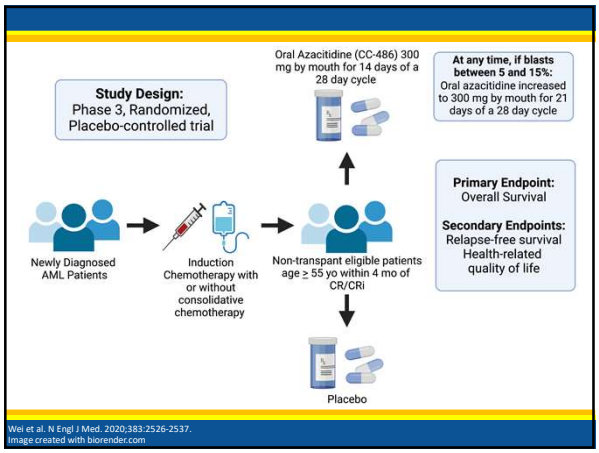
Remaining Questions and Limitations

- Criteria for fitness
- What is the optimal dose/schedule of venetoclax?
  - Dosing strategy with drug interactions
- Choice of hypomethylating agent
  - Azacitidine x 7 days
  - Decitabine x 5 days
  - Decitabine x 10 days (early data suggests promising ORR)
- Role in favorable risk disease
- Role in secondary AML
  - MF, PV, ET, and CML progressed to AML not included
  - vs CPX-351

Oral Azacitidine (CC-486) – QUAZAR AML-001

Inclusion Criteria	Exclusion Criteria
Patients age ≥ 55 years old with de novo or secondary AML (MDS-AML) in CR/CRi following intensive chemotherapy induction ▪ With or without consolidation chemo	CR/CRi after hypomethylating agent therapy Favorable risk AML (CBF, APL) MPN-AML (including CML) Prior BMT or candidate for BMT at screening

Wei et al. N Engl J Med. 2020;383:2526-2537.



Results

		Oral Azacitidine (n=238)	Placebo (n=234)
Baseline Demographics No. (%)	Median Age	68 (range 55-86)	68 (range 55-82)
	ECOG 0-1	217 (91)	217 (92)
	ECOG 2-3	21 (9)	17 (7)
AML Characteristics No. (%)	De novo AML	213 (89)	216 (92)
	sAML	25 (11)	18 (8)
	Intermediate risk	203 (85)	203 (87)
	Adverse risk	35 (15)	31 (13)
	Receipt of Consolidation Chemo		
	Yes	186 (78)	192 (82)
	No	52 (22)	42 (18)
	Measurable Residual Disease*	103 (43)	116 (50)

*Measured with flow cytometry with 0.1% threshold for positivity

Wei et al. N Engl J Med. 2020;383:2526-2537.

Results

	Oral Azacitidine (n=238)	Placebo (n=234)	P-value
Primary Endpoint			
Overall Survival	24.7 mo	14.8 mo	P<0.001
Secondary Endpoints			
Relapse Free Survival	10.2 mo	4.8 mo	P<0.001
FACIT Fatigue Scale	No significant difference in scores throughout treatment		
EQ-5D-3L health utility index scores	No significant difference in scores throughout treatment		

Wei et al. N Engl J Med. 2020;383:2526-2537.

Subgroup Analysis of 2-year Overall Survival

	Oral Azacitidine (n=238)	Placebo (n=234)	95% CI
Consolidation			
Yes	50.8% (n=186)	39.2% (n=192)	1.4 to 21.7
No	50.0% (n=52)	27.4% (n=42)	3.2 to 42.0
Consolidation Cycles			
1 – 2	50.8% (n=180)	37.6% (n=179)	2.9 to 23.7
3	50.0% (n=6)	61.5% (n=13)	-59.5 to 36.4
MRD Status At Randomization			
Positive	39.5% (n=103)	22.0% (n=116)	5.3 to 29.8
Negative	58.6% (n=133)	51.7% (n=111)	-5.8 to 19.5

Wei et al. N Engl J Med. 2020;383:2526-2537.

Results

Patients requiring escalated dosing:

- Oral azacitidine – 21%; time to escalated dosing – 9.2 mo
  - Restoration of CR/CRi status: 10 of 43 patients (23%)
  - Overall survival: 22.8 mo
- Placebo – 17%; time to escalated dosing – 6.0 mo
  - Restoration of CR/CRi status: 4 of 35 patients (11%)
  - Overall survival: 14.6 mo

Subsequent Therapies:

- Oral azacitidine: 137 patients (58%); 96% of patients who relapsed
  - 15 patients (6%) underwent HSCT; of these, 9 were relapsed
- Placebo: 170 patients (73%); 94% of patients who relapsed
  - 32 patients (14%) underwent HSCT
- Of the entire population: 33% received intensive chemotherapy as salvage

Wei et al. N Engl J Med. 2020;383:2526-2537.

Adverse Events

Common Adverse Events:

- Neutropenia
  - Oral aza (44%) vs. placebo (26%)
- Thrombocytopenia
  - Oral aza (33%) vs. placebo (27%)
- Nausea
  - Oral aza (65%) vs. placebo (24%)
- Vomiting
  - Oral aza (60%) vs. placebo (10%)
- Diarrhea
  - Oral aza (50%) vs. placebo (21%)

Grade ≥ 3 Adverse Events:

- Febrile Neutropenia
  - Oral aza (12%) vs placebo (8%)

Dose Interruptions:

- Oral aza (43%) vs. placebo (17%)

Wei et al. N Engl J Med. 2020;383:2526-2537.

Limitations

- High number of patients (33%) were able to receive intensive salvage chemotherapy after relapse
  - Questions legitimacy and ethics of stopping consolidation early (< 4 cycles) for maintenance therapy in this subset of patients
- Patients proceeded to transplant in either group, notably 14% of patients in the placebo arm
  - Possible improvement in functional status, but baseline ECOG 0-1 92% suggests otherwise
- Most patients did not receive consolidation or only received 1-2 cycles
  - Likely to have contributed to the benefit of continued therapy with oral azacitidine
  - MRD negative patients did not appear to benefit from oral azacitidine maintenance (2-yr OS: 58.6% vs. 51.7%; 95% CI, -5.8 to 19.5)
- Not compared to commercially available IV azacitidine or decitabine
  - AWP of oral azacitidine (14 days): $25,389.70
  - AWP of IV azacitidine (7 days): as low as $491.40 for BSA = 2.0 m^2
  - Do not have health-related quality of life outcomes to compare IV to PO
- Funded and supported by manufacturer

Wei et al. N Engl J Med. 2020;383:2526-2537.

So where does oral azacitidine fit into AML treatment?

- Study findings heavily confounded by substandard care
- Hypomethylating agents may be reasonable choices for maintenance in patients unable to proceed to BMT or finish high-dose consolidation chemotherapy due to a reduction in functional status or new-onset organ dysfunction following induction CR/CRi
  - Choice of IV azacitidine, IV decitabine, and PO azacitidine
  - NCCN guidelines endorse PO azacitidine as an option in this setting
- Reduction in clinic visits and infusion chair time vs IV azacitidine
  - May improve quality of life
  - Costs of infusion chair care and time may offset some of the PO azacitidine cost difference
  - Increases chair availability for other patients

NCCN. Acute Myeloid Leukemia. V3.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

Learning Assessment #2

The VIALE-A trial found an overall survival benefit of adding venetoclax to azacitidine therapy for patients with AML.

A. True

B. False

Nine approvals in 4 years…
So where are we now?

Updated Treatment Recommendations from NCCN v3.2021

Patients < 60 years old

Favorable Risk Cytogenetics (CBF-AML)	7 + 3 + GO (preferred) 7 + 3 (category 1) FLAG-IDA + GO (category 2B)
FLT3+ AML	7 + 3 + midostaurin
tAML, antecedent MDS/CMML-AML, and AML-MRC	7 + 3 (category 1) Liposome-encapsulated daunorubicin and cytarabine (category 2B)
Poor Risk Cytogenetics with TP53mut	Consider alternative induction strategies

NCCN. Acute Myeloid Leukemia. V3.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

Updated Treatment Recommendations from NCCN v3.2021

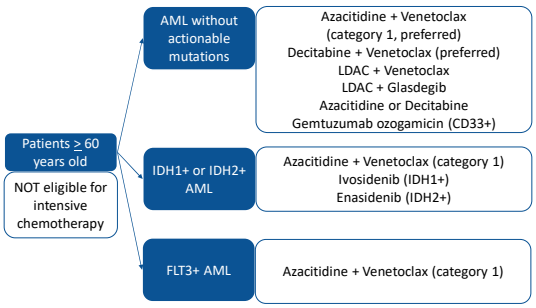
Patients ≥ 60 years old

Eligible for intensive chemotherapy

Favorable Risk Cytogenetics (CBF-AML)	7 + 3 + GO 7 + 3
FLT3+ AML	7 + 3 + midostaurin
tAML, antecedent MDS/CMML-AML, and AML-MRC	Liposome-encapsulated daunorubicin and cytarabine (category 1)
Poor Risk Cytogenetics	Azacitidine + Venetoclax Decitabine + Venetoclax LDAC + Venetoclax Azacitidine or Decitabine (category 2B)

NCCN. Acute Myeloid Leukemia. V3.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

Updated Treatment Recommendations from NCCN v3.2021



NCCN. Acute Myeloid Leukemia. V3.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

Considerations in Elderly AML (> 60 years old)

- Determination of Fitness
- Favorable vs Intermediate/Poor Risk
- Urgency of Treatment
- tAML or secondary AML
- Patient Goals

Learning Assessment #3

Patient MB is a 78 yo female with PMH of HTN and T2DM admitted to the hematology service with leukocytosis (WBC 36k) and concerns for acute leukemia.

Bone marrow biopsy: hypercellular marrow with 70% blasts; flow cytometry is consisted with newly diagnosed AML.

FISH: No abnormalities (for t(15;17), t(8;22), inv(16), t(16;16))

FLT3 PCR: FLT3-ITD mutation POSITIVE

Next Generation Sequencing: IDH1 mutation POSITIVE, DNMT3A mutation POSITIVE

Which of the below therapy options is the most appropriate first-line therapy:

A. Daunorubicin 60 mg/m2 IV x 3 days and cytarabine 100 mg/m2 IV over 24h x 7 days
B. Azacitidine 75 mg/m2 IV x 7 days and venetoclax with escalation to 400 mg by mouth x 28 days
C. Gilteritinib 120 mg by mouth once daily
D. Ivosidenib 500 mg by mouth once daily

Ongoing Trials and Future Directions

2021 → ?

Notable Ongoing Trials

Population	Study	Intervention	Preliminary Results
FLT3+ AML	Phase I/II: NCT02236013	7 + 3 + gilteritinib	Study complete, results pending ASH 2020: CR/CRi 81.6% (31 of 38 pts)
FLT3+ AML and MDS-EB2 (fit)	Phase III: NCT04027309	7 + 3 + midostaurin vs gilteritinib	Study ongoing
FLT3+ AML (unfit)	Phase III: NCT02752035	Azacitidine + gilteritinib vs azacitidine alone	Study ongoing ASH 2020: CR/CRi 67% (10/15 pts)
FLT3+ and CBF+ AML (fit)	Phase I/II: NCT04385290	7 + 3 + midostaurin + gemtuzumab ozogamicin	Study ongoing
R/R AML (fit)	Phase II: NCT03629171	CPX-351 + venetoclax (7 days)	Study ongoing ASH 2020: ORR 44%
AML (fit, age 18-59)	Phase II: NCT03573024	Azacitidine + venetoclax	Study ongoing
TP53 mut AML	Phase III: NCT04778397	Magrolimab (CD47 checkpoint inhibitor) + azacitidine vs azacitidine + venetoclax OR intensive induction chemotherapy	Study ongoing

Wang et al. Poster presented at ASH Annual Meeting and Exposition, December 5, 2020, Virtual.
Kadia et al. Poster presented at ASH Annual Meeting and Exposition, December 5, 2020, Virtual.
NIH Clinicaltrials.gov. Available at www.clinicaltrials.gov

Notable Ongoing Trials

Population	Study	Intervention	Preliminary Results
R/R AML	Phase II: NCT04746235	Venetoclax + decitabine/cedurazidine	Study ongoing
IDH1+ and IDH2+ AML or MDS-EB2 (fit)	Phase III: NCT03839771	7 + 3 + ivosidenib OR enasidenib	Study ongoing
Secondary AML in age 18-59	Phase II: NCT04269213	CPX-351	Study ongoing
IDH1+ AML (unfit)	Phase III: NCT03173248	Azacitidine + ivosidenib	Study ongoing Phase I/II: CR/CRh: 69.6%, CR: 60.9%; median time to CR: 3.7mo
IDH2+ AML (unfit)	Phase I/II: NCT02677922	Azacitidine + enasidenib	Study ongoing Phase I/II: CR/CRh: 71%, CR: 50%; median time to CR: 5.0mo
AML	Phase I: NCT04075747	CPX-351 + midostaurin (FLT3), enasidenib (IDH2), OR venetoclax (no targetable mutations)	Study ongoing
R/R FLT3+ AML	Phase I: NCT03625505	Venetoclax + Gilteritinib	Study ongoing CR: 8.1%, CRi: 8.1%, MLFS: 54.1%

DiNardo et al. J Clin Oncol. 2020;39:57-65.
DiNardo et al. J Clin Oncol. 2020;38:15_suppl, 7501-7501.
Daver et al. Blood. 2020;136 (supplement 1):20-22.
NIH Clinicaltrials.gov. Available at www.clinicaltrials.gov

Additional Ongoing Trials and Investigational Therapies

Population	Study	Intervention	Preliminary Results
R/R AML	Phase I/II: NCT02152956	Flotetuzumab (CD3-CD123 BiTE)	CR/CRh 11.7%
MLL rearranged AML	Phase I/II: NCT03724084	7 + 3 + Pinometostat	Study ongoing
R/R AML	Phase I/II: NCT04351022	CD38 CAR T product	Study ongoing
R/R FLT3+ AML	Phase I/II: NCT05023707	FLT3 CAR T product	Study ongoing
AML	Phase I/II: NCT04629443	S64315 (MCL1 inhibitor) + azacitidine	Study ongoing
AML with MRD	Phase I/II: NCT04623216	Sabatolimab (TIM-3 inhibitor) with or without azacitidine	Study ongoing
AML	Phase I/II: NCT04086264	IMGN632 (CD123-directed ADC) with or without azacitidine and/or venetoclax	Study ongoing
TP53mut AML	Phase I/II: NCT03745716	APR-246 (eprenetapopt) + azacitidine vs azacitidine	Study ongoing, Phase III trial in MDS ongoing

Uy et al. Blood. 2021;137(6):751-762.
NIH Clinicaltrials.gov. Available at www.clinicaltrials.gov

Learning Assessment #4

Ongoing clinical trials combining commercially available agents include:

A. Azacitidine with enasidenib
B. CPX-351 with venetoclax
C. 7 + 3 with midostaurin vs 7 + 3 with gilteritinib
D. All of the above

Updates in Acute Myeloid Leukemia

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