NEW THERAPIES IN ACUTE MYELOID LEUKEMIA (AML)

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OBJECTIVES

- Recognize new medications that received FDA approval for the treatment of AML in 2017 and 2018
- Identify targetable genetic mutations in AML and the FDA approved medications used to target these mutations
- Discuss key trials that lead to the FDA approvals of new drugs
- Summarize common side effects of these agents and their management

AUDIENCE RESPONSE

- 1. What is your practice setting?
  - A. Academic medical center
  - B. Community hospital
  - C. Outpatient/specialty pharmacy
  - D. Industry
  - E. Other

AUDIENCE RESPONSE

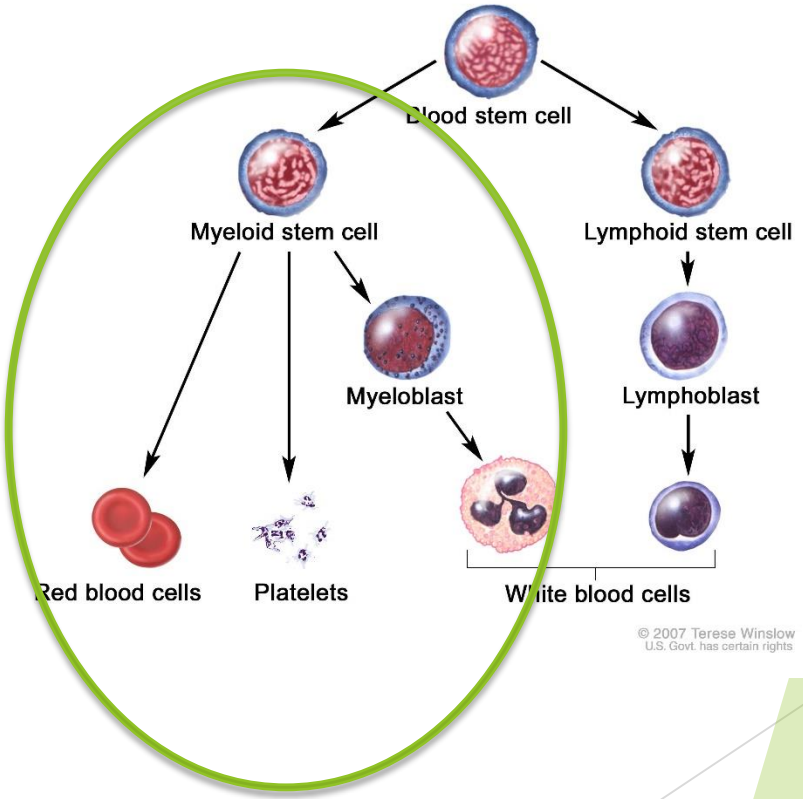
- 2. Do you primarily practice in the inpatient or outpatient setting?
  - A. Inpatient
  - B. Outpatient

AUDIENCE RESPONSE

- 3. What is your specialty?
  - A. Malignant hematology! (yah!)
  - B. Benign hematology
  - C. Solid malignancies (thanks for coming to this topic)
  - D. Hematopoietic stem cell transplant (HSCT)
  - E. General hematology/oncology (I do all the things)
  - F. I'm a learner (trying to figure out what I want to do with my life)
  - G. Other (what are you doing here?!)

AML

- Heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts
  - Peripheral blood
  - Bone Marrow
  - Other tissues
- Characterized by impaired hematopoiesis and bone marrow failure

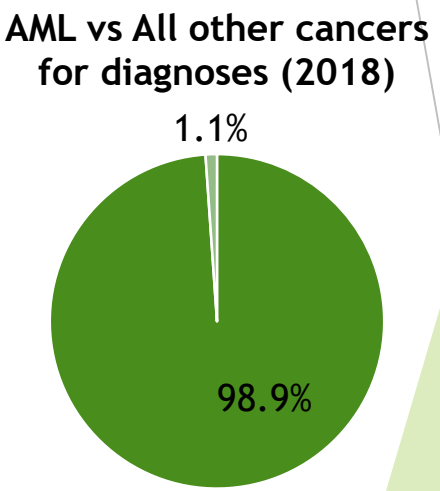


NCCN. Acute Myeloid Leukemia. V1.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf
NCI. AML. Available at: https://www.cancer.gov/types/leukemia/patient/adult-aml-treatment-pdq

Statistics

- Estimated new cases and deaths in the U.S. in 2018

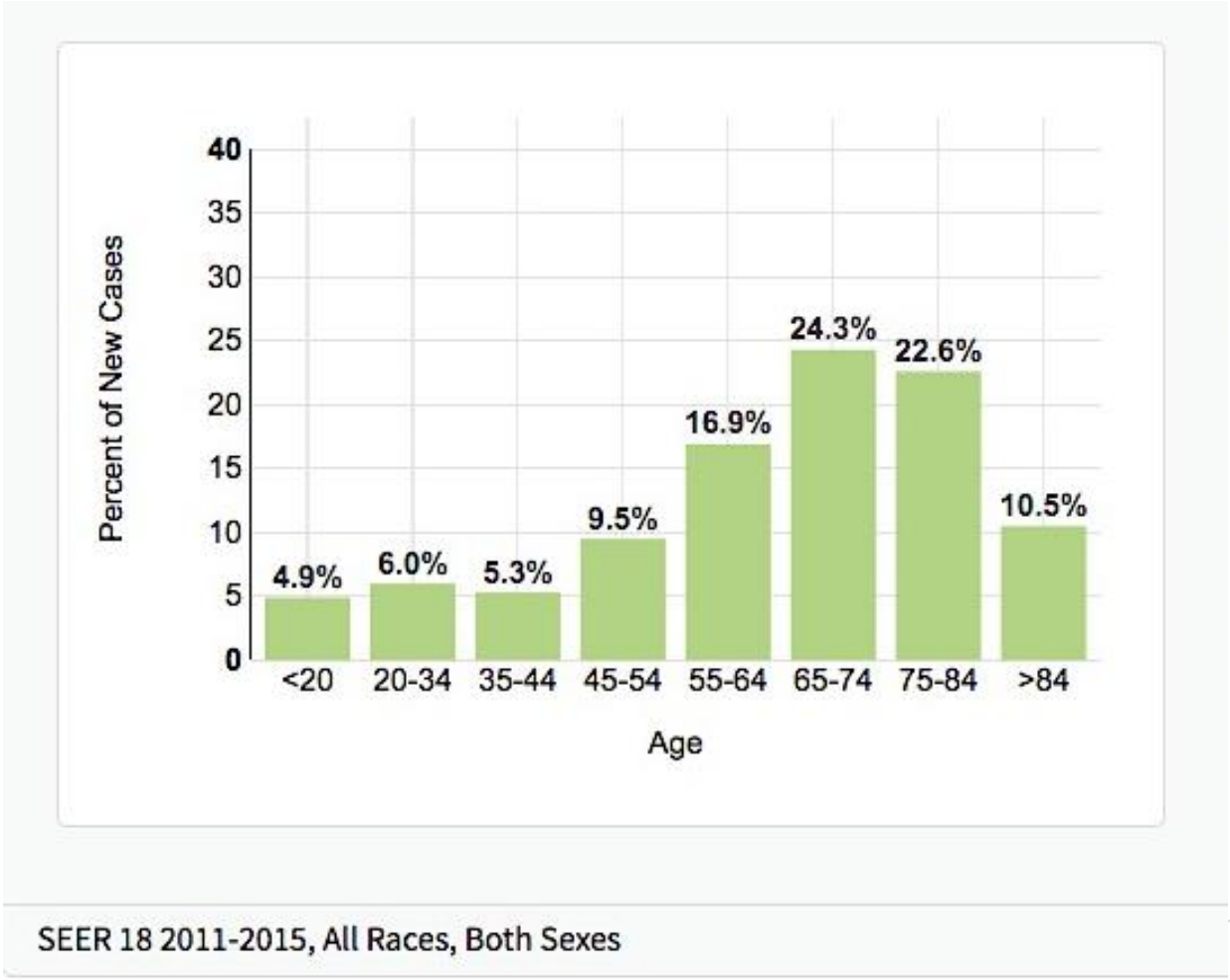
	Common Types of Cancer	Estimated New Cases 2018	Estimated Deaths 2018
1	Breast Cancer	266,120	40,920
2	Lung Cancer	234,030	154,050
3	Prostate Cancer	164,690	29,430
4	Colorectal Cancer	140,250	50,630
5	Melanoma of Skin	91,270	9,320
10	Leukemia	**60,300**	24,370
	AML	**19,520**	10,670



- Average age at diagnosis: 68

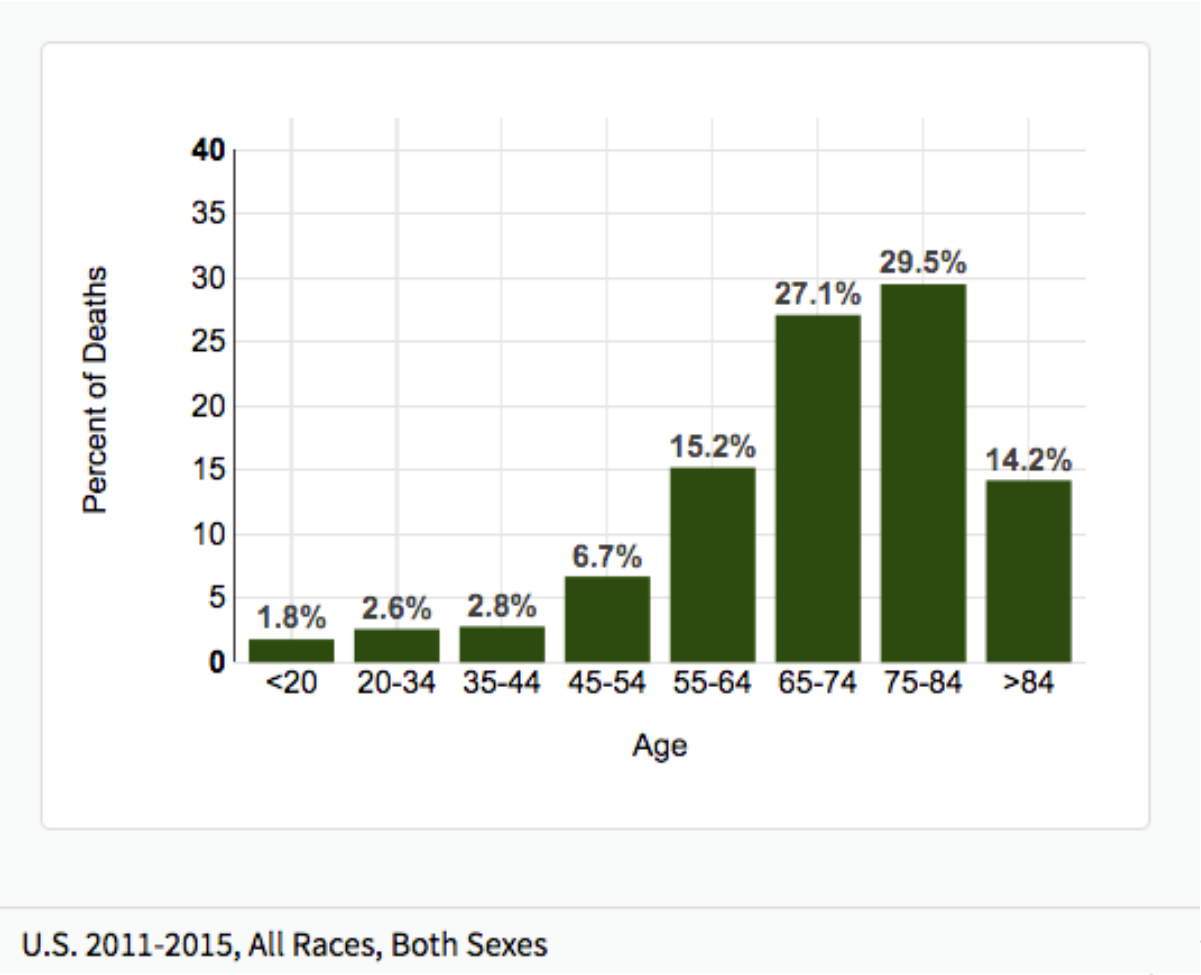
Fast Stats: An interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. Available on: https://seer.cancer.gov/faststats.

Percent of New Cases by Age



SEER Cancer Stat Facts: Acute Myeloid Leukemia. National Cancer Institute. Bethesda, MD. Available on: https://seer.cancer.gov/statfacts/html/amyl.html

Percent of Deaths by Age



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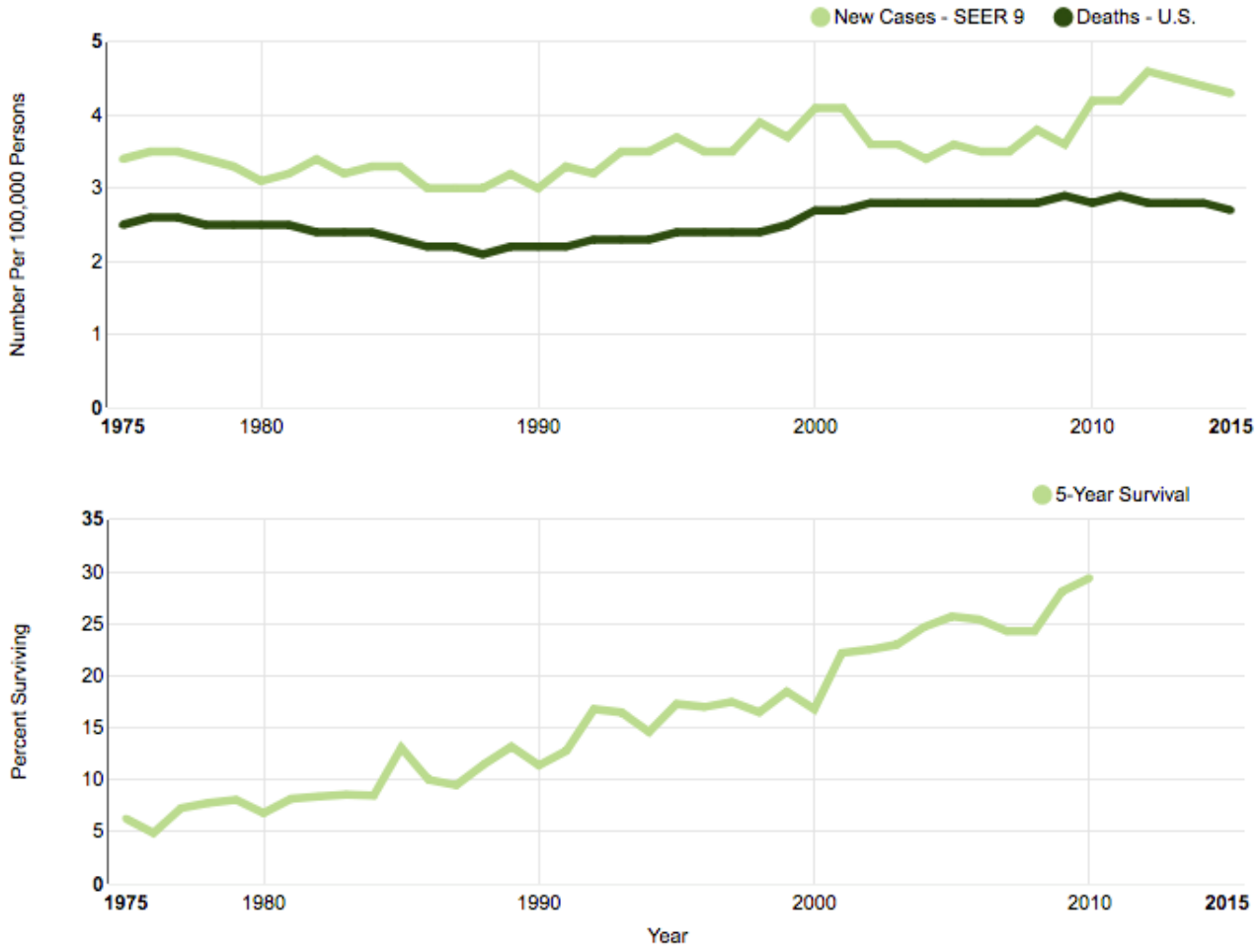
AML Trends



SEER Cancer Stat Facts: Acute Myeloid Leukemia. National Cancer Institute. Bethesda, MD. Available on: https://seer.cancer.gov/statfacts/html/amyl.html

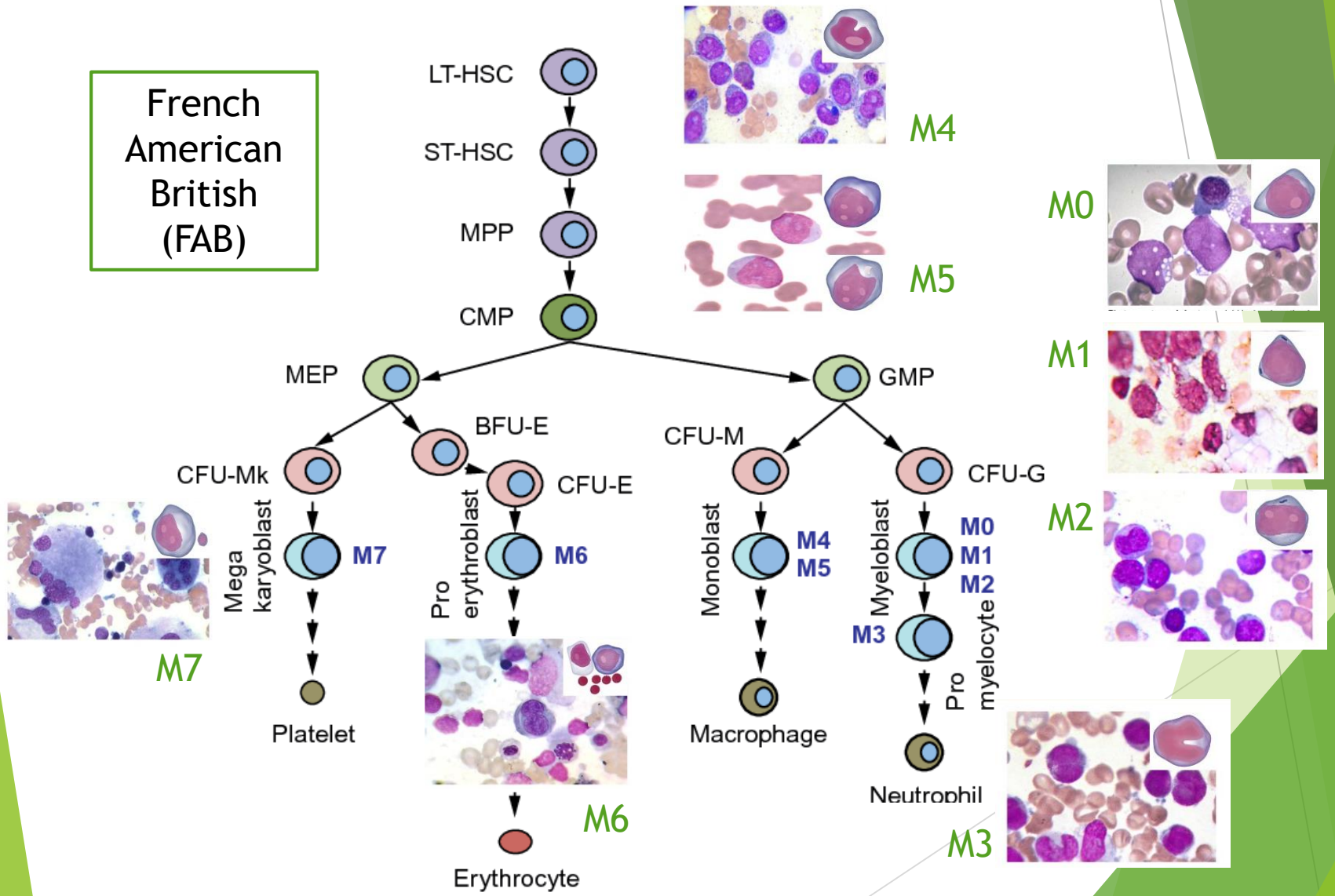
Diagnosis

- 2016 World Health Organization (WHO) Classification: Presence of > 20% blasts in the bone marrow or peripheral blood
  - Core binding factors: t(15;17), t(8;21), or t(16;16)
- Tests to establish diagnosis
  - Complete blood count with differential
  - Bone marrow aspirate
  - Bone marrow biopsy
  - Immunophenotyping
- Genetic analyses
  - Cytogenetics
  - Screening for gene mutations and rearrangements

Döhner H et al. Blood. 2017. 129(4): 424-447
Arber D et al. Blood. 2016. 127(20): 2391-2405

Classification

French
American
British
(FAB)



Fukuda Y et al.Advances in cancer research. 2015:171-96

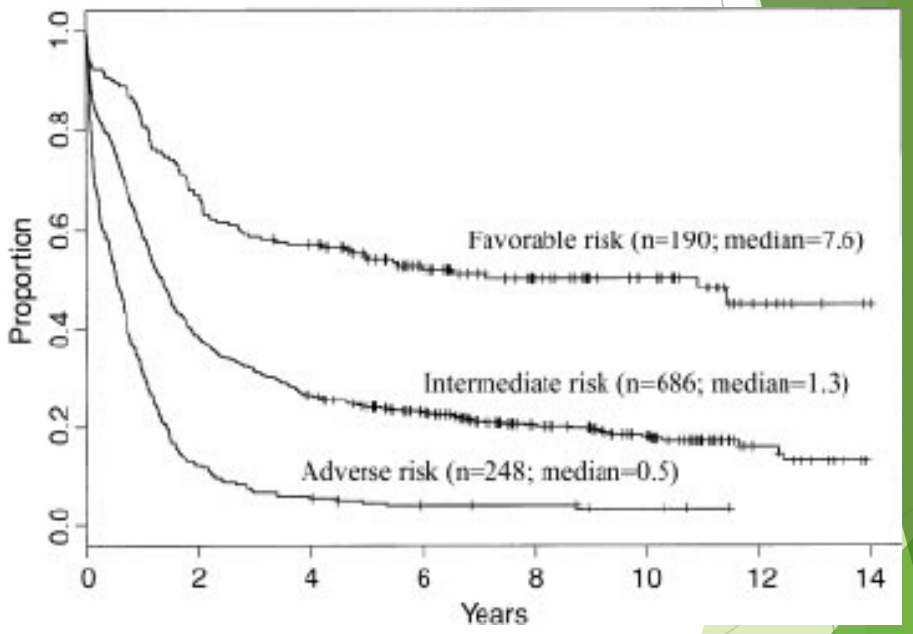
WHO Classification

- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
  - APL with *PML-RARA*
  - AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
  - AML with t(6;9)(p23;q34.1);*DEK-NUP214*
  - AML with inv(3)(q21.3q26.2) or t(3;3(q21.3;q26.2); *GATA2*, *MECOM*
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
  - *Provisional entity: AML with BCR-ABL1*
  - AML with mutated *NPM1*
  - AML with biallelic mutations of *CEBPA*
  - *Provisional entity: AML with mutated RUNX1*
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, NOS
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic/monocytic leukemia
  - Pure erythroid leukemia
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis (TAM)
- Myeloid leukemia associated with Down syndrome

Arber D et al. Blood. 2016. 127(20): 2391-2405

Risk Stratification

- Karyotype represents the single most important prognostic factor for predicting remission rates, risk of relapse, and overall survival
- SWOG/ECOG Intergroup study 5- year survival rates
  - Favorable cytogenetics: 55%
  - Intermediate cytogenetics: 24%
  - Adverse cytogenetics: 5%



NCCN. Acute Myeloid Leukemia. V1.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf
Byrd JC et al. Blood 2002; 100;100:4325-4336

NCCN Risk Stratification

Risk Status	Cytogenetics	Molecular Abnormalities
Favorable Risk	Core binding factor: inv(16), t(16;16), t(8:21), t(15;17)	Normal cytogenetics: • NPM1 mutation in the absence of FLT3-ITD or • CEBPA mutation
Intermediate Risk	• Normal cytogenetics • t(9;11) • Other non-defined	• Core binding factors with KIT mutation • Mutated NPM1 and FLT3-ITD • Wild type NPM1
Poor / Adverse Risk	• Complex (≥3 clonal chromosomal abnormalities) • Monosomal karyotype • -5, 5q-, -7, 7q- • 11q23 – non t(9;11) • inv(3), t(3;3) • t(6;9) • t(9;22)	Normal cytogenetics: • With FLT3-ITD mutation • TP53 mutation • Mutated RUNX1 • Mutated ASXL • Wild-type NPM1 and FLT3-ITD

**NCCN = National Comprehensive Cancer Network

NCCN. Acute Myeloid Leukemia. V1.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

Prevalence of Genetic Mutations

Signal Transduction Pathway	
JAK2V617F	<1%
CSF3R	1%
FLT3-ITD	32%
FLT3-TKD	12%
KRAS, NRAS	12-14%
PTPN11	4%
KIT	4%
Epigenetic Regulation	
ASXL1	30%
EZH2	2%
TET2	8%
DNMT3A	26%
IDH1and IDH2	20%

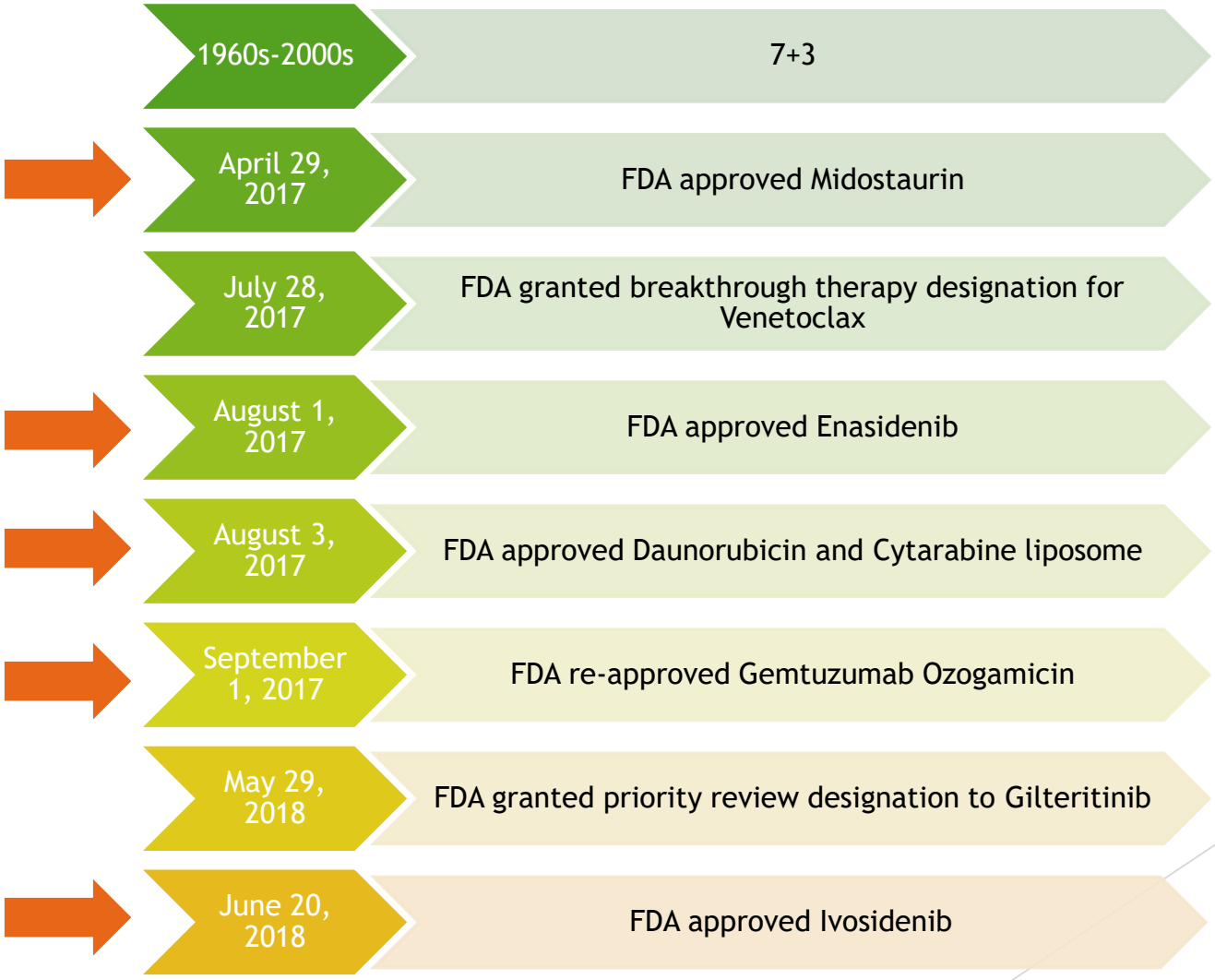
Transcriptional Regulation	
TP53	8%
RUNX1	10%
ETV6	2%
BCOR	4%
CEBPA	6-14%
WT1	6%
RNA regulation	
SF3B1	2%
SRSF2	5%
U2AF1	3%
Other	
NPM1	27-54%
SETBP1	<1%

Arber D et al. Blood. 2016. 127(20): 2391-2405
Tremblay D et al. Oncology (Williston Park). 2018. 32(4):e38-e44.

SELF ASSESSMENT QUESTION 1

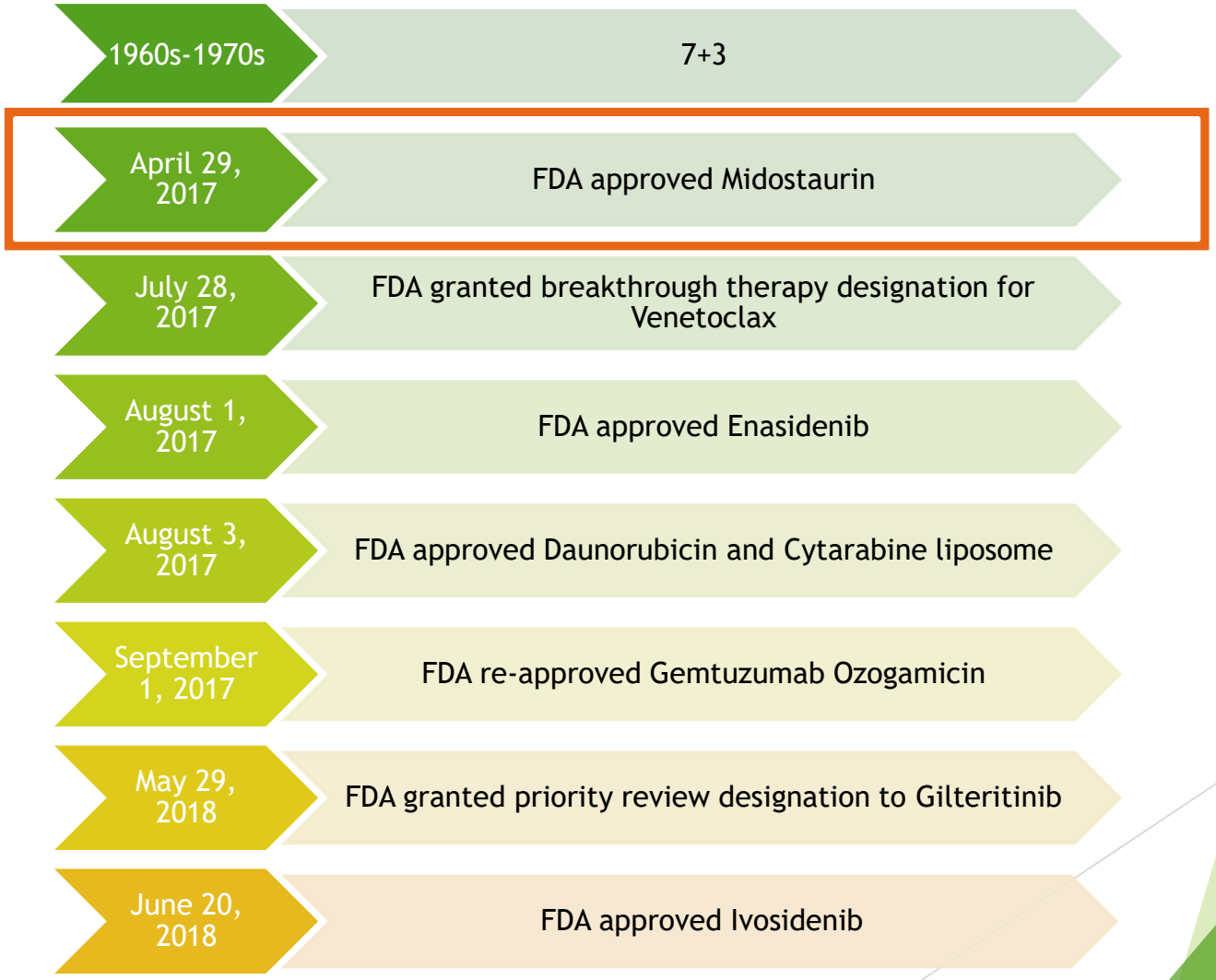
- 1. Which of the following is true regarding mutations in AML?
  - A. CEBPA is associated with a poor prognosis and there is a FDA approved agent to target this mutation
  - B. FLT-3 is associated with a good prognosis and there is no FDA approved agent to target this mutation
  - C. Only 20% of AML patients have either an IDH1 or IDH2 mutation and the prognosis associated with these mutations is controversial
  - D. There are multiple FDA approved medications that target IDH1 mutations

AML Treatment Timeline



Wei AH, et. al. Blood. 2017. 30(23): 2469-2472

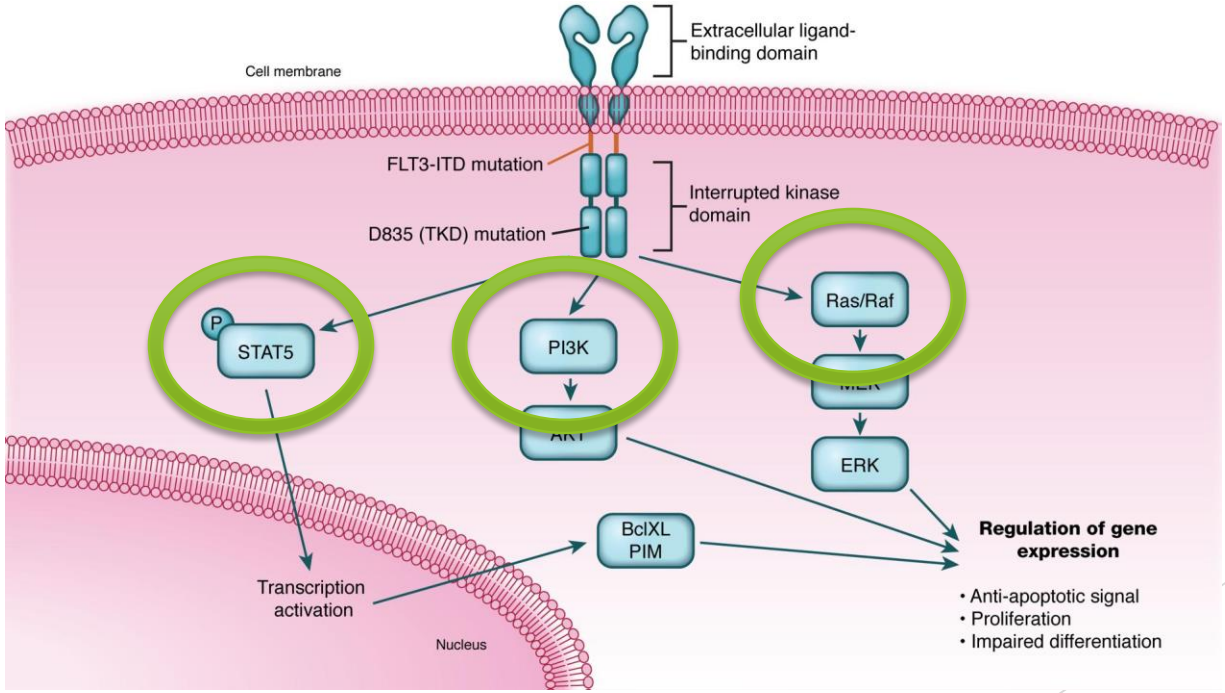
AML Treatment Timeline



Wei AH, et. al. Blood. 2017. 30(23): 2469-2472

FMS-like Tyrosine Kinase (FLT-3)

- One of the most common mutations detected in AML
- Type III receptor tyrosine kinase which regulates normal growth and differentiation of CD34+ hematopoietic cells *via* signaling through multiple pathways



Gallogly MM et al. Ther Adv Hematol. 2017. 8(9): 245–261.
Kavanah S et al. JCI Insight. 2017. 2(18):e95679.

FMS-like Tyrosine Kinase (FLT-3)

- Overall incidence ~30%
  - Internal tandem duplication (ITD): ~23%; in-frame insertion mutations within the juxtamembrane domain
  - Tyrosine Kinase Domain (TKD): ~7%; point mutations
- FLT3-ITD mutation
  - Independent risk factor for higher relapse, lower disease-free survival (DFS), event-free survival (EFS), and overall survival (OS) rates
  - Unfavorable molecular risk marker in AML by the NCCN
- FLT3-TKD mutation
  - NOT an independent risk factor for poor outcomes

Gallogly MM et al. Ther Adv Hematol. 2017. 8(9): 245–261.

MIDOSTAURIN

Mechanism	Multi-kinase inhibitor that inhibits FLT-3 ITD and TKD, protein kinase C, c-KIT, PDGFRs α/β, CDK1, VEGF receptor KDR, src, Fgr, and Syk
Place in therapy	Treatment of adult patients with newly diagnosed FLT3 mutation-positive AML, in combination with standard therapy
Dosing	50 mg PO BID days 8-21 of 7+3 induction and high dose cytarabine (HiDAC) consolidation
Metabolism	Substrate of CYP3A4 (major); inhibits OAT1A1/SLCO1A1; induces MRP2
Cost (AWP)	25 mg capsules #28: $4,497→ $8,994 per cycle

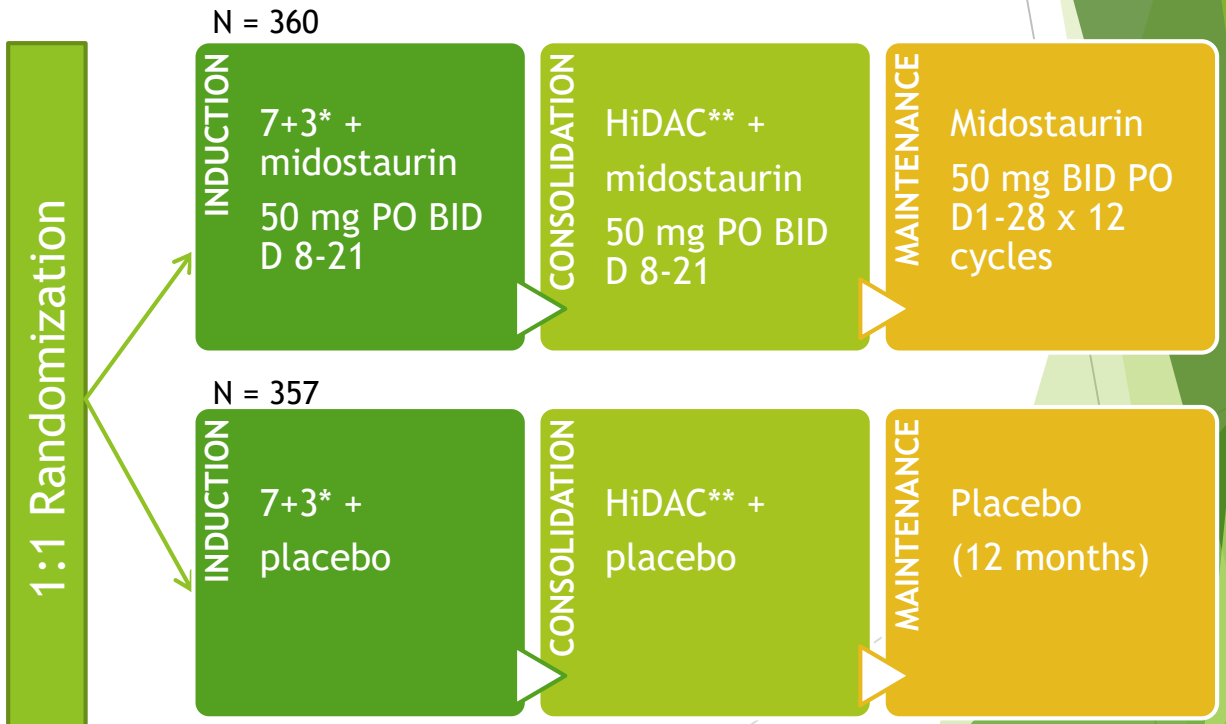
Rydapt (midostaurin) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; April 2017

RATIFY Trial: CALGB 10603

Trial Design	Endpoints
Multi-institutional, multi-national, randomized, double-blind, placebo-controlled	Primary: OS Secondary: EFS, DFS, adverse events (ADEs)

Eligibility:

- Adults 18-59 years of age
- Newly diagnosed AML (not therapy-related)
- Received no prior antineoplastic therapy
- FLT3 mutation
- Bilirubin <2.5x ULN
- Absence of other major coexisting illnesses



*7+3 = daunorubicin 60 mg/m2 x 3 days + cytarabine 200 mg/m2 x 7 days
**HiDAC = 3g/m2 BID on Days 1, 3, 5

Stone RM et al. N Eng J Med. 2017. 377(3):454 - 464

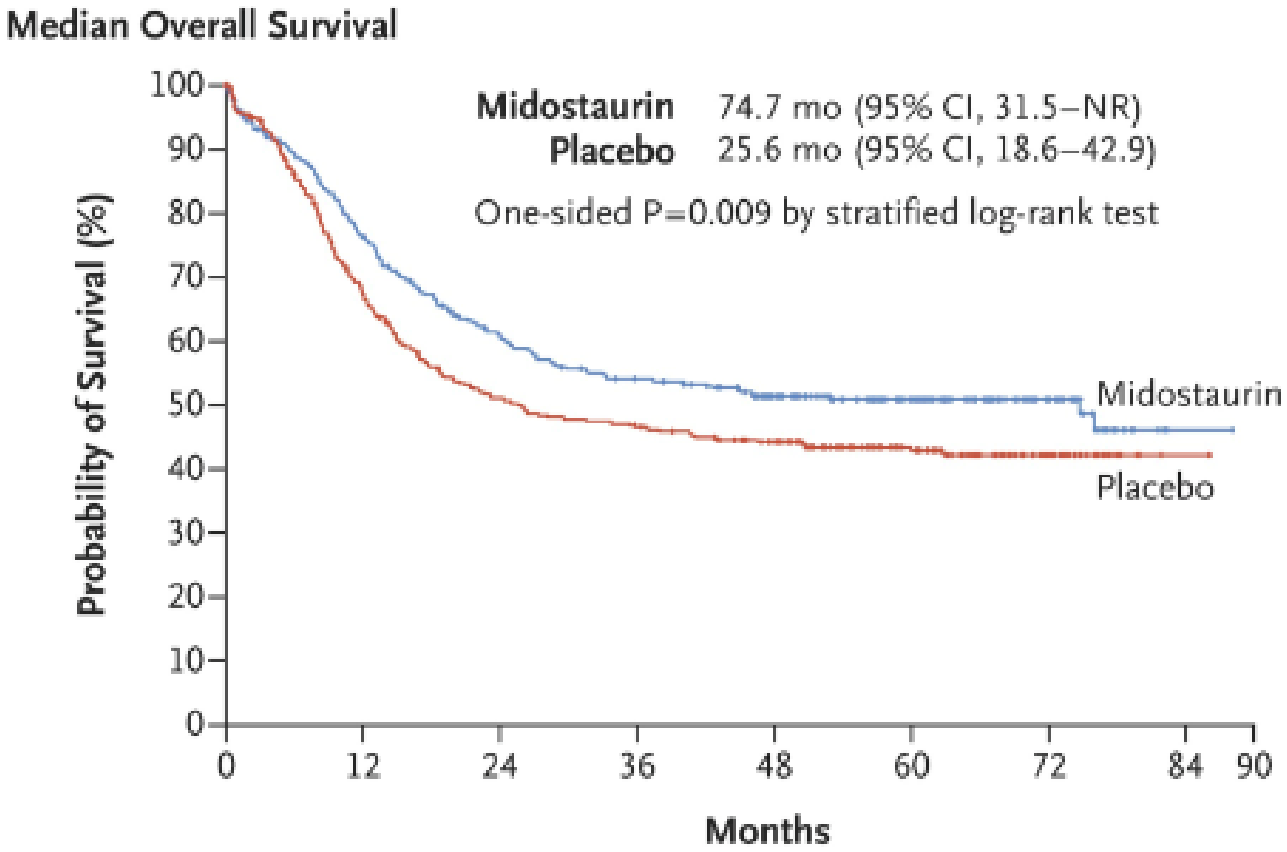
RATIFY Trial: RESULTS

Primary Outcome	Midostaurin (n=360)	Placebo (n=357)	P-value
Median OS – mo. (95% CI)	74.7 (31.5 – not reached)	25.6 (18.6 – 42.9)	P=0.009

Secondary Outcomes	Midostaurin (n=360)	Placebo (n=357)	P-value
EFS – median – mo. (95% CI)	8.2 (5.4 – 10.7)	3.0 (1.9 – 5.9)	P = 0.002
DFS – median – mo. (95% CI)	26.7 (19.4 – not reached)	15.5 (11.3 – 23.5)	P = 0.01
CR - % (95% CI)	58.9 (53.6 – 64)	53.5 (48.2 – 58.8)	P = 0.15
HSCT in 1st remission – n(%)	101 (28.1)	81 (22.7)	P = 0.10

Stone RM et al. N Eng J Med. 2017. 377(3):454 - 464

RATIFY Trial: RESULTS



Stone RM et al. N Eng J Med. 2017. 377(3):454 - 464

RATIFY Trial: SAFETY

Adverse Effect (Grade 3, 4, 5)	Midostaurin (n=360) N (%)	Placebo (n=357) N (%)	P-value
Thrombocytopenia	346 (97)	342 (97)	0.52
Neutropenia	338 (95)	339 (96)	0.86
Anemia	329 (93)	311 (88)	0.03
Febrile neutropenia	290 (82)	292 (82)	0.84
Rash	50 (14)	27 (8)	0.008
Nausea	20 (6)	34 (10)	0.05

Count Recovery (Days)	Midostaurin Median (IQR)	Placebo Median (IQR)
Absolute neutrophil count (ANC) >500/μL	26 (24-30)	26 (22-31)
Platelet count >100,000/μL	21 (19-23)	21 (19-24)

IQR = interquartile range

Stone RM et al. N Eng J Med. 2017. 377(3):454 - 464

Clinical Pearls: MIDOSTAURIN

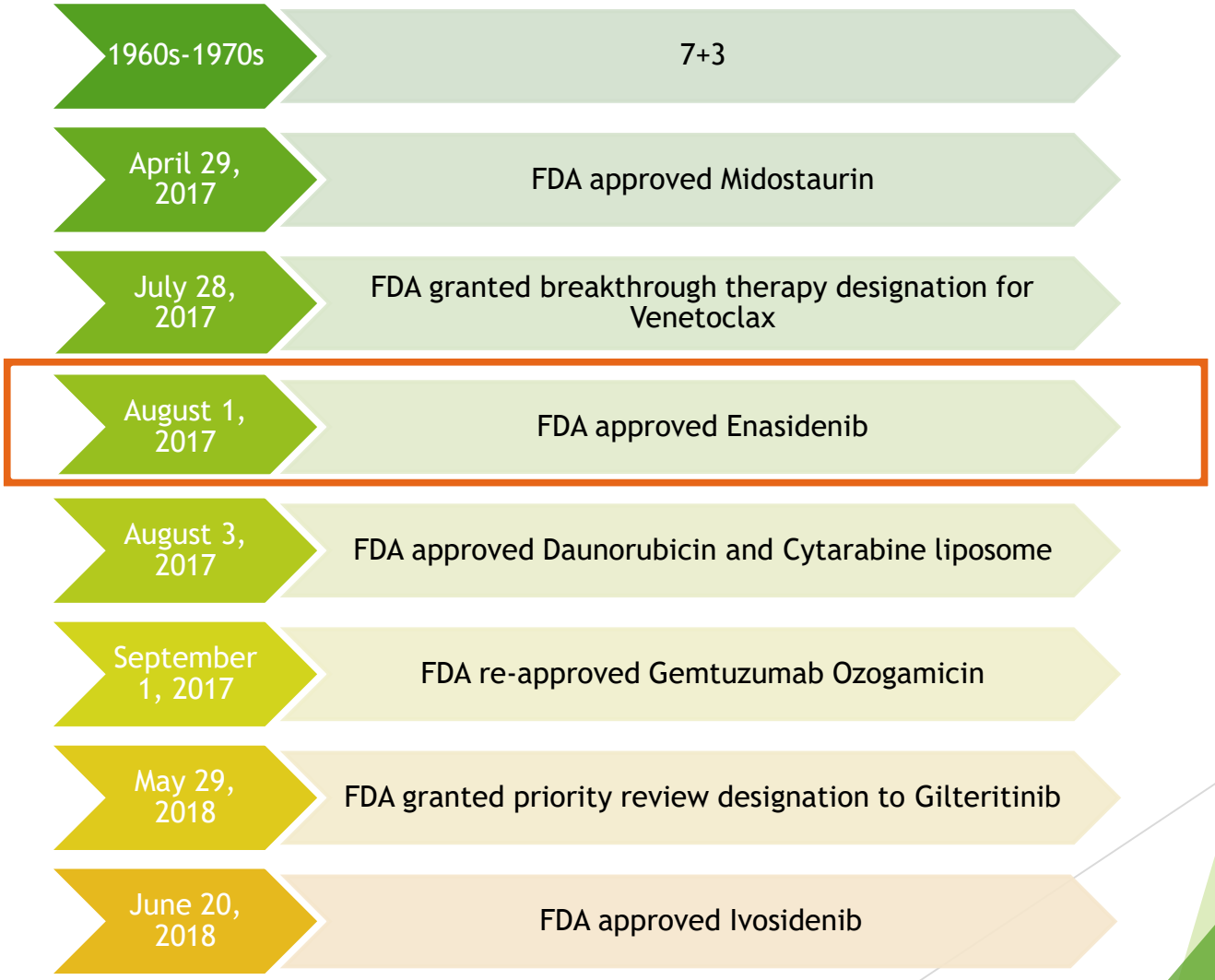
- Moderate-High emetogenicity
  - May need to schedule anti-emetics
- QTc prolongation
- Watch for DDI – CYP3A4 inhibitors
  - ?? Fungal prophylaxis
- $$ COST $$
  - Check for co-pays with insurance companies
  - Novartis Oncology Universal Co-Pay Card
    - Commercially insured patients pay $10/month
  - RYDAPT NOW Access program (Patient Assistance Now Oncology)

Rydapt (midostaurin) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; April 2017
Available at: https://www.us.rydapt.com/acute-myeloid-leukemia/patient-support/financial-resources/

SELF-ASSESSMENT QUESTION 2

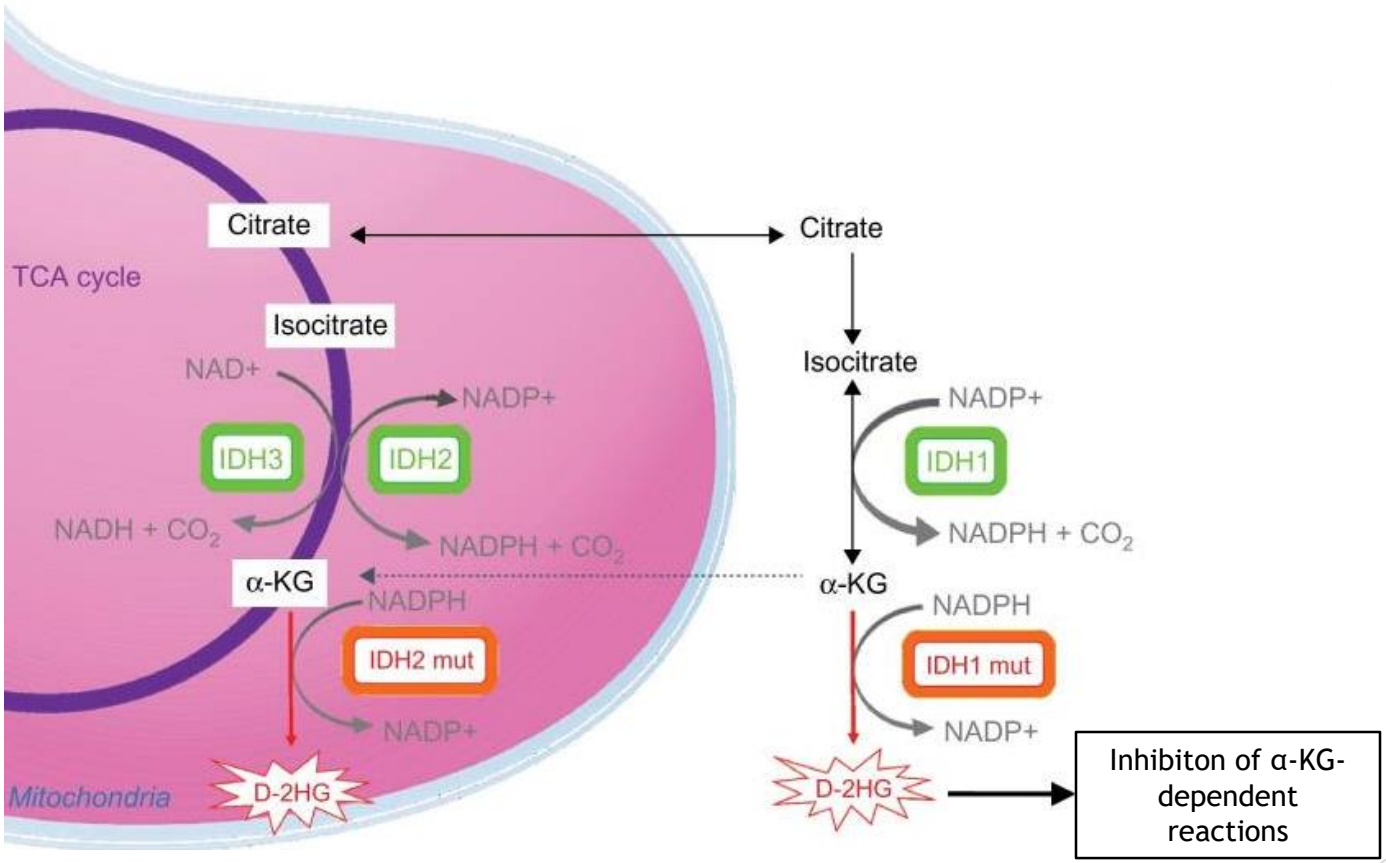
- 2. Which of the following statements are true regarding the RATIFY trial?
  - A. Overall survival was significantly longer in the midostaurin group than in the placebo group
  - B. Only patients with a FLT-3 ITD mutation had a response to midostaurin
  - C. The most common grade 3, 4 adverse reactions associated with midostaurin were febrile neutropenia and nausea
  - D. Midostaurin was administered on days 1-28 of each cycle

AML Timeline



Wei AH, et. al. Blood. 2017. 30(23): 2469-2472

Isocitrate Dehydrogenase (IDH)

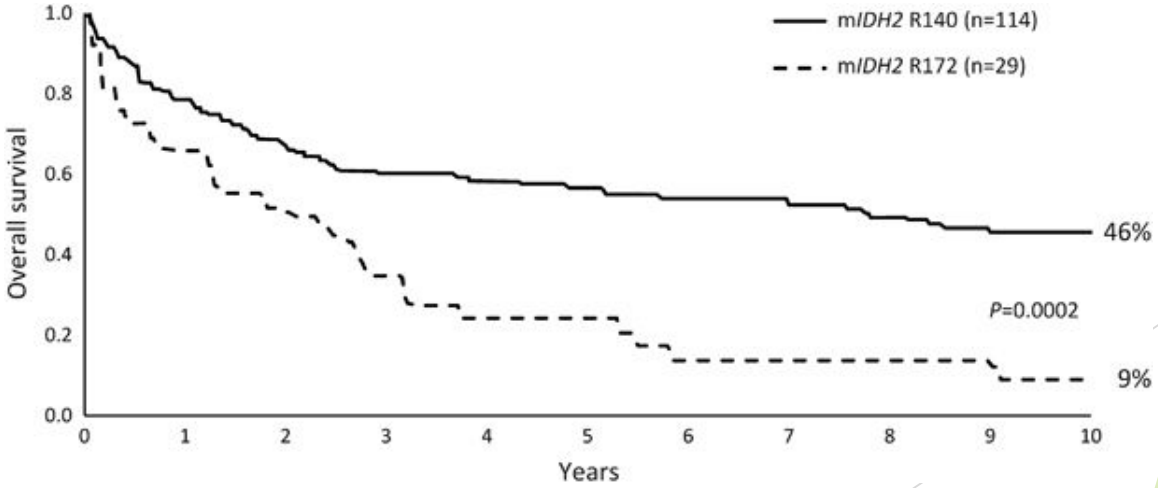


- Increased histone methylation
- Increased DNA methylation
- Impaired cell differentiation

Mondesir J et al. J Blood Med. 2016; 7: 171–180.

IDH1/2 mutations

- Incidence: ~20%
  - IDH1 mutation: 7-9%
  - IDH2 mutation: 8-12%
    - R140 – more likely to be accompanied by mutated NPM1
    - R172
- Prognostic impact of IDH1 and 2 mutations in AML remains controversial



Dohner H, et al. N Engl J Med 2015; **373**: 1136–1152
Green CL et al. Blood 2011; 118: 409–412
NCCN. Acute Myeloid Leukemia. V1.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pd

ENASIDENIB

Mechanism	Small molecule inhibitor of the IDH2 enzyme (inhibits both R140 and R172 IDH2 isoforms)
Place in therapy	Treatment of adult patients with relapsed or refractory (R/R) AML with an IDH2 mutation
Dosing	100 mg PO daily until disease progression
Cost (AWP)	100 mg tablets: $994.88 each → $29,846 per month

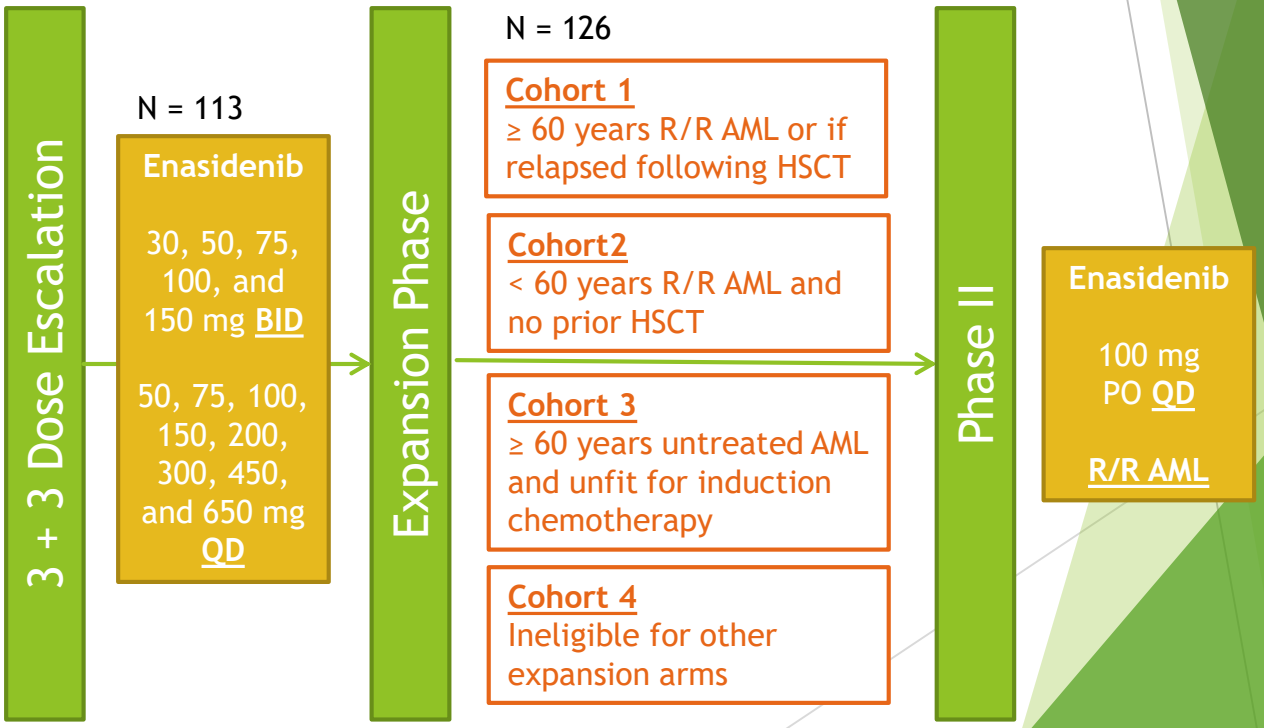
Idhifa (enasidenib) [prescribing information]. Summit, NJ: Celgene Corporation; August 2017

Enasidenib in Mutant-IDH2 R/R AML

Trial Design	Endpoints
Multi-center, phase 1/2, first-in-human study	Primary: Safety and maximum tolerated dose (MTD) Secondary: PK/PD profiles and clinical activity of enasidenib

Eligibility:

- ≥ 18 years of age
- Confirmed mutant-IDH2 advanced myeloid malignancies (AML/MDS)
- ECOG 0-2



Stein EM, et. al. Blood. 2017; 130(6):722-31

Baseline Characteristics

Characteristic	Enasidenib 100 mg QD (n=199)
Age, years, median (range)	68 (19-100)
Male, n (%)	103 (52)
Relapsed AML, n(%)	95 (48)
Refractory AML, n(%)	104 (52)
Prior HSCT	25 (13)
Prior lines of therapy, n(%)	
1	89 (45)
2	64 (32)
≥3	46 (23)
ECOG*, n(%)	
0	46 (23)
1	124 (62)
2	28 (15)

*ECOG=Eastern Cooperative Oncology Group performance status

Stein EM, et. al. Blood. 2017; 130(6):722-31

SAFETY

Grades 3 or ADEs occurring in ≥2% of all patients n (%)	Enasidenib 100 mg QD (n=153)
Hyperbilirubinemia	13 (8)
IDH differentiation syndrome	11 (7)
Anemia	10 (7)
Thrombocytopenia	8 (5)
Tumor lysis syndrome	3 (2)
Decreased appetite	2 (1)
Leukocytosis	2 (1)
Fatigue	2 (1)
Nausea	2 (1)
Lipase increased	2 (1)

- Enasidenib was generally well-tolerated but nearly all experienced ADEs
- Most common ADEs: indirect hyperbilirubinemia, nausea, and diarrhea
- Enasidenib-related grade 3-4 ADEs occurred in 41% (n = 99/239) patients
- Median number of treatment cycles: 5.0 (range 1–25)
- MTD was not reached at doses of up to 650 mg daily
  - Prolonged dosing with 650 mg not well-tolerated

Stein EM, et. al. Blood. 2017; 130(6):722-31

Differentiation Syndrome

- IDH-inhibitor-associated differentiation syndrome (IDH-DS): 23 patients
  - Grade 3-4: 15 patients
  - Managed with systemic corticosteroids:19 patients
- Mean time to onset: 48 days (range 10-340 days)
- Interrupted therapy: 10 patients
  - Permanent discontinuation not required
- Non-dose dependent, non-infectious leukocytosis: 41 patients
  - Primarily within first 2 cycles
  - Leukocytosis not necessarily accompanied by IDH-DS

Stein EM, et. al. Blood. 2017; 130(6):722-31

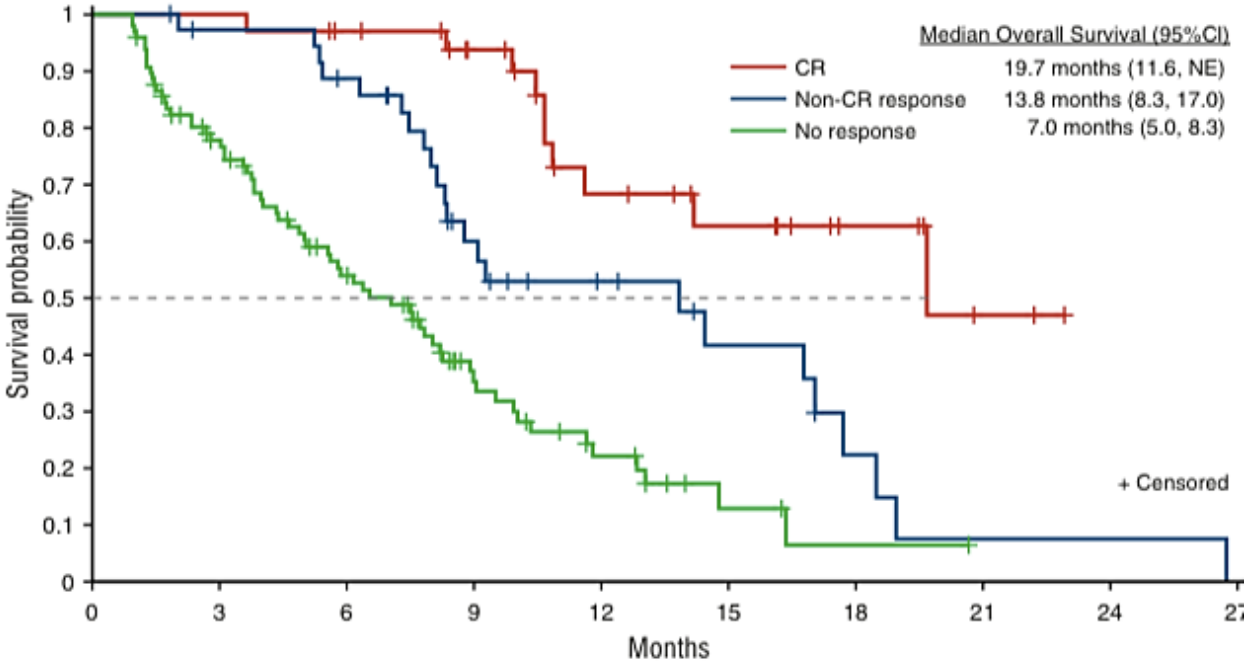
EFFICACY

Outcomes for R/R AML	100 mg QD (n=199)
ORR, n(%)	65 (33)
Best Response	
CR, n(%)	37 (19)
CRi, n(%)	9 (4)
PR, n(%)	4 (4)
Morphologic leukemia-free, n(%)	15 (8)
Stable disease, n(%)	94 (47)
Time to first response (CR/CRi), Median (range)	1.9 months (0.5-7.5)
Duration of response (CR/CRi), Median	8.2 months
Time to CR/CRi, Median (range)	3.7 months (0.6-11.2)

- Median follow up: 9.7 months (range 3.7-20.8)
- Discontinued enasidenib and went to HSCT: 17 (11%)
- ORR
  - IDH2-R172: 53.3%
  - IDH2-R140: 35.4%
- CR
  - IDH2-R172: 24.4%
  - IDH2-R140: 17.7%

Stein EM, et. al. Blood. 2017; 130(6):722-31

EFFICACY



Patients at risk:

CR	34	34	31	25	15	11	6	2	0	
Non-CR response	37	34	30	17	11	7	3	1	1	0
No response	97	68	43	20	10	3	1	0		

CR, complete remission

Stein EM, et. al. Blood. 2017; 130(6):722-31

Clinical Pearls: ENASIDENIB

- IDH-DS

Symptoms of IDH-DS	%
Acute respiratory distress represented by dyspnea and/or hypoxia	68
Pulmonary infiltrates	73
Pleural effusion	45
Renal impairment	70
Fever	36
Peripheral edema with rapid weight gain	21
Pericardial effusion	18

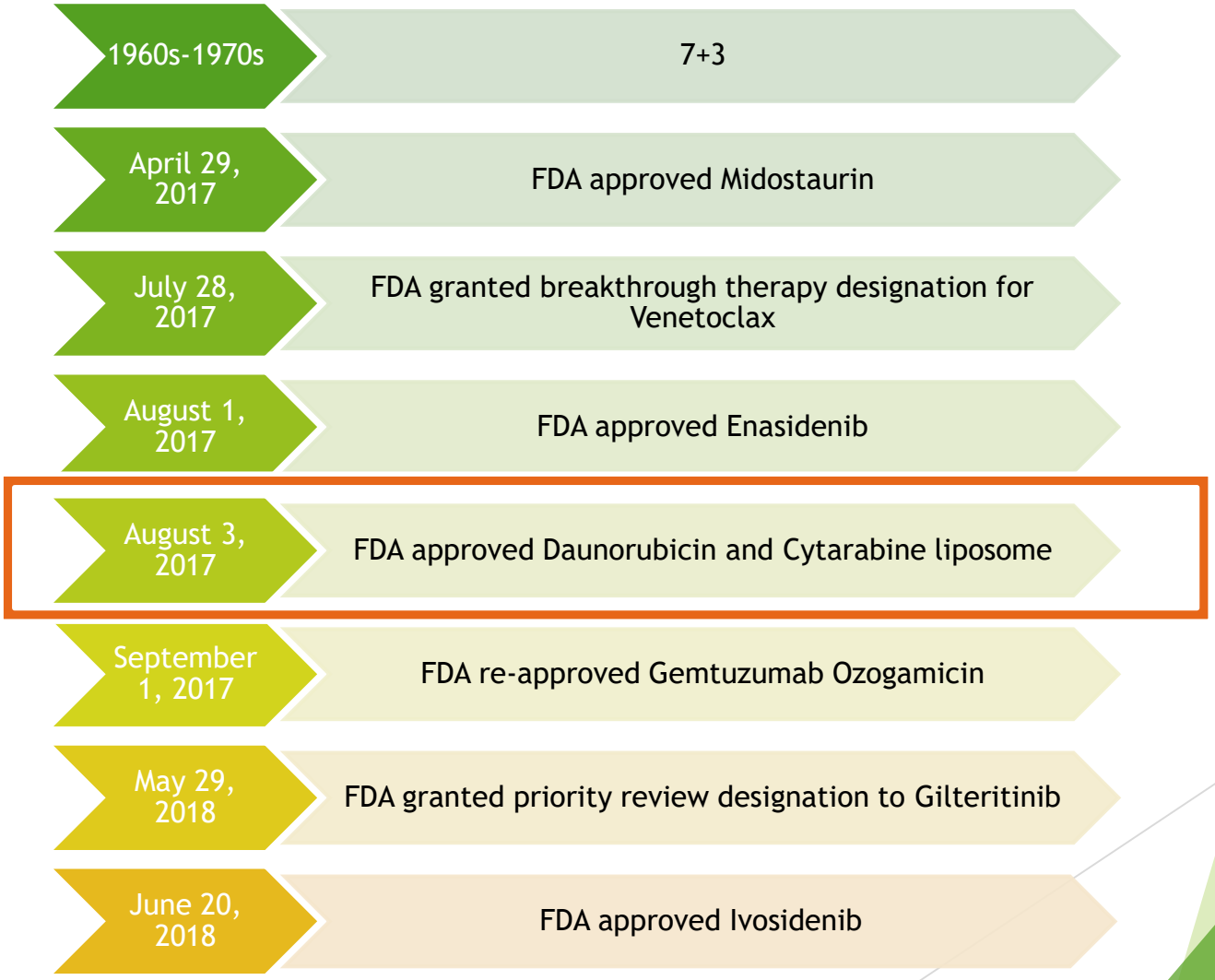
- Treatment
  - Dexamethasone 10mg BID
  - Hydroxyurea (>WBC 30 x 10^9/L)
  - Hold therapy if severe pulmonary/renal symptoms persist after initiating steroids or if leukocytosis is not resolved with hydroxyurea
- Moderate-High emetogenicity
  - May need to schedule anti-emetics
- Treat for minimum of 6 months
- Dose adjust for bilirubin >3x ULN – 50 mg daily
- $$COST$$
  - Check for co-pays with insurance companies
  - Celgene commercial co-pay program
    - $25 co-pay
  - Patient assistance program

Idhifa (enasidenib) [prescribing information]. Summit, NJ: Celgene Corporation; August 2017

SELF ASSESSMENT QUESTION 3

- 3. Patient DS is a 67 year old male who started on enasidenib 1 month ago for his relapsed AML. He presents today in clinic with complaints of fever, shortness of breath, and edema. Labs are obtained and you notice that his white blood cell count is elevated to 40,000 $x10^3$ u/L His chest X-ray is positive for a pleural effusion. Which of the following is <u>not</u> true regarding his therapy?
  - A. He is most likely experiencing symptoms of differentiation syndrome
  - B. He is most likely experiencing tumor lysis syndrome
  - C. Hydroxyurea should be used to cytoreduce this patient
  - D. Dexamethasone 10 mg twice daily should be initiated

AML Timeline



Wei AH, et. al. Blood. 2017. 30(23): 2469-2472

Daunorubicin and cytarabine liposome (CPX-351)

Mechanism	Combination product (daunorubicin and cytarabine) with fixed 1:5 molar ratio
Place in therapy	Adults with newly-diagnosed therapy related AML or AML with myelodysplasia-related changes
Dosing	**Dosed using daunorubicin component** Induction: 44 mg/m2 on days 1, 3, and 5 Consolidation: 29 mg/m2 on days 1 and 3
Cost (AWP)	100-44 mg vial (1): $9,300.00

Vyxeos (daunorubicin and cytarabine [liposomal]) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals Inc; August 2017

2016 WHO Classification

- AML with myelodysplasia-related changes
  - Morphologic detection of multilineage dysplasia (defined as the presence of >50% dysplastic cells in at least 2 cell lines)
  - A history of MDS
  - Presence of an MDS-related cytogenetic abnormality

Complex karyotype (3 or more abnormalities)	
Unbalanced abnormalities	**Balanced abnormalities**
-7del/(7q)	t(11;16)(q23.3;p13.3)
del(5q)/t(5q)	t(3;21)(q26.2;q22.1)
i(17q)/t(17p)	t(1;3)(p36.3;q21.2)
-13/del(13q)	t(2;11)(p21;q23.3)
del(11q)	t(5;12)(q32;p13.2)
del(12p)/t(12p)	t(5;7)(q32;q11.2)
idic(X)(q13)	t(5;17)(q32;p13.2)
	t(5;10)(q32;q21.2)
	t(3;5)(q25.3;q35.1)

  - Removed del(9q) because of association with NPM1 or biallelic CEBPA mutations and its apparent lack of prognostic significance in those settings

Arber D et al. Blood. 2016. 127(20): 2391-2405

SO…What is so unique about daunorubicin and cytarabine liposome (CPX-351)??

- "7+3" regimen represents a cytokinetically rational approach to combination chemotherapy
- Ratio of individual agents in a combination determines the nature of action
- Ratiometric approach aims at controlling drug ratios following systemic administration
- 100 nm bilamellar liposomal formulation of cytarabine and daunorubicin in a fixed 5:1 molar ratio
- Selectively ingested by leukemia cells providing enhanced efficacy and increased therapeutic index

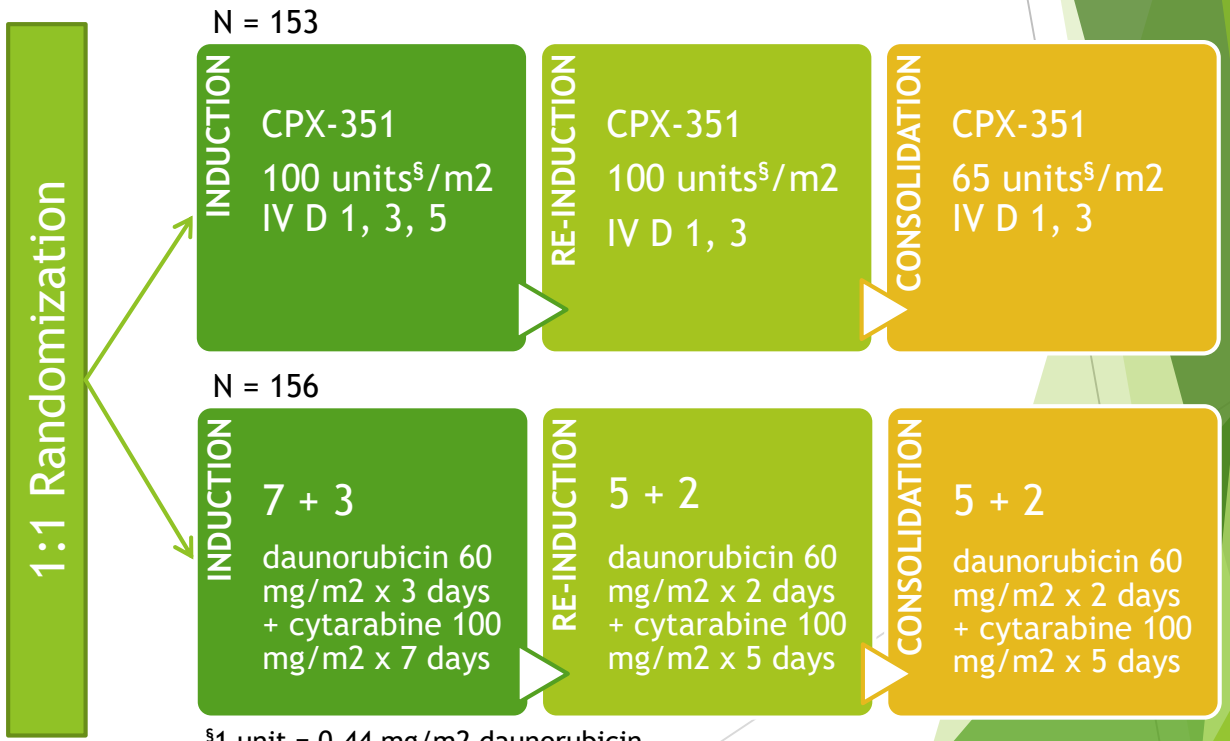
Raut LS. South Asian J Cancer. 2015. 4(1): 38–40.
Feldman EJ et al. J Clin Oncol. 2011. 10; 29(8): 979–985.

Phase III CPX-351 vs 7+3 in older patients with newly diagnosed high risk AML

Trial Design	Endpoints
Randomized, multicenter, open-label, active-controlled	Primary: OS Secondary: CR, EFS, CR+CRi, and 60-day mortality, remission duration, proportion receiving HSCT, ADEs

Eligibility:

- Adults 60-75 years of age
- Untreated AML with a history of prior cytotoxic treatment, antecedent MDS/CMML, or AML with MDS-related cytogenetic abnormalities
- ECOG 0-2
- Scr <2, Tbili <2, AST/ALT <3x ULN
- EF ≥ 50%



§1 unit = 0.44 mg/m2 daunorubicin

Lancet JE. J Clin Oncol. 2016 34:15_suppl, 7000-7000
Available at: https://clinicaltrials.gov/ct2/show/NCT01696084

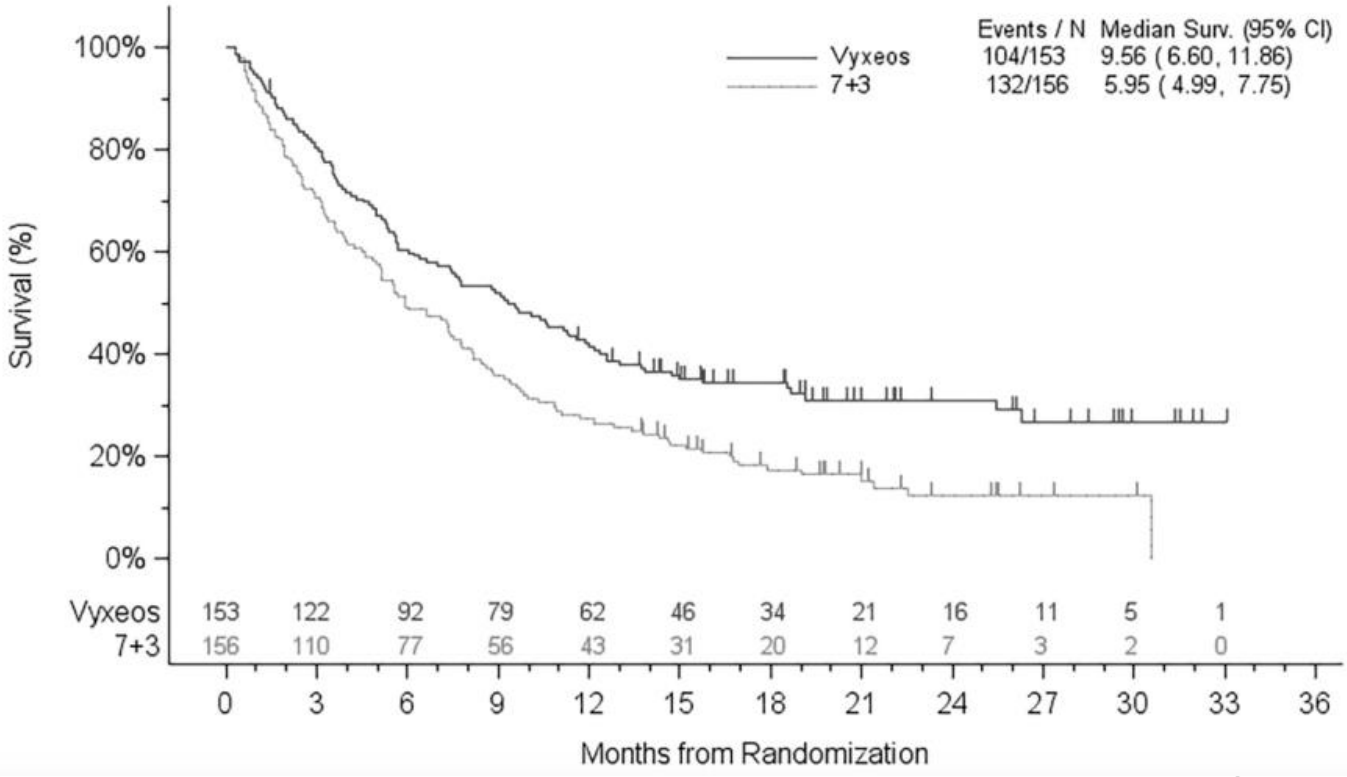
CPX351 vs 7+3: Results

Primary Outcome	CPX-351 (n=153)	7+3 (n=156)	HR	P-value
Median OS – mo. (95%CI)	9.56 (6.6, 11.9)	5.95 (5.0, 7.8)	0.69 (0.52, 0.9)	P=0.005

Secondary Outcomes	CPX-351 (n=153)	7+3 (n=156)	HR	P-value
CR – n(%)	58 (38)	41 (26)	---	P =0.036
60 day mortality – n(%)	21 (13.7)	32 (21.2)	---	---
Overall rate of HSCT – n(%)	52 (34)	39 (25)	---	---

Vyxeos (daunorubicin and cytarabine [liposomal]) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals Inc; August 2017
Lancet JE. J Clin Oncol. 2016 34:15_suppl, 7000-7000

Overall Survival, ITT Population



Vyxeos (daunorubicin and cytarabine [liposomal]) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals Inc; August 2017
Lancet JE. J Clin Oncol. 2016 34:15_suppl, 7000-7000

CPX-351: SAFETY

- Most common serious ADEs (≥ 5%): dyspnea, myocardial toxicity, sepsis, pneumonia, febrile neutropenia, bacteremia and hemorrhage
- Adverse reactions led to discontinuation in 18% (n=28) of CPX-351 patients and 13% (n=20) in the control arm
- Most common adverse reactions (≥ 25%): Hemorrhagic events, febrile neutropenia, rash, edema, nausea, mucositis, diarrhea, constipation, musculoskeletal pain, fatigue, abdominal pain, dyspnea, headache, cough, decreased appetite, arrhythmia, pneumonia, bacteremia, chills, sleep disorders, and vomiting
- Prolonged cytopenias:

	Induction 1		Consolidation	
	CPX-351 N=58 n(%)	7+3 N=34 n(%)	CPX-351 N=48 n(%)	5+2 N=32 n(%)
Prolonged thrombocytopenia*	16 (28)	4 (12)	12 (25)	5 (16)
Prolonged neutropenia*	10 (17)	1 (3)	5 (10)	1 (3)

*Platelets < 50 $x10^3/\mu L$ or neutrophils < 0.5 $x10^3/\mu L$ lasting past cycle day 42 in the absence of active leukemia

Vyxeos (daunorubicin and cytarabine [liposomal]) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals Inc; August 2017
Lancet JE. J Clin Oncol. 2016 34:15_suppl, 7000-7000

Clinical Pearls: VYXEOS®

- Dosed using the daunorubicin component – 44 mg/m2
  - 5mg/ml for the amount of cytarabine in the infusion
- PURPLE shimmery infusion
  - > 1 hour to prepare
- Nadir bone marrow evaluation days 14-21
- Prolonged cytopenias
  - Watch for bleeds and infectious complications
- Don't forget to check LVEF
- $$ COST $$
  - Inpatient vs outpatient administration
  - JumpStart program – reimbursement support

Vyxeos (daunorubicin and cytarabine [liposomal]) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals Inc; August 2017
Available at: https://vyxeospro.com/support-materials/

AML Timeline

1960s-1970s	7+3
April 29, 2017	FDA approved Midostaurin
July 28, 2017	FDA granted breakthrough therapy designation for Venetoclax
August 1, 2017	FDA approved Enasidenib
August 3, 2017	FDA approved Daunorubicin and Cytarabine liposome
September 1, 2017	FDA re-approved Gemtuzumab Ozogamicin
May 29, 2018	FDA granted priority review designation to Gilteritinib
June 20, 2018	FDA approved Ivosidenib

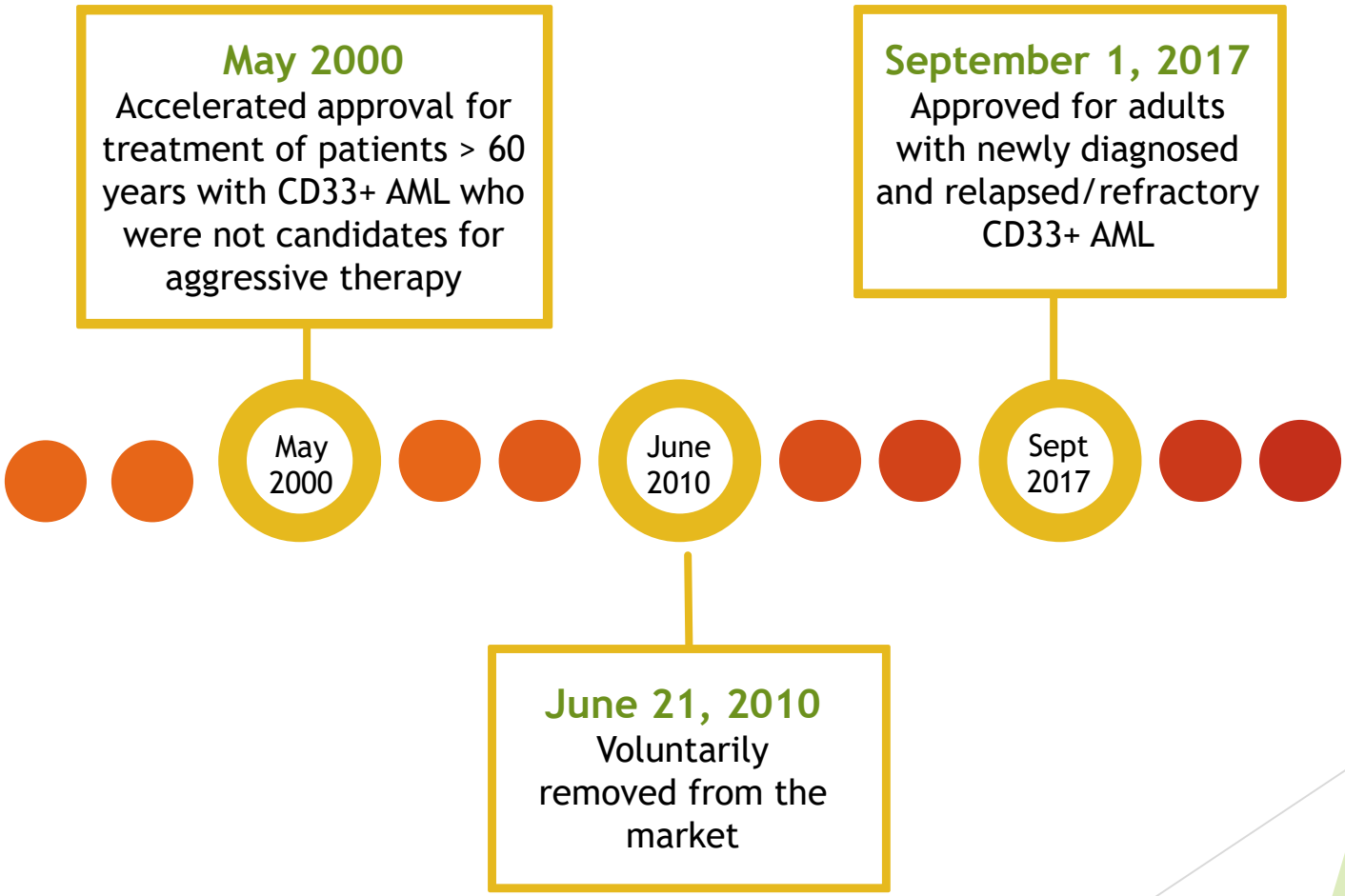
Wei AH, et. al. Blood. 2017. 30(23): 2469-2472

GEMTUZUMAB OZOGAMICIN

Mechanism	Humanized anti-CD33 monoclonal antibody conjugated with calicheamicin, a potent antitumor anthracycline antibiotic
Place in therapy	▪ Initial therapy as monotherapy or in combination with 7+3 ▪ Monotherapy in R/R CD33-positive AML
Dosing (R/R)	Induction: 3 mg/m2 (max 4.5 mg/dose) on days 1, 4, and 7 Consolidation: 3mg/m2 (max 4.5 mg/dose) on day 1
Cost (AWP)	4.5 mg vial: $9,840.0 → $29,520 per course (4.5 mg doses x3 doses)

Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; September 2017

History of GEMTUZUMAB OZOGAMICIN



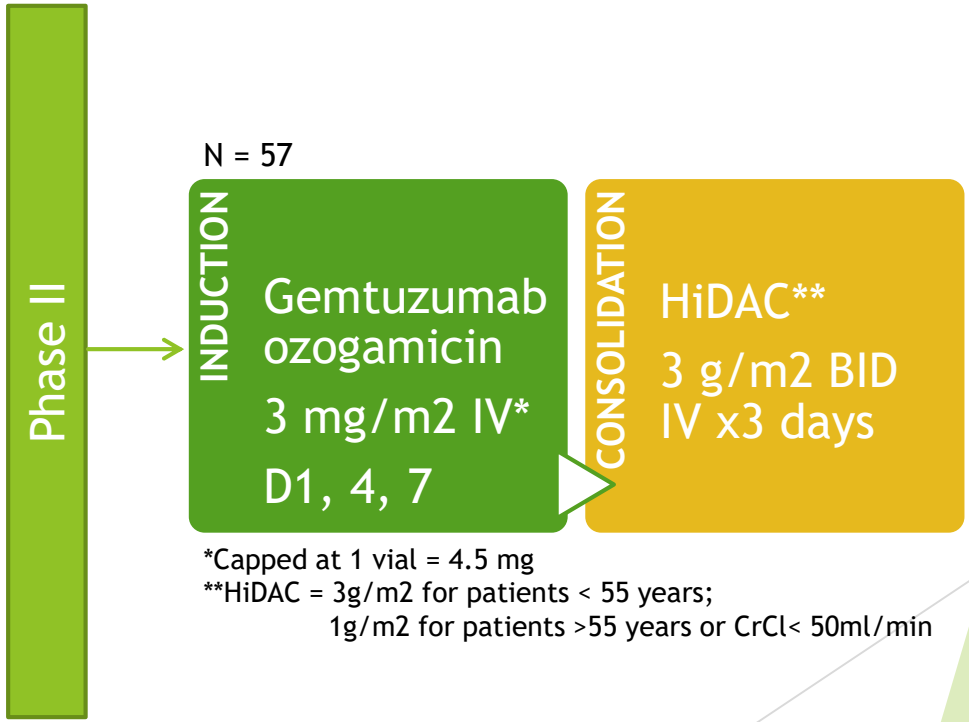
Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; September 2017

MyloFrance-1 Trial

Trial Design	Endpoints
Phase 2, single-arm, multicenter, open-label	CR, CRp, ORR, OS, cumulative incidence of relapse, relapse free survival, ADEs

Eligibility:

- Adults > 18 years of age
- CD33+ AML in first relapse
- First remission duration ≥ 3months and ≤ 18 months
- Without secondary leukemia or prior HSCT
- ECOG ≤ 2
- SCr <180/µL
- AST/ALT < 2x ULN



*Capped at 1 vial = 4.5 mg
**HiDAC = 3g/m2 for patients < 55 years;
1g/m2 for patients >55 years or CrCl< 50ml/min

Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; September 2017

Mylo-France-1 Trial: RESULTS

Efficacy Results	N=57
ORR, n(%)	19 (33.3)
CR, n(%)	15 (26)
CRp, n(%)	4 (7)
OS median	8.4 months
Cumulative incidence of relapse at 1 year	57.4%
Relapse Free Survival	11.6 months

Recovery	Median
ANC > 500/µl	23 days
Platelets >50,000/µL	20 days

ADEs (Grade 3 >1% patients)	
Sepsis	31.5%
Fever	15.8%
Rash	10.5%
Pneumonia	7%
Bleeding	7%
Mucositis	3.5%
Diarrhea	1.75%
Headaches	1.75%
Tachycardia	1.75%
Edema	1.75%

LIVER toxicities:
NO incidence of veno-occlusive disorder (VOD);
Grade 1 /2 hyperbilirubinemia (n=4), AST (n=23) and ALT (n=9) elevations

Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; September 2017

Clinical Pearls: GEMTUZUMAB OZOGAMICIN

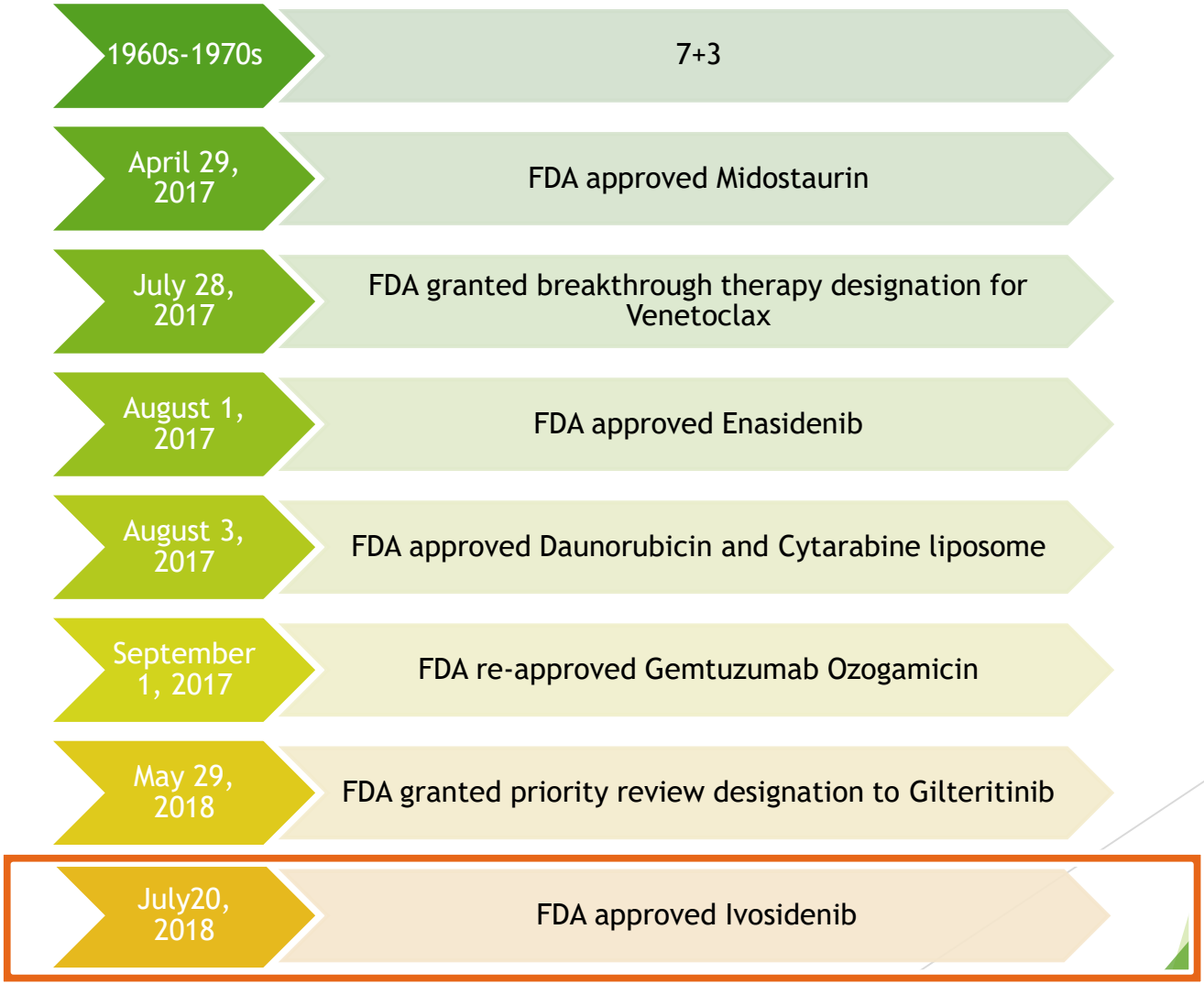
- Watch out for dosing and indication!
  - 3 different indications – all slightly different dosing
  - Place in therapy is still controversial (front line setting)
- Infusion reactions
  - Pre-medicate: Acetaminophen (1 hour before) + diphenhydramine (1 hour before) + corticosteroid (within 30 min of infusion)
  - If patient has a reaction, stop infusion, medicate, and when resolved, initiate at half the rate
- VOD [BOXED WARNING]?
  - Discontinue therapy!
- Prepare the drug **IN THE DARK**
  - Protect the bag from light (but not the line)

Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; September 2017

SELF ASSESSMENT QUESTION 4

- 4. Which of the following medications was FDA approved in 2017 and 2018 for the treatment of AML that is considered “first in class”?
  - A. Sorafenib
  - B. Enasidenib
  - C. Gilteritinib
  - D. Crenolanib

AML Timeline



Wei AH, et. al. Blood. 2017. 30(23): 2469-2472

IVOSIDENIB

Mechanism	Small molecule inhibitor of the IDH1 enzyme
Place in therapy	Treatment of adult patients with relapsed or refractory (R/R) AML with an IDH1 mutation
Dosing	500 mg PO daily until disease progression
Metabolism	Primarily metabolized by CYP3A4
Cost (AWP)	N/A (250 mg tablets)

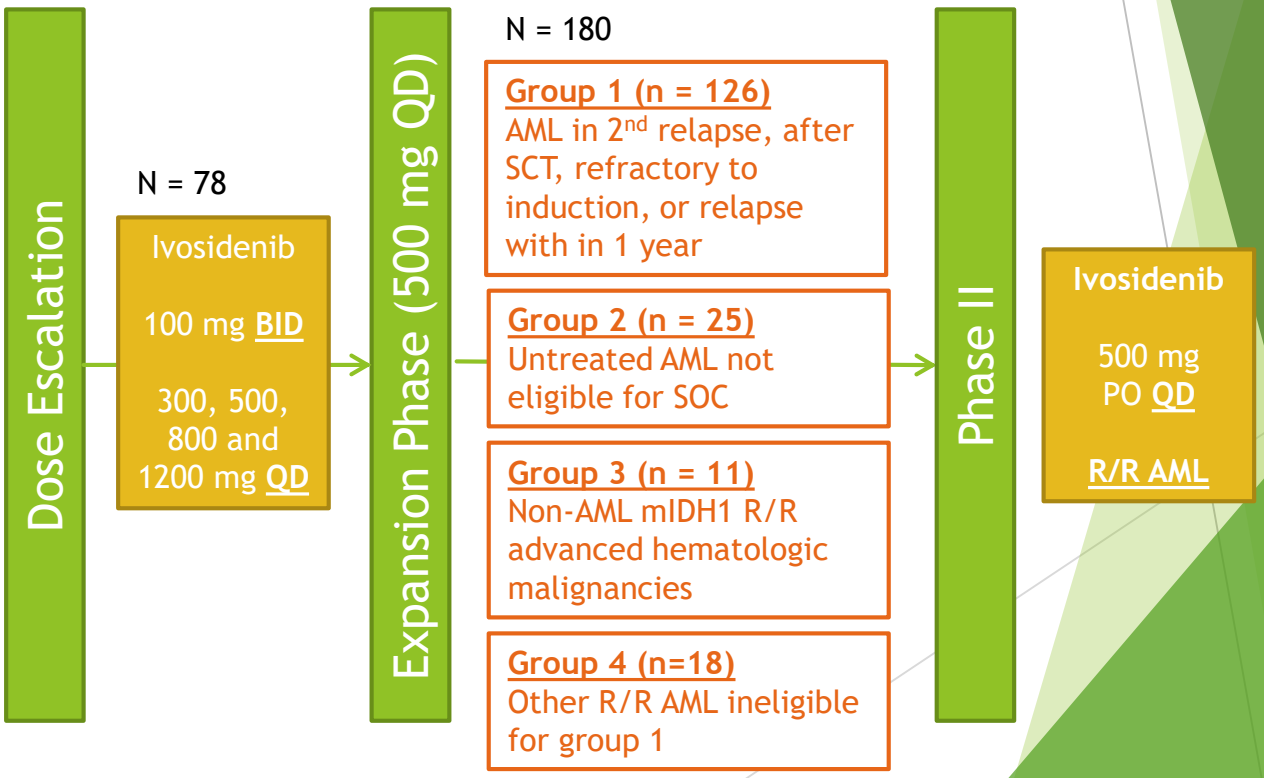
Tibsovo (ivosidenib) [prescribing information]. Cambridge, MA: Agios Pharmaceuticals, Inc.; July 2018

Ivosidenib in Mutant-IDH1 R/R AML

Trial Design	Endpoints
Multi-center, phase 1 dose-escalation and dose-expansion study	Primary: Safety and MTD and recommended phase 2 dose and to assess clinical activity in R/R patients who received 500 mg QD dosing Secondary: PK/PD and clinical activity in others

Eligibility:

- ≥ 18 years of age
- Confirmed mutant- IDH1 advanced myeloid malignancies (AML/MDS)
- ECOG 0-2
- Tbili ≤ 1.5 x ULN; AST/AST ≤ 3x ULN
- SCr ≤ 2 x ULN or CrCl ≥ 40 mL/min



NiDardo CD, et. al. N Engl J Med. 2018; 378:2386-2398

EFFICACY

Outcomes for R/R AML	500 mg QD (n=179)
ORR, n(%)	70 (39.1)
Best Response	
CR, n(%)	39 (21.9)
CRi, n(%)	21 (11.7)
PR, n(%)	0 (0)
Morphologic leukemia-free, n(%)	10 (5.6)
Stable disease, n(%)	69 (38.5)
Time to first response (CR/CRi), Median (range)	1.9 months (0.8-4.7)
Duration of response (CR/CRi), median	6.5 months
Time to CR/CRi, median Range	2 months (0.9-5.6)

- Median follow up: 14.8 months (range 0.2-30.3)
- Median OS: 8.8 months
  - No response : 3.9 months
- 18 month survival rate (CR/CRi): 50.1%

NiDardo CD, et. al. N Engl J Med. 2018; 378:2386-2398

SAFETY

Common ADEs (≥20% of patients) n (%)	Ivosidenib 500 mg QD (n=179)
Diarrhea	55 (30.7)
Leukocytosis	53 (29.6)
Febrile neutropenia	51 (28.5)
Nausea	50 (27.9)
Fatigue	46 (25.7)
Dyspnea	44 (24.6)
QT prolongation	44 (24.6)
Peripheral edema	39 (21.8)
Anemia	39 (21.8)
Pyrexia	38 (21.2)
Cough	37 (20.7)

- Ivosidenib was generally well-tolerated but nearly all (98.9%) experienced ADEs
- Ivosidenib-related grade 3-4 ADEs occurred in 37 patients (20.7%)
  - QTc prolongation was highest (7.8%)
- IDH-DS occurred in 29 (11.2%) patients
  - Median time to onset: 29 days (range: 5 to 59)
  - No discontinuations or dose reductions due to IDH-DS

NiDardo CD, et. al. N Engl J Med. 2018; 378:2386-2398

Clinical Pearls: IVOSIDENIB

- Moderate-High emetogenicity
  - May need to schedule anti-emetics
- Do not administer with a high-fat meal
- WATCH FOR DDIs!!!
  - QTc prolongation:
    - Avoid concomitant use; if not possible monitor closely
    - If >500 msec, hold therapy. Resume with reduced dose of 250 mg when QTc returns to within 30 msec of baseline or ≤ 480 msec
  - CYP3A4:
    - Strong or moderate inhibitors: consider alternative therapies
      - If STRONG inhibitor is unavoidable, reduce dose to 250 mg once daily
    - Strong inducers: avoid use
    - Substrates: consider alternative therapies
      - An inducer of CYP3A4 and 2C9 – watch out for use with CYP3A4/2C9 substrates
  - Treat for a minimum of 6 months

Tibsovo (ivosidenib) [prescribing information]. Cambridge, MA: Agios Pharmaceuticals, Inc.; July 2018

NEW KIDS ON THE BLOCK
– AML version -

FLT-3 +

- Midostaurin
- First in class FLT-3 inhibitor
- Newly diagnosed AML

IDH1/2 mutated

- Enasidenib (IDH2)
- Ivosidenib(IDH1)
- First in class IDH1 and IDH2 inhibitor
- R/R AML

High Risk

- Daunorubicin + Cytarabine liposome
- Optimize “7+3”
- 5:1 molar ratio
- Newly diagnosed AML

CD33 +

- Gemtuzumab ozogamicin
- Welcome back!
- First line and R/R AML

NEW THERAPIES IN ACUTE MYELOID LEUKEMIA (AML)

Maho Hibino, PharmD, BCOP

Oncology Clinical Specialist

Wake Forest Baptist Health

August 3, 2018