Updates in the Management of Acute Myeloid Leukemia

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2017 TOPA Conference

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I have no conflicts of interest with relation to the content of this presentation

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Objectives

- Describe mechanism of action of novel agents in treatment of AML
- Discuss data and place in therapy for newly approved agents
- Review recent data regarding dosing and scheduling of standard of care regimens

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Audience Participation

How many agents have been approved for AML treatment this year?

A. One
B. Two
C. Three
D. Four

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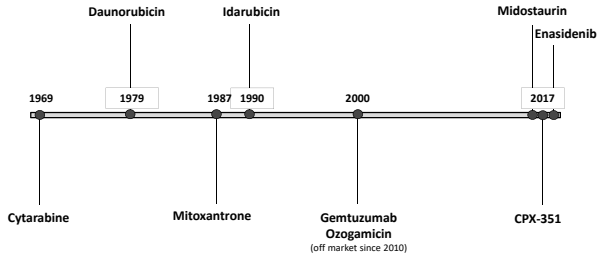
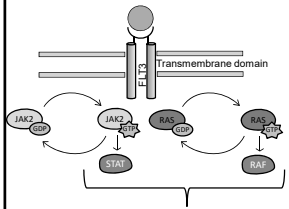
Timeline of Approved Drugs for AML



FLT-3 Mutation in AML



- Present in ~20-30% of all AML
- FLT3-ITD associated with high-risk disease
- FLT3-TKD has unclear prognostic significance
- **Midostaurin (Rydapt)** inhibits multiple kinases including mutated FLT3 (ITD and TKD)

Survival and uncontrolled proliferation

Hassanein M, et al. *Clinical Lymphoma, Myeloma & Leukemia 2016*. 16(10):543-9.

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RATIFY trial

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Induction (1-2 cycles) | Consolidation | Maintenance

Patient with treatment naïve FLT3-mutated AML Age 18-60 yo (N=717)

- 7+3* + Midostaurin (n = 360) → HIDAC + Midostaurin (n = 231) → Midostaurin For 12 cycles (n = 120)
- 7+3* + Placebo (n = 357) → HIDAC + Placebo (n = 210) → Placebo (n = 85)

*daunorubicin 60 mg/m2 and cytarabine 200 mg/m2

Phase III randomized double blind trial

Baseline Characteristic	Midostaurin	Placebo	P
Age, median (range)	47.1 (19-60.9)	48.6 (19-59.8)	0.22
Subtype of FLT3			1.00
TKD n(%)	84 (22.5)	81 (22.7)	
ITD, n(%)	279 (77.5)	276 (77.3)	

Grade III-V AEs	Midostaurin n(%)	Placebo n(%)	P
Rash or desquamation	50 (14)	27 (8)	0.008
Anemia	329 (93)	311 (88)	0.03
Nausea	20 (6)	34 (10)	0.05

Stone RM, et al. NEJM 2017. 377:454-64.

RATIFY trial

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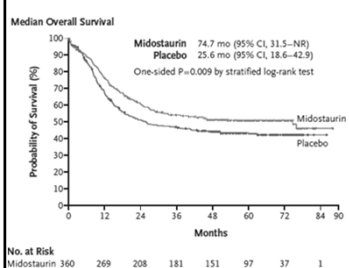

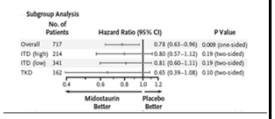

Midostaurin (Rydapt) Quick Facts

Administration	50 mg (2 tablets) twice daily Day 8 through 21 with meal
Metabolism	CYP3A4
Drug interactions	Azole antifungals*
Additional kinases inhibited	KIT (WT and D816V mutant) PDGFRα/β VEGFR2 Protein kinase C family
Renal/Hepatic impairment	safe in T. bili < 3x ULN & CrCL > 30 ml/min

*Thought to contribute to grade IV pulmonary edema and infiltrates in 2 patients leading to death and subsequently prohibited

Stone RM, et al. NEJM 2017. 377:454-64.
Stone RM, et al. NEJM 2017. CALGB 10603 Protocol

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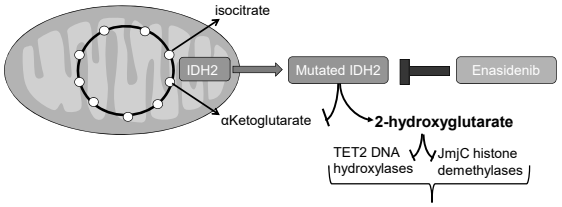
IDH-2 mutations in AML



Block in cellular differentiation and progression to leukemia

Cantor JR, et al. *Cancer Discovery, 2012.*
http://cancerdiscovery.aacrjournals.org/content/2/10/881

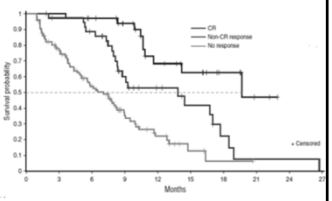
Enasidenib in R/R AML

Patients with Relapse/Refractory mutant-IDH2 AML/MDS aged ≥18 yrs and ECOG 0-2 (N = 176) → **Enasidenib once daily Expansion cohort – 100 mg daily** (n = 109)

Phase I/II open label dose escalation study

	Expansion cohort (n=109)	All doses (n=176)
ORR[1]	42 (38.5)	71 (40.3)
CR[1]	22 (20.2)	34 (19.3)
CRi[1]	7 (6.4)	12 (6.8)
PR[1]	3 (2.8)	11 (6.3)
Time to CR[2]	3.7 (0.7-11.2)	1.9 (0.5-9.4)
DoR in patients attaining CR[2]	8.8 (5.3 – NR)	8.8 (6.4-NR)

[1]n (%), [2]median mo. (range)



Stein, et al. *Blood, 2017.*130(6):722-731.

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Enasidenib (Inhifa) in R/R AML

Adverse Events Grade III or IV n(%)	100 mg daily (n=153)
Hyperbilirubinemia	13 (8)
IDH Differentiation syndrome	11 (7)
Anemia	10 (7)
Thrombocytopenia	8 (5)

Enasidenib Quick Facts

Approval	Mutations detected with FDA approved Abbott assay
Administration	100 mg (2 tablets) daily
Metabolism	Inhibits various CYP enzymes and UGT1A1
DDI	Contraception
Hepatic impairment	50 mg daily if T.bili > 3xULN for 2 wks w/o AST/ALT elevation

Differentiation Syndrome (DS)

- Occurs later that ATRA-DS (3-4 mo post start)
- Associated with the following:
  - New/worsening progressive dyspnea
  - Increasing O_2 demands
  - Radiologic evidence of new or worsened bilateral pulmonary involvement
  - peripheral edema, with rapid weight gain
  - ↑Serum Creatinine
  - Rash
- **Recommendation for DS Management**
  - Start corticosteroids
  - Interrupt enasidenib is severe pulmonary symptoms and/or renal dysfunction for > 48 hours of treatment with steroids

Stein, et al. *Blood, 2017.*130(6):722-731.

CPX-351 (Vyxeos)

- Based on concept of rate dependent synergistic antitumor activity
- 100-nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- Dosing & Frequency:
  - Induction: dauno 44 mg/m^2 & Ara-C 100 mg/m^2
  - Consolidation: dauno 29 mg/m^2 & Ara-C 65 mg/m^2

Vyxeos [package insert]. Jazz Pharmaceuticals, Palo Alto, CA.2017

CPX-351 in Treatment Related AML

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Patient with treatment naïve Treatment related or AML-MRC Age 60-75 yo (N=309)

INDUCTION (1-2 cycles)	Consolidation (1-2 cycles)
CPX-351 D1,3,5 Re-induction: CPX-351 D1&3 (n = 153)	**CPX-351 D1 & 3** (n=49)
7+3* Re-induction: 5+2 (n = 156)	**5+2** (n=33)

*daunorubicin 60 mg/m2 and cytarabine 100 mg/m2

Phase III open label

Baseline Characteristics	Overall N (%)
Median age, yr	68 (60-75)
ECOG PS 0-1	172 (88)
Treatment related AML	62 (20)
Antecedent heme disorder	166 (54)
MR cytogetenic abnormalities	77 (25)

Lancet JE, et al. ASCO 2016. Abstract 7000. Vyxeos (package insert). Jazz Pharmaceuticals. 2017

CPX-351 in Treatment Related AML

Response	CPX-351	7+3	P
OS[1]	9.56 (6.6 – 11.86)	5.95 (4.99-7.75)	0.005
EFS[1]	2.53 (2.07-4.99)	1.31 (1.08-1.64)	0.021
CR +CRi	47.7 %	33.3 %	0.016

[1]median (95% CI)

Adverse Events	CPX-351 n (%)	7+3 n (%)
Febrile Neutropenia	104 (68%)	107 (71)
Hypertension	16 (10%)	8 (5%)
Bacteremia	15 (10%)	3 (2%)
Decreased EF	8 (5%)	8 (5%)

OS post-HCT CPX-351 (n = 52) vs 7+3 (n = 39): NR vs 10.25 mos (HR: 0.46; 95% CI: 6.21-16.69; *P* = .0046)

Things to Consider:
- Less patients in control arm received consolidation (33 vs. 21%)
- HSCT in CR1 was higher in CPX-351 arm (20% vs. 12%)
- Overall rate of HSCT was higher in CPX-351 arm (34% vs. 25%)
- Non-tradiational consolidation strategy

Venetoclax

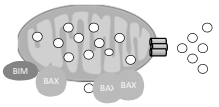
Stress signaling in BCL-2 overexpressing cells

Apoptosis blockade via BAX/BAK inhibition → Cell survival

Effect of Venetoclax (BH3 mimetic)

inhibition

BAX/BAK released →



Caspase mediated cell death

Anderson et al. *Semin Hematol*, 2014. 51:219-227.
Modified from CCO Oncology

Venetoclax +Ara-C in untreated AML

Pts ≥ 65 yrs of age with untreated AML, ineligible for standard induction tx, no active CNS involvement

Phase I (3+3 design)

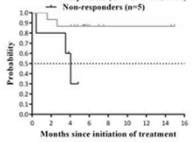
VEN + Ara-C*
600-mg VEN, n = 8;
800-mg VEN,* n = 10

Phase II

VEN + Ara-C*
(N = 53)
All pts, 600-mg VEN

*Ara-C = 20mg/m^2 D1-10 SQ every 28 days

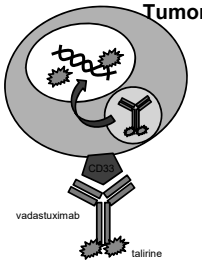
Figure 1. Overall survival in responders vs. non-responders



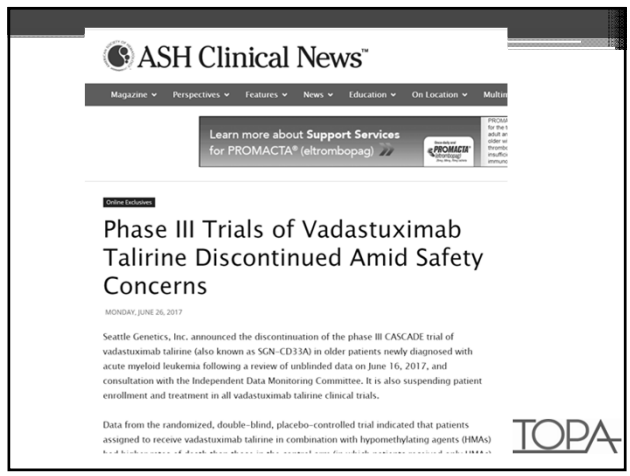
Response	Ven 600 mg n(%)
CR	21
CRi	33
CR + CRi*	54
PR	7
ORR (CR + CRi + PR)	61
Resistant/progressive disease	38

Wei AH, et al. ASH 2016. Abstract 387.

Vadastuximab talirine (SGN-CD33)



- Combination w HMA (ASH Abstract 592)
- Combination w 7+3 (ASH Abstract 211)
- Monotherapy in elderly (ASH Abstract 591)



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Phase III Trials of Vadastuximab Talirine Discontinued Amid Safety Concerns

MONDAY, JUNE 26, 2017

Seattle Genetics, Inc. announced the discontinuation of the phase III CASCADE trial of vadastuximab talirine (also known as SGN-CD33A) in older patients newly diagnosed with acute myeloid leukemia following a review of unblinded data on June 16, 2017, and consultation with the Independent Data Monitoring Committee. It is also suspending patient enrollment and treatment in all vadastuximab talirine clinical trials.

Data from the randomized, double-blind, placebo-controlled trial indicated that patients assigned to receive vadastuximab talirine in combination with hypomethylating agents (HMAs)

Daunorubicin vs. Idarubicin

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Patient with treatment naïve AML receiving 7+3 induction
Age 15-65 yo
(N=299)

- **Idarubicin 12 mg/m²** Cytarabine 200 mg/m² (n = 149)
- **Daunorubicin 90 mg/m²** Cytarabine 200 mg/m² (n = 150)

Phase III randomized open label non-inferiority of AD vs. AI

Baseline Characteristic	AI n (%)	AD n (%)	P
Leukemia			0.035
De Novo	142 (95.3)	133 (88.7)	
Secondary	7 (4.7)	17 (11.3)	
Cytogenetic Risk			0.004
Good	27 (18.6)	35 (23.5)	
Intermediate	97 (66.9)	73 (49.0)	
Poor	21 (14.5)	41 (27.5)	
FLT3-ITD	27 (20.9)	17 (13.5)	0.116

Outcomes	AI n (%)	AD n (%)	P
CR 1st cycle	106 (71.7)	100(66.7)	0.403
Overall CR	120 (77.6)	112 (74.7)	0.224
4yr OS	51.1%	54.7%	0.756
4yr EFS	45.5%	50.8%	0.772

Lee JH et al. J Clin Oncol, 2017. 35(24):2754-2762

AD vs. AI in FLT3-ITD Subgroup

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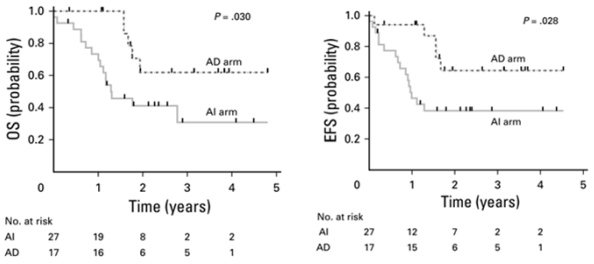
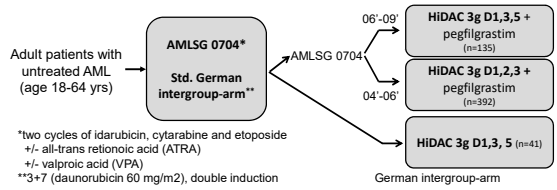


Lee JH et al. J Clin Oncol, 2017. 35(24):2754-2762

Condensed vs. Standard HiDAC

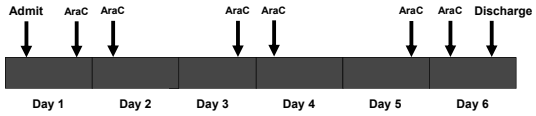


*two cycles of idarubicin, cytarabine and etoposide
+/- all-trans retionoic acid (ATRA)
+/- valproic acid (VPA)
**3+7 (daunorubicin 60 mg/m2), double induction

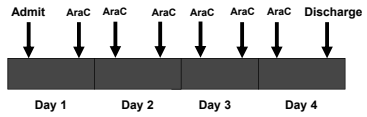
Büchner et al. J Clin Oncol. 2012;30:3604-10, NCT00151242
Jaramillo. ASH 2016 Abstract 337

Standard vs. Revised Consolidation

Standard HDAC



HDAC-123



Jaramillo. ASH 2016 Abstract 337

Outcomes

Outcomes	D1,2,3 vs. D1,3,5
Hematologic recovery	Condensed regimen: 4 days shorter (p<0.0001) Pegfilgrastim addition: 2 day further reduction (p< 0.0001)
Rate of infections	Condensed regimen lower: P<0.0001 Pegfilgrastim addition lower (p=0.002)
Days in hospital and PLT transfusions	Significantly lower (per authors)
OS and RFS	No difference (p=0.48 and p=0.90 respectively)

Jaramillo. ASH 2016 Abstract 337

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Summary of Developments in AML

- New standard of care regimen for FLT3 mutated AML
- Several new options in R/R disease
  - Enasidenib (FDA approved)
  - Venetoclax (FDA Breakthrough designation)
- New ways of dosing and scheduling chemotherapeutics
  - Daunorubicin dosing in FLT3 positive AML
  - Condensed HIDAC

In the pipeline…

- Gemtuzumab ozogamicin comeback
  - 5-trial meta-analysis demonstrating GO addition benefit
  - OS benefit in patients > 60yo not eligible for intensive regimens
- Ivosidenib (IDH-1 inhibitor)
  - Ongoing trials in combination and monotherapy
- Venetoclax (BCL-2 inhibitor)
  - Ongoing trials in combination and monotherapy
- CD-33 directed CAR-T cell therapy

Hills RK, et al. Lancet Oncol. 2014
Amadori S, et al. J Clin Oncol. 2016

Updates in the Management of Acute Myeloid Leukemia

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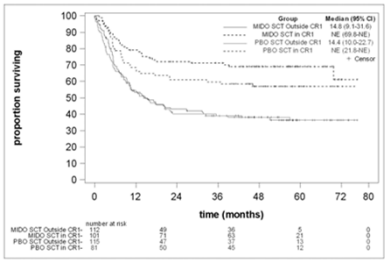
RATIFY trial – Supplementary Appendix

FIGURE S3A. Post-transplant Kaplan-Meier survival curves by arm and timing of transplant.

MIDO vs PBO in CR1: Stratified on *FLT3* subtype, two-sided log-rank p=0.07

MIDO vs PBO outside CR1: Stratified on *FLT3* subtype, two-sided log-rank p=0.85



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Median survival times in months. CI=confidence interval.