

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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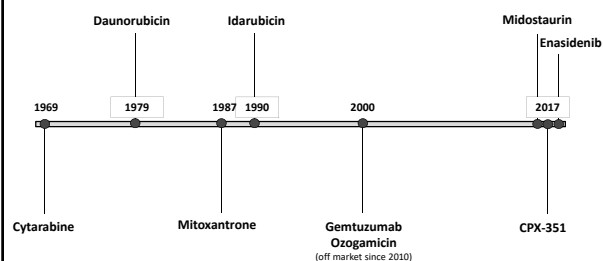
Audience Participation

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

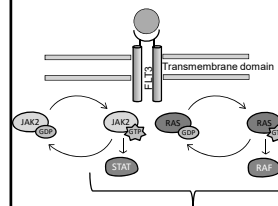
- A. One
B. Two
C. Three
D. Four

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Timeline of Approved Drugs for AML



FLT-3 Mutation in AML

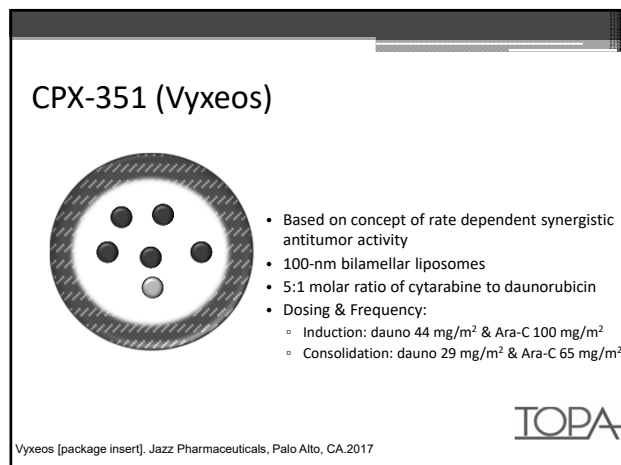
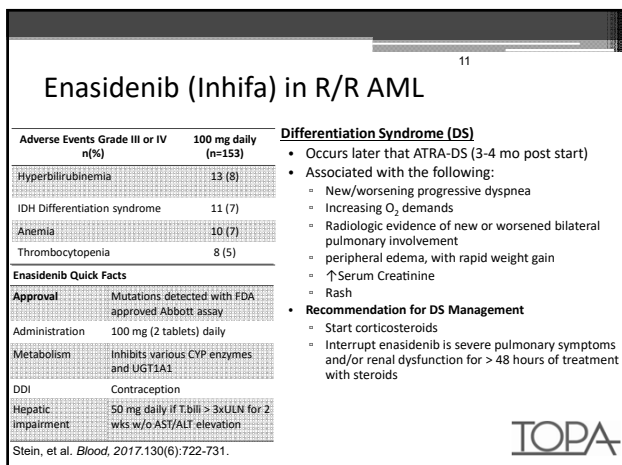
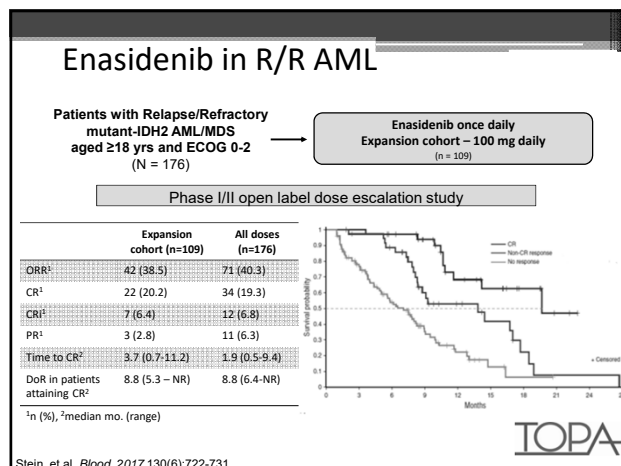
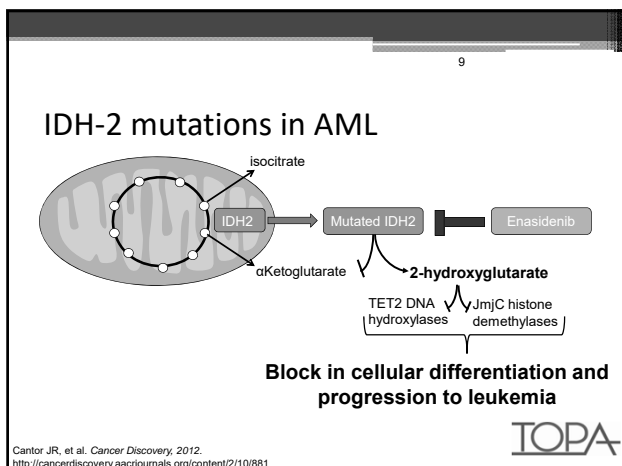
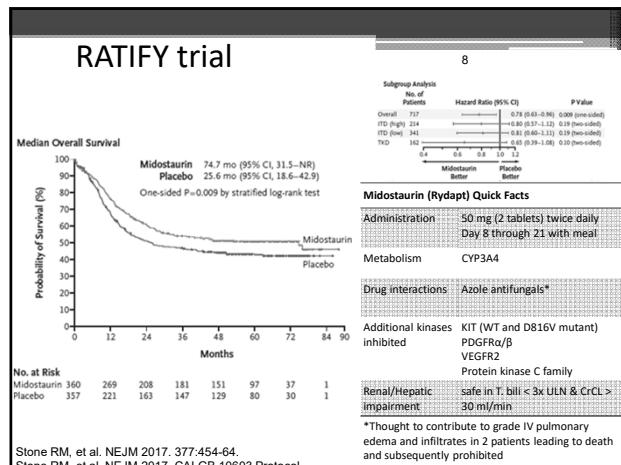
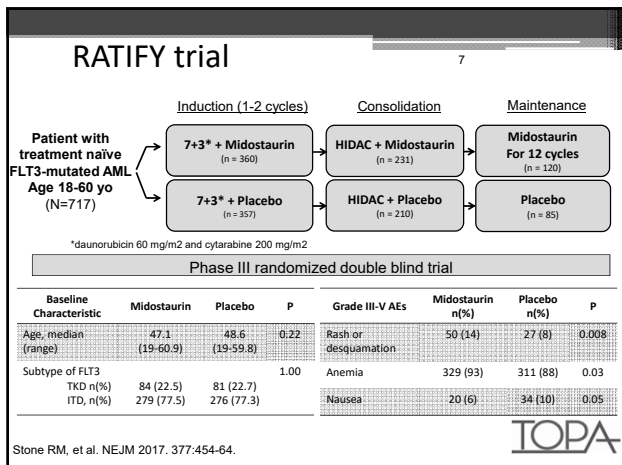


- Present in ~20-30% of all AML
- FLT3-ITD associated with high-risk disease
- FLT3-TKD has unclear prognostic significance
- **Midostaurin (Rydapt)** inhibits multiple kinases including mutated FLT3 (ITD and TKD)

Survival and uncontrolled proliferation

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

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CPX-351 in Treatment Related AML

13

Patient with treatment naïve Treatment related or AML-MRC Age 60-75 yo (N=309)
 *daunorubicin 60 mg/m2 and cytarabine 100 mg/m2

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

Consolidation (1-2 cycles)
 CPX-351 D1 & 3 (n=49)
 5+2 (n=33)

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 cytogenetic abnormalities	77 (25)

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

CPX-351 in Treatment Related AML

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

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

*median (95% CI)

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-traditional consolidation strategy

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Venetoclax

Stress signaling in BCL-2 overexpressing cells

BCL-2 → Apoptosis blockade via BAX/BAK inhibition → Cell survival

Effect of Venetoclax (BH3 mimetic)

BCL-2 → BAX/BAK released → Caspase mediated cell death

inhibition

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

Venetoclax +Ara-C in untreated AML

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/m² D1-10 SQ every 28 days

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

Probability

Months since initiation of treatment

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

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

Vadastuximab talirine (SGN-CD33)

Tumor Cell

vadastuximab

talirine

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

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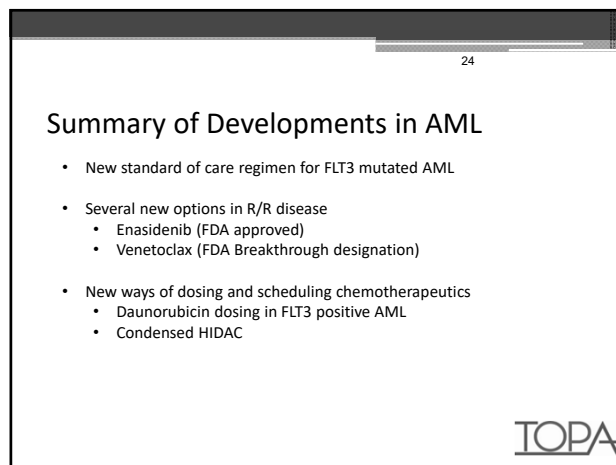
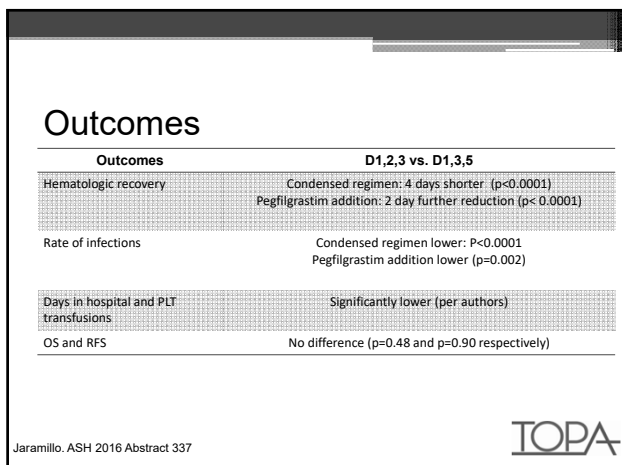
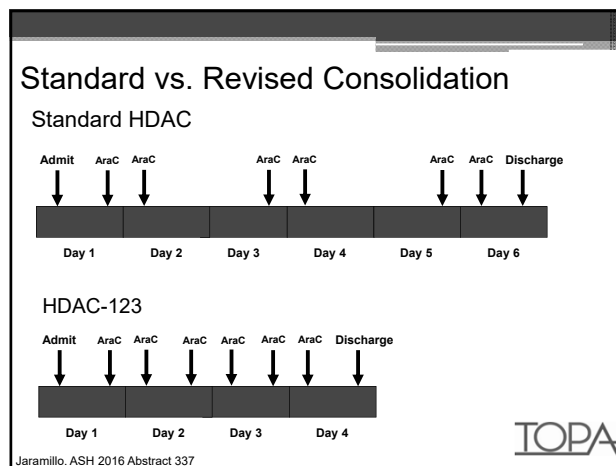
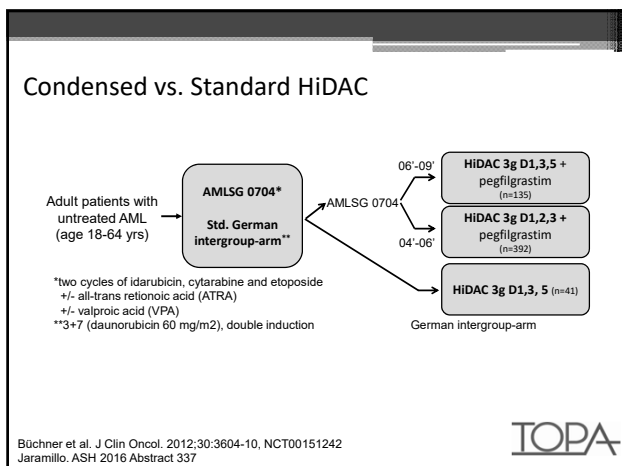
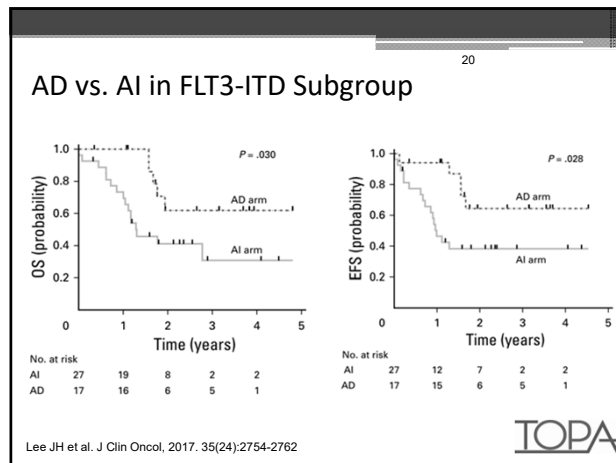
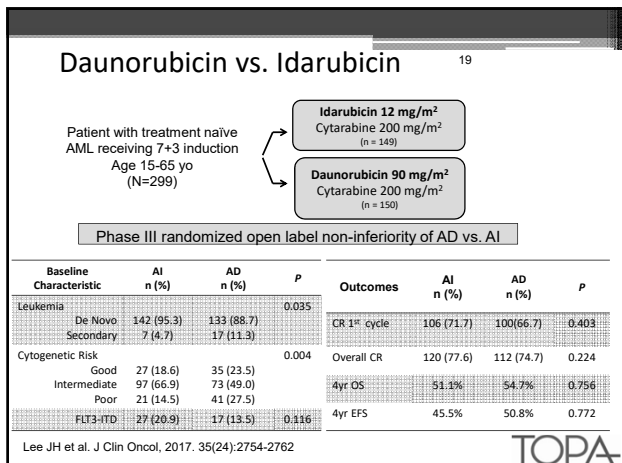
Phase III Trials of Vadastuximab Talirine Discontinued Amid Safety Concerns

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)

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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

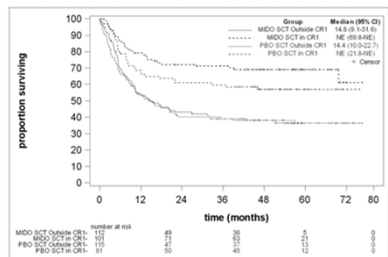
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RATIFY trial – Supplementary Appendix

FIGURE S3A. Post-transplant Kaplan-Meier survival curves by arm and timing of transplant.
 MDO vs PBO in CR1: Stratified on FLT3 subtype, two-sided log-rank p=0.07
 MDO vs PBO outside CR1: Stratified on FLT3 subtype, two-sided log-rank p=0.85



Median survival times in months. CI=confidence interval.

