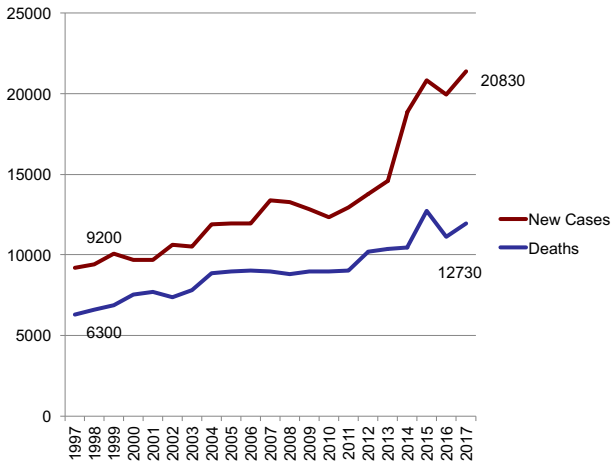
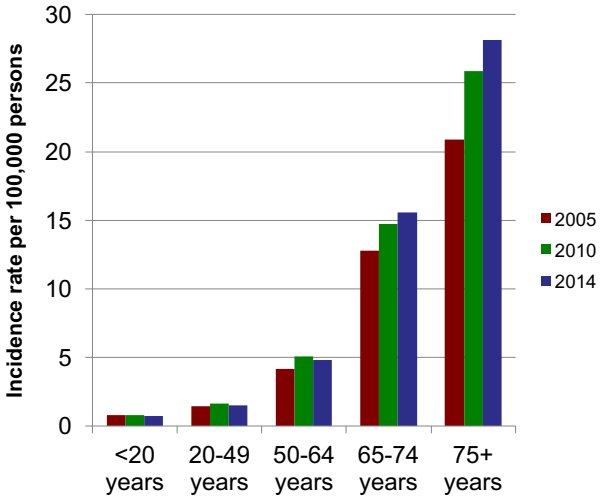
Acute Myeloid Leukemia
Progress at last

Bruno C. Medeiros, MD
September 9, 2017

- Introduction
- Mechanisms of leukemogenesis
- Emerging therapies in AML
  - Previously untreated AML
  - Relapsed and refractory patients

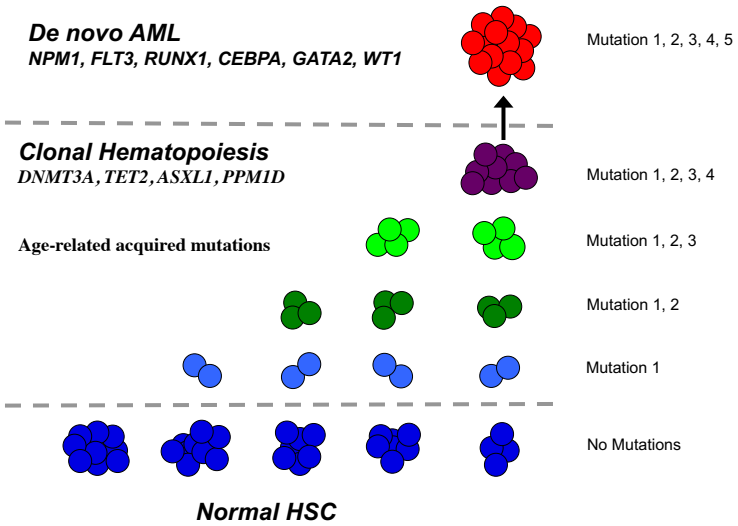
AML - Age Specific Incidence Rates in the U.S.

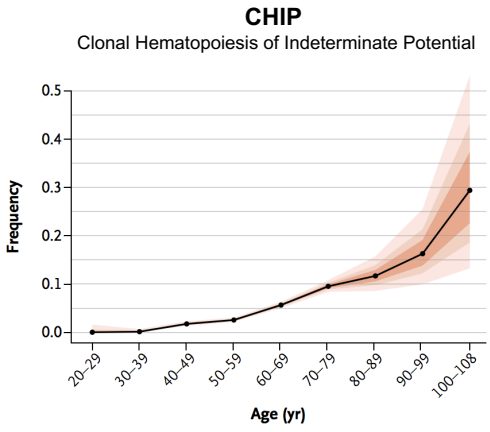




Sources: Cancer Facts & Figures 2013; American Cancer Society; 2013; http://seer.cancer.gov/faststats/; http://globocan.iarc.fr

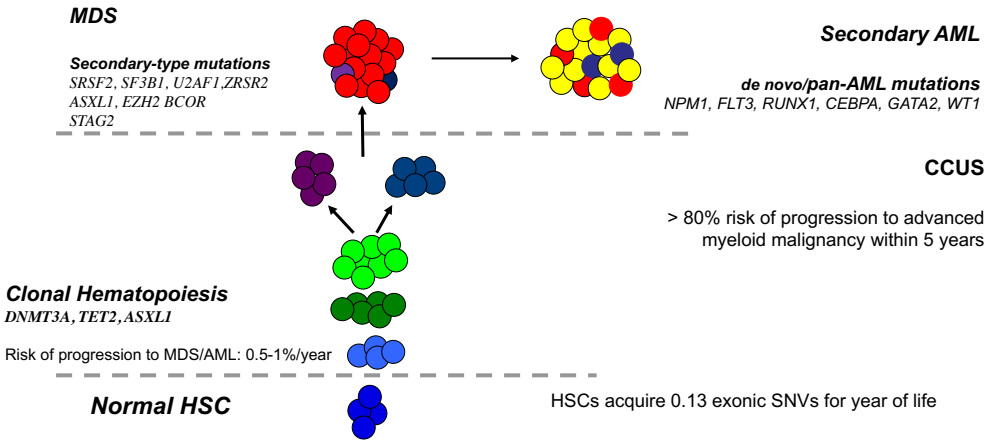
Model for the Clonal Evolution of HSC into Myeloid Malignancies





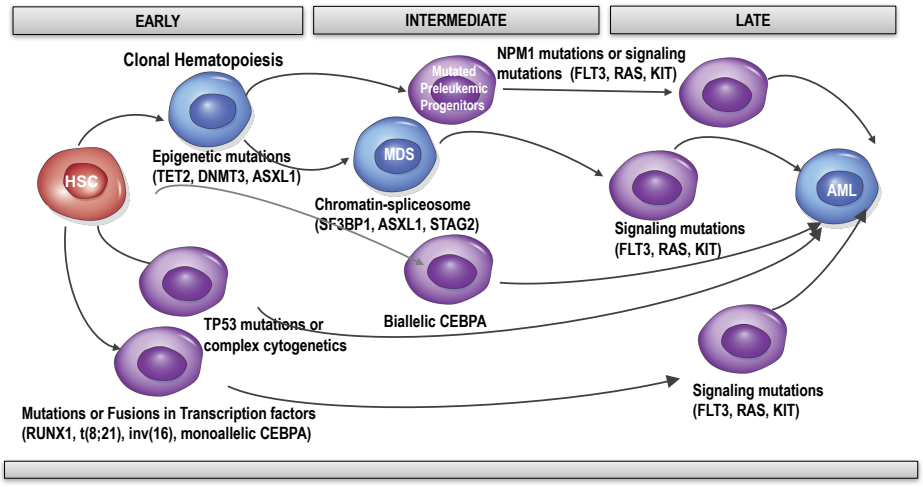
Jaiswal S et al. N Engl J Med 2014;371:2488-98.

Model for Clonal Evolution in secondary AML



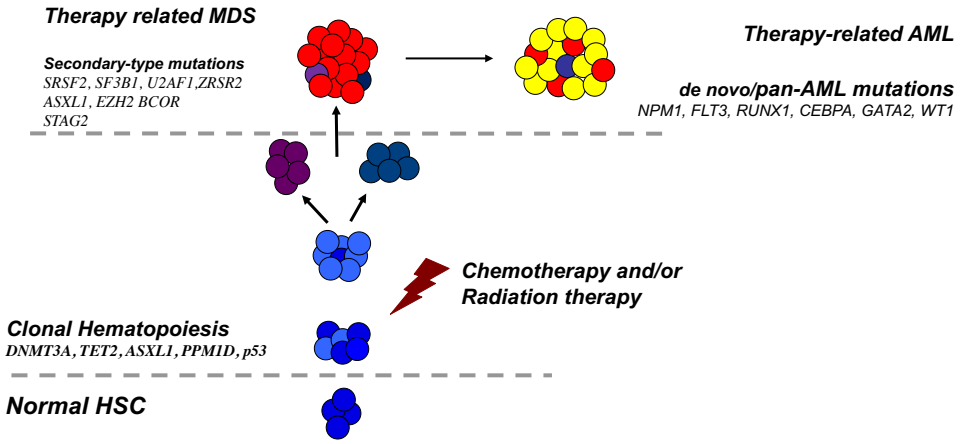
Leukemogenesis

Involves continuous genetic, epigenetic evolution and clonal diversification

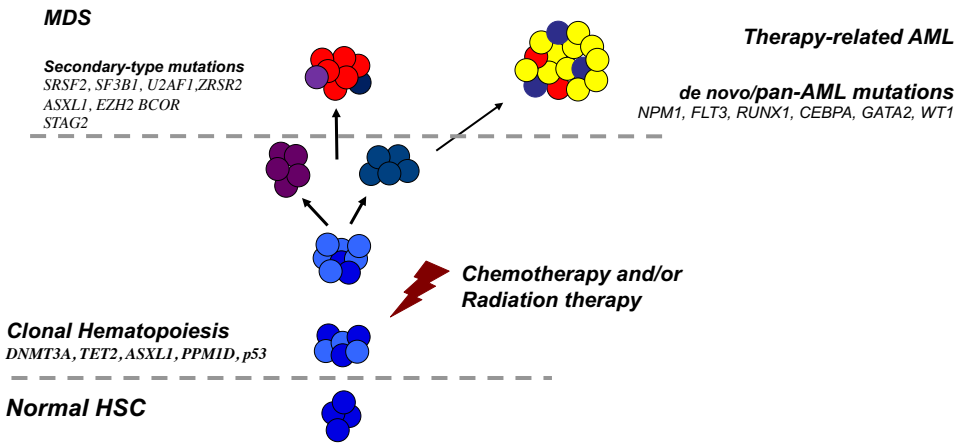


[1] Viny A et al. NEJM. 2016; 374: p2282-2284 ; [2] Li S et al. Current Opinion in Genetics & Development. 2016; 36:100-106

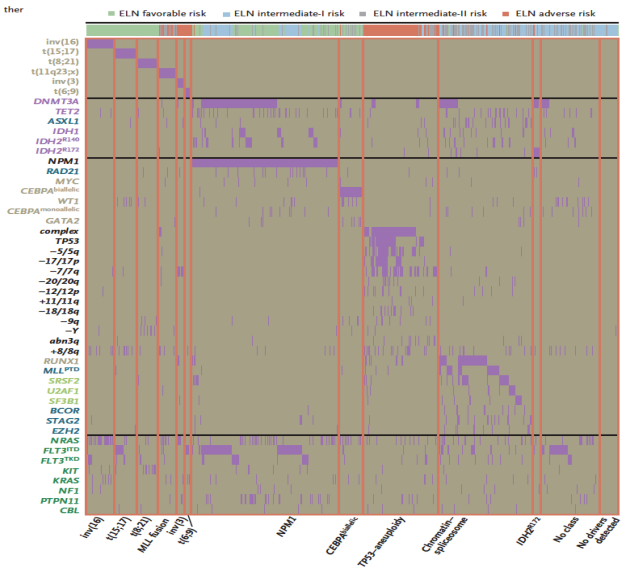
Model for Clonal Evolution in therapy-related AML

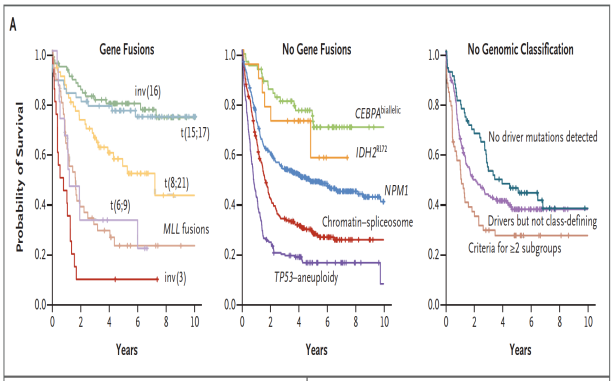


Model for Clonal Evolution in therapy-related AML

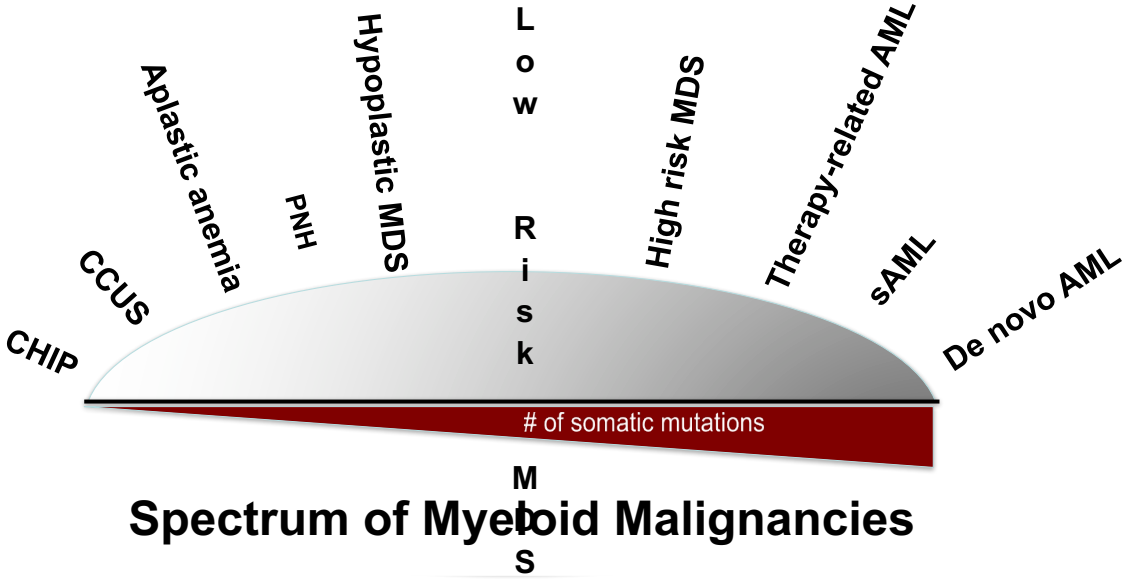


Molecular Heterogeneity in AML





Papaemmanuil E et al. N Engl J Med 2016;374:2209-21.



Spectrum of Myeloid Malignancies

Induction Chemotherapy in AML

Cancer Chemother Rep. 1973 Nov-Dec;57(4):485-8.

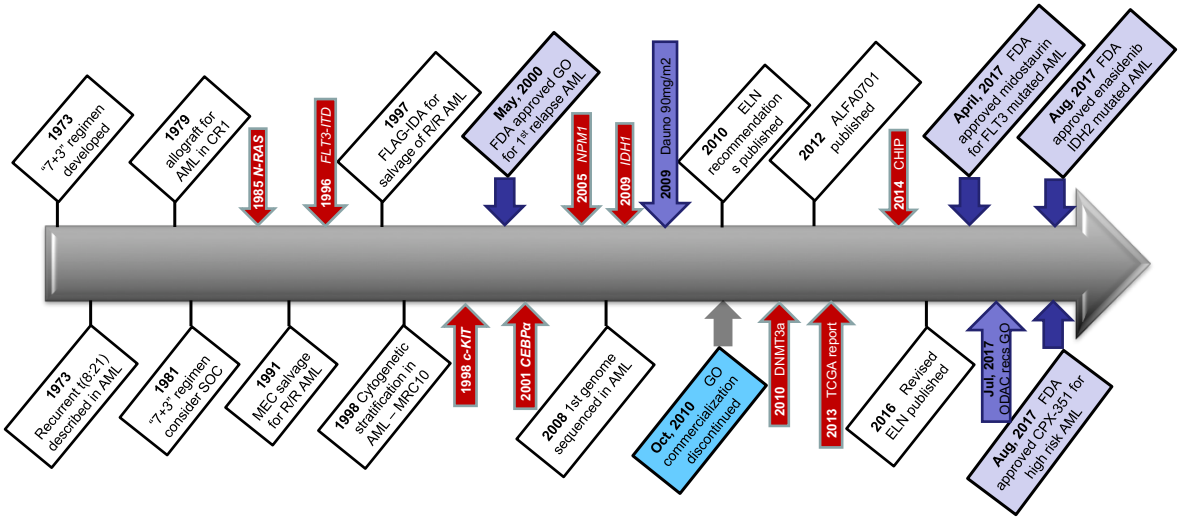
Cytosine arabinoside (NSC-63878) and daunorubicin (NSC-83142) therapy in acute nonlymphocytic leukemia.

Yates JW, Wallace HJ Jr, Ellison RR, Holland JF.

- Ara C 100 mg/m^2/day continuously for 7 days
- DNR 45 mg/m^2/day by rapid injection for 3 days

- N = 8 previously untreated adult patients with AML
  - All 5 patients < 60 years of age sustained complete remission.
  - All > 60 years (67, 76, 78) failed to achieve a complete remission.
- The CR rate for previously untreated AML patients was 63%.

Timeline of discoveries in AML



FLT3 MUTATED AML

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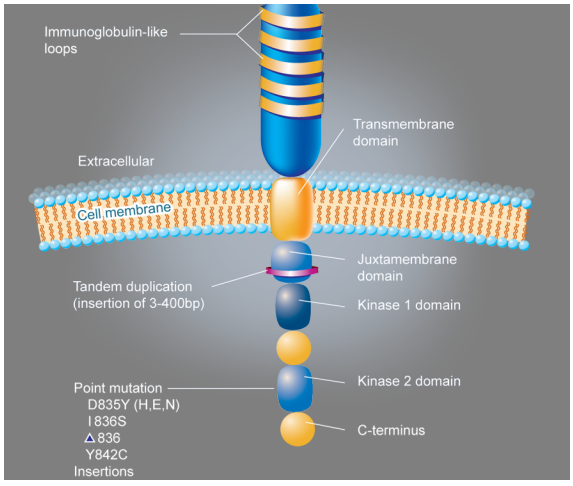
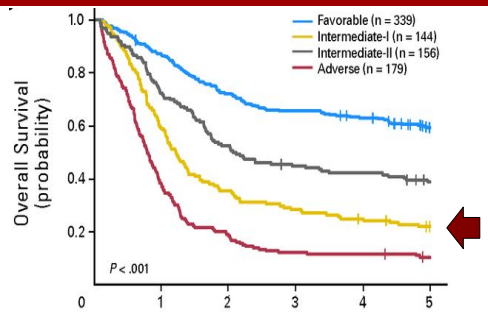
FLT3 in AML



2010 ELN Classification



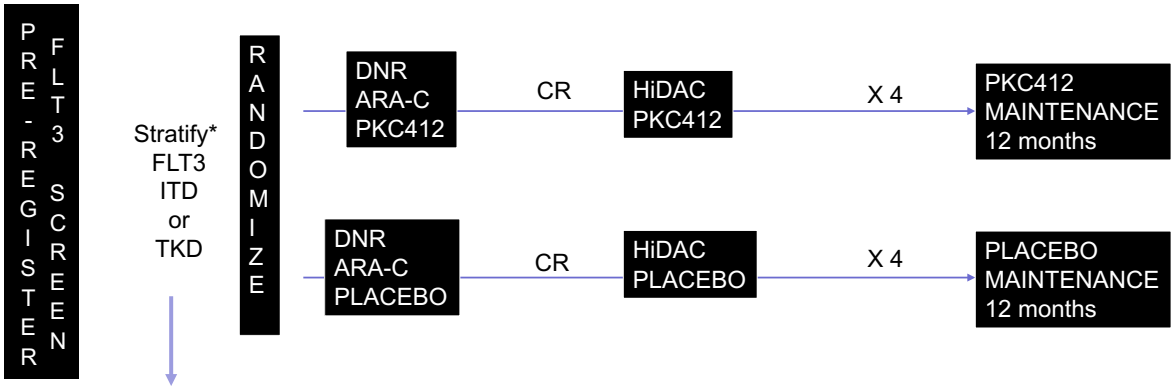
2017 ELN Classification

Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Midostaurin

- PKC412 developed as a VEGF and PKC inhibitor
  - known FLT3 (both ITD and TKD) inhibitor (IC_{50} <10 nM)
- Drug has biological activity
  - limited single agent activity in advanced FLT3 mutant AML
- PKC412 50 mg 2x/daily given for 14 days can be safely combined with chemotherapy in upfront AML

Schema



FLT3 WILD TYPE not eligible for enrollment

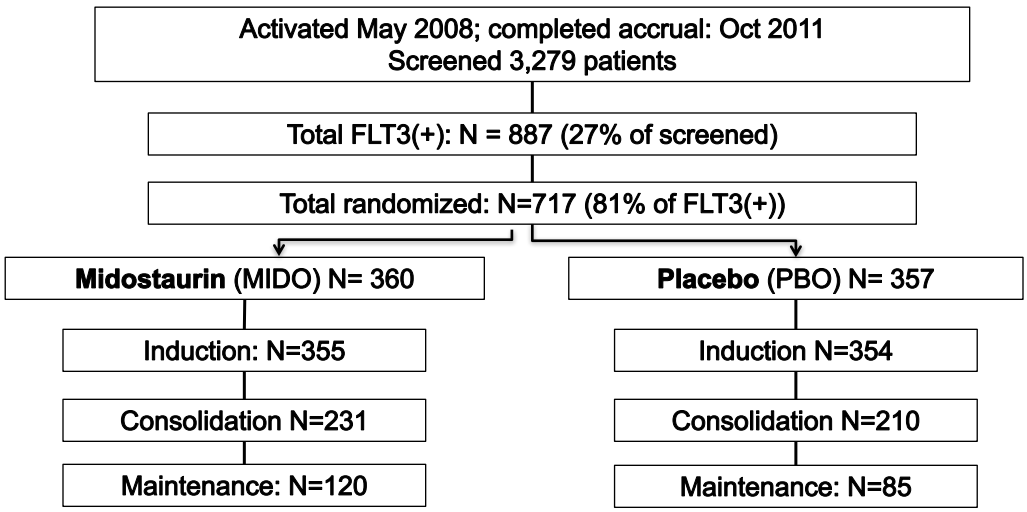
Study drug is given on Days 8-21 after each course of chemotherapy, and Days 1-28 of each 28 day Maintenance cycle.

* Stratification: TKD; ITD with allelic ratio <0.7; ITD with allelic ratio >=0.7

Protocol Therapy

- Induction: daunorubicin 60 mg/m2 IVP days 1-3, cytarabine 200 mg/m2/d d 1-7 via IVCI, midostaurin 50 mg po bid or placebo days 8-22
  - marrow on day 21. If residual AML, repeat above
- Consolidation (4 cycles): cytarabine 3 gm/m2 over 3h q 12h days 1, 3, and 5
  - midostaurin 50 mg po bid or placebo days 8-21
- Maintenance: midostaurin 50 mg po bid or placebo days 1-28 x 12 cycles
- Transplant not specifically mandated

Consort Diagram



Patient Characteristics

	MIDO (N=360)	PBO (N=357)	p value
Age (years), median (range)	47.1 (19.0-100.2)	48.6 (18.0-60.9)	0.27
Gender			0.045
Female	187 (51.9%)	212 (59.4%)	
Male	173 (48.1%)	145 (40.6%)	
FLT3 Stratification Group			0.995
FLT3 TKD (No ITD)	81 (22.5%)	81 (22.7%)	
ITD Allelic ratio <0.7 (+/- FLT3 TKD)	171 (47.5%)	170 (47.6%)	
ITD Allelic ratio ≥0.7 (+/- FLT3 TKD)	108 (30.0%)	106 (29.7%)	

Toxicity Profile

Grade 3-4	MIDO	PBO	p *
NON-HEMATOLOGIC	n (%)	n (%)	
Febrile Neutropenia	288 (81%)	290 (82%)	0.92
Infection	143 (40%)	133 (38%)	0.49
Diarrhea	54 (15%)	55 (16%)	1.00
Hypokalemia	46 (13%)	60 (17%)	0.17
Pain	47 (13%)	45 (13%)	0.91
Infection - Other (Specify)	42 (12%)	43 (12%)	1.00
ALT, SGPT	44 (12%)	33 (9%)	0.23
Rash/desquamation	47 (13%)	27 (8%)	0.02
Fatigue (asthenia, lethargy, malaise)	32 (9%)	38 (11%)	0.53

* 2-sided Fisher's Exact p

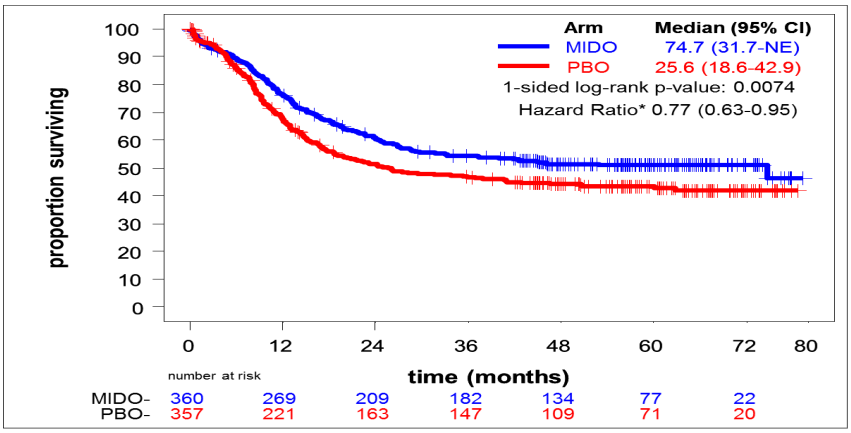
Grade 5 Adverse Events	MIDO	PBO
Death NOS	5	6
Infection	4	7
Hemorrhage, CNS	1	2
Pneumonitis	3	0
Cardiac ischemia	1	1
Colitis	2	0
Hypotension	1	0
Febrile Neutropenia	0	1
Perforation, GI	0	1
Potassium serum	0	1
Renal failure	1	0
Total Grade 5 AEs	18 (5.0%)	19 (5.3%)

2-sided Fisher's Exact p = 1.0

Response Rates

	MIDO (N=360)	PBO (N=357)	Fisher's exact p (2-sided)
Initial CR (within 60 days)	212	191	
Rate	59%	54%	0.15
Time to CR, median (range)	35 days (20-60)	35 days (20-60)	
Initial CR (at any time)	244	216	
Rate	68%	61%	0.04
Time to CR, median (range)	37 days (20-192)	36 days (20-108)	

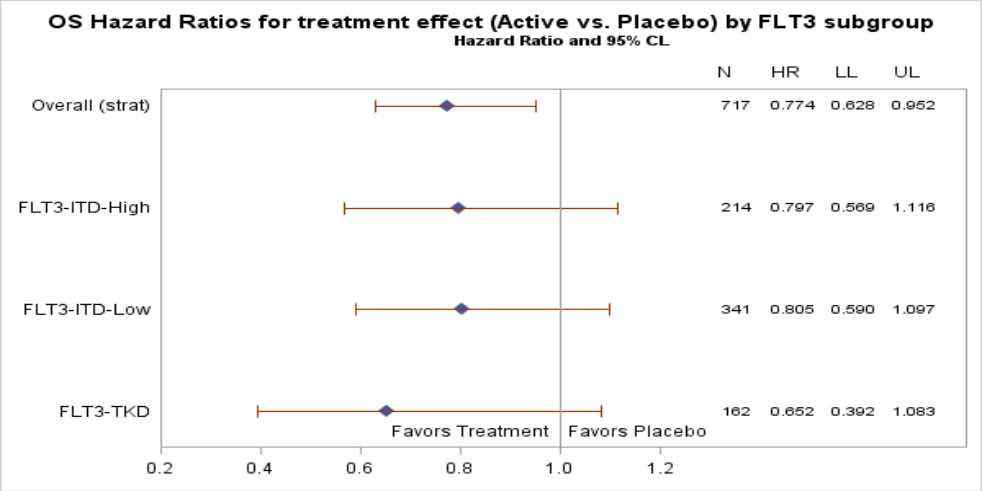
Overall Survival - Primary ITT Analysis



- 5 year survival rate: Mido 50.9% vs. PBO 43.3%
- Median follow-up time for survivors: 56.7 mo (range: 0.1, 79.2)

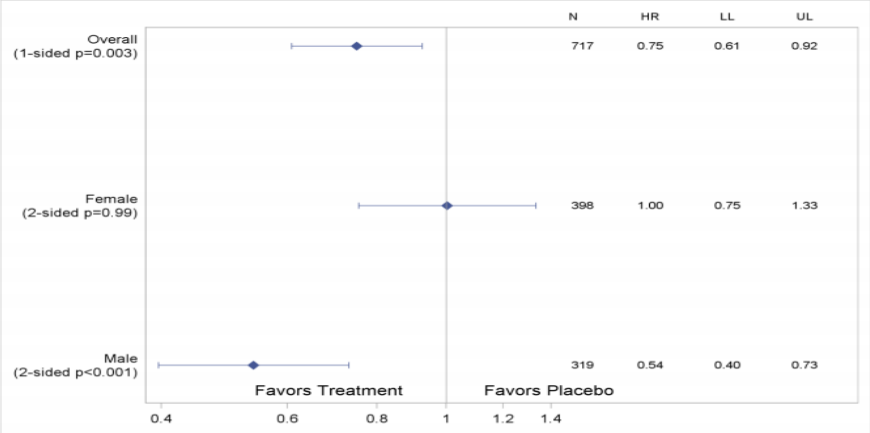
NE: not estimable
* controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)

Forest Plot of OS by FLT3 status

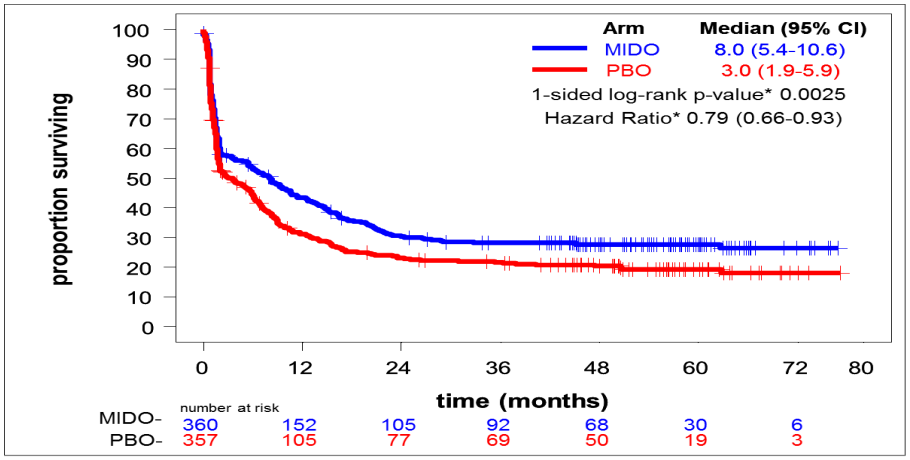


Mido effect on OS was similar across FLT3 subtypes

Overall Survival HRs by gender



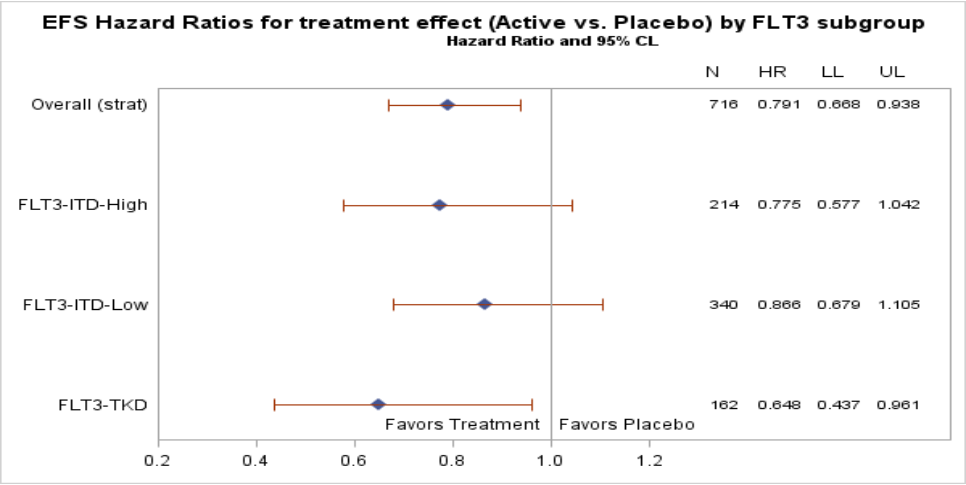
Event-Free Survival



- Event: first of: no CR within 60 days, relapse or death
- 5 year EFS rate: Mido 27.6% vs. PBO 19.3%

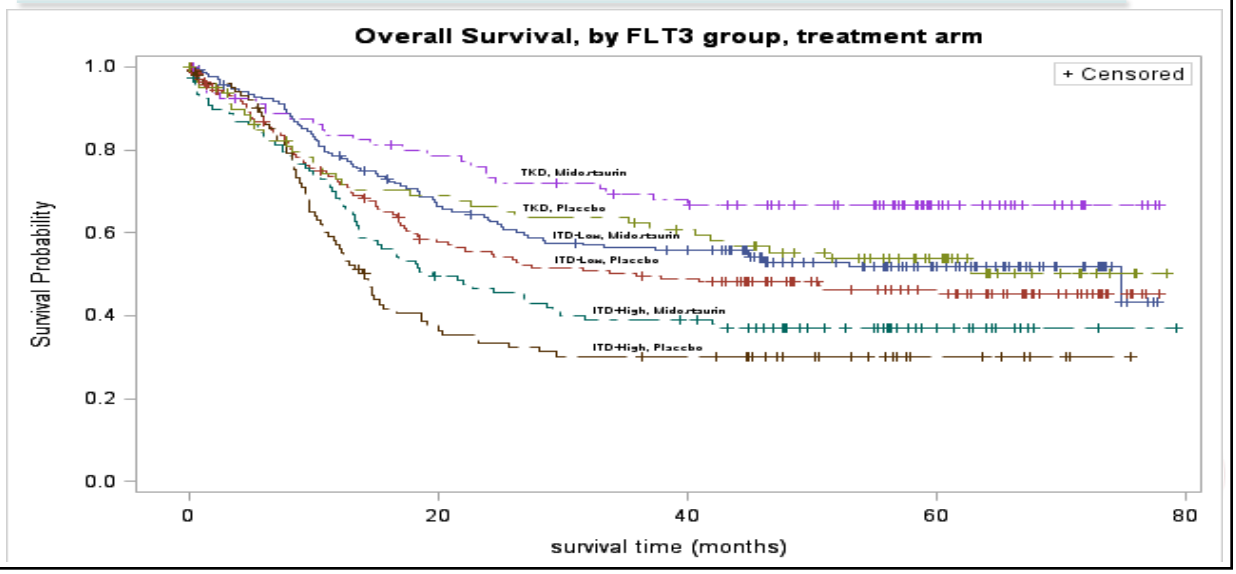
* controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)

Forest Plot of EFS by FLT3 status

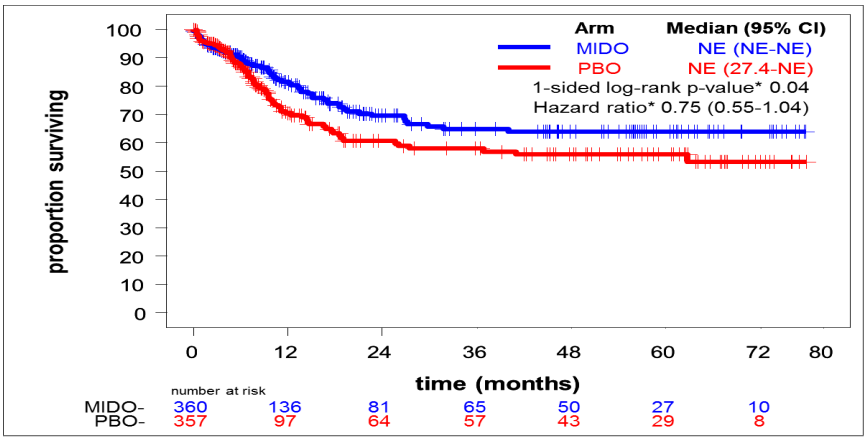


Mido effect on EFS was similar across FLT3 subtypes

Overall Survival according to FLT3 stratification



Overall Survival - Censored at time of transplant

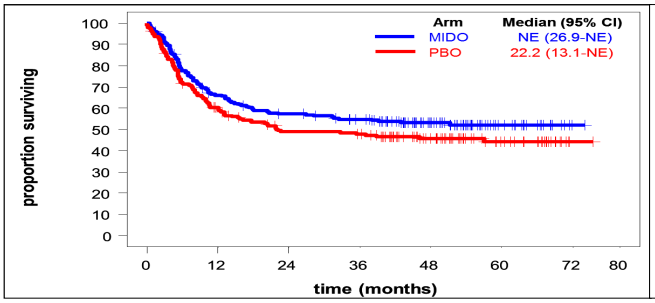


- 5 year survival rate: Mido 63.8% vs. PBO 55.7%

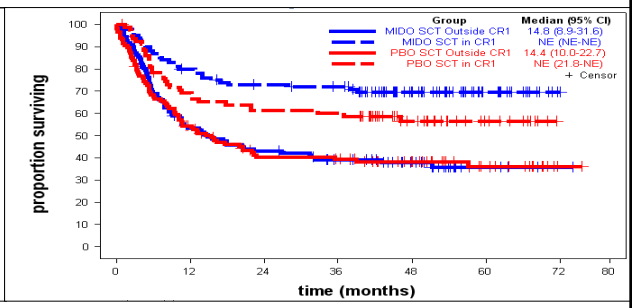
NE: not estimable
* controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)

Overall Survival post-transplant

All Transplants



SCT in/outside of CR1



NE: not estimable

Post-Hoc Analysis

- 428 patients had NPM1 testing performed
  - *NPM1*^{mut}/*FLT3*-ITD^{low} (n=85)
  - *NPM1*^{mut}/*FLT3*-ITD^{high} (n=159)
  - *NPM1*^{wt}/*FLT3*-ITD^{low} (n=75)
  - *NPM1*^{wt}/*FLT3*-ITD^{high} (n=109)

- Overall response rates and OS data to be presented at ASH 2017
- Impact of maintenance therapy to be presented at ASH 2017

GEMTUZUMAB OZOGOMYCIN IN AML

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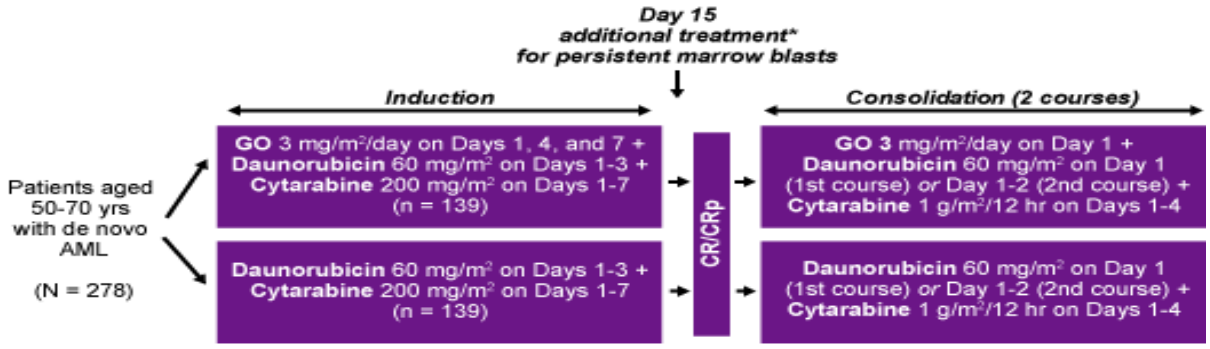
ALFA 0701



CRp, CR with incomplete platelet recovery.
*Patients with persistent marrow blasts > 10% at Day 15 received additional daunorubicin 35 mg/m² on Days 1-2 + cytarabine 1 g/m²/12 hrs on Days 1-3.

Patients with previous MPN or MDS (sAML) or exposure to chemotherapy or radiotherapy (t-AML) were not eligible

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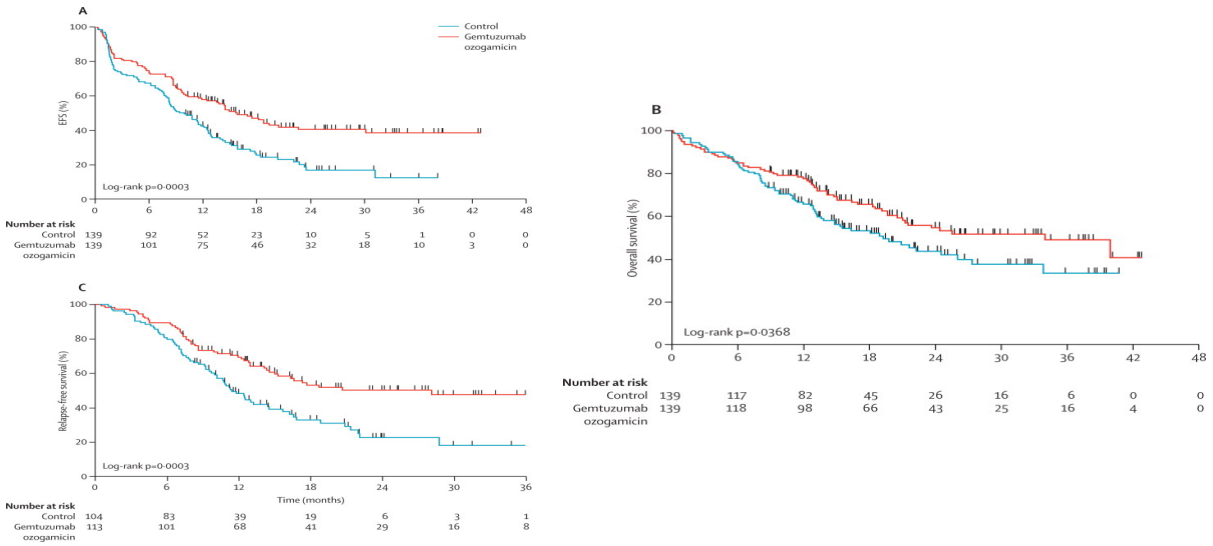
Castaigne S, et al. *The Lancet*. 2012; 379,1508–1516.

ALFA 0701



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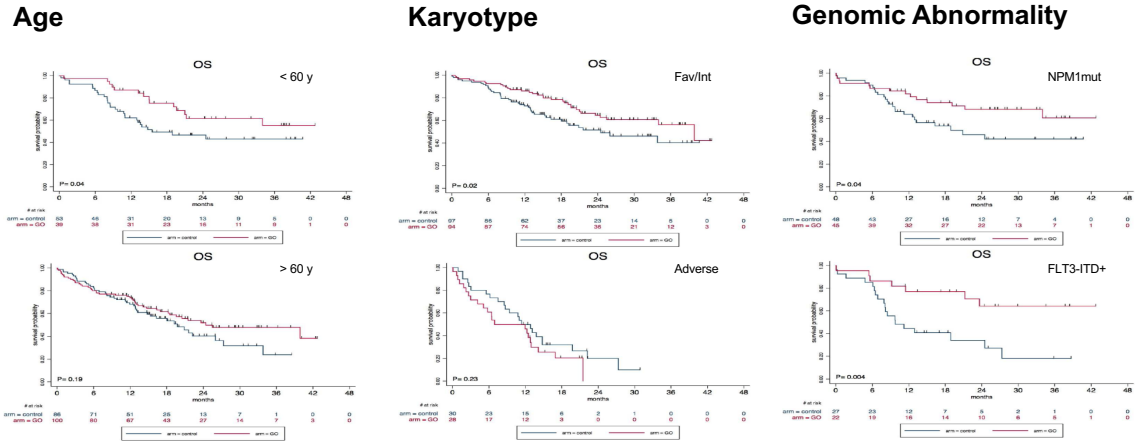
Castaigne S, et al. *The Lancet*. 2012; 379:508–1516.

Subgroup analyses



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Castaigne S, et al. *The Lancet*. 2012; 379:508–1516.

HIGH RISK AML

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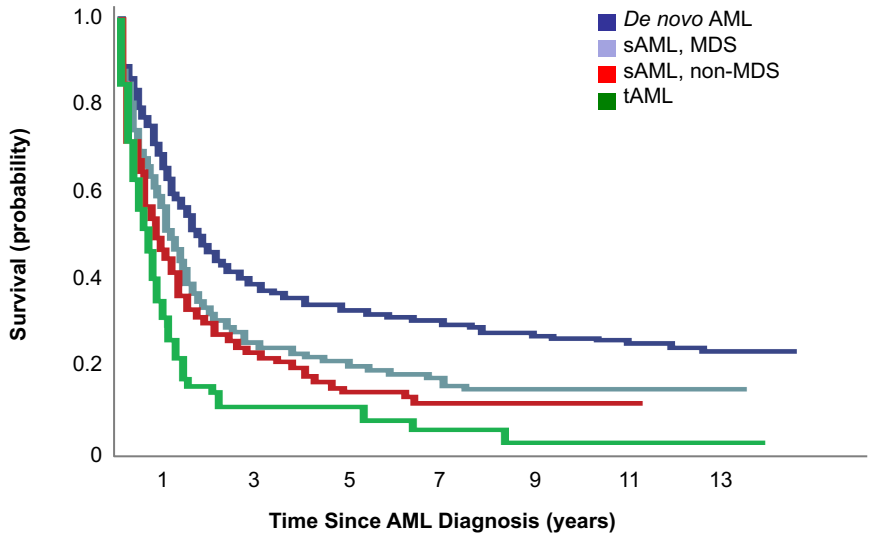
Secondary AML



Granfeldt-Osgard, et al. *J Clin Oncol.* 2015;33:3641

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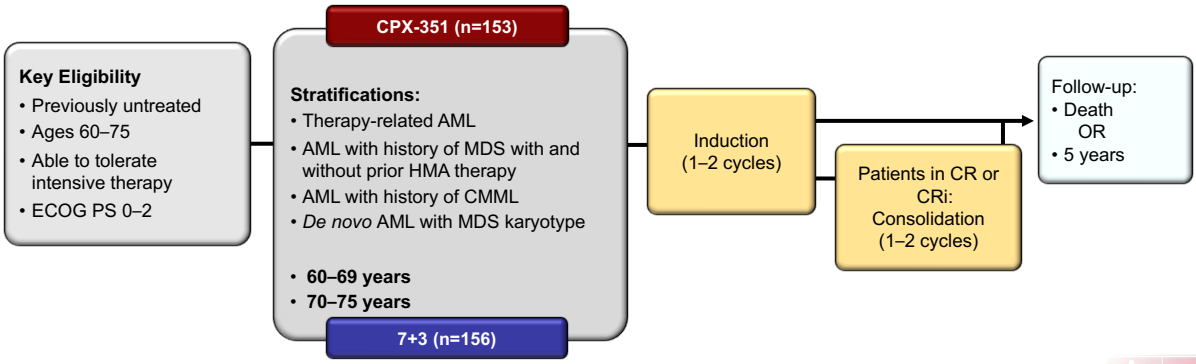
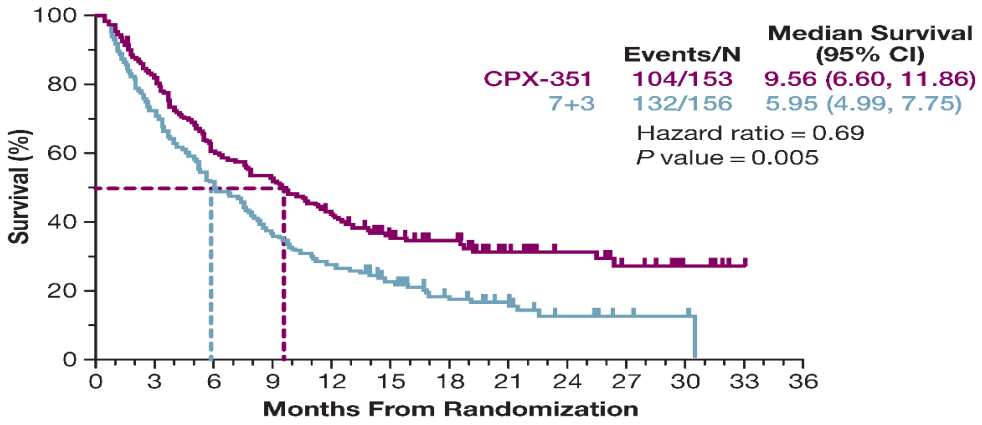
CPX-351 Phase III Study Design

- Randomized, open-label, parallel-arm, standard therapy–controlled
  - 1:1 randomization



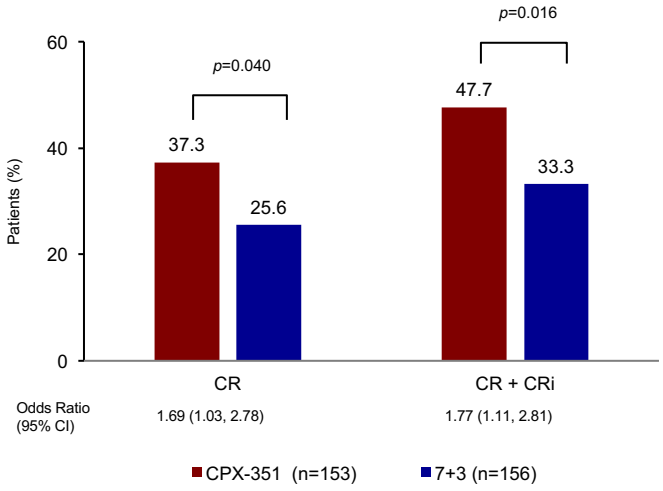
Lancet J et al. ASCO, 2016

Clinical Results of Phase III Study



Lancet J et al. ASCO, 2016

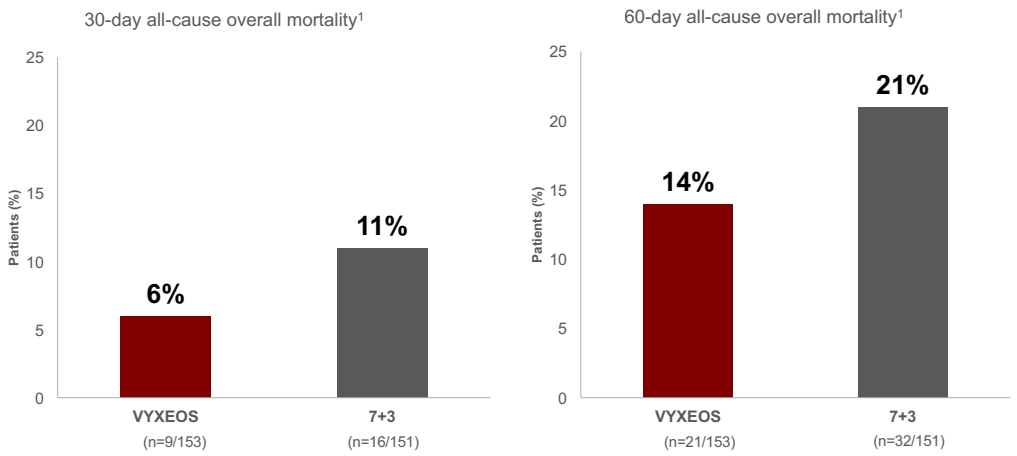
Response Rate and 60-day Mortality



39 **Lancet J et al. ASCO, 2016**

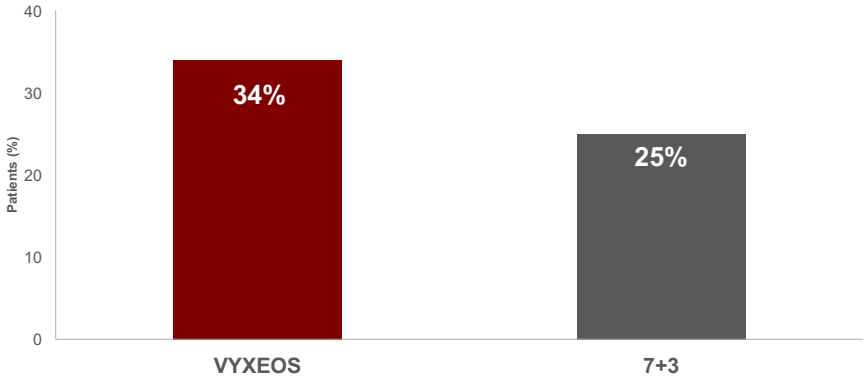
Overall all-cause early mortality

VYXEOS was associated with lower 30- and 60-day mortality rates compared to 7+3[1]



Study 301: overall rate of HSCT[a]

More patients received an HSCT after treatment with VYXEOS[1]

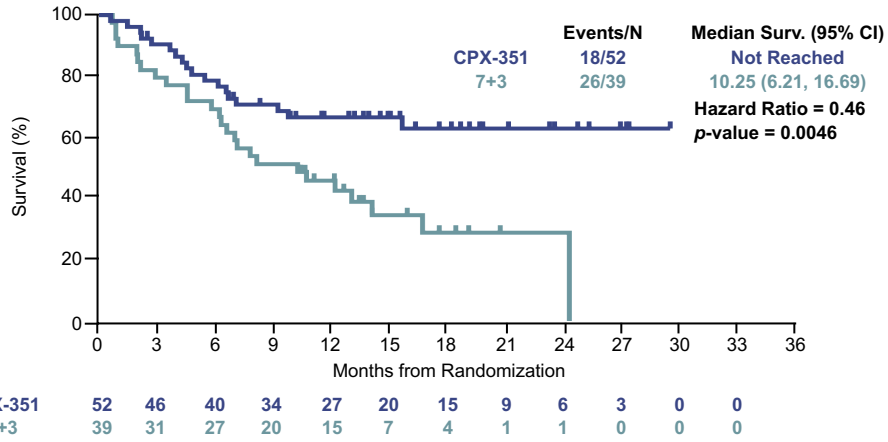


[a]Induction failure, first CR, or as salvage after response.

HSCT=hematopoietic stem cell transplant.

Landmark Analysis at Time of Transplant

KAPLAN-MEIER CURVE FOR OVERALL SURVIVAL LANDMARKED AT STEM CELL TRANSPLANT
ITT ANALYSIS POPULATION



CPX-351	52	46	40	34	27	20	15	9	6	3	0	0
7+3	39	31	27	20	15	7	4	1	1	0	0	0

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Lancet J et al. ASCO, 2016

Treatment setting

- Consolidation with VYXEOS was frequently administered in the outpatient setting without diminished overall survival, as compared with the 7+3 arm and patients in the VYXEOS arm who were hospitalized during consolidation administration

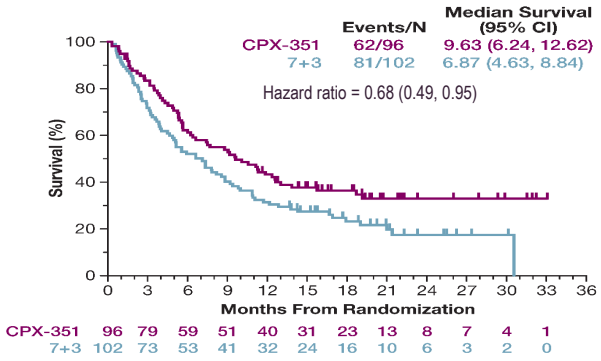
	Inpatient		Outpatient	
	VYXEOS	7+3	VYXEOS	7+3
Consolidation 1, n/N (%)	24/49 (49%)	30/32 (94)	25/49 (51)	2/32 (6)
Median OS, months	14.72	9.26	25.43	6.87
Hazard ratio (95% CI)	0.55 (0.25, 1.21)		0.10 (0.01, 1.11)	
Consolidation 2, n/N (%)	9/23 (39)	12/12 (100)	14/23 (61)	0/12 (0)
Median OS, months	Not reached	14.31	26.32	–
Hazard ratio (95% CI)	0.45 (0.09, 2.36)		–	

Kolitz JE, et al. Poster 7036 presented at: American Society of Clinical Oncology Annual Meeting, June 2-6, 2017, Chicago, IL.

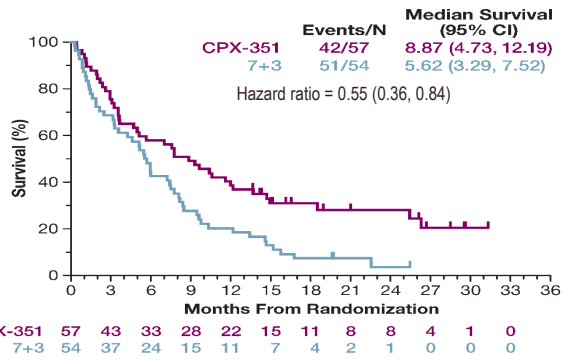
Exploratory analysis by age

- Median OS was significantly longer in the VYXEOS arm versus the 7+3 arm for both stratification age subgroups

Aged 60–69 years



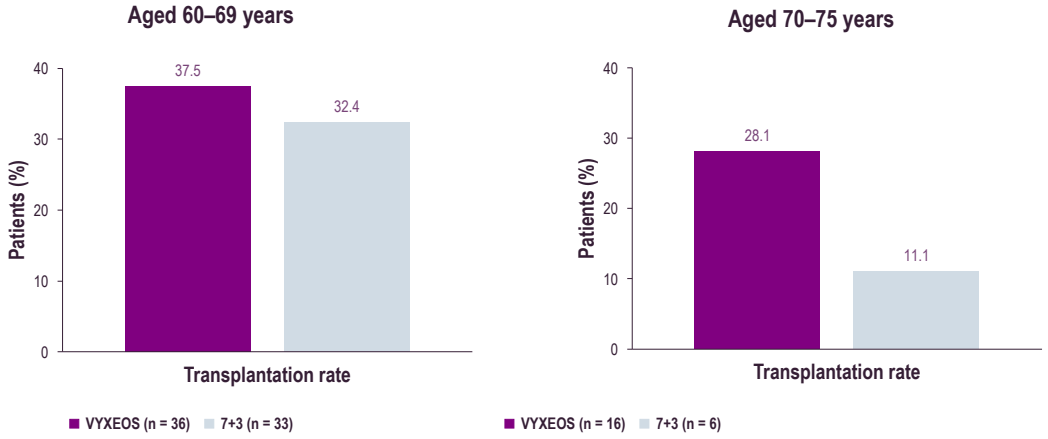
Aged 70–75 years



- The safety profile of CPX-351 in transplanted patients was comparable between age subgroups
- Grade 3-4 adverse events and events resulting in death were generally similar between the arms

Lancet J, et al. *Biol Blood Marrow Transplant* . 2017;23(3):S38-S39.

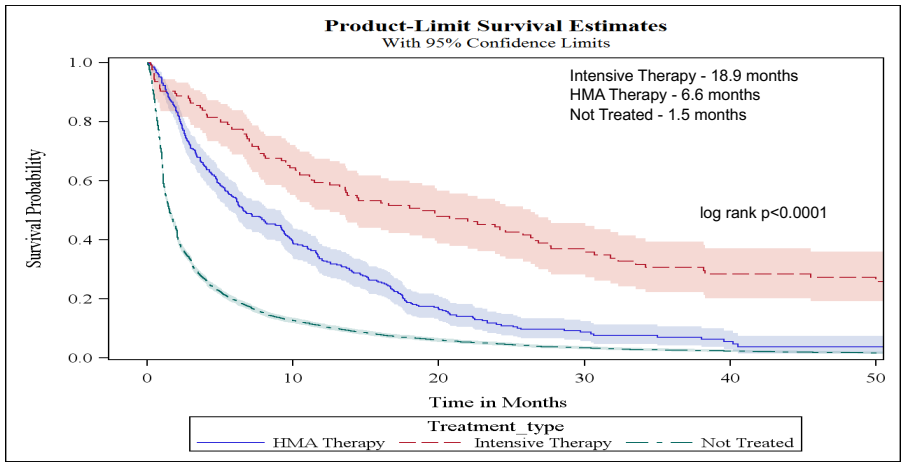
Allogeneic transplantation rates



Note: Percentages reflect number with endpoint out of column total. Odds ratios are calculated with the 7+3 arm as the reference group.

Lancet J, et al. *Biol Blood Marrow Transplant* . 2017;23(3):S38-S39.

Survival AML > 65 years

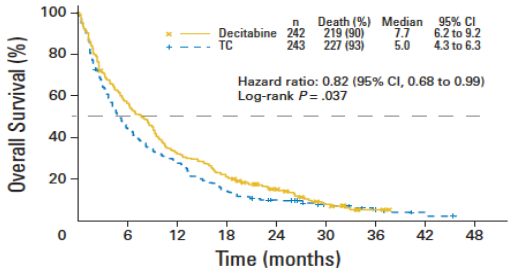


~50% of all AML patients > 65 years receive no anti-leukemia therapy

Medeiros BC et. Ann Hematol. 2015

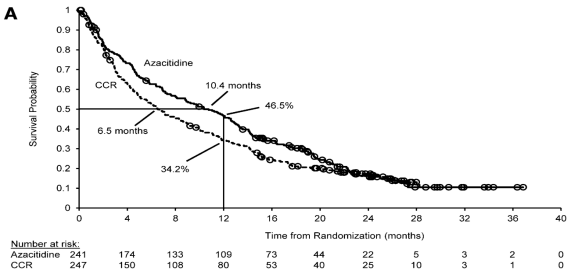
Inhibitors of DNMTs in AML

Decitabine



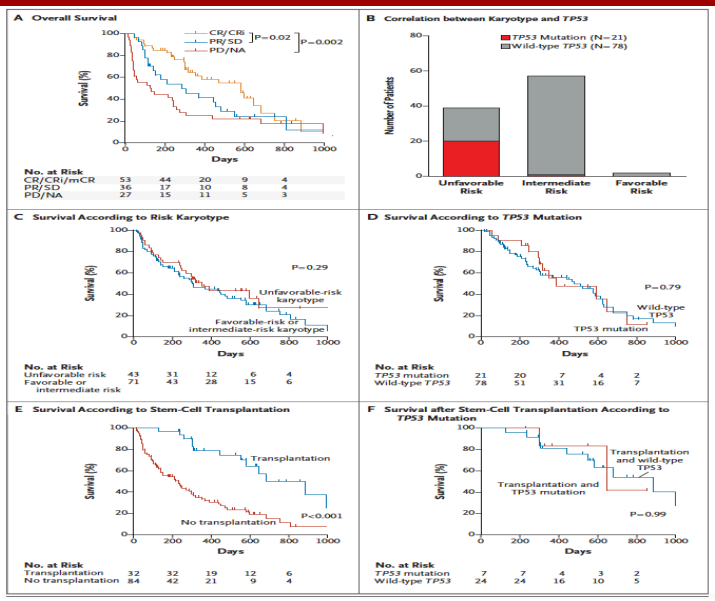
J Clin Oncol 2012; 30:2670-2677

Azacitadine



Dombret H et al. Blood. 2015;126(3):291-9

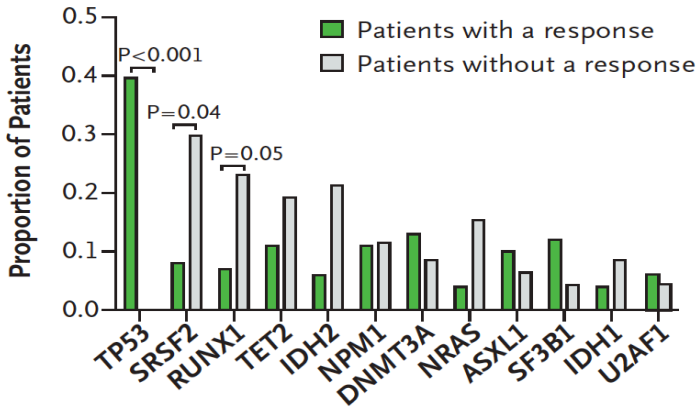
Decitabine in *p53* mutated AML



Welch JS et al. NEJM, 2016:375,2023

Decitabine in *p53* mutated AML

Response



Welch JS et al. NEJM, 2016:375,2023

BCL-2 inhibitor in AML

Eligibility

Adult patients ≥65 years of age with untreated AML who are not eligible for standard induction therapy due to comorbidity or other factors
Adverse or intermediate-risk cytogenetic

Phase 1b Safety
PK & Dose Finding

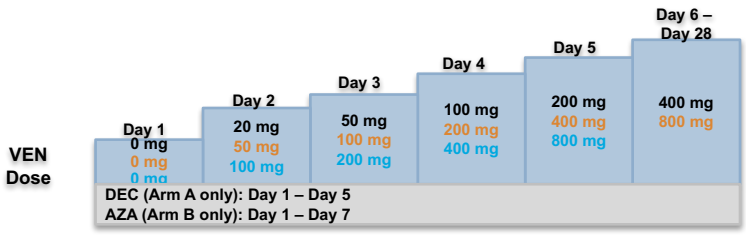
VEN + DEC (ARM A)
20 mg/m² D1–5, IV 28-D cycles
N=~24

VEN + AZA (ARM B)
75 mg/m² D1–7, IV/SC 28-D cycles
N=~24

One HMA combo at RP2D

Expansion stage for confirmation of safety and efficacy

VEN + HMA
N=40



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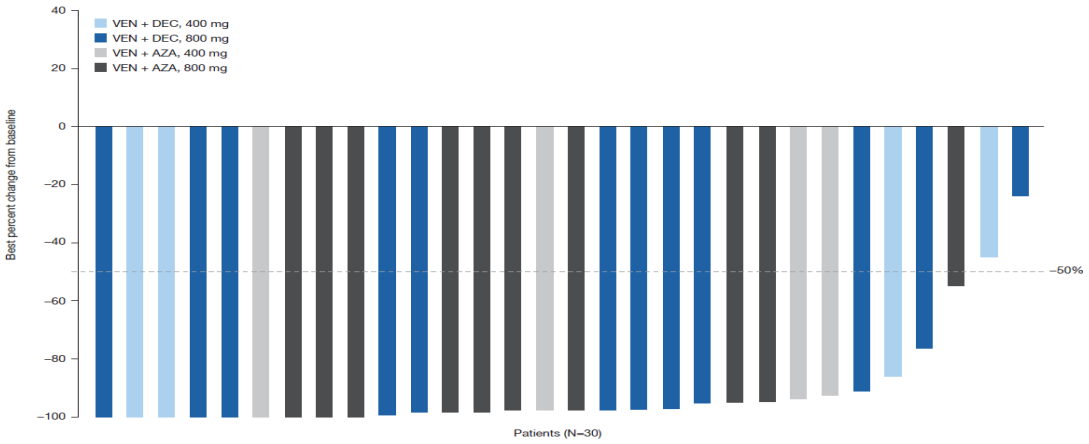
Change in Bone Marrow Blast Count

- 28 of the 30 patients (93%) with bone marrow evaluation had more than 50% reduction at assessment
- 24 patients achieved CR/CRi. Median time to CR/CRi was 29.5 days (range: 24−112 days)



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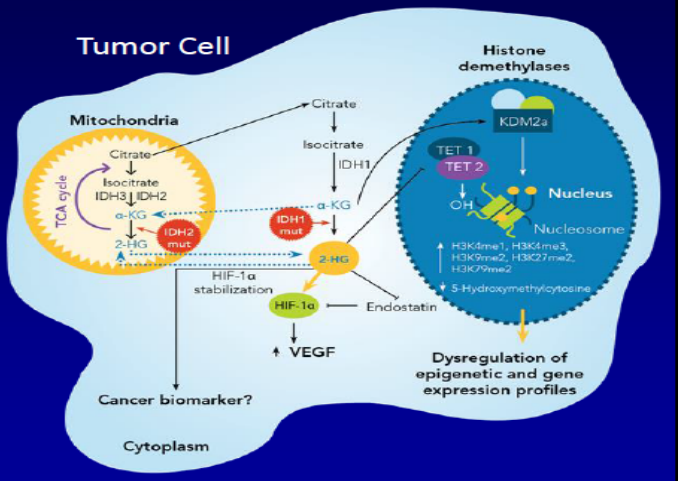
IDH2 MUTATED AML

STANFORD UNIVERSITY

Isocitrate Dehydrogenase (IDH) Mutations as a Target in AML

- **IDH is an enzyme of the citric acid cycle**
- **Mutant *IDH2* produces 2-hydroxyglutarate (2-HG), which alters DNA methylation and leads to a block in cellular differentiation**
- **AG-221 (CC-90007) is a selective, oral, potent inhibitor of the mutant *IDH2* (m*IDH2*) enzyme**



AML, acute myeloid leukemia; IDH, isocitrate dehydrogenase; 2-HG, 2-hydroxyglutarate; m*IDH2*, mutated IDH2

Phase 1/2 Study Design

Dose Escalation
Completed

- Advanced heme malignancies with IDH2 mutation
- Continuous 28 day cycles
- Cumulative daily doses of 30-650 mg

Expansion Phase I
completed (n=25 pts per arm)

- RR-AML age ≥60, or any age if relapsed post-BMT
- RR-AML age <60, excluding pts relapsed post-BMT
- Untreated AML pts age ≥60 who decline standard of care
- Any hematologic malignancy ineligible for other arms

Phase 2
Ongoing

AG-221
100 mg PO QD

RR-AML
(N ≈ 125)

Key Endpoints:

- **Safety, tolerability, MTD, DLTs**
- **Response rates as assessed by local investigator per IWG criteria**
- **Assessment of clinical activity**

9

Response

	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (N = 209)
Overall Response (CR, CRp, CRi, mCR, PR)	**59 (37%)** [95%CI: 30%, 45%]	**10 (42%)** [22%, 63%]	**7 (50%)** [23%, 77%]	**79 (38%)** [31%, 45%]
CR	**29 (18%)** [95%CI: 13%, 25%]	**4 (17%)** [5%, 37%]	**3 (21%)** [5%, 51%]	**37 (18%)** [13%, 24%]
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	22 (11%)
SD	72 (45%)	9 (38%)	6 (43%)	96 (46%)
PD	10 (6%)	1 (4%)	0	11 (5%)
Not evaluable	18 (11%)	4 (17%)	1 (7%)	23 (11%)

- Overall response by IDH mutation type: R140Q 36% / R172K 42%

CR, complete response; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete hematologic recovery; mCR, marrow CR; PR, partial response; SD, stable disease; PD, progressive disease

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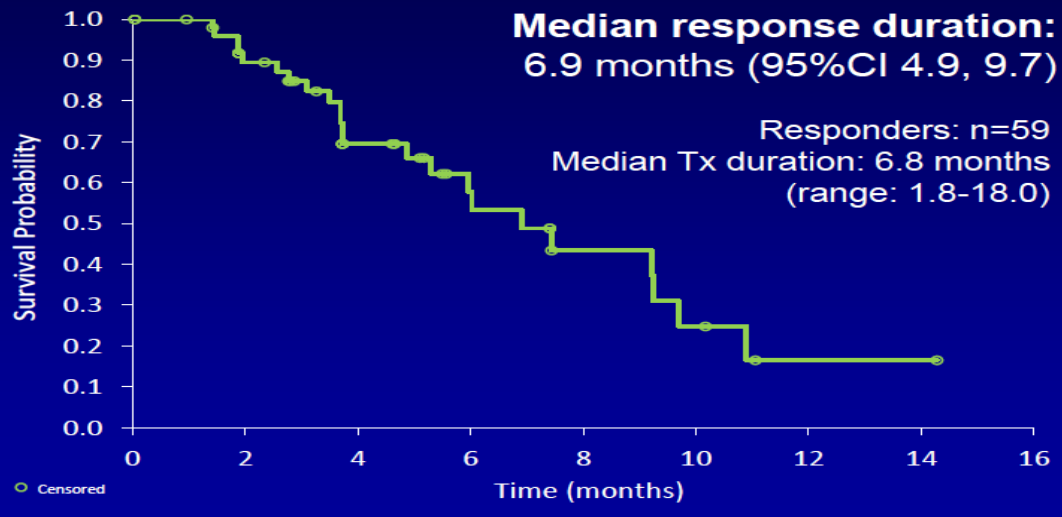
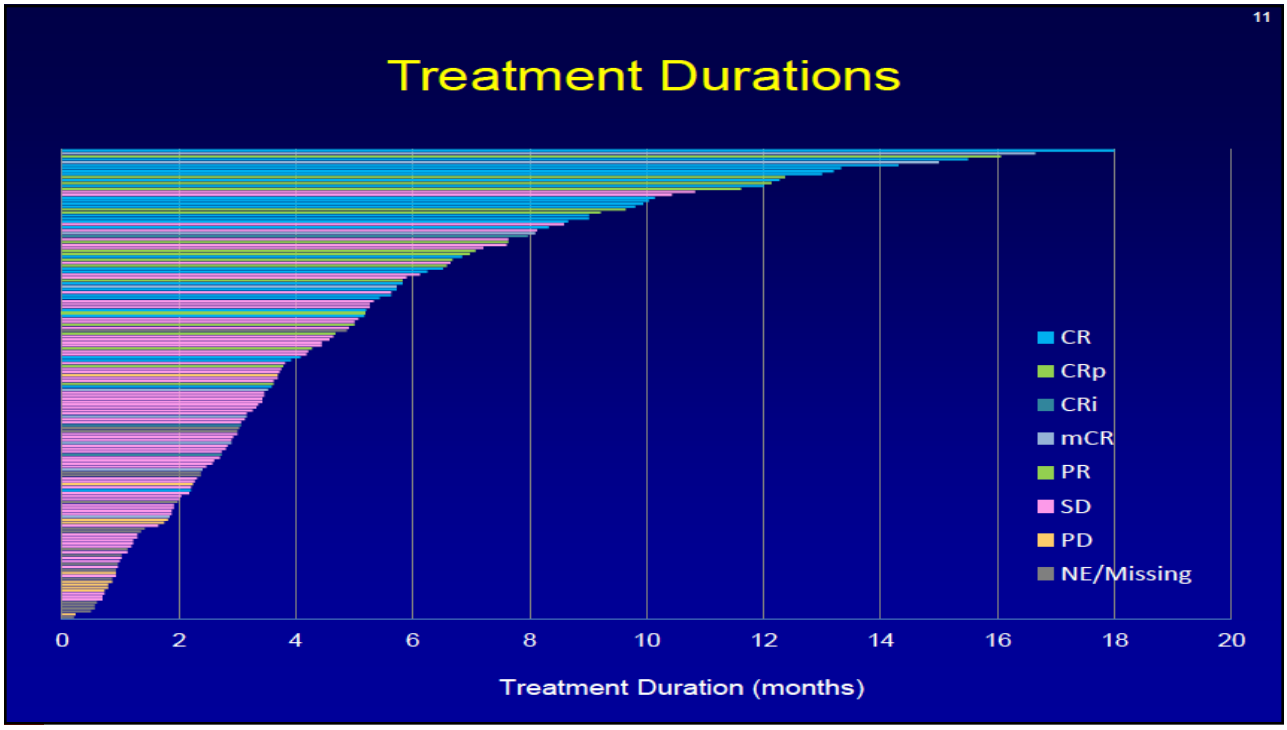
Duration of Response: RR-AML



Median response duration:
6.9 months (95%CI 4.9, 9.7)

Responders: n=59
Median Tx duration: 6.8 months
(range: 1.8-18.0)



AML: Treatment Algorithm

AML

< 60 years

> 60 years

Fit for Induction chemotherapy

Fit for Induction chemotherapy

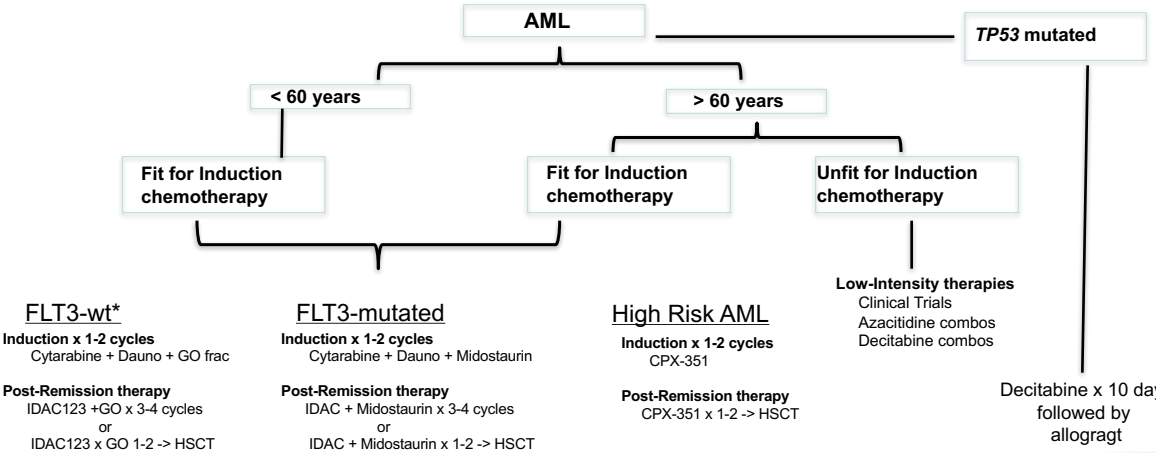
Unfit for induction chemotherapy

Induction Chemotherapy x 1-2 cycles
Cytarabine + Ida or Dauno

Post-Remission therapy
Consolidation Chemotherapy x 3-4 cycles
or
Chemotherapy x 1-2 cycles followed by HSCT

Low-Intensity therapies
Clinical Trials
Azacitidine
Decitabine

AML: Updated Treatment Algorithm



Relapsed/Refractory IDH2 mutated AML - Enasidenib

Q&A

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