Terapia della LAM: il sogno sta diventando realtà?

Sergio Amadori

Fondazione GIMEMA

Roma

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Disclosures

- Advisory Boards
  - AbbVie
  - Novartis
  - Pfizer

Standard treatment paradigm

7+3
HDAC/IDAC

Allo (Auto)
HSCT

HMAs
LDAC

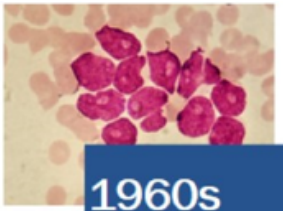
Age <60y

- CR 70-80%
- Cure ~40%

Age >60y

- CR 40-60%
- Cure ~10%

History of AML therapy



2000: Gemtuzumab approved in US in R/R but withdrawn in 2010 due to toxicities

1960s 1970s 1980s 1990s 2000s 2010s 2020s

2012: Decitabine approved for older AML in EU, but not in US

2015: Azacitidine approved for older AML > 30% blasts in EU

Chemotherapy first introduced for AML in 1960s

Allogeneic stem-cell transplantation shows OS advantage in younger AML patients

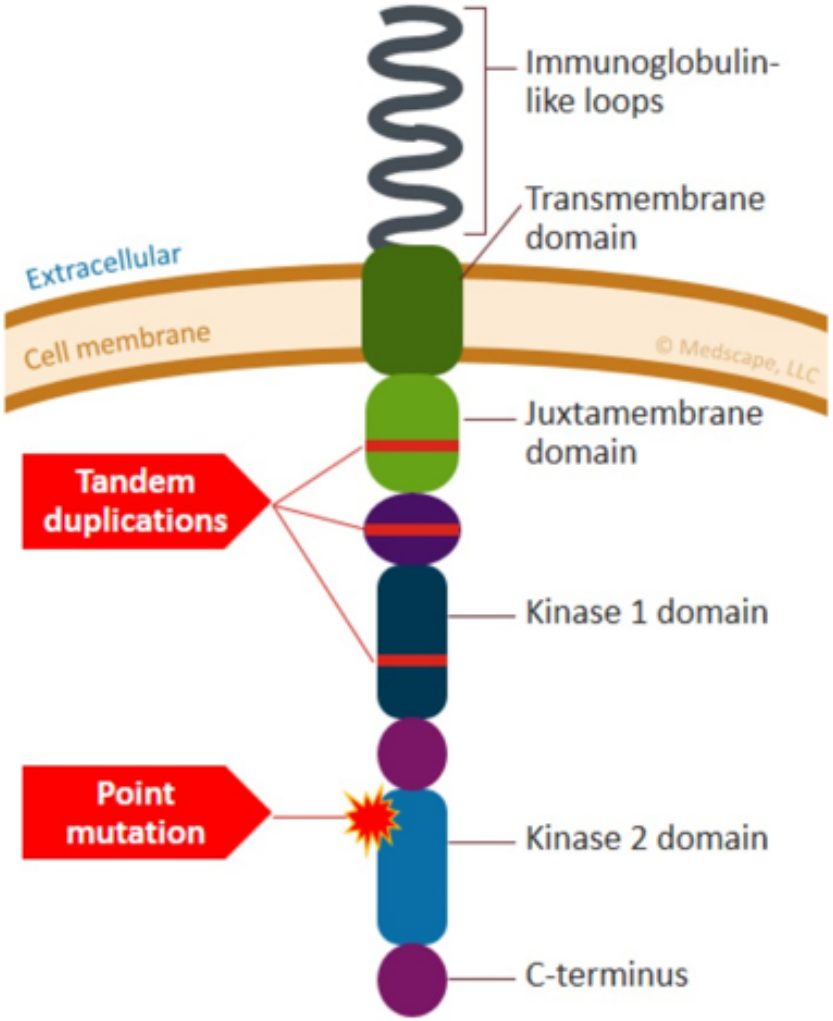
Cytarabine + anthracycline regimens (3+7) become standard of care for AML in 1970s

2017-18

FLT3 (Inhib)	• **Midostaurin** (FDA-2017; ND-AML + chemo induc/consol) • **Gilterinib** (FDA, 2018; R/R AML)
CD33 (ADC)	• **GO** (FDA-2017; ND-CD33+ AML + chemo, or single agent older pts, or R/R adults and peds)
IDH (Inhib)	• **Enasidenib** (FDA-2017; R/R AML with mIDH2) • **Ivosidenib** (FDA-2018; R/R AML with mIDH1)
BCL-2 (Inhib)	• **Venetoclax** (FDA-2018; ND-AML older pts + HMA or LDAC)
Sonic Hh (Inhib)	• **Glasdegib** (FDA-2018; ND-AML older pts + LDAC)
CPX-351	• **Cytotoxic** (FDA-2017; ND t-AML or AML with MRC)

DiNardo CD et al, Nat Rev Clin Onc 2019

Targeting mFLT3

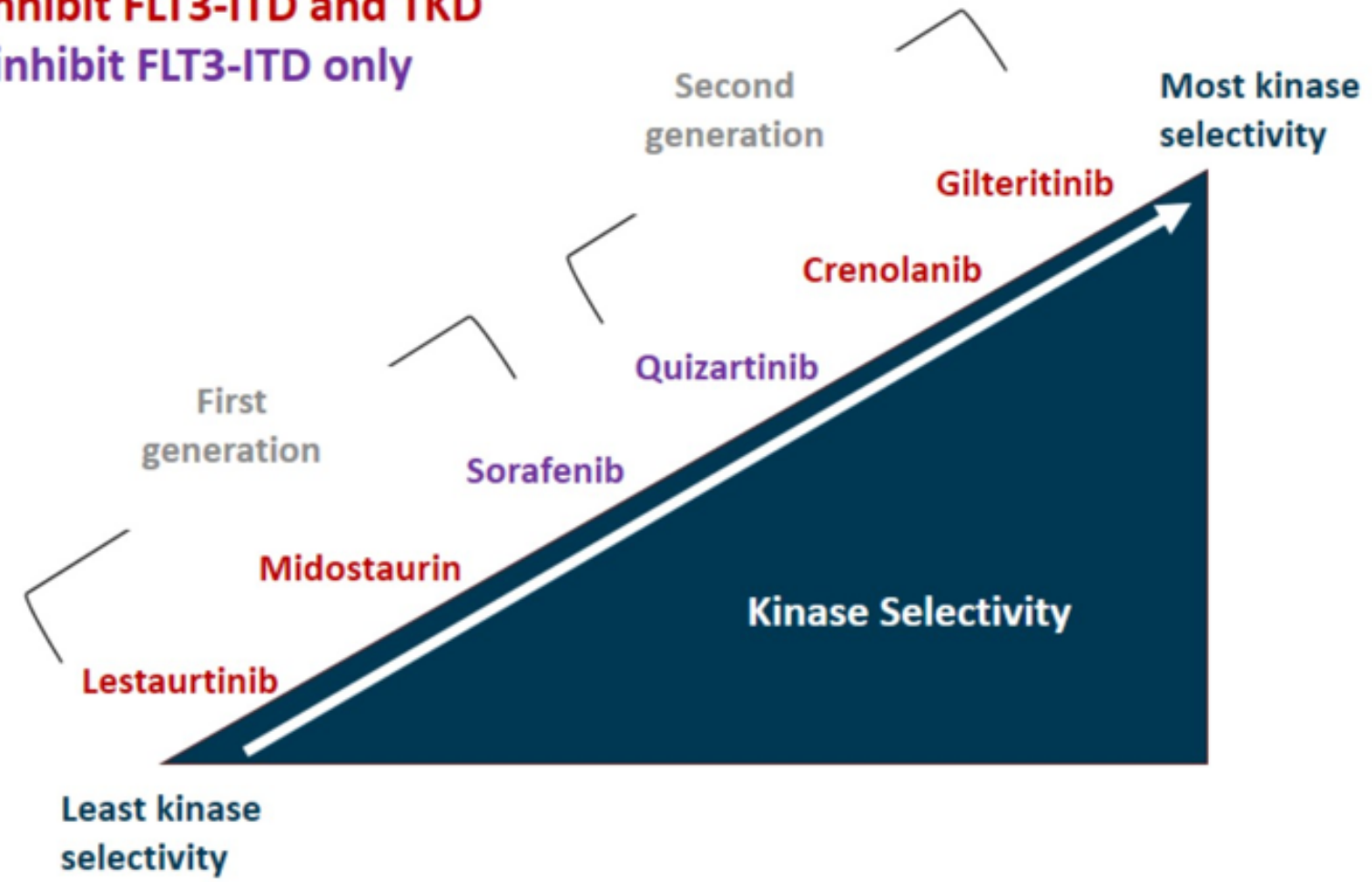


- *FLT3* mutations lead to constitutive activation of *FLT3* receptor
- *FLT3*-ITD mutations
  - Although CR rate is not typically negatively affected, the mutation is associated with poor prognosis due to higher relapse rate
  - Found in ≈25% to 30% of cytogenetically normal AML
- *FLT3*-TKD mutations
  - Found in ≈5% of cytogenetically normal AML
  - Prognostic significance unclear

Pemmaraju N et al, Cancer 2011

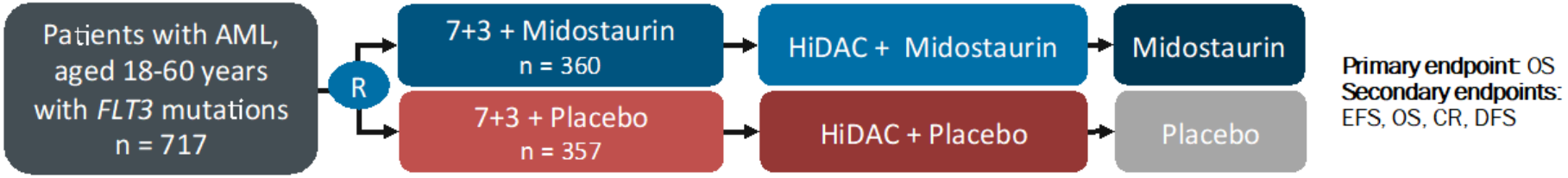
FLT3i in clinical development

Type I – inhibit FLT3-ITD and TKD
Type II – inhibit FLT3-ITD only

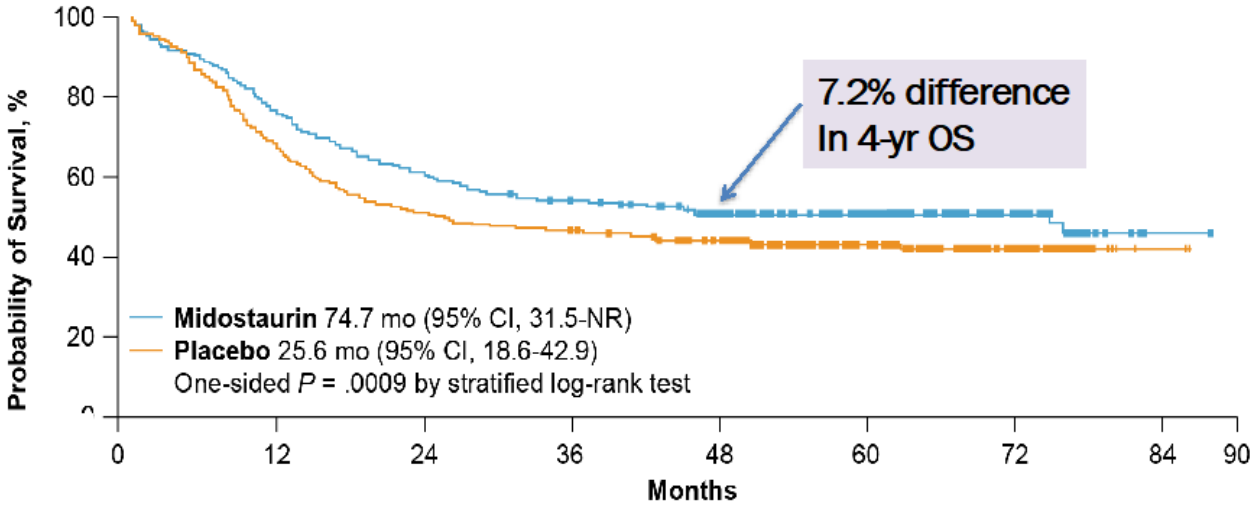


Galanis A et al, Blood 2014; Lee LY et al, Blood 2017; Garcia JS and Stone RM, Hematol Oncol Clin N Am 2017

Midostaurin (RATIFY trial)

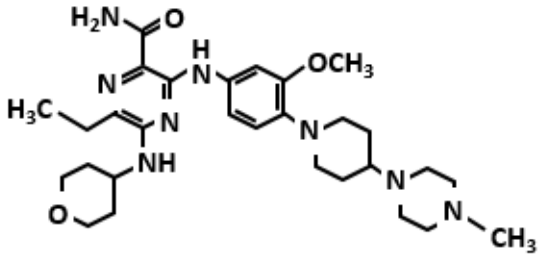


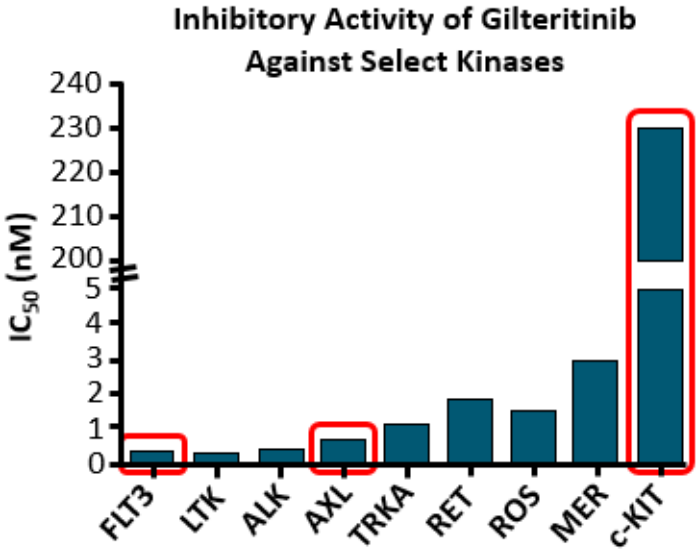
- 717 patients randomized (ITD-low, high and TKD)
- CR rate: 58.9% vs 53.5%
- Median OS: 74.7 vs 25.6 months
- AlloSCT rate (182 underwent SCT in CR1)
  - In CR1, 28.1% vs 22.7%
  - Overall, 59% vs 55%



Stone RM et al, NEJM 2017

Gilterinib



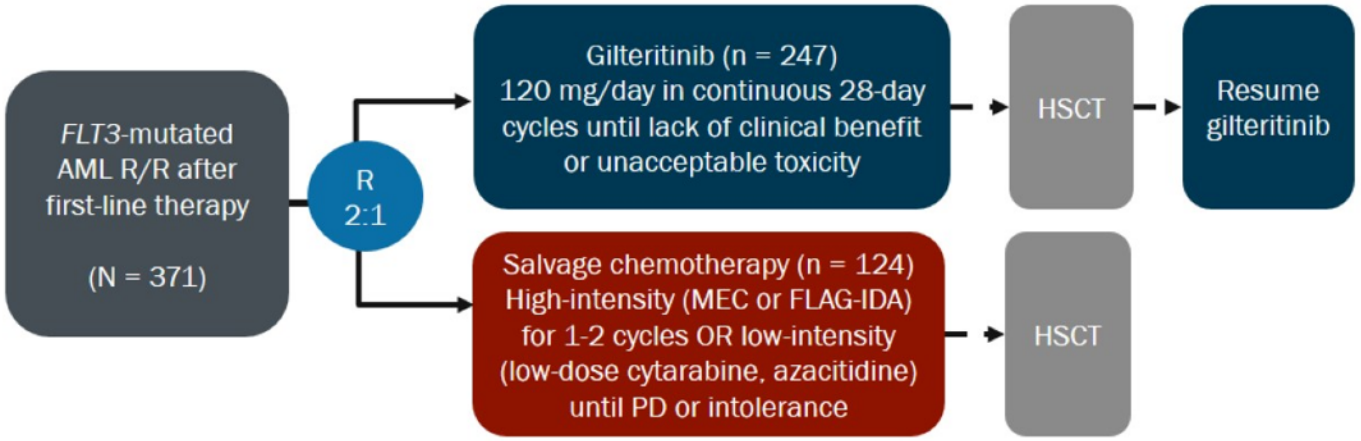


- Active against the tyrosine kinase domain mutations that confer resistance to quizartinib and sorafenib

FLT3 Receptor Subtype	Gilteritinib IC_{50} (nM)
WT	5
Molm14 (ITD)	1.8
TF/ITD	1.4
Ba/F3 ITD	0.7
Ba/F3 D835Y	0.5
Ba/F3 D835H	1.9
Ba/F3 D835V	0.7
Ba/F3/ITD F691L	17.6

Lee LY et al, Blood 2017

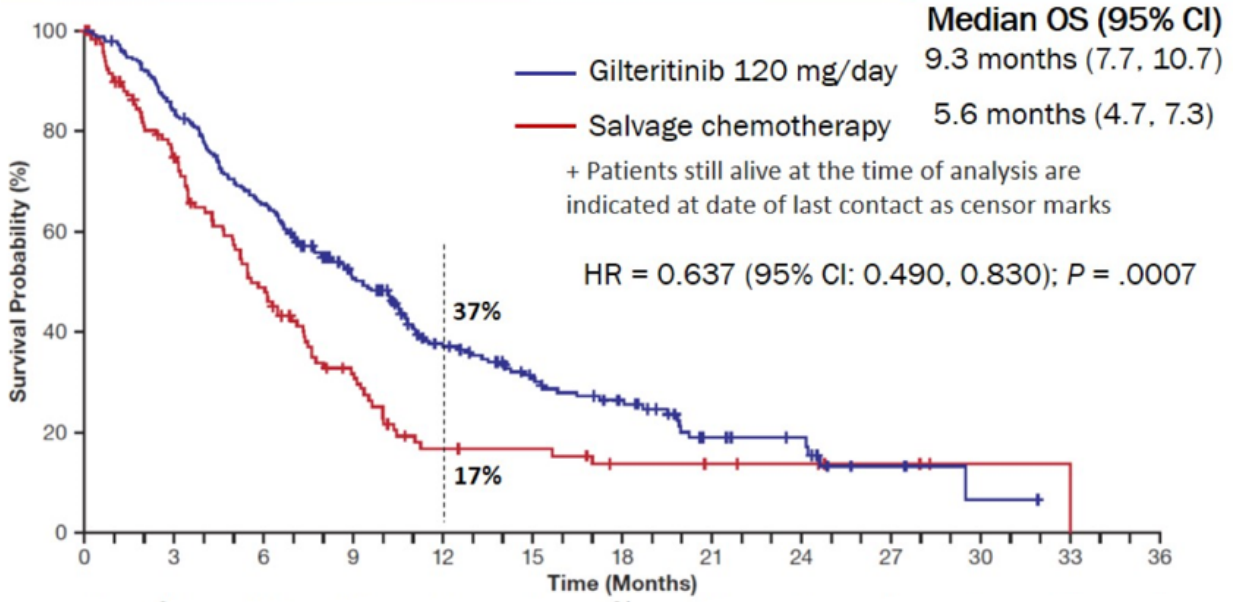
Admiral trial (phase 3)



Primary E/P

OS, CR/CRh

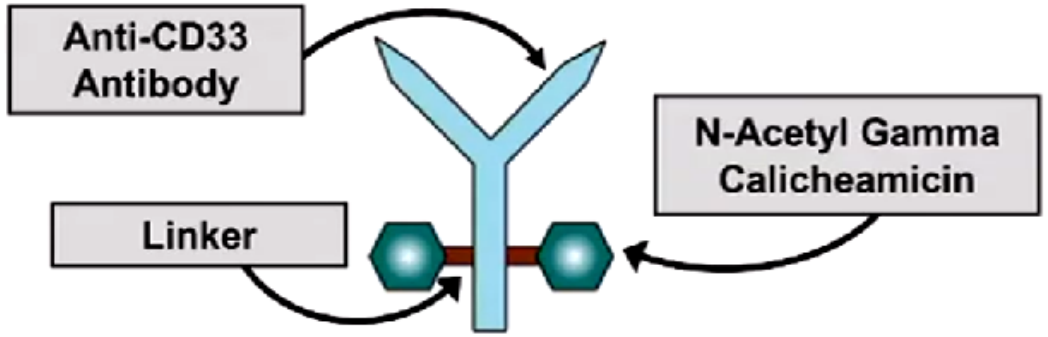
	Gilterinib (N=247)	SC (N=124)	P
CR/CRh	34%	15%	.0001
CR	21%	11%	.01



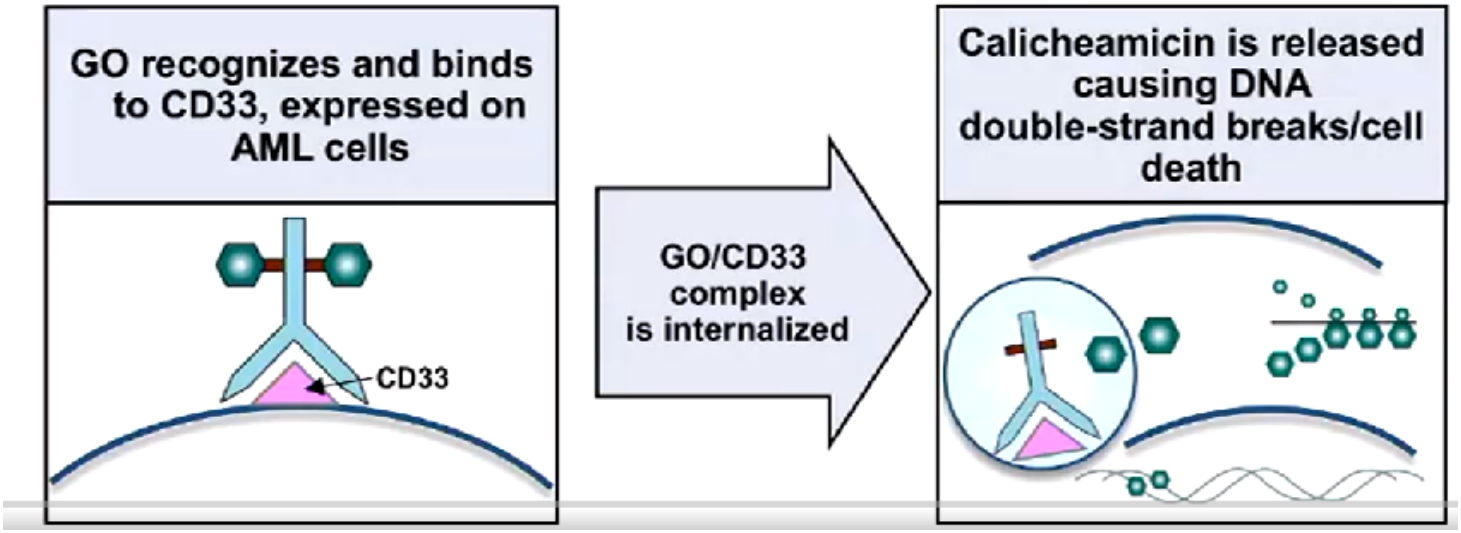
Perl AE et al, EHA 2019

Targeting CD33

Gemtuzumab ozogamicin (GO)

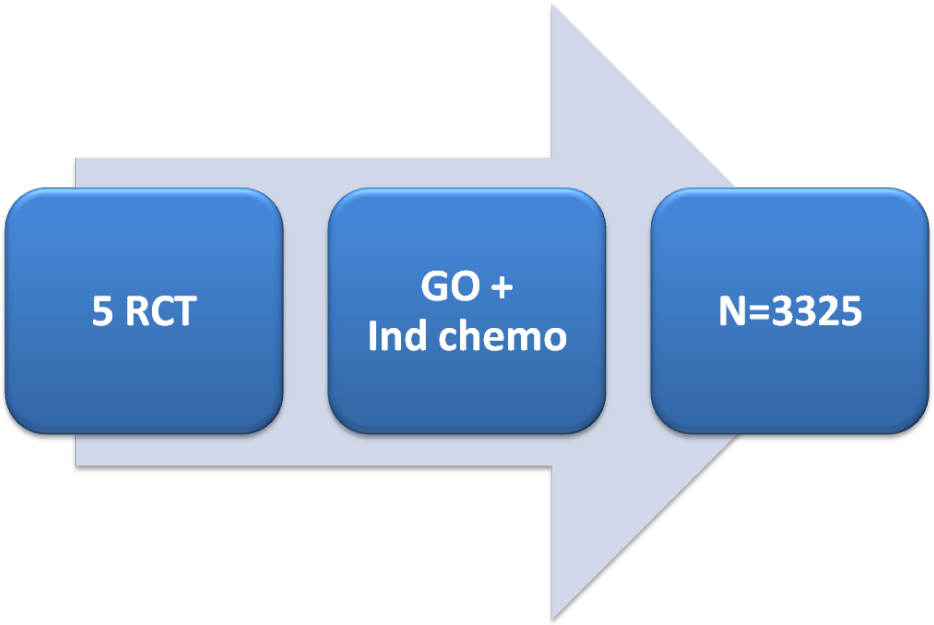


Mechanism of Action



GO in induction therapy

Meta-analysis of 5 randomized trials



Younger pts

- SWOG 0106
- MRC AML15
- GOELAMS 2006/IR

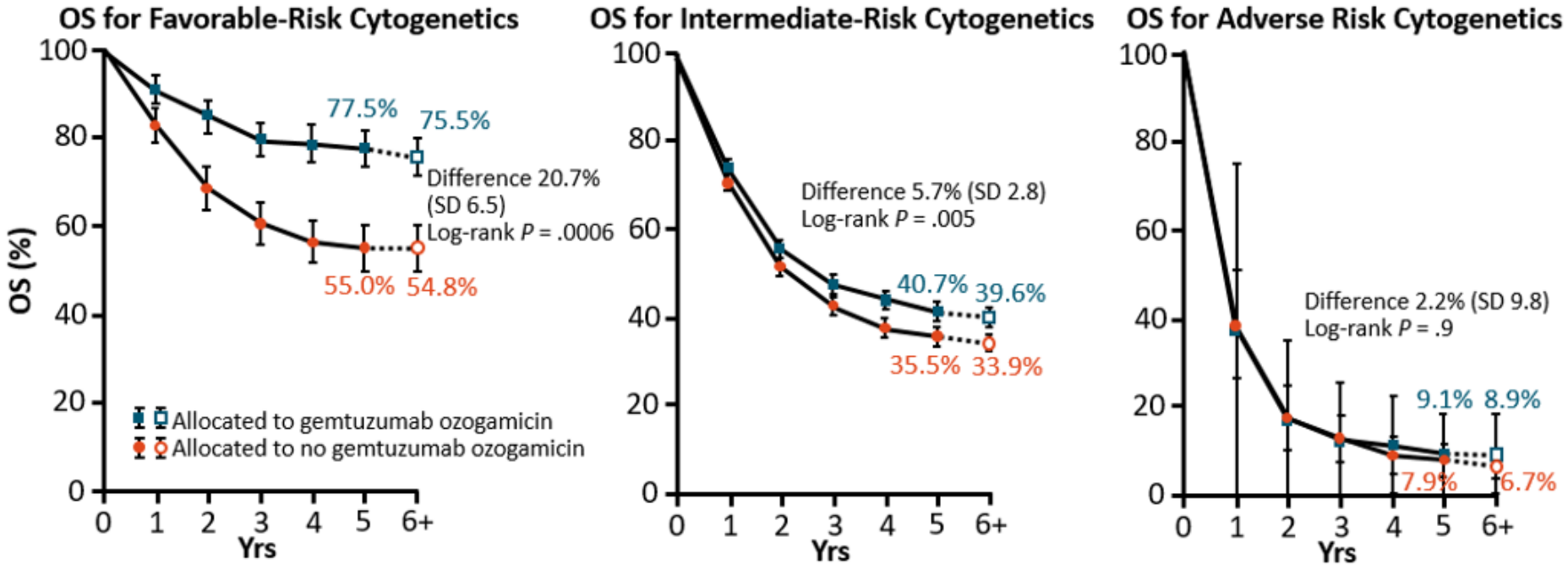
Older pts

- ALFA 0701
- NCRI AML16

Hills RK et al, Lancet Oncol 2014

Survival

GO has no impact on remission rates but reduces relapse risk (p<0.0001) and prolongs OS (p<0.0001)

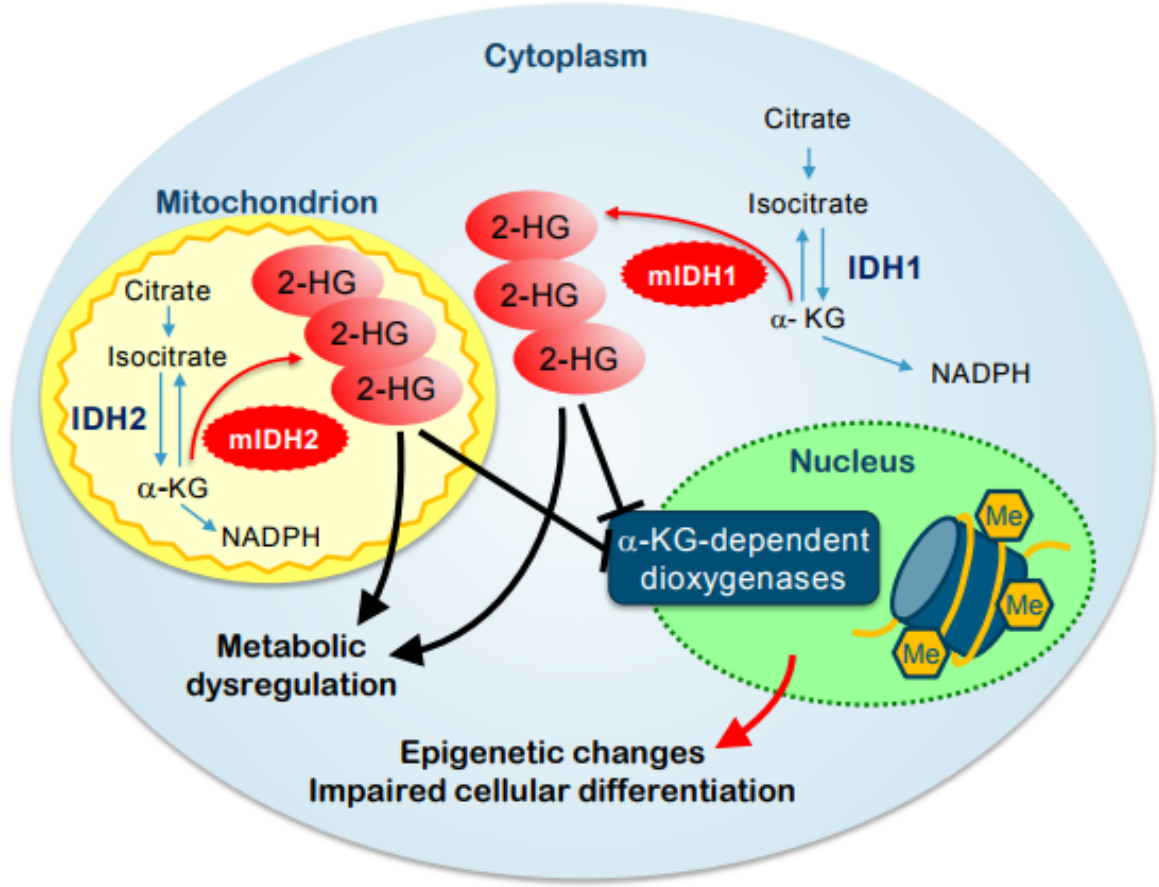


Targeting mIDH

mIDH (1,2) is seen in ~20% of AML

Results in accumulation of the oncometabolite 2-HG which inhibits a-KG dependent reactions

2-HG leads to DNA and histone hypermethylation, and a resultant block in differentiation

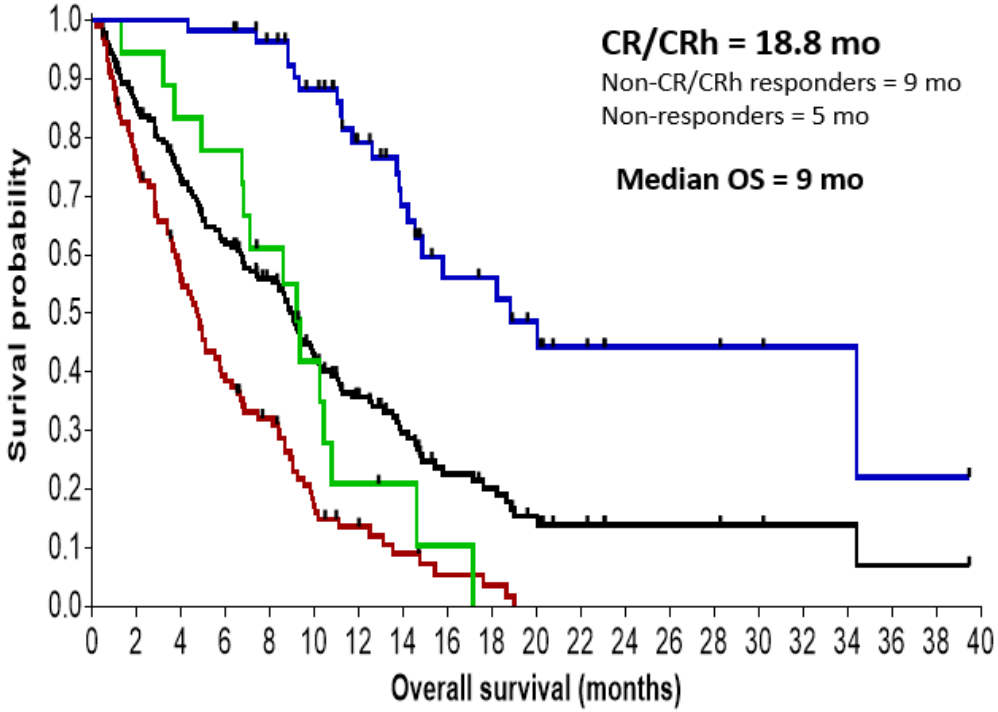


DiNardo CD et al, Leukemia 2016

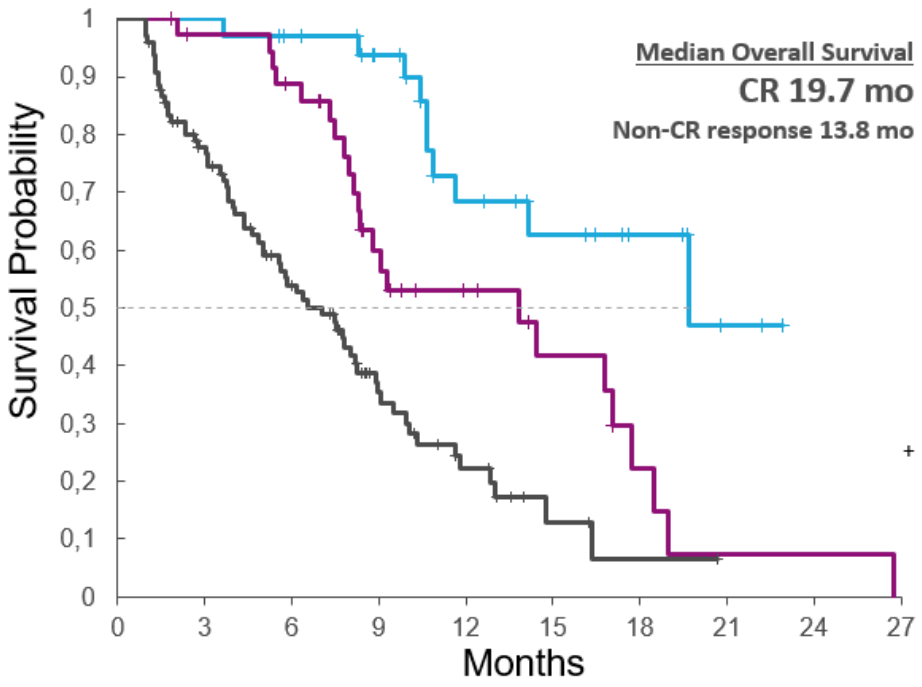
mIDH-inhibitor monotherapy in R/R AML

CR rate ~20%
CR/CRh rate ~30%
ORR ~40%

Ivosidenib (IDH1 inhibitor)



Enasidenib (IDH2 inhibitor)

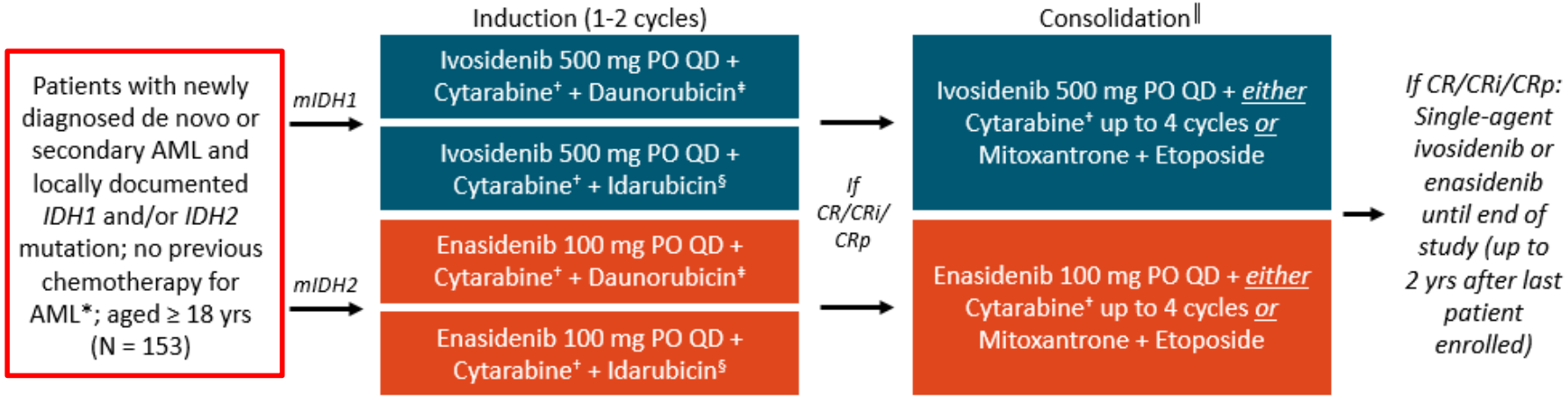


DiNardo CD et al, NEJM 2018; Stein EM et al, Blood 2017

mIDH inhibitors in ND-AML

Phase 1 study

- Interim analysis of open-label, multicenter phase I trial with 6 + 6 design for evaluating safety, followed by cohort expansion (data cutoff: August 1, 2018)



*In those with secondary AML, prior treatment (including hypomethylating agents) for MDS or other previous hematologic disorders permitted.
†Cytarabine given at 200 mg/m²/day x 7 days. ‡Daunorubicin given at 60 mg/m²/day x 3 days. §Idarubicin 12 mg/m²/day x 3 days.
‖In patients proceeding to transplant, ivosidenib and enasidenib are discontinued.

- Primary endpoint: safety and tolerability
- Secondary, exploratory endpoints: clinical activity, MRD status by flow cytometry, *IDH* mutation clearance by digital PCR

Stein EM et al, ASH 2018

Outcomes

Best Response,* n (%)	Ivosidenib + CT			Enasidenib + CT		
	All (n = 49)	de novo (n = 34)	Secondary AML (n = 15)	All (n = 89)	de novo (n = 56)	Secondary AML (n = 33)
CR + CRi/CRp	39 (80)	31 (91)	8 (53)	64 (72)	43 (77)	21 (64)
▪ CR	35 (71)	27 (79)	8 (53)	50 (56)	36 (64)	14 (42)
▪ CRi/CRp	4 (8)	4 (12)	--	14 (16)	7 (13)	7 (21)
MLFS	3 (6)	1 (3)	2 (13)	11 (12)	6 (11)	5 (15)
PR	1 (2)	--	1 (7)	1 (1)	--	1 (3)
Treatment failure	6 (12)	2 (6)	4 (27)	13 (15)	7 (13)	6 (18)

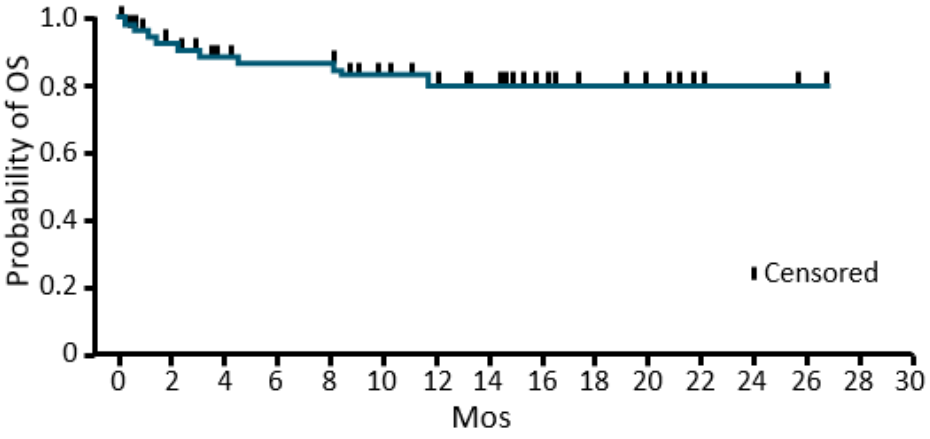
30-d mortality

- IVO arm 5%, ENA arm 5%

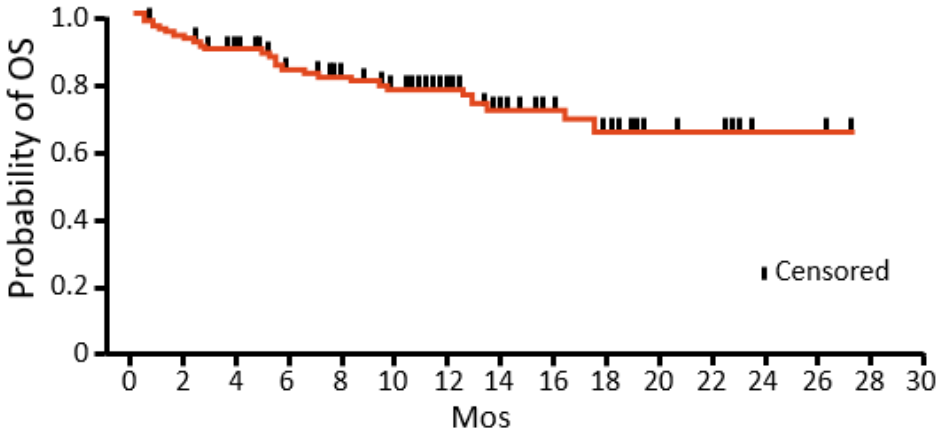
60-d mortality

- IVO arm 8%, ENA arm 9%

Ivosidenib in Patients With *IDH1*-Mutated AML

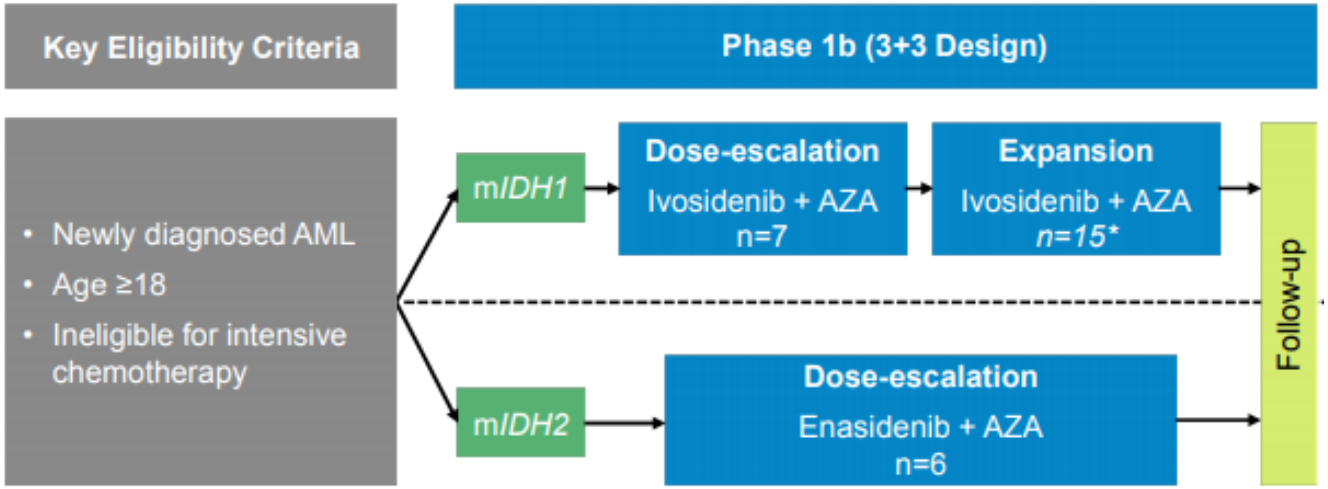


Enasidenib in Patients With *IDH2*-Mutated AML



Stein EM et al, ASH 2018

ENA or IVO + AZA



Parameter, n (%)	Ivosidenib 500 mg + AZA (N = 23)	Enasidenib 100/200 mg + AZA (N = 6)
Overall response*	18 (78)	4 (67)
CR	10 (44)	3 (50)
CRi/CRp	5 (22)	0
PR	0	0
MLFS	3 (13)	1 (17)

DiNardo CD et al, ASCO 2018

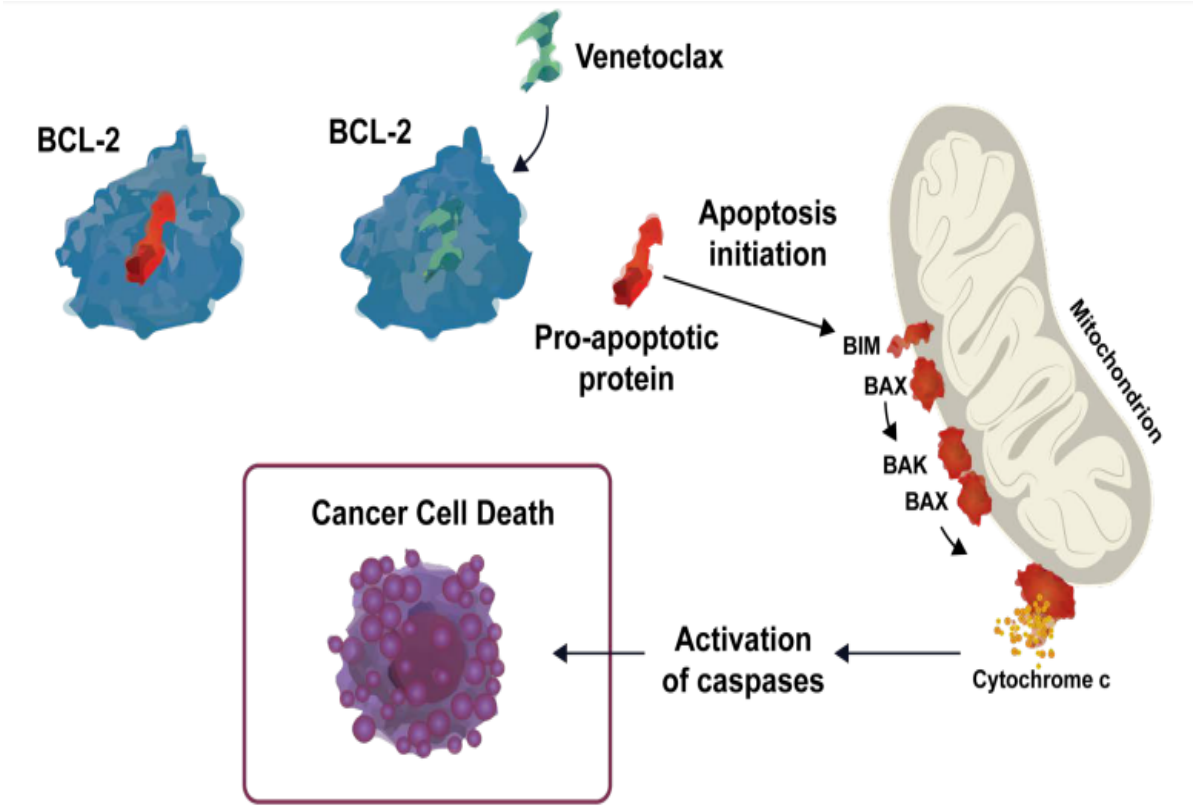
Targeting BCL-2

BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering proapoptotic proteins

Venetoclax is an oral BCL-2 selective inhibitor

Binds to BCL-2 freeing proapoptotic proteins that initiate apoptosis

Phase 2 study in R/R AML: ORR 19%

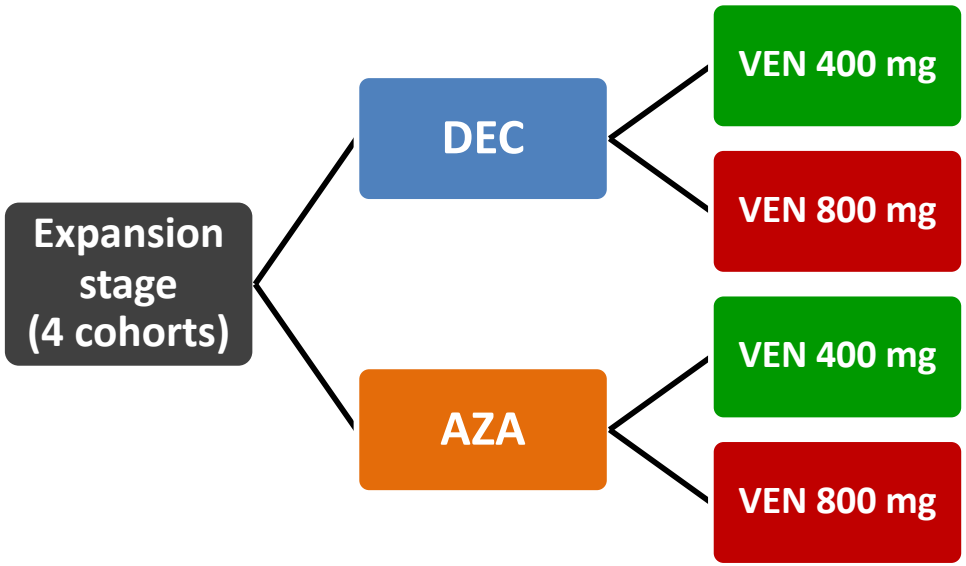


Konopleva M et al, Cancer Discov 2016; Roberts AW et al, Clin Cancer Res 2017

VEN + HMAs in ND older AML

Phase 1b, open-label, multicenter study with dose-escalation and expansion stages

- **VEN + DEC (20 mg/m2 iv, D1-5, 28d cycles) or VEN + AZA (75 mg/m2 iv/sc, D1-7, 28d cycles)**



Eligibility criteria

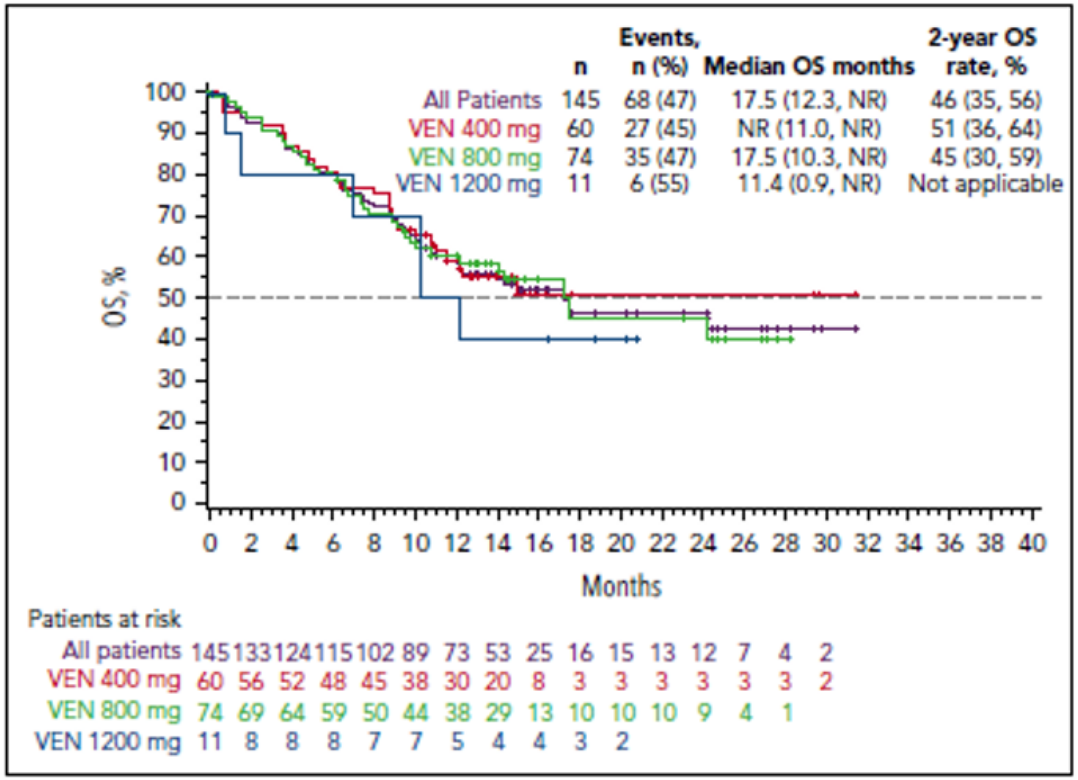
- Patients ≥65y with untreated AML; Int/Adv CG; ECOG ≤2; ineligible for standard induction therapy

Objectives

- Primary: efficacy and safety
- Secondary: CR, CRi, DOR, OS

DiNardo CD et al, Blood 2019

Results



CR + CRi = 97 (67%)

Median DOR = 11.3 mos (8.9 – NR)

Median OS = 17.5 mos (12.3 – NR)

Subgroup Results

Subgroup	Evaluable for responses/OS, n (%)	CR + CRi, n (%)	n for Median duration of CR + CRi	Median duration of CR + CRi, (95% CI)	Median OS, mo (95% CI)
All patients	145	97 (67)	97	11.3 (8.9, NR)	17.5 (12.3-NR)
Cytogenetic risk					
Intermediate	74 (51)	55 (74)	55	12.9 (11, NR)	NR (17.5-NR)
Poor	71 (49)	42 (60)	42	6.7 (4.1, 9.4)	9.6 (7.2-12.4)
Age					
≥75 y	62 (43)	40 (65)	40	9.2 (6.4, 12.5)	11 (9.3-NR)
<75 y	83 (57)	57 (69)	57	12.9 (9.2, NR)	17.7 (14.2-NR)
AML					
De novo	109 (75)	73 (67)	73	9.4 (7.2, 11.7)	12.5 (10.3-24.4)
Secondary	36 (25)	24 (67)	24	NR (12.5, NR)	NR (14.6-NR)

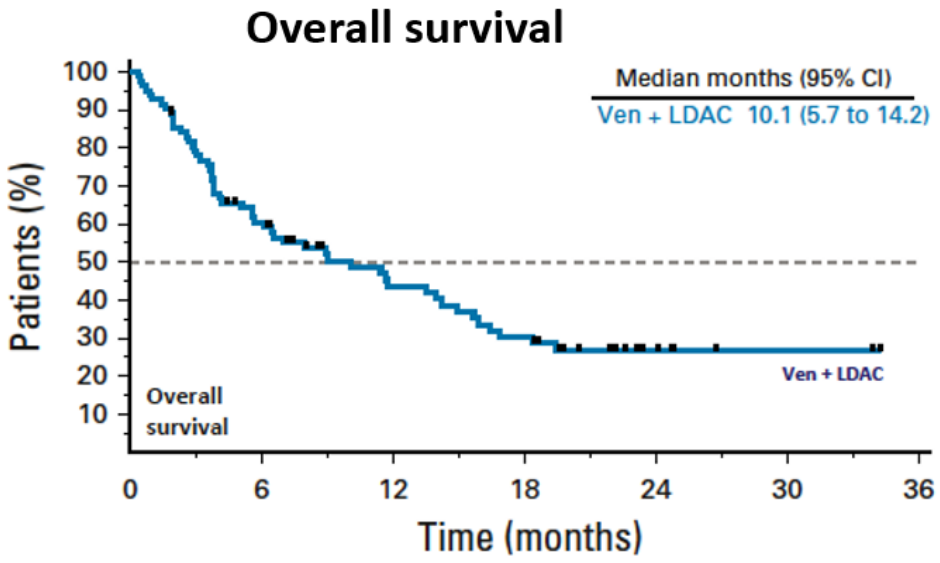
VEN + LDAC (phase 1/2)

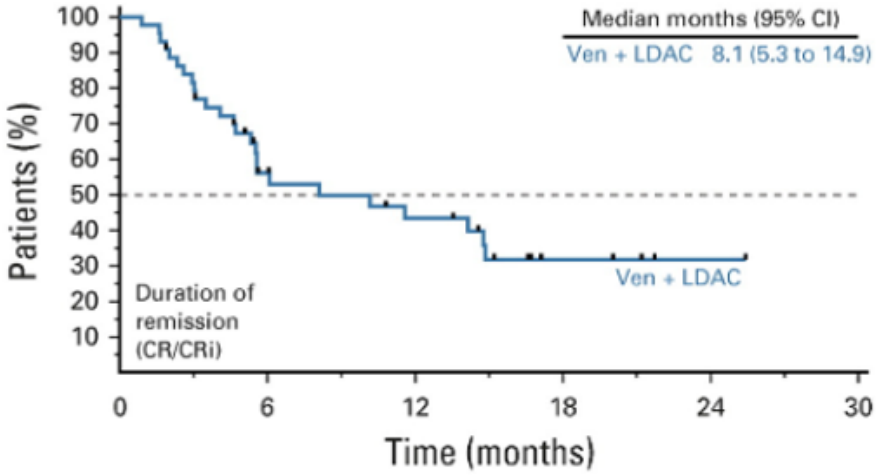
Elderly pts with ND-AML unfit for IC
(Median age 74y, 66-87)

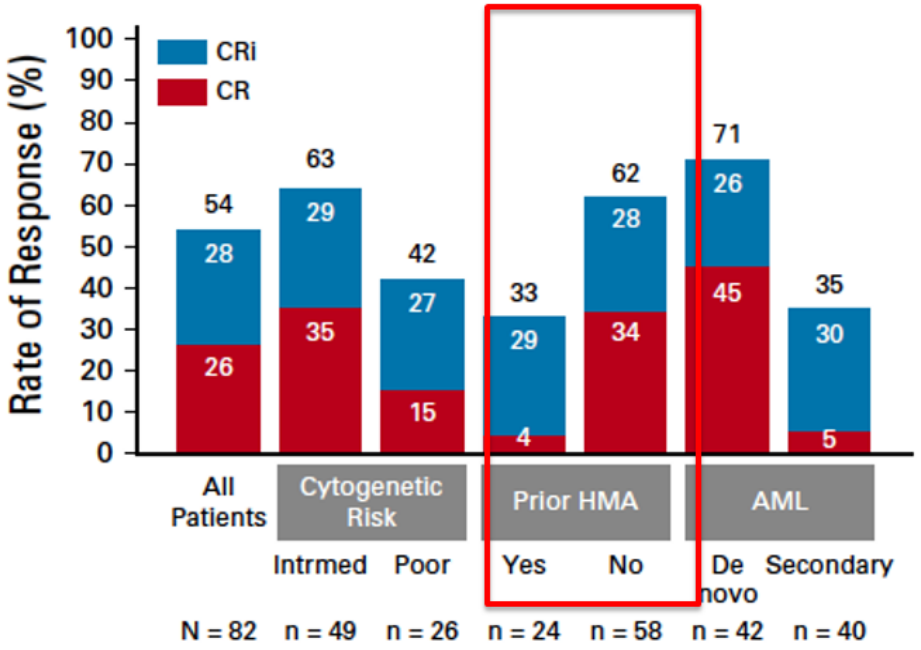
VEN 600 mg PO QD on days 1 – 28*
LDAC 20 mg/m^2 SC QD on days 1 – 10
(28-day cycles)

Wei A et al, JCO 2019

Results





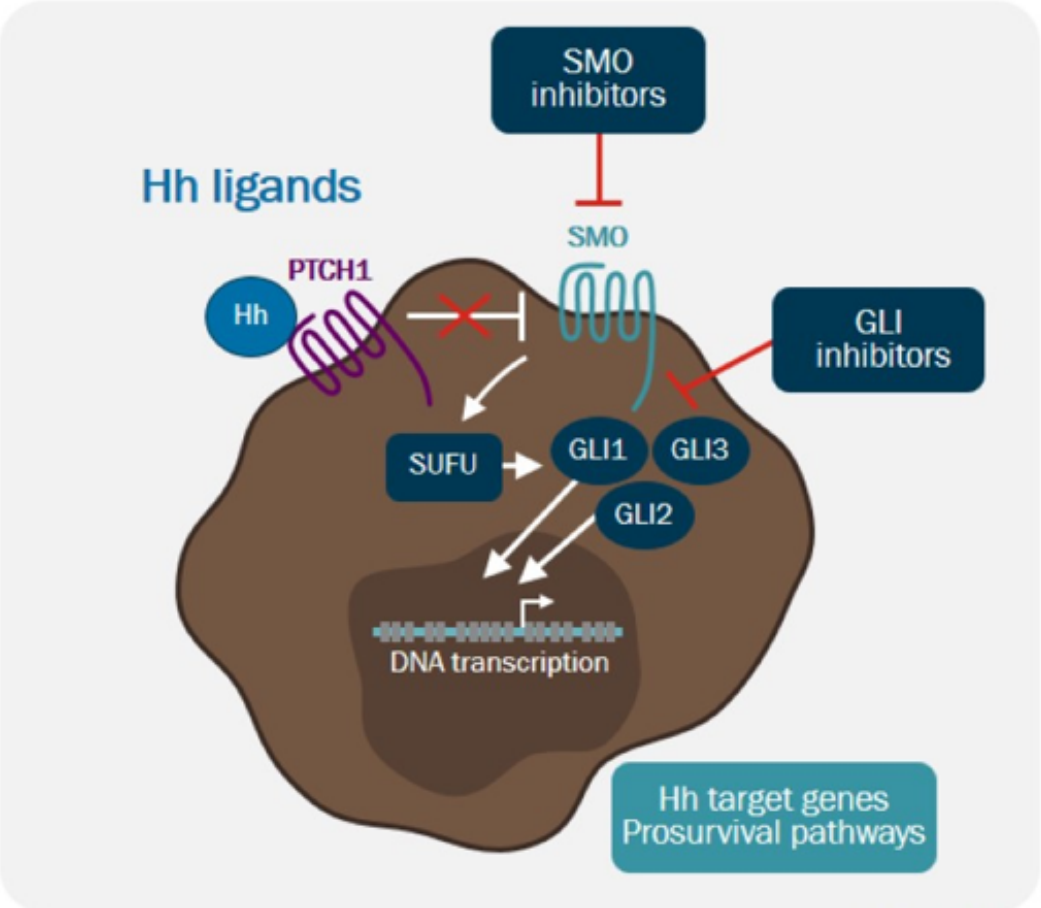


TP53mut: 30% IDHmut: 72%

NPM1mut: 89% FLT3 mut: 44%

Targeting Hh pathway

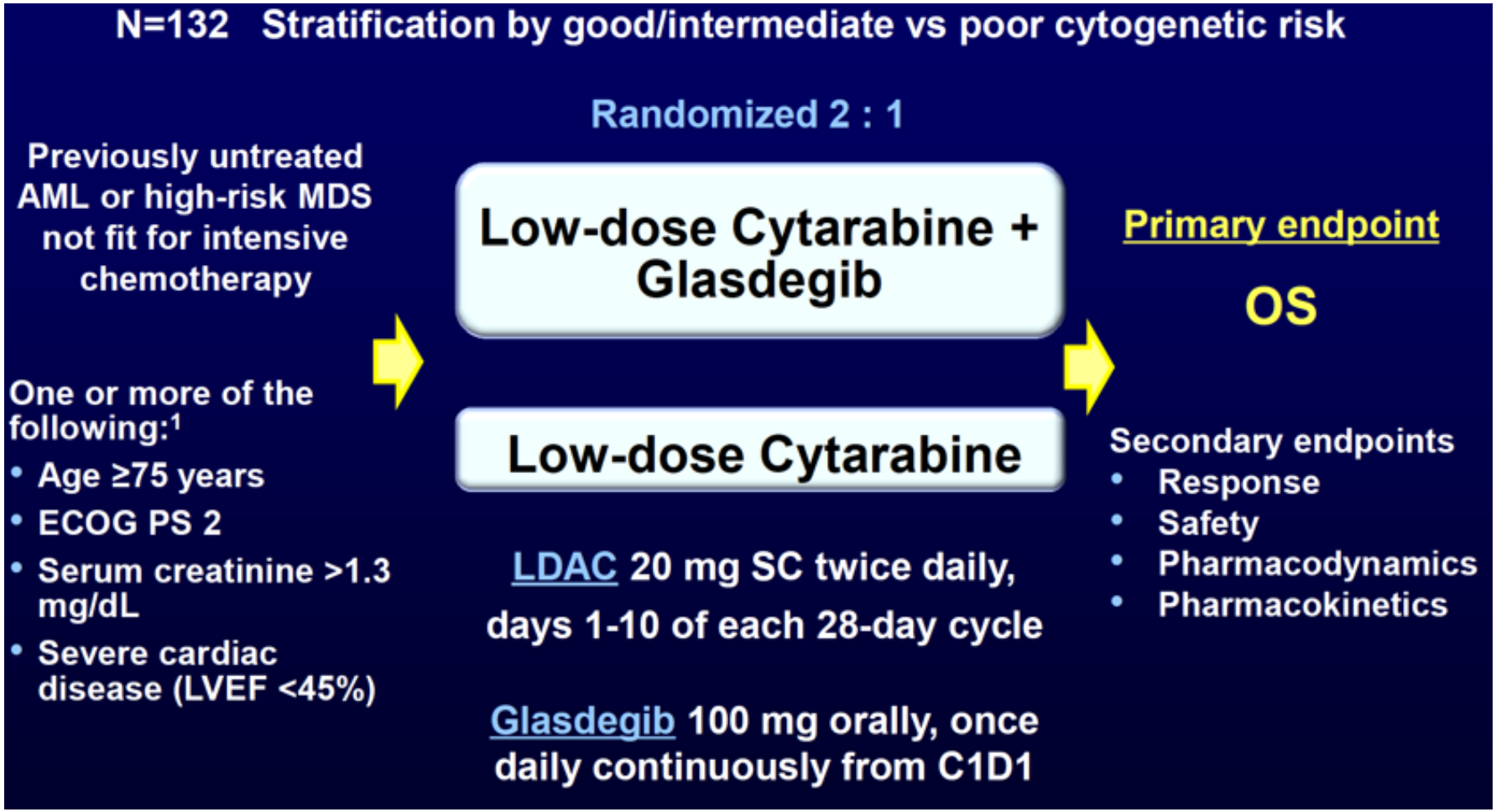
- The Hh-Pathway is aberrantly activated in AML/MDS, promoting cancer stem cell maintenance
- Hh inhibition reduces leukemia stem cells
- Glasdegib is a potent, selective, oral SMO inhibitor
- Single agent activity in advanced AML/MDS



Khan AA et al, Br J Haematol 2015; Martinelli G et al, Lancet Haematol 2015

GLA±LDAC in AML/HR-MDS

BRIGHT 1003 (Ph 2)

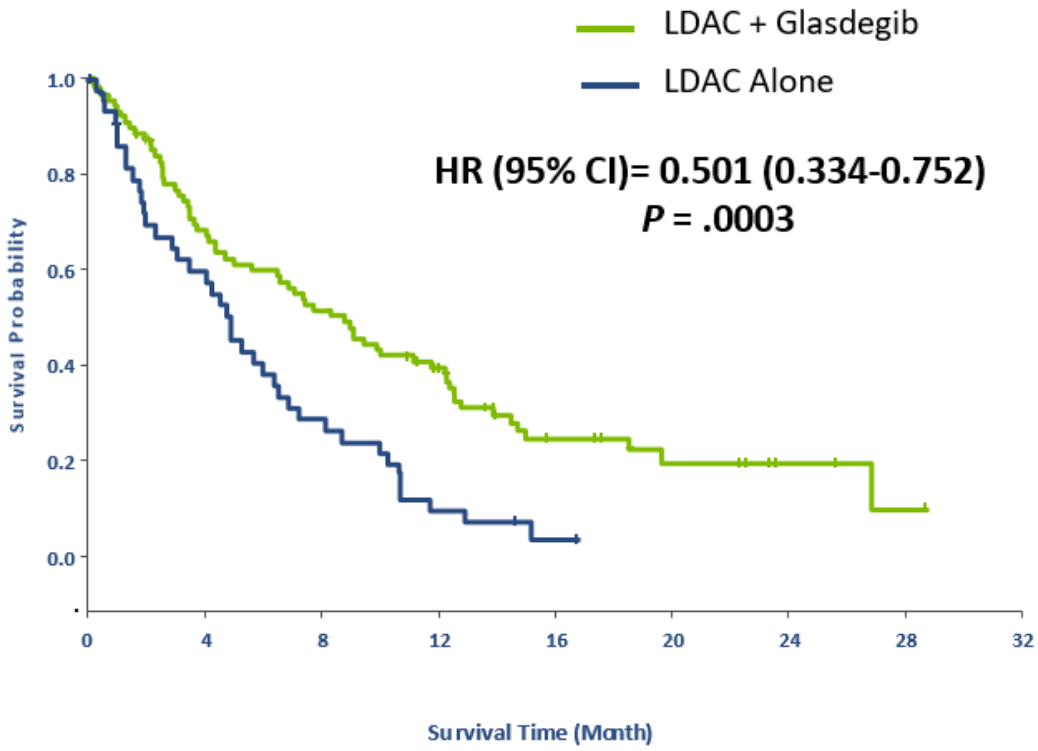


Cortes JE et al, Am J Hematol 2018

Results

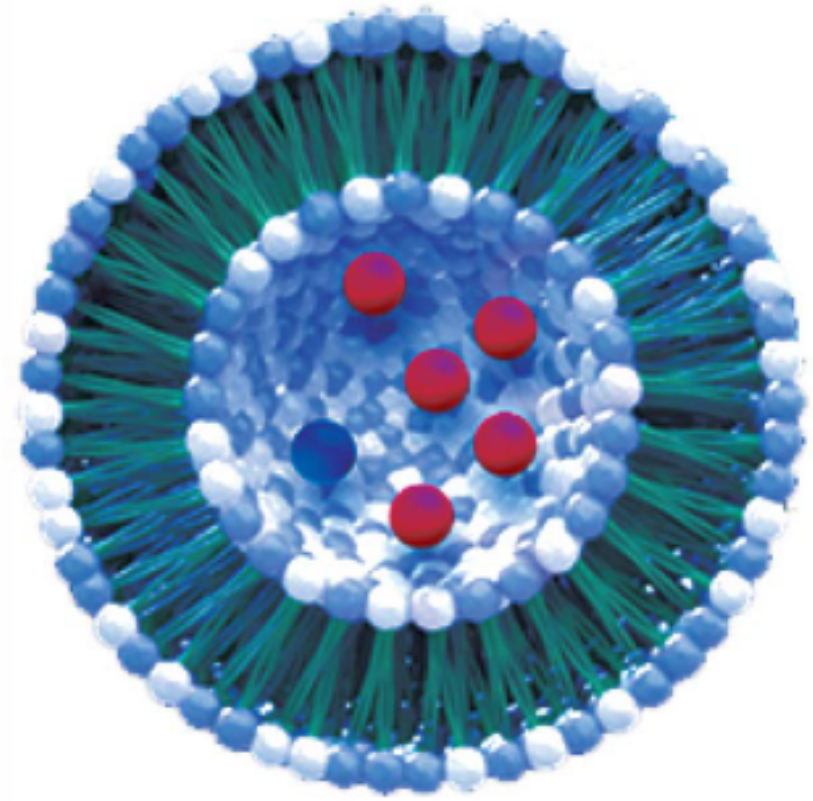
Phase II study in pts with AML and high-risk myelodysplastic syndrome (N = 132)

	LDAC + Glasdegib (n = 88)	LDAC Alone (n = 44)
Median age, yrs (range)	77 (63-92)	75 (58-83)
Good/Int CG, n (%)	52 (60)	25 (57)
CR/CRi (n, %)	**20 (23)**	**2 (4.5)**
Median OS (mos)	**8.8 mos**	**4.9 mos**



Liposomal Cytarabine + Dauno

CPX-351



- CPX-351 a 5:1 molar ratio of cytarabine:daunorubicin
- Formulation provides synergistic leukemia cell killing in vitro[1]
- In humans
  - CPX-351 preserved delivery of the 5:1 drug ratio for > 24 hours
  - Drug exposure maintained for 7 days[2]
- Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]

Treatment of adults with newly diagnosed tAML or AML-MRC

Aug 3, 2017

APPROVED FDA

[1]Tardi P et al, Leuk Res 2009; [2]Feldman EJ et al, JCO 2011; [3]Lim WS et al, Leuk Res 2010

CPX-351 vs 3+7 in Elderly HR-AML

ND high-risk/secondary AML; aged 60 to 75 years; able to tolerate intensive therapy; PS 0-2; N = 309

R

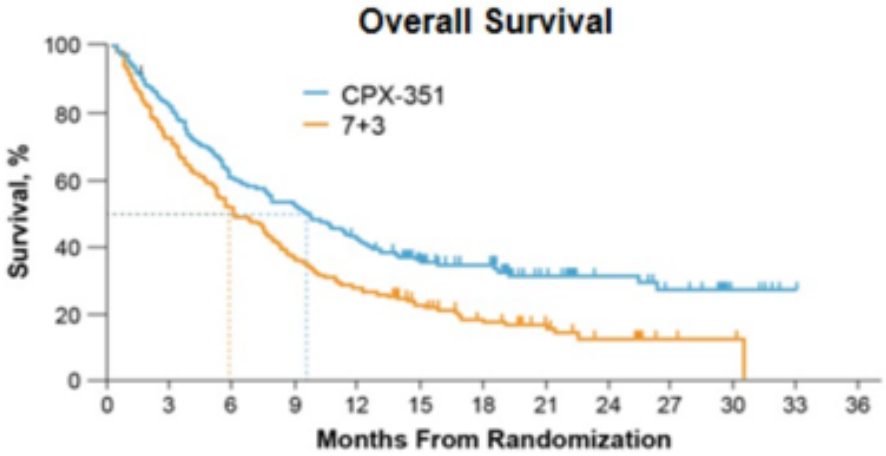
- CPX-351; n = 153
- 7+3; n = 156

Induction (1-2 cycles)

CR or CRi: Consolidation (1-2 cycles)

Follow-up: Death *or* 5 y

Primary endpoint: OS



	CPX-351 n = 153	7+3 n = 156	OR; *P*
CR + CRi, %	47.7	33.3	1.77; .016
HSCT rate, %	34.0	25.0	1.54; .097
Median OS, mo	9.56	5.95	HR = .69; .003
Deaths ≤ 60 d, %	13.7	21.2	*P* = .097

- Improved outcomes across age groups and AML subtypes with liposomal cytarabine/daunorubicin
- Incidence of nonhematologic AEs comparable between arms

Lancet JE et al, JCO 2018