How I treat High-Risk AML

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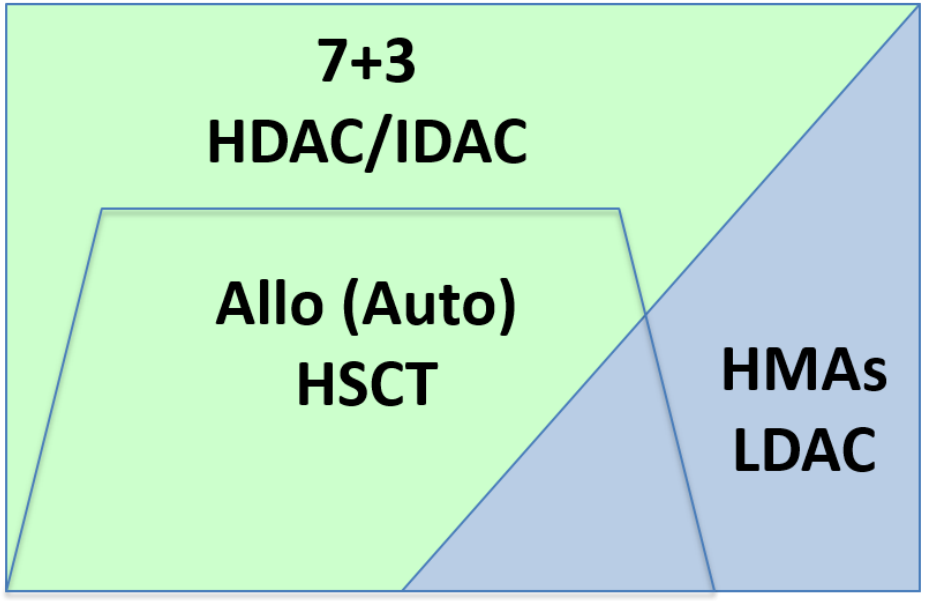
Torino, 09/2018

Current treatment paradigms



Age <60y

- CR 70-80%
- Cure ~40%

Age >60y

- CR 40-60%
- Cure ~10%

Burnett AK, ASH 2012

What defines HR-AML

Clinical features

- Advanced age (>75y)
- Medical co-morbidities, Poor PS
- sAML, tAML

Biological features

- Adverse cytogenetics
- Unfavorable molecular abnormalities
- MRD+

Why is HR-AML high risk?

Poor clinical features

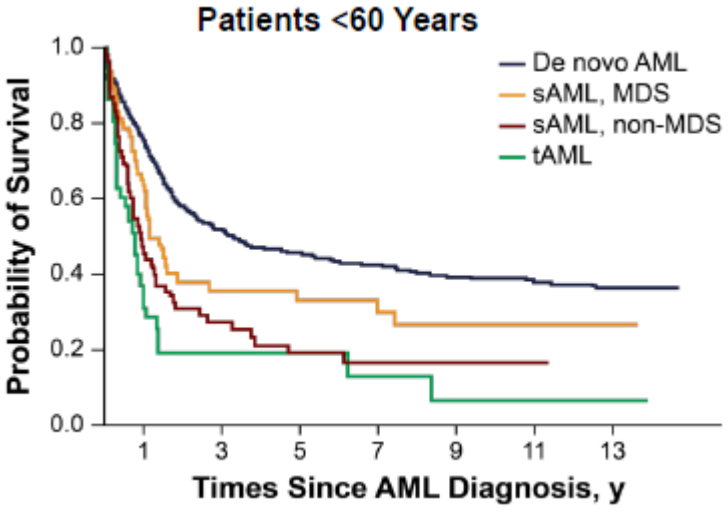
+

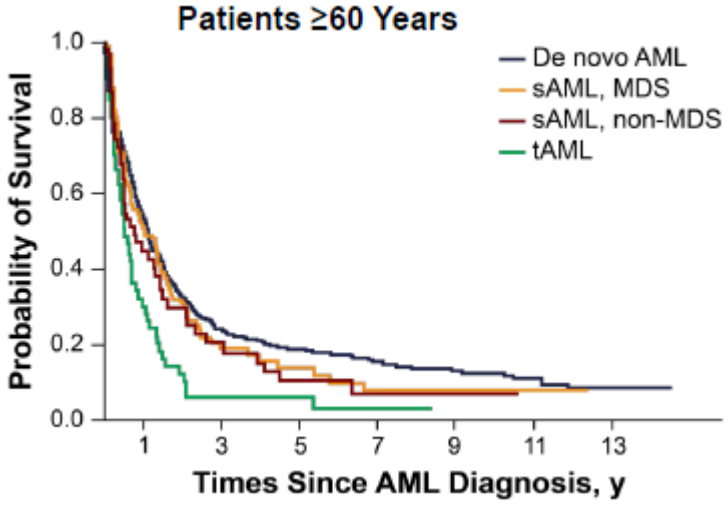
Adverse biology

→

Drug resistance

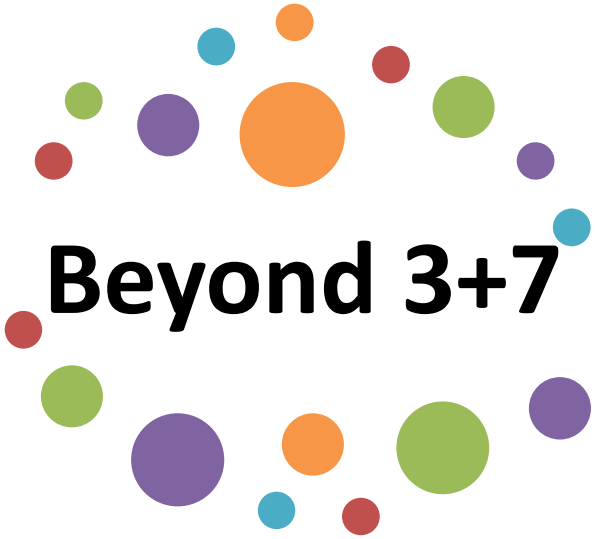
- poor response to induction
- high relapse rate





Granfeldt Ostgard LS et al, JCO 2015

How can we do better?



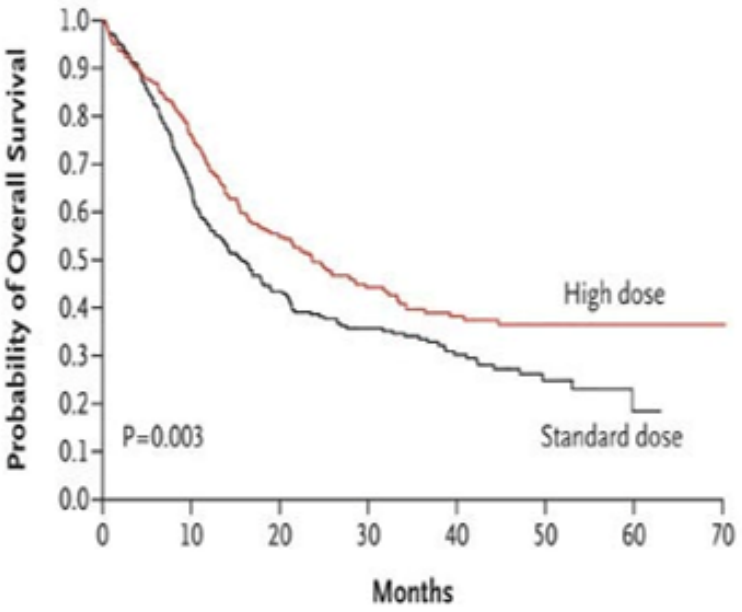
- Optimization of induction therapy
- New drugs
- Better strategies

Dauno intensification?

ECOG 1900 trial: (n=647)

Dauno **45 vs 90**mg/m² in course 1

57% vs 71% CR rate (p<0.001)

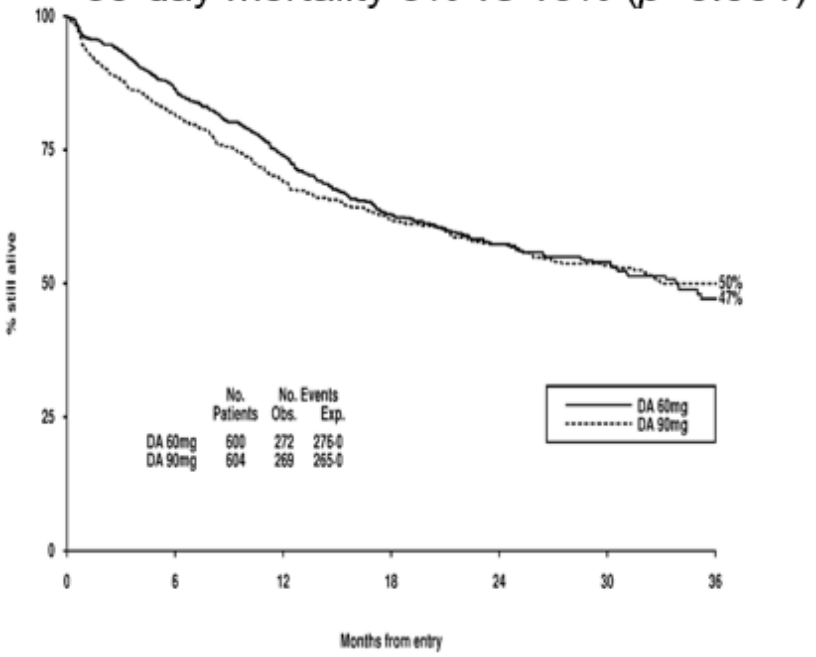


NCRI AML17 study: (n=1204)

Dauno **60 vs 90**mg/m² in course 1

73% vs 73% CR rate

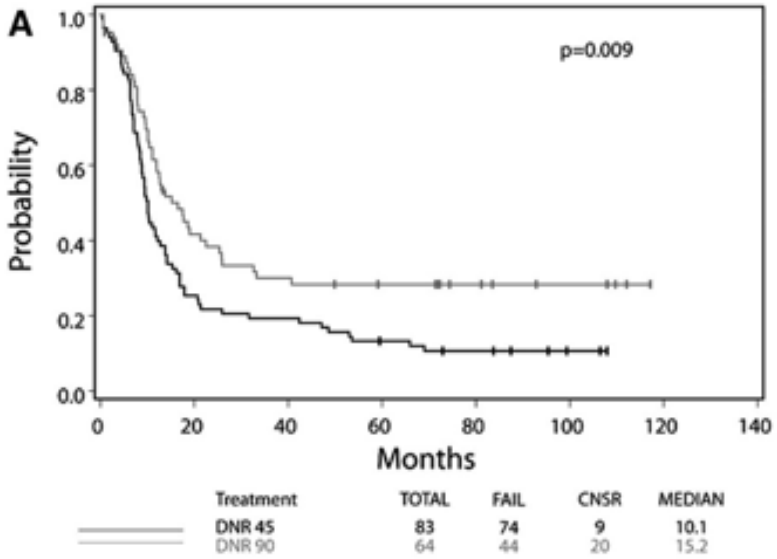
60-day mortality 5% vs 10% (*p*=0.001)

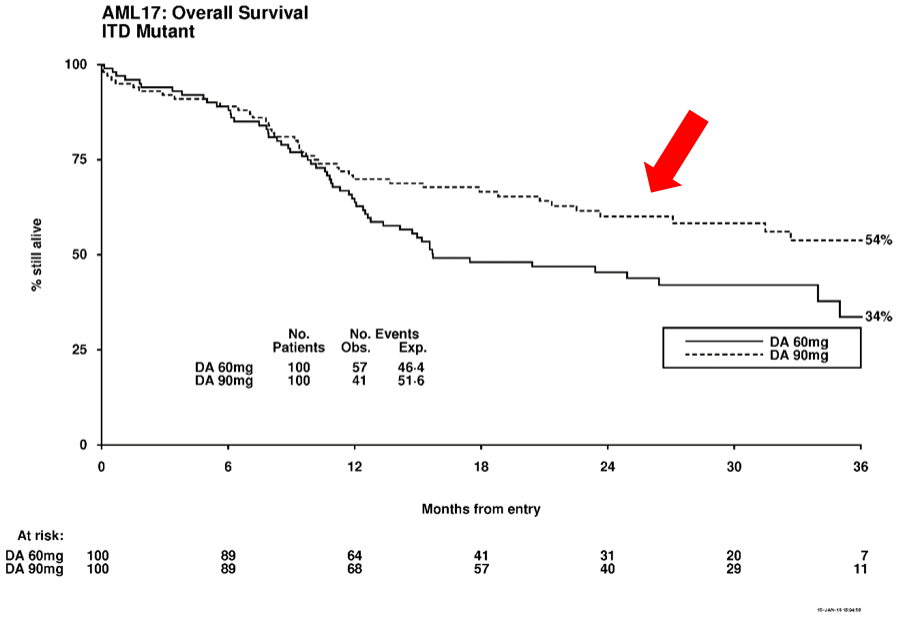


Fernandez HF et al, NEJM 2009; Burnett AK et al, Blood 2016

Dauno/90 for FLT3-ITDm AML?

FLT3-ITD^{mut}



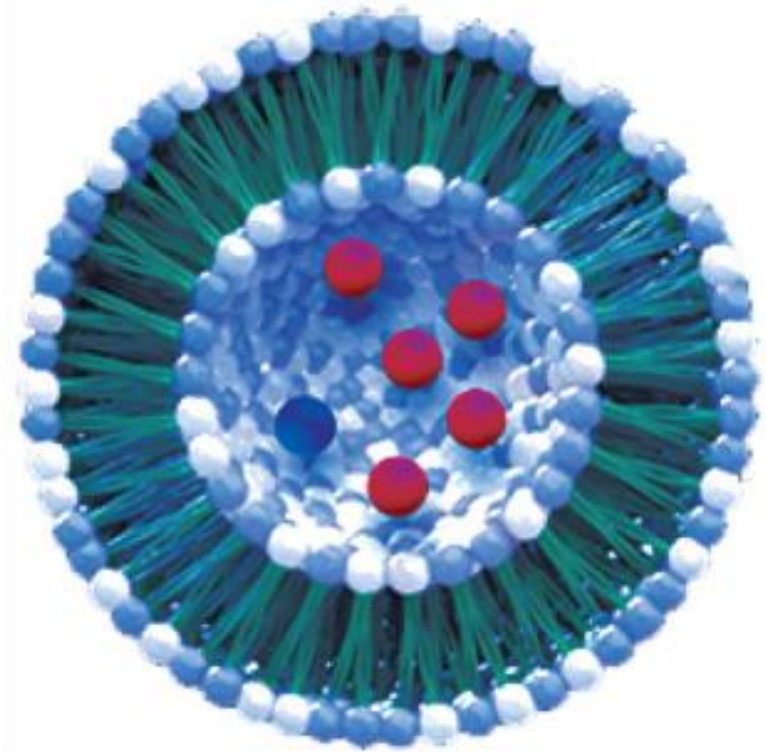


ECOG 1900

Luskin MR et al, Blood 2016; Burnett AK et al, Blood 2016

New drugs: CPX-351

Vyxeos



- 1:5 molar ratio of daunorubicin to cytarabine
- Synergistic activity in both in vitro and animal models
- 100-nm bilamellar liposomes
- 1 unit = 0.44 mg daunorubicin plus 1 mg cytarabine (1:5 molar ratio) complexed with copper
- Targets bone marrow and preferentially targets leukemic compared with normal marrow progenitors

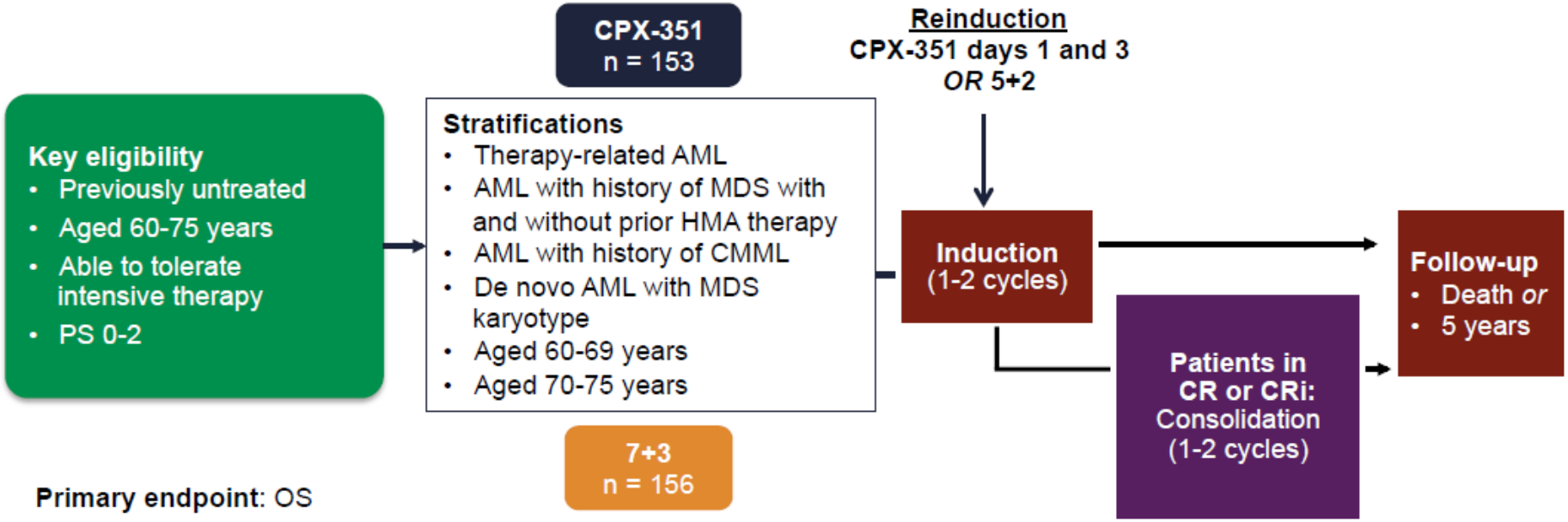
Treatment of adults with newly diagnosed tAML or AML-MRC

Aug 3, 2017

APPROVED FDA

Lancet JE et al, Blood 2014

CPX-351 vs 3+7 in HR-AML (phase 3)

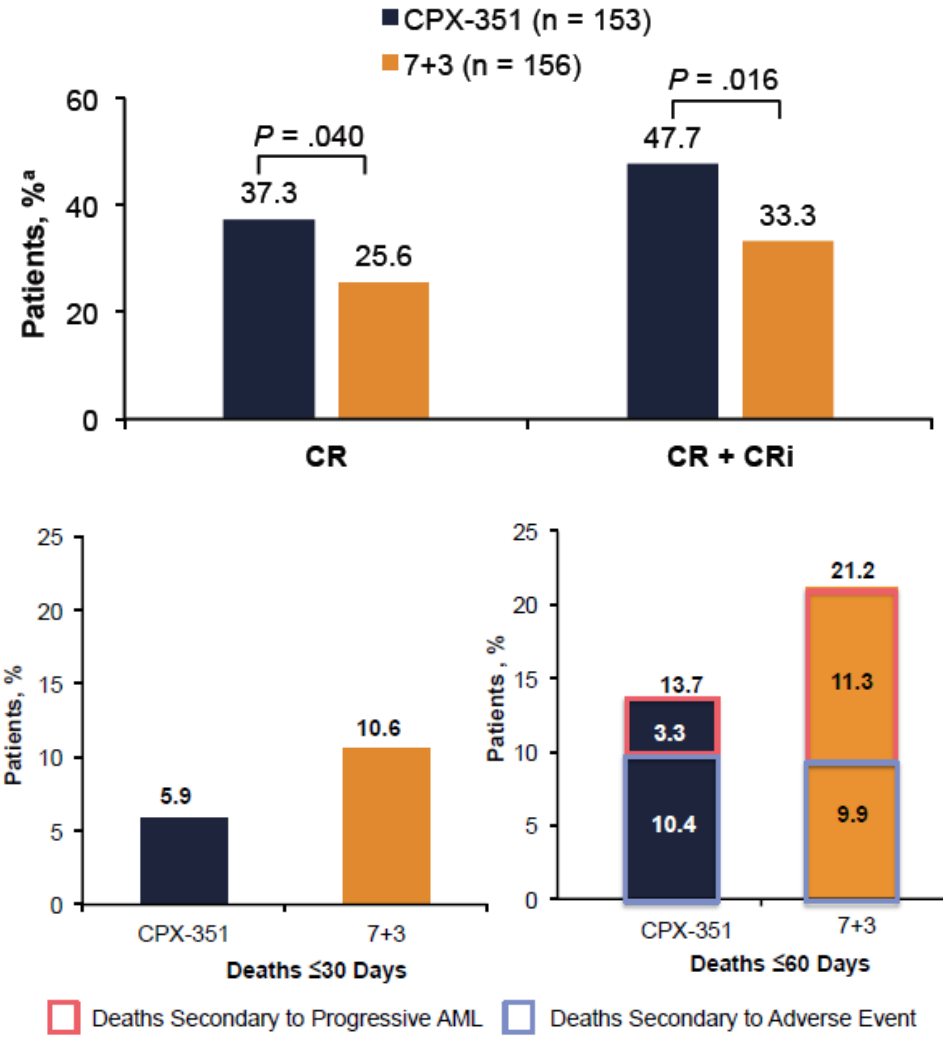


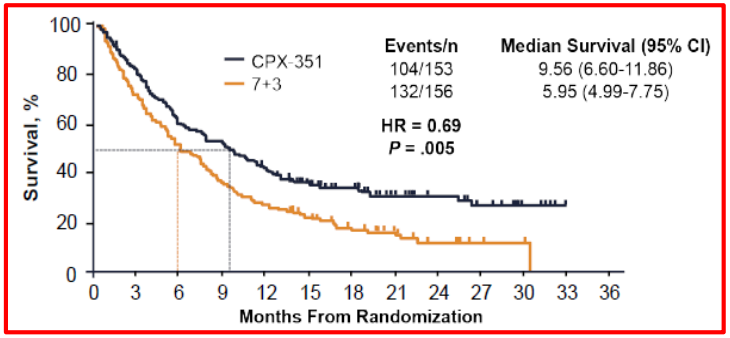
Primary endpoint: OS

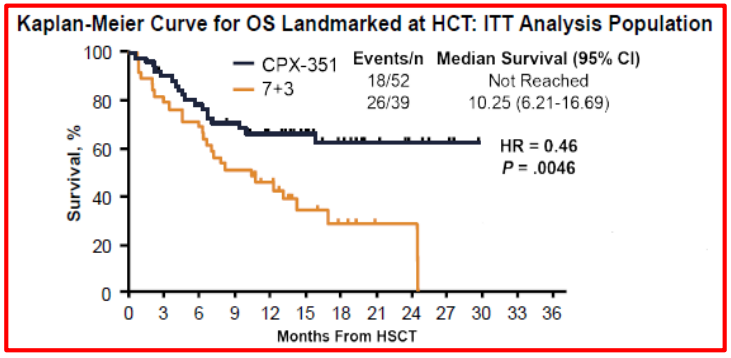
Induction
- CPX-351 44 mg/100 mg per m^2 IV days 1, 3, 5
- Cytarabine 100 mg/m^2/day x 7 plus daunorubicin 60 mg/m^2/day x 3

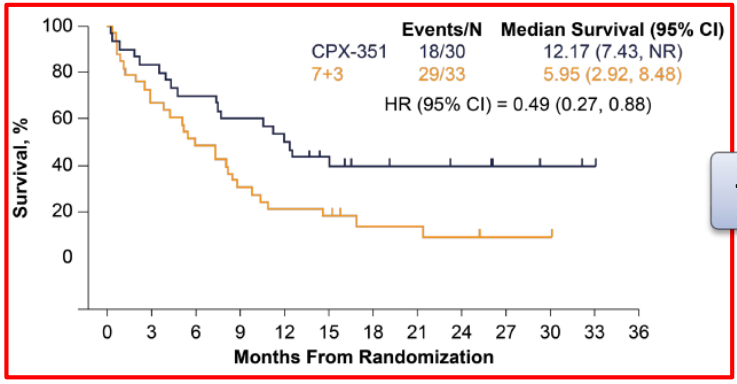
Consolidation
- CPX-351 29 mg/65 mg per m^2 IV days 1, 3
- Cytarabine 100 mg/m^2/day x 5 plus daunorubicin 60 mg/m^2/day x 2

CPX-351 vs 3+7 in HR-AML





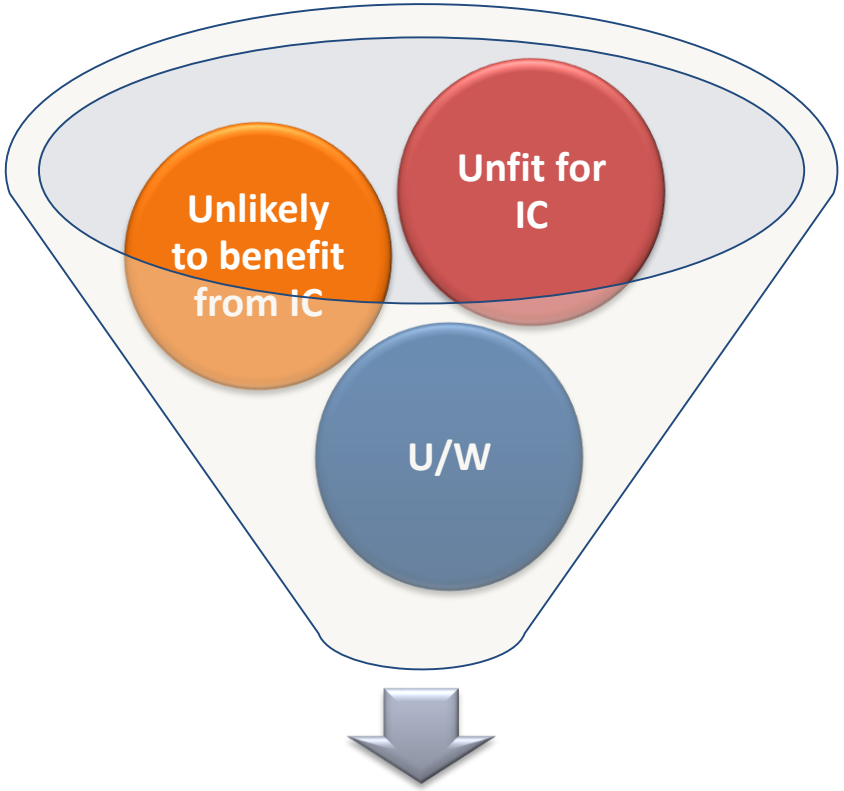




tAML

Lancet JE et al, ASH 2016, EHA 2017

Can lower-intensity therapies improve care in elderly patients?

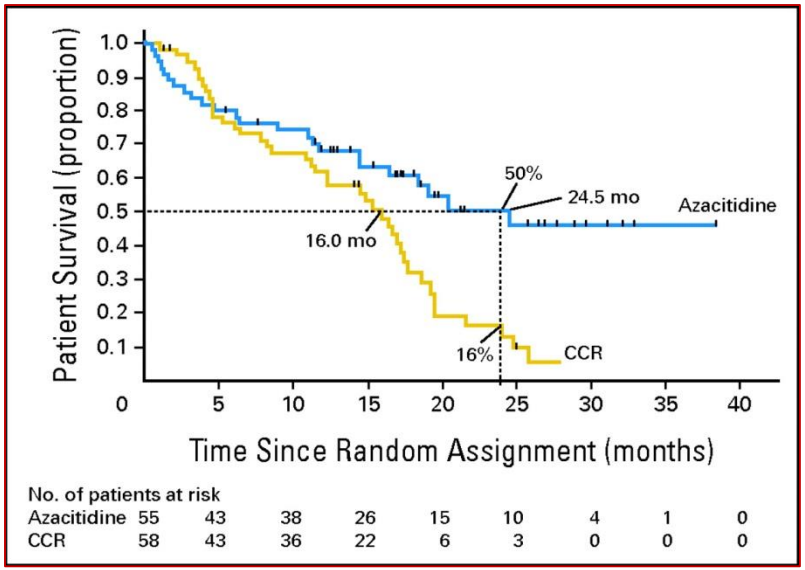


Epigenetic therapy as a new paradigm

Azacitidine Prolongs OS in LBC-AML

- **AZA-001 (N=358, INT-2/HR MDS)**
- **113 patients with 20-30% BM blasts**
- **Median age 70 years (50-83)**
- **55 random to AZA, 58 to CCR (47% BSC, 34% LDAC, 19% IC)**
- **AZA 75 mg/m^2/d sc x 7 days (median 8 cycles)**

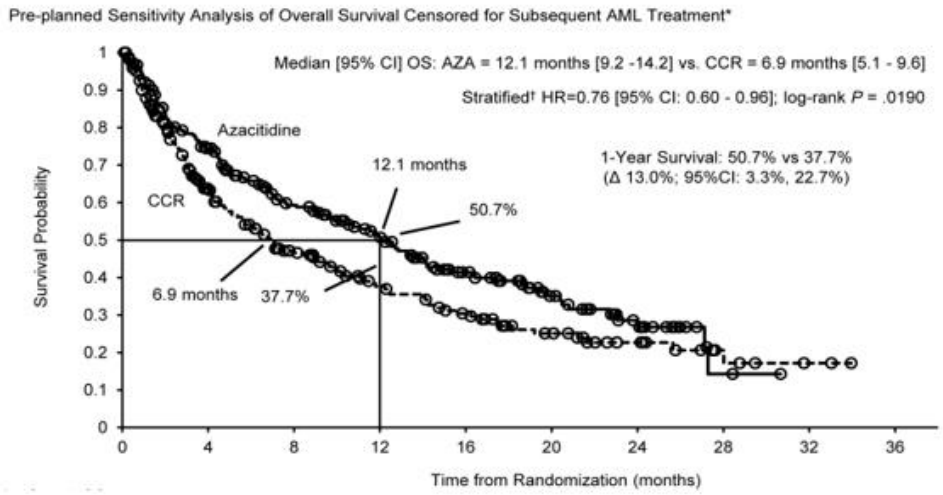
	AZA	CCR	*P*-value
Median OS (mo)	24.5	16.0	0.005
2-year OS (%)	50	16	0.001
CR (%)	18	16	NS
Hospitalizat (pt-yr)	3.4	4.3	0.03
Infection (pt-yr)	0.58	1.14	0.003

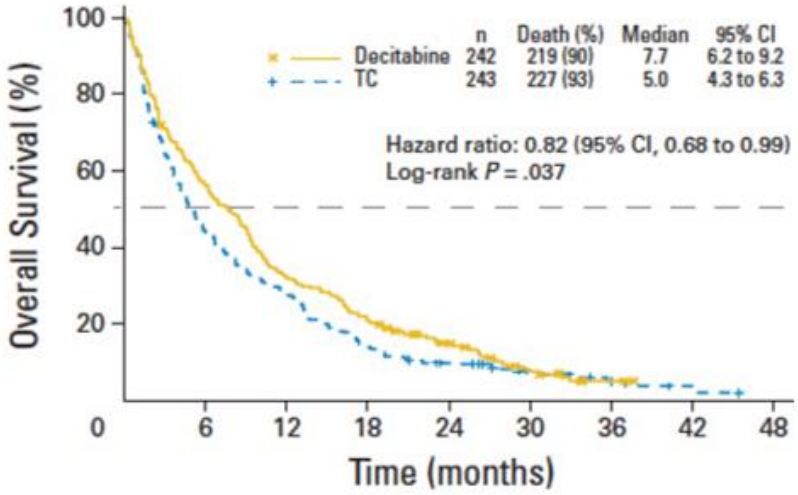


Fenaux et al, JCO 2010

HMAs vs TC in AML (phase 3 trials)

Overall Survival





Dombret H et al, Blood 2015; Kantarjian HM et al, JCO 2012

HOVON-97 (phase 3)

- Randomized, multicenter feasibility study

Pts ≥ 60 yrs of age with AML* and < 5% bone marrow blasts after 2 cycles of chemotherapy (N = 116)

*Excluded: FAB M3, t(15;17), RAEB, RAEB-t with IPSS ≥ 5.

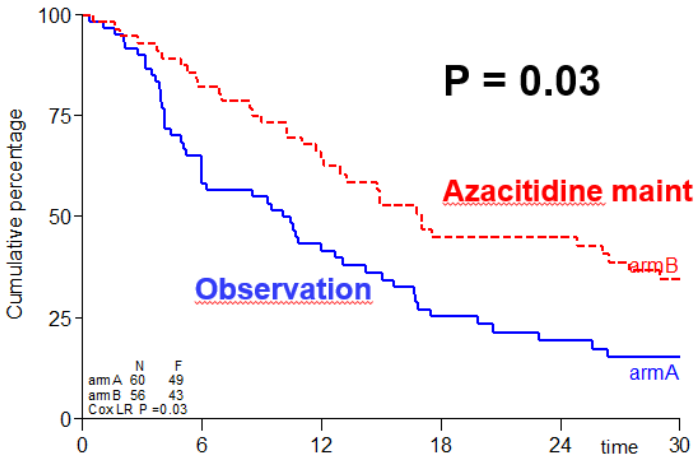
Azacitidine Maintenance
50 mg/m², Days 1-5 Q4W
for ≤ 12 cycles until relapse
(n = 56)

Observation
(n = 60)

Follow-up ≥ 5 yrs

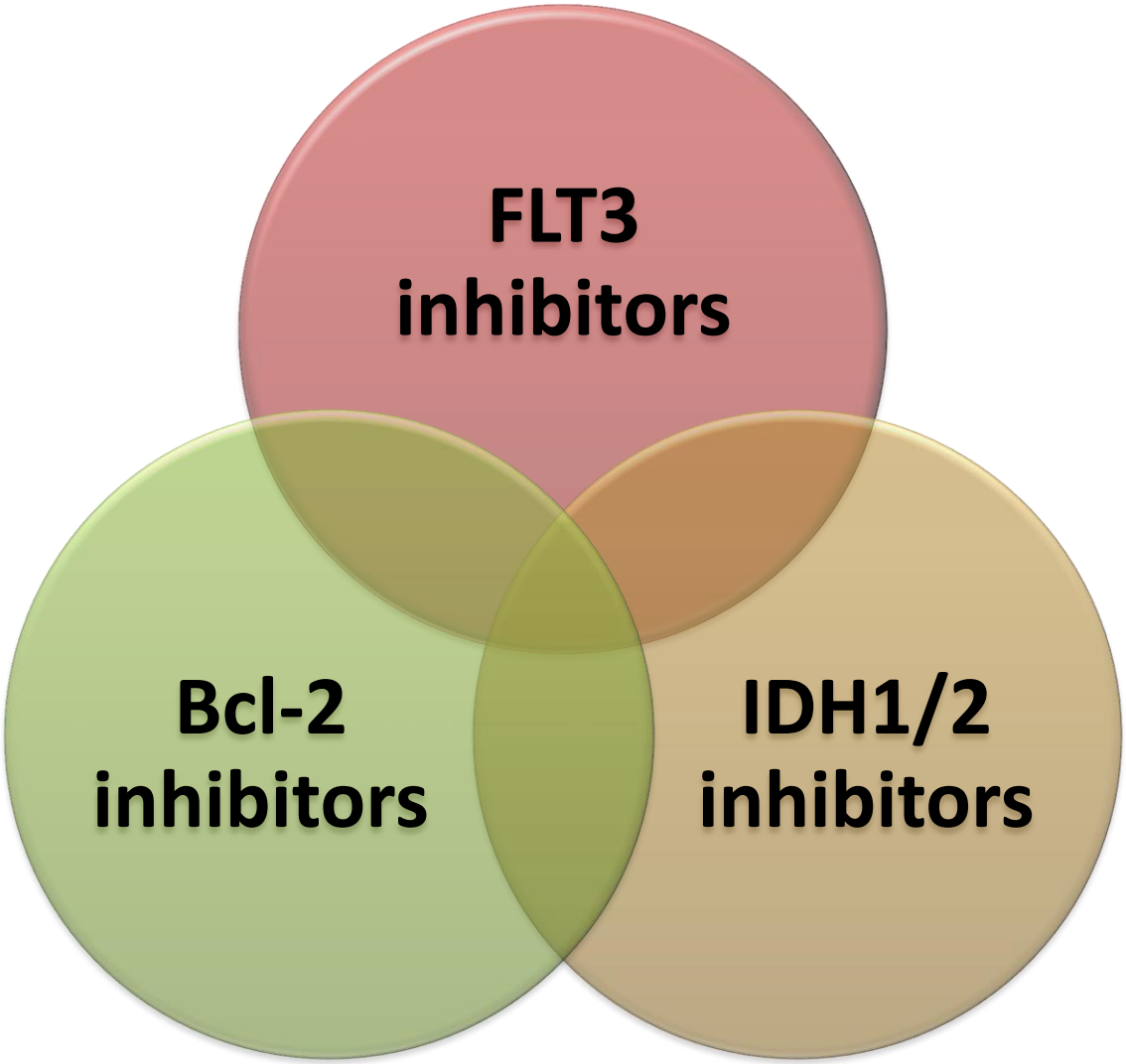
- Primary endpoint: DFS (time to relapse or death)

DFS

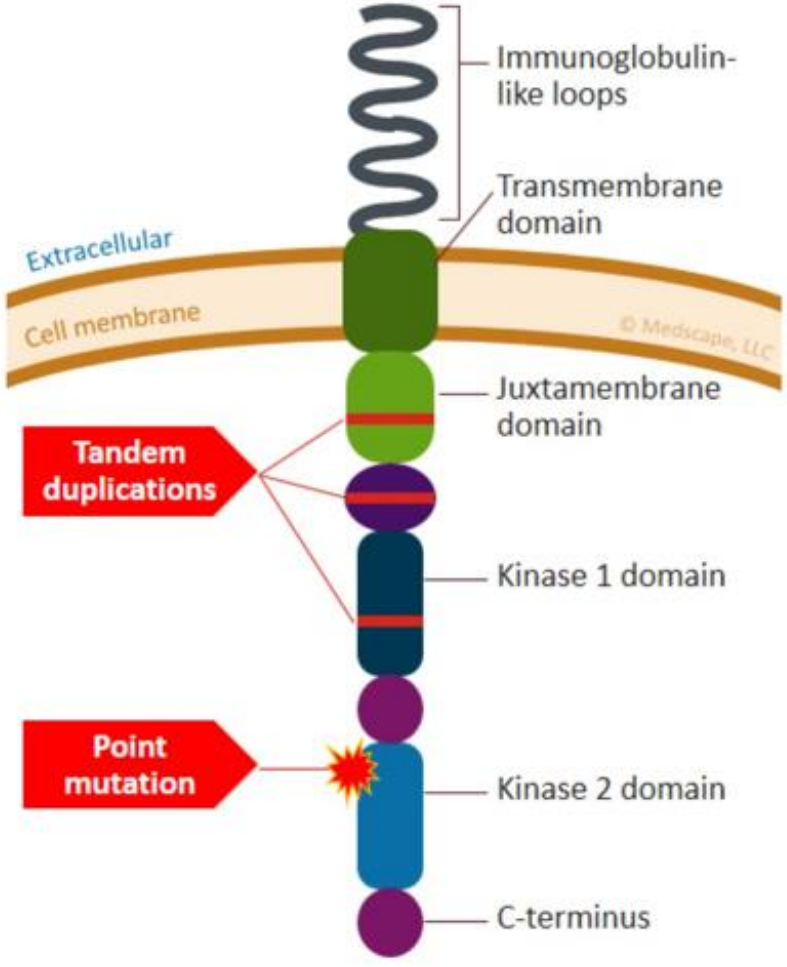


Huls G et al, ASH 2017

Targeted agents to watch….



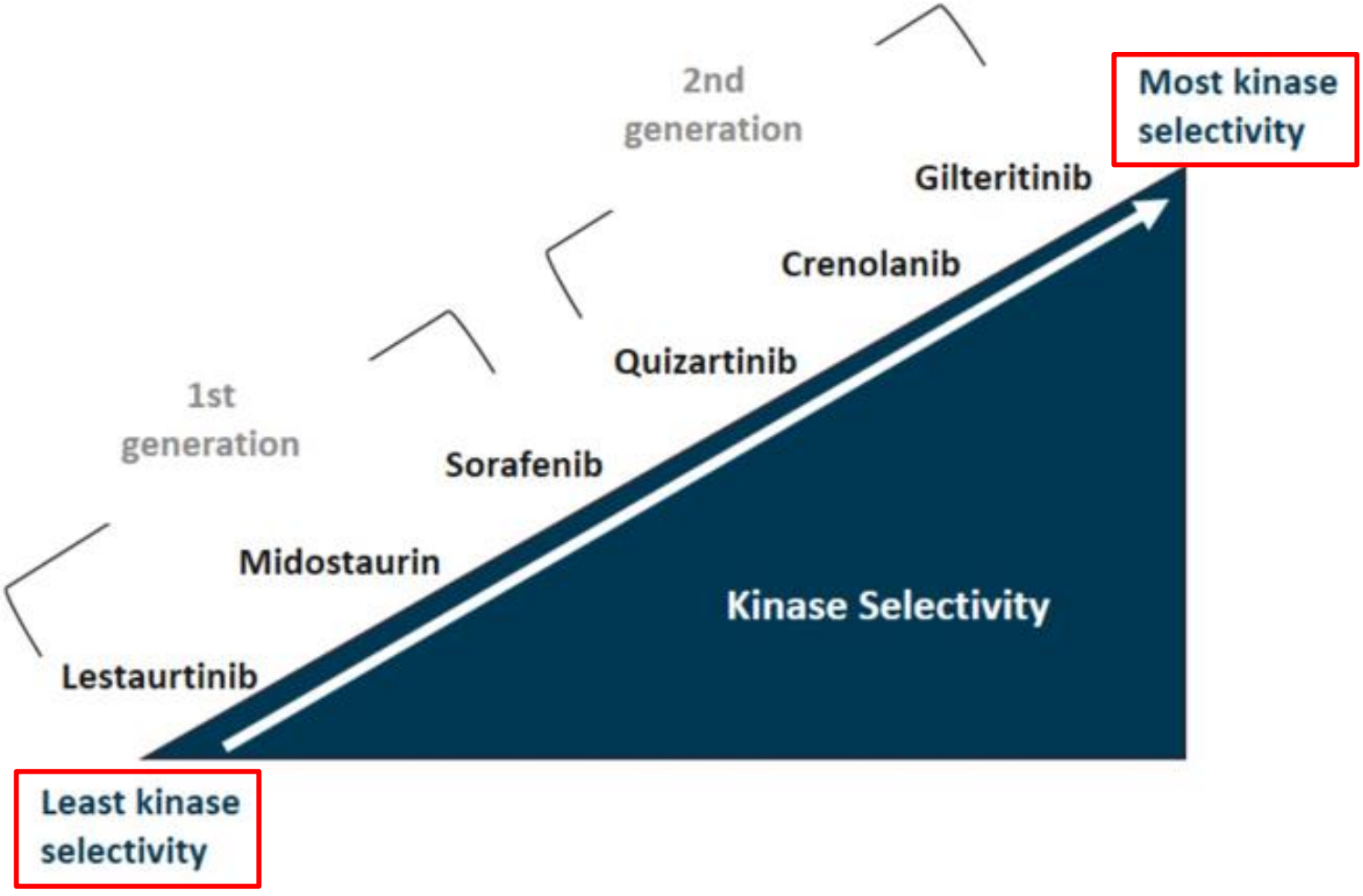
Targeting mFLT3



- *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

FLT3 inhibitors in clinical development



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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

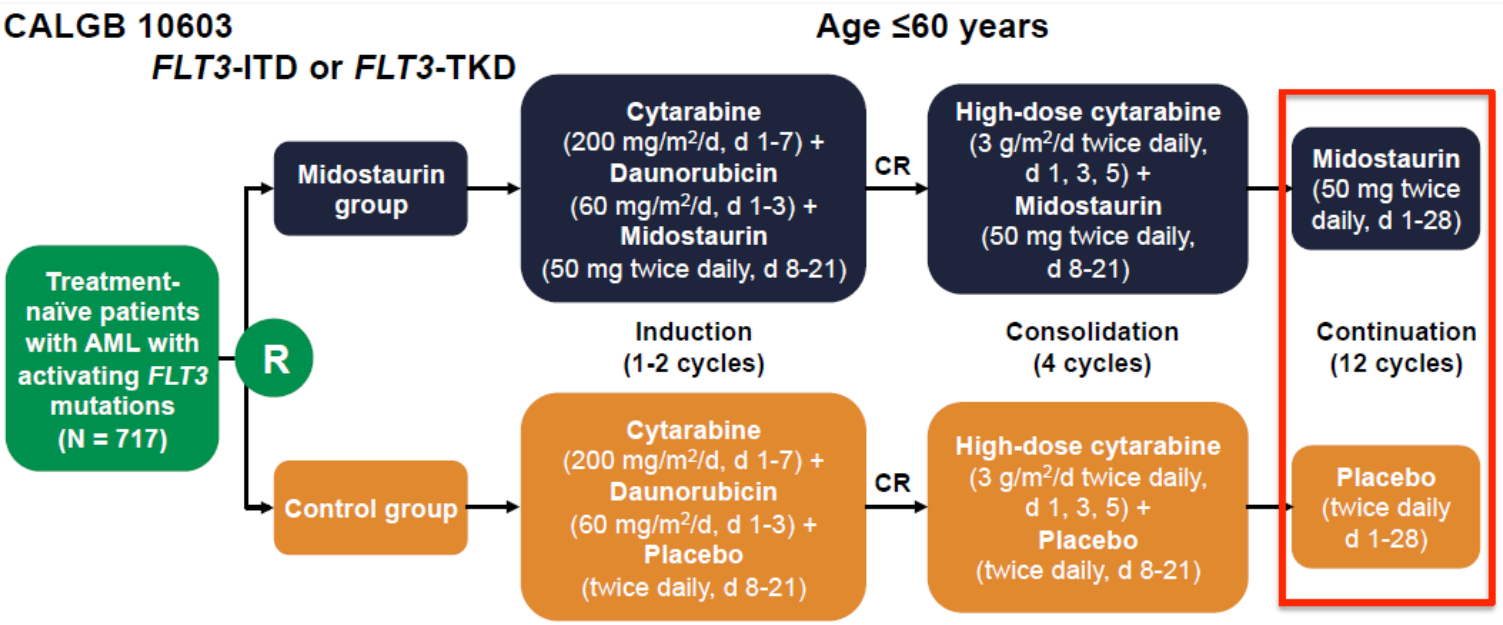
Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

R.M. Stone, S.J. Mandrekar, B.L. Sanford, K. Laumann, S. Geyer, C.D. Bloomfield, C. Thiede, T.W. Prior, K. Döhner, G. Marcucci, F. Lo-Coco, R.B. Klisovic, A. Wei, J. Sierra, M.A. Sanz, J.M. Brandwein, T. de Witte, D. Niederwieser, F.R. Appelbaum, B.C. Medeiros, M.S. Tallman, J. Krauter, R.F. Schlenk, A. Ganser, H. Serve, G. Ehninger, S. Amadori, R.A. Larson, and H. Döhner

FDA-approved (April 2017)

Stone RM et al, NEJM 2017

RATIFY trial

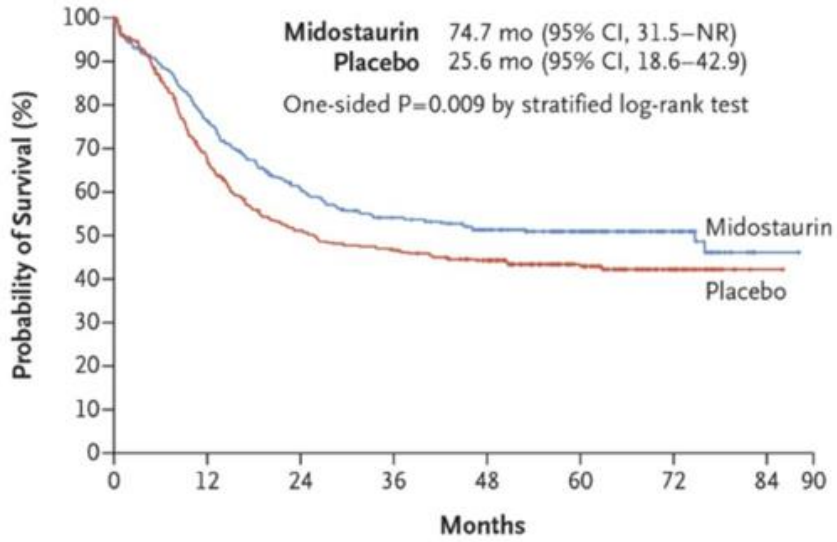


mEFS	mRFS	mOS
8.2 vs 3.0 mos	26.7 vs 15.5 mos	74.7 vs 25.6 mos
P = .002	*P* = .001	*P* = .009

Stone RM et al, NEJM 2017

Overall Survival

22% reduced risk of death in midostaurin arm

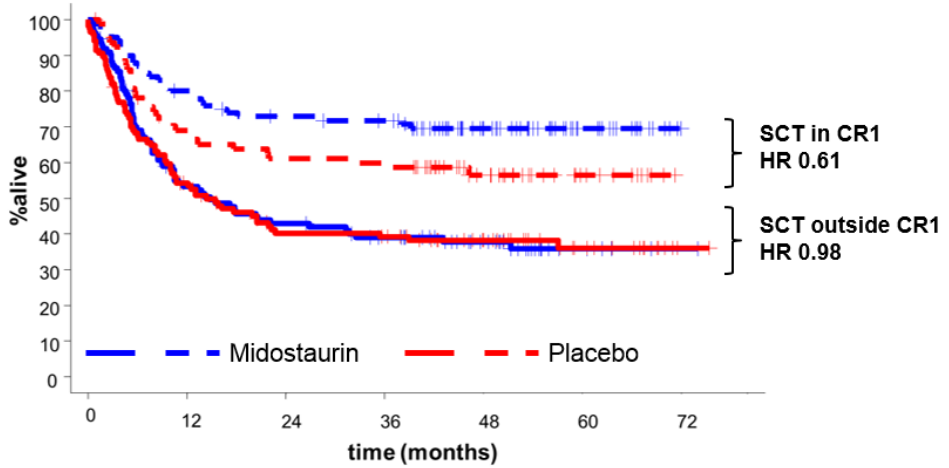


Mido benefit maintained in FLT3m subtypes

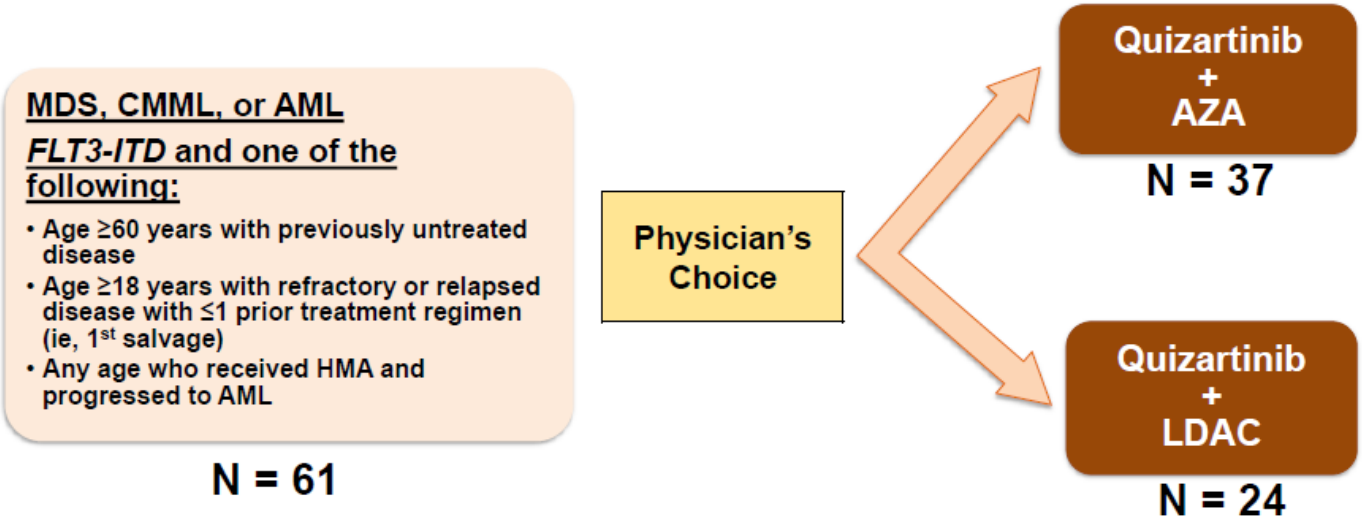
ITDm (H/L ratio)

TKDm

post-SCT



Quizartinib + AZA or LDAC



Best Response, n (%)	Quizartinib + Azacitidine	Quizartinib + Cytarabine	All Patients
CR	8 (22)	2 (8)	10 (16)
CRp	2 (5)	5 (21)	7 (12)
CRi	15 (41)	7 (29)	22 (36)
CRc (CR + CRp + CRi)	25 (68)	14 (58)	39 (64)
OR (CRc + HI + PR)	26 (70)	16 (67)	42 (69)
NR	9 (24)	8 (33)	17 (28)
60-day mortality	2 (5)	0	2 (3)

Swaminathan M et al, ASH 2017

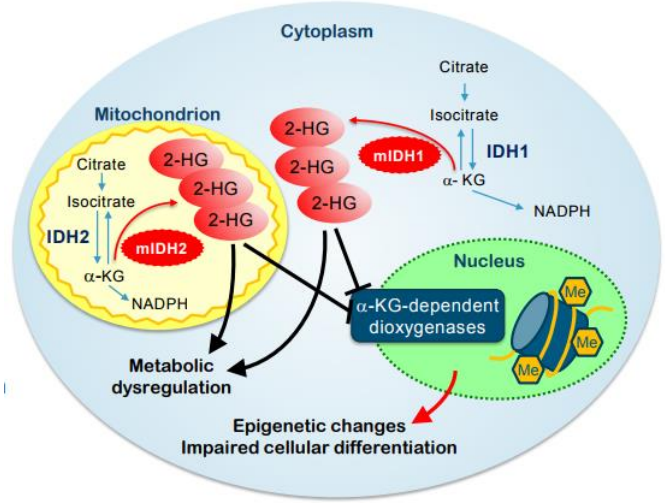
Targeting mIDHs

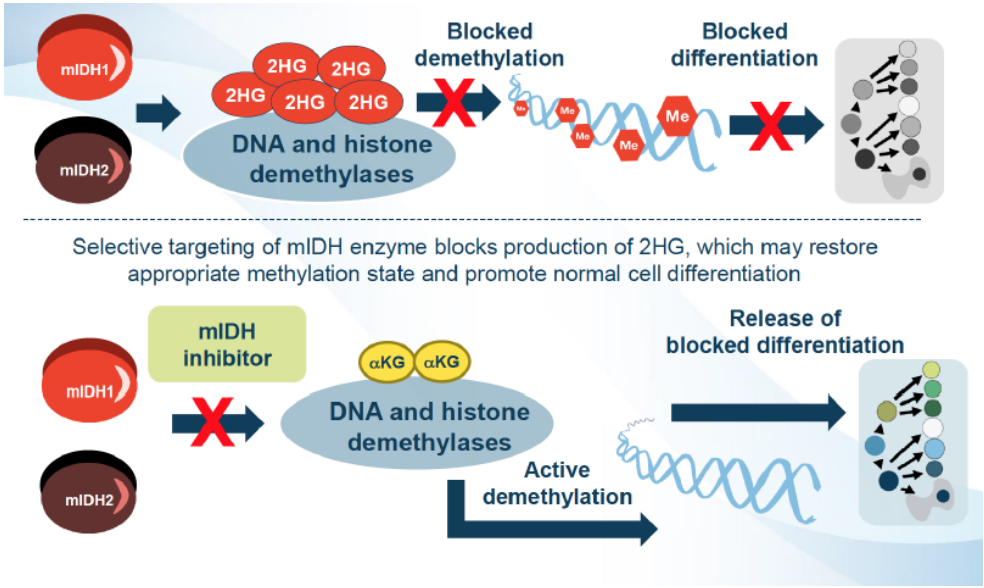
IDHs are critical enzymes of the citric acid cycle

Mutant IDH 1 or 2 is seen in 15-20% of patients with AML

mIDH results in accumulation of 2-HG, leading to DNA+histone ipermethylation and a block in differentiation

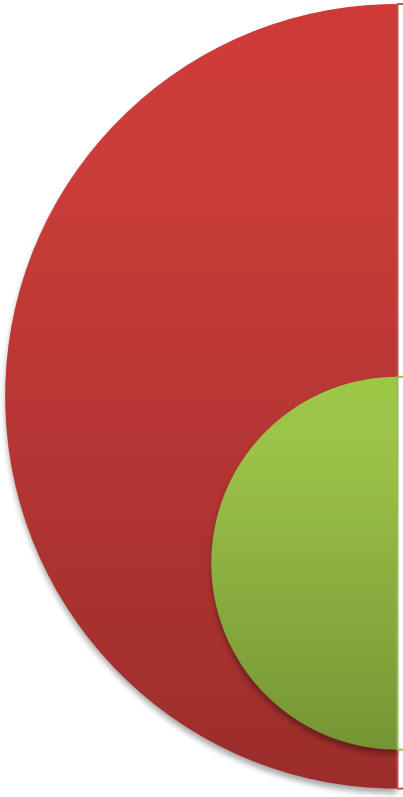
Ivosidenib (AG-120) and Enasidenib (AG-221) are oral inhibitors of mIDH1 and mIDH2, respectively





DiNardo CD et al, Leukemia 2016

mIDH inhibitors in R/R AML

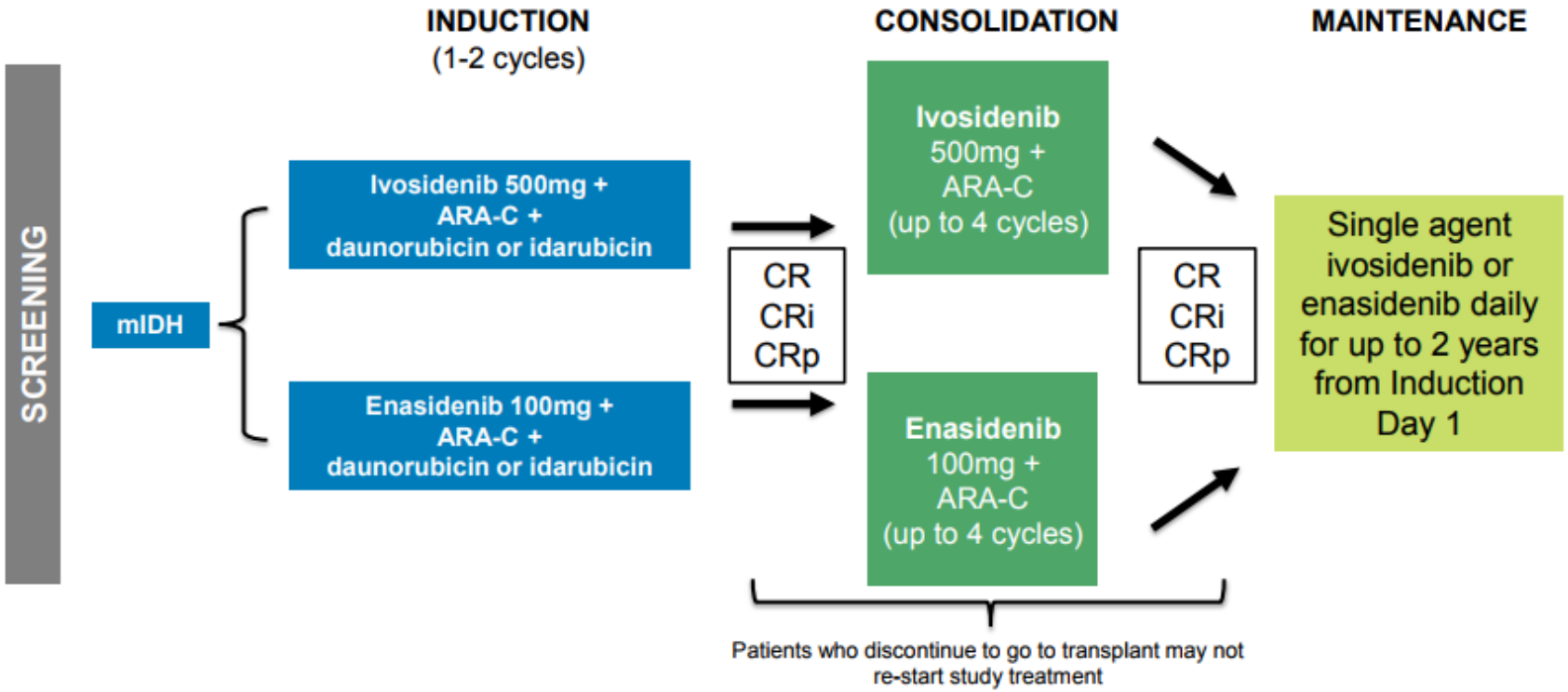


Enasidenib[1] (mIDH2 inhib)	• Monotherapy • 40.3% ORR (CR 19.3%) • Med-OS 9.3 mos • FDA-approved (08/2017)
Ivosidenib[2] (mIDH1 inhib)	• Monotherapy • 41.6% ORR (CR 21.6%) • Med-OS 8.8 mos • FDA-approved (07/2018)

[1]Stein EM et al, Blood 2017; [2]DiNardo CD et al, NEJM 2018

mIDH inhibitors in ND-AML

Phase 1 study



Stein EM et al, ASH 2017

Best response

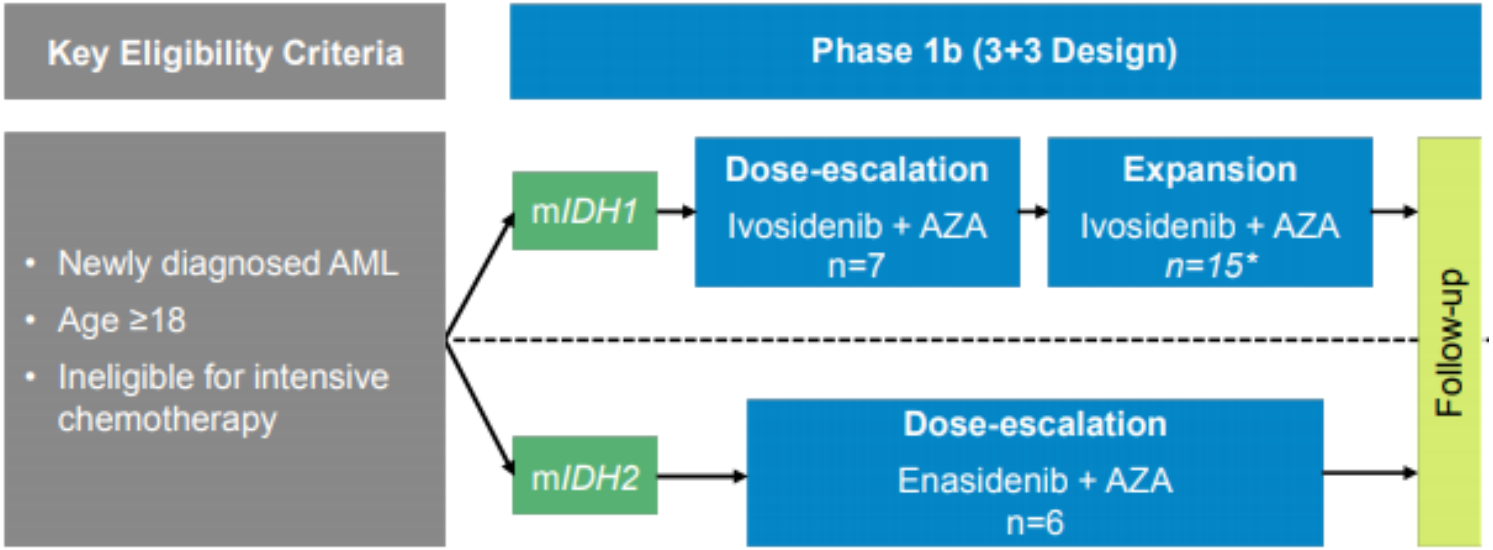
Response, n (%)	Ivosidenib (AG-120) + CT			Enasidenib (AG-221) + CT		
	All (n=30)	*De novo* (n=21)	sAML (n=9)	All (n=50)	*De novo* (n=27)	sAML (n=23)
CR+CRi/CRp	23 (77)	19 (91)	4 (44)	31 (62)	18 (67)	13 (57)
CR	19 (63)	15 (71)	4 (44)	25 (50)	16 (59)	9 (39)
CRi/CRp	4 (13)	4 (19)	-	6 (12)	2 (7)	4 (17)
MLFS	1 (3)	-	1 (11)	10 (20)	4 (15)	6 (26)
PR	2 (7)	1 (5)	1 (11)	-	-	-
Persistent disease	2 (7)	1 (5)	1 (11)	5 (10)	2 (7)	3 (13)
NE	2 (7)	-	2 (22)	4 (8)	3 (11)	1 (4)

Ivo or Ena + CT generally well tolerated

Response rates encouraging, especially in sAML

Phase 3 planned

mIDH inhibitors + AZA in ND-AML



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

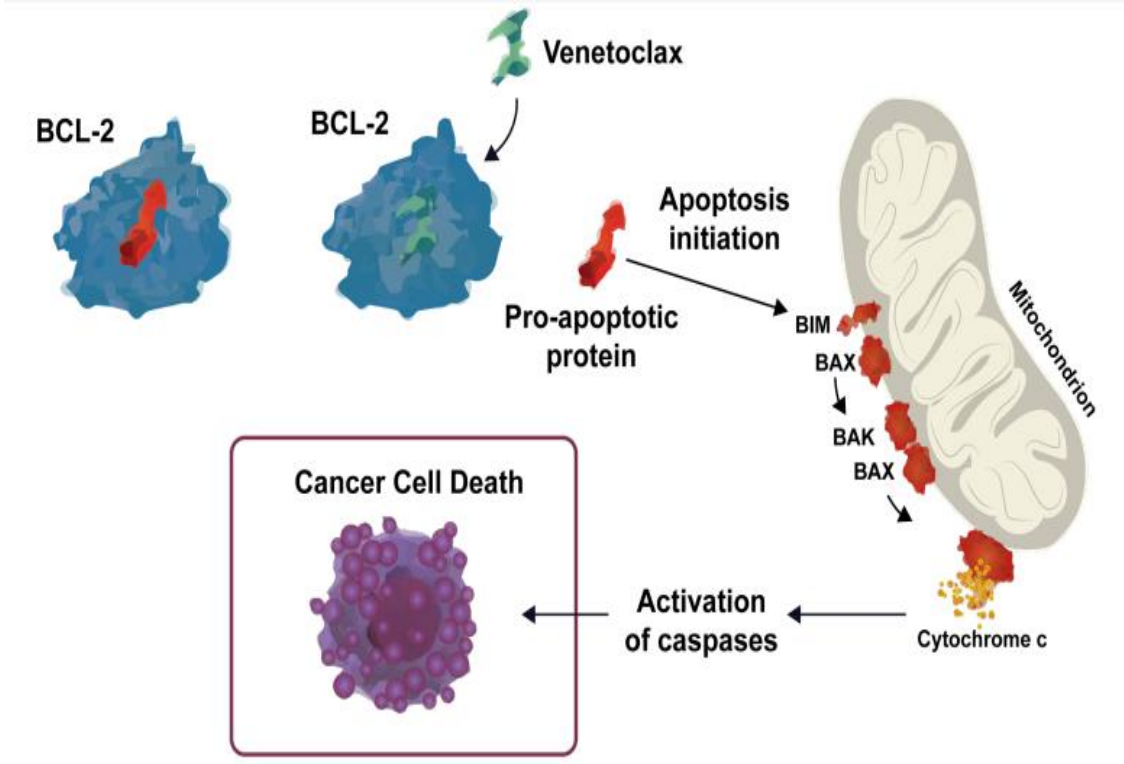
Targeting BCL-2

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%



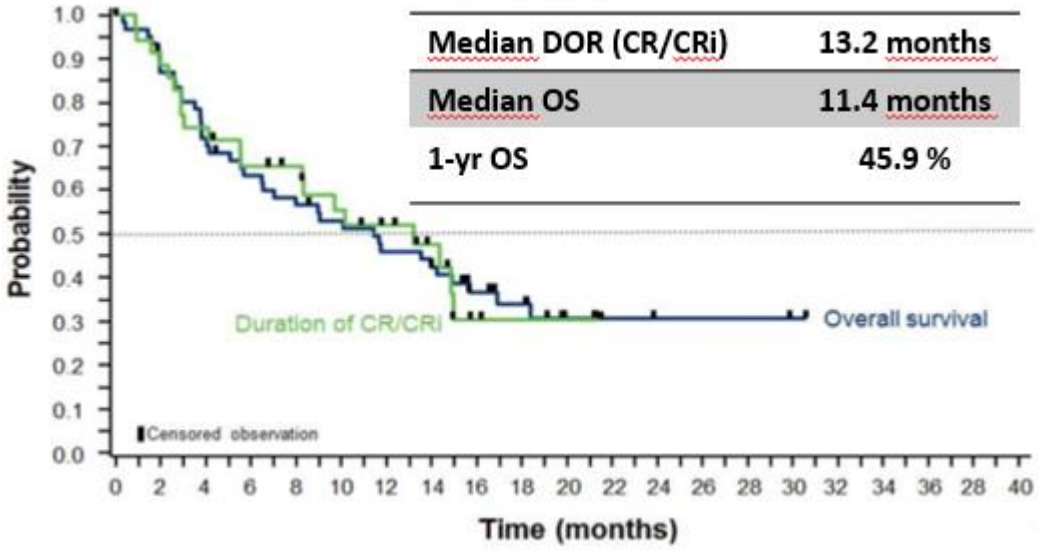
Konopleva M et al, Cancer Discov 2016; Roberts AW et al, Clin Cancer Res 2017

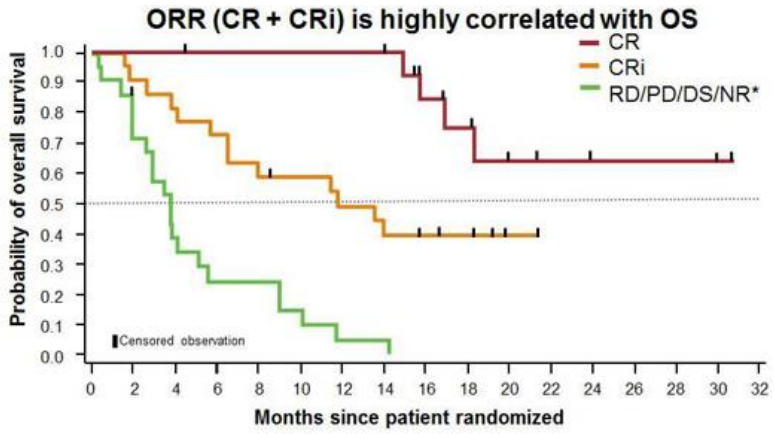
VEN + LDAC (phase 1/2)

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

Response	Overall (N = 61)	Intermediate Cytogenetics (n = 37)	Adverse Cytogenetics (n = 19)	No Prior HMA (n = 44)	Prior HMA (n = 17)	Secondary AML (n = 27)
CR + CRi	62	76	47	66	53	52
▪ CR	26	35	15	32	12	11
▪ CRi	36	41	32	34	41	41
PR	2	3	0	2	0	0

30/60-d mortality: 3%/13%





Wei A et al, ASH 2017

VEN+HMAs in ND-AML (phase 1b)

Outcome	All Patients* (N = 145)	Venetoclax 400 mg		Venetoclax 800 mg	
		Azacitidine (n = 29)	Decitabine (n = 31)	Azacitidine (n = 37)	Decitabine (n = 37)
CR + CRi, %	**67**	**76**	**71**	**57**	**73**
▪ CR	37	38	45	30	38
▪ CRi	30	38	26	27	35
MRD negativity in patients with CR/CRi, n/N (%)	**28/97 (29)**	**10/22 (45)**	**7/22 (32)**	**7/21 (33)**	**3/27 (11)**
Median DoR in patients with CR/CRi, mos (95% CI)	**11.3 (8.9-NR)**	**NR (5.6-NR)**	**12.5 (5.1-NR)**	**11.7 (4.6-12.9)**	**9.2 (5.9-NR)**
▪ Intermediate risk	12.9 (11.0-NR)	--	--	--	--
▪ Poor risk	6.7 (4.1-9.4)	--	--	--	--
▪ de novo AML	9.4 (7.2-11.7)	--	--	--	--
▪ Secondary AML	NR (12.5-NR)	--	--	--	--
Median OS, mos (95% CI)	**17.5 (12.3-NR)**	**NR (11.0-NR)**		**17.5 (10.3-NR)**	

*Including 11 patients who received venetoclax at 1200 mg.

- **CR/CRi rates in subgroups: intermediate-risk cytogenetics, 74%; poor-risk cytogenetics, 59%; de novo AML, 67%; secondary AML, 67%; aged < 75 yrs, 69%; aged ≥ 75 yrs, 64%**

- Deaths after starting venetoclax: ≤ 30 days, n = 5 (3%); ≤ 60 days, n = 11 (8%)
- No laboratory or clinical TLS observed
- Comparable AE rates with decitabine vs azacitidine

DiNardo CD et al, ASCO 2018

AML: Progress at last!

FDA-approv of 5 new drugs in 2017-18!

Biological understanding of AML improving

More than 300 AML clinical trials ongoing, testing >40 novel agents

Clinical trials to move the field forward