LEUCEMIE ACUTE : RUOLO DELLE TERAPIE TARGET

Leucemia acuta mieloblastica

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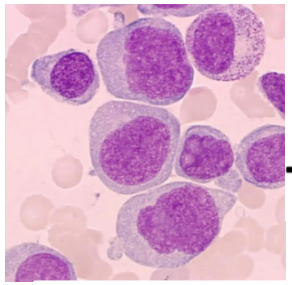
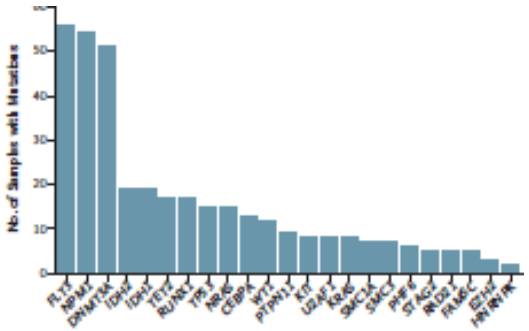
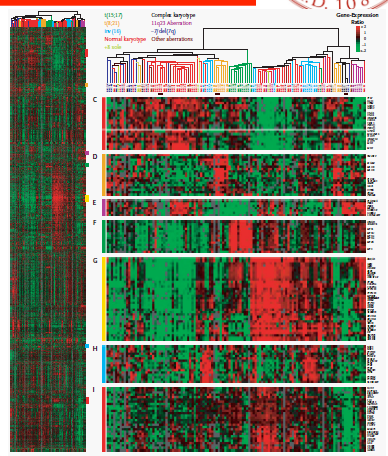
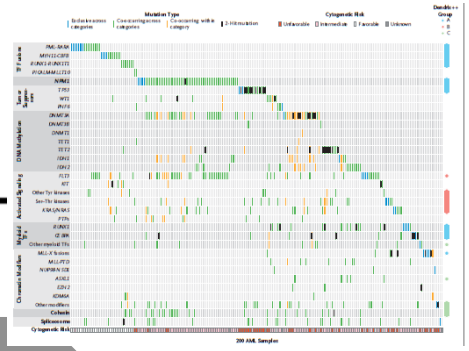
Historical progress in AML: the knowledge of biology







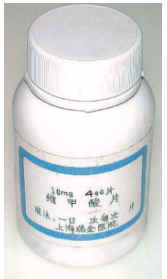


FLT3 -ITD
MLL -PTD
MYST3-CREBBP
NPM1-MLF1
NUP98-HOXA9
PICALM-MLLT10
WT1
FUS-ERG
MLL-ELL
RUNX1-MECOM
CBFB-MYH11
MLL-MLLT3
MLL-MLLT4
NF1
DEK-NUP214
MLL-MLLT1
RUNX1-RUNX1T1
KRAS
NRAS
PML-RARA
BCR-ABL
TP53
KIT
MLL-MLLT10
RUNX1
PTPN11
CEBPA
FLT3 -TKD
NUP98-NSD1
CBL
NPM1
SF3B1
SRSF2
U2AF1
ZRSR2
DDX41
GATA2/MECOM
DNMT3A
ASXL2
EZH2
STAG1
ASXL1
IDH2
RAD21
IDH1
SMC1A
SMC3
TET2
STAG2

1985 1990 1995 2000 2005 2010 2015

1970 1980 2000

1973: **Cytarabine** and **Daunorubicin** «**3+7**» AML protocol

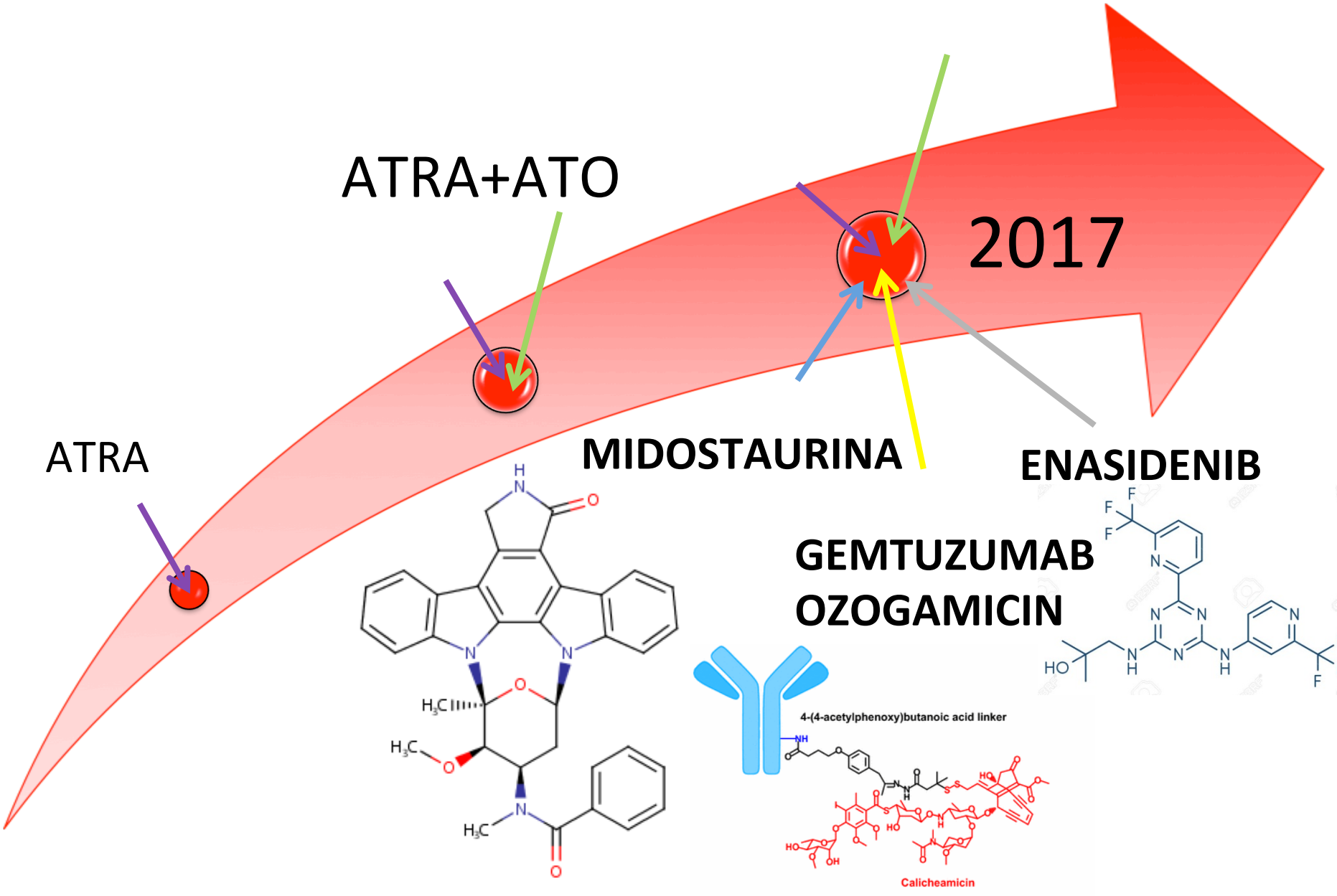


1988: **ATRA** in APL

2000: **ATO** in APL

Grimwade D. et al, Blood 2016;127(1):29-41
TCGA AML, N Engl J Med 2013;368(22):2059-74

2017 FDA approval of new target therapy in AML



Higher effectiveness **Reduced toxicity**

↑ **OS**

Molecular target in AML

Signal transduction genes 59%
FLT3, NRAS, c-KIT, PTPN11

Tumor-suppressor genes 16%
TP53, WT1, PHF6

DNA modification genes 44%
DNMT3A, TET2, IDH1/2

Chromatin modifiers 30%
MLL-fusions, ASXL1, EZH2, MLL-PTS

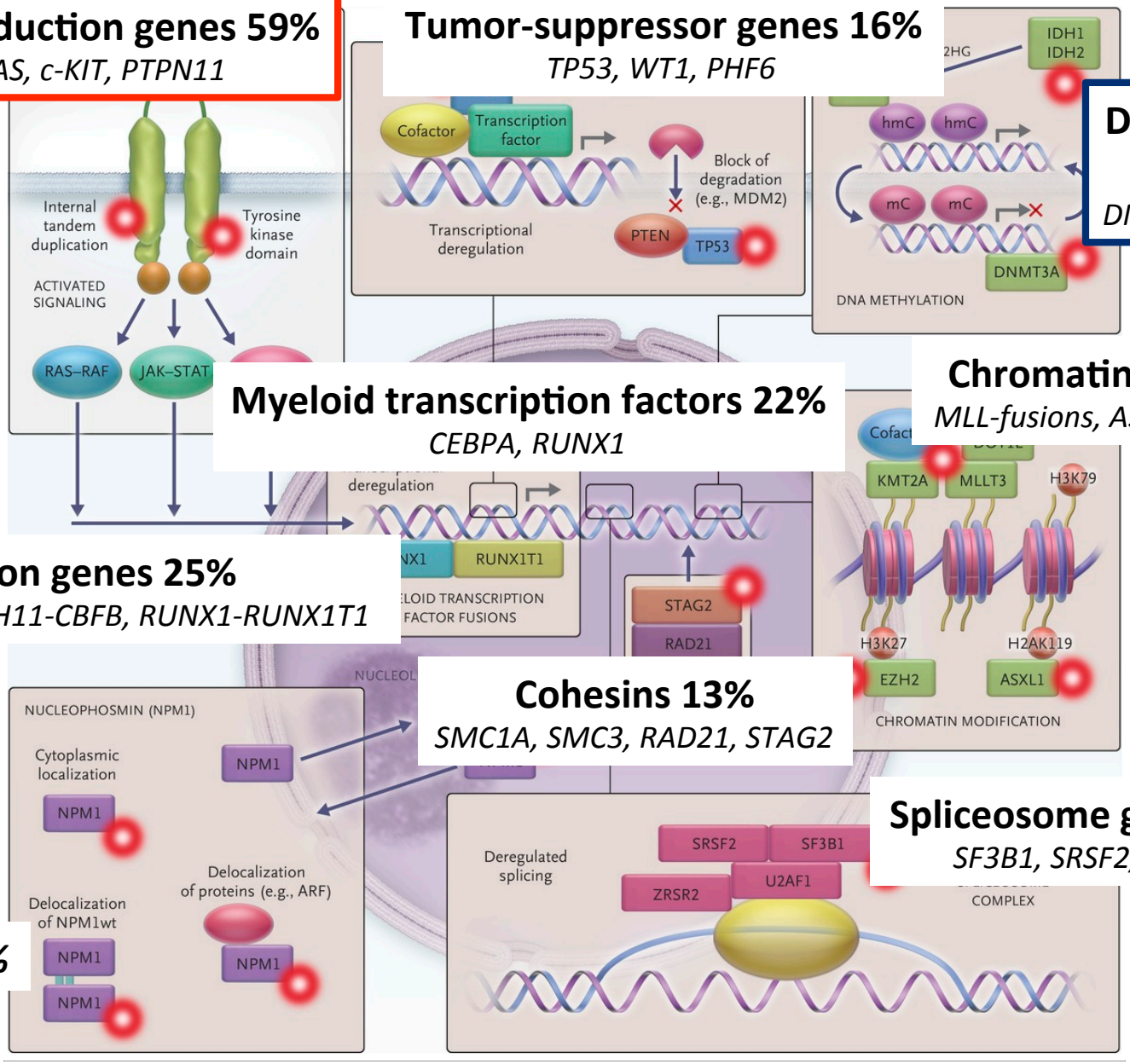
Myeloid transcription factors 22%
CEBPA, RUNX1

Fusion genes 25%
PML-RARA, MYH11-CBFB, RUNX1-RUNX1T1

Cohesins 13%
SMC1A, SMC3, RAD21, STAG2

Spliceosome genes 14%
SF3B1, SRSF2, U2AF1

NPM1 27%



Dohner H. et al N Engl J Med 2015;373:1136-52

Target therapy in AML

1. **Mutation-targeted** agents
   - FLT3 inhibitors
   - IDH inhibitors

2. **Non mutation**-targeted agents
   - BCL-2 inhibitors
   - epigenetic modifiers , novel HMAs
   - BET inhibitors, LSD inhibitors, DOT1L inhibitors

3. **Targeted delivery** of cytotoxic agents
   - ADCs

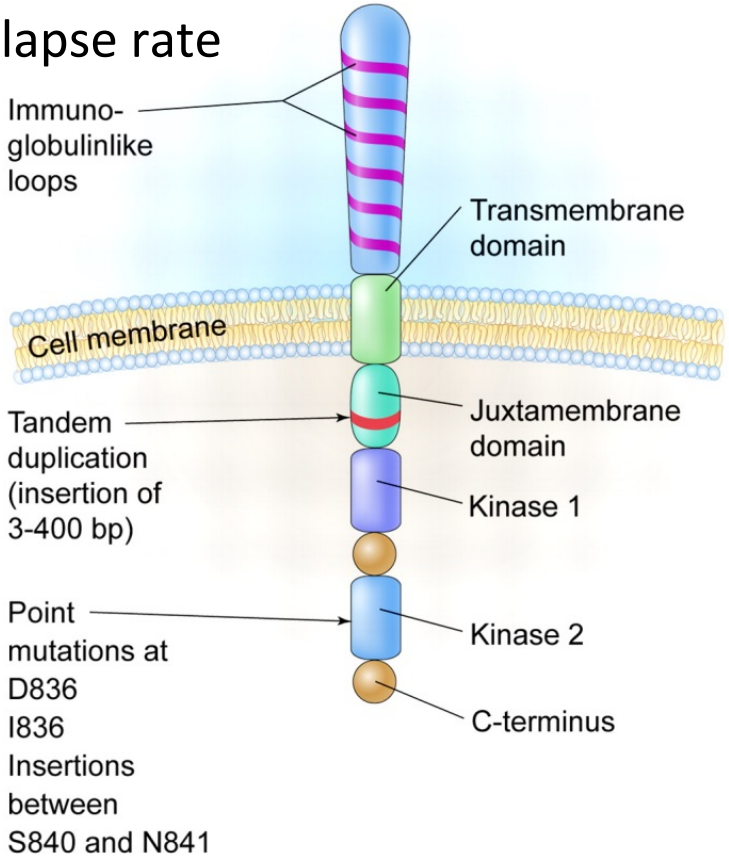
Perl A.E. et al. Blood Advances 2017;1(24):2281-2294

FLT3 as molecular target in AML

- Mutations in the fms-related tyrosine kinase 3 gene (**FLT3**) are present in **30%** of **newly diagnosed AML**
  - **75% ITD** mutation
    - Poor prognosis owing to a high relapse rate
  - **8% TKD** mutation
    - No clear effect on prognosis

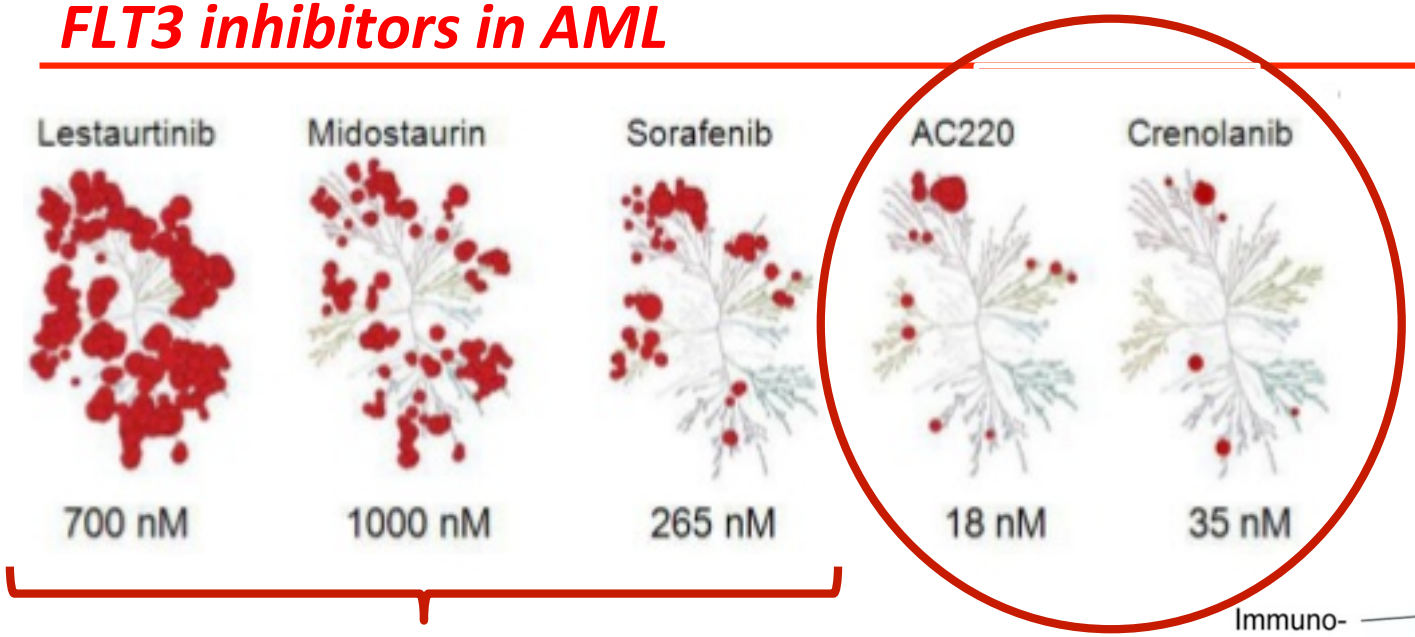
- **Most** single **frequent «driver» mutations** in adult AML

- Elevated FLT3-ITD mutant/WT ratio associated with **worse outcomes** but more responsive to FLT3-directed therapies



Litzow M. R. et al, Blood 2005;106(10):3331; Thiede C. et al, Blood 2002;99:4326-35; Pratz K. et al, Blood 2010;115:1425-32

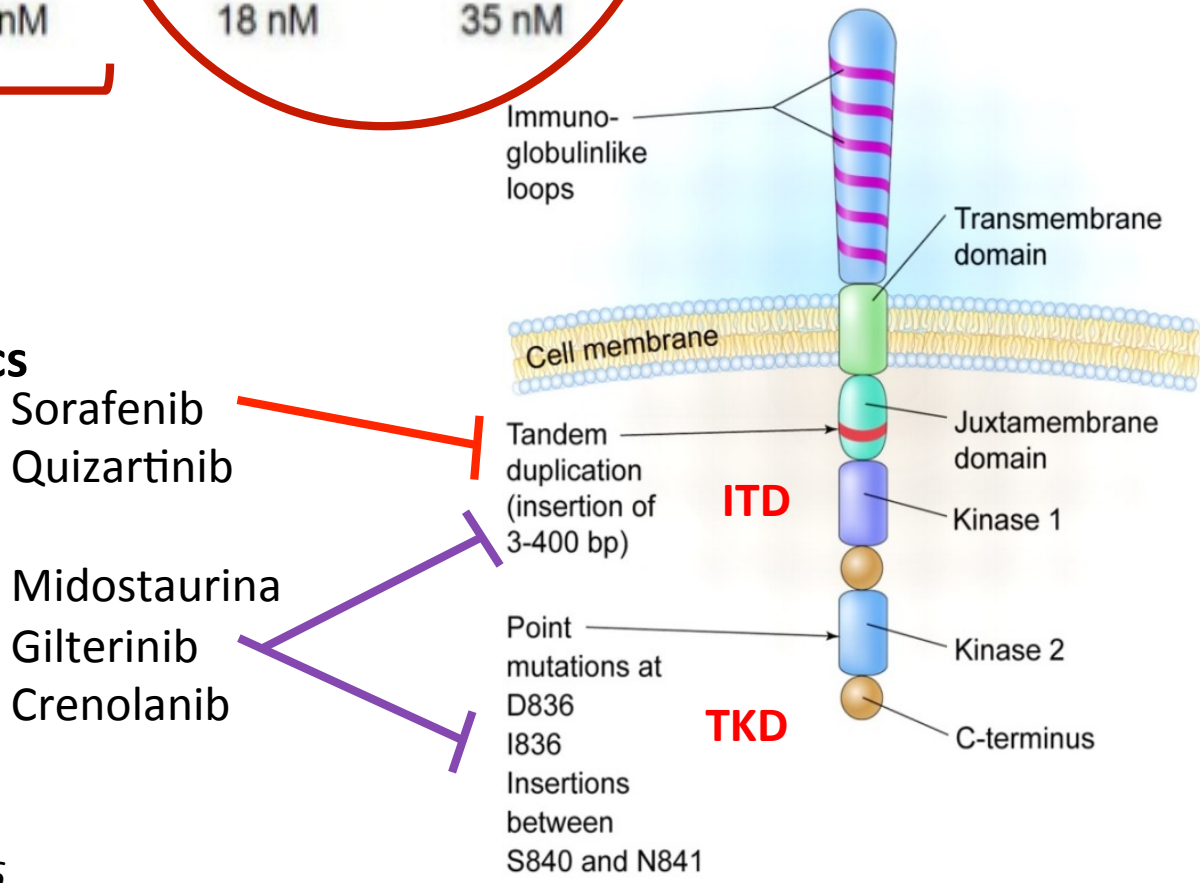
FLT3 inhibitors in AML



First generation FLT3 TKIs

Second generation FLT3 TKIs

- **Poor** kinase **selectivity**
- Complicated **pharmacokinetics** properties
- **Transient reduction** in the number of **blasts** in blood, marrow or both



Stone R.M. et al, Blood 2005;10554-60;
Smith B.D. et al, Blood 2004;103:3669-76

FLT3 inhibitors in AML

- **Quizartinib single agent** (30-60 mg/die)
  - QTc prolongation at higher doses (90-120 mg)
  - **CRc** (CR+CRp+CRi) **46-54%**
  - Induction of terminal **granulocytic differentiation**
  - Rapid **acquisition** of resistance (emerging of **FLT3-TKD** mutations)

- **Crenolanib single agent** (100 mg three times daily)
  - CR/CRi **37**% in TKI naïve and **15**% in pts previously treated with TKIs

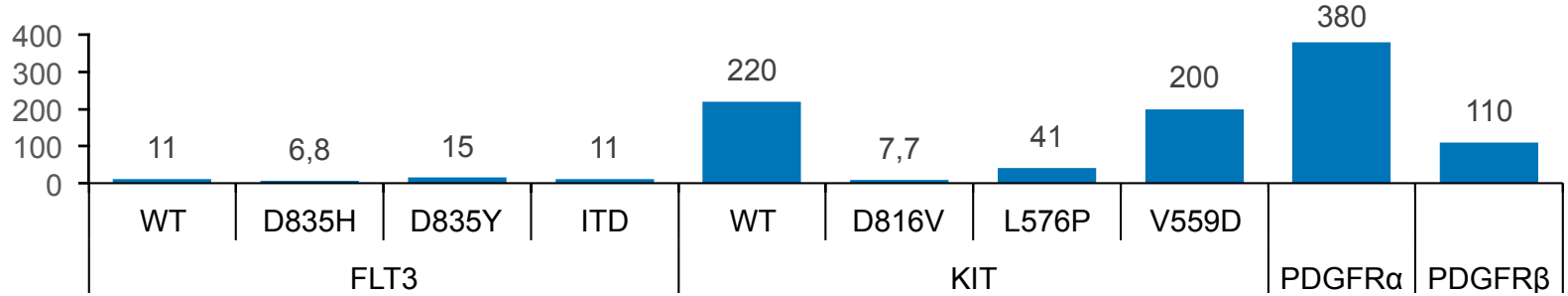
- **Gilterinib single agent** (120 mg/die)
  - CRc **30**%

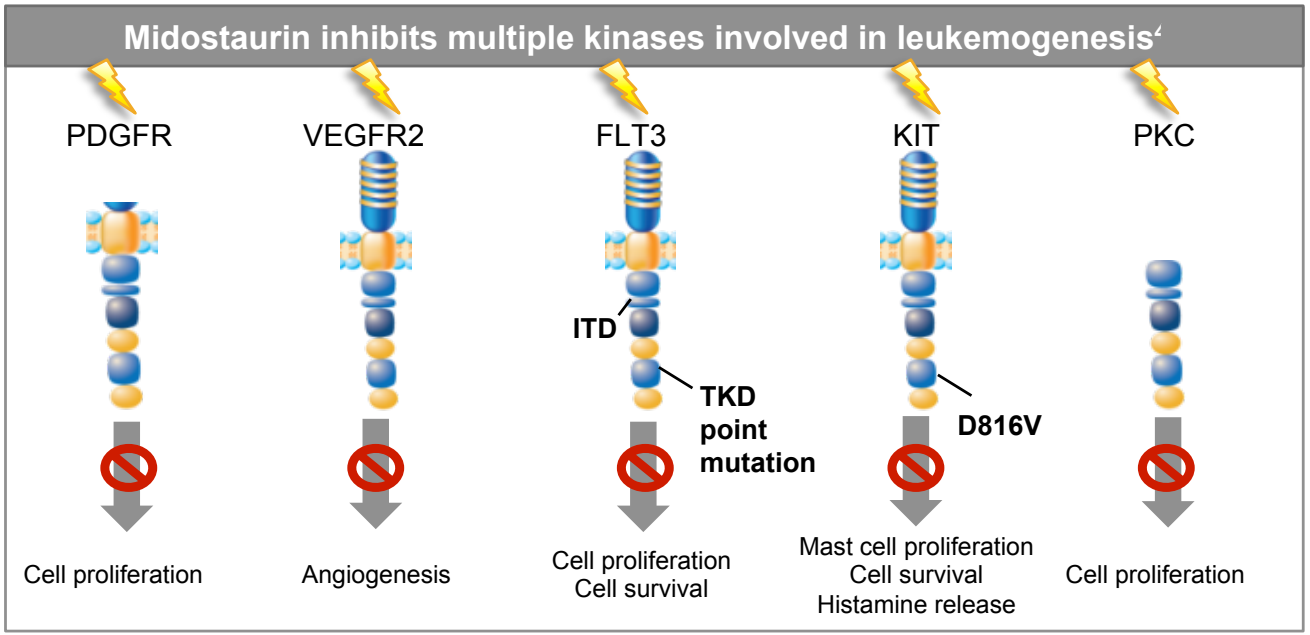
Cortes J.E. et al, Blood 2012;120,48; Levis M.J. et al, Blood 2012;120,673; Cortes J.E. et al, JCO 2016;34,7008; Perl A.E. et al, Lancet Oncol 2017;18,1061-1075.

1^ generation FLT3 inhibitor: MIDOSTAURIN

FDA approved for newly diagnosed AML in combination with standard intensive chemotherapy

- *In vitro* midostaurin inhibits **FLT3-WT** as well as **FLT3-ITD** and **FLT3-TKD** (D835H and D835Y)





Weisberg E. et al. Cancer Cell 2002;1:433–43; Stone RM. et al. Leukemia 2012;26:2061–68.

1^ generation FLT3 inhibitor: MIDOSTAURIN

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

RATIFY

Phase **3 randomized**, **double-blind**, placebo-controlled study of **midostaurin** in combination with **standard induction/consolidation chemotherapy** and as **single agent maintenance** therapy in newly diagnosed adult patients (aged 18-60 years) with *FLT3* mutated AML

RATIFY protocol

Patients with **newly diagnosed AML** ≥ 18 to < 60 years with activating ***FLT3* mutations**

Stratification by TKD and ITD (ratio < 0.7 vs ≥ 0.7)

(n=717)

R

Induction (1-2 cycles)	CR	Consolidation (up to 4 cycles)	CR	Postconsolidation (up to 12 cycles)
Midostaurin (50 mg bid, days 8-21)		**Midostaurin** (50 mg bid, days 8-21)		**Midostaurin** (50 mg bid, days 1-28)
Daunorubicin (60 mg/m²/day, days 1-3)		**High-dose cytarabine** (3 g/m²/day q12h, days 1, 3, and 5)		
Cytarabine (200 mg/m²/day, days 1-7)				
Placebo (bid, days 8-21)		**Placebo** (bid, days 8-21)		**Placebo** (bid, days 1-28)
Daunorubicin (60 mg/m²/day, days 1-3)		**High-dose cytarabine** (3 g/m²/day q12h, days 1, 3, and 5)		
Cytarabine (200 mg/m²/day, days 1-7)				

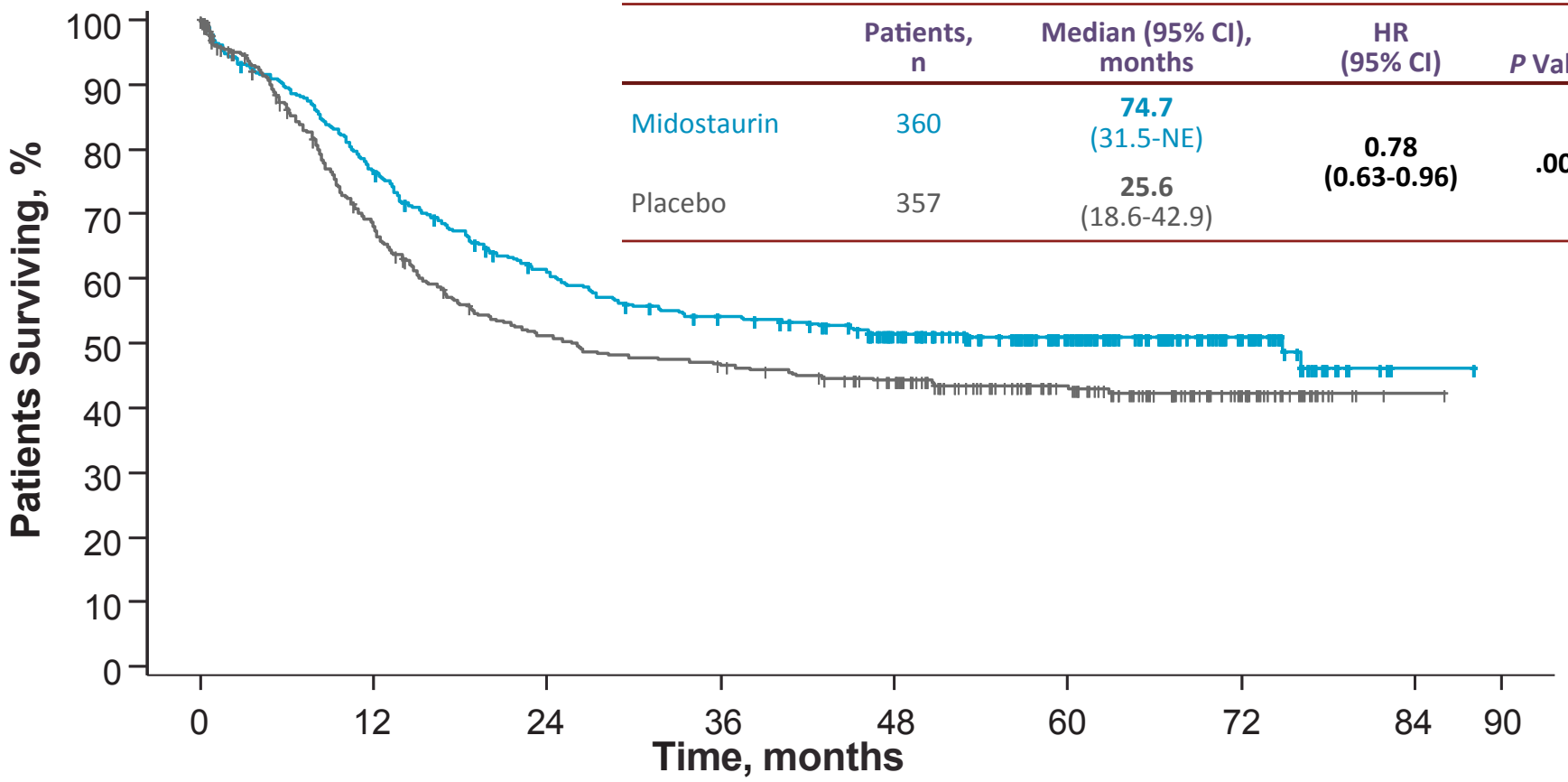
Primary endpoint: OS

Key secondary endpoint: EFS

Stone RM. et al. NEJM 2017;377(5):454-64.

RATIFY protocol: OS noncensored for SCT

*Primary endpoint: **22% reduced risk** of **death** in the midostaurin arm vs placebo*



	Patients, n	Median (95% CI), months	HR (95% CI)	*P* Value[b]
Midostaurin	360	**74.7** (31.5-NE)	**0.78 (0.63-0.96)**	**.009**
Placebo	357	**25.6** (18.6-42.9)		

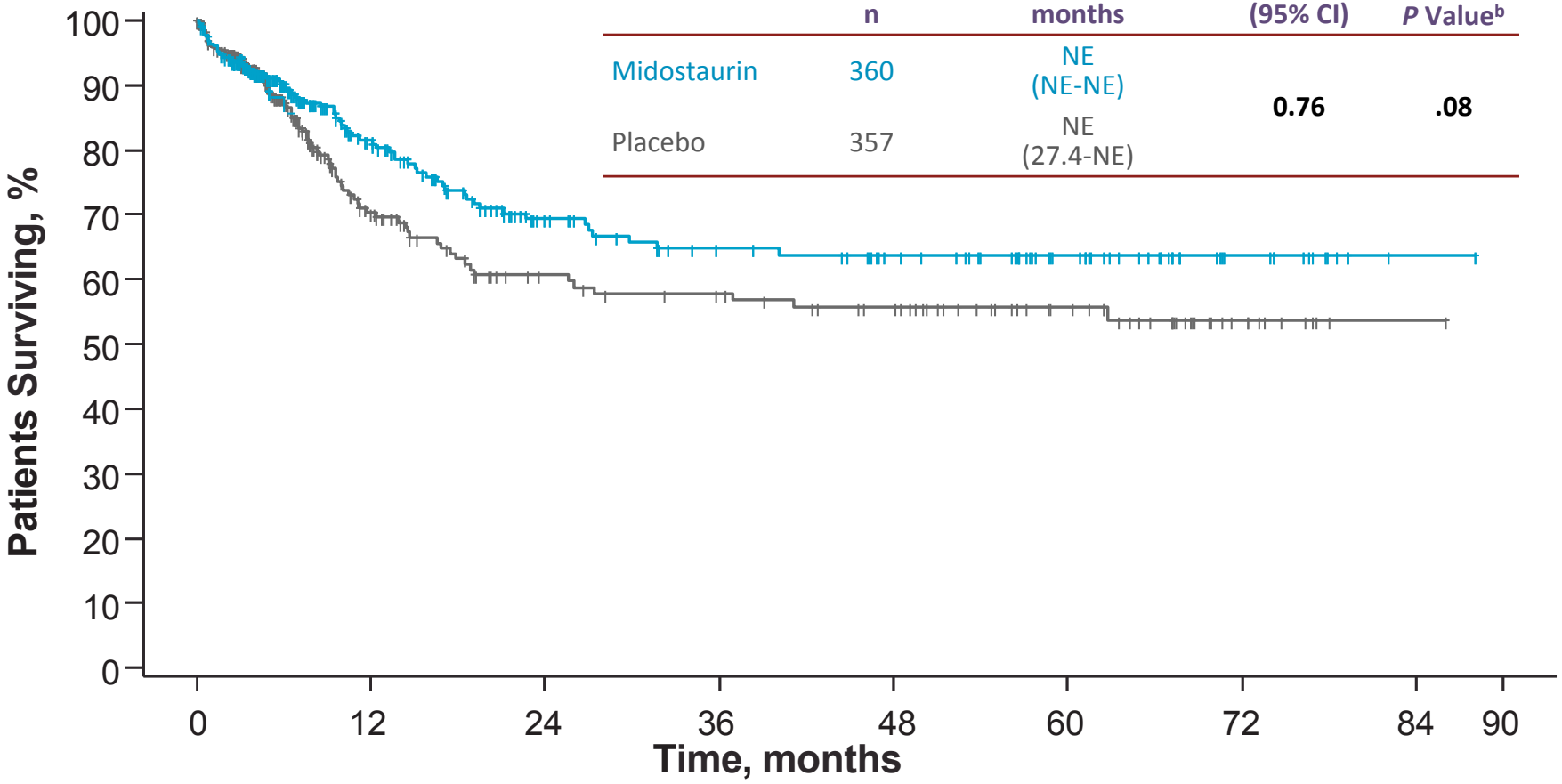
Midostaurin	360	269	209	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1

Stone RM. et al. NEJM 2017;377(5):454-64.

RATIFY protocol: OS censored at time of SCT

Secondary endpoint

	Patients, n	Median (95% CI), months	HR (95% CI)	*P* Value[b]
Midostaurin	360	NE (NE-NE)	**0.76**	**.08**
Placebo	357	NE (27.4-NE)		



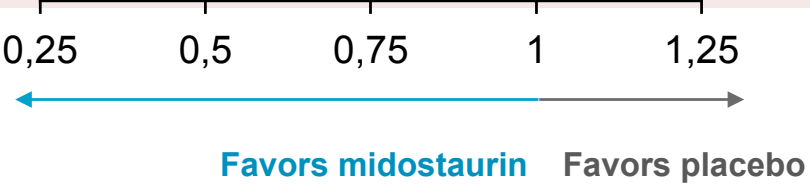
Midostaurin	360	136	80	64	54	35	13	1
Placebo	357	97	64	57	49	32	10	1

Stone RM. et al. NEJM 2017;377(5):454-64.

RATIFY protocol: consistent effect on OS by FLT3 status

Secondary endpoint

	N	HR (95% CI)	HR (95% CI)	*P* Value[a]
Overall (stratified)	717		0.78 (0.63-0.96)	.009
FLT3-ITD high	214		0.80 (0.57-1.12)	.19
FLT3-ITD low	341		0.80 (0.60-1.11)	.19
FLT3-TKD	162		0.65 (0.39-1.08)	.10

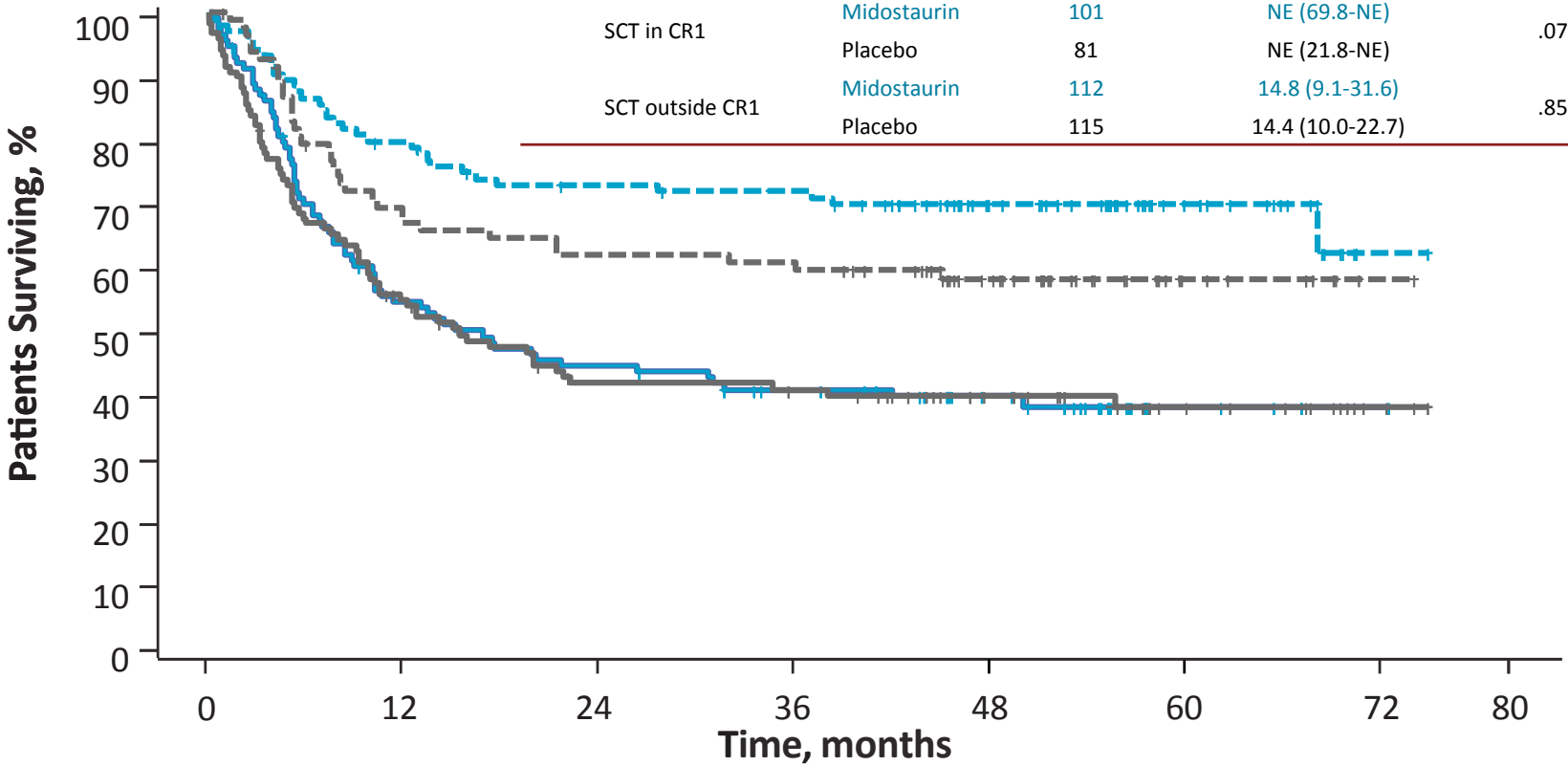


Stone RM. et al. NEJM 2017;377(5):454-64.

RATIFY protocol: OS by timing of SCT

Secondary endpoint

		Patients, n	Median (95% CI), months	*P* Value[a]
SCT in CR1	Midostaurin	101	NE (69.8-NE)	.07
	Placebo	81	NE (21.8-NE)	
SCT outside CR1	Midostaurin	112	14.8 (9.1-31.6)	.85
	Placebo	115	14.4 (10.0-22.7)	



SCT in CR1	Midostaurin	101	71	63	21	0
	Placebo	81	50	45	12	0
SCT outside CR1	Midostaurin	112	49	36	5	0
	Placebo	115	47	37	13	0

Stone RM. et al. NEJM 2017;377(5):454-64.

RATIFY protocol: OS by timing of SCT

Secondary endpoint

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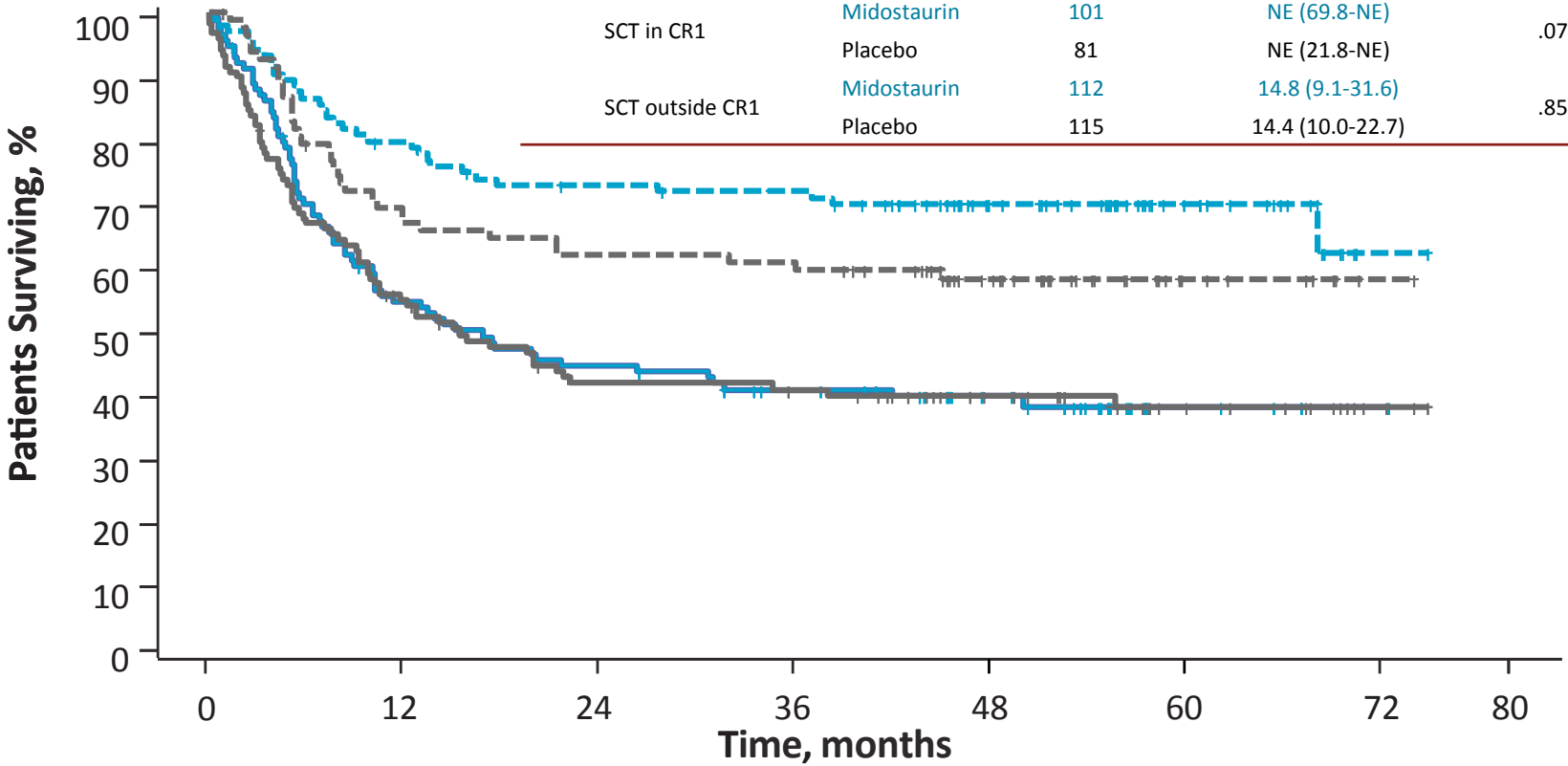

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	Placebo	115	47	37	13	0

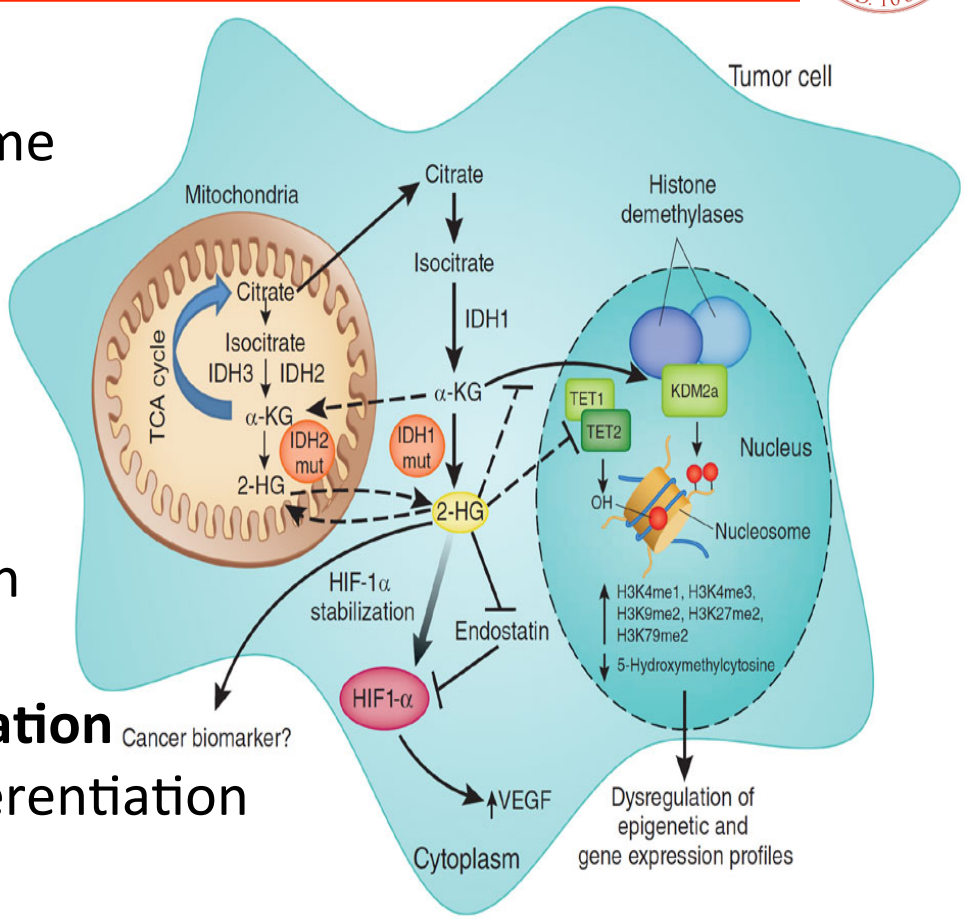
Stone RM. et al. NEJM 2017;377(5):454-64.

Phase III trial with 1^ and 2^ generation FLT3 inhibitors

- **Leustartinib (CEP-701)** **x no difference in CR and OS**
  - Chemo +/- leustartinib in relapsed/refractory FLT3+ AML (*Levis M. et al Blood 2011*)
  - Chemo +/- leustartinib in newly diagnosed FLT3+ AML (*Burnett A. et al ASH 2014*)
- **Sorafenib** v better 3 ys-**EFS** (**22**% vs **40**%) **x increase grade 3 toxicity**
  - Chemo +/- sorafenib in older AML patients (*Serve H. et al JCO 2013*)
  - Chemo +/- sorafenib in younger AML patients (*Rölling C. et al Lancet Oncol 2015*)
- **Quizartinib** **v** **CRc 46-54%** in R/R FLT3-ITD+AML *(Cortes et al 2012; Levis et al 2012);* **longer survival after SCT** (*Hills et al 2017*)
  - Quizartinib vs salvage chemotherapy in relapsed/refractory FLT3 ITD AML (QuANTUM-R)
  - Chemo +/- quizartinib in newly diagnosed FLT3 ITD AML (QuANTUM-First)
- **Gilterinib (ASP2215)** **v CRc 30%** in R/R FLT3+AML (*Perl* et al 2017)
  - ASP2215 vs salvage chemotherapy in relapsed/refractory FLT3 AML
  - ASP2215 vs placebo as maintenance therapy after SCT in FLT3-ITD AML

IDH1-2 as molecular target in AML

- **IDH** is a critical metabolic enzyme in the citric acid cycle
- IDH**1** in **cytoplasm** and IDH**2** in **mithocondria**
- Cancer-associated IDH mutation produces **2-hydroxyglutarate** leading to **epigenetic dysregulation** and blocks normal cellular differentiation



- IDH mutations occur in **~ 20%** of AML in conserved active site (**IDH1-R132, IDH2-R172 or-R140**)
- **Founder mutations**

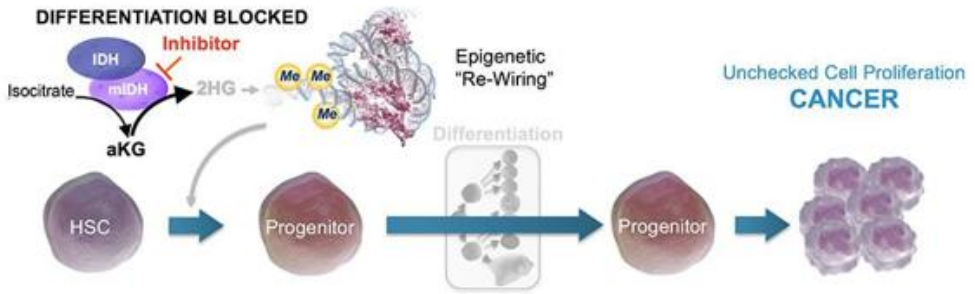
Dang L. et al, Trends Mol Med 2010; 16(9):387-97; Chou WC. et al, Leuk 2011;25(2):246-53; Patel J.P. et al, N Engl J Med 2012;366:1079-89; Prensner R.J. et al, Nat Med 2011;17:291–293

IDH2 inhibitor: ENASIDENIB

FDA approved for relapsed/refractory AML with IDH2 mutation

- **Enasidenib (AG-221)** is a first-in-class, oral, selective, small-molecule covalent inhibitor of R140Q and R172K-mutated IDH2
- Marrow blast from mutant-*IDH2* AML patients exposed to AG-221 ex-vivo produce **mature fully functioning neutrophils** with conserved mutant IDH2 allele frequency
- **159 relapsed/refractory** AML patients:
  - **CR/CRp**: **20**%; ORR **40**%; median duration of response: **6.9** months; median OS **9.3** months

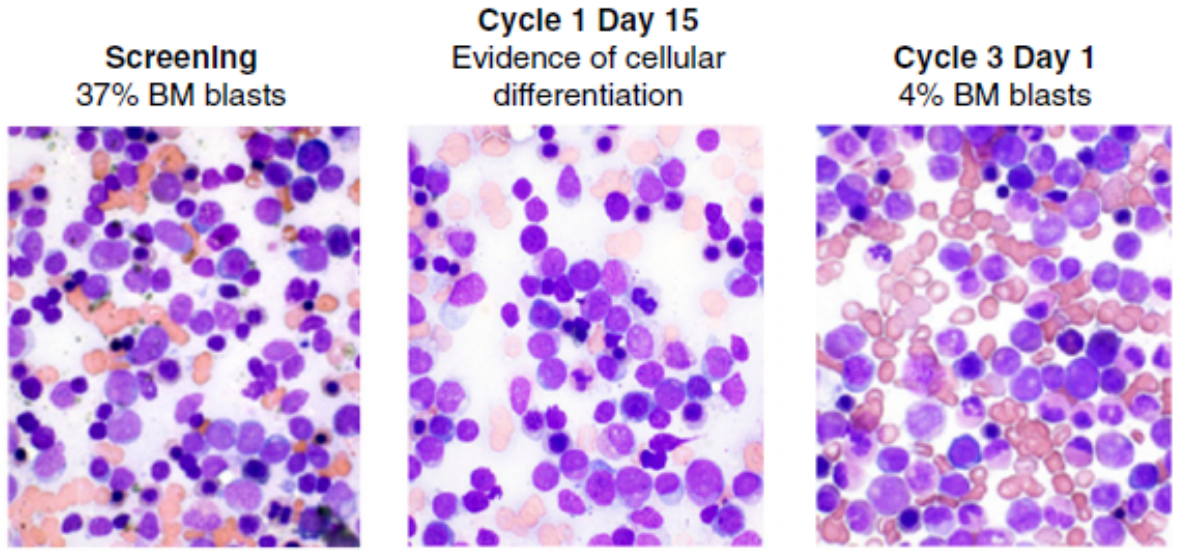
- Primary mechanism of response: terminal **differentiation of leukemic blasts**
  - **12% differentiation syndrome**

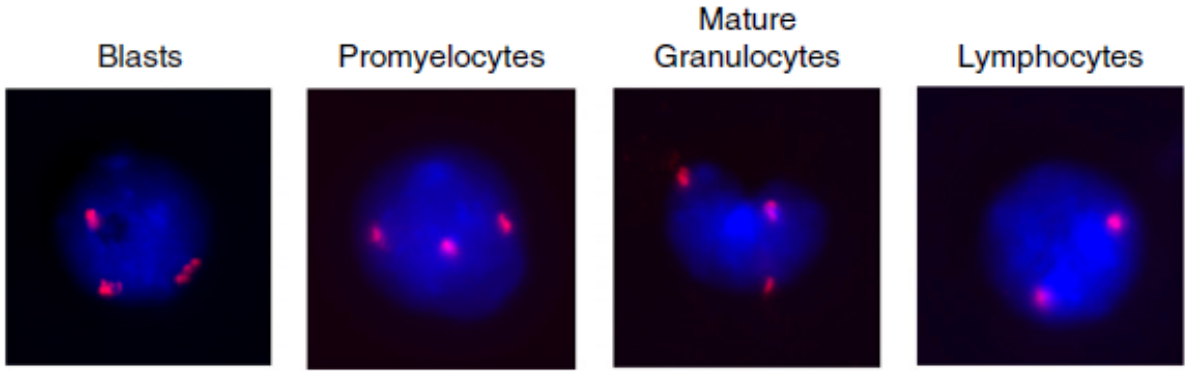


Stein EM. et al, Blood 2017; 130(6):722-731;

IDH2 inhibitor: ENASIDENIB

FDA approved for relapsed/refractory AML with IDH2 mutation





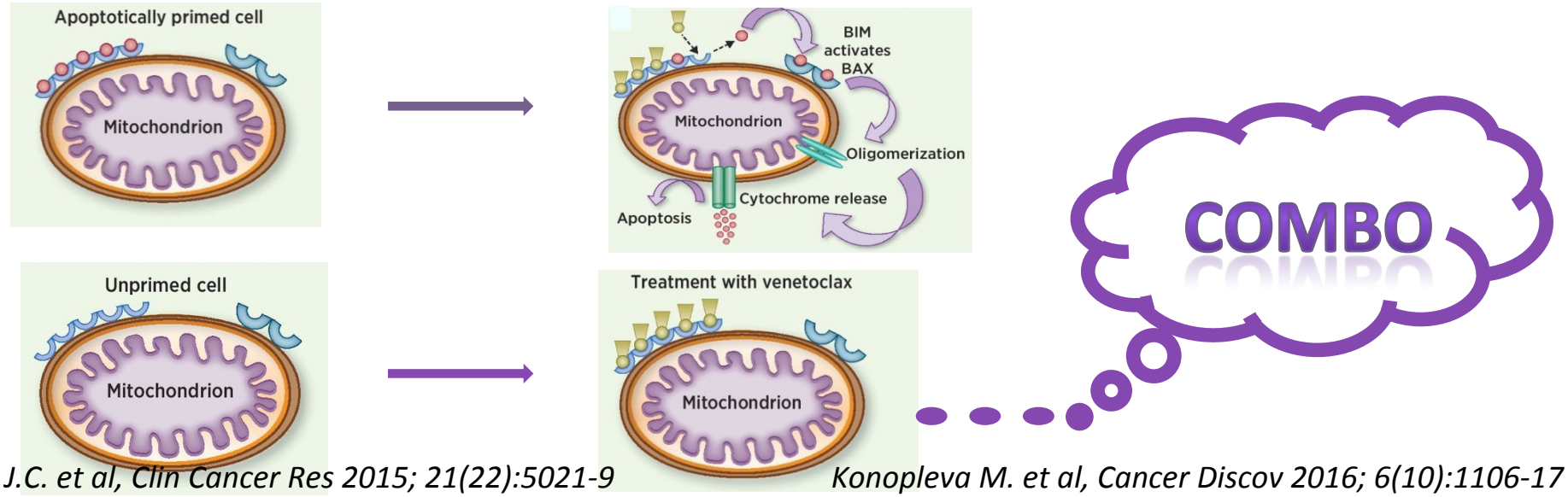
Stein EM. et al, Blood 2017; 130(6):722-731;

Non mutation targeted agents: antiapoptotic

- BCL2 is an **antiapoptotic** protein
- High BCL2 expression in myeloblasts (unlike CLL specific genetic alteration are not known)
- BCL2 **over**expression implicated in the **maintenance** and **survival** of AML cells *in vitro*
- BCL2 overexpression associated with **resistance** to **chemotherapy** and poor survival in AML patients
- **Unique role** in **LSC** survival → potential to eliminate chemotherapy resistant LSC sparing normal hematopoietic stem cell

BCL2 inhibitor: VENETOCLAX single agent

- Venetoclax is a highly selective, potent, orally bioavailable **BCL2 inhibitor**
- Single agent activity in **relapsed/refractory** (n=30) or **unfit** (n=2) AML patients:
  - Median age **71** yrs (range 19-84)
  - Rump-up dosing from 20 mg until **800 mg** within 6 days
  - **19**% (6/32) ORR
    - 2 CR and 4 CRi
    - **33%** ORR (4/12) in **IDH1/IDH2** mutated patients



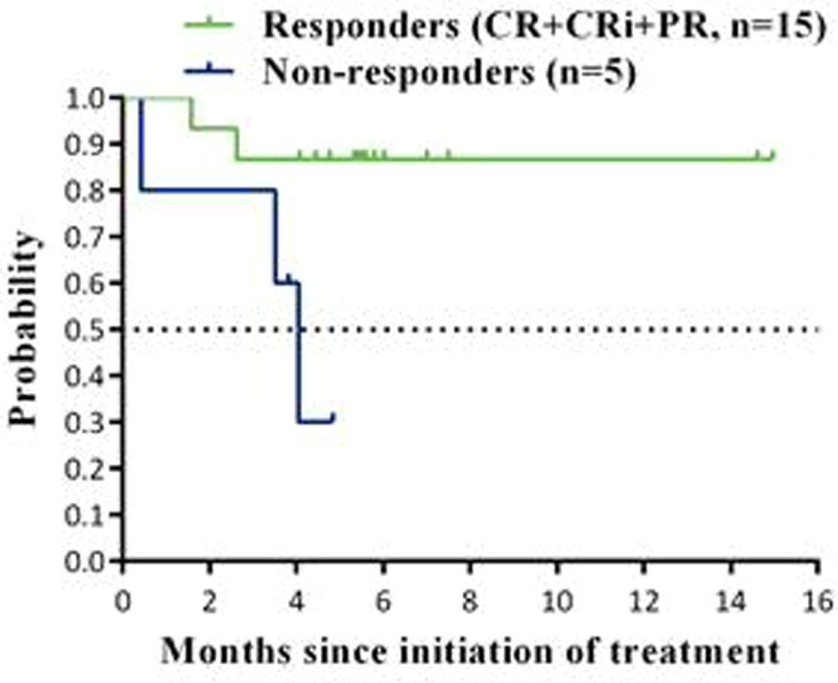
Gibson J.C. et al, Clin Cancer Res 2015; 21(22):5021-9

Konopleva M. et al, Cancer Discov 2016; 6(10):1106-17

BCL2 inhibitor: VENETOCLAX associations

- Phase II **Venetoclax** plus **low-dose cytarabine** in treatment-naive AML patients aged ≥ 65 years:
  - 20 AML pts; median age **75** yrs (range 66-87)
  - Ven **600 mg** plus LDAC **20 mg/m²** days 1-10
  - **75**% (15/20) **ORR**
    - 14/20 (**70**%) **CR+Cri**
  - Median time to best response **30** days (23-169)

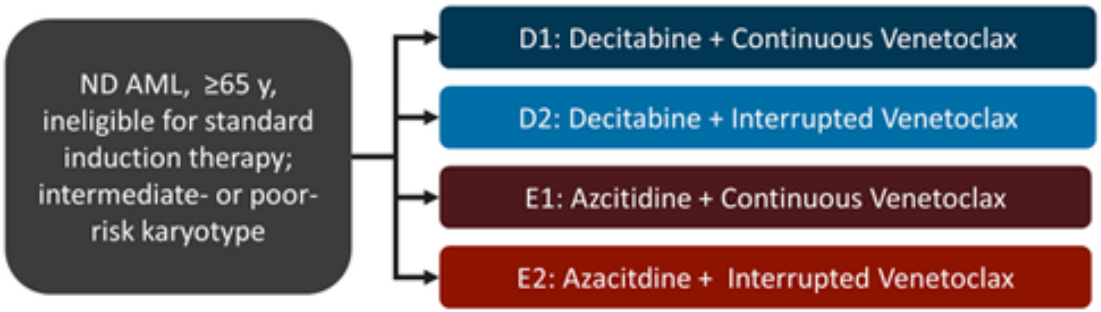
12-months OS estimate
for all patients: **74.7**%
for responders: **86.7**%



Wei A. et al, Blood 2016;128:102

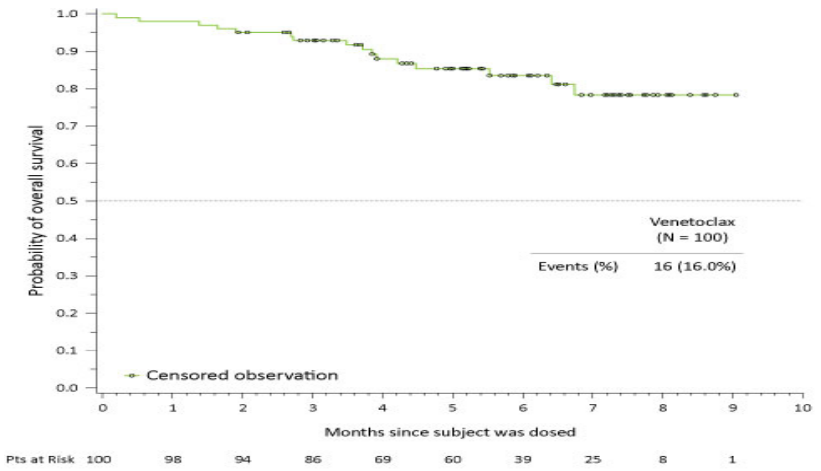
BCL2 inhibitor: VENETOCLAX associations

- Phase 1b **Venetoclax** plus standard dose **decitabine** or **azacitidine** in treatment-naive AML patients aged ≥ 65 years:
  - 57 AML pts; 23 group A; 22 group B; 12 group C (+ posaconazole)
  - RP2D: 2 dose cohorts ven: **continuous 400 mg** and **interrupted 800 mg**
  - **61**% (35/57) **CR/CRi**
  - **60**% (27/45) **CR/CRi** in group A and B
- Expansion stage: 100 pts (25 pts in each arm) median age 74 years (65-86): ORR **68**%



Decitabine: 20 mg/m²/d IV, days 1 to 5; AZA: 75 mg/m²/d SQ or IV, days 1 to 7; venetoclax: continuous 400 mg (arm 1) or interrupted

Objective Response	Arm D1 (n=25)	Arm D2 (n=25)	Arm E1 (n=25)	Arm E2 (n=25)
CR and CRi, %	76	68	72	56



Di Nardo C.D. et al, Lancet Oncol 2018;19(2):216-28; Pratz K. et al EHA 2017 abstract S472

Venetoclax + azacytidine in elderly AML

Phase 3 study

- Open-label, randomized, double-blind, placebo controlled study

Untreated AML, elderly and adult **ineligible for standard** induction therapy

→ **Azacitidine + Venetoclax**
75 mg/m^2 Days **1-7**, IV/SC
400 mg 1-28 days
28-day cycles

Safety, PK, dose finding

→ **Azacitidine + PLACEBO**
75 mg/m^2 Days **1-7**, IV/SC
1-28 days
28-day cycles

- **Endpoints**:
  - **Primary: OS, CR/CRi**
  - **Secondary**: EFS, CR/CRi rate at the end of cycle 1, QoL
  - **Exploratory**: biomarkers predictive of response, MRD, BCL2 expression

Potluri J. et al, ASCO 2017, Abstract TPS7069

TAKE HOME MESSAGE

THERE IS A ROLE FOR TARGET THERAPY IN AML?

- Several novel potential molecular target unveiled by high throughput genomics
  - ✓ **Extensive analysis** are currently **recommended** by ELN
- **New standard of care** for **FLT-mutated AML**
  - ✓ Higher response rate achieved with intensive chemo-combination
- **Chemo-free** strategy is the goal

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BOLOGNAIL
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SEZIONE DI BOLOGNA ONLUS

Grazie per l' attenzione !