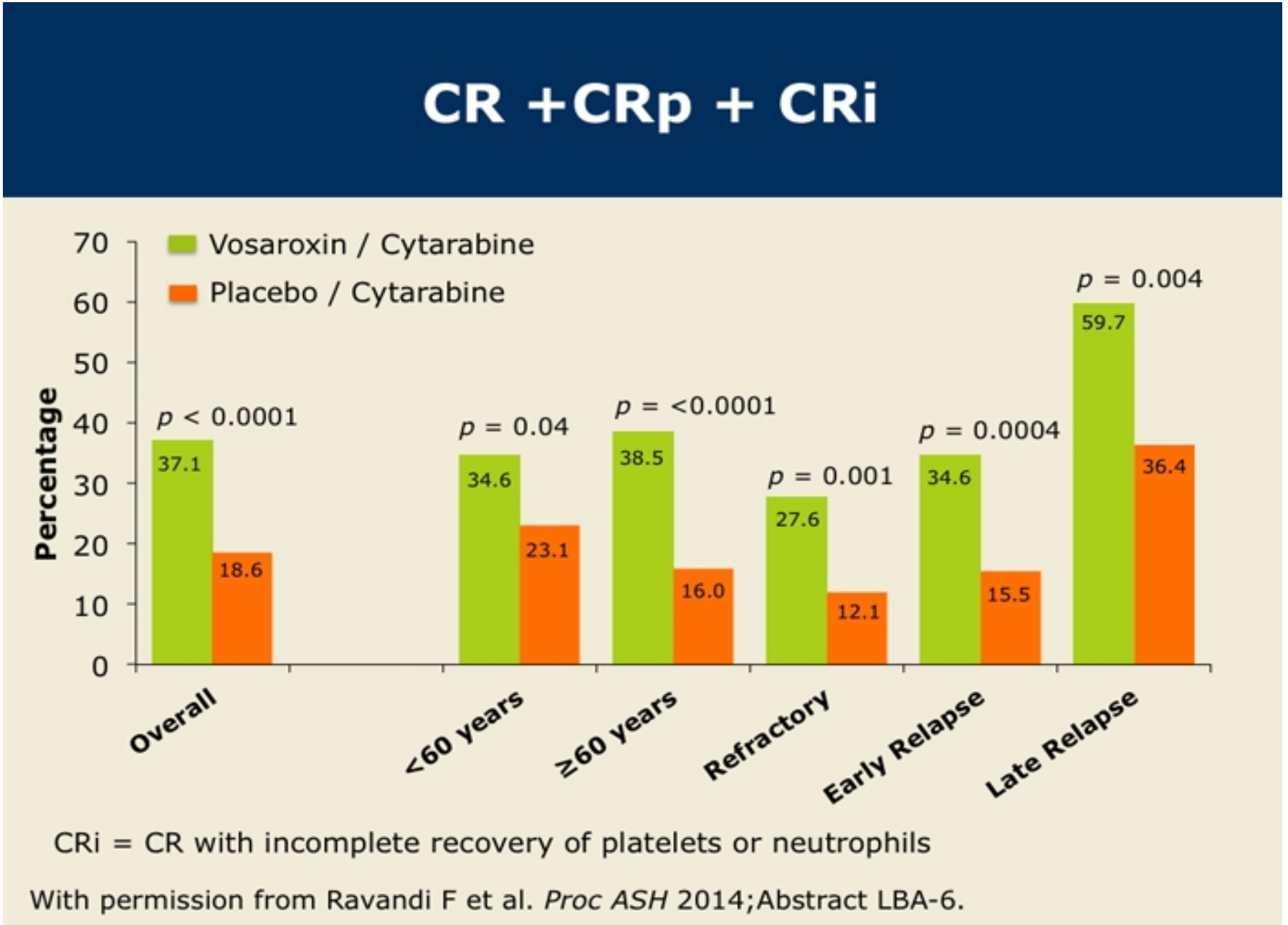
New Drugs in AML

- **New version of old drugs**
  - CPX-351
  - Topo II inhibitors (Vosaroxin)
- **Epigenetic modifiers**
  - HMA
  - HDAC
  - IDH1/2 inhibitors
  - DOT1L inhibitors
  - Bromo-domain inhibitors
- **Inhibitors of signaling pathways**
  - FLT3 inhibitors
  - PLK1 inhibitors (Volasertib)
- **Apoptosis inducers**
  - Bcl-2 inhibitors (ABT-199)
- **Immunotherapy**
  - AB conjugates (SGN-CD33A)
  - BiTEs
  - Vaccines
  - CAR-T

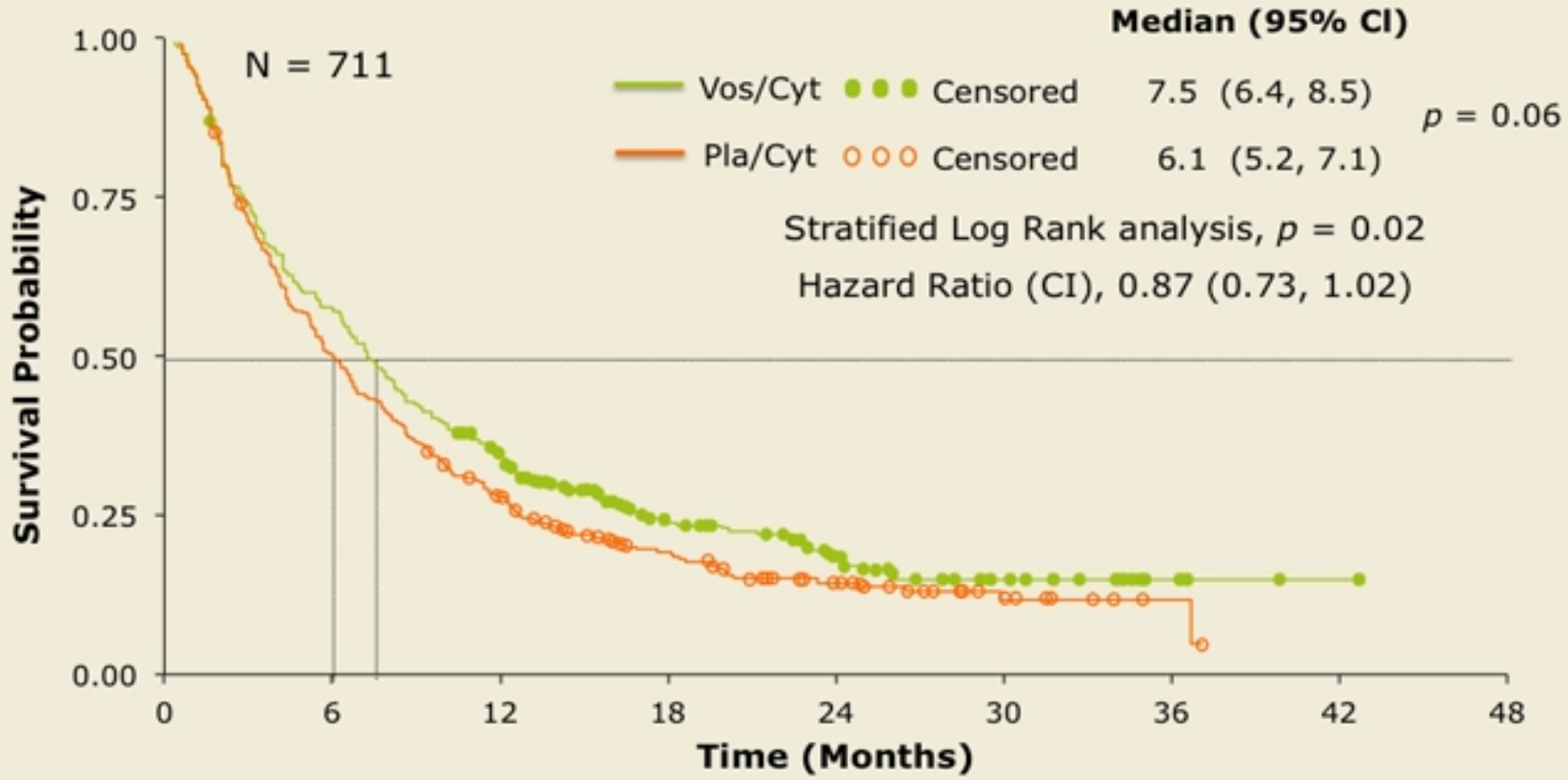
THE VALOR TRIAL



CRi = CR with incomplete recovery of platelets or neutrophils

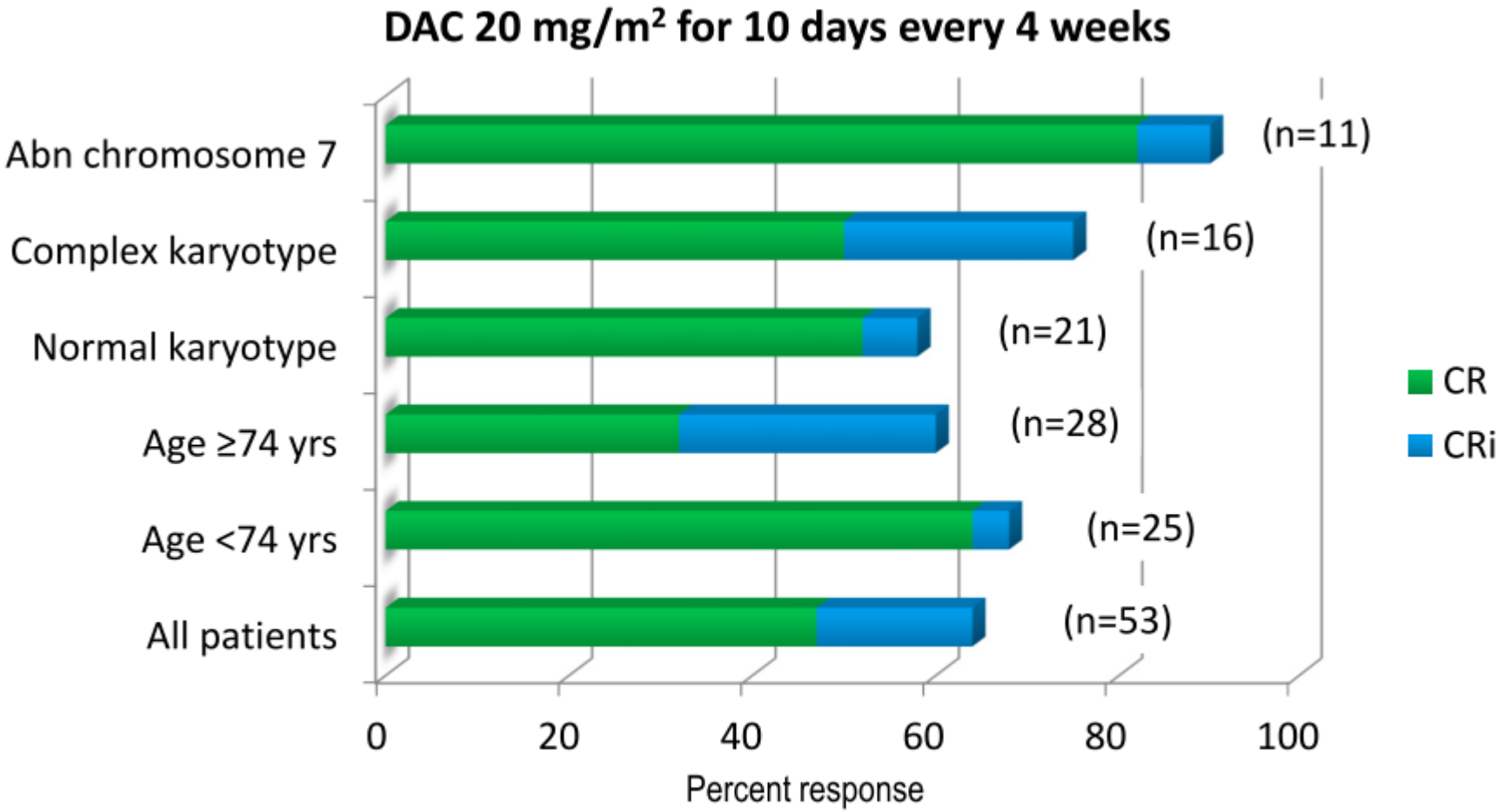
With permission from Ravandi F et al. *Proc ASH* 2014;Abstract LBA-6.

Overall Survival: Intent-to-Treat



With permission from Ravandi F et al. *Proc ASH* 2014;Abstract LBA-6.

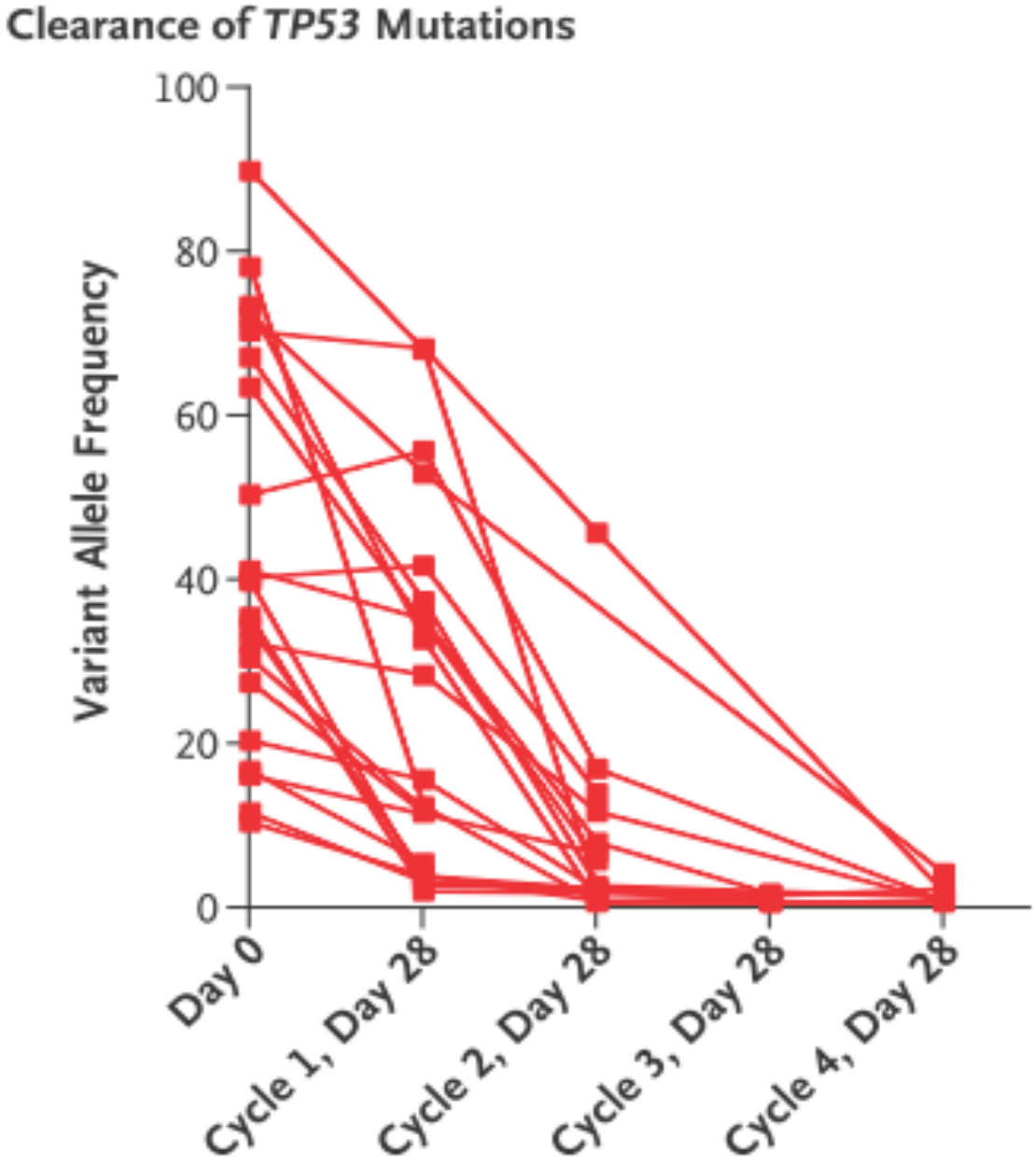
Phase 2 clinical trial of decitabine for elderly patients with *de novo* AML



AML, acute myeloid leukaemia; CR, complete remission; CRi, complete remission with incomplete haematological recovery of peripheral blood counts; DAC, decitabine

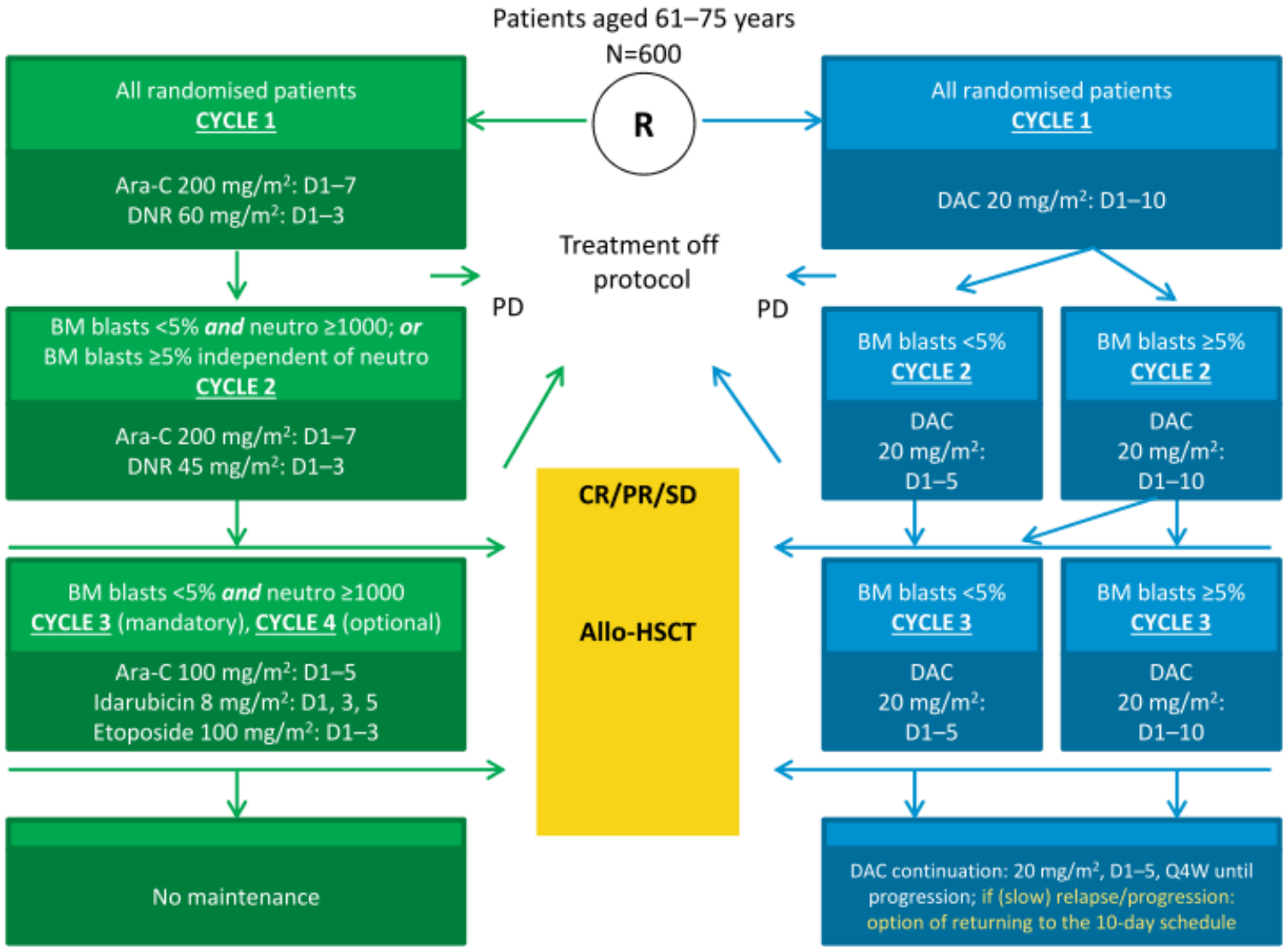
Blum et al. Proc Natl Acad Sci U S A. 2010;107:7473-8.

TP53 and decitabine in AML and MDS



Welch et al. N Engl J Med 2016;375:2023-6.

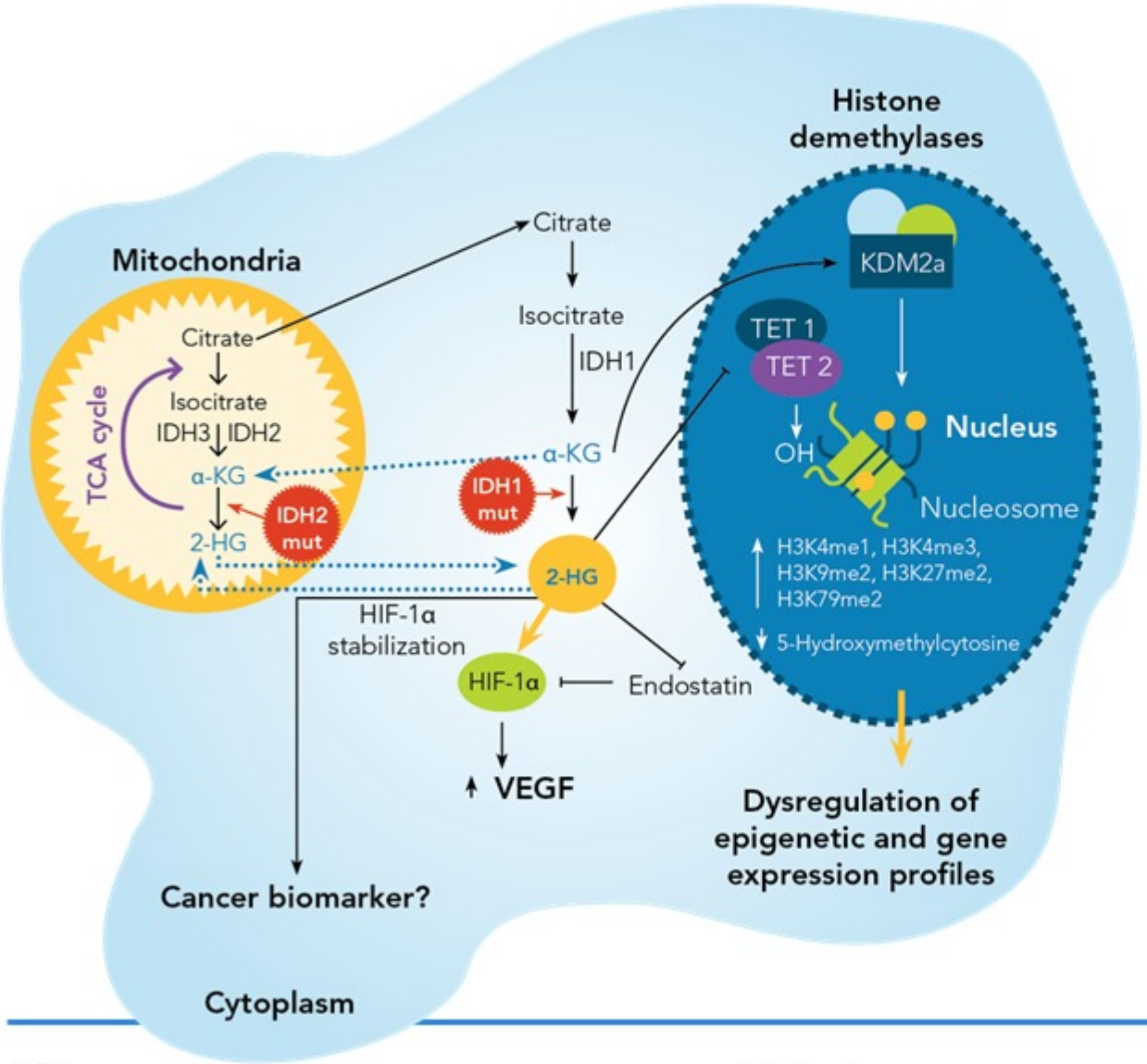
EORTC/GIMEMA AML1301 protocol



Allo-HSCT, allogeneic haematopoietic stem cell transplantation; AML, acute myeloid leukaemia; Ara-C, cytarabine; BM, bone marrow; CR, complete remission; D, day; DAC, decitabine; DNR, daunorubicin; EORTC, European Organisation for Research and Treatment of Cancer; GIMEMA, Italian Adult Haematological Malignancies Group; PD, progressive disease; PR, partial remission; Q4W, once every 4 weeks; SD, stable disease

www.clinicaltrials.gov/ct2/show/NCT02172872.

IDH in AML



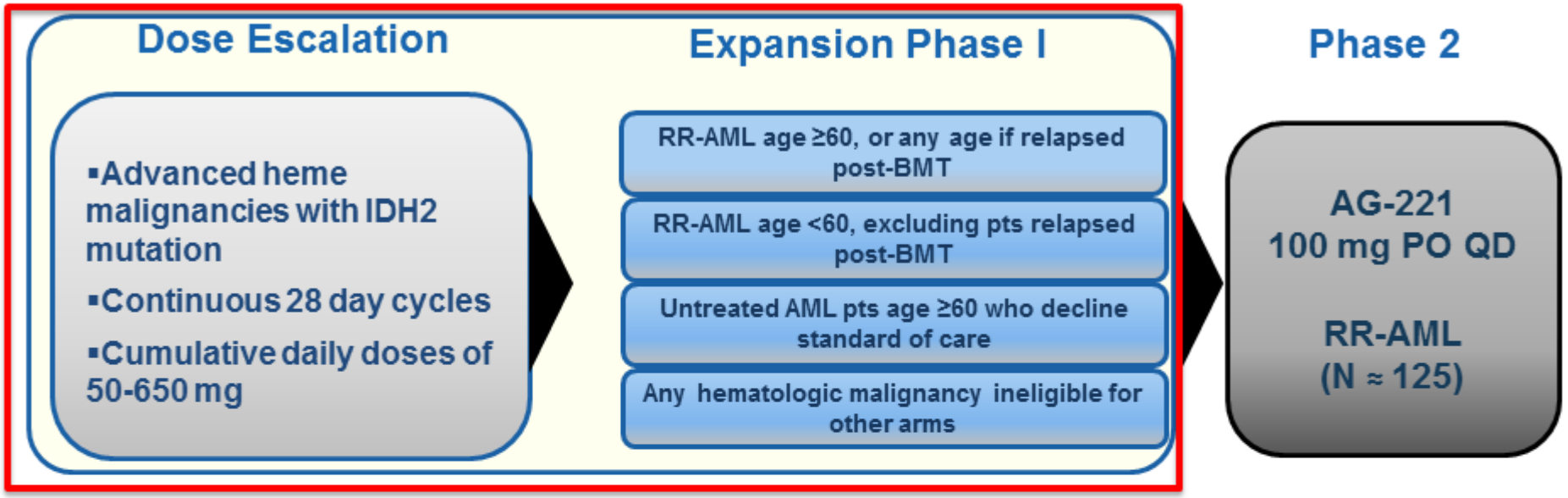
- IDH is a critical metabolic enzyme in the citric acid cycle
- IDH1 in cytoplasm and IDH2 in mitochondria
- Cancer-associated IDHm produces 2-hydroxyglutarate (2-HG) and blocks normal cellular differentiation

Prensner and Chinnaiyan Nature, 2011

Current IDH inhibitors in Clinical Trials for Acute Myeloid Leukemia

- AG-221 (Agios/Celgene) – IDH 2 inhibitor
- AG-120 (Agios) – IDH1 inhibitor
- IDH-305 (Novartis) – IDH1 inhibitor
- AG-881 (Agios/Celgene) – Dual IDH1/IDH2 inhibitor
- FT-2102 (Forma) – IDH1 inhibitor

Phase 1/2 Study Design – IDH2 inhibitor AG-221 (Celgene/Agios)



Key Endpoints:

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

Stein EM, et. al. Blood 2015 126:323

Baseline Characteristics

Data cut-off: 1 Sept 2015	All (N = 209)	RR-AML (n=159)
Age (years), median (range)	69 (19–100)	68 (19–100)
Gender, % M/F	56/44	50/50
IDH2 mutation, n (%)		
R140	146 (70)	109 (69)
R172	50 (24)	41 (26)
ECOG PS, n (%)		
0-1	161 (77)	120 (76)
2	41 (20)	34 (21)
Diagnosis, n (%)		
RR-AML	159 (76)	159 (100)
Untreated AML	24 (11)	-
MDS	14 (7)	-
Other	12 (6)	-
Number of prior Tx, median (range)	-	2 (1–6)

Response

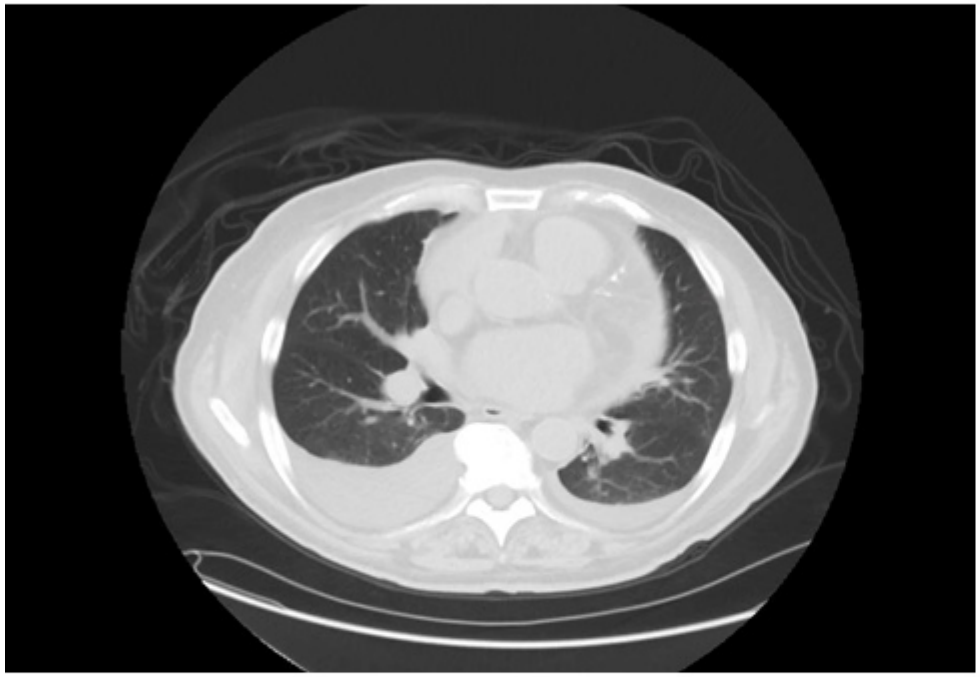
	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (N = 209)
Overall Response (CR, CRp, CRi, mCR, PR)	59 (37%)	10 (42%)	7 (50%)	79 (38%)
CR	29 (18%)	4 (17%)	3 (21%)	37 (18%)
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	22 (11%)
SD	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%)

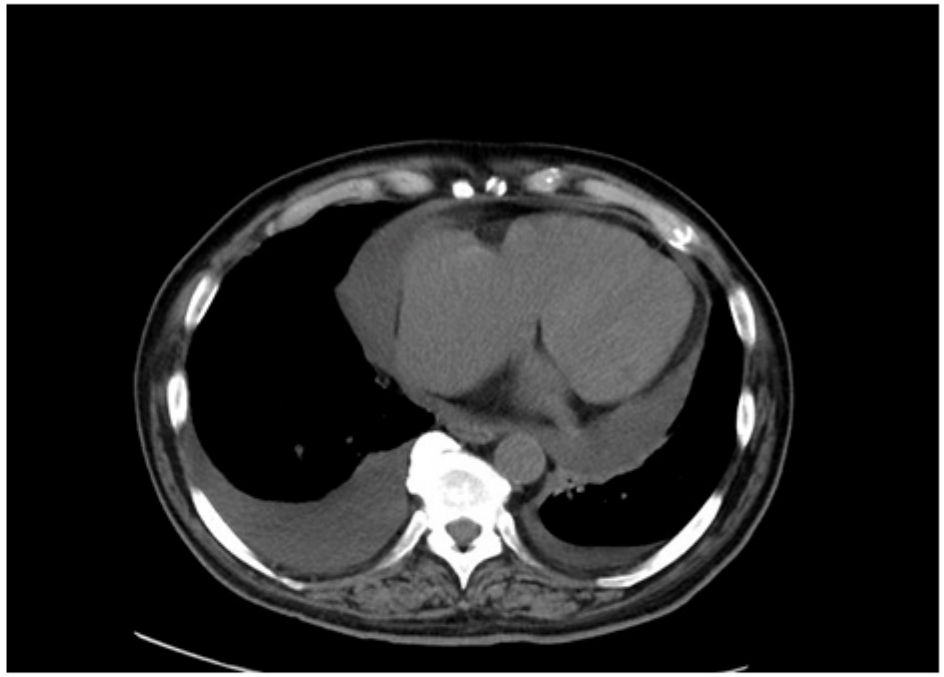
- Overall response by IDH mutation type: R140Q 36% / R172K 42%

Most Frequent Treatment Emergent Adverse Events (≥15% of patients)

	Any Grade	Grade ≥3
Preferred Term	%	
Nausea	32	2
Diarrhea	28	3
Fatigue	28	6
Hyperbilirubinemia	27	10
Decreased appetite	27	3
Febrile neutropenia	27	26
Dyspnea	23	5
Pyrexia	23	4
Cough	22	0
Vomiting	20	1
Constipation	19	<1
Anemia	18	12
Peripheral edema	18	2
Thrombocytopenia	16	12

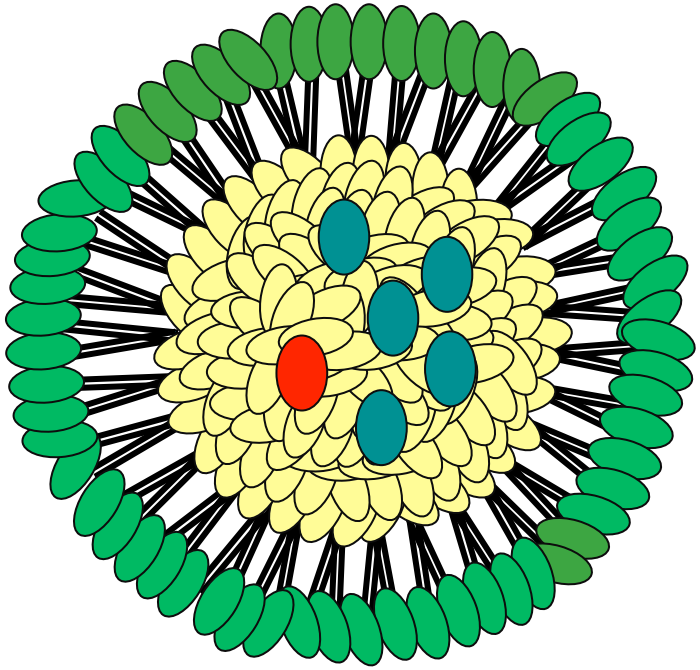
CT Chest – February 11, 2016





- Started Dexamethasone 10mg bid with rapid resolution of symptoms
- Rapid taper of dex without recurrence of symptoms

CPX-351 Uses a Nano-Scale Delivery Complex



- 100-nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

Lancet JE, et al. ASCO 2016. Abstract 7000.

CPX-351: Phase 2 trial vs ARA-C / DNR in older adults with untreated AML

n=127 randomized 2:1 to CPX-351 or 3+7

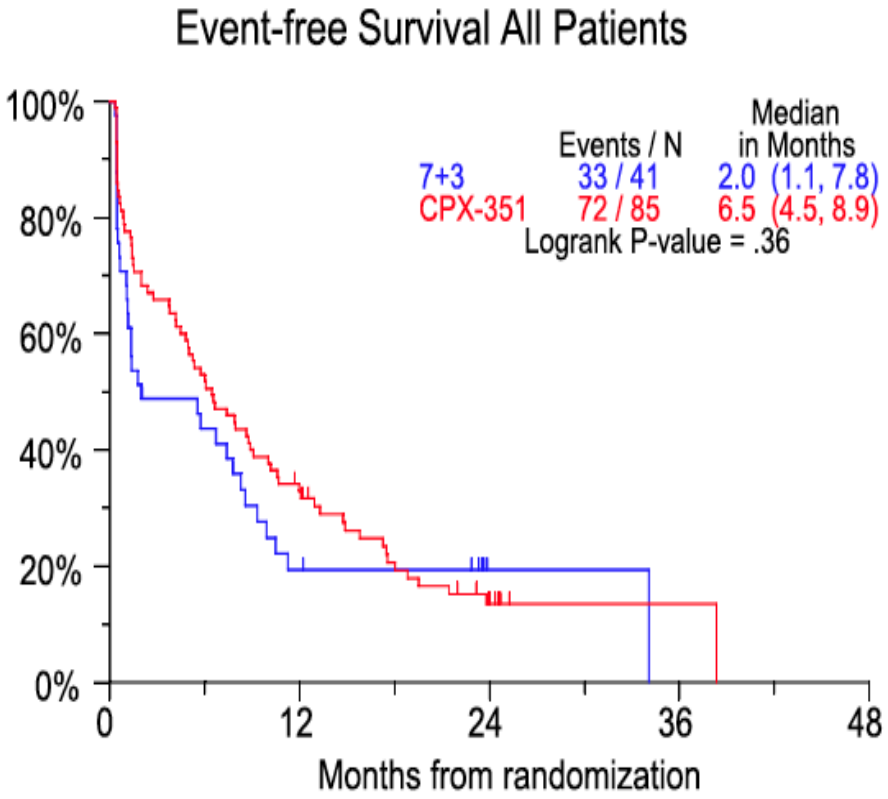
	CPX-351*	3+7	*P*
CR, n (%)	41/84 (48.8%)	20/41 (48.8%)	
CRi, n (%)	15/84 (17.9%)	1/41 (2.4%)	
Overall, n (%)	56/84 (66.7%)	21/41 (51.2%)	**0.07**

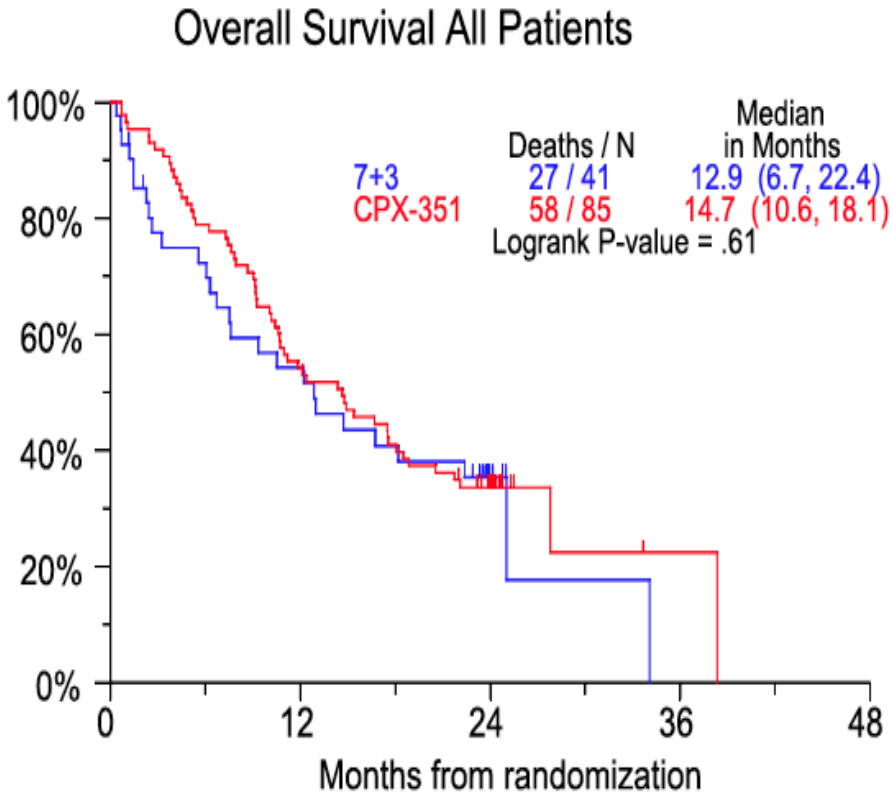
***Liposomal formulation of daunorubicin and cytarabine at an "optimal" (1:5) molar ratio**

CPX-351 = 100 U/m^2, day 1-3-5
ARA-C = 100 mg/m^2, day 1-7
DNR = 60 mg/m^2, day 1-3

Lancet et al. Blood 2014;123:3239-46.

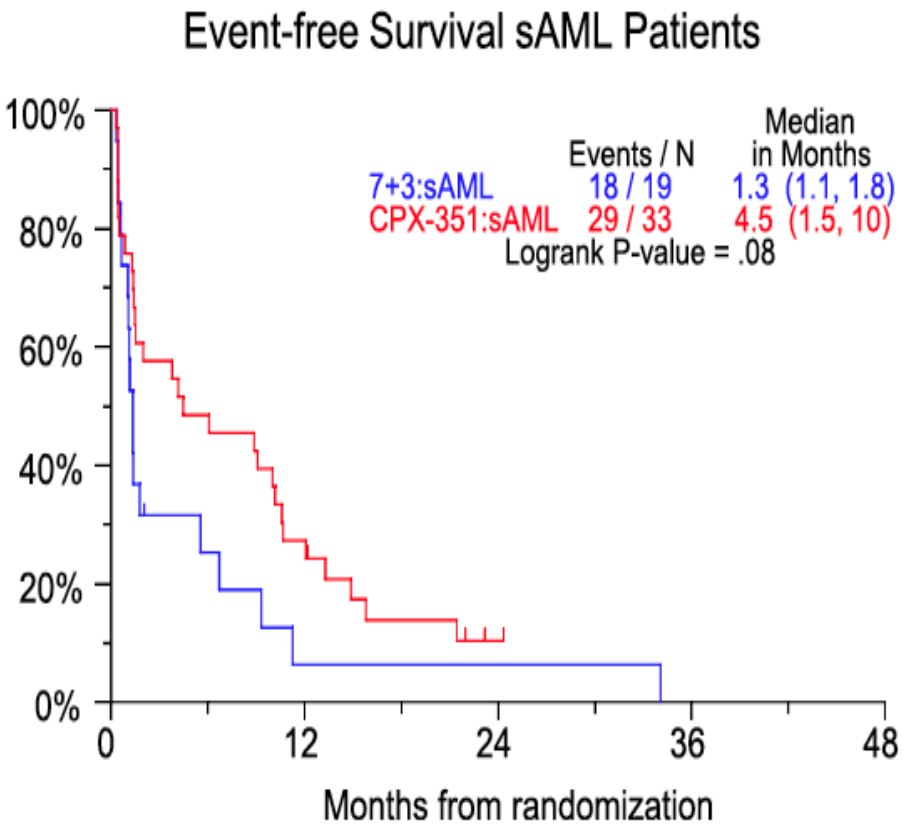
CPX-351: Phase 2 trial vs ARA-C / DNR in older adults with untreated AML

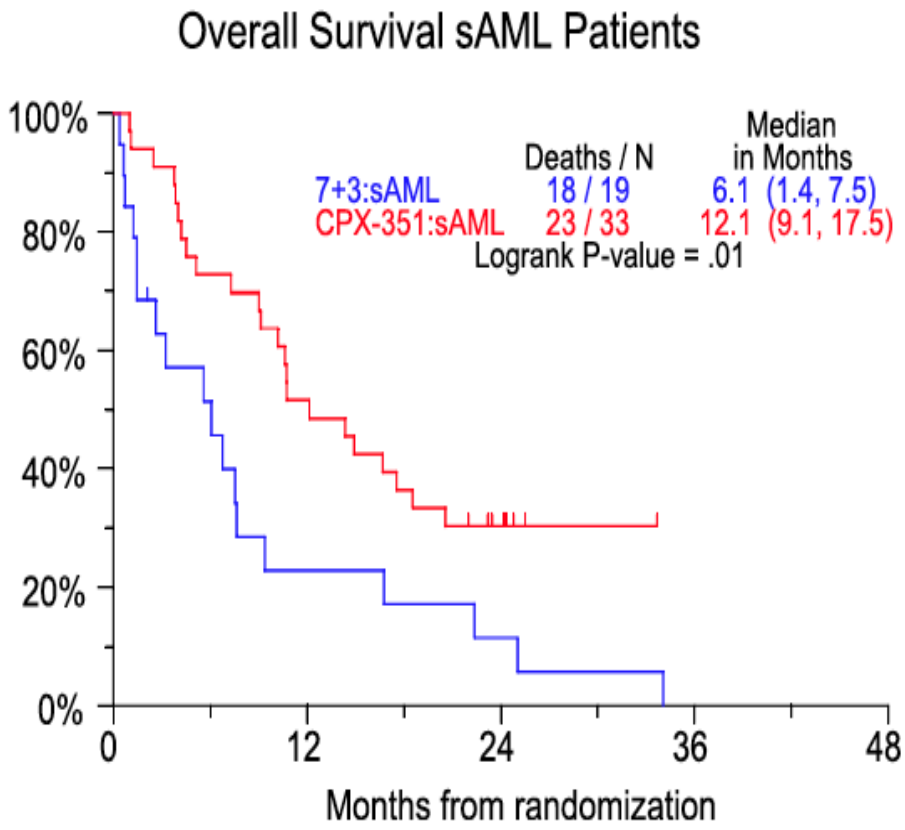




Lancet et al. Blood 2014;123:3239-46.

CPX-351: Phase 2 trial vs ARA-C / DNR in older adults with untreated AML





sAML, secondary AML

Lancet et al. Blood 2014;123:3239-46.

Phase 3 study: Open-label, randomized Phase 3 study of CPX-351 vs daunorubicin (60 mg/m^2)-cytarabine for sAML in patients aged 60–75 years[1]

CPX-351 significantly improves response rate over 3+7 in FLT3-ITD^{mut} AML

Group	CR+CRi rate n(%)		P-value
	CPX arm	3+7 arm	
FLT3^{mut} (all)	**15/22 (68.2)**	**5/20 (25.0)**	**0.007**
FLT3 ITD+	12/19 (63.1)	3/13 (23.0)	
FLT3 TKD+	3/3 (100)	2/7 (28.6)	

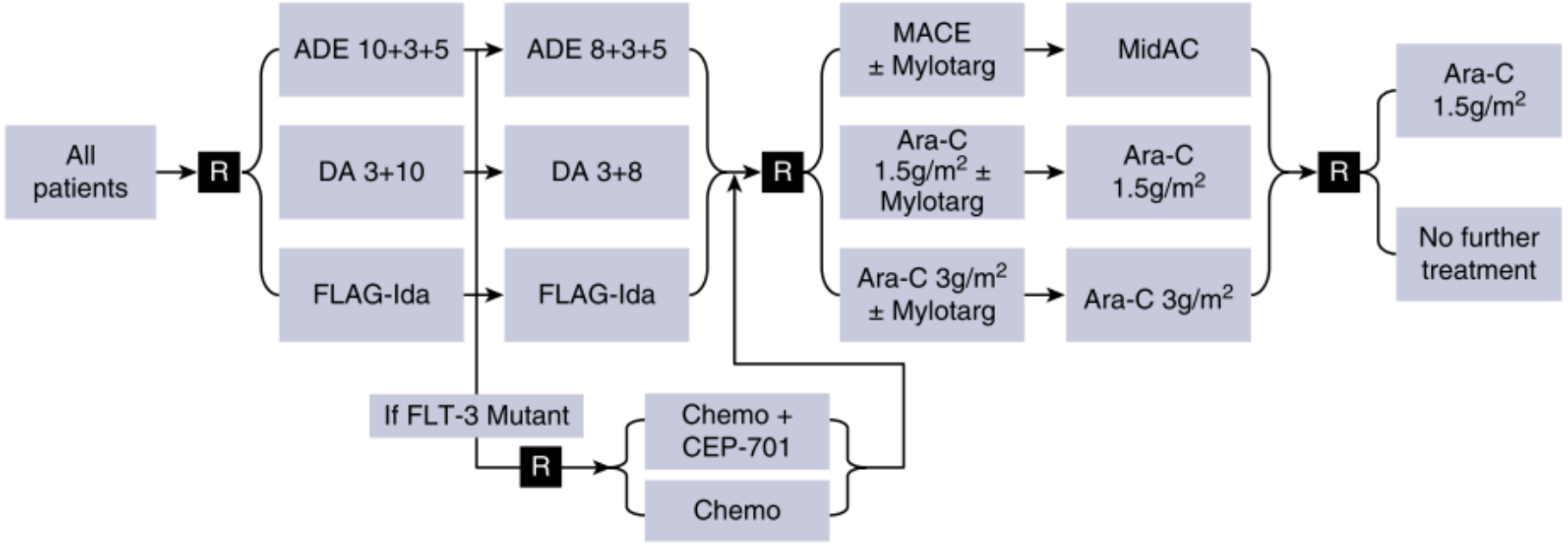
Lancet et al. EHA 2016. Abstract S502.

New Drugs – FLT3 Inhibitors

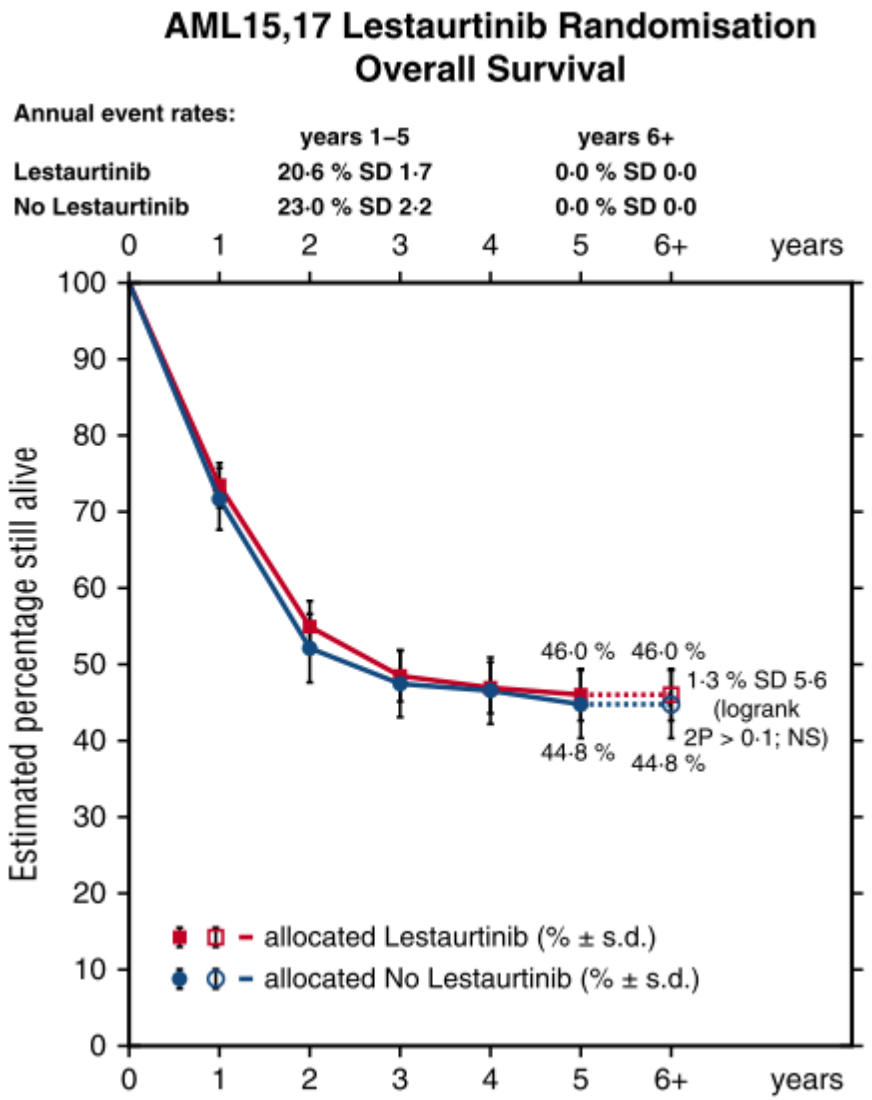
- Leustartinib (CEP-701)
- Midostaurin (PKC-412)
- Sorafenib
- Quizartinib (AC220)
- Crenolanib
- Gilteritinib

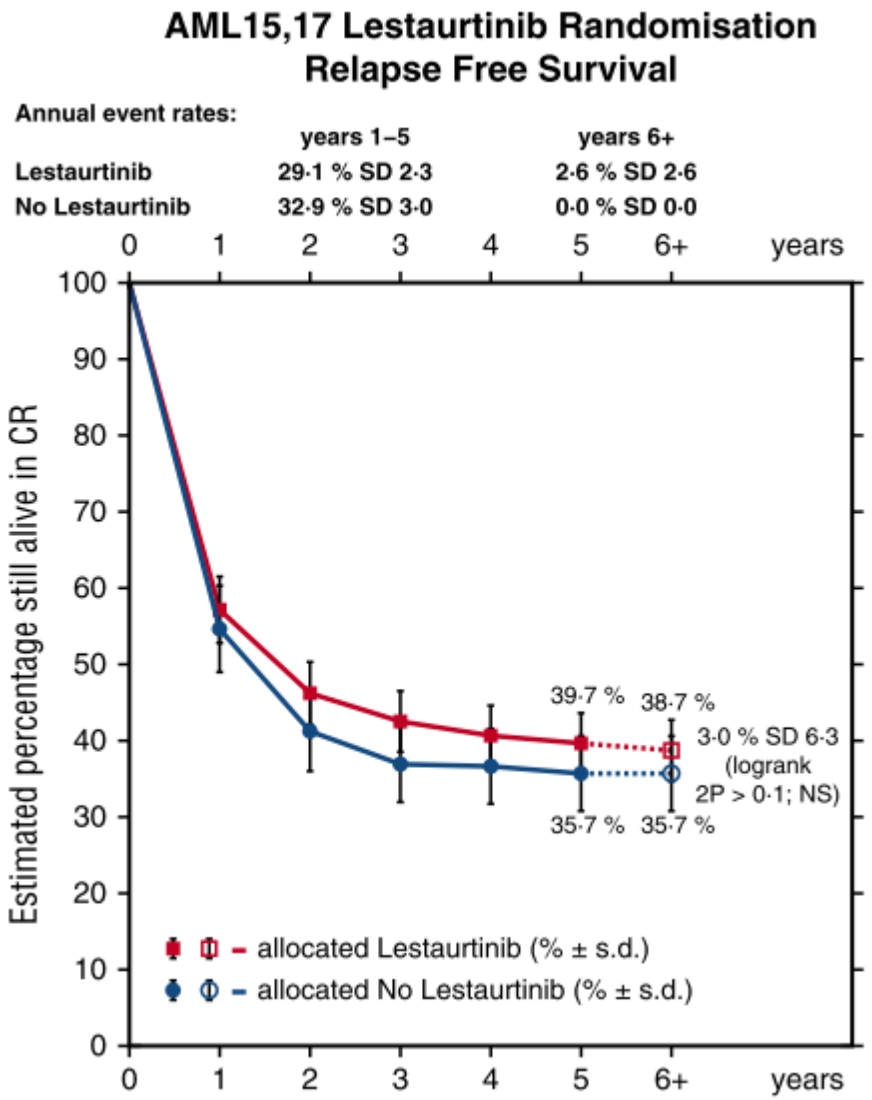
A randomized assessment of adding the kinase inhibitor lestaurtinib to first-line chemotherapy for FLT3-mutated AML

Steven Knapper,[1] Nigel Russell,[2] Amanda Gilkes,[3] Robert K. Hills,[4] Rosemary E. Gale,[5] James D. Cavenagh,[6] Gail Jones,[7] Lars Kjeldsen,[8] Michael R. Grunwald,[9] Ian Thomas,[4] Heiko Konig,[10] Mark J. Levis,[11] and Alan K. Burnett[1]



Knapper et al. Blood 2017.





Knapper et al. Blood 2017.

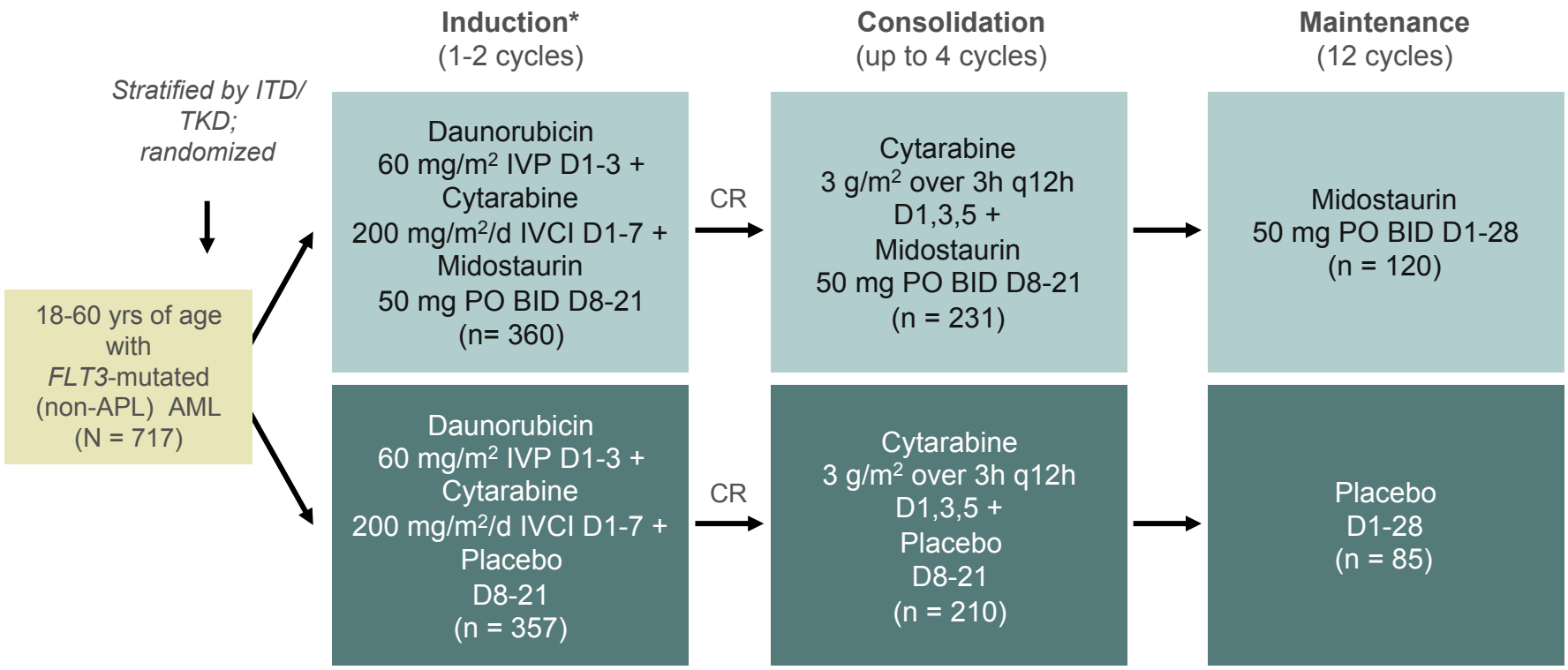
Leustartinib

- No clinical benefit seen after the addition of leustartinib to CHT

- Lower relapse rate and improved OS in those achieving sustained levels of FLT3 plasma inhibitory activity

Knapper et al. Blood 2017.

RATIFY: Study design

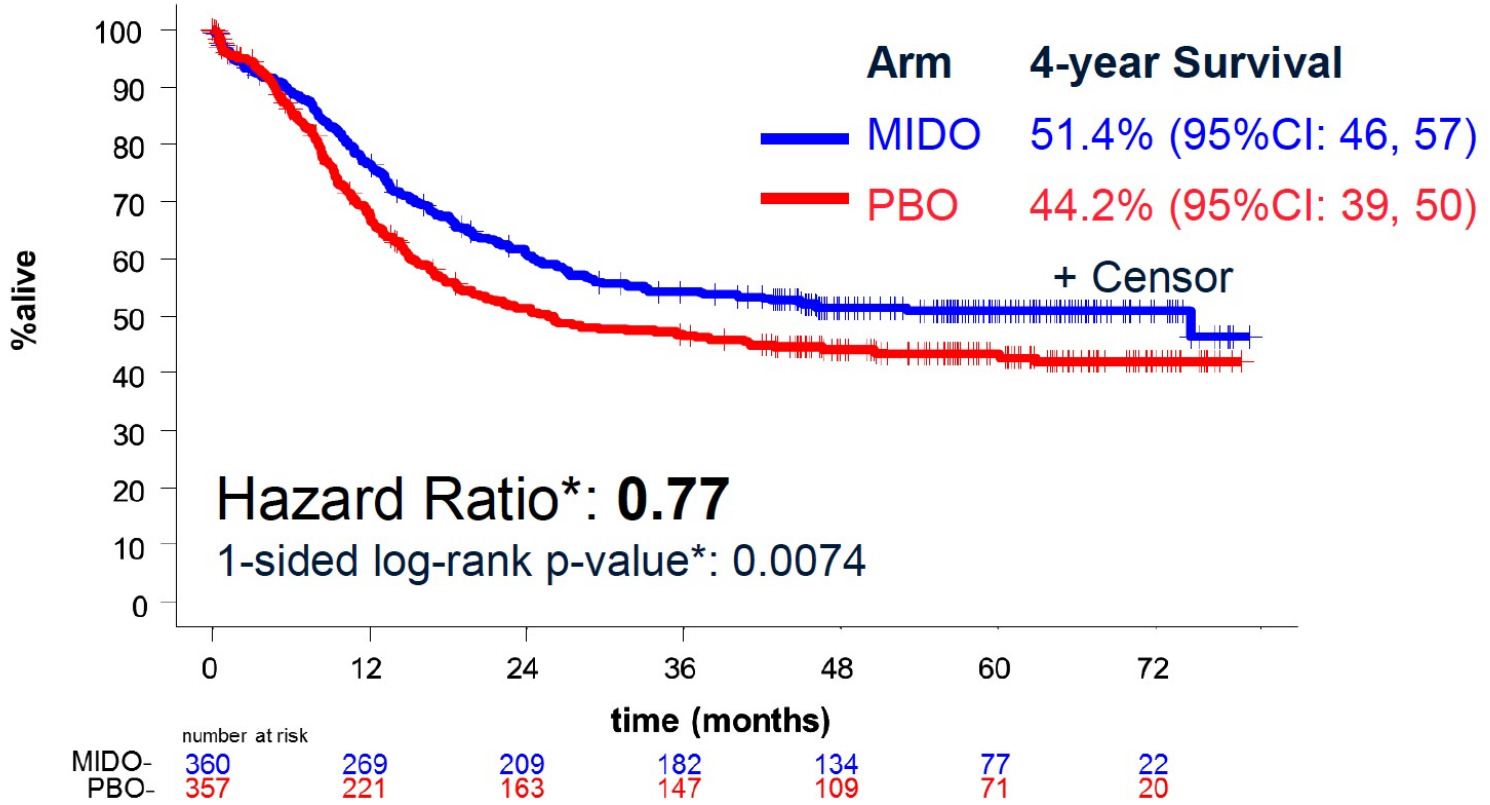


*Hydroxyurea allowed for ≤ 5 days prior to induction therapy.

- Double-blind, placebo-controlled, randomized phase III study
  - Primary endpoint: OS (not censored for SCT)

Stone et al. ASH 2015. Abstract 6.

Overall survival (primary endpoint)
23% reduction in risk of death in midostaurin arm

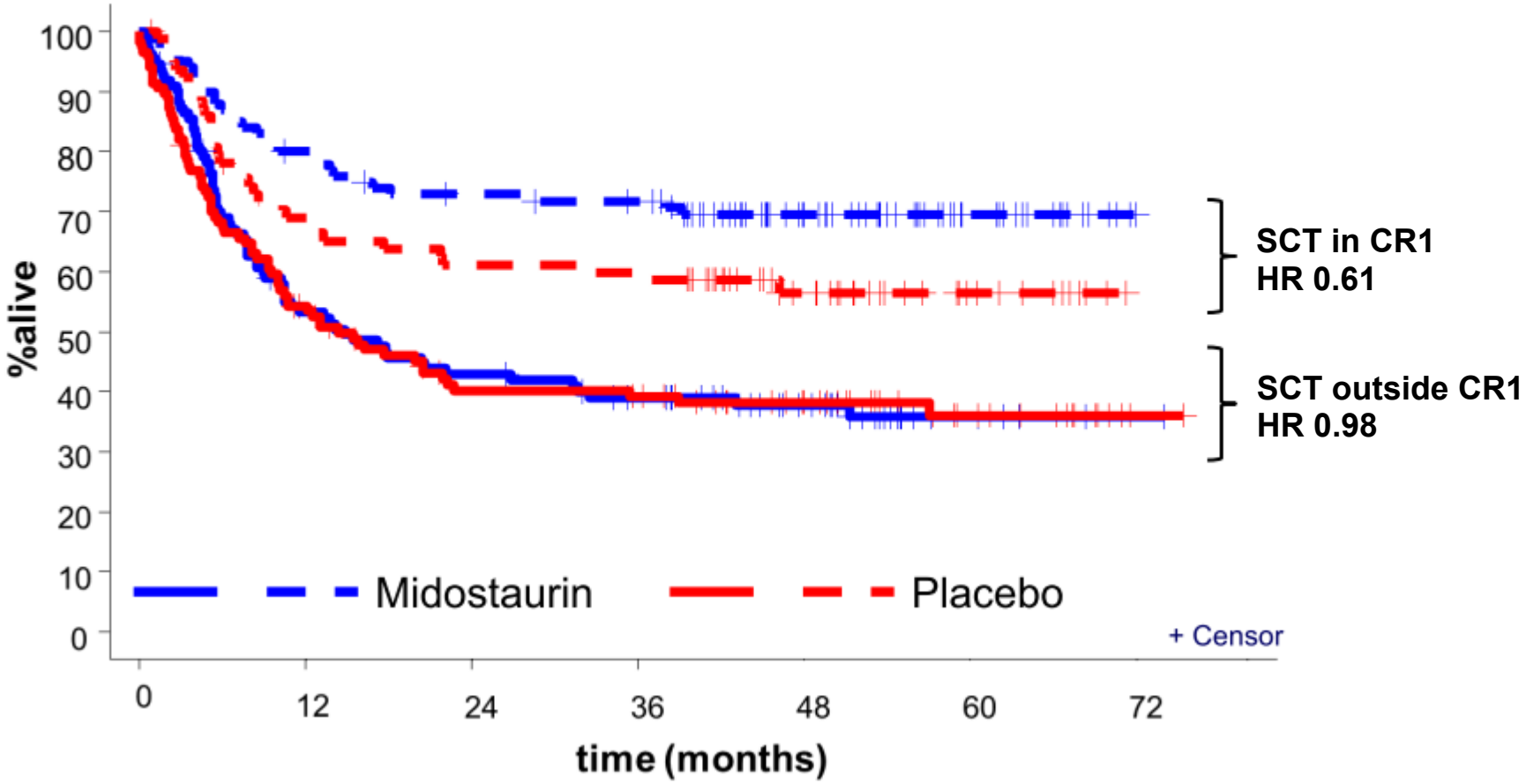


Median OS: midostaurin 74.7 months (31.7–NE); placebo 25.6 months (18.6–42.9)

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

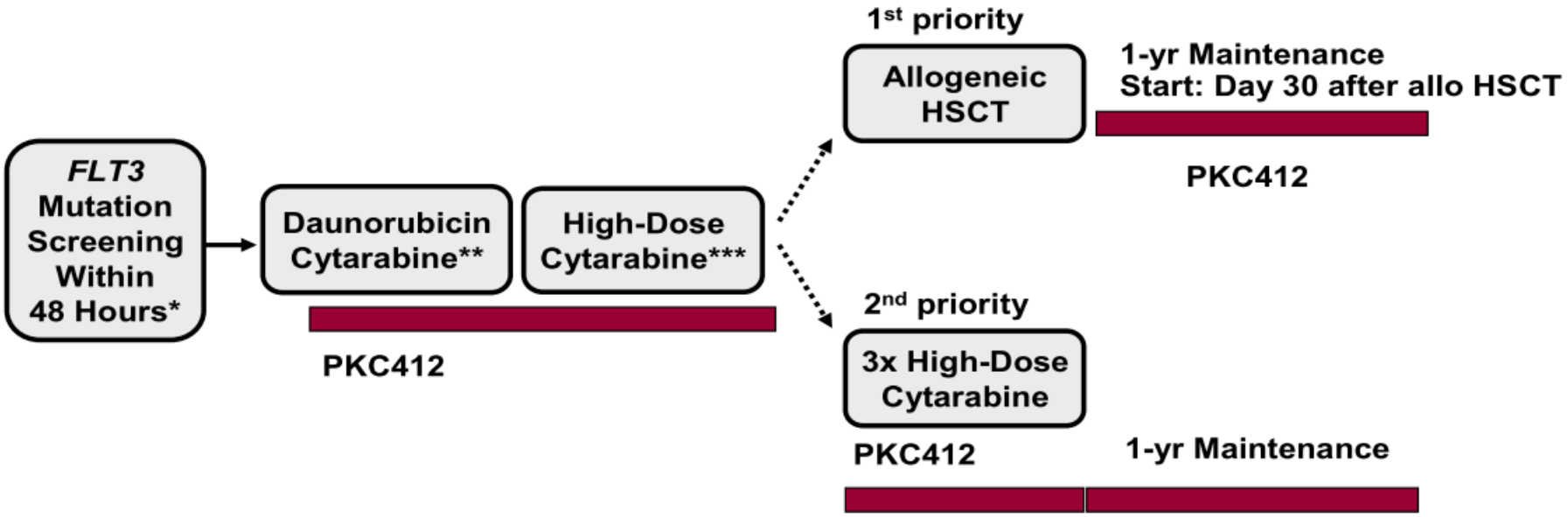
Stone et al. ASH 2015. Abstract 6.

Overall survival censoring patients at transplant



Stone et al. ASH 2015. Abstract 6.

AMLSG 16-10



* Patients may receive hydroxyurea during screening phase

** Optional 2nd cycle in patients achieving PR after cycle I

*** Cytarabine: 18-65 years, 3g/m², q12hr, day 1,3,5; >65 years, 1g/m², q12hr, day 1,3,5; optional for patients before allogeneic HSCT

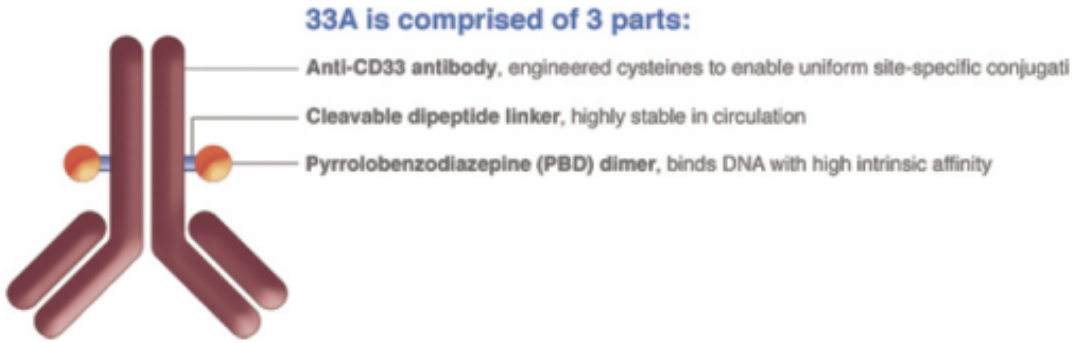
Schlenk RF, et al. Blood. 2015;126: Abstract 322

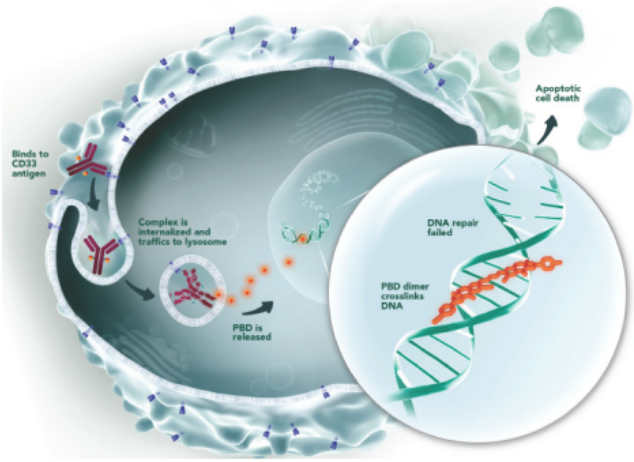
PKC-412: points for considerations

- We don’t know how mido exactly works
  - ✓ Primarily FLT3 inhibitor?
  - ✓ Anthracycline enhancer?
- Does it work in ITD low burden status?
- Does it work in FLT3mut/NPM1mut AML?
- Will PKC-412 treatment benefit everyone equally?
  - ✓ RATIFY trial not powered to look at patients subsets

Stone RM & Luger SM, ASH Clinical News, July 2016.

Anti-CD33 mAbs





SGN-CD33A mAb (vadastuximab talirine)

- Fully humanized anti-CD33 mAb linked with a pyrrolobenzodiazepine dimer (PBD), which binds DNA with high intrinsic affinity
- In xenotransplanted mice, it exhibits a potent cytotoxicity against p53 mutated or MDR-1 efflux positive AML cells
- It exhibits synergy with HMAs to enhance anti-leukemic activity
- CR rate 29% in a escalating Phase 1 study of relapsed/refractory AML

HMA, hypomethylating agent; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease

Stein & Tallman. Blood 2016;127:71-8.
Feldman. Clin Lymphoma Myeloma Leuk 2015;15 Suppl:S91-3.
Kung Sunderland et al. Blood 2013;122:1455-63.

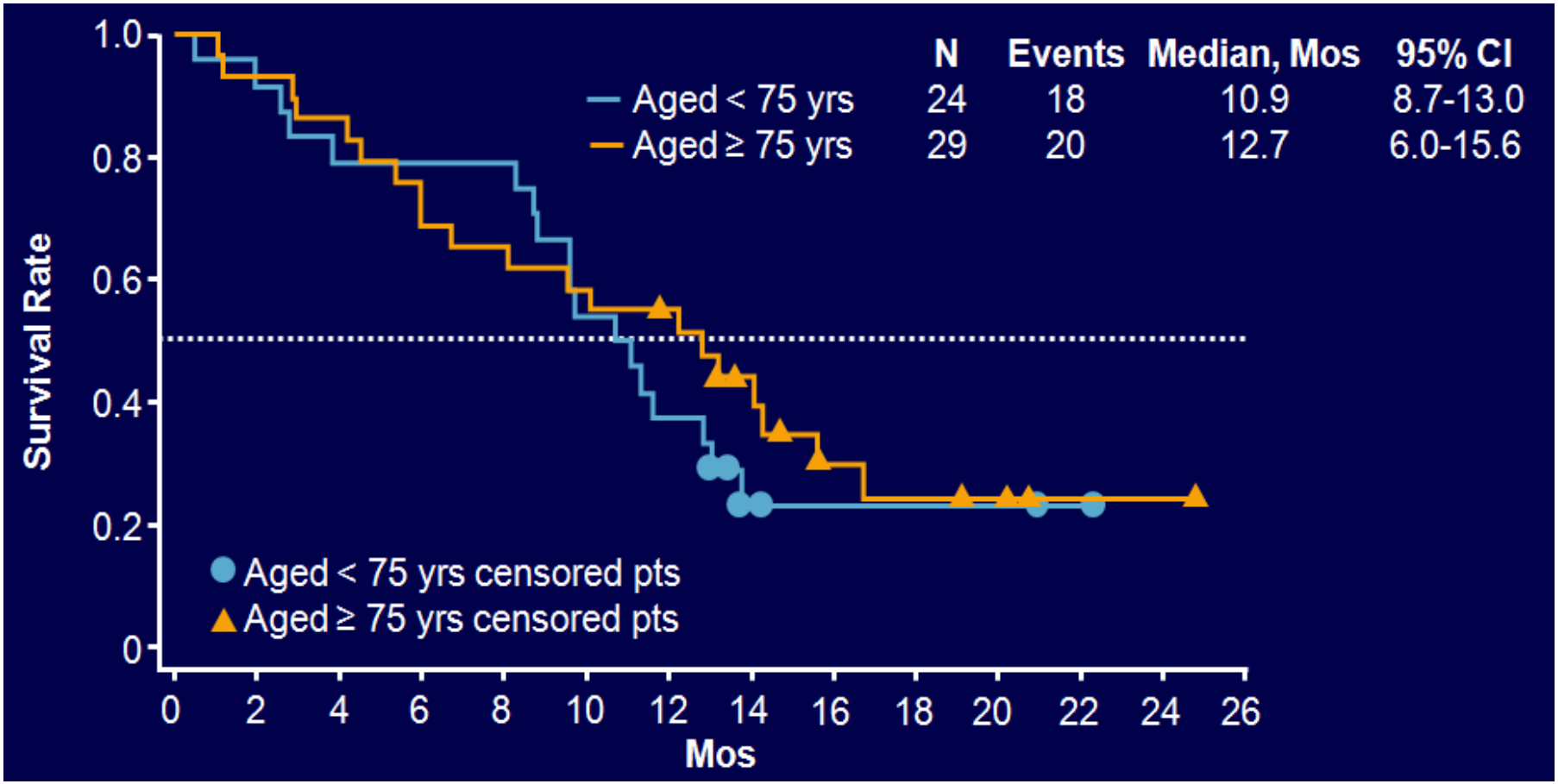
Anti-CD33 mAb: SGN-CD33A + HMA

Phase I study of SGN-CD33A in combination with an HMA (AZA or DAC) (NCT01902329)

Treatment and patients	Outcomes
▪ **SGN-CD33A 10 µg/kg IV, every 4 weeks on the last day of HMA** ▪ 53 patients treated ▪ Median age: 75 years ▪ Median BM blast infiltration: 46% ▪ 5 patients (9%) previously treated ▪ 19 patients (36%) with adverse cytogenetics risk	▪ 49/53 evaluable for efficacy ▪ **37/49 (76%) achieved CR + CRi + PR** (1) ▪ Median time to response: 2 cycles ▪ 13/17 (76%) with adverse cytogenetic risk achieved remission ▪ Median RFS in CR / CRi patients: 6.9 months ▪ 37 pts (70%) still alive with a median follow-up of 4.9 months ▪ Combination well tolerated and capable of inducing deep and durable remission

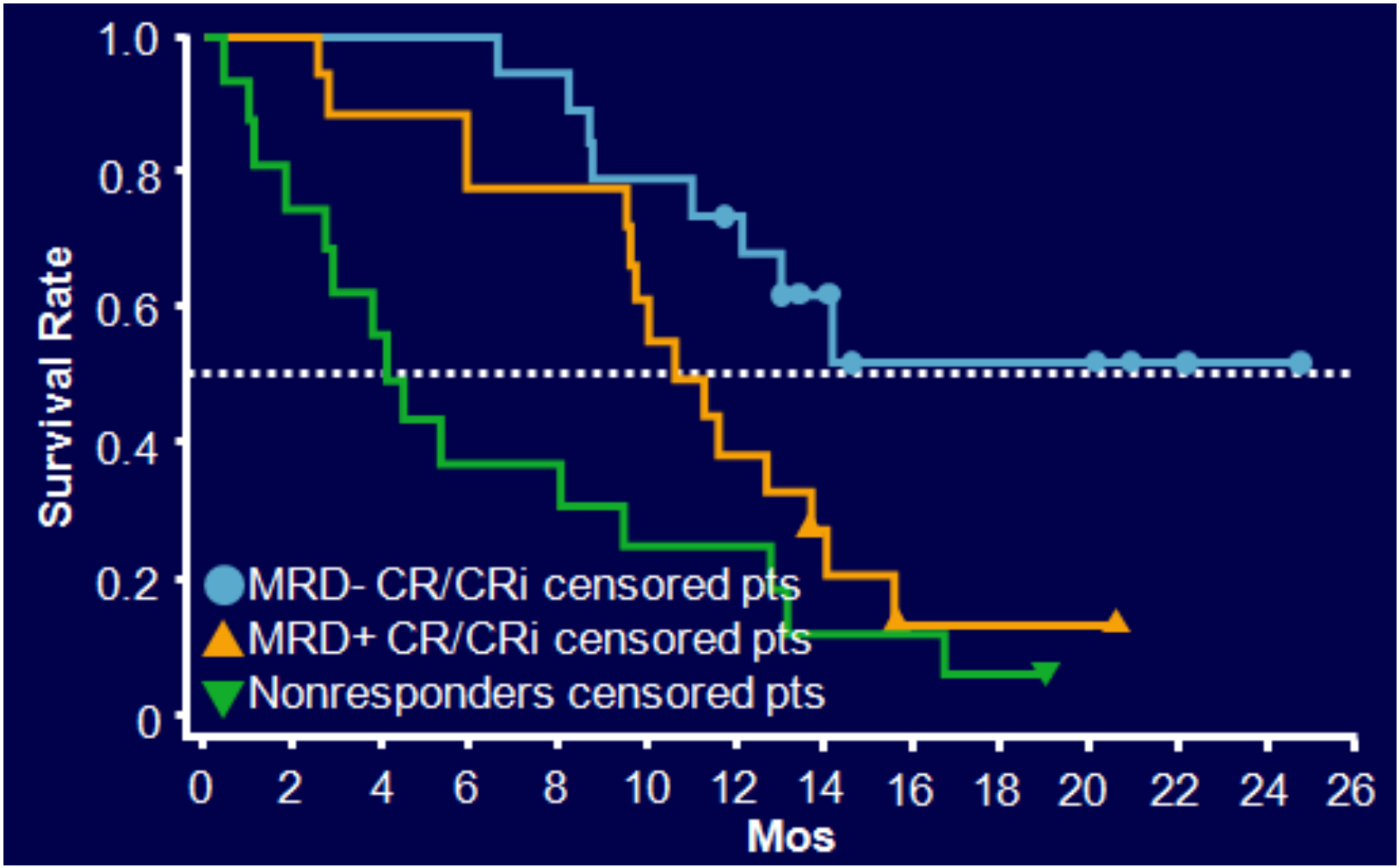
Fathi et al. EHA 2016. Abstract S503.

SGN-CD33A + HMA: OS by age



Fathi et al. EHA 2016. Abstract S503.
Fathi et al. ASH 2016. Abstract 591.

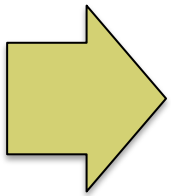
SGN-CD33A + HMA: OS by MRD status



Fathi et al. EHA 2016. Abstract S503.
Fathi et al. ASH 2016. Abstract 591.

Anti-CD33 mAb

Phase 3 enrolling



CD33A + HMA
vs
HMA alone

NOTE: Some Phase 1 studies of SGN-CD33A have been put on hold after 6 patients were identified with hepatotoxicity, including several cases of veno-occlusive disease, with 4 fatal events

Venetoclax + low-dose cytarabine in treatment-naïve AML patients aged ≥ 65 years

- Venetoclax 600 mg orally once daily on days 2–28 of Cycle 1 and days 1–28 of subsequent cycles
- A 5-day dose ramp-up schedule was followed to reach the 600 mg dose
- LDAC 20 mg/m^2 was administered s.c. daily on days 1–10 in 28-day cycles
- 20 patients enrolled
  - n=8 in an escalation phase
  - n=12 in an expansion phase
- Median age: 74 years (range 66–87)
- 8/20 patients (40%) had an antecedent hematologic disorder

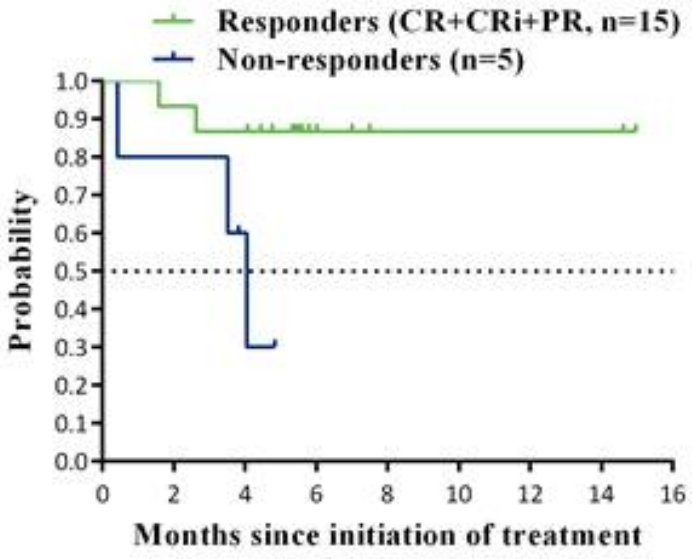
Wei et al. ASH 2016. Abstract 102.

Venetoclax + low-dose cytarabine in treatment-naïve AML patients aged ≥ 65 years

ORR and 12-month OS estimates

	All patients n=20	Prior HMA n=2	No prior HMA n=18	Prior MPN n=2	No prior MPN n=18
ORR (CR + CRi + PR), n (%)	**15 (75%)**	2 (100%)	13 (72%)	0	15 (83%)
12-month OS estimate (95% CI)	**74.7% (49.4–88.6)**	NA	71.8% (44.9–87.2)	NA	83.3% (56.8–94.3)

OS in responders vs non-responders



Wei et al. ASH 2016. Abstract 102.

New Drugs in AML – Conclusions

- 1998–2017, 4 drugs registered for AML therapy
  - GO (withdrawn, re-filed)
  - AZA
  - DAC
  - Midostaurin (approved by FDA pending with EMEA)
- Enroll into clinical trials
- Pivotal role of cooperative groups
  - Scientific questions
- Post-marketing studies
  - Long-term efficacy / toxicity of registered drugs