FLT3 inhibitors in AML

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Disclosures- Richard M. Stone, MD

- **Consulting relationships:**
  - **AbbVie; Agios; Amgen; Arog; Celator; Celgene (includes DSMB and steering committee); Janssen, Juno, Karyopharm, Merck, Novartis, Pfizer, Roche; Seattle Genetics; Sunesis (DSMB); Xenetic**
- **Securities, employment, promotional activities, intellectual property, gifts, grants**
  - **None**

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Brigham and Women's Hospital

Yawkey Center (Clinic)

FLT3 inhibitors in AML: Outline

- FLT3 inhibitors: background
- FLT3 inhibitors- single agent
- FLT3 inhibitors + chemo
- The Future

Key Points from de novo AML genome atlas

- **AML genomes have fewer mutations than most other adult cancers (n=13, 5 of which are aomg the 23 recurrently mutated genes)**
- **9 Key categories:**
  - **transcription-factor fusions (18%)**
  - **nucleophosmin (*NPM1*) (27%)**
  - **tumor-suppressor genes (16%)**
  - **DNA-methylation–related genes (44%)**
  - **signaling genes (59%)**
  - **chromatin-modifying genes (30%)**
  - **myeloid transcription-factor genes (22%)**
  - **cohesin-complex genes (13%)**
  - **spliceosome-complex genes (14%).**

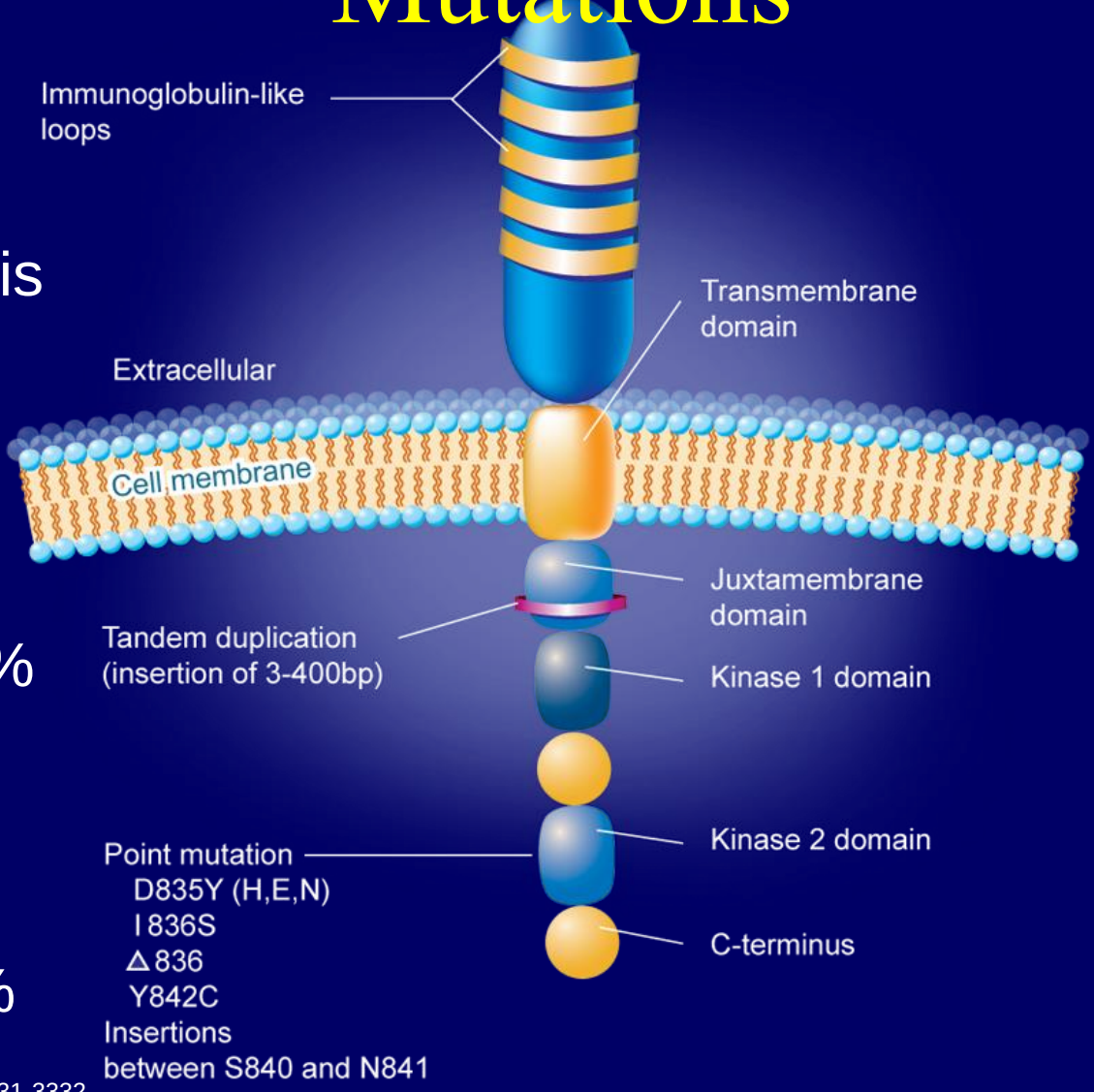
The Cancer Genome Atlas Research Network
N Engl J Med 2013; 368:2059-2074.

Reasons why single agent targeted tx in AML may not be ideal

- Clonal Heterogeneity
  - Need to use chemo to simplify clonal architecture
- Must hit a founder mutation to have a chance
  - We don't have good drugs yet for founder mutations such as DNMT3, TP53, TET2, ASXL1, EZH2
    - IDH inhibitors a possible emerging exception
- Resistance mechanisms (secondary mutations in target, off target effects, up regulation of ligand- with chemo)

FLT3 Structure and Activating Mutations

Over-expression is common



25-30%

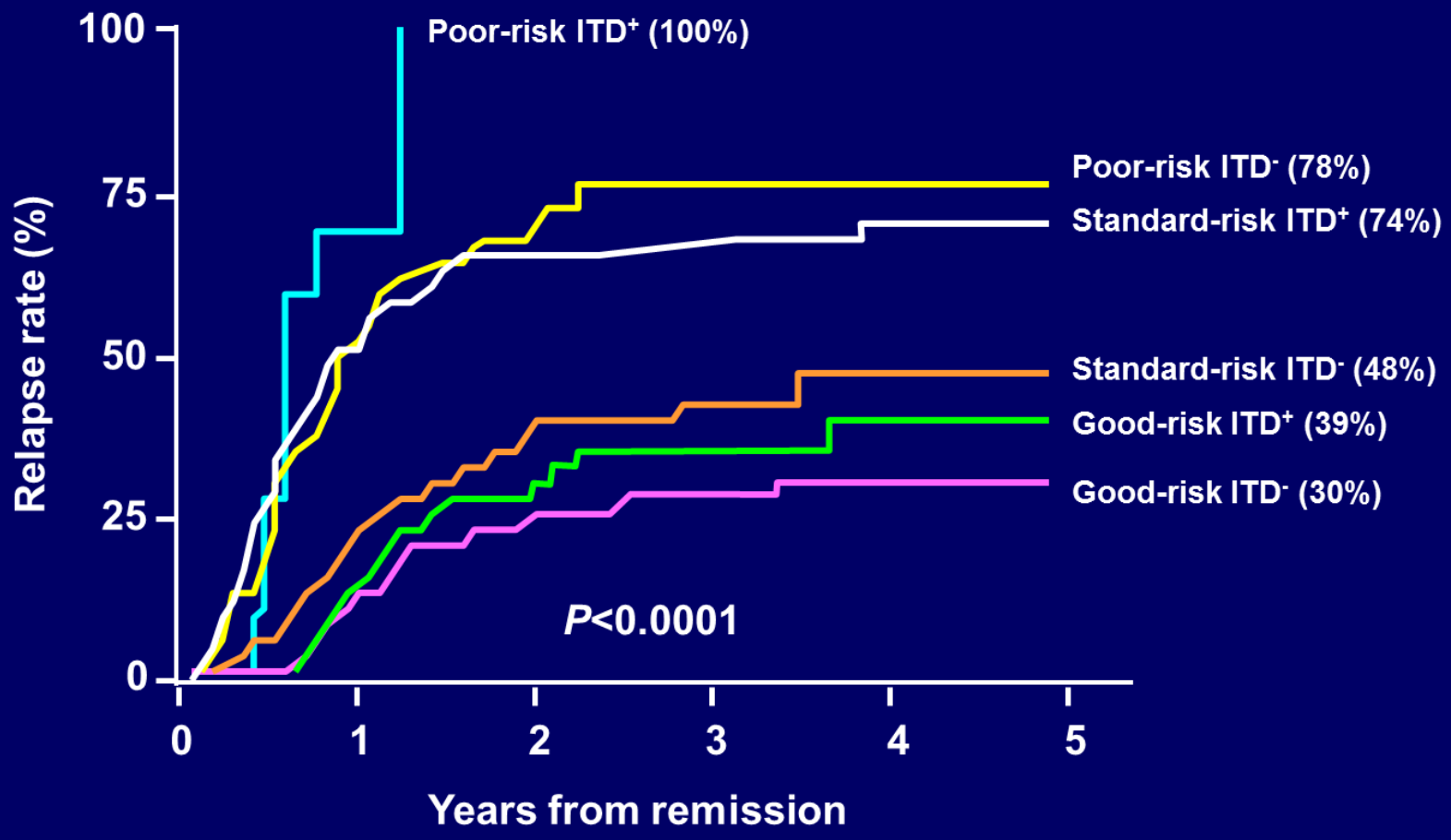
5-10%

Both mutations cause spont dimerization,

ligand independent growth, and MPD in murine model

Litzow MR. *Blood*. 2005;106:3331-3332.

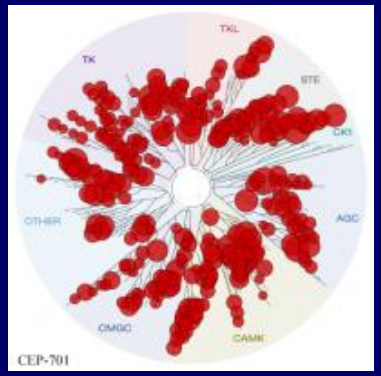
Flt3 ITD and relapse



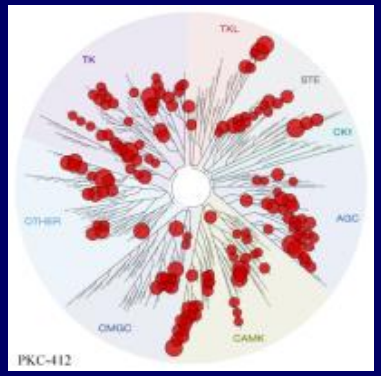
Kotarridis PD, et al. Blood. 2001;98:1752-1759.

FLT 3 inhibitors in prior studies

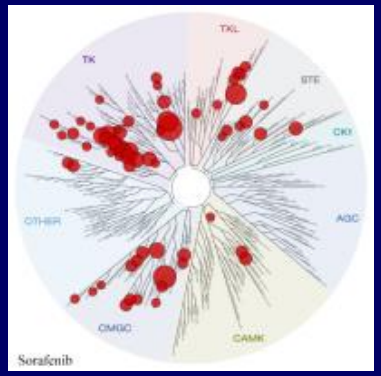
	IC_{50} (medium)[a]	IC_{50} (plasma)[b]
Lestaurtinib	2 nM	700 nM
Midostaurin	6 nM	~1000 nM
Sorafenib	3 nM	~265 nM
Quizartinib	1 nM	18 nM



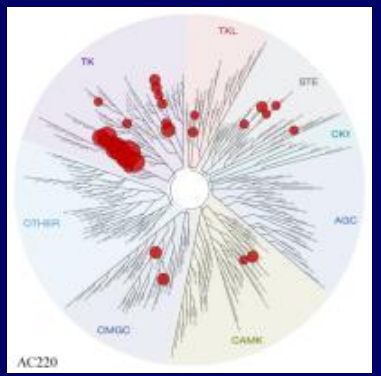
Lestaurtinib
(CEP-701)



Midostaurin
(PKC-412)



Sorafenib



Quizartinib
(AC220)

a – Molm-14 cells incubated in RPMI/10% FBS *b - Molm-14 cells incubated in plasma*

Pratz et al. Blood 2010;115(7):1425-32

Human kinome image generated using TREEspot™ software tool and reprinted with permission from KINOMEscan™, a division of DiscoveRx Co.

Background

- Midostaurin (PKC412; N-benzoylstaurosporine) is a potent FLT3 (both ITD and TKD) inhibitor (IC_{50} <10 nM) (also inhibits VEGFR, PKC, KIT, and PDGFR)[1, 2]

- Midostaurin specifically inhibits growth of leukemic cell lines made factor independent by transfection of activating *FLT3* mutation (ITD or D835Y)[2]

- Midostaurin increased survival in a murine BMT model of *FLT3* ITD myeloproliferative disorder [3]

1. Propper DJ et al. *J Clin Oncol*. 2001; 19:1485-1492.
2. Weisberg E, et al. *Cancer Cell*. 2002;1:433-443.
3. Kelly LM, et al. *Blood*. 2002;99:310-318

Phase II Trial of PKC412: Clinical Activity (75 mg po TID)

- >50% reduction in BM blasts: 5/20 (25%)
  - 2 patients with <5% blasts; 1 on D 28, 1 on D 60*
- >50% reduction in PB blasts: 14/20 (70%)
- 7 (35%) with clinical benefit:

Baseline PB blasts	110K	65K	21K	5K	16K	71K	46K
Best response	0, D 29	.06K, D 42	0, D 50	0.1K, D 22	0, D 15	0, D 57	0, D 51

- Comparable results with imatinib with CML-blast crisis
  - 31% HEME RESPONSE (8% CR, 18% RTC, 4% NEL

Stone et al, Blood, 2005

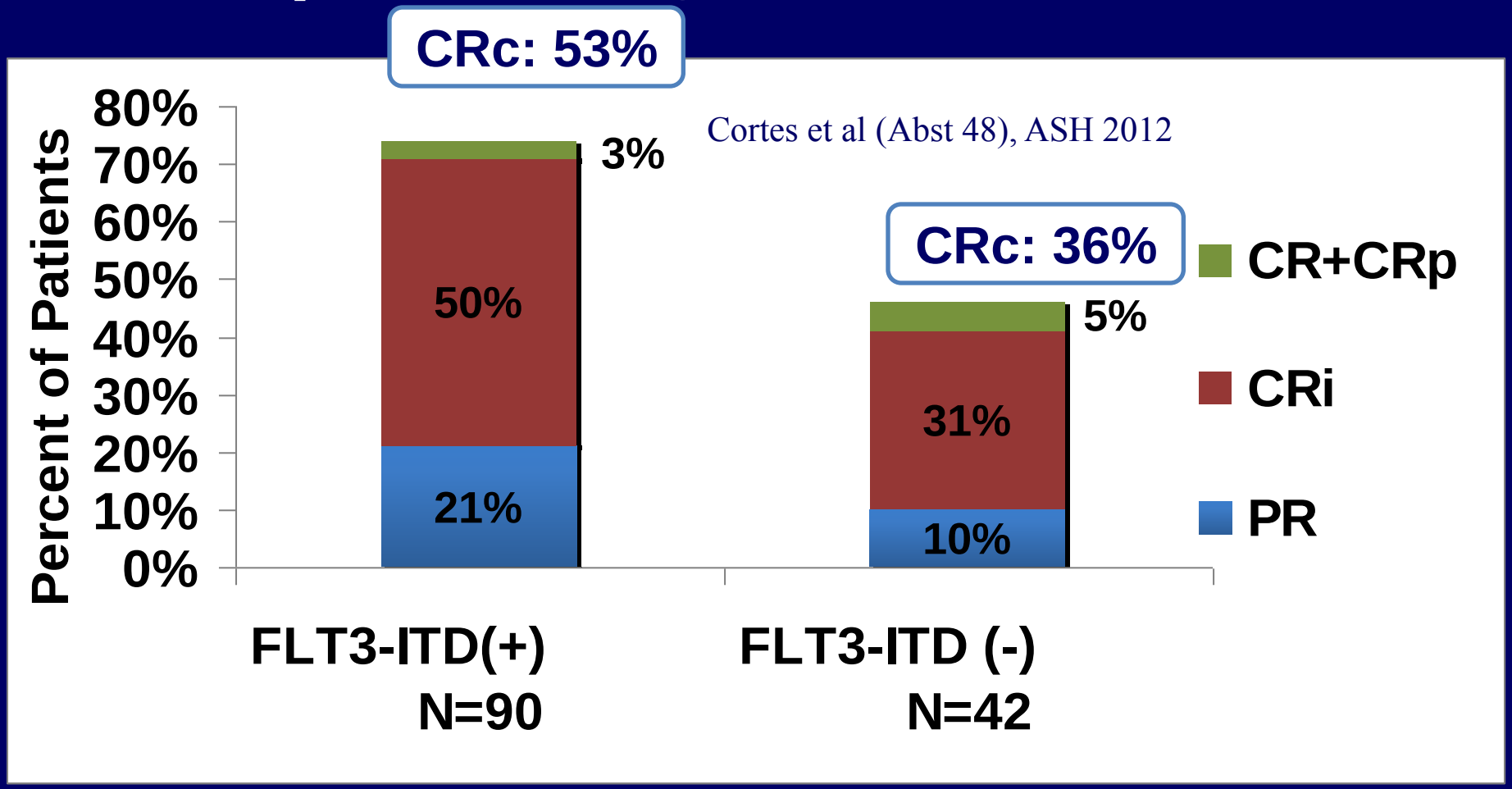
Study 2104: Single Agent Midostaurin Induces Blast Reduction But Not CR

Response	75 mg TID FLT3mut n=20	50 or 100 mg BID FLT3mut n=35	50 or 100 mg BID FLT3wt n=57
Complete response	0/20	0/35	0/57
Partial response	1/20	1/35 [in 100 mg BID cohort]	0/57
50% PB blast or BM reduction	14/20 (70%)	25/35 (71%) [67% for 50 mg BID & 76% for 100 mg BID]	24/57 (42%) [50% for 50 mg BID & 33% for 100 mg BID]

Generally well tolerated

- Nausea/vomiting, diarrhea, and fatigue
- < 10% of patients experienced grade 2 or grade 3 events at doses ≤ 100 mg/day
- Hematologic toxicity was uncommon
- Fischer et al, JCO, 2010

Phase 2 of Quizartinib in AML: Response to Quizartinib; Cohort 1



- 70% of FLT3-ITD(+) and 55% of FLT3-ITD(-) patients refractory to last prior therapy achieved at least a PR
- Median CRc duration: 10.4 wks for FLT3-ITD(+), 9.3 wks for FLT3-ITD(-)

Clinical Response to Gilteritinib Treatment by *FLT3* Mutation or TKI Status

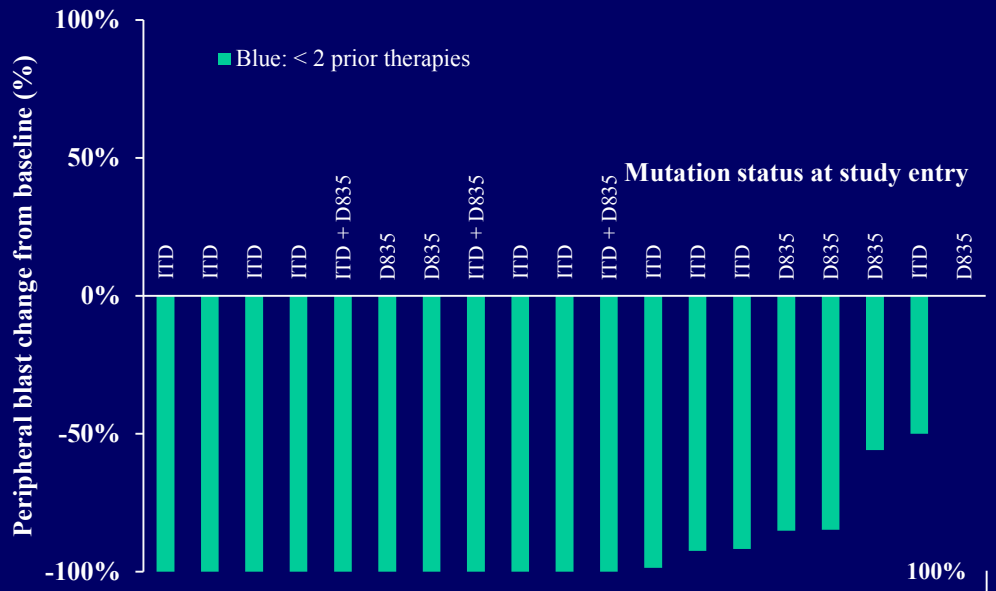
Clinical Response	≥80 mg Gilteritinib				
	Mutation Type			TKI Status	
	FLT3-ITD only	*FLT3*-D835 only	ITD and D835	Prior TKI	TKI Naïve
	N = 142	N = 11	N = 9	N = 40	N = 127
CR	16 (11)	0	0	2 (5)	14 (11)
CRp	11 (8)	0	0	3 (8)	8 (7)
CRi	38 (27)	1 (9)	4 (44)	9 (23)	35 (28)
PR	15 (11)	2 (18)	0	5 (13)	13 (10)
CRc (CR+CRp+CRi)	**65 (46)**	**1 (9)**	**4 (44)**	**14 (35)**	**57 (45)**
ORR (CRc+PR)	**80 (56)**	**3 (27)**	**4 (44)**	**19 (48)**	**70 (55)**

Data presented as n (%).
CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; ITD, internal tandem duplication; ORR, overall response rate; PR, partial response.

midostaurin, crenolanib also 'hit' ITD and tyrosine kinase domain (TKD); quizartinib potent ITD inhibitor

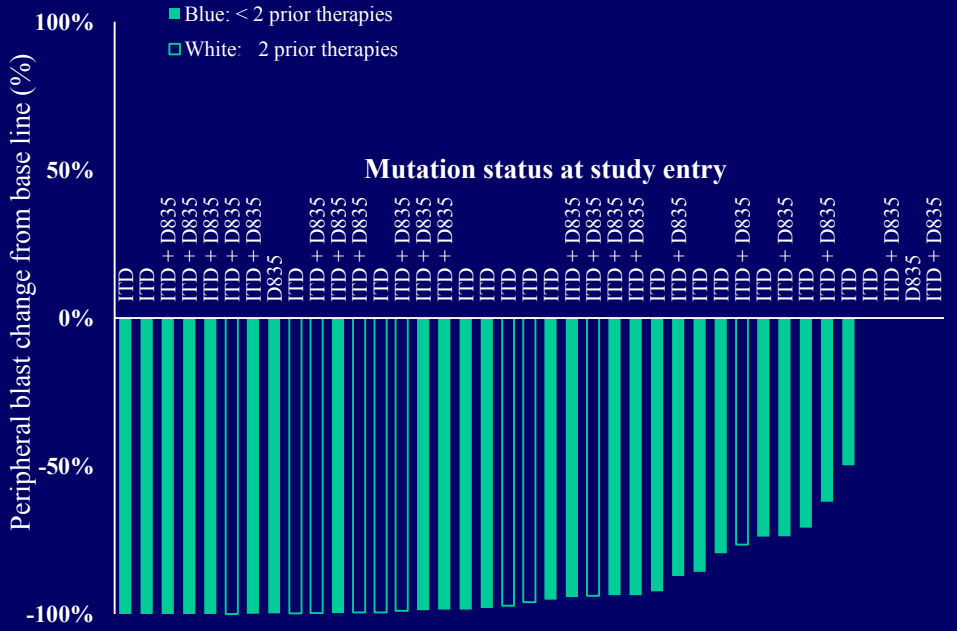
Altman J, et al. *Blood.* 2015;126: Abstract 321.

Crenolanib: Peripheral Leukemic Blasts in FLT3/ITD, FLT3/D835 and FLT3/ITD+FLT3/D835



TKI Naïve - No MDS		
Total evaluable patients	18	
CR/CRi	7	39%
PR	2	11%
ORR (CR+PR)	9	50%
Blast Response	7	39%
Clinical Benefit (CR +PR+HI)	16	89%
RD	2	11%

TKI Treated - No MDS		
Total evaluable patients	36	
CRi	6	17%
PR	5	14%
ORR (CR+PR)	11	31%
Blast Response	14	39%
Clinical Benefit (CR +PR+HI)	25	69%
RD	11	31%



Ongoing single agent phase III trials

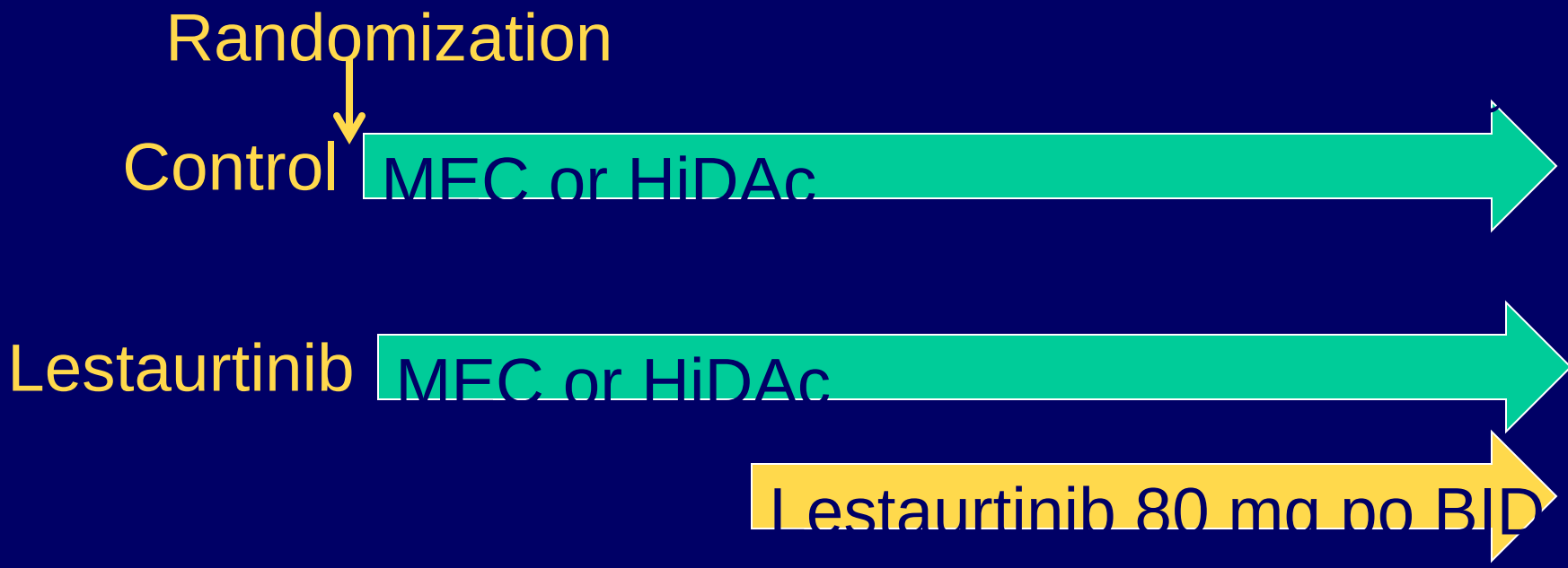
- Quizartinib v dealer's choice chemo (including 'low' and high dose) in FLT3ITD relapsed AML, less than 6 month disease-free interval
- Gilteritinib v dealer's choice chemo (including 'low' and high dose) in FLT3ITD and or TKD relapsed AML

A Cautionary Tale – CEP701 (Lestaurtinib)

- Originally developed as inhibitor of neurotrophic tyrosine kinase receptor 1
- Potent Flt3 ITD autophopshorylation inhibitor – IC50 (nM) 1.5
- Well-tolerated with modest responses as single agent in phase II trials (Smith, Blood 2004)
- Phase III trial with 224 Flt3 mutant AML patients in first relapse randomized to chemo alone or chemo + lestaurtinib, primary endpoint → CR

Cephalon 204: Trial Design

- AML in first relapse with FLT3 mutation



Primary Outcome: CR
Secondary outcome: Survival

Control patients eligible for crossover

Levis et al Blood 2012

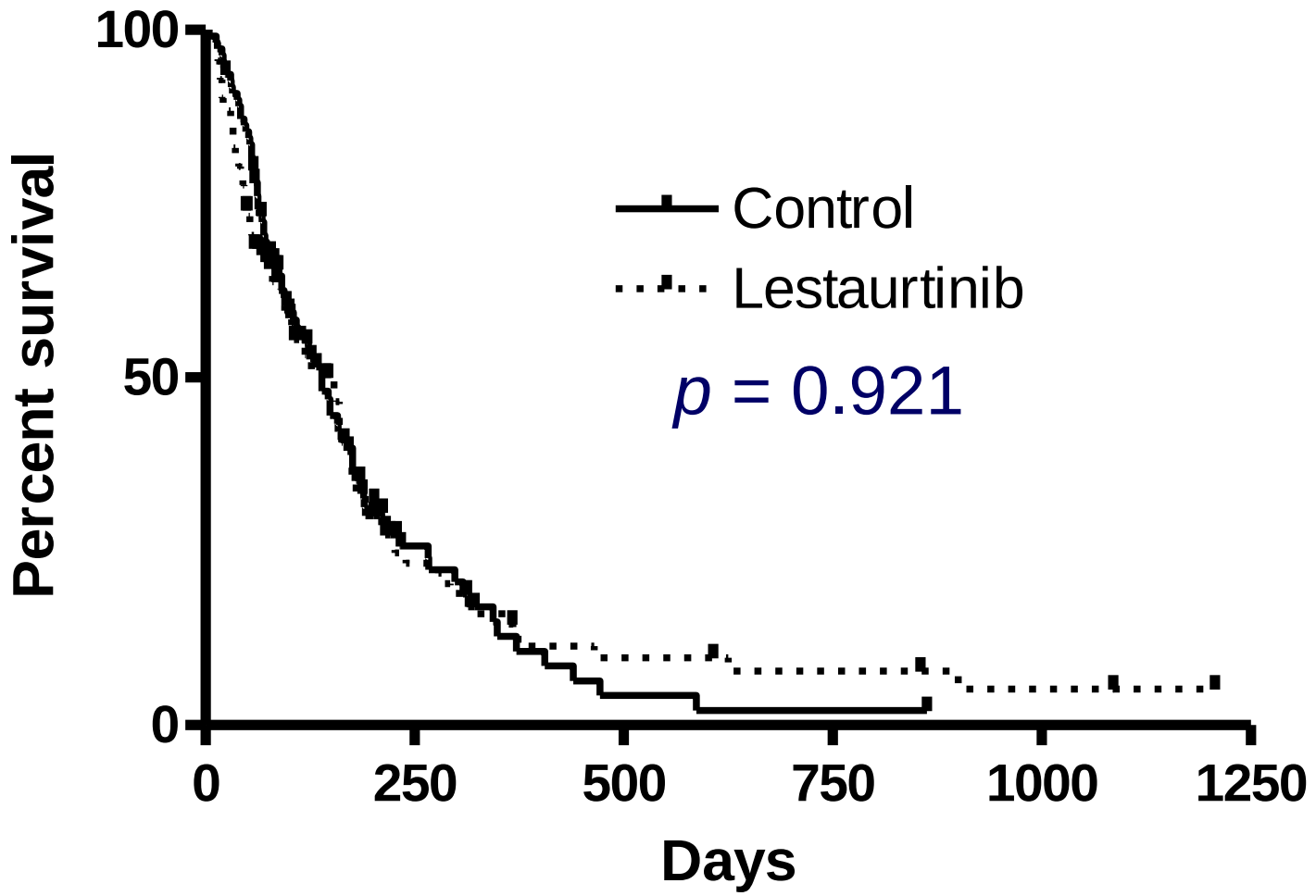
CEP 204: Results

Parameter	Chemotherapy only	Chemotherapy + Lestaurtinib	*p* value
Number of total patients	112	112	1.00
CR (%)	13 (12%)	19 (17%)	0.25
CRp (%)	10 (9%)	10 (9%)	1.00
Total CR/CRp (%)	23 (21%)	29 (26%)	0.35
1st remission 1-6 months, CR/CRp (%)	6 (11%)	10 (19%)	0.42
1st remission ≥ 6 months, CR/CRp (%)	17 (29%)	19 (32%)	0.84
< 50 years of age, CR/CRp (%)	4 (12%)	9 (27%)	0.21
≥ 50 years of age, CR/CRp (%)	19 (24%)	20 (25%)	1.00

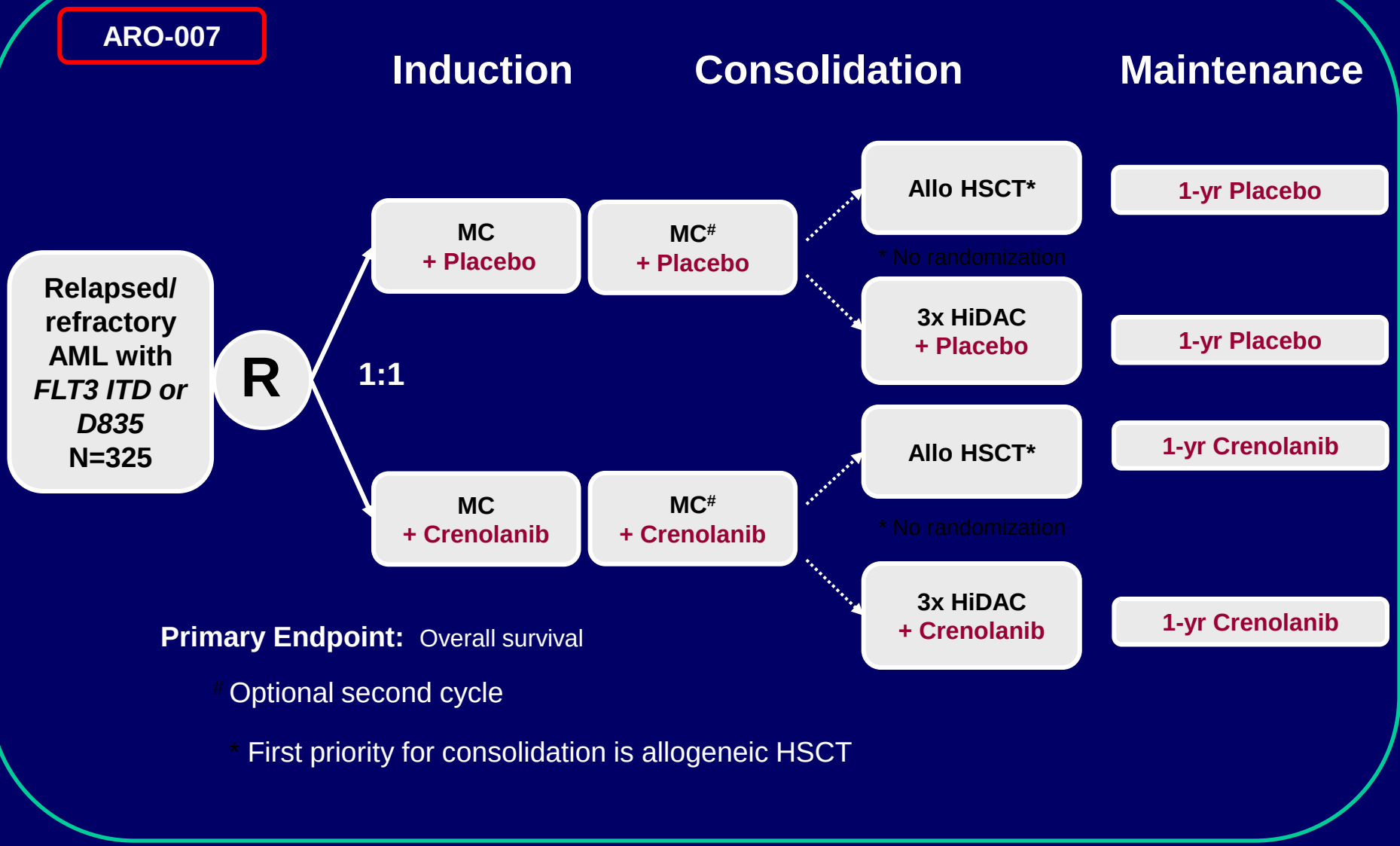
Safety Parameter	Chemotherapy only	Chemotherapy + Lestaurtinib	*p* value
Death Within 30 Days of Start of Treatment	7/109 (6%)	13/111 (12%)	0.24
Grade 3 or 4 AE	101/109 (93%)	104/111 (94%)	0.8
Serious AE	49/109 (45%)	61/111 (55%)	0.18

But plasma levels of drug too low in most pts

Cephalon 204 trial: Overall Survival



Double-blind, placebo controlled, randomized Study of Chemotherapy + Crenolanib in Relapsed or Refractory FLT3 mutant AML

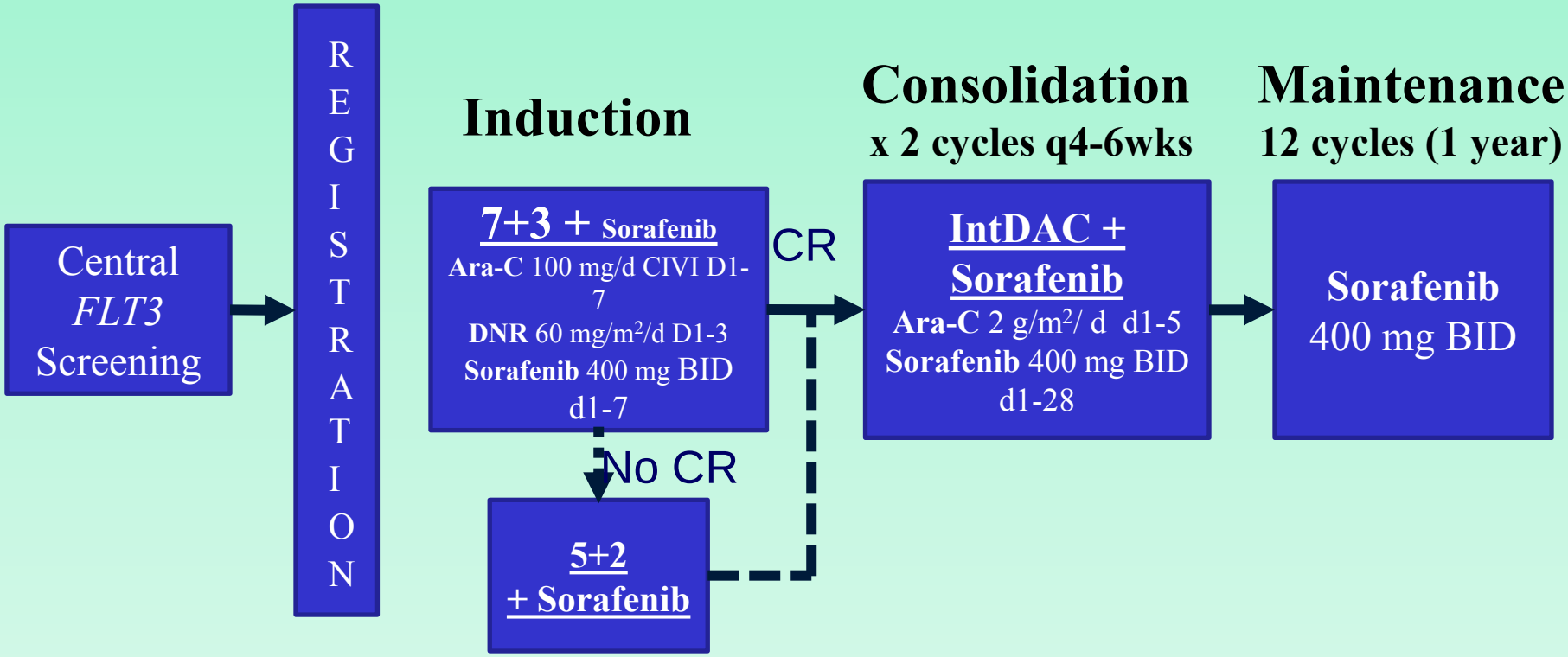


Sorafenib in AML

- MD Anderson phase I/II sorafenib + IA (Ravandi)
  - 17/18 pts morph CR/CRp (94%, 95% CI 73-99)
- Compassionate use sorafenib, use post-alloSCT
- SAL trial >60 yrs (Serve)
  - Randomized phase II of 201 pts
  - No improvement in EFS or OS with early TRM for sorafenib
- SORAML trial <60 yrs (Röllig)
  - Randomized phase II of 276 pts
  - Median EFS of 21 mo (95% CI, 9-32) vs 9 months (4-15) for sorafenib without difference in OS
  - Trend for improved RFS and OS in *FLT3*-ITD

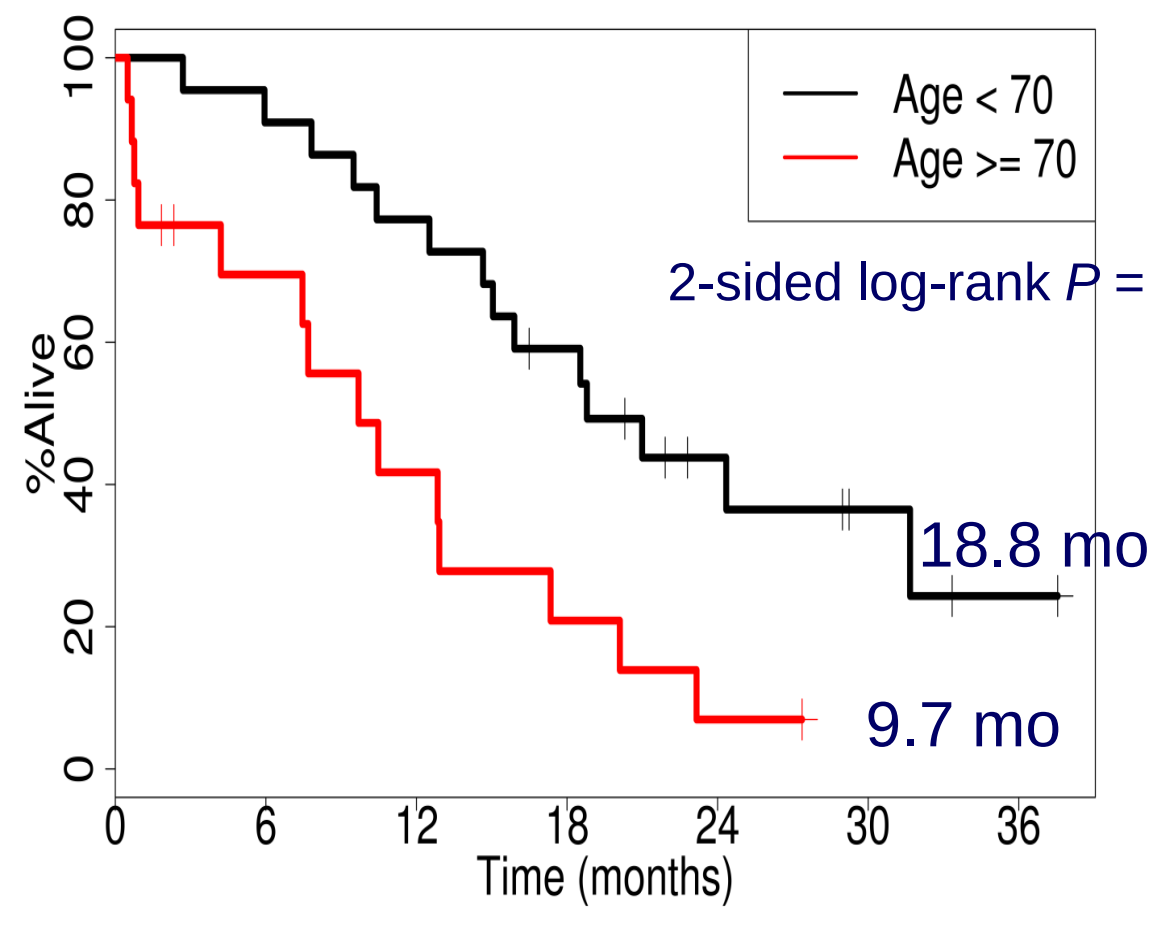
Clin Oncol. 2010;28(11):1856-1862. Metzelder S, et al. *Blood*. 2009;113(26):6567-6571. Serve H, et al. *J Clin Oncol.* 2013;31(25):3110-3118. Röllig C, et al. *Lancet Oncol.* 2015;16(16):1691-1699

Schema



Uy G, et al. *Blood.* 2015;126: Abstract 319.

Overall Survival by Age



Uy G, et al. *Blood.* 2015;126: Abstract 319

PKC412 plus chemo in newly diagnosed, previously untreated AML: Treatment Plan

- Induction Chemotherapy
  - DNR 60 mg/m^2 d1, 2, 3 plus ara-C 100 mg/m^2 IVCI d1-7
- Post-remisssion chemotherapy
  - ara-C 3 gm/m^2 over 3h q 12h d1, 3, and 5 x 3 cycles
- PKC412
  - 100 mg po bid begin d1 (simultaneous) OR d8 (sequential) of each cycle
  - give continuously during induction and post-CR

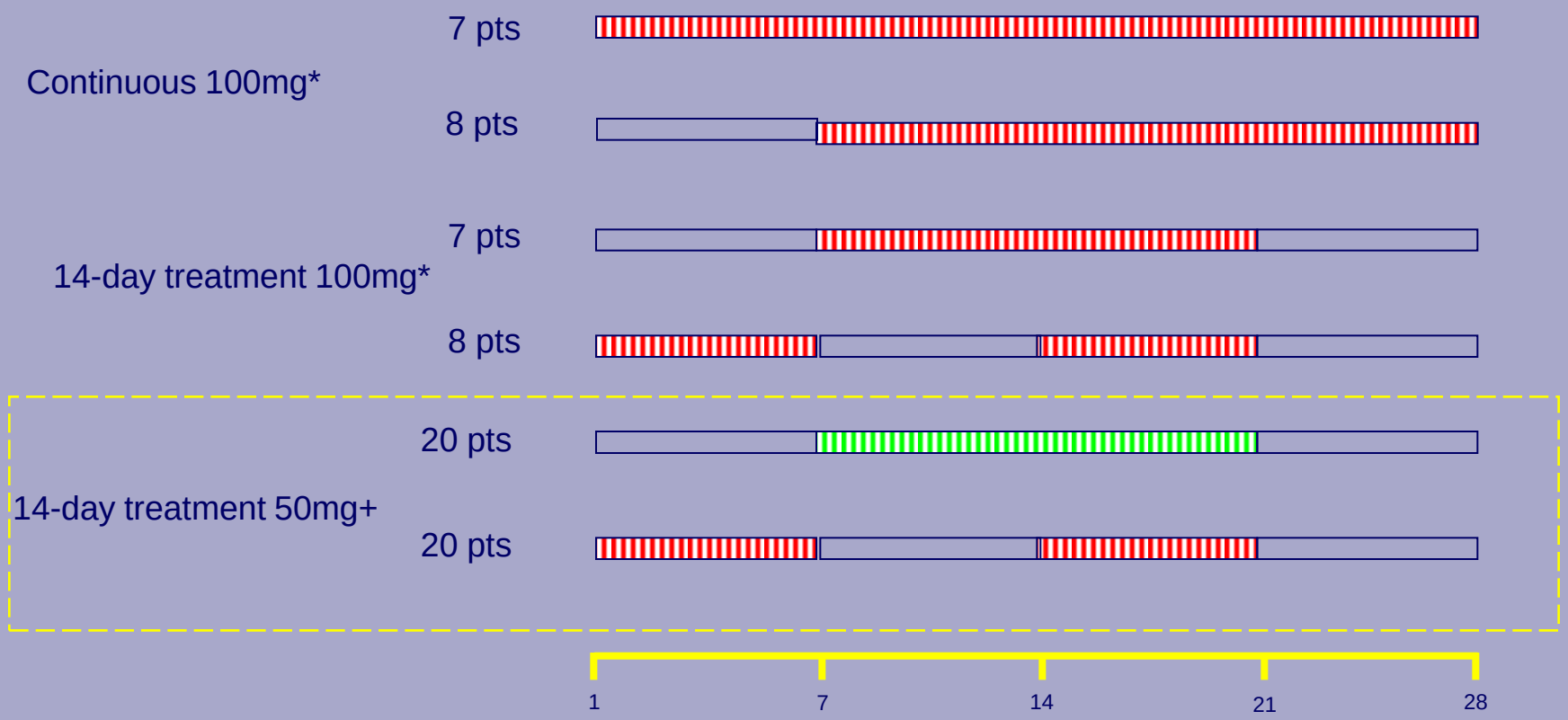
Study Induction Scheme by Cohort

PKC412 dosed bid

Dauno 60mg/sqm i.v.

DDD

ara-C 100mg/sqm c.i.v.

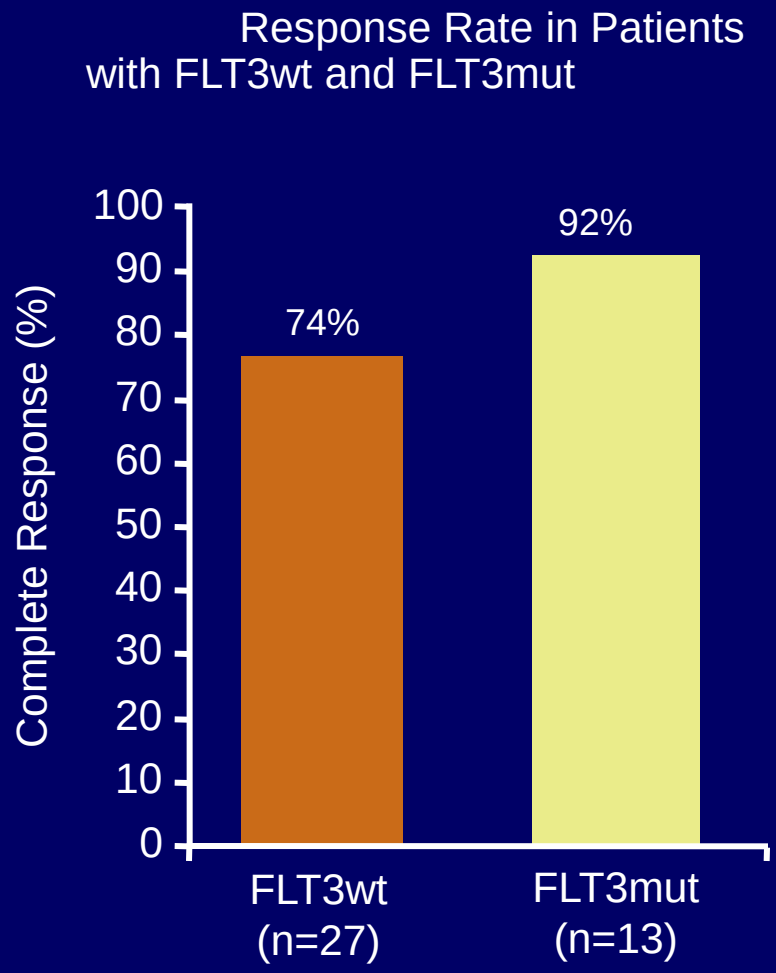


*AE rate, dt GI tox too high

Efficacy

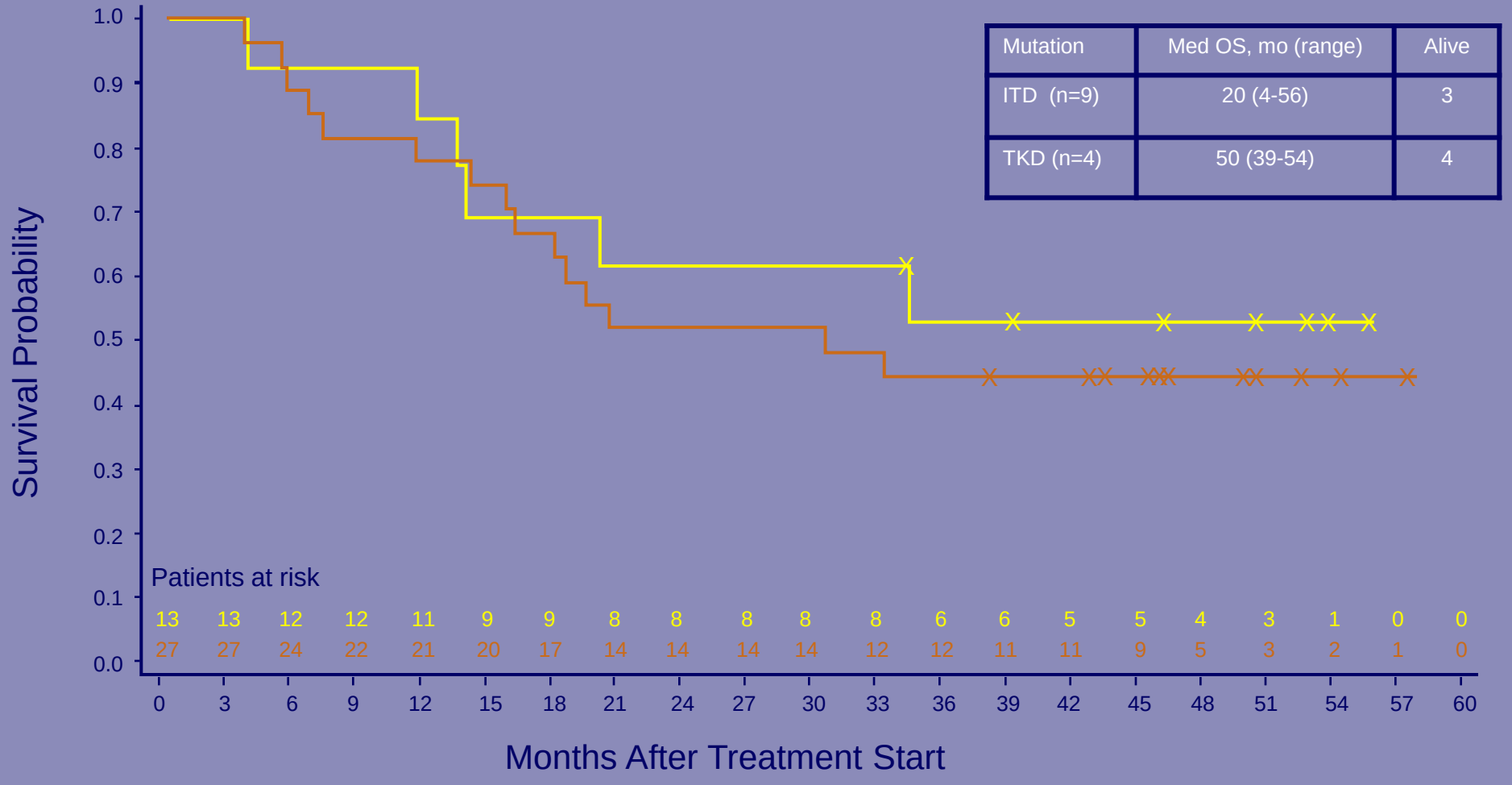
- 80% Complete Response (CR) rate (32/40)
- 92% of FLT3mut patients had a CR
- Trend toward higher CR in FLT3mut patients
- No significant difference in response rates or duration of remission between the sequential and concomitant schedules

90% CR rate also w soraf+IA; Ravandi et al JCO, 2010



Stone, Leukemia, 2012

Similar Survival Seen in Previously Untreated Patients With FLT3mut and FLT3wt Blasts



Mutation	Med OS, mo (range)	Alive
ITD (n=9)	20 (4-56)	3
TKD (n=4)	50 (39-54)	4

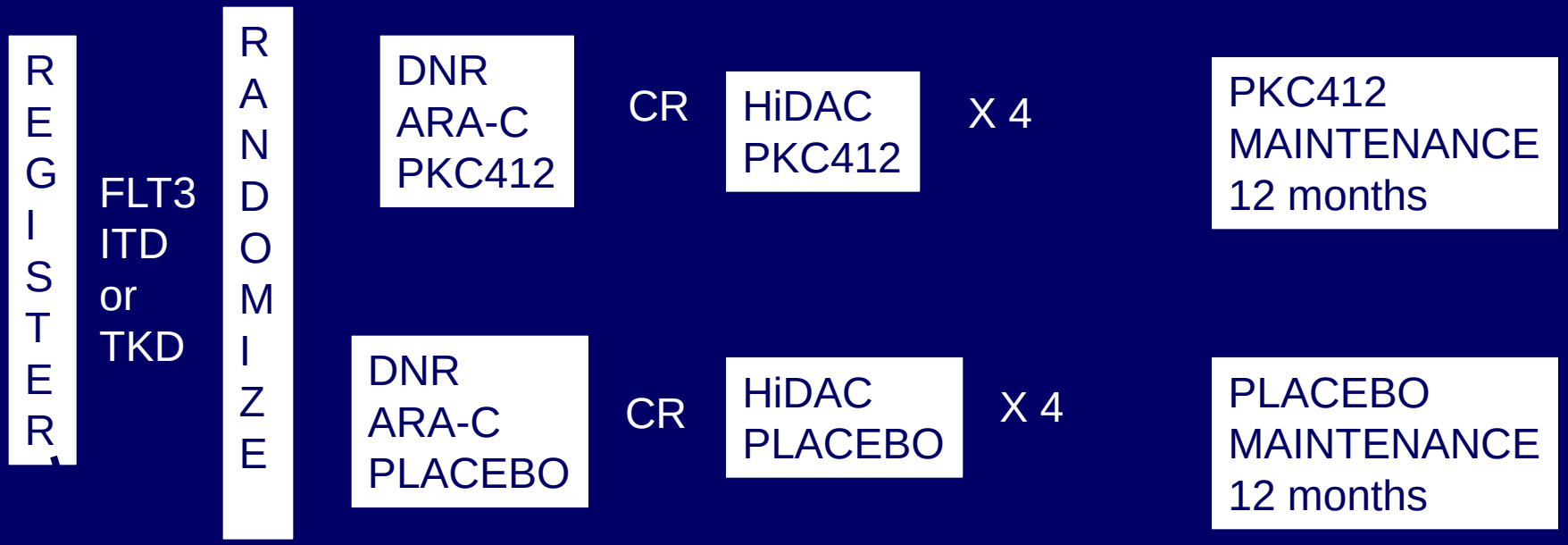
Stone, Leukemia, 2012

The Multi-Kinase Inhibitor Midostaurin (M) Prolongs Survival Compared with Placebo (P) in Combination with Daunorubicin (D)/Cytarabine (C) Induction (ind), High-Dose C Consolidation (consol), and As Maintenance (maint) Therapy in Newly Diagnosed Acute Myeloid Leukemia (AML) Patients (pts) Age 18-60 With *FLT3* Mutations (muts): An International Prospective Randomized (rand) P-Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance])

Abstract 6

Stone RM, Mandrekar S, Sanford BL, Geyer S, Bloomfield CD, Dohner K, Thiede C, Marcucci G, Lo-Coco F, Klisovic RB, Wei A, Sierra J, Sanz MA, Brandwein JM, de Witte T, Niederwieser D, Appelbaum FR, Medeiros BC, Tallman MS, Krauter J, Schlenk RF, Ganser A, Serve H, Ehninger G, Amadori S, Larson RA, Dohner H

CALGB 10603: Prospective Phase III, double-blinded randomized study of induction and consolidation +/- Midostaurin (PKC412) in newly diagnosed patients < 60 years old with FLT3 mutated AML



Not on STUDY:
FLT3 WILD TYPE

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

Key Eligibility Criteria

- Age 18-60, normal end-organ function
- Documented AML (non-APL)
- *FLT3* mutation centrally determined prior to enrollment
  - Assessed at one of 9 academic labs around the world
  - Results within 48h
- Up to 5 days of hydroxyurea allowed prior to start of treatment while awaiting results of mutation analysis

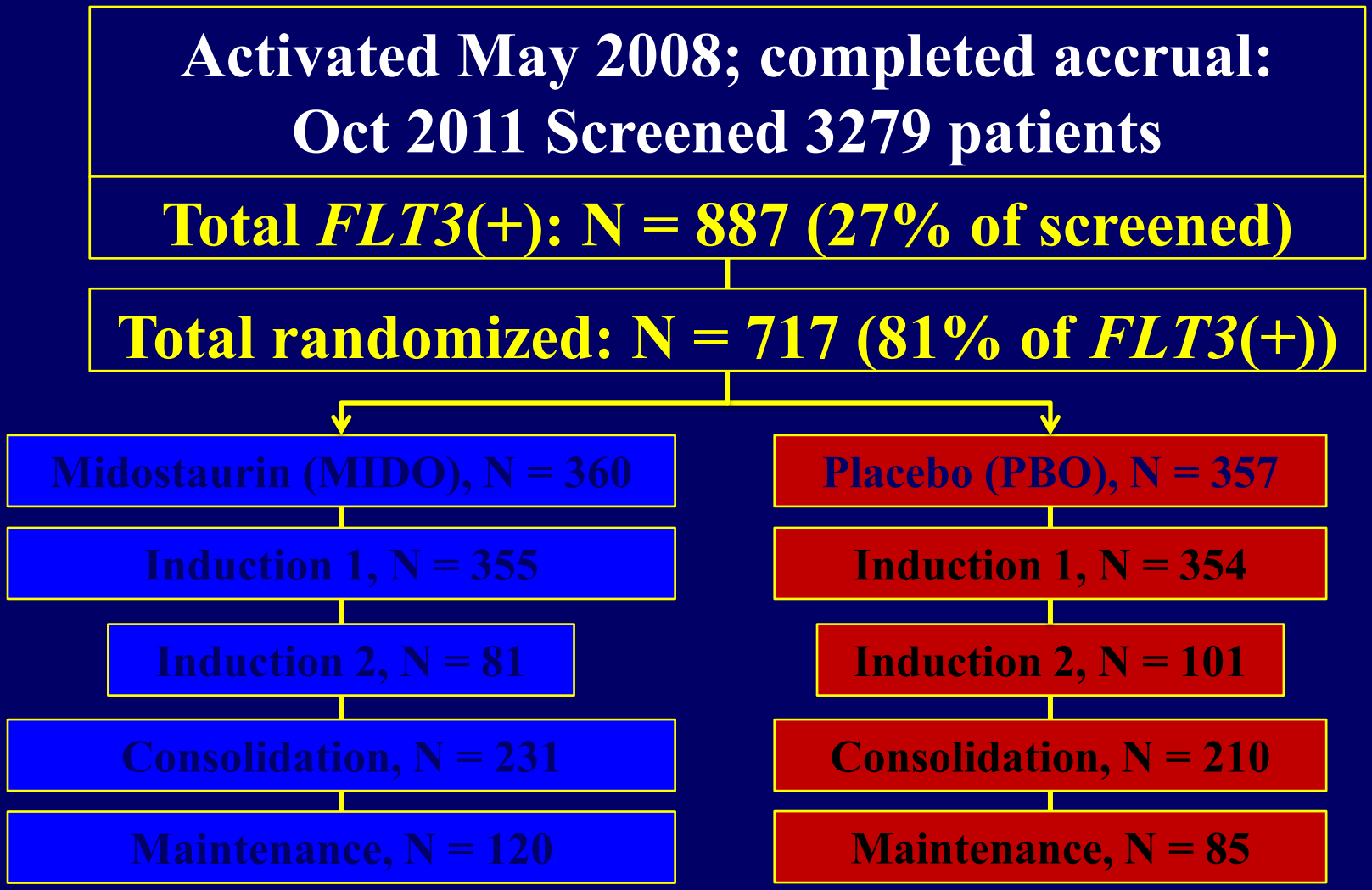
Protocol Therapy

Induction (2nd cycle given based on d21 marrow)	**daunorubicin**	60 mg/m^2 IVP days 1-3
	cytarabine	200 mg/m^2/d d 1-7 via IVCI
	midostaurin or placebo	50 mg po bid days 8-21
Consolidation (up to 4 cycles)	**cytarabine**	3 gm/m^2 over 3h q 12h days 1, 3, and 5
	midostaurin or placebo	50 mg po bid days 8-21
Maintenance	**midostaurin or placebo**	50 mg po bid days 1-28 x 12 cycles

- Transplant not specifically mandated

Stone R, et al. *Blood.* 2015;126: Abstract 6.

Consort Diagram



Stone RM, et al. *Blood.* 2015;126: Abstract 6.

Patient Characteristics

	MIDO (N = 360)	PBO (N = 357)	*P* value
Age (years), median (range)	47.1 (19.0-59.8)	48.6 (18.0-60.9)	.27
Gender			.045
Female	187 (51.9%)	212 (59.4%)	
Male	173 (48.1%)	145 (40.6%)	
FLT3 stratification Groups			.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%)	

MIDO, midostaurin

Complete Response Rates

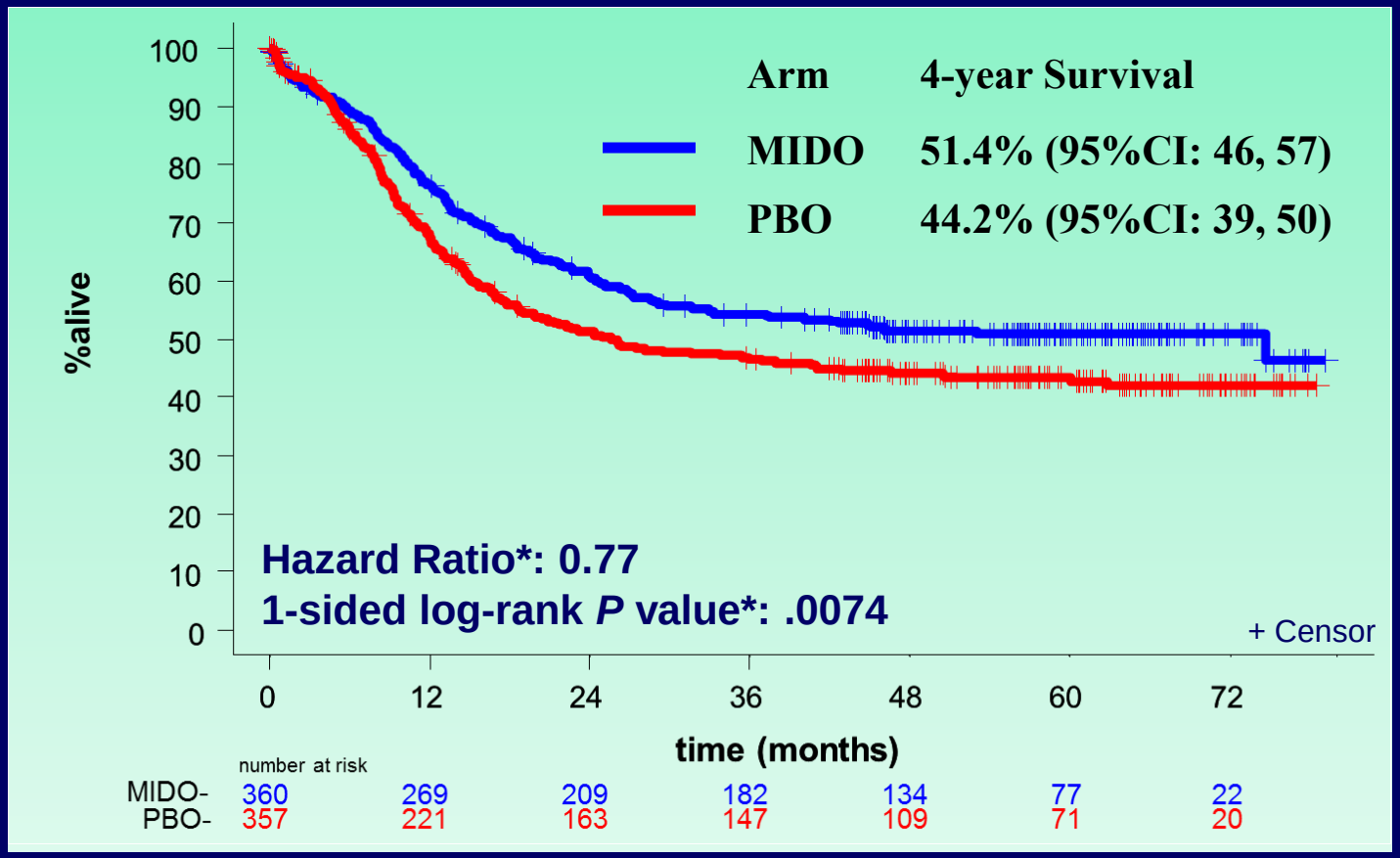
	MIDO (N = 360)	PBO (N = 357)	*P**
CR by day 60	212	191	
Rate	59%	53%	.15
Time to CR, median (range)	35 days (20-60)	35 days (20-60)	
CR in induction/consolidation**	239	211	
Rate	66%	59%	.045
Time to CR, median (range)	37 days (20-99)	36 days (20-112)	

**Includes all CRs reported within 30 days of ending protocol therapy

Stone RM, et al. *Blood.* 2015;126: Abstract 6.

Overall Survival (Primary Endpoint)

23% Reduced Risk of Death in the MIDO Arm



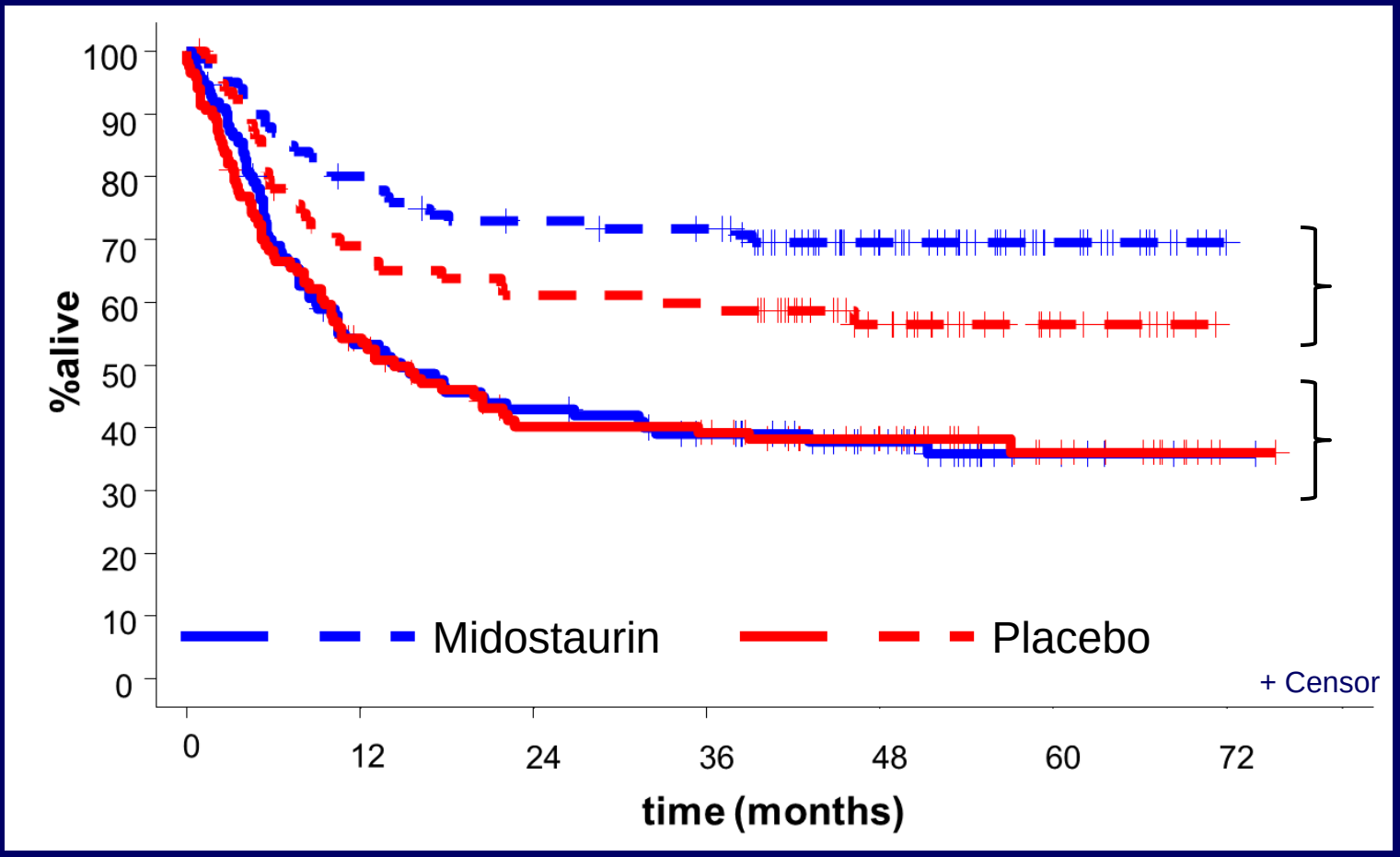
- **Median OS**: MIDO 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months

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

Stone RM, et al. *Blood.* 2015;126: Abstract 6.

Overall Survival: Post-Transplant

Treatment With MIDO Increases OS After SCT in CR1



SCT in CR1
HR 0.61

SCT outside CR1
HR 0.98

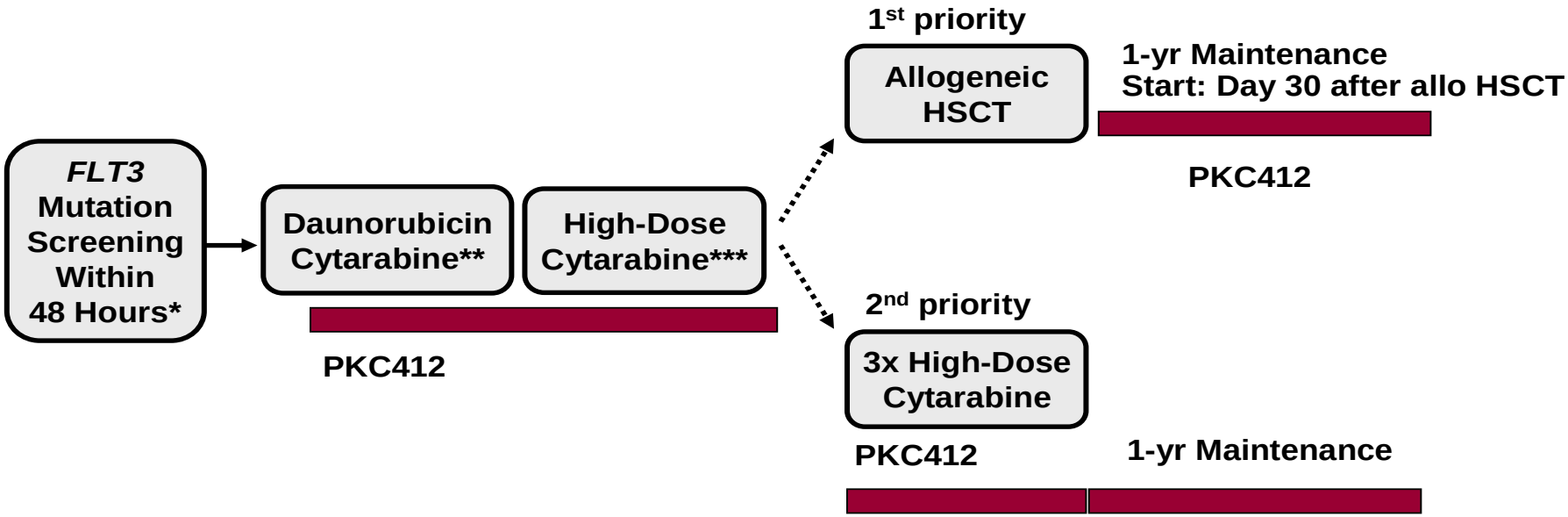
Conclusions

- **Midostaurin, a mult-itargeted kinase inhibitor, improves OS when added to standard chemo with one year maintenance in newly diagnosed pts aged 18-60 with ITD and TKD *FLT3* mutant AML, and represents a new standard of care**
- OS and EFS benefit was consistent in uncensored as well as censored analyses, despite high SCT rate
- Safety profile similar in each arm
- An international academic-industry collaborative AML study based on genotype at dx is feasible

Stone R, et al. *Blood.* 2015;126: Abstract 6.

Study Design

AMLSG 16-10 (Clinicaltrials.gov identifier, NCT01477606; EudraCT Number, 2011-003168-63)



* Patients may receive hydroxyurea during screening phase

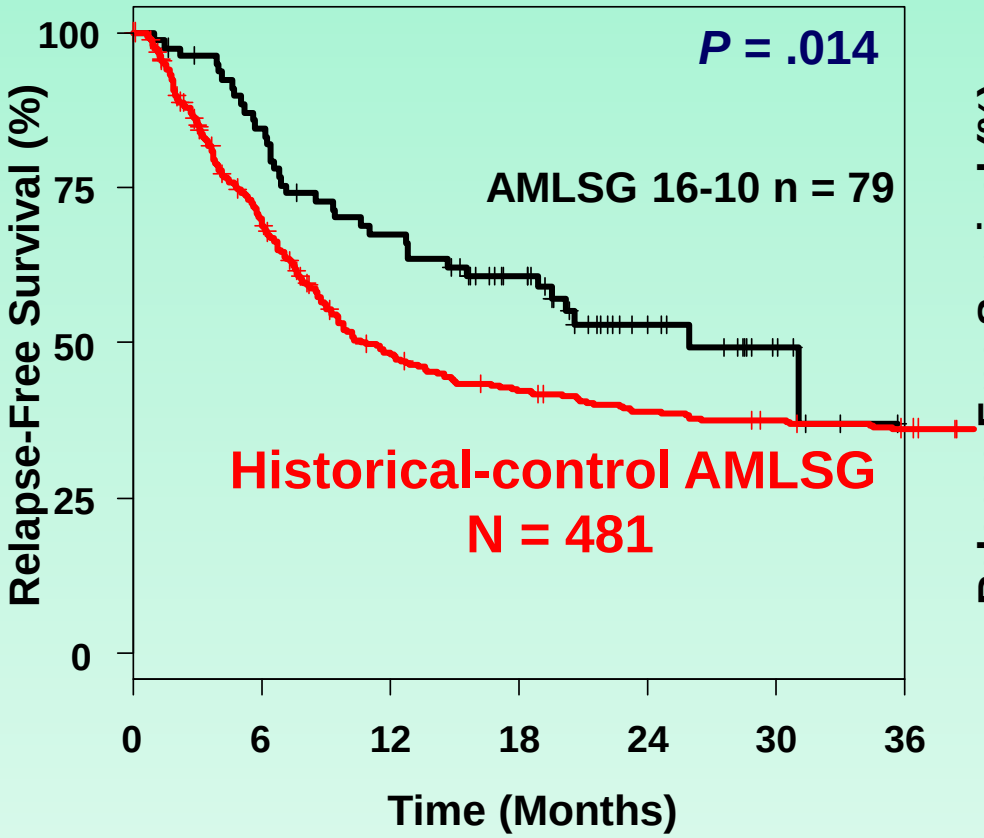
** Optional 2nd cycle in patients achieving PR after cycle I

*** 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

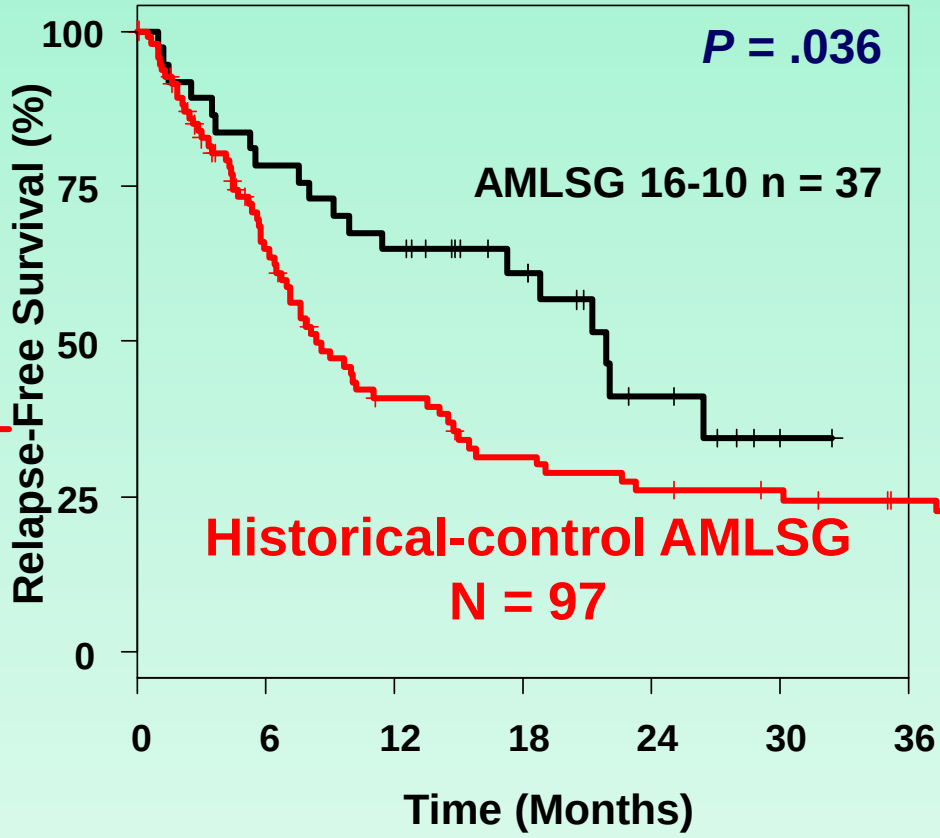
Schlenk RF, et al. *Blood.* 2015;126: Abstract 322.

AML With *FLT3*-ITD
AMLSG 16-10 Compared to Historical Controls

Age 18-<60 yrs



Age 60-70 yrs



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

FLT3 inhibitors in AML: conclusions

- Midostaurin plus chemo f/b alloSCT emerging as a new standard of care in ages 18-60
- Role of specific and nonspecific *FLT3* inhibitors being explored as single agents +/- chemo, in different settings (older [e.g with HMA], relapse, post-SCT, *FLT3* WT status)
- Is this really about FLT3 inhibtion (Would a potent FLT3 inhibitor v multi-targeted agent be better) ?
  - Off target primary resistance mechanisms described (CCND3, encodes cyclin 3) (Smith et al , ASH abst 677, 2015)

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