FLT-3 inhibitors in AML

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Disclosures

- Advisory board: Pfizer, Novartis, Jazz, Celgene, Seattle Genetics, Astellas
- Research grants: Celgene, Novartis, Amgen
- Speaker: Novartis, Celgene, Pfizer, Gilead

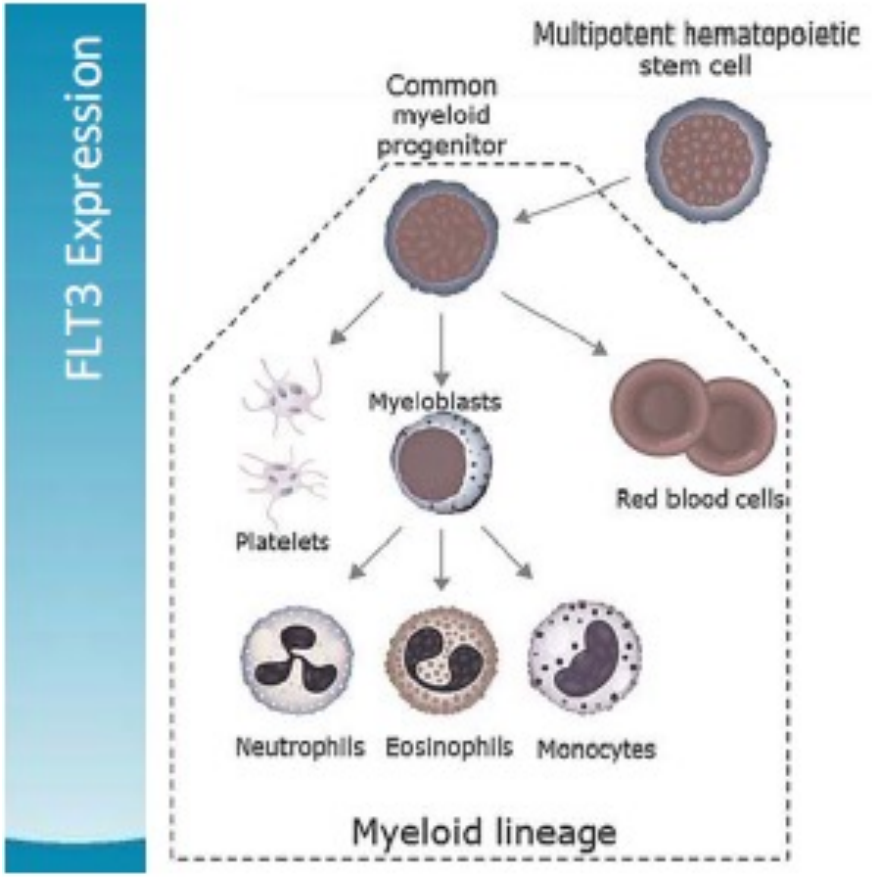
Index

- FLT3: The gene and the receptor
- The prognostic impact and the transplant indications
- FLT3 inhibitors

FLT3 in normal hematopoiesis

FLT3

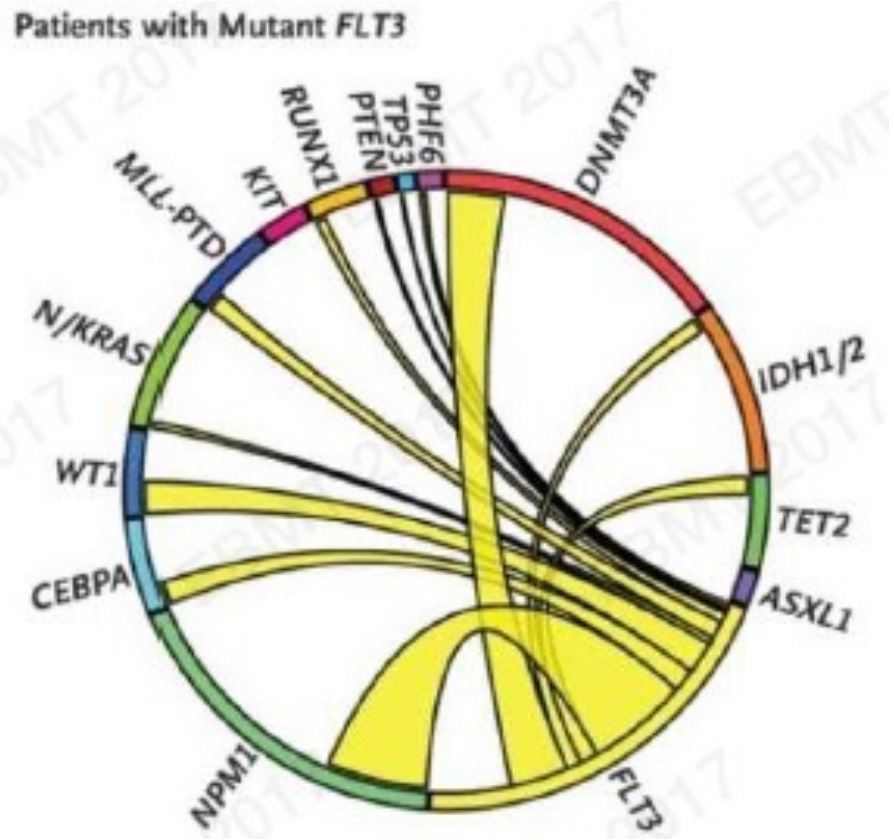
- Member of the type III receptor tyrosine kinase subfamily that includes c-KIT, c-FMS, and PDGFR-α/β
- Essential for proliferation and differentiation of myeloid progenitor cells
- Expression decreases as myeloid cells progress to their terminally differentiated states



FLT3, FMS-like tyrosine kinase 3; PDGFR, platelet-derived growth factor receptor.

Janeway CA, et al. Chapter 1: Basic Concepts in Immunology. In: *Immunobiology*. 6th edition. New York, NY: Garland Science. 2. Fey MF, et al. *Ann Oncol*. 2007;18:i9–i13.

Sequencing the entire coding regions of TET2, ASXL1, DNMT3A, CEBPA, PHF6, WT1, TP53,EZH2, RUNX1, PTEN FLT3, NPM1, HRAS, KRAS, NRAS, KIT, IDH1 and IDH2

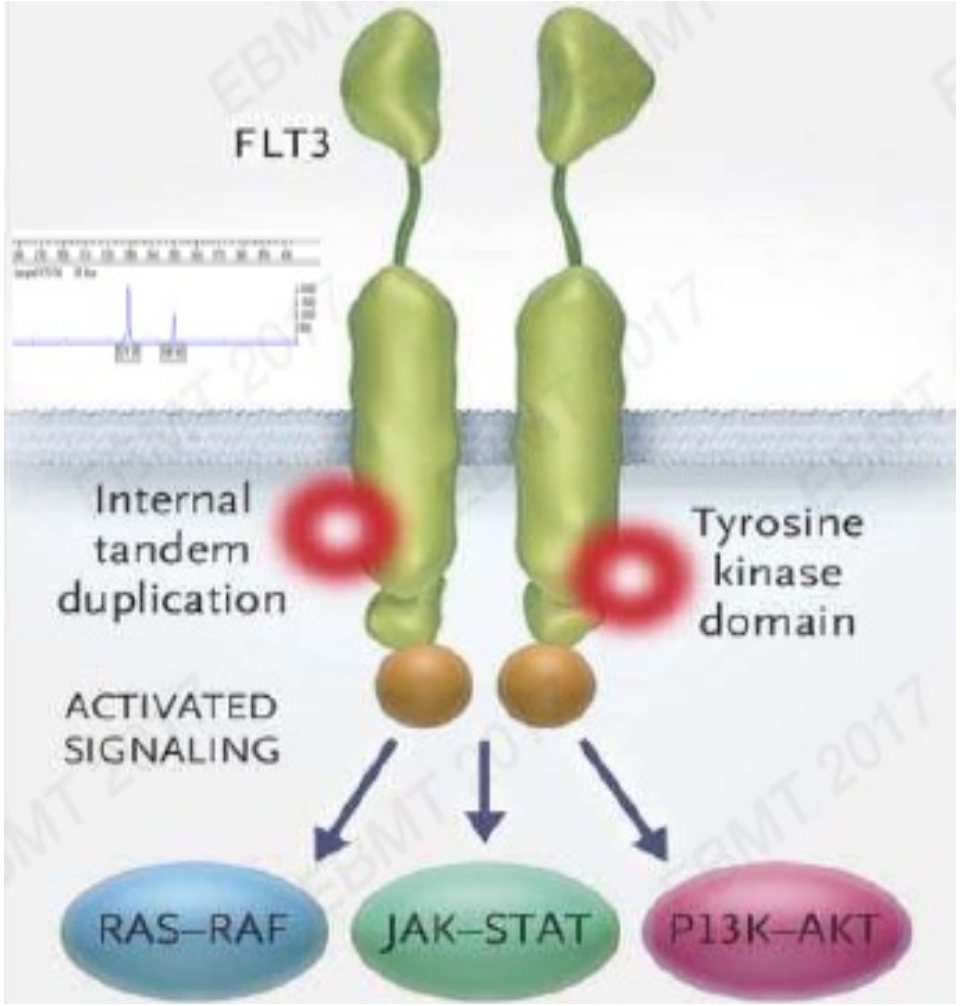


Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

ITD, internal tandem duplication; TKD, tyrosine kinase domain

Patel JP *et al*. *NEJM* 2012;366:1079–1089.

FLT3 mutations: Pathophysiology



FLT3-ITD

Drive proliferation and/or reduce apoptosis

Distinct AML presentation:

- High WBC count
- Increased myeloid blast cells in BM and PB

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

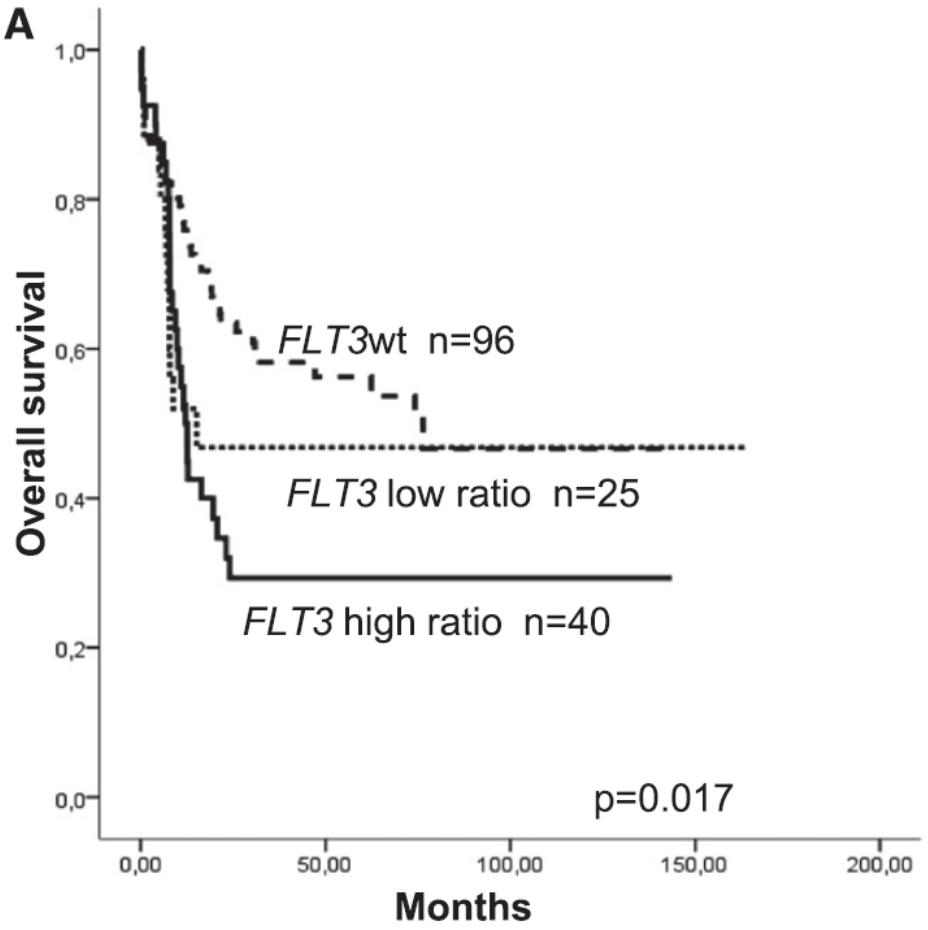
2 Fey MF. *Ann Oncol*. 2007;18:i9–i13. 3. Gale RE et al. *Blood*. 2005;106:3768-3776.

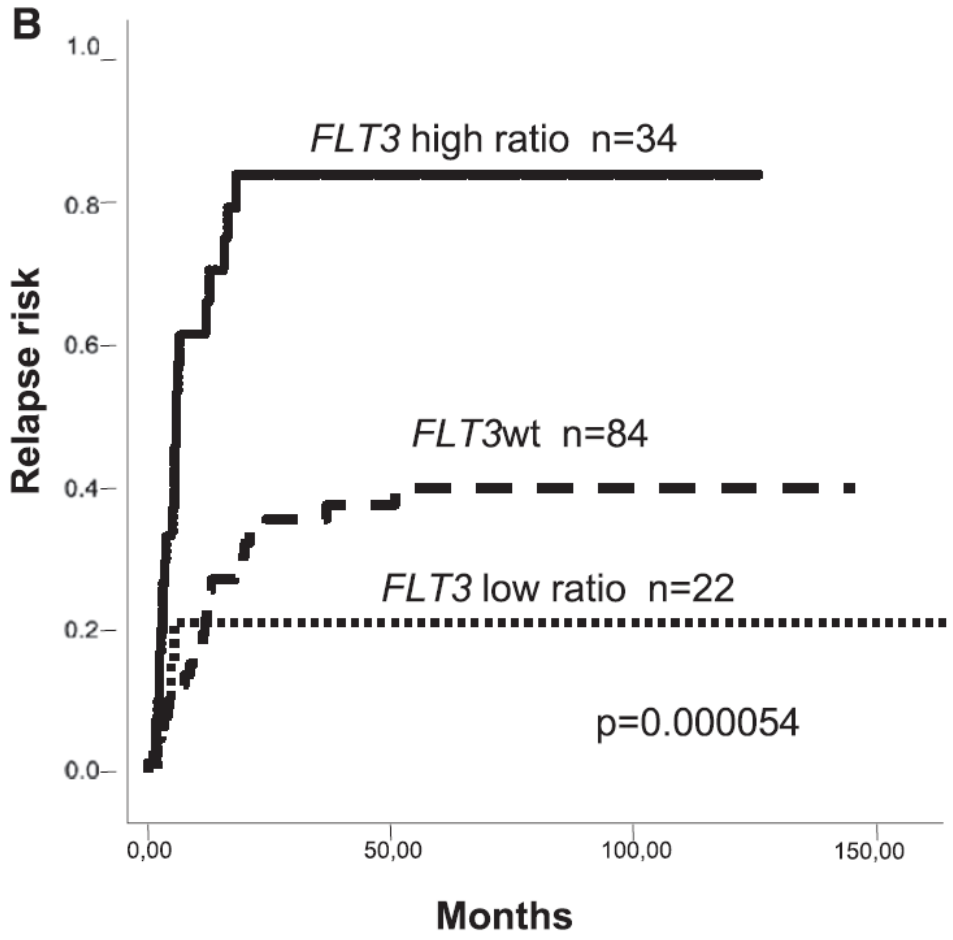
CETLAM AML-12: Characteristics (n=426)

Age, yrs; median (range) 18-35, 36-60, >60	55 (18-70) 48 (11%), 225 (52%), 160 (37%)
Gender; male/female	222 (52%) / 204 (48%)
WBC x10^9/l; median (range) >50, >100	10,3 (0.08-530) 92 (22%), 48 (12%)
MRC Favorable Intermediate; NK / Abn K Adverse	45 (11%) 272 (68%); 202 / 70 86 (21%)
ELN Favorable Intermediate I Intermediate II Adverse	117 (29%) 82 (21%) 108 (27%) 94 (23%)
Mutations in MRC Intermediate NPM1+FLT3-ITD neg **NPM1+FLT3-ITD Low ratio** **NPM1+FLT3-ITD High ratio** **NPM1-FLT3 pos** CEBPA mut / Triple mut neg	 73 (28%) **21 (8%)** **38 (14%)** **31%** **25 (9%)** 4 (2%) / 102 (39%)

FLT3 mutations: prognostic impact

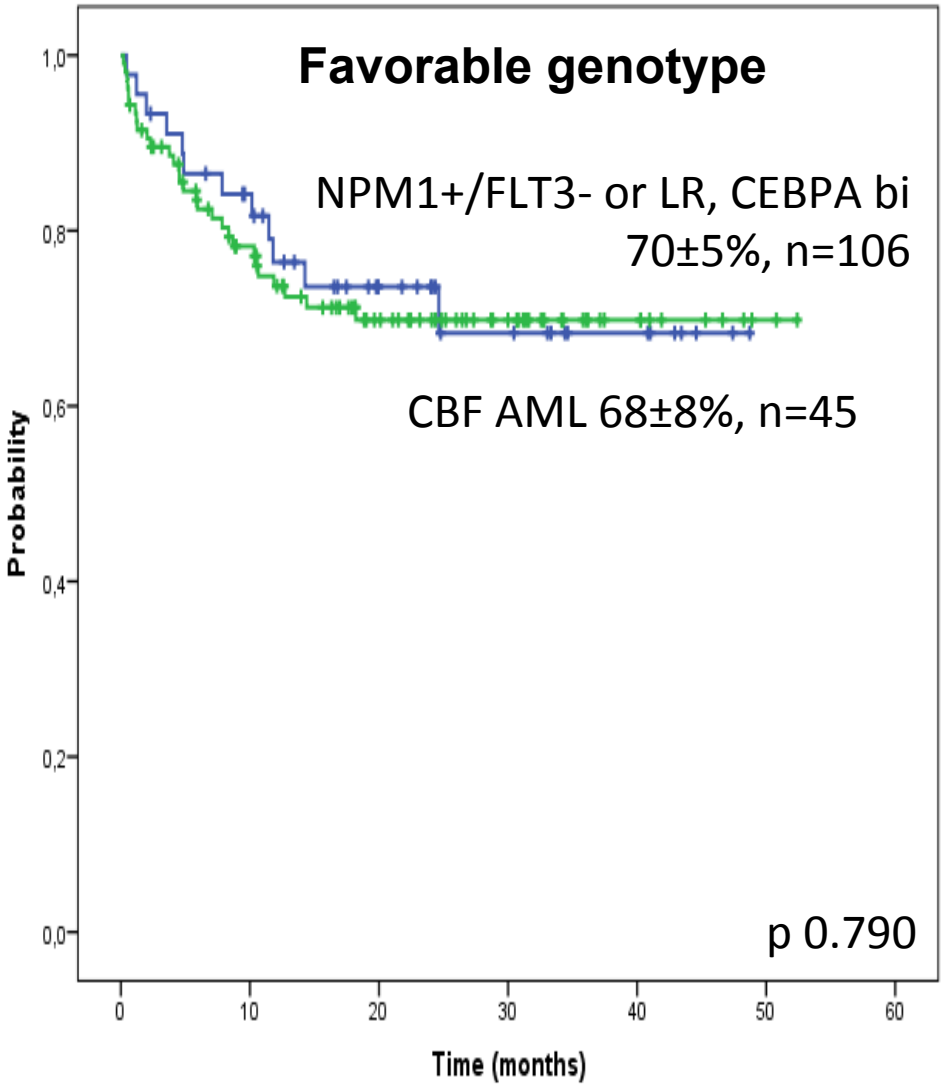
Favorable outcome of patients with acute myeloid leukemia harboring a low-allelic burden *FLT3*-ITD mutation and concomitant *NPM1* mutation: relevance to post-remission therapy

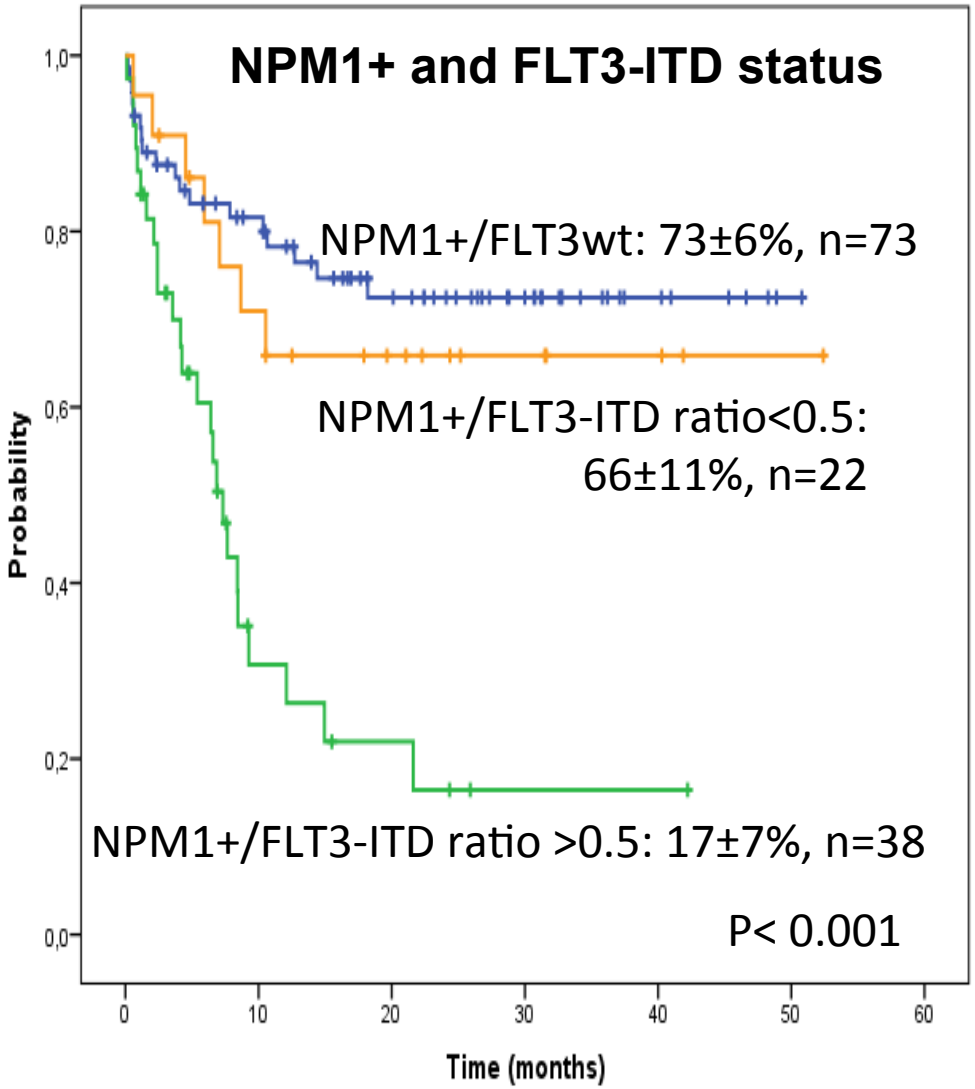




Marta Pratcorona, BLOOD, 4 APRIL 2013 • VOLUME 121, NUMBER 14

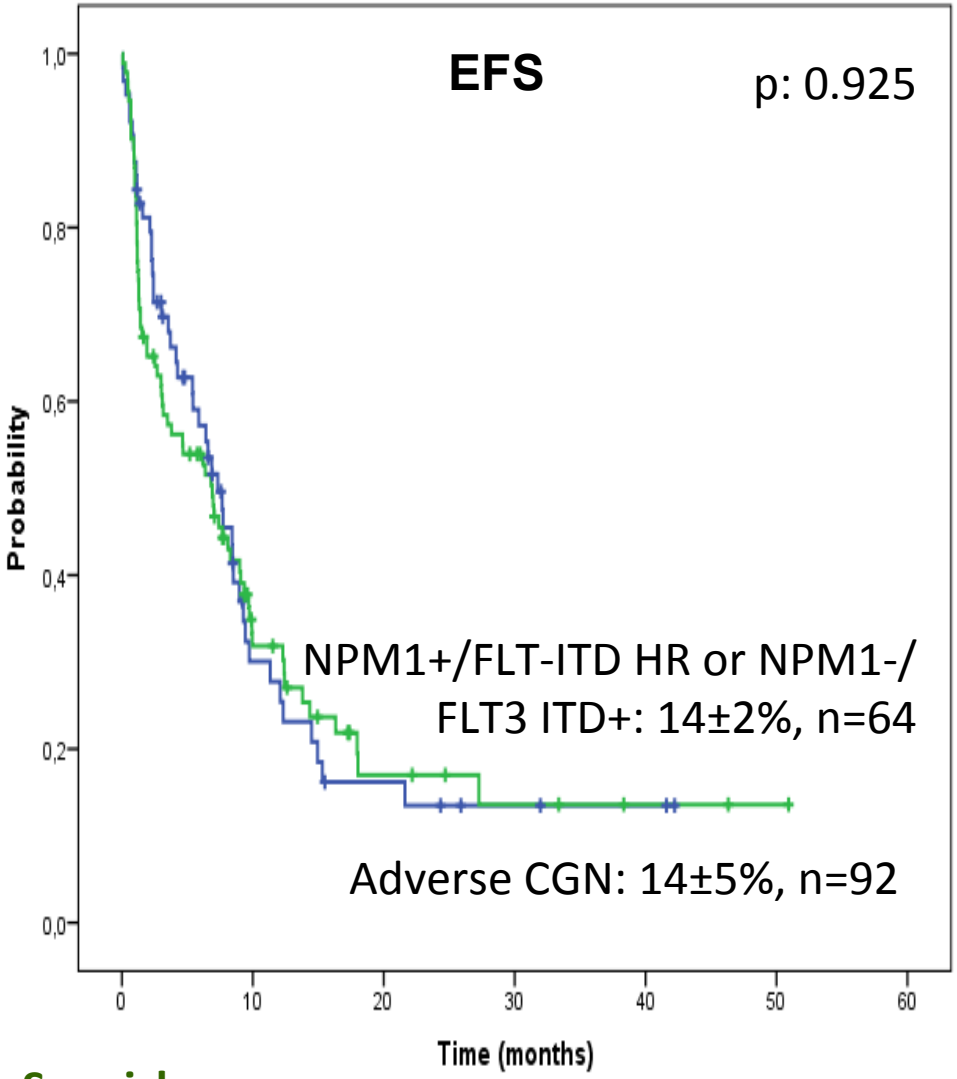
CETLAM AML-12: Event-free Survival

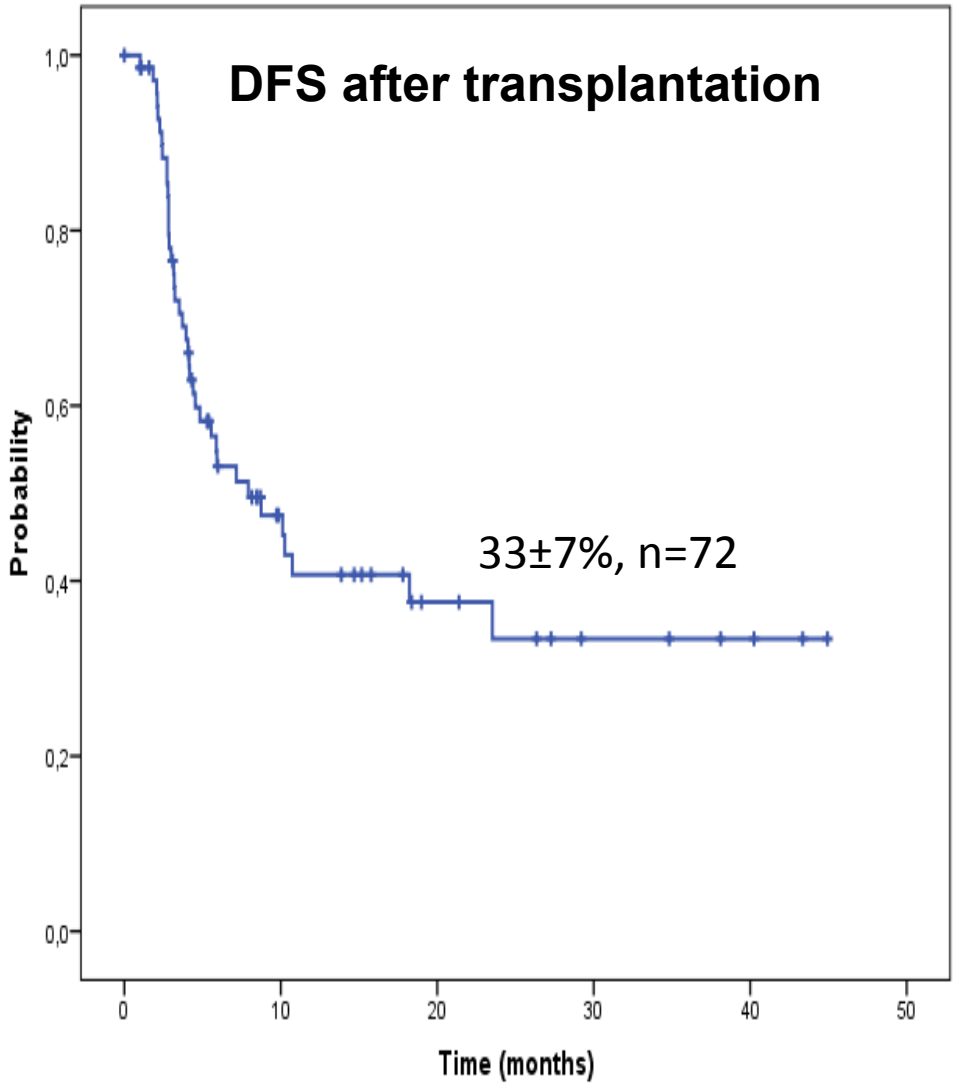




Spanish
CETLAM

CETLAM AML-12: Adverse risk (Genetics and/or MRD+)





Spanish CETLAM

ELN 2017: AML risk stratification by genetics

Favourable	• t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* • **Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}** • Biallelic mutated *CEBPA*
Intermediate	• **Mutated *NPM1* and *FLT3*-ITD^{high}** • **Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions)** • t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* • Cytogenetic abnormalities not classified as favourable or adverse
Adverse	• t(6;9)(p23;q34.1); *DEK-NUP214* • t(v;11q23.3); *KMT2A* rearranged • t(9;22)(q34.1;q11.2); *BCR-ABL1* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype, monosomal karyotype • **Wild-type *NPM1* and *FLT3*-ITD^{high}** • Mutated *RUNX1* • Mutated ASXL1 • Mutated TP53

Dohner H *et al*. *Blood* 2017;129:424–447

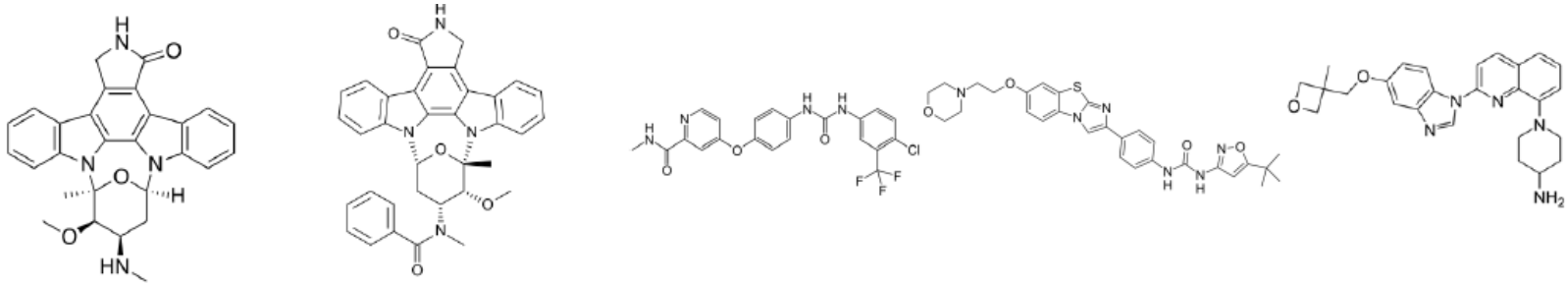
Impact of FLT3-ITD mutations in newly diagnosed acute promyelocytic leukemia treated with ATRA and ATO or ATRA and chemotherapy

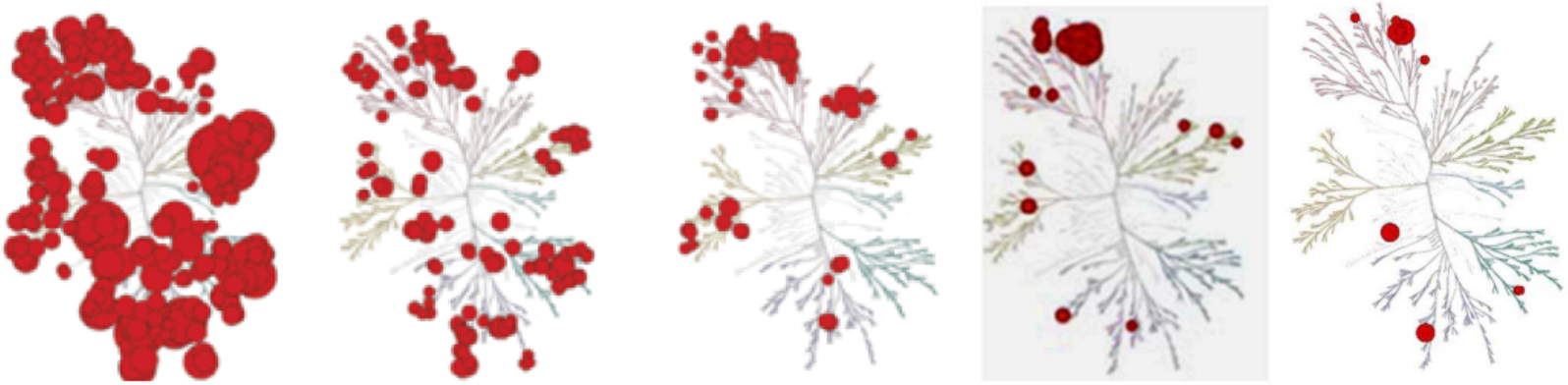
- FLT3-ITD mutations had no significant impact on either event-free survival (EFS) or cumulative incidence of relapse in patients receiving ATRA-ATO, whereas a trend for inferior EFS was observed in FLT3-ITD-positive patients receiving ATRA-CHT.
- ATRA-ATO may abrogate the negative prognostic impact of FLT3-ITD.

Cicconi L et al. Leukemia. 2016 Oct;30(10):1987-1992

FLT3 inhibitors in clinical trials

Tyrosine Kinase Inhibitors: Selectivity and Potency





Staurosporine Midostaurin Sorafenib Quizartinib Crenolanib

Karaman MW, et al. Nature Biotechnology 2008;26 (1):127-132
Zarrinkar PP, et al. Blood. 2009;114(14):2984-2992.
Crenolanib KinomeScan assay, DiscoveRx, 2010.

Gilteritinib

FLT3 inhibitors (I)

	Specificity	Available data	Ongoing or recently completed trials
Sorafenib	Non-specific but potent inhibitor of FLT3/ITD RTK	Leads to transient reductions in marrow and circulating myeloblasts **Improves EFS in combination with chemotherapy in younger patients, regardless of *FLT3* mutational status**	Phase II **sorafenib with HMA therapy as upfront approach for *FLT3/ITD*-mutant patients** (NCT02196857) **Phase maintenance sorafenib after HSCT for FLT3/ITD AML** (EudraCT 2010-018539-16)
Midostaurin	Non-specific inhibitor of FLT3	Transient peripheral responses as monotherapy in *FLT3*-mutant **AML Improves overall survival in combination with conventional chemotherapy in younger *FLT3*-mutant patients**	**Phase II randomized midostaurin monotherapy following stem cell transplant (NCT01883362)**
Quizartinib	Selective and potent inhibitor of FLT3/ ITD RTK	**As monotherapy, CR and CRi in sizeable proportion of relapsed *FLT3/ITD*-mutant patients Ongoing trials are evaluating quizartinib in combination with conventional therapies**	**Combined with HMA QuANTUM-R: quizartinib vs conventional salvage QuANTUM-First: Phase III quizartinib with conventional CT in *FLT3/ITD* (NCT02668653)**

Modified from Amir T. Fathi & Yi-Bin Chen, *Eur J Haematol.* 2017;98:330–336

The NEW ENGLAND JOURNAL of MEDICINE

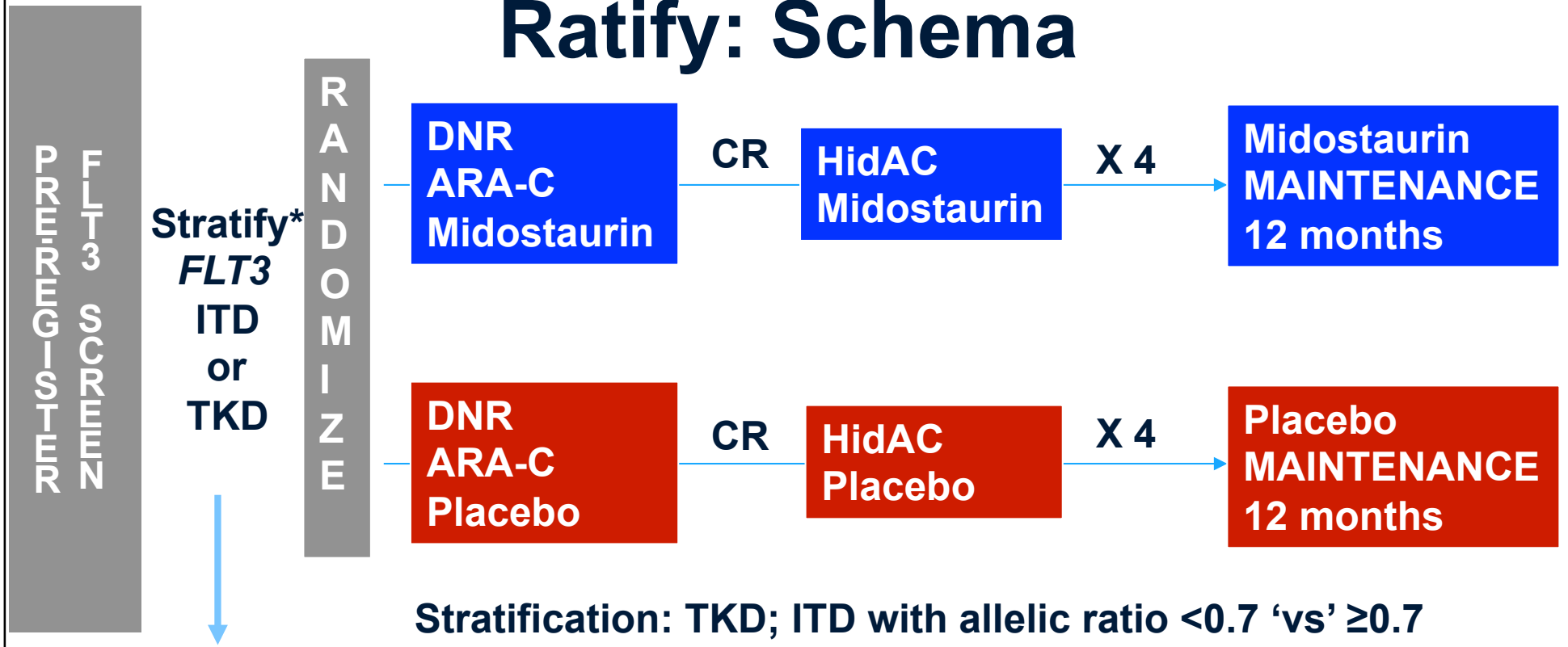
ORIGINAL ARTICLE

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

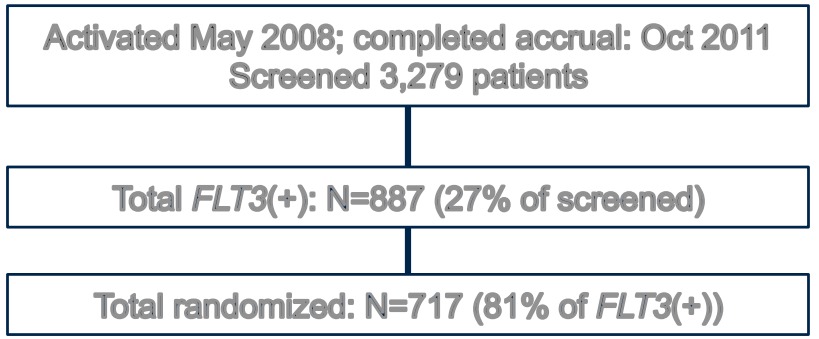
N Engl J Med. 2017 Aug 3;377(5):454-464.

Ratify: Schema



Stratification: TKD; ITD with allelic ratio <0.7 'vs' ≥0.7

***FLT3* WILD TYPE not eligible for enrollment**

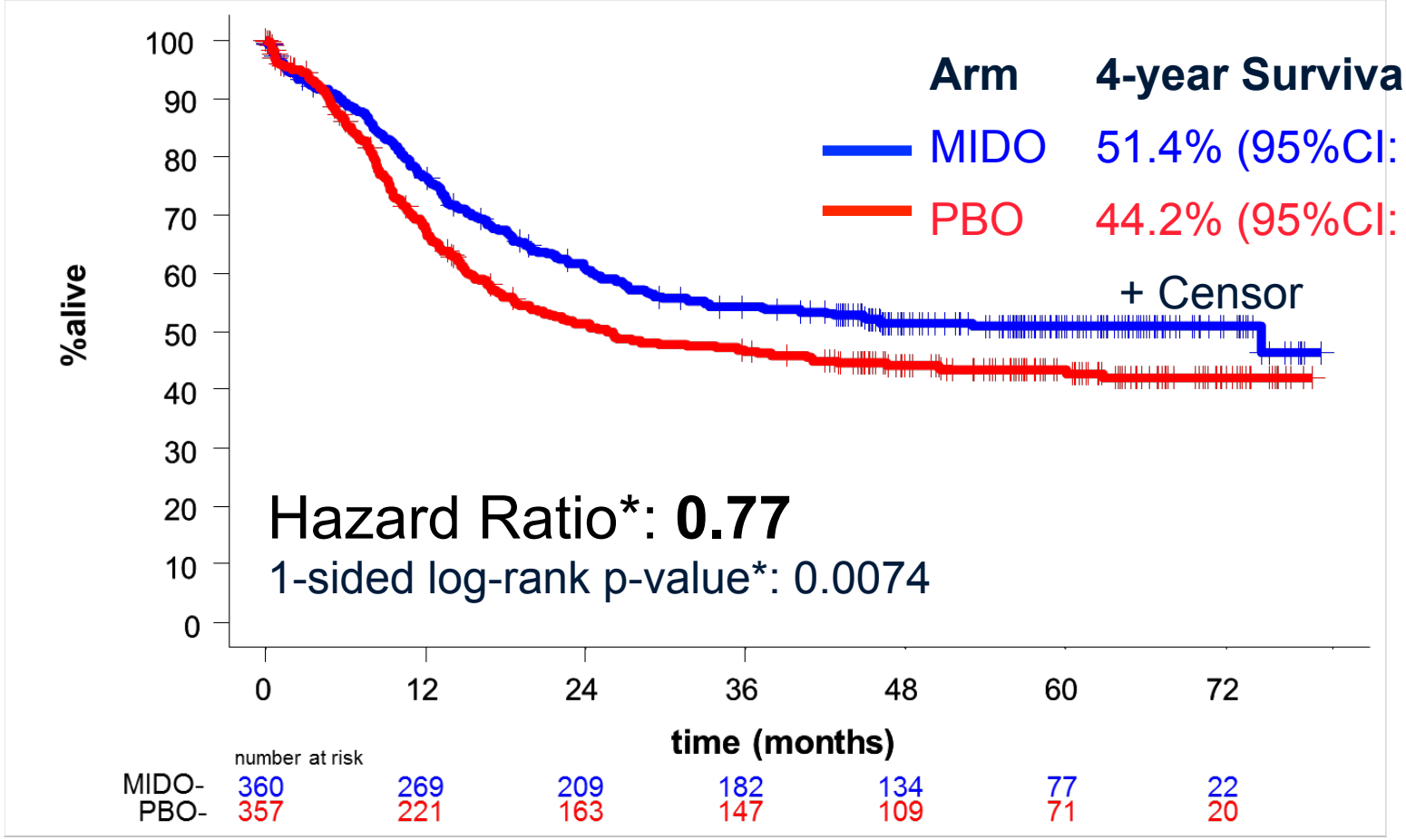


ARA-C, cytarabine; DNR, daunorubicin; HidAC, high-dose cytarabine.

Stone, et al. *Blood*. 2015;126:[abstract 6].

Overall Survival (Primary Endpoint)

23% reduced risk of death in the Mido arm



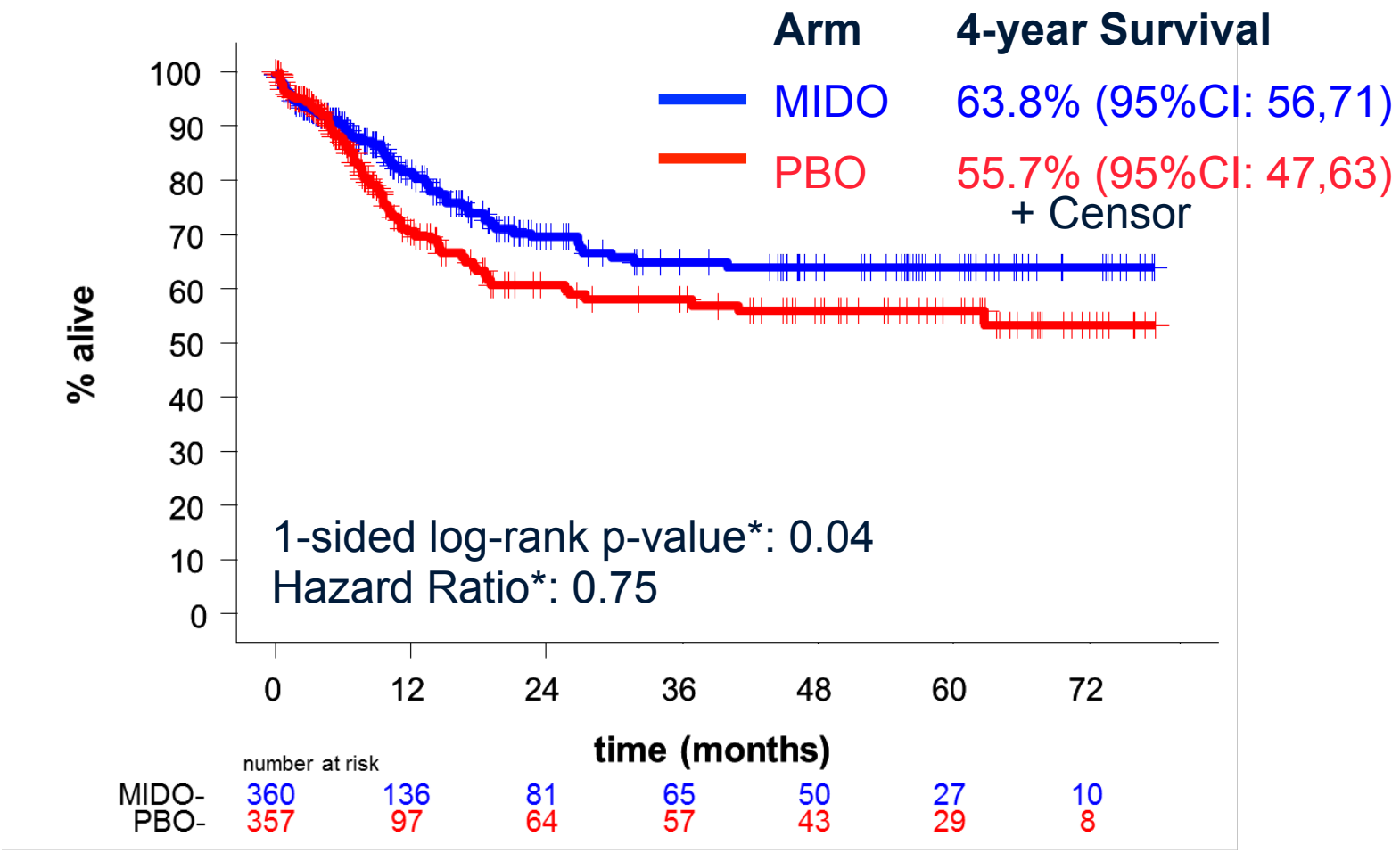
- **Median OS**: Mido 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months
  NE: not estimable
  * controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Stone, et al. *Blood*. 2015;126:[abstract 6].

Overall Survival

Censored at time of transplant

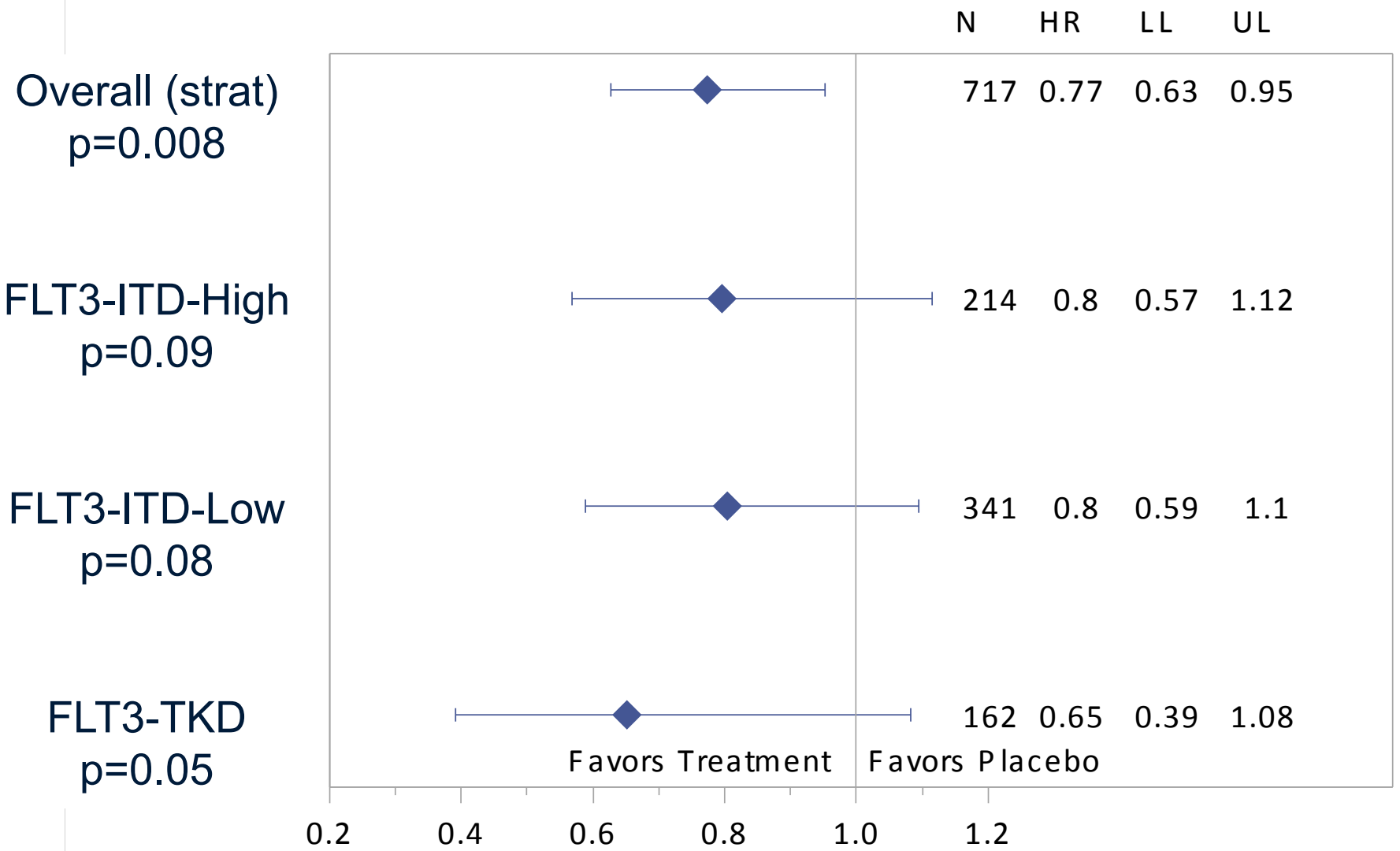


Medians not reached

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

Stone, et al. *Blood*. 2015;126:[abstract 6].

Consistent Effect on OS by *FLT3* status

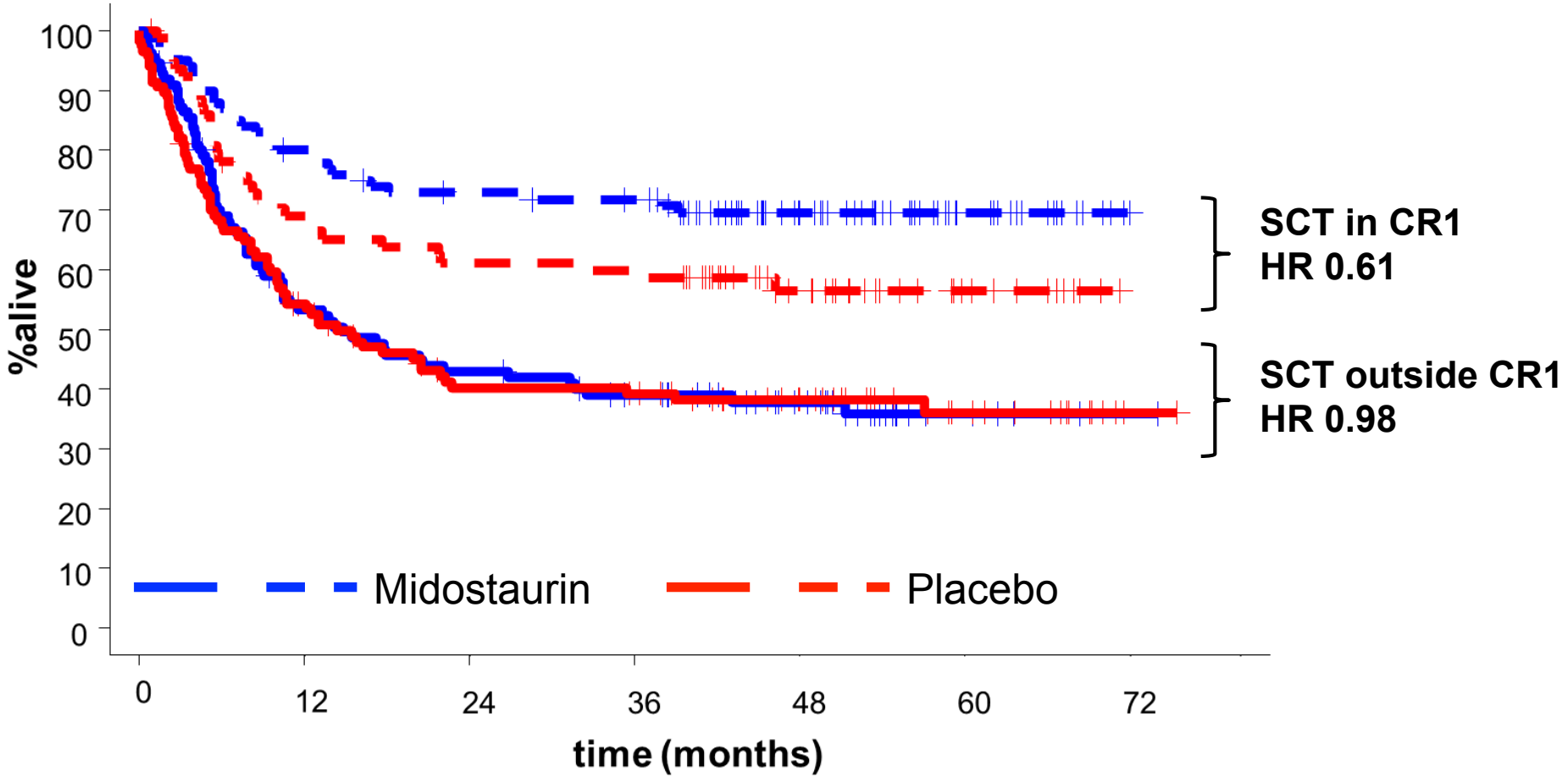


Confidence intervals are two-sided; p-values are one-sided.
HR: Hazard Ratio, LL: Lower Limit; UL: Upper Limit;
strat: stratified by FLT3 status; ITD-low: Allelic ratio < 0.7; ITD-high: Allelic ratio ≥ 0.7

Stone, et al. *Blood*. 2015;126:[abstract 6].

Overall Survival - Post-transplant

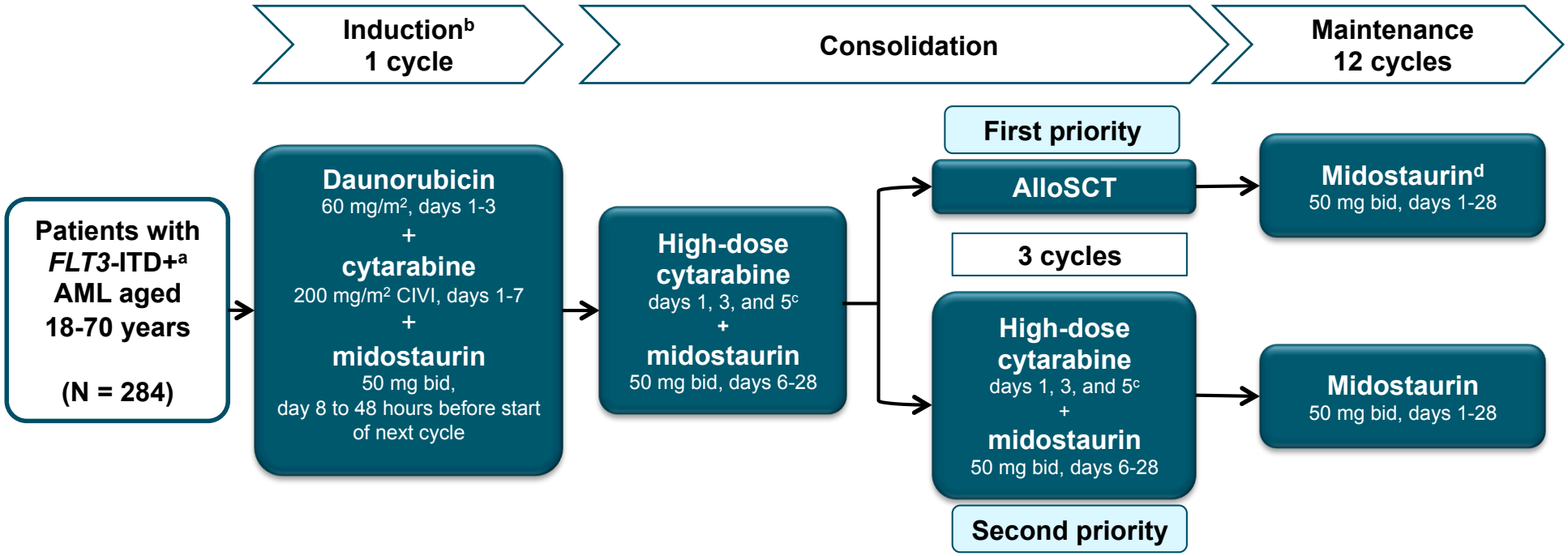
Treatment with Mido increases OS after SCT in CR1



+ Censor

Stone, et al. *Blood*. 2015;126:[abstract 6].

Phase 2 DE02T Trial (AMLSG 16-10): Midostaurin + Chemotherapy in Patients With *FLT3*-ITD+ AML



Primary endpoint: EFS

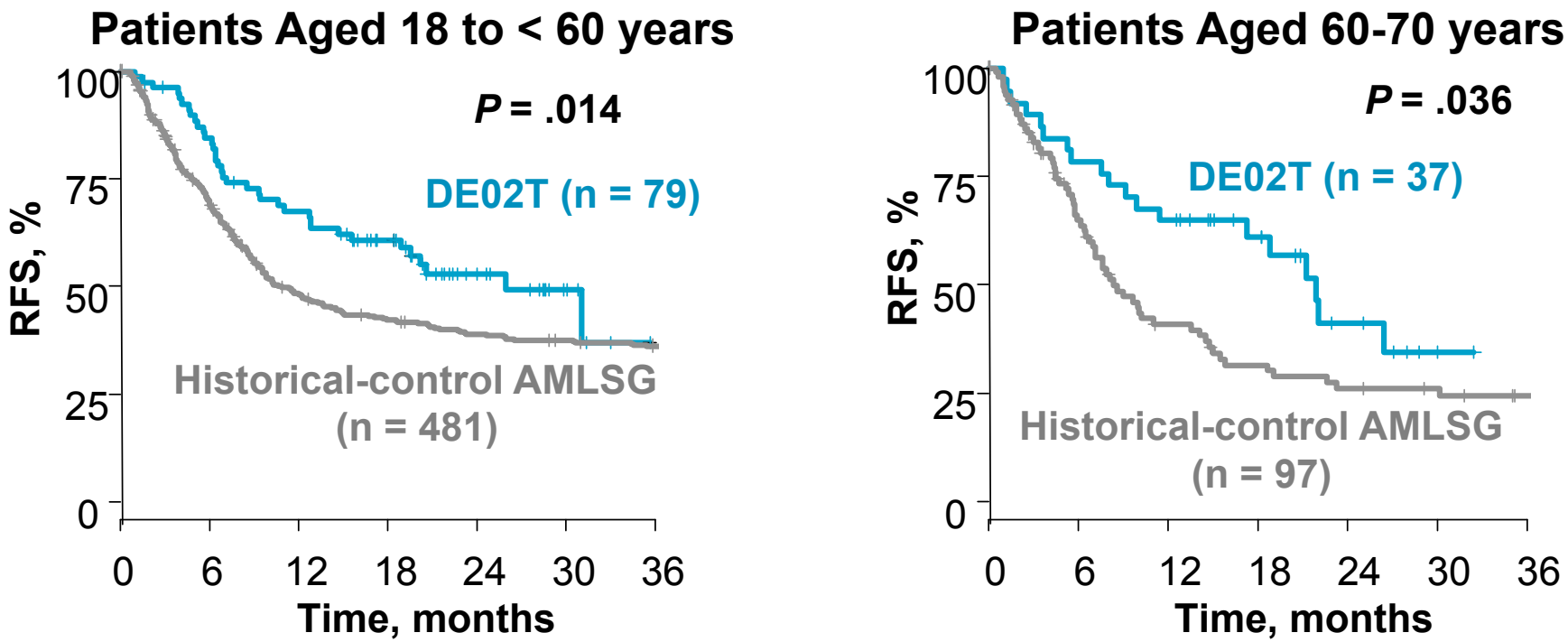
Secondary endpoints: CR rate, relapse-free survival, OS, cumulative incidence of relapse and death in CR, plasma inhibitory activity, safety, quality of life

[a] Allelic ratio > 0.05 by Genescan-based fragment length analysis required to be *FLT3*-ITD positive.
[b] During induction, patients achieving PR after cycle 1 can receive an optional cycle 2.
[c] Age-appropriate cytarabine dose on days 1, 3, and 5: 18-65 years 3 g/m² q12h; > 65 years 1 g/m² q12h; optional for patients before alloSCT.
[d] Start midostaurin 30 days post alloSCT in patients who received alloSCT.

1. Kayser S, et al. *Blood*. 2013;122(suppl): [abstract 1283].
2. https://clinicaltrials.gov/ct2/show/NCT01477606. Accessed October 27, 2015.

Phase 2 DE02T Trial (AMLSG 16-10): Midostaurin + Chemotherapy in Patients With *FLT3*-ITD+ AML – RFS

Patients in the DE02T study had improved RFS vs historical control



Adding midostaurin to intensive induction and consolidation therapy (ie, high-dose cytarabine or alloSCT) and as post-consolidation maintenance in patients ≤ 70 years was feasible and rates of relapse were lower in patients with a high *FLT3*-ITD allelic ratio-
No impact of age and dose adaptation on outcome.

AMLSG, Acute Myeloid Leukemia Study Group.

Schlenk R, et al. ASH 2015. Abstract 322. Oral presentation.

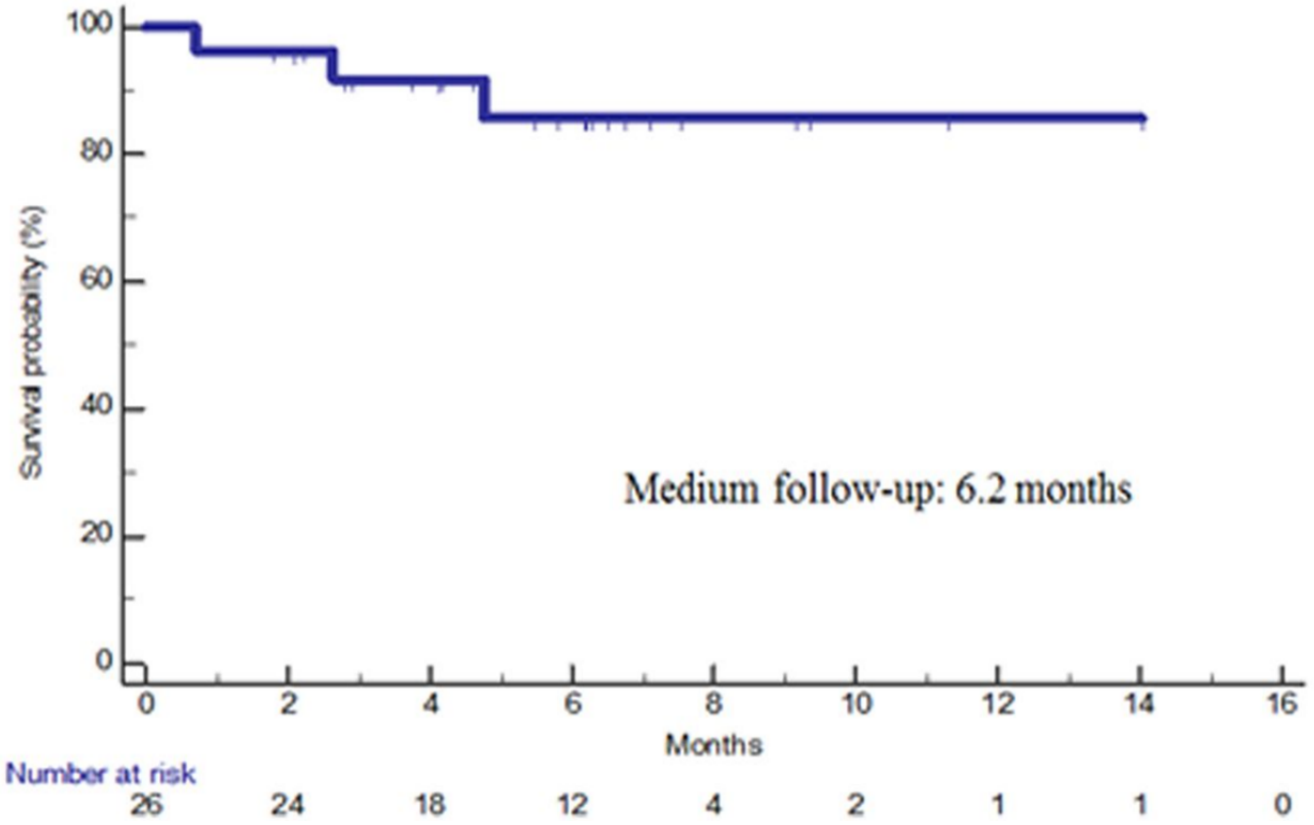
Blood 2016 128:449

	Specificity	Available data	Ongoing or recently completed trials
Crenolanib	Active against both *FLT3/ITD* and *FLT3-TKD* mutation variants	**Multiple ongoing trials of this agent are in progress, including in the frontline and relapsed/ refractory settings**	Safety study of crenolanib combined **with upfront induction in *FLT3*-mutant patients (NCT02283177)** Phase I/II trial of crenolanib combined **with re-induction regimens for R/R *FLT3*-mutantpatients** (NCT02626338) Pilot study of crenolanib combined **with salvage regimens for R/R patients, regardless of *FLT3*-mutation** status (NCT02400281) **Crenolanib maintenance following stem cell transplant** (NCT02400255
Gilteritinib	Selective FLT3 inhibitor, which can target both FLT3*/ITD* and *FLT3-TKD*	Remains under study in clinical trials. **Composite remission rate of 46% among relapsed / refractory *FLT3*-mutant patients**	Phase III randomized study of **gilteritinib vs conventional salvage CT among *FLT3*-mutant** Phase II/III study of gilteritinib **combined with HMA therapy** Phase I study of **gilteritinib combined with conventional induction CT** Phase III study of **gilteritinib maintenance among *FLT3*-mutant patients in first remission** Phase III randomized study of **maintenance gilteritinib after HSCT for patients with FLT3/ITD AML CR1**

Modified from Amir T. Fathi & Yi-Bin Chen, *Eur J Haematol.* 2017;98:330–336

Crenolanib, a Type I FLT3 TKI, Can be Safely Combined with Cytarabine and Anthracycline Induction Chemotherapy and Results in High Response Rates in Patients with Newly Diagnosed FLT3 Mutant Acute Myeloid Leukemia (AML)

Figure 1. Overall Survival in Newly Diagnosed FLT3 mutant AML



Eunice S. Wang et al. Blood 2016;128:1071

FLT3-ITD AML: Approaches to further investigate

Mechanisms of Resistance to FLT3 Inhibitors and the Role of the Bone Marrow Microenvironment

Ghiaur G, Levis M. Hematol Oncol Clin North Am. 2017Aug;31(4):681-692. doi: 10.1016/j.hoc.2017.04.005. PMID: 28673395.

Combination with immunotherapy

Tyrosine kinase inhibition increases the cell surface localization of FLT3-ITD and enhances FLT3-directed immunotherapy of acute myeloid leukemia. Reiter K, et al. Leukemia. 2017 Aug 14. doi: 10.1038/leu.2017.257. PMID: 28895560.

Intensification of therapy resulted in a reduced relapse risk

Gemtuzumab Ozogamicin in induction therapy

(Castaigne S, et al. Lancet 2012; 379: 1508–16.)

High-dose daunorubicin in induction therapy

(Burnett AK, et al. Blood. 2016;128(3):449-52.)

FLT3 mutated AML: Summary

FLT3-ITD is a negative prognostic factor in newly diagnosed intensively treated AML.

FLT3-ITD, in the absence of NPM1 mutation or despite this if the allelic ratio is high, favours the indication of allogeneic hematopoietic transplantation in first CR.

The FLT3-inhibitor midostaurin given in younger adults (<60 years) with activating *FLT3* mutations during induction therapy before an allogeneic HCT performed in first CR significantly improves outcome.

Important clinical trials evaluating novel and more specific FLT3 inhibitors are ongoing.