Treatment Options for Patients with AML Harboring FLT3 Mutations

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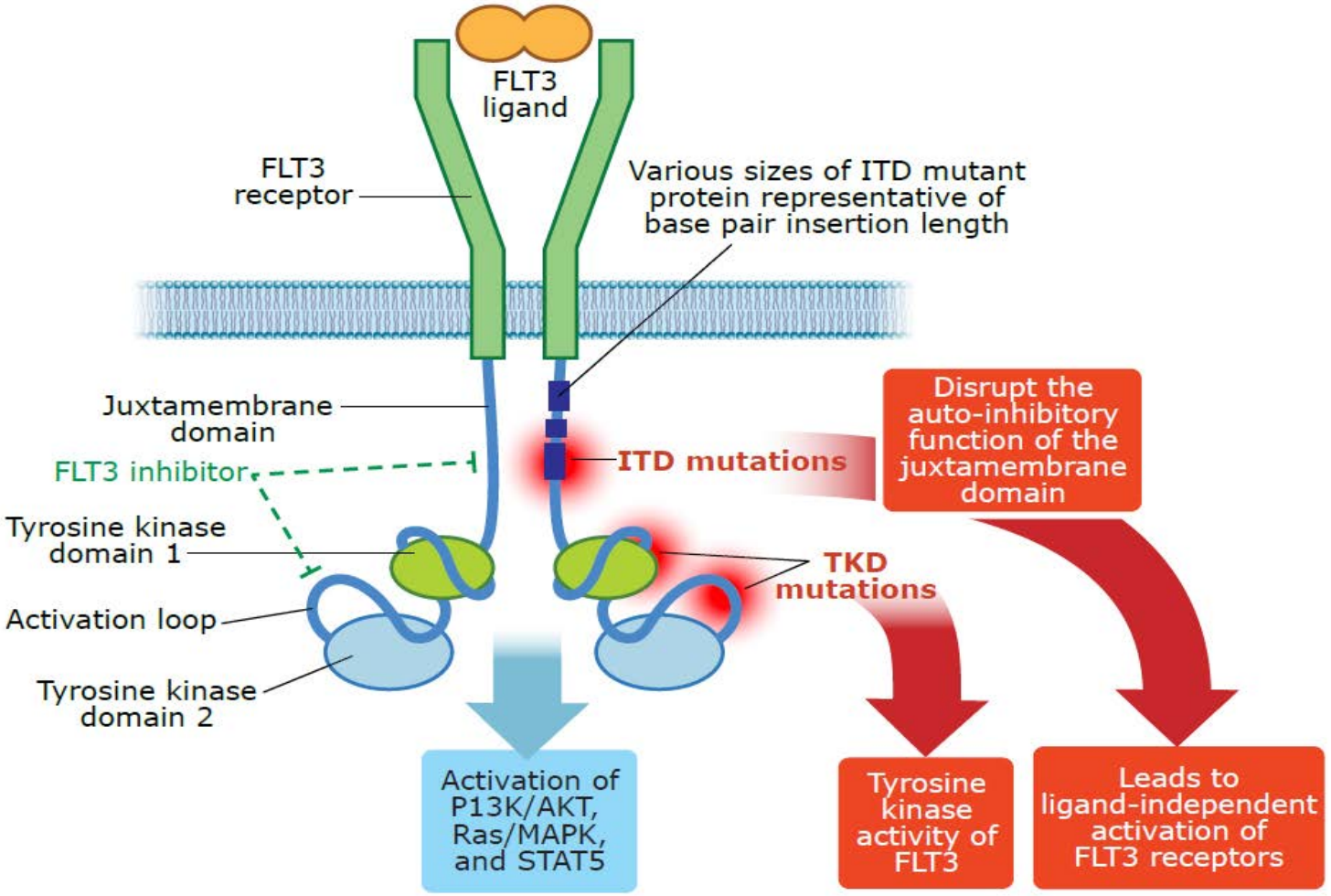
FLT3 mutations in AML



- Incidence
  - *FLT3*-ITD 20-25%
  - *FLT3*-TKD 5-10%
- Clinical features
  - Leukocytosis
  - High marrow blast percent
  - Proliferative disease
- Genetic associations
  - Diploid karyotype
  - NPM1 mutation
  - t(6;9)
  - t(15;17)
- Frequently subclonal
  - gained at relapse/progression
  - sometimes lost at relapse/progression

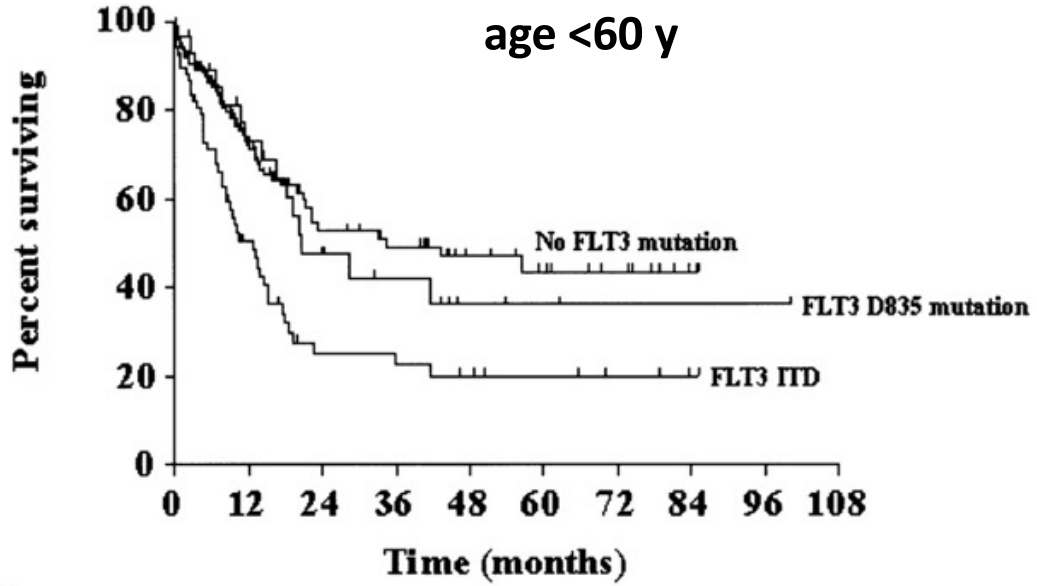
ITD= internal tandem duplication
TKD= tyrosine kinase domain

Slide courtesy of Ashkan Emadi

Courtesy of Alexander Perl, MD

FLT3 mutations: prognostication

Untreated *FLT3*-ITD+ AML, age <60 y



Number at risk									
No FLT3 mutation	125	67	31	26	16	12	8	3	0
FLT3 D835 mutation	28	18	11	7	3	2	1	1	1
FLT3 ITD	67	25	10	9	7	5	3	1	0

Table 5. 2017 ELN risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	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 favorable 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*#

Allelic ratio is defined by PCR (*not* NGS)

There is no harmonized standard for ITD:WT allelic ratio

Courtesy of Alexander Perl, MD

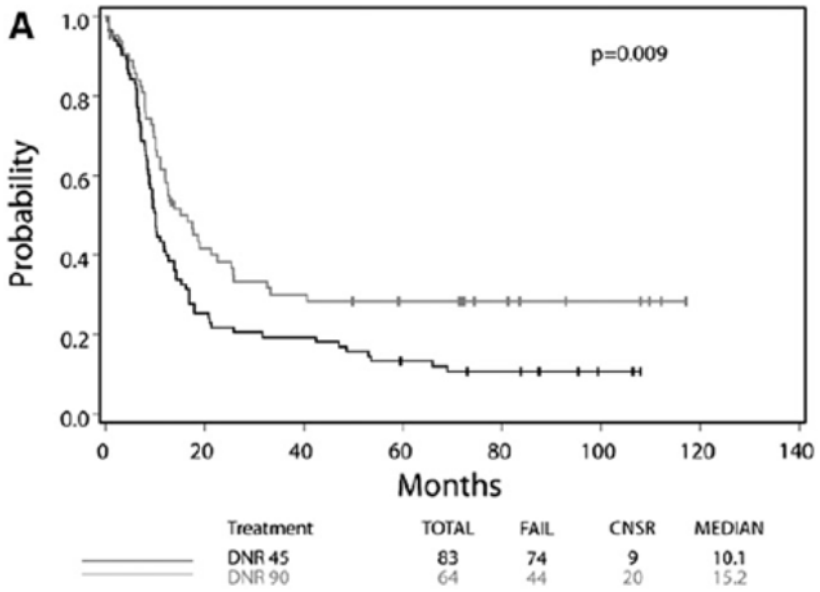
Döhner H, et al. Blood. 2017 Jan 26;129(4):424-447

Papaemmanuil E, et al. *N Engl J Med*. 2016 Sep 1;375(9):900-1

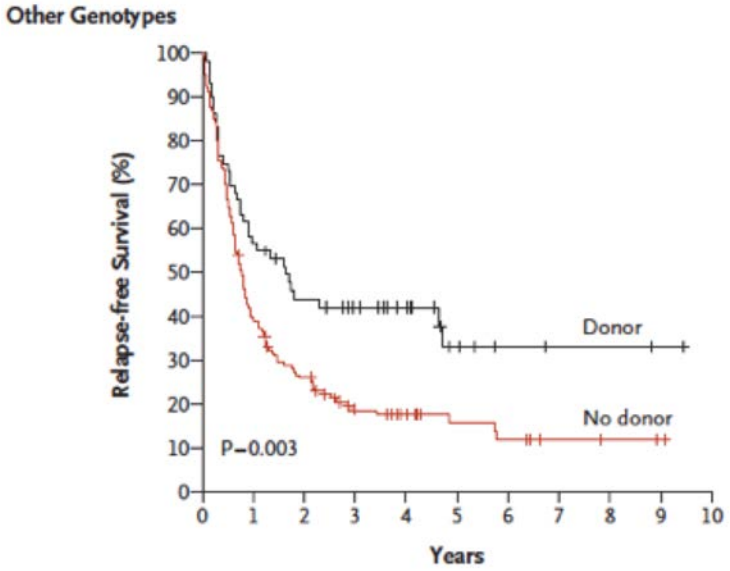
Fröhling S et al. *Blood*. 2002;100:4372-4380.

3 therapies improve FLT3-ITD+ AML cure rates

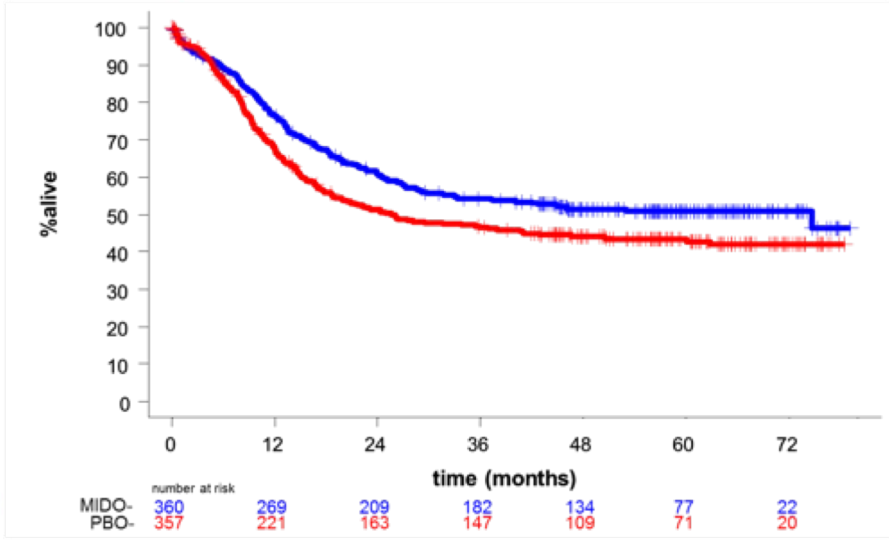
High dose daunorubicin



First remission AlloHSCT



Midostaurin



Note: includes FLT3-ITD (77%) and FLT3-D835 (23%)
57% underwent alloHSCT

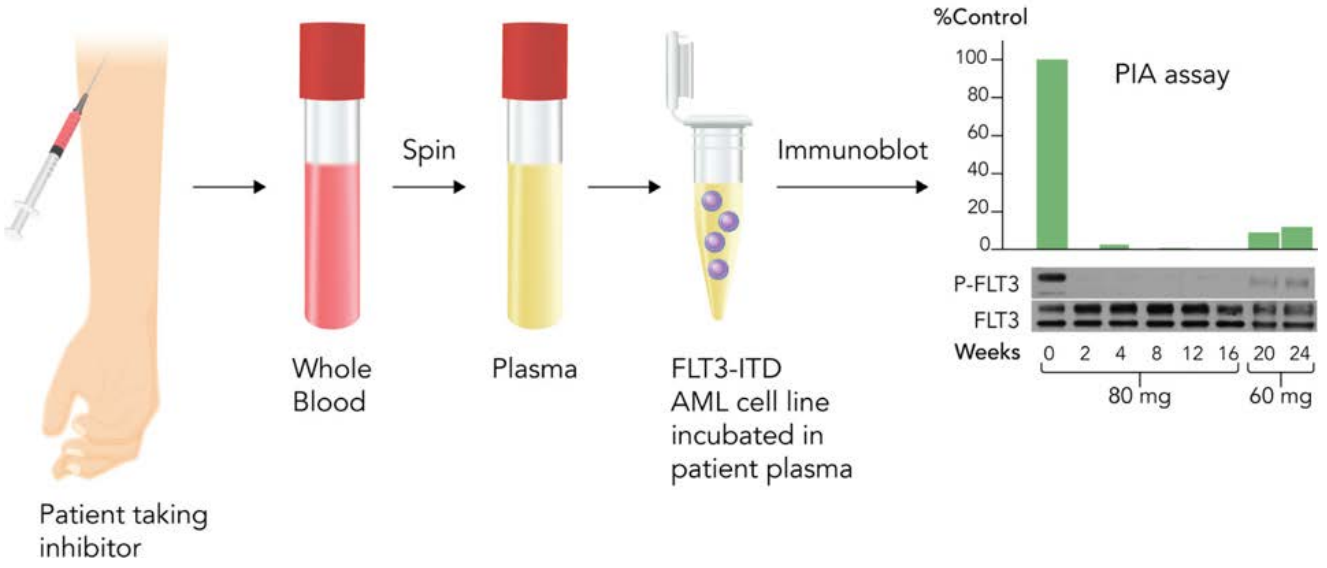
Courtesy of Alexander Perl, MD

Luskin MR, et al. *Blood*. 2016 Mar 24;127(12):1551-8
Schlenk RF, et al. N Engl J Med. 2008 May 1;358(18):1909-18.
Stone RM, et al. *N Engl J Med*. 2017 Aug 3;377(5):454-464

Potency and selectivity of FLT3 inhibitors

		IC_{50} (medium)	IC_{50} (plasma)	Single agent clinical activity	Kinase inhibition
1st gen	Lestaurtinib	2 nM	700 nM	-	**Type 1**
	Midostaurin	6 nM	~1000 nM	-	**Type 1**
	Sorafenib	3 nM	~265 nM	+/-	**Type 2**
2nd gen	Quizartinib	1 nM	18 nM	+	**Type 2**
	Crenolanib	2 nM	48 nM	+	**Type 1**
	Gilteritinib	3 nM	43 nM	+	**Type 1**

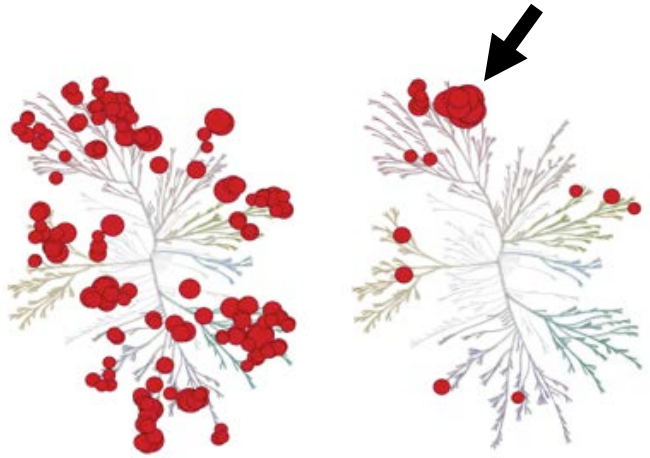
The plasma inhibitory activity (PIA) assay for FLT3



Courtesy of Alexander Perl, MD

Type 2 inhibitors: resistance due to FLT3-D835
Type 1 inhibitors: active against FLT3-D835, limited potential for on-target resistance

Class 3 RTK's:
FLT3, KIT, CSF1R, PDGFRA/B

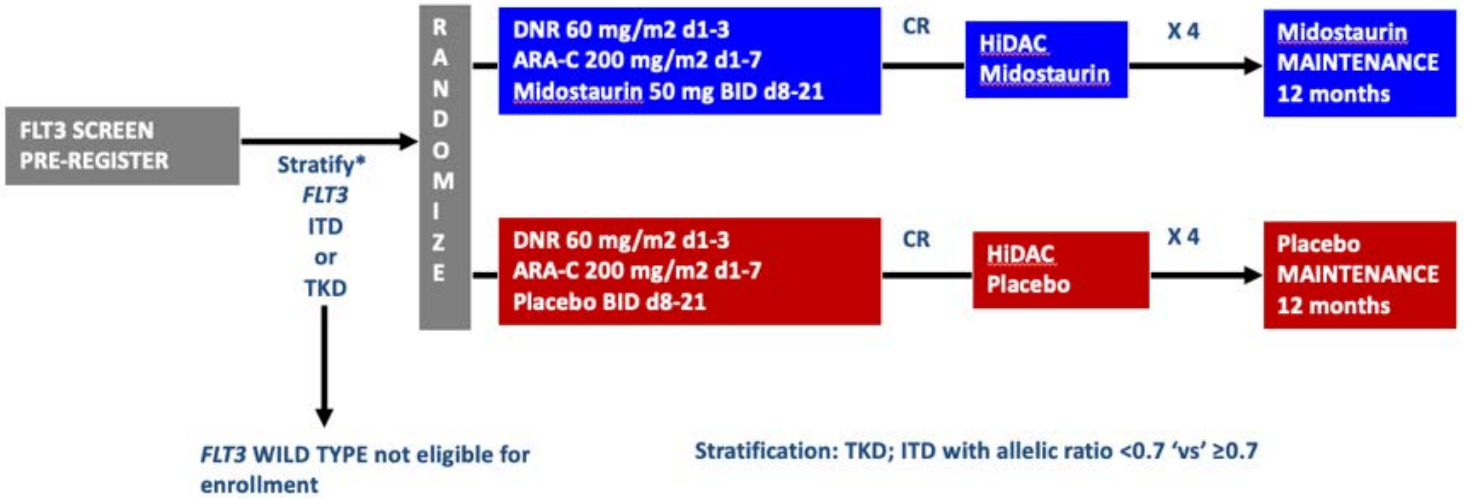


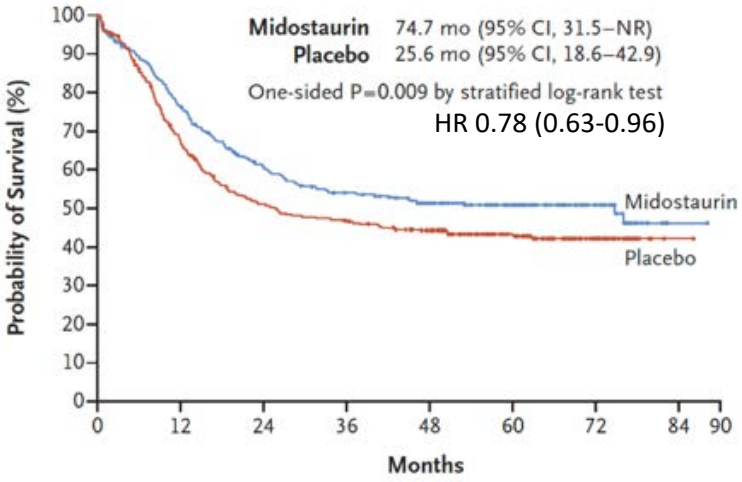
Midostaurin **Quizartinib**

Pratz KW, et al. Blood 2010;115(7):1425-32
Zarrinkar PP, et al. Blood. 2009 Oct 1;114(14):2984-92
Galanis A, et al. Blood 2014 Jan 2;123(1):94-100
Levis M, Perl AE. Blood Adv. 2020 Mar 24;4(6):1178-1191
Smith CC, et al. Nature. 2012 Apr 15;485(7397):260-3
Tarver TC, et al. Blood Adv. 2020 Feb 11;4(3):514-524

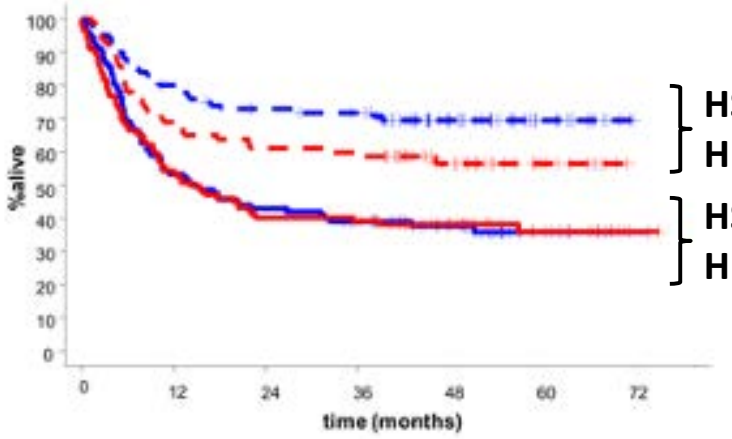
Current frontline standard of care: 7+3 + midostaurin

RATIFY/C10603





- 22% reduction in risk of death compared to 7+3 + placebo
  - Midostaurin was given during induction, consolidation, maintenance
  - OS benefit maintained when censored for HSCT
  - No post-HSCT maintenance in study
  - Transplanted patients benefitted from midostaurin prior to HSCT



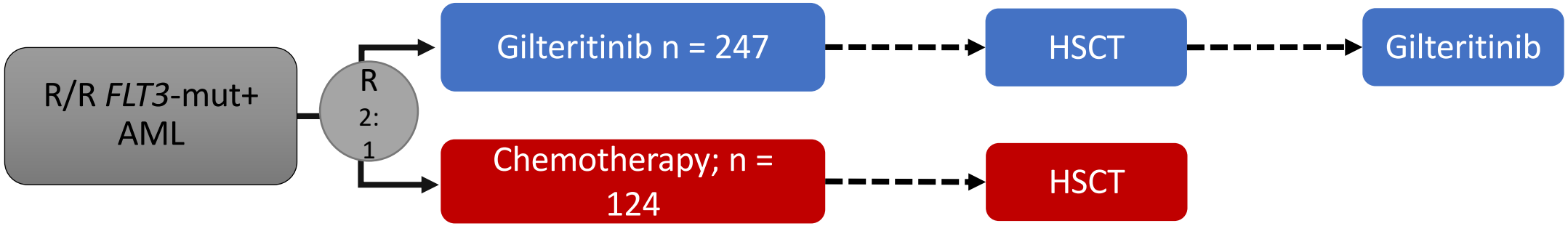
- Toxicity of midostaurin similar to placebo
  - Rashes more frequent with midostaurin
  - Nausea, diarrhea common with prolonged administration

Courtesy of Alexander Perl, MD

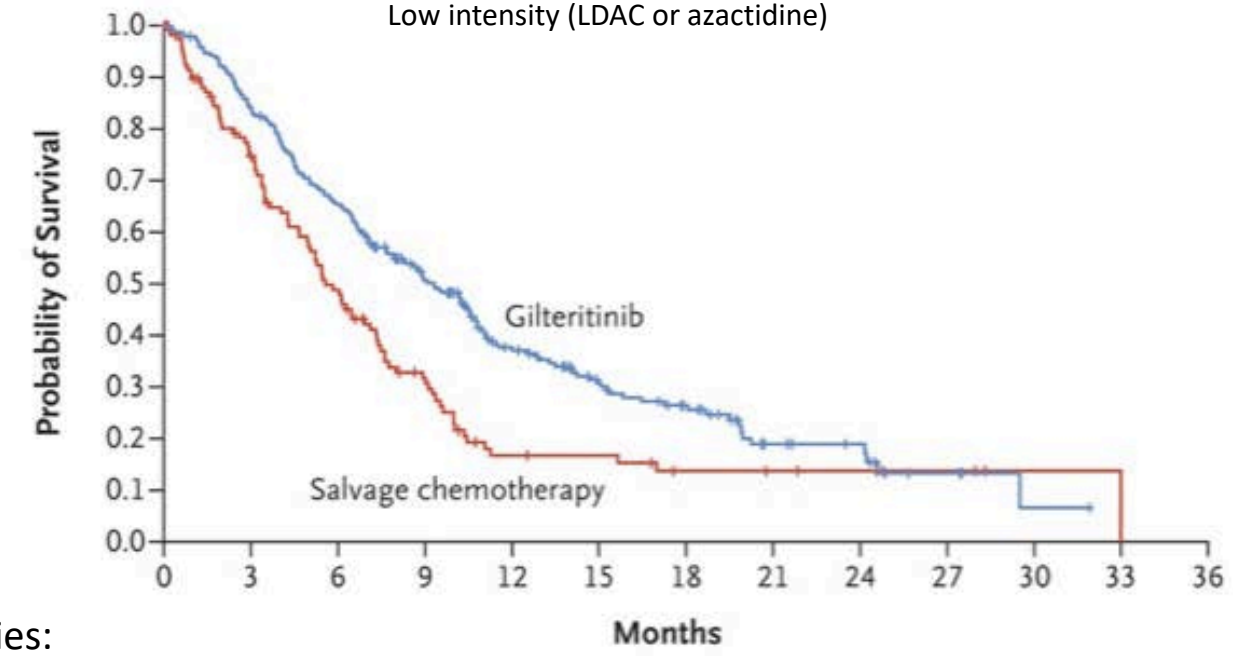
Stone RM, et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464

Current relapsed/refractory standard of care: gilteritinib

Gilteritinib Phase 3 (ADMIRAL)



High intensity (MEC or FLAG-IDA)
Low intensity (LDAC or azactidine)



	Median Overall Survival (95% CI) *mo*
Gilteritinib	9.3 (7.7–10.7)
Salvage Chemotherapy	5.6 (4.7–7.3)

Hazard ratio for death, 0.64 (95% CI, 0.49–0.83)
P<0.001

CR/CRh

34%
15.3%

- Gilteritinib toxicities:
  - Cytopenias, elevation of LFTs, CPK, fevers/rashes (Sweet's syndrome)
  - Uncommon toxicities: differentiation syndrome, QT prolongation

Courtesy of Alexander Perl, MD

Perl AE, et al. *N Engl J Med.* 2019;381:1728-1740.

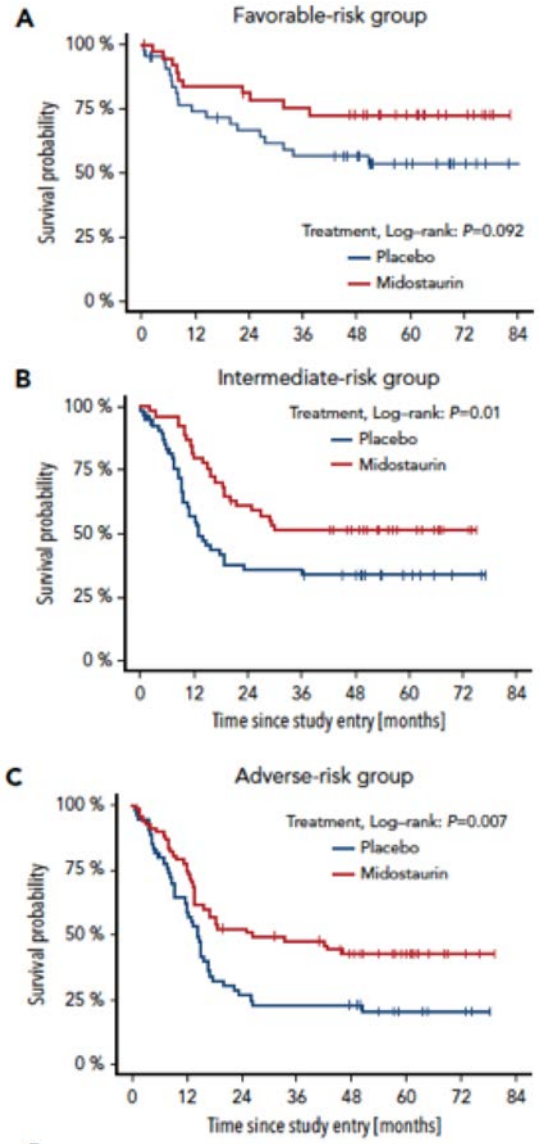
Ongoing questions in the FLT3 world

- The NCCN guidelines only recommend midostaurin for intermediate risk karyotype $FLT3^{mut+}$--does it work in other patients?
- Do FLT3-TKD+ patients benefit from midostaurin?
- Which $FLT3^{mut+}$ patients need transplant?
- Should I give TKI maintenance after transplant?
- Should I give midostaurin or a newer FLT3 inhibitor with induction?
- What should newly diagnosed $FLT3^{mut+}$ unfit patients receive?

Courtesy of Alexander Perl, MD

Midostaurin for FLT3-ITD+ AML: ELN risk and role of transplant

ELN risk category: midostaurin vs. placebo



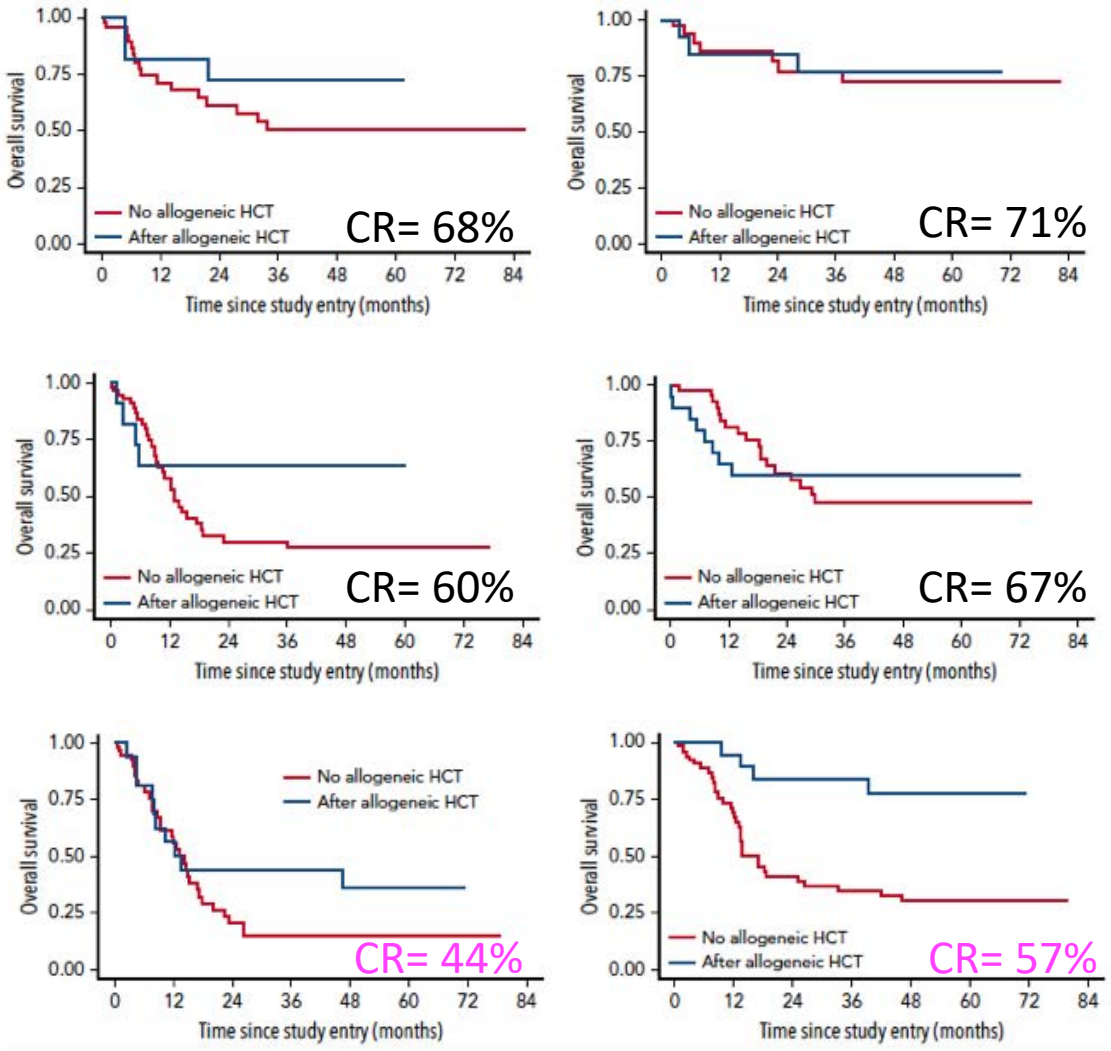
Favorable
NPM1+/low AR

Intermediate:
NPM1+/high AR
Or
NPM1-WT/low AR

Adverse:
NPM1-WT/high AR

Low AR= FLT3-ITD:WT <0.5
High AR= FLT3-ITD:WT ≥0.5

Benefit of transplant vs. consolidation/maintenance

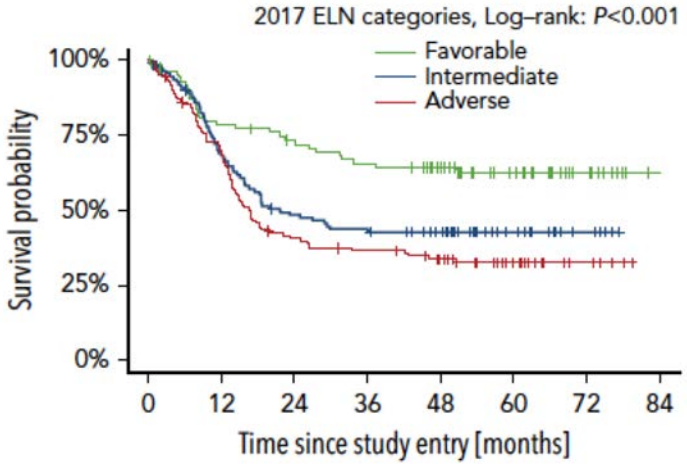


Dohner K, et al. *Blood*. 2020 Jan 30;135(5):371-380

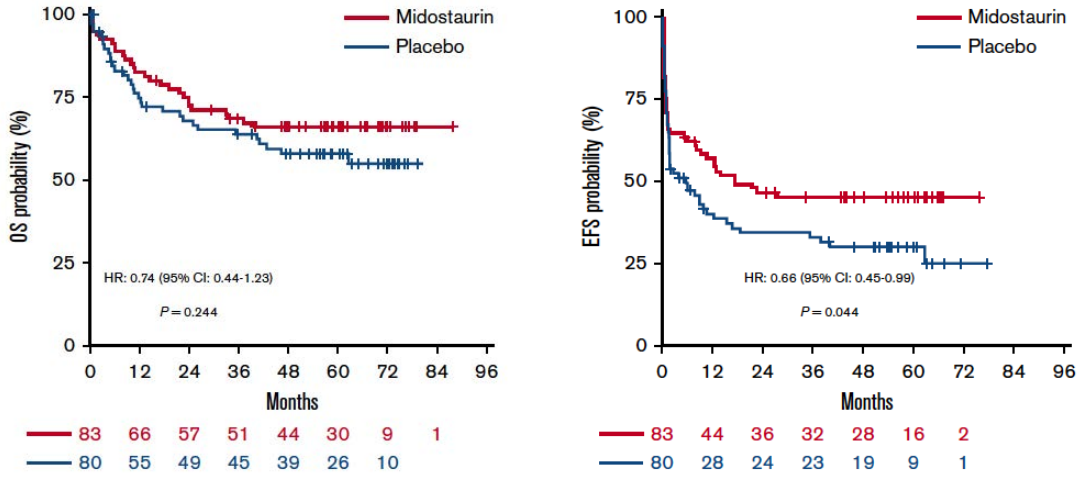
Courtesy of Alexander Perl, MD

RATIFY: FLT3-TKD+ patients

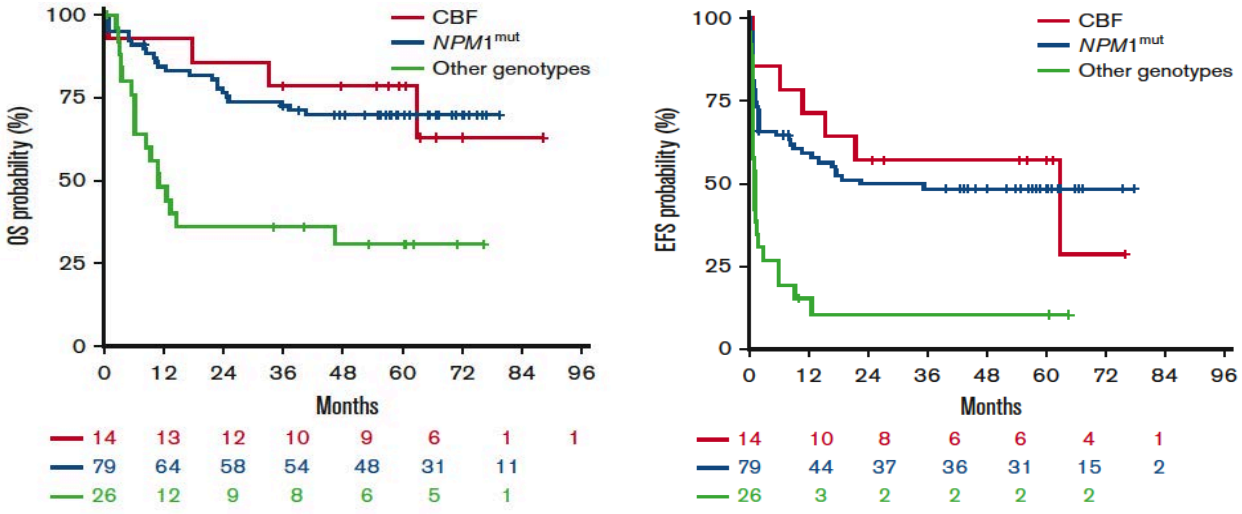
FLT3-ITD+ (both arms)



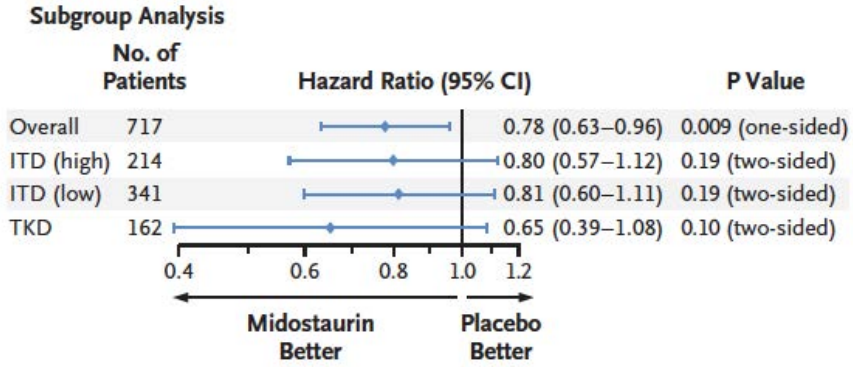
FLT3-TKD+ (by treatment arm)



FLT3-TKD+ (both arms)



Courtesy of Alexander Perl, MD



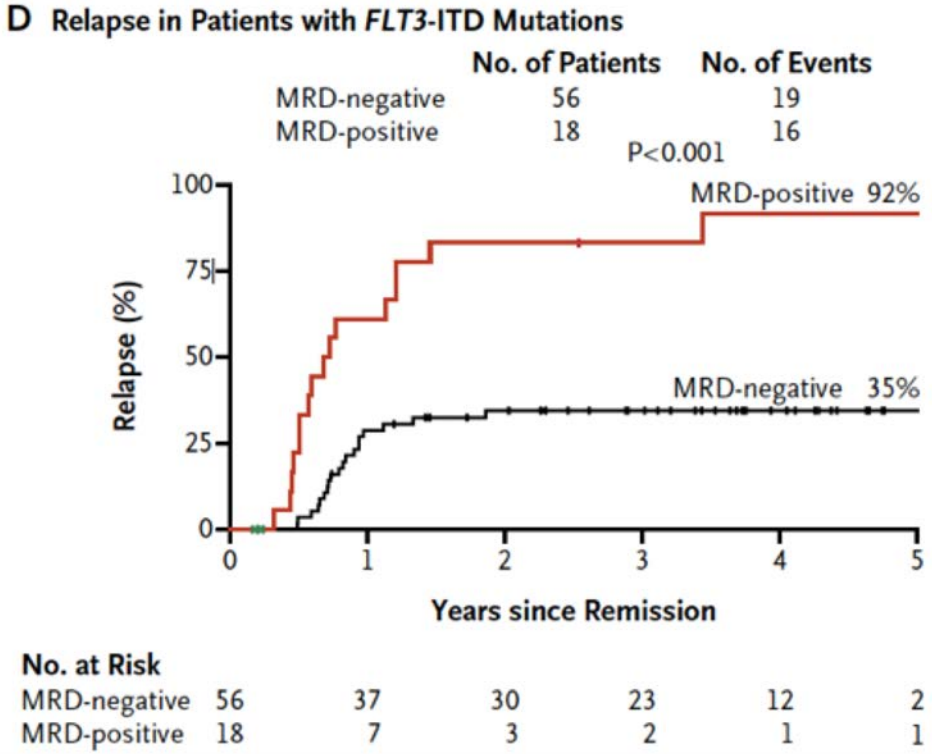
~75% of FLT3-TKD+ on RATIFY were ELN favorable

- 59% NPM1+, 15% CBF+

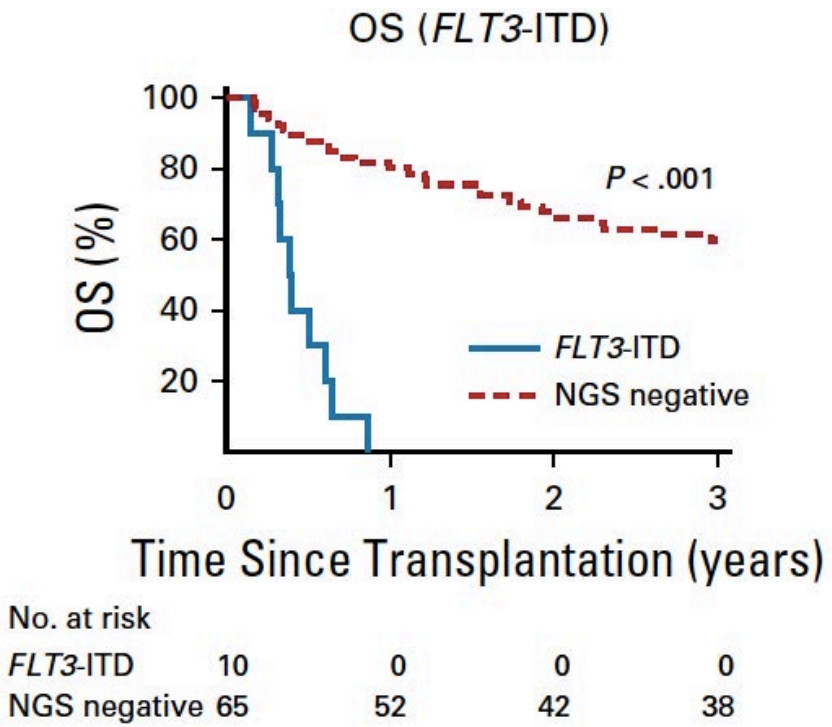
Stone RM, et al. *N Engl J Med*. 2017 Aug 3;377(5):454-464
Dohner K, et al. *Blood*. 2020 Jan 30;135(5):371-380
Voso MT, et al. *Blood Adv.* 2020 Oct 13;4(19):4945-4954

Role of MRD in FLT3-ITD+ AML

FLT3-ITD+ patients: MRD status using peripheral blood RT-PCR for NPM1 mutation after two induction cycles



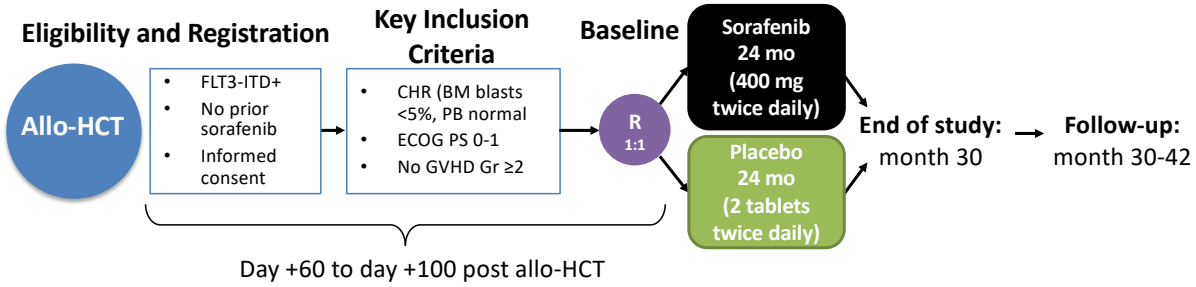
Pre-HSCT peripheral blood FLT3-ITD NGS (cutoff 0.1%)



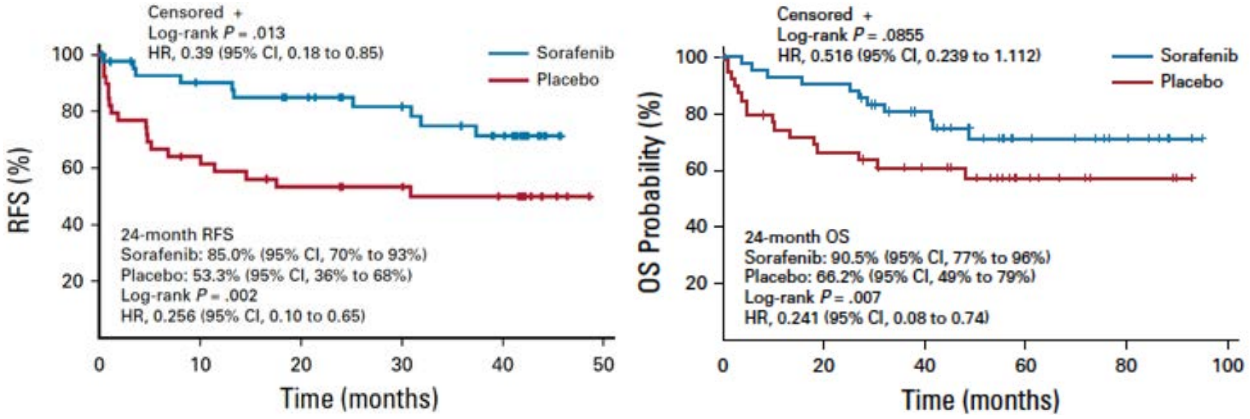
Hourigan CS, et al. *J Clin Oncol.* 2020 Apr 20;38(12):1273-1283.
Ivey A, et al. *N Engl J Med.* 2016 Feb 4;374(5):422-33

Courtesy of Alexander Perl, MD

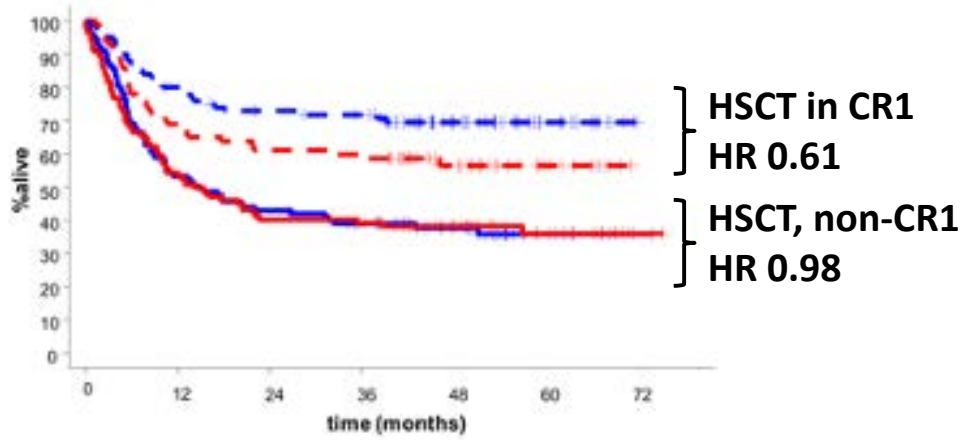
Post-transplant maintenance



SORMAIN



C10603/RATIFY



Potential importance of post-HSCT maintenance

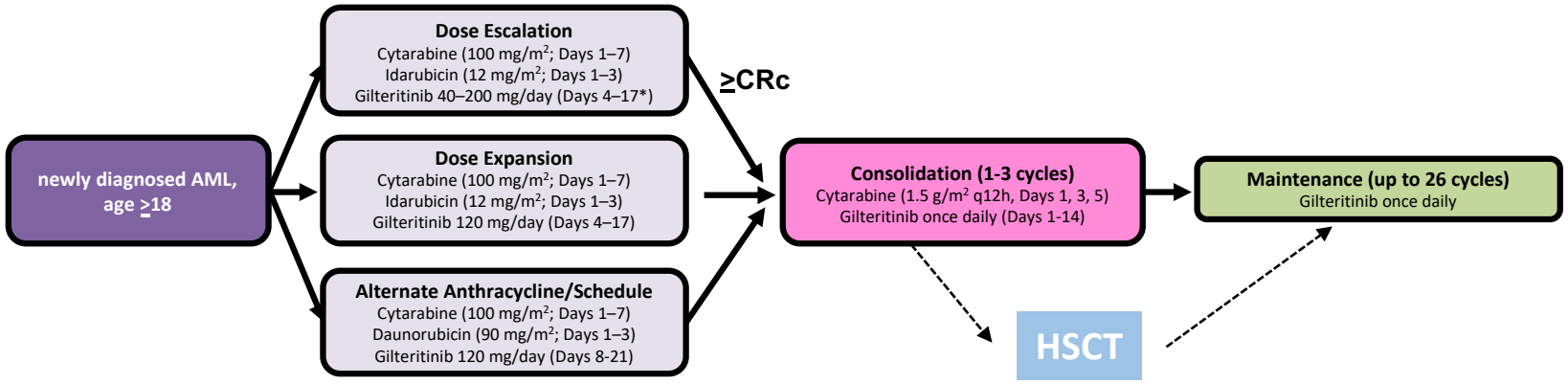
- Sorafenib (vs. placebo) x 2 years post-HSCT improved RFS (n=83)
- Sorafenib (vs. observation) x 6 months post-CR1 HSCT improved RFS and OS (n=227)
- Phase 3 gilteritinib vs. placebo maintenance post-CR1 HSCT has fully enrolled (BMT-CTN 1506/MORPHO, n=346), collected pre-HSCT MRD

Burchert A, et al. *J Clin Oncol.* 2020 Sep 10;38(26):2993-3002
Xuan Y, et al. *Lancet Oncol.* 2020 Sep;21(9):1201-1212
Stone RM, et al. *N Engl J Med.* 2017 Aug 3;377(5):454-464

Courtesy of Alexander Perl, MD

Newer FLT3 inhibitors in frontline intensive therapy?

Combination: gilteritinib + intensive chemotherapy for newly diagnosed FLT3mut+ AML



up to 2 induction cycles permitted; HSCT followed by maintenance allowed without leaving study

Response FLT3^{mut+} (n=33†)	N (%)
CR	22 (66.7)
CRp	1 (3.0)
CRi	8 (24.2)
PR	0
NR	2 (6.1)
CRc‡	31 (93.9)

Trial	Phase (N)	Control	Maintenance	Primary endpoint	status
Quantum-FIRST (quizartinib)[1]	3 (539)	Placebo	1-3 years	EFS, OS	Enrollment complete
ARO-021 (crenolanib)[2]	3 (510)	Midostaurin	1 year	EFS	Ongoing (US)
PrECOG 0905 (gilteritinib)[3]	2 (170)	Midostaurin	None	FLT3^{mut}(-) CRc	Ongoing (US)
HOVON 156 (gilteritinib)[4]	3 (768)	Midostaurin	1 year	EFS	Ongoing (Europe)

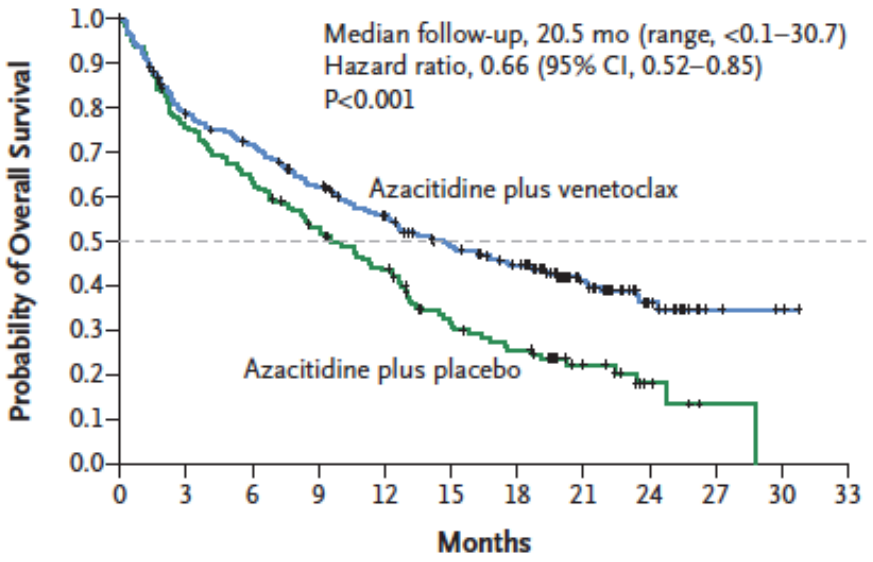
Pratz KW, et al. *Blood* 2018; 132 (Supplement 1): 564

Courtesy of Alexander Perl, MD

1. NCT02668653
2. NCT03258931
3. NCT03836209
4. NCT04027309

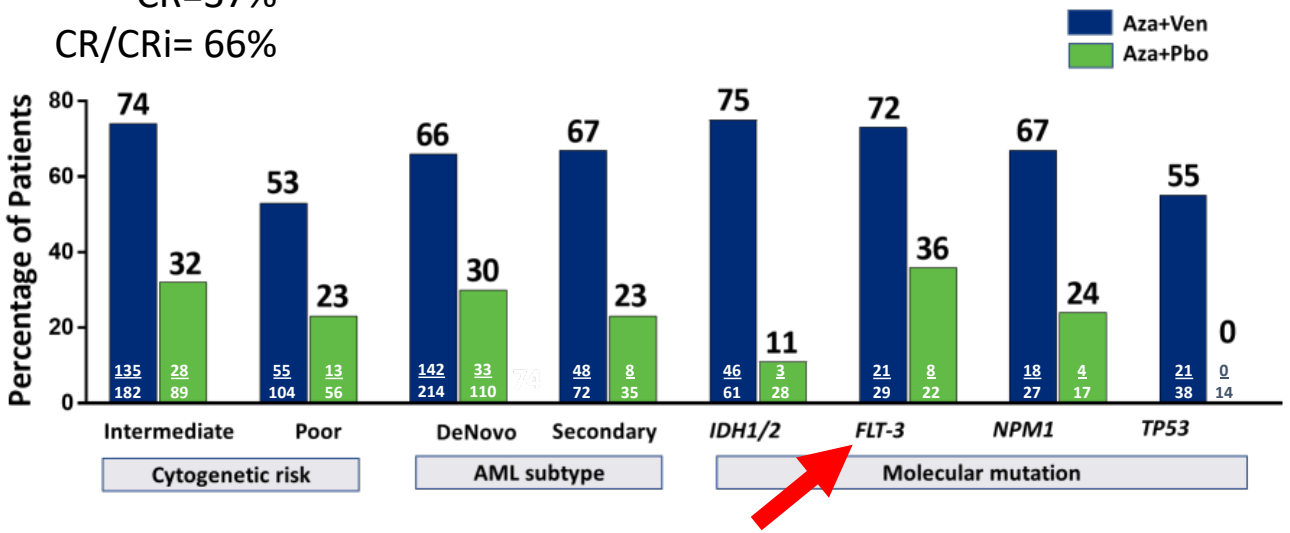
VIALE-A Response Rates (CR+CRi) by Subgroups

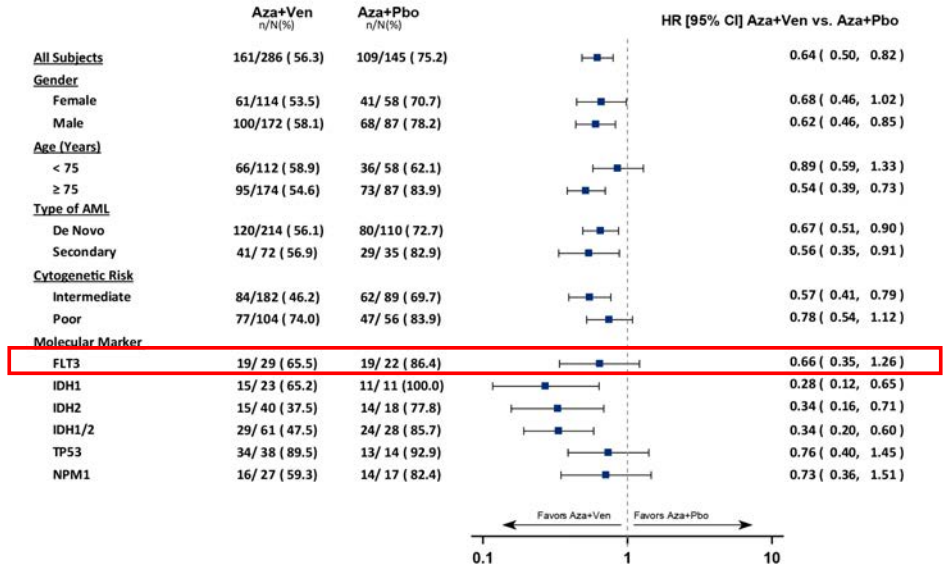
AZA + venetoclax vs. AZA/placebo



HMA + ven: median OS= 14.7 mo
HMA + PBO: median OS=9.6 mo

CR=37%
CR/CRi= 66%





Age >60 unfit or age >75 fit/unfit
All non-CBF subtypes, no prior HMA

Courtesy of Alexander Perl, MD

Conclusions

- Therapeutic advances, particularly FLT3 inhibitors, have improved survival for $FLT3^{mut+}$ AML

- Intensively treated patients should receive midostaurin
  - Regardless of karyotype, ITD vs TKD, presence of other mutations, etc.
  - Possible exception: CBF receiving GO or CPX-351 (await safety data)
  - RCTs will clarify if 2nd gen. TKIs (e.g. gilteritinib) are superior to midostaurin in 7+3

- HSCT and/or maintenance still appear important
  - Nearly all my FLT3-ITD+ patients still go to CR1 HSCT
  - Likely some MRD(-) patients do not benefit from CR1 HSCT
  - Until trials mature, post-HSCT maintenance is recommended, esp if still FLT3-ITD+ at time of HSCT

- Unfit patients benefit from venetoclax/azacitidine as frontline therapy
  - Role of frontline FLT3 TKI to be determined

Courtesy of Alexander Perl, MD

Case #1

- 66 YO woman presents with recurrent tonsilitis, arthralgias/bone pain, and fevers over 2 months
- Labs:
  - WBC= 15K, monocytes/promonocytes 19%, dysplastic PMNs
  - Hgb= 6.7
  - Plts= 66
  - Normal cardiac, hepatic, and renal function.
- Admitted for transfusions and IV abx. No drainable abscess
- BMBx: read as CMML-2:
  - hypercelular, with dysplastic erythroid and MKCs, and marked monocytosis, L shifted myeloids.
  - Aspirate: blasts 11% by flow, no manual count done due to hemodilution
  - karyotype 47, XX, +8
  - NGS: mutations in NPM1 (VAF 42%), PTPN11, and FLT3-D835Y (VAF 10%)
- Comorbidities: diabetes, obesity.
- She is retired from work in the pharmaceutical industry, is fit and has an ECOG PS=1

Courtesy of Alexander Perl, MD

Case #1

What should her treatment be?

A) Azacitidine
B) Venetoclax + azacitidine
C) Azacitidine + midostaurin
D) CPX-351 followed by transplant
E) 7 + 3 + midostaurin

Courtesy of Alexander Perl, MD

Case 1 continued

- Marrow re-aspirated, showing 22% blasts:
  - a diagnosis of AML with mutated NPM1 is made
  - I recommend treating patients with a *de novo,* fulminant presentation of “MDS” but NPM1 mutation be treated as de novo AML, regardless of blast %
- She is induced with daunorubicin, cytarabine, and midostaurin
  - She enters CR1 with first cycle
  - NPM1 remains detectable by quant NGS in CR
  - Consolidated with Cytarabine 1500 mg/m2 q12h x 6 doses with midostaurin
  - NPM1 is undetectable after first consolidation cycle ($<1 \times 10^{-4}$)
- 3 cycles of consolidation are planned (ongoing)
  - She is risk-averse to transplant consideration; we will consider oral azacitidine post-consolidation

Courtesy of Alexander Perl, MD

Montalban-Bravo G, et al. *Blood Adv.* 2019 Mar 26;3(6):922-933

Case 2

- 53 YO previously well woman presents (in early 2017) with progressive DOE of 2 weeks duration
  - laboratory tests show hyperleukocytosis (WBC= 301K) with >95% blasts and she is leukapheresed
- Marrow biopsy diagnoses her with AML with myelodysplasia-related changes
  - Karyotype: 46,XX,i(17)(q10)
  - PCR: FLT3-ITD+ (ITD:WT allelic ratio: 0.5), no other mutations on 68 gene NGS panel
- She is induced with 7 + 3 but is refractory after two cycles, genetics unchanged from dx.
- She enrolls on a phase 3 clinical trial of a FLT3 inhibitor vs. standard chemotherapy
  - randomizes to control arm and does not respond
- She receives sorafenib and azacitidine
  - peripheral blasts clear and marrow blasts decrease to <10% after two cycles.
  - FLT3-ITD remains detectable by PCR
- She undergoes a myeloablative HSCT from her HLA-identical sibling.
  - she tolerates transplant well, engrafts with full donor chimerism, and has no detectable FLT3-ITD in marrow
  - She is started on post-HSCT sorafenib maintenance on day +50.

Courtesy of Alexander Perl, MD

Case 2 (continued)

- 2 Years post-HSCT, she has developed cGHVD for which she undergoes a pulse and taper of prednisone and photopheresis
  - Unfortunately, her leukemia then relapses, while still on sorafenib
  - FLT3 PCR testing shows her relapse is again FLT3-ITD+, without FLT3-D835

- What should her therapy be?
- Would any testing alter this recommendation?

Courtesy of Alexander Perl, MD

Case 2 (continued)

- Resistance to FLT3 inhibitors can be from several causes
  - Immunologic/loss of GVL
  - Clonal evolution with new on-target mutations (e.g. FLT3-D835 on sorafenib; FLT3-F691L on gilteritinib)
  - Clonal evolution with new off-target mutations (e.g. ras pathway)
  - Selection for FLT3-WT clones

- Therapy for cases with prior TKI is uncertain
  - Only 12% of patients on ADMIRAL had prior TKI
  - Ras pathway mutations commonly emerge at gilteritinib progression
  - If Ras pathway mutations were present at study gilteritinib remained active

- This patient enrolled on a clinical trial of venetoclax + gilteritinib and entered CR2.
  - She remains on study therapy at 14 months duration without relapse and with full donor chimerism

Courtesy of Alexander Perl, MD

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