ManagingAML

The Evolving Standard of Care in AML: FLT3 Inhibitors

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Welcome to *Managing AML*. I am Dr. Alexander Perl. Today I will review the evolving standard of care in AML, specifically FLT3 inhibitors. In this presentation, I will summarize the diagnosis and prognosis of FLT3 mutated AML, the role of FLT3 inhibitors in the treatment of patients with this mutation, outline the efficacy and safety amongst current and emerging FLT3 inhibitors for the treatment of AML, and incorporate individual patient and treatment-related factors into decision-making processes for patients with AML.

Speaker Disclosure

- **Consultant:** Arog Pharmaceuticals, Inc., Asana BioSciences, LLC., Astellas Pharma US, Inc., Daiichi Sankyo, Inc., Novartis AG, and NewLink Genetics Corporation

- **Off-label discussion:** Use of sorafenib in AML

These are my disclosures.

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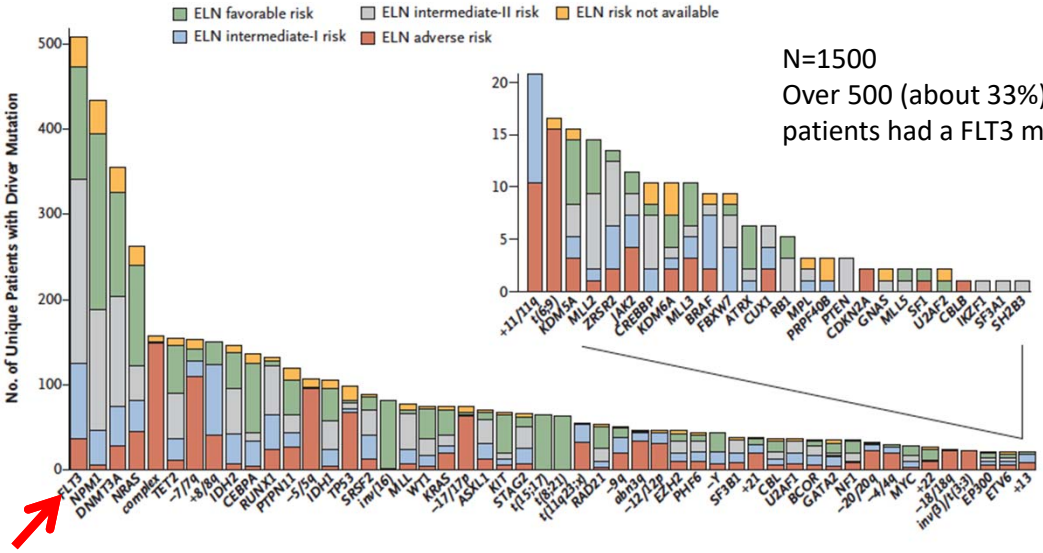
Gene Mutations in AML



Papaemmanuil E, et al. *N Engl J Med.* 2016;374(23):2209-2221.

The first thing to know about FLT3 mutations in AML is that they are quite common. Indeed, FLT3 is the most commonly mutated gene in AML. We see this from a very large-scale genomic study done in Germany by Elli Papaemmanuil of Memorial Sloan Kettering where she looked across the genome at every mutation mutated in AML and looked to sequence all of these genes in a large dataset of over 1500 patients. Over 500 of these or about a third of the patients had mutations in FLT3.

Clinical Importance of FLT3 Mutations

- FLT3 mutations are common
  - Incidence ~33% of AML
  - High WBC, high marrow blast %
  - Two major types of mutations (ITD and D835)
  - Often intermediate risk karyotype (with either NPM1 or DNMT3A mutation, or both)
- FLT3-ITD mutations are prognostic
  - Excellent CR rates, but high relapse rates
  - Transplant reduces relapse rate
- New therapies for patients with FLT3 mutations improve survival
  - Multi-kinase inhibitor midostaurin (approved)
  - Selective FLT3 inhibitors (under FDA review)

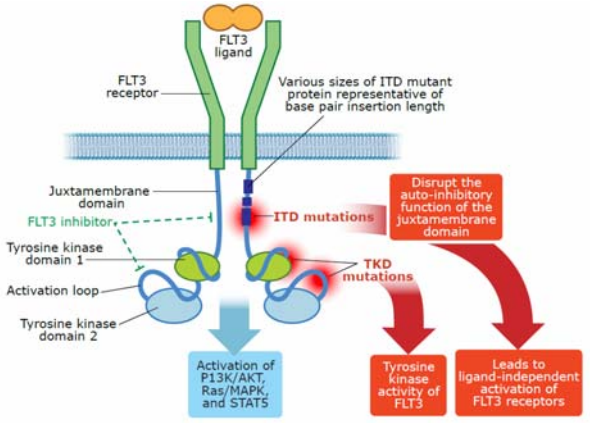


Figure courtesy of Ashkan Emadi, MD, PhD

Papaemmanuil E, et al. *N Engl J Med*. 2016;374(23):2209-2221.; Thiede C, et al. *Blood*. 2002;99(12):4326-4335.; Brunet S, et al. *J Clin Oncol*. 2012;30(7):735-741.; Stone RM, et al. *N Engl J Med*. 2017;377(5):454-464.; Cortes JE, et al. EHA 2018. Abstract LB2600.

We know that FLT3 mutations occur largely in two flavors. One are internal tandem duplication mutations shown in the cartoon diagram on the right which occur in about 20% or 21% of patients with AML who are newly diagnosed, and an additional 10% of patients will have an activation loop mutation in the tyrosine kinase domain, often at the residue D835. These two different mutations have a common clinical phenotype which is that these patients often, though not always, present with very high white blood cell count, and their bone marrows often have a high blast percentage. The two different mutations have differing prognostic effects, which I will show you in a minute, where FLT3-ITD mutations are generally considered more sinister and have particularly high relapse rates. If we look at the karyotypes of patients with FLT3 mutations, they usually fall into the intermediate risk group. They often will have a normal karyotype and they are commonly seen in patients who have either NPM1 mutations, DNMT3A mutations, or both mutations.

Now, in terms of clinical effects, what FLT3 mutations do is they increase the relapse rate, in particular FLT3-ITD mutations increase relapse rates. The complete remission rates to induction chemotherapy for patients with FLT3 mutations are actually quite good and are largely not affected by the presence of the mutation if you look at patients by their karyotype. But unfortunately, if these relapses occur, they tend to occur early in the course of therapy, so patients may go into remission for only a few weeks or a few months, fall out of remission and because of the short first remission duration often do not respond well to salvage chemotherapy at that point, and at least a very poor survival for patients with FLT3-ITD mutations. For this reason, because we know functionally FLT3 is a receptor tyrosine kinase, it activates downstream signaling that promotes the growth of leukemic cells, impairs their differentiation and contributes to their survival even in the context to chemotherapy. An inhibitor of FLT3 kinase might be very desirable and drugs that targeted FLT3 have been in development for approximately 15 years. Recently drugs that inhibited FLT3 as multi-kinase inhibitors were approved — importantly the drug midostaurin was approved last year for the therapy of patients with FLT3 mutations in combination with intensive daunorubicin and Ara-C based chemotherapy. And more selective and more potent FLT3 inhibitors have been developed since that time to really maximize the effects of inhibiting FLT3.

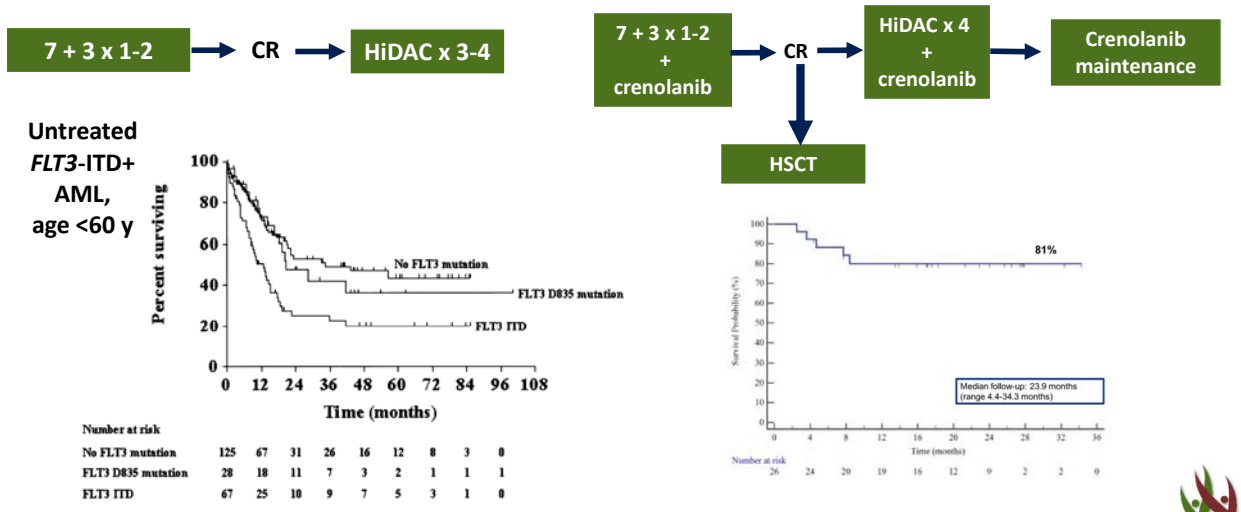
Diagnosis of FLT3 Mutations

- Polymerase chain reaction (PCR)
  - More rapid, results return in few days
  - Detects both ITD and D835
  - ? role for ITD:WT allelic ratio among patients with NPM1 mutation
- Next-generation sequencing (NGS)
  - Time consuming, results can take several weeks
  - Can miss large ITD inserts, allele burden unreliable
  - Detects FLT3 mutations other than ITD or D835
  - Detects other gene mutations (eg, NPM1, DNMT3A, IDH1/2, TP53, etc.)
- Both tests require myeloblasts

How do we diagnose FLT3 mutations? Well, there really are several different approaches, but most commonly we use PCR or polymerase chain reaction or next-generation sequencing or NGS. These two tests are commonly done at diagnosis, but really you do want to do both studies, not one or the other. There are reasons for this. The PCR is advantageous because we get the fastest result and it may be actually more sensitive at picking up FLT3-ITD mutations which can be missed by some next-generation sequencing panels. The PCR is also faster at getting us a result, and we know from the study that showed that midostaurin's addition to induction chemotherapy improve survival that you want to get an answer pretty quickly. On that study, patients were treated with midostaurin on day 8 of therapy and were given 14 days of treatment. One problem with the next-generation sequencing is that the results may not come out for three weeks, and thus, the window to treat the patient during induction may be lost, and again, there is a survival benefit to adding midostaurin early in therapy. You do not want to miss that window. I recommend sending PCR even if you are sending next-generation sequencing. It is helpful later on to know that the FLT3 mutation is there on the odd chance that a low level FLT3-ITD might be missed by PCR and picked by next-generation sequencing. We sometimes do see that. And one advantage of next-generation sequencing panels is we can see the whole complement of different mutations in the leukemia, not just FLT3 itself, and that can give us important prognostic information and might help inform other therapies that we might want to add at some point, such as IDH mutations, or give us useful information that might help us make a transplant versus consolidation chemotherapy for post-remission therapy. This test can be very helpful in that regard.

Now, importantly both of these tests require myeloblasts. Next-generation sequencing can pick up mutations in cells that are either immature or mature, but one problem with it and PCR is the FLT3 mutations may show up only in the blasts and maybe even only in a subset of the blast because FLT3 we think of as being a late mutation in the process of leukemogenesis. We see patients who have FLT3 mutations in perhaps only 10% of their blasts, and if there is a wild type and a mutant type, we might be down at the very lowest levels of sensitivity in a patient who had 20% blasts in the bone marrow. For this reason, a negative result on a FLT3 testing if it did not actually have at least 10% blast in the sample cannot really be trusted. We want to make sure that the samples that are tested have enough blasts to detect a mutation if it is really there.

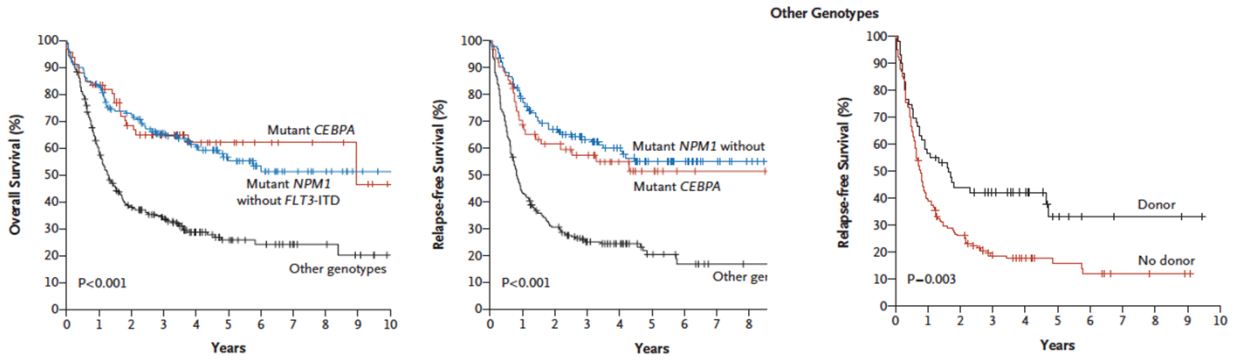
Progress for FLT3 Mutated AML



HiDAC=high-dose AraC; HSCT=hematopoietic stem cell transplant
Fröhling S, et al. *Blood*. 2002;100:4372-4380.; Walter RB, et al. EHA 2018. Abstract PF227.

Over the years we have seen — as I have mentioned that patients who have FLT3 mutations had worst survival than patients without these mutations, and it was particularly true for FLT3-ITD mutations which are the bottom curve as shown on the left from a study done in Germany in 2002. In that study, patients received 7 and 3 cytarabine and anthracycline for up to two cycles, and then three to four cycles of high dose Ara-C. While that is a standard treatment recommendation for patients before the development of FLT3 inhibitors, we know that these days we see better outcomes. And on the right is a more modern study where patients were given a more modern treatment approach and this included the FLT3 inhibitor crenolanib. And as you can see instead of being a very low curve there for FLT3 mutations, it is really at the top of the survival curve. We know with proper therapy, patients with FLT3 mutations can do very well, but it is important to recognize that you need to diagnose these patients and you need to treat them with these newer drugs to see these kinds of outcomes. And so 7 and 3 followed by high dose Ara-C really is not a good enough therapy anymore for this subset.

Outcome of Normal Karyotype AML

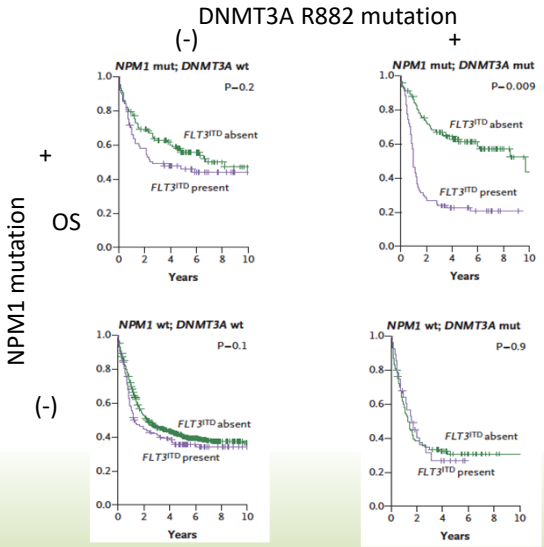


Schlenk RF, et al. *N Engl J Med*. 2008;358(18):1909-1918.

One major advance in the treatment of patients with FLT3 mutations, in particular for FLT3-ITD mutations, is the incorporation of allogeneic transplant in first remission. This was recognized in the mid-2000s, and this study from the AMLSG from Germany published in the *New England Journal of Medicine* by Richard Schlenk shows that patients with certain genotypes and normal karyotype had really much better outcomes than others. In this study, they were trying to highlight the outcomes that were improved in patients who had nucleophosmin mutation or CEBP-alpha mutation in the absence of FLT3-ITD. If you look at all the other genotypes with normal karyotype AML, the have considerably worse outcomes, and if you look at those patients who had a donor versus those without a donor, on this study that allocated 80% of patients to transplant, you can see those with a donor did better. And from this, we infer that FLT3-ITD benefits in terms of survival from allogeneic transplant in first remission because it falls into the black curve at the bottom that is labeled 'Other Genotypes.'

Risk Prognostication in the Era of NGS

- NPM1, DNMT3A, and FLT3-ITD are the three most common gene mutations in AML
  - Complex prognostic interactions
- DNMT3A + FLT3-ITD has poor survival
  - True regardless of NPM1 status
- European classification (ELN) prognosticates from FLT3-ITD allele burden
  - This is neither standardized nor widely available in US



Papaemmanuil E, et al. *N Engl J Med.* 2016;374(23):2209-2221.

We also know from more recent data that the combination of nucleophosmin mutation and FLT3-ITD softens the benefit of an NPM1 mutation significantly, and there is an interaction with DNMT3A R882 mutations. We see all three mutations which again are all quite common in AML here from, again, the study from Elli Papaemmanuil. These are the three most common mutations and they are often commutated in one combination or another; and all the permutations are shown here with the NPM1 mutations on the top row, the DNMT3A mutations on the right column, and every permutation with or without a FLT3 mutation shown within the figures. FLT3-ITD here is the bottom curve on all four figures. But the biggest difference is where we see all three mutations together — that's the top right — where FLT3-ITD, NPM1 and DNMT3A triple mutation has a very poor outcome, as is also true for any combination of DNMT3A and FLT3-ITD.

We know that we get additional information from next-generation sequencing that is better than just testing for an NPM1 mutation or FLT3-ITD which would have been the standard up until recently. So there really is value in adding a next-generation sequencing at diagnosis to help risk stratify patients.

FLT3 Inhibitors

	IC_{50} (medium)	IC_{50} (plasma)
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)

Pratz KW, et al. *Blood.* 2010;115(7):1425-1432.; Zarrinkar PP, et al. *Blood*. 2009;114(14):2984-2992.

I did mention that there are FLT3 inhibitors that have been now approved for therapy, and I want to highlight some of the drugs that have come along in the past decade. First starting with the first generation of FLT3 inhibitors which are the top three shown on this table here, and then show you the kinase activity below. Lestaurtinib, midostaurin and sorafenib came from first generation of drugs that were designed almost as FLT3 inhibitors by accident, not by design, because they inhibited so many kinases as is shown by the kinome-binding assays below which have a kinase inhibition in vitro shown in red for every kinase in the human kinome, and the size of the bubble is proportional to the degree of inhibition by the drug. As you can see lestaurtinib on the very left is quite nonselective and equipotent against many different targets, and this does not actually get a lot of more selective as you go to midostaurin or sorafenib. What we see with the more modern inhibitor quizartinib is that there really is only potent inhibition of a small number of kinases and very few kinases actually light up with this assay. What is also notable about quizartinib is that the amount of effective drug is shown on the right column in terms of its IC50 or inhibition concentration 50% in the plasma which is a better indication of how active these drugs will be in the clinic than whether these drugs work in vitro against leukemia cells that have FLT3 mutations, which is shown on the left column. Quizartinib has substantially more selectivity for FLT3 and much more potency and it is much bioavailable, meaning it is a much better FLT3 inhibitor in patients, and when it inhibits FLT3 it is inhibiting very little else.

First-Generation FLT3 Inhibitors

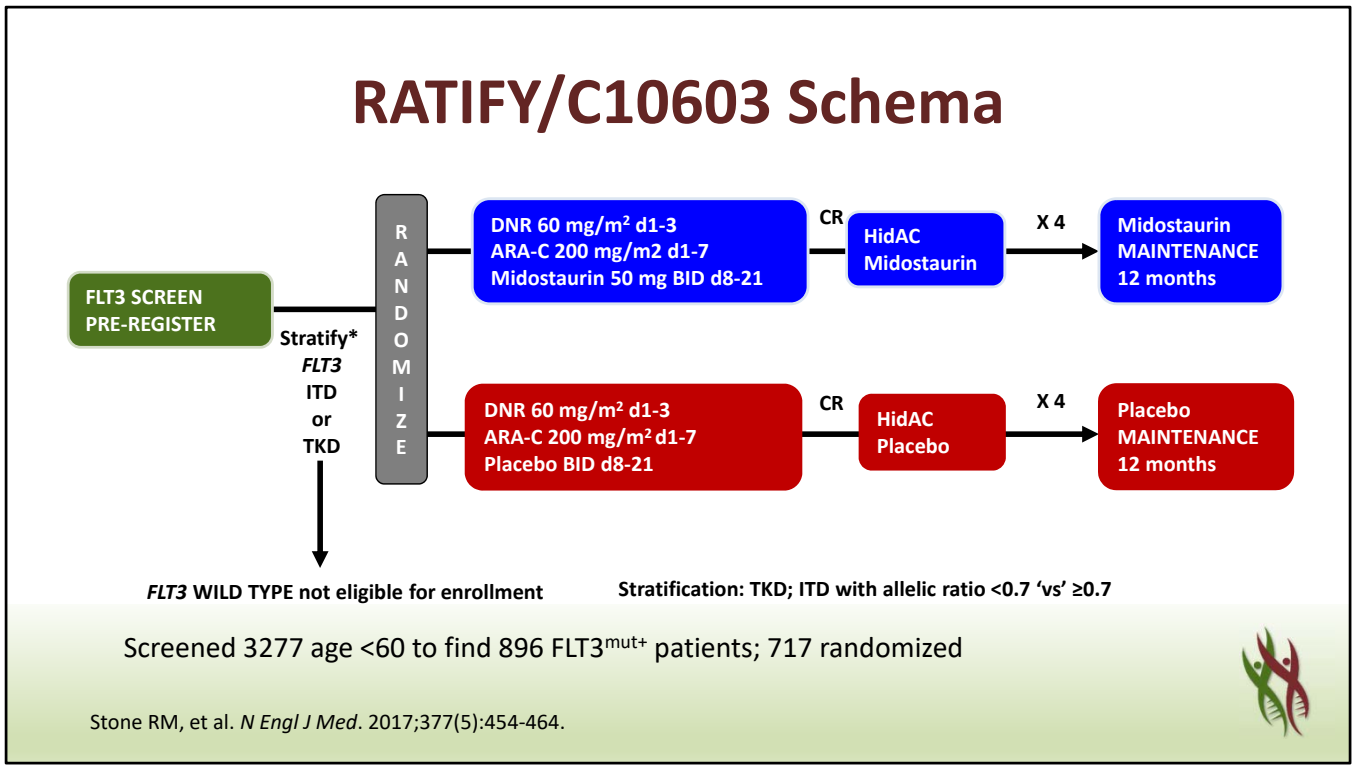
- Modest clinical responses
  - Clearance of peripheral blood or extramedullary blasts
  - Activity in both FLT3 mutated and WT patients
  - Limited/no reduction in marrow blasts
- Quickly moved to combination regimens
  - Midostaurin plus induction chemotherapy
  - Sorafenib plus induction chemo
  - Sorafenib plus azacitidine
  - Of note, while active, sorafenib/aza tolerability has been challenging, especially in unfit patients
    - Cytopenias, fatigue/asthenia, hand/foot, diarrhea, HTN

Sorafenib is not FDA approved for use in patients with AML

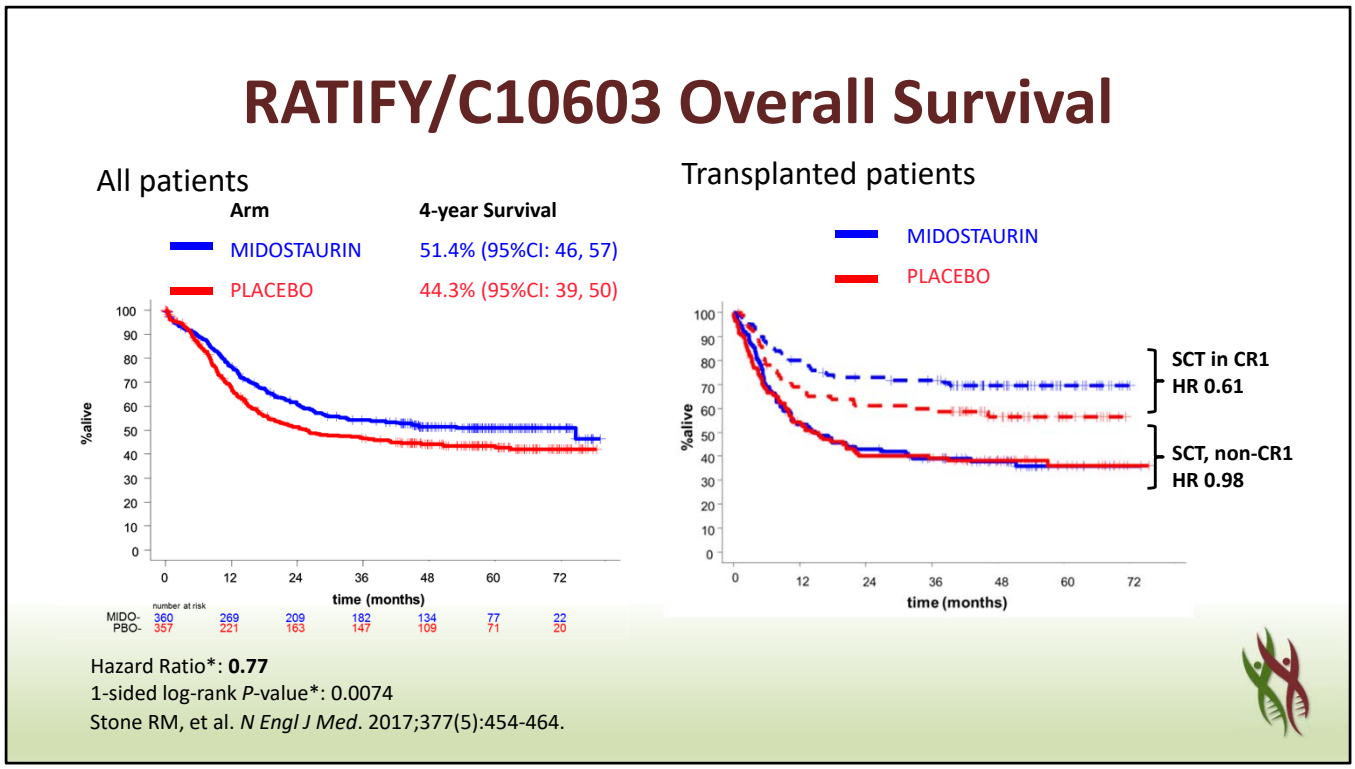
Fischer T, et al. *J Clin Oncol*. 2010;28(28):4339-4345.; Stone RM, et al. *Leukemia*. 2012;26(9):2061-2068.; Röllig C, et al. *Lancet Oncol*. 2015; 16(16):1691-1699.; Ohanian M, et al. *Am J Hematol.* 2018 Jul 20. [Epub ahead of print].; Ravandi F, et al. *Blood*. 2013;121(23):4655-4662.

The first-generation FLT3 inhibitors when they were tested in patients had really modest clinical responses. They would lead to reductions or clearance of peripheral blood blasts or extramedullary blasts, but we would do bone marrow biopsies on these patients and see relatively little change from pretreatment to on-the-drug even if the patients had no evidence of circulating leukemia. We could not use these responses as a single agent to bridge to a transplant or expect that the patient would get really durable response, and indeed, these patients typically would grow through these drugs within a matter of a few weeks to maybe a month or two. Those drugs were quickly moved to combination regimens, and there they were much more successful. I have already alluded to the data with midostaurin which improved overall survival. Sorafenib plus induction chemotherapy has been shown to improve event-free survival, though not overall survival, and sorafenib plus azacytidine has been shown to be a tolerable regimen in patients who are unfit for induction chemotherapy or for patients who relapse who do not have other options. So those are uses of first-generation inhibitors that we think give patients potentially clinical benefit, and note importantly that none of these are single agent use of the first-generation inhibitor.

The Evolving Standard of Care in AML: FLT3 Inhibitors



I am going to move on to the RATIFY study which was the pivotal trial of midostaurin, the schema of which is shown here. This was a really monumental study that was done internationally and led by the CALGB Cooperative Group, really all the three US cooperative groups as well as a large number of patients enrolled in Europe. And this study screened newly diagnosed patients from ages 18 to 60 who had a diagnosis of AML but were of unknown FLT3 mutation status. Patients had a diagnostic bone marrow sent and within 48 hours were told whether they had a FLT3-ITD or TKD mutation and thus would be eligible to be randomized. From 3277 patients, they found almost 900 patients with FLT3 mutations and randomized 717 of these patients. We do not have any outcome data on the almost 200 patients who did not undergo randomization, but nonetheless had the target mutation. But we do have data on the 717 who were randomized to either 7 and 3 using daunorubicin, Ara-C and midostaurin, or daunorubicin, Ara-C and a placebo. Patients who entered remission after one to two cycles of this induction went on to receive up to four cycles of high dose Ara-C with either the midostaurin or placebo that had been assigned from the randomization, and then a year of maintenance with again the same drug as single agent. And these are the outcomes from the study.



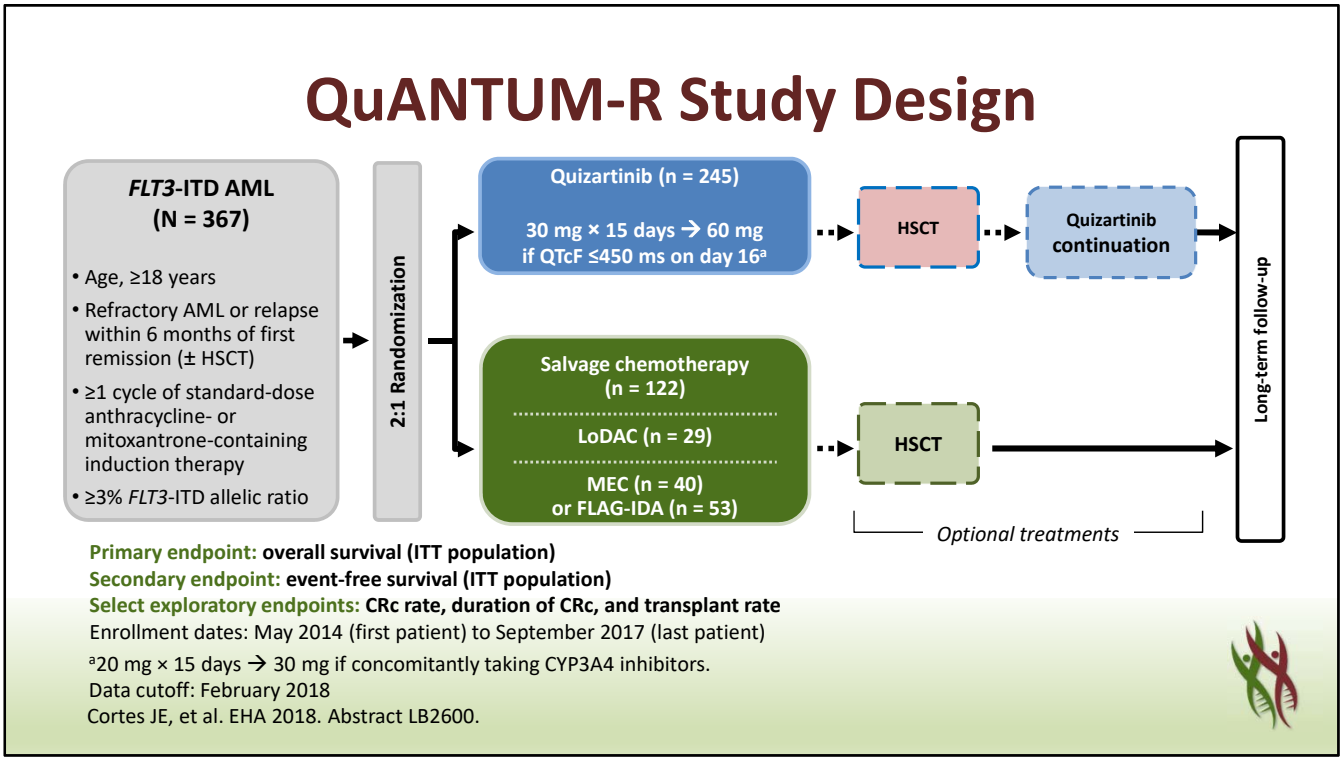
Midostaurin therapy was associated with a 7% overall survival or 22% relative increase in overall survival compared to placebo which was highly statistically significantly improved. And notably, patients who went from diagnosis to remission to transplant in first remission showed a sustained benefit from the prior midostaurin therapy, even though these patients did not receive midostaurin maintenance, which suggested the quality of therapeutic response may be actually better in the midostaurin treated group if these patients went to transplant in first remission. This is an important advance and really the first time that a third drug has been shown to add to the overall survival of 7 and 3 therapy after about 40 years of clinical trials. This was an important advance in the field and really improved outcomes for patients with FLT3 mutations who now see fewer relapses with the addition of midostaurin therapy. There are some caveats to these data, however. First is, as I noted, we do not know what happened to the 200 patients who could not be randomized, and it is possible there is a subset that does not see this benefit or perhaps the benefit is even greater in those patients, but they could not be enrolled on. We also do not know whether we can extrapolate this data to older patients, although importantly the drug was approved for the treatment of FLT3 mutated AML without an age range, and so it is allowed to be used for that purpose on label. And then lastly, we do not know whether this could be improved by a newer drug that has either more potency against FLT3 or more selectivity, but that is currently being tested.

Newer FLT3 Inhibitors

Drug	Half life (dosing)	D835 activity	Selectivity	Single agent Relapse/refractory	Toxicities (mostly grade 1/2)
Quizartinib (AC220)	Long (once daily)	No	Narrow, inhibits KIT	Phase 3 completed: Quizartinib improves OS compared to investigator's choice salvage chemo	Myelosuppression Dysgeusia QT prolongation[1, 2]
Crenolanib	Short (TID)	Yes	Narrow, spares KIT	N/A (Phase 3 with chemo ongoing)	Fluid retention LFT elevation Nausea/vomiting[3]
Gilteritinib (ASP2215)	Long (once daily)	Yes	Narrow spares KIT	Phase 3 enrollment complete, results expected late 2018	Myelosuppression LFT elevation Diarrhea[4]

[1]Cortes JE, et al. *Lancet Oncol*. 2018;19(7):889-903.; [2]Cortes JE, et al. *Blood*. 2018;132(6):598-607. [3]Cortes, JE, et al. ASCO 2016. Abstract 7008. [4]Perl AE, et al. *Lancet Oncol*. 2017;18(8):1061-1075.

So what are those drugs? I have mentioned quizartinib, crenolanib, and gilteritinib are newer drugs that have been developed because of their greater potency both in vitro and also in vivo in terms of inhibiting FLT3 kinase. They differ in terms of their pharmacokinetic properties, with quizartinib and gilteritinib being given once daily and crenolanib being given three times a day. They also differ in terms of their activity against FLT3-ITD and D835 where all the drugs inhibit FLT3-ITD, but only crenolanib and gilteritinib inhibit FLT3 D835 tyrosine kinase domain mutations. There is some selectivity for KIT amongst quizartinib which may contribute to myelosuppression. This is less prominent with the other two drugs, and all of these have either completed phase 3 development in relapsed patients or about to undergo phase 3 development. The toxicity of these drugs are largely overlapping in that they are generally easy drugs to take as a single agent. They all can have some GI disturbances, either dysgeusia, some nausea, and perhaps some diarrhea, and that varies a little bit from drug to drug. One important thing to note with quizartinib, and this was particularly true when the drug was first developed at much higher doses, is that the drug could cause QT prolongation in a significant number of patients. For this reason, further development of quizartinib was done at much lower doses and that side effect seems to be largely eliminated, though it still requires monitoring. The other drugs do have side effects, but I would not say any of these are really limiting or require very close monitoring during therapy.



As I have mentioned, quizartinib is undergoing phase 3 development and quizartinib as a single agent has already completed a study in which it was used as a single agent to treat patients with relapsed FLT3-ITD positive AML, and that study was just released in terms of its impact upon overall survival, and the study was indeed positive. The study called the QuANTUM-R Study tested the addition of quizartinib as a single agent in comparison to investigators' choice of one of three salvage chemotherapy regimens in patients who had FLT3-ITD positive AML that had relapsed within six months of initial remission. Patients could have received a prior transplant as well and remained still eligible for the study. These patients were randomized at study entry to either quizartinib 2 to 1 or the salvage chemotherapy, and they had to be treated with whatever was selected as the optimal salvage regimen for the patient if they were randomized to the chemotherapy arm. Patients who responded to quizartinib and went to transplant could go back on the quizartinib as maintenance and then were followed for survival thereafter.

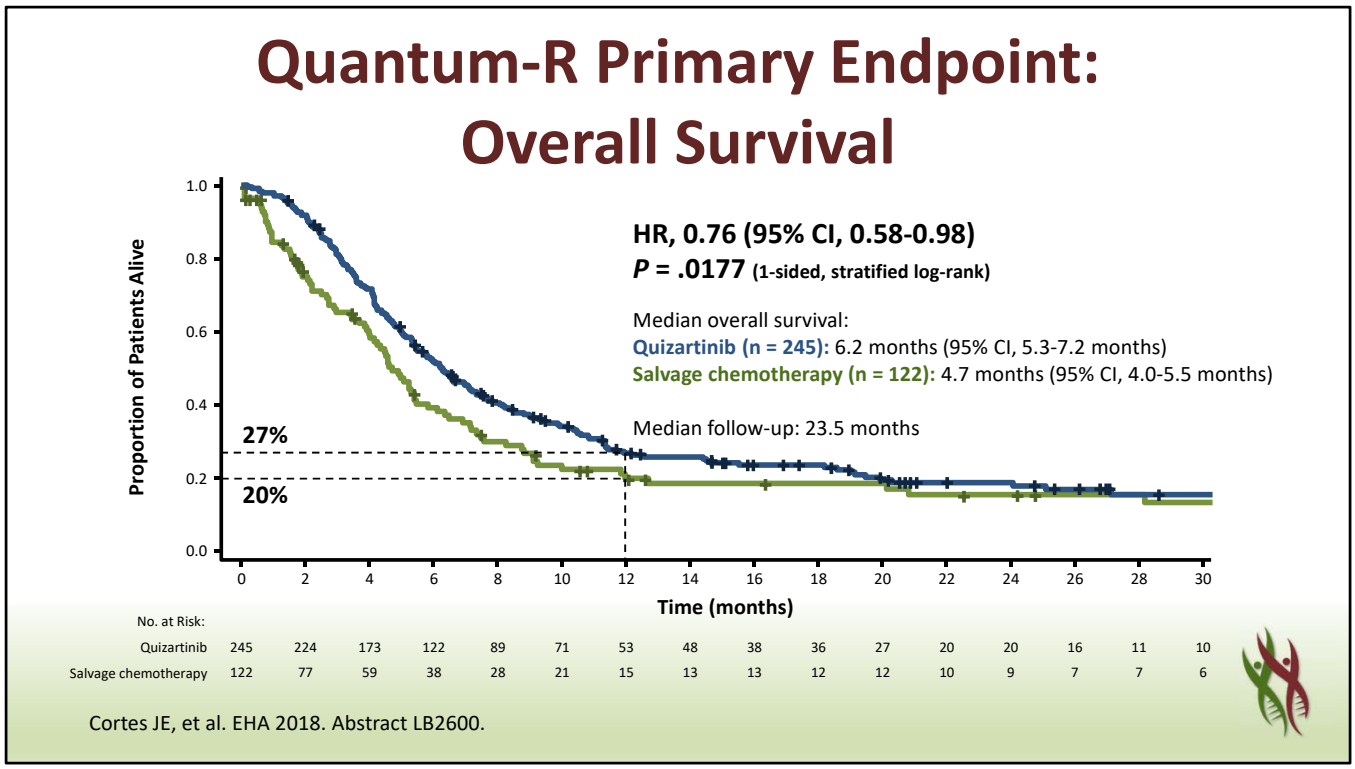
QuANTUM-R Responses

Best response	Percentage (95% CI)	
	Quizartinib n = 245	Salvage Chemotherapy n = 122
CRc[a]	48 (42-55)	27 (19-36)
CR	4 (2-7)	1 (0-5)
CRp	4 (2-7)	0 (0-3)
CRi	40 (34-47)	26 (19-35)
PR	21 (16-27)	3 (1-8)
ORR (CRc + PR)	69 (63-75)	30 (22-39)
No response	25 (20-31)	37 (28-46)
Non-evaluable	5 (3-9)	33 (25-42)

[a]Nominal *P* = .0001 for between-group comparison of CRc

Duration of CRc: quizartinib 12 weeks; salvage chemo 5 weeks
HSCT rate: quizartinib 32%; salvage chemo 12%
QT prolongation >500 ms: quizartinib 3%; salvage chemo 0
Cortes JE, et al. EHA 2018. Abstract LB2600.

This study results were recently presented as a plenary session at the EHA meeting in 2018 and we see the results here in terms of secondary endpoint of complete remissions which were substantially higher in the quizartinib arm than in the salvage chemotherapy arm with about twice as many composite CR responses. And I would note that the number of true complete remissions was low in both arms. This is a very high-risk group. What we see is actually more commonly a complete remission with incomplete count recovery in either of these treatment approaches, but twice as many of those responses were seen in the quizartinib arm as in the salvage chemotherapy arm.



And the overall survival, which was the primary endpoint, was also statistically significantly improved by the quizartinib arm with 27% of patients alive at a year from randomization as compared to 20% in the chemotherapy arm. Quizartinib as therapy for relapse or refractory AML improves the survival of FLT3-ITD positive patients.

Clinical Quizartinib Resistance

Table 1 | Summary of FLT3 kinase domain mutations in patients relapsed on AC220

Subject number	Sex	Age (years)	Prior therapy	Karyotype at enrolment	Karyotype at relapse	Blasts in relapse sample (%)	New mutation at relapse	ITD$^+$ clones with mutation	Weeks on study
1009-003	F	75	7+3	45~54,XX,+3,+6,+7, +8,+13,+14,+21, +22[cp15]/46,XX[5]	52,XX,+3,+6,+7,+8, +10,+12,+13[cp7]/46, XX[14]	90	D835F	6/15	12
1011-006	M	70	7+3, low-dose cytarabine	Normal	ND	10	D835Y	4/15	8
1011-007	F	56	7+3, HAM	Normal	46,XX,del(11) (p?13p?15) [12]/46,XX[9]	80	F691L D835V	4/24 5/24	11
1005-004	F	60	Cytarabine and mitoxantrone	Normal	Normal	92	F691L	9/22	19
1005-006	M	43	7+3, MEC, allogeneic stem cell transplant	6,XY,t(1;15)(p22;q15)	ND	59	D835Y	8/17	6
1005-007	F	59	7+3, HDAC	Normal	ND	39	D835V	9/21	23
1005-009	M	68	Cytarabine and mitoxantrone	Normal	ND	58	D835Y	8/14	19
1005-010	M	52	7+3, HDAC, mitoxantrone and etoposide	46,XY,t(4;12)(q26;p11.2), t(8;14)(q13;q11.2)	ND	22	F691L	6/18	20

All patients achieved morphological bone marrow blasts of ≤5% at best response. 7+3, low-dose cytarabine for 7 days plus 3 days anthracycline; HAM, high-dose cytarabine plus mitoxantrone; HDAC, high-dose cytarabine; MEC, mitoxantrone, etoposide, cytarabine. ND, not done.

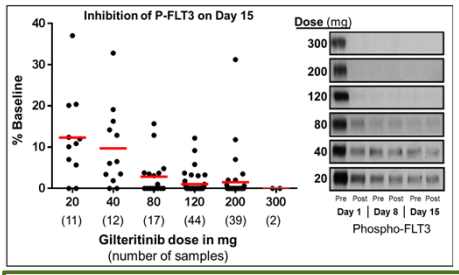
- Acquired FLT3 TKD mutations validate FLT3 inhibition
- Deep sequencing: polyclonal resistance

Smith CC, et al. *Nature.* 2012;485(7397):260-263.

Now, there are some limitations to quizartinib therapy, one of which is as I mentioned is that this is only active against FLT3-ITD mutations. A problem that we see is also that different FLT3 mutations such as those that occur in the tyrosine kinase domain at D835 or at other residues such as F691 can lead to either reactivation of the kinase by the mutation itself or a lack of binding of the drug to inhibit the kinase, again, leading to activation and growth of the leukemia that contains both the FLT3-ITD and then this new mutation. This process is analogous to what we see with resistance to imatinib in CML where in that context a newer drug that inhibits both the target mutation and the resistance mutations is more effective at controlling the disease in patients who have advanced phases of their disease in particular. Obviously, you would want to develop a drug in this setting that would inhibit both FLT3-ITD and also these resistance mutations, and that is where the second generation of drugs were developed that include crenolanib and gilteritinib as these are active against both FLT3-ITD and also these TKD mutations.

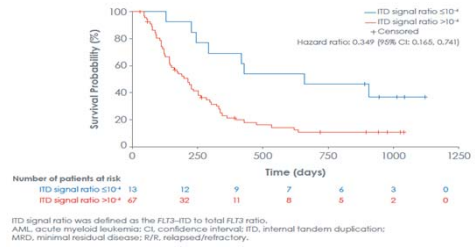
The Evolving Standard of Care in AML: FLT3 Inhibitors

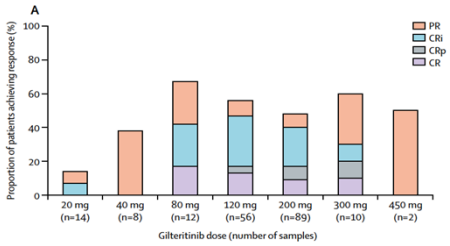
Gilteritinib Pharmacodynamic Effects and Clinical Responses

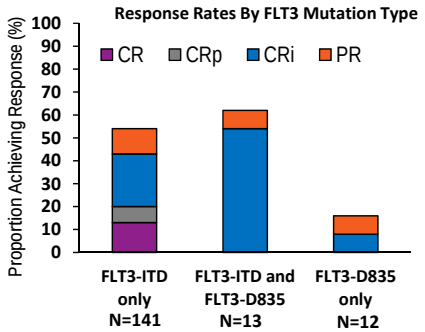


Plasma Inhibitory Activity (PIA) against p-FLT3

Gilteritinib ≥80 mg/day in FLT3^{mut+} Patients
Median OS: 31 weeks (range: 1.7–61 weeks)
Median Duration of Response: 20 weeks (range: 1.1–55 weeks)
Median Time to Best Response: 7.2 weeks (range: 3.7– 52 weeks)







Perl AE, et al. *Lancet Oncol*. 2017;18(8):1061-1075.; Levis MJ, et al. *Blood Adv*. 2018;2(8):825-831.

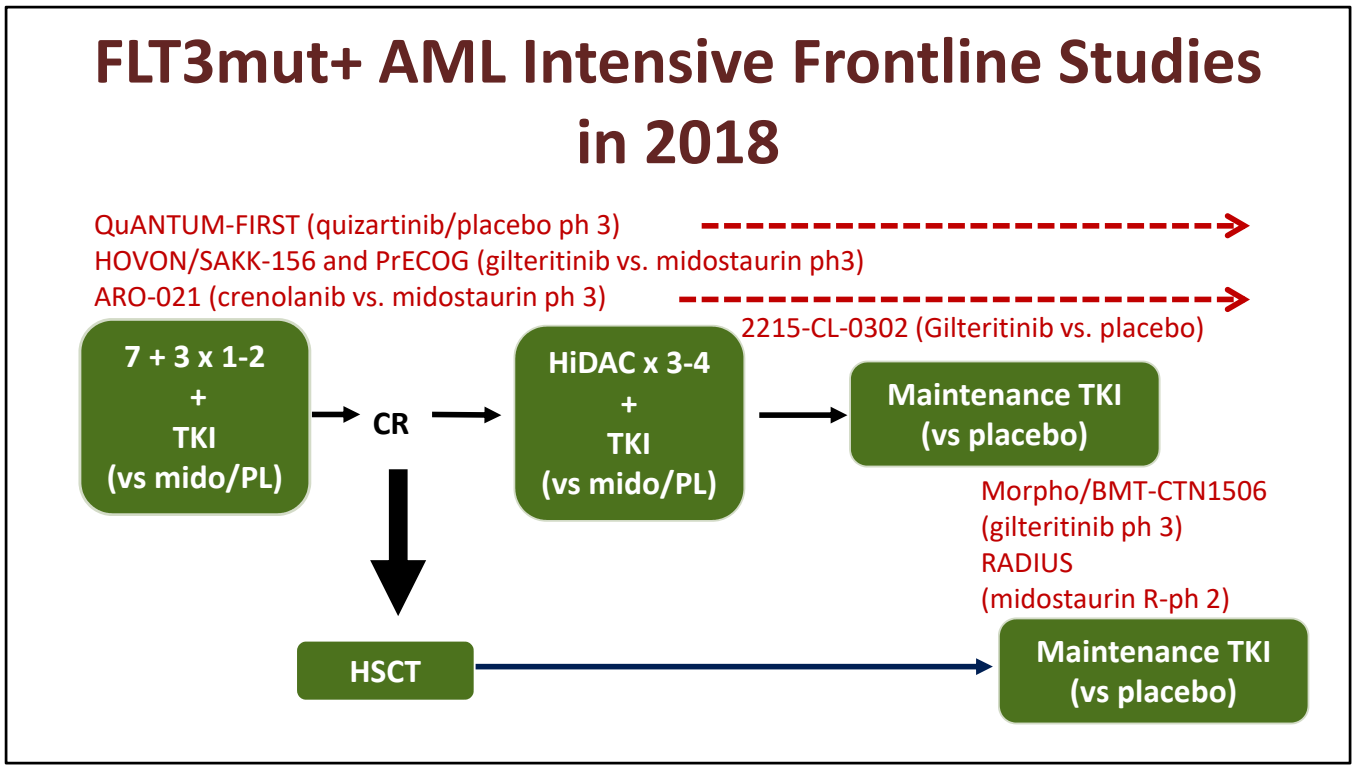
Here is an example of one of these drugs which was recently published called gilteritinib. We see on the left that as we did the phase 1 development of gilteritinib, we got to a dose of 80 mg or higher which completely extinguished FLT3 signaling and that higher doses really did not impair FLT3 signaling any better because it was maximal at that dose and became more consistent in higher doses, and that the response rates paired with the inhibition of target. You see some responses in the lower doses of gilteritinib, but they pretty much hit a plateau at 80 mg and up, and so 120 mg has been the dose that has been developed since that time. And when we look at patients treated at FLT3 inhibitory doses of gilteritinib, not only is there a response rate in about half of the patients with a composite complete remission and about 40% of patients who have FLT3-ITD mutation, but we see an equal number of patients achieve these responses, who have both FLT3-ITD and FLT3 D835 mutation, and again that is the genotype that we see resistance to quizartinib with. Notably patients with the D835 only mutation had a lower response rate with a caveat that this is a small number of patients. We did note that patients who had responses to gilteritinib could induce differentiation of their clone and maintain their FLT3 mutation during response. Some patients also cleared the FLT3 mutation and we could watch this go away during therapy even to very low levels. What is shown at the bottom left is the patients in blue who had clearance of their FLT3-ITD mutation had substantially better survival than patients who did not. It may be that is important in terms of selecting the best responses to FLT3 inhibitor therapy.

Current Regulatory Status of FLT3 Inhibitors

- Midostaurin—APPROVED
  - Frontline in combination with intensive induction/consolidation
  - Also as maintenance in European Union (not FDA approved for this use in US)
- Gilteritinib (ASP2215)—NDA filed, priority review
  - PDUFA: 11/29/2018
  - Phase 3 completed single agent for 1st relapse/refractory AML, FLT3mut+
  - OS read out: late 2018 (co-primary endpoint)
- Quizartinib (AC220)—NDA TBA
  - Phase 3 single agent for first relapse (CR1 or post-HSCT <6 mo), FLT3-ITD+
  - EHA 2018: Quizartinib improved OS (primary endpoint)
- Crenolanib
  - Undergoing phase 3 studies in frontline and relapsed FLT3mut+ patients

At present, the regulatory status of FLT3 inhibitors includes drugs that are approved such as midostaurin, which is approved for frontline therapy in combination with intensive induction and consolidation. Something I did not mention about the RATIFY Study is that study included a year of maintenance therapy, but subsequent post-hoc analysis of that trial did not identify that the maintenance therapy improved survival. It is possible that could be true if a study were specifically powered to answer that question, but that study really did not have enough patients who underwent maintenance to really answer the question. It is approved for maintenance in the EU, but it is not approved for maintenance in the US.

For gilteritinib, I have just shown you the data from, and that drug based on the phase ½ and interim data that has come off its phase 3 ,which has a very similar design to the QuANTUM-R Study I showed you, is currently under review by the FDA and we expect to have a ruling on whether it is approved by the end of November. That study has completed its phase 3, and the survival outcomes and response data, we hope to have available soon. Quizartinib, as I have mentioned, had a positive phase 3 study as a single agent for first relapse of FLT3-ITD positive patients which was presented earlier this year. The drug presumably will be submitted for regulatory review likely later this year. And crenolanib is just starting its phase 3 development, we hopefully will see very nice results from this drug which in many ways resembles gilteritinib with the exception that it has to be given more frequently.

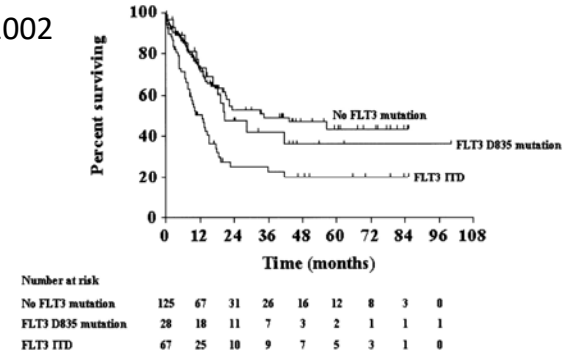


So where do we stand in terms of optimal therapy for patients with FLT3 mutations who are fit and eligible for intensive chemotherapy? I have already shown you the data with midostaurin added to 7 and 3. Also, this gives us a backbone for what we might do for patients who want to go in clinical trials to see if the newer drugs can outperform midostaurin. Around the time that the midostaurin data were read out, quizartinib had already entered a phase 3 study where it was compared to placebo. That is called the QuANTUM First Study. So that study is ongoing, though largely enrolling outside of the US because of the availability of midostaurin. There will be a Dutch study as well as a US study combining gilteritinib with induction chemotherapy and comparing that to the same induction chemotherapy with midostaurin, and crenolanib will use a very similar design, adding that drug to 7 and 3 in post remission high dose Ara-C. All of these studies include maintenance therapy. Many of these studies will encourage patients to go onto transplant, and while those studies will include a maintenance arm, there is also a stand alone study looking at maintenance FLT3 inhibitor after bone marrow transplant as there are also stand alone maintenance studies after postremission chemotherapy for patients that could not be captured on the frontline studies. All of those studies are ongoing at this point, and there is a lot of activity to see just what is the best FLT3 inhibitor and at what stage is it really important to add these drugs. Is the benefit largely seen in induction? Is it seen in maintenance? Where does it really come from?

The Evolving Standard of Care in AML: FLT3 Inhibitors

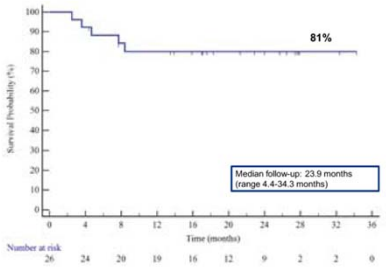
Future Directions

2002



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

2018



- Survival is improving for FLT3 mutated AML
  - This is due to improved diagnostics and new therapies
  - Induction/consolidation has benefited from adding midostaurin
  - More potent/selective inhibitors are currently under FDA review
  - These agents are undergoing evaluation in the frontline setting
  - ?role for post-consolidation or post-HSCT maintenance
- Novel agent + FLT3 inhibitor trials are in development
  - For patients unfit for intensive induction
  - For patients who are relapsed/refractory

Walter RB, et al. EHA 2018. Abstract PF227.; Fröhling S, et al. *Blood*. 2002;100:4372-4380.

As for future directions, I think we are certainly making progress in terms of improving survival for patients who get the most aggressive approaches, adding FLT3 inhibitors to intensive chemotherapy and then going to transplant and maybe even from the addition of maintenance therapy. We can see very good survivals now in FLT3 mutated AML, as shown on the right, from a phase 2 study adding crenolanib to 7 and 3 therapy postremission high dose Ara-C and patients who went to transplant could get maintenance. We can see really quite good outcomes in the context of adding the new FLT3 inhibitors to frontline therapy. Again, we have not refined which is the best drug and which are the patients that really benefit, and so that is an ongoing question. The other thing we have not figured out is what about patients who are not candidates for these intensive approaches? Are there lower intensity approaches that we could use with FLT3 inhibitors added to low intensity therapy that might actually have good outcomes? I have already mentioned that sorafenib can be added to azacitidine therapy. What about the newer FLT3 inhibitors or what about adding midostaurin? All of those are reasonable frontline approaches. And while we also have IDH inhibitors that are now inhibited for patients with IDH mutations, I should note that about 20% of patients with FLT3 mutations also have an IDH mutation, and so there are actually patients with both of these drugs, and those combinations will be tested.

As you might imagine, venetoclax is getting a lot of press these days from data where it was added to either low dose Ara-C or hypomethylating agents, and studies to combine venetoclax with FLT3 inhibitors are already underway. So these drugs are in development both with standard chemotherapy, with novel chemotherapy agents, and I think it is a very exciting time in the world of treating patients with FLT3 mutations because we are really moving the survival bars up, the response bars up, and all of this is headed towards hopefully a day when we have fewer toxicities of therapies because we need to rely less and less on the intensive approaches that I have just outlined for you.

Key Points

- FLT3 mutated AML, especially FLT3-ITD, is common and often highly aggressive
  - High CR rates, but also high relapse rates
- Effective approaches to improve survival (fit patients)
  - Refer FLT3-ITD early for transplant evaluation
  - Add midostaurin to induction chemotherapy of both FLT3-ITD and TKD (days 8-21)
  - Consider clinical trials of newer, more potent FLT3 inhibitors (especially relapsed/refractory or unfit)

In conclusion, FLT3 mutated AML, especially FLT3-ITD positive AML, is quite common and often highly aggressive in the clinic. While remission rates are high, prior to the development of FLT3 inhibitors, relapse rates were really unacceptably high as well. The addition of these new drugs has improved survival, but we have really seen those gains in fit patients. At present, midostaurin is the only approved drug to treat FLT3 mutated AML, but as I have mentioned there are a number of drugs that are either close to FDA review or are already under FDA review based on very promising data from either early phase studies or now phase 3 data. I would encourage — if you have patients with these mutations or if you do not know if your patients have these mutations but have this phenotype, refer them for evaluation at centers that have these trials because we really can potentially improve their outcomes. This is true through all stages of disease from frontline therapy all the way through to maintenance therapy after either transplant or post consolidation.

Key Points

- First-generation (multi-kinase) inhibitors like midostaurin
  - Have modest single-agent activity
  - Should be used in the context of combination therapy
  - Midostaurin + induction (fit); sorafenib + azacitidine (unfit, FLT3-ITD only)
- Second-generation (selective, potent) FLT3 inhibitors (quizartinib, gilteritinib, crenolanib)
  - Have significant clinical activity as single agents--outpatient therapy
  - Improve survival of relapsed/refractory patients (quizartinib)
  - Undergoing testing to determine their role in frontline treatment

The first-generation FLT3 inhibitors like midostaurin it seems are best used in combination with other active agents in AML rather than as single agents. But we can use these with either low intensity therapy or higher intensity therapy and there is probably a benefit in both context, although from randomized studies have only proven that benefit with intensive chemotherapy. And there is very promising data from second-generation drugs such as quizartinib, gilteritinib, or crenolanib now coming out, already some positive phase 3 studies, and we await the phase 3 results from gilteritinib and crenolanib in the near future.

Thanks for your attention.