ManagingAML

Managing High-Risk and Relapsed/Refractory AML: Where Is Research Headed Next?

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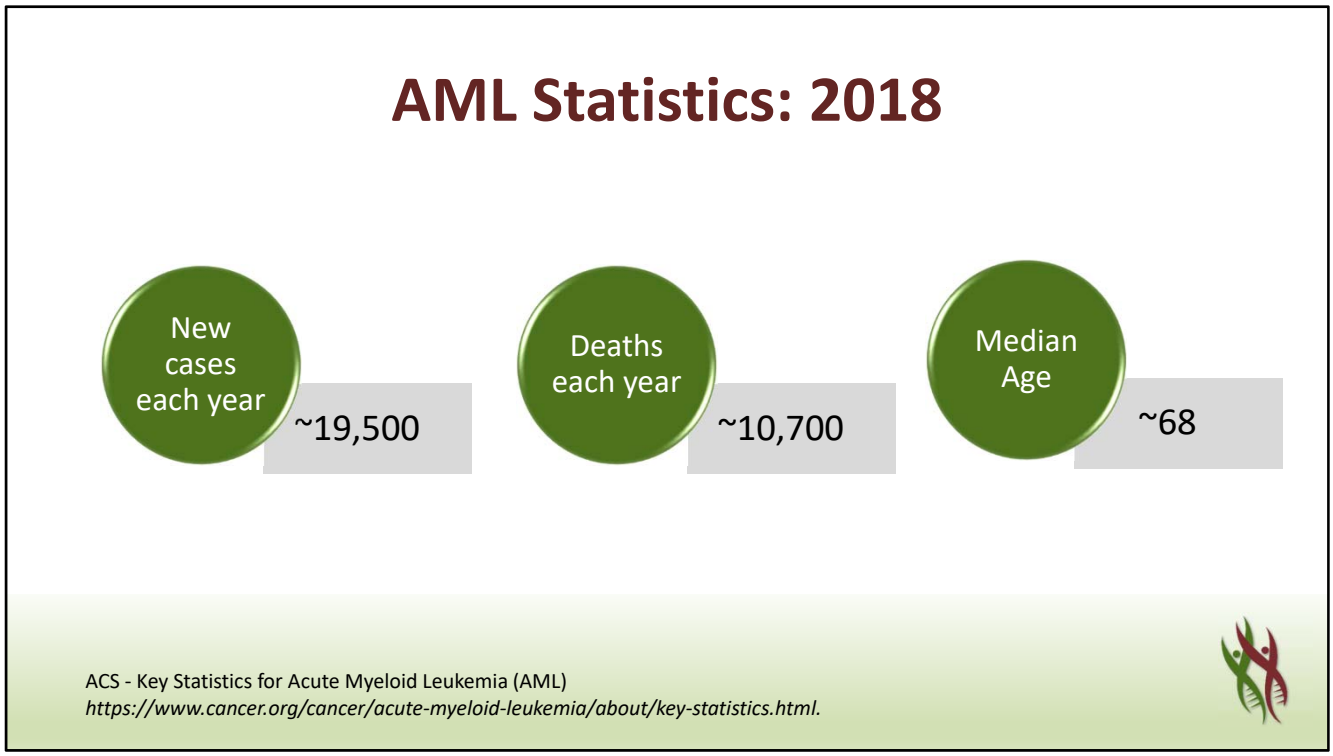
Welcome to this presentation on the management of acute myeloid leukemia. I am Dr. Amir Fathi, the Director of the Leukemia Program at Massachusetts General Hospital. Today I will review the management of higher-risk AML, as well as relapsed/refractory AML (R/R AML), and where research development is headed for this disease. Specifically, in this presentation I will describe the emerging role of FLT3, IDH1, and IDH2 inhibitors in AML, and I will discuss the paradigm for non-intensive upfront treatment of older of or less functionally robust patients with this disease.

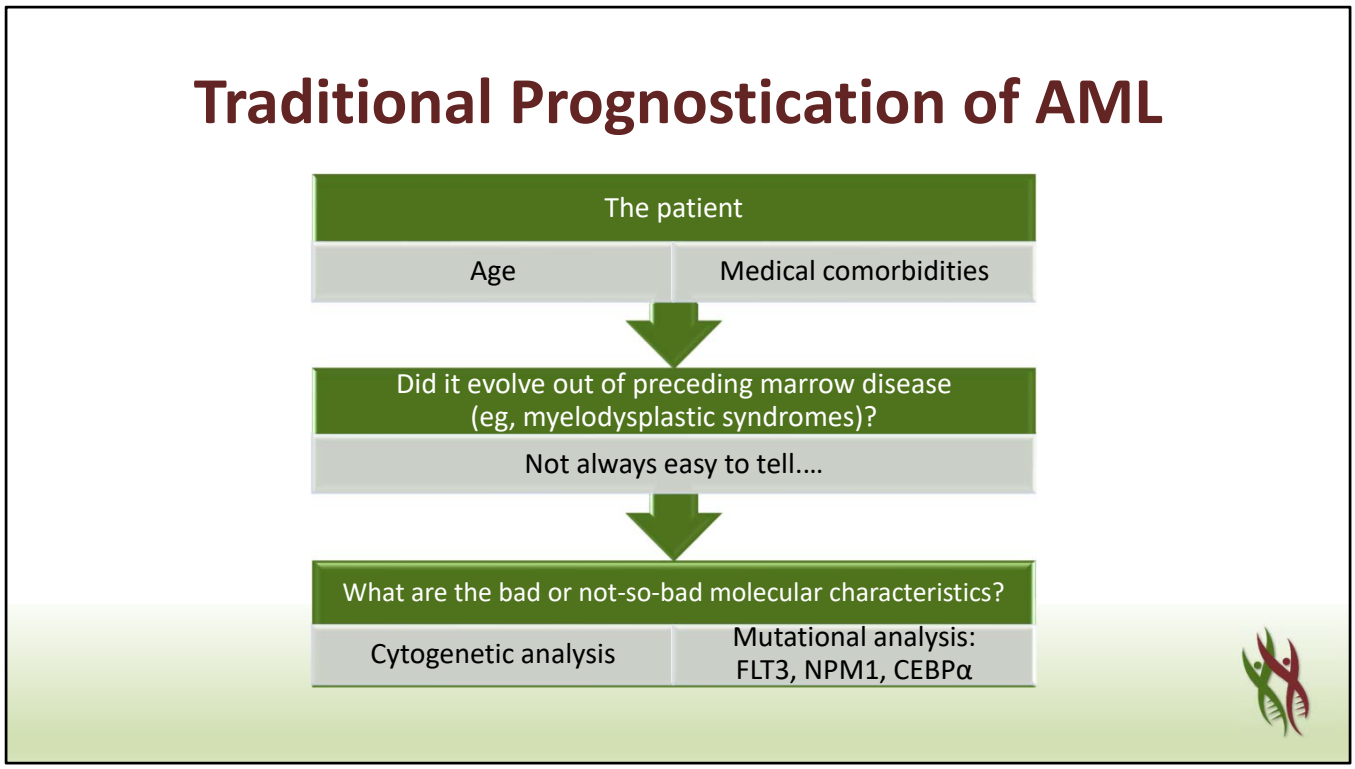
Speaker Disclosure

- **Consultant:** Celgene Corporation, Clear Creek Bio, Inc., Novartis AG, and Takeda Oncology
- **Advisory Activities:** Agios, Astellas Pharma US, Inc., and Jazz Pharmaceuticals plc

These are my disclosures.



Let us start with some statistical information regarding acute myeloid leukemia. These are the most recent numbers for patients with this disease. There are approximately 20,000 new cases of AML in the United States every year, and a large proportion of those patients also die from their disease. Importantly, the median age of AML is 68 and appears to increase every year as our population also ages. It is important to note that approximately half of patients with AML are in their 70s and 80s, an age group which is also impacted by other comorbidities as well as overall functional decline. This is an important issue, especially when considering options for treatment and more intensive versus less intensive approaches to the therapy of this disease.



The traditional prognostication of AML is presented here. This has not substantially changed over the course of the last two decades. There are certain factors that are patient-specific such as the patient's age as well as their other comorbid conditions. In older patients, generally speaking, other comorbidities may impact the ability of the clinician to treat the patient intensively with chemotherapy. These comorbidities may include cardiac dysfunction, renal insufficiency, hepatic disease, and functional limitations. All of these things can limit ability to provide intensive chemotherapy in patients with AML. There are also disease-specific factors to consider. Did the AML arise out of antecedent marrow malignancy, which may have been more indolent? If AML is secondary, meaning arising out of something else, it is oftentimes much harder to achieve remission with traditional treatment; as opposed to de novo AML, which means leukemia that arose out of a normal marrow. Also, there are other disease-specific factors to consider. The leukemic blasts may have certain cytogenetic abnormalities within them or certain mutations that may be better risk in terms of therapeutic response to upfront conventional treatment. These patient-specific and disease-specific factors did go into the traditional prognostication of AML, in terms of whether patients did well or did poorly with treatment.

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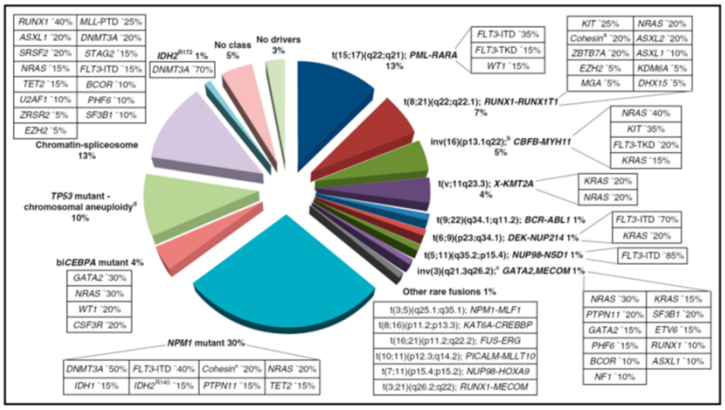
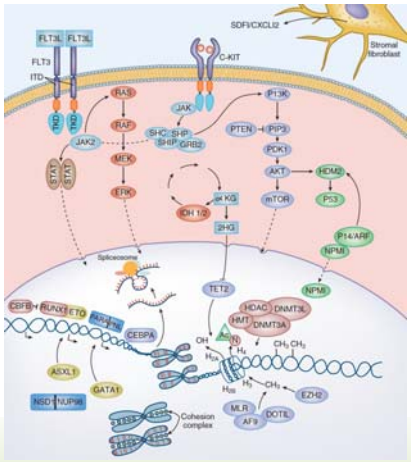
However, over the course of the last decade especially, there has been a range of developments in terms of understanding the complex underpinnings of the disease. Specifically, new mutations – or mutations that have been there from the beginning but were newly discovered – have come to our attention. These include IDH mutations, TET2 mutations, EZH2 mutations, as well as ASXL1 mutation.

The Complexity of AML





Dohner H. et al. *Blood*. 2017;129(4):424-447.; Brunner AM, Graubert TA. Pathobiology of Acute Myeloid Leukemia. In: *Hematology.* (7th Ed). 2018;913-923.

This complexity is also demonstrated here. If you look at the pie graph, you can see that patients with AML are not a homogenous group. They are markedly heterogeneous, with small pieces of the pie demonstrating the different subpopulations of the disease with different molecular features. These molecular features contribute in a complex fashion to the genesis of AML, but also may provide targets for therapy, which we will get to in this talk.

Traditional Induction Chemotherapy

- Cytarabine (continuous infusion or bolus)
- Anthracycline
  - Typically daunorubicin or idarubicin
- Various regimens (7+3, IA, AcDVP16, etc.)
- CR rate 75% (includes those needing two courses)

Ellison RR, et al. *Blood*. 1968;32(4)507-523.; Rai KR, et al. *Blood*. 1981;58:1203-1212.

Before we do that, let's talk about the traditional approach to the treatment of AML, which unfortunately did not change for a period of almost four decades. The initial papers are presented here. As you can see, they occurred in the late 1960s and early 1970s, and the traditional treatment of AML generally involved two classes of chemotherapy drugs. One was called cytarabine, which is a highly effective chemotherapeutic agent especially in acute myeloid leukemia, and the other class are anthracyclines. There are two that have been incorporated into induction chemotherapies, daunorubicin and idarubicin. Anthracyclines and cytarabine have been included together in various chemotherapy regimens that have been used to try to induce a remission, hence, the name induction. These include 7+3, IA, as well as others that have been used across the country. Suffice it to say, these induction chemotherapy regimens are relatively similar in the rate of response that they lead to. The rate of response is approximately 70% to 75% of patients. Patients with a new diagnosis of AML are oftentimes, if eligible or appropriate for intensive treatment, admitted to the hospital. They receive chemotherapy, usually over a period of five to seven days. Their marrow empties as a result of that chemotherapy and following that there is a period of recovery and then assessment by another marrow biopsy to see if a remission has been achieved. That first phase of treatment for AML is called induction. The goal of induction is to achieve remission.

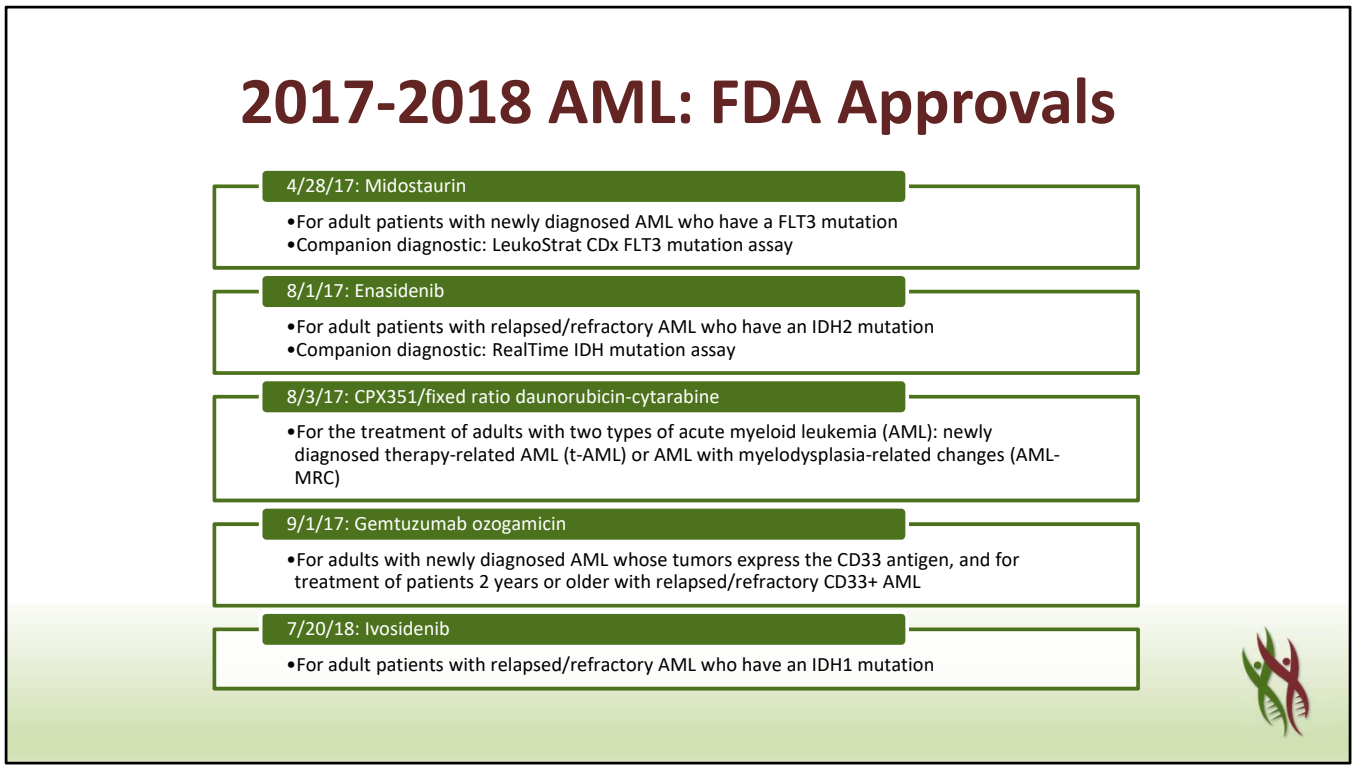
Consolidation

- Most common: High-dose cytarabine (HiDAc)
  - Mayer: 3 g/m^2 IV BID Days 1, 3, 5 for 3-4 cycles
  - Several alternates (eg, 1.5 g IV q12 x 6 days)
- Allogeneic stem cell transplant

Mayer RJ, et al. *N Engl J Med.* 1994;331(14):896-903.

The second phase of traditional treatment is called consolidation. The goal of consolidation is to achieve a cure. What is cure? Cure is three to five years of remission, an arbitrary definition. Therefore, the goal of consolidation is to prolong the initial remission achieved after induction, if we are lucky enough to achieve it, to a period of three to five years at which point we can arbitrarily call it a cure and move on from there. The likelihood of relapse at three to five years is very low. Consolidation can either be chemotherapy or it can be a bone marrow transplant. Generally speaking, for patients who have lower-risk disease, we give consolidated chemotherapy: typically repeated cycles of high doses of cytarabine in an effort to eliminate any molecular residual disease left in the patient. But usually for intermediate, and also for strictly higher-risk patients, we use consolidated allogeneic stem cell transplant, since this is a more intensive approach to consolidation in an effort to eliminate any residual disease and to cure the patient.

This was the paradigm that I mentioned in the last two slides for the traditional approach to the therapy of AML. Induction, hope for remission (about 75% of patients achieve remission), followed by consolidation: either chemotherapy consolidation for lower-risk patients or intermediate-risk patients who do not have appropriate donors for stem cell transplant, or consolidated transplant for intermediate risk patients who have donors and for higher-risk patients. The hope is to cure those patients. Nevertheless with this paradigm of induction and consolidation, a large proportion of patients who are either refractory to initial chemotherapy, or even if they achieved remission with induction, subsequently relapsed. Therefore, the likelihood of long-term remission and cure for patients with AML with this traditional approach has hovered around 25% to 35%, which is very suboptimal.



We had not had substantial advances in the field until fairly recently, especially in the years 2017 and 2018. We've had multiple approvals for targeted therapies and novel approaches to the treatment of AML: these are listed here. Midostaurin was initially approved for use in patients with FLT3-mutated AML and appropriate for induction chemotherapy. Patients received induction with 7+3, and if they had FLT3 mutation, midostaurin would be added on day 8. Enasidenib, the IDH2 inhibitor, and ivosidenib, the IDH1 inhibitor, have been approved for use in patients with IDH2 and IDH1 mutations respectively, and who have relapsed and refractory IDH-mutated AML. The fixed ratio daunorubicin-cytarabine liposomal drug called CPX351 was also recently approved based on phase 3 data for use in patients with secondary AML or MDS-related AML. Finally, the antibody drug conjugate gemtuzumab ozogamicin has also been FDA-approved for use in certain populations in the upfront and the relapsed and refractory setting.

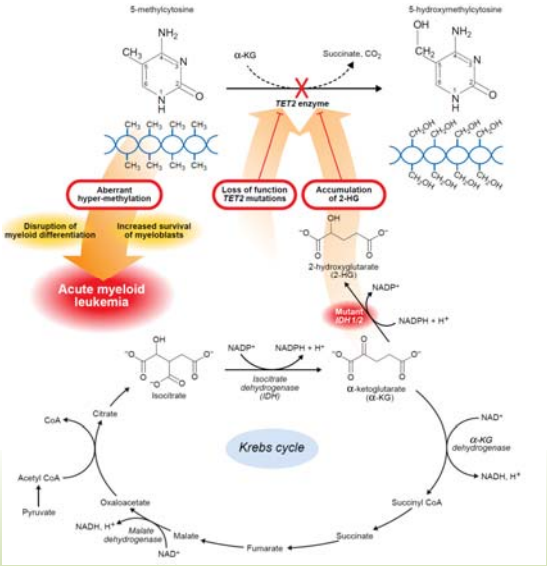
Emerging Therapies

IDH Inhibitors

Let's focus our attention on IDH inhibitors.

IDH1/2-Mutant AML

- First description of IDH1 mutations in ~8% of patients with AML, associated with normal cytogenetic status (cn-AML)[1]
- Subsequent studies found a larger subset, ~15%, of patients with mutations in the IDH2 gene
- IDH proteins, essential to the Krebs Cycle, catalyze decarboxylation of isocitrate to α-ketoglutarate (α-KG) in cytoplasm (IDH1) and mitochondria (IDH2)
- Mutant IDH enzymes catalyze an NADPH-dependent reduction of α-KG to 2-hydroxyglutarate (2-HG)
- This leads to accumulation of 2-HG onco-metabolite in IDH-mutant tumors



[1]Mardis ER, et al. *N Engl J Med*. 2009;361(11):1058-1066.; Ward PS, et al. *Cancer Cell*. 2010;17(3):225-234.; Gross S, et al. *J Exp Med.* 2010;207(2):339-344.; Dang L, et al. *Nature*. 2009;462:739-744.

In 2009, a publication in the *New England Journal of Medicine* first described IDH1 mutations in a subset of patients with AML. IDH stands for isocitrate dehydrogenase. Isocitrate dehydrogenase is a key enzyme in the Krebs cycle and helps catalyze the conversion of isocitrate dehydrogenase to alpha ketoglutarate, ultimately leading to the production of ATP. IDH1 mutations were initially discovered in AML and a short time after, IDH2 mutations were also discovered. Both of these altered IDH enzymes do not lead to the classic enzymatic reaction we see with normal IDH proteins. Instead, the altered IDH1 and IDH2 proteins help catalyze the conversion of alpha ketoglutarate to the oncometabolite 2-hydroxyglutarate, which leads to suppression of the key enzyme called TET2. TET2 is involved in the methylation of key genes that mediate maturation and differentiation of myeloid precursors. When TET function is suppressed by 2HG, which is built up as a result of the aberrant IDH enzymes, these normal genes are inappropriately hypermethylated and turned off, and the myeloid precursors no longer appear to mature and differentiate normally. Hence, the phenotype of acute myeloid leukemia and the accumulation of these precursor malignant leukemic cells in the marrow; 2-hydroxyglutarate can actually be measured in the blood, urine, and marrow, and is a marker of disease in patients with IDH-mutated AML.

Enasidenib in Mutant *IDH2* Relapsed or Refractory Acute Myeloid Leukemia

Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, Stone RM, DeAngelo DJ, Levine RL, Flinn IW, Kantarjian HM, Collins R, Patel MR, Frankel AE, Stein A, Sekeres MA, Swords RT, Medeiros BC, Willekens C, Vyas P, Tosolini A, Xu Q, Knight RD, Yen KE, Agresta S, de Botton, Tallman MS

Blood. 2017;130(6):722-731.

Let us talk about the IDH2 inhibitor enasidenib in patients with AML.

Activity in Relapsed/Refractory AML

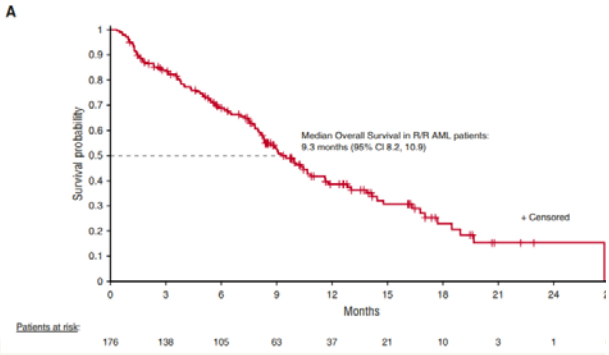
	Relapsed or refractory AML									
	Enasidenib 100 mg per day (n = 109)					All doses (N = 176)				
Response	No.	%	95% CI	Median	Range	No.	%	95% CI	Median	Range
ORR*†	42	38.5	29.4-48.3			71	40.3	33.0-48.0		
Best response										
CR	22	20.2	13.1-28.9			34	19.3	13.8-25.9		
CR with incomplete hematologic recovery/CR with incomplete platelet recovery	7	6.4				12	6.8			
Partial remission	3	2.8				11	6.3			
Morphologic leukemia-free state	10	9.2				14	8.0			
Stable disease‡	58	53.2				85	48.3			
Progressive disease§	5	4.6				9	5.1			

Stein EM, et al. *Blood*. 2017;130(6):722-731.

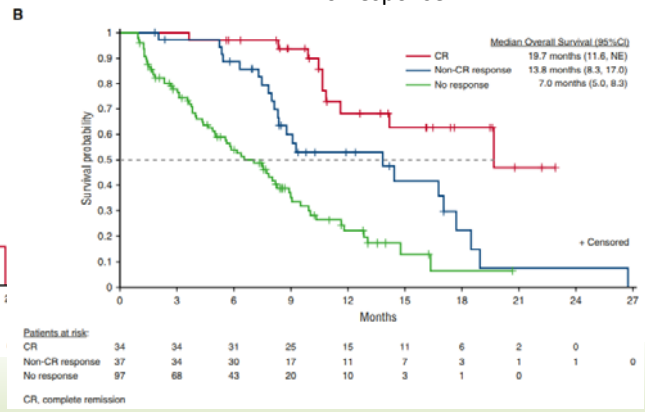
Enasidenib was studied in various populations of patients with myeloid malignancy and a key cohort in the initial dose escalation and dose expansion studies looked specifically at patients with relapsed and refractory AML. These are patients who have gone beyond initial rounds of treatment and have either failed to respond or have relapsed disease following initial response and now require treatment. These patients did receive on-trial the IDH2 inhibitor enasidenib, and in this population at least, there was a fairly impressive overall response rate of approximately 40%, and a composite remission rate that approximated 20%; in this patient population that is quite remarkable. Looking at all doses of the drug used on these trials, the same proportion of response was seen on-study.

Overall Survival

Overall Survival: Patients with R/R AML



Overall survival: Patients with R/R AML in CR, Patients with Non-CR Hematologic Response, or No Response



Stein EM, et al. *Blood*. 2017;130(6):722-731.

These are the survival curves for patients with relapsed and refractory AML who had received enasidenib. As you can see, those individuals who achieved remission – and even those patients who did not achieve remission but had some degree of response – had a fairly impressive median overall survival. The patients achieving remission appeared to have a median overall survival that approached 20 months, which is quite remarkable in this patient population. Those non-CR responders also had a fairly impressive median overall survival of 14 months.

Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML

DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, Swords R, Collins RH, Mannis GN, Pollyea DA, Donnellan W, Fathi AT, Pigneux A, Erba HP, Prince GT, Stein AS, Uy GL, Foran JM, Traer E, Stuart RK, Arellano ML, Slack JL, Sekeres MA, Willekens C, Choe S, Wang H, Zhang V, Yen KE, Kapsalis SM, Yang H, Dai D, Fan B, Goldwasser M, Liu H, Agresta S, Wu B, Attar EC, Tallman MS, Stone RM, Kantarjian HM

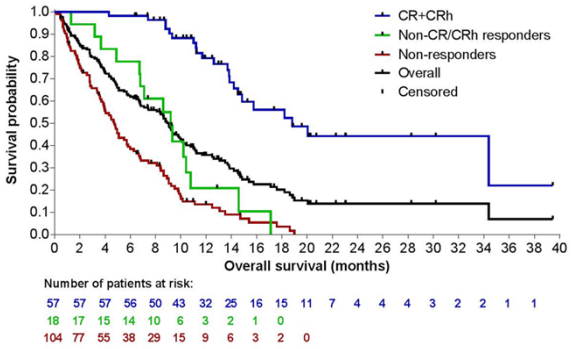
N Engl J Med. 2018;378(25):2386-2398.

Similarly, with the IDH1 inhibitor ivosidenib, there was an impressive rate of response

Activity

- Responders had better OS than nonresponders, with the greatest survival probability seen in patients who achieved CR + CRh
- Responders achieved a DOR of up to ~10 months

Overall Survival by Best Response in R/R AML 500 mg (n=179)



Number of patients at risk:

CR+CRh	57	57	57	56	50	43	32	25	16	15	11	7	4	4	4	3	2	2	1	1
Non-CR/CRh responders	18	17	15	14	10	6	3	2	1	0										
Non-responders	104	77	55	38	29	15	9	6	3	2	0									

	Months
Overall survival, median [95% CI]	
CR + CRh	18.8 [14.2, NE]
Non-CR/CRh responders	9.2 [6.7, 10.8]
Nonresponders	4.7 [3.7, 5.7]
All	9.0 [7.1, 10.0]
Overall follow-up, median (range)	15.3 (0.2-39.5)

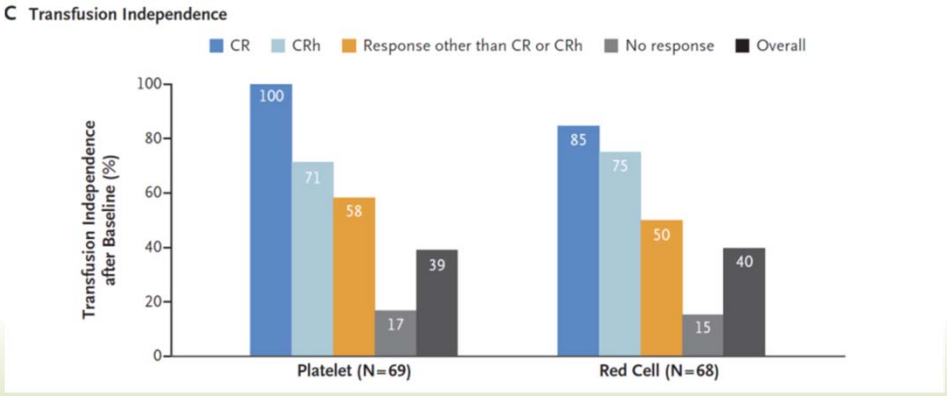
Duration of Response	CR + CRh	CR	Overall Response
Median [95% CI], months	8.2 [5.6, 12.0]	10.1 [6.5, 22.2]	6.5 [5.5, 10.1]

Non-CR/CRh responders include CRi, CRp, and MLFS who are not CRh.
Nonresponders=all others including those with best response of SD, PD, or not evaluable (NE).
DOR=duration of response
Pollyea D, et al. ASCO 2018. Abstract 7000.

that can be demonstrated here, which was fairly similar to that seen in enasidenib respectively in the IDH2-mutated patient population. Again, those patients who had responses seemed to do better in terms of overall survival versus those who had no response.

Ivosidenib Phase 1: Results (Continued)

Transfusion independence was observed across all response categories in R/R AML 500 mg patients who were dependent at baseline



Stein EM, et al. *Blood*. 2017;130(6):722-731.

It is important to note the traditional responses of remission and CRi or CRh were not the complete picture when it comes to IDH inhibitors. In the dose escalation and dose expansion study of ivosidenib, transfusion independence was also seen across the patient populations treated with IDH inhibition. As you can see, a large proportion of patients treated achieved transfusion independence; remarkably, almost all individuals who achieved a complete remission, but also those individuals who did not. Even in patients who had no response, a subset of them achieved transfusion independence, which is important in terms of quality of life in our patients with AML, many of whom with active disease require multiple visits to the hospital for transfusions. When we are able to eliminate the need for transfusions, we do have a very positive impact on the quality of life.

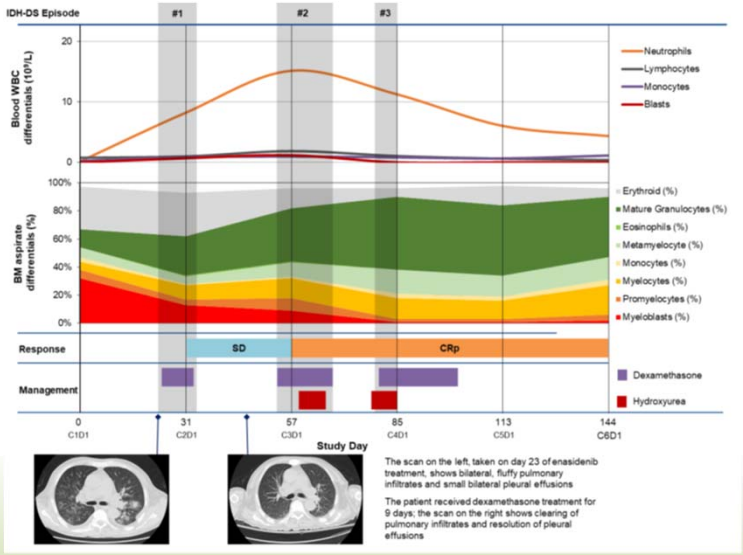
Differentiation Syndrome Associated with Enasidenib, a Selective Inhibitor of Mutant Isocitrate Dehydrogenase 2: Analysis of a Phase 1/2 Study

Fathi AT, DiNardo CD, Kline I, Kenvin L, Gupta I, Attar EC, Stein EM, de Botton S; AG221-C-001 Study Investigators

JAMA Oncol. 2018;4(8):1106-1110.

IDH inhibitors have a unique toxicity profile. In general, they are very well-tolerated. However, a subset of patients can develop symptoms and signs of what is called differentiation syndrome. As was mentioned earlier, IDH inhibitors appear to inhibit the activity of the altered IDH enzyme. As a result, 2HG levels are suppressed, the block on differentiation is released, and cells again differentiate.

IDH-Differentiation Syndrome



Fathi AT, et al. *JAMA Oncol.* 2018;4(8):1106-1110.

Sometimes, the differentiation can be quite robust and lead to a cytokine-mediated syndrome called a differentiation syndrome. This differentiation syndrome can have a relatively heterogeneous presentation, which can include unexplained fevers, pulmonary infiltrates, pleural effusions, rash, and renal insufficiency. In patients who are treated with IDH inhibitors, especially in those in whom there is evidence of differentiation in the peripheral blood in the marrow, there can also be a manifestation of a differentiation syndrome, which can be severe and lethal if it's not appropriately recognized. This particular figure is from a paper that was published to describe the differentiation syndrome associated with the IDH2 inhibitor enasidenib, and represents a typical patient treated with the drug who experienced the syndrome. As can be seen in the top figure, this patient's peripheral blood after initiating enasidenib demonstrated a steady rise in neutrophils or granulocytes, which is a good response to treatment, especially in the peripheral blood. Concurrent with that, there was an increase in maturing granulocytes and myeloid precursors in the marrow. That's the middle part of the figure here. The green being the mature granulocytes expanding and the red being the leukemic blasts decreasing. As one can see, concurrent with this, there was multiple episodes of differentiation syndrome, which for this patient included unexplained fevers and pulmonary manifestations. The gray vertical bar graphs demonstrate the three separate episodes of differentiation syndrome. Each episode was treated with dexamethasone as well as the use of hydroxyurea, which was specifically used to manage any leukocytosis that occurred coincidentally with the differentiation syndrome. Differentiation syndrome does not have to include leukocytosis but it oftentimes occurs concurrently with leukocytosis.

IDH-Differentiation Syndrome

Table 1. Frequency of Signs and Symptoms Consistent With IDH-DS[a]

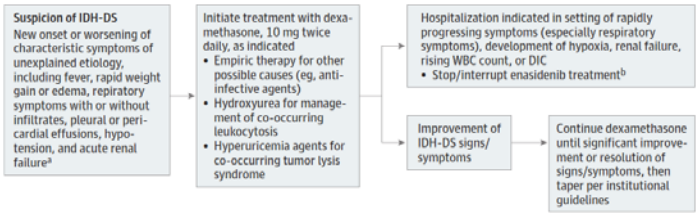
Sign or Symptom	Patients With IDH-DS, No. (%) (n = 33)[b]
Dyspnea	28 (85)
Unexplained fever (body temperature of 38.0°C for 2 d)	26 (79)
Pulmonary infiltrates	24 (73)
Hypoxia	19 (58)
Acute kidney injury (CTCAE grade ≥2)	14 (42)
Pleural effusion	14 (42)
Bone pain or arthralgia	9 (27)
Lymphadenopathy	8 (24)
Rash	8 (24)
Disseminated intravascular coagulopathy	7 (21)
Edema or weight gain of >5 kg from screening	7 (21)
Pericardial effusion	5 (15)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events[14]; IDH-DS, isocitrate dehydrogenase differentiation syndrome.

[a] Signs and symptoms included in this table are based on retrospective differentiation syndrome review committee review of clinical records.

[b] Patients may have had multiple symptoms.

Figure. Differentiation Syndrome Review Committee Amended Protocol for Isocitrate Dehydrogenase Differentiation Syndrome (IDH-DS) Diagnosis and Management



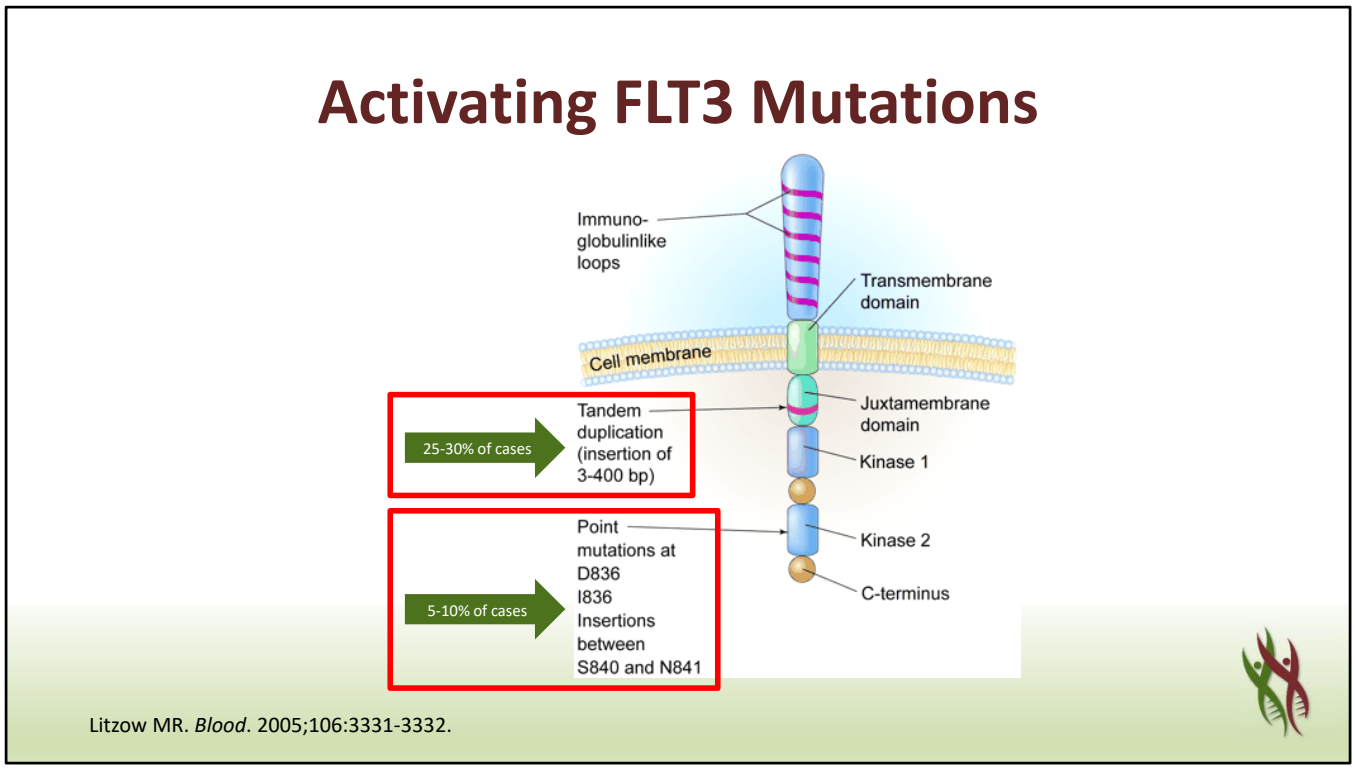
Fathi AT, et al. *JAMA Oncol.* 2018;4(8):1106-1110.

This led to recommendations regarding the recognition of differentiation syndrome in patients treated with IDH inhibitors and the typical signs and patterns. Unfortunately, many of these signs and patterns of differentiation syndrome are nonspecific and can also accompany other conditions seen on patients with AML such as infection, heart disease, and kidney disease. Secondary causes that may explain the signs and symptoms should be ruled out or at least treated effectively. But if the manifestation does not get better and is getting rapidly worse, empiric treatment with dexamethasone is recommended. Certainly, if leukocytosis or an elevated white count is also occurring and progressing rapidly, concurrent administration of hydroxyurea to control the white count is also recommended. Once the symptoms and signs of a presumed differentiation syndrome are improved on steroids, the steroids can be tapered over a period of days. In fact, if this is differentiation syndrome that is causing these symptoms, steroids should lead to a relatively prompt response.

Emerging Therapies

FLT3 Inhibitors

Let's move on to FLT3 mutations and FLT3 inhibitor therapy in AML.



FLT3 stands for FMS-like tyrosine kinase 3. It is a receptor tyrosine kinase, which shares similarities with other receptor tyrosine kinases known in human biology.
There is an extracellular domain, a cell membrane domain, and an intracellular domain, which are a feature of these receptor tyrosine kinases. The alterations typically occur on the intracellular portion of the receptor tyrosine kinase. The most common mutation is the internal tandem duplication mutation, which affects approximately a quarter of patients with AML, the so-called FLT3-ITD mutation. Approximately, 7% of patients have another type of FLT3 mutation called the TKD mutation, which are point tyrosine kinase domain mutations that also impact the intercellular part of the FLT3 tyrosine receptor kinase. When the FLT3 receptor tyrosine kinase is altered as a result of a mutation, it becomes less dependent on its ligand, the FLT3 ligand. As a result, the receptor becomes more active and the cells receive an uncontrolled signal to replicate and divide. Patients with FLT3 mutations typically present with very proliferative disease and a monocytic leukemia. A series of FLT3 inhibitors have been studied over the course of the last decade. The first generation of these FLT3 inhibitors were relatively nonspecific and less potent.

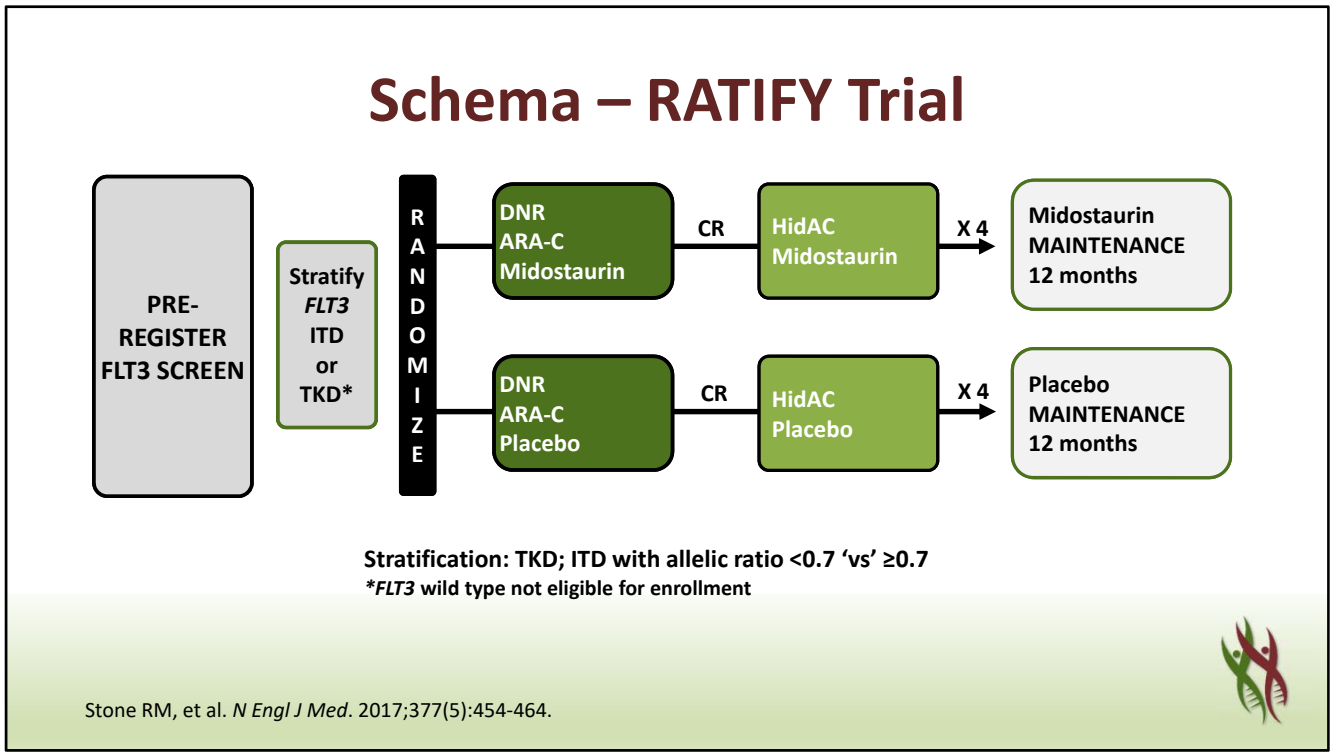
Midostaurin Plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation

Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, Thiede C, Prior TW, Döhner K, 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, Döhner H

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

Among these was the FLT3 inhibitor midostaurin, which in monotherapy studies did not lead to any significant proportion of patients achieving deep responses or impressive rates of remission.

Managing High-Risk and Relapsed/Refractory AML: Where Is Research Headed Next?

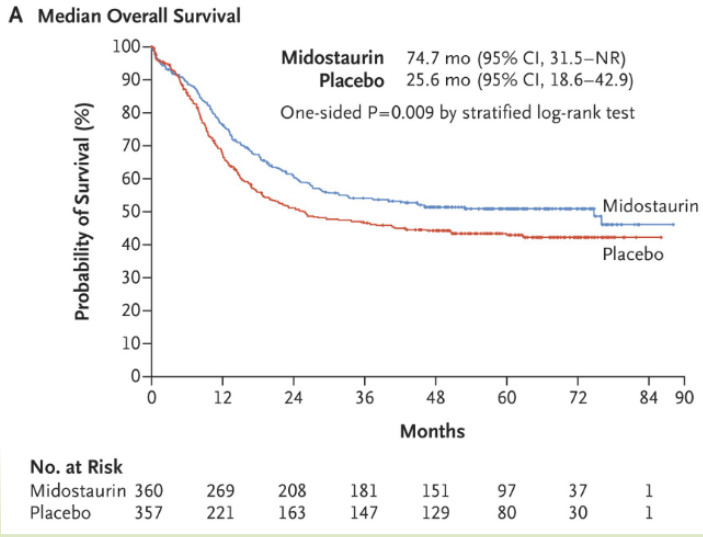


Stone RM, et al. *N Engl J Med*. 2017;377(5):454-464.

However, in combination with chemotherapy, it appeared to be quite promising, ultimately leading to a large phase 3 trial that compared 7+3 with placebo, to 7+3 with midostaurin. This study was conducted in younger patients with FLT3 activating mutations and combined midostaurin with induction, consolidation, and maintenance.

Managing High-Risk and Relapsed/Refractory AML: Where Is Research Headed Next?

Overall Survival



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

These results were presented a few years ago demonstrating a survival advantage in those patients who received midostaurin plus 7+3 as opposed to those who received 7+3 plus placebo. This led to the first of a series of FDA-approvals specifically in patients with FLT3 mutated AML.

Selective Inhibition of FLT3 by Gilteritinib in Relapsed or Refractory Acute Myeloid Leukaemia: A Multicentre, First-in-Human, Open-label, Phase 1-2 Study

Perl AE, Altman JK, Cortes J, Smith C, Litzow M, Baer MR, Claxton D, Erba HP, Gill S, Goldberg S, Jurcic JG, Larson RA, Liu C, Ritchie E, Schiller G, Spira AI, Strickland SA, Tibes R, Ustun C, Wang ES, Stuart R, Röllig C, Neubauer A, Martinelli G, Bahceci E, Levis M

Lancet Oncol. 2017;18(8):1061-1075.

As mentioned, midostaurin is certainly not the only FLT3 inhibitor in development. A second and third generation of FLT3 inhibitors are currently under study and many of these drugs are much more potent and much more specific for the FLT3 receptor tyrosine kinase. Among these is the FLT3 inhibitor gilteritinib, which has been studied in various settings.

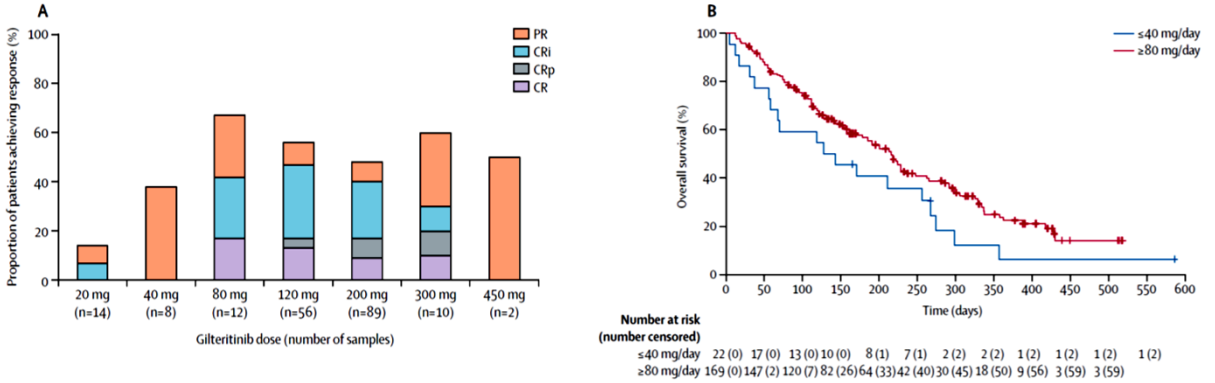
Antileukemic Response to Gilteritinib in Patients with R/R AML

Antileukemic Response	FAS Patient Population (n=249)	FLT3^{WT}(n=58)	FLT3^{mut+}	
			All Patients (n=191)	Patients Receiving ≥80 mg/d (n=169)
Complete remission (CR)	19 (8% [5, 12])	1 (2% [0, 9])	18 (9% [6, 15])	18 (11% [6, 16])
Complete remission with incomplete platelet recovery (CRp)	10 (4% [2, 7])	0	10 (5% [3, 9])	10 (6% [3, 11])
Complete remission with incomplete hematologic recovery (CRi)	46 (19% [14, 24])	4 (7% [2, 17])	42 (22% [16, 29])	41 (24% [18, 31])
Partial Remission (PR)	25 (10% [7, 15])	2 (3% [0, 12])	23 (12% [8, 18])	19 (11% [7, 17])
Composite complete remission (CRc)	**75 (30% [25, 36])**	**5 (9% [3, 19])**	**70 (37% [30, 44])**	**69 41% (33, 49)**
Overall response (ORR)	**100 (40% [34, 47])**	**7 (12% [5, 23])**	**93 (49% [41, 56])**	**88 (52% [44, 60])**
Duration of response (weeks)	17 (14, 29)	12 (3, 17)	20 (14, 33)	20 (14, 33)
Overall survival (weeks)	25 (20, 30)	17 (11, 21)	30 (23, 33)	31 (24, 59)

Data are number of patients (% [95% Confidence Interval]), or median (95% CI). The full analysis set included all patients who received at least one dose of study drug and who had at least one datapoint post-treatment.
FLT3^{mut+}= FLT3 mutation-positive; FLT3^{wt}=FLT3 wild type
Perl AE, et al. *Lancet Oncol.* 2017;18(8):1061-1075.

As mono therapy in relapsed and refractory AML it leads to composite complete remission rates that hover between 35% and 45% in relapse and refractory patient populations. This is quite remarkable.

Gilteritinib Dosing and Response



Perl AE, et al. *Lancet Oncol.* 2017;18(8):1061-1075.

A dose of 120 mg, and specifically doses above 80 mg a day, seem to lead to the highest rate of response, and this drug is currently under study for further clinical development.

Quizartinib Significantly Prolongs Overall Survival in Patients with FLT3-Internal Tandem Duplication-Mutated (MUT) Relapsed/Refractory AML in the Phase 3, Randomized, Controlled QuANTUM-R Trial

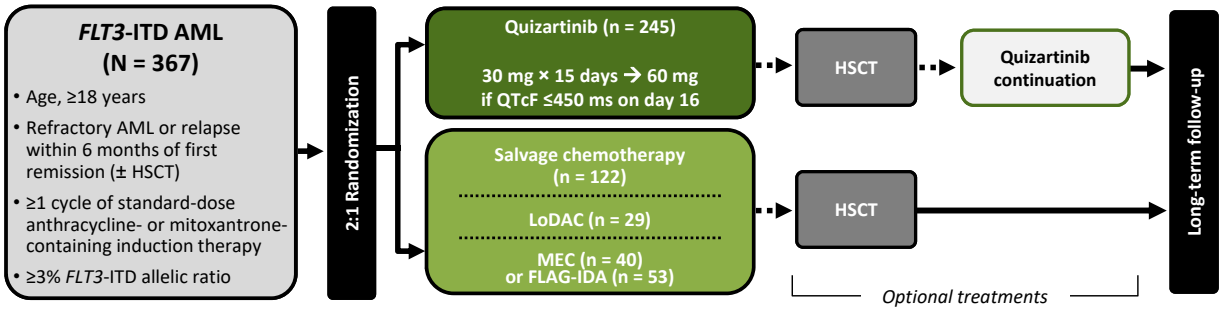
Cortes J, Khaled S, Martinelli G, Perl AE, Ganguly S, Russell N, Krämer A, Dombret H, Hogge D, Jonas BA, Yu-Hung Leung A, Mehta P, Montesinos P, Radsak M, Sica S, Arunachalam M, Holmes M, Kobayashi K, Namuyinga R, Ge R, Yver A, Zhang Y, Levis MJ

EHA 2018. Abstract LB2600.

Quizartinib, another potent and selective FLT3 inhibitor, was also studied as monotherapy and has also been studied in combination with conventional chemotherapies.

Managing High-Risk and Relapsed/Refractory AML: Where Is Research Headed Next?

QuANTUM-R Global Phase 3: Study Design



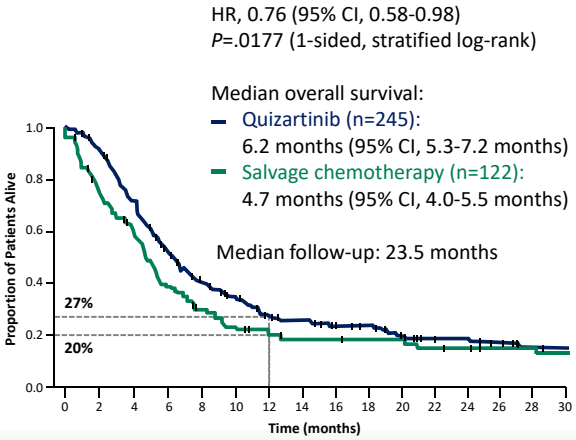
- The study allowed participation regardless of whether the patient had received stem cell transplantation; patients assigned to the quizartinib arm were allowed to resume this treatment following transplantation
- Patients who had previously received an FLT inhibitor (with the exception of midostaurin) were excluded from the trial
- **Primary endpoint**: overall survival (OS) in the ITT population
- **Secondary endpoints**: objective response rate (ORR) and event-free survival (EFS) in the ITT population

FLAG-IDA=fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin; HSCT=hematopoietic stem cell transplantation; LoDAC=low-dose cytarabine; MEC=mitoxantrone, etoposide, and intermediate-dose cytarabine
Cortes J, et al. EHA 2018. Abstract LB2600.

As monotherapy, this study was recently compared to other salvage regimens for relapsed and refractory AML, specifically FLT3-mutated relapsed and refractory AML.

QuANTUM-R: Results

- Patients who received single-agent quizartinib had a 24% reduction in the risk of death compared to patients who received salvage chemotherapy
- The median OS was 6.2 months for patients treated with quizartinib and 4.7 months for patients treated with salvage chemotherapy
- Estimated survival probability at 1 year was 27% for patients who received quizartinib and 20% for patients who received salvage chemotherapy
- Impressive results for a single agent in this difficult-to-treat patient population (presenter comment)



CI=confidence interval; HR=hazard ratio
Cortes J, et al. EHA 2018. Abstract LB2600.

In comparison to other traditional salvage approaches, the FLT3 inhibitor quizartinib was recently shown to have a survival advantage in patients who have FLT3-mutated AML. Specifically, there was a 24% reduction in the risk of death compared to patients who received the traditional salvage chemotherapy for those patients who received quizartinib. The median overall survival was also significantly improved for patients getting quizartinib compared to those individuals receiving salvage chemotherapy. Salvage chemotherapy included traditional chemotherapy regimens such as low-dose cytarabine and FLAG.

Emerging Therapies

Novel Combinations for Older Patients

Let us move on to talk about novel combinations for older patients.

AML Survival by Age

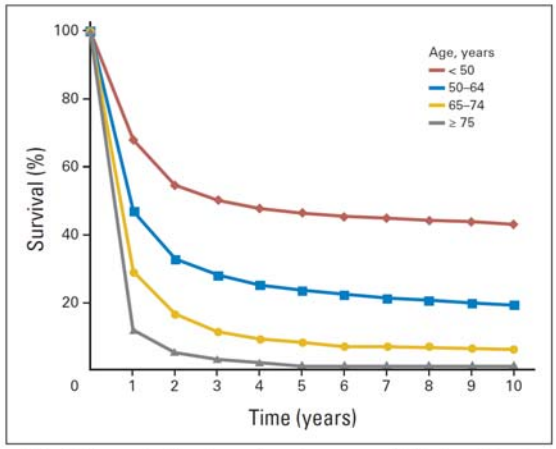
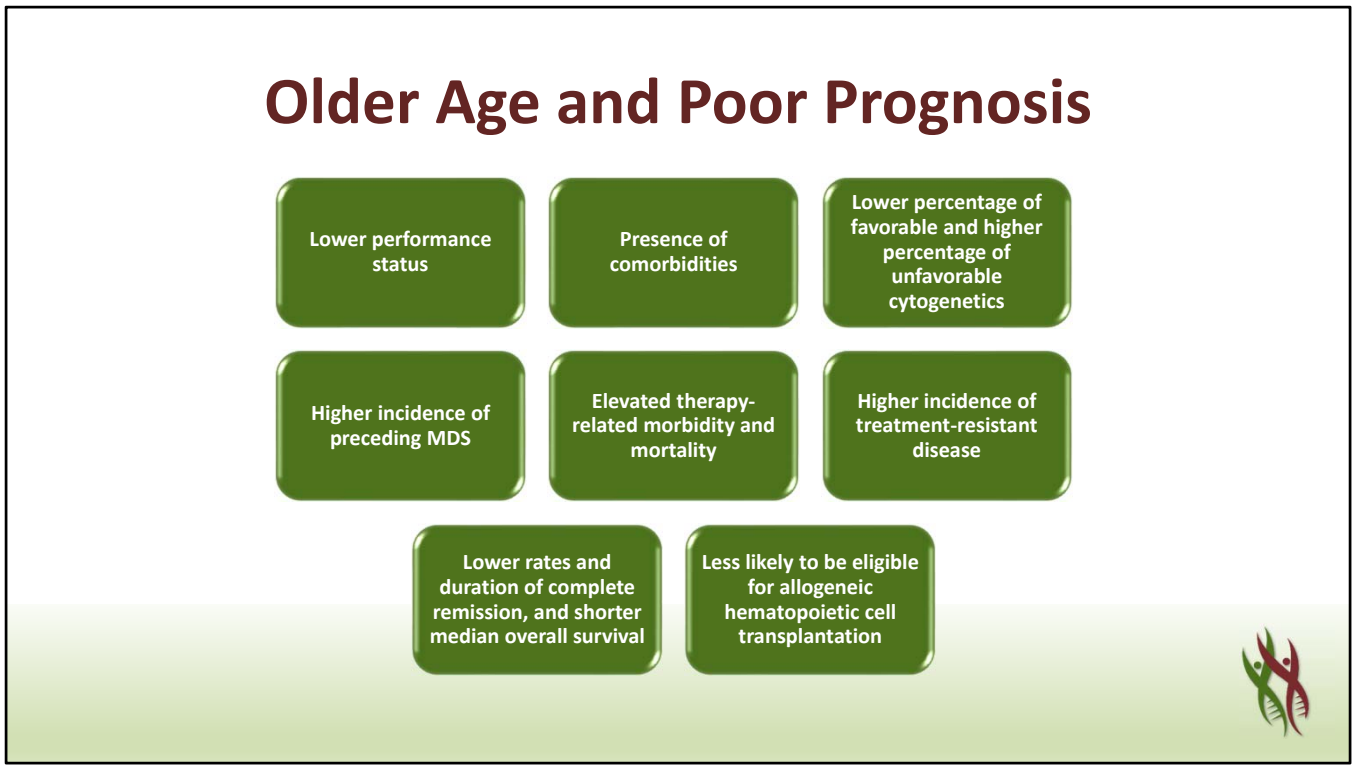


Fig 1. Relative survival by time and age for acute myeloid leukemia based on SEER data.

Klepin H, et al. *J Clin Oncol*. 2014;32(24):2541-2552.

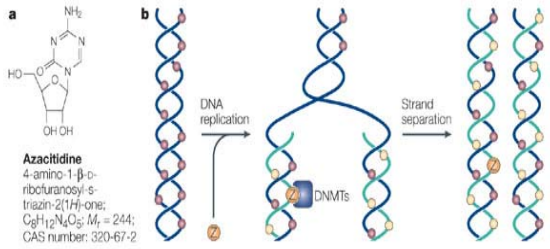
As can be seen by this figure, as patients age, their outcomes in terms of survival are markedly worse.



Many factors contribute to why patients who are older do worse in terms of AML. Patients who are older have a lower performance status and are more likely to have substantial comorbid disease. Their disease specifically seems to have less favorable, and a higher percentage of unfavorable, molecular markers. MDS, a pre-leukemic condition that may lead to secondary AML, is more common in older patients; and secondary AML by itself has a worse prognosis. There is an elevated risk of therapy-related morbidity and mortality in older patients, a higher incidence of therapy-resistant disease. Because of all this, they have lower rates and duration of complete remission and a shorter median overall survival. Also because of the above, these patients are much less likely to be eligible for curative paradigms of treatment in terms of consolidation, which include bone marrow transplant.

Hypomethylating Therapies

- Less intensive treatment, increasingly used for less robust or older patients in whom it is better tolerated with lower rate of toxicity
- Typically administered in clinic
- Can lead to therapeutic responses, including transfusion independence, decrease in leukemic burden and, less commonly, remissions
- However, responses often transient, with leukemic progression and brief post-HMA survival



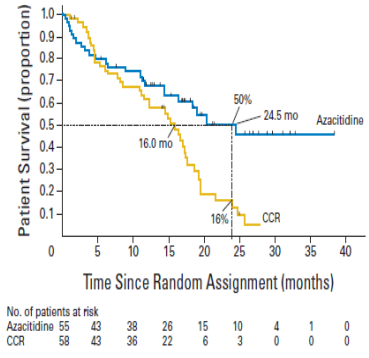
Issa JP, et al. *Nat Rev Drug Discov.* 2005;4(4):275-276.

For older patients, hypomethylating therapies have emerged as a less intensive treatment. These agents are better-tolerated and have a lower rate of toxicity. They can also be administered in the clinic. Hypomethylating agents at the doses that we generally use are thought to decrease the aberrant hypermethylation in genes that are key for differentiation and maturation, and release the block on differentiation. Once the block on differentiation is released, those cells can mature. Therefore, over time we see an improvement in the marrows of patients who are receiving treatment with hypomethylating therapy, and hopefully a reduction in blasts and an improvement in their transfusion dependence. Therefore, the substantial proportion of patients who receive hypomethylating therapies can have therapeutic responses, and a small subset can achieve remission. However, responses are often transient, with leukemic progression and brief survival after initiation of therapy.

Managing High-Risk and Relapsed/Refractory AML: Where Is Research Headed Next?

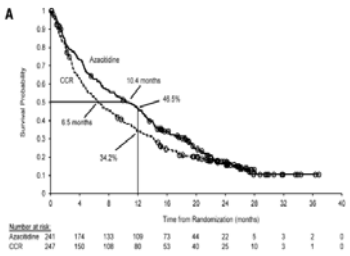
Hypomethylating Therapy Among Older Adults

Azacitidine Prolongs Overall Survival Compared with Conventional Care Regimens in Elderly Patients with Low Bone Marrow Blast Count AML



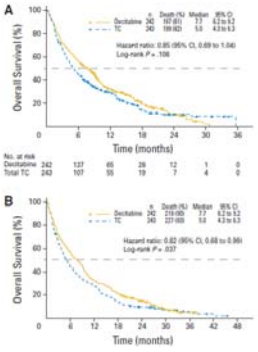
CR rate: 18% (10/55)

International Phase 3 Study of Azacitidine vs Conventional Care Regimens in Older Patients with Newly Diagnosed AML with >30% Blasts



	Azacitidine (n = 241)	
	No.	%
Hematologic response*		
CR + CRi	67	27.8
CR	47	19.5
CRi	20	8.3

Multicenter, Randomized, Open-Label, Phase III Trial of Decitabine vs Patient Choice, with Physician Advice, of Either Supportive Care or Low-Dose Cytarabine for the Treatment of Older Patients with Newly Diagnosed AML



Response	Supportive Care (n = 28) No.	%	Cytarabine (n = 215) No.	%	Total TC (n = 243) No.	%	Decitabine (n = 242) No.	%
CR	1	3.6	17	7.9	18	7.4	38	15.7
CRi	1	3.6	6	2.8	7	2.9	24	9.9
CRp	0	0	1	0.5	1	0.4	5	2.1
CR + CRp	1	3.6	18	8.4	19	7.8*	43	17.8*

Fenaux P, et al. *J Clin Oncol.* 2010;28(4):562-569.; Dombret H, et al. *Blood*. 2015;126(3):291-299.; Kantarjian H, et al. *J Clin Oncol*. 2012;30(21):2670-2677.

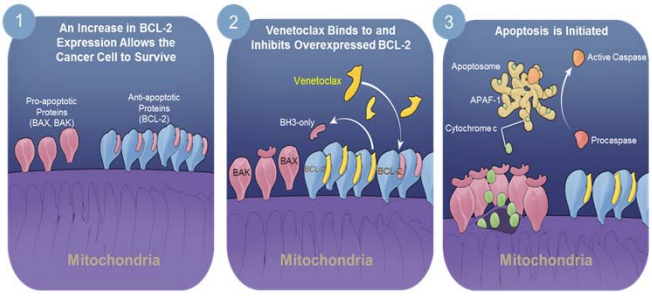
A series of studies have looked at azacitidine and decitabine, which are the typical hypomethylating agents we use in patients with AML, and have compared them to traditional salvage approaches. In these studies, the rate of remission that has been seen in patients receiving hypomethylating therapy hovers between 18% and 35%.

HMAs in AML

Can We Maintain Tolerability But Enhance Efficacy?

Given this relatively low rate of remission and suboptimal survival in our older patient population, many have wondered whether we can maintain the tolerability of hypomethylating agent therapy but add to its efficacy; perhaps by incorporating and combining hypomethylating agents with targeted agents.

Venetoclax: Selective BCL-2 Inhibitor



- Venetoclax is a potent, orally bioavailable agent[1] with demonstrated single-agent activity in:
  - AML cell lines and primary patient samples[2]
  - Heavily pretreated relapsed/refractory AML patients[3]
- Venetoclax was shown to synergize with HMA in preclinical models, suggesting that combination with HMA may be a promising approach in AML[4]
- Reporting from ongoing phase 1b, open-label, nonrandomized, dose-escalation trial of venetoclax in combination with decitabine or azacitidine in older (≥65 years), treatment-naive AML patients (NCT02203773)

[1]Souers A, et al. *Nat Med*. 2013;19:202-208. [2]Pan R, et al. *Cancer Discov.* 2014;4:362-375. [3]Konopleva M, et al. ASH 2014. Abstract 118. [4]Tsao T, et al. *Ann Hematol.* 2012;91:1861-1870.

Venetoclax is a novel and selective BCL2 inhibitor. BCL2 is an anti-apoptotic protein that is increasingly expressed in patients with AML. As monotherapy, venetoclax seems to have a fairly modest response rate in patients with this disease. However, in combination with hypomethylating agents, venetoclax appears to lead to fairly prominent rates of response.

Safety and Preliminary Efficacy of Venetoclax with Decitabine or Azacitidine in Elderly Patients with Previously Untreated AML: A Non-randomized Open-label, Phase 1b Study

DiNardo CD, Pratz KW, Letai A, Jonas BA, Wei AH, Thirman M, Arellano M, Frattini MG, Kantarjian H, Popovic R, Chyla B, Xu T, Dunbar M, Agarwal SK, Humerickhouse R, Mabry M, Potluri J, Konopleva M, Pollyea DA

Lancet Oncol. 2018;19(2):216-228.

Specifically in newly diagnosed patients who are not induction eligible, the combination of hypomethylating therapy with venetoclax seems to lead to high rates of complete remission and complete remission with incomplete recovery in approximately 60% to 70% of patients.

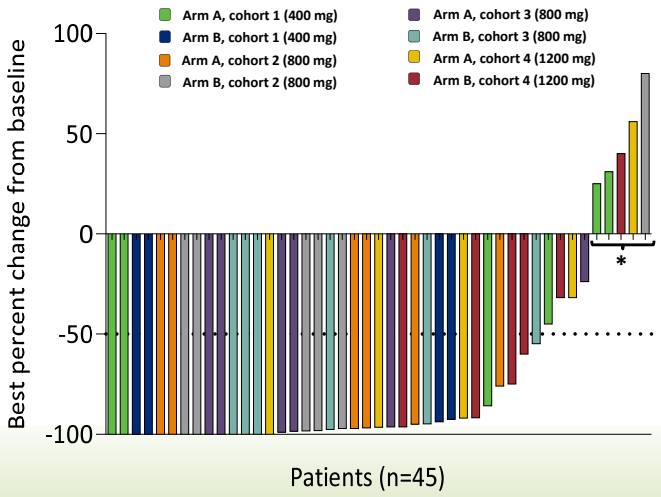
Response Rates

	Group A (n = 23)	Group B (n = 22)	Group C (n = 12)
Complete remission	8 (35%)	6 (27%)	0
CRi	6 (26%)	7 (32%)	8 (67%)
Partial remission	1 (4%)	0	0
Morphologically leukemia-free state	2 (9%)	5 (23%)	0
Resistant disease	3 (13%)	2 (9%)	3 (25%)
Non-evaluable	3 (13%)	2 (9%)	1 (8%)
Complete remission and CRi	14 (61%)	13 (59%)	8 (67%)
Overall response	15 (65%)	13 (59%)	8 (67%)
Overall outcome*	17 (74%)	18 (82%)	8 (67%)

Group A (venetoclax and intravenous decitabine); Group B (venetoclax and subcutaneous or intravenous azacitidine); Group C (venetoclax and decitabine sub-study with the oral CYP3A inhibitor posaconazole).
*Including overall response and MLFS.
Venetoclax is not FDA approved for use in patients with AML.
DiNardo CD, et al. *Lancet Oncol*. 2018;19(2):216-228.

This rate of response is highly promising and was seen in early phase studies of the combination of hypomethylating therapy and venetoclax. Venetoclax is currently FDA-approved for use in chronic lymphocytic leukemia and has been used by clinicians in the off-label setting for patients with AML in combination with hypomethylating therapy. Nevertheless, we are awaiting results of more advanced phase studies of the combination of hypomethylating therapy and venetoclax to determine whether the combination will be promising in the future.

Bone Marrow Blast Count



*5 patients non-evaluable, did not complete cycle 1
DiNardo CD, et al. *Lancet Oncol*. 2018;19(2):216-228.; Pollyea D, et al. ASCO Annual Conference 2016.

In early studies of the combination of venetoclax and hypomethylating therapy, there was definitely a substantial decrease in bone marrow blast burden in the majority of treated patients, and this leads to significant promise in patients receiving this combination.

Reasons for Optimism

- Improved outcomes due to better prognostication, patient selection, and supportive care
- Emergence of effective, targeted therapies
- Novel combinations for older patients that can maintain tolerability and enhance outcomes
- Will the next decade see more approved AML therapies than the last four decades combined?

In conclusion, there is much promise in our field. There are improved outcomes due to better prognostication, patient selection, and supportive care. There is an emergence of effective and targeted therapies. Novel combinations for older patients appear to be emerging that enhance efficacy and maintain tolerability. But there is much work to be done. The majority of patients with AML are yet to be curable or cured. Will the next decade see more approvals in terms of novel therapies for AML? That is yet to be seen but I remain optimistic. Thank you so much for listening.