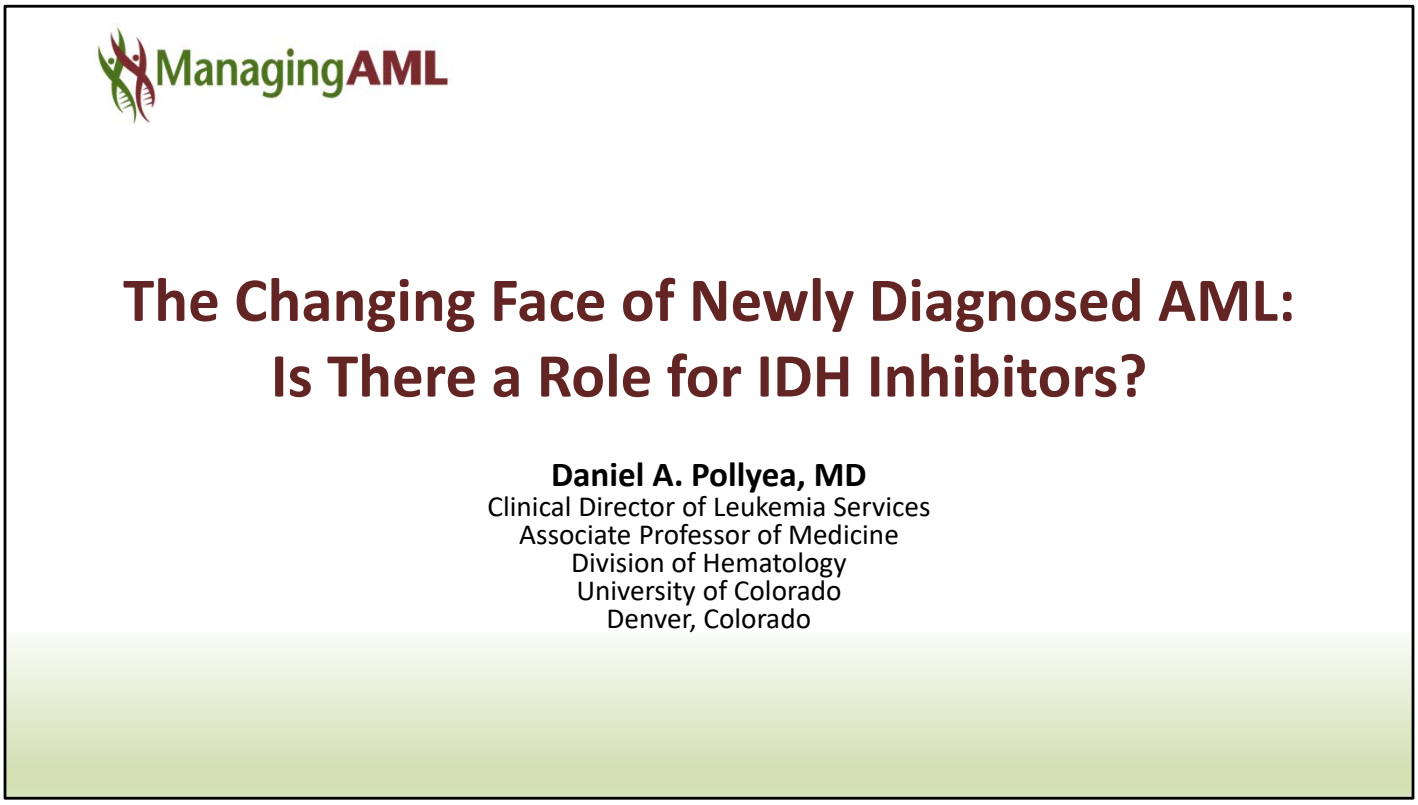


Hi. Welcome to *Managing AML*. My name is Dr. Dan Pollyea and I'm an Associate Professor of Medicine at the University of Colorado, School of Medicine.

Today's Activity

- Outline the clinical imperative for mutational testing for IDH mutations during prognosis of AML and the implications of IDH1 and IDH2 mutations on prognosis
- Compare and contrast trial endpoints of elimination of minimal residual disease versus mutational clearance and relate each to its clinical impact in newly diagnosed AML patients
- Describe promising clinical trials of IDH1 and IDH2 inhibitors for AML, both alone and in combination with other therapies in the frontline setting
- Identify newly diagnosed AML patients who are candidates for clinical trials of IDH1 and IDH2 inhibitors

In today's activity, I will outline the clinical imperative for mutational testing for IDH mutations during prognosis of AML and the implications of IDH1 and IDH2 mutations on prognosis. I will compare and contrast trial endpoints of elimination of minimal residual disease versus mutational clearance and relate each to its clinical impact in newly diagnosed AML patients. I will describe promising clinical trials of IDH1 and IDH2 inhibitors for AML, both alone and in combination with other therapies in the frontline setting, and we will identify newly diagnosed AML patients who are candidates for clinical trials of IDH1 and IDH2 inhibitors.

AML: The First Cancer Genome Sequenced

Table 2. Tier 1 Mutations.*

Annotated Gene	Mutation Type	Annotation	SIFT Prediction	Conservation Score	Base Conservation	Variant Frequency			Best Probe†
						Skin	Tumor	cDNA	
						%			
CDC42	Missense	S30L	Tolerated	597	1	1.03	49.27	46.3	27,990
NRAS	Missense	G12D	Deleterious	616	1	0.66	43.00	42.0	7,468
IDH1	Missense	R132C	Deleterious	445	1	0.81	46.06	63.9	11,400
IMPG2	Missense	G834D	Deleterious	472	0.018	0.67	46.22	0.4	NA
ANKRD26	Missense	K1300N	Deleterious	444	1	0.70	51.73	33.1	514
LTA4H	Missense	F107S	Tolerated	539	0.946	0.68	45.28	47.9	12,138
FREM2	Missense	Q2077E	Tolerated	464	1	0.37	48.92	0‡	NA
C19orf62	Splice-site	Exon 5-1	NA	444	1	0.27	38.71	38.8	5,021
SRRM1	Silent	P691	NA	553	0.988	0.97	46.61	ND	12,858
PCDHA6	Silent	A731	NA	NS	0.423	0.66	49.75	ND	Absent
CEP170	In-frame insertion	Codon 177 in-frame ins L	NA	513	1	0.28	28.57	52.0	15,298
NPM1	Frame-shift insertion	W288fs	NA	689	1	0	45.46	85.4	27,150

Mardis ER, et al. *N Engl J Med.* 2009;361(11):1058-1066.

The really interesting thing about this whole story starts back a little over 10 years ago and this story begins with the first patient with cancer to ever have their full genome sequenced, and that patient happened to be a patient with acute myeloid leukemia or AML. And just from that one patient, shown here in the *New England Journal Medicine* paper, we learned a tremendous amount of information that would really change the landscape of this disease. One of those many things that we learned was that there was in this one particular patient, a mutation in the gene called isocitrate dehydrogenase, and there's two isoforms of that gene, and in this case it is isoform 1, IDH1. While it was known that IDH1 could be mutated in other types of cancers, very little was known or understood about what this gene did or how it may be contributing to leukemia in the case of this patient.

IDH1 and IDH2 are Recurrently Mutated

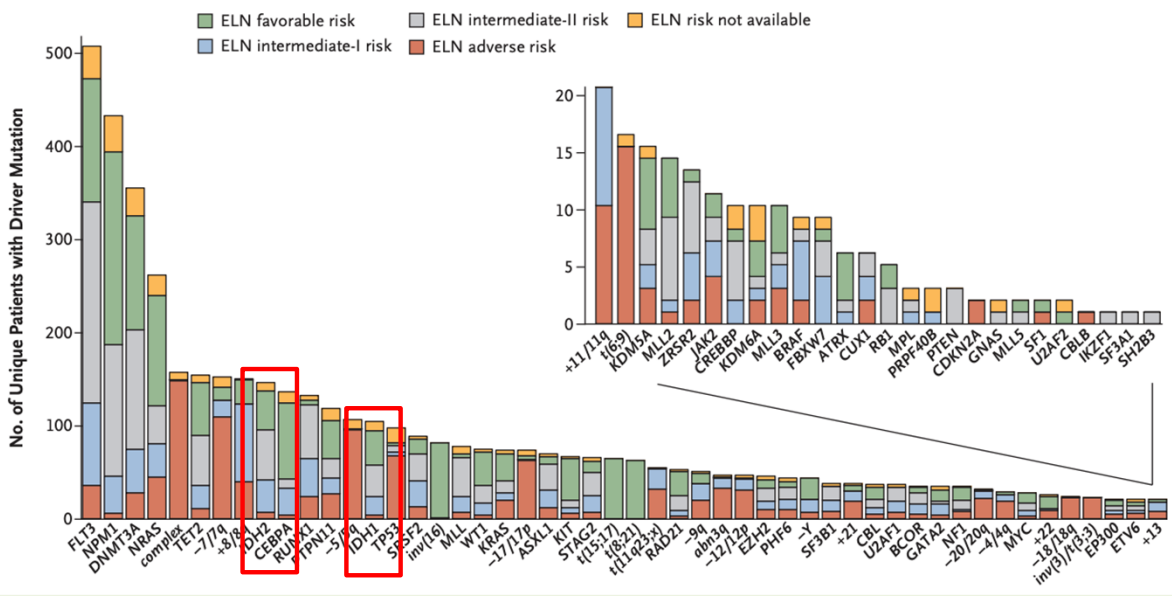
Table 1. (Continued.)

Characteristic	Value
Mutation — no./total no. (%)	
NPM1	54/200 (27)
FLT3	56/200 (28)
DNMT3A	51/200 (26)
IDH1 or *IDH2*	39/200 (20)
NRAS or *KRAS*	23/200 (12)
RUNX1	19/200 (10)
TET2	17/200 (8)
TP53	16/200 (8)

Cancer Genome Atlas Research Network, et al. *N Engl J Med.* 2013;368(22):2059-2074.

The investigators went back and looked at a library of patient samples, in this case several hundred, and found that in fact IDH was a recurrent mutation in those patients, so upwards of 20% of patients that they later did targeted sequencing for had a mutation in IDH1 or IDH2. So, all along kind of right under our noses was this very commonly mutated gene in this disease that we had before been completely unaware of. A lot of progress has occurred over a very short period of time to identify the reasons why this mutation contributes to leukemia and as you will see even new therapies to target patients with this mutation.

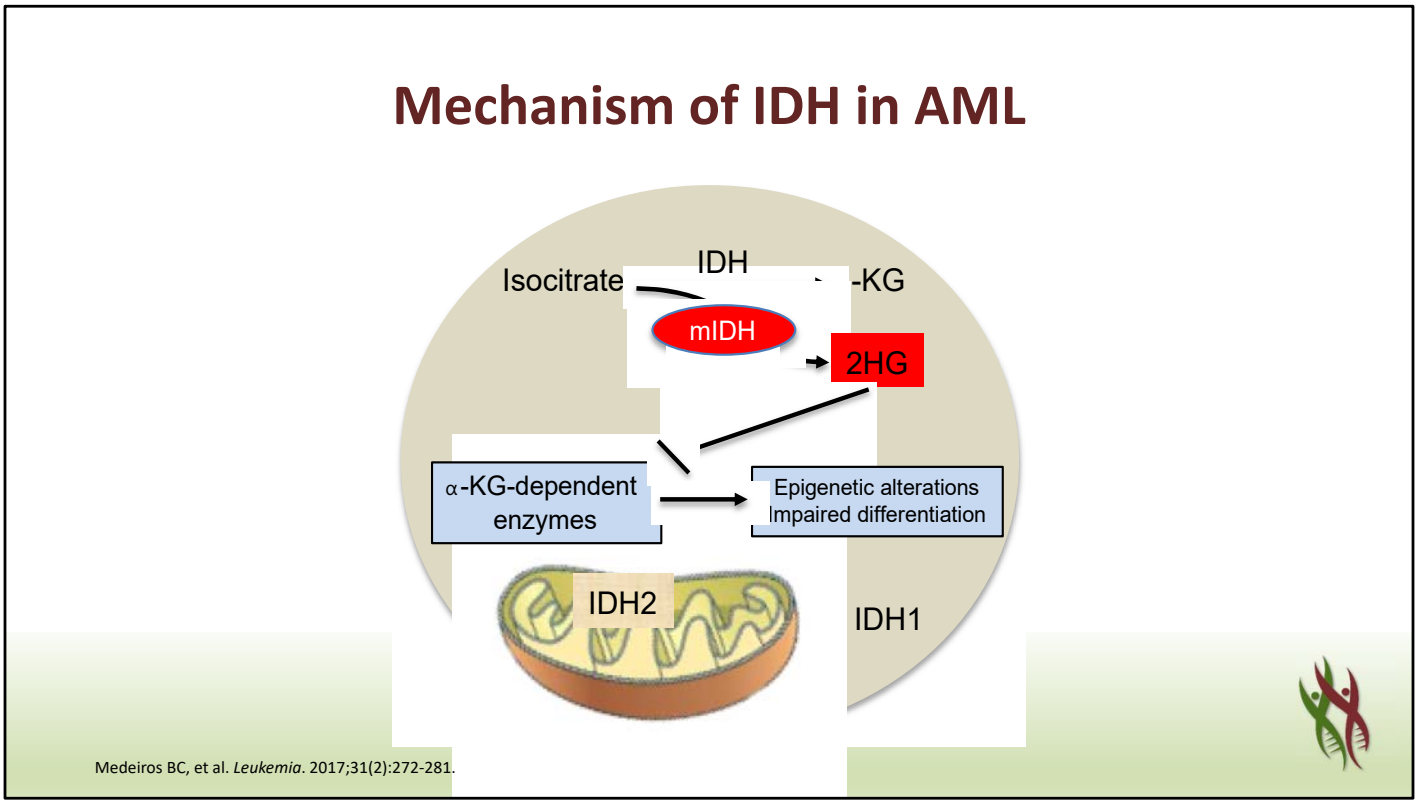
The Changing Face of Newly Diagnosed AML: Is There a Role for IDH Inhibitors?



Papaemmanuil E, et al. *N Engl J Med.* 2016;375(9):900-901.

Here is another way to look at the genomic landscape of AML. This is a large series, also published in the *New England Journal of Medicine* of many, many AML patients and they are here divided up by their different mutational profiles. You can see that some genes are very common or frequent, lots of genes are less frequent, and highlighted here for you is the incidence of IDH2 and IDH1 showing as we discussed previously, these are pretty common recurrent mutations in this disease, but they also exist within a landscape of other mutations.

The Changing Face of Newly Diagnosed AML: Is There a Role for IDH Inhibitors?



What is the significance of IDH when it comes to AML? The field has very rapidly done the work to help figure this very important question out, and it goes back to you have to first understand what the function of isocitrate dehydrogenase is, so when you think all the way back to your molecular biology class and if you remember the Krebs's cycle, one of the really important ways that a cell makes energy, IDH is a critical gene that is involved in a normal process of the Krebs's cycle. It has a job converting isocitrate to something called alpha-ketoglutarate and then if you remember that Krebs's cycle, other genes and other enzymes convert further proteins along this cycle to make energy, and that is how the cells do energy, that is how they do metabolism.

In the presence of a mutated copy of IDH, you re-route this whole process and instead of converting isocitrate to alpha-ketoglutarate, you divert this process and you form something call 2-hydroxyglutarate or 2-HG. And 2-HG, is made in huge quantities compared to the normal levels of alpha-ketoglutarate and this 2-HG is now referred to as the first-known oncometabolite because very high levels of 2-HG interfere with all the enzymes in the body that are dependent on normal levels of alpha-ketoglutarate, and because these are so structurally similar, the thing is you just outcompeting all the alpha-ketoglutarate dependent enzymes for their alpha-ketoglutarate to hydroxyglutarate is binding there instead and it is causing derangement and problems and in this case impairment of differentiation, which leads to leukemia. As I mentioned before, there's two isoforms of this gene, IDH1 exists in the cytoplasm and IDH 2 exists in the mitochondria, but both of them have the similar function with respect to the Krebs's cycle and mutations in either gene can lead to leukemic processes.

Prognostic Implications of IDH

Table 2. *IDH* mutations in AML: frequency and clinical outcomes

	All mIDH		mIDH1-*R132*		mIDH2 *(all)*		mIDH2-*R140*		mIDH2-*R172*	
Study	*Frequency*	*Prognosis*	*Frequency*	*Prognosis*	*Frequency*	*Prognosis*	*Frequency*	*Prognosis*	*Frequency*	*Prognosis*
Abbas *et al.*[51] (*N* = 893)	17%	↔ OS	6%	↔ OS	11%	↔ OS	8.3%	↔ OS	2.6%	↔ OS
Aref *et al.*[37a] (*N* = 211)	19%	↓ OS ↔ CR	8.5%	NR	10.4%	NR	9.5%	NR	1%	NR
Boissel *et al.*[43] (*N* = 520)	NR	NR	9.6%	↑ RR[a] ↓OS[a]	NR	NR	NR	NR	3.0%	↑ RR[a] ↓OS[a]
Chotirat *et al.*[50] (*N* = 230)	19.1%	↔ OS	8.7	↔ OS	10.4%	↔ OS	8.7%	↔ OS	1.7%	↔ OS
Chou *et al.*[40] (*N* = 446)	18.2%	↑ OS (trend)	6.1%	↓ OS (trend)	12.1%	↑ OS ↔ DFS ↔ RFS	9.2%	NR	2.9%	NR
DiNardo *et al.*[35] (*N* = 826)	20%	↔ OS ↔ CR	7.1%	↔ OS ↔ CR	12.8%	↔ OS ↔ CR	10%	NR	2.7%	NR
Feng *et al.*[48] (*N* = 8121)	NR	NR	4.4–9.3%	↓ OS ↔ CR ↓CR[a]	NR	NR	NR	NR	NR	NR
Green *et al.*[55] (*N* = 1473)	17%	NR	7%	↔ OS	10%	NR	8%	↑ OS	2.0%	↓ OS
Marcucci *et al.*[10a] (*N* = 358)	33.0%	NR	13.7%	↔ OS ↓DFS	19.3%	↔ OS ↓CR	15.6%	↔ OS	3.6%	↓ CR ↔ OS
Paschka *et al.*[38] (*N* = 805)	16%	↓ OS in NPM1^{mut}/no FLT3-ITD^{wta}	7.6%	↔ OS	8.7%	↔ OS	6.0%	↔ OS	2.7%	↔ OS
Patel *et al.*[42] (*N* = 398)	14.1%	↑ OS in NPM1^{mut}/FLT3-ITD^{wta}	5.8%	↑ OS	8.3%	↑ OS	6.0%	↑ OS	2.3%	NR
Ravandi *et al.*[57] (*N* = 358)	30%	↔ OS ↔ CR ↔ EFS	7%	↔ OS[b] ↔ CR ↔ EFS	14%	↔ OS ↔ CR ↔ EFS	NR	NR	NR	NR
Schnittger *et al.*[106] (*N* = 1414)	NR	NR	6.6%	↓ OS (trend) ↓EFS ↑RR	NR	NR	NR	NR	NR	NR
Thol *et al.*[52a] 153 MDS, 53 AML	NR	NR	NR	NR	12.1%	↔ OS ↔ CR	11%	NR	1.1%	NR
Wagner *et al.*[11a] (*N* = 275)	NR	NR	10.9%	↔ OS[c] ↔ CR ↔ RFS	NR	NR	NR	NR	NR	NR
Willander *et al.*[9] (*N* = 189)	21.7%	NR	7.9%	↔ OS[c]	13.7%	NR	11.1%	↓ OS	2.6%	↑ OS
Yamaguchi *et al.*[49] (*N* = 233)	16.7%	↓ OS ↓CR ↔ RFS	8.6%	NR	8.2%	NR	7.3%	NR	0.9%	NR

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; DFS, disease-free survival; EFS, event-free survival; IDH, isocitrate dehydrogenase; m*IDH*, mutant *IDH*; mut, mutation; NR, not reported; OS, overall survival; RFS, relapse-free survival; RR, relapse rate; wt, wild type; '↔', no effect; ↑, improved; ↓, worsened. [a]Limited to cytogenetically normal AML. [b]*IDH1* G105 single-nucleotide polymorphism (SNP) had no effect on OS. [c]*IDH1* SNP rs11554137 was an adverse prognostic factor for OS.

Medeiros BC, et al. *Leukemia*. 2017;31(2):272-281.

We know about the incidence of this gene mutation. We know a little bit about the biology of this gene mutation. What is its prognostic significance? We have become used to certain gene mutations in AML having a good or poor risk of prognosis and with IDH, you can see, as reflected by this table from a recent publication, it is really all over the map. I think there is no general consensus today as to what the prognosis overall of an IDH1 or IDH2 mutation is, probably because numbers are too small, still a little bit early, but really there is no clear prognostic impact from either an IDH1 or IDH2 mutation. With more time, more patient samples, more experience, that may change, but at the moment, we do not think of this as having an overtly prognostic impact on this disease.

Current Landscape of IDH Inhibitors in AML

- Enasidenib
  - FDA approved for relapsed/refractory IDH2+ AML
- Ivosidenib
  - FDA approved for relapsed/refractory IDH1+ AML
  - FDA approved for newly diagnosed IDH1+ AML not eligible for induction chemotherapy
- Olutasidenib
  - In clinical development for IDH1+ AML/MDS
- Vorasidenib
  - Dual IDH1/IDH2 inhibitor (not being developed for AML)

Liu X, et al. *Biomark Res*. 2019;7:22.; Megías-Vericat JE, et al. *Blood Lymphat Cancer*. 2019;9:19-32.

As I mentioned before, not only is this an important contributing factor to our understanding of the biology of this disease, but it is also an opportunity, so the presence of an IDH mutation makes the question of whether you can impair or inhibit patients with leukemia with mutant copies of IDH with a specific targeted therapy, and there is definitely precedence for this in our field. We have FLT3 inhibitors, working on other targeted gene mutational inhibitors, and the same thought was conceived very early on after the discovery that IDH was a recurrently mutated gene in this disease. In a very short period of time, an incredibly short period of time, we now have two FDA-approved IDH inhibitors for this disease. Enasidenib is an inhibitor of IDH2 and this has FDA-approval for relapsed and refractory AML patients with an IDH2 mutation. Ivosidenib is the other approved IDH inhibitor. This is a targeted therapy against IDH1, so patients with an IDH1 mutation can benefit from ivosidenib and it is FDA-approved for two indications. It is also approved for relapsed/refractory AML, as is enasidenib. But it has an additional approval that we will talk about for a newly diagnosed IDH1 positive AML patient who is not eligible for standard intensive induction chemotherapy, now there is a labeled indication for ivosidenib in that setting. Other drugs are under investigation as IDH inhibitors. Olutasidenib is a new IDH1 inhibitor that is under clinical investigation and vorasidenib is a dual IDH1 and IDH2 inhibitor that is currently not being developed specifically for AML but being developed for perhaps other solid tumor patients with IDH mutations.

Guideline Recommendations

- Per NCCN recommendations, all newly diagnosed patients should have a comprehensive next-generation sequencing panel performed (including IDH1/IDH2)
- IDH is a stable mutation but recommended to repeat this panel at known or suspected relapse

Megías-Vericat JE, et al. *Blood Lymphat Cancer*. 2019;9:19-32.

Recommendations related to IDH testing and treatment have made their way in the standard guideline of recommendations. For instance, the National Comprehensive Cancer Network recommends that all newly diagnosed AML patients should have comprehensive next-generation sequencing performed as part of the diagnostic workup and every comprehensive panel should include tests for IDH1 and IDH2. In addition, there are recommendations to repeat this screening at relapse or suspected relapse. Now, IDH is a fairly stable mutation, so when present at diagnosis it is almost always present at relapse, but sometimes the allele frequency or the burden of IDH at diagnosis may be too low to really appreciate, but at relapse it is sort of becomes more apparent. So it is always a good idea to repeat the sequencing at relapse because of this therapeutic opportunity at the moment.

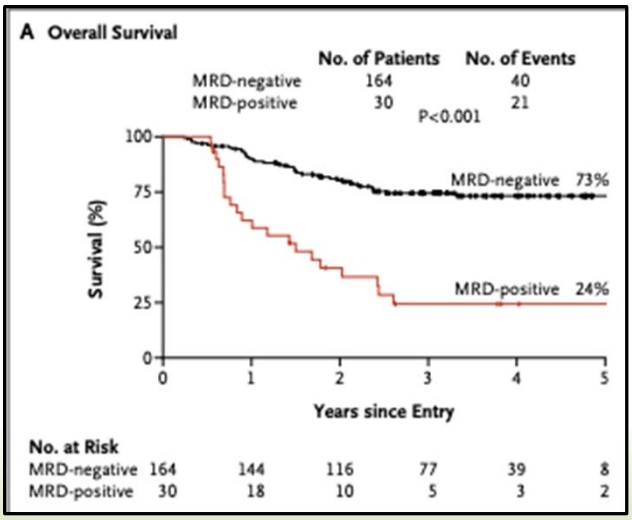
Measurable Residual Disease (MRD)

- Defined as the residual cell population that remains after a patient achieves a remission
- Detection methods not uniform
- Poor prognostic impact

Schuurhuis GJ, et al. *Blood.* 2018;131(12):1275-1291.

Let's talk about measurable residual disease, also sometimes called minimal residual disease or MRD. This is defined as the residual cell population that remains after a patient has achieved a clinical remission. The ways to detect MRD in the clinical setting are really still not very uniform, different places do this different ways and there is different ways to define this. There is no real consensus on this yet, but it is fairly well understood or accepted that the presence of MRD when a patient is in and otherwise clinical remission has a poor prognostic impact.

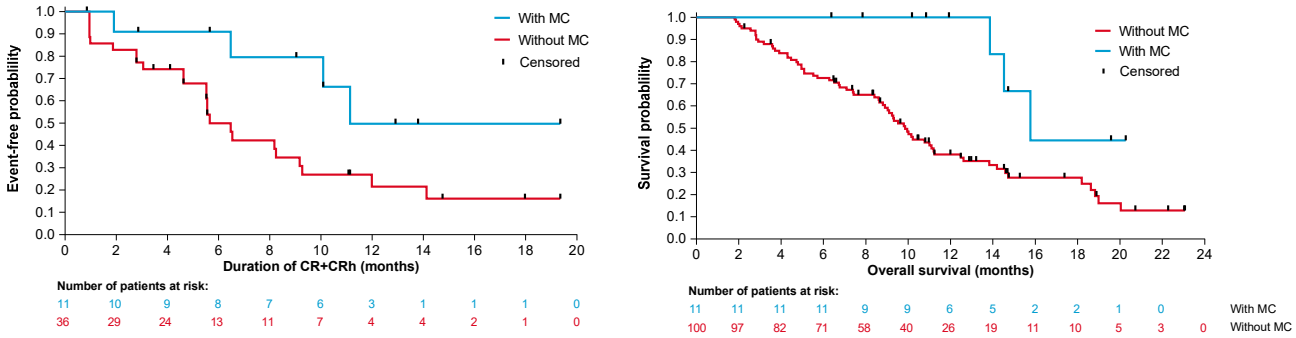
Defining MRD by Genetic Sequencing of NPM1



Ivey A, et al. *N Engl J Med.* 2016;374(5):422-433.

One way to define MRD is by genetic sequencing of particular gene mutations. One of the most common mutations in AML, upwards of a third of AML patients have this, is a mutation of a gene called nucleophosmin or NPM1. What this data shows from the *New England Journal of Medicine* a couple of years ago is that in patients who have an NPM1 mutation, detecting residual evidence of this with a really specific detection technique called digital droplet PCR, if it is detectable, these are all patients who achieved a remission, the prognosis is much worse. This is a survival curve showing overall survival for patients who are MRD negative versus MRD positive, and you can see a big difference in these curves with favorability toward the patients who achieved MRD negativity.

Potential to Use IDH1 as an MRD Marker



Pollyea D, et al. EHA 2018. Abstract S1560.

When we are talking about IDH, that presents an opportunity for MRD testing in this disease or with this gene as well. The data are a lot more preliminary. The numbers are not as big, but with what preliminary data we do have, it appears to be a very similar story. The presence of IDH, either 1 or 2, as a residual disease marker has prognostic impact. In this figure, we are showing IDH1, and the persistence of IDH1 in patients who achieve a remission is associated with an inferior event-free survival and overall survival compared to patients who clear all evidence of this disease or of the gene mutation with a really sensitive detection technique.

Frontline Use of IDH Inhibitors

- Ivosidenib approved as a single agent
- Other opportunities for single-agent use and in combination with other therapies

Helwick C. *The ASCO POST*. January 2, 2019.

Moving on, we have talked about the role for IDH inhibitors and the FDA-approved label for enasidenib and ivosidenib, but what about taking a more aggressive approach toward targeting IDH in the earlier setting. Enasidenib and ivosidenib are both approved in the relapsed/refractory setting. As we discussed, ivosidenib is now approved as a single agent in the upfront setting, but I think there are a lot of other opportunities we're excited about using these drugs, sometimes in combination in the upfront setting, to try to improve the impact that they will have.

IDH Inhibitors as Single Therapies in Newly Diagnosed AML Patients

Therapy	IDH Isoform	N	ORR	OS	Citation
Enasidenib	IDH2	39	31%	11 months	Pollyea, et al. *Leukemia*. 2019
Ivosidenib	IDH1	33	55%	13 months	Roboz, et al. *Blood*. 2020

First, let's just think about them as single agents, enasidenib the IDH2 inhibitor, ivosidenib the IDH 1 inhibitor. As we discussed, ivosidenib is approved as a single agent in newly diagnosed AML patients. Based on this data here, a very small number of patients, 33 patients, and there is 55% overall response rate in that setting and overall survival of about a year. Enasidenib is not approved but has similar data as a single agent in IDH2 positive newly diagnosed AML patients who were not felt to be suitable candidates for any other therapy.

The Changing Face of Newly Diagnosed AML: Is There a Role for IDH Inhibitors?

Enasidenib as a Single Agent

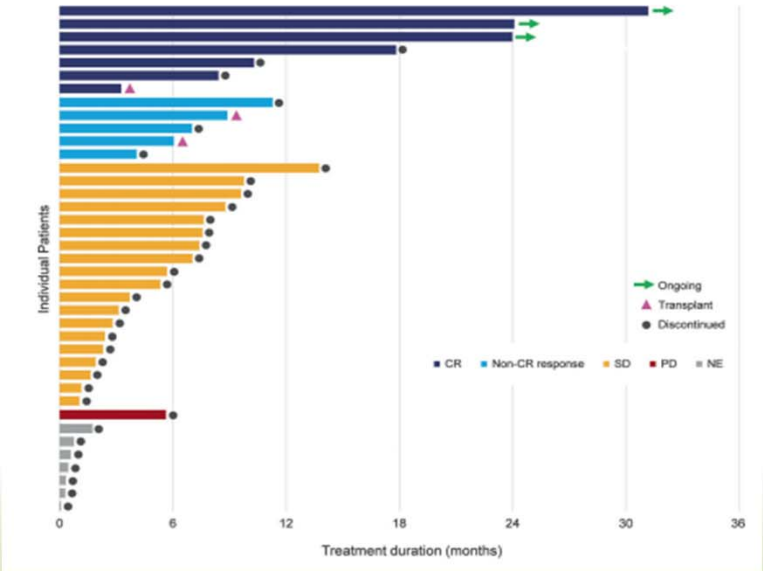


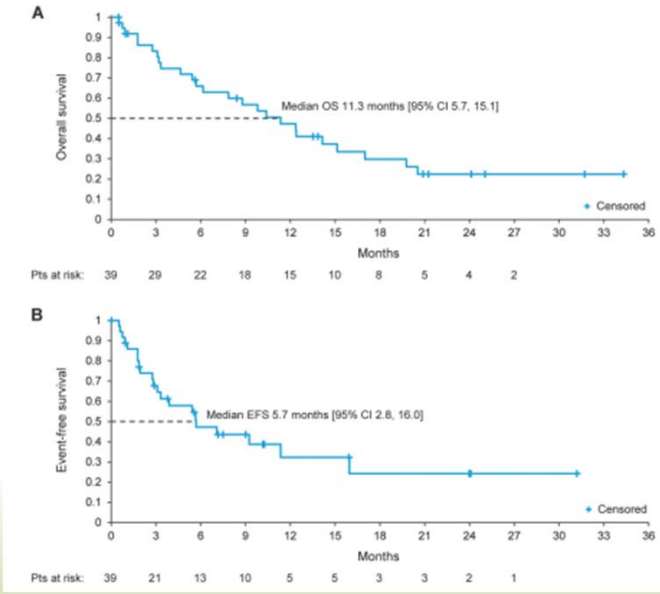
Table 3 Hematologic responses, times to response, and durations of response

	Patients with newly diagnosed AML $N = 39$
Overall response rate (ORR),[a] n(%)	**30.8% (12/39)**
95% CI	17.0, 47.6
Best response, n(%)	
Complete remission (CR)	7 (18)
CR with incomplete count recovery (CRi/CRp)	1 (3)
Partial remission	2 (5)
Morphologic leukemia-free state	2 (5)
Stable disease,[b] n(%)	19 (49)
Disease progression, n(%)	1 (3)
Not evaluable,[c] n(%)	7 (18)
Time to first response, months, median (range)	1.9 (1.0–3.8)
Time to best response, months, median (range)	3.7 (1.0–12.9)
Duration of any response, months, median [95% CI]	NR [7.4, NR]
Time to CR, months, median (range)	5.6 (3.4–12.9)
Duration of CR, months, median [95% CI]	NR [3.7, NR]

Pollyea DA, et al. *Leukemia.* 2019;33(11):2575-2584.

Just digging into this a little bit more, here are the enasidenib swim-lane plots and you can see the dark blue on top are the patients who achieved a complete remission. You can see some of these remissions have been quite durable. The overall response rate as I mentioned before is about 31%. There are some complete remissions in that group. It works fairly quickly. The time to the first response is about two months. You can see that as of the time of the publication of this paper, the duration of response had not yet been reached, at least the median had not been reached.

OS and EFS for Single-Agent Enasidenib



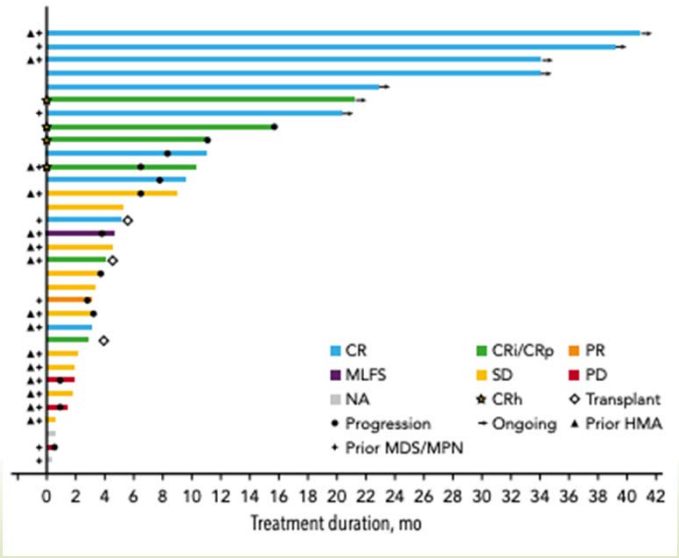
Pollyea DA, et al. *Leukemia.* 2019;33(11):2575-2584.

And then here are overall survival and event-free survival curves for enasidenib as a single agent in this population, so you can see as I said before, about a year for the overall survival.

The Changing Face of Newly Diagnosed AML: Is There a Role for IDH Inhibitors?

Ivosidenib as a Single Agent in AML

Response category	Ivosidenib 500 mg, n = 33*
CR + CRh rate, n (%) [95% CI]	14 (42.4) [25.5-60.8]
Time to CR/CRh, median (range), mo	2.8 (1.9-12.9)
Duration of CR/CRh, median [95% CI], mo	NE [4.6 to NE]
CR rate, n (%) [95% CI]	10 (30.3) [15.6-48.7]
Time to CR, median (range), mo	2.8 (1.9-4.6)
Duration of CR, median [95% CI], mo	NE [4.2 to NE]
CRh rate, n (%) [95% CI]	4 (12.1) [3.4-28.2]
Time to CRh, median (range), mo	3.7 (1.9-12.9)
Duration of CRh, median [95% CI], mo	6.5 [2.8 to NE]
ORR by IWG, n (%) [95% CI]†	18 (54.5) [36.4-71.9]
Time to first response, median (range), mo	1.9 (0.9-3.6)
Duration of response, median [95% CI], mo	NE [4.6 to NE]
Best response by IWG, n (%)	
CR	10 (30.3)
CRi or CRp	6 (18.2)
PR	1 (3.0)
MLFS	1 (3.0)
SD	10 (30.3)
PD	3 (9.1)
Not assessed	2 (6.1)

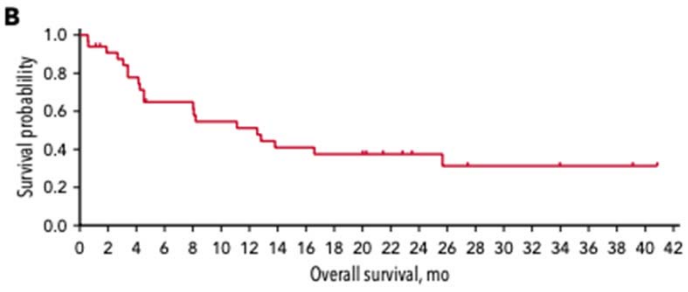


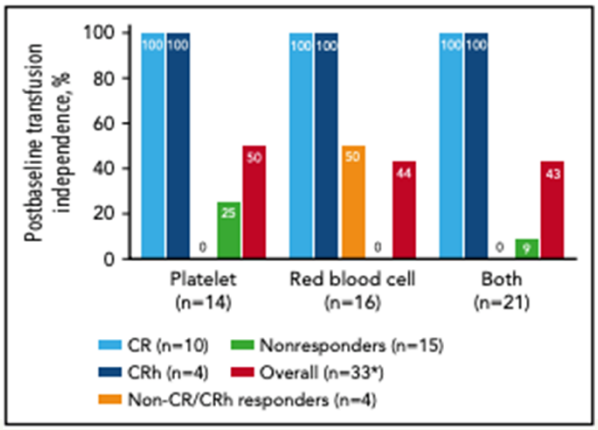
Roboz JG, et al. *Blood*. 2020;135(7):463-471.

Similar data for ivosidenib, single-agent, IDH1 positive, newly diagnosed AML, you can see on the right this swim-lane plot show patients who achieved complete remissions often have fairly durable complete remissions. The complete remission rate as you can see in the table on the left, similar to that which we discussed for enasidenib and similar time to response and median response durations.

The Changing Face of Newly Diagnosed AML: Is There a Role for IDH Inhibitors?

OS and Transfusion Independence for Ivosidenib as a Single Agent in AML





Roboz JG, et al. *Blood*. 2020;135(7):463-471.

Overall survival is shown on the left here for ivosidenib and it is also very interesting to note and to appreciate the table on the right because this is something that seems to be unique to these targeted therapies compared to more traditional chemotherapy agents that we have. This shows the percentage of patients who achieved transfusion independence. You can see that of course the blue colors as you would expect by definition, patients who achieve complete remissions have blood count recovery, but what is very interesting is that there are patients who do not achieve the historically defined outcomes for responses who are achieving benefit with respect to transfusion independence. And this is part of what has led to the approval of this therapies and their sort of beneficial impact on quality of life. There are scenarios where even patients who do not achieve traditionally defined responses can have real benefits from these therapies with respect to transfusion impendence, so something to keep in mind when thinking about selecting these treatments.

IDH Inhibitors with Azacitidine for Newly Diagnosed AML Patients

Outcomes	Ivosidenib + AZA (n = 23)	Enasidenib + AZA (n = 68)
Overall response rate	18 (78.3%)	46 (68%)
Median duration of response	Not estimable	Not estimable
Complete remission rate	14 (60.9%)	34 (50%)

DiNardo C, et al. ASH 2019. Abstract 643.

What about combining IDH inhibitors with other therapies in the upfront setting? Well, these studies are underway. They are still fairly immature. This is a study that was presented at ASH 2019. Ivosidenib or enasidenib plus azacitidine in newly diagnosed patients, you can see that there may be a higher response rate than we came to expect in the setting of this single agent alone, so definitely some promise there for patients newly diagnosed with IDH mutations who are not good candidates for intensive induction chemotherapy.

IDH Inhibitor with 7+3 for Newly Diagnosed AML

Response, n (%)	Ivosidenib (AG-120) + chemotherapy			Enasidenib (AG-221) + chemotherapy		
	All (n=49)	*De novo* (n=34)	sAML (n=15)	All (n=89)	*De novo* (n=56)	sAML (n=33)
CR+CRi/CRp	**39 (80)**	31 (91)	8 (53)	**64 (72)**	43 (77)	21 (64)
CR	**35 (71)**	27 (79)	8 (53)	**50 (56)**	36 (64)	14 (42)
CRi/CRp	**4 (8)**	4 (12)	-	**14 (16)**	7 (13)	7 (21)
MLFS	**3 (6)**	1 (3)	2 (13)	**11 (12)**	6 (11)	5 (15)
PR	**1 (2)**	-	1 (7)	**1 (1)**	-	1 (3)
Treatment failure	**6 (12)**	2 (6)	4 (27)	**13 (15)**	7 (13)	6 (18)

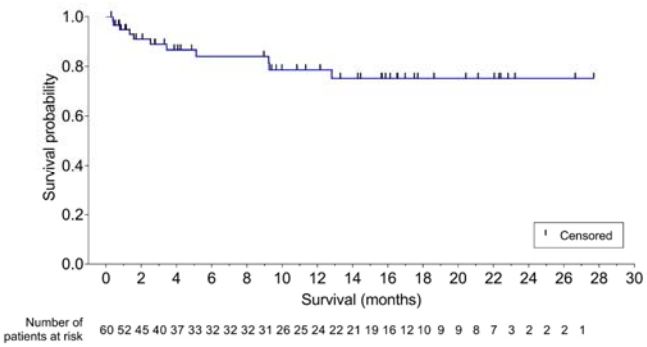
Stein M, et al. *Blood.* 2018;132(Supplement 1):560.

And then what about patients who are good candidates for induction chemotherapy who have IDH mutations, would there be benefit from adding an IDH inhibitor to the traditional backbone in the intensive induction chemotherapy that we called 7 + 3? You can see again, fairly early results presented now a year and a half ago at the ASH meeting, you can see that for both ivosidenib and enasidenib we're just showing here response rates. This is really the only data we have. This looks to be a viable option with respect to, it is not shown here, but tolerability looked fairly good. It is a little hard to assess in a single-arm setting what impact the addition of an IDH inhibitor might have on response with a therapy like induction chemotherapy that has a very high response rate on its own. But I think over time, the survival data will be very helpful in parsing out the success of a strategy like this. So, it is certainly where the field is hopeful things will go to improve on standard induction chemotherapy with the addition more targeted therapies.

The Changing Face of Newly Diagnosed AML: Is There a Role for IDH Inhibitors?

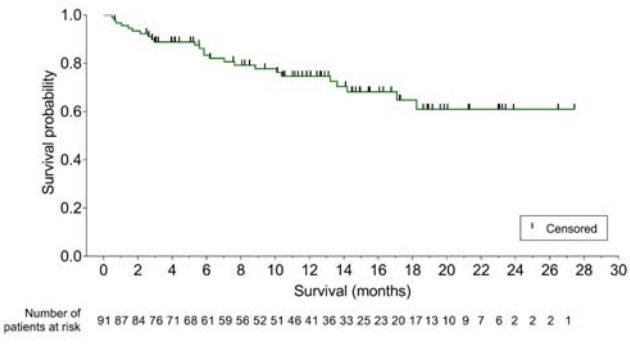
Overall Survival

Ivosidenib



- 79% probability of being alive at 1 year after Induction Day 1
- Median overall survival not yet estimable

Enasidenib



- 75% probability of being alive at 1 year after Induction Day 1
- Median overall survival not yet estimable

Stein M, et al. *Blood.* 2018;132(Supplement 1):560.

And then following up on this, a very early look at the survival and I think again we need more time to see how this holds up, but very promising strategies.

Ongoing Phase III Studies of IDH Inhibitors in Newly Diagnosed AML

Study	Setting	Centers
Unfit for Induction Chemotherapy		
Ivosidenib vs Placebo + Azacitidine	Newly diagnosed IDH1+ AML	Multiple (includes US)
Fit for Induction Chemotherapy		
Ivosidenib or Enasidenib with Induction, Consolidation and Maintenance	Newly diagnosed IDH1/IDH2+ AML	Netherlands

There are some important phase 3 studies ongoing using IDH inhibitors for newly diagnosed patients. I have divided them into two rough categories. Those who are unfit for induction chemotherapy, there is an ivosidenib versus placebo plus azacitidine clinical trial to really get at the benefit of the addition of ivosidenib to azacitidine in newly diagnosed IDH1 positive AML patients, that is a worldwide study. Then in Europe, in particular, they are more aggressively looking at the addition of an IDH inhibitor with induction, consolidation, and maintenance in newly diagnosed IDH positive AML patients.

Thank you so much for viewing this activity. I hope this was helpful.