ManagingAML

Are IDH2 Inhibitors Right for Your AML Patient?

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Welcome to Managing Acute Myeloid Leukemia, or AML. I am Dr. Hetty Carraway, and today I will review whether IDH2 inhibitors are right for your AML patient. During the course of this presentation, I will review the prognosis for adult patients diagnosed with AML; summarize the role of IDH2 inhibitors in the diagnosis, prognosis, and treatment of patients with IDH2-mutated AML; outline a treatment plan for AML patients with IDH2 mutation in the relapsed or refractory setting, taking into consideration patient selection, proper administration, and potential adverse events; as well as identify the latest updates in emerging data related to safety and efficacy of IDH2 inhibitors currently in clinical trials.

Conflict of Interest Disclosure

- **Research Funding:** Celgene
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- **Discussion of Off-Label Drug Use:** The drugs discussed as part of clinical trials have not yet been approved by the FDA but are all under investigation for MDS and/or AML

These are my disclosures.

Are IDH2 Inhibitors Right for Your AML Patient?

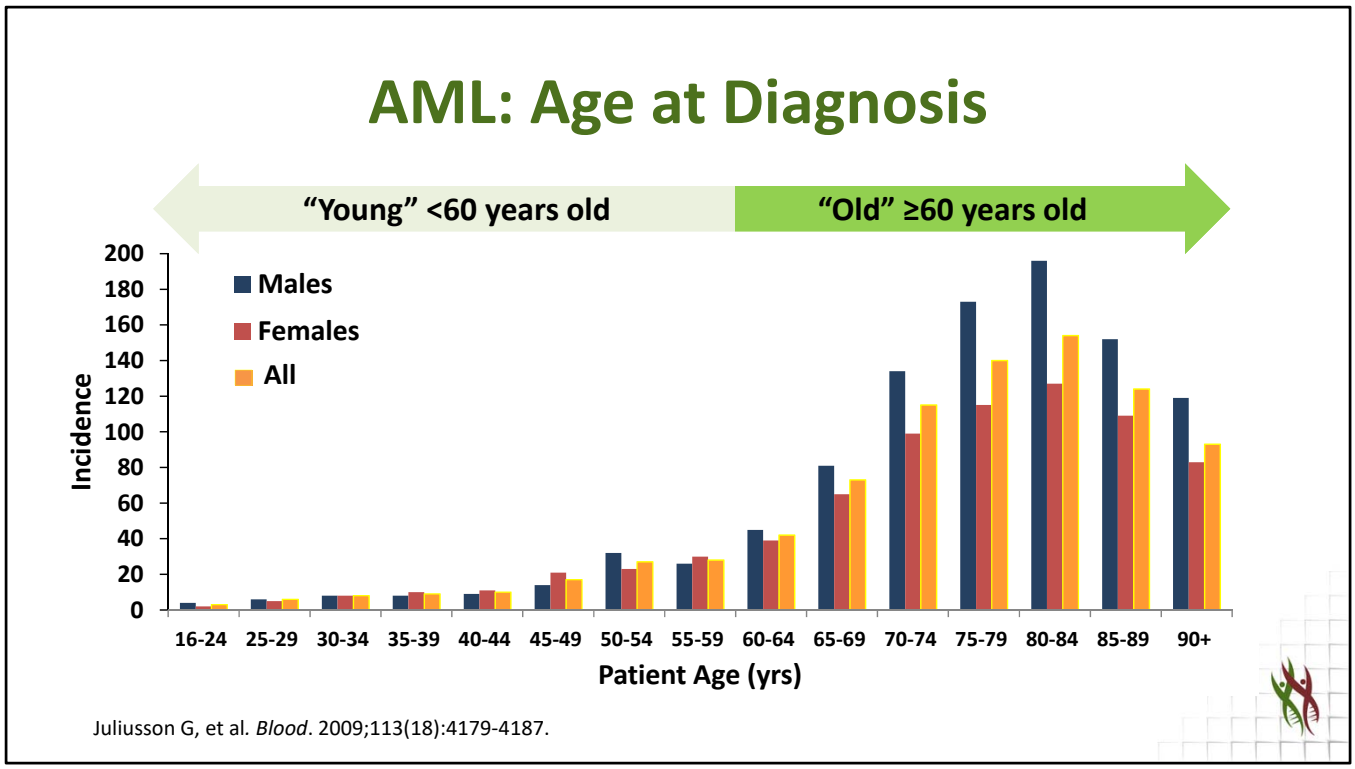
AML Statistics

- 21,380 new cases of AML annually*
- 10,590 deaths from AML*
- Uncommon before age of 45, average age 68 years
- Slightly more common among men than women
- The majority of adults with AML achieving a CR will relapse and a minority of such patients are cured
- Prognostic factors include age, karyotype, mutational status, and duration of CR1

*2018 statistics estimate 19,520 new cases and 10,670 deaths annually
American Cancer Society. Cancer Statistics 2017. *CA: A Cancer Journal for Clinicians. www.cancer.org.*; American Cancer Society. Key Statistics for AML. *https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html*

AML affects about 21,000 patients annually. Unfortunately, over 50% of those patients die directly from acute myeloid leukemia. The diagnosis of AML is uncommon before the age of 45 and the average age of diagnosis is 68. It is slightly more common among men than women. The majority of adults with AML achieving complete remission will ultimately relapse, and a minority of such patients are cured. The prognostic factors in treating patients with AML include age, cytogenetics, mutational status, and the duration of their first complete remission.

Are IDH2 Inhibitors Right for Your AML Patient?



Juliusson G, et al. *Blood*. 2009;113(18):4179-4187.

Here you can see AML in old and young patients and the incidence related to their age. Young patients are typically defined as under the age of 60, and older patients are usually defined as greater than or equal to the age of 60. You can see here the blue bars reflect incidence in males and red bars reflect incidence in females. In general, you can see a spike in the incidence after the age of 60 which annotates the typical population for patients diagnosed with AML.

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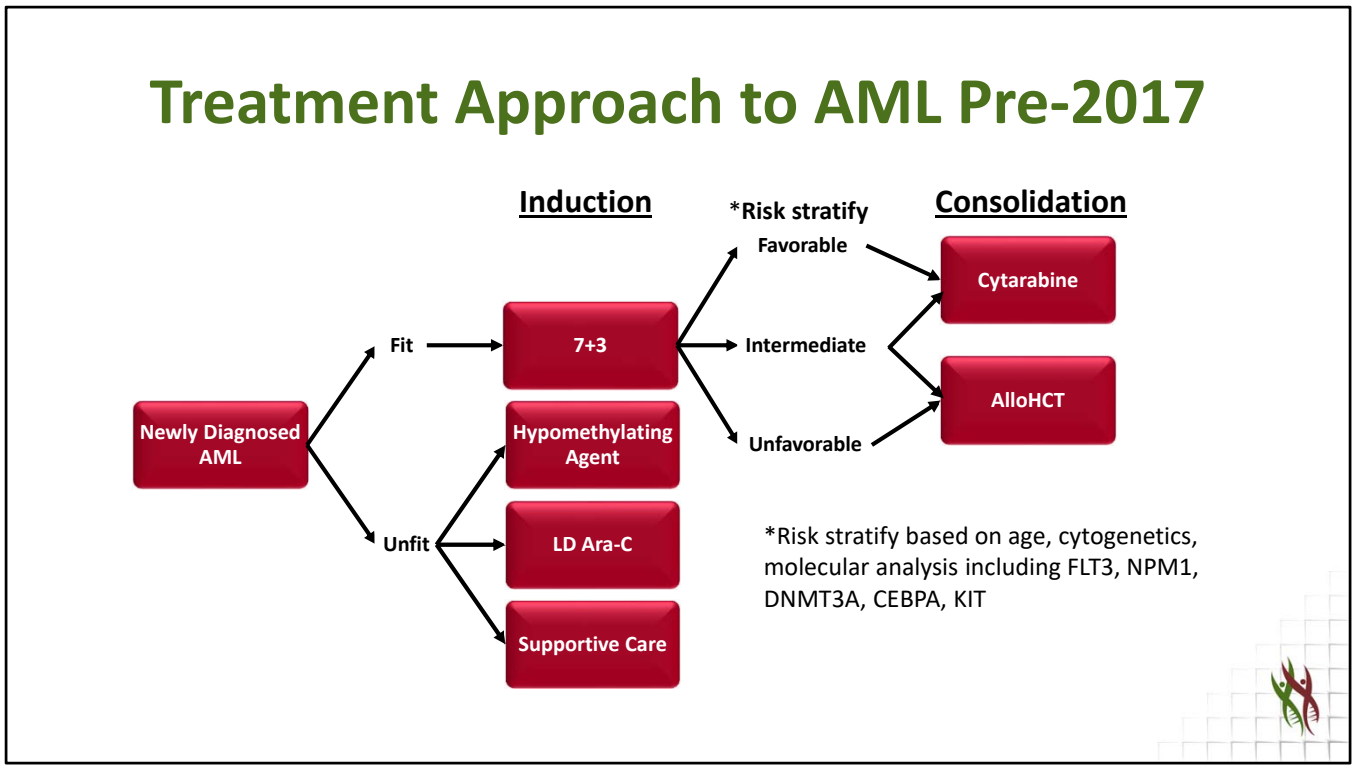

A typical treatment approach to AML before 2017 included evaluating patients and separating them into a population that would be able to undergo therapy with induction chemotherapy such as 7+3 (cytarabine plus an anthracycline). For those patients undergoing intensive chemotherapy, we would stratify those patients based on their chromosome and mutational status as to whether or not they were favorable, intermediate, or unfavorable. For those patients highest at risk, if they were appropriate for bone marrow transplant, those patients in the intermediate and unfavorable category would then receive consolidation with a transplant. Whereas those in the favorable or intermediate category that were not transplant candidates or not needing transplant, they would receive consolidation chemotherapy with cytarabine. Furthermore, those patients that were not able to tolerate induction chemotherapy typically proceeded with hypomethylating therapy, low-dose cytarabine, or supportive care. As noted here, many of the patients were again risk stratified based on age, cytogenetics, and molecular analysis, including the mutations annotated on this slide.

How Do Older Adults Compare with "7+3"?

	Older Adults >60	Younger Adults <60
Complete Remission Rates	40-55%	65-85%
Treatment Related Mortality	15-25%	5-10%
5-Year Overall Survival	5-10%	30-40%

Based on CALGB and MRC trials in which adults of all ages were eligible
Burnett AK, et al. *J Clin Oncol.* 2013;31(27):3360-3368.

When we think about our patients that are older, over the age of 60, as we discussed in the prior slide, you can see the complete remission rates for that population pale in comparison to those that are younger, to the tune of 40% to 55% CR rates compared to 65% to 85% CRs. Additionally, treatment-related mortality is higher in the older adults ranging from 15% to 25%. You can see ultimately the five-year overall survival for those patients that are older is in typical single digits.

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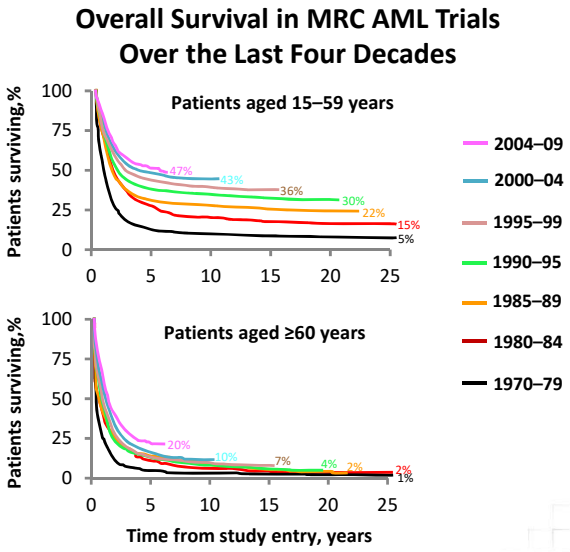
Lack of Progress for AML Patients >60 Years Old

- Over the last 40 years, survival has improved for AML patients <60 years of age
- Little progress has been made for the long-term survival for patients >60 years of age



Burnett AK. *ASH Education Book.* 2012;2012:1-6.

These data highlight the fact that our older patients really do not do well. Additionally, when we look over the last 40 years, you can see here that survival has improved for AML patients under the age of 60. You can see in the most recent timeline from 2004 to 2009, represented by the pink line on the top chart, there was 47% survival for patients age 15 to 59, compared to 20% survival for those patients that are over the age of 60. Thus, over the last 40 years, survival has improved for AML patients under the age of 60, but little progress has been made for the long-term survival for patients over the age of 60.

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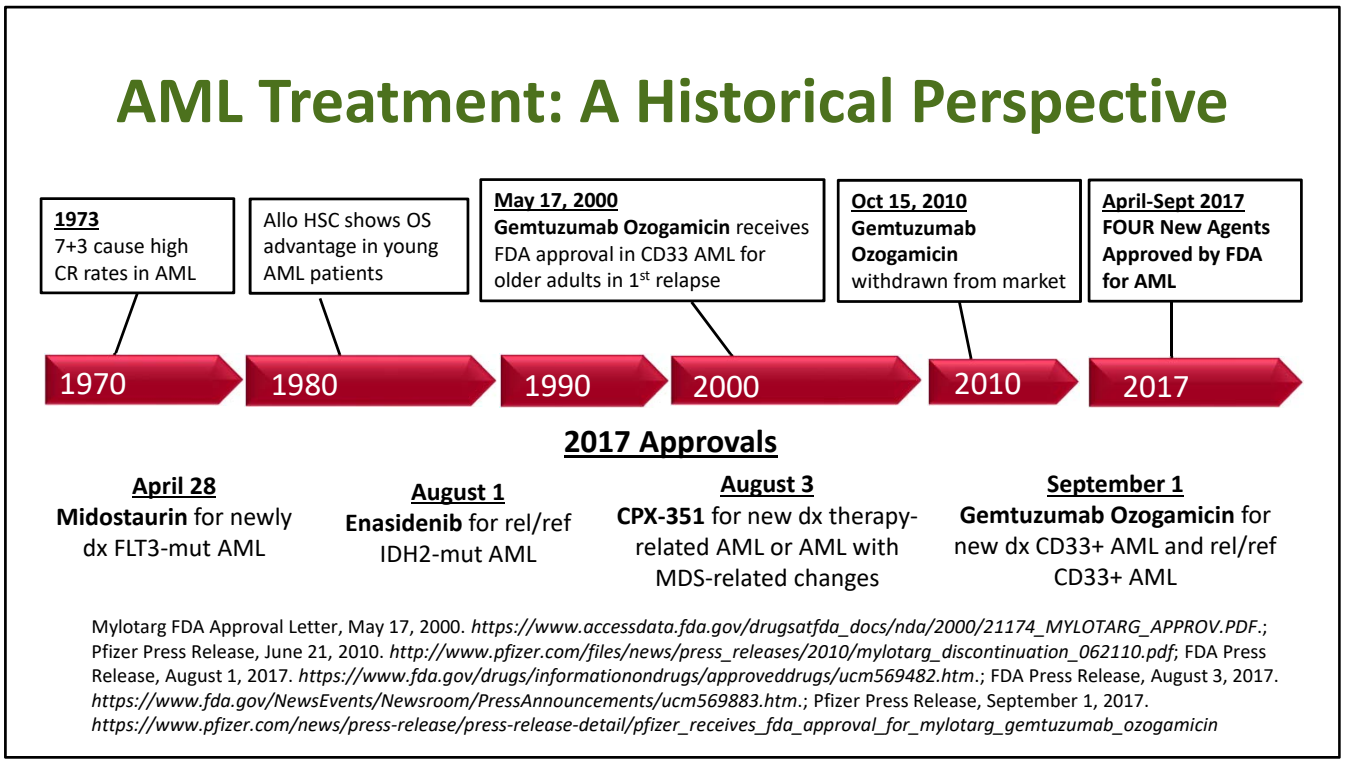
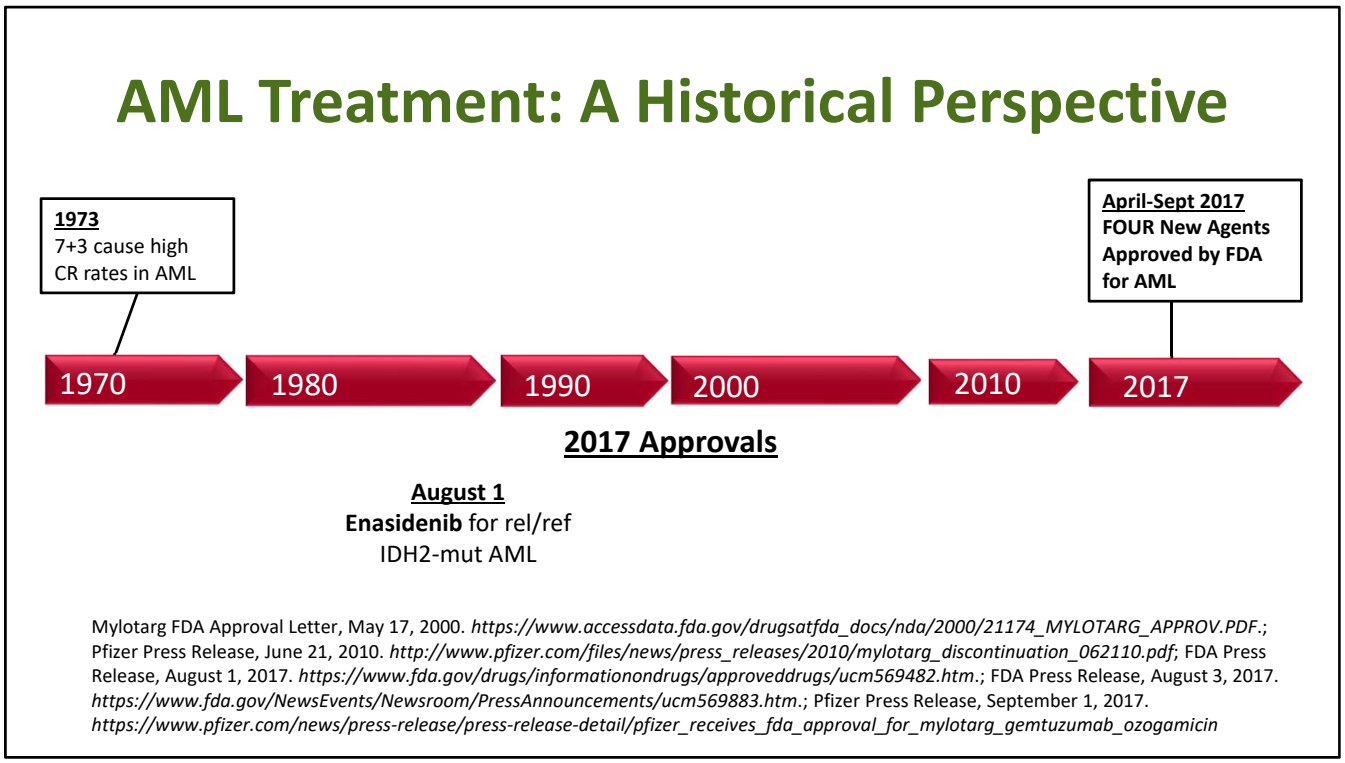


Mylotarg FDA Approval Letter, May 17, 2000. *https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21174_MYLOTARG_APPROV.PDF.*; Pfizer Press Release, June 21, 2010. *http://www.pfizer.com/files/news/press_releases/2010/mylotarg_discontinuation_062110.pdf*; FDA Press Release, August 1, 2017. *https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm569482.htm.*; FDA Press Release, August 3, 2017. *https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm569883.htm.*; Pfizer Press Release, September 1, 2017. *https://www.pfizer.com/news/press-release/press-release-detail/pfizer_receives_fda_approval_for_mylotarg_gemtuzumab_ozogamicin*

2017 was marked by new approvals. The historical perspective annotated here shows you how long it took for novel agents to be approved for patients diagnosed with AML. 2017 was a pretty fantastic year for novel agents emerging for patients with a diagnosis of AML. You can see in 1970 that 7+3 was found to bring on complete remission rates in patients with AML. Transplant came on the scene in 1980. Gemtuzumab was approved in 2000 then came off the market 10 years later.

Furthermore, when we think about what happened in 2017, midostaurin was approved for newly diagnosed FLT3 mutated acute myeloid leukemia patients. In addition, enasidenib was approved for relapsed/refractory IDH2 mutated positive patients with AML. CPX-351 was also approved for newly diagnosed therapy related AML, or AML with MDS related changes. Gemtuzumab ozogamicin for newly diagnosed CD33 AML patients in relapsed/refractory CD33-positive AML was also approved.

Are IDH2 Inhibitors Right for Your AML Patient?

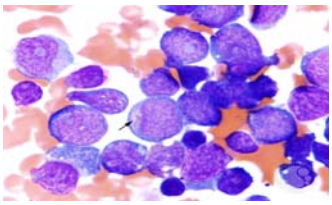


During this talk, we will focus specifically on enasidenib for relapsed/refractory IDH2 mutated-positive patients with AML.

Are IDH2 Inhibitors Right for Your AML Patient?

Case

- 69-year-old-female presents with a significant PMHx of IDH2 and DNMT3a positive AML (normal karyotype 46, XX [20]) for which she was treated with 7+3 induction two months ago
- She has a new onset of fevers and flu-like symptoms. Unfortunately, her CBC reveals WBC count of 32,000 with 68% circulating blasts
- Bone marrow biopsy confirms relapsed AML with blasts expressing MPO, CD13, CD33, CD117. Repeat molecular studies confirm IDH2 pos status*
- She has a ECOG PS of 2 and would like to get therapy but would prefer to be home rather than hospitalized.



*FDA approved test: Abbott RealTime IDH2 Assay

Let us jump to a case to lead off the discussion. This is a 69-year-old female who presents with a significant past medical history of IDH2 and DNMT3A-positive AML. She has a normal karyotype for which she was treated with induction 7+ 3 two months ago. She has a new onset of fevers and flu-like symptoms. Unfortunately, her CBC reveals a white count that is elevated, at 32,000 with 68% circulating blasts. A bone marrow biopsy confirms a relapsed AML with blasts expressing MPO, CD13, CD33 and CD117. Repeat molecular studies confirm an IDH2-positive status. She has an ECOG performance status of 2 and would like to get therapy, but she tells you she prefers to be home rather than hospitalized for that therapy.

Are IDH2 Inhibitors Right for Your AML Patient?

Case

- 69-year-old female presents with a significant PMHx of IDH2 and DNMT3a positive AML (normal karyotype 46, XX [20])
- Best option for this patient who desires outpatient based therapy includes:

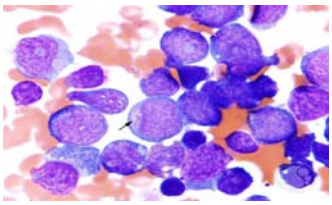
A. Induction with cytarabine and daunorubicin

B. Low-dose cytarabine (20 mg/m^2 SC x 10 days)

C. Enasidenib 100 mg PO QD

D. Oral etoposide

E. Best supportive care (transfusions, antibiotics)

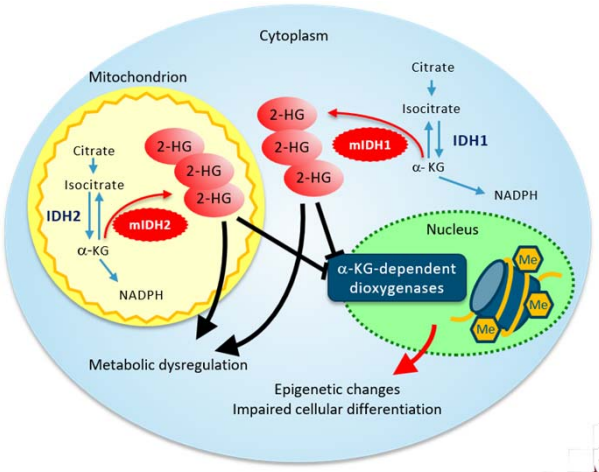


Based on this case, the best option for this patient who desires outpatient-based therapy includes (a) induction with cytarabine and daunorubicin, (b) low-dose cytarabine, (c) enasidenib 100 mg PO QD, (d) oral etoposide, or (e) best supportive care with transfusions and antibiotics. And I would say at this point that we will highlight the selection that I think is the answer here: enasidenib 100 mg PO QD and we will talk a little bit more about why that is the case.

Are IDH2 Inhibitors Right for Your AML Patient?

Isocitrate Dehydrogenase-2 (IDH2) Mutations in AML

- IDH are critical enzymes of the citric acid cycle
- IDHs convert Isocitrate to αKG
- Mutant *IDH2 (mIDH2)* confers a gain of function resulting in conversion of αKG to 2-HG
- 2-HG alters DNA methylation/ blocks cellular differentiation
- m*IDH2* in ~8-19% AML



IDH=isocitrate dehydrogenase; 2-HG=2-hydroxyglutarate; m*IDH2*=mutated IDH2
Stein E, et al. *Blood.* 2017: blood-2017-04-779405.; Dohner H, et al. *N Engl J Med*. 2015;373(12) 1136-1152.

We do know that isocitrate dehydrogenase 2 (or IDH2) mutations exist in patients with AML, and we know the presence of these mutations confer a gain of function resulting in conversion of alpha-ketoglutarate to 2-hydroxyglutarate. These IDH enzymes are critical enzymes of the citric acid cycle and they do convert isocitrate to alpha-ketoglutarate. What happens in the mutated state when IDH2 is mutated, you can see that as we just discussed, isocitrate is converted to alpha-ketoglutarate with IDH2 and in the mutated state you can see alpha-ketoglutarate becomes 2-hydroxyglutarate. The presence of this 2-hydroxyglutarate alters DNA methylation and blocks cellular differentiation. There can be an accumulation of 2-hydroxyglutarate when patients have a mutated IDH2 positive state. We also know that mutated IDH2 exists or is positive in about 8% to 19% of patients diagnosed with AML.

Are IDH2 Inhibitors Right for Your AML Patient?

Enasidenib (AG-221/CC-90007)

- Selective, oral, potent inhibitor of mIDH2 enzyme
- Safety and efficacy evaluated in open-label, single-arm, multicenter phase I/II dose escalation and expansion study in adults with R/R AML with and IDH2 mutation
- Most patients received 100 mg PO QD
- Efficacy was established on basis of:
  1. Rate of complete response (CR)
  2. Rate of complete response with hematologic recovery (CRh) (CRh: plts >50 and ANC >500)
  3. Duration of response (DOR: time since first response of CR/CRh to relapse or death)
  4. Rate of conversion from transfusion dependent to transfusion independent

Stein E, et al. *Blood.* 2017: blood-2017-04-779405.

Enasidenib (or AG 221 or CC 90007) is a selective oral potent inhibitor of mutated IDH2 enzyme. Its safety and efficacy were evaluated in an open-label, single arm, multicenter, phase 1/2 dose escalation and expansion study in adults with relapsed/refractory AML that had a positive IDH2 mutation. Most patients in the study received 100 mg a day, and we will talk a little bit about some of the subsets in that larger study, specifically focusing on those patients that only received 100 mg a day. The efficacy of this agent was established on the basis of rate of complete response, rate of complete response with hematologic recovery (CRh) and duration of response. Duration of response was defined as time since first response of CR or CRh to relapse or death, as well as rate of conversion from transfusion dependent to transfusion independent.

Are IDH2 Inhibitors Right for Your AML Patient?

Baseline Demographic and Disease Characteristics for AML Patients Treated with Enasidenib 100 mg PO QD

Demographic and disease characteristics	R/R AML (N=99)
Median age in years	68 (range 19-100)
Median time from AML dx in months (172 pts)	11.3 (range 1.2-129.1)
ECOG PS 0 ≥ 1	 46 (23%) 152 (76%)
IDH2 Mutation Location R140 R172	 155(78%) 44(22%)
Prior HSCT	25 (13%)
Cytogenetic risk Missing Intermediate Poor	 47 (24%) 98 (49%) 54 (27%)
Transfusion dependent at baseline	157 (79%)
Number of prior anticancer regimens 1 ≥ 2	 45% 55%

Stein E, et al. *Blood.* 2017: blood-2017-04-779405.

You can see here the baseline demographic and disease characteristics for those AML patients treated with 100 mg a day of enasidenib. You can see the median age for those patients was 68 years of age. Again, this population included those patients that were only given 100 mg a day. The study itself had a larger cohort of patients and you will see that in the upcoming slides, but here we will specifically focused on the 99 patients that were relapsed/refractory and received only 100 mg of enasidenib. You can see, by and large, many patients had an ECOG performance status of 1 or 2. You can see that annotated as greater than or equal to 1, 76% of the patients fit into that category. The majority of patients, 78% of patients had an IDH mutation at R140 compared to R172 (you will see in the upcoming slides why I am pointing that out). A small percentage of patients had a prior bone marrow transplant. You can see here annotated in the cytogenetic risk, many patients had intermediate or poor risk cytogenetics: 49% and 27%, respectively. The majority of patients were transfusion-dependent at baseline, and 55% of patients had greater than or equal to two prior anticancer regimens for their AML.

Are IDH2 Inhibitors Right for Your AML Patient?

Investigator Reported Responses Among AML Patients Treated with Enasidenib

	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			
Not evaluable	2	1.8				3	1. 7			
Time to first response, mo				1.9	0.5-9.4				1.9	0.5-9.4
Duration of response, mo			3.8-9.7	5.6				3.9-7.4	5.8	
Time to CR, mo				3.7	0.7-11.2				3.8	0.5-11.2
Duration of response in patients who attained CR, mo ‖			5.3-NR	8.8				6.4-NR	8.8	

Responses were evaluated by study investigators and classified according to the 2003 revised International Working Group criteria for AML[22]
CR, complete remission; NR, not reached.
*ORR includes patients with CR, CR with incomplete hematologic recovery, CR with incomplete platelet recovery, partial remission, or morphologic leukemia-free state.
†Of 9 patients with extramedullary disease at study entry, 1 patient achieved CR with incomplete platelet recovery, 5 patients maintained stable disease, 1 patient experienced disease progression, and 2 patients were not evaluable for response.
‡Stable disease was defined as failure to achieve a response but not meeting criteria for disease progression for a period of more than 8 weeks.
§Patients must have had previous partial remission or stable disease. For patients with 5% to 66% bone marrow blasts at nadir, progressive disease was defined as a >50% increase in bone marrow blast count percentage from the nadir and a blast percentage of ≥20%; for patients with >67% bone marrow blasts at nadir, progressive disease was defined as a doubling of the nadir absolute peripheral blood blast count with a final absolute peripheral blood blast count of $>10 \times 10^9$/L.
‖Date of first documented response to date of relapse, disease progression, or death.

Stein E, et al. *Blood.* 2017: blood-2017-04-779405.

When we look at the investigator-reported responses among AML patients treated with enasidenib, you can see here what I was referring to on the earlier slides where we have the larger population of relapsed/refractory AML and we the cohort of enasidenib that was treated only with 100 mg a day. Because this was a dose escalation study, there were 176 other patients that were treated with doses up to and including 600 mg a day. Overall response rate here annotated in the 100 mg per day arm was 38.5%, compared to 40.3% for all doses. The CR rate in the 100 mg per day dose was 20.2%, similar to all doses at 19.3%. CR with incomplete platelet recovery was 6.4%, partial remission was 2.8%, and morphologic leukemia-free state was 9.2%, with similar percentages in the all-dose cohort. Furthermore, I think it is important to pay attention to the fact that there is some evidence of stabilization of disease annotated here at 53% in the 100 mg per day cohort, and closer to 48% in the all doses cohort. About 5% of patients had progressive disease and about 2% of patients were not evaluable. Importantly, we will talk about this in the upcoming slides looking at the time to first response, duration of response, and time to complete remission.

Are IDH2 Inhibitors Right for Your AML Patient?

Enasidenib (AG-221/CC-90007)

- Median follow up 6.6 months (0.4-27.7)
- 37 patients (19%) achieved CR and 9 (4%) CRh
- ORR was 40.3% (95% CI, 33-48%)
- 87.3% of responding patients attained first response by cycle 5
- Median time to first response 1.9 months (range, 0.5-9.4 months)
- Median duration of response 8.2-9.6 months

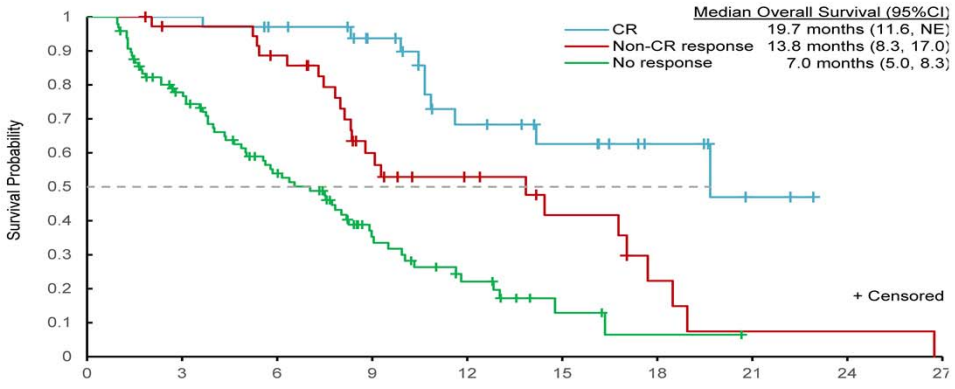
Stein E, et al. *Blood.* 2017: blood-2017-04-779405.

For this cohort, you can see the median follow-up was about 6.6 months. Again, just to highlight in the 100 mg per day cohort, 19% achieved a complete remission and 4% achieved a complete remission with partial hematologic response.

The overall response was 40.3%, and 87.3% of responding patients attained their first response by cycle 5. What that means is that five months in, 87% had their first response by that duration of time. Importantly, median time to first response was 1.9 months and median duration of response was 8.2 to 9.6 months.

Are IDH2 Inhibitors Right for Your AML Patient?

Overall Survival Relapsed/Refractory AML Patients on Enasidenib



Patients at risk:

CR	34	34	31	25	15	11	6	2	0
Non-CR response	37	34	30	17	11	7	3	1	1	0
No response	97	68	43	20	10	3	1	0	

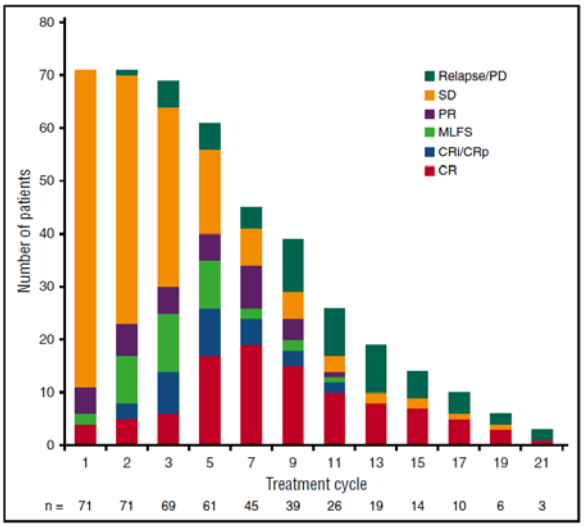
CR, complete remission

Stein E, et al. *Blood.* 2017: blood-2017-04-779405.

You can see annotated here the overall survival for relapsed/refractory AML patients on enasidenib, the blue line highlights those patients that achieved a complete response. You can see the median overall survival for that cohort was 19.7 months. For those patients that had no responses (the green line here) had a median overall survival of 7 months. Again, when we were discussing some of the stable disease, there are patients that have a non-CR response with a median overall survival of 13.8 months.

Are IDH2 Inhibitors Right for Your AML Patient?

Evolution of Response During Treatment of Responding Patients (N=71)



Stein E, et al. *Blood.* 2017: blood-2017-04-779405.

One of the reasons why I particularly like this graph is it describes and demonstrates better the evolution of response during treatment of responding patients. These are all patients that have some type of response, whether it is a CR, PR, or even stabilization of disease. The CR represents the red boxes, and by treatment cycle 7, you can see the highest number of patients around the 7th cycle, which then falls off by cycle 19, very similar to the data that we just walked through in terms of median time to response. You do see that there is a large bar for stabilization of disease that also falls off with some period of time, so this graph is a nice pictorial of the data that we just walked through and is a nice visual to keep in your mind's eye.

Are IDH2 Inhibitors Right for Your AML Patient?

Treatment-related Adverse Events (TRAEs) (≥ Grade 3-4) Occurring in ≥2% of All Patients

	Enasidenib 100 mg per day (n = 153)		All patients (N = 239)	
TEAE	No.	%	No.	%
Hyperbilirubinemia*	13	8	29	12
IDH differentiation syndrome†	11	7	15	6
Anemia	10	7	12	5
Thrombocytopenia‡	8	5	15	6
Tumor lysis syndrome	5	3	8	3
Decreased appetite	3	2	6	3
Leukocytosis	2	1	6	3
Fatigue	2	1	6	3
Nausea	2	1	5	2
Lipase increased	2	1	5	2

A TRAE was defined as any event that began or worsened on or after the start of enasidenib use until 28 days after the last dose and was considered by their treating physician to be possibly or probably related to enasidenib.
*Includes preferred terms "hyperbilirubinemia" and "blood bilirubin increased." †Preferred term is "retinoic acid syndrome" ‡Includes preferred terms "thrombocytopenia" and "platelet count decreased"
Stein E, et al. *Blood.* 2017: blood-2017-04-779405.

What happens to our patients that are on this particular therapy and what are the things that we should look out for? Here, we see the treatment-related adverse events that are greater than or equal to grade 3 or 4. These were annotated by occurring in greater than or equal to 2% of all patients that were on therapy. Highlighted here are those patients that received 100 mg a day compared to all of the patients. One thing that I want you to remember is that patients can have hyperbilirubinemia; 8% of the population that was receiving 100 mg a day. Patients that do have hyperbilirubinemia, we think that it is related to the UGT1A1 system and the way that the drug is metabolized. Many of the patients that have a high bilirubin do not have elevations of other liver function tests like AST, ALT and alkaline phosphatase. In that setting, they were able to stay on the agent and did not need a dose reduction or dose interruption.

Furthermore, the things that we will talk about in the upcoming slides are the differentiation syndrome that you see here listed as IDH differentiation syndrome in 7% of patients. There are patients that have anemia, thrombocytopenia, tumor lysis syndrome, as well as some issues with fatigue and nausea, but pretty minimal with single-digit numbers. I would like to point out that there is some percentage of patients that have an increase in their white count and that typically is managed by initiating hydroxyurea and following their counts and making sure that their white count stays below 20,000.

I have fielded questions from other colleagues and patients whether the patients that are having a high white count or differentiation syndrome are more likely to be responding to the agent. There does not appear to be a correlation between those two entities in terms of adverse event and responses.

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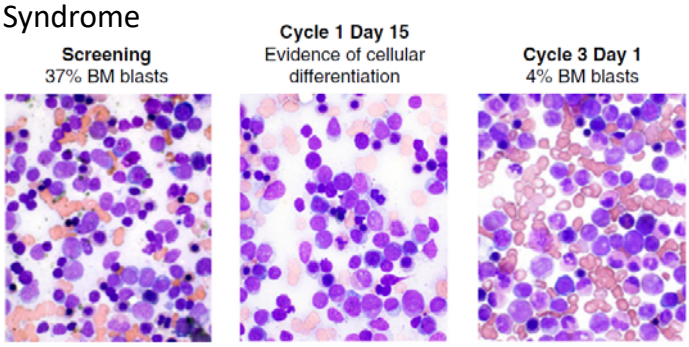
Evidence of Differentiation With Targeted IDH2 Inhibition

- **Black Box Warning:** Differentiation Syndrome
- Can be fatal if not treated
- 10 days to 5 months from start of therapy
- **Symptoms:** Fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural/pericardial effusions, bone pain, hepatic renal or multi-organ dysfunction
- **Treatment:** Administer systemic corticosteroids and hemodynamic monitoring. Stop enasidenib if the symptoms do not improve after 48 hours



IDHIFA (enasidenib) Highlights of Prescribing Information. Celgene Corporation. August 2017.

What I do want to drive home is that there is evidence of differentiation with targeted IDH2 inhibition and there is a black box warning that you should be aware of and knowledgeable about which is differentiation syndrome with enasidenib. This is an entity that can be fatal if it is not treated and it can happen anywhere from 10 days to 5 months from the start of therapy. Depicted here you can see at screening a predominance of blasts (37% blasts), from a slide of patient's bone marrow, and by day 15, you can see evidence of cellular differentiation. Then on cycle 3 day 1, you can see a decrease in the percentage of blasts and further differentiation with neutrophils and other differentiated cells. For those patients that have differentiation syndrome, they typically will present with symptoms such as fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural/pericardial effusions, bone pain, or other multiorgan dysfunction, whether it is hepatic or renal or multiorgan. The treatment for these patients is to administer systemic corticosteroids and begin hemodynamic monitoring. If patients do not get better after 48 hours, there are instructions with regard to stopping the enasidenib if the symptoms do not improve, or if the patients end up having true issues and respiratory distress needing ventilator support. There is more information, of course, that we can provide with regard to that.

Are IDH2 Inhibitors Right for Your AML Patient?

Response Among Patients with and without IDH-DS

Response Among Patients with and without IDH-DS		
Patient Response	IDH-DS (N=33)	No IDH-DS (N=248)
Overall Response	15 (45.5%)	93 (37.5%)
CR	6 (18.2%)	49 (19.8%)
CRi/CRp	6 (18.2%)	16 (6.5%)
PR	2 (6.1%)	14 (5.7%)
MLFS	1 (3.0%)	14 (5.7%)
Stable Disease	16 (48.5%)	121 (48.8%)
Disease Progression	1 (3.0%)	14 (5.7%)

No differences in clinical responses based on presence/absence of IDH-DS

Fathi A, et al. *JAMA* Jan 18, 2018. [Epub ahead of print].

One of the things that I alluded to earlier is that I field lots of questions about whether or not patients that had differentiation syndrome are more likely to be responders to this drug. You can see here the response among patients with and without IDH differentiation syndrome: 33 patients with differentiation syndrome compared to those patients without differentiation syndrome. This was reviewed by Dr. Fathi and presented in JAMA at the beginning of this year. You can see that there were equal overall responses (45% versus 37%) with equivalent CR rates (18% versus 19%) as well as CRI CRP. Ultimately the conclusion of this investigation was that there were no differences in clinical responses based on the presence or absence of IDH differentiation syndrome.

Does Site of IDH2 Mutation Matter? Can We Predict Responders?

- Patients with IDH2-R140 mutations ORR 35.4% CR 17.7%
- Patients with IDH2-R172 mutations ORR 53.3% CR 24.4%

- Extent of 2-HG suppression from baseline at cycle 2 day 1 was not correlated with clinical responses among all patients or within either site mutation subgroup
- Clinical activity was observed at all enasidenib doses (50-650 mg PO QD)

Other questions might be does the site of the IDH2 mutation matter and can we predict those patients that are going to be responders? As we discussed earlier, the majority of patients have an IDH2 mutation located at R140, and the overall response rate for those patients was 35% with a CR rate of 17.7%. Patients with an IDH2 mutation located at R172 had an overall response rate of 53.3% and a CR rate of 24.4%. Ultimately, it was determined that there were not differences in real terms for patients with R140 versus R172, although it does seem that there appears to be somewhat of an improved overall response rate, but patients with R172 really are much less frequent than those with R140. Furthermore, we do have an accumulation of 2-hydroxyglutarate so you could imagine measuring the suppression of 2-hydroxyglutarate as a correlate. Interestingly, the extent of 2-hydroxyglutarate suppression from baseline at cycle 2 day 1 was not correlated with clinical responses among all patients, or within either site mutation group. Again, we did talk about some of the data for all the other doses that were included in this dose escalation study, and clinical activity was observed at all enasidenib doses from 50 mg to 650 mg once a day.

Are IDH2 Inhibitors Right for Your AML Patient?

How Do We Improve Therapy?

- **How does IDH2 positive AML relapse despite targeted therapy (enasidenib)?** Annotation of clonal evolution at time of relapse in IDH2m R/R AML patients treated with enasidenib
  - At relapse, no "new" IDH2 mutation at new IDH2 sites (like bcr-abl or FLT3) but rather acquired additional mutations that highlight bypass pathways which re-impose differentiation arrest
    - Acquire IDH1 R132 and result in increase in 2HG
    - Deletion of chromosome 7
    - Gain of function mutations that result in cell proliferation (FLT3, CSF3R)
    - Acquire mutation in hematopoietic transcription factors (GATA2, RUNX1)
- Expect to hear more about clonal progression and how best to sequence agents and/or combine to eradicate mother clone

Quek L, et al. *Blood*. 2017;130:724.

Ultimately, we would love for all of our patients to respond to targeted therapy, so of course we are talking about how we can improve therapy. There was some interesting work presented at ASH 2017 looking at how IDH2-positive AML relapses despite the targeted therapy. Understanding the mechanisms of resistance may help us to target those patients that are not responding or lose response, so Quek, et al., noted the clonal evolution at the time of relapse in those patients with IDH2-mutated AML treated with enasidenib. This work demonstrated that, at relapse, there were no new IDH2 mutations at new IDH sites as we typically see in patients that have bcr-abl or FLT3 mutations, but rather they acquired additional mutations that highlight bypass pathways which reimpose a differentiation arrest. For example, there may be an acquisition of an IDH1 mutation that results in an increase in 2-hydroxyglutarate or deletion of chromosome 7; or a gain of function mutation that results in cell proliferation like FLT3 or CSF3R; and other mechanisms. I think further work is needed to see if there are new mutations that occur in IDH2 and IDH1 space. More work is ongoing with that and I expect to hear more in this upcoming year.

Furthermore, we will hear more as well about clonal progression and how best to sequence the agents and/or combine them to eradicate the mother clone. We will talk more about the ongoing studies that we are eager to hear results on.

Are IDH2 Inhibitors Right for Your AML Patient?

Ongoing Clinical Trials with Enasidenib

Combination clinical trials ongoing

1. Azacitidine plus enasidenib ongoing in upfront IDH2 positive AML[1]
   - Decitabine fell off due to Bayesian design, await results and long-term follow up
   - Promising response rates, but await durability
2. Induction chemotherapy (7+3) plus enasidenib in upfront IDH2 positive AML[2]
   - Early addition of enasidenib
   - Unclear if this will be synergistic early versus late (IDH mutated leukemia has impaired DNA damage response and if given an inhibitor early this may decrease chemotherapy affect[3])

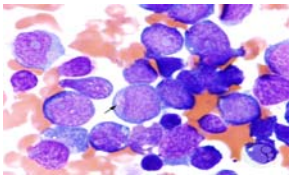
[1]DiNardo D, et al. *Blood*. 2017;130:639. [2]Stein E, et al. *Blood.* 2017: blood-2017-04-779405.
[3]Molenaar R, et al. *Blood*. 2017;130:568.

I just wanted to highlight the other studies that are going on, not only using enasidenib as a single agent, but potentially combining it with chemotherapy agents. For example, azacitidine plus enasidenib is ongoing in the upfront IDH2-positive AML setting. In this study led by DiNardo, et al., decitabine fell off due to a Bayesian design, and there are promising response rates, but we await durability. Additionally, induction chemotherapy plus enasidenib in the upfront IDH2-positive AML mutated population really adds the early introduction of enasidenib in the upfront 7+3 setting. It is unclear if this will be synergistic early versus late, primarily because when cells harbor this IDH mutation, we know that it means that those cells have an impaired response to DNA damage. If we give the inhibitor to eradicate this mutation, it may decrease the chemotherapy effect on the leukemia cell, but this is yet to be seen. We really do not know what the outcome of this study will show and potentially it will be positive, so we are eager to see the results of this study as well.

Are IDH2 Inhibitors Right for Your AML Patient?

Case

- 69-year-old female presents with a significant PMHx of IDH2 and DNMT3a positive AML (normal karyotype 46, XX [20]). Enasidenib was started and her WBC continued to increase while on 100 mg PO QD for the first week
- Hydroxyurea 500 mg PO QD was started along with enasidenib and this controlled her WBC to less than 20K. She remained on therapy for duration of 9 months and gained transfusion independence by cycle 3
- She had progression of disease by 10 months whereupon a new FLT3 mutation was detected and she enrolled on a clinical trial as her next therapy



Let us go back to our case, our 69-year-old female who presents with a past medical history of IDH2-positive DNMT3A-positive AML. As we described, enasidenib was started and her white count continued to increase while on this therapy for the first week. Hydroxyurea was initiated along with enasidenib, and this controlled her white count to less than 20,000 and she remained on therapy for a duration of nine months and gained transfusion independence by cycle 3. Unfortunately, she had progression of disease by 10 months whereupon a new FLT3 mutation was detected and she enrolled on a clinical trial as her next therapy.

Are IDH2 Inhibitors Right for Your AML Patient?

Key Points

- IDH2 mutations occur in 8-19% of AML patients
- Inhibition with enasidenib 100 mg by mouth daily is a reasonable outpatient option for relapsed or refractory AML patients with positive IDH2 mutation
- Be mindful of toxicities including differentiation syndrome, increased WBC and total bilirubin, and know management of these side effects
- Stable disease may be meaningful in this population, need to keep patients on therapy to cycle 4 (4 months) to determine response
- Clinical trials ongoing to evaluate combination therapy with hypomethylating agents and/or induction chemotherapy to aid in improving upfront outcomes
  - Toxicity profiles and drug-drug interactions
  - Delivery of therapy (overlapping vs sequential)

To conclude. I would like to leave you with these key takeaway points. IDH2 mutations occur in about 8% to 19% of AML patients. Inhibition with enasidenib 100 mg by mouth daily is a reasonable outpatient option for relapsed or refractory AML patients with positive IDH2 mutation. Be mindful of toxicities including differentiation syndrome, increased white blood cell count, and a rise in the total bilirubin. Know how to manage these, or at least know how to figure out what to do for these expected side effects in some of the population. Stable disease may be meaningful in this population and we need to keep patients on therapy to at least cycle 4 (four months of therapy), in order to determine their response to the therapy.

As we discussed, clinical trials are ongoing to evaluate combination therapy with hypomethylators and/or induction chemotherapy to aid in improving upfront outcomes for our patients with AML. Obviously, we are aware of toxicity profiles and drug-drug interactions in that setting, and we need to be mindful of whether or not we should be doing overlapping or sequential therapy in the delivery of those combinations.

Are IDH2 Inhibitors Right for Your AML Patient?

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I want to thank you for viewing this activity, and also thank the Taussig Cancer Center and the Cleveland Clinic and the Faculty on the Leukemia Program that work as a team to deliver care to our patients affected by myeloid disorders; the research nurses, our Taussig nurses, our data managers, and our lab research staff really help us to do what we do every day and we are grateful to do it. Thank you for being here today, I appreciate it.