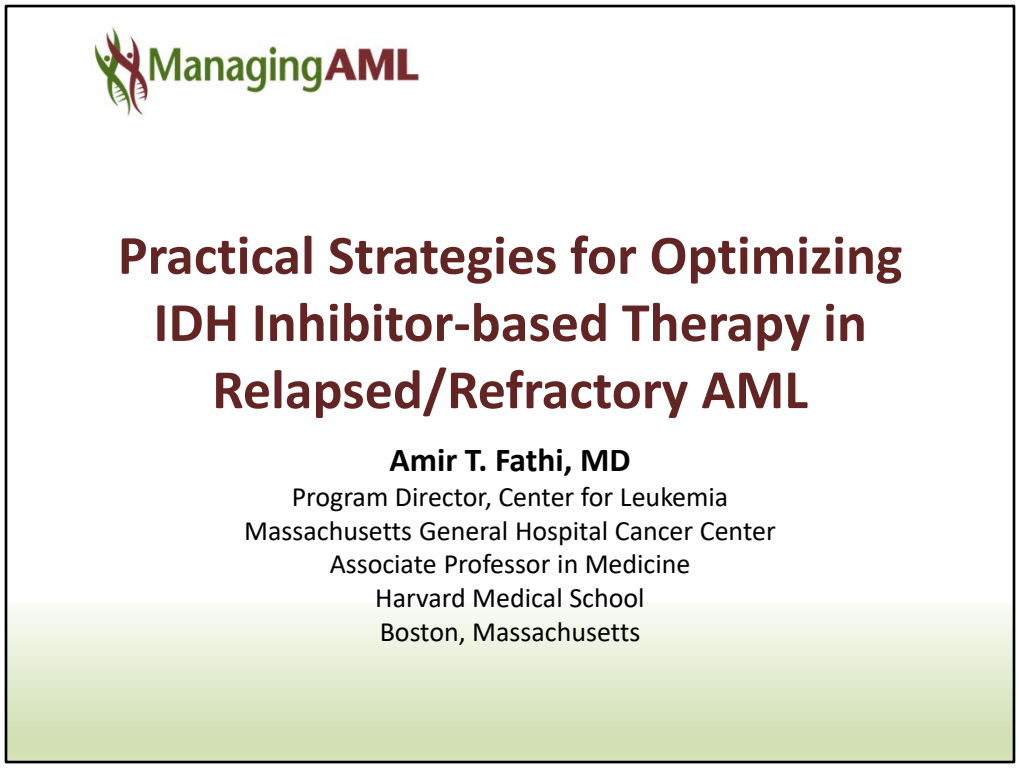
Practical Strategies for Optimizing IDH Inhibitor-based Therapy in Relapsed/Refractory AML



Welcome to *Managing AML*. My name is Dr. Amir Fathi. Today, I will be discussing practical strategies for optimizing IDH inhibitor-based therapy in relapsed or refractory acute myeloid leukemia.

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Learning Objectives

- Identify mutational testing strategies that should be used to identify AML patients with IDH1 and IDH2 mutations
- Outline approaches for management and monitoring of acute myeloid leukemia related to expected time to therapeutic response seen with IDH inhibitors
- Describe symptoms of differentiation syndrome associated with these agents, timing of symptom onset, and proactive management strategies that will minimize the impact of this treatment-related adverse event called differentiation syndrome
- Identify other treatment-related adverse events associated with the use of IDH inhibitors in acute myeloid leukemia and correlate each with appropriate and effective management strategies

During this presentation, I will identify mutational testing strategies that should be used to identify AML patients with IDH1 and IDH2 mutations; outline approaches for management and monitoring of acute myeloid leukemia related to expected time to therapeutic response seen with IDH inhibitors; describe symptoms of differentiation syndrome associated with these agents, timing of symptom onset, and proactive management strategies that will minimize the impact of this treatment-related adverse event called differentiation syndrome; and identify other treatment-related adverse events associated with the use of IDH inhibitors in acute myeloid leukemia and correlate each with appropriate and effective management strategies.

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Traditional Prognostication of AML

- The patient…
  - Age
  - Medical comorbidities
- Did it evolve out of preceding marrow disease (eg, myelodysplastic syndromes)?
  - Not always easy to tell…
- What are the bad or not-so-bad molecular characteristics?
  - Cytogenetic analysis
  - Mutational analysis: FLT3, NPM1, CEBPα

There is a traditional prognostication to acute myeloid leukemia, the most basic ways to prognosticate AML are related to patient age as well as medical comorbidity. Age is an imperfect surrogate of many other prognostic factors because older patients generally have a higher burden of comorbidity, have compromised organ function, and also often present with higher-risk molecular features. It is also important to know whether the acute myeloid leukemia arose from a preceding indolent or long-term marrow malignancy such as myelodysplastic syndrome. These secondary forms of AML that arise from another form of malignancy are oftentimes much higher risk and have a poor prognosis. Disease specific features such as chromosomal changes or certain mutations can also have prognostic impact. Certain mutations like FLT3 have, in general, a poor prognosis. NPM1 mutations and biallelic C/EBPα alterations are thought to have a more favorable prognosis.

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ELN Molecular and Cytogenetic Risk Groups

Table 1. European LeukemiaNet Standardized Reporting System for Correlation of Cytogenetic and Molecular Genetic Data in AML With Clinical Data[12]

Genetic Group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	–5 or del(5q)
	–7
	abnl(17p)
	Complex karyotype*

Abbreviations: AML, acute myeloid leukemia; ITD, internal tandem duplication.
*Complex karyotype is defined as three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions: t(8;21), inv(16) or t(16;16), t(15;17), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3).

Mrózek K, et al. *J Clin Oncol*. 2012;30(36):4515-4523.

Using mutational and chromosomal data, we are able to place patients roughly into prognostic groups of adverse, intermediate, and favorable risk and hopefully make a determination of whether these patients should pursue a more aggressive route of treatment, particularly in consolidation, such as with bone marrow transplant, or folks that have a more favorable risk feature be treated without bone marrow transplant in an effort to cure these patients.

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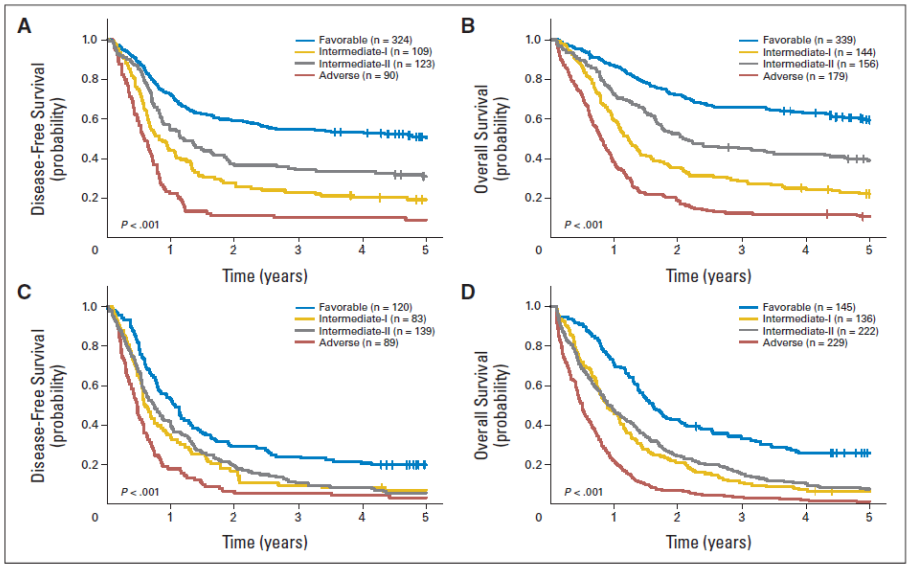

Fig 4. Outcome of patients with primary acute myeloid leukemia classified into the four European LeukemiaNet genetic groups according to the European LeukemiaNet recommendations. (A) Disease-free survival and (B) overall survival of patients younger than age 60 years; (C) disease-free survival and (D) overall survival of patients age 60 years or older.

Mrózek K, et al. *J Clin Oncol*. 2012;30(36):4515-4523.

The prognostic risks whether they are adverse risk, intermediate risk, or favorable risk can be splayed out across patient populations. Here, we have older groups displayed at the bottom in panel C and D and younger groups displayed up top on panels A and B with survival and disease-free survival being demonstrated. As can be seen in the blue lines demonstrating favorable risk disease, those patients generally do better. Those individuals who have adverse risk disease as displayed by the red lines do worse. Of course, in older patients, the lines are much closer to each other. Even favorable risk patients who are older do not do as well.

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AML Gets More Complex!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Recurring Mutations Found by Sequencing an Acute Myeloid Leukemia Genome

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

DNMT3A Mutations in Acute Myeloid Leukemia

JOURNAL OF CLINICAL ONCOLOGY — ORIGINAL REPORT

IDH1 and *IDH2* Gene Mutations Identify Novel Molecular Subsets Within De Novo Cytogenetically Normal Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study

OPEN ACCESS Freely available online — PLOS | ONE

EZH2 Mutations Are Related to Low Blast Percentage in Bone Marrow and -7/del(7q) in De Novo Acute Myeloid Leukemia

JOURNAL OF CLINICAL ONCOLOGY — ORIGINAL REPORT

TET2 Mutations Improve the New European LeukemiaNet Risk Classification of Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study

ASXL1 mutations identify a high-risk subgroup of older patients with primary cytogenetically normal AML within the ELN Favorable genetic category

Over the course of the last 10 to 15 years, AML has become more complex, or at least our knowledge of AML has become more refined and we know much more about the various mutations and molecular alterations that define it. In addition to what we knew previously such as with FLT3 mutations, NPM1 mutations, C/EBPα mutations, now there are a whole host of other alterations that have been discovered in AML that speak to the complexity of the disease.

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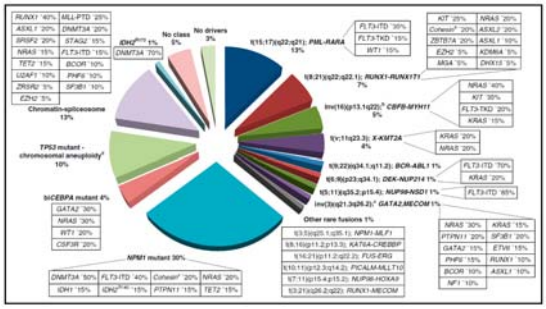
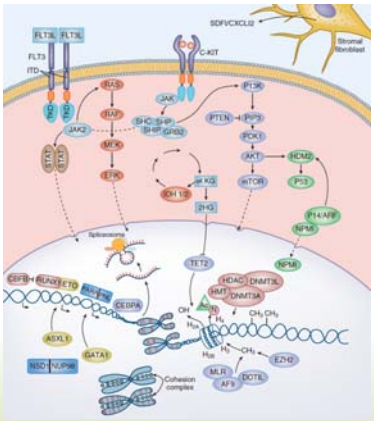


Dohner H, et al. *Blood*. 2017;129(4):424-447.



Brunner AM, Graubert TA. *Nat Med*. 2018;24(1):7-9.

Here, we have a pie graph demonstrating the various different types of acute myeloid leukemia that can be characterized by molecular alterations, as well as the various molecular underpinnings of the disease, again, highlighting the complexity and the related challenge that comes with this condition and it's therapy. And in fact, when I round on my leukemia patients in the hospital, every room that I enter, unfortunately, I encounter probably a wholly different disease. In one room, I may encounter a 50-year-old patient with newly diagnosed de novo FLT3-mutated AML; in another room, I might see a 75-year-old who's had years of marrow malignancy and now has secondary AML that arises from that malignancy; in another room, I might see a 45-year-old female who had breast cancer, received chemotherapy and/or radiation, and as a result of that exposure developed secondary therapy-related AML. All those patients, if you look at their blood underneath the microscope, you will see leukemic blasts swimming around, but the molecular features of those blasts are markedly different and, therefore, their responsiveness to treatment or traditional chemotherapy is going to be different.

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The Last Decade - New Era of Therapeutics

- FLT3 inhibition
  - Midostaurin
  - Gilteritinib
- IDH inhibition
  - Enasidenib
  - Ivosidenib
- BCL2 inhibition
  - Venetoclax
- Antibody-drug conjugates
  - Gemtuzumab ozogamicin
- Liposomal formulations of chemotherapy
  - CPX-351

So over time, in the last 30 to 40 years, traditional chemotherapy has been a big hammer that has attempted to hit multiple different small nails with inconsistent and oftentimes inadequate success. Over the last decade, however, we have found ways to target specific alterations and, therefore, specific subpopulations of patients that may benefit from these new targeted therapies. Among these are IDH inhibitors for IDH1 or IDH2-mutated patients, the topic of my presentation today.

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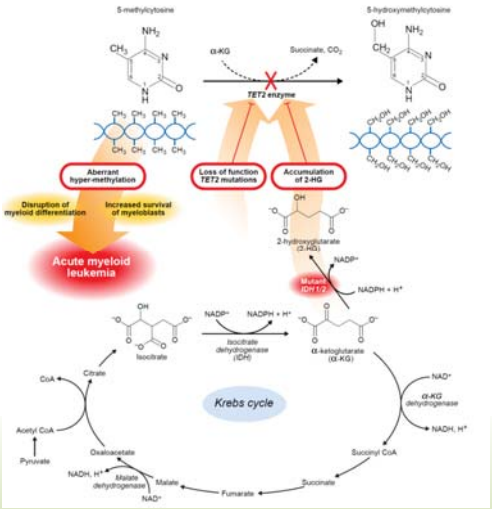
IDH1/2-mutant AML

- Mardis, et al. *N Engl J Med*. 2009: First description of IDH1 mutations in ~8% of patients with AML, associated with normal cytogenetic status (cn-AML)
- 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



Ward PS, et al. *Cancer Cell.* 2010;17:225-234.; Gross S, et al. *J Exp Med*. 2010;207:339-344.; Dang L, et al. *Nature*. 2009;462:739-744.

So, as a way of background, in 2009, IDH1 mutations were first described in acute myeloid leukemia in less than 10% of patients. But these were enriched in populations including cytogenetically normal AML or AML with NPM1 mutations. Subsequent studies done in the years that followed revealed that IDH mutations were also seen in AML and actually were more common than IDH1 mutations. Where do IDH proteins play a role? Well, IDH stands for isocitrate dehydrogenase, and it's a key enzyme in the Krebs cycle. It catalyzes the decarboxylation of isocitrates or α-ketoglutarate and in that process helps to form ATP and energy for the cell, IDH1 resides in the cytoplasm, IDH-2 in the mitochondria, doing similar functions.

When the IDH enzymes are altered, however, due to mutations, the same enzymatic process does not take place. The altered IDH enzymes actually catalyze a different reaction. They convert α-ketoglutarate to 2-hydroxyglutarate, a metabolite that's usually present at low levels. But when you have the altered IDH enzyme, the 2-HG is produced as a result of the catalyzation of that enzymatic reaction, and there is a high buildup of 2-HG in the cell and in the blood. 2-HG is an oncometabolite, it actually inhibits certain key enzymes including TET enzymes. TET enzymes are important for the process of demethylation. So, when we have a scenario where 2-HG is inappropriately and exorbitantly produced, we have suppression of TET enzymes and, as a result, hypermethylation across the genome. What does methylation do?

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Methylation suppresses the normal differentiation and maturation of myeloid cells by suppressing genes that are important for maturation and differentiation. So, in stepwise fashion, what ends up happening or at least is thought to happen are that these altered IDH enzymes resulting from IDH mutations lead to production of high levels of 2-HG. 2-HG suppresses a key enzyme called TET as well as other key enzymes. That process leads to an aberrant hypermethylation and suppression of key genes that are important for the process of maturation and differentiation. Because there is hypermethylation in certain key promoter regions, these genes are inappropriately turned off and cells forget to mature and differentiate normally causing a leukemogenic phenotype immature or aberrant malignant cells in the bone marrow.

IDH Mutational Testing

- PCR or next-generation sequencing (NGS), are commonly used for mIDH detection
- Mutations are on exon 4, and typically affect IDH1 protein at a single residue R132, or IDH2 at two residues, R140 and R172
- Many centers perform mutational analyses with NGS using myeloid malignancy gene panels

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

How do we test for IDH mutations and IDH mutated AML? Well, PCR testing or next-generation sequencing are the most commonly used modalities for detection of these abnormalities. The IDH mutations are existent on exon 4 and typically affect the IDH1 protein at a single residue, R132, although there are exceptions or IDH-2 at two residues, R140 and R172. Variety of academic centers perform these mutational analyses with next-generation sequencing using a different myeloid malignancy gene panels.

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blood

Prepublished online October 16, 2012;
doi:10.1182/blood-2012-06-438267

Prospective serial evaluation of 2-hydroxyglutarate, during treatment of newly diagnosed acute myeloid leukemia, to assess disease activity and therapeutic response

Amir T. Fathi, Hossein Sadrzadeh, Darrell R. Borger, Karen K. Ballen, Philip C. Amrein, Eyal C. Attar, Julia Foster, Meghan Burke, Hector U. Lopez, Christina R. Matulis, Katherine M. Edmonds, A. John Iafrate, Kimberly S. Straley, Katharine E. Yen, Samuel Agresta, David P. Schenkein, Cedric Hill, Ashkan Emadi, Donna S. Neuberg, Richard M. Stone and Yi-Bin Chen

Original Article

Isocitrate Dehydrogenase 1 and 2 Mutations, 2-Hydroxyglutarate Levels, and Response to Standard Chemotherapy for Patients With Newly Diagnosed Acute Myeloid Leukemia

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Let's move on and talk about 2-HG which, as I mentioned, is that oncometabolite that's inappropriately produced in patients who have this altered enzyme. You can actually measure 2-HG or 2-hydroxyglutarate in the blood, in the serum, in the urine, in the cerebrospinal fluid of patients who are affected by IDH mutations.

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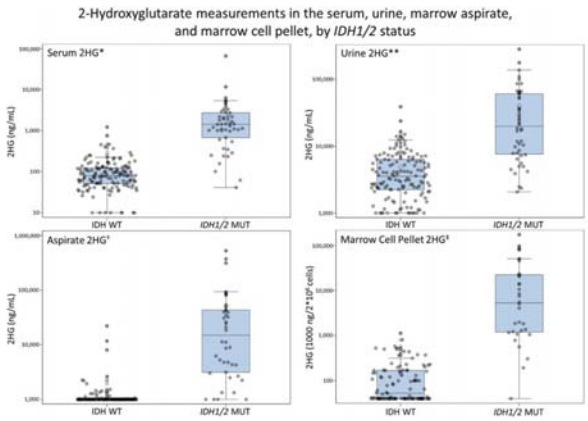

TABLE 2. Test Characteristics Based on the Optimal 2HG Cutoff by Compartment

				23% Prevalence	
Compartment	2HG Cutoff	Sensitivity	Specificity	PPV	NPV
Serum	534.5 ng/mL	0.8039	0.9882	0.9535	0.9438
Urine	16,650 ng/mL	0.5600	0.9877	0.9333	0.8798
Marrow aspirate	2210 ng/mL	0.8837	0.9660	0.8837	0.9660
Marrow pellet	1146 ng/2 × 10^6 cells	0.7813	1.000	1.000	0.9478

Abbreviations: 2HG, 2-hydroxyglutarate; NPV, negative predictive value; PPV, positive predictive value.

Brunner AM, et al. *Cancer*. 2019;125:541-549.

Here is a few bar graphs that tell you clearly that individuals who have IDH mutations have very high levels of serum 2-HG and urine 2-HG, and you can see that individuals who have IDH wild type AML have very low levels of serum and urine 2-HG, and healthy donors that we've looked at also have low levels of 2-HG. So in many ways, 2-HG is a biomarker of the presence of IDH-mutated AML. It can also provide you with fairly good specificity, positive predictive value, and negative predictive value for the presence of IDH-mutated AML, and you can follow 2-HG in the blood and urine of patients who are undergoing treatment for IDH-mutated AML.

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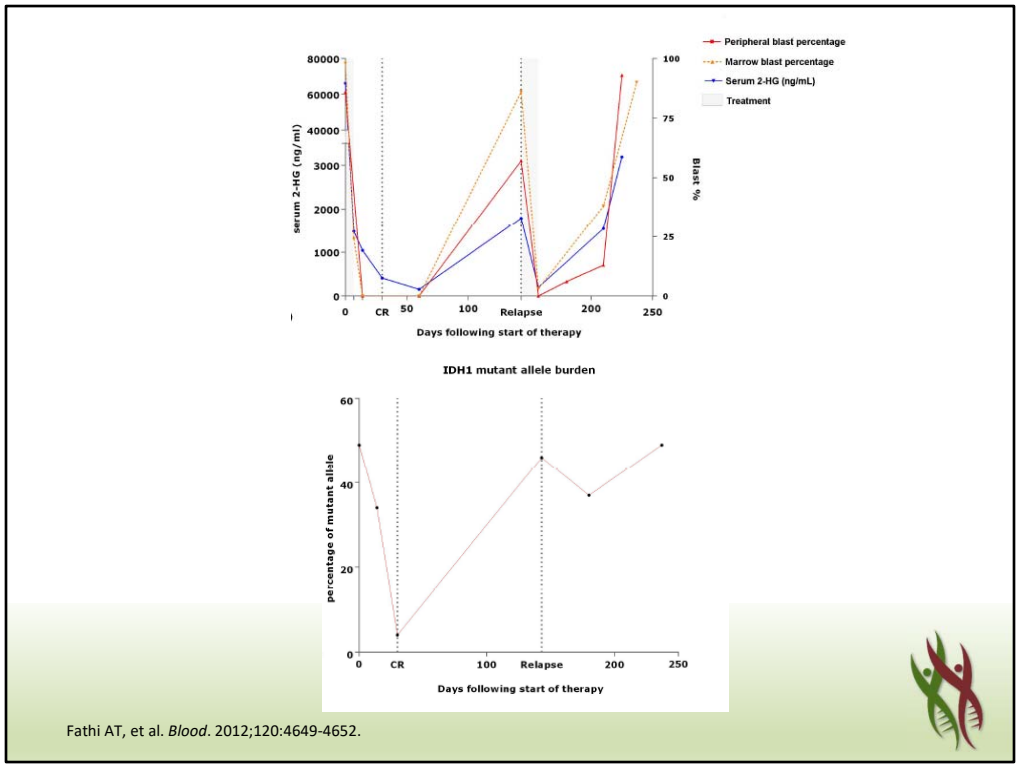

Fathi AT, et al. *Blood*. 2012;120:4649-4652.

Here is one representative patient whose blasts go down represented by red during a therapy of AML. Concurrently, there is a marked suppression of 2-HG as well that follows the decrease in peripheral blasts. There is an increase in peripheral blasts and serum 2-HG with relapse of disease and a subsequent response to treatment followed by unfortunately a second relapse and end of life. This is a typical presentation that you would follow with a patient who is relapsing multiple times with IDH-mutated AML. These markers of 2-HG and disease burden also follow the allelic burden of IDH mutations that can be detected in the blood.

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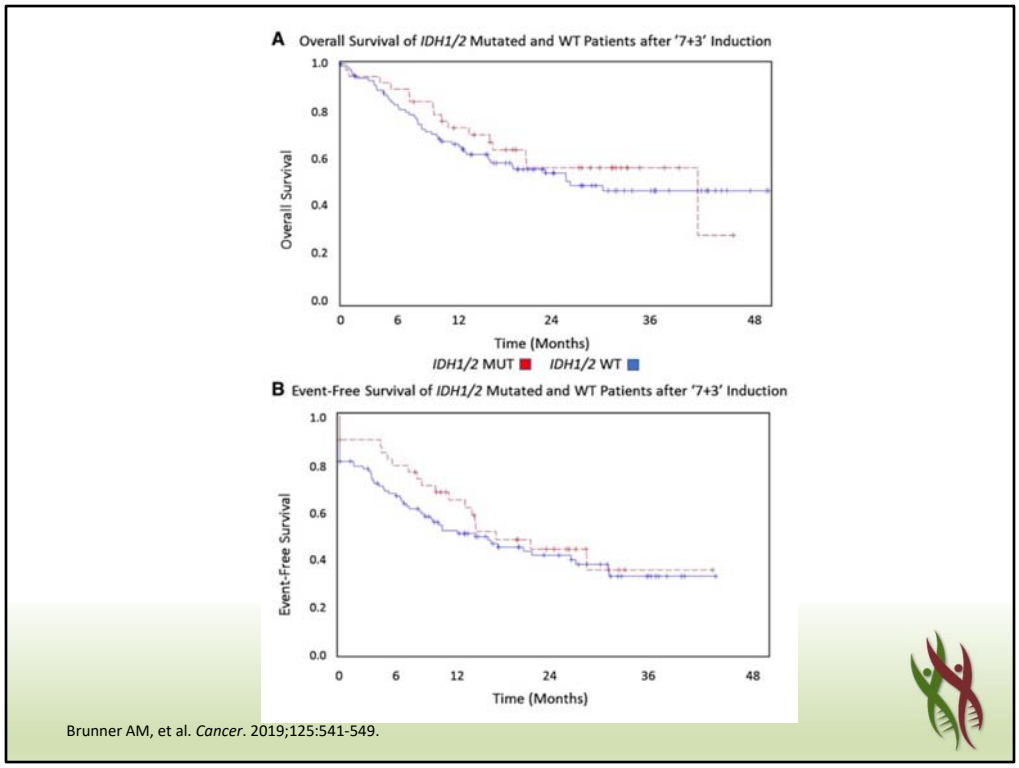

Brunner AM, et al. *Cancer*. 2019;125:541-549.

Do IDH mutations have prognostic impact? We mentioned that FLT3 mutations have, in general, a poor prognostic impact and NPM1 mutations, for example, have a better prognostic impact. Do IDH mutations have a similar impact in patients with acute myeloid leukemia? Well, different studies largely retrospective have provided conflicting data. In our patient groups, we looked prospectively and found that there was no substantial prognostic impact of IDH mutations, whether you have them or not, did not seem to affect response and outcomes after traditional upfront chemotherapy.

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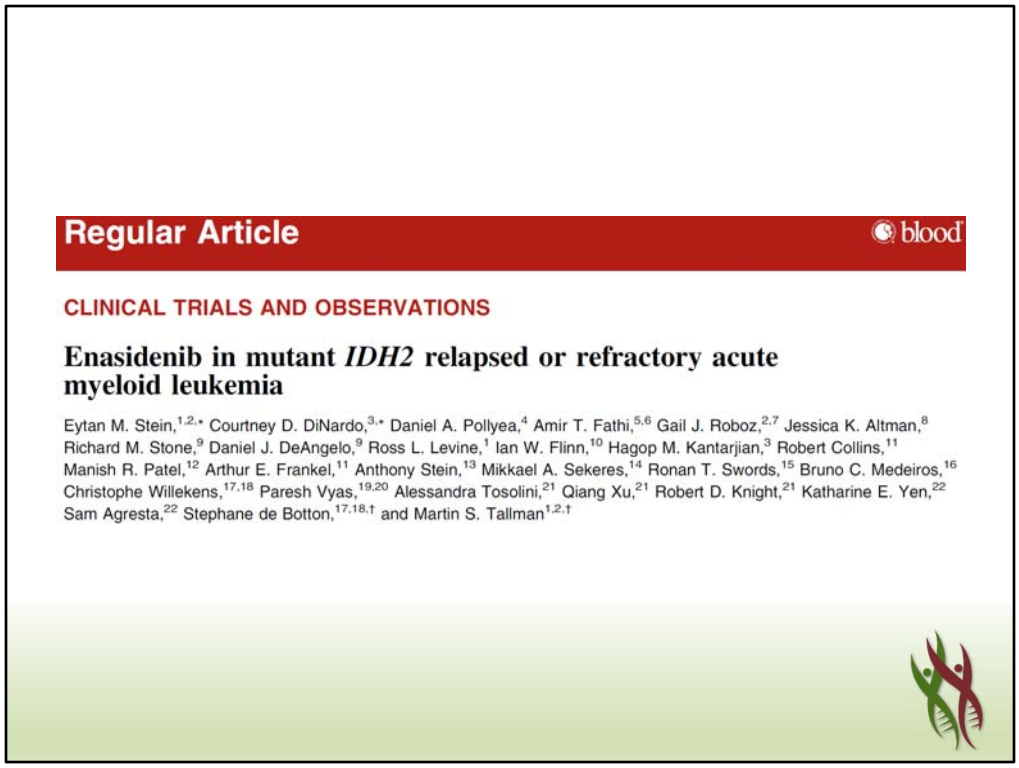

Regular Article

blood

CLINICAL TRIALS AND OBSERVATIONS

Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia

Eytan M. Stein,[1,2,*] Courtney D. DiNardo,[3,*] Daniel A. Pollyea,[4] Amir T. Fathi,[5,6] Gail J. Roboz,[2,7] Jessica K. Altman,[8] Richard M. Stone,[9] Daniel J. DeAngelo,[9] Ross L. Levine,[1] Ian W. Flinn,[10] Hagop M. Kantarjian,[3] Robert Collins,[11] Manish R. Patel,[12] Arthur E. Frankel,[11] Anthony Stein,[13] Mikkael A. Sekeres,[14] Ronan T. Swords,[15] Bruno C. Medeiros,[16] Christophe Willekens,[17,18] Paresh Vyas,[19,20] Alessandra Tosolini,[21] Qiang Xu,[21] Robert D. Knight,[21] Katharine E. Yen,[22] Sam Agresta,[22] Stephane de Botton,[17,18,†] and Martin S. Tallman[1,2,†]

We talked about 2-HG as a potential biomarker, we talked about the potential prognostic impact of IDH mutations, now let's move on to talk about targeted therapies for patients with IDH-mutated AML.

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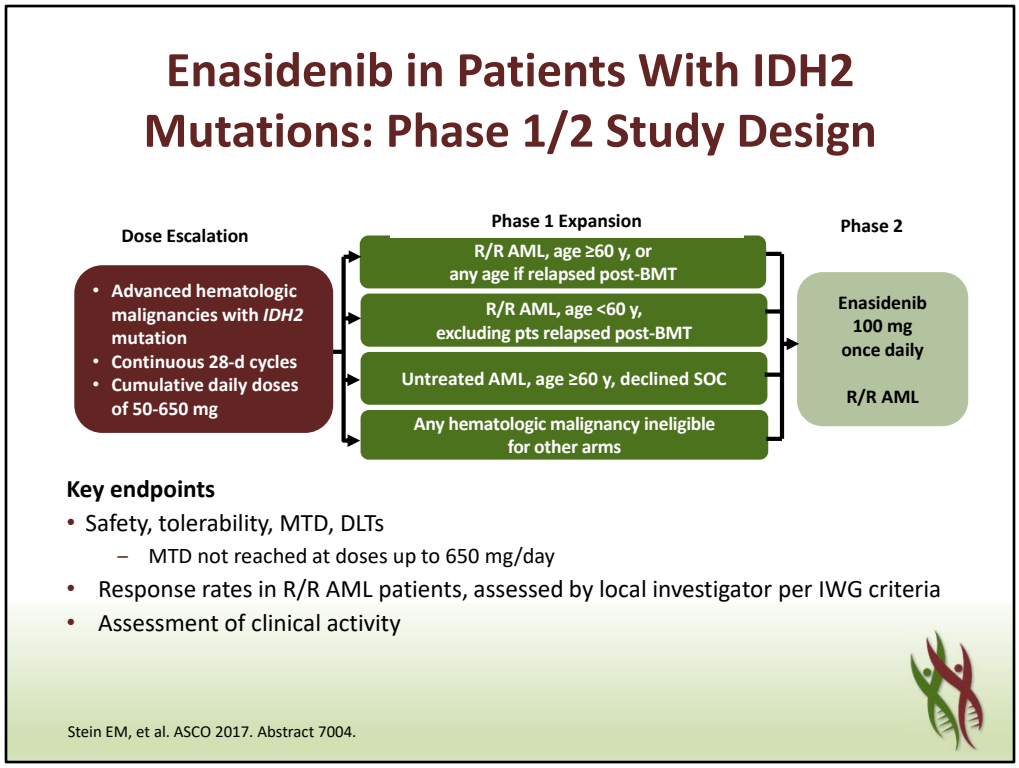

The first drug that emerged as a targeted inhibitor of IDH2 was enasidenib and was initially studied in various populations, predominantly in folks who have relapsed or refractory acute myeloid leukemia. This was the dose escalation and expansion study, ultimately, a phase 2 study that looked at various cohorts of patients that had IDH2-mutated AML. The study sought to assess safety tolerability as well as the maximum tolerated dose and ultimately gain an appreciation for the efficacy of this IDH2 inhibitor in patients with IDH2-mutated AML.

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Enasidenib in Patients With IDH2 Mutations: Grade 3-4 TEAEs (≥2% Patients)

Table 2. Treatment-related TEAEs of grades 3 or 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

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

The predominant adverse events that were seen on study are represented here. Hyperbilirubinemia, typically indirect bilirubinemia, was seen in a subset of patients, although its clinical impact was not that substantial. On the other hand, IDH differentiation syndrome could be severe in patients and often needs to be monitored closely for and managed very rigorously since it is a potentially lethal sequela of treatment with IDH inhibitors; we will get to that shortly. Other toxicities were less commonly seen with this targeted agent and cytopenias were, in general, relatively uncommon.

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Molecular remission and response patterns in patients with mutant-*IDH2* acute myeloid leukemia treated with enasidenib

Eytan M. Stein,[1,2,*] Courtney D. DiNardo,[3,*] Amir T. Fathi,[4,5,*] Daniel A. Pollyea,[6] Richard M. Stone,[7] Jessica K. Altman,[8] Gail J. Roboz,[2,9] Manish R. Patel,[10] Robert Collins,[11] Ian W. Flinn,[12] Mikkael A. Sekeres,[13] Anthony S. Stein,[14] Hagop M. Kantarjian,[3] Ross L. Levine,[1] Paresh Vyas,[15] Kyle J. MacBeth,[16] Alessandra Tosolini,[17] Jason VanOostendorp,[17] Qiang Xu,[17] Ira Gupta,[17] Thomas Lila,[16] Alberto Risueno,[18] Katharine E. Yen,[19] Bin Wu,[19] Eyal C. Attar,[19] Martin S. Tallman,[1,2,†] and Stéphane de Botton[20,21,†]

	R/R AML	
	Enasidenib, 100 mg/d (n = 214)	All doses (N = 280)
ORR, % (n/N) [95% CI]*	38.8 (83/214) [32.2%-45.7%]	39.6 (111/280) [33.9%-45.6%]
CR + CRi/CRp rate, % (n/N)	29.0 (62/214)	27.9 (78/280)
Best response		
CR, n (%) [CR rate 95% CI]	42 (19.6) [14.5-25.6]	53 (18.9) [14.5-24.0]
CRi/CRp, n (%)	20 (9.3)	25 (8.9)
PR, n (%)	9 (4.2)	17 (6.1)
MLFS, n (%)	12 (5.6)	16 (5.7)

	Refractory to intensive chemotherapy (n = 40)	Refractory to lower-intensity therapy (n = 44)†	Relapsed following any prior AML therapy (n = 130)
ORR, n (%) [95% CI]*	15 (37.5) [22.7-54.2]	19 (43.2) [28.4-59.0]	49 (37.7) [29.4-46.6]
CR, n (%)	4 (10.0)	12 (27.3)	26 (20.0)
CRi/CRp, n (%)	4 (10.0)	2 (4.5)	14 (10.8)
OS, median (95% CI), mo	12.4 (8.2-22.9)	8.0 (5.6-11.7)	8.1 (7.0-9.3)

I wanted to provide some data regarding the response rates seen with IDH2 inhibition with this agent and enasidenib. These were predominantly relapsed and refractory patients who, in general, do not have a very high response rate with conventional therapies that are also highly toxic. With a pill that you take once a day, relatively well tolerated, there was an overall response rate in relapsed/refractory AML of about 40% and particularly complete remissions in about 20% to 30% of patients and that is very promising for a well-tolerated drug. In addition, looking at specific subgroups of patients who were treated with enasidenib, you can appreciate that the responses were preserved in individuals who are refractory to prior intensive chemotherapy, those were refractory to prior lower intensity therapy, and those individuals who had relapse following any prior therapy. So, in general, the rates of response seem to be preserved across multiple different clinical groups.

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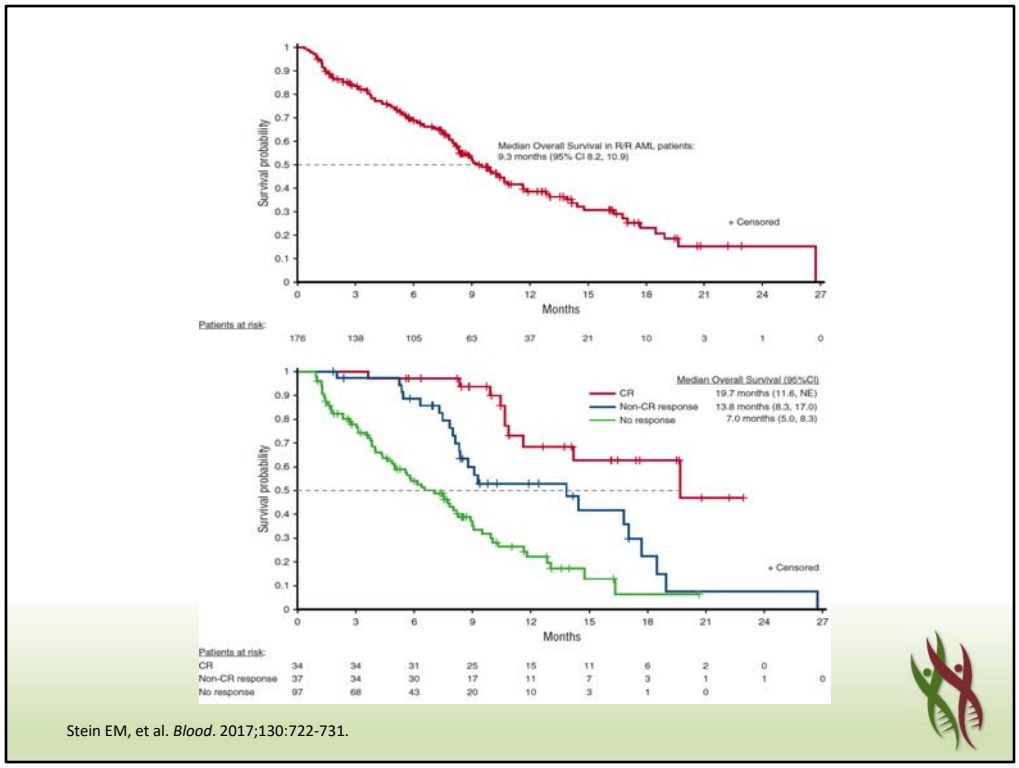

Stein EM, et al. *Blood*. 2017;130:722-731.

These are the survival curve seen with enasidenib in these populations. The median overall survival was approximately nine months but patients that responded with complete remissions or even those who had non-complete remission responses such as those with partial responses or morphologic leukemia-free states also had relatively good median overall survival of 19.7 months and 13.8 months, respectively. So if there was some degree of response that was seen, at least in a substantial subset of patients treated with this well-tolerated treatment, these folks had very prolonged overall survival, ultimately, leading to the approval of this drug for patients with relapsed or refractory IDH2-mutated AML.

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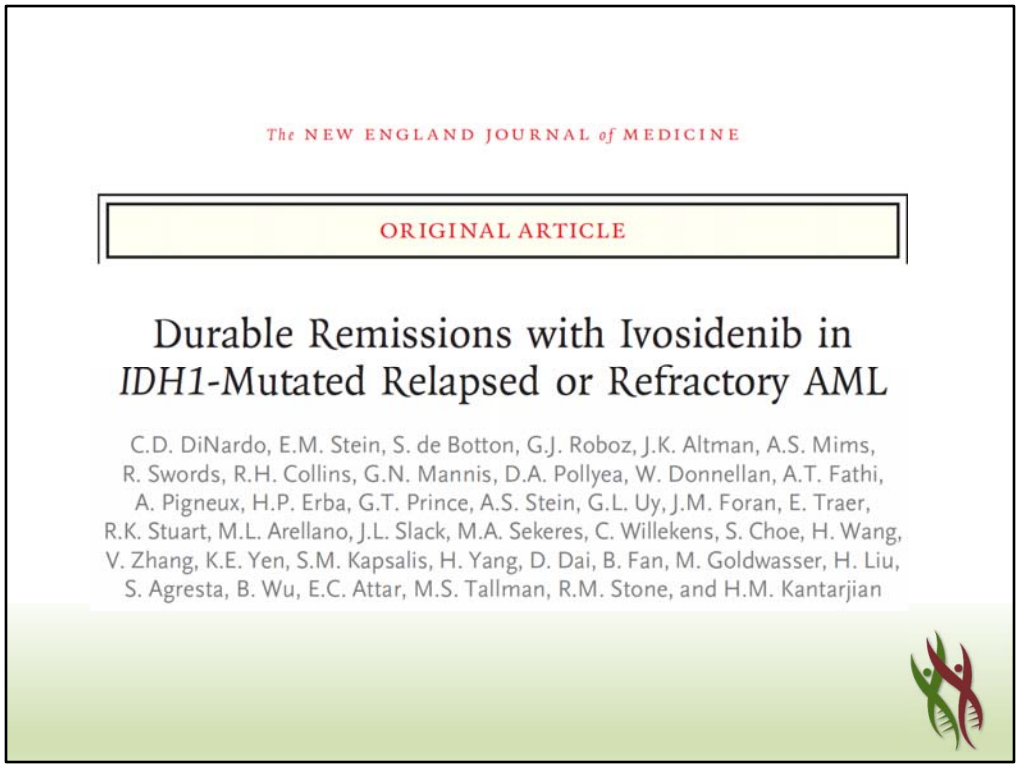
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

C.D. DiNardo, E.M. Stein, S. de Botton, G.J. Roboz, J.K. Altman, A.S. Mims, R. Swords, R.H. Collins, G.N. Mannis, D.A. Pollyea, W. Donnellan, A.T. Fathi, A. Pigneux, H.P. Erba, G.T. Prince, A.S. Stein, G.L. Uy, J.M. Foran, E. Traer, R.K. Stuart, M.L. Arellano, J.L. Slack, M.A. Sekeres, C. Willekens, S. Choe, H. Wang, V. Zhang, K.E. Yen, S.M. Kapsalis, H. Yang, D. Dai, B. Fan, M. Goldwasser, H. Liu, S. Agresta, B. Wu, E.C. Attar, M.S. Tallman, R.M. Stone, and H.M. Kantarjian

Let's move on to ivosidenib. The IDH1 inhibitor similarly studied across various patient populations, but specifically enriched for individuals who had relapsed/refractory AML.

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Single-Arm, Open-Label, Multi-Center Study of Ivosidenib

Dose Escalation
Enrollment Complete

Patients with m*IDH1*+ advanced hematologic malignancies
Oral AG-120 daily in continuous 28-day cycles
Doses: 100 mg twice daily; 300, 500, 800, 1,200 mg once daily

Dose Expansion
500 mg Once Daily in Continuous 28-d Cycles

- **R/R AML in 2nd+ relapse, relapse after SCT, refractory to induction or reinduction, or relapse within 1 year (n = 125)**
- **Untreated AML not eligible for SOC (n = 25)**
- **Other non-AML m*IDH1* R/R advanced hematologic malignancies (n = 25)**
- **Other R/R AML (n = 25)**

Dose escalation objectives

Primary	Safety and tolerability, identification of MTD and/or recommended phase 2 dose
Secondary	Assessment of clinical activity by investigators using modified 2003 International Working Group criteria in AML
Exploratory	Determination of m*IDH1* variant allele frequency (VAF) by next-generation sequencing (NGS)

DiNardo CD, et al. ASH 2017. Abstract 725.

Similar study design is shown here as was seen with enasidenib, multiple cohorts looked at including relapsed/refractory AML as well as untreated AML and other forms of hematologic malignancy, again, the primary endpoint of the study was safety and tolerability, but we did also look at an early appreciation of efficacy.

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Phase 1 Study of Ivosidenib in AML: Grade ≥3 TEAEs (≥1% Patients)

Event	Relapsed or Refractory AML and Starting Dose of Ivosidenib of 500 mg Daily (N=179)	Overall Population (N=258)
	no. of patients (%)	
≥1 Treatment-related adverse event of grade 3 or higher	37 (20.7)	66 (25.6)
Prolongation of the QT interval on ECG	14 (7.8)	18 (7.0)
IDH differentiation syndrome†	7 (3.9)	12 (4.7)
Anemia	4 (2.2)	6 (2.3)
Thrombocytopenia	3 (1.7)	5 (1.9)
Leukocytosis	3 (1.7)	3 (1.2)
Febrile neutropenia	1 (0.6)	3 (1.2)
Diarrhea	1 (0.6)	3 (1.2)
Platelet count decreased	3 (1.7)	3 (1.2)
Hypoxia	2 (1.1)	3 (1.2)

DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398.

As opposed to enasidenib, which saw a minority of patients developed bilirubinemia, the adverse event of interest here was prolonged QT interval seen on EKG, which was seen in the minority of patients. Similarly, IDH differentiation syndrome was also seen among this cohort of patients in a minority and could be lethal. It was important to monitor for this entity and closely manage it if there was suspicion for it.

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Phase 1 Study of Ivosidenib in AML: Response

Response	Primary Efficacy Population (N=125)	Relapsed or Refractory AML (N=179)	Untreated AML (N=34)†
CR or CRh			
No. of patients	38	54	12
% (95% CI)	30.4 (22.5–39.3)	30.2 (23.5–37.5)	35.3 (19.7–53.5)
Median time to CR or CRh (range) — mo	2.7 (0.9–5.6)	2.0 (0.9–5.6)	2.8 (1.9–2.9)
Median duration of CR or CRh (95% CI) — mo	8.2 (5.5–12.0)	6.5 (5.5–11.1)	NE (1.0–NE)

DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398.

Again, there was a promising rate of response with ivosidenib monotherapy, at least among the primary efficacy population the median time to complete remission or CRH was 2.7 months. For patients who had relapsed or refractory AML, it was two months. The median duration of CR was eight months for at least all patients that were seen on study; and for relapsed/refractory patients, 6.5 months.

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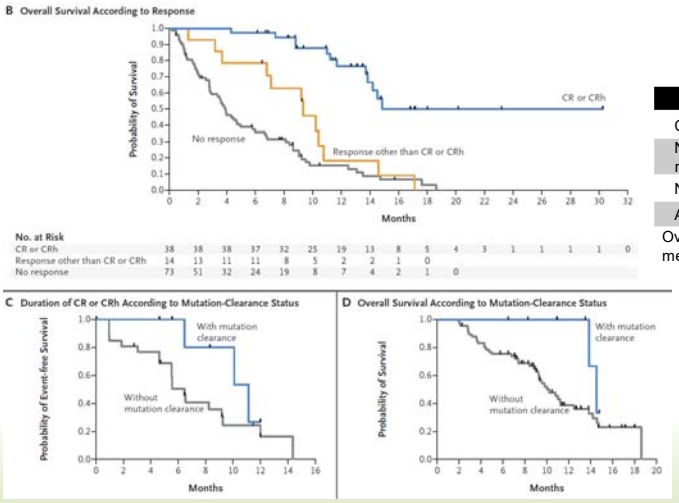
Phase 1 Study of Ivosidenib in AML: Response



CR + CRh	NE [13.8-NE]
Non-CR/CRh responders	9.3 [3.7-10.8]
Nonresponders	3.9 [2.8-5.8]
All	8.8 [6.7-10.2]
Overall follow-up, median (range)	14.8 (0.2-30.3)

DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398.; DiNardo CD, et al. ASH 2017. Abstract 725.

Here is the survival curves that again demonstrate that individuals who had a response to treatment seem to do particularly well, and individuals who cleared their IDH1 mutation at the timing of response doing particularly well also. The rates of response for patients on this study were approximately, again, around 40% with CR and CRH affecting approximately 30% of patients, and those individuals who responded seem to have very high median overall survival, and even those who had non-CR responders having median overall survival of nine months, which is promising in this patient population.

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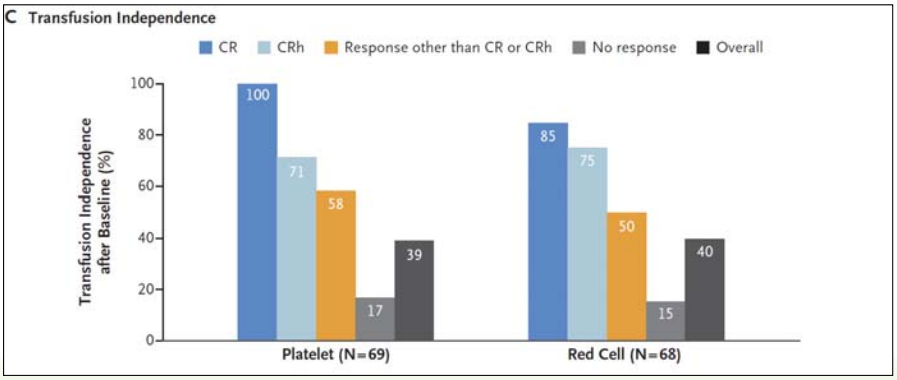
Phase 1 Study of Ivosidenib in AML: Response

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



DiNardo CD, et al. *N Engl J Med*. 2018;378(25):2386-2398.

In addition to complete remission and survival, there was also an impact on quality of life for these patients, which is increasingly relevant for relapsed/refractory AML, particularly on older patients. Many individuals who responded and many who did not respond with traditional complete remission established transfusion independence on therapy, meaning that they had less need for red cell transfusions and platelet transfusions. Even individuals who had no response, 17% achieved platelet transfusion independence and 15% achieved red cell transfusion independence, which again has great clinical impact among these groups of patients.

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Ivosidenib – Newly Diagnosed Patients

(Study AG120-C-001)

Endpoint	Ivosidenib (500 mg daily) N=28
CR[1] n (%)	8 (28.6)
95% CI	(13.2, 48.7)
Median DOCR[2] (months)	NE[3]
95% CI	(4.2, NE)
CRh[4] n (%)	4 (14.3)
95% CI	(4.0, 32.7)
Observed DOCRh[2] (months)	2.8, 4.6, 8.3, 15.7+
CR+CRh n (%)	12 (42.9)
95% CI	(24.5, 62.8)
Median DOCR+CRh[2] (months)	NE[3]
95% CI	(4.2, NE)

Ivosidenib – Prescribing Information

A table here describes what was seen in individuals receiving ivosidenib who did not have relapsed/refractory disease but rather newly diagnosed disease, and again among this population, we see that the rate of complete remission was 28.6% and that of CRH was 14.3%, together combined for a CR/CRH percentage of 42.9%, again highly promising. The number of patients obviously is smaller than individuals who had relapsed/refractory disease, total of 28 patients, presented here with newly diagnosed AML. But this data has helped lead to the approval of this drug, also in the newly diagnosed patients who are not eligible for intensive therapy or maybe older and therefore their options are limited. So, the ivosidenib IDH1 inhibitor is now approved for relapsed/refractory IDH1-mutated AML, but also in the newly diagnosed setting for individuals who may not be eligible for upfront conventional therapies.

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JAMA Oncology | Brief Report

Differentiation Syndrome Associated With Enasidenib, a Selective Inhibitor of Mutant Isocitrate Dehydrogenase 2

Analysis of a Phase 1/2 Study

Amir T. Fathi, MD; Courtney D. DiNardo, MD; Irina Kline, MD; Laurie Kenvin, BSN; Ira Gupta, MD; Eyal C. Attar, MD; Eytan M. Stein, MD; Stephane de Botton, MD, PhD; for the AG221-C-001 Study Investigators

As mentioned, I wanted to briefly discuss differentiation syndrome associated with IDH inhibitors. We look back at the initial phase 1/2 study of enasidenib IDH2 inhibitor and tried to characterize differentiation syndrome among the patients that were studied on that trial.

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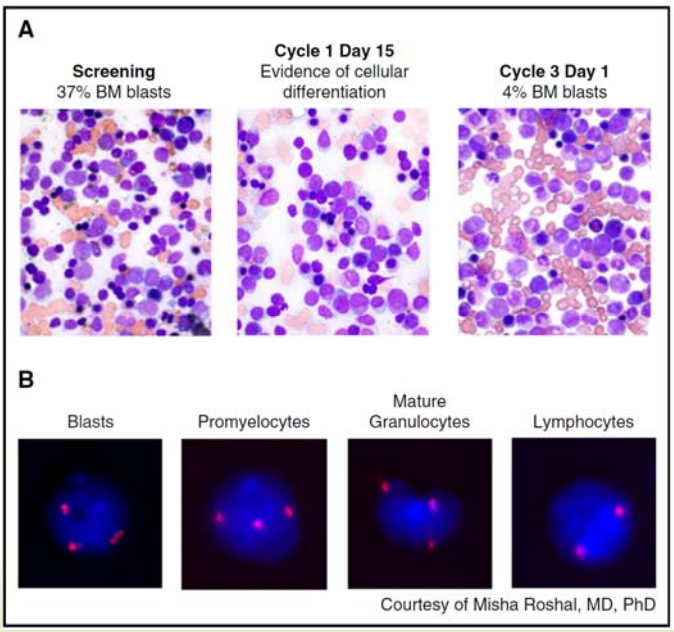
Practical Strategies for Optimizing IDH Inhibitor-based Therapy in Relapsed/Refractory AML



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

Just to sort of discuss how responses are seen with IDH inhibitors, here we have a representative patient who at screening, had substantial involvement of leukemia in the marrow; thereafter, by day 15 of treatment, there was already signs of differentiation and maturation reflective of the underlying mechanism of action of this drug, and by the beginning of cycle three, which is about 60 days following startup treatment, we actually see suppression of leukemic blasts and evidence of marked differentiation and normal myeloid maturation. However, those myeloid cells that appear normal still have the remnant abnormality of the blast. As an example in the bottom panel you see, this patient had a trisomy in their chromosomal analysis at baseline. Those blasts that were seen had three copies of a chromosome. As the patient underwent treatment, you can see that the mature granulocytes that resulted from treatment and for all intents and purposes appeared normal and normal functioning still had the chromosomal alteration, suggesting that the process of response was through differentiation, which then goes to show you that the syndrome that may emerge as a result of differentiation therapy should be seen concurrent with therapy among these patients and differentiation syndrome is thought to result from the various cytokine-mediated inflammatory cascades that result from the underlying differentiation triggered by these treatments.

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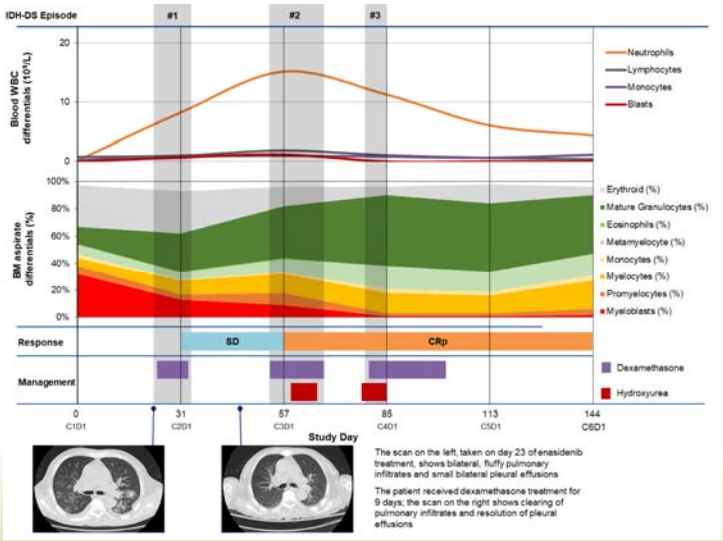
IDH-Differentiation Syndrome



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

Here is a patient, for example, who approximately on beginning of cycle two of treatment started to have episodes of pulmonary symptomatology, namely shortness of breath, cough, and a CTM is shown at the bottom left there, shows infiltrates, as well as an unexplained fever. Secondary causes, infectious causes, are looked at and they're not necessarily convincing. At around the same time, you see a rise in maturing granulocytes as well as a reduction and blasts in the bone marrow as shown in the bottom panel. You see, there is that decrease in that red proportion of cells over time and at the top panel arise in that orange line, which is the normal maturing granulocytes. The gray bars that you see throughout are episodes of differentiation syndrome, again, these are vague symptoms of respiratory symptomatology, fevers, and each time the patient is treated with steroids and has a resolution of symptoms. Concurrent with these episodes of differentiation syndrome, you may have leukocytosis as the cells are maturing and expanding in the peripheral blood, that can be managed with hydroxyurea.

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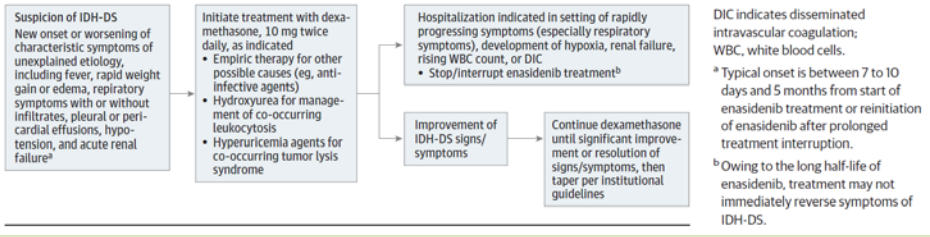
IDH-Differentiation Syndrome

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)

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



DIC indicates disseminated intravascular coagulation; WBC, white blood cells.

[a] Typical onset is between 7 to 10 days and 5 months from start of enasidenib treatment or reinitiation of enasidenib after prolonged treatment interruption.

[b] Owing to the long half-life of enasidenib, treatment may not immediately reverse symptoms of IDH-DS.

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

So we actually went through and looked at all the patients that were treated in the phase 1/2 study and found symptoms and signs that might be suggestive of differentiation syndrome. These included dyspnea, unexplained fever, pulmonary infiltrates, hypoxia, kidney injury, pleural and pericardial effusions, bony pains and rash and the most common of these were basically respiratory symptoms and fevers. Our recommendation was that if there was suspicion of IDH differentiation syndrome, and if there was reasonable time to rule out secondary causes of fever and respiratory symptoms, patients should be treated relatively urgently with dexamethasone at 10 mg twice daily. If the symptoms are sufficiently rapid, where there is no time to rule out secondary causes and there is sufficient suspicion for differentiation syndrome, dexamethasone at 10 mg twice daily should still be started because if you wait sufficiently for the differentiation syndrome to get worse it can become a lethal entity. Hospitalization may be necessary in patients who are rapidly progressive. If patients respond to dexamethasone, it's suggestive that the process was likely related to differentiation, although as we know dexamethasone response can be nonspecific. As patients respond and get better to steroids therapy, the dexamethasone dosing can be down tapered and ultimately discontinued, but there needs to be substantial improvement in symptoms. Leukocytosis and DIC also known as disseminated intravascular coagulation are entities that can be seen in conjunction with differentiation syndrome and should be managed separately. So if individuals have high rapidly rising white blood cell counts that occur with differentiation syndromes they may be in need of hydroxyurea. Similarly, management of coagulopathies may also be necessary, such as with transfusional support, and if there is also a concurrent tumor lysis, tumor lysis syndrome should also be monitored for and vigilantly managed.

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Ongoing Studies

- Enasidenib or ivosidenib + HMA therapy in patients with ND AML not eligible for intensive chemotherapy
- AGILE: global, phase 3, ivosidenib + azacitidine vs placebo + azacitidine in patients with ND AML
- Enasidenib or ivosidenib in combination with standard AML induction and consolidation therapy in patients with ND AML
- HOVON 150/AMLSG: international, phase 3, randomized, ivosidenib with induction, consolidation and maintenance in ND AML or MDS-EB2 eligible for IC

DiNardo CD, et al. *J Clin Oncol* ,2019;37:Abstract 7011.; Stein E, et al. *Blood*. 2018;132:Abstract 560.

Table 4. Response rates

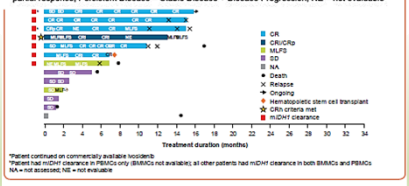
Response parameter	All patients N=23
CR, n (%) [95% CI]	14 (60.9) [38.5, 80.3]
Time to CR, median (range), months	3.7 (0.8–15.7)
Duration of CR, median [95% CI], months	NE [9.3, NE]
CR+CRh,* n (%) [95% CI]	16 (69.6) [47.1, 86.8]
Time to CR+CRh, median (range), months	2.8 (0.8–11.5)
Duration of CR+CRh, median [95% CI], months	NE [12.2, NE]
CRh, n (%)	2 (8.7)
ORR, n (%) [95% CI]	18 (78.3) [56.3, 92.5]
Time to response, median (range), months	1.8 (0.7–3.8)
Duration of response, median [95% CI], months	NE [10.3, NE]

	Ivosidenib (AG-120) + chemotherapy			Enasidenib (AG-221) + chemotherapy		
Response, n (%)	All (n=41)	*De Novo* (n=28)	sAML (n=13)	All (n=77)	*De novo* (n=45)	sAML (n=32)
CR+CRi/CRp	32 (78)	26 (93)	6 (46)	53 (69)	33 (73)	20 (63)
CR	27 (66)	22 (79)	5 (39)	42 (55)	28 (62)	14 (44)
CRi/CRp	5 (12)	4 (14)	1 (8)	11 (14)	5 (11)	6 (19)
MLFS	2 (5)	-	2 (15)	10 (13)	4 (9)	6 (19)
PR	1 (2)	0	1 (8)	1 (1)	-	1 (3)
Persistent disease	2 (5)	1 (4)	1 (8)	9 (12)	6 (13)	3 (9)
NE	4 (10)	1 (4)	3 (23)	4 (5)	2 (4)	2 (6)

Best Response from any time on study is shown

*Patients who have at least one post-baseline response assessment on or after Induction Day 21 or who discontinued treatment before having a response assessment.

CR = Complete Remission; CRi = CR with incomplete hematologic recovery; CRp = CR with incomplete platelet recovery; MLFS = morphologic leukemic-free state for patients with AML; PR = partial response; Persistent Disease = Stable Disease + Disease Progression; NE = not evaluable



*Patient continued on commercially available ivosidenib
†Patient had mIDH1 clearance in PBMCs only (BMMCs not available); all other patients had mIDH1 clearance in both BMMCs and PBMCs
NA = not assessed; NE = not evaluable

We discussed the trials that have been completed to date with enasidenib, the IDH2 inhibitor and ivosidenib, the IDH1 inhibitor while there are also ongoing studies that are looking at these agents in combination with conventional therapies such as with hypomethylating agents and with induction chemotherapy. Here, we have some preliminary data that has been presented in the last few years looking at the combination of hypomethylating agents and IDH inhibitors. This particular table and graphic shows patients treated with ivosidenib and we see that the complete remission rate is actually, at least in a limited number of patients, quite high when you combine IDH inhibitors with hypomethylating agents, of course, we need more robust, comprehensive data to emerge to tell us whether this is promising and likely additional clinical trials which will follow. There are ongoing randomized studies that are seeking to answer these questions in terms of the promise of IDH inhibitors with hypomethylating agents. Similarly, the combination of IDH inhibitors with induction intensive chemotherapy has also been presented and shows relatively promising rates of response in individuals who have at least de novo non-therapy, non-secondary AML.

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FDA Approvals for AML

- **4/28/17: Midostaurin (Rydapt)**
  - For adult patients with newly diagnosed AML who have a *FLT3* mutation
  - Companion diagnostic: LeukoStrat CDx *FLT3* mutation assay
- **8/1/17: Enasidenib (Idhifa)**
  - For adult patients with relapsed/refractory AML who have an *IDH2* mutation
  - Companion diagnostic: RealTime *IDH* mutation assay
- **8/3/17: CPX351/fixed ratio daunorubicin-cytarabine (Vyxeos)**
  - for the treatment of adults with two types of acute myeloid leukemia (AML): newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
- **9/1/17: Gemtuzumab ozogamicin (Mylotarg)**
  - For adults with newly diagnosed AML whose tumors express the CD33 antigen, and for treatment of patients 2 years or older with relapsed/refractory CD33+ AML
- **7/20/18: Ivosidenib (Tibsovo)**
  - For adult patients with relapsed/refractory AML who have an *IDH1* mutation
  - For newly diagnosed *IDH1*-mutated patients ≥ age 75 or with comorbidity precluding intensive therapy (May 2019)
- **11/21/18: Glasdegib (Daurismo) and low dose cytarabine**
  - For adult patients with newly diagnosed AML who are ≥ age 75 or are ineligible for induction due to comorbidity
- **11/21/18: Venetoclax (Venclexta) and hypomethylating therapy (or low dose cytarabine)**
  - For adult patients with newly diagnosed AML who are ≥ age 75 or are ineligible for induction due to comorbidity
- **11/28/18: Gilteritinib (Xospata)**
  - For adult patients with relapsed/refractory AML who have a *FLT3* mutation

In summary, I wanted to provide a list of the amazing advances we've seen in the FDA approvals we've had for acute myeloid leukemia. Over the course of the last two years, just in 2017 and 2018 alone, we've had a host of approvals for various patient populations, which include the topic that we discussed today, namely IDH1 and IDH2 inhibitors, ivosidenib and enasidenib, respectively.

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Future of AML Therapy – 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
- Novel chemotherapeutic approaches for higher-risk populations
- Will this decade see more approved AML therapies than the last four decades combined?

So reasons for optimism in AML, in general, there are improved outcomes due to better prognostication, patient selection, and supportive care. There is an emergence of effective targeted therapies which include IDH inhibitors, novel combinations for older patients are emerging, and being studied such as the combination of IDH inhibitors with conventional treatments such as hypomethylating agents and induction chemotherapies, novel chemotherapeutic approaches for high-risk patients are also being looked at, and I'm very optimistic and look forward to subsequent years and ask the question, will the upcoming decade produce more approvals for AML than all of the decades that we've seen, and I think there is certainly room for optimism in that regard.

Thank you so much for your attention.

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