

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## Enasidenib for Relapsed/Refractory Acute Myeloid Leukemia With *IDH2* Mutations: Optimizing the Patient Experience



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### H&O What is the mechanism of action of enasidenib?

**GR** Enasidenib (Idhifa, Celgene/Agios) is an oral, small molecule inhibitor of mutant isocitrate dehydrogenase 2 (*IDH2*) enzymes. *IDH2* mutations occur in approximately 15% of patients with acute myeloid leukemia (AML). The mutant proteins catalyze production of the oncometabolite 2-hydroxyglutarate (2-HG). This change results in several downstream epigenetic effects that are related to the growth and proliferation of AML, including hypermethylation and blocked differentiation of hematopoietic cells. Enasidenib inhibits mutant *IDH2* enzymes and results in decreased 2-HG levels and differentiation of leukemic cells.

### H&O What clinical trial data led to the approval of enasidenib for AML?

**GR** The US Food and Drug Administration (FDA) has approved enasidenib for the treatment of adult patients with relapsed or refractory AML with an *IDH2* mutation. The trial that led to approval included approximately 200 patients with relapsed/refractory *IDH2*-mutated AML, and showed that enasidenib resulted in durable responses, including complete remissions, in about 20% of patients.

### H&O What is known about use in the frontline setting?

**GR** Although enasidenib has not been approved for

patients with newly diagnosed *IDH2*-mutated AML, a small number of newly diagnosed patients were treated as part of the original clinical trial, and about 20% of them attained complete remission. Some of these patients have enjoyed prolonged responses and might reasonably be called “super responders.” An important goal of further research is to determine how to identify those newly diagnosed patients who might do well enough with enasidenib monotherapy that they could avoid concomitant chemotherapy. Also, there are ongoing clinical trials evaluating the efficacy and safety of enasidenib in combination with other agents, such as standard chemotherapy and azacitidine (Vidaza, Celgene), for the treatment of newly diagnosed patients. There are many unanswered questions. For example, what are the best combination partners for enasidenib, and should it be administered concomitantly or sequentially with other agents?

### H&O What are typical patient expectations about AML?

**GR** AML is the most common acute leukemia in adults. It is well-recognized as a highly lethal disease. Worldwide, the overall survival is often less than a year. Most patients with AML who are older than 60 years are worried about long-term survival and they know that, historically, remission rates are low. In highly selected patients older than 60 years, remission rates can reach as high as 50% to 60%, but the duration of remission is generally short. For much older patients, especially those who are frail or have other illnesses, the outcomes are very poor. In fact, many older

## Treatment of Acute Myeloid Leukemia: A Patient's Perspective

Ralph Hills

In December 2014, I underwent a physical. A few days later, the doctor's receptionist called and told me to make an immediate appointment at our local cancer center. "Why would I do that?" I asked. But she had no other information to give me.

I visited a nearby hospital in Connecticut with Dorcas, my wife. Dorcas is key to the story, as my primary full-time caregiver. We spoke with an oncologist, who told us 4 things. My diagnosis was a serious and advanced blood cancer called acute myeloid leukemia (AML). The oncologist prescribed multiple cycles of chemotherapy. He suggested we go home and get my affairs in order. Then he recommended that we obtain a second opinion in New York City.

After that meeting, I was resigned and without hope. We went home and cried.

I am now most grateful for the oncologist's recommendation to obtain a second opinion. We went to Weill Cornell Medical Center and met with Dr Gail Roboz. Dr Roboz ordered blood and bone marrow tests. Her first treatment recommendation was two 30-day cycles of chemotherapy, which disappointed me because it sounded like the original plan. Dorcas and I returned home, and we arranged for treatment at the local cancer center.

My chemotherapy was scheduled to begin on a Monday. The Sunday evening before, Dr Roboz called me from the ski slopes of Colorado. She asked if I would consider changing my treatment plan. Unbeknownst to Dorcas and me, Dr Roboz had ordered specialized genetic tests, which disclosed that I had a mutation that might respond to a new, nonchemotherapy treatment. Dr Roboz was clear that the decision was ours, but the fact that she called late on a Sunday night while on vacation seemed to amplify the promise of this new treatment. Aware of the harsh side effects and limited survival benefits of chemotherapy at my age, Dorcas and I chose the mystery drug.

I enrolled in a trial of AG-221, now known as enasidenib. The drug is administered orally, once a day. Except for trips to New York City every 2 weeks for tests, I was able to stay home during treatment. For

the first 5 months, I was terribly sick. I slept for 24 hours on most days. I was barely mobile, and I could not ingest anything other than water and nutritional supplements. I lost 45 pounds. My blast cell percentage exceeded 70%. My eyes and skin were yellow with jaundice, and I had gallbladder trouble and serious digestive tract issues.

Some cancer patients have told me that they dread waking up in the morning and facing their day. For me, however, waking up each morning was a pleasant surprise; my situation felt that desperate. I was alive, but only because of treatment with enasidenib. My blast count decreased from 70%, to 42%, to 20%, to 12%. (Now, my blast count is zero.)

By September 15, 2015, I could sip soup. It took another 6 months for my digestive tract issues to resolve. Since April 2016, I have been slowly regaining my strength. I am still receiving treatment with enasidenib, which I began more than 42 months ago.

The world has changed since my diagnosis in 2014.

Congress and Medicare are now supporting the use of new genetic tests. I consider it a miracle that Dr Roboz tested me for genetic mutations. In past years, there was no reason to perform these tests because the targeted therapies did not exist. In 2017, the FDA approved 4 drugs for patients with AML.

I credit the doctors, the drug company, and my wife and other caregivers for my survival. However, I was recently told that my willingness to enroll in a clinical trial is a key factor. Most clinical trials are designed for patients with relapsed or refractory disease. In the United States, only 3% of patients elect to enter a clinical trial as their first line of treatment. A bill currently in Congress aims to improve patient access to experimental treatments in clinical trials.

With the exception of that first phone call in December 2014, every step of this journey has been filled with luck. Because I have been so lucky, I can give hope to the next 23,000 families who are impacted by a diagnosis of AML each year. I consider every single day a bonus.



Ralph and Dorcas Hills

AML patients worldwide are not offered any treatment at all.

For patients with AML who are aged 18 years to approximately 60 years, rates of remission and overall survival have improved throughout the past few decades. However, they remain far from what patients want to hear, with 5-year overall survival rates of approximately 40% to 50% for unselected patients. Even in 2018, patients who receive a diagnosis of AML are still hearing devastating news. The rare exceptions would include patients with favorable molecular subtypes.

### **H&O** What do you tell your patients about treatment with enasidenib?

**GR** There is definitely an exciting aspect to being treated with a targeted therapy. In particular, I find that patients are excited to hear about the science behind enasidenib and its mechanism of action. The problem is that most patients assume that if their disease has a target, then they will be cured by treatment with a corresponding targeted therapy. So, I try to be careful not to “oversell” targeted therapy to patients. I tend to be somewhat measured and realistic when presenting enasidenib and other targeted therapies to patients, to ensure they understand that having a “targetable” leukemia does not at all guarantee a cure, or even remission.

### **H&O** What are the potential adverse events?

**GR** I find that patients tend to assume that pills are not as strong as intravenous therapies, and I caution patients that even though enasidenib is administered orally as a pill, it is still a powerful drug. I prepare patients for several different side effects, including an important one called differentiation syndrome. Both doctors and patients must be prepared for potentially rapid escalation of blood counts that might be associated with fever, shortness of breath, and low oxygen levels. Differentiation syndrome occurs with some frequency, and it is described in the prescribing information for both doctors and patients. Patients require close monitoring and sometimes hospitalization. Some patients require multiple weekly blood tests until their white blood cell count stabilizes. Also, most patients require both packed red blood cell and platelet transfusions.

The toxicity profile of enasidenib is much easier to tolerate than that of conventional cytotoxic chemotherapies. That being said, “easier than chemotherapy” does not mean easy. Patients may experience gastrointestinal side effects, such as nausea, vomiting, and diarrhea. There can be some changes in appetite. Hematologic side effects might require transfusions. As with all leukemia patients,

infections can occur. Patients should be counseled to expect these events. They should undergo regular symptom checks to determine whether antiemetics, antidiarrheals, or other supportive measures are needed to ensure they can remain on therapy as prescribed, which is important. I favor aggressive monitoring of laboratory parameters, especially hepatic and renal parameters, as abnormalities, especially in the bilirubin, are quite common.

### **H&O** How does monitoring incorporate bone marrow biopsies?

**GR** After treatment with enasidenib, the appearance of bone marrow can differ from what is seen after cytotoxic chemotherapy. A bone marrow biopsy performed 2 weeks, 4 weeks, or even 6 weeks after treatment with enasidenib is likely to still show significant disease. Both patients and practitioners should recognize that responses to enasidenib can take many weeks. If a patient is tolerating the treatment well, I favor continuing it for at least 8 to 12 weeks to allow for a response to develop. There are reports of patients who did not achieve a complete remission, but did maintain stable disease, which may offer clinical benefits by reducing the number of transfusions or improving performance status.

To summarize, do not assume that an early bone marrow biopsy showing residual disease means that enasidenib is ineffective. It may take many weeks to confirm the full impact of treatment and to achieve maximal response to treatment.

### **H&O** Are there any ongoing clinical trials of enasidenib?

**GR** There are several ongoing trials of enasidenib, both industry-sponsored and investigator-initiated. We are hopeful that research will continue because there are many unanswered questions. For example, should enasidenib be combined with standard cytotoxic intensive chemotherapy in the upfront setting? What are the possibilities for combining enasidenib with hypomethylating agents? What are the optimal timing, schedule, and dose of the combination of enasidenib with other treatment programs? These important questions must be answered in clinical trials.

Preliminary data for combination regimens suggest that there may be significant differences between administering enasidenib concomitantly vs sequentially. The optimal strategy is not yet known, and both doctors and patients should be hopeful that accrual to clinical trials will continue briskly. Also, it is important to note that the potential use of enasidenib in combination with other treatments is not only for patients with newly diagnosed

disease, but also for those with relapsed disease. In the relapsed AML setting, there is, unfortunately, plenty of room for further improvement in the rates of overall response, remission, and duration of response.

### Disclosure

*Dr Roboz has performed consulting for AbbVie, Amphivena Therapeutics, Argenx, Array BioPharma Inc., Astex Pharmaceuticals, Bayer, Celgene, Celltrion, CTI BioPharma, Eisai, Genoptix, Immune Pharmaceuticals, Janssen Pharmaceutica, Jazz Pharmaceuticals, MedImmune, Novartis, Orsenix, Pfizer, Roche/Genentech, Sunesis Pharmaceuticals, and Sandoz. She has received research support from Cellectis.*

### Suggested Readings

ClinicalTrials.gov. An efficacy and safety study of AG-221 (CC-90007) versus

conventional care regimens in older subjects with late stage acute myeloid leukemia harboring an isocitrate dehydrogenase 2 mutation (IDHENTIFY). Identifier: NCT02577406. <https://clinicaltrials.gov/ct2/show/NCT02577406>. Accessed April 10, 2018.

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