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COMMENTARY

Deep Dive into Targeted Therapies: Understanding IDH1-Mutant AML Treatments [Podcast]

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Abstract: This podcast episode reviews recent advances in the treatment of IDH1-mutant acute myeloid leukemia (AML), focusing on the mechanisms, efficacy, and safety profiles of approved IDH1 inhibitors. The purpose is to present expert insights and clinical data from key trials that underscore the clinical benefits of these targeted therapies. Through discussion of key findings from pivotal clinical trial studies, including data supporting the use of these agents in both newly diagnosed and relapsed or refractory (R/R) settings, the episode highlights significant outcomes such as increased overall response and prolonged duration of remission in patients treated with IDH1 inhibitors. The analysis examines critical factors including treatment sequencing, combination regimens, and toxicity management, particularly the monitoring and mitigation of differentiation syndrome and QT interval prolongation. Emphasis is placed on the clinical rationale for individualized therapy selection and the importance of repeat mutation testing at diagnosis and relapse to guide treatment decisions. The results obtained from these clinical trials provide evidence that integrating oral targeted agents into the management of relapsed or refractory AML improves patient outcomes, especially for older or unfit patients who cannot undergo intensive chemotherapy. In conclusion, the episode demonstrates that the evolving use of IDH1 inhibitors, supported by rigorous clinical evidence, represents a promising advance in AML treatment by offering more precise, effective, and tolerable therapeutic options.

Keywords: acute myeloid leukemia, IDH inhibitors, ivosidenib, olutasidenib, molecular testing, relapsed, refractory

This podcast series is part of a wider, accredited independent educational program, The AML Expert Series: Innovations in Molecular Testing, Emerging Therapies & Targeted Treatments. The episode reviews pivotal clinical trials supporting the use of IDH1-targeted agents, with a focus on response rates, remission durability, and survival outcomes across various lines of therapy. Expert faculty also address treatment sequencing strategies, considerations for incorporating combination regimens, and management of common and serious adverse events such as differentiation syndrome and QTc prolongation. Practical guidance is provided to support personalized therapy selection and optimize patient outcomes. Supported by an independent educational grant from Rigel.

Transcript

Voiceover

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program entitled The AML expert series: Innovations in molecular testing, emerging therapies and targeted treatments it is intended for healthcare professionals only and is supported by an independent educational grant from Rigel.

Chapter 1 Introduction

Amer Zeidan [00:40]: Hi, everyone. Thank you so much for joining us today. We are going to have a fantastic educational program with the titled "Deep Dive into Targeted Therapies: Understanding IDH1-Mutant AML Treatment"s, where we will be discussing the mechanism of action, the safety, the selection of therapies, the efficacy and the combination and sequencing of IDH1 inhibitors.

Amer Zeidan [01:06]: So my name is Amer Zeidan. I am a professor of medicine at Yale University. And it's a true pleasure to be joined today by a top expert in the field, Dr. DiNardo, who has been very instrumental in approval of some of those therapies that we will be discussing today. Courtney, thank you so much for joining us. Do you want to introduce yourself?

Courtney DiNardo [01:27]: Sure. Yes. Thank you so much. It's a pleasure to be here. My name's Courtney DiNardo. I am here at MD Anderson in Houston, Texas. And, yeah, just very much looking forward to discussion with you today on IDH inhibitors.

Amer Zeidan [01:43]: Perfect. Thank you. So, as I think many of our audience knows that management of acute myeloid leukemia (AML) has seen significant changes over the last decade, we understood that those patients should not be treated the same way, not in one uniform treatment, the same way we used to do it 10 years ago when we gave either intensive chemotherapy therapy or hypomethylating agents. And we clearly understood that the importance of precision medicine or individualized treatment, because there are different drivers for different subsets of AML. And probably the best management is going to be directed towards those specific providers, including, for example, *FLT3* mutations, *IDH1* and *[IDH]2* mutations, and other subsets that I think are being understood more, such as *TP53* and *KRAS*, and *RAS*, et cetera.[1]

Chapter 2 IDH1-Mutations in Leukemogenesis

Amer Zeidan [02:33]: So, this episode is going to focus more on IDH inhibitors, particularly IDH1 inhibitors.[2–5] And maybe we can start, Courtney, by explaining to the audience what is an *IDH1*-mutation and how does it contribute to the leukemogenesis in some patients with acute myeloid leukemia?

Courtney DiNardo [02:52]: Sure. So *IDH1*-mutations are not kind of the most common mutation, but they are actually quite prevalent in acute myeloid leukemia. About 8, up to 10% of patients can have an *IDH1*- mutation.[6,7] And the *IDH1*-mutations are interesting in that it creates this specific mutation that creates what's called an oncometabolite, where you have this essentially poisoning of the cells, where it creates, like, scientifically, what's called a hypermethylated phenotype. But what it's doing is it's preventing kind of that normal myeloid maturation. And so these cells get stuck in the in the leukemia blast phase and helps to promote malignancy and leukemia in that way.[1]

Amer Zeidan [03:44]: And I think the recognition of this pathway has been a very important step in the development of therapies, which I think it's always very satisfying to us as, you know, clinical researchers to see discoveries in the lab get translated into therapies that help our patients.

Chapter 3 Mechanism of Action of IDH1-Inhibitors

Amer Zeidan [04:03]: So maybe you can overview for us the currently approved therapies for *IDH1* as well as some of the major clinical trials that looked at these drugs.

Courtney DiNardo [04:14]: Yeah, because you have this kind of altered mutation creating this oncometabolite, the question is, you know, can you turn that off? So, so there have. There has been the development of actual mutant-targeted IDH inhibitors. Both *IDH1* and *IDH2*. We will not talk about as much today, but kind of you get these two different mutations leading to this kind of abnormal physiology that have figured out how to create molecules that can turn it off. So for the *IDH1* story, the first IDH1 inhibitor was a compound called ivosidenib.[4]

Courtney DiNardo [04:53]: And there is now a second IDH1 inhibitor that's now also approved called olutasidenib.[8] So just as background, we now have two IDH1 inhibitors, and they both function as small molecules. They are oral therapies

that kind of turn off that abnormal mutant process that's happening and allow cells to kind of normally differentiate, to turn into the normal myeloid counterparts that they are supposed to.

Courtney DiNardo [05:21]: So just briefly, you know, when you asked about, about a summary of the trials, the first one, ivosidenib, was approved in the relapse setting for patients with *IDH1*-mutation. So you have to have this mutation for the IDH inhibitors to work.

Chapter 4 Clinical Trials: Efficacy Data

Courtney DiNardo [05:37]: And in the ivosidenib study, we saw about a kind of a 30% response rate and about a 40%, what we call overall response rate. So, I should clarify, so like a complete remission or a complete remission with incomplete count recovery, it's about 30%.[9] And then when you kind of open it up to include any sort of response, about 40%.[9] And that was significant, right. So you have about a third or more of patients, you know, becoming transfusion independent that were previously needing transfusions, you know, improving counts, oral outpatient therapy leading to improved quality of life.

Courtney DiNardo [06:14]: And so the ivosidenib was approved and then olutasidenib, was approved more recently with very similar kind of data in the relapse setting. So again, a composite remission rate of about 30%, a response rate of about 40%.[10] So when you look at the numbers they are quite similar. So we have two different kind of excellent drugs that are approved. One thing that's a little bit notable about olutasidenib is that the duration of the remissions seem to last a little bit longer. And so whether these were not, of course, randomized trials compared against each other, so whether they were different populations or whether there is something kind of unique that olutasidenib is leading to longer remissions is something that was notable in those two approval studies.

Courtney DiNardo [06:58]: And then the third study I want to mention, the last one I want to mention is the AGILE study.[11] So that's where we have taken the IDH inhibitors, which work well as a single agent in the relapse setting. And kind of the concept, of course, is to try to move it to the front line where we are giving it in combinations for effective frontline therapy. And so the AGILE study looked at kind of a standard treatment, azacitidine with the IDH1 inhibitor, ivosidenib (AZA-IVO).[11,12] And in the setting for older patients not fit for intensive chemotherapy getting AZA-IVO, we saw composite remissions of over 50% with an overall survival in a randomized fashion, like an overall survival of over two years, so 29 months, which is pretty remarkable for that older unfit AML population.[11] So those are kind of the three, I think, most impactful trials leading to kind of approved settings to be using the IDH1 inhibitors.

Amer Zeidan [07:55]: Yeah, and I think this kind of exemplifies the typical paradigm of development in oncology, where we start with single agent in the refractory/relapse setting, and once we have an effective and safe drug, we go to the front line and in combinations. And as you mentioned, there are also ongoing trials, of course, with triplets and with intensive chemotherapy. And it's very satisfying to kind of see, I think that the increased number of trials that are looking at these agents.

Amer Zeidan [08:27]: Like you, I struggle to kind of completely differentiate between the two drugs. We had I think a very interesting discussion with Dr. Wang as well about some of that. And how do we choose between these two agents? And I always, you know, people think a lot about chronic myeloid leukemia (CML) as a paradigm for the development of multiple good agents to treat the same disease. And how do you sequence between them and how do you follow them?

Amer Zeidan [08:58]: Just for the audience, do you check for specific mutations based on which you would use these drugs? Or how do you think about sequencing them in your practice?

Chapter 5 Sequencing Treatment

Courtney DiNardo [09:10]: So there's no specific kind of mutation or co-mutation that I am aware of that would make me want to use ivosidenib over olutasidenib or vice versa. For me it's more of a side effect profile would be that the easiest way to discriminate. So for instance ivosidenib does have a QTC signal and so you have to be monitoring EKGs.[12] So if I had a patient that is on multiple different QT prolonging agents and has or maybe a family history or a personal history of cardiomyopathy or a QTC abnormality, that would be something to maybe make me opt more for olutasidenib.

Courtney DiNardo [09:51]: Whereas a olutasidenib has an AE side effect profile of transaminitis and so which, which ivosidenib does not.[13] So if I have a patient who had, you know, maybe at baseline has a mild transaminitis or is on other things leading to a transaminitis, that might be kind of one reason I would choose one over the other.

Courtney DiNardo [10:14]: The, only other thing I would say in terms of selecting one versus the other is I think there's good data on olutasidenib in the post venetoclax (VEN) setting and ivosidenib just does not have that peer reviewed data that I am, that I am aware of.[14] And so when you are in the olutasidenib study of the single agent in the relapse setting there was, still for me rather surprising like 50% response rate, like 30% true CR/CRH and about a 50% response rate in patients that had already failed venetoclax, which tends to be a really challenging population where there are not as many good responses in the post-VEN setting.[10] So if I do have a patient that's had a frontline regimen with maybe Aza-VEN and I am wanting to use an IDH1 inhibitor as a second line, I might opt for olutasidenib and have given that data.[13,14]

Amer Zeidan [11:08]: Yeah, I think all of these are excellent observations and I think many in the field I struggle to how biologically kind of explain these kind of trends that have been kind of seen in some of those trials. And of course, we do not have head-to-head comparisons, but you know, I think at the end of the day two good drugs, but like any good effective drug they do come with some side effects which you kind of touch on a little bit.

Chapter 6 Safety Profiles and Management of Adverse Events

Amer Zeidan [11:34]: But how do you in your practice monitor and manage these side effects?

Courtney DiNardo [11:39]: Yeah, I mean, the side effects are pretty well tolerated oral therapies. So, I think the most important thing is to realize that these are things that can have side effects. So, you do want to monitor your patient the first month or two when a patient is on a new therapy, even though it's oral, I do not say, you know, come back and see me in three months. You do want to be following labs and being on top of things. For olutasidenib the transaminitis is something I am watching for. So I am making sure to be monitoring liver function tests (LFTs), in addition to, you know, the complete blood count (CBC) and the general chemistries with ivosidenib, it's the QT monitoring. So making sure I am doing monthly EKGs at the beginning so that if there is a QT signal, I can maybe drop something else they are on that could also be affecting the QT. The main side effect with both of the IDH inhibitors, which is true for the IDH2 inhibitor, enasidenib, also is differentiation syndrome (DS).[15–18]

Courtney DiNardo [12:35]: So about 12 to 15% of patients that are getting an IDH inhibitor as a single agent will have differentiation syndrome, which is really nonspecific.[19] So you are not going to know you have a patient with DS unless you are thinking about it because it's nonspecific, like fevers and shortness of breath and effusions and things that are so easy for us to call infection or call relapse leukemia.

Courtney DiNardo [13:02]: And so being aware of that constellation and starting steroids is really important. That tends to happen usually in the end of the first cycle, early into the second cycle when you are using an IDH inhibitor. So those are the main side effects I think about.

Amer Zeidan [13:15]: Yeah, and I share your experience that these drugs are generally among the easiest of drugs to kind of deal with. They are very well tolerated, but of course, very important to pay attention to development of differentiation syndrome, which, you know, can sometimes sneak on you and can significantly cause problems if you do not pay close attention to it.

Amer Zeidan [13:36]: So, Courtney, you discussed very nicely the trials that led to the current approval of these agents as a monotherapy in the relapsed refractory setting and in combination with azacitidine, and also as a single agent for older unfit patients with acute myeloid leukemia who have the *IDH1*-mutation for ivosidenib.

Chapter 7 Clinical Trials: Combination Treatments

Amer Zeidan [13:58]: Can you tell us more about the ongoing trials that are looking at these agents in combinations? And you have been a pioneer of several of those trials.

Courtney DiNardo [14:08]: Sure. So I think, one of the main questions which we did not talk about is, how do I know whether to prioritize an IDH inhibitor or venetoclax, right? When I have a newly diagnosed *IDH1* patient, should I use a hypomethylating agent and an IDH1 inhibitor or should I use a hypomethylating agent and venetoclax? And so I think what I am struck by in the AGILE study is really the impressive overall survival and the well tolerated nature of

azacitidine and ivosidenib. So, I like that idea. But we are only getting like 55% of people responding to AZA-IVO. Right. It's not 100%. We need to do better. And so that's where kind of these triplet trials, many of them are kind of ongoing at our institution that we have started. And I think I do not want to get out there and say everyone should be putting their patient with an *IDH1*-mutation on a triplet, I do not think we are there yet, but I have been really encouraged by the fact that we are seeing response rates now up towards like 90% when you are putting a hypomethylating agent, an IDH1 inhibitor and venetoclax together and we are shortening the venetoclax durations.[20] When we do it this way, they are only getting 14 days of venetoclax. So maybe preventing some of the more prolonged myelosuppression that you could see if you were giving it continuously. And, and what's going to really matter is, are we seeing more patients become (minimal residual disease) MRD negative, get deeper remissions, have those remissions last longer?

Courtney DiNardo [15:44]: And you know, the studies are still relatively early, but we are seeing really strong signals that, you know, MRD negative rates are upwards of 85%.[21] Survival looks really good. We are not seeing early mortality from this combination. So, I think that's something that is actually moving forward.

Courtney DiNardo [16:02]: In Europe, an AMLSG HOVON study that's going to be looking at kind of AZA-IVO versus AZA-IVO-VEN as a triplet to see if this really is kind of a new well-tolerated and more effective strategy.[22,23]

Amer Zeidan [16:16]: Yeah, and this is all very exciting clearly for our patients. Maybe we can touch a little bit on the intensive chemo combinations. And again, some of those trials were done initially in the US as a single arm. But I think similar to what you just mentioned, the randomized trials are happening now in Europe.

Courtney DiNardo [16:34]: Yeah, so that's another. I mean, when we talk about *IDH1*-mutations, we are usually talking about older, more frail patients because on average they tend to be older. But there is, you know, certainly a percentage of younger patients who have IDH mutations. There was a non-randomized Phase 2 study looking at just standard 7 and 3 intensive chemo with ivosidenib and responses look good.[24]

Courtney DiNardo [16:58]:It was an older, you know, like we were just saying. The average patient in that study was over 60, which is pretty, you know, is on the older age for these, you know, intensive chemotherapy studies. About a third were secondary, had already had myelodysplastic syndrome (MDS) before, so a pretty high-risk population. And, in that, given that population, the fact that three quarters of patients responded and survival looked good, I think is encouraging and suggests that adding an IDH1 inhibitor to intensive chemotherapy kind of makes sense that that should be an effective strategy similar to the way we add FLT3 inhibitors to *FLT3* mutated patients.[25–27]

Courtney DiNardo [17:37]: And so there's a very large again, HOVON AMLSG study in Europe that has finished enrolling.[23] So all the patients have enrolled and they are just following them now for, for those survival endpoints in a placebo controlled randomized study. So hopefully I have heard maybe towards the end of this year or next year we will have some results to see if adding an IDH inhibitor to intensive chemo improves outcomes too.

Amer Zeidan [17:59]: Yeah, and I think that would be clearly amazing news to our patients. You know, I think really, really great drugs. The main problem is the relative rarity of these mutations, around 5 to 7% with *IDH1*.[7]

Amer Zeidan [18:17]: However, when you add them up together with the *IDH2* mutation and *FLT3* mutations and other, you know, evolving targetable mutations such as *NPM-1* for inhibitors, etc. I think most of the patients with AML, like you said, should really be considered for clinical trials these days as we continue hopefully to try to improve the outcomes further for our patients.[28]

Chapter 8 Key Takeaways and Conclusion

Amer Zeidan [18:39]: We are coming to the end of this podcast, but maybe you can give our audience your kind of key take home messages about the evolving landscape of IDH1 mutant acute myeloid leukemia.

Courtney DiNardo [18:55]: So I think my gestalt is that the IDH inhibitors are very effective for *IDH1* mutated disease. I think people kind of hear a lot about how effective venetoclax is for IDH mutated leukemias. And I think that's true, especially for *IDH2*. You know, *IDH2*-mutated patients respond incredibly well to venetoclax based therapy. *IDH1* do okay with then, but I think they do even better with IDH inhibitors. So, I think that is maybe the story I would say is that it's a rare mutation, but if you see it, it's important because it might make you want to think I should be prioritizing a regimen that includes an IDH inhibitor. They are well tolerated and they are effective. And hopefully in the future we will be combining them together to make really effective curative strategies.

Amer Zeidan [19:44]: Yeah, and I think it's important to remember, as you mentioned, that these mutations should be checked for not only at diagnosis, but also at subsequent time points. Because even if you did not use an IDH1 inhibitor because, you know, people wanted to move quickly with treatment and the patient got AZA-VEN or got intensive chemo and subsequently relapse, I think IDH1 inhibitor certainly is a reasonable option at relapse. And these are approved drugs, I think, you know, in addition to the trials you mentioned, the role of maintenance, I think is something that is being kind of explored post-transplant, because still many of those patients would relapse post-transplant.

Amer Zeidan [20:29]: And I think there is increasing interest in post-transplant strategies. So with that, I like to thank you very much for your excellent discussion and thoughts and I would like to thank our audience for listening and I would encourage all of our audience to watch the entire video podcast series.

Amer Zeidan [20:50]: Thank you so much and have a good day.

Abbreviations

AML, acute myeloid leukemia; AE, adverse events; AZA-IVO, Azacitidine-Ivosidenib; AZA-IVO-VEN, Azacitidine-Ivosidenib-Venetoclax; CBC, complete blood count; CR, complete remission; CRH, complete remission with partial hematologic recovery; CML, chronic myeloid leukemia; DS, differentiation syndrome; MRD, minimal residual disease; MDS, myelodysplastic syndrome; 2-HG, oncometabolite 2-hydroxyglutarate; VEN, venetoclax.

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