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COMMENTARY

Advancing AML Treatment: Evidence-Based Regimens and Guideline Updates for Targeted Treatments in R/R AML [Podcast]

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Abstract: Acute myeloid leukemia (AML) is a heterogeneous malignancy characterized by diverse genetic mutations, including *IDH1* and *IDH2*, which are present in approximately 15–20% of cases. Recent clinical practice guidelines, including the 2025 NCCN guidelines, emphasize the importance of comprehensive mutational profiling at diagnosis and at relapse to guide targeted treatment strategies for patients with refractory or relapsed (R/R) AML. IDH1-mutations, which occur in 5–7% of AML cases, result in the production of the oncometabolite 2-hydroxyglutarate (2-HG), disrupting cellular differentiation. IDH1-inhibitors, such as ivosidenib and olutasidenib, block this aberrant metabolic pathway, allowing for differentiation and apoptosis of leukemia cells. Given the rarity of these mutations, comprehensive molecular testing remains essential to optimize therapeutic decision-making.

Keywords: IDH1 inhibitors, ivosidenib, olutasidenib, molecular testing, NCCN guidelines, targeted therapy, molecular profiling

This podcast series is part of a wider, accredited independent educational program titled "The AML Expert Series: Innovations in Molecular Testing, Emerging Therapies & Targeted Treatments." This episode, Advancing AML Treatment: Evidence-Based Regimens and Guidelines for R/R AML Management, provides practical insights into how emerging data and evolving clinical guidelines are reshaping treatment strategies for relapsed/refractory acute myeloid leukemia (R/R AML). Supported by an independent educational grant from Rigel.

Transcript

Voiceover

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Chapter 1 Introduction

Amer Zeidan [00:40]: Hi, everyone. Thank you for joining us. Welcome to our medical education program called Advancing AML Treatment: Evidence-Based Regimens and Guidelines for Refractory and Relapse Acute Myeloid Leukemia. My name is Amer Zeidan and a professor of medicine at Yale University. I focus on the management of patients with acute myeloid leukemia (AML) and myelodysplastic leukemia (MDS). It's my pleasure to be joined today by Dr. Wang. Eunice, do you want to introduce yourself?

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Eunice Wang [01:10]: Hi. Thank you so much. My name is Dr. Eunice Wang and I'm a professor of oncology and the chief of the Leukemia Service at the Roswell Park Comprehensive Cancer Center in Buffalo, New York. Thanks so much for inviting me.

Amer Zeidan [01:24]: Thank you so much for joining us. In the context of this discussion, we are going to be talking about the management of refractory and relapsed acute myeloid leukemia (R/R AML), focusing on some of the new evidence supporting the use of novel drugs and we have seen a number of them have been approved. In addition, we will discuss the guidelines for the management of these R/R AML patients and how we decide on the choice of the treatment for those patients.

Chapter 2 Guideline Updates

Amer Zeidan [01:50]: To start with, Eunice, maybe you can introduce us to the guidelines that you think are most helpful for our colleagues in the community and how do they approach the patients with refractory/relapsed acute myeloid leukemia, especially those with targetable mutations such as *FLT3* and *IDH* mutations.

Eunice Wang [02:15]: I think in the community it's really important to recognize that there are a number of guidelines that have come out over the last few years.[1–4] There was the American Society of Clinical Oncology (ASCO) clinical practice guidelines in 2020[5] there was the American Society of Hematology (ASH) clinical guidelines for management of older AML patients newly diagnosed.[6] And as always, there are the National Comprehensive Cancer Network (NCCN) guidelines which are updated on an annual basis and we do have the most recent version of that from 2025.[7] All of these guidelines really highlight for the community provider taking care of patients with AML or suspected AML, the importance of doing a complete mutational profile and diagnostic workup in all patients.

Eunice Wang [03:01]: Now, the NCCN which is the most recently updated guideline, really stresses that comprehensive mutational profile done at the time of diagnosis as well as at relapse is really key to selection of the appropriate therapy for these patients.[7]

And these include what we call actionable or targetable molecular aberrations, specifically *FLT3, IDH1, IDH2*, as well as a number of what we call secondary mutations which have been identified in the last classification system (the European Leukemia Net), as being diagnostic of what we use to call secondary leukemias.[2,8]

Eunice Wang [03:43]: So I think it's imperative that we all take the time to run these analyses, I think the NCCN does emphasize that expedient obtaining of the results is key for selection of therapy.[2] And for patients that have relapsed AML, the initial NCCN guideline says it is really important to identify, for example, the same mutations *(IDH1, IDH2*, and *FLT3)*, particularly for older patients who are not eligible for intensive chemotherapy.[9]

Eunice Wang [04:20]: So I think this is a change from in the past, where just morphological confirmation of AML or maybe flow was the only thing that we needed.

Amer Zeidan [04:28]: I think that's very important, clearly, as similar to other tumors, we transition into an individualized or personalized approach of choosing therapies rather than treating all patients with refractory disease the same way. And I think it does also emphasize the need to get molecular assessment not only at the time of diagnosis, but also at the time of relapse because of the new drugs that are available and I think some of these drugs such as IDH inhibitors have been important *IDH* occur in around 15 to 20% of patients, primarily *IDH2* but *IDH1* also is relatively rare, but something we see around 5 to 7% of patients have those mutations.[10–13]

Chapter 3 Evidence-Based Regimens

Amer Zeidan [05:19]: Maybe you can walk us, Eunice, through the approved drugs for patients with *IDH1* mutation. And can you describe the mechanism of action of those drugs?

Eunice Wang [05:31]: Sure. *IDH1* or isocitrate dehydrogenase is something that we remember from biochemistry, the Krebs cycle, in medical school. And it's actually a very unique mechanism of tumorigenesis or leukemogenesis in this situation.[14] So what happens is that typically this isocitrate dehydrogenase gene catalyzes transformation of isocitrate to alpha-ketoglutarate (αKG), which then is really important for the Krebs cycle, normal metabolism etc.

Eunice Wang [06:04]: When you have a mutation in this IDH1 enzyme, what happens is it then converts αKG into what we call an oncometabolite, 2-hydroxyglutarate (2HG). Elevated levels of 2HG actually affect chromatin modification and lead to differentiation arrest.[10]

So leukemia cells are stuck in a very immature stage. What happens is when you block that particular mutant enzyme you are able to revert 2HG back backwards, and so you get rid of this oncometabolite. Then the cells actually differentiate and undergo terminal apoptosis.

Eunice Wang [06:49]: So it's not a drug like conventional cytotoxic chemotherapies that target really rapidly growing cells that we're really used to, it's actually what we term a differentiation agent. So the small molecule inhibitors that convert or target that mutant enzyme, there's actually 2 of them, in the market.[11,12]

Eunice Wang [07:10]: Ivosidenib was approved several years ago as the first small molecule inhibitor targeting the mutant *IDH1*. Olutasidenib was approved a couple of years ago as a second-generation small molecule inhibitor. Both of these result in complete remission rates either with or without incomplete hematologic recovery, of about 20 to 30%.[14]

Eunice Wang [07:32]: Olutasidenib, the most recent agent, has about an overall response rate of 48%.[15,16] Ivosidenib as a single agent in the relapsed/refractory setting is similar. The difference in the two agents are maybe a little bit in their side effects abut also in the fact that with the olutasidenib, even though about the same percentage of patients went into remission or had a response, the duration of the response that we saw with the olutasidenib was much longer with that median duration not of 11–12 months but actually up to 29 months.[15,17]

Eunice Wang [08:04]: We know now that many of our older patients treated with lower intensity therapy (venetoclax- and azacitidine-based therapy), can recur.[18] Olutasidenib, interestingly enough, has been shown to work in patients in the relapsed setting who have received prior venetoclax.[19]

Eunice Wang [08:22]: Now that we have a couple of agents to target IDH1, I think I would agree with you that at the time of relapse, it's imperative to recheck for these mutations. They're very uncommon, but we do get clonal evolution and selection of different clones with emergence of different clones. So even if there's a chance that maybe 1 out of 10 of your patients has an *IDH1*-mutation, it can be key in being able to offer these oral chemotherapy drugs with response rates just to single agent therapy.

Chapter 4 Practical Implications for Oncologists

Amer Zeidan [08:57]: Thank you so much for this excellent summary. I think, Eunice, in the refractory life setting, both of those drugs were approved based on single arm trials because it's a relatively rare subset of AML. There is no randomized trials comparing these drugs. So how do you decide on which one to use in your clinic and how do you advise oncologists in practice to decide? Do you do a chronic myeloid leukemia (CML) like approach where you go by comorbidities, or is it by one drug being once a day versus twice a day? Or how do you decide?

Eunice Wang [09:40]: I think just like people choose other tyrosine kinase inhibitors or small molecule inhibitors, it is a little bit of an art, not necessarily a science. I think that there are clearly differences, ivosidenib and olutasidenib are both *IDH1* inhibitors, there are slight differences. Both of them result in differentiation syndrome, which is something that we see with acute promyelocytic leukemia, weight gain, pulmonary infiltrates, effusions, and pericardial effusions.[14,20] This is something that we see commonly on both.

Eunice Wang [10:16]: I think that my preference would be to see what I think would be the best benefit for patients. I know that there's a lot of data with ivosidenib. We've clearly used it in the upfront setting. I think that it depends a little bit on pretreatment. A lot of us with our *IDH1*-mutated patients, if we are doing that diagnostic workup at the time of diagnosis, patients may be treated per the randomized trial. There are trials of these *IDH1* inhibitors, but you're right, there are not randomized trials in the relapsed refractory setting. But we have the AGILE trial in the upfront setting that randomized patients with *IDH1*-mutant AML to receive ivosidenib and azacitidine (Ivo-Aza) versus azacitidine (Aza) alone, with clear superiority for the Ivo-Aza arm.[18]

So I think if a patient has already received ivosidenib in the upfront setting, I'm more likely obviously not to reuse that drug. I also think that there's good data with olutasidenib in patients who have received prior venetoclax azacitidine (Ven-Aza) upfront. There's some anecdotal data, again not randomized, that patients who got Ven-Aza upfront do not do as well with ivosidenib. So a lot of it is obviously selection of the drug based on side effects with increased QTC prolongation but I think a lot of it is what I think about is what did they get in the upfront setting.

Chapter 5 Real-World Applications

Amer Zeidan [11:38]: Yes, I think you summarized very nicely some of the discussion about the combinations as well as the sequencing. You highlighted olutasidenib might potentially work better based on limited evidence after venetoclax failure compared to ivosidenib. But I'm interested from your clinical experience, outside of the literature. How was your personal experience with both of those agents?

Eunice Wang [12:08]: I think both of the agents are really well tolerated. I think that there is a risk and I think it's even a black box warning for ivosidenib and enasidenib, the IDH2 inhibitors, that these induce differentiation syndrome.[21–24] We have seen some evidence of differentiation syndrome with all of these agents, all of the *IDH* inhibitors. But if you're on the lookout for it and you're able to manage it, I think that that's not a huge barrier. In my hands, both olutasidenib and ivosidenib have been very, very well tolerated, both as single agents and as well as in combination studies within the upfront setting.

Eunice Wang [12:50]: I haven't had major toxicities and we have actually seen patients that do very well. Ivosidenib is also indicated not only in the upfront setting in combination with AZA or as monotherapy but ivosidenib is also indicated for patients that have *IDH1*-mutant MDS. Again, in all of these settings, I've seen evidence of count recovery and responses. However you have to remember that these are differentiation agents. As I'm sure in your experience as well, which I'd love to hear about, you can't expect that patients are going to have a response within one or even two or three cycles. So as long as they're tolerating drug and you're supporting them with transfusions and so forth, you need to hang in there. We saw with both olutasidenib and with ivosidenib patients do at maybe 20–30% get transfusion independence if they are transfusion dependent at baseline; but it's at about 56 days.[15,17]

Eunice Wang [13:51]: So it's important to recognize supportive care as long as these patients are tolerating drug and to wait for a response. We've had some very nice responses, particularly in older patients who aren't eligible for transplant. High quality of life is something that they treasure.

And the oral administration and the tolerability, I think is a key advantage of these drugs. And again you think to yourself, why would I want to check for these *IDH*-mutations if they are so rare like you said, 5–10%, at most 20% for all the IDH1/2 inhibitors.[13,25] But I think if you have the option to offer a precision medicine approach with these agents, I think it's really worth it.

Amer Zeidan [14:35]: Yes. My experience has been largely along the lines of your experience. I think these drugs in the relapsed/refractory setting are clearly effective, well tolerated oral options. They don't cure patients, so clearly I think we need better combinations and to treat patients more in the frontline setting. I have actually struggled to differentiate between the two agents in terms of both of them have somewhat relatively limited data in the relapsed/refractory setting. But to my eye, there's a lot of similarities. Similar to what you said also in the *IDH1*-mutated MDS second line setting, ivosidenib is an approved drug. Actually olutasidenib also has evidence and is also listed in the NCCN as an option in that setting.[26]

Amer Zeidan [15:36]: I think in the frontline setting in combination with azacitidine, we have AGILE data at Phase 3 level so I tend to use ivosidenib more in that setting. But in terms of monitoring for QTC and differentiation syndrome, and liver enzyme issues, etc, I tend to think of them similarly. I would say maybe ivosidenib might be a little bit easier to give because it is once a day compared to twice a day with olutasidenib. But I think overall the two drugs are very similar.

Chapter 6 Expert Insights on Real-World Outcomes

Amer Zeidan [16:17]: You started kind of talking about some of the patient experiences and especially older patients who have limited survival with these kind of advanced situations. With refractory/relapsed AML, the survival is generally less than a year, and it's important to try to keep the patient out of the hospital and with the best of quality of life as possible. Can you think of one or two success stories or situations where you thought that these drugs made a huge difference?

Eunice Wang [16:52]: Well, I think that one of the key differences between the two agents, and I agree with you that they're both well tolerated with difference between once a day (ivosidenib) versus twice a day (olutasidenib). I think one of the puzzling things, and I don't know that we know the reason for this, is that in the trial leading to olutasidenib FDA approval, in largely ivosidenib naive and venetoclax naive R/R AML patients, the median duration of response in those 153 patients in that trial, was an astonishing 29 months, it is unheard of for patients with relapse/refractory setting to have

a survival of over two years.[15,27–29] And there is recent five-year data for olutasidenib that demonstrated that some even four years out there were some patients that were still alive.[30]

Eunice Wang [17:36]: I do not know and understand why that is they seem to be similar compounds, obviously a newer generation. But that has me intrigued. I do have some patients that have gotten upfront therapy with VEN-AZA approach, I really am tending to prefer the IDH1 inhibitor (ivosidenib) plus AZA for upfront therapy of my *IDH*-mutant AML patients, I feel like this is a great approach and you don't get the same toxicities with long term administration that you get with venetoclax plus hypomethylating agent (HMA) for these patients.[31,32]

Eunice Wang [18:13]: I do also have patients that have been on long term IDH1/IDH2 with IVO, enasidenib, and olutasidenib that are out two or three years just taking monotherapy as an outpatient. For example, I have a patient who's in his 80s who is just taking an IDH inhibitor and we have finally moved to seeing him every three months because he is month 29 or 32 and he just does not see a purpose in coming to see me every month if he's doing so well on monotherapy. So I think there are some patients for whom these drugs offer the possibility of long-term survival.

Eunice Wang [19:03]: There are certainly resistance mechanisms that have been documented. Patients that have co-mutations in the *RAS* gene tend not to respond as well. But I think that overall to start thinking about integrating even for those rare populations is great. Similarly some of these patients we are doing less toxic allogeneic stem cell transplantation. So some of these elderly individuals, if you're able to get them into remission (even though it's only 20 or 30%), you might render them possibly candidates for transplant. I don't have any of those per se in my practice.

Chapter 7 Closing Remarks/Take Home Messages

Amer Zeidan [19:38]: I think a very nice outline, we are running short on time but I think that the main messages is the importance of molecular testing to look for these mutations and individualizing therapy for patients with acute myeloid leukemia. While these IDH mutations are relatively rare, we now have good effective oral drugs that are generally well tolerated and I think are important to think about when we see these R/R AML patients. Eunice, any closing remarks?

Eunice Wang [20:18]: I think one key take home message is one must do the mutation profiling at diagnosis as well as at relapse to identify what we call actionable or targetable mutations for which there now are oral, well tolerated, safe medications that result in true complete remissions (CRs) and in some cases long term remissions.

Amer Zeidan [20:36]: Thank you so much Dr. Wang for this excellent discussion and thank you to the audience for listening. I encourage everybody to listen to the video podcast series and upcoming episode three, which will focus on the mechanisms of action and the safety profile of IDH1 inhibitors.

Thank you so much for listening and have a good day.

Abbreviations

AML, acute myeloid leukemia; Aza-Ivo, Azacitidine-Ivosidenib; Aza-Ivo-Ven, Azacitidine-Ivosidenib-Venetoclax; DS, differentiation syndrome; FLO, flow cytometry; HMA, hypomethylating agent; MRD, minimal residual disease; MDS, myelodysplastic syndrome; 2-HG, oncometabolite 2-hydroxyglutarate; VEN, venetoclax; ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; αKG, alpha-ketoglutarate; NCCN, National Comprehensive Cancer Network.

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References

1. Arber DA, Borowitz MJ, Cessna M, et al. Initial diagnostic workup of acute leukemia: guideline from the College of American Pathologists and the American Society of Hematology. *Arch Pathol Lab Med*. 2017;141(10):1342–1393.
2. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345–1377. PMID: 35797463. doi:10.1182/blood.2022016867
3. Pollyea DA, Altman JK, Assi R, et al. Acute myeloid leukemia, version 3.2023, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2023;21(5):503–513. PMID: 37156478. doi:10.6004/jnccn.2023.0025
4. Heuser M, Ofran Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;24 Suppl 6:vi138–43.
5. de Haas V, Ismaila N, Advani A, et al. Initial diagnostic work-up of acute leukemia: ASCO clinical practice guideline endorsement of the College of American Pathologists and American Society of Hematology Guideline. *J Clin Oncol*. 2019;37(3):239–253. Erratum in: J Clin Oncol. 2019;37(7):612. PMID: 30523709; PMCID: PMC6338392. doi:10.1200/JCO.19.00155. doi:10.1200/JCO.18.01468
6. Sekeres MA, Guyatt G, Abel G, et al. American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. *Blood Adv*. 2020;4(15):3528–3549. PMID: 32761235; PMCID: PMC7422124. doi:10.1182/bloodadvances.2020001920
7. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 2.2025. National Comprehensive Cancer Network; 2025. Available from: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed March 10, 2025.
8. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424–447. PMID: 27895058; PMCID: PMC5291965. doi:10.1182/blood-2016-08-733196
9. Percival ME, Lai C, Estey E, Hourigan CS. Bone marrow evaluation for diagnosis and monitoring of acute myeloid leukemia. *Blood Rev*. 2017;31(4):185–192. PMID: 28190619; PMCID: PMC5513766. doi:10.1016/j.blre.2017.01.003
10. Fruchtman H, Avigan ZM, Waksal JA, et al. Management of isocitrate dehydrogenase 1/2 mutated acute myeloid leukemia. *Leukemia*. 2024;38:927–935. doi:10.1038/s41375-024-02246-2
11. Merchant SL, Culos K, Wyatt H. Ivosidenib: IDH1 inhibitor for the treatment of acute myeloid leukemia. *J Adv Pract Oncol*. 2019;10(5):494–500. PMID: 33457062; PMCID: PMC7779565. doi:10.6004/jadpro.2019.10.5.7
12. Cortes J, Fenaux P, Yee K, et al. Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed/refractory mIDH1 acute myeloid leukemia. Results from a planned interim analysis of a Phase 2 pivotal clinical trial. *Blood*. 2022;140(suppl 1):6193–6196. doi:10.1182/blood-2022-167330
13. Messina M, Piciocchi A, Ottone T, et al. Prevalence and prognostic role of IDH mutations in acute myeloid leukemia: results of the GIMEMA AML1516 protocol. *Cancers*. 2022;14:3012. doi:10.3390/cancers14123012
14. Issa GC, DiNardo CD. Acute myeloid leukemia with IDH1 and IDH2 mutations: 2021 treatment algorithm. *Blood Cancer J*. 2021;11:107. doi:10.1038/s41408-021-00497-1
15. de Botton S, Fenaux P, Yee K, et al. Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed or refractory IDH1-mutated AML. *Blood Adv*. 2023;7(13):3117–3127. PMID: 36724515; PMCID: PMC10362540. doi:10.1182/bloodadvances.2022009411
16. Rigel Pharms (2022) REZLIDHIA™ (olutasidenib) capsules, for oral use [package insert]. South San Francisco, CA: Rigel Pharms; 2022.
17. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with Ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386–2398. PMID: 29860938. doi:10.1056/NEJMoa1716984
18. Montesinos P, Recher C, Vives S, et al. Ivosidenib and Azacitidine in IDH1-mutated acute myeloid leukemia. *N Engl J Med*. 2022;386(16):1519–1531. PMID: 35443108. doi:10.1056/NEJMoa2117344
19. Cortes J, Jonas BA, Schiller G, et al. Olutasidenib in post-venetoclax patients with mutant isocitrate dehydrogenase 1 (mIDH1) acute myeloid leukemia (AML). *Leuk Lymphoma*. 2024;65(8):1145–1152. PMID: 38538632. doi:10.1080/10428194.2024.2333451
20. Woods AC, Norsworthy KJ. Differentiation syndrome in acute leukemia: APL and beyond. *Cancers*. 2023;15(19):4767. PMID: 37835461; PMCID: PMC10571864. doi:10.3390/cancers15194767
21. Issa GC, Stein EM, DiNardo CD. How I treat acute myeloid leukemia with differentiation therapy. *Blood*. 2025;145(12):1251–1259. PMID: 38976876; PMCID: PMC11952016. doi:10.1182/blood.2024024008
22. Myers RA, Wirth S, Williams S, Kiel PJ. Enasidenib: an oral IDH2 inhibitor for the treatment of acute myeloid leukemia. *J Adv Pract Oncol*. 2018;9(4):435–440. PMID: 30719396; PMCID: PMC6347084.
23. IDHIFA® (enasidenib tablets, for oral use) [package insert]. Boston, MA: Servier Pharmaceuticals LLC; 2025.
24. TIBSOVO® (ivosidenib tablets) [package insert]. Boston, MA: Servier Pharmaceuticals LLC; 2023.
25. ElNahass YH, Badawy RH, ElRefaey FA, et al. IDH mutations in AML patients; a higher association with intermediate risk cytogenetics. *Asian Pac J Cancer Prev*. 2020;21:721–725. doi:10.31557/APJCP.2020.21.3.721
26. Greenberg PL, Stone RM, Abaza Y, et al. NCCN clinical practice guidelines in oncology for myelodysplastic syndromes, version 2.2025. *J Natl Compr Cancer Netw*. 2025;23(3):66–75. doi:10.6004/jnccn.2025.0013

27. Wang ES, Cortes JE, Watts JM, et al. Time to response and overall survival in patients with mIDH1 relapsed/refractory acute myeloid leukemia treated with olutasidenib. *Blood*. 2024;144(Supplement 1):1514. doi:10.1182/blood-2024-198504
28. Woods AC, Norsworthy KJ, Choe M, et al. FDA approval summary: olutasidenib for adult patients with relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase 1 mutation. *Clin Cancer Res*. 2025;31(1):12–17. PMID: 39475462; PMCID: PMC11703669. doi:10.1158/1078-0432.CCR-24-2196
29. Venugopal S, Watts J. Olutasidenib: from bench to bedside. *Blood Adv*. 2023;7(16):4358–4365. PMID: 37196640; PMCID: PMC10432604. doi:10.1182/bloodadvances.2023009854
30. Cortes J, Jonas BA, Watts JM, et al. Olutasidenib for mutated IDH1 acute myeloid leukemia: final five-year results from the phase 2 pivotal cohort. *J Clin Oncol*. 2024;42(suppl 16):6528. doi:10.1200/JCO.2024.42.16_suppl.6528
31. Ucciero A, Pagnoni F, Scotti L, et al. Venetoclax with hypomethylating agents in newly diagnosed acute myeloid leukemia: a systematic review and meta-analysis of survival data from real-world studies. *Cancers*. 2023;15(18):4618. PMID: 37760587; PMCID: PMC10526951. doi:10.3390/cancers15184618
32. Madarang E, Lykon J, Zhao W, et al. Venetoclax and hypomethylating agents in octogenarians and nonagenarians with acute myeloid leukemia. *Blood Neoplasia*. 2024;1(2):100016. doi:10.1016/j.bneo.2024.100016