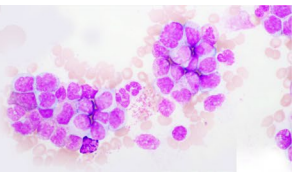
Applying Evolving Targeted Therapy in Acute Myeloid Leukemia



Editor's Note: This is a transcript of an online course released in October 2023. It has been lightly edited for clarity. To obtain credit for participation, CLICK HERE.

What is AML?

What is acute myeloid leukemia (AML)? AML is the proliferation of immature myeloid precursors, also known as blasts, that lose the ability to differentiate into mature cells. It's the accumulation of these immature myeloid precursors that stay ineffective, as well. that affects normal production of other cell lines, such as mature granulocytes, red blood cells and platelets. And this results in anemia, bleeding risk from thrombocytopenia, and infection from neutropenia, which underlie all the morbidity and mortality related to AML.

The estimated new cases of AML in the United States in 2022 was 20,050 cases and this led to estimated deaths in 2022 of 11,540. In terms of the percentages of all new cancer cases, AML is a rare form of cancer, representing 1%, and that represents 1.9% of all cancer deaths. Looking at longer-term survival, the 5-year relative survival from 2012 to 2018 is 30.5%, and the hope is that this number will improve with the recent advances in the field and approval of new medications for AML in the last few years.

When you think about treating AML, one of the main things we think about is are patients going to be a candidate or not for standard induction chemotherapy? And this has been an issue that's been at the forefront of the field for a long time, and many different approaches have been proposed to determine one's fitness. In the end of the day, there's really no age limit for who is a candidate for induction chemotherapy, although, in practice, a lot of people will think it's about the age of 75 years. There are cytogenetic and molecular studies that are involved in determining this appropriateness for induction chemotherapy or not, and there's been a movement recently to get more rapid readouts of molecular studies, such as FLT3 and NPM-1, as well as a number of other things like FISH and other molecular markers, hopefully within the first 3 to 5 days of presentation.

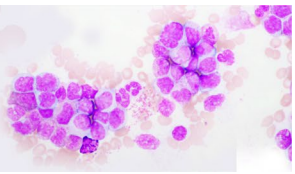
Other important issues for determining candidacy for induction chemotherapy are the patient's comorbidities, often related to aging, and these can include cardiovascular disease, diabetes, history of other cancers, etc. There are tools to kind of assess the impact of comorbidities. The one that's used often is the HCT-CI, which stands for hematopoietic cell transplantation-specific comorbidity index.

There are also other tools, like ECOG performance status and Karnofsky performance status, and these can help to determine whether one is fit or not. And there was an attempt to quantify fitness using criteria that were proposed by Ferrara et al, and these were adopted by the FDA and basically include things like age, performance status, other medical comorbidities.

ASCO Guidelines for Geriatric Oncology also recommend minimal assessment for functionality, comorbidity, falls, depression, cognition and nutrition. Tools that are available to determine the extent of chemotherapy toxicity risk include the CARG, Cancer and Aging Research Group, the Chemotherapy Risk Assessment Scale for High-Age Patients, also known as CRASH. There are tools to predict mortality, such as the Geriatric-8 or Vulnerable Elders Survey-13. There are tools to assess cognition, such as the Mini-Cog, and tools to assess depression, such as the Geriatric Depression Scale.

Supposing a patient was deemed fit or appropriate for standard induction chemotherapy, what does that even mean? Well, the standard—really the basic standard induction chemotherapy, if you will—is known as 7+3, and this includes 7 days of continuous infusion cytarabine at 100-200 mg/m^2 plus 3 days of an anthracycline, which is usually daunorubicin at 60-90 mg/m^2 or idarubicin at 12 mg/m^2. Hence the 7+3 name. In younger adults, this leads to complete remission rates of 60% to 80%. And the number is lower, but still promising, in older adults, that were just defined, by the way, at 60 or above, of 40% to 60%.

I've said that the 7+3 is the background. Well, there's a number of other targets and frontline treatment considerations that have emerged in the last few years. Not only that, but many of these are



involved in treatment of relapsed or refractory patients as well. BCL-2 is now targeted by a medication called venetoclax, which is a BCL-2 inhibitor. CD33-positive AML can be targeted by the monoclonal antibody gemtuzumab ozogamicin, which is an antibody/drug conjugate where the antibody is linked to the chemotherapy agent—the anti-CD47 antibody, actually known as magrolimab—which targets the "don't eat me" signal on the cells. There's the FLT3/ITD or FLT3/TKD inhibitors. These include midostaurin, crenolanib, gilteritinib and quizartinib. These are small molecule inhibitors. There's the IDH1 as a target and there's a drug called ivosidenib, and there's a new drug called olutasidenib. IDH2 is targeted by enasidenib and there's also a small molecular inhibitor of the smoothened receptor at the Hedgehog pathway known as glasdegib.

Now, a new agent has also been developed to affect the AML microenvironment through its interactions with a protein called E-selectin and this interaction is targeted by a drug called uproleselan, also known as GMI-1271. Many of these are still investigational, but some have been approved for use in AML, including the most recent approval on July 20, 2023, this year, of quizartinib.

A little more context about these molecular targets in frontline consideration. The first one I'll mention is venetoclax, which is a BCL-2 inhibitor. And it is approved by the US FDA in combination with azacitidine, decitabine or low-dose cytarabine for newly diagnosed AML in adults aged 75 years or older, or those who are younger who have comorbidities that preclude the use of intensive induction chemotherapy. And notably, azacitidine and decitabine are also known as hypomethylating agents, so again these are acceptable partners for venetoclax, as is low-dose cytarabine. These have really become standard of care for the older, unfit patients with AML.

The next drug is gemtuzumab ozogamicin, again an antibody drug conjugate, and this drug targets CD33. It's taken up by cells that express CD33, internalized and the calicheamicin drug is released from the antibody carrier. This was approved for the treatment of newly diagnosed CD33-positive AML in adults, and treatment of relapsed/refractory CD33-positive AML in adults and pediatric patients 2 years and older. And it's given with induction and/or with consolidation.

Another drug, called magrolimab, again this targets CD47. It's a monoclonal antibody targeting CD47. It blocks the "don't eat me" signal which leads to the immune system with monocytes ingesting or eating, if you will, the abnormal cells that, like the cancer cells, in terms of AML, so potentially MDS and even other cancers that express CD47, leading to exhaustion. potentially. This is still investigational and so it's not approved by the FDA, and clinical trials are ongoing in multiple disease types.

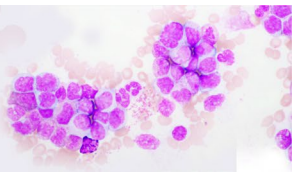
We summarized new FLT3 ITD or TKD inhibitors. And when I say ITD, that refers to the internal tandem duplication patient, which is the most common FLT3 mutation in AML. TKD stands for tyrosine kinase domain mutations. And all 3 of the drugs on the screen here can inhibit both ITD and TKD mutations.

Crenolanib is still investigational, and while promising in early phase studies, the larger phase 3 studies have yet to read out. That story, as of yet, is incomplete.

Gilteritinib is approved by the FDA as monotherapy for relapsed/refractory AML and is being studied in newly diagnosed FLT3-positive and TKD-positive AML in combination with chemotherapy. That data is eagerly anticipated.

Midostaurin has been approved by the FDA for newly diagnosed FLT3-positive AML in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation without any age restrictions. This was based on a study called the RATIFY trial and it increased overall survival in adults for a better outcome posttransplant if the patients received midostaurin during induction, and one possible reason for this was due to reduced pretransplant MRD. It's also not indicated as a single agent induction therapy for treatment of patients with AML.

Another FLT3 inhibitor, quizartinib, is only active against the FLT3 ITD mutation and this is now



approved. This was approved in July of this year [2023] for newly diagnosed FLT3-ITD-positive AML in combination with standard cytarabine and anthracycline induction, cytarabine consolidation, and maintenance after cytarabine consolidation without age restrictions. This is based on the QuANTUM-First phase 3 trial that showed that it improved survival for the quizartinib arm compared to the placebo arm. Some other notes about this study: they did include patients up to age 75 years; this is not active against the FLT3 TKD mutational process; there's a potential resistance mechanism; and the approval came with a REMS program.

Next is the IDH inhibitors. ivosidenib is an IDH1 inhibitor. It's approved for the treatment of AML with IDH1 mutation. Newly diagnosed patients who are 75 years or older or who have comorbidities that preclude the use of intensive induction chemotherapy. It's also approved for relapsed/refractory AML with IDH1 mutation. In newly diagnosed patients, it can be given as monotherapy or in combination with azacitidine, and this is based on something called the AGILE trial. And one needs to monitor for differentiation syndrome.

The second IDH1 inhibitor, called olutasidenib, was also approved by the FDA for relapsed/refractory AML with IDH1 mutation. Similarly to ivosidenib, it needs monitoring for differentiation syndrome.

There's an IDH2 inhibitor that's been approved by the FDA for treatment of IDH2-positive relapsed/refractory AML, known as enasidenib and, like the other IDH inhibitors, this is a class effect, one has to monitor for differentiation syndrome.

The last drug on this list is an investigational agent that targets E-selectin and affects the interaction between blasts and the microenvironment by inhibiting this E-selectin and binding to E-selectin ligand. And this is a drug called uproleselan, also known as GMI-1271. And this is studied in a phase 1 study, including frontline and some combination with 7+3 or in relapsed/refractory patients in combination with MEC, which stands for mitoxantrone, etoposide and cytarabine. There were promising results in this phase 1 and, of course, this agent needs confirmatory, randomized clinical trials in order to be considered a potential treatment for AML.

The next drug is the smoothened receptor inhibitor, again which is part of the Hedgehog pathway. This drug is called glasdegib and it's actually approved by the FDA. It's in combination with low-dose cytarabine for the treatment of newly diagnosed AML in patients 75 years or older, or those younger patients with comorbidities that preclude the use of intensive induction chemotherapy. This drug has not been studied in patients with severe renal impairment or moderate-to-severe hepatic impairment.

Case 1 - Maggie

Maggie is a 60-year-old woman who presents to her PCP with fever, fatigue, dyspnea, and easy bruising.

- Comorbidities- none
- Current medications- none
- Vital signs
  - HR 110/min
  - BP 118/82 mmHg
  - RR 24/min
  - SPO_2 96%
  - T 37.5°C

Physical exam

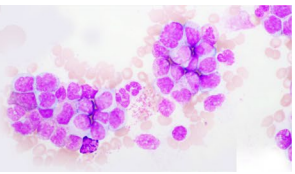
- Pallor, petechiae throughout her abdomen and ecchymosis to bilateral lower and upper extremities; otherwise unremarkable.
- ECOG 1

Labs

- WBC $40x10^9$/L with 80% blasts
- ANC $200x10^9$/L
- Hgb 7.2 g/dL
- Platelets $12x10^9$/L
- SCr 1.4 mg/dL
- Uric acid 9.5 mg/dL

Bone marrow biopsy with aspirate reveals:

- Cellularity 80% (hypercellular) with 90% blasts consistent with AML
- Cytogenetics normal



- NGS mutated NPM1 and FLT3-ITD high allele burden

She is admitted to the medical oncology service for

- Transfusion support
- Management of tumor lysis syndrome
- Infectious workup with preemptive antibiotics
- Echocardiogram to assess medical fitness prior to receiving induction therapy

What is the most appropriate next step?

A. Send HLA typing
B. Start standard induction with 7+3
C. Start standard induction 7+3 plus midostaurin
D. Do not start any treatment until WBC <25x10^9/L

The correct answer among these choices is to start standard induction with 7+3 plus midostaurin and I'll explain here in a second why. It should be noted if HLA testing is available, this should be done ideally before treatment when there's still white cells.

The reason that 7+3 plus midostaurin is appropriate for this patient is that she is 60 years old, she is fit for induction chemotherapy and she has a FLT3-ITD mutation. There was a study called the RATIFY trial which led to the FDA approval of midostaurin. The RATIFY trial was a phase 3, randomized, placebo-controlled trial and enrolled 717 patients. Patients were given daunorubicin 60 mg/m^2 and cytarabine 200 mg/m^2 and they were also given either midostaurin on days 8 to 21 or placebo on days 8 to 21. This was a positive study and it showed that the midostaurin improved survival over placebo. At 4 years, the overall survival was 51.4% on the midostaurin arm compared to 44.3% on the placebo arm. Interestingly, despite a better survival, there was not a significant difference in remission rate at 60 days of clinical therapy, although it numerically favored midostaurin at 58.9% compared to 53.5%. In 2017, the FDA approved midostaurin for newly diagnosed FLT3-positive AML in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

The standard induction, again, is cytarabine 200 mg/m^2 continuous IV for 7 days plus daunorubicin 60 mg/m^2 IV on days 1 through 3. Notably, idarubicin at 12 mg/m^2 IV days 1 through 3 is used by many centers in lieu of the daunorubicin, and then the midostaurin is given at 50 mg BID days 8 to 21. For consolidation, the regimen used high-dose cytarabine or HiDAC, 3 g/m^2 given IV over 3 hours every 12 hours on days 1, 3 and 5, plus midostaurin 50 mg twice a day on days 8 to 21. There was a maintenance phase on the RATIFY trial of midostaurin 50 mg BID daily for up to a year. The maintenance regimen, however, was not part of the FDA label in the United States as the RATIFY trial was not powered to show this.

In terms of toxicities that are seen with midostaurin compared to placebo in the RATIFY trial, as you can imagine the rates of hematologic toxicities grade 3 or higher are very high on a study like this where everyone is getting intense chemotherapy, that is not surprising. One can look for differences between the 2 arms and you'll note that there is more incidence of anemia and more incidence of rash in the midostaurin arm at grade 3 or worse, compared to placebo. The rates of the thrombocytopenia and neutropenia, febrile neutropenia, and infection are similar.

Case 1 – Maggie Continued

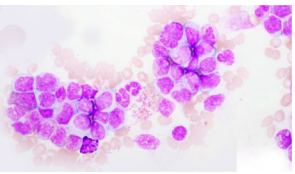
Maggie was started on:

- Cytarabine 200 mg/m^2 CIV D1-7
- Daunorubicin 90 mg/m^2 IV D1-3
- Midostaurin 50 mg BID D8-21

D14: hypocellular marrow with no evidence of disease

D30:

- ANC 1000/μL
- Platelets 82x10^9/L
- Bone marrow biopsy and aspirate pathology revealed:
  - 45% cellularity (normocellular) with no detectable blasts
  - Cytogenetics normal
  - No mutations found on NGS (next generation sequencing testing)



What is the next step?

A. Give 4 cycles of HiDAC consolidation + midostaurin followed by midostaurin maintenance
B. Switch to salvage regimen FLAG-IDA
C. Start consolidation HiDAC + midostaurin followed by allogeneic HSCT
D. Make a referral to palliative care and a hospice program

Of these answers, I would consider C, start consolidation with high-dose cytarabine plus midostaurin followed by allogeneic transplant, to be the correct answer out of the bunch. In this case, the RATIFY trial, there was an increase in overall survival noted in the midostaurin arm in patients who went on to allogeneic transplant in first remission compared to those who were transplanted later in their course of treatment. Typically, patients with FLT3-ITD-positive AML are referred to transplant unless transplant at first remission, is pretty typical.

Transplants are not ready right away and so they often take sometimes even a few months or more to set up, and so those patients will undergo consolidation with high-dose cytarabine plus midostaurin, in this case, while the transplant is being arranged.

Here is some data from RATIFY with regards to transplant. The 28.1% of the patients on the midostaurin arm went to transplant at first remission compared to 22.7% on the placebo arm. In terms of the median, overall survival of those who went to transplant was not reached in the range of 69.8 months to not reached for the midostaurin arm, was also not reached in the placebo arm with a range of 21.8 months to not reached. The 4-year overall survival for transplanted patients in the midostaurin arm was 63.7% compared to 55.7% in the placebo arm. Those statistics did not reach the 0.05, however they trended in favor of midostaurin.

CASE 2 – Joseph

Joseph is a 72-year-old man sent to the ED by his PCP for fever, fatigue, dyspnea, and easy bruising.

PMH:

- Coronary artery disease
- Diabetes mellitus
- Spinal stenosis resulting in chronic pain
- Prostate cancer in CR post prostatectomy and XRT.

Current medications: several

Vitals signs

- HR 98/min
- BP 134/80 mmHg
- RR 28/min
- SPO_2 96%
- T 37.0 C

Physical exam:

- Frail and cachectic appearing, holosystolic murmur, bibasilar crackles, petechiae to abdomen and wet purpura post oropharynx.
- ECOG 2

Labs

- WBC $22x10^9$/L, 80% blasts
- ANC $0.2x10^9$/L
- Hgb 6.5 g/dL
- Platelets $9x10^9$/L
- SCr 1.4 mg/dL
- Uric acid 10 mg/dL

Bone marrow biopsy reveals:

- Cellularity 70% (hypercellular) with 80% blasts
- Cytogenetics abnormal with del(5q)
- NGS no actionable biomarkers

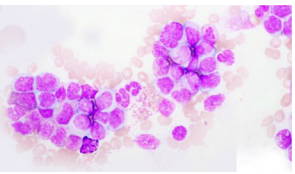
Echocardiogram: ejection fraction 45%

Joseph is deemed medically unfit due to:

- ECOG 2 due to chronic pain from spinal stenosis
- Ejection fraction 45%

What are the next steps?

A. Start hypomethylating agent plus venetoclax
B. Start standard 7+3 induction treatment
C. Start lenalidomide
D. Enroll onto a hospice program



The correct answer is start hypomethylating agent plus venetoclax based on the list that is shown here. We determined that this patient is not a good candidate for standard 7+3 induction because of their decreased EF and their increased performance status which is a 2. Lenalidomide might be an option for an MDS patient with deletion 5q who primarily has anemia, but would not be the appropriate first-line therapy for a patient with AML. Enroll onto a hospice program is an interesting choice. There are some patients who choose not to do therapy and, in that case, a hospice program may be reasonable considering the poor survival and treatment. A number of datasets have shown, however, that any form of therapy in AML is associated with superior survival compared to no treatment.

For patients who are motivated to treat, answer A would be the most appropriate answer.

The reason we would choose A is because of the VIALE-A trial. And this was a randomized trial, placebo-controlled, that enrolled 431 older patients with AML. They had to be 75 years or older or they had to be considered ineligible for intensive induction chemotherapy based on criteria that were derived from the Ferrara criteria. The treatment was azacitidine at standard dosing, 75 mg/m^2, given IV on days 1 through 7, plus venetoclax, to a target dose of 400 mg orally daily, days 1 through 28, or placebo orally, days 1 through 28.

The trial was positive, and at the median follow-up of 28.5 months the median overall survival in the aza-ven arm was 14.7 months compared to 9.6 months in the aza-placebo arm, which was statistically significant. The complete response rate was also higher on the aza-ven arm, 36.7%, compared to 17.9% in the aza-placebo arm. The composite remission rate, which we'll define as CR plus CRi, that rate was 66.4% in the aza-ven arm compared to 28.3% in the aza-placebo arm. Notably, the responses were seen regardless of cytogenetic risk and mutations and there was also a faster time to response in the aza-ven arm compared to the aza-placebo arm. with a median time to remission of 1.3 months vs 2.8 months. The results of this study led to the approval in 2020 of adults with newly diagnosed AML, aged greater than or equal to 75 years who are ineligible for intensive induction chemotherapy of venetoclax in combination with HMA. There was also a study that showed some benefit in combination with low-dose cytarabine, so the label included low-dose cytarabine as a potential partner with venetoclax.

Case 2 – Joseph Continued

Joseph was started on:

- Azacitidine 75 mg/m2 IV D1-7
- Venetoclax 400 mg D1-28

D21, he meets sepsis criteria:

- WBC 0.4x10^9/L
- ANC 0x10^9/L
- Hgb 6.8 g/dL
- Platelets 24x10^9/L

Bone marrow biopsy and aspirate: hypocellular with no evidence of disease

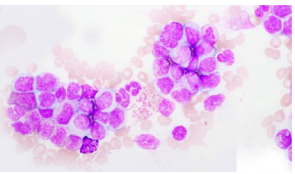
Current medications:

- Piperacillin/tazobactam, posaconazole, acyclovir

What is the next step to control infection?

A. Transfuse 1U PRBCs
B. Start daily G-CSF until ANC >500
C. Hold venetoclax
D. Reduce venetoclax dose by 50%

In this case, it would be reasonable to do B, start daily G-CSF until ANC is greater than 500 because, at this point, the patient has cleared the disease from the bone marrow which shows a morphological remission-free state. The neutrophils are still 0, so getting the neutrophils above 500 will help the patient recover from the infection. Transfusing red blood cells might help with the patient's energy level, but it shouldn't have a big impact on treatment of the infection. Holding venetoclax is a potential option that is being explored more. and current practice would not technically be standard of care without instruction on how to use it. Reduction of the venetoclax dose by 50% is not recommended except when there is concurrent use of a CYP3A4 inhibitor that requires a reduction of venetoclax dose.



Some dose adjustment considerations that were derived from the VIALE-A trial. For patients with grade 4 neutropenia plus or minus fever or grade 4 thrombocytopenia, these were some of the instructions. If it occurred prior to achieving remission, which is the case here in this example, in most cases do not interrupt HMA plus venetoclax prior to achieving remission.

If the first occurrence that occurred after achieving remission that lasts for greater than 7 days, then the next cycle of HMA-venetoclax was delayed and the blood counts were monitored and, upon resolution of the blood counts to grade 1 or 2, resume HMA-venetoclax at the previous dose.

For subsequent occurrences in cycles after achieving remission and lasting for more than 7 days, same story, delay the next cycle of HMA plus venetoclax and monitor blood counts. Upon resolution to grade 1 or 2, resume HMA-venetoclax at the previous dose and reduce venetoclax duration by 7 days during subsequent cycles. In other words, give it for 21 days instead of 28.

The formal guidance was to do this after the second occurrence of these events in patients who have achieved remission and that's why, in this case, the patient who had yet to officially achieve a remission, the interruption of venetoclax was not the ideal answer. Instead, trying to get the recovery of the neutrophils so the patient can recover from their infection.

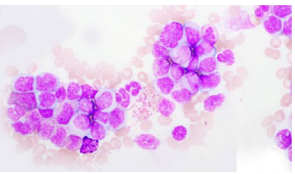
Another consideration when you use venetoclax-HMA therapy is tumor lysis syndrome and the TLS incidence was infrequent in the VIALE-A trial. This was rates during treatment for CLL, much more common in CLL. In the VIALE-A trial, the TLS rate was 1% in the HMA-venetoclax arm and 0% in the placebo arm. As a result, the potential risk of TLS, the dosing recommendations are to start with a short ramp-up and this would be 100 mg on day 1, 200 mg on day 2 and 400 mg on day 3 and beyond. Notably, the dose of venetoclax should also be adjusted, as I mentioned before, depending on the concurrent medications, such as a CYP3A4 inhibitor. We frequently use such medications in AML. These are the antifungal drugs that are commonly prescribed for patients with AML and so one has to be very careful of the dosing of venetoclax, especially when considering concurrent medications.

Back to TLS. We should consider frequent lab draws in patients during their initial treatment and their ramp-up. Patients are usually given hydration, IV hydration, and allopurinol, and sometimes they're even given rasburicase if their uric acid is high or becomes high as a result of treatment.

In terms of patients after they achieve remission and you want to consider this to be continuation therapy—or some people call it consolidation maintenance—the standard HMA dosing is usually maintained, decitabine 20 mg/m^2 on days 1 through 5, or azacitidine 75 mg/m^2 days 1 through 7 and the venetoclax is given for 400 mg per day for days 1 through 21 of the 28-day cycle. This would be kind of the standard dosing. In terms of some other considerations, the treatment is usually continued until progression, intolerance, transplant, or I always say the patient decision to stop is always a reasonable consideration. If one of those criteria are not met, I typically will continue the treatment. Patients should get a bone marrow biopsy after cycle 1 for response assessment, and typically we'll do another bone marrow biopsy after cycle 2 if there wasn't a response after cycle 1 and so on, every cycle until remission. In patients who achieved an early remission, we'll often repeat a bone marrow at cycle 4 to see if the response is deepening or not.

There's again no data to support stopping treatment in responding patients once a CR or MRD-negative CR is achieved. If the CR is not achieved, there can be benefits to continue the treatment. There are some patients who will respond after several cycles, including upwards of 4 cycles or more, and so there are some late responders. Other patients might benefit from decreased transfusion dependency and improved cytopenia.

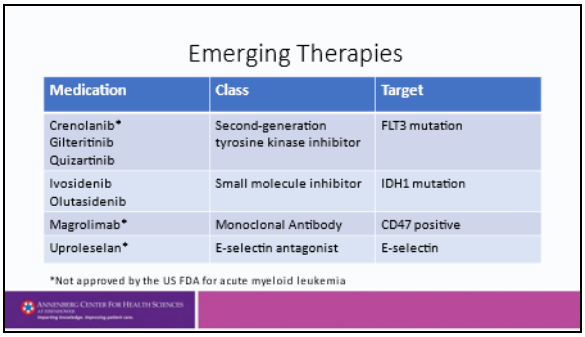
A lot of these management strategies for venetoclax and decitabine, venetoclax and azacitidine or venetoclax and low-dose cytarabine are evolving with increasing clinical use. I think it's important to keep learning and attending



educational seminars and discussions that talk about how current practice is, such as dose reductions of venetoclax down to 21 days or potentially to shorter periods of time, extension of cycles beyond 28 days, sometimes up to 6 weeks, is commonly done. Sometimes the doses of the hypomethylating agents will be decreased for patients who have ongoing issues with cytopenia. There's a lot of things that can be done to improve the tolerability of treatment and to allow patients to maintain their treatment, and hopefully keep themselves in remission.

Emerging Therapies

This table shows a number of potential new drugs, including some that are already approved and some that are still investigational.



Emerging Therapies

Medication	Class	Target
Crenolanib* Gilteritinib Quizartinib	Second-generation tyrosine kinase inhibitor	FLT3 mutation
Ivosidenib Olutasidenib	Small molecule inhibitor	IDH1 mutation
Magrolimab*	Monoclonal Antibody	CD47 positive
Uproleselan*	E-selectin antagonist	E-selectin

*Not approved by the US FDA for acute myeloid leukemia

Such drugs include FLT3 inhibitors, like crenolanib, gilteritinib and quizartinib. These are second-generation tyrosine kinase inhibitors, again that target FLT3.

Ivosidenib and olutasidenib, both small molecule inhibitors, so IDH1 and so they target IDH1 mutation.

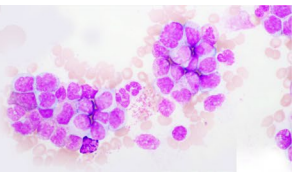
Magrolimab is a monoclonal antibody blocking CD47, so this can target anything that's CD47-positive, such as AML and a number of other diseases.

Uproleselan is an E-Selectin antagonist that disrupts the interaction between E-Selectin and E-Selectin ligand and affects the interaction of the AML cells with their microenvironment. Several are not approved by the FDA yet.

One drug is crenolanib and this is being studied in a randomized, phase 3 trial and this trial is looking at crenolanib vs midostaurin with induction and consolidation and in the maintenance phase. This is a 510-patient trial, randomized 1:1 with either crenolanib or midostaurin in combination with standard of care, including transplant. The advantages of this design is the use of midostaurin as a control arm instead of placebo and the study is also, again, looking at a large patient size and including patients looking at maintenance phase treatment. The primary outcome is event-free survival at 5-year follow-up. Secondary outcomes can include overall survival, relapse-free survival, composite complete remission rate, and duration of response. This is an ongoing trial, so there are no results to report yet, and the trial is recruiting.

The next study to highlight is one with gilteritinib, also a FLT3 inhibitor, and this is a study with gilteritinib vs midostaurin in combination with induction and consolidation chemo followed by 1 year of maintenance in patients with newly diagnosed AML and MDS EB 2 with FLT3 mutations eligible for intensive chemotherapy. This is also a large, randomized, phase 3, multicenter, open label trial. Patients are randomized—768, it's a very large trial—randomized to get either gilteritinib or midostaurin in combination with intense chemotherapy, standard of care chemotherapy followed by a year of maintenance. The strength of this design is the use of midostaurin as the control arm instead of placebo because midostaurin, at the time of this trial design, is standard of care for patients with FLT3 mutations. The primary outcome is event-free survival up to 45 months and there's a number of secondary outcomes that are being looked at, including overall survival, CR rate after induction, CR/CR1 rate after induction cycle 1, cycle 2, relapse-free survival, cumulative incidence of relapse, cumulative incidence of death, CR without MRD, adverse events, time to hematologic recovery, allogeneic transplant, quality of life, and global health status. There are no results to report yet. This is a trial is still recruiting.

Quizartinib, this was the QuANTUM-First study and this trial has completed. This was a combination of quizartinib with standard of care chemotherapy compared to placebo plus standard of care



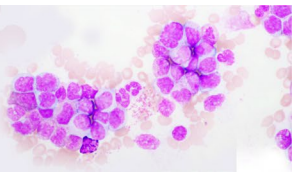
chemotherapy with up to 3 years of maintenance. This is for patients with FLT3-ITD-positive AML. A large phase 3 trial including 539 patients randomized 1:1 to get quizartinib vs placebo in combination with standard of care chemotherapy, including maintenance, with the primary outcome of overall survival. Secondary outcomes included event-free survival, complete remission, composite complete remission, relapse, death, complete remission with MRD negativity. The results have now been published recently in *The Lancet* with Dr. Erba as first author, and this was in 2023. It showed a median follow-up of 39.2 months. The median overall survival with quizartinib was 31.9 months vs 15.1 months in the placebo arm. The rates of CR, composite CR, CR with MRD negativity and composite CR with MRD negativity was similar between arms. In terms of the grade 3 or more AEs, they were similar between the 2 arms, 92% with quizartinib, 90% with placebo. The most common AEs included febrile neutropenia, hypokalemia, pneumonia, and neutropenia, which was more common in the quizartinib group. Because of the positive endpoint of this trial showing an improved overall survival with quizartinib over placebo, this was approved by the FDA on July 20, 2023, with a REMS program.

I wanted to highlight again the way that the treatment is given on this study and the study did enroll patients all the way up to age 75 years, so it was age 18 to 75 years, and they all had FLT3-ITD-positive AML. This is worth noting because quizartinib is not active against a TKD mutation. Patients all got cytarabine at standard dose days 1 through 7 and they got a choice of either investigator choice or physician choice of daunorubicin or idarubicin, given in the standard fashion on days 1 through 3, again the so-called 7+3 regimen. Quizartinib at 40 mg was given daily on days 8 through 21. On the other arm, placebo was also combined with 7+3 and given on days 8 through 21. They could get up to 2 cycles of induction.

Consolidation was given up to 4 cycles and used standard high-dose cytarabine, in combination with quizartinib 40 mg and patients could go to transplant. On the control arm, it was the same basic story with high-dose cytarabine up to 4 cycles with placebo, and patients could go to transplant as well.

There was a continuation phase or maintenance phase up to 3 years with quizartinib 60 mg daily vs placebo daily.

Another drug that I'm highlighting is ivosidenib, which is an IDH1 inhibitor. In the AGILE trial, it was combined with azacitidine in older patients with untreated AML with IDH1 mutation and those patients were either 75 years or older or unfit for standard induction. This is a multicenter, double-blind, randomized, placebo-controlled phase 3 trial and patients got oral ivosidenib 150 mg per day on days 1 through 28 in combination with azacitidine 75 mg/m^2 given subcutaneous or IV on days 1 through 7, so again, standard azacitidine dosing vs standard azacitidine, with placebo given daily days 1 through 28. The primary outcome was event-free survival and the secondary outcomes included things like complete remission rate, overall survival, CR rate plus CRh rate which is partial hematologic recovery, objective response rate, CR plus CRi rate, duration of CR, duration of other responses like CRh, Cri and time to response calculations including CR, CRh, Cri. At a median follow-up at 12.4 months, the event-free survival at 12 months favored azacitidine plus ivo at 37% event-free survival at 12 months vs 12% on the placebo arm. This was again significant, with a hazard ratio of 0.33. The overall survival also favored azacitidine plus ivo vs. placebo which was 24 months in the aza-ivo arm vs 7.9 months in the azacitidine-placebo arm. The CR rate was 47.2% in the ivo-aza combo vs 14.9% in the azacitidine-placebo combo. The rates of AEs, actually in some cases less in the ivo-aza arm, 28% febrile neutropenia compared to 34% in the placebo-aza arm. Neutropenia was higher in the ivo-aza arm, 27% vs 16%. There was grade 2 or more differentiation syndrome seen in 14.1% of patients in the ivo-aza arm and 8.2% in the aza-placebo arm. On the results of this trial, the FDA approved the combination of ivosidenib and azacitidine for newly diagnosed patients older or unfit for induction chemotherapy with IDH1-positive AML. There was already an approval in place for ivosidenib as a monotherapy, in either newly diagnosed or relapsed/refractory AML from the



results of the phase 1 trial, but this AGILE trial led to the approval of the combination therapy.

Next is olutasidenib. This is another IDH1 inhibitor and so this was an open-label of olutasidenib, also known as FT-2102, with or without azacitidine in patients with AML or MDS with an IDH1 mutation. This was a multicenter, open-label, phase 1/2 trial. Patients were given a number of different doses of olutasidenib, 150 mg daily BID or 300 mg daily, as a monotherapy or in combination with standard azacitidine dosing until disease progression, unacceptable toxicity or transplant. Primary outcomes included dose-limiting toxicities, maximum tolerated dose, maximum evaluated dose and recommended phase 2 dose. There were 32 patients treated with monotherapy and 46 with combination therapy. Median follow-up was 8.3 months in monotherapy, 10.1 months in combo therapy. There were no DLTs seen in the dose-escalation cohorts. In terms of overall responses, in treatment-naive AML, monotherapy produced a 25% overall response and there was a 77% overall response in combination therapy. For relapsed/refractory AML patients with IDH1 mutation, monotherapy produced a 41% response rate and 46% in combination. In terms of the most common grade 3 or worse AEs, the monotherapy, those included thrombocytopenia, febrile neutropenia, anemia and the recommended phase 2 dose was 150 mg twice daily. This drug was approved by the FDA on December 1, 2022, and has been added as a recommended agent in the guidelines for the treatment of relapsed/refractory AML with an IDH1 mutation.

Next, I'll mention magrolimab. This is a CD47 antibody, as I mentioned before, so this was a study looking at magrolimab vs placebo in combination with venetoclax and azacitidine in patients with AML. This is also known as the ENHANCE-3 trial. This was a randomized, double-blind, placebo-controlled, phase 3 trial, a large study with 432 patients. Again, magro vs placebo in combination with aza-ven and primary outcomes include complete remission and survival up to 5 years. Other outcomes include rate of remission with MRD, rate and duration of CR, transfusion independence and event-free survival. There's no results yet and this study is currently recruiting.

The next drug is uproleselan. This is an E-selectin antagonist. This interrupts the interaction between E-selectin and E-selectin ligand that links the blasts to the microenvironment. This is a study to determine the efficacy of the drug in combination with chemotherapy for relapsed/refractory AML, and this is another large, randomized, double-blind, placebo-controlled, phase 3 trial. It's 388 patients with uproleselan vs placebo in combination with MEC or FAI. FAI is fludarabine, cytarabine, and idarubicin. The primary outcome is overall survival up to 5 years and secondary outcomes include rate of mucositis and overall response rate. This is also a trial that has not yet reported, so there's no data to report yet, and the trial is active, but not recruiting.