Hello and welcome to our program, *Acute Myeloid Leukemia, Incorporating the Latest Advances into Nursing Practice*. I am Sandy Kurtin, Director of Advanced Practice at the University of Arizona Cancer Center and a nurse practitioner, and today I will share insights to help you remain up-to-date in the advances made in AML.

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Disclosures

- Formal Advisory Activities/Consultant:
  - BMS/Celgene, Takeda, Incyte, Novartis, Astra Zeneca, Amgen, Pharmacyclics, and Jazz

These are my disclosures.

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Today's Activity

- Discuss nursing considerations for patients with AML who are receiving frontline induction and post remission therapy
- Provide best supportive care or palliative measures for patients with relapsed/refractory AML to mitigate the toxic effects associated with current medications
- Describe the current landscape of approved therapies for AML, including considerations for dosing, administration, side-effect monitoring and management
- Provide patient/family education on the risks and benefits of treatment options to facilitate shared decision making

Here are the learning objectives. We are going to talk about nursing considerations for patients with AML who are receiving frontline induction and post-remission therapy. We are going to talk about best supportive care, palliative measures for patients with relapsed/refractory AML to mitigate any adverse events associated with current medications, and we are going to discuss the current landscape of approved therapies for AML including considerations for dosing, administration, side-effect monitoring, and management, and last we will talk about patient and family education and how this is important in mitigating these risks.

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Overview of AML

So, let's first talk about an overview of AML.

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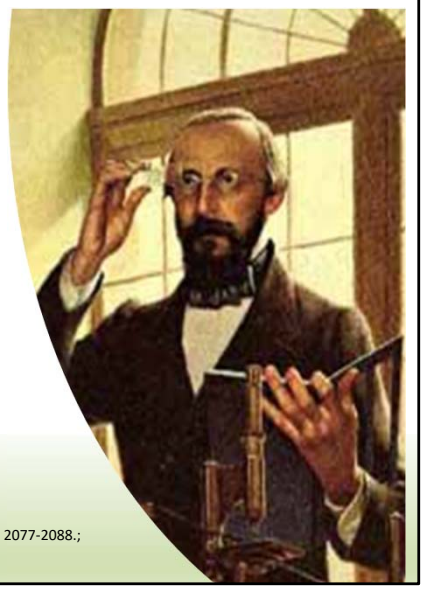
Acute Myelogenous Leukemia

- A clonal hematopoietic stem cell cancer within the myeloid continuum of diseases that originate in hematopoietic progenitor cells
- First described in 1845 by Dr. Rudolph Virchow
- Diagnosis requires evaluation of both peripheral blood and bone marrow
  - Presence of at least 20% myeloid blasts (immature cells) in the blood or bone marrow is required
- Categorized based on morphology when reviewed by a pathologist and the genetic signature of the disease



Gilliand G, Reffel G. Molecular biology of acute leukemias. In: *Cancer: Principles and Practice of Oncology.* 2005 Edition; 2077-2088.; Dohner H, et al. *Blood.* 2017;129:424-447.

AML or acute myelogenous leukemia is a clonal hematopoietic stem cell cancer within the myeloid continuum of diseases. This originates in hematopoietic progenitor cells and this group of diseases or disease was first described in 1845 by Rudolf Virchow. This diagnosis is complex. It requires evaluating both peripheral blood and bone marrow. We know that the definition by the World Health Organization in 2008 changed the definition of AML to require at least 20% blasts. Prior to that 30% blasts was the threshold. This is categorized by how the cells look, or morphology, and more recently, very specifically looking at cytogenetic and molecular attributes of the disease to better categorize the risk profile.

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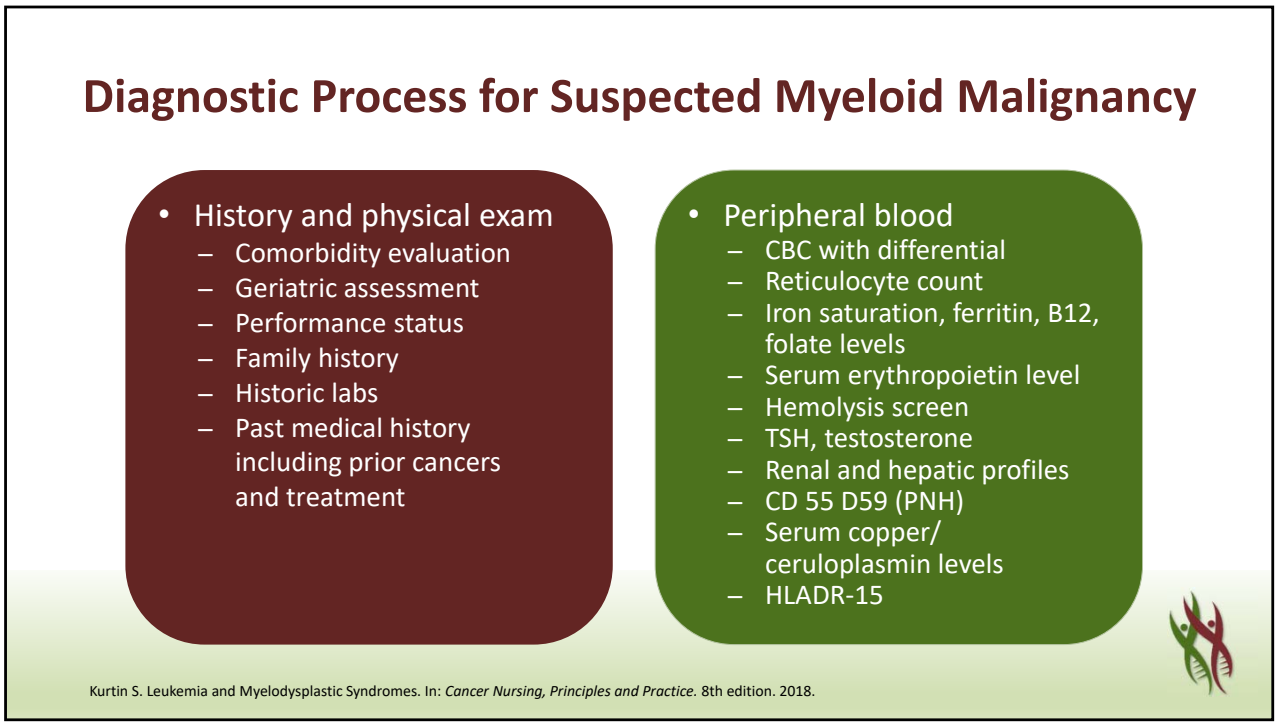

Part of that diagnostic work-up that we perform is looking at the history and physical, so the presence of comorbidities, many of these patients are older adults, some are younger. We are going to do a geriatric or frailty assessment, look at performance status, family history, historic labs, and then looking at any other history of cancer; this becomes very important when we start talking about secondary AML and we will talk about that in more detail later. We are going to look at the peripheral blood and this includes and all of the possible reasons someone might have cytopenias, in particular anemia, so iron, B12, folate for instance, serum erythropoietin levels, and such.

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Diagnostic Process for Suspected Myeloid Malignancy

- Bone marrow biopsy and aspiration
  - Hematopathology
    - Bone marrow blasts (%): >20% myeloblasts is diagnostic for AML
    - Cellularity (normal is 100 – patient's age)
    - Cell morphology (eg, dysplasia)
  - Metaphase cytogenetics
  - Iron stain
  - Reticulin stain for fibrosis
  - Cytogenetic and genetic testing
- Selected imaging based on symptoms

Kurtin S. Leukemia and Myelodysplastic Syndromes. In: *Cancer Nursing, Principles and Practice.* 8th edition. 2018.

Ultimately, there needs to be a tissue diagnosis, so much like we would do a breast biopsy in a breast cancer patient or do a colonoscopy with biopsy in a colon cancer patient, we need a tissue biopsy. And for patients with hematological malignancies, specifically myeloid malignancies, the bone marrow and biopsy aspirate and trephine biopsy are what meet this requirement. So we are going to look for that 20% threshold for blasts. We are going to look for cellularity, which should be 100 minus your age, and depending on the kind of leukemia or whether it is secondary or de novo, we are going to expect different things here, and then we are going to look for the presence of abnormal morphology, so in patients who have treatment-related MDS that has evolved into AML, or MDS that has evolved into AML itself, we are going to probably see the presence of dysplasia. We are going to look at metaphase cytogenetic, so this is basically those 20 metaphases that you see on a standard cytogenetic report, the presence or absence of iron or fibrosis, and then ultimately we are going to send it for a variety of cytogenetic and molecular testing.

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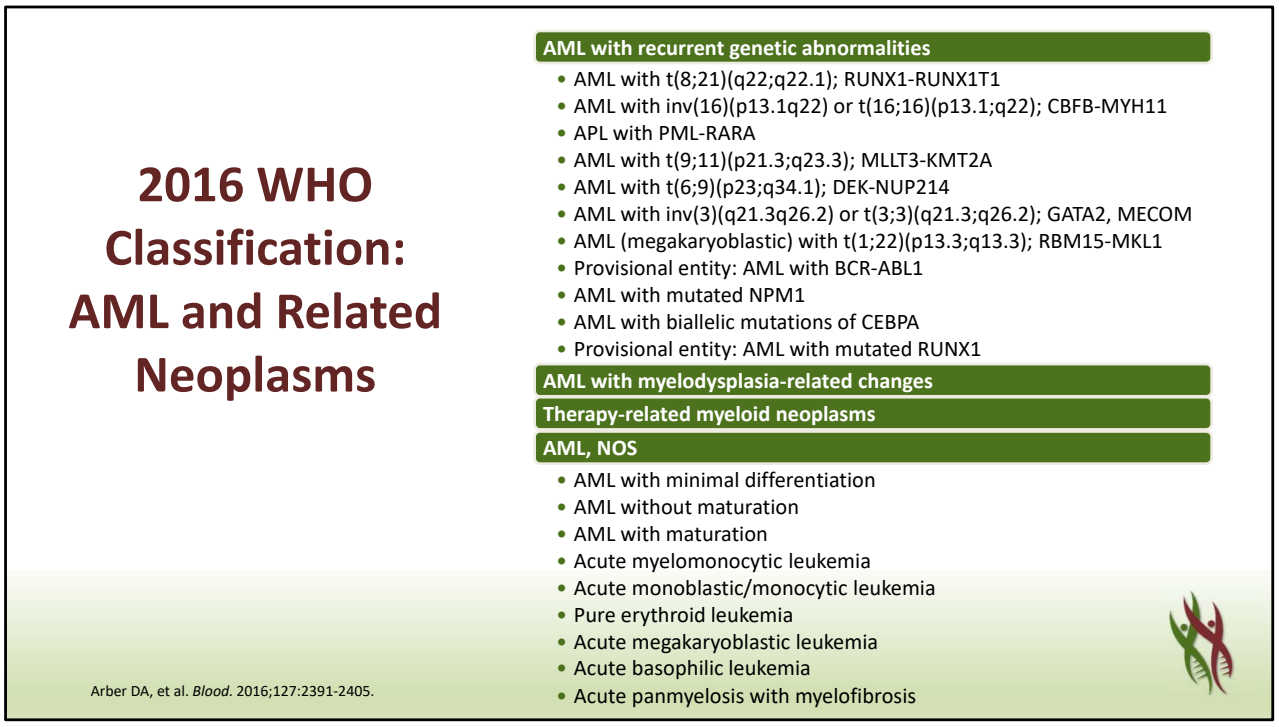

This is the 2016 World Health Organization classification and you can see that this is completely defined by the cytogenetic and molecular attributes, and so this has become very complex. It requires a skilled hematopathologist and skilled clinicians to identify the specific subtype of disease.

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Genetic Profile of AML

- AML is a complex, dynamic disease, characterized by multiple genetic abnormalities
- More than one genetic abnormality can be present at any time during the disease
  - These abnormalities may change over time
- There are different types of AML, each associated with variable prognosis and treatment approaches

Estey EH. *Am J Hematol.* 2018;93:1267-1291.; Dohner H, et al. *Blood.* 2017;129:424-447.

These are the various genetic subtypes, and I know that the cartoon here is relatively small and we do not expect you to remember or know all of these, but it is very important to understand that there are several different sub-categories in this nomenclature that are related to prognosis, and in some cases dictate our approach to treatment.

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De Novo AML

- De novo AML occurs in patients of all ages
- The onset is usually abrupt with symptoms progressing over days to a few weeks
- Most patients present with fevers, infections, bruising or bleeding, fatigue, bone pain, and in some cases, skin nodules

- High-risk features include:
  - Not a candidate for intensive therapy
  - Physiological age
  - Poor performance status/frailty
  - Complex or poorly controlled comorbidities
  - AML-related genetic factors

So, let us first talk about de novo AML. De novo means from the start, so this is AML that just happens, tends to be very abrupt. These are people that a week ago were just fine and suddenly they become quite ill very quickly, often presenting to the emergency room and are found to have very high white counts or also sometimes low platelets and other cell lines like anemia, and are then noted to have AML. So they may have fevers, infections, bruising, bleeding, fatigue, bone pain, and in some cases skin nodules, although that tends to happen later on. We want to look at risk features. Are they a candidate for a bone marrow transplant? Because ultimately that is the only cure for the majority of these patients or potential cure. We are going to look at physiological age, if they are much older we are going to be suspicious of an antecedent myeloid malignancies such as MDS. We are going to look at their performance status and frailty. Can they endure intensive induction therapy? And then what kind of comorbidities they have and then what are those other risk factors.

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2017 ELN Risk Stratification by Genetics: AML

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{Low}
	Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD^{High}
	Wild type NPM1 without FLT3-ITD or with FLT3-ITD^{Low} (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	Cytogenetic abnormalities not classified as favorable or adverse

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

When we look at the cytogenetic and molecular abnormalities we categorize them into favorable, intermediate, or poor risk. These are the lists of favorable and intermediate molecular and cytogenetic abnormalities.

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2017 ELN Risk Stratification by Genetics: AML

Risk Category	Genetic Abnormality
Adverse	t(6;9)(p23;q34.1); DEK-NUP214
	t(v;11q23.3); KMT2A rearranged
	t(9;22)(q34.1;q11.2); BCR-ABL1
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM (EVI1)
	-5 or del(5q); -7; -17/abnormal (17p)
	Complex karyotype; monosomal karyotype
	Wild type NPM1 and FLT3-ITD^{High}
	Mutated RUNX1
	Mutated ASXL1
	Mutated TP53

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

Then we have those that are very adverse, and in these patients in particular, these are either associated with likely antecedent myeloid malignancies or we know that they are likely going to be refractory to standard therapy.

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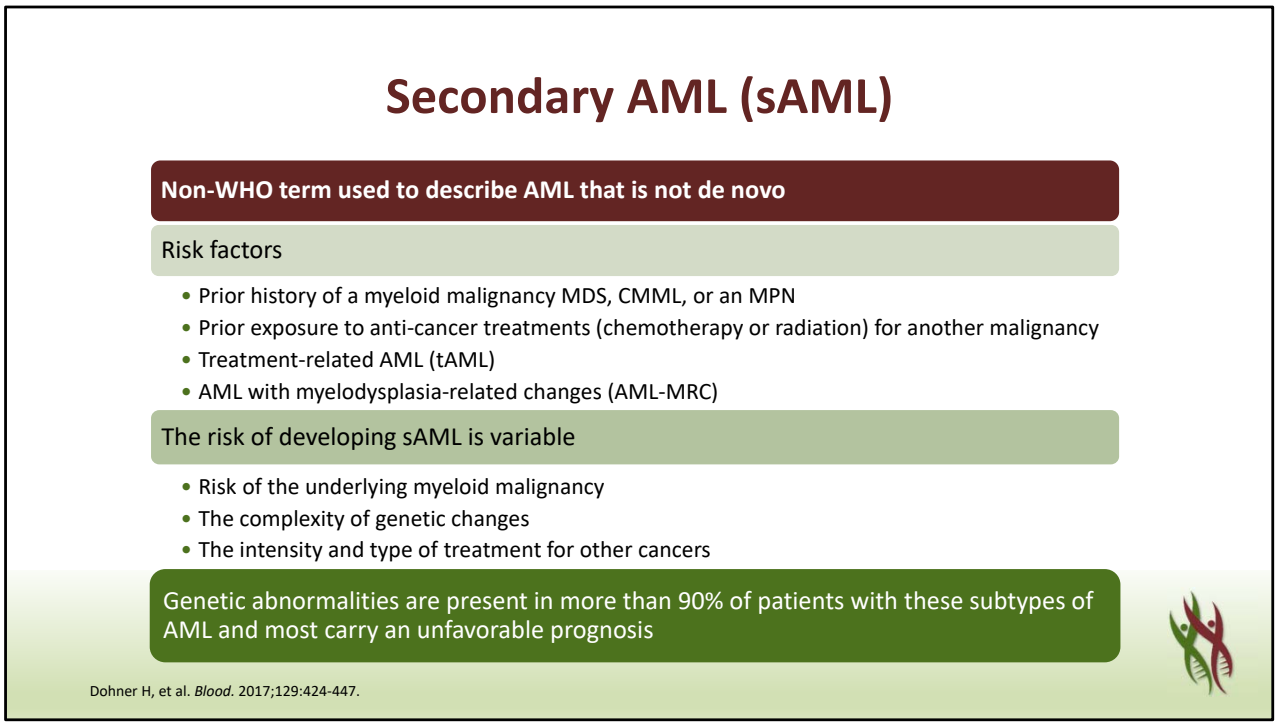

Let us talk about secondary AML. This is a non-World Health Organization term, but basically it means that this did not just happen on its own, that there is a secondary process, so they either have a prior history of a myeloid malignancy, most commonly MDS, CMML, or a myeloproliferative neoplasm, or MPN, or they have had prior exposure to anti-neoplastic therapy, either chemotherapy, targeted therapies in some cases, or radiation therapy. This is considered to be treatment-related AML, and then in this category is AML with myelodysplasia-related changes or AML-MRC. The risk of developing AML in these cases is variable and it has to do with the underlying malignancy, the complexity of genetic changes, and the intensity and the type of treatment for the other cancers. They are all associated with genetic abnormalities and instability and are present in more than 90% of patients with these subtypes of AML.

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Treatment-related AML (tAML)

Risk Factors:

- Prior exposure to anti-cancer treatments (chemotherapy or radiation) for another malignancy

Early onset (3 years):
- Topoisomerase II inhibitors – Etoposide, teniposide, topotecan, doxorubicin
- MLL gene (11q23) most common, t(8;21), t(15;17), AML1 (21q;22)

Late onset (5-10 years):
- Therapeutic alkylators – Cytoxan, melphalan or radiation
- Chromosome 5 or 7 abnormalities most common, 17p, del(3p)

- The risk of developing sAML is variable
  - Risk of the underlying myeloid malignancy
  - The complexity of genetic changes
  - The intensity and type of treatment for other cancers
- Genetic abnormalities are present in more than 90% of patients with these subtypes of AML and most carry an unfavorable prognosis

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

Let's talk about treatment-related AML, we know that this can include either chemotherapy or radiation. We know that it is time-sensitive; so we have early onset, so this is within three years of the primary therapy for that other malignancy, and we know there are certain drugs associated with secondary or treatment-related AML. Those are the Topo II inhibitors like etoposide, doxorubicin, and other anthracyclines. We know that these are associated with the MML gene which is the translocation 11;23 and these tend to confer an unfavorable prognosis. We also know that there are those patients that have a late onset, so this is very difficult. It is all very difficult, but these are patients that may have been treated 5 or 10 years ago and they come back and they have developed cytopenias and you may think it is their primary malignancy, for instance in the case of a lymphoma, but in fact they have treatment-related AML. These are things like Cytoxan (cyclophosphamide) one of the most common drugs that we use, melphalan or radiation, so we see a number of patients for instance who have had pelvic radiation for either gynecological tumors or prostate cancer in this category, and they tend to have chromosome 5 or 7 abnormalities or 17p, all of which are unfavorable. So again the risk is underlying myeloid malignancy, the complexity of the genetic changes, and the intensity and type of treatment.

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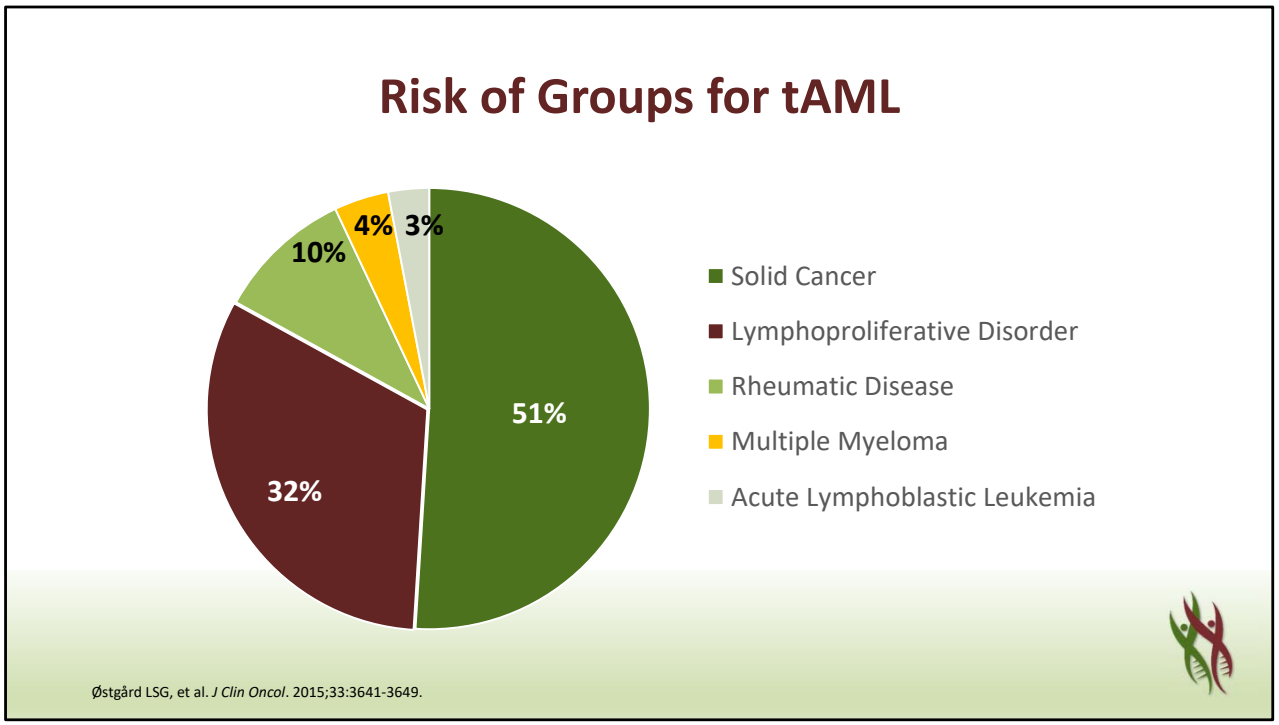

These are some of those diagnostic groups that are associated or have that risk of treatment-related AML based on the disease itself and the drugs and/or radiation that we used to treat them. So different solid tumors, the lymphoproliferative disorders such as the lymphomas, rheumatic diseases, we give some of these drugs such as methotrexate in people with rheumatoid arthritis, sometimes over many, many years, multiple myeloma which is a plasma cell dyscrasia, part of the lymphoproliferative disorders, and then an acute lymphoblastic leukemia where people may receive treatment for two or three years.

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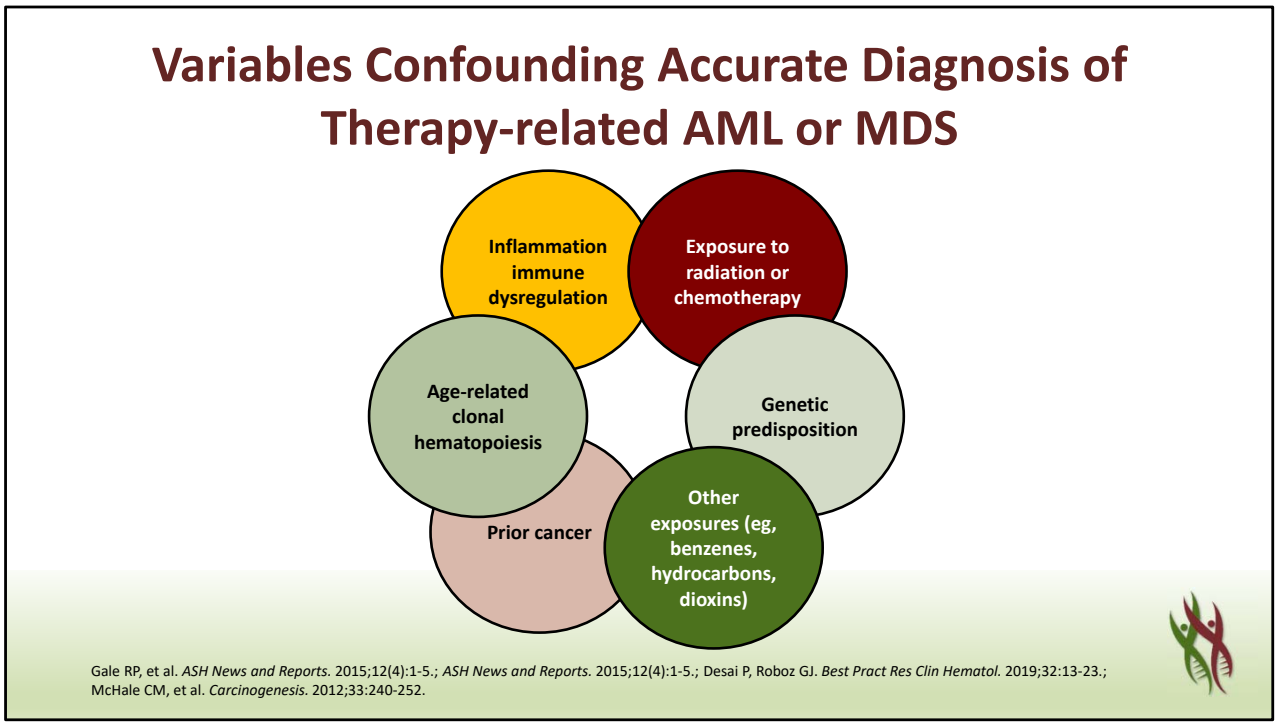

These are the variables that make it difficult to sometimes diagnose this, and so again it takes us all to be vigilant and aware of what the risk factors are and then a very skilled hematopathologist to be able to discern sometimes very subtle changes on the bone marrow biopsy and aspirate sample. We are going to look for prior exposure, we are going to look for other exposures, are they a smoker for instance? Have they had a prior history of cancer? Do they have age-related clonal hematopoiesis, so there is a subtype there, and/or is there a history of long-term inflammation or immune dysregulation as is the case in some of our autoimmune disorders?

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AML with Myelodysplasia-related Changes (AML-MRC)

- **Clinical history**
  - Prior history of a myeloid malignancy MDS, CMML, or an MPN
- **Morphology**
- **Multilineage dysplasia** dysgranulopoiesis, dyserythropoiesis, and/or dysmegakaryopoiesis ***in >50% of ≥2 cell lineages in the absence of genetic abnormalities defining the category of recurrent genetic abnormalities***

≥3 unrelated abnormalities, not including the recurrent genetic abnormalities encountered in AML	
Unbalanced abnormalities: deletions, additions, inversions	−7/del(7q)
	del(5q)/t(5q)
	i(17q)/t(17p)
	−13/del(13q)
	del(11q)
	del(12p)/t(12p)
	idic(X)(q13)
Balanced abnormalities: translocations	t(11;16)(q23.3;p13.3)
	t(3;21)(q26.2;q22.1)
	t(1;3)(p36.3;q21.2)
	t(2;11)(p21;q23.3)
	t(5;12)(q32;p13.2)
	t(5;7)(q32;q11.2)
	t(5;17)(q32;p13.2)
	t(5;10)(q32;q21.2)
	t(3;5)(q25.3;q35.1)

Arber DA, et al. *Blood.* 2016;127:2391-2405.

Then we look at AML with myelodysplasia-related changes or AML-MRC, and this is a very specific subtype. We know that these patients all carry variable risk of leukemic transformation over the course of their disease. We are going to look at MDS, CMML, and myeloproliferative neoplasms specifically. We are going to look for specific dysplasia in one or more cell lines, so in this case multi-lineage dysplasia, meaning multiple cell lines, red blood cell, white blood cell, and platelets. If there is greater than 50% in two or more cell lines in the absence of genetic abnormalities, this actually meets the diagnostic criteria for AML-MRC, so again very important to have a complete review, a good sample and then complete review of the bone marrow sample to be able to account for whether that 50% exists, and there are specific cytogenetic and molecular attributes that are listed here that are also a part of that diagnostic criteria and the new World Health Organization classification.

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Key Takeaways

- The diagnosis of myeloid malignancies has become increasingly complex
- Accurate classification of MDS and AML requires hematopathology's, physicians, and other clinicians with expertise in myeloid malignancies
- The patient's history is a critical component of the diagnostic process
- Genetic and cytogenetic abnormalities are prevalent in myeloid malignancies, are prognostic, and in some cases predictive
- It is not going to get any easier – we need to embrace the science and learn how to translate it for patients, caregivers, and other lay people

Key takeaway in this diagnostic process is that this is becoming increasingly complex. We understand that we really need a good sample of bone marrow biopsy and aspirate, sometimes we do not get a good enough sample and may need to repeat that, so you need to make sure that the person performing the bone marrow biopsy and aspirate understands how to get a good sample, that we have an adequate specimen, and that we ask all of the questions of that sample at the time we collect it. We are going to look at the patient's history. This is critical, and then we are going to evaluate the bone marrow and biopsy aspirate sample for the presence of these genetic and cytogenetic abnormalities.

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Therapy in Frontline Induction, Post-remission and Relapsed/Refractory Settings

Now let us talk about treatment, so we have made the diagnosis and we are going to talk about treatment, both in the frontline induction therapy, and then in post remission and relapsed/refractory settings.

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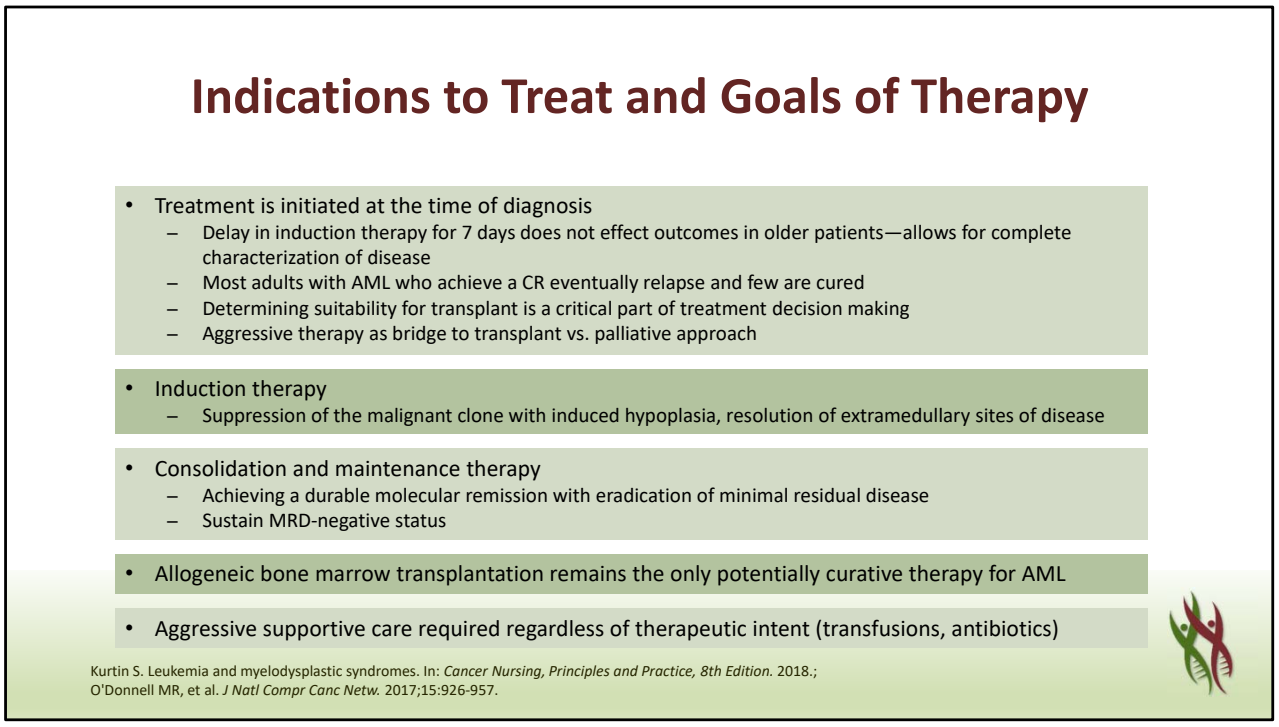

So really important that in acute myeloid leukemia, regardless of subtype, we generally start treatment immediately; in de novo AML that happens usually within a matter of days. These patients often present with very high white blood cell counts, a significant number of blasts, and we start treatment right away. In older patients where we suspect they may have an antecedent myeloid malignancy, we may be able to delay this induction for up to seven days, and there was a good study that supports this. This allows us to really tailor that therapy for the specific population. Most patients with AML, particularly older adults, will eventually relapse and few are cured, so our question upfront is are they eligible for a hematopoietic stem cell transplant and do they have available donors? And we are going to ask that question right away so that we can plan on our long-term treatment. Our goal in induction therapy is to suppress that malignant clone, so we want to reduce the number of blasts right away. We need to empty out the marrow so they become pancytopenic, and then hopefully as that recovers there will be healthy cells that repopulate the bone marrow. Ultimately one cycle of treatment, as with any cancer, is not enough, and we are going to need to consolidate those patients and this can be done in a number of ways, but basically this is where we are really looking at achieving a depth of response to erase any molecular evidence of disease. We talked about many of those molecular attributes, we want to make sure that those are no longer detectable in these patients. During this process, patients can become very, very sick and often experience febrile neutropenia or other treatment-related toxicities, and so aggressive supportive care is always expected.

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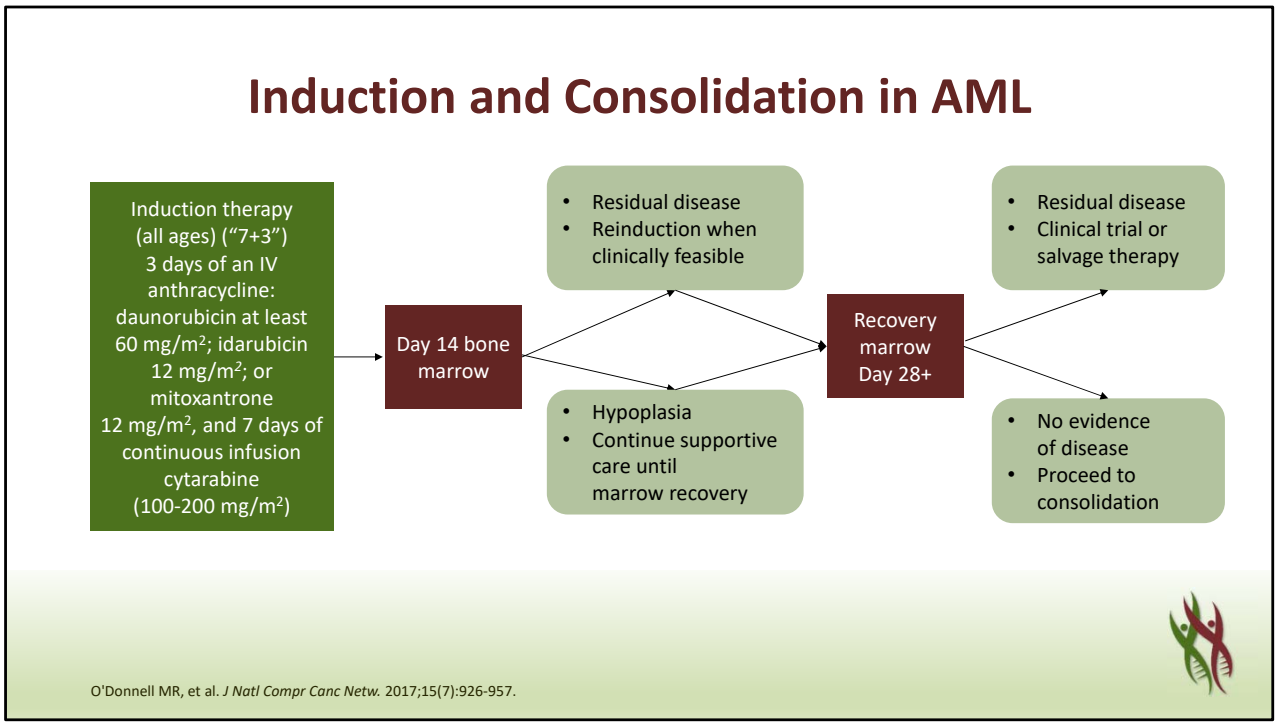

This is how that looks in a schema, so we are going to start induction therapy. This is usually aggressive chemotherapeutic regimen still today, and the most common of those has been 7+3, less frequently in patients who have impaired cardiac function, we may modify that slightly, and then basically we are going to check a day-14 marrow. What that is going to answer for us is did we empty out the marrow, is there no longer the presence of excess blasts, and were there absence of cytogenetic abnormalities? We allow that to recover if they do not meet the criteria for the absence of these blasts, we are going to have to reinduce them, otherwise at that recovery point typically we would do a day 28 marrow and we are going to answer the question is what grew back healthy or not? So if that day-28 marrow shows residual disease, we are going to remove salvage therapy. If there is no evidence of disease then we are going to move to consolidation.

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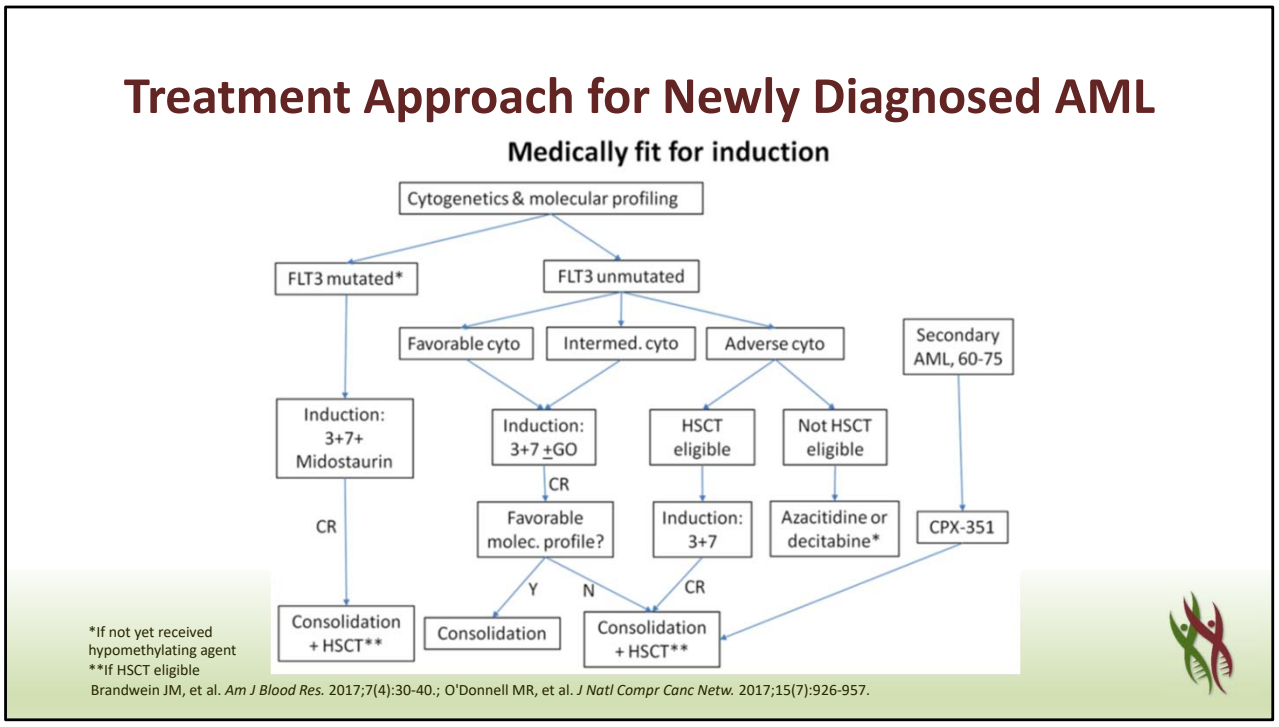

For the medically fit patient, these are people that we would expect to be eligible for a bone marrow transplant, we are also going to evaluate for actionable targets. One of the common actionable targets in AML is something called FLT3, and if they are FLT3 positive, we are going to add a FLT3 inhibitor to their induction and to their consolidation, and we know that these are particularly high-risk patients in terms of relapse. We are going to try to move them to transplant as soon as we achieve a molecular remission. If they do not have a FLT3 mutation and they have favorable cytogenetics, there are different regimens that we can consider, and if they have secondary AML, so this is that older population where we suspect that it came from an antecedent myeloid malignancy, we know that standard 7+3 induction therapy really does not work and we are going to look at alternative options such as CPX-351 and then plus or minus transplant if they are eligible for that. And some of these patients who initially are quite sick, if we get their disease under control, may actually be eligible for transplant.

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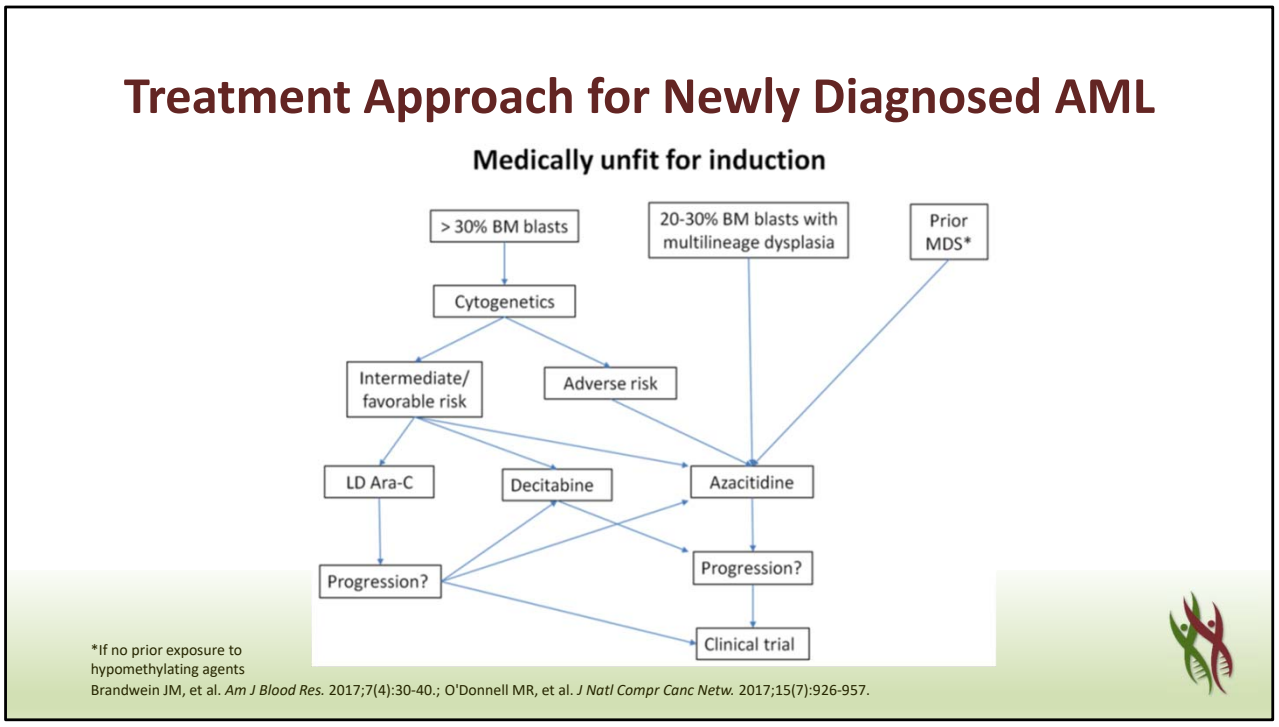

If they are unfit and they have greater than 30% bone marrow blasts we are going to really look at a more palliative approach to therapy, so this is somebody who we believe really is not going to be eligible for a transplant upfront and/or if they have multi-lineage dysplasia, so they are in that AML-MRC category, we are going to think about possibly hypomethylating agents and/or if they do improve with time and there's improvement in fitness, we can consider some of the other things we discussed in the prior slide.

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Induction Therapy with 7+3: 44 Years Later

- In 1973, Yates and colleagues reported results from an AML regimen of 7 days of cytarabine and 3 days of daunorubicin, aka "7+3"
- 40 years later, 7+3 induction therapy continues to benefit patients with AML
  - CR rate in younger patients: 60% to 75%
  - CR rate in patients older than age 60 years: 35% to 50%
- Relapse is inevitable for the majority of patients
- Current trials are focused on adding agents to the 7+3 over the course of treatment, changing the pharmacokinetics of daunorubicin + cytarabine, or finding new targets/pathways that are actionable

Yates JW, et al. *Cancer Chemother Rep.* 1973;57:485-488.; Murphy T, et al. *Expert Opin Pharmacother.* 2017:1-16.

Let's talk about 7+3, I have been doing this for 36 years and that's just been the mainstay of what we do for a very long time, so not quite 44 years but almost. In 1973, this is when this regimen was developed, and this is basically seven days of cytarabine, or Ara-C, and three days of daunorubicin, so thus the 7+3. We know that this does not work very well in a subset of patients, particularly those patients with secondary AML and/or people who are older and may not be able to tolerate this therapy. We know that relapse is inevitable for the majority of these patients, and we have ongoing trials to identify new targets and pathways.

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Low-intensity Treatment

- Azacitidine: 75 mg/m^2, SC, d1-7, every 4 weeks, until progression
- Decitabine: 20 mg/m^2, IV, d1-5, every 4 weeks, until progression
- Low-dose cytarabine (20 mg every 12 hours, SC, d1-10, every 4 weeks; until progression); not recommended in patients with adverse-risk genetics
- Best supportive care, including hydroxyurea, for patients who cannot tolerate any antileukemic therapy, or who do not wish any therapy

There is low-intensity treatment, again this is palliative, and this can be the hypomethylating agents, either azacitidine or decitabine as I mentioned, and there are different ways to administer these drugs. We know that low-dose cytarabine offers an option for some of these patients, and then again we would apply best supportive care, either along with these approaches or as individual therapy in a purely palliative setting.

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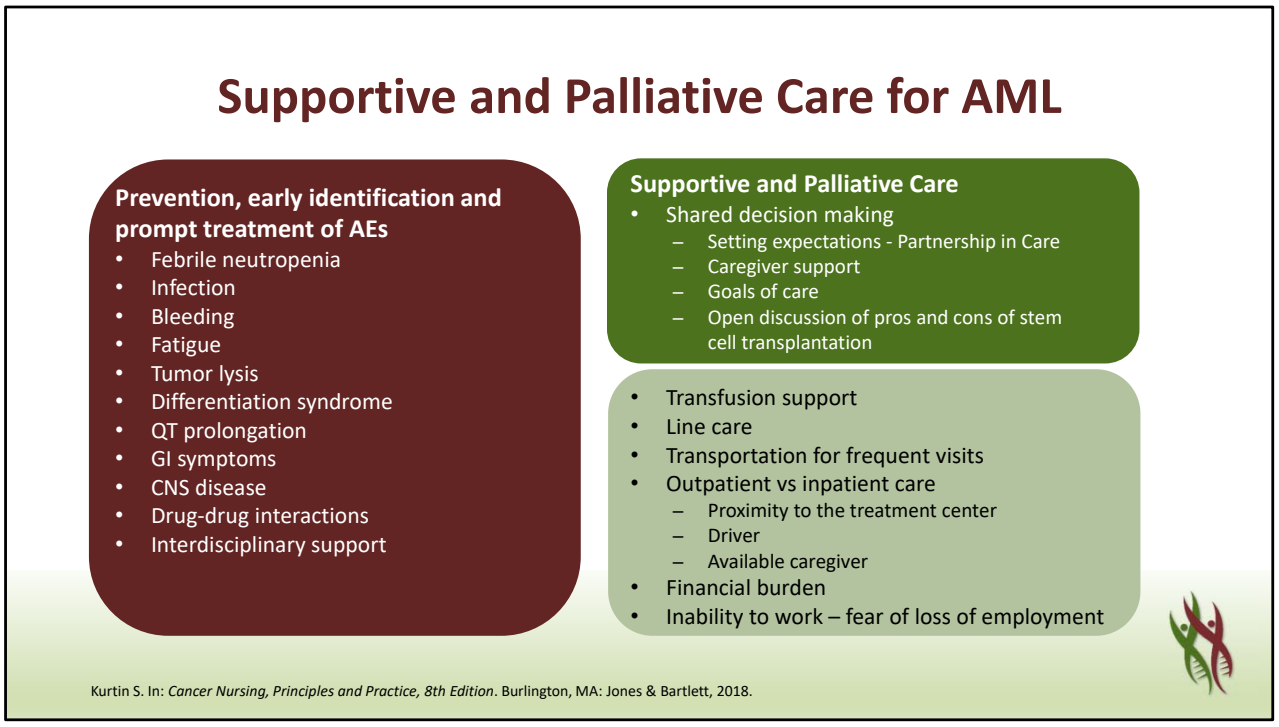

Some of that supportive and palliative care means that we are going to mitigate adverse events and treat those aggressively. We also are going to apply transfusion support, line care, antibiotics, really begin to look at where do they live in proximity to the treatment setting, consider financial burden, and in many cases we have very difficult conversations with these patients about the goals of care.

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Current and Emerging Therapies for AML

Now let's talk about some of the newer therapies that have evolved for AML.

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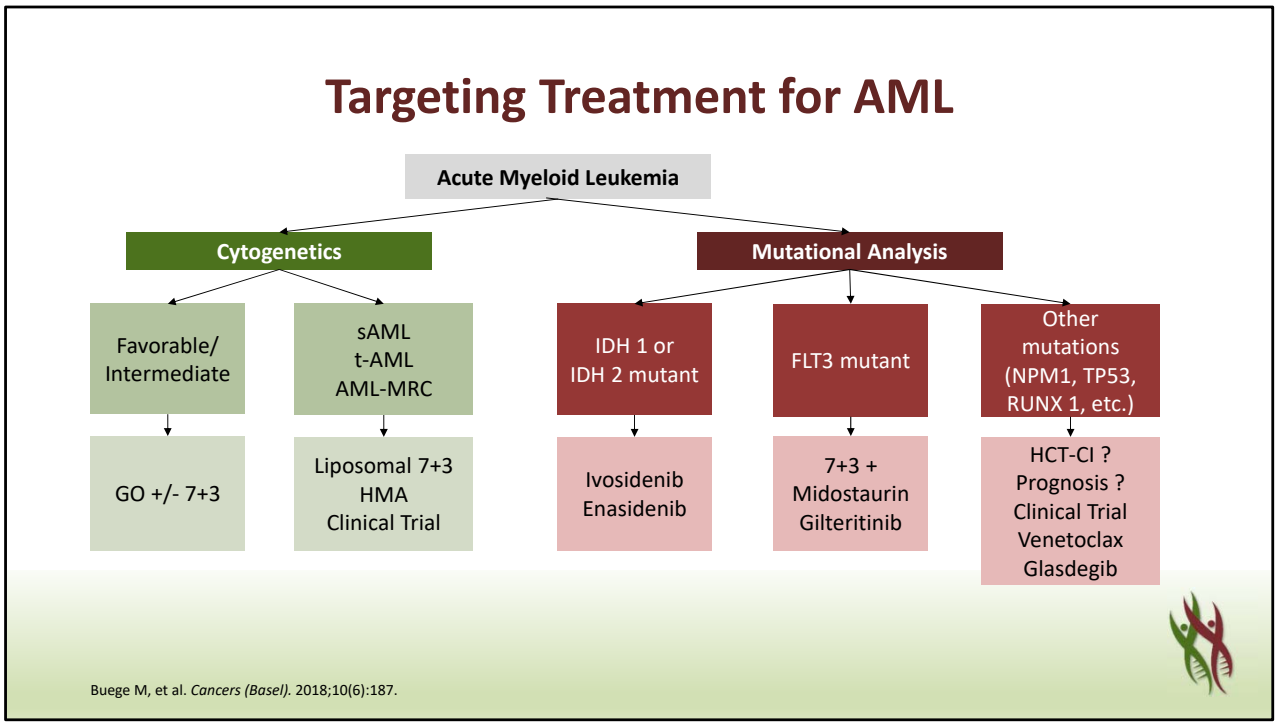

Again, we are going to look at first the diagnosis, we are going to look at cytogenetics, are they favorable or unfavorable? And most of the ones that are unfavorable are associated with the secondary AML treatment-related AML and AML-MRC. In that case we know that those patients do not respond as well to the 7+3 regimen and we have newer therapies such as the liposomal 7+3 CPX that we talked about earlier. We can use hypomethylating agents here, and we always want to consider clinical trials for these patients. If they have favorable or intermediate cytogenetics, they may be able to have what we call the GO regimen, plus or minus 7+3, and then we look at mutational analysis. Do they have any actionable targets? So IDH-1 and IDH-2 inhibitors are available in patients who carry this mutation. We talked about FLT3 previously, and then there are selected other mutations where we know these patients have particularly high-risk disease or perhaps more favorable disease, and we are going to treat them in a different way.

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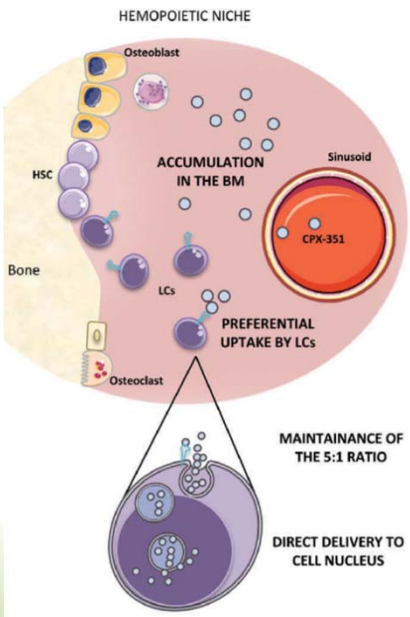

Liposomal Daunorubicin and Cytarabine (CPX-351): Mechanism of Action

- Uptake into the hematopoietic niche (bone marrow)
- Liposomes persist in the bone marrow and are taken up by leukemia cells to a greater extent than by normal bone marrow cells in a murine model
- Liposomes undergo degradation, releasing daunorubicin and cytarabine within the intracellular environment

Lim WS, et al. *Exp Hematol.* 2011;39:741-750.

The first thing, let us talk about liposomal daunorubicin and cytarabine or CPX-351. This is a liposomal compound, as we have talked about. These liposomes tend to be taken up better in the bone marrow and linger longer in the bone marrow, this was demonstrated in murine models, and then they undergo degradation, releasing these active compounds of daunorubicin/cytarabine directly into the intracellular environment which just where these abnormal cells reside.

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Liposomal Daunorubicin and Cytarabine

- Indications: adults with newly diagnosed t-AML or AML-MRC
- Liposomal cholesterol membrane of cytarabine and daunorubicin in a 5:1 molar ratio

Dosing

Induction:
Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2; liposome over 90 minutes on days 1, 3, and 5 and on days 1 and 3 for subsequent cycles of induction, if needed

Consolidation:
Daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 liposome over 90 minutes on days 1 and 3

Daunorubicin and cytarabine liposomal product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209401s000lbl.pdf

This is indicated for adults with newly diagnosed therapy-related acute myeloid leukemia, and you can see how we note that is t-AML or AML with myelodysplasia-related changes or AML-MRC. This is not your grandmother's 7+3 as we say. This does linger in the marrow and there are a couple of really key points: Number 1 is that it is a 5:1 molar ratio. The dosing looks different because of the liposomal compound, and we will go through that in a little bit more detail, but it is not going to be given in the same way as the 7+3, and we may see some differences in bone marrow recovery because of that increased uptake of the liposomal compound. We also know that consolidation will look different than the induction of 7+3 so where we do 7+3 in induction and consolidation, you are going to see a day 1, 3 and 5 in the induction and then you are going to see a days 1 and 3 in the consolidation setting.

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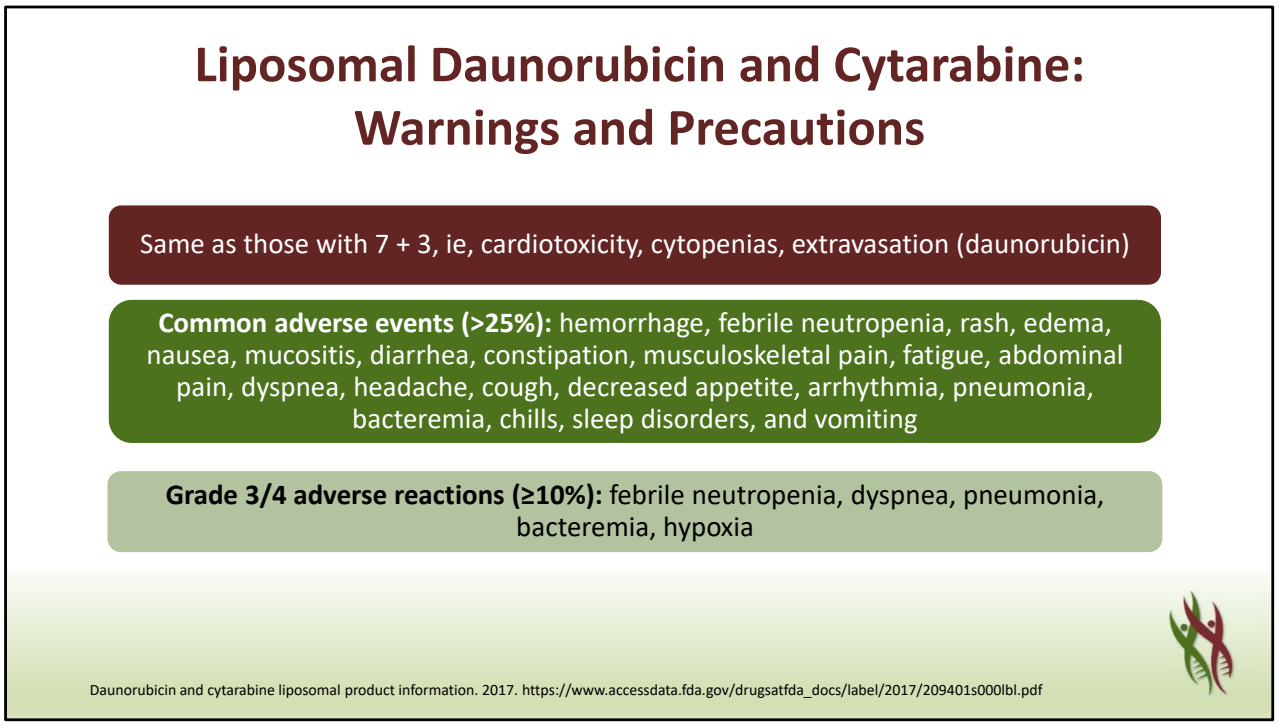

Even though that administration guideline looks different, the toxicities can be very similar and we have to apply the same safety considerations, particularly for cardiotoxicity associated with anthracyclines. The cytopenias, as I mentioned, may be prolonged, and so we are going to have to rethink that day-28 marrow for instance, and then this compound still carries that risk of extravasation because of the daunorubicin.

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CPX-351: Safety—Similar in the Two Arms

Grade ≥3 AEs (≥5% patients), n (%)	CPX-351 (n = 153)	7+3 (n = 151)
Febrile neutropenia	104 (68)	107 (71)
Pneumonia	30 (20)	22 (15)
Hypoxia	20 (13)	23 (15)
Sepsis	14 (9)	11 (7)
Hypertension	16 (10)	8 (5)
Respiratory failure	11 (7)	10 (7)
Fatigue	11 (7)	9 (6)
Bacteremia	15 (10)	3 (2)
Reduced ejection fraction	8 (5)	8 (5)

Lancet JE, et al. *J Clin Oncol.* 2018;36:2684-2692.

The common adverse events are very similar to the standard 7+3, so all of those things associated with pancytopenia--mucositis, diarrhea, musculoskeletal pain can be seen, and then we are going to need to look again at that cardiotoxicity.

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CPX-351: Prolonged Time to Recovery of Cytopenias Associated with CPX-351

	Induction		Consolidation (at least 1 consolidation)	
	CPX-351 (n = 58) n (%)	7+3 (n = 34) n (%)	CPX-351 (n = 48) n (%)	7+3 (n = 32) n (%)
Prolonged thrombocytopenia	16 (28)	4 (12)	12 (25)	5 (16)
Prolonged neutropenia	10 (17)	1 (3)	5 (10)	1 (3)

Platelets <50,000 or neutrophils <500 lasting past day 42 in the absence of active leukemia

Lancet JE, et al. *J Clin Oncol.* 2018;36:2684-2692.

This is the comparison data looking at CPX-351 and 7+3, so you can see they are almost identical with the exception of the prolonged cytopenias, and particular thrombocytopenia, so when we normally treat AML with 7+3, we expect that marrow to bottom out at day 14, recover at day 28. When we are applying CPX-351 we need to really rethink that because that may not be what happens at day 28, and we do not want to panic and think that either they have not responded or they are not recovering, we need to give it a little bit more time, so you can see here that this prolonged cytopenia was not uncommon in the patients receiving this liposomal compound.

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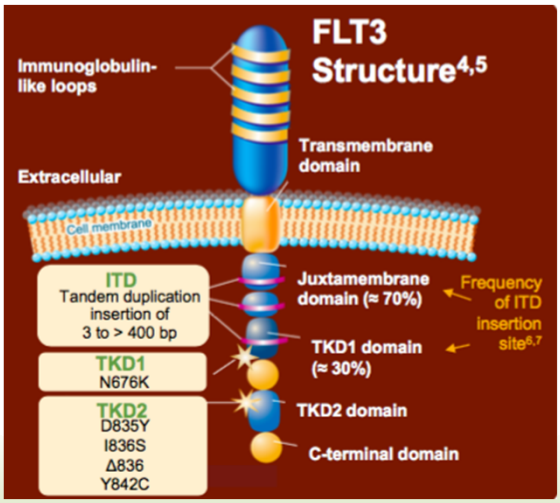
FLT3 and AML

- Type III transmembrane receptor tyrosine kinase
  - Same family as KIT, PDGFR-α/β
- Highly expressed on hematopoietic progenitors and required for myeloid differentiation
- Mutations in the *FLT3* gene cause constitutive activation of the receptor - Most common mutation is the ITD
- Small molecule oral agents



Fathi AT, et al. *Eur J Haematol.* 2017;98:330-336.; Gurnari C, et al. *Cancers.* 2020;12(2):357.; Image reprinted with permission: Pemmaraju N, et al. *Cancer.* 2011;117(15):3293-3304.

Now let's talk about other approaches to therapy. This is FLT3 and AML, so FLT3 is a type III transmembrane receptor tyrosine kinase or a protein. This is in the same family as KIT and PDGFR, alpha and beta. It turns out that these are highly expressed on hematopoietic progenitor cells, which is where the AML cells originate as we discussed earlier, and that mutations in this FLT3 gene are constitutively activated on the receptor and that basically makes the cells behave badly and not listen to feedback mechanisms.

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FLT3-targeted Agents for AML

Drug	Targets	Status
Sorafenib	FLT3, c-KIT, PDGFR, RAF, VEGRF	Approved
Midostaurin	FLT3, c-KIT, PDGFR, PKC, VEGFR	Approved
Gilteritinib	FLT3, AXL	Approved
Quizartinib	FLT3, c-KIT, PDGFR, RET	Investigational
Crenolanib	FLT3, PDGFR	Investigational

Fathi AT, et al. *Eur J Haematol.* 2017;98:330-336.; Gurnari C, et al. *Cancers.* 2020;12(2):357.

It turns out we have a number of small molecular oral agents that can target FLT3. Some of them are more specific to FLT3, many of them have off-target effects, and this will have to do with how what we see in their toxicity profiles.

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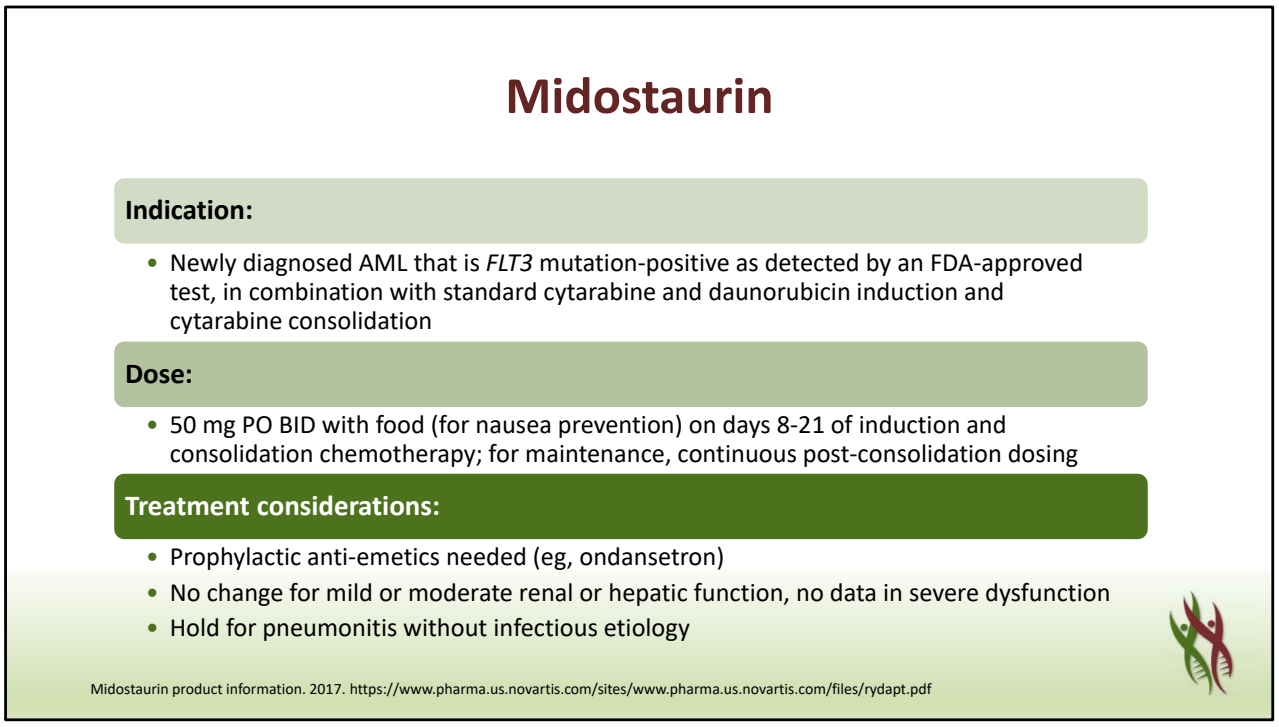

The first drug approved was midostaurin, so this is indicated for newly-diagnosed AML that has this FLT3 mutation and this is based on FDA-approved tests. This is given as an oral agent 50 mg twice-daily with food and it is given days 8 through 21, so 14 days of treatment, but waiting a week after their standard induction therapy. It can be also added to consolidation, and there is some research looking at maintenance therapy. This can add to nausea and vomiting, so we need to make sure that they have anti-emetics available and want to hold it for any pneumonitis without infectious etiology as there can be some cases of pulmonary toxicity.

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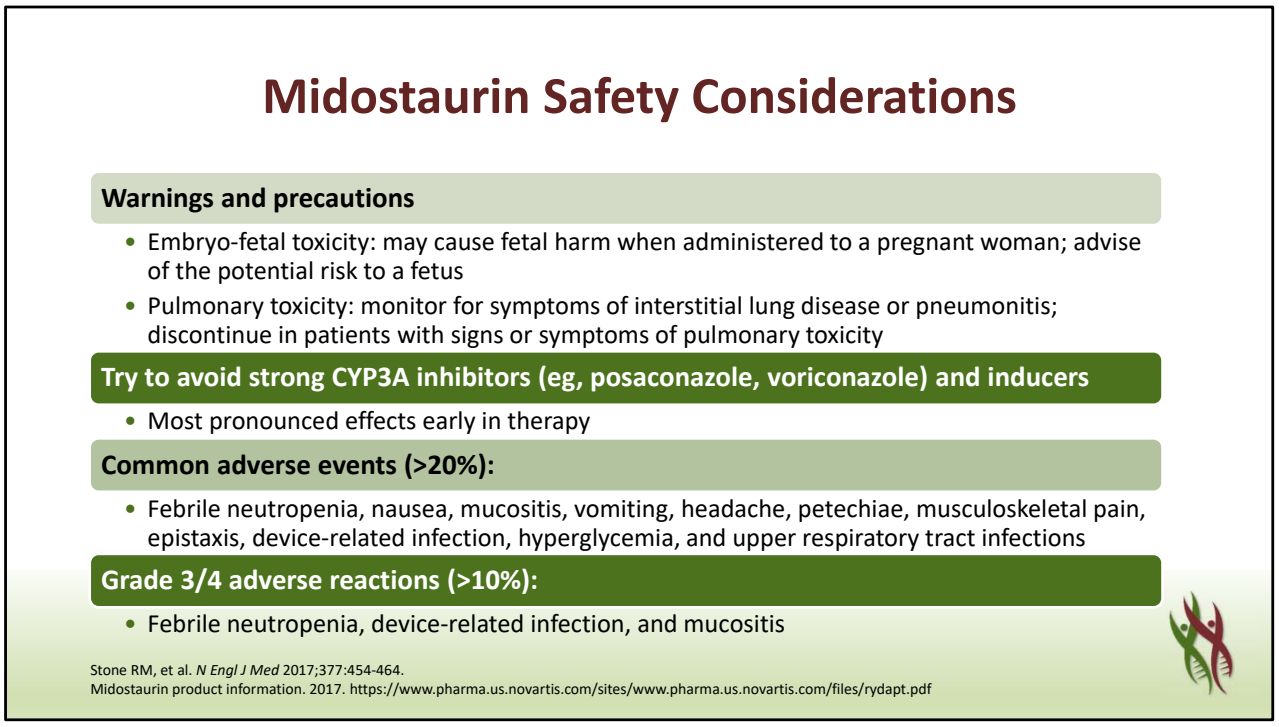

Other warnings and precautions are embryo fetal toxicity. This is true of most things we use for AML, and then I mention the pulmonary toxicity. It is an oral compound and so we do need to be aware of SIT3a inhibitors, the most common of these being anti-fungal agents which are commonly applied to patients with AML because they are cytopenic, sometimes for prolonged periods of time. So we talked about the common adverse events.

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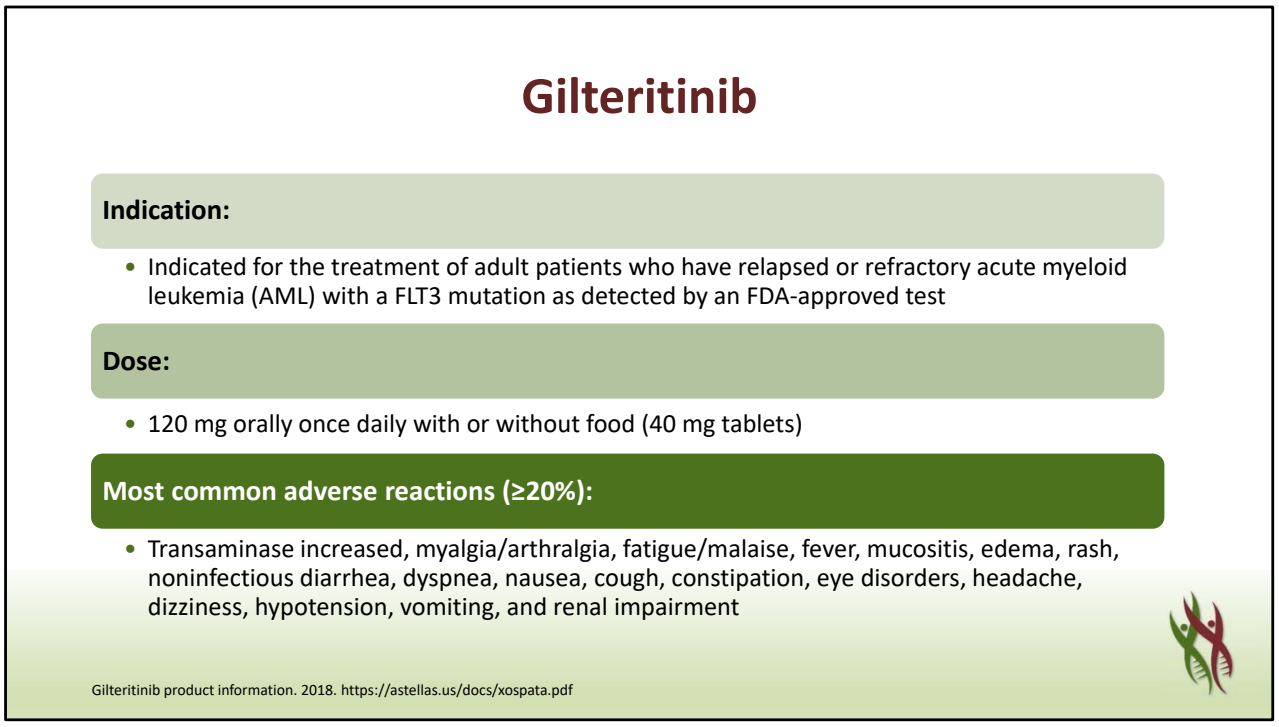

The second compound is gilteritinib, and this is indicated for the treatment of adult patients who have relapsed or refractory AML and with the FLT3 mutation. The dosing here is 120 mg once daily with or without food, these come in 40 mg tablets, and the most common adverse events are transaminase increase, bone and muscle pain, fatigue, again things that are associated with cytopenias because these are people with AML who have also undergone either induction or consolidation therapy, and then we can see some renal impairment and GI toxicity.

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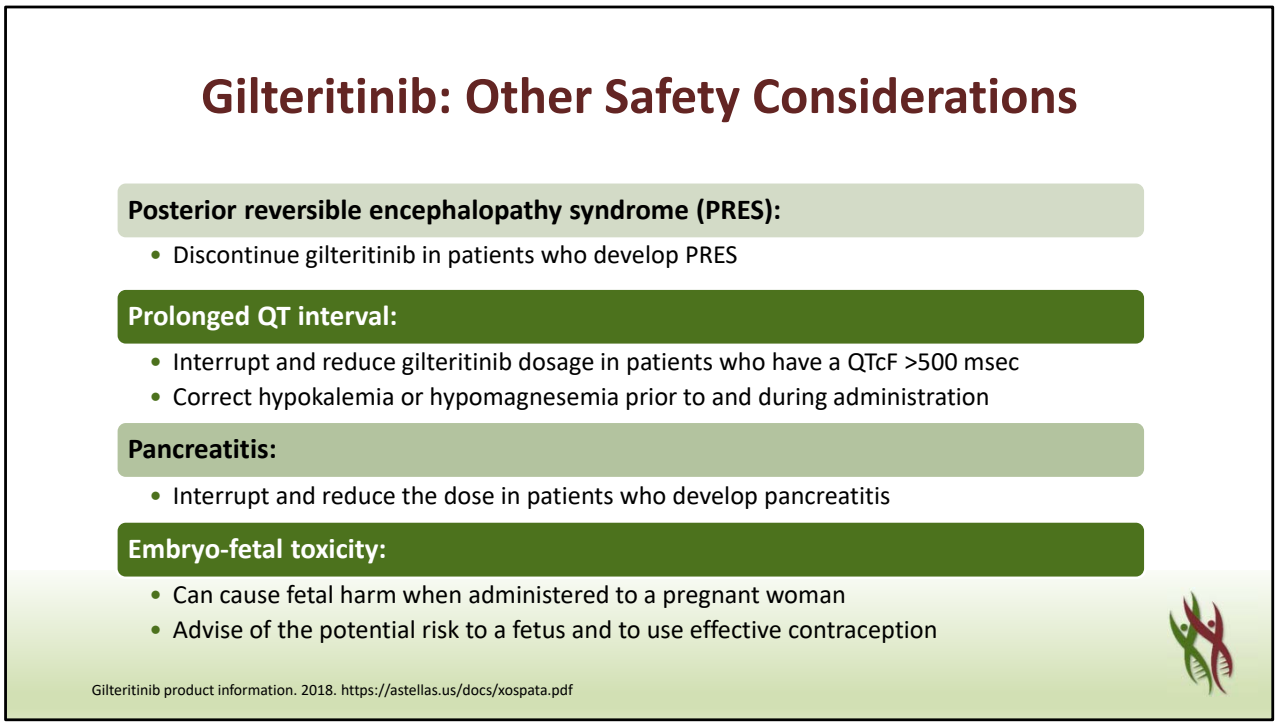

Also very rarely you can see posterior reversible encephalopathy or PRES syndrome, and in the presence of that you would discontinue this drug completely. You can also see prolonged QT intervals and so we are going to be monitoring these patients with baseline EKGs and periodic EKGs for anybody who is symptomatic. We are also going to correct hypokalemia and hypomagnesemia to reduce the possibility of QT prolongation. Cases of pancreatitis were reported in the studies and so we do need to monitor for that which requires amylase and lipase monitoring, and then again embryo fetal toxicity is a consideration.

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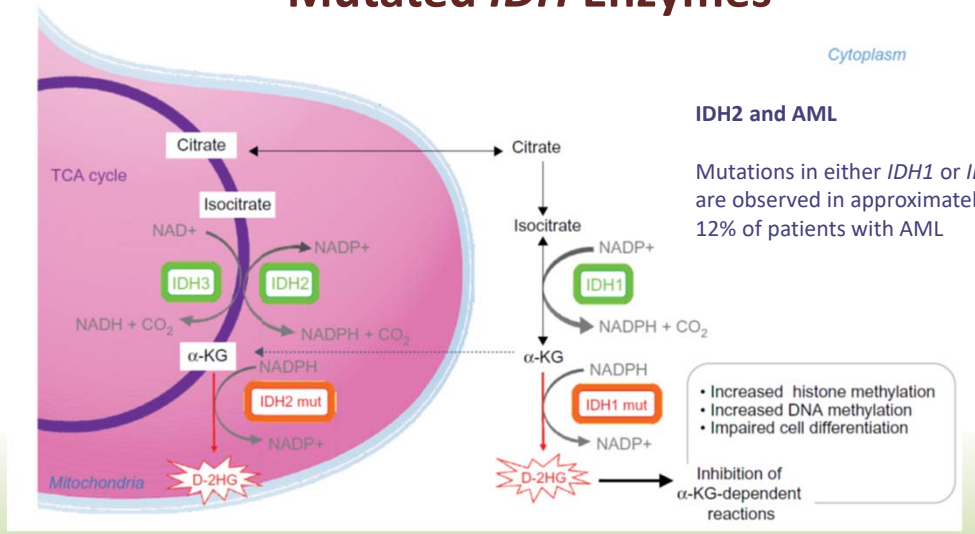
Enzymatic Activities of Wild Type and Mutated *IDH* Enzymes



IDH2 and AML

Mutations in either *IDH1* or *IDH2* are observed in approximately 12% of patients with AML

Mondesir J, et al. *J Blood Med.* 2016;7:171-180.

Now let's talk about some of the other targeted therapies. What we are looking at is IDH-1 and IDH-2 inhibitors, and so mutations in either IDH-1 or IDH-2 are observed in approximately 12% of patients with AML, and this takes us back to the Krebs cycle, way back when which most of us do not want to revisit, but there are elements of that that obviously have to do with cellular development and differentiation, and so these compounds can offer a good treatment option for those patients that carry those mutations, again, actionable targets.

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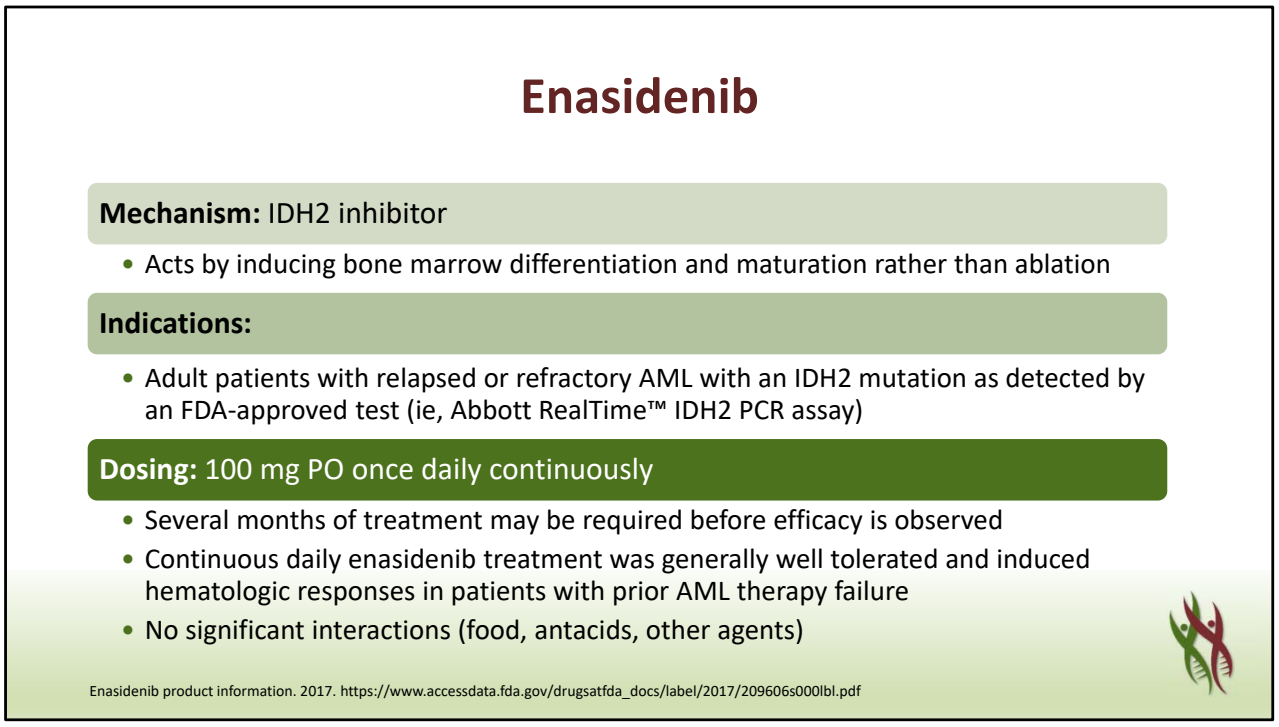

The first of these drugs is enasidenib. This is an IDH-2 inhibitor and this acts by inducing bone marrow differentiation in maturation rather than ablation. The presence of these mutations basically inhibit the normal development of these cells and by giving these inhibitors you can overcome that and reinduce differentiation and maturation. This is indicated for adults with relapsed and refractory AML, again they have to have documented IDH-2 mutations, and the dosing here is 100 mg once daily. This is given basically until progression or unacceptable toxicity. It can take a long time to see benefits, so unlike induction therapy where we are going to look for 14 days and they have no evidence of blasts, this may actually take several weeks or months to see the full benefit of patients. The continuous daily dosing is generally well tolerated and can induce hematological responses in patients with prior AML therapy, and I have a few patients that I have seen who have done very well on these compounds. There are no significant interactions with food, antacids or other agents, but there are warnings and precautions.

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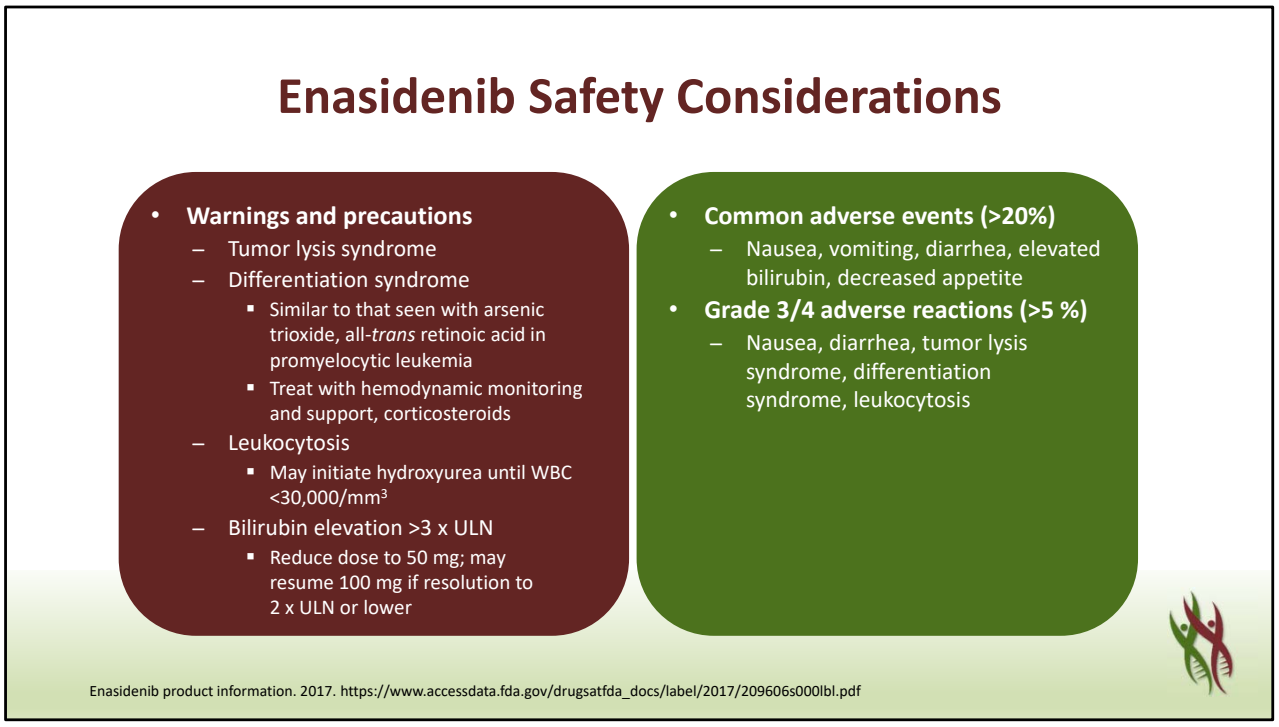

You can see tumor lysis syndrome or tumor lysis-like syndrome, again this is a differentiation process so as those cells are dividing and differentiating you can be breaking down cells as well, which is the characteristic of tumor lysis. There is a very specific differentiation syndrome that can be seen. We have seen this historically in acute promyelocytic leukemia where we also use differentiation agents, and so it is very important to familiarize yourself with that, and we will talk about it briefly a little bit later. You can see initial leukocytosis, again, these cells are being induced back into differentiation and maturation so you can see an initial spike. It is very important to discriminate that from progression of disease. You can also see some elevated bilirubin, that also comes from this differentiation process, primarily from red blood cells. Some of the adverse events, nausea, vomiting, and diarrhea are the most common, and then grade 3/4 adverse events, again we talked about tumor lysis syndrome, differentiation syndrome, and leukocytosis.

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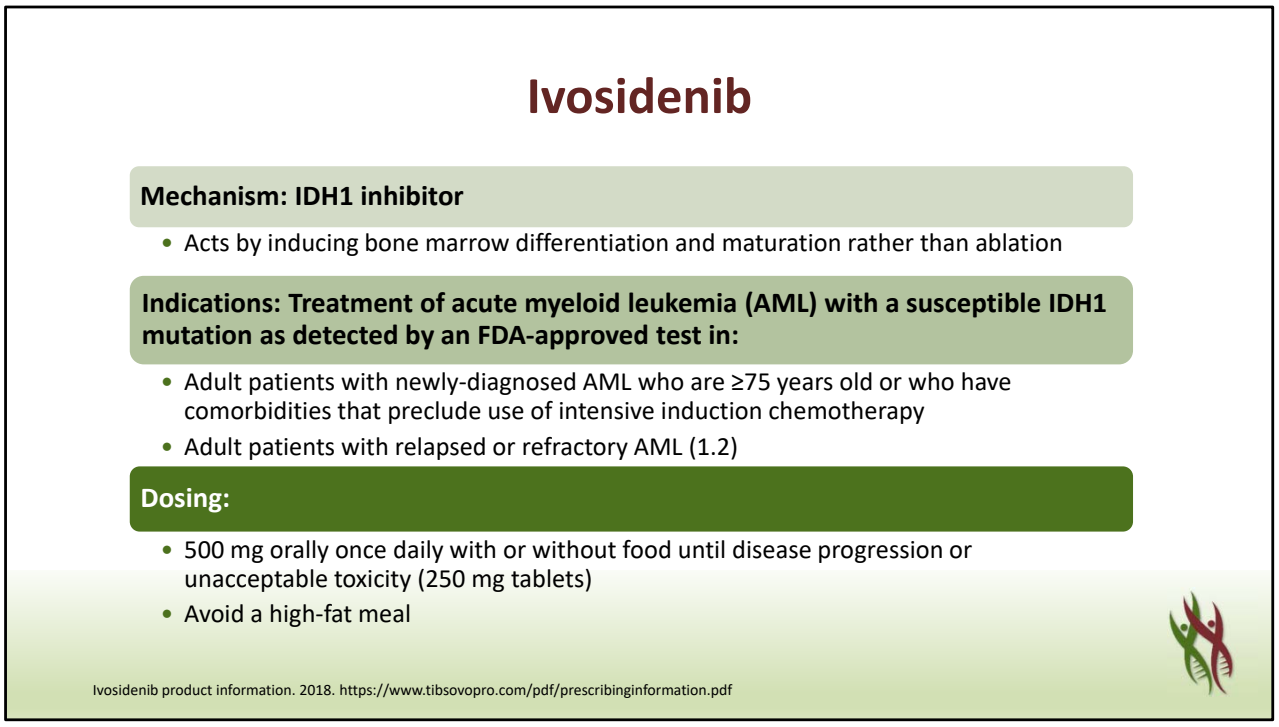

Then the IDH-1 inhibitor ivosidenib acts also by inducing bone marrow differentiation and maturation rather than ablation on a different target, so they are all in that same general pathway but different components of it. This is indicated for the treatment of acute myeloid leukemia with the susceptible IDH-1 mutation, again needing to achieve that through an FDA-approved test, and this is for adults with newly-diagnosed AML who are over the age of 65 or have comorbidities that preclude intensive induction therapy or with patients that have relapsed or refractory AML. Dosing is 500 mg once daily with or without food, again until disease progression or an acceptable toxicity. It is important to understand where we are using these kinds of agents, if there is an aberrant pathway with a mutation, in the absence of a hematopoietic stem cell transplant, specifically an allogeneic stem cell transplant, that aberrant pathway will persist and if we remove these drugs that are targeting these actionable targets, that aberrant pathway will resume and you will begin to see that abnormal function again, so that is the rationale behind until disease progression or unacceptable toxicity. Want to avoid taking this with a high-fat meal.

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Warning and certain precautions, you can see QT prolongation, rarely Guillain-Barre syndrome, so this is similar to the PRES syndrome that we talked about previously but very important to do these neurological assessments for patients, and if any of these signs and symptoms are present, you need to do a complete work-up including an MRI of the brain and discontinue therapy. Other adverse events very similar to what we have discussed with the other IDH inhibitor, and then laboratory abnormalities can be seen that indicate either the presence of tumor lysis or LFT elevation.

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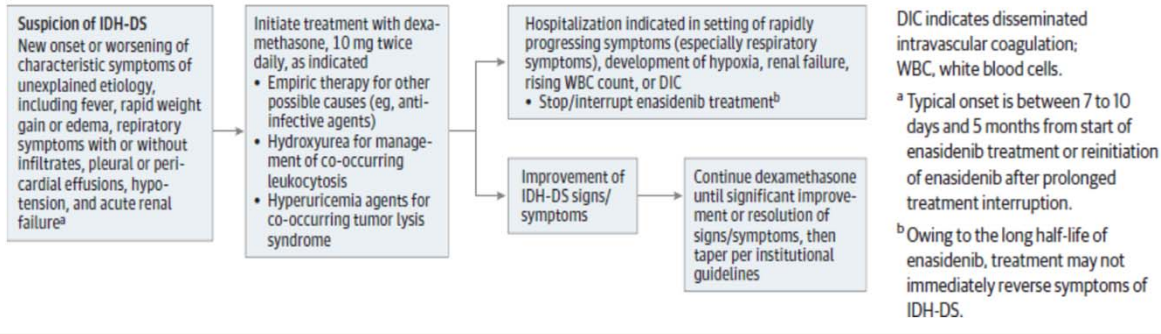
Differentiation Syndrome Review Committee Amended Protocol for Isocitrate Dehydrogenase Differentiation Syndrome (IDH-DS) Diagnosis and Management



Fathi AT, et al. *JAMA Oncol.* 2018;4(8):1106-1110.

Here's the differentiation syndrome, there was a review committee that basically identified the key features of this, and it is very important to familiarize yourself with the signs and symptoms for these patients if you are treating somebody on here. If in doubt we give steroids. This is the empiric therapy to overcome that process. It is important to understand that there are other things that can mimic this process, particularly infectious etiologies that may cause similar pulmonary symptoms, which is the primary concern here. These patients can also have a very rapid weight gain and symptoms of fluid overload, including pleural effusions and pericardial effusions. We want to watch these patients very, very carefully. You can see less commonly DIC, but that is something if they are having bleeding or bruising we are going to want to evaluate.

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IDH Differentiation Syndrome (IDH-DS)

- 11.7% (33/281) of study participants were identified as having possible or probable IDH-DS
  - Median age = 70 years (range, 38–80 years)
  - 60.6% were male
  - 39.4% (13/33) had concomitant leukocytosis
  - Other risk factors: >20% blasts, >1 prior therapy
- Median time to onset = 30 days (range, 7-129 days)
- Most frequent manifestations
  - Dyspnea
  - Fever
  - Pulmonary infiltrates
  - Hypoxia
- Enasidenib dosing was interrupted for 15 patients (45.5%), but permanent discontinuation of treatment was not required

Fathi AT, et al. *JAMA Oncol.* 2018;4(8):1106-1110.

In IDH-associated differentiations, IDH inhibition differentiation syndrome, 11.7% of study participants basically showed that this was likely the cause, so there are a lot of other reasons people may have these symptoms, very important to understand that because if this is not truly differentiation syndrome, we want to continue to give them their IDH inhibitor therapy, so very important to understand this phenomena, get the appropriate diagnosis, provide aggressive supportive care, and understand if this is truly the case, can they continue their IDH inhibition therapy with concurrent steroids? The other thing that is really important is those steroids need to be continued until this is completely resolved. You do not want to give them just a burst of steroids and then abruptly stop because if this is differentiation syndrome, those cells are already in that process and it may take a while for this to resolve. So very important to look at the duration of steroid therapy.

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Gemtuzumab Ozogamicin

- Mechanism: anti-CD33 monoclonal antibody-drug conjugate with calicheamicin
- Indications: treatment of newly diagnosed CD33-positive AML in adults and treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older
- Dosing: premedicate with corticosteroid, acetaminophen, diphenhydramine

Newly diagnosed, de novo AML (combination regimen)	Newly diagnosed AML (single-agent regimen)	Relapsed or refractory AML (single-agent regimen)
• Induction: 3 mg/m^2 (up to one 4.5 mg vial) on days 1, 4, and 7 in combination with daunorubicin and cytarabine • Consolidation: 3 mg/m^2 on day 1 (up to one 4.5 mg vial) in combination with daunorubicin and cytarabine	• Induction: 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8 • Continuation: for patients without evidence of disease progression following induction, up to 8 continuation courses of 2 mg/m^2 day 1 every 4 weeks	• 3 mg/m^2 on days 1, 4, 7

Gemtuzumab ozogamicin product information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761060lbl.pdf

Then we talked about the GO regimen or gemtuzumab ozogamicin. This is a drug that we used years ago and then it was taken off the market for a period of time because we did not really understand the adverse event profile. This is an anti-CD 33 monoclonal antibody. It is a conjugate, so it is conjugated with calicheamicin, which is sort of the carrier molecule if you will, and this is indicated for patients with newly-diagnosed CD33 positive AML in the relapsed/refractory setting or in the newly diagnosed population. It is also approved for pediatric patients 2 years and older. These patients, it is monoclonal antibodies, so all of the principles of monoclonal antibodies apply, so premedication to avoid hypersensitivity reactions, and you can see the dosing here for induction and consolidation, and some difference in the regimens that we use for newly diagnosed and relapsed/refractory patients.

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Gemtuzumab Ozogamicin Safety Considerations

- **Warnings and precautions**
  - Hepatotoxicity, including severe or fatal hepatic VOD, aka sinusoidal obstruction syndrome
  - Infusion-related reactions (including anaphylaxis); monitor patients during and for at least 1 hour after the end of the infusion; interrupt the infusion, administer steroids or antihistamines, or permanently discontinue treatment as necessary
  - Hemorrhage: severe, including fatal, hemorrhage may occur at recommended doses; monitor platelet counts frequently
- Common adverse events (>15%): hemorrhage, infection, fever, nausea, vomiting, constipation, headache, increased AST, increased ALT, rash, and mucositis
  - Grade 3/4 adverse reactions (≥20%): fatigue, thrombocytopenia, neutropenia, infection, anemia, febrile neutropenia

Fathi AT, et al. *JAMA Oncol.* 2018;4(8):1106-1110.

It also has warnings and precautions, one of the big things that we saw in the early clinical trials was hepatotoxicity, in particular people who have had a previous bone marrow transplant they may have developed veno-occlusive disease and so hepatic failure can be seen, so very important to know what was their prior therapy and have they had a prior allogeneic stem cell transplant. We talked about hypersensitivity reactions. This is a monoclonal antibody and in some patients, hemorrhage was seen, including fatal hemorrhage, and as so with any patient with AML who develops thrombocytopenia or has a risk of developing DIC, we need to pay particular attention to bleeding risk. Other than that we talked about LFT elevation and hepatotoxicity, but you can also see a rash, fever, nausea, and vomiting.

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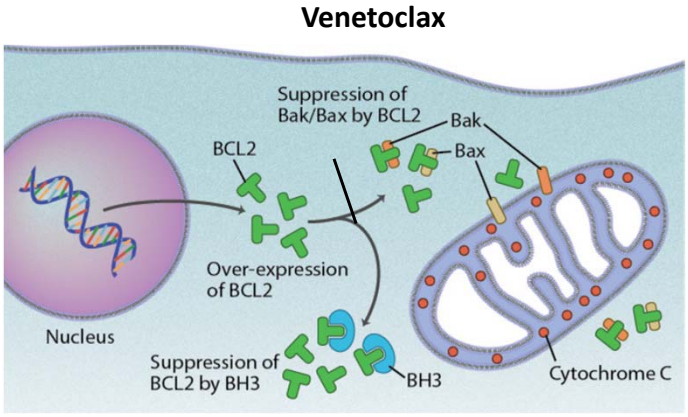
BCL-2 Inhibition in AML: Venetoclax

- Venetoclax is a highly selective, orally bioavailable BH3 mimetic that specifically targets BCL-2, but lacks affinity for BCL-XL and MCL-1
- BCL-2 proteins play a critical role in mitochondrial mediated apoptosis
- BCL-2 is overexpressed in AML
- AML cells are primed for BCL-2 inhibition



Cassier PA, et al. *Br J Cancer.* 2017;117(8):1089-1098.; Original illustration by David Baker, from Kurtin S, et al. *JADPRO* 2017 in print.

The next group of drugs are BCL-2 inhibitors in AML. This is a very recent development, specifically here venetoclax. We know that BCL-2 plays a role in hematopoietic development and that the overexpression of BCL-2 is associated with apoptosis or programmed cell death, and so BCL-2 is in the mitochondria of the cell. It happens to be overexpressed in AML and so it makes sense that these cells are primed for BCL-2 inhibition.

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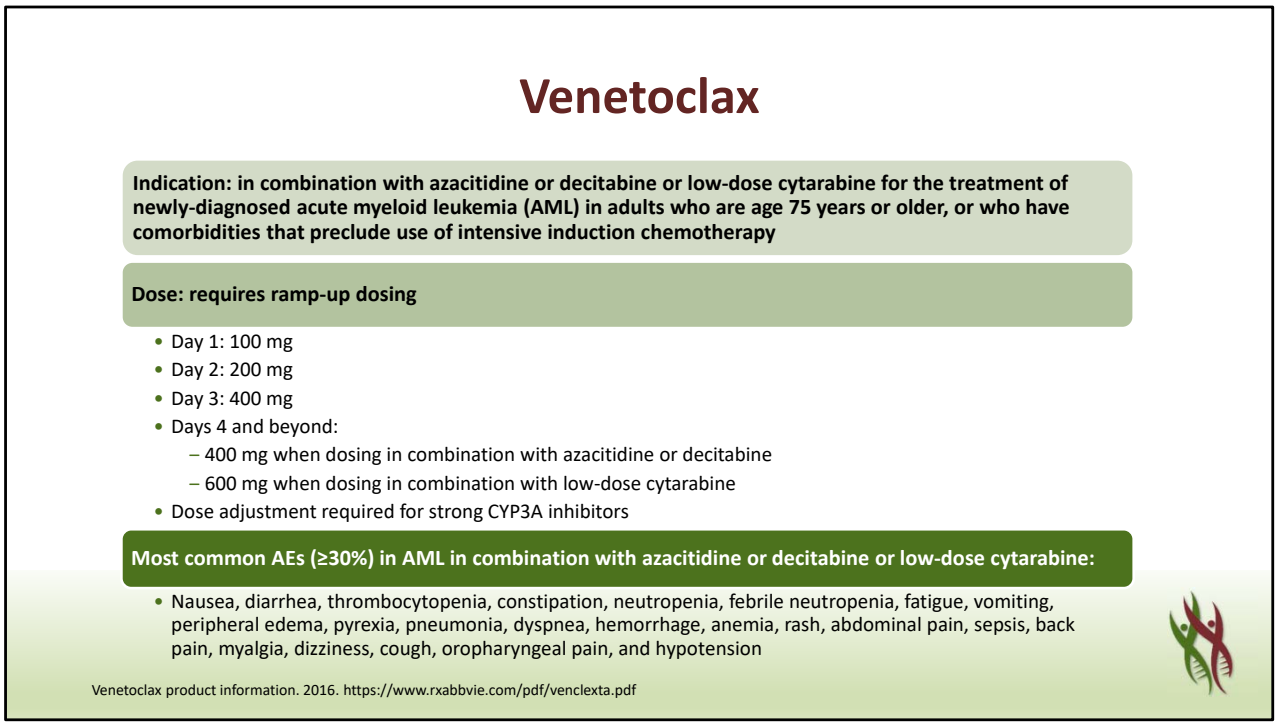

Venetoclax is an oral compound. We have used this in a number of other hematopoietic malignancies but this is approved in combination with the hypomethylating agent, either azacitidine or decitabine, or low-dose cytarabine for either newly-diagnosed patients with AML over the age of 75 who are not eligible for induction therapy or stem cell transplant. This ramped up dosing is very different than the ramped up dosing we use for our lymphoid malignancies where we use this compound, so you basically are going to do day 1, 2, 3 by incremental increase from 100, 200 to 400 which is the final dosing. There is indication for a 600 mg dosing when used with low-dose cytarabine. Very important that there are significant drug-drug interactions, again particularly with antifungal agents that may be commonly used with AML patients, FF and so we need to really rethink what we are doing, if we are not using a purine analog like high-dose Ara-C or 7+3, we are going to have to really figure out do we really need to have an antifungal drug on hand. If that is necessary, then you would not ramp up to these higher doses because the compound becomes too toxic and people develop severe cytopenias. Some of the other toxicities associated with venetoclax include GI toxicities. You again can see a rash, you may see bone pain, and then other things that are common in these patients who may develop infections.

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Venetoclax Safety Considerations

Warnings and precautions

- Tumor lysis syndrome (TLS): anticipate TLS; assess risk in all patients
- Neutropenia: monitor blood counts and for signs of infection; manage as medically appropriate.
- Infections: monitor for signs and symptoms of infection and treat promptly
- Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment

Venetoclax product information. 2016. https://www.rxabbvie.com/pdf/venclexta.pdf

Warnings and precautions, again tumor lysis syndrome, particularly in anybody that has a high blast count or a high white blood cell count. Most of the time patients with AML-MRC, people that have antecedent myeloid malignancies, most of those patients actually present with cytopenias and this is less of a concern but it is not a risk of 0, so you need to assess those patients carefully. Again cytopenias may be significant in these patients and dose modification may be required. They are going to be at increased risk for infections because we are suppressing BCL-2, F which also has to do with the normal development of B-lymphocytes which provide us humoral immunity. This can have a teratogenicity associated with it, so embryo fetal risk, and we are going to have to counsel patients on that.

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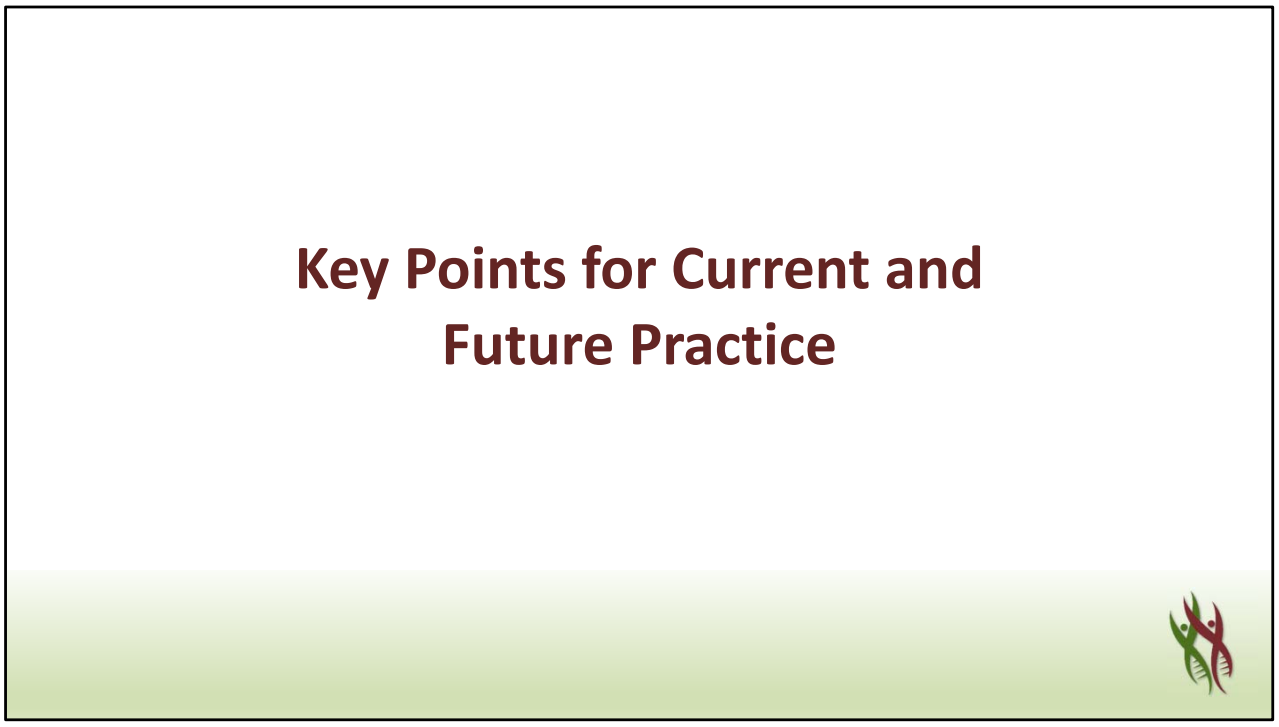

Key points for current and future practice.

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Clinical Challenges and Best Practice

- Selection of the best therapy for the individual patient
  - Requires appropriate testing to allow risk stratification
  - Access to drugs on time
- Outpatient management and monitoring
- Preserving future treatment options
  - Managing comorbidities
  - Limiting severity of AEs
- Adverse events – new but old
- Time to best response – shifting paradigms
- Treatment of the older AML patient

We have to be very specific in the diagnostic process so that we can risk-stratify patients and really choose the best therapy based on their individual disease characteristics. We want to be sure that we access drugs in a timely manner, and again we saw a variety of dosing regimens that can be used. Some of these are oral compounds, many remain injectable drugs. If we can we need to try to do outpatient management as much as possible, but there are very specific criteria that need to be met for outpatient management of these patients. Always one of our goals is to preserve future treatment options and we do this by managing comorbidities, so for instance if we are giving them an anthracycline-containing regimen we are going to want to make sure that we are monitoring ejection fraction and the presence of anti-cardiotoxicity. Similarly, if there are hepatotoxicity or renal toxicity associated with treatment, we need to carefully monitor this so that this does not exclude them from having drugs that are cleared through a hepatic or renal pathways. The adverse events, some of these are things we have known for a long time, those of you that have been in practice a long time may be familiar with some of these toxicities such as differentiation syndrome, for instance, from other compounds, and we need to reapply those principles to the current therapy. Time to best response, we talked about the liposomal compound CPX-351 where that day-14 and day-28 paradigm really does not apply and we need to rethink our expectations for bone marrow recovery so that we are not changing therapy prematurely and we are treating people in the best way possible, given the mechanism of action of the individual drug, and then very specifically, how best to treat the older patients or frail patients with AML, understanding that many of these people have antecedent myeloid malignancies and standard approaches to therapy like 7+3 are not likely to provide benefit.

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Where to Go From Here? Emerging Therapies

Drug	Targets/Pathways
Olutasidenib	IDH type 1
Vorasidenib	IDH type 1 and 2
Vismodegib	Inhibition of Smoothened (SMO)
Sonidegib	Inhibition of Smoothened (SMO)
Taladegib	Inhibition of Smoothened (SMO)
Guadecitabine	Inhibition of DNA methyltransferase
Rigosertib	Ras/Raf/MAPK Pathway inhibitor
Pevonedistat	Selective NEDD8 inhibition
Panobinostat	HDAC inhibitor
APR-246	Tp53
Idasanutlin	Mdm2
Milademetan	Mdm2

Dohner H, et al. *Blood.* 2017;129(4):424-447.; Gurnari C, et al. *Cancers.* 2020;12(2):357.

So where do we go from here? There are a number of emerging therapies, all of these are based on ongoing clinical trials. There are some novel targets being explored like smoothened, or SMO for instance, the RAS/RAF and map kinase pathways. There are NEDD8 inhibitors that are being explored, and then MDM2 inhibition using either some of these newer compounds that are in clinical trials. So we always want to consider a clinical trial for patients, this is how we have come to have all of the drugs that are currently available, and so if patients are eligible for a clinical trial that is always a consideration.

Thank you for joining me for this presentation. I hope this information will be useful to you in the care of your patients.

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