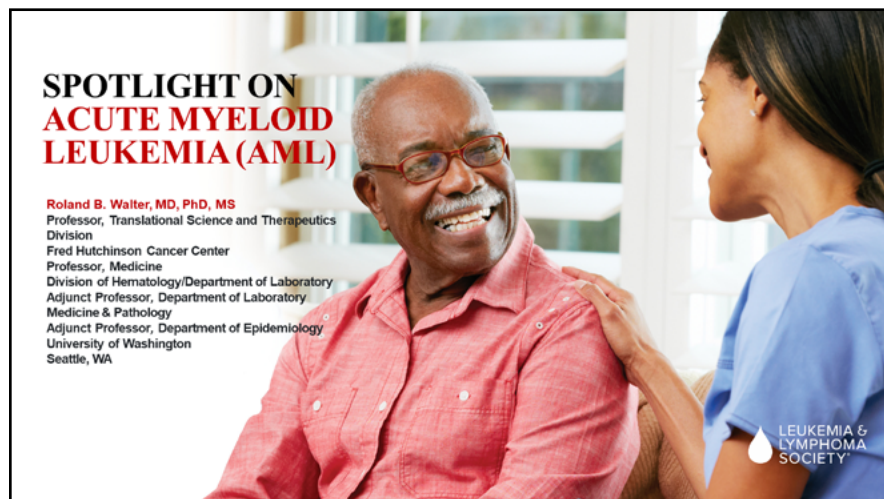


Spotlight on Acute Myeloid Leukemia (AML)

April 26, 2023 **Speaker:** Roland B. Walter, MD, PhD, MS



Slide 1: SPOTLIGHT ON ACUTE MYELOID LEUKEMIA (AML)



Slide 2: WELCOMING REMARKS


Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society I would like to welcome all of you. Thank you all for joining us today.


LLS helps you navigate cancer treatment and ensures that you or your loved one has access to quality, affordable, and coordinated care. The need for new treatments for AML (acute myeloid leukemia) remains urgent, which is why LLS has invested approximately one-quarter of its research dollars annually in AML, reaching more than \$142 million over the past decade. Please continue to inform us of what you need during this time and please continue to let us be there for you.

And now Steve Buechler, who was diagnosed with AML in 2016, will share some of his story with us.

WELCOMING REMARKS
SPOTLIGHT ON ACUTE MYELOID LEUKEMIA



Steve Buechler
Acute Myeloid Leukemia (AML Survivor)
Podcast Guest, *The Bloodline with LLS*
Author, *How Steve Became Ralph*
Facilitator, *Pen My Path* Writing Workshops through [LLS Community](#)



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Slide 3: WELCOMING REMARKS

Steve Buechler:

Hello. My name is Steve Buechler and I would like to welcome all of you to today's program. I'm an AML survivor. In June of 2016 I was asymptomatic, but a routine physical exam showed that my white blood cell count was dangerously low. That triggered a bone marrow biopsy that revealed AML. In 48 hours, I went from feeling perfectly fine to intensive treatment for a lethal disease. I was rushed into treatment with induction chemotherapy and a 37-day hospital stay. But it got me into remission.

That bought me time to consider options and receive a double umbilical cord blood transplant in October of 2016. Nothing about it was easy, but I hit the treatment trifecta: remission with first induction, full donor engraftment within 3 weeks, and no graft-versus-host disease. My oncologist called me a statistical outlier, but her sweet words meant even more when she proclaimed this is as good as it gets.

And now, 6½ years out, fully recovered, and considered cured. That outcome has prompted me to pay it forward as a multifaceted volunteer, patient advocate, writing workshop instructor, and author in the cancer community. Through that volunteering, I found LLS to be a tremendously valuable resource for blood cancer patients.

This month on April 21st, we celebrated AML World Awareness Day, the one day of the year when people from across the world raise awareness of AML. To bring more awareness, I was featured on an LLS podcast episode that was released in honor of AML World Awareness Day. Be sure to learn more about AML and my story on LLS's patient podcast, *The Bloodline with LLS*. Look for the title, *Healing Through Writing, an Odyssey Through Acute Myeloid Leukemia*.

LLS has been at the front of the fight to cure cancer. They've invested nearly \$1.6 billion in research. The need for new treatments for AML remains urgent, which is why The Leukemia & Lymphoma Society has invested approximately one-quarter of its research dollars annually in the disease, more than \$100 million over the past decade.

Our understanding of the molecular basis for AML has dramatically improved over the past 10 years. This knowledge, along with technological improvements in new therapeutic approaches for cancer, is changing the outcome for patients with AML for the better.

Thank you for joining today's program. We are fortunate to have an esteemed key opinion leader to provide us all with important updates as to new therapies and how we and our caregivers can look to have a good quality of life.

Spotlight on Acute Myeloid Leukemia (AML)


April 26, 2023 **Speaker:** Roland B. Walter, MD, PhD, MS

I will now turn the program back to you, Lizette.

Ms. Figueroa-Rivera:

Thank you, Steve, for sharing. And to hear more about his story please listen to his podcast episode on *TheBloodline.org*, as well as through his book, which is filled with life lessons and living and thriving with cancer.

We'd like to acknowledge and thank AbbVie Inc. and Bristol Myers Squibb for their support.



FACULTY
SPOTLIGHT ON ACUTE MYELOID LEUKEMIA (AML)



Roland B. Walter, MD, PhD, MS
Professor, Translational Science and
Therapeutics Division
Fred Hutchinson Cancer Center
Professor, Medicine
Division of Hematology/Department of Laboratory
Adjunct Professor, Department of Laboratory
Medicine & Pathology
Adjunct Professor, Department of Epidemiology
University of Washington
Seattle, WA



Slide 4: FACULTY

Ms. Figueroa-Rivera:

It is my pleasure to introduce Dr. Roland B. Walter from the Fred Hutchinson Cancer Center and the University of Washington in Seattle, Washington, who will be discussing the advances in acute myeloid leukemia.

Dr. Walter, I'm privileged to turn the program over to you.



 Fred Hutch
Cancer Center

**Spotlight on
Acute Myeloid Leukemia (AML)**

Roland B. Walter, MD PhD MS

UW Medicine

Slide 5: SPOTLIGHT ON ACUTE MYELOID LEUKEMIA (AML)

Dr. Roland Walter:

Thank you very much. Good morning, everyone. It's a real pleasure and honor to spend this hour with you today and discuss the recent developments in the treatment of AML.

Disclosures

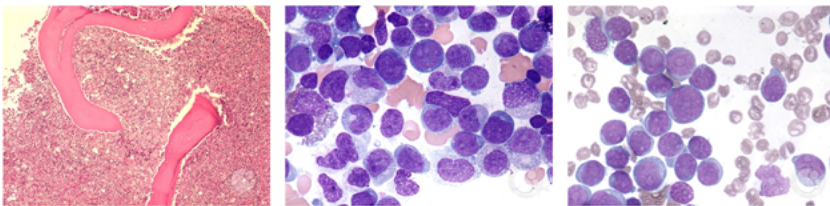
- Laboratory research support: Celgene, ImmunoGen, Janssen, Pfizer
- Clinical trial support: Amgen, Aptevo, ImmunoGen, Janssen, Jazz, Kura, MacroGenics
- Consultancy: Abbvie, Adicet, Amphivena, BerGenBio, Bristol Myers Squibb, GlaxoSmithKline, ImmunoGen, Kura, Orum

Slide 6: DISCLOSURES

My disclosures for laboratory research support, clinical trial support, and consulting, mostly done in the area of AML, are summarized on this slide.

Acute myeloid leukemia (AML)

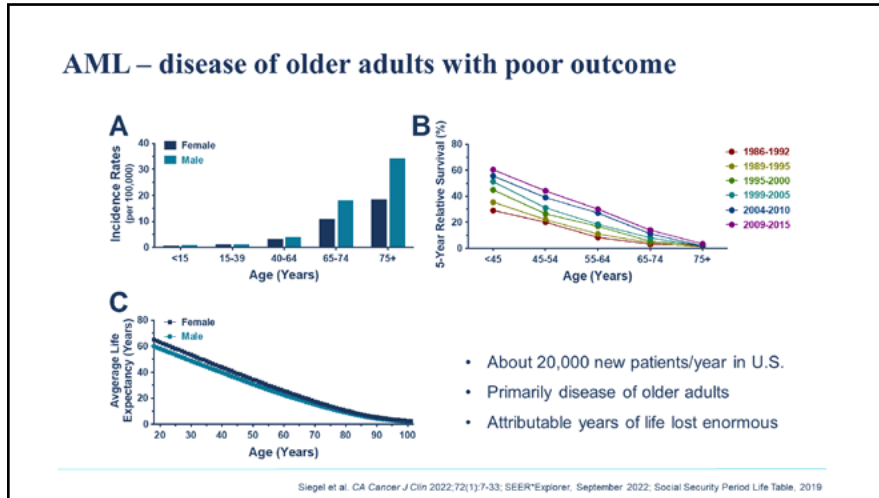
- Diverse group of aggressive blood cancers
- Cells defective in maturation, accumulate at various stages of incomplete maturation/function
- AML cells interfere with production of normal blood cells
 - Weakness/fatigue, infection, bleeding



Images: American Society of Hematology Image Bank

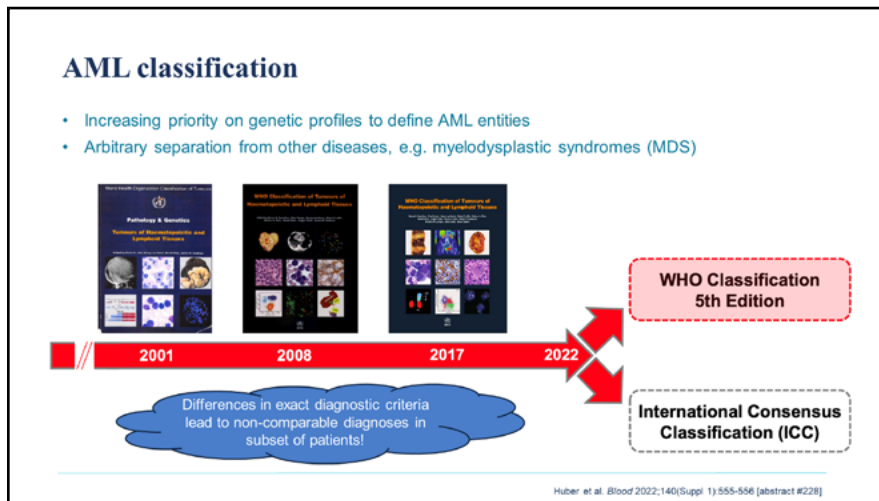
Slide 7: ACUTE MYELOID LEUKEMIA (AML)

We now understand that what we call AML really encompasses a diverse group of aggressive blood cancers. They all have in common that they stem from very early white blood cells that go awry and lose their ability to mature normally and accumulate in the bone marrow, blood, and sometimes other tissues. The leukemia cells interfere with the production of normal blood cells, which then manifests as weakness, fatigue, susceptibility to infection, and bleeding, and occasionally simply leads to an overwhelming accumulation of leukemia cells, all problems that can be life-threatening and ultimately life-limiting.



Slide 8: AML – DISEASE OF OLDER ADULTS WITH POOR OUTCOME

About 20,000 patients face a new diagnosis of AML per year in the United States. AML can occur at any age but is primarily a disease of older individuals. The likelihood of being a long-term survivor after a diagnosis of AML increases with increasing age. With poor outcomes even today, individuals older than age 60 or so, a very substantial number of years of life are lost when you compare survival expectation of older adults with AML with the average life expectancy of healthy people of the same age living in the United States. Just as one example, the typical life expectancy of a person diagnosed with AML around age 70 is measured in months, whereas an average 70-year-old person is predicted to live for another 15 years or so.



Slide 9: AML CLASSIFICATION

The pathologists help us classify AML and distinguish AML from other blood disorders. The separation is not always clear and clean. In many instances the boundaries used to separate AML from other disorders are arbitrary and are changing over time. Many years ago, the diagnosis of AML was primarily based on the shape and staining characteristics of cells under the microscope. More and more different subtypes of AML are classified based on genetic profiles.

A new headache for us is that in 2022 two separate classification systems have been introduced, although similar, but are not identical. Hopefully, we can resolve this before it causes too many problems for patients and care providers alike.

European LeukemiaNet (ELN) genetic risk classification

Increasing complexity with refinements from genetic data

ELN 2010 ¹		ELN 2017 ²		ELN 2022 ³	
Genetic group	Subsets	Risk category ^a	Genetic abnormality	Risk category ^a	Genetic abnormality
Favorable	t(8;21)(q22;q22): RUNX1-RUNX1T1 inv(16)(p13;q22) or t(16;16)(p13;q22): CBFB-MYH11 Mutated NPM1 without FLT3-ITD (normal karyotype) Mutated CEBPA (normal karyotype)	Favorable	t(8;21)(q22;q22): RUNX1-RUNX1T1 inv(16)(p13;q22) or t(16;16)(p13;q22): CBFB-MYH11 Mutated NPM1 without FLT3-ITD or with FLT3-ITD ^{b,c} Biallelic mutated CEBPA	Favorable	<ul style="list-style-type: none"> • t(8;21)(q22;q22): RUNX1-RUNX1T1 • inv(16)(p13;q22) or t(16;16)(p13;q22): CBFB-MYH11 • Mutated NPM1 without FLT3-ITD • NPM1 alone mutated CEBPA
Intermediate ^d	Mutated NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 and FLT3-ITD (normal karyotype)	Intermediate	Mutated NPM1 and FLT3-ITD ^{b,c} Wild-type NPM1 without FLT3-ITD or with FLT3-ITD ^{b,c} (without adverse-risk genetic lesions) t(9;11)(p21;q23.3): MLL3-KMT2A2 t(9;22)(q34;q11): DEK-NUP214	Intermediate	<ul style="list-style-type: none"> • Mutated NPM1 with FLT3-ITD • Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions) • t(9;11)(p21;q23.3)/MLL3-KMT2A2 • t(9;22)(q34;q11)/DEK-NUP214 • Cyto-genetic and/or molecular abnormalities not classified as favorable or adverse
Intermediate ^e	t(8;11)(p22;q23): MLL3-MLL Cytogenetic abnormalities not classified as favorable or adverse ^f	Adverse	t(8;11)(p22;q23): MLL3-MLL t(9;22)(q34;q11): DEK-NUP214 t(1;1)(q23;q23): KMT2A rearranged t(9;22)(q34;q11): BCR-ABL1 inv(3)(q26;q29) or t(3;21)(q26;q21): GATA2-MECOM1/1 -5 or del(5q) -7, del(17q): complex karyotype Mutated ASXL1 Mutated TP53	Adverse	<ul style="list-style-type: none"> • t(8;11)(p22;q23): MLL3-MLL • t(9;22)(q34;q11)/DEK-NUP214 • t(1;1)(q23;q23)/KMT2A rearranged^g • t(9;22)(q34;q11)/BCR-ABL1 • t(3;21)(q26;q29)/GATA2-CREBBP • inv(3)(q26;q29) or t(3;21)(q26;q29)/GATA2-MECOM1/1 • t(5q) del(5q) -7, -17 del(17q): complex karyotype^h • Mutated ASXL1, BCR, EDN2, RUNX1, SF3B1, SRSF2, STAG2, UDAF1, and/or ZNF921 • Mutated TP53

¹Döhner et al. Blood 2010;115(3):453-474. ²Döhner et al. Blood 2017;128(4):424-447. ³Döhner et al. Blood 2022;140(12):1345-1377

Slide 10: EUROPEAN LEUKEMIANET (ELN) GENETIC RISK CLASSIFICATION

Different subtypes of AML respond differently to therapy and have different prognoses. On an individual patient level, our ability to predict exactly what will happen is unfortunately far from perfect, even today. That said, our most helpful information regarding prognosis comes from the genetic makeup of the leukemia cells. As we learn more and more about genetic changes and how they affect response to therapy and prognosis, the risk classification schemes have become more and more complex. However, we still somewhat crudely put patients into 3 different risk categories: favorable, intermediate, and adverse, which is helpful to guide treatment decision-making, as we will discuss later.

Genetic predisposition – increasingly recognized

Important for: choice of donor for transplant, health surveillance strategies, relatives who share causative gene variant, etc.

- Should be considered for all patients regardless of age
- Increasing list of pathogenic and likely pathogenic gene variants
- Certain disorders associated with specific characteristics (e.g. platelet defects, organ dysfunction)
- Clinical features prompting consideration of testing for genetic predisposition:

Clinical features
Personal history of 2 cancers, 1 of which is a hematopoietic malignancy (skin does not count)
Personal history of a hematopoietic malignancy plus
<ul style="list-style-type: none"> • Another relative with two generations with another hematopoietic malignancy or • Another relative with two generations with a solid tumor diagnosed at age 50 or younger, or • Another relative with two generations with another hematopoietic malignancy
Presence of a hematopoietic gene variant in tumor profiling that could be a germline clone, especially if that variant is present during remission ^a
Age at diagnosis of hematopoietic malignancy at an earlier age than average (eg, MDS diagnosed < 40y)
Germline status of a variant is confirmed by
<ul style="list-style-type: none"> • No presence in 1000 Genomes or other sources not likely to undergo neutral selection frequency (eg, palindromic ATRX deletions on chr 16) • Inclusion AND at a variant allele frequency consistent with the germline (generally concordant between 2x10⁶ and 10⁷) • No presence in at least two relatives of a variant allele frequency consistent with the germline

- Testing may require culture, genetic testing of skin cells

Döhner et al. Blood 2022;140(12):1345-1377

Slide 11: GENETIC PREDISPOSITION – INCREASINGLY RECOGNIZED

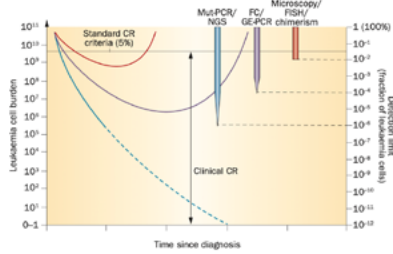
As a result of the increasing understanding of the genetic changes that underlie AML, we now know that the subset of the patients diagnosed with AML, perhaps 10 or 15%, have a genetic predisposition. This is important for the care of these patients. For example, for the decision who to choose as a donor for a transplant and to come up with the best health surveillance strategies and may be important for relatives who might share similar genetic changes in their DNA and might also be at higher than average risk of developing AML or other cancers.

We think of genetic predisposition particularly strongly if patients present at relatively young age, but it really can affect patients across the entire age range. Besides age, the concern may come up because of other abnormalities that are found on physical exam or because of a suspicious family history.

Treatment response assessment

Provides important prognostic information, guides further treatment decision making

- Traditional gold standard:** microscopic assessment of blood and bone marrow
 - Many patients achieving "complete remission (CR)" relapse
- Increasingly used:** measurable residual disease (MRD) testing
 - Detects AML cells below microscopy threshold
 - Improves prognostication, outcome prediction



Hourigan & Karp. Nat Rev Clin Oncol 2013;10(8):460-471

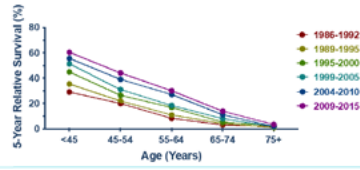
Slide 12: TREATMENT RESPONSE ASSESSMENT

Essential for the care of patients with AML is the assessment of how a particular treatment works. Traditionally, this is assessed on bone marrow and blood samples via microscope. However, it is known for a very long time that achievement of a remission, a state when we can no longer find leukemia cells with the microscope, is not the same as being cured. In other words, the microscope is not good enough to find relevant leukemia cells, and this is depicted on the cartoon where you can see that the patient can have very substantial amounts of leukemia cells left, yet we cannot see them any more with the microscope.

This has sparked interest in methodologies that can detect leukemia cells in situations where the microscope fails. Several methods are now available for the testing of what is called measurable residual disease or MRD. MRD testing, while it has its own challenges, is increasingly important as it improves our ability to risk stratify patients and to predict outcomes.

AML therapy over time: until ~5 years ago

- Begin of modern AML treatment era in 1973** (introduction of "7+3")
- Relatively simple treatment algorithm**
 - Medically fit ("younger") -> cure possible: induction chemotherapy, choice of post-remission therapy
 - Medically unfit ("older") -> cure not possible: low-intensity chemotherapy or best supportive care
- Highly variable outcomes**
- Slow outcome improvements** with advances in supportive care and hematopoietic cell transplantation



Data source: <https://seer.cancer.gov/csr/previous.html>

Slide 13: AML THERAPY OVER TIME: UNTIL ~5 YEARS AGO

Now that we've covered some of the basics of AML diagnosis, risk stratification, and prognosis, let's talk about AML therapy.

The modern era of AML therapy started 50 years ago with the introduction of a 2-drug chemotherapy called 7+3.

The treatment algorithm has been simple and largely unchanged until about 5 years ago. For medically fit patients, cure was considered possible and treatment was given with intensive chemotherapy with or without a transplant. For medically unfit patients, on the other hand, cure was not felt possible and either low-dose chemotherapy, such as low-dose cytarabine or azacitidine or decitabine, was given or treatment was focused entirely on supportive care. With improvements in the latter and more widespread use of transplants, outcomes have nonetheless gradually improved over the years, at least for younger patients.

Induction chemotherapy for fit adults with AML

- **Most common: "7+3" chemotherapy**
 - Cytarabine (intermediate dose) x 7 days, anthracycline (daunorubicin, idarubicin) x 3 days
 - Typically given inpatient (~1 month hospital stay) for monitoring, supportive care
 - Side effects: nausea/vomiting, loss of appetite, mouth sores, diarrhea/constipation, low blood counts (bleeding, fever/infections)
 - **Alternative: high-dose cytarabine-based therapies (e.g. FLAG-Ida, CLAG-M)**
 - Slightly more efficacious than 7+3
 - Slightly more toxic than 7+3
 - Fewer relapses but similar overall survival compared to 7+3
- ❖ Goal: induction of complete remission

Döhner et al. Blood 2022;140(12):1345-1377

Slide 14: INDUCTION CHEMOTHERAPY FOR FIT ADULTS WITH AML

Even today, 7+3 remains the most widely used intensive chemotherapy regimen for AML. It uses one drug, cytarabine, for 7 days and a second drug for 3 days. Because of the need for close patient monitoring and supportive care, including frequent use of blood and platelet transfusions, patients receive this treatment typically in the hospital and remain there for about a month or so until the blood counts recover.

Besides low blood counts and associated risks, like bleeding and infection, other typical side effects are nausea/vomiting on occasion, loss of appetite, mouth sores, and diarrhea or constipation.

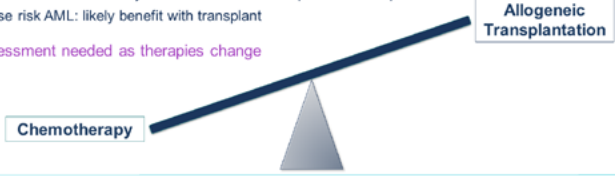
There are alternatives available to 7+3, those are slightly more intense, like FLAG-Ida. Compared to 7+3, many studies have shown that such regimens are perhaps slightly more efficacious, but they're also slightly more toxic. As a result, while relapses are less common, overall survival appears similar to what is obtained with 7+3, and because of that, these more intense regimens have not really replaced 7+3 so far.

The hope is that intensive chemotherapy induces a remission, which is obtained in 60 to 80% of younger adults and 40 to 60% of older adults with newly diagnosed AML.

Post-remission (“consolidation”) therapy in AML

Additional chemotherapy vs. allogeneic hematopoietic cell (“bone marrow”) transplantation?

- Balancing risks and benefits for optimal outcome
 - Transplantation: more effective in preventing AML relapse, higher risk of short- and long-term toxicities
- Question: are risks with transplantation worth the benefit of better disease control?
 - Favorable risk AML: likely no benefit with transplant if good response to chemotherapy
 - Intermediate risk AML: likely some benefit with transplant in some patients
 - Adverse risk AML: likely benefit with transplant
- ❖ Re-assessment needed as therapies change



Slide 15: POST-REMISSION (“CONSOLIDATION”) THERAPY IN AML

Achievement of a complete remission is not the same as being cured and additional therapy is required to reduce the risk of AML relapse. This is typically done with additional courses of chemotherapy or the use of a transplant. What strategy leads to best outcomes depends on the type of AML. Transplant is more effective in preventing disease relapses than additional chemotherapy but is also more toxic in the short and the long run. Thus the question the patient and the physician have to answer is whether the risks with transplant are worth the benefit of better disease control. Very crudely speaking, for patients with favorable risk AML, there is likely no benefit with a transplant in first remission if there was a good response to induction chemotherapy. On the other hand, for patients with adverse risk AML, there is likely benefit with transplant. For patients with intermediate risk AML, there may be some benefit with transplant, although the magnitude of the benefit may be relatively small.

Treatment of relapsed/refractory AML

Area of great unmet medical need

- Overall poor outcomes with currently available therapies, especially if
 - Short remission duration, older age, non-favorable cytogenetic risk, prior allogeneic transplant
- Many conventional chemotherapy regimens available, no clear “winner”
- Molecular re-evaluation important to identify actionable mutations
- If treatment successful, strongly consider allogeneic transplant
 - Only cure for primary refractory AML, best chance of cure for relapsed AML

➢ PLEASE CONSIDER PARTICIPATION IN CLINICAL TRIALS TESTING NEW THERAPIES

Slide 16: TREATMENT OF RELAPSED/REFRACTORY AML

Relapse in AML occurs relatively early, typically within 3 to 5 years after achieving a remission, but sometimes within just a matter of months. The earlier the relapse, the more difficult the relapse is to treat. Many chemotherapy regimens have been used for people with AML that has relapsed or has not responded to initial chemotherapy in the first place, which is what’s called a refractory AML, but none of these therapies was found better than any others.

Finding a targetable mutation with one of the newly approved drugs we will talk about very soon can be helpful. And transplantation plays an important role as potentially curative treatment. All in all, however, there are great unmet

needs for people with relapsed or refractory AML. With this, this is an area where many clinical trials that test new drugs exist and we often consider participation in clinical trials as the best possible treatment option, given how often currently available treatments do not work.

AML therapy over time: last ~5 years

- **Approval of 10 new drugs since 2017**
- **Substantially increased treatment options**
 - Outcomes may improve incrementally
- **Treatment algorithms are changing**
 - Blurrier line between intensive and non-intensive therapy
 - Blurrier line between “curative” and “palliative” therapy
- ❖ **Treatment decision-making has become more nuanced/complex**

Slide 17: AML THERAPY OVER TIME: LAST ~5 YEARS

The treatment of AML has dramatically changed in the last 5 years with approval of 10 new drugs. These drugs have substantially increased our treatment options and, as I will show you, led to some improvements in outcomes in some instances over what can be accomplished with 7+3 or low-dose standard chemotherapy.

With these new drugs now available, the lines between intensive and non-intensive therapy and between curative and palliative therapy have become blurrier, and treatment decision-making has become a lot more complex.

Shared decision-making

Information exchange between patient and clinicians to decide on right choice for this individual in that specific situation

- **Unique challenges for patients with AML**
 - Little warning about illness
 - Requirement for urgent treatment initiation, prolonged hospitalizations
 - **Difficulty processing information on prognosis, treatment**
- **In busy clinical environment, process not used well**
 - Time pressures, conflicting priorities
 - Lack of clinician training in how to operationalize in practice, information “broadcasting”
- **Various frameworks might help shared decision-making, e.g. “COD”**
 - “C”: emphasize/discuss that there is choice
 - “O”: list/describe the options
 - “D”: coming to decision

LeBlanc. Semin Oncol Nurs 2016;35(6):150958

Slide 18: SHARED DECISION-MAKING

Especially when there are several treatment options and there isn’t necessarily a medically right or wrong path, shared decision-making between the patient and the clinician becomes really important to find the right choice for this particular situation.

As you all know, there are unique challenges for patients with AML related to how unexpectedly the disease often presents and how quickly treatment decisions need to be made. The concept of shared decision-making is thought of

as the gold standard for decision-making for cancer patients today, but the research indicates that this process is not used very well for various reasons.

Several frameworks have been developed to help with shared decision-making. One example is COD where the C emphasizes that there is a choice to make, the O then describes the options that are available, and the D then concludes with the actual coming to a decision.

Newly approved drugs for AML since 2017


Drug	Drug class	Indication
CC-486	Oral formulation of azacitidine	• Adults with AML who achieved first CR/CRi after intensive chemotherapy and are unable to complete intensive curative therapy
CPX-351	Liposomal formulation of cytarabine/daunorubicin (IV)	• Adults with newly-diagnosed 1-AML, or AML with myelodysplasia-related changes
Enasidenib	Inhibitor of mutant IDH2 (oral)	• Adults with relapsed/refractory AML with IDH2 mutation
Gemtuzumab ozogamicin	CD33 antibody-drug conjugate (IV)	• Adults with newly-diagnosed CD33+ AML • Adults and children age ≥2 with relapsed/refractory CD33+ AML
Gilteritinib	2 nd generation tyrosine kinase inhibitor (oral)	• Adults with relapsed/refractory FLT3-mutated AML
Glasdegib	Inhibitor of hedgehog signaling pathway (oral)	• With low-dose cytarabine for adults ≥75 years or if unfit for intensive chemotherapy
Ivosidenib	Inhibitor of mutant IDH1 (oral)	• Adults with relapsed/refractory AML with IDH1 mutation • Adults with newly diagnosed AML with IDH1 mutation if ≥75 years or unfit for intensive chemotherapy
Midostaurin	1 st generation tyrosine kinase inhibitor (oral)	• Adults with newly-diagnosed FLT3-mutated AML, with cytarabine/daunorubicin induction and cytarabine consolidation
Olotasidenib	Inhibitor of mutant IDH1 (oral)	• Adults with relapsed/refractory AML with IDH1 mutation
Venetoclax	Selective BCL-2 inhibitor (oral)	• With azacytidine/decitabine or low-dose cytarabine for adults ≥75 years or if unfit for intensive chemotherapy

Slide 19: NEWLY APPROVED DRUGS FOR AML SINCE 2017

Except for 2 drugs, CC-486 and CPX-351, all newly approved drugs are targeting agents either in the form of an antibody-based therapeutic or a small molecule inhibitor. My goal in the remainder of this presentation will be to describe the efficacy and side effect profiles of these 10 drugs and discuss how they are currently used in the treatment of patients with AML.

CD33-targeted immunotherapy

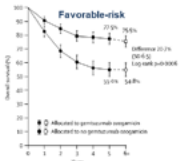
CD33: expressed on some AML blasts in almost all patients, possibly AML stem cells in some¹



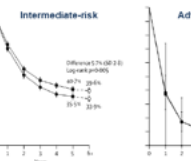
Gemtuzumab ozogamicin
CD33 antibody conjugated to potent toxin (calicheamicin-γ₁ derivative)

- Single agent activity in newly-diagnosed and relapsed/refractory AML²
- Reduces relapses, prolongs survival when added to intensive induction chemotherapy³

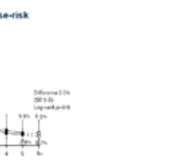
Favorable-risk



Intermediate-risk



Adverse-risk



• Side effects: infusion toxicities, severely low blood counts, liver toxicity (veno-occlusive disease/sinusoidal obstruction syndrome)

¹Walter et al. Blood 2012;119(26):6198-6208; ²Godwin et al. Leukemia 2017;31(9):1855-1865; ³Hills et al. Lancet Oncol 2014;15(9):988-996

Slide 20: CD33-TARGETED IMMUNOTHERAPY

Antibodies have long been pursued for AML therapy. Many of the efforts have focused on a cell surface protein called CD33 as target. This is because CD33 is expressed on at least some leukemia cells in almost all patients with AML. In some patients CD33 may also be displayed on underlying leukemia stem cells.

By far, the most tested CD33 targeted therapeutic is gemtuzumab ozogamicin or GO, an antibody drug conjugate

that is using a toxic calicheamicin derivative to kill leukemia cells. Initially approved because of single-agent activity in about 25% of patients with relapsed or refractory AML, its best documented value to date lies in the use with intensive chemotherapy in the up-front setting, where the drug reduces relapse risk and prolongs survival, particularly in patients with favorable risk disease. This benefit was the foundation for the regular approval in both the United States and Europe. However, the therapeutic window of GO is narrow. A profound decrease in white blood cells and platelets is the most common clinically important side effect because CD33 is also expressed on normal blood cells.

Less common, but potentially fatal, is a particular type of liver toxicity. Worth mentioning also is that premedications are used to minimize the risk of infusion toxicities when the drug is given.

Liposomal 7+3 (CPX-351)

CPX-351: 100 nM bilamellar liposomes, delivers constant ratio of cytarabine and daunorubicin

- Approved for adults with therapy-related AML or AML with myelodysplasia-related changes
- In these patients, better outcomes with CPX-351 than conventional 7+3
 - Higher response rates
 - Slightly lower 30- and 60-day mortality (fewer deaths from progressive AML)
 - Outcomes seem particularly improved in patients who subsequently undergo allogeneic transplant
 - Side effects: similar to 7+3 but less mucositis

Lancet et al. J Clin Oncol 2018;36(28):2684-2692; Lancet et al. Lancet Haematol 2021;8(7):e481-e491; Cartoon: Mayer et al. Int J Nanomedicine 2019;14:3819-3830

Slide 21: LIPOSOMAL 7+3 (CPX-351)

Interesting from a drug design perspective is CPX-351, which is a liposomal form of 7+3. Liposomes are tiny bubbles made out of the same materials as cell membranes. For adults with therapy-related AML or AML with MDS-related changes, a randomized study has shown that CPX-351 leads to better outcomes than old fashioned 7+3, with this benefit particularly marked in patients who then went on to get a transplant.

The side effects with CPX-351 are similar to those seen with 7+3, except that mucositis, that is mouth sores or other problems with the GI tract, are less common. While the drug is well tolerated in general, it is not widely used, at least partly related to the drug cost and challenges for the hospitals to get reimbursement for it.

FLT3 inhibitors

- FLT3 mutations found in ~30% of AML
 - Internal tandem duplication (ITD): ~30%
 - Tyrosine kinase domain mutation (TKD): 7-10%

Drug	IC ₅₀ (medium)	IC ₅₀ (plasma)	Single agent clinical activity	Kinase inhibition
1st Generation				
Lestauritinib	2 nM	700 nM	-	Type I
Midostaurin	6 nM	~1,000 nM	-	Type I
Sorafenib	3 nM	~265 nM	+/-	Type II
2nd Generation				
Quizartinib	1 nM	18 nM	+	Type II
Crenolanib	2 nM	48 nM	+	Type I
Gilteritinib	3 nM	43 nM	+	Type I

Class 3 RTKs: FLT3, KIT, CSF1R, PDGFRA/B

Midostaurin (PKC412) **Quizartinib (AC220)**

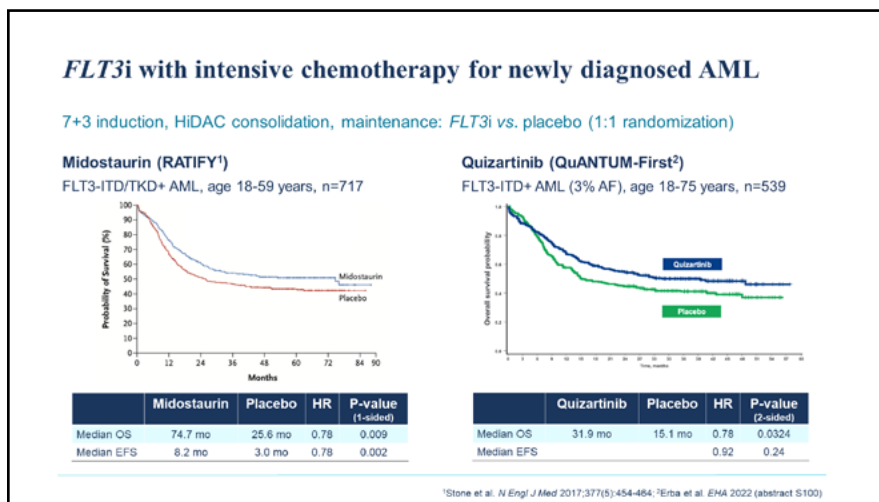
Side effects: gastrointestinal toxicity, skin rash, low blood counts, differentiation syndrome, drug/drug interactions

Zarrinkar et al. Blood 2009;114(14):2984-2992; Pratz et al. Blood 2010;115(7):1425-1432; Smith et al. Nature 2012;485(7397):269-263; Galanis et al. Blood 2014;123(1):94-100; Daver et al. Leukemia 2019;33(2):299-312; Tarver et al. Blood Adv 2020;4(3):514-524

Slide 22: FLT3 INHIBITORS

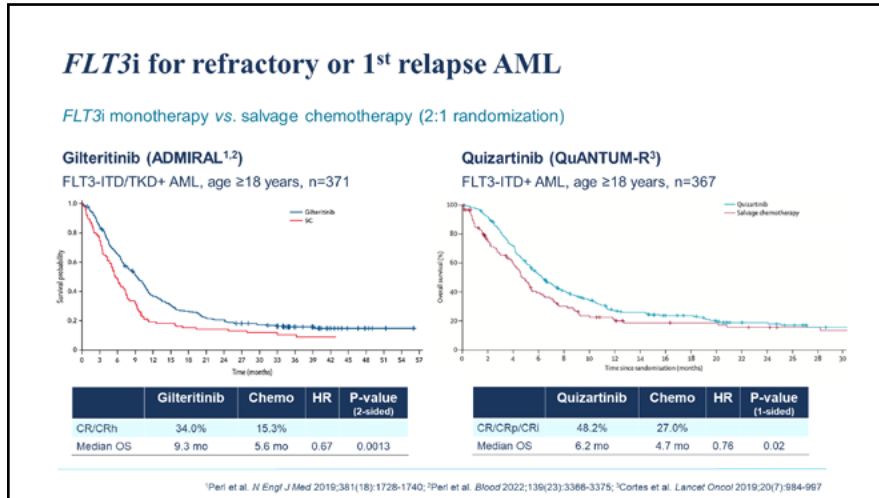
FLT3 is a gene that makes a protein that is involved in the formation and growth of new blood cells. Mutated forms of the *FLT3* gene may cause an overactive *FLT3* protein to be made. Such mutations occur in approximately 30% of patients with AML. It's therefore no surprise that major efforts in drug development have focused on inhibitors for this protein. Several agents have entered clinical testing. They distinguish themselves from each other by how potent they are in inhibiting *FLT3*, by how selectively they inhibit *FLT3*, and what type of *FLT3* mutation they inhibit.

The side effect profile for the individual *FLT3* inhibitors differ slightly, but in general these oral drugs cause some gastrointestinal toxicity, skin rash, and low blood counts. Sometimes they lead to a complication called differentiation syndrome when the leukemia cells regain the ability to mature, then accumulate in large numbers and cause potentially life-threatening problems. The pharmacists and physicians will also need to watch for interactions with other drugs and adjust drug dosages accordingly.



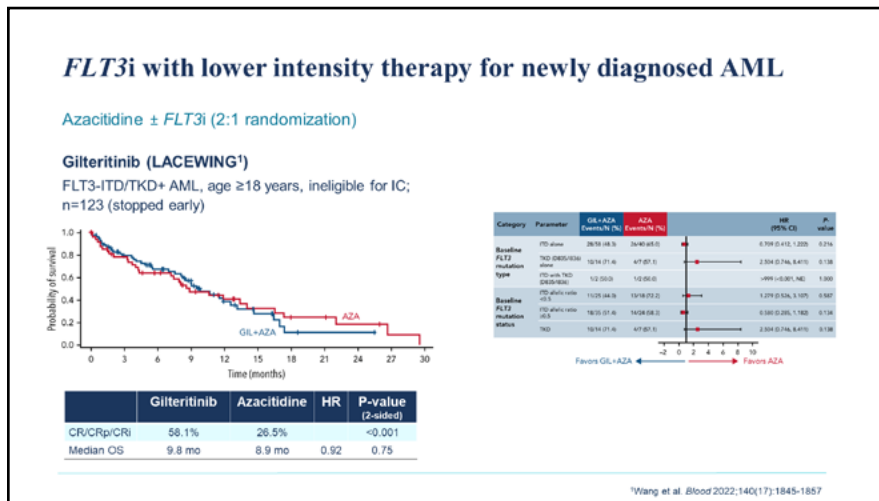
Slide 23: FLT3I WITH INTENSIVE CHEMOTHERAPY FOR NEWLY DIAGNOSED AML

Two large, randomized trials have tested the value of adding a *FLT3* inhibitor to standard induction, consolidation, and maintenance treatment for patients with previously untreated AML, the RATIFY trial, which tested midostaurin in 717 adults and the QuANTUM-First trial, which tested quizartinib in 539 patients. Both trials showed improved survival in the patients treated with the *FLT3* inhibitor, with the magnitude of benefit being the same in these trials. Based on these results, midostaurin was approved by the FDA for use with intensive chemotherapy for adults with newly diagnosed AML. The results with quizartinib are very recent and it is certainly possible that this drug will eventually also get approved.



Slide 24: *FLT3i* FOR REFRACTORY OR 1ST RELAPSE AML

Two relatively large, randomized trials have compared single-agent treatment with a *FLT3* inhibitor to standard salvage chemotherapy for patients with refractory or first relapse AML, the ADMIRAL trial, which tested gilteritinib (XOSPATA[®]) in 371 adults and the QuANTUM-R trial, which tested quizartinib in 367 patients. In both trials the response rate with the *FLT3* inhibitor was higher than the standard salvage chemotherapy. The roughly 3.5 months longer survival with gilteritinib was considered meaningful enough by the regulatory authority to grant market approval, whereas the roughly 1.5 months improvement in survival with quizartinib was not, however. And quizartinib was denied approval.



Slide 25: *FLT3i* WITH LOWER INTENSITY THERAPY FOR NEWLY DIAGNOSED AML

Unlike for use with intensive chemotherapy in the up-front setting or as a single agent in the relapse/refractory setting, the value of *FLT3* inhibitors together with lower intensity treatment is currently unclear. Perhaps the most pertinent example for this is the LACEWING trial, which randomized patients with newly diagnosed AML considered ineligible for intensive chemotherapy between azacitidine alone, so one of the standard low-intensity therapies, or azacitidine plus gilteritinib. The trial was stopped early because there was no evidence of improved survival with gilteritinib, even though the remission rate in the gilteritinib arm was more than double than that with the *FLT3* inhibitor – than without the *FLT3* inhibitor.

BCL-2 inhibition

BCL-2: allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins

Venetoclax (ABT-199/GDC-0199): oral, selective BCL-2 inhibitor

- Relatively low response rate as single agent in relapsed/refractory AML¹
- High response rates and broad activity in combination with lower-intensity therapy in newly diagnosed AML^{2,3}
- Main side effects: severely low blood counts (myelosuppression), infections

¹Konopleva et al. *Cancer Discov* 2016;6(10):1106-1117; ²Wei et al. *J Clin Oncol* 2019;37(15):1277-1284; ³Dinardo et al. *Blood* 2019;133(1):7-17
cartoon: Mihaylova et al. *Exp Hematol* 2018;61:10-25

Slide 26: BCL-2 INHIBITION

Arguably, the biggest impact on the landscape of AML therapy came with the use of venetoclax (VENCLEXTA®), an oral inhibitor of BCL-2. BCL-2 is a protein that helps cancer cells to live by blocking a type of cell death called apoptosis. Initially tested as a single agent in adults with relapsed or refractory AML, the drug did not appear very effective. However, in subsequent Phase I and II studies, remarkably high response rates and survival estimates were observed across a broad range of patients with disease-related characteristics. When venetoclax was combined with either azacitidine or decitabine or low dose cytarabine in adults with newly diagnosed AML, myelosuppression, that is low blood counts, was quickly recognized as a clinically important drug toxicity with venetoclax.

Venetoclax with lower intensity therapy for newly diagnosed AML

Low intensity therapy ± venetoclax for adults **unfit** for intensive chemotherapy (2:1 randomization)

VIALE-C^{1,2}

Prior HMA therapy permissible, n=211

	Ven/LDAC	LDAC	HR	P-value (2-sided)
CR/CRi	48.3%	13.2%	0.70	<0.001
Median OS*	6.4 mo	4.1 mo		0.04

*Unplanned analysis with +6 mo follow-up

VIALE-A³

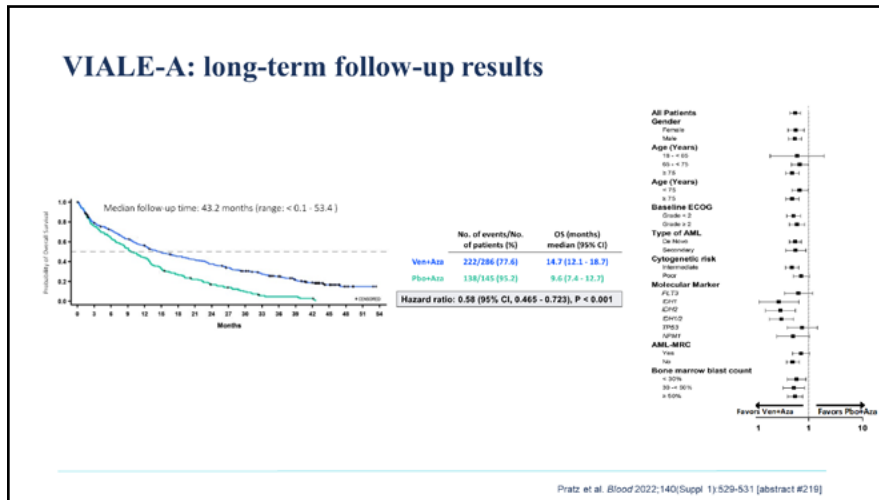
Prior HMA not permissible, n=431

	Ven/Aza	Aza	HR	P-value (2-sided)
CR/CRi	66.4%	28.3%	0.66	<0.001
Median OS	14.7 mo	9.6 mo		<0.001

¹Wei et al. *Blood* 2020;135(24):2137-2145; ²Wei et al. *Blood* 2022;140(25):2754-2756; ³Dinardo et al. *N Engl J Med* 2020;383(7):617-623

Slide 27: VENETOCLAX WITH LOWER INTENSITY THERAPY FOR NEWLY DIAGNOSED AML

Two randomized trials have assessed the value of adding venetoclax to lower intensity therapeutics in adults considered unfit for intensive chemotherapy, the VIALE-C trial testing the addition to low-dose cytarabine in 211 patients and the VIALE-A trial testing the addition to azacitidine in 431 patients. As a main difference between the trials, the VIALE-C trial, but not the VIALE-A trial, allowed prior therapy with azacitidine or decitabine. In both trials the remission rates were substantially higher with the combination treatment. With a significant improvement in survival seen with the addition of venetoclax to azacitidine, this combination has now become a new standard of care for adults with newly diagnosed AML considered unfit for intensive chemotherapy.



Slide 28: VIALE-A: LONG-TERM FOLLOW-UP RESULTS

Very recently, longer term outcomes of the randomized trial with azacitidine and venetoclax, that is the VIALE-A trial, have been reported at a large international meeting. What was shown was reassuring, that the earlier results showing improvement in outcome over the use of azacitidine alone were confirmed. Perhaps more importantly, analyses of several patient subsets indicated that this benefit seemed to hold up across individual types of patients and AML.

Inhibitors of mutant IDH

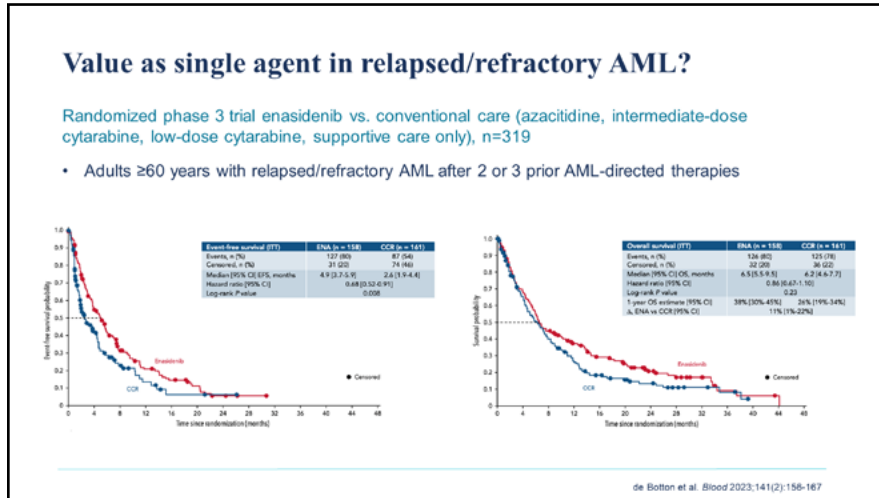
- Somatic *IDH1* and *IDH2* mutations result in accumulation of oncometabolite (2-HG)
 - Epigenetic changes, impaired cellular differentiation
- Found in 6-10% (*mIDH1*) and 9-13% (*mIDH2*) of AML
- Inhibitors of *mIDH* have single agent activity in AML

Inhibitor	n	CR/CRh rate at RP2D	Duration of CR	Differentiation syndrome
Ivosidenib (<i>mIDH1</i> inhibitor) ¹	258	30.4%	9.3 mo	10.6%
Olutasidenib (<i>mIDH1</i> inhibitor) ²	147	34.7%	25.9 mo	14%
Enasidenib (<i>mIDH2</i> inhibitor) ³	239	26.6%	8.8 mo	7%

¹D'Nardo et al. N Engl J Med 2018;378(25):2396-2398; ²Cortes et al. ASH 2022 [abstract]; ³Stein et al. Blood 2017;130(8):722-731

Slide 29: INHIBITORS OF MUTANT IDH

IDH genes make proteins that help break down fats for energy and protect cells from harmful molecules. Somatic mutations in *IDH1* or *IDH2* occur in a significant subset of cases of AML. These mutations are relevant and result in the accumulation of an abnormal metabolite that leads to an inability of the blood cells to mature fully. Oral inhibitors that have been developed are interesting in that they only inhibit the mutant form of *IDH*. So far 3 inhibitors have been approved: ivosidenib, and very recently olutasidenib, both inhibitors of mutant *IDH1*, and enasidenib, an inhibitor of mutant *IDH2*.

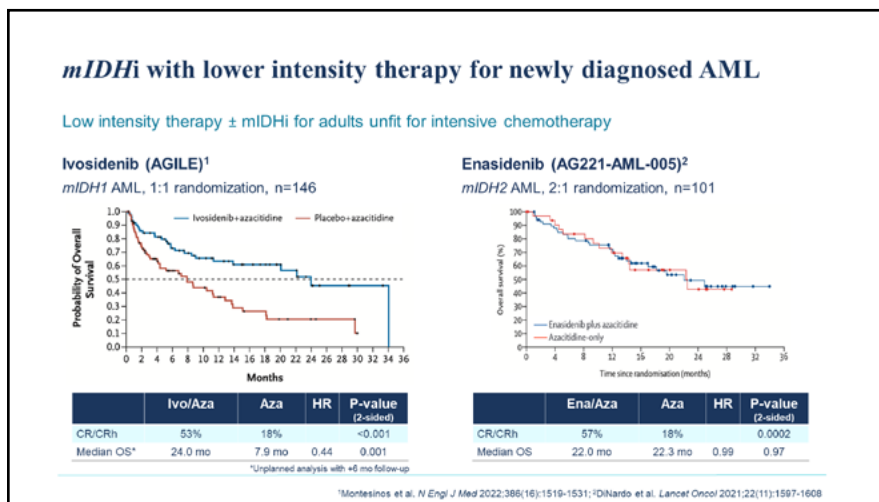


Slide 30: VALUE AS SINGLE AGENT IN RELAPSED/REFRACTORY AML?

All these drugs have single-agent activity in patients with relapsed or refractory AML, leading to remissions in a quarter to a third of treated patients, with some of these remissions being quite durable.

As a class effect and consistent with the effect of mutant *IDH*, these inhibitors cause differentiation syndrome in up to 10 to 15% of patients as a main clinically important and potentially dangerous side effect.

That said, while the drugs have single-agent activity, how helpful they are when used alone is a bit uncertain in my mind. For example, when comparing single-agent enasidenib against a conventional salvage chemotherapy, a reasonably large, randomized trial found no significant difference in survival, even though the event-free survival was slightly longer.



Slide 31: MIDHI WITH LOWER INTENSITY THERAPY FOR NEWLY DIAGNOSED AML

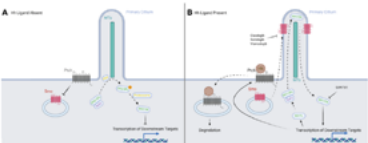
Two relatively small, randomized trials have assessed the value of adding an *IDH* inhibitor to azacitidine in adults considered unfit for intensive chemotherapy: the AGILE trial, testing the addition of ivosidenib in 146 patients, *IDH1* mutation, and the AG221 trial, testing the addition of enasidenib in 101 patients with *IDH2* mutations. In both trials the combination therapy was associated with a roughly 3-fold higher remission rate, however only with ivosidenib, but not enasidenib, survival was substantially prolonged when added to azacitidine.

Since azacitidine plus ivosidenib causes less problems with low blood counts than azacitidine plus venetoclax, but outcomes look comparable, some experts have advocated for this *IDH* inhibitor doublet treatment to be used instead of venetoclax plus azacitidine in patients with *IDH1* mutations.

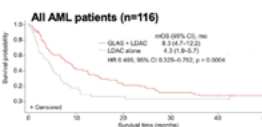
Glasdegib for previously untreated secondary AML

- Hedgehog pathway: involved in AML cell survival, resistance to chemotherapy, radiotherapy¹
- Glasdegib: potent oral inhibitor of Smoothened

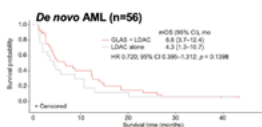
- Phase 2 BRIGHT AML 1003: newly-diagnosed AML (n=116)/high-risk MDS (n=16), age ≥55 years, unfit^{2,3}
- 2:1 randomization glasdegib (100mg daily)/low-dose cytarabine (LDAC, 10/28 days) vs. LDAC



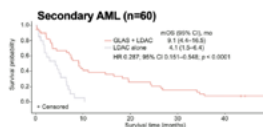
All AML patients (n=116)



De novo AML (n=56)



Secondary AML (n=60)



¹Lemos and Merchant. *Front Oncol* 2022;12:960943; ²Cortes et al. *Leukemia* 2019;33(2):379-389; ³Heuser et al. *Ann Hematol* 2021;100(5):1181-1194

Slide 32: GLASDEGIB FOR PREVIOUSLY UNTREATED SECONDARY AML

The second to last new drug to be mentioned is glasdegib, an oral inhibitor of the Hedgehog pathway, a signaling pathway involved in AML cell survival and resistance to chemotherapy and radiation therapy. Drug approval was based on a randomized trial showing that the addition of glasdegib to low dose cytarabine improved survival, particularly in patients with secondary AML. Despite this benefit, I believe it is fair to say that the drug's not widely used, at least not in the United States, at least partly because the outcomes with the combination therapy may not appear better and what one might expect with azacitidine alone. However, the drug is currently undergoing testing in combination with azacitidine or with intensive induction chemotherapy.

Maintenance therapy for AML

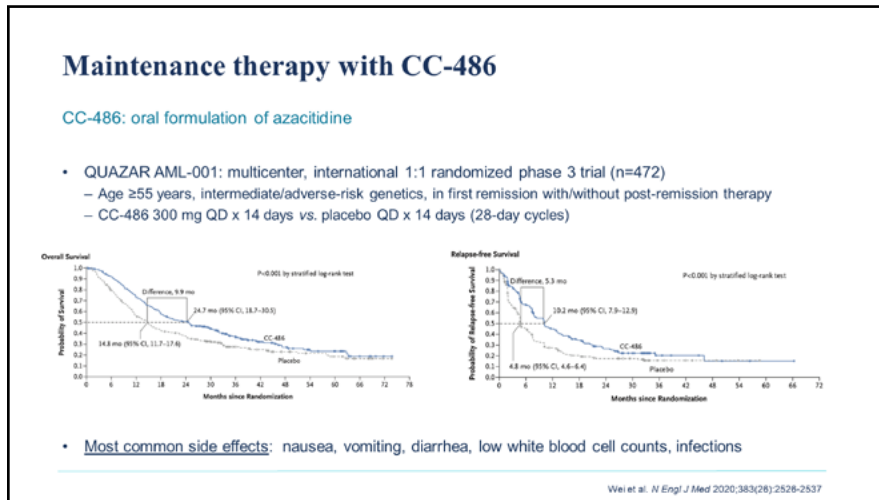
- Investigated for over 40 years
- Large number of randomized controlled trials
 - Immunotherapies (IL-2, BCG vaccine, interferon-alpha)
 - Conventional cytotoxic chemotherapy
 - Small molecule inhibitors (e.g. tyrosine kinase inhibitors)
- Improved disease-free (but not overall) survival: low-dose IL-2 plus histamine dihydrochloride
 - Approved by EMA in 2008 (hardly used)

Rashidi et al. *Blood* 2016;128(6):763-773

Slide 33: MAINTENANCE THERAPY FOR AML

The 9 drugs discussed so far have been approved for use in the up-front setting or in patients with relapsed or refractory AML. In contrast, the 10th drug brings renewed interest in maintenance treatment for AML that is lower intensity treatment given over a prolonged period of time to patients who have achieved a remission. Maintenance therapy options have been explored for 40 years in AML. Most of the agents tested have been found to be ineffective. The only exception to this rule so far has been a rather obscure combination therapy that was approved for use in

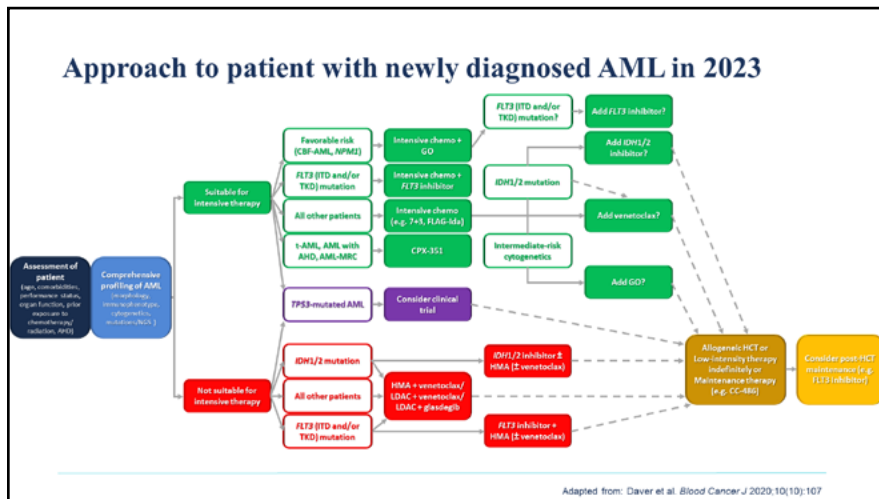
Europe about 15 years ago but has never found regular usage.



Slide 34: MAINTENANCE THERAPY WITH CC-486

This is now likely going to change with the availability of CC-486, which is an oral formulation of azacitidine. A large, randomized study recently showed that older adults who were in first remission after receiving conventional induction chemotherapy, and possibly consolidation chemotherapy, had significantly longer survival and relapse-free survival when receiving a 2-week on / 2-week off schedule of CC-486, compared to receiving placebo.

While there are some side effects with CC-486, such as nausea, vomiting, diarrhea, low blood counts, and infections, CC-486 may now offer a treatment option, perhaps particularly in patients for one reason or another who do not go on to receive a transplant.



Slide 35: APPROACH TO PATIENT WITH NEWLY DIAGNOSED AML IN 2023

So how does this fit altogether? The landscape of AML therapy has dramatically changed in the last 5 years with the approval of 10 new drugs. Although these drugs mostly only slightly improve outcomes over what can be accomplished with 7+3, a low-dose standard chemotherapy, we have now moved towards personalized selection of therapy that takes into consideration both the characteristics of the patient, age, comorbidities, performance status, organ functions among others, as well as the molecular and genetic characteristics of the leukemia. At least for now, the question about fitness for intensive chemotherapy has remained central, but the disease characteristics influence

the selection of therapy more and more and increasingly supersedes fitness in importance for treatment decision-making.

Conclusions

Some progress made but ongoing need for new therapies

- **Increasing understanding of genetic basis of AML**
 - Changing disease classification, risk stratification
 - Identification of new rational drug targets
- **10 new drugs approved since 2017**
 - Treatment algorithms continue to evolve
 - Blurrier line between “curative” intensive and “palliative” non-intensive therapy
 - New standard of care for patients “unfit” for intensive chemotherapy
- **No replacement for allogeneic HCT (yet)**
- ❖ **For many patients, current therapies insufficient – participation in clinical trials important to evaluate new drugs**

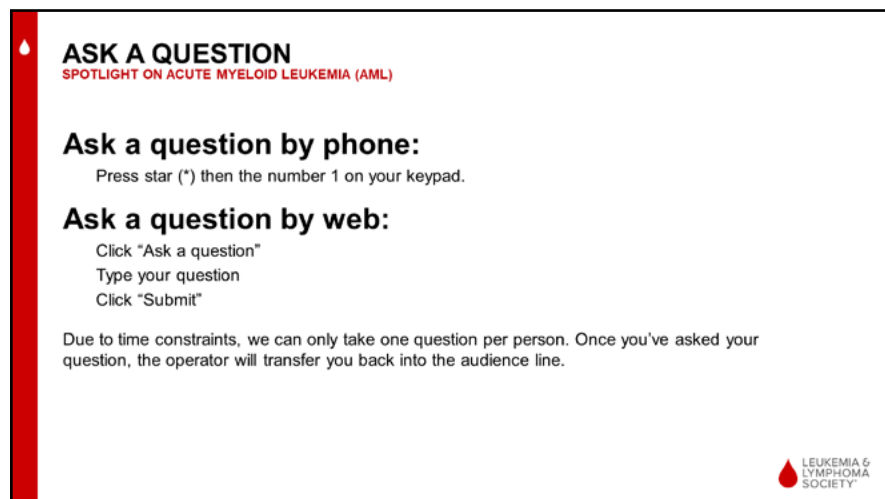
Slide 36: CONCLUSIONS

As I hope I was able to show you in this relatively short presentation, we have made significant progress in AML. A better understanding of disease biology has led to an improved ability to classify patients and stratify them according to their expected prognosis. The 10 drugs that have been approved since 2017 have been a very welcome addition to our treatment armamentarium, have enabled us to move toward the more personalized selection of therapies, and have given us a new standard of care for patients we consider unfit for intensive chemotherapy.

It is important to recognize though that our treatment algorithms are currently in flux and change rapidly and what I showed you today is likely going to be outdated soon. Ultimately, one hope is that we could eventually move away from the need to transplant patients, but so far there is no replacement in sight.

Finally, I am sure you have appreciated from the clinical trial results I showed you just how much need there still is for additional therapies in AML and how important it is to participate in clinical trials, testing new drugs, to bring us closer to finding cures for more and more patients with AML.

And with this, I would like to stop and thank you very much for your attention. I’m very happy to take any questions and comments you will have for me.




ASK A QUESTION
SPOTLIGHT ON ACUTE MYELOID LEUKEMIA (AML)

Ask a question by phone:
Press star (*) then the number 1 on your keypad.

Ask a question by web:
Click "Ask a question"
Type your question
Click "Submit"

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.



Slide 37: ASK A QUESTION

Ms. Figueroa-Rivera:

And thank you so much, Doctor, for the great information that you provided for us regarding AML.

As you mentioned it is now time for the question-and-answer portion of our program .

And we'll take the first question from our web audience.

Doctor, Angela is asking... what are the possibilities of a recurrence of AML or other types of leukemia or lymphomas after a successful BMT, bone marrow transplant?

Dr. Walter:

That's a very good and important question. Thank you for asking it. The outcomes vary quite widely with transplant for a number of reasons. What we learned is that one of the key reasons for this variability is how much disease a patient has at the time of the transplant. And this is where this MRD testing, that I briefly mentioned, plays an important and really pivotal role.

For patients that go into a transplant and have no disease at any levels that we can measure, outcomes are substantially better than for patients that go into a transplant, the same transplant, yet still have even small amounts of disease that we can detect with one of the fancy methodologies that we have. And just to sort of give you a ballpark of ideas at our institution, the likelihood of disease recurrence for a patient, for an adult patient that goes to transplant, in remission without any MRD, is about 20 to 25%, so that's the relapse risk in the first 3 years, and survival expectations are in the order of 70 to 75%. For patients that are in remission, but still have some amount of MRD detectable, the numbers are roughly flipped, so the relapse rates are in the order of 70 to 75% and the survival expectations are about 20 to 25% in 3 years down the road. So, substantially different depending on how much disease you have at the time of transplant.

There're other factors that also matter.

Ms. Figueroa-Rivera:

Sure, thank you so much, Doctor, and thank you, Angela, for your question. The next question we'll take from the telephone audience, please.

Operator:

Certainly. We have a question from Elise. Elise, go ahead.

Elise:

Yes, thank you, Doctor, for your presentation. The young man that gave the initial opening with having no GVHD, I can't tell you how lucky he is. My husband is a transplant, bone marrow transplant survivor from AML, *FLT3*, 13 years as of Sunday, but he has very bad graft-versus-host and I was wondering what the doctor thinks because not very much else has helped of medical marijuana. Thank you.

Dr. Walter:

Thank you for this question. I think it highlights one of the real challenges with transplantation, one of the risks associated with transplant, right? I mentioned in the presentation that from an efficacy standpoint, transplant is more effective in preventing leukemia relapse than chemotherapy, so if we could do this without any side effects, we would want to do this for everybody. But that's obviously not the case, even today. And, graft-versus-host disease, so this immune fight of the transplanted cells against normal cells in the patient is one of the biggest challenges in transplantation, even today.

There's some improvements made, they're sort of gradual improvements in the medications that are available to prevent graft-versus-host disease from happening in the first place, some improvements in the treatment of it, but the improvements are slow and many patients are still left with graft-versus-host disease complications that sometimes last for a very long time, as seemingly was in the case of this question.

And it's a real challenge that sometimes requires help from a lot of different specialties and different drugs that can help, including the one that was mentioned before.

Ms. Figueroa-Rivera:

Thank you. And we have questions in regard to AML and monosomy 7. I know that different people on the line have different types of subtypes of AML and can you speak to if certain subtypes have different types of treatment?

Dr. Walter:

Yes. Thank you for this question. So yes, there are certain subtypes where we now have a pretty good understanding that some therapies are more helpful than others. Some of them I mentioned before, for example, for the favorable risk subset, this CD33 targeting drug, gemtuzumab ozogamicin, has provided a benefit. For the patients with *FLT3* abnormalities, the *FLT3* inhibitors do provide some benefit. For certain genetic alterations we understand that they're fairly common, like monosomy 7 is an example that we see fairly regularly. And we have a pretty good understanding of some of these mutations or changes, what they mean prognostically, for example, monosomy 7 has been associated with a lesser likelihood of responding well to chemotherapy. But for many of these genetic abnormalities, we don't have yet a therapy that works particularly well and monosomy 7 is an example where we don't have a drug specifically available for this type of abnormality.

Ms. Figueroa-Rivera:

Thank you. And also, the person with the monosomy 7 is a younger patient, so younger than 30, is it something that will be treated different when you're a younger patient versus an older patient?

Dr. Walter:

That is a good question. The answer is yes perhaps. So, there's this sort of gray zone between pediatric AML, right, and adult AML, where patients may get treated either by the pediatricians or by the adult leukemia doctors. And at least in another type of acute leukemia, acute lymphoblastic leukemia, it's been shown that for this very young subset of adults with acute leukemia, for some reason the regimens that were developed by the pediatricians seem to work better than those that we had commonly used for adult patients.

So, for a really young person, it is possible that a pediatric clinic might be willing to treat a patient and might give slightly different therapies than one would give as an adult oncologist. How the treatments really compare are much less clear in AML than it is in acute lymphoblastic leukemia, but it's very possible that the treatments might differ.

For a young adult, what we would typically do with a monosomy 7 patient would be, since we will consider it an adverse risk characteristic, is to induce a remission with some form of intensive chemotherapy and then work towards an allogeneic bone marrow transplant. And of course, for a young person with a monosomy 7, the question certainly has to come up whether there's a genetic predisposition involved and which again might influence who you might choose as a donor, for example.

Ms. Figueroa-Rivera:

Thank you. And we'll take the next question from our telephone audience, please.

Operator:

Thank you. The next question comes from Tammy. Go ahead, Tammy.

Tammy:

Hi, thank you so much for the presentation. I was just wondering if you can comment at all on cell therapies like CAR T or NK cell therapy, what seems promising, especially in pediatrics?

Dr. Walter:

Thank you for this question. So, in general, I don't know the pediatrics field in too much detail, but in general there is or there has been great enthusiasm for cell therapies in AML, largely because they have proven to be quite effective again for the other type of acute leukemia, acute lymphoblastic leukemia, where CAR T cells have really made a major impact in the treatment landscape. The same is true for a different type of drug that engages T cells, the bispecific antibodies again have been shown to be very, very effective in patients with ALL. So that has sparked a lot of enthusiasm to test similar drugs in AML, CAR T cells, bispecific antibodies, or other cell therapies.

I think the verdict is still out for some of the bispecific antibody therapies. There's now, at least data reported from sort of early phase experiences, and I'd say the general experience is perhaps a little disappointing in that the efficacy, so how effective these drugs are against the leukemia cells, doesn't appear as marked as it's been in ALL. But the toxicity profiles are clearly there and are substantial. And so that has maybe dampened the enthusiasm a little bit, but there's still a lot of effort ongoing with CAR cells, for example. But I think the verdict is really out how helpful they're ultimately going to be.

And I think to some degree that is the same for NK cell therapies that were mentioned. That's a type of therapy that takes advantage of natural killer cells or NK cells to fight leukemia cells. And there's a lot of, sort of laboratory data and sort of early phase uncontrolled clinical data that make a case that these NK cell therapies could be quite effective, but a lot of the data really comes from small trials that are not controlled very well and from individual

institutions, and we really need more data to get a better sense of how effective they ultimately are going to be. And there're quite a few efforts ongoing with these types of therapies. But again, just like for the CAR-T cells, for the NK cell therapies, the verdict ultimately is still out.

Ms. Figueroa-Rivera:

Thank you. And our next question comes from Gloria. Gloria is asking... what do you recommend for managing the side effect of fatigue from venetoclax and Vidaza® treatment?

Dr. Walter:

That is a very good and very tough question because some of the fatigue, as many of you know, is related to just having somewhat low blood counts. But, as many in the audience probably know, even transfusing people will not get rid of the fatigue and it may get more intense as the treatment continues. So I think it will ultimately resolve or improve with some therapy, so it's a situation where one has to find some kind of a balance between giving therapy and taking breaks in between. And depending on how effective the treatment worked, possibilities might be to dose-reduce the treatment or to introduce slightly longer gaps between the individual cycles and try to find a better balance there. But it's a challenging one because we're all afraid if we're giving too much time between the individual therapies that the leukemia cells have too much time to grow back, so it's a real tradeoff to do.

I think other things that people have sort of advocated for is to try to be active as good as you can, be physically active, go on walks and sports as much as you can, and try to maintain some physical fitness level that might ultimately help with this fatigue as well to some degree.

Ms. Figueroa-Rivera:

Thank you. And our next question comes from Annie. Annie is asking... can you speak more about how MRD predicts outcomes? Does positive MRD always mean relapse and are there ways of knowing when relapse might happen?

Dr. Walter:

Oh, that is a very good question, thank you for asking it. So, the MRD field is a very important field today. Because numerous studies have shown that for people that got treated the same way and entered a remission, so we can no longer find leukemia cells on a microscope, those that we still find MRD, either by flow cytometry or any of the molecular testing methods, outcomes for those people are worse than for people that do not have MRD. And that's measured by higher relapse rates and by shorter survival. Many, many studies have shown this, there's very little doubt about it.

Now there are problems with MRD testing. They're not standardized and many of the methodologies vary widely between different institutions. So, if you get MRD testing done in Institution A, that may be very, very different from what you get in Institution B. So that's one challenge. So, you have to really know how it was measured and what that place knows about how good is their assay. There're very, very big differences between the assays.

But there's also, and this is where the question goes to, there are challenges, statistical challenges with MRD testing. Not every person that has MRD will relapse, but the opposite is true, too, not everybody who doesn't have MRD will not relapse. So, there are quote-unquote false negatives, so people that have no MRD, but they will still relapse, and there's false positives, people that we measure MRD and they will not relapse. And that may have to do with the fact that we're trying to look for residual leukemia cells with our fancy tests, but what we really are in need of being able to do is find the leukemia cells that are capable of causing relapse. Not all leukemia cells can do that. Many leukemia cells don't have that capability. And we don't really understand how these rare cells that cause leukemia relapse distinguish themselves from the many cells that don't have the capability. So, we may measure a leukemia cell that is

unable to cause a relapse and that may be reflected by an MRD test that is positive, but the person will not relapse. So, it's not a black and white answer with the test. It does provide some guidance on relapse risk overall.

The timing question is a little bit more difficult. I think in general, one can say that people that don't have MRD, their relapse rates are lower, as I mentioned, and they tend to relapse later. People that are measured to have MRD, their relapse risk is higher and the relapses do occur earlier. But I'm not aware of good data that would say if your MRD test is X, Y, or Z that means your relapse is going to happen in 2 or 3 months. In fact, it's well known that the dynamic of the relapses can vary very, very significantly between individual patients, between weeks to sometimes many, many months, despite the fact that an MRD test may be positive.

Ms. Figueroa-Rivera:

Thank you. And Pam is asking if a FISH test is adequate for testing MRD?

Dr. Walter:

Well, yes and no. So, FISH test typically measures genetic changes in about 200 to 500 cells, right? So, if you do the math, that means the sensitivity is not more than one in a few hundred. So, if a FISH test, and that's more than you get, that's better than if you're just looking at karyotyping, which usually looks at 20 cells or 30 cells, so you're gaining some sensitivity. And if a FISH test is abnormal, it tells you something about residual disease that you might have not seen by microscope. But it's not nearly as sensitive as flow cytometry, which probably detects one in 10,000, sometimes one in 100,000 cells or one of the molecular tests, which can go down to maybe one in 100,000 to one in a million cells. So, if a FISH test is negative, the sensitivity is not good enough to have good confidence that there's no MRD. So, we don't think of FISH testing as a classic MRD testing method, just because it's not quite sensitive enough.

Again, if it's abnormal, it's informative.

Ms. Figueroa-Rivera:

Thank you. And the next question is coming from Ron. Ron is asking about the vaccine schedule for AML patients in active treatment. So, flu, pneumonia vaccines?

Dr. Walter:

Thank you for that question. So, I think the really clear distinguish is the issue of live vaccine versus dead vaccine. And, keeping in mind that the efficacy of a vaccine may not be the same. For example, a flu shot is a dead vaccine, right? So, the worst in some ways that can happen, other than some side effects, is that the flu vaccine doesn't work. So we have a relatively low threshold to use flu vaccines in the setting of AML therapies, and that is depending on the state of immune suppression a patient's in and maybe the treatments that a person gets, the likelihood that that person will raise a response to the vaccine is not going to be as good as for a clinical normal person. But that's different from live vaccines where there's a real danger to do this in an immune compromised patient and this is particularly important after an allogeneic transplant, where we might use flu vaccines as early as 6 months after transplant because I think we hope that at that time the immune system is capable of developing some immune response. And we're going through the childhood vaccine series about a year after transplant with dead vaccines, but we hold off on live vaccines for much longer because of the worry that live vaccines actually could cause disease in a person that is severely immune suppressed.

Ms. Figueroa-Rivera:

Thank you. And Lee is asking, has any connection been established between exposure to Agent Orange in the Vietnam War and the diagnosis of AML?

Dr. Walter:

Let me answer this more generally. I don't know the literature exactly on this particular exposure, but it is well described that chemical exposures are associated with an increased risk of leukemia, including AML. That's been shown for many chemicals, quite convincingly. Now the challenge is that this is a link that's been made on an epidemiology level. That means you need to look at a lot of people and you will find that the risk is higher among people that were exposed to a particular chemical than in people that were not exposed to that chemical. For any individual patient presenting with leukemia, though, it is very difficult or impossible to say whether that exposure has anything to do with the leukemia occurrence.

In the example that was mentioned here, so if a patient had Agent Orange exposure and presents with AML, you might know from epidemiology studies, that increased the risk of AML, but we would have no real ability to say that that particular AML in that particular patient was truly quote-unquote caused by the Agent Orange exposure. That's unfortunately very difficult or impossible to conclude.

Ms. Figueroa-Rivera:

Thank you. And our last question today, Doctor, Lillian asks, I'm very thankful that I'm a 10-year allogeneic transplant thriver. I have lived very carefully, but enjoyably. I've been masking for 10 years and happy to do so. Am I cured? Should I continue to avoid crowds?

Dr. Walter:

That is a very good question. So first of all, congratulations with this outcome, I think this is really inspiring, this is what we really hope to accomplish more and more with our patients, right? What we do know is that the likelihood of relapse after a transplant is time-dependent, with the vast majority of relapses occurring within 3 to 5 years. After 3 to 5 years there's still occasionally a relapse, but the likelihood of relapse is much, much, much lower. So, it may be impossible to truly say cured, cured, cured, because there's always a rare patient that does relapse. But the chance of that happening is very small, particularly after 10 years.

So, this is probably as close to a cure as we are in AML, acknowledging that there's a very rare patient that might relapse, even after 15 or 20 years, but it's really not the typical. Unlike other cancers where this is much more common that these late relapses can occur.

As far as precautions, one advice is to probably do what people feel comfortable doing. From a medical side of things, we have tried for many years to isolate people, you know, these bubble wrap tents, many, many years ago, where we put people in tents and we kind of really removed them from the environment and this has really all proven to be not helpful. So what we currently recommend is that people are cognizant about avoiding overtly sick people, maybe avoiding overt crowds, because you never know who might be sick in a crowd, so like quote-unquote crowd control in the acute settings of transplant, in the first year, for example, or in the height of going through induction chemotherapy, but with an improved immune system, particularly many years after transplant and presumably off immune suppressive therapy, the immune system probably is good enough that there shouldn't be any additional precaution necessary, over what one would typically do for a normal, quote-unquote, a normal healthy person.

Ms. Figueroa-Rivera:

Well, thank you for your question, Lillian, and we are glad that you are doing well.

And a special thank you to Dr. Walter for volunteering your time today with us and your expertise.

LLS EDUCATION & SUPPORT RESOURCES



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Slide 38: LLS EDUCATION & SUPPORT RESOURCES

If we weren't able to get to your question today or you want more information, you may speak to an Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or reach us by email at LLS.org/ContactUs.


LLS EDUCATION & SUPPORT RESOURCES



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The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org

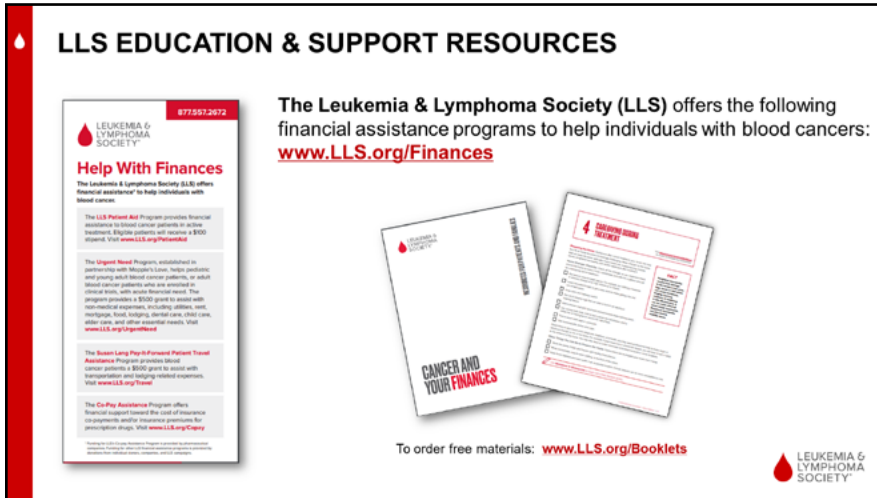


Slide 39: LLS EDUCATION & SUPPORT RESOURCES

As a reminder, you can download and print the slides, as well as view today's program, from our website at LLS.org/Programs.

Spotlight on Acute Myeloid Leukemia (AML)

April 26, 2023 **Speaker:** Roland B. Walter, MD, PhD, MS



LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: www.LLS.org/Finances

Help With Finances
The Leukemia & Lymphoma Society (LLS) offers financial assistance* to help individuals with blood cancers.

The **LLS Patient Aid** Program provides financial assistance for out-of-pocket costs associated with treatment. Eligible patients will receive a \$500 annual grant. Visit www.LLS.org/PatientAid


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Slide 40: LLS EDUCATION & SUPPORT RESOURCES

Again, we'd like to acknowledge and thank AbbVie Inc. and Bristol Myers Squibb for their support of this program.



THANK YOU

We have one goal: A world without cancer.



Slide 41: THANK YOU

Dr. Walter, thank you again for your time with us today and on behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye and we wish you well.

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