

## Transcript

The slide features a large, light gray teardrop shape in the center. The title "What's on the Horizon for Acute Myeloid Leukemia?" is written in red text across the top of the teardrop. Below the title, the speaker's name and credentials are listed in black text. In the top right corner of the slide, there is a red rectangular box containing the Leukemia & Lymphoma Society logo and name.

What's on the Horizon for  
Acute Myeloid Leukemia?

**What's on the Horizon for  
Acute Myeloid Leukemia?**

**David P. Steensma, MD, FACP**  
*Senior Physician, Adult Leukemia Program*  
Division of Hematological Malignancies  
Dana-Farber Cancer Institute  
*Associate Professor of Medicine*  
Harvard Medical School  
Boston, MA

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### Slide 1. What's on the Horizon for Acute Myeloid Leukemia?

**Lizette Figueroa-Rivera:**

Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, I would like to welcome all of you. Special thanks to Dr. David P. Steensma for volunteering his time and expertise with us today.

Before we begin, I'd like to introduce Dr. Elisa Weiss, The Leukemia & Lymphoma Society's Senior Vice President of Patient Access and Outcomes, who will share a few words. Elisa, please go ahead.

**Elisa Weiss:**

Thank you, Lizette. I would like to add my welcome to the patients, caregivers and healthcare professionals attending the program today.

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancers. Our vision is a world without blood cancer. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

As the world's largest voluntary health agency dedicated to fighting blood cancers, The Leukemia & Lymphoma Society is leading the charge to dramatically improve outcomes for patients with acute myeloid leukemia or AML.

The Leukemia & Lymphoma Society began funding AML research at our inception more than 66 years ago, and about 26% of our annual research budget funds AML research.

In the past 5 years alone, we have invested nearly \$100 million in AML research with a focus on understanding the underlying causes of the disease, to develop better therapies and save more lives

With advances in genomics we can now identify and target specific types of AML. This precision medicine approach is the key to developing new therapies for patients.

LLS is leading the Beat AML Master Trial, a groundbreaking collaborative clinical trial that is testing several novel targeted therapies for patients with AML. This collaborative clinical trial involves multiple medical institutions, drug companies and the FDA, all of whom have committed to working together to drive this master clinical trial forward. For more information on our innovative research I invite you to visit our website at [www.LLS.org](http://www.LLS.org).

# What's on the Horizon for Acute Myeloid Leukemia?

November 2, 2017

Speaker: David P. Steensma, MD, FACP

We're fortunate to have as our presenter today, Dr. David P. Steensma, one of the nation's leading experts in acute myeloid leukemia. We appreciate his dedication to supporting our mission and his commitment in caring for patients living with blood cancers. I'd like to thank him for providing us today with important information on AML.

And now I'll turn the program back to Lizette.

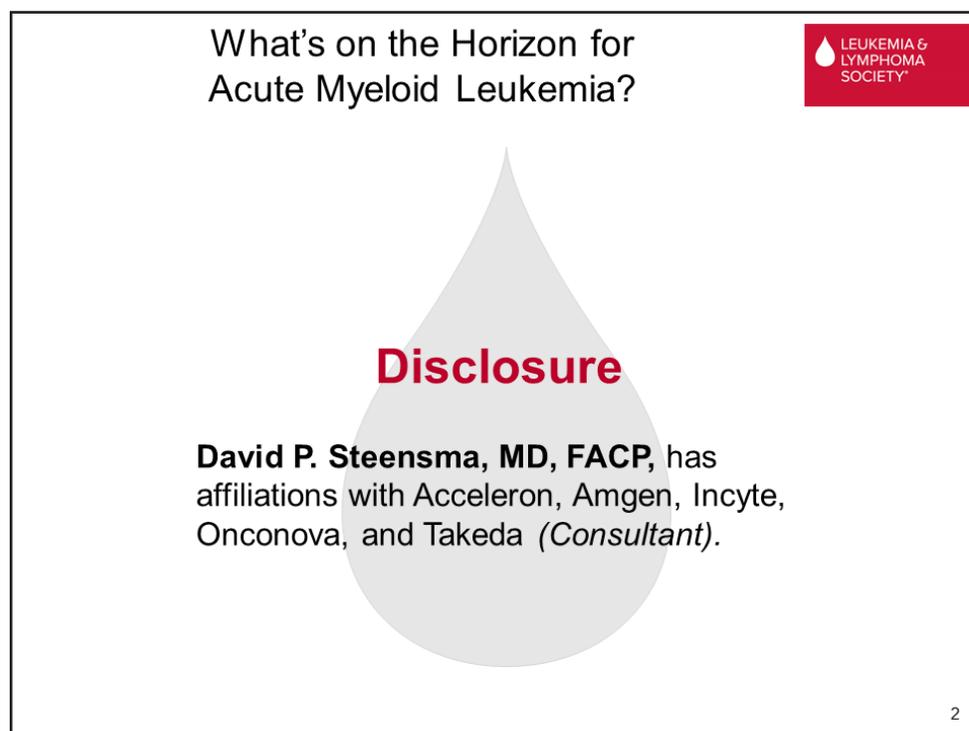
## **Lizette Figueroa-Rivera:**

Thank you, Elisa. And we would like to acknowledge and thank Agios, Celgene and Novartis for support of this program.

I am now pleased to introduce Dr. David P. Steensma, Senior Physician in the Adult Leukemia Program, Division of Hematological Malignancies, at Dana-Farber Cancer Institute, and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts. Dr. Steensma, I'm privileged to turn the program over to you.

## **Dr. Steensma:**

Well, thank you, it's an honor to be with you today to be presenting on behalf of The Leukemia & Lymphoma Society, who do so much wonderful work supporting our patients with these difficult conditions, and those who are their families, friends, loved ones and caregivers.



What's on the Horizon for  
Acute Myeloid Leukemia?



**Disclosure**

David P. Steensma, MD, FACP, has  
affiliations with Acceleron, Amgen, Incyte,  
Onconova, and Takeda (*Consultant*).

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## **Slide 2. Disclosure**

### **Dr. Steensma:**

It has been an exciting year for AML in the sense that we've had four new FDA approvals, the first approvals we've had in decades for new drugs for these diseases, and there's more on the horizon.

I realize our audience today is made up of people who maybe have just been diagnosed or their loved one has just been diagnosed, and others who have been on this journey for quite some time, and so hopefully there will be something today for everyone.

## Definitions and Risk Assessment

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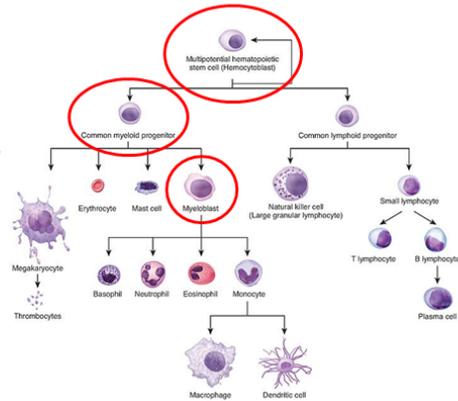
### **Slide 3. Definitions and Risk Assessment**

I'd like to start, for those who are newer to this disease, by talking a bit about definitions and about how we decide which patients are high risk and which patients are lower risk with risk being the likelihood that the leukemia will take their life.

## Definitions

- AML is a hematological cancer: “Clonal” proliferation of myeloid precursor cells (immature white blood cells), unable to mature
- These malignant “blasts” accumulate in marrow, blood, and sometimes other tissues
  - 20% blasts = acute leukemia
- These abnormal cells inhibit production of red blood cells, platelets, and mature neutrophils / granulocytes

Blood cell production (hematopoiesis)



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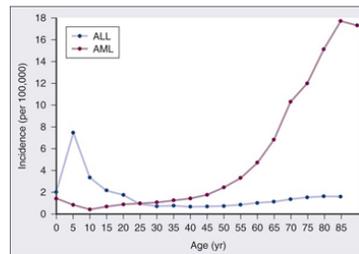
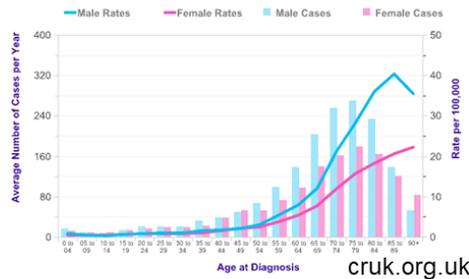
### Slide 4. Definitions

First the definitions. So acute myeloid leukemia is a hematologic cancer in which a clone of cells, that is to say a number of copies of genetically identical cells, which are unable to mature and form healthy blood cells, increase in the bone marrow and crowd out other blood cells, so that the bone marrow cannot make healthy red cells, white cells, or platelets. When the number of these immature cells, which are called blast cells, gets to 20% or more, it's called acute leukemia. There are several different types of acute leukemia, but the majority in adults is acute myeloid leukemia and that's defined by the specific type of white cell that has in fact turned cancerous.

## AML – By The Numbers



- New US cases each year: ~21,000
- Deaths each year: ~11,000
- Median age: ~67 years



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### Slide 5. AML – By the Numbers

Now how common is this disease? Well, in the United States leukemia is tracked by the SEER (Surveillance, Epidemiology, and End Results Program) Registry of the National Cancer Institute (NCI). This incorporates data from little states, big states, from rural areas, urban areas, from red states, blue states, to try to get a comprehensive picture of what leukemia and other cancers are like in the US. From this registry, we've learned that there are more than 20,000 new cases each year, so if you have been recently diagnosed you are far from alone. This is not as common certainly as lung cancer or breast cancer, but it is a common enough malignancy that there are many others going through this.

About half of the patients who are diagnosed ultimately will pass away and half will live and be cured of the disease.

It's more common in older folks. As we get into the 60s and 70s, the genetic mutations that cause this become more common. And it is slightly more common in men than it is in women, for reasons that are still not clear.

## Prognostication in AML

- **Who** is the patient?
  - Age
  - Medical “co-morbidities” (i.e., other problems)
- Did it evolve out of **preceding marrow disease** (e.g. myelodysplastic syndromes (MDS))?
  - Not always easy to tell...
- Is it a consequence of **therapy for another cancer?** (“therapy-related AML”)
- What are the **biological characteristics?**
  - Cytogenetic (chromosome) analysis
  - DNA mutational analysis: *FLT3*, *NPM1*, *CEBPA*, etc



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### Slide 6. Prognostication in AML

Now when we think about how a patient is going to do, when we first meet that patient and we try to look into the crystal ball and say is this patient likely to be cured, how difficult is it going to be, there's a lot of information that we try to integrate to make an assessment. We want to know who is the patient, what's their age, because older patients don't do as well as younger ones. Do they have other medical problems? If a person is completely healthy other than the leukemia, they're likely to do better than if they have a bad heart or bad lungs or bad kidneys. Did their acute leukemia just come out of the blue or did it evolve out of one of the preceding conditions such as myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN)? Patients whose disease has evolved out of such conditions tend to have a more dangerous disease. It's not always easy to tell because some people just don't go to the doctor that often. They may have had such a phase and not known it.

Is it a consequence of a therapy for another cancer, so-called therapy-related AML? For instance, a woman had breast cancer 5 years earlier, she was treated for that, cured of that, and unfortunately because of the chemo-radiation, damage to the bone marrow led to acute leukemia. That's the most difficult form of AML, the so-called therapy-related.

And then we want to know about the intrinsic characteristics of the disease, and I'll talk more about that in just a moment. This includes what the chromosomes are in the leukemia cells and what specific DNA mutations, what specific DNA letter changes are present in the cells. These are rarely inherited, they're usually acquired.

## Cytogenetics (chromosomes, karyotype)

### “Good-risk”

- Translocation t(15;17) - Acute promyelocytic leukemia (APML, APL)
  - ~10%... A different disease
- t(8;21) and inv(16),
  - ~15%, “Core binding factor” alterations

### “Poor-Risk”

- Chromosome 7 deletion
- Chromosome 5 deletion
- t(6;9)
- Complex (i.e., 3 or more abnormalities)
- Chromosome 11 translocations at 11q23
- Chromosome 17p abnormalities

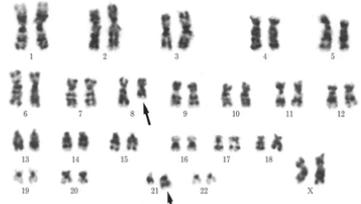


Figure 2. The karyotype at the diagnosis of AML. 146, XX, 68,21t(8;21)(q22;q22)

### “Intermediate”

- Normal
- One or two (non-bad) abnormalities

Sakai et al Internal Medicine 43: 582-586, 2004.

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## Slide 7. Cytogenetics (chromosomes, karyotype)

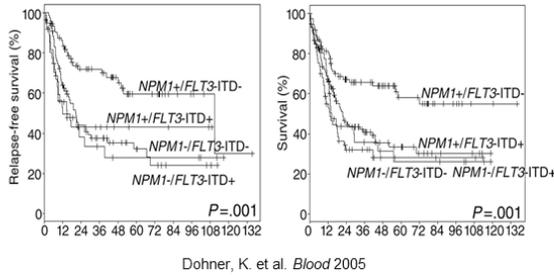
So, we do what's called a karyotype, where we have cytogeneticist, a laboratory scientist, grow the cells and then spread out the chromosomes and stain them and count them and look. And there are several forms of leukemia based on the cytogenetics that tend to be better risk. The majority of these patients will be cured. This includes the 15;17 translocation, where a bit of chromosome 15 gets on 17 and vice versa. That defines a condition called acute promyelocytic leukemia (APL), which we won't talk about anymore because it really is a different disease. When I started training it was not considered or treated differently from the other AML, but now it is, has different drugs and a different approach.

Then there's the so-called core binding factor leukemias, that's an 8;21 translocation, and an inversion where the middle part of chromosome 16 has flipped around. Those patients tend to have a better prognosis.

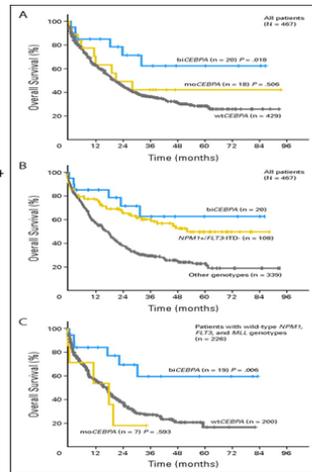
A large proportion, however, fit into the poor risk group, where they have abnormalities of chromosome 5 or 7, where they have a complex chromosome pattern with multiple different abnormalities, or abnormalities of chromosome 11 or 17. And we're learning more and more about the genetics, about what makes these leukemias tick.

Then there's the intermediate risk leukemias where the chromosomes may actually be normal or where there's one or two abnormalities that are not mentioned.

## Prognostically important genes: *NPM1*, *FLT3* and *CEBPA*



*NPM1* mutation: Favorable  
*FLT3* ITD: Unfavorable  
*FLT3* TKD (D835/D836): Controversial  
*CEBPA* one mutation: Unfavorable  
*CEBPA* two mutations: Favorable



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### Slide 8. Prognostically important genes: *NPM1*, *FLT3* and *CEBPA*

Now in the last 10 years it's become routine to measure for DNA mutations in 3 genes – *NPM1*, *FLT3* and *CEBPA*. The first 2 are by far the most important. And *NPM1*, if the leukemia cell has a mutation in that, the patient tends to do a little bit better. If they have it in *FLT3* they tend to do a little bit worse. And *CEBPA* is a little bit more complicated, depends on whether there's 1 mutation or 2.

## European LeukemiaNet (ELN) Molecular and Cytogenetic Risk Groups

**Table 1.** European LeukemiaNet Standardized Reporting System for Correlation of Cytogenetic and Molecular Genetic Data in AML With Clinical Data<sup>1,2</sup>

Genetic Group	Subsets
Favorable	t(8;21)(q22;q22); <i>RUNX1-RUNX1T1</i> inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i> Mutated <i>NPM1</i> without <i>FLT3-ITD</i> (normal karyotype) Mutated <i>CEBPA</i> (normal karyotype)
Intermediate-I	Mutated <i>NPM1</i> and <i>FLT3-ITD</i> (normal karyotype) Wild-type <i>NPM1</i> and <i>FLT3-ITD</i> (normal karyotype) Wild-type <i>NPM1</i> without <i>FLT3-ITD</i> (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); <i>MLL3-MLL</i> Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21;q26.2) or t(3;3)(q21;q26.2); <i>RPN1-EVI1</i> t(6;9)(p23;q34); <i>DEK-NUP214</i> t(v;11)(v;q23); <i>MLL</i> rearranged -5 or del(5q) -7 abn(17p) Complex karyotype*

Abbreviations: AML, acute myeloid leukemia; ITD, internal tandem duplication.  
\*Complex karyotype is defined as three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions: t(8;21), inv(16) or t(16;16), t(15;17), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3).

Mrozek K et al. *J Clin Oncol* 2012

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### Slide 9. European LeukemiaNet (ELN) Molecular and Cytogenetic Risk Groups

And all that's factored into how patients are classified using risk groups such as this European LeukemiaNet model. And that helps us decide who is likely to be cured with chemo alone and who's going to need a transplant, if they can get one.

# Outcome by ELN Risk Group

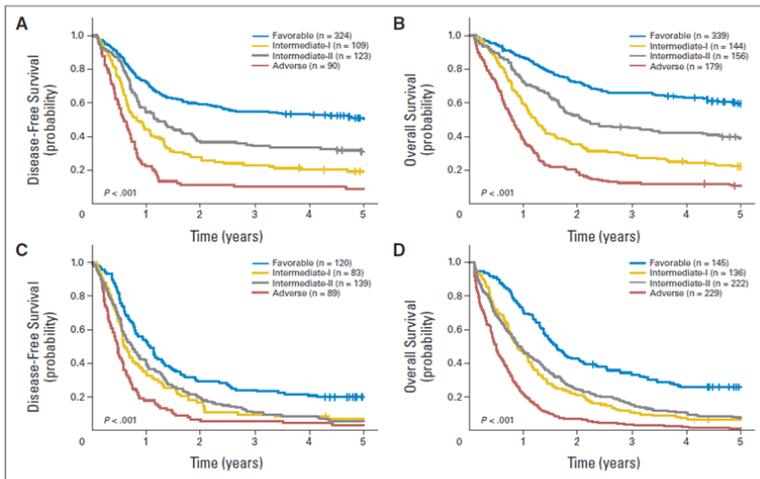


Fig 4. Outcome of patients with primary acute myeloid leukemia classified into the four European LeukemiaNet genetic groups according to the European LeukemiaNet recommendations. (A) Disease-free survival and (B) overall survival of patients younger than age 60 years; (C) disease-free survival and (D) overall survival of patients age 60 years or older.

Mrozek K et al. *J Clin Oncol* 2012

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## Slide 10. Outcome by ELN Risk Group

Now if you look at those ELN risk groups, you can see that patients do quite differently in terms of their overall survival and their survival free of leukemia. The images on this slide are called Kaplan-Meier curves and they're bread and butter of hematology-oncology practice. On the left part of the graph, it's the overall survival or the overall proportion of patients who are alive and free from disease, and in the bottom axis, the X axis is time. And so, you can see, for instance, in graph B there, if you're on the blue line, the favorable line, 100% of the patients are alive at baseline and a year later it's about 95%. And even if you go out to 5 years it's still about 75%. If you're in the adverse risk group, already by year 2 that red line is down about 20%. So, you can see these risk groupings really do have a major difference in terms of outcomes for patients. And so, it's important to know that.

## AML Survival by Age

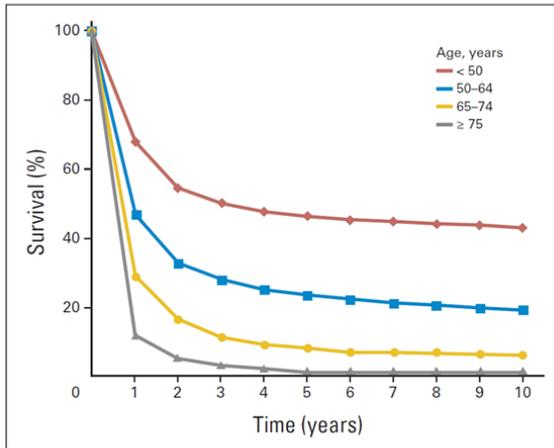


Fig 1. Relative survival by time and age for acute myeloid leukemia based on SEER data.

Klepin et al. JCO 2014

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### Slide 11. AML Survival by Age

Age also makes a huge difference. The red line on this slide is people who are under 50, the yellow line, those who are 65 and 74, and again you can see long term, 10 years later, big differences in how folks do. And that certainly influences how we counsel patients.

## Why Do Older Patients with AML Have A Poorer Prognosis?

- Frailer and more commonly have other health problems
- Less favorable and more unfavorable cytogenetics
- Higher incidence of preceding MDS
- Elevated therapy-related morbidity and mortality
- Higher incidence of treatment-resistant disease
- Lower rates and duration of complete remission, and shorter median overall survival
- Less likely to be eligible for allogeneic hematopoietic cell transplantation



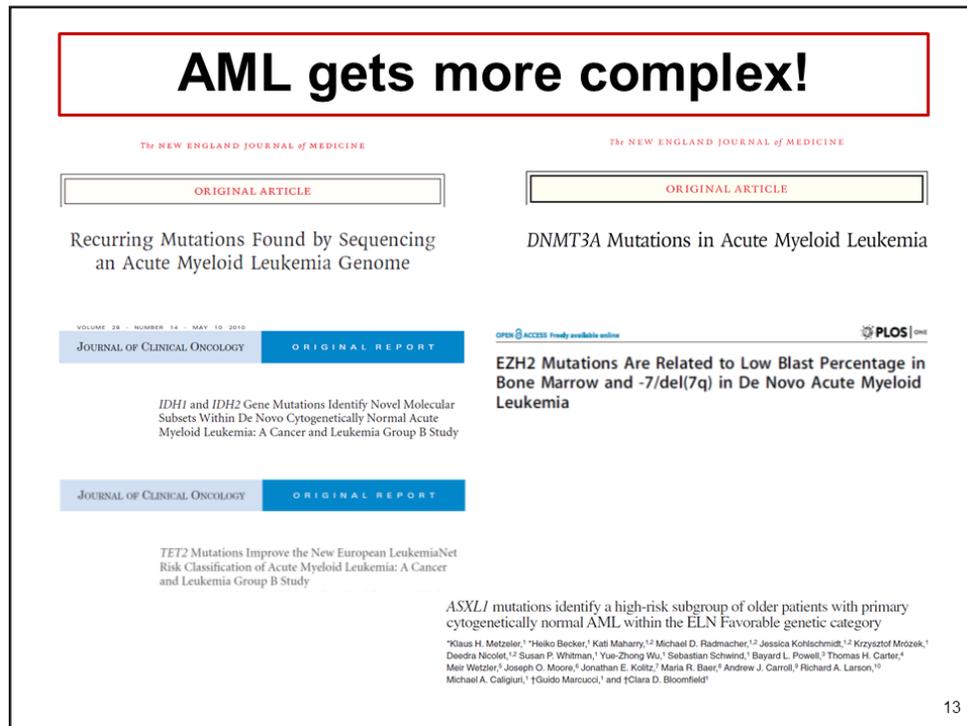
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### Slide 12. Why Do Older Patients with AML Have a Poorer Prognosis?

Why is it that older patients do worse? Well, they're more likely to have other health problems that make it difficult to treat the leukemia. They tend to have more complex DNA changes, as a result of lifetimes of injury or errors in copying by the DNA in the cells. You know, all through our lives these stem cells, these seed cells in the bone marrow, they're copying their

DNA, every day they have to copy 3 billion letters. And you can imagine just like a Medieval scribe copying a manuscript, you know, every once in a while, they screw up, they make a mistake, they put the wrong letter in. And most of the time that makes no difference, we can still read the word the monk wrote, even if it's an A instead of an E. But sometimes it does make a difference and the word meaning changes and that's exactly the same process that happens in the cells in the bone marrow. And so, as we go through life we can actually measure the number of mutations and they increase with time.

Older patients are more likely to have prior MDS or another condition, and they're less likely to get in remission and less likely to be candidates for a stem cell transplant, which we do up to about age 75 now if a person is healthy otherwise.



**AML gets more complex!**

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Recurring Mutations Found by Sequencing an Acute Myeloid Leukemia Genome

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

DNMT3A Mutations in Acute Myeloid Leukemia

VOLUME 28 NUMBER 14 MAY 10 2010

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

OPEN ACCESS Freely available online

PLOS ONE

EZH2 Mutations Are Related to Low Blast Percentage in Bone Marrow and -7/del(7q) in De Novo Acute Myeloid Leukemia

IDH1 and IDH2 Gene Mutations Identify Novel Molecular Subsets Within De Novo Cytogenetically Normal Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

TET2 Mutations Improve the New European LeukemiaNet Risk Classification of Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study

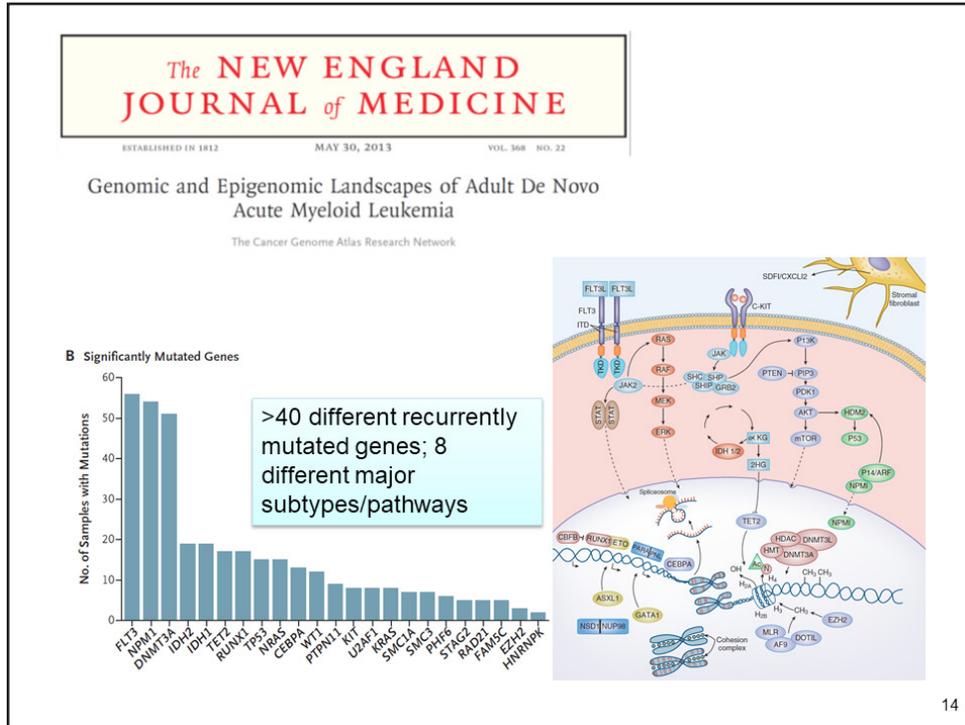
ASXL1 mutations identify a high-risk subgroup of older patients with primary cytogenetically normal AML within the ELN Favorable genetic category

\*Klaus H. Metzeler,<sup>1</sup> \*Helko Becker,<sup>1</sup> Kati Maharry,<sup>1,2</sup> Michael D. Radmacher,<sup>1,2</sup> Jessica Köhlschmidt,<sup>1,2</sup> Krzysztof Młózek,<sup>1</sup> Deedra Nicollet,<sup>1,2</sup> Susan P. Whitman,<sup>1</sup> Yue-Zhong Wu,<sup>1</sup> Sebastian Schwind,<sup>1</sup> Bayard L. Powell,<sup>3</sup> Thomas H. Carter,<sup>4</sup> Meir Wetzler,<sup>5</sup> Joseph O. Moore,<sup>6</sup> Jonathan E. Kollitz,<sup>7</sup> Maria R. Baer,<sup>8</sup> Andrew J. Carroll,<sup>9</sup> Richard A. Larson,<sup>10</sup> Michael A. Caligiuri,<sup>1</sup> †Guido Marcucci,<sup>1</sup> and †Clara D. Bloomfield<sup>1</sup>

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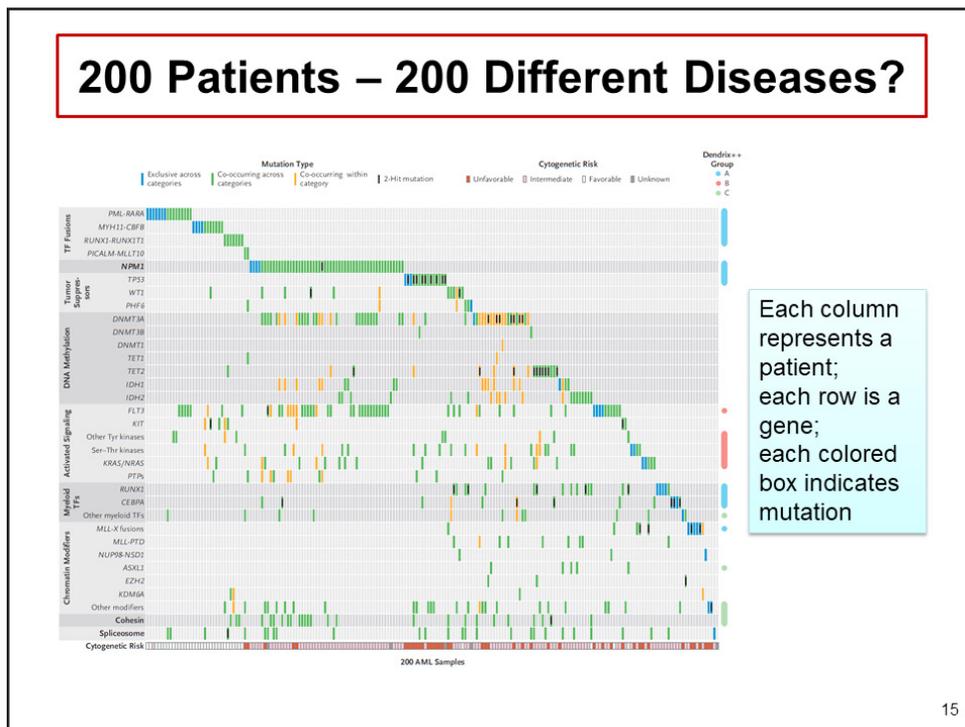
## Slide 13. AML gets more complex!

Now in the last few years there've been a lot of different, very exciting genome sequencing studies that have disclosed a bunch of new mutations that affect both how we understand how leukemia evolves and increasingly how patients are treated. Here are 6 key papers first describing 6 different mutations that are common in patients with AML. And each of these modifies the risk and for several of these we have targeted therapies such as IDH1 and 2, the first drug for which was approved just a few months ago.



Slide 14. Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia

Now overall, we now know about more than 40 different mutated genes in AML and they cluster into a bunch of different pathways. FLT3, NPM1 and DNMT3A are the most common, but the others definitely are highly recurrent and do matter in terms of how we approach patients.

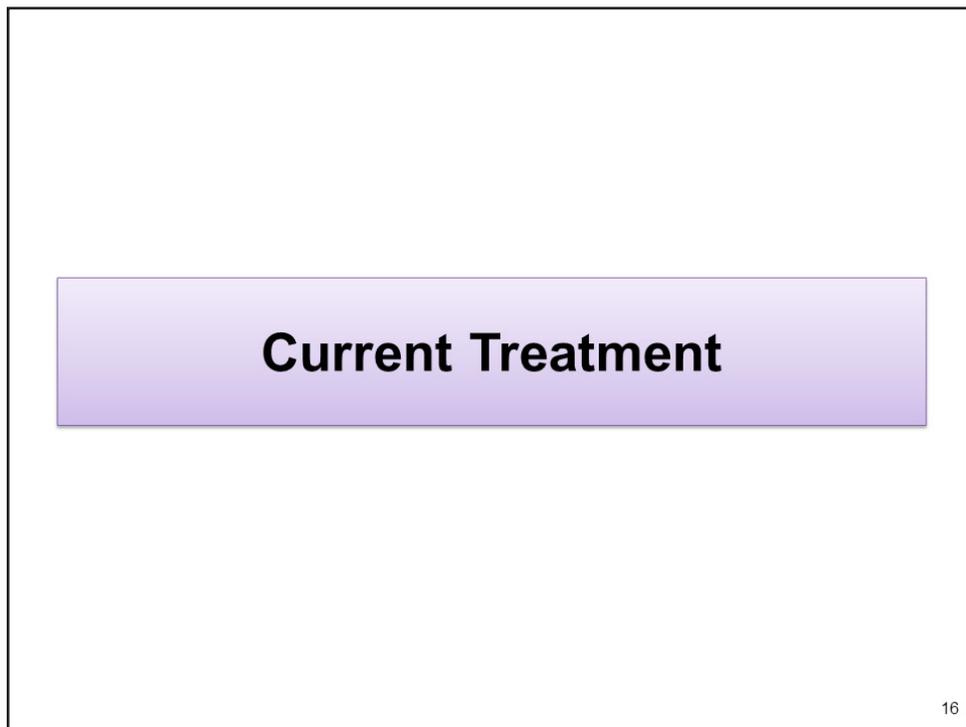


Slide 15. 200 Patients – 200 Different Diseases?

Now this has gotten actually quite complicated and this figure I think demonstrates the challenge that leukemia drug developers have and that we have as physicians caring for patients with these diseases. So, each column here is a patient,

each row is a gene, and you can see from the sort of – if it's mutated it's colored in – and you can see from the scattered pattern of these gene mutations, that of these 200 patients with AML who underwent sequencing, there was hardly a one that had the same gene complement, the same mutations as the other person. And so do we have to come up with 200 different regimens for these 200 different patients?

Well, probably not, but we probably do need to come up with 20 or 30 different approaches, and this is what clinicians are working on right now. This is part of the Beat AML Trial that LLS is leading, where patients, depending on their genotype, are assigned to one regimen versus another.

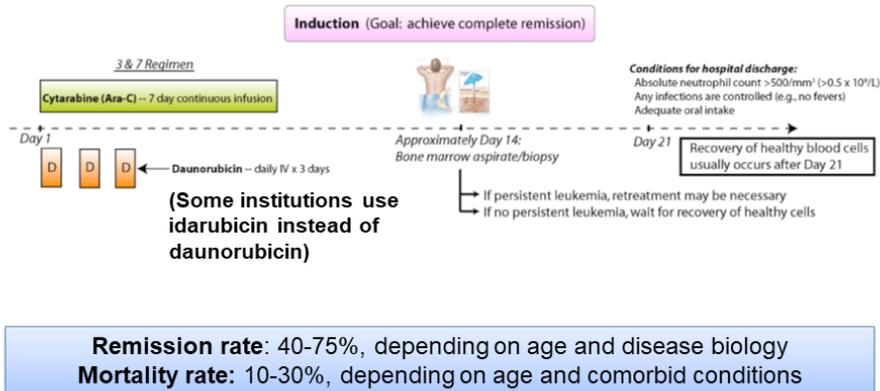


### Slide 16. Current Treatment

So that's a bit about the genetic diversity about AML, how it's defined, how we assess, how likely patients are to do well long term or need a transplant. Let's get into treatment.

## “3&7” or “7+3” – The Standard Remission Induction Approach for “Fit” Patients From 1973-2017

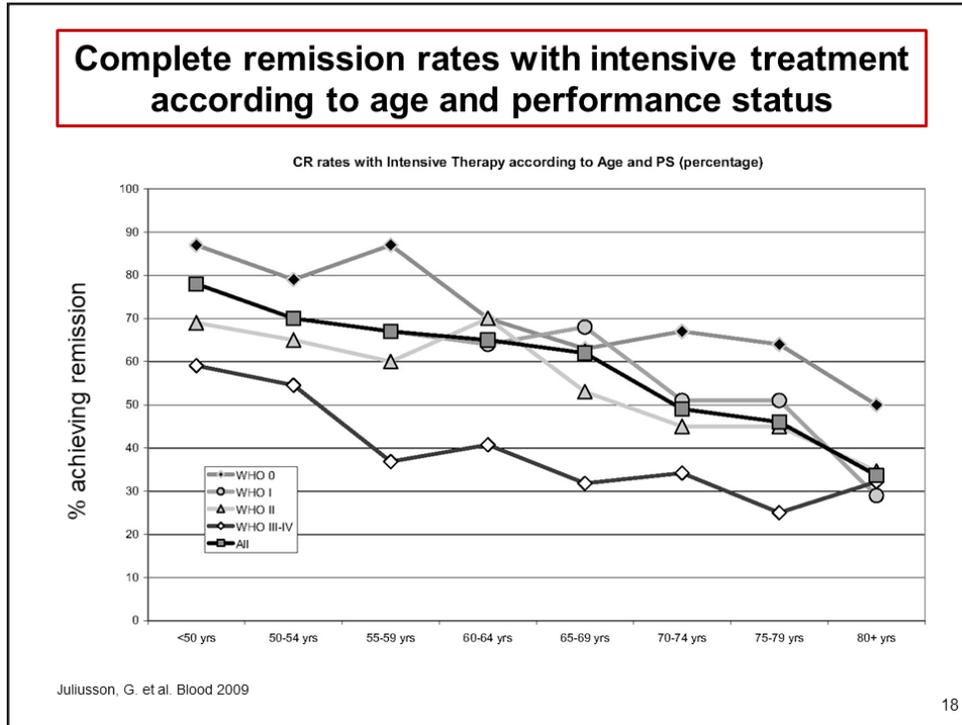
### Standard Non-Protocol Therapy for Acute Myeloid Leukemia (AML)



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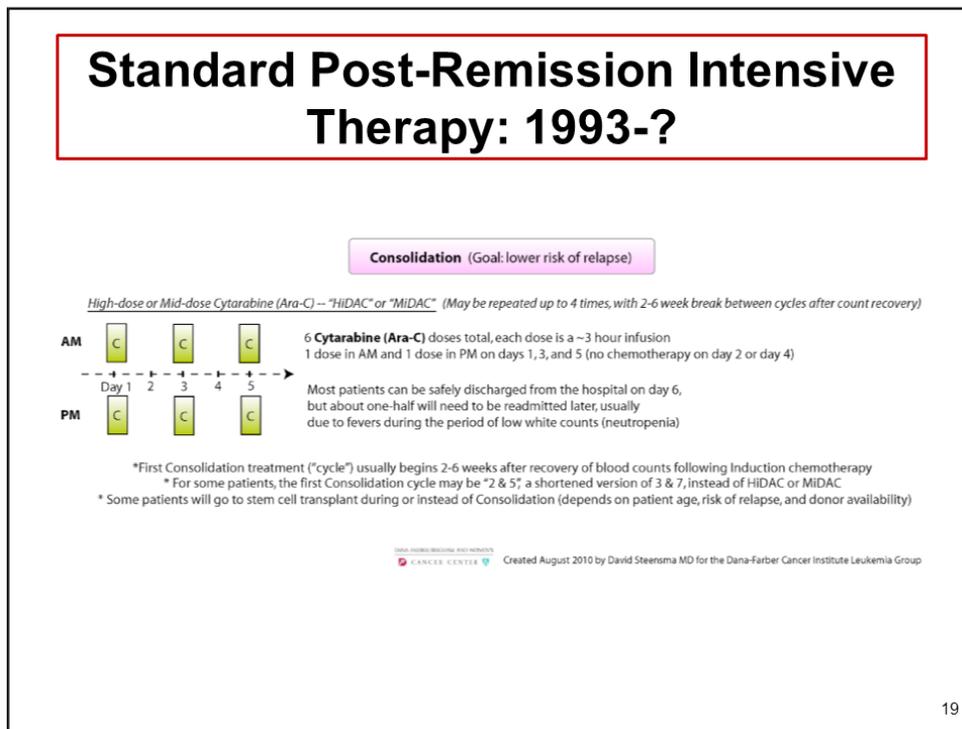
### Slide 17. “3&7” or “7+3” – The Standard Remission Induction Approach for “Fit” Patients From 1973-2017

Now since I was a little guy in the 1970s, playing Little League Baseball, until this year, we were using the same regimen for chemotherapy of AML. And it wasn't for want of trying to make it better. There were dozens and dozens of clinical trials, adding new drugs, changing schedules, changing doses, and almost none of them improved over what's called 3&7 or 7+3, the standard approach for fit patients, that is for patients who can tolerate such a regimen. And what it involves is a seven day continuous infusion of Ara-C or cytarabine, one chemotherapy medicine, and then 3 IV pushes of either daunorubicin or idarubicin, which are really equivalent. Then about 2 weeks after starting a bone marrow biopsy is done. You look and see the leukemia cells; do they appear to be gone? If they're gone then we just wait for healthy cells to recover, which usually happens about 10 days later and then the patient can go home. If they're not gone then we typically repeat a version of 3&7, often shorter, 2&5. And for some patients we actually switch to a different therapy.



**Slide 18. Complete remission rates with intensive treatment according to age and performance status**

Depending on age and other conditions, this can induce a remission rate of up to 75-80%, but at the cost of a mortality rate, ie, a death rate in the hospital of between 10% and 25% to 30%, depending on the age and condition of the patient.



**Slide 19. Standard Post-Remission Intensive Therapy: 1993-?**

This is a very large study from Sweden here which shows what the complete remission rate is with intensive treatment, according to both age of the patient, with the younger folks on the left, and performance status. Performance status is a measure of how functional a person is. So, if they're able to get up and go to work, they have WHO (World Health

Organization) zero performance status. If they're in bed or a chair much of the day they have 3 or 4 performance status and their outcomes are not as good.

But it's not a bad regimen, it does work for a lot of people, has saved many lives over the years, it's just that it's not where we need to be. And that's why there's so much interest in moving beyond this.

Now once a person achieves a remission, then what do we do? Well, 1 of 2 things. For patients with high risk disease we tend to refer them for transplant if they can get it. For the good risk leukemias or those who don't have transplant as an option, we'll typically do up to 4 cycles of a cytarabine-based chemotherapy. That's usually about 5 or 6 days long and some places do that as an outpatient, some do it as an inpatient, and it generally is better tolerated than the initial induction.

### Emerging Approaches

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**Slide 20. Monitoring for CML response needs improvement**

So, what's coming?

## 2017 Acute Myeloid Leukemia FDA Approvals



- 4/28/17: **Midostaurin** (Rydapt™; Novartis)
  - For adult patients with newly diagnosed AML who have a FLT3 mutation
  - Companion diagnostic: Invivoscribe LeukoStrat CDx FLT3 mutation assay
- 8/1/17: **Enasidenib** (Idhifa™; Agios)
  - For adult patients with relapsed/refractory AML who have an IDH2 mutation
  - Companion diagnostic: Abbott m2000 RealTime IDH2 mutation assay
- 8/3/17: **CPX351** / fixed ratio daunorubicin-cytarabine (Vyxeos™; Jazz)
  - For adults with either of two types of AML: newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
- 9/1/17: **Gemtuzumab ozogamicin** (Mylotarg™; Pfizer)
  - For adults with newly diagnosed AML whose tumors express the CD33 antigen (CD33+), and for treatment of patients 2 years or older with relapsed/refractory CD33+ AML

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### Slide 21. 2017 Acute Myeloid Leukemia FDA Approvals

Well, I mentioned this has been a big year for leukemia drug development. We've had 4 drugs approved. In April midostaurin, also known as Rydapt®, that's a FLT3 inhibitor and it's specifically for patients with AML who have a FLT mutation, that's about 30% of patients. In August we had 2 approvals, 2 days apart, enasidenib, also known as Idhifa®, this is for patients with relapsed/refractory disease who have an IDH2 mutation, although it is also effective in patients who've just been newly diagnosed.

And then CPX351, this is the same 2 medicines that are in 3&7, daunorubicin and cytarabine, but they're put in a little lipid particle, little very nanomolar, very high tech particle that gets more into the bone marrow where you want it, and less other places like the lining of the gut or the mouth or the heart or places you don't want it. You want it just to go to the leukemia cells and we haven't been able to do that with 3&7. CPX351 does it a little better.

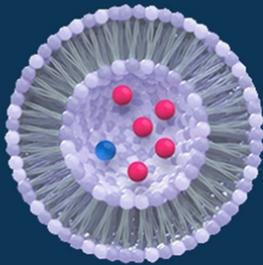
The study for CPX351 showed that there was a survival advantage, but only for a specific group of patients, who we'll talk about in just a moment.

And then finally gemtuzumab ozogamicin, this drug was actually originally approved in 2000 and then some studies showed that it wasn't probably being used right, it wasn't as safe or effective as had originally looked, and so was taken off the market in 2010. But then additional studies showed, well, if we used it a different way it actually was quite effective and helpful and so the FDA said alright, we'll reapprove this. And this is an antibody directed against a marker called CD33, which is present on the leukemia cells in a large proportion of patients. So, this drug is back as well.

It's likely that by the end of the year we'll have another approval, ivosidenib, which is an IDH1 inhibitor, and we may have others as well.

## CPX-351 Structure

### CPX-351 Uses a Nano-Scale Delivery Complex



- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

Source: Celator

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### Slide 22. CPX-351 Structure

So, let's just go through each of these in turn. So CPX351 uses a nano-scale delivery complex, so these little fatty capsules called liposomes, and they have 5 of the pink molecules, cytarabine for every one of daunorubicin.

## CPX-351 Trial Design

### Randomized Phase 3 Trial of CPX-351 vs "7+3" in Older Patients with sAML

Primary Endpoint:  
Overall Survival

#### Eligibility

- Previously untreated sAML or tAML
- Ages 60- 75
- Able to tolerate intensive therapy
- PS 0-2

#### CPX-351

100 units/m<sup>2</sup> IV days 1, 3, 5  
Up to 2 inductions and 2 consolidations

#### 7+3

Daunorubicin 60 mg/m<sup>2</sup>  
Cytarabine 100 mg/m<sup>2</sup>

Source: Celator

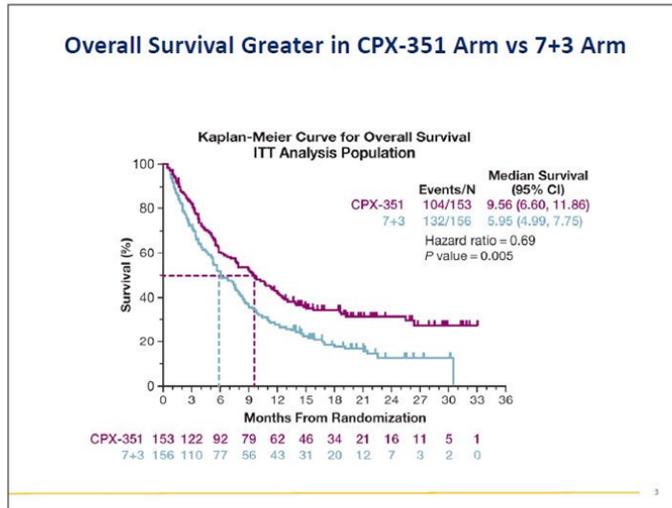
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### Slide 23. CPX-351 Trial Design

This was studied in a randomized trial in which patients between 60 and 75, who had either therapy-related AML or secondary AML, after prior MDS or myelofibrosis, they could get enrolled. And they either got the standard 7&3 or they got CPX351. Now CPX351 is a little easier to give because instead of being a seven day continuous infusion where you're hooked up to an IV pole and you can't take a shower, etcetera, it's given over a couple of hours on day 1, day 3 and day

5. It's also a very pretty purple and some of our nurses have very much liked the color of this compared to daunorubicin, which is kind of a nasty orange look.

## CPX-351 Trial Result

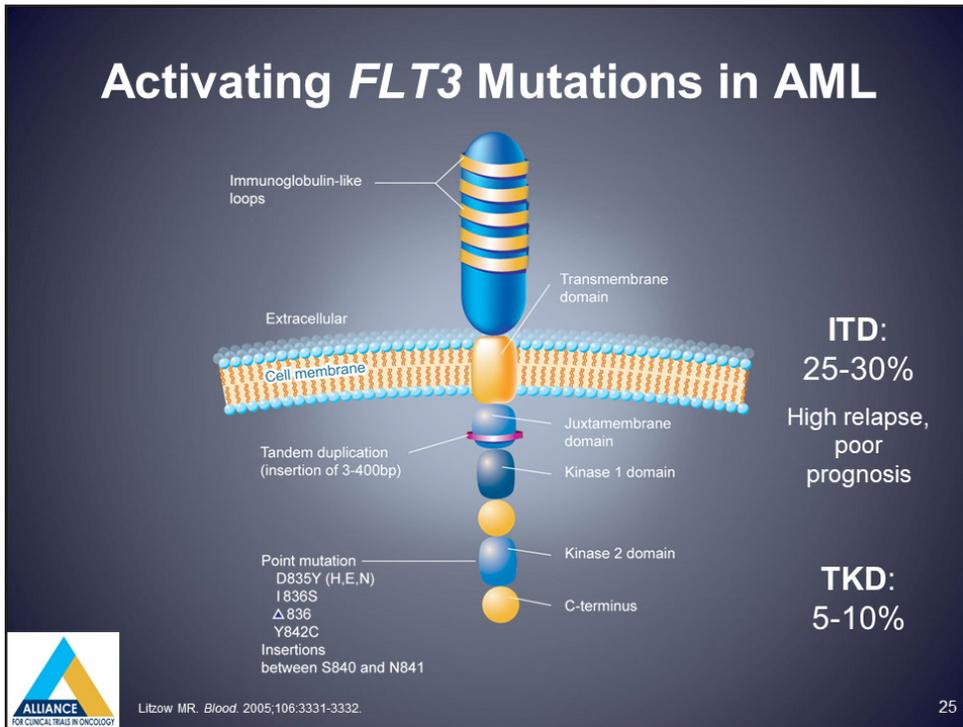


Lancet J et al ASCO 2016 annual meeting

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### Slide 24. CPX-351 Trial Result

But anyway, so half of the patients got one, half got the other, and the patients who got the CPX351, that's the purple line here, you can see after a few months they were more likely to be alive than those who got the 7&3, the standard therapy. So by 9 months it was a pretty substantial difference; 50% were alive who got CPX351, 30% who got 7&3. So, I've used this drug in my own patients, we now have it on our formulary here, and for that subset between 60 and 75 who have higher risk AML, this is certainly a very reasonable choice.



**Slide 25. Activating *FLT3* Mutations in AML**

I mentioned FLT3. Twenty-five to 35% of patients have activating mutations in this complex. You can see a picture of it here, the little squiggly things are the cell surface and then the thing that looks like a cricket bat or an antenna, that is the actual FLT3 signaling molecule. When it's mutated it's like a switch that's turned on all the time, like pushing the gas all the time without the brake, and the cell divides and becomes a leukemic cell.



## **A Phase III Randomized Double-blinded Study Of Chemotherapy +/- Midostaurin (PKC412) In Newly Diagnosed Adults aged 18-60 with *FLT3* Mutated Acute Myeloid Leukemia (AML)**

Richard M. Stone, Sumithra Mandrekar, Ben L Sanford, Susan Geyer, Clara D. Bloomfield, Konstanze Dohner, Christian Thiede, Guido Marcucci, Francesco Lo-Coco, Rebecca B. Klisovic, Andrew Wei, Jorge Sierra, Miguel A. Sanz, Joseph M. Brandwein, Theo de Witte, Dietger Niedewieser, Frederick R. Appelbaum, Bruno C. Medeiros, Martin S Tallman, Jurgen Krauter, Richard F. Schlenk, Arnold Ganser, Hubert Serve, Gerhard Ehninger, Sergio Amadori, Richard A. Larson, and Hartmut Dohner

Participants: ALLIANCE/CALGB, AMLSG, CETLAM, ECOG, EORTC, GIMEMA, NCIC, OSHO, PETHEMA, SAL, SWOG

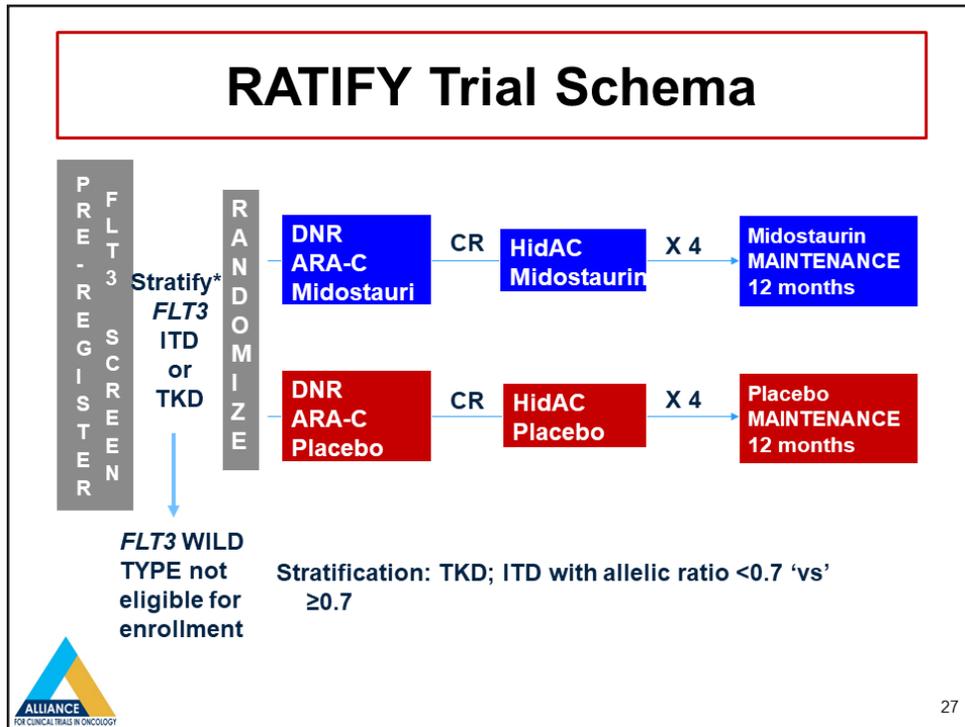
CTEP sponsored, Novartis provided drug and sponsored outside North America, and Alliance (formerly CALGB) chaired study, collected data and performed analysis



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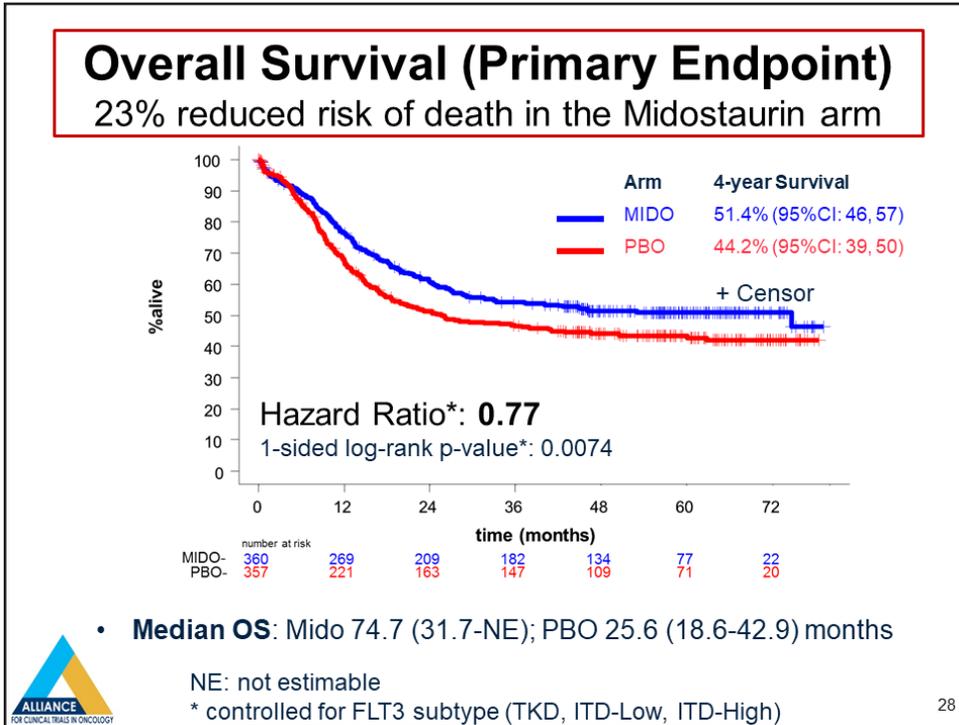
### **Slide 26. A Phase III Randomized Double-blinded Study Of Chemotherapy +/- Midostaurin (PKC412) In Newly Diagnosed Adults aged 18-60 with *FLT3* Mutated Acute Myeloid Leukemia (AML)**

And for many years people have tried to come up with inhibitors that affected this. And there's now 6 or 7 of them out there. But the first one that was studied by my colleague Rich Stone here in Boston and a number of associates, this compared the standard chemotherapy with midostaurin versus the standard chemotherapy with placebo.



**Slide 27. RATIFY Trial Schema**

Now a note about placebos. Very few trials in oncology, at least in the leukemia world, are placebo-controlled. The only time that they're placebo-controlled is when somebody is already getting a standard therapy or there is no standard therapy for their condition. So here it would have been unethical to say, okay, these people are getting midostaurin, these people aren't, and then we're not going to give them anything else. So, everybody got the standard treatment, it was just one group got midostaurin in addition, and the other got a placebo. So that's an ethical design. Because we didn't know, the midostaurin could have been worse, it could have just added side effects without improving remissions or survival.

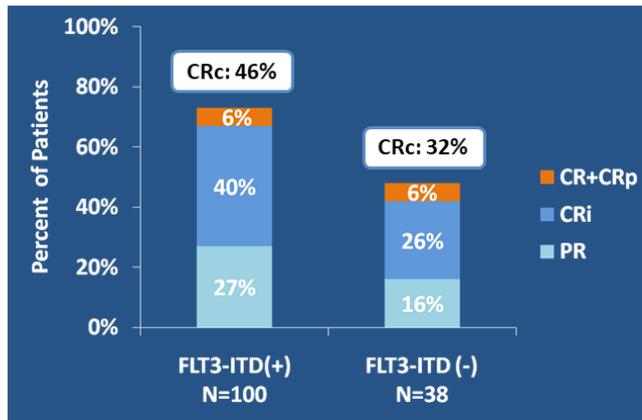


**Slide 28. Overall Survival (Primary Endpoint)**

But in this case, in contrast to a number of other studies, which didn't show a survival benefit, there was a survival benefit. It was modest, it was at 3 years, 36 months, there was about a 7% survival difference, which is a small benefit. We still have more work to do certainly, but if you're 1 of those 7 out of 100, that's a big deal for you. And so, this drug got approved and it's something that we're routinely using now.

Sorafenib is another FLT3 inhibitor that is approved for kidney cancer and liver cancer, but where we can sometimes get it, and some doctors use that.

## Phase 2 Study of Quizartinib in AML: Response Rate



- Median duration of response: 12.1 weeks FLT3-ITD(+) & 7.0 weeks FLT3-ITD(-)
- 75% of FLT3-ITD(+) and 48% of FLT3-ITD(-) patients refractory to their last prior therapy, achieved at least a PR to quizartinib

Levis et al ASH 2015

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### Slide 29. Phase 2 Study of Quizartinib in AML: Response Rate

There's also a couple of new ones in development that aren't approved yet, so one of them is shown here, quizartinib, this in patients with relapsed or refractory AML and refractory means they didn't respond to their prior therapy, had a 46% response rate in those that had the specific mutation called ITD.

## Clinical Response to Gilteritinib Treatment by FLT3 Mutation or TKI Status

Clinical Response	≥80 mg Gilteritinib				
	Mutation Type			TKI Status	
	FLT3-ITD only N=142	FLT3-D835 only N=11	ITD and D835 N=9	Prior TKI N=40	TKI Naïve N=127
CR	16 (11)	0	0	2 (5)	14 (11)
CRp	11 (8)	0	0	3 (8)	8 (7)
CRi	38 (27)	1 (9)	4 (44)	9 (23)	35 (28)
PR	15 (11)	2 (18)	0	5 (13)	13 (10)
<b>CRc (CR+CRp+CRi)</b>	<b>65 (46)</b>	<b>1 (9)</b>	<b>4 (44)</b>	<b>14 (35)</b>	<b>57 (45)</b>
<b>ORR (CRc+PR)</b>	<b>80 (56)</b>	<b>3 (27)</b>	<b>4 (44)</b>	<b>19 (48)</b>	<b>70 (55)</b>

Data presented as n (%).

CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; ORR, overall response rate; PR, partial response.



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### Slide 30. Clinical Response to Gilteritinib Treatment by FLT3 Mutation or TKI Status

And then gilteritinib, it's another one that's moving forward. And this drug as well had a complete response rate of over 40% in those with the mutation who were treated with it.

So, both of these, plus a couple of other drugs like crizotinib, are being studied in patients and at least have a chance of approval down the road.

## IDH1/2-mutant AML

- Mardis et al, NEJM 2009: First description of *IDH1* mutations in ~8% of patients with AML, associated with normal cytogenetic status (cn-AML).
- Subsequent studies found a larger subset, ~15%, of patients with mutations in the *IDH2* gene.
- IDH proteins, essential to the Krebs Cycle, catalyze decarboxylation of isocitrate to  $\alpha$ -ketoglutarate ( $\alpha$ -KG) in cytoplasm (*IDH1*) and mitochondria (*IDH2*).
- Mutant IDH enzymes catalyze an NADPH-dependent reduction of  $\alpha$ -KG to 2-hydroxyglutarate (2-HG).
- This leads to accumulation of 2-HG onco-metabolite in IDH-mutant tumors.

Ward et al. Cancer cell, 2010, Gross et al. J Exp Med 207:339-44, 2010, Dang et al. Nature 462:739-44, 2009.

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**Slide 31. IDH1/2-mutant AML**

So, what about the IDH mutations? So, what these do is these actually are present in about 15 to 20% of patients with AML, and they affect the way that the cell uses energy. And there's this cycle called the Krebs cycle, if there's any biochemists on the call or in fact anybody who took cell biology 101 in college, they had to memorize this Krebs cycle at one point. We torture our first year medical students with making them memorize it because it does have different implications in various aspects of medicine.

But what this mutation does, it's an enzyme in the Krebs cycle that gets mixed up and it changes the way that the cells grow and divide, and leads to the cell becoming malignant. This mutation is not restricted to AML, there's a few other tumors like brain tumors that also have IDH mutations.

### Response to Enasidenib (AG-221) in AML/MDS

	RR-AML (n = 159)	Untreated AML (n = 24)	MDS (n = 14)	All (N = 209)
<b>Overall Response</b> (CR, CRp, CRi, mCR, PR)	<b>59 (37%)</b> [95%CI: 30%, 45%]	<b>10 (42%)</b> [22%, 63%]	<b>7 (50%)</b> [23%, 77%]	<b>79 (38%)</b> [31%, 45%]
<b>CR</b>	<b>29 (18%)</b> [95%CI: 13%, 25%]	<b>4 (17%)</b> [5%, 37%]	<b>3 (21%)</b> [5%, 51%]	<b>37 (18%)</b> [13%, 24%]
CRp	1 (1%)	1 (4%)	1 (7%)	3 (1%)
CRi	3 (2%)	0	0	3 (1%)
mCR	9 (6%)	1 (4%)	3 (21%)	14 (7%)
PR	17 (11%)	4 (17%)	0	22 (11%)
SD	72 (45%)	9 (38%)	6 (43%)	96 (46%)
PD	10 (6%)	1 (4%)	0	11 (5%)
Not evaluable	18 (11%)	4 (17%)	1 (7%)	23 (11%)

- Overall response by IDH mutation type: R140Q 36% / R172K 42%

CR, complete response; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete hematologic recovery; mCR, marrow CR; PR, partial response; SD, stable disease; PD, progressive disease

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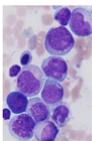
### Slide 32. Response to Enasidenib (AG-221) in AML/MDS

Enasidenib, the second drug to get approved this year, formerly known as AG-221, in those patients it had a complete response rate of about 18% and an overall response rate of almost 40%. This is useful, this particular drug, as a bridge to transplant for some patients. I've treated a number of my own patients with it who have then been able to go on and get transplant. And now it's being added to chemotherapy, just like midostaurin was.

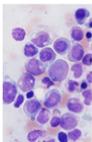
### Clinical activity of AG-120 in R/R AML

Patient achieved CR by end of Cycle 1

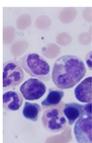
Screening  
44% blasts



Cycle 1  
Day 15  
3% blasts



Cycle 1  
Day 28  
2% blasts



	Dose escalation	
	R/R AML n=63	Overall N=78
CR, n (%)	10 (16)	14 (18)
CRi/CRp, n (%)	8 (13)	8 (10)
PR, n (%)	1 (2)	2 (3)
mCR/MLFS, n (%)	2 (3)	6 (8)
SD, n (%)	27 (43)	30 (38)
PD, n (%)	8 (13)	8 (10)
NE, n (%)	7 (11)	10 (13)
<b>ORR, n (%)</b> [95% CI]	<b>21 (33)</b> [22, 46]	<b>30 (38)</b> [28, 50]

DiNardo et al ASH 2016

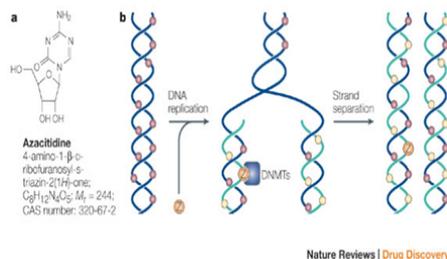
Data cut off date 1 August 2016  
CR = complete response; CRi = CR with incomplete neutrophil recovery; CRp = CR with incomplete platelet recovery; PR = partial response; mCR/MLFS (marrow CR/morphologic leukemia-free state) = <5% blasts in bone marrow, no hematologic recovery; SD = stable disease; NE = not evaluable; ORR = overall response rate (CR + CRi + CRp + PR + mCR/MLFS)

### Slide 33. Clinical activity of AG-120 in R/R AML

So, AG-120, ivosidenib, is also active for patients who have an IDH1 mutation instead of an IDH2, and again with an overall response rate of between 30 and 40%.

## DNA Hypomethylating Therapies

- Less intensive treatment, increasingly used for frailer or older patients
- Typically administered in outpatient clinic
- Can lead to therapeutic responses, including transfusion independence, decrease in leukemic burden, and less commonly, remissions
- However, responses often transient, with leukemic progression and brief post-HMA survival
- **Decitabine** and **azacitidine** FDA approved for MDS (and AML with 20-30% blasts)
- Development: guadecitabine (SGI-110), CC-486, ASTX727



Issa JP, et al. Nature Reviews Drug Discovery 2005.

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### Slide 34. DNA Hypomethylating Therapies

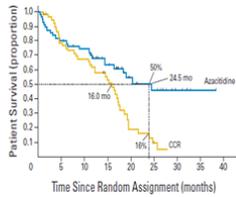
Okay, so the so-called DNA hypomethylating therapies, so what these are, there's 2 of them that are out there on the market. One is azacitidine or Vidaza®, the other is decitabine or Dacogen®. They are not as intense as intensive chemotherapy with 3&7. They don't make people lose their hair, they tend not to make people very sick, but they can lead to responses. Now they probably don't cure anybody, but they certainly can, particularly for the older or frailer patient who's not a good candidate for intensive therapy, they can induce a remission in many of those patients and extend life and help them feel better.

Unfortunately, we don't know ahead of time how to predict who's going to respond to these drugs and some patients have only a very brief response. These drugs, what they do, the way they work, is by changing the way the DNA is folded and the way the DNA is transcribed, the way genes are turned on and turned off. And to be honest, even though azacitidine was approved 13 years ago, 2004, for myelodysplastic syndromes and low blast count AML, and even though decitabine was approved in 2006, we still don't really understand how it is that these drugs work. But they are available, and many patients have been treated with them.

There's a couple of other drugs in the same class that are moving forward. There's an oral form of azacitidine called CC-486, there's an oral form of decitabine called ASTX727. These are both active agents that are currently being studied in randomized trials. And then there's guadecitabine or SGI-110, that's kind of like a super decitabine. It seems to be more potent in some patients for whom decitabine didn't work, responded, and that drug is moving forward in randomized trials as well, to see if it's any better than what we have now. So, this is an area of particular interest.

## Hypomethylating Therapy among Older Adults

Azacitidine Prolongs Overall Survival Compared With Conventional Care Regimens in Elderly Patients With Low Bone Marrow Blast Count Acute Myeloid Leukemia

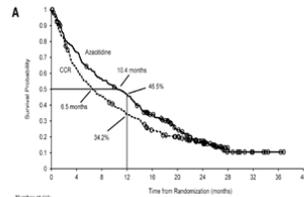


No. of patients at risk	Azacitidine	Conventional Care
0	55	58
5	43	43
10	38	36
15	26	22
20	15	6
25	10	3
30	4	0
35	1	0
40	0	0

CR rate: 18% (10/55)

Fenaux P, et al. JCO 2010

International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

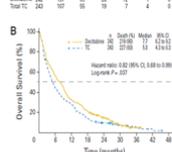
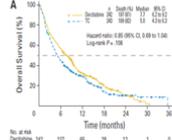


No. at risk	Azacitidine	Conventional Care
0	241	247
4	114	133
8	108	128
12	73	108
16	44	80
20	22	53
24	5	40
28	3	25
32	2	10
36	1	3
40	0	1

Azacitidine (n = 241)		
	No.	%
<b>Hematologic response*</b>		
CR + CRi	67	27.8
CR	47	19.5
CRi	20	8.3

Dombret H, et al. Blood 2015

Multicenter, Randomized, Open-Label, Phase III Trial of Decitabine Versus Patient Choice, With Physician Advice, of Either Supportive Care or Low-Dose Cytarabine for the Treatment of Older Patients With Newly Diagnosed Acute Myeloid Leukemia



Response	Supportive Care (n = 228)		Cytarabine (n = 215)		Total TC (n = 243)		Decitabine (n = 242)	
	No.	%	No.	%	No.	%	No.	%
CR	1	3.6	17	7.9	18	7.4	38	15.7
CRi	1	3.6	6	2.8	7	2.9	24	9.9
CRp	0	0	1	0.5	1	0.4	5	2.1
CR + CRp	1	3.6	18	8.4	19	7.8*	43	17.8*

Kantarjian H, et al. JCO 2012

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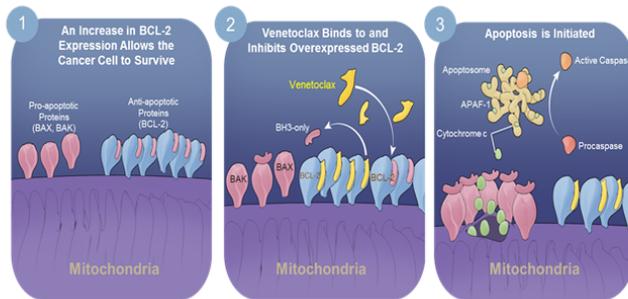
TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes

Weich et al. NEJM 2016

### Slide 35. Hypomethylating Therapy among Older Adults

Now again, a complete response rate, where all the blood counts go to normal and the blasts go away, that's not very high, it's only about 15 to 20%. But the rate in which we see benefit is higher than that, closer to 40%. And there are some groups, like those with TP53 mutations, who would do very poorly with intensive chemotherapy most likely, for whom decitabine seems to be particularly effective. So that's become kind of our go-to drug for patients with TP53 mutation. Based on a paper last year, Washington University in St. Louis published in the New England Journal of Medicine, in collaboration with a group in Chicago, so that type of therapy is out there.

## Venetoclax: An Oral Selective BCL-2 Inhibitor



- Venetoclax was shown to synergize with HMA in preclinical models, suggesting that combination with HMA may be a promising approach in AML
- FDA approved for CLL
- Reported: phase 1b, open-label, nonrandomized, dose-escalation trial of venetoclax in combination with DEC or AZA in older ( $\geq 65$  years), treatment-naive AML patients (NCT02203773)
- *Ongoing: randomized trials in up-front and relapsed/refractory AML*

1. Souers A, et al. *Nat Med*. 2013;19:202-8; 2. Pan R, et al. *Cancer Discov*. 2014;4:362-75; 3. Konopleva M, et al. 56<sup>th</sup> Annual American Society of Hematology; December 6-9, 2014; Abstract 118; 4. Tsao T, et al. *Ann Hematol*. 2012;91:1861-70.

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### Slide 36. Venetoclax: An Oral Selective BCL-2 Inhibitor

How can we make that better? Well, there's a drug approved for CLL, chronic lymphoid leukemia, called venetoclax and it also is useful in some forms of lymphoma. And what it does is it kind of primes cells to die by inhibiting a factor called BCL2, that's like a survival message for them. And a very provocative study from our colleagues down in Houston, combining venetoclax plus either decitabine or azacitidine, showed a very high response rate with this combination. And so randomized trials are ongoing.

## Venetoclax + HMA Efficacy in AML

Overall Response, n (%)	Arm A (VEN + DEC)		Arm B (VEN + AZA)		Total
	VEN 400 mg (n=6)	VEN 800 mg (n=12)	VEN 400 mg (n=4)	VEN 800 mg (n=12)	
					N=34
CR+CRi	3 (50)	9 (75)	4 (100)	7 (58)	23 (68)
ORR (CR+CRi+PR)	3 (50)	10 (83)	4 (100)	7 (58)	24 (71)
CR+CRi+PR+MLFS	3 (50)	11 (92)	4 (100)	10 (83)	28 (82)

- 27/45 (60%) patients achieved CR/CRi, 1/45 (2%) had partial remission (PR), and 4/45 (9%) patients achieved morphologic leukemia free state (MLFS) when treated at all dose levels
- 23/34 (68%) patients achieved CR/CRi when treated at 400 and 800mg dose levels
- Median time to CR/CRi was 1 month (range, 0.8–3.8)
- The median duration of response was 8.4 months (95% CI = 6.8—not reached)
- 7/45 (16%) patients experienced morphologic relapse after achieving a CR or CRi
- Median time on study was 3.2 months (range, 0.2–14.6)

Dinardo C, ASH 2015, Abstract 327  
 Pollyea D, ASCO 2016, Abstract 7009.

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### Slide 37. Venetoclax + HMA Efficacy in AML

So over 70% of the patients had a response to this combination, which is better than we'd expect just from azacitidine or decitabine alone. So, lots of excitement right now around this combination. We've used this for some patients off-study when azacitidine or decitabine weren't helping them anymore. It's not an FDA-approved indication, but if the patient can afford it and venetoclax is over \$10,000 a month, then we can sometimes get this, and it may help a few people. But definitely better to do it in a study if we can get somebody on a trial and learn formally from that.

The cost of these drugs, it's all astronomical. They're all ridiculously expensive. And I'm not going to talk about that much more. I know this is a huge issue for LLS trying to support patients and their families. And I practiced – it was in the UK for 2 years – nobody in the UK goes bankrupt because of not being able to afford the drugs, but it certainly happens here, and so that's something our leaders need to sort out.

### Vadastuximab Talirine (SGN-CD33A; 33A) Proposed Mechanism of Action in Combination with HMA

**Anti-CD33 antibody**, engineered cysteines to enable uniform site-specific conjugation  
**Cleavable dipeptide linker**, highly stable in circulation  
**Pyrrolobenzodiazepine (PBD) dimer**, binds DNA with high intrinsic affinity

Labels in diagram: Binds to CD33 antigen, Increased CD33 cell surface density, Complex is internalized and traffics to lysosome, PBD dimer is released, Increased PBD dimer binding to DNA, DNA repair failed, PBD dimer crosslinks DNA, Apoptotic cell death.

Vadastuximab talirine (SGN-CD33A; 33A) is an investigational agent, and its safety and efficacy have not yet been established. ©2015 Seattle Genetics, Inc. All rights reserved.

Fathi AT et al. ASH 2015 38

**Slide 38. Vadastuximab Talirine (SGN-CD33A; 33A)**

Vadastuximab is an example of a class of therapy in which antibodies are bound to a poison and the antibody binds only to the leukemia cells, only to cells that have the particular marker that the antibody is going after, in this case it's CD33. Now vadastuximab turned out to have some more side effects than was anticipated and so for the moment development of this is suspended. But this is the exact same mechanism that gemtuzumab or Mylotarg®, which is now FDA approved, uses.

### Vadastuximab Best Clinical Response: Efficacy Evaluable Patients

Efficacy Evaluable	All N=49	Secondary AML <sup>d</sup> N=22	FLT3/ITD+ N=5	Age ≥75 years N=26
<b>Remission Rate (CR + CRi)</b>	<b>73%</b>	<b>77%</b>	<b>100%</b>	<b>65%</b>
CR	47%	50%	80%	38%
CRi (p) <sup>a</sup>	20%	18%	20%	19%
CRi (n) <sup>b</sup>	6%	9%	0	8%
mLFS <sup>c</sup>	2%	5%	0	4%
<b>ORR (CR + CRi + mLFS)</b>	<b>76%</b>	<b>82%</b>	<b>100%</b>	<b>69%</b>

But... 7/2017, development on hold due to excess deaths in randomized study; FDA and sponsor evaluating

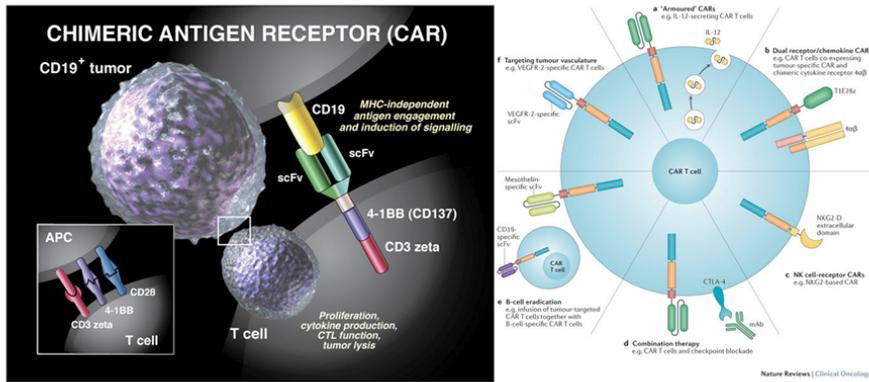
<sup>a</sup> CRi (p)= CR with ANC ≥1000/uL, incomplete platelet recovery  
<sup>b</sup> CRi (n)= CR with platelets ≥100,000/uL, incomplete neutrophil recovery  
<sup>c</sup> mLFS = morphologic leukemia-free state  
<sup>d</sup> Defined as therapy-related AML, AML evolved from prior MDS, or de novo AML with MDS-related cytogenetics

Fathi AT et al. ASH 2015 39

**Slide 39. Vadastuximab Best Clinical Response: Efficacy Evaluable Patients**

And it can lead to a very high remission rate. And so, the FDA is evaluating vadastuximab specifically. There's other CD33 antibodies in development, and I show that just because it's so similar to how Mylotarg works.

## Chimeric Antigen Receptor T (CAR-T) Cells: An Advance for ALL; Will They Be Useful Someday for AML?



Barrett DM et al *Curr Opin Pediatr* 2014;26(1):43-49  
 Jackson H et al *Nature Reviews Clinical Oncology* 13, 370–383 (2016)

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### Slide 40. Chimeric Antigen Receptor T (CAR-T) Cells: An Advance for ALL; Will They Be Useful Someday for AML?

Now CAR-T cells, chimeric antigen receptor T-cells, they make a lot of headlines. We had an approval in lymphoid leukemia, we had an approval in lymphoma just a couple of weeks ago, but will this ever be feasible for myeloid leukemias? The problem with CART-T cells in myeloid leukemia as compared to lymphoids is the target. So CD19 is a marker on B cells that are malignant and lymphoma and CLL and acute lymphoid leukemia, and if you target the patient's own immune cells by making them – bioengineering them to fight off these B cells, it gets rid of all the B cells in the body. And we can live without B cells, it turns out, we can get a monthly infusion of gammaglobulin and we can survive, but if you did that in a myeloid leukemia cell, you did that against, say, CD33, well, some of the neutrophils, the normal white cells important in fighting bacteria, they also express the CD33 and we can't live without them, there's no like infusion that you can get to make up for that. So, we don't know how to do this yet for myeloid diseases, but we'll get there, I'm confident, because there's lots of different CAR-T constructs that are being developed right now. Some of them have what's called the suicide gene, where you can put them in for a while, they clean up the leukemia cells, so they don't become a permanent force, you can turn them off and end the deployment. And so, I think one of those strategies is going to be successful.

## Immune Checkpoint Inhibitors: A Breakthrough In Solid Tumors, What About AML?

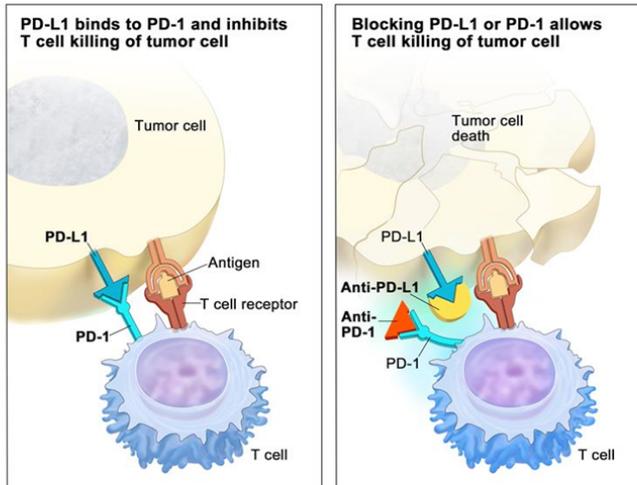


Image Source: NCI

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### Slide 41. Immune Checkpoint Inhibitors: A Breakthrough In Solid Tumors, What About AML?

A very similar concept, a lot of our colleagues in solid tumors are treating their patients with immune checkpoint inhibitors that, you know, cancer is really a failure of the immune system, including AML. The patient's own immune system should recognize those cells as abnormal and fight them off, but it doesn't. And that's because the cancer cells trick the immune system into thinking they belong there. These immune checkpoint inhibitors break through the trickery and say, hey, no, this really is a tumor cell, kill it, don't just ignore it. And those can be very effective. I mean Jimmy Carter had metastasis to his brain from a tumor and he got one of these and achieved a complete remission in a 90 year old man. That's pretty remarkable.

These don't seem to have as much activity in AML as we'd like and so we're trying to figure out why that is and can we modify them or use them in combination to do better.

# What's Next For AML? "Personalized" Medicine

## Personalized medicine approach to treating AML

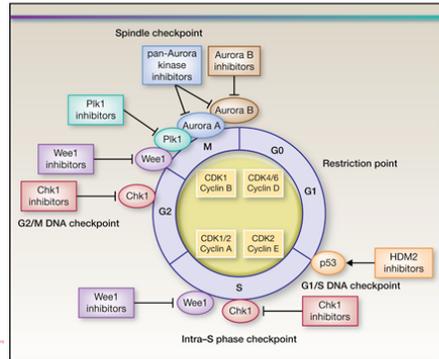
The Leukemia & Lymphoma Society (LLS) and the Knight Cancer Institute at Oregon Health & Science University are leading a pioneering collaboration to develop a precision medicine approach to improve outcomes for patients with acute myeloid leukemia (AML), a particularly devastating cancer of the blood and bone marrow. LLS provided \$2.2 million to fund Beat AML, and here is how the collaboration will work:

**1** In coordination with the Knight Cancer Institute, Stanford University, UT Southwestern Medical Center and Dana-Farber Cancer Institute will collect data from 500 AML patient samples within 3 years.

**2** Drug and biotech companies will work with the collaboration to test drug compounds that target mutations independent of drug resistance progression. Any drug/compound will be first to test a therapeutic.

**3** LLS will perform genetic sequencing to identify mutations in the patient samples collected.

**4** LLS will work with Knight Cancer's bioinformatics team to apply the technology to systematic computational analysis of the mutation data collected.



Gojo I, Karp J. Clin Can Res Dec 2014

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## Slide 42. What's Next For AML? "Personalized" Medicine

So, what's next for AML? Well, as I mentioned, personalized medicine, this Beat AML Trial, very exciting, there's lots and lots of different studies of specific mutations and, you know, I think 20 years from now we'll be treating AML completely differently from how we are now, where instead of lots and lots of people getting 3&7, everybody will be getting the specific inhibitors that are necessary for their particular case of leukemia, their particular profile.

# Stem Cell (Bone Marrow) Transplantation

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## Slide 43. Stem Cell (Bone Marrow) Transplantation

Well, I want to leave plenty of time for your questions and so I'm just going to finish up in the next 2 or 3 minutes to talk about stem cell or bone marrow transplantation, which are really synonyms.

## Transplant ≈ “Rebooting the System”



www.leadingwithtrust.com

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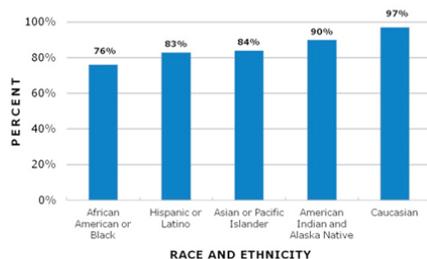
### Slide 44. Transplant = “Rebooting the System”

This is at the heart of it a way of getting over and overcoming that immune checkpoint limitation, of basically rebooting the patient’s own immune system.

## What Needs To Be Done Before Transplant? Donor Identification



Likelihood of Finding a Matching Adult Donor



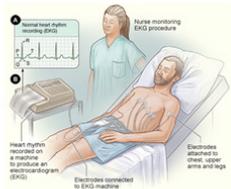
SOURCE: National Marrow Donor Program / Be The Match 2013 fiscal year reports.

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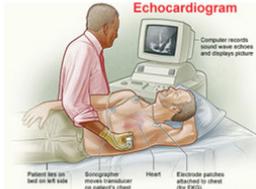
### Slide 45. What Needs To Be Done Before Transplant? Donor Identification

And what we do with transplant is to take cells from a donor and Be the Match, the National Marrow Donor Program, is very good at helping find matches. And it definitely depends on your ethnic background, how likely is to be found, but even for minority groups the majority have a match donor out there, so you have to find a donor because you have to get new immune and bone marrow cells.

## Typical Pre-Transplant Testing



Electrocardiogram (ECG)



Echocardiogram



Pulmonary function tests (PFTs, spirometry)



Dental exam and cleaning



Updated marrow biopsy



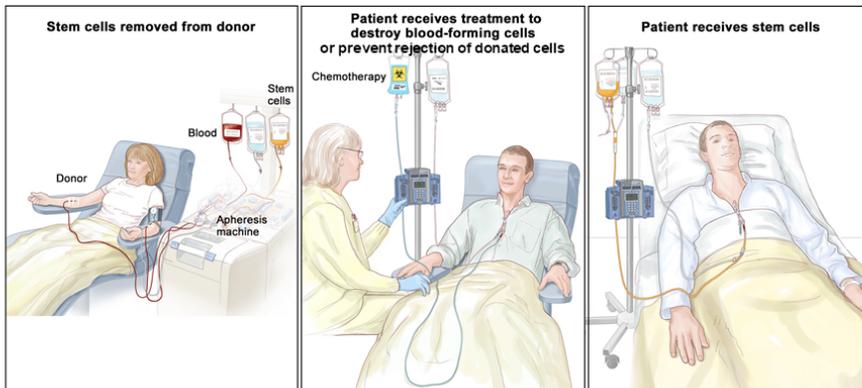
Blood tests: *tissue type, antibodies, blood type, infection markers, organ function*

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### Slide 46. Typical Pre-Transplant Testing

And then there's a lot of testing that takes place before the pre-transplant occurs.

## Allogeneic Hematopoietic Stem Cell Transplant (Allo-HSCT)



Source: NCI

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### Slide 47. Allogeneic Hematopoietic Stem Cell Transplant (Allo-HSCT)

And once all that – you know, the dental exam and the heart tests, the patient has some sort of treatment to either wipe out the patient's own bone marrow or at least prevent rejection of the donated cells, they receive the stem cells just like a transfusion, and then those stem cells go to work.

### Transplant Trends

- **Older fit patients** are increasingly considered eligible (up to ~75 years)
- Increasing use of half-matched “**haplo**” **transplant** (usually parent/child)
  - Randomize transplant of haplo vs cord blood
- Increasing elective use of **bone marrow rather than blood stem cells** as donor source
  - Requires an operation, but may reduce graft-versus-host (GVH)
- Increasing use of post-transplant **preventive or pre-emptive therapy**
  - e.g., sorafenib after FLT3 AML allo-SCT
- Monitoring and treatment of graft-versus-host and infection is improving

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#### Slide 48. Transplant Trends

Increasingly the age is going up where we consider this. When I was a student we didn't do this in people over age 50. Now we do people who are 75 years old almost every day.

There's also increasing use of what's called haplo-transplant, these are half-matched, usually a child, or for pediatric patients a parent, who can only be half-matched sort of by definition.

We're also using more bone marrow than blood stem cells, just in the last few years, which requires an operation, but may reduce graft-versus-host disease. And increasingly we're seeing use of post-transplant therapy such as sorafenib for FLT3 mutated disease.

There's also been some improvements in graft-versus-host disease and infection, but these remain very, very difficult problems to deal with.

### Conclusions

- FDA approval of 4 new AML drugs in 2017!
  - Hopefully the beginning of a wave
- Biological understanding of AML is improving
- More than 300 AML clinical trials ongoing, testing >40 different novel compounds
  - Clinical trials are the only way to move the field forward
- Transplant is more broadly applied, outcomes improving

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#### Slide 49. Conclusions

So, in conclusion, the FDA has approved four new AML drugs this year and hopefully that's the beginning of a wave of new approvals. Our biological understanding of the disease is improving, there's lots more genes that we understand, lots of good basic science going on, trying to understand what the pathways are that AML depends on in the cell and how we can gum those up selectively.

Last time I looked at [clinicaltrials.gov](http://clinicaltrials.gov) a few weeks ago, there were more than 300 active trials and more than 40 compounds being tested, so that's really the only way we're going to move this field forward.

And then transplant is increasingly being used and outcomes are slowly improving. We're not where we need to be yet.

## Thank You!



Yawkey Center,  
Dana-Farber Cancer Institute



Harvard Medical School quadrangle

As of February 2017, Dana-Farber currently has  
**533 therapeutic clinical trials**  
in progress to treat cancers like:

Metastatic breast cancer  
Lung cancer  
Multiple myeloma  
Leukemia



**2,156**  
adults participated  
in a clinical trial at  
Dana-Farber in 2016

Resources for clinical trials: Dana-Farber.org, Clinicaltrials.gov, DFHCC, Harvard.edu  
Sources: Dana-Farber's Early Drug Development Center and Clinical Trials Office

### DFCI Adult Leukemia Clinical Program

Richard Stone MD  
Daniel Deangelo MD PhD  
Martha Wadleigh MD  
Gregory (Goyo) Abel MD MPH  
Jacqueline S Garcia MD  
Eric S Winer MD  
Marlise Luskin MD  
Ilene Galinsky RN NP  
Mary Gerard PA-C  
Adriana Penicaud PA-C  
Katherine Edmonds RN NP

### Research Collaborators

Benjamin Ebert MD PhD  
R. Coleman Lindsley MD PhD  
Andrew Lane MD PhD  
David Frank MD PhD  
Tony Letai MD PhD

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### Slide 50. Thank You!

So, thank you from Boston. This is our adult leukemia program, led by my colleagues Rich Stone and Dan DeAngelo is our research director, and there's lots of basic scientists we meet with. We're fortunate to have lots of bright scientists around who are always coming up with new ideas for us to try and that makes this is a very exciting place to work.

## What's on the Horizon for Acute Myeloid Leukemia?



### Q&A Session

#### 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.

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### Slide 51. Q&A Session

And with that we'll take some of your questions.

## What's on the Horizon for Acute Myeloid Leukemia?

November 2, 2017

Speaker: David P. Steensma, MD, FACP



### **Lizette Figueroa-Rivera:**

Thank you so much, Dr. Steensma. It's now time for the question and answer portion of our program.

And we'll take the first question from our web audience. Doctor, Rob is asking if anywhere in the U.S. or abroad people are studying or addressing relapse prevention, utilizing diet, exercising, potassium, Vitamin C in high doses?

### **Dr. Steensma:**

So, the answer is definitely yes in terms of people addressing relapse prevention. And we're actually going to see at the American Society of Hematology (ASH) national meeting next month a large study from Europe in which they treated patients who were showing signs of relapse with azacitidine and were able to get them back in remission.

The Vitamin C story is actually kind of interesting. There's a lot of interest because it's shown to be particularly helpful maybe in folks with TET-2 mutations, but we don't know that yet, whether those observations in mice and in cell line models will translate into the clinic.

As far as diet and exercise are concerned, that definitely makes a difference. Our ability to stay physically active and to eat enough calories to try to minimize weight loss. But as being formally studied, that's a very difficult thing. As you saw, even just addressing with targeted agents, given the diversity of disease, that's tough.

But there are certainly groups that are looking at physical activity in terms of quality of life and in terms of long-term outcomes.

### **Lizette Figueroa-Rivera:**

Thank you, Doctor, and we'll take the next question from the telephone audience, please.

### **Operator:**

Thank you. Our question comes from Katie. Please state your question.

### **Katie:**

Hi, Doctor, I read on the slide that in some cases older patients are receiving transplant, but it's typically under 75. Are there ever any exceptions to that rule for extremely, extremely healthy individuals who are over 75, having a success with transplant? Thank you.

### **Dr. Steensma:**

It's a very good question and we don't have an absolute limit at our center of 75. We have transplanted a selected group who are just a little bit older than that, 76, 77, 78, who have no other major problems and are quite fit and active. The problem is, you know, once you start getting into that age group, even if somebody looks good on the outside and continues to stay active and intellectually engaged, etcetera, they still have 78 year old kidneys and a 78 year old liver and that's what makes the transplant often difficult in such patients.

### **Lizette Figueroa-Rivera:**

Thank you, Doctor. And our next question comes from the web. Kelly states my father passed away from AML as did his two biological brothers and his brother's son, my cousin, who died at age 4. Is it common to have a familial link and do my sister and I need to be concerned for our future?

### **Dr. Steensma:**

That's a great question. And there are certainly families that have a predisposition to leukemia and we're learning more and more about these. Several different new genes have been described just in the last couple of years. We knew, for instance, for about ten years about a gene called RUNX1 and for longer than that about a gene called TP53. In the last five years we've learned about GATA2 inherited mutations and about DDX41 inherited mutations. So, it is reasonable, given your strong family history, because that is certainly one that is a bit of a flag, to see a genetic counselor, to talk about the testing that is available. There are different panels that can assess this.

I would emphasize, though, for the majority of folks this is a random event. This is a copying mix-up by the cell and it's not something they're predisposed to, they have no family history, their kids are not at increased risk for getting it. So that's a common question folks ask, are my kids at risk for this. And for most families the answer is no, but there are some exceptions and we're better able to define those now.

## What's on the Horizon for Acute Myeloid Leukemia?

November 2, 2017

Speaker: David P. Steensma, MD, FACP



**Lizette Figueroa-Rivera:**

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

**Operator:**

Thank you. Our next question comes from Darcie from Pennsylvania. Please state your question.

**Darcie:**

Yes, Doctor, thank you for taking my call. I am an allo stem cell transplant for the past four and a half years and in remission. When they tested me at University of Penn I had a faulty gene. Can this – should the gene be targeted instead of giving a chemo regimen?

**Dr. Steensma:**

Do you know what that gene is, did you tell you which gene it is?

**Darcie:**

It was a something sex-fly.

**Dr. Steensma:**

Oh, probably ASXL1, does that sound, right?

**Darcie:**

I'm not really sure of the first or the last part of that. All I remember is him saying sex-fly something.

**Dr. Steensma:**

We don't have a targeted agent for AS601 yet. But you've done quite well with 4 and a half years post-transplant and hopefully that remission will continue.

**Lizette Figueroa-Rivera:**

Thank you, Doctor. And also, it's very important to speak with your treatment team about any of the mutations that you might have, so you know if there's anything that can actually help you and if there's something that is coming down the pike that might be able to assist you.

Tom asks, Doctor, if one is in remission, what are the signs of relapse?

**Dr. Steensma:**

The most common signs are change in the blood counts and so that's why we commonly monitor patients' blood counts. We don't always do bone marrow biopsies if the counts are stable. Different institutions have different protocols for how frequently to do those, but the blood counts are often the first sign. And sometimes patients rarely will have a new lump on the skin or a new neurologic sign, because some of the relapses, especially after transplant, can be outside the bone marrow and other places. But the majority by far are picked up by changes in the blood counts.

And I know that it always, you know, when patients come see me, that always makes them nervous, even if they are far out from their treatment, waiting for that blood count result, and I'm very sympathetic to that and try to – as soon as I find out that result, I go in and tell the patient, even if I'm not quite ready to see them yet, because it's often difficult for people to think of anything else and we understand that.

**Lizette Figueroa-Rivera:**

Sure, thank you. And we'll take the next question from the phone audience, please.

**Operator:**

Our next question comes from Steven from New Mexico. Please state your question.

**Steven:**

Thank you. I wonder if you're familiar with a drug that's just coming over the horizon for AML, called venetoclax, was called ABT199 in the trial. It's approved for CLL. I've been taking it for the last couple of months and it just completely turned around my blood counts, they are bounding into the correct ranges. And we don't know what to do next because – are you aware of any long-term data or what do you know about venetoclax?

## What's on the Horizon for Acute Myeloid Leukemia?

November 2, 2017

Speaker: David P. Steensma, MD, FACP



**Dr. Steensma:**

Yeah, so that was one of the drugs that I mentioned and showed a few slides with. So, it's certainly of interest combining this with therapy or using it in people who are no longer responding to therapy. We've had not much long-term data. There were patients, the longest that patients have been treated with that is probably about two years now, because we just heard reports last year of the combination approach with azacitidine or decitabine. So certainly, of interest. There's randomized trials going on, giving patients either azacitidine alone or azacitidine plus venetoclax, ABT199, and this is certainly something that a lot of us are very interested in and excited about, and where there is anecdotal use outside a study also.

**Steven:**

If I can continue my anecdote for another second, I'm taking just the pills, not any chemicals. I'm in a relapse after getting 7+3 about three years ago. But I've – so yeah, it's working and we're wondering what to do next, maybe it's over.

**Dr. Steensma:**

Well, I hope so for your sake very much, I'm glad to hear it's working. There have certainly been folks who've responded to single therapy with venetoclax as well. We don't have long term data to help us decide yet what to do next.

**Lizette Figueroa-Rivera:**

Thank you. And Doctor, we'll take the next question from the web. Darlene is asking what is the standard of care for frequency or continuation of bone marrow biopsies 5 years post-remission with PCR at .01 or lower?

**Dr. Steensma:**

Yeah, so there is no standard for doing it. I usually won't do a bone marrow beyond five years if the patient's counts continue to look okay. However, some colleagues will continue to do them. I don't find it adds a lot of additional information if the blood counts are stable. But different institutions do have different practices.

**Lizette Figueroa-Rivera:**

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

**Operator:**

Thank you. Our next question comes from Linda from Texas. Please state your question.

**Linda:**

My mother recently died, I guess it was 2 months ago tomorrow, from AML, and it hit her out of the blue. And I have chronic ITP or low platelet count, I have had for about the last 3 or 4 years. And I just wanted to know is there any connection between that and developing AML or any form of leukemia?

**Dr. Steensma:**

That's a very good question. So, there is not a connection between ITP and leukemia. And first of all, sorry for your loss. Anniversaries of when we've lost our loved ones often can be quite difficult times, and so my sympathies on the loss of your mom.

So, it is true that there's not a connection between ITP and AML. However, there certainly have been people who've been thought to have ITP because they have a germline mutation in either RUNX1 or 2 more recently described genes, AMKRD26 and ETV6. And so that would be certainly something if you – especially if you have other family members who have what looks like ITP, almost every patient that I've seen who've had those inborn germline hereditary mutations, was misdiagnosed as ITP because ITP is so much more common than those inborn mutations. And so, it would be worth at least talking about it with your doctor, now that we know more or given your family history.

**Lizette Figueroa-Rivera:**

Thank you, Doctor. And again, Linda, sorry for your loss.

The next question does come from our web audience, Doctor. Alice is asking about maintenance therapy options for AML after remission is obtained in first round of decitabine.

**Dr. Steensma:**

Yeah, so good question, and we know that with maintenance therapy that that is necessary usually to maintain a remission for patients treated with decitabine. There's not clear benefit of maintenance after more intensive chemotherapy, although

there will be some data presented next month showing a potential benefit for that approach in a randomized trial from Europe.

So, I usually tell patients if we're treating your AML with decitabine, if we stop, the disease is going to come back within a few months and so as long as a patient is tolerating it and remaining in remission, we continue that. Unless they end up doing something else like going onto a transplant or going onto a clinical study. So, with decitabine, with azacitidine maintenance seems to be important to continue to maintain the remission.

**Lizette Figueroa-Rivera:**

Thank you, Doctor. And the next question comes from our telephone audience, please.

**Operator:**

Thank you. Our next question comes from John from Connecticut. Please state your question.

**John:**

Thank you. Thank you, Doctor, for your very informative words to all of us. My question is more general. How do hospitals get selected for clinical trials and how much of that information then gets shared with hospitals who have not been selected?

**Dr. Steensma:**

Thank a great question, John. So, most of the time hospitals are selected for clinical trials for three reasons: they see the patients with the condition that might benefit; they have an investigator there who's interested in participating in the clinical trial at their site; and they have the research infrastructure to do clinical studies. And that latter part is what often gets us because not every center has a research infrastructure. Many community practices, they'd love to do trials but it's difficult for them. So that's why most clinical trials are done at academic centers.

Now that being said, if you're being treated in a community practice, your doctor may be doing a very good job at keeping up on what research developments are in the field and there's a number of different venues for keeping up. So we do web seminars like this for healthcare professionals, for instance, that's one way. A more common way is at meetings and there are continuing medical education meetings. I co-chair a couple of them each year, and there's usually one of them – there's hundreds and hundreds of people there who are all doctors practicing in the community and caring for patients with blood cancers. And so that's another opportunity for them. And then they can also read the literature, the journals, you know, many people get the Journal of Clinical Oncology or Blood or the New England Journal of Medicine or usually a combination, and these will often have up-to-date studies and then sometimes review articles.

So that's how places get picked for clinical trials. A center that doesn't see a lot of patients with AML, it's not going to be worth their while to do an AML trial. And if it's a small center they may not have all the research pharmacists and clinical research coordinators and such to be able to do the study. But they can still keep up and still follow developments in the field and give up-to-date care.

And as far as sharing of information, there's lots of venues by which we do that. Something that happens in Europe today, I'll know by next week if it's a significant development. So, we really are I think much better as a field about communicating than 20 years ago.

**Lizette Figueroa-Rivera:**

Thank you, that was an excellent question. And our last question today comes from Ron. Ron's asking are there any environmental factors that have been proven to cause AML?

**Dr. Steensma:**

That's a great question, Ron, and it's something that's actually quite difficult to study because we all have so many environmental exposures and then studying those exposures, we have to take into account our own personal degree of exposure and our own sort of genetic background and such, and so the whole thing becomes very challenging.

That being said, we know that cigarette smoking is a risk factor for blood cancers, including AML. We know that AML increased in frequency in Hiroshima and Nagasaki after the atomic bomb. We know that people with certain types of occupations that work with certain types of chemicals in the same class as benzene and – have a lot of exposure to kerosene or gasoline, are at increased risk as well. So that's a complicated area to sort of get our hands around, but there definitely are some environmental risk factors.

The vast majority of people, though, with AML, we're learning that it is really just bad luck, it really is something that the cell just happened to screw up and copy itself incorrectly on a bad day. And so, you know, most people they're not going to be able to say, oh, I was in this situation and that's why I got the disease.

**Lizette Figueroa-Rivera:**

Thank you for your question, Ron, which was our final question today. And thank you, Dr. Steensma, for your continued dedication to patients.

For those of you who participated in today's program, we hope the information presented today will assist you and your family in your next steps.

## The Leukemia & Lymphoma Society Offers:

- **Information Resource Center:** Information Specialists, who are master's level oncology professionals, are available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  - **EMAIL:** [infocenter@LLS.org](mailto:infocenter@LLS.org)
  - **TOLL-FREE PHONE:** 1-800-955-4572
- **Free Education Booklets:**
  - [www.LLS.org/booklets](http://www.LLS.org/booklets)
- **Free Telephone/Web Programs:**
  - [www.LLS.org/programs](http://www.LLS.org/programs)
- **Live, weekly Online Chats:**
  - [www.LLS.org/chat](http://www.LLS.org/chat)



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### Slide 52. The Leukemia & Lymphoma Society Offers:

If we weren't able to get to your question today or you want more information about our Beat AML Master Trial, you may speak to an Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or you can reach us by email at [infocenter@LLS.org](mailto:infocenter@LLS.org).

## The Leukemia & Lymphoma Society Offers:

- **Support Resources:** LLS Community, discussion boards, blogs, support groups, financial assistance and more: [www.LLS.org/support](http://www.LLS.org/support)
  - **NEW LLS Podcast, *The Bloodline with LLS!*** Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients. [www.thebloodline.org](http://www.thebloodline.org)
- **Education Video:** Free education videos about survivorship, treatment, disease updates and other topics: [www.LLS.org/educationvideos](http://www.LLS.org/educationvideos)
- **Patti Robinson Kaufmann First Connection Program:** Peer-to-peer program that matches newly diagnosed patients and their families: [www.LLS.org/firstconnection](http://www.LLS.org/firstconnection)
- **Free Nutrition Consults:** Telephone and email consultations with a Registered Dietitian: [www.LLS.org/nutrition](http://www.LLS.org/nutrition)
- **What to ask:** Questions to ask your treatment team: [www.LLS.org/whattoask](http://www.LLS.org/whattoask)



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### Slide 53. The Leukemia & Lymphoma Society Offers:

Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions that you might have about support, including financial assistance for treatment.

Again, we'd like to acknowledge and thank Agios, Celgene and Novartis for support of this program.



**THANK  
YOU FOR  
PARTICIPATING!**

**We have one goal:  
A world without  
blood cancers**

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### Slide 54. Thank You For Participating!

Dr. Steensma, thank you again for volunteering 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.