Transcript

Slide 1. Welcome & Introductions

Lizette Figueroa-Rivera:
Hello, everyone, on behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you.

We have over 250 people participating from across the United States and several countries around the world including Bermuda, Canada, Egypt, India, Poland, and the United Kingdom.

Special thanks to Dr. Hillard M. Lazarus for volunteering his time and expertise with us today.

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

Dr. Elisa Weiss:
Thank you, Lizette. I'd like to add my welcome to the patients, caregivers, and healthcare professionals from around the world who are attending the program today.

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer. For more than 60 years, LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients. To date we have invested over $1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates, we are the leading source of free blood cancer information, education, and support, and we touch patients in their communities through our 56 chapters across the United States.

LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatments and ensuring that they have access to quality, affordable and coordinated care.

We are very fortunate to have Dr. Hillard Lazarus as our presenter today. Dr. Lazarus is one of the nation's leading experts in leukemia. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers.

Dr. Lazarus, thank you very much for providing us with important information today on adult ALL.

And now, I'd like to turn the program back to Lizette.

Lizette Figueroa-Rivera:
Thank you, Elisa.

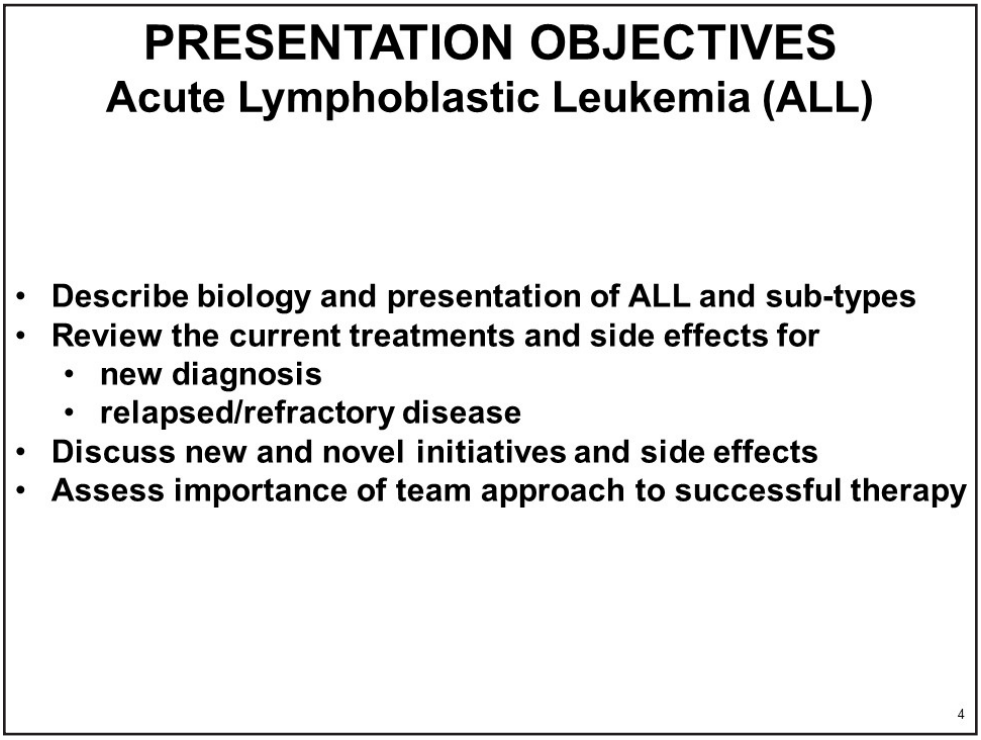
We would like to thank our supporters for this program, Amgen, The Leukemia & Lymphoma Society, and Shire.

Slide 2. Treating Adult Acute Lymphoblastic Leukemia (ALL)

I'm now pleased to introduce Dr. Hillard Lazarus, Professor of Medicine at Case Western Reserve University in Cleveland, Ohio. Dr. Lazarus, I'm privileged to turn the program over to you.

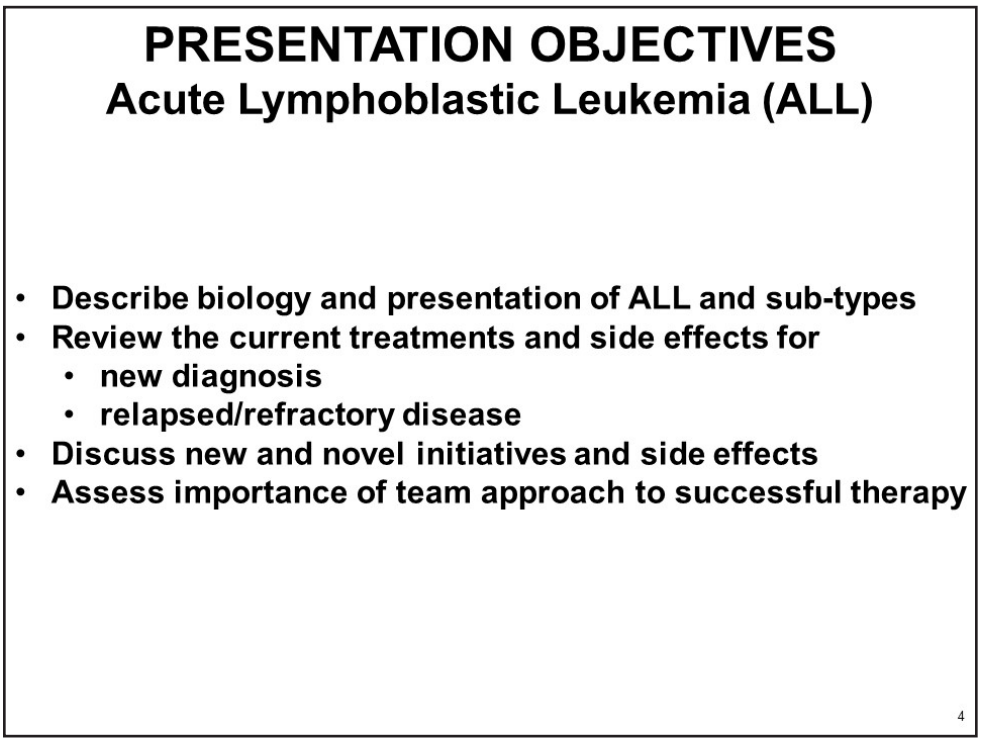
Slide 3. Disclosure

Dr. Hillard Lazarus:
Thank you very much. I'm very pleased to be able to present. This slide are my disclosures.



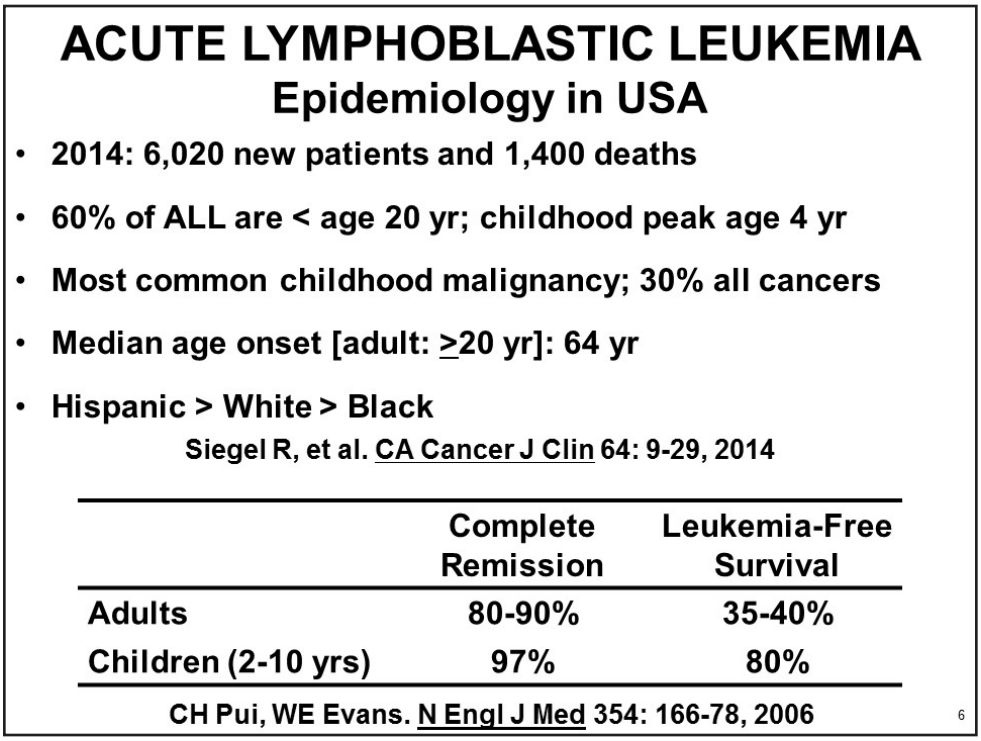
Slide 4. Presentation Objectives

What I'm going to do in the time allotted me is to describe the biology and presentation of various subtypes of acute lymphoblastic leukemia, and review the current and new treatments as well as the side effects for those patients with newly diagnosed disease and for those who have relapsed and refractory disease, as well as discuss some of the more novel approaches, and emphasize the team approach to a successful therapy.



Slide 5. Annual Incidence of ALL SEER Data: By Age Groups

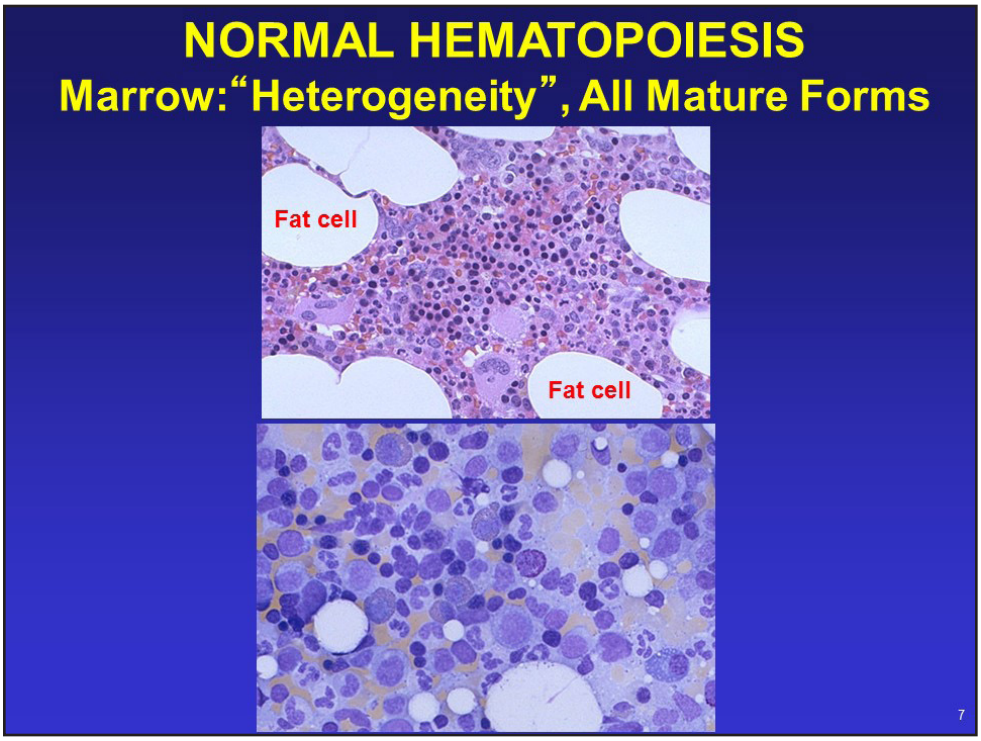
The incidence of acute lymphoblastic leukemia is shown on this slide. It's predominantly a disease of young adults and children, although older adults are affected. As you can see, the peak incidence in young adults and children is approximately 4 years of age, but older adults certainly are affected. And in fact, 64 on the right-hand side of the panel shows the age of onset for older adults.



Slide 6. Acute Lymphoblastic Leukemia Epidemiology in USA

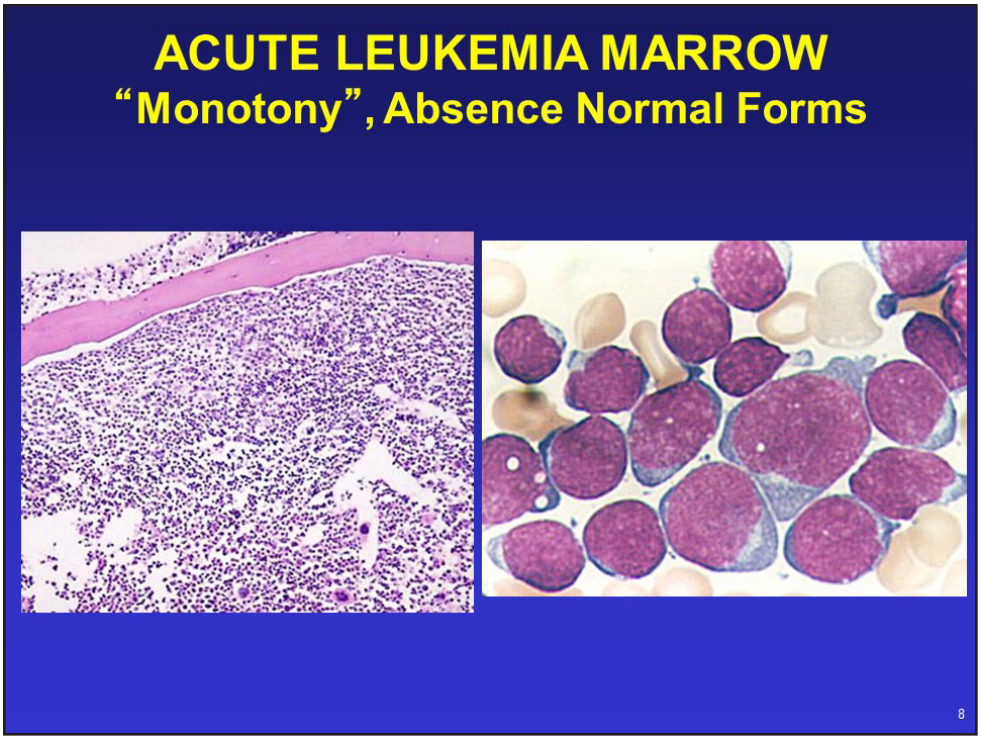
The effect on the population in the United States is approximately 6,000 new patients diagnosed yearly, which results in almost 1,500 deaths. This is the most common malignancy in childhood and represents about a third of all cancers, but as stated earlier, about – a fair number of older adults will get acute leukemia with a peak of age 64.

Hispanics are affected more commonly than Caucasians, and you can see on the bottom part of this slide that the benefit of treatment to children is much greater than adults. In children ages 2 to 10 years of age, it's nearly 100 percent eradication of disease, with an 80 percent leukemia-free survival, which is much better than adults, where complete remissions are only 80 to 90 percent and only approximately 35 or 40 percent will experience leukemia-free survival.



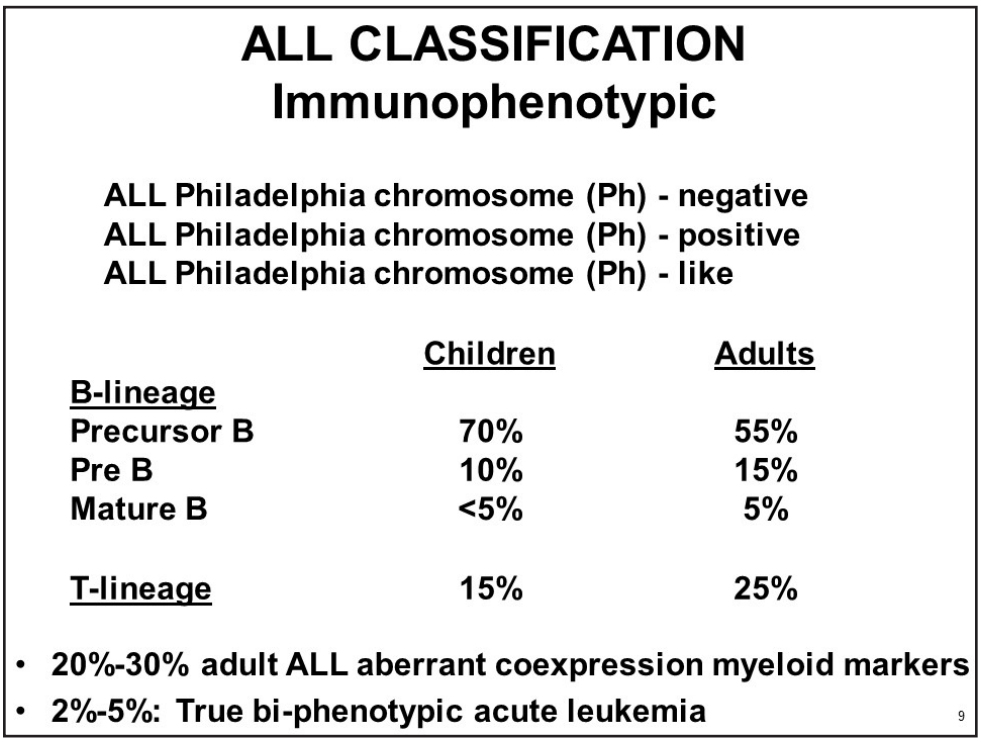
Slide 7. Normal Hematopoiesis: Marrow: "Heterogeneity", All Mature Forms

For those of you who are not familiar with photomicrographs, this is a picture of normal bone marrow that's magnified, what you would see under the microscope, and the top part is a lower power view of a bone marrow that's been smeared on a slide, and there are clearer areas that are labeled fat, but the cellular, the heavier areas in the center, are blown up on the lower portion of the slide, and what is very obvious is that there are all kinds of shapes and sizes and color cells, so the bone marrow, which is the factor for making blood, makes many kinds of cells and that's shown here. And so the term is heterogenous or many kinds of cells.



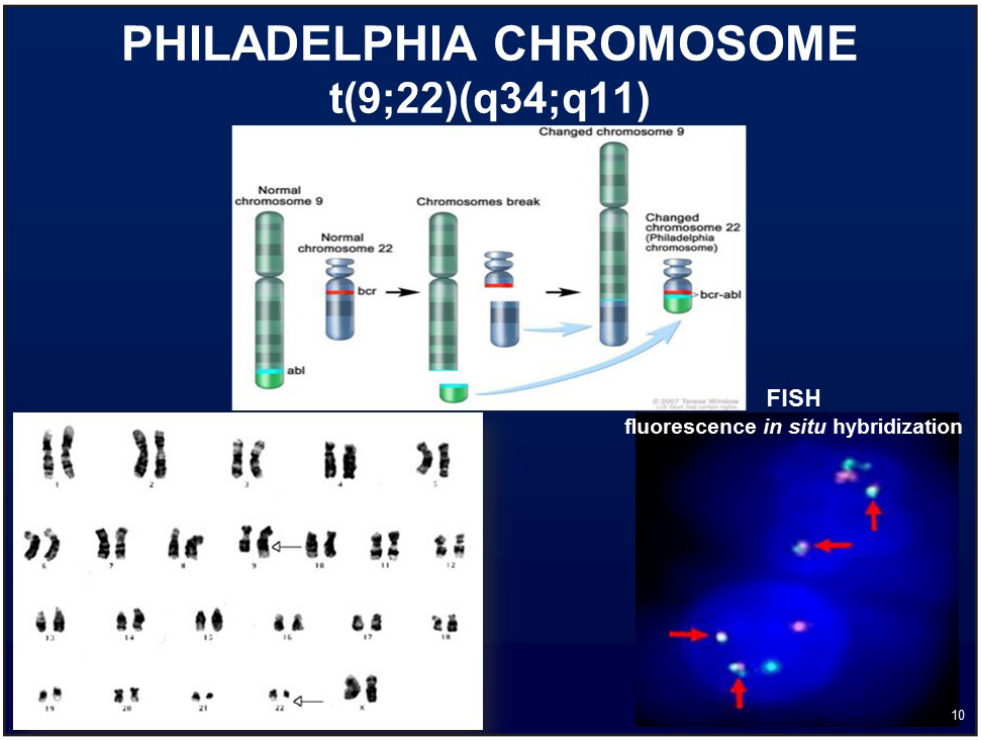
Slide 8. Acute Leukemia Marrow: "Monotony", Absence Normal Forms

This is in contrast to what one would see under the microscope for acute lymphoblastic leukemia in the bone marrow. On the left is a lower power view, and you can see the pink is a piece of bone, and this is a monotonous population of cells. They're all pretty much large and round, which goes along with this clonality of leukemia and the term monotony is very accurate.



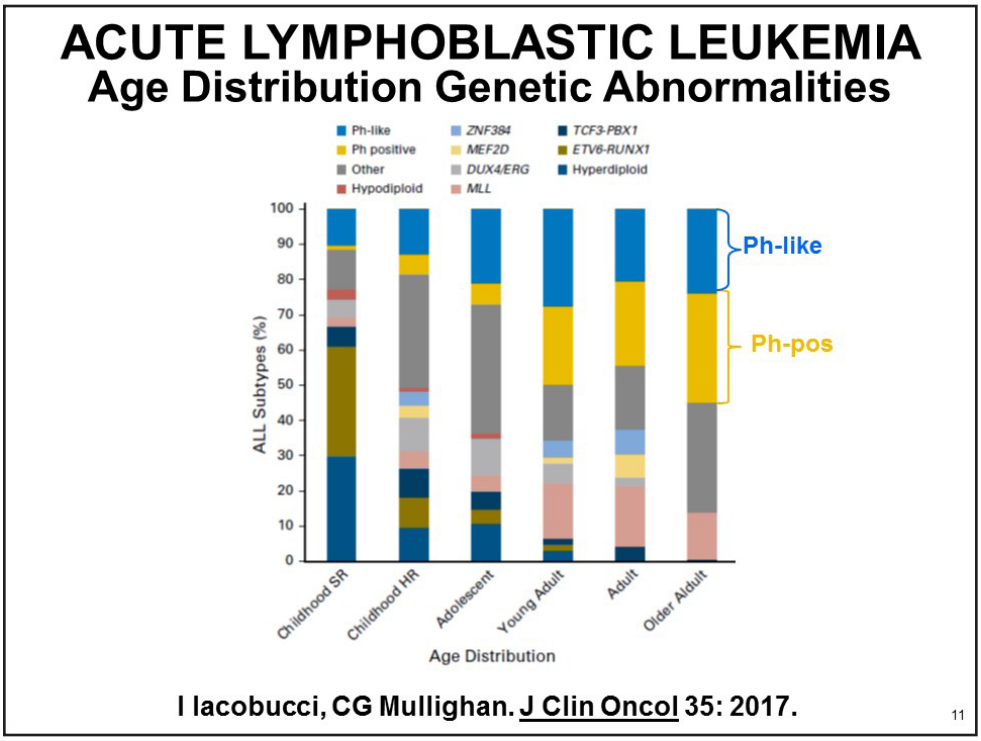
Slide 9. ALL Classification: Immunophenotypic

There are three clinical immunophenotypic presentations which I will discuss in more detail. Philadelphia chromosome, positive Philadelphia chromosome, negative, and a new entity known as Philadelphia chromosome-like. That's looking at the disease from a cytogenetics perspective. But also from an immunophenotypic perspective or what the cells look like when monoclonal antibodies are used to define their subsets. Most of the acute lymphoblastic leukemia patients fall under the category of B cells and there is a lesser percentage of T cells. Shown on the bottom of this slide, there are some patients whose disease reflects both T and B cell, and in fact, there's a very small percentage of patients that are what are called mixed phenotypic, where myeloid features are associated, and this is a relatively uncommon group of patients.



Slide 10. Philadelphia Chromosome

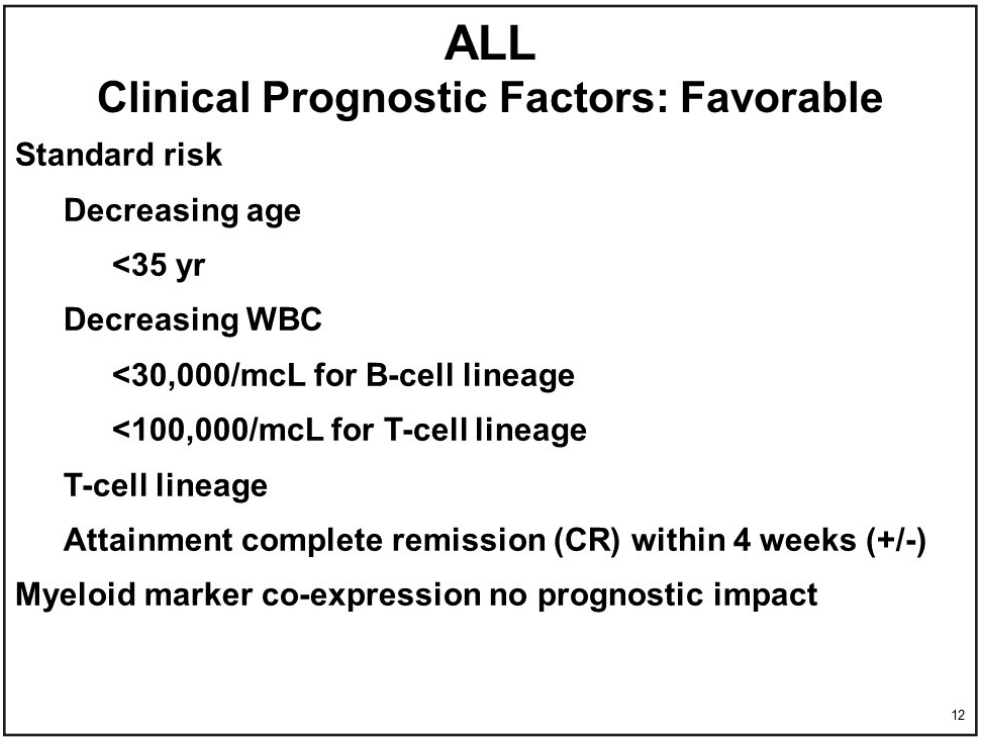
The Philadelphia chromosome was originally described in 1960 and it was really the beginning of the cytogenetics as we understand disease. What's happened, for reasons that are unclear, whether it's cosmic radiation or genetics or whatever, somehow part of chromosome number 9 in a cell and part of chromosome number 22 are switched and this switching results, as you can see on the top panel on the right side, with the creation of a fusion piece of DNA that results in a fusion protein, and we call this the BCR-ABL. The panel on the left shows a standard presentation of a karyotype, what chromosomes look like when they're frozen in division, and you can see the two arrows point to the reciprocal two products. And on the right side, which is what's called fluorescent in situ hybridization or FISH, you can see that within each affected cell the arrows point to the combination of the BCR and ABL. BCR-ABL basically is putting the gas pedal down in this cell and makes the cell grow out of control and hence the leukemia behavior.



Slide 11. Acute Lymphoblastic Leukemia: Age Distribution Genetic Abnormalities

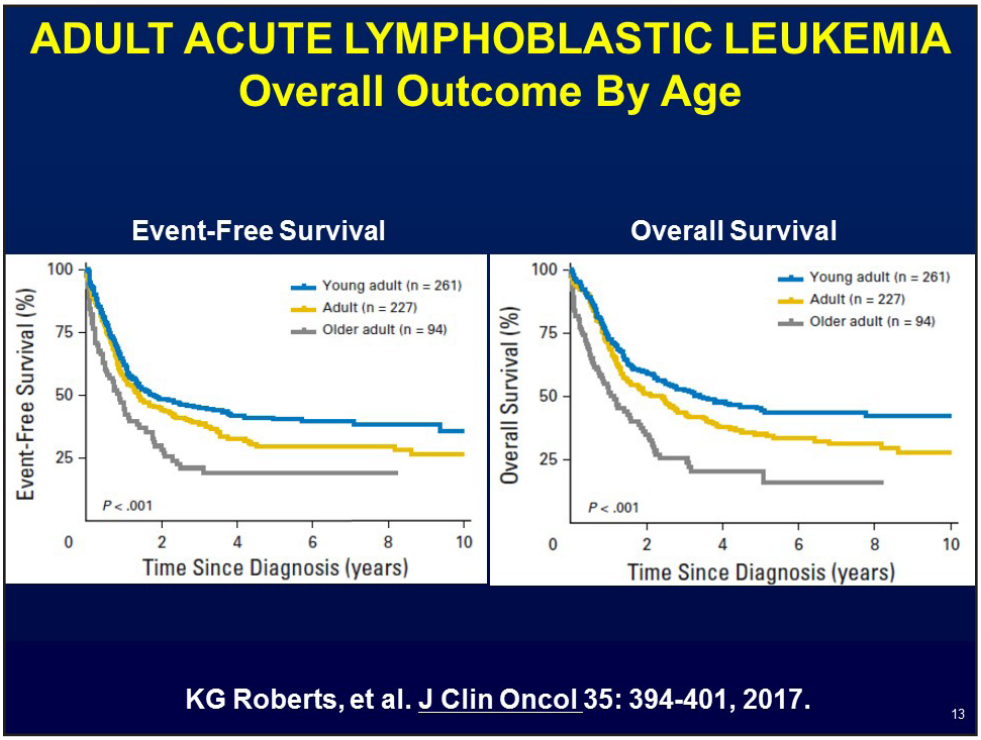
The genetic abnormalities in acute lymphoblastic leukemia, as for all leukemias, are relatively varied and are significant, but this slide shows several of these features as a function of age. You'll notice in the yellow, which is the Philadelphia chromosome, which is abbreviated Ph-positive, that on the left the children, as we go from left to right, the age increases. The yellow band is very rare in young children, but as one gets older the likelihood of a person having a Philadelphia chromosome-positive leukemia increases to about a third in most and certainly by as many as 50 percent in the older patients.

Also shown on this slide, which I'll talk about later, is this new entity known as Philadelphia chromosome-like leukemia, and this is a disease that is represented across all age groups.



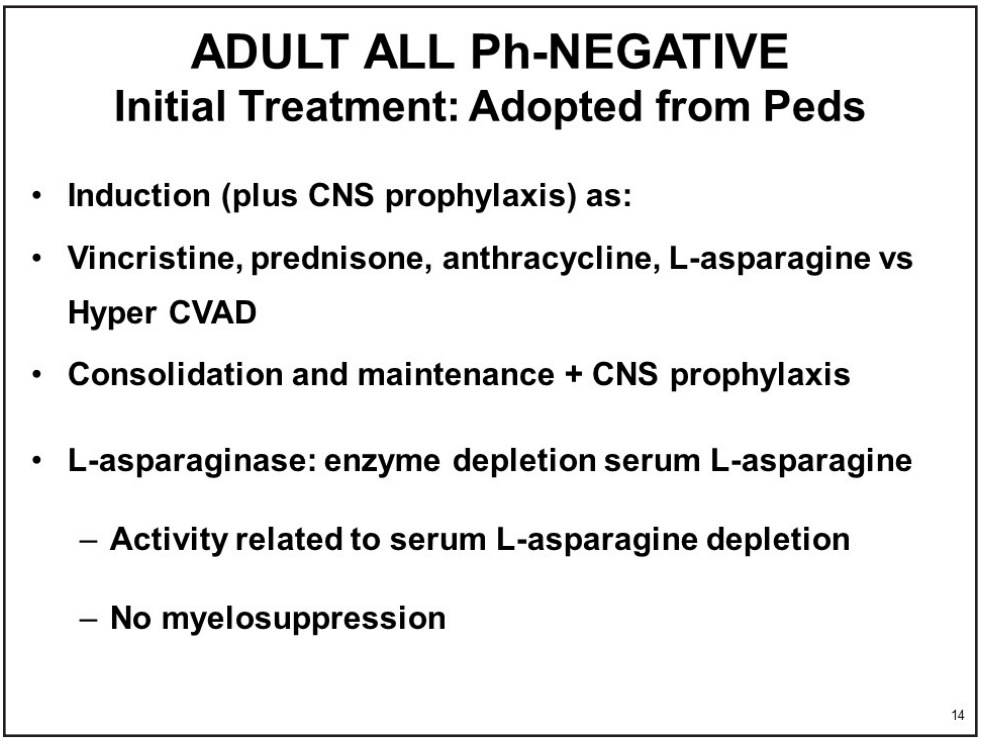
Slide 12. ALL Clinical Prognostic Factors: Favorable

The behavior of the genetics can be looked at in the context of clinical features. And this slide basically shows some of the clinical and other features that indicate to the caregivers and the patient, him or herself, as to whether the disease is likely to be a more favorable outcome or less favorable. So you can see that for patients who are younger, under the age of 35, those whose disease comes to medical attention without being very high in white blood cell counts, 30,000 or less for the B cell lineage and less than 100,000 for the T cell lineage, which has a better prognosis in general, and if a patient who receives treatment goes into a complete remission within 4 weeks. These are all favorable and, in myeloid co-expression in lymphoid leukemia, do not have a prognostic impact.



Slide 13. Adult Acute Lymphoblastic Leukemia: Overall Outcome by Age

The outcome shown on this slide by age is very striking. You can see on the left panel event-free survival and on the right panel overall survival, these are on the vertical axis, as a function of time, and you can see that for the younger adults the likelihood of having no disease out to ten years is quite good at 50 percent, but as a patient gets older when the disease becomes manifest, the overall prognosis drops to the yellow line and finally for an older patient drops to the gray line and is of greater concern.



Slide 14. Adult ALL Ph-Negative Initial Treatment: Adopted from Peds

Now how do we approach the treatment? Pediatricians led the way, as I showed you in one of the early slides, pediatric acute lymphoblastic leukemia is a common disease and for many decades the pediatricians worked out how best to give a cocktail of medications including vincristine, prednisone, anthracycline, L-asparaginase and other treatments, sometimes put together in a certain recipe. One shown here is called Hyper CVAD. And the idea is to get rid of the disease at the start or to get it under control in the initial weeks, which is referred to as induction. And then after the disease is under control, then to mop up and get rid of any remaining leukemia, what's known as consolidation and maintenance.

Acute lymphoblastic leukemia is one of the diseases that has a nasty habit of crossing the blood–brain barrier and going into the brain, and so patients who have this disease require therapy to prevent the spread of the blood and bone marrow cancer cells into the brain.

One of the big additions to the management is the addition of a drug called L-asparaginase. This is a bacterial enzyme that has been derived and purified and can be given to patients and it is very specific in getting rid of acute lymphoblastic leukemia, and has the benefit of not causing damage to the bone marrow. The concept is that acute lymphoblastic leukemia cells cannot live without this amino acid asparagine. And so giving this enzyme eliminates asparagine from the blood and will starve away the leukemia cells, but normal cells can make asparagine, so it doesn't hurt them.

ALL Ph NEGATIVE
How Old Too Old For Peds Regimen?

Patients	N	CR rate	Induction death rate	5-year CIF	5-year CITRM		5-year EFS
					w/o SCT censoring	with SCT censoring	
All patients	787	92%	5.5%	30.5%	17%	12%	52%
Patients aged 18-24y	200	98.5%	0.5%	32.7%	7.6%	1.8%	60%
Patients aged 25-34y	172	95.3%	1.7%	29.4%	12.7%	6.4%	58%
Patients aged 35-44y	171	87.7%	7.6%	31.0%	15.0%	11.3%	54%
Patients aged 45-54y	151	89.4%	6.6%	26.7%	22.4%	16.7%	50%
Patients aged 55y+	93	79.6%	18.3%	33.0%	39.7%	38.4%	26%

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15

Slide 15. All Ph Negative: How Old is too Old for Peds Regimen?

The problem with L-asparaginase, I'll show on subsequent slides, these intensive regimens that I described that were generated in pediatrics, the cocktail of vincristine, prednisone, anthracycline, L-asparaginase and others, can be more and more toxic as a person gets older. And what's shown on this slide is how old is somebody too old to get these intensive pediatric regimens. You can see here that patients up to the age of 55 can do quite well, have reasonable efficacy with not horrific side effects, until someone gets to be about the age of 55, and you can notice on the bottom line the outcomes are not nearly as good and so we need other strategies and need to be more careful.

ADULT ACUTE LYMPHOBLASTIC LEUKEMIA
L-Asparaginase: Unique Toxicities

- Hypersensitivity
  - Neutralizing antibodies
- Liver dysfunction
  - Elevation liver enzymes and bilirubin
  - Low serum albumin
- Hemostasis
  - Bleeding: low clotting factors
  - Clotting: low anti-thrombin III, protein S
- Pancreatitis
- Diabetes mellitus
- Neurological (lethargy, somnolence)

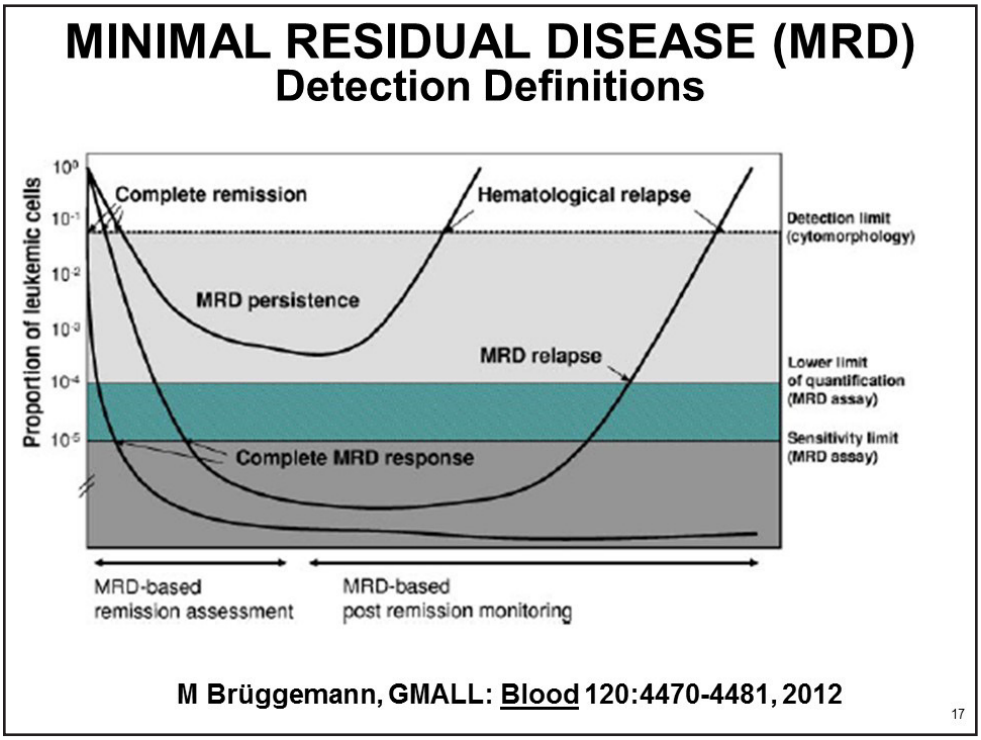
16

Slide 16. Adult Acute Lymphoblastic Leukemia: L-Asparaginase: Unique Toxicities

One of the problems as one gets older is the toxicity of L-asparaginase as I mentioned. Because the drug is made from a bacterium, it has the potential of inducing not only significant allergic side effects, but also the body can make antibodies and neutralize its effects.

Its main side effects, besides the allergic reactions, are damage to the liver, and a liver is a critical organ for either help eliminating blood clots by making anti-blood clot factors, but also bleeding can occur, so this liver damage can result in either excessive bleeding or excessive clotting.

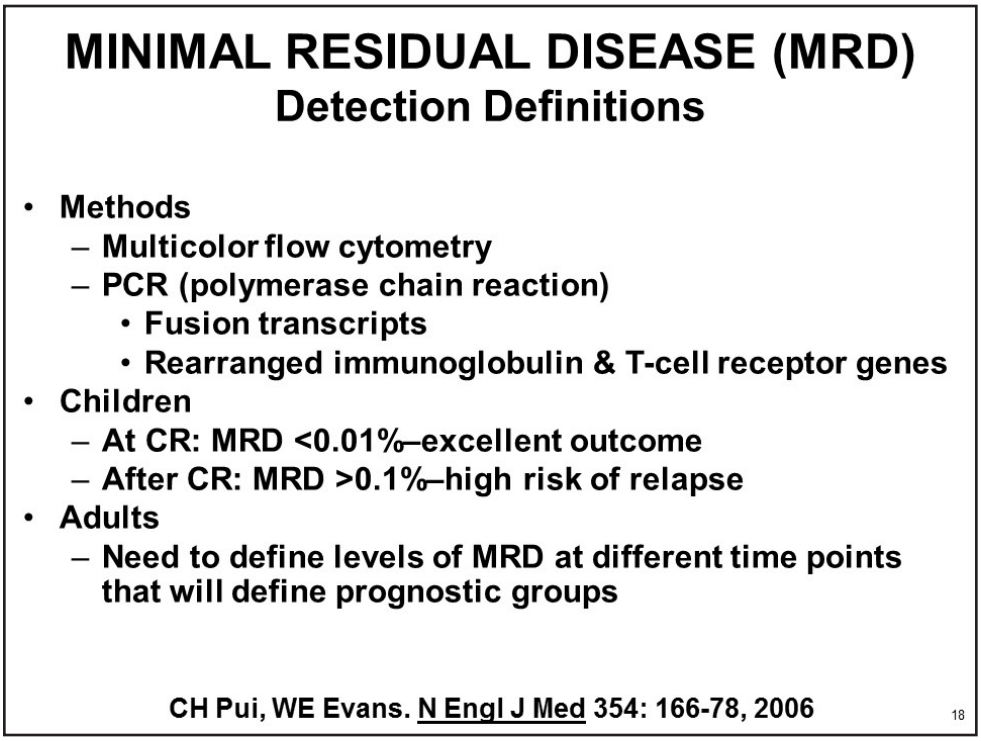
L-asparaginase also can damage the pancreas, pancreatitis, cause diabetes, and even cause neurologic damage, which may be severe in some patients.



Slide 17. Minimal Residual Disease (MRD): Detection Definitions

Now one of the major scientific advances in the last decade or so is the recognition that one can detect disease going beyond the microscope and looking at the blood under the microscope and the bone marrow. And as I showed you in the beginning with those photomicrographs, showing what the disease looks like, that's very good for looking at gross disease, but doesn't really help for a needle in a haystack, where one leukemia cell undetected can over time grow and become many billions of leukemia cells and result in severe problems.

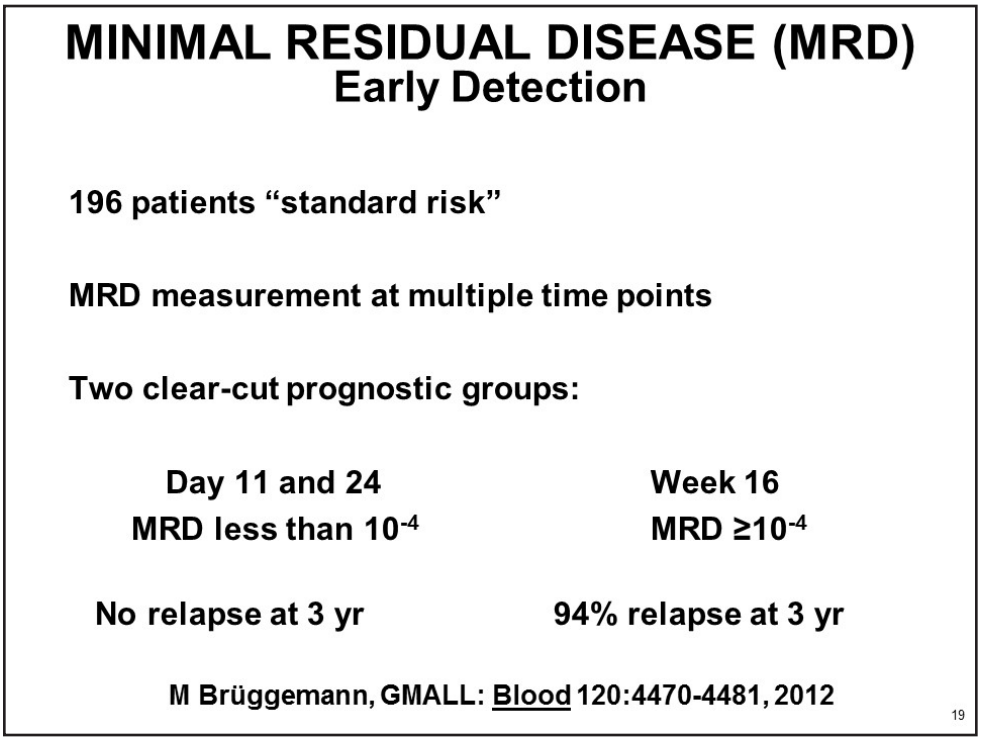
This slide shows that as treatments are given and one lowers the amount of leukemia in the body, using very sophisticated analysis, you can detect the needle in the haystack, the one in a million cells, and the goal is to get on the bottom, below detectable or measurable residual disease, and that's where the body's own immune system comes into play and will help eliminate the disease. So, you can see these bottom curves show that with negative minimal residual disease, the likelihood of the disease coming back is quite small and helps guide practitioners to know whether to continue treatment.



Slide 18. Minimal Residual Disease (MRD): Detection Definitions

The definition for minimal residual disease is complicated. It's basically looking at blood or bone marrow with either flow cytometry, where monoclonal antibodies are reacted to pick up cells, or to look for specific targets like some of the fusion transcripts that I illustrated, the BCR-ABL and Philadelphia chromosome disease, or other components of the cancer, immunoglobulin or T receptor genes.

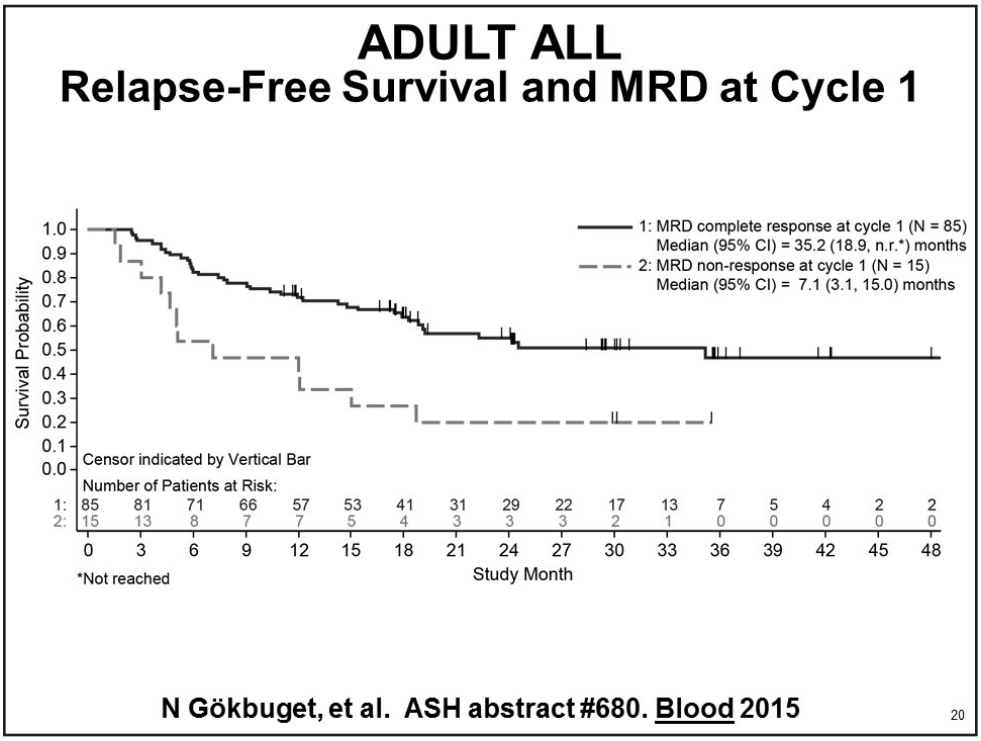
I'll show on subsequent slides some of these outcomes, but basically the earliest work was done in children, in which investigators showed that if the minimal residual disease was less than .01 percent at the time a morphologic complete remission was obtained, outcome was excellent, but with persistence it looked like the disease was going to be headed either for an overt or actually in an overt relapse. And so we're now doing this, as the pediatricians have done, in adults, and we're looking at it over various time points.



Slide 19. Minimal Residual Disease (MRD): Early Detection

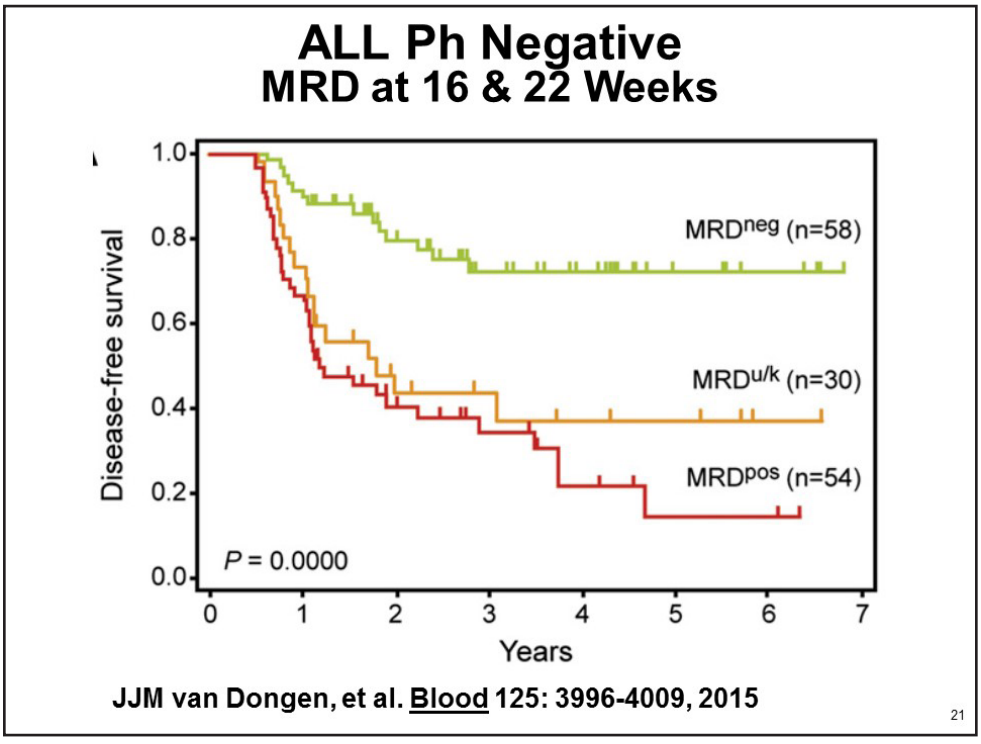
This slide shows one such example of a 200 patient study, where they looked at blood and marrow samples for minimal residual disease, using the sophisticated tools, probing the marrow and blood that I described, and there are two clear-cut prognostic groups from this information.

One was that early on if a patient received treatment and minimal residual disease could essentially not be detected, that is MRD is less than 1 in 10,000 cells, those patients did terrific and none of them relapsed when they were followed out to 3 years. But on the other hand, if by week 16 the disease was still active and one could detect 1 in 10,000 leukemia cells, relapse was inevitable and those patients did not do well.



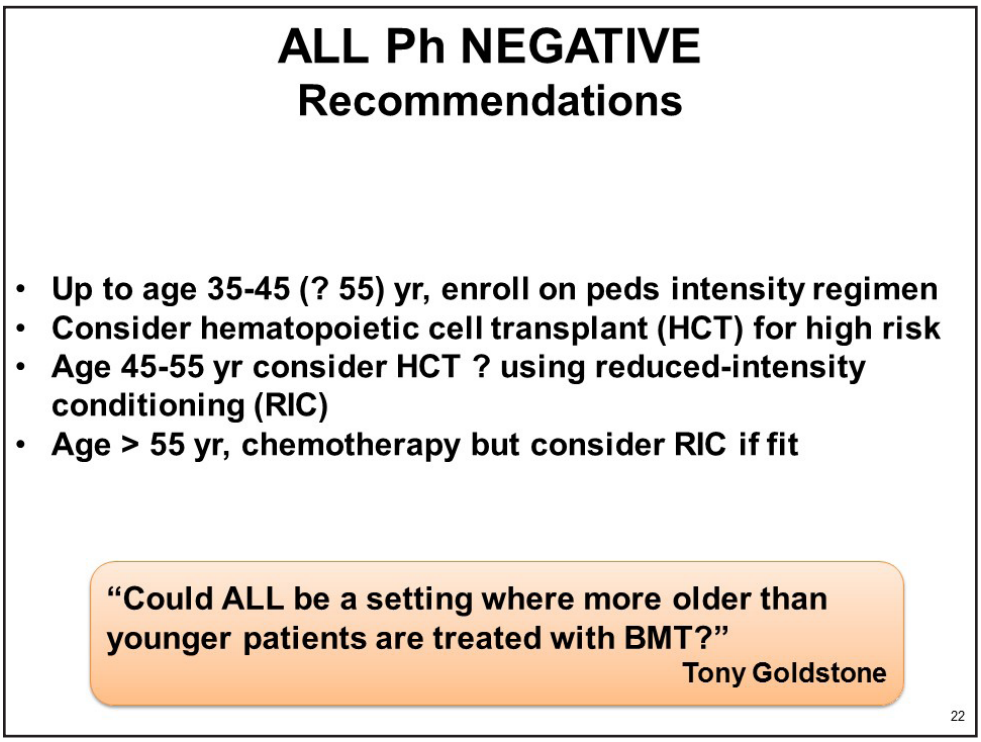
Slide 20. Adult ALL: Relapse-Free Survival and MRD at Cycle 1

This is illustrated graphically in another study, where you see on the top panel the probability of surviving is much better in a patient in morphologic complete remission, who has no detectable minimal residual disease, versus a patient on the dotted curve, where survival probability is much less when followed over time because the minimal residual disease becomes overt disease.



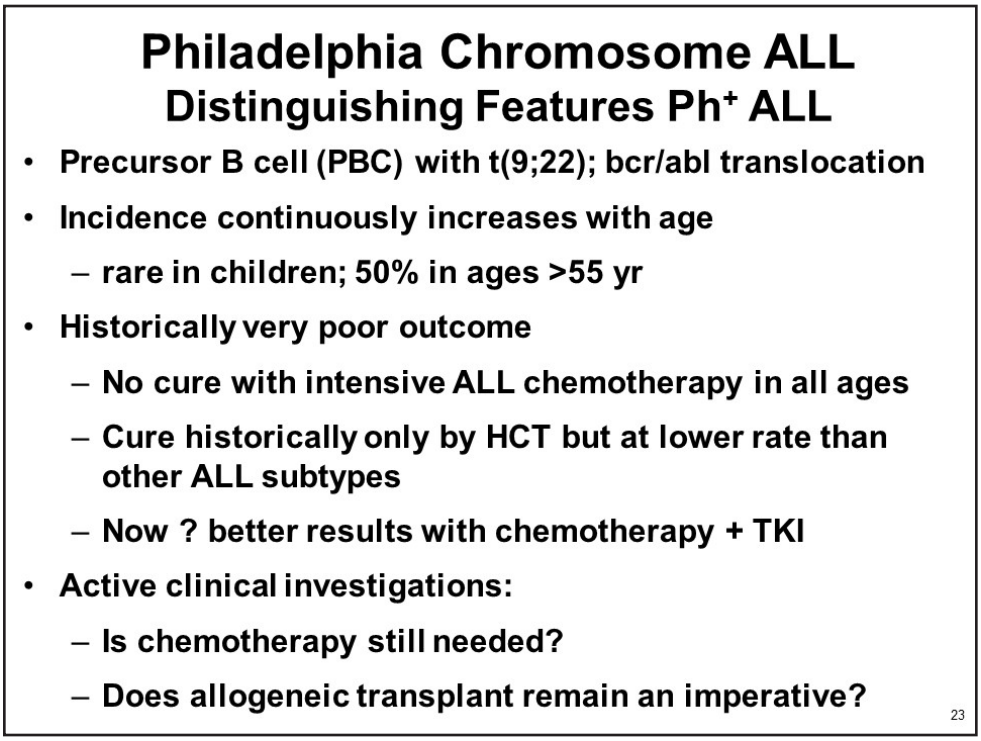
Slide 21. ALL Ph Negative: MRD at 16 & 22 Weeks

This is another example. Again, on the vertical axis is disease-free survival versus a function of many years. You can see on the top panel that when a patient received treatment and had no detectable minimal residual disease 16 and 22 weeks after treatment, patient outcome was terrific in contrast to those patients where the disease could still be demonstrated on the lower curves.



Slide 22. ALL Ph Negative: Recommendations

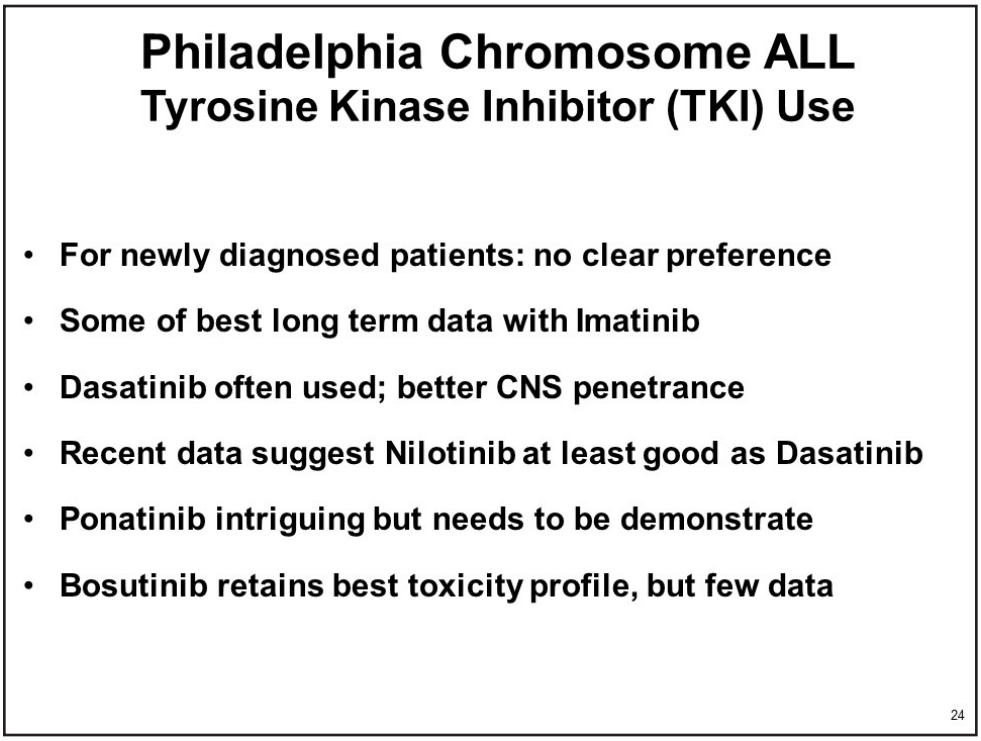
Recommendations therefore for approaching a patient who has Philadelphia chromosome negative acute lymphoblastic leukemia is to try, if possible, to utilize an intensive pediatric-like regimen that I described, certainly in people into their mid-40s and maybe up to age 55 as I showed you, and reserve a hematopoietic blood or marrow transplant for those who are high risk, while those people who are a little bit older might be able to get a transplant. The transplant conditioning should not be as intense. Those patients can't tolerate it. We refer to that as reduced intensity conditioning. And finally, those patients over 55, this is a very tough group of patients, they don't do as well with chemotherapy. If they are fit they should be considered to transplant. And now we have a paradox, and I use this quote from my colleague Tony Goldstone in the United Kingdom, could ALL be a setting where more older than younger patients are treated with bone marrow transplant? So, it is an interesting paradox.



Slide 23. Philadelphia Chromosome ALL: Distinguishing Features Ph+ ALL

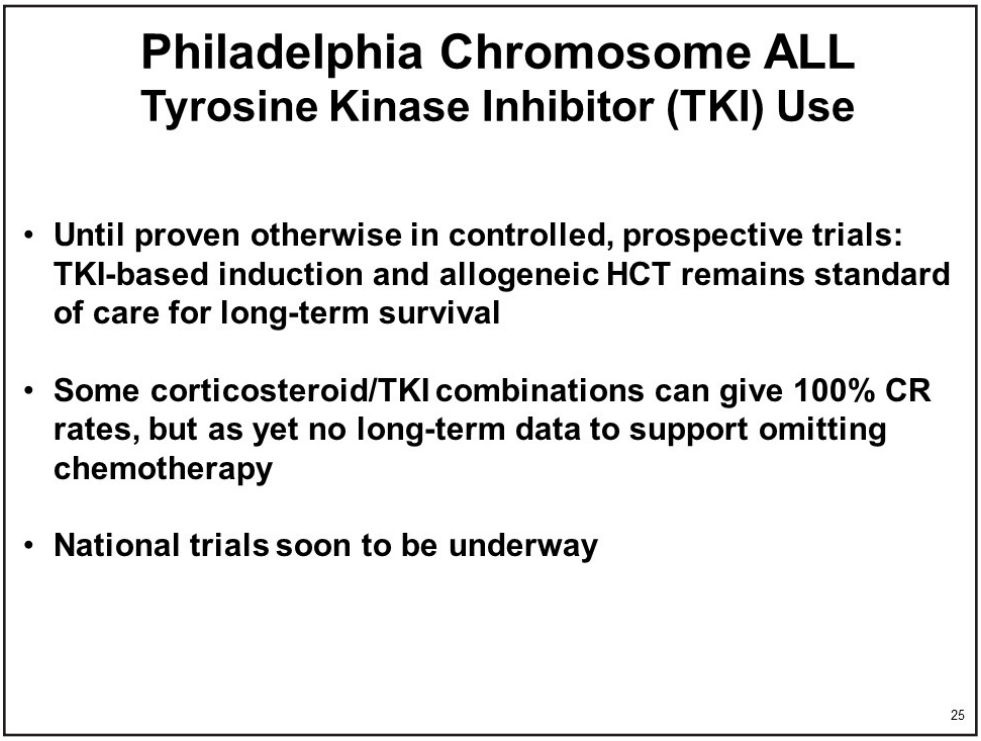
Now switching from Philadelphia chromosome negative to Philadelphia chromosome positive disease, this is a disease, as I showed early on, is very uncommon in younger children, but the incidence increases with age, certainly at least 30 percent in most adults and up to 50 percent of adults over the age of 55 will have the Philadelphia chromosome that can be demonstrated.

Initially and historically this disease was thought to be much worse than Philadelphia chromosome negative, without any cures, and the only really effective treatment was a blood or bone marrow transplant. Now with the introduction of these new drugs called tyrosine kinase inhibitors, which I'll show in a subsequent slide, the playing field has been leveled and in fact it's not clear that we even will in the future need chemotherapy or allogeneic transplant in as many patients because the tyrosine kinase agents have really made a significant difference.



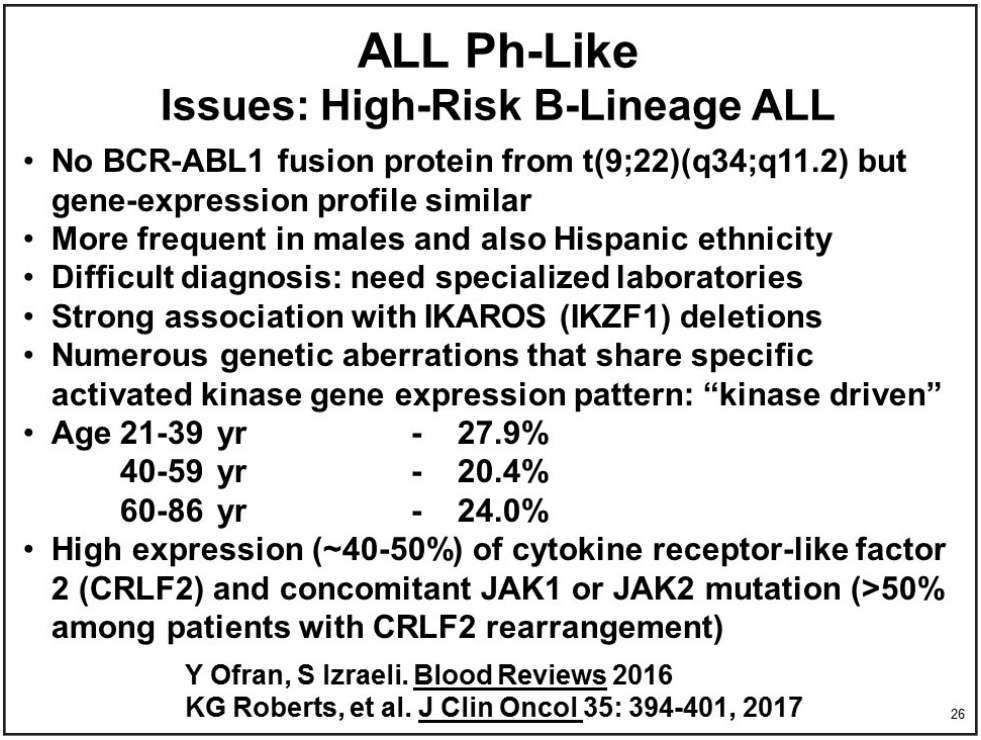
Slide 24. Philadelphia Chromosome ALL: Tyrosine Kinase Inhibitor (TKI) Use

These are drugs that specifically target and block the gas pedal analogy as I used from the Philadelphia chromosome, that genetic recombination of genes from chromosome 9 and 22, that makes the cell run at a high rate. These small molecules go in and block that and kill the cell. There have been many of these drugs that have been created. The first was imatinib or also known as Gleevec® in the late 1990s, but there have been many others. There's a drug called dasatinib or Sprycel®. It's a smaller molecule and it gets into the brain better than the other ones, and I remind you about this disease penetrating the brain. There are other drugs, nilotinib or Tasigna® is the name, ponatinib, these are all very effective drugs and each seems to have a different role. And finally a newer agent bosutinib, this is a drug that might have the best toxicity profile because all these drugs can suppress normal bone marrow, and bosutinib does not have effects on C-kit, and therefore it might be one that can be used with less marrow toxicity.



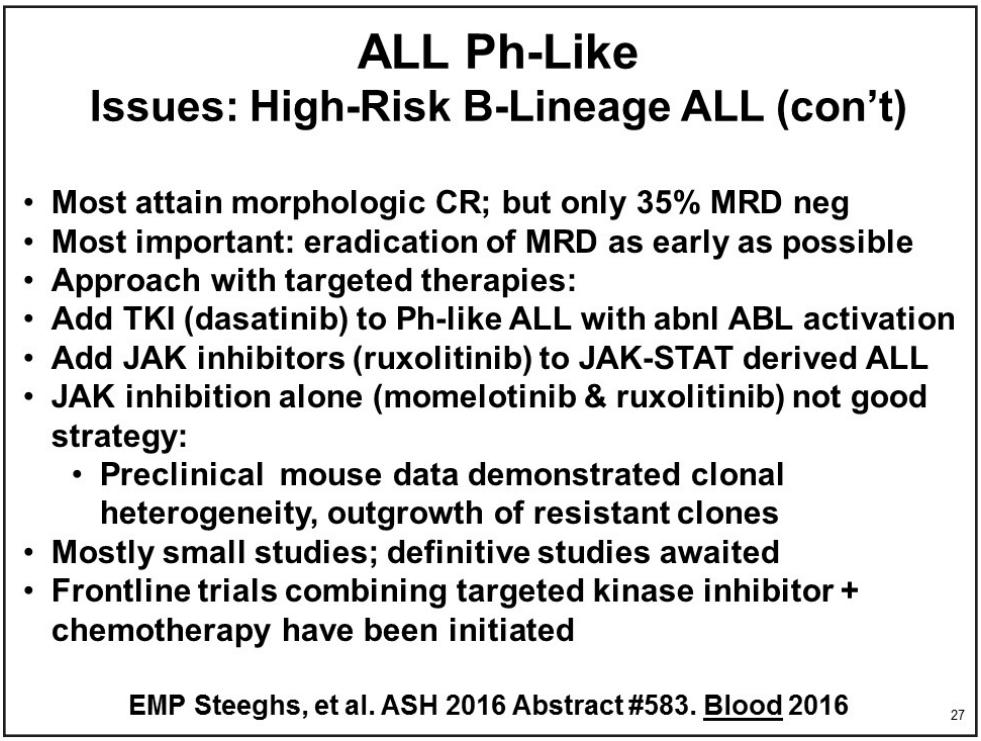
Slide 25. Philadelphia Chromosome ALL: Tyrosine Kinase Inhibitor (TKI) Use

Until otherwise proven, however, the use of tyrosine kinase inhibitors in combination with chemotherapy and allogeneic transplant is essentially the standard of care for long-term survival in all patients, but there have been data that suggest that corticosteroids like prednisone and dexamethasone in combination with tyrosine kinase inhibitors can give 100 percent complete remission rates. These patients haven't been followed that long, so national trials are underway. But it's a very interesting thought process to realize that eventually we may be able to eliminate chemotherapy and even transplantation in some patients that are affected with Philadelphia chromosome disease.



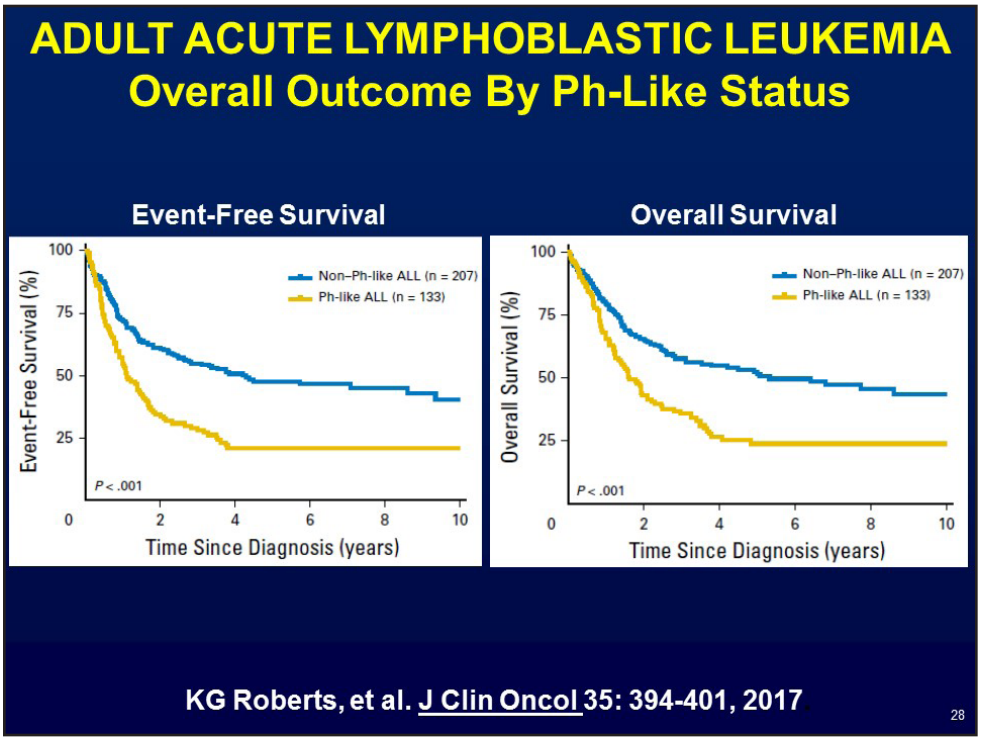
Slide 26. ALL Ph-Like Issues: High-Risk B-Lineage ALL

Now the last big group is high risk acute lymphoblastic leukemia-like. This does not have the Philadelphia chromosome, but it does have a very aggressive profile, it's more common in males and Hispanics, and specialized laboratories need to be able to diagnose this disease because it's not so easy to recognize. IKAROS deletions, this is B cell proliferation, are affected, and this disease can affect all age groups. And the problem is if you have cytokine receptor factors that account for this aggressive biology, and these factors need to be targeted, JAK1 and JAK2 mutations, to help eliminate the disease.



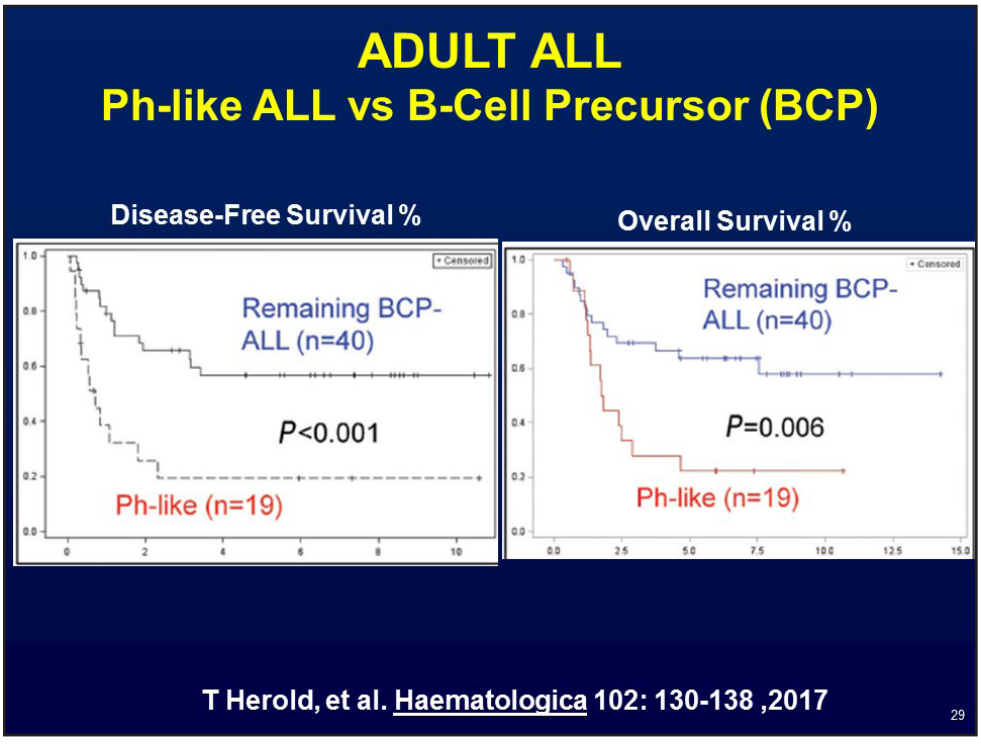
Slide 27. ALL Ph-Like Issues: High-Risk B-Lineage ALL (con't)

What's shown on this slide is that the paradox here, that while most patients attain a morphologic complete remission initially, only a third of these are minimal residual disease negative, meaning the disease is going to get active and result in serious problems for the patient. And so the approach has been to add in these targeted therapies, the tyrosine kinase inhibitors to the regimen, along with agents that block other of these cytokine problems, the JAK inhibitors, such as ruxolitinib, and these drugs all have to be given in combination because animal experiments have shown that very quickly the leukemia cells will become resistant and will not be effective unless they're combined, and so the front line trials will combine the targeted kinase inhibitors, whether they're tyrosine kinase or JAK inhibitors and all these, along with chemotherapy. Stay tuned, we're just scratching the surface of how to approach this disease.



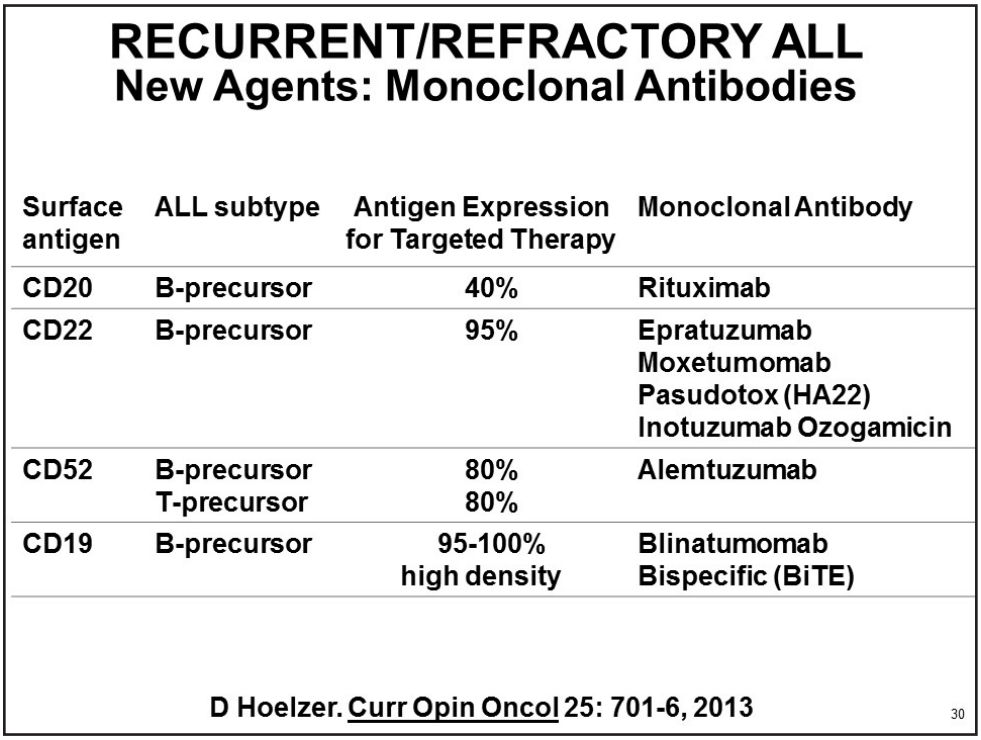
Slide 28. Adult Acute Lymphoblastic Leukemia: Overall Outcome by Ph-Like Status

This slide and the next one point out that the outcome for patients who have the Philadelphia chromosome-like disease is much worse than the other forms of acute lymphoblastic leukemia. So, the blue is the non-Philadelphia chromosome-like, the left panel is event-free survival, and the right is overall survival, and you can see that the yellow is not nearly as good in this large series.



Slide 29. Adult ALL: Ph-Like ALL vs B-Cell Precursor (BCP)

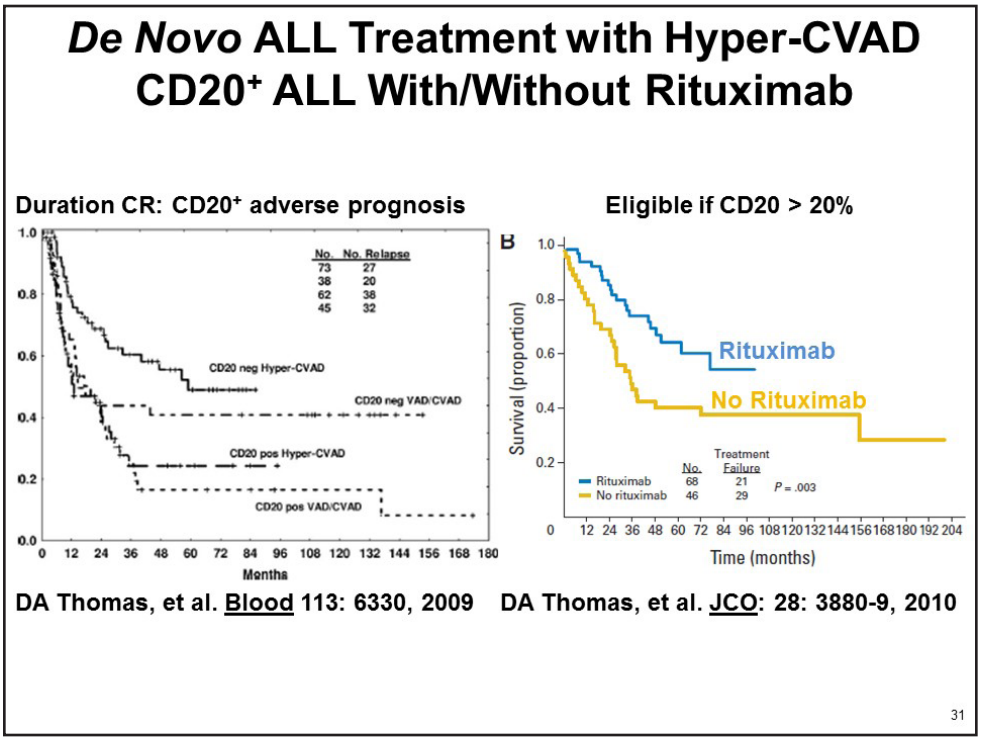
And here on this slide is a smaller series that just was published, again showing that the Philadelphia chromosome-like patients on the bottom occurs, do not fare nearly as well, and there's much more research that needs to be undertaken before we can start to get our arms around that disease.



Slide 30. Recurrent/Refractory ALL: New Agents: Monoclonal Antibodies

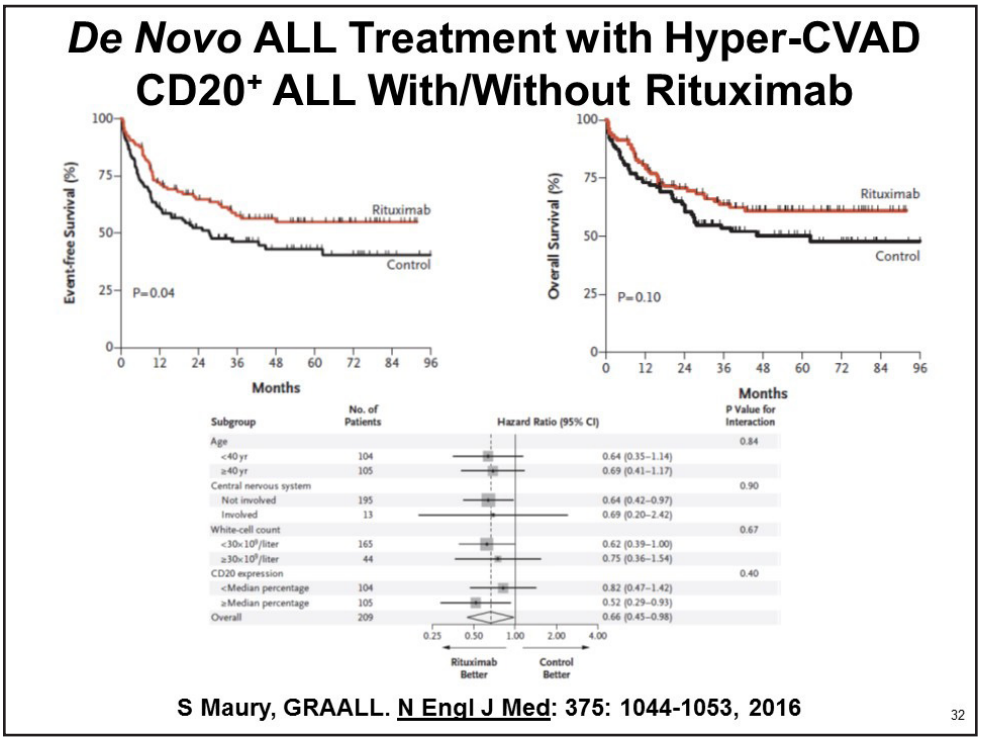
Now one of the major additions to the treatment of leukemia in addition to chemotherapy has been the implementation of monoclonal antibodies. These are like guided missiles. They are proteins that are given intravenously and target to seek out the leukemia cell. They look for something on the cell surface, the antigen or epitope on the cell, and they go by different names. One of the most commonly used drugs in the world is a drug called rituximab that targets B cells that express CD20 shown on the left. That's not all that common in acute lymphoblastic leukemia and it's especially of interest in people who have disease who have relapsed, and this is really the role for where monoclonal antibodies are making a big impact in the relapsed setting.

You can see in the middle of this slide that there are antibodies, anti-CD22, anti-CD19, that have much greater specificity, and the likelihood of the antibody having more efficacy would be demonstrated.



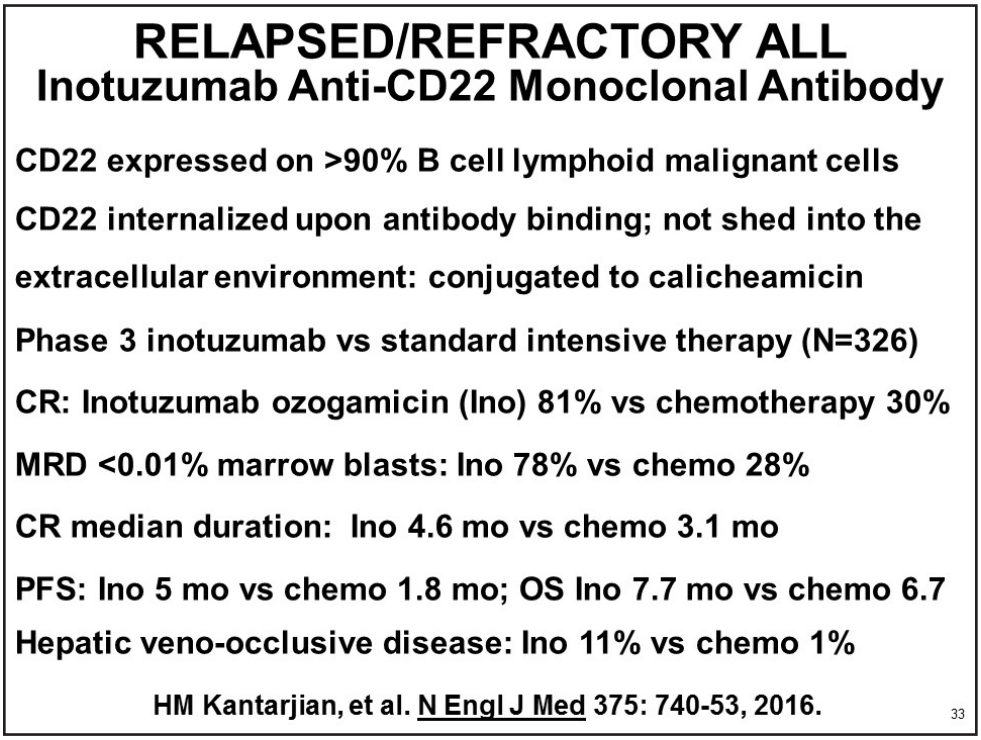
Slide 31. De Novo ALL Treatment with Hyper-CVAD CD20+ ALL With/Without Rituximab

Now historically patients at MD Anderson who were given rituximab when compared to patients who were not given rituximab did much better. And you can see they did this because leukemias that express CD20 is a worse group of patients – but you can see that the group who got rituximab did better. And that prompted these investigators to move forward with a prospective randomized trial in patients who would be eligible, whose disease was CD20 positive.



Slide 32. De Novo ALL Treatment with Hyper-CVAD CD20+ ALL With/Without Rituximab

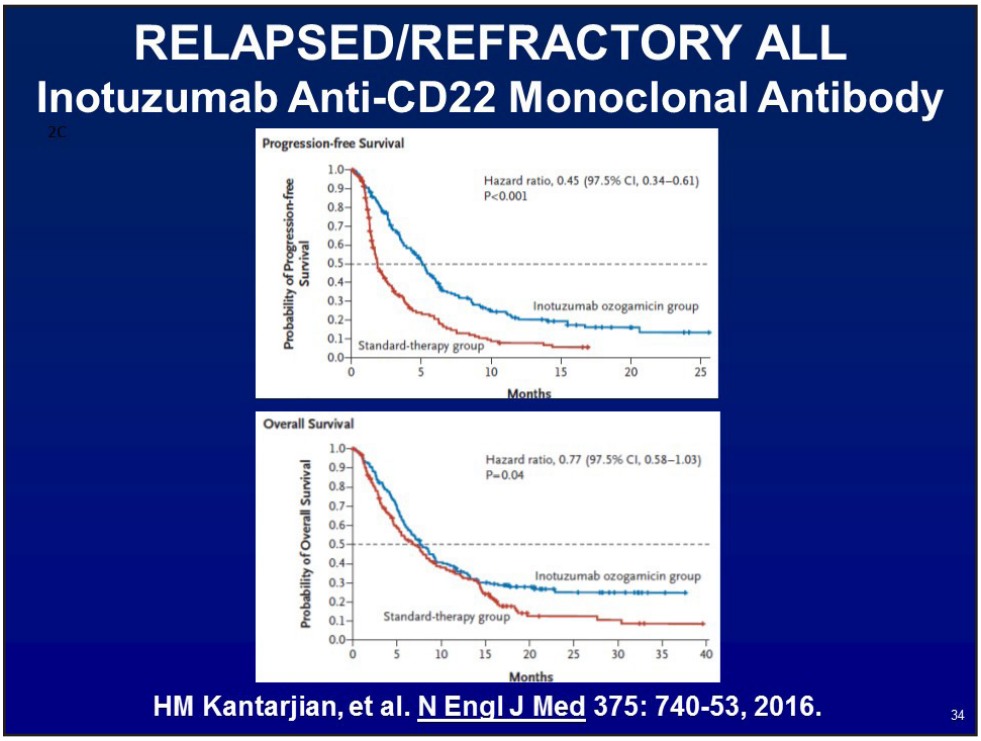
And again, you can see here on these survival plots over time, that those individuals assigned to get rituximab had a much better disease-free and overall survival rate compared to the control group, who did not get the drug, and really got this monoclonal antibody field started.



Slide 33. Relapsed/Refractory ALL: Inotuzumab Anti-CD22 Monoclonal Antibody

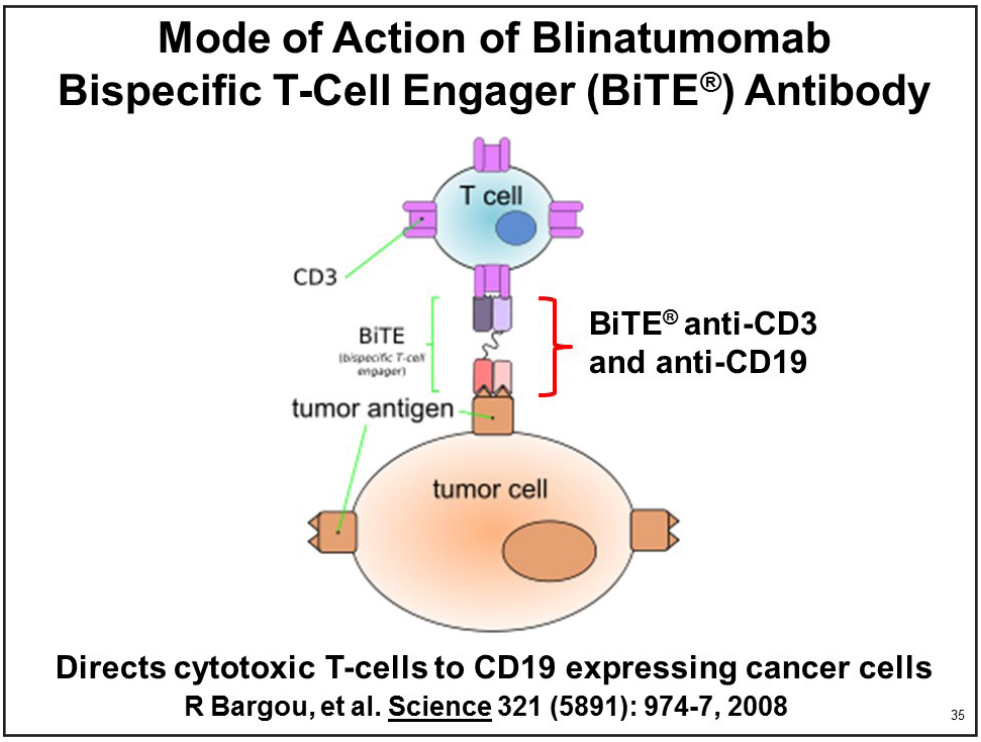
There are others that are out there. I'm going to share with you information on two specific kinds. One is known as inotuzumab. This in contrast to rituximab, which targets CD20, inotuzumab is an immunoconjugate, meaning it targets CD22 on the leukemia cell, which most, about 95 percent of leukemia ALL present this. And it's hooked up to a bomb, in other words, it's a guided missile that delivers a payload. The antibody is given intravenously, it reacts with the leukemia cell, and unlike other antibodies the epitope on the surface is not shed, but like the Trojan horse, the cell pulls in the whole antibody along with this bomb or payload, known as calicheamicin, a very potent drug. And so, it's killing the leukemia cell by putting this poison inside the cell and you can see, and I'll show on the next slide a graphic, that the complete remission rates in patients getting chemotherapy plus this monoclonal immunoconjugate, had a much, much better outcome, 80 percent versus 30 percent complete remissions, with a longer remission duration in the relapse setting. This can permit patients to go on and get other therapies as a bridge.

There is a downside, of course. The calicheamicin may have associated with it liver toxicity and in the patients in this prospective trial who got the antibody immunoconjugate, there was an 11 percent incidence of hepatic veno-occlusive disease versus only 1 percent in the group who just got the chemotherapy.



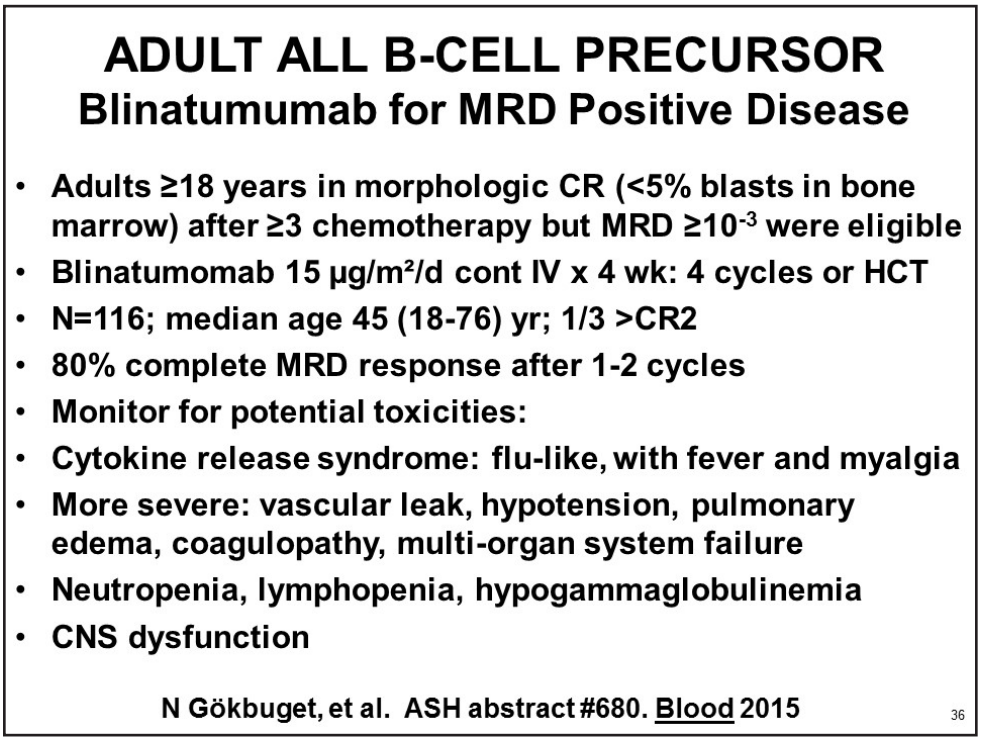
Slide 34. Relapsed/Refractory ALL: Inotuzumab Anti-CD22 Monoclonal Antibody

And this is shown graphically here. Again, this prospective trial, you can see that the likelihood of overall survival in relapsed leukemia is much better in the group who had the addition of the inotuzumab ozogamicin immunoconjugate compared to just chemotherapy alone.



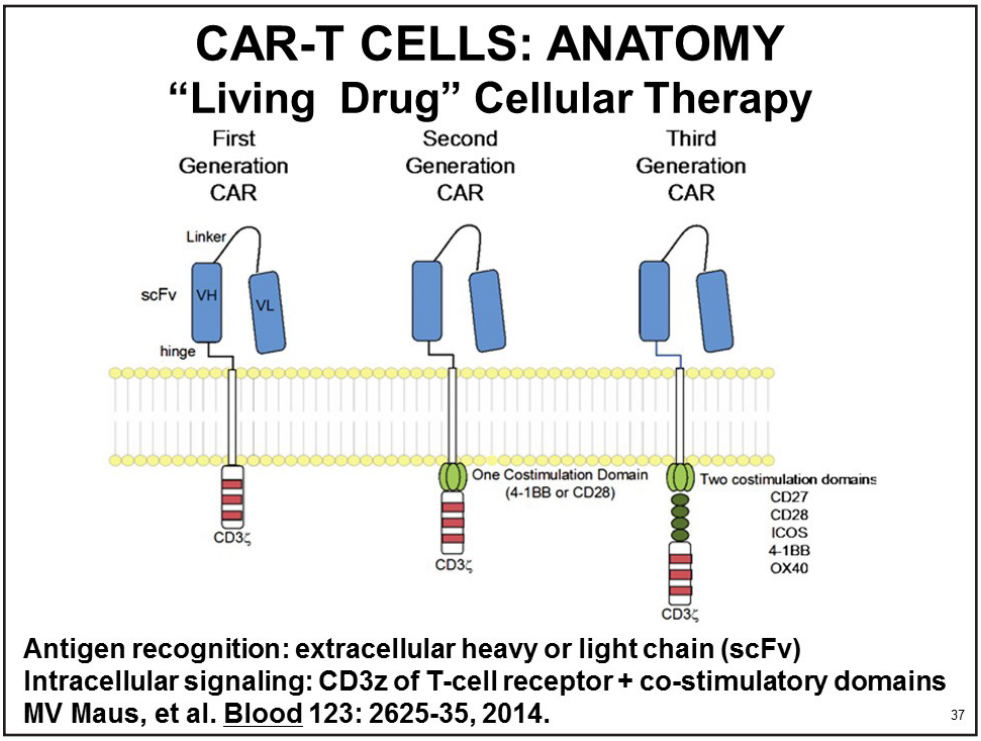
Slide 35. Mode of Action of Blinatumomab Bispecific T-Cell Engager (BiTE®) Antibody

The final antibody that I'm going to speak to is a very, very novel drug. It goes by the term BiTE, which stands for bispecific T-cell engager antibody, and unlike the other antibodies that were just targeting the antibody to hit the surface of the cell and either kill it directly or have it get internalized and kill, this is a very interesting way of getting the host's own immune system to target the acute leukemia. So, the term BiTE means that the antibody works to pull the host's own T cells, these are normal T cells that fight cancer, into close proximity with the tumor cell. So, the CD3 on the normal T cell of the host is now hooked up with the cell, bringing in contact with a CD19 positive leukemia cell, and this approach, the drug is called blinatumomab, has been used very effectively in those patients who have MRD positive disease. And several studies, one of which is shown here, this drug, which has to be continuously infused over 4 weeks, was able to get a complete remission, which was MRD negative, after 1 or 2 cycles. So many of those patients could go on and get a transplant.



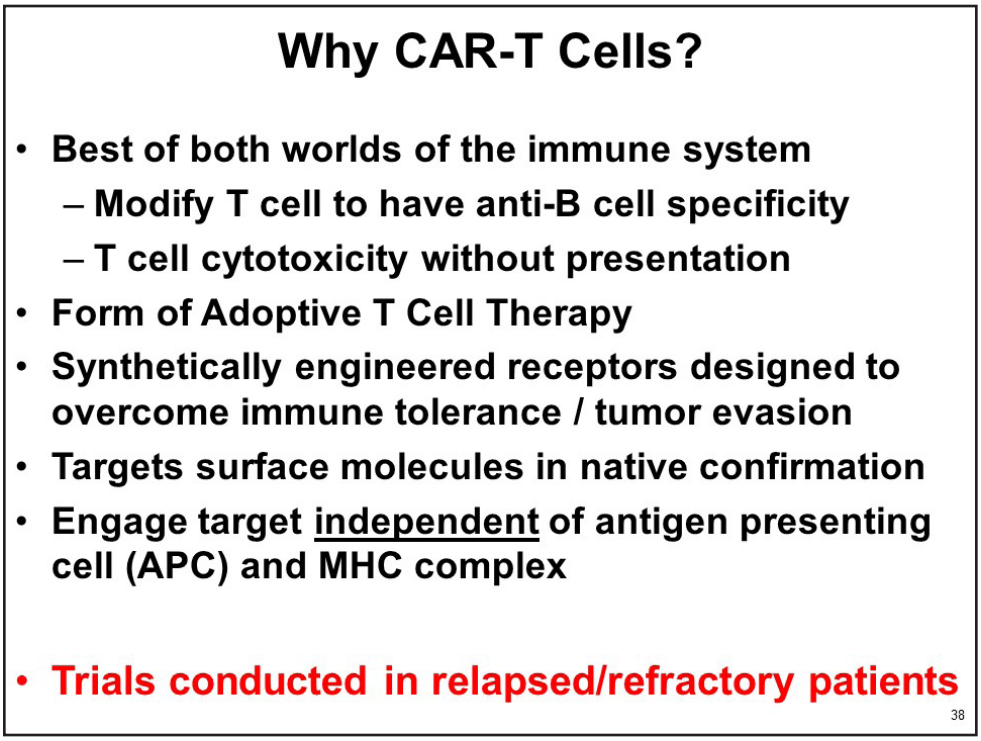
Slide 36. Adult ALL B-Cell Precursor: Blinatumumab for MRD Positive Disease

Now the problem with this approach is that by killing the leukemia cells, there's a release of cytokines, which can make people very, very sick. More commonly fevers and chills and muscle aches are common, but some patients experience severe cytokine release syndrome with interference of blood vessel function, so that they get hypotension, they get pulmonary edema, blood clotting and multi-system organ failure, along with marrow suppression, and even central nervous system dysfunction. So one has to be very, very careful in how these drugs are used because of the cytokine release syndrome.



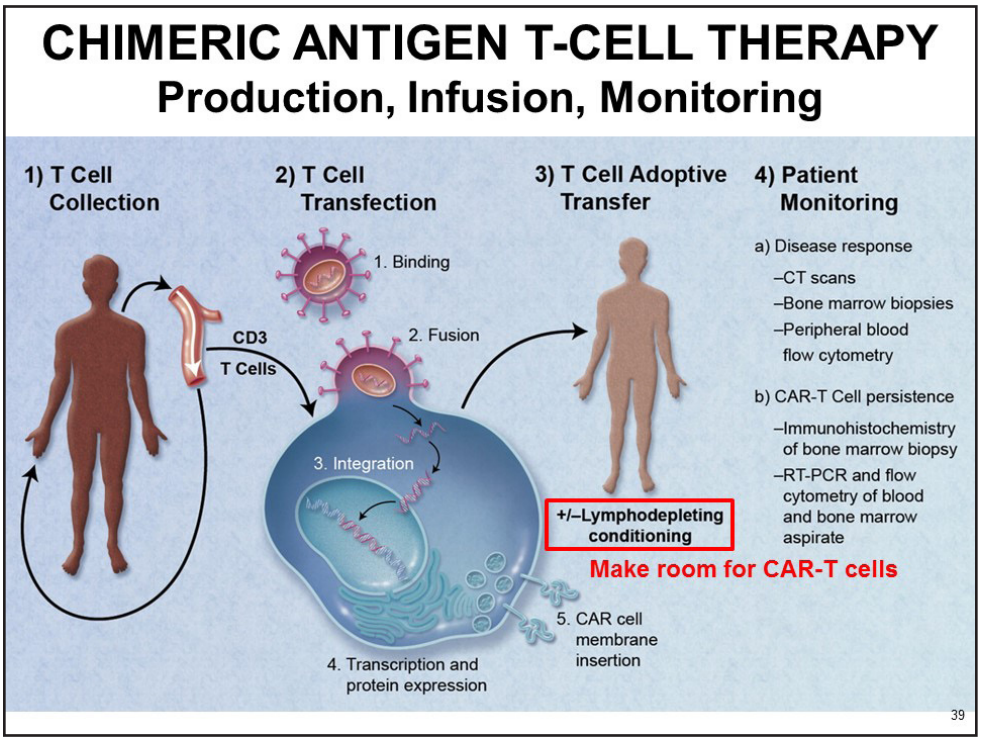
Slide 37. CAR-T Cells: Anatomy "Living Drug" Cellular Therapy

The final therapeutic intervention that I wanted to describe is probably the most novel and the one that's got the most newsworthy, and that is what are referred to as CAR-T cells. And this is more than just your usual therapy. This is a living drug, that's the best way to describe it. The idea here is to take a T cell, which usually has to be educated by the host, and converted into a B cell, where the education has already been done, and then this cell will go on and circulate in the recipient's blood and bone marrow system and go on and just kill cells, leukemia cells over and over again, over a long period of time. There have been many generations of CAR-T cells shown on this slide, first, second and third generation. Basically, the top part of the molecule is where the cell is directed. In this case most therapies are against CD19. The internal part of the molecule, down at the base of the slide, is basically the machinery for this converted cell to have machinery to replicate and divide and sustain its life, so it could go day after day after day, unlike a drug which is out of the system.



Slide 38. Why CAR-T Cells?

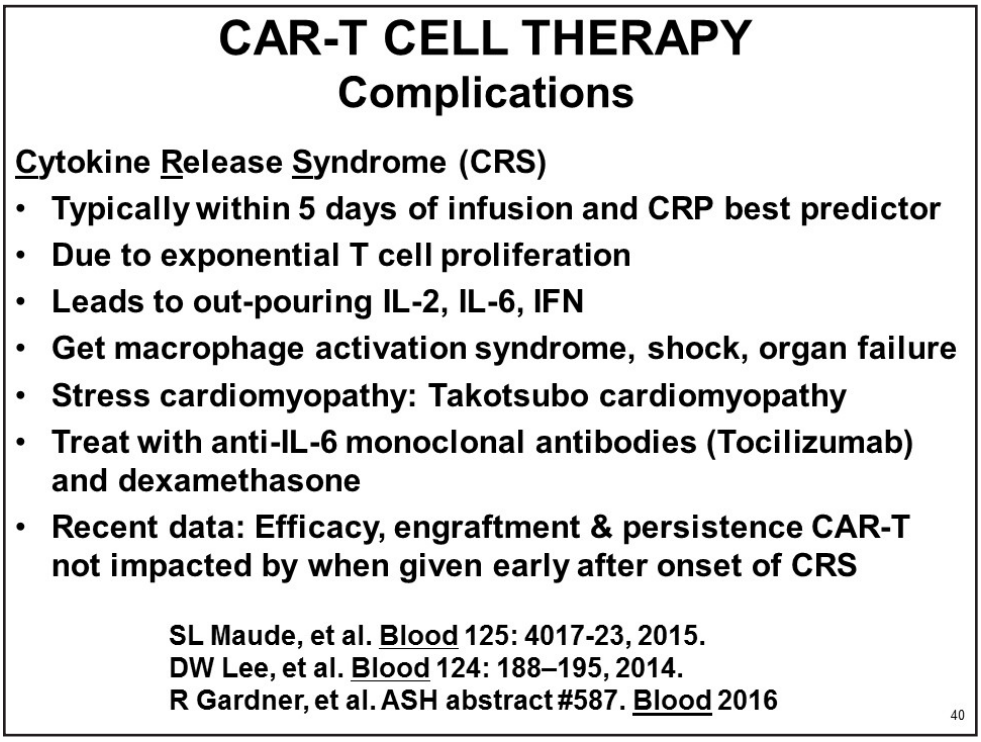
Now the CAR-T, as I've said, is to modify T cells, so they have B cell specificity and they can be educated without having been told by the immune system what to do. So this is a form of adoptive T cell therapy and it can be engineered in a variety of ways to target a variety of diseases.



Slide 39. Chimeric Antigen T-Cell Therapy: Production, Infusion, Monitoring

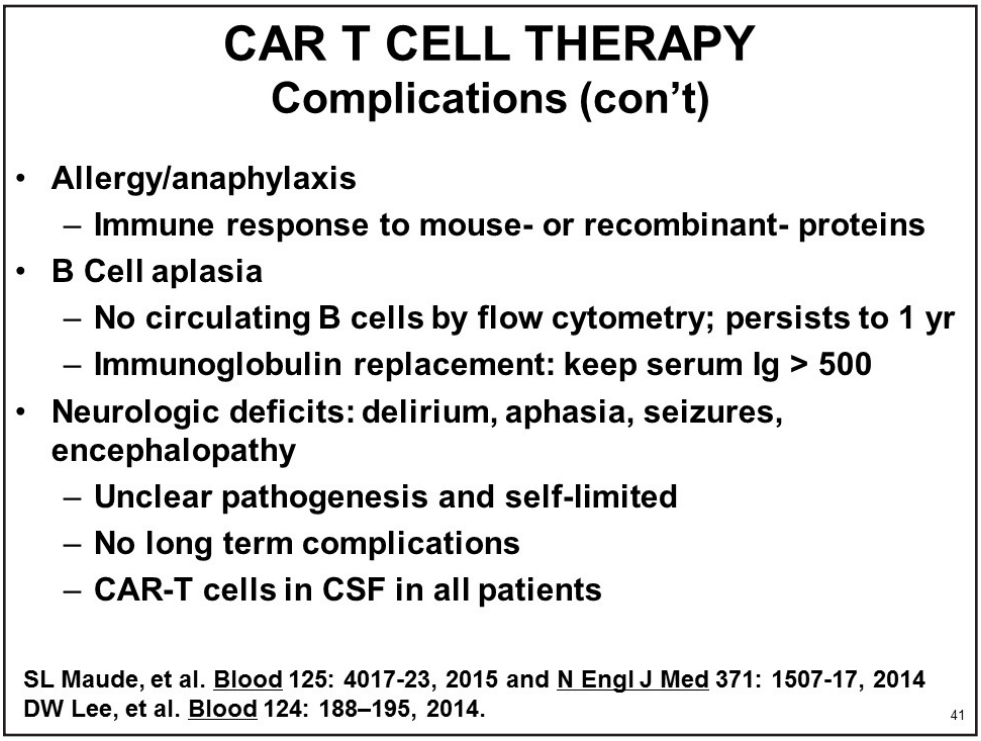
The initial work and most of the work to date is in the treatment of relapsed or refractory disease. This is a cartoon that shows how a CAR-T cell can be done, can be created for a specific patient. So, the patient in this case can undergo an apheresis procedure, where blood is collected and then those cells are purified, and through transfection with a virus, the properties can be transmitted genetically into the cell and make the cell a CAR-T cell to express the B cell properties of reacting to and targeting CD19 acute lymphoblastic leukemia, and then it can be infused intravenously to do its thing.

Now I'll remind the audience that these cells need a place to grow and divide, so before the person just gets these CAR-T cells, they have to get so-called lymphodepleting conditioning, highlighted in the red, and to get rid of the person's own lymphoid cells and allow the CAR-T cells now to grow and divide and to do their thing.



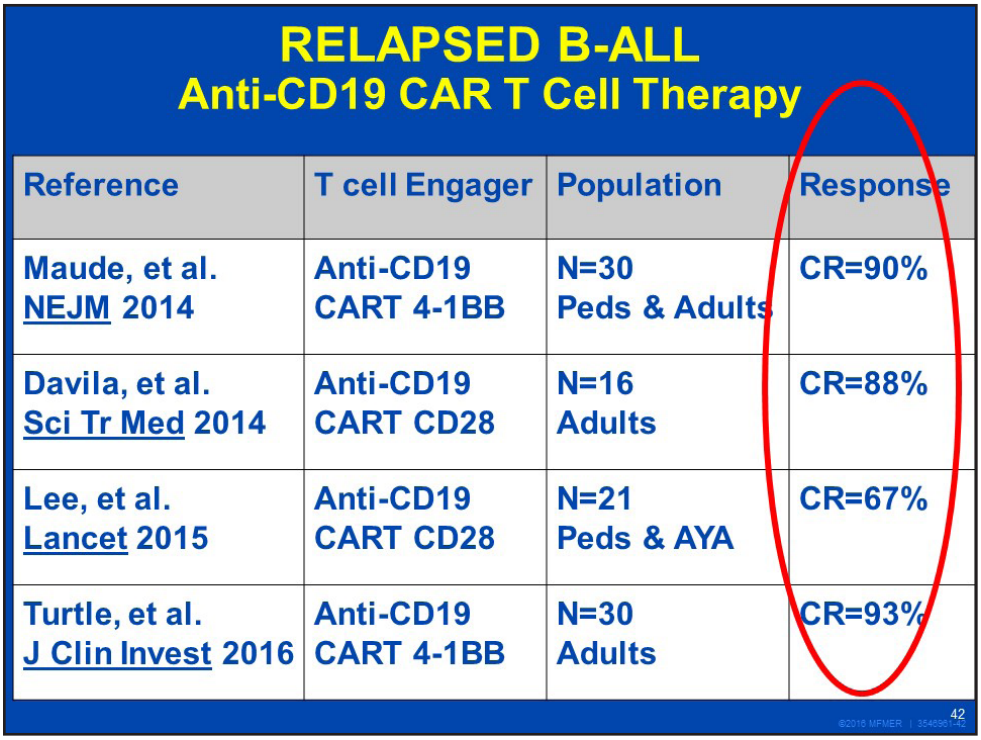
Slide 40. CAR-T Cell Therapy: Complications

Now the CAR-T cell, it also is associated with this dreaded cytokine release syndrome. This usually occurs earlier, it can be predicted by looking for elevation in C-reactive protein, and it's due to this exponential proliferation of these cells. They get into the host. The field has been cleared for them. And they have an outpouring of all these very active cytokines, IL-2, IL-6 and interferon, and the body may not like that and there can be significant side effects, including shock and organ failure, and even a specific kind of heart failure called stress cardiomyopathy. Now fortunately, there are a lot of other monoclonal antibodies that can neutralize some of these cytokines. One is known as tocilizumab, and this drug will help in reducing the toxicity of the CAR-T and can hopefully prevent some of these significant problems.



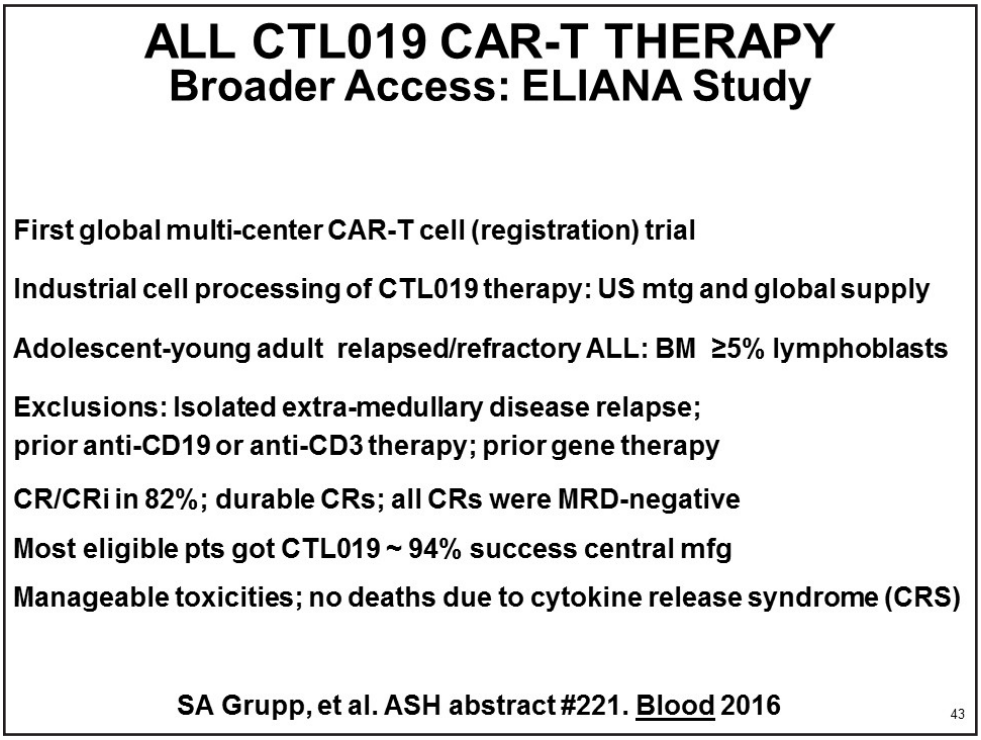
Slide 41. CAR-T Cell Therapy: Complications (con't)

But one needs to be aware that there may be other side effects of this approach, including just like with L-asparaginase, we have the allergic reactions because there're recombinant proteins in there. Targeting B cells essentially eliminates the B cell leukemia, but also may eliminate a person's ability to make antibody from B cells, and they may require immunoglobulin replacement. And just like with the blinatumomab, BiTE antibody that I showed, neurologic deficits may be significant. It's unclear why these occur, but they can be very severe and can range from delirium to seizure to encephalopathy, and it is something that requires very sophisticated supportive care to get the patient through that treatment.



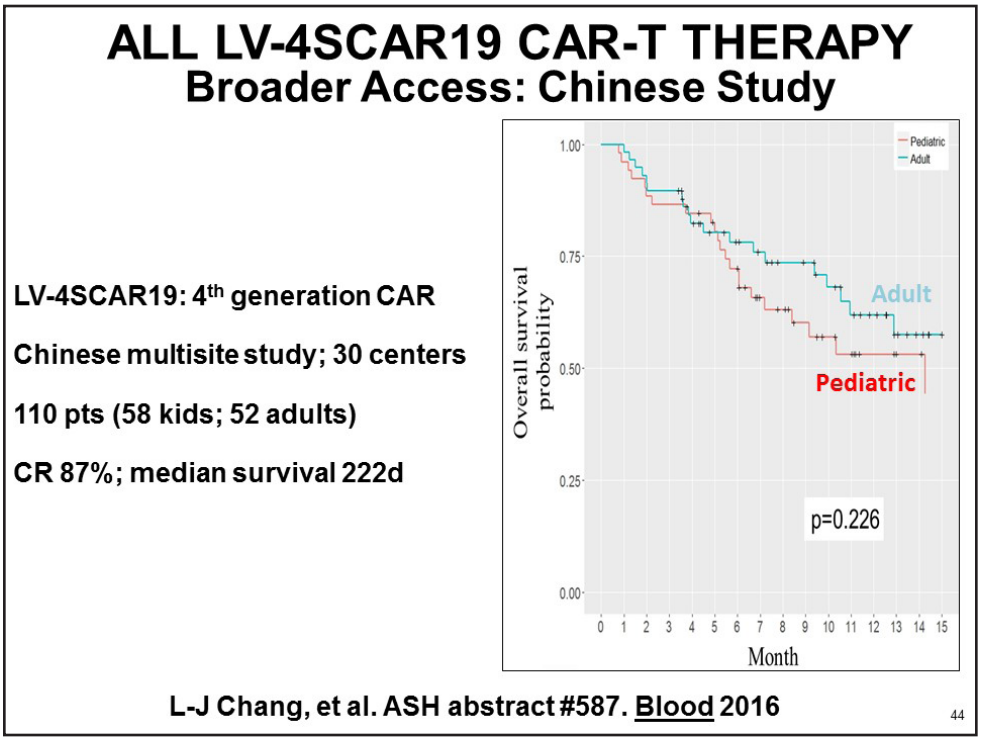
Slide 42. Relapsed B-ALL: Anti-CD19 CAR-T Cell Therapy

Now how effective are they? These are 4 different, albeit very small studies, that have been presented relatively recently, but notice in relapsed acute lymphoblastic leukemia that's CD19, the complete remission rate is astounding again. So the toxicity price to pay can be offset by the extensive efficacy.



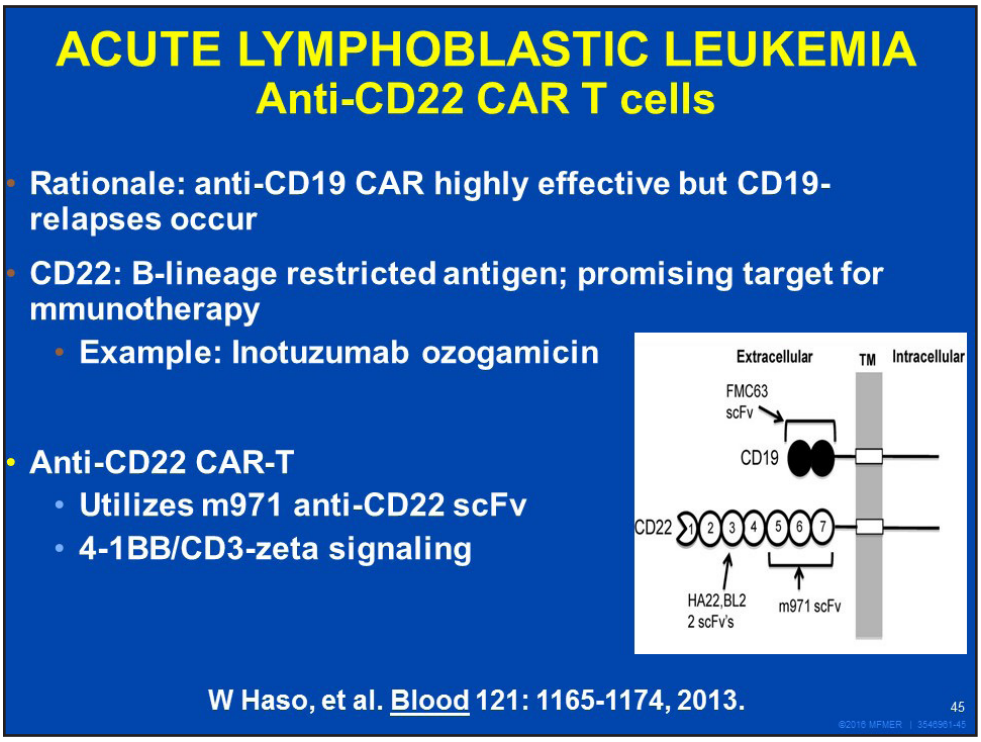
Slide 43. ALL CTL019 CAR-T Therapy Broader Access: ELIANA Study

And so, the question is can this be given as an off-the-shelf product? So this slide and the next slide speak to that. The patients – these are now commercially available and there have been several so-called registration trials, one is shown here in the United States where an industrial cell processing and then distribution of the CAR-Ts for patients that had relapsed acute lymphoblastic leukemia has been undertaken, 80 percent complete remission rates, where all of the complete remissions were MRD negative, and this presentation showed that, yes, this is certainly a potential way to go, an off-the-shelf product, and the toxicities with following the specific guidelines were very manageable. And none of the patients died from cytokine release syndrome, which was not the case when these trials were first undertaken a number of years ago.



Slide 44. ALL LV-4SCAR19 CAR-T Therapy Broader Access: Chinese Study

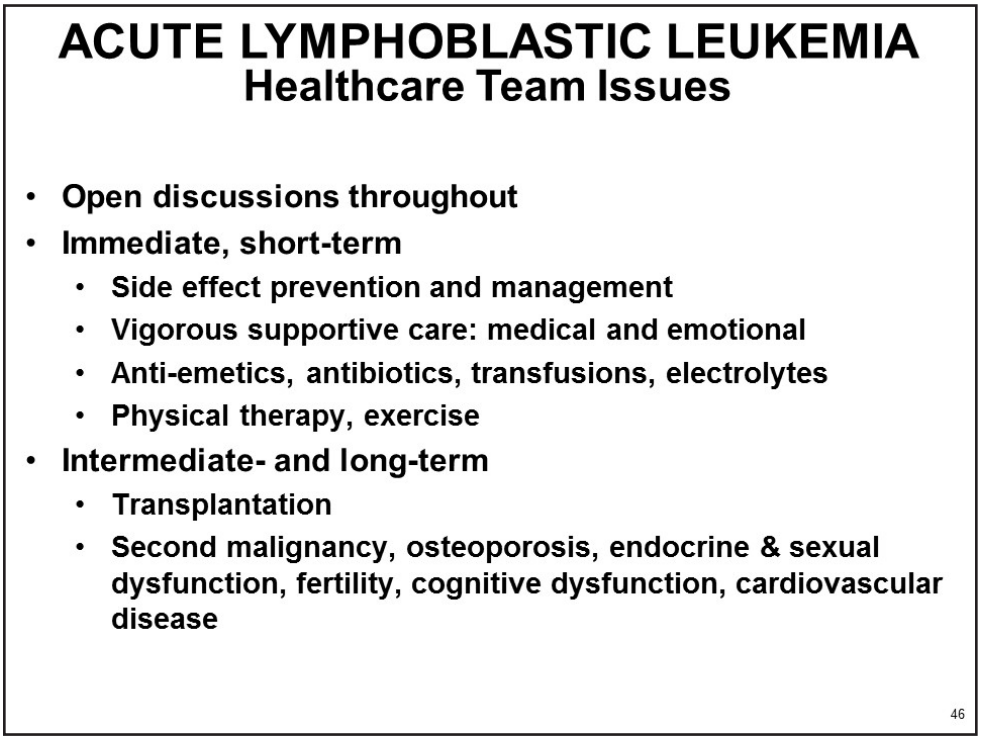
Now this is another trial showing that this can be done in other parts of the world. This is the so-called CAR-T specific therapy from China, where they did in 30 centers 110 patients and had an 87 percent complete remission rate. So, it's a very exciting strategy. It is not perfect.



Slide 45. Acute Lymphoblastic Leukemia: Anti-CD22 CAR T cells

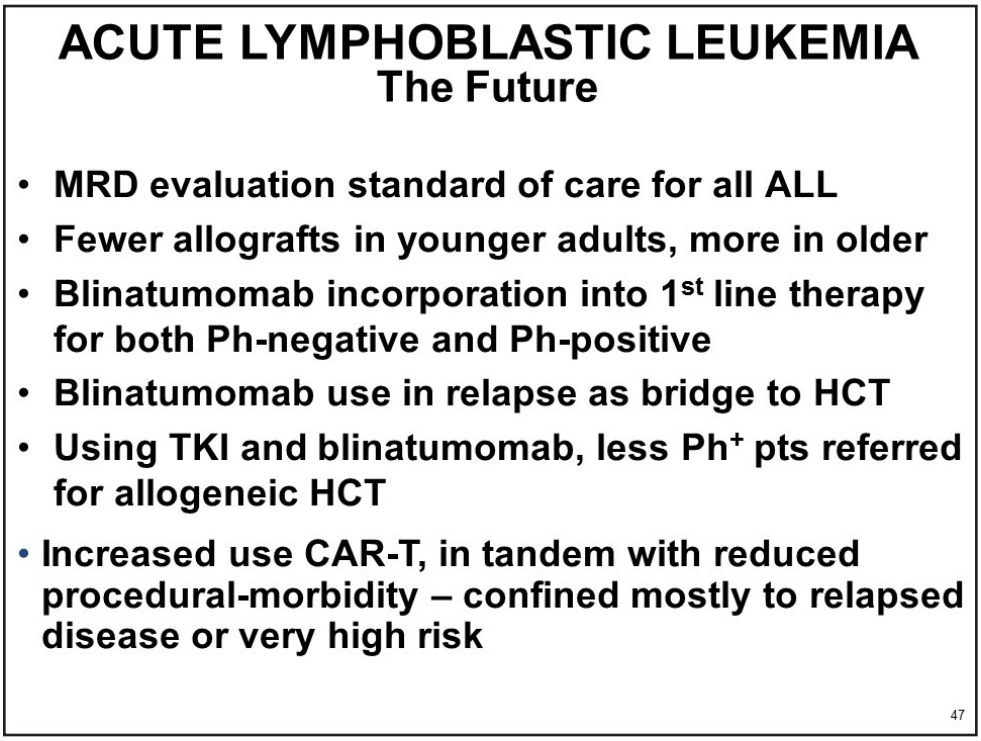
If one uses a CAR-T to kill off the CD19, it is very possible that the leukemia cells will mutate and there may be other – a need for treating other kinds of cells that have emerged. And this basically shows that there can be a CD22 CAR-T. This is

much like the inotuzumab trial that I showed earlier as an antibody, but remember this is a living drug. These cells hopefully will grow and survive and circulate for many months or maybe even longer in the patients, and may be able to overcome the side effects of the leukemia and prevent recurrence in the relapsed setting.



Slide 46. Acute Lymphoblastic Leukemia: Healthcare Team Issues

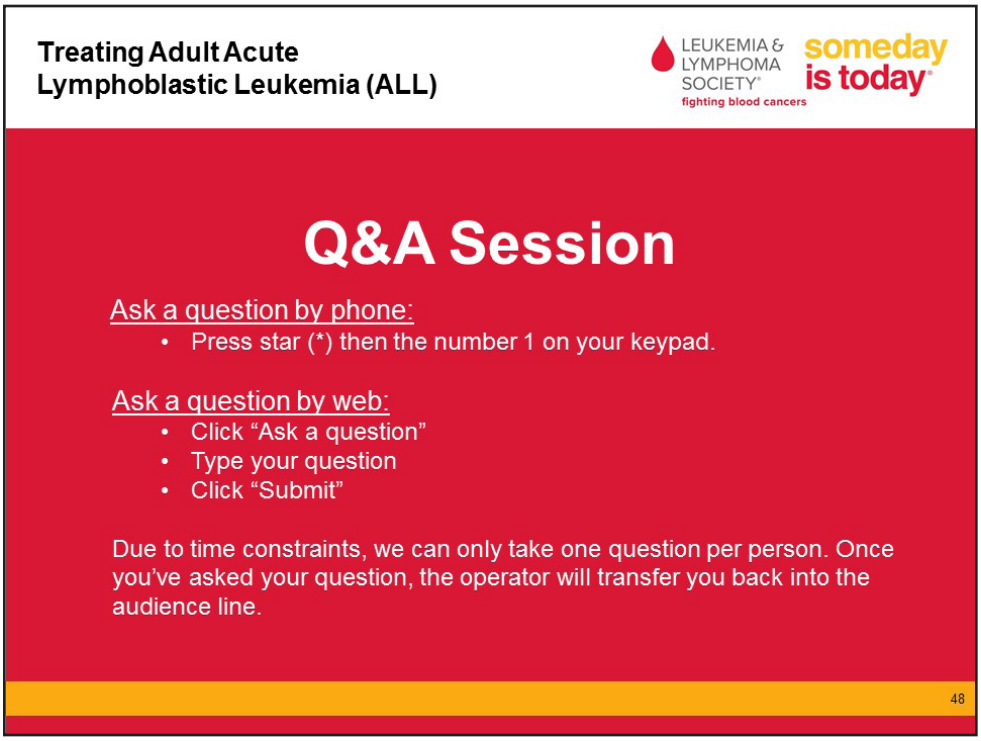
So, this is my last slide, I think. Just point out that it is incredibly important that treating these diseases requires the expertise of many, – as one says, it takes a village. Not only do all the caregivers have to be onboard, but obviously the patients and their families have to understand what the game plan is, not only in the immediate and the short-term situation where side effects of these dangerous treatments require vigorous supportive care, including anti-nausea medications, antibiotics, transfusions and electrolytes, but also some of these other approaches including getting the patient moving, physical therapy. And finally dealing with the emotional insult and providing as much psychological and emotional support as possible. Getting that patient to the next phase. Hopefully the patient is feeling better, and that patient may be a transplant candidate. And then, of course, there's another constellation of late effects that have to be addressed, including increased risk of second malignancy, endocrine abnormalities in young children, there's cognitive dysfunction, and, of course, in adults, cardiovascular disease.



Slide 47. Acute Lymphoblastic Leukemia: The Future

So, the future for the treatment of acute lymphoblastic leukemia is extremely bright. I pointed out the implementation of minimal residual disease. This has really helped understand whether a person needs more treatment or not, and is also very useful from a prognostic standpoint. And paradoxically, there are fewer allogeneic transplants that are being done in younger adults, and actually we're doing more in the older adults.

I talked about some of the newer interventions, such as the blinatumomab, BiTE antibody, which is now being looked at not just in the relapsed setting, but is actually being looked as front-line therapy in both Philadelphia chromosome positive and Philadelphia chromosome negative disease. It's now used a lot as a bridge to transplant. And of course, the implementation of tyrosine kinase inhibitors plus corticosteroids, we're really now winning the battle against the dreaded Philadelphia chromosome positive disease. And then finally I ended with the increased use of the CAR-Ts. Yes, there is a potential morbidity and even mortality, but now with greater experience we understand how to use these products, and they're now off-the-shelf and it's a very, very exciting field indeed.



Slide 48. Q&A Session

So, I'll thank you for your time and attention and the program is now open for questions.

Lizette Figueroa-Rivera:
Thank you so much, Dr. Lazarus, for your very informative presentation.

It's now time for our question and answer portion of our program.

We'll take our first question from the web audience. Doctor, Tristin asks, what are the expected outcomes for adult T cell ALL with chemotherapy alone versus stem cell transplant outcomes?

Dr. Hillard Lazarus:
So, the approach to T cell ALL is a little different because, as I alluded to early on in the presentation, it's got a better prognosis. It's one of the unusual – most T cell diseases do worse in humans than B cells – this is the one exception. A large number of patients will derive considerably good benefit and not need to proceed to an allogeneic transplant. I think that reserving the transplant for people with high risk, again, a white blood cell count of over 100,000, is an indicator of high risk T cell ALL, and that patient might be considered to transplant. But the likelihood of getting a complete remission and going on to a better outcome is at least 60 percent and in some series considerably higher in the adults. So, transplant is used less frequently unless it's in either high risk or in the relapsed setting.

Lizette Figueroa-Rivera:
Thank you, Doctor. And the next question comes from James. James asks, what are the options for treatment if there's a relapse after stem cell transplant? And that was the original treatment regimen done in a young adult of 24 years old.

Dr. Hillard Lazarus:
So, it's unfortunate that transplantation is not a perfect solution. Certainly, there are significant side effects, graft-versus-host disease and organ injury. But also, relapse can be a problem and it depends on how the transplant is performed. In a younger patient, we usually use what's called a myeloablative regimen, which means that basically throwing the kitchen sink at the leukemia. A-24-year old more likely than not would have gotten a myeloablative. And so, if a person has had a myeloablative transplant, the likelihood of them being able to get a second transplant is limited. And certainly, they wouldn't

be a candidate for a while because the effects of the myeloablative must have worn off. It's less of a problem in the less intensive transplant, the so-called reduced intensity conditioning. But again, tincture of time, it depends on how much disease a person has, can a person be stabilized to get enough disease control and enough time for them to heal to go on and get something else.

So, there are a number of options of what to do after transplant. One is what is called a donor lymphocyte infusion. This is where one goes back to the original donor and collects the T cells and the NK cells and the immune cells from the donor, usually out of the blood, and those cells are then given as a transfusion. And they often can go into a person and get good disease control. Usually a donor lymphocyte infusion has to be given in conjunction with chemotherapy.

There are the monoclonal antibodies that I described, the blinatumomab, BiTE antibody is one, the inotuzumab is others. There are a number of treatments. And then of course, the CAR-T given in the post-transplant setting, not a lot of data, but is a possibility.

So, I guess could a person also get a second transplant? Again, it depends on how the transplant was done, who was the donor. Oftentimes a second transplant, when it's performed for the reason of relapsed disease, we often will choose a different donor because whatever it was about the first donor, that should have helped eliminate the cancer, that was the not the case.

So, there's a lot of options, but it really depends on how a person is doing, how much damage they had from the first transplant, how much active disease they have, and whether their overall performance is good.

Lizette Figueroa-Rivera:
Thank you, Doctor. And the next question comes from Lauren. She asks, can you speak to the role of MRD in the post-stem cell transplant setting. For example, if MRD persists 1 month post-stem cell transplant, 2 months and so on.

Dr. Hillard Lazarus:
This is an incredibly informative, but an incredibly complicated area, because I made it sound very easy to say, oh, it's MRD, you do this test, you do that test. It's not as simple as that. There is some degree of variability because there actually have been patients where MRD positivity was not associated with progression of disease. We don't understand why that's the case. And clearly there have been patients who are MRD negative, where for other reasons, the disease gets active.

So, I think in general what we are trying to do is to prospectively understand the best way to monitor this. Most of the time the MRD is sent through a sophisticated central laboratory and trying to understand the best way to proceed, if the MRD is coming down, that usually indicates a positive – but persistence of MRD beyond a certain period of time usually is a negative prognostic sign and means that some other intervention is in order.

But it's a really complicated area and what we're trying to do in the national trials is to understand this better by doing serial, sending serial samples over time, to sophisticated reference laboratories, where the MRD is done uniformly and gives us the best information. So, global recommendations, there's no definitive answer at this point. Stay tuned for more information.

Lizette Figueroa-Rivera:
Thank you, Doctor. And Ruth asks, I am one and a half years post-transplant and still have issues with graft-versus-host disease and energy levels. Is that common, does it get better?

Dr. Hillard Lazarus:
So, congratulations for being a year and a half after your transplant. Graft-versus-host disease is a two-edged sword, the agony and the ecstasy in the sense that the cells from the donor are recognizing the tumor, this case I presume leukemia, and eliminating the leukemia, but also, it's a nonspecific recognition. So, the donor cells are certainly killing the leukemia, but may be killing or damaging the recipient's organs.

The term is chronic graft-versus-host disease when the onset is beyond 100 days. And it's a very characteristic condition that is hard to address. The most effective treatment when it works is corticosteroids, prednisone or drugs like that, and

they can control or eliminate the graft-versus-host disease for periods of time. The problem is that if it's persistent, many, many other treatments are tried.

One of the Holy Grails of the transplant field, to try to figure out, number one, how to get some graft-versus-tumor or graft-versus-host disease without having it overwhelming. In many patients if the patient can be sustained for a sufficient period of time, eventually over time the graft-versus-host disease may lessen and may go away. There's lots of very new agents that are out there.

And it also depends on the organ that's affected. For example, I mentioned the tyrosine kinase inhibitors. Gleevec in low doses has actually been very effective in chronic graft-versus-host disease of the skin. That was an unexpected benefit. But some of these other treatments are out there and are being explored, have not been as successful.

So hopefully the affected person can hang in there and the graft-versus-host disease eventually will lessen.

Lizette Figueroa-Rivera:
Thank you, Doctor. And our last question today comes from Carmel. Carmel asks, what nutrition and/or supplements can be given to someone being treated with chemotherapy, when neutrophils are low?

Dr. Hillard Lazarus:
So that's a very common question. When the neutrophils are low, the body's defenses are down and taking in things like lettuce, unwashed vegetables, may have – they don't affect people who aren't immunocompromised, but clearly are a problem for people who don't have a line of defense like neutrophils. And so, the patients are cautioned about eating unwashed vegetables and they have to eat cooked foods and all that sort of thing.

To my knowledge, for the most part, there aren't any magical supplements that can be given that seem to be conveying terrific properties. In fact, some people who take supplements may get into trouble. There are well recorded examples of supplements either causing organ damage or causing interference with treatment.

So, I would urge consultation with the dietician at the medical center and with the caregivers to understand, but some things like the usual vitamins, Vitamin D, things like that, certainly aren't going to harm the recipient. But one needs to be very careful when neutropenic with regards to diet and with regards to taking in other things that may actually interfere with the current treatment that's being prescribed.

Slide 49. Support Resources

Lizette Figueroa-Rivera:
Thank you, Dr. Lazarus, for sharing your time and expertise with us today.

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.

If you weren't able to get to your question today, you can call The Leukemia & Lymphoma Society's Information Specialists at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or you can reach us by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you may have about support, including financial assistance for treatment.

Again we would like to thank Amgen, The Leukemia & Lymphoma Society, and Shire for supporting this program.

As a reminder, you can download and print the slides as well as listen to the audio of today's program from our website.

Dr. Lazarus, 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.