Treatment Advancements for Acute Lymphoblastic Leukemia (ALL) in Children and Adults

Operator
Greetings, and welcome to Treatment Advancements for Acute Lymphoblastic Leukemia in Children and Adults, a live telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you. You may begin.

Welcoming Remarks

Lizette Figueroa-Rivera
Good day, everyone. On behalf of The Leukemia and Lymphoma Society, a warm welcome to all of you. We have over 400 people participating from across the United States, as well as other countries, including Canada, Indonesia, Ireland, Poland, and Venezuela. Special thanks to Dr. Cuglievan and Dr. Short for volunteering their time and sharing their expertise with us today.

LLS is at the forefront of the fight to cure cancer. We have invested nearly $1.3 billion in research. The five-year survival rate for a child with leukemia 50 years ago was three percent. But with the advent of combination chemotherapy as standard of care in the 1960s, increasing understanding of the disease, and more recent discoveries of novel therapeutics, cures are now possible in children.

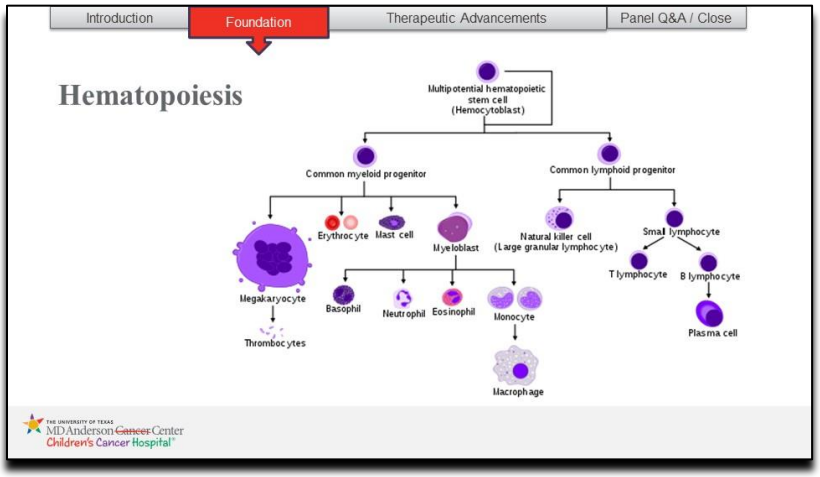
LLS has been at the forefront in improving outcomes for patients with ALL. LLS supported pioneering work at the University of Pennsylvania, where researchers helped develop the first CAR T-cell immunotherapy for ALL, which attained approval from the U.S. Food and Drug Administration in 2017. There is still much work to be done and LLS is, again, leading the charge for ongoing and future work in the ALL landscape, both in pediatrics, as well as in adults, where there remains tremendous, unmet medical need.

In adults, despite advances in management, the backbone of front-line therapy remains multi-agent chemotherapy, and for patients who can tolerate it, allogeneic stem cell transplantation. LLS is currently supporting new research through 26 active academic grants to explore every avenue, to further improve outcomes for ALL patients. As the leading source of free blood cancer information, education, and support for patients, survivors, families, and healthcare professionals, LLS helps you navigate your cancer treatment and ensures yo u have access to quality, affordable, and coordinated care. Research will help us achieve an end to cancer. In the meantime, patients need help before, during, and after their diagnosis and treatment and LLS is the leading, non-profit that does just that.

For this program, we would like to acknowledge and thank Kite, A Gilead Company, for their support. Following the presentation, we will take questions from the audience.

Disclosures

I am now pleased to introduce our speakers, Dr. Branko Cuglievan, Assistant Professor, Department of Pediatrics at The University of Texas, MD Anderson Cancer Center; and Dr. Nicholas Short, Assistant Professor, Department of Leukemia at The University of Texas, MD Anderson Cancer Center in Houston, Texas. Dr. Cuglievan, I'm now privileged to turn the program over to you.



Hematopoiesis

Branko Cuglievan, MD
My name is Branko Cuglievan. I'm the Section Chief for Hematological Malignancies here at MD Anderson. And it's a pleasure to be here. So today, we're going to talk about pediatric leukemia, and particularly ALL. So, the first thing, and I know this is in focusing advancements, but I want to take one or two minutes to discuss pediatric cancer, as a whole, so that you take perspective in the whole talk.

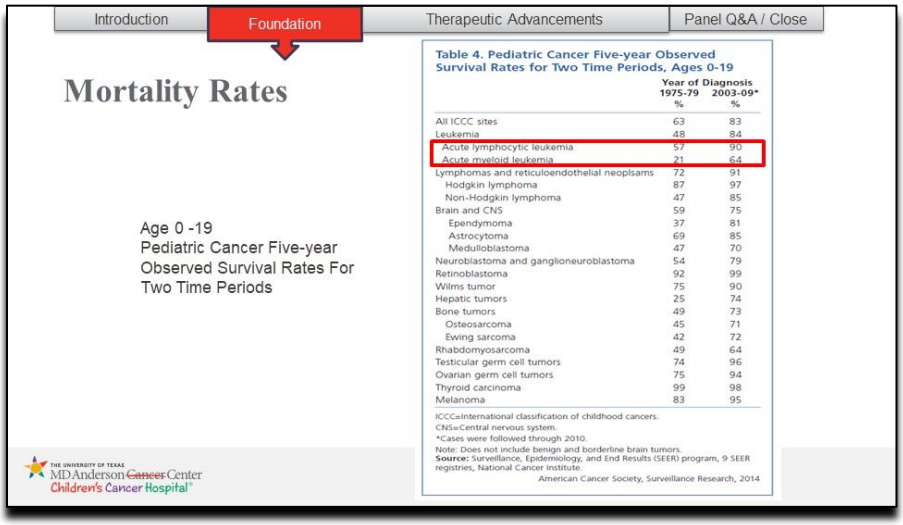
And then, after my talk, you'll have Dr. Short, who's an amazing physician and colleague and he's also going to share amazing data to you guys. So when you think of cancer and you think of breast cancer in adults, colon cancer, lung cancer, you're talking about 200,000 cases for breast, 200,000 cases for colon, et cetera, right? When you talk about pediatric cancer, as a whole, I'm not talking about lung cancer or breast now. I'm talking as a whole, pediatric cancer. You're talking about 15,000 cases, total.

So, it's very rare compared to adults, right? Among those 15,000 cases, 30 percent, so 5,000, are leukemias. And that's great, 'cause there's not many. But once you take that bucket of 5,000 cases, you need to divide them in B-ALL, T-ALL, Ph-like, Ph-positive, B-cell or, infant ALL, and so on and so forth. And eventually, you end up having buckets of these small number of diseases, which, like I said before, it's great. But, that will have an impact in drug discovery, because if Dr. Short calls me tomorrow and tells me, Branko, I have this drug that we should advance it in pediatrics, I need numbers, number of patients, to enroll in a study to finally complete my study and see if it worked or not, the drug. When you have a small number of patients in these leukemias, a trial can take ten years to complete. And in those ten years, Dr. Short's going to call me and say, what happened? You didn't find an answer to that and maybe the answer was that it didn't work. So we need to find new mechanisms to discover therapies in children. And we will see that in this talk.

So this first slide is hematopoiesis. This happens in the bone marrow. If you take a bone and you cut it in half, it's not empty inside. What's inside the bone, it's called the bone marrow. And this was probably one of the ugliest diagrams that I had to see when I was in med school.

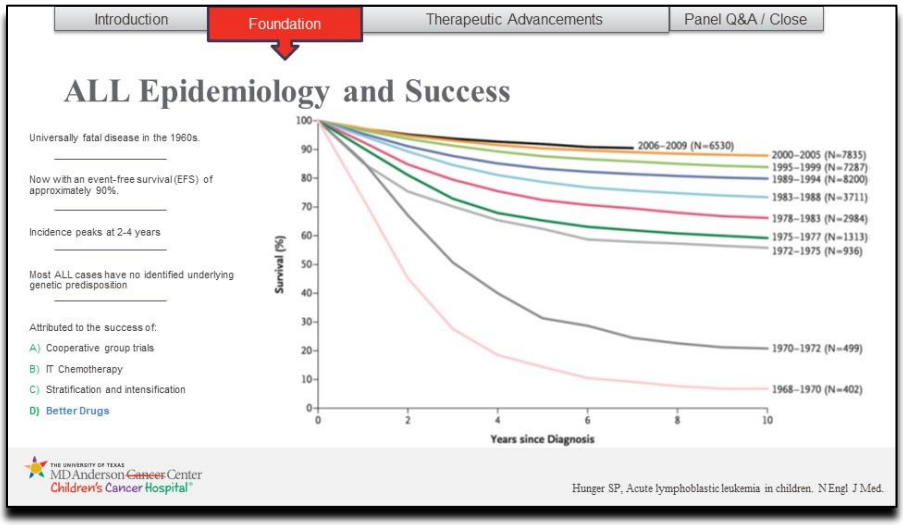
And it's incredible how I'm, now I'm specialized in this field. The way I explain this, is you have this stem cell, here, on the top, which I would call it, like a sort of chairman, right? And then, you have two, independent, and separate directors. One is the myeloid director -- myeloid progenitor, and the other one is the lymphoid director, or progenitor. They don't talk to each other, even though they come from the same stem cell, they don't talk to each other -- different headquarters. And they differentiate, or they develop, or they mature into highly functioning immune cells. For example, in the myeloid progenitor, you have the eosinophils or the neutrophils, the macrophages, the monocytes. The myeloid director converts or becomes or differentiates into that. In the lymphoid, which is the area of the talk, same thing happens -- the cells mature, grow, develop into a full-blown lymphocyte that will fight for infections for you.

What happens in leukemia, is that there's an -- a block differentiation or maturity. And this is not on a structural block. It's that the cell, that lymphocyte, not the person who has the leukemia, but that cell, the genetic information on that cell suddenly has a problem and does not allow the cell to mature and differentiate into a full-blown lymphocyte, preparing you to fight infections. And this happens in the early development of the cell, so it's a baby cell and that's why it's called blast, for baby cell. It's a baby blast cell that doesn't mature. And that's when leukemia happens, when there's an accumulation of these blast cells that are not able to move forward into the process of development.



Mortality Rates

And we've done really well, as you can see here, in acute lymphoblastic leukemia. Years ago -- we've done a significant improvement. This says that we are in 90 -- we're probably 98, 99, in some cases. And in AML, we're still not doing as good as we would like. There's data showing that we're closer to 70 percent. Hopefully, we can go better than that.

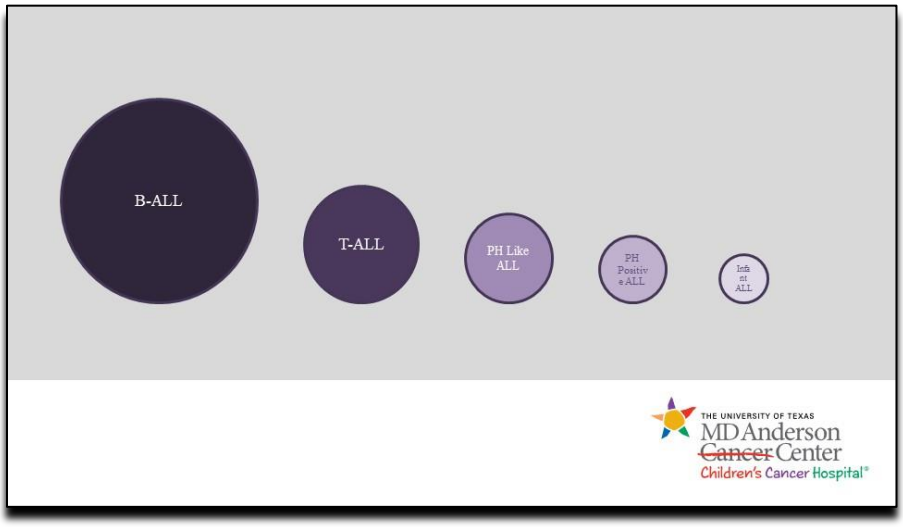


ALL Epidemiology and Success

And the success in ALL, this is a Kaplan -Meier curve, and you're going see it throughout. So, this curve, what you're going to see here is survival here, on the left. And then, you're going to see the years to diagnosis.

And this graph is important in cancer, because we try to see what's the rate of cure. So if I put the example of what's the chances, here in Houston, of living after being bitten by a mosquito bite, for example, it would be a straight line, at 100 percent. Right? A straight line at 100 percent. You can see here, in ALL, in what happens, is that years ago, the survival was 10 percent. And then, we've gone up to 20, 30, 40, 50, and now we're doing better.

And that's thanks to many things. Number one, we've done, a comparative group, to join forces with different hospitals across the world, because we need to find that problem I mentioned in the beginning, of isolating all these small groups. We need to get all together to find a solution and -- and treat and do these trials, with everybody joining forces. But also, because we've been able to isolate, we are the patients that need more chemo, transplant. Which are the patients that need less chemo. Also, we have newer therapies and also, we've known, which are the types of leukemia that, for example, relapse quite often in the spine. And we need to do lumbar punctures to all of these patients, right?



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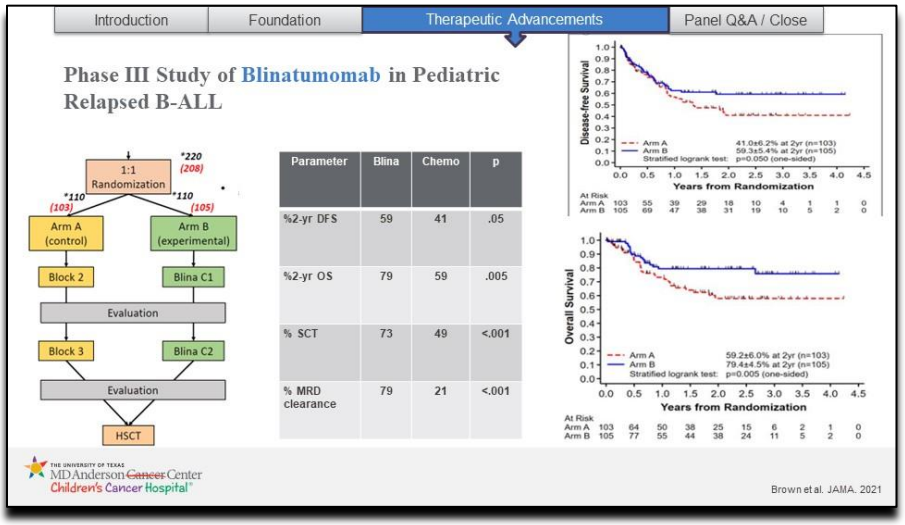
But if I try to do this in 12 minutes, and I try to select which are the leukemia, the ALL types that have the biggest advancements, I would say they are B-ALL, T-ALL, Ph-like ALL, Ph-positive ALL, and infant ALL.

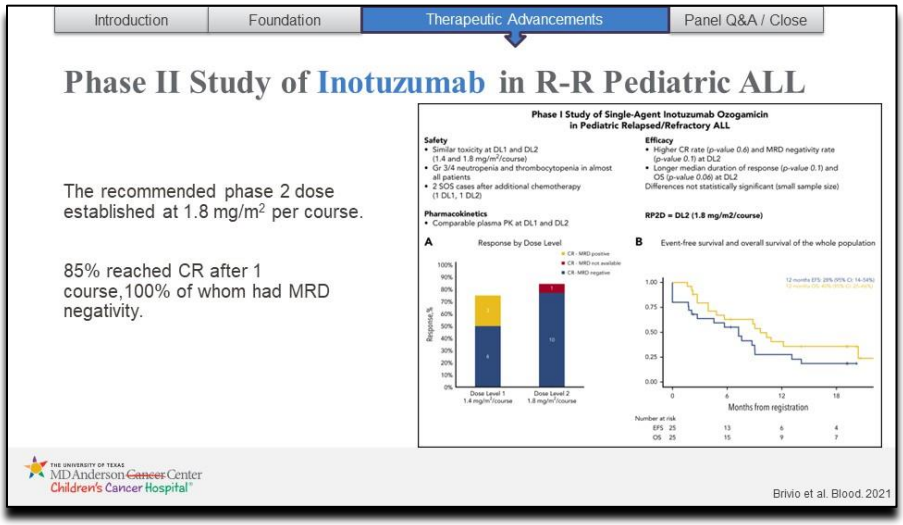


Phase III Study of Blinatumomab in Pediatric Relapsed B-ALL

Probably the biggest discovery, which was translated as all of these drugs from adults to pediatrics, was blinatumomab (Blincyto®). Blinatumomab is an antibody. It's a monoclonal antibody. It's actually called a BiTE [bispecific T cell engager], a BiTE antibody because it joins, or it stimulates your immune system, also to fight against this leukemia, which, targets a tag that the lymphocytes have. It's called CD19. So it doesn't cause any hair loss or any mucositis or all the anemia, thrombocytopenias, and all the complications that were seen in the past with all these leukemias.

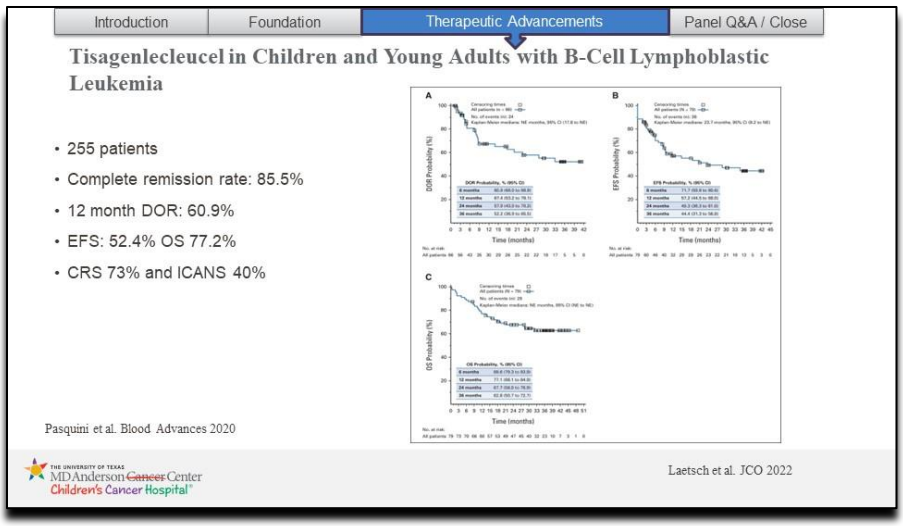
And this study was done in pediatrics, where they randomized patients who relapsed with ALL. So they pretty much said, and it was a study done by Pat Brown here in the United States. And there was, in parallel study done by Franco Locatelli in Europe. And what they did was, okay, we have 200 patients who relapsed with ALL. And we're going to randomize them. A hundred are going go to get more chemo or a hundred are going go to go get this amazing, you know, immunotherapy that has been working in adults and see what happens.

Well, the study needed to shut down early, because everybody who was in the blinatumomab arm was doing much better. And now, eventually, all the relapse patients that were in the chemotherapy arm were moved into the blinatumomab arm. As you can see here, Kaplan-Meier curves again, the blue lines, patients with Blina did much better than the ones with chemo. You can see that here, again.



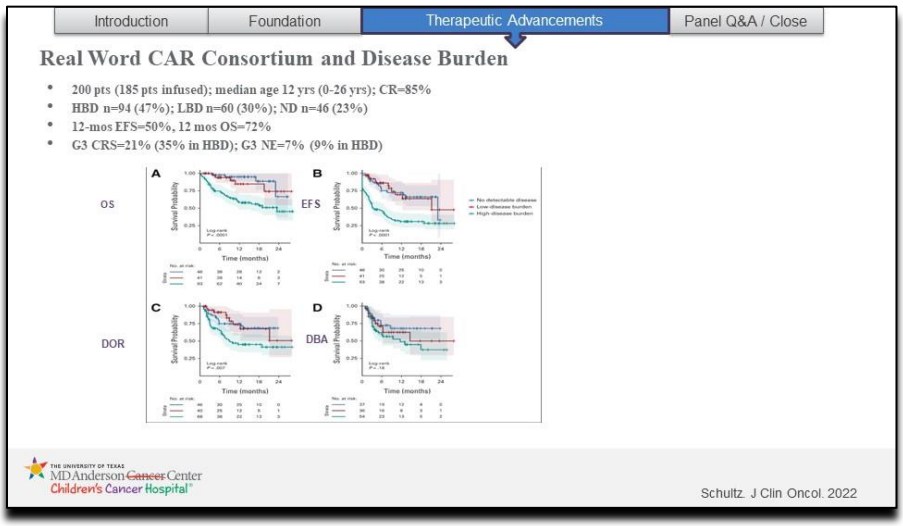
Phase II Study of Inotuzumab in R-R Pediatric ALL

Inotuzumab (Besponsa®) is sort of a cousin in mechanism with blinatumomab. It's also an antibody. It's not chemo. It doesn't have the toxicities of chemo. It has other immune-mediated problems, that we can talk about later. But this was phase I study done in Europe. And this study, what it did, it did not randomize the patients with leukemia to get A versus B. It pretty much received a bunch of patients with ALL who had relapsed and they gave them Inotuzumab. And 85 percent of these patients achieved a remission and were MRD [minimal/measurable residual disease] negative. So it was a fascinating response and that's why blinatumomab and inotuzumab, now, in 2023, are used in front-line ALL. Meaning if somebody's newly diagnosed with ALL, they will get these drugs in the front-line.



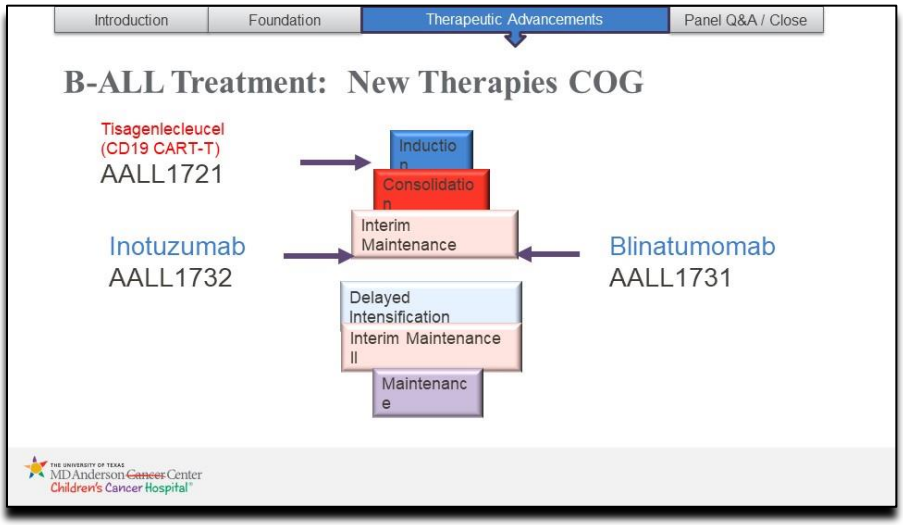
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

Subsequently, is the CAR T-cell therapy. Probably, many of you already are aware of that. It got FDA designation of a new type of living drug in 2017, after seeing phenomenal responses. What they do, is they take your healthy cells, they take them to the lab. They engineer them, and then they re-infuse them into you after four weeks. And that new mechanism, of this living drug, has helped us achieve phenomenal responses, as you can see here. Almost 85 percent of responses. What we have been learning, though, is that, as time goes by, the efficacy starts dropping. And we need to know which are the patients who we should start using this with and in what context and when. There is still 50 percent or more of patients that are cured only by using this -- this sort of technology.



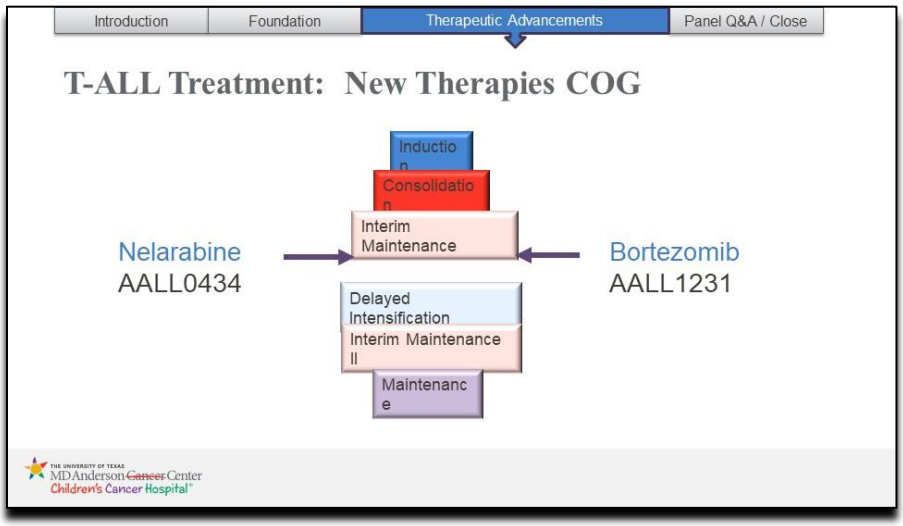
Real Word CAR Consortium and Disease Burden

There's a new study that was published last year that has shown that patients who have less disease amount, or less burden of disease, seem to do better with CAR T. So the next question for the future is should we proceed to do this CAR T when patients are almost in remission, and in different time points? And that's something that we are investigating and we can talk further. And I think Dr. Short will also talk about this.



B-ALL Treatment: New Therapies COG

So, currently, the standard for ALL, for B-cell ALL has this -- all these phases -- induction, consolidation, interim maintenance, and so on and so forth. And these are all the new drugs that are being tested. Of course, they cannot be tested all at the same time, because if we make progress and we go from 95 to 99 percent, we won't know which of these really made it. So, these are all independent studies that are seeing and analyzing these interventions, independently.

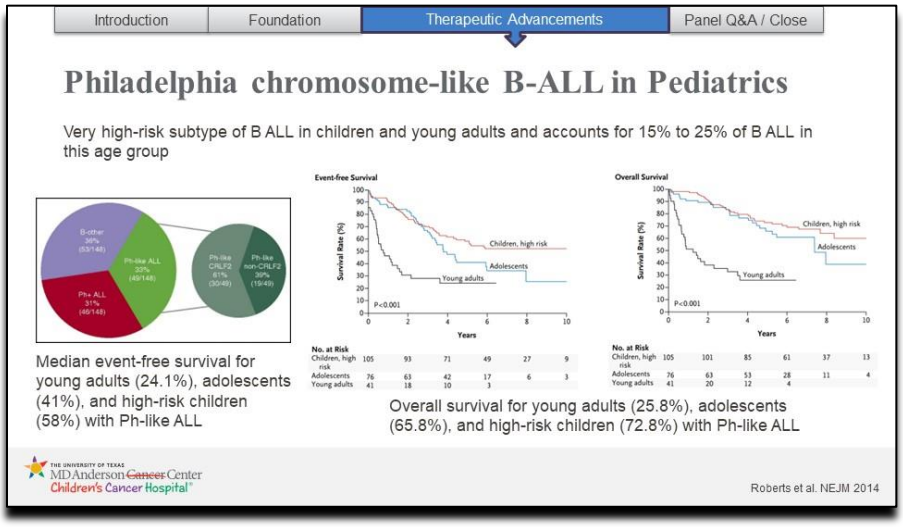


T-ALL Treatment: New Therapies COG

In T-cell, the progress has been slower, because when we think of all ALL, that it's 3,500, three-thousand-five-hundred cases, only 15 percent of those are T-cells. So, it takes much longer to discover new drugs, because the studies take much longer. But these were two very important studies that happened almost at the same time.

In this backbone of drugs that we are sharing, that pretty much are shared with B-cell ALL, nelarabine (Arranon®) and radiation was added. And in those patients, the cure rate was 92 percent for T-cell ALL -- was a significant advancement. And, in parallel, bortezomib (Velcade®) was done in a separate study, but these children were not radiated. And the survival was 88 percent.

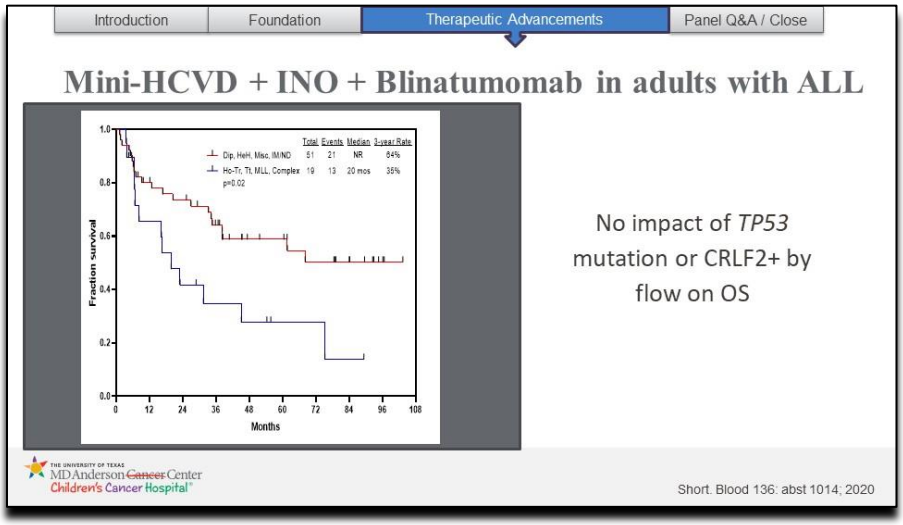
So now, there's a discussion among the T-cell group as to should we use nelarabine up front or bortezomib up front? The new study to be designed is including nelarabine and bortezomib will be used in a different context.



Philadelphia chromosome-like B-ALL in Pediatrics

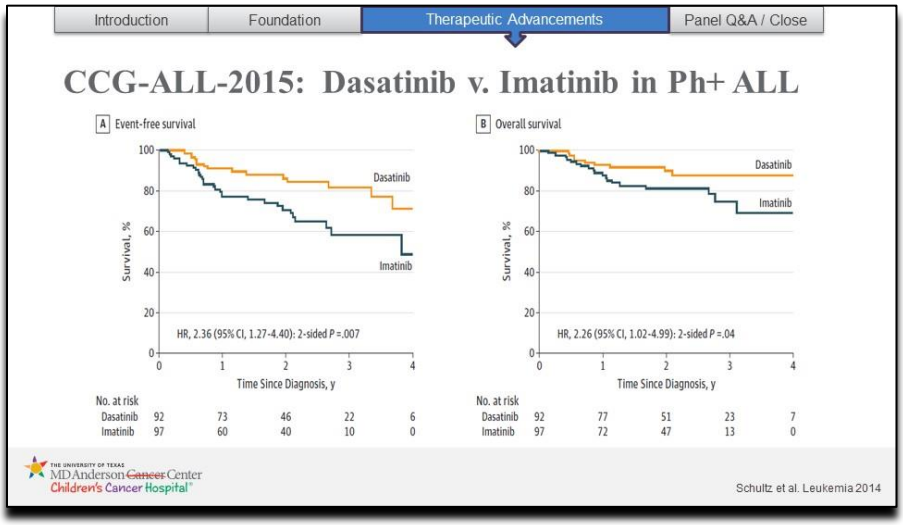
When we think of Ph-like, or Philadelphia-chromosome-like B-ALL, we need to think of a disease that it's coming in young adults, and in teenagers -- very common in Hispanics. The most common marker that we see in these leukemias are CRLF2s.

In this cell, that's the leukemia cell, all of these cells express as a CRLF2, or JAK2, these markers. And when we treat them with chemotherapy, they are very resistant. Very often, these patients are MRD positive at the end of induction, for example, and some of these patients need to be taken into transplants. We've done several studies trying to address how can we improve the outcomes of these children, because usually, or lately, it's been between 65 to 72 percent, when you have the other groups that are 95 percent.



Mini-HCVD + INO + Blinatumomab in adults with ALL

So we need to do better, right? But there's not really a directed drug that has improved outcomes. Recently, Dr. Short and his group, in adults, shared this data with me, that adding blinatumomab, or these antibodies, and inotuzumab to these patients, perhaps even sequentially, meaning blina first and then, later on ino, might be eliminating the high-risk factor of CRLF2. We'll have to see if this is real, if this maintains, and if this can be, you know, passed on into children.

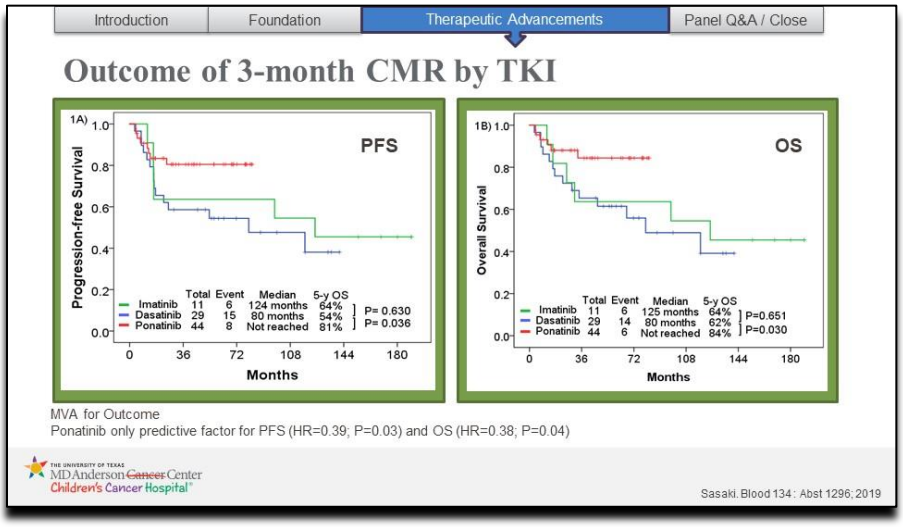


CCG-ALL-2015: Dasatinib v. Imatinib in Ph+ ALL

For Philadelphia-positive ALL, many years ago, these patients were treated only with chemotherapy until later, we found out that patients who have Philadelphia-positive ALL have this translocation, this chromosomal fusion that, again, it's not on the body of the patient. It's in the leukemia cell that created a protein that made these cells divide quicker and faster. That's the Philadelphia tyrosine kinase.

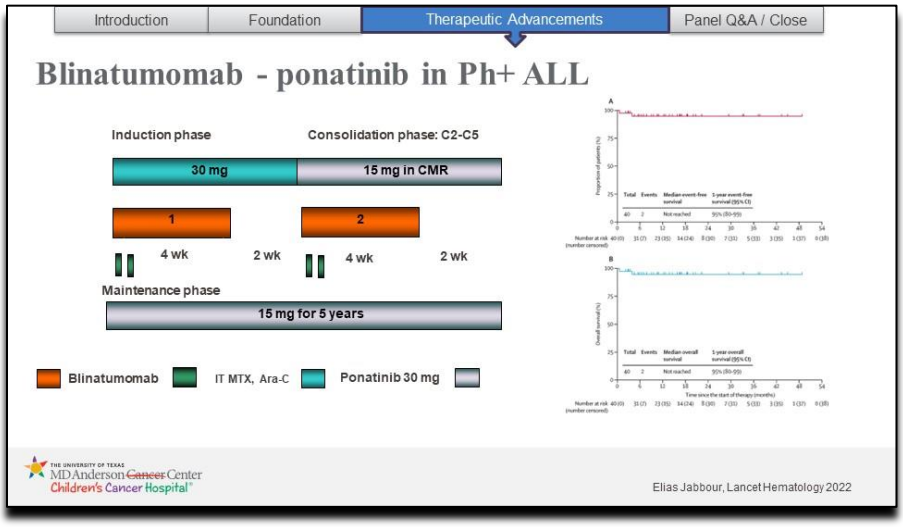
And then, we decided, many years ago, to give chemo to these patients, but to sprinkle a tyrosine kinase blocker. At that time, was called imatinib, or Gleevec®. The survival in children increased from 50 percent to 85 percent. Well, now the data, the plan in pharmaceutical companies, is to see which is the best TKI, or tyrosine kinase inhibitor, is there a new one that's better?

So this was a study done in China, that compared for patients who had Philadelphia-positive ALL, either dasatinib (Sprycel®) or imatinib. And the results in this study in China was the dasatinib was significantly better.



Outcome of 3-month CMR by TKI

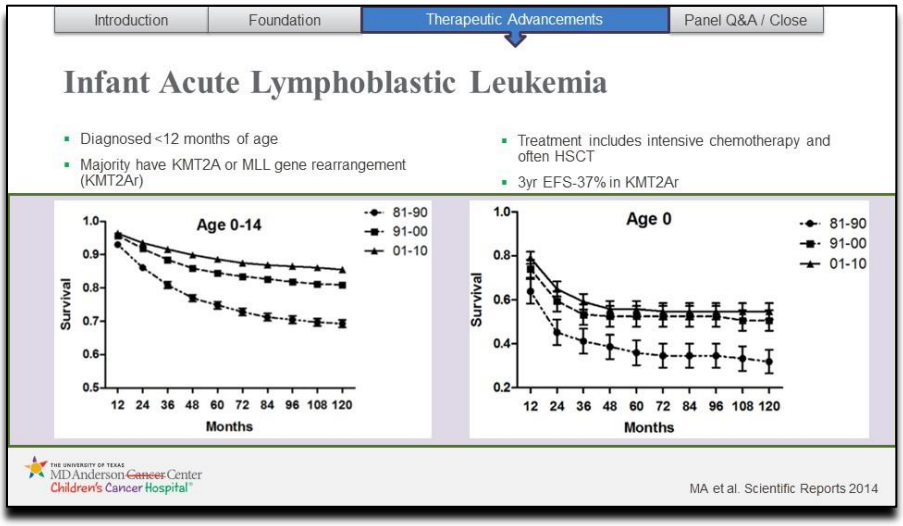
Interestingly, at the same time, now the adults have shown that there's even better TKIs that we could use in pediatrics. In particular, in this study, you can see in this Kaplan-Meier curve, that ponatinib (Iclusig®), in red, was superior to dasatinib and to imatinib, by far. The question is, should we now start using, you know, ponatinib in children, with chemotherapy?



Blinatumomab - ponatinib in Ph+ ALL

But brilliantly, what they are doing, and we are extrapolating now to pediatrics, is that they are trying to stay away from chemotherapy. And what they're doing is they are using the blinatumomab that we were talking at the beginning, that has very low toxicity, very good profile, in combination with ponatinib. Of course, we will have to see the side effects of ponatinib in children. Most of these

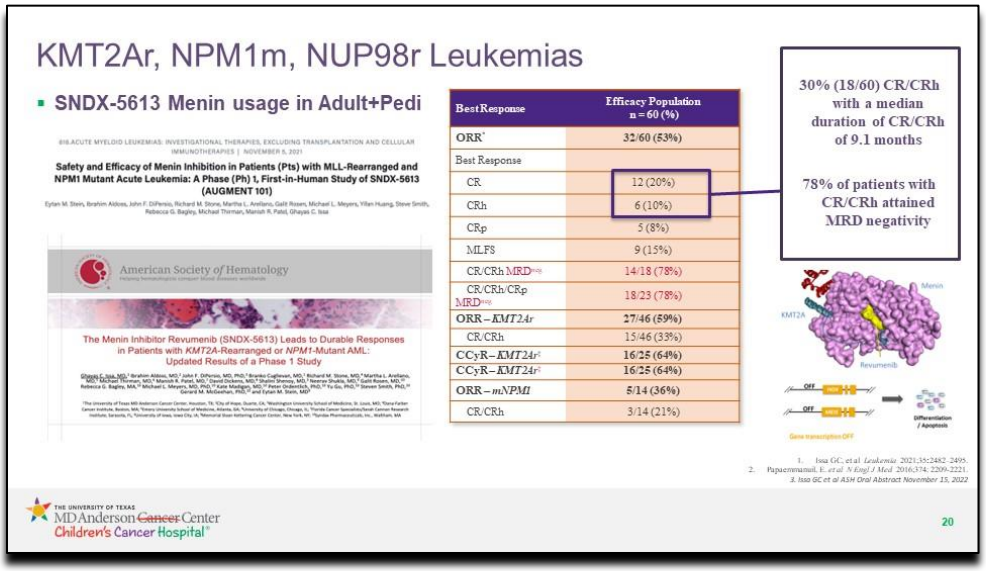
tyrosine kinase inhibitors in pediatrics affect growth. So you don't necessarily want to use them at a high dose and for a long time.



Infant Acute Lymphoblastic Leukemia

And finally, the last topic I wanted to talk about is infant acute lymphoblastic leukemia. This is very rare. When you think of all leukemias, it's one percent. So it's very, very rare. It's a very small group. But their chances of cure is incredibly low. The chances of cure of these children, who are infants, under 12 months of age, is 37 percent. We need to do better. We need to find solutions to that. We know that those who present with disease under then six months of age, do even worse. And those who have a white cell count over 300,000 do even worse than everybody.

For many years, we've tried to do different things, and nothing seems to improve the outcome of these children.



KMT2Ar, NPM1m, NUP98r Leukemias

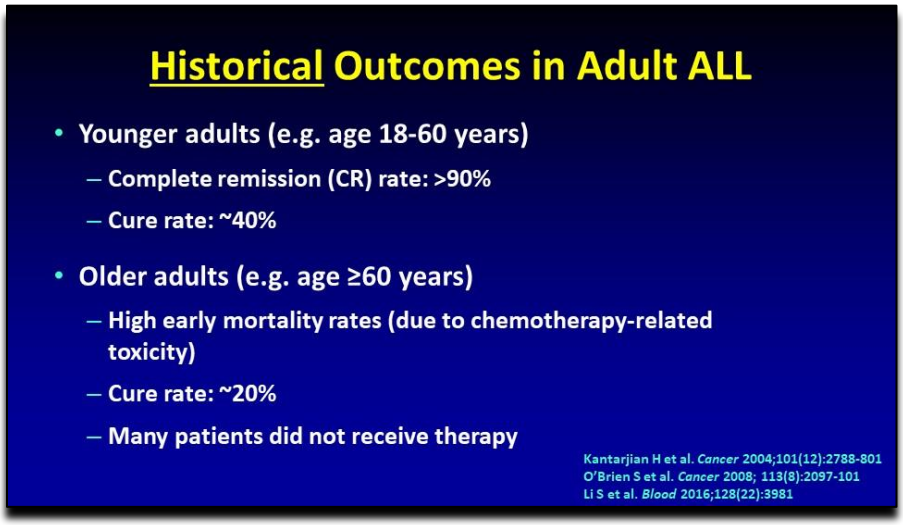
But up to last year, there's a new compound that targets KM2TA, which is a fusion, it's a protein, that it's present in 75 percent of these children. And, with the data, that it's preliminary, is that when this drug is being used in patients who have KM2TA fusions, we don't know the data yet in infants. But

when this is used in KM2TA fusions, that what we see in infant ALL, the response has been phenomenal.

I foresee that, in the future, this will be advanced into front-line, infant ALL and, perhaps, combined with blina, (blinatumomab), inotuzumab, or even CAR T, or even something sequential. I'm happy to take any questions at the end. But as of now, I want to introduce my dear friend, Dr. Short, who's a phenomenal physician and he can proceed with the talk. Thank you so much.

Treatment Advances for Acute Lymphoblastic Leukemia in Adults

Nicholas Short, MD
Great. Thank you, Branko, for that excellent discussion. And so, I will move to discussing treatment advances in ALL, specifically in adults. But they'll be some very similar themes, as Dr. Cuglievan just discussed.



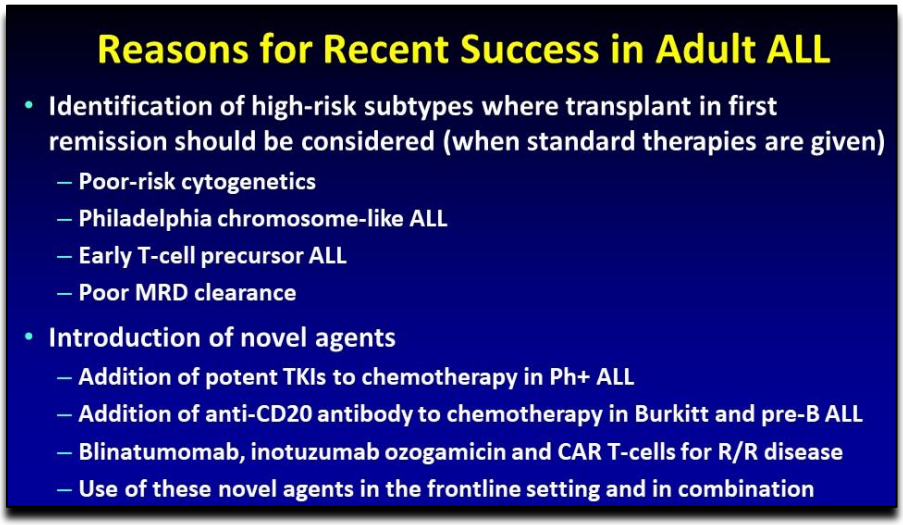
Historical Outcomes in Adult ALL

So just to set the expectations with the historical outcomes in adult ALL, and I emphasize historical, because we've made a lot of progress, which I'll show in a bit.

But in younger adults, which for us, is patients up to about age 60 years of age -- historically, with intensive chemotherapy, we can get very high rates of remission. So, over 90 percent of patients

would achieve a remission. However, unfortunately, only a minority of those patients would be cured. And we would typically be able to cure around 40 percent of patients.

For older adults, those patients who are 60 years of age and older, the outcomes are significantly worse. And this is because they have a higher, early rates of mortality, largely due to chemotherapy-related toxicity. The cure rate is historically only around 20 percent. And actually, many patients who presented to their doctor, who are over 60 with new, adult ALL, historically, have been sent to hospice because it was thought to be relatively futile to offer treatment, because there was really nothing effective for these patients. Now, again, fortunately a lot has changed.



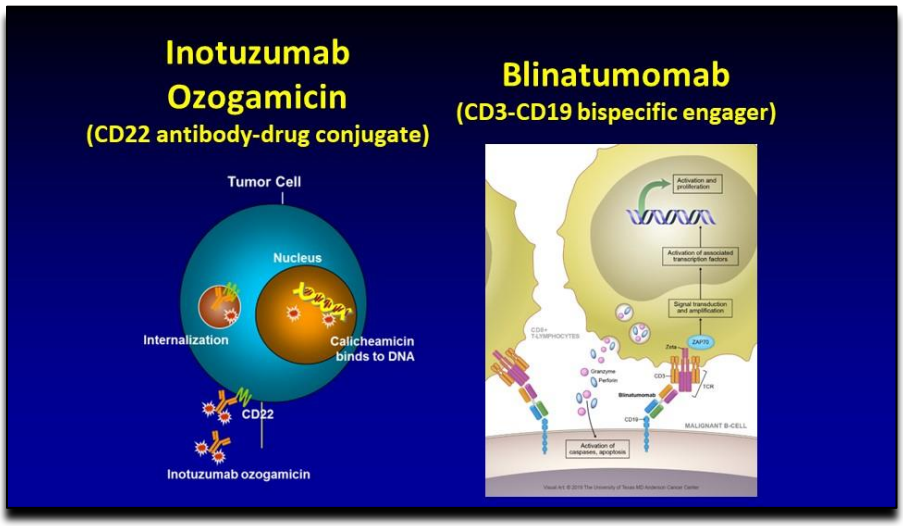
Reasons for Recent Success in Adult ALL

We've had some recent successes in adult ALL, and I'll describe them in a bit. But there's a couple reasons for this. One is identification of some high-risk, subtypes of disease where transplant in first remission should at least be considered when we use standard therapies. There are some core risk, cytogenetic features, so the chromosomal changes that occurred, which can be associated with higher rates of relapse.

Patients with Philadelphia chromosome-like ALL, as Dr. Cuglievan discussed. Within T-cell ALL, there's a specific subtype called early T-cell precursor ALL, that we know has particularly poor outcomes. And we're also appreciating more of the important role of measurable residual disease, or MRD, as a marker of how well the leukemia has responded to treatment. What we'll discuss a lot in this talk, though, is how the introduction of new drugs has really started to improve, significantly, the outcome of the patients with adult ALL.

So, again, the importance of these BCR-ABL tyrosine kinase inhibitors for patients who filled up chromosome positive ALL, have certainly improved outcomes. For patients with ALL that expresses a certain marker, called CD20, we know that we should be giving these patients an anti-CD20 antibody, such as rituximab (Rituxan®). In the relapsed, refractory setting, we have approvals of different immunotherapies, such as blinatumomab, inotuzumab ozogamicin, and CAR T-cells.

And now what we're doing, is we're taking these effective drugs in the relapsed, refractory setting and moving them into the beginning, into the front-line setting, with the hope of curing patients in the very beginning, without waiting for relapse, to then give these drugs.

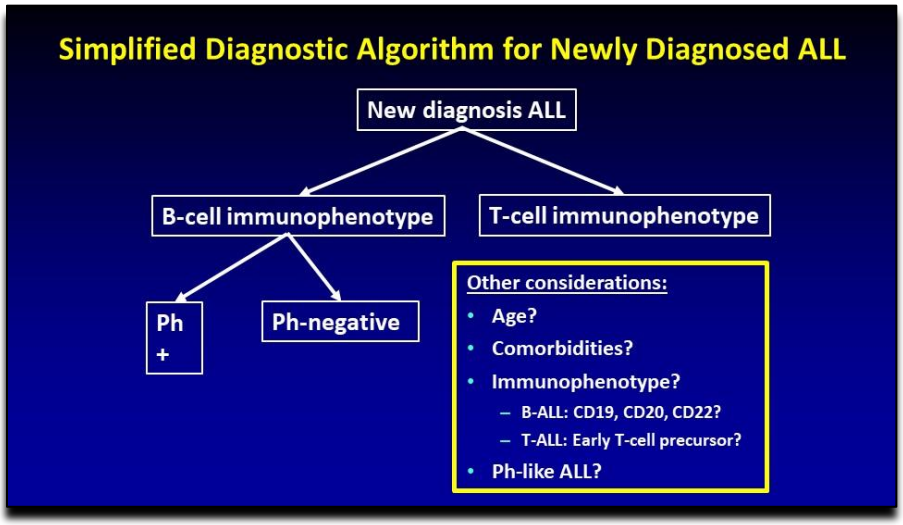


Image

So as I mentioned, these are two of the very important drugs that we have at our disposal now. We won't go over the data in relapsed, refractory disease, although we're happy to discuss it in the Q&A, but essentially, both of these drugs, inotuzumab ozogamicin, and blinatumomab have been shown, in randomized studies, in the relapsed, refractory setting, in B-cell ALL, to improve survival for adults, compared to conventional chemotherapy. So now, when a patient with ALL, if they relapse, we now treat them with immune-based therapies, rather than with chemotherapy.

Inotuzumab is what's called an antibody drug conjugate. It targets CD22, which is a marker on most ALL. It's an antibody therapy, so an immune therapy that delivers a drug specifically to those CD22-positive leukemia cells. And as was mentioned before, blinatumomab is an immune therapy that gets T-cells, CD3-positive T-cells, the patient's own functional T-cells that are meant for immune [response], that kill off abnormal cells in the body.

And it brings them up right against the CD19-positive leukemia cells, with the goal of stimulating the 34 patient's immune system to fight off the leukemia.



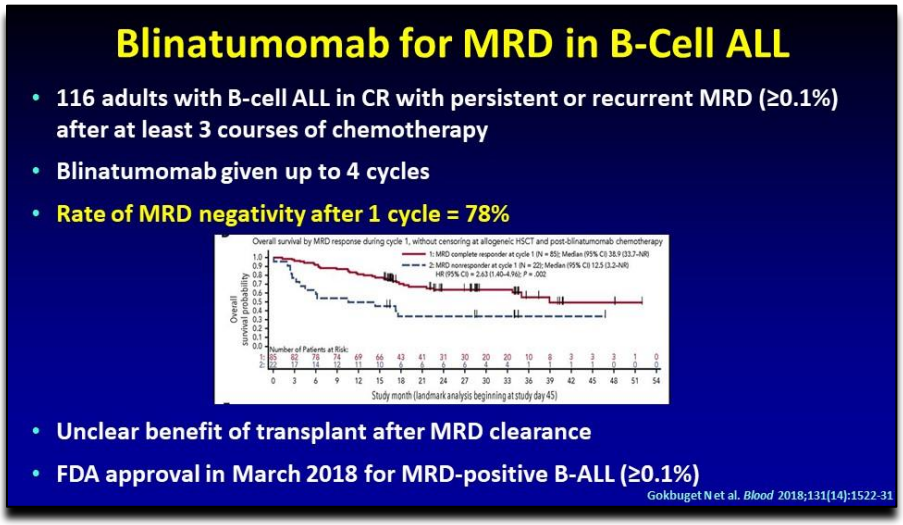
Simplified Diagnostic Algorithm for Newly Diagnosed ALL

If we're thinking about, you know, a new patient with a new diagnosis of ALL, how do I think of it, just very broadly, in terms of classification, so we can decide on the treatment? So, patients about 75

percent of patients have B-cell ALL, and 25 percent have T-cell ALL. Within the B-cell ALL, I want to further subdivide it, and do they have Philadelphia chromosome positive B-cell ALL or Philadelphia chromosome negative?

And then, there are other considerations that are going to impact the type of therapy that I would recommend. So, what is the patient's age? What kind of co-morbidities do they have? Are they very sick and have diabetes and heart issues? Are they, otherwise, very healthy, aside from the leukemia? What's the immunophenotype? So, again, what are the markers that the leukemia expresses? Does it express CD20? Does it express CD19? Does it express CD22? Because we have targets for all of these.

In the T-cell ALL, do they have the early T-cell precursor immunophenotype, which we know is more aggressive, and we usually recommend transplant for those patients. And then, also, do they have what's called Philadelphia-chromosome-like ALL, which means that they don't have that BCR-ABL Philadelphia chromosome fusion, but they have a disease that behaves similarly, but without that exact, genetic abnormality.

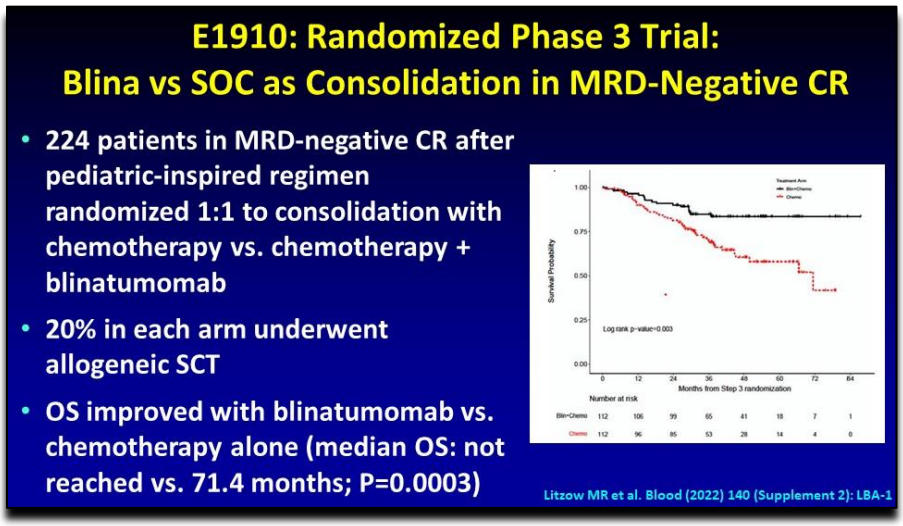


Blinatumomab for MRD in B-Cell ALL

So, as mentioned, we have these different drugs at our disposal. One application, specifically blinatumomab, is for treatment of MRD positive, B-cell ALL. So, for example, this is a study in patients with B-cell ALL, who got initial chemotherapy and then they still had residual disease, called MRD, after at least three cycles of chemotherapy. So, historically, we would always call it remission if a patient achieved less than 5 percent blasts in the marrow.

But now, we have better tests that can look for smaller amounts of disease. And so, this is called MRD. So basically, when you look under the microscope, these patients are in remission but when we use this other, more sensitive test, we can see that they have residual disease. So, in this study, blinatumomab, for up to four cycles, was given, and almost 80 percent of patients became MRD negative after just one cycle of treatment. And this translated to those patients who achieved MRD negativity, which was a vast majority, had better survival than those patients who did not.

Now one big question is, when we treat patients with blinatumomab, and they become MRD negative, which fortunately the vast majority do, do we need to follow this up with a stem cell transplant? And that's still an open question. But based on these data, the FDA approved blinatumomab for patients with MRD-positive, B-cell ALL.

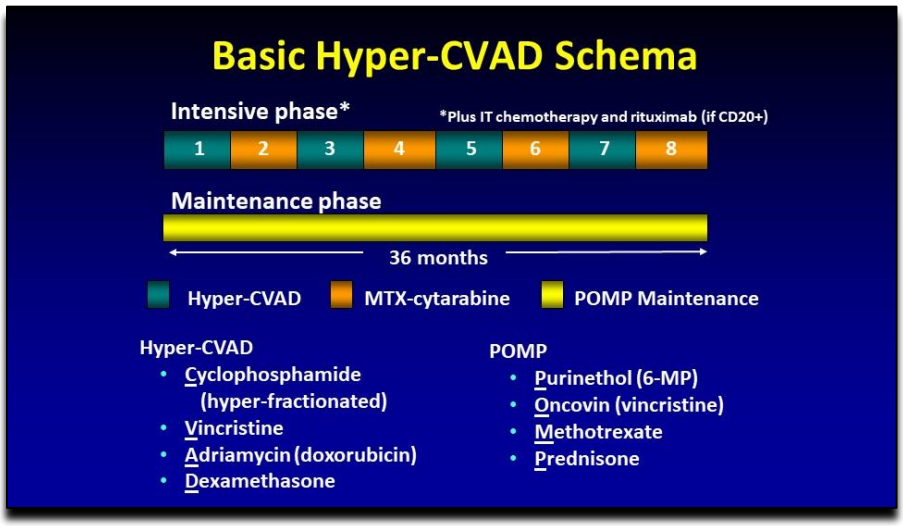


E1910: Randomized Phase 3 Trial: Blina vs SOC as Consolidation in MRD-Negative CR

And now we have new data supporting the routine use of blinatumomab in the front-line setting. And this is sort of, like, hot off the presses, in that it was just presented at our most recent hematology meeting in this last December.

And this was a study where they took patients who were getting standard chemotherapy in the front-line setting, with B-cell ALL. And we know that blinatumomab is a drug that we should give if patients have residual disease, if they have MRD-positive disease. But this study took patients even who were MRD negative, who by all accounts, we couldn't detect any more leukemia, after some initial chemotherapy, and it randomized them, to either give them blinatumomab with chemotherapy or give them chemotherapy alone.

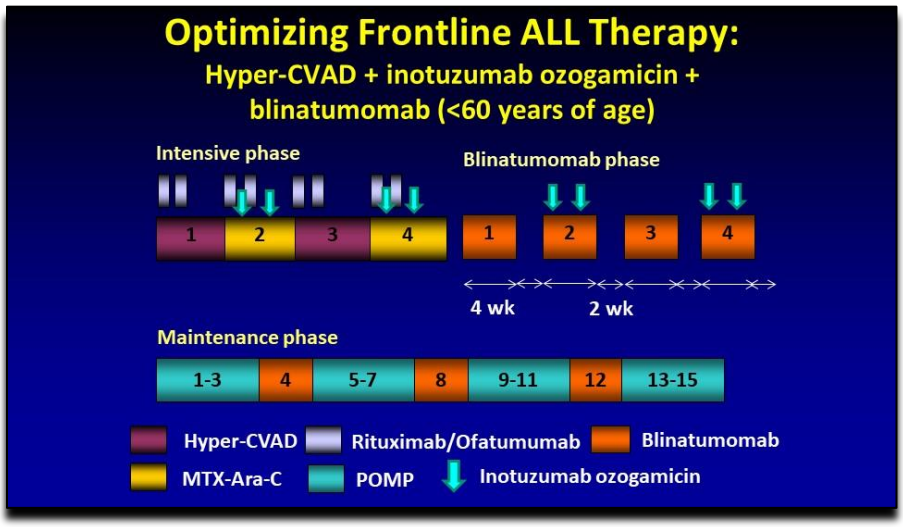
And importantly, the addition of blinatumomab improved the survival significantly, compared to chemotherapy alone. And so now, this is a very new kind of shift in our thinking. But I would consider this, now, a new standard of care for patients with newly diagnosed B-cell ALL, to receive blinatumomab as part of their regimen, regardless of whether or not they have or they do or not have residual disease, MRD.



Basic Hyper-CVAD Schema

I'll talk a lot about what are approaches at MD Anderson for patients with new ALL. So we use a regimen called Hyper-CVAD. And this is a common regimen that's used at a lot of other institutions. And basically, just to show you what the historical Hyper-CVAD looked like. It's eight cycles of intensive chemotherapy, followed by three years of a lower-intensity therapy maintenance called POMP.

Patients also should receive intrathecal chemotherapy. This is the chemotherapy through the spinal tap, into the spine and the fluid around the spine and brain, to prevent leukemia from coming back into that area. And also, patients would always receive rituximab, which targets that CD20 that's positive on up to about half of patients with B-cell ALL.

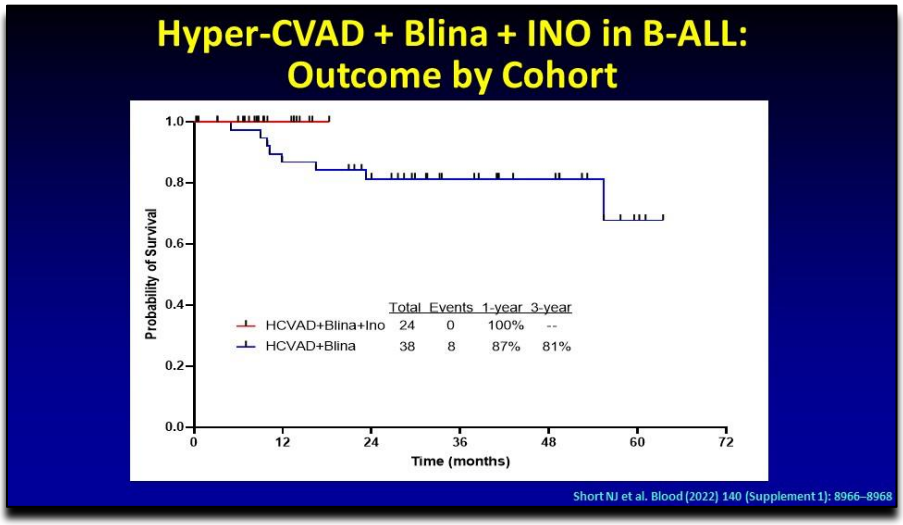


Optimizing Frontline ALL Therapy: Hyper-CVAD + inotuzumab ozogamicin + blinatumomab (<60 years of age)

So this is how we've attempted to optimize, further, the Hyper-CVAD regimen. And this is what we're doing now. And this is just to give you a glimpse of what I really I think will be future treatment for ALL, and certainly for the patients we treat here at MD Anderson, this is what we give to them. So what we've done, instead of eight cycles of Hyper-CVAD, we've now decreased it to four cycles. And we follow that four cycles of chemotherapy with blinatumomab, regardless of the MRD status. So, four

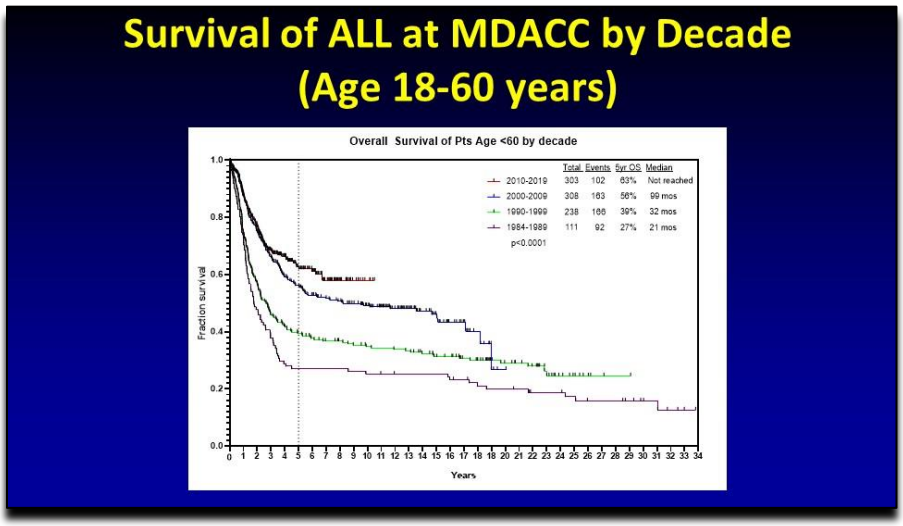
cycles of chemotherapy, followed by four cycles of blinatumomab, and then the maintenance phase, rather than being three years of chemotherapy it is now only about a year and a half.

And we alternate the standard, low-dose maintenance therapy with a cycle of blinatumomab. And you can see three months of maintenance therapy, one month of blinatumomab. And in addition, we've recently added inotuzumab ozogamicin another drug that we know is effective in the relapsed, refractory setting. We've added that into several of the courses of treatment. So we're trying to give all those the most effective drugs, that we know work in the relapsed, refractory setting, but give them in patients -- when patients are newly diagnosed. And we use this regimen in patients up to 60 years of age, because it is in an intense regimen, because of the Hyper-CVAD chemotherapy.



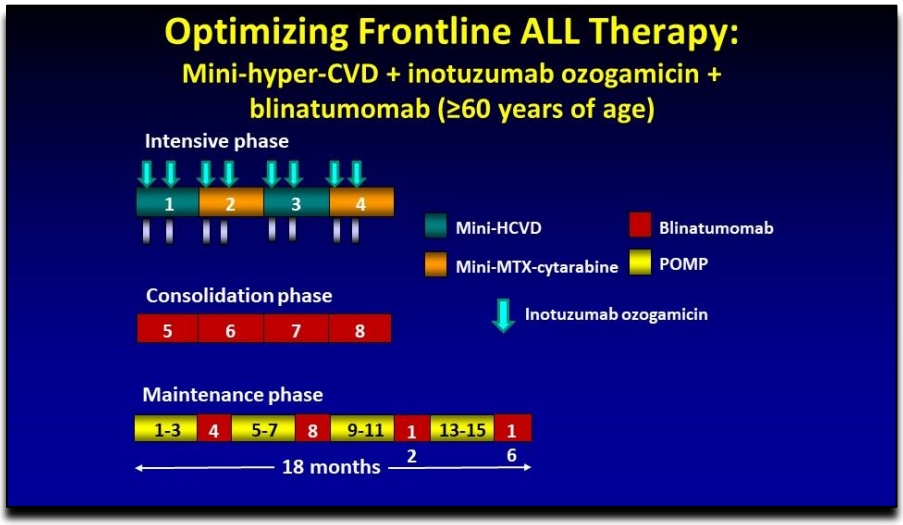
Hyper-CVAD + Blina + INO in B-ALL: Outcome by Cohort

And these are the Kaplan-Meier curves, the survival data. So we see when the patients, before the addition of inotuzumab, so those patients who received Hyper-CVAD plus blinatumomab, at three years, over 80 percent of them, 81 percent, were still alive, which in the world of adult ALL, is actually quite good. Because our outcomes have not yet reached those that Dr. Cuglievan just discussed with pediatric ALL. And it's still early, but when we look at the group of patients that have received both inotuzumab and blinatumomab, we can see that, so far, none of them have died. So we see very encouraging data with the addition of both of these drugs in the front-line setting, and this is an ongoing study. And, we will see if this is maintained with longer follow-up.



Survival of ALL at MDACC by Decade (Age 18-60 years)

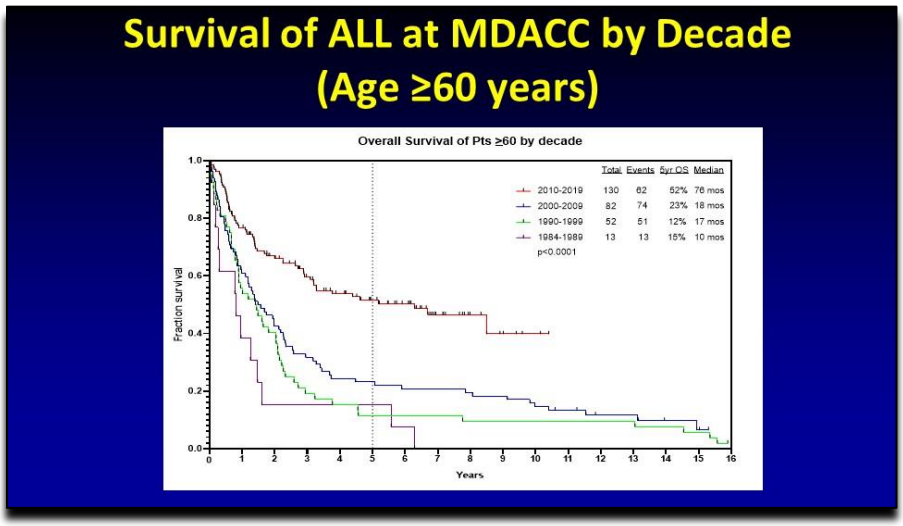
So just to show you, in another way, that this is really making meaningful impacts for patients. So if we look at the survival of patients, at our institution, at MD Anderson, by decade, these are adult patients I'm showing here, between 18 and 60 years of age. You can see, with every decade, we've made improvements. And now, in the most recent decade, well, this is actually up until 2019, we were achieving about five-year survival of about 60 to 65 percent. And we hope, in this next decade, as we're using inotuzumab and blinatumomab, that that will be even better.



Optimizing Frontline ALL Therapy: Mini-hyper-CVD + inotuzumab ozogamicin + blinatumomab (≥60 years of age)

For patients who are older, who are 60 years of age and older, we don't want to give the strong, Hyper-CVAD chemotherapy, but use a regimen called mini-hyper-CVD.

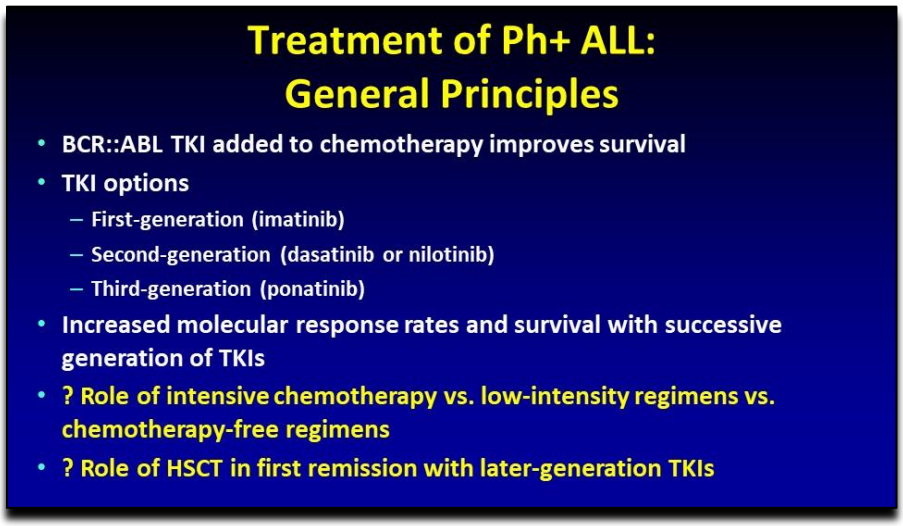
So this is basically standard, Hyper-CVAD, but we reduce all of the doses of the chemotherapy and we remove the A, the anthracycline, that's one particular drug that particularly causes a lot of potential toxicity. So we give them the mini-CVD chemotherapy for four cycles, followed by four cycles of blinatumomab, and then the maintenance phase is, again, POMP, low-dose chemotherapy maintenance, along with blinatumomab. And, patients also receive inotuzumab integrated into this regimen, as well, which is those turquoise arrows.



Survival of ALL at MDACC by Decade (Age ≥60 years)

And we've been doing this for a while. And you can see, this is another way of survival of patients with ALL treated at MD Anderson, by decade. Those patients who are 60 years of age and older. And you can see, unfortunately, up until about 2010, we made, maybe, some minor changes. But you can see the outcomes of older patients with ALL were really quite dismal. But you see a very dramatic improvement in the outcomes, since 2010, which is around when we started using this regimen.

And now, we have five-year survival rates over 50 percent. And this is much better than we saw, historically. And actually, is almost on par with what we get in younger patients. And I think it just shows the importance of using these lower, these immunotherapies in the front-line setting, rather than waiting to use them in the relapsed, refractory setting.

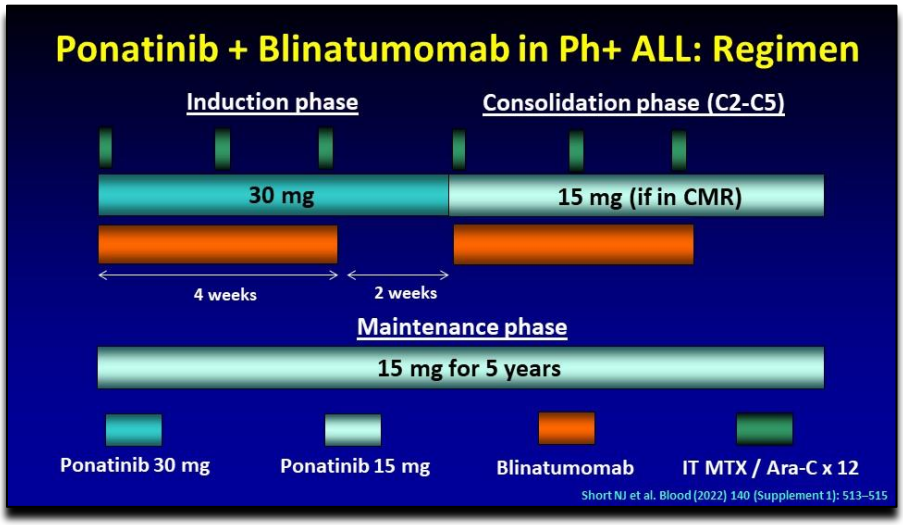


Treatment of Ph+ ALL: General Principles

Moving onto Philadelphia-chromosome positive ALL, just as some general principles. We know that, as Dr. Cuglievan discussed, that we should be adding a tyrosine kinase inhibitor, a pill, against BCR-ABL. It'll, along with chemotherapy, that improves survival for patients with Philadelphia-chromosome positive ALL. There are various options available, but the first drug developed for this was imatinib (Gleevec®).

Then, there are what's called second-generation tyrosine kinase inhibitors. These include dasatinib (Sprycel®) or nilotinib (Tasigna®). And then, more recently, we have a third generation inhibitor, called ponatinib (Iclusig®). And what we tend to see, across studies, is that when you use a later-generation, tyrosine kinase inhibitor, we typically get deeper levels of remission, which are associated with better, long-term survival.

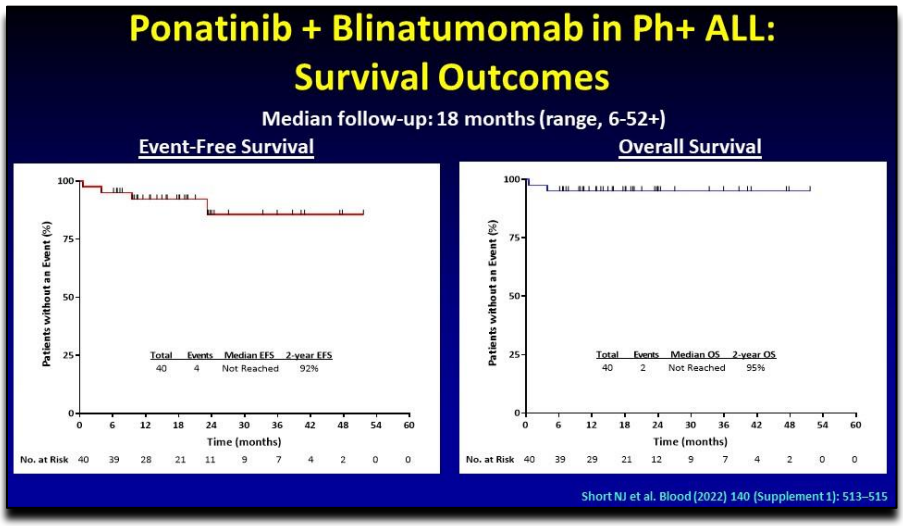
And now the big question in the field, is what's the role of intensive chemotherapy for these patients? Do we need to use intensive chemotherapy for Philadelphia-chromosome positive ALL? Or, can we use low-intensity regimens or even chemotherapy-free regimens? And also, what's the role of transplant for these patients? Because, historically, we would say if you have Philadelphia-chromosome positive ALL, you needed to get chemotherapy with a tyrosine kinase inhibitor and then go to transplant. And now, that's changing, where I think many patients do not necessarily need a transplant, with this subtype of ALL.



Ponatinib + Blinatumomab in Ph+ ALL: Regimen

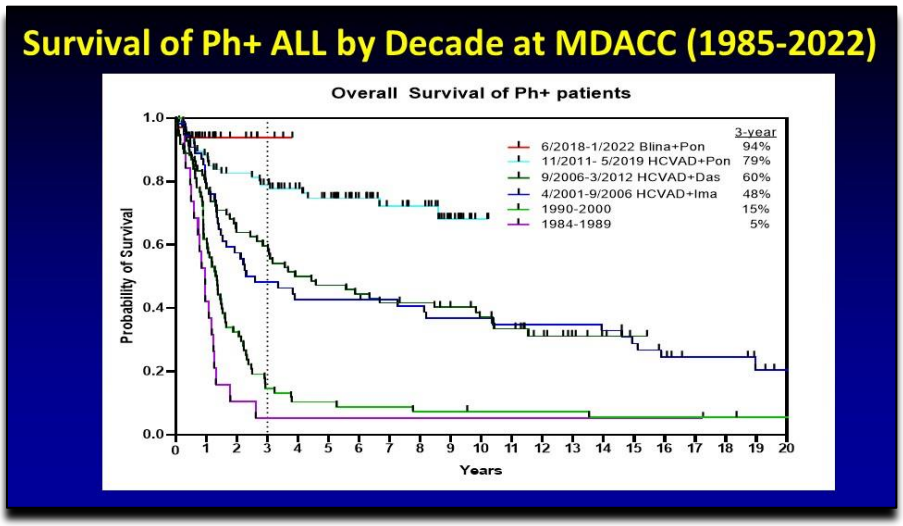
This is a regimen that we're using at MD Anderson. And it's ponatinib and blinatumomab. So ponatinib, one of those tyrosine kinase inhibitors, along with blinatumomab, which is an immune therapy. And note, that this is a chemotherapy-free regimen. So, we're using immunotherapy and pills.

We treat patients with five cycles of blinatumomab, along with continuous use of ponatinib. The only chemotherapy that we do give is we still give the chemotherapy into the spinal fluid to prevent relapse.



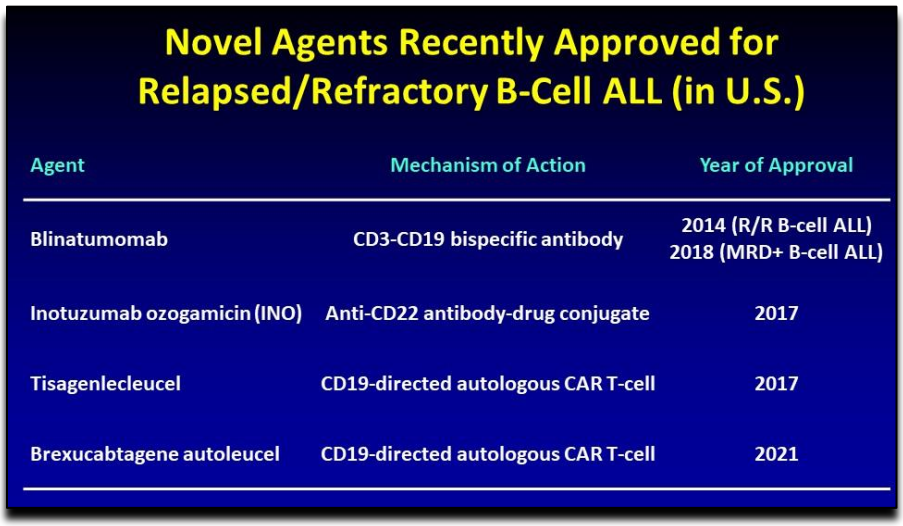
Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes

And we've seen very encouraging outcomes with this regimen. You can see the two-year survival is 95 percent. And this is much better than we've ever seen, historically. And importantly, we only transplanted one out of these 40 patients. So we're seeing these excellent outcomes, despite not transplanting the vast majority of patients.



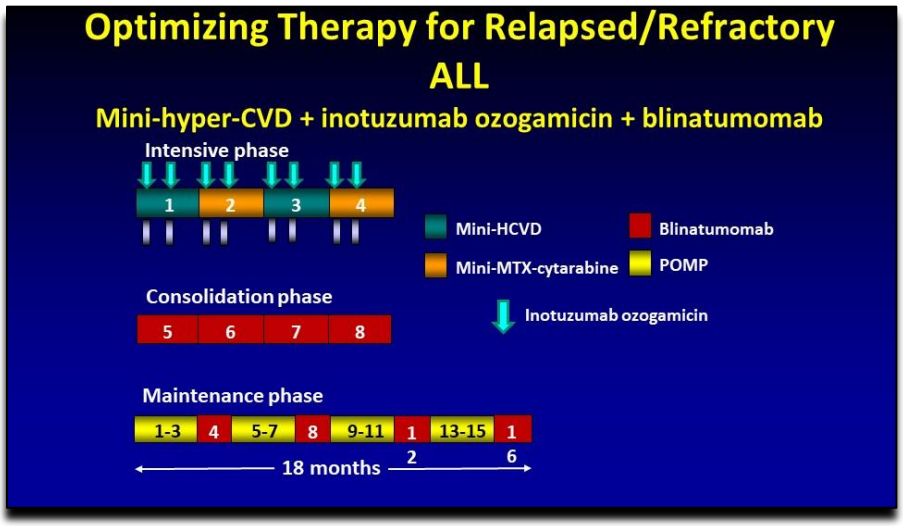
Survival of Ph+ ALL by Decade at MDACC (1985-2022)

And just to highlight how these incremental advances and, more recently, this chemotherapy-free regimen have improved outcomes for patients with ALL, Ph-positive ALL, this is the same curve, looking at the outcomes of patients with Philadelphia-chromosome positive ALL at MD Anderson, by decade, and really by treatment era. And you can see there is a significant improvement when we initially added imatinib and dasatinib, that's the dark blue and green curves. You can see that there was an improvement, when we first added these tyrosine kinase inhibitors. There was another big improvement when we started using a more potent tyrosine kinase inhibitor, ponatinib. And then now, we need longer-term follow-up, but we think what's going be the next iteration is this chemotherapy-free regimen, where we hope that we're going to have less toxicity, but also even better outcomes.



Novel Agents Recently Approved for Relapsed/Refractory B-Cell ALL (in U.S.)

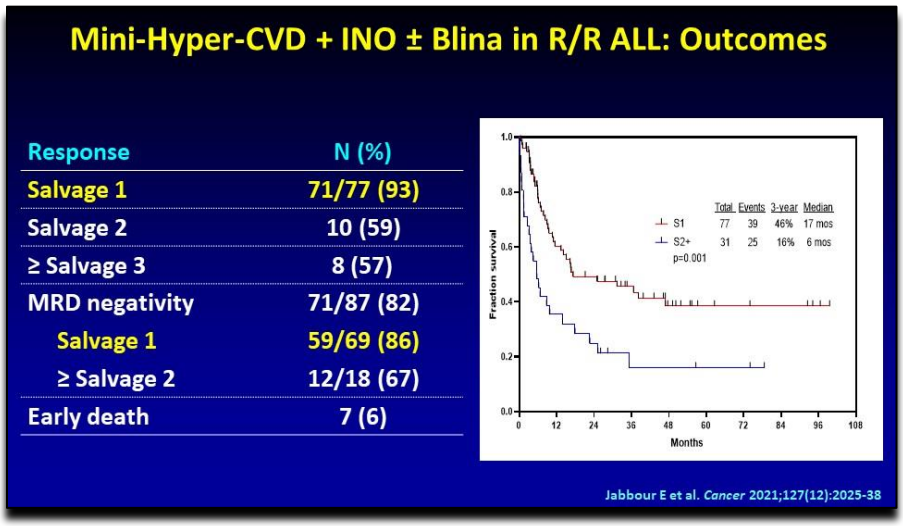
Moving very briefly to relapsed, refractory ALL. We've already talked about most of these drugs, because we're talking about using them, in the front-line setting. But, again, we have blinatumomab, inotuzumab ozogamicin, and we have two CAR T-cell products that target CD19, tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®).



Optimizing Therapy for Relapsed/Refractory ALL

What are we using at MD Anderson for patients with relapsed, refractory B-cell ALL? Well, we use that same regimen I showed you in the older patients -- mini-hyper CVD, so low-dose chemotherapy, combined with inotuzumab and blinatumomab.

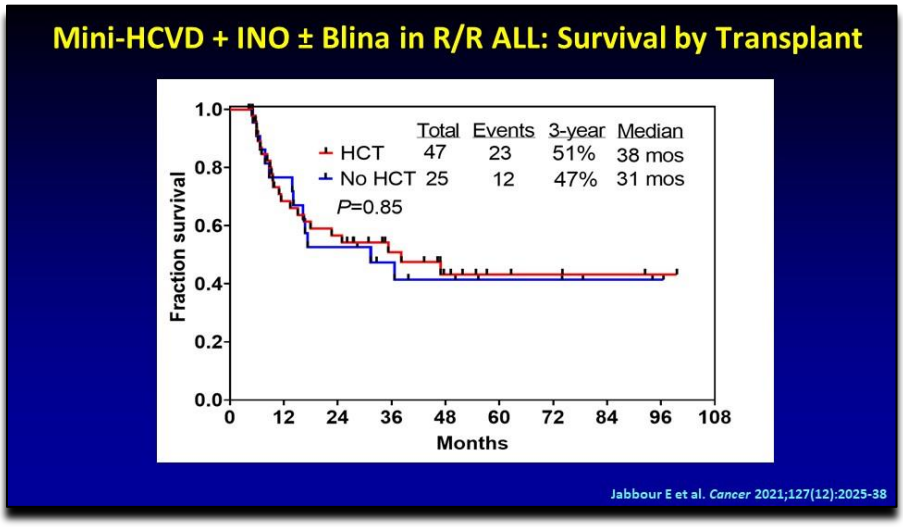
And so we use that in patients, if they have initial chemotherapy, and then they subsequently relapse or if they don't respond to it.



Mini-Hyper-CVD + INO ± Blina in R/R ALL: Outcomes

And we see very high -- you know, relapsed, refractory disease is a very difficult situation. However, we see very high rates of response, particularly when treated in first-salvage, which means the first treatment that someone receives after they initially relapse or after their first refractory to front-line therapy.

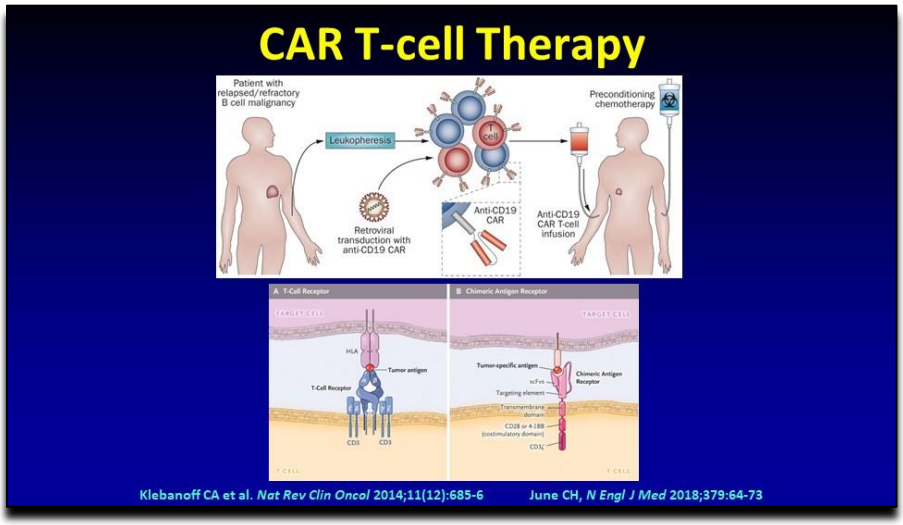
So 93 percent of patients treated in this context respond. The vast majority of them, 86 percent, achieve MRD-negativity, which we know is a very important endpoint in ALL therapy. And in first salvage, we actually see a three-year survival rate of around 45 to 50 percent. And this, compared to historically, patients with relapsed, refractory ALL, the long-term survival was at best 10 to 20 percent. So we think we're making very significant improvements by using all of these drugs together, rather than individually. Altogether, low-dose chemotherapy, inotuzumab, blinatumomab -- looks like it's improving outcomes for patients.



Mini-HCVD + INO ± Blina in R/R ALL: Survival by Transplant

And one big, kind of provocative finding that we found, was that when look at, do patients need to go to transplant after we give them this regimen? So, kind of the paradigm for relapsed, refractory ALL is that if you get them and -- the goal is to get the patient into remission and then after that, as soon as they're in remission, send them to transplant, because that, historically, was viewed as the only curative to treatment for patients with relapsed, refractory disease.

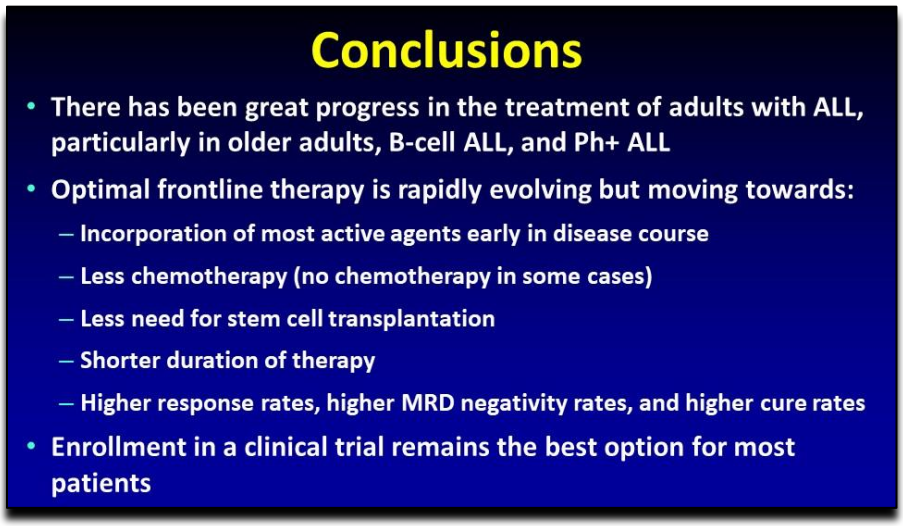
However, when we would look at analysis for patients who received this regimen and we look at those patients who went to transplant, or didn't, you can see that these curves, the survival outcomes, are almost exactly the same, between those patients who go to transplant and don't. And so now, the future challenge is identifying those patients who should go to transplant after a regimen like this and those patients who are likely to have long-term remissions and maybe even be cured without the need for transplant.



CAR T-cell Therapy

We won't discuss too much about CAR T-cell therapy, but this is another option that's available, especially for patients after they've had inotuzumab and blinatumomab. As Dr. Cuglievan discussed, this is where we manufacture this product, this cellular therapy, from a patient's own T-cells. So we take the T-cells, like you're giving a blood transfusion, we take the T-cells from a patient with leukemia. We go and engineer them in the lab to specifically target the leukemia, specifically CD19, which is a marker on the leukemia cells.

And then, we reinfuse it back to the patient. And with this, we can see very high rates of response. And again, the question for this is, if a patient responds, do we then need to send them to transplant or is this therapy potentially curative by itself? And I think that's still a very open question.

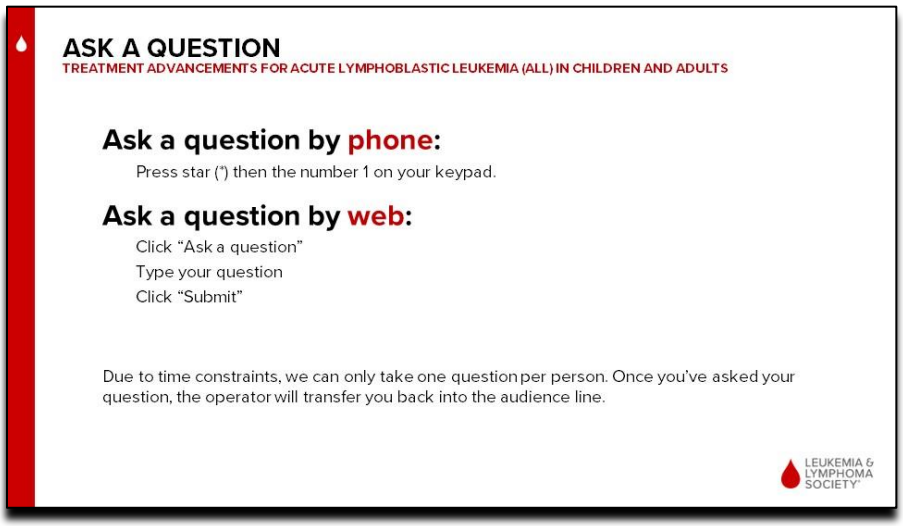


Conclusions

And with that, I'll conclude, just to say that there's been great progress in the treatment of adults with ALL, particularly in older adults, B-cell ALL, and in patients with Philadelphia-chromosome positive ALL.

The optimal treatment for front-line therapy for ALL is really rapidly evolving. But generally moving toward using these more potent, immune therapies in the front-line setting, earlier in the disease course, using less chemotherapy or even chemotherapy-free regimens in some cases, less need for stem-cell transplant, shortening the duration of therapy, which will, hopefully, lead to better quality of life for patients, and, importantly, what we believe we're seeing with this, is higher response rates, higher rates of MRD-negativity, and ultimately, what's important, is higher cure rates.

And I would just conclude, finally, with just emphasizing that I think enrollment in clinical trials still remains the best option for most patients. And this is the best way for patients to have access to these very innovative approaches that are ongoing. And I thank you very much for your attention and look forward to the Q&A.



Ask A Question

Lizette Figueroa-Rivera
I want to thank you both, Dr. Cuglievan and Dr. Short, for your very informative presentations. It is time for our question-and-answer portion of our program. And for everyone's benefit, if you can keep your questions general in nature, without many personal details.

And we'll start with a question from the web. Dr. Cuglievan, one of your patient's fathers, Brian, is asking, around two years ago, nelarabine (Arranon®) and bortezomib (Velcade®) for T-cell was fairly new treatment for pediatric patients. Have there been advancements in treatment for relapsed, T-cell patients and are you seeing any sort of success with these drugs?

Branko Cuglievan, MD
Great question. Thank you, very much, Brian. What you're saying is true. There is new drugs that are being tested for relapsed, T-cell ALL. One of them is venetoclax (Venclexta®). There was a nice study in *Cancer Discovery*, that combined venetoclax and navitoclax in patients with -- ETP [early T-cell precursor] pediatric patients with early, T-cell leukemia in relapse, did very well. So that might be moved, in the short-term, into front-line.

Daratumumab (Darzalex®) has also been studied and that will also be moved into the upcoming study. There's going be an arm that tests CD38, daratumumab for those patients. But if I have to ask to think of one, I would say the CAR T CD7. There's a study that's early, was done in China. And it's showing outstanding responses. I cannot tell you how long do they last or what sort of problems we will have enrolling kids on that study. But there are new things that are moving that way. But there's nothing right now that would be an ideal standard of care for relapsed, T-cell ALL.

Lizette Figueroa-Rivera
Thank you. And we'll take the next question from our phone audience, please.

Operator
Thank you. This question comes from Allison, calling from California. Please go ahead and state your question.

Allison
My question is, when I hear you say a cure, what constitutes as a cure? How many years in remission, or MRD negative, do you need to be in order to be considered cured?

Nicholas Short, MD
That's a great question. I can speak to that from the adult [point of view], and I don't know if the criteria are a little bit different for pediatrics. The challenge is, unfortunately, we can never tell a patient that they are cured. Because we have seen rare cases, where leukemia can come back five or 10 years later. Very, very rare, though. So, there's no number, where I can say 100 percent likely that this is a cure. It's a likelihood.

So what I tell patients is, every month that goes by, if you're still in a good remission, it becomes more and more likely that you are cured or will be cured. On average, if someone really wants to ask and says, you know, when would you consider, on average that it's very likely that I'm cured? I say basically after you've completed therapy and if two years -- two to three years after that, there's still no evidence of any disease and, you're doing well and there is no evidence of disease, that accounts for what very, very likely, so I would say 95 percent plus chance that that patient is cured. But, unfortunately, we can never say for sure.

Lizete Figueroa-Rivera
Thank you. And the next question is for Dr. Cuglievan. Jonathan is asking, what are the risks or side effects of blinatumomab?

Branko Cuglievan, MD
So, there's -- the biggest risk, I would say, or side effects that we are seeing is, some patients are developing immune reactions to that, which we call it CRS [cytokine release syndrome] sort of reactions, you know? Your body is having this flu-like illness secondary to the infusion, you can have that. There are some pediatric patients, particularly patients who are overweight or patients who have, for example, Down Syndrome, that are having seizures, as well. You see patients having fevers. And I'm trying to think if there's something else that I'm missing that you're seeing in adults, Nick.

Nicholas Short, MD
No, and I think one thing I would say, I think the most important thing about blinatumomab side effects is yes, we can see cytokine release, which is like this flu-like syndrome that can occur with it, or neurotoxicity, so headaches, confusion, or even seizures. But the important thing about blinatumomab is these are rapidly reversible, by stopping the blinatumomab and usually giving steroids.

So, it's important to distinguish that these are short-term side effects that can happen while you're on the treatment. But they're not really long-term side effects, for the most part, that we see with blinatumomab, which I think is very different than we see with chemotherapy, where patients can have long-term manifestations for years, and for the rest of their life, from the chemo that they received.

Lizette Figueroa-Rivera
Thank you. And doctors, this could be for both of you. Katherine is asking about ALL in the young adult population. She says, I believe there are different outcomes and studies for this group.

Nicholas Short, MD
Yeah, there is an overlap, where -- and we actually may have slightly different approaches, even though we're from the same institution. So, you want to start?

Branko Cuglievan, MD
Oh, yeah. So first of all, for those who -- young adults, you know, overcome the age -- adolescent to young adult, this 15 to 39, right? And -- there are studies that have been done in the past. I think it was called GB study, that showed that when these young adults, or some of these young adults were treated with the pediatric studies, the outcomes w ere very good. I think it was 73, 75 percent, compared to what it was before, in the area of chemotherapy. But now, with all the advances that, you know, the adults have done and the inclusion of all these immunotherapies, I would say that, probably, the treatment of these young adults is even superior to that. And probably Nick can talk to that.

Nicholas Short, MD
Yeah, so I think it's an area of controversy. And so, I don't think that there's any good data. There is some data suggesting maybe to use what's called a pediatric-inspired regimen, which is a regimen that has a lot of asparaginase (various brands), which is particular -- in front, that's commonly used in ALL. But that may be better. However, there's no good data -- there's no really high-quality data.

There's no randomized data, which is the best quality data that we have available. We did a study at our institution, MD Anderson, where we looked back at patients who had received a pediatric-inspired regimen compared to Hyper-CVAD, which we consider a, quote-unquote, "adult regimen." And we saw no differences. So I think the most important thing is to be treated at a place where the doctor feels very comfortable and has delivered that regimen very frequently.

So if they are used to giving pediatric-inspired regimens and they know how to manage all the toxicities, then that's probably the best thing to get. And if they're treated at a place that gives Hyper-CVAD all the time and is very good at managing those toxicities, then that's the treatment that you should receive. And I don't think that there's really a lot of reason to think that one is strongly better -- is significantly better than the other one.

Lizette Figueroa-Rivera
Thank you so much. And Dr. Short, this question is for you. Dave and Danny both have questions about Philadelphia-chromosome positive, so Ph-positive ALL. The latest research about maintenance and ongoing TKI (tyrosine kinase inhibitor) use, will that be something that is utilized for the rest of their lives?

Nicholas Short, MD
So that's a very good question and that's an area that we're very interested at looking into. So for patients who get chemo -- like chemotherapy and q tyrosine kinase inhibitor, and then they go to transplant, there's some data to suggest that, perhaps, you only need about two years of treatment afterwards, that there may not be a benefit to giving more than two additional years of the TKI, post-transplant.

So that's typically what we would do. And assuming that the patient is MRD negative, so we're monitoring that PCR (polymerase chain reaction test) and we see that, you know, it's remaining negative, after two years, it's a discussion with the patient, potentially stopping therapy. Now that we're moving away from doing-- as much transplant, that's where it's a bit harder. Because we get anxious -- we didn't do a trans [transplant]-- let's say we give them chemotherapy with a TKI or we give them ponatinib and blinatumomab, for example, and they have a great response.

But how long do we need to continue that? We didn't transplant them, so are we saying that, at some point, the disease is entirely gone and we can stop? We don't know the answer to that question. In our studies, what we're recommending, is patients receive at least five years of TKI maintenance. So if they get, for example, ponatinib and blinatumomab, they get that for a while. And then, once they're done with all the blinatumomab and they're just on the single agent TKI, to get that for at least five years.

Then, I sit down with my patients and I say look: we don't have a lot of data. If they're tolerating well and they don't want to stop, then I say, let's not stop. Some patients are very anxious to stop. They say I've been on this for a long time. When can I stop? After five years is a reasonable time.

That's assuming that all of their numbers are looking good, all the MRD tests are negative. We have PCR and also now use a new test called next-generation sequencing MRD. And also, if anyone -- if a patient is going to stop their tyrosine kinase inhibitor, I'm going to be monitoring extra carefully after that, watching very carefully and making sure that we don't see any evidence of emerging MRD. Because if we do, then I would want to re-start that.

Lizette Figueroa-Rivera
Thank you so much. And we'll take the next question from our telephone audience, please.

Operator
This question comes Katie, calling from Washington. Please state your question.

Katie
This is sort of a two-part question. First of all, are the new protocols being used for adult T-cell ALL, or how are they being used? And then, the second part is, what are the side effects, or post-treatment effects of the new regimens, that are an improvement over, doing a stem-cell transplant?

Nichlas Short, MD
So if I understand it, so, basically for an adult T-cell ALL, what are the new regimens? So, you know, I will be honest we talked about a lot of exciting things in B-cell ALL. There certainly are exciting things in T-cell ALL, but it's been moving more slowly. One thing I can just speak to what we're doing at our institution, for a new adult T-cell ALL would be, we're still giving chemotherapy, so Hyper-CVAD.

We are introducing nelarabine. So Dr. Cuglievan had, I think, mentioned some benefit of adding nelarabine in the front-line setting for patients with T-cell ALL in children, and we've adopted that and we're using that in adults. We also are using asparaginase, even though asparaginase is typically only a component of, quote-unquote, "pediatric regimens." We started to incorporate asparaginase into the Hyper-CVAD regimen for patients with T-cell ALL.

And we've also added venetoclax (Venclexta®), which is another pill that is approved in some other leukemias and, you know, there's some good data, some laboratory data, suggesting that it might be effective. So we're incorporating all of those -- chemotherapy, venetoclax, nelarabine, asparaginase, all under the front-line setting. And we're hoping that we're going to further improve outcomes.

As far as the longer-term side effect, I mean for T-cell ALL, there's not a lot of long-term toxicity from these drugs, aside from the chemotherapy itself. So, the backbone, Hyper-CVAD can come with potential toxicity. Anthracyclines from the Hyper-CVAD can cause cardiac toxicity, although that's relatively rare. The vincristine (various brands) can cause neurotoxicity, so peripheral nerve damage. That usually gets better with time, but not in all patients. And, of course, complications from chemotherapy can persist, such as bad infections or other things.

So, but with the other therapies we talked about, in B-cell ALL, we're not seeing a lot of longer-term toxicities. As I mentioned, blinatumomab, for example, most of the toxicities, or almost all of the toxicities, are just while the patient is receiving it. And once you stop it, those toxicities generally don't persist.

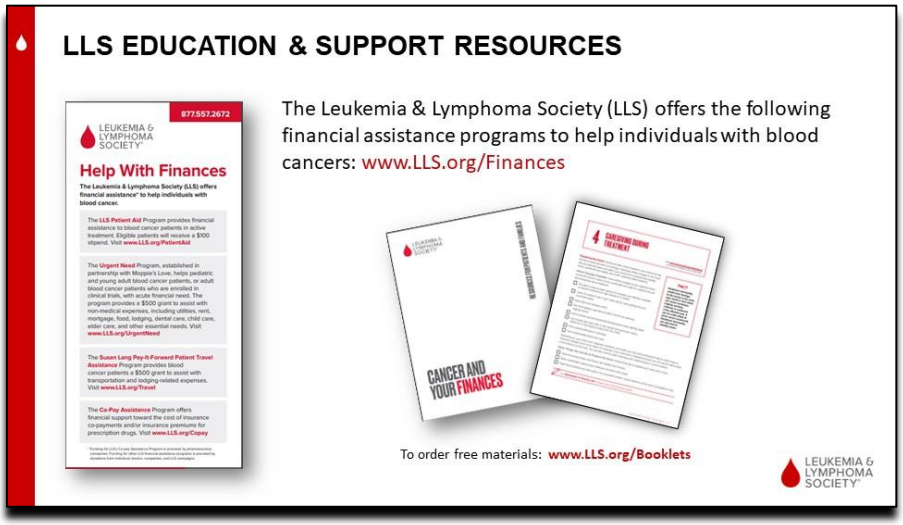
Lizette Figueroa-Rivera
Thank you. And I know you're mentioning side effects, people are asking about side effects, like neuropathy. Are there any other side effects that you're able to treat for patients?

Nicholas Short, MD
Branko, I know you see a different type of side effects, with all of the steroids and other things. You want to talk a little about that in pediatrics, because I know that that's a major move toward managing long-term toxicity for patients -- children who've received these regimens.

Branko Cuglievan, MD
Yeah, so, I mean, it's a broad question. We have a clinic that manages these long-term toxicities. So, if the question is what are the common toxicities that we see, in the long-term. You see, for example, because of all the LPs (lumbar punctures) and all the chemo, some of these children end up having some intellectual disabilities, or ADHD (Attention-deficit/Hyperactivity Disorder), for example. That's well studied.

Some of the patients that have TKIs have some growth restriction. Not too bad, but you see it with the TKIs we were talking about -- ponatinib, imatinib, dasatinib -- you see that. Patients that get steroids, because the regimen has a lot of steroids, have problems with glucose. They can end up having diabetes. Some of them, particularly patients who are overweight, can develop problems in bones, like, the bones become very fragile and they have some necrosis (death of cells or tissue) of the bones.

You also can see some cardiac problems, but like Dr. Short said, it's not very common. You can also see fertility issues, depending. From all of that, I mean, when you think of how many patients we treat and how many have these complications, it's very, very small, the percentage. But it's something that we need to talk about. But the biggest problem is transplant. From all of these, the biggest problem is transplant. And you also need to remember there is something called therapy-related leukemias, and -- and these patients can also have it, while it's kind of rare.



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Lizette Figueroa-Rivera
Thank you, so much and thank you so much, again, for answering all of these questions and for sharing your expertise with us today. And, thank you for your continued dedication to our blood cancer patients.

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If we weren't able to get your question today, you can contact an LLS Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572, from 9 a.m. to 9 p.m., Eastern Time. Or, go to LLS.org/InformationSpecialist, to chat online. Or email us at LLS.org/ContactUs. LLS also has a Clinical Trial Support Center, where clinical trial nurse navigators will personally assist you throughout the entire clinical trial process. And you may reach them at LLS.org/Navigation.

Thank You

Again, we would to acknowledge and thank Kite, A Gilead Company.

On behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Please let us know what you need from us during this time and take good care.