00:00:00.000 --> 00:00:02.534 What about what come the live audience?
00:00:02.540 --> 00:00:05.092 And I want to welcome everybody who’s joining
00:00:05.092 --> 00:00:07.920 us today on zoom for the Sun Special Lecture.
00:00:07.920 --> 00:00:12.176 So I will be introducing Dr Sears
00:00:12.176 --> 00:00:14.320 and today’s lecture honoree.
00:00:14.320 --> 00:00:17.732 And and then Doctor Zaiden, who is on zoom
00:00:17.732 --> 00:00:19.400 will be introducing Patrick and Harden.
00:00:19.400 --> 00:00:22.392 So the Blanche Tom and lecture series was
00:00:22.392 --> 00:00:25.380 established in 2012 by Doctor Marvin Sears.
00:00:25.380 --> 00:00:28.188 Dr Sears was a longtime chair and founder
00:00:28.188 --> 00:00:30.589 of Ophthalmology and visual science at Yale.
00:00:30.590 --> 00:00:33.290 And the lecture was established
00:00:33.290 --> 00:00:33.290 in honor of his mother,
Lange Tolman, who passed away from acute myelogenous leukemia. This was actually the first lecture series dedicated solely to hematologic malignancies at Yale and it is intended to bring to Yale pioneers that have made major contributions to our understanding of the current trends in hematologic malignancies and in particular leukemia. So doctors Aiden, I welcome you to introduce Doctor Kantarjian.
but anyone more suited to give this lecture about new developments on leukemia because he has been a major force in many of the new developments over the last few decades, really in leukemia, both in AML and CLL and CML as well.

So Doctor Kantarjian is a professor and chair of the Department of leukemia at the University of Texas and the Anderson. He’s also the Samsung Distinguished Leukemia chair in cancer medicine. His research has focused on translation and clinical development therapeutics in
00:01:38.375 --> 00:01:40.865 leukemia over the last three decades.

00:01:40.870 --> 00:01:43.445 He had made significant contributions

00:01:43.445 --> 00:01:46.020 that improved our understanding of

00:01:46.095 --> 00:01:48.797 both the prognosis as well as the

00:01:48.797 --> 00:01:51.381 survival of patients of CMLL as

00:01:51.381 --> 00:01:54.915 well as discoveries of decitabine

00:01:54.915 --> 00:01:56.790 and clofarabine in the treatment

00:01:56.790 --> 00:01:58.700 of leukemias and many other.

00:01:58.700 --> 00:01:59.072 Medications.

00:01:59.072 --> 00:01:59.816 In fact,

00:01:59.816 --> 00:02:02.048 he and his group have contributed

00:02:02.048 --> 00:02:04.801 to more than 20 developments in this space.

00:02:04.801 --> 00:02:06.870 He has been an author of more than

00:02:06.870 --> 00:02:12.846 peer reviewed publications,
and he actually has been a major advocate of clinical research. He has mentored hundreds of leukemia doctors and researchers all over the US and the world and has been a big advocate for introduction and use of Therapy across the world, especially in low resource countries. So it’s really a pleasure to have doctor Kantarjian and who are very grateful to have you speak to us today about acute and plastic leukemia. Thank you.

Thank you very much, Doctor Zeidan. It’s really a great honor and a
pleasure to give it the talk at Yale and
particularly the special Tallman talk.
But I’m going to do is review the
progress and research in acute
lymphocytic leukemia as it stands today.
And a lot of the things I’m going
to say may be very different from
what you view all treatment today.
So bear with me,
I’ll try to get you through the information.
And perhaps convince you that the
times are changing very quickly.
These are my conflicts of interest.
So this is the standard of care
in acute lymphocytic leukemia
as it stands today we give.
A lot of intensive chemotherapy with 15 chemotherapy drugs over three years in childhood there L on the left side the investigators have reported your rates of up to 80%. On the right side is the data and adult L MD Anderson. So up till 2010 we were able to claim A5 year survival of maybe 50%. This is regardless of age and it has improved since 2010, but I’m going to show you that. That even the red curve is outdated in 2022. So it’s important to just keep an open mind about the things.
which I’m going to mention, because I truly believe what I will show will be the next standard of care and maybe five years from now. So one of the questions is why is still there 30% difference or 40% difference in the cure rate between childhood and adult L? With intensive chemotherapy, so this is because of four subsets uh which have different incidences and prognosis. So in childhood all the hyper deployed and ETV 6 runx 1 constitute half and these have a favorable prognosis with intensive chemotherapy in contrast historically Philadelphia.
positive and Philadelphia like L which constitute 50% of adult. L and the 15% of childhood L These have had unfavorable outcomes with intensive chemotherapy.

I’m going to show you that this does not apply anymore, neither for Philadelphia positive nor for the Philadelphia like it.

So if you use the intensive chemotherapy for three years, what is the cost of this traditional intensive chemotherapy?

So you’re using a lot of chemotherapy over three years.
00:05:25.860 --> 00:05:27.780 This could be manageable
NOTE Confidence: 0.83799161
00:05:27.780 --> 00:05:29.700 and the ivory towers,
NOTE Confidence: 0.83799161
00:05:29.700 --> 00:05:31.440 leukemia centers of excellence.
NOTE Confidence: 0.83799161
00:05:31.440 --> 00:05:35.279 But if you apply this to the Community
NOTE Confidence: 0.83799161
00:05:35.279 --> 00:05:38.154 practice and emerging nations among
NOTE Confidence: 0.83799161
00:05:38.154 --> 00:05:40.277 poorer and disadvantaged populations,
NOTE Confidence: 0.83799161
00:05:40.277 --> 00:05:42.262 there's a very high dropout
NOTE Confidence: 0.83799161
00:05:42.262 --> 00:05:44.920 rate due to the socioeconomic.
NOTE Confidence: 0.83799161
00:05:44.920 --> 00:05:47.950 Conditions as well as in the
NOTE Confidence: 0.83799161
00:05:47.950 --> 00:05:49.465 infrastructure and support.
NOTE Confidence: 0.83799161
00:05:49.470 --> 00:05:51.420 Even then the frontline therapy
NOTE Confidence: 0.83799161
00:05:51.420 --> 00:05:53.622 will cost half $1,000,000 in the
NOTE Confidence: 0.83799161
00:05:53.622 --> 00:05:55.686 United States and if the patients
NOTE Confidence: 0.83799161
00:05:55.686 --> 00:05:57.004 relapse that’s $2,000,000.
NOTE Confidence: 0.83799161
00:05:57.004 --> 00:06:00.952 And moreover there are multiple long term
NOTE Confidence: 0.83799161
00:06:00.952 --> 00:06:03.549 complications including organ dysfunctions,
healthcare issues, psychological and social issues. So what is the solution to this? Let me try to show you some data from other nations. So this is Peru and India and these are recent reports and what they show is accurate and childhood L not of 80 or 90% but in the range of 60 to 70% if you go to the older patients see. These are the patients that we treat more commonly. The cure rate is anywhere from 10 to 27% and this is simply because. The intensive chemotherapy for three years
00:06:43.358 --> 00:06:46.438 is not feasible among many of the patients.
NOTE Confidence: 0.805844978421053
00:06:46.440 --> 00:06:49.203 So the solution in my view is to try
NOTE Confidence: 0.805844978421053
00:06:49.203 --> 00:06:52.012 to develop different regimens which
NOTE Confidence: 0.805844978421053
00:06:52.012 --> 00:06:53.872 incorporate the newer treatments which
NOTE Confidence: 0.805844978421053
00:06:53.872 --> 00:06:56.399 have been discovered in the last 10 years.
NOTE Confidence: 0.805844978421053
00:06:56.400 --> 00:06:58.014 So for example,
NOTE Confidence: 0.805844978421053
00:06:58.014 --> 00:07:01.242 the third generation BCR able kinase
NOTE Confidence: 0.805844978421053
00:07:01.242 --> 00:07:04.315 inhibitors like PONATINIB in Philadelphia
NOTE Confidence: 0.805844978421053
00:07:04.315 --> 00:07:08.291 positive all and also incorporating.
NOTE Confidence: 0.805844978421053
00:07:08.291 --> 00:07:12.399 New antibodies that target CD19CD20
NOTE Confidence: 0.805844978421053
00:07:12.399 --> 00:07:15.033 and CD22 and perhaps consider that
NOTE Confidence: 0.805844978421053
00:07:15.033 --> 00:07:18.086 the best role of the car T cells
NOTE Confidence: 0.805844978421053
00:07:18.086 --> 00:07:20.440 is not an active salvage disease.
NOTE Confidence: 0.805844978421053
00:07:20.440 --> 00:07:23.401 But as a consolidation in remission and
NOTE Confidence: 0.805844978421053
00:07:23.401 --> 00:07:25.768 first second transplant also we need
NOTE Confidence: 0.805844978421053
00:07:25.768 --> 00:07:28.162 to measure the disease in better ways.
So there’s a way that’s called next generation sequencing that measures the immunoglobulin heavy chain of the particular all it can analyze up to 3,000,000. Yes.

And this will allow us to decide on changing the therapy and the duration of therapy.

This is a seven month regiment which I’m hoping may become some form of a standard of care five years from now.
This is not fiction. We did these studies now and ALS salvage with good results and we have moved it to the older patients. So this is something that is happening. So this is a regimen that contains blinatumomab, rituximab, inotuzumab, and we do a condensed approach with chemotherapy. So rather than sequencing the chemotherapy followed by blinatumomab, we are doing it as a condensed regiment. So this is something that can be improved upon.
I'll show you some of the results. So why do I believe that it is time to break with the 40 year old tradition? I believe so because in Philadelphia, non-chemotherapy regimens without the transplant are giving outstanding results. Also in the pre-bial less chemotherapy for shorter durations in combination with these antibodies are improving the outcome significantly. I'm not sure about this because we do not have Antibodies, which are broadly available.
to treat T cell L,

But I'll show you some of the data with the incorporation of venetoclax and asparagine is nelarabine at the end.

Now, anytime you break with tradition. It bothers some of the skeptics, the traditionalist. So I'm showing this slide just to show you how times change.

This was the time when ARC was discovered at three as the treatment for AML.

And there was a debate then between Dr Crosby, and Doctor Friedrich. And the question was,
even though we have arasse, should we treat or not treat acute myeloid leukemia? So the answer is obvious. Today we treat almost all leukemias, but it was not obvious 50 years ago. And this was 15 years after I was born. So what? What? What? Seems unusual or. Out of the norm can become very quickly standard of care, uh within a lifetime. So I think the Anderson, we developed the Hyper C Weather Regiment in 1992.
We changed the CNS prophylaxis from radiation therapy to intrathecal that became a standard of care. In 2000. We added the rituximab to workout and three BL. This was confirmed in randomized trials which were published in 2017 and this has become a standard of care in Philadelphia. Positive it was only in 2000. The satanic followed by transplant in 2017 and this has become a standard of care in Philadelphia. Positive it was only in 2000. The satanic followed by transplant.
00:11:10.588 --> 00:11:13.734 is what is currently the standard of care in the United States in 2022.

And I’ll show you that it’s probably old fashioned, outdated and perhaps obsolete.

The big breakthrough came of course with the discovery of the new antibodies that were highly effective, more effective.

The big breakthrough came of course with the discovery of the new antibodies that were highly effective, more effective.

And intensive chemotherapy and which targeted 2 of the cluster designation so blinatumomab bispecific T cell engager that targets CD19 and CD22.

And intensive chemotherapy and which targeted 2 of the cluster designation so blinatumomab bispecific T cell engager that targets CD19 and CD22.
So on the left side I show the again the data and the younger patients. So this is patients up to the age of 60 and since 2010 there is an improvement. So now the five year survival is over 60%. On the right side is the data with mini CD in Oblina which started in 2010 and this is where we had a big improvement in the five year survival from 20% to about 50%. So we still use the Hyper Siva in contrast to many other places where pediatric inspired regimens are used because it’s easier to incorporate it into the newer targeted therapies and...
because at our institution we found that Hyper Cvad which is also a pediatric inspired regimen performed as well as the asparaginase containing regimens during the induction. Now for people who use the Hyper Cvad, I would like to draw your attention to a review in cancer which gives you some vignettes and pearls as to how to reduce the myelosuppression complications. The key issue is in the event courses where reduce the methotrexate by 24 percent, and the RC from 3 to 2 grams per meter square.
But there are other small clues to improve the toxicities of this regime.

Now, when I'm going to show you the research at MD Anderson, you're going to be wondering why we're resorting to Bayesian designs with signal arm trials. And I'll try to explain my position, but also why is it that different regiments have been developed differently? And this is essentially because a lot of the times it is what we propose and the drug companies offer us in terms of free drugs, so.
Uh, the evolution of a lot of Ind studies at MD Anderson where based on if and when the antibodies were available and free on island studies as well as on the maturing Bayesian based data. So we started with the mini CVD in 2010, we added the BLINATUMOMAB later in 2015 and the younger patients, the Hyper Cvd started in 2018. And I’ll show you that. And I mentioned that those dense mini CVD started only September 2021 and we opened this study for the older AML year later.
So I’m going to show you some of the evolution of these studies. So let’s start with Philadelphia positive and then in 2000, this diagnosis was a death sentence unless the patient had an allogeneic donor. So if the patients did not have a donor even zone, 90% of them went in a complete remission with intensive chemotherapy. They almost all relapsed and died. If they had the donor, we gave them the transplant and their mission and the cure rate was about 30 to 40%. At MD Anderson,
we added the imatinib to Hyper Cvad in 2000.

Allogeneic transplant was almost always done in first complete remission.

In 2006, we replaced that with the SA T in it and we started doing the transplant only if the patients were still PCR positive in 2010, because 20% of the relapses were with the T315I clone.

We replace the satanic with ponatinib, the patients who are living longer.

10 to 15% were developing CNS leukemia with the 8 intraceuticals.

So we increased this to 12 intraceuticals.
and we did the transplant less and only if there was no major molecular response in 2017 we switched. So this was the drastic change eliminating chemotherapy and transplant and using two targeted therapies for net and Lina tuna. So I’m going to show you the sequence of the studies but. I’d like to draw your attention that none of these studies were randomized trial. And I’m gonna come back to this for the sake of the younger students and others because they, we and they have been indoctrinated the only way to advance
research in medicine and in cancer

is in through randomized trials.

And I'm going to probably state

that that depends on where we are.

So this is the progress in

Philadelphia positive L before 2000,

the patients died since 2002,

the cure rate or survival improved to 40%.

Since 2010 it went to A5

year survival of 70%.

Now the hyper Cvd Desatino was taken by the SW Oncology group.

It was tested in a single arm

trial and they found that they
could reproduce the data from the single institution CR rate of 88% and a three-year survival of 70%. And they showed at that time that doing allogeneic transplant in first remission improved the outcome. So this became and is still the standard of care in the United States. I perceive that this afternoon followed by allogeneic transplant in first complete remission. Now people question whether the satanic was superior to imatinib and they waited for the randomized trials. So this randomized trial did
not come from the United States, it came actually from China where children with Philadelphia positive were randomized to chemotherapy with these satanic or imatinib. And that study showed clearly that the four year survival was superior with desatinik 88 versus 69% but notice on either. From the results are better than in adult L, so this is a common scene. Children with L do better than adults with L, whether they receive intensive chemotherapy, allogeneic transplant, or any other modalities so far.
Now the hyper Cvad, Ponatinib started in 2010 because Ponatinib was toxic. We reduced the dose very quickly to 30 milligrams in CR to 15 milligrams in complete molecular response and we published the data on the 86 patients treated with this regimen. CR 800%, PCR negativity 84%, five year survival shown on the left side 75% and now we have a longer follow-up, so we. This is very solid data, but for the first time on the right side of the slide we showed that perhaps allogeneic transplantation is not necessary in all patients.
So the blue curve is actually the patients who did undergo transplantation either by physician or by patients choice. So this was 1/4 of the patients and they did worse. The 12 intraceuticals abrogated or eliminated the CNS leukemia. So now we're sticking with 12 intraceuticals and this is the best we could do to convince people who wish for the randomized trials. We did the propensity score analysis that showed that ponatinib was superior to desatinib in our institutional studies. Now in the meantime,
Lena and Inotuzumab were undergoing the single and randomized trials. And the randomized trials showed that in the subset of patients with Philadelphia positive L refractory relapsed blinatumomab and INOTUZUMAB were superior to intensive chemotherapy in terms of improving the CRA and perhaps improving survival modesty. So because of this, we went to a regiment in 2017. That skipped the intensive chemotherapy and skipped the transplant. And we use Ponatinib and blinatumomab during the induction and then blinatumomab for five cycles.
The Ponatinib is as of today indefinitely, but based on the NGH smurd studies, we're thinking to follow a strategy similar to CML where if the patients are NGS, MRD negative for five years, maybe we'll stop the treatment, but we're not there yet. But let me show you the data which is going to be published in Lancet hematology in the next couple of months. So we treated 63 patients, where newly diagnosed Philadelphia positive L, so if you look at those patients in the middle column, the CR rate is universal.
complete molecular response rate also in most of the patients and for the first time they estimated 2 to three years survival is 95%. So this is better than anything we’ve ever had and only one of the 43 patients went to transplant. Now for patients with refractory relapsed Philadelphia positive AML or CML chronic phase that evolved into the lymphoid blastic phase, the outcome is still bad. So we still use the hyper Cvad, ponatinib, blinatumomab in those two subsets. And this is to show you how quickly the patients achieve PCR negativity.
So if you treat Philadelphia positive CLL, you are used to the fact that the PCR does not become negative till three to six months into a remission. Here I show and we did this the PCR weekly simply to see whether we’re going to see some major signal and we were surprised to notice that within the four weeks of induction therapy, 2/3 of the patients became PCR negative and before the next course, 3/4 of the patients had become PCR negative. So very quick achievement of PCR negativity and NGS MRD negativity. And now I show the survival in the
red with the ponatinib blinatumomab

compared to the hyper cvad ponatinib.

So the question is will you do a randomized study today comparing poneto?

See that? Um, imagine it.

So this is an important question and I have to tell you that this is a randomized study that’s ongoing in Europe.

So you have to decide is this randomized trial which provides equipoise,

which is the basis of a randomized trial,

meaning that the investigator does not know whether one or the other arms

of the randomization is superior.

So as I mentioned,
we still use intensive chemotherapy with ponatinib blinatumomab in CML chronic phase that evolves into a blastic phase and refractory relapsed Philadelphia positive L and then in two other rare subsets. So patients with Philadelphia positive L but where the fish is positive on the mature granular sites, these are patients mostly with P210, Philadelphia positive L and another rare. Upset, which we did not think existed, but we had now 7 cases of Philadelphia positive L and CRLF two. These do badly and they need
Now next I’m going to move to Philadelphia like so for the students and the fellows. Philadelphia Lucky L is an L entity where the cytogenetics do not show the translocation 922 and the molecular studies do not show the BCR able translocation molecular events, but they have a genomic profile which is identical to Philadelphia positive all and different from the other subsets of all. So what we’ve learned is Philadelphia, like L has a bad prognosis with intensive chemotherapy. On the left side is the data from Saint Jude,
00:24:34.870 --> 00:24:37.054 on the right side is the data from MD Anderson.

00:24:37.054 --> 00:24:37.990 And what you notice is historically with intensive chemotherapy,

00:24:37.990 --> 00:24:40.654 the cure rate in children was 25%.

00:24:40.654 --> 00:24:41.986 The cure rate and adult also was below 20%.

00:24:41.990 --> 00:24:45.169 We now know that this is more common in Hispanics because they have got a 3 variant that increases CRF2,

00:24:45.169 --> 00:24:49.930 so they have a lot of Philadelphia like.

00:24:49.930 --> 00:25:04.412 So Philadelphia like LL is divided into 2 entities.

00:25:04.420 --> 00:25:06.510 So Philadelphia like LL is 1/4 of pre BL,

00:25:06.510 --> 00:25:08.182 divided into 2 entities.

00:25:08.190 --> 00:25:12.900 So this is just 1/4 of pre BL,

00:25:12.900 --> 00:25:17.000 but 50% of Hispanics pre B all,

00:25:17.000 --> 00:25:19.968 most of them 80% have CRLF two
over expression and half of these have a Jack mutation. So if you take 100 patients with L25, we’ll have Philadelphia like Disease, 20 will be CRLF, 2 overexpressed and 10 of them. Will be Jack 2 mutated and these are bad. These patients may still need the allogeneic transplantation, but otherwise the other Philadelphia like I’ll show you do well with the addition of the antibodies. Then there’s an uncommon subset, so five of the 100 or 20% of the Philadelphia like that have able translocations.
So this is not the BCR able, but they are able translocations to other genes and these patients. Respond to BCR able kinase inhibitors. So here I show it more schematically. In blue are the translocations of able one. To other genes that produce enable translocation that responds to the BCR able kinase inhibitors also the same applies to PDGFR beta translocations. So these patients with Abel or PD GFR fusions, we treat them on the Philadelphia positive protocols. There is another subset with not
00:26:41.908 --> 00:26:44.835 Jack 2 mutations but with Jack to
NOTE Confidence: 0.88114062631579
00:26:44.835 --> 00:26:46.990 translocations and it is possible.
NOTE Confidence: 0.88114062631579
00:26:46.990 --> 00:26:48.700 That these may respond to resolution
NOTE Confidence: 0.88114062631579
00:26:48.700 --> 00:26:51.208 and we do not know and they are rare,
NOTE Confidence: 0.88114062631579
00:26:51.210 --> 00:26:53.982 so we haven’t been able to
NOTE Confidence: 0.88114062631579
00:26:53.982 --> 00:26:56.780 treat them on our studies.
NOTE Confidence: 0.88114062631579
00:27:01.190 --> 00:27:03.122 24 patients with essentially
NOTE Confidence: 0.88114062631579
00:27:03.122 --> 00:27:05.054 able translocations were treated
NOTE Confidence: 0.88114062631579
00:27:05.054 --> 00:27:07.820 with BCR able kinase inhibitors
NOTE Confidence: 0.88114062631579
00:27:07.820 --> 00:27:09.545 and intensive chemotherapy.
NOTE Confidence: 0.88114062631579
00:27:09.550 --> 00:27:12.707 And they showed in this study that
NOTE Confidence: 0.88114062631579
00:27:12.707 --> 00:27:15.054 like Philadelphia positive all these
NOTE Confidence: 0.88114062631579
00:27:15.054 --> 00:27:16.886 patients who receive chemotherapy
NOTE Confidence: 0.88114062631579
00:27:16.886 --> 00:27:19.662 and BCR ABL kinase inhibitor have
NOTE Confidence: 0.88114062631579
00:27:19.662 --> 00:27:22.656 a high response rate close to 90%


and the four year survival of 60%.

So these able.

Mislocated lol.

We treat the same way as Philadelphia positive L.

So to summarize,

Philadelphia like L has the same genomic profile as Philadelphia positive L,

but not the 922 translocation and not the BCR able molecular events.

It constitutes 25% of the adults.

Historically it has a poor prognosis,

but not anymore.

It is more common among Hispanics

and it is 2 distinct entities.
The CRF2 overexpressed and they’re able translocated. Which we treat like Philadelphia positively. And so the newer approaches are actually improving the outcome in both of these entities.

Next I’m going to talk about the therapeutic revolution in the particular subset of CRF2 overexpression. It comes from 2 subsets. The first one are the newer antibodies including antibody drug conjugates and by specific T cell engagers that are targeting
CD19, CD20, and CD22.

So you may be aware of the CD 20 bytes which have shown very high efficacy in lymphoma. So we'd like to use them to replace rituximab.

And that way we have 3 antibodies which are highly effective.

On the right side are the cartel cells, which are a revolution in both lymphoma and myeloma.

But I think for them to be important in the L, they have to be used in the setting of minimal residual disease.

So in 2009 at MD Anderson,
we were aware of the INOTUZUMAB studies and lymphoma.
And so we convinced the company to give us an investigator in this study, which we did initially with single dose per course and then in fractionated doses and that study matured into 90 patients that showed Mario CR rate of 58%.
In the meantime, the randomized trials and lymphoma with INOTUZUMAB failed. So the company went ahead with the randomized trial and I show here the data in the randomized trial.
So there were two studies. Two parallel trials with Blinatumomab and these were both randomized. Trials that compared the antibodies to intensive chemotherapy and both showed that blinatumomab and inotuzumab were superior to intensive chemotherapy in refractory relaxed.

I want you all to also notice that even though we reported Amaro CR rate in the MD Anderson. Actually the randomized trial showed higher mercy RA than our institutional study.
So both these agents became FDA approved in 2014 and in 2017 as single agents for the treatment of refractory relapse AML. But what you see is the benefit is very modest. So very quickly we decided this is not how we are going to use them and we incorporated them rapidly into the standard chemotherapy.

The design of the original study was four cycles of intensive chemotherapy and because the prevailing notion was you cannot dose dense.
because the chemotherapy kills the these T cells, so theoretically blinatumomab would be less effective. The company allowed us only to use it in sequence and then we shorten the duration of the maintenance from two years to one year. And later on the other company allowed us to add inotuzumab. So we had two of the antibodies as three drugs that we incorporated into the high perceived blinatumomab inotuzumab. So we are going to publish the data in the 1st again unless it
hematology in the next couple of months.

The CR8 was 100%, MRD negativity 95% and for the first time in pre BLA in adult pre BL the three-year survival was 85%.

On the right side I showed the data since we added the inotuzumab, so by adding inotuzumab.

To the high perceived blinatumomab we improved the outcome, perhaps because we so far have not seen any relapses.

So that’s why I think that this is perhaps a potential standard of care in the future.

Now let’s look at the data compared to the
00:32:43.016 --> 00:32:45.912 previous high perceived ofatumumab, a 20%
NOTE Confidence: 0.823395777692308
00:32:45.912 --> 00:32:48.894 difference in the survival at three years.
NOTE Confidence: 0.823395777692308
00:32:48.900 --> 00:32:52.986 And this shows the subset in blue of patients
NOTE Confidence: 0.823395777692308
00:32:52.986 --> 00:32:56.516 with Philadelphia like disease where the
NOTE Confidence: 0.823395777692308
00:32:56.516 --> 00:33:00.220 survival is not anymore 20% as I showed you,
NOTE Confidence: 0.823395777692308
00:33:00.220 --> 00:33:04.210 but it has gone up to 70% and this shows the.
NOTE Confidence: 0.823395777692308
00:33:04.210 --> 00:33:06.616 Survival with or without the transplant,
NOTE Confidence: 0.823395777692308
00:33:06.620 --> 00:33:09.524 again suggesting that the role of
NOTE Confidence: 0.823395777692308
00:33:09.524 --> 00:33:12.028 transplant is not that important
NOTE Confidence: 0.823395777692308
00:33:12.028 --> 00:33:15.360 and not for all patients with ALS.
NOTE Confidence: 0.823395777692308
00:33:15.360 --> 00:33:17.576 So I showed you the top two slides,
NOTE Confidence: 0.823395777692308
00:33:17.580 --> 00:33:20.828 the top two studies from MD Anderson and
NOTE Confidence: 0.823395777692308
00:33:20.828 --> 00:33:24.539 what you see is this is a common trend now.
NOTE Confidence: 0.823395777692308
00:33:24.540 --> 00:33:27.908 So even though randomized trials has been or
NOTE Confidence: 0.823395777692308
00:33:27.908 --> 00:33:31.818 is the standard of care in Cancer Research,
what you see is many of the studies from Germany, France and other places, they are using single arm trials in order to optimize the regimens before taking them to a final randomized. One and they are showing similar data with high CR rates and high survival rates. Now, I mentioned randomized trial and Bayesian designs for several times and I want to explain myself perhaps not to the senior physicians who. May be skeptical about this, but perhaps for the fellows and students who have been educated to appreciate randomized trials as the only way to
00:34:18.698 --> 00:34:22.345 advance research in medicine and in cancer.

00:34:22.350 --> 00:34:25.514 So we started the studies with INOTUZUMAB

00:34:25.514 --> 00:34:29.010 in 2010, with BLINATUMOMAB in 2012.

00:34:31.690 --> 00:34:37.318 These drugs were FDA approved in

00:34:31.690 --> 00:34:37.318 2014 and 17 in 2022 a decade later.

00:34:37.318 --> 00:34:40.810 W e still use Blinatumomab and inotuzumab

00:34:40.913 --> 00:34:43.967 as single agents in ASL solvers.

00:34:43.970 --> 00:34:46.706 W e have not yet established the

00:34:46.706 --> 00:34:49.239 combinations as a standard of care.

00:34:49.240 --> 00:34:50.018 Now what?

00:34:50.018 --> 00:34:52.352 Let’s go back to the history

00:34:52.352 --> 00:34:53.730 of randomized trials.

00:34:53.730 --> 00:34:57.517 What people may not know is the

00:34:57.517 --> 00:35:00.288 randomized trial started only in 1955.

00:35:00.288 --> 00:35:02.128 The first randomized trial in
cancer was done by Doctor Friedrich. This was a time when he was at the NIH and he showed a correlation between low platelets and bleeding. So people ask him to do a randomized trial where he gave fresh blood and he showed that the bleeding decreased. In those days, we did not have to resist machines, so he was asked to do a randomized trial of fresh blood versus stored blood. To show that fresh blood would reduce the bleeding in children with a L and he showed that when the trial turned to be positive, they accused him of falsifying the data.
So this shows you a trend that perhaps a randomized trials are established today, but maybe we can question them. So let me tell you why we should question them. So today in Europe there is a phase three study of 1. Versus intensive chemotherapy, imagine. I do not believe there is real equipoise, so the basis of all randomized trials. Is that they assume there’s the knowledge equipoise. So you’re sitting in the room with the patient and you say, I’m going to randomize you to this.
protocol and I truly and honestly do not believe that the new treatment is better than the old one. Now randomized trials are OK if you are in a research desert. So if you were in 1965 or 1970 or 1980 where there was very little to offer to the patients, you could do a randomized trial with the new drug X or if you have a highly curable disease like ALS today, we are in the land of research plenty. There are multiple targeted therapies in ASL and if you do a randomized trial that randomizes, the patients to the standard of
care versus standard of care versus drug X that the results of that randomized trial will be outdated by the time the data matures. And if you think about it, our whole life experience is actually not randomized. It’s Bayesian. The way we raise our children, the schools we choose for them, the restaurants we choose, the careers, the partners. You do not go out 50 times with a new person and 50 times with another new person and then look at your experience and decide which
one you're going to marry.

You actually switch from person A to B&C. Very quickly and gain a cumulative experience that allows you to decide on what to do.

Now in the editorials you may have read those two examples, which are obvious examples. So parachutes were not based on randomized trials. We did not throw 50 people without a parachute and 50 people with a parachute from airplanes to decide that parachutes save lives. And the same applied to seatbelts and so on.

Now for the young people,
they search Google all the time

So there are Google algorithms that we

So I’m going to propose that perhaps

So think about it and see if it’s
something that could that could maybe challenge the concept of randomized trials and this is not new knowledge. So what you notice is that the A today is approving. Several drugs not based on randomized trials, but based on the results of even phase one studies and we were told historically that phase one studies are purely to identify toxicities and the phase two dose. Now we know that there are several drugs like crizotinib and non small cell lung cancer and then roughly in Melanoma that were approved based

60
on the results of Phase 1/2 trials.

So I’m going to propose at least for a L which is a land of the resource plenty that we hold the randomized styles because they will slow the progress and the discoveries and replace them with Bayesian trials. Actually randomized trials which are poorly designed can give you false leads. So there was in fact an all study using a pediatric inspired regimen. It was a cooperative trial in the United States that had. Randomized patients to using a regimen with ASPARAGINASE and inotuzumab.
I objected vehemently to that study because I said that Asparaginase and Inotuzumab will cause vino and occlusive disease and mortality. This was not believed and the study was stopped two months ago after 400 patients were entered because as expected, there was a higher mortality in the investigational arm because of the anticipated synergistic toxicity of asparaginase and inotuzumab. So I think at least in ASL we have to revert to single arm trials until we optimize the regimen that could.
be compared to the standard of care.

Now next I’m going to discuss minimal residual disease.

I’m going to draw your attention to figure this is, this is patients with adult AL who are in remission and who are MRD positive.

So what you see is their cure rate is at best 10% compared to over 50% for the patients who become MRD negative by any methodology. But this was mostly by flow cytometry.

So this is. Where we started using BLINATUMOMAB for five courses in the setting of MRD positive L in first or second remission we observed that 80%
00:41:40.100 --> 00:41:42.902 of the patients became MRD negative
00:41:42.902 --> 00:41:46.718 and the four year survival was not 10%,
00:41:46.720 --> 00:41:48.860 it went up to 60%.
00:41:48.860 --> 00:41:51.852 And on the right side I showed that
00:41:51.852 --> 00:41:54.800 the effect of transplant was minimal.
00:41:54.800 --> 00:41:56.977 So perhaps this is where we can
00:41:56.977 --> 00:41:58.400 do the cartel cells.
00:41:58.400 --> 00:42:01.544 Instead of transplant,
00:42:01.544 --> 00:42:02.990 because if you avoid the
00:42:02.990 --> 00:42:06.006 transplant related mortality,
00:42:06.010 --> 00:42:08.578 maybe the cure rate will be even higher.
00:42:08.578 --> 00:42:11.428 to Measure Mart not by flow
00:42:11.428 --> 00:42:14.048 but by the next generation sequencing
NOTE Confidence: 0.8738667475
for the immunoglobulin heavy chain that looks at the million to three million cells. So this is a study in the older AL, so I’m going to show you an update for just for information purposes. So this is the study that we did and we took from the L salvage where we did minimal chemotherapy with inotuzumab and added the BLINA TUMOMAB later on. And we showed that by matched analysis that the new study was superior to the old study of Hyper Siva. The question? Is can we do a randomized trial and what it would be the control arm now that there’s a significant difference in
the outcome compared to historical data? And this is the same happening elsewhere. So in the United States there was a single arm swork trial of chemotherapy with blinatumomab and similar studies were conducted again in Germany and Australia and by the French group. All of them are single arm trials combining chemotherapy with one of the two antibodies producing high CR rates and good early outcomes. Now in this LL, as I mentioned, we do not have an antibody. But what we have is something that might work,
so intensive chemotherapy with a lot of methotrexate and asparaginase and recently we have seen that nelarabine works there and venetoclax might work. So we have started combining these drugs in a trial and error formulation. And the other thing that is important is the fact that T cell L, there’s a subset of T cell AL shown here that has a genomic profile more like AML. I think this is the precursor T cell all where we need to start considering treatments that incorporate AML therapies. So this is the subset of the cell L with methylation profile. Identical to acute myeloid leukemia
and perhaps these are the patients that should be treated like M so this is the multiple reiterations of the hyper cvad asparaginase, nelarabine regimen and not yet ready for prime time, but in the past two studies where we added venetoclax and nelarabine asparaginase, we’re getting survivals not of 60%, but over 70%. And we are, we hope that this will continue with the updates. Now one of the questions is then when do we use allogeneic transplantation in remission.
So we still use it in the patients with translocation 11q23IN precursor TLL and patients with complex karyotypes, so abnormalities more than five and in the Philadelphia-like L with CRLF two with JAK2 mutations otherwise. This constitutes about maybe 15 to 20% of adult AML where we still use allogeneic transplant today and where we may use CAR T cells in the future. This is an update in the AL solver. So this is where it all started. So even though I'm showing it at the end because it's L salvage, this is where all the research
started with the MACD, you know to Zuma blinatumomab and I showed the update in the 112 patients treated so far, marrow CR 88%, MRD negativity, define occlusive disease after we fractionated the inotuzumab. And kept the doors has gone from 9% to 1%. AML relapse used to be again death sentence and the overall 112 patients. The five year survival is 30%. Since we added the blinatumomab we have shown like in the younger patients when we added in auto blina.
00:46:34.801 --> 00:46:37.447 we showed an improvement in the
survival and the salvage when we added
BLINATUMOMAB to the mini CD you know.

00:46:43.290 --> 00:46:46.038 We have shown an improvement in
the three-year survival to 50%.

00:46:49.581 --> 00:46:52.640 the potential five year survival is now
40% and we do not see a difference with
or without alot transplant because I
think we’re losing a lot of patience.

00:47:05.519 --> 00:47:09.720 So if we do the car T cells maybe we’ll
improve the survival further than 40%.

00:47:09.720 --> 00:47:11.020 Now people may say, well,
we have the cartee cells,
why have you ignored them?
So on the left side, I showed you data with inotuzumab. We're not curing too many patients, maybe 20%. And we need the transplant here in the middle or the newer car T cells, the approved car T cells for the older patients and what you see is the two year survival is probably 20%. And now I show you the the UM in blue, the post amendment where the three-year survival is 50%. So I think in L salvage if I have a patient who has relapsed, I would use the mini CVD in obinisa.
and then I would do the Carticel to improve the potential cure rate.

Now why have I insisted several times on the CART sales to be tested in minimal residual disease? I think the car T cells today are being used the same way we use allogeneic transplant in the 1970s in active disease and we’re curing 20 to 30%. If we start using the car T cells and minimal residual disease the same way as allogeneic transplant is used today, then perhaps we will cure many more of them. Now people will object to this saying,
well no, you need active disease to expand the car T cells. But the real world data shows that in fact when you do the car T cells in minimal residual disease, you potentially cure more patients than if you do it in the setting of minimal residual disease. So in summary, I think in Philadelphia positive Ponatinib BLINATUMOMAB will be the future form of therapy and I think the future of pre BL will
be with much less chemotherapy for shorter duration combined with the antibodies using the car T cells in the setting of minimal residual disease and monitoring patients by next generation MRD. Now can we do better than this? So this is what I showed you with what I call the break or the dose dense mini CBD regimen and this is what we are testing today in older all and we may move it to younger all. So this is very similar to what you do in lymphoma, the need of car T cell consolidation,
but can we do better than this.

So you may be aware that.

There are T cell engagers which target more than CD19 or CD20.

This is what we call the Tetra.

This is not science fiction.

These will be developed and there are also cartee cells which target more than one target.

So it is possible that in the future we will use very little chemotherapy to induce the patients in remission.

Consolidate them with the Tetra.
specific T cell engagers and then

we’ll further consolidate them

with Karti cells.

So in total duration of therapy

of three to four months,

which will not be toxic and which

will be highly effective and

potentially highly curable.

Thank you for your attention and

I’m happy to answer any questions.

Did I thank you for this absolutely fantastic

lecture? And we actually have hematology

faculty and trainees in the room.

So I encourage everybody to

ask questions in person.

You’re welcome to come up to the
00:51:06.587 --> 00:51:08.770 podium or I'm happy to repeat

00:51:08.770 --> 00:51:10.780 your questions from the audience.

00:51:10.780 --> 00:51:13.335 And then are you seeing

00:51:13.335 --> 00:51:15.379 questions from in soon?

00:51:20.980 --> 00:51:22.340 So I don't see questions

00:51:22.340 --> 00:51:25.280 in either that. Question.

00:51:27.180 --> 00:51:29.715 OK. Thank you for that

00:51:29.715 --> 00:51:30.729 excellent presentation.

00:51:30.730 --> 00:51:33.622 I think the pH positive word is largely

00:51:33.362 --> 00:51:35.980 driven by what happens at MD Anderson.

00:51:35.980 --> 00:51:37.515 And it's interesting to see

00:51:37.515 --> 00:51:39.833 it's negative disease and ALS is

00:51:39.393 --> 00:51:40.828 going that direction as well.

00:51:40.830 --> 00:51:44.316 Thank you for those excellent slides.

00:51:44.320 --> 00:51:46.518 You show a couple of interesting but
equally provocative slides, right?

Innovate and leaner trials,

when published historically

compared them against standard of

chemo while the Cartesian trials.

At INA and Lena failure in my mind,

those were probably more refractory diseases.

Based on the CR and the MRD rate

that are reported across Kartes as

is approved with the FDA agents.

What’s the hesitation of you

trying them first?

And why are we still pursuing with Inar

Deena approaches with chemotherapy?

I think the answer to that

will lead to my next question.
So that’s a very important question. And the answer to this is I do not compare the single agent antibodies to the cartica results, but you have to do is compare the hyper cvad in oblina and salvage to the Carticel. So with the cart cells, if you take 100 patients, you’re infusing probably only 2/3 of them because you lose some of the patients. In the process with the mini CD and Oblina you are treating 100% of the patients and you’re getting a mirror CR rate of 85% and that does not negate the need and potential.
use of either allogeneic transplant or Cathy cell as a consolidation. So I do not see the antibodies and Carty cells as either or or competitive modalities, I see them as in fact synergistic modalities that. Have to be used in the proper sequence. I think that begs the question, since we’re competing for the CD19 targets with Lena and Carti, why not just stick to your mini hyper Cvd prasina to Zoom app and then a different target, right? Because it’s 19 or 22 expressions. Because the bigger question of how to sequence this,
should blina be avoided, especially in car? Likely coordinating patients or however you design it, because there are some issues of competing for the same antigenic targets. So that’s an important question and the Carticel experts have always brought the issue. If you treat the patients with blinatumomab, you may lose the target. And there were data that showed that the outcome may be worse. But there is this real world data which I’ve shown you have updated the
results and they’ve shown that the results were worse with blinatumomab only in the patients who failed blinatumomab and the patients who respond to blinatumomab when they relapse. And they get the car T cells, the results are still as good. So it was a selection of the patients who are refractory to blinatumomab who were also refractory to the cartesius. So I have no hesitation and no issues with using blinatumomab before the car T cells, because loss of the target is minimal, if at all, and also because the updated data. Does not show that exposure to blinatumomab
worsens the outcome of the car T cells.
It was an epiphenomenon of the patients who are refractory, truly refractory to blina that also are refractory to the cortices.
OK. Thank you. And last comment was going to make was now I’ll let others take the question because a couple of my other colleagues have to go for Nicola.
I guess you have just one question.
Have you noticed that you know by maybe not running phase three trial randomized trials, but these early phase trials that you
have better inclusion of you know, people who may be more hesitant to enroll in trials, so underrepresented population. Well that’s one issue because as I mentioned today with all the targeted therapies with the multitudes of targeted therapies, it’s very difficult for an investigator. We truly and transparently states a situation of equipoise, meaning that you tell the patient, look, I have hyper cvad. Um. Imagine versus ponatinib, blinatumomab and I truly believe that I do not know the answer to to that, to that strategy.
So I think if you tell the patient, look, we have gathered all our knowledge and to the best of my knowledge this is a trial that will help you. First, it would reduce the restrictive eligibility criteria, which was. You can negotiate better within your own Ind studies and in single ARM trials to reduce the obstacles. And second, you probably can convince the patients better that what you're offering them is truly what you believe is best for them. Thank you so much Doctor Baldev, come on to the podium.
00:56:47.590 --> 00:56:49.005 Doctor Contagion, thank you very
NOTE Confidence: 0.652388093333333
00:56:49.005 --> 00:56:50.137 much for excellent presentation.
NOTE Confidence: 0.652388093333333
00:56:50.140 --> 00:56:53.094 My question is about use of Ponatinib
NOTE Confidence: 0.652388093333333
00:56:53.094 --> 00:56:55.074 and BLINATUMOMAB and pH positive
NOTE Confidence: 0.652388093333333
00:56:55.074 --> 00:56:57.016 L so you know this is applicable
NOTE Confidence: 0.652388093333333
00:56:57.016 --> 00:56:58.735 to younger and older patients and
NOTE Confidence: 0.652388093333333
00:56:58.735 --> 00:57:00.744 obviously there is a lot of concern
NOTE Confidence: 0.652388093333333
00:57:00.744 --> 00:57:02.527 about the natib related toxicity.
NOTE Confidence: 0.652388093333333
00:57:02.530 --> 00:57:03.955 Would you see any contraindications
NOTE Confidence: 0.652388093333333
00:57:03.955 --> 00:57:06.034 and what do you think about long
NOTE Confidence: 0.652388093333333
00:57:06.034 --> 00:57:07.534 term use of management after
NOTE Confidence: 0.652388093333333
00:57:07.534 --> 00:57:08.990 you finished initial treatment,
NOTE Confidence: 0.652388093333333
00:57:08.990 --> 00:57:10.230 how long should we continue?
NOTE Confidence: 0.793629846666667
00:57:11.240 --> 00:57:13.825 So you’re absolutely correct that
NOTE Confidence: 0.793629846666667
00:57:13.825 --> 00:57:15.893 Ponatinib has significant toxicities.
NOTE Confidence: 0.793629846666667
00:57:15.900 --> 00:57:18.643 That’s why we reduce it from 45.
Actually in the ponatinib Lina, we start with 30 milligrams and we reduce it to 15 milligrams usually within a month as I showed you. But your question is very legitimate. What do we do with all the patients who have already existing arterial occlusive events or cardiovascular events. So in those situations there’s. One could design a trial with Bosutinib Blinatumomab. Or with the satanic Blinatumomab, but you’re going to encounter perhaps relapse rate of maybe 10 to 20% with 315I clones.
You hope that the Blinatumomab will suppress these clones, and if you try to design a regimen like this, I would encourage to use the blinatumomab starting day one with the induction rather than as the Italians did where they used it three months into a remission. So today if I have a patient with cardiovascular contraindications, arterial occlusive events. Then by all means I could start them with with desatino blinatumomab, but then you have to somehow carve out a time space where you give them ponatinib to try to eliminate those perhaps 10% of the patients.
who can relapse with the T315 icron. Alternatively you can see what the residual disease is left with next generation sequencing and if you see it there then you can. So following with Jim, next Gen sequencing rather than with PCR is what you suggest because you know PCR is reasonably sensitive as well. So the PCR detects 100,000 cells. The NGS when successful can measure 3,000,000 cents. We’re doing both of them. Another interesting finding which
I didn’t mention is we have patients who are NCGS negative and PCR positive at low levels. So you could say, well is this a fluke, how can that be? And we think that the eggs, because it measures the immunoglobulin heavy chain is looking only at the lymphoblast. But there could be some BCR able signals in the myeloid cells which will not cause an ACL relapse. And in fact this is what we are noticing. There’s a subset of patients who are NGS MRD negative, PCR positive at low level 0.01 or 0.1%.
NOTE Confidence: 0.811219101666667
01:00:00.810 --> 01:00:03.491 so we’re not sending them to transplant
NOTE Confidence: 0.811219101666667
01:00:03.491 --> 01:00:05.999 if they are NGS MRD negative.
NOTE Confidence: 0.811219101666667
01:00:06.000 --> 01:00:07.578 But we haven’t published on this.
NOTE Confidence: 0.811219101666667
01:00:07.580 --> 01:00:08.528 It’s A twist.
NOTE Confidence: 0.8402872825
01:00:10.560 --> 01:00:14.340 To some patients so more specialized
NOTE Confidence: 0.8402872825
01:00:14.340 --> 01:00:16.710 than what? What one needs to know.
NOTE Confidence: 0.654074203384615
01:00:17.590 --> 01:00:19.280 And duration of Inactive and
NOTE Confidence: 0.654074203384615
01:00:19.280 --> 01:00:20.632 younger patients receive treatment
NOTE Confidence: 0.654074203384615
01:00:20.632 --> 01:00:22.418 with minor ponatinib combination.
NOTE Confidence: 0.827764602
01:00:22.690 --> 01:00:24.010 So we do not know,
NOTE Confidence: 0.827764602
01:00:24.010 --> 01:00:25.886 but here’s what we’re going to do.
NOTE Confidence: 0.827764602
01:00:25.890 --> 01:00:28.946 We’re going to adopt strategy similar to CML.
NOTE Confidence: 0.827764602
01:00:28.950 --> 01:00:31.098 We’re going to say if the
NOTE Confidence: 0.827764602
01:00:31.098 --> 01:00:32.530 patient is NCGS negative,
NOTE Confidence: 0.827764602
01:00:32.530 --> 01:00:34.950 MRD negative for five years,
NOTE Confidence: 0.827764602
we are going to either stop the treatment for toxicities or accidentally if the patient doesn’t want it or perhaps in the future on purpose, we’re going to tell them you have been NGS, MRD negative for five years. They think the disease is not going to relapse and perhaps ponatinib will buy you more problems than benefits. So we’re going to stop and see what happens the same way as we do in chronic myeloid leukemia with the concept of treatment free remission. But we’re not there yet. We need to get to a population of patients who are NGS MRD negative.
for five years or at least three years to offer them that kind of a treatment option if they have toxicities or side effects.

Thank you.

Right. I think we're at the top of the hour at Doctor Kantarjian. Thank you so much for this absolutely spectacular lecture. And Dr Sears, thank you for bringing these amazing advances to our lecture hall today.

So thank you so much and thank you, Amar, for the wonderful introduction.
01:01:38.092 --> 01:01:39.967 inviting me to this special lecture.