Disclosures.

An outline for my talk today would be to briefly talk about 6 important studies. One is a randomized trial comparing best supportive care against allogeneic transplant for patients with MD S between ages of 50 to 75. Yes second study would be looking into an owl way of mobilizing stem cells. Studies 3, four and five are addressing pharmacologic and cellular manipulations to decrease the risk of graft versus host disease. Post allogeneic stem cell
transplant and the final study.

We will briefly talk about evolving role of what consolidation is prior to allogeneic stem cell transplantation.

In modern era, we will not focus too much about autologous transplantation because my colleagues in lymphoma and myeloma section. I have tested on that concept and once the arrows done I’m going to pass on the talk to Iris for chimeric T cell talk.

The first study was a BMT CTN 1102. This randomized study was a biologic assessment study to be biologically assigned to receive.
another public stem cell transplant.

People should have identified a donor between the 90 days of consenting for this MDS study.

Math sibling donors and matched unrelated donors were load.

They were all expected to undergo stem cell transplantation within six months.

Subjects between ages 50 to 75 were included.

Only primary Arduino MD S with the intermediate two or high risk by PSS were included in the study.

All these candidates were meant to be in a traditional sense be acceptable to undergo reduced intensity transportation study.
Randomized people to either get randomized

260 questions to transplantation, or 124 patients.

2 best supportive care or whatever

other options individual centers

would offer to those.

So here are the results from that study.

The primary endpoint of the trial

was a prior overall survival.

Looking into the donor and the

no donor arms here 3 or estimate

overall survival was 47.9% for

those who had a donor against at

26.6% for people who did not have a

donor at the time of randomization.
Game when they do the sensitivity analysis, excluding subjects, are assigned to the node on around who either died or withdrew prior to the 90 research window. For the sooner the eventual outcome did not change with the adjusted overall survival of 48% for the donor arm against the 28.1% for the non donor when they specifically looked into the different subgroups for analysis. Use of rat hyperventilation agents. Age groups less than 65 against greater than 65 duration of MBS, less than three months or greater than. Reminds I PS is risk groups that
00:02:50.125 --> 00:02:53.233 donor am sent it to do better

00:02:53.233 --> 00:02:55.037 for the overall survival.

00:02:55.040 --> 00:02:58.507 One of the secondary endpoints of this

00:02:58.510 --> 00:03:00.025 video is to look into leukemia free survival.

00:03:00.025 --> 00:03:00.934 latest plastic syndromes.

00:03:02.170 --> 00:03:05.040 They don’t around again came out superior.

00:03:05.040 --> 00:03:07.090 Three year leukemia free survival

00:03:07.090 --> 00:03:09.550 of 35.8% compared to the node

00:03:11.600 --> 00:03:13.730 Adjusting with the sensitivity analysis

00:03:13.730 --> 00:03:16.519 again the leukemia free survival was 35.9%.

00:03:16.520 --> 00:03:18.980 The donor arm against the 21.8%

00:03:18.980 --> 00:03:21.241 for the node and are similar to
the prior slide within subgroups

for all different variables that looked into leukemia.

Free survival advantage was seen with the transplantation.

This is a slide that is showing as treated analysis.

Again, showing the superiority for both overall survival and leukemia free survival.

Absolute improvement for overall survival study,

one point 4% for the transplantation arm was 28.4% for the leukemia free survival again for the transplantation.

So one of the conclusions of this
randomized study for a very long time,

the field of Miller Park,

stem cell transplantation

and who to transplant,

who not to transplant was based

upon Markov decision modeling.

This is the first randomized trial

comparing best supportive care of

best available care against the

random against allogeneic stem cell

transplantation in a randomized manner.

Specifically, in a Common Age group

where we encountered this disease,

so such patients,

if they have a suitable donor,
this leads to improved overall survival through leukemia free survival and again after we ask our patients to undergo transplantation, a question that gets asked is can you know, is this covered by Medicare? Historically, we had to report those outcomes now within the subgroup analysis, we’re clearly able to show that for people greater than 65 in less than 65. Transportation is a good option. I think that goes against transportation. Is there are reports that talk
about decreased quality of life post transplantation, so the study had designed.

I didn’t show you that like the study. I designed a quality of life measurement at different time points for both the arms and it shows that the quality of life was no different or definitely not included in the transportation. Finally, as I want to emphasize that overall, there’s a very strong advantage for stem cell transplantation, particularly to have a match sibling donor or a mass unrelated donor identified.
early in the course of their treatment.

I have next study talks about how to mobilize stem cells at.

Traditionally we walked in stem cell sources through several modes, either with G, CSF mobilized the donor bone marrow transplant ago for bone marrow aspiration, or resemble cord blood transplants. There are many different limitations for each one of those things, but the communist platform is G. CSF mobilized peripheral blood graphs.

Usually, in order to achieve that, we have to give about four
00:05:51.372 --> 00:05:53.080 to five days of injection.

00:05:53.080 --> 00:05:55.180 This is kind of a time sensitive

00:05:55.180 --> 00:05:57.368 process and with every day we keep

00:05:57.368 --> 00:05:59.650 giving G CSF phenotype of sounds that

00:05:59.650 --> 00:06:01.930 we generate along with Democratic stem

00:06:01.930 --> 00:06:04.254 cells changes with those T cells that

00:06:04.254 --> 00:06:06.465 are then more likely to induce both

00:06:06.465 --> 00:06:09.055 acute and chronic graft versus host disease.

00:06:09.060 --> 00:06:11.209 Currently there is an urgent need rather

00:06:11.209 --> 00:06:13.728 than unmet need for rapid mobilizing agents.

00:06:13.730 --> 00:06:16.124 One compound that we tend to use

00:06:16.124 --> 00:06:17.843 Explorer EXE firing people who

00:06:17.843 --> 00:06:19.715 do not mobilize with G CSF.

00:06:19.720 --> 00:06:21.718 It’s a CX here for inhibitor.

00:06:21.720 --> 00:06:24.380 It does generate a lot of cells.
But can only mobilize adequate number of cells that we feel are desirable in about 60 to 65% of patients. So in order to come with a rapid solution, people have been looking for alternative options in terms of how to do. CXE R2 seems to be a potential target, so here in this study that we should have presented by the audience they using akcija to organist MDT at 145 along with product support to try and see if a single day mobilization is possible to generate * **** wit emitter Partick stem cells in addition to Olympus suppressive properties of the T cells. So here is a condensed version of
The results that I'm presenting. The study included healthy volunteers, about 12 of them, of which 92% of those volunteers mobilized 20 CD, 34 cells per microliters combination. That is the M GTA145 plus player XFR compared to only 57% of the patients achieving the same target with single agent product so far. Just in case you're wondering what is the 20 CD 34 cells for Michael later before the subjects are put on a fresh this machine, we do a peripheral blood CD 4 count. Most centers would not put people in machine if the count is less than 10.
Here it’s showing that they’ve got a decent number of count 2020 CD 34 cells per microliter, suggesting that the cell, what we can predict preparing the machine. This is a decent deal, expecting a good outcome for decent collection at the end of the day. The Peaks cell concentration that we found in the peripheral with the combination was 40 CD 34 cells from Mike later again that suggest that the robust aggressive the cells that they were able to achieve with this combinations. Eight of those donors went voted the combination underwent a phrases
and the median sell those that were

00:08:06.037 --> 00:08:07.993 collected was 4,000,000 cells per cagey

00:08:07.993 --> 00:08:09.937 of their sippy and what’s expected.

00:08:09.940 --> 00:08:11.872 So that’s a very good number in

00:08:11.872 --> 00:08:13.769 terms of the overall picture.

00:08:13.770 --> 00:08:17.066 How we look at it. Then the design.

00:08:17.066 --> 00:08:17.710 Some industry.

00:08:17.710 --> 00:08:19.756 Most experiment with the primary transparent

00:08:19.756 --> 00:08:21.880 secondary transplant on the left hand side.

00:08:21.880 --> 00:08:24.127 There able to show that using this

00:08:24.127 --> 00:08:26.383 combination they were able to show at

00:08:26.383 --> 00:08:28.237 23 fold higher engraftment compared to

00:08:28.300 --> 00:08:30.226 using donors were mobilized with just

00:08:30.226 --> 00:08:32.698 five days alone or plexi for single agent.

00:08:32.698 --> 00:08:34.889 The graph on the right hand side
basically show the survival for such mice.

Post engraftment was pretty good compared to the alternative options. This study has kind of been an exciting development in that now people are now exploring alternatives to G, CSF and basically trying to mobilize a phenotype of cells that are immunosuppressive to make sure the graph can stain. But at the same time they're able to generate enough of HSBC's to re populate post updated conditioning therapies.

For the next three studies were going to talk about graph versus host disease, as many of you know,
allogeneic stem cell transplantation is a curative intent treatment, but the graph versus host disease can have significant mortality and morbidity, especially chronic graft versus host disease, can be seen in about 30 to 70% of the patients main frontline therapy. For these patients, we do use corticosteroids. Approximately about 50% of patients, either dependent on it or eventually become refractory. The only FDA approved drugs in their second line setting is the drug in Brittany.
People in the CLL vertebrae familiar

The overall response rate was about 67% in that in the CRL about 21%.

It’s interesting to note the median time to response was close to three months on that study.

However, there was a D. Saint reduction in Cortico steroid use from 29 to 12.5 again pretty late in the game by up by both.

Week 49 after initiating at a
median follow up for 14 months.

In that study 71% of the patients at discontinue the drug due to toxicities.

Again, the other important point to note here is that there are currently no drugs approved in this space.

Based on the randomization.

This led to the reach three study which was studying ruxolitinib against best available therapy in patients with steroid refractory or steroid dependent.

Chronic graft versus host disease.

This was a multinational trial led by Doctor Zaiser.
Here’s the study.

Design included patients greater than 12 years of age who either had steroid refractory independent chronic graft versus host disease. It had to be moderate to severe, as defined here below. That is lack of response or disease progression after Prednisone greater than a MacBook per day for more than a week, or disease progression with Prednisone greater than point, buy mixed bag per day are a milligram per kilogram every other day for greater than four weeks are increasing the dose of Prednisone.
00:11:05.665 --> 00:11:07.475 to greater than .25 milligrams.

00:11:07.480 --> 00:11:07.832 Today,

00:11:07.832 --> 00:11:09.240 after two unsuccessful attempts

00:11:09.240 --> 00:11:10.648 to taper the dose,

00:11:10.650 --> 00:11:12.054 obviously you’re worried about

00:11:12.054 --> 00:11:13.107 the graft rejection.

00:11:13.110 --> 00:11:15.216 So prior to the study enrollment,

00:11:15.220 --> 00:11:16.980 we had to confirm everybody

00:11:16.980 --> 00:11:18.036 had decent engraftment.

00:11:18.040 --> 00:11:21.560 The randomization was stratified by

00:11:21.560 --> 00:11:24.045 Great people were allowed to go either

00:11:24.045 --> 00:11:26.543 on ruxolitinib 10 milligrams to be ID

00:11:26.543 --> 00:11:28.595 those on the backbone of steroids.

00:11:28.600 --> 00:11:30.652 Percent minus calcineurin inhibitors

NOTE Confidence: 0.7914078
or best available therapy.

NOTE Confidence: 0.7914078

About six cycles.

NOTE Confidence: 0.7914078

Were given in the intervention

NOTE Confidence: 0.7914078

alarm and then the analysis was done

NOTE Confidence: 0.7914078

correctly to the start of summer cycle.

NOTE Confidence: 0.7914078

At the end of 6 cycle people around

NOTE Confidence: 0.7914078

the best available therapy are what

NOTE Confidence: 0.7914078

allowed indeed to crossover the excellent in.

NOTE Confidence: 0.7914078

If there was a need,

NOTE Confidence: 0.7914078

the primary endpoint of the study

NOTE Confidence: 0.7914078

was overall response rate at Week

NOTE Confidence: 0.7914078

as defined by the NIH consensus

NOTE Confidence: 0.7914078

criteria and the key secondary

NOTE Confidence: 0.7914078

endpoints were failure free

NOTE Confidence: 0.7914078

survival and

NOTE Confidence: 0.8022639

modified lease symptom scale.
Assessing the responses at Week 24.

This is just a slide to show that across the two arms age, sex, TV, IDF, chronic GV HD the criteria on the score were well matched.

The overall response rate, when assessed after six months or weeks 24, was higher in the proximity bomb. It was 49.7% almost doubled compared to the 25.6% seen with the best available therapists. The CRH was about 6.7% or says 3%.

Achieving a CR in the setting is extremely hard, although it may look like the
sea animals aren’t that high.

What we really need to take into account is the OR or are you know when you talk to people who take transportation. It will be agrees that this is a good endpoint. Rather than focusing on CR alone. When they looked into failure free survival at week 24, failure fix around being defined as a time to the earliest of recurrence of underlying disease or the start menu. Systemic treatment for chronic GVHD or death. But the rock selection of arm it was not raised,
but as it was 5.7 months with the observation log.

One thing that is often understood, he did incorporate that is the symptom scale modified.

Lee Symptom Scale is well validated in chronic GVHD setting, investigators were able to show that for patients who are investigational arm had a better quality of life as is being measured by the symptomatic score with a 24.2% here compared to the 11% the controller.

Which is the best overall response
00:13:42.842 --> 00:13:44.360 rate right? But again,
NOTE Confidence: 0.8165663
00:13:44.360 --> 00:13:46.700 with the intervention arm with excellent
NOTE Confidence: 0.8165663
00:13:46.700 --> 00:13:49.486 and M it was 76.4% compared to 60.4%.
NOTE Confidence: 0.8165663
00:13:49.486 --> 00:13:51.718 But the best available therapy are
NOTE Confidence: 0.8165663
00:13:51.718 --> 00:13:54.114 the median duration or best overall
NOTE Confidence: 0.8165663
00:13:54.114 --> 00:13:56.796 response was 6.2 four months unpaid but
NOTE Confidence: 0.8165663
00:13:56.796 --> 00:14:01.000 was not reached in their excellent in a bar.
NOTE Confidence: 0.8165663
00:14:01.000 --> 00:14:03.994 In conclusion this is the first
NOTE Confidence: 0.8165663
00:14:03.994 --> 00:14:05.990 successful randomized phase three
NOTE Confidence: 0.8165663
00:14:06.069 --> 00:14:08.680 trial for the chronic GV HD space,
NOTE Confidence: 0.8165663
00:14:08.680 --> 00:14:11.428 or excellent in a demonstrated significantly
NOTE Confidence: 0.8165663
00:14:11.428 --> 00:14:14.019 higher overall response rate at Week 24.
NOTE Confidence: 0.8165663
00:14:14.020 --> 00:14:16.310 There was improvement in failure
NOTE Confidence: 0.8165663
00:14:16.310 --> 00:14:17.684 free survival significantly
NOTE Confidence: 0.8165663
00:14:17.684 --> 00:14:19.380 improved symptom improvement.
NOTE Confidence: 0.8165663
00:14:19.380 --> 00:14:20.454 There was hype.
It was the highest best overall response rate at Week 24 with excellent.

The most frequent adverse event seemed the setting was similar to what we’ve seen in acute GBS resetting when we use our excellent name, namely anemia and thrombocytopenia.

Based on this finding, there is increasing enthusiasm to start using this drug as a second line setting.

The other important progress in the chronic GV HD space is in studying this pathway called the rock Pot Rock here stands for through associated coiled coil protein kinase pathway.
Rock essentially comes in two isoforms, rock one and Rock 2. These are sitting three on TuneIn kinases. Most of this study is coming systemic sclerosis, another autoimmune disease models where altering rock to re balance the immune system, which down regulates drugs that’s blocking the rock. Two parter. Basically, downregulate proinflammatory side intensity at 17 and it also increases your Excel production. In addition, what is interesting about this pathway is that it also controls
multiple pro fibrotic processes,
including myofibroblast activation.
Rock is a downstream of major Pro.
Fibrotic mediators mediate stress fiber formation.
It also regulates transcription of several pro fibrotic genes.
It is important because when you study chronic GV HD,
there are milder versions of GV HD where people are just ocular or oral GST,
which is not really that much of morbid GST.
In contrast, that sclerotic, longer sclerotic pericardium,
those are the most serious one
where inflammation with fibrosis

eventually lead to bad outcomes.

So a drug which controls inflammation

alters the fibrotic trajectory

is a big welcome into the field.

Study results are being eagerly awaited in the field for the last couple of years based on its mechanisms.

And here’s a slide on the right hand side that was presented initially in 2018 and that ECT.

And they’re trying to find the dose.

That intention to treat analysis about 59% of the patients showed overall response rate in that state.

The inclusion criteria included people
or greater than two prior lines of therapy and a significant number of those have more than four organ involved, and many of those are traditionally classified as what we call as a severe chronic GV HD. This lady is recapitulating what the study design was on the left of the eligibility criteria, which is basically age greater than five prior lines of therapy. They were allowed to go on the one of two arms either once a day. Those are twice a day.
Those you would continue to tell clinically significant progression or unacceptable toxicity with the primary endpoint looking in four or R as per the consensus criteria and secondary endpoints with safety duration of response, at least symptoms care.

Can you free survival and overall survival? The study population was well balanced for both the once a day dose and twice a day dose on the right hand side is giving you the overall output for all of those things. There was nothing significantly different between these two groups, but what is of interest here?
Ways there were several people.

Approximately 30% of the patients had used up ibrutinib.

Other option ruxolitinib bugs are option, suggesting that the drug the design of the study should be interpreted taking into account what are currently approved, or at least what’s commonly used in the field.

It has issues with gastrointestinal stuff in terms of diarrhea, nausea, which is a common thing that we encounter in our patient population.
When we looked at specifically the great prior higher events, pneumonia, hypertension, hyperglycemia, or some of the common events that might come across. Again, keep in mind chronic GVHD patients are highly immunocompromised and infections are not uncommon.

The primary endpoint was easily met for both the arms. It was 73% with once a day, those 77% with the twice a day dose. What was presented in this Patch was basically the 12 months follow compared to the previous presentations.
Offered to show that seven patients were able to reach a CR Interestingly median time to the response in the studies four weeks, which is a welcome change. Here’s the responses across the different subgroups they were interested in, no matter whether using it once a day or twice a day. Whether they had severe chronic GV HD screening or not, but it was refractory and refractory number of organs involved. prior originate are excellent in it,
this drug was able to show good overall response rate. The duration of Response rather than median duration of response was 50 weeks and about 60% of the patients maintain responses for greater than five months. Can you see survival six months? This ones reporting at 12 months of failure free survival at 58% is an extremely encouraging data for this field. Overall survival again is impressive, but 89% understanding the mortality that comes with chronic graft versus host disease. Additional endpoints that they talk about is reduction in the doors.
They were able to show that the main cortico steroid dose reduction was possible in about 44% of the people. It was higher in those who responded. Obviously 52% and lower in those who are not responding about 17% in addition to the steroids calcineurin inhibitor dose reduction was also possible with. More patients in the treatment arm able to do that with compared to what we’ve seen historically in other trials. Symptoms scale The least scale as I presented you earlier on. Again, it was a meaningful difference with both.
00:20:14.114 --> 00:20:15.870 responders or nonresponders achieving
NOTE Confidence: 0.7602978
00:20:15.870 --> 00:20:18.360 improvement in their symptoms scores.
NOTE Confidence: 0.7602978
00:20:18.360 --> 00:20:20.820 In conclusion this drug element Bell
NOTE Confidence: 0.7602978
00:20:20.820 --> 00:20:23.566 incident is well tolerated and has
NOTE Confidence: 0.7602978
00:20:23.566 --> 00:20:25.646 achieved clinically meaningful outcomes.
NOTE Confidence: 0.7602978
00:20:25.650 --> 00:20:27.705 Response rates are greater than
NOTE Confidence: 0.7602978
00:20:27.705 --> 00:20:29.756 70% with both treatment arms,
NOTE Confidence: 0.7602978
00:20:29.756 --> 00:20:31.801 including in patients who failed
NOTE Confidence: 0.7602978
00:20:31.801 --> 00:20:33.479 ibrutinib and Jack inhibitors.
NOTE Confidence: 0.78034705
00:20:36.110 --> 00:20:37.727 Switching gears will talk about the cells.
NOTE Confidence: 0.78034705
00:20:37.730 --> 00:20:39.550 The reason for graft versus host disease
NOTE Confidence: 0.78034705
00:20:39.550 --> 00:20:41.827 or the T cells that are coming here.
NOTE Confidence: 0.78034705
00:20:41.830 --> 00:20:43.774 The trial initially done at Stanford
NOTE Confidence: 0.78034705
00:20:43.774 --> 00:20:46.519 is explored to see if we can isolate
NOTE Confidence: 0.78034705
00:20:46.519 --> 00:20:48.254 self populations to decrease after
NOTE Confidence: 0.78034705
00:20:48.254 --> 00:20:49.989 sostis is historically the way
we’ve tried to diploid cells are XY or we try to extract pantycelyn, please or use drugs like ATG Witcher invite. We’re depleting agents toxin is more recent addition to the field of transplantation, initially they showed that regulatory cells which in the PD 1 field with solid tumors as a different meaning, is a welcome change in the post transplantation setting because it in users tolerance decreases GV HD.
So the design the study with the my love letter transplant setting wherein you would give your chemotherapy or radiation and then subsequently confuse equal volumes of regulatory T cells and conventional cells. So basically and a -- 2 prior to transplantation. Amateur quite stem cells and T. Rex cells were extracted out, kept and then infused, and a 0 two days later the conventional cells were then infused into the recipient. Here instead of a conventional two or a combination of suppression regiments, they were able to show that single agent,
even a suppressive. Agents like tacrolimus was adequate.

The amount of total cells that they chose would 3,000,000 T cells and almost everybody got more than two million CD 34 positive cells, which is what we normally like in the transportation context. Extrapolating the data, they now went at a multi site level and showed that when you try to go commercial, it’s feasible showed on the left hand side the CD 34 purity.
00:22:29.160 --> 00:22:31.827 comes with it for mobilizing the donor.
NOTE Confidence: 0.8181829

00:22:31.830 --> 00:22:34.511 Collecting at a site shipping it to
NOTE Confidence: 0.8181829

00:22:34.511 --> 00:22:36.762 this company would then analyze extract
NOTE Confidence: 0.8181829

00:22:36.762 --> 00:22:40.037 HSP season T Rex to one bag and then
NOTE Confidence: 0.8181829

00:22:40.037 --> 00:22:42.485 conventional T cells to another back.
NOTE Confidence: 0.8181829

00:22:42.490 --> 00:22:45.514 They were able to show that that process
NOTE Confidence: 0.8181829

00:22:45.514 --> 00:22:47.739 work efficiently and the rest of this,
NOTE Confidence: 0.8181829

00:22:47.740 --> 00:22:49.840 like basically show the clinical data,
NOTE Confidence: 0.8181829

00:22:49.840 --> 00:22:51.868 were able to show this interphil
NOTE Confidence: 0.8181829

00:22:51.868 --> 00:22:53.220 engraftment later engagement and
NOTE Confidence: 0.8181829

00:22:53.280 --> 00:22:54.740 time of hospital discharges,
NOTE Confidence: 0.8181829

00:22:54.740 --> 00:22:56.840 or all favoring this novel approach.
NOTE Confidence: 0.8181829

00:22:56.840 --> 00:22:58.164 What is more important,
NOTE Confidence: 0.8181829

00:22:58.164 --> 00:23:00.690 or patients is graft versus host disease,
NOTE Confidence: 0.8181829

00:23:00.690 --> 00:23:03.259 both grades two or higher acute graft
NOTE Confidence: 0.8181829

00:23:03.259 --> 00:23:05.534 versus host disease and chronic GBS T
as shown on the left hand side here was significantly lowered when they use this design of infusing regulatory T cells. Along with the conventional cells at different time points. GPS direction is important, So what happens to the relapse? A good out point for that is what we call the GFS on the right hand side there able to show that GFS was significantly better with using this novel approach and TRM was almost nonexistent with this approach, suggesting and paving way for future study designs for cell manipulation to
decrease graph versus host disease,
with a special emphasis on regulatory T cells.
In this last light,
we're going to talk about how they feel if consolidation is evolving.
Loading my colleague presented a couple of weeks ago and this interesting trial from oral is cited in in terms of how this is a game changer to the field of transplantation, the drug has now been approved.
To recap, essentially patients get intensive chemotherapy at the time of recruitment.
These people are all in the older
00:24:07.435 --> 00:24:09.891 age group and were thought not
00:24:09.891 --> 00:24:11.855 eligible to receive transplantation,
00:24:11.860 --> 00:24:14.612 but 44% of the patient get one cycle
00:24:14.612 --> 00:24:16.321 of intensive chemo consolidation
00:24:16.321 --> 00:24:19.435 and 38% get second layer of chemo
00:24:19.435 --> 00:24:21.600 consolidation and then their random
00:24:21.675 --> 00:24:24.015 honest to get either placebo osrs
00:24:24.015 --> 00:24:26.291 study agent which was CC-486 which
00:24:26.291 --> 00:24:28.843 is or a laser sighted in in that
00:24:28.850 --> 00:24:30.960 there was overall survival advantage
00:24:30.960 --> 00:24:33.949 as shown in the right top corner.
00:24:33.950 --> 00:24:36.218 I adore you present it as an extension of
00:24:36.218 --> 00:24:38.666 that people have now done subgroup analysis,
00:24:38.670 --> 00:24:40.764 coming back to the left hand
00:24:40.764 --> 00:24:43.153 side here Doctor Way and up to
00:24:43.153 --> 00:24:45.630
remind you are able to show that.
Irrespective of consolidation,
whether they got consolidation or not. Are they got one consolidation or greater than or equal to two consolidation there showing that CC 4X6 was able to improve overall survival and relapse free survival?
I’m not showing the slide but in the more recent ECD a couple of weeks ago as an extension of this study, investigators showed that many people in the placebo arm. Went on to get eventual allogeneic stem cell transplantation and they
make a case suggesting that we are getting more transplantation at higher frequency in that arm. Basically did not alter the eventual overall survival, however, we should keep in mind the study was not designed to answer that question, so that leads us to the next segment of this as to how we can address limitations and propel understandings of allogeneic stem cell transplant, so in this coming year ALR several study designs to do this in the backdrop of. Was that animal study design
working with Doctor Probie?

We have a multicenter study that we are initiating's, been supported by Celgene.

That is basically looking into the potential role of novel consolidation regiments.

We all know that reaching CR is a major milestone in AML.

The question is, how long do you need to consolidate them prior to you get them to the allogeneic transplantation in that premise, using some immunological correlates will be studying the role of epigenetic priming post consolidation.
And also using the concept of Fortaleza cited in increasing regulatory T cell output to decrease GV HD in the post transplantation setting, we have designed a study that will look into an extended period use of over laser setting prior to transplantation and post transplantation with the hope of decreasing both GST and relaxed survival and that would start recording. So this study has implications to the satellite centers because many of these patients after transferring will go back to you as primary and
that's something you guys would be able to get access to the drugs and treat them in the practice.

The other two studies of interest is led by my boss that are open. We looking into the role of allogeneic stem cell transplantation for patients who are relapsed refractory setting. There are many new drugs that are coming. I didn’t have a chance to talk all about them up for all of them, but I have is 1 set strike which is using Radionucleotide to target CD 45. Comparing against the conventional care which is currently ongoing and
there’s also a multicenter trial. As you know, afflict Rena bitter guilty name is approved to treat relapsed refractory AML. But now we’re studying that in a randomized fashion to see if preventing relapse is better rather than treating relapsing refractory AML. And that’s a study that’s currently ongoing with that. I’d like to thank you all and I would ask you all to hold your questions at the end of it while I pass on. So the more interesting phase of T cell engineering talks by my colleague,
00:27:36.260 --> 00:27:36.820 Doctor Sophie,  
NOTE Confidence: 0.82386875  
00:27:36.820 --> 00:27:37.940 thank you very much.  
NOTE Confidence: 0.5139432  
00:27:45.490 --> 00:27:46.618 Thank you, Louise.  
NOTE Confidence: 0.84160817  
00:28:03.250 --> 00:28:06.850 So I’ll focus my talk today on cellular  
NOTE Confidence: 0.84160817  
00:28:06.850 --> 00:28:09.538 therapies for B cell malignancy’s.  
NOTE Confidence: 0.84160817  
00:28:09.540 --> 00:28:11.272 These are my disclosures.  
NOTE Confidence: 0.84160817  
00:28:11.272 --> 00:28:14.523 And I’d like to start by reminding  
NOTE Confidence: 0.84160817  
00:28:14.523 --> 00:28:17.338 everyone of the approved city  
NOTE Confidence: 0.84160817  
00:28:17.338 --> 00:28:20.102 19 cortisol products that are  
NOTE Confidence: 0.84160817  
00:28:20.102 --> 00:28:23.056 currently on the market for B cell.  
NOTE Confidence: 0.84160817  
00:28:23.060 --> 00:28:25.616 Non Hodgkin lymphoma is we have  
NOTE Confidence: 0.84160817  
00:28:25.616 --> 00:28:27.881 exit Captain James I’ll alusil  
NOTE Confidence: 0.84160817  
00:28:27.881 --> 00:28:31.241 targeting City 19 with the city 28  
NOTE Confidence: 0.84160817  
00:28:31.241 --> 00:28:33.120 costimulatory domain tyssa gentle  
NOTE Confidence: 0.84160817  
00:28:33.120 --> 00:28:36.046 occlusal also targeting CD 19 with a  
NOTE Confidence: 0.84160817  
00:28:36.046 --> 00:28:38.254 four one baby costimulatory domain.
The newly approved lie.

So Captain Jean meluso.

With a four one baby costimulatory domain, these are all approved for large cell lymphoma and transformed follicular lymphoma, whereas T Sergeant occlusal is currently the only approved product. Also for the treatment of relapsed refractory pediatric LL and then finally a recent another recent approval last year of Brexit captain Jean Autolux so in mental relapse, refractory mantle cell lymphoma. Targeting CD19 with the CD 28 costimulatory domain for relapsed
refractory large cell lymphoma,

transformed follicular lymphoma.

The overall response rates seen in clinical trials have varied between 50 and upwards of 80%.

Complete remission rates, however, are only in the order of 40 to 50%.

This is significantly improved compared to the previously established standards of care.

But still leaves some room for improvement and then with Brexit catagen and mantle cell lymphoma.

Also very remarkable results with overall response rates of 93% and complete response rates of 67%.
Looking at studies of these cellular therapies and some of the risk factors associated with worse progression, it has become clear that there are some factors that are patient related and some that are treatment related. For example, having a very poor performance, equal performance status prior to receiving car T cell therapy and also very elevated LDH have actually been shown to be very poor prognostic markers for progression free and overall survival. And this is a study just published.
in JCO this year where they did multivariable models in patients treated with AXI cottage inside alusil. And again they really showed clear distinction between the progression free survival and overall survival curves in patients that had poor performance status and high disease burden as represented by elevated LDH levels. You know what about the biology of the tumor itself? What we know now is that anywhere from 1/4 to 30% of patients with relapsed refractory, large cell lymphoma, who progress after cortisol therapy. 1/4 of them will have loss of
CD 19 in their tumor biopsies.

So not all patients, but at least in some this is responsible for their relapse.

A very important study published in Nature of Medicine also this year by Nirav Shah at University of Medicine, Wisconsin, looked at specific anti-CD 20 and CD19 car sales for relapsed diffuse large B cell lymphoma and they have seen a 40% of patients having ongoing response rates. The follow-up is still short on this study.
but there were definitely complete remission rates, including in patients with previously received CD 19, car T cell therapy, and they did not see loss of CD 19 in any of the progressing patient tumors. In addition to antigen CD 19 antigen Escape, the tumor micro environment is very important as well, with PDL one upregulation which can contribute to car T cell exhaustion, and so this brings me to a very important study called Alexander Auto Three that was presented. Initially at ASCO where they
looked at targeting Bicistronic, assisting with a bicistronic vector target targeting CD 19 and CD 22 and the importance of this is that there are two independent cars that are delivered in a single retroviral vector. They have humanized binders and in addition to the four one baby costimulatory domains, there’s also an OX40 costimulatory domain, which. Would lead to improved persistence, and so from this study presented at ASCO now we have the Auto 3 Alexander study that was presented at this year’s ASH where in addition to dewali.
targeting CD 19 and CD 22 they also edit Pember Lizum app in relapsed refractory diffuse large B cell lymphoma. They had a cohort of patients that received the cortisol therapy alone and then they had another cohort that received three doses of pembrolizumab every two weeks, just one dose of Pembroke on day one following conditioning and. Based on the MTD that was established from the phase one. There is currently an ongoing phase two looking at efficacy for relapsed refractory diffuse large B cell lymphoma.
So these are some of the characteristics. As you can see, the median age was 59 years, but they did give this cortisol therapy to patients up to the age of 83. The majority of them had high risk features, 55% were double hit, dual overexpresses or even triple hits. At the majority, 71% had stage four disease and the majority were relapsed. Actually, about 50% were both relapsed and refractory and interesting, Lee. With this novel technology, they saw that great three of
cytokine release syndrome,
NOTE Confidence: 0.8052864
or grades three and above of
NOTE Confidence: 0.8052864
neurotoxicity were quite low.
NOTE Confidence: 0.8052864
So CRS over grades three and above.
NOTE Confidence: 0.8052864
Only 2% and neurotoxicity City
NOTE Confidence: 0.8052864
green above only four percent.
NOTE Confidence: 0.8052864
Importantly,
NOTE Confidence: 0.8052864
none of these patients received any
NOTE Confidence: 0.8052864
prophylactic measures to prevent the
NOTE Confidence: 0.8052864
development of CRS or neurotoxicity.
NOTE Confidence: 0.8052864
An overall,
NOTE Confidence: 0.8052864
the number of patients that received
NOTE Confidence: 0.8052864
tocilizumab was low at 16%.
NOTE Confidence: 0.8052864
And an patients did not receive steroids.
NOTE Confidence: 0.89521617
So what are the results?
NOTE Confidence: 0.89521617
As you can see, particularly if
we go to the higher dose levels of the cell therapy product, the overall response. Rate is 87% with 73% complete response rates. It’s still early, so durability remains unclear, but the patients, particularly the patients, were achieved. Complete remission actually have had ongoing complete remission beyond three months. And also when we look at the cellular kinetics by best overall response, you can see that. Particularly in patients who achieved
CR PR as designated here in green, they have ongoing persistency beyond 18 months. So CRP are associated with higher expansion and longer persistence. In conclusion, auto three is well tolerated with low rates of C, Rs and neurotoxicity. Particularly higher grades. They did also include an outpatient cohort and more than half of the patients were managed in the outpatient setting without requiring admission. None of them were into baited, and the complete response.
rates were particularly high. Especially if we look at the higher cortisol dose levels. With a CR rate of 73%.

So the next study that I will talk about that I found very interesting and I will just give you a bit of a background here, is that about 20 to 30% of these relapsed refractory diffuse large B cell informers were actually found to have either mutations or copy number loss in City 58.
was published in Uncle Target.

That has looked at TP 53 and 358 and here just to focus on wild type CD 58 versus mutated both in terms of progression free but also overall survival. Both patients who had mutations in city 58 and patients who had copy number loss actually had a much poorer progression free and overall survival. And why is that important? It turns out to be 58 is actually the receptor of for the city. Of the city to molecule that’s expressed by T cells and also by natural killer cells and its
expression is necessary for T cell and NK cell mediated cytotoxicity. So in this study published, it actually presented as an oral abstract by Misner. They looked at city 58 mutations in circulating tumor DNA by cap seek and also looked at city 58 expression by email, looked at a city 58 history, and as you can see, patients who carried these city 58 mutations in their tumors actually had much worse progression free survival compared to wild type patients and
also when it looked at CD58, expression by IHC. And again this is a pre-treatment.

Precarity and this is. They had used exit captain Jean style Alusil. What they saw is that the complete remission rates were actually much lower in the patient group who had low levels of CD58. Expression and even in the patients with a C58 loss who responded to treatment, at best they had a short PR and then they progressed. And so, um. So this was very interesting.
So how can we circumvent that and how can we probe the biology of the car T cell responses towards tumors that are lacking? This functional city 58 So what the authors did is they generated the city 58 knockout via CRISPR and they integrated a city to Costimulation within cars so when you look here on the left they actually generated. They looked as a control it either CD19 or CD22 targeting cars that were similar to exit cottage inside Alusil or Tisagenlecleucel that are on the market and they actually did not see any response.
However, when they integrated a city too. 

Costimulation here represented in red 

what they saw is that that actually 

overcame the loss of CD 58 in tumor cells. 

And when you look at the percent 

higher in the cells that had. 

That contained CV 2 and you know initially 

they incorporated city two in SIS and 

that did not result in any responses in vivo. 

However, when they introduced it in 

trends that actually did the trick. 

So they put in an additional, 

so to speak. 

City two receptor entrance, 

and that’s what mediated significant
antitumor activity in vivo. Anet overcame the city 58 knockout. So this data was actually extremely important, in my view, because it shows us that city two Co. Stimulation is very important. This wasn’t known before we, we thought that these car T cells were already endowed with all the necessary costimulation that they needed. However, we now know based on this study, that there are other Co stimulators on the surface of the tumor cells, such as CD 58 that also really matter and that they can drive car T cell efficacy.
So this CD 5832 is a novel axis for car resistance. It’s important in large cell lymphoma because, as I said to you 25 to 30% of patients will have either city 58 loss or mutations. And if we engineer cars, integrating City two signaling entrance we can overcome this city 58. Lawson reestablished car efficacy. And this is important because there are other cancers like multiple myeloma, Hodgkin lymphoma as well as solid tumors like colon cancer for example that do carry city 58 loss and mutations, and we expect that in the next...
couple of years there will be. Cortisol studies looking at this. Another study that I found of interest was also this abstract. where they looked at Amick, expression and tumor infiltrated the cells in patients who received his agenda cluzel in the Juliet study for lymphoma and what they were able to show was that having a baseline Nick negative Myc positive studies make positive study was actually here in blue. Associated with a worse probability of. Survival and then also having fewer tumor infiltrating CD 3 positive cells were
was also associated with poorer outcomes.

And particularly, if those infiltrating cells had.

Exhausted immunophenotype

so I talked to you about how this works in the relapse refractory setting and what we can do in that setting to overcome resistance.

But what about patients who never go into remission with their frontline therapy?

So this study Zooma, 12, looked at exit cottage inside Alusil, in patients with very high risk.

large diffuse large B cell

lymphoma in the first line.

Um and at ash they
00:44:32.298 --> 00:44:33.990 presented the interim efficacy,

NOTE Confidence: 0.83085793

00:44:33.990 --> 00:44:35.818 safety and PK data,

NOTE Confidence: 0.83085793

00:44:35.818 --> 00:44:38.103 so patients qualified for this

NOTE Confidence: 0.83085793

00:44:38.103 --> 00:44:40.997 study if they had high grade B

NOTE Confidence: 0.83085793

00:44:40.997 --> 00:44:43.299 cell lymphoma with Mick and BCL,

NOTE Confidence: 0.83085793

00:44:43.300 --> 00:44:45.410 two or BCL six translocations,

NOTE Confidence: 0.83085793

00:44:45.410 --> 00:44:49.026 so double hit or triple hit large cell

NOTE Confidence: 0.83085793

00:44:49.026 --> 00:44:52.362 lymphoma with an epic score of three

NOTE Confidence: 0.83085793

00:44:52.362 --> 00:44:55.457 or above before enrollment they had to

NOTE Confidence: 0.83085793

00:44:55.457 --> 00:44:59.160 have had at least 2 lines of an anti CD.

NOTE Confidence: 0.83085793

00:44:59.160 --> 00:45:00.750 20 monoclonal antibody.

NOTE Confidence: 0.83085793

00:45:00.750 --> 00:45:03.630 Sorry not 2 lines but two cycles and

NOTE Confidence: 0.83085793

00:45:03.630 --> 00:45:06.015 enter second containing regimen and they

NOTE Confidence: 0.83085793

00:45:06.015 --> 00:45:09.207 had to have had a positive PET scan

NOTE Confidence: 0.83085793

00:45:09.207 --> 00:45:11.776 after two Step 2 cycles of treatment

NOTE Confidence: 0.83085793
they enrolled them look at free stem. They had the option of getting some non chemotherapy bridging such as radiation or maybe REVLIMID. And then they give them flu side conditioning and a single infusion of access cell. Again, median was 61 years old, but they treated patients up to the age of 86. They all had advanced stage disease, 53% were double hit or triple hit as determined by fish. A 72% had. Keeping score of greater than or equal to 3. And when they looked at overall
NOTE Confidence: 0.84949166
00:45:51.882 --> 00:45:54.494 response rates, remarkably high 85% and
NOTE Confidence: 0.84949166
00:45:54.494 --> 00:45:57.520 CR rate for these patients was 74%,
NOTE Confidence: 0.84949166
00:45:57.520 --> 00:45:59.680 and they have followed them.
NOTE Confidence: 0.84949166
00:45:59.680 --> 00:46:02.704 The median follow-up was a 9.5 months,
NOTE Confidence: 0.84949166
00:46:02.710 --> 00:46:05.734 so not very long follow up yet,
NOTE Confidence: 0.84949166
00:46:05.740 --> 00:46:08.164 but it’s important to realize that
NOTE Confidence: 0.84949166
00:46:08.164 --> 00:46:10.806 the majority of these patients with
NOTE Confidence: 0.84949166
00:46:10.806 --> 00:46:13.662 double or triple hit INFORMALS will
NOTE Confidence: 0.84949166
00:46:13.662 --> 00:46:15.698 actually relapse within a year.
NOTE Confidence: 0.84949166
00:46:15.700 --> 00:46:16.996 Post initial therapy.
NOTE Confidence: 0.84949166
00:46:16.996 --> 00:46:19.153 So so you know, really.
NOTE Confidence: 0.84949166
00:46:19.153 --> 00:46:21.268 Really great outcomes and the
NOTE Confidence: 0.84949166
00:46:21.268 --> 00:46:24.069 most common grade three and above
NOTE Confidence: 0.84949166
00:46:24.069 --> 00:46:26.149 adverse events were encephalopathy.
NOTE Confidence: 0.84949166
00:46:26.150 --> 00:46:29.643 In 16% of the patients and cytopenias
NOTE Confidence: 0.84949166
there was one grade 5 adverse event that occurred on the study due to COVID-19.
When they looked at cortisol expansion and compared that to their Zuma one study where people had had relapsed refractory disease, what they saw is that the car T cell expansion was significantly greater in this study in summer 12 compared to Zuma one. And that perhaps, maybe because these patients had very little treatment before they went on to party. There was higher frequency of CCR seven 3045 RAT cells in the pre infusion product which
was associated with a greater expansion. Again, this is suggestive of improved T cell fitness in the first line treatment. So it’s this study you know well doesn’t have very long follow up. It does provide us with some insights into the pharmacology of access L for patients who are exposed to fewer prior therapies. Now I’m going to shift gears to relapse refractory indolent non Hodgkin lymphoma. I’ll present you the data from Zuma five with AXI Cap to Gene and then from ilaris study with tisagenlecleucel cell so. In this study zoomify,
they looked at follicular and marginal zone lymphoma patients who had relapsed after two or more lines of therapy. This was the study design. Again, very standard flu Cy followed by Access L. They all had to have had anti CD 20 monoclonal antibody plus an alkylating agent with their prior therapies. 68% of the patients had refractory disease and importantly, over half of the patients had actually progressed within two years from their initial therapy, which is this P OH, D20 four group that we now know
00:48:39.111 --> 00:48:41.455 is associated with worse survival
NOTE Confidence: 0.84949166

00:48:41.455 --> 00:48:44.165 in both follicular lymphoma and
NOTE Confidence: 0.84949166

00:48:44.165 --> 00:48:46.756 marginal zone lymphoma when they
NOTE Confidence: 0.84949166

00:48:46.756 --> 00:48:49.396 looked at the overall response rates
NOTE Confidence: 0.84949166

00:48:49.396 --> 00:48:52.890 very high again in the above 90%.
NOTE Confidence: 0.84949166

00:48:52.890 --> 00:48:53.878 And CRA,
NOTE Confidence: 0.84949166

00:48:53.878 --> 00:48:56.348 it’s also very high anywhere
NOTE Confidence: 0.84949166

00:48:56.348 --> 00:48:59.190 from 70 to 80% progression free.
NOTE Confidence: 0.84949166

00:48:59.190 --> 00:49:02.010 Survival was actually noted to be
NOTE Confidence: 0.84949166

00:49:02.010 --> 00:49:05.040 longer in the follicular lymphoma group
NOTE Confidence: 0.84949166

00:49:05.040 --> 00:49:08.046 compared to the marginal as opposed
NOTE Confidence: 0.84949166

00:49:08.131 --> 00:49:10.909 to the marginal Zone lymphoma group.
NOTE Confidence: 0.84949166

00:49:10.910 --> 00:49:13.748 But the response rates importantly were
NOTE Confidence: 0.84949166

00:49:13.748 --> 00:49:16.749 consistent across all of the subgroups,
NOTE Confidence: 0.84949166

00:49:16.750 --> 00:49:18.616 including Flipi score,
NOTE Confidence: 0.84949166
00:49:18.616 --> 00:49:22.348 high tumor burden or prior therapies.
NOTE Confidence: 0.84949166
00:49:22.350 --> 00:49:25.608 And the median duration of response,
NOTE Confidence: 0.84949166
00:49:25.610 --> 00:49:28.335 particularly in the follicular lymphoma
NOTE Confidence: 0.84949166
00:49:28.335 --> 00:49:33.110 Group, has not been reached and.
NOTE Confidence: 0.84949166
00:49:33.110 --> 00:49:38.241 Is a 78% duration of response in
NOTE Confidence: 0.84949166
00:49:38.241 --> 00:49:41.906 patients who, with follicular lymphoma,
NOTE Confidence: 0.84949166
00:49:41.906 --> 00:49:44.834 who achieved a CR.
NOTE Confidence: 0.84090036
00:49:46.960 --> 00:49:49.744 There were important to note a
NOTE Confidence: 0.84090036
00:49:49.744 --> 00:49:52.163 grade three and above adverse
NOTE Confidence: 0.84090036
00:49:52.163 --> 00:49:55.010 events in 86% of the patients.
NOTE Confidence: 0.84090036
00:49:55.010 --> 00:49:57.410 Most of them were cytopenias
NOTE Confidence: 0.84090036
00:49:57.410 --> 00:50:02.056 and infections and their worst
NOTE Confidence: 0.84090036
00:50:02.060 --> 00:50:05.140 one of which was related to multisystem
NOTE Confidence: 0.84090036
00:50:05.140 --> 00:50:07.727 organ failure with cytokine release
NOTE Confidence: 0.84090036
00:50:07.727 --> 00:50:11.279 syndrome and another one due to
coccidioidomycosis infection.

So the other important thing to note is that 82% of patients experienced some grade of cytokine release syndrome. The only 7% experienced grade three and above. Almost half the patients received socialism AB and 17% received corticosteroids.

As far as neurologic events, 60% at any grade, neurologic events an almost 20% had grade three and above neurologic events. 36% of patients received steroids for neurologic toxicity, so when they looked at serum cytokine levels,
they saw that cortisol peak levels were associated with grade three and above.

It kinds like interferon gamma L6 TNF Alpha. It were also associated with grade three and above neurologic events.

So the response rates were very high, but as I've just shown you there is still significant toxicity with this treatment, particularly for follicular and marginal zone.

Lymphoma is where we now do have available other available therapeutic options.

This is a sort of a similar design study. The Ilara which looked at this urgent occlusal for follicular lymphoma and.
And I will not spend much time. Suffice it to say that the complete response rates and overall response rates were extremely high with this therapy as well, but it was better tolerated, and indeed they did not have any cases of Grade 3 or above cytokine release syndrome. There was very little use of anti-cytokine therapy and very low rate of severe neurologic events of only 1% so. You know, it’s important to again keep in mind that these treatments are not created equal and that there are differences between them.
some of which have to do with the costimulatory domain, but many of which have to do with other parts of the design.

So toxicities are very different and there’s much work to be done to see how they will stack up against other types of treatments, particularly these novel.

I will now briefly shift gears to mantle cell lymphoma, which also remains an unmet need.

As you can see with one year and five year outcomes relative in terms...
NOTE Confidence: 0.84090036
00:53:02.013 --> 00:53:05.031 of relative survival that are worse
NOTE Confidence: 0.84090036
00:53:05.116 --> 00:53:07.420 compared to follicular lymphoma
NOTE Confidence: 0.84090036
00:53:07.420 --> 00:53:10.300 in marginal zone lymphoma and
NOTE Confidence: 0.84090036
00:53:10.300 --> 00:53:12.796 certainly lower cure rates compared
NOTE Confidence: 0.84090036
00:53:12.796 --> 00:53:15.670 to diffuse large B cell lymphoma.
NOTE Confidence: 0.84090036
00:53:15.670 --> 00:53:19.590 So this is the study that got.
NOTE Confidence: 0.84090036
NOTE Confidence: 0.84090036
00:53:21.690 --> 00:53:23.265 Captain Jean approved,
NOTE Confidence: 0.84090036
00:53:23.270 --> 00:53:25.900 published in New England Journal
NOTE Confidence: 0.84090036
00:53:25.900 --> 00:53:28.530 in 2020 targeting CD 19,
NOTE Confidence: 0.84090036
00:53:28.530 --> 00:53:31.650 where you see that the overall
NOTE Confidence: 0.84090036
00:53:31.650 --> 00:53:34.320 response rate was very high,
NOTE Confidence: 0.84090036
00:53:34.320 --> 00:53:37.470 93% and 67% of patients actually
NOTE Confidence: 0.84090036
00:53:37.470 --> 00:53:39.045 achieved complete remission.
NOTE Confidence: 0.84090036
00:53:39.050 --> 00:53:42.188 These were patients that had relapsed
NOTE Confidence: 0.84090036

88
refractory disease and the duration of response is quite durable, with a plateau in this curve.

I'm reaching three years now. As so, um, this is the transcendent study. The mantle cell cohort. This was just presented at ASH and this is looking at lysosome now in mantle cell lymphoma.

This product is different from AXA capture Gene because it has a defined composition of T of CD8 and CD4T cell components that are administered separately at equal target doses. So flu Cy conditioning lies to sell and they had two dose levels.
70% of patients had more than or equal to three prior therapies. A 75% had received prior ibrutinib, including 31% that were refractory to ibrutinib, 25% a quarter had received prior Boneta klaxon there were 16% of patients that were also refractory to prior Boneta clocks. There was a significant number of patients, 41% that had blastoid morphology, 22% with P50. Three mutations and the majority of patients. 2/3 of patients actually had an elevated key. proliferation index, 67 which we know is associated with worse
outcomes in mantle cell lymphoma.

When we look at the toxicity.

I’m with Lisa cell CRS grade three and above very low 3% and Grade 3 or above neurotoxicity 12.5%.

When they looked at response by subgroup, again remarkable that the overall response rates and complete response rates in patients with High Ki 67 blastoid morphology or P53 mutations are actually quite so.

Miller to the group that does not have any of these poor features.

The median follow-up is still relatively short 5.9 months.

This type of therapy works fast
within a month. You see the responses. And when they looked at the cellular kinetics, what they saw is that at one year sick there was life cell persistence in 67% and 33% even out to two years. Am so now they are ongoing with enrollment at the higher dose level. Dose level 2. And and again, this is remarkable for mantle cell lymphoma with no significant toxicity, grade three toxicity. What about CLL? This study transcend CLL 004,
looked at lice or sell in

NOTE Confidence: 0.820293

relapse CLL and very interesting.

NOTE Confidence: 0.820293

Lee had very high complete response

NOTE Confidence: 0.820293

rates of 45% and and really

NOTE Confidence: 0.820293

high rates of undetectable MRD,

NOTE Confidence: 0.820293

both in the blood flow and in

NOTE Confidence: 0.820293

the bone marrow by NGS and even

NOTE Confidence: 0.820293

when they looked at patients with

NOTE Confidence: 0.820293

failed BTK here in the second.

NOTE Confidence: 0.820293

Bar what failed BTK or or phonetic lacks.

NOTE Confidence: 0.820293

They had a very impressive

NOTE Confidence: 0.820293

rates of complete response,

NOTE Confidence: 0.820293

so this was already presented at

NOTE Confidence: 0.820293

Ash of 2019 and what was actually

NOTE Confidence: 0.820293

presented this year at Ash was.

NOTE Confidence: 0.820293

A combination of lice,
a cell with a brute nip based on preclinical data that shows that imbrued nip can improve car T cell, anti tumor efficacy and reduce the rates of cytokine release syndrome. So this was the study patients had progressed on ibrutinib or they had mutations of BTK and they had no contraindication to restarting ibrutinib. And they were again very high risk patients in all groups. 100% had some high risk features like deletion 17, P 53, mutation complex karyotype, 100% had priori brute Nip,
100% were relapsed refractory to ibrutinib and. Half of the patients had actually seen vanetta clocks, in addition to two BTK inhibitors. When we looked at grade three cytokine release syndrome, only 5% again and or logic toxicity grade three and above similar to mantle cell lymphoma. Only 16%. Um, complete response rates, particularly when you look at dose level 200% overall response rate 67% complete
response rate and the majority of patients had undetectable MRD. In their blood. So in summary, you have very rapid responses, high overall response rate, high rates of CR with lysis cell and ibrutinib. And even though this is no direct comparison, it certainly looks better than the data with lysis cell alone for relapsed refractory CLL. So I just wanted to I know we’re running out of time, but for people who treat leukemia, I did want to mention some of the upcoming studies in a allow that are important,
including the comparison of tisagenlecleucel

cell versus plain attuma Bob or I know,

choose a map, Osaka mice and this

choose a map, Osaka mice and this

Cassiopeia,

which looks at his agenda occlusal in

which looks at his agenda occlusal in

patients who are MRD positive after

patients who are MRD positive after

first line therapy and then also summa

first line therapy and then also summa

for looking at exit cap to gene in

for looking at exit cap to gene in

patients with relapsed refractory LL.

patients with relapsed refractory LL.

So so with that,

So so with that,

you know I’d like to end and and

you know I’d like to end and and

I’m happy to take any questions.

I’m happy to take any questions.

OK. So, Doctor Gordon Dr Sophie.

OK. So, Doctor Gordon Dr Sophie.

Thanks for those great reviews.

Thanks for those great reviews.

We do have a number of questions.
All remind people who are listening.

If you have questions, submit them in the Chatter Q&A section.

I will start with some questions about Milo dysplasia,

This is for Doctor Gowda. And I’ll just paraphrase this given the results of the randomized trial led by Doctor Cutler.

Mild displeasure. Should we in? Should we be considering haploidentical transplant in older
01:00:59.742 --> 01:01:01.460 high risk MD’s patients low? 
NOTE Confidence: 0.8303818
01:01:01.460 --> 01:01:04.120 What do you think? 
NOTE Confidence: 0.8303818
01:01:04.120 --> 01:01:04.370 It’s 
NOTE Confidence: 0.9250498
01:01:04.370 --> 01:01:06.340 a great question, I think. 
NOTE Confidence: 0.9250498
01:01:06.340 --> 01:01:08.340 It was an exclusion criteria in this trial, 
NOTE Confidence: 0.9250498
01:01:08.340 --> 01:01:10.746 so that’s the number one point. 
NOTE Confidence: 0.9250498
01:01:10.750 --> 01:01:12.222 Essentially, this pistol betas 
NOTE Confidence: 0.9250498
01:01:12.222 --> 01:01:14.430 lingered on for as many years 
NOTE Confidence: 0.9250498
01:01:14.491 --> 01:01:16.267 as we’ve all been doing this. 
NOTE Confidence: 0.9250498
01:01:16.270 --> 01:01:19.396 That haploidentical outcomes similar to 
NOTE Confidence: 0.9250498
NOTE Confidence: 0.9250498
01:01:21.580 --> 01:01:23.764 There has never been a randomized 
NOTE Confidence: 0.9250498
01:01:23.764 --> 01:01:25.220 study in this population. 
NOTE Confidence: 0.9250498
01:01:25.220 --> 01:01:27.355 There are multiple registry studies 
NOTE Confidence: 0.9250498
01:01:27.355 --> 01:01:29.063 that have shown feasibility’s. 
NOTE Confidence: 0.9250498
01:01:29.070 --> 01:01:31.310 And then also just studies that shows
01:01:31.310 --> 01:01:34.181 you kind of laid these people so you have
01:01:34.181 --> 01:01:36.847 to take all those with a pinch of salt.
01:01:36.850 --> 01:01:39.020 I would say enter specific protocol based.
01:01:39.020 --> 01:01:40.845 Certainly worth considering that the
01:01:40.845 --> 01:01:42.987 reason that prospective study that says
01:01:42.987 --> 01:01:45.043 in elderly people Apple may not be that
01:01:45.043 --> 01:01:47.110 but there are at the same time you do the
01:01:47.110 --> 01:01:49.460 mismatches in the registry limitations.
01:01:49.526 --> 01:01:51.766 There are equal numbers that
01:01:51.770 --> 01:01:53.325 There are equal numbers that
01:01:53.325 --> 01:01:56.684 So if you think there’s a high risk
01:01:56.684 --> 01:01:59.297 disease and there’s no really good option.
01:01:59.300 --> 01:02:00.395 I would certainly get an
01:02:00.395 --> 01:02:01.490 Apple down and go forward.
OK alright thanks Doctor Assoufia

question about car T cells.

Given the encouraging Zuma 12 results or were car T cells child at all and frontline setting for high risk lymphoma. So this is the first study that I know of where this is being tested in up front, in upfront lymphoma and that’s why they chose such a high disease risk. Group of patients that had double or triple hit disease or were primary refractory on PET scan.

Do you think this data is sufficient?
01:02:45.880 --> 01:02:48.540 We should consider this.

01:02:48.540 --> 01:02:50.958 Or this requires further study and end insurance approval, of course.

01:02:53.630 --> 01:02:56.006 Yeah, I mean, I think that the duration is short.

01:02:56.006 --> 01:02:58.200 we need longer duration,

01:02:58.200 --> 01:03:01.926 at least beyond the year.

01:03:01.930 --> 01:03:04.010 For these patients, you know.

01:03:04.010 --> 01:03:05.060 That being said,

01:03:05.060 --> 01:03:07.510 we have treated here and also other institutions have reported that PET scan after two cycles of therapy does not have the same prognostic significance in large cell lymphoma that it has in Hodgkin lymphoma,
and that indeed we are able to cure.

Um, many of those patients when we complete six cycles of therapy so.

I certainly don’t think that based on these data, you know we would change standard of care.

I think that this requires you know further further follow up.

Right, and I think that most importantly, we really need to see the data in relapsed refractory disease.

As to how this stacks up to too high dose therapy and autologous stem cell rescue, I think if indeed there is an improvement in cure rates with that approach.

For these patients,
01:04:01.352 --> 01:04:04.683 I think that will be a stronger push to
move it to frontline for high risk groups.

01:04:09.140 --> 01:04:10.396 Right, right?

01:04:14.164 --> 01:04:17.889 OK couple of questions on the
graft versus host disease studies.

01:04:19.570 --> 01:04:22.650 I from Doctor Challace,
do we have a sense of what?

01:04:22.650 --> 01:04:25.740 Best alternative therapies patients received.

01:04:27.380 --> 01:04:32.300 Did any receive a brute nib?

01:04:33.620 --> 01:04:39.007 Although that may refer to the crossover.

01:04:39.010 --> 01:04:41.020 I probably also know the answer to this.
01:04:41.020 --> 01:04:43.068 I don’t know if you want me to feel this one or.
NOTE Confidence: 0.826792846153846
01:04:44.100 --> 01:04:45.400 Yeah, sure yeah.
NOTE Confidence: 0.826792846153846
01:04:46.262 --> 01:04:47.986 It says it says.
NOTE Confidence: 0.826792846153846
01:04:47.990 --> 01:04:50.270 Why was the local investigator on this study so best alternative?
NOTE Confidence: 0.826792846153846
01:04:50.270 --> 01:04:52.740 Therapy was a long list of standard non FDA approved treatments ’cause there aren’t any FDA approved treatments for chronic GV HD, but they did include ibrutinib.
NOTE Confidence: 0.826792846153846
01:05:00.094 --> 01:05:02.679 They included photo pheresis.
NOTE Confidence: 0.826792846153846
01:05:02.680 --> 01:05:04.840 Other agents for Mycophenolate sirolimus occasionally and the
brute name was added to this trial.

Pretty early on, and so patients did receive many of those best alternative therapies.

In comparison, and that was up to investigators choice, corollary, question, how do you recite decide between ruxolitinib and a brute.

Take a stab at that. Yeah, I think we should understand that I put in the beta was approved based on Phase 1B.

In another, we really didn’t have many drugs.
Well, certainly it’s challenging. You know, practice. We see a lot of cases with Orange ebstein a little bit of Raskin GV HD. Those stones care of us. I’m really excited about this new drug that Katie, especially for what we traditionally called the marleybone versions of GST, including highly fibrotic questions of that and those are the ones that kill. Your patience is defining it highly immunosuppressive, right? So, coming back to her then, I think I might be tempted to use it earlier on again in a clinical trial design,
NOTE Confidence: 0.7581872
01:06:16.880 --> 01:06:17.228 because.
NOTE Confidence: 0.7581872
01:06:17.228 --> 01:06:18.620 It’s not a prude,
NOTE Confidence: 0.7581872
01:06:18.620 --> 01:06:20.608 although we are waiting for the approval
NOTE Confidence: 0.7581872
01:06:20.608 --> 01:06:22.449 to come through anytime I might be
NOTE Confidence: 0.7581872
01:06:22.449 --> 01:06:24.515 tempted to try that if it's a highly
NOTE Confidence: 0.7581872
01:06:24.515 --> 01:06:26.040 fibrotic question earlier on but.
NOTE Confidence: 0.7581872
NOTE Confidence: 0.7581872
01:06:27.452 --> 01:06:29.217 Your name can be significant
NOTE Confidence: 0.7581872
01:06:29.217 --> 01:06:31.379 in my personal biased opinion.
NOTE Confidence: 0.7581872
01:06:31.380 --> 01:06:33.207 Set opinions with Rocks is an issue,
NOTE Confidence: 0.7581872
01:06:33.210 --> 01:06:33.672 but again,
NOTE Confidence: 0.7581872
01:06:33.672 --> 01:06:35.058 in this trial the show that
NOTE Confidence: 0.7581872
01:06:35.058 --> 01:06:36.394 quality of life cytoopenias taking
NOTE Confidence: 0.7581872
01:06:36.394 --> 01:06:38.038 all that into account rocks was
NOTE Confidence: 0.7581872
01:06:38.038 --> 01:06:39.730 way better compared to the other,
NOTE Confidence: 0.7581872
so I may be tempted to use that up front and we’re already doing it in some of our cases, but it’s not studied in a randomized fashion. It’s worth studying it. If somebody sponsors that kind of a study.

So when you short answer the data support for ruxolitinib is probably a more active agent. The I’ll add the ibrutinib study required inflammatory erythema in the skin or oral GV HD is entry criteria. So as you said, it was probably a group of patients. Might be a little bit easier to treat those particular clinical scenarios, whereas ruxolitinib seems to be a more broadly active agent and it
doesn’t cause atrial fibrillation, which is an issue with the brunette. Um? OK, another Milo dysplasia question. Given the recent randomized study from MD Anderson showing no improvement in outcome with maintenance, Ivy is a sighted in versus placebo. This is post transplant in AML and MD S. Do we think or Eliza would be different? So I’m glad I’m with paying attention to MD Anderson clinical trial output very closely, and I guess he likes those results with that background. I think we should first dichotomize those two things,
So what battle showed was.
NOTE Confidence: 0.8174205

Every come are getting randomized and they’ve only median
NOTE Confidence: 0.8174205

of 4 cycles of that was given.
NOTE Confidence: 0.8174205

As for the trial right?
NOTE Confidence: 0.8174205

And it was tested in a randomized fashion that turned out to be negative.
NOTE Confidence: 0.8174205

We can argue that Ivy and oral,
NOTE Confidence: 0.8174205

despite mechanistic things,
NOTE Confidence: 0.8174205

are not the same drug.
NOTE Confidence: 0.8174205

What we’re trying to achieve is
NOTE Confidence: 0.8174205

couple of two different things.
NOTE Confidence: 0.8174205

There’s some confusion now with the CC-486 clinical trial data as to what
NOTE Confidence: 0.8174205

is the right timing for the transplant.
NOTE Confidence: 0.8174205

because it’s very cleverly
articated by the company in terms of how this needs to be done. So we all agree CR one is a major entry point, especially for intermediate and advanced rest. How many cycles of consolidations are needed? It’s an open field, unlike the hydac for the good risk groups. So if we can create outpatient based regiments with oral set aside in equal and drug. And the rationale that we build for the trial is the initial scandura trial from Cornell,
where they show that epigenetic priming enhances cancer test is an antigen exposure now antigen expression that makes the T cell attack better. You generate a lot of tumor infiltrating lymphocytes with epigenetic priming, so you kind of also make the people less fragile coming into the transparent by rather than giving hydac equivalent intensity, you make it better.

Third, in the pre transplantation setting this synergy when you prime with epigenetic agents.

Bracton Alcalay to yourself
and cyclophosphamide. So those are the 3 concepts in the pre transplantation setting. The post transplantation setting. When you continue that as a maintenance again, that’s the dichotomy between BI tools file and mine. Is that increase the regulatory T cell expressions, which is beneficial for GST. But there’s also a lot of data that epigenetics increases hedging idea or expression which then makes it easier for the T cell attack that makes
01:09:51.641 -- 01:09:53.340 relapse less likely because there’s
NOTE Confidence: 0.8174205
NOTE Confidence: 0.8174205
01:09:55.560 -- 01:09:57.476 We’re redefining consolidation differently.
NOTE Confidence: 0.8174205
01:09:57.476 -- 01:10:01.156 Trying to get into the space of a
NOTE Confidence: 0.8174205
01:10:01.156 -- 01:10:03.021 traditional hydac plus hydac against
NOTE Confidence: 0.8174205
01:10:03.021 -- 01:10:04.529 probably lower intensity therapy,
NOTE Confidence: 0.8174205
01:10:04.530 -- 01:10:06.414 which can be given an extended
NOTE Confidence: 0.8174205
01:10:06.414 -- 01:10:09.149 period of time at the target on
NOTE Confidence: 0.8174205
01:10:09.149 -- 01:10:10.556 decreasing events downstream,
NOTE Confidence: 0.8174205
01:10:10.560 -- 01:10:13.288 either due to relapse GST so that those
NOTE Confidence: 0.8174205
01:10:13.288 -- 01:10:15.665 are some of the subtle differences
NOTE Confidence: 0.8174205
01:10:15.665 -- 01:10:18.095 in how this can be interpreted.
NOTE Confidence: 0.7608803
01:10:20.090 -- 01:10:22.278 OK, one last question.
NOTE Confidence: 0.7608803
01:10:22.278 -- 01:10:25.013 I were there patients with
NOTE Confidence: 0.7608803
01:10:25.013 -- 01:10:27.215 bronchiolitis obliterans and the
NOTE Confidence: 0.7608803
01:10:27.215 -- 01:10:30.372 Rockstar study an important question.
Alright, do you recall? It’s not clear to me. I mean, I think this is abstract. I want to look at the paper myself to see what it is, but the initial dose finding study they said greater than four organ involvement. And there was a lot of multiple people at severe chronic GV HD. I’m assuming there was some representation of Bill, but I want to look at the fine print before it comes out, especially for all the noise it’s
making saying it’s antifibrotic.

and anti-inflammatory.

That would be a breakthrough.

Right, so I think we probably need to wrap up.

There’s a kudos to Doctor Trophy for pronouncing the Carty names.

I’m sure I was.

I was very impressed actually and thank you so much buddy else.

Can do that? Yeah yeah thank you so much Stewart for moderating such a lively Q&A.

And thank you Doctor Sufyan Gowda for such amazing talks.

I would also like to thank
01:11:33.982 --> 01:11:36.070 me go day to work very hard behind the scenes to get this series going and this is recorded as we discussed all of the recordings will be available. You can claim CME credit if you provide us some feedback about how we can improve this going forward and. Hopefully next year we will have a hybrid model of in person and virtual component and looking forward for a great 2021 for everybody. Thank you so much and looking forward to next year post Ash. Thank you. Excellent, thank you.