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
00:00:30.030 --> 00:00:31.830 transplant and the final study.

00:00:31.830 --> 00:00:33.858 We will briefly talk about evolving role of what consolidation is prior to

00:00:36.419 --> 00:00:37.947 allogeneic stem cell transplantation.

00:00:37.950 --> 00:00:38.778 In modern era,

00:00:38.778 --> 00:00:40.710 we will not focus too much about autologous transplantation because my

00:00:40.774 --> 00:00:42.678 colleagues in lymphoma and myeloma section.

00:00:42.678 --> 00:00:45.534 I have tested on that concept and once

00:00:45.540 --> 00:00:48.516 the arrows done I’m going to pass on

00:00:48.516 --> 00:00:51.259 the talk to Iris for chimeric T cell talk.

00:00:48.516 --> 00:00:51.259 the talk to Iris for chimeric T cell talk.

00:00:51.259 --> 00:00:54.517 So the first study was a BMT CTN 1102.

00:00:54.520 --> 00:00:58.012 This randomized study was a

00:00:58.020 --> 00:00:59.710 biologic assessment study to be

00:00:59.710 --> 00:01:00.640 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,

NOTE Confidence: 0.8365025

excluding subjects,

NOTE Confidence: 0.8365025

are assigned to the node on around

NOTE Confidence: 0.8365025

who either died or withdrew prior

NOTE Confidence: 0.8365025

to the 90 research window.

NOTE Confidence: 0.8365025

For the sooner the eventual outcome did

NOTE Confidence: 0.8365025

not change with the adjusted overall

NOTE Confidence: 0.8365025

survival of 48% for the donor arm

NOTE Confidence: 0.8365025

against the 28.1% for the non donor

NOTE Confidence: 0.8365025

when they specifically looked into

NOTE Confidence: 0.8365025

the different subgroups for analysis.

NOTE Confidence: 0.8365025

Use of rat hyperventilation agents.

NOTE Confidence: 0.8365025

Age groups less than 65 against

NOTE Confidence: 0.8365025

greater than 65 duration of MBS,

NOTE Confidence: 0.8365025

less than three months or greater than.

NOTE Confidence: 0.8365025

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.

00:03:00.940 --> 00:03:02.170 Clonal evolution here.

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 --> 00:03:11.600 on around which was 20.6%.

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...
00:04:50.686 --> 00:04:51.750 about decreased quality of life post transplantation,

00:04:51.804 --> 00:04:53.019 so the study had designed.

00:04:53.020 --> 00:04:54.530 I didn’t show you that like the study.

00:04:54.530 --> 00:04:56.938 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.

00:05:01.321 --> 00:05:03.552 Finally, as I want to emphasize that overall, there’s a very strong advantage for stem cell transplantation,

00:05:03.552 --> 00:05:05.382 particularly to have a match sibling donor or a mass unrelated donor identified

00:05:05.382 --> 00:05:08.380 was not included in the transportation.

00:05:08.380 --> 00:05:11.316 Finally,

00:05:08.747 --> 00:05:11.316 as I want to emphasize that overall,

00:05:11.320 --> 00:05:13.150 there’s a very strong advantage for stem cell transplantation,

00:05:13.150 --> 00:05:14.614 particularly to have a match sibling donor

00:05:14.620 --> 00:05:17.273 or a mass unrelated donor identified

00:05:17.273 --> 00:05:19.936
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
to five days of injection.

This is kind of a time sensitive process and with every day we keep giving G CSF phenotype of sounds that we generate along with Democratic stem cells changes with those T cells that are then more likely to induce both acute and chronic graft versus host disease. Currently there is an urgent need rather than unmet need for rapid mobilizing agents. One compound that we tend to use Explorer EXE firing people who do not mobilize with G CSF. It’s a CX here for inhibitor. 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 eel, 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 collected was 4,000,000 cells per cagey of their sippy and what’s expected. So that’s a very good number in terms of the overall picture. How we look at it. Then the design. Most experiment with the primary transparent secondary transplant on the left hand side. There able to show that using this combination they were able to show at 23 fold higher engraftment compared to using donors were mobilized with just five days alone or plexi for single agent. 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 graft versus host disease complication that ensures 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 with this drug and that study was not based on randomized trial is based on a single arm study where they study about 42 patients. 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 two .125 again pretty late in the game by up by both Week 49 after initiating at a
NOTE Confidence: 0.7914078
00:10:08.876 --> 00:10:10.892 median follow up for 14 months.
NOTE Confidence: 0.7914078
00:10:10.892 --> 00:10:14.028 In that study 71% of the patients at
NOTE Confidence: 0.7914078
00:10:14.028 --> 00:10:16.710 discontinue the drug due to toxicities.
NOTE Confidence: 0.7914078
00:10:16.710 --> 00:10:17.023 Again,
NOTE Confidence: 0.7914078
00:10:17.023 --> 00:10:18.901 the other important point to note
NOTE Confidence: 0.7914078
00:10:18.901 --> 00:10:20.927 here is that there are currently
NOTE Confidence: 0.7914078
00:10:20.927 --> 00:10:22.973 no drugs approved in this space.
NOTE Confidence: 0.7914078
00:10:22.980 --> 00:10:24.100 Based on the randomization.
NOTE Confidence: 0.7914078
00:10:24.100 --> 00:10:26.545 This led to the reach three study which
NOTE Confidence: 0.7914078
00:10:26.545 --> 00:10:28.325 was studying ruxolitinib against best
NOTE Confidence: 0.7914078
00:10:28.325 --> 00:10:30.568 available therapy in patients with steroid,
NOTE Confidence: 0.7914078
00:10:30.570 --> 00:10:31.890 refractory or steroid dependent.
NOTE Confidence: 0.7914078
00:10:31.890 --> 00:10:33.540 Chronic graft versus host disease.
NOTE Confidence: 0.7914078
00:10:33.540 --> 00:10:35.200 This was a multinational
NOTE Confidence: 0.7914078
00:10:35.200 --> 00:10:37.275 trial led by Doctor Zaiser.
NOTE Confidence: 0.7914078

20
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.
to greater than .25 milligrams.

Today, after two unsuccessful attempts to taper the dose, obviously you’re worried about the graft rejection. So prior to the study enrollment, we had to confirm everybody had decent engraftment. The randomization was stratified by chronic graft versus host disease. Great people were allowed to go either on ruxolitinib 10 milligrams to be ID and on the backbone of steroids. Percent minus calcineurin inhibitors.
or best available therapy.

About six cycles.

Were given in the intervention

alarm and then the analysis was done

correctly to the start of summer cycle.

At the end of 6 cycle people around

the best available therapy are what

allowed indeed to crossover the excellent in.

At the end of 6 cycle people around

the best available therapy are what

allowed indeed to crossover the excellent in.

If there was a need, the primary endpoint of the study

was overall response rate at Week

as defined by the NIH consensus

criteria and the key secondary

endpoints were failure free

survival and

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 GV HD 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
rate right? But again, with the intervention arm with excellent and it was 76.4% compared to 60.4%. But the best available therapy are the median duration or best overall response was 6.2 four months unpaid but was not reached in their excellent in a bar. In conclusion this is the first successful randomized phase three trial for the chronic GV HD space, or excellent in a demonstrated significantly higher overall response rate at Week 24. There was improvement in failure free survival significantly improved symptom improvement. 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 which down regulates 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. 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, or twice 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 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.

Here is the safety and tolerability. 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 GVHD screening or not, but it was refractory and refractory number of organs involved. Number of prior lines of therapy 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 rasterizer reported 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
responders or nonresponders achieving improvement in their symptoms scores. In conclusion this drug element Bell incident is well tolerated and has achieved clinically meaningful outcomes. Response rates are greater than 70% with both treatment arms, including in patients who failed ibrutinib and Jak inhibitors. Switching gears will talk about the cells. The reason for graft versus host disease or the T cells that are coming here. The trial initially done at Stanford is explored to see if we can isolate self populations to decrease after sostis is historically the way.
we’ve tried to diploid cells are XY or we try to extract pantycelyn, plead or use drugs like ATG Witcher invite. We’re depleting agents toxin is more recent addition to the field of transplantation, which kinds of depletes the cell in the setting of haploidentical transplantation? What investigators at Stanford Ed. Was in the preclinical models. 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 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. Amateur quite stem cells and T. Rex cells were extracted out, kept and then infused, and a 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
NOTE Confidence: 0.8181829
00:24:07.435 --> 00:24:09.891 age group and were thought not
NOTE Confidence: 0.8181829
00:24:09.891 --> 00:24:11.855 eligible to receive transplantation,
NOTE Confidence: 0.8181829
00:24:11.860 --> 00:24:14.612 but 44% of the patient get one cycle
NOTE Confidence: 0.8181829
00:24:14.612 --> 00:24:16.321 of intensive chemo consolidation
NOTE Confidence: 0.8181829
00:24:16.321 --> 00:24:19.435 and 38% get second layer of chemo
NOTE Confidence: 0.8181829
00:24:19.435 --> 00:24:21.600 consolidation and then their random
NOTE Confidence: 0.8181829
00:24:21.675 --> 00:24:24.015 honest to get either placebo osrs
NOTE Confidence: 0.8181829
00:24:24.015 --> 00:24:26.291 study agent which was CC-486 which
NOTE Confidence: 0.8181829
00:24:26.291 --> 00:24:28.843 is or a laser sighted in in that
NOTE Confidence: 0.8181829
00:24:28.850 --> 00:24:30.960 there was overall survival advantage
NOTE Confidence: 0.8181829
00:24:30.960 --> 00:24:33.949 as shown in the right top corner.
NOTE Confidence: 0.8181829
00:24:33.950 --> 00:24:36.218 I adore you present it as an extension of
NOTE Confidence: 0.8181829
00:24:36.218 --> 00:24:38.666 that people have now done subgroup analysis,
NOTE Confidence: 0.8181829
00:24:38.670 --> 00:24:40.764 coming back to the left hand
NOTE Confidence: 0.8181829
00:24:40.764 --> 00:24:43.153 side here Doctor Way and up to
NOTE Confidence: 0.8181829
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
00:25:15.861 --> 00:25:17.613 make a case suggesting that we
00:25:17.613 --> 00:25:18.930 are getting more transplantation
00:25:18.930 --> 00:25:21.240 at higher frequency in that arm.
00:25:21.240 --> 00:25:22.965 Basically did not alter the
00:25:22.965 --> 00:25:24.305 eventual overall survival, however,
00:25:24.305 --> 00:25:26.745 we should keep in mind the study was
00:25:26.745 --> 00:25:29.169 not designed to answer that question,
00:25:29.170 --> 00:25:31.340 so that leads us to the next
00:25:31.340 --> 00:25:34.224 segment of this as to how we can
00:25:34.224 --> 00:25:35.728 address limitations and propel.
00:25:35.730 --> 00:25:36.765 Understands of allogeneic
00:25:36.765 --> 00:25:37.800 stem cell transplant,
00:25:37.800 --> 00:25:40.760 so in this coming year ALR several study
00:25:40.760 --> 00:25:43.540 designs to do this in the backdrop of.
00:25:43.540 --> 00:25:45.350 Was that animal study design
00:25:45.350 --> 00:25:46.473
working with Doctor Probie?
We have a multicenter study
That we we 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 relapse 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
00:29:18.232 --> 00:29:20.736 refractory large cell lymphoma,
NOTE Confidence: 0.84160817
00:29:20.740 --> 00:29:22.627 transformed follicular lymphoma.
NOTE Confidence: 0.84160817
00:29:22.627 --> 00:29:25.772 The overall response rates seen
NOTE Confidence: 0.84160817
00:29:25.772 --> 00:29:28.464 in clinical trials have varied
NOTE Confidence: 0.84160817
00:29:28.464 --> 00:29:31.164 between 50 and upwards of 80%.
NOTE Confidence: 0.84160817
00:29:31.170 --> 00:29:33.574 Complete remission rates, however,
NOTE Confidence: 0.84160817
00:29:33.574 --> 00:29:38.298 are only in the order of 40 to 50%.
NOTE Confidence: 0.84160817
00:29:38.300 --> 00:29:40.808 This is significantly improved
NOTE Confidence: 0.84160817
00:29:40.808 --> 00:29:43.316 compared to the previously
NOTE Confidence: 0.84160817
00:29:43.316 --> 00:29:45.289 established standards of care.
NOTE Confidence: 0.84160817
00:29:45.290 --> 00:29:47.900 But still leaves some room for
NOTE Confidence: 0.84160817
00:29:47.900 --> 00:29:50.245 improvement and then with Brexit
NOTE Confidence: 0.84160817
00:29:50.245 --> 00:29:52.835 catagen and mantle cell lymphoma.
NOTE Confidence: 0.84160817
00:29:52.840 --> 00:29:55.200 Also very remarkable results with
NOTE Confidence: 0.84160817
00:29:55.200 --> 00:29:58.031 overall response rates of 93% and
NOTE Confidence: 0.84160817
00:29:58.031 --> 00:30:00.386 complete response rates of 67%. 
Looking at studies of these cellular therapies and some of the risk factors associated with worse progression, free survival and overall survival, 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
NOTE Confidence: 0.8383559
multivariable models in patients
NOTE Confidence: 0.8383559
multivariable models in patients treated with AXI cottage inside alusil.
NOTE Confidence: 0.8383559
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 what about
the biology of the tumor itself?
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% response rate. The follow-up is still short on this study.
but there were definitely complete remission rates, including in patients with previously received CD 19, 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...
00:32:56.360 --> 00:32:58.240 looked at targeting Bicistronic,

00:32:58.240 --> 00:33:00.885 assisting with a bicistronic vector

00:33:00.885 --> 00:33:04.803 targetting CD 19 and CD 22 and

00:33:04.803 --> 00:33:07.554 the importance of this is that there

00:33:07.640 --> 00:33:10.460 are two independent cars that are

00:33:10.460 --> 00:33:13.262 delivered in a single retroviral vector.

00:33:13.262 --> 00:33:16.489 They have humanized binders and in addition

00:33:16.489 --> 00:33:19.860 to the four one baby costimulatory domains,

00:33:19.860 --> 00:33:21.740 there’s also an OX40

00:33:21.740 --> 00:33:23.245 costimulatory domain, which.

00:33:23.245 --> 00:33:26.070 Would lead to improved persistence,

00:33:26.070 --> 00:33:28.611 and so from this study presented at

00:33:28.611 --> 00:33:31.824 ASCO now we have the Auto 3 Alexander

00:33:31.824 --> 00:33:34.384 study that was presented at this

00:33:34.384 --> 00:33:37.408 year’s ASH where in addition to dewali

NOTE Confidence: 0.8052864
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,
as well as a third cord that received 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
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, or grades three and above of neurotoxicity were quite low. So CRS over grades three and above. Only 2% and neurotoxicity City green above only four percent. Importantly, none of these patients received any prophylactic measures to prevent the development of CRS or neurotoxicity. An overall, the number of patients that received tocilizumab was low at 16%. And an patients did not receive steroids. 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. And there was this study that
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, history, chemistry 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 city 58, 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 CD 58. Expression and. Even though even in the patients with a C 58 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
NOTE Confidence: 0.8078168
00:41:22.775 --> 00:41:25.428 antitumor activity in in Vivo Anet
NOTE Confidence: 0.8078168
00:41:25.428 --> 00:41:27.368 overcame the city 58 knockout.
NOTE Confidence: 0.8078168
00:41:27.370 --> 00:41:29.902 So this data was actually extremely
NOTE Confidence: 0.8078168
00:41:29.902 --> 00:41:31.620 important, in my view,
NOTE Confidence: 0.8078168
00:41:31.620 --> 00:41:35.419 because it it shows us that City two Co.
NOTE Confidence: 0.8078168
00:41:35.420 --> 00:41:37.116 Stimulation is very important.
NOTE Confidence: 0.8078168
00:41:37.116 --> 00:41:39.236 This wasn’t known before we,
NOTE Confidence: 0.8078168
00:41:39.240 --> 00:41:42.552 we thought that these car T cells were
NOTE Confidence: 0.8078168
00:41:42.552 --> 00:41:45.526 already endowed with all the necessary
NOTE Confidence: 0.8078168
00:41:45.526 --> 00:41:47.594 costimulation that they needed.
NOTE Confidence: 0.8078168
00:41:47.600 --> 00:41:50.896 However, we now know based on this study,
NOTE Confidence: 0.8078168
00:41:50.900 --> 00:41:53.336 that there are other Co stimulators
NOTE Confidence: 0.8078168
00:41:53.336 --> 00:41:56.270 on the surface of the tumor cells,
NOTE Confidence: 0.8078168
00:41:56.270 --> 00:41:59.807 such as CD 58 that also really matter and
NOTE Confidence: 0.8078168
00:41:59.807 --> 00:42:03.290 that they can drive car T cell efficacy.
NOTE Confidence: 0.82577026
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.

In humans. 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 you know 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
presented the interim efficacy, safety and PK data, so patients qualified for this study if they had high grade B cell lymphoma with Mll and BCL, two or BCL six translocations, so double hit or triple hit large cell lymphoma with an epic score of three or above before enrollment they had to have had at least 2 lines of an anti CD. have had at least 2 lines of an anti CD. 20 monoclonal antibody. Sorry not 2 lines but two cycles and enter second containing regimen and they had to have had a positive PET scan after two Step 2 cycles of treatment
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 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
00:47:18.337 --> 00:47:21.240 was associated with a greater expansion.

00:47:21.240 --> 00:47:24.586 Again, this is suggestive of improved T cell fitness in the first line treatment.

00:47:28.290 --> 00:47:31.195 So it’s this study you know well doesn’t have very long follow up.

00:47:31.195 --> 00:47:33.780 It does provide us with some insights into the pharmacology of access L for patients who are exposed to fewer prior therapies.

00:47:33.780 --> 00:47:36.384 Now I’m going to shift gears to relapse refractory indolent non Hodgkin lymphoma.

00:47:36.384 --> 00:47:38.120 I’ll present you the data from Zuma five with AXI Cap to Gene and then from ilaris study with tisagenlecleucel cell so.

00:47:40.719 --> 00:47:43.060 I’ll present you the data from Zuma.

00:47:48.550 --> 00:47:51.469 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
00:48:41.455 --> 00:48:44.165 in both follicular lymphoma and
00:48:44.165 --> 00:48:46.756 marginal zone lymphoma when they
00:48:46.756 --> 00:48:49.396 looked at the overall response rates
00:48:49.396 --> 00:48:52.890 very high again in the above 90%.
00:48:52.890 --> 00:48:53.878 And CRA,
00:48:53.878 --> 00:48:56.348 it’s also very high anywhere
00:48:56.348 --> 00:48:59.190 from 70 to 80% progression free.
00:48:59.190 --> 00:49:02.010 Survival was actually noted to be
00:49:02.010 --> 00:49:05.040 longer in the follicular lymphoma group
00:49:05.040 --> 00:49:08.046 compared to the marginal as opposed
00:49:08.131 --> 00:49:10.909 to the marginal Zone lymphoma group.
00:49:10.910 --> 00:49:13.748 But the response rates importantly were
00:49:13.748 --> 00:49:16.749 consistent across all of the subgroups,
00:49:16.750 --> 00:49:18.616 including Flipi score,
high tumor burden or prior therapies.

And the median duration of response, particularly in the follicular lymphoma Group, has not been reached and.

Is a 78% duration of response in patients who, with follicular lymphoma, who achieved a CR.

There were important to note a grade three and above adverse events in 86% of the patients. Most of them were cytopenias and infections and their worst three Grade 5 adverse events, one of which was related to multisystem organ failure with cytokine release 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, 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 kind kinds like interferon gamma L6 TNF Alpha. 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
refractory disease and the duration
NOTE Confidence: 0.84090036
of response is quite durable,
NOTE Confidence: 0.84090036
with a plateau in this curve.
NOTE Confidence: 0.9070388
I'm reaching three years now.
NOTE Confidence: 0.9070388
As so, um, this is the transcendent study.
NOTE Confidence: 0.9070388
The mantle cell cohort.
NOTE Confidence: 0.9070388
This was just presented at ASH
NOTE Confidence: 0.9070388
and this is looking at lysosome
NOTE Confidence: 0.9070388
now in mantle cell lymphoma.
NOTE Confidence: 0.9070388
This product is different from AXA
NOTE Confidence: 0.9070388
capture Gene because it has a defined
NOTE Confidence: 0.9070388
composition of T of CD8 and CD4T
NOTE Confidence: 0.9070388
cell components that are administered
NOTE Confidence: 0.9070388
separately at equal target doses.
NOTE Confidence: 0.9070388
So flu Cy conditioning lies to
NOTE Confidence: 0.9070388
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 actually had an elevated key. proliferation index, 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 relapse CLL and very interesting. Lee had very high complete response rates of 45% and really high rates of undetectable MRD, both in the blood flow and in the bone marrow by NGS and even when they looked at patients with failed BTK here in the second. They had a very impressive rates of complete response, so this was already presented at Ash of 2019 and what was actually presented this year at Ash was. 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
NOTE Confidence: 0.8644943
00:58:47.565 --> 00:58:51.397 response rate and the majority of
NOTE Confidence: 0.8644943
00:58:51.397 --> 00:58:53.917 patients had undetectable MRD.
NOTE Confidence: 0.8644943
00:58:53.920 --> 00:58:56.960 In their in their blood.
NOTE Confidence: 0.8644943
00:58:56.960 --> 00:59:00.456 So in summary, you have very rapid responses,
NOTE Confidence: 0.8644943
00:59:00.460 --> 00:59:02.956 high overall response rate, high rates
NOTE Confidence: 0.8644943
00:59:02.956 --> 00:59:06.138 of CR with lysis cell and ibrutinib.
NOTE Confidence: 0.8644943
00:59:06.140 --> 00:59:09.628 And even though this is no direct comparison,
NOTE Confidence: 0.8644943
00:59:09.630 --> 00:59:11.630 it certainly looks better than
NOTE Confidence: 0.8644943
00:59:11.630 --> 00:59:14.207 the data with lysis cell alone
NOTE Confidence: 0.8644943
00:59:14.207 --> 00:59:16.187 for relapsed refractory CLL.
NOTE Confidence: 0.8644943
00:59:16.190 --> 00:59:19.235 So I just wanted to I know
NOTE Confidence: 0.8644943
00:59:19.235 --> 00:59:21.429 we’re running out of time,
NOTE Confidence: 0.8644943
00:59:21.430 --> 00:59:24.046 but for people who treat leukemia,
NOTE Confidence: 0.8644943
00:59:24.050 --> 00:59:28.082 I did want to mention some of the upcoming.
NOTE Confidence: 0.8644943
00:59:28.090 --> 00:59:31.247 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 is the Auburn phase three study, Cassiopeia, which looks at his agenda occlusal in patients who are MRD positive after first line therapy and then also summa for looking at exit cap to gene in patients with relapsed refractory LL. So so with that, you know I’d like to end and and I’m happy to take any questions. OK. So, Doctor Gordon Dr Sophie. 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 and. I'll start with some questions about Milo dysplasia, starting from the top. This is for Doctor Gowda. And I'll just, I'll 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 donors?
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
you kind of laid these people so you have to take all those with a pinch of salt. I would say enter specific protocol based. Certainly worth considering that the reason that prospective study that says in elderly people Apple may not be that great for email from the registry again, but there are at the same time you do the mismatches in the registry limitations. There are equal numbers that suggest it’s efficacious. So if you think there’s a high risk disease and there’s no really good option. I would certainly get an 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. I’ll follow up with my own question. Do you think this data is sufficient?
We should consider this.

Or this requires further study and end insurance approval, of course.

Yeah, I mean, I think that the duration is short,

we need longer duration,

at least beyond the year.

For these patients, you know.

That being said,

we 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,
I think that will be a stronger push to move it to frontline for high risk groups.

Right, right?

OK couple of questions on the graft versus host disease studies.

I from Doctor Challace, do we have a sense of what? Monoclonal antibodies. Did any receive a brute nib? And now it’s just.

Did anyone receive rocks? Although that may refer to the crossover.

Hello diary, I probably also know the answer to this.
I don’t know if you want me to feel this one or.

Yeah, sure yeah.

So yes.

It says it says.

Why was the local investigator on this study so best alternative?

Therapy was a long list of standard non FDA approved treatments ’cause there aren’t any FDA approved treatments for for chronic GV HD, but they did include ibrutinib.

They included photo pheresis.

Those were common ones.

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 based on this phase, three data looks like. Take a stab at that. Yeah, I think we should understand that I put in the beta was approved based on Phase 1B. Phase two study design. 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, 025, 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,
because.

It's not a prude, although we are waiting for the approval to come through anytime I might be tempted to try that if it's a highly fibrotic question earlier on but.

Side effects of reboot.

Your name can be significant in my personal biased opinion.

Set opinions with Rocks is an issue, but again,

in this trial the show that quality of life cytopenias taking all that into account rocks was way better compared to the other,
so I may be tempted to use that up front and we’re already doing it in some of our case this, 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.

Every every come are getting randomized and they’ve only median.

As for the trial right?

And it was it was tested in a randomized fashion that turned out to be negative.

We can argue that Ivy and oral, despite mechanistic things, are not the same drug.

What we're trying to achieve is couple of two different things.

There’s some confusion now with the clinical trial data as to what is the right timing for the transplant, because it’s very cleverly
NOTE Confidence: 0.8174205
01:08:33.344 --> 01:08:35.600 articulated by the company in terms of how this needs to be done.
NOTE Confidence: 0.8174205
01:08:35.661 --> 01:08:37.418 So we all agree CR one is a major entry point,
NOTE Confidence: 0.8174205
01:08:39.415 --> 01:08:40.790 especially for intermediate and advanced rest.
NOTE Confidence: 0.8174205
01:08:40.790 --> 01:08:42.620 How many cycles of consolidations are needed?
NOTE Confidence: 0.8174205
01:08:44.760 --> 01:08:46.108 It’s an open field, unlike the hydac for the good risk groups.
NOTE Confidence: 0.8174205
01:08:46.108 --> 01:08:49.030 So if we can create outpatient based regiments with oral set aside in equal and drug.
NOTE Confidence: 0.8174205
01:08:49.030 --> 01:08:51.232 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 then 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 three 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,
01:10:58.296 --> 01:10:59.380 making saying it’s antifibrotic
NOTE Confidence: 0.81454706
01:10:59.430 --> 01:11:00.350 and anti-inflammatory.
NOTE Confidence: 0.81454706
01:11:00.350 --> 01:11:01.890 That would be a breakthrough.
NOTE Confidence: 0.7963529
01:11:04.350 --> 01:11:06.612 Right, so think we we
NOTE Confidence: 0.7963529
01:11:06.612 --> 01:11:08.460 probably need to wrap up.
NOTE Confidence: 0.7963529
01:11:08.460 --> 01:11:11.490 There’s a kudos to Doctor Trophy
NOTE Confidence: 0.7963529
01:11:11.490 --> 01:11:14.120 for pronouncing the Carty names.
NOTE Confidence: 0.7963529
01:11:14.120 --> 01:11:15.444 I’m sure I was.
NOTE Confidence: 0.7963529
01:11:15.444 --> 01:11:17.672 I was very impressed actually and
NOTE Confidence: 0.7963529
01:11:17.672 --> 01:11:21.104 thank you so much buddy else.
NOTE Confidence: 0.7963529
01:11:21.110 --> 01:11:23.742 Can do that? Yeah yeah thank you so
NOTE Confidence: 0.7963529
01:11:23.742 --> 01:11:25.979 much Stewart for moderating such a,
NOTE Confidence: 0.7963529
01:11:25.980 --> 01:11:28.068 you know, a very lively Q&A.
NOTE Confidence: 0.7963529
01:11:28.070 --> 01:11:30.116 And thank you Doctor Sufyan doctor
NOTE Confidence: 0.7963529
NOTE Confidence: 0.7963529
01:11:31.900 --> 01:11:33.982 I would also like to thank
01:11:33.982 --> 01:11:36.070 me go day to work very

01:11:36.070 --> 01:11:38.507 hard behind the scenes to get this

01:11:38.507 --> 01:11:40.950 series going and this is recorded as

01:11:40.950 --> 01:11:42.685 we discussed all of the

01:11:42.685 --> 01:11:44.073 recordings will be available.

01:11:44.080 --> 01:11:46.376 You can claim CME credit if you

01:11:46.376 --> 01:11:49.027 provide us some feedback about how we

01:11:49.027 --> 01:11:51.415 can improve this going forward and.

01:11:51.420 --> 01:11:53.959 Hopefully next year we will have

01:11:53.960 --> 01:11:56.795 a hybrid model of in person and

01:11:56.795 --> 01:11:59.055 virtual component and looking forward

01:11:59.055 --> 01:12:01.600 for a great 2021 for everybody.

01:12:01.600 --> 01:12:04.138 Thank you so much and looking

01:12:04.138 --> 01:12:06.680 forward to next year post Ash.

01:12:06.680 --> 01:12:11.104 Thank you. Excellent, thank you.