Today we're going to give an update on cellular therapies and stem cell transplant.

From ash, this session will be moderated by myself and Doctor Delgado and Doctor Stuart Seropian, who's our director of the stem cell transplant program, and also joined us and will help moderate the session together with low Heath and myself.

So we will get started.
will give some updates on cortisol therapy for hematologic malignancies, so I’m going to go ahead and get started, so thank you again for joining everyone. I will probably leave the questions for the end. So these are my disclosures. And just to give everyone a little bit of a background today. I’m just going to show a general schematic for car T cells, so as you know, car T cell therapy. Has been approved in the last five years to treat patients with hematologic malignancies. The T cells are genetically modified.
to target tumor cells and this can be done in the absence of MHC one and two. Expression on the surface of the tumor cells.

So there’s a targeting domain. That binds to the antigen on the cell surface.

There’s a linker, and then there’s a costimulatory domain that gives this car T cells, proliferative capacity, and AT cell activation domain.

So we have currently multiple FDA approved car T cell therapies. It’s hard to believe the majority of them are approved in the setting of.
B cell lymphoma.

So we have four products currently

Also counted in Merluza Lantis again coucil,

and they’re currently approved for

patients with relapsed refractory

B cell lymphoma after at least

two lines of systemic therapy.

Brecksville Cottage in was recently

approved in patients with mantle

cell lymphoma as well as in

adults with relapsed refractory B.

Cell A allows so these are two more

recent approvals and then in the

multiple myeloma arena the target

is bmet and I’m happy to say that
we not only have I decapped agenda

cluzel approved in patients with

with failed at least four lines of

prior therapy but very recently.

There’s a new approval of Celtic

the Loosle in the same

refractory patient population.

So this is the summary of the

efficacy after two lines of therapy

efficacy after two lines of therapy

for the currently approved products.

As you can see,

there are very high overall response

rates from the three randomized

phase three trials.

Complete response rates vary anywhere
between 40 to 58% and you can see that about 40% of patients.
There's a 40% progression free survival. Basically at two years, which is definitely not bad for.
Refractory patient population that otherwise would have. Expected very poor outcomes.
The toxicity is as you are familiar with by now are.
Twofold cytokine release syndrome and neurologic toxicity, which. It happens in the majority of patients, however,
grade three to four CRS and neurologic toxicity fortunately are less common,
and there's some variability between the products in terms of the grades and severity of CRS, and neurologic toxicity.

So what was exciting at this year's ASH was that there have been efforts made to move these CAR T cell therapies further up front in the treatment of patients with lymphoma. Given that this type of therapy is doing so well in the relapse refractory setting, could it potentially replace autologous stem cell transplant so there were three...
studies that were presented and are currently published and those resume as seven with Axicabtagene sailu. So Belinda with the decision Chzel and the transform study with Lisa Captain Marlow so and they looked at high risk diffuse large B cell lymphoma patients that were either refractory. First line treatment, which is usually our job. Or that relapse early after first line treatment, and patients were randomized to either cortisol therapy or the standard of care which is salvage therapy with autologous stem cell transplant.
So I will start with Zuma 7. Basically, this is again an autologous second generation CD19 directed car T cell therapy that’s currently approved after two lines of therapy and in the study design is that patients had relapsed refractory disease within 12 months of adequate first line chemo it was intended to proceed to autologous stem cell transplant so they were stratified by first line treatment response. And second line age adjusted it be in demised access L 2 * 10 they were in demised access L 2 * 10 to the 6th chord, T cells per KG.
After receiving some Lymphodepletion

Kiem Lympho,

depleting chemotherapy and cytoxan,

or the standard of care which was two to three cycles of investigator selected.

Usually platinum based chemotherapy.

'cause that’s what we use in practice,

either rice or our depth.

And patients that achieved either complete or partial response went on to achieve to receive a stem cell transplant.

Whereas patients that did not achieve a CR or PR were off protocol and this is important as you’ll see in a distinction with Belinda trial this Zuma seven study did not allow for
any bridging therapy prior to car T.

And there was no crossover, so patients who did not respond and could not go on to transplant or did not crossover to the Axis alarm. Some of them actually 56% did receive subsequent cellular in no therapy. But that was not done on trial. So you know what happened to these patients? Well, you see that they enrolled 359 and 180 received access.

Actually, we randomized accela 179 the standard of care, we randomized accela 179 the standard of care,
and then when you look at what happened to them out of 100 and 8178 underwent leukapheresis 172 receiving for depletion chemotherapy and 170 received access selling fusion. So 94% of the starting patients. Actually received access out which they were randomized to, whereas in the standard of care arm out of 179 patients. Only about 64 of them received. Stem cell trench transplant, which is 36% of patients, and this actually is not uncommon in clinical practice because many of these patients end up for one
NOTE Confidence: 0.84452435
00:08:24.826 --> 00:08:26.430 reason or another.
NOTE Confidence: 0.84452435
00:08:26.430 --> 00:08:29.028 Not responding to the salvage chemotherapy,
NOTE Confidence: 0.84452435
00:08:29.030 --> 00:08:31.450 or they develop organ toxicity.
NOTE Confidence: 0.84452435
00:08:31.450 --> 00:08:32.978 They may not have.
NOTE Confidence: 0.84452435
00:08:32.978 --> 00:08:35.078 By that point, their lympho depleted,
NOTE Confidence: 0.84452435
00:08:35.078 --> 00:08:37.750 so they may not have fit T cells.
NOTE Confidence: 0.84452435
00:08:37.750 --> 00:08:38.686 They may not.
NOTE Confidence: 0.84452435
00:08:38.686 --> 00:08:40.870 They may not have fit stem cells
NOTE Confidence: 0.84452435
00:08:40.941 --> 00:08:42.908 for us to be able to collect.
NOTE Confidence: 0.84452435
00:08:42.910 --> 00:08:46.870 So a minority actually made it to transplant.
NOTE Confidence: 0.84452435
00:08:46.870 --> 00:08:49.888 So when we look at the
NOTE Confidence: 0.84452435
00:08:49.890 --> 00:08:50.942 baseline characteristics,
NOTE Confidence: 0.84452435
00:08:50.942 --> 00:08:53.572 they were pretty well distributed
NOTE Confidence: 0.84452435
00:08:53.572 --> 00:08:55.150 among the groups.
NOTE Confidence: 0.84452435
00:08:55.150 --> 00:08:56.734 As you can see,
NOTE Confidence: 0.84452435
74% of patients were primary refractory.

And then 26% of patients had relapsed within a 12 months.

There were some high grade B cell lymphomas, including double and triple hit,

17% duel over X pressers,

and Mick rearranged patients.

So when we look at the event free survival, which was their primary end point for the study,

you can see that the 24 month event free survival was 40.5% in the access of ARM compared to only 16.

.3% in the standard of care arm, and that was actually true when they
looked at each of the individual.

Subgroups by age response to first line therapy and whether they had high grades at B cell lymphoma, including double, triple hit or double expresser lymphoma.

And when you look at the complete response rates, so overall response was 83% in the access alarm and 50% in standard of care and complete remission rates were 65 versus 32%.

So there is some confounding in terms of looking at the overall survival benefits, because as I mentioned earlier,
56% of patients in the standard care arm received subsequent cellular immunotherapy of protocol. So this is the event free survival curve, here again showing a dramatic improvement. Median event free survival two months versus 8.3 months in the access alarm, the hazard ratio favored accessible for all of the different subgroups, including really high risk disease. Again, this is reflected in the progression free survival curves that separated and then when you look at the median overall survival was 35 months in the standard of care arm and it was
not reached in the axle arm and.

You know it, it’s going again to be difficult to see.

It’s curbs here that in terms of overall survival that are dramatically different from each other.

nearly three times more patients that were randomized to access L received definitive therapy versus standard of care, and there was a significant improvement in event free survival and response rate compared to standard of care.

So this Soma 7 May actually mark a paradigm shift where you access L.
should be considered the new standard of care for patients with second line relapse. Refractory large B cell lymphoma.

This is the transform study, so it looked at Lisa Captain Marlow, but the I just want to point out that this car T cell therapy is slightly different from access L because there's a defined composition of CD8 and CD4T cell components that are. Expanded separately, and then they're administered to the patient in equal target dosing. So when we looked at the study design,
It's very similar. This did allow some bridging therapy, but then they performed a PET scan prior to lymphodepletion and Light and Lisle. And if there was no response by 9 weeks or progression at anytime, a crossover to the lysis alarm was allowed. So when you look at the event free survival again with a median follow-up of six months, there was a significant improvement there of 63.3% in event free survival of 63.3% compared to 33.4% at six months, and that held continue to hold at 12
00:13:04.519 --> 00:13:07.242 months even though there was some decline.
NOTE Confidence: 0.818740913
00:13:07.250 --> 00:13:11.133 So 44.5% versus 23.7%.
NOTE Confidence: 0.818740913
00:13:11.133 --> 00:13:13.498 Now again very similar results.
NOTE Confidence: 0.818740913
00:13:13.500 --> 00:13:17.329 So what we saw in Zuma 7?
NOTE Confidence: 0.818740913
00:13:17.330 --> 00:13:19.542 The complete response rates
NOTE Confidence: 0.818740913
00:13:19.542 --> 00:13:22.307 in the Lisle arm were
NOTE Confidence: 0.945483056666667
00:13:22.310 --> 00:13:24.710 66% versus only 39% in
NOTE Confidence: 0.945483056666667
00:13:24.710 --> 00:13:27.220 the standard of care arm.
NOTE Confidence: 0.87196846
00:13:29.830 --> 00:13:32.350 This is progression free survival.
NOTE Confidence: 0.87196846
00:13:32.350 --> 00:13:36.316 Again, even looking at 12 month
NOTE Confidence: 0.87196846
00:13:36.316 --> 00:13:40.580 data that is 52% in the Lisle
NOTE Confidence: 0.87196846
00:13:40.580 --> 00:13:44.014 arm compared to 33.9% in the in.
NOTE Confidence: 0.87196846
00:13:44.014 --> 00:13:46.169 The standard of care arm.
NOTE Confidence: 0.87196846
00:13:46.170 --> 00:13:49.224 So significant improvement in PFS median
NOTE Confidence: 0.87196846
00:13:49.224 --> 00:13:53.587 PFS in the light in the Lysol CAP to gene.
NOTE Confidence: 0.87196846
00:13:53.590 --> 00:13:58.790 The lysis alarm was 14.8 months.

20
Versus only 5.7 months in the standard of care arm, which was the transplant arm and you know this is overall survival. Median overall survival was not reached in the Lisle arm and it was 16.4 months in the standard of care arm. The third phase three study was Belinda, which this is kymriah. Basically the autologous CD19 CAR T cell therapy and this is the study design. Patients were looking for ease that screening. They did receive optional bridging with a platinum based chemotherapy and.
The standard of care arm received salvage rice or or depth investigators investigators choice.

They then underwent a week six pet scan, and then they were received either to sigend, occlusal or standard of Care now the difference here being that patients who did not achieve a complete remission actually ended up receiving. Multiple lines of platinum based therapy and including a different platinum based therapy altogether so they may have had two different two or three different salvage regimens here. By the time they actually made
00:15:33.490 --> 00:15:37.389 it to stem cell transplant.

00:15:37.390 --> 00:15:37.950 And.

00:15:40.290 --> 00:15:44.454 The fact that they looked at this.

00:15:44.454 --> 00:15:47.499 They they based a lot of the UM.

00:15:47.500 --> 00:15:52.529 A lot of the criteria for non response.

00:15:52.529 --> 00:15:55.490 on the Week 6 assessment actually did

00:15:55.572 --> 00:16:02.406 So the patient characteristics

00:16:02.406 --> 00:16:04.358 were relatively equally

00:16:04.358 --> 00:16:06.878 distributed between the two arms.

00:16:06.880 --> 00:16:09.538 The median time from initial diagnosis.

00:16:09.540 --> 00:16:11.188 The randomization was similar

00:16:11.188 --> 00:16:13.660 about 8 months in both groups

00:16:13.660 --> 00:16:15.844 and the median time from the most

00:16:15.844 --> 00:16:17.781 recent relapse or progression to

NOTE Confidence: 0.778544301428571

NOTE Confidence: 0.942135833333333
randomization was about 1.4 months.

In the decision Lochloosa and 1.1 months in the standard of care arm.

So if you look now at, you know what patients are received. You can see that in the T sigend occlusal arm, almost 50% of patients received more than one cycle of. Chemotherapy prior to their lymphodepletion and then in the standard of care arm, 97% of patients received multiple cycles of chemotherapy, and, importantly, the median time to the actual infusion of the T cells and that isagen occlusal
arm was extremely long at 52 days and even in the United States was 41 days. But particularly in Europe, was longer at 57 days. So when they looked, surprisingly, when they looked at the event free survival, which was their primary endpoint, that was actually disappointingly the same in both the tisagenlecleucel and standard of care arm, so. You know why? Why did this happen? I mean, why was this study different from the prior to when you look at the
Week 6 assessment that they did after these patients received bridging therapy or salvage chemotherapy, you can see that in that isagen lochloosa ORM. 26% of patients actually had progressive disease compared to 14% in the standard of care arm, so they progressed before they were able to receive the lymphodepleting regimen and Corti. So they investigators for the study did point that out, that the progressive disease at week six was more frequent in patients in that isagen lochloosa ORM.
arm versus the standard of care and.
There were multiple meetings and and experts in the field were asked about why they thought that Belinda failed to show an improvement in event free survival. And there are several factors for this that I’m sure will guide their the development of future trials for them. So the first was the longtime to infusion with that Kymriah in Belinda 52 days compared to 29 days. Abelinda allowed multiple lines of chemotherapy, as bridging therapy,
which was different from Zuma 7 and transform. And Belinda also used lower dosing of lympho depleting agents, which are important for to obtain Disease Control in these patients that are not as heavily pretreated right because these patients had only received one prior line of therapy. So in Belinda, Cytoxan was only 900 milligram per meter squared over three days, and fludarabine was 75 per meter squared, whereas the other two trials had a higher cytoxan dose of 1500 milligrams and 90 milligrams.
Perimeter squared off loader being over three days. There were some differences in disease criteria. So Zuma 7 for example, enrolled only diffuse large B cell lymphoma patients whereas transform lymphoma patients whereas transform and Belinda allowed patients with 3B follicular lymphoma, which one could argue may be less aggressive. And the Belinda Trials definition of event free survival actually counts failure to achieve a response at the week 12 assessment as a negative incident. But due to the long gap to treatment,
some patients may not adequately respond to kymriah at that point, and they responded to kymriah after the 12 week mark without any additional therapy. So several factors for White failed. So what is Novartis going to do? Are they gonna pursue another trial using the same product? You know, trying to mimic the other two studies? They have moved away from that. They have moved on and what they actually announced was this a next generation platform that’s called T Charge that aims to revolutionize car T cell therapy and what it does
00:20:49.818 --> 00:20:52.268 is that it preserves T cell stemness
00:20:52.268 --> 00:20:54.824 the ability to self renew and mature
00:20:54.824 --> 00:20:57.659 that results in a product that has
00:20:57.659 --> 00:20:59.177 greater proliferative potential
00:20:59.177 --> 00:21:02.330 and fewer exhausted T cells and.
00:21:02.330 --> 00:21:05.430 They already presented at Ash.
00:21:05.430 --> 00:21:08.986 Now data from two first in human
clinical trials.
00:21:08.986 --> 00:21:10.510 So Y TB323IN lymphoma and PHE
885 in multiple myeloma.
00:21:10.510 --> 00:21:17.093 So there were two scientific posters
00:21:17.093 --> 00:21:19.812 that went along with the 1st in
human clinical trials and what they
00:21:19.812 --> 00:21:23.038 basically showed is that this T cell T
Give us a product that retains the immunophenotype, the of the input leukapheresis material, where naive and T central memory cells that are City 45 RO negative and CCR 7 positive are actually preserved as you see here.

As opposed to the traditional manufacturing approaches where the cells are.

So the the thought is that these cells this is the time will reduce the manufacturing time basically to less than
than two days because these cells are going to be able to go into the patient and expand and proliferate in vivo. So when you look again, these are called violent plots, there is. The Y TB323 core T cells here actually showed very similar central memory. T cell phenotype and stemness gene signatures as the input material here in red compared to to the standard autologous city 19 product where there's more of a T factor, memory phenotype and. The Stemness high signature is retained in the the new product where TP323
versus low stamina signature in the

conventional autologous product,

and this what this did is that it actually

when you they looked at a tumor model,

it showed better in vivo

This is a traditional manufacturing

and this is the T charge platform

where you can see that even

as low overdose as .1 times.

Went to the six here shown in blue.

Gives a response compared to .5.

Times tends to the six in the

traditional manufacturing so

fewer cells are actually a car.

T cells are required for tumor suppression
and even when they looked at the expansion.

The that they looked at in the blood by flow cytometry.

These cells were very potent and they actually had much better expansion. So there C Max was 40 times higher and AUC in the 1st 21 days was 33 times higher for Y TB323 as compared to their traditional manufacturing.

So this is what they used in the first in human study in patients with relapsed diffuse, large B cell lymphoma. And they saw some very encouraging data.

They had two dose levels and they treated about 20 patients.
15 patients who received this product at those level 2. They had a very high complete response rate of 73%. And they didn’t. Importantly. Also they didn’t see any safety signals beyond what was known and expected with the kymriah. So so. I think that all of the future studies that we’re going to see coming out of Novartis will be utilizing this platform and at some point they will probably compare this to the standard of care which is autologous stem cell transplant and this eventually I think,
NOTE Confidence: 0.8323023
00:25:24.010 --> 00:25:25.615 will replace kymriah.
NOTE Confidence: 0.8323023
00:25:25.615 --> 00:25:28.825 So just to shift gears quickly
NOTE Confidence: 0.8323023
00:25:28.825 --> 00:25:30.969 towards multiple myeloma,
NOTE Confidence: 0.8323023
00:25:30.970 --> 00:25:32.152 as you know,
NOTE Confidence: 0.8323023
00:25:32.152 --> 00:25:34.516 bmet is highly expressed and malignant.
NOTE Confidence: 0.8323023
00:25:34.520 --> 00:25:37.030 Plasma cells and multiple myeloma,
NOTE Confidence: 0.8323023
00:25:37.030 --> 00:25:40.066 and then higher concentrations of soluble
NOTE Confidence: 0.8323023
00:25:40.066 --> 00:25:43.239 BCMA are associated with poor outcomes,
NOTE Confidence: 0.8323023
00:25:43.240 --> 00:25:46.126 and that’s why this presented a
NOTE Confidence: 0.8323023
00:25:46.126 --> 00:25:48.830 very rational target for therapy.
NOTE Confidence: 0.8323023
00:25:48.830 --> 00:25:51.146 There’s a lot of competition in
NOTE Confidence: 0.8323023
00:25:51.146 --> 00:25:53.425 terms of antibody drug conjugates
NOTE Confidence: 0.8323023
00:25:53.425 --> 00:25:55.408 and bispecific antibodies,
NOTE Confidence: 0.8323023
00:25:55.410 --> 00:25:58.090 but in terms of car T cell therapies.
NOTE Confidence: 0.8323023
00:25:58.090 --> 00:25:59.410 The advantages that hopefully
NOTE Confidence: 0.8323023
it's a one and done deal.

If you have a good product and you don't have to continuously infuse antibodies.

So currently either captured in blue and Celtic after Geno Deluso are both approved in patients who've had four lines of therapy exposures to immunomodulatory agent proteasome inhibitors and also anti CD 38 monoclonal antibody like daratumumab.

So BB 2121 was the first product approved. This is the phase one two data with BCM a directed CAR T cells in multiple myeloma.

BB 2121 was the first product approved. So BB 2121 was the first product approved.
31% complete response rate in a heavily pretreated patient population. However, disappointingly, the median progression free survival was only about a year, and so people realize very early that. Uhm? Something else that needed to be done and that we need to improve upon this product. So Elk, RB 38 M is a car construct that actually has CV targeting 2 bfhne epitopes instead of 1. So it targets both VH1 and VH two, and when they looked at the data, the overall response rate was 100%.
00:27:24.413 --> 00:27:27.262 with complete response rate of 76%.

NOTE Confidence: 0.784530236470588

00:27:27.262 --> 00:27:30.454 And there's also another product where.

NOTE Confidence: 0.784530236470588

00:27:30.460 --> 00:27:32.624 Which is fully humanized,

NOTE Confidence: 0.784530236470588

00:27:32.624 --> 00:27:35.329 and that's enriched for early

NOTE Confidence: 0.784530236470588

00:27:35.329 --> 00:27:36.840 memory phenotype,

NOTE Confidence: 0.784530236470588

00:27:36.840 --> 00:27:38.772 so this kind of kills two

NOTE Confidence: 0.784530236470588

00:27:38.772 --> 00:27:40.060 birds with one stone.

NOTE Confidence: 0.784530236470588

00:27:40.060 --> 00:27:42.660 The cells hopefully persist longer,

NOTE Confidence: 0.784530236470588

00:27:42.660 --> 00:27:45.820 but because of their memory,

NOTE Confidence: 0.784530236470588

00:27:45.820 --> 00:27:49.200 early memory phenotype, but.

NOTE Confidence: 0.784530236470588

00:27:49.200 --> 00:27:49.964 Also,

NOTE Confidence: 0.784530236470588

00:27:49.964 --> 00:27:53.020 and being fully humanized,

NOTE Confidence: 0.784530236470588

00:27:53.020 --> 00:27:56.562 there is less development of of antibodies

NOTE Confidence: 0.784530236470588

00:27:56.562 --> 00:27:59.574 that result in destruction of these.

NOTE Confidence: 0.784530236470588

00:27:59.580 --> 00:28:03.171 Court T cells soak artitude one was

NOTE Confidence: 0.784530236470588

00:28:03.171 --> 00:28:06.370 a phase 1B2 study of Celtic catagen
all deluso and they presented at ash
their two year update and this is
very similar in terms of leukapheresis
lymphodepletion with fludarabine
then they had the soul to sell.
Just important to note that 87% of
patients were triple class refractory
and 42% were pentad drug refractory so
very heavily pretreated and resistant.
Patient population.
When you look at their overall
response rates.
I mean dramatic 97.9% and when you
look at stringent complete response
extremely high 82.5% the median
time to first response was quick
a month and median time to CR or
two point 9 months.
The percentage of patients that
are remaining progression free
at two years with 60.5%.
So that was better than what we
saw with the with Ida Captain Jean.

Which is you know important
in terms of quality of life?
And preservation of organ function.
So when we look at PFS and overall survival,
the two year PFS was a 71% median PFS and not reached compared to 60.5%.

Here in blue for patients who all comers compared to patients who achieve stringent CR that did significantly better in terms of progression. In patients who were MRD negative.

So, so that’s what denoted here in blue and. And as expected, the stringent CR patients would have better outcomes. And if you look at progression free and overall survival by MRD status again, significantly better. In patients who were MRD negative.
And MRD negativity negative patients actually maintain their progression free survival beyond the year.

So I'm going to switch gears now finally to a LL briefly.

But importantly, we now do not have just the tisagenlecleucel approval for a LL up to 25 years old. We also have Rex Cottage in Auto Lusso, recently approved in adults with relapsed refractory B cell.

So Ileana was in. Children and young adults are showing a significant improvement.
00:31:04.973 --> 00:31:07.912 in event free and overall survival
00:31:07.912 --> 00:31:09.812 with this agenda Clouseau.
00:31:11.708 --> 00:31:14.068 In this patient population,
00:31:14.068 --> 00:31:16.908 including patients who did not
00:31:16.908 --> 00:31:19.193 go onto to receive an allogeneic
00:31:19.271 --> 00:31:21.683 is zooma 3 with Brexit captain
00:31:21.683 --> 00:31:24.700 Jean with that showed 70.9% CR.
00:31:28.900 --> 00:31:31.475 Pretty high in adults with
00:31:31.475 --> 00:31:33.020 relapsed refractory LL,
00:31:33.020 --> 00:31:34.975 so this has already previously
00:31:34.975 --> 00:31:35.757 been published.
00:31:35.760 --> 00:31:38.868 But to point out what was interesting
00:31:38.868 --> 00:31:42.648 at ASH is that patients are relapsing
mainly because they’re losing CD 19
and so a lot of effort has gone into
finding ways to mitigate that risk.
So either by giving dual cars like City 1920.
Two giving off the shelf CAR products or
by re infusing CAR T cells in patients
who may be at high risk of free labs.
And so this was a study from CHOP at
Upenn in children and young adults
with relapsed refractory LL and they
basically followed patients from.
The time of their first scene,
Carty and if they had,
if they were minimal residual disease,
positive if they relapsed,
or if they saw that they had early B
cell recovery and or city 19 hematogen's in the bone marrow they basically re infuse them with the autologous CAR. T cell products within six months of their initial treatment and. Were reinfused because of him at Agones. Actually the majority of them 76% achieved a complete remission and also patients who had early B cell recovery but did not have measurable disease. A good proportion of them achieved CR without needing consolidation with a transplant. However, patients who were reinfused for non
response actually all of them pretty much.

Did not respond to the car T product,

so the clinical implications

for this are that cortisol re

infusions can prolong be sold.

A plasia in a subset of patients

with short car persistence and

this can reduce risk of relapse.

Rain fusions can induce remission

in patients with prior relapse,

but the remissions have limited durability,

and really it does not make sense to

reinfuse patients who were refractory

the first time around because

none of them actually responded.

So this is just the class effects
NOTE Confidence: 0.71652823375
00:33:51.135 --> 00:33:53.040 of the immune responses,
NOTE Confidence: 0.71652823375
00:33:53.040 --> 00:33:54.736 CRS, and neurologic toxicity.
NOTE Confidence: 0.71652823375
00:33:54.736 --> 00:33:57.870 You see that they’re very very variable
NOTE Confidence: 0.71652823375
00:33:57.870 --> 00:34:00.730 amongst the products in terms of
NOTE Confidence: 0.71652823375
00:34:00.730 --> 00:34:02.930 both CRS and neurologic toxicity,
NOTE Confidence: 0.71652823375
00:34:02.930 --> 00:34:04.565 and so then.
NOTE Confidence: 0.71652823375
00:34:04.565 --> 00:34:08.124 The the less disease burden patients have.
NOTE Confidence: 0.71652823375
00:34:08.124 --> 00:34:12.029 At the time of treatment at the better,
NOTE Confidence: 0.71652823375
00:34:12.030 --> 00:34:15.117 the outcomes and and the less toxicity.
NOTE Confidence: 0.71652823375
00:34:15.120 --> 00:34:16.765 And this is this is a lesson
NOTE Confidence: 0.71652823375
00:34:16.765 --> 00:34:17.470 that we’ve learned.
NOTE Confidence: 0.71652823375
00:34:17.470 --> 00:34:20.557 So the studies now are moving to
NOTE Confidence: 0.71652823375
00:34:20.560 --> 00:34:22.140 incorporate these therapies earlier
NOTE Confidence: 0.71652823375
00:34:22.140 --> 00:34:24.967 in the disease course or to debulk
NOTE Confidence: 0.71652823375
00:34:24.967 --> 00:34:26.912 the patients before we actually
NOTE Confidence: 0.71652823375

49
00:34:26.912 --> 00:34:28.468 give them the products.
NOTE Confidence: 0.71652823375
00:34:28.470 --> 00:34:31.406 And and I think that’s all I have.
NOTE Confidence: 0.71652823375
00:34:31.410 --> 00:34:33.831 So what I’m going to do is I’m going
NOTE Confidence: 0.71652823375
00:34:33.831 --> 00:34:36.177 to pass it over to to low heath.
NOTE Confidence: 0.96360756625
00:34:36.180 --> 00:34:38.084 And then we’ll do questions at the end.
NOTE Confidence: 0.742589505625
00:34:57.610 --> 00:34:58.801 Good afternoon everyone.
NOTE Confidence: 0.742589505625
00:35:01.183 --> 00:35:02.737 Anika I thank you for that
NOTE Confidence: 0.742589505625
00:35:02.737 --> 00:35:04.909 beautiful presentation that
NOTE Confidence: 0.742589505625
00:35:04.910 --> 00:35:07.046 Yeah, these are the people who led the
NOTE Confidence: 0.742589505625
00:35:07.046 --> 00:35:10.527 Objectives are DOC today would be
NOTE Confidence: 0.742589505625
00:35:10.530 --> 00:35:13.038 to mainly look into the therapeutic
NOTE Confidence: 0.742589505625
00:35:13.040 --> 00:35:15.422 avenues in which allogeneic stem
cell transplant has been making progress in order to reduce some of the complications associated with it, which ultimately results in a better curative promise on the quality of life. I’m going to present a trial wherein we’re going to use pre and post transplant. In addition to standard immunosuppression, for patients with acute GVHD, also present 2 two phase two trials looking a chronic DVT targeting different pathways. This was a trial that was like that MGS.
There was a multi site study led by Doctor Hobson team. Basically the study is looking to use ruxolitinib which is a Jack anybody prior to during and after stem cell transplantation for patients with primary or secondary modified process. So for those of you who manage my life, I process. This is a very common slide. The disease can be classified into five different categories. Things on the left here usually get managed conservatively, or using cytokines and things symptomatic splenomegaly patients.
We use ruxolitinib, and more recently the strike has been approved. Once they start coming intermediate risk or have bad gene signatures or higher very high risk. OK, those are the people if they’re eligible for transplant, they’ll be considered for stem cell transplantation of clinical trials. This is just a slide that shows that for the groups here, starting from grey, yellow, and blue median, overall survival is less.
Those are the people that are normally considered for a stem cell. Transplantation based on clinical scenarios. So why is it that stem cell transplantation, although being curative, has been a little bit of a problem for us? Most of these patients have a fibrotic condition. Have you know Mega League and patients who come in with splenomegaly at the time of transplantation generally tend to do poorly compared to others. You can consider options to take over spleen do variation, surgery and things like that,
but it has its own infectious risk, robotic risk which ultimately decreases the promise of transplant. In addition, we’ve seen people have poor graft function graph failure rates can be up to 15%. That all adds up to the non relapse mortality and there are some transwitch reports. Pretty high rates of GVHD and on the left mortality for my life I process compared to other people. The real question is if regulating even the rest of the drugs which
are now making foray into the field of my life I process, is it possible to continue this truck in a longer term? Because, as I said, Jackie Ken has implications on symptomatic control for people who have multiple process can decrease the screen size or the last couple of years. We've learned that this drug is pretty active in both acute and chronic GVHD. Now we have a label for it. If people are being a Jack iffy and you start with prior to transplantation, there are some reports which suggest that it can manifest in cytokine release syndrome.
Kind of clinical spectrum and there have been efforts to see if this drug can continue on. And there are also people who think if you suddenly stop it will rebound or bounce back and things like that which ultimately has negative impact. So the real question this study is trying to answer is, is it safe, effective to use a drug pre and post transplantation? This is a study schema. It included patients with mild fibrosis, both primary and secondary pre transplantation they would start a drug at 5 milligrams which is a lower dose around day minus 14 continued.
with conditioning regimen.

Use it in the post transplant period.

Reevaluate the patients at day 30 post transplantation,

at which time if the Council recovered,

you bump them up to the 10 milligrams vid dose,

which is what we kind of use it in our set.

The key inclusion for mainly adult patient population, as I said,

both primary and secondary.

This is a classification system.

This is a dip system that intermediate 1 risk group in addition to adverse molecular markers or people greater than intermediate 2 running through that,
they went with the Disney intensity

regimen as receipts was 140 or lesser

dose commonly used regimen prophylaxis.

Methotrexate and climbers was

applied in the set.

Here is some characteristics.

I know it’s a busy slide,

but all that I want you to focus

on is that most of these people,

about 85% of the people in this

trial had a split omegle coming in.

The study largely consisted of

match related and unrelated donors,

about 85% of the people in this

trial had a split omegle coming in.

The study largely consisted of

match related and unrelated donors,
when putting in a post transplant period is housing grafman. This is a pretty mild toxic drug. People can have deep cytopenias and here’s a report and they thirty 23124 patients had engrafted. On the platelet count tend to lag behind a little bit, whether it’s the drug, whether it’s the spleen. It’s debatable, you follow them up today, 60 neutrophils have recovered, or the platelets still lags behind by around a little more than 100 days, almost everybody recovers their platelet count.
I’m here with the clinical outcomes that are reported. The one year OS is about 77% the one year cumulative incidence of relapse is about 17%. One year. Incidence of chronic GVHD is 14%. I think it’s also important in the six months incidence of great leader for acute, which can be lethal. It’s about four percent is kind of impressive. So based on this trial now people are starting to contemplate the C. Yes, this drug has benefits in pre and post transplantation setting in terms of the high risk.
In population, maybe this can be translated into clinically. We will now just switch gears and go to an acute graft history that is presented by Minnesota Group. This was a phase two study a couple of years ago. They presented their phase one data that was published in Blood Advances, Dr. Holton and ET al had led this study. Basically, the rationale behind using human chorionic troepen and epidermal growth factor is that. Acute GVHD happens. It’s usually in the setting of an immune attack due to the discordance.
00:41:04.416 --> 00:41:06.450 between the recipient and the host.
00:41:06.450 --> 00:41:07.890 Communist therapeutic interventions that we apply are all deeply immunosuppressive.
00:41:07.890 --> 00:41:10.050 But by the time the immune cells have caused destruction to the epithelial lining.
00:41:10.050 --> 00:41:12.732 In the absence of anything else, we continue to escalate him in a suppression,
00:41:12.732 --> 00:41:15.449 but here they’re trying to come up with the concept of using tissue repair mechanisms by using growth factor support mechanisms like epidermal growth factors.
00:41:15.450 --> 00:41:16.728 We also know the concept of pregnancy.
00:41:16.730 --> 00:41:18.826 We’ve all known that HCG is kind of taller rising rising,
00:41:18.830 --> 00:41:20.830 it increases the regular population
00:41:35.618 --> 00:41:37.290 compared to conventional subpopulation.
NOTE Confidence: 0.633647803583333

00:41:37.290 --> 00:41:39.414 It also has impact on anabolic
NOTE Confidence: 0.633647803583333

00:41:39.414 --> 00:41:40.830 sides of metabol ISM,
NOTE Confidence: 0.633647803583333

00:41:40.830 --> 00:41:43.018 and as I said.
NOTE Confidence: 0.633647803583333

00:41:43.020 --> 00:41:46.920 GF also decreases and regulation,
NOTE Confidence: 0.633647803583333

00:41:46.920 --> 00:41:48.708 which is kind of being thought
NOTE Confidence: 0.633647803583333

00:41:48.708 --> 00:41:50.935 as a marker of inflammation in
NOTE Confidence: 0.633647803583333

00:41:50.935 --> 00:41:53.350 addition to promoting promoting it.
NOTE Confidence: 0.633647803583333

00:41:53.350 --> 00:41:55.708 More and more T cell metabolic
NOTE Confidence: 0.633647803583333

00:41:55.708 --> 00:41:57.723 studies suggests that bit rate
NOTE Confidence: 0.633647803583333

00:41:57.723 --> 00:41:59.049 seems to promote expansion,
NOTE Confidence: 0.633647803583333

00:41:59.049 --> 00:42:00.801 which is kind of a thing we like
NOTE Confidence: 0.633647803583333

00:42:00.801 --> 00:42:02.449 in the field of transplantation.
NOTE Confidence: 0.633647803583333

00:42:02.450 --> 00:42:05.072 Unlike neoplasms where T Rex are not
NOTE Confidence: 0.633647803583333

00:42:05.072 --> 00:42:07.389 well liked upon but to develop tolerance,
NOTE Confidence: 0.633647803583333

00:42:07.390 --> 00:42:09.832 we, like any agents that increases
direct population.
So based on their phase one design they now where they identified 2000 units. Sorry, 2000 units as appropriate dose, and they included two risk groups. In Minnesota, High Risk Group and the. Second line therapeutic group. I can give references for this at a later stage. They were used to drug subq every other day for seven days in addition to the high dose steroids, which is the commonest Firstline agent we use for the second line cohort,
they would use this combination
the same dose subq.
Or if you’re going to use it at 5000 units for those who are refractory was given every other day for 14 days in addition to the standard of care and that standard of care was left with the physicians based on their choice.
This is just a brief synopsis of what were the cohorts like.
Largely, I wanted to focus on the fact that in the first line cohort, most of those people were stage three to four lower GI GVHD, three to four lower GI GVHD,
which is what is more challenging
to manage in the second line cohort that did have a few skin cases, that was stage three or four, they have some pictures in their presentation. I'm not showing that, but they were pretty bad skin stays, but regardless, most of them are a grade three to four acute GVHD, which is kind of challenging to manage. Here are the response rates in the acute GVHD clinical drug development. 28 year responses being kind of validated as a nice marker to predict responses,
so date 28 for all patient cohorts.

There was a 57% CR and 11% had partial responses for the high risk Minnesota Risk Group to see.

Our rate was 64% in the second line, it was 50% CR rates.

And here's a non elapsed mortality can easily lead to that.

This is for the entire cohort in the dark clients for the high risk group.

And this is for the second line group.

The P value was not significant, but based on those who are responding.

CR or PR is not responding.

There seems to be a train that the non relapse mortality at two years.
00:44:05.413 --> 00:44:07.373 is declining with this information.
00:44:07.380 --> 00:44:10.004 And here is the same analysis for overall
00:44:10.004 --> 00:44:11.898 survival based on the whole cohort.
00:44:11.900 --> 00:44:13.996 And this is for those who are responding
00:44:14.000 --> 00:44:15.710 based on this kind of response
00:44:15.710 --> 00:44:17.650 we elicit with this intervention.
00:44:17.650 --> 00:44:19.904 When they presented the causes of that,
00:44:19.910 --> 00:44:22.304 it’s really interesting that happens to be
00:44:22.304 --> 00:44:24.467 a communist cause of death, right?
00:44:24.467 --> 00:44:25.986 About half of the patients had died,
00:44:25.990 --> 00:44:28.027 with a median follow-up of 17 months.
00:44:28.030 --> 00:44:30.228 Relapse is the second most common stuff,
00:44:30.230 --> 00:44:31.680 and infections and organ damage
00:44:31.680 --> 00:44:32.550 with common livery,
00:44:32.550 --> 00:44:34.310 and that didn’t seem to be that much.
But again, it's a small patient population.

In summary, I think they show that the response rate of 68 percent is pretty reasonably accepted, and doesn't significantly impact on relapse.

Mortality based on the fact that people are still dying with GST and relapses, they're recommending either using biomarkers, and they have some nice profile of metabolic stuff that they reported which I can talk to you later on.

But it's kind of now in development in the field that we don't necessarily have to keep thinking about escalating immunosuppression,
but now we need to start focusing. On getting the right immunomodulation in addition to tissue repair pathway drugs. In the other half of the talk, I’m going to talk about chronic GVHD. For some of us who do this on a daily basis, we see this in up to about 50% of patient population use of post transplant cyclophosphamide has brought that number down, but most people don’t get it because cyclophosphamide does have some issues in terms of infection, cardiac toxicity and other things, and again it’s largely applied in
00:45:37.570 --> 00:45:38.900 the setting of unrelated donors
NOTE Confidence: 0.573978271428571
00:45:38.900 --> 00:45:40.832 and not commonly used in massively
NOTE Confidence: 0.573978271428571
00:45:40.832 --> 00:45:41.476 donor transplantation.
NOTE Confidence: 0.573978271428571
00:45:41.480 --> 00:45:43.000 For those who develop,
NOTE Confidence: 0.573978271428571
00:45:43.000 --> 00:45:45.410 chronic steroids has been the workhorse
NOTE Confidence: 0.573978271428571
00:45:45.410 --> 00:45:47.034 for multiple multiple decades.
NOTE Confidence: 0.573978271428571
00:45:47.040 --> 00:45:48.520 About half of those patients
NOTE Confidence: 0.573978271428571
00:45:48.520 --> 00:45:50.000 eventually need second line treatment
NOTE Confidence: 0.573978271428571
00:45:50.051 --> 00:45:51.128 for disease progression.
NOTE Confidence: 0.573978271428571
00:45:51.130 --> 00:45:53.710 And they don’t tend to do well at that stage.
NOTE Confidence: 0.573978271428571
00:45:53.710 --> 00:45:54.886 Up until a year,
NOTE Confidence: 0.573978271428571
00:45:54.886 --> 00:45:56.650 year and half ago really didn’t
NOTE Confidence: 0.573978271428571
00:45:56.714 --> 00:45:58.570 have that many drugs in Brittany
NOTE Confidence: 0.573978271428571
00:45:58.570 --> 00:46:00.460 was approved a few years ago.
NOTE Confidence: 0.573978271428571
00:46:00.460 --> 00:46:01.552 Based on this trial,
NOTE Confidence: 0.573978271428571
00:46:01.552 --> 00:46:02.644 it’s a boutique inhibitor.
As you all know, the overall response rate was 67%, CR was 21% in that period, and we have two drugs belimo saddle which is a rock to inhibition. That's not only has anti-inflammatory properties, but it also kind of targets the scarring part of it, which is kind of a novel mechanisms. Here the overall rate was 73% in the CR. CRA despite being low the PR was high but based on the fact that it targets the scarring pathway, it’s been approved recently.
In addition to controlling given.

NOTE Confidence: 0.794081502857143

Uh, I spoke to you earlier on.

NOTE Confidence: 0.794081502857143

Fracture GBST in the last six months.

NOTE Confidence: 0.794081502857143

It’s also been approved for chronic GVHD.

NOTE Confidence: 0.794081502857143

Again, the rates of CR is close to about 50%.

NOTE Confidence: 0.794081502857143

Most of these drugs are approved for people who fail at least two or more lines of therapy,

NOTE Confidence: 0.794081502857143

but these lines of response rate suggests there is still more that’s needed to optimize the speed.

NOTE Confidence: 0.794081502857143

One of the yes, which is kind of not that commonly explored,

NOTE Confidence: 0.794081502857143

but it’s kind of.

NOTE Confidence: 0.794081502857143

It’s a welcome change.

NOTE Confidence: 0.794081502857143

It’s commonly,
we think about jobs as a T cell mediated pathway. This work that was presented by Stephanie Lee’s group from Fred Hutch is now looking into targeting macrophage driven chronic drug Physiology colony stimulating factor 1 receptor mediated pathways. Once someone is circulating, they can get into the tissues and then they can differentiate in either. I’m wondering 2 phenotypes of macrophages, which one being pro inflammatory, this being anti inflammatory. But now people are looking into
developing drugs against tests
which promotes this differentiation
to decrease the inflammation and
the drug that I'm going to talk
is a CC colony stimulating
factor 1 receptor antibody.
Inhibition of that starts to
decrease 5 process and make bring about
changes in collagen structure which
kind of then has impact and tissue
healing for people with chronic dry.
The drug is exactly exactly map.
As I said, it's a humanized IgG.
monoclonal antibody binds to
CSF 1 receptor.
In addition, it also binds to oil 34,
which has informative properties in the skin.

It’s administered over 30 minutes for every two to four weeks.

It’s highly effective in decreasing the fiber optic signals on the nonclassical monocytes.

In addition, using this intermittent dosing pathway, they found that you know gives opportunities to keep the drugs going frequently because the cells do.

So in the mean time this was a phase one two study design.

They wanted to test the phase one about 17 patients,
a point

15.5133 given over Q4 weeks at Q2 weeks,

and then they went to the phase expansion at 1 milligram per kilogram.

That included a larger number

Presented here is a baseline characteristics for patients.

A quick summary of this is that most of these people were heavily treated that more than half of the people in both phase one and two.

I had four or more organs involved consistent with modern tactics.

People have been exposed to Brittany and which is the rock number that I showed.
00:49:10.930 --> 00:49:12.058 I'm there, basically show that there's no differences
00:49:19.020 --> 00:49:21.279 Uh, and the drug seems to be pretty well tolerated across both groups.
00:49:22.878 --> 00:49:23.960 The discontinuation rate, although seems to be high,
00:49:26.298 --> 00:49:28.295 and about 30% in the phase one, and about 58% are still continuing.
00:49:33.400 --> 00:49:34.650 More interestingly, the response rate.
00:49:34.650 --> 00:49:37.150 is the response rate.
especially with this one milligram per KQ, 2 weeks our sponsor seems to be pretty durable and same is the case with three milligrams per kick and when you look around their best overall response rates and time from responses, that’s reasonably impressive, but time to responsive. One month it’s something that you don’t often see, and that’s a welcome change. The next question people come commonly ask is how about organ specific responses? Well, light light Gray or blue ish the CR rates in the dark ones. is the CR rates in the dark ones. The PR lower GI?
Everybody seems to have good responses. What's of interest to us is the Giants and the skin, which seems to be PR based on its antifibrotic mechanisms. People ask me what happens to the lung, which is more common and challenging to handle? Seems like you know at least five out of 15 patients is a reasonable one for CR. When it types the lung, and and about 88% at serious skin sclerosis are baseline close to 16% on improvement in sclerosis. Another aspect that we tend to ignore.
00:50:41.645 --> 00:50:43.719 is you might have clinical manifestation,
NOTE Confidence: 0.649108285555556
00:50:43.720 --> 00:50:45.520 but what about the quality of
NOTE Confidence: 0.649108285555556
00:50:45.520 --> 00:50:46.720 lives and symptom burden?
NOTE Confidence: 0.649108285555556
00:50:46.720 --> 00:50:48.939 And here’s just a graph in somebody
NOTE Confidence: 0.649108285555556
00:50:48.939 --> 00:50:50.502 that’s depicting that across the
NOTE Confidence: 0.649108285555556
00:50:50.502 --> 00:50:52.820 dose people had good responses
NOTE Confidence: 0.649108285555556
00:50:52.820 --> 00:50:54.860 in the symptom scale.
NOTE Confidence: 0.649108285555556
00:50:54.860 --> 00:50:55.500 In conclusion,
NOTE Confidence: 0.649108285555556
00:50:55.500 --> 00:50:57.100 I think the investigators were
NOTE Confidence: 0.649108285555556
00:50:57.100 --> 00:50:59.065 able to show that targeting
NOTE Confidence: 0.649108285555556
00:50:59.065 --> 00:51:00.487 monocyte macrophage pathway,
NOTE Confidence: 0.649108285555556
00:51:00.490 --> 00:51:04.434 the CSF one receptor ligand seems to be
NOTE Confidence: 0.649108285555556
00:51:04.434 --> 00:51:07.422 meaningful leads to decent response rates.
NOTE Confidence: 0.649108285555556
00:51:07.430 --> 00:51:10.190 Sclerosis seems to go down on it now.
NOTE Confidence: 0.649108285555556
00:51:10.190 --> 00:51:12.206 There’s a trial that they’re going
NOTE Confidence: 0.649108285555556
00:51:12.206 --> 00:51:13.550 to randomize different doses,
potentially as a group with contemplating participating in this thing, but it’s kind of opened up the concept of targeting monocyte macrophages in addition to the T cell thing that we commonly pursued in chronic GVHD. On the last day that I’m going to talk about is a better set, this was a study that was done at Boston. Abbott stepped as you all know, is a T cell costimulation modulator, after recognizing the APKS would interact with them and the CD 20 would normally interact with the CD 86.
For this is necessary for T cell activation, proliferation and production of inflammatory mediators, whereas inhibits this pathway by targeting CD 1886, this costimulation doesn’t happen and the hypothesis here is that if you somehow can prevent this T cell costimulation, maybe the proliferation activation doesn’t happen. That leads to decrease chronic dry. About six months ago I know I’m using the six months one year commonly because that’s how frequently the drugs are
NOTE Confidence: 0.616817497777778
00:52:14.850 --> 00:52:15.950 getting approved in this space.
NOTE Confidence: 0.616817497777778
00:52:15.950 --> 00:52:16.416 Recently, the drug was actually approved for prevention of acute GVHD.
NOTE Confidence: 0.616817497777778
00:52:18.746 --> 00:52:21.050 Yeah, mainly for unrelated donors,
NOTE Confidence: 0.616817497777778
00:52:23.230 --> 00:52:25.170 so this is a study in the backdrop of that,
NOTE Confidence: 0.616817497777778
00:52:25.170 --> 00:52:26.822 but obviously the context is in a chronic dbcontext,
NOTE Confidence: 0.616817497777778
00:52:26.822 --> 00:52:28.887 so people are wanting to say yes.
NOTE Confidence: 0.616817497777778
00:52:28.890 --> 00:52:30.444 This is a drug that’s not going to be commonly used.
NOTE Confidence: 0.616817497777778
00:52:30.450 --> 00:52:32.790 What happens in the chronic dry setting? So the design was this close to 40
NOTE Confidence: 0.616817497777778
00:52:32.790 --> 00:52:35.184 patients who had both are bleeding
NOTE Confidence: 0.616817497777778
00:52:35.190 --> 00:52:37.142 and reduced density transplants
NOTE Confidence: 0.616817497777778
00:52:39.060 --> 00:52:40.432
and declared themselves steroid refractory and the definition of that was persistent science. Despite use of steroids, they were to be getting this to stand mix for cake, which is what was acute GVHD. Dose was every two weeks for three doses and then they would go on to get it for every four weeks for three doses based on the clinical response, there was no response will come off that a clinical response for
their continuation was allowed. The aim was to look into the rates of overall response rates and see how things were playing out. And this is just a description of things. Go on the oral response rate was 49%. Unfortunately, CR was zero and most of them were PR responses. This is just a spread across different organs. In the interest of time, I’m going to quit that and this is the slide that basically shows.
its importance to Ryan has been the main drug that we've used quite a few other people were able to decrease down their dose of steroids, which has long term implications on their metabolic health, mental health, cardiovascular risk and things like that. So with that the investigators conclude now a 50% objective response rate or are in the cirrhotic factory is a welcome change. Importantly, there was a durable reduction in prednisone dosing overtime infections were uncommon in this context.
and infusions were pretty well tolerated. Their ongoing studies, correlate's and biomarkers, and things like that.

With that, I'll end the top and thank everybody for coming and I'll open it up for the audience. So we’re going to open this up to questions. Now you can feel free to ask them or write them down in the chat. For each of the talks. And maybe in the meantime, I'll just ask Lohith. Do you think that given the good
efficacy we've seen with ruxolitinib
in patients with steroid refractory?
and given the safe the what seems
to be fairly good safety profile of
the human chorionic gonadotropin?
Do you see a role for the combination
in terms of steroid sparing effects
in this patient population?
I don’t know if there is such
a trial that’s already been.
That University of Minnesota is doing or not,
but that would seem like a
reasonable trial to conduct.
Yeah, I think I think that’s
that’s a great question, Alice.
Obviously, the CR rates around 60 to 70% based on which trial you look around it or our response rate.
Real question is the day 28 is the magic bullet, at least in most trials.
How much are we going to? Miles suppressed?
The good thing about this drug is it’s not deeply Mila suppressive right?
There’s always been this concern in the field that if the inflammation kicks in and the tissue is wiped out. You’re in a losing cause that that
combination makes rational sense, but I’m not certain the group is pursuing this. Clearly, I think what it’s showing is we just probably need to start thinking and deescalating immunosuppression sooner rather than keep harping on it, which is what we’ve done for many decades. Hopefully we’ll get a good antimotility drugs, good tissue, healing, drugs going forwards, and this seems to be the right start. But there’s a question in the chat about the mechanism of rock
NOTE Confidence: 0.730805488
00:56:23.830 --> 00:56:25.610 two and Rock 2 inhibition. Can you

NOTE Confidence: 0.928397435714286
00:56:25.620 --> 00:56:28.770 tell us a little more about that? So.

NOTE Confidence: 0.52708664666667
00:56:31.510 --> 00:56:33.285 I think it’s mass general

NOTE Confidence: 0.52708664666667
00:56:33.285 --> 00:56:35.476 identified a few years ago.

NOTE Confidence: 0.52708664666667
00:56:35.476 --> 00:56:38.860 They came up with this idea that.

NOTE Confidence: 0.52708664666667
00:56:38.860 --> 00:56:41.508 You know, just like most things you know,

NOTE Confidence: 0.52708664666667
00:56:41.510 --> 00:56:43.338 we have anti-inflammatory drugs.

NOTE Confidence: 0.52708664666667
00:56:43.338 --> 00:56:45.623 But we don’t really have

NOTE Confidence: 0.52708664666667
00:56:45.623 --> 00:56:47.629 good antifibrotic trucks.

NOTE Confidence: 0.52708664666667
00:56:47.630 --> 00:56:49.835 I think this rock pathway has been

NOTE Confidence: 0.52708664666667
00:56:49.835 --> 00:56:51.700 shown in systemic sclerosis and,

NOTE Confidence: 0.52708664666667
00:56:51.700 --> 00:56:53.758 at least in this clematis GBST,

NOTE Confidence: 0.52708664666667
00:56:53.760 --> 00:56:57.004 most models targeting rock

NOTE Confidence: 0.52708664666667
00:56:57.004 --> 00:57:01.059 Pathway Rock 2 results in.

NOTE Confidence: 0.52708664666667
00:57:01.060 --> 00:57:03.236 Grease scarring, decreased fibrosis,

NOTE Confidence: 0.52708664666667
00:57:03.236 --> 00:57:05.406 and decreased fibrosis.

NOTE Confidence: 0.52708664666667
00:57:05.406 --> 00:57:08.788 Thank you.
and that was the rationale for that.

Considering most of chronic GVHD, people have facial involvement, synovitis myositis and things. There's a lot of interest that's going on a couple of our dermatology colleagues and our banking. These samples at least my patients. Uh, trying to address what are the synergistic things that we could use? In addition to the rock pathway that further subprocess fibrotic mechanisms, because really, we do see that some of them come up with contracted arms and things like that and that has functional implications.
More importantly, it’s not deeply immunosuppressive, and that’s a welcome change. Rates of infections are low and Stating that this is something that you had in the car, I say I’ve seen good responses even in lung GVHD, but I think as a special code I would like to see a little more to see if that brings up on field changing shift, but that’s still a work in progress. There’s also a question for Aris about immune approaches. Postcard T to enhance attention.
00:58:07.920 --> 00:58:10.670 of cells for continued response.
00:58:10.670 --> 00:58:12.018 Thank you. Touched on that a little bit with that new Novartis platform.
00:58:12.018 --> 00:58:14.510 But people doing other things try and get car T cells to persist to work better afterwards that you heard of.
00:58:16.494 --> 00:58:21.620 Yeah, well, I mean so.
00:58:21.620 --> 00:58:24.470 So the humanizing party is 1 approach to for them to persist better.
00:58:28.649 --> 00:58:32.148 Again looking at the central memory phenotypes are using enriching for that particular patient population is another is another approach to to enhance retention.
00:58:34.500 --> 00:58:37.640 You know, the other thing is that they do have these Cortese that secrete cytokines,
00:58:52.120 --> 00:58:53.365 so that’s another.

00:58:53.365 --> 00:58:54.610 That’s another approach.

00:58:56.970 --> 00:59:06.590 And in fact there was actually an abstract at ASH that I didn’t show,

00:59:06.590 --> 00:59:10.598 Releasing, you know with AB McCourtie

00:59:10.598 --> 00:59:13.147 releasing cytokines that enhance proliferation so so there are multiple approaches and actually.

00:59:13.147 --> 00:59:15.832 Come. You know, sometimes that can be a double edged sword, right?

00:59:15.832 --> 00:59:19.709 multiple approaches and actually.

00:59:19.710 --> 00:59:21.792 Because these cells can proliferate very rapidly and then you have to think about a switch to turn them off because they can become a very toxic,
but you can combine them.

You can do basically like City

Chen is doing at Yale,

a dual knock in knockout, where you can.

Knockout pretty one, so I mean,

that’s that’s another approach, right?

So so looking at the micro environment,

can we actually can we actually.

can we actually can we actually.

_get cells that are less exhausted

by stimulating by by affecting

the micro environment.

For example,

those efforts are going on in CLL

where there is a real problem with

persistence of these court T cells,

so those are all or you
know the other thing is.

At CAR T cells like one of the labs is doing here with Sally Sue, you know, with the targeting low antigen density, for example T cells. So that’s another approach so that once they may. Progress after regular karty, or if you see decreased antigen expression, is to actually target them with the party that has higher avidity, so those are some of the approaches for to enhance the retention of these cells and continued response.
So so I have one question for you is that? Why it has come up in there has already been a trial, but given the favorable results, at least from the Zuma 7 trial. Do you foresee a time when Carty are used even? In high risk patients, as part of their initial therapy, as opposed to waiting for disease, refactoriness or relapse.

Well, I mean different from the Zuma. For example, right? They took really high risk patients and they stratified them by pet after
two cycles and patients that were pet positive went on to get to get Carty and the outcomes were pretty good. You know the problem is I think we need to get a little bit longer follow-up because. You know patients who have a positive PET scan after two cycles you know may still go on to achieve complete remission at the end of 6 cycles of therapy, so I don’t know if it’s ever going to make it to to frontline. It may. It’s not. We’re not there yet. I think that what companies are doing now, though they are sponsoring trials where they pay for the collection of T cells.
early on in somebody’s presentation.

And they saved them in the event that patients do relapse and they will probably.

Sell that information.

Sell those to pharmaceutical companies that are designing trials.

That’s interesting, so so, so that’s going on because I think it’s really important to collect the cells as early as possible when they’re fit before people have a lot of chemotherapy.

So so you know there may.

I mean,

the FDA hasn’t even approved yet, right?

For they haven’t even approved access
L or based on or Lisle based on

the Zuma 7 and transform results.

I think that’s the next step.

Because I think it should be approved,

‘cause clearly there’s a PFS benefit in

that patient population over transplant,

so I think that’s going to be

probably the first approval,

and then after that you know

we’re looking at.

Yeah,

potentially incorporating it in

people with double hit lymphomas

or primary refractory disease.

Incorporating it early on.
Alright, well we're a few minutes after the hour, so, great presentations, great questions and discussion. Thanks everybody. Have a good weekend. Thank you everyone.