Thank you so much for coming. You know, we are getting back to full in person and I know there are a lot of people on Zoom as well. So thank you so much for coming today.

And I will be talking about immune checkpoint inhibition and Novant therapies for myelodysplastic syndromes. These are my disclosures and this is the outline.

I’m going to cover 4 areas that have seen a lot of developments in the last few years.
as well as risk stratification and response assessment MD’s,
the evolving therapies for lower risk MD’s,
high risk MD’s and then specifically about the immune checkpoint inhibition efforts that I have been trying to
kind of doing in these disease areas.
So what are myelodysplastic syndromes,
neoplasms finally because for a long time myelodysplastic syndromes were thought of as syndrome
or pre leukemia or a disorder,
but they are actually cancers and this has been formally diagnosed by The Who.
They are basically uncommon only four in 100,000 a year, 20,000 cases of MD’s in the US. However, the median ages in the early 70s and the number of patients with MD’s has been increasing because we have more and more cancer survivors. I share many patients with many of you on the solid pumor side because those patients have secondary myelodysplastic syndromes and those can be among the most challenging patients to treat. And you can see here another fact that emphasizes the malignant nature of MD’s.
So this is the five year survival of patients with MD’s in Violet and you can see it’s 31%, very close to what you get with AML which is 25% but much worse than some of the more common solid tumors such as breast and lung when you take all the patients together. Again further emphasizing the malignant nature of these conditions. And more recently, we also understood that there is a large number of people who go through a process called clonal hematopoiesis of indeterminate potential or CHIP. And this is a condition that happens
in up to 10% of people older than 70. And some of those progress to MD's, and some don’t, but they are also associated with inflammation and cardiovascular risk and many other syndromic dysfunction across the body. This is why multiple disciplines including cardiology have been interested in this. And for that more and more cancer centers have been interested in establishing clinics for chip and seekers. And here our newest recruit, Dr. Lourdes Mendez has taken over this aspect and I think this is going to...
become very important in the coming years.
The management of MD’s, as I’m going to show you in a little bit,
has been difficult to get new therapies. And part of this is because of the
large heterogeneity of the disease.
This is a schema showing the genetic landscape of MD’s.
And you can see here that there are more than 40 recurrently abnormal somatic mutations that can happen in patients.
However, less than six of those happen in more than 10% of patients.
Therefore, there are many different driver genes and developing therapies that work across the spectrum for patients.
00:03:12.601 --> 00:03:14.976 with MD’s has been quite challenging.

00:03:14.980 --> 00:03:16.865 Another I think challenging feature

00:03:16.865 --> 00:03:19.100 has been the classification of MD’s.

00:03:19.100 --> 00:03:20.420 And over the years,

00:03:20.420 --> 00:03:22.400 how do you separate MD’s from

00:03:22.467 --> 00:03:24.417 AML has been a moving target.

00:03:24.420 --> 00:03:27.686 Historically A+ count of 30% was used

00:03:27.686 --> 00:03:30.793 and then this was changed to 20% most

00:03:30.793 --> 00:03:34.244 recently last year and this created a

00:03:34.244 --> 00:03:37.500 huge difficulty in the field is the

00:03:37.500 --> 00:03:40.100 target blast count has been moved to 10%.

00:03:40.100 --> 00:03:42.634 So now there is this new entity

00:03:42.634 --> 00:03:45.149 called MD’s slash AML which is 10 to

00:03:45.149 --> 00:03:47.373 19% blast and this is causing a lot

00:03:47.373 --> 00:03:49.071 of confusion for patients especially
that the PATH reports get released immediately to patient nowadays or they are being told that you have MD’s by 1 classification and AML by another classification.

And to address this issue, we actually have worked with a large number of international colleagues to establish international consortium of MD’s. This is an effort that involves many experts across the world to try to come up with a unified way of classifying the disease. And indeed we have put together more than 70 cases, which by the numbers of MD’s is
quite actually quite large of highly annotated cases to try to come up with one unified classification.

There’s another update of this effort that will be presented in ASH in an oral fashion this year and hopefully the paper will be published soon so that we can have one common way in which we can talk to patients with MD’s. After that.

What is important is the risk stratification. Why is that important? Because patients with MD’s have variable prognosis. Some patients can live for multiple years.
00:04:54.930 --> 00:04:56.592 years while other patients have
NOTE Confidence: 0.87494814
00:04:56.592 --> 00:04:58.137 prognosis that’s almost akin to
NOTE Confidence: 0.87494814
00:04:58.137 --> 00:04:59.900 that of acute leukemia patients,
NOTE Confidence: 0.87494814
00:04:59.900 --> 00:05:01.315 meaning that the prognosis can
NOTE Confidence: 0.87494814
00:05:01.315 --> 00:05:03.554 be less than six to nine months
NOTE Confidence: 0.87494814
00:05:03.554 --> 00:05:05.474 and therefore having good risk
NOTE Confidence: 0.87494814
00:05:05.474 --> 00:05:07.539 stratification systems is very important.
NOTE Confidence: 0.87494814
00:05:07.540 --> 00:05:07.814 Historically,
NOTE Confidence: 0.87494814
00:05:07.814 --> 00:05:10.280 you can see in this table four of the
NOTE Confidence: 0.87494814
00:05:10.334 --> 00:05:12.589 most commonly used stratification systems.
NOTE Confidence: 0.87494814
00:05:12.590 --> 00:05:14.550 All of them rely on the number of
NOTE Confidence: 0.87494814
00:05:14.550 --> 00:05:16.279 the plast in the bone marrow as
NOTE Confidence: 0.87494814
00:05:16.279 --> 00:05:17.950 well as the karyotypic abnormalities
NOTE Confidence: 0.87494814
00:05:17.950 --> 00:05:19.870 and the blood counts.
NOTE Confidence: 0.87494814
00:05:19.870 --> 00:05:20.203 However,
NOTE Confidence: 0.87494814
00:05:20.203 --> 00:05:22.534 none of those were very good because
for a long time we and others have shown that some of the patients that are called lower risk MD’s die quickly die within two years of diagnosis. More than 1/4 of those lower risk MD’s patients and it was clear that these prognostic risk scores are not capturing the whole spectrum. And we also have shown that among patients with therapy related MD’s, which historically have been considered very high risk disease, some of them do OK, do better than some of the other patients.
And that's again reflective of the variability on prognosis of those patients. And this is why it's important to apply good risk stratification process for every patient. After all of this basically the IPSSM, the molecular IPSS was finally published after a large international effort in the New England Journal of Evidence. You can see the Bernard ET al Citation. But the short of this is that it incorporated the molecular alterations in the calculation and that led to a more accurate risk stratification picture. And we have shown in a large analysis of two phase,
phase two and phase three trials that were presented last year in ASH that this system does lead to upstaging of patients. You can see in red the high risk patients by the old scoring system, the Ipss, then the revised Ipss, then most recently the molecular IPSS. And you can see that the number of patients who are being diagnosed now as high risk disease because their prognosis is indeed poor, is becoming higher and therefore more of those patients are being directed for aggressive treatments. The last area I want to cover before we go
to therapeutics is the response criteria. This is actually a very important area because response criteria have been quite problematic in MD’s. And I can tell you that it’s my belief and several of my colleagues at the same believe that it has impeded drug development in MD’s. Why is that? Because some of the issues with the response criteria have led to certain medications moving from phase one to phase three. That probably should not have been the case. And this is why we have many Phase 3 failures in MD’s.
So again using a large international effort over the last two years that was coordinated through the international working group, we have revised these response criteria and this consensus proposal for revised international working group criteria has been now published and it started to be implemented in some clinical trials protocols. We have been in discussions with the FDA as well about implementing this in, I’m hopeful that this will become a more uniform way of looking at clinical trial
to further like establish their efficacy of therapeutics in a more consistent fashion. And we are validating this using WD database which will look both at the international working group criteria as well as the IPSSM. We actually have this database again with 15 different centers. Six of those presentations are going to be upcoming in ASH, two of them are oral presentations by Doctor Tarek Iwan and by our newer newest recruit Dr. Ian Beversdorf. So I think this is going to
further validate these response criteria as the way to establish, establish them as a way to approve medications in the future. So now moving from classification and response assessment to other therapies and you are looking here at the approved therapies in the top line by the FDA and in the lower line by the EMA. And what you can quickly see compared to many solid tumours is that we don’t have many approved therapies. This has been a very frustrating Rd. for drug development in MD’s and
in high risk MD’s. For example,

we did not have a drug approved in

the last 20 years until the year 2020.

So I’m going to show you the main

therapies that we currently have

available and how we are finally breaking

through that deadlock of therapeutic
evolution and we are starting I think

to have better therapies come along.

The traditional approach of

treating patients with lower risk MD’s

depends on symptom control because we

cannot currently cure these patients.

The only way to cure a patient with

MD’s with bone marrow transplant,

but bone marrow transplants are
usually reserved for patients who have higher risk disease, not lower risk disease. For patients with anaemia, the standard treatment would be ESA’s however, those drugs are not active except in less than 1/2 of patients, and the response last less than 12 months. And I’m going to show you how this landscape has changed in the last couple of years. So the first I think major improvement was the introduction and final approval of this drug called luspetercept.
what is luspetercept, the silicon trap. It works on a pathway called transforming growth factor pathway. These ligands suppress erythropoiesis, especially late erythropoiesis and using this ligand trap has led to restoration of effective erythropoiesis and ultimately improved transition independence. This led to transition independence in around 40% of patients in the phase three Middle East trial which was the landmark paper published in the New England Journal of Medicine. And based on this this drug was approved.
And we have subsequently published additional follow up from this trial that showed that this drug not only lead to high rates of transfusion independence but it actually also leads to significant reduction in transfusions for patients who do not become transfusion dependent and lead to hematologic improvements.

And this year the major development in lower risk MD’s has been the final publication of the commands trial which looked at the activity of specter sit in the frontline setting. So this is comparing it against
erythropoiesis stimulating agents in patients with ringsidroplasts and without ringsidroplasts. So this was a primary analysis. This paper is now out in The Lancet journal showing that patients who received Los Pertoset achieved 60% transition independence, almost double that what you expect with patients who receive ESA. So clearly a very active drug and it’s moving to the frontline treatment of MD’s which is a fundamental change in how we treat patients with lower risk MD’s. We are trying to move this further through two other trials.
One is the element trial, which is a large phase three trial that will be looking at patients who are not transfusion dependent. Here we are trying to move the bar higher and we are trying to prevent patients from even becoming transfusion dependent by treating them at an earlier stage of their anaemia. So this trial which will open at TLI think will be very important as a landmark trial in the management of MD’s if it’s positive because it would be the first time we get a drug...
potentially approved for patients who are not yet transfusion dependent. And another phase three trial that we are working on with the sponsor basically is looking at the use of the drug at maximal doses because we currently many of the patients are not being escalated to the right dose that leads to highest response rate. So I think starting with the higher response with the higher dose is going to increase the response rate and potentially open the door for more and more patients responding to this drug. And this trial is also up going to open ATL another drug that I think generated
a lot of interest is Amitelestad.
This is a first in class telomerase inhibitor. So telomerase activity in patients with MD’s has been associated with high risk disease and inhibition of the telomerase it has led to restoration of effective erythropoiesis in a large phase two trial. This is a drug that’s given intravenously every four weeks and in a phase two trial lead to 40% transfusion independence. So this was taken to a phase three trial. We have presented the data of this paper in Asch or sorry in ASCO.
2023 and the paper is now in Lancet in press where patients were randomized to receive hematillostat versus placebo.

Again those are patients who are heavily transfusion dependent with lower risk MD’s and you can see here that the rate of transfusion dependence was similar to phase two trial with 40% compared to 15%.

And importantly, the degree of hemoglobin elevation was almost 3 grams on average from a hemoglobin of 8 to hemoglobin of 11.

So quite active and the durability
NOTE Confidence: 0.34587935
00:14:13.318 --> 00:14:15.812 is very good, It’s around 51 weeks,
NOTE Confidence: 0.34587935
00:14:15.812 --> 00:14:18.230 which fought by MD’s criteria is
NOTE Confidence: 0.34587935
00:14:18.311 --> 00:14:19.880 actually pretty good.
NOTE Confidence: 0.34587935
00:14:19.880 --> 00:14:21.581 So this drug is currently in front
NOTE Confidence: 0.34587935
00:14:21.581 --> 00:14:23.274 of the FDA for consideration of
NOTE Confidence: 0.34587935
00:14:23.274 --> 00:14:25.388 approval and if it gets approved it
NOTE Confidence: 0.34587935
00:14:25.451 --> 00:14:27.565 will offer another I think very good
NOTE Confidence: 0.34587935
00:14:27.565 --> 00:14:29.128 opportunity for our patients with
NOTE Confidence: 0.34587935
00:14:29.128 --> 00:14:31.396 lower risk MD’s to become transition free,
NOTE Confidence: 0.34587935
00:14:31.400 --> 00:14:33.360 which is very important moving
NOTE Confidence: 0.34587935
00:14:33.360 --> 00:14:34.928 to high risk MD’s.
NOTE Confidence: 0.34587935
00:14:34.930 --> 00:14:37.874 This is where we have more of our
NOTE Confidence: 0.34587935
00:14:37.874 --> 00:14:40.090 recent failures I would say in
NOTE Confidence: 0.34587935
00:14:40.090 --> 00:14:41.930 in development of new therapies.
NOTE Confidence: 0.34587935
00:14:41.930 --> 00:14:43.694 This figure I’m showing you has not
NOTE Confidence: 0.34587935
really changed in the last almost 20 years.

So patients who are candidates for transplant go for transplant and those who are not receive hypomythylating agents.

However, we know that hypomuthilating agent treatment by itself is not great. The long term survival only if you use HMA without going to transplant is less than 4% and for that reason we strongly encourage patients to consider transplant whenever possible, but also try to build up on HMA therapy to improve outcomes.
And this is kind of a summary of three different real life studies that we have done that show that the real life outcomes with Hmas are actually much worse than what you see in clinical trials with immediate survival of only one year on average for patients with high risk MD’s. Again further emphasizing the point for new therapies for patients with high risk MD’s and we have tried, we have tried for a very long time over the last 20 years. Unfortunately this graveyard of combinations of drugs that were added.
to hypomithilating agents keep expanding.

The latest addition was this drug magrolimab which works on the CD 47 pathway. This is a very exciting drug has generated a lot of excitement early on but unfortunately a recent press release couple of months ago showed that phase three trial of this drug was negative. We can talk in another time once the data is publicly released about the reasons for failure and how we can try to come up out of this system. The good news is that we have other drugs that are more exciting and potentially could lead to approval.
One of them is venetoclax. So venetoclax is an oral BCL 2 inhibitor. This is already approved for patients with acute myeloid leukemia who are older. The frontline phase two trial should show CR responses of around 35% and across the genetic spectrum of MD’s we have published a phase 1P study that shows that adding venetoclax to HMA is actually active in the HMA failure setting, which is a very difficult setting to treat patients in. It leads to responses as well as transition independence. But the pivotal phase three trial is...
fully accrued now it’s called Verona.

This trial might change the landscape of how high risk MD’s is, is going to be treated.

This is the scheme of the trial that we presented a couple of years ago.

This trial is now fully accrued.

It’s the results are actually expected by early 2024 and if this trial is possible, it would lead to a new standard of care.

Now moving to immune dysregulation myeloid malignancies and this is an area where I have personally invested quite a bit of time trying to develop new therapies for both MD’s and acute myeloid leukemia.
So we know that the most effective treatment for patients with MD’s and AML is bone marrow transplant, which is effectively an immune intervention. We know there is significant dysfunction in the immune system happens in patients with MD’s and AML both at diagnosis but also during the progression of the disease. There is both quantitative and qualitative abnormalities that happen in the T cells including the regulatory T cells, but also in the macrophages and the ANKAE cells.
And study after study have shown that these increase in frequency as the disease progresses. The question has been always are these pathogenic, are they basically mediating the progression and the resistance of AML and MD’s or are they basically adhering, they are just a phenomena that comes with the progression of the disease. And the first trial I think that generated a lot of interest of immune checkpoint inhibition which clearly in solid tumors have led to a major revolution, but in blood tumors has not led to the same impact so far.
However, the Dana Farber group published this trial using Epilumab which is a CTL A4 inhibitor approved for multiple solar tumors. Now it was a small phase one study, but it was done in the post transplant setting where the drug was given for patients who relapse after transplant and what they have shown that the drug was tolerated. There were some GVHD but generally it was well tolerated for the most part and they were able to achieve 5 responses, 5 complete remissions out of 13 patients, which again was a proof of principle.
that immune checkpoint inhibition post transplant does actually work. And this generated a number of trials looking at the drug in MD’s and AML. This is one of the trials, one of the early trials that I have worked on actually when I was at Hopkins and later moved it to Yale. It was multicentre, it was in the post relapse setting for patients with MD’s. So this was not after transplant, this was after HMA failure in patients with MD’s. And while we have shown that the drug was well tolerated,
we could manage the immune related adverse events effectively similar to what they do in solid tumors.

The clinical responses were generally very low and the drug was not clinically active. We did achieve some disease stabilisation but stable disease always very tricky in MD’s to figure out is it related to the biology of the disease being indolent in some patients or is it related to the activity of the drug. However, among those patients who had stable disease, we have conducted extensive correlative testing with Leo Loznick at Hopkins.
And we have shown that there was an increase in the frequency of Icos, which is costimulatory molecule, but this was not basically associated with increase in the peripheral T cell receptor diversity in terms of association with the response. And I think trying to find biomarkers for patients has been one of the also challenging areas in immune checkpoint inhibition in MD’s. Of course single arm trials as I mentioned are not very definitive in any kind of activity. Some of those phase one trials
have shown positive signals, but the definitive way to achieve that would be with a randomized trial and we worked with the Celgene slash BMS to develop this trial of randomized trial. This was the only randomized published trial to date of immune checkpoint inhibition both in MD’s and AML. So patients with MD’s or AML in two separate cohorts, more than 210 patients were randomized to receive azacitidine or azacitidine with durvalumab. Many of you are probably familiar
with this PDL 1 inhibitor which is approved to multiple solid tumors and has shown overall survival prolongation in several settings. However, again this was a negative trial. You can see here complete overlap in the overall survival and progression free survival cares and no difference in the primary endpoint which was the overall response rate. So this was disappointing. We try to understand better why is that the case, why did the drug not lead to improvement? So the first theory is that one common thing we see with MD’s trials is that
when you add a drug in top of MD’s, you lead to less exposure of azacitidine which is the only drug shown to improve survival. And therefore maybe adding the volumab has led to reduced exposure of Aza and that’s why we did not see benefit. But you can see in this analysis in the green bars that the number of cycles between the two arms was actually similar and most patients have received more than four cycles. So it doesn’t seem like this underlines the lack of therapeutic efficacy to the right.
You can see also that there was similar hypomethylation which how we think how those drugs hypomethylating agents work and no difference between the two arms. So doesn’t seem like there was antagonism there. We also tried to see if there was an increased expression in PDL 2 as a mechanism to bypass the PDL 1 inhibition and that also was not the case. So none of those mechanisms seem to suggest why the drug did not work. What was actually quite surprising is that when we conducted serial flow cytometric analysis, we did not see T cell expansion in
00:23:07.874 --> 00:23:11.576 diversity or in quantity by flow cytometry,
00:23:11.576 --> 00:23:13.938 neither in the bone marrow or in the
00:23:13.938 --> 00:23:15.924 peripheral blood between the two arms.
00:23:15.930 --> 00:23:19.030 And this was particularly surprising
00:23:19.030 --> 00:23:21.190 because there has been a prevailing
00:23:21.190 --> 00:23:23.118 theory that the reason why immune
00:23:23.118 --> 00:23:24.418 checkpoint inhibition does not
00:23:24.418 --> 00:23:27.076 work in AML is that once you give
00:23:27.076 --> 00:23:28.344 it subsequent lines, third,
00:23:28.344 --> 00:23:28.932 fourth line,
00:23:28.932 --> 00:23:30.990 that the immune system has been beat
00:23:31.046 --> 00:23:32.570 up a lot by the chemotherapy.
00:23:32.570 --> 00:23:34.874 So here we were giving it in the
00:23:34.874 --> 00:23:36.519 frontline sitting and still it did
00:23:36.519 --> 00:23:37.830 not lead to immune stimulation.
And the last thing we tried to do with this trial is to look at substance of patients because here you are putting all newcomers together and maybe certain subsets of patients benefit better. So we tried to look at 2 specific subsets, patients who have TP 53 mutations, which have been shown to have a microenvironment in the bone marrow that is more immunosuppressive and might be more amenable to immune checkpoint inhibition based on multiple sources as well as patients who have splicing factor mutations, which Omar Abdullah have from...
Sloan Kettering and others have shown could be more susceptible to immune checkpoint inhibition. However, we also did not see any activity in those patients who have TB. This analysis was presented by Yan in a couple of years at ASH and is currently under consideration for publication. So we tried to think further about how can we overcome this immune checkpoint resistance for patients and one theory was, that myeloid derived suppressor cells could be a mediating resistance. This was based on solid tumours and we replicated the data.
Doctor Tikkun Kim who's currently at Vanderbilt was here at TL did very nice preclinical trials that suggested that there could be the benefit of combining a drug that targets myeloid derived suppressor cells such as entenostat which is a Estonia acetylase inhibitor with with Pimpro or PD1 inhibitor. And based on these preclinical data, this was translated to a clinical trial, multi centre phase one trial that was conducted in collaboration with the UM one group under Pat Larosso with the theory again that adding Antinostat would suppress myeloid giraffe, suppress our cells and therefore
allow pimprolismab to exert its immune chip point inhibition. So that the trial has been presented by Anne, I’m not going to go through the results because again unfortunately it was clinically negative. We are currently going through the correlative data to understand what led to the failure of the clinical data. However, I think there are more exciting agents. One of them is sabatolimab. So sabatolimab is a novel immune checkpoint inhibitor. Sabatolimab targets term 3.
So term 3 is not only expressed on T cells and medias immune checkpoint inhibition, but it’s also expressed in leukemia stem cells and leukemia plast and targeting. Preclinical data has suggested a potential not only efficacy but a functional mechanism in which it can lead to immune checkpoint inhibition but also direct targeting of the leukemia stem cells. So the stimulus MD’s one trial was the first randomized trial with this drug. This trial randomized patients to receive HMA versus HMA with sabatolimab and the primary endpoint was complete.
response and progression free survival.

We presented this data in ASH last year. Currently the manuscript is under review and while the trial did not meet its end point, there was no significant statistically improvement in complete remission or progression free survival. You can see that there was a late separation in the curve of the progression free survival and some trend toward improvement with the PFS. So we also sub analyse these data and what we have found is that patients who have lower disease...
burden seem to benefit more.

However, of course this is ad hoc analysis, exploratory analysis.

But what was also exciting is among the patients who achieved response as you can see in the red, patients who achieved The Who got the combination seems to have doubled the duration of response compared to those who have HMA alone, which again suggests that the combination might deepen the response leading to longer duration of activity.

So the stimulus MD’s two is a large randomized phase three trial of Sabatolimab plus Aza versus Sabatolimab alone and
00:27:45.136 --> 00:27:48.094 this trial again is fully accrued more
00:27:48.094 --> 00:27:51.270 than 530 patients enrolled on this trial.
00:27:51.270 --> 00:27:53.180 This trial is also expected to report by early 2024.
00:27:55.236 --> 00:27:57.866 So between venetoclax and sabatolimab,
00:28:00.078 --> 00:28:02.365 hopefully one of those two at least will be positive and change the landscape
00:28:02.365 --> 00:28:05.249 of how we treat patients with high risk MD's.
00:28:05.250 --> 00:28:07.511 So moving to the AML front where
00:28:07.511 --> 00:28:11.530 we have also tried to move some of those concepts forward.
00:28:11.530 --> 00:28:14.378 So the plus AML one is a randomized phase two trial an IAT that is also running through the UM 1 mechanism
00:28:14.378 --> 00:28:17.620 with Pat Larosso Rory has been doctor
Shalis has been working on this with me and this trial is actively enrolling.

We have more than 40 patients right now where patients are getting 7 + 3 versus 7 + 3 with pemprolizumab.

The primary endpoint is MRD negative CR, another randomized phase two trial that we are working through the same mechanism as last ML2 and this trial looks at older patients where the combination is is a citedine with venetoclax plus minus Pemprolizumab. This trial is also through the UM 1 mechanism and through both of those trials and in collaboration with CMAC, which is a cancer immunotherapy.
monitoring group.

Within C Tib, we are conducting an extensive set of correlative studies who are also collaborating with Doctor Jerry Radic from the Hajj to look at MRD negativity through different more sensitive techniques including circulating tumor DNA and at the level of the stem cells and looking at as I mentioned that other leukaemia and a specific T cell activation and a number of other I think important studies. Finally on the same front we have the plasty ML3 trial which is a
phase two trial looking at combining IDH inhibitors with pimprolism AB. This is based on preclinical data suggesting that patients who have IDH mutations also have immunosuppressed microenvironment. So Doctor Lourdes Mendez and Dr. Max Stoll at Hutch who I forgot to put his picture sorry are working on this trial and hopefully this trial is approved by Merck and hopefully it’s going to open next year. And lastly on that front, we also have another trial with the triplet is Evan Sabatolimab. This is a phase two trial which
00:30:15.025 --> 00:30:17.085 enrolled more than 80 patients.

00:30:17.090 --> 00:30:20.408 We presented the data lost ash and

00:30:20.410 --> 00:30:22.685 for the only for the safety cohort,

00:30:22.690 --> 00:30:25.090 the full set of data has not been

00:30:25.090 --> 00:30:28.198 presented and I think we have shown

00:30:28.198 --> 00:30:30.122 extensively that immune checkpoint

00:30:30.122 --> 00:30:33.182 inhibition while can be difficult in

00:30:33.182 --> 00:30:35.605 patients with leukaemia is difficult

00:30:35.605 --> 00:30:37.930 to administer for multiple reasons.

00:30:37.930 --> 00:30:38.826 For example,

00:30:38.826 --> 00:30:41.066 our patients are often have

00:30:41.066 --> 00:30:41.962 deep thrombocytopenia,

00:30:41.970 --> 00:30:43.170 so we cannot biopsy them.

00:30:43.170 --> 00:30:44.414 If the patient has

00:30:44.414 --> 00:30:45.658 inflammation in their lung,
sometimes it’s difficult to know
is this a fungal infection or is
this pneumonitis And in solid
tumours it’s easy or not
at least easier to go and get a
biopsy out of the lung.
biopsy out of the lung.
But in our patients it’s very
difficult to get biopsies.
We’re also hesitant to give steroids
many times because of fungal infections
that are common in our patients.
So conducting immune checkpoint
inhibition trials in patients
with MD’s is a bit challenging.
However it is it can be done and this
is retrospective analysis that was done
by Doctor Shalas in you’re looking at
our own data showing that the number
of immune related adverse events was
somewhat similar to what is seen in
patients with solid tumors when they
get immune checkpoint inhibition.
But also importantly that we are not seeing
excess mortality when we use these agents.
So I think it’s certainly feasible.
I think it’s certainly has a
way to kind of move forward and
one of those agents I have deep
confidence is going to be positive.
But I think another important
concept that we need to apply is
biomarker selection of patients,
because currently we are unrolling all newcomers regardless of their susceptibility to immune checkpoint inhibition. And I keep making the analogy of trying to treat patients with IDH or all patients with an IDH inhibitor when you only should treat the ones with the IDH 1 mutation or the same thing with the EGFR. So we really should select patients who are more likely to respond to the specific pathway. This is an example of I think a nice effort looking at an immune effector signature to try to
define subset of patients.
This is clearly retrospective,
but I think this is what should be applied in clinical trials
in a prospective fashion,
so we can select patients who are more likely to respond.
So and I’d like to thank the colleagues in the leukemia and myeloid malignancy program,
including our wonderful MPs and the fellows and mentors and collaborators. All of them have been working with us,
but also importantly our clinical research team who has been fundamental.
to all those clinical trials that I’ve just shown you and have been extremely productive even during COVID and all the staffing shortages that we had over the years.

And at the end I’d like to thank all the organizations that helped fund my research and all the collaborators and happy to take any questions.

Have a great time and let me apologize for not being here yesterday.

I realized I was supposed to notice I heard you again well on your own It’s it’s a pretty impressive body of work that that we’ve seen over these past few years.
What do we know about and I thought this team eventually was when I was here, but is there any fundamental difference in MD’s in younger individuals than those who are, you know, more typically, so the occasional 40 or 50 year old person, you see it because this heavy year, 80 year old. Yeah, this is actually a very important question. So the majority of MD’s patients are older than 65, around 85% of patients are older than 65.
but generally tend to be two big areas. One of them is previous exposure to chemotherapy or radiation in the context of solid tumours, usually breast cancer actually is a common setting where we see patients who have received radiation or chemo and have secondary cancer. But the second big area is genomic predisposition. So there are a number of patients who have for example underlying Franconia’s anemia or plastic anemia or some kind of hereditary predisposition. The number of those predisposition genes actually has been increasing.
or we are discovering more and more of them and it’s quite fascinating.

For example, there is one called DDX 4, one that we did not know about until you know a few years ago and it turned out that 10% of patients with AML and MD’s have that.

And those are I think important because they underlie different, different clinical behaviour.

Those patients for example tend to be more indolent. I have a 96 year old patient with AML who has DDX 41 germline and it’s just mind boggling to
me that you think that someone carried this mutation until she was 95 to develop finally AML. So those tend to happen in older patients. There are other ones that tend to happen at a younger age. But I think the biggest message usually, I usually say regarding younger patients the MD’s is you have to look for other things because there are many things that mimic MD’s and you want to make sure what you are dealing with is indeed MD’s because the treatment is, is different.
Yes.

Yeah, this is a very good question.

And actually this has always come up in our discussions with you know, with IR, BS and regulators. And there’s actually a large chunk of evidence based on as I mentioned, the problems that most of the trials that we have done in the field have been single arm trials. So most of what we have right now is anecdotal experience.

We are not seeing overall, if you look at the entirety of data, we’re not seeing an increased incidence.
00:36:41.218 --> 00:36:45.450 of GVHD that is of high severity.
NOTE Confidence: 0.46399102
00:36:45.450 --> 00:36:48.264 However, we have never had a randomized
NOTE Confidence: 0.46399102
00:36:48.264 --> 00:36:50.820 trial that would look at this in both
NOTE Confidence: 0.46399102
00:36:50.820 --> 00:36:52.777 in both arms and This is why I think
NOTE Confidence: 0.46399102
00:36:52.777 --> 00:36:54.809 our tube last trials are going to be
NOTE Confidence: 0.46399102
00:36:54.809 --> 00:36:56.663 very important because we have two
NOTE Confidence: 0.46399102
00:36:56.663 --> 00:36:58.878 arms and patients from both arms are
NOTE Confidence: 0.46399102
00:36:58.878 --> 00:37:01.216 going to transplant and I think this
NOTE Confidence: 0.46399102
00:37:01.216 --> 00:37:04.442 is going to give us a good sense of that.
NOTE Confidence: 0.46399102
00:37:04.442 --> 00:37:06.188 The, the other argument I always
NOTE Confidence: 0.46399102
00:37:06.188 --> 00:37:08.726 say is that while there could be a
NOTE Confidence: 0.46399102
00:37:08.726 --> 00:37:10.847 potential that you could increase GVHD,
NOTE Confidence: 0.46399102
00:37:10.847 --> 00:37:12.382 there’s also a potential that
NOTE Confidence: 0.46399102
00:37:12.382 --> 00:37:13.860 you could actually increase GVL,
NOTE Confidence: 0.46399102
00:37:13.860 --> 00:37:14.180 right,
NOTE Confidence: 0.46399102
00:37:14.180 --> 00:37:16.420 because the way GVL is a graft
versus leukemia effect and this is how we think transplant can work. So I think it’s always a risk benefit and I don’t think you can answer that without a randomized data. This is something we are certainly keeping a very close eye on in our different trials and the regulators have been also kind of keeping a close eye on this. And I have to say in in our practice we usually try to say stop the immune checkpoint inhibitor like you know in the last six weeks before transplant 6 to 8 weeks ideally just.
because of that theoretical concern. I would say at the end is that in immune checkpoint inhibitors are approved in some in substance of lymphoma and in that setting there has not they have not seen that issue as much. So I guess we’ll, you know, we’ll have to wait and see for AML and MD’s. So I guess we’ll, you know, we’ll have to wait and see for AML and MD’s. Yeah, this is a great question And part of why I did not divulge and like go too much into this is that this methylation business has been
I think one of the most challenging aspects of Steve Gorwin, he used to hate calling these hypomethylating agents because we are not even 100% sure that this is how they actually work. You know, we always like to call them DNMT3 inhibitors. In those trials that I presented they did not do like specific methylation. But we still don’t fully understand what because you are seeing a mix of hyper methylation, hyper methylation depending on where.
you are looking within the genome and until now we don’t fully understand the mechanism of action of these drugs. I did not go into this because of, of, you know, the nature of the audience here. But I think one of the biggest challenges in my own view about why we could not go beyond HMAS is that we are stuck with this schedule that is at the approved seven days we could not go beyond HMAS is that we are stuck with this schedule that is at the approved seven days of azacitidine in every single trial that we have. And this is a myelosuppressive combination and trying to add things to it has been quite challenging.
But currently it’s not considered ethical to randomize, you know, without including the seven days of HMA because it’s the only drug that has been want to improve our all survival. But you’re right, I mean there could be trials, there could be agents that could antagonize that methylation or it could be the other way around where this methylation is negatively impacting it. So that has been a big, I think, problem, Nathaniel.
we know that those therapies result in quite profound immune suppression and not only they, they’re also quite lymphopenic when you have 0.1. So does it make sense to give them concurrently? I mean, you’re trying to mount some different response at the same time, completely suppressing their chemo, so it doesn’t make sense to get them concurrently. Or would you have a more clever way where you perhaps cumulate the marrow, allow them to recover, have some given or reconstitution and then, you know, yeah.
So there are people working on concepts like this where they are giving it around the time of immune reconstitution as you mentioned.

I think 2 points on this front is that they actually have combined and solid tumours. They have multiple and you know, Barbara and others know more about this like solid tumours where you are giving chemo with immune therapy and it seems like it has worked, but their drugs are not as lymphodepleting as ours. But the other thing we actually
have tried to do on these trials,

I did not go into this into detail is that we moved the initiation of the immune checkpoint inhibition to day eight.

So rather than waiting until day 21 when you know all the cells have have died.

So around the aid, the idea of doing it early is similar to that you have.

This is when you have all the antigens being, you know, from the dying cells coming out and trying to activate lymphocytes at that at that point.

But you’re right,

I mean this is another I think big
NOTE Confidence: 0.27404776
00:41:53.104 --> 00:41:54.798 challenge of when what is the exact
NOTE Confidence: 0.27404776
00:41:54.798 --> 00:41:58.494 time to to use these these drugs has
NOTE Confidence: 0.27404776
00:41:58.494 --> 00:42:00.114 been somewhat kind of frustrating
NOTE Confidence: 0.27404776
00:42:00.114 --> 00:42:02.688 I have to say with with both PD1,
NOTE Confidence: 0.27404776
00:42:02.690 --> 00:42:05.210 PDL 1 so far and because multiple
NOTE Confidence: 0.27404776
00:42:05.210 --> 00:42:06.613 trials have been negative.
NOTE Confidence: 0.27404776
00:42:06.613 --> 00:42:09.197 So it might be that none of those
NOTE Confidence: 0.27404776
00:42:09.197 --> 00:42:11.350 pathways are you know what really
NOTE Confidence: 0.27404776
00:42:11.350 --> 00:42:13.734 is important in the MLN MD’s and
NOTE Confidence: 0.27404776
00:42:13.734 --> 00:42:15.342 maybe the Sabatoli map that I
NOTE Confidence: 0.27404776
00:42:15.342 --> 00:42:17.090 just showed or some other.
NOTE Confidence: 0.27404776
00:42:17.090 --> 00:42:18.890 You know there are other,
NOTE Confidence: 0.27404776
00:42:18.890 --> 00:42:21.010 I did not go on to this as well in detail,
NOTE Confidence: 0.27404776
00:42:21.010 --> 00:42:23.222 but they are lag three, they are Lil RP4.
NOTE Confidence: 0.27404776
00:42:23.222 --> 00:42:25.486 There are a number of other immune
NOTE Confidence: 0.27404776
75
checkpoint pathways that are also being tested in MD’s and AML.

Yes, with...and that has not led to clinical improvement in solid tumors. So the development has been largely focused on the MD’s space. They have a, the company has sponsored trials where they are combining different immune checkpoint inhibitors and actually sabatorimab with other drugs.
So those I think could give you an idea, but from a regulatory path, you know you’re as I was saying a little bit earlier is you have to combine with HMA to kind of get your first approval and then I think you know contagion, hago. Contagion also said like the real research starts once a drug is approved like you really need to get like something like once it’s approved, I think you can do all kinds of concepts but the initial focus is always on trying to kind of get the trial that leads to approval and then you can do all these kind of bigger concepts.
You can do them now in a small phase one study, but not in a large setting.

Yes, Sir.

I think this is a very good question. Clearly the post transplant setting is a very important development area because most of our patients unfortunately despite transplant they they relapse. So I think with the epilogue map, the trial, the New England Journal paper I showed you, people have had a very tough time replicating these, I would say outside of, you know, occasional responses. So most people are not using Epilomab.
of kind of label to to give it.
And most of those responses by the way happened in the extramedullary relapses like skin disease and probably that speaks to different microenvironment between the bone marrow, versus the bone marrow relapse.
In terms of your other questions specific about the TM3, there’s actually a trial giving TM3 inhibitor post transplant. I didn’t go into this one, but this one is ongoing and I believe there could be presentations.
in the near future about this. I'm not involved in it. Yeah. No. I think again, like,
you know, I think it's like we're getting out like that. Sit right. Sitting.
Could you phrase your hand? Is there any evidence that that prevents basically the development of MPs or weighted MPs or AFL? Just thinking of like ways to sort of look at that rather than a code reading with like MD's. This is actually an area.
that is getting more attention now because of what I showed at the beginning like this chip slash seeker spectrum where clonal hematopoiesis. We are seeing some of this actually in solid tumors. For example a breast cancer patient under you know underlying more and more people are doing these next Gen. sequencing and then the patient turned out to have TP 53 mutation chip like the blood counts are completely normal but she has TP53 mutation. And one of the increasing questions that are being asked like you know
the oncologists are afraid to give chemotherapy because that TP53 clone could expand and lead to MD’s or or AML. So I would say this is an evolving area. Currently we don’t think immune checkpoint inhibition would work. Most of the trials that are looking at agents are looking at things that are very non-toxic. Let me put it this way because those are patients with good counts generally and normal bone marrow. So they are like they are trials of vitamin C and you know inflammation, anti-inflammatory agents etcetera. However those drugs can be given together.
One of the things actually we benefited from doing these trials is that I have a number of patients I share with our colleagues here that need some, you know, that need immune checkpoint inhibition. I have multiple patients including with Barbara where they are on some kind of immune checkpoint inhibitor and they have MD’s now and I need to give them azacitidine because they have MD’s and we have been doing this in a number of patients and for the most part is pretty safe.
be a horrendous situation.

It’s still a horrendous situation.

You have two active tumours,

MD’s and solid tumour,

but many of those patients used to get only supportive care and nothing else.

But now we for the most part because immune checkpoint inhibitors generally will not lower your blood count.

So they are able to give them even with patients with MD’s and I’m able to treat the patient with azacitidine because it does not worsen their immunosuppression.

You can give it safely.

But again,
this I think how to prevent clonal evolution is I think is an important area as well.
OK. Thank you so much my e-mail if anybody has any questions then.