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.

The first one is updates and classification
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

So what are myelodysplastic syndromes,

neoplasm.

You can see that we actually have

kind of doing in these disease areas.

So what are myelodysplastic syndromes,

neoplasm.

You can see that we actually have

formally added the name 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 tumor 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, 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.
with MD’s has been quite challenging. Another I think challenging feature has been the classification of MD’s. And over the years, how do you separate MD’s from AML has been a moving target. Historically A+ count of 30% was used and then this was changed to 20% most recently last year and this created a huge difficulty in the field is the target blast count has been moved to 10%. So now there is this new entity called MD’s slash AML which is 10 to 19% blast and this is causing a lot of confusion for patients especially.
that the PATH reports get released immediately to patients nowadays or they are being told that you have MD’s by one classification and AML by another classification. And to address this issue, we actually have worked with a large number of international colleagues to establish an 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 70,000 cases, which by the numbers of MD’s is
00:04:25.558 --> 00:04:27.896 quite actually quite large of highly annotated cases to try to come up with one unified classification.

00:04:27.896 --> 00:04:30.087 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.

00:04:32.230 --> 00:04:33.970 What is I think important is the risk stratification. Why is that important? Because patients with MD’s have variable prognosis. Some patients can live for multiple...
years while other patients have prognosis that’s almost akin to that of acute leukemia patients, meaning that the prognosis can be less than six to nine months and therefore having good risk stratification systems is very important. Historically, you can see in this table four of the most commonly used stratification systems. All of them rely on the number of the plast in the bone marrow as well as the karyotypic abnormalities and the blood counts. However,
for a long time we and others have shown that some of the patients that are called lower risk MD’s die quickly. 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 of the disease severity. 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.
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 their assessment and I’m hopeful that this will become a more uniform way of looking at clinical trial
to further like establish their confidence in the efficacy of therapeutics in a more consistent fashion. We are validating this using the 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 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 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 erythropoiesis stimulating agents. 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 the specter sit in the frontline setting. So this is comparing it against
Erythropoiesis stimulating agents in patients with ringsidroplasts and without ringsidroplasts. 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 a 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
NOTE Confidence: 0.34587935
00:13:02.934 --> 00:13:04.790 a lot of interest is Amitelestad.
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00:13:04.790 --> 00:13:07.520 This is a first in class telomerase
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00:13:07.910 --> 00:13:10.275 So telomerase activity in patients
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00:13:10.275 --> 00:13:12.950 with MD’s has been associated with
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00:13:18.874 --> 00:13:21.119 in a large phase two trial.
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00:13:21.120 --> 00:13:24.284 This is a drug that’s given intravenously
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00:13:24.284 --> 00:13:27.050 every four weeks and in a phase two trial
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00:13:27.050 --> 00:13:28.562 lead to 40% transfusion independence.
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00:13:28.562 --> 00:13:32.240 So this was taken to a phase three trial.
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00:13:32.240 --> 00:13:35.159 We have presented the data of this
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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...
It’s around 51 weeks, which fought by MD’s criteria is actually pretty good. So this drug is currently in front of the FDA for consideration of approval and if it gets approved it will offer another I think very good opportunity for our patients with lower risk MD’s to become transition free, which is very important moving to high risk MD’s. This is where we have more of our recent failures I would say in development of new therapies. This figure I’m showing you has not
00:14:43.694 --> 00:14:45.690 really changed in the last almost 20 years.
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00:14:45.690 --> 00:14:47.690 So patients who are candidates
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00:14:49.757 --> 00:14:52.571 and those who are not the receive
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00:14:52.571 --> 00:14:53.375 hypomythylating agents.
NOTE Confidence: 0.34587935
00:14:53.380 --> 00:14:53.900 However,
NOTE Confidence: 0.34587935
00:14:53.900 --> 00:14:56.500 we know that hypomuthilating agent
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00:14:56.500 --> 00:15:00.909 the long term survival only if you
NOTE Confidence: 0.34587935
00:15:00.909 --> 00:15:02.946 use HMA without going to transplant
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00:15:02.946 --> 00:15:06.024 is less than 4% and for that reason
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00:15:06.024 --> 00:15:08.670 we strongly encourage patients
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00:15:08.747 --> 00:15:10.440 transplant whenever possible,
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00:15:10.440 --> 00:15:13.160 but also try to build up on HMA
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00:15:13.160 -- 00:15:14.968 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 hypomethylating agents keep expanding.
The latest addition was this drug magrolimab which works on the CD 47 pathway.
This is a very, this 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 I guess in a 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 PCL 2 inhibitor. This is already approved for patients with acute myeloid leukemia who are older. The frontline phase two trial should have 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. 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 are adhering, 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, 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
diversity or in quantity by flow cytometry, neither in the bone marrow or in the peripheral blood between the two arms. And this was particularly surprising because there has been a prevailing theory that the reason why immune checkpoint inhibition does not work in AML is that once you give it subsequent lines, third, fourth line, that the immune system has been beat up a lot by the chemotherapy. So here we were giving it in the frontline sitting and still it did 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 micro environment 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 53. 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 we can 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 Tikun 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 Pimpro or PD1 inhibitor. And based on these preclinical data, this was translated to a clinical trial, a 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 mediates 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. 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.
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 than 530 patients enrolled on this trial. This trial is also expected to report by early 2024.

So between venetoclax and sabatolimab, hopefully one of those two at least will be positive and change the landscape of how we treat patients with high risk MDS.

So moving to the AML front where we have also tried to move some of those concepts forward. The plus AML one is a randomized phase two trial an IAT that is also running through the UM 1 mechanism 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 a citudeine 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.
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00:29:06.542 --> 00:29:08.720 we are conducting an extensive set
NOTE Confidence: 0.66074306
00:29:08.789 --> 00:29:11.441 of correlative studies who are also
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00:29:11.441 --> 00:29:13.209 collaborating with Doctor Jerry
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00:29:13.280 --> 00:29:16.308 Radic from the Hajj to look at MRD
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00:29:35.590 --> 00:29:37.872 Finally on the same front we have
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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 micro environment. 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.
enrolled more than 80 patients.

We presented the data lost ash and for the only for the safety cohort, the full set of data has not been presented and I think we have shown extensively that immune checkpoint inhibition while can be difficult in patients with leukaemia is difficult to administer for multiple reasons. For example, our patients are often have deep thrombocytopenia, so we cannot biopsy them. If the patient has 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. 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 can be done and this 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, 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.

We do see MD’s in younger patients,
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 1 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 for 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
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carried this mutation until she was
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finally AML.
NOTE Confidence: 0.29407984
So those tend to happen in older patients.
NOTE Confidence: 0.29407984
There are other ones that tend
NOTE Confidence: 0.29407984
to happen at a younger age.
NOTE Confidence: 0.29407984
But I think the biggest message usually,
NOTE Confidence: 0.29407984
I usually say regarding younger
NOTE Confidence: 0.29407984
patients the MD’s is you have to
NOTE Confidence: 0.29407984
look for other things because there
NOTE Confidence: 0.29407984
are many things that mimic MD’s
NOTE Confidence: 0.29407984
and you want to make sure what
NOTE Confidence: 0.29407984
you are dealing with is indeed
NOTE Confidence: 0.29407984
MD’s because the treatment is,
NOTE Confidence: 0.29407984
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.
of GVHD that is of high severity.

However, we have never had a randomized trial that would look at this in both arms and This is why I think our tube last trials are going to be very important because we have two arms and patients from both arms are going to transplant and I think this is going to give us a good sense of that.

The other argument I always say is that while there could be a potential that you could increase GVHD, there’s also a potential that you could actually increase GVL, because the way GVL is a graft.
00:37:16.420 --> 00:37:18.376 versus leukemia effect and this is how we think transplant can work.
00:37:20.260 --> 00:37:22.412 So I think it’s always a risk benefit and I don’t think you can answer that without a randomized data.
00:37:28.871 --> 00:37:30.924 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.
00:37:39.488 --> 00:37:42.622 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 aspect of you know Steve Gorwin, he used to be like 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 site specific methylation. But we still don’t fully understand what because you are seeing a mix of hyper methylation.
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 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, and their drugs are not as lymphodepleting as ours. But the other thing we actually
00:41:25.654 --> 00:41:27.080 have tried to do on these trials,
NOTE Confidence: 0.27404776
00:41:27.080 --> 00:41:29.050 I did not go into this into detail is that
NOTE Confidence: 0.27404776
00:41:29.097 --> 00:41:31.127 we moved the initiation of the immune
NOTE Confidence: 0.27404776
00:41:31.127 --> 00:41:32.519 checkpoint inhibition to day eight.
NOTE Confidence: 0.27404776
00:41:32.520 --> 00:41:35.448 So rather than waiting until day 21 when
NOTE Confidence: 0.27404776
00:41:35.450 --> 00:41:36.970 you know all the cells have have died.
NOTE Confidence: 0.27404776
00:41:36.970 --> 00:41:38.214 So around the aid,
NOTE Confidence: 0.27404776
00:41:38.214 --> 00:41:40.450 the idea of doing it early is
NOTE Confidence: 0.27404776
00:41:40.450 --> 00:41:41.710 similar to that you have.
NOTE Confidence: 0.27404776
00:41:41.710 --> 00:41:44.050 This is when you have all the antigens being,
NOTE Confidence: 0.27404776
00:41:44.050 --> 00:41:44.708 you know,
NOTE Confidence: 0.27404776
00:41:44.708 --> 00:41:46.682 from the dying cells coming out
NOTE Confidence: 0.27404776
00:41:46.682 --> 00:41:48.504 and trying to activate lymphocytes
NOTE Confidence: 0.27404776
00:41:48.504 --> 00:41:50.324 at that at that point.
NOTE Confidence: 0.27404776
00:41:50.330 --> 00:41:51.074 But you’re right,
NOTE Confidence: 0.27404776
00:41:51.074 --> 00:41:53.104 I mean this is another I think big
challenge of when what is the exact
time to use these drugs has been somewhat frustrating
I have to say with both PD1, PDL 1 so far and because multiple trials have been negative.
So it might be that none of those pathways are really important in the MLN MD’s and maybe the Sabatoli map that I showed or some other.
You know there are other, I did not go on to this as well in detail, but they are lag three, they are Lil RP4.
There are a number of other immune
checkpoint pathways that are also being tested in MD’s and AML.

Yes, with TM3 without the PD one. Yeah, so I did not go through that the solid tumor literature with TM3 but they actually had a big trial combined TM3 and PD1 and that has not led to clinical improvement in solid tumours. 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, but not in a large setting. Yes, Sir.

Again, 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 relapse. So most people are not using Epilomab
NOTE Confidence: 0.290338
00:45:18.603 --> 00:45:20.995 of kind of label to to give it.
NOTE Confidence: 0.290338
00:45:21.000 --> 00:45:23.191 And most of those responses by the
NOTE Confidence: 0.290338
00:45:23.191 --> 00:45:25.127 way happened in the extramedullary
NOTE Confidence: 0.290338
00:45:25.127 --> 00:45:27.166 relapses like skin disease and
NOTE Confidence: 0.290338
00:45:27.166 --> 00:45:28.781 probably that speaks to different
NOTE Confidence: 0.290338
00:45:28.781 --> 00:45:30.320 microenvironment between the bone marrow,
NOTE Confidence: 0.290338
00:45:30.320 --> 00:45:31.571 between the extramedullary
NOTE Confidence: 0.290338
00:45:31.571 --> 00:45:33.664 versus the bone marrow relapse.
NOTE Confidence: 0.290338
00:45:33.664 --> 00:45:36.208 In terms of your other questions
NOTE Confidence: 0.290338
00:45:36.208 --> 00:45:37.840 specific about the TM3,
NOTE Confidence: 0.290338
00:45:37.840 --> 00:45:40.360 there’s actually a trial giving
NOTE Confidence: 0.290338
00:45:40.360 --> 00:45:41.400 TM3 inhibitor post transplant.
NOTE Confidence: 0.290338
00:45:41.400 --> 00:45:42.960 I didn’t go into this one,
NOTE Confidence: 0.290338
00:45:42.960 --> 00:45:45.025 but this one is ongoing and I
NOTE Confidence: 0.290338
00:45:45.025 --> 00:45:46.676 believe there could be presentations
NOTE Confidence: 0.290338

79
00:45:46.676 --> 00:45:48.794 in the near future about this.
NOTE Confidence: 0.290338
00:45:48.800 --> 00:45:49.958 I'm. I'm not involved in it.
NOTE Confidence: 0.46746305
00:46:07.150 --> 00:46:09.214 Yeah. No. I I think again, like,
NOTE Confidence: 0.46746305
00:46:09.214 --> 00:46:10.318 you know, I think it's like
NOTE Confidence: 0.46746305
00:46:10.318 --> 00:46:11.269 we're getting out like that.
NOTE Confidence: 0.46746305
00:46:11.270 --> 00:46:12.188 Sit right. Sitting.
NOTE Confidence: 0.46746305
00:46:23.180 --> 00:46:23.580 Yes,
NOTE Confidence: 0.26404873
00:46:41.910 --> 00:46:43.308 sorry, Could you phrase your hand?
NOTE Confidence: 0.26404873
00:46:50.710 --> 00:46:54.790 Is there any evidence that that
NOTE Confidence: 0.26404873
00:46:54.790 --> 00:46:57.390 prevents basically the development
NOTE Confidence: 0.26404873
00:46:57.390 --> 00:47:02.190 of an MPs or weighted MPs or AFL?
NOTE Confidence: 0.26404873
00:47:02.190 --> 00:47:04.050 Just thinking of like ways to
NOTE Confidence: 0.26404873
00:47:04.050 --> 00:47:06.101 sort of look at that rather
NOTE Confidence: 0.26404873
00:47:06.101 --> 00:47:07.710 than a code reading with like
NOTE Confidence: 0.5107637
00:47:10.790 --> 00:47:14.070 yeah, I think inhibiting development of
NOTE Confidence: 0.5107637
00:47:14.070 --> 00:47:17.534 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 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. So this in the past used to
00:48:48.597 --> 00:48:50.138 be a horrendous situation.
NOTE Confidence: 0.66263217
00:48:50.140 --> 00:48:51.260 It’s still a horrendous situation.
NOTE Confidence: 0.66263217
00:48:51.260 --> 00:48:52.860 You have two active tumours,
NOTE Confidence: 0.66263217
00:48:52.860 --> 00:48:54.104 MD’s and solid tumour,
NOTE Confidence: 0.66263217
00:48:54.104 --> 00:48:56.676 but many of those patients used to get
NOTE Confidence: 0.66263217
00:48:56.676 --> 00:48:58.620 only supportive care and nothing else.
NOTE Confidence: 0.66263217
00:48:58.620 --> 00:49:00.924 But now we for the most part because
NOTE Confidence: 0.66263217
00:49:00.924 --> 00:49:02.259 immune checkpoint inhibitors generally
NOTE Confidence: 0.66263217
00:49:02.259 --> 00:49:04.377 will not lower your blood count.
NOTE Confidence: 0.66263217
00:49:04.380 --> 00:49:06.580 So they are able to give them even
NOTE Confidence: 0.66263217
00:49:06.580 --> 00:49:08.296 with patients with MD’s and I’m
NOTE Confidence: 0.66263217
00:49:08.296 --> 00:49:09.946 able to treat the patient with
NOTE Confidence: 0.66263217
00:49:10.012 --> 00:49:11.817 azacitidine because it does not
NOTE Confidence: 0.66263217
00:49:11.817 --> 00:49:12.840 worsen their immunosuppression.
NOTE Confidence: 0.66263217
00:49:12.840 --> 00:49:14.340 You can give it safely.
NOTE Confidence: 0.66263217
00:49:14.340 --> 00:49:15.114 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.