WEBVTT

NOTE duration:"00:49:36"

NOTE recognizability:0.534

NOTE language:en-us

NOTE Confidence: 0.5386517

00:00:00.000 --> 00:00:02.196 Thank you so much for coming.

NOTE Confidence: 0.5386517

00:00:02.200 --> 00:00:03.894 You know, we are getting back to

NOTE Confidence: 0.5386517

00:00:03.894 --> 00:00:05.671 full in person and I know there are

NOTE Confidence: 0.5386517

00:00:05.671 --> 00:00:07.400 a lot of people on Zoom as well.

NOTE Confidence: 0.5386517

00:00:07.400 --> 00:00:09.240 So thank you so much for coming today.

NOTE Confidence: 0.5386517

00:00:09.240 --> 00:00:11.711 And I will be talking about immune

NOTE Confidence: 0.5386517

00:00:11.711 --> 00:00:13.385 checkpoint inhibition and Novant

NOTE Confidence: 0.5386517

00:00:13.385 --> 00:00:15.597 therapies for myelodysplastic syndromes.

NOTE Confidence: 0.5386517

00:00:15.600 --> 00:00:16.720 These are my disclosures

NOTE Confidence: 0.5386517

00:00:16.720 --> 00:00:18.120 and this is the outline.

NOTE Confidence: 0.5386517

00:00:18.120 --> 00:00:20.640 I'm going to cover 4 areas that have seen a

NOTE Confidence: 0.5386517

00:00:20.699 --> 00:00:23.155 lot of developments in the last few years.

NOTE Confidence: 0.5386517

00:00:23.160 --> 00:00:25.904 The first one is updates and classification

NOTE Confidence: 0.5386517

00:00:25.904 --> 00:00:28.344 as well as risk stratification

NOTE Confidence: 0.5386517

00:00:28.344 --> 00:00:30.716 and response assessment MD's,

NOTE Confidence: 0.5386517

00:00:30.720 --> 00:00:33.478 the evolving therapies for lower risk MD's,

NOTE Confidence: 0.5386517

00:00:33.480 --> 00:00:35.646 high risk MD's and then specifically

NOTE Confidence: 0.5386517

00:00:35.646 --> 00:00:37.475 about the immune checkpoint inhibition

NOTE Confidence: 0.5386517

00:00:37.475 --> 00:00:39.874 efforts that I have been trying to

NOTE Confidence: 0.5386517

00:00:39.874 --> 00:00:42.513 kind of doing in these disease areas.

NOTE Confidence: 0.5386517

00:00:42.520 --> 00:00:44.320 So what are myelodysplastic syndromes,

NOTE Confidence: 0.5386517

00:00:44.320 --> 00:00:44.661 neoplasm.

NOTE Confidence: 0.5386517

00:00:44.661 --> 00:00:47.048 You can see that we actually have

NOTE Confidence: 0.5386517

00:00:47.048 --> 00:00:49.306 formally added the name neoplasms finally

NOTE Confidence: 0.5386517

00:00:49.306 --> 00:00:51.568 because for a long time myelosplastic

NOTE Confidence: 0.5386517

00:00:51.629 --> 00:00:53.832 syndromes were thought of as syndrome

NOTE Confidence: 0.5386517

00:00:53.832 --> 00:00:56.688 or pre leukemia or a disorder,

NOTE Confidence: 0.5386517

00:00:56.688 --> 00:00:58.956 but they are actually cancers and this

NOTE Confidence: 0.5386517

00:00:58.956 --> 00:01:01.440 has been formally diagnosed by The Who.

NOTE Confidence: 0.5386517

00:01:01.440 --> 00:01:03.168 They are basically uncommon

NOTE Confidence: 0.5386517

00:01:03.168 --> 00:01:05.760 only four in 100,000 a year,

NOTE Confidence: 0.5386517

00:01:05.760 --> 00:01:08.756 20,000 cases of MD's in the US.

NOTE Confidence: 0.5386517

00:01:08.760 --> 00:01:09.028 However,

NOTE Confidence: 0.5386517

00:01:09.028 --> 00:01:10.904 the median ages in the early 70s

NOTE Confidence: 0.5386517

00:01:10.904 --> 00:01:13.115 and the number of patients with MD's

NOTE Confidence: 0.5386517

00:01:13.115 --> 00:01:15.115 has been increasing because we have

NOTE Confidence: 0.5386517

00:01:15.115 --> 00:01:16.755 more and more cancer survivors.

NOTE Confidence: 0.5386517

00:01:16.760 --> 00:01:19.064 I share many patients with many of you

NOTE Confidence: 0.5386517

00:01:19.064 --> 00:01:21.958 on the solid pumor side because those

NOTE Confidence: 0.5386517

00:01:21.958 --> 00:01:23.886 patients have secondary myelodysplastic

NOTE Confidence: 0.5386517

00:01:23.886 --> 00:01:26.715 syndromes and those can be among the

NOTE Confidence: 0.5386517

00:01:26.715 --> 00:01:28.510 most challenging patients to treat.

NOTE Confidence: 0.5386517

00:01:28.510 --> 00:01:31.062 And you can see here another fact that

NOTE Confidence: 0.5386517

00:01:31.062 --> 00:01:33.268 emphasizes the malignant nature of MD's.

NOTE Confidence: 0.5386517

00:01:33.270 --> 00:01:35.433 So this is the five year survival

00:01:35.433 --> 00:01:37.256 of patients with MD's in Violet

00:01:37.256 --> 00:01:38.906 and you can see it's 31%,

00:01:38.910 --> 00:01:40.646 very close to what you get with

00:01:40.646 --> 00:01:42.586 AML which is 25% but much worse

00:01:42.586 --> 00:01:44.768 than some of the more common solid

00:01:44.768 --> 00:01:46.994 tumors such as breast and lung when

00:01:46.994 --> 00:01:49.358 you take all the patients together.

00:01:49.360 --> 00:01:51.296 Again further emphasizing the

00:01:51.296 --> 00:01:53.716 malignant nature of these conditions.

00:01:53.720 --> 00:01:55.484 And more recently,

00:01:55.484 --> 00:01:58.713 we also understood that there is a

00:01:58.713 --> 00:02:00.750 large number of people who go through

00:02:00.812 --> 00:02:03.022 a process called clonal hematopoiesis

00:02:03.022 --> 00:02:05.232 of indeterminate potential or CHIP.

00:02:05.240 --> 00:02:07.949 And this is a condition that happens

NOTE Confidence: 0.5386517

00:02:07.949 --> 00:02:11.140 in up to 10% of people older than 70.

NOTE Confidence: 0.5386517

00:02:11.140 --> 00:02:13.324 And some of those progress to MD's

NOTE Confidence: 0.5386517

00:02:13.324 --> 00:02:14.260 and some don't,

NOTE Confidence: 0.5386517

00:02:14.260 --> 00:02:17.086 but they are also associated with

NOTE Confidence: 0.5386517

00:02:17.086 --> 00:02:18.499 inflammation and cardiovascular

NOTE Confidence: 0.5386517

00:02:18.499 --> 00:02:20.831 risk and many other syndromic

NOTE Confidence: 0.5386517

00:02:20.831 --> 00:02:22.615 dysfunction across the body.

NOTE Confidence: 0.5386517

00:02:22.620 --> 00:02:24.972 This is why multiple disciplines including

NOTE Confidence: 0.5386517

00:02:24.972 --> 00:02:27.020 cardiology have been interested in this.

NOTE Confidence: 0.5386517

00:02:27.020 --> 00:02:28.868 And for that more and more cancer

NOTE Confidence: 0.5386517

00:02:28.868 --> 00:02:30.442 centers have been interested in

NOTE Confidence: 0.5386517

00:02:30.442 --> 00:02:32.620 establishing clinics for chip and seekers.

NOTE Confidence: 0.5386517

00:02:32.620 --> 00:02:35.165 And here our newest recruit, Dr.

NOTE Confidence: 0.5386517

00:02:35.165 --> 00:02:37.235 Lourdes Mendez has taken over this

NOTE Confidence: 0.5386517

00:02:37.235 --> 00:02:40.065 aspect and I think this is going to

NOTE Confidence: 0.5386517

00:02:40.065 --> 00:02:42.740 become very important in the coming years.

NOTE Confidence: 0.5386517

00:02:42.740 --> 00:02:43.540 The management of MD's,

NOTE Confidence: 0.5386517

00:02:43.540 --> 00:02:45.458 as I'm going to show you in a little bit,

NOTE Confidence: 0.5386517

00:02:45.460 --> 00:02:47.420 has been difficult to get new therapies.

NOTE Confidence: 0.5386517

00:02:47.420 --> 00:02:49.956 And part of this is because of the

NOTE Confidence: 0.5386517

00:02:49.956 --> 00:02:51.539 large heterogeneity of the disease.

NOTE Confidence: 0.5386517

00:02:51.540 --> 00:02:53.580 This is a schema showing the

NOTE Confidence: 0.5386517

00:02:53.580 --> 00:02:54.940 genetic landscape of MD's.

NOTE Confidence: 0.87494814

00:02:54.940 --> 00:02:57.127 And you can see here that there are more

NOTE Confidence: 0.87494814

00:02:57.127 --> 00:02:58.946 than 40 recurrently abnormal somatic

NOTE Confidence: 0.87494814

00:02:58.946 --> 00:03:01.220 mutations that can happen in patients.

NOTE Confidence: 0.87494814

00:03:01.220 --> 00:03:03.332 However, less than six of those

NOTE Confidence: 0.87494814

00:03:03.332 --> 00:03:05.794 happen in more than 10% of patients.

NOTE Confidence: 0.87494814

00:03:05.794 --> 00:03:08.116 Therefore, there are many different driver

NOTE Confidence: 0.87494814

00:03:08.116 --> 00:03:10.171 genes and developing therapies that

NOTE Confidence: 0.87494814

00:03:10.171 --> 00:03:12.601 work across the spectrum for patients

NOTE Confidence: 0.87494814

00:03:12.601 --> 00:03:14.976 with MD's has been quite challenging.

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

00:03:47.373 --> 00:03:49.071 of confusion for patients especially

NOTE Confidence: 0.87494814

00:03:49.071 --> 00:03:51.477 that the PATH reports get released

NOTE Confidence: 0.87494814

00:03:51.477 --> 00:03:53.263 immediately to patient nowadays or

NOTE Confidence: 0.87494814

00:03:53.263 --> 00:03:55.419 they are being told that you have

NOTE Confidence: 0.87494814

00:03:55.420 --> 00:03:58.564 MD's by 1 classification and AML

NOTE Confidence: 0.87494814

00:03:58.564 --> 00:04:00.136 by another classification.

NOTE Confidence: 0.87494814

00:04:00.140 --> 00:04:02.060 And to address this issue,

NOTE Confidence: 0.87494814

00:04:02.060 --> 00:04:04.804 we actually have worked with a large

NOTE Confidence: 0.87494814

00:04:04.804 --> 00:04:07.115 number of international colleagues to

NOTE Confidence: 0.87494814

00:04:07.115 --> 00:04:09.775 establish international consortium of MD's.

NOTE Confidence: 0.87494814

00:04:09.780 --> 00:04:12.084 This is an effort that involves

NOTE Confidence: 0.87494814

00:04:12.084 --> 00:04:14.277 many experts across the world to

NOTE Confidence: 0.87494814

00:04:14.277 --> 00:04:16.621 try to come up with a unified way

NOTE Confidence: 0.87494814

00:04:16.694 --> 00:04:18.578 of classifying the disease.

NOTE Confidence: 0.87494814

00:04:18.580 --> 00:04:20.800 And indeed we have put together

NOTE Confidence: 0.87494814

00:04:20.800 --> 00:04:23.304 more than 70 more than 7000 cases,

NOTE Confidence: 0.87494814

00:04:23.304 --> 00:04:25.558 which by the numbers of MD's is

NOTE Confidence: 0.87494814

00:04:25.558 --> 00:04:27.896 quite actually quite large of highly

NOTE Confidence: 0.87494814

00:04:27.896 --> 00:04:30.087 annotated cases to try to come up

NOTE Confidence: 0.87494814

00:04:30.087 --> 00:04:32.229 with one unified classification.

NOTE Confidence: 0.87494814

00:04:32.230 --> 00:04:33.970 There's another update of this effort

NOTE Confidence: 0.87494814

00:04:33.970 --> 00:04:36.124 that will be presented in ASH in an

NOTE Confidence: 0.87494814

00:04:36.124 --> 00:04:37.540 oral fashion this year and hopefully

NOTE Confidence: 0.87494814

00:04:37.597 --> 00:04:39.186 the paper will be published soon so

NOTE Confidence: 0.87494814

00:04:39.186 --> 00:04:41.955 that we can have one common way in

NOTE Confidence: 0.87494814

00:04:41.955 --> 00:04:45.979 which we can talk to patients with MD's.

NOTE Confidence: 0.87494814

00:04:45.980 --> 00:04:46.528 After that.

NOTE Confidence: 0.87494814

00:04:46.528 --> 00:04:48.720 What is I think important is the risk

NOTE Confidence: 0.87494814

00:04:48.780 --> 00:04:50.764 stratification. Why is that important?

NOTE Confidence: 0.87494814

00:04:50.764 --> 00:04:51.908 Because patients with MD's

NOTE Confidence: 0.87494814

00:04:51.908 --> 00:04:52.980 have variable prognosis.

NOTE Confidence: 0.87494814

00:04:52.980 --> 00:04:54.930 Some patients can live for multiple

NOTE Confidence: 0.87494814

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

NOTE Confidence: 0.87494814

00:05:22.534 --> 00:05:25.112 for a long time we and others have

NOTE Confidence: 0.87494814

00:05:25.112 --> 00:05:27.506 shown that some of the patients that

NOTE Confidence: 0.87494814

00:05:27.506 --> 00:05:30.068 are called lower risk MD's die quickly

NOTE Confidence: 0.87494814

00:05:30.070 --> 00:05:31.870 die within two years of diagnosis.

NOTE Confidence: 0.87494814

00:05:31.870 --> 00:05:34.355 More than 1/4 of those lower risk

NOTE Confidence: 0.87494814

00:05:34.355 --> 00:05:36.655 MD's patients and it was clear that

NOTE Confidence: 0.87494814

00:05:36.655 --> 00:05:38.240 these prognostic risk scores are

NOTE Confidence: 0.87494814

00:05:38.307 --> 00:05:40.187 not capturing the whole spectrum

NOTE Confidence: 0.87494814

00:05:40.190 --> 00:05:41.558 of the disease severity.

NOTE Confidence: 0.87494814

00:05:41.558 --> 00:05:44.144 And we also have shown that among

NOTE Confidence: 0.87494814

00:05:44.144 --> 00:05:46.350 patients with therapy related MD's,

NOTE Confidence: 0.87494814

00:05:46.350 --> 00:05:47.790 which historically have been

NOTE Confidence: 0.87494814

00:05:47.790 --> 00:05:49.590 considered very high risk disease,

NOTE Confidence: 0.87494814

00:05:49.590 --> 00:05:51.790 some of them do OK,

NOTE Confidence: 0.87494814

00:05:51.790 --> 00:05:53.910 do better than some of the other patients.

NOTE Confidence: 0.9671921

00:05:53.910 --> 00:05:56.178 And that's again reflective of the

00:05:56.178 --> 00:05:58.669 variability on prognosis of those patients.

00:05:58.670 --> 00:06:00.805 And This is why it's important to

00:06:00.805 --> 00:06:03.054 apply good risk stratification

00:06:03.054 --> 00:06:05.646 process for every patient.

00:06:05.650 --> 00:06:07.996 After all of this basically the IPSSM,

00:06:07.996 --> 00:06:09.832 the molecular IPSS was finally published

00:06:09.832 --> 00:06:11.802 after a large international effort in

00:06:11.802 --> 00:06:13.806 the New England Journal of Evidence.

00:06:13.810 --> 00:06:17.090 You can see the Bernard ET al Citation.

00:06:17.090 --> 00:06:19.786 But the short of this is that it

00:06:19.786 --> 00:06:21.332 incorporated the molecular alterations

00:06:21.332 --> 00:06:25.175 in the calculation and that led to a more

00:06:25.175 --> 00:06:27.487 accurate risk stratification picture.

00:06:27.490 --> 00:06:29.807 And we have shown in a large

00:06:29.807 --> 00:06:31.330 analysis of two phase,

NOTE Confidence: 0.9671921

00:06:31.330 --> 00:06:33.521 phase two and phase three trials that

NOTE Confidence: 0.9671921

00:06:33.521 --> 00:06:35.825 were presented last year in ASH that this

NOTE Confidence: 0.9671921

00:06:35.825 --> 00:06:38.800 system does lead to upstaging of patients.

NOTE Confidence: 0.9671921

00:06:38.800 --> 00:06:40.888 You can see in red the high risk

NOTE Confidence: 0.9671921

00:06:40.888 --> 00:06:42.838 patients by the old scoring system,

NOTE Confidence: 0.9671921

00:06:42.840 --> 00:06:44.916 the Ipss, then the revised Ipss,

NOTE Confidence: 0.9671921

00:06:44.920 --> 00:06:47.320 then most recently the molecular IPSS.

NOTE Confidence: 0.9671921

00:06:47.320 --> 00:06:49.184 And you can see that the number of

NOTE Confidence: 0.9671921

00:06:49.184 --> 00:06:50.569 patients who are being diagnosed

NOTE Confidence: 0.9671921

00:06:50.569 --> 00:06:52.297 now as high risk disease because

NOTE Confidence: 0.9671921

00:06:52.297 --> 00:06:53.878 their prognosis is indeed poor,

NOTE Confidence: 0.9671921

00:06:53.880 --> 00:06:55.845 is becoming higher and therefore

NOTE Confidence: 0.9671921

00:06:55.845 --> 00:06:58.280 more of those patients are being

NOTE Confidence: 0.9671921

00:06:58.280 --> 00:07:01.610 directed for aggressive treatments.

NOTE Confidence: 0.9671921

00:07:01.610 --> 00:07:03.650 The last area I want to cover before we go

NOTE Confidence: 0.9671921

00:07:03.699 --> 00:07:05.685 to therapeutics is the response criteria.

NOTE Confidence: 0.9671921

00:07:05.690 --> 00:07:08.408 This is actually a very important

NOTE Confidence: 0.9671921

00:07:08.408 --> 00:07:10.611 area because response criteria have

NOTE Confidence: 0.9671921

00:07:10.611 --> 00:07:12.462 been quite problematic in MD's.

NOTE Confidence: 0.9671921

00:07:12.462 --> 00:07:15.538 And I can tell you that it's my

NOTE Confidence: 0.9671921

00:07:15.538 --> 00:07:17.614 belief and several of my colleagues

NOTE Confidence: 0.9671921

00:07:17.614 --> 00:07:19.882 at the same believe that it has

NOTE Confidence: 0.9671921

00:07:19.882 --> 00:07:21.770 impeded drug development in MD's.

NOTE Confidence: 0.9671921

00:07:21.770 --> 00:07:22.532 Why is that?

NOTE Confidence: 0.9671921

00:07:22.532 --> 00:07:24.056 Because some of the issues with

NOTE Confidence: 0.9671921

00:07:24.056 --> 00:07:25.788 the response criteria have led

NOTE Confidence: 0.9671921

00:07:25.788 --> 00:07:27.208 to certain medications moving

NOTE Confidence: 0.9671921

00:07:27.208 --> 00:07:28.977 from phase one to phase three.

NOTE Confidence: 0.9671921

00:07:28.980 --> 00:07:31.020 That probably should not have been the case.

NOTE Confidence: 0.9671921

00:07:31.020 --> 00:07:33.302 And This is why we have many

NOTE Confidence: 0.9671921

00:07:33.302 --> 00:07:34.939 Phase 3 failures in MD's.

NOTE Confidence: 0.9671921

00:07:34.940 --> 00:07:37.952 So again using a large international

NOTE Confidence: 0.9671921

00:07:37.952 --> 00:07:40.770 effort over the last two years

NOTE Confidence: 0.9671921

00:07:40.770 --> 00:07:43.179 that was coordinated through the

NOTE Confidence: 0.9671921

00:07:43.179 --> 00:07:44.658 international working group,

NOTE Confidence: 0.9671921

00:07:44.660 --> 00:07:47.350 we have revised these response

NOTE Confidence: 0.9671921

00:07:47.350 --> 00:07:50.040 criteria and this consensus proposal

NOTE Confidence: 0.9671921

00:07:50.040 --> 00:07:51.832 for revised international working

NOTE Confidence: 0.9671921

00:07:51.832 --> 00:07:54.520 group criteria has been now published

NOTE Confidence: 0.9671921

00:07:54.586 --> 00:07:56.644 and it started to be implemented

NOTE Confidence: 0.9671921

00:07:56.644 --> 00:07:58.466 in some clinical trials protocols.

NOTE Confidence: 0.9671921

00:07:58.466 --> 00:08:01.217 We have been in discussions with the

NOTE Confidence: 0.9671921

00:08:01.217 --> 00:08:04.200 FDA as well about implementing this in,

NOTE Confidence: 0.9671921

00:08:04.200 --> 00:08:07.260 in their assessment and I'm hopeful

NOTE Confidence: 0.9671921

00:08:07.340 --> 00:08:10.224 that this will become a more uniform

NOTE Confidence: 0.9671921

00:08:10.224 --> 00:08:12.916 way of looking at clinical trial

NOTE Confidence: 0.9671921

00:08:12.916 --> 00:08:15.296 to further like establish their

NOTE Confidence: 0.9671921

00:08:15.296 --> 00:08:18.113 the efficacy of therapeutics in a

NOTE Confidence: 0.9671921

00:08:18.113 --> 00:08:19.367 more consistent fashion.

NOTE Confidence: 0.9671921

00:08:19.370 --> 00:08:22.010 And we are validating this using

NOTE Confidence: 0.9671921

00:08:22.010 --> 00:08:24.262 WD database which will look both

NOTE Confidence: 0.9671921

00:08:24.262 --> 00:08:25.977 at the international working group

NOTE Confidence: 0.9671921

00:08:25.977 --> 00:08:27.645 criteria as well as the IPSSM.

NOTE Confidence: 0.9671921

00:08:27.645 --> 00:08:30.220 We actually have this database

NOTE Confidence: 0.9671921

00:08:30.220 --> 00:08:33.050 again with 15 different centers.

NOTE Confidence: 0.9671921

00:08:33.050 --> 00:08:34.650 Six of those presentations are

NOTE Confidence: 0.9671921

00:08:34.650 --> 00:08:36.729 going to be upcoming in in ASH,

NOTE Confidence: 0.9671921

00:08:36.730 --> 00:08:39.046 two of them are oral presentations

NOTE Confidence: 0.9671921

00:08:39.046 --> 00:08:41.370 by Doctor Tarek Iwan and by

NOTE Confidence: 0.9671921

00:08:41.370 --> 00:08:43.125 our newer newest recruit Dr.

NOTE Confidence: 0.9671921

00:08:43.130 --> 00:08:43.852 Ian Beversdorf.

NOTE Confidence: 0.9671921

00:08:43.852 --> 00:08:46.379 So I think this is going to

NOTE Confidence: 0.9671921

00:08:46.379 --> 00:08:48.521 further validate these response

NOTE Confidence: 0.9671921

00:08:48.521 --> 00:08:53.010 criteria as the way to establish,

NOTE Confidence: 0.9671921

00:08:53.010 --> 00:08:55.008 establish them as a way to

NOTE Confidence: 0.9671921

00:08:55.008 --> 00:08:56.850 approve medications in the future.

NOTE Confidence: 0.9671921

00:08:56.850 --> 00:08:59.160 So now moving from classification

NOTE Confidence: 0.9671921

00:08:59.160 --> 00:09:01.470 and response assessment to other

NOTE Confidence: 0.9671921

00:09:01.540 --> 00:09:03.722 therapies and you are looking here

NOTE Confidence: 0.9671921

00:09:03.722 --> 00:09:05.937 at the approved therapies in in the

NOTE Confidence: 0.9671921

00:09:05.937 --> 00:09:08.133 top line by the FDA and in the lower

NOTE Confidence: 0.62744665

00:09:08.201 --> 00:09:09.177 line by the EMA.

NOTE Confidence: 0.62744665

00:09:09.180 --> 00:09:10.902 And what you can quickly see compared

NOTE Confidence: 0.62744665

00:09:10.902 --> 00:09:12.848 to many solid tumours is that we

NOTE Confidence: 0.62744665

00:09:12.848 --> 00:09:14.293 don't have many approved therapies.

NOTE Confidence: 0.62744665

00:09:14.300 --> 00:09:16.134 This has been a very frustrating Rd.

NOTE Confidence: 0.62744665

00:09:16.140 --> 00:09:18.732 for drug development in MD's and

NOTE Confidence: 0.62744665

17

00:09:18.732 --> 00:09:21.172 in high risk MD's. For example,

NOTE Confidence: 0.62744665

00:09:21.172 --> 00:09:24.020 we did not have a drug approved in

NOTE Confidence: 0.62744665

00:09:24.099 --> 00:09:26.979 the last 20 years until the year 2020.

NOTE Confidence: 0.62744665

00:09:26.980 --> 00:09:29.140 So I'm going to show you the main

NOTE Confidence: 0.62744665

00:09:29.140 --> 00:09:30.734 therapies that we currently have

NOTE Confidence: 0.62744665

00:09:30.734 --> 00:09:33.058 available and how we are finally breaking

NOTE Confidence: 0.62744665

00:09:33.114 --> 00:09:35.139 through that deadlock of therapeutic

NOTE Confidence: 0.62744665

00:09:35.140 --> 00:09:37.359 evolution and we are starting I think

NOTE Confidence: 0.62744665

00:09:37.359 --> 00:09:39.658 to have better therapies come along.

NOTE Confidence: 0.62744665

00:09:39.660 --> 00:09:41.520 So the traditional approach of

NOTE Confidence: 0.62744665

00:09:41.520 --> 00:09:43.815 treating patients with lower risk MD's

NOTE Confidence: 0.62744665

00:09:43.815 --> 00:09:46.047 depends on symptom control because we

NOTE Confidence: 0.62744665

00:09:46.047 --> 00:09:48.099 cannot currently cure these patients.

NOTE Confidence: 0.62744665

00:09:48.100 --> 00:09:50.036 The only way to cure a patient with

NOTE Confidence: 0.62744665

00:09:50.036 --> 00:09:51.819 MD's with bone marrow transplant,

NOTE Confidence: 0.62744665

00:09:51.820 --> 00:09:53.420 but bone marrow transplants are

NOTE Confidence: 0.62744665

00:09:53.420 --> 00:09:54.700 usually reserved for patients

NOTE Confidence: 0.62744665

00:09:54.700 --> 00:09:56.297 who have higher risk disease,

NOTE Confidence: 0.62744665

00:09:56.300 --> 00:09:57.680 not lower risk disease.

NOTE Confidence: 0.62744665

00:09:57.680 --> 00:09:59.060 For patients with anaemia,

NOTE Confidence: 0.62744665

00:09:59.060 --> 00:10:02.126 the standard treatment would be ESA's

NOTE Confidence: 0.62744665

00:10:02.126 --> 00:10:03.659 erythropoiesis stimulating agents.

NOTE Confidence: 0.62744665

00:10:03.660 --> 00:10:06.282 However, those drugs are not active

NOTE Confidence: 0.62744665

00:10:06.282 --> 00:10:09.389 except in less than 1/2 of patients,

NOTE Confidence: 0.62744665

00:10:09.390 --> 00:10:11.442 40% and the response last less

NOTE Confidence: 0.62744665

00:10:11.442 --> 00:10:12.468 than 12 months.

NOTE Confidence: 0.62744665

00:10:12.470 --> 00:10:14.990 And I'm going to show you how this landscape

NOTE Confidence: 0.62744665

00:10:14.990 --> 00:10:17.429 has changed in the last couple of years.

NOTE Confidence: 0.62744665

00:10:17.430 --> 00:10:19.712 So the first I think major improvement

NOTE Confidence: 0.62744665

00:10:19.712 --> 00:10:21.828 was the introduction and final approval

NOTE Confidence: 0.62744665

00:10:21.828 --> 00:10:23.623 of this drug called luspetercept,

NOTE Confidence: 0.62744665

00:10:23.630 --> 00:10:24.830 what is luspetercept,

NOTE Confidence: 0.62744665

00:10:24.830 --> 00:10:26.030 the silicon trap.

NOTE Confidence: 0.62744665

00:10:26.030 --> 00:10:28.142 It works on a pathway called

NOTE Confidence: 0.62744665

00:10:28.142 --> 00:10:29.550 transforming growth factor pathway.

NOTE Confidence: 0.62744665

00:10:29.550 --> 00:10:32.246 These ligands suppress erythropoiesis,

NOTE Confidence: 0.62744665

00:10:32.246 --> 00:10:34.268 especially late erythropoiesis

NOTE Confidence: 0.62744665

00:10:34.270 --> 00:10:36.340 and using this ligand trap has

NOTE Confidence: 0.62744665

00:10:36.340 --> 00:10:38.390 led to restoration of effective

NOTE Confidence: 0.62744665

00:10:38.390 --> 00:10:40.508 erythropoiesis and ultimately

NOTE Confidence: 0.62744665

00:10:40.508 --> 00:10:42.626 improved transition independence.

NOTE Confidence: 0.62744665

00:10:42.630 --> 00:10:45.240 This led to transition independence in

NOTE Confidence: 0.62744665

00:10:45.240 --> 00:10:47.748 around 40% of patients in the in the

NOTE Confidence: 0.62744665

00:10:47.748 --> 00:10:49.515 phase three Middle East trial which

NOTE Confidence: 0.62744665

00:10:49.515 --> 00:10:51.357 was the landmark paper published in

NOTE Confidence: 0.62744665

00:10:51.357 --> 00:10:53.587 the New England Journal of Medicine.

NOTE Confidence: 0.62744665

00:10:53.590 --> 00:10:56.398 And based on this this drug was approved.

NOTE Confidence: 0.62744665

00:10:56.400 --> 00:10:58.265 And we have subsequently published

NOTE Confidence: 0.62744665

00:10:58.265 --> 00:11:00.473 additional follow up from this trial

NOTE Confidence: 0.62744665

00:11:00.473 --> 00:11:02.440 that showed that this drug not only

NOTE Confidence: 0.62744665

00:11:02.440 --> 00:11:04.557 lead to high rates of transfusion

NOTE Confidence: 0.62744665

00:11:04.557 --> 00:11:06.422 independence but it actually also

NOTE Confidence: 0.62744665

00:11:06.422 --> 00:11:08.260 leads to significant reduction in

NOTE Confidence: 0.62744665

00:11:08.260 --> 00:11:10.450 transfusions for patients who do not

NOTE Confidence: 0.62744665

00:11:10.511 --> 00:11:12.395 become transfusion dependent and

NOTE Confidence: 0.62744665

00:11:12.395 --> 00:11:14.279 lead to hematologic improvements.

NOTE Confidence: 0.62744665

00:11:14.280 --> 00:11:16.158 And this year the major development

NOTE Confidence: 0.62744665

00:11:16.158 --> 00:11:18.815 in lower risk MD's has been the final

NOTE Confidence: 0.62744665

00:11:18.815 --> 00:11:20.495 publication of the commands trial

NOTE Confidence: 0.62744665

00:11:20.495 --> 00:11:22.563 which looked at the activity of the

NOTE Confidence: 0.62744665

00:11:22.563 --> 00:11:24.636 specter sit in the frontline setting.

NOTE Confidence: 0.62744665

00:11:24.636 --> 00:11:27.708 So this is comparing it against

NOTE Confidence: 0.62744665

00:11:27.708 --> 00:11:29.346 erythropoiesis stimulating agents

NOTE Confidence: 0.62744665

00:11:29.346 --> 00:11:31.530 in patients with ringsidroplasts

NOTE Confidence: 0.62744665

00:11:31.593 --> 00:11:33.348 and without ringsidroplasts.

NOTE Confidence: 0.62744665

00:11:33.350 --> 00:11:34.988 So this was a primary analysis.

NOTE Confidence: 0.62744665

00:11:34.990 --> 00:11:38.366 This paper is now out in The Lancet

NOTE Confidence: 0.62744665

00:11:38.366 --> 00:11:40.494 journal showing that patients who

NOTE Confidence: 0.62744665

00:11:40.494 --> 00:11:42.198 received Los Pertoset achieved

NOTE Confidence: 0.62744665

00:11:42.198 --> 00:11:43.470 60% transition independence,

NOTE Confidence: 0.62744665

00:11:43.470 --> 00:11:45.990 almost double that what you expect

NOTE Confidence: 0.62744665

00:11:45.990 --> 00:11:47.656 with patients who receive ESA.

NOTE Confidence: 0.62744665

00:11:47.656 --> 00:11:50.000 So clearly a very active drug and it's

NOTE Confidence: 0.62744665

00:11:50.063 --> 00:11:51.857 moving to the frontline treatment of

NOTE Confidence: 0.62744665

00:11:51.857 --> 00:11:54.131 MD's which is a fundamental change in

NOTE Confidence: 0.62744665

00:11:54.131 --> 00:11:56.907 how we treat patients with lower risk MD's.

NOTE Confidence: 0.62744665

00:11:56.907 --> 00:11:59.289 We are trying to move this

NOTE Confidence: 0.62744665

00:11:59.289 --> 00:12:01.549 further through two other trials.

NOTE Confidence: 0.62744665

00:12:01.550 --> 00:12:03.110 One is the element trial,

NOTE Confidence: 0.62744665

00:12:03.110 --> 00:12:05.091 which is a large phase three trial

NOTE Confidence: 0.62744665

00:12:05.091 --> 00:12:07.230 that will be looking at patients

NOTE Confidence: 0.62744665

00:12:07.230 --> 00:12:09.265 who are not transfusion dependent.

NOTE Confidence: 0.62744665

00:12:09.270 --> 00:12:10.789 Here we are trying to move the

NOTE Confidence: 0.62744665

00:12:10.789 --> 00:12:11.440 bar higher and

NOTE Confidence: 0.34587935

00:12:11.489 --> 00:12:13.337 we are trying to prevent patients

NOTE Confidence: 0.34587935

00:12:13.337 --> 00:12:14.569 from even becoming transfusion

NOTE Confidence: 0.34587935

00:12:14.625 --> 00:12:16.185 dependent by treating them at a

NOTE Confidence: 0.34587935

00:12:16.185 --> 00:12:17.607 earlier stage of their anaemia.

NOTE Confidence: 0.34587935

00:12:17.607 --> 00:12:20.246 So this trial which will open at

NOTE Confidence: 0.34587935

00:12:20.246 --> 00:12:22.971 TLI think will be very important as

NOTE Confidence: 0.34587935

00:12:22.971 --> 00:12:24.597 a landmark trial in the management

NOTE Confidence: 0.34587935

00:12:24.597 --> 00:12:26.624 of MD's if it's positive because it

NOTE Confidence: 0.34587935

00:12:26.624 --> 00:12:28.978 would be the first time we get a drug

NOTE Confidence: 0.34587935

00:12:28.980 --> 00:12:31.080 potentially approved for patients who

NOTE Confidence: 0.34587935

00:12:31.080 --> 00:12:33.180 are not yet transfusion dependent.

NOTE Confidence: 0.34587935

00:12:33.180 --> 00:12:34.980 And another phase three trial that

NOTE Confidence: 0.34587935

00:12:34.980 --> 00:12:37.011 we are working on with the sponsor

NOTE Confidence: 0.34587935

00:12:37.011 --> 00:12:38.950 basically is looking at the use of

NOTE Confidence: 0.34587935

00:12:39.009 --> 00:12:41.060 the drug at maximal doses because we

NOTE Confidence: 0.34587935

00:12:41.060 --> 00:12:42.881 currently many of the patients are

NOTE Confidence: 0.34587935

00:12:42.881 --> 00:12:44.932 not being escalated to the right dose

NOTE Confidence: 0.34587935

00:12:44.940 --> 00:12:47.670 that leads to highest response rate.

NOTE Confidence: 0.34587935

00:12:47.670 --> 00:12:49.553 So I think starting with the higher

NOTE Confidence: 0.34587935

00:12:49.553 --> 00:12:51.520 response with the higher dose is going

NOTE Confidence: 0.34587935

00:12:51.520 --> 00:12:53.170 to increase the response rate and

NOTE Confidence: 0.34587935

00:12:53.221 --> 00:12:55.461 potentially open the door for more and

NOTE Confidence: 0.34587935

00:12:55.461 --> 00:12:57.573 more patients responding to this drug.

NOTE Confidence: 0.34587935

00:12:57.573 --> 00:13:01.349 And this trial is also up going to open ATL,

NOTE Confidence: 0.34587935

00:13:01.350 --> 00:13:02.934 another drug that I think generated

NOTE Confidence: 0.34587935

00:13:02.934 --> 00:13:04.790 a lot of interest is Amitelestad.

NOTE Confidence: 0.34587935

00:13:04.790 --> 00:13:07.520 This is a first in class telomerase

NOTE Confidence: 0.34587935

00:13:07.520 --> 00:13:07.910 inhibitor.

NOTE Confidence: 0.34587935

00:13:07.910 --> 00:13:10.275 So telomerase activity in patients

NOTE Confidence: 0.34587935

00:13:10.275 --> 00:13:12.950 with MD's has been associated with

NOTE Confidence: 0.34587935

00:13:12.950 --> 00:13:14.710 high risk disease and inhibition

NOTE Confidence: 0.34587935

00:13:14.710 --> 00:13:17.318 of the telomerase it has led to

NOTE Confidence: 0.34587935

00:13:17.318 --> 00:13:18.874 restoration of effective erythropoiesis

NOTE Confidence: 0.34587935

00:13:18.874 --> 00:13:21.119 in a large phase two trial.

NOTE Confidence: 0.34587935

00:13:21.120 --> 00:13:24.284 This is a drug that's given intravenously

NOTE Confidence: 0.34587935

00:13:24.284 --> 00:13:27.050 every four weeks and in a phase two trial

NOTE Confidence: 0.34587935

00:13:27.050 --> 00:13:28.562 lead to 40% transfusion independence.

NOTE Confidence: 0.34587935

00:13:28.562 --> 00:13:32.240 So this was taken to a phase three trial.

NOTE Confidence: 0.34587935

00:13:32.240 --> 00:13:35.159 We have presented the data of this

NOTE Confidence: 0.34587935

00:13:35.160 --> 00:13:39.200 paper in in Asch or sorry in ASCO

NOTE Confidence: 0.34587935

00:13:39.200 --> 00:13:41.900 2023 and the paper is now in Lancet in

00:13:41.900 --> 00:13:44.971 press where patients were randomized to

00:13:44.971 --> 00:13:47.127 receive hematillostat versus placebo.

00:13:47.130 --> 00:13:49.188 Again those are patients who are

00:13:49.188 --> 00:13:50.560 heavily transfusion dependent with

00:13:50.617 --> 00:13:52.810 lower risk MD's and you can see here

00:13:52.810 --> 00:13:54.758 again that the rate of transfusion

00:13:54.758 --> 00:13:57.038 dependence was similar to phase two

00:13:57.038 --> 00:14:00.138 trial with 40% compared to 15%.

00:14:00.138 --> 00:14:01.530 And importantly,

00:14:01.530 --> 00:14:03.565 the degree of hemoglobin elevation

00:14:03.565 --> 00:14:05.193 is actually quite prominence.

00:14:05.200 --> 00:14:07.252 So the hemoglobin increase was almost

00:14:07.252 --> 00:14:09.643 3 grams on average from a hemoglobin

00:14:09.643 --> 00:14:11.557 of eight to hemoglobin of 11.

00:14:11.560 --> 00:14:13.318 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

00:14:43.694 --> 00:14:45.690 really changed in the last almost 20 years.

NOTE Confidence: 0.34587935

00:14:45.690 --> 00:14:47.690 So patients who are candidates

NOTE Confidence: 0.34587935

00:14:47.690 --> 00:14:49.690 for transplant go for transplant

NOTE Confidence: 0.34587935

00:14:49.757 --> 00:14:52.571 and those who are not the receive

NOTE Confidence: 0.34587935

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

NOTE Confidence: 0.34587935

00:14:56.500 --> 00:14:58.618 treatment by itself is not great.

NOTE Confidence: 0.34587935

00:14:58.620 --> 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

NOTE Confidence: 0.34587935

00:15:02.946 --> 00:15:06.024 is less than 4% and for that reason

NOTE Confidence: 0.34587935

00:15:06.024 --> 00:15:07.788 we strongly encourage patients

NOTE Confidence: 0.34587935

00:15:07.788 --> 00:15:08.670 to consider

NOTE Confidence: 0.40800372

00:15:08.747 --> 00:15:10.440 transplant whenever possible,

NOTE Confidence: 0.40800372

00:15:10.440 --> 00:15:13.160 but also try to build up on HMA

NOTE Confidence: 0.40800372

00:15:13.160 --> 00:15:14.968 therapy to improve outcomes.

NOTE Confidence: 0.40800372

00:15:14.970 --> 00:15:17.178 And this is kind of a summary of

NOTE Confidence: 0.40800372

00:15:17.178 --> 00:15:18.661 three different real life studies

NOTE Confidence: 0.40800372

00:15:18.661 --> 00:15:21.062 that we have done that show that the

NOTE Confidence: 0.40800372

00:15:21.062 --> 00:15:23.000 real life outcomes with Hmas are

NOTE Confidence: 0.40800372

00:15:23.000 --> 00:15:24.924 actually much worse than what you

NOTE Confidence: 0.40800372

00:15:24.924 --> 00:15:26.832 see in clinical trials with immediate

NOTE Confidence: 0.40800372

00:15:26.832 --> 00:15:28.800 survival of only one year on average

NOTE Confidence: 0.40800372

00:15:28.800 --> 00:15:30.449 for patients with high risk MD's.

NOTE Confidence: 0.40800372

00:15:30.450 --> 00:15:32.935 Again further emphasizing the point

NOTE Confidence: 0.40800372

00:15:32.935 --> 00:15:35.856 for new therapies for patients with

NOTE Confidence: 0.40800372

00:15:35.856 --> 00:15:37.958 high risk MD's and we have tried,

NOTE Confidence: 0.40800372

00:15:37.958 --> 00:15:39.846 we have tried for a very long

NOTE Confidence: 0.40800372

00:15:39.846 --> 00:15:41.538 time over the last 20 years.

NOTE Confidence: 0.40800372

00:15:41.540 --> 00:15:43.244 Unfortunately this graveyard of

NOTE Confidence: 0.40800372

00:15:43.244 --> 00:15:45.800 combinations of drugs that were added

NOTE Confidence: 0.40800372

29

00:15:45.867 --> 00:15:48.337 to hypomthilating agents keep expanding.

NOTE Confidence: 0.40800372

00:15:48.340 --> 00:15:50.536 The latest addition was this drug

NOTE Confidence: 0.40800372

00:15:50.536 --> 00:15:53.179 magrolimab which works on the CD 47 pathway.

NOTE Confidence: 0.40800372

00:15:53.180 --> 00:15:55.140 This is a very,

NOTE Confidence: 0.40800372

00:15:55.140 --> 00:15:57.667 this drug has generated a lot of

NOTE Confidence: 0.40800372

00:15:57.667 --> 00:15:59.675 excitement early on but unfortunately

NOTE Confidence: 0.40800372

00:15:59.675 --> 00:16:02.219 a recent press release couple of

NOTE Confidence: 0.40800372

00:16:02.219 --> 00:16:04.560 months ago showed that phase three

NOTE Confidence: 0.40800372

00:16:04.560 --> 00:16:06.638 trial of this drug was negative.

NOTE Confidence: 0.40800372

00:16:06.638 --> 00:16:09.320 We can talk I guess in a in another

NOTE Confidence: 0.40800372

00:16:09.388 --> 00:16:12.027 time once the data is publicly released

NOTE Confidence: 0.40800372

00:16:12.027 --> 00:16:14.195 about the reasons for for failure and

NOTE Confidence: 0.40800372

00:16:14.195 --> 00:16:17.230 how we can try to come up out of this system.

NOTE Confidence: 0.40800372

00:16:17.230 --> 00:16:19.518 The good news is that we have other

NOTE Confidence: 0.40800372

00:16:19.518 --> 00:16:21.734 drugs that are more exciting and

NOTE Confidence: 0.40800372

00:16:21.734 --> 00:16:23.704 potentially could lead to approval.

NOTE Confidence: 0.40800372

00:16:23.710 --> 00:16:25.230 One of them is venetoclax.

NOTE Confidence: 0.40800372

00:16:25.230 --> 00:16:28.230 So venetoclax is an oral PCL 2 inhibitor.

NOTE Confidence: 0.40800372

00:16:28.230 --> 00:16:31.184 This is already approved for patients with

NOTE Confidence: 0.40800372

00:16:31.184 --> 00:16:33.429 acute myeloid leukemia who are older.

NOTE Confidence: 0.40800372

00:16:33.430 --> 00:16:35.878 The frontline phase two trial should

NOTE Confidence: 0.40800372

00:16:35.880 --> 00:16:39.986 CR responses of around 35% and across

NOTE Confidence: 0.40800372

00:16:39.986 --> 00:16:42.899 the genetic spectrum of MD's we have

NOTE Confidence: 0.40800372

00:16:42.899 --> 00:16:45.090 published a phase 1P study that shows

NOTE Confidence: 0.40800372

00:16:45.157 --> 00:16:47.221 that adding venetoclax to HMA is

NOTE Confidence: 0.40800372

00:16:47.221 --> 00:16:49.920 actually active in the HMA failure setting,

NOTE Confidence: 0.40800372

00:16:49.920 --> 00:16:51.540 which is a very difficult

NOTE Confidence: 0.40800372

00:16:51.540 --> 00:16:53.160 setting to treat patients in.

NOTE Confidence: 0.40800372

00:16:53.160 --> 00:16:55.926 It leads to responses as well

NOTE Confidence: 0.40800372

00:16:55.926 --> 00:16:57.309 as transition independence.

NOTE Confidence: 0.40800372

00:16:57.310 --> 00:17:00.498 But the pivotal phase three trial is is

NOTE Confidence: 0.40800372

00:17:00.498 --> 00:17:02.106 fully accrued now it's called Verona.

NOTE Confidence: 0.40800372

00:17:02.110 --> 00:17:04.180 This trial might change the

NOTE Confidence: 0.40800372

00:17:04.180 --> 00:17:06.949 landscape of how high risk MD's is,

NOTE Confidence: 0.40800372

00:17:06.950 --> 00:17:08.870 is going to be treated.

NOTE Confidence: 0.40800372

00:17:08.870 --> 00:17:10.502 This is the scheme of the trial that

NOTE Confidence: 0.40800372

00:17:10.502 --> 00:17:11.868 we presented a couple of years ago.

NOTE Confidence: 0.40800372

00:17:11.870 --> 00:17:13.466 This trial is now fully accrued.

NOTE Confidence: 0.40800372

00:17:13.470 --> 00:17:15.955 It's the results are actually expected by

NOTE Confidence: 0.40800372

00:17:15.955 --> 00:17:19.544 early 2024 and if this trial is possible,

NOTE Confidence: 0.40800372

00:17:19.550 --> 00:17:22.457 it would lead to a new standard of care.

NOTE Confidence: 0.40800372

00:17:22.460 --> 00:17:24.990 Now moving to immune dysregulation

NOTE Confidence: 0.40800372

00:17:24.990 --> 00:17:27.520 myeloid malignancies and this is

NOTE Confidence: 0.40800372

00:17:27.598 --> 00:17:29.474 an area where I have personally

NOTE Confidence: 0.40800372

00:17:29.474 --> 00:17:31.560 invested quite a bit of time trying

NOTE Confidence: 0.40800372

00:17:31.618 --> 00:17:34.260 to develop new therapies for both

NOTE Confidence: 0.40800372

00:17:34.260 --> 00:17:36.860 MD's and acute myeloid leukemia.

NOTE Confidence: 0.40800372

00:17:36.860 --> 00:17:38.799 So we know that the most effective

NOTE Confidence: 0.40800372

00:17:38.799 --> 00:17:40.214 treatment for patients with MD's

NOTE Confidence: 0.40800372

00:17:40.214 --> 00:17:41.816 and AML is bone marrow transplant,

NOTE Confidence: 0.40800372

00:17:41.820 --> 00:17:44.260 which is effectively is an

NOTE Confidence: 0.40800372

00:17:44.260 --> 00:17:45.236 immune intervention.

NOTE Confidence: 0.40800372

00:17:45.240 --> 00:17:47.075 We know there is significant

NOTE Confidence: 0.40800372

00:17:47.075 --> 00:17:48.910 dysfunction in the immune system

NOTE Confidence: 0.40800372

00:17:48.980 --> 00:17:51.297 happens in patients with MD's and AML

NOTE Confidence: 0.40800372

00:17:51.297 --> 00:17:53.186 both at diagnosis but also during

NOTE Confidence: 0.40800372

00:17:53.186 --> 00:17:54.916 the progression of the disease.

NOTE Confidence: 0.40800372

00:17:54.920 --> 00:17:57.030 There is both quantitative and

NOTE Confidence: 0.40800372

00:17:57.030 --> 00:17:59.140 qualitative abnormalities that happen in

NOTE Confidence: 0.40800372

00:17:59.203 --> 00:18:01.875 the T cells including the regulatory T cells,

NOTE Confidence: 0.40800372

00:18:01.880 --> 00:18:03.555 but also in the macrophages

NOTE Confidence: 0.40800372

00:18:03.555 --> 00:18:05.026 and the ANKAE cells.

NOTE Confidence: 0.40800372

00:18:05.026 --> 00:18:07.822 And study after study have shown

NOTE Confidence: 0.40800372

00:18:07.822 --> 00:18:10.305 that these increase in frequency

NOTE Confidence: 0.40800372

00:18:10.305 --> 00:18:12.365 as the disease progresses.

NOTE Confidence: 0.29320434

00:18:12.370 --> 00:18:13.870 The question has been

NOTE Confidence: 0.29320434

00:18:13.870 --> 00:18:15.370 always are these pathogenic,

NOTE Confidence: 0.29320434

00:18:15.370 --> 00:18:17.430 are they basically mediating the

NOTE Confidence: 0.29320434

00:18:17.430 --> 00:18:20.050 progression and the resistance of AML and

NOTE Confidence: 0.29320434

00:18:20.050 --> 00:18:22.073 MD's or are they basically are adhering,

NOTE Confidence: 0.29320434

00:18:22.073 --> 00:18:24.460 they are just a phenomena that comes

NOTE Confidence: 0.29320434

00:18:24.521 --> 00:18:26.567 with the progression of the disease.

NOTE Confidence: 0.29320434

00:18:26.570 --> 00:18:28.538 And the first trial I think that generated

NOTE Confidence: 0.29320434

00:18:28.538 --> 00:18:30.785 a lot of interest of immune checkpoint

NOTE Confidence: 0.29320434

00:18:30.785 --> 00:18:32.480 inhibition which clearly in solid

NOTE Confidence: 0.29320434

00:18:32.536 --> 00:18:34.489 tumors have led to a major revolution,

NOTE Confidence: 0.29320434

00:18:34.490 --> 00:18:37.490 but in in in blood tumors has not

NOTE Confidence: 0.29320434

00:18:37.490 --> 00:18:40.489 led to the same impact so far.

NOTE Confidence: 0.29320434

00:18:40.490 --> 00:18:42.560 However, the Dana Farber group

NOTE Confidence: 0.29320434

00:18:42.560 --> 00:18:44.630 published this trial using Epilumab

NOTE Confidence: 0.29320434

00:18:44.701 --> 00:18:46.875 which is a CTL A4 inhibitor

NOTE Confidence: 0.29320434

00:18:46.875 --> 00:18:49.450 approved for multiple solar tumors.

NOTE Confidence: 0.29320434

00:18:49.450 --> 00:18:52.290 Now it was a small phase one study,

NOTE Confidence: 0.29320434

00:18:52.290 --> 00:18:54.341 but it was done in the post

NOTE Confidence: 0.29320434

00:18:54.341 --> 00:18:55.952 transplant setting where the drug

NOTE Confidence: 0.29320434

00:18:55.952 --> 00:18:57.980 was given for patients who relapse

NOTE Confidence: 0.29320434

00:18:57.980 --> 00:18:59.765 after transplant and what they have

NOTE Confidence: 0.29320434

00:18:59.765 --> 00:19:01.423 shown that the drug was tolerated.

NOTE Confidence: 0.29320434

00:19:01.423 --> 00:19:03.824 There were some GVHD but generally it

NOTE Confidence: 0.29320434

00:19:03.824 --> 00:19:06.728 was well tolerated for the most part and

NOTE Confidence: 0.29320434

00:19:06.728 --> 00:19:10.100 they were able to achieve 5 responses,

NOTE Confidence: 0.29320434

00:19:10.100 --> 00:19:13.040 5 complete remissions out of 13 patients,

NOTE Confidence: 0.29320434

00:19:13.040 --> 00:19:15.231 which again was a proof of principle

NOTE Confidence: 0.29320434

00:19:15.231 --> 00:19:16.640 that immune checkpoint inhibition

NOTE Confidence: 0.29320434

00:19:16.640 --> 00:19:18.680 post transplant does actually work.

NOTE Confidence: 0.29320434

00:19:18.680 --> 00:19:21.720 And this generated a a number of trials

NOTE Confidence: 0.29320434

00:19:21.720 --> 00:19:24.333 looking at the drug in MD's and AML.

NOTE Confidence: 0.29320434

00:19:24.333 --> 00:19:26.199 This is one of the trials,

NOTE Confidence: 0.29320434

00:19:26.200 --> 00:19:28.272 one of the early trials that I have

NOTE Confidence: 0.29320434

00:19:28.272 --> 00:19:30.264 worked on actually when I was at

NOTE Confidence: 0.29320434

00:19:30.264 --> 00:19:32.200 Hopkins and later moved it to Yale.

NOTE Confidence: 0.29320434

00:19:32.200 --> 00:19:33.379 It was multicentre,

NOTE Confidence: 0.29320434

00:19:33.379 --> 00:19:36.130 it was in the post relapse setting

NOTE Confidence: 0.29320434

00:19:36.205 --> 00:19:37.877 for patients with MD's.

NOTE Confidence: 0.29320434

00:19:37.880 --> 00:19:39.560 So this was not after transplant,

NOTE Confidence: 0.29320434

00:19:39.560 --> 00:19:42.224 this was after HMA failure in

NOTE Confidence: 0.29320434

00:19:42.224 --> 00:19:43.556 patients with MD's.

NOTE Confidence: 0.29320434

00:19:43.560 --> 00:19:44.934 And while we have shown that

NOTE Confidence: 0.29320434

00:19:44.934 --> 00:19:46.400 the drug was well tolerated,

NOTE Confidence: 0.29320434

00:19:46.400 --> 00:19:48.470 we could manage the immune related

NOTE Confidence: 0.29320434

00:19:48.470 --> 00:19:49.850 adverse events effectively similar

NOTE Confidence: 0.29320434

00:19:49.907 --> 00:19:51.511 to what they do in solid tumors.

NOTE Confidence: 0.29320434

00:19:51.511 --> 00:19:53.917 The clinical responses were generally very

NOTE Confidence: 0.29320434

00:19:53.917 --> 00:19:57.190 low and the drug was not clinically active.

NOTE Confidence: 0.29320434

00:19:57.190 --> 00:19:59.848 We did achieve some disease stabilisation

NOTE Confidence: 0.29320434

00:19:59.848 --> 00:20:02.313 but stable disease always very tricky

NOTE Confidence: 0.29320434

00:20:02.313 --> 00:20:04.801 in MD's to figure out is it related

NOTE Confidence: 0.29320434

00:20:04.868 --> 00:20:07.276 to the biology of the disease being

NOTE Confidence: 0.29320434

00:20:07.276 --> 00:20:09.390 indolent in some patients or is it

NOTE Confidence: 0.29320434

00:20:09.390 --> 00:20:11.350 related to the activity of the drug.

NOTE Confidence: 0.29320434

00:20:11.350 --> 00:20:11.745 However,

NOTE Confidence: 0.29320434

00:20:11.745 --> 00:20:14.510 among those patients who had stable disease,

NOTE Confidence: 0.29320434

00:20:14.510 --> 00:20:16.815 we have conducted extensive correlative

NOTE Confidence: 0.29320434

00:20:16.815 --> 00:20:19.740 testing with Leo Loznick at Hopkins.

NOTE Confidence: 0.29320434

00:20:19.740 --> 00:20:22.012 And we have shown that there was an

NOTE Confidence: 0.29320434

00:20:22.012 --> 00:20:24.157 increase in the frequency of Icos

NOTE Confidence: 0.29320434

00:20:24.157 --> 00:20:26.013 which is costimulatory molecule,

NOTE Confidence: 0.29320434

00:20:26.013 --> 00:20:30.006 but this this was not basically

NOTE Confidence: 0.29320434

00:20:30.006 --> 00:20:32.136 associated with increase in the

NOTE Confidence: 0.29320434

00:20:32.136 --> 00:20:34.500 peripheral T cell receptor diversity in

NOTE Confidence: 0.29320434

00:20:34.500 --> 00:20:36.660 terms of association with the response.

NOTE Confidence: 0.29320434

00:20:36.660 --> 00:20:39.698 And I think trying to find biomarkers

NOTE Confidence: 0.29320434

00:20:39.698 --> 00:20:42.989 for patients has been one of the

NOTE Confidence: 0.29320434

00:20:42.989 --> 00:20:45.364 also challenging areas in immune

NOTE Confidence: 0.29320434

00:20:45.364 --> 00:20:47.450 checkpoint inhibition in MD's.

NOTE Confidence: 0.29320434

00:20:47.450 --> 00:20:49.235 Of course single arm trials

NOTE Confidence: 0.29320434

00:20:49.235 --> 00:20:51.450 as I mentioned are not very,

NOTE Confidence: 0.29320434

00:20:51.450 --> 00:20:53.418 are not very definitive in any

NOTE Confidence: 0.29320434

00:20:53.418 --> 00:20:54.402 kind of activity.

NOTE Confidence: 0.29320434

00:20:54.410 --> 00:20:56.330 Some of those phase one trials

NOTE Confidence: 0.29320434

00:20:56.330 --> 00:20:57.610 have shown positive signals,

NOTE Confidence: 0.29320434

00:20:57.610 --> 00:20:59.350 but the definitive way to achieve

NOTE Confidence: 0.29320434

00:20:59.350 --> 00:21:01.234 that would be with a randomized

NOTE Confidence: 0.29320434

00:21:01.234 --> 00:21:03.498 trial and we worked with the with

NOTE Confidence: 0.29320434

00:21:03.498 --> 00:21:06.426 the Celgene slash BMS to develop

NOTE Confidence: 0.29320434

00:21:06.426 --> 00:21:08.674 this trial of randomized trial.

NOTE Confidence: 0.29320434

00:21:08.674 --> 00:21:11.026 This was the only randomized published

NOTE Confidence: 0.29320434

00:21:11.026 --> 00:21:13.267 trial to date of immune checkpoint

NOTE Confidence: 0.29320434

00:21:13.267 --> 00:21:15.361 inhibition both in MD's and AML.

NOTE Confidence: 0.69711691

00:21:15.370 --> 00:21:17.836 So patients with MD's or AML

NOTE Confidence: 0.69711691

00:21:17.836 --> 00:21:19.480 in two separate cohorts,

NOTE Confidence: 0.69711691

00:21:19.480 --> 00:21:21.420 more than 210 patients were

NOTE Confidence: 0.69711691

00:21:21.420 --> 00:21:22.972 randomized to receive azacitidine

NOTE Confidence: 0.69711691

00:21:22.972 --> 00:21:25.120 or azacitidine with dorvalumab.

NOTE Confidence: 0.69711691

00:21:25.120 --> 00:21:26.866 Many of you are probably familiar

NOTE Confidence: 0.69711691

00:21:26.866 --> 00:21:29.167 with this PDL 1 inhibitor which is

NOTE Confidence: 0.69711691

00:21:29.167 --> 00:21:30.952 approved to multiple solid tumors

NOTE Confidence: 0.69711691

00:21:30.952 --> 00:21:33.045 and has shown overall survival

NOTE Confidence: 0.69711691

00:21:33.045 --> 00:21:35.240 prolongation in in several settings.

NOTE Confidence: 0.69711691

00:21:35.240 --> 00:21:37.515 However, again this was a negative trial.

NOTE Confidence: 0.69711691

00:21:37.520 --> 00:21:39.620 You can see here complete overlap in

NOTE Confidence: 0.69711691

00:21:39.620 --> 00:21:41.210 the overall survival and progression

NOTE Confidence: 0.69711691

00:21:41.210 --> 00:21:43.106 free survival cares and no difference

NOTE Confidence: 0.69711691

00:21:43.106 --> 00:21:44.842 in the primary endpoint which

NOTE Confidence: 0.69711691

00:21:44.842 --> 00:21:46.587 was the overall response rate.

NOTE Confidence: 0.69711691

00:21:46.590 --> 00:21:48.126 So this was disappointing.

NOTE Confidence: 0.69711691

00:21:48.126 --> 00:21:50.046 We try to understand better

NOTE Confidence: 0.69711691

00:21:50.046 --> 00:21:51.627 why is that the case,

NOTE Confidence: 0.69711691

00:21:51.630 --> 00:21:53.910 why did the drug not lead to improvement?

NOTE Confidence: 0.69711691

00:21:53.910 --> 00:21:56.806 So the first theory is that one common

NOTE Confidence: 0.69711691

00:21:56.806 --> 00:21:59.146 thing we see with MD's trials is that

NOTE Confidence: 0.69711691

00:21:59.146 --> 00:22:01.267 when you add a drug in top of MD's,

NOTE Confidence: 0.69711691

00:22:01.267 --> 00:22:03.409 you lead to less exposure of

NOTE Confidence: 0.69711691

00:22:03.409 --> 00:22:05.292 azacitidine which is the only

NOTE Confidence: 0.69711691

00:22:05.292 --> 00:22:07.147 drug shown to improve survival.

NOTE Confidence: 0.69711691

00:22:07.150 --> 00:22:09.262 And therefore maybe adding the volumab

NOTE Confidence: 0.69711691

00:22:09.262 --> 00:22:11.851 has led to reduced exposure of Aza and

NOTE Confidence: 0.69711691

00:22:11.851 --> 00:22:14.080 that's why we did not see benefit.

NOTE Confidence: 0.69711691

00:22:14.080 --> 00:22:16.229 But you can see in this analysis

NOTE Confidence: 0.69711691

00:22:16.229 --> 00:22:18.483 in the green bars that the number

NOTE Confidence: 0.69711691

00:22:18.483 --> 00:22:20.522 of cycles between the two arms was

NOTE Confidence: 0.69711691

00:22:20.522 --> 00:22:22.052 actually similar and most patients

NOTE Confidence: 0.69711691

00:22:22.052 --> 00:22:23.996 have received more than four cycles.

NOTE Confidence: 0.69711691

00:22:24.000 --> 00:22:26.568 So it doesn't seem like this

NOTE Confidence: 0.69711691

00:22:26.568 --> 00:22:29.304 underlines the lack of therapeutic

NOTE Confidence: 0.69711691

00:22:29.304 --> 00:22:30.621 efficacy to the right.

NOTE Confidence: 0.69711691

00:22:30.621 --> 00:22:32.938 You can see also that there was similar

NOTE Confidence: 0.69711691

00:22:32.938 --> 00:22:35.400 hypomethylation which how we think how

NOTE Confidence: 0.69711691

00:22:35.400 --> 00:22:37.150 those drugs hypomethylating agents work

NOTE Confidence: 0.69711691

00:22:37.150 --> 00:22:39.598 and no difference between the two arms.

NOTE Confidence: 0.69711691

00:22:39.600 --> 00:22:41.575 So doesn't seem like there

NOTE Confidence: 0.69711691

00:22:41.575 --> 00:22:42.760 was antagonism there.

NOTE Confidence: 0.69711691

00:22:42.760 --> 00:22:45.096 We also tried to see if there was

NOTE Confidence: 0.69711691

00:22:45.096 --> 00:22:46.970 an increased expression in PDL 2

NOTE Confidence: 0.69711691

00:22:46.970 --> 00:22:49.477 as a mechanism to bypass the PDL 1

NOTE Confidence: 0.69711691

00:22:49.477 --> 00:22:51.917 inhibition and that also was not the case.

NOTE Confidence: 0.69711691

00:22:51.920 --> 00:22:54.594 So none of those mechanisms seem to

NOTE Confidence: 0.69711691

00:22:54.600 --> 00:22:57.799 suggest why the drug did not work.

NOTE Confidence: 0.69711691

00:22:57.800 --> 00:22:59.785 What was actually quite surprising

NOTE Confidence: 0.69711691

00:22:59.785 --> 00:23:02.370 is that when we conducted serial

NOTE Confidence: 0.69711691

00:23:02.370 --> 00:23:03.960 flow cytometric analysis,

NOTE Confidence: 0.69711691

00:23:03.960 --> 00:23:07.874 we did not see T cell expansion in

NOTE Confidence: 0.69711691

00:23:07.874 --> 00:23:11.576 diversity or in quantity by flow cytometry,

NOTE Confidence: 0.69711691

00:23:11.576 --> 00:23:13.938 neither in the bone marrow or in the

NOTE Confidence: 0.69711691

00:23:13.938 --> 00:23:15.924 peripheral blood between the two arms.

NOTE Confidence: 0.69711691

00:23:15.930 --> 00:23:19.030 And this was particularly surprising

NOTE Confidence: 0.69711691

00:23:19.030 --> 00:23:21.190 because there has been a prevailing

NOTE Confidence: 0.69711691

00:23:21.190 --> 00:23:23.118 theory that the reason why immune

NOTE Confidence: 0.69711691

00:23:23.118 --> 00:23:24.418 checkpoint inhibition does not

NOTE Confidence: 0.69711691

00:23:24.418 --> 00:23:27.076 work in AML is that once you give

NOTE Confidence: 0.69711691

00:23:27.076 --> 00:23:28.344 it subsequent lines, third,

NOTE Confidence: 0.69711691

00:23:28.344 --> 00:23:28.932 fourth line,

NOTE Confidence: 0.69711691

00:23:28.932 --> 00:23:30.990 that the immune system has been beat

NOTE Confidence: 0.69711691

00:23:31.046 --> 00:23:32.570 up a lot by the chemotherapy.

NOTE Confidence: 0.69711691

00:23:32.570 --> 00:23:34.874 So here we were giving it in the

NOTE Confidence: 0.69711691

00:23:34.874 --> 00:23:36.519 frontline sitting and still it did

NOTE Confidence: 0.69711691

00:23:36.519 --> 00:23:37.830 not lead to immune stimulation.

NOTE Confidence: 0.69711691

00:23:37.830 --> 00:23:39.930 And the last thing we tried to

NOTE Confidence: 0.69711691

00:23:39.930 --> 00:23:42.493 do with this trial is to look at

NOTE Confidence: 0.69711691

00:23:42.493 --> 00:23:44.188 substance of patients because here

NOTE Confidence: 0.69711691

00:23:44.188 --> 00:23:45.983 you are putting all newcomers

NOTE Confidence: 0.69711691

00:23:45.983 --> 00:23:47.908 together and maybe certain subsets

NOTE Confidence: 0.69711691

00:23:47.908 --> 00:23:49.860 of patients benefit better.

NOTE Confidence: 0.69711691

00:23:49.860 --> 00:23:52.092 So we tried to look at 2 specific subsets,

NOTE Confidence: 0.69711691

00:23:52.100 --> 00:23:54.656 patients who have TP 53 mutations,

NOTE Confidence: 0.69711691

00:23:54.660 --> 00:23:56.876 which have been shown to have a micro

NOTE Confidence: 0.69711691

00:23:56.876 --> 00:23:58.751 environment in the bone marrow that

NOTE Confidence: 0.69711691

00:23:58.751 --> 00:24:00.326 is more immunosuppressive and might

NOTE Confidence: 0.69711691

00:24:00.326 --> 00:24:02.696 be more amenable to immune checkpoint

NOTE Confidence: 0.69711691

00:24:02.696 --> 00:24:04.336 inhibition based on multiple sources

NOTE Confidence: 0.69711691

00:24:04.336 --> 00:24:06.664 of data as well as patients who

NOTE Confidence: 0.69711691

00:24:06.664 --> 00:24:08.300 have splicing factor mutations,

NOTE Confidence: 0.69711691

00:24:08.300 --> 00:24:09.830 which Omar Abdullah have from

44

NOTE Confidence: 0.69711691

00:24:09.830 --> 00:24:11.360 Sloan Kettering and others have

NOTE Confidence: 0.26679423

00:24:11.410 --> 00:24:13.190 shown could be more susceptible

NOTE Confidence: 0.26679423

00:24:13.190 --> 00:24:14.614 to immune checkpoint inhibition.

NOTE Confidence: 0.26679423

00:24:14.620 --> 00:24:18.913 However, we also did not see any any

NOTE Confidence: 0.26679423

00:24:18.913 --> 00:24:22.537 activity in those patients who have TB 53.

NOTE Confidence: 0.26679423

00:24:22.540 --> 00:24:25.564 This analysis was presented by Yan in a

NOTE Confidence: 0.26679423

00:24:25.564 --> 00:24:28.709 couple of years at ASH and is currently

NOTE Confidence: 0.26679423

00:24:28.709 --> 00:24:30.540 under consideration for publication.

NOTE Confidence: 0.26679423

00:24:30.540 --> 00:24:34.426 So we tried to think further about how

NOTE Confidence: 0.26679423

00:24:34.426 --> 00:24:37.084 can we overcome this immune checkpoint

NOTE Confidence: 0.26679423

00:24:37.090 --> 00:24:40.926 resistance for patients and one theory was,

NOTE Confidence: 0.26679423

00:24:40.930 --> 00:24:43.000 is that myeloid derived suppressor

NOTE Confidence: 0.26679423

00:24:43.000 --> 00:24:45.890 cells could be a mediating resistance.

NOTE Confidence: 0.26679423

00:24:45.890 --> 00:24:47.912 This was based on solid tumours

NOTE Confidence: 0.26679423

00:24:47.912 --> 00:24:49.650 and we replicated the data.

NOTE Confidence: 0.26679423

00:24:49.650 --> 00:24:52.110 Doctor Tikkun Kim who's currently at
NOTE Confidence: 0.26679423

00:24:52.110 --> 00:24:55.523 Vanderbilt was here at TL did very nice
NOTE Confidence: 0.26679423

00:24:55.523 --> 00:24:57.643 preclinical trials that suggested that
NOTE Confidence: 0.26679423

00:24:57.643 --> 00:25:00.152 there could be the benefit of combining
NOTE Confidence: 0.26679423

00:25:00.152 --> 00:25:02.330 a drug that targets myeloid derived
NOTE Confidence: 0.26679423

00:25:02.395 --> 00:25:04.330 suppressor cells such as entenostat
NOTE Confidence: 0.26679423

00:25:04.330 --> 00:25:06.756 which is a Estonia acetylase inhibitor
NOTE Confidence: 0.26679423

00:25:06.756 --> 00:25:10.260 with with Pimpro or PD1 inhibitor.
NOTE Confidence: 0.26679423

00:25:10.260 --> 00:25:12.180 And based on these preclinical data,
NOTE Confidence: 0.26679423

00:25:12.180 --> 00:25:15.057 this was translated to a clinical trial,
NOTE Confidence: 0.26679423

00:25:15.060 --> 00:25:18.105 multi centre phase one trial that was
NOTE Confidence: 0.26679423

00:25:18.105 --> 00:25:21.105 conducted in collaboration with the UM
NOTE Confidence: 0.26679423

00:25:21.105 --> 00:25:24.290 one group under Pat Larosso with the
NOTE Confidence: 0.26679423

00:25:24.290 --> 00:25:25.840 theory again that adding Antinostat
NOTE Confidence: 0.26679423

00:25:25.840 --> 00:25:27.190 would suppress myeloid giraffe,
NOTE Confidence: 0.26679423

00:25:27.190 --> 00:25:28.875 suppress our cells and therefore

NOTE Confidence: 0.26679423

00:25:28.875 --> 00:25:30.560 allow pimprolismab to exert its

NOTE Confidence: 0.26679423

00:25:30.620 --> 00:25:32.148 immune chip point inhibition.

NOTE Confidence: 0.26679423

00:25:32.150 --> 00:25:34.868 So that the trial has been presented by Anne,

NOTE Confidence: 0.26679423

00:25:34.870 --> 00:25:36.613 I'm not going to go through the

NOTE Confidence: 0.26679423

00:25:36.613 --> 00:25:37.803 results because again unfortunately

NOTE Confidence: 0.26679423

00:25:37.803 --> 00:25:39.347 it was clinically negative.

NOTE Confidence: 0.26679423

00:25:39.350 --> 00:25:41.630 We are currently going through the

NOTE Confidence: 0.26679423

00:25:41.630 --> 00:25:43.966 correlative data to understand what led

NOTE Confidence: 0.26679423

00:25:43.966 --> 00:25:46.822 to the failure of the clinical data.

NOTE Confidence: 0.26679423

00:25:46.830 --> 00:25:47.256 However,

NOTE Confidence: 0.26679423

00:25:47.256 --> 00:25:50.354 I think there are more exciting agents.

NOTE Confidence: 0.26679423

00:25:50.354 --> 00:25:52.764 One of them is sabatolimab.

NOTE Confidence: 0.26679423

00:25:52.770 --> 00:25:54.795 So sabatolimab is a novel

NOTE Confidence: 0.26679423

00:25:54.795 --> 00:25:56.010 immune checkpoint inhibitor.

NOTE Confidence: 0.26679423

00:25:56.010 --> 00:25:57.278 Sabatolimab targets term 3.

NOTE Confidence: 0.26679423

00:25:57.278 --> 00:26:01.009 So term 3 is not only expressed on T cells

NOTE Confidence: 0.26679423

00:26:01.009 --> 00:26:03.204 and medias immune checkpoint inhibition,

NOTE Confidence: 0.26679423

00:26:03.210 --> 00:26:05.723 but it's also expressed in leukemia stem

NOTE Confidence: 0.26679423

00:26:05.723 --> 00:26:08.088 cells and leukemia plast and targeting.

NOTE Confidence: 0.26679423

00:26:08.090 --> 00:26:08.906 Term 3IN.

NOTE Confidence: 0.26679423

00:26:08.906 --> 00:26:10.946 Preclinical data has suggested a

NOTE Confidence: 0.26679423

00:26:10.946 --> 00:26:13.430 potential not only efficacy but a

NOTE Confidence: 0.26679423

00:26:13.430 --> 00:26:15.010 potential   functional mechanism

NOTE Confidence: 0.26679423

00:26:15.010 --> 00:26:18.035 in which it can lead to immune

NOTE Confidence: 0.26679423

00:26:18.035 --> 00:26:20.245 checkpoint inhibition but also direct

NOTE Confidence: 0.26679423

00:26:20.245 --> 00:26:22.760 targeting of the leukemia stem cells.

NOTE Confidence: 0.26679423

00:26:22.760 --> 00:26:25.320 So the stimulus MD's one trial was the

NOTE Confidence: 0.26679423

00:26:25.320 --> 00:26:27.238 first randomized trial with this drug.

NOTE Confidence: 0.26679423

00:26:27.240 --> 00:26:29.600 This trial randomized patients to

NOTE Confidence: 0.26679423

00:26:29.600 --> 00:26:32.488 receive HMA versus HMA with sabatolimab

NOTE Confidence: 0.26679423

00:26:32.488 --> 00:26:35.656 and the primary endpoint was complete

NOTE Confidence: 0.26679423

00:26:35.656 --> 00:26:38.320 response and progression free survival.

NOTE Confidence: 0.26679423

00:26:38.320 --> 00:26:40.960 We presented this data in ASH last year.

NOTE Confidence: 0.26679423

00:26:40.960 --> 00:26:43.325 Currently the manuscript is under

NOTE Confidence: 0.26679423

00:26:43.325 --> 00:26:45.050 review and while the the trial

NOTE Confidence: 0.26679423

00:26:45.050 --> 00:26:46.700 did not meet its end point,

NOTE Confidence: 0.26679423

00:26:46.700 --> 00:26:48.960 there was no significant statistically

NOTE Confidence: 0.26679423

00:26:48.960 --> 00:26:50.768 improvement in complete remission

NOTE Confidence: 0.26679423

00:26:50.768 --> 00:26:52.859 or progression free survival.

NOTE Confidence: 0.26679423

00:26:52.860 --> 00:26:55.316 You can see that there was a late

NOTE Confidence: 0.26679423

00:26:55.316 --> 00:26:57.482 separation in the curve of the

NOTE Confidence: 0.26679423

00:26:57.482 --> 00:26:59.332 progression free survival and some

NOTE Confidence: 0.26679423

00:26:59.340 --> 00:27:01.776 trend toward improvement with the PFS.

NOTE Confidence: 0.26679423

00:27:01.780 --> 00:27:03.852 So we also sub analyse these data

NOTE Confidence: 0.26679423

00:27:03.852 --> 00:27:06.309 and what we have found is that

NOTE Confidence: 0.26679423

00:27:06.309 --> 00:27:08.184 patients who have lower disease

NOTE Confidence: 0.26679423

00:27:08.184 --> 00:27:09.938 burden seem to benefit more.

NOTE Confidence: 0.26679423

00:27:09.938 --> 00:27:13.330 However, of course this is ad hoc analysis,

NOTE Confidence: 0.26679423

00:27:13.330 --> 00:27:14.076 exploratory analysis.

NOTE Confidence: 0.26679423

00:27:14.076 --> 00:27:16.314 But what was also exciting is

NOTE Confidence: 0.26679423

00:27:16.314 --> 00:27:18.077 among the patients who achieved

NOTE Confidence: 0.26679423

00:27:18.077 --> 00:27:20.610 response as you can see in the red,

NOTE Confidence: 0.26679423

00:27:20.610 --> 00:27:22.220 patients who achieved The Who

NOTE Confidence: 0.26679423

00:27:22.220 --> 00:27:24.213 got the combination seems to have

NOTE Confidence: 0.26679423

00:27:24.213 --> 00:27:25.848 doubled the duration of response

NOTE Confidence: 0.26679423

00:27:25.848 --> 00:27:28.048 compared to those who have HMA alone,

NOTE Confidence: 0.26679423

00:27:28.050 --> 00:27:30.440 which again suggests that the

NOTE Confidence: 0.26679423

00:27:30.440 --> 00:27:32.830 combination might deepen the response

NOTE Confidence: 0.66074306

00:27:32.901 --> 00:27:36.750 leading to longer duration of activity.

NOTE Confidence: 0.66074306

00:27:36.750 --> 00:27:39.862 So the stimulus MD's two is a large

NOTE Confidence: 0.66074306

00:27:39.862 --> 00:27:42.670 randomized phase three trial of Sabatolimab

NOTE Confidence: 0.66074306

00:27:42.670 --> 00:27:45.136 plus Aza versus Sabatolimab alone and

NOTE Confidence: 0.66074306

00:27:45.136 --> 00:27:48.094 this trial again is fully accrued more

NOTE Confidence: 0.66074306

00:27:48.094 --> 00:27:51.270 than 530 patients enrolled on this trial.

NOTE Confidence: 0.66074306

00:27:51.270 --> 00:27:53.180 This trial is also expected

NOTE Confidence: 0.66074306

00:27:53.180 --> 00:27:55.236 to report by early 2024.

NOTE Confidence: 0.66074306

00:27:55.236 --> 00:27:57.866 So between venetoclax and sabatolimab,

NOTE Confidence: 0.66074306

00:27:57.870 --> 00:28:00.078 hopefully one of those two at least will

NOTE Confidence: 0.66074306

00:28:00.078 --> 00:28:02.365 will be positive and change the landscape

NOTE Confidence: 0.66074306

00:28:02.365 --> 00:28:05.249 of how we treat patients with high risk MD's.

NOTE Confidence: 0.66074306

00:28:05.250 --> 00:28:07.511 So moving to the AML front where

NOTE Confidence: 0.66074306

00:28:07.511 --> 00:28:09.530 we have also tried to move

NOTE Confidence: 0.66074306

00:28:09.530 --> 00:28:11.530 some of those concepts forward.

NOTE Confidence: 0.66074306

00:28:11.530 --> 00:28:14.378 So the plus AML one is a randomized

NOTE Confidence: 0.66074306

00:28:14.378 --> 00:28:17.620 phase two trial an IAT that is also

NOTE Confidence: 0.66074306

00:28:17.620 --> 00:28:20.530 running through the UM 1 mechanism

NOTE Confidence: 0.66074306

00:28:20.530 --> 00:28:23.722 with Pat Larosso Rory has been doctor

NOTE Confidence: 0.66074306

00:28:23.722 --> 00:28:26.675 Shalis has been working on this with me

NOTE Confidence: 0.66074306

00:28:26.675 --> 00:28:28.670 and this trial is actively enrolling.

NOTE Confidence: 0.66074306

00:28:28.670 --> 00:28:31.400 We have more than 40 patients right

NOTE Confidence: 0.66074306

00:28:31.400 --> 00:28:33.565 now where patients are getting 7 +

NOTE Confidence: 0.66074306

00:28:33.565 --> 00:28:35.865 3 versus 7 + 3 with pemprolizumab.

NOTE Confidence: 0.66074306

00:28:35.865 --> 00:28:40.730 The primary endpoint is MRD negative CR,

NOTE Confidence: 0.66074306

00:28:40.730 --> 00:28:42.555 another randomized phase two trial

NOTE Confidence: 0.66074306

00:28:42.555 --> 00:28:45.044 that we are working through the same

NOTE Confidence: 0.66074306

00:28:45.044 --> 00:28:47.144 mechanism as last ML2 and this trial

NOTE Confidence: 0.66074306

00:28:47.144 --> 00:28:49.159 looks at older patients where the

NOTE Confidence: 0.66074306

00:28:49.159 --> 00:28:51.482 combination is is a citedine with

NOTE Confidence: 0.66074306

00:28:51.482 --> 00:28:54.170 venetoclax plus minus Pemprolizumab.

NOTE Confidence: 0.66074306

00:28:54.170 --> 00:28:58.010 This trial is also through the UM 1

NOTE Confidence: 0.66074306

00:28:58.010 --> 00:29:00.280 mechanism and through both of those

NOTE Confidence: 0.66074306

00:29:00.280 --> 00:29:02.450 trials and in collaboration with CMAC,

NOTE Confidence: 0.66074306

00:29:02.450 --> 00:29:04.650 which is a cancer immunotherapy

NOTE Confidence: 0.66074306

00:29:04.650 --> 00:29:05.453 monitoring group.

NOTE Confidence: 0.66074306

00:29:05.453 --> 00:29:06.542 Within C Tib,

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

00:29:11.441 --> 00:29:13.209 collaborating with Doctor Jerry

NOTE Confidence: 0.66074306

00:29:13.280 --> 00:29:16.308 Radic from the Hajj to look at MRD

NOTE Confidence: 0.66074306

00:29:16.308 --> 00:29:18.940 negativity through different more

NOTE Confidence: 0.66074306

00:29:18.940 --> 00:29:20.914 sensitive techniques including

NOTE Confidence: 0.66074306

00:29:20.914 --> 00:29:23.450 circulating tumor DNA and at the

NOTE Confidence: 0.66074306

00:29:23.450 --> 00:29:25.946 level of the stem cells and looking

NOTE Confidence: 0.66074306

00:29:25.946 --> 00:29:29.432 at as I mentioned that other leukaemia

NOTE Confidence: 0.66074306

00:29:29.432 --> 00:29:31.997 specific T cell activation and a

NOTE Confidence: 0.66074306

00:29:31.997 --> 00:29:35.590 number of other I think important studies.

NOTE Confidence: 0.66074306

00:29:35.590 --> 00:29:37.872 Finally on the same front we have

NOTE Confidence: 0.66074306

00:29:37.872 --> 00:29:40.363 the plasty ML3 trial which is a

NOTE Confidence: 0.66074306

00:29:40.363 --> 00:29:42.523 phase two trial looking at combining

NOTE Confidence: 0.66074306

00:29:42.597 --> 00:29:44.907 IDH inhibitors with pimprolism AB.

NOTE Confidence: 0.66074306

00:29:44.910 --> 00:29:47.316 This is based on preclinical data

NOTE Confidence: 0.66074306

00:29:47.316 --> 00:29:50.022 suggesting that patients who have IDH

NOTE Confidence: 0.66074306

00:29:50.022 --> 00:29:52.090 mutations also have immunosuppressed

NOTE Confidence: 0.66074306

00:29:52.090 --> 00:29:53.124 micro environment.

NOTE Confidence: 0.66074306

00:29:53.130 --> 00:29:55.608 So Doctor Lourdes Mendez and Dr.

NOTE Confidence: 0.66074306

00:29:55.610 --> 00:29:58.418 Max Stoll at Hutch who I forgot to

NOTE Confidence: 0.66074306

00:29:58.418 --> 00:30:01.403 put his picture sorry are working on

NOTE Confidence: 0.66074306

00:30:01.403 --> 00:30:03.564 this trial and hopefully this trial

NOTE Confidence: 0.66074306

00:30:03.564 --> 00:30:05.586 is approved by Merck and hopefully

NOTE Confidence: 0.66074306

00:30:05.586 --> 00:30:07.409 it's going to open next year.

NOTE Confidence: 0.66074306

00:30:07.410 --> 00:30:08.690 And lastly on that front,

NOTE Confidence: 0.66074306

00:30:08.690 --> 00:30:10.610 we also have another trial with

NOTE Confidence: 0.66074306

00:30:10.610 --> 00:30:12.374 the triplet is Evan Sabatolimab.

NOTE Confidence: 0.66074306

00:30:12.374 --> 00:30:15.025 This is a phase two trial which

NOTE Confidence: 0.66074306

00:30:15.025 --> 00:30:17.085 enrolled more than 80 patients.

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

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

NOTE Confidence: 0.66074306

00:30:44.414 --> 00:30:45.658 inflammation in their lung,

NOTE Confidence: 0.66074306

00:30:45.660 --> 00:30:47.430 sometimes it's difficult to know

NOTE Confidence: 0.66074306

00:30:47.430 --> 00:30:49.896 is this a fungal infection or is

NOTE Confidence: 0.66074306

00:30:49.896 --> 00:30:51.486 this pneumonitis And in solid

NOTE Confidence: 0.66074306

00:30:51.486 --> 00:30:52.860 tumours it's easy or not

NOTE Confidence: 0.7563334

00:30:52.860 --> 00:30:54.860 at least easier to go and get a

NOTE Confidence: 0.7563334

00:30:54.860 --> 00:30:56.629 biopsy out of the of the lung.

NOTE Confidence: 0.7563334

00:30:56.629 --> 00:30:58.327 But in our patients it's very

NOTE Confidence: 0.7563334

00:30:58.327 --> 00:30:59.538 difficult to get biopsies.

NOTE Confidence: 0.7563334

00:30:59.540 --> 00:31:01.430 We're also hesitant to give steroids

NOTE Confidence: 0.7563334

00:31:01.430 --> 00:31:03.422 many times because of fungal infections

NOTE Confidence: 0.7563334

00:31:03.422 --> 00:31:05.456 that are common in our patients.

NOTE Confidence: 0.7563334

00:31:05.460 --> 00:31:07.828 So conducting immune checkpoint

NOTE Confidence: 0.7563334

00:31:07.828 --> 00:31:09.758 inhibition trials in patients

NOTE Confidence: 0.7563334

00:31:09.758 --> 00:31:12.084 with MD's is a bit challenging.

NOTE Confidence: 0.7563334

00:31:12.084 --> 00:31:14.964 However it is it can be done and this

NOTE Confidence: 0.7563334

00:31:14.964 --> 00:31:17.350 is retrospective analysis that was done

NOTE Confidence: 0.7563334

00:31:17.350 --> 00:31:20.068 by Doctor Shalas in you're looking at

NOTE Confidence: 0.7563334

00:31:20.068 --> 00:31:22.420 our own data showing that the number

NOTE Confidence: 0.7563334

00:31:22.491 --> 00:31:24.771 of immune related adverse events was

NOTE Confidence: 0.7563334

00:31:24.771 --> 00:31:27.313 somewhat similar to what is seen in

NOTE Confidence: 0.7563334

00:31:27.313 --> 00:31:29.221 patients with solid tumors when they

NOTE Confidence: 0.7563334

00:31:29.221 --> 00:31:30.821 get immune checkpoint inhibition.

NOTE Confidence: 0.7563334

00:31:30.821 --> 00:31:34.280 But also importantly that we are not seeing

NOTE Confidence: 0.7563334

00:31:34.280 --> 00:31:37.059 excess mortality when we use these agents.

NOTE Confidence: 0.7563334

00:31:37.060 --> 00:31:38.500 So I think it's certainly feasible.

NOTE Confidence: 0.7563334

00:31:38.500 --> 00:31:40.786 I think it's certainly has a

NOTE Confidence: 0.7563334

00:31:40.786 --> 00:31:43.820 way to kind of move forward and

NOTE Confidence: 0.7563334

00:31:43.820 --> 00:31:45.885 one of those agents I have deep

NOTE Confidence: 0.7563334

00:31:45.885 --> 00:31:47.698 confidence is going to be positive.

NOTE Confidence: 0.7563334

00:31:47.700 --> 00:31:49.685 But I think another important

NOTE Confidence: 0.7563334

00:31:49.685 --> 00:31:52.771 concept that we need to apply is

NOTE Confidence: 0.7563334

00:31:52.771 --> 00:31:54.819 biomarker selection of patients,

NOTE Confidence: 0.7563334

00:31:54.820 --> 00:31:58.630 because currently we are unrolling all

NOTE Confidence: 0.7563334

00:31:58.630 --> 00:32:01.930 newcomers regardless of their susceptibility

NOTE Confidence: 0.7563334

00:32:01.930 --> 00:32:04.710 to immune checkpoint inhibition.

NOTE Confidence: 0.7563334

00:32:04.710 --> 00:32:07.118 And I keep making the analogy of

NOTE Confidence: 0.7563334

00:32:07.118 --> 00:32:09.488 like trying to treat patients with

NOTE Confidence: 0.7563334

00:32:09.488 --> 00:32:11.524 IDH or all patients with an IDH

NOTE Confidence: 0.7563334

00:32:11.524 --> 00:32:13.170 inhibitor when you only should treat

NOTE Confidence: 0.7563334

00:32:13.170 --> 00:32:14.948 the ones with the IDH 1 mutation

NOTE Confidence: 0.7563334

00:32:14.948 --> 00:32:16.785 or the same thing with the EGFR.

NOTE Confidence: 0.7563334

00:32:16.790 --> 00:32:18.848 So we really should select patients

NOTE Confidence: 0.7563334

00:32:18.848 --> 00:32:20.935 who are more likely to respond

NOTE Confidence: 0.7563334

00:32:20.935 --> 00:32:22.268 to the specific pathway.

NOTE Confidence: 0.7563334

00:32:22.268 --> 00:32:25.132 This is an example of I think a

NOTE Confidence: 0.7563334

00:32:25.132 --> 00:32:27.382 nice effort looking at an immune

NOTE Confidence: 0.7563334

00:32:27.382 --> 00:32:29.047 effector signature to try to

00:32:29.047 --> 00:32:30.568 define subset of patients.

00:32:30.570 --> 00:32:31.774 This is clearly retrospective,

00:32:31.774 --> 00:32:33.922 but I think this is what should

00:32:33.922 --> 00:32:35.327 be applied in clinical trials

00:32:35.327 --> 00:32:36.540 in a prospective fashion,

00:32:36.540 --> 00:32:38.490 so we can select patients who

00:32:38.490 --> 00:32:40.320 are more likely to respond.

00:32:40.320 --> 00:32:43.085 So and I'd like to thank the

00:32:43.090 --> 00:32:45.375 our colleagues in the leukemia

00:32:45.375 --> 00:32:47.203 and myeloid malignancy program,

00:32:47.210 --> 00:32:52.096 including our wonderful MPs and the

00:32:52.096 --> 00:32:54.726 fellows and mentors and collaborators.

00:32:54.730 --> 00:32:55.970 All of them have been working with us,

00:32:55.970 --> 00:32:57.975 but also importantly our clinical

00:32:57.975 --> 00:33:00.458 research team who has been fundamental

00:33:00.458 --> 00:33:02.906 to all those clinical trials that

NOTE Confidence: 0.7563334

00:33:02.906 --> 00:33:05.801 I've just shown you and have been

NOTE Confidence: 0.7563334

00:33:05.801 --> 00:33:07.405 extremely productive even during

NOTE Confidence: 0.7563334

00:33:07.405 --> 00:33:09.778 COVID and all the staffing shortages

NOTE Confidence: 0.7563334

00:33:09.778 --> 00:33:12.130 that we had over the years.

NOTE Confidence: 0.7563334

00:33:12.130 --> 00:33:14.137 And at the end I'd like to thank all

NOTE Confidence: 0.7563334

00:33:14.137 --> 00:33:16.312 the organizations that helped fund my

NOTE Confidence: 0.7563334

00:33:16.312 --> 00:33:18.207 research and all the collaborators

NOTE Confidence: 0.7563334

00:33:18.265 --> 00:33:20.047 and happy to take any questions.

NOTE Confidence: 0.31525552

00:33:27.400 --> 00:33:29.688 Have a great time and let me apologize

NOTE Confidence: 0.31525552

00:33:29.688 --> 00:33:31.639 for not being here yesterday.

NOTE Confidence: 0.31525552

00:33:31.640 --> 00:33:35.180 I realized I was supposed to notice

NOTE Confidence: 0.31525552

00:33:35.180 --> 00:33:38.212 I heard you again well on your

NOTE Confidence: 0.31525552

00:33:38.212 --> 00:33:41.350 own It's it's a pretty impressive

NOTE Confidence: 0.31525552

00:33:41.350 --> 00:33:45.398 body of work that that that we've

NOTE Confidence: 0.31525552

00:33:45.398 --> 00:33:49.154 seen over these past few years.

NOTE Confidence: 0.31525552

00:33:49.160 --> 00:33:51.788 What do we know about and I thought this

NOTE Confidence: 0.31525552

00:33:51.788 --> 00:33:54.157 team eventually was when I was here,

NOTE Confidence: 0.31525552

00:33:54.160 --> 00:33:56.795 but is there any fundamental

NOTE Confidence: 0.31525552

00:33:56.795 --> 00:33:59.600 difference in MD's in younger

NOTE Confidence: 0.31525552

00:33:59.600 --> 00:34:02.202 individuals than those who are,

NOTE Confidence: 0.31525552

00:34:02.202 --> 00:34:03.266 you know, more typically,

NOTE Confidence: 0.31525552

00:34:03.270 --> 00:34:05.990 yes, age, you know,

NOTE Confidence: 0.31525552

00:34:05.990 --> 00:34:08.750 so the occasional 40 or 50 year old person,

NOTE Confidence: 0.31525552

00:34:08.750 --> 00:34:10.304 you see it because this heavy year,

NOTE Confidence: 0.31525552

00:34:10.310 --> 00:34:11.870 80 year old. Yeah,

NOTE Confidence: 0.29407984

00:34:11.870 --> 00:34:13.788 this is actually a very important question.

NOTE Confidence: 0.29407984

00:34:13.790 --> 00:34:15.610 So the majority of MD's

NOTE Confidence: 0.29407984

00:34:15.610 --> 00:34:17.430 patients are older than 65,

NOTE Confidence: 0.29407984

00:34:17.430 --> 00:34:20.838 around 85% of patients are older than 65.

NOTE Confidence: 0.29407984

00:34:20.840 --> 00:34:22.758 We do see MD's in younger patients,

NOTE Confidence: 0.29407984

00:34:22.760 --> 00:34:26.497 but generally tend to be two big areas.

NOTE Confidence: 0.29407984

00:34:26.497 --> 00:34:28.291 One of them is previous exposure

NOTE Confidence: 0.29407984

00:34:28.291 --> 00:34:30.191 to chemotherapy or radiation in

NOTE Confidence: 0.29407984

00:34:30.191 --> 00:34:32.116 the context of solid tumours,

NOTE Confidence: 0.29407984

00:34:32.120 --> 00:34:33.812 usually breast cancer actually

NOTE Confidence: 0.29407984

00:34:33.812 --> 00:34:36.640 is 1 common setting where we see

NOTE Confidence: 0.29407984

00:34:36.640 --> 00:34:38.095 patients who have received radiation

NOTE Confidence: 0.29407984

00:34:38.095 --> 00:34:39.920 or chemo and have secondary cancer.

NOTE Confidence: 0.29407984

00:34:39.920 --> 00:34:42.560 But the second big area is

NOTE Confidence: 0.29407984

00:34:42.560 --> 00:34:43.270 genomic predisposition.

NOTE Confidence: 0.29407984

00:34:43.270 --> 00:34:46.110 So there are a number of patients who

NOTE Confidence: 0.29407984

00:34:46.177 --> 00:34:47.850 have for example underlying Franconia's

NOTE Confidence: 0.29407984

00:34:47.850 --> 00:34:50.010 anemia or plastic anemia or some

NOTE Confidence: 0.29407984

00:34:50.063 --> 00:34:51.887 kind of hereditary predisposition.

NOTE Confidence: 0.29407984

00:34:51.890 --> 00:34:56.210 The number of those predisposition

NOTE Confidence: 0.29407984

00:34:56.210 --> 00:34:58.050 genes actually has been increasing

NOTE Confidence: 0.29407984

00:34:58.050 --> 00:35:00.617 or we are discovering more and more

NOTE Confidence: 0.29407984

00:35:00.617 --> 00:35:02.609 of them and it's quite fascinating.

NOTE Confidence: 0.29407984

00:35:02.610 --> 00:35:04.850 For example, there is one called DDX 4,

NOTE Confidence: 0.29407984

00:35:04.850 --> 00:35:07.034 one that we did not for know about

NOTE Confidence: 0.29407984

00:35:07.034 --> 00:35:09.250 until you know a few years ago and

NOTE Confidence: 0.29407984

00:35:09.250 --> 00:35:11.310 it turned out that 10% of patients

NOTE Confidence: 0.29407984

00:35:11.310 --> 00:35:13.530 with AML and MD's have that.

NOTE Confidence: 0.29407984

00:35:13.530 --> 00:35:16.452 And those are I think important

NOTE Confidence: 0.29407984

00:35:16.452 --> 00:35:18.381 because they underlie different,

NOTE Confidence: 0.29407984

00:35:18.381 --> 00:35:19.764 different clinical behaviour.

NOTE Confidence: 0.29407984

00:35:19.764 --> 00:35:22.069 Those patients for example tend

NOTE Confidence: 0.29407984

00:35:22.069 --> 00:35:23.638 to be more indolent.

NOTE Confidence: 0.29407984

00:35:23.640 --> 00:35:26.376 I have a 96 year old patient with

NOTE Confidence: 0.29407984

00:35:26.376 --> 00:35:28.716 AML who has DDX 41 germline and

NOTE Confidence: 0.29407984

00:35:28.716 --> 00:35:30.690 it's just just mind boggling to

NOTE Confidence: 0.29407984

00:35:30.757 --> 00:35:33.001 me that you think that someone

NOTE Confidence: 0.29407984

00:35:33.001 --> 00:35:35.191 carried this mutation until she was

NOTE Confidence: 0.29407984

00:35:35.191 --> 00:35:36.756 95 to develop finally AML.

NOTE Confidence: 0.29407984

00:35:36.760 --> 00:35:39.280 So those tend to happen in older patients.

NOTE Confidence: 0.29407984

00:35:39.280 --> 00:35:40.732 There are other ones that tend

NOTE Confidence: 0.29407984

00:35:40.732 --> 00:35:42.410 to happen at a younger age.

NOTE Confidence: 0.29407984

00:35:42.410 --> 00:35:44.370 But I think the biggest message usually,

NOTE Confidence: 0.29407984

00:35:44.370 --> 00:35:44.657 I,

NOTE Confidence: 0.29407984

00:35:44.657 --> 00:35:46.092 I usually say regarding younger

NOTE Confidence: 0.29407984

00:35:46.092 --> 00:35:48.097 patients the MD's is you have to

NOTE Confidence: 0.29407984

00:35:48.097 --> 00:35:49.693 look for other things because there

NOTE Confidence: 0.29407984

00:35:49.693 --> 00:35:51.274 are many things that mimic MD's

NOTE Confidence: 0.29407984

00:35:51.274 --> 00:35:53.054 and you want to make sure what

NOTE Confidence: 0.29407984

00:35:53.054 --> 00:35:54.626 you are dealing with is indeed

NOTE Confidence: 0.29407984

00:35:54.626 --> 00:35:56.050 MD's because the treatment is,

NOTE Confidence: 0.29407984

00:35:56.050 --> 00:35:57.208 is is different.

NOTE Confidence: 0.8515997

00:35:59.650 --> 00:36:00.010 Yes.

NOTE Confidence: 0.46399102

00:36:12.970 --> 00:36:14.405 Yeah, this is a very good question.

NOTE Confidence: 0.46399102

00:36:14.410 --> 00:36:16.363 And actually this has always come up

NOTE Confidence: 0.46399102

00:36:16.363 --> 00:36:17.969 in our discussions with you know,

NOTE Confidence: 0.46399102

00:36:17.970 --> 00:36:19.450 with IR, BS and regulators.

NOTE Confidence: 0.46399102

00:36:19.450 --> 00:36:21.970 And there's actually a large chunk

NOTE Confidence: 0.46399102

00:36:21.970 --> 00:36:24.410 of evidence based on as I mentioned,

NOTE Confidence: 0.46399102

00:36:24.410 --> 00:36:26.432 the problems that most of the

NOTE Confidence: 0.46399102

00:36:26.432 --> 00:36:28.650 trials that we have done in the

NOTE Confidence: 0.46399102

00:36:28.650 --> 00:36:30.210 field have been single arm trials.

NOTE Confidence: 0.46399102

00:36:30.210 --> 00:36:32.674 So most of what we have right

NOTE Confidence: 0.46399102

00:36:32.674 --> 00:36:34.650 now is anecdotal experience.

NOTE Confidence: 0.46399102

00:36:34.650 --> 00:36:36.450 We are not seeing overall,

NOTE Confidence: 0.46399102

00:36:36.450 --> 00:36:38.650 if you look at the entirety of data,

NOTE Confidence: 0.46399102

00:36:38.650 --> 00:36:41.218 we're not seeing an increased incidence

NOTE Confidence: 0.46399102

65

00:36:41.218 --> 00:36:45.450 of GVHD that is 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 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

NOTE Confidence: 0.46399102

00:37:16.420 --> 00:37:18.376 versus leukemia effect and this is

NOTE Confidence: 0.46399102

00:37:18.376 --> 00:37:20.260 how we think transplant can work.

NOTE Confidence: 0.46399102

00:37:20.260 --> 00:37:22.412 So I think it's always a risk benefit

NOTE Confidence: 0.46399102

00:37:22.412 --> 00:37:24.762 and I don't think you can answer

NOTE Confidence: 0.46399102

00:37:24.762 --> 00:37:26.597 that without a randomized data.

NOTE Confidence: 0.46399102

00:37:26.597 --> 00:37:28.871 This is something we are certainly

NOTE Confidence: 0.46399102

00:37:28.871 --> 00:37:30.924 keeping a very close eye on in our

NOTE Confidence: 0.46399102

00:37:30.930 --> 00:37:32.515 different trials and the regulators

NOTE Confidence: 0.46399102

00:37:32.515 --> 00:37:34.413 have been also kind of keeping

NOTE Confidence: 0.46399102

00:37:34.413 --> 00:37:35.688 a close eye on this.

NOTE Confidence: 0.46399102

00:37:35.690 --> 00:37:39.488 And I have to say in in our practice

NOTE Confidence: 0.46399102

00:37:39.488 --> 00:37:42.622 we usually try to say stop the

NOTE Confidence: 0.46399102

00:37:42.622 --> 00:37:44.252 immune checkpoint inhibitor like you

NOTE Confidence: 0.46399102

00:37:44.252 --> 00:37:46.505 know in the last six weeks before

NOTE Confidence: 0.46399102

00:37:46.505 --> 00:37:48.750 transplant 6 to 8 weeks ideally just

NOTE Confidence: 0.46399102

00:37:48.750 --> 00:37:50.850 because of that theoretical concern.

NOTE Confidence: 0.46399102

00:37:50.850 --> 00:37:53.127 I would say at the end is that in

NOTE Confidence: 0.46399102

00:37:53.130 --> 00:37:55.050 immune checkpoint inhibitors are

NOTE Confidence: 0.46399102

00:37:55.050 --> 00:37:58.682 approved in in in some in substance

NOTE Confidence: 0.46399102

00:37:58.682 --> 00:38:01.490 of lymphoma and in in that setting

NOTE Confidence: 0.46399102

00:38:01.490 --> 00:38:03.200 like Hodgkin's disease and generally

NOTE Confidence: 0.46399102

00:38:03.267 --> 00:38:05.220 there has not they have not seen

NOTE Confidence: 0.46399102

00:38:05.220 --> 00:38:06.579 that that issue as much.

NOTE Confidence: 0.46399102

00:38:06.580 --> 00:38:07.672 So I guess we'll,

NOTE Confidence: 0.46399102

00:38:07.672 --> 00:38:08.218 you know,

NOTE Confidence: 0.46399102

00:38:08.220 --> 00:38:11.460 we'll have to wait and see for AML and MD's.

NOTE Confidence: 0.46399102

00:38:11.460 --> 00:38:11.700 Yes.

NOTE Confidence: 0.55645

00:38:29.390 --> 00:38:31.126 Yeah, this is a great question And

NOTE Confidence: 0.55645

00:38:31.126 --> 00:38:33.087 part of why I did not divulge and

NOTE Confidence: 0.55645

00:38:33.087 --> 00:38:35.190 like go too much into this is that

NOTE Confidence: 0.55645

00:38:35.190 --> 00:38:36.670 this methylation business has been

NOTE Confidence: 0.55645

00:38:36.670 --> 00:38:39.125 I think one of the most challenging

NOTE Confidence: 0.55645

00:38:39.125 --> 00:38:40.850 aspect of you know Steve Gorwin,

NOTE Confidence: 0.55645

00:38:40.850 --> 00:38:43.440 he used to be like he used to hate

NOTE Confidence: 0.55645

00:38:43.440 --> 00:38:44.848 calling these hypomethylating agents

NOTE Confidence: 0.55645

00:38:44.848 --> 00:38:47.135 because we we are not even 100% sure

NOTE Confidence: 0.55645

00:38:47.135 --> 00:38:48.710 that this is how they actually work.

NOTE Confidence: 0.55645

00:38:48.710 --> 00:38:49.940 You know, we always like to

NOTE Confidence: 0.55645

00:38:49.940 --> 00:38:52.990 call them DN MT3 inhibitors.

NOTE Confidence: 0.55645

00:38:52.990 --> 00:38:56.340 I guess the big answer is that in those

NOTE Confidence: 0.55645

00:38:56.340 --> 00:38:58.970 trials that I presented they did not

NOTE Confidence: 0.55645

00:38:58.970 --> 00:39:00.720 do like site specific methylation.

NOTE Confidence: 0.55645

00:39:00.720 --> 00:39:02.934 But we still don't fully understand

NOTE Confidence: 0.55645

00:39:02.934 --> 00:39:04.851 what because you are seeing

NOTE Confidence: 0.55645

00:39:04.851 --> 00:39:06.716 a mix of hyper methylation,

NOTE Confidence: 0.55645

00:39:06.720 --> 00:39:08.240 hyper methylation depending on where

NOTE Confidence: 0.55645

00:39:08.240 --> 00:39:10.318 you are looking within the genome and
NOTE Confidence: 0.55645

00:39:10.318 --> 00:39:12.271 until now we don't fully understand the
NOTE Confidence: 0.55645

00:39:12.271 --> 00:39:13.757 mechanism of action of these drugs.
NOTE Confidence: 0.55645

00:39:13.760 --> 00:39:16.672 I did not go into this because of,
NOTE Confidence: 0.55645

00:39:16.672 --> 00:39:17.800 of, you know,
NOTE Confidence: 0.55645

00:39:17.800 --> 00:39:19.396 the nature of of the audience here.
NOTE Confidence: 0.55645

00:39:19.400 --> 00:39:21.710 But I think one of the biggest
NOTE Confidence: 0.55645

00:39:21.710 --> 00:39:23.676 challenges in my own view about why
NOTE Confidence: 0.55645

00:39:23.676 --> 00:39:25.696 we could not go beyond HMAS is that
NOTE Confidence: 0.55645

00:39:25.696 --> 00:39:27.190 we are stuck with this schedule
NOTE Confidence: 0.55645

00:39:27.190 --> 00:39:29.265 that is at the approved seven days
NOTE Confidence: 0.55645

00:39:29.265 --> 00:39:30.780 of azacitidine in every single
NOTE Confidence: 0.55645

00:39:30.780 --> 00:39:32.272 trial that we have.
NOTE Confidence: 0.55645

00:39:32.272 --> 00:39:34.137 And this is a myelosuppressive
NOTE Confidence: 0.55645

00:39:34.140 --> 00:39:35.766 combination and trying to add things
NOTE Confidence: 0.55645

00:39:35.766 --> 00:39:37.859 to it has been quite challenging.

NOTE Confidence: 0.55645

00:39:37.860 --> 00:39:39.876 But currently it's not

NOTE Confidence: 0.55645

00:39:39.876 --> 00:39:41.748 considered ethical to randomize,

NOTE Confidence: 0.55645

00:39:41.748 --> 00:39:42.660 you know,

NOTE Confidence: 0.55645

00:39:42.660 --> 00:39:45.089 without including the seven days of HMA

NOTE Confidence: 0.55645

00:39:45.089 --> 00:39:47.341 because it's the only drug that has

NOTE Confidence: 0.55645

00:39:47.341 --> 00:39:49.670 been want to improve our all survival.

NOTE Confidence: 0.55645

00:39:49.670 --> 00:39:50.243 But you're right,

NOTE Confidence: 0.55645

00:39:50.243 --> 00:39:51.389 I mean there could be trials,

NOTE Confidence: 0.55645

00:39:51.390 --> 00:39:53.718 there could be agents that could

NOTE Confidence: 0.55645

00:39:53.718 --> 00:39:55.520 antagonize that methylation or it could

NOTE Confidence: 0.55645

00:39:55.520 --> 00:39:57.768 be the other way around where this

NOTE Confidence: 0.55645

00:39:57.768 --> 00:39:59.708 methylation is negatively impacting it.

NOTE Confidence: 0.55645

00:39:59.710 --> 00:40:02.548 So that has been a big,

NOTE Confidence: 0.55645

00:40:02.550 --> 00:40:04.590 I think, problem, Nathaniel.

NOTE Confidence: 0.26580712

00:40:17.650 --> 00:40:21.290 Like those seven the therapy,

NOTE Confidence: 0.26580712

00:40:21.290 --> 00:40:24.022 we know that those therapies

NOTE Confidence: 0.26580712

00:40:24.022 --> 00:40:26.803 result in quite profound immune

NOTE Confidence: 0.26580712

00:40:26.803 --> 00:40:28.968 suppression and not only they,

NOTE Confidence: 0.26580712

00:40:28.970 --> 00:40:30.727 they're also quite lymphopenic when you have

NOTE Confidence: 0.26580712

00:40:32.850 --> 00:40:36.954 0.1. So does it make sense to

NOTE Confidence: 0.26580712

00:40:36.954 --> 00:40:38.864 give them concurrently? I mean,

NOTE Confidence: 0.26580712

00:40:38.864 --> 00:40:40.586 you're trying to mount some different

NOTE Confidence: 0.27404776

00:40:43.990 --> 00:40:44.870 response at the same time,

NOTE Confidence: 0.27404776

00:40:44.870 --> 00:40:47.110 completely suppressing their chemo,

NOTE Confidence: 0.27404776

00:40:47.110 --> 00:40:49.190 so it doesn't make sense

NOTE Confidence: 0.27404776

00:40:49.190 --> 00:40:50.478 to get them concurrently.

NOTE Confidence: 0.27404776

00:40:50.478 --> 00:40:53.050 Or would you have a more clever way

NOTE Confidence: 0.27404776

00:40:53.050 --> 00:40:54.966 where you perhaps cumulate the marrow,

NOTE Confidence: 0.27404776

00:40:54.966 --> 00:40:56.476 allow them to recover,

NOTE Confidence: 0.27404776

00:40:56.476 --> 00:40:59.310 have some given or reconstitution and

NOTE Confidence: 0.27404776

00:41:00.870 --> 00:41:01.766 then, you know, yeah.

00:41:01.766 --> 00:41:03.110 So there are people working on

00:41:03.154 --> 00:41:04.546 concepts like this where they are

00:41:04.546 --> 00:41:06.391 giving it around the time of immune

00:41:06.391 --> 00:41:07.547 reconstitution as you mentioned.

00:41:07.550 --> 00:41:09.660 I think 2 points on this front is that they

00:41:09.709 --> 00:41:11.719 actually have combined and solid tumours.

00:41:11.720 --> 00:41:13.676 They have multiple and you know,

00:41:13.680 --> 00:41:15.228 Barbara and others know more about

00:41:15.228 --> 00:41:16.786 this like solid tumours where you

00:41:16.786 --> 00:41:18.202 are giving chemo with immune therapy

00:41:18.202 --> 00:41:19.839 and it seems like it has worked,

00:41:19.840 --> 00:41:20.599 but they're, yeah,

00:41:20.599 --> 00:41:22.117 their drugs are not as lymph,

00:41:22.120 --> 00:41:24.520 you know, lymphodepleting as ours.

00:41:24.520 --> 00:41:25.654 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

00:41:53.104 --> 00:41:54.798 challenge of when what is the exact

00:41:54.798 --> 00:41:58.494 time to to use these these drugs has

00:41:58.494 --> 00:42:00.114 been somewhat kind of frustrating

00:42:00.114 --> 00:42:02.688 I have to say with with both PD1,

00:42:02.690 --> 00:42:05.210 PDL 1 so far and because multiple

00:42:05.210 --> 00:42:06.613 trials have been negative.

00:42:06.613 --> 00:42:09.197 So it might be that none of those

00:42:09.197 --> 00:42:11.350 pathways are you know what really

00:42:11.350 --> 00:42:13.734 is important in the MLN MD's and

00:42:13.734 --> 00:42:15.342 maybe the Sabatoli map that I

00:42:15.342 --> 00:42:17.090 just showed or some other.

00:42:17.090 --> 00:42:18.890 You know there are other,

00:42:18.890 --> 00:42:21.010 I did not go on to this as well in detail,

00:42:21.010 --> 00:42:23.222 but they are lag three, they are Lil RP4.

00:42:23.222 --> 00:42:25.486 There are a number of other immune

00:42:25.486 --> 00:42:27.716 checkpoint pathways that are also

00:42:27.716 --> 00:42:30.159 being tested in MD's and AML.

00:42:30.160 --> 00:42:30.340 Yes,

00:42:30.340 --> 00:42:30.520 with

00:42:50.680 --> 00:42:52.718 the the actually TM3 without the PD one.

00:42:52.720 --> 00:42:55.492 Yeah, so I did not go through that the

00:42:55.492 --> 00:42:57.740 solid tumor literature with TM3 but

00:42:57.740 --> 00:43:00.341 they actually had a big trial combined

00:43:00.341 --> 00:43:03.580 TM3 and PD1 and that has not led to

00:43:03.580 --> 00:43:05.805 clinical improvement in solid tumours.

00:43:05.810 --> 00:43:07.630 So the development has been

00:43:07.630 --> 00:43:10.018 largely focused on the MD's space.

00:43:10.018 --> 00:43:13.346 They have a, the company has sponsored

00:43:13.346 --> 00:43:16.238 trials where they are combining different

00:43:16.238 --> 00:43:18.110 immune checkpoint inhibitors and

00:43:18.110 --> 00:43:20.450 actually sabatorimab with other drugs.

NOTE Confidence: 0.4381587

00:43:20.450 --> 00:43:24.794 So those I think could give you know an idea,

NOTE Confidence: 0.4381587

00:43:24.794 --> 00:43:26.524 but from a regulatory path,

NOTE Confidence: 0.4381587

00:43:26.530 --> 00:43:29.041 you know you're as I was saying a little

NOTE Confidence: 0.4381587

00:43:29.041 --> 00:43:31.477 bit earlier is you have to combine with

NOTE Confidence: 0.4381587

00:43:31.477 --> 00:43:34.370 HMA to kind of get your first approval

NOTE Confidence: 0.4381587

00:43:34.370 --> 00:43:37.334 and then I think you know contagion, hago.

NOTE Confidence: 0.4381587

00:43:37.334 --> 00:43:39.080 Contagion also said like the real

NOTE Confidence: 0.4381587

00:43:39.130 --> 00:43:41.027 research starts once a drug is approved

NOTE Confidence: 0.4381587

00:43:41.027 --> 00:43:43.010 like you really need to get like

NOTE Confidence: 0.4381587

00:43:43.010 --> 00:43:44.405 something like once it's approved,

NOTE Confidence: 0.4381587

00:43:44.410 --> 00:43:46.471 I think you can do all kinds of concepts

NOTE Confidence: 0.4381587

00:43:46.471 --> 00:43:48.433 but the initial focus is always on

NOTE Confidence: 0.4381587

00:43:48.433 --> 00:43:50.537 trying to kind of get the trial that

NOTE Confidence: 0.4381587

00:43:50.537 --> 00:43:52.478 leads to approval and then you can

NOTE Confidence: 0.4381587

00:43:52.478 --> 00:43:54.730 do all these kind of bigger concepts.

NOTE Confidence: 0.4381587

00:43:54.730 --> 00:43:56.170 You can do them now in a small phase

NOTE Confidence: 0.4381587

00:43:56.170 --> 00:43:59.370 one study, but not in a large setting.

NOTE Confidence: 0.4381587

00:43:59.370 --> 00:43:59.890 Yes, Sir.

NOTE Confidence: 0.04401749

00:44:17.120 --> 00:44:17.160 I

NOTE Confidence: 0.290338

00:44:51.290 --> 00:44:53.126 Again, I think this is a very good question.

NOTE Confidence: 0.290338

00:44:53.130 --> 00:44:55.853 Clearly the post transplant setting is a

NOTE Confidence: 0.290338

00:44:55.853 --> 00:44:57.907 very important development area because

NOTE Confidence: 0.290338

00:44:57.907 --> 00:44:59.967 most of our patients unfortunately

NOTE Confidence: 0.290338

00:44:59.967 --> 00:45:01.956 despite transplant they they relapse.

NOTE Confidence: 0.290338

00:45:01.956 --> 00:45:05.250 So I think with the epilogue map, the trial,

NOTE Confidence: 0.290338

00:45:05.250 --> 00:45:07.970 the New England Journal paper I showed you,

NOTE Confidence: 0.290338

00:45:07.970 --> 00:45:09.806 people have had a very tough

NOTE Confidence: 0.290338

00:45:09.806 --> 00:45:10.724 time replicating these,

NOTE Confidence: 0.290338

00:45:10.730 --> 00:45:14.666 I would say outside of, you know,

NOTE Confidence: 0.290338

00:45:14.666 --> 00:45:15.532 occasional responses.

NOTE Confidence: 0.290338

00:45:15.532 --> 00:45:18.603 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

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

NOTE Confidence: 0.5107637

00:47:17.534 --> 00:47:19.358 that is getting more attention now

NOTE Confidence: 0.5107637

00:47:19.358 --> 00:47:21.501 because of what I showed at the

NOTE Confidence: 0.5107637

00:47:21.501 --> 00:47:23.259 beginning like this chip slash seeker

NOTE Confidence: 0.5107637

00:47:23.318 --> 00:47:25.310 spectrum where clonal hematopoiesis.

NOTE Confidence: 0.5107637

00:47:25.310 --> 00:47:26.582 We are seeing some of this

NOTE Confidence: 0.5107637

00:47:26.582 --> 00:47:27.430 actually in solid tumors.

NOTE Confidence: 0.5107637

00:47:27.430 --> 00:47:30.348 For example a breast cancer patient

NOTE Confidence: 0.5107637

00:47:30.348 --> 00:47:34.454 under you know underlying more and

NOTE Confidence: 0.5107637

00:47:34.454 --> 00:47:35.973 more people are doing these next Gen.

NOTE Confidence: 0.5107637

00:47:35.980 --> 00:47:37.624 sequencing and then the patient turned

NOTE Confidence: 0.5107637

00:47:37.624 --> 00:47:40.014 out to have TP 53 mutation chip like

NOTE Confidence: 0.5107637

00:47:40.014 --> 00:47:41.564 the blood counts are completely

NOTE Confidence: 0.5107637

00:47:41.564 --> 00:47:43.136 normal but she has TP53 mutation.

NOTE Confidence: 0.5107637

00:47:43.136 --> 00:47:45.044 And one of the increasing questions

NOTE Confidence: 0.5107637

00:47:45.044 --> 00:47:47.218 that are being asked like you know

NOTE Confidence: 0.5107637

00:47:47.218 --> 00:47:49.165 the oncologists are afraid to give

NOTE Confidence: 0.5107637

00:47:49.165 --> 00:47:51.122 chemotherapy because that TP53 clone

NOTE Confidence: 0.5107637

00:47:51.122 --> 00:47:54.500 could expand and lead to MD's or or AML.

NOTE Confidence: 0.5107637

00:47:54.500 --> 00:47:56.858 So I would say this is an evolving area.

NOTE Confidence: 0.5107637

00:47:56.860 --> 00:47:58.415 Currently we don't think immune

NOTE Confidence: 0.5107637

00:47:58.415 --> 00:47:59.659 checkpoint inhibition would work.

NOTE Confidence: 0.5107637

00:47:59.660 --> 00:48:01.800 Most of the trials that are looking

NOTE Confidence: 0.5107637

00:48:01.800 --> 00:48:03.480 at agents are looking at things

NOTE Confidence: 0.5107637

00:48:03.480 --> 00:48:04.320 that are very

NOTE Confidence: 0.66263217

00:48:06.400 --> 00:48:08.094 non-toxic. Let me put it this way

NOTE Confidence: 0.66263217

00:48:08.094 --> 00:48:09.807 because those are patients with good

NOTE Confidence: 0.66263217

00:48:09.807 --> 00:48:11.673 counts generally and normal bone marrow.

NOTE Confidence: 0.66263217

00:48:11.680 --> 00:48:13.840 So they are like they are trials of

NOTE Confidence: 0.66263217

00:48:13.840 --> 00:48:16.000 vitamin C and you know inflammation,

NOTE Confidence: 0.66263217

00:48:16.000 --> 00:48:18.319 anti-inflammatory agents etcetera.

NOTE Confidence: 0.66263217

00:48:18.320 --> 00:48:20.756 However those drugs can be given together.

NOTE Confidence: 0.66263217

00:48:20.760 --> 00:48:22.888 One of the things actually we benefited

NOTE Confidence: 0.66263217

00:48:22.888 --> 00:48:24.983 from doing these trials is that I have

NOTE Confidence: 0.66263217

00:48:24.983 --> 00:48:26.908 a number of patients I share with

NOTE Confidence: 0.66263217

00:48:26.908 --> 00:48:28.780 our colleagues here that need some,

NOTE Confidence: 0.66263217

00:48:28.780 --> 00:48:30.340 you know that that need immune

NOTE Confidence: 0.66263217

00:48:30.340 --> 00:48:30.860 checkpoint inhibition.

NOTE Confidence: 0.66263217

00:48:30.860 --> 00:48:32.860 I have multiple patients including

NOTE Confidence: 0.66263217

00:48:32.860 --> 00:48:35.138 with Barbara where they are on some

NOTE Confidence: 0.66263217

00:48:35.138 --> 00:48:36.709 kind of immune checkpoint inhibitor

NOTE Confidence: 0.66263217

00:48:36.709 --> 00:48:39.022 and they have MD's now and I need to

NOTE Confidence: 0.66263217

00:48:39.084 --> 00:48:40.649 give them azacitidine because they

NOTE Confidence: 0.66263217

00:48:40.649 --> 00:48:42.848 have MD's and we have been doing

NOTE Confidence: 0.66263217

00:48:42.848 --> 00:48:45.046 this in a number of patients and

NOTE Confidence: 0.66263217

00:48:45.046 --> 00:48:46.966 for the most part is pretty safe.

NOTE Confidence: 0.66263217

00:48:46.966 --> 00:48:48.597 So this in the past used to

NOTE Confidence: 0.66263217

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,

NOTE Confidence: 0.66263217

00:49:15.114 --> 00:49:17.436 this I think how to prevent

NOTE Confidence: 0.66263217

00:49:17.436 --> 00:49:19.535 clonal evolution is I think is

NOTE Confidence: 0.66263217

00:49:19.535 --> 00:49:21.100 an important area as well.

NOTE Confidence: 0.88644993

00:49:25.200 --> 00:49:28.040 OK. Thank you so much my e-mail

NOTE Confidence: 0.88644993

00:49:28.040 --> 00:49:29.480 if anybody has any questions then.