Typically this is a CME event composed of six sessions. We already had the first session for multiple myeloma on January 15th and the lymphoid malignancy session last week. Today will be updating you on the myeloid malignancy and next week we have an update on pediatric leukemia and also adult acute lymphoblastic leukemia. February 12th will be classical or non benign hematology and we will conclude on February 19th with cell therapy and transplantation updates. So as you can tell,
there are many great abstracts that are being presented in ash this year, and it’s very difficult to try to cover all of these, especially with the time limitation. So here the abstracts that have been selected in this session and in the other sessions basically are chosen for their highest impact, and the ones that are most relevant clinically, especially in areas of unmet clinical need with decided to group them basically by the disease area AML MD’s.
Of course, that doesn’t mean that the other abstracts that are not presented are not as great. It just as time limitation, and also important to remember that a lot of the abstracts contain preliminary information and preliminary data, and they have not been peer reviewed or finalize or published. So these results always have to be taken with that consideration in mind. We also like to thank all the authors of those abstracts who have shared their slides. With us for this presentation at the end of the entire Series A recording.
00:01:41.830 --> 00:01:44.216 of this session and the other sessions

00:01:44.216 --> 00:01:46.806 will be available on the subsequent week.

00:01:46.810 --> 00:01:49.386 An slice of each presentation that will

00:01:49.386 --> 00:01:51.844 also be available for your review and

00:01:51.844 --> 00:01:54.560 for people who cannot make the live event.

00:01:54.560 --> 00:01:57.264 At the end of the six session series,

00:01:57.270 --> 00:01:58.965 CME Credit will be provided

00:01:58.965 --> 00:02:00.660 for those who claim it.

00:02:00.660 --> 00:02:05.079 You will have to fill a quick form and.

00:02:05.080 --> 00:02:07.660 Supply some feedback to claim the

00:02:07.660 --> 00:02:10.990 CME credit at the end of the series.

00:02:10.990 --> 00:02:12.630 So today we’ll be covering

00:02:12.630 --> 00:02:13.614 the myeloid neoplasms.

00:02:13.620 --> 00:02:15.270 As you can see here,

00:02:15.270 --> 00:02:17.573 I will be updating you for Milo

NOTE Confidence: 0.8444918
dysplastic syndromes then, Doctor Orish Alice will update us on acute myeloid leukemia and finally doctor, but also full update us on myeloproliferative. Neoplasm's will try to stick to the times that you can see here so that we can allow some time for questions in the last 10 minutes. We can stay a few minutes beyond one. For those of you who can stay if there are many questions as well. So I'll start with the updates on my latest ostick syndromes. So these are my disclosures. So I'm just as many of you know,
their management is really highly risk adaptive. It’s somewhat unusual compared to other malignancy’s in which the interventions vary significantly all the way from observation. For patients with lower risk, MD S All the way to recommending a very aggressive intervention, like allogenic bone marrow transplantation for patients who have very aggressive disease, which have a prognosis almost like acute myeloid leukemia. In the most aggressive forms of Andy’s,
00:03:17.510 --> 00:03:19.974 this is actually a schema from 2013,
NOTE Confidence: 0.8444918
00:03:19.980 --> 00:03:23.180 and the reason I’m showing you this one.
NOTE Confidence: 0.8444918
00:03:23.180 --> 00:03:26.618 From seven or eight years ago is because.
NOTE Confidence: 0.8444918
00:03:26.620 --> 00:03:28.744 Not much really has changed in
NOTE Confidence: 0.8444918
00:03:28.744 --> 00:03:31.011 the schema in the management of
NOTE Confidence: 0.8444918
00:03:31.011 --> 00:03:33.699 Andy as until last year until 2020
NOTE Confidence: 0.8444918
00:03:33.699 --> 00:03:36.898 and in 2020 we have the first 2
NOTE Confidence: 0.8444918
00:03:36.898 --> 00:03:38.071 approvers basically since
NOTE Confidence: 0.8375796
00:03:38.080 --> 00:03:40.936 2006 so we had 14 years without any
NOTE Confidence: 0.8375796
00:03:40.936 --> 00:03:43.557 approvals for Andy’s until 2020 when we
NOTE Confidence: 0.8375796
00:03:43.557 --> 00:03:46.479 have two drugs that have been approved.
NOTE Confidence: 0.8375796
00:03:46.480 --> 00:03:49.014 One of them is last battleship which
NOTE Confidence: 0.8375796
00:03:49.014 --> 00:03:51.449 is a transforming growth factor beta,
NOTE Confidence: 0.8375796
00:03:51.450 --> 00:03:54.120 an inhibitor disinhibits. Elegant and.
NOTE Confidence: 0.8375796
00:03:54.120 --> 00:03:56.124 This is recommended for patients who
NOTE Confidence: 0.8375796
00:03:56.124 --> 00:03:58.543 have lower risk MD’s who have any
meandering senior class and other drug,

was an oral decitabine.

An oral version of this item,

in that we will be talking about,

but this was also approved in late 2024 patients with high risk MD's.

So I think it’s important to start the presentation by highlighting that high unmet need for patients with high risk MD's.

So these are some real life analysis that showed that despite the introduction of hypomethylating agents in for treatment for high risk MD

as the outcomes or me and pull the overall responses is around 40 to 50%.
However, the complete response rate is only around 15% and most of those responses are limited and most patients die from the disease relatively quickly. You can see here previous real life analysis that we conducted for patients who receive is cited in or decide to be in and you can see the median overall survival for older patients. And this was a serious Medicare analysis was eleven months while for patients who were younger and were referred to tertiary big centers in the MD's Clinical Research Consortium. The median overall survival was 17 months.
So basically it’s much lower than what is generally described in the literature.

On 24 months, and for patients who progress after receiving those hypomethylating agents, their survival is even worse.

This is an important study that was published by our colleague, Doctor to my Propay, showing that the median survival was only five months.

Basically after failure of hypomethylating agents and I think all of this data highlight the significant unmet need that we should not just routinely
use hypomethylating agents.

But we should try to improve the outcomes of patients.

So going to some of the major highlights from the ash meeting, I will start with this one.

This is a drug that I just mentioned. Oral deci TB in that has just been approved in August 2020, so decide to be in the reason why you cannot give this ITB in orally. Citadine dominates as well as in the liver, so you have significant first pass effect.

is because it’s highly metabolised in the gut by this enzyme. Citadine dominates as well as in the liver, so you have significant first pass effect.

So what was done here in to develop
this drug which is called in covi.

Is to combine decided being with an inhibitor of this city in Germany is called sisters OR and the combination in phase one.

Phase two trials was shown to result in similar pharmacodynamic and pharmacodynamic.

Activities to the Ivy decided mean, so this combination was taken to a phase three trial that looked at pharmacokinetic equivalence as a final end point, and this trial was presented in 2019 and you can see A at the bottom.

The final conclusion, which you have 99% equivalence pharmacokinetic equivalence.
between oral and IV decitabine.

However, the follow-up from this study was somewhat limited and an important update. Was presented in the American Society of Hematology meeting this year by Doctor Savona, and this trial is actually a trial. We participated in many of you in the care centers, so we thank you for that.

So the update from the certain study showed that the complete response rate was around 22% and the median overall survival after median follow-up of 24 months has not yet been reached and the median duration...
00:07:26.614 --> 00:07:28.726 of best response was 12 months.
00:07:28.730 --> 00:07:31.350 So I think well.
00:07:31.350 --> 00:07:33.966 The follow up still needs to be longer.
00:07:33.970 --> 00:07:36.546 It’s important to know that for now it
00:07:36.546 --> 00:07:38.974 seems that oral version of Decitabine is
00:07:38.974 --> 00:07:41.808 very similar to how we decide to be in,
00:07:41.810 --> 00:07:43.916 and I think we have a lot of data
00:07:43.916 --> 00:07:46.090 now suggesting that it can be
00:07:46.090 --> 00:07:47.960 completely replacing the IBD side
00:07:48.024 --> 00:07:49.989 been as monotherapy for Andy’s.
00:07:49.990 --> 00:07:52.662 And on this note also I like to
00:07:52.662 --> 00:07:54.965 highlight that many of you are aware
00:07:54.965 --> 00:07:57.560 that there is an oral version of is
00:07:57.560 --> 00:08:00.210 cited in the CC-486 or on your leg.
00:08:00.210 --> 00:08:01.850 That has been approved,
but this is was only approved in AML on your egg Aurora.

Laser sighted in is very different in pharmacokinetics. Ann for Neko Dynamics. Then I be decided in an. Then Ivy is exciting in and therefore should not be used in MD as its only approved for AML and I think it should be used only in that sitting and AML only in the maintenance setting. After achieving remission with intensive chemotherapy and not as a replacement as monotherapy or. In combination with Venator class so this is important to note.
I think another combination that’s attracting a lot of attention as a combination of hypomethylating agents with Veneto class. So this is an update that was presented by Doctor Garcia and her colleagues in the frontline setting, so this is a phase One piece study that looked at combination of SSI tied in with Veneto class and this is a single arm study and they provided an update here in around 78 patients and what you can see is a very high CR rates. So the CR rate is around 40%.
Monotherapy is only around 15% to 20% at best and the overall response rate is around 80%. The responses, as you can see, were durable around 13 months and the median follow up on the study was somewhat short 16 months, but the survival so far, especially for those patients who have complete responses, appear quite significant. However, I think these data are important to take into consideration still early. A single arm. We don’t have randomized data and we have many drugs that
shown excellent data as monotherapy, but when they went to randomized setting they did not basically show improvement in overall survival and I think This is why it’s important to wait for the randomized data before this could be used as a, you know a setting in like in routine clinic. Another I think important study is the one we conducted here at at Yale in collaboration with many other centers. And we also provided an update from this data in the American Society of Hematology here.
in the relapsed or refractory setting,
and as you can see, the response rate is around 40% total.
Around 7% of those have complete responses,
but many of those who have more complete responses also achieved significant hematologic improvement.

So there are significant clinical benefits.
But also as you can see on the right side, the median overall survival of all patients was 12 months,
which compares favorably than the four to six months that I showed you earlier.
in the typical refractory relapsed MD setting and even patients who have more OCR have significant survival. As you can see with 15 months, this is single ARM study, not randomized, and I think we need more data before this could be used in routine clinical practice. There are important differences in how financial classes used in real life setting or for Andy as compared to AML for example. Veneto class was given only for 14 days,
not the 28 days that are given in AML.

And that’s important because MTS patients might not tolerate the same degree of myelosuppression that their male patients who tend to be somewhat younger than on average and MD’s patients.

So we have now around a nice face retrial. The Verona trial, which is looking at, is cited in versus cases cited in with venetoclax in the frontline setting.

among patients with high risk MBS and this study is going to open at Yale. We are also opening at a number of daycare centers and I encourage you to enroll patients on it to see if
this setup we actually will change the standard management of high risk MD's. Another update that was prevent presented in the American state of Mythology meeting was on this drug people, and it is that which is the 1st in class need it inhibitor. So this this is an upstream of the proteasome and it was shown in early phase trials in combination with their society into lead to improvement and responses. This trial randomized patients, but this was a randomized phase two trial in which not only patients with
MD as but also patients with illegal plastic, AML and CML were randomized to receive. Cited in alone or as a sighted in with people needed stat and this trial also was actually open here at at year and what you can see here or the subgroup analysis of the patients who had higher risk and the S which were a total of 67 patients. This paper this this was just also published in Leukemia Journal. What you can see is that there was like a marginal improvement in event free survival, but the primary endpoint of the study the overall survival was not improved. And I think most notable here is that the overall response rate,
but especially the CR rate, was significantly higher with the combination compared to the monotherapy and was more durable. There is a phase three trial of the same. Basically, design of P1 is a sighted in compared to azacitidine alone. This trial, actually called the Panther trial, has fully accrued and we expect results from the study soon. So I think this also could potentially be a practice changing if the if there is us are posted. How about immunotherapy?
Many of you use immune checkpoint inhibitors such as anti PD-L1 for routinely management of solid tumors. We've been trying to use these drugs for some time now in high risk myeloid malignancy and so far a lot of the data has been single arm. This is what I'm showing you is a presentation from ASH 2019 in which we showed with colleagues from other centers in a randomized phase two study that the combination of is cited in with the anti PDL one door.
volume app which is approved for several solid tumors did not improve outcomes compared to other sighting.

However I think this is probably just related to PD L1. And does not extend necessarily to other classes of immune checkpoint inhibitors. And on that note, another immune checkpoint inhibitor called sabatella mob or MPG 453. Is basically being studied in combination with hypomethylating agents, not only for high risk MD’s, but also for AML patients and the data from what was presented in
in 2018 this year showed this is a single arm again phase one study, but it showed the CR rate of 23% which is slightly higher than what you expect with monotherapy, but the overall response rate was 64%, and what you can see on the right hand is that there was encouraging durability. Of the combination, especially with patients who have long or very high risk disease, and I would note the side effect profile here it does not seem to add myelosuppression to the exercise again alone, and also importantly, the incidence of immune related
NOTE Confidence: 0.8049437
00:15:16.866 --> 00:15:19.039 effects seems to be low with this.
NOTE Confidence: 0.8049437
00:15:19.040 --> 00:15:20.520 With this particular agent,
NOTE Confidence: 0.8049437
00:15:20.520 --> 00:15:22.370 so appears on this data.
NOTE Confidence: 0.8049437
00:15:22.370 --> 00:15:24.220 There are ongoing several study.
NOTE Confidence: 0.8049437
00:15:24.220 --> 00:15:27.444 We just completed a cruel to a randomized
NOTE Confidence: 0.8049437
00:15:27.444 --> 00:15:30.624 phase two study in higher risk MD S of.
NOTE Confidence: 0.82144034
00:15:30.630 --> 00:15:32.814 Is there with the battle map versus
NOTE Confidence: 0.82144034
00:15:32.814 --> 00:15:35.306 is alone and this study is completed
NOTE Confidence: 0.82144034
00:15:35.306 --> 00:15:37.532 accrual and we expect the results
NOTE Confidence: 0.82144034
00:15:37.601 --> 00:15:39.484 in the next one to two years.
NOTE Confidence: 0.82144034
00:15:39.490 --> 00:15:40.802 There’s another face retrial
NOTE Confidence: 0.82144034
00:15:40.802 --> 00:15:42.770 that will open here as well.
NOTE Confidence: 0.82144034
00:15:42.770 --> 00:15:44.410 Called the stimulus MD S2,
NOTE Confidence: 0.82144034
00:15:44.410 --> 00:15:46.714 which is a randomized phase three
NOTE Confidence: 0.82144034
00:15:46.714 --> 00:15:48.939 of the same combination is with
NOTE Confidence: 0.82144034
00:15:48.939 --> 00:15:51.109 the battle map versus Asia and we
NOTE Confidence: 0.82144034
00:15:51.109 --> 00:15:53.143 have our as well a frontline study
NOTE Confidence: 0.82144034
00:15:53.143 --> 00:15:55.390 with a 7 is events a battle map.
NOTE Confidence: 0.82144034
00:15:55.390 --> 00:15:57.572 All of those are open at at
NOTE Confidence: 0.82144034
00:15:57.572 --> 00:15:59.192 yet another interesting immune
NOTE Confidence: 0.82144034
00:15:59.192 --> 00:16:01.480 checkpoint inhibitor is the CD 47.
NOTE Confidence: 0.82144034
00:16:01.480 --> 00:16:03.965 Anti CD 47. They don’t eat me.
NOTE Confidence: 0.82144034
00:16:03.970 --> 00:16:05.690 Signal inhibitor mag rolling up
NOTE Confidence: 0.82144034
00:16:05.690 --> 00:16:07.778 what was presented in ash this
NOTE Confidence: 0.82144034
00:16:07.778 --> 00:16:09.892 year was an update and what the
NOTE Confidence: 0.82144034
00:16:09.892 --> 00:16:11.851 authors shown the significant plus
NOTE Confidence: 0.82144034
00:16:11.851 --> 00:16:13.575 reduction among all patients.
NOTE Confidence: 0.82144034
00:16:13.580 --> 00:16:16.002 But the data was most impressive in
NOTE Confidence: 0.82144034
00:16:16.002 --> 00:16:18.251 patients who have TP 53 mutations
NOTE Confidence: 0.82144034
00:16:18.251 --> 00:16:20.525 in which the median overall survival
NOTE Confidence: 0.82144034
00:16:20.525 --> 00:16:22.480 among patients who had TP 50.
Three was 12 months, which is higher than what we typically expect it to nine months. Generally in patients who have this mutation. So this drug now is being studied. In a randomized trial called the enhance in high risk MD’s whether they have TP 53 or not, magherally map with laser versus is alone, but also there are efforts to study it in acute myeloid leukemia patients as well, especially those with TP 53. This is a transplant abstract and as I mentioned, there is a separate transplant.
presentation that will happen at the end of the series, but I just wanted to highlight this the conclusion from this because this is in my view, one of the most important abstracts from this because it showed in a randomized trial data, so here this was randomized. All the data that we have about MD’s improving survival in high risk MD’s patients compared to hypomethylating agents alone is based on Markov decision analysis and modeling, but this is the first randomized trial to actually show.
An absolute improvement in overall survival and the three year survival for donor versus no donor arm.

And I think what is very important is this study allowed patients after the age of 75.

And this is important to get out there, that because we still see patients who are like 72 who come to us very later and their scores and being told they were not candidates for transplant.

So I think it’s important to know that even patients up to the age of 75 could be considered for curative therapy and they should be referred for big Centers for clinical trials.
as transplant consideration

NOTE Confidence: 0.82144034

in the last couple of minutes.

NOTE Confidence: 0.82144034

I will talk about lower risk MD’s

NOTE Confidence: 0.82144034

as I mentioned was partnership has

NOTE Confidence: 0.82144034

been approved after ESA failure.

NOTE Confidence: 0.82144034

For patients who have RingCentral

NOTE Confidence: 0.82144034

plastic anemia from lower risk MD’s now,

NOTE Confidence: 0.82144034

this drug is being studied in the

NOTE Confidence: 0.82144034

frontline setting in the commands trial,

NOTE Confidence: 0.82144034

so this is it’s being studied compared

NOTE Confidence: 0.82144034

to low Earth roelle powerton and

NOTE Confidence: 0.82144034

this or a potent procrit and this

NOTE Confidence: 0.7745304

is in the frontline setting and regardless

NOTE Confidence: 0.7745304

so whether you have ringstad or plus or not,

NOTE Confidence: 0.7745304

you could be randomized to either a

NOTE Confidence: 0.7745304

proton or low spatter set and this trial
is open in the care centers as well.

So many of you will be able to enroll in it.

Another interesting drug is the emitted step, which is the 1st in class telomerase inhibitor which has been shown also to improve transfusion independence.

Regardless of having RingCentral Plus or not and some of those responses which occur in 42% of patients were at durable.

Now we have actually an open study here. The High Merge study the phase three so this is a randomized study after he has a failure so frontline we have the commands in lower risk and be as. Refractory, we have the Hymer study.
00:19:07.524 --> 00:19:09.891 for patients after failure of PSA
NOTE Confidence: 0.7745304
00:19:09.891 --> 00:19:11.925 in which patients are randomized to
NOTE Confidence: 0.7745304
00:19:11.925 --> 00:19:14.110 him until a stat versus placebo.
NOTE Confidence: 0.7745304
00:19:14.110 --> 00:19:16.886 In the last minute I wanna show you
NOTE Confidence: 0.7745304
00:19:16.886 --> 00:19:18.877 another like non interventional study
NOTE Confidence: 0.7745304
00:19:18.877 --> 00:19:22.415 that we did in patients with MD S who
NOTE Confidence: 0.7745304
00:19:22.415 --> 00:19:24.903 have lower who have anemia and as you
NOTE Confidence: 0.7745304
00:19:24.910 --> 00:19:27.790 know one of the open questions in MDSS.
NOTE Confidence: 0.7745304
00:19:27.790 --> 00:19:29.746 When do you transfuse patients with
NOTE Confidence: 0.7745304
00:19:29.746 --> 00:19:32.281 MD S and many people use different
NOTE Confidence: 0.7745304
00:19:32.281 --> 00:19:34.983 cut off seven or eight of hemoglobin?
NOTE Confidence: 0.7745304
00:19:34.990 --> 00:19:37.293 Here we used verified quality of life
NOTE Confidence: 0.7745304
00:19:37.293 --> 00:19:39.120 instrument in a investigator initiated
NOTE Confidence: 0.7745304
00:19:39.120 --> 00:19:41.822 effort led by Doctor Go in Table.
NOTE Confidence: 0.7745304
00:19:41.830 --> 00:19:43.082 Go on Dana Farber.
NOTE Confidence: 0.7745304
00:19:43.082 --> 00:19:45.835 And we looked at the quality of life
improvement before and after transfusion
and what we have shown is that most
patients 2/3 of patients did not
experience an improvement in their
quality of life after transfusion.
So I think that puts into question
our practice of Troy.
Using patients based on hemoglobin
cut offs of aid,
and I think it’s important to try
to study this in more extensive
sitting about what is the right cut
off for transfusions in,
especially in the outpatient setting.
For patients with ambie rather than
using random cut offs of hemoglobin.

So this is my last slide and I will give the floor now to my colleague Doctor Rory Challis who will update us on acute myeloid leukemia.

Updates from the ash.

Thank you and we'll be happy all of us will be taking questions.

At the end of that seminar at 12:50, thanks.

OK, How are we looking? How are we looking?

Every seeing a full slide who every seeing a full slide who?

screws two screens again? Sorry.

Standard technical difficulties.

Yeah, I think you need to swap your

screens. Let’s try this again.

Yes.

Looks good.

You're seeing one. Yes, one scream.

You're good to go alright? Do this by then.

Sorry bout that.

OK.

Alright one screen we're good to go so.

Thanks for the introduction.

I'll be specifically focusing on

the highlights presented this past

meeting as they pertain to AML.

I have no disclosures, so.

Again, you’re still seeing one screen, right?
OK, it's a bit hard to really focus in on really a select few updates from an entire years worth of. I would say progress in the field. So I'll try to really focus on agents with which we already have some familiar that Phillip familiarity, but also some new combinations or regiments, some of which you can guess we're going to include the BCL two inhibitor of medical acts. All of these are all the studies I'll be discussing are going to be interventional of only really try to give some minimal background so it's really focused on the updates themselves.
So jump right in. As many of you are. Aware Gilteritinib is a flip through inhibitor, which in the Admiral trial was shown to improve survival when compared with classical salvage chemotherapy in their refractory setting. The preclinical data does support some synergy when Gilteritinib is combined with a BCL two inhibitor.
00:23:09.979 --> 00:23:12.348 and those data prompted the launch of  
NOTE Confidence: 0.85143447
00:23:12.348 --> 00:23:14.504 the trial that I'll be talking about.  
NOTE Confidence: 0.85143447
00:23:14.510 --> 00:23:16.658 In brief, you can see here,  
NOTE Confidence: 0.85143447
00:23:16.660 --> 00:23:19.164 so this was done in the context of  
NOTE Confidence: 0.85143447
00:23:19.164 --> 00:23:21.299 the following trial schema patients,  
NOTE Confidence: 0.85143447
00:23:21.300 --> 00:23:22.724 as you guessed it,  
NOTE Confidence: 0.85143447
00:23:22.724 --> 00:23:24.148 had relapsed refractory disease,  
NOTE Confidence: 0.85143447
00:23:24.150 --> 00:23:25.734 including wild type patients.  
NOTE Confidence: 0.85143447
00:23:25.734 --> 00:23:27.714 In the dose escalation phase,  
NOTE Confidence: 0.85143447
00:23:27.720 --> 00:23:30.177 without you know, a low white counts.  
NOTE Confidence: 0.85143447
00:23:30.180 --> 00:23:31.940 They really had controlled proliferation.  
NOTE Confidence: 0.85143447
00:23:31.940 --> 00:23:33.820 They received standard phonetic lacks  
NOTE Confidence: 0.85143447
00:23:33.820 --> 00:23:35.700 4 milligrams in combination with  
NOTE Confidence: 0.85143447
00:23:35.754 --> 00:23:37.578 either guilt 80 or 120 milligrams,  
NOTE Confidence: 0.85143447
00:23:37.580 --> 00:23:39.995 which the latter of which is the  
NOTE Confidence: 0.85143447
00:23:39.995 --> 00:23:42.507 standard dose that was studied in Phase
00:23:42.507 --> 00:23:44.970 3 testing, and this was later expanded,
00:23:44.970 --> 00:23:46.374 so the demographics were,
00:23:46.374 --> 00:23:48.836 for the most part, I would say,
00:23:48.836 --> 00:23:50.596 expected with regards to age,
00:23:50.600 --> 00:23:52.819 set of genetic risk given the inclusion
00:23:52.819 --> 00:23:54.819 criteria that I mentioned before,
00:23:54.820 --> 00:23:56.684 a majority of patients.
00:23:56.684 --> 00:23:58.548 Did have ITD mutations?
00:23:58.550 --> 00:23:59.304 Of note,
00:23:59.304 --> 00:24:01.189 65% of patients received prior
00:24:01.189 --> 00:24:03.521 therapy with the flip three inhibitor
00:24:03.521 --> 00:24:05.783 and a third enrolled after they
00:24:05.783 --> 00:24:08.419 had a relapse after allogeneic
00:24:08.419 --> 00:24:10.607 metaplastic stem cell transplantation.
00:24:10.610 --> 00:24:12.445 All patients experienced an adverse
NOTE Confidence: 0.85143447
event in nearly all grade three,

with unsurprisingly, was being cytopenias.

You know,
given the combination with medical access,
you know a very well known Milo
toxic amount suppressive agent,
but perhaps some contribution of guilt.
And as well,
three patients were reported as having
laboratory tumor lysis syndrome with
only one of these having clinical TLS,
only 60% of patients,
at least as of last follow-up,
discontinued the drug due to adverse events.

Of note,
no patients died within a month of dosing,
but six died with up to 60 days out.

Amongst 41 adult patients, only three achieved CR or 7% specifically.

However, 27% of patients achieved a less than CR remission, which here was inclusive of CR or CR P.

Half of patients achieved MFS or morphologic leukemia Free State again, in the context of the Netflix related mileage suppression.

Amongst responders, the median time to response was one month, but best responses were observed up to four months out.
No more could differences in response or the types of response for that matter were apparent after accounting for prior filter exposure other than maybe a little less or chance of CR. As you can see here, 7.3 versus one quote versus 3.6%. The median overall survival for the overall cohort was 12.3 months and specifically not reached, including an unreached lower limit of the 95% confidence interval for ITD patients. Clear differences in survival were noted based on prior filter exposure, so I would say in some the addition of
attacks appears to augment the efficacy of guilt monotherapy in this situation, which based on the Admiral trial I had mentioned before, predicts a median survival around 9 and a half months. This is at the expense of near double hematologic toxicity, which I think we can all agree is attributable to the phonetic LAX, but of course. Just heating some caution and saying it appears to increase the efficacy outside of a randomized clinical trial, so this isn’t of course need.
to at least confirm this.
This likely benefit here.
Jump into the next update.
I have 40 or so older patients with AML.
Have generally a poor outcomes,
but there there is some variance
noted to improve these outcomes.
Ventures like the following are underway,
so next I’d like to discuss the
interim results of a striking study
of cladribine and lodosa Terrapín,
which is essentially a double
nucleoside backbone and Aza,
both with the addition of an ethics course.
The double clad plus Ldac backbone
has been previously studied this.
This isn’t showing here in this slide with alternating decide to be as treatment for newly diagnosed.

Older patients with AML and this led to a composite CR of 68%, including CR 50%.

Quite quite nice with a median OS of well over a year.

It appears 14.8 months with quite low mortality.

This scheme is a little complex, but essentially like I mentioned, received clad plus idac with van with.
As you can see here, the standard dose reductions for CYP 3A four inhibitor use receive this for cycle one, with cycle to being the same three drugs but less clad and a little bit less fanatical acts with cycle three switching the nucleoside backbone for Asia on the standard schedule, again with phonetic lacks for 14 days, similar to cycle two. So basically patients received. As you can see here and they can move.
00:27:59.334 --> 00:28:00.319 highlighter or whatever,

00:28:00.320 --> 00:28:02.318 but patients received a * 2 then

00:28:02.318 --> 00:28:05.304 B * 2 and then back and forth back

00:28:05.304 --> 00:28:07.978 and forth for up to 18 cycles.

00:28:07.980 --> 00:28:10.225 So here the patient characteristics

00:28:10.225 --> 00:28:15.638 note 40% of patients for older.

00:28:15.638 --> 00:28:17.648 Sorry older than 70 years,

00:28:17.650 --> 00:28:20.874 by porous I,

00:28:20.880 --> 00:28:23.100 genetics ANAN would be would be

00:28:23.100 --> 00:28:25.310 generally expected given this population,

00:28:25.310 --> 00:28:27.675 although nearly half were ellenor

00:28:27.675 --> 00:28:32.381 after accounting for the relevant
molecular features on top of genetics. Amongst the 54 patients that today have been accrued and are in fact invaluable with a median one cycle or month to responses, striking 78% achieved CR and basically all except three achieved MFC MRD negativity. Basically, MRD negativity negativity by flow centric analysis including CRIA composite CR rate of 93% was rendered which is simply amazing and perhaps I really should have saved this safest route for the end so. One of the more striking updates from ASH with regards to the response rates.
However, it’s not all about response rates for the patient not proceeding to therapy, really care about event-based outcomes like survival in evaluating survival and a medium median of 14.2 months. The OS and RFS curves were essentially the same, meaning OS was reached was not reached. Sorry, and 60% of patients were still alive at two years after starting therapy again. Quite amazing considering the fact that half of patients were.
Yellen adverse risk. Sorry

00:29:42.750 --> 00:29:44.660 However, this is just some.
NOTE Confidence: 0.8340789

00:29:46.460 --> 00:29:47.570 You know, some smaller kind
NOTE Confidence: 0.8340789

00:29:47.570 --> 00:29:50.146 of subpopulation analysis.
NOTE Confidence: 0.8340789

00:29:50.146 --> 00:29:53.880 You can see that when accounting for
NOTE Confidence: 0.8340789

00:29:53.880 --> 00:29:55.360 set of genetic risk and Dylan risk,
NOTE Confidence: 0.8340789

00:29:55.360 --> 00:29:59.862 not surprising differences
NOTE Confidence: 0.8340789

00:29:59.862 --> 00:30:01.011 are in fact observed.
NOTE Confidence: 0.8340789

00:30:01.011 --> 00:30:02.740 Patients proceeding to
NOTE Confidence: 0.8340789

00:30:02.740 --> 00:30:04.112 transplant with these patients,
NOTE Confidence: 0.8340789

00:30:04.112 --> 00:30:07.878 which when compared with the
frocks not getting to transform with 69% but a difference, did not reach statistical significance. Likely in the setting of just, you know, obviously a small early phase study.

So just going to switch gears a little bit with AML, gears a little bit with AML, one of the first decision we have to make is whether patient is quote unquote intensive therapy eligible or not. The first 2 trials I mentioned were really geared towards patients that are intensive therapy ineligible.
intensive therapy generally felt to be the standard of care for those who are eligible with some specific exceptions? Of course if prompted debate, but that’s a discussion for another. Another presentation. Here is the schema for a trial also out of MD Anderson and evaluating the addition of genetic lacks. To CPX, 3/5 one or the brand name being fix EOS which is standard of care for patients with AML MRC and therapy quote unquote related AML. The design included cohort for adults with newly diagnosed AML as well as looks. Factory disease, with the latter
allowing prior phonetics exposure. Quite important criterion. A dose escalation phase or safety run included.

Of course, all the patients, irrespective of whether they were Dinovo slash, newly diagnosed or realtor factory. Of note CPX 3/5 one was given at the standard dose on label. Essentially event began fairly quickly on day two with a three day ramp up to a target dose of 400, again with the standard dose reductions you would expect or should
00:31:37.620 --> 00:31:39.235 be considering with concurrency 3A
NOTE Confidence: 0.7932578
00:31:39.235 --> 00:31:41.230 four inhibition as well as toxicities
NOTE Confidence: 0.7932578
00:31:41.230 --> 00:31:42.522 prompted prompting dropping to
NOTE Confidence: 0.7932578
00:31:42.522 --> 00:31:44.741 lower dose levels as they came up.
NOTE Confidence: 0.7932578
00:31:44.741 --> 00:31:46.890 Essentially this was then was given for
NOTE Confidence: 0.7932578
00:31:46.957 --> 00:31:48.769 three weeks during induction as well
NOTE Confidence: 0.7932578
00:31:48.769 --> 00:31:51.428 As for 20 three weeks during each cycle.
NOTE Confidence: 0.7932578
00:31:51.430 --> 00:31:51.808 Consolidation.
NOTE Confidence: 0.7932578
00:31:51.808 --> 00:31:55.210 In this case they allowed up to four cycles.
NOTE Confidence: 0.7932578
00:31:55.210 --> 00:32:00.600 in contrast to the standard on label CPX 351.
NOTE Confidence: 0.7932578
00:32:00.600 --> 00:32:02.950 Monotherapy consolidation.
NOTE Confidence: 0.7932578
00:32:02.950 --> 00:32:04.570 Here the characteristics of the
NOTE Confidence: 0.7932578
00:32:04.570 --> 00:32:06.554 patients who had a broad range
NOTE Confidence: 0.7932578
00:32:06.554 --> 00:32:08.384 of age instead of genetic risk,
NOTE Confidence: 0.7932578
00:32:08.390 --> 00:32:10.707 I'll call your attention to the right
where you can see that 30% of patients had disease characterized by the presence of a TP 53 mutation and after including ASL one and runx one mutations, the majority of patients did in fact have guillain adverse risk disease. Only 6% of patients achieved CR, but CR CRA was the rate of CRC. I was 39% still fairly low with a median one cycle time to response. The most common reason for coming off of study was actually proceeding to transplant. This occurred in 31 patients were but generally 50 half of the patient population. The most common grade 3 plus
ease were human logic in nature,

pneumonia amongst other infections didn’t.

Did also occur 30 and 60 day mortality were weren’t nominal

10% at 30 days and 20% at 60 days,

so a fairly toxic regimen with again relatively limited efficacy in comparison to the other guys I’ve presented.

The median overall survival was six months with a 6 month OS rate of about 53%.

Just to be specific and 46% at one year.

So not terribly different.

6 versus 12 months among responders, the median OS and RFS were not reached,

and the six month OS and RFS were essentially about 8590%.
You can see that patients without prior medical exposure did better. However, again, given the small numbers, this did not reach statistical significance. Sticking with intensive therapy eligible patients. What about adding then to other intensive backbones beyond CPX 351, here’s a schema which demonstrates that patients with both newly diagnosed disease and relapse refractory disease received a fairly standard flag. Ida regimen and dosing with Medical X added, especially specifically during days.
one through 14 at a target dose of 400 in standard target dose, but not without a ramp up and then high debt consolidation had been incorporated. Days one through 14. So a complex slide, but hopefully that kind of summed it up. Here are the patient demographics or sorry patient characteristics specifically, noting that the relapse refractory cohorts were a bit more enriched for adverse risk disease. And as you would otherwise expect and 38% had received prior allogeneic Amanda poetic stem cell transplant. The toxicity was what you would
NOTE Confidence: 0.79211825
00:34:40.328 --> 00:34:42.303 expect with intensive therapy and
NOTE Confidence: 0.79211825
00:34:42.303 --> 00:34:44.313 addition of class including based on
NOTE Confidence: 0.79211825
00:34:44.313 --> 00:34:48.838 what I just presented. For C PX351.
NOTE Confidence: 0.79211825
00:34:48.840 --> 00:34:52.701 CRC is 90% and in the newly diagnosed cohort
NOTE Confidence: 0.79211825
00:34:52.701 --> 00:34:55.830 60 to 75% in the roaster factory cohorts.
NOTE Confidence: 0.79211825
00:34:55.830 --> 00:35:00.998 So and fairly good rates of MRD negativity.
NOTE Confidence: 0.79211825
00:35:01.000 --> 00:35:04.664 And this is essentially just looking at at.
NOTE Confidence: 0.79211825
00:35:04.670 --> 00:35:06.390 Based on their disease,
NOTE Confidence: 0.79211825
00:35:06.390 --> 00:35:07.834 the disease cohort specifically.
NOTE Confidence: 0.79211825
00:35:07.834 --> 00:35:10.689 So I’ll just kind of wrap it up
NOTE Confidence: 0.79211825
00:35:10.689 --> 00:35:12.555 with just promise two more slides.
NOTE Confidence: 0.79211825
00:35:12.560 --> 00:35:14.270 So those updates for therapies
NOTE Confidence: 0.79211825
00:35:14.270 --> 00:35:15.296 we already had.
NOTE Confidence: 0.79211825
00:35:15.300 --> 00:35:17.190 But what about just one update
NOTE Confidence: 0.79211825
00:35:17.190 --> 00:35:19.080 on an agent or regimen?
00:35:19.080 --> 00:35:21.126 We do not yet really have.
00:35:21.130 --> 00:35:23.545 This is Google Map or the this
00:35:23.545 --> 00:35:25.249 is the humanized anti CD.
00:35:25.250 --> 00:35:26.965 IgG, four monoclonal antibody
00:35:26.965 --> 00:35:28.680 product from from Gilead Sciences,
00:35:28.680 --> 00:35:29.988 relevant as tumor expression
00:35:29.988 --> 00:35:31.950 of CD 47 prompts evasion from
00:35:32.012 --> 00:35:33.480 an 80 minute surveillance.
00:35:33.480 --> 00:35:34.509 Specifically macrophage mediated.
00:35:34.509 --> 00:35:36.224 Microcytosis and in fact pre
00:35:36.224 --> 00:35:37.729 clinical data support that AML,
00:35:37.730 --> 00:35:38.878 leukemic blast doing factor,
00:35:38.878 --> 00:35:41.200 or enriched for CD 47 Express expression.
00:35:41.200 --> 00:35:43.054 So this was studied in combination
00:35:43.054 --> 00:35:44.980 with Asia and a phase one.
00:35:44.980 --> 00:35:48.102 B2 trial that armored actually touched on
NOTE Confidence: 0.79211825
00:35:48.102 --> 00:35:51.199 earlier most in the context of high risk
NOTE Confidence: 0.79211825
00:35:51.199 --> 00:35:54.837 MD S but I'll just focus on the AML cohort.
NOTE Confidence: 0.79211825
00:35:54.840 --> 00:35:55.230 Specifically,
NOTE Confidence: 0.79211825
00:35:55.230 --> 00:35:56.400 90 except sorry,
NOTE Confidence: 0.79211825
00:35:56.400 --> 00:35:58.550 70% porous surgeon attics 70% P
NOTE Confidence: 0.79211825
00:35:58.550 --> 00:36:00.310 three mutations with a robust
NOTE Confidence: 0.79211825
00:36:00.371 --> 00:36:02.466 median vaf which would otherwise
NOTE Confidence: 0.79211825
00:36:02.466 --> 00:36:04.561 predict biallelic loss of function.
NOTE Confidence: 0.79211825
00:36:04.570 --> 00:36:06.122 So essentially a very,
NOTE Confidence: 0.79211825
00:36:06.122 --> 00:36:06.510 very,
NOTE Confidence: 0.79211825
00:36:06.510 --> 00:36:11.450 very poorest population and not the
NOTE Confidence: 0.79211825
00:36:11.450 --> 00:36:14.026 toxicity profile was generally what
NOTE Confidence: 0.79211825
00:36:14.026 --> 00:36:16.506 other than I'd say a mild transient
NOTE Confidence: 0.79211825
00:36:16.506 --> 00:36:18.595 on targeting me that was reversible.
NOTE Confidence: 0.79211825
Know whether grade 3/4 plus 80s and no immune related AE’s given macros mechanism of action.

This is a slide hammer showed you this is the AML cohort, essentially a 20% rate of see better in comparison to generate 20% rate of expected as a monotherapy.

60 ish percent, essentially with essentially in the waterfall plot.

Here nearly all patients experiencing Meryl Blast percentage reduction with many being robust reductions.

The median OS at last day to cut off of patients in the trial was
18.9 months and even after isolating patients that had a P3 mutation.

And we still 12.9 months, which to be honest is the longest median OS I believe ever reported for this population, so quite striking as you can see, four or five patients are still alive more than two years out, so quite impressive. So I am a little bit over and I apologize to Nikolai. Mostly this is raw, conclude my section and look forward any questions at the end.
So next I'd like to introduce Doctor Nikolai Pedulla civilly discussing the ash 2020 updates in there almost perfect NPS. Alright, thank you Oriel let me share my slides with you. How does it look? Does it look like one screen? We don’t see slides head. Sadly you don’t see slides OK, just a second. We just see you. Oh interesting. Alright, so hold on let me escape from here. And so I’ll do this. How about now? Do you see two right and I need to swap? No, we still don’t see them.
You don’t see them.

Did you share a video girl OK?

Yep, now we see alright.

You see this one slide right?

Alright, OK,

Alright so I’ll be talking about.

Milo proliferative neoplasms and I had to be selective because of the time frame,

so this are my disclosures.

I’ll go over 4 studies and the first one was presented as a late breaking abstract is not the interventional study I thought would be important to mention.

I just have one slide about it.

This is about driver mutation,
The methods used by UK investigators included studying 10 patients with Jack. Two mutations of this is Jack. This patients were between H20 and 76. The single cell derived hematopoietic colonies were studied.
using whole exome sequencing. There was targeted resequencing of longitudinal blood samples from the stem patients and something which is still not clear very clear to me, but they were able to create those. Polygenetic trees or of hematopoiesis, allowing them to understand when initial driver mutation occurred as the result it was found that mpanza originate from driver mutation quite very early in life, including before birth, and then there is lifelong clonal expansion and evolution.
Results are quite amazing because they tell us that this Jack two mutation, which eventually leads to development of MPN late at life, is present in utero and perhaps if we can understand how it develops and evolves, we may use some preventative strategies in the future to prevent expansion of this clone or its evolution.

Moving onto interventional studies, first of all, I will talk about CML and again another late breaking abstract second. I will talk about one study using new drug for Milo fibrosis patients.
and finally I'll finish with the study for PVR patients. So the second study I would like to talk about looked at a synonym also known as 001. This is the first class stamp inhibitor. An stamp is specifically targeting the BCR ABL one inhibitor which is different to advertising kinese inhibitors which targeting ATP pocket on April 1. So as you can see on the cartoon from New England Journal Medicine article discussing Phase One.
results with this medication.

There is Mr Lated and terminal

which auto inhibits able one

an with BCR ABL translocation.

This N terminal piece of.

Peace is gone,

so you have PCR and now there is

no auto inhibition and there is

constitutive activation of ABL kinase

Aciman app targets that fork it and

can allosterically inhibit PCR able?

So as you can see,

the other tiki eyes we have currently

in practice and use in practice

go to ATP binding site and the

Aciman app actually affects able
one kinase inhibits able one kinase using this mirror style pocket, hence the name specifically targeting the able Morris to pocket. So it works even when mutations like T315Y inhibit ability of the tiki eyes to inhibit able one. Like in this particular situation, in the cartoon you can see that the teising kinase inhibitor cannot attach to the pocket due to change of its confirmation, but a synonym still able to attach to Bristol Pocket inhibiting able one kinase. So this is a phase three study was
Simonette versus Design IP in patients with chronic phase CML previously treated with at least two tiki eyes, this is an important study because the drug is now undergoing review for approval and I'm hoping that it will be available as yet another medication to treat chronic myeloid leukemia later this year. So the selection criteria listed and patients were included had chronic phase two or more GIS used before and patients have to change treatment either because they were intolerant or resistant to treatment and so
the patients was 2315 I mutation or V299L mutations were excluded because pursuit Nip is not. So this is specifically the study which didn’t include T315I mutated patients. This particular group of patients was addressed by the Phase One study and the drug is active against the BCR with this particular mutation, so patients were randomized. As you can see in two to one fashion, and the demographics were slightly different in two groups I highlighted. In yellow here that a similar patients
there were more men than women.  
Also in a similar patients, the switch of therapy was less likely to be due to lack of efficacy and more likely due to taller ability and that basically is characteristic of a group of patients which may be more responsive to the next line of treatment.  
And finally also in a similar barm less patience than in pursuit. Newbomb received three or more tikis. So this is the primary endpoint of this study which showed improved major molecular response rate at 24 weeks at six months, and the difference between two
00:44:38.505 --> 00:44:41.170 groups was twelve point 2%.

00:44:41.170 --> 00:44:42.965 So taking into consideration the differences between two groups I

00:44:42.965 --> 00:44:44.760 showed on previous slide that the logistic regression analysis was done and showed that odds ratios adjusted for those things which were different in two groups were quite similar towards ratios without adjustment, which gives us hope that the improved outcome in a similar treated patients is not related to the difference in the population.

00:45:01.008 --> 00:45:04.960 So the side effect profiles a lot of patients get different side effects,
but overall a similar patients have less side effects than positive treated patients.

One thing I would like to highlight here that a similar group there were two deaths related to arterial embolism won an ischemic stroke. Another Iman positive patients. One patient died due to septic shock, so the side effect profile was different, so anemia and thrombo cytopenia. Sorry, Trump said opinion neutropenia were similar in both groups and then GI side effects in the left abnormalities were more common in bosutinib treated patients.

So in conclusion, this assemble study was the first control study
00:45:48.012 --> 00:45:50.220 comparing tiki’s for treatment.
00:45:50.220 --> 00:45:51.753 Assistant Intolerant CML population and assimilate,
00:45:51.753 --> 00:45:53.286 which is first class stamp inhibitor,
00:45:53.290 --> 00:45:56.356 showed superior efficacy compared with
00:45:56.360 --> 00:45:58.875 bosutinib with favorable side effect profile,
00:45:58.875 --> 00:46:02.000 so this is upcoming hopefully.
00:46:02.000 --> 00:46:06.130 Approved in the near future treatment option for CML patients,
00:46:06.130 --> 00:46:11.474 particularly with resistant and
00:46:11.474 --> 00:46:14.526 after treatment with two different guys.
00:46:14.530 --> 00:46:16.690 Also, the drug is effective in
00:46:16.690 --> 00:46:18.740 treating patients with T315I mutation,
00:46:18.740 --> 00:46:21.407 so moving on to the next study.
I wanted to present today you will understand towards the end why pick this particular one? There are a number of drugs where there are a number of drugs being developed in patients with myelofibrosis. I think they’re up to 10. A phase three randomized phase three studies in this field. So this particular study presented by John Mascarenhas is about CPI, 0610. Bromodomain angusta terminal domain protein or BET inhibitor in combination with reflective for Jack inhibitor naive Milo fibrosis patients or manifest study. So one word about bet so bromodomain and
extra terminal domain protein promote. 

Symptoms of Milo fibrosis by activating bet targeted genes leading to increase production of cytokines responsible for inflammation, extramental hematopoiesis, and bone marrow fibrosis. All manifestations of patients with primary myelofibrosis as well as modify process after PD and 80 so the other influence of bat is activations of target genes leading to aberrant erythroid differentiation as well as aberrant megakaryocytic differentiation. And this patients may have an email.
00:47:40.440 --> 00:47:40.762 Thrombocytopenia,
NOTE Confidence: 0.800081
00:47:40.762 --> 00:47:41.728 as you know.
NOTE Confidence: 0.800081
00:47:41.728 --> 00:47:44.578 So CPI 610 inhibits bat and may suppress
NOTE Confidence: 0.800081
00:47:44.578 --> 00:47:47.146 cytokine production as well as promote
NOTE Confidence: 0.800081
00:47:47.146 --> 00:47:49.535 erythroid differentiation as well as
NOTE Confidence: 0.800081
00:47:49.535 --> 00:47:51.008 normalized megakaryocytic differentiation.
NOTE Confidence: 0.800081
00:47:51.010 --> 00:47:53.176 So let’s see how this drug
NOTE Confidence: 0.800081
00:47:53.176 --> 00:47:55.689 did in this phase two studies.
NOTE Confidence: 0.800081
00:47:55.690 --> 00:47:57.250 So first of all,
NOTE Confidence: 0.800081
00:47:57.250 --> 00:47:59.200 the study had three arms,
NOTE Confidence: 0.800081
00:47:59.200 --> 00:48:01.540 so they are mine going present.
NOTE Confidence: 0.800081
00:48:01.540 --> 00:48:04.480 Today’s I’m three which looked at Jack
NOTE Confidence: 0.800081
00:48:04.480 --> 00:48:06.856 inhibitor naive patients and use the
NOTE Confidence: 0.800081
00:48:06.856 --> 00:48:08.944 combination of CPI 610 and Rosslyn.
NOTE Confidence: 0.800081
00:48:08.950 --> 00:48:12.460 If the other two arms were add on CPI,
NOTE Confidence: 0.800081
00:48:12.460 --> 00:48:14.064 six dental clinic patients
who didn’t have full benefit.

From Brooklyn balloon treatment and monotherapy with CPI,

this study was also presented as an abstract as a poster during ash meeting,

so I’m three,

basically Jack inhibitor naïve Milo fibrosis patients who need treatment.

They received two drugs,

rock Solid Nap standard of care but in additional CPI 0610 better hitter.

So this drug better hitter was administered two weeks on two weeks,

one week off and.
The endpoints which we were looked at was spleen volume response 35% spleen world in response at 24 weeks as well as total symptom score 50%.

So this is primary endpoint which basically it was achieved by 67% of patients so again the drug probably worked a little bit better for patients who are low risk but it was compatible 72.73% for intermediate 16.0.

Four 66% for intermediate to high risk based on the IP SS and IP address. Most of the patients cadres, reduction of spleen volume only one had increased. This is out of 70 patients studied,
00:49:30.010 --> 00:49:32.152 so the second endpoint at the
NOTE Confidence: 0.8362344
00:49:32.152 --> 00:49:33.580 symptoms decreased by 50%.
NOTE Confidence: 0.8362344
00:49:33.580 --> 00:49:36.522 Again, this was seen in 57% of patients.
NOTE Confidence: 0.8362344
00:49:36.522 --> 00:49:39.329 Most of the patients get this clinical
NOTE Confidence: 0.8362344
00:49:39.329 --> 00:49:41.425 benefit in the study at week 24,
NOTE Confidence: 0.8362344
00:49:41.430 --> 00:49:46.213 so one of the interesting finding when
NOTE Confidence: 0.8362344
00:49:43.789 --> 00:49:48.235 you start looks lit up in patients
NOTE Confidence: 0.8362344
00:49:46.213 --> 00:49:48.235 with myelofibrosis you expect a dip
NOTE Confidence: 0.8362344
00:49:48.299 --> 00:49:50.359 in hemoglobin about three points,
NOTE Confidence: 0.8362344
00:49:50.360 --> 00:49:53.400 so here the dip was not as deep.
NOTE Confidence: 0.8362344
00:49:53.400 --> 00:49:55.278 And then, as you can see,
NOTE Confidence: 0.8362344
00:49:55.280 --> 00:49:56.222 hemoglobin improved overtime.
NOTE Confidence: 0.8362344
00:49:56.222 --> 00:49:58.106 In fact, baseline increased a little
NOTE Confidence: 0.8362344
00:49:58.106 --> 00:50:00.430 bit higher than the baseline, so this.
NOTE Confidence: 0.8362344
00:50:00.430 --> 00:50:03.055 Awful actually looks at patients who had
NOTE Confidence: 0.8362344

86
hemoglobin more than 10 and less than 10, but didn’t require transfusions.

And as you can see, after initial small dip there is improvement in anemia in this subgroup of patients, which is quite impressive. So one other thing, at the bone marrow’s biopsies were done at the beginning as well as during the study and there was improvement in fibrosis. Great in 1/3 of patients and most of the improvements observed were observed during the first six months of treatment. Only two patients get worsening of fibrosis and you can see that there...
is also a sign that there is improved
air throughout differentiation and
normalization of megakaryocytic
histopathology.
So the side effects the CPI 16 in
combination with Link was generally
well tolerated. 87% reported at least one
treatment emergent adverse event.
44% reported, one grade,
treatment emergent adverse event.
So the most common ones were
haematological and now this was
an email from both cytopenia.
Of course this may be manifestations
of the disease itself,
NOTE Confidence: 0.8362344

the most common and non human to
NOTE Confidence: 0.8362344

logic was diarrhea or which was
NOTE Confidence: 0.8362344

mild moderate Grade 1 two so.
NOTE Confidence: 0.8362344

Great five were two events.
NOTE Confidence: 0.8362344

Multiorgan failure with due to
NOTE Confidence: 0.8362344

sepsis times two.
NOTE Confidence: 0.8362344

So overall the drug was pretty
NOTE Confidence: 0.8362344

reasonably well tolerated.
NOTE Confidence: 0.8362344

The combination of drugs I have
NOTE Confidence: 0.8362344

to say because we’re looking at
NOTE Confidence: 0.8362344

the side effect profile of two
NOTE Confidence: 0.8362344

drugs administered together.
NOTE Confidence: 0.8362344

So finally conclusions 67% of patients
NOTE Confidence: 0.8362344

achieve CVR 35 comparing to historical phase,
NOTE Confidence: 0.8362344

three studies simplifying comfort studies.
This looks better even though we cannot compare apples to oranges in those studies with ruxolitinib alone, the response was 28 to 42%. 57% in the study achieved improvement and symptoms. 50% reduction of symptoms and there were improvement in bone marrow findings suggestive of potential disease modification. So it was well tolerated combination an phase three study is planned and this would be a randomized study for treatment. Naive patients looks lit up against ruxolitinib Sir, plus CPI six 110 versus wrestling.
00:52:11.420 --> 00:52:12.190 plus placebo,
NOTE Confidence: 0.8362344
00:52:12.190 --> 00:52:14.500 which allows crossover down the road.
NOTE Confidence: 0.8362344
00:52:14.500 --> 00:52:18.770 We are planning to open it at Yale this year.
NOTE Confidence: 0.8362344
00:52:18.770 --> 00:52:22.220 So the final study I want to present is PG
NOTE Confidence: 0.7385071
00:52:22.310 --> 00:52:25.516 300 study hepcidin mimetic as you know,
NOTE Confidence: 0.7385071
00:52:25.520 --> 00:52:28.299 hepcidin was discovered about 20 years ago,
NOTE Confidence: 0.7385071
00:52:28.300 --> 00:52:30.495 master regulator why and metabolism
NOTE Confidence: 0.7385071
00:52:30.495 --> 00:52:33.096 with high hepcidin level shutting down
NOTE Confidence: 0.7385071
00:52:33.096 --> 00:52:35.434 for a port and transport of ferritin.
NOTE Confidence: 0.7385071
00:52:35.440 --> 00:52:38.563 And so the reason to use it in polycythemia
NOTE Confidence: 0.7385071
00:52:38.563 --> 00:52:41.378 Vera is of course this patient need
NOTE Confidence: 0.7385071
00:52:41.378 --> 00:52:44.350 phlebotomies as the main part of their
NOTE Confidence: 0.7385071
00:52:44.350 --> 00:52:46.954 treatment which lead to iron deficiency.
NOTE Confidence: 0.7385071
00:52:46.960 --> 00:52:49.396 Perhaps keep citing analog PG 300?
NOTE Confidence: 0.7385071
00:52:49.400 --> 00:52:51.892 Can do this instead by shutting down
NOTE Confidence: 0.7385071
00:52:51.892 --> 00:52:55.084 availability of iron to every throw pesis so
NOTE Confidence: 0.7385071
00:52:55.084 --> 00:52:57.144 eligibility requirement PV diagnosed based
NOTE Confidence: 0.7385071
00:52:57.211 --> 00:52:59.710 on most recent to double check criteria,
NOTE Confidence: 0.7385071
00:52:59.710 --> 00:53:01.672 three phlebotomies in the last six
NOTE Confidence: 0.7385071
00:53:01.672 --> 00:53:03.888 months or more necessary primary endpoint
NOTE Confidence: 0.7385071
00:53:03.888 --> 00:53:06.018 is proportion of patients randomized
NOTE Confidence: 0.7385071
00:53:06.018 --> 00:53:08.504 withdrawal period whose cymatic Rick is
NOTE Confidence: 0.7385071
00:53:08.504 --> 00:53:10.409 maintained without need for phlebotomy.
NOTE Confidence: 0.7385071
00:53:10.410 --> 00:53:12.395 Secondary endpoint response at Week
NOTE Confidence: 0.7385071
00:53:12.395 --> 00:53:15.123 29 as well as improvement in symptoms
NOTE Confidence: 0.7385071
00:53:15.123 --> 00:53:17.328 using MP NTSS. So complicated schema.
NOTE Confidence: 0.7385071
00:53:17.328 --> 00:53:19.704 What we're looking at is just
NOTE Confidence: 0.7385071
00:53:19.704 --> 00:53:21.489 initial phase of this study.
NOTE Confidence: 0.7385071
NOTE Confidence: 0.7385071
00:53:22.190 --> 00:53:23.940 Patients enrolled who went through
NOTE Confidence: 0.7385071
00:53:23.940 --> 00:53:25.828 the first part of the study.
NOTE Confidence: 0.7385071

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Those finding at 28 weeks.

There’s those escalation,

trying to identify how much

subcutaneous injections once a week.

You need to control phlebotomy

and you know when you identify it.

You kind of continue with that dose.

Then you reach the second part of

the study blinded withdrawal.

Some patients continue real thing others

and switch to placebo to see how it’s

going to affect the phlebotomy requirement.

And finally,

there is open label extension so

that the report only dealt with

this red part of the study.
And as you can see in the red dots are phlebotomy requirements. Before initiation of the study, before the 1st dose and then after the first was only three patients required one phlebotomy Chen, those were getting the low level of the medication with which was further escalated. So pretty impressive effectiveness. As you can see, ferritin increasing significantly, showing that iron deficiency is gone. Total symptom score improving with time. And this is subset you can see improved concentration,
00:54:22.580 --> 00:54:24.188 fatigue, itching for writers,
NOTE Confidence: 0.7385071
00:54:24.188 --> 00:54:25.796 and though this is.
NOTE Confidence: 0.7385071
00:54:25.800 --> 00:54:27.912 The scoring system used to assess
NOTE Confidence: 0.7385071
00:54:27.912 --> 00:54:29.320 MPN scores MPN symptoms.
NOTE Confidence: 0.7385071
00:54:29.320 --> 00:54:31.848 We can say that perhaps some of it
NOTE Confidence: 0.7385071
00:54:31.848 --> 00:54:34.318 is related to the fact that iron
NOTE Confidence: 0.7385071
00:54:34.318 --> 00:54:36.522 deficiency is gone because I am
NOTE Confidence: 0.7385071
00:54:36.522 --> 00:54:38.387 deficiency can cause the symptoms
NOTE Confidence: 0.7385071
00:54:38.387 --> 00:54:40.232 as well was well tolerated.
NOTE Confidence: 0.7385071
00:54:40.232 --> 00:54:42.696 More than 90% had drug related adverse
NOTE Confidence: 0.7385071
00:54:42.696 --> 00:54:45.156 events, but all of them were sorry,
NOTE Confidence: 0.7385071
00:54:45.160 --> 00:54:47.920 not more than 90% of those who had
NOTE Confidence: 0.7385071
00:54:47.920 --> 00:54:49.739 adverse events were great one,
NOTE Confidence: 0.7385071
00:54:49.740 --> 00:54:52.204 so I would like to conclude by
NOTE Confidence: 0.7385071
00:54:52.204 --> 00:54:53.260 summarizing this study.
NOTE Confidence: 0.7385071
00:54:53.260 --> 00:54:55.015 It was PG 300 subcutaneously
00:54:55.015 --> 00:54:56.419 administered once a week,
00:54:56.420 --> 00:54:59.509 was safe and well tolerated, no Grade 3/4.
00:54:59.509 --> 00:55:01.724 Adverse events related to treatment.
00:55:01.730 --> 00:55:04.145 It was effective in eliminating
00:55:04.145 --> 00:55:06.077 the therapeutic phlebotomy's and
00:55:06.077 --> 00:55:08.405 reversing iron deficiency impact on
00:55:08.405 --> 00:55:10.620 previous symptoms is being studied,
00:55:10.620 --> 00:55:13.380 and this study is also planned
00:55:13.380 --> 00:55:16.239 for opening at Yell this year.
00:55:19.670 --> 00:55:21.806 Thank you Nikolaj and Rory great
00:55:21.806 --> 00:55:24.299 talks and I think very important
00:55:24.300 --> 00:55:26.232 updates from from the meeting
00:55:26.232 --> 00:55:28.548 since we’re a little bit overtime,
00:55:28.550 --> 00:55:30.300 will actually take 10 minutes
beyond 1:00 PM for any questions,
NOTE Confidence: 0.8375762

but I will start with a question for Doctor.  
NOTE Confidence: 0.8375762

But also as he needs to go out  
NOTE Confidence: 0.8375762

at 1:00 PM for another meeting.
NOTE Confidence: 0.8375762

Actually two questions.
NOTE Confidence: 0.8375762

So one of them is.  
NOTE Confidence: 0.8375762

Are there any immediately practice changing  
NOTE Confidence: 0.8375762

updates you take from from the ash meeting?  
NOTE Confidence: 0.8375762

In terms of what we do today today and the  
NOTE Confidence: 0.8375762

second question is from Doctor Isufi,  
NOTE Confidence: 0.8375762

she's asking whether the ampion  
NOTE Confidence: 0.8375762

driver mutations were acquired  
NOTE Confidence: 0.8375762

that were acquired in nutri,  
NOTE Confidence: 0.8375762

worthy, germline or somatic.  
NOTE Confidence: 0.8375762

Also please free to type your  
NOTE Confidence: 0.8375762

questions and if you want to
ask live or any can unmute, you just just indicating the chat Nikolai so no immediate practice changing presentations. I think a similar but the drug for CML will be. Changing our practice when the drug and if the drug is approved, which I think should be you know towards the end of 2021, so you know I presented two studies where the drugs are very interesting and for that reason this studies will be available to our patients at Yale. So in regards to the mutations in utero, no.
Those are somatic mutations.

Those are not germline mutations.

This is somatic mutations which acquired.

So Doctor God actually follows up on the CML presentation and he’s asking if this drug is actually approved.

Does that change your calculation and whether you transplant patients would CML as they go through multiple tiki eyes and maybe to follow up on that?

Like would you put this drug ahead of assertive in your kind of lines of therapy?

If the drug is approved?

Or how would you approach it?

Yeah, so you know,

I, I think it’s too early to say
if this is going to eliminate transplant for some of our patients.

So, but yes, you know, based on the study which I presented today, it may be before positive for patients who had two tiki eyes prior. You know, looking at the results here. So unless there are other questions for doctor adults, if I will go to Doctor Challace.

So Rory, any immediate practice changing abstracts for what people do to leukemia in their practices right now, whether in the community or in the academic centers that you
00:57:54.484 --> 00:57:56.788 take out from the ash meeting.
NOTE Confidence: 0.7030181
00:57:58.250 --> 00:57:59.228 Great question. Thanks
NOTE Confidence: 0.7030181
00:57:59.230 --> 00:58:01.528 amarum. I guess I'll kind of piggyback,
NOTE Confidence: 0.7030181
00:58:01.530 --> 00:58:03.532 but Nikolai said I mean at the
NOTE Confidence: 0.7030181
00:58:03.532 --> 00:58:05.790 moment I would say nothing imminent.
NOTE Confidence: 0.7030181
00:58:05.790 --> 00:58:07.434 Clearly some interesting interim data,
NOTE Confidence: 0.7030181
00:58:07.434 --> 00:58:09.069 although not yet practice changing.
NOTE Confidence: 0.7030181
00:58:09.070 --> 00:58:11.697 I'm most interested in the data for Kinetic
NOTE Confidence: 0.7030181
00:58:11.697 --> 00:58:13.988 lacks added to the dual nucleoside therapy.
NOTE Confidence: 0.7030181
00:58:13.990 --> 00:58:14.980 Cladribine motive sutera
NOTE Confidence: 0.7030181
00:58:14.980 --> 00:58:16.700 been alternating with visa.
NOTE Confidence: 0.7030181
00:58:16.700 --> 00:58:18.874 You know, it's hard to argue with 93%
NOTE Confidence: 0.7030181
00:58:18.874 --> 00:58:21.256 CRC or I rate with you know meeting one
NOTE Confidence: 0.7030181
00:58:21.256 --> 00:58:23.630 cycle response and meeting OS not reached.
NOTE Confidence: 0.7030181
00:58:23.630 --> 00:58:25.370 This compares very favorably with you.
NOTE Confidence: 0.7030181
00:58:25.370 --> 00:58:27.980 Know that the data phrase event you know 15
months OS on the median OS on Bailey a trial.

However, we've learned this year a few times over.

Unfortunately, that single arm studies of agents, despite great clinical
despite great clinical
preclinical rationale, a priority.

Or excellent similar data can fall short, so this needs to
be confirmed in a randomized study.

The same goes for Magnolia Map, which is currently being evaluated
in phase three in comparison days,
amount of therapy, but the double
edged sword you know, pretty

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exciting preclinical data is very exciting. Single arm data begets more. Add on therapy notes with Phase one trial of triplet with days of medical acts makrolon map. Now Aizen Gilteritinib phonetic lacks, so I mean there’s kind of divergent goals here. But to answer your question directly, I’d say nothing that’s immediately practice changing, but. Excited for this to be a different conversation, maybe a few months to a year.
Yeah, look a lot of exciting agents in development. This is a question from Doctor Isufi about Sabbato Lima. Basically, she’s asking whether this targets the leukemia stem cell or does it work as an immune activator and this is a great question arrested. There’s a lot of ongoing research on this issue, but currently the thinking is that it’s a dual targeting drug, meaning that there is direct evidence that it affects the leukemia stem cells by interfering with.
One of the leg and that is important for self renewal of the leukemic stem cells, and I think this is an interesting differentiator from other immune checkpoint activators, but there is also clearly data that also activates the immune response at the level of the T cells. How do we dissect the clinical efficacy in terms of being related to one or the other? I think it’s a question that we are currently exploring and ongoing clinical trials, but I think this would be very important to explore.
I think there’s a question here from Doctor Gowda about CD 447. Inhibition is asking whether CD 47 inhibition does not cause many immune side effects. Thoughts, this is actually a good question. I will let also really give his his insight. I think this is one of the important things in terms of like. Issue related to like single arm studies and needing to know more data. So CD 47 is actually expressed in most of their cells in the normal body. However, they seem to be overexpressed by the leukemia cells and the idea here is that you’re exploring a therapeutic
01:01:02.715 --> 01:01:06.187 window where using the CD 47 you are
NOTE Confidence: 0.8176035
01:01:06.187 --> 01:01:08.449 preferentially targeting the leukemia cells.
NOTE Confidence: 0.8176035
01:01:08.449 --> 01:01:11.227 However, because City 47 is also
NOTE Confidence: 0.8176035
01:01:11.227 --> 01:01:13.040 expressed on. Red blood cells.
NOTE Confidence: 0.8176035
01:01:13.040 --> 01:01:14.790 We do see hemolytic anemia,
NOTE Confidence: 0.8176035
01:01:14.790 --> 01:01:16.878 and some of those patients which
NOTE Confidence: 0.8176035
01:01:16.878 --> 01:01:19.373 can be actually quite severe and it
NOTE Confidence: 0.8176035
01:01:19.373 --> 01:01:21.437 has to be managed quite carefully,
NOTE Confidence: 0.8176035
01:01:21.440 --> 01:01:23.190 especially during the initial phases.
NOTE Confidence: 0.8176035
01:01:23.190 --> 01:01:25.654 And This is why they prime this drug
NOTE Confidence: 0.8176035
01:01:25.654 --> 01:01:28.002 and carefully monitor patients, it, etc.
NOTE Confidence: 0.8176035
01:01:28.002 --> 01:01:30.450 But I think it’s a very good question
NOTE Confidence: 0.8176035
01:01:30.517 --> 01:01:32.827 about why no activity against other
NOTE Confidence: 0.8176035
01:01:32.827 --> 01:01:35.438 CD 47 expressing cells are being seen.
NOTE Confidence: 0.8176035
01:01:35.440 --> 01:01:37.890 I think what’s gonna tell us really?
NOTE Confidence: 0.8176035
01:01:37.890 --> 01:01:40.634 The answer is once we see randomized
data and try to. You know, explore whether some of the things that get attributed to the disease, for example, are really disease related or some kind of subtle immune related adverse events. But I think what is clear. Is we are not seeing the typical immune adverse effects that are seen with the PD one or CTL A4 type of drugs such as pneumonitis colitis. It doesn’t seem that this is commonly seen or do you have any additional insights on this that was very well said?
I mean, I think the key points are the transient, presumed immune mediated hemolytic anemia, which really is why do you know the priming dose is sort of incorporated, but I think you’re right. I mean, there’s some element of specificity for those cells on which CD47 is just enriched. Which happens to be within cells, and I mean outside of like you said, and I mean outside of like you said, subtle or maybe even delayed immune IR A ES that sort of thing. And I think we have what median fourteen 1516 months of follow up?
I mean, maybe there are delayed events that did not yet occurred, but I think it comes down to specificity and more of a different mechanism of action comparison. So you know more of a direct cell effect.

Thank you so much for a few minutes past hour. Be very cognizant of the time. On a Friday afternoon, I’d like to thank everybody who joined us for this session and if there are any additional questions, feel free to.
email their speakers directly.

Thank you so much and looking forward to seeing you next week with their next session next Friday.

Have a great weekend everyone.

Thank you.