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. And my love I almyra prefective neoplasms.
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important to remember that a lot of the abstracts contain preliminary information and preliminary data, and they have not been peer reviewed or finalize or published.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.
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 be cause.
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
NOTE Confidence: 0.8375796
00:03:58.543 --> 00:04:00.577 meandering senior class and other drug,
NOTE Confidence: 0.8375796
00:04:00.580 --> 00:04:01.940 was an oral decitabine.
NOTE Confidence: 0.8375796
00:04:01.940 --> 00:04:03.980 An oral version of this item,
NOTE Confidence: 0.8375796
00:04:03.980 --> 00:04:06.360 in that we will be talking about,
NOTE Confidence: 0.8375796
00:04:06.360 --> 00:04:09.237 but this was also approved in late
NOTE Confidence: 0.8375796
00:04:09.237 --> 00:04:11.719 2024 patients with high risk MD's.
NOTE Confidence: 0.8375796
00:04:11.720 --> 00:04:14.504 So I think it's important to start the
NOTE Confidence: 0.8375796
00:04:14.504 --> 00:04:16.454 presentation by highlighting that high
NOTE Confidence: 0.8375796
00:04:16.454 --> 00:04:19.599 unmet need for patients with high risk MD S.
NOTE Confidence: 0.8375796
00:04:19.600 --> 00:04:21.952 So these are some real life analysis
NOTE Confidence: 0.8375796
00:04:21.952 --> 00:04:23.934 that showed that despite the
NOTE Confidence: 0.8375796
00:04:23.934 --> 00:04:25.738 introduction of hypomethylating agents
NOTE Confidence: 0.8375796
00:04:25.738 --> 00:04:28.426 in for treatment for high risk MD
NOTE Confidence: 0.8375796
00:04:28.426 --> 00:04:30.697 as the outcomes or me and pull the
NOTE Confidence: 0.8375796
00:04:30.697 --> 00:04:33.196 overall responses is around 40 to 50%.
NOTE Confidence: 0.8375796
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, 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.

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
NOTE Confidence: 0.8375796
00:06:10.468 --> 00:06:13.007 this drug which is called in covi.

NOTE Confidence: 0.8375796
00:06:13.010 --> 00:06:15.873 Is to combine decided being with an
NOTE Confidence: 0.8375796
00:06:15.873 --> 00:06:18.474 inhibitor of this city in Germany
NOTE Confidence: 0.8375796
00:06:18.474 --> 00:06:21.066 is called sisters OR and the
NOTE Confidence: 0.8375796
00:06:21.066 --> 00:06:22.579 combination in phase one.
NOTE Confidence: 0.8375796
00:06:22.580 --> 00:06:25.572 Phase two trials was shown to result in
NOTE Confidence: 0.8375796
00:06:25.572 --> 00:06:27.570 similar pharmacodynamic and pharmacodynamic.
NOTE Confidence: 0.8306338
00:06:29.720 --> 00:06:32.216 Activities to the Ivy decided mean,
NOTE Confidence: 0.8306338
00:06:32.220 --> 00:06:35.172 so this combination was taken to a phase
NOTE Confidence: 0.8306338
00:06:35.172 --> 00:06:37.809 three trial that looked at pharmacokinetic
NOTE Confidence: 0.8306338
00:06:37.809 --> 00:06:40.539 equivalence as a final end point,
NOTE Confidence: 0.8306338
00:06:40.540 --> 00:06:43.578 and this trial was presented in 2019
NOTE Confidence: 0.8306338
00:06:43.578 --> 00:06:46.776 and you can see A at the bottom.
NOTE Confidence: 0.8306338
00:06:46.780 --> 00:06:49.685 The final conclusion, which you have 99%
NOTE Confidence: 0.8306338
00:06:49.690 --> 00:06:50.938 equivalence pharmacokinetic equivalence
NOTE Confidence: 0.8306338
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 care centers, have referred patients for us, so we thank you for that. The update from the certain study showed that the complete response rate was around 22% and the median overall survival after 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 --> 00:07:41.808 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 --> 00:08:01.850 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
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%. Remember that the CR rate would is cited in.
Monotherapy is only around 15% to 20% at best and the overall response rate is around 80%. The responses, as you can see, sorry for that responses were durable around 13 months and the median follow up on the study was somewhat short 16 months, 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 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 and transfusion independence of.

Latest on blood. As you can see, 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, One PD, L1, CLU for routinely for management of solid tumors, we’ve been trying to use these drugs for some time now in high risk MD ASAN myeloid malignancy really and so far a lot of the data has been single arm and. A single center data. 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 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
00:15:16.866 --> 00:15:19.039 Effects seems to be low with this.

00:15:19.040 --> 00:15:20.520 With this particular agent,

00:15:20.520 --> 00:15:22.370 so appears on this data.

00:15:22.370 --> 00:15:24.220 There are ongoing several study.

00:15:24.220 --> 00:15:27.444 We just completed a cruel to a randomized

00:15:27.444 --> 00:15:30.624 phase two study in higher risk MD S of.

00:15:30.630 --> 00:15:32.814 Is there with the battle map versus

00:15:32.814 --> 00:15:35.306 is alone and this study is completed

00:15:35.306 --> 00:15:37.532 accrual and we expect the results

00:15:37.601 --> 00:15:39.484 in the next one to two years.

00:15:39.490 --> 00:15:40.802 There’s another face retrial

00:15:40.802 --> 00:15:42.770 that will open here as well.

00:15:42.770 --> 00:15:44.410 Called the stimulus MD S2,

00:15:44.410 --> 00:15:46.714 which is a randomized phase three

00:15:46.714 --> 00:15:48.939 of the same combination is with

NOTE Confidence: 0.82144034
the battle map versus Asia and we have our as well a frontline study with a 7 is events a battle map. All of those are open at yet another interesting immune checkpoint inhibitor is the CD 47. Anti CD 47. They don’t eat me. Signal inhibitor mag rolling up what was presented in ash this year was an update and what the authors shown the significant plus reduction among all patients. But the data was most impressive in patients who have TP 53 mutations in which the median overall survival 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.
00:16:53.875 --> 00:16:55.271 presentation that will happen
NOTE Confidence: 0.82144034
00:16:55.271 --> 00:16:56.900 at the end of the series,
NOTE Confidence: 0.82144034
00:16:56.900 --> 00:16:58.928 but I just wanted to highlight
NOTE Confidence: 0.82144034
00:16:58.928 --> 00:17:00.624 this the conclusion from this
NOTE Confidence: 0.82144034
00:17:00.624 --> 00:17:02.310 because this is in my view,
NOTE Confidence: 0.82144034
00:17:02.310 --> 00:17:04.254 one of the most important abstracts
NOTE Confidence: 0.82144034
00:17:04.254 --> 00:17:06.207 from this ash becausw it showed
NOTE Confidence: 0.82144034
00:17:06.207 --> 00:17:07.707 in a randomized trial data,
NOTE Confidence: 0.82144034
00:17:07.710 --> 00:17:09.300 so here this was randomized.
NOTE Confidence: 0.82144034
00:17:09.300 --> 00:17:11.548 All the data that we have about MD’s
NOTE Confidence: 0.82144034
00:17:11.548 --> 00:17:13.540 improving survival in high risk MD’s
NOTE Confidence: 0.82144034
00:17:13.540 --> 00:17:14.912 patients compared to hypomethylating
NOTE Confidence: 0.82144034
00:17:14.912 --> 00:17:16.930 agents alone is based on Markov
NOTE Confidence: 0.82144034
00:17:16.930 --> 00:17:18.210 decision analysis and modeling,
NOTE Confidence: 0.82144034
00:17:18.210 --> 00:17:20.148 but this is the first randomized
NOTE Confidence: 0.82144034
00:17:20.148 --> 00:17:21.440 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 well as transplant consideration

I will talk about lower risk MD’s

For patients who have RingCentral

this drug is being studied in the

frontline setting in the commands trial,

so this is it’s being studied compared

to low Earth roelle powerton and

this or a potent procrit and this

in the frontline setting and regardless

so whether you have ringstad or plus or not,

you could be randomized to either a

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 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.
for patients after failure of PSA

In which patients are randomized to him until a stat versus placebo.

In the last minute I wanna show you another like non interventional study.

In patients with MD S who have lower who have anemia and as you know one of the open questions in MDSS.

When do you transfuse patients with MD S and many people use different cut off seven or eight of hemoglobin?

Here we used verified quality of life instrument in a investigator initiated effort led by Doctor Go in Table.

Go on Dana Farber.

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 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 ambius rather than
00:20:14.808 --> 00:20:16.909 using random cut offs of hemoglobin.
NOTE Confidence: 0.7745304
00:20:16.910 --> 00:20:19.295 So this is my last slide and I will
NOTE Confidence: 0.7745304
00:20:19.295 --> 00:20:21.735 give the floor now to my colleague
NOTE Confidence: 0.7745304
00:20:21.735 --> 00:20:23.987 Doctor Rory Challis who will update
NOTE Confidence: 0.7745304
00:20:23.987 --> 00:20:25.927 us on acute myeloid leukemia.
NOTE Confidence: 0.7745304
00:20:25.930 --> 00:20:27.302 Updates from the ash.
NOTE Confidence: 0.7745304
00:20:27.302 --> 00:20:29.778 Thank you and we’ll be happy all
NOTE Confidence: 0.7745304
00:20:29.778 --> 00:20:31.836 of us will be taking questions.
NOTE Confidence: 0.7745304
00:20:31.840 --> 00:20:34.280 At the end of that seminar at 12:50,
NOTE Confidence: 0.7745304
00:20:34.280 --> 00:20:34.590 thanks.
NOTE Confidence: 0.78832996
00:20:52.070 --> 00:20:53.700 OK, How are we looking?
NOTE Confidence: 0.78832996
00:20:53.700 --> 00:20:55.646 Every seeing a full slide who
NOTE Confidence: 0.78832996
00:20:55.646 --> 00:21:00.100 screens two screens again? Sorry.
NOTE Confidence: 0.78832996
00:21:00.100 --> 00:21:01.828 Standard technical difficulties.
NOTE Confidence: 0.80935025
00:21:07.370 --> 00:21:09.786 Yeah, I think you need to swap your
NOTE Confidence: 0.80935025
00:21:09.790 --> 00:21:11.310 screens. Let’s try this again.
Yep. How’s that? That looks good, not yet ticket.

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 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.
00:22:39.052 --> 00:22:40.496 So jump right in.

00:22:40.500 --> 00:22:42.720 As many of you are.

00:22:42.720 --> 00:22:44.460 Aware Gilteritinib is a flip through inhibitor,

00:22:44.460 --> 00:22:45.765 which in the Admiral trial was shown to improve survival when compared with classical salvage chemotherapy in their refractory setting.

00:22:53.596 --> 00:22:55.948 So its approval for such over the outcomes for these patients treated with guilt, or it never guilt are still quite poor.

00:23:05.825 --> 00:23:07.850 The preclinical data does support some synergy when Gilteritinib is combined with a BCL two inhibitor.
and those data prompted the launch of the trial that I'll be talking about. In brief, you can see here, so this was done in the context of the following trial schema patients, as you guessed it, had relapsed refractory disease, including wild type patients. In the dose escalation phase, without you know, a low white counts. They really had controlled proliferation. They received standard phonetic lacks 4 milligrams in combination with either guilt 80 or 120 milligrams, which the latter of which is the standard dose that was studied in Phase
testing, and this was later expanded, so the demographics were, for the most part, I would say, expected with regards to age. set of genetic risk given the inclusion criteria that I mentioned before, a majority of patients. Did have ITD mutations? Of note, 65% of patients received prior therapy with the flip three inhibitor and a third enrolled after they had a relapse after allogeneic transplantation. All patients experienced an adverse event.
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 nine 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.
00:26:22.994 -- 00:26:24.520 to at least confirm this.
NOTE Confidence: 0.8010021

00:26:24.520 -- 00:26:25.708 This likely benefit here.
NOTE Confidence: 0.77116615

00:26:27.760 -- 00:26:29.490 Jump into the next update.
NOTE Confidence: 0.77116615

00:26:29.490 -- 00:26:32.381 I have 40 or so older patients with AML.
NOTE Confidence: 0.77116615

00:26:33.820 -- 00:26:35.590 Have generally a poor outcomes,
NOTE Confidence: 0.77116615

00:26:35.590 -- 00:26:37.564 but there there is some variance
NOTE Confidence: 0.77116615

00:26:37.564 -- 00:26:39.480 noted to improve these outcomes.
NOTE Confidence: 0.77116615

00:26:39.480 -- 00:26:41.610 Ventures like the following are underway,
NOTE Confidence: 0.77116615

00:26:41.610 -- 00:26:43.794 so next I’d like to discuss the
NOTE Confidence: 0.77116615

00:26:43.794 -- 00:26:45.989 interim results of a striking study
NOTE Confidence: 0.77116615

00:26:45.989 -- 00:26:47.979 of cladribine and lodosa Terrapín,
NOTE Confidence: 0.77116615

00:26:47.980 -- 00:26:49.750 which is essentially a double
NOTE Confidence: 0.77116615

00:26:49.750 -- 00:26:51.166 nucleoside backbone and Aza,
NOTE Confidence: 0.77116615

00:26:51.170 -- 00:26:53.994 both with the addition of an ethics course.
NOTE Confidence: 0.77116615

00:26:54.000 -- 00:26:56.124 The double clad plus Ldac backbone
NOTE Confidence: 0.77116615

00:26:56.124 -- 00:26:57.890 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 for an 8 week rates of mortality.

So this is the actual trial. This scheme is a little complex,

but essentially like I mentioned, older,

newly diagnosed patients with AML received clad plus ldac 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. I don’t.

I don’t know how to use a
highlighter or whatever, but patients received a \textit{2} then \textit{B} \textit{2} and then back and forth back and forth for up to 18 cycles.

So here the patient characteristics as of the first day to cut off 40\% of patients for older.

Sorry older than 70 years, 25\% were had disease characterized by porous I, generally expected given this population, although nearly half were ellenor.

European leukemia net poor risk 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

Hadelin adverse risk disease.

However, this is just some.

You know, some smaller kind of subpopulation analysis.

You can see that when accounting for set of genetic risk and Dylan risk, not surprising differences are in fact observed.

I would note that 11 patients or 2524% of the 45 responding.

Patients proceeding to transplant with these patients, patients really enjoying more than 90% survival at one year, which when compared with the
NOTE Confidence: 0.8340789
00:30:07.878 --> 00:30:09.634 folks not getting to transform
NOTE Confidence: 0.8340789
00:30:09.634 --> 00:30:11.339 with 69% but a difference,
NOTE Confidence: 0.8340789
00:30:11.339 --> 00:30:13.054 did not reach statistical significance.
NOTE Confidence: 0.8340789
00:30:13.060 --> 00:30:15.118 Likely in the setting of just,
NOTE Confidence: 0.8340789
00:30:15.120 --> 00:30:15.806 you know,
NOTE Confidence: 0.8340789
00:30:15.806 --> 00:30:17.864 obviously a small early phase study.
NOTE Confidence: 0.7932578
00:30:20.240 --> 00:30:21.825 So just going to switch
NOTE Confidence: 0.7932578
00:30:21.825 --> 00:30:23.750 gears a little bit with AML,
NOTE Confidence: 0.7932578
00:30:23.750 --> 00:30:25.750 one of the first decision we have to
NOTE Confidence: 0.7932578
00:30:25.750 --> 00:30:28.218 make is whether patient is quote unquote
NOTE Confidence: 0.7932578
00:30:28.218 --> 00:30:30.123 intensive therapy eligible or not.
NOTE Confidence: 0.7932578
00:30:30.130 --> 00:30:32.062 The first 2 trials I mentioned were
NOTE Confidence: 0.7932578
00:30:32.062 --> 00:30:33.707 really geared towards patients that
NOTE Confidence: 0.7932578
00:30:33.707 --> 00:30:35.227 are intensive therapy ineligible.
NOTE Confidence: 0.7932578
00:30:35.230 --> 00:30:36.980 But what about patients receiving
NOTE Confidence: 0.7932578
00:30:36.980 --> 00:30:39.034 intensive therapy generally felt to be
NOTE Confidence: 0.7932578
00:30:39.034 --> 00:30:41.058 the standard of care for those who are
NOTE Confidence: 0.7932578
00:30:41.058 --> 00:30:42.888 eligible with some specific exceptions?
NOTE Confidence: 0.7932578
00:30:42.890 --> 00:30:44.480 Of course if prompted debate,
NOTE Confidence: 0.7932578
00:30:44.480 --> 00:30:46.400 but that’s a discussion for another.
NOTE Confidence: 0.7932578
00:30:46.400 --> 00:30:47.052 Another presentation.
NOTE Confidence: 0.7932578
00:30:47.052 --> 00:30:49.660 Here is the schema for a trial also
NOTE Confidence: 0.7932578
00:30:49.718 --> 00:30:51.674 out of MD Anderson and evaluating
NOTE Confidence: 0.7932578
00:30:51.674 --> 00:30:53.380 the addition of genetic lacks.
NOTE Confidence: 0.7932578
00:30:53.380 --> 00:30:56.084 To CPX, 3/5 one or the brand name
NOTE Confidence: 0.7932578
00:30:56.084 --> 00:31:01.886 being fix EOS which is standard of care for patients with AML MRC and
NOTE Confidence: 0.7932578
00:31:01.886 --> 00:31:04.246 therapy quote unquote related AML.
NOTE Confidence: 0.7932578
00:31:04.250 --> 00:31:06.924 The design included cohort for adults with
NOTE Confidence: 0.7932578
00:31:06.924 --> 00:31:09.188 newly diagnosed AML as well as looks.
NOTE Confidence: 0.7932578
00:31:09.190 --> 00:31:10.955 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
be considering with concurrency 3A

four inhibition as well as toxicities

prompted prompting dropping to lower dose levels as they came up.

Essentially this was then was given for three weeks during induction as well.

As for 20 three weeks during each cycle.

Consolidation.

In this case they allowed up to four cycles.

Of consolidation,

in contrast to the standard on label CPX 351.

Monotherapy consolidation.

Here the characteristics of the patients who had a broad range of age instead of genetic risk,

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 this is another trial. 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

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

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 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?
NOTE Confidence: 0.79211825
We do not yet really have.

This is Google Map or the this

is the humanized anti CD.

47 IgG, four monoclonal antibody

relevant as tumor expression

specifically macrophage mediated.

Microcytosis and in fact pre

clinical data support that AML,

leukemic blast doing factor,

or enriched for CD 47 Express expression.

So this was studied in combination

with Asia and a phase one.

B2 trial that armored actually touched on
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 --> 00:36:09.210 very poorest population and not the

NOTE Confidence: 0.79211825

00:36:09.210 --> 00:36:11.450 toxicity profile was generally what

NOTE Confidence: 0.79211825

00:36:11.450 --> 00:36:14.026 you would expect with as a monotherapy

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.

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
00:36:51.025 --> 00:36:53.557 18.9 months and even after isolating
patients that had a P3 mutation.

00:36:53.557 --> 00:36:56.317 And we still 12.9 months,
which to be honest is the longest
median OS I believe ever reported
for this population,

00:36:56.320 --> 00:37:01.867 so quite striking as you can see,
four or five patients are still
alive more than two years out,

00:37:01.867 --> 00:37:03.097 so quite impressive.

00:37:03.100 --> 00:37:05.354 Mostly this is raw,
conclude my section and look
forward any questions at the end.

00:37:05.360 --> 00:37:07.274 I apologize to Nikolai.

00:37:07.274 --> 00:37:09.240 I apologize to Nikolai.

00:37:09.240 --> 00:37:10.143 I apologize to Nikolai.

00:37:10.143 --> 00:37:12.674 I apologize to Nikolai.

00:37:12.674 --> 00:37:14.090 I apologize to Nikolai.
So next I’d like to introduce Doctor Nikolai Pedulla 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,
acquisition in pH, negative MPs, and this study managed to show that this mutations are quite as early as in utero until disease develops decades later. So the goal of the study was timing of driver, mutation, acquisition, and clonal expansion evolution dynamics of the clones. The methods used by UK investigators included studying 10 patients with Jack. Two mutations of this is Jack two mutation for Stevens. 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.
So this. 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 able 001. This is the first class stamp inhibitor. An stamp is specifically targeting the BSL 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.
00:41:22.133 --> 00:41:24.680 results with this medication.
NOTE Confidence: 0.71176875
00:41:24.680 --> 00:41:27.344 There is Mr Lated and terminal
NOTE Confidence: 0.71176875
00:41:27.344 --> 00:41:29.668 which auto inhibits able one
NOTE Confidence: 0.71176875
00:41:29.668 --> 00:41:31.958 an with BCR ABL translocation.
NOTE Confidence: 0.71176875
00:41:31.960 --> 00:41:35.920 This N terminal piece of.
NOTE Confidence: 0.71176875
00:41:35.920 --> 00:41:37.066 Peace is gone,
NOTE Confidence: 0.71176875
00:41:37.066 --> 00:41:40.362 so you have PCR and now there is
NOTE Confidence: 0.71176875
00:41:40.362 --> 00:41:43.542 no auto inhibition and there is
NOTE Confidence: 0.71176875
00:41:43.542 --> 00:41:46.091 constitutive activation of ABL kinase
NOTE Confidence: 0.71176875
00:41:46.091 --> 00:41:49.129 Aciman app targets that fork it and
NOTE Confidence: 0.71176875
00:41:49.129 --> 00:41:51.706 can allosterically inhibit PCR able?
NOTE Confidence: 0.71176875
00:41:51.706 --> 00:41:54.376 So as you can see,
NOTE Confidence: 0.71176875
00:41:54.380 --> 00:41:57.418 the other tiki eyes we have currently
NOTE Confidence: 0.71176875
00:41:57.418 --> 00:41:59.941 in practice and use in practice
NOTE Confidence: 0.71176875
00:41:59.941 --> 00:42:02.580 go to ATP binding site and the
NOTE Confidence: 0.78682363
00:42:02.666 --> 00:42:05.166 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 different drugs and 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 drugs used before and patients have to change treatment because they were intolerant or resistant to treatment and so
00:43:18.530 --> 00:43:21.212 the patients was 2315 I mutation

00:43:21.212 --> 00:43:23.737 or V299L mutations were excluded

00:43:23.737 --> 00:43:26.160 because pursuit Nip is not.

00:43:26.160 --> 00:43:27.900 Active against this mutation.

00:43:27.900 --> 00:43:31.094 So this is specifically the study which

00:43:31.094 --> 00:43:33.629 didn’t include T315I mutated patients.

00:43:33.630 --> 00:43:36.546 This particular group of patients was

00:43:36.546 --> 00:43:39.745 addressed by the Phase One study and

00:43:39.745 --> 00:43:42.468 the drug is active against the BCR

00:43:42.552 --> 00:43:45.307 ABL with this particular mutation,

00:43:45.310 --> 00:43:47.146 so patients were randomized.

00:43:47.146 --> 00:43:51.380 As you can see in two to one fashion,

00:43:51.380 --> 00:43:53.530 and the demographics were slightly

00:43:53.530 --> 00:43:56.620 different in two groups I highlighted.

00:43:56.620 --> 00:43:59.350 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 barb 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

00:44:42.965 --> 00:44:44.760 differences between two groups I

00:44:44.819 --> 00:44:47.003 showed on previous slide that the

00:44:47.003 --> 00:44:48.843 logistic regression analysis was done

00:44:48.843 --> 00:44:50.763 and showed that odds ratios adjusted

00:44:50.763 --> 00:44:52.681 for those things which were different

00:44:52.681 --> 00:44:54.583 in two groups were quite similar

00:44:54.583 --> 00:44:56.310 towards ratios without adjustment,

00:44:56.310 --> 00:44:58.690 which gives us hope that the improved

00:44:58.690 --> 00:45:01.008 outcome in a similar treated patients

00:45:01.008 --> 00:45:03.456 is not related to the difference

00:45:03.456 --> 00:45:04.960 in the population.

00:45:04.960 --> 00:45:07.584 So the side effect profiles a lot of

00:45:07.584 --> 00:45:09.858 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 thrombocytopenia. 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 tiks for treatment.

00:45:50.220 --> 00:45:51.753 Assistant Intolerant CML

00:45:51.753 --> 00:45:53.286 population and assimilate,

00:45:53.290 --> 00:45:56.356 which is first class stamp inhibitor,

00:45:56.360 --> 00:45:58.875 showed superior efficacy compared with

00:45:58.875 --> 00:46:02.000 bosutinib with favorable side effect profile,

00:46:02.000 --> 00:46:06.130 so this is upcoming hopefully.

00:46:06.130 --> 00:46:09.950 Approved in the near future

00:46:09.950 --> 00:46:11.474 particularly with resistant and

00:46:11.474 --> 00:46:12.236 intolerant disease.

00:46:12.240 --> 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,
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.
Thrombocytopenia, as you know. So CPI 610 inhibits bat and may suppress cytokine production as well as promote erythroid differentiation as well as normalized megakaryocytic differentiation. So let’s see how this drug did in this phase two studies. So first of all, the study had three arms, so they are mine going present. Today’s I’m three which looked at Jack inhibitor naive patients and use the combination of CPI 610 and Rosslyn. If the other two arms were add on CPI, six dental clinic patients
NOTE Confidence: 0.800081
00:48:14.064 --> 00:48:16.069 who didn’t have full benefit.
NOTE Confidence: 0.800081
00:48:16.070 --> 00:48:17.810 From Brooklyn balloon treatment
NOTE Confidence: 0.800081
00:48:17.810 --> 00:48:19.550 and monotherapy with CPI,
NOTE Confidence: 0.800081
00:48:19.550 --> 00:48:19.972 0610,
NOTE Confidence: 0.800081
00:48:19.972 --> 00:48:22.926 this study was also presented as an
NOTE Confidence: 0.800081
00:48:22.926 --> 00:48:26.080 abstract as a poster during ash meeting,
NOTE Confidence: 0.800081
00:48:26.080 --> 00:48:27.385 so I’m three,
NOTE Confidence: 0.800081
00:48:27.385 --> 00:48:29.560 basically Jack inhibitor naïve Milo
NOTE Confidence: 0.800081
NOTE Confidence: 0.800081
00:48:31.730 --> 00:48:33.418 They received two drugs,
NOTE Confidence: 0.800081
00:48:33.418 --> 00:48:36.476 rock Solid Nap standard of care but
NOTE Confidence: 0.800081
00:48:36.476 --> 00:48:39.128 in additional CPI 0610 better hitter.
NOTE Confidence: 0.800081
00:48:39.130 --> 00:48:41.746 So this drug better hitter was
NOTE Confidence: 0.800081
00:48:41.746 --> 00:48:44.349 administered two weeks on two weeks,
NOTE Confidence: 0.800081
00:48:44.350 --> 00:48:46.546 one week off and.
NOTE Confidence: 0.800081
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%. Reduction of symptoms by 24 weeks. 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 7273% for intermediate 160. It was compatible 7273% for intermediate 160. 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,
so the second endpoint at the symptoms decreased by 50%.

Again, this was seen in 57% of patients. Most of the patients get this clinical benefit in the study at week 24, so one of the interesting finding when you start looks lit up in patients with myelofibrosis you expect a dip in hemoglobin about three points, so here the dip was not as deep. And then, as you can see, hemoglobin improved overtime. In fact, baseline increased a little bit higher than the baseline, so this. Awful actually looks at patients who had
hemoglobin more than 10 and less than 10,
NOTE Confidence: 0.8362344

but didn’t require transfusions.
NOTE Confidence: 0.8362344

And as you can see,
NOTE Confidence: 0.8362344

after initial small dip there is improvement
NOTE Confidence: 0.8362344

in anemia in this subgroup of patients,
NOTE Confidence: 0.8362344

which is quite impressive.
NOTE Confidence: 0.8362344

So one other thing,
NOTE Confidence: 0.8362344

at the bone marrow’s,
NOTE Confidence: 0.8362344

their biopsies were done at the
NOTE Confidence: 0.8362344

beginning as well as during the study
NOTE Confidence: 0.8362344

and there was improvement in fibrosis.
NOTE Confidence: 0.8362344

Great in 1/3 of patients and most of
NOTE Confidence: 0.8362344

the improvements observed were observed
NOTE Confidence: 0.8362344

during the first six months of treatment.
NOTE Confidence: 0.8362344

Only two patients get worsening of
NOTE Confidence: 0.8362344

fibrosis and you can see that there
00:50:35.338 --> 00:50:38.292 is also a sign that there is improved
NOTE Confidence: 0.8362344
00:50:38.292 --> 00:50:41.188 air throughout differentiation and
NOTE Confidence: 0.8362344
00:50:41.188 --> 00:50:43.360 normalization of megakaryocytic
NOTE Confidence: 0.8362344
00:50:43.360 --> 00:50:44.084 histopathology.
NOTE Confidence: 0.8362344
00:50:47.418 --> 00:50:48.708 So the side effects the CPI 16 in
NOTE Confidence: 0.8362344
00:50:50.036 --> 00:50:51.168 combination with Link was generally
NOTE Confidence: 0.8362344
00:50:51.170 --> 00:50:54.002 well tolerated.
NOTE Confidence: 0.8362344
00:50:54.002 --> 00:50:55.890 87% reported at least one
NOTE Confidence: 0.8362344
00:50:55.890 --> 00:51:00.489 treatment emergent adverse event.
NOTE Confidence: 0.8362344
00:51:00.490 --> 00:51:02.386 44% reported, one grade,
NOTE Confidence: 0.8362344
00:51:02.386 --> 00:51:05.580 three treatment emergent adverse event.
NOTE Confidence: 0.8362344
00:51:05.580 --> 00:51:07.488 So the most common ones were
NOTE Confidence: 0.8362344
00:51:07.488 --> 00:51:09.420 haematological and now this was
NOTE Confidence: 0.8362344
00:51:09.420 --> 00:51:11.425 an email from both cytopenia.
NOTE Confidence: 0.8362344
00:51:11.425 --> 00:51:13.425 Of course this may be manifestations
NOTE Confidence: 0.8362344
88
of the disease itself,

the most common and non human to

logic was diarrhea or which was

mild moderate Grade 1 two so.

Great five were two events.

Multiorgan failure with due to

sepsis times two.

So overall the drug was pretty

reasonably well tolerated.

The combination of drugs I have

to say because we’re looking at

the side effect profile of two

drugs administered together.

So finally conclusions 67% of patients

achieve CVR 35 comparing to historical phase,

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 and a randomized study for treatment. Naive patients looks lit up against ruxolitinib Sir,
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
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
Those finding at 28 weeks.
NOTE Confidence: 0.7385071
There's those escalation,
NOTE Confidence: 0.7385071
trying to identify how much
NOTE Confidence: 0.7385071
subcutaneous injections once a week.
NOTE Confidence: 0.7385071
You need to control phlebotomy
NOTE Confidence: 0.7385071
and you know when you identify it.
NOTE Confidence: 0.7385071
You kind of continue with that dose.
NOTE Confidence: 0.7385071
Then you reach the second part of
NOTE Confidence: 0.7385071
the study blinded withdrawal.
NOTE Confidence: 0.7385071
Some patients continue real thing others
NOTE Confidence: 0.7385071
and switch to placebo to see how it's
NOTE Confidence: 0.7385071
going to affect the phlebotomy requirement.
NOTE Confidence: 0.7385071
And finally,
NOTE Confidence: 0.7385071
there is open label extension so
NOTE Confidence: 0.7385071
that the report only dealt with
NOTE Confidence: 0.7385071
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 see, ferritin increasing significantly, showing that iron deficiency is gone. Total symptom score improving with time. This is subset you can see improved concentration,
fatigue, itching for writers, and though this is.
The scoring system used to assess MPN scores MPN symptoms. We can say that perhaps some of it is related to the fact that iron deficiency is gone because I am deficient can cause the symptoms as well was well tolerated. More than 90% had drug related adverse events, but all of them were sorry, not more than 90% of those who had adverse events were great one, so I would like to conclude by summarizing this study. It was PG 300 subcutaneously.
00:54:56.420 --> 00:54:59.509 was safe and well tolerated, no Grade 3/4.

00:55:04.145 --> 00:55:08.405 reversing iron deficiency impact on

00:55:10.620 --> 00:55:13.380 previous symptoms is being studied, and this study is also planned


00:55:19.670 --> 00:55:21.806 Thank you Nikolaj and Rory great

00:55:24.300 --> 00:55:26.232 updates from the meeting

00:55:26.232 --> 00:55:28.548 since we’re a little bit overtime,

00:55:30.300 will actually take 10 minutes
beyond 1:00 PM for any questions, but I will start with a question for Doctor. But also as he needs to go out at 1:00 PM for another meeting. Actually two questions. So one of them is. Are there any immediately practice changing updates you take from the ash meeting? In terms of what we do day today and the second question is from Doctor Isufi, she's asking whether the ampion driver mutations were acquired that were acquired in nutri, worthy, germline or somatic. Also please free to type your 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 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 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
take out from the ash meeting.

NOTE Confidence: 0.7030181

Great question. Thanks

NOTE Confidence: 0.7030181

I guess I'll kind of piggyback, but Nikolai said I mean at the moment I would say nothing imminent.

Clearly some interesting interim data, although not yet practice changing.

I'm most interested in the data for Kinetic lacks added to the dual nucleoside therapy.

I know that the data phrase event you know 15
00:58:27.980 --> 00:58:31.480 months OS on the median OS on Bailey a trial.

00:58:31.480 --> 00:58:31.805 However,

00:58:31.805 --> 00:58:34.410 we've learned this year a few times over.

00:58:34.410 --> 00:58:34.740 Unfortunately,

00:58:34.740 --> 00:58:36.695 that single arm studies of agents,

00:58:36.695 --> 00:58:37.670 despite great clinical

00:58:37.670 --> 00:58:38.978 preclinical rationale, a priority.

00:58:40.400 --> 00:58:41.946 Or excellent similar data can

00:58:41.946 --> 00:58:43.800 fall short, so this needs to

00:58:43.800 --> 00:58:45.650 be confirmed in a randomized study.

00:58:45.650 --> 00:58:47.506 The same goes for Magnolia Map,

00:58:47.506 --> 00:58:49.046 which is currently being evaluated

00:58:49.046 --> 00:58:50.907 in phase three in comparison days,

00:58:50.907 --> 00:58:52.760 amount of therapy, but the double

00:58:52.760 --> 00:58:55.538 edged sword you know, pretty

NOTE Confidence: 0.733859
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
window where using the CD 47 you are preferentially targeting the leukemia cells. However, because City 47 is also expressed on Red blood cells. We do see hemolytic anemia, and some of those patients which can be actually quite severe and it has to be managed quite carefully, especially during the initial phases. And this is why they prime this drug and carefully monitor patients, it, etc. But I think it’s a very good question about why no activity against other CD 47 expressing cells are being seen. I think what’s gonna tell us really? 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. Which happens to be within cells, and I mean outside of like you said, and I mean 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.